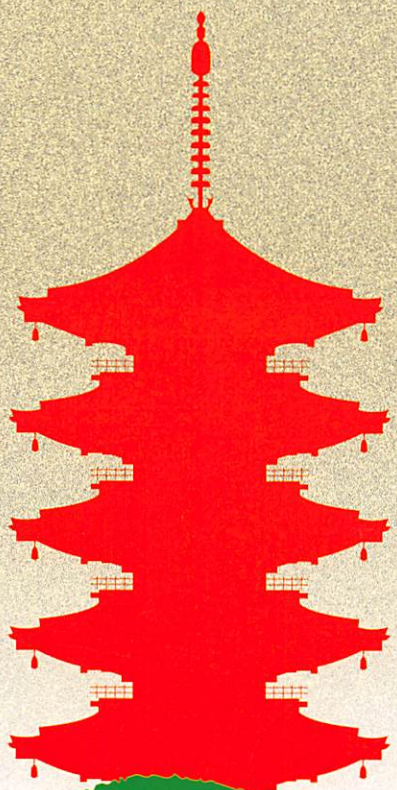
The First International Symposium on Process Chemistry (ISPC 08)

(2008 Summer Symposium of the Japanese Society for Process Chemistry)

Abstracts



J. S. P. C.

The Japanese Society for Process Chemistry

Organizer:
The Japanese Society for Process Chemistry
Support:
The Chemical Society of Japan
The Pharmaceutical Society of Japan
Japan Society for Bioscience, Biotechnology, and Agrochemistry
The Society of Synthetic Organic Chemistry, Japan
The Kinki Chemical Society, Japan
The Society of Separation Process Engineers, Japan
The Chemical Daily Co., Ltd.

July 28(Mon)−30(Wed), 2008
Venue:
Kyoto International Conference Center

ダイセルキラルカラム®

早急にキラル化合物を入手したいお客様へ

カラム法によるキラル分取でお客様の開発スピードをUP!!

mg~kg

お客様		ダイセル
問合せ		打合せ（直ちに営業がお伺い致します）
	約1週間で見積提出	秘密保持に関する確認書提出
検討用ラセミ体ご提供（30mg～）		分離条件検討、安定性試験、見積提出（※原則として、ここまでの費用は頂きません）
発注 分取用ラセミ体ご提供	発注から納品まで約10日間	HPLC分取 SFC分取 SMB分取
納品		

お問合せ・資料請求は、

chiral@daicel.co.jp

東京:03-6711-8222　大阪:06-6342-6161

http://www.daicelchiral.com/

Innovation for Tomorrow
ダイセル化学工業株式会社
CPIカンパニー Chiral Pharmaceutical Ingredients

●東日本　〒108-8230 東京都港区港南2-18-1 JR品川イーストビル14F　TEL.03-6711-8222（直）
●西日本　〒530-0001 大阪市北区梅田3-4-5　毎日インテシオ20F　TEL.06-6342-6161（直）

The First International Symposium on Process Chemistry (ISPC 08)
(2008 Summer Symposium of the Japanese Society for Process Chemistry)

Abstracts

J. S. P. C.

The Japanese Society for Process Chemistry

July 28(Mon)-30(Wed), 2008

Venue:
Kyoto International Conference Center

Organizer:
The Japanese Society for Process Chemistry
Support:
The Chemical Society of Japan
The Pharmaceutical Society of Japan
Japan Society for Bioscience, Biotechnology, and Agrochemistry
The Society of Synthetic Organic Chemistry, Japan
The Kinki Chemical Society, Japan
The Society of Separation Process Engineers, Japan
The Chemical Daily Co., Ltd.

Greetings from the Chairman of ISPC 08

Welcome to ISPC 08 !

On behalf of the organizing committee, I would like to extend a wholehearted welcome to all the participants to ISPC 08, the First International Symposium on Process Chemistry, in conjunction with the 2008 Summer Symposium of the Japanese Society for Process Chemistry (JSPC).

JSPC was founded in 2001, just the beginning of this century, after several symposia and sincere discussions between process chemistry directors of industries and university professors.

JSPC aims to promote and encourage the development of process chemistry in various directions among members. Process chemistry includes synthetic chemistry, analytical chemistry, chemical technology, solid state chemistry, environmental science, regulations, patent problem and so on, to mention but a few.

JSPC has regular symposia twice a year, summer and winter, after the foundation commemorative symposium was held in 2002. Members of JSPC belong to industries, especially pharmaceutical ones, manufacturers of intermediates, universities, and so on. The number of participants to symposia is yearly increasing. Furthermore, JSPC has a seminar called "Process Chemistry Lounge" in which all participants will stay in the same accommodation and discuss all areas of process chemistry.

JSPC believes that the Society will have a key feature to advance and improve process chemistry in this century. It is our great pleasure to hold the international symposium, ISPC 08, this year, organized by JSPC.

Process chemistry now occupies an important hub position between substance creative chemistry and their commercial production. Without its strong activity, no useful compounds would be produced in an efficient manner on a large industrial scale.

ISPC 08 will be a truly international symposium covering all aspects of process chemistry.

The symposium will include keynote lectures by top runners of process chemistry in the world, selected short communications, poster presentations, and exhibitions. Mutual understanding among participants will be actively deepened in coffee break of the lectures, welcome reception, and banquet.

Kyoto, the symposium place, is a historical city which was the capital of Japan from 794 until 1868 before the captal was moved to Tokyo. It has a reputation worldwide as Japan's most beautiful city, and you will discover so many unparalled collections of palaces, temples, and shirines. You could enjoy these beautiful and historical places in addition to the Symposium.

Takayuki Shioiri

Takayuki Shioiri
Chairman of the Organizing Committee of ISPC 08
President of the Japanese Society for Process Chemistry

Organizing Committee

■Chair

Takayuki Shioiri	(Meijo Univ.)

■Members

Kunisuke Izawa	(Ajinomoto)
Toshiro Konoike	(Shionogi)
Hironao Sajiki	(Gifu Pharm. Univ.)
Shigeru Soda	(Eisai)
Yoo Tanabe	(Kwansei Gakuin Univ.)
Kiyoshi Tomioka	(Kyoto Univ.)

■Advisory Board

Takahiko Akiyama	(Gakushuin Univ.)
Hidetsura Cho	(Tohoku Univ.)
Kenji Inoue	(Kaneka)
Koji Kagara	(Ohara)
Satoru Kuraoka	(Mitsubishi Tanabe)
Toshiaki Mase	(Banyu)
Akihiko Miyadera	(Daiichi Sankyo)
Takashi Mukuta	(Astellas)
Yasushi Murai	(Meiji Seika)
Yuzuru Saito	(Takeda)
Masakatsu Shibasaki	(Univ. of Tokyo)
Ichiro Shinkai	(Beta Chem)
Kinichi Tadano	(Keio Univ.)
Takumi Tanaka	(Wako)
Kuniaki Tatsuta	(Waseda Univ.)

To Participants of The First International Symposium on Process Chemistry (ISPC 08)

* Those who had registered in advance are advised to show to the receptionists before entering the venue the registration confirmations that we had previously mailed to them. Name-card holders are to be collected after the symposium.
* Neither photographing nor videotaping is allowed at the symposium.
* Please set cell phones to silent mode.
* Light clothes are recommended for the symposium.
* A cloakroom is available.

To Poster Presenters

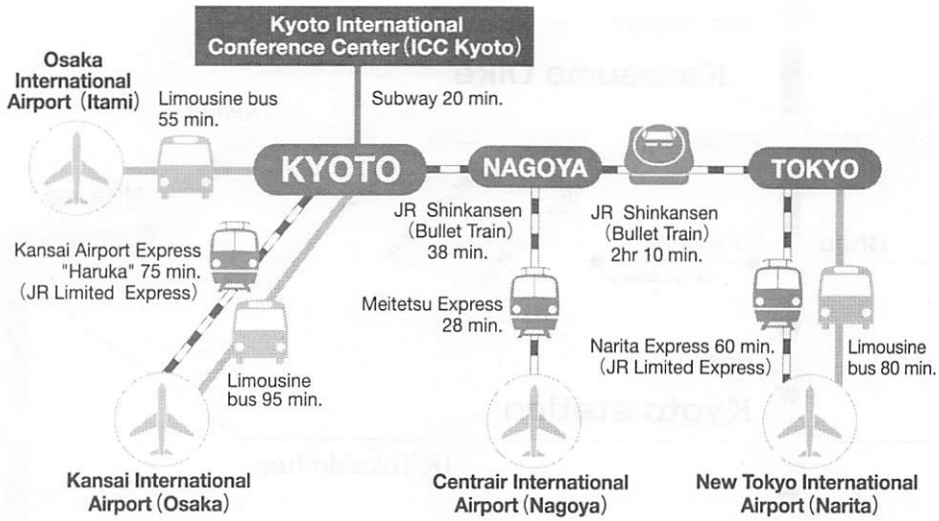
* Poster presenters need not check-in at the reception desks.
* The venue for the poster presentation is Annex Hall. Poster presenters need to have their posters in place by 2:30 p.m., July 29, at the latest and keep them up for two days. Please start putting them away at 4:30 p.m., July 30, when the poster session is scheduled to end, and finish by 6 p.m., when the symposium is to come to a close.
* Oral presenters need to come to the front of the entrance of the Main Hall at the following times:

  12:40 p.m. on July 29 1:10 p.m. on July 30

Access

Easy International Access

Located on the main Shinkansen (Bullet Train) Line,
Kyoto is directly accessible from NARITA (Tokyo),
Centrair (Nagoya) and
KANSAI (Osaka) International Airports.

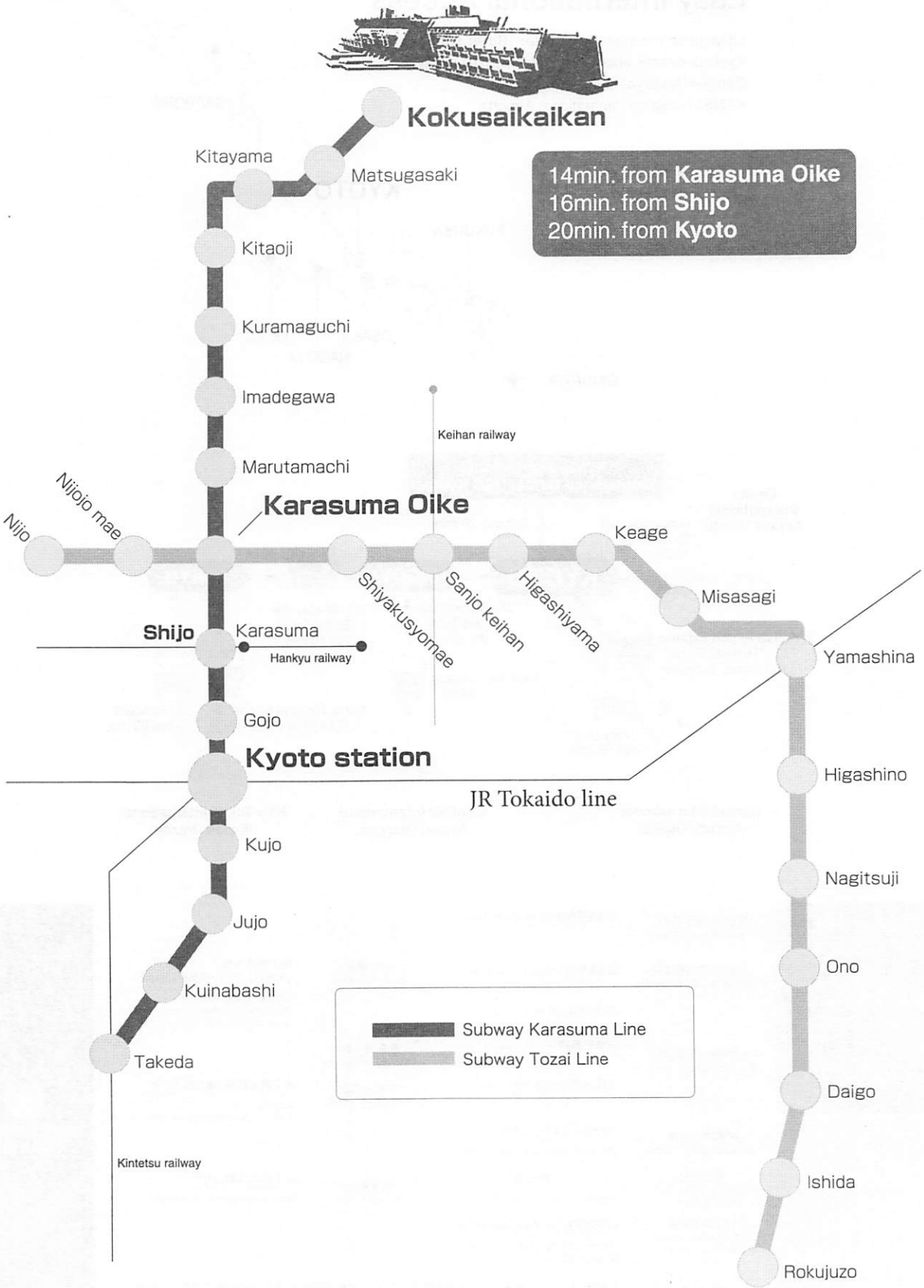


鉄道をご利用の場合 Access by rail	東京・中部方面より From Tokyo and Chubu	東海道新幹線 (JR Tokaido Shinkansen)	JR京都駅 JR Kyoto station	地下鉄烏丸線 (京都駅より20分・四条駅より16分) Subway: Karasuma Line (From Kyoto station, 20 min.; from Shijo station, 16 min.)
	九州・中国方面より From Kyushu and Chugoku	山陽新幹線 (JR Sanyo Shinkansen)		
	大阪・神戸方面より From Osaka and Kobe	JR京都線 (JR Kyoto Line)		
		阪急京都線 (Hankyu Kyoto Line)	四条烏丸駅 Shijo Karasuma station	
		京阪本線 (Keihan Main Line)	京阪三条駅 Keihan Sanjo station	地下鉄東西線・烏丸線 (20分) Subway: Tozai Line & Karasuma Line (20 min.)
飛行機をご利用の場合 Access by air	関西国際空港 Kansai International Airport	JR特急「はるか」(75分) JR Haruka Airport Express (75 min.)	JR京都駅 JR Kyoto station	
	大阪空港 Osaka International Airport (Itami)	リムジンバス (約55分) Limousine bus (approx. 55 min.)		地下鉄烏丸線 (20分) Subway: Karasuma Line (20 min.)
	中部国際空港 Centrair International Airport (Nagoya)	名鉄空港快速特急+東海道新幹線 (約80分) Meitetsu Express + JR Shinkansen (approx. 80 min.)		
お車をご利用の場合 Access by road	名神高速道路 Meishin Expressway	京都南I.C.または京都東I.C.より市内道路表示の「国立京都国際会館」を目印にお越しください。(40分) Take the Kyoto South or Kyoto East exit and follow the signs to "Kyoto International Conference Center." (40 min.)		

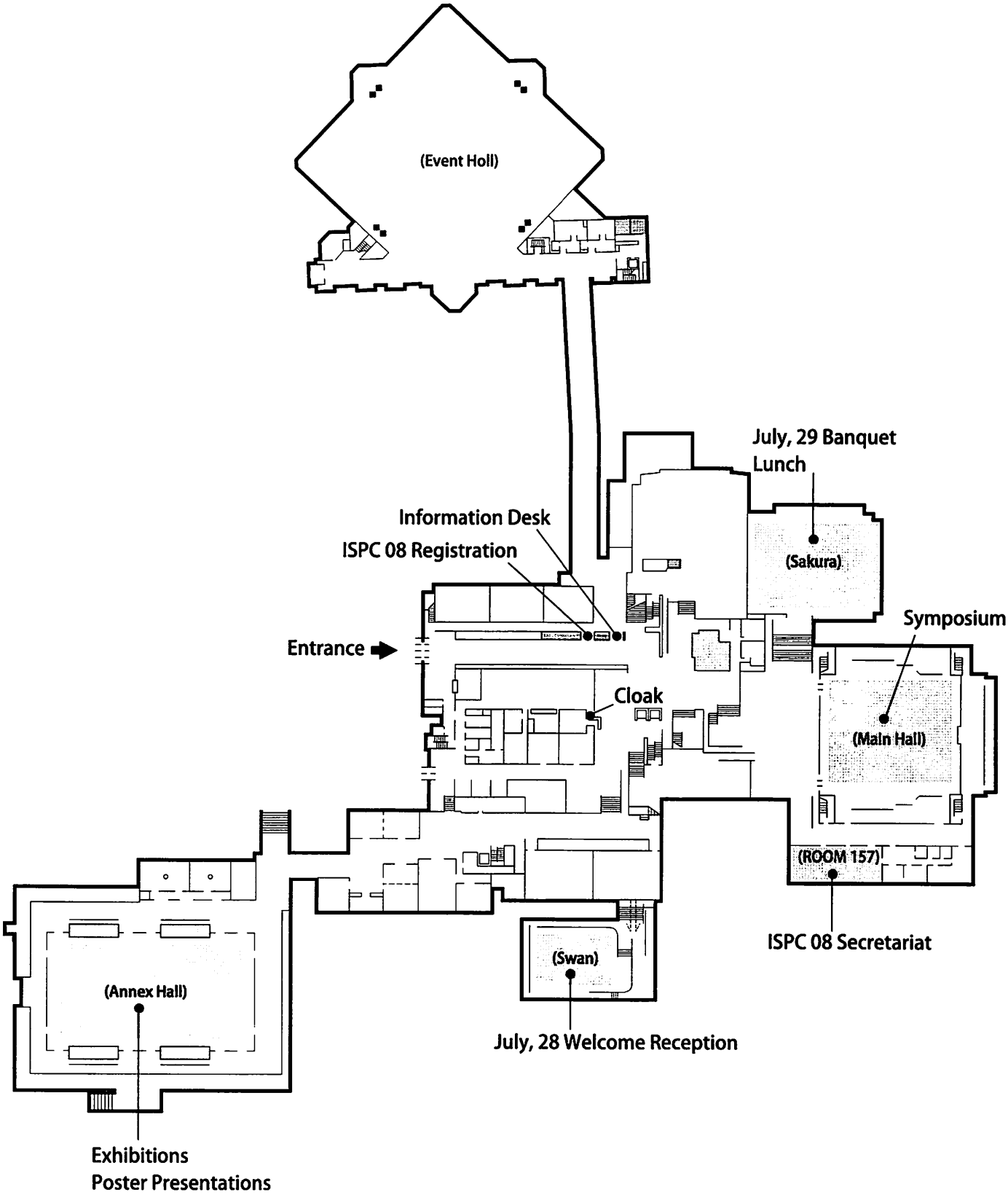
国立京都国際会館
ICC Kyoto

ICC Kyoto **Subway Line**

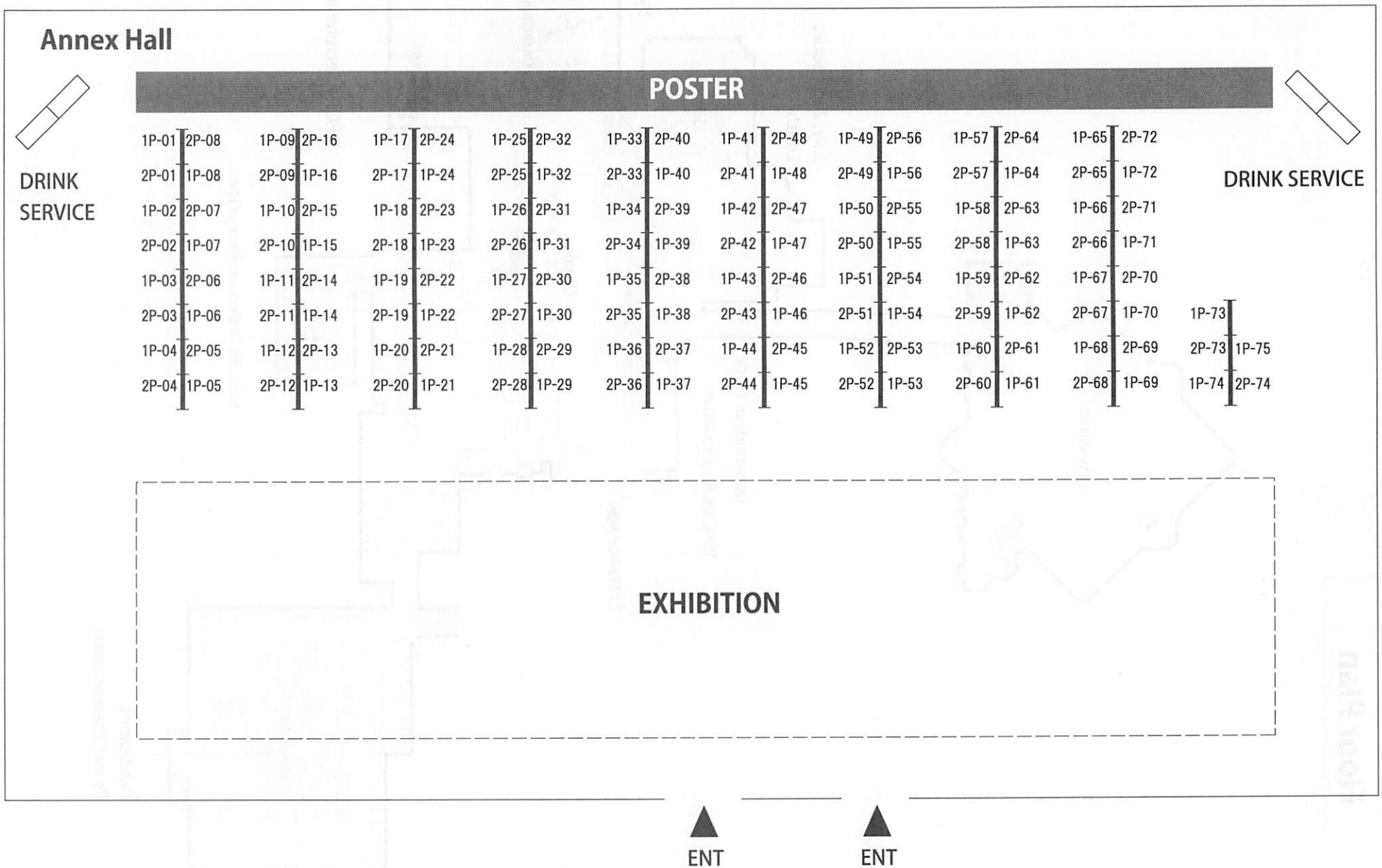
Kyoto International Conference Center



Floor Plan


(Event Holl)
July, 29 Banquet
Lunch
(Sakura)
Information Desk
ISPC 08 Registration
Entrance
Symposium
Cloak
(Main Hall)
(ROOM 157)
ISPC 08 Secretariat
(Swan)
(Annex Hall)
July, 28 Welcome Reception
Exhibitions
Poster Presentations

Poster Floor Layout



The First International Symposium on Process Chemistry (ISPC 08)

(The Japanese Society for Process Chemistry 2008 Summer Symposium)

Program

(**Main Hall** is used unless otherwise stated.)

July 28 (Mon)

15:30-17:00	**Registration**
17:00-19:00	**Welcome Reception** (*Banquet Hall Swan*)

July 29 (Tue)

8:30	**Registration**
9:00-9:10	**Opening Remarks** Takayuki Shioiri (*Meijo Univ., Japan*)
9:10-9:50	**From Milligrams to Tons: The Importance of Synthesis & Process**
(K−1)	**Research in the Development of New Drugs**
(Keynote Lecture)	**Martin Karpf** (*F. Hoffmann-La Roche, Switzerland*)
	Chair: Toshiro Konoike (*Shionogi, Japan*)
9:50-10:20	**Streamlining Synthesis via C-H Oxidation**
(K−2)	**M. Christina White** (*Univ. of Illinois, Urbana-Champaign, USA*)
(Keynote Lecture)	*Chair:* Hironao Sajiki (*Gifu Pharm. Univ., Japan*)
10:20-10:35	**Coffee Break**
10:35-11:05	**Design of Dynamic Salt Catalysts Based on Acid–Base Combination**
(K−3)	**Chemistry**
(Keynote Lecture)	**Kazuaki Ishihara** (*Nagoya Univ., Japan*)
	Chair: Yoo Tanabe (*Kwansei Gakuin Univ., Japan*)
11:05-11:35	**Enzymo-Metallic Dynamic Kinetic Resolution as a New Tool for Chiral**
(K−4)	**Synthesis**
(Keynote Lecture)	**Mahn-Joo Kim** (*Pohang Univ. of Sci. & Tec., Korea*)
	Chair: Kenji Inoue (*Kaneka, Japan*)
11:35-12:05	**Matching Chemistry with Chemical Engineering for Optimum Design**
(K−5)	**and Performance of Pharmaceutical Processing**
(Keynote Lecture)	**Aniruddha B. Pandit** (*Univ. of Mumbai, India*)
	Chair: Koji Kagara (*Ohara, Japan*)
12:05-13:00	**Lunch** (*Banquet Hall Sakura*)

13:00-14:30	**Oral Presentation**
	(1P-03, 1P-20, 1P-22, 1P-24, 1P-31, 1P-38, 1P-43, 1P-49, 1P-55)
	Chair: Toshiaki Mase (*Banyu, Japan*)
14:30-16:30	**Poster Presentation (1P-01～1P-75)** (*Annex Hall*)
16:30-16:35	**Break**
16:35-17:05	**Boron Reagents in Process Chemistry: Excellent Tools for Selective**
(K－6)	**Reductions**
(Keynote Lecture)	**Karl Matos** (*BASF Corporation, USA*)
	Chair: Yoshiharu Iwabuchi (*Tohoku Univ., Japan*)
17:05-17:45	**Asymmetric Oxidation with Hydrogen Peroxide, an Effective and**
(K－7)	**Versatile Oxidant**
(Keynote Lecture)	**Tsutomu Katsuki** (*Kyushu Univ., Japan*)
	Chair: Masakatsu Shibasaki (*Univ. of Tokyo, Japan*)
18:00-20:30	**Banquet** (*Banquet Hall Sakura*)
	Chair: Kinichi Tadano (*Keio Univ., Japan*)

July 30 (Wed)

9:00-9:40	**Process Development of HIV Integrase Inhibitor S-1360**
(K－8)	**Toshiro Konoike** (*Shionogi, Japan*)
(Keynote Lecture)	*Chair:* Ichiro Shinkai (*Beta Chem, Japan*)
9:40-10:10	**An Entirely New Methodology for Synthesizing Perfluorinated**
(K－9)	**Compounds**
(Keynote Lecture)	**Takashi Okazoe** (*Asahi Glass, Japan*)
	Chair: Noritada Matsuo (*Sumitomo Chem., Japan*)
10:10-10:40	**New Methods for the Functionalization of Aromatic Compounds**
(K－10)	**Keith Fagnou** (*Univ. of Ottawa, Canada*)
(Keynote Lecture)	*Chair:* Yujiro Hayashi (*Tokyo Univ. of Science, Japan*)
10:40-10:55	**Coffee Break**
10:55-11:25	**Byproduct-Free C-C Bond Formation via Catalytic Hydrogenation**
(K－11)	**and Transfer Hydrogenation**
(Keynote Lecture)	**Michael J. Krische** (*Univ. of Texas at Austin, USA*)
	Chair: Takahiko Akiyama (*Gakushuin Univ., Japan*)

11:25-11:55	**Commercialization of a Sodium Hydride Mediated Arylation Process**
(K－12)	**Mark Butchko** (*Eli Lilly, USA*)
(Keynote Lecture)	*Chair:* Norio Hashimoto (*Astellas, Japan*)
11:55-13:00	**Lunch** (*Banquet Hall Sakura*)
13:00-13:30	**General Assembly of JSPC**
13:30-14:30	**Oral Presentation**
	(2P-02, 2P-08, 2P-18, 2P-30, 2P-37, 2P-49)
	Chair: Yasushi Murai (*Meiji Seika, Japan*)
14:30-16:30	**Poster Presentation (2P-01～2P-74)** (*Annex Hall*)
16:30-16:35	**Break**
16:35-17:05	**JSPC Award for Excellence 2007 Lecture**
	Chair: Takumi Tanaka (*Wako, Japan*)
(A－1)	**Process development of a key building block for anti-AIDS drugs by proline catalyzed enatio-selective direct cross aldol reaction**
	Tetsuya Ikemoto*, Yosuke Watanabe, Junichi Tomokawa, Takehiko Kawakami, Yasuo Uekita, Isao Kurimoto
	(*Sumitomo Chem., Japan*)
(A－2)	**Catalytic Reduction of Carboxamides by Hydrosilanes**
	Hideo Nagashima*, Hidehiro Sasakuma, Nariaki Harada, Hironori Tsutsumi, Yukihiro Motoyama
	(*Kyushu Univ., Japan*)
(A－3)	**Development of One-pot Synthesis of New Antiarthritic Drug Candidate S-2474 with High E-Selectivity**
	Takemasa Hida*, Katsuo Oda, Hideo Nogusa, Toshiaki Masui
	(*Shionogi, Japan*)
17:05-17:45	**Design Space for Drug Substance - the Approach used for**
(K－13)	**Vandetanib**
(Keynote Lecture)	**David Haywood** (*AstraZeneca, UK*)
	Chair: Kunisuke Izawa (*Ajinomoto, Japan*)
17:45-17:50	**Release of JSPC Awardees for Excellence 2008**
17:50-18:00	**Closing Remarks** Kiyoshi Tomioka (*Kyoto Univ., Japan*)

Poster Program

Poster Program

July 29 (Tue)

Oral Presentation 13:00-14:30 (Main Hall) **◆Oral Presenter**
Discussion 14:30-16:30 (Annex Hall)

1P-01 **A New Ethereal Solvent:CycloPentyl Methyl Ether(CPME) for Process Innovation and Green Chemistry**
Kiyoshi Watanabe* (Zeon Corporation, Japan)
Yasuhiro Torisawa (Takasaki University of Health and Welfare, Japan)

1P-02 **Efficient Approaches to S-Alkyl-N-alkylisothioureas :Syntheses of Histamine H3 Antagonist Clobenpropit and Its Analogues**
Hiroki Yoneyama, Mifuyu Yasunaga, Lisa Araki, Shinya Harusawa*
(Osaka University of Pharmaceutical Sciences, Japan)
Kouta Hatano, Atsushi Yamatodani (Osaka University, Japan)

1P-03 ◆ **A Practical Synthesis of the PDE4 inhibitor KW-4490**
Arata Yanagisawa*, Koichiro Nishimura ,Tetsuya Nezu, Kyoji Ando, Ayako Maki, Eiichiro Imai, Shin-ichiro Mohri (Kyowa Hakko Kogyo, Japan)

1P-04 **Solvent-free Synthesis of Heterocycles Using Carbon Dioxide (1 atm)**
Takumi Mizuno*, Takeo Nakai, Masatoshi Mihara
(Osaka Municipal Technical Research Institute, Japan)

1P-05 **A One-Pot Procedure for Acetylation or Trifluoroacetylation of Amines Using Acetic Acid or Trifluoroacetic Acid as an Acylating Reagent**
Yasuo Kikugawa*, Junpei Otaka, Naohiro Oshima, Hiroshi Yamazaki, Takesi Sakamoto
(Josai University, Japan)

1P-06 **Highly stereoselective α-O-sialylation with N,N-Ac,Boc laurylthio sialoside in CPME**
Kiyoshi Ikeda*, Keisuke Miyamoto, Masayuki Sato
(School of Pharmaceutical Sciences, University of Shizuoka, Japan)

1P-07 **Properties of diol type silica in the chromatography separation**
Kazunori Nobuhara*, Mitsuhiro Kamimura, Takako Inoue, Makoto Kawai, Ryuji Orii
(Fuji Silysia Chemical Ltd., Japan)

1P-08 **Recycle effect on Mass-Transfer Efficiency Improvement in Multi-Pass Mass Exchangers**
Chii-Dong Ho*, Jr-Wei Tu (Tamkang University, Taiwan)

1P-09 **Molecular sieves supported Pd catalyst (Pd/MS5A) for chemoselective hydrogenation**
Tomohiro Maegawa*, Masatsugu Kato, Ayako Tani, Tohru Takahashi, Yasunari Monguchi, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

1P-10 **Regioselective protection of sugars catalyzed by organotin**
Yuki Kubo*, Yosuke Demizu, Osamu Onomura (Nagasaki University, Japan)

1P-11 **Process Development using automated reactor -kinetics of nitroso reaction-**
Takashi Naka*, Yasunari Takayasu, Hiroshi Iwamura
(Mitsubishi Tanabe Pharma Corporation, Japan)

1P-12 **Change in neuron aggregation and neurite fasciculation on EVAL membranes modified with different diamines**
Tai-Horng Young* (National Taiwan University, Taiwan)

1P-13 **Process Development of a Novel Na Ion channel Blocker E2070**
Manabu Kubota*, Atsushi Kamata, Naoyuki Shimomura (Eisai Co., Ltd., Japan)

1P-14 **Copper-catalyzed C-H activation/C-O bond formation for the synthesis of benzoxazoles**
Satoshi Ueda*, Hideko Nagasawa (Gifu Pharmaceutical University, Japan)

1P-15 **Photocuring of Acrylated Dendrimer**
Syang-Peng Rwei* (National Taipei University of Technology, Taiwan)

1P-16 **Asymmetric Synthesis of Cyclic Aza-Morita-Baylis-Hillman Reaction Products Using Pd-DIAPHOX Catalyst System**
Tetsuhiro Nemoto*, Takashi Fukuyama, Kazumi Kakugawa, Yuko Maruyama, Yasumasa Hamada (Chiba University, Japan)

1P-17 **Pd/PEI : Partial hydrogenation catalyst of alkynes to alkenes**
Shigeki Mori*, Tomoyuki Ohkubo, Takashi Ikawa, Akira Kume, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

1P-18 **Design and construction of biocatalyst for multistep reaction, and development of biotransformation-organic synthesis composite process -Process development of chiral intermediate (EVAL)-**
Motoko Hayashi*, Norihiro Kimoto, Hiroaki Yamamoto, Kiyoshi Ikura, Naohiro Hashikawa (Daicel Chemical Industries, Ltd., Japan)

1P-19 **Industrial Scale Application of Umicore's Leading Edge Catalysts & Technologies**
Yoshiaki Horiguchi* (Umicore Japan K.K., Japan)

1P-20 ◆ **Control of Primary Nucleation by Utrasonic Irradiation**
Izumi Hirasawa* (Waseda University, Japan)

1P-21 **DMEAD : A Separation-Friendly Reagent for Mitsunobu Reaction**
Kazutake Hagiya, Yasuhiro Sakamoto, Masao Miyatake, Hikaru Tanaka, Hideki Tatsumi (Toyo Kasei Kogyo Co., Ltd., Japan)
Takashi Sugimura (University of Hyogo, Japan)

1P-22 ◆ **An Efficient Synthesis of the PKCb Inhibitor JTT-010 Using a Novel Cyclopropane Ring-Opening Reaction with Indole**
Takashi Inaba*, Masahiro Tanaka, Minoru Ubukata, Takafumi Matsuo, Katsutaka Yasue, Katsuya Matsumoto, Yasuyuki Kajimoto, Takashi Ogo (Japan Tobacco Inc., Japan)

1P-23 **Some Case studies of Process chemistry at Shanghai ChemPartner Development of a Practical Route for the Manufacture of 3-Deoxy Ribose derivatives**
Yunaqiang Li*, Jianchun Liao, Weihua He (Shanghai ChemPartner, China)

1P-24 ◆ **Towards Advanced Molecular Build-up in One-Pot by Catalytic Multicomponent Reaction**
Kiyosei Takasu*, Tohru Tanaka, Yu Ogawa, Yoshiji Takemoto (Kyoto University, Japan)

1P-25 **Synthetic Method of Colorless 4-Carbamoylimidazorium-5-olate**
Chihiro Kondo*, Yusuke Higuchi, Nobuo Kato (Osaka University, Japan)
Makoto Sunagawa (Teikyo Heisei University, Japan)

1P-26 **Novel Palladium-on-Carbon Catalyst, Pd/C[Ph2S], for Chemoselective Hydrogenation**
Yukio Takagi, Masatoshi Yoshimura*, Shinobu Takao, Tomoteru Mizusaki
(N. E. Chemcat Corporation, Japan)
Hironao Sajiki, Yasunari Monguchi, Tomohiro Maegawa, Akinori Mori
(Gifu Pharmaceutical University, Japan)

1P-27 **Hydrogenation of Aromatic Nuclei : Practical Synthesis Cyclohexanol Derivatives**
Kiichiro Yaguchi*, Akira Akashi, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki
(Gifu Pharmaceutical University, Japan)

1P-28 **Transition Metal Catalyzed Construction of Indole Nucleus under CO Conditions**
Yasuhiro Sakurai*, Yasuo Sirai, Tomohisa Utsunomiya, Norio Tanaka
(Nissan Chemical Industries, Ltd., Japan)

1P-29 **Synthesis of Carbonyl Compounds through Aerobic Photo-oxidation**
Akichika Itoh, Norihiro Tada, Shin-ichi Hirashima*, Hiroki Nakayama
(Gifu Pharmaceutical University, Japan)

1P-30 **Design and development of new catalyst systems**
: Palladium/BRIDP for efficient coupling reactions
Tohru Kobayashi*, Ken Suzuki, Noboru Sayo
(Takasago International Corporation, Japan)

1P-31 ◆ **Development of Protecting Group Free Catalytic O-Selective Acylation of Aminoalcohols**
Takashi Ohshima*, Takanori Iwasaki, Yusuke Maegawa, Yukiko Hayashi, Kazushi Mashima
(Osaka University, Japan)

1P-32 **Development of Recyclable Ruthenium Catalysts for Aerobic Oxidation**
Utilizing Poly (N-isopropylacrylamide)-Based Polymer
Hiromi Hamamoto*, Yasuyoshi Miki (Kinki University, Japan)
Masahiro Kudoh, Hideyo Takahashi, Hideaki Natsugari, Shiro Ikegami (Teikyo University, Japan)

1P-33 **Pd/C-catalyzed dehalogenation of aromatic halides and its application to degradation of PCBs**
Shinji Ishihara*, Akiko Ido, Tomohiro Maegawa, Yasunari Monguchi, Hisamitsu Nagase,
Hironao Sajiki (Gifu Pharmaceutical University, Japan)
Sueo Wada (Nagara Bionics Co., Ltd., Japan)

1P-34 **Synthetic Studies on a NR2B Antagonist**
Akira Ogawa*, Osamu Saku, Noriko Koizumi, Tsutomu Matsumura, Tomokazu Watanabe,
Koichiro Nishimura, Iwao Chujo (Kyowa Hakko Kogyo, Japan)

1P-35 **Total Synthesis of Natural Products Using a Radical Cascade**
Tsuyoshi Taniguchi*, Hiroyuki Ishibashi (Kanazawa University, Japan)

1P-36 **Production of chiral amines including adamantyl groups by optical resolution**
Taichi Akimoto*, Tetsuro Watadani, Shigeki Nunomura, Yukio Takahashi
(Daito Chemical Co., Ltd., Japan) Isao Fujii (Tokai university, Japan)

1P-37 **Organic synthesis utilizing tetrahydropyran-boron complex**
Hiroshi Yasuda*, Yoshihiko Maeda (Showa Denko K.K., Japan)
Takeshi Oriyama, Ryoichi Chiba (Ibaraki University, Japan)

1P-38 ◆ **Construction of Quaternary Chiral Center by Asymmetric Transfer Claisen Rearrangemant**
Kazuhiko Watabe, Kazumi Okuro, Masaru Mitsuda* (Kaneka Corporation, Japan)

1P-39 **Scaffold Approach for Solid-phase synthesis of quinazoline derivatives**
Yong Cai*, Hongjun Zhang, Yongping Yu (Chemik Co., Ltd., China)
Yandong Zhang (Zhejiang University, China)

1P-40 **Design and Synthesis of Macrosphelide Aza-analogues**
Yuta Kobayashi*, Yuji Matsuya, Hideo Nemoto (University of Toyama, Japan)

1P-41 **Synthesis and Bioactivity of Macrosphelide-based Artificial Compounds**
Yuji Matsuya*, Takanori Kawaguchi, Kanwal Ahmed, Qing-Li Zhao, Takashi Kondo, Hideo Nemoto (University of Toyama, Japan)

1P-42 **Ru/C-catalyzed a-position selective deuteration of alcohols**
Yuta Fujiwara*, Yuya Inagaki, Yasunari Monguchi, Tomohiro Maegawa, Hironao Sajiki (Gifu Pharmaceutical University, japan)

1P-43 ◆ **Pd/C-catalyzed, Solvent-free and Solid-Phase Suzuki-Miyaura Coupling Reaction**
Yuki Fujita *, Shota Hashimoto, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

1P-44 **Practical synthesis of heterobiaryl derivatives**
Azusa Tsutsui*, Satoko Sako, Yoshiaki Kitamura, Takahiro Udzu, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

1P-45 **Mild hydrogenation of carbonyl compounds using Pt/C as a catalyst**
Youhei Iwasaki*, Yuta Fujiwara, Yasunari Monguchi, Tomohiro Maegawa, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

1P-46 **Pd/C-catalyzed, ligand-free Suzuki-Miyaura reaction**
Yasunari Monguchi*, Yoshiaki Kitamura, Satoko Sako, Takanori Kurita, Tomohiro Maegawa, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

1P-47 **Meerwein's reagent-Catalyzed Sol-Gel Polycondensations Giving Silanol Free Silica gel**
Toyoshi Shimada*, Yogesh Jorapur, Yoshifumi Maegawa, Hiroki Nakagawa, Takeru Hasegawa (Nara National College of Technology, Japan)
Norihiro Mizoshita, Takao Tani, Shinji Inagaki (Toyota Central R&D Labs., Inc., Japan)

1P-48 **Development of Separation and Analysis Method for Ab Peptide Based on Biomembrane Abnormarity ~ Membrane Chip Analysis Can Brighten a Potential Aspect of Alzheimer Disease**
Toshinori Shimanouchi*, Haruyuki IshiiI, Vu Thi Huong, Keiichi Nishiyama, Hiroshi Umakoshi, Ryoichi Kuboi (Osaka University, Japan)

1P-49 ◆ **Biomembrane Process Chemistry and Separation Technology ~ Design and Development of Antioxidative LIPOzyme in One-Pot Based on Molecular Recognition Function of Liposome**
Hiroshi Umakoshi*, Le Quoc Tuan, Kengo Morimoto, Toshinori Shimanouchi, Ryoichi Kuboi (Osaka University, Japan)

1P-50 **Autoxidation Resistant Cyclopentyl Methyl Ether (CPME)**
Kazuhisa Sakakibara*, Hayato Hosino (Yokohama National University, Japan)
Kiyoshi Watanabe (Zeon Corporation, Japan)

1P-51 **Dirhodium(II)-Catalyzed Enantioselective Hetero-Diels-Alder Reaction**
Masahiro Anada*, Takuya Washio, Yuudai Watanabe, Naoyuki Shimada, Shunichi Hashimoto (Hokkaido University, Japan)

1P-52 **Enzyme-catalyzed enantiomeric resolution of tamiflu intermediates**
Manabu Hamada*, Seiichiro Ogawa, Toshinori Higashi, Keiko Inami, Kazuo Umezawa, Takeshi Sugai (Keio University, Japan)
Nakamura Kaoru (Kyoto University, Japan)

1P-53 **Studies of Solvent Effects in the Selective Monohydrolysis of Symmetric Diesters**
Satomi Niwayama*, Hezhen Wang, Hanjoung Cho (Texas Tech University, USA)
Yoshikazu Hiraga (Hiroshima University, Japan)

1P-54 **Esterification of Polyalcohol in water**
Risa Maeda*, Yuusaku Yokoyama, Hiroaki Okuno (Toho University, Japan)

1P-55 ◆ **Chemists' Scale-Up Challenges**
Asayuki Kamatani* (Pfizer Global Research and Development, UK)

1P-56 **Template Synthesis Process of Porous Polymers**
Wei-Chi Lai*, Shen-Chen Tseng (Tamkang University, Taiwan)

1P-57 **Chemical Immobilization of DNA on porous PVDF membranes for biomedical applications**
Dar-Jong Lin, Hsu-Hsien Chang, Liao-Ping Cheng* (Tamkang University, Taiwan)
Dong-Tsamn Lin, Tai-Horng Young (National Taiwan University, Taiwan)

1P-58 **Graft polymerization of Poly(vinyl acetate) to a Corn Starch and Its Blends with Polyhydroxybutyrate**
Trong-Ming Don*, Wei-Wei Shun (Tamkang University, Taiwan)

1P-59 **Chiral Bronsted Acid-Catalyzed Enantioselective Friedel-Crafts Alkylation of Indole with a,b-Unsaturated Ketones**
Tsubasa Sakamoto*, Junji Itoh, Kohei Fuchibe, Keiji Mori, Takahiko Akiyama (Gakushuin University, Japan)

1P-60 **Chiral Bronsted Acid-Catalyzed Enantioselective Aza-Darzens Reaction**
Tohru Suzuki*, Kohei Fuchibe, Keiji Mori, Takahiko Akiyama (Gakushuin University, Japan)

1P-61 **DMSO Promoted SN2' Reaction of Organozinc Compounds**
Koji Kobayashi*, Hiroshi Naka, Yoshinori Kondo (Tohoku University, Japan)

1P-62 **New synthetic methods by using MAC reagents**
Tomoyuki Kawamura* (Kwansei Gakuin University, Japan)
Kenji Yatsuzuka, Masaki Kamiya, Hisao Nemoto (The University of Tokushima, Japan)

1P-63 **Concise Synthesis of Oligosaccharides Using Fluorous Method**
Kenji Osumi*, Kohtaro Goto, Yuriko Hirose, Mamoru Mizuno (The Noguchi Institute, Japan)

1P-64 **Friedel-Crafts Acylation of Activated Aromatic Compounds Using a Catalytic Amount of Zinc**
Masatoshi Mihara*, Hiroki Suzuki, Takeo Nakai, Toshiyuki Iwai, Takatoshi Ito, Takumi Mizuno, Toshinobu Ohno (Osaka Municipal Technical Research Institute, Japan)
Yoshio Ishino (Asahi Chemical Co., Ltd., Japan)

1P-65 **Development of Immobilized Phosphonium Bromide for Cyclic Carbonate from Epoxide**
Takashi Sakai, Yoshihiro Tsutsumi*, Tadashi Ema (Okayama University, Japan)

1P-66 **Total synthesis of halipeptins**
Kazuishi Makino*, Sousuke Hara, Youhei Koma, Masaru Sakaguchi, Yasumasa Hamada (Chiba university, Japan)

1P-67 **Microbial reclamation of squid pens for the production of proteases and biofertilizer**
San-Lang Wang* (Tamkang University, Taiwan)

1P-68 **A Novel Synthesis of 3-Sulfanylphenols**
Yasuhiro Sato*, Sunao Mitsui, Hideki Tatsumi (Toyo Kasei Kogyo Co., Ltd., Japan)

1P-69 **Ortho-Selective Cross-Coupling of Dihalobenzene Derivatives**
Shunpei Ishikawa*, Kei Manabe (RIKEN, Japan)

1P-70 **Chemo-Structural Processes in Polyhydrosilanes**
Liviu Sacarescu*, Mihaela Simionescu, Gabriela Sacarescu
(Petru Poni Institute of Macromolecular Chemistry, Romania)

1P-71 **Polysilane Structures with Conformational Photocontrol**
Gabriela Sacarescu*, Liviu Sacarescu, Mihaela Simionescu, Gabriela E Hitruc
(Petru Poni Institute of Macromolecular Chemistry, Romania)

1P-72 **Microwave Assisted Hydrosilylation Processes**
Mihaela Simionescu*, Gabriela Sacarescu, Liviu Sacarescu
(Petru Poni Institute of Macromolecular Chemistry, Romania)
Ionel Mangalagiu (Al. I. Cuza University, Romania)

1P-73 **Regioselective Diels-Alder Reactions of Silylbenzynes**
: Convergent Synthesis of Polysubstituted Biaryls
Sho-ichi Takayanagi*, Takashi Ikawa, Yuki Morikawa, Shinya Mohri, Masaya Tsubakiyama, Masahiro Egi, Shuji Akai (University of Shizuoka, Japan)
Yasufumi Wada (Osaka University, Japan)
Yasuyuki Kita (Osaka Univ. and Ritsumeikan Univ., Japan)

1P-74 **Mo-Au Combo Catalysis for Rapid 1,3-Rearrangement of Propargyl Alcohols into α,β-Unsaturated Carbonyl Compounds**
Masahiro Egi, Noboru Fujiwara*, Yoshiko Yamaguchi, Shuji Akai
(University of Shizuoka, Japan)

1P-75 **Radical Alkylations of Carbonyl Compounds**
JinYoung Lee*, Misun Lee, Sunggak Kim (KAIST, Korea)

July 30 (Wed)

Oral Presentation 13:30-14:30 (Main Hall) **◆Oral Presenter**
Discussion 14:30-16:30 (Annex Hall)

2P-01 **Chlorine gas free synthesis of isothiazolo[5,4-b]pyridin-3-ones**
Masao Shimizu* (National Institute of Advanced Industrial Science and Technology, Japan)
Yusuke Higuchi, Takeo Konakahara (Tokyo University of Science, Japan)

2P-02 ◆ **The asymmetric reaction of acetaldehyde catalyzed by organocatalysis**
Yujiro Hayashi*, Takahiko Itoh, Seiji Aratake, Hayato Ishikawa (Tokyo University of Science, Japan)

2P-03 **Overcoming The Issues Of Precious Metal Contamination Within Catalysed Reactions**
David J. Evans*, Mohammed Nisar, Thomas E. O. Screen, Michael R. Pitts,
Angus J. P. Stewart-Liddon (Reaxa Limited, UK)

2P-04 **Asymmetric Synthesis of dihydrobenzofurans and chromans via planar chiral enolates**
Tomoyuki Yoshimura*, Keisuke Tomohara, Takeo Kawabata (Kyoto Unversity, Japan)

2P-05 **Towards the Gram-Scale Synthesis of Spongistatin 1**
Helmut Kraus*, Alejandro Diéguez-Vázquez (University of Cambridge, UK)

2P-06 **Enzymatic Resolution and Evaluation of Enantiomers of cis-5'-Hydroxythalidomide**
Takeshi Yamamoto*, Masayuki Takashima, Shuichi Nakamura, Norio Shibata, Takeshi Toru
(Graduate School of Engineering, Nagoya Institute of Technology, Japan)

2P-07 **Enantioselective Synthesis of Spirobilactams via the Intramolecular Double Buchwald -Hartwig Reaction**
Kazuhiro Takenaka*, Noriyuki Itoh, Hiroaki Sasai (Osaka University, Japan)

2P-08 ◆ **A ternary complex reagent for an asymmetric conjugate Michael addition of lithium ester enolates with enoates**
Yasutomo Yamamoto*, Hirokazu Suzuki, Yorinobu Yasuda, Kiyoshi Tomioka
(Kyoto University, Japan)

2P-09 **Synthesis and spectroscopic properties of novel azo dyes derived from phthalimide**
Hyun yung Lee, Oh tak Kwon*, Jae hong Choi (Kyungpook National University, Korea)
Wilson Jung (Eastwell Co., Ltd., Korea)

2P-10 **Synthesis of alkali-clearable phthalimidyl dyes and their colorimetric properties**
Hyun yung Lee*, Oh tak Kwon, Jae hong Choi (Kyungpook National University, Korea)
Wilson Jung (Eastwell Co., Ltd., Korea)

2P-11 **Catalytic Enantioselective Petasis Reaction**
Naoto Inakoshi*, Eric N Jacobsen (Harvard University, USA)

2P-12 **Enantioselective Conjugate Addition of Hydrazines to a,b-Unsaturated imides Synthesis of Chiral Pyrazolidinones**
Takahiro Soeta* (Kanazawa University, Japan) Mukund P. Sibi (North Dakota State University, USA)

2P-13 **The study of in-situ monitoring to radical polymerization process using by fiber mid infrared spectroscopy**
Daisuke Sasakura*, Kazuo Osaki, Tsuyoshi Miura (Bruker Optics K.K., Japan)

2P-14 **Catalytic asymmetric hydrogenation using environment conscious new BINAP polymer**
Yoshinori Takamatsu*, Gakuto Goshima, Naomi Takenaka (Kyoeisha Chemical Co., Ltd., Japan)
Kenji Toribatake, Hiroshi Shibaguchi, Toyohiro Nagano, Toyoshi Shimada
(Nara National College of Technology, Japan)

2P-15 **Improving the enantioselectivity of Candida antarctica lipase B for kinetic resolution of butyl tetrahydrofuran-2-carboxylate**
Sojung Park*, Suhyun Jung, Seongsoon Park (Sungshin Women's University, Korea)

2P-16 **Carbon Nanofiber-Supported Metal Nanoparticles as Efficient Catalysts for Hydrogenation Reactions**
Yukihiro Motoyama*, Mikihiro Takasaki, Kenji Higashi, Keita Tsuji, Hideo Nagashima
(Kyushu University, Japan)

2P-17 **The Polymer-Supported Dirhodium(II) Catalyst for Asymmetric Intramolecular C-H Insertion Reactions**
Koji Takeda*, Tadashi Ohara, Masahiro Anada, Hisanori Nambu, Shunichi Hashimoto
(Hokkaido University, Japan)

2P-18 ◆ **Novel Asymmetric Catalytic Oxidation Approach to Esomeprazole**
Jian Liao*, Tian Tian, Jin Zhu, Jingen Deng (Chinese Academy of Sciences, China)

2P-19 **Enantioselective Michael Addition Reaction using FBSM**
Tatsuya Furukawa*, Satoshi Mizuta, Shuichi Nakamura, Norio Shibata, Takeshi Toru
(School of Engineering, Nagoya Institute of Technology, Japan)

2P-20 **Enantioselective Synthesis of (R)-Convolutamydine A with Novel N-Heteroarylprolinamide**
Noriyuki Hara*, Hiroki Nakashima, Shuichi Nakamura, Norio Shibata, Takeshi Toru
(School of Engineering, Nagoya Institute of Technology, Japan)

2P-21 **Organocatalytic Enantioselective Hydrophosphonylation of Sulfonylimines Having Heteroarylsulfonyl Group**
Akiko Yamamura*, Hiroki Nakashima, Shuichi Nakamura, Norio Shibata, Takeshi Toru
(School of Engineering, Nagoya Institute of Technology, Japan)

2P-22 **A Novel C2-Symmetric Chiral Bis(imidazoline) Ligands : Highly Enantioselective Friedel-Crafts Alkylation of Indoles with Ethyl 3,3,3-Trifluoropyruvate**
Yuko Nakamura*, Kotaro Tsuji, Kengo Hyodo, Shuichi Nakamura, Norio Shibata, Takeshi Toru
(School of Engineering, Nagoya Institute of Technology, Japan)

2P-23 **Chemoselective hydrogenation of nitro functionalities in the presence of olefins using Os/C-catalyst**
Mutsumi Sato*, Keiji Oono (Wako Pure Chemical Industries, Ltd., Japan)
Yasunari Monguchi, Tomohiro Maegawa, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

2P-24 **Preparation method of Pd/C(en)catalyst in water**
Keiji Oono*, Mutsumi Sato (Wako Pure Chemical Industries, Ltd., Japan)
Yasunari Monguchi, Tomohiro Maegawa, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

2P-25 **Solvent effect on oxidation of alkylbenzene using hydrogen peroxide**
Takeo Nakai*, Toshiyuki Iwai, Masatoshi Mihara, Takatoshi Ito, Takumi Mizuno
(Osaka Municipal Technical Research Institute, Japan)

2P-26 **Cinchona alkaloid-catalyzed asymmetric aldol-type reactions using trifluoropyruvates**
Shinichi Ogawa*, Hiroyuki Fujimoto, Norihito Iida, Shuichi Nakamura, Norio Shibata, Takeshi Toru
(School of Engineering, Nagoya Institute of Technology, Japan)

2P-27 **Ring-Opening Reaction of α- and β-Pinene in Hot -Compressed Water without Additives**
Tomomi Kawahara*, Toshiyuki Sato, Akiko Kawai-Nakamura, Hiizu Iwamura, Toshihiko Hiaki
(Nihon University, Japan)
Kiwamu Sue (National Institute of Advanced Industrial Science and Technology, Japan)

2P-28 **Synthesis of Polyacene in Hot-Compressed Water without Additives**
Takenori Sawada*, Toshiyuki Sato, Akiko Kawai-Nakamura, Hiizu Iwamura, Toshihiko Hiaki
(Nihon University, Japan)
Kiwamu Sue (National Institute of Advanced Industrial Science and Technology, Japan)

2P-29 **Pd-perovskite applied to catalytic organic reaction**
Mitsuhiro Yamada*, Hiroyuki Morikawa, Junzo Nokami, Shun-ichi Murahashi
(Okayama University of Science, Japan)
Yoshiki Hayakawa, Kimiyoshi Kaneko (Hokko Chemical Industry Co., Ltd., Japan)

2P-30 ◆ **Optimization of Crystallization Experiments Using In-Process Particle Size Characterization : Lasenetec and PVM**
Eric J Hukkanen*, Benjamin Smith (Mettler-Toledo AutoChem, Inc., USA)

2P-31 **Efficient Catalytic Process Using Dendritic Catalyst**
Ken-ichi Fujita*, Takahito Muraki ,Masato Kujime (AIST, Japan)

2P-32 **Process Development of MCP-1R antagonist TEI-E00526**
Hiroaki Makino*, Asahi Kawana, Yoshinori Satou, Takumi Takeyasu (Teijin Pharma Limited, Japan)

2P-33 **New syntheses of diaryl ketones and diaryl 1,2-diketones : Nucleophilic aroylation with arylaldehydes by N-heterocyclic carbene catalysis**
Yumiko Suzuki*, Shinya Ota, Yoshinori Fukuta, Abu Bakar Md., Takashi Tanoi, Masayuki Sato
(University of Shizuoka, Japan)

2P-34 **The development of micro chemical process development aiming the perfect control of exlplosive atmosphere**
Tomoya Inoue*, Satoshi Hamakawa, Fujio Mizukami, (CCP-AIST, Japan)
Yoshikuni Kikutani (IMT, Japan) Kazuma Mawatari (KAST, Japan)
Takehiko Kitamori (KAST, The University of Tokyo, Japan)

2P-35 **Synthesis of Benzazoles**
Yuhei Yamamoto*, Takahiro Itoh, Tosiaki Mase (Banyu Pharmaceutical, Japan)

2P-36 **Rapid Parallel Development for Three Adenosine A1/A2a Receptor Antagonists**
Ryoki Orii*, Hiroyoshi Matsubara, Takashi Kikuchi, Norio Hashimoto, Shunsuke Goto
(Astellas Pharma Inc., Japan)

2P-37 ◆ **Process Intensification Assisted by Zeolite Membranes**
Tomoya Inoue*, Takako Nagase, Yasuhisa Hasegawa, Yoshimichi Kiyozumi, Satoshi Hamakawa,
Fujio Mizukami (CCP-AIST, Japan) Toshikazu Nishide (Nihon University, Japan)

2P-38 **Development of Polymer Incarcerated Osmium Catalysts**
Yasunori Tuchiya,* Ryo Akiyama, Hidekazu Oyamada (ERATO, JST, Japan)
Shu Kobayashi (The Univ. of Tokyo ; ERATO, JST, Japan)

2P-39 **Basic Study on Separation by Mild Adsorption in Supercritical CO2**
Kazuyuki Chihara,* Mai Hikita, Wada Taichi, Ryota Suzuki (Meiji University, Japan)

2P-40 **Mild, powerful, and robust acylation and tosylation utilizing N-methylimidazole (NMI) agents : synergy effect of different amine bases**
Hidefumi Nakatsuji*, Mami Morimoto, Kanako Ueno, Yoo Tanabe
(Kwansei Gakuin University, Japan)

2P-41 **Highly stereocomplementary method for the preparation of tri-substituted olefins and its application 2-arylcarbapenem synthesis**
Kanako Ueno*, Hidefumi Nakatsuji, Yoo Tanabe (Kwansei Gakuin University, Japan)

2P-42 **Development of asymmetric Ti-Claisen condensation directed for process chemistry : application to asymmetric total syntheses of two natural products**
Ryohei Nagase*, Mikiko Sugi, Yumiko Oguni, Tomonori Misaki, Yoo Tanabe
(Kwansei Gakuin University, Japan)

2P-43 **Catalyst-free Efficient Reactions in DMSO**
Tomoko Kakinuma*, Ryoichi Chiba, Katsuyuki Iwanami, Masaru Aoyagi, Takeshi Oriyama
(Ibaraki University, Japan)

2P-44 **BF3・THP-promoted [3+2] Cycloaddition of N-Tosylaziridines with Nitriles.**
Hitomi Urai*, Ryoichi Chiba, Takeshi Oriyama (Ibaraki University, Japan)
Hiroshi Yasuda, Yoshihiko Maeda (Showa Denko K.K., Japan)

2P-45 **Attractive role of sugar ester W/O microemulsion phase on lipid hydrolysis by lipase to provide highest reactivity**
Aki Uehara*, Masanao Imai, Isao Suzuki (Nihon University, Japan)

2P-46 **Production of biodiesel from algal oil using microwave-based transesterification process**
Ching-An Peng*, Guen-Yen Chen, Wen-Yi Tsai (National Taiwan University, Taiwan)

2P-47 **Highly cis-selective synthesis of a,b-unsaturated amides by Horner -Wadsworth-Emmons reaction**
Kaori Ando*, Yuko Tarumi (Gifu University, Japan)

2P-48 **Cinchona Alkaloids /TMAF Combination -Catalyzed Nucleophilic Enantioselective Trifluoromethylation of Aryl Ketones**
Hiroyuki Kawai*, Satoshi Mizuta, Hiroyuki Fujimoto, Akiti Surendar, Shuichi Nakamura, Norio Shibata, Takeshi Toru
(Graduated School of Engineering, Nagoya Institute of Technology, Japan)

2P-49 ◆ **Scale up of hydrogenation reactions in continuous processes**
Laszlo Urge*, (Thales Nano Inc., Hungary)

2P-50 **Synthesis of PVDF-g-PMMA by Atom Transfer Radical Polymerization**
Dar-Jong Lin*, Liao-Ping Cheng, Chun-Liang Lin, Chang-Li Lin (Tamkang University, Taiwan)

2P-51 **Effect of Ligands on Pd-Catalyzed Hydroarylation of Ethyl Propiolate**
Tsugio Kitamura*, Juzo Oyamada (Saga University, Japan)

2P-52 **Tetrabutylammonium Fluoride-Induced Dehydrobromination of Vinyl Bromides to Terminal Acetylenes**
Masaru Okutani, Yuji Mori* (Meijo University, Japan)

2P-53 **AZADOs : Highly Active Oxidation Catalysts for Alcohols -Discovery and Characterization-**
Masaki Tomizawa*, Masatoshi Shibuya, Yusuke Sasano, Iwao Suzuki, Fabio Pichierri, Yoshiharu Iwabuchi (Tohoku University, Japan)

2P-54 **New application of oxoammonium Salt-based catalysts**
Masatoshi Shibuya*, Masaki Tomizawa, Takahisa Sato, Yoshiharu Iwabuchi
(Tohoku university, Japan)

2P-55 **Aerobic oxidation of alcohols using AZADOs**
Yoshiharu Iwabuchi, Masatoshi Shibuya, Masaki Tomizawa, Yuji Osada*, Yusuke Sasano
(Tohoku university, Japan)

2P-56 **Practical Synthesis of Highly Efficient Organocatalysts for Oxidation of Alcohols : AZADO, 1-Me-AZADO and ABNO**
Yusuke Sasano*, Masatoshi Shibuya, Masaki Tomizawa, Yoshiharu Iwabuchi
(Tohoku University, Japan)

2P-57 **Oxidative degradation analysis of organic ethers**
Arata Kimura*, Hayato Kitoh, Atsumi Miyake (Yokohama National University, Japan)
Kiyoshi Watanabe (Zeon Corporation, Japan)

2P-58 **Mild preparation of substituted indolizines and indole from simple aromatic precursors using (trimethylsilyl) diazomethane**
Sean P Brown*, Liusheng Zhu, Marc Vimolratana, Julio C Medina (Amgen, USA)

2P-59 **Non-degraded expression and one-step purification of yeast ALD6 enzyme in E. coli**
Wei-Jyh Shiah, Yu-Chun Chen, Ming-Kai Chern* (Tamkang University, Taiwan)

2P-60 **Reusable chaperone-conjugated magnetic nanobeads in production of a functionally active biocatalyst**
Suhyun Jung*, Seongsoon Park (Sungshin Women's University, Korea)

2P-61 **Deveropment and application of odorless thiol reagents**
Manabu Matoba*, Tetsuya Kajimoto, Manabu Node (Kyoto Pharmaceutical University, Japan)

2P-62 **Development of selective C-N bond crevage utilizing N-halosuccinimide**
Tsunefumi Watanabe*, Noboru Hayama, Takahiro Katoh, Minoru Ozeki, Tetsuya Kajimoto, Manabu Node (Kyoto Pharmaceutical University, Japan)

2P-63 **Construction of Three Contiguous Stereogenic Centers via Asymmetric Michael Addition Using Chiral Amino Ether as a Chiral Reagent**
Shunsuke Ochi*, Minoru Ozeki, Takahiro Katoh, Tetsuya Kajimoto, Manabu Node
(Kyoto Pharmaceutical University, Japan)

2P-64 **Adsorption kinetic of chitosan from three source**
Feng-Chin Wu* (National United University, Taiwan)

2P-65 **Adsorption kinetic of chitosan from three source**
Ru-Ling Tseng* (National United University, Taiwan)

2P-66 **Bioconversion of aromatic compounds using Escherichia coli expressing Cytochrome P450**
Toshihiko Otomatsu* (KNC Laboratories Co., Ltd., Japan)

2P-67 **Synthesis of indole derivatives under microwave conditions**
Li-Jian Ma*, Zhenwu Mei, Tomoyo Kusuyama, Tsutomu Inokuchi (Okayama University, Japan)

2P-68 **High-performance method of TEMPO-oxidation of alcohols**
Zhenwu Mei*, Li-Jian Ma, Tsutomu Inokuchi (Okayama University, Japan)
Hiroyuki Kawafuchi (Toyama National College of Technology, Japan)

2P-69 **Highly Enantioselective Dynamic Kinetic Resolution of 1,2-Diarylethanols by a Lipase-Ruthenium Couple**

Sol Kim*, Yun Kyung Choi, Yunwoong Kim, Cheolwoo Kim, Jaiwook Park, Mahn-Joo Kim (POSTECH, Korea)

2P-70 **New One-Pot Synthesis of Malonic Acid Derivatives**

Akichika Itoh*, Norihiro Tada, Hiroki Nakayama, Naohiko Kanai (Gifu Pharmaceutical University, Japan)

2P-71 **Nickel/Lewis acid-catalyzed carbocyanation reaction of unsaturated compoudns**

Yoshiaki Nakao*, Akira Yada, Shiro Ebata, Yasuhiro Hirata, Tomoya Yukawa, Tamejiro Hiyama (Kyoto University, Japan)

2P-72 **Nickel/Lewis acid-catalyzed hydroheteroarylation reaction of alkynes**

Kyalo Stephen*, Kanyiva Yoshiaki Nakao, Tamejiro Hiyama (Kyoto University, Japan)

2P-73 **Dynamic Kinetic Resolution of Primary Amines by Lipase-Palladium Cocatalysis**

Kiwon Han*, Yoon Kyung Choi, Cheolwoo Kim, Jaiwook Park, Mahn-Joo Kim (POSTECH, Korea)

2P-74 **Micronization of Pharmaceutical Compounds by Supercritical Fluid Technology**

Yan-Ping Chen* (National Taiwan University, Taiwan)

Muoi Tang (Chinese Culture University, Taiwan)

Keynote Speakers' Profile

K−1 Martin Karpf (F. Hoffmann-La Roche, Switzerland)
K−2 M. Christina White (Univ. of Illinois, Urbana-Champaign, USA)
K−3 Kazuaki Ishihara (Nagoya Univ., Japan)
K−4 Mahn-Joo Kim (Pohang Univ. of Sci. & Tec., Korea)
K−5 Aniruddha B. Pandit (Univ. of Mumbai, India)
K−6 Karl Matos (BASF Corporation, USA)
K−7 Tsutomu Katsuki (Kyushu Univ., Japan)
K−8 Toshiro Konoike (Shionogi, Japan)
K−9 Takashi Okazoe (Asahi Glass, Japan)
K−10 Keith Fagnou (Univ. of Ottawa, Canada)
K−11 Michael J. Krische (Univ. of Texas at Austin, USA)
K−12 Mark Butchko (Eli Lilly, USA)
K−13 David Haywood (AstraZeneca, UK)

CURRICULUM VITAE

Martin Karpf

1965 - 1971	Studies of Natural Sciences, University of Zürich
1972	Diploma in Chemistry, University of Zürich
1973 - 1977	Doctoral Dissertation with Prof. A.S. Dreiding, University of Zürich "*On the Way from 12- to 15-membered Ring Systems*"
1978	Post-doctoral fellow with Prof. A.S. Dreiding
1979	Post-doctoral fellow with Prof. C. Djerassi, Stanford University - Synthesis of optically active cyclopropane derivatives - Synthesis of marine steroids
1980 - 1984	Head assistant, University of Zürich Research work aiming at an appointment as university lecturer
1981	Award of the Swiss Chemical Society for the *"Discovery of a Novel Thermal Reaction for the Synthesis of 5-membered Ring Systems"*
1984	Inaugural Dissertation (Habilitation) *"Organic Synthesis at High Temperature: Discovery, Investigation and Application of the α-Alkynone Cyclisation"*
1985	Venia legendi for Organic Chemistry, University of Zürich
1985 - 1995	Lecturer at the University of Zürich
1985 - 2000	Group leader at the Synthesis & Process Research Department, Non-Clinical Development of the Pharma Division of F. Hoffmann-La Roche Ltd, Basel, dealing with synthesis & process research for new pharmaceuticals
1988	Promoted to Deputy
1991	Roche Lecturer "Chemical Process Research on "*The Synthetic Problems Encountered between Research and Production*"
1994	Promoted to Scientific Expert
since 2000	Head of Synthesis, Process Research & Catalysis
2006	Promoted to Distinguished Scientist

K – 2

M. Christina White

M. Christina White was born in Athens, Greece where she lived until the age of five. She received her undergraduate degree in biochemistry at Smith College, where she worked with Professor Stuart Rosenfeld in the area of host-guest chemistry. After a brief stint in the biology graduate program at Johns Hopkins University working with Professor Christian Anfinsen, she began her doctoral studies in chemistry under the direction of Professor Gary Posner. During that time, she initiated the hybrid Vitamin D_3 analog program in his group.

In 1999, she joined Professor Eric Jacobsen's labs at Harvard University as an NIH postdoctoral fellow. During this time, she developed the first synthetically useful methane monooxygenase (MMO) mimic system for catalytic epoxidations with hydrogen peroxide. Christina began her independent career as a member of the chemistry faculty at Harvard University in July of 2002. She joined the department of chemistry at the University of Illinois in the summer of 2005, where she is currently an Assistant Professor of Chemistry. Her group's research interests center around the development of highly selective C—H functionalization methods for streamlining the process of complex molecule synthesis. She has received numerous awards including the Camille and Henry Dreyfus New Faculty Award (2002), the NSF CAREER Award (2006), the Eli Lilly Grantee Award (2007), the Alfred P. Sloan Research Fellowship (2008), the BMS Unrestricted "Freedom to Discover" Grant (2008), and the Pfizer Award for Creativity in Organic Chemistry (2008).

CURROCULUM VITAE (14 May, 2008)

Kazuaki Ishihara

Furo-cho, Chikusa, Nagoya 464-8603, Japan
Phone: +81-52-789-3331; Fax: +81-52-789-3222
E-mail: ishihara@cc.nagoya-u.ac.jp

BIRTH

Birthed at Aichi Prefecture, Japan on 26 April, 1963.

EDUCATION

B. of Eng., Sch. of Eng., Nagoya University (1985); M. of Eng., Grad. Sch. of Eng., Nagoya University (1987); D. of Eng., Grad. Sch. of Eng., Nagoya University (1991) [Visiting scholar under the supervision of Professor Clayton H. Heathcock at Department of Chemistry, University of Berkeley, California, USA for three months in 1987.]

POSITIONS HELD

Postdoctoral Fellow under the supervision of Professor E. J. Corey at Harvard University, USA (1991); Assistant Professor, Grad. Sch. of Eng., Nagoya University, Japan (1992); Assistant Professor, Grad. Sch. of Eng., Nagoya University, Japan (1994); Associate Professor, Research Center of Waste and Emission Management, Nagoya University, Japan (1997); Associate Professor, Grad. Sch. of Eng., Nagoya University, Japan (2001); Professor, Grad. Sch. of Eng., Nagoya University, Japan (2002)

HONORS & AWARDS

(1) JSPS Fellowship for Japanese Junior Scientists (1988–1991)
(2) Yamada Science Foundation Fellowship for Studying Abroad (1991–1992)
(3) The 10th Inoue Research Award for Young Scientists (1994)
(4) The 45th Young Chemist Award from the Chemical Society of Japan (1996)
(5) Thieme Chemistry Journal Award (2001)
(6) The 2nd Green & Sustainable Chemistry Award from the Minister of Education, Culture, Sports, Science and Technology (2003)
(7) The 1st JSPS Prize (2005)
(8) BCSJ(Bulletin of the Chemical Society of Japan) Award (2005)
(9) Lectureship Awards (from Korea and Taiwan) in "0th International Conference on Cutting-Edge Organic Chemistry in Asia (2006)
(10) Japan/UK GSC Symposium Lectureship in Japan/UK Green Sustainable Chemistry Symposium (2007)
(11) The 21st Japan IBM Science Prize (2007)

PRINCIPLE AREAS OF RESERACH

1981–1991	Studies on stereoselective reactions of chiral acetals
1991–1992	Design of asymmetric Diels–Alder catalysts
1992–	Design of chiral Brønsted acid–Lewis acid combined catalysts
1995–	Design of superacids
1996–	Design of dehydrative condensation catalysts
1999–	Design of artificial cyclases for synthesizing optically active polycyclic terpenoids
2000–	Design of recoverable and reusable catalysts
2002–	Design of acid–base combined catalysts

His current research is the development of catalytic organic reactions and processes directed towards green chemistry.

PUBLICATIONS

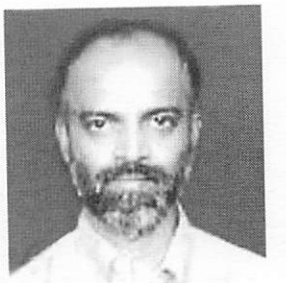
Communications and full papers: **143**; Patents: **47**; Reviews and Books **60**; Interpretive articles **21**; Lectures at International Conferences: **31**

Mahn-Joo Kim
Department of Chemistry
Pohang University of Science and Technology
Pohang, Korea

Brief CV

KIM, Mahn-Joo (b. 1955), B.S. 1977, Kangwon National University; M.S. 1981, Seoul National University (J. Suh); Ph.D. 1987, Harvard University (G. M. Whitesides); Postdoctoral Fellow, 1987-1988, Texas AM University (C.-H. Wong); Guest Scientist, 1996-1997, The Scripps Research Institute (C.-H. Wong); Assistant, Associate, and Full Professor, 1988-present, POSTECH. *Organic, Enzyme, and Nano Chemistry*: asymmetric synthesis by biocatalysis, nanocatalysis, and nanobiocatalysis; functionalization and applications of nanomaterials.

Tel: 82-54-279-2112, Fax: 82-54-279-0654, E-mail: mjkim@postech.ac.kr.



BIO-DATA

Name : Dr.A.B.Pandit
Date of Birth : 7th December, 1957
Designation : UGC, Research Scientist 'C', Professor with University Institute of Chemical Technology (UICT), University of Mumbai
Educational Background : B.Tech. (Chem), Institute of Technology, Banaras Hindu University, 1980.
Ph.D.(Tech), UDCT, 1984.

Professional/Teaching experience:

Associate Lecturer: UDCT, 1984
Research Associate: Dept. of Chem. Eng., Cambridge, U.K., 1984-1990
UGC Research Scientist, 'B' (Reader's Grade): UDCT, Mumbai, 1991-1995.
UGC Research Scientist, 'C' (Professor's Grade): UDCT, 1996 onwards

Important Awards:

Prof. R.A. Rajadyaksha Best Teacher award, UDCT, 1995, 1997,2000, 2001, 2004, 2006, 2007.
VASVIK award, 1996
Fellow, Maharashtra Academy of Sciences 1997
ISTE-IPCL award for guiding work of Mr. Shrikant Palaskar awarded as Second best Master's thesis award on National level, 1998
INAE award for guiding the work of Mr. Nilesh Vichare awarded as Best M.Tech. Innovative project award, 2000
IIChE- Artemis Biotech award for guiding the work of Mr. Nilesh Vichare awarded as the Best Master's thesis on National Level, 2000
IIChE - Herdilia award for excellence in basic research, 2001
Best paper presentation award at CHEMCON-2002 on national level co-authored with Ms. Preeti Sangave, 2002
Distinguished Alumnus award, Institute of Technology-Banaras Hindu University, 2004
IIChE-Dr. Dr. A.V. Ramarao's Foundation award for the Best Ph.D. Thesis/Research award in Chemical Engineering/Technology for the year 2004 **(Guide)**
Fellowship of Indian National Academy of Engineering (2006)
Fellowship of Indian Academy of Sciences (2008)

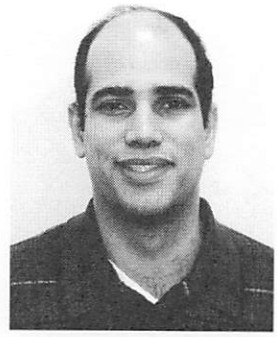
Research Interests: Multiphase Reactors, Cavitation Phenomena, Thin film Dynamics and Environmental Engineering.

Significant research achievements:

Combination of excellent theoretical analysis and innovative, simple experimental techniques has lead to the development of performance correlations for multiphase reactors and has resulted into novel reactor modifications and reactors to enhance the specific performance parameters. The work in the area of hydrodynamic cavitation is likely to bring this emerging technology in the forefront, which has been languishing, in the confines of laboratory.

A unique creative approach of using the fundamental information to develop performance correlations and explanation for anomalous behaviour has resulted into a focussed design methods and criteria for commonly used multiphase contactors and some novel cavitation based reactors. Several of these designs are in successful commercial operation.

K－6



Karl Matos, Manager, Research & New Product Development at BASF Corporation at Evans City, Pennsylvania, was born in 1970 in New Haven, Connecticut (USA). He received his B. S. in 1991 and Ph.D. in 1998 under the supervision of Professor John A. Soderquist from the University of Puerto Rico. His graduate work at the University of Puerto Rico focused on the mechanistic features of the Suzuki-Miyaura alkyl group transfer and organoborane conversions with borabicyclo[3.3.2]decanes. In 1999, he worked as a post-doctoral research associate with Professor John A. Soderquist (University of Puerto Rico) to develop a scaleable process to prepare chiral borabicyclo[3.3.2]decane derivatives for asymmetric synthesis. After completing his post-doctoral assignment, he joined Callery Chemical Company (now part of BASF Corporation) in 1999. His industrial scientific work has involved developing large-scale processes of new boron reagents for technologies such as the Suzuki-Miyaura coupling reaction and optimizing key parameters in the asymmetric reduction of ketones with the Corey catalyst.

Curriculum vitae of Tsutomu Katsuki

Current Employment and Status:

Professor of Chemistry
Kyushu University

Addresses: Department of Chemistry, Faculty of Science, Graduate School,
Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581
Fax:+81-92-642-2607
E-mail: katsuscc@mbox.nc.kyushu-u.ac.jp

Date of Birth: September 23, 1946
Place of Birth: Saga, Japan

Education:
B. Sc., Kyushu University, 1969
M. Sc., Kyushu University, 1971
D. Sc., Kyushu University, 1976

Professional Experience:

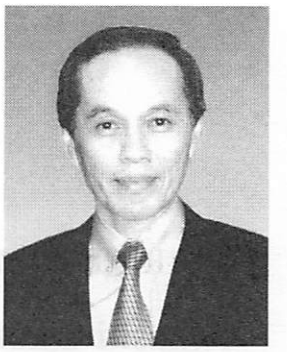
Research Associate, Kyushu University (with Professor Masaru Yamaguchi)	1971-1988
Postdoctoral Fellow, Stanford University and Massachusetts Institute of Technology (with Professor K. Barry Sharpless)	1979-1981
Professor, Kyushu University	1988-present

Current Research Interest:

construction of new metal-based asymmetric catalysts and development of ecologically sustainable and stereoselective methods for chemical transformation.

Award and lectureshio:

Inoue Science Award (1996)
Synthetic Organic Chemistry Award, Japan (1998)
Molecular Chirality Award (2001)
Award for the Chemical Society of Japan (2002)
Ryoji Noyori Prize (2005)



CURRICULUM VITAE

Toshiro Konoike

CMC Development Laboratories,
Shionogi & Co., Ltd
1-3, Kuise Terajima 2-chome, Amagasaki,
Hyogo 660-0813, Japan
Phone: 81-6-6401-8305; Fax: 81-6401-1309
E-mail: toshiro.konoike@shionogi.co.jp

BIRTH:

1948, Osaka, Japan.

EDUCATION:

B.S.: 1971, Faculty of Engineering, Kyoto University (Professor T. Matsuura)
M.S: 1973, Faculty of Engineering, Kyoto University (Professor T. Saegusa)
Ph.D. 1976, Kyoto University, Kyoto, Japan (Professor T. Saegusa)
Major: Organic synthesis, organo-copper and silver chemistry
Dissertation: ''Synthetic Chemistry via Metal Enolate Intermediates''

EMPLOYMENT HISTORY:

1976-1990: Research Scientist, Shionogi Research Laboratories
1984-1986: Postdoctoral fellow, Professor Alan P. Kozikowski , University of Pittsburgh, Pennsylvania
1990-1994: Manager, Drug Discovery Research Laboratories
1994-1997: Deputy Manager, Drug Discovery Research Laboratories
1997-2000: General Manager of Organic Process R & D Laboratories
2000-2004: General Manager of Manufacturing Technology R & D Laboratories
2004-2008: General Manager of Bulk Chemicals Process R & D Laboratories
2008- : Principal Scientist of CMC Development Laboratories, Shionogi & Co.

RESEARCH AREAS:

Synthetic chemistry of antibiotics
Medicinal chemistry of cardiovascular drugs
Asymmetric synthesis of enantiopure drugs
Process chemistry of pharmaceuticals

CURRICULUM VITAE (May, 2008)

Takashi Okazoe

Shinyurakucho Bldg., 1-12-1 Yurakucho, Chiyoda-ku, Tokyo 100-8405, Japan
Phone: +81-3-3218-5448; Fax: +81-3-3218-7858
E-mail: takashi-okazoe@agc.co.jp

BIRTH

Birthed at Sapporo, Japan on 25 April, 1961.

EDUCATION

Bachelor of Engineering, Faculty of Engineering, Kyoto University (1985);
Master of Engineering, Graduate School of Engineering, Kyoto University (1987)

POSITIONS HELD

Researcher, Research Center, Asahi Glass Co., Ltd. (1987);
Group Leader, Research Center, Asahi Glass Co., Ltd. (1999);
Manager, Planning and Coordination Office, AGC Chemicals, Asahi Glass Co., Ltd. (2006)

AWARDS

The 48th Technology Award from the Society of Synthetic Organic Chemistry, Japan (2006)

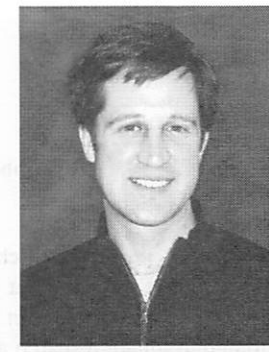
PRINCIPLE AREAS OF RESERACH

1987–1997	Development of fluorinated pharmaceuticals
1997–2005	Development of fluorinated materials
2005–	Planning of R&D strategy

PUBLICATIONS

Communications and full papers: **24**;
Patents: **100**;
Reviews: **2**

K – 10



Keith Fagnou, Associate Professor

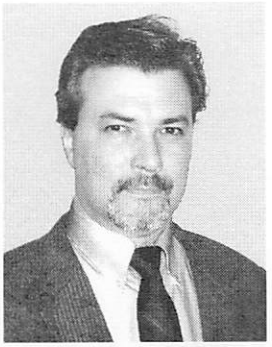
DEGREES:
Ph.D. Organic Chemistry, University of Toronto, 2002 (Supervisor: Mark Lautens)
M.Sc. Organic Chemistry, University of Toronto, 2000
B.Ed., University of Saskatchewan, 1995

EMPLOYMENT HISTORY:

2007-present	Associate Professor with tenure, University of Ottawa
2002-2007	Assistant Professor, University of Ottawa
1998-2002	Graduate Student in Organic Chemistry, University of Toronto, Dept. of Chemistry
1999 / 2000	NSERC Summer Research Associate, AstraZeneca Research Center, Montreal, PQ
1995-1996	High School Teacher, Ecole Canadienne Française/St. Joseph HS Saskatoon, SK
1990-1998	Naval Reserve Officer (Lieutenant (N)), Dept. of National Defense

ACADEMIC HONOURS AND AWARDS (Since 2003):
Sloan Research Fellow 2008
Merck Process Award 2007, 2008
Eli Lilly Grantee, 2007-2009
NSERC Accelerator Supplement Grantee, 2007-2009
Amgen Young Investigator's Award 2007
Astra Zeneca Award for Chemistry 2007
University of Ottawa Research Chair in Novel Catalytic Transformations 2007-2012
University of Ottawa Young Researcher of the Year Award 2006
Ichikizaki Award for Young Chemists 2006
Boehringer Ingelheim Young Investigator Award in Organic Chemistry 2005
Cottrell Research Scholar Award 2005
Ichikizaki Award for Young Chemists 2005
Premier's Excellence in Research Award 2004
John Charles Polanyi Prize in Chemistry 2003

RECENT PUBLICATIONS:
"C2, C5 and C4 Azole *N*-Oxide Direct Arylation Including Room Temperature Reactions" Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276-3277.
"Site-Selective sp^2 and Benzylic sp^3 Palladium-Catalyzed Direct Arylation" Campeau, L.-C.; Schipper, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266.
"High Yielding Palladium-Catalyzed Intramolecular Alkane Arylation Reactions" Lafrance, M.; Gorelsky, S.I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570-14571.
"Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene Cross-Coupling" Stuart, D.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072-12073.
"Catalytic Cross-Coupling Reactions with Unactivated Arenes" Stuart, D.R.; Fagnou, K. *Science* **2007**, *316*, 1172-1175.
"Palladium-Catalyzed Benzene Arylation: Incorporation of Catalytic Pivalic Acid as a Proton Shuttle and a Key Element in Catalyst Design" Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496-16497.
"Palladium-Catalyzed Diazine N-Oxide Cross Coupling Reactions with Aryl Chlorides, Bromides and Iodides" Leclerc, J.-P.; Fagnou, K. *Angew. Chem Int. Ed.* **2006**, *45*, 7781-7786.

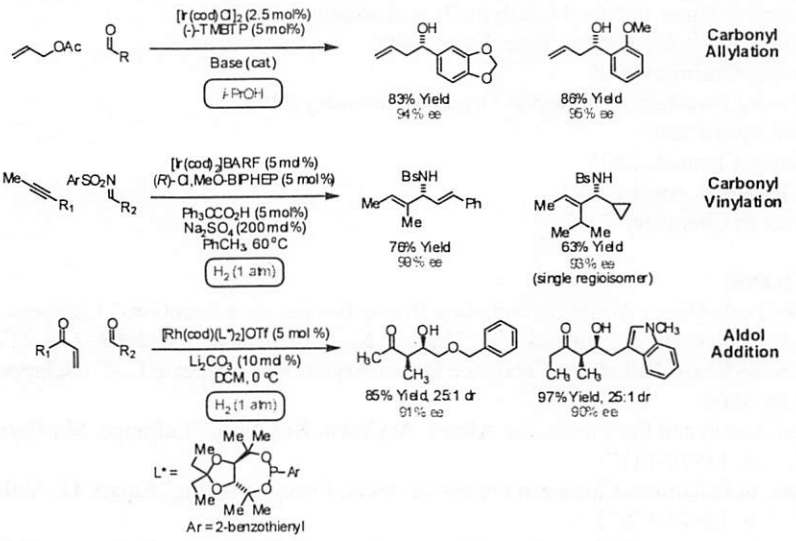


Biographical Sketch - Professor Michael J. Krische
University of Texas at Austin

Biography: Professor Michael J. Krische obtained a B.S. degree in Chemistry from the University of California at Berkeley, where he performed research under the tutelage of Professor Henry Rapoport. After one year of study abroad as a Fulbright Fellow, he initiated graduate research at Stanford University under the mentorship of Professor Barry Trost as a Veatch Graduate Fellow. Following receipt of his Ph.D. degree, he worked with Jean-Marie Lehn at the Université Louis Pasteur as an NIH Post-Doctoral Fellow. In Fall 1999, Professor Krische was appointed Assistant Professor at the University of Texas at Austin. He was promoted directly to Full Professor in Fall 2004 and in Fall 2007 he received the Robert A. Welch Chair in Science.

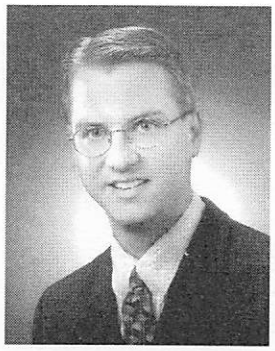
Selected Honors and Awards: Novartis Chemistry Lectureship (2008), Presidential Green Chemistry Award (2007), Dowpharma Prize (2007), ACS Elias J. Corey Award (2007), Solvias Ligand Prize (2006), Society of Synthetic Chemistry Japan Lectureship (2005), Johnson & Johnson Focused Giving Award (2005), Dreyfus Teacher Scholar Award (2003), Alfred P. Sloan Research Fellowship (2003), Cottrell Scholar Award (2002), Frasch Foundation Award in Chemistry (2002), Lilly Grantee Award (2002), National Science Foundation-CAREER Award (2000), Maître de Conference, Collége de France (1999), NIH Post-Doctoral Fellow (1997), Veatch Graduate Fellow (1995), Sigma Xi Grantee (1991), Fulbright Fellow (1990).

Research Interests: Asymmetric hydrogenation accounts for over half the chiral compounds made by man, withstanding physical or enzymatic resolution. Whereas conventional hydrogenation involves *C-H bond formation*, our research establishes hydrogenation as a method for *C-C bond formation*. We have shown that hydrogenation and transfer hydrogenation may be used to couple diverse π-unsaturated reactants to carbonyl compounds, imines and even alcohols offering a byproduct-free alternative to stoichiometrically preformed organometallics in a range of classical C=X (X = O, NR) addition processes. These studies represent the first systematic efforts to exploit hydrogenation in C-C couplings beyond hydroformylation and define a departure from the use of preformed organometallic reagents in carbonyl addition.



Selected Publications

- "Diastereo- and Enantioselective Hydrogenative Aldol Coupling of Vinyl Ketones: Design of Effective Monodentate TADDOL-Like Phosphonite Ligands," Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2747.
- "Enantioselective Iridium Catalyzed Imine Vinylation: Optically Enriched Allylic Amines *via* Alkyne-Imine Reductive Coupling Mediated by Hydrogen," Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644.
- "Enantioselective Reductive Coupling of Acetylene to *N*-Arylsulfonyl Imines *via* Rhodium Catalyzed C-C Bond Forming Hydrogenation: (*Z*)-Dienyl Allylic Amines," Skucas, E.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242.
- "Enantioselective Reductive Coupling of 1,3-Enynes to Heterocyclic Aromatic Aldehydes and Ketones *via* Rhodium Catalyzed Asymmetric Hydrogenation: Mechanistic Insight into the Role of Brønsted Acid Additives," Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448.



Mark A. Butchko, Ph.D.

Eli Lilly and Company
Tippecanoe Laboratories, TL31
1650 Lilly Road
Lafayette, IN 47909-9201
(765) 477-4602
butchko_mark_a@lilly.com

Education

- **University of Notre Dame**: Ph.D. in Chemistry, 2000. Doctoral Research under the direction of Professor Xavier Creary. Thesis: *Intramolecular Carbene Rearrangements: Experimental and Theoretical Studies.*
- **King's College**: B.S., Chemistry, 1994.

Experience

- **Eli Lilly and Company, Tippecanoe Laboratories (Lafayette, IN)**:
  2000-2003: Senior Organic Chemist, Chemical Process R&D
  2004-2005: Principal Research Scientist, Chemical Process R&D
  2005-2008: Manager, Manufacturing Science & Technology
- **Eli Lilly and Company, Lilly Technology Center (Indianapolis, IN)**:
  2008-: Manager, Quality Assurance, Chemical Process R&D

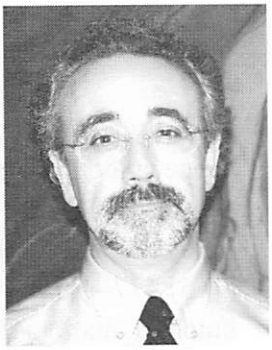
Areas of Experience

- Mechanistic Organic Chemistry
- Chemical Process Research & Development
- Manufacturing Science & Technology
- Active Pharmaceutical Ingredient (API) Commercialization
- Process Validation
- cGMP Manufacturing
- Process Safety Management

Publications

- Creary, X.; Butchko, M.A. "β-Trimethylsilyl Cyclopropylcarbenes", *J.Org.Chem.* **2001**, 66, 1115-1121.
- Creary, X.; Butchko, M.A. "The Bicyclo[2.2.2]octyl Carbene System as a Probe for Migratory Aptitudes of Hydrogen to Carbenic Centers", *J.Am.Chem.Soc.* **2001**, *123*, 1569-1578.
- Creary, X.; Butchko, M.A. "β-Silylcarbenes from Isolable Diazosilanes", *J.Org.Chem.* **2002**, *67*, 112-18.

K – 13



Dr Haywood received his BSc and PhD degrees from the University of Kent at Canterbury, and carried out post-doctoral work in synthetic photochemistry at the University of London, before joining Glaxo as a development chemist in 1980.

He worked on a number of development projects in the Chemical Development department before transferring to the Glaxo manufacturing organisation in 1990. Three years later he moved to Singapore to manage the plant and process commissioning of the new multi-purpose facility at Glaxo's site there. Upon completion of this work he moved back to the UK and became Technical Department Head at Glaxo's cephalosporin manufacturing facility in Ulverston, Cumbria.

Following the merger with Welcome, he also took on responsibility for the technical department based at Welcome's Dartford site and for Outsourcing group which had the responsibility for identifying and carrying out technology transfer to external suppliers of intermediates and Bulk Drug.

He left GlaxoWelcome in 1997 and joined Astra in the UK as the local Head of Process R&D. Over the next few years he developed the UK group before taking over as VP at the Macclesfield Process R&D group following the merger with Zeneca. In 2002 he was made Global VP of Process R&D. His group currently consists of ~800 staff based on four sites; two in the UK, one in Södertälje, Sweden and one in Bangalore, India.

Besides being VP of Global Process R&D, Dr Haywood is also the Chairman of AstraZeneca India Pvt. Ltd. and Site Manager of the Charnwood R&D Site in the UK.

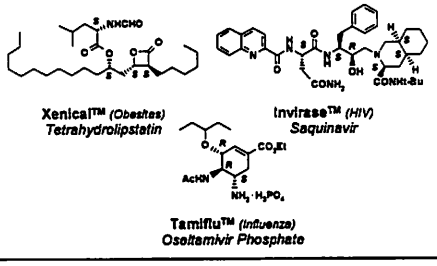
Graphical Abstract

Keynote Lecture

K-1

From Milligrams to Tons: The Importance of Synthesis & Process Research in the Development of new Drugs

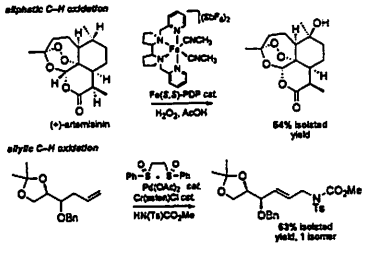
Martin Karpf
Synthesis & Process Research, F. Hoffmann-La Roche Ltd



K-2

Streamlining Synthesis via C-H Oxidation

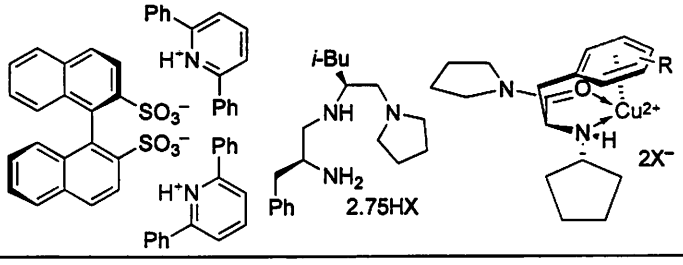
M. Christina White
Department of Chemistry, University of Illinois, Urbana, Il USA



K-3

Design of Dynamic Salt Catalysts Based on Acid–Base Combination Chemistry

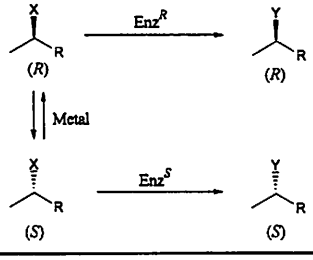
Kazuaki Ishihara*
Graduate School of Engineering, Nagoya University



K-4

Enzymo-Metallic Dynamic Kinetic Resolution as a New Tool for Chiral Synthesis

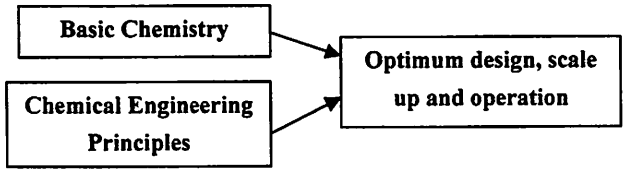
*Mahn-Joo Kim and Jaiwook Park
Department of Chemistry
Pohang University of Science and Technology,
Pohang, Korea



K-5

Matching Chemistry with Chemical Engineering for Optimum Design and Performance of Pharmaceutical Processing

Aniruddha B. Pandit
Chem. Eng. Dept. UICT, Mumbai 400 019 India

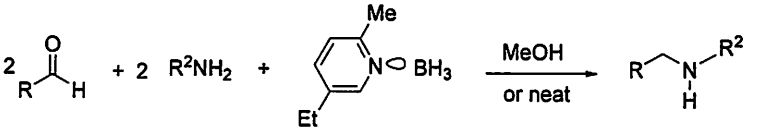


K-6

Boron Reagents for Process Chemistry: Excellent Tools for Selective Reductions

Karl Matos*, Elizabeth R. Burkhardt, Brian M. Coleridge

BASF Corporation

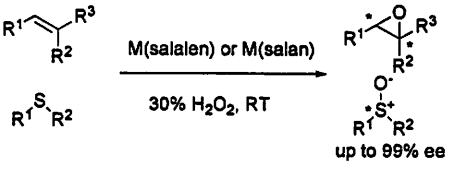


K-7

Asymmetric Oxidation with Hydrogen Peroxide, an Effective and Versatile Oxidant

Tsutomu Katsuki

Department of Chemistry, Graduate School, Kyushu university

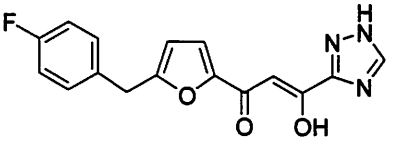


K-8

Process Development of HIV Integrase Inhibitor S-1360

Toshiro Konoike*

CMC Development Laboratories, Shionogi & Co., Ltd.



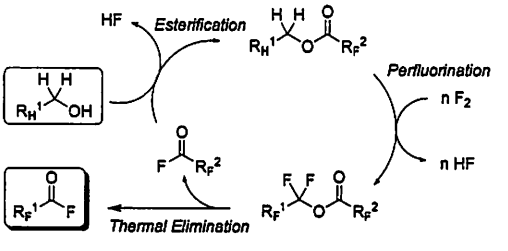
S-1360

K-9

An Entirely New Methodology for Synthesizing Perfluorinated Compounds

Takashi Okazoe,* Hirokazu Takagi, Daisuke Shirakawa

AGC Chemicals, Asahi Glass Co., Ltd.

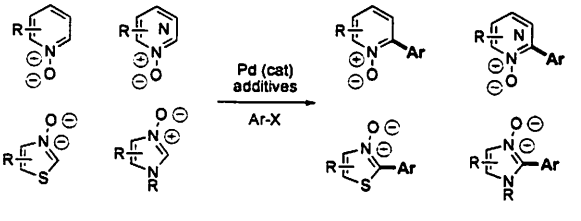


K-10

New Methods for the Functionalization of Aromatic Compounds

Keith Fagnou*

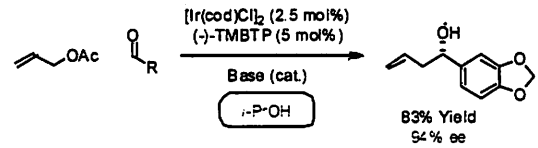
Dept. of Chemistry, University of Ottawa, Canada



K-11

Formation of C-C Bonds via Catalytic Hydrogenation and Transfer Hydrogenation

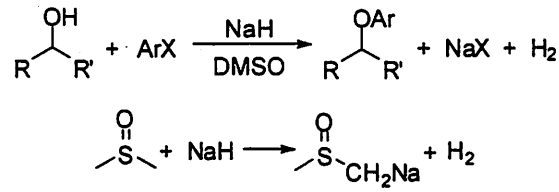
Michael J. Krische*
University of Texas at Austin, Department of Chemistry and Biochemistry



K-12

Commercialization of a Sodium Hydride Mediated Arylation Process

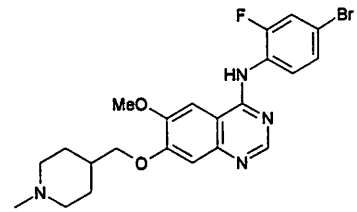
Mark A. Butchko
Eli Lilly and Company, Manufacturing Science & Technology, Tippecanoe Laboratories, Lafayette, IN (USA)



K-13

Design Space for Drug Substance – the approach used for vandetanib

David Haywood
Global Process R&D, AstraZeneca



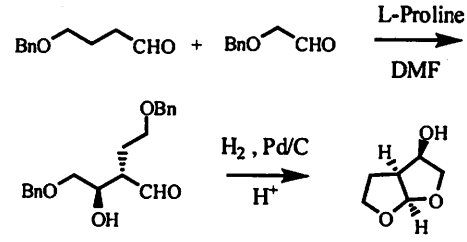
Vandetanib

Award Lecture

A-1

Process development of a key building block for anti-AIDS drugs by proline catalyzed enatio-selective direct cross aldol reaction

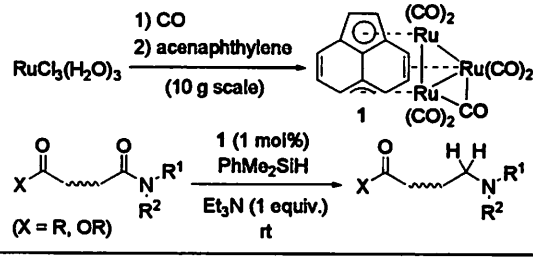
Tetsuya Ikemoto,* Yosuke Watanabe, Jun-ichi Tomokawa, Takehiko Kawakami, Yasuo Uekita, Isao Kurimoto
Fine Chemicals Research Laboratory,
Sumitomo Chemical Co., Ltd.



A-2

Development of Practical and Scalable Synthesis of a Triruthenium Cluster Catalyst and Amide-Selective Silane Reduction

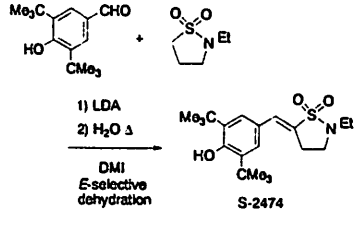
Hideo Nagashima,* Hidehiro Sasakuma, Nariaki Harada, Hironori Tsutsumi, Yukihiro Motoyama
Institute for Materials Chemistry and Engineering,
Graduate School of Engineering Sciences, Kyushu University



A-3

Development of One-pot Synthesis of New Antiarthritic Drug Candidate S-2474 with *E*-selectivity

Takemasa Hida,* Katsuo Oda, Toshiaki Masui, Hideo Nogusa
CMC Development Laboratories., Shionogi & Co., Ltd.

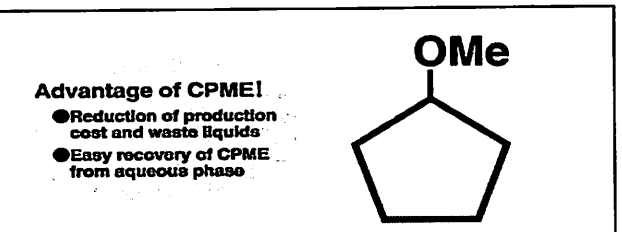


Poster Presentation
July 29 (Tue)

1P-01

A New Ethereal Solvent:CPME for Process Innovation and Green Chemistry

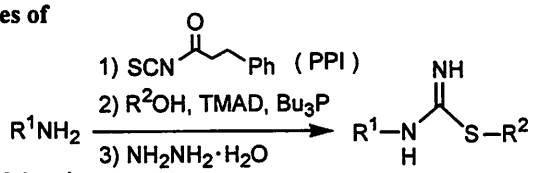
Kiyoshi Watanabe[1]*, Yasuhiro Torisawa [2]
[1,]*Specialty Chemicals Division, ZEON CORPORATION,
[2] Faculty of Pharmacy, Takasaki University of Health and Welfare



1P-02

Efficient Approaches to *S*-Alkyl-*N*-alkylisothioureas : Syntheses of Histamine H_3 Antagonist Clobenpropit and Its Analogues

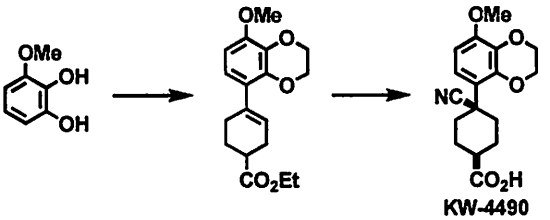
Hiroki Yoneyama[1], Mifuyu Yasunaga[1], Lisa Araki[1],
Kouta Hatano[2], Atsushi Yamatodani[2], Shinya Harusawa[1*]
[1]Osaka University of Pharmaceutical Sciences
[2]Graduate School of Allied Health Sciences, Faculty of Medicine, Osaka University



1P-03

A Practical Synthesis of the PDE4 inhibitor, KW-4490

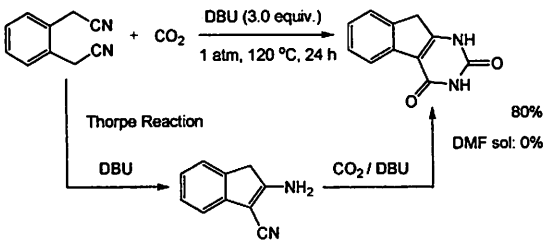
Arata Yanagisawa,* Koichiro Nishimura, Tetsuya Nezu,
Kyoji Ando, Ayako Maki, Eiichiro Imai, and Shin-ichiro Mohri
Sakai Research Laboratories, Pharmaceutical Research Center,
Kyowa Hakko Kogyo Co., Ltd.



1P-04

Solvent-free Synthesis of Heterocycles Using Carbon Dioxide (1 atm)

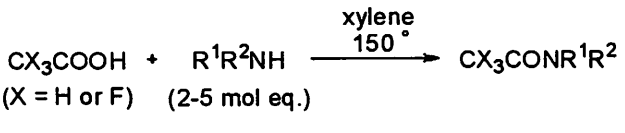
Takumi Mizuno,* Takeo Nakai,
Masatoshi Mihara
Osaka Municipal Technical Research Institute



1P-05

A One-Pot Procedure for Acetylation or Trifluoroacetylation of Amines Using Acetic Acid or Trifluoroacetic Acid as an Acylating Reagent

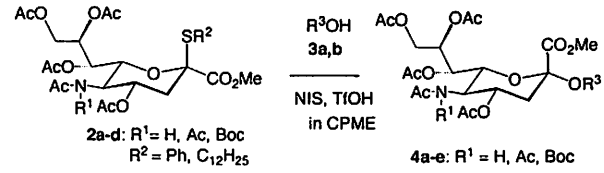
Yasuo Kikugawa,* Junpei Otaka, Hiroshi Yamazaki,
Naohiro Oshima, and Takeshi Sakamoto
Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan



1P-06

Highly stereoselective α-*O*-sialylation with *N,N*-Ac,Boc laurylthio sialoside in CPME

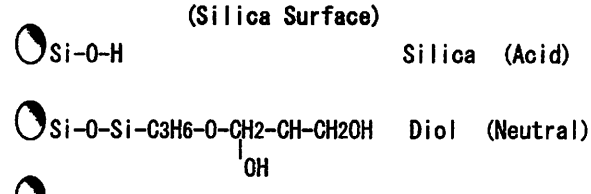
Kiyoshi Ikeda,*Keisuke Miyamoto, Masayuki Sato
School of Pharmaceutical Sciences, University of Shizuoka, Japan



1P-07

Properties of diol type silica in chromatography separation

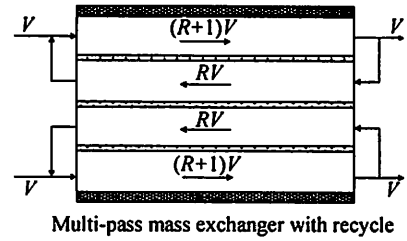
Kazunori Nobuhara, Mitsuhiro Kamimura, Takako Inoue, Makoto Kawai, Ryuji Orii
Fuji-Silysia Chemical Co., Ltd.



1P-08

Recycle effect on Mass-Transfer Efficiency Improvement in Multi-Pass Mass Exchangers

Chii-Dong Ho,* Jr-Wei Tu
Department of Chemical and Materials Engineering, Tamkang University, Tamsui, Taipei 25137, Taiwan

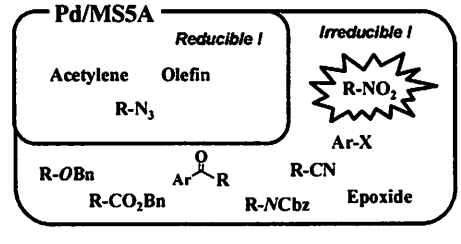


Multi-pass mass exchanger with recycle

1P-09

Molecular Sieves supported Pd Catalyst (Pd/MS5A) for Chemoselective Hydrogenation

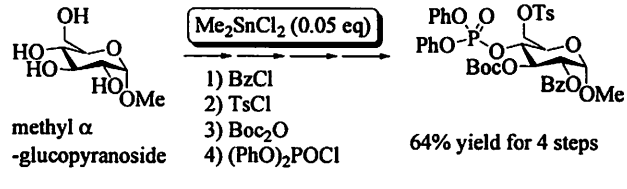
Tomohiro Maegawa,* Masatsugu Katoh, Ayako Tani, Tohru Takahashi, Yasunari Monguchi, Hironao Sajiki
Lab. of Med. Chem., Gifu Pharmaceutical University



1P-10

Regioselective protection of sugars catalyzed by organotin

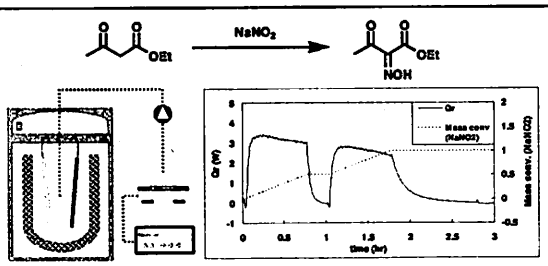
*Yuki Kubo, Yosuke Demizu, Osamu Onomura
Graduate School of Biomedical Sciences, Nagasaki University.



1P-11

Process Development Using Automated Reactor
- Kinetics of Nitroso Reaction -

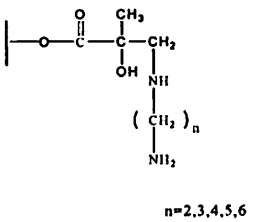
Takashi Naka,* Yasunari Takayasu and Hiroshi Iwamura
Process Chemistry Research Department
Mitusbishi Tanabe Pharma Corporation



1P-12

Change in neuron aggregation and neurite fasciculation on EVAL membranes modified with different diamines

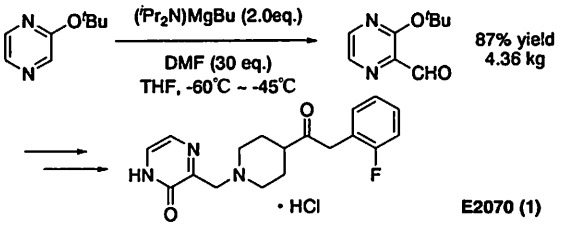
Tai-Horng Young (Email: thyoung@ntu.edu.tw)
Inst. Biomed. Eng., National Taiwan University, Taipei, Taiwan



1P-13

Process Development of a Novel Na-Ion channel Blocker E2070

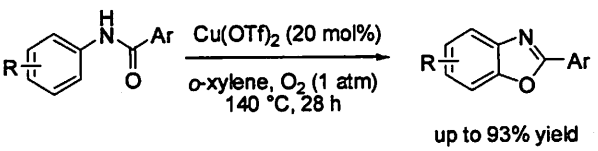
Manabu Kubota,* Atsushi Kamada, Ken Furukawa, Hiroshi Kuroda, Mamoru Miyazawa, Yuichi Kimoto, Naoyuki Shimomura
API Research Laboratories, Eisai Co., Ltd.



1P-14

Copper-Catalyzed C–H Activation/C–O Bond Formation for the Synthesis of Benzoxazoles

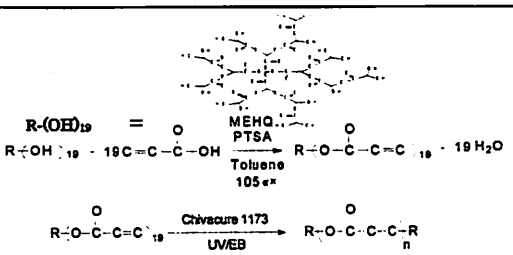
Satoshi Ueda,* Hideko Nagasawa
Laboratory of Medicinal and Pharmaceutical Chemistry, Gifu Pharmaceutical University



1P-15

Photocuring of Acrylated Dendrimer

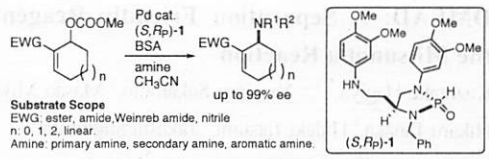
Syang-Peng Rwei*, National Taipei University of Technology



1P-16

Asymmetric Synthesis of Cyclic Aza-Morita-Baylis-Hillman Reaction Products Using Pd-DIAPHOX Catalyst System

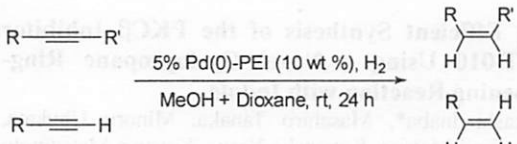
Tetsuhiro Nemoto, Takashi Fukuyama, Kazumi kakugawa, Yuko Maruyama, and Yasumasa Hamada
Graduate School of Pharmaceutical Sciences, Chiba University



1P-17

Pd/PEI : Partial hydrogenation catalyst of alkynes to alkenes

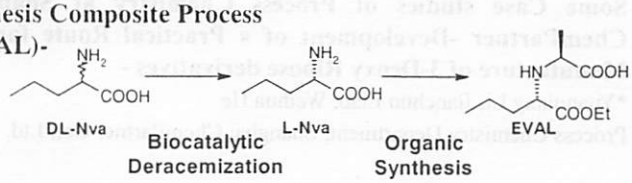
Shigeki Mori,* Tomoyuki Ohkubo, Takashi Ikawa, Akira Kume, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University



1P-18

Design and Construction of Biocatalyst for Multistep Reaction, and Development of Biotransformation-Organic Synthesis Composite Process -Process Development of Chiral Intermediate (EVAL)-

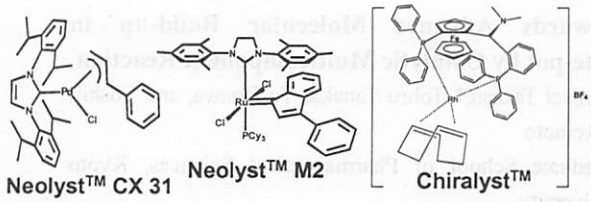
Motoko Hayashi,* Norihiro Kimoto, Hiroaki Yamamoto, Kiyoshi Ikura, Naohiro Hashikawa
Daicel Chemical Industries, Ltd.



1P-19

Industrial Scale Application of Umicore's Leading Edge Catalysts & Technologies

Yoshiaki Horiguchi*
Precious Metals Chemistry
Umicore Japan KK.

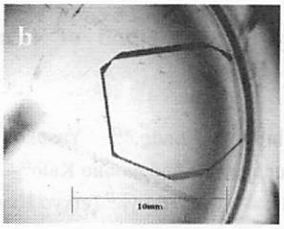


1P-20

Control of Primary Nucleation for Organic Substance by Ultrasonic Irradiation

Izumi Hirasawa* Waseda University.

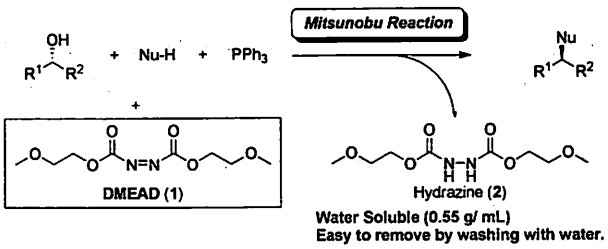
A grown crystal from a nuclei induced by US



1P-21

DMEAD: A Separation Friendly Reagent for the Mitsunobu Reaction

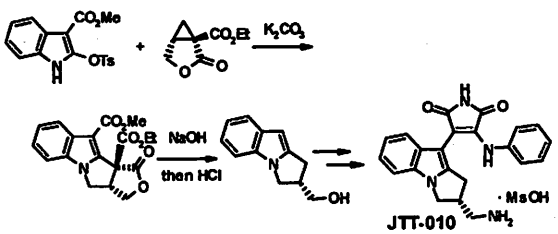
Kazutake Hagiya,*[1,2] Yasuhiro Sakamoto,[1] Masao Miyatake,[1] Hikaru Tanaka,[1] Hideki Tatsumi,[1] Takashi Sugimura[2]
[1]TOYO KASEI KOGYO Co., Ltd. [2]University of Hyogo



1P-22

An Efficient Synthesis of the PKCβ Inhibitor JTT-010 Using a Novel Cyclopropane Ring-Opening Reaction with Indole

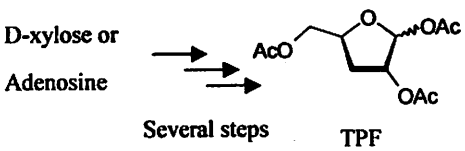
Takashi Inaba*, Masahiro Tanaka, Minoru Ubukata, Takafumi Matsuo, Katsutaka Yasue, Katsuya Matsumoto, Yasuyuki Kajimoto, Takashi Ogo
Central Pharmaceutical Research Institute, Japan Tobacco Inc.



1P-23

Some Case studies of Process Chemistry at Shanghai ChemPartner -Development of a Practical Route for the Manufacture of 3-Deoxy Ribose derivatives -

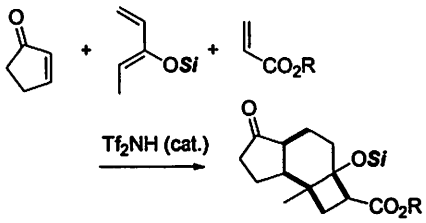
*Yuanqiang Li, Jianchun Liao, Weihua He
Process Chemistry Department, Shanghai ChemPartner Co., Ltd.



1P-24

Towards Advance Molecular Build-up in One-pot by Catalytic Multicomponent Reaction

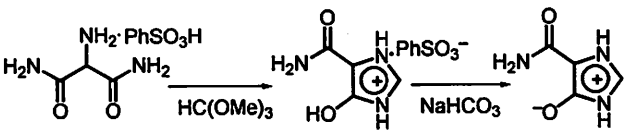
Kiyosei Takasu,* Tohru Tanaka, Yu Ogawa, and Yoshiji Takemoto
Graduate School of Pharmaceutical Sciences, Kyoto University.



1P-25

Synthetic Method of 4-carbamoylimidazolium-5-olate

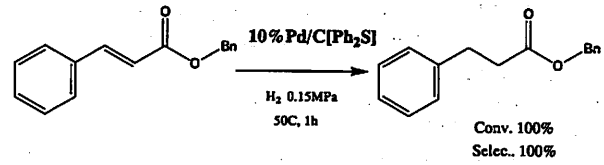
Chihiro Kondo,*[a] Yusuke Higuchi,[a] Makoto Sunagawa,[b] and Nobuo Kato[a]
[a]Osaka University, [b]Teikyo Heisei University



1P-26

Novel Palladium-on-Carbon Catalyst, Pd/C[Ph2S], for Chemoselective Hydrogenation

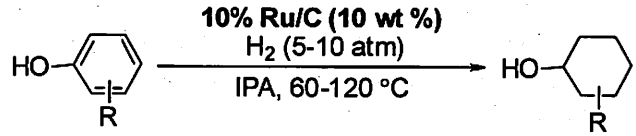
Tomoteru Mizusaki, Shinobu Takao, Masashi Endo,
* Masatoshi Yoshimura, Yukio Takagi
N.E. Chemcat Corporation



1P-27

Hydrogenation of Aromatic Nuclei: Practical Synthesis of Cyclohexanol Derivatives

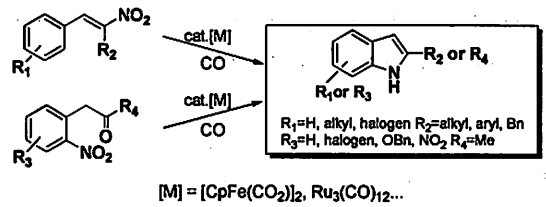
Kiichiro Yaguchi, * Akira Akashi, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki



1P-28

Transition Metal Catalyzed Construction of Indole Nucleus under CO Conditions

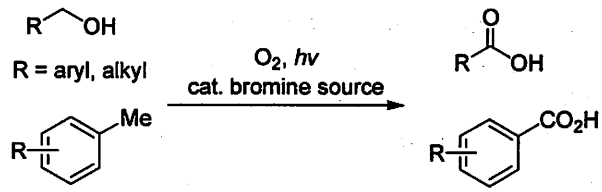
* Yasuhiro Sakurai, Yasuo Shirai, Tomohisa Utsunomiya, Norio Tanaka
Nissan Chemical Industries, LTD.



1P-29

Synthesis of Carbonyl Compounds through Aerobic Photo-oxidation

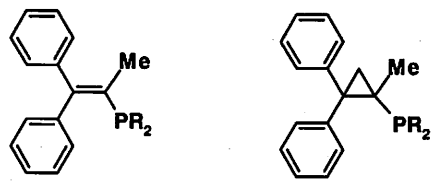
Akichika Itoh, Norihiro Tada, Shin-ichi Hirashima,* Hiroki Nakayama
Gifu Pharmaceutical University



1P-30

Design and development of new catalyst systems: Palladium/BRIDP for efficient coupling reactions

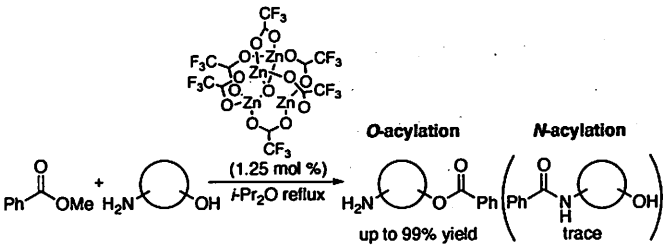
Tohru Kobayashi,* Ken Suzuki, Noboru Sayo
Corporate Research & Development Division,
Takasago International Corporation



1P-31

Development of Protecting Group Free Catalytic *O*-Selective Acylation of Aminoalcohols

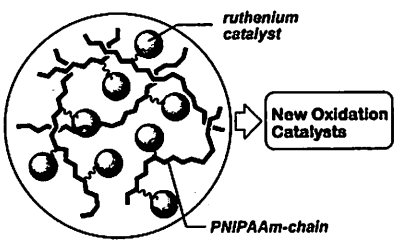
Takashi Ohshima,* Takanori Iwasaki, Yusuke Maegawa, Kazushi Mashima
Department of Chemistry, Graduate School of Engineering Science, Osaka University



1P-32

Development of Recyclable Ruthenium Catalysts for Aerobic Oxidation Utilizing Poly(*N*-isopropylacrylamide)-Based Polymer

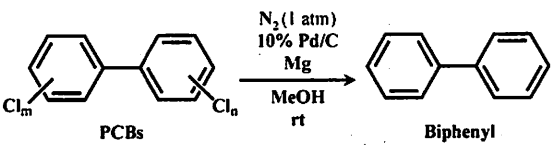
Hiromi Hamamoto[1,2],* Masahiro Kudoh[2], Hideyo Takahashi[2], Hideaki Natsugari[2], Shiro Ikegami[2], Yasuyoshi Miki[1]
School of Pharmaceutical Sciences, Kinki University[1]
School of Pharmaceutical Sciences, Teikyo University[2]



1P-33

Pd/C-catalyzed dehalogenation of aromatic halides and its application to degradation of PCBs

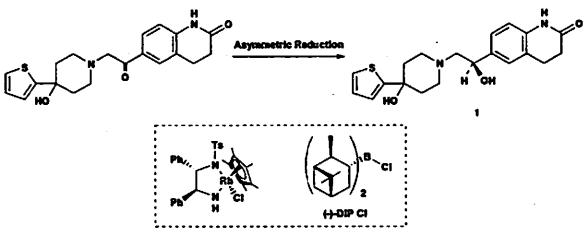
Shinji Ishihara,*[ab] Akiko Ido,[a] Tomohiro Maegawa,[a] Yasunari Monguchi,[a] Sueo Wada,[b] Hisamitsu Nagase,[a] Hironao Sajiki[a]
[a]Gifu Pharmaceutical University. [b]Nagara Bionics Co., Ltd.



1P-34

Synthetic Studies on an NR2B Antagonist

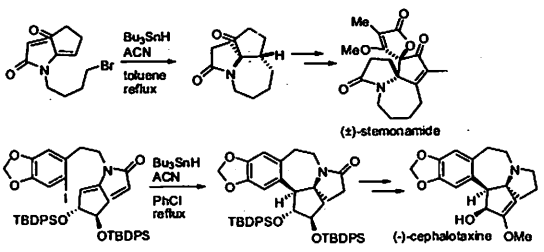
A. Ogawa,* O. Saku, N. Koizumi, T. Matsumura, T. Watanabe, K. Nishimura, I. Chujo
Sakai Research Laboratories, Kyowa Hakko Kogyo Co., Ltd.



1P-35

Total Synthesis of Natural Products Using a Radical Cascade

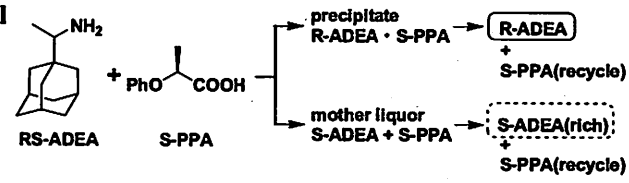
Tsuyoshi Taniguchi,* Hiroyuki Ishibashi
Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University.



1P-36

Production of Chiral Amines including Adamantyl Groups by Optical Resolution

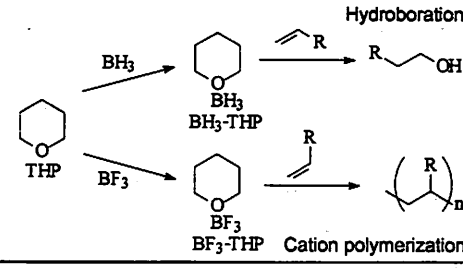
Taichi Akimoto,*[1] Tetsuro Watadani,[1] Shigeki Nunomura,[1] Yukio Takahashi,[1] Isao Fujii[2] ;[1]Daito Chemical Co., Ltd, [2]Dept. of Biological Sci. and Tech.,Tokai University



1P-37

Organic synthesis utilizing tetrahydropyran-boron complex

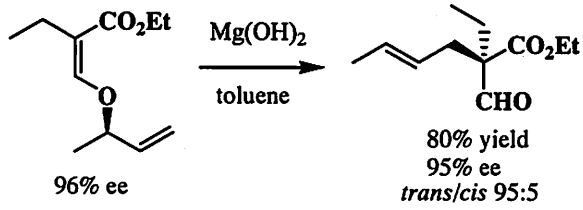
Hiroshi Yasuda,* Yoshihiko Maeda
Corporate R&D Center, Showa Denko K.K.
Takeshi Oriyama, Ryoichi Chiba
Faculty of Science, Ibaraki University



1P-38

Construction of Quaternary Chiral Center by Asymmetric Transfer Claisen Rearrangement

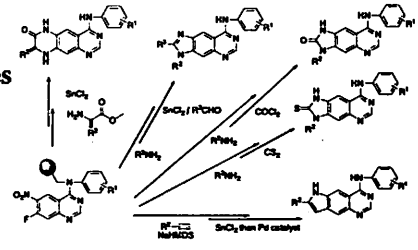
Kazuhiko Watabe, Kazumi Okuro, Masaru Mitsuda*
Frontier Biochemical and Medical Research Laboratories, Kaneka Corporation



1P-39

Scaffold Approach for Solid-phase synthesis of quinazoline derivatives

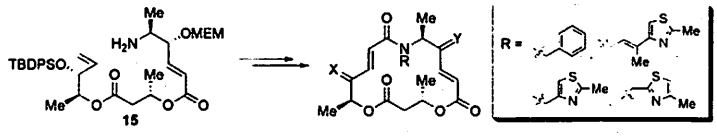
Yong Cai[1]*, Hongjun Zhang[1], Yandong Zhang[2], Yongping Yu[1,2]
[1]Chemik Co., Ltd. P. R. China
[2]College of Pharmaceutical Science, Zhejiang University, P.R.China



1P-40

Design and Synthesis of Macrosphelide Aza-analogues

Yuta Kobayashi.* Yuji Matsuya, Hideo Nemoto
Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama.

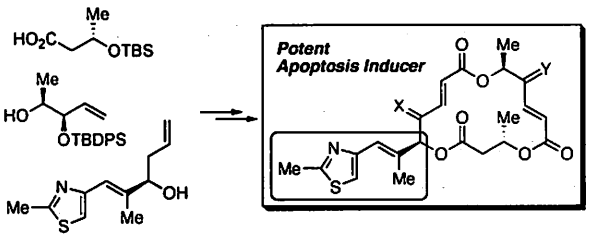


1P-41

Synthesis and Bioactivity of Macrosphelide -based Artificial Compounds

Yuji Matsuya,* Takanori Kawaguchi, Kanwal Ahmed, Qing-Li Zhao, Takashi Kondo, Hideo Nemoto

Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama

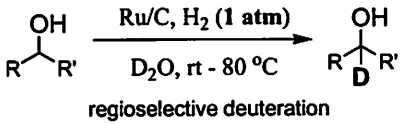


1P-42

Ru/C-Catalyzed α-position selective deuteration of alcohols

Yuta Fujiwara,* Yuya Inagaki, Yasunari Monguchi, Tomohiro Maegawa, Hironao Sajiki

Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University

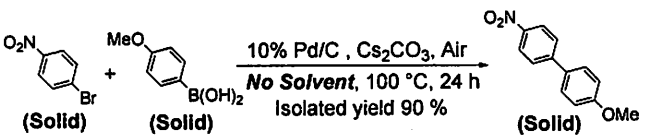


1P-43

Pd/C-catalyzed, Solvent-free and Solid-Phase Suzuki-Miyaura Coupling Reaction

Yuki Fujita,* Shota Hashimoto, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki

Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University

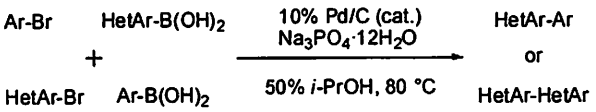


1P-44

Practical synthesys of heterobiaryl derivatives

Azusa Tsutsui,* Satoko Sako, Yoshiaki Kitamuira, Takahiro Udzu, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki

Gifu Pharmaceutical University

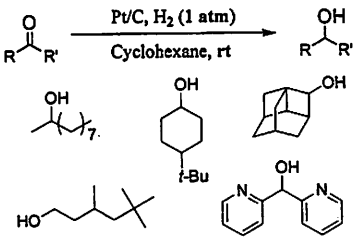


1P-45

Mild hydrogenation of carbonyl compounds using Pt/C as a catalyst

Youhei Iwasaki,* Yuta Fuijiwara, Yasunari Monguchi, Tomohiro Maegawa, Hironao Sajiki

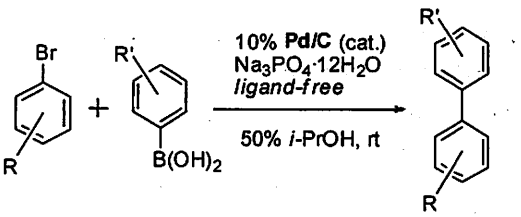
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University



1P-46

Pd/C-catalyzed, Ligand-free Suzuki-Miyaura Reaction

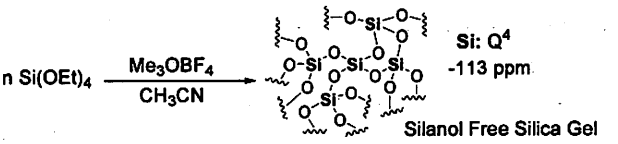
Yasunari Monguchi,* Yoshiaki Kitamura, Satoko Sako, Takanori Kurita, Tomohiro Maegawa, Hironao Sajiki
Gifu Pharmaceutical University



1P-47

Meerwein's reagent-Catalyzed Sol-Gel Polycondensations Giving Silanol Free Silica gel

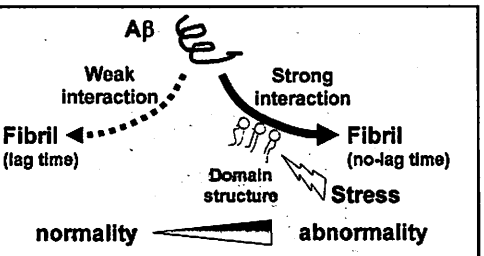
Toyoshi Shimada,* Yogesh Jorapur[†,‡], Norihiro Mizoshita[§,‡], Yoshifumi Maegawa[†], Hiroki Nakagawa[†], Takeru Hasegawa[†], Takao Tani[§,‡], Shinji Inagaki[§,‡]
[†]Department of Chemical Engineering, Nara National College of Technology. [§]Toyota Central R&D Laboratories, Inc. and [‡]CREST, JST



1P-48

Development of Separation and Analytic Method for Aβ Peptide Based on Biomembrane Abnormarity ~Membrane Chip Analysis Can Brighten a Potential Aspect of Alzheimer Disease~

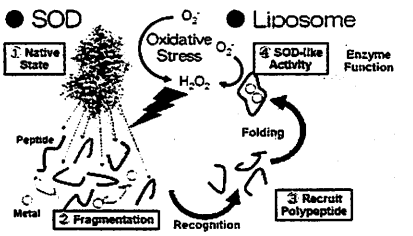
Toshinori Shimanouchi, Haruyuki Ishii, Vu Thi Huong, Keiichi Nishiyama, Hiroshi Umakoshi, Ryoichi Kuboi
Grad. Sch. of Engineering Science, Osaka Univ.



1P-49

Biomembrane Process Chemistry and Separation Technology ~ Design and Development of Antioxidative LIPOzyme in One-Pot based on Molecular Recognition Function of Liposome Biomembrane

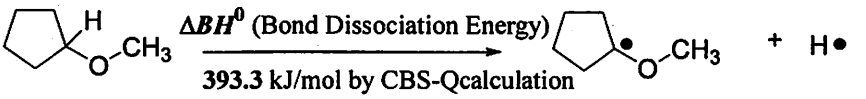
Hiroshi Umakoshi, Le Quoc Tuan, Kengo Morimoto, Toshinori Shimanouchi, Ryoichi Kuboi
Grad. Sch. of Engineering Science, Osaka Univ.



1P-50

Autoxidation Resistant Cyclopentyl Methyl Ether (CPME).

* Kazuhisa Sakakibara, Hayato Hoshino, and Kiyoshi Watanabe[1]
Dept. Appl. Chem.
Yokohama Natl. Univ.
1. Zeon Corporation

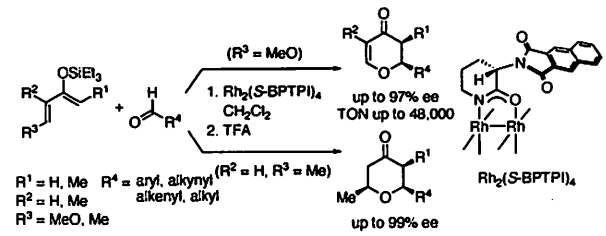


1P-51

Dirhodium(II)-Catalyzed Enantioselective Hetero-Diels–Alder Reaction

Masahiro Anada,* Takuya Washio, Yuudai Watanabe, Naoyuki Shimada, Shunichi Hashimoto

Faculty of Pharmaceutical Sciences, Hokkaido University

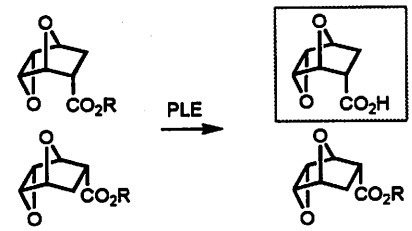


1P-52

Enzyme-catalyzed enantiomeric resolution of tamiflu intermediates

Manabu Hamada,* Kaoru Nakamura, Seiichiro Ogawa, Toshinori Higashi, Keiko Inami, Kazuo Umezawa, Takeshi Suga

Faculty of Pharmacy, Keio University

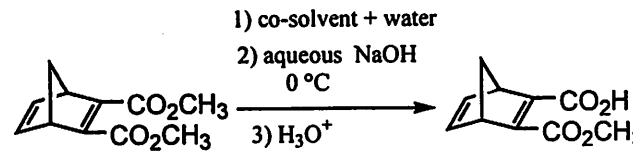


1P-53

Studies of Solvent Effects in the Selective Monohydrolysis of Symmetric Diesters

Satomi Niwayama,[a,*] Hezhen Wang,[a] Hanjoung Cho,[a] Yoshikazu Hiraga[b]

a: Department of Chemistry and Biochemistry, Texas Tech University, U.S.A.
b:Department of Chemistry, Hiroshima University, Japan

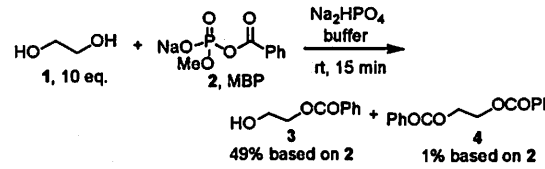


1P-54

Esterification of Polyalcohol in water

Risa Maeda,* Yuusaku Yokoyama, Hiroaki Okuno

Department of Pharmaceutical Sciences, Toho University

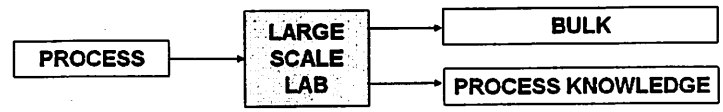


1P-55

Chemists' Scale-Up Challenges

Asayuki Kamatani*

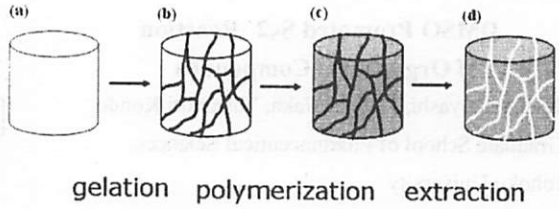
Pfizer Global Research and Development, UK



1P-56

Template Synthesis Process of Porous Polymers

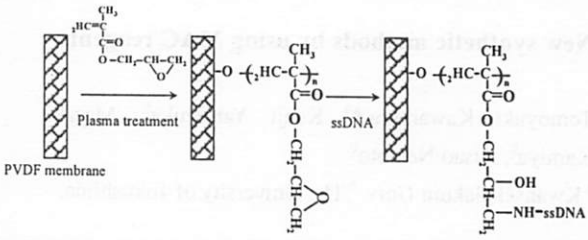
Wei-Chi Lai,* Shen-Chen Tseng
Department of Chemical and Materials Engineering, Tamkang University, Tamsui, Taipei 25137, Taiwan



1P-57

Chemical Immobilization of DNA on porous PVDF membranes for biomedical applications

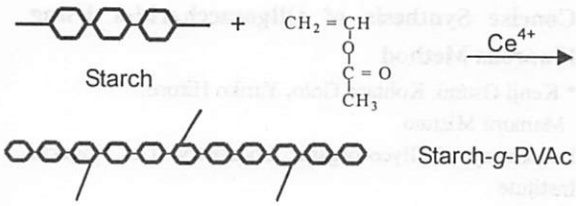
D-J Lin, D-T Lin, T-H Young, H-H Chang, L-P Cheng*
*Department of Chemical and Materials Engineering, Tamkang University, Taipei, Taiwan 25137



1P-58

Graft Polymerization of Poly(vinyl acetate) to a Corn Starch and Its Blends with Polyhydroxybutyrate

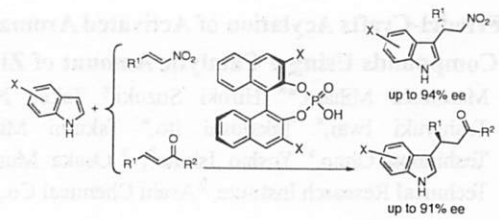
Trong-Ming Don,* Wei-Wei Shun
Department of Chemical and Materials Engineering, Tamkang University, Taipei County, Taiwan



1P-59

Chiral Brønsted Acid-Catalyzed Enantioselective Friedel-Crafts Alkylation of Indole with α,β-Unsaturated Ketones

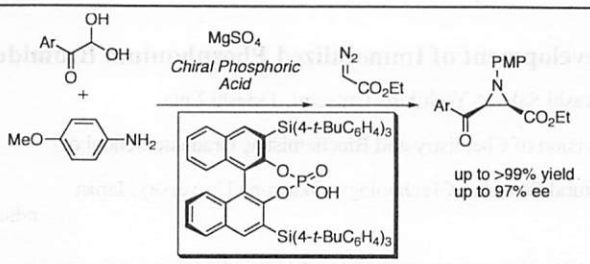
Tsubasa Sakamoto*, Junji Itoh, Kohei Fuchibe, Keiji Mori, Takahiko Akiyama
Department of Chemistry, Faculty of Science, Gakushuin University.



1P-60

Chiral Brønsted Acid Catalyzed Enantioselective aza-Darzens Reaction

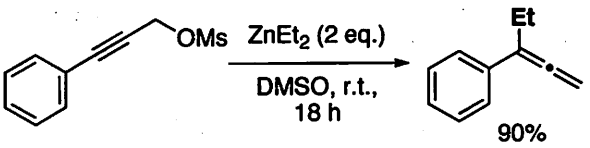
Tohru Suzuki,* Kohei Fuchibe, Keiji Mori, Takahiko Akiyama
Department of Chemistry, Gakushuin University.



1P-61

DMSO Promoted S_N2' Reaction of Organozinc Compounds

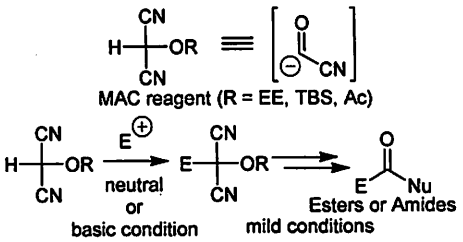
* Koji Kobayashi, Hiroshi Naka, Yoshinori Kondo
Graduate School of Pharmaceutical Sciences, Tohoku University



1P-62

New synthetic methods by using MAC reagents

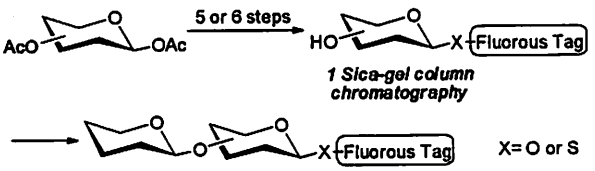
Tomoyuki Kawamura,*[a] Kenji Yatsuzuka[b], Masaki Kamiya[b], Hisao Nemoto[b]
[a] Kwansei Gakuin Univ. [b] The University of Tokushima.



1P-63

Concise Synthesis of Oligosaccharides Using Fluorous Method

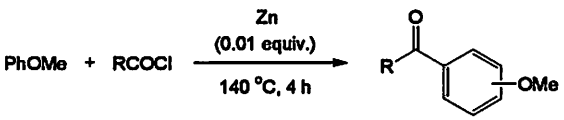
* Kenji Osumi, Kohtaro Goto, Yuriko Hirose, Mamoru Mizuno
Laboratory of Glyco-organic Chemistry, The Noguchi Institute



1P-64

Friedel-Crafts Acylation of Activated Aromatic Compounds Using a Catalytic Amount of Zinc

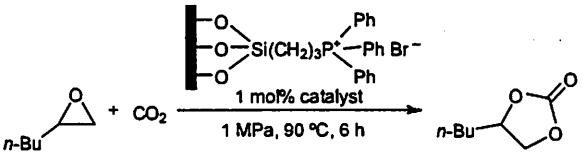
Masatoshi Mihara,*[a] Hiroki Suzuki,[a] Takeo Nakai,[a] Toshiyuki Iwai,[a] Takatoshi Ito,[a] Takumi Mizuno,[a] Toshinobu Ohno,[a] Yoshio Ishino[b]; [a] Osaka Municipal Technical Research Institute, [b] Asahi Chemical Co., Ltd.



1P-65

Development of Immobilized Phosphonium Bromide for Cyclic Carbonate from Epoxide

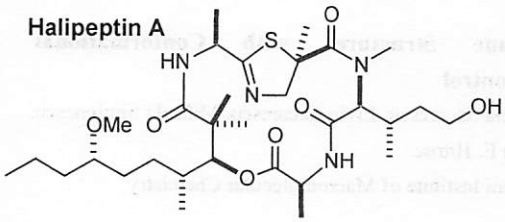
Takashi Sakai,* Yoshihiro Tsutsumi. Tadashi Ema
Division of Chemistry and Biochemistry, Graduate School of Natural Science of Technology, Okayama University, Japan



1P-66

Total Synthesis of Halipeptins

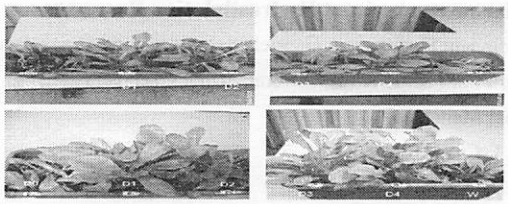
Kazuishi Makino, Sousuke Hara, Youhei Koma,
Masaru Sakaguchi, Yasumasa Hamada*
Graduate School of Pharmaceutical Sciences,
Chiba University



1P-67

Microbial Reclamation of Squid Pen for the Production of Proteases and Biofertilizer

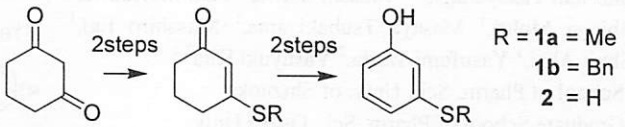
San-Lang Wang,* Tsai-Yi Huang, Chun-Yuan Wang
Graduate Institute of Life Sciences, Tamkang University



1P-68

A Novel Synthesis of 3-Sulfanylphenols

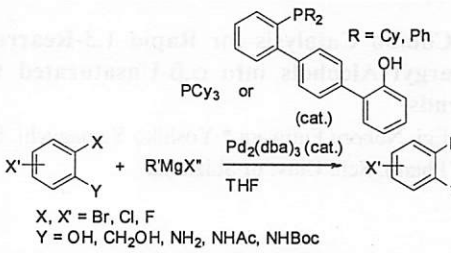
Yasuhiro Sato,* Sunao Mitsui, Hideki Tatsumi
Fine Chemicals Research Laboratory, Chemicals Research Center, TOYO KASEI KOGYO Co., Ltd.



1P-69

Ortho-Selective Cross-Coupling of Dihalobenzene Derivatives

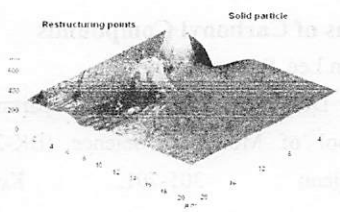
Shunpei Ishikawa,* Kei Manabe
Manabe Initiative Research Unit, RIKEN



1P-70

Chemo-Structural Processes in Polyhydrosilanes

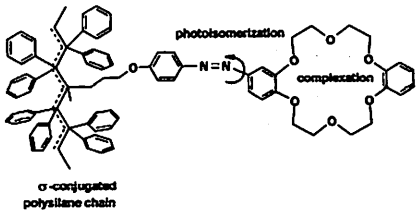
* Liviu Sacarescu, Mihaela Simionescu, Gabriela Sacarescu
Petru Poni Institute of Macromolecular Chemistry



1P-71

Polysilane Structures with Conformational Photocontrol

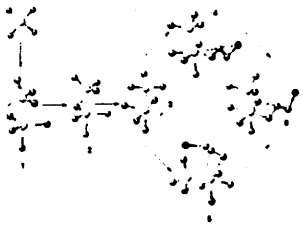
* Gabriela Sacarescu, Liviu Sacarescu, Mihaela Simionescu, Gabriela E. Hitruc
Petru Poni Institute of Macromolecular Chemistry



1P-72

Microwave Assisted Hydrosilylation Processes

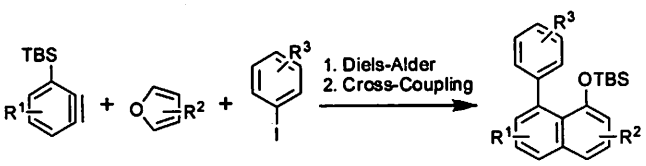
* Mihaela Simionescu, Gabriela Sacarescu, Liviu Sacarescu
Petru Poni Institute of Macromolecular Chemistry
Ionel Mangalagiu
Al. I. Cuza University



1P-73

Regioselective Diels-Alder Reactions of Silylbenzynes: Convergent Synthesis of Polysubstituted Biaryls

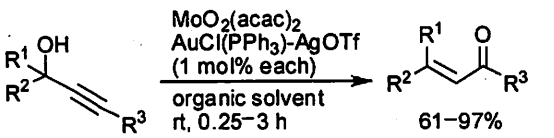
Sho-ichi Takayanagi,[1,*] Takashi Ikawa,[1] Yuki Morikawa,[1] Shinya Mohri,[1] Masaya Tsubakiyama,[1] Masahiro Egi,[1] Shuji Akai,[1] Yasufumi Wada,[2] Yasuyuki Kita[2,3]
[1]School of Pharm. Sci., Univ. of Shizuoka
[2]Graduate School of Pharm. Sci., Osaka Univ.
[3]School of Pharm. Sci., Ritsumeikan Univ.



1P-74

Mo-Au Combo Catalysis for Rapid 1,3-Rearrangement of Propargyl Alcohols into α,β-Unsaturated Carbonyl Compounds

Masahiro Egi, Noboru Fujiwara,* Yoshiko Yamaguchi, Shuji Akai
School of Pharm. Sci., Univ. of Shizuoka

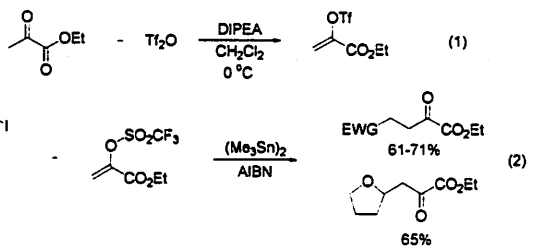


R^1, R^2 = H, alkyl, aryl; R^3 = H, alkyl, aryl, OPh, N(Bn)Ts

1P-75

Radical Alkylations of Carbonyl Compounds

JinYoung Lee,* Misun Lee, Sunggak Kim
Center for Molecular Design & Synthesis and Department of Chemistry, School of Molecular Science (BK-21), KAIST, Daejeon 305-701, Korea

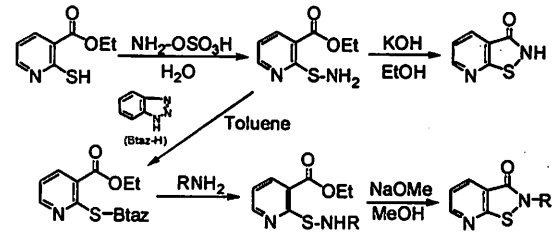


Poster Presentation
July 30 (Wed)

2P-01

Chlorine Gas Free Synthesis of Isothiazolo[5,4-*b*]pyridin-3-ones

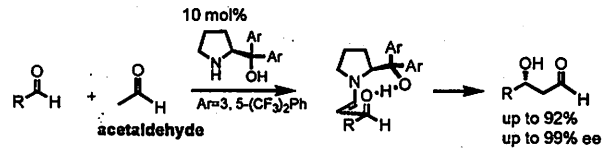
Masao Shimizu,*[1)] Yusuke Higuchi,[2)] Takeo Konakahara[2)]
1) National Institute of Advanced Industrial Science and Technology (AIST); 2) Faculty of Science and Technology, Tokyo University of Science



2P-02

The asymmetric reaction of acetaldehyde catalyzed by organocatalysis

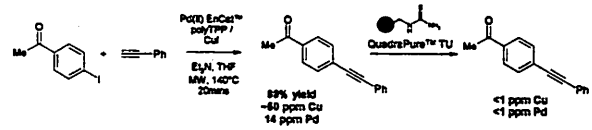
Yujiro Hayashi,* Takahiko Itoh, Seiji Aratake, Hayato Ishikawa
Faculty of Engineering, Tokyo University of Science



2P-03

Overcoming The Issues Of Precious Metal Contamination Within Catalysed Reactions

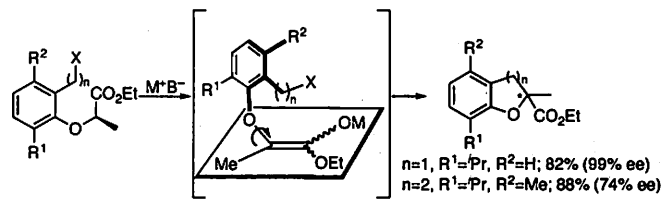
David J. Evans,* Mohammed Nisar, Thomas E. O. Screen, Michael R. Pitts, Angus J. P. Stewart-Liddon
Reaxa Limited, Hexagon Tower, Manchester, M9 8ZS, UK



2P-04

Asymmetric Synthesis of Dihydrobenzofurans and Chromans via Planar Chiral Enolates

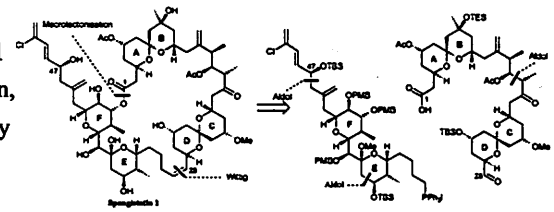
*Tomoyuki Yoshimura, Keisuke Tomohara, and Takeo Kawabata
Institute for Chemical Research, Kyoto University



2P-05

Studies Towards a Gram-Scale Synthesis of Spongistatin 1

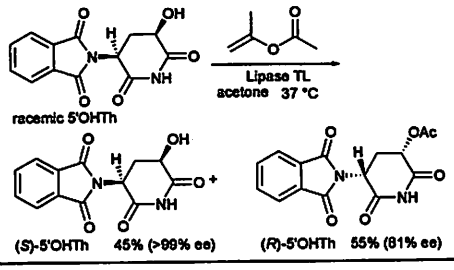
Helmut Kraus,* Alejandro Diéguez-Vázquez, Matthew O'Brien, Yukihito Sumino, Takashi Tsunoda, Day-Shin Hsu and Steven V. Ley
University of Cambridge, Department of Chemistry, Lensfiled Road, Cambridge, CB2 1EW, UK



2P-06

Enzymatic Resolution and Evaluation of Enantiomers of *cis*-5'-Hydroxythalidomide

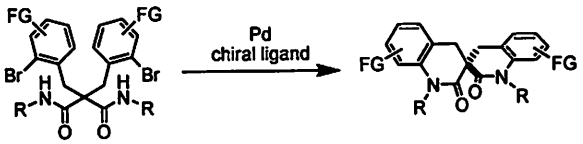
Takeshiu Yamamoto,* Masayuki Takashima, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Graduate School of Engineering, Nagoya Institute of Technology



2P-07

Enantioselective Synthesis of Spirobilactams via the Intramolecular Double Buchwald-Hartwig Reaction

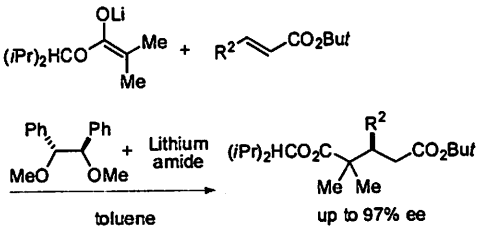
* Kazuhiro Takenaka, Noriyuki Itoh, Hiroaki Sasai
The Institute of Scientific and Industrial Research, Osaka University



2P-08

A ternary complex reagent for an asymmetric conjugate Michael addition of lithium ester enolates with enoates

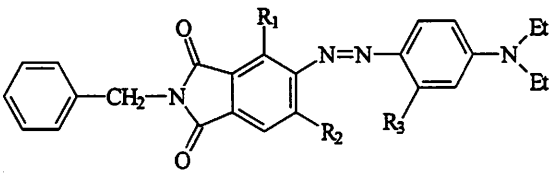
Yasutomo Yamamoto,* Hirokazu Suzuki, Yorinobu Yasuda, Kiyoshi Tomioka
Graduate School of Pharmaceutical Sciences, Kyoto University



2P-09

Synthesis and spectroscopic properties of novel azo dyes derived from phthalimide

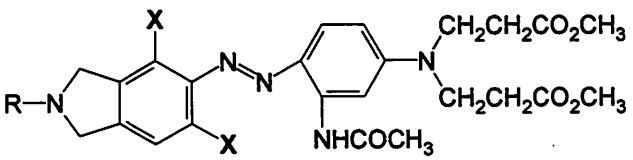
*Oh Tak Kwon, Hyun Yung Lee, Jae Hong Choi, Wilson Jung
Department of Textile System Engineering,
Kyungpook National University, Korea



2P-10

Synthesis of alkali-clearable phthalimidyl dyes and their colorimetric properties

*Hyun Young Lee, Jae Hong Choi,
Jeong Min Jeon, Wilson Jung[c*]
Department of Textile System Engineering,
Kyungpook National University & Eastwell Co. Ltd

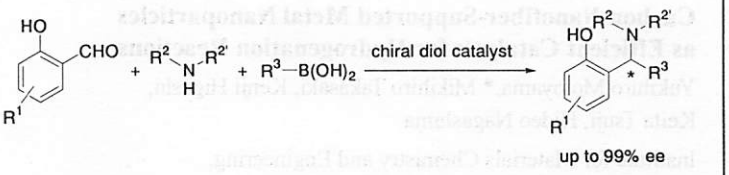


2P-11

Catalytic Enantioselective Petasis Reaction

Naoto Inakoshi,* Eric N. Jacobsen

Department of Chemistry and Chemical Biology, Harvard University

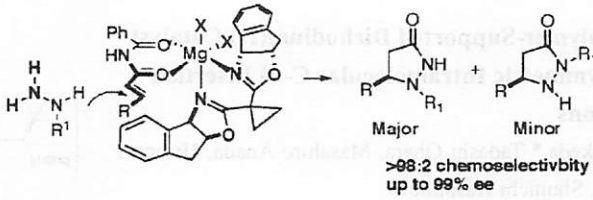


2P-12

Enantioselective Conjugate Addition of Hydrazines to α,β-Unsaturated imides. Synthesis of Chiral Pyrazolidinones.

Takahieo Soeta*, Mukund P. Sibi

Department of Chemistry, North Dakota State University, Fargo, ND, 58105.

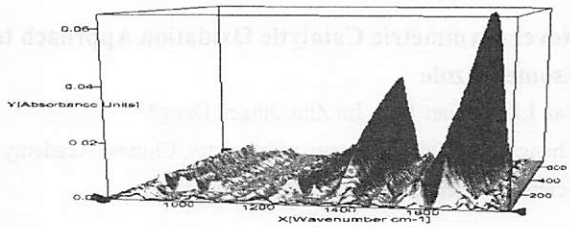


2P-13

The study of in-situ monitoring to radical polymerization process using by fiber mid infrared spectroscopy.

Daisuke Sasakura,* Kazuo Osaki, Tsuyoshi Miura

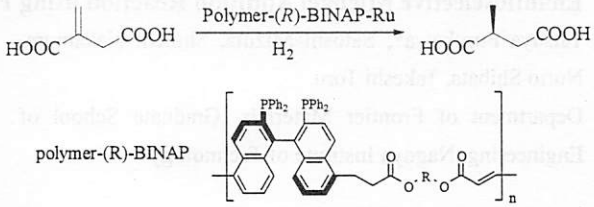
Application Division ,Bruker Optics K.K.



2P-14

Catalytic asymmetric hydrogenation using environment conscious new BINAP polymer

Yoshinori Takamatsu,[1,*] Gakuto Goshima,[1] Naomi Takenaka,[1] Kenji Toribatake,[2] Hiroshi Shibaguchi,[2] Toyohiro Nagano,[2] Toyoshi Shimada[2] [1]Kyoeisha Chemical Co.,Ltd. Nara Laboratory. [2]Nara National College of Technology.

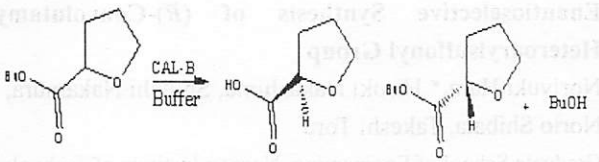


2P-15

Improving the enantioselectivity of *Candida antartaca* lipase B for kinetic resolution of butyl tetrahydrofuran-2-carboxylate

* Sojung Park, Suhyun Jung , Seongsoon Park

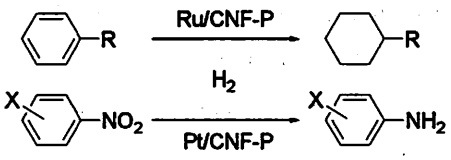
Department of Chemistry, Sungshin Women's University



2P-16

Carbon Nanofiber-Supported Metal Nanoparticles as Efficient Catalysts for Hydrogenation Reactions

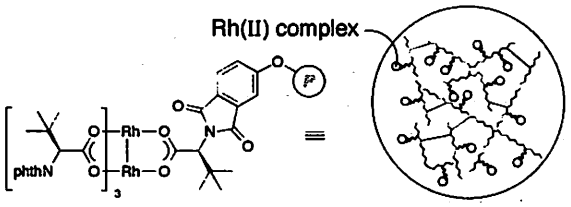
Yukihiro Motoyama,* Mikihiro Takasaki, Kenji Higashi, Keita Tsuji, Hideo Nagashima
Institute for Materials Chemistry and Engineering, Graduate School of Engineering Sciences, Kyushu University



2P-17

The Polymer-Supported Dirhodium(II) Catalyst for Asymmetric Intramolecular C–H Insertion Reactions

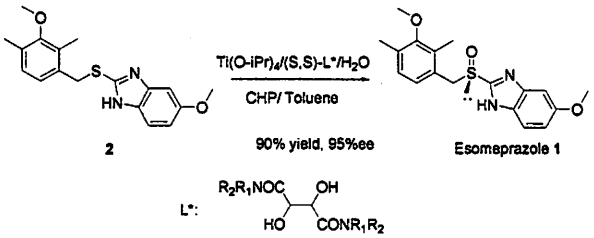
Koji Takeda,* Tadashi Ohara, Masahiro Anada, Hisanori Nambu, Shunichi Hashimoto
Faculty of Pharmaceutical Sciences, Hokkaido University



2P-18

Novel Asymmetric Catalytic Oxidation Approach to Esomeprazole

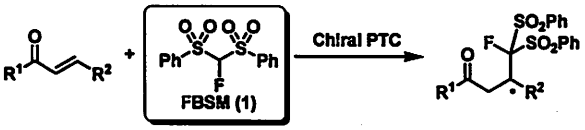
Jian Liao,* Tian Tian, Jin Zhu, Jingen Deng*
Chengdu Insititute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041, P. R. China



2P-19

Enantioselective Michael Addition Reaction using FBSM

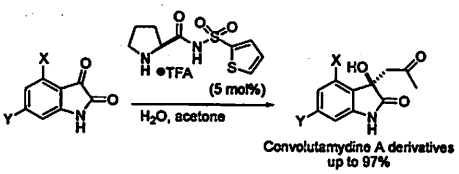
Tatsuya Furukawa*, Satoshi Mizuta, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology



2P-20

Enantioselective Synthesis of (*R*)-Convolutamydine A using Novel Organocatalyst Having Heteroarylsulfonyl Group

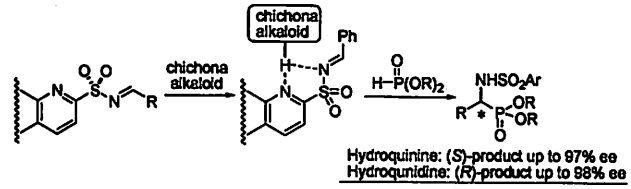
Noriyuki Hara,* Hiroki Nakashima, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Graduate School of Engineering, Nagoya Institute of Technology



2P-21

Organocatalytic Enantioselective Hydrophosphonylation of Sulfonylimines Having Heteroarylsulfonyl Group

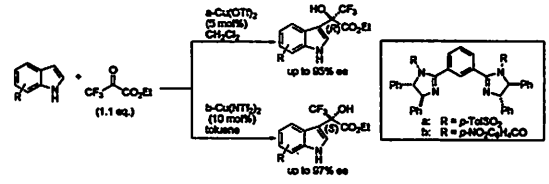
Akiko Yamamura,* Hiroki Nakashima, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Graduate School of Engineering, Nagoya Institute of Technology



2P-22

A Novel C2-Symmetric Chiral Bis(imidazoline) Ligands: Highly Enantioselective Friedel-Crafts Alkylation of Indoles with Ethyl 3,3,3-Trifluoropyruvate

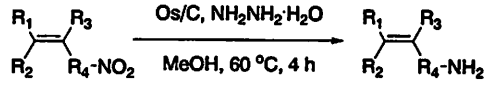
Yuko Nakamura,* Kotaro Tsuji, Kengo Hyodo, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Graduate School of Engineering, Nagoya Institute of Technology



2P-23

Chemoselective hydrogenation of nitro functionalities in the presence of olefins using Os/C-catalyst

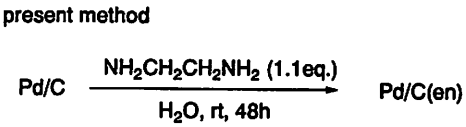
Mutsumi Sato,[1]* Keiji Oono,[1] Yasunari Monguchi,[2] Tomohiro Maegawa Hironao Sajiki[2]
[1] Wako Pure Chemical Industries, Ltd. [2] Gifu Pharmaceutical University



2P-24

Preparation method of Pd/C(en) catalyst in water

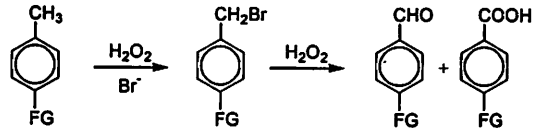
Keiji Oono,[1]* Mutsumi Sato,[1] Yasunari Monguchi,[2] Tomohiro Maegawa,[2] Hironao Sajiki[2]
[1] Wako Pure Chemical Industries, Ltd. [2] Gifu Pharmaceutical University



2P-25

Solvent Effect on Oxidation of Alkylbenzene Using Hydrogen Peroxide

Takeo Nakai,* Toshiyuki Iwai, Masatoshi Mihara, Takatoshi Ito, Takumi Mizuno
Osaka Municipal Technical Research Institute

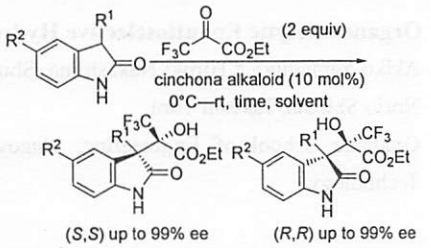


2P-26

Cinchona Alkaloid-catalyzed Asymmetric Aldol-type Reactions Using Trifluoropyruvates

Shinichi Ogawa*, Hiroyuki Fujimoto, Norihito Iida, Shuichi Nakamura, Norio Shibata, Takeshi Toru

Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology

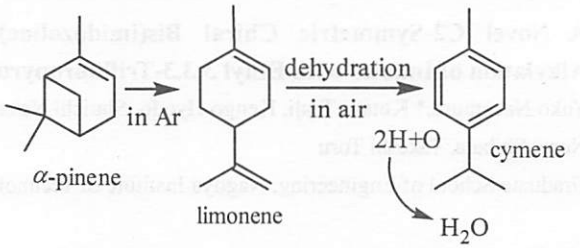


2P-27

Ring-Opening Reaction of α- and β-pinene in Hot, Compressed Water without Any Additive

Tomomi Kawahara,* Toshiyuki Sato, Akiko Kawai-Nakamura, Kiwamu Sue, Hiizu Iwamura, Toshihiko Hiaki

College of Industrial Technology, Nihon University

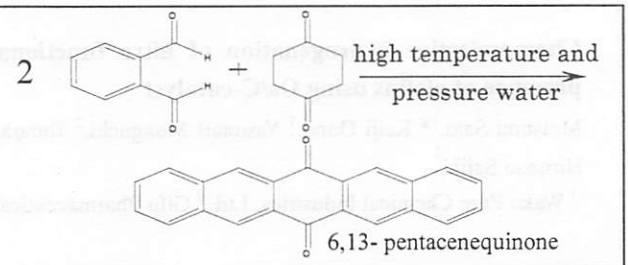


2P-28

Synthesis of Polyacenequinones in Hot, Compressed Water in the Absence of Added Catalysts

Takenori Sawada*, Toshiyuki Sato, Akiko Kawai-Nakamura, Kiwamu Sue, Hiizu Iwamura, Toshihiko Hiaki

College of Industrial Technology, Nihon University



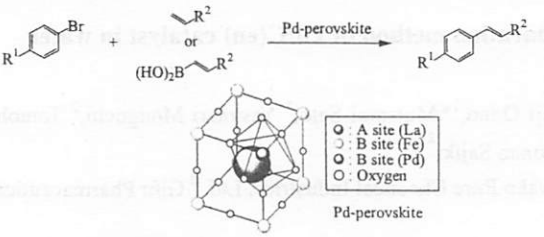
2P-29

Pd-perovskite applid to catalytic organic reaction

Mitsuhiro Yamada,[a,*] Hiroyukli Morikawa,[a] Junzo Nokami, [a] Yoshiki Hayakawa,[b] Kimiyoshi Kaneko,[b] Shun-ichi Murahashi[a]

[a]Fuculty of Engneering, Okayama University of Science

[b]Hokko Chemical Industry Co., Ltd.

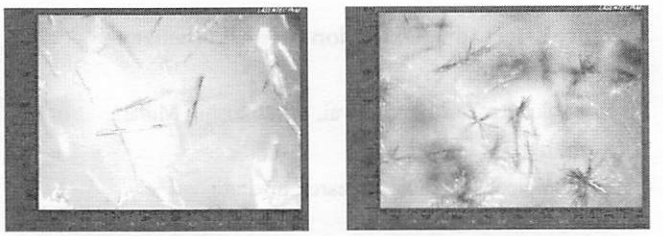


2P-30

Optimization of Crystallization Experiments Using In-Process Particle Size Characterization: Lasenetec and PVM

Eric Hukkanen,* Benjamin Smith

Mettler-Toledo Autochem, Inc.

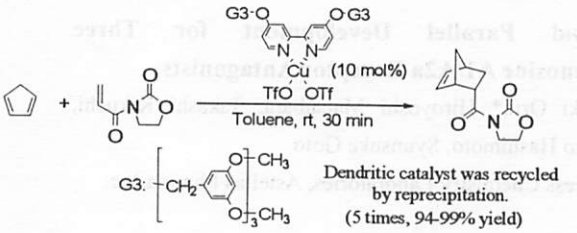


2P-31

Efficient Catalytic Process Using Dendritic Catalyst

Ken-ichi Fujita,* Takahito Muraki, Masato Kujime

National Institute of Advanced Industrial Science and Technology (AIST)

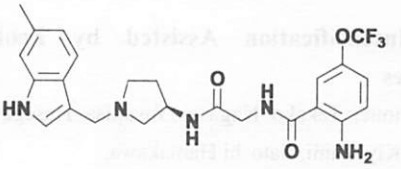


2P-32

Process Development of MCP-1R antagonist TEI-E00526

Hiroaki Makino,* Asahi Kawana, Yoshinori Satou, Takumi Takeyasu

Pharmaceutical Products Research Laboratories, Teijin Pharma Limited



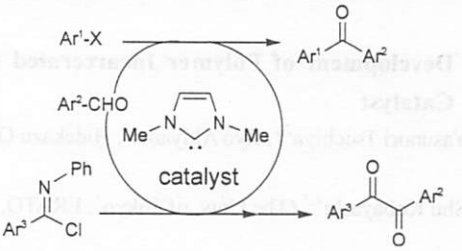
TEI-E00526

2P-33

New Syntheses of diaryl ketones and Diaryl 1,2-Diketones: Nucleophilic Aroylation with Arylaldehydes by *N*-Heterocyclic Carbene Catalysis

Yumiko Suzuki,* Shinya Ota, Yoshinori Fukuta, Abu Bakar Md., Takashi Tanoi, Masayuki Sato

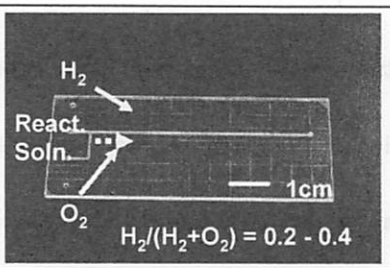
School of Pharmaceutical Sciences, University of Shizuoka



2P-34

Development of micro chemical process by intensive controls of exlplosive atmosphere

*Tomoya Inoue, Yoshikuni Kikutani, Satoshi Hamakawa, Kazuma Mawatari, Fujio Mizukami, and Takehiko Kitamori

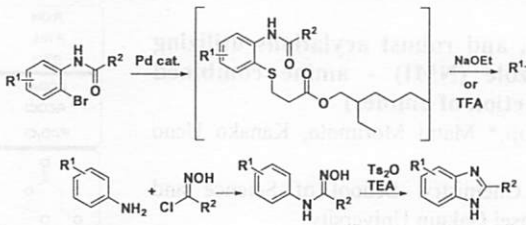


2P-35

Synthesis of Benzazoles

Yuhei Yamamoto,* Takahiro Itoh, Toshiaki Mase

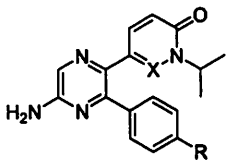
Process Research Preclinical Development, Banyu Pharmaceutical Co., Ltd.



2P-36

Rapid Parallel Development for Three Adenosine A1/A2a Receptor Antagonists

Ryoki Orii,* Hiroyoshi Matsubara, Takashi Kikuchi, Norio Hashimoto, Syunsuke Goto
Process Chemistry Laboratories, Astellas Pharma Inc.

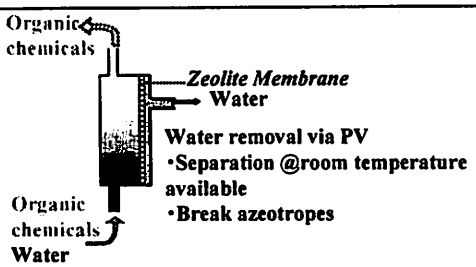


FR277446 X=N , R=H
FR294063 X=H , R=H
FR295854 X=H , R=F

2P-37

Process Intensification Assisted by Zeolite Membranes

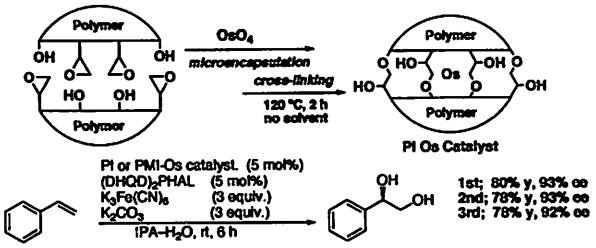
*Tomoya Inoue, Takako Nagase, Yasuhisa Hasegawa, Yoshimichi Kiyozumi, Satoshi Hamakawa, Toshikazu Nishide, and Fujio Mizukami



2P-38

Development of Polymer Incarcerated Osmium Catalyst

Yasunori Tsuchiya[2]*, Ryo Akiyama[2], Hidekazu Oyamada[2], Shū Kobayashi[1,2] (The Univ. of Tokyo[1]; ERATO, JST[2])



2P-39

Basic Study on Separation by Mild Adsorption in Supercritical CO_2

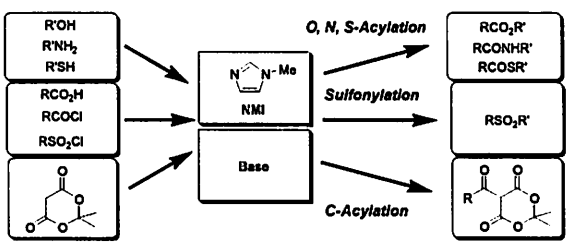
Kazuyukli Chihara* , Mai Hikita, Taichi wada and Ryota Suzuki
Department of Industrial Chemistry, Meiji university,

Adsorption of aromatic organics on activated carbon, MSC and siliceous Y-type zeolite in supercritical CO_2 fluid were measured, using a super critical fluid chromatograph. Moment analyses of pulse response of aromatic organics were performed to get the apparent adsorption equilibrium constant, K* from the retention time of response peaks and the mass transfer steps with diffusivity in micro pore from second central moment of response peaks.

2P-40

Mild, powerful, and robust acylations utilizing *N*-methylimidazole (NMI) - amine combined catalyst (joint action of amines)

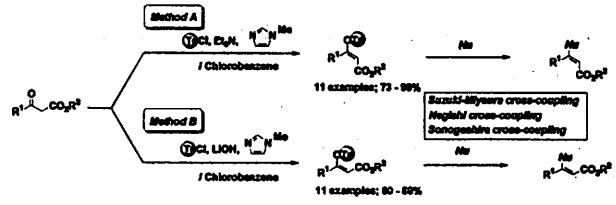
Hidefumi Nakatsuji,* Mami Morimoto, Kanako Ueno and Yoo Tanabe
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University



2P-41

Highly stereocomplementary method for the preparation of tri-substituted olefins and its application to 2-arylcarbapenem synthesis

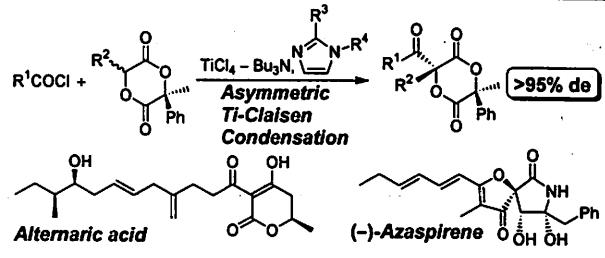
Kanako Ueno,* Hidefumi Nakatsuji, Yoo Tanabe
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University



2P-42

Development of asymmetric Ti-Claisen condensation directed for process chemistry: application to asymmetric total syntheses of two natural products

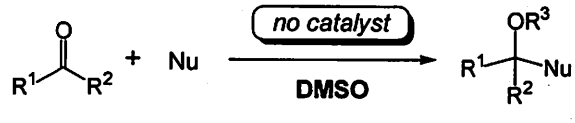
Ryohei Nagase,* Mikiko Sugi, Yumiko Oguni, Tomonori Misaki, Yoo Tanabe
School of Science and Technology, Kwansei Gakuin Univ.



2P-43

Catalyst-free Efficient Reactions in DMSO

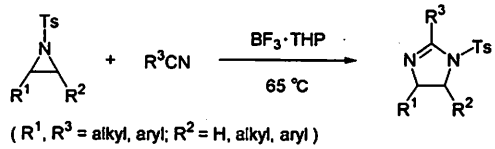
Tomoko Kakinuma,* Ryoichi Chiba, Katsuyuki Iwanami, Masaru Aoyagi, Takeshi Oriyama
Department of Chemistry, Faculty of Science, Ibaraki Univ.



Nu : $TMSCF_3$, BzCN, $NCCO_2R$, CH_3NO_2...etc

2P-44

BF_3·THP-promoted [3+2]Cycloaddition of *N*-Tosylaziridines with Nitriles



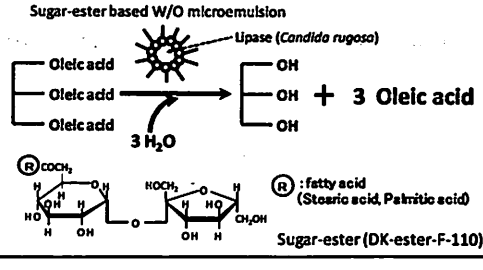
(R^1, R^3 = alkyl, aryl; R^2 = H, alkyl, aryl)

Hitomi Urai,[1]* Ryoichi Chiba,[1] Hiroshi Yasuda,[2] Yoshihiko Maeda,[2] Takeshi Oriyama[1]
Department of Chemistry, Faculty of Science, Ibaraki Univ.,[1] Corporate R&D Center, Showa Denko K. K.[2]

2P-45

Attractive role of sugar ester W/O microemulsion phase on lipid hydrolysis by lipase to provide highest reactivity

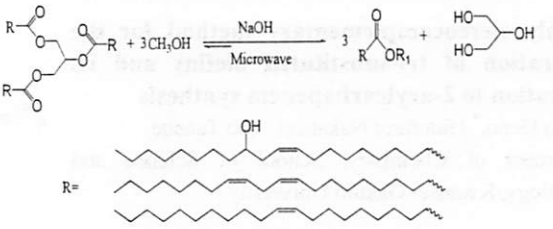
*Aki Uehara, Masanao Imai, Isao Suzuki
Course in Bioresource Utilization Sciences,
Graduate School of Bioresource Sciences, Nihon University



2P-46

Production of Biodiesel from Algal Oil Using Microwave-based Transesterification Process

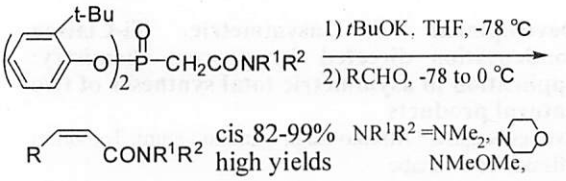
Ching-An Peng,* Guen-Yen Chen, Wen-Yi Tsai
Department of Chemical Engineering, National Taiwan University



2P-47

Highly cis-selective synthesis of α,β-unsaturated amides by Horner-Wadsworth-Emmons reaction

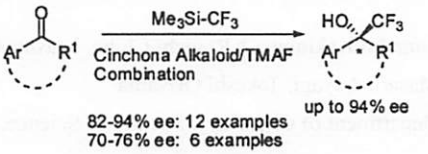
Kaori Ando,* Yuko Tarumi
Dept. of Chemistry, Faculty of Eng., Gifu University



2P-48

Cinchona Alkaloids/TMAF Combination-Catalyzed Nucleophilic Enantioselective Trifluoromethylation of Aryl Ketones

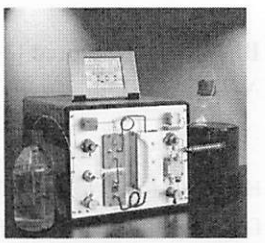
Hiroyuki Kawai,* Satoshi Mizuta, Surendar Akiti, Hiroyuki Fujimoto, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Graduate School of Engineering, Nagoya Institute of Technology



2P-49

Scale-up of hydrogenation reactions in continuous processes

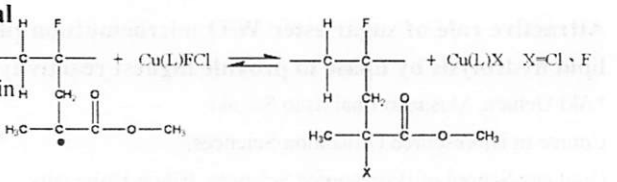
*Laszlo Urge, Zsolt Otvos, Attila Wootsch, Eszter Varga, Ferenc Darvas
ThalesNano Inc.



2P-50

Synthesis of PVDF-g-PMMA by atom transfer radical polymerization

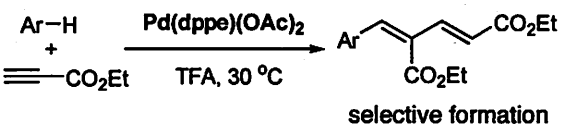
Dar-Jong Lin, Liao-Ping Cheng, Chun-Liang Lin, Chang-Li Lin
Department of Chemical and Materials Engineering, Tamkang University, Tamsui, Taipei 25137, Taiwan



2P-51

Effect of Ligands on Pd-Catalyzed Hydroarylation of Ethyl Propiolate

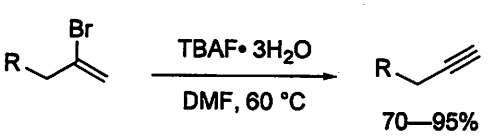
Tsugio Kitamura,* Juzo Oyamada
Department of Chemistry and Applied Chemistry, Saga University



2P-52

Tetrabutylammonium Fluoride-Induced Dehydrobromination of Vinyl Bromides to Terminal Acetylenes

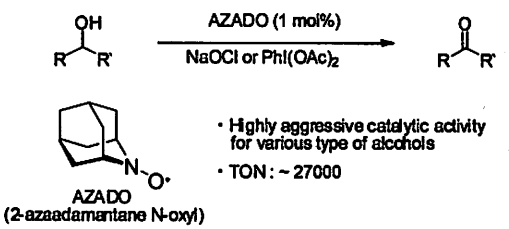
Masaru Okutani and Yuji Mori*
Faculty of Pharmacy, Meijo University



2P-53

AZADOs : Highly Active Oxidation Catalysts for Alcohols -Discovery and Characterization-

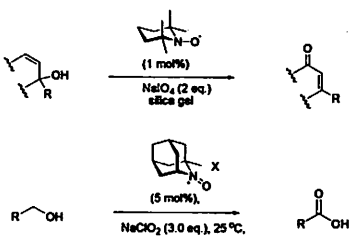
*Masaki Tomizawa[1], Masatoshi Shibuya[1], Yusuke Sasano[1], Iwao Suzuki[1], Fabio Pichierri[2], Yoshiharu Iwabuchi[1]
[1]Graduate School of Pharmaceutical Sciences and
[2]Graduate School of Engineering, Tohoku University



2P-54

New Application of Oxoammonium Salt-based Catalysts

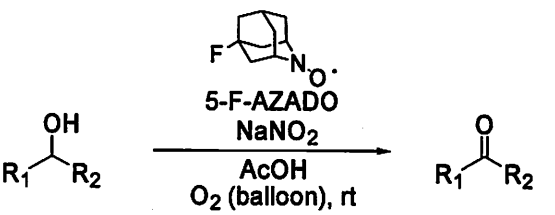
* Masatoshi Shibuya, Takahisa Sato, Masaki Tomizawa, Yoshiharu Iwabuchi
Graduate School of Tohoku University



2P-55

Aerobic Oxidation of Alcohols using AZADOs

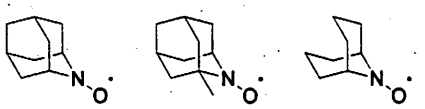
*Yuji Osada, Masatoshi Shibuya, Masaki Tomizawa, Yusuke Sasano, Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University.



2P-56

Practical Synthesis of Highly Efficient Organocatalysts for Oxidation of Alcohols: AZADO, 1-Me-AZADO and ABNO

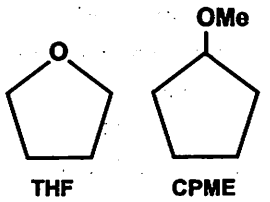
Yusuke Sasano*, Masatoshi Shibuya, Masaki Tomizawa, Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University



2P-57

Oxidative degradation analysis of organic ethers

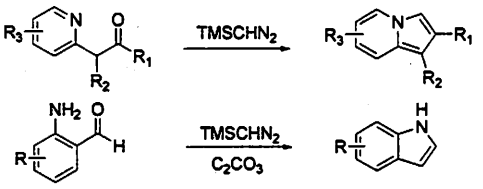
Arata Kimura[1*], Hayato Kitoh[1], Atsumi Miyake[1], Kiyoshi Watanabe[2]
1 Yokohama National University
2 Zeon Corporation



2P-58

A mild preparation of substituted indolizines and indole from simple aromatic precursors using (trimethylsilyl)diazomethane

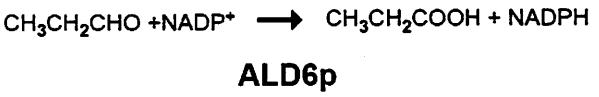
Liusheng Zhu, Marc Vimolratana, Sean P. Brown,* Julio C. Medina
Amgen Inc. 1120 Veterans Blvd., South San Francisco, CA, 94080



2P-59

Non-degraded expression and one-step purification of yeast ALD6 enzyme in *E. coli*

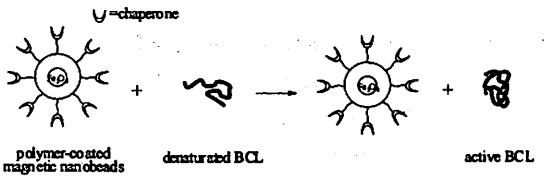
Wei-Jyh Shiah, Yu-Chun Chen, *Ming-Kai Chern
Graduate Institute of Life Sciences, Tamkang University, Taiwan



2P-60

Reusable chaperone-conjugated magnetic nanobeads in production of a functionally active biocatalyst

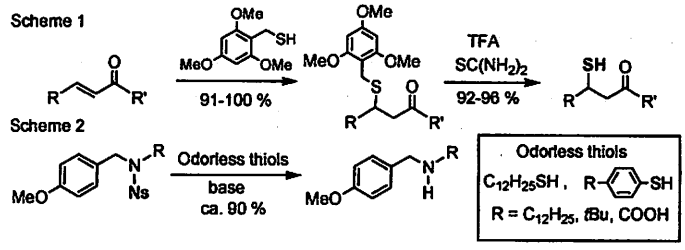
*Suhyun Jung and Seongsoon Park
Department of Chemistry, Sungshin Women's University



2P-61

Development and application of odorless thiol reagents

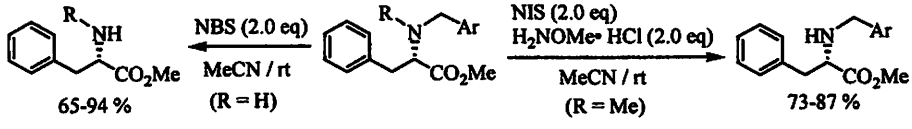
Manabu Matoba,* Tetsuya Kajimoto, Manabu Node
Department of Pharmaceutical Manufacturing Chemistry, 21st COE, Kyoto Pharmaceutical Univ.



2P-62

Deveropment of selective C-N bond crevage utilizing *N*-halosuccinimide

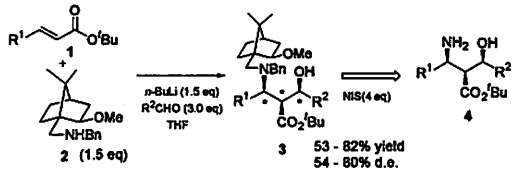
Tsunefumi Watanabe,* Noboru Hayama, Takahiro Katoh, Minoru Ozeki, Tetsuya Kajimoto, Manabu Node
Department of Pharmaceutical Manufucturing Chemistry, Kyoto Pharmaceutical University



2P-63

Construction of Three Contiguous Stereogenic Centers *via* Asymmetric Michael Addition Using Chiral Amino Ether as a Chiral Reagent

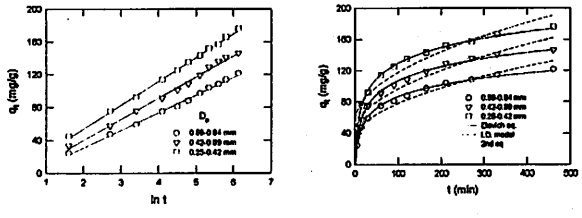
Shunsuke Ochi,* Minoru Ozeki, Takahiro Katoh,
Tetsuya Kajimoto and Manabu Node
Department of Pharmaceutical Manufacturing Chemistry, Kyoto Pharmaceutical Univ.



2P-64

Adsorption Kinetic of Three Particle Size Chitosan

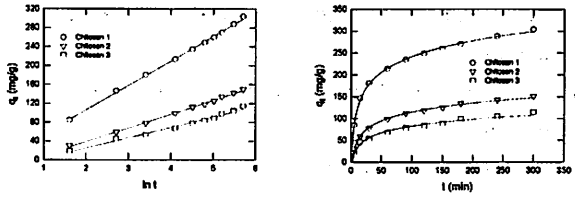
Feng-Chin Wu,*[1] Pin-Hsueh Wu[2], Ru-Ling Tseng[2]
Department of Chemical Engineering, National United University



2P-65

Adsorption Kinetic of Chitosan from Three Source

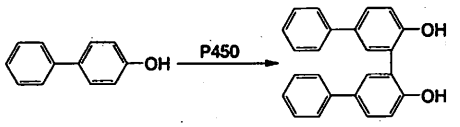
Ru-Ling Tseng,*[1] Pin-Hsueh Wu[1], Feng-Chin Wu[2]
Department of Safety, Health and Environmental Engineering, National United University



2P-66

Bioconversion of aromatic compounds using *Escherichia coli* expressing cytochrome P450

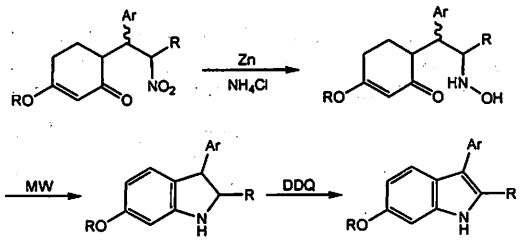
Toshihiko Otomatsu,[a]* Liming Bai[a], Naoya Fujita[a], Kazutoshi Shindo[b], Norihiko Misawa[c]
[a]KNC Bio Research Center, Technology Development Dept., KNC Laboratories Co., Ltd.; [b]Department of Food and Nutrition, Japan Women's University; [c]Marine Biotechnology Institute (Present address: Central Laboratories for Frontier Technology, Kirin Holdings Co., Ltd.)



2P-67

Synthesis of indole derivatives under microwave conditions

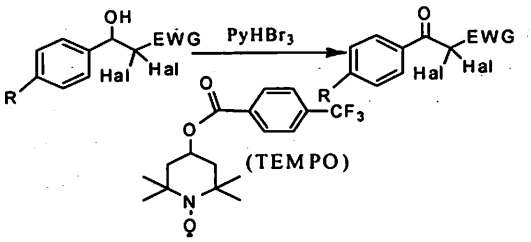
Li-Jian Ma, Zhen-Wu Mei, Tomoyo Kusuyama, and Tsutomu Inokuchi*
Okayama University



2P-68

High-performance method of TEMPO-oxidation of alcohols

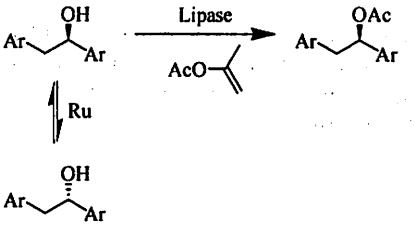
Zhen-Wu Mei[1], Li-Jian Ma[1], Hiroyuki Kawafuchi[2], Tsutomu Inokuchi[1*]
[1]Okayama University, [2]Toyama National College of technology



2P-69

Dynamic Kinetic Resolution of 1,2-Diarylethanols by Lipase-Ruthenium Cocatalysis

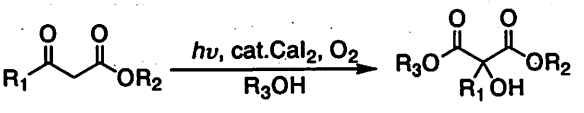
*Sol Kim, Yun Kyung Choi, Yunwoong Kim, Cheolwoo Kim, Jaiwook Park, Mahn-Joo Kim
Department of Chemistry, Pohang University of Science and Technology, Pohang, Korea



2P-70

New One-Pot Synthesis of Malonic Acid Derivatives

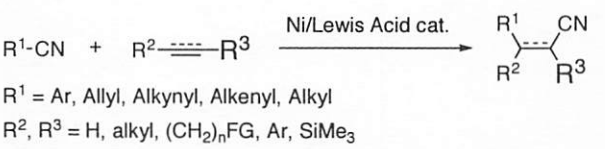
Akichika Itoh,* Norihiro Tada, Hiroki Nakayama, Naohiko Kanai
Gifu Pharmaceutical University.



2P-71

Nickel/Lewis Acid-catalyzed Carbocyanation Reaction of Unsaturated Compounds

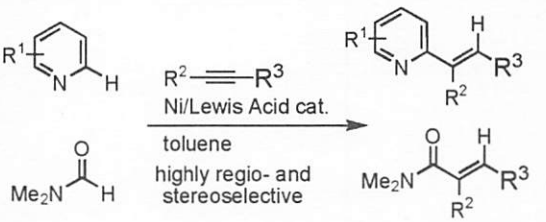
Yoshiaki Nakao,* Akira Yada, Shiro Ebata, Yasuhiro Hirata, Tomoya Yukawa, Tamejiro Hiyama
Kyoto University



2P-72

Nickel/Lewis Acid Catalyzed hydrohetero-arylation and Hydrocarbamoylation of Unsaturated Bonds

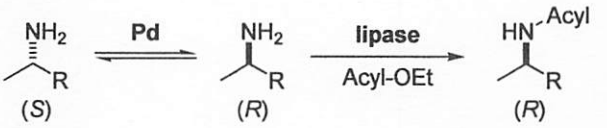
Kyalo Stephen Kanyiva,* Hiroaki Idei, Yoshiaki Nakao, Tamejiro Hiyama
Graduate School of Engineering, Kyoto University



2P-73

Dynamic Kinetic Resolution of Primary Amines by Lipase-Palladium Cocatalysis

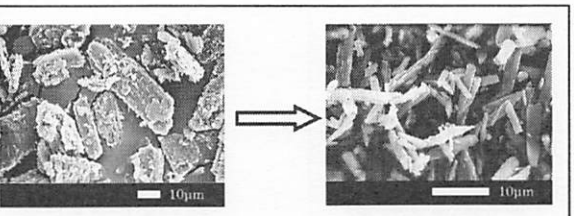
* Kiwon Han, Yoon Kyung Choi, Chelwoo Kim, Jaiwook Park, Mahn-Joo Kim
Pohang University of Science and Technology



2P-74

Micronization of Pharmaceutical Compounds by Supercritical Technology

Yen-Ming Chen[(1)], Yan-Ping Chen*[(1)] and Muoi Tang[(2)]
Dept. of Chemical Engineering, (1) National Taiwan University, (2) Chinese Culture University, Taipei, Taiwan



Original DCA SAS treated DCA

Abstracts

Keynote Lectures

K-1 ~ K-13

July 29 & 30

K-1 (Keynote Lecture)

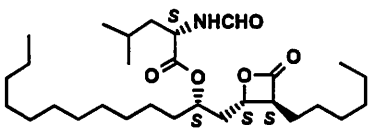
From Milligrams to Tons: The Importance of Synthesis & Process Research in the Development of new Drugs

Martin Karpf

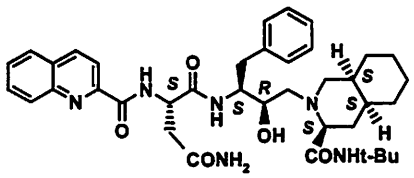
Synthesis & Process Research
Technical Sciences, Pharmaceuticals Division
F. Hoffmann-La Roche Ltd
CH-4070 Basel Switzerland
martin.karpf@roche.com

An essential part of the multidisciplinary development process of new, innovative pharmaceuticals is the search for and the development and production of novel biologically active compounds. In this context organic synthesis not only plays a key role in the search for new clinical candidates but also represents an indispensable tool for the subsequent exploration, evaluation and development of short, efficient, safe, reproducible, scalable, economical and ecological production routes with technical potential. In addition to the problems of structural and stereochemical complexity, the new synthesis has to take into account the basic requirements and limitations of a potential industrial process.

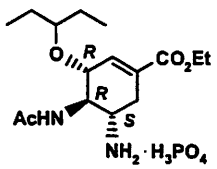
In the current presentation the role and importance of synthesis & process research including catalysis in the development process of new drugs from the discovery chemistry synthesis up to technical route will be discussed and exemplified on various examples shown below in view of large scale production requirements. The lecture will concentrate on the synthetic strategies and tactics applied to drug candidates in order to create on time technically feasible chemical syntheses suitable for further technical development and optimization aiming at future large scale industrial production.



Xenical™ *(Obesitas)*
Tetrahydrolipstatin



Invirase™ *(HIV)*
Saquinavir



Tamiflu™ *(Influenza)*
Oseltamivir Phosphate

For leading references see:

Xenical R. Birk, M. Karpf, K. Püntener, M. Scalone, M. Schwindt, U. Zutter, *Chimia* **2006**, *60*, 561; *Org. Proc. Res. & Dev.* **2007**, in press.

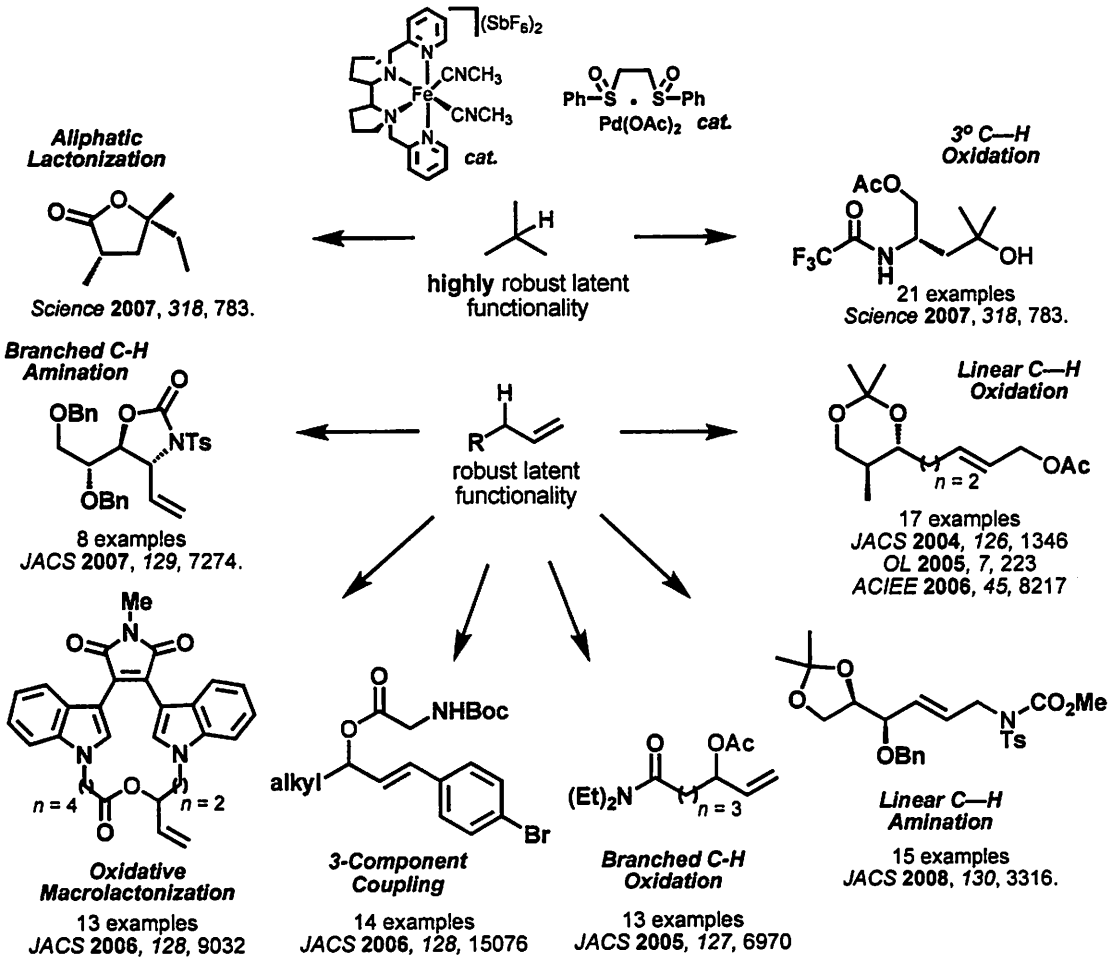
Invirase W. Goehring, S. Gokhale, H. Hilpert, F. Roessler, M. Schlageter, P. Vogt, *Chimia* **1996**, *50*, 532.

Tamiflu S. Abrecht, P. Harrington, H. Iding, M. Karpf, R. Trussardi, B. Wirz, U. Zutter, *Chimia* **2004**, *58*, 621; *Chimia* **2007**, *61*, 93.

Streamlining Synthesis via C—H Oxidation

M. Christina White*
Department of Chemistry, Roger Adams Laboratory,
University of Illinois, Urbana, IL 61801, USA

Among the frontier challenges in chemistry in the 21st century are (1) increasing control of chemical reactivity and (2) synthesizing complex molecules with higher levels of efficiency. Although it has been well demonstrated that given ample time and resources, highly complex molecules can be synthesized in the laboratory, too often current methods do not allow chemists to match the efficiency achieved in Nature. This is particularly relevant for molecules with non-polypropionate-like oxidation patterns (e.g. Taxol). Traditional organic methods for installing oxidized functionality rely heavily on acid-base reactions that require extensive functional group manipulations (FGMs) including wasteful protection-deprotection sequences. Due to their ubiquity in complex molecules and inertness to most organic transformation, C—H bonds have typically been ignored in the context of methods development for total synthesis. Highly selective



oxidation methods, similar to those found in Nature, for the direct installation of oxygen, nitrogen and carbon functionalities into allylic and aliphatic C—H bonds of complex molecules and their intermediates will be discussed. Unlike Nature which uses elaborate enzyme active sites, we rely on the subtle electronic and steric interactions between C—

H bonds and small molecule transition metal complexes to achieve high selectivities. Our current understanding of these interactions gained through mechanistic studies will be discussed. Novel strategies for streamlining the process of complex molecule synthesis enabled by these methods will be presented. Collectively, we aim to change the way that complex molecules are constructed by redefining the reactivity principles of C—H bonds in complex molecule settings.

For further reading please see:

Aliphatic C—H Oxidation:

- Chen, M.S.; White, M.C. "A Predictably Selective Aliphatic C—H Oxidation Reaction for Complex Molecule Synthesis." *Science*, **2007**, *318*, 783-787.

Allylic C—H Oxidation:

- Delcamp, J.H.; White, M.C. "Sequential Hydrocarbon Functionalization: Allylic C—H Oxidation/Vinylic C—H Arylation." *J. Am. Chem. Soc.* **2006**, *128*, 15076-15077.
- Fraunhoffer, K.J.; Prabagaran, N.; Sirios, L.E.; White, M.C. "Macrolactonization via Hydrocarbon Oxidation." *J. Am. Chem. Soc.* **2006**, *128*, 9032-9033.
- Chen, M.S.; Prabagaran, N.; Labenz, N.; White, M.C. "Serial Ligand Catalysis: A Highly Selective Allylic C-H Oxidation." *J. Am. Chem. Soc.* **2005**, *127*, 6970-6971.
- Chen, M.S.; White, M.C. "A Sulfoxide-Promoted, Catalytic Method for the Regioselective Synthesis of Allylic Acetates from Monosubstituted Olefins via C-H Oxidation." *J. Am. Chem. Soc.* **2004**, *126*, 1346-1347.

Allylic C—H Amination:

- Reed, S.A.; White, M.C. "Catalytic Intermolecular Linear Allylic C—H Amination via Heterobimetallic Catalysis." *J. Am. Chem. Soc.*, **2008**, *130*, 3316-3318.

- Fraunhoffer, K.J.; White, M.C. "syn-1,2-Amino Alcohols via Diastereoselective Allylic C—H Amination." *J. Am. Chem. Soc.* **2007**, *129*, 7274-7276.

Streamlining Synthesis Strategies:

- Covell, D.J.; Vermeulen, N.A.; Labenz, N.A.; White, M.C. "Polyol Synthesis via Hydrocarbon Oxidation: De Novo Synthesis of L-Galactose." *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 8217-8220.

- Fraunhoffer, K. J.; Bachovchin, D.A.; White, M.C. "Hydrocarbon Oxidation vs. C-C Bond Forming Approaches for Efficient Syntheses of Oxygenated Molecules." *Org. Lett.* **2005**, *7*, 223-226.

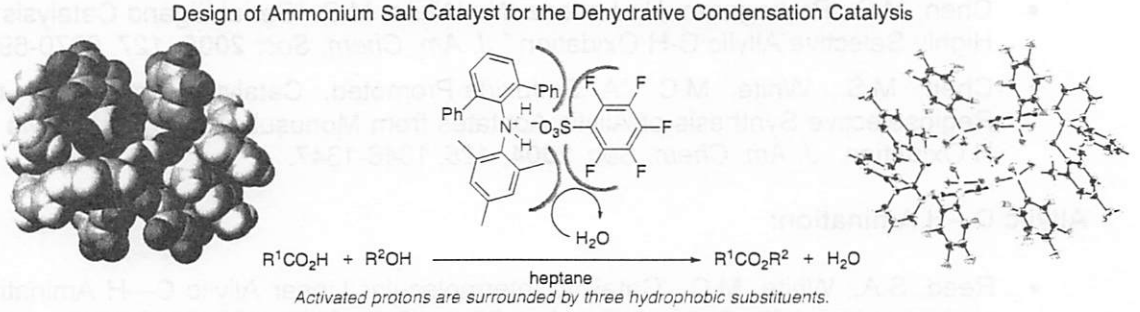
Design of Dynamic Salt Catalysts Based on Acid–Base Combination Chemistry

Kazuaki Ishihara*
Graduate School of Engineering, Nagoya University
Furo-cho, Chikusa, Nagoya 464-8603, Japan
ishihara@cc.nagoya-u.ac.jp

Acid–base combined catalysts bearing versatile functions can be created by the self-assembly between acidic and basic molecules which are designed.[1] In particular, dynamic salt complexes are very attractive as artificial enzymes because of their structural flexibility like natural enzymes. Recently, we developed several highly functional dynamic salt catalysts based on the acid–base combination chemistry.[1]

Bulky diarylammonium pentafluorobenzenesulfonates catalyzed the dehydrative condensation of an equimolar mixture of carboxylic acids and alcohols under heating conditions in heptane even without the removal of water produced.[2,3] These dynamic salt complexes behave as reverse micelles.[2c]

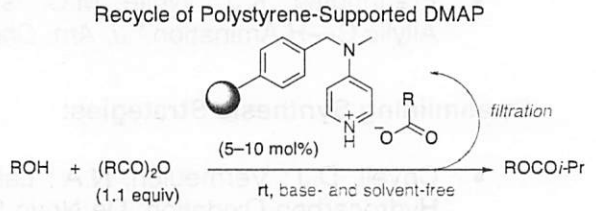
Design of Ammonium Salt Catalyst for the Dehydrative Condensation Catalysis



Activated protons are surrounded by three hydrophobic substituents.

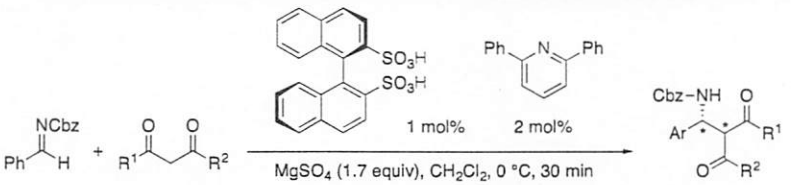
DMAP is an excellent nucleophilic catalyst for the acylation of alcohols with carboxylic anhydrides. In general, the acylation is carried out in the presence of stoichiometric amounts of tertiary amine such as *i*-Pr_2EtN in suitable solvents because carboxylic acids were produced together esters. We found that the acylation proceeded well even in the absence of any auxiliary bases under solvent-free conditions.[4]

Recycle of Polystyrene-Supported DMAP



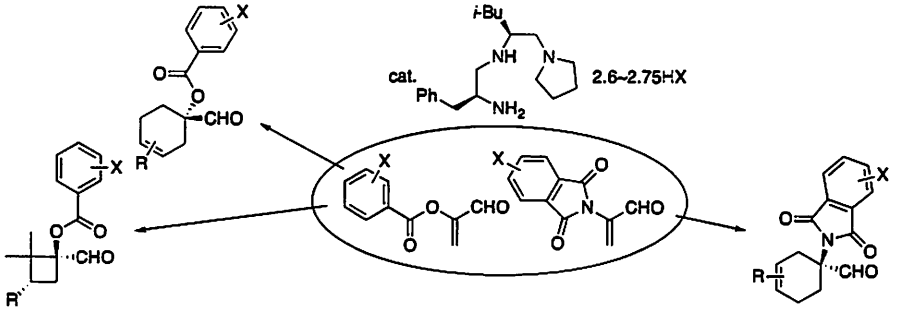
Chiral ammonium salt of (*R*)-1,1'-binaphthyl-2,2'-disulfonic acid and 2,6-diphenylpyridine catalyzed the enantioselective Mannich-type reaction of *N*-Cbz- and *N*-Boc-aldimines with 1,3-diketones and 3-oxocarboximides.[5]

Design of Chiral Ammonium Salt Catalysts for the Mannich-type Reaction



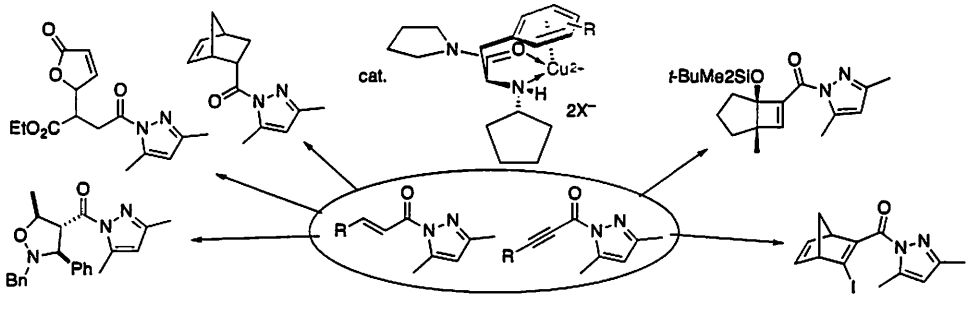
Chiral ammonium salt of H_2N-L-Phe-L-Leu-$N(CH_2CH_2)_2$-reduced triamine and HX catalyzed the enantioselective [2+4] and [2+2] cycloaddition reactions of α-(acyloxy)- or α-(phtalimido)acroleins thorough the corresponding aldiminium intermediates.[6] Thus, synthetically valuable optically active α,α-dialkyl-substituted α-hydroxyaldehydes and α-amino aldehyde derivatives were synthesized.

Design of Chiral Ammonium Salt Catalysts for [2+4] and [2+2] Cycloaddition Reactions



Chiral Cu(II) cation–π complex of L-phenylalanine amide was a highly effective catalyst for the enantioselective [2+4] and [2+2] cycloaddition reactions of not only α-unsubstituted acrylamides but also propiolamides.[7] The [2+4] cycloaddition reaction of cyclic dienes with acetylenic dienophiles may provide a concise method for the preparation of chiral bicyclic 2,5-diene ligand candidates for the asymmetric catalysis of Rh and Ir. To the best our knowledge, this is the first example of the enantioselective [2+2] cycloaddition reaction of alkynes.

Design of Small-molecule Chiral Catalysts Based on Cation–π Interaction



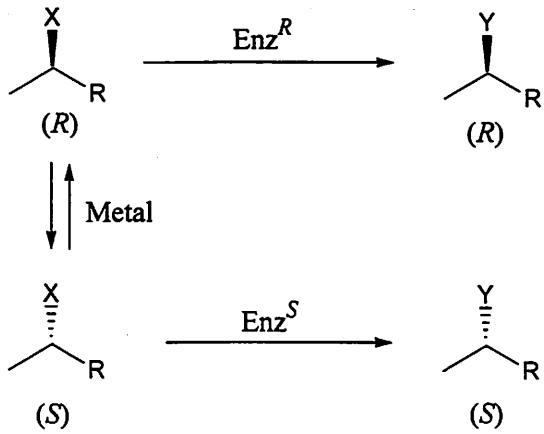
References

1. For an account, see: Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686.
2. (a) Ishihara, K.; Nakagawa, S.; Sakakura *J. Am. Chem. Soc.* **2005**, *127*, 4168. (b) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Tetrahedron* **2006**, *62*, 422. (c) Sakakura, A.; Watanabe, H.; Nakagawa, S.; Ishihara, K. *Chem. Asian J.* **2007**, *2*, 477. (d) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Nature Protocols* **2007**, *2*, 1746.
3. For Ph_2NH_2OTf, see: (a) Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahderon Lett.* **2000**, *41*, 5249. For $C_6F_5NH_3OTf$, see: (b) Funatomi, T.; Wakasugi, K.; Misaki, T.; Tanabe, Y. *Green Chem.* **2006**, *8*, 1022.
4. Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc.* **2007**, *129*, 14775.
5. Hatano, M.; Maki, T.; Arinobe, M.; Moriyama, K.; Ishihara, K. to be submitted.
6. (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504; *127*, 13079 (additions and corrections). (b) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930. (c) Ishihara, K.; Nakano, K. to be submitted.
7. (a) Ishihara, K.; Fushimi, M. *Org. Lett.* **2006**, *8*, 1921. (b) Ishihara, K.; Fushimi, M.; Akakura, M. *Acc. Chem. Res.* **2007**, *40*, 1049. (c) Ishihara, K.; Fushimi, M. *J. Am. Chem. Soc.* **2008**, *130*, ASAP.

Enzymo-Metallic Dynamic Kinetic Resolution as a New Tool for Chiral Synthesis

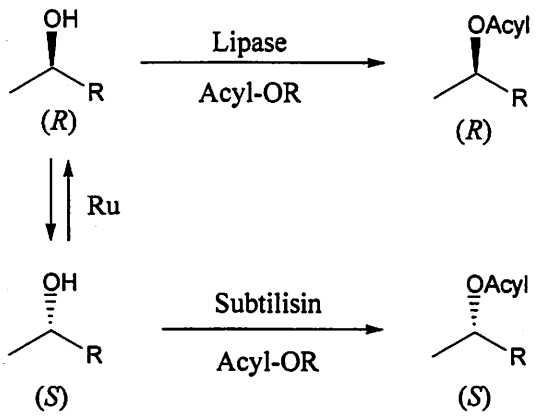
*Mahn-Joo Kim and Jaiwook Park
Department of Chemistry, Pohang University of Science and Technology,
San-31 Hyojadong, Pohang 790-784, Korea
mjkim@postech.ac.kr

We are developing methods using enzyme and metal in combination for the dynamic kinetic resolution (DKR) of racemic molecules.[1] In this approach, enzymes are used as the enantioselective resolution catalysts and metal or metal complexes as the racemization catalysts (Scheme 1).



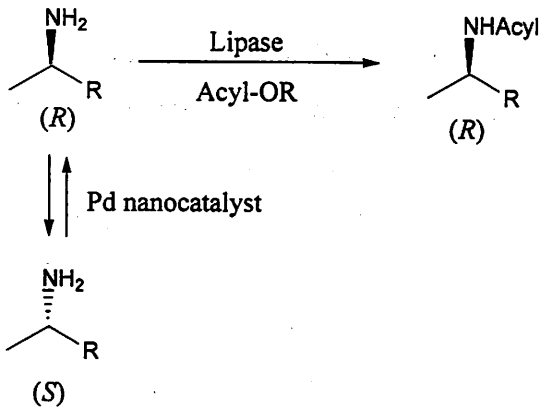
Scheme 1. Dynamic kinetic resolution by enzyme-metal combination

Intensive studies have been done to search for highly efficient racemization catalysts. It was found that Ru-based complexes were highly effective as the racemization catalysts for the DKR of secondary alcohols. They were combined with (*R*)-selective lipase or (*S*)-selective subtilisin for the conversion of a wide range of secondary alcohols to the corresponding (*R*)- or (*S*)-esters via DKR. In many cases, high enantiomeric excesses (98–99% ee) were obtained with yields approaching 100% (Scheme 2).[2]



Scheme 2. DKR of secondary alcohols by enzyme-metal combinations

An immobilized Pd nanocatalyst, Pd/AlO(OH), was prepared as the racemization catalyst for the DKR of primary amines. It was highly active and recyclable. The efficient DKRs of both benzylic and aliphatic amines were accomplished by the combination of a lipase with the Pd nanocatalyst (Scheme 3). In most cases, high yields and excellent optical purities were obtained.[3]



Scheme 3. DKR of primary amines by enzyme-metal combinations

References

1. Reviews: (a) M.-J. Kim, Y. Ahn, J. Park, *Curr. Opin. Biotechnol.* **2002**, *13*, 578. (b) M.-J. Kim, Y. Ahn, J. Park, *Bull. Kor. Chem. Soc.* **2005**, *26*, 1. (c) Y. Ahn, S.-B. K o, M.-J. Kim, and J. Park, *Coord. Chem. Rev.* **2008**, *252*, 647. (d) M.-J. Kim, J. Pa rk, and Y. Ahn, *Biocatalysis in the Pharmaceutical and Biotechnology Industries*, Pat el, R. N., Ed., CRC Press: Boca Raton, Fl, **2007**; Chapter 8, pp 249-272. (e) M.-J. Kim, J. Park, Y. Ahn, and O. R. Krishna, *Future Directions in Biocatalysis*, Matsuda, T. N., Ed., Elsevier: Amsterdam, The Netherlands, **2007**; Chapter 4, pp 59-80.
2. (a) J. H. Choi, Y. H. Kim, S. H. Nam, S. T. Shin, M.-J. Kim, J. Park, *Angew. Che m. Int. Ed.* **2002**, *41*, 2373. (b) M.-J. Kim, Y. I. Chung, Y. K. Choi, H. K. Lee, D. Kim, J. Park, *J. Am. Chem. Soc.* **2003**, *125*, 11494. (c) J. H. Choi, Y.K. Choi, Y.H. Kim, E.S. Park, E.J. Kim, M.-J. Kim, J. Park, *J. Org. Chem.* **2004**, *69*, 1972. (d) N. Kim, S.-B. Ko, M. S. Kwon, M.-J. Kim, J. Park, *J. Org. Chem.* **2007**, *72*, 6860. (e) S.-B. Ko, B. Baburaj, M.-J. Kim, J. Park, *Org. Lett.* **2008**, *10*, 1295. (f) M.-J. Kim, Y. K. Choi, S. Kim, D. Kim, K. Han, S.-B. Ko, J. Park, *Org. Lett.* **2008**, *10*, 1295.
3. (a) M.-J. Kim, W.-H. Kim, K. Han, Y.K. Choi, J. Park, *Org. Lett.* **2007**, *9*, 1157. (b) K. W. Han, J. Park, M.-J. Kim, *J. Org. Chem.* in press.

K-5 (Keynote Lecture)

Matching Chemistry with Chemical Engineering for Optimum Design and Performance of Pharmaceutical Processing

Prof. A.B. Pandit
Chemical Engineering Department
Institute of Chemical Technology,
Matunga, Mumbai 400 019
India

Abstract:

The success of pharmaceutical industry is controlled by two important factors viz. Discovery of new molecule/drug having medicinal properties and Translating the laboratory scale manufacturing practices to industrial production scale.

Most of the time, the above two activities are performed in series i.e. first the molecule is discovered; its synthesis strategies are standardized and then handed over to the manufacturing team. The manufacturing team faces many difficulties in the scaling up of the laboratory scale processes as during the synthesis activities, the equipments and strategies used for conducting the reactions, separation and purification processes are not amenable to the scale up as these factors are generally ignored by the chemists involved in the synthesis work.

For successful implementation of the transformation from lab scale to industrial scale technology, a chemist and a chemical engineer need to work together. The chemist will understand the alternative routes of synthesis, operating conditions for the same, while the chemical engineer will keep on putting restrictions and limitations on these based on the available knowledge base of the various unit operations involved in the same. Many a times the time span of these unit operations such as filtration, drying, mixing, heat transfer are significantly different on laboratory and industrial scale, which affects the yield, conversion, purity etc. sometimes rendering the industrial processes economically unviable.

In the present talk, the role of chemical engineering unit operations in addressing the above issues will be discussed with some specific examples. Reaction and reactor engineering design concepts, selection criteria for equipments such as those required for crystallization, filtration and drying will be discussed. Some comments on the limitations of the available equipments to translate the laboratory scale processes to industrial processes will also be made. An optimized strategy for the drug development and manufacturing will be proposed.

K-6 (Keynote Lecture)

Boron Reagents for Process Chemistry: Excellent Reagents for Selective Reduction

Karl Matos*, Elizabeth R. Burkhardt, Brian M. Coleridge

BASF Corporation, 1424 Mars-Evans City Road, Evans City, PA 16033

karl.matos@basf.com

Boranes and borohydride reagents have found utility in synthesis routes to a number of pharmaceutical and other products. Boron reagents have become increasingly important for catalytic reactions and other organic transformations of highly complex functionalized molecules. Some of the highlights include asymmetric reductions, Suzuki-Miyaura cross-coupling and the introduction of functional groups such as alcohols and amines. Because of their unique properties and high selectivities, these reagents have become a valuable part of the organic chemistry toolbox and found their way into a number of commercial applications.

Reductive amination of aldehydes and ketones with boranes is an important direct transformation of carbonyl compounds into amines. Amines are ubiquitous functionalities in current drugs and active pharmaceutical intermediates. In this important carbon-nitrogen bond forming process, aldehydes or ketones are reacted with ammonia, primary or secondary amines in the presence of a reducing agent to produce primary, secondary and tertiary amines, respectively. In the interest of efficient processes, the intermediate imine is not pre-formed. Therefore, the reducing agent used must be stable to conditions for the *in situ* formation of the imine or iminium ion since water is a co-product. In addition, the reduction of the ketone or aldehyde must be slower than imine formation and reduction to avoid alcohol by-products

In order to successfully carry out a direct reductive amination, the choice of the reducing agent is very critical. Three acid stable reducing agents are sodium cyanoborohydride, sodium triacyloxyborohydrides, and amine boranes. Industrial use of sodium cyano-borohydride is unattractive due to toxicity and the large excess needed. Sodium triacetoxyborohydride, STAB, although quite selective for reductive amination, has only one hydride and is insoluble in most common organic solvents. In addition, STAB is often used in excess and cannot be utilized in protic solvents such as methanol which favors imine formation. Catalytic hydrogenation has limited use with compounds containing double bonds, triple bonds or hydrogen sensitive functionalities in the substrate. Other reagents are non-selective in their reducing properties or are decomposed in acidic media precluding an *in situ* direct reductive amination.

Amine boranes are effective reagents to carry out reductive aminations due to their acid stability and functional group compatibility. Amine boranes derived from primary or secondary amines suffer from incorporation of the amine, therefore, are only appropriate for reduction of pre-formed imines. Amine boranes derived from tertiary amine or aromatic amines do not incorporate into the imine intermediate. In general, tertiary amine borane complexes are much less reactive than aromatic amine borane complexes.

Although pyridine borane (PYB) has been demonstrated in successful reductive aminations, even at large scale, it has a shelf-life of only 6 months and decomposes above 54 °C. Commercially available 2-picoline borane (PICB, mp 44-45 °C) has been demonstrated as a viable replacement for pyridine borane in reductive aminations. Since liquid reagents can be easily contained and transferred from drums or cylinders via pipes, we have designed a liquid aromatic amine borane, 5-ethyl-2-methylpyridine borane (PEMB). Thermal test have demonstrated the thermal stability of PEMB is greater than pyridine borane.

Because of the strong interaction of the nitrogen in pyridine compounds with Lewis acidic borane, 5-ethyl-2-methylpyridine borane (PEMB) is relatively stable towards hydrolysis (5% per day in water/THF) and methanolysis (6% per day). PEMB is highly soluble in tetrahydrofuran and toluene, up to at least 70 wt%, but it is essentially insoluble in aliphatic hydrocarbon solvents.

In summary, the advantageous properties of PEMB are the liquid physical state, the thermal stability at ambient temperatures, and the slow reaction with protic solvents. These characteristics of PEMB make it an attractive amine borane for selected reductions. The utility of PEMB in reductive aminations are demonstrated in this article to promote this compound as a direct replacement for PYB.

K-7 (Keynote Lecture)

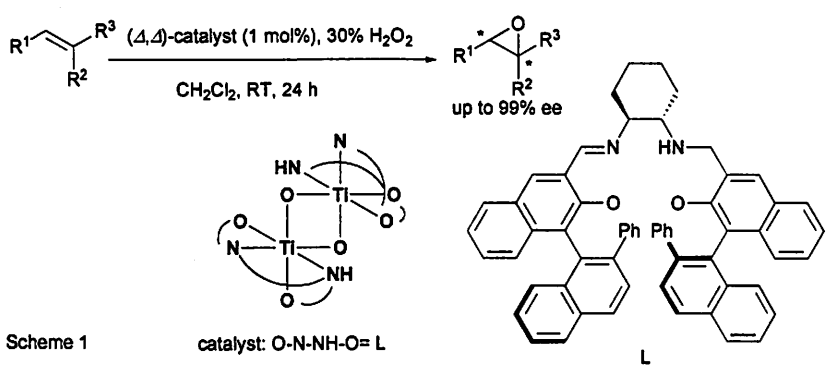
Asymmetric Oxidation with Hydrogen Peroxide, an Effective and Versatile Oxidant

Tsutomu Katsuki
Department of Chemistry, Faculty of Science, Graduate School, Kyushu University
Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan
katsuscc@mbox.nc.kyushu-u.ac.jp

Asymmetric oxidation is a potent tool for introducing functional group(s) to organic compounds and it has been widely used not only in laboratory research but also pharmaceutical and agrochemical industrials. Thus, many excellent catalysts for asymmetric oxidation have been introduced and high stereoselectivity has been achieved in many oxidations. However, enhancement of ecological sustainability as well as selectivities in chemical transformation is strongly required for realizing green chemistry. Ecological sustainability of organic oxidation significantly depends on the oxidant and solvent. Thus, intensive effort has been devoted to development of asymmetric oxidations using a highly atom-efficient and green oxidant that co-produce only innocuous waste.

Active oxygen content of hydrogen peroxide is as high as 47% and it generates only water after the oxygen atom transfer. In particular, aqueous hydrogen peroxide is commercially available, cheap, and easy-to handle. Thus, asymmetric oxidation using hydrogen peroxide as the oxidant is a current topic of interest.

We focused our attention on a divalent nature of hydrogen peroxide that allows a chelate formation with a metal ion. We first examined asymmetric oxidation of sulfides using di-μ-oxo Ti(salen) complex as catalyst in the presence of urea hydrogen peroxide adduct. The oxidation proceeded with high enantioselectivity and good chemical yields; however, this reaction condition could not be applied to asymmetric epoxidation.[1]



Scheme 1

Fortunately, we discovered that di-μ-oxo Ti(salalen) complex, one imino bond-reduced derivative of salen complexes (salalen = salen/salan hybrid), served as an efficient catalyst for asymmetric epoxidation (Scheme 1).[2] Although the structure of the catalyst was complex and its synthesis is not very easy, we found that di-μ-oxo Ti(salan) complex which can be readily synthesized serves as the catalyst as efficiently as the titanium(salalen) complex (Figure 1).[3] Moreover, this procedure can be applied to the synthesis of acid-sensitive epoxide in the presence of phosphate buffer on a molar scale.[4] It is noteworthy that the procedure using the metal(salalen) complex can be successfully applied to the asymmetric epoxidation of non-activated olefins.[5] We recently reexamined asymmetric oxidation using hydrogen peroxide as oxidant and found that an aluminum(salalen) complex efficiently catalyzed asymmetric oxidation of sulfides using aqueous hydrogen peroxide.[5] Moreover, we for the first time achieved highly enantioselective oxidation of sulfides using aqueous hydrogen peroxide in water without adding any detergent by using iron(salan) complex as catalyst.[6]

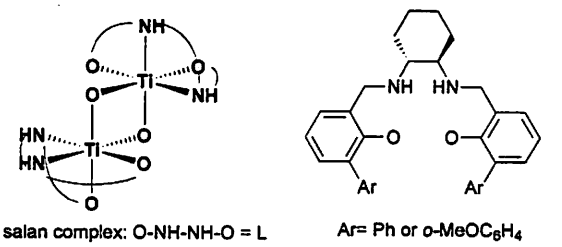


Figure 1

In this paper, we will discuss the potential of aqueous hydrogen peroxide as the terminal oxidant for asymmetric epoxidation and oxidation of sulfides.

1) B. Saito, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 3873-3876.

2) K. Matsumoto, Y. Sawada, B. Saito, K. Sakai, T. Katsuki, *Angew. Chem. Int. Ed.* **2005**, *44*, 4935-4939.

3) a) Y. Sawada, K. Matsumoto, S. Kondo, H. Watanabe, T. Ozawa, K. Suzuki, B. Saito and T. Katsuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 3478-3480. b) K. Matsumoto, Y. Sawada, and T. Katsuki, *Synlett,* **2006**, 3545-3547.

4) Y. Shimada, S. Kondo, Y. Ohara, K. Matsumoto, and T. Katsuki, *Synlett* **2007**, 245-2447.

5) a) T. Yamaguchi, K. Matsumoto, B. Saito and T. Katsuki, *Angew. Chem. Int. Ed.* **2007**, *46*, 4729-4731. b) K. Matsumoto, T. Yamaguchi, J. Fujisaki, B. Saito, and T. Katsuki, *Chem. Asian J.* **2008**, *3*, 351-358.

6) H. Egami and T. Katsuki, *J. Am. Chem. Soc.* **2007**, *129*, 8940-8941.

Process Development of HIV Integrase Inhibitor S-1360

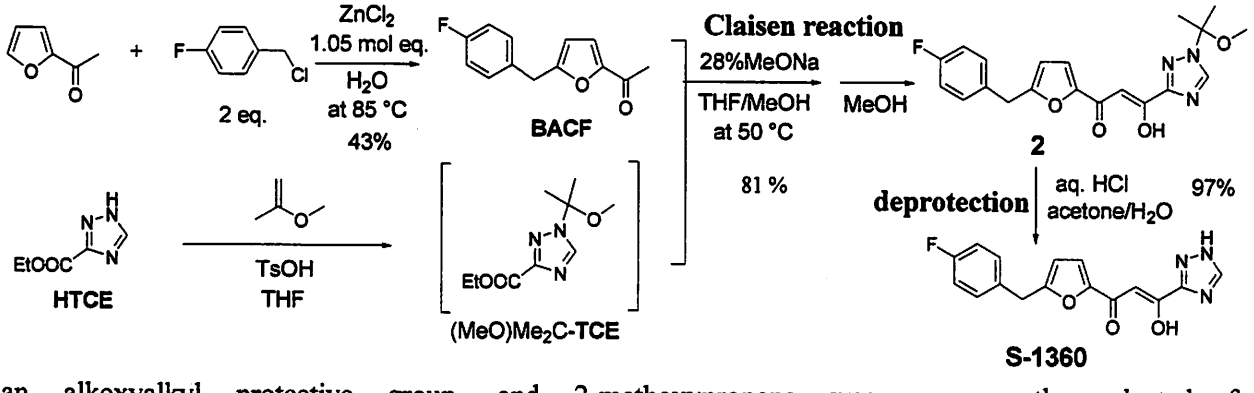
Toshiro Konoike
CMC Development Laboratories, Shionogi & Co., Ltd.
1-3, Kuise-Terajima 2-chome, Amagasaki, Hyogo 660-0813, Japan
toshiro.konoike@shionogi.co.jp

Impacts of process chemistry on speed development and manufacturing cost is described in the lecture. A practice of process chemistry is shown using a drug candidate for AIDS, focusing on safety, environment, robustness and productivity of the synthetic process of **S-1360**, a potent inhibitor of HIV integrase.

A discovery route of S-1360 was a long multi-step synthesis and it had a number of drawbacks for a large scale preparation. Two reactants, benzyl acetyl furan (BACF) and triazole ester (HTCE), for the Claisen reaction were prepared by a multi-step synthesis in a poor yield, and strong base LDA employed for the Claisen reaction is expensive. A bulky trityl group for protection of HTCE is not economical in terms of atom economy, and it required tedious procedure to remove a trityl residue after deprotection.

In order to establish an efficient and scalable synthesis of S-1360, we have solved those issues which included practical synthesis of starting materials, economical conditions for the Claisen reaction, and an efficient protection–deprotection sequence. The final synthetic scheme is shown in Scheme 1. Starting material BACF was prepared from 2-acetylfuran and 4-fluorobenzyl chloride by the Friedel–Crafts alkylation by aqueous $ZnCl_2$. A variety of vinyl ethers was surveyed for a protecting reagent of HTCE to

Scheme 1. Pilot Production of S-1360



an alkoxyalkyl protective group, and 2-methoxypropene was consequently selected for 1-methoxy-1-methylethyl protective group. The Claisen reaction was carried out uneventfully when sodium methoxide in methanol was employed in place of LDA–THF in a discovery route, and the final intermediate **2** was isolated by dilution of the reaction mixture by methanol. The final deprotection was facile, and S-1360 was precipitated by diluting the mixture with water.

References

(1) Izumi, K.; Kabaki, M; Uenaka, M.; Shimizu, S. *Org. Process Res. Dev.* **2007**, *11*, 1059.
(2) Shimizu, S.; Endo. T.; Izumi, K.; Mikamiyama, H. *Org. Process Res. Dev.* **2007**, *11*, 1055.

An Entirely New Methodology for Synthesizing Perfluorinated Compounds

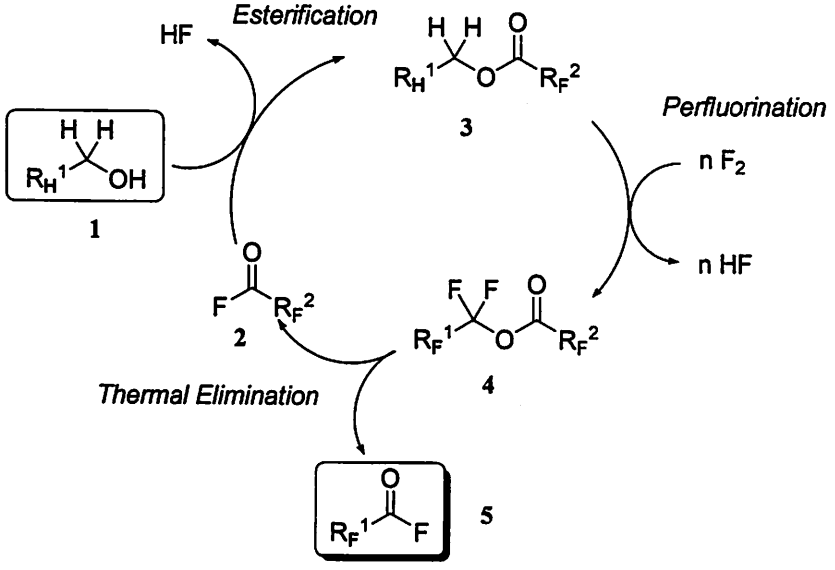
Takashi Okazoe,* Hirokazu Takagi, Daisuke Shirakawa
AGC Chemicals, Asahi Glass Co., Ltd.
Shinyurakucho Bldg., 1-12-1 Yurakucho, Chiyoda-ku, Tokyo, 100-8405, Japan
takashi-okazoe@agc.co.jp

Perfluorinated compounds are important precursors for materials, which are used as a both thermally and chemically resistant material in industrial areas, and are building blocks especially in recent medical, and pharmaceutical applications.[1] However, it has been difficult to synthesize new perfluorinated compounds because the reactivity of fluorinated compounds is restricted.

Liquid-phase direct fluorination is a powerful tool to make perfluorinated compounds.[2] Especially, Exfluor-Lagow elemental fluorine process is effective under mild conditions.[3] Lagow *et al.* reported direct fluorination of nonfluorinated compounds with relatively simple structure.

The liquid-phase direct fluorination of a small molecule such as a monomer precursor was examined, however, it was not appropriate for a large scale.[4a] In some cases, reaction in the vapor phase due to high volatility of the substrate partly took place and led to an explosion.

In order to solve this problem, we have developed the PERFECT process (Scheme 1).[4a] The name "PERFECT" is the abbreviation of *PERFluorination of an Esterified Compound then Thermal elimination*. By employing a higher-molecular weight partially-fluorinated ester **3**, which is synthesized from nonfluorinated alcohol **1** and perfluorinated acyl fluoride **2**, as the substrate for direct fluorination, any dangerous vapor-phase reactions can be avoided.

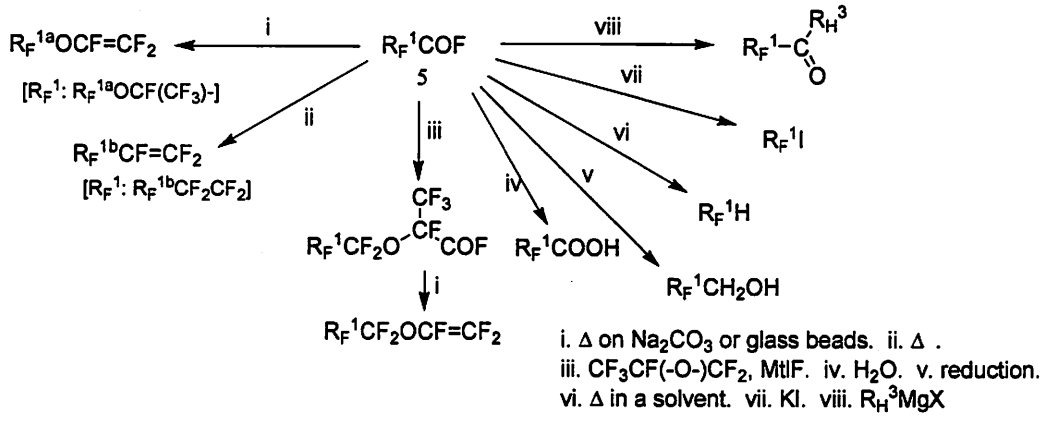


Scheme 1. Typical "PERFECT" process

By using the PERFECT process, various perfluoroacyl fluorides can be synthesized. The synthesis of perfluorinated propyl vinyl ether, which is the monomer of perfluoroalkoxy copolymer (PFA), the synthesis of various perfluoroacyl fluorides, and the synthesis of the monomers for ion exchange membrane (Flemion®) have been acheived.[4] When a secondary alcohol is employed as the hydrocarbon starting material, the corresponding perfluorinated ketone is obtained.[5]

This methodology has advantages over other direct fluorination methods as follows. (1) It avoids dangerous vapor-phase reaction by employing a substrate, which has a lower vapor pressure. (2) It significantly increases the solubility of the substrate in the perfluorinated solvent used for the liquid-phase fluorination, compared to non-fluorinated ester. (3) It is easier to synthesize the partially-fluorinated substrate because perfluorinated acyl fluorides are available from the conventional manufacturing process.

Examples of the building blocks derived from the "PERFECT" product are shown in Scheme 2.



Scheme 2. Building blocks derived from the "PERFECT" product

By utilizing the "PERFECT" method, we have created a new fluorinated surfactant, and a new lubricant for hard disk drives[6]. The synthesis of molecules for these materials will also be discussed.

References

1 a) T. Hiyama, *Organofluorine Compounds*, Springer, Berlin, **2000**. b) R. D. Chambers, *Fluorine in Organic Chemistry, 2nd Ed.*, Oxford, **2004**.

2 J. Hutchinson, G. Sandford, *Top. Curr. Chem.* **1997**, *193*, 1.

3 T. R. Bierschenk, T. Juhlke, H. Kawa, R. J. Lagow, *US Patent* 5093432, **1992**.

4 a) T. Okazoe, K. Watanabe, M. Itoh, D. Shirakawa, H. Murofushi, H. Okamoto, S. Tatematsu, *Adv. Synth. Catal.* **2001**, *343*, 215. b) T. Okazoe, K. Watanabe, M. Itoh, D. Shirakawa, H. Murofushi, H. Okamoto, S. Tatematsu, *J. Fluorine Chem.* **2001**, *112*, 109. c) T. Okazoe, E. Murotani, K. Watanabe, M. Itoh, D. Shirakawa, K. Kawahara, I. Kaneko, S. Tatematsu, *J. Fluorine Chem.* **2004**, *125*, 1695. d) T. Okazoe, K. Watanabe, M. Itoh, D. Shirakawa, K. Kawahara, S. Tatematsu, *J. Fluorine Chem.* **2005**, *126*, 521.

5 T. Okazoe, K. Watanabe, M. Itoh, D. Shirakawa, H. Takagi, K. Kawahara, S. Tatematsu, *Bull. Chem. Soc. Jpn.*, **2007**, *80*, 1611.

6 D. Shirakawa, K. Sonoda, K. Ohnishi, *IEEE Trans. Magn.*, **2007**, *43*, 1.

K-10 (Keynote Lecture)

New Methods for the Functionalization of Aromatic Compounds

*Keith Fagnou
Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, ON, Canada K1N 6N5
keith.fagnou@uottawa.ca

While transition metal catalyzed cross couplings have been successfully employed with a wide range of halides and organometallics, some substrate classes still pose significant challenges. This is the case with 2-pyridyl organometallics, whose frequent instability and difficult synthesis severely limits their application. For example, while the coupling of 2-halopyridines with aryl boronic acids is well precedented, the inherent instability of 2-pyridyl boronic acid makes successful cross-couplings with this nucleophile rare. In recent years, direct arylation has emerged as an attractive alternative to typical cross-coupling reactions. In direct arylation, one of the pre-activated cross-coupling partners (typically the organometallic species) is replaced by an unfunctionalized arene. Consistent with an electrophilic aromatic substitution (S_EAr) pathway, electron-rich heterocyclic arenes have featured prominently in recent developments. While some simple arenes can now be used direct arylation reactions with π-electron-deficient heteroarenes, such as azines and diazines, remains a challenging goal.

An underlying challenge associated with direct arylation is that all aspects of reactivity are governed by the inherent properties of the heterocycle itself. In non-ideal cases, this can complicate issues of regiocontrol and/or necessitate the use of very forcing reaction conditions. Methods to manipulate the reactivity of the heterocyclic substrate are thus invaluable, especially if new or improved reactivity/regiocontrol can be achieved. Azole direct arylation reactions, which are believed to be facilitated in most cases by azole π-nucleophilicity at C5 and C-H acidity at C2, are illustrative. In most cases, arylation at C5 is preferred, although the formation of C5/C2 double arylation side-products is commonplace. C2 arylation has been achieved through the use of copper additives and palladium catalysis, but a broadly applicable process remains to be identified. Very high reaction temperatures are commonly required and a successful C4 arylation has not been described.

This presentation will describe the use of azine and diazine *N*-oxides as commercially available or easily prepared, inexpensive, bench stable replacements for problematic 2-metallaazines, diazines and azoles. Direct arylation reactions of pyridine *N*-oxides occur in good yield with complete selectivity for the 2-position with a wide range of aryl chlorides and iodides. While achieving reactivity from diazine substrates may have been complicated by the presence of the free nitrogen atom that could bind and poison the catalyst and the fact that they are more π-electron-deficient and less nucleophilic than pyridine *N*-oxides, excellent reactiviy is also obtained with many of these substrates. For example, a broad range of pyrazine

and pyridazine *N*-oxides react in high yield. More challenging are pyrimidine *N*-oxides, which require the use of a copper co-catalyst to achieve acceptable outcomes. This presentation will also describe how the *N*-oxide group not only imparts a dramatic increase at all positions of azole substrates, but also changes the weak azole bias for C5 > C2 arylation to a reliable C2 > C5 > C4 reactivity profile. This permits high yielding, regioselective and room temperature arylation at C2, high yielding arylation at C5, and the first examples of arylation at C4 - providing a unique opportunity for exhaustive functionalization the azole core.

This presentation will also deal with aspects of regioselectivity and reactivity and highlights the use of the *N*-oxide cross-coupling strategy in the preparation of medicinally significant targets. An overview of ongoing mechanistic studies will also be presented that should provide insight into the reasons for the beneficial reactivity imparted by the *N*-oxide fragment in arene cross-couplings that may have borader significance in the functionalization of other arenes via this strategy.

K-11 (Keynote Lecture)

Formation of C-C Bonds via Catalytic Hydrogenation and Transfer Hydrogenation

Michael J. Krische
University of Texas at Austin, Department of Chemistry and Biochemistry
1 University Station (A5300), Austin, Texas 78712
mkrische@mail.utexas.edu

Asymmetric hydrogenation accounts for over half the chiral compounds made by man, withstanding physical or enzymatic resolution. Whereas conventional hydrogenation involves *C-H bond formation*, our research demonstrates that catalytic hydrogenation may be exploited as a general protocol for *C-C bond formation*. Specifically, we have shown that hydrogenation may be used to couple diverse π-unsaturated reactants to carbonyl compounds and imines. By intercepting organometallic that arise transiently under hydrogenation conditions, one overcomes the necessity of utilizing preformed organometallic reagents in a range of classical C=X (X = O, NR) addition processes, including aldol addition (via enone-carbonyl coupling), carbonyl and imine vinylation to furnish allylic alcohols and amines (via alkyne- carbonyl and alkyne-imine coupling), and carbonyl allylation (via allene-carbonyl coupling).

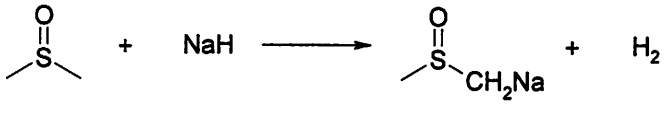
Under transfer hydrogenation conditions employing isopropanol as terminal reductant, related C=X (X = O, NR) addition processes are achieved. Additionally, by taking advantage of hydrogen already embedded within an alcoholic reactant, one may achieve carbonyl addition from the alcohol oxidation level, representing a direct method for the formal C-H functionalization of alcohols. Thus, carbonyl addition is achieved with equal facility from the aldehyde or alcohol oxidation level. By taking advantage of this new concept for alcohol-unsaturate C-C coupling, we have developed catalytic protocols for highly enantioselective carbonyl allylation from the aldehyde or alcohol oxidation level employing allyl acetate as the allyl donor.

These studies represent the first systematic efforts to exploit hydrogenation in C-C couplings beyond hydroformylation and define a departure from the use of preformed organometallic reagents in carbonyl and imine addition. Future studies will focus on the activation of feedstock chemicals (e.g. alpha-olefins, glycerol and bio-ethanol) in hydrogenative and transfer hydrogenative C-C bond forming processes with goal of achieving inexpensive and byproduct-free routes to useful chiral building blocks.

Commercialization of a Sodium Hydride Mediated Arylation Process

Mark A. Butchko (Eli Lilly, USA)

The use of sodium hydride in a full-scale commercial manufacturing process will be presented. An overview of the initial synthetic route for duloxetine drug substance will be provided as an example. Particular emphasis will be placed on the arylation reaction conditions that have been used to manufacture the penultimate intermediate to duloxetine. The potential interaction between sodium hydride and DMSO solvent to form dimsyl anion will be discussed primarily, along with appropriate controls that have been established to ensure a safe manufacturing process.



K-13 (Keynote Lecture)

Design Space for Drug Substance - approach used for vandetanib

David Haywood*
AstraZeneca Global Process R&D, AstraZeneca R&D Charnwood
Bakewell Road, Loughborough LE12 8AB UK
david.haywood2@astrazeneca.co.uk

Quality by Design (QbD) is a conceptual approach to the development of manufacturing processes for pharmaceuticals being championed by the FDA. The objective of the approach is to assure the safety and efficacy of medicines by developing robust well-understood manufacturing processes tailored to meet these needs. Fundamental to the approach is the identification of the critical quality attributes required of the product and tracking these back through the manufacturing process to identify and understand the key drivers affecting these quality measures. By focusing process development activities on understanding and controlling the key factors that impact the critical quality attributes of the drug product, quality can be "designed into" the manufacturing processes. The AZ approach has relied extensively on the application of analytical and mechanistic chemistry skills to achieve comprehensive process understanding.

The benefits of this approach are that it supports a Right First Time manufacturing philosophy based on meeting the requirements of the drug product and promises greater regulatory flexibility for continuing process improvement. Some of the challenges lie in realising these benefits for API manufacture to support the challenges facing life cycle management.

Aspects of the QbD approach will be illustrated with examples from the development of vandetanib that is progressing through the FDA's pilot program for the new pharmaceutical quality assessment system (PQAS).

Abstracts

Award Lectures

A-1 ～ A-3

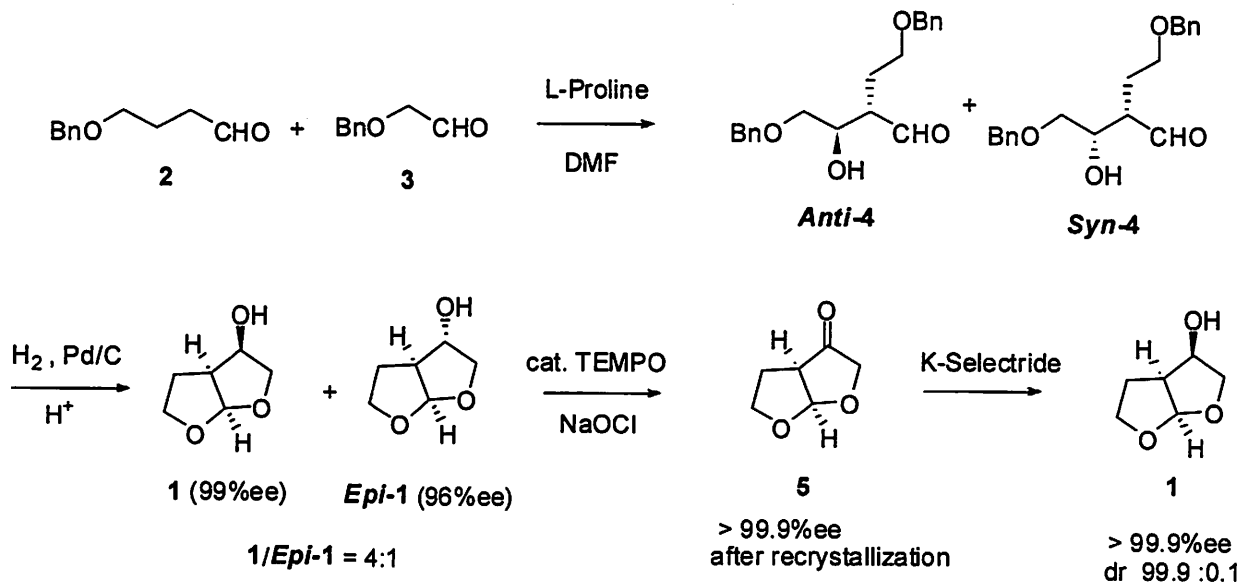
July 30

Process development of a key building block for anti-AIDS drugs by proline catalyzed enatio-selective direct cross aldol reaction

Tetsuya Ikemoto,* Yosuke Watanabe, Jun-ichi Tomokawa,
Takehiko Kawakami, Yasuo Uekita, Isao Kurimoto
Fine Chemicals Research Laboratory, Sumitomo Chemical Co., Ltd.,
3-1-21, Utajima, Nishiyodogawa-ku, Osaka 555-0021, Japan
ikemotot2@sc.sumitomo-chem.co.jp

A bis-tetrahydrofuranyl (bis-THF) moiety has been utilized in the design of a number of potent HIV protease inhibitors. Much effort had been given to the synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro [2,3-*b*]furan-3-ol (bis-THF-ol) **1**,[1] however, further improvement of the synthetic method is still required from an industrial point of view.

On the other hand, much attention has been focused on organocatalysis recently since the group of List and Barbas reported on the intramolecular direct cross-aldol reaction between ketones and aldehydes in 2000.[2] In 2002, MacMillan's group reported on the proline catalyzed highly enantioselective direct cross aldol reaction between aldehydes.[3] It was a truly amazing report indeed, however, we felt that industrial application was not so easy for the following reasons. The content of the desired product in the reaction mixture would be low because an excess amount of aldehydes would have to be used in order to obtain a practical yield, and as a result various kinds of undesired and unstable cross-aldol and self-aldol products which possess similar properties would be produced. Therefore it was thought that the purification would be difficult at an industrial level.



However, if the direct cross-aldol reaction between aldehyde **2** and aldehyde **3** successfully proceeds to give the desired ***Anti*-4** as a major product, it seemed that it might be possible to convert this aldehyde to the stable bis-THF-ol **1** by introducing the cyclization process sequentially and separating it from other non-cyclized aldol adducts. Thus we tried the proline catalyzed direct cross-aldol reaction between 1 equivalent of aldehyde **2** and 2 equivalent of aldehyde **3** in dimethylformamide (DMF). Fortunately the reaction proceeded very well to obtain ***Anti*-4** as a major product. The aldol adduct obtained was extracted with *tert*-butyl methyl ether (TBME) and concentrated under reduced pressure. However, the aldol adduct was gradually decomposed even at 30℃ when the concentration time was prolonged. Thus we decided not to concentrate the solution. That is to say, the aldol adducts in TBME was added to the solution of 2-propanol and 35% HCl, and hydrogenized in the presence of 10% Pd/C under a pressure of 0.5 MPa. As a result we successfully obtained the desired bis-THF-ol **1** and ***Epi*-1.** However we noticed that the yield tended to be lower when the reduction time was prolonged. We thought that this was due to the instability of the aldol adduct in the presence of the strong acid. Thus we tried the dropwise addition of cooled aldol adduct in TBME with a pressure pump to the reaction vessel containing the mixture of Pd/C, HCl aqueous solution and 2-propanol pressurized by hydrogen at 0.5 MPa beforehand. As a result, the yield was stabilized at around 60% (**1** + ***Epi*-1**) even when the addition time was prolonged to 12 h. The product was successfully obtained by single distillation as a mixture of bis-THF-ol **1** (99%ee) and ***Epi*-1** (96%ee) (***1*/*Epi*-1** = 4:1).

Though the pure compound **1** was of course obtained by conventional column chromatography, its separation was difficult by industrial means, for example by distillation. Furthermore undesired ***Epi*-1** had to be discarded. Thus we tried to convert the mixture **1** and ***Epi*-1** to the ketone **5** by TEMPO oxidation. The oxidation proceeded successfully to give the crystalline ketone **5** (98%ee), followed by single recrystallization from 2-propanol to afford an almost pure product **5** (>99.9%ee) with around 80% isolated yield. Then we finally tried the diastereoselective reduction of ketone **5.** Simple $NaBH_4$ reduction at -15℃ showed high diastereoselectivity (*dr*=98:2) to give bis-THF-ol **1** with 94% isolated yield. Though this was already a satisfactory result for us, we also tried other reduction conditions. As a result, we were able to reduce the ketone **5** to bis-THF-ol **1** in a quantitative yield with a diastereoselectivity of 99.9:0.1 by using K-selectride® at -70℃.

In summary, we have found a practical method for the synthesis of bis-THF-ol **1** using a proline catalyzed enantio-selective direct cross aldol reaction as the key reaction. This method was successfully scaled-up and proven to be environmentally friendly and economical on an industrial scale.

References

1) For a representative example, see: Ghosh, A. K.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 505.

2) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem.* Soc. **2000**, *122*, 2395.

3) (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem.* Soc. **2002**, *124*, 6798. (b) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152.

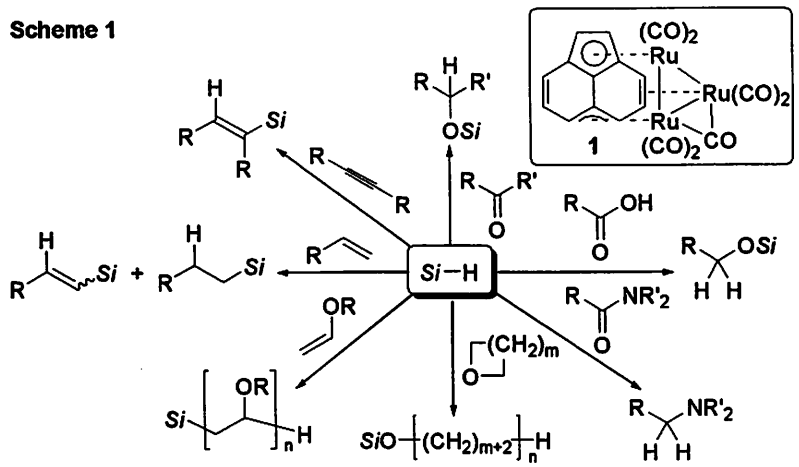
A-2 (Award Lecture)

Development of Practical and Scalable Synthesis of a Triruthenium Cluster Catalyst and Amide-Selective Silane Reduction

Hideo Nagashima,* Hidehiro Sasakuma, Nariaki Harada, Hironori Tsutsumi, and Yukihiro Motoyama
Institute for Materials Chemistry and Engineering,
Graduate School of Engineering Sciences, Kyushu University
6-1, Kasuga-koen, Kasuga, Fukuoka 816-8580, Japan
nagasima@cm.kyushu-u.ac.jp

A triruthenium carbonyl cluster having an acenaphthylene as a face-capping ligand (**1**) is stable to air and moisture, and can be stored under aerobic conditions for over a year. Treatment of **1** with hydrosilans results in facile activation of the Si-H bond leading to catalytic hydrosilylation of alkenes and alkynes, hydrosilane-reduction of aldehydes, ketones, and carboxylic acid derivatives, ring-opening polymerization of cyclic ethers, and addition polymerization of vinyl ethers (Scheme 1). We reported earlier a synthetic route of **1** from $Ru_3(CO)_{12}$ and acenaphthylene (purity >99%), in which the mixture was heated in heptane under reflux for 36 h, and the resulting crude product was purified by silica gel column chromatography for removal of a small amount of a by-product, (μ_3, η^2, η^3, η^5-acenaphthylene)$Ru_4(CO)_9$. This method is reliable but has drawbacks in the high-cost of acenaphthylene with >99% purity (¥ 14,700 / 100 mg) and chromatographic purification using a large amount of solvents (ether 2.6 L and hexane 1.5 L for isolation of 1 gram of **1**). There are apparently problems in the cost and large-scale synthesis of **1**. We report here an improved and practical synthetic procedure of **1** with excellent safety and cost.

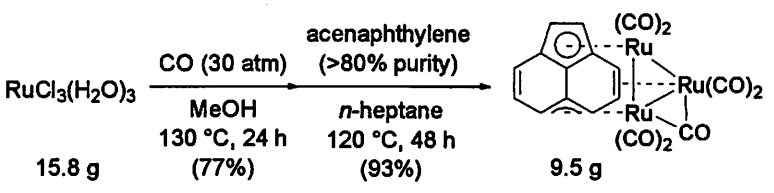
Scheme 1



The first step is synthesis of $Ru_3(CO)_{12}$, in which treatment of 15.8 g of $RuCl_3 \cdot 3H_2O$ with CO (30 atm) in methanol at 130 °C for 24 h. The reaction with no stirring followed by slow cooling of the reaction mixture to room temperature results in instant formation of $Ru_3(CO)_{12}$ as orange crystals. Pure $Ru_3(CO)_{12}$ is available in 77% isolated yield by washing of the crystals with methanol. The second step is treatment of the resulting $Ru_3(CO)_{12}$ with 80% purity of acenaphthylene. Acenaphthylene with 80% purity is cheap and

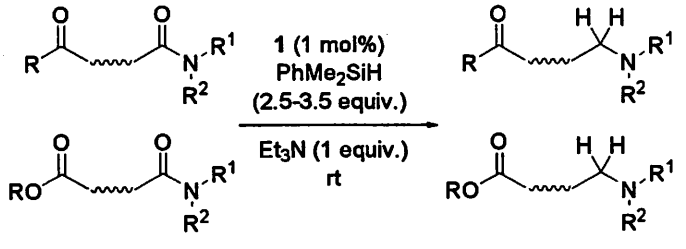
commercially available (¥ 7,400 / 25 g), which contains 20% of acenapthene. The acenaphthylene (80%) in *n*-heptane is allowed to react with $Ru_3(CO)_{12}$ (10.0 g) at 120 °C for 48 h to give **1** as orange solids. During the reaction, acenaphthene, which is not reactive with $Ru_3(CO)_{12}$, being removable by washing the crude **1** with hexane after the reaction. The crude **1** contains a small amount of the Ru_4 by-product; however, it is easily removable by recrystallization from a mixture of CH_2Cl_2 and hexane. The yield of **1** by this method reaches 93% (Scheme 2). The procedure using cheap and low purity acenapthylene and skipping the chromatographic purification step results in lowering the cost of **1**, one twelfth as much as that of **1** with the original procedure.

Scheme 2



As shown in Scheme 1, the ruthenium cluster **1** catalyzes various organic and polymer synthesis. One of the most useful reactions is hydrosilane reduction of carboxamides. In a typical example, treatment of *N,N*-dimethyl-3-phenylpropionamide (10 mL, 56 mmol) with $PhMe_2SiH$ (19 mL, 123 mmol) in the presence of **1** (365 mg, 0.56 mmol) in THP (4.5 mL) at room temperature for 75 min gave *N,N*-dimethyl-3-phenylpropylamine in 91% yield (8.32 g), which is reported in Organic Synthesis. Interesting discovery is "selective poisoning" of the catalyst species by amines. The rate of the hydrosilane reduction of *N,N*-demethyldecanamide (amide) is compared with methyl decanoate (ester) and 2-decanone (ketone); experiments suggest the order, amides ≥ esters > ketones in the absence of amines. Addition of 1 equiv. of Et_3N to the reaction medium completely kills the reactivity of hydrosilanes towards the reduction of esters and ketones with remaining the reactivity of amides. Application of this Et_3N effect to reduction of amido esters and amido ketones resulted in selective reduction of amides with remaining the other carbonyl functions intact (Scheme 3). Related papers are listed in References.

Scheme 3



References

(1) Nagashima, H.; Suzuki, A.; Iura, T.; Ryu, K.; Matsubara, K. *Organometallics* **2000**, *19*, 3579.

(2) Matsubara, K.; Iura, T.; Maki, T.; Terasawa, J.; Nagashima, H. *J. Org. Chem.* **2002**, *67*, 4985.

(3) Matsubara, K.; Terasawa, J.; Nagashima, H. *J. Organomet. Chem.* **2002**, *660*, 145.

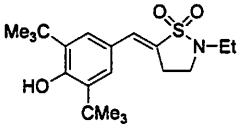
(4) Nagashima, H.; Itonaga, C.; Yasuhara, J.; Motoyama, Y.; Matsubara, K. *Organometallics* **2004**, *23*, 5779.

(5) Motoyama, Y.; Itonaga, C.; Ishida, T.; Takasaki, M.; Nagashima, H. *Org. Synth.* **2005**, *82*, 188.

Development of One-pot Synthesis of New Antiarthritic Drug Candidate S-2474 with High *E*-Selectivity

Takemasa Hida,* Katsuo Oda, Toshiaki Masui, Hideo Nogusa
CMC Development Laboratories, Shionogi & Co., Ltd.
1-3, Kuise Terajima 2-chome, Amagasaki, Hyogo 660-0813, Japan

(*E*)-(5)-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (S-2474, **1**), which was discovered at Shionogi Research Laboratories, shows potent inhibitory effects on both cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LO) and is anticipated to be promising as an antiarthritic drug.[1] The stereoselective formation of *E*-olefin and development of a short route are key point in this study and the details are discussed in this presentation.

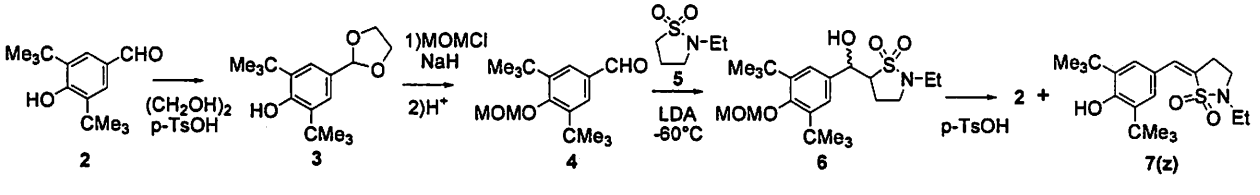


S-2474 1

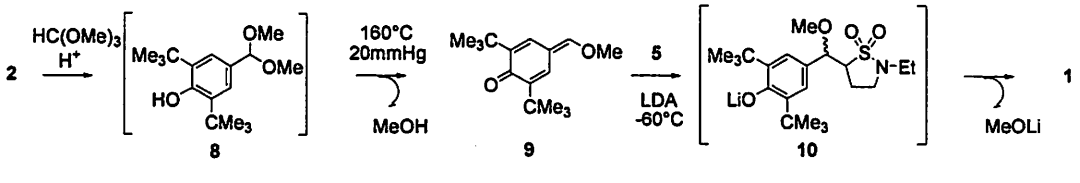
Synthetic route of S-2474 on medicinal chemistry

We already had two synthetic routes of **1** , however there were some ploblems for industrial manufacturing in the following. The original synthetic route (Scheme 1) required five reactions and chromatographic purification because dehydration of **6** produced the *Z*-isomer **7** of S-2474 as a by-product (*E*/*Z* = 84/16). The overall yield was only 19.8%. Another synthetic route was developed by Inagaki et al. using a quinone methide derivative as an equivalent of the protected *p*-hydroxybenzaldeyde derivative (Scheme 2).[2] Although the overall yield was improved to 71.2% and the generation of **7** could be controlled, this route had a problem with respect to scale-up manufacturing. Quinone methide derivative **9** underwent sublimation and its preparation required a very high temperature reaction in vacuo (160°C, 20–100 mmHg).

Scheme 1 First generation route (medicinal route).



Scheme 2 Second generation route (Kilo-Lab route).



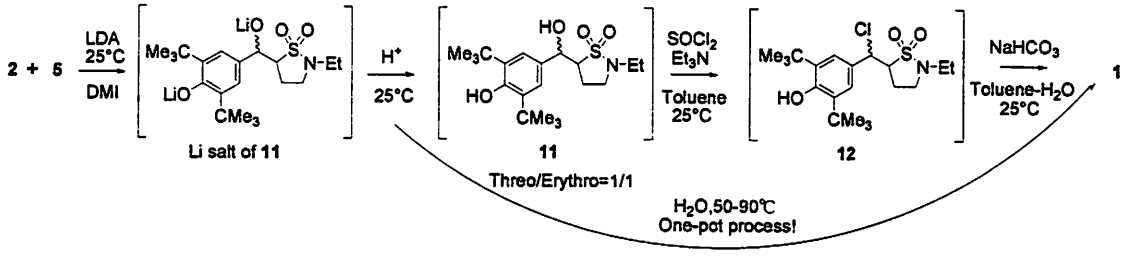
Development of process route of S-2474 (telescoping and one-pot process)[3]

We developed a new synthetic route for pilot manufacturing. Aldol-type condensation of **2** and **5** was carried out with LDA. The resulting mixture was quenched under acidic condition at room temperature, and then chlorination of hydroxy group and its dechlorination with aq. $NaHCO_3$ gave **1** with high *E*-selectivity

(Scheme 3). These three reactions were carried out with telescoped process. The isolated yield of **1** was 82.5%. This route does not need any severe reaction conditions and it was applicable for pilot scale manufacturing. However we further tried to develop much better process as described in the following section.

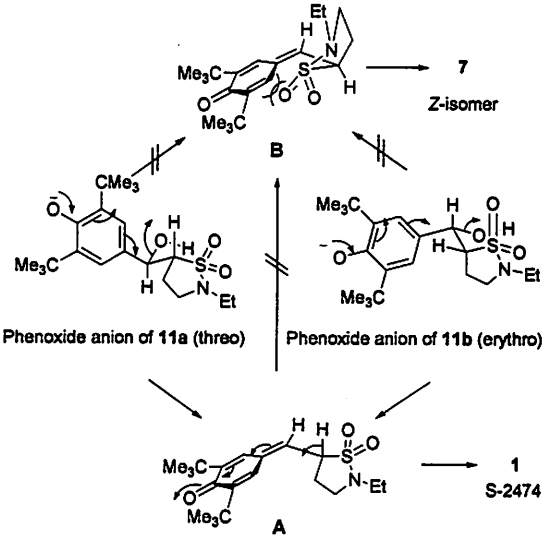
Careful monitoring of the reaction showed that a very small amount of **1** was generated when the lithium salt of **11** was quenched. The yield of **1** seemed to be affected by the exothermic heat of quenching. We estimated that **1** was obtained directly without chlorination and dechlorination and optimized the dehydration condition. The dehydration preferred the basic condition to the acidic. Addition of water and heating to 50–90 °C gave **1** as a single isomer on the benzylidene double bond (Scheme 3, from **11** to **1**). The isolated yield of **1** was 84.1%.

Scheme 3 Telescoped process of **1**



Reaction mechanism

Aldol compound **11** is a mixture of threo and erythro isomers. *Z*-isomer **7** could be given by E2 elimination of threo isomer, however no *Z*-isomer was detected in this one-pot process. We clarified the reaction mechanism via the quinone methide form as shown in Figure 1. In fact, dehydration of protected phenol (*p*-methoxy benzene type) derivative did not proceed. We hypothesized that phenoxide anions, threo isomer **11a** and erythro isomer **11b**, would give the same intermediate **A** which is controlled by steric hindrance of the sulfonyl and the aryl groups.



Reference

1. Inagaki, M.; Tsuri, T.; Jyoyama, H.; Ono, T.; Yamada, K.; Kobayashi, M.; Hori, Y; Arimura, A; Yasui, K.; Ohno, K.; Kakudo, S.; Koizumi, K.; Suzuki, R.; Kato, M.; Kawai, S.; Matsumoto, S. *J. Med. Chem.* **2000**, *43*, 2040.

2. Inagaki, M.; Haga, N.; Kobayashi, M.; Ohta, N.; Kamata, S.; Tsuri, T. *J. Org. Chem.* **2002**, *67*, 125.

3. Oda, K.; Hida, T.; Sakata, T.; Nagai, M.;Sugata, Y.; Masui, T.; Nogusa, H., *Org. Process, Res. Dev.* in press.

Abstracts

Poster Presentation

1 P-01 ～ 1P-75

July 29

1P-01

A New Ethereal Solvent:CycloPentylMethylEther(CPME) for Process Innovation and Green Chemistry

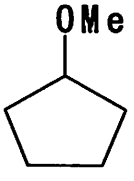
*Kiyoshi Watanabe [1], Yasuhiro Torisawa [2]

[1] Specialty Chemicals Division, ZEON CORPORATION,

1-6-2 Marunouchi, Chiyoda-ku, Tokyo, 100-8246, Japan,kw@zeon.co.jp

[2]Faculty of Pharmacy, Takasaki University of Health and Welfare, Takasaki, Gunma 370-0033, Japan

1. Physical Properties of CPME compared to various ethers



CPME is a new process solvent with such preferable characters as high boiling point (106 °C) with small evaporation energy, low formation of peroxides, relative stability under acidic or basic conditions, formation of azeotropes with water, low affinity for water and coupled with narrow explosion range.

	CPME	THF	2-MeTHF	MTBE	Et_2O	Dioxane
Density (20℃)[g/cm^3]	0.86	0.89	0.85	0.74	0.71	1.03
Vapor specific gravity (air = 1)	3.45	2.49	2.97	3.1	2.56	3.3
Boiling point[℃]	106	65	80	55	34.6	101
Melting point[℃]	<-140	-108.5	-136	-110	-116.3	11.8
Viscosity (20℃)[cP]	0.55	0.55	0.6(25℃)	0.35	0.2448	1.31
Surface tension (20℃)[mN/m]	25.17	26.4	Unknown	19.8	17.3	33.74
vaporization energy (bp) [Kcal/kg]	69.2	98.1	89.7	81.7	86.08	98.6
Specific heat (20℃)[Kcal/kg·K]	0.4346	0.469	Unknown	0.51	0.5385	0.41
Refractive index (20℃)	1.4189	1.407	1.406	1.369	1.353	1.422
Solubility parameter [cal/ml]	8.4	9.5	8.52	Unknown	7.4	Unknown
Dielectric constant(25℃)	4.76	7.58	7	2.6	4.197	2.227
Dipole moment [D]	1.27 (calcd.)	1.7	Unknown	1.4	1.12	0.45
Azeotropic point with water [℃]	83(a)	64	71(b)	52.9(c)	34.2	87.8
Solubility in water [g/100g]	1.1 (23℃)	∞	14	4.8	6.5	∞
Solubility of water in the solvent [g/100g]	0.3 (23℃)	∞	4.4	1.4	1.2	∞
Flash point [℃]	-1	-14.5	-11	-28	-45	12
Ignition point [℃]	180	205	270	224	180～190	180
LogPow	1.59	0.47	Unknown	0.94	0.89	-0.42
Explosion range [vol%]	1.1-9.9	1.84-11.8	1.5-8.9	1.6-8.4	1.85-48	2-22

azeotrope (wt%)
a composition= CPME:83.7,H_2O:16.3
b composition= MeTHF: 89.4,H_2O: 10.6
c composition= MTBE: 96.5%,H_2O: 3.5

2. CPME for Process Innovation and Green Chemistry

Pinner reaction is selected as a representative example. Nitriles can react with methanol in the presence of g.HCl in ethers to give imidates·HCl, very important intermediates for the synthesis of heterocyclic compounds. We surveyed this reaction both in the conventional system (dioxane-ether) and in CPME system. The conventional conditions have many disadvantages; 1) use of toxic dioxane, 2) dangerous concentration process with ethers, and 3) instability of ethers under acidic conditions. On the other hand, in CPME system, products can be obtained in high yield only by filtration / washing because of the low solubility of salt ,the high hydrophobicity of CPME and it's stability to acidic media.

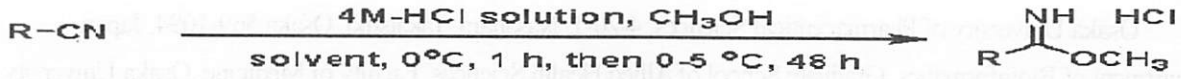
Solvent unification by the single use of CPME makes a series of unit operations (reaction, work-up,

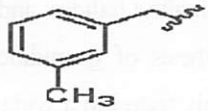
isolation) simple and short, so CPME can contribute to GSC in the following viewpoints.

(1) Reduction of the wastes and water

(2) Replacement of the hazardous or dangerous solvents

(3) Recovery and reuse of CPME

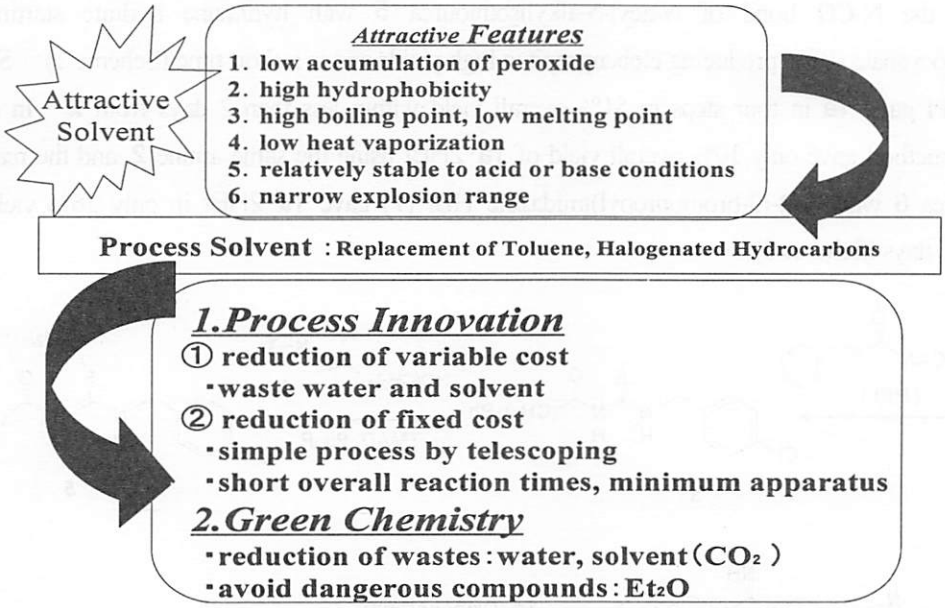


R	solution	solvent	Yield (%)
	1,4-Dioxane	Et_2O	86 [a]
	CPME	CPME	90 [b]
	CPME	CPME	89 [b]
	CPME	CPME	91 [b]

a) U.S.Pat.No.: US 6806380 B2
b) Work-up of CPME process is only filtration and washing.

3.Conclusion

CPME can thus contribute to many stages in modern synthesis from laboratory to plant scale operation. Attractive features of CPME are summarized in the following scheme and other applications are summarized in the review article shown below.



Reference

1.Watanabe,K.; Yamagiwa, N.; Torisawa, Y. *Org. Process Res. Dev.* **2007**, *11*, 251.

2. Zeon Corporation, Specialty Chemicals Division, *CPME Catalog & Technical Data* (2006).

1P-02

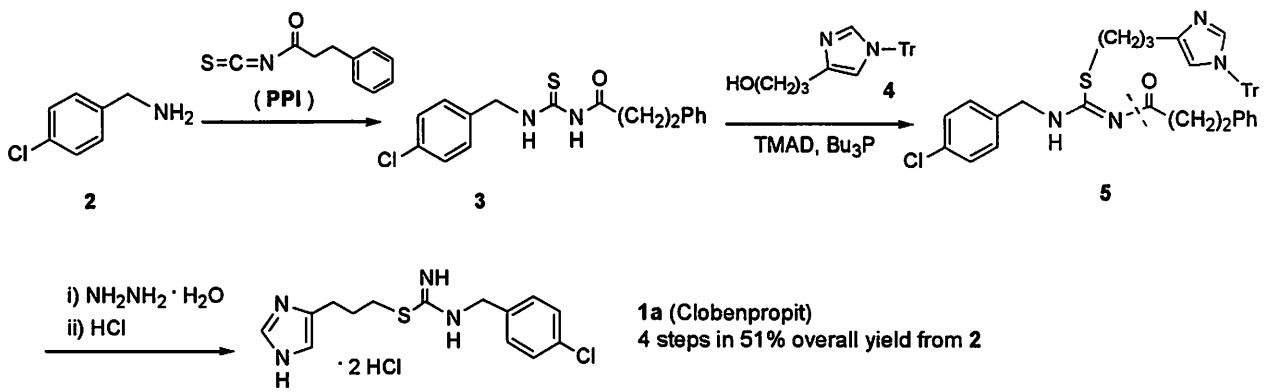
Efficient Approaches to *S*-Alkyl-*N*-alkylisothioureas: Syntheses of Histamine H_3 Antagonist Clobenpropit and Its Analogues[1)]

Hiroki Yoneyama[1], Mifuyu Yasunaga[1], Lisa Araki[1], Kouta Hatano[2],
Atsushi Yamatodani[2], Shinya Harusawa[1]*,
[1]Osaka University of Pharmaceutical Sciences, 4-20-1, Nasahara, Takatsuki, Osaka 569-1094, Japan
[2]Department of Bioinformatics, Graduate School of Allied Health Sciences, Faculty of Medicine, Osaka University, Osaka 565-0871, Japan
harusawa@gly.oups.ac.jp

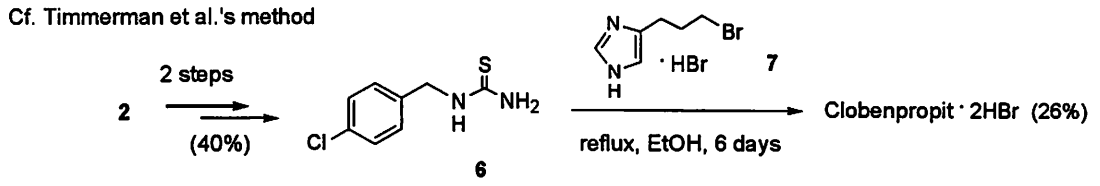
S-Alkylisothioureas **1** and their salts **1**·HX are synthesized by mainly reacting thioureas with alkyl halides, and other methods have been little employed so far. They are crucial intermediates for the synthesis of guanidines and heterocyclic systems. In recent years, the isothiourea-functional group has been increasingly found in a wide range of biologically active molecules, including NO synthase-inhibitors and Na^+/Ca^{2+} exchanger-inhibitors.

On the other hand, the histamine H_3 receptor (H_3R) is a presynaptic autoreceptor that is mainly localized in the central nervous system (CNS) and acts to modulate the biosynthesis and release of histamine from histaminergic neurons. H_3R antagonists increase central histamine levels and may therefore be useful for the treatment of a variety of CNS disorders, including eating disorder, schizophrenia, narcolepsy, epilepsy and cognitive disorders, and attention-deficit hyperactivity disorder (ADHD). Among H_3R antagonists, clobenpropit (**1a**), which was developed by Timmerman and co-workers, has been widely used in pharmacology as a potent prototype of H_3R antagonists.[1)]

We herein report two efficient synthetic approaches to *S*-alkylisothioureas **1**.[2)] In particular, one approach involves direct cleavage of the N-CO bond of *N*-acyl-*S*-alkylisothiourea **5** with hydrazine hydrate starting from 3-phenylpropionyl isocyanate (PPI), producing clobenpropit in high yields and in a short time (Scheme 1). Synthetic method using the PPI gave **1a** in four steps in 51% overall yield within less than 2 days from **2**. In contrast, Timmerman et al.'s method gave only 10% overall yield of **1a**·2HBr using the same amine **2**, and the reaction of 4-chlorobenzylthiourea **6** with 4(5)-(3-bromopropyl)imidazole·HBr (**7**) gave **1a**·2HBr in only 26% yield under reflux in ethanol for 6 days (Scheme 2).[1)]



Scheme 1



Scheme 2

To demonstrate the applicability of this method using PPI, several analogues of clobenpropit were synthesized : the precursor of ^{125}I-labeled iodophenpropit, novel *p*-carborane-containing isothioureas (**1b** and **1c**), piperidine analogue (**1d**, FUB 661), and novel pyrrolidine and morpholine (**1e**) analogues (Fig.).

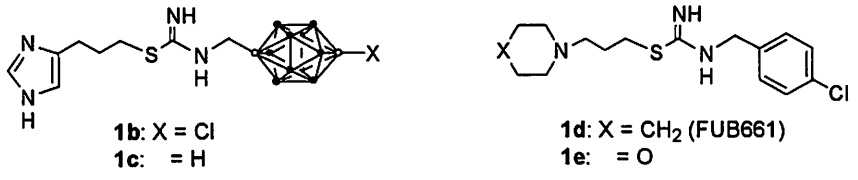
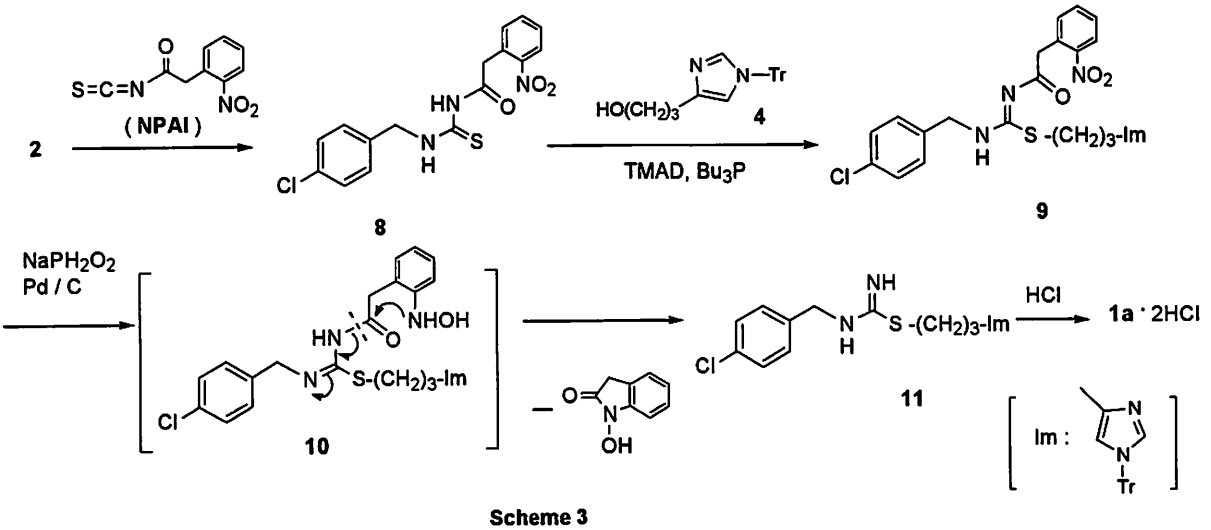


Fig.

Among them, brain microdialysis experiments showed that FUB 661 and morpholine analogues **1e** increased moderately histamine realease by 130-140% and 140-150%, respectively.

We next directed our interest to the alternative synthesis of clobenpropit using intramolecular amide cleavage with use of 2-nitrophenylacetyl isothiocyanate (NPAI). Synthetic method using the NPAI gave clobenpropit in four steps in 54% overall yield within less than 2 days from **2** (Scheme 3).



Scheme 3

The utility of those two approaches was proved by the syntheses of clobenpropit and its analogues. The two approaches are expected to supply a variety of H_3R ligand candidates having the isothiourea moiety by which their biological activities could be assessed.

1) H. Timmerman *et al.*, *Eur. J. Med. Chem.*, **27**, 511 (1992); 2) S. Harusawa *et al.*, *J. Org. Chem.*, **73**, 2096 (2008).

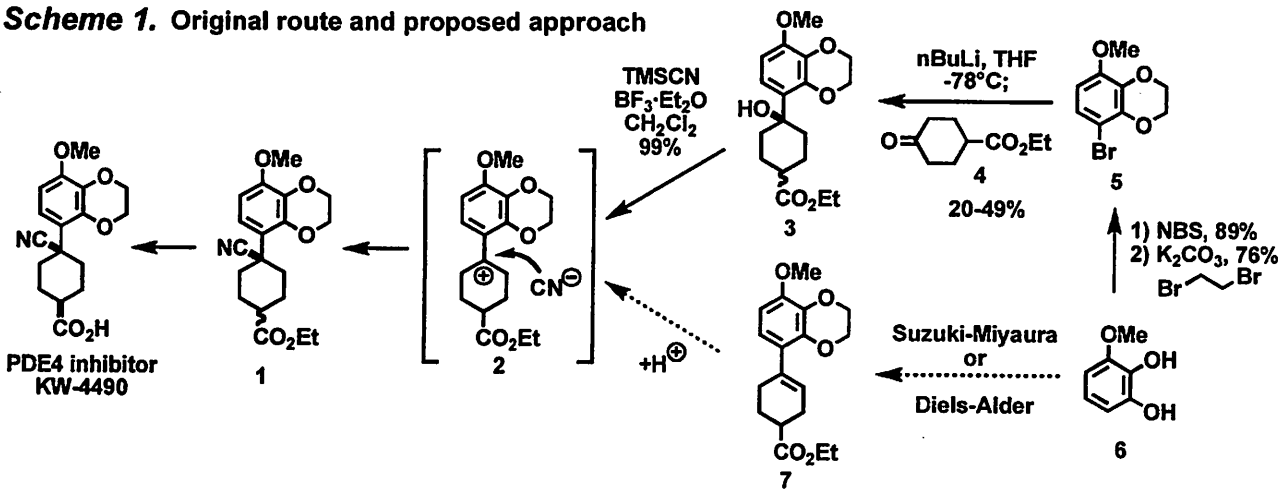
1P-03

A Practical Synthesis of the PDE4 inhibitor, KW-4490

Arata Yanagisawa,*,† Koichiro Nishimura, Tetsuya Nezu, Kyoji Ando,
Ayako Maki, Eiichiro Imai, and Shin-ichiro Mohri
Sakai Research Laboratories, Pharmaceutical Research Center, Kyowa Hakko Kogyo Co., Ltd.
1-1-53, Takasu-cho, Sakai-ku, Sakai, Osaka, 590-8554, Japan
arata.yanagisawa@kyowa.co.jp

KW-4490 was identified at Kyowa Hakko as a potent phosphodiesterase 4 (PDE4) inhibitor for the treatment of asthma and chronic obstructive pulmonary disease (COPD).[1] The original synthesis was suitable for gram-scale delivery, but not for large-scale production (Scheme 1). Aryllithium addition to ketone **4** was problematic because of low yield, poor reproducibility, and necessity of column chromatography due to difficulty in crystallizing alcohol **3**. On the other hand, the following cyano substitution was high-yield and robust.[2] With the concept that the intermediate cation **2** is stabilized by the oxygen substituents, we envisioned that cyclohexene **7** might be a new precursor for nitrile **1** in presence of Brønsted acid and cyanide source (Scheme 1), even though hydrocyanation of such highly substituted olefins has been very limited.[3]

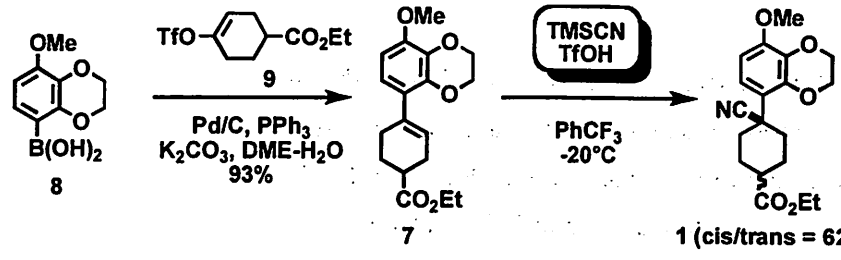
Scheme 1. **Original route and proposed approach**



Suzuki-Miyaura cross coupling of boronic acid **8** and enol triflate **9**, prepared from **5** and **4**, respectively, gave cyclohexene **7**. Then, **7** was subjected to screening of various Brønsted acids in presence of trimethylsilyl cyanide. As a result, the proposed hydrocyanation did proceed when triflic acid was used (Scheme 2). Use of a slightly excess amount of triflic acid than trimethylsilyl cyanide was essential, which implies that residual triflic acid generates cation **2**.

With some issues in large-scale preparation of both **8** and **9**, we have established more scalable synthesis of **7** (Scheme 3). 1,2-Dibromoethane treatment of catechol **6**, selective Friedel-Crafts acetylation, and vinyl Grignard addition afforded alcohol **11**. Without purification, **11** was heated (ca. 100°C) in presence of pyridinium *p*-toluenesulfonate and ethyl acrylate. Quick formation of diene **12** and subsequent

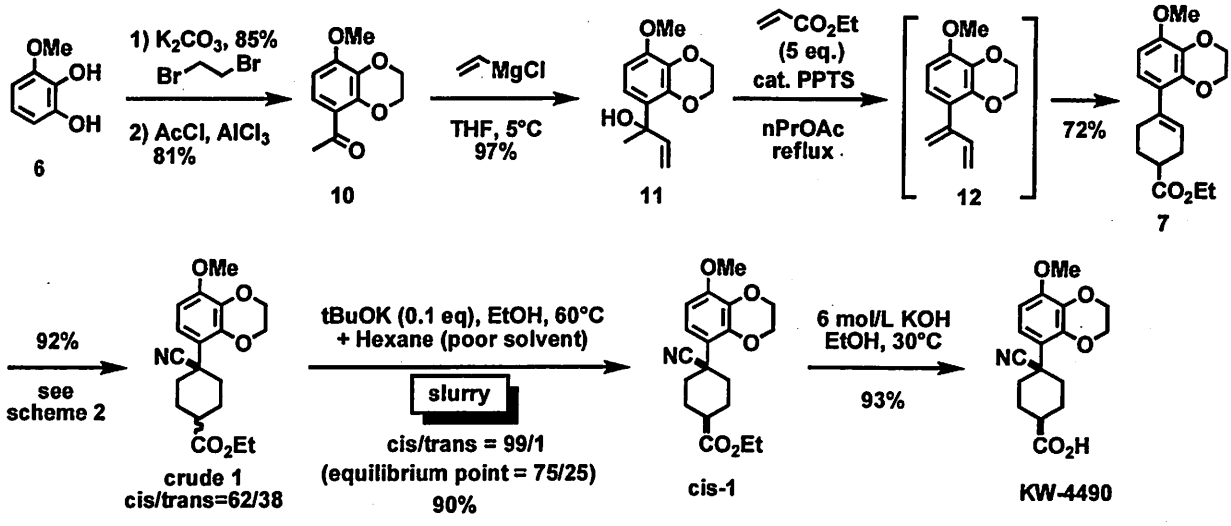
Scheme 2. **Acid-mediated hydrocyanation of 7**



TMSCN	TfOH	Yield
1.5 eq.	0.5 eq.	2%
2.0 eq	2.1 eq.	92%

conversion to Diels-Alder adduct **7** were observed in one-pot. Ca. 16% of regio-isomer of **7** was formed, but was successfully removed by recrystallization. After the above hydrocyanation process of **7**, recovery of **trans-1** via base-induced isomerization was required because of the poor cis/trans selectivity. With observation that **cis-1** is less soluble than **trans-1**, we conducted crystallization-induced dynamic resolution of crude **1** (cis/trans = 62/38). In solution state, the isomerization stopped at thermodynamic equilibrium point (75/25), but in slurry state, the ratio came up to 99/1. Finally, hydrolysis of **cis-1** gave KW-4490.

Scheme 3. **Process route *via* Deils-Alder and crystallization-induced dynamic resolution of cis-1**



In summary, the synthesis was achieved in 7 steps and 37% overall yield, and produced multikilogram quantities of KW-4490. In the poster session, generality of the acid-mediated hydrocyanation, and improvement of the Diels-Alder regioselectivity will be presented.

References

† Current address: Medicinal Chemistry Research Laboratories, Pharmaceutical Research Center, 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8731, Japan.

1) a) Yanagawa K. the 26th medicinal chemistry symposium, Sagamihara 2007, 2P-29. b) Ohshima E.; Yanagawa K.; Manabe H.; Miki I.; Masuda Y. PCT Int. Appl. WO0164666 A1, 2001.

2) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331.

3) North M. in Comprehensive Organic Functional Group Transformations, Pergamon, Oxford, 1995: Vol. 3, p. 614.

1P-04

Solvent-free Synthesis of Heterocycles Using Carbon Dioxide (1 atm)

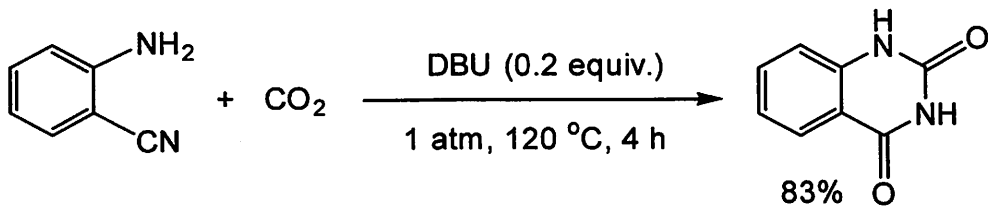
Takumi Mizuno,* Takeo Nakai, Masatoshi Mihara
Osaka Municipal Technical Research Institute
1-6-50, Morinomiya, Joto-ku, Osaka 536-8553, Japan
tmizuno@omtri.city.osaka.jp

1*H*-Quinazoline-2,4-dione derivatives have been interesting for their biological activities, and have been widely used as a key structure of medicines. For instance, 7-chloro-1*H*-quinazoline-2,4-dione is an important intermediate of medicines (FK 366 (Zenarestat®) and KF31327). FK 366 (Zenarestat®) showed the effect for an aldose reductase inhibitor, and was produced for a remedy of complications of diabetes mellitus, and KF31327 was developed as a heart disease remedy and an impotence medicine. Also, 6,7-dimethoxy-1*H*-quinazoline-2,4-dione is a key intermediate for the production of the effective α_1-adrenergic blocker (Prazosin, Bunazosin, and Doxazosin), are useful for antihypertensives.

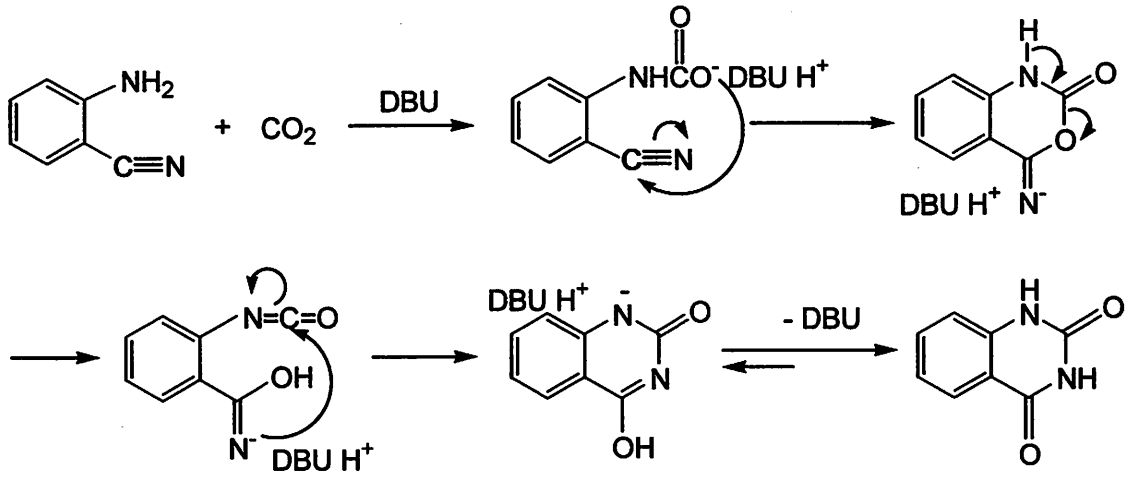
Supercritical carbon dioxide as a substitution for organic solvents is of a great importance, because of both for the toxicity for human and the environmental problems of organic solvents. Recently, we showed a successful result of synthesis of 1*H*-quinazoline-2,4-diones in excellent yields with supercritical carbon dioxide (100 atm, 80 °C) as a reactant and a solvent, in the presence of DBU (0.1 equiv.).[1] However, it is not easy reaction procedure using high pressure of carbon dioxide.

Therefore, if solvent-free synthesis of substituted 1*H*-quinazoline-2,4-diones from 2-aminobenzonitriles using only carbon dioxide (1 atm) and catalytic amount of base is established, it would be one of the ideal organic reactions.

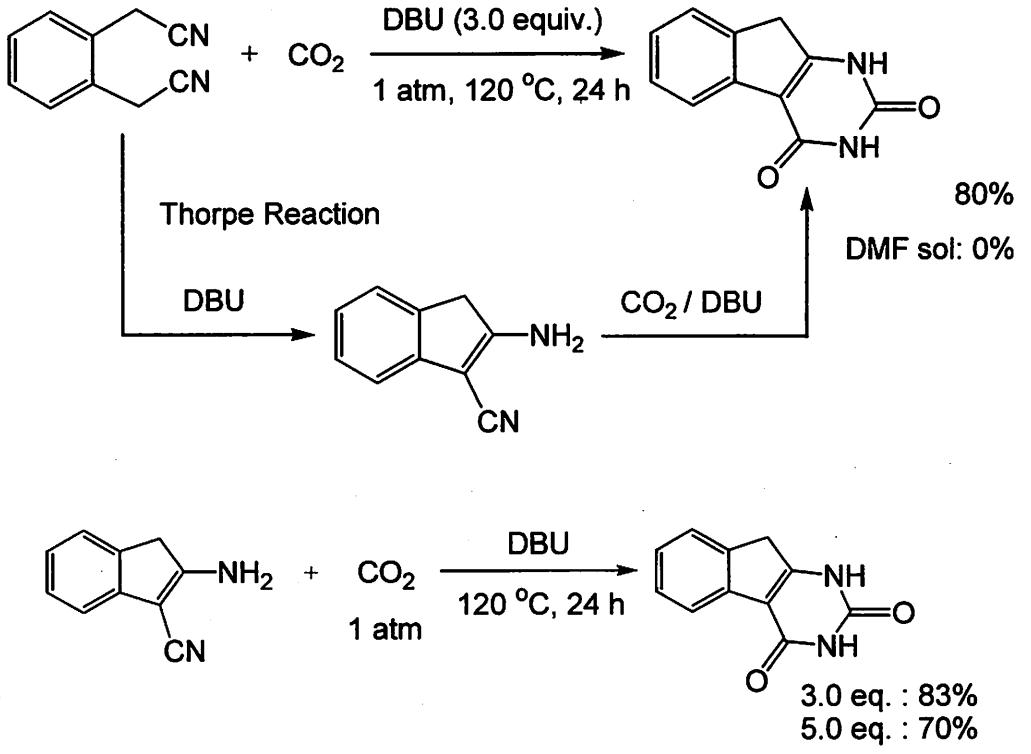
Then, under solvent-free conditions, 1*H*-quinazoline-2,4-diones were afforded in good to excellent yields from 2-aminobenzonitriles with only carbon dioxide (1 atm) and catalytic amount of base (DBU or DBN). For example, 6,7-dimethoxy-1*H*-quinazoline-2,4-dione which is an intermediate of medicines was synthesized successfully in a 97% yield, using 0.2 equiv. of DBU under CO_2 (1 atm) at 120 °C.[2]



Scheme shows a plausible pathway for the formation of 1*H*-quinazoline-2,4-dione from 2-aminobenzonitrile with carbon dioxide aided by catalytic amount of DBU. The carbonylation with carbon dioxide generates a carbamate salt in the presence of catalytic DBU. Then, nucleophilic cyclization followed by rearrangement by the way of isocyanate intermediate affords the final product. In this reaction system, formation of isocyanate intermediate assisted by *o*-cyano group seems to be important.



Next, we also developed heterocycle synthesis with carbon dioxide (1 atm) under solvent-free conditions. Heterocyclic compound (9*H*-indeno[2,1-*d*]pyrimidine-2,4(1*H*,3*H*)-dione) was afforded in good to excellent yields through an intermediate by Thorpe reaction, from *o*-phenylenediacetonitrile with only carbon dioxide (1 atm) and excess amount of base (DBU or DBN) at 120 °C.



References

1) T. Mizuno, T. Iwai, Y. Ishino, *Tetrahedron Lett.*, 2004, **45**, 7073.

2) T. Mizuno, M. Mihara, T. Nakai, T. Iwai, T. Ito, *Synthesis*, 2007, 2524.

1P-05

A One-Pot Procedure for Acetylation or Trifluoroacetylation of Amines Using Acetic Acid or Trifluoroacetic Acid as an Acylating Reagent

Yasuo Kikugawa,* Junpei Otaka, Hiroshi Yamazaki, Naohiro Oshima, and Takeshi Sakamoto
Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan
kikugawa@josai.ac.jp

The acetylation and trifluoroacetylation of amino groups are important fundamental transformations in organic chemistry. A variety of reagents, catalysts, and methods for *N*-acetylation and *N*-trifluoroacetylation have been reported. Most of these, however, have drawbacks and limitations due to either formation of undesirable by-products and/or handling issues on a plant scale. Considering the importance of *N*-acetylation and *N*-trifluoroacetylation in laboratory and industry, an efficient and convenient *N*-acylation method is still desirable. To this end it is evident that the use of acetic acid or trifluoroacetic acid alone is both economically and environmentally advantageous.

In the present study, we have developed an environmentally- and eco-friendly acetylation or trifluoroacetylation method using acetic acid or trifluoroacetic acid as an acetylating reagent.

Acetylation of Amines

The reaction of aniline with acetic acid first appeared in 1912. Müller reported that aniline reacted with acetic acid under reflux removing generated water from the reaction mixture to afford acetanilide in high yield.[1]

We have undertaken the examination of this method and found that anilines were acetylated in acetic acid in high yield without removing generated water during reaction. The results are presented in Table 1.

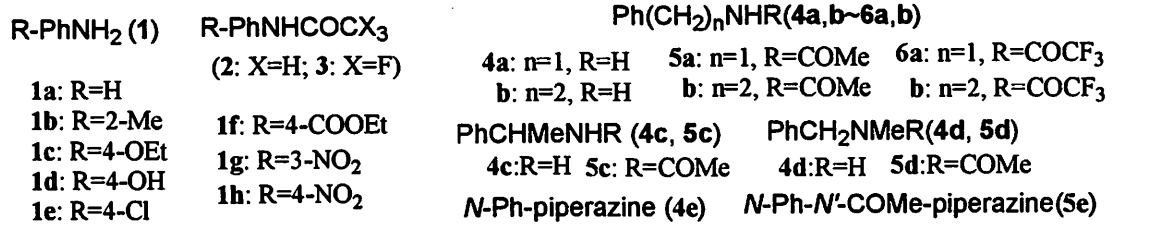


Table 1. Acetylation of arylamines in refluxing AcOH

Starting compound	Reaction time (h)	Product	Yield (%)
1a	6	**2a**	98
1b	3	**2b**	70
1c	5	**2c**	90
1d	8	**2d**	78
1e	3.5	**2e**	94
1f	5	**2f**	87
1g	4	**2g**	85
1h	8	**2h**	87

Table 2. Acetylation of aliphatic amines in refluxing xylene containing AcOH

Starting compound	AcOH mol. eq.	Reaction time (h)	Product	Yield (%)
4a	5	5	**5a**	95
4a	2	4.5	**5a**	93
4b	5	5.5	**5b**	95
4c	5	6	**5c**	91
4d	5	8	**5d**	89
4e	5	8.5	**5e**	86
4e	--*	8.5	**5e**	22*

* Solvent: AcOH alone. See Table 1.

Next, we have applied the method of acetylation of arylamines to acetylate aliphatic amines. However, the reaction proceeded only in poor yields. We examined reaction conditions, and found that when the amount of acetic acid was reduced to 2-5 molar equivalents to an amine in refluxing xylene, the yields were dramatically increased. Acetylation of a wide variety of aliphatic amines was successful without removing water formed in the reaction and gave the desired compounds in good to excellent yields. The results are presented in Table 2.

Trifluoroacetylation of Amines

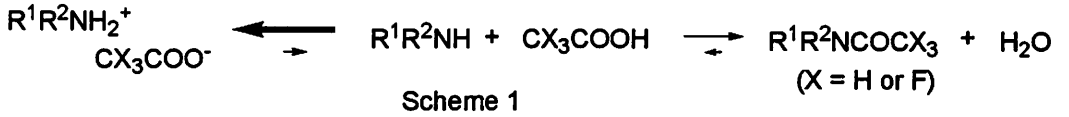
Initially, we examined the trifluoroacetylation of aniline (**1a**) with trifluoroacetic acid (TFA) in various solvents (Et_2O, THF, TFA, toluene, and xylene). The use of large excess of TFA provided the TFA salt of aniline alone. When the amount of TFA was reduce, the yield was dramatically increased.

Table 3. Trifluoroacetylation of amines in refluxing xylene

Starting compound	Method[a]	Reaction time (h)	Product	Yield (%)
4a	A	5.5	**5a**	94(92)[b]
4b	A	7	**5b**	86
4c	A	2	**5c**	68(98)[b]
4d	B	6.5	**5d**	62(95)[b]
4e	A	3	**5e**	92
1f	A	2.5	**5f**	88
1g	A	2	**5g**	94
1h	B	5.5	**5h**	89
4a	A	5	**6a**	(90)[b]
4b	A	5	**6b**	(70)[b]

[a] A: TFA (2 eq) was used. B: TFA (4 eq) was used.
[b] Pyridinium trifluoroacetate was used instead of TFA.

On the basis of these preliminary results, the application of this procedure to various amines was investigated. The results are presented in Table 3. In this case it is worth noting that the presence of electron-withdrawing groups such as nitro, ester, and chloro groups in anilines facilitates the trifluoroacetylation, whereas the electron-releasing group has less an effect. However, use of pyridinium trifluoroacetate instead of TFA improved the yields very much. At high temperature (150 °C), the reaction between TFA and an amine has two routes, one of which is to form a salt by the nucleophilic attack of the amine to the hydrogen and the other is to form an amide by the nucleophilic attack of the amine on the carbonyl carbon. The presence of a free amine and TFA in the reaction mixture is required for trifluoroacetamide formation.



Scheme 1

In excess TFA solution, the concentration of a free amine is reduced because of formation of the TFA salt and this results in less efficient amide formation. Addition of an equimolar amount of pyridine to TFA is effective in the trifluoroacetylation of rather strongly basic anilines which have *p*Ka values similar to pyridine.

Low cost and availability of the reagent, and the ease of operation and workup make this method a useful addition to the available methodologies.

References

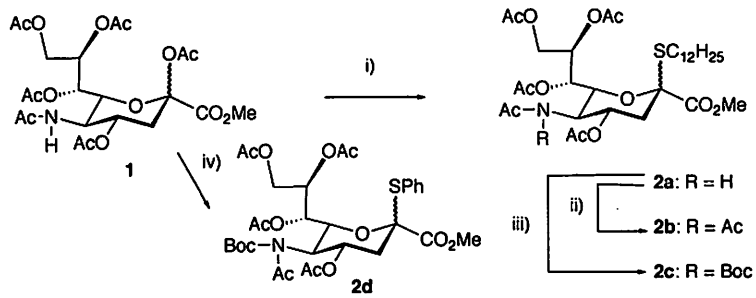
1. Müller, P. *Chemiker-Zeitung* **1912**, *36*, 1049.

1P-06

Highly stereoselective α-*O*-sialylation with *N,N*-Ac,Boc laurylthio sialoside in CPME

Kiyoshi Ikeda,* Keisuke Miyamoto, Masayuki Sato
School of Pharmaceutical Sciences, University of Shizuoka,
52-1 Yada, Suruga-ku, Shizuoka-shi, 422-8526, Japan
ikeda@ys2.u-shizuoka-ken.ac.jp

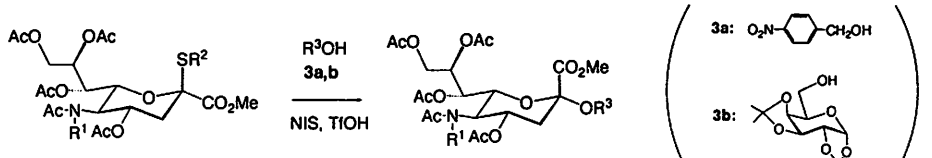
N-Acetylneuraminic acid (sialic acid, Neu5Ac) and its various analogs are critical components of many glycoconjugates involved in biologically important ligand-receptor interactions.[1] The development of an efficient method of *O*-sialylation has been a challenging task in the field of sialic acid chemistry.[2] One important trend focuses on the utilization of the thioglycoside of sialic acids for milder and stereoselective *O*-glycosylation. Matsuoka group reported thioglycoside of sialic acids with a lauryl moiety to avoid the unpleasant odor of thiols employed for thioglycoside formation, and its application to stereo-selective *O*-sialylation.[3] We report the preparation of novel *N,N*-diacyl analogs of sialic acid **2** with a laurylthio moiety and their application to stereoselective *O*-sialylation.[4] As shown in Scheme 1, three laurylthio glycosides with NHAc, NAc_2 and *N,N*-Boc,Ac at the C-5 position (**2a**, **2b** and **2c**, respectively) and a *N,N*-Boc,Ac phenylthio glycoside **2d** were synthesized and tested for their reactivity and α-selectivity in sialylation.



Scheme 1. Reagents and conditions: (i) 1-dodecanethiol, $BF_3 \cdot OEt_2$, CH_2Cl_2, rt, 24 h, 84%; (ii) isopropenyl acetate, PTSA, 65°C, 17 h, 89%; (iii) Boc_2O, DMAP, THF, reflux, 4 h, 99%; (iv) 1) thiophenol, $BF_3 \cdot OEt_2$, CH_2Cl_2, rt, 24 h, 89%, 2) Boc_2O, DMAP, THF, reflux, 20 h, 90%.

The glycosylation between **2b** and 1.5 molar equivalent of **3a** using 3.0 molar equivalent of NIS and 1.0 molar equivalent of TfOH and MS 3 Å in CH_3CN at -40 °C gave the glycoside **4a** in 70% yield (α : β = 1 : 1.8, entry 1). A small increment of α-selectivity of **2c** glycosylation with **3a** was observed (79%, α : β = 1.3 : 1, entry 2). High α-selectivity in condensation of **2c** with **3a** in CPME was observed (85%, α : β = 10 : 1, entry 3). The sialylation of **2a** with **3a** in CPME was nonselective, together with the formation of the 2,3-dehydro glycal derivative (11%, entry 4). The glycosylation of **2d** with **3a** catalyzed by NIS/TfOH in CPME at -40 °C gave **4b** in inferior yield (59%) and α-selectivity (α : β = 6 : 1, entry 5). When the reaction of **2c** with **3b** was carried out in CH_3CN at -40 °C, an increment of α-selectivity was observed (62%, α : β = 2.2 : 1, entry 6). The sialylation of **2c** with **3b** in CPME at -40 °C showed remarkable improvement in both the glycosylation yield (quantitative) and α-selectivity (only α-anomer, entry 7). Coupling of **2a** with **3b** in CPME at -40 °C resulted in the formation of **4e** with 77% (α : β = 1.9 : 1, entry 8).

Table 1. Glycosylation reaction with C-5 *N*-protected sialic acid derivatives **2a-d**

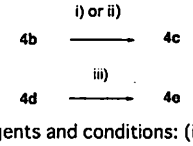


2a (R^1= H, R^2 = $C_{12}H_{25}$), 2b (R^1= Ac, R^2 = $C_{12}H_{25}$)
2c (R^1= Boc, R^2 = $C_{12}H_{25}$), 2d (R^1= Boc, R^2 = Ph)

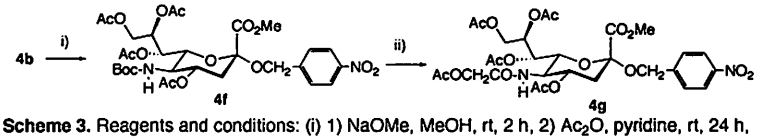
4a-e: R^1 = H, Ac, Boc

Entry	Glycosyl donor 2	Glycosyl acceptor 3	Condition	Product 4	Yield % (α/β ratio)
1	2b	3a	CH_3CN, -40 °C	4a	70 (1 : 1.8)
2	2c	3a	CH_3CN, -40 °C	4b	79 (1.3 : 1)
3	2c	3a	CPME, -40 °C	4b	85 (10 : 1)
4	2a	3a	CPME, -40 °C	4c	77 (1 : 1)
5	2d	3a	CPME, -40 °C	4b	59 (6 : 1)
6	2c	3b	CH_3CN, -40 °C	4d	62 (2.2 : 1)
7	2c	3b	CPME, -40 °C	4d	quant. (α only)
8	2a	3b	CPME, -40 °C	4e	77 (1.9 : 1)

Removal of the *N*-Boc group of **4b** with $Yb(OTf)_3$-SiO_2 or TFA-CH_2Cl_2 gave **4c** in 84% or 96% yield, respectively. Deprotection of the *N*-Boc group of **4d** with $Yb(OTf)_3$-SiO_2 smoothly proceeded to give the *N*-Ac sialoside **4e** in 81% yield (Scheme 2). Transformation of *N,N*-Ac,Boc group of **4b** into an *N*-glycolyl group was easily performed via selective *N*-deacetylation of the Ac-*N*-Boc carbamate, followed by subsequent Boc group removal of **4f**, and reacylation to give **4g** (Scheme 3).



Scheme 2. Reagents and conditions: (i) $Yb(OTf)_3$-SiO_2, rt, 48 h, 84%; (ii) TFA-CH_2Cl_2 (1 : 4), rt, 1 h, 96%; (iii) $Yb(OTf)_3$-SiO_2, rt, 48 h, 81%.



Scheme 3. Reagents and conditions: (i) 1) NaOMe, MeOH, rt, 2 h, 2) Ac_2O, pyridine, rt, 24 h, 75% over two steps; (ii) 1) TFA-CH_2Cl_2 (1 : 4), rt, 1 h; 2) $AcOCH_2COCl$, pyridine, rt, 24 h, 90% over two steps.

In summary, the combination of the 5-*N*-Boc group of laurylthio sialoside **2c** and CPME as a solvent enhanced the reactivity and α-selectivity of the sialyl donor during sialylation. We are currently applying this methodology to the synthesis of other oligosaccharides.

1. Rosenberg, A. *Biology of Sialic Acids*; Plenum: New York, London, 1995.
2. Boons, G.-J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539.
3. Matsuoka, K. *et al.*, *Tetrahedron Lett.* **2004**, *45*, 9383.
4. Ikeda, K. *et al.*, *Tetrahedron Lett.* **2007**, *48*, 7431.

1P-07

Properties of diol type silica in chromatography separation

Kazunori Nobuhara, Mitsuhiro Kamimura, Takako Inoue, Makoto Kawai, Ryuji Orii
Fuji-Silysia Chemical Co., Ltd.
2-1846 Kozoji-ch,o kasugai-shi, Aichi 487-0013,Japan
nobuhara@fuji-silysia.co.jp

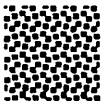
Surface modification of silica has been attempted to acquire unique adsorption property. Also, it has been developed a technique to introduce hydroxyl bond on silica surface [1]; however, diol type silica was not widespread in chromatography field because a small advantage was found. We reviewed the production process and characteristics of diol silica and found out unique properties which ordinary silica doesn't have at normal phase chromatography.

(Surface characteristics of diol silica)

Si-O-Si-C3H6-O-CH2-CH-CH2 (Nuetral)
OH OH

Alcoholic hydroxyl(C-OH) without ionicity exsist on silica surface.
Mild hydrogen bond occur on the surface.

(Surface characteristics of silica gel)



Si-O-H
Si-O-H (Acid) Si-O^{-} ◀···▶ N^{+}<

Ionic adsorption between silanol bond and amine

Silanol bonds on silica surface are polarized and indicate high hydrogen-bonding. Also, acidic characteristics show ionic strong adsorption against basic compounds.

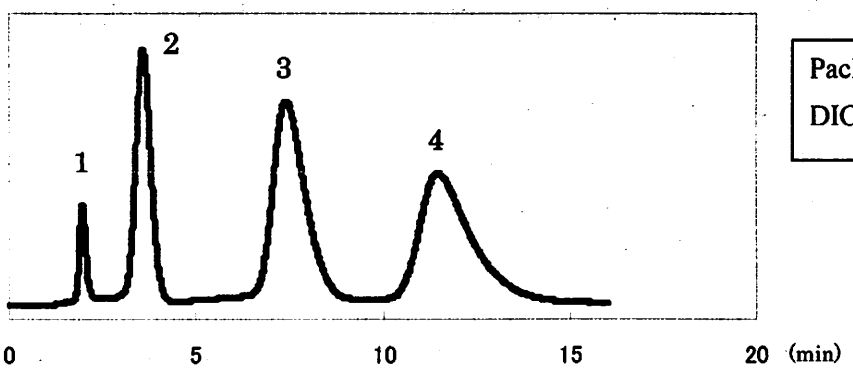
The figure1-3 show the chromatograms of standard substances by diol silica, silica gel and NH silica. The results of separation by Diol silica are excellent separation in spite of neutral, acidic, and basic compounds. On the other hands, pyridine of basic compound cannot be eluted by silica gel and, phenol of acid compound cannot be eluted by NH silica.

(Conditions)

Column	: Cartridge Size 60 (28x100mm)
Mobile phase	: 10% ethyl acetate/n-hexane(w/w)
Flow rate	: 28ml/min
Detector	: UV254nm 0.32aufs

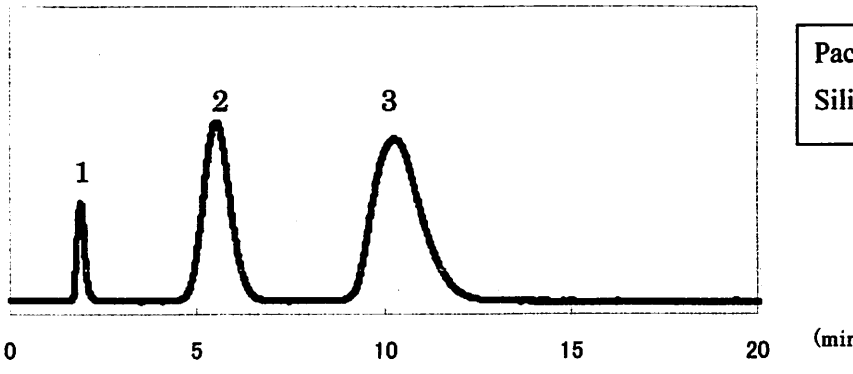
Samples

1. Benzen	(to)
2. Dibutyl phthalate	(neutral compound)
3. Phenol	(acidic compound)
4. Pyridine	(basic compound)



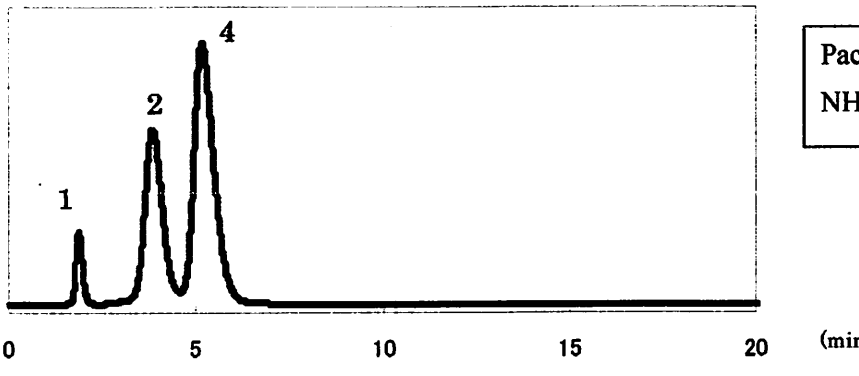
Packing media :
DIOL 40-75 micron

Fig.1



Packing media :
Silica gel 40-75 micron

Fig.2



Packing media :
NH silica 40-75 micron

Fig.3

Diol silica can be applied normal phase chromatography and has following unique properties compared with ordinary silica gel.

Silica gel :**Si-OH (Silanol bond)** strong adsorption, minus charge

Diol silica :**C-OH (Alcoholic hydroxyl)** mild adsorption, neutral charge

1. Same separation property as silica gel with weaker polar character at normal phase.
2. Specific strong adsorption property against phenolic compounds.
3. No strong adsorption property like a silica gel and superior separation property to basic compounds.

Refrence

(1) 'Porous Silica' K.K.Unger Elsevier Scientific Publishing Company (1979)

1P-08

Recycle effect on Mass-Transfer Efficiency Improvement in Multi-Pass Mass Exchangers

Chii-Dong Ho,* Jr-Wei Tu
Department of Chemical and Materials Engineering, Tamkang University
151 Ying-Chuan Road, Tamsui, Taipei 25137, Taiwan
cdho@mail.tku.edu.tw

The mass transfer phenomena of a multi-pass mass exchanger with three permeable membranes inserted was investigated theoretically in this study. An external recycle operation was also applied to the multi-pass mass exchanger to improve the mass transfer efficiency of device. The theoretical formulation was developed based on mass balance and the analytical solutions were obtained by using the orthogonal expansion technique and the eigenfunction expanding in power series. Compared to the single-pass devices without membrane inserted and external recycle, the theoretical results showed that the considerable mass-transfer efficiency improvement can be obtained while the recycle ratio and channel thickness ratio are suitably selected under the operating conditions of interest.

The working dimensions of the multi-pass exchanger are thickness W, length L, and width B ($>>W$), the thickness of four subchannels a, b, c and d are W_a, W_b, W_c and W_d, respectively, and the subchannel thickness ratio are $b_{ab} = W_a/W_b$ and $b_{dc} = W_d/W_c$. The inserting membranes are the ideal membranes and the solute can diffuse freely through the membrane. This mass transfer problem of multistream systems is so-called conjugated Graetz problems. The theoretical model of the multi-pass mass exchanger is developed by the following assumptions: constant physical properties of fluid, negligible end effects and axial diffusion effects, and no concentration polarization on the permeable membranes. The theoretical concentration distributions can be solved by using the orthogonal expansion technique and the eigenfunction expanding in power series. The mass-transfer efficiency of the multi-pass mass exchanger with external recycle can be expressed by the average Sherwood number.

The calculating results of the outlet concentration and average Sherwood numbers and are illustrated in this study The results show that both the outlet concentration and the average Sherwood numbers increase with increasing the mass-transfer Greatz number, Gz_m, and with decreasing the subchannel thickness ratio and recycle ratio. Comparing to the single-pass devices, the membrane-inserted multi-pass mass exchangers with recycle perform higher mass-transfer efficiency. In a conclusion, the mass transfer efficiency of a mass exchanger can be improved by introducing the recycle operation and inserting the membranes.

1P-09

Molecular Sieves Supported Pd Catalyst (Pd/MS5A) for Chemoselective Hydrogenation

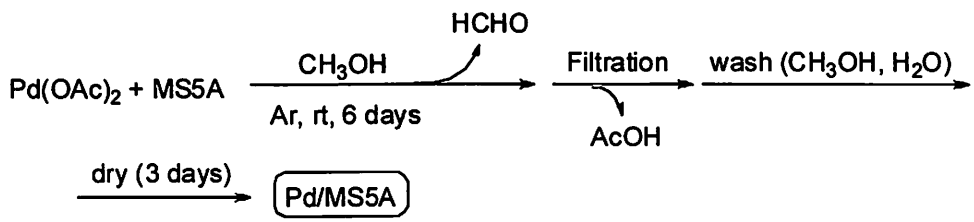
Tomohiro Maegawa,* Masatsugu Katoh, Ayako Tani, Tohru Takahashi, Yasunari Monguchi, Hironao Sajiki
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University.
5-6-1 Mitahora-higashi, Gifu, 502-8585, Japan
maegawa@gifu-pu.ac.jp

Introduction

A number of heterogeneous catalysts supported by synthetic polymer, activated carbon, silica gel or alumina are widely utilized in a variety of fields. Palladium on charcoal (Pd/C) is one of the most useful heterogeneous catalysts, especially for the hydrogenation of diverse organic compounds by some advantages such as ready availability, ease of storage and handling and reusability. The inhomogeneous nature is however, problem of activated carbon made from naturally-derived peat or sawdust and it might cause the difference of the catalyst activity of Pd/C. It is important to develop novel, reproducible and heterogeneous Pd catalysts supported by artificial materials possessing constant quality. Therefore, we chose the zeolite as the support for the heterogeneous Pd catalyst. Molecular sieves, a kind of zeolites possessing microporous structure, are used as dehydrating reagent and it can also absorb small molecules such as Pd nanoparticles. Therefore we planed to prepare the zeolite supported Pd catalyst which would be expected to play the hydrogenation catalyst as well as the small cage and reaction field for the reaction.

Experimental result

We have already developed the fibroin (silk protein) supported Pd catalyst (Pd/Fib) for the chemoselective hydrogenation. To prepare the zeolite supported Pd catalyst, we employed the similar procedure to the preparation of Pd/Fib (Scheme 1). The solution of $Pd(OAc)_2$ and molecular sieve 5Å (MS 5A) in CH_3OH was stirred at room temperature for 6 days then filtered and washed with CH_3OH and H_2O. Drying the collected gray solid in vacuo for 3 days afforded the 5% Pd/MS5A catalyst.



Scheme 1. Preparation of Pd/MS5A

We first conducted the hydrogenation of 2-benzyloxy-2'-propenylbenzene (Table 1, Entry 1) to examine

the catalyst activity of 5% Pd/MS5A. Consequently, the chemoselective hydrogenation proceeded and only the alkene was reduced remaining the benzyl ether under the conditions. To develop the 5% Pd/MS5A as a chemoselective hydrogenation catalyst, we examined the hydrogenation of various substrates. The reducible functionalities under the Pd/C catalyzed hydrogenation conditions such as benzyl ether, benzyl ester, *N*-Cbz, aromatic carbonyl and so on, are torelant for the 5% Pd/MS5A catalyzed hydrogenation conditions. Only less-hindered alkene, alkyne and azide functionalities are reduced under the conditions. Surprisingly, nitro group remain intact (Table 1, Entry 6) while it is well-known that the nitro group is highly susceptible to the hydrogenation. Since nitro compounds can be widely utilized as row materials of pharmaceuticals and pesticides, it is important to develop the hydrogenation method of the other reducible functional groups in the presence of a nitro group. When substrate containing a nitro group was hydrogenated under 5% Pd/MS5A-catalyzed conditions, the only alkene and alkyne functionalities were smoothly reduced without affecting the nitro group (Table 2). Further application of the 5% Pd/MS5A catalyst to the hydrogenation of diverse substrates and the structural and physical characterizations of the catalyst are in progress.

Table 1. 5% MS5A catalyzed hydrogenation

Substrate —(5% Pd/MS5A (10 wt %); H_2, CH_3OH, rt, 24 h)→ Product

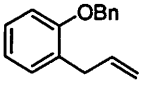
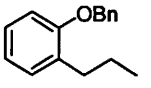
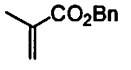
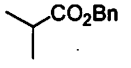
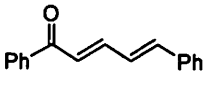
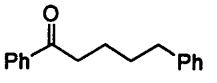
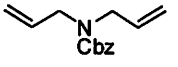
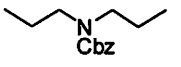
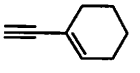
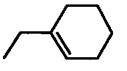
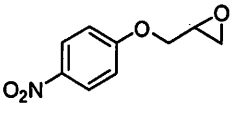
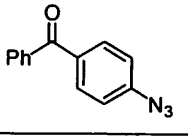
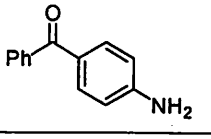
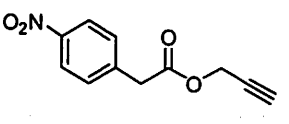
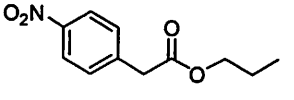
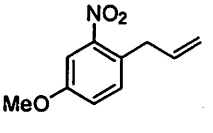
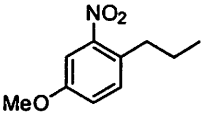
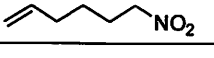
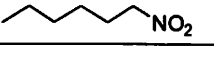
Entry	Substrate	Product	Yield (%)
1			99
2			95
3			100
4			100
5			100
6		recovery	95
7			75

Table 2. 5% Pd/MS5A catalyzed hydrogenation with the substrate with nitro group

Substrate —(5% Pd/MS5A (10 wt %); H_2, CH_3OH, rt, 24 h)→ Product

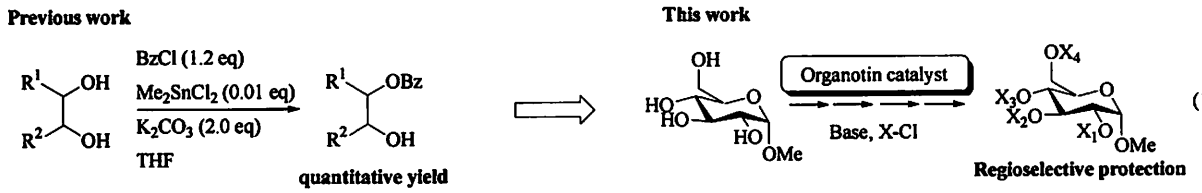
Entry	Substrate	Product	Yield (%)
1			94
2			92
3			100

1P-10

Regioselective protection of sugars catalyzed by organotin

*Yuki Kubo, Yosuke Demizu, Osamu Onomura
Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan
onomura@nagasaki-u.ac.jp

Modified sugars are biologically important, and widely used in medicinal, pharmaceutical, and agricultural chemistry. Since their preparation from easily available sugars needs tedious protection and deprotection of several hydroxyl groups, it is worthwhile to develop versatile tool for the regioselective protection of their hydroxyl groups. Last year, Hung[1] reported one-pot protection of carbohydrates, and Kawabata[2] exploited a catalytic one-step process for regioselective acylation of β-glcopyranoside. In the case of both methods, there is some limitation of substrates. On the other hand, we have reported the selective monobenzoylation of 1,2-diols using organotin catalyst.[3] This catalytic system is based on the concept that a coordination of 1,2-diols with tin ion might form an activated five-membered intermediate in which the coordinated hydroxyl group is much activated than those of un-coordinated ones and the monobenzoylated products were obtained with high efficiency. We wish to present herein the application of this catalytic system to the regioselective continuous protection of several α- and β-pyranosides.



First, we tried monobenzoylation of methyl α-glucopyranoside **1a** using Me_2SnCl_2 (0.05 eq) as a catalyst, DIPEA (2.0 eq) as a base, and BzCl (1.2 eq) (Eq. 2). As a result, 2-*O*-benzoylated compound **2a** was regioselectively obtained in 82 % yield.

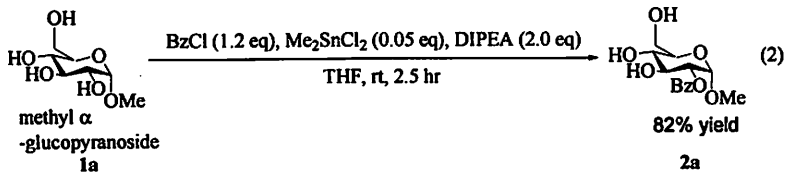


Table 1 summarizes the monobenzoylation of several methyl α- and β-pyranosides **1b-f** (Eq. 3). Methyl β-glucopyranoside **1b** was monobenzoylated at the 6-position in 79 % yield (entry1), while methyl α-galactopyranoside **1c**, β-galactopyranoside **1d**, and methyl α-mannopyranoside **1e** were protected at the 3-position (entries 2 and 3). Monobenzoylation of methyl β-xylopyranoside **1f** occured at the 4-position to give **2f** in 68 % yield (entry 4).

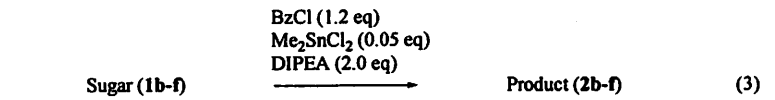
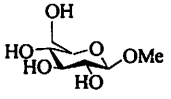
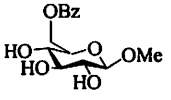
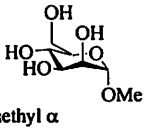
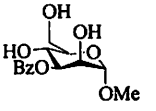
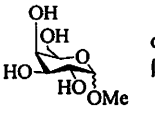
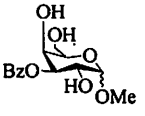
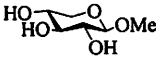
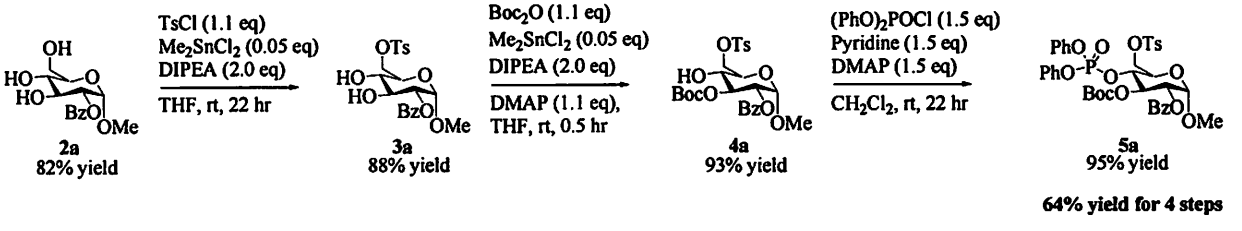


Table 1.

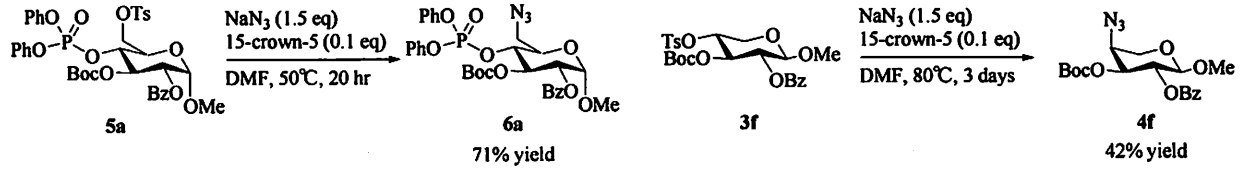
Entry	Sugar		Product	Yield	Entry	Sugar		Product	Yield
1	 methyl β -glucopyranoside	1b		2b 79%	3	 methyl α -mannopyranoside	1e		2e 97%
2	 methyl α- or β- -galactopyranoside	α: 1c β: 1d		2c α : 84% 2d β : 78%	4	 methyl β -xylopyranoside	1f		2f 68%

Next, the differential protection of 2-*O*-benzoylated **2a** were done stepwise catalyzed by Me_2SnCl_2 as follows (Eq. 4). Namely, **2a** was regioselectively tosylated to afford 6-*O*-tosylated **3a** in 88 % yield, then transformed into 3-*O*-*tert*-butoxycarbonylated **4a** in 93 %, and finally 4-*O*-(diphenyl)phosphated **5a** was obtained in 95 % yield. Total yield for 4 steps was 64%.



(4)

Conveniently, compounds **5a** and **3f** have tosyloxy substituent which is a good leaving group. The reaction with NaN_3 through S_N2 mechanism proceeded smoothly to give the azides **6a** and **4f** with moderate to good yield (Eq. 5).



(5)

In summary, we have accomplished the regioselective protection of several α- and β-pyranosides with high regioselectivity. Details will be presented during the poster session.

References

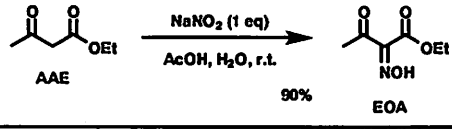
1) S.-C. Hung, *et al.*, *Nature*, **2007**, *446*, 896-899.
2) T. Kawabata, *et al*, *J. Am. Chem. Soc.* **2007**, *129*, 12890-12895.
3) Y. Matsumura, *et al*, *Tetrahedron Lett.* **1998**, *39*, 5601-5604.

1P-11

Process Development Using Automated Reactor
- Kinetics of Nitroso Reaction -

Takashi Naka,* Yasunari Takayasu and Hiroshi Iwamura
Process Chemistry Research Department, Mitsubishi Tanabe Pharma Corporation
14, Sunayama, Kamisu, Ibaraki 314-0255, Japan
Naka.Takashi@md.mt-pharma.co.jp

Nitroso derivative of ethyl acetoacetate is the important intermediate for the syntheses of nitrogen containing compounds. However, safety issue related to the thermal stability of the nitroso compound is envisaged. Herein we report the process development of nitrosation of ehyl acetoacetate (AAE) using several kinds of automated reactors in the reaction enthalpy point of view.

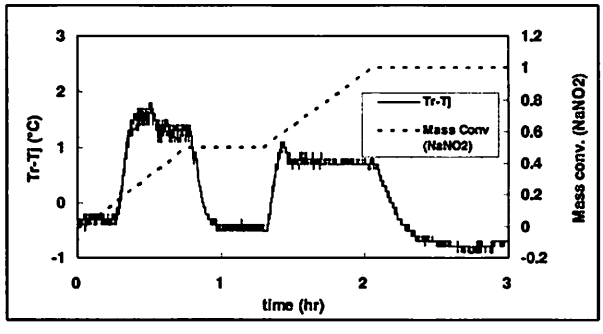


Item	AAE	EOA
DSC	Onset Temp. : 147 ℃ ΔH : 45 J / g	Onset Temp. : 144 ℃ ΔH : 1285 J / g

1. Advantage 2410™ experiment[1)]

Advantage 2410™ is useful for the reaction screening with parallel tube (2-10 mL). Tr (°C) and Tj (°C) can be recorded during the reaction. Nitrosation of AAE was fairly clean and the addition of $NaNO_2$ aqueous solution was exothermic (Figure 1). Furthermore, heat evolution could be controlled with $NaNO_2$ supply.

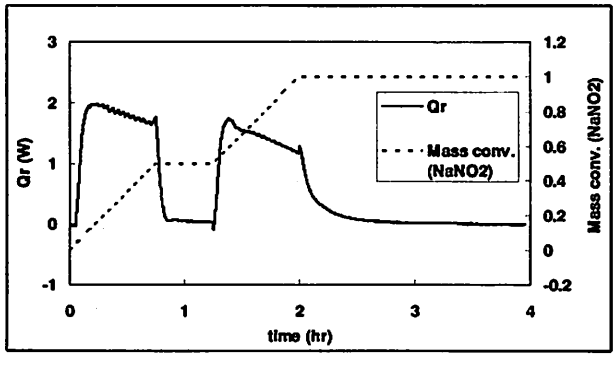
Figure 1. Advantage 2410™ experiment



2. Multi Max™ experiment[2)]

Multi Max™ is useful for the reaction optimization with parallel reactor (20-50 mL). Tr (°C), Tj (°C) can be recorded during the reaction. U•A (W/K) can also be estimated. No significant residual reaction enthalpy was observed (Figure 2). Approximate reaction enthalpy was determined to be 138 kJ / mol (AAE). On the basis of constant specific heat capacity, the adiabatic temperature rise was estimated at 244 K. These results required more detailed safety assessment because thermal stability tests about the product (EOA) indicated a self-heating exotherm onset at 144 °C.

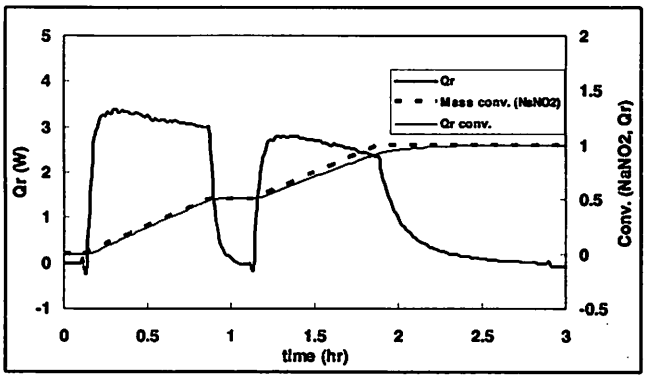
Figure 2. Multi Max™ experiment



3. RC1 ™ experiment[2)]

RC1™ is useful for the accurate measurement of reaction calorimetry. Tr (°C), Tj (°C) can be recorded during the reaction. U•A (W/K) and Cpr (J/kg•K) can also be estimated. The reaction enthalpy was determined to be 127 kJ / mol (AAE) (Figure 3). On the basis of an experimental determination of specific heat capacity, the adiabatic temperature rise was observed at 221 K.

Figure 3. RC1™ experiment



4. Super CRC™ experiment[3)]

Reaction rate and kinetic parameter were estimated using Super CRC™ for the purpose of safety evaluation (Figure 4). The Arrhenius plot suggested the reaction rate dependency on the reaction temperature (Figure 5). These results suggested the reaction rate of nitrosation could be controlled under the operation conditions.

Figure 4. Super CRC™ experiment

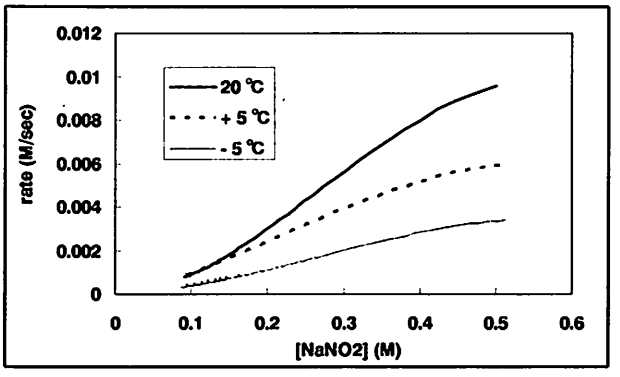
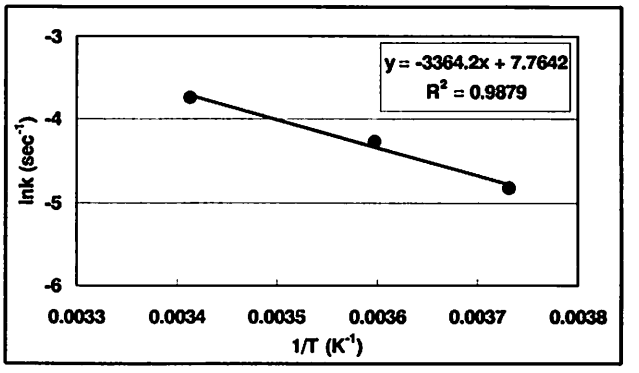


Figure 5. Arrhenius plot of nitrosation



In summary, we have reported the process development of nitrosation using automated reactors. The reaction screening including exothermic behavior was performed. The approximate and the accurate reaction enthalpy were determined. The kinetic analyses for the safety evaluation were performed. Essential and detailed sets of data on nitrosation were collected and the process for a large scale manufacturing was established.

References

1) Advantage 2410 ™ is available from Biotage. http://www.biotage.com

2) Multi Max ™ and RC1 ™ are available from Mettler Toredo. http://www.mt.com

3) Super CRC™ is available from Omnical Technology Inc. http://www.omnicaltech.com

1P-12

Change in neuron aggregation and neurite fasciculation on EVAL membranes modified with different diamines

Tai-Horng Young
Manufacturing Technology Research Laboratories, Chemical Development Dept., Shionogi & Co., Ltd.
Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan
thyoung@ntu.edu.tw

Abstract

In the present study, we modified poly (ethylene-co-vinyl alcohol) (EVAL) membranes by the covalent bonding of diamine via epoxidation of surface hydroxyl groups to analyze the effect of grafted diamine with different carbon-chain length on the cultured cerebellar granule neurons. Morphological studies showed neurons seeded on the diamine-immobilized EVAL membrane were able to survive and regenerate with formation of an extensive neuritic network. Furthermore, cultured neurons showed that the presence of diamine with different carbon-chain length was capable of providing a magic environment to effectively regulate the neuron development, but mediated neuronal activity with equal efficacy. The short-chain amine stimulated neuron aggregation and neurite fasciculation, whereas the long carbon-chain diamine maintained single neuron distribution with the defasciculated feature of the neurite. Although it is known that positively charged amine molecules can interact directly with cell surface proteoglycans to mediate cell attachment, this study further demonstrated that the terminal primary amine with different carbon-chain length is involved in mediating cellular response to regulate neuron migration and guidance of neurite growth pattern. This indicates a delicate interaction of neuron with the immobilized diamine molecules on the EVAL membrane surface.

Results and Discussion

It is well documented that the physical and chemical characteristics of biomaterial surface govern cellular responses and ultimately affect the success of tissue engineering applications. For neuron cells, amine-containing materials are known to play a role in neuronal survival by ionic interactions between specific positively charged domains and negatively charged sulfate and carboxylate groups of the cell surface proteoglycans [1,2]. The objective of the present study was to determine whether amine bonded to different carbon-chain length have different influences on neuronal behavior *in vitro*. This was achieved by immobilizing different chain-length diamines on the EVAL membrane. These prepared membranes appeared similar surface morphologies and contact angles as determined by comprehensive surface investigation.

First, five amines affected the neuronal activity in a similar manner. However, small

alterations in chain length resulted in obvious changes in neuron aggregation and neurite outgrowth pattern. Cells cultured on EVAL membranes modified with shorter carbon-chain diamines showed a greater tendency to aggregate, reflecting the influence of substrate on cell migration. Conversely, EVAL membranes modified with long carbon-chain diamine such as 1,6-diaminohexane allowed cells to adhere more firmly than other membranes. Phase contrast images showed that only non-aggregated distribution and defasciculated pattern were on membranes during the culture period. Such phenomena were not attributable to differences in the surface morphologies and hydrophobic effects of modified substrates, since all prepared membranes exhibited the dense structure with similar contact angles. Thus, it is likely not only terminal primary amine itself, but also the carbon-chain length of diamine act directly on the neuron and neurite migration in some way.

In summary, neuronal response to the terminal primary amines can be affected by subtle changes in carbon-chain length. It is not clear why carbon-chain length can govern their cell response now. However, our results showed neurons are more likely to attach firmly to EVAL membranes immobilized with long carbon-chain diamine. It is reasonable to assume that neurons form aggregates on EVAL membranes modified with short carbon-chain diamines via migration after close intercellular contact can be reached. Acheson et al hypothesized that a balance between the interactions of cell-substrate and cell-cell plays a key role in determining cell migration [3]. When neurons are seeded on the low neuron-adhesive surface, dominance of cell-cell interaction results in cell aggregation since the cell-substrate interaction is too low to obstruct cell migration. Therefore, the substrate surface facilitates neuron migration and neuron aggregation is enhanced. Similarly, changes in the degree of fasciculation also reflect a shift in the balance between these two competing forces. Decrease of neurite-substrate interaction results in neurite migration to produce thicker fascicles. Conversely, enhancement of cell-substrate interaction makes neuron migration and aggregation more difficult. Thus, the increased presence of methylene groups are assumed to increase the flexibility of immobilized diamine, and in turn the positively charged amines are easier to interact with cell surface proteoglycans, which may account for the observed overall inhibition in neuron and neurite migration on the modified EVAL membranes.

References

1. Harada J, Sugimoto M, Brain Res 1997; 753: 251-259.
2. Abe K, Chu PJ, Shirahata A, Samejima K, Saito H, Brain Res 1997; 766: 281-284.
3. Acheson A, Sunshine JL, Rutishauser U, J Cell Biol 1991; 114: 143-153.

1P-13

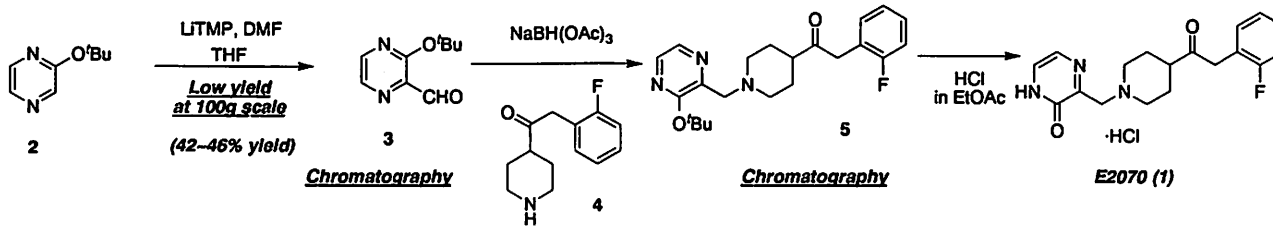
Process Development of a Novel Na-Ion Channel Blocker E2070

Manabu Kubota*, Atsushi Kamada, Ken Furukawa, Hiroshi Kuroda, Mamoru Miyazawa, Yuichi Kimoto, and Naoyuki Shimomura
API Research Laboratories, Eisai Co., Ltd.
22-Sunayama, Kamisu-shi, Ibaraki, 314-0255, Japan
m-kubota@hhc.eisai.co.jp

Introduction:

E2070 (1) is being developed as a novel Na-ion channel blocker for the treatment of pain associated with diabetic neuropathy and post-herpetic neuralgia. Medicinal synthetic route of E2070 (1) is shown in Scheme 1. In this route, 1) improvement of formylation step, and 2) elimination of two column chromatography purifications were considered as critical subjects for process development.

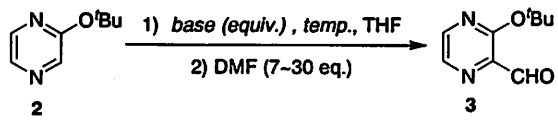
Scheme 1. Medicinal Synthetic Route of E2070 (1)



Results and Discussion:

Since LiTMP mediated formylation gave low total mass recovery (Table 1, entry 1), we assumed that the instability of pyrazine anion generated from LiTMP was issue. Then we applied magnesium reagents which had been reported as strong base (Table 1, entry 2, 3).[1), 2)] An initial attempt using Hauser's reagent revealed that excess equivalent was required to obtain moderate yield (Table 1, entry 2). This indicated a possibility of the existence of active species in Hauser's reagent by Schlenk-like equilibrium (Figure 1).

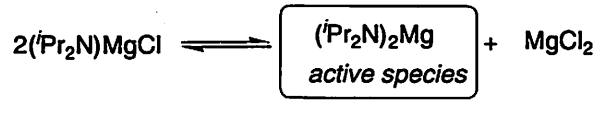
Table 1. Comparison between LiTMP and Magnesium reagents



entry	base	equiv.	temp (°C)	yield of 3 (%)	yield of 2 (%)
1	LiTMP	1.2	-78	59%	23%
2	$(^iPr_2N)MgCl$[2)]	6	-12	67%	-[1)]
3	$(^iPr_2N)_2Mg$	3	-20	70%	16%
4	$(^iPr_2N)MgBu$	2	-20	84%	11%

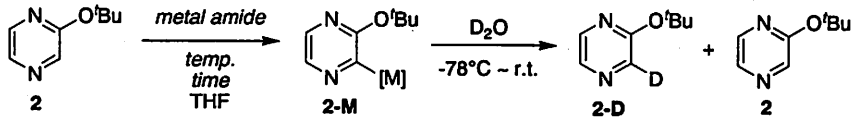
1) No data 2) Hauset's reagent

Figure 1 Schlenk-like equilibrium hypothesis



Based on the hypothesis, we applied $(^iPr_2N)_2Mg$ for D_2O quenching experiment to check anion formation (Table 2). As expected, 3 equivalent of $(^iPr_2N)_2Mg$ gave 77% D-incorporation (Table 2, entry 2). We speculated that the insufficient incorporation was due to protonation by diisopropylamine regenerated by deprotonation. In order to solve this issue, $(^iPr_2N)MgBu$ was designed, in which the Bu group was expected to work as a scavenger of diisopropylamine. This magnesium monoamide reagent afforded 85% of D-incorporation with 2 equivalent (Table 2, entry 3). The results of formylation reaction (Table 1, entry 3, 4) well reflected the results of these D_2O quenching experiments.

Table 2. Study of Anion Formation by D_2O Quenching Experiment

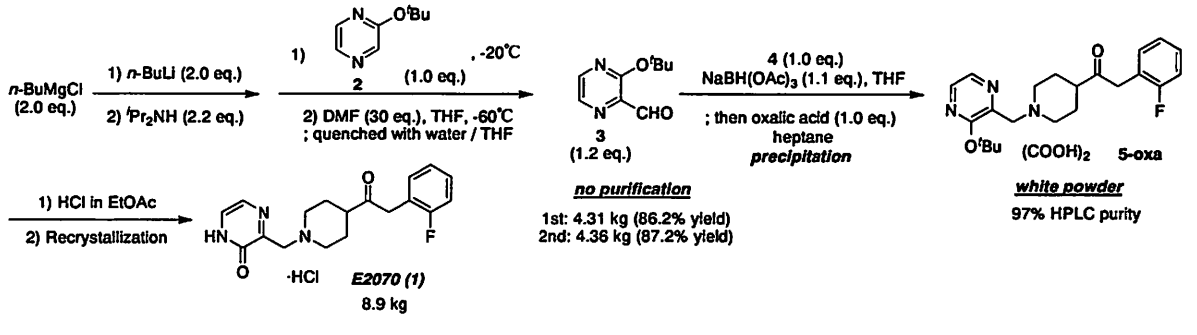


entry	metal amide	equiv.	temp (°C)	time (h)	D-conv. (%)[1)]	2 + 2-D (%)[2)]
1	LiTMP	3	-50	1.5	-	58%
2	$(^iPr_2N)_2Mg$	3	-20	2.0	77%	99%
3	$(^iPr_2N)MgBu$	2	-20	14	85%	97%

1) Determined by *1H*-NMR analysis
2) Determined by GC analysis. The yield of **2+2-D** reflects the stability of **2-M**

Using $(^iPr_2N)MgBu$ which was prepared from Bu_2Mg, we succeeded in developing new and practical formylation process (Scheme 2).[3)] *To the best of our knowledge, this was the first example of the magnesium monoamide being applied to direct anion formation of hetero aromatic compounds.* Additionally, elimination of two chromatographic steps was also achieved as results of the improvement of the formylation step and the successful isolation of **5** as oxalic acid salt with excellent purity. The detail of the process development will be introduced in the poster session.

Scheme 2. Procedure for pilot manufacturing of **4**



References:

1. Review; Knochel, P et al Angew. Chem. Int. Ed. 2003, 42(36), 4302 and references cited therein.
2. (a) Eaton, P. E. et al *J. Am. Chem. Soc.*, **1989**, *111*, 8016 (b) Schleckler, W. et al *J. Org. Chem.* **1995**, *60*, 8414 (c) Shilai, M.; Kondo, Y. et al *J. Chem. Soc., Perkin Trans 1*, **2001**, 442-444
3. A. Kamada, M. Kubota, PCT int. Appl. WO 05/030714, 2005.

1P-14

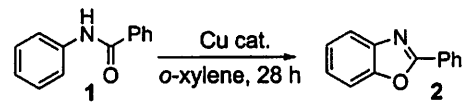
Copper-Catalyzed C–H Activation/C–O Bond Formation for the Synthesis of Benzoxazoles

*Satoshi Ueda, Hideko Nagasawa
Laboratory of Medicinal and Pharmaceutical Chemistry, Gifu Pharmaceutical University
5-6-1, Mitahora-higashi, Gifu, 502-8585, Japan
sueda@gifu-pu.ac.jp, hnagasawa@gifu-pu.ac.jp

Over the past decades, transition-metal catalyzed intramolecular C–N/O bond forming reaction has proven to be an integral process for the formation of C–N/O linkages in the synthesis of heterocyclic compounds.[1] While the reaction provides desirable products by coupling of an aryl or vinyl halides with an N/O nucleophiles with extrusion of the hydrohalic acid, the overall process requires prehalogenation step. A potentially more efficient process would involve oxidative coupling of an unfunctionalized arene directly with N/O nucleophiles, thus obviating the necessity for prehalogenation of the substrate. We paid attention to the fact that aminoacyl group served as directing group in several *ortho* C–H functionalization of anilides, and envisaged that, benzoxazoles could be produced via *ortho* C–H bond activation and subsequent intramolecular coupling with amide oxygen of the anilides.

In order to examine the feasibility of the intramolecular oxidative C–O coupling, we first examined the reaction of benzanilide **1a**. After screening of a range of transition-metal sources, solvents and temperature, we found that the reaction occured in *o*-xylene in the presence of $Cu(OTf)_2$ (20 mol%) at 140 °C under an atmosphere of air to provided 2-phenylbenzoxazole **2a** in 39% yield (Table 1, entry 1). Higher reaction temperatures could increase yield (entry 2). Further investigations revealed that the desired benzoxazole could be obtained in 81% yield under O_2 atmosphere at 140 °C (entry 3). When the amount of the catalyst was reduced to 10 mol% under the O_2 condition, yield was dropped to 50% (entry 4). Modification of copper source had great influence on the reaction outcome. The reaction could proceed with the use of Cu(OTf), $Cu(OAc)_2$ or $Cu(ClO_4)_2$, albeit with lower yield (entries 5-7). On the other hand, $CuCl_2$ or $CuBr_2$ did not afford any desired product, small amount of *o*-halogenated product was detected instead (entries 8-9). Substituent diversity was achieved using the optimized reaction condition (Table 2). The reaction of benzanilides with electron-donating alkyl or alkoxy group at the *meta* or *para* position gave the corresponding benzoxazoles in high yield (Table 2, entries 1-2 and 9-10). Sterically demanding ortho substituted substrates provided the corresponding benzoxazoles in

Table 1. Copper-catalyzed cyclization of *N*-phenylbenzamide



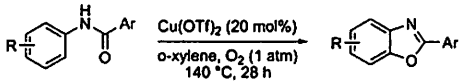
Entry	Cu catalyst (mol%)	Temp (°C)	Gas (1 atm)	Yield (%)[a]
1	$Cu(OTf)_2$ (20)	140	Air	39
2	$Cu(OTf)_2$ (20)	160	Air	89[b]
3	$Cu(OTf)_2$ (20)	140	O_2	81
4	$Cu(OTf)_2$ (10)	140	O_2	50
5	Cu(OTf) (20)	140	O_2	22
6	$Cu(OAc)_2$ (20)	140	O_2	11
7	$Cu(ClO_4)_2$ (20)	140	O_2	38
8	$CuCl_2$ (20)	140	O_2	0
9	$CuBr_2$ (20)	140	O_2	0

[a]Yield of isolated product. [b]1,2-dichlorobenzene was used as solvent.

moderate yield (entries 11 and 12), indicating that steric congestion around the amide decreases the reaction efficacy.

The presence of either halogen or electron-withdrawing groups was tolerated but resulted in slightly decreased reactivity and some recovered substrate (entries 4-8 and 16). The regioselectivity of the cyclization markedly depends on the arene substituents. Thus, C–O bond formation took place exclusively at the less sterically hindered position in the reaction of *meta* methyl- or methoxy-substituted anilides, to give 2-5-disubstituted benzoxazoles (entries 9 and 10). N-(Naphthalen-2-yl)benzamide also cyclized exclusively at the less sterically hindered β-position (entry 13). On the other hand, the substrate with a pyrrolidine-2-one group at the *meta* position cyclized at the more sterically hindered position to give 2-7-disubstituted benzoxazole as the sole product in 81 % yield (entry 15). Similar results were obtained for the substrate with *meta* methoxycarbonyl substituent which cyclized exclusively at the 2-position of the anilide to give 2-7-disubstituted benzoxazoles (entry 16). Substituent diversity of the 2-aryl group was also achieved. From the reactions of various substrates with substituents at *para* position of the benzamide ring, the corresponding 2-arylbenzoxazoles were obtained in generally good yield (entries 17-22). Thiophen-2-yl group ring could also be introduced at the C2 position of the benzoxazole (entry 23).

Table 2. Synthesis of substituted 2-arylbenzoxazoles.



Entry	Substrate	Product		Yield (%)[a]
1			(R = Me)	92
2			(R = OEt)	91
3			(R = Ph)	72
4			(R = CO_2Me)	40[b]
5			(R = COPh)	63
6			(R = F)	80
7			(R = Cl)	76
8			(R = Br)	61
9			(R = Me)	86
10			(R = OMe)	93
11			(R = Me)	51
12			(R = OMe)	55
13				75
14				70
15				82
16				61[c]
17			(R = Et)	85
18			(R = OMe)	89
19			(R = CO_2Me)	83
20			(R = Cl)	78
21			(R = Br)	72
22			(R = I)	81
23				44[d]

[a]Yields of isolated product. [b]With 41% substrate recovery. [c]Reaction time = 48 h. [b]With 39% substrate recovery.

In summary, we have developed a novel copper-catalyzed intramolecular oxidative C–O coupling reaction for the efficient synthesis of 2-arylbenzoxazoles from readily available benzanilides. The catalytic cycle was achieved by use of molecular oxygen as terminal oxidant that produce water as sole theoretical by-product. Since this approach should offer advantages in turms of simplicity and performance, including low cost, harmlessness and high regioselectivity, it may adequately complement the commonly used procedures for the synthesis of benzoxazoles.

1) G. Evindar, R. A. Batey, *J. Org. Chem.* **2006**, 71, 1802; G. Evindar, R. A. Batey, *Org. Lett.* **2003**, 5, 133.

1P-15

Photocuring of Acrylated Dendrimer

Syang-Peng Rwei*,
Institute of Organic and Polymeric Materials,
National Taipei University of Technology,
f10714@ntut.edu.tw

Abstract

In this study, PDSC was utilized to monitor the UV curing process for dendrimer and linear oligomer with various acrylated groups. Experimental results show that even within a slight increase of MW for the linear-type oligomers, a remarkable increase in viscosity against the branch number was observed. In contrast, a dendritic oligomer containing the same number of branches does have much lower viscosity. Furthermore, the conversion of hydroxyl groups into acrylic group for the dendritic-type oligomer would make the viscosity slightly decrease due to the extinguishing of the hydrogen bonds. Regarding to the effect of acrylated branch number on the curing reaction, the conversion and curing rate was found to increase first and then reaches the maximum at the number of 5. The acceleration of double bond reaction within a dense group of multiacrylate sites causes the initial rise, however, the steric effect of the branches to hinder the simultaneous free-radical propagation results in a negative tendency as the branch number further increase in a curing process of dendrimers. Finally, the inhomogeneity of cross linking density for dendrimers cause less hardness and lower T_d values than the linear ones. Nevertheless, cured dendrimer with 19 acrylated branches can provide a film with low viscosity, satisfied hardness (6H), reasonable T_d (290 °C) and superior refractive index (1.5).

Keywords: UV curing, Photo-DSC, linear oligomer, dendrimer, acrylated branch number

1P-16

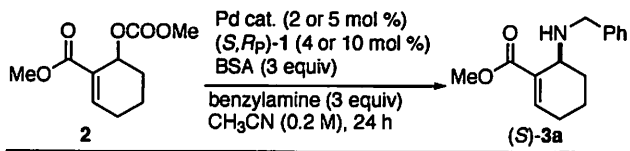
Asymmetric Synthesis of Cyclic Aza-Morita-Baylis-Hillman Reaction Products Using Pd-DIAPHOX Catalyst System

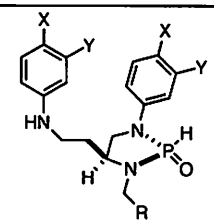
Tetsuhiro Nemoto,* Takashi Fukuyama, Kazumi Kakugawa, Yuko Maruyama, and Yasumasa Hamada
Graduate School of Pharmaceutical Sciences, Chiba University
1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan
tnemoto@p.chiba-u.ac.jp

Catalytic enantioselective aza-Morita-Baylis-Hillman (aza-MBH) reaction provides functionalized chiral allylic amines. To date, several asymmetric catalysts for intermolecular aza-MBH reaction have been developed. In contrast, there are no reports of a catalytic asymmetric intramolecular aza-MBH reaction. Deracemization of cyclic MBH adduct derivatives using Pd-catalyzed asymmetric allylic amination is an alternative strategy to synthesize chiral aza-MBH adducts.[1] These backgrounds led us to examine this type of transformation using Pd-chiral diaminophosphine oxide (DIAPHOX) catalyst systems. In this presentation, we report a general and highly enantioselective synthesis of aza-MBH adducts using Pd-catalyzed asymmetric allylic amination.[2]

We first selected asymmetric allylic amination of 2-methoxycarbonyl 2-cyclohexenol derivatives **2** with benzylamine as the model reaction, because the cyclic products such as **3a** are not readily accessible using the asymmetric aza-MBH reaction (Table 1). Although cyclic adduct **3a** with low enantiomeric excess was obtained when an acetate derivative (26% ee) and a pentafluorobenzoate derivative (31% ee) were used as substrates, allylic amination of carbonate derivative **2** proceeded in the presence of 2.5 mol % of $[\eta^3\text{-}C_3H_5PdCl]_2$ (5 mol % of Pd catalyst) and 10 mol % of (S,R_P)-**1a** at 4 °C, affording **3a** in 91% yield and 87% ee. The effect of the ligand structure revealed that the introduction of electron-donating groups onto the aromatic rings attached to the nitrogen atoms increases the enantioselectivity, and the 3,4-dimethoxy-type ligand (S,R_P)-**1f** was best for asymmetric induction. Moreover, enantioselectivity was increased when the reaction was performed at a lower temperature. Using 2 mol % of Pd catalyst and 4 mol % of (S,R_P)-**1f**, cyclic product **3a** was obtained in 99% yield with 99% ee (entry 8).

Table 1. Optimization of the Reaction Conditions



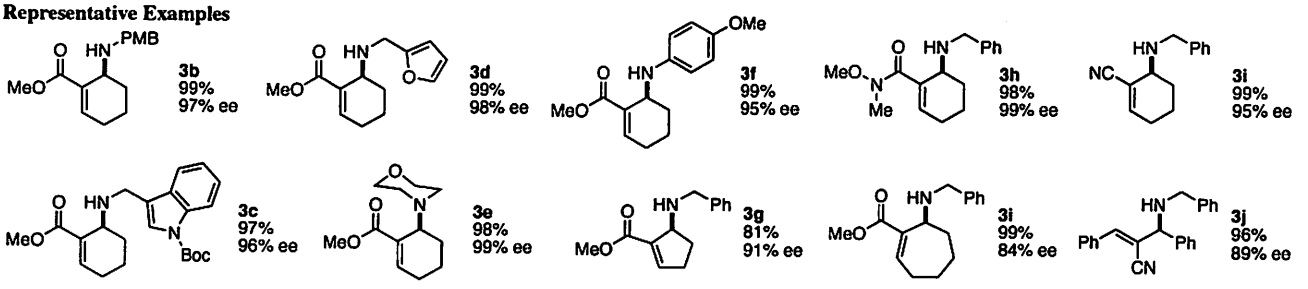
entry	DIAPHOX		temp.	yield	ee
1[a]		**1a**	4 °C	91%	87% ee
2[a]		**1b**	4 °C	92%	69% ee
3[a]		**1c**	4 °C	97%	83% ee
4[a]		**1d**	4 °C	99%	71% ee
5[a]		**1e**	4 °C	96%	90% ee
6[a]		**1f**	4 °C	99%	94% ee
7[b]		**1f**	4 °C	99%	94% ee
8[b]		**1f**	−30 °C	99%	99% ee

1a: X = H, Y = H, R = C_6H_5
1b: X = H, Y = H, R = 1-naphthyl
1c: X = H, Y = H, R = 2-naphthyl
1d: X = CF_3, Y = H, R = C_6H_5
1e: X = OCH_3, Y = H, R = C_6H_5
1f: X = OCH_3, Y = OCH_3, R = C_6H_5

[a] 5 mol % of the Pd catalyst and 10 mol % of **1** were used.
[b] 2 mol % of the Pd catalyst and 4 mol % of **1** were used.

Having developed efficient conditions, we next examined the scope and limitation of different substrates. When 2 mol % of Pd catalyst and 4 mol % of (S,R_P)-**1f** were used, asymmetric allylic amination

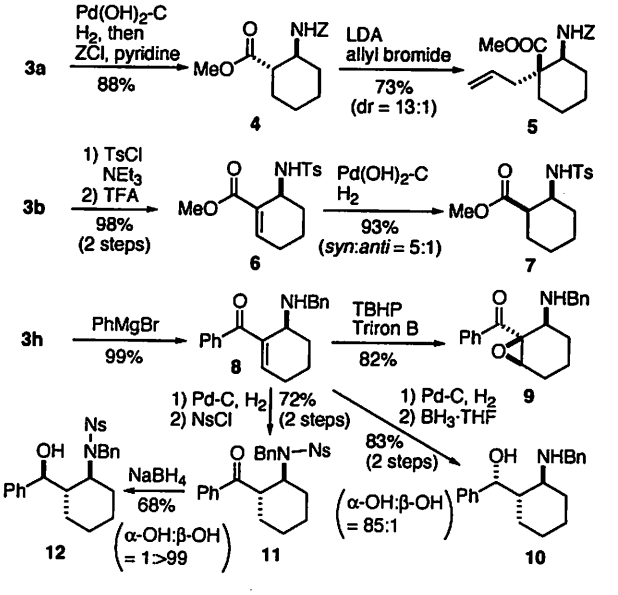
Representative Examples



of **2** using various amines proceeded efficiently to provide the corresponding products in excellent yield and enantiomeric excess. Other cyclic substrates with a five-membered ring and a seven-membered ring were also applicable to this reaction, affording the corresponding chiral allylic amines in 91% ee and 84% ee, respectively. Furthermore, a substrate with a nitrile group, as well as the Weinreb amide-type substrate, could be utilized for this reaction system, giving the corresponding products in excellent yield and enantiomeric excess. In addition, asymmetric allylic amination of 1,3-diphenylallyl carbonate derivative proceeded at 4 °C to provide the corresponding product in 89% ee.

To demonstrate the usefulness of these chiral allylic amines, several diastereoselective modifications were performed (Scheme 1). Both olefin hydrogenation and debenzylation of **3a** using $Pd(OH)_2$-C, followed by protection of the resulting free amine with a carbobenzyloxy (Z) group, afforded the cyclic *anti*-β-amino acid derivative **4** in 88% yield as a single diastereomer. On the other hand, protection of **3b** with a tosyl group, followed by treatment with TFA, gave α,β-unsaturated ester **6** in 98% yield. This product could be transformed into the cyclic *syn*-β-amino acid derivative **7** with good diastereoselectivity (*syn*:*anti* = 5:1). The usefulness of these compounds was further demonstrated. After the formation of lithium enolate of **4**, diastereoselective alkylation was performed using allyl bromide as an electrophile, affording the product with an all-carbon quaternary stereocenter in 73% yield with high diastereoselectivity (dr = 13:1). Weinreb amide-type adduct **3h** reacted with a Grignard reagent at –40 °C to provide the corresponding enone **8** in 99% yield. This enone could be converted into α,β-epoxy ketone **9** and *syn-anti*-1,3-aminoalcohol **10** in a highly diastereoselective manner. In addition, conversion of **8** into a *N*-nosyl-protected compound **11**, followed by treating with $NaBH_4$, gave *syn-syn*-1,3-aminoalcohol **12** with excellent diastereoselectivity.

Scheme 1. Diastereoselective Modifications



References. 1) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057. 2) (a) Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, *9*, 927. (b) Nemoto, T.; Tamura, S.; Sakamoto, T.; Hamada Y. submitted. 3) Nemoto, T.; Masuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. Lett.* **2005**, *7*, 4447.

1P-17

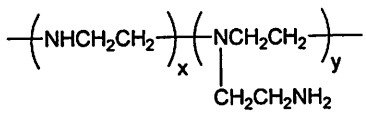
Pd/PEI : Partial hydrogenation catalyst of alkynes to alkenes

Shigeki Mori,* Tomoyuki Ohkubo, Takashi Ikawa, Akira Kume, Tomohiro Maegawa, Yasunari Monguchi and Hironao Sajiki
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University
5-6-1 Mitahora-higashi, Gifu, 502-8585, Japan
yakuhin@gifu-pu.ac.jp

The selective partial hydrogenation of alkynes to alkenes represents an important class of chemical transformations that have found extensive use in the construction of enormous bioactive molecules, natural products, industrial materials and so on. The important transformation has mainly been accomplished under ordinary hydrogen pressure at room temperature using heterogeneous transition metal catalysts such as the Lindlar catalyst [Pd/$CaCO_3$-Pb$(OAc)_2$ in conjunction with quinoline][1], Pdc[2], phosphinated PI Pd[3], Au nanoparticle[4], and Ni nanoparticles[5] to date although the smooth over-reduction of *mono*-substituted (terminal) alkynes to the corresponding alkanes usually proceeded. Therefore, much attention has been attracted for the development of novel partial hydrogenation catalyst of alkynes (including *mono*-substituted alkynes) to alkenes that can provide excellent selectivity without any additives and/or pretreatments.

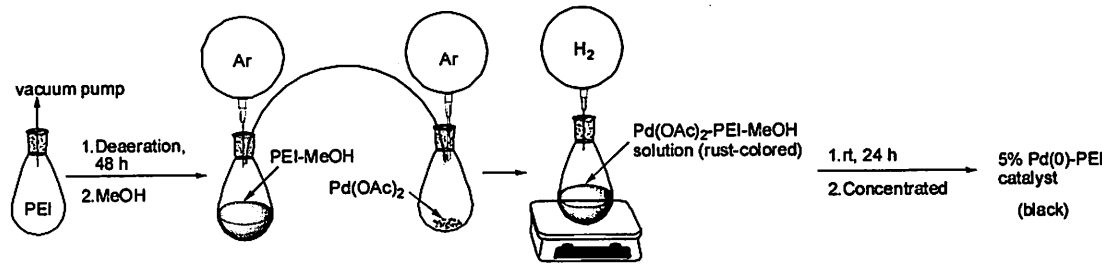
Recently, we have developed chemoselective hydrogenation methods by the addition of nitrogen-containing bases as a catalytic poison to the reaction media.[6] Moreover, we have developed the palladium on carbon-ethylenediamine complex [Pd/C(en)] as an isolable chemoselective hydrogenation catalyst.[7] During our further effort to develop a new Pd catalyst for the hydrogenation possessing the different chemoselectivity, we found that polyethyleneimine (Figure 1: PEI, branched polymer, average molecular weight approximately 25,000) is likely to be a good carrier of highly poisoned Pd(0) metal. Thus, we made a challenge to develop PEI-poisoned Pd catalyst [Pd(0)-PEI catalyst] for the partial hydrogenation of alkynes including both *mono*- and *di*-substituted alkynes to alkenes.[8]

Figure 1 Structure of PEI



After the detailed investigation for the preparation of the Pd(0)-PEI catalyst, we developed the general preparation methods that were indicated in Scheme 1. First, the MeOH solution of deaerated-PEI was poured into the round bottom flask containing $Pd(OAc)_2$ under Ar atmosphere. Next, the resulting rust-colored solution was stirred under H_2 atmosphere at room temperature for 24 h and the solution gradually changed the color to black. After concentration *in vacuo,* the black gummy 5% Pd(0)-PEI catalyst was obtained. When the catalyst was applied for the hydrogenation of *di*-substituted alkynes, the partial hydrogenation proceeded with excellent selectivity regardless of alkyl or aryl substituents (Figure 2).

Scheme 1 Preparation Method of Pd(0)-PEI Catalyst



We next applied the Pd(0)-PEI catalyst to the partial hydrogenation of *mono*-substituted (terminal) alkynes (Figure 3). Amazingly, a variety of *mono*-substituted alkynes possessing an alkyl or aryl group were selectively hydrogenated to alkenes although the solvent-tuning (addition or use of the coordinating solvent such as dioxane) was necessary. Furthermore, other reducible functionalities such as *N*-Cbz protective group, benzyl ester, benzyl ether and *O*-TBS group could universally be tolerated under the hydrogenation conditions.[8]

Figure 2

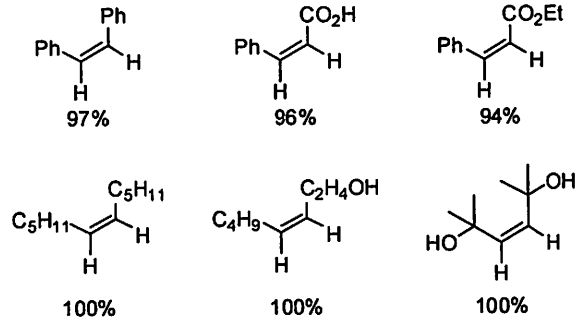
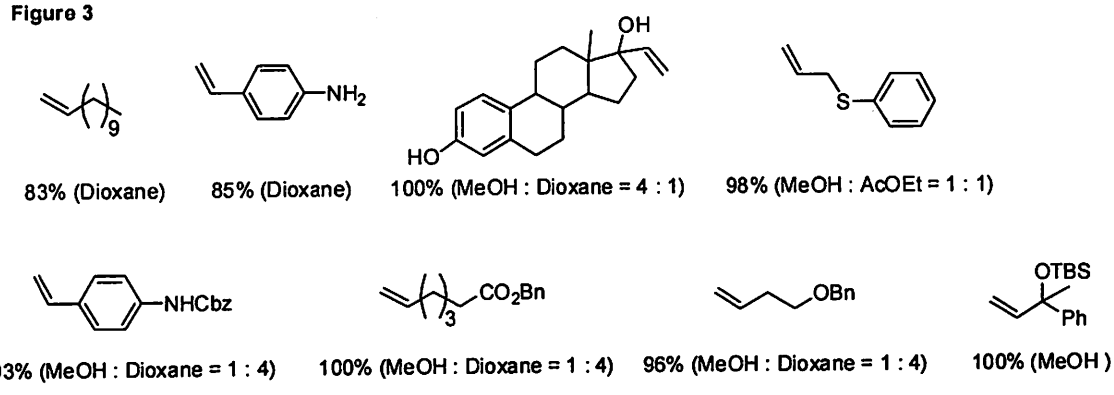


Figure 3



[Reference]

[1] Lindlar, H. *Helv. Chim. Acta,* **1952**, *35*, 446.

[2] Brunet, J. -J.; Caubere, P. *J. Org. Chem.* **1984**, *49*, 4058.

[3] Nishio, R.; Sugiura, M.; Kobayashi, S. *Org. Biomol. Chem.* **2006**, *4*, 992.

[4] Segura, Y.; López, N.; Pérez-Ramíez, J.; *J. Catal.* **2007**, *247*, 383.

[5] Alons, F.; Osante, I.; Yus, M. *Adv. Synth. Catal.* **2006**, *348*, 305-308.

[6] Sajiki, H.; Hirota, K. Tetrahedron, **1998**, *54*, 13981.

[7] Sajiki, H.; Hattori, K.; Hirota, K. *J. Org. Chem.* **1998**, *63*, 7990.

[8] Sajiki, H.; Mori, S.; Ohkubo, T.; Ikawa, T.; Kume, A.; Maegawa, T.; Monguchi, Y. *Chem. Eur. J.* **2008**, in press

1P-18

Design and Construction of Biocatalyst for Multistep Reaction, and Development of Biotransformation-Organic Synthesis Composite Process -Process Development of Chiral Intermediate (EVAL)-

Motoko Hayashi,* [a] Norihiro Kimoto, [a] Hiroaki Yamamoto, Kiyoshi Ikura, Naohiro Hashikawa
Life Science Development Center, CPI Company, Daicel Chemical Industries, Ltd.
1-1 Shinko-cho, Myoko, Niigata, 944-8550 Japan
biochem@daicel.co.jp
[a] Corporate R&D Center, R&D Management, Daicel Chemical Industries, Ltd.
1239 Shinzaike, Aboshi-ku, Himeji, Hyogo, 671-1283 Japan

EVAL (*N*-[1-(*S*)-(ethoxycarbonyl)butyl]-(*S*)-alanine) is an important intermediate for an ACE inhibitor, which is made up of optically active unnatural amino acid L-norvaline (L-Nva, (*S*)-2-aminopentanoic acid). We developed economical process for EVAL with an efficient process for L-Nva using biocatalytic reactions by novel designed recombinant microorganism, followed by chemical synthetic steps.

1. L-Nva Process

We worked out our strategy for enzymatic deracemization of DL-amino acid. Starting from DL-amino acid, D-amino acid is converted into L-amino acid, whereas L-amino acid remains unchanged, to give L-amino acid in theoretically 100% yield. In case of L-Nva, it has additional advantages because the DL-amino acid is commercially available at a low price. Conversion of D-Nva to L-Nva can be divided into two reactions, oxidative deamination of D-Nva to corresponding keto acid, 2-oxopentanoic acid (KVA), followed by reductive amination or transamination of KVA to L-Nva. We planned to design novel biocatalyst, which can perform these reactions by multiple enzyme system in single cell. The process would be the most efficient because we can conduct the reaction with good reproducibility by one-time cultivation of single microorganism.

Our strategy is made up of four tactics and each target has been achieved as follows:

1) D-amino acid oxidase for the first step; Screened and found from *Candida boidinii* (CbDAO),
2) L-phenylalanine dehydrogenase for the second step; Screened and found from *Thermoactinomyces intermedius* (TiPheDH),
3) Solvent resistant enzyme which regenerate coenzyme (NADH) and is essential for the reductive amination; Selected modified formate dehydrogenase from *Mycobacterium vaccae* (McFDH), and
4) Catalase, which decompose hydrogen peroxide that degrades Nva; Introduced gene of catalase.

We constructed a plasmid expressing these four genes of enzymes, and introduced it into *Escherichia coli* HB101. Although all four enzymes expressed with high efficiency, our initial attempt of deracemization using this recombinant *E. coli* resulted L-Nva in only 70% yield remaining 12% of KVA. We assumed that this is because of difference of required reaction conditions. Oxidative deamination requires oxygen,

whereas reductive amination is carried out under anaerobic condition. So, the reaction conditions were optimized, in which the oxidative deamination to KVA was performed under aerobic condition, and then aeration was stopped for reductive amination to L-Nva. As a result, reaction yield was improved in 90% yield with >99.9% e.e. We also developed purification process from the reaction mixture to give L-Nva of high purity in high yield.

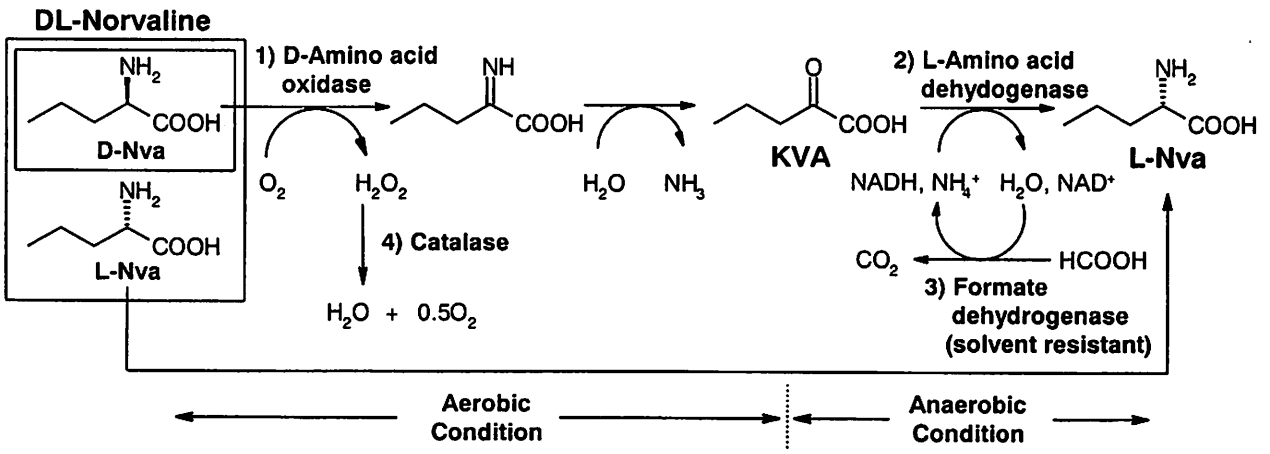


Figure 1. Deracemization of DL-Nva to L-Nva

2. EVAL Process

EVAL was derived from L-Nva by the process shown in Figure 2 at pilot plant scale.

In our scale-up development, there were some issues. One of those was safety issue at the coupling of L-Nva-OEt with D-LA(OTs)-OBn which is a derivative of D-lactic acid. In our laboratory process, D-LA(OTs)-OBn was added into L-Nva-OEt at one time and the reaction was conducted with no solvent. It was difficult to control reaction speed with proper heat removal at large scale. For the issue, we succeeded to modify some reaction conditions to assure safety with keeping the reaction performance. Another issue was diastereomer formation at the coupling. The reaction went by S_N2 at α-position of D-LA(OTs)-OBn to give (*S, S*) isomer, but some (*S, R*) isomer was formed. In addition, amount of (*S, R*) isomer varied by unknown factor, which hasn't been certain yet. We tried to reduce the formation of (*S, R*) isomer, and simultaneously sought alternative resolutions. As a result, we established a robust crystallization procedure for EVAL to remove undesired diastereomer efficiently.

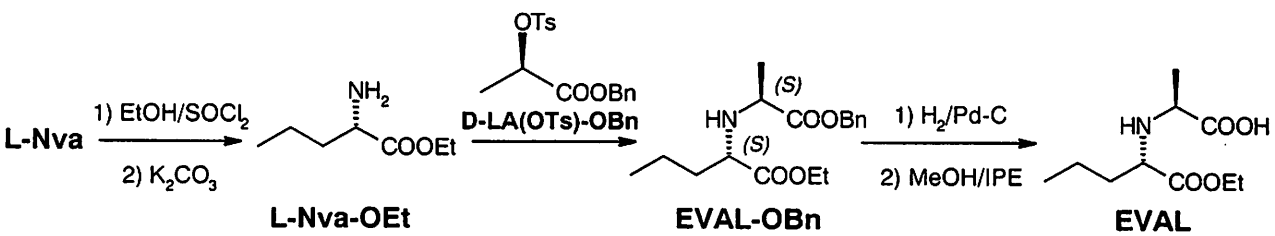


Figure 2. Manufacturing Process of EVAL

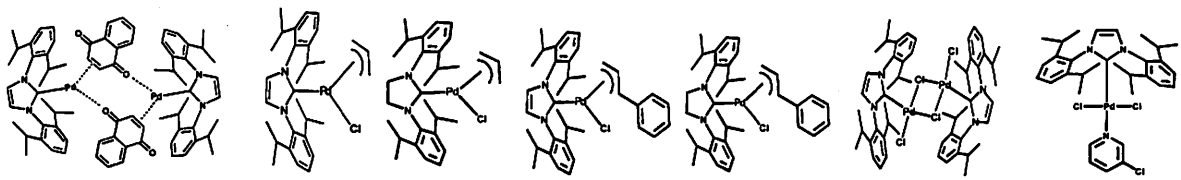
Industrial Scale Application of Umicore's Leading Edge Catalysts & Technologies

Yoshiaki Horiguchi*
Precious Metals Chemistry, Umicore Japan KK
Aoyama Building 5th floor, 2-3 Kita-Aoyama 1-chome, Minato-ku, Tokyo, 107-0061, Japan
yoshiaki.horiguchi@ap.umicore.com

Umicore is an international group focusing on metals and materials sciences. Its Business Unit Precious Metals Chemistry manufactures and provides world-wide bulk scale precious metal chemicals and catalysts, along with customised metal separation and recovery technologies, allowing its customers to develop reliable and cost effective reaction processes. In this paper, we would like to show three classes of our homogeneous precious metal catalysts, which is dedicated to industrial applications in life science/fine chemical industries.

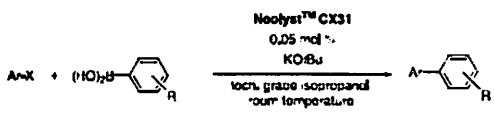
1. Highly Active N-Heterocyclic Carbene-Pd Catalysts for Various Coupling Reactions

Umicore has developed, in industrial scales, N-heterocyclic carbene-Pd (NHC-Pd) catalysts, Neolyst™ CX series, licensed by Matthias Beller and Steve Nolan.



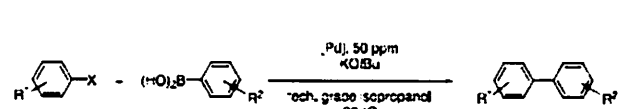
CX 11 CX 21 CX 23 CX 31 CX 32 CX 41 PEPPSI

These catalysts exhibit very attractive properties and catalytic performances for process chemists as follows: 1. air stable both during storage and reaction, 2. simple catalysis protocols without *in situ* preparation, 3. very high catalytic performance in general, 4. very low catalyst loading possible, up to 10 ppm to the substrate, 5. versatile coupling reactions possible (Suzuki-Miyaura coupling, Kumada reaction, Negishi reaction, Heck reaction, carbonylation, ketone arylation, Buchwald-Hartwig amination, etc), 6. broad range of aryl halides applicable (Ar-Cl, Ar-OTs and, Het-Cl), 7. robust, reproducible process possible without vigorous air-free operations, 8. potentially easy work-up for removal of Pd residue. Following tables show some examples of Suzuki-Miyaura coupling and Buchwald-Hartwig amination.



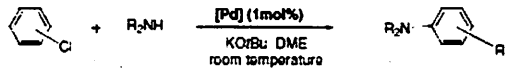
entry	Ar-X	boronic acid	product	time (h)	yield (%)[a]
1				15	83
2				15	94
3				15	93

Reaction conditions: aryl halide, 1 mmol, boronic acid 1.05 mmol, Neolyst™ CX31, 0.05 mol %, KOtBu 1.1 mmol, technical grade isopropanol, 1 mL. [a]Isolated yields average of two runs.



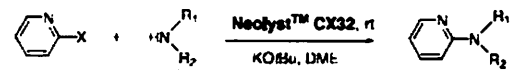
entry	Ar-X	boronic acid	product	[Pd]	time (h)	yield (%)[a]
1				Neolyst™ CX31	3	93
				Neolyst™ CX21	3	92
2				Neolyst™ CX21	3	91

Reaction conditions: aryl chloride 1 mmol, boronic acid, 1.05 mmol, KOtBu, 1.1 mmol, tech. grade isopropanol, 1 mL. [a]Isolated yields average of two runs.



amine	chloride	product	catalyst	time	GC conv. (%)[c]
			CX21	5 h	98
			CX23	2.5 h	99
			CX31	2 h	100
			CX32	20 min	100
			CX21	20 h	31[c]
			CX23	20 h	62[c]
			CX31	5 h	100
			CX32	5 min	100
			CX21	20 h	73[c]
			CX23	15 h	90[c]
			CX31	6 h	98
			CX32	1.5 h	97

[a]Reaction conditions: aryl chloride, 1 mmol; amine, 1.1 mmol; **Neolyst™ CX catalysts**, 1 mol %; KOtBu, 1.1 mmol; DME, 1 mL. [b]Isolated yields, average of two runs. [c]No further conversion

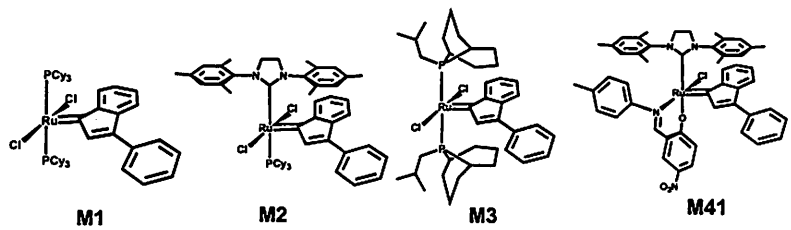


aryl halide	amine	cat. loading (mol %)	time	yield(%)[a]
		1	1 min	100
		0.1	5 min	93
		0.001	48 h	95
		0.001	20 h	94[b]
		1	15 min	98
		0.1	1 h	99
		0.001	50 h	73
		0.001	40 h	93[b]

Reaction conditions: halopyridine, 1 mmol; amine, 1.1 mmol; KOtBu 1.1 mmol; DME 1 mL.[a] GC yields (hexamethylbenzene as internal standard) average of two runs.[b] T = 80 °C.

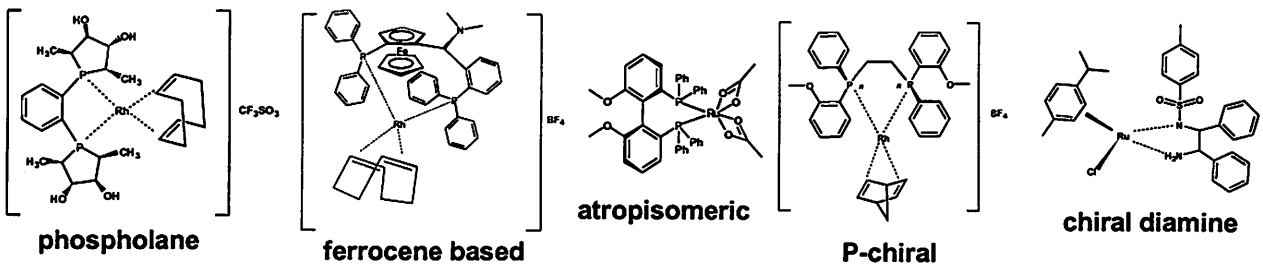
2. Ru-Based Metathesis Catalysts

There are a series of Ru-based metathesis catalysts, Neolyst™ M series, from the first generation to the third generation. These catalysts exhibit high performances in ROMP, RCM, and CM applications, comparable to the Grubbs catalysts. Umicore offers user friendly IP included supply, resulting in royalty free usage for the commercial production.



3. Precious Metal-Ligand Complexes for Highly Effective Asymmetric Hydrogenations

Umicore has expertise to develop and manufacture broad range of precious metal-ligand (ML) complexes, Chiralyst™ series, as depicted below in industrial scales. This technology would enable process chemists to develop highly efficient asymmetric hydrogenation processes. ML complexes provide you the following benefits compared to *in situ* systems: 1. potentially higher %ee, chemical yield, s/c and less side reactions, 2. enhanced stability of ML complexes compared to precious metal precursors and chiral ligands, 3. simplified protocol without *in situ* catalysts formation, 4. increased process stability: robust process, 5. potential better cost performance compared to *in situ* system.



1P-20

Control of Primary Nucleation for Organic Substance by Ultrasonic Irradiation

...

* Izumi Hirasawa, Takanori Kodera, Naoki Kominami,, Masahiro Kurotani

Major in Applied Chemistry, Graduate School of Advanced Sci. & Engr., Waseda University.
3-4-1, Ohkubo, Shinjyuku, Tokyo 169-8555, Japan
izumih@waseda.jp

The purpose of our study is to understand ultrasonic primary nucleation phenomena for controlling final product size via the number of primary nuclei.

In our previous study, the effect of ultrasonic irradiation on the number of nuclei was investigated in the same supersaturated condition, as a result two novel phenomena were observed. Firstly, there was a region where ultrasonic irradiation inhibits primary nucleation. Secondly, a specific amount of energy was needed to activate primary nucleation. From these results, it was expected that the ultrasonic energy needed to activate primary nucleation has a certain relation to the energy necessary to form a stable nucleus.

Therefore, we investigated the three queries; whether ultrasonic irradiation inhibits and activates primary nucleation at other degrees of supersaturation or not, whether the final crystal size relates to the number of nuclei or not, and whether the ultrasonic energy needed to activate primary nucleation relates to the energy necessary to form a stable nucleus, or not.

Batch cooling crystallization experiments were done to observe the effect of supersaturation and ultrasonic irradiation conditions (output ant irradiation time) on induction time for primary nucleation, number of crystals and average size of product crystals in organic substance system.

Firstly, ultrasonic irradiation inhibits and activates primary nucleation, determined by degree of supersaturation and ultrasonic irradiation conditions. Secondly, the final crystal size increased or decreased due to the number of nuclei, which contributes to the quality of product crystals. Therefore, it was indicated that ultrasonic energy could create a desired crystal size by obtaining suitable nucleation.

Thirdly, the ultrasonic energy needed to activate primary nucleation E_{crit} decreased with decreases in the energy necessary to form a stable nucleus ΔG_{crit}. From this result, we can propose the criteria to determine the effect of ultrasonic irradiation on the primary nucleation by showing the diagrams correlating ΔG_{crit} with E_{crit} (Figure 1).

This kind of relationship was recognized in Arginine, Vanillin, and Ethyl Paraben, and correlated in the same figure, although the tendencies were different affected by the kinds of substances, temperature and volumetric ratio of solvent. Effect of temperature and volumetric ration of solvent ia considered to affect not only suersaturation ratio, but also cavitation energy.

And application of sono-crystallization is also discussed. Sono-crystallization process has been developed by Prosonix Co., Ltd in England, and many experiments were done to verify the applicability to the pharmaceutical field. Authors started cooperation study with Prosonix Co., Ltd.. Authors have proposed

the sono-crystallization process, as shown in Figure 2

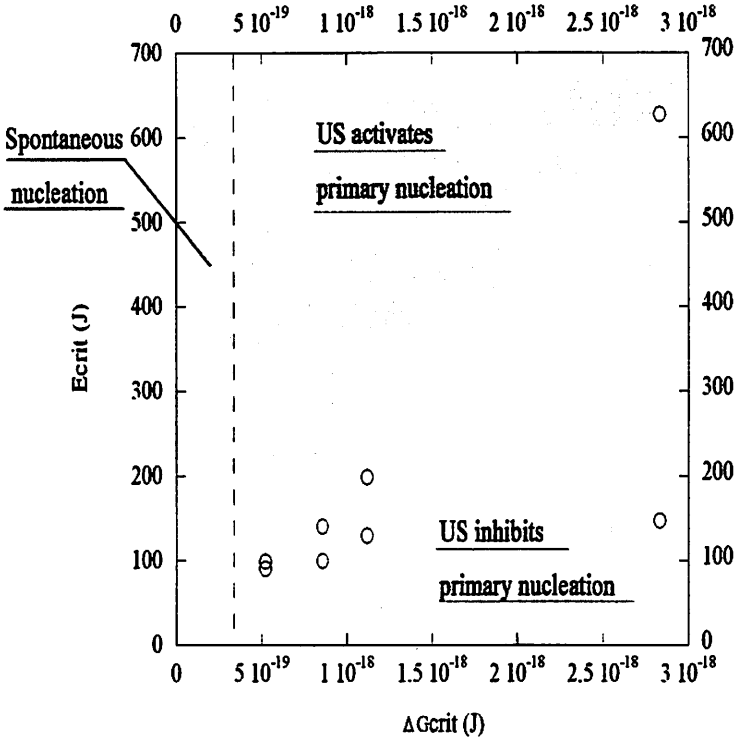


Figure 1 Diagram correlating ΔG_{crit} with E_{crit}.
(Aspirin Case)

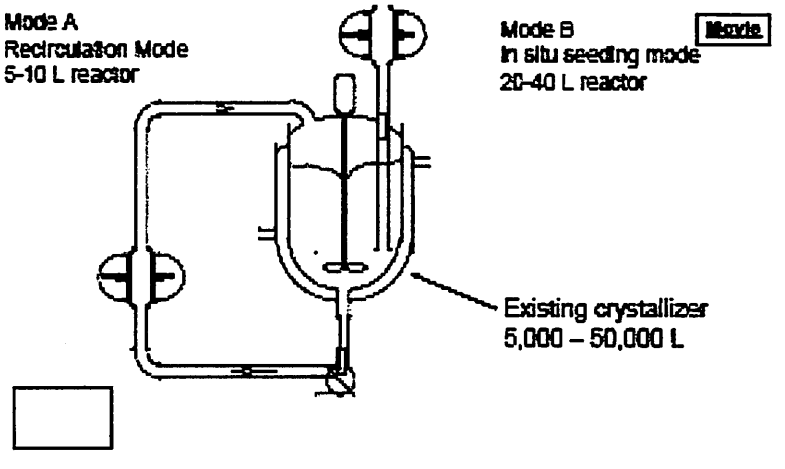


Figure 2 An example of sonoicrystallizatrion process

1P-21

DMEAD: A Separation-Friendly Reagent for the Mitsunobu Reaction

Kazutake Hagiya,*[1,2] Yasuhiro Sakamoto,[1] Masao Miyatake,[1] Hikaru Tanaka,[1] Hideki Tatsumi,[1] Takashi Sugimura[2]

[1]*Chemicals Research Center, Toyo Kasei Kogyo Co., Ltd.*

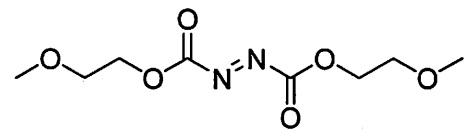
2900, Sone-Cho, Takasago-City, Hyogo, 676-0082, Japan

kazutake-hagiya@toyokasei-kogyo.co.jp, URL: http://www.toyokasei-kogyo.co.jp/

[2]*Graduate School of Material Science, University of Hyogo*

Simple separation process is indispensable in fine chemical production if the target product is accompanied with a large amount of co-products. Removal of co-products is generally achieved by extraction, recrystallization, distillation, or column chromatography. Among these methods, column purification is useful in a laboratory small scale synthesis. However, it may not be employed for a large scale production because of productivity, cost, and environmental issue. The Mitsunobu reaction is popular with organic chemists to synthesize pharmaceuticals, agrochemicals, and bioactive natural products, but has the co-product problem. This reaction is carried out with a starting alcohol, a pronucleophile (carboxylic acids, phenols, thiols, imides, etc.), triphenylphosphine, and diethyl or diisopropyl azodicarboxylate (DEAD, EtOOC-N=N-COOEt or DIAD, *i*PrOOC-N=N-COO*i*Pr) to give the corresponding product. The special feature of the reaction is the complete stereo inversion at an alcohol function. However, a stoichiometric amount of triphenylphosphine oxide and the hydrazinedicarboxylate from DEAD or DIAD is also generated, which cause the increase of production cost and environmental burden in a large scale production. Especially, removal of the hydrazinedicarboxylate from DEAD or DIAD is difficult for the reason of the moderate solubility in solvents and polarity. To circumvent this problem, many separation-friendly reagents alternative to DEAD and DIAD have been developed.[(1),(2),(3)] Still these methods have the problems in cost and availability.

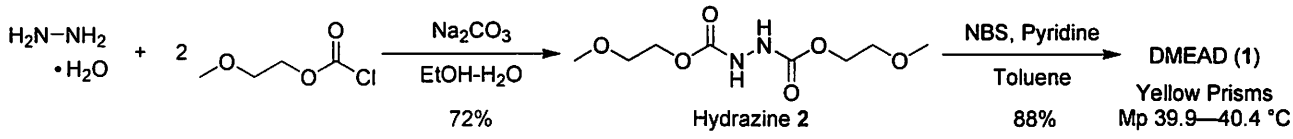
Here, we have developed Di-2-methoxyehyl azodicarboxylate (DMEAD, **1**) as the new Mitsunobu reagent to solve this problem. Co-produced di-2-methoxyethyl hydrazinedicarboxylate (**2**) is easily separable by extraction with water and is reusable to produce DMEAD.[(4)] DMEAD has been commercialized by Toyo Kasei Kogyo Co., Ltd. in Japan. In the poster session, we will describe the physical property, application for the Mitsunobu reaction, and the advantages.



DMEAD (**1**)

Figure 1. Structure of DMEAD (**1**)

DMEAD (**1**) is easily prepared in two steps from hydrazine hydrate and 2-methoxyethyl chloroformate in good yield (Scheme 1). The solubility of **2**, which is also a co-product in the Mitsunobu reaction, is very good in water (0.55 g/mL) in compared with chloroform (0.25) and ethyl acetate (0.1), ether and toluene (<0.01). The observed solubility supports our molecular design intended to separate **2** after the reaction by extraction with water.



Scheme 1. Preparation of DMEAD (**1**)

The decomposition temperature of DMEAD is lower than that of DEAD and DIAD by DSC (Differential scanning calorimetry) analysis (Table 1.), but the crystalline DMEAD must have an advantage in the stability at rt. In fact, DMEAD maintained its crystalline form for more than three months at rt and over one year at 5 °C.

Table 1. DSC analysis of the reagents

Reagent	Decomposition Temp. (°C)	Decomposition Energy (J/g, exothermic)
DMEAD (**1**)	210	930
DEAD	227	1090
DIAD	249	1000

The useful separation and reuse process of the Mitsunobu reaction was demonstrated by using DMEAD (Figure 2.) as follows: to a solution of (*S*)-2-octanol (2 g, 15.4 mmol) of 96% enantiomeric excess (ee), benzoic acid (16.9 mmol), and triphenylphosphine (16.9 mmol) in diethyl ether was added dropwise a diethyl ether solution of DMEAD (16.9 mmol) at rt. After two hours, the reaction mixture was washed with water, and the aqueous layer obtained was re-extracted with diethyl ether. The aqueous layer contained only the hydrazinedicarboxylate **2**, and recovery of sufficiently pure **2** to reuse was accomplished by a single recrystallization in 75% yield (based on the employed amount of DMEAD). The organic layer was dried, concentrated, and suspended in hexane. After the filtration of the slurry, 79% yield (based on the employed amount) of triphenylphosphine oxide was obtained as a crystalline. The filtrate was concentrated and purified by a short column chromatography to give the (*R*)-benzoate product in 89% yield (96% ee).

We could overcome the separation issue of the Mitsunobu reaction by the molecular design of DMEAD.

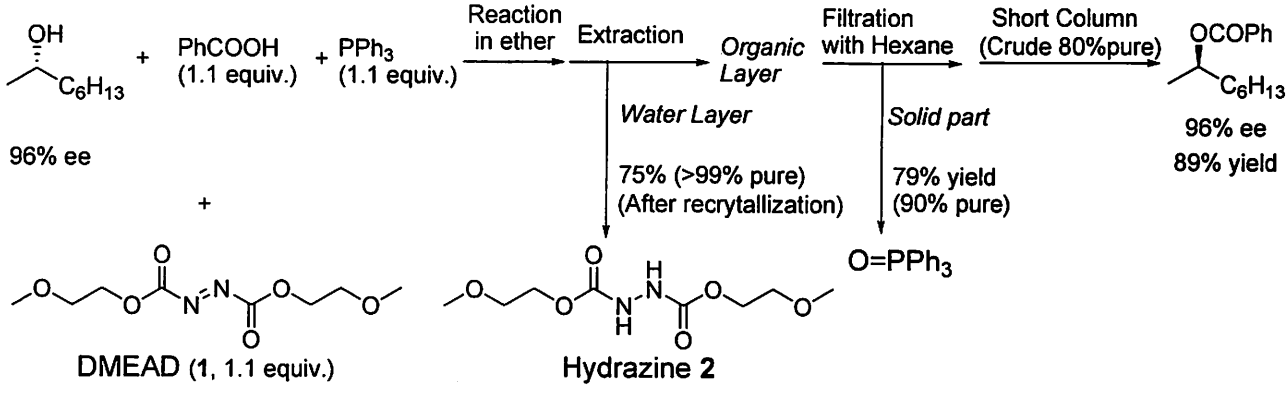


Figure 2. A procedure for the Mitsunobu reaction by using DMEAD

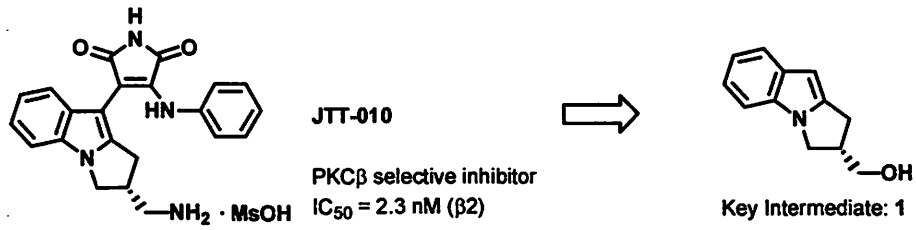
References: (1) For reviews, see: R. Dembinski, *Eur. J. Org. Chem.* **2004**, 2763; S.Dandapani, D. P. Curran, *Chem. Eur. J.* **2004**, 10, 3130. (2) J. C. Poupon, A. A. Boezio, A. B. Charette, *Angew. Chem., Int. Ed.* **2006**, 45, 1415. (3) B. H. Lipshutz, D. W. Chung, B. Rich, R. Corral, *Org. Lett.* **2006**, **8**, 5069. (4) Preliminary results were reported. T. Sugimura, K. Hagiya, *Chem. Lett.* **2007**, 36, 566.

1P-22

An Efficient Synthesis of the PKCβ Inhibitor JTT-010 Using a Novel Cyclopropane Ring-Opening Reaction with Indole

Takashi Inaba*, Masahiro Tanaka, Minoru Ubukata, Takafumi Matsuo, Katsutaka Yasue, Katsuya Matsumoto, Yasuyuki Kajimoto, Takashi Ogo
Central Pharmaceutical Research Institute, Japan Tobacco Inc.
1-1, Murasaki-cho, Takatsuki Osaka, 569-1125, Japan
takashi.inaba@ims.jti.co.jp

We recently identified JTT-010, a new structural class of protein kinase C-β (PKCβ)-selective inhibitor that possesses indole-fused, chirally substituted pyrrolidine as a core.[1] In this symposium, we present a new synthetic route to indole-fused pyrrolidines via a cyclopropane ring-opening reaction, which was applied successfully to the synthesis of JTT-010.

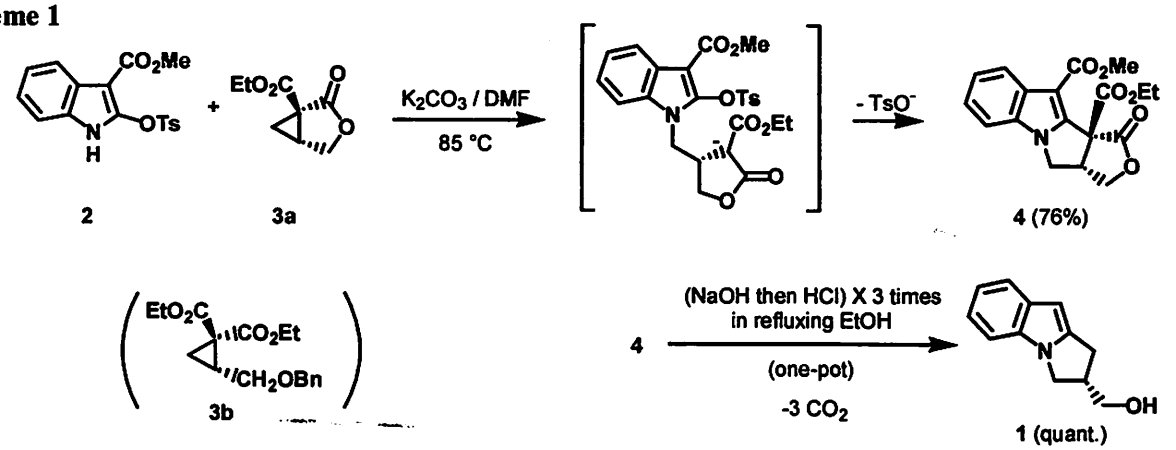


The efficiency of JTT-010 production depends on the practicality of the preparation of key intermediate **1**, which is an indole-fused, chirally substituted pyrrolidine. In our early discovery stage, the preparation of **1** involved an enzymatic method, which required multiple protection-deprotection and column chromatography separation steps.[1] Bergman's and Ellman's group independently synthesized one of our PKCβ inhibitors to demonstrate the effectiveness of their asymmetric Rh-catalyzed C-H bond activation of 1-allylindoles. Although this route was straightforward, the ee of the resulting synthetic equivalent of **1** was 90%.[2]

To synthesize **1** efficiently in an optically pure form, we envisioned a one-step tandem bond construction using a chirally substituted cyclopropane ring-opening reaction. After several attempts, we found that the reaction of lactone-fused cyclopropane **3a**, obtained from (*R*)-epichlorohydrin and diethyl malonate in one step, with indole **2** proceeded smoothly in the presence of K_2CO_3 in DMF to give the desired **4** in 76% yield (Scheme 1). The mechanism of this reaction involves nucleophilic attack by the nitrogen atom of **2** on the cyclopropane methylene carbon of **3a** to generate a carbanion that is stabilized by the ester groups. The carbanion attacks the carbon atom that bears the TsO leaving group to complete the net insertion of an indole N(1)-C(2) unit, thereby generating chirally substituted pyrrolidine **4** (Scheme 1). When the non-fused cyclopropane **3b** was employed instead of **3a**, the desired pyrrolidine was not obtained. The higher reactivity found in **3a** is thought to arise from its highly strained lactone-fused structure. By taking advantage of the characteristic features of indole-2-acetic acids and indole-3-carboxylic acids, the three carboxyl groups in **4** could be removed simultaneously. By simple alkaline hydrolysis followed by

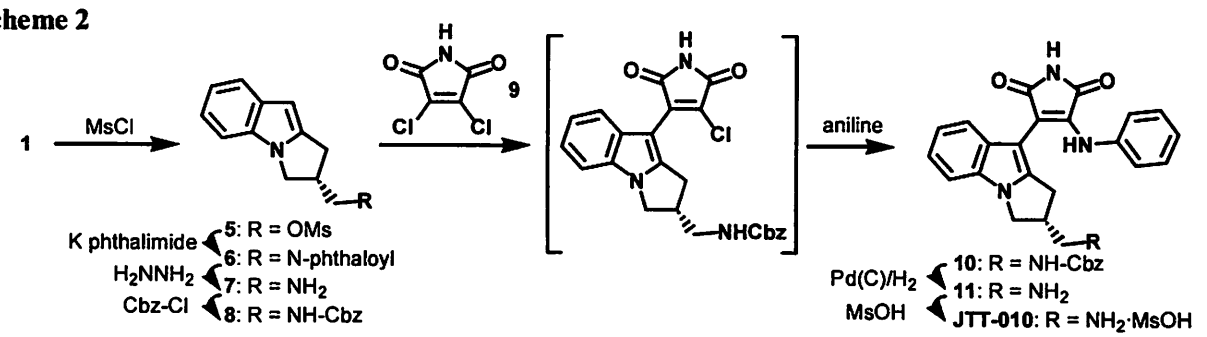
heating under acidic conditions, the one-pot triple decarboxylation was accomplished to quantitatively afford optically pure **1**.

Scheme 1



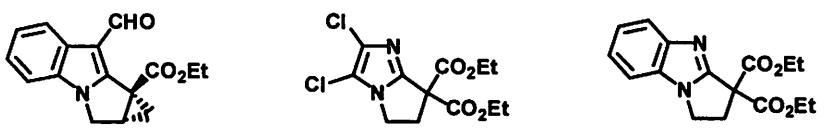
1 was converted to **8** through **5**, **6**, and **7** with one-pot Gabriel synthesis followed by Cbz protection (78% overall yield from **4**). One-pot sequential replacement of each of two chlorine atoms of **9** with **8** and then with aniline, a transformation that has not been reported previously for an *N*-unprotected maleimide, provided **10**. Hydrogenolysis of the Cbz protection with Pd-carbon followed by recrystallization gave **11** from **8** in 51% yield. **11** was then transformed to a MsOH salt to provide JTT-010 (Scheme 2). Consequently, the incorporation of the novel cyclopropane ring-opening reaction (Scheme 1) and the one-pot sequential replacement reaction using **9** (Scheme 2) dramatically shortened the synthetic route to JTT-010. The new route contains no chromatographic separation or low-temperature reaction.

Scheme 2



In this symposium, we also would like to present synthesis of other indole- and imidazole-fused pyrrolidines using the cyclopropane ring-opening reaction shown here (Chart 1). Pyrrolidines fused with heteroaromatics are often found as a core structure in a variety of compounds of biological interest, in addition to the PKC inhibitors identified by us and others.

Chart 1



References: 1) *Bioorg. Med. Chem.* **2006**, *14*, 5781. 2) *Org. Lett.* **2006**, *8*, 1745. 3) *Org. Lett.* **2007**, 9, 3331.

1P-23

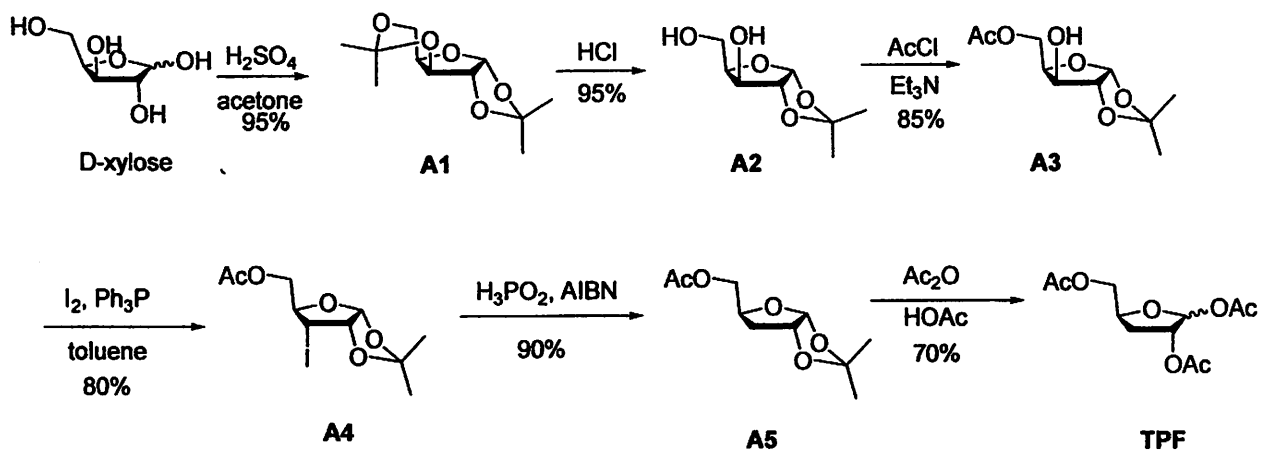
Some Case studies of Process Chemistry at Shanghai ChemPartner
Development of a Practical Route for the Manufacture of 3-Deoxy Ribose derivatives

*Yuanqiang Li, Jianchun Liao, Weihua He
Process Chemistry Department, Shanghai ChemPartner Co., Ltd.
720 Cailun Road, Zhangjiang Hi-tech Park, Pudong New Area, 201203 Shanghai, China
yqli@chempartner.cn

For many years, the design of modified nucleosides has been a focal point for research in medicinal chemistry. Recently, a number of modified nucleosides with 3-deoxyribose unit were found exhibiting a broad spectrum of intriguing activities as anti-virus and anti-tumor reagents, and some of the reagents have already entered clinical trails. Up to now, the report of synthesis 3-deoxyribose derivatives are rare, and the existing methods only be applied on small scale. Along with the increased requirement of 3-deoxyribose derivatives, a new synthetic route which is practical for the manufacturing of large quantity is highly desired. We have developed several new processes which allowed us to prepare 3-deoxy ribose (**TPF**) derivatives from kg scale to hundred kg scale.

The first new route was started with D-xylose (**Scheme 1**), the key of this route is the iodination of the intermediate **A3**, followed by deiodination to give the 3-deoxy intermediate **A5**. This route can be carried out on kg scale, and the total yield is 39%. The drawback of this route is that all the intermediates are liquid, and could not be purified by crystallization, which caused the difficulty in purification of the final product. The final product needs to be purified by column chromatography, and sometime it can not meet the required specification.

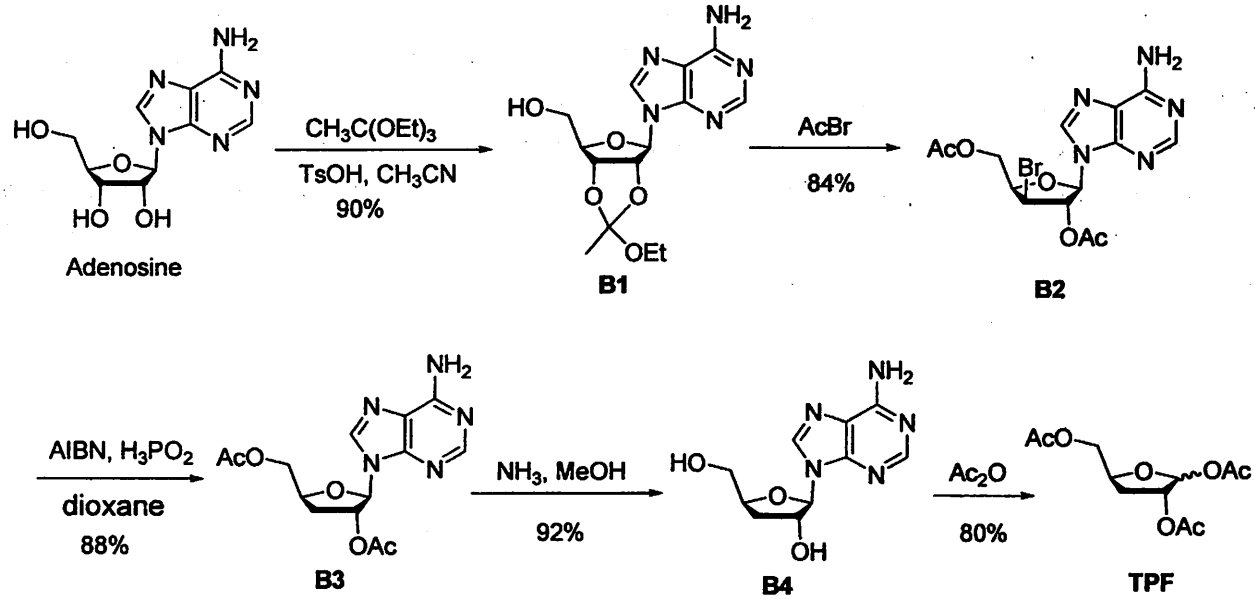
Scheme 1



A new process has been developed and is shown in **Scheme 2**. The synthesis starts with adenosine, which is commercial available. The key step is the debromination reaction of the intermediate **B2**, which is normally only occurred under irradiation or using toxic HgCN as debromination reagent. A novel

debromination condition for **B2** was investigated, which gave the 3-deoxyribose intermediate **B3** in high yield. The whole step of new route reduces to five steps comparing to 6 steps of the D-xylose route, and the total yield was improved to 48%. Intermediates **B2** and **B4** can be purified by crystallization, and a purification condition for **TPF** was also developed as well. The production of 3-deoxyribose derivatives can be carried out in hundred kg scale.

Scheme 2



The detailed information of the process development of this project will be claimed in the poster session.

1P-24

Towards Advanced Molecular Build-up in One-pot by Catalytic Multicomponent Reaction

Kiyosei Takasu,* Tohru Tanaka, Yu Ogawa, and Yoshiji Takemoto
Graduate School of Pharmaceutical Sciences, Kyoto University,
Yoshida Sakyo-ku, Kyoto 606-8501, Japan
kay-t@pharm.kyoto-u.ac.jp

A variety of natural and non-natural substances that contain polycyclic rings and an assortment of stereogenic centers have been found to exhibit attractive and specific biological activities. Owing to this, synthetic organic chemists are constantly confronted with the task of developing new reactions that can be used to prepare these complex targets in concise fashions starting from simple and readily available materials. An innovative strategy developed for this purpose relies on the use of highly convergent cascade reactions and multicomponent reactions. Major advantages of these, in which multiple covalent bonds are formed in single steps, include operational simplicity, time- and cost-saving, atom economy, environmental benignancy, and applicability to diversity-oriented synthesis and combinatorial chemistry. A lot of researchers have developed a variety of cascade and multicomponent reactions. In case of typical cascade and/or multicomponent reactions, a reactive site (functionality) of an intermediate, which is produced in the previous step, is directly utilized in the subsequent bond-forming reaction (Figure 1a). Thus, the mode of multiple bond-formation in the cascade reaction would be simply defined by the substrates. On the contrary, we intrigued, if the reactive site formed in the previous step can move to another position selectively during the cascade reaction, variety modes of multiple bond-formation can be achieved in a single operation (Figure 1b). We wish describe herein cascade multicomponent reaction, which consists of (4 + 2) cycloaddition, isomerization, and (2 + 2) cycloaddition, to give highly functionalized bicyclo[4.2.0]octanes from readily available substrates. Its related chemistry also will be discussed.

We recently reported cascade (4 + 2)-(2 + 2) cycloaddition catalyzed by an acidic catalyst, such as triflic imide (Tf_2NH), as illustrated in Scheme 1.[1,2] Thus, Diels-Alder reaction of 2-siloxydiene **2** with enone **1** gives silyl enol ether **4**, and then (2 + 2) cycloaddition of formed **4** with α,β-unsaturated ester **3** afforded tricyclo[6.3.0.0^{3,6}]undecane **5**. In the process, the silyl enol ether moiety formed in the initial step directly

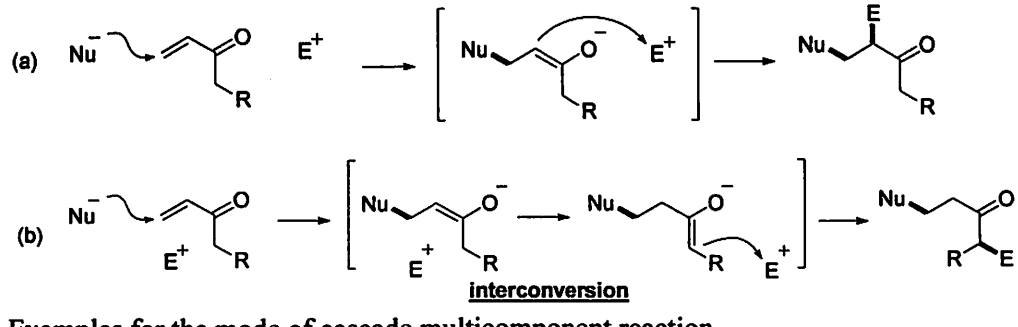
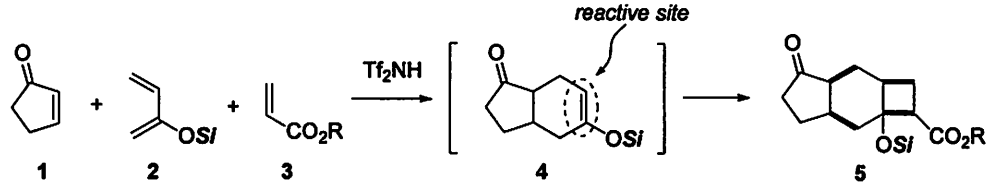
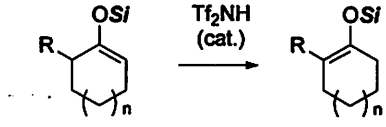


Figure 1. Examples for the mode of cascade multicomponent reaction.
A bold line means a newly generated bond in the cascade reaction. (a) the reactive site formed in the initial step directly reacts with the next substrate (traditional mode). (b) the reactive site formed in the initial step moves to another position, and then reacts with the next substrate (advanced mode).

participates in the subsequent bond formation reaction. During the course of our continuous study, we have found Tf_2NH catalyzes isomerization of kinetically stable silyl enol ethers into thermodynamically stable one (Scheme 2).

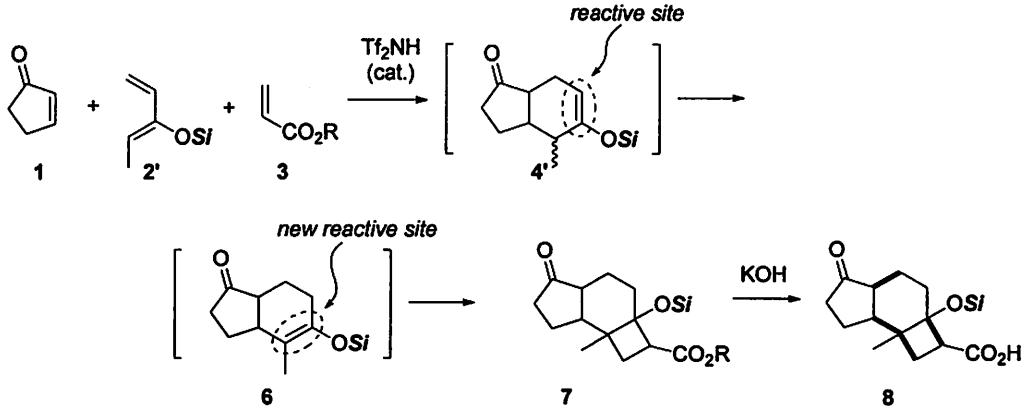


Scheme 1. Tf_2NH-catalyzed (4 + 2)-(2 + 2) cascade cycloaddition (A bold line means a newly generated bond.)



Scheme 2. Tf_2NH-catalyzed isomerization of silyl enol ethers.

With optimized conditions for the isomerization in hand, we designed a new cascade multicomponent reaction involving an isomerization process during a cascade reaction (Scheme 3). After a mixture of **1** and **2'** was treated with a catalytic amount of Tf_2NH at -40 °C to furnish intermediate **6** by Diels Alder reaction and the subsequent isomerization, addition of acrylate **3** to the resulting mixture furnished tricyclo[6.3.0.0^{2,5}]undecane **7**. The product could be easily purified by crystallization after hydrolysis into **8**. The position of the reactive site (silyl enol ether moiety) selectively changes during the cascade reaction. As the result, the different mode of multiple bond-formation can be achieved (Schemes 1 vs 3). It is noteworthy that Tf_2NH catalyzes three mechanistically distinct reactions, such as Diels-Alder reaction, isomerization of silyl enol ether, (2 + 2) cycloaddition, in one-pot. We expect that our developed cascade process would be a powerful strategy for construction of structurally complex molecules, such as naturally occurring substances, in a rapid manner.



Scheme 3. Tf_2NH-catalyzed (4 + 2)-isomerization-(2 + 2) cycloaddition reaction (A bold line means a newly generated bond.)

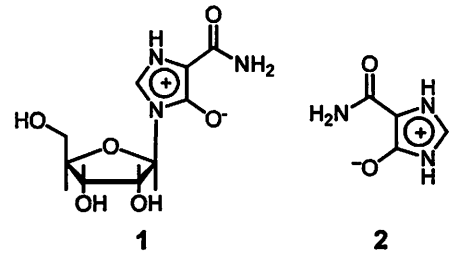
Ref) 1. Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, 126, 1352-1353.
2. Takasu, K.; Inanaga, K.; Ihara, M. *Tetrahedron Lett.* **2008**, in press.

1P-25

Synthetic Method of 4-Carbamoylimidazolium-5-olate

Chihiro Kondo,*[a] Yusuke Higuchi,[a] Makoto Sunagawa,[b] and Nobuo Kato[a]
[a]The Institute of Scientific and Industrial Research, Osaka University
8-1, Mihogaoka, Ibaraki, Osaka 567-0047, Japan
[b]Department of Pharmaceutical Science, Teikyo Heisei University
2289, Uruido, Ichihara, Chiba 290-0193, Japan
ckondo33@sanken.osaka-u.ac.jp

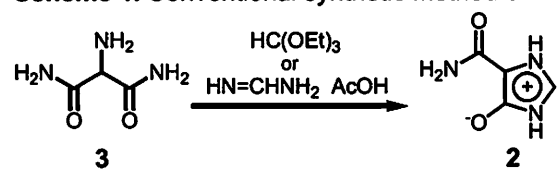
Bredinin (**1**) is a nucleoside type of compound containing an imidazol derivative as a base unit and was isolated from the culture filtrate of *Eupenicillium brefeldianum* M-2166 in 1974. It is reported that **1** shows selective cytotoxity against L5178Y cells derived from malignant lymphoma of mouse.[1] Today, **1** is clinically used as an immunosuppressive agent.



The aglycone of **1**, 4-carbamoylimidazolium-5-olate (**2**) (SM-108) also has potent antitumor activities against various tumors and, especially, has the excellent medicinal properties for myelodysplastic syndromes (MDS).[2] MDS is the hematopoietic stem cells disorder characterized by peripheral cytopenias in combination with a hyperplastic bone marrow. The problem is that some patients with MDS are prone to contract acute myelocytic leukemia (AML) within months to a few years. Though the rate of progression of symptoms is relatively low, there has been few chemotherapies for MDS. Therefore, **2** has attracted attention as a candidate of a new chemotherapeutic. Actually, the Phase II clinical trial had been conducted by Sumitomo Pharmaceuticals Co., Ltd in 1980s. However, the development of **1** discontinued because of the limited marketability in those days and the instability of **2**. However, as the number of patients of MDS is increasing nowadays, we tried to solve the latter problem to lead the pharmaceutical development of **2** once again.

2 has been conventionally synthesized by the condensation reaction of aminomalonamide (**3**) with triethyl orthoformate or formamidine acetate (**Scheme 1**).[3] However, the dark-blue-colored by-products are produced in this synthetic process and the removal of the colorants by recrystallization and/or the charcoal treatment are in vain. The purification method by use of anion exchange resin has been reported to obtain highly-pure colorless **2**.[4] However, the use of a large excess of resin is not suitable for an industrial process. Hence, we decided to improve the synthetic route to obtain colorant-free **2** directly.

Scheme 1. Conventional synthetic method of **2**

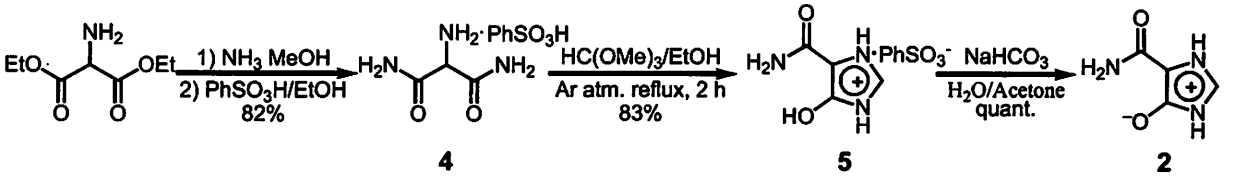


When the reaction was conducted in the air, argon gas or a sealed tube, the degree of the coloring of crude **2** was restrained in this order. Therefore, it is clear that oxidation process must be involved in the coloring process. Besides, a colorless aqueous solution of purified **2** turned blue in a few weeks. Contrarily, an aqueous solution of the salt of **2** with benzenesulfonic acid is stable and no coloration was observed even

after a few months. These observations clearly demonstrate that **2** is stable under the acidic conditions and the coloration proceeds in basic and oxidative conditions. Actually, both of the reactant **3** and the product **2** can act as base, and two equivalents of ammonia are generated during the condensation reaction in case of the use of formamidine acetate. The key to develop a new synthetic procedure was the selection of an appreciate reagent, and the amount and the strength of acid to maintain the reaction medium slightly acidic. We found that orthoformate is the choice as a reagent because a catalytic amount of the strong acids accelerated the condensation reaction from **3** to **2**, whereas acidic conditions significantly retarded the reaction rate of the condensation between **3** and formamidine acetate. Then, we investigated acids that can maintain appropriate acidity of the reaction medium. As a result, benzenesulfonic acid was the best choice to afford the colorless and crystalline salt of **2**, because the salt precipitated out from the medium during the reaction and, therefore, the acidity of the medium was controlled nearly constant from the beginning to the end point of the reaction.

The new synthetic procedure is shown below. Firstly, crude **3** obtained by ammonolysis of diethyl aminomalonate was purified as a salt (**4**) with benzensulfonic acid. The salt, **4**, could be used directly to the condensation reaction with trimethyl orthoformate in ethanol afforded colorless salt (**5**) of **2** in good yield by simple filtration after the completion of the reaction. Finally, we succeeded in getting colorless **2** by neutralizing **5** with sodium hydrogencarbonate, taking advantage of the difference of the solubility with sodium benzenesulfonate (**Scheme 2**).

Scheme 2. New synthetic procedures for colorant-free **2**



This synthetic process of SM-108 (**2**) is quite simple and suitable for large-scale preparation. Furthermore, benzenesulfonic acid salt (**5**) of **2** can be stored without any decomposition over months.

references

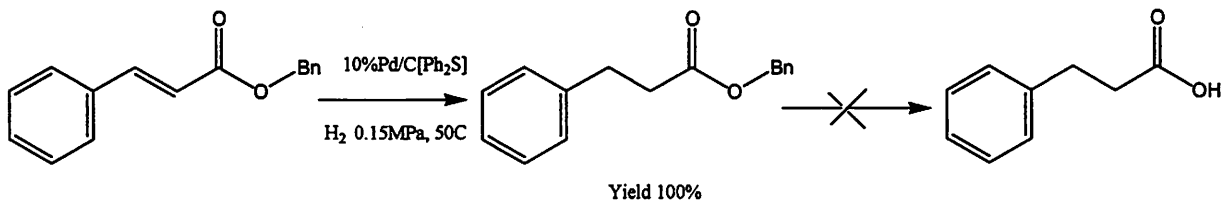
1. K. Mizuno, M. Tsujino, M. Takada, M. Hayashi, K. Atsumi, *J. Antibiot.*, **27**, 775 (1974).
2. K. Kimura, K.Yamada, Y. Uzuka, T. Masaoka, M. Hirano, R. Ohno, M. Ogawa, Gan to Kagaku Ryoho. Cancer & Chemotherapy, 16, 123 (1989).
3. E. Schipper, A. R. Day, *J. Am. Chem. Soc.*, **74**, 350 (1952).; T. Atsumi, Y. Takebayashi, J. Katsube, H. Yamamoto, JP51088965; P. D. Cook, D. J. McNamara, JP59170075.
4. T. Atsumi, F. Kishimoto, Y. Tarumi, J. Katsube, S. Ogino, H. Yamamoto, JP Application No. S52-118468.

1P-26

Novel Palladium-on-Carbon Catalyst, Pd/C[Ph2S], for Chemoselective Hydrogenation

Tomoteru Mizusaki, Shinobu Takao, Masashi Endo,* Masatoshi Yoshimura, Yukio Takagi
Technical Center of Chemical Catalysts, N.E. Chemcat Corporation
678, Ipponmatsu, Numazu, Shizuoka, 410-0314, Japan
masatoshi.yoshimura@ne-chemcat.co.jp
Akinori Mori, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki
Department of Medicinal Chemistry, Gifu Pharmaceutical University
5-6-1, Mitahora-higashi, Gifu, 502-8585, Japan

Palladium-on-carbon catalyst is a popular catalyst for hydrogenation. But due to its high reactivity, the catalyst normally cannot distinguish the functional groups on substrates. Sajiki[1] et al. recently reported on the novel palladium-on-carbon catalyst modified with diphenyl sulfide which shows excellent selectivity on hydrogenation reactions. For example, in the case of benzyl cinnamate as a substrate, 10%Pd/C[Ph2S] shows 100% selectivity toward the hydrogenation of the double bond keeping benzyl protecting group untouched, while the benzyl protecting group were liberated on our standard catalyst (10%Pd/C) under the same condition. This catalyst shows hydrogenation selectivity toward carbon-carbon double bond, triple bonds or nitro groups over carbonyls, benzyl or benzyloxycarbonyl protecting groups.



Scheme 1

About the preparation of this catalyst, characteristic about this catalyst is that it is tolerant to the excessive dope of diphenyl sulfide and its reactivity is relatively unaffected by the amount of diphenyl sulfide introduced on the catalyst, while other sulfur containing compounds are often strongly poisonous to palladium and their excessive dope on the catalyst ends up in the complete loss of reactivity. This means that this catalyst is easy to prepare, but still excess of diphenyl sulfide on the catalyst can be eluted into the reaction media during the reaction and can be the contaminant to the product. In this work, we optimized the amount of the diphenyl sulfide added to Pd/C and found not only that the elution of diphenyl sulfide can be minimized, but also the reactivity is improved (Fig. 1).

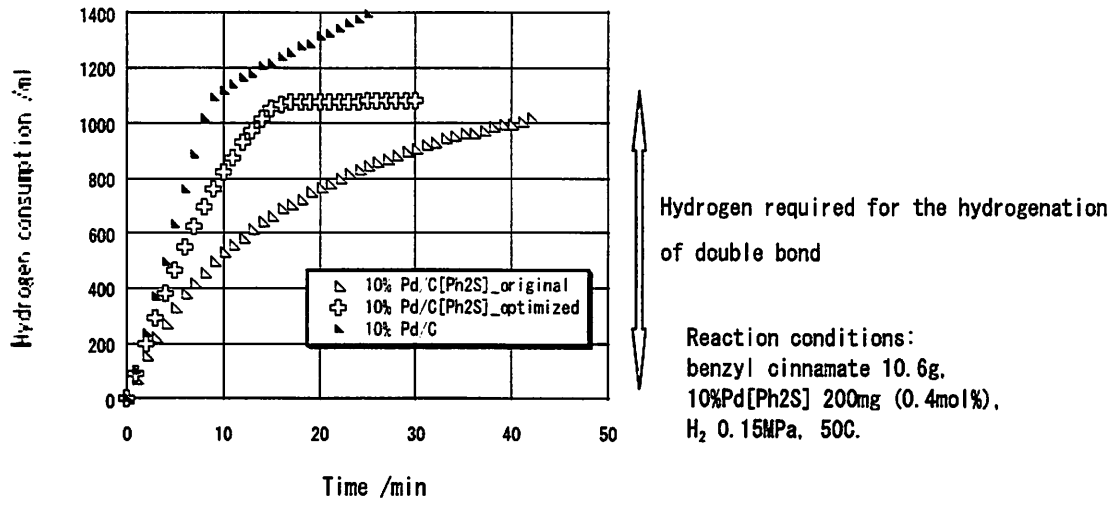


Fig. 1. Hydrogen consumption during the hydrogenation reaction of benzyl cinnamate.

As shown in the first run in the recycling test (Table 1), the sulfur content in the reaction media after the reaction was only 1 ppm which was originally 5 ppm before the optimization of the preparation process.

Table 1. Results of the catalyst recycling test on the hydrogenation of benzyl cinnamate

# of runs	Conversion[%]	Selectivity[%]	Pd [ppm]	S[ppm]
1	100	100	<1	1
2	100	100	<1	1
3	100	100	1	<1
4	100	100	<1	1
5	100	100	<1	1

This catalyst was also proved to be robust on the repeated usage. Its reactivity and selectivity is unchanged throughout the test (up to 5 times). This possibility of catalyst recycling can be advantageous from the economical point of view.

Regarding the role of diphenyl sulfide, although some data is reported in the literature, it still left ambiguous. In this work, several 10%Pd/C[Ph2S] samples with different amount of diphenyl sulfide were analyzed by XPS, EPMA. These results are compared with other samples doped with another sulfur containing compound. The detailed results and the speculation on the origin of selectivity in hydrogenation reactions will be discussed in the presentation.

Reference

1. A. Mori, T. Mizusaki, M. Kawase, T. Maegawa, Y. Monguchi, S. Takao, Y. Takagi, H. Sajiki, *Adv. Syn. Cat.* **2008**, *350*, 406.

1P-27

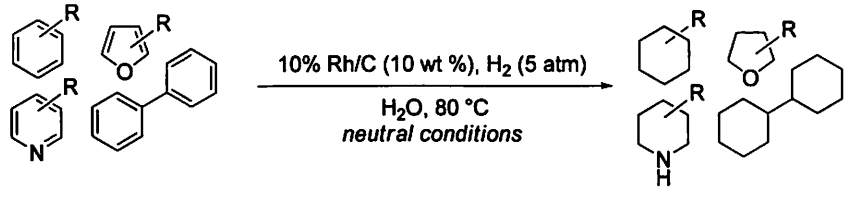
Hydrogenation of Aromatic Nuclei : Practical Synthesis of Cyclohexanol Derivatives

Kiichiro Yaguchi, * Akira Akashi, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University.
6-1, Mitahora-higashi 5-chome, Gifu, 502-8585, Japan
yakuhin@gifu-pu.ac.jp

【Introduction】

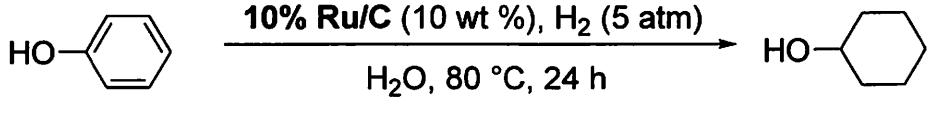
Cyclohexanol derivatives are important intermediates of natural products, pharmaceuticals, chemical raw materials and so on. There are some synthetic methods of cyclohexanol derivatives, for example, (1) the oxidation of cyclohexane derivatives and (2) the reduction of cyclohexanone derivatives, although they still have some problems, such as low selectivity and limitation of the applicability. The hydrogenation of phenol derivatives is one of the significant methods for the synthesis of cyclohexanols. Such methods are effective for the industrial process although the drastic conditions (for example: addition of a strong acid or base and high reaction temperature and pressure) are necessary because of the resonance stabilization of the aromatic ring. Therefore, the development of facile and mild hydrogenation method of phenol derivatives has been strongly desired. Recently we have developed a convenient and efficient hydrogenation of aromatic rings catalyzed by heterogeneous 10% Rh/C (80 °C in water under 5 atm of hydrogen pressure, Scheme 1, *Synlett.* **2006**, 1440). It is applicable to the hydrogenation of diverse aromatic compounds including the heterocycles under mild and neutral conditions.

Scheme 1



While the use of Rh/C as a catalyst is rather difficult for the application of this method to the industrial process in point of cost, the Ru/C-catalyzed reaction will be a much more cost-effective and applicable method. We recently found the hydrogenation of phenolic nuclei was also achieved under 10% Ru/C-catalyzed mild reaction conditions (Scheme 2).

Scheme 2

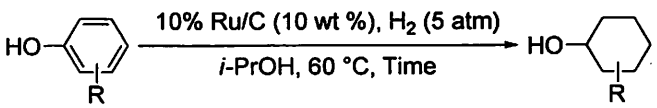


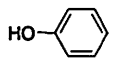
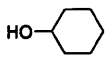
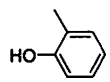
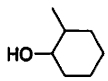
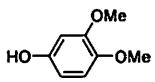
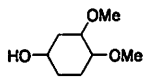
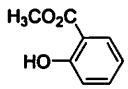
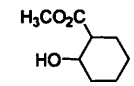
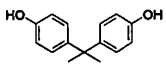
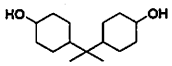
【Experimental Results】

To optimize the reaction conditions of Ru/C catalyzed hydrogenation of phenol, we first examined the effect of solvents. The hydrogenation proceeded efficiently in alcoholic media and *i*-PrOH was chosen as the best solvent of this reaction.

The present reaction was widely applicable to the reduction of diverse phenolic nuclei. Phenol was easily hydrogenated at 60 °C for 3 h under 5 atm hydrogen pressure (Table 1, Entry 1). Other phenol derivatives bearing electron-donating and electron-withdrawing groups were also hydrogenated to the corresponding cycloaliphatic alcohols (Entries 2-4). While the hydrogenation of bisphenol A, which is used as a synthon of functional materials, was not complete at 60 °C, the increase of the reaction temperature to 90 °C was effective for the completion of the hydrogenation (Entry 5). Furthermore, the application of additional heat and H_2 pressure to the reaction led to the completion of the nuclei-hydrogenation of even relatively-stable substrates. In fact, estrone was completely hydrogenated in *i*-PrOH at 120 °C under 10 atm of hydrogen pressure whereas the reaction was not completed at 90 °C under 5 atm of hydrogen pressure (Scheme 3).

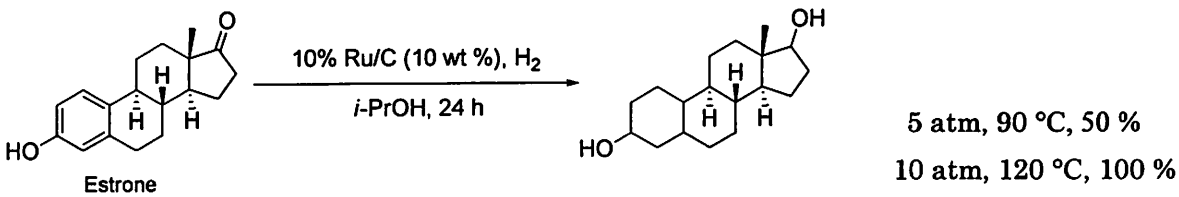
Table 1. Ru/C Catalyzed Hydrogenation of Various Phenols



Entry	Substrate	Time (h)	Product	Conv. (%)
1		3		100
2		5		100
3		24		100
4		8		100
5		21[a]		100

[a] At 90 °C.

Scheme 3



The present reaction could provide an environmental friendly and practical method of the hydrogenation of phenols. This method will provide the new strategy for the synthesis of cyclohexanol derivatives in the industrial scale.

【Acknowledgement】

This work was supported in part by the 2008 Foundation Nagase Science Technology Development.

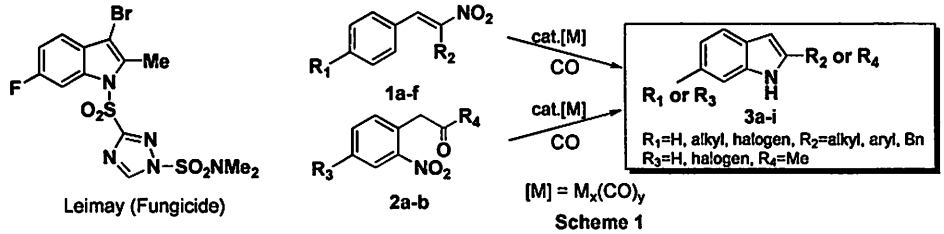
1P-28

Transition Metal Catalyzed Construction of Indole Nucleus under CO Conditions

*Yasuhiro Sakurai, Yasuo Shirai, Tomohisa Utsunomiya, Norio Tanaka
Technical Development Division, Onoda Plant, Nissan Chemical Industries, Ltd.
6903-1, Onoda, Sanyoonoda-shi, Yamaguchi, 756-0093, Japan
sakuraiy@nissanchem.co.jp

The transition metal-catalyzed reductive N-heterocyclization of organic nitro compounds employing carbon monoxide as the stoichiometric reductant is a powerful and essential tool for construction of N-contained heterocycles[1]. Among the various N-contained heterocycles, indole is one of the most interesting ring because of its potentiality as the substructure of biologically active compounds in pharmaceutical and agrochemical field. There have been reported several transition metal-catalyzed indole syntheses in the presence of CO so far, but they utilizes 2-nitrostyrene derivatives as a starting material and comparatively expensive metal catalyst[2]. From the viewpoint of accessibility to prerequisite material and cost of catalyst, the development of efficient and versatile synthetic method is desired.

Nissan Chemical Industries, LTD. has just launched new fungicide Leimay®, which shows excellent activity against vine downy mildew, potato late blight and other plant diseases caused by Phycomycetes fungi. In the course of process research for the efficient synthesis of indole moiety of Leimay, we have found new synthetic approaches starting from readily accessible two different substrates, (E)-β-nitrostyrene **1** and 2-nitrophenylacetone **2** (Scheme 1)[3]. Herein, we wish to report that reductive cyclization of **1** and **2** in the presence of transition metal catalysts under CO atmosphere, producing substituted indoles **3** in good to excellent yields.



Scheme 1

First the reaction of (E)-*p*-fluoro-β-nitrostyrene **1a** (R_1=F, R_2=Me) in toluene in the presence of catalytic amount of metal carbonyl complex was examined and the results are summarized in Table **1**. When using $Co_2(CO)_8$, $Ru_3(CO)_{12}$, $Rh_6(CO)_{16}$ and $Fe(CO)_5$ as a catalyst, the reaction proceeded and gave the expected 6-fluoro-2-methylindole **3a** in modest yields (entry 1-4). From the economical point of view it was attractive that the reaction proceeded by iron catalyst. Encouraged by this result, various iron catalysts were screened, then it was found that $[CpFe(CO)_2]_2$ was the most efficient catalyst in this reaction and **3a** was obtained in 76% yield (entry 6). To probe the scope of this iron-catalyzed reaction, varieties of substituted (E)-β

-nitrostyrene were subjected to the representaive reaction conditions : 4mol% $[CpFe(CO)_2]_2$ in toluene. The results are summarized in Table 2. The substituent effect of R_1 on the product yield was not clearly shown (entry 1-3). In contrast, the yield was highly affected by R_2 and it was increased as the alkyl chain became long (entry 4-6). We assume that this is due to the stability of the nitrene intermediate, although no further mechanistic insights are available at this time.

Table 1. Reductive cyclization of 1a (R_1=F, R_2=Me) to 3a catalyzed by metal carbonyl complex

entry	catalyst	P_{CO} (kgf/cm^2)	temp (°C)	time (h)	yield[a)] (%)
1	$Co_2(CO)_8$	60	190	5	18
2	$Ru_3(CO)_{12}$	65	190	5	27
3	$Rh_6(CO)_{16}$	60	190	5	20
4	$Fe(CO)_5$	60	190	5	45
5	$Fe_3(CO)_{12}$	50	120	6	0
6	$[CpFe(CO)_2]_2$	70	120	5	76

Reaction conditions; substrate 3mmol, catalyst 4mol%(run1, 3-6), 5mol%(run2), solvent toluene, a) Determined by HPLC.

Table 2. Reductive cyclization of 1a-f to 3a-f catalyzed by $[CpFe(CO)_2]_2$

entry	substrate R_1	R_2	P_{CO} (kgf/cm^2)	temp (°C)	time (h)	yield[a)] (%)	conv.[a)] (%)
1	*p*-Cl	Me	50	120	5	66	100
2	H	Me	50	150	7	38	100
3	*p*-Me	Me	50	120	5	68	81
4	*p*-F	H	50	120	7	0	38
5	*p*-F	Me	70	120	5	76	100
6	*p*-F	Et	50	120	3	92	99

Reaction conditions; substrate 3mmol, $[CpFe(CO)_2]_2$ 4mol%, solvent toluene, a) Determined by HPLC.

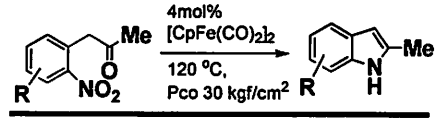
To apply above catalytic reaction to another substrates, further investigation was continued and it was discovered that 2-nitrophenylacetone derivatives **2** can be adopted (Table 3). Thus, reaction of **2a** (R_3=F, R_4=Me) in toluene in the presence of 4mol% $[CpFe(CO)_2]_2$ at 120 ℃ for 5 h under Pco 50 kgf/cm^2 gave **3a** in 91% yield (entry 4). Other catalyst systems such as $Ru_3(CO)_{12}$-1,10-Phen, $PdCl_2(PPh_3)_2$-$SnCl_2$ were also effective (entry 5-6). In addition the functional groups on the benzene ring that are generally sensitive to hydrogenation conditions like Br, Cl, OBn are compatible with this reaction conditions (Table 4).

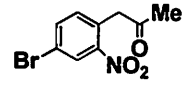
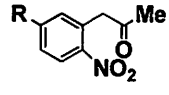
Table 3. Reductive cyclization of 2a (R_3=F, R_4=Me) to 3a catalyzed by various transition-metal catalyst

entry	catalyst	additive	P_{CO} (kgf/cm^2)	temp (°C)	time (h)	yield[a)] (%)	conv.[a)] (%)
1	$Fe(CO)_5$	none	50	200	4	14	79
2	$Fe_2(CO)_9$	none	50	200	4	16	78
3	$Fe_3(CO)_{12}$	none	50	200	4	17	81
4	$[CpFe(CO)_2]_2$	none	50	120	5	91	99
5	$Ru_3(CO)_{12}$	1,10-Phen[b)]	50	150	5	90	100
6	$PdCl_2(PPh_3)_2$	$SnCl_2$	20	120	8	86	100

Reaction conditions; substrate 3mmol, catalyst 4mol% (run1-5), 5mol% (run6),additive 8mol% (run5), 50mol% (run6), solvent toluene (run1-5) dioxane (run6), a) Determined by HPLC, b) 1,10-phenanthroline

Table 4. Functional tolerance of substrates



substrate		yield(%)
	2b	93
 R = Cl	2c	94
R = OBn	2d	82

References and Notes

1) S. Cenini and F. Ragaini, *Catalytic reductive carbonylation of organic nitro compounds,* KLUWER ACADEMIC PUBLISHERS (1997)

2) (a) C. Crotti, S. Cenini et al., *J. C. S. Chem. Commun.*, 784 (1986). (b) M. Akazome, T. Kondo, Y. Watanabe, *Chem. Lett.*, 769 (1992). (c) S. Cenini, C. Crotti et al. *J. Mol. Cat.*, 203 (1994). (d) B. C. Soderberg and J. A. Shriver, *J. Org. Chem.*, 5838 (1997).

3) (a) Y. Shirai, T. Utsunomiya, N. Tanaka, JP 2002-241364, (b) Y. Sakurai, T. Utsunomiya, N. Tanaka, JP 2005-35991

1P-29

Synthesis of Carbonyl Compounds through Aerobic Photo-oxidation

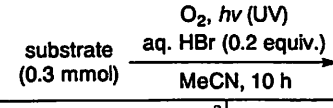
Akichika Itoh, Norihiro Tada, Shin-ichi Hirashima,* Hiroki Nakayama
Gifu Pharmaceutical University
5-6-1, Mitahora-higashi, Gifu, 502-8585, Japan
itoha@gifu-pu.ac.jp

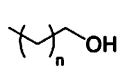
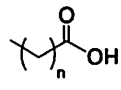
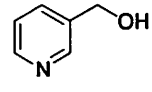
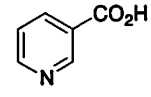
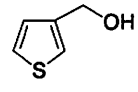
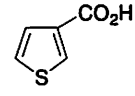
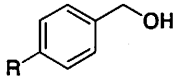
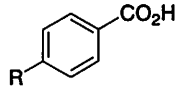
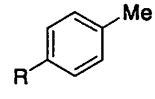
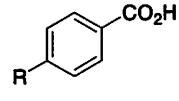
Oxidation is a most important transformation in organic synthesis; however, these reactions essentially involve the use of large quantities of heavy metals and complex organic compounds, which generate large amount of waste, and are not at all environmentally benign. On the other hand, recently, catalytic oxidation processes with molecular oxygen, which generate little waste, have been reported by many researchers. Molecular oxygen has received much attention as an ultimate oxidant, since it produces theoretically only water with a certain suitable catalyst and is inexpensive and of large atom efficiency than that of other oxidants. With this background in mind, we examined aerobic photo-oxidation, and obtained the following findings.

1. Aerobic Photo-oxidation under UV Irradiation.

We found that a methyl group at the aromatic nucleus and alcohols were oxidized directly to the corresponding carboxylic groups in the presence of a catalytic amount of bromine sources such as LiBr, aq.HBr and Br_2 under UV irradiation (<400 nm) (Table 1). [1)] Aliphatic primary alcohols afford the corresponding carboxylic acids in moderate yields; however, aliphatic secondary alcohols were less reactive than primary alcohols (entries 1-3). The corresponding benzoic acids were obtained in high yield regardless of an electron-donating or electron-withdrawing group at aromatic nucleus when using benzyl alcohols (entries 4-6). Heterocyclic compounds also afforded the corresponding carboxylic acids in high yields (entries 7 and 8). Although an electron-donating group at aromatic nucleus, in general, enhanced the reaction rate, an electron-withdrawing group retarded it when using a methyl group at the aromatic nucleus as substrate (entries 9-13).

Table 1 Aerobic Photooxidation under UV Irradiation in the Presence of aq. HBr.



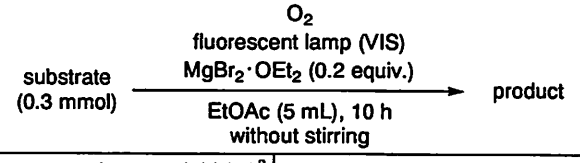
entry	substrate	product	yield (%)[a]	entry	substrate	product	yield (%)[a]
1	 n = 10		69[b]	7			100
2	n = 4		66				
3			57[c]	8			83
4	 R = -*t*Bu		99	9	 R = -^{t}Bu		98[d]
5	R = -OMe		92	10	R = -OMe		87[d]
6	R = -Cl		100	11	R = -Cl		50[d]
				12	R = -CN		53[d]
				13	R = -NO_2		87[d,e]

[a] All yields are for pure, isolated products. [b] The reaction was carried out using 0.14 equiv. of aq. HBr. [c] The reaction was carried out for 20 h. [d] The reaction was carried out in EtOAc. [e] The reaction was carried out for 36 h.

2. Aerobic Photo-oxidation under VIS Irradiation.

The reaction mentioned above becomes safe, economical and steady, and the equipment is more easily installed, if visible light (VIS) from a fluorescent lamp is applicable instead of UV from a high pressure mercury lamp. This is the driving force of our continued wide-ranging studies on this oxidation with a new bromine source, and we have found that $MgBr_2 \cdot OEt_2$ is suitable for this purpose (Table 2). [2] Aliphatic primary alcohols afforded the corresponding carboxylic acids in good yields; however, secondary alcohols were found to give the products in modest yields (entries 1-3). Benzyl alcohols were also found to give the corresponding benzoic acids in high yield (entries 4-11). Furthermore, 3-thiophenemethanol afforded 3-thiophenecarboxylic acid in 81% yield (entries 12). In the case of a methyl group at the aromatic nucleus, an electron-donating group at aromatic nucleus accelerates the reactions, and afforded the corresponding carboxylic acids in high yield (entries 13-15). Although an electron-withdrawing group retarded the reaction, yield of the products were high for a longer reaction time (entries 17 and 18).

Table 2 Aerobic Photooxidation under Visible Irradiation in the Presence of $MgBr_2 \cdot OEt_2$.



entry	substrate	product	yield (%)[a]
1	n = 10		84
2	n = 4		64
3			49[b]
4	R = -H		96
5	R = -tBu		89
6	R = -OMe		93
7	R = -Cl		69[c]
8	R = -NO_2		89
9			60
10	R = 1-CH_2OH		78
11	R = 2-CH_2OH		92
12			81
13	R = -^{t}Bu		98
14	R = -OMe		99
15	R = -Ph		99
16	R = -Cl		87
17	R = -CN		86[b]
18	R = -NO_2		90[b]

[a] All yields are for pure, isolated products. [b] The reaction was carried out for 36 h. [c] 4-Chlorobenzoic anhydride was also obtained in 25% yield.

This new form of oxidation reaction is interesting in keeping with the notion of green chemistry due to the non-use of heavy metals and halogenated solvents, waste reduction, use of molecular oxygen and safe reagents.

References

1) A. Itoh, S. Hashimoto, Y. Masaki, *Synlett*, 2639 (2005); A. Itoh, S. Hashimoto, T. Kodama, Y. Masaki, *Synlett*, 2107 (2005); S. Hirashima, S. Hashimoto, Y. Masaki, A. Itoh, *Tetrahedron*, **62**, 7887 (2006); S. Hirashima, A. Itoh, *Synthesis*, 1757 (2006).

2) S. Hirashima, A. Itoh, *Green Chem.*, **9**, 318 (2007); S. Hirashima, A. Itoh, *Photochem. Photobiol. Sci.*, *6*, 521 (2007).

1P-30

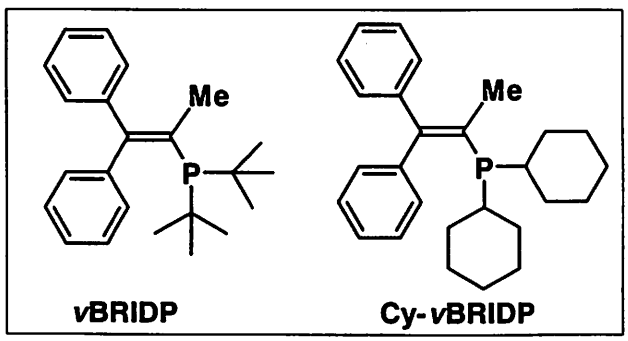
Design and development of new catalyst systems: Palladium/BRIDP for efficient coupling reactions

Tohru Kobayashi,* Ken Suzuki, Noboru Sayo
Corporate Research & Development Division,Takasago International Corporation
4-11, 1-Chome, Nishi-Yawata, Hiratsuka City, Kanagawa 254-0073, Japan
tohru_kobayashi@takasago.com

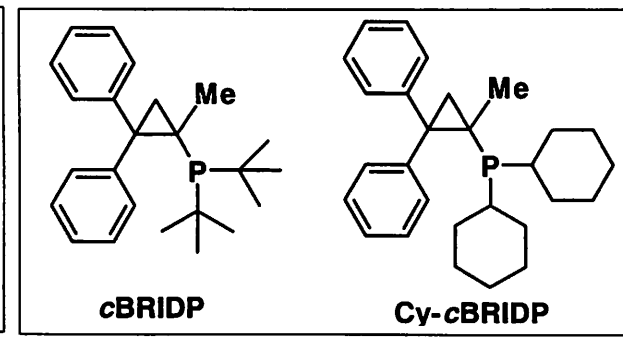
In the pharmaceutical and chemical industries, Pd-catalyzed cross coupling reactions have often been used for carrying out key bond formations. While many phosphines and carbenes have been known as the ligands that efficiently mediate carbon-heteroatom and carbon-carbon bond formations, there is still a demand for ligands that enable to open up the options in order to apply to various substrates.

Initial efforts towards the coupling reaction with applicable aryl halides have used generally available phosphine ligands such as (o-tolyl)$_3$P and BINAP.[1] Although aryl bromides have successfully been used for coupling reactions, employment of less active aryl chlorides has had limited success. Considering applications for industrial processes, the choice of aryl chloride is extremely significant because of its lower cost and better availability.

Characteristics that efficient ligands reported recently have in common are electron-richness and steric hindrance.[2] To develop a more effective phosphine ligand by strengthening these characteristics, we designed two types of new phosphine ligands, BRIDPs. Based on a vinylphosphine structure, a series of diphenylvinylphosphines, *v*BRIDPs were synthesized.[3] A methyl substituent at the α-position on the phosphine could make the ligand more sterically hindered around the phosphorus. To increase electron density of the ligand, the β-position was substituted by two phenyl moieties where could enjoy modifying with substituent groups. On the other hand, a *c*BRIDPs series featured by a cyclopropane structure was designed to add the more increasing common characteristics to *v*BRIDPs.[4] The cyclopropane brought three hindered alkyl substituents to the phosphorus as effective trialkylphoshpine such as t-Bu$_3$P and Ad$_2$PBu.[5] In the point that a spatial relationship between a phosphorus and a phenyl group on the ligands influences the reactivity, *c*BRIDPs virtually have the same as *v*BRIDPs and others.[6]

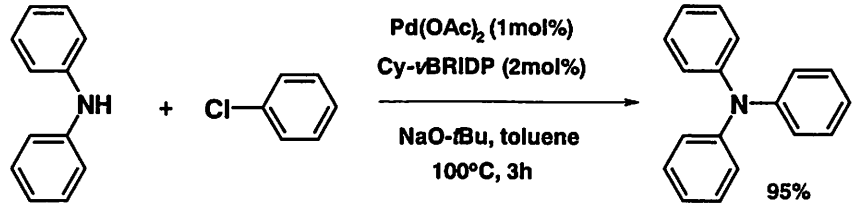


*v*BRIDPs

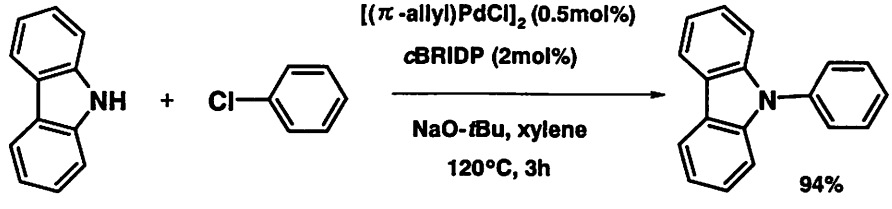


*c*BRIDPs

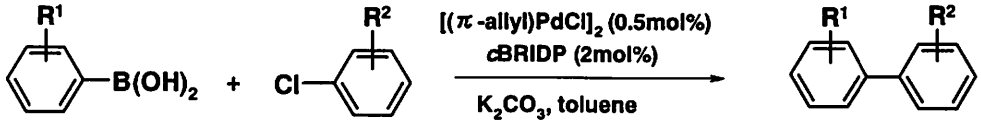
Pd-catalyzed carbon-nitrogen bond formation has become an important synthetic reaction in the past 20 years. First, we examined the general coupling reaction of aryl halides with amines using Cy-*v*BRIDP, which was one of the most effective phosphines among the BRIDPs series. A catalyst system that consists of Pd/Cy-*v*BRIDP was active for the reaction of aryl chlorides. For example, the reaction of chlorobenzene with diphenylamine gave triphenylamine in 95% yield. Both electron-rich and electron-poor aryl chlorides could be also converted to the corresponding tertiary amines from secondary amines.



A Pd/*c*BRIDPs system efficiently catalyzed the arylamination of aryl chlorides as well. The reactions of chlorobenzene with carbazole was successfully completed in 3h to afford *N*-phenylcarbazole in 94%.



In addition, Suzuki-Miyaura coupling reactions and α-arylation of ketones using the Pd/BRIDPs catalytic system were successful for both electron-rich and electron-poor aryl chlorides.



R^1=H, R^2=*o*-CO_2Me; 96%
R^1=*p*-Me, R^2=*p*-OMe; 96%

References:

1) a) J .P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118,* 7215; b) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1995**, *34,* 1348; c) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, 36, 3609.

2) a) J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2047; b) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125.

3) K. Suzuki, Y. Hori, T. Nishikawa, T. Kobayashi, *Adv. Synth. Catal.* **2007**, *349*, 2089.

4) K. Suzuki, Y. Hori, T. Kobayashi, *Adv. Synth. Catal.* **2008**, *350*, 652.

5) a) M. Nishiyama, Y. Koie, *Tetrahedron Lett.* **1998**, *39*, 617; b) T. Yamamoto, M. Nishiyama, Y. Koie, *Tetrahedron Lett.* **1998**, *39*, 2367; c) A. Zapf, M. Beller, *Chem. Com.* **2005**, 431.

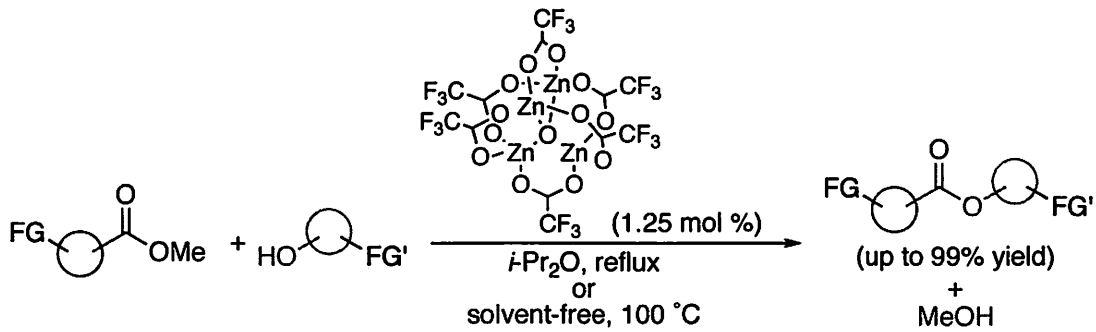
6) a) D. Zim, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 2413; b) E. R. Strieter, D. G. Blackmond, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125,* 13978; c) J. P. Wolfe, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1999**,*38,* 2413.

1P-31

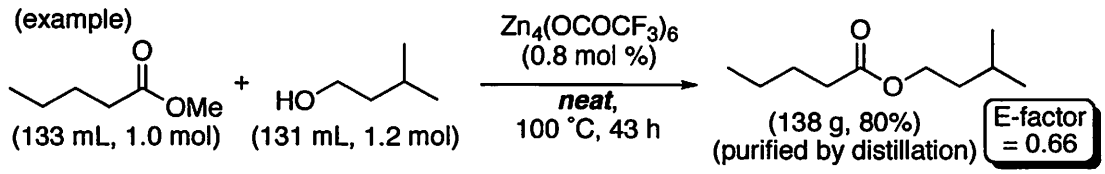
Development of Protecting Group Free Catalytic *O*-Selective Acylation of Aminoalcohols

Takashi Ohshima,* Takanori Iwasaki, Yusuke Maegawa, Kazushi Mashima
Department of Chemistry, Graduate School of Engineering Science, Osaka University
1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan
ohshima@chem.es.osaka-u.ac.jp

Over the last few decades, the quest for the most economic ways to the formation of chemical bonds has become a matter of increasing importance among both industrial and academic research units. Thus, in order to develop highly atom-economical and environmentally benign synthetic process, we have focused on the development of highly selective and practical direct catalytic reactions. Recently, we developed the direct conversion of esters to oxazolines using a catalytic amount of a novel trifluoroacetate-bridged μ-oxo-tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$.[1] Because this catalysis proceeds through acylation and cyclodehydration reactions, which utilize a cooperative mechanism of zinc ions similar to that of aminopeptidase and efficient multimetallic catalysts, the zinc cluster is expected to efficiently catalyze the acylation of alcohols in a manner similar to metalloenzyme. In fact, we found that the zinc cluster is highly efficient catalyst for transesterification of various methyl esters with various primary and secondary alcohols.[2] The mild reaction conditions enabled the reactions of various functionalized substrates to proceed in good to high yield. A large-scale reaction under solvent-free conditions proceeded with a low E-factor value (0.66), indicating the high environmental and economical advantage of the present catalysis.

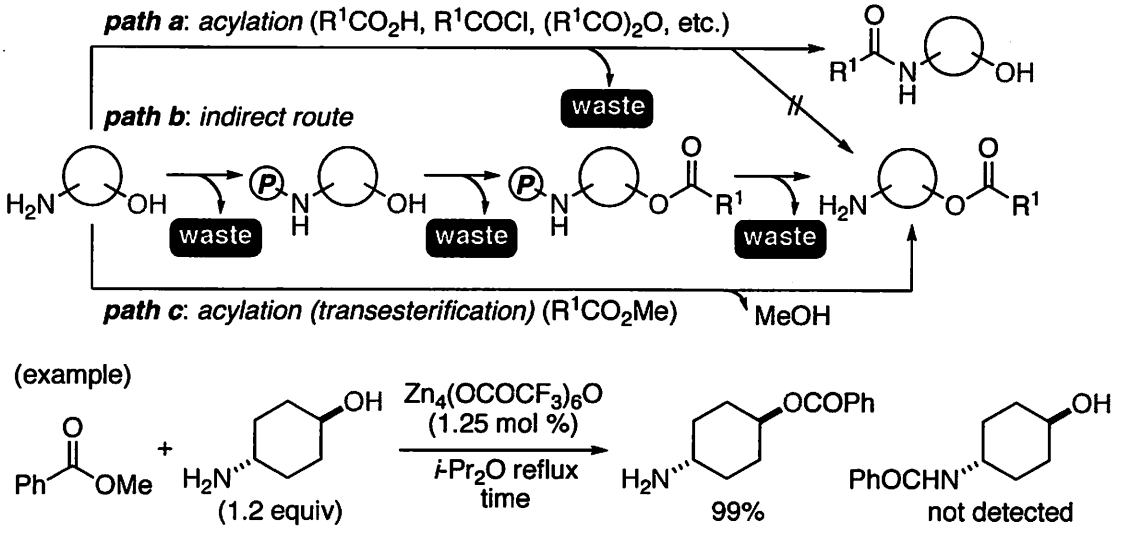


FG = Boc, Cbz, and Fmoc carbamates, acetal, amide, *tert*-Bu ester, enone, triene, etc.



Acylation of alcohols (esterification) and amines (amidation) is one of the most fundamental and widely used reactions in both organic and biologic reactions. As the nucleophilicity of the amino group is much greater than that of the hydroxyl group, the amine can be selectively acylated to give the corresponding amide, even in the presence of excess alcohols and/or water. This chemoselectivity has been well utilized

for several highly efficient amidation reactions such as the Schotten-Baumann reactions (*path a*). On the other hand, selective *O*-acylation (*path c*) is quite difficult to perform in ordinary organic reaction, even though lipase catalyzes highly selective *O*-acylation in the presence of primary alkyl amines. When an aminoester is targeted, the only feasible route is indirect protection-deprotection process including in situ protection with acid (*path b*). The requirement for such a multistep transformation decreases the atom-economy of this process. Moreover, some notable exception aside, any acylation, including esterification and amidation, using carboxylic acid, acid chloride, or acid anhydride requires a stoichiometric amount of the condensing reagent or base, resulting in the formation of more than a stoichiometric amount of unwanted chemical waste. To comply with the demand for an environmentally benign process, reversing the normal chemoselectivity of path a and minimizing waste are very important. The ideal method leading to the development of a new transformation without using protecting groups is a direct catalytic conversion of aminoalcohol to aminoester in a highly chemoselective manner (*path c*); however, there are no examples of such a reaction using an artificial catalyst. Here, we show that acylation using the zinc cluster efficiently catalyzes a highly chemoselective acylation of hydroxyl groups in the presence of primary and secondary alkyl amino groups to afford the corresponding esters in high yields.[3] Furthermore, the present method can be applied to the direct conversion of aminoalcohols to the corresponding aminoesters, providing an option for developing a new transformation without the use of protecting groups. Our strategy towards achieving these results was to assemble metal ions to be a starting point for the development of further enzyme-like chemoselective reactions.



(1) Ohshima, T.; Iwasaki, T.; Mashima, K. *Chem. Comm.* **2006**, 2711.

(2) Iwasaki, T.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *J. Org. Chem. in press.*

(3) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A. Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944.

1P-32

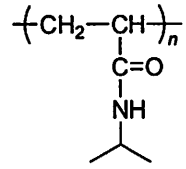
Development of Recyclable Ruthenium Catalysts for Aerobic Oxidation Utilizing Poly(*N*-isopropylacrylamide)-Based Polymer

Hiromi Hamamoto[1,2],* Masahiro Kudoh[2], Hideyo Takahashi[2], Hideaki Natsugari[2], Shiro Ikegami[2], Yasuyoshi Miki[1]

School of Pharmaceutical Sciences, Kinki University[1]
3-4-1 Kowakae, Higashi-Osaka, Osaka 577-8502, Japan
School of Pharmaceutical Sciences, Teikyo University[2]
Sagamiko, Sagamihara, Kanagawa 229-0195, Japan
hamamoto@phar.kindai.ac.jp

Due to significant advantages over homogeneous catalysts such as ease of recovery and recycling, atom utility, and enhanced stability, solid-supported (heterogeneous) catalysts have gained increasing attention in the last few years. The development of heterogeneous catalytic oxidation systems that use molecular oxygen as a primary oxidant, which is readily available and produces water as the sole by-product, is of paramount importance.[1] Many attempts have been directed toward the heterogenization of soluble catalytic species, and various supports with differing physical properties have been explored. The use of inorganic supports, such as hydroxyapatite, microporous zeolite, mesoporous silica, etc., is effective in the creation of recyclable aerobic oxidation systems. In contrast, examples of metal catalysts supported on functional polymers for aerobic oxidation are still limited, even though they may possess multifunctional advantages and could allow material applications.

Poly(*N*-isopropylacrylamide)[PNIPAAm]-based polymers have intrinsically temperature-responsive behavior and undergo thermally reversible changes between water-soluble and -insoluble states across a lower critical solution temperature (LCST) from 30°C to 40°C. Owing to this unique characteristic, they have been applied in various fields such as drug-delivery systems, column packing materials, and cell culture substrates. In the course of our research on the utilization of PNIPAAm as a catalyst support material, PNIPAAm-bound catalyst was found to be useful in the development of recyclable oxidation systems[3]. We report here a novel design of a PNIPAAm-bound ruthenium catalyst developed for use in conjunction with molecular oxygen.



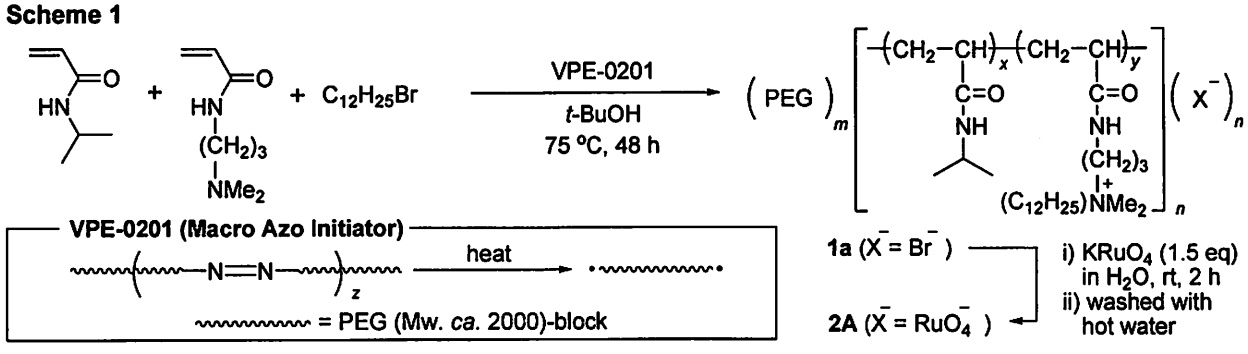
PNIPAAm
Poly(*N*-isopropylacrylamide)

Ruthenium complexes have great potential for the catalytic oxidation reaction of various compounds. Among the ruthenium complexes, the peruthenate ion shows promising catalytic properties for various oxidative transformations. Tetrapropylammonium perruthenate alone is an active catalyst for the oxidation of alcohols if the water can be removed *in situ* by adding activated molecular sieves to the reaction system. Although the use of a polystyrene-based resin yielded polymer-bound perruthenate, it is still quite difficult to recycle, possibly due to oxidative degradation of the polymer support.

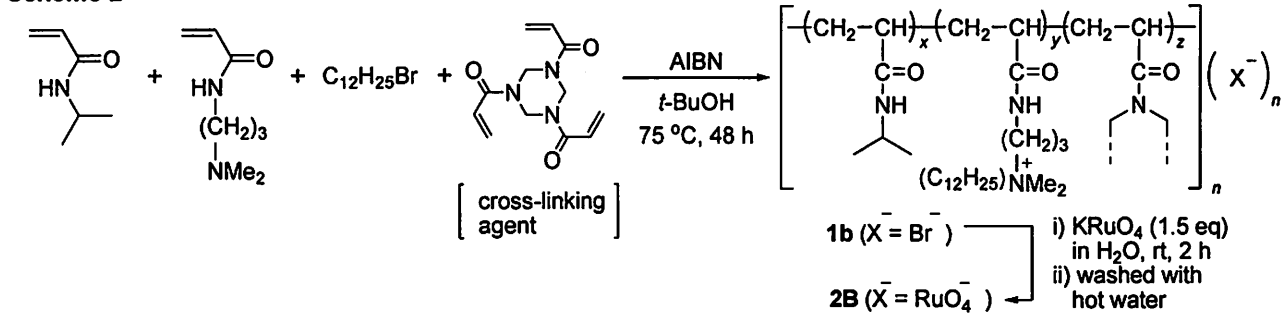
Scheme 1 and 2 show the preparation of the new PNIPAAm-bound ruthenium catalysts (**2**). The PEG block-containing PNIPAAm chain (**1a**) was easily prepared using the azo compound 4,4'-azobis(4-cyanovaleric acid)-PEG copolymer (VPE-0201) as a polymerization initiator, while the

cross-linked PNIPAAm (**1b**) was prepared using AIBN in the presence of cross-linking agent. Subsequent complexation with perruthenate in water afforded the new polymer-bound ruthenium catalyst **2A** and **2B**.

Scheme 1

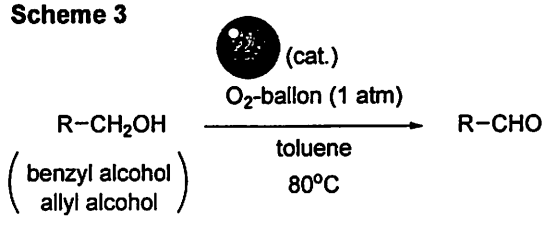


Scheme 2

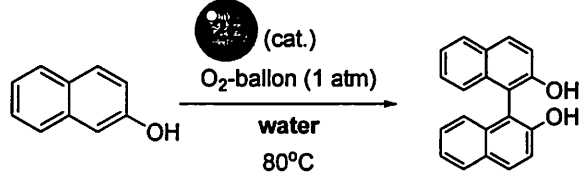


PEG-PINIPAAm-Ru (**2A**) showed highly activity in the oxidation of alcohol to carbonyl compounds with molecular oxygen, while cross-linked-PNIPAAm-Ru (**2B**) was effective for the oxidative biaryl coupling reaction of naphtols and substituted phenols with molecular oxygen. In addition, the recovered catalyst could also be used for consecutive reactions without any significant loss of catalytic efficacy in both cases (Schemes 3 and 4).

Scheme 3



Scheme 4



In summary, we developed a polymer-supported ruthenium catalyst and demonstrated its efficiency in aerobic oxidation. The utility of the PNIPAAm version of a heterogeneous catalyst and ease of catalyst preparation may offer multifunctional advantages in further applications. In addition, the results described here will enhance the utility of PNIPAAm polymers in the field of organic synthesis.

References

1) Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3058

2) (a) Haskins, M.; Guillet, J. E. *J. Macromol. Sci. Chem.* **1968**, *2*, 1441. (b) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163.

3) (a) Hamamoto, H.; Suzuki, Y.; Yamada, Y. M. A.; Tabata, H.; Takahashi, H., Ikegami, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 4536. (b) Hamamoto, H.; Kudoh, M.; Takahashi, H. Ikegami, S. *Org. Lett.* **2006**, *8*, 4015. (c) Hamamoto, H.; Kudoh, M.; Takahashi, H.; Natsugari H. Ikegami, S. *Chem. Lett.* **2007**, *36*, 632. (d) Hamamoto, H.; Suzuki, Y.; Takahashi, H., Ikegami, S. *Adv. Synth. Cat.* **2007**, *349*, 2685. (e) Hamamoto, H. Ikegami, S. *Yuki Gosei Kagaku Kyokaishi* , **2008**, 66, 205-214.

1P-33

Pd/C-catalyzed dehalogenation of aromatic halides and its application to degradation of PCBs

Shinji Ishihara,*[ac] Akiko Ido,[b] Tomohiro Maegawa,[a] Yasunari Monguchi,[a] Sueo Wada,[c] Hisamitsu Nagase,[b] Hironao Sajiki[a]

[a]Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University
5-6-1 Mitahora-higashi, Gifu, 502-8585, Japan

[b]Laboratory of Hygienics, Gifu Pharmaceutical University
5-6-1 Mitahora-higashi, Gifu, 502-8585, Japan

[c]Reserch and Development Section, Nagara Bionics Co., Ltd.
47 Nakano, Kasamatsu-cho, Hashima-gun, Gifu, 501-6034, Japan
sishihara@nabioweb.co.jp

Polychlorinated biphenyls (PCBs) had been used as insulating fluids for transformers and other electrical equipments, since they were recognized as persistent organic pollutants (POPs) which possibly cause cancer or/and hormone disruption. The production, import and use of PCBs were totally prohibited in 1974, and all PCB wastes must be legally disposed in environmental sound manner by July, 2016 in Japan. PCB degradation methods so far developed, however, have a serious problem; these methods require harsh conditions such as high heat, high pressure, and strongly basic conditions due to the chemical stability of PCBs. The time limit for the PCB waste disposal is coming up soon. Therefore, the immediate development of safe and reliable PCB degradation methods is expected.

Recently, we found the use of Et_3N remarkably and selectively enhanced the catalytic activity of palladium on carbon (Pd/C) toward the hydrodechlorination of aromatic chlorides under hydrogen atmosphere.[1),2)] The dechlorination method utilizing Pd/C-Et_3N system could be applied to the degradation of PCBs and DDT,[3)-5)] and the construction of PCB degradation plant is now in progress.[6)] In this symposium, we will present the novel catalytic PCB dechlorination method under milder conditions which never require hydrogen gas.

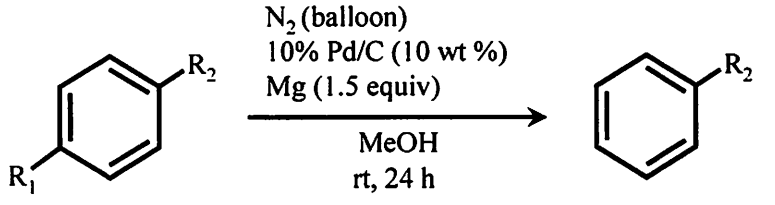
When a mixture of *p*-chlorobenzoic acid as a model substrate, 10% Pd/C (10 wt % of the substrate), and magnesium metal (1.5 equiv) in MeOH was stirred at room temperature under nitrogen atmosphere, the dechlorination was completed within 24 h. Other metal in place of magnesium was also investigated, but it was found that magnesium was the best choice. The combination of Pd/C-Mg-MeOH was then applied to the dechlorination of a variety of aromatic halides. As a result, aromatic halides that bear either an electron-donating group (Table 1, entry 1–4) or electron-withdrawing group (Table 1, entry 5–8) on the benzene ring were efficiently dehalogenated in the absence of hydrogen. We finally applied the present dehalogenation method to the degradation of PCBs. Although the addition of 2.2 equiv of magnesium metal towards the average chlorine number per a molecule (ACN) was necessary, Aroclor 1242 (ACN = ca.

3.1) underwent complete dechlorination within two hours to give a nontoxic biphenyl as a single product (Scheme 1).

Furthermore, the dechlorination of both Aroclor 1248 (ACN = 4.0) and Aroclor 1254 (ACN = 5.0) also smoothly proceeded.

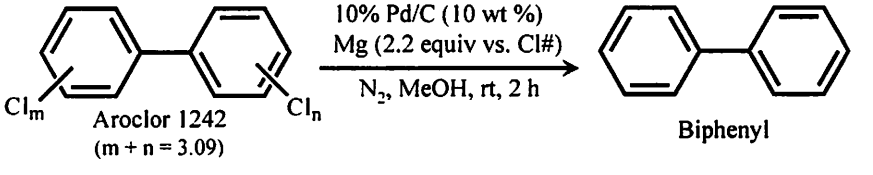
The present Pd/C-catalyzed dehalogenation of aromatic halides in the presence of magnesium metal was achieved at ambient pressure and temperature under inactive gas atmosphere (without hydrogen gas). The method could be successfully applied to the degradation of PCBs based on the dechlorination. These results are very promising for the development of the PCB degradation plant with high safety.

Table 1 Dehalogenation of aromatic halides



Entry	Substrate R_1	Substrate R_2	Conversion (%)
1	-Cl	-OH	100 (86)
2	-Cl	$-NH_2$	100 (70)
3	-Br	$-NH_2$	100 (71)
4	-Br	$-NHCOCH_3$	100 (69)
5	-Cl	$-COC_6H_5$	100 (81)
6	-Cl	$-CONH_2$	100 (70)
7	-Cl	$-COCH_3$	100 (91)
8	-Br	$-COCH_3$	100 (82)

Conversion yields were determined by GC-Mass and isolated yields were indicated in parenthesis.



Scheme 1 Degradation of Aroclor 1242 (PCBs)

References

1) Sajiki, H. et al. *Tetrahedron Lett.* **2002**, *43*, 7247.

2) Monguchi, Y. et al. *Tetrahedron* **2006**, *62*, 7926.

3) Monguchi, Y. et al. *Tetrahedron* **2006**, *62*, 8384.

4) Sajiki, H. et al. *Tetrahedron Lett.* **2002**, *43*, 7251.

5) Kume, A. et al. *Appl. Catal. B: Environ.* **2008**, in press.

6) Ishihara, S. et al. J.S.P.C. 2007 summer symposium abstracts book, 2P-25, p150.

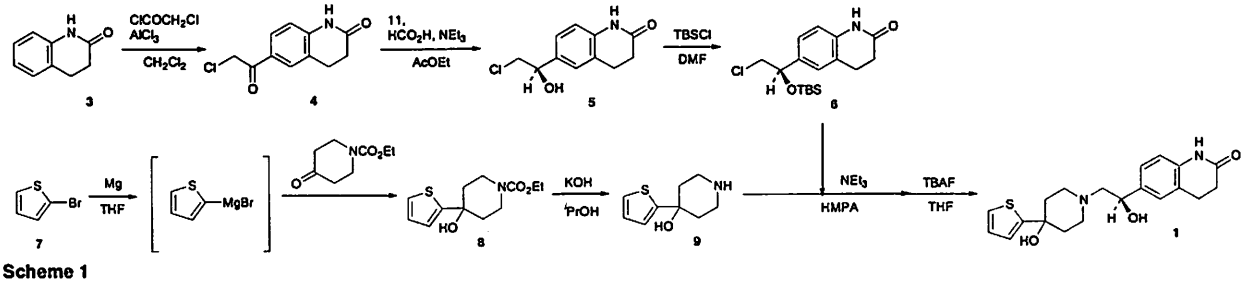
1P-34

Synthetic Studies on an NR2B Antagonist

Akira Ogawa,* Osamu Saku, Noriko Koizumi, Tsutomu Matsumura, Tomokazu Watanabe, Koichiro Nishimura, Iwao Chujo
Sakai Research Laboratories, Kyowa Hakko Kogyo Co., Ltd.
1-1-53, Takasu-cho, Sakai-ku, Sakai, Osaka, 590-8554, Japan
akira.ogawa@kyowa.co.jp

Process development of selective NMDA/NR2B antagonist **1**[1] is described. The synthesis features asymmetric reduction of beta-aminoketone **2**.

Compound **1** was originally synthesized by the coupling of piperidine derivative **9** with protected chloroalcohol **6**, which was prepared by asymmetric reduction of alfa-chloroketone **4** with Rh-diamine catalyst **11** reported by Noyori and co-workers[2] (Scheme 1). Taking into account the large-scale synthesis, this route had several issues. Though the asymmetric reduction of chloroketone **4** was carried out in the early stage of the synthesis, the resulting chiral alcohol **5** was unstable under basic conditions and it had the property of racemizing in easy (Figure 1). Therefore, the protection-deprotection process of the hydroxy group was necessary. Furthermore, it seemed to be preferable to prevent the use of CH_2Cl_2 (which might cause a negative environment impact) in the Friedel-Crafts reaction and Mg metal in the Grignard reaction (which was highly exothermic and potentially uncontrollable reaction). For these reasons, we decided to investigate an alternative strategy for the large-scale production of **1**.



Scheme 1

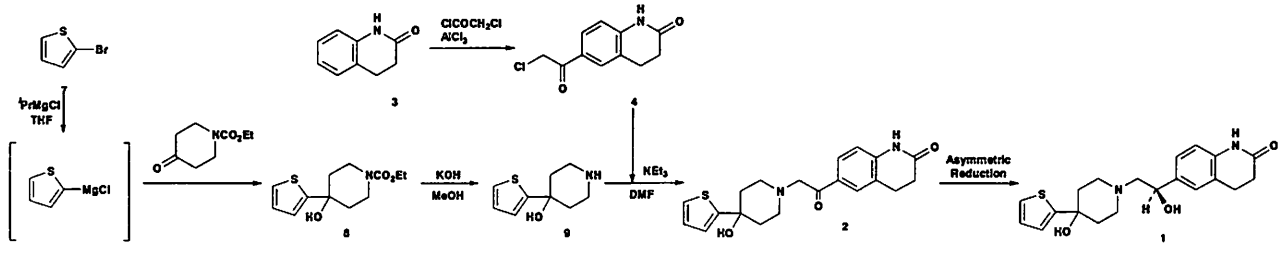
Figure 1

We focused the asymmetric reduction of beta-aminoketone **2** to obtain the chiral target compound **1** (Scheme 2). Though we also tried the optical resolution of racemic **1** using the diastereomeric salt methods or the enzymatic methods at the same instance, they were failed.

The beta-aminoketone **2** was easily prepared by the substitution reaction of piperidine derivative **9** chloroketone **4**. In the synthesis of **4**, we improved the Friedel-Crafts reaction conditions to use

chloroacetyl chloride instead of CH_2Cl_2 as a solvent. On the other hand, we established alternative method for the preparation of Grignard reagent using the halogen-Mg exchange reaction of 2-bromothiophene with ^{i}PrMgCl. Under these conditions, the reaction proceeded at 10℃ and the exothermic heat was controllable by adjusting the dropping rate of ^{i}PrMgCl solution.

Considering the asymmetric reduction of ketones, a great number of reagents and catalysts have been reported. Among them, we chose four different types of method (Figure 2) and tried asymmetric reduction of aminoketone **2**. The oxazaborolidine **10** mediated asymmetric reduction with borane gave complex mixture. Although desired alcohol **1** was obtained with high enantioselectivity (91%ee) by the asymmetric hydrogenation using Rh-phosphine complex **12**, pressurized condition was required and the conversion ratio was low. Both the transfer hydrogenation with Rh-diamine catalyst **11**[3] and asymmetric reducion by (-)-DIP-Cl[4] gave alcohol **1** in good yield with high enantioselectivity (99%ee and 95%ee, respectively). Regarding the transfer hydrogenation with catalyst **11**, the reaction completed only when HCO_2H was used as the hydrogen donor. On the other hand, it was found that the addition of $^{i}Pr_2NEt$ was essential for proceeding the reduction by (-)-DIP-Cl. After optimization of the process of both reaction conditions, we carried out the production of several hundred grams of **1**. As the results, the prolongation of the reaction period was observed in the transfer hydrogenation method, and we were concerned the reproducibility of reaction in further scale-up. Thus the DIP-Cl was selected as the reducing agent for large scale production and the process was demonstrated on multi-kilogram scale.



Scheme 2

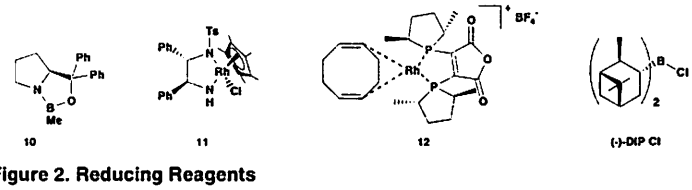


Figure 2. Reducing Reagents

References

1. WO 2005/097782.
2. WO 97/20789.
3. JP 2006/312626.
4. *J. Org. Chem.* 1985, 50, 5448-5450.

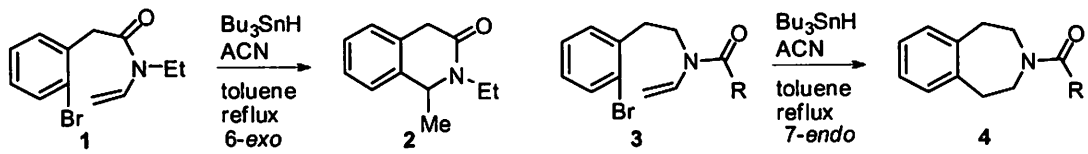
1P-35

Total Synthesis of Natual Products Using a Radical Cascade

Tsuyoshi Taniguchi,* Hiroyuki Ishibashi
Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology,
Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan
isibasi@p.kanazawa-u.ac.jp

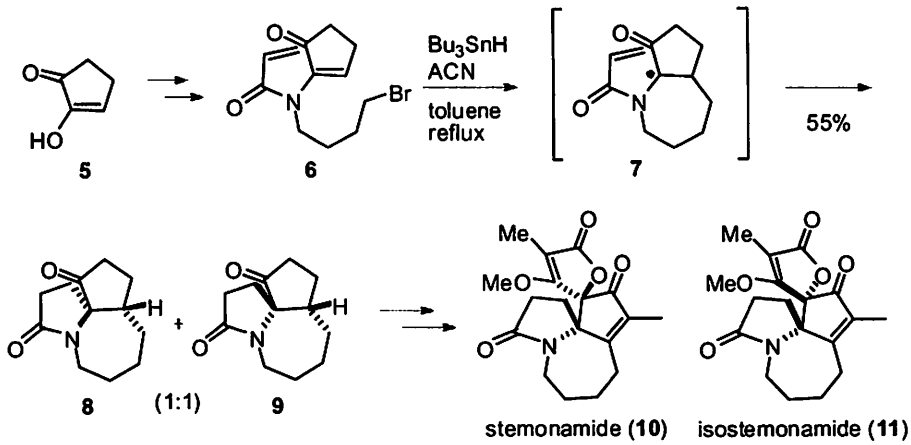
Radical cyclization has been a powerful tool in organic synthesis. In particular, the reaction is efficient in the synthesis of complex polycyclic natural products.

Recently, our investigation on the regioselectivety of radical cyclizations discovered 6-*exo* and 7-*endo* selective radical cyclization onto enamides.[1] Treatment of enamide **1** with Bu_3SnH in presence of ACN (1,1'-azobiscyclohexanecarbonitrile) gave 6-*exo* cyclization product **2**, whereas, enamide **3** gave 7-*endo* cyclization product **4**.

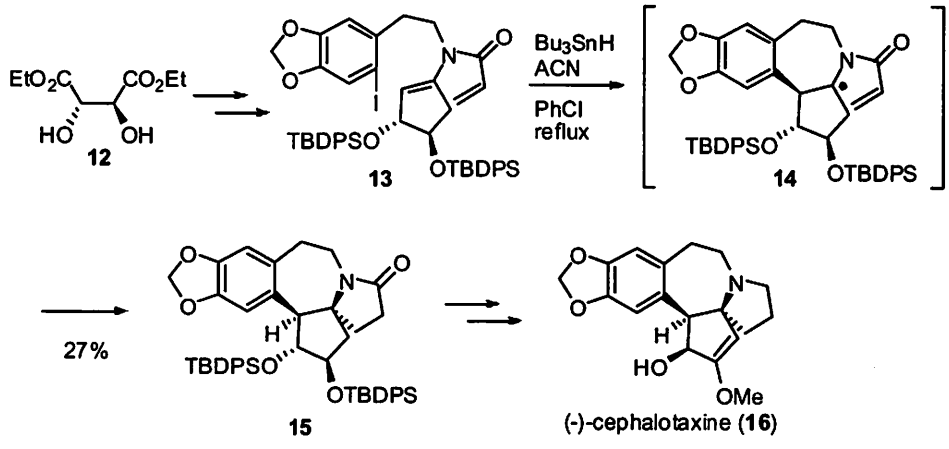


We assumed that the later process was useful for the concise construction of azepine skeleton. Herein, we wish to report the successful total synthesis of stemonamides and cephalotaxine using a radical cascade involving 7-*endo* selective cyclization onto enamides.

Stemonamide (**10**) and isostemonamide (**11**) were isolated from the roots of *Stemona japonica* that are used in Japanese and Chinese folk medicine.[2] The complex tricyclic skeleton of these alkaloids was easily constructed by using a radical cascade. Treatment of enamide **6**, which was prepared from 1,2-cyclopentanedione (**5**) in 4 steps, with Bu_3SnH/ACN in boiling toluene gave a mixture of two isomers **8** and **9**, through 7-*endo* cyclization of **6** followed by 5-*endo* cyclization of the resultant α-amidoyl radical **7**. Compounds **8** and **9** were converted to (±)-stemonamide (**10**) and (±)-isostemonamide (**11**) through some chemical transformations, respectively.[3]



Similarly, asymmetric total synthesis of (–)-cephalotaxine (**16**), isolated from plants of *Cephalotaxus* family whose extraction showed potent antileukemic activity,[4] was achieved using a radical cascade involing 7-*endo* selective cyclizations. Treatment of optically active compound **13**, which was prepared from diethyl D-tartrate (**12**), with Bu_3SnH/ACN in boiling chlorobenzene gave a radical cascade product **15** via radical intermediate **14** in a stereoselective manner. Subsequent chemical transformation of compound **15**, involing deprotection, oxidation, *O*-methylation and reduction of carbonyl groups, provided (–)-cephalotaxine (**16**).



Above successful radical cascade gave us the way to the complex polycyclic skeleton of alkaloids. Further studies directed toward synthesis of other alkaloids and their derivatives using the radical cascade strategy are now in progress.

Reference

(1) (a) Ishibashi, H.; Ohata, K.; Niihara, M.; Sato, T.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 547. (b) Ishibashi, H.; Kato, I.; Takeda, Y.; Kogure, M.; Tamura, O. *Chem. Commun.* **2000**, 1527. (c) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922.

(2) Ye, Y.; Qin, G.-W.; Xu, R.-S. *J. Nat. Prod.* **1994**, *57*, 665.

(3) Taniguchi, T.; Tanabe, G.; Muraoka, O.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 197.

(4) Miah, M. A. J.; Hudlicky, T.; Reed, J. W. Cephalotaxus alkaloids. In The Alkaloids; Academic Press: New York, 1998; Vol. 51, pp. 199-269.

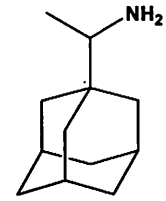
Production of Chiral Amines including Adamantyl Groups by Optical Resolution

Taichi Akimoto,*[1] Tetsuro Watadani,[1] Shigeki Nunomura,[1] Yukio Takahashi,[1] Isao Fujii[2]
[1]Daito Chemical Co., Ltd, Suka 2700, Hiratsuka, Kanagawa, 254-0022, Japan
[2]Dept. of Biological Sci. and Tech.,Tokai University, Nishino 317, Numazu, Shizuoka, 410-0321, Japan
t-akimoto@dcg.co.jp

[Introduction]

Racemic rimantadine, *RS*-1-(1-adamantyl)ethylamine (*RS*-ADEA), possesses some antagonistic properties against N-methyl-D-aspartic acid (NMDA) and is used as an anti-parkinsonic drug.[1] *RS*-ADEA is also an orally administered antiviral drug used to treat and prevent influenza A infection.[2] Previous studies suggest that the M2 coat protein in virus envelope, a proton channel, plays an important role in the susceptibility of influenza A virus to inhibition by *RS*-ADEA. The production of chiral amines has great importance in the pharmaceutical industry, such as chiral switch. On the other hand, adamantane derivatives have been applied to electrical or optoelectrical materials because of its significant physicochemical properties: transparency in deep-UV to Vis region, high temperature resistance, low permittivity and so on. In the frontier, excimer laser exposure (ArF) has been applied in semiconductor productions, and this process requires a photoresist made from adamantane derivatives.[3] Potentially chiral control of adamantane derivatives will educe some oriented structure and polarization property in materials.

The chiral resolution of *RS*-ADEA has been reported using gas chromatography method,[4),5)] but it is not suitable for practical use. Optical resolution and asymmetric synthesis are the prime choice of methodologies to obtain synthetic homochiral compounds. *RS*-ADEA and optical resolution agents have been applied in the diastereomer salt separation. In this study, we focus on production of chiral ADEA, and clarify the inherent structures of *R*-ADEA diastereomer salt with (*S*)-2-phenoxypropionic acid (*S*-PPA) by X-ray analysis.



RS-ADEA

[Methods & Results]

Resolution: RS-ADEA and resolving agent, which is one enantiomer of PPA, ibuprofen, ketoprofen, 2-phenylproponic acid, 2-(2-naphtyl)glyconic acid, tartaric acid and dibenzoyl tartaric acid (*R,R*-BzTA), were dissolved in an aqueous acetone at reflux. The solutions were slowly cooled at room temperature, and diastereomer salts were obtained after a few days in vials. A series of obtained ADEA complexes were given in Table 1. The bonding ratios of ADEA to resolution agents were determined by ^{1}H-NMR and non aqueous titration. The absolute configurations of the resolved ADEA were determined by comparing their specific rotation signs with that from *R*-ADEA/*S*-PPA complex, which absolute configuration was directly determined by following X-ray analysis. The enantiomeric purities were determined by HPLC analysis with chiral separation column after modification by *p*-tert-butylbenzoic chloride. The

Table 1 Diastereomer separation with resolving agents.

Resolving agent	Blending ratio[1)]	Bonding ratio[1)]	Yield[2)] / %	Optical purity[3)] / %ee (stereo)	Efficency[4)] / %
S-2-Phenoxy propionic acid	2	1	53	85 (*R*)	47
S-Ibuprofen	2	1	43	55 (*S*)	24
S-Ketoprofen	2	1	75	9.2 (*S*)	7
R-2-Phenyl propionic acid	2	1	86	40 (*R*)	34
R-2-(2-Naphtyl) glyconic acid	2	1	91	5.2 (*R*)	4.7
R,R-Tartaric acid	4	2	90	25 (*R*)	23
R,R-Dibenzoyl tartaric acid	4	2	83	53 (*R*)	44

1) The ratio of *R/S*-AEDA to resolving agent, 2) The yield is diastereomer salt's, 3) The optical purity is diastereomer salt's, 4) The efficiency is yield x optical purity.

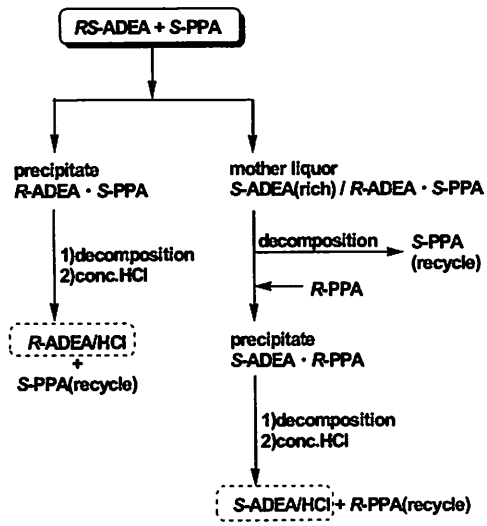


Fig. 1 optical separations of *R/S*-ADEA with PPA

first optical separations with *S*-PPA and *R,R*-BzTA show high resolution efficiencies. PPA was selected because of its versatile resolving agent and chemical stability against racemization and decomposition. The complex with *S*-PPA were recrystallized from various organic solvents such as methanol, ethanol, 2-propanol, acetonitrile and so on, but crystals from aqueous solvents of methanol, ethanol and acetone were of higher enantiomeric purity. After the second crystallization with *S*-PPA, the enantiomeric purity was determined to be >98% ee. After acid treatment, R-ADEA hydrochloride salt was recoverd from organic solution. *S*-PPA is also recycled by double decomposition. From the mother liquor excluded *S*-PPA, *S*-ADEA hydrochloride salt was similarly separated with *R*-PPA. It shows that the process was easy and practical to be obtained enantiomers of ADEA shown in Fig. 1.

Table 2 Crystal and experimental data

	R-ADEA / *S*-PPA
Formula	$C_{12}H_{22}N$ / $C_9H_9O_3$
Formula weight	345.47
Crystal system	Monoclinic
Space group	$P2_1$
Z	2
a / Å	13.1326(2)
b / Å	7.0015(2)
c / Å	10.6319(3)
b / °	100.05(8)
V / Å^3	964.4(5)
Dx/ g cm^{-3}	1.192
No. of reflections used	2187
2θmax/ ° with Cu Ka	149.8
$R1$	0.063
$(\Delta/\sigma)_{max}$	<0.0001

X-ray analysis: One planar colorless crystal of R-ADEA / S-PPA complex with a size of 0.4 x 0.3 x 0.3 mm was used for diffraction experiments. The crystal and experimental data are given in Table 2. The structure of complex with S-PPA was solved by direct methods and refined by the full-matrix least-squares. The absolute configuration was chosen to correspond to that of *S*-PPA. Non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were refined isotropically. All calculations were carried out with the program package WinGX32.

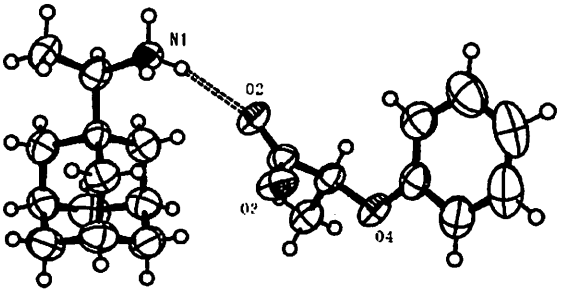


Fig. 2 Crystal Structure of R-ADEA/S-PPA

ORTEP drawing of R-ADEA/S-PPA is shown in Fig. 2. The crystal structure demonstrates the molecular recognition between R-ADEA and *S*-PPA with hydrogen bond and CH...π interaction. The deprotonated *S*-PPA molecules have an almost identical structure, as we have already reported.[6),7)] The *R*-ADEA molecule also displays a deprotonated structure, which is novel in the Cambridge Structural Database.

Physicochemical properties: The phase-transitions of *R*-ADEA hydrochloride salt was measured by DSC equipment: Shimadzu Inst. Co. Ltd., DSC-60; N_2 gas flow 100mL/min; 3.2×10^{-3} g of samples; a heating rate of 5 Kmin^{-1} from 297 to 573 K. *R*-ADEA hydrochloride is heat stable up to 513K, in which the exothermic reaction was observed.

[Conclusions]

We confirmed a reproducible optical separation process of R/S-ADEA using PPA. High purity enantiomers were obtained by decomposition via diastereomer salt formation. The absolute configuration was directly defined by X-ray analysis, in which the molecular recognition system of diastereomer salt was cleared.

[References]

1) Evidente V G; Adler C H et al., Clinical neuropharmacology(1999), **22(1)**, 30-2.
2) Koff W C; Knight V, J. of virology(1979), **31(1)**, 261-3.
3) Takechi, S; Kaimoto, Y et al, J. of Photopolymer Sci. and Tech.(1992), **5(3)**, 439-45.
4) Fukuda E K; Edom R W, J. of Chromatography(1988), **431**, 343-352
5) Fukuda E K; Garland W A et al., Biochemical Chromatography(1992), **6**, 12-15.
6) Watadani, T; Takahashi et al., Analytical Sci. Online (2004), **20**, x141-x142.
7) Fujii, I; Watadani, T et al., Analytical Sci. Online (2006), **22(4)**, x75-x76.

1P-37

Organic synthesis utilizing tetrahydropyran-boron complex

Hiroshi Yasuda,* Yoshihiko Maeda
Corporate R&D Center (Kawasaki), Showa Denko K.K.
5-1, Ogimachi, Kawasaki-ku, Kawasaki, Kanagawa 210-0867 Japan, Hiroshi_Yasuda@sdk.co.jp
Takeshi Oriyama, Ryoichi Chiba
Faculty of Science, Ibaraki University, 2-1-1, Bunkyo, Mito 310-8512 Japan, tor@mx.ibaraki.ac.jp

The synthesis, properties, and reactions of the boron trifluoride-tetrahydropyran (BF_3-THP) complex and borane-tetrahydropyran (BH_3-THP) were examined. BF_3-THP may be isolated as a pure material only after reduced-pressure distillation; its structure was confirmed by NMR. It was also clarified in a thermal decomposition experiment that BF_3-THP rapidly decomposes at approximately 200°C. BF_3-THP shows a slightly weaker Lewis acidity than BF_3-Et_2O, and it has the following advantages: minimal change in color during storage under ambient air, limited amount of smoking owing to insensitivity to humidity, and small changes in purity, all of which make it easy to handle and store. BF_3-THP is used as a catalyst in cationic polymerizations. In contrast, it is easy to prepare the BH_3-THP complex when BH_3 is absorbed by THP. The storage stability of BH_3-THP is much higher than that of BH_3-THF. It was clarified that reactivity and selectivity of BH_3-THP are equivalent to BH_3-THF during hydroboration and reduction reactions.

BF_3-THP complex

Synthesis: BF_3-THP was synthesized by introducing BF_3 gas to THP. The crude product was subjected to reduced-pressure distillation (bp.55°C/ 15 mmHg) to obtain BF_3-THP of 99% purity or more (yield: 91%).

Structure: In the ^{1}H-NMR(Fig.1) and ^{13}C-NMR(Fig.2) spectra, a shift of OCH_2 to a lower magnetic field was observed in BF_3-THP compared with THP alone. This tendency is also observed in the spectra of BF_3-Et_2O and Et_2O. Therefore, we speculate that THP exists as a complex rather than individually. With respect to ^{11}B-NMR(160 MHz, internal standard boric acid, -19.52 ppm), a chemical shift similar to that observed for BF_3-Et_2O and BF_3-THP was found, which also supports the notion that BF_3-THP exists as a complex.

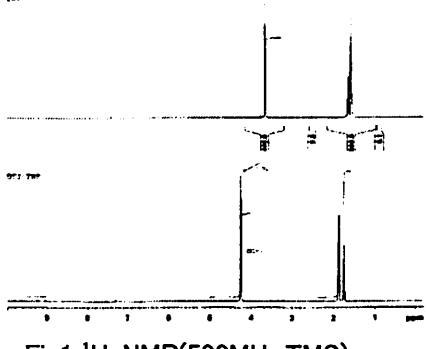


Fig1 ^{1}H-NMR(500MHz,TMS)

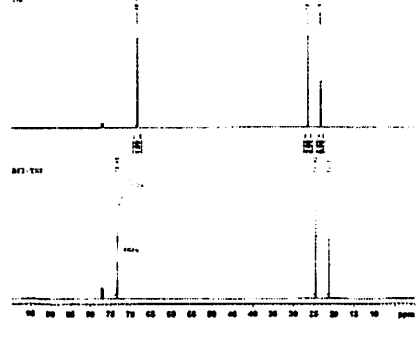


Fig2 ^{13}C-NMR(126MHz,CDCl3)

Stability: The thermal decomposition of BF_3-THP was carried out. Figure 3 shows the results for differential scanning calorimetry (DSC). As shown in Fig. 3, it was found that BF_3-THP produces heat gradually at approximately 190 °C and rapidly at approximately 200 °C.

Reaction: Cationic polymerization was carried out. In the polymerization of methylstyrene, the reaction proceeds at a lower temperature, the molar mass of the polymer is higher, and the polymer is more active when BF_3-THP is used as a catalyst (Fig. 4). In a solvent-free reaction, the polymerization is uncontrollable, and it is also difficult to control the reaction when BF_3-Et_2O is used as a catalyst. On the other hand, a mild polymerization takes places and the reaction is easy to control when BF_3-THP is used as a catalyst.

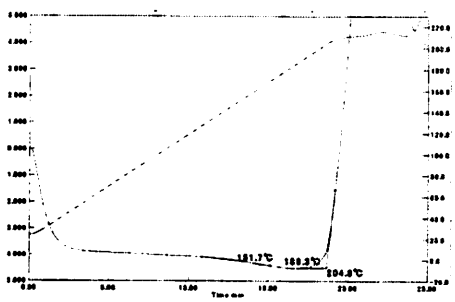
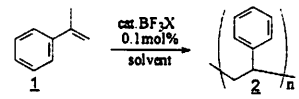


Fig3 DSC of BF_3-THP



run	BF_3X	solvent	temp.(°C)	2 Mw
1	Et_2O	Toluene	0–14	312
2	THP		0–4	4357
3	Et_2O	DCM	0–11	336
4	THP		0–6	4767
5	Et_2O	–	0–133	6576
6	THP		0–22	5031

Fig4 Cationic polymerization of methylstyrene

BH_3-THP complex

Synthesis: Diborane is produced using sodium borohydride and dimethyl sulfate in diglyme. The diborane produced is absorbed by THP to prepare the BH_3-THP complex. The concentration (0.82 mol/l) was measured using a gas burette. BH_3-THF was prepared using a similar method.

Structure: Analyses of proton, carbon, and boron NMR of BH_3-THP were carried out. Although the presence of BH_3 in THP was confirmed, concrete proof for its existence in the form of the BH_3-THP complex was not obtained.

Stability: BH_3-THP (complex? or solution?), BH_3-THF (complex? or solution?), and BH_3-THF (reagent) were stored at room temperature (approximately 30 °C) during summer to evaluate their stabilities in terms of the rate of alcohol production, which is associated with the decomposition of the cyclic ether (Fig. 5). For both complexed(?) and reagent BH_3-THF, the amount of the decomposed material, n-butanol, gradually increased, whereas for BH_3-THP, the formation of the decomposed material, n-pentanol, was not observed.

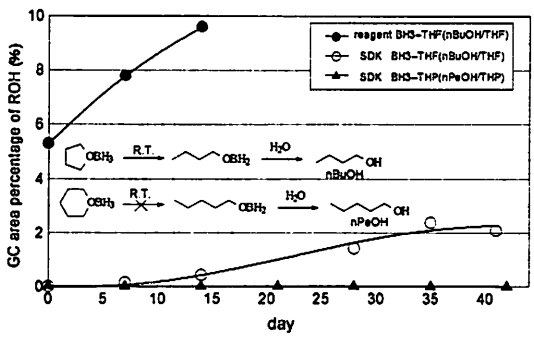
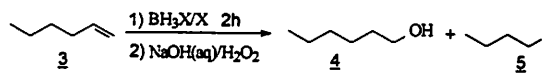


Fig5 Stability of borane-cyclic ether complex



BH_3X/X	temp.(°C)	4	5	yield(%)
THF	0–14	93.5	6.5	98
THP	0–4	93.2	6.8	98

Fig6 Hydroboration of terminal olefin

Reaction: The hydroboration of a terminal olefin (Fig. 6) were carried out using BH_3-THP. No difference in the reactivity, selectivity, and product yield between BH_3-THP and BH_3-THF was observed during either reaction. THP-derived by-products were also not detected. BH_3-THP showed a reactivity equivalent to that of BH_3-THF, and the storage stability of BH_3-THP was excellent.

1P-38

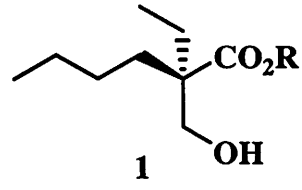
Construction of Quaternary Chiral Center by Asymmetric Transfer Claisen Rearrangement

Kazuhiko Watabe, Kazumi Okuro, and Masaru Mitsuda*
Frontier Biochemical and Medical Research Laboratories, Corporate Research and Development, Kaneka Corporation
1-8, Miyamae-machi, Takasago-cho, Takasago, Hyogo 676-8688, Japan
masaru.mitsuda@kaneka.co.jp

Asymmetric synthesis has made remarkable progress since the middle of the 20th century. Pioneers in this realm realized a variety of asymmetric reactions (e.g.; asymmetric hydrogenation, epoxydation, aldol type reaction, Diels Alder reaction, and other reactions). Plenty of researchers have been struggling to develop advanced asymmetric reactions that proceed highly stereoselectively for a wide range of substrates. Nowadays, it seems as if any chiral molecules could be produced by the asymmetric synthesis reported in the abundant literature. However, most of the process researchers know that there still remain several problems to be solved for practical preparations of valuable chiral products.

Construction of a quaternary stereo center is a typical subject focused as a new frontier of the asymmetric synthesis. Especially, few methods have been reported for general synthesis of the quaternary chiral compound, in which the chiral carbon atom is bonded to four different carbon substituents.

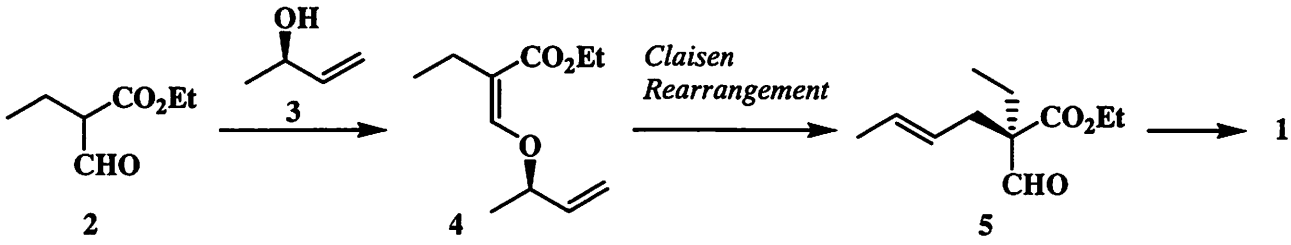
(*R*)-2-Ethyl-2-hydroxymethylhexanoic acid derivative (**1**) is an important compound as a key intermediate of hypolipidemics. It has a quaternary chiral center bonded to four different carbon groups, two of which are similar simple alkyl chains, ethyl and *n*-butyl group. This structural feature posed our challenge for an efficient asymmetric synthesis of **1.** Significant effect enough for chiral discrimination might not be expected by any enantioselective manner (including simple optical resolution) because of high similarity of steric or electrostatic property among the carbon substituents.



1

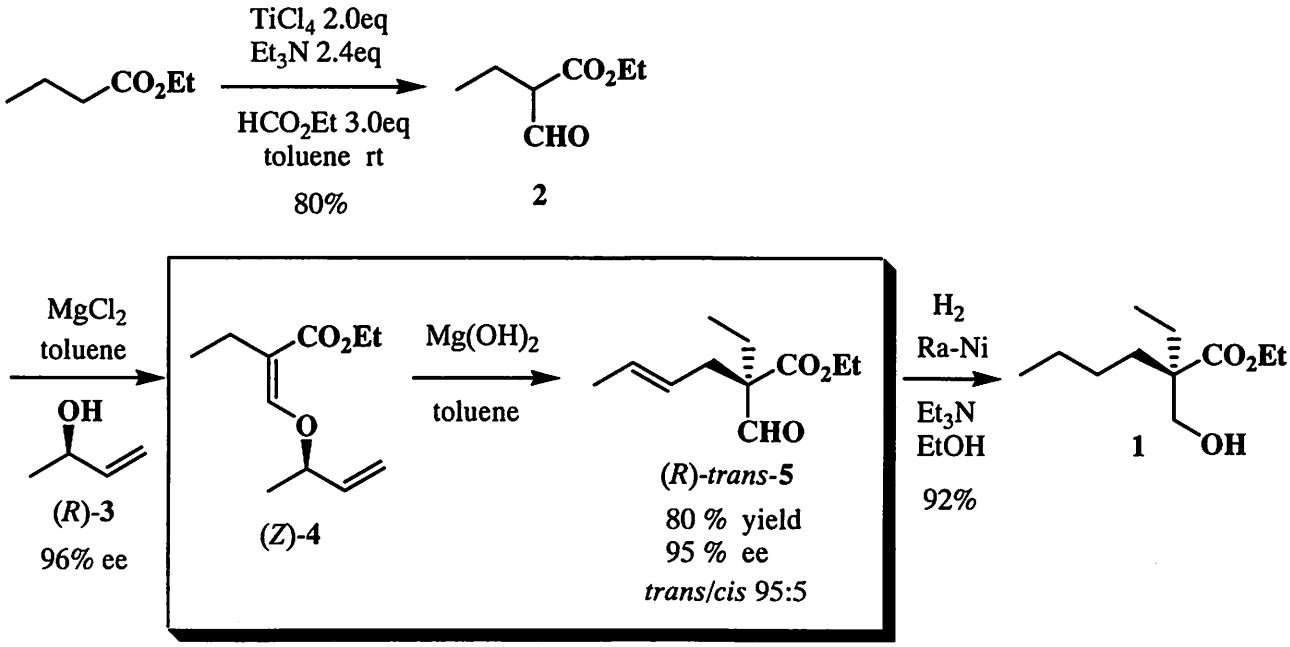
Tackling a process development of compound **1**, we found asymmetric transfer Claisen rearrangement was a powerful methodology for introducing chirality on the quaternary carbon atom with carbon substituents. Thus, as shown in **Scheme 1**, chirality of the allylic moiety in **4**, introduced by simple chiral alcohol **3**, was transferred in high ratio to the newly formed quaternary carbon atom on complicated compound **5**.

Scheme 1 *Asymmetric transfer Claisen rearrangement*



The compound **2**, prepared from ethyl *n*-butyrate and ethyl formate according to Tanabe's method was condensed with the chiral alcohol **3** in the presence of $MgCl_2$ to give the enol ether **4**. It is noteworthy that a single geometric isomer of **4** was obtained in this reaction. Claisen rearrangement of **4** to **5** was promoted by various electron deficient metal catalysts. The best result was observed in $Mg(OH)_2$ catalyzed reaction in terms of a chemical yield and asymmetric transfer efficiency. Finally, the α-formyl ester **5** was hydrogenated by Raney nickel catalyst under an atmospheric pressure of H_2 to give target compound **1**. Total synthetic process to **1** is summarized in **Scheme 2**.

Scheme 2 *Summary of the total synthetic process to target compound* (**1**)



In summary, we developed a new methodology for constructing quaternary chiral center bonded to four different carbon units by using asymmetric transfer claisen rearrangement. With this technology, complicated chiral compound **1** was synthesized from simple chiral compound **3** in high yield and high asymmetric efficiency.

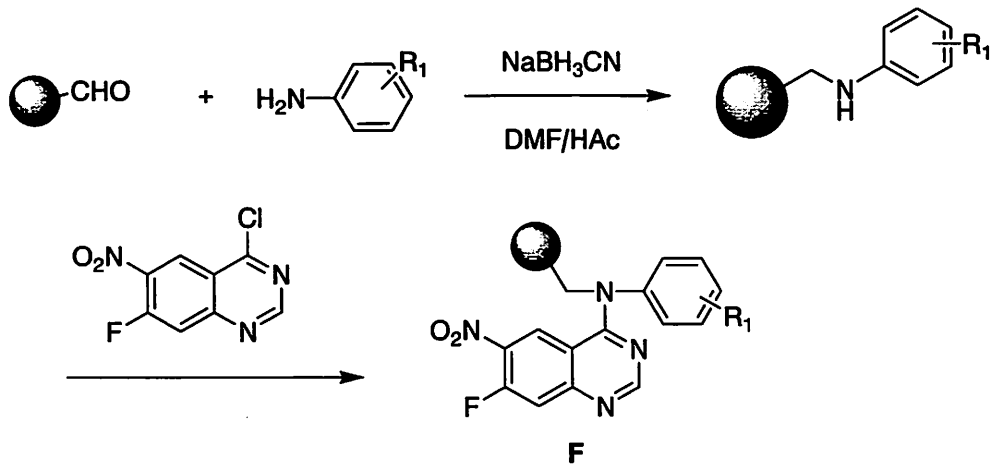
1P-39

Scaffold Approach for Solid-phase synthesis of quinazoline derivatives

Yong Cai,[1]* Hongjun Zhang,[1] Yandong Zhang,[2] Yongping Yu[1,2]
[1]Chemik Co., Lid. 2225, 55 Yunshi Street, Ningbo 315010, P.R.China
[2]College of Pharmaceutical Science, Zhejiang University, Hangzhou 310058, P.R. China
cai@chemik.com, yyu@zju.edu.cn

Quinazoline compounds have been well-recognized for their pharmacological properties such as anticonvulsant, sedative, antihypertensive, vasodilator, anti-inflammatory, antibiosis, phosphodiesterase inhibitors and fibrinogen receptor antagonists.

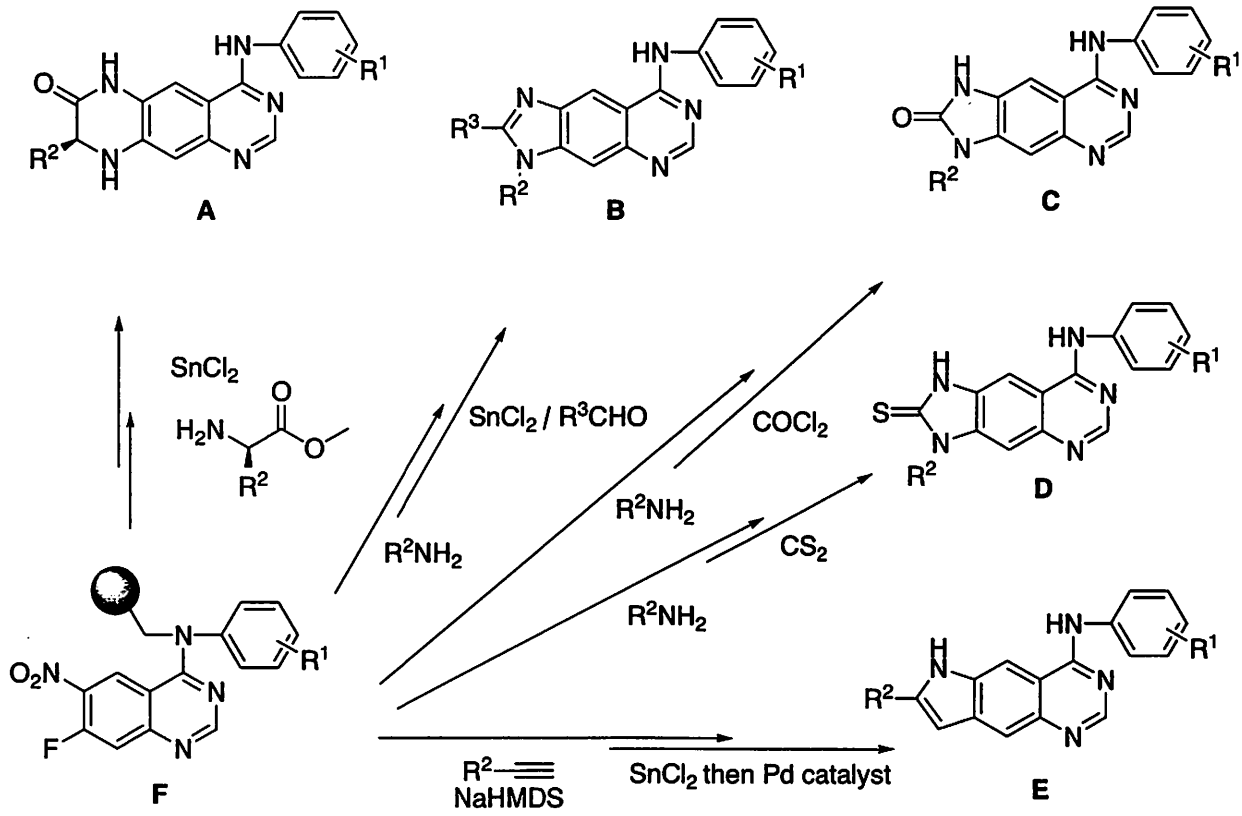
Five different structures of quinazolines were synthesized on solid phase using 4-chloro-7-fluoro-6-nitroquinazoline as a new scaffold. Starting from aldehyde resin, arylamines were attached on the resin by reductive amination reaction. The resin-bound arylamines were then reacted with 4-chloro-7-fluoro-6-nitroquinazoline to afford corresponding structure **F**[1]. Based on the reactions between resin-bound compound **F** and various building blocks, different quinazoline derivatives were synthesized.



Scheme 1 Solid-Phase Synthesis of Scaffold F

The reaction of resin-bound compound **F** and amino acid methyl esters followed by reduction of nitro group and ring formation reaction afforded quinazoline derivatives with structure **A**. The S_NAr reaction of resin-bound compound **F** and alkyl amines followed by reduction of nitro group and imidazo ring formation with alkyl aldehydes afforded quinazoline derivatives with structure **B**. The reaction of resin-bound compound **F** and alkyl amines followed by reduction of nitro group and ring formation

reaction by triphosgene afforded quinazoline derivatives with structure **C**. The reaction of resin-bound compound **F** and alkyl amines followed by reduction of nitro group and thionylated ring formation reaction by CS_2 afforded quinazoline derivatives with structure **D**. The reaction of resin-bound compound **F** and substituted acetylenes followed by reduction of nitro group and ring formation reaction catalyzed by Pd complex afforded quinazoline derivatives with structure **E** (**Scheme 2**).



Scheme 2 Solid-phase Synthesis of Quinazoline derivatives

The screening of synthesized quinazolines libraries in different assays for identification of active compounds will be reported in due course.

Ref:

1) **Yandong Zhang, Yongping Yu, et al.** ***J. Comb. Chem.*****, 9 (1), 9 -11, 2007**

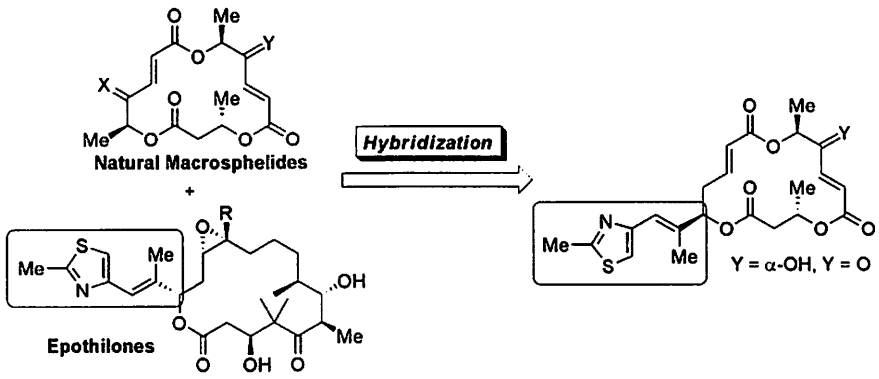
1P-40

Design and Synthesis of Macrosphelide Aza-analogues

Yuta Kobayashi,* Yuji Matsuya, Hideo Nemoto
Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama.
2630 Sugitani, Toyama 930-0194, Japan
nemotoh@pha.u-toyama.ac.jp

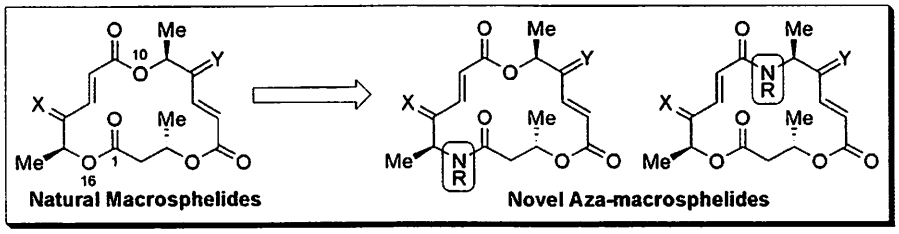
Macrosphelides, 16-membered natural macrolide compounds, have been reported to exhibit potent cell-cell adhesion inhibitory activity, immunosuppressive activity, and anti-tumor activity. We have recently discovered that some of natural macrosphelides and its analogues can activate apoptotic program in human lymphoma U937 cells. The structural characteristics of macrosphelides are associated with epothilones, natural macrolides which possess the same 16-membered lactone framework. Epothilones have been reported to exhibit extraordinarily potent cytotoxicity and induce apoptotic cell death. We have previously reported design and synthesis of novel hybrid compounds composed of the 16-membered trilactone core structure of macrosphelides and the thiazole-containing side chain of epothilones, aiming at increase of apoptosis inducing activity of macrosphelides (**Figure 1**). These studies led to discovery of some hybrid compounds showing the significantly improved activity.

Figure 1. Hybridization of Macrosphelides and Epothilones



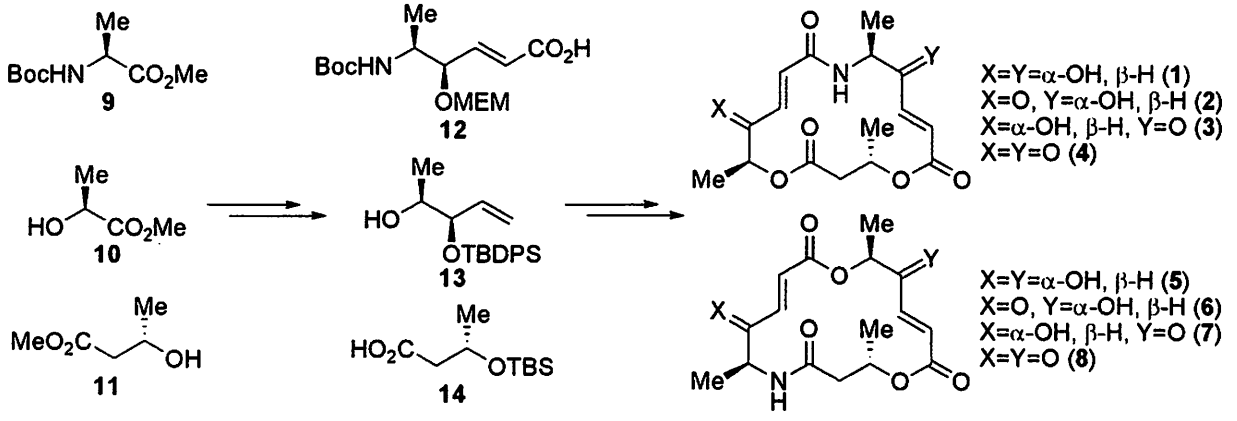
Because it has also been reported that replacement of a part of the epothilone skeleton with a nitrogen atom remarkably affects the bioactivity of epothilones, we designed novel macrosphelide lactam-analogues as a part of structure-activity rerationship study (**Figure 2**).

Figure 2. Novel Macrosphelide Lactam-analogues



The synthesis of the lactam-analogues was investigated based on an efficient synthetic strategy of natural macrosphelides we have already developed, taking advantage of its broad applicability. In practice, three chiral blocks (**12**), (**13**) and (**14**) were prepared from methyl *N*-Boc-L-alanate (**9**), methyl L-lactate (**10**) and methyl (*S*)-3-hydroxybutyrate (**11**), respectively according to established methods. Then they were combined and cyclized to afford the lactam-analogues (**1**)-(**8**) with a high efficiency (**Figure 3**).

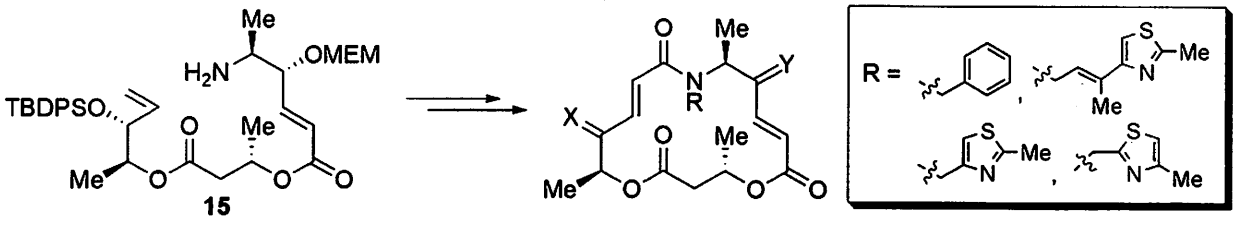
Figure 3. Synthesis of Lactam-analogues (**1**)-(**8**)



In addition to (**1**)-(**8**), we have achieved synthesis of *N*-modified lactam-analogues having a thiazole-containing side chain, taking the previous finding into consideration.

In this case, we applied reductive amination of various aldehydes with (**15**), common synthetic intermediate of (**1**)-(**4**), leading to the synthesis of 10-aza derivatives having variable side chains on the nitrogen atom.

Figure 4. Synthesis of *N*-modified Lactam-analogues



Now we are trying to introduce the other side chain to 10-aza macrosphelides and synthesis of *N*-modified 16-aza macrosphelides. In this symposium, we will report details of efficient synthesis of macrosphelide aza-analogues and their bioactivities.

1P-41

Synthesis and Bioactivity of Macrosphelide-based Artificial Compounds

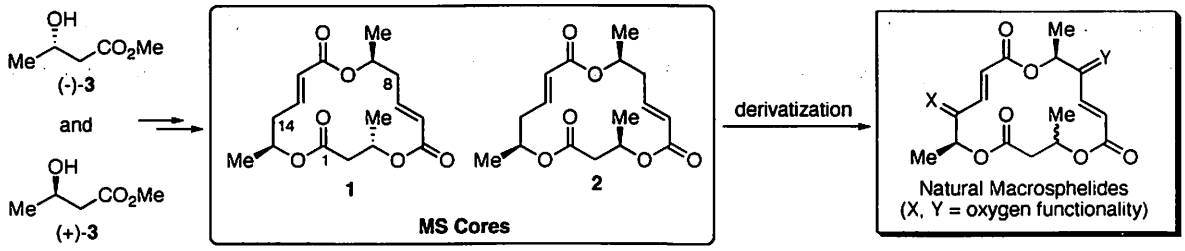
Yuji Matsuya,* Takanori Kawaguchi, Kanwal Ahmed, Qing-Li Zhao, Takashi Kondo, Hideo Nemoto
Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama,
2630 Sugitani, Toyama 930-0194, Japan
nemotoh@pha.u-toyama.ac.jp

Organic molecules derived from natural resources have provided a rich pool of new drug discovery. Because natural products themselves often possess undesirable properties for a practical drug such as serious side-effects and instability in living cells, even if they exhibit an ideal biological activity in vitro, an "artificial" structure rationally designed considering bioactive "natural" product structure may provide a novel and useful lead for a discovery of a new therapeutic agent. We have been engaged in the studies directed toward design, synthesis, and biological assessment of the compounds having a simplified, hybridized, or model structure inspired by various naturally-occurring compounds. For the in-depth SAR researches and the production of new medicine, development of efficient, simple, short-step, and high-yielding synthetic process is an essential task.

Macrosphelides, whose structural characteristic is a common 16-membered trilactone framework, have been reported to exhibit potent inhibitory activity against adhesion of human leukemia HL-60 cells to human-umbilicalvein endothelial cells (HUVECs). In addition, macrosphelide B and relating compounds have been found to exert inhibitory activity against tumor cell growth (colon 26-L5 adenocarcinoma cells). These studies have revealed that macrosphelides can be a potential lead compound for development of a new anticancer chemotherapeutic agent. In the course of our studies on macrosphelides, we first found the apoptosis-inducing activity of several macrosphelides. Two strategies have been utilized for advancing these studies; 1) synthesis of simplified core structures of macrosphelides and their divergent derivatization, and 2) new design of macrosphelide-epothilone hybrid compounds.

(1) Macrosphelide Core (MS Core) Strategy

We envisaged that the simplified core compounds (MS Cores) might serve as a potential precursor of a variety of macrosphelide analogues, including natural compounds, through various chemical manipulations (Scheme 1).

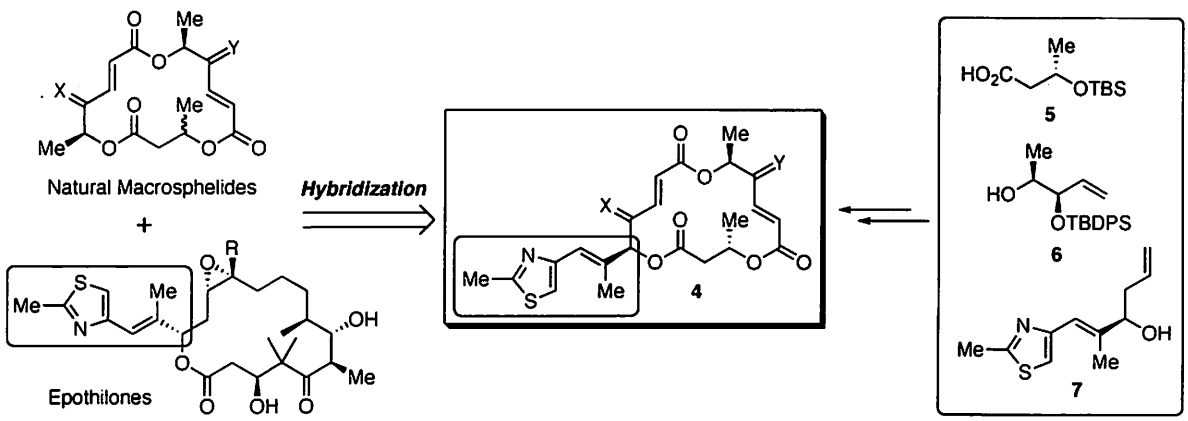


Scheme 1. Macrosphelide Core (MS Core) Strategy for Synthesis of Various Derivatives

This MS Core strategy has several advantages as follows; (1) all three chiral centers in MS Cores (**1** and **2**) can be derived from a sole chiral block, methyl 3-hydroxybutyrate (**3**), (2) availability of both enantiomers of methyl 3-hydroxybutyrate (**3**) makes accessible to two types of MS Core as well as their non-natural enantiomers, (3) the simplified structures of MS Cores compared to those of the natural compounds allow the synthetic routes to be very simple (11 steps, overall 37.2%), making large-scale synthesis possible, (4) various chemical transformations of MS Cores will be applicable at the 8- and 14-allylic positions and the conjugated enone moieties, providing a large number of macrosphelide-like compounds.
Biological evaluation of several derivatives synthesized by above strategy led to discovery of apoptosis-inducing activity against human lymphoma U937 cells (particularly, X = Y = O).

(2) <u>Design and Synthesis of Macrosphelide-Epothilone Hybrid Compounds</u>

To improve the potential of macrosphelides as an anticancer agent, we undertook new molecular design of several artificial macrosphelides. We took notice that the structural characteristics of macrosphelides are associated with natural macrolide epothilones, possessing the same 16-membered lactone framework. Epothilones have been reported to inhibit microtubule dynamics in living cells and consequently exhibit extraordinarily potent cytotoxicity. In addition, epothilones are known to induce apoptotic cell death, which is suggested to have close correlation with the tumor cell growth inhibitory effects. Thus, we designed novel hybrid compounds (**4**) composed of the 16-membered trilactone core structure of macrosphelides and the thiazole-containing side chain of epothilones (Scheme 2).



Scheme 2. Design of Hybrid Compounds of Macrosphelides and Epothilones

The syntheses were accomplished starting from readily available chiral units (**5**, **6**, and **7**) through a successive esterification sequence and simple functional group manipulations. Examination of the apoptosis inducing activity revealed that some of the hybrid compounds **4** exhibited significantly improved activity at 1 μM concentration. It is an important note that none of the natural-type macrosphelides displayed any apoptosis inducing ability at the same concentration.

In this symposium, we will present details of the efficient synthesis of macrosphelide-based compounds, utilizing operationally simple reaction sequences.

1P-42

Ru/C-Catalyzed α-position selective deuteration of alcohols

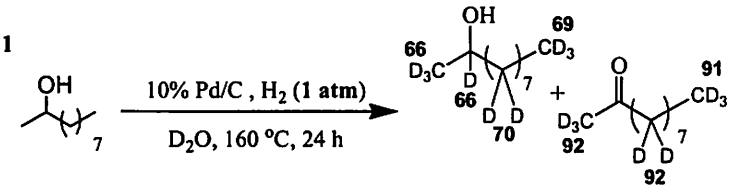
*Yuta Fujiwara, Yuya Inagaki, Yasunari Monguchi, Tomohiro Maegawa and Hironao Sajiki
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University
5-6-1 Mitahora-higashi, Gifu 502-8585, Japan
yakuhin@gifu-pu.ac.jp

Deuterium-labelled compounds are widely used as solvents for NMR spectroscopy, tools for the elucidation of metabolism and reaction mechanism, and so on. Accordingly, the increase in demand for deuterium-labelled compounds has led to accelerate the development of efficient syntheses of deuterated compounds. Especially, a regioselective-deuteration method of alcohols is effective for determination of complicate compounds, such as glycosides, by the simplification of ^{1}H NMR charts. The regioselective deuteration at α-positions of the hydroxyl group in secondary or primary alcohols has been mainly achieved by three methods: 1) stoichiometric deuteride-addition to carbonyl compounds (ketones and aldehydes) using deuterated reducing reagents ($NaBD_4$ and $LiAlD_4$), 2) transition metal-catalyzed deuterogenation of carbonyl compounds, 3) H-D exchange reaction which can directly incorporate deuterium atom into target materials. However, these former methods have several problems in respect to costs, handling and atom efficiency on deuterium sources. Generally H-D exchange reaction is a powerful method to prepare deuterated compounds, although there are quite a few regioselective deuteration methods at vicinal-OH of alcohols were reported.

We have previously reported an efficient Pd/C-catalyzed H-D exchange reaction of alkylbeznene derivatives[1], amino acids[2], nucleosides[3], and hydrocarbons[4] in D_2O as a deuterium source under hydrogen atmosphere.

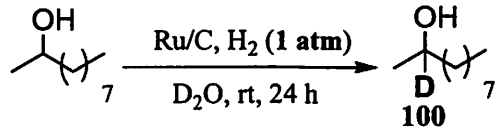
Furthermore, we have also reported a novel Pd/C-catalyzed H-D exchange reaction of aliphatic secondary alcohols and ketones via redox reactions[5] (Scheme 1).

Scheme 1



During the course of these investigations, we found that Ru/C efficiently catalyzes the regioselective H-D exchange reaction at the adjacent position to a hydroxyl group of the aliphatic secondary alcohol (α-position) (Scheme 2). Herein, we report that regioselective H-D exchange reaction of aliphatic alcohol utilizing Ru/C-H_2-D_2O system efficiently and regioselectively proceeded under mild reaction conditions.

Scheme 2



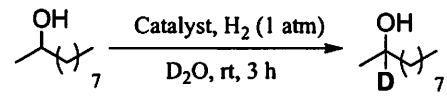
regioselective deuteration

[Experimental results]

First, we examined the difference of the catalyst activity among various carbon-supported transition metal catalysts toward the deuteration of 2-decanol (Table 1). Ru/C was only an effective catalyst for the regioselective deuteration at the α-position (Entry 1), and other heterogeneous catalysts were not effective for the desirable deuteration (Entries 2-6). After further optimization, the best result of the efficiency of deuterium incorporation was achieved with 5% Ru/C at 50 °C.

Next, various alcohols were employed under optimized conditions to explore the scope of the reaction. In the case of primary alcohols and polyols, although the application of heat at 80 °C was required, various aliphatic alcohols were quantitatively deuterated (Figure 1).

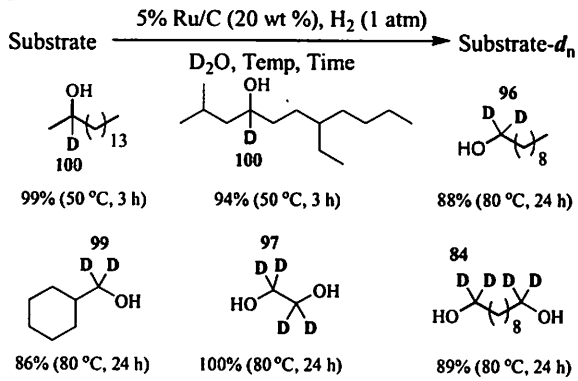
Table 1



Entry	Catalyst (10 wt %)	D content (%)
1	10% Ru/C	87
2	10% Pd/C	--[a]
3	10% Rh/C	--[a]
4	10% Ir/C	--[a]
5	10% Pt/C	--[b]
6	10% Au/C	--[c]

a) Ketones were detected by ^{1}H NMR.
b) Byproduct was detected by ^{1}H NMR.
c) Other positions were slightly deuterated.

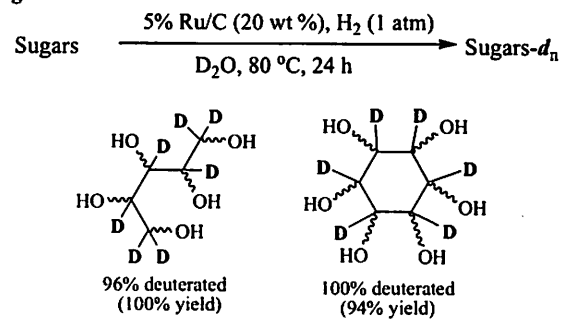
Figure 1



In summary, we have developed the α-position selective H-D exchange reaction of aliphatic alcohols utilizing Ru/C-D_2O-H_2 system. This method can be carried out under mild reaction conditions and efficiently incorporate the deuterium atoms using D_2O, which is the attractive deuterium source in respect to low cost and toxicity. Our ongoing efforts are seeking to expand the scope and limitation of this method and to probe the reaction mechanism.

These results encouraged us to carry out the further application of this reaction to the carbohydrates. Although the deuteration of D-glucose gave no anticipated glucose-d7, the product seemed to be deuterated sorbitol according to ^{1}H NMR analysis. Accordingly, we changed the target to sugar alcohols. And various sugar alcohols, such as xylitol and inositol were efficiently deuterated (Figure 2).

Figure 2



References

(1) *Org. Lett.* **2004**, *6*, 1485 ; *Chem. Eur. J.* **2007**. *13*, 4052 ; *Synlett* **2002**, 1149 ; *Chem. Eur. J.* **2008**.
(2) *Synlett* **2005**, 845. (3) *Heterocycles* **2005**, *66*, 361. (4) *Angew. Chem. Int. Ed.*, in press
(5) *J. Org. Chem.* **2007**, *72*, 2143.

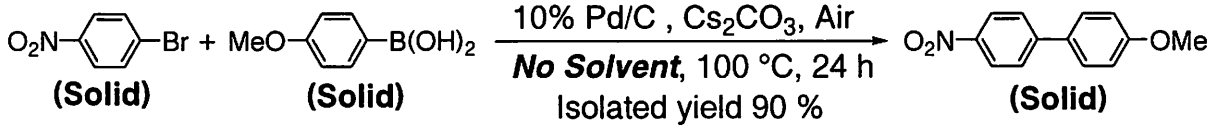
1P-43

Pd/C-catalyzed, Solvent-free and Solid-phase Suzuki-Miyaura coupling Reaction

Yuki Fujita,* Shota Hashimoto, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University
5-6-1 Mitahora-higashi, Gifu, 502-8585, Japan
yakuhin@gifu-pu.ac.jp

Abstract: Pd/C is one of the most useful heterogeneous catalysts in organic synthesis, because it can be safely handled and removed from the reaction mixture by a simple filtration. Recently, we found that Pd/C-catalyzed Suzuki-Miyaura coupling reaction efficiently proceeded only by blending the solid substrates, inorganic base and 10% Pd/C under solvent-free (solid-phase) reaction conditions (Scheme 1).

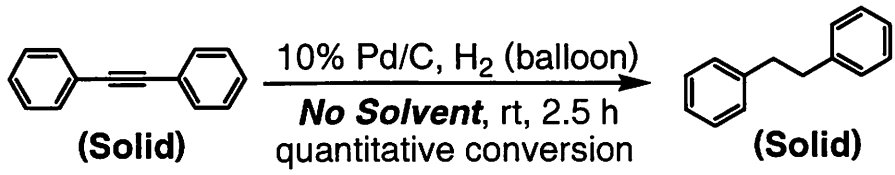
Scheme 1. Suzuki-Miyaura Coupling Reaction under *Solvent-free* Reaction Conditions



The palladium-catalyzed Suzuki-Miyaura coupling reaction, which involves the cross-coupling reaction between aryl halides and aryl boronic acids, is one of the most powerful and convenient synthetic methods for the preparation of biaryl derivatives that are often found as the structural unit in the pharmaceuticals, agrochemicals, natural products, and functional polymers. The Suzuki-Miyaura coupling reaction has many advantages such as tolerance of a wide range of functional groups, low toxicity, easy handling of reagents and so on. We have recently reported a mild and efficient ligand-free Pd/C-catalyzed Suzuki-Miyaura coupling reaction at room temperature in the presence of a mild inorganic base in aqueous or alcoholic media.[1]

Solvent-free catalytic processes in organic synthesis, which can reduce the consumption of environmentally unfriendly solvents and the size of the reaction vessels, would be able to achieve the significant energy saving. In spite of the great promise, the solvent-free catalytic reactions have been hardly examined, since an efficient contact of a solid catalyst with a solid substrate has been recognized to be an absolute requirement for the smooth reaction progress. Recently, we found that the solvent-free hydrogenation efficiently proceeded only by blending the solid diphenylacetylene as a substrate and a catalytic amount of Pd/C under hydrogen atmosphere (balloon) at room temperature (Scheme 2), and we have established the generality of the solvent-free hydrogenation method.[2]

Scheme 2 Hydrogenation of Diphenylacetylene under *Solvent-free* Conditions



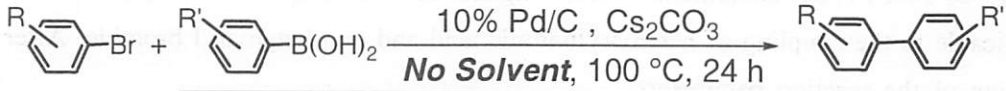
Herein, we report a ligand- and solvent-free Pd/C-catalyzed Suzuki-Miyaura coupling reaction only by blending the solid substrates an inorganic base, and heterogeneous Pd/C catalyst.

Fig.1 constant-temperature incubator

After the detailed optimization of the reaction conditions, we found that 1.5 mol % of 10% Pd/C catalyzed the reaction of 4-bromonitrobenzene with 4-methoxyphenylboronic acid (1.5 equiv) in the presence of 1.5 equiv of Cs_2CO_3 as the base using a constant-temperature incubator (ca. 100 ℃) (Fig.1). We then explored the scope and limitations of the applicable substrates for the coupling (Table 1).

As shown in Table 1, a wide range of aryl bromides were smoothly cross-coupled with aryl boronic acids, such as 4-methoxyphenylboronic acid, 2-methoxyphenylboronic acid, and 4-acethylphenylboronic acid, to afford the corresponding biaryls in good yields. It is noteworthy that the cross-coupling reaction between solid substrates could proceed to give the solid products under absolute solid-phase conditions.

Table 1 Scope and Limitation



Entry	R	R'	Yield (%)
1	4-NO_2	4-MeO	90
2	4-NO_2	2-MeO	100
3	4-NO_2	4-COMe	100
4	4-CN	4-MeO	88
5	4-NO_2	4-CH_3	74

In conclusion, we have developed a Pd/C-catalyzed, solvent-free and solid-phase Suzuki-Miyaura coupling reaction. This methodology can provide a facile, efficient and environmentally friendly heterogeneous process due to the simplicity, the wide applicability of substrates, the use of less toxic reagent without any ligands and solvents. To the best of our knowledge, this is the first report for the general synthesis of various biaryl compounds by the heterogeneous catalyzed cross-coupling reaction under solvent-free conditions. We will introduce more details including practical procedures about the Suzuki-Miyaura reaction under solid-solid-solid-phases.

References

1. Maegawa, T.; Kitamura, Y.; Sako, S.; Udzu, T.; Sakurai, A.; Tanaka, A.; Kobayashi, Y.; Endo, K.; Bora, U.; Kurita, T.; Kozaki, A.; Monguchi, Y.; Sajiki, H. *Chem. Eur. J.* **2007**, *13*, 5937-5943.
2. a) 127th Annual Meeting of the Pharmaceutical Society of Japan, **2007**, Toyama, Japan
   b) 2007 Summer Symposium of the Japanese Society for Process Chemistry, **2007**, Tokyo, Japan
   c) The 33rd Symposium on Progress in Organic Reactions in the Life Sciences, **2007**, Nagasaki, Japan

1P-44

Practical synthesis of heterobiaryl derivatives

Azusa Tsutsui, *Satoko Sako, Yoshiaki Kitamura, Takahiro Udzu, Tomohiro Maegawa, Yasunari Monguchi, Hironao Sajiki

Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University

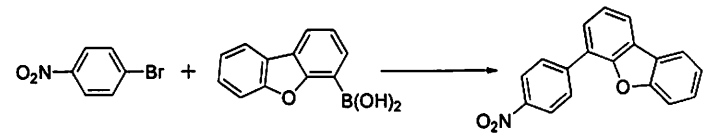
5-6-1 Mitahorahigashi, Gifu, 502-8585, Japan

yakuhin@gifu-pu.ac.jp

Suzuki-Miyaura coupling reaction, which involves the palladium-catalyzed cross-coupling reaction between aryl halides and arylboronic acids, produces biaryl skeletons often included as partial structures in pharmaceuticals, natural products and functional materials. Significant efforts have been focused on the development of the combination of palladium catalysts and ligands for the efficient reaction progress. Most developed protocols, however, used homogeneous catalysts which are difficult to handle and remove from the reaction mixture. Furthermore, they are mainly applicable to the construction of simple non-hetero aryl-aryl units, and are usually difficult to apply to the synthesis of heterobiaryl compounds.

Recently, we have developed an efficient non-hetero biaryl Suzuki-Miyaura coupling reaction using Pd/C-Na_3PO_4-50% *i*-PrOH combination without ligands at room temperature,[1] but the reaction system was not applicable to the coupling of heteroarylboronic acid and non-heteroaryl bromide. After considerable exploration of the reaction parameters, we found that the application of heat (80 °C) was the most important variable to enhance the reaction progress; the reaction of 4-bromonitrobenzene with 4-dibenzofuranboronic acid (1.5 equiv) in the presence of 10% Pd/C (3.5 mol% as Pd metal) and $Na_3PO_4 \cdot 12H_2O$ (3.5 equiv.) in 50% *i*-PrOH at 80 °C was completed within 1 h with 98% yield.

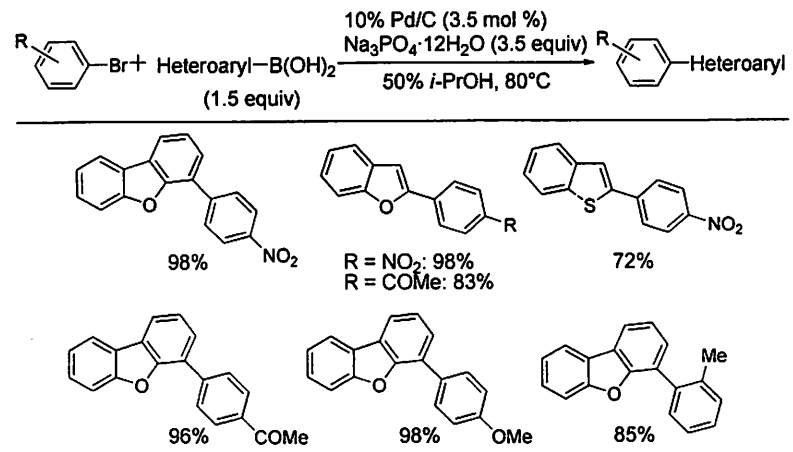
Scheme 1 Suzuki-Miyaura coupling between 4-bromobenzene and 4-dibenzofuranboronic acid



arylboronic acid (1.1 equiv.), 10% Pd/C (3.5 equiv.), 50% *i*-PrOH, rt 0%

arylboronic acid (1.5 equiv.), 10% Pd/C (3.5 equiv.), 50% *i*-PrOH, 80°C 98%

Scheme 2 Suzuki-Miyaura coupling of aryl bromide with heteroarylboronic acid

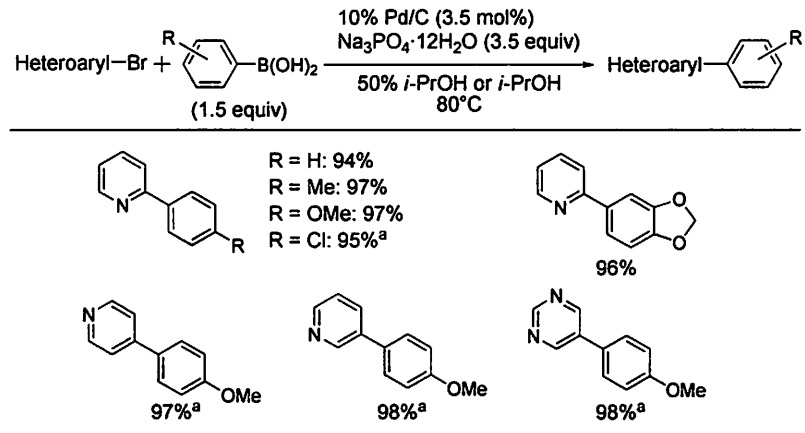


As shown in Scheme 2, a wide range of non-heteroaryl bromides bearing an electron-withdrawing group or an electron-donating group clearly reacted with heteroaryl boronic acids.[2]

We next investigated the coupling between heteroaryl

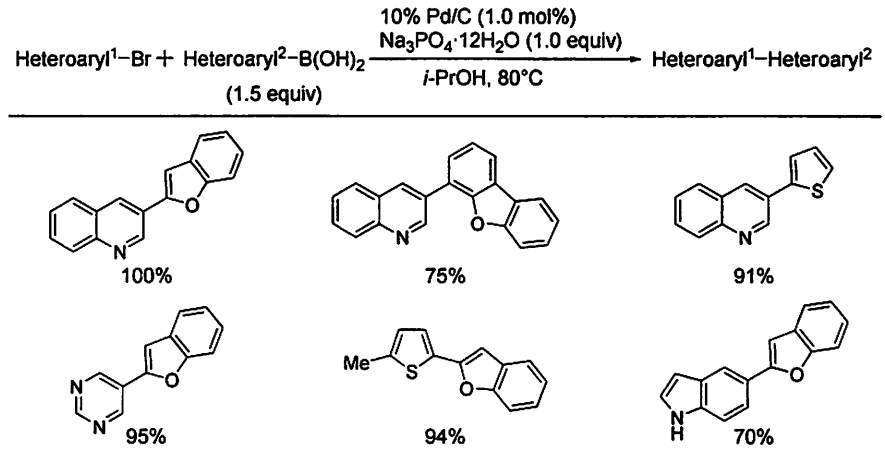
bromides and non-hetroarylboronic acids. The reactions of 2-bromopyridine with a series of electron-neutral to electron-rich phenylboronic acids produced the desired heterobiaryl products in 94–97% yields. However, the use of 4-chloroboronic acid or 3- and 4-bromopyridines as substrates was incomplete even after 24 h, while the reaction progress was remarkably improved in *i*-PrOH in place of 50% *i*-PrOH as the solvent and the desired products were provided in more than 95% yields (Scheme 3). Further application of the reaction conditions to the coupling between heteroarylboronic acids and heteroaryl bromides was successfully achieved to give the corresponding heterobiaryl compounds in good yields (Scheme 4).[2] It is noteworthy that the present protocol is applicable to the cross-coupling of sulfur-containing heterocycles, since the reaction of such substrates has previously been plagued by several limitations involving protodeboronation (hydrolysis or solvolysis) and catalyst poisoning of the sulfur atom.

Scheme 3 Suzuki-Miyaura coupling of heteroatyl bromide with arylboronic acid



[a] *i*-PrOH was used as the solvent.

Scheme 4 Suzuki-Miyaura coupling of heteroaryl bromide with heteroarylboronic acid



We have developed a mild and efficient protocol for the ligand-free and heterogeneous Pd/C-catalyzed hetero Suzuki-Miyaura coupling reaction.[2] To the best of our knowledge, this methodology is the first to be reported which has widespread application for the synthesis of various hetrobiaryl compounds using a heterogeneous catalyst under ligand-free conditions. We anticipate that this approach will offer an alternative synthetic strategy for the practical construction of heterobiaryl compounds. In this symposium, we will also present the reuse test of the catalyst and the application of wet-type Pd/C instead of dry-type one and discuss the water effect on the cross-coupling reaction.

References: 1) (a) Maegawa, T. et al. *Chem. Eur. J.* **2007**, *13*, 5937–5943. (b) Kitamura, Y. et al. *Tetrahedron.* **2007**, *63*, 10596–10602.
2) Kitamura, Y. et al. *Chem. Commun.* **2007**, 5069–5071.

1P-45

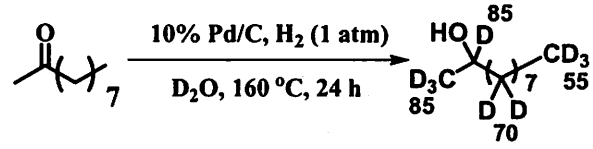
Mild hydrogenation of carbonyl compounds using Pt/C as a catalyst

*Youhei Iwasaki, Yuta Fujiwara, Yasunari Monguchi, Tomohiro Maegawa and Hironao Sajiki
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University
5-6-1 Mitahora-higashi, Gifu 502-8585, Japan
yakuhin@gifu-pu.ac.jp

[Introduction] Reduction of carbonyl groups is a convenient tool to prepare corresponding alcohols. It has been mainly achieved by three methods: 1) Hydride-addition using stoichiometric amount of reducing reagents ($NaBH_4$ and $LiAlH_4$), 2) enzyme-catalyzed biochemical reduction, 3) transition-metal catalyzed hydrogenation. Especially, transition-metal catalyzed hydrogenation is of advantage on industrial and laboratory-scale reductions in respect to handling and low cost.

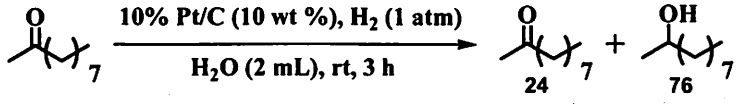
Heterogeneous hydrogenation of ketone is preferable to homogeneous one in terms of easy work-up, reuse and application to industry. However, the harsh conditions such as high temperature and/or pressure, acidic or basic conditions and excess amount of catalyst are required, especially for aliphatic carbonyl compounds. Therefore, the development of efficient and mild hydrogenation of carbonyl groups catalyzed by heterogeneous catalysts has been desired.

Scheme 1



During our continuous study of the H-D exchange reaction, we found that Pd/C catalyze the H-D exchange reaction of aliphatic ketone derivatives accompanied with the reduction of the carbonyl group (Scheme 1, *J. Org. Chem.* **2007**, *72*, 2143). After optimization of reaction conditions, Pt/C was found to be an effective catalyst for the hydrogenation of aliphatic ketones under mild conditions (Scheme 2). We describe that the efficient hydrogenation of carbonyl compounds at room temperature under ordinary hydrogen pressure.

Scheme 2

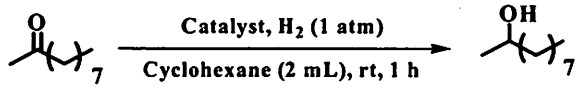


The hydrogenation of aliphatic ketones proceeded at rt under ordinary hydrogen pressure!!

[Experimental results]

First, we studied the difference of the catalyst activity among various carbon-supported transition metal catalysts (Table 1). Interestingly, the reaction proceeded only with Pt/C or Rh/C and the other heterogeneous catalysts were not effective for the reaction. It is obvious Pt/C was the most efficient catalyst for the hydrogenation of 2-decanone.

Table 1



*Yield was determined by ^{1}H NMR.

Catalyst	Yield (%)	Catalyst	Yield (%)	Catalyst	Yield (%)
10% Pt/C	100	10% Pd/C	NR	10% Ir/C	NR
10% Rh/C	79	10% Ru/C	NR	10% Au/C	NR

We also investigate the solvent effect of the hydrogenation (Scheme 3). As a result, the reaction proceeded in cyclohexane, H_2O and *i*-PrOH, and cyclohexane was chosen as the most effective solvent.

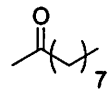
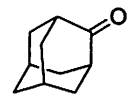
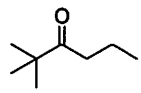
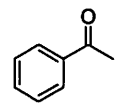
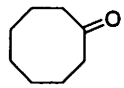
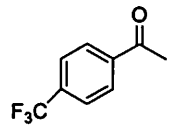
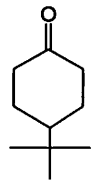
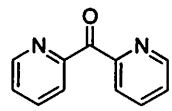
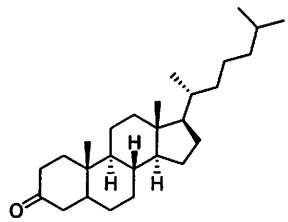
In the case of aliphatic ketones as a substrate including structurally rigid cholestanone and adamantanone, hydrogenation efficiently proceeded to give the corresponding secondary alcohols in quantitative yields with high selectivity (Table 2, Entries 1-6).

These results encouraged us to carry out the further application to aromatic ketones (Table 2, Entries 7 and 8). Although small amount of cyclohexane derivatives derived from the hydrogenation of both the ketone and aromatic ring were detected on ^{1}H NMR, hydrogenation of ketones efficiently proceeded and corresponding aromatic secondary alcohols were obtained in high selectivity. In the case of di-2-pyridyl ketone, only the corresponding secondary alcohol was obtained by the selective hydrogenation of the carbonyl group (Table 2, Entry 9).

In conclusion, we have developed the mild, efficient and Pt/C-catalyzed hydrogenation of aliphatic ketones under heterogeneous conditions. The present method can be carried out under ordinary H_2 pressure at room temperature. The further application to the reduction of the other carbonyl compounds, such as aldehyde and ester is underway.

Table 2

Substrate (0.5 mmol) —**10% Pt/C (10 wt %), H_2 (1 atm)**, **cyclohexane (2 mL), rt, Time**→ **Product**

Entry	Substrate	Entry	Substrate
1	 96% (1 h)	6	 100% (3 h)
2	 85% (1 h)	7	 >99%(6h)[a]
3	 99% (6 h)	8	 94%(5h)[a]
4	 90%(2h)	9	 98%(3h)[b]
5	 93% [c] (6 h)		

a : ^{1}H NMR yield.
b : Yield of stereoisomeric mixture.
c : In *i*-PrOH.

1P-46

Pd/C-catalyzed, ligand-free Suzuki-Miyaura reaction

Yasunari Monguchi,* Yoshiaki Kitamura, Satoko Sako. Takanori Kurita, Tomohiro Maegawa, Hironao Sajiki
Department of Medicinal Chemistry, Gifu Pharmaceutical University
5-6-1 Mitahora-higashi, Gifu, 502-8585, Japan
monguchi@gifu-pu.ac.jp

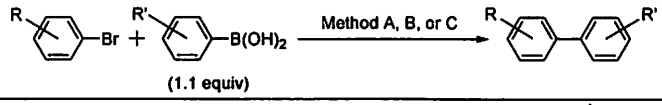
Palladium-catalyzed Suzuki-Miyaura coupling reaction involving the cross-coupling between aryl halides and aryl boronic acids is one of the most powerful and convenient synthetic methods for the preparation of biaryls as well as alkenes which are structural components of natural products, agrochemicals, pharmaceuticals, and polymers such as organic EL materials. Suzuki-Miyaura coupling reaction has many advantages: tolerating a wide range of functional groups, low toxicity and easy handling of reagents. Traditional Suzuki-Miyaura coupling reactions were generally employed with homogeneous palladium catalysts in the presence of phosphine ligands. However, they possess some serious drawbacks in the availability, stability, toxicity, reusability, and cost of the palladium complexes and phosphine ligands. Furthermore, the products are frequently contaminated with residual Pd and ligands because of the difficulty of the separation. Palladium on carbon (Pd/C) is one of the most common heterogeneous catalysts because of its availability, easy handling, and reusability, and many applications of Pd/C for Suzuki-Miyaura coupling reactions have been reported. However, some additives such as phosphine ligands and quaternary ammonium salt, and/or application of heat, microwave irradiation and pressure are required for the effective reaction progress. Therefore, the development of a mild, efficient, and ligand-free Pd/C-catalyzed Suzuki-Miyaura coupling reaction in aqueous media has been desired from the environmental and economical points of view.

We initially found that stirring a mixture of 4-bromonitrobenzene and phenylboronic acid in the presence of 10% Pd/C and Na_2CO_3 in MeOH promote a cross-coupling reaction even without ligands. Detailed optimization of the reaction conditions led to the following three combinations of reagents: Method A, Pd/C (1.5 mol %)–$NaHCO_3$ (3.5 equiv)–MeOH; Method B, Pd/C (1.5 mol %)–Na_2CO_3 (1.5 equiv)–50% aqueous EtOH; Method C, Pd/C (0.5 mol %)–$Na_3PO_4 \cdot 12H_2O$ (3.5 equiv)–50% aqueous *i*-PrOH.

We next explored the scope and limitation of substrates for the optimal conditions (Table 1). A variety of aryl bromides bearing an electron-withdrawing group such as nitro, aldehyde, ester, and carboxylic acid as well as an electron-donating group such as methyl, hydroxyl, and methoxy groups coupled with phenylboronic acid in high yields. Regarding aryl boronic acids, the coupling reaction of electron-rich arylboronic acid such as 2-, 3-, or 4-methoxyphenylboronic acid efficiently proceeded compared with non-substituted phenylboronic acid. On the other hand, a phenylboronic acid possessing an electron-withdrawing group (COMe) indicated a lower reactivity, and the reaction with 4-bromoanisole could not complete in the cases of Methods A and B even after 48 h, while the use of $Na_3PO_4 \cdot 12H_2O$ as a

base (Method C) gave a gratifying result. Hence, the combination of $Na_3PO_4 \cdot 12H_2O$–50% *i*PrOH indicates higher reactivity for the present Pd/C-catalyzed Suzuki-Miyaura coupling reaction and it may be attributed to the difference of basicity.

Table 1 Pd/C-catalyzed Suzuki-Miyaura coupling between arylboronic acids and arylbromides.



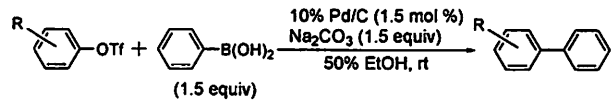
			Method A[a]		Method B[b]		Method C[c]	
Entry	R	R'	Time (h)	Yield (%)[d]	Time (h)	Yield (%)[d]	Time (h)	Yield (%)[d]
1	4-NO_2	H	4	96	3	97	3.5	93
2	4-CHO	H	5.5	94	3	98	3	91
3	4-CO_2Et	H	24	92	12	99	6	99
4	2-Me	H	4.5	92	3.5	90	4	90
5	4-OH	H	25	93	11	90	3.5	91
6	4-CO_2H	H	25	91	8	94	3.5	100
7	4-OMe	H	48	98	24	91	24	93
8	4-OMe	2-OMe	8	100	9	93	6	90
9	4-OMe	3-OMe	24	90	12	91	10	96
10	4-OMe	4-OMe	24	94	11	96	5	95
11	4-OMe	4-COMe	48	45[e]	48	77[e]	48	100

[a] The reaction was carried out using 10% Pd/C (1.5 mol %), $NaHCO_3$ (3.5 equiv), and MeOH at rt. [b] The reaction was carried out using 10% Pd/C (1.5 mol %), Na_2CO_3 (1.5 equiv), and 50% aqueous EtOH at rt. [c] The reaction was carried out using 10% Pd/C (0.5 mol %), $Na_3PO_4 \cdot 12H_2O$ (3.5 equiv), and 50% aqueous EtOH at rt. [d] Isolated yield. [e] The reaction was incomplete.

We then explored the application of the present method to the coupling of aryl triflates. Aryl triflates are important starting materials for metal-catalyzed coupling reactions because of their ease of preparation from phenol derivatives, although they are known to be less reactive than the corresponding iodides and bromides in the Suzuki-Miyaura coupling reactions. Diverse aryl triflates possessing either an electron-withdrawing or -donating substituent on the aromatic ring smoothly underwent the coupling reaction in high yields using Method B without remarkable hydrolysis of the triflate moiety even under alcoholic and/or aqueous basic reaction conditions (Table 2).

This methodology will provide a facile, efficient and environmentally-friendly Suzuki-Miyaura coupling reaction because of wide applicability to various substrates, the use of less toxic reagents, and the mild reaction conditions. In this symposium, we will present more details of the reaction including further application to the stilbene synthesis, the use of wet-type Pd/C which hardly ignites, reusability of Pd/C, and no leaching of palladium metal in the reaction media.

Table 2 Application of aryl triflates.



Entry	R	Time (h)	Yield (%)[a]
1	4-NO_2	24	95
2	H	24	97
3	4-CN	24	98
4	4-CHO	24	95
5	4-CO_2Me	24	91
6	4-Cl	24	93
7	4-F	24	92
8	4-OMe	48	90
9	4-NHCOMe	48	90

[a] Isolated yield.

References: (1) Maegawa, T. et al. *Chem. Eur. J.* **2007**, *13*, 5937–5943. (2) Kitamura, Y. et al. *Tetrahedron* **2007**, *63*, 10596–10602.

1P-47

Meerwein's reagent-Catalyzed Sol-Gel Polycondensations Giving Silanol Free Silica gel

Toyoshi Shimada,*[†,‡] Yogesh Jorapur,[†,‡] Norihiro Mizoshita,[§,‡] Yoshifumi Maegawa,[†] Hiroki Nakagawa,[†] Takeru Hasegawa,[†] Takao Tani,[§,‡] Shinji Inagaki[§,‡]

[†]Department of Chemical Engineering, Nara National College of Technology, 22 Yata-cho, Yamatokoriyama, Nara 639-1080, Japan, [§]Toyota Central R&D Laboratories, Inc., Nagakute, Aichi 480-1192, Japan, and [‡]Core Research for Evolutional Science and Technology (CREST), JST, 4-1-8

shimada@chem.nara-k.ac.jp

Since the first studies by Ebelman,[1] metal alkoxides such as $Si(OR)_4$, $Al(OR)_3$ and $Ti(OR)_4$ have been used as popular sol-gel precursors for production of functional materials.[2] Recently, we have reported triallylsilanes or diallylethoxysilanes as reactive sol-gel precursors for organosilica hybrid materials.[3] To date, sol-gel polymerizations to yield silica or organosilica gels have been carried out under acidic or basic reaction conditions, always providing silanol groups on the surface of the gels.[2] However, quite a few residual silanols in the gels sometimes result in functional deterioration due to hydrophilicity, local conductivity, and hydrogen bonding.[4]

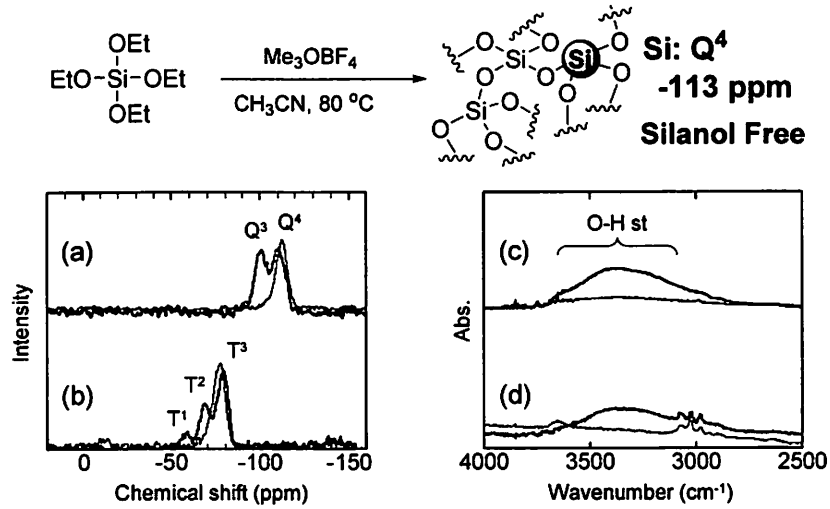
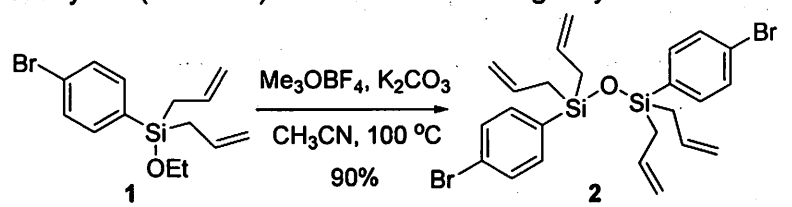


Figure 1. ^{29}Si MAS NMR (a: silica, b: biphenylene-silica) and FT-IR (ATR, c: silica, d: biphenyl-silica) spectra for the silica and biphenyl-silica gels prepared by the Meerwein's reagent-catalyzed (red lines) or conventional sol-gel synthesis.



Scheme 1. Synthesis of Disiloxanes Catalyzed by Meerwein's reagent

The present report proposes a novel trimethyloxonium tetrafluoroborate (Meerwein's reagent)-catalyzed sol-gel process in the absence of water, giving highly-condensed and silanol-free silica or organosilica gels, and also provides insight into the role of Meerwein's reagent[5] for Si–O–Si bond formation with a plausible mechanism.

Tetraethoxysilane or 4,4'-bis(triethoxysilyl)biphenyl was reacted with catalytic amount of Meerwein's reagent in distilled acetonitrile at rt and then at 80 °C. The resulting precipitates were washed several

times with acetonitrile, dried in vacuum and then characterized using FT-IR and ^{29}Si MAS NMR. For comparison, gels were prepared from the same precursors by conventional sol-gel synthesis and characterized. An intense signal was observed in the NMR spectrum for both the silica (red line in Fig. 1a, -113 ppm: denoted as Q^4 species[6]) and biphenyl-silica (red line in Fig. 1b, -77 ppm: denoted as T^3 species) gels derived by the Meerwein's reagent-catalyzed synthesis. These results indicate that all the Si-OEt bonds are reacted to form Si-O-Si bonds, giving highly-condensed (no residual ethoxy groups) and silanol-free gels. On the other hand, the conventional synthesis resulted in silica or biphenyl-silica gels having Q^3 (black line in Fig. 1a) and $T^{1\text{-}2}$ (black line in Fig. 1b) species, respectively, in the NMR spectra. The FT-IR results showed no silanol groups only for the silica (red line in Fig. 1c) and biphenyl-silica (red line in Fig. 1d) gels derived by the Meerwein's reagent-catalyzed synthesis, in good agreement with the NMR results.

To elucidate the reaction mechanism, condensation of a relatively less reactive precursor, 4-bromophenyl(diallylethoxy)silane **1**[7], was studied instead of TEOS In the presence of Me_3OBF_4 and potassium carbonate, **1** provided disiloxane **2** in high yield (90%) (*Scheme 1*).

In summary, we proposed a novel trimethyloxonium tetrafluoroborate-catalyzed sol-gel polycondensation to yield highly-condensed and silanol-free silica or organosilica gels and revealed the reaction mechanism.

References and notes

(1) Ebelman, M. *Ann. Chimie Phys.* **1846**, *16*, 129.

(2) (a) Mehrotra, R. C. *J. Non-Cryst. Solids* **1988**, *100*, 1. (b) Brinker, C. J.; Scherer, G. W. *Sol-Gel Science*; Academic Press: New York, 1990. (c) Hench, L.; West, J. K. *Chem. Rev.* **1990**, *90*, 33. (d) Shea, K. J.; Loy, D. A. *Acc. Chem. Res.* **2001**, *34*, 707. (e) Lu, Z.-L.; Linder, E.; Mayer, H. A. *Chem. Rev.* **2002**, *102*, 3543.

(3) (a) Shimada, T.; Aoki, K.; Shinoda, Y.; Nakamura, T.; Tokunaga, N.; Inagaki, S.; Hayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 4688. (b) Aoki, K.; Shimada, T.; Hayashi, T. *Tetrahedron Asymmetry* **2004**, *15*, 1771. (c) Kapoor, M. P.; Inagaki, S.; Ikeda, S.; Kakiuchi, K.; Suda, M.; Shimada, T. *J. Am. Chem. Soc.* **2005**, *127*, 8174.

(4) (a) Jozwiak, W. K.; DallaLana, I. G.; Fiedorow, R. *J. Catal.* **1990**, *121*, 183. (b) Ugliengo, P.; Saunders, V.; Garrone, E. *J. Phys. Chem.* **1990**, *94*, 2260. (c) Yu, S.; Wong, T. K. S.; Hu, X.; Pita, K. *Thin Solid Films* **2004**, *462-463*, 311. (d) Su, K.; Bujalski, D. R.; Eguchi, K.; Gordon, G. V.; Ou, D.-L.; Chevalier, P.; Hu, S.; Boisvert, R. P. *Chem. Mater.* **2005**, *17*, 2520. (e) Thakar, N.; Schildhauer, T. J.; Buijs, W.; Kapteijin, F.; Moulijn, J. A. *J. Catal.* **2007**, *248*, 249.

(5) Meerwein, H.; Hinz, G.; Hofmann, P.; Kroning, E.; Pfeil, E. *J. Prakt. Chem.* **1937**, *147*, 257.

(6) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; John Wiley & Sons, Ltd.: New York, 2000; Chapter 10.

(7) Maegawa, Y.; Nagano, T.; Yabuno, T.; Nakagawa, H.; Shimada, T. *Tetrahedron* **2007**, *63*, 11467.

1P-48

Development of Separation and Analytic Method for Aβ Peptide Based on Biomembrane Abnormarity
~Membrane Chip Analysis Can Brighten a Potential Aspect of Alzheimer Disease~

Toshinori Shimanouchi, Haruyuki Ishii, Vu Thi Huong, Keiichi Nishiyama,
Hiroshi Umakoshi, Ryoichi Kuboi
Grad. Sch. of Eng. Sci., Osaka Univ. 1-3, Machikaneyama-cho Toyonaka, Osaka, 560-8531, Japan
msb@cheng.es.osaka-u.ac.jp

Dynamic function of cell membrane attracts much interest of many researchers because environmental signals (stimuli or stress) are normally recognized on the membrane surface and the first responses against the signals should be elucidated there. Currently, the oxidation of the membrane component and the domain structure on the membrane are believed to cause many kinds of diseases and disorders. It is reported that oxidations of the membrane component are caused by oxidant and biomolecules [1]. Oxidative stresses perturb membrane structures and functions of cells and lead to their death. It is also reported that either the damaged membrane or the raft structure on the membrane strongly interacts with an amyloidogenic protein, which trigger Alzheimer's Disease (AD) [2].

The approaches using genome and proteome have contributed to the elucidations of processes and causes of diseases and disorders. The obtained information is, however, not enough because previous approaches have not been based on cell membranes. There is a possibility that the approach by the biomembranes may open the new perspective in the above disease.

Liposome, a closed bilayer phospholipid membrane, is a useful tool for mimicking a cell membrane, which has the closed lipid membrane structure prior to an encapsulation of various molecules. Many researchers have designed the tools using these properties. The presented techniques are the sensor systems to detect the liposome-protein interaction, such as surface plasmon resonance (SPR)[3], immobilized liposome chromatography (ILC)[4]. These methods have the possibility of the clarification of the relationship between the membrane property and the process or causative mechanism of Alzheimer disease. For the purpose, the design of the (damaged) liposome-based analysis system, *i.e.* membrane chip, is important.

In this study, the immobilized liposome device was first prepared for the analysis of the interaction between the target causative protein of Alzheimer disease, Aβ, and liposome. Based on the separation of Aβ from the other non-amyloidgenic protein, we investigated the relationship of the membrane damage with the Aβ-(damaged) membrane interaction. In the preparation of the immobilized-liposome quartz crystal microbalance (IL-QCM) system, the liposomes including Egg Phosphoethanolamine (PE) were immobilized on QCM electrode by amino coupling method described before[5,6]. Self-assembly monolayers (SAMs) of carboxyl thiol were formed on the electrode and carboxyl group of SAMs were activated. In the preparation of oxidatively damaged liposome, 1-stearoyl-2-arachdonyl-phosphatidylcholine (SAPC) pre-oxidized by $CuSO_4/H_2O_2$ was incorporated into 1,2-dimyrstoyl phosphatidylcholine (DMPC).

The immobilization of *intact* liposome was confirmed by using the IL-QCM method. This method easily gives us the information on the protein binding on the liposome membranes. The protein binding was observed to be dependent on their hydrogen bonding instability (HBi). This HBi propensity determines the amyloidgenicity of protein. In the case of Aβ, which is a causative protein of Alzheimer disease, the large HBi was obtained in comparison with the other cytoplasmic proteins with low HBi. Furthermore, the interaction between Aβ and liposome with either domain structure or damaged lipid was stronger than that in the case of liposome without domain (the ILC method) (**Figure 1**). These experimental results show that the oxidatively damaged membrane could detect and separate Aβ from other proteins This interaction is found to be predominated by HBi of protein and lipid membrane on a basis of the dielectric dispersion analysis (data not shown).

In order to analyze the influence of the selective separation of amyloidgenic protein against its conformational change, its amyloid fibril formation was monitored. The resulting fibril formation was drastically affected by the presence of oxidatively damaged DMPC/oxidized-SAPC liposome, suggesting that the selective separation of Aβ by the damaged membrane probably plays a key role for the induction of amyloid fibril formation.

[References]

1) A.Girotti, *J. Lipid Res.* **39** 1528 (1998)

2) A.Kakio and K. Matsuzaki *et al.*, *Biochem. Biophys. Res. Commun.* **303** 514 (2003)

3) G. Anderluh *et al.*, *Anal. Biochem.* **344**, 43-52 (2005)

4) N. Yoshimoto, M.Yoshimoto, K.Yasuhara, T.Shimanouchi, H.Umakoshi, R.Kuboi, *Biochem.Eng.J.*, **29**, 174-181 (2006)

5) H.Jung, H. Ishii, R.Kuboi *et al.*, *Membrane* **32**, 294-301 (2007)

6) S.Morita, M.Nukui, R.Kuboi, *J.Coll.Inter.Sci.*, **298**, 672-678 (2006)

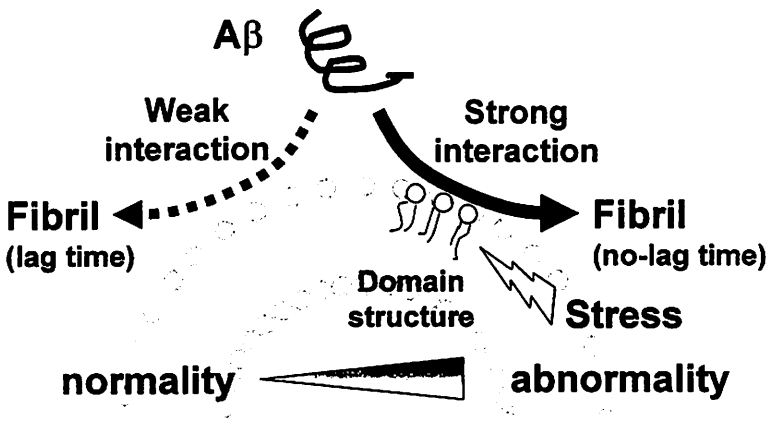


Figure 1 Interaction between Aβ and lipid membrane in the presence or absence of damaged lipid domain.

1P-49

Biomembrane Process Chemistry and Separation Technology ~ Design and Development of Antioxidative LIPOzyme in One-Pot based on Molecular Recognition Function of Liposome Biomembrane

Hiroshi Umakoshi, Le Quoc Tuan, Kengo Morimoto, Toshinori Shimanouchi, Ryoichi Kuboi*
Div. of Chemical Engineering, Grad. Sch. of Engineering Science, Osaka Univ.
1-3 Machikaneyama-cho, Toyonaka, Osaka 560-8531, Japan
kuboi@cheng.es.osaka-u.ac.jp

A fusion of process chemistry and separation technology becomes an important issue when one should achieve a SQDCE (Safety, Quality, Delivery, Cost, and Environment) in process design and development. A biological cell is a minimal unit of "life", where complexed and parallel biochemical reactions, molecular transport, and selective separation are cooperatively achieved in well-organized manner through the interaction among various active interfaces (biomembranes). A new process chemistry, life-environment friendly biomembrane-based process chemistry, could be established through the utilization of the highly-organized strategy of the biological membranes.

A "Biomembrane" is a key interface to achieve an integration of production and separation of target materials. A "Membranomics" is gradually recognized as an important research methodology to investigate the potential functions of biomembrane and to apply them for the bioprocess design[1)]. A model biomembrane, liposome, possesses several benefits in the recognition of (bio)molecules, where it can recognize them with (i) electrostatic, (ii) hydrophobic interaction, and (iii) stabilization effect of hydrogen bonds in the hydrophobic lipid environment[2)]. A molecular recognition with high selectivity can be achieved by the simple liposome membrane on its surface through the combination of (i)-(iii)[2)]. A novel biomembrane-based catalysis can be designed and developed by integrating the above recognition sites and a simple catalytic center on the liposome surface. Some examples to achieve the above requirement have previously been reported as LIPOzyme (liposome + enzyme)[3)-12)]. A process design utilizing LIPOzyme chemistry and the recognition (separation) functions of model-biomembrane (liposome) is the basic strategy in "Biomembrane Process Chemistry (BMPC)". In the following, the design of LIPOzyme has been introduced by employing the "Anti-Oxidative" LIPOzyme as an example of the BMPC applications.

1. SOD LIPOzyme Design through Recognition (Separation) of Minimal Elements by Liposome. The peptide fragment of H_2O_2-treated Cu,Zn-superoxide dismutase (SOD) was found to be reactivated with liposomes prepared by POPC[4,7,10,12)]. The H_2O_2-treated SOD, which lost their activity at different incubation times, were dramatically reactivated only by adding POPC liposomes, resulting in 1.3~2.8 times higher enzymatic activity. The ultrafiltration and RP-HPLC analysis of H_2O_2-treated SOD co-incubated with liposomes shows that some specific peptide fragments of the oxidized and fragmented SOD can interact with POPC liposomes. The effect of several kinds of liposomes on their recruited activity of oxidized and fragmented SOD was furthermore investigated. The addition of zwitterionic liposomes with high membrane fluidity or

that with positive charge was found to increase the SOD-like activity of fragmented SOD although the negatively charged liposome has no effect on its activity. The SOD-like activity was found to be strongly dependent on the adsorbed amount of the peptides on the liposome surface. The analyzed characteristics of the peptide, together with the above findings, imply that the liposome-recruited activity of the fragmented SOD was strongly related with the recognition of the SOD fragment by the liposome caused by the combination of electrostatic and hydrophobic interaction, and hydrogen bonding between the peptide and liposome membrane. These results show the possibility of LIPOzyme chemistry where the POPC liposomes can act as molecular and metal chaperones for stress-damaged peptides and the liposomes can recruit the potentially active fragment of SOD among the lethally damaged SOD fragments to elucidate the antioxidative function.

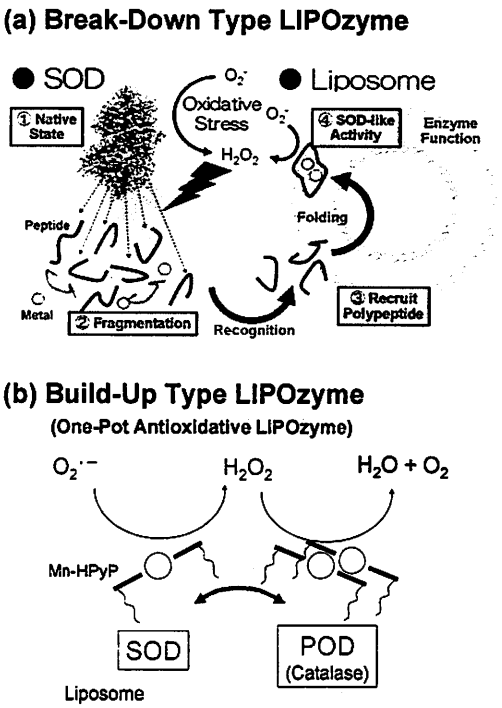


Fig.1 Schematic Illustration of LIPOzymes

2. Antioxidative LIPOzyme Design through Assembly (Reconstruction) of Minimal Elements on Liposome Surface. An antioxidative liposome catalysis that mimics both superoxide dismutase (SOD) and peroxidase (POD) activities has been developed by using the liposomes modified with lipophilic Mn-(5,10,15,20-tetrakis[1-hexadecylpyridium-4-yl]-21H,23H-porphyrin) (Mn-HPyP)[4-8] or Dodecanoyl-His (Dodec-His)[9]. In the former case, the SOD- and POD-like activities of the Mn-HPyP modified liposome were first investigated by varying the type of phospholipid. Higher SOD-like activity was obtained in the case of DPPC and DMPC liposomes, in which the ligands were well-dispersed on the membrane in the liquid crystalline phase. The POD-like activity was maximal in the case of DMPC liposome, in which the Mn-HPyP complex was appropriately clustered on the membrane in the gel phase. Based on the above results, the co-induction of the SOD and POD activities to eliminate the superoxide and also hydrogen peroxide as one-pot reaction was finally performed by using the Mn-HPyP modified DMPC liposome, resulting in the increase of the efficiency of the elimination of both superoxide and hydrogen peroxide.

It is expecting that the fusion of "separation technology" and "process chemistry" could be achieved in the BMPC through LIPOzyme chemistry and their separation functions-utilizing process design.

[References]

(1)R. Kuboi *et al.*, *Seibutsu Kogaku*, **5**, 201 (2004), (2) R. Kuboi and H Umakoshi, *Solv. Extr. Res. Dev., Japan*, **13**, 9 (2006), (3) H. Nagami *et al.*, *Biochem. Eng. J.*, **21**, 221 (2004), (4) H. Nagami *et al.*, *J. Biosci. Bioeng.*, **99**, 423 (2005), (5) N. Yoshimoto *et al.*, *J Biosci Bioeng.*, **100**, 455 (2005), (6) H. Umakoshi *et al.*, *Membrane (Maku)*, **32**, 287 (2007), (7) L. Q. Tuan *et al.*, *Langmuir*, **24**, 350 (2008), (8) H. Umakoshi *et al.*, *Langmuir*, **24**, 4451 (2008), (9) H. Umakoshi *et al.*, *Maku (Membrane).*, in press (2008), (10) L. Q. Tuan *et al.*, *Langmuir*, submitted, (11) B. T. Huong *et al.*, *Langmuir*, accepted (2008), (12) L. Q. Tuan *et al.*, *Maku (Membrane)*, in press (2008)

1P-50

Autoxidation Resistant Cyclopentyl Methyl Ether (CPME).

*Kazuhisa Sakakibara, Hayato Hoshino, and Kiyoshi Watanabe[1]
Department of Applied Chemistry, Yokohama National University.
79-5,Tokiwadai, Hodogaya-ku, Yokohama, 240-8501, Japan
mozart@ynu.ac.jp
1.Research & Development Center, Zeon Corporation.
1-6-2, Marunouchi, Chiyoda-ku, Tokyo, 100-8246, Japan

1. Purpose of this Research Cyclopentyl methyl ether(CPME: CAS No. 5614-37-9) is widely known as an autoxidation resistant ether, and has been used as a highly safer solvent in the process of the industrial production. Why CPME is so stable against autoxidation and leading to the less production of peroxides ? The reason was investigated by evaluating the bond dissociation energy (ΔBH^0) theoretically of the C-H bond (*tert*-hydrogen) at the α-position of an ether oxygen in CPME. Intrinsic structual and IR spectroscopic features of CPME being consistent with this autoxidation resisitive characteristic have been also studied.

2. Theory to evaluate the bond dissociation energy First of all, the data for the heat of formation (ΔH_f^0) of CPME radical (CPME*) is requisite to evaluate the bond dissociation energy of the C-H bond in CPME (ΔBH^0). As there are no available accurate experimental data, a theoretical method via an isodesmic reaction (1) to evaluate the heat of formation of CPME* (ΔH^0_f(CPME*)) has been adopted.

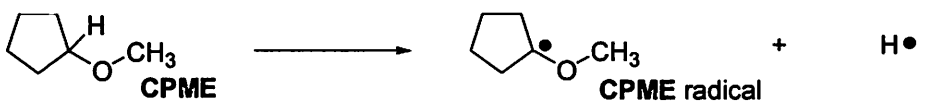
$$\text{CPME*} + CH_3OCH_3 \rightarrow \text{CPME} + CH_3OCH_2^* \qquad (1)$$

As the reaction enthalpy (ΔH^0_{rec}) of this isodesmic reaction is expressed as eq.2, the heat of formation of CPME* at 298K ($\underline{\Delta H^0_{f298}(\text{CPME*})}$) can be evaluated by putting the reported heats of formation data for CPME, CH_3OCH_3, and CH_3OCH_2* into eq.2 after calculating this reaction enthalpy (ΔH^0_{rec}). In order to obtain reliable energy data, CBS-Q//MP2-6-31+G* calculations including zero-point energy correction (normal mode vibrational analyses) were carried out with the Gaussian 03 program.

$$\Delta H^\circ_{rec} = \Delta H^\circ_{f298}(\text{CPME}) + \Delta H^\circ_{f298}(CH_3OCH_2^*) - \underline{\Delta H^\circ_{f298}(\text{CPME*})} - \Delta H^\circ_{f298}(CH_3OCH_3) \qquad (2)$$

The bond dissociation energy of the C-H bond of the α-position of ether oxygen can be written as in eq. 3 by using the energy difference of the heats of formation ($\delta\Delta H_f^\circ$) of the ether radical and parent ether and the heat of formation of the hydrogen radical H*.

$$\mathbf{\Delta BH^\circ_{298}(C\text{–}H{:}ether)} = \Delta H^\circ_{f298}(\text{ether radical}) - \Delta H^\circ_{f298}(\text{parent ether}) + \Delta H^\circ_{f298}(H^*) \qquad (3)$$



3. Results and Discussion The reported heats of formation[1] and calculated energies to estimate the reaction enthalpy (ΔH^0_{rec}) of the isodesmic reaction (1) were summarized in Table 1. By using these data, the heat of formation of the CPME radical (CPME*) was calculated to be –47.9 kJ/mol. The heat of formation of the hydrogen radical $\Delta H^\circ_{f298}(H^*)$ is 218 kJ/mol from the literature.

Table 1 The reported heats of formation[1] and calculated energies to estimate the reaction enthalpy (ΔH^0_{rec}) of the isodesmic reaction (1)

species	ΔH_f^0/ kJ mol^{-1}	Energy (298 K)/ hartree CBS-Q//MP2-6-31+G*
CPME	-223.2	-310.464550
CPME*		-309.816714
CH_3OCH_3	-184.1	-154.744492
CH_3OCH_2*	1.3	-154.092823

By putting the determined value of ΔH°_{f298}(H*) into eq 3, the bond dissociation energy for the C-H bond at the α-position of the ether oxugen in CPME (ΔBH°_{298}(C–H$_\alpha$:CPME)) was evaluated to be **393.3** kJ/mol.

In Table 2, the literature data for the bond dissociation energy (ΔBH°) of relevant ethers are compiled together with the heats of formation (ΔH_f°) of the ether radicals and parent ethers. It should be noticed that the theoretically evaluated bond dissociation energy for the C–H bond of CPME is larger by 2 – 3 kJ/mol than those of diisopropyl ether (IPE) and THF which are liable to produce peroxides as by-products. Autoxidation resistive *tert*-butyl methyl ether (*t*BuOMe) is assumed to have a stronger C–H bond than CPME from the bond dissociation energy data shown in Table 2.

Table 2 Heats of formation of ether radicals and the bond dissociation energies for the C-H bond at the α-position of the ether oxygen at 298 K

species	Literature values[1]			Bond dissociation Energy(ΔBH°_{298}) / kJ mol^{-1}
	ΔH_f° / kJ mol^{-1}		δH_f° / kJ mol^{-1}	
	ether	ether radical		
MeOMe*	-184.1	1.3	185.4	403.4
*t*BuOMe*	-283.6	-102.7	180.9	398.9
THF*	-184.1	-10.5	173.6	391.6
EtOEt*	-251.5	-70.0	181.5	399.5
*i*PrO*i*Pr	-318.8	-146.0	172.8	390.8
CPME*	-223.2	-47.9	175.3	**393.3**

Why is the ΔBH° of the C–H bond of CPME so strong and resistive to autoxidation though it is a *tert*-hydrogen? Investigating the optimized structures of CPME* by MP2/6-31+G* calculation, it was found that bond angle strain at the radical carbon atom in CPME* was noticeable in the structural change from CPME (sp^3) to CPME*(sp^2). The rather stronger C-H bond in CPME reflects on characteristic lower frequency number of this C-H stretching vibration (~ 2820 cm^{-1}) which comes from the specific conformation where interactions then occur between the lone pair on the oxygen and the C-H bond which lies in a *trans* position to it.

4. References. 1. a) V. E. Tumanov, et al., *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 1641. b) C.-C. Chen, et al., *J. Phys. Chem. A.* **2003**, *107*, 4351.

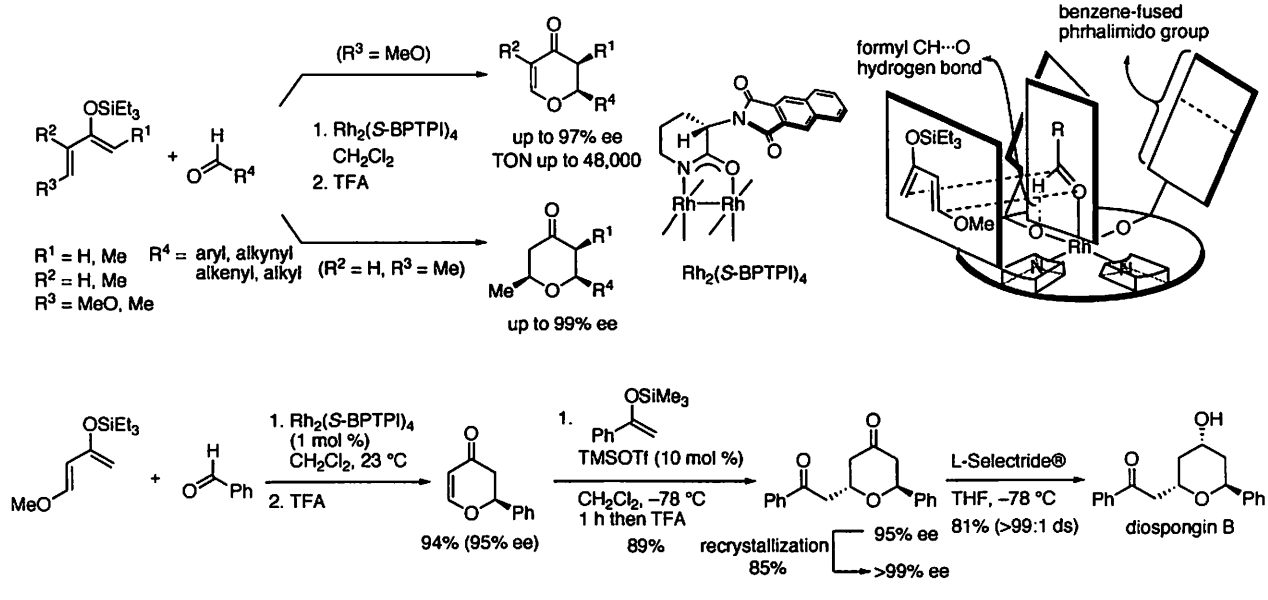
1P-51

Dirhodium(II)-Catalyzed Enantioselective Hetero-Diels–Alder Reaction

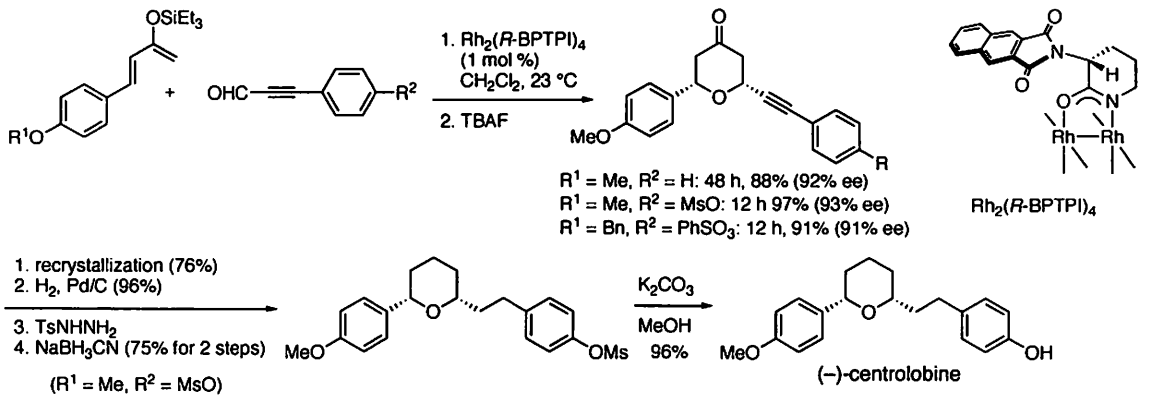
Masahiro Anada,* Takuya Washio, Yuudai Watanabe, Naoyuki Shimada, Shunichi Hashimoto
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan
hsmt@pharm.hokudai.ac.jp

In recent years, tremendous progress has been made in the development of chiral Lewis acids as catalysts for a diverse range of enantioselective reactions. Aside from the superiority in diazo decomposition, the dirhodium(II) complex with vacant coordination sites at the axial position of each octahedral rhodium is Lewis acidic since the molecule has a great avidity for axial ligands. Consequently, this important feature provides a great incentive to develop dirhodium(II) complexes as a new class of chiral Lewis acid catalysts.[1]

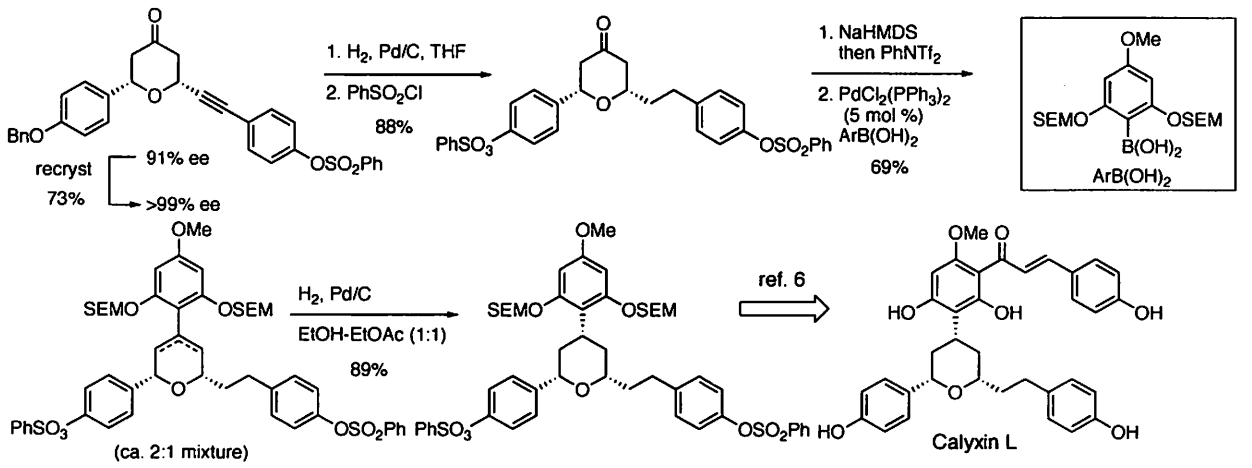
We have found that Rh_2(*S*-BPTPI)$_4$, a dirhodium(II) carboxamidate complex which incorporates (*S*)-3-(benzene-fused-phthalimido)-2-piperidinonate as bridging ligands, is a highly efficient catalyst for *endo*- and enantioselective hetero-Diels–Alder reactions.[2] The Rh_2(*S*-BPTPI)$_4$ catalytic system provides a great flexibility in the nature of aldehyde substrates as well as the substitution pattern on Danishefsky-type and monooxygenated dienes, wherein essentially perfect diastereoselectivity and high levels of enantioselectivity ranging from 90 to 99% ee have been achieved. Selected reactions can proceed smoothly with very low catalyst loadings (0.0075-0.002 mol %) without compromising the yield or enantioselectivity. The turnover number as high as 48,000 achieved here is probably one of the highest ever reported to date for Lewis acid catalyzed asymmetric reactions. The stereochemical outcome of the present reaction can be rationalized by the model based on the crystal structure of its analogue Rh_2(*S*-PTPI)$_4$ coupled with the formyl C–H···O hydrogen bond concept proposed by Corey.[3] The efficiency of the present protocol has been verified well by a short-step synthesis of diospongin B.



As an extension of our work, we addressed the enantioselective synthesis of diarylheptanoid natural products containing a tetrahydropyran ring. The HDA reaction between 4-aryl-substituted 2-siloxy-1,3-diene and phenylpropargylaldehydes using 1 mol % of Rh_2(*R*-BPTPI)$_4$ proceeded in 48 h, and, after treatment with TBAF, gave *cis*-2,6-disubstituted tetrahydropyranone as a sole product with 92% ee. We found that the use of aldehyde phenylpropargylaldehyde bearing a methanesulfonyloxy substituent as the electron-withdrawing group proceeded smoothly to completion within 12 h, and, after desilylation, gave exclusively the *cis*-2,6-disubstituted tetrahydropyran-4-one with 93% ee. Hydrogenation of triple bond, reduction of carbonyl group and hydrolysis followed by removal of the methanesulfonyl group provided (−)-centrolobine in 40% overall yield.[4]



The effectiveness of the present protocol has also been demonstrated by the asymmetric formal synthesis of calyxin L.[5]



(1) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366. (2) M. Anada, T. Washio, N. Shimada, S. Kitagaki, M. Nakajima, M. Shiro, S. Hashimoto, *Angew. Chem. Int. Ed.*, **2004**, *43*, 2665. (3) Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321. (4) Washio, T.; Yamaguchi, R.; Abe, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron* **2007**, *63*, 12037. (5) Washio, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2007**, *18*, 2606. (6) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176.

1P-52

Enzyme-catalyzed enantiomeric resolution of tamiflu intermediates

Manabu Hamada,[1,3] * Kaoru Nakamura,[2] Seiichiro Ogawa,[1] Toshinori Higahi,[3] Keiko Inami,[3] Kazuo Umezawa,[1] Takeshi Sugai[3]

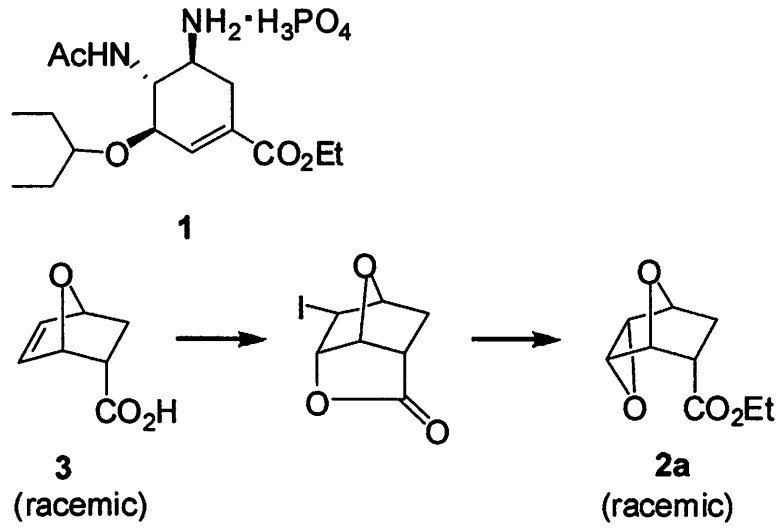
[1] Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Yokohama 223-8522, Japan

[2] Institute of Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

[3] Faculty of Pharmacy, Keio University, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan

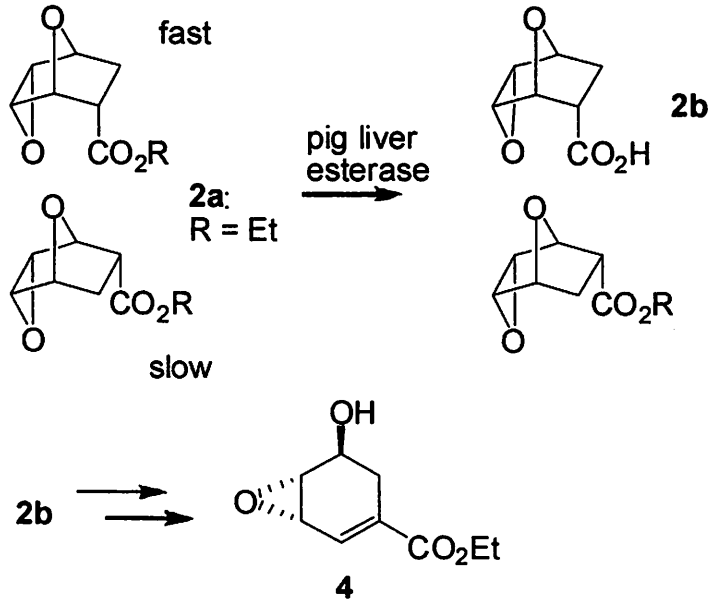
gaku1115@z2.keio.jp

Recently, syntheses of tamiflu **1** based on the asymmetric synthesis are extensively studied, towards the exploitation of new industrial production, which has currently depended upon naturally occurring shikimic acid as the starting material. We turned our attention to Terashima's approach,[1] which had been reported as the racemic tamiflu synthesis, and are examining the enzyme-catalyzed kinetic optical resolution of some compounds related to Terashima's intermediates.



The targets are racemic tricyclic *endo*-epoxycarboxylic acid esters **2**, which are readily available according to the following route, *i.e.*, the Diels-Alder reaction between furan and acrylic acid and subsequent iodolactonization of *endo*-adduct, hydrolysis together with epoxy ring formation, then esterification.[2]

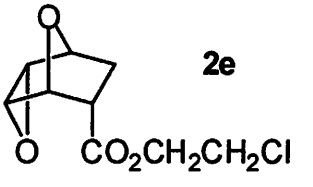
Toward this end, wide range of hydrolytic enzymes involving microbial and mammal proteases, lipases, and esterases were examined on the enantioselective hydrolysis of the racemic ethyl ester **2a**. This ester turned out to be rather poor substrate, and among the attempted enzymes only pig liver esterase afforded the corresponding acid **2b**. Even in this case, the reaction was very



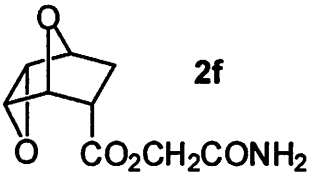
slow, and the hydrolysis proceeded as low as 33% conversion after the prolonged reaction. The product **2b** was converted to literary known ester **4** by way of two steps, and the absolute configuration was determined as shown in the scheme. The enantiomeric ratio of the enzyme-catalyzed kinetic resolution was also estimated to be 11 at this stage.

In terms of the efficiency and enantioselectivity of enzyme-catalyzed kinetic resolution, the "fast" enantiomer should have higher *k*cat as well as low *K*m. There was no effect of lowering the size of ester from ethyl to methyl **2c** (E = 6.5). Then we substituted the ethyl group of **2a** to more electron-withdrawing, chloromethyl group **2d**, however, it was too labile under the enzyme-catalyzed hydrolytic conditions. Another attempt for applying electron-wighdrawing, 2-chloroethyl ester **2e** and carbamylmethyl ester **2f** showed contrasting results. The enantiomeric ratio of the former, **2e**, was excellent (E = 50), however, the latter, **2f**, only resulted in very low reactivity as well as low enantioselectivity (E = 5).

substrate	R	conv. (%)	E value
2c	CH_3	32	6.5
2a	CH_2CH_3	33	11
2d	CH_2Cl		
2e	CH_2CH_2Cl	50	51
2f	CH_2CONH_2	26	5
2g	CH_2CF_3	50	9



2e



2f

The chloroethyl ester moiety of our "fast isomer" fits very well on the "hydrophobic pocket" of Jones' proposed active site model of pig liver esterase,[3] and the acceleration of the hydrolysis of fast isomer was supported. On the other hand, it was suggested that a strong interaction between carbamyl group and another "polar site" of PLE allowed the ester carbonyl group far from the nucleophilic hydroxyl group of serine residue, responsible for the enzyme-catalyzed hydrolysis. The introduction of another electron-withdrawing and hydrophobic trifluoroethyl group in **2g**, disappointingly, resulted in the unexpected enhancement of the hydrolysis of "slow enantiomer" to give a lower E (9) value.

In summary, we found pig liver esterase-catalyzed highly enantioselective resolution of racemic ester **2e** toward tamiflu intermediates, and further investigation on efficient method of preparation of substrate as well as the optimization of enzyme-catalyzed hydrolysis are now under way.

1) Terashima, S., Ujita, K., Kuwayama, T., Sugioka, T., Shimizu. K., Kanehira, K., WO 01/47906 A1.

2) Ogawa, S.; Iwasawa, Y.; Nose, T.; Suami, T.; Ohba, S.; Ito, M.; Saito, Y. *J. Chem. Soc. Perkin 1* **1985**, 903-906.

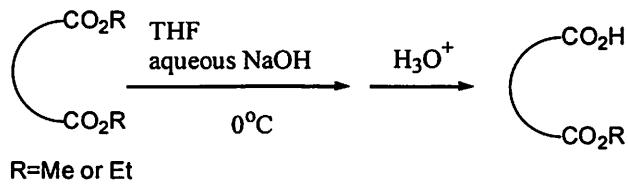
3) Jones, J. B. *Can. J. Chem.* **1993**, *71*, 1273-1282.

1P-53

Studies of Solvent Effects in the Selective Monohydrolysis of Symmetric Diesters

Satomi Niwayama,*[,a] Hezhen Wang,[a] Hanjoung Cho,[a] Yoshikazu Hiraga[b]
a:Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, U.S.A.
b: Department of Chemistry, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526, Japan
E-mail: satomi.niwayama@ttu.edu

Monohydrolysis of symmetric diesters without reliance on enzymes has been challenging. Limited examples have been reported for selective saponification of symmetric diesters,[1] but in most cases, complex mixtures of the starting diesters, half-esters, and diacids are formed even with the use of one equivalent of the base, and separation and purification of the half-esters has been a difficult task. However, we previously reported highly efficient selective monohydrolysis with the use of an aqueous NaOH solution in THF-water media at around 0°C (Scheme 1).[2,3] This reaction enables selective monohydrolysis of a series of symmetric diesters, yielding the corresponding half-esters in high to quantitative yields under these straightforward conditions. Because half-esters are important building blocks, this reaction is expected to have great synthetic versatility, and therefore we have been expanding the scope of this reaction from various points of view.



Scheme 1. Selective Monohydrolysis of Symmetric Diesters

One of the most remarkable differences between this monohydrolysis reaction and classical saponification is the reaction media. The use of the aqueous NaOH or KOH solution in the THF-water media at 0°C instead of a solid base and an alcohol medium makes the reaction mixture clean. Therefore, we have studied the influence of solvents by changing the proportion of THF as well as the type of co-solvent.[4]

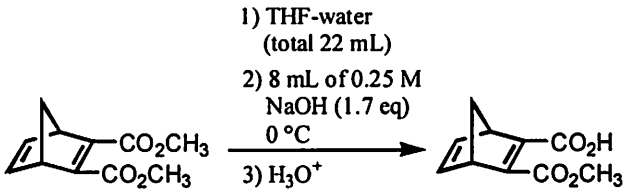
First, in the selective monohydrolysis of dimethyl bicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylate, **1**, we changed the proportion of THF as the co-solvent, keeping all other initially reported conditions constant (Table 1).[2] These results clearly indicate that decreasing the proportion of THF to below 7% does not influence the reaction rates significantly, but increasing the proportion of THF diminishes the rates tremendously. This tendency perhaps reflects the solubility of THF in water, and the increased proportion of THF is anticipated to decrease the exposure of the carbomethoxy group to the aqueous NaOH. Therefore, it appears that the optimal proportion of the THF as a co-solvent is approximately the proportion reported previously.[2]

Table 2 summarizes the results of changing a variety of co-solvents under the same conditions, which are 7% of co-solvent and the same reaction tempetarture.[2] From these results, it is apparent that methylene chloride, which has little miscibility with water, decreases the reaction rate significantly due to the reduced exposure of the carboalkoxy group to the aqueous NaOH. This result is similar to the cases in which large percentages of THF are applied as shown in Table 1. On the other hand, other co-solvents that are water-miscible to a small or great extent do not change the reaction rate significantly. The isolated yields of half-ester **2** appear to be highest when THF, acetonitrile, or no co-solvent is used, and slightly decrease when an alcohol is used as a co-solvent. These results indicate that the decreased yields may be due to the formation of a small amount of the corresponding diacid, and/or to the difficulty of extracting the product. Overall, THF or acetonitrile appears to be the best co-solvent among the solvents tested in this study for this selective monohydrolysis reaction.

Therefore, we conclude that in the reaction mixture, the small amount of THF or acetonitrile is dissolved in the larger amount of water, making one aqueous phase, and that the diester participates in the reaction as the second

phase, and the monohydrolysis occurs at the interface between the aqueous phase and the diester. The major role of THF or acetonitrile as a co-solvent is likely that of dispersing the starting diesters more smoothly to the reaction medium. This role is particularly advantageous when the starting diester is a solid, while the conditions free of an organic solvent are also anticipated to offer another practical advantage as a green reaction.

Table 1. Effects of Volume of THF in the Monohydrolysis of **1**

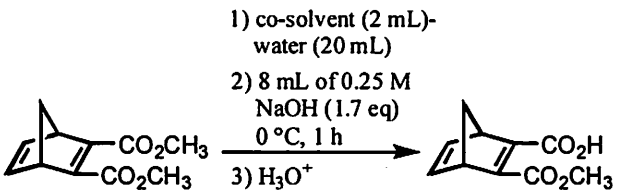


1 (1.2 mmol) **2**

Volume (mL) of THF[a]	Time	Yield (%)[b]	Reaction rate constant ($L \cdot mol^{-1} \cdot s^{-1}$)
22 (73%)	8 h	88 (0)	$3.26 \pm 0.02 \times 10^{-3}$
18 (60%)	6 h 30 min	81 (1.2)	$6.06 \pm 0.12 \times 10^{-3}$
14 (47%)	5 h 20 min	84 (0.4)	$1.10 \pm 0.02 \times 10^{-2}$
10 (33%)	3 h	90 (1.6)	$2.06 \pm 0.23 \times 10^{-2}$
6 (20%)	70 min	94 (1.2)	$2.56 \pm 0.06 \times 10^{-2}$
2 (7%)[c]	70 min	>99 (0)	$4.70 \pm 0.02 \times 10^{-2}$
1 (3%)	70 min	>99 (0)	$4.81 \pm 0.10 \times 10^{-2}$
0 (0%)	70 min	>99 (0)	$4.59 \pm 0.07 \times 10^{-2}$

[a] Percentage of THF(v/v) is shown in parentheses.
[b] Isolated yield of **2**. Recovered **1** is shown in parentheses.
[c] The same conditions reported in reference 2.

Table 2. Effects of Co-solvents in the Monohydrolysis of **1**



1 (1.2 mmol) **2**

Co-solvent	Yield (%)[a]	Reaction rate constant ($L \cdot mol^{-1} \cdot s^{-1}$)
THF[b]	>99 (0)	$4.70 \pm 0.02 \times 10^{-2}$
CH_3CN	>99 (0)	$4.85 \pm 0.40 \times 10^{-2}$
methanol	90 (0.8)	$3.73 \pm 0.50 \times 10^{-2}$
ethanol	86 (0)	$3.48 \pm 0.06 \times 10^{-2}$
2-propanol	88 (0.8)	$3.29 \pm 0.02 \times 10^{-2}$
CH_2Cl_2	9 (89)	$8.60 \pm 0.27 \times 10^{-4}$
None	>99 (0)	$4.59 \pm 0.07 \times 10^{-2}$

[a] Isolated yield of **2**. Recovered **1** is shown in parentheses.
[b] The same conditions reported in reference 2.

We also applied this solvent effect to selective monohydrolysis of diesters of molanic acid derivatives, and found that the use of acetonitrile instead of THF improved the yields of the half-esters to some extent. Recently, water-mediated reactions have become important as environmentally friendly reactions in green chemistry. To our knowledge, the reaction described here is among the first examples of water-mediated reactions being applied to desymmetrization.

References:

1 For example, (a) Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 5897-5905; (b) Vecchi, A.; Melone, G. *J. Org. Chem.* **1959**, *24*. 109-110; (c) Strube, R. E. *Org. Synth.* **1963**, Col. Vol. IV, 417-419; (d) Hutchinson, C. R.; Nakane, M.; Gollman, H.; Knutson, P. L. *Org. Synth.* **1990**, Col. Vol. VII, 323-326; (e) Robertson, A.; Sandrock, W. F., *J. Chem. Soc.* **1933**, 1617-1618; (f) Grakauskas, V.; Guest, A. M. *J. Org. Chem.* **1978**, *43*, 3485-3488.

2. Niwayama, S. *J. Org. Chem.* **2000**, *65*, 5834-5836.

3. Niwayama, S. US Serial No. 60/932.629.

4. Niwayama, S.; Wang, H.; Hiraga, Y.; Clayton, J. C. *Tetrahedron Lett.* **2007**, *48*, 8508-8510.

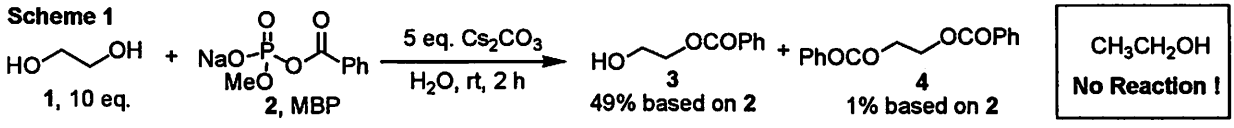
1P-54

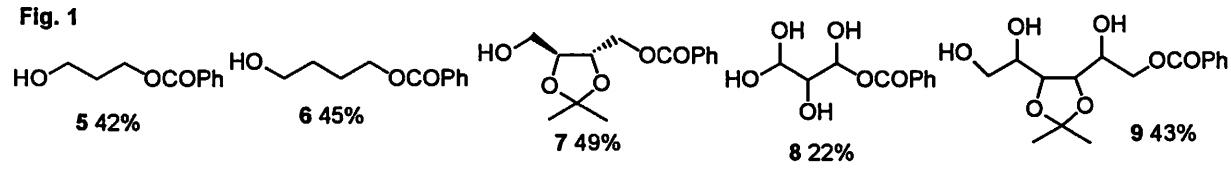
Esterification of Polyalcohol in Water

Risa Maeda,* Yuusaku Yokoyama, Hiroaki Okuno
Department of Pharmaceutical Sciences, Toho University
3-3-1, Miyama, Funabashi, Chiba, 274-8510, Japan
yokoyama@phar.toho-u.ac.jp

Esterification of alcohol is usually carried out in anhydrous condition. Since biologically important polyols such as glycerol, sugar, are only soluble in water, extra hydroxyl groups should be protected for selective reaction and for solubilization to organic solvent. In biological system, however, esterification of glycerol and ribose proceeded without protection by the help of enzymes during biosynthesis of lipids or peptides. We wish to report here the successful esterification of polyols in water using sodium methyl benzoyl phosphate (MBP), which is water soluble acylating reagent developed by Kluger.[1)]

A mixture of ethylene glycol (**1**, 10 *eq.*) and MBP (**2**) in the presence of $CsCO_3$ (5 *eq.*) was kept for 2 h at room temperature (Scheme 1). The reaction proceeded in homogeneous clear solution to give 49% of mono-ester (**3**) accompanied with small amount of di-ester (**4**). Although other diols or polyols gave mono-esters (**5-9**) selectively in moderate yields under similar condition, ethanol did not give the product at all.





Next, we investigated the reaction of ethyleneglycol (**1**) with MBP (**2**) (scheme 1) by changing $CsCO_3$ to various metal salts in order to clarify the key factor for the enhancement of this esterification. Table 1 shows the results. Although kind of alkali metal cations did not affect the results (runs 1-4), counter anion seemed to be very important; only carbonate ion were effective and other neutral or weak basic salts such as $CsNO_3$, CsCl and CsOAc, CsC_2O_4 did not act as catalysts (runs 5-8). Since aqueous solution of alkali metal carbonate is strongly basic (pH 12-13), we considered that, if more weak basic carbonate salt could be used, the yield would be much improved by suppressing hydrolysis. Therefore, we chose triethylammonium carbonate as a weak basic carbonate salt (pH 10). The yield, however, was decreased to 10% (run 9), and it took 24 h to give 37% yield (run 10).

Table 1

run	Additive	Mono-ester (3)	Di-ester (4)
1	Cs_2CO_3	49 %	1 %
2	Rb_2CO_3	48 %	1 %
3	K_2CO_3	42 %	2 %
4	Na_2CO_3	45 %	0.5 %
5	$CsNO_3$	-	-
6	CsCl	-	-
7	AcOCs	-	-
8	$Cs_2C_2O_4$	10 %	-
9	$(HEt_3N)_2CO_3$	10%	-
10	$(HEt_3N)_2CO_3$	37%[a)]	1%

[a)] Reaction time is 24 h

From above results, it came to our mind that important factor might not be carbonate ion but basicity of the solution. Therefore, we attempted the same reaction (scheme 1) under strong basic condition without using carbonate salt. The results are shown in Table 2. The addition of triethylamine (pH 13) gave 39% yield after 2h (run 1), but, surprisingly, the short reaction time (15 min) increased the yield 51% (run 2). Next we investigated this reaction maintaining the pH constantly using phosphate buffer. The reaction slowed down seriously under pH 10 (runs 5 and 6), but the reaction proceeded at pH 11-12 to give the product in 47-50% yields (runs 3 and 4).

Table 2

run	base	pH	time	Mono-ester (3)	Di-ester (4)
1	Et_3N (10 *eq.*)	13	2 h	39 %	2 %
2	Et_3N (10 *eq.*)	13	15 min	51 %	2 %
3	Phosphate Buffer	12	15 min	47 %	3 %
4	Phosphate Buffer	11	15 min	51 %	2 %
5	Phosphate Buffer	10	15 min	12 %	0.1 %
6	Phosphate Buffer	9	15 min	0.7 %	-

Although Klugar reported that the rate of esterification of polyols was enhanced by the addition of $La(OTf)_3$ or $Sc(OTf)_3$, our finding that basic condition (> pH 12) is a key factor for the enhancement of the esterification (not hydrolysis !) in water is the first examples. More precise investigation for factors of rate enhancement and application to the synthesis of the complex molecules are now in progress.

[1)] R. Kluger, *et. al.*, *J. Am. Chem. Soc.*, **2004**, *126*, 1071.

1P-55

Chemists' Scale-Up Challenges

Asayuki Kamatani*
Pharmaceutical Sciences, Pfizer Ltd.
Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom
asayuki.kamatani@pfizer.com

Process chemists' responsibilities in pharmaceutical industries continue to rise as the structure of target molecules is becoming more complex and there is a higher chance of a novel reaction process going into a plant scale in a short period of time.

In contrast, ironically, their opportunities to participate in these scale-up processes are starting to decrease as the equipments in general-purpose pilot plants became complicated and more difficult for chemists to use. In particular, chemists in some of the pharmaceutical companies are losing opportunities to oversee manufacture of GMP batches as they are not fully trained to take part.

On the other hand, scaling-up reactions in simple round-bottomed flasks creates safety concerns as the batch size increases, particularly in sizes between 10–20 L and beyond as the total weight of the flask with the reaction mixture gets bigger that makes it hard to support by regular clamps and lab jacks. One of the possible solutions to this issue is the use of heating mantles, but so many incidents related to this equipment as an ignition source creates another safety-related worry. The other concern on this approach is the fact that the results from these flask experiments often do not represent what can happen in the pilot plant primarily due to poor mixing and heat transfer issues.

At Pfizer Sandwich laboratories in UK, a simple training program was recently developed to allow chemists use two 15-L reactor systems (glass-lined and Hastelloy; manufactured by Ken Kimble Ltd.) configured similarly to the ones in the pilot plant. This allowed them to scale-up their reactions in their own hands with minimum barrier but not compromising safety. Since opening this facility in early 2007, more than 70 chemical reactions were performed by chemists themselves in these fixed reactors. The processes scaled up in this facility include reactions requiring operation under cryogenic temperature, air-sensitive reactions involving transition metal catalysts and crystallization to upgrade enantiomeric excess. During the runs chemists have an opportunity to learn how their reaction can behave in a large scale reactor, gain data to understand what is going on in the reactor, and develop a solution to some unexpected results or issues while the process is run.

Of all the major operations in a reaction (set-up, charging reagents, running, quench, extraction, solvent exchange and isolation), interestingly, the most common step chemists find "unexpected" is crystallization,

where they learn how valuable it is to execute analysis before filtration to avoid loss of the desired products. Solvent exchange (using either jacketed vessel or Rotavapor) can also be a pitfall for them as the efficiency of solvent involves so many factors (heat transfer, vapor pressure, nitrogen sweep) that proper analysis of solvent composition is essential in order to reproduce the results in small scales. In a sharp contrast, chemists generally do not find unexpected issues on reaction itself, although visual insights on large scale reactions have always been valuable for record.

Examples from these processes, with key observations and learning that proved valuable to transfer to engineers and operators in the pilot plant will be presented.

1P-56

Template Synthesis Process of Porous Polymers

Wei-Chi Lai,* Shen-Chen Tseng
Department of Chemical and Materials Engineering, Tamkang University
151 Ying-Chuan Road, Tamsui, Taipei 25137, Taiwan
wclai@mail.tku.edu.tw

Techniques of template synthesis process of porous polymers have been the subject of numerous studies over the past decades. Such techniques often utilized nano-scale templates mixed with monomers and initiators. Careful polymerization of the monomeric solvent results in nanostructured polymers with embedded templates. The size and morphology of the templates used plays an important role in the properties of the resulting polymers. Templates extracted in organic solvent yield nanoporous materials that could prove useful in a variety of applications on account of their unique nanostructure. Such applications include: use as membranes, mesoporous catalysts, stationary phases for chromatography, and even as chemical or biosensors.

Techniques of template synthesis of porous polymers include: micellar templating, liquid crystal templating organogel templating and so on. The primary disadvantage of micellar and liquid crystal templating results from the μm-sized aggregates formed during synthesis, leading to the loss of nano-structures. The resulting materials in such cases are opaque and heterogeneous. By comparison, if the molecules self-organize into a network and yield the physical gelation, these molecules are then able to maintain a self-assembled nano-structure during polymerization. Therefore, the organogel templating technique may overcome the shortcomings of the other two methods.

We propose a new method for preparing nanostructured materials using self-assembled templates formed by organogels. 1,3:2,4-Dibenzylidene sorbitol (DBS) is a sugar derivative that is capable of self-assembling into a 3-D nanofibrillar network at relatively low concentrations in some organic solvents and polymer melts. In this work, we induced the formation of such nanofibrils in organic monomers such as styrene. Subsequently, we synthesized the styrene using general thermal-initiated polymerization. The resulting materials would be a transparent solid or film containing nanofibrils from DBS organogels. The final self-assembled microstructure was examined using atomic force microscopy (AFM). This study revealed that self-assembled entities could indeed be preserved during polymerization, and the resulting nanofibrils ranged from 10 nm to 100 nm in diameter. The BET data show that the porous samples obtained after the removal of DBS organogels by washing with ethanol had a greater specific surface area.

1P-57

Chemical immobilization of DNA on porous PVDF membranes for biomedical applications

Dar-Jong Lin[1], Dong-Tsamn Lin[2], Tai-Horng Young[2], Hsu-Hsien Chang[1], Liao-Ping Cheng[1,*]
[1]Department of Chemical and Materials Engineering, Tamkang University, Taipei, Taiwan
[2]Department of Laboratory Medicine, College of Medicine, National Taiwan University, Taipei 10016, Taiwan
lpcheng@mail.tku.edu.tw

Microporous poly (vinylidene fluoride) (PVDF) membranes are often prepared by the so-called immersion-precipitation method, in which a casting dope composed of polymer dissolved in a solvent is immersed in a nonsolvent bath to induce polymer precipitation. Thereafter, the precipitate is dried to form a porous membrane. A wide variety of morphologies can be obtained simply by controlling the conditions of the casting dope and the precipitation bath. At one extreme, the membrane may exhibit an asymmetric morphology being composed of tight skin, macrovoids, and cellular pores. On the other hand, it can also be totally open and uniformly packed by interlinked crystal entities. In most cases, however, crystal particles and cellular pores are all present to form a mixed morphology. That is, PVDF surfaces with very different porosities are available to us. It is then of great interest to investigate how the surface morphology affects the efficiency of immobilization on these membranes; in particular, the final products find biomedical applications.

In the current work, attempts were made to immobilize single strand deoxyribonucleic acid (ss-DNA) on PVDF membrane substrates. PVDF membranes with different porous surface morphologies were prepared by immersion-precipitation from coagulation baths of different strengths. On these membranes single strand deoxyribonucleic acid (ss-DNA) was covalently immobilized by a dual step procedure. First, glycidyl methacrylate (GMA) was grafted on the PVDF substrate by the technique of plasma-induced polymerization. PVDF membrane was plasma-irradiated and then exposed to air to form peroxides, which decomposed into free radicals $-CO\cdot$ at an elevated temperature and/or in the presence of Fe^{2+} (e.g., Mohr salt). These radicals served to initiate the free radical polymerization of GMA monomers to produce

PGMA on the surface of the PVDF membrane. ss-DNA was then reacted with PGMA by opening of the epoxy rings at the attack of amines of ss-DNA to form amino-alcohols.

Nowadays, while immobilization of enzyme has reached a stage of maturity, DNA is being emerging as a new target for research. Owing to its excellent ability to interact with proteins, DNA is considered to possess great potential in biomedical applications (e.g., protein adsorbent, biosensor, etc.). Recently, Kado et al. immobilized ss-DNA on polyester microfibers by way of a spacer (e.g., poly(glycidyl methacrylate), poly(acrylic acid), etc.) that were previously ozone-grafted on the microfibers. A marked improvement in immobilization yield was reported being attributed to the much larger surface available than beads or sheets that was conventionally used for the same purpose. The DNA-immobilized microfibers were shown to exhibit very well antibody adsorption capabilities. However, because the surfaces of the microfibers were essentially nonporous, the immobilization yields were still limited to a relatively low level (e.g., 0.047 $\mu g/cm^2$ for a PGMA spacer). To increase the immobilization yield and to understand how strong effect the substrate's surface morphology causes, a series of PVDF membrane substrates with very different surface porosities were prepared and DNA was immobilized on them. In addition, the anti-DNA antibody adsorption tests were performed on the DNA-immobilized membranes to see their adsorption capabilities.

The highest attainable graft density of PGMA on PVDF membrane was 0.3 mg/cm^2, which was the case when a highly porous PVDF membrane was employed as the substrate. For immobilization of ss-DNA, the yield was found to depend significantly on the reaction temperature and pH. The maximal value was 48.5 $\mu g/cm^2$. Furthermore, adsorption tests of anti-DNA antibody were carried out on membranes with and without immobilized ss-DNA using serum obtained from systemic lupus erythematosus patients. The results indicated that the immobilized DNA could effectively adsorb the antibody in the serum.

1P-58

Graft Polymerization of Poly(vinyl acetate) to a Corn Starch and Its Blends with Polyhydroxybutyrate

Trong-Ming Don,* Wei-Wei Shun
Department of Chemical and Materials Engineering, Tamkang University
151 Ying-chuan Rd., Tamsui, Tapei County, Taiwan 25137
tmdon@mail.tku.edu.tw

Recently, much attention has been paid to environmentally-friendly materials, because of growing environmental concern for sustainable development. Poly(hydroxyalkanoates) (PHAs) are a class of biodegradable aliphatic polyesters naturally produced by a variety of bacteria under a condition of excess carbon source. The first identified member of PHA family is polyhydroxybutyrate (PHB), which is often compared to isotactic polypropylene due to their similar melting temperatures, crystallinity degrees and tensile strengths. However, PHB is a brittle and expensive material. To lower its cost, it was intended to blend PHB with a cheaper corn starch. Yet, due to their immiscibility, phase separation occurs extensively which results in very poor film formability. In this study, corn starch was thus pre-grafted with poly(vinyl acetate) (PVAc) which has been proved to be miscible with PHB. Hopefully, grafted PVAc chains would help corn starch to be well-dispersed in PHB matrix. Another potential advantage of incorporating PVAc component is the material's toughness can be increased since PVAc is known as a leathery polymer.

Graft copolymerization of synthetic polymers to polysaccharide chains has been studied for many years, especially in cellulose. In this way, new materials with desired properties can be obtained by the chemical combination of natural and synthetic polymers. To effectively graft PVAc chains to corn starch, ceric ion (Ce^{4+}) was used as the initiator for free radical graft polymerization. The reaction mechanism has been well described in literatures. Briefly, when ceric ion is added into starch solution, it oxidizes pyranose rings of starch (St) to produce free radicals ($Ce^{4+} + St \rightarrow Ce^{3+} + St\bullet + H^{+}$). Once free radicals are generated on the starch main chain, graft polymerization of monomer then takes place immediately following the traditional chain polymerization. In this way, starch graft copolymer is thus produced. Besides copolymer, PVAc homopolymer can also be obtained mainly due to the chain transfer reaction, where free radical is transferred to VAc monomer and thus initiating homopolymerization. Therefore, graft copolymerization and homopolymerization compete with each other for the monomer. In this study, corn starch was first gelatinized at 90°C for 1h. It was then cooled down to 50°C for the grafting reaction. Ceric ammonium nitrate initiator dissolved in nitric acid solution was poured into the gelatinized starch solution, followed by the addition of VAc monomer. After 4 h of reaction, a latex solution was obtained. To determine the amount of PVAc grafted to corn starch, PVAc homopolymer was removed by using a Soxhlet extraction with acetone solvent. Structure of the starch-*g*-PVAc copolymer was confirmed by FTIR analysis, which revealed absorption peaks of both starch and PVAc. For example, starch has absorption peaks at 579, 855, 1649, 3315 cm^{-1}; and those peaks characteristic of PVAc are 1742 (C=O), 2925 (CH_2) and 2975 cm^{-1} (CH_3).

From gravimetric analysis, total monomer conversion (amount of reacted monomer/initial addition of monomer), grafting efficiency (amount of grafted PVAc chains/amount of reacted monomer) and grafting ratio (amount of grafted PVAc chains/amount of starch) were 85%, 16% and 0.27, respectively. Molecular weights of PVAc homopolymer and grafted PVAc chains were measured using a GPC technique and found to be 8.2×10^4 and 8.5×10^4 g/mol, respectively.

After drying, the synthesized PVAc-modified corn starch was then blended with PHB at different compositions using a solution blending method with DMSO as a co-solvent. Differential scanning calorimeter was used to measure glass transition temperature (T_g), crystallization temperature (T_c) and melting point (T_m) of blends, from which miscibility of the PHB and PVAc-modified corn starch was evaluated. The results showed that PHB was indeed miscible with PVAc chains in PVAc-modified starch from the evidence that there was only one T_g in all the blends. SEM pictures showed this miscibility could help starch particles uniformly dispersed in PHB matrix with good bonding. PHB had a T_g at 2.3°C and increased with the composition of PVAc-modified corn starch. A Gordon-Taylor equation with a k value of 0.11 could describe the T_g-composition relationship in the blends very well. The equation is shown as follows: $1/T_{g,blend} = (w_1 T_{g,1} + k w_2 T_{g,2})/(w_1 + k w_2)$, where w_1 and w_2 are weight fractions of PHB and PVAc-modified starch, respectively; and $T_{g,1}$ and $T_{g,2}$ are glass transition temperatures of PHB and PVAc-modified starch, respectively.

Thermal gravimetric analysis was carried out to understand their thermal stability. PHB had a one-stage degradation behavior with the maximum-rate degradation temperature at 274°C under nitrogen atmosphere. A two-stage degradation behavior was observed for the PVAc-modified corn starch. The first stage with a maximum-rate degradation temperature at 360°C was caused by the starch and the pendant acetate groups in PVAc chains. The second stage with a maximum-rate degradation temperature at 484°C was due to the degradation of PVAc main chains. There was still 7.6% of char yield at 600°C for PVAc-modified starch, where no residual char was found for PHB. For the blends, a three-stage degradation behavior was found and the maximum-rate degradation temperature of the first stage caused by PHB component increased with increasing the composition of PVAc-modified corn starch. This indicates that the addition of PVAc-modified starch can increase thermal stability of PHB, which help mechanical processing by increasing the processing window. Maximum-rate degradation temperatures of the second- and third-stage in the blends were caused by the PVAc-modified starch and had the same degradation temperatures as those in pure form.

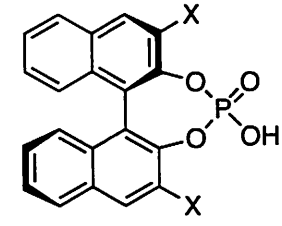
However, it is known that PVAc is unable to be degraded by microorganisms, which would raise questions on the biodegradability of PHB/PVAc-modified starch blends. Therefore, PVAc-modified starch was treated with methanol/alkaline solution, converting to poly(vinyl alcohol)-modified starch. It was found by FTIR analysis that the ester absorption peak at 1742 cm^{-1} of PVAc completely disappeared after methanolysis, proving successful conversion of PVAc to PVA. This PVA-modified starch will then be blended with PHB and properties of the blends will be evaluated in the near future.

1P-59

Chiral Brønsted Acid-Catalyzed Enantioselective Friedel-Crafts Alkylation of Indole with α,β-Unsaturated Ketones

Tsubasa Sakamoto*, Junji Itoh, Kohei Fuchibe, Keiji Mori, Takahiko Akiyama
Department of Chemistry, Faculty of Science, Gakushuin University
1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588, Japan
takahiko.akiyama@gakushuin.ac.jp

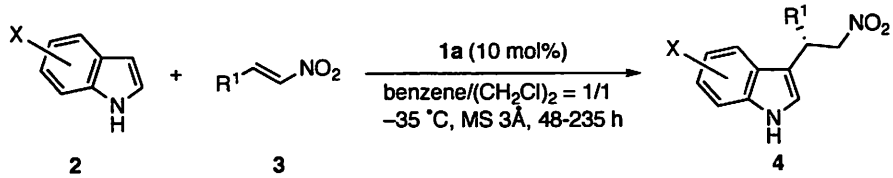
Development of an efficient chiral catalyst continues to be one of the most important goal of organic synthesis. We have recently synthesized chiral cyclic phosphoric acids **1**,[1] starting from (*R*)-BINOL, and found they are efficient chiral Brønsted acid catalysts for the nucleophilic addition[2] and the cycloaddition reaction toward imines,[3] and so on. However, in the most of reactions catalyzed by the catalyst **1**, imine was employed as the electrophile. In order to expand the synthetic utility of the phosphoric acid catalysis, we investigated other electrophiles and have found that nitroalkenes and α,β-unsaturated ketones proved to be suitable substrates for the 1,4-addition of indoles.



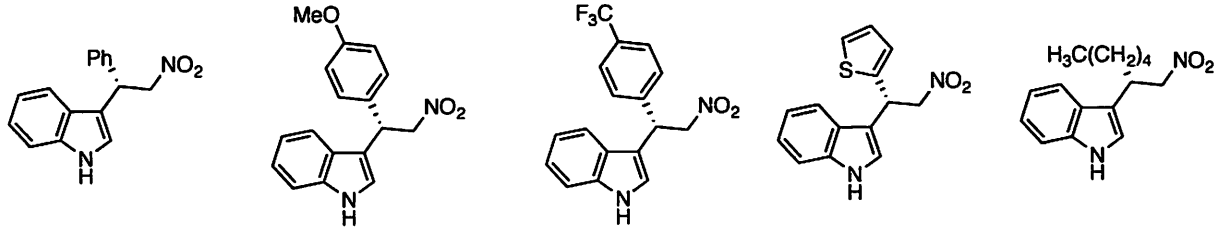
Chiral Phosphoric Acid
1a: X=$SiPh_3$
1b: X=2,4-$(CF_3)_2C_6H_3$

1. *Friedel-Crafts alkylation of indoles with nitroalkenes*[4]

A variety of phosphoric acids were screened as catalysts for the Friedel-Crafts alkylation reaction of indole with β-nitrostyrene, and phosphoric acid **1a** (X=$SiPh_3$) was turned out to be the most effective. We found that addition of activated MS 3Å is crucial and could afford the corresponding adducts **4** in a good yield and high enantioselectivity. A wide range of indole derivatives and nitroalkenes participated in the **1a**-catalyzed Friedel-Crafts alkylation reactions and the corresponding adducts were obtained in good yields and with excellent enantioselectivities in all the cases examined.



2 **3** **4**



4a: 76%, 91% ee **4b**: 74%, 91% ee (−20 °C) **4c**: 84%, 91% ee **4d**: 71%, 90% ee **4e**: 77%, 90% ee (With 20 mol% of **1a**)

On the other hand, 1-methylindole gave a racemic adduct in a low yield. This result suggests that the presence of hydrogen on nitrogen of indole is essential for the reaction, and we propose the ternary transition state (Figure 1).

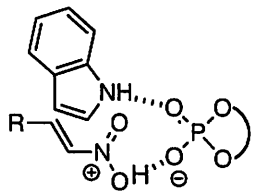
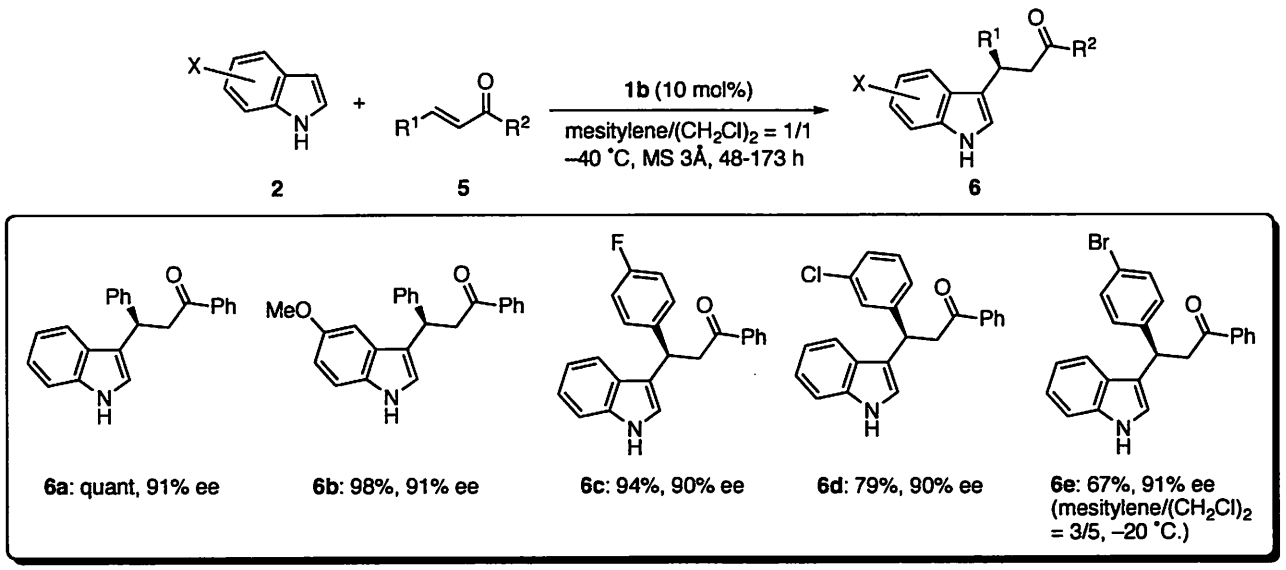


Figure 1

2. ***Friedel-Crafts alkylation of indoles with α,β-unsaturated ketones***

Next, we focused on the Friedel-Crafts alkylation reaction of indole with α,β-unsaturated ketones. A phosphoric acid **1b**, bearing 2,4-$(CF_3)_2C_6H_3$ group on 3,3'-position, proved to be the most effective as a catalyst. Treatment of indoles **2** with α,β-unsaturated ketones **5** with phosphoric acid **1b** (10 mol%) and activated MS 3Å at –40 °C in mesitylene/dichloroethane gave indole derivatives **6** with high yields and enantioselectivities.



References

1) For reviews, see: a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999-1010. b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744-5758.

2) a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568. b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583-2585. c) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2005**, *347*, 1523-1526. d) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756-6764.

3) a) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141-143. b) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796-4798. c) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070-13071.

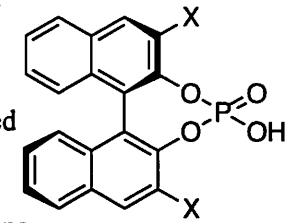
4) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 4016-4018.

1P-60

Chiral Brønsted Acid Catalyzed Enantioselective aza-Darzens Reaction

Tohru Suzuki,* Kohei Fuchibe, Keiji Mori, Takahiko Akiyama
Department of Chemistry, Faculty of Science, Gakushuin University
1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588, Japan
takahiko.akiyama@gakushuin.ac.jp

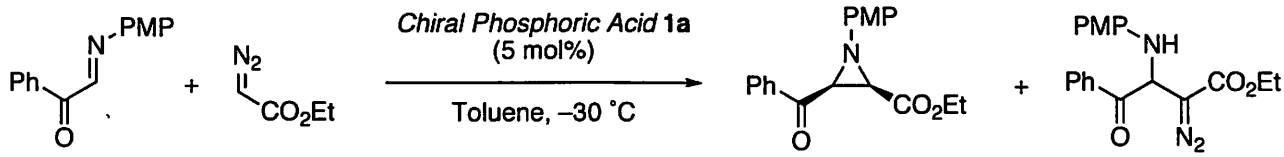
Development of efficient chiral catalyst continues to be one of the most important goal of synthetic organic chemistry. Recently, chiral Brønsted acid catalysis has emerged as a new type of chiral catalysis. We have recently synthesized chiral cyclic phosphoric acids **1**, starting from (*R*)-BINOL, and demonstrated their catalytic activity as chiral Brønsted acid in the Mannich-type reactions,[1] hydrophosphonylation reactions,[2] aza Diels-Alder reactions.[3] β-Amino esters, α-amino phosphonates, and dihydropyridone derivatives were obtained respectively with excellent enantioselectivities.[4]



1

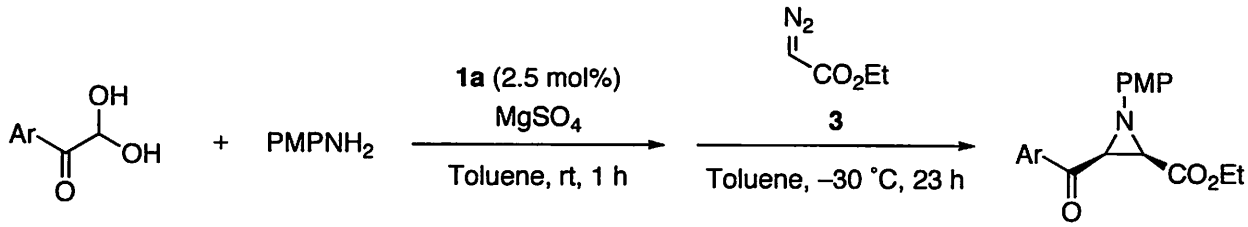
Aziridines are versatile intermediates of great value in organic synthesis because ring opening of chiral aziridine is a potent method for the synthesis of optically active amines. We wish to present herein chiral Brønsted acid catalyzed enantioselective aza-Darzens reaction leading to aziridines.

We studied the reaction of **2a** and **3b** in the presence of **1** and found that **1a**(X=Si(4-*t*-BuC_6H_4)$_3$) proved to the most effective as a catalyst for the aza-Darzens reaction. On treatment of α-imino ketone **2a** with α-diazoacetate **3** in the presence of chiral phosphoric acid (5 mol%) **1a** in toluene at −30 °C, substituted aziridine **4a** was obtained in 72% yield with 94% ee accompanied by **5a**.



2a **3** **4a** 72%, 94% ee **5a** 10%, 38% ee

We tried three-component aza-Darzens reaction, starting from phenylglyoxal hydrate, *p*-anisidine, and α-diazoacetate. Gratifyingly, both the chemical yield and ee were improved and **4a** was obtained in 95% yield with 97% ee under the influence of 2.5 mol% of **1a**, and the formation of **5a** was suppressed. A range of substituted phenylglyoxal derivatives gave the corresponding aziridines in excellent yields and ee (Table). Use of activated aldimine derived from phenyl glyoxal is crucial for the formation of the aziridine.

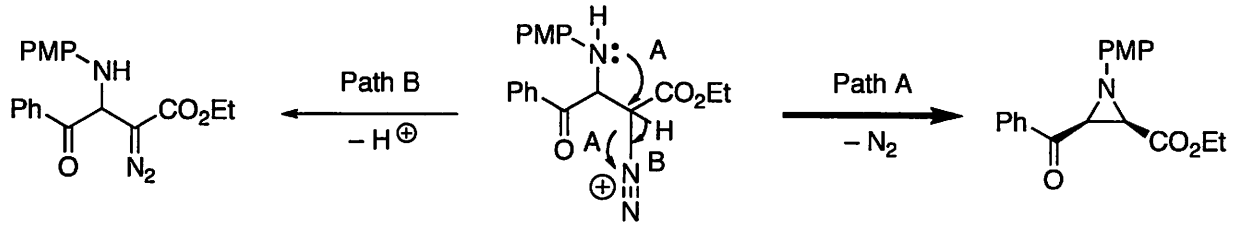


4

Table Three-component Aza-Darzens Reaction

Entry	Ar	Yield of **4**/%	ee of **4**/%
1	Ph	95	97
2	4-BrC_6H_4	93	93
3	4-MeC_6H_4	94	92
4	4-$MeOC_6H_4$	98	95
5	4-ClC_6H_4	>99	94

The aziridination proceeded by nucleophilic attack of α-diazoacetate to generate an intermediate **6**, which subsequently underwent intramolecular nucleophilic addition to afford an aziridine **4a** (Path A). Terada et al already reported chiral phosphoric acid catalyzed asymmetric direct alkylation,[5] in which α-diazoester was obtained exclusively via path B. The contrasting results may be ascribed to the nucleophilicity of the nitrogen. We employed PMP (*p*-methoxyphenyl) substituted imine whereas Terada's group employed *N*-acyl imine.



5a **6** **4a**

In summary, chiral phosphoric acid catalyzed three component aza-Darzens reactions have been developed and the corresponding aziridines were obtained with excellent enantioselectivities.

References

1) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.
2) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583.
3) (a) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (b) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796.
4) For reviews, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.
5) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360.

1P-61

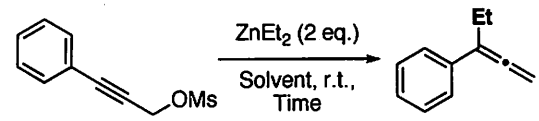
DMSO Promoted S_N2' Reaction of Organozinc Compounds

*Koji Kobayashi, Hiroshi Naka, Yoshinori Kondo
Graduate School of Pharmaceutical Sciences, Tohoku University
Aramaki Aza Aoba 6-3, Aoba-ku, Sendai 980-8578, Japan
ykondo@mail.pharm.tohoku.ac.jp

Organozinc reagents have been widely used as soft nucleophiles in organic synthesis and the control of nucleohilicity is highly important for desired selective transformations. Various methods have been utilized for promotion of the reactivity, and conventionally ate complexation or transmetalation has been employed. In connection with our recent studies on the reactivity control of organozinc reagents, we focused our interest on solvent effects for promoting the reactivity of organozinc reagents. In this presentation, we wish to report S_N2' reaction to propargyl eletrophiles of organozinc reagents using the dramatic effect of DMSO.

Solvent is one of most important parameters in organic reaction. The solvents effects of organometallic reactions have been studied energetically, not only on improvement of solubility of metal salt but also on change of oligomeric complex structures, on acceleration of the reaction, and on the reaction selectivity. These effects depend on the physicochemical nature of solvents (polarity, donor number and acceptor number, *etc.*). Therefore, it is considered to be very attractive reaction issue to investigate the relationship between the solvents and reactivities of organometallic reagents. DMSO has been regarded as an excellent polar solvent for various organic reactions, but recognized as uncommon solvent for organozinc reactions with uncertain advantage.

In preliminary experiment, the reaction of diethylzinc and 3- phenylpropargyl mesylate (**1**) in various organic solvents was carried out at room temperature (Table 1). In nonpolar solvents such as CH_2Cl_2 and toluene, the reaction did not proceed at all (Entry 1,2 Table 1). In polar solvents such as THF and CH_3CN, no reaction was observed (Entry 3,4 Table 1). To our surprise, in polar and strong donor ability solvent such as DMF and DMSO, the S_N2' reaction was dramatically promoted, and the target allene (**2**) was obtained (Entry 5,6 Table 1). The best result (90%) was obtained when DMSO was employed as a solvent. The solvent polarity (E_T) of CH_3CN is largely similar to DMF (43.8) and DMSO (45.0). On the other hand, the donor numbers (*DN*), DMF (26.6) and DMSO (29.8) are higher values than CH_3CN (14.1). The highest *DN* solvent gave the most excellent result.



1 **2**

Table 1. Solvent Effect of S_N2' Reaction[a]

Entry	Solvent	E_T	*DN*	Time(h)	Yield (%)[b]
1	CH_2Cl_2	41.1	-	24	n.r.
2	Toluene	33.9	-	24	n.r.
3	THF	37.4	20.0	24	n.r.
4	CH_3CN	46.0	14.1	24	n.r.
5	DMF	43.8	26.6	24	43
6	**DMSO**	45.0	29.8	18	**90**

[a] All reactions were carried out using 3-phenyl propargyl mesylate (1) (0.3 mmol) and diethylzinc (0.6 mmol) at r.t.. [b] Isolated yield.

In order to examine further scope and limitations, reactions using other substrates were investigated. 3-phenyl-1-phenethylpropargyl mesylate (**1a**) and 3-butyl-1-phenethylpropargyl mesylate (**1b**) reacted smoothly to give corresponding 1,2,2-trisubstituted allene (Table 2 Entry 1,2). Various substituents on the aromatic ring of the 3-phenyl propargyl mesylate (**2c-h**) were compatible this allene synthesis. Substitution with electron-donating methoxy is acceptable for the reaction corresponding allene **2c** was obtained in good yield (Table 2 Entry 3). However, yields of allenes **2d, e** were moderate when methyl subustituted substrate **1d, e** were utilized (Table 2 Entry 4,5). The tolerance of alkokycarbonyl group (**1f**), cyano group (**1g**) and bromo substituent (**1h**) in the allene synthesis is considered to be synthetically important (Table 2 Entry 6-8). The reaction of the substrate with terminal alkyne **1i** was also found to be successful and 1,3-disubsutituted allene **2i** was selectively obtained in high yield (Table 2, Entry 9). It is noteworthy that no deprotonation of terminal alkyne was observed during the reaction. The allenylsilyl compound **2j** was obtained from trimethylsilylated substrte **1j** using similar reaction conditions (Table 2, Entry 10). The high functional group tolerance of this allene synthesis using organozinc reagents in DMSO is considered to be more advantageous over conventional oganometallic nucleophiles.

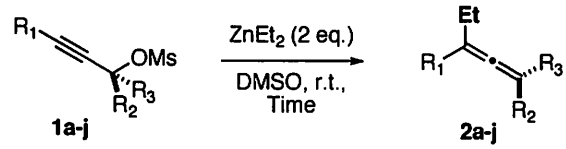
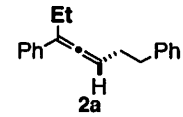
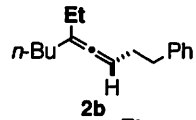
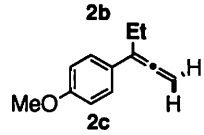
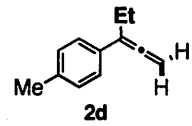
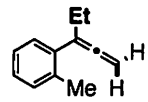
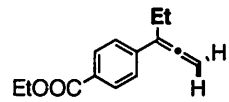
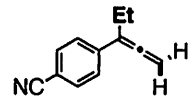
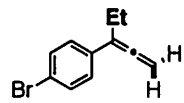
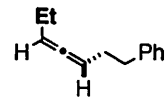
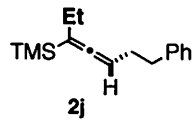


Table 2. Additoin to Other Propargyl Mesylates[a]

Entry	Product	Time(h)	Yield (%)[b]
1	 **2a**	24	90
2	 **2b**	24	69
3	 **2c**	24	74
4	 **2d**	24	44
5	 **2e**	24	59
6	 **2f**	22	88
7	 **2g**	16	71
8	 **2h**	16	74
9	 **2i**	24	86
10	 **2j**	24	59

[a] All reactions wer carried out using propargyl mesylate (1) (0.3 mmol) and diethylzinc (0.6 mmol) at r.t.. [b] Isolated yield.

In conclusion, the S_N2' reaction of propargyl electrophile with organozinc reagents was dramatically improved in DMSO. Further investigation on the scope and limitation of this reaction and mechanistic studies are underway.

1P-62

New synthetic methods by using MAC reagents

Tomoyuki Kawamura, *[a] Kenji Yatsuzuka,[b] Masaki Kamiya,[b] Hisao Nemoto[b]

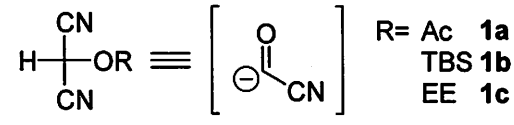
[a] Department of Chemistry, School of Science and Technology, Kwansei Gakuin University
2-1 Gakuen Sanda 669-1337, Japan

[b] Division of Pharmaceutical Chemistry, Institute of Health Biosciences, Graduate School of the University of Tokushima, 1-78 Sho-machi, Tokushima 770-8505, Japan

cln70396@kwansei.ac.jp

Carbon-carbon bond formation reaction between electrophiles and Masked Acyl Cyanide (MAC) reagents (H-MAC-R **1**), developed our research group, proceeds under mild basic or neutral conditions in excellent yields.[1] Recently, we developed acylated MAC reagent (H-MAC-Ac **1a**). In this report, we describe one-pot reaction by using H-MAC-Ac.[2]

Figure

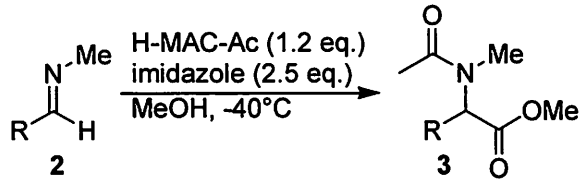


1
MAC reagent

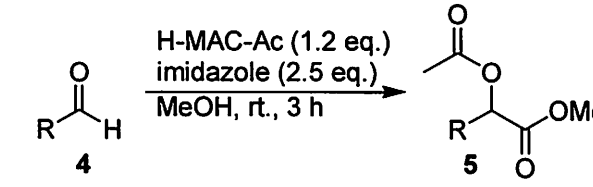
We have reported that silylated MAC reagent (H-MAC-TBS **1b**) enables one-pot reaction with aldehydes and alcohols to give α-siloxy esters.[3] However, silylated MAC reagent did not exhibit similar reaction with *N*-alkylated imines. In contrast, the use of noble acylated MAC reagent (H-MAC-Ac **1a**) was effective in facilitating the reaction of C=X double bond.

Three components, an imine (or aldehyde), an alcohol and an acylated MAC reagent (H-MAC-Ac **1a**), were coupled in one-portion to produce α-amino acid derivative **3** (or α-acyloxy ester **5**) in excellent yields. For this one-pot reaction, imidazole as an additional base gave the best results. When alcohol was used as a solvent, best results was obtained for imines and aromatic aldehydes.

Table Reaction of H-MAC-Ac with various electrophiles (aldimines and aldehydes).



entry	R	time (h)	yield (%)
1	C_6H_5	3	99
2	4-CH_3O-C_6H_4	3	88
3	4-NO_2-C_6H_4	5	82
4	$C_6H_5CH_2CH_2$	3	83
5	$(CH_3CH_2)_2CH$	5	81
6	4-$(C_2H_5O)CH$-C_6H_4	5	82

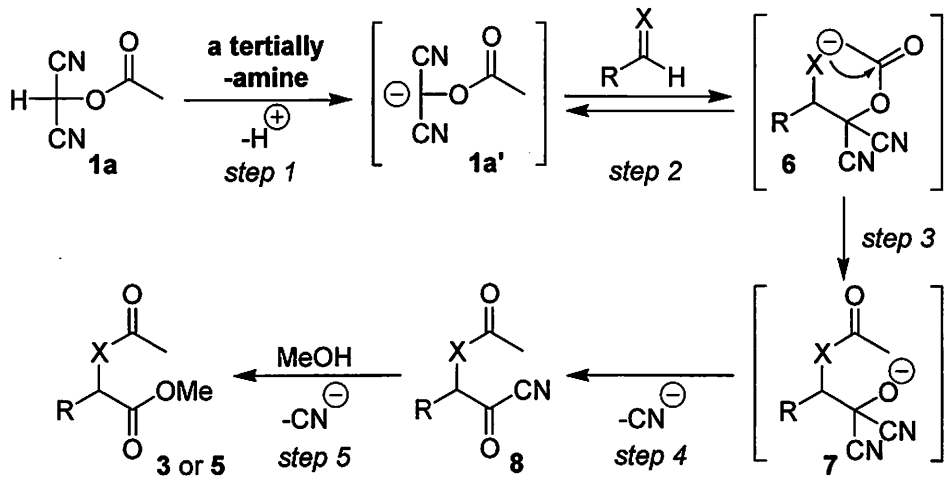


entry	R	yield (%)
1	C_6H_5	84
2[1]	4-CH_3O-C_6H_4	81
3	4-NO_2-C_6H_4	91
4[2]	$C_6H_5CH_2CH_2$	92
5[2]	$(CH_3CH_2)_2CH$	75

[1] H-MAC-Ac (3.0 eq.).
[2] MeOH (3.0 eq.) in diethyl ether at -20°C for 24 h.

The proposed mechanism is illustrated in **Scheme**. First, a tertiary amine deprotonates **1a** to genarate carbanion **1a'** (*step 1*), followed by nucleophilic addition to C=X double bond gives intermediate **6** (*step 2*). Miguration of acyl group of **1a** from oxygen to anionic X could intramolecularly occur to give **7** (*step 3*). The elimination of hydrogen cyanide from **7** generates the acyl cyanide **8** (*step 4*). Finally, **3** (or **5**) can be produced from **8** with methanol (*step 5*).

Scheme Proposed mechanism



By the acylated MAC reagents, our developed three-component reactions will be more applicable in organic synthesis since availability of various acylated derivatives is higher than that of organosilyl derivatives.

Reference

1) Nemoto, H. *Yuki Gousei Kagaku Kyoukaishi*, **2004**, *62*, 347.

2) Nemoto, H.; Kawamura, T.; Miyoshi, N. *J. Am. Chem. Soc.* **2005**, *127*, 14546.

3) Nemoto, H.; Ma, R.; Li, X.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2001**, *42*, 2145.

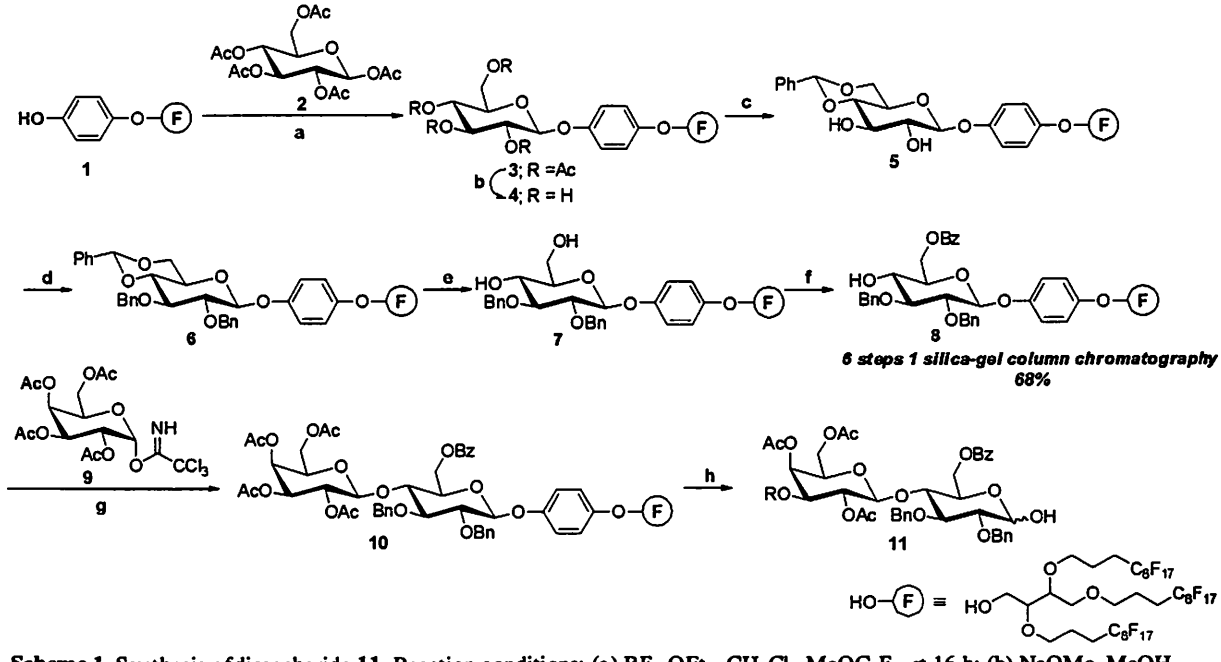
1P-63

Concise Synthesis of Oligosaccharides Using Fluorous Method

* Kenji Osumi, Kohtaro Goto, Yuriko Hirose, Mamoru Mizuno
Laboratory of Glyco-organic Chemistry, The Noguchi Institute
11-8-1, Kaga, Itabashi-ku, Tokyo, 173-0003, Japan
osumi@noguchi.or.jp

Oligosaccharides have been found to play prominent roles in physiological processes and diseases.[1] Because of the limited availability of structurally defined oligosaccharides in nature, the chemical synthesis of these compounds has contributed to advances in glycobiology.[2] Recently, fluorous chemistry has been used to increase the efficiency of oligosaccharide synthesis by reducing the number of purification steps required.[3] However, this improvement in efficiency is limited to the glycosylation steps. Monosaccharide units are still prepared by classical organic synthesis, which requires much labor. In this study, we describe the efficient synthesis of monosaccharides and oligosaccharides by the use of both heavy and light fluorous methods.

First, we investigated the synthesis of disaccharide **11** by using the heavy fluorous method (Scheme 1). Glycosyl acceptor **8** was synthesized in 6 steps, with 68% overall yield, from heavy fluorous tag **1**.[4] In

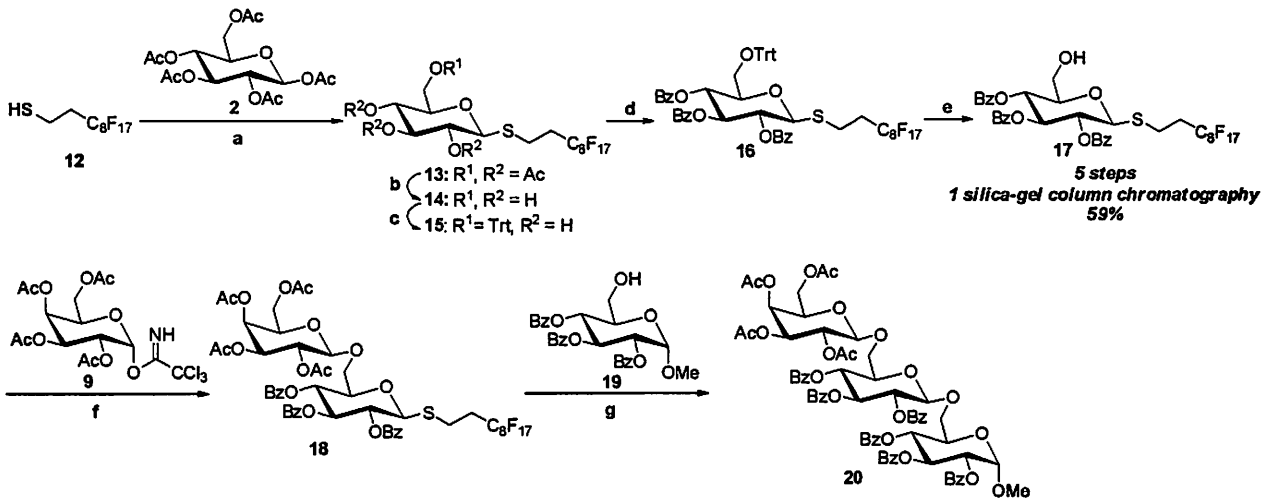


Scheme 1. Synthesis of disaccharide **11**. Reaction conditions: (a) $BF_3 \cdot OEt_2$, CH_2Cl_2-$MeOC_4F_9$, rt 16 h; (b) NaOMe, MeOH-$MeOC_4F_9$, rt 30 min; (c) $PhCH(OMe)_2$, CSA, MeCN-$MeOC_4F_9$, rt 1h; (d) BnBr, NaH, 15-Crown-5, THF, rt 20 h; (e) 95% aq TFA, CH_2Cl_2, 0 °C, 1 h; (f) BzCl, Et_3N, CH_2Cl_2-$MeOC_4F_9$, −20 °C, 14 h, then silica-gel column chromatography; 68% from **1**; (g) TMSOTf, CH_2Cl_2-$MeOC_4F_9$, −10 °C, 1 h, 79%; (h) CAN, EtCN-PhMe-H_2O, 0 °C, 5 h, 74%.

the synthesis of **8**, each fluorous synthetic intermediate (**3**–**7**) was straightforwardly obtained by a simple fluorous-organic solvent partition. Consequently, glycosyl acceptor **8** was obtained after only one silica-gel

column chromatographic purification step. The coupling reaction of glycosyl acceptor **8** with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (9) in the presence of TMSOTf gave fluorous disaccharide **10**, with 79% yield. Finally, the fluorous tag of **10** was removed by CAN to give the desired disaccharide **11** with 74% yield. In this method, disaccharide **11** was obtained in only three silica-gel column chromatographic purification steps from the starting heavy fluorous tag **1**.

Next, we investigated the synthesis of trisaccharide **20** by the light fluorous method (Scheme 2). The glycosyl acceptor **17** was obtained from a commercially available fluorous thiol **12** in five steps, with 59%



Scheme 2. Synthesis of trisaccharide **20**. Reaction conditions: (a) $BF_3 \cdot OEt_2$, CH_2Cl_2, rt 20 h; (b) NaOMe, MeOH-THF, rt 4.5 h; (c) TrtCl, DMAP, Et_3N, DMF, rt 48 h; (d) BzCl, Pyridine, rt 19 h; (e) CSA, LiCl, $CHCl_3$-MeOH, rt 25 h, then silica-gel column chromatography; 59% from **12**; (f) TMSOTf, CH_2Cl_2, −40 °C, 2 h, 77%; (g) NBS, TMSOTf, $(CH_2Cl)_2$, −20 °C to rt, 22 h, 97%.

overall yield. In the synthesis of **17**, each fluorous intermediate (**13–16**) was obtained by a simple fluorous – solid phase extraction. Consequently, glycosyl acceptor **17** was obtained after one silica-gel column chromatographic purification step. Glycosyl acceptors **17** and **9** were coupled in the presence of TMSOTf to give fluorous disaccharide **18**, with 77% yield. Disaccharide **18** was used directly for the coupling reaction with methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**19**) in the presence of NBS-TMSOTf to give the desired trisaccharide **20**, with 92% yield. By this method, trisaccharide **20** was obtained in three silica-gel column chromatographic purification steps from the starting light fluorous tag **12**.

References

[1] Varki, A., *Glycobiology* **1993**, *3*, 97.

[2] Davis, B. G., *Chem. Rev.* **2002**, *102*, 579.

[3] (a) Mizuno, M.; Goto, K.; Miura, T.; Inazu, T. *QSAR Comb. Sci.* **2006**, *8*, 955. (b) Carrel, F. R.; Geyer, K.; Codée, J. D. C.; Seeberger, P. H. *Organic Lett.* **2007**, *9*, 2285 and references cited therein.

[4] Goto, K.; Mizuno, M., *Tetrahedron Lett.* **2007**, *48*, 5605.

1P-64

Friedel-Crafts Acylation of Activated Aromatic Compounds Using a Catalytic Amount of Zinc

Masatoshi Mihara,*[a] Hiroki Suzuki,[a] Takeo Nakai,[a] Toshiyuki Iwai,[a] Takatoshi Ito,[a] Takumi Mizuno,[a] Toshinobu Ohno,[a] Yoshio Ishino[b]

[a] Osaka Municipal Technical Research Institute, 1-6-50 Morinomiya, Joto-ku, Osaka 536-8553, Japan

[b] Asahi Chemical Co., Ltd., 2-4-2 Technoport, Yonozu, Mikuni-cho, Sakai, Fukui 913-0038, Japan

mihara@omtri.city.osaka.jp

The Friedel-Crafts acylation of aromatic compounds is one of the most fundamental transformations in organic synthesis. The acylation generally requires more than one equivalent of a Lewis acid because of its complexation with the ketone product. Moreover, the Lewis acid complex with the ketone is destroyed upon workup, leading to serious problems due to a large amount of toxic waste, particularly in large-scale industrial processes. Therefore, the development of catalytic Friedel-Crafts acylation is increasingly important in order to circumvent these problems.

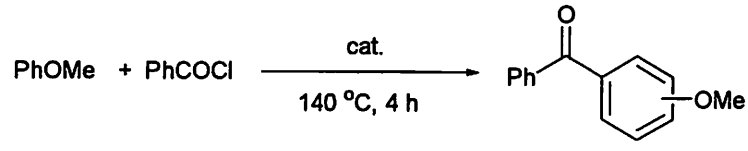
Zinc-mediated reactions have received considerable attention due to their selectivity and easy handling. On the other hand, although zinc has been shown to catalyze the acylation of aromatic hydrocarbons in earlier reports, its potentiality toward the acylation has hitherto been almost overlooked because of the lack of detailed information on the quantity of zinc used and the requirement of an extremely high temperature and a long reaction time. Furthermore, zinc was recently reported to be useful for the Friedel-Crafts acylation[1] but a stoichiometric amount of zinc is still required for operating with high activity under their reaction conditions. Herein, we would like to describe Friedel-Crafts acylation of activated aromatics using a catalytic amount of zinc.

To explore the utility of zinc for the catalytic Friedel-Crafts acylation, we investigated the model reaction of anisole with benzoyl chloride in the presence of various amounts of zinc (Table 1). It is very interesting to note that the yield of the acylated product increased as the quantity of zinc used was decreased, as shown in entries 1–3. The reaction with 1 equiv. of zinc did not afford an appreciable yield due to the generation of complex mixtures, including 4-benzoylanisole (entry 1). In contrast, the use of 0.01 equiv. of zinc resulted in a smooth acylation to afford the desired aromatic ketone in high yield; moreover, when the amount of zinc was decreased to 0.0025 equiv., no decrease in the yield was observed (entries 3 and 4). In addition, the coexistence of sulfuric acid (0.026 equiv.) in the presence of 0.01 equiv. of zinc caused an improvement in the yield (entry 5). On the other hand, the reaction without any catalyst afforded only a 13% yield of the product (entry 6). Consequently, zinc is considered to be a useful catalyst for the acylation of anisole.

The catalytic acylation was successfully carried out with other acyl chlorides to afford the corresponding ketones in good to excellent yields (Table 2). Both aromatic and aliphatic acyl chlorides were efficiently subjected to the acylation reaction. These acylations afforded the para-isomer as a major product, thereby

indicating a high regioselectivity.

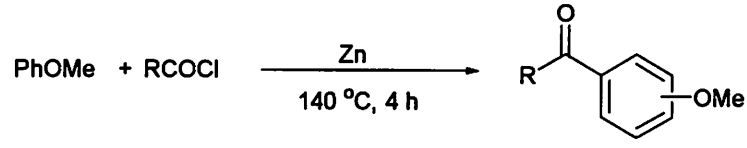
Table 1 Friedel-Crafts acylation of anisole with benzoyl chloride in the presence of zinc[a]



Entry	Cat.	Equiv.	Yield (%)
1	Zn	1	31
2	Zn	0.1	75
3	Zn	0.01	90
4	Zn	0.0025	90
5	Zn/H_2SO_4	0.01/0.026	98
6	-	-	13

[a] Reaction conditions: anisole (20 mL), benzoyl chloride (1.2 mL, 10 mmol).

Table 2 Catalytic acylation of anisole with acyl chlorides using zinc[a]



R	Yield (%)	Ratio of *o*/*p*[b]
Ph	90	8/92
3-MeC_6H_4	91	5/95
4-MeC_6H_4	93	4/96
Et	72	2/98
Me	50	3/97

[a] Reaction conditions: anisole (20 mL), acyl chlorides (10 mmol), zinc (0.01 equiv.).
[b] The ratio of *o*/*p* was determined by GC analysis.

It was observed that the reaction of anisole with benzoyl chloride afforded 4-methoxybenzophenone in 87% yield when zinc chloride was used in place of zinc metal under the conditions shown in entry 3 of Table 1. Thus, zinc chloride appears to be the true catalyst generated *in situ*. However, since Gupta et al. reported that zinc itself assumes the major role of catalyst in the zinc-mediated acylation of anisole,[1b] the contributions of other active species are under investigation.

References

1 (a) Meshram, H. M.; Reddy, G. S.; Reddy, M. M.; Yadav, J. S. *Synth. Commun.* **1998**, *28*, 2203.
(b) Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* **2003**, 2877.

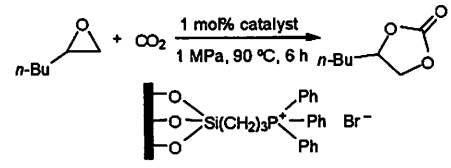
1P-65

Development of Immobilized Phosphonium Bromide for Cyclic Carbonate from Epoxide

Takashi Sakai,* Yoshihiro Tsutsumi, Tadashi Ema
Division of Chemistry and Biochemistry, Graduate School of Natural Science of Technology,
Okayama University, Tsushima, Okayama, 700-8530, Japan
tsakai@cc.okayama-u.ac.jp

Chemical fixation of CO_2 to synthesize a useful compound is one of the most important and challenging subjects in synthetic organic chemistry. Although CO_2 is one of the greenhouse gases, it is a non-toxic, abundant, and recoverable C_1 building block. One method for the CO_2 fixation is the coupling reaction with epoxides to synthesize five-membered cyclic carbonates, which can be used as aprotic polar solvents, monomers for polycarbonates, and fine chemical intermediates. Cyclic carbonates have been synthesized from the corresponding 1,2-diols and a highly toxic gas, phosgene. In the past decade, however, many catalysts for synthesizing cyclic carbonates from CO_2 and epoxides have been developed to surpass the phosgene method. [1, 2] Some of them have problems, such as harsh reaction conditions (a high temperature and pressure) and the use of organic solvent or a Lewis base co-catalyst.

Here we demonstrated a high-throughput combinatorial strategy to find a highly active organic–inorganic hybrid catalyst for the production of cyclic carbonates from CO_2 and epoxides. The best hybrid catalyst with high catalytic activity and reusability was prepared by the coupling of 3-(triethoxysilyl)-propyltriphenylphosphonium bromide and mesoporous silica.

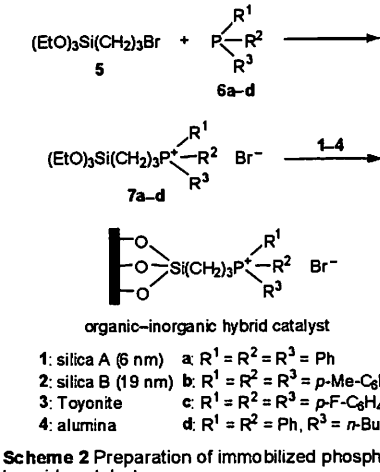


Scheme 1 Immobilized phosphonium bromide for cyclic carbonate from epoxides and CO_2

We found that the pore size of silica is important for catalysis; mesoporous silica with the mean pore size of 19 nm exhibited much better performance than silica with that of 6 nm. Solvent-free and metal-free reactions proceeded successfully under milder conditions, and the catalyst could be recycled ten times. We also wish to report an unexpected effect of the substituent attached to the phosphorus atom on catalytic activity.[3]

The synthetic scheme for the immobilized catalysts is shown in Scheme 2. We succeeded in the isolation of the desired phosphonium bromide **7a** by the reaction of **5** and **6a** using MeCN as a solvent. A similar procedure gave other phosphonium bromides **7b–c** as a powder and **7d** as a viscous oil in good yields.

Phosphonium bromides **7a–d** were immobilized on a variety of inorganic supports: two kinds of silica gel (silica A and silica B), Toyonite, and alumina. Silica A and B have the mean pore sizes of 19 nm and 6 nm, respectively. Toyonite is a porous ceramic support prepared from kaolin minerals by the hydrothermal treatment under

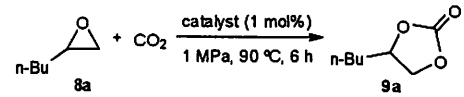


Scheme 2 Preparation of immobilized phosphonium bromide catalysts.

acidic conditions and has a mean pore size of 60 nm. Alumina used in this study is basic aluminium oxide developed for the purpose of chromatography.

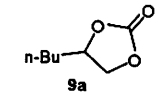
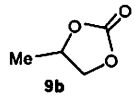
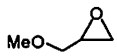
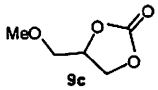
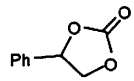
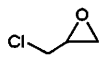
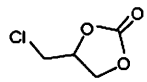
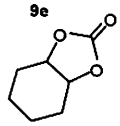
The coupling reaction of CO_2 (1 MPa) with 1,2-epoxyhexane (**8a**) at 90 °C for 6 h as the model reaction was conducted (Table 1). The control reactions using tetraphenylphosphonium bromide (entry 13) and 3-(triethoxysilyl)propyltriphenylphosphonium bromide (**7a**) (entry 14) were also conducted giving 1% and 38% conversions, respectively. However, silica gel-immobilized catalyst **1a** and **2a** dramatically increased the conversion up to 99% (entries 1 and 2). On the other hand, Toyonite (porous ceramic support prepared from kaolin mineral) immobilized catalyst **3a** and alumina immobilized catalyst **4a** gave lower conversion, respectively (90% and 52%, entries 3 and 4). We suppose that the acidity of the OH group on the surface of inorganic support is an important factor for the coupling reaction.

Table 1 Synthesis of cyclic carbonate **9a** from CO_2 and 1,2-epoxyhexane (**8a**) with phosphonium bromide catalyst



Entry	Catalyst	Conversion (%)
1	**1a**	99
2	**2a**	>99
3	**3a**	90
4	**4a**	52
5	**1a** (0.5 mol%)	90
6	**2a** (0.5 mol%)	64
7	**1b**	>99
8	**1c**	96
9	**1d**	99
10	**3b**	44
11	**3c**	70
12	**3d**	55
13	$PPh_4^+Br^-$	1
14	**7a**	38

Table 2 Synthesis of various cyclic carbonates using immobilized catalyst **1a**

Substrate	Product	Time (h)	Yield (%)
8a	 **9a**	6	99
8b	 **9b**	6	99
 **8c**	 **9c**	12	88
8d	 **9d**	6	86
 **8e**	 **9e**	20	85
8f	 **9f**	24	21

Next, we investigated the substituent effect of the phosphonium moiety. Silica gel-immobilized catalysts (**1a** ~**d**) were found to have highest activities and substituent effect wasn't clear. On the other hand, the catalytic activity of the Toyonite immobilized catalysts decreased by the difference of the substituent in the following order: **3a** >**3c**>**3d**>**3b**. We concluded to use the catalyst **1a** for further application to other epoxides because of the high catalytic activity and synthetic accessibility (Table 2).

In conclusion, we could have developed a higher active and robust organic-inorganic hybrid catalyst for the synthesis of cyclic carbonates from CO_2 and epoxides under milder conditions. The catalyst can be reused at least 10 times with 97% conv.

1. Caló, V.; Nacci, A.; Monopoli, A.; Fanizzi, A. *Org. Lett.* **2002**, *4*, 2561.
2. Takahashi, T.; Watahiki, T.; Kitazume, S.; Yasuda, H.; Sakakura, T. *Chem. Commun.*, **2006**, 1664.
3. Sakai, T.; Tsutsumi, Y.; Ema, T. *Green Chem.* **2008**, *10*, 345.

1P-66

Total Synthesis of Halipeptins

Kazuishi Makino, Sousuke Hara, Youhei Koma, Masaru Sakaguchi, Yasumasa Hamada*
Graduate School of Pharmaceutical Sciences, Chiba University
Yayoi-cho, Inage-ku, Chiba, 263-8522, Japan
hamada@p.chiba-u.ac.jp

Halipeptins A is a novel 16-membered cyclodepsipeptide isolated from the marine sponge *Halicona* sp. by Gomez-Paloma and co-workers in 2001, and exhibits potent anti-inflammatory properties *in vivo* that exceed those of well-established drugs such as indomethacin and naproxen (Figure 1). In addition to their impressive biological activities, their intriguing structures bearing (2*S*,3*S*)-*N*-methyl-5-hydroxyl isoleucine (*N*-MeOHIle) and highly substituted decanoic acid derivative (HTMMD) prompted us and other groups to initiate efforts directed towards the total synthesis. Herein, we describe a total synthesis of halipeptin A and relatives. Our synthesis includes coupling of the ester and amide segment at HTMMD/(ala)Thz site, and final macrocyclization at the *N*-MeOHIle/Ala site. Synthesis of the ester segment (HTMMD-Ala) was shown Scheme 1. Aldol **5** prepared by Kiyooka's chiral oxazaborolidinone-catalyzed aldol reaction was converted to aldehyde **6** by a sequence of reduction of ester, protection of 1,3-diol as a isopropylideneacetal, deprotection of benzyl ether, and oxidation. The synthesis of sulfone **9** began with MacMillan's proline-catalyzed α-oxiamination of pantanal **7** and reductive removal of the anilino group to afford (*S*)-pentan-1,2-diol **8** with >99% ee. Protection of diol as a benzylideneacetal, regioselective reductive ring opening, introduction of mercaptophenyltetrazole, and oxidation with mCPBA gave sulfone **9**. The Julia-Kociensky coupling of **6** and **9** was performed by using KHMDS in 63% yield. Simultaneous cleavage of benzyl ether and reduction of double bond in **10** using Raney Ni (W-2) under hydrogen atmosphere, *O*-methylation, and deprotection of isopropylideneacetal gave HTMMD building block **11**. The introduction of (*S*)-Ala residue to highly hindered hydroxyl group at C3 of HTMMD building block was attained by transesterification under acidic conditions (Scheme 2). After regioselective esterifi-

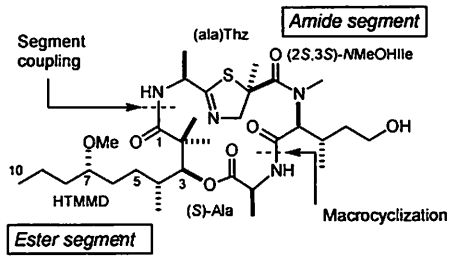
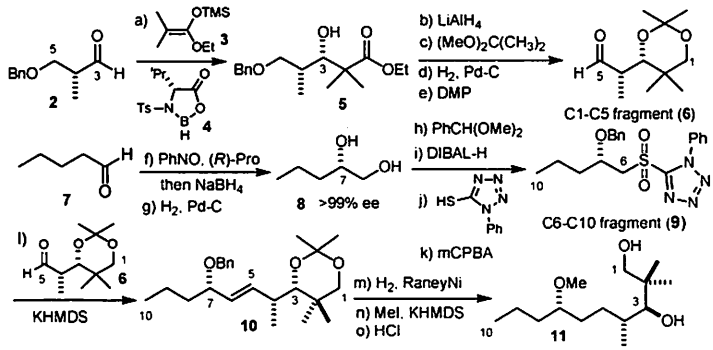


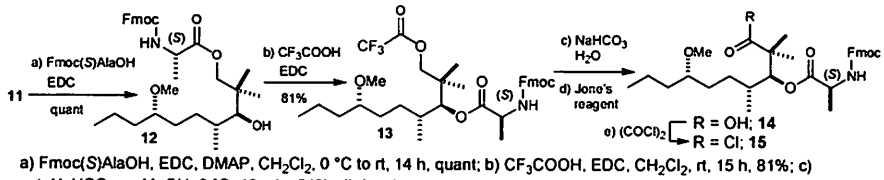
Figure 1. Structure of Halipeptin A (1)



Reagents and conditions:
a) 3, 4, -78°C, 2 h, 82%, >99 : 1; b) $LiAlH_4$, rt, 5.5 h; c) 2,2-dimethoxypropane, TsOH·H_2O, CH_2Cl_2, rt, 15 h, 83% (2 steps); d) H_2, Pd-C, AcOEt, rt, 17 h, 98%; e) DMP, CH_2Cl_2, rt, 4 h, 94%; f) PhNO, (*R*)-proline, $CHCl_3$, 4°C, 2 h; then $NaBH_4$, EtOH-$CHCl_3$, 5°C, 35 min, >99% ee (determined by HPLC); g) H_2, Pd-C, CH_3OH, rt, 17 h, 94% (from 7); h) benzaldehyde dimethylacetal, TsOH·H_2O, $PhCH_3$, rt, 17.5 h, 77%; i) DIBAL-H, CH_2Cl_2, -17 to -10°C, 1.5 h, 94%; j) 5-mercapto-1-phenyl tetrazole, DEAD, PhP_3, THF, rt, 9.5 h, 94%; k) mCPBA, CH_2Cl_2, 0°C to rt, 3 h, 99%; l) 6, KHMDS, DME, -65°Cto rt, 16 h, 63%; m) H_2(4.5 atm), Raney-Ni, C_2H_5OH, rt, 22 h, 95%; n) KHMDS, MeI, THF, -78°C to rt, 5 h, 86%; o) 6 N HCl, CH_3OH (4 : 1), 0°C to rt, 3 h.

Scheme 1

cation at C1 hydroxyl group of diol **11** with Fmoc-(*S*)-Ala-OH using EDC/DMAP, the obtained ester **12** was treated with CF_3COOH and EDC in CH_2Cl_2 to give desired product **13** by trans-esterification of (*S*)-Ala residue from C1 to more sterically hindered C2 hydroxyl group in excellent yield (81%) without epimerization. Removal of trifluoroacetyl group of **13** under mild basic conditions, oxidation of primary alcohol to carboxylic acid with Jones' reagent, and treatment of oxalyl chloride afforded acid chloride **15**.

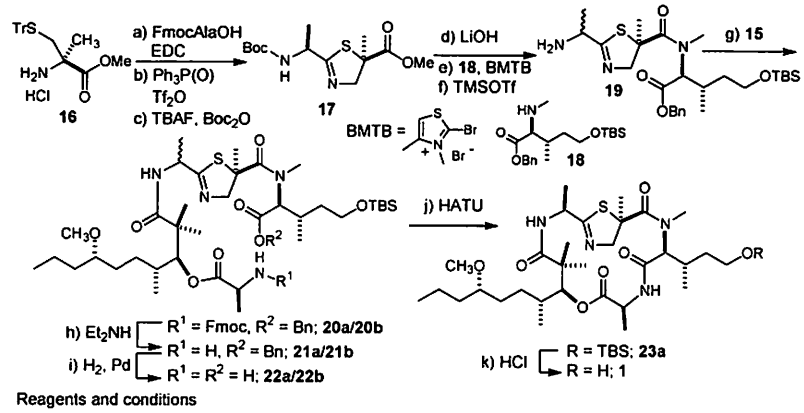


a) Fmoc(*S*)AlaOH, EDC, DMAP, CH_2Cl_2, 0 °C to rt, 14 h, quant; b) CF_3COOH, EDC, CH_2Cl_2, rt, 15 h, 81%; c) satuNaHCO$_3$aq, MeOH, 0 °C, 10 min, 81%; d) Jone's reagent, acetone, -15 to 0°C, 3 h; e) $(COCl)_2$, CH_2Cl_2, rt, 5 h.

Scheme 2

As depicted in Scheme 3, the amide segment was prepared from the known protected α-methylcystein **16**. Condensation of **16** with Fmoc-(*S*)-Ala-OH using EDC, deprotective cyclization of the dipeptide **17** with triphenylphosphine oxide and triflic anhydride, and exchange of protective group from Fmoc to Boc afforded thiazoline **17**. After saponification of methyl ester **17**, the coupling of *N*-MeOHIle derivative **18** was attained by use of BMTB as an activating reagent in the presence of DIEA in 94% yield. However, epimerization of α-position of thiazoline occurred in saponification step and two inseparable isomers were determined by ^{1}H-NMR. Deprotection of the Boc group with TMSOTf provided amide segment **19**.

Coupling of acid chloride **15** and amine **19** gave a mixture of linear product **20a** and epimer **20b** at α-position of thiazoline in 89% yield. Fortunately, protection-free precursor form the respective deprotection of the Fmoc group and the benzyl ester was separable with epimer, and desired isomer **22a** was obtained in 40% yield along with 35% yield of epimer **22b**. Macrolactamization of **22a** with HATU and DIEA proceeded with partial racemization at the *N*-MeOHIle residue and afforded a separable mixture of desired product **23a** (61%) and *N*-Me OHIle epimer **23b** (29%). Final deprotection of the TBS group in **23a** was carried out using 4 M HCl-dioxane, which caused again epimerization at α-position of thiazoline. Pure halipeptin A (**1**) was obtained after chromatographic purification in 35% yield.



Reagents and conditions

a) Fmoc(*S*)AlaOH, EDC, DIEA, CH_2Cl_2, 0°C to rt, 10.5 h, 70%; b) $Ph_3P(O)$, Tf_2O, CH_2Cl_2, -18 to -10°C, 3.5 h, 75%; c) TBAF, THF-DMF (5 : 1), 0°C to rt, 5 h; then Boc_2O, rt, 2 h, 87%; d) LiOH, THF-H_2O (4 : 1), 0°C to rt, 1.5 h; e) (2*S*,3*S*)-*N*-MeOHIle(**18**), BMTB, DIEA, 0°C to rt, 94%; f) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h; g) DIEA, CH_2Cl_2, 0°C to rt, 6.5 h, 89% (from **14**); h) Et_2NH-CH_3CN (1 : 1), 0°C to rt, 1.5 h, 97%; i) H_2, Pd-black, CH_3OH-buffer (10 : 1), rt, 8 h, **22a**: 40% (+ thiazoline epimer **22b**: 35%); j) HATU, DIEA, CH_2Cl_2, rt, 24 h, **23a**: 61% (+ *N*-MeOHIle epimer **23b**: 29%); k) 4 N HCl-dioxane, Et_2O, 0°C to rt, 4 h, **1**: 35% (+ thiazoline epimer: 50%).

Scheme 3

Referrences

1. Hara, S.; Makino, K.; Hamada, Y. *Tetrahedron*, **2004**, *60*, 8031-8035.
2. Hara, S.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 1081-1085.

1P-67

Microbial Reclamation of Squid Pen for the Production of Proteases and Biofertilizer

San-Lang Wang*, Tsai-Yi Huang, Chun-Yuan Wang

Graduate Institute of Life Sciences, Tamkang University, Taipei 251, Taiwan

E-mail address: sabulo@mail.tku.edu.tw (S.L. Wang)

The application of probiotic bacteria in food products is increasing due to potential health benefits associated with the consumption of these bacteria (Ong et al., 2007). *Lactobacillus* is the predominant genus of lactic acid bacteria found in milk samples. The genus *Lactobacillus* has been associated with a proteolytic activity (Ong et al., 2007; Oneca et al., 2007; Morea et al., 2007; Jung et al., 2007; Tavaria and Malcata, 2003), however, data concerning of proteases from lactobacilli are more limited (Wang et al., 2008; Degraeve and Martial-Gros, 2003). Bioconversion of squid pen has been proposed as a waste treatment alternative to the disposal of chitin containing seafood proceesing wastes (Wang et al., 2008; Wang et al., 2006; Lavall et al., 2007). Squid pen contains abundant protein and chitin and its mineral salts are much lower than those of shrimp or crab shell. Therefore, we have previously investigated microbial reclamation of squid pen for the production of lactobacilli protease, and published the first report on the production and purification of extracellular proteases from lactobacilli (Wang et al., 2008). In this study, isolated from the same infant vomited split milk, we found *L. paracasei* subsp *paracasei* TKU010, which is the same species as *L. paracasei* subsp *paracasei* TKU012. When *L. paracasei* subsp *paracasei* TKU010 was cultured in a squid pen powder medium, besides the protease activity displayed, the culture supernatant possessed vegetable growth enhancing effect, which was not found with TKU012. Considering the potential of these enzymes to be used in biotechnological process and the fact that the vegetable growth enhancing effect of the culture supernatant of squid pen fermented by lactobacilli has not been reported, the current work presents the purification and characterization of a protease obtained from *L. paracasei* subsp *paracasei* TKU010, comparison with the peptide mass mapping of *L. paracasei* subsp *paracasei* TKU012 protease, and the vegetable growth enhancing effect of the culture supernatant of squid pen fermented by lactobacilli.

The effect of culture supernatant of *L. paracasei* TKU010 on the growth rate of lettuce and cabbage seedlings was investigated. The addition of culture supernatant enhanced the growth of both lettuce and cabbage seedlings. Better results of the total weight and total length (552%, 152%) and (250%, 152%), respectively, were observed for lettuce and cabbage treated with the fourth day of the culture supernatant compared with the control group. The best vegetable enhancing activity was with the culture supernatant after 4 days of fermentation. Consequently, if TKU010 would be used to produce biofertilizer with vegetable growth enhancing effect, the culture time had better be the fourth day. However, the optimized culture time for protease production was at the third day. Based on the above facts, the vegetable enhancing activities in the culture supernatant could be related to the products of the proteolysis reactions rather than the protease itself. In other words, vegetable enhancing compounds could be amino acids and peptides from the hydrolysis of the SPP proteins by proteases. Although fermentation under the same condition with TKU012, which belongs to the same species *L. paracasei* subsp

paracasei as TKU012, no growth enhancing effect was observed (data not shown). Besides, it is possible that the growth enhancing effect was not totally (or partly) owing to the amino acids and peptides from the hydrolysis of the SPP proteins by proteases, but originated from other metabolites produced by TKU010 rather than hydrolyzates of the SPP proteins. Therefore, the role of protease on plants requires further investigation.

Both TKU010 serine protease and TKU012 metalloprotease were produced by the strains of the same species *L. paracasei* subsp *paracasei* and had similar molecular weight (49 kDa). However, the culture supernatant of squid pen powder fermented by these two lactobacilli strains showed obvious difference in vegetable growth enhancing effect. Consequently, peptide mass mapping was used to compare the sequence difference between TKU010 protease and TKU012 protease. Peptide mass mapping was performed by Mission Biotech Co. (Taipei, Taiwan) using LC/MS as described in previous paper (Wang et al., 2008). Peptide masses obtained were searched against a comprehensive nonredundant protein sequence data base (NCBINr) using the Mascot program for protein identification. The spectra matched nine tryptic peptides that could be correlated to a protein of unknown function (GenBank accession number gi999638) from *Serratia* protease (serralysin) (E.C.3.4.24.40) with 35% sequence coverage (Katsuya et al., 1985), As for the results of TKU012 (Wang et al., 2008), the masses of seven peptides can be matched with that deduced from the amino acid sequence of metalloprotease of *Serratia marcescens* (GenBank accession number gi47240). From the comparison between the peptide mass mappings of TKU010 and TKU012 protease, it was shown that these two proteases had 7 similar peptides. Besides, TKU010 protease had two more peptides, than TKU012, AATTGYDAVDDLLHYHER and QTFTHEIGHALGLSHPGDYNAGEGNPTYR. Among them, the peptide of AATTGYDAVDDLLHYHER is the N-terminal initial sequence of *Serratia* protease (serralysin). These structural differences between TKU010 protease and TKU012 protease might be the reason for the above different properties including the vegetable growth enhancing effect.

Acknowledgement

This work was supported in part by a grant of the National Science Council, Taiwan (NSC96-2313-B-032-002-MY3).

References

Wang SL, Yeh PY (2008) Purification and characterization of a chitosanase from a nattokinase producing strain *Bacillus subtilis* TKU007 using shrimp shell powder as a medium. Process Biochem 43:132-138.

Wang SL, Wang CY, Huang CY (2008) Microbial reclamation of squid pen for the production of a novel extracellular serine protease by *Lactobacillus paracasei* subsp *paracasei* TKU012. Biores Technol 99:3411-3417.

Wang SL, Chen SJ, Wang CL (2008) Purification and characterization of chitinases and chitosanases from a new species strain *Pseudomonas* sp. TKU015 using shrimp shells as a substrate. Carbohydr Res 343:1171-1179.

Liang TW, Chen YZ, Yen YH, Wang SL (2007) The antitumor activity of the hydrolysates of chitinous materials hydrolyzed by crude enzyme from *Bacillus amyloliquefaciens* V656. Process Biochem 42: 527-534.

1P-68

A Novel Synthesis of 3-Sulfanylphenols

Yasuhiro Sato,* Sunao Mitsui, Hideki Tatsumi
Fine Chemicals Research Laboratory, Chemicals Research Center, TOYO KASEI KOGYO Co., Ltd.
2900, Sone-cho, Takasago-City, Hyogo, 676-0082, Japan
yasuhiro-satou@toyokasei-kogyo.co.jp

3-Sulfanylphenols (1) have attracted much attention as starting materials for heterocyclic compounds including pharmaceuticals. Generally, preparation of (1) is achieved by *S*-substitution of 3-mercaptophenol (2) [1]. However, most of the reported methods for synthesizing (2) require explosive diazonium salts [2),4)], toxic hydrogen sulfide [3)], or Grignard reagents [4)]. A versatile and safe method for synthesizing (1) is required for a stable supply.

Among the starting material of (1), we propose here commercially available 1, 3-cyclohexanedione. In this presentation, we will describe the synthetic method of 3-sulfanylphenols (1) from inexpensive 1, 3-cyclohexanedione (3) in four steps including a new sulfanylaromatization system as a key step. Synthesis of 3-mercaptophenol (2) will be also indicated.

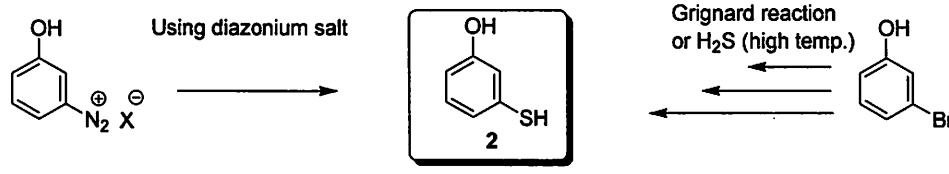


Figure 1. Reported Synthesis of (2)

1) Synthesis of 3-Sulfanylphenols (1)

The chlorinated cyclohexenone (4) was easily prepared from (3) using phosphorusoxychloride in quantitative yield. We assumed that the intermediate (3') is readily formed, and then converted to (4) slowly only in toluene. Addition of DMF is favorable for the smooth formation of (4) from (3'). Sulfanylcyclohexenone (5) was obtained by the reaction of (4) with corresponding thiols under basic condition in good yield.

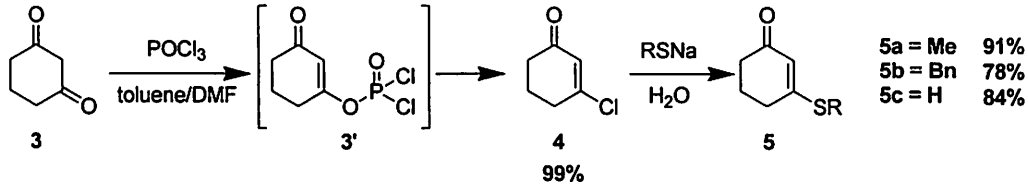


Figure 2. Synthesis of (5) from 1, 3-Cyclohexanedione (3)

Aromatization of (**5a**) or (**5b**) was carried out with acetic anhydride in the presence of sulfuric acid at 70°C, followed by hydrolysis under basic condition to afford (**1a**) in moderate yield, or (**1b**) in excellent yield. However, (**5c**) gave complex mixture under the same reaction condition.

The aromatization mechanism is shown in Figure 3. We assume that the intermediate (**5'**) is formed by sulfonation of (**5**) at fast, then acetylation at the keto group and the sulfonyl group is occurred to give intermediate (**5"**). Finally, acetylated 3-sulfanylphenols (**6**) is obtained by thermal decomposition of (**5"**). This synthetic method is widely applicable to various 3-sulfanylphenols by using corresponding thiols to react with (**4**).

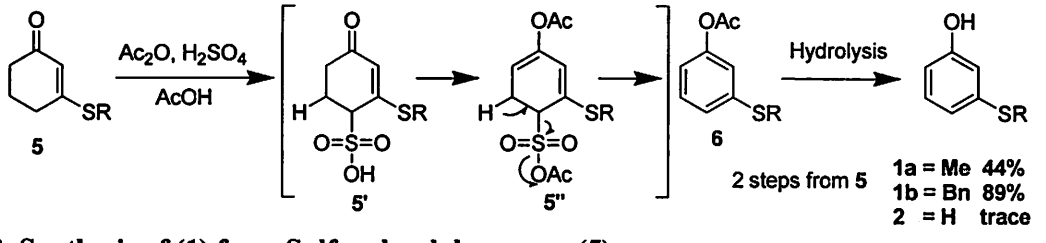


Figure 3. Synthesis of (1) from Sulfanylcyclohexenone (5)

2) Synthesis of 3-mercaptophenol (2)

We applied the above method to prepare 3-mercaptophenol (**2**). The thiouronium salt (**7**) was easily prepared from (**4**) using thiourea in quantitative yield, then (**7**) was aromatized using acetic anhydride in the presence of sulfuric acid at 70°C, followed by hydrolysis under basic condition to give (**2**) as a pale brown liquid in low yield. We assume that aromatization of the thiouronium salt (**7**) proceeds accompanied with many side reactions.

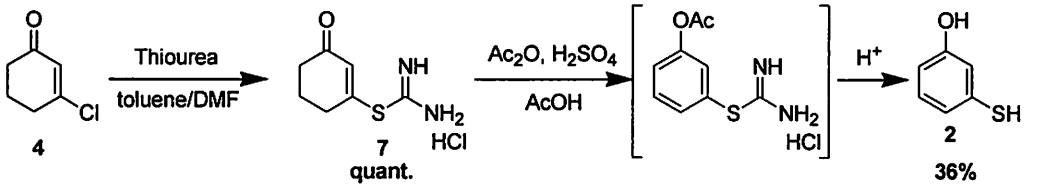


Figure 4. Synthesis of (2) from Chlorocyclohexenone (4)

Details will be discussed in poster session.

References

1) *US pat.* 2074851. 2) Watson, E.R.; Dutt, S., *J. Chem. Soc.*, **1922**, 121, 2415. 3)Shagun, L. G.; Deriglazova, E. S.; Kashik, T. V.; Deryagina, E. N.; Voronkov, M, G., *J. Org. Chem. USSR* (*Engl. Transl.*) **1978**, 14, 173. 4) Zhang, Mingbao; Ryckman, David; Chen, Guohua; Macmillan, Eric; Duquette, Jason, *Synthesis*, **2003**, 112.

1P-69

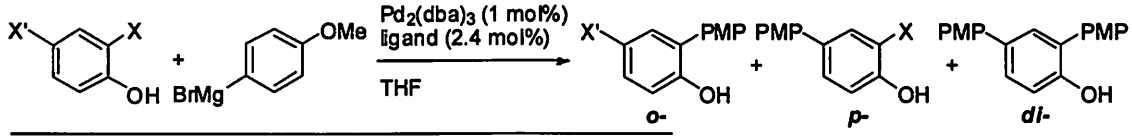
Ortho-Selective Cross-Coupling of Dihalobenzene Derivatives

Shunpei Ishikawa,* Kei Manabe
Manabe Initiative Research Unit, RIKEN
2-1 Hirosawa, Wako, Saitama 351-0198, Japan
keimanabe@riken.jp

Site-selective cross-coupling of dihalogenated arenes constitutes a practical method for the synthesis of multifunctionalized aryl compounds. For dihalogenated heteroarenes, many examples of site-selective cross-coupling exist. In contrast, only a few examples have been reported for dihalogenated benzene derivatives, and the reactions mainly occur at less electronically negative carbons. Thus, it is generally difficult to achieve site-selective cross-coupling reactions that occur preferentially at more electronically negative carbons. If the carbons are at more sterically hindered positions, the reactions are even more difficult to achieve. In this study, we investigated palladium-catalyzed cross-coupling of dihalogenated derivatives such as phenols and anilines with Grignard reagents. In general, the presence of a free OH or NH_2 group in a substrate significantly retards cross-coupling, because deprotonation of these groups by Grignard reagents generates a highly electron-donating oxido or amide group and electronically retards oxidative addition. Moreover, the reaction at ortho position is thought to be difficult because of its steric hinderance.

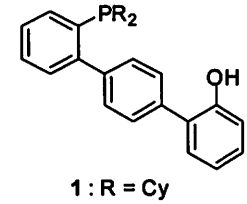
First, the reaction of 2,4-dibromophenol with *p*-methoxyphenylmagnesium bromide (PMPMgBr) was examined (**Table 1**, entries 1-3). The reaction using **1** was found to proceed very smoothly with high ortho-selectivity, while the reactions using non-hydroxylated phosphine such as PCy_3 proceeded slowly and non-selectively. Moreover, the yield of ortho-arylated product was much improved by changing the substituent on phosphine atom from Cy group to Ph group (**2**). Use of **1** or **2** exhibited high ortho-selectivity in the cross-coupling of several substrates such as 2,5-dibromophenol, 2,4-dibromoaniline and 2,5-dibromoaniline, or in the cross-coupling with 2-thienylmagnesium bromide and BnMgBr.

Table 1. Cross-coupling of dihalogenated phenols.



PMP = *para*-methoxyphenyl

entry	X,X'	ligand	T (°C)	time (h)	*o-*	*p-*	*di-*
1	2,4-Br	PCy_3	25	24	21%	14%	38%
2		**1**	25	2	71%	0%	16%
3		**2**	25	2	89%	0%	4%
4	2,4-Cl	PCy_3	50	4	80%	0%	0%
5		**1**	50	4	99%	0%	0%
6	4-Br-2-Cl	PCy_3	50	2	5%	34%	13%
7		**2**	50	2	58%	4%	22%
8	2,4-F	PCy_3	50	24	71%	0%	0%
9		**1**	50	24	49%	0%	0%



1 : R = Cy
2 : R = Ph

On the other hand, the reaction of 2,4-dichlorophenol with PMPMgBr using **1** or **2** was found to proceed in complete ortho-selectivity, and the diarylated product which was produced in the reaction of dibromobenzene derivatives was not observed at all (entry 5). Remarkably, complete ortho-selectivity was realized even with a simple PCy_3 (entry 4) although the reaction rate with PCy_3 was slower than that with **1** or **2**. The reaction of 2,4-dichloroanisole under the same conditions did not give the cross-coupled products. This result strongly suggests that the presence of a protic group in the substrates is essential for rate acceleration at the ortho-position. Effectiveness of the hydroxylated phosphines **1** and **2** was demonstrated by the reaction of 4-bromo-2-chlorophenol (entry 7). The Cl group at the ortho-position reacted preferentially over the Br group. This unusual selectivity was not observed in the reaction with PCy_3 (entry 6).

Use of fluorobenzenes as substrates is a challenging task due to strong fluorine-carbon bond, and ortho-selective cross-coupling of substrates with electron-donating groups has not been reported so far. The reaction of 2,4-difluorophenol with PhMgBr was investigated and found to proceed in high ortho-selectivity both with **1** and PCy_3 (entries 8, 9). It is noted that **1** was inferior to PCy_3 in this case.

To reveal the reason for these reactivities and selectivities for each halogen with each ligand obtained above, we then investigated the kinetic studies. In the reactions of 2-bromophenol and 2,4-dichlorophenol using **1**, the initial rate kinetics for the concentration of substrates gave saturation behavior (**Figure 1**, left). In the reactions of 4-bromophenol and 2,4-difluorophenol using **1** on the other hand, the initial rate kinetics did not show saturation behavior (**Figure 1**, middle). In contrast, the rate kinetics of the reaction using PCy_3 did not show saturation behavior for all substrates (**Figure 1**, right). On account of these results, reaction mechanisms could be proposed as **Figure 2**. Considering the saturation kinetics on substrates, the reactions of Br and Cl at ortho-position using **1** were assumed to proceed in Michaelis-Menten mechanism, and high reaction rate and high selectivity could be achieved by catalyst control. On the other hand, the reactions of Cl and F using PCy_3 were assumed to proceed by substrate control, in which Lewis acidic Mg facilitates oxidative addition of the ortho C-X bond to Pd. These studies would contribute to the research for the synthesis of multisubstituted benzene derivatives.

Figure 1. Initial rate kinetics on the concentration of substrates.

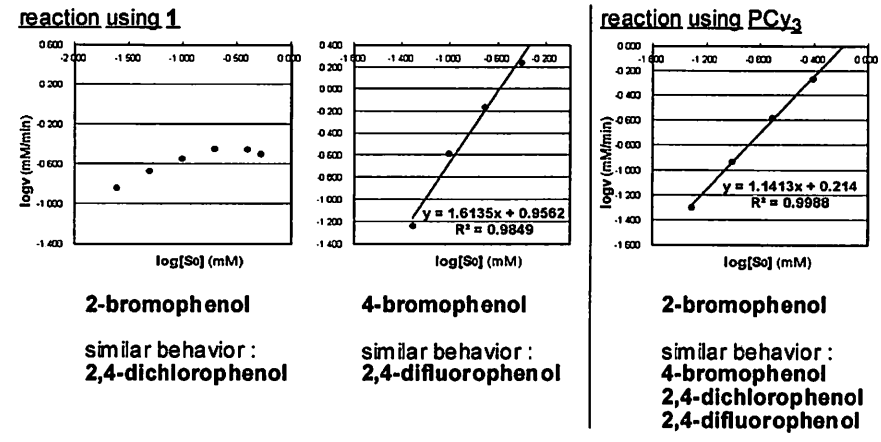
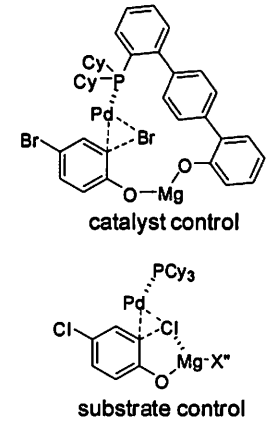


Figure 2. Proposed transition states.



1P-70

Chemo-Structural Processes in Polyhydrosilanes

* Liviu Sacarescu, Mihaela Simionescu, Gabriela Sacarescu
Petru Poni Institute of Macromolecular Chemistry, Inorganic Polymers Dept.
Aleea Grigore Ghica Voda 41 A, 700487, Iasi, Romania
livius@icmpp.ro

In recent years intense research has been dedicated in the modification of a wide variety of material properties simply by reducing the material domain size in order to obtain quantum non-negligible effects. Semiconductor materials have been the subject of the majority of this work, particular attention being paid to silicon. Silicon quantum size effects have been exploited to investigate properties like: photoluminescence, melting and sintering, band gap energy, physical strength of derivative ceramics and phosphorescence. Due to the importance of silicon in modern technology, modifications of its properties have a major impact on leading industrial sectors including: electronics, aerospace, computers, energy and sensors.

Polysilanes are well known merely as precursors for silicon carbide and their exploitation as a possible source for optoelectronic materials is just in the beginning. Research in this field proved that UV irradiation or thermal processing of polysilanes under certain conditions, lead to a slight enrichment in elemental silicon especially when the material is deposed as a thin layer. This property could be useful as a different approach to obtain polycrystalline silicon structures and layers by taking advantage of specially designed highly reactive soluble oligo- and polysilanes.

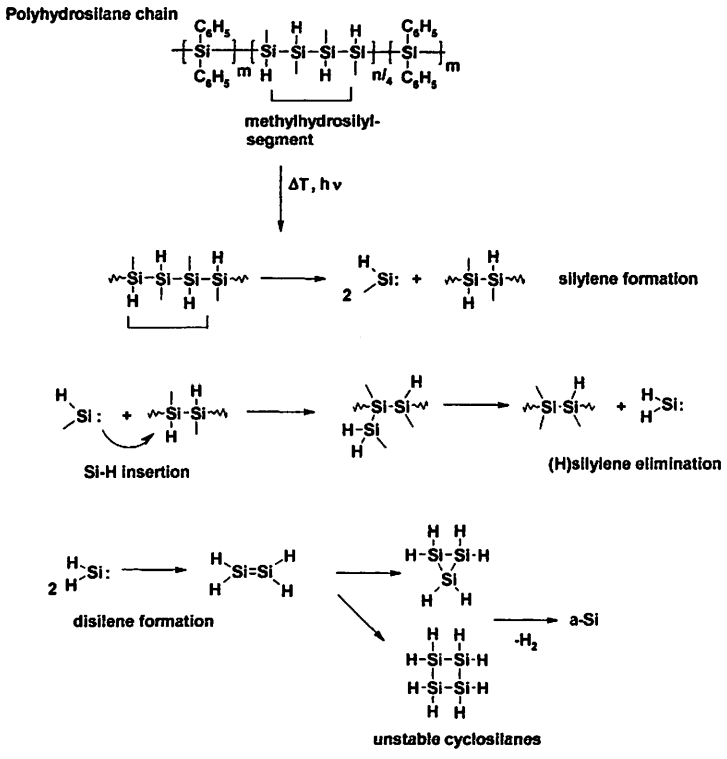
This work presents the chemo-structural effects due to the methylhydrosilyl groups enclosed within a polydiphenylsilane chain. It is shown that this specific structure is capable of producing small particles of elemental silicon with controllable dimension and possesses a long-ordered helical conformation with extended σ-electrons delocalization.

To investigate these processes polyhydrosilanes with various contents of methylhydrosilyl groups were synthesized by homogeneous coupling of methyldichlorosilane with diphenyldichlorosilane. Spectral analysis techniques combined with atomic force and polarized light microscopy were used to reveal insides of the silicon particles formation mechanism within the polymeric matrix.

The enclosure of methylhydrosilyl fragments within the polydiphenylsilane chain causes major chemo-structural effects. Therefore, the coupling of the stiff diphenylsilyl segments through methylhydrosilyl's eliminates the internal conformational tensions allowing the rearrangement of the polysilane structure with the formation of an ordered helical conformation. The decrease of the chain fractioning frequency allows the polydiphenylsilyl segments to reach a higher conjugative dimension improving the symmetry of the emissive electronic transitions.

On the other side, the chemical processes involving the participation of the Si-H groups cause the formation of elemental silicon particles. An explanation of the elemental silicon formation within polyhydrosilanes should start from the synthesis moments when highly reactive silylene intermediates appear as a result of

both alkaline dehalogenation of methyldichlorosilane during the Wurtz-Fittig-like condensation or thermo-photolytic scission of the already formed methylhydrosilyl- segments. Thereafter, silylenes insert within the relatively week Si-H bond, by initial formation of a donor-acceptor complex followed by a [1-2]-atom shift. This reaction leads to the appearance of a relatively unstable carbohydridosilane branching group attached to the silicon atoms in the immediate neighboring of the Si-H reactivities. These structures create local conformational distortions and could participate to Kumada rearrangements with crosslinking of the polysilane chains leading to formation of the embedded silicon structures visible on the polyhydrosilanes film surface. Due to the complex action of the highly reactive sylilene, the insertion reaction could take also a different course by elimination of the dihydrosilylene with lower stabilization energy. Further, the highly reactive dihydrosilylene species participate to dimerization reactions with formation of unstable disilene and cyclic oligosilanes. Because of the composition, these structures based only on silicon and hydrogen atoms could generate elemental silicon as solid particles mounted within the polymeric matrix.



The linear methylhydrosilyl structure manifests a high structural instability due to the presence of methylhydrosilylene reactive species in the earlier stages of the synthesis process. Adjusting of the comonomers molecular ratio made possible the control over the dimension of these particles down to the nanometric level.

Exploitation of these intriguing properties of polyhydrosilanes opens new possibilities for applications aiming to the quantum dimension of optoelectronics.

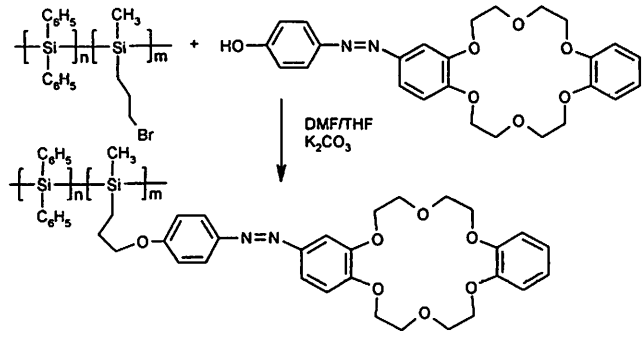
1P-71

Polysilane Structures with Conformational Photocontrol

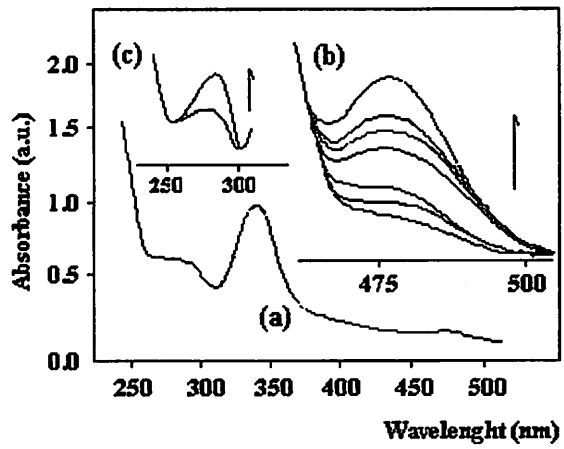
* Gabriela Sacarescu, Liviu Sacarescu, Mihaela Simionescu, Gabriela E. Hitruc
Petru Poni Institute of Macromolecular Chemistry, Inorganic Polymers Dept.
Aleea Grigore Ghica Voda 41 A, 700487, Iasi, Romania
gsacarescu@icmpp.ro

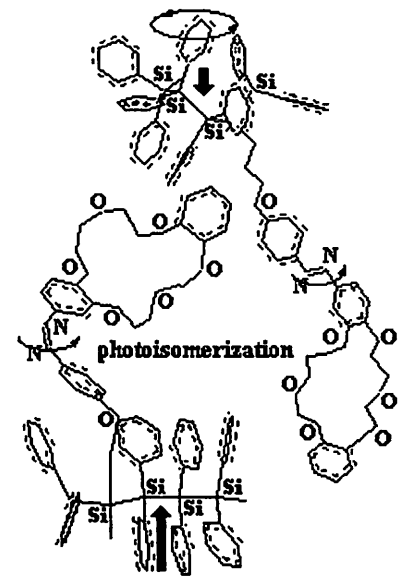
During the last years, an increasing number of papers has described various methods to obtain unusual polysilanes structures. These works cover complex research domains such as quantum conductors (QWR) or polymer-metal complexes and present an increasing amount of information on their semiconducting or NLO intriguing properties. This paper is a step ahead to a new polysilane structure and presents the synthesis of a new poly[diphenyl-co-methyl(propyl-oxyphenylazo-dibenzo-18-crown-6)]silane, PSADF. The azocrown side segments play a double part: they allow the trans-cis isomerizations induced by irradiation with a specific UV wavelength on one side and provide the polysilane with the electrochemical sensitivity of the crown ether units on the other.

The synthesis procedure starts from poly[diphenyl-co-methyl(bromopropyl)]silane (PSBDF) which was obtained through the addition of allyl bromide to soluble poly[diphenyl-co-methyl(H)]silane. At high temperature, in anhydrous solvent (DMF), PSBDF undergoes a modified Williamson reaction with (4-hydroxyphenylazo)dibenzo-18-crown-6.



It is known that the azobenzene derivatives undergo trans-cis photoisomerizations in UV light with a temporary and local change of shape and polarity. The process is reversible and reversion from cis to trans isomer state takes place thermally or by irradiation in visible spectrum. The photoisomerization of PSADF was performed by irradiation of the polymer solutions in DMSO with a 400 nm filtered UV light and recording the 480 nm absorption band corresponding to the n–π* transition of the azobenzene unit in cis conformation. This procedure was chosen because the azo group π–π* transitions overlap with the polysilane σ–σ transitions on one side, and to protect the polysilane chain against photodecomposition on the other. UV irradiation caused an increase in the intensity of the 480 nm absorption band until a photostationary state was reached and about 65 – 70% of azobenzene segments were in cis configuration. By heating at moderate temperature (70 ^{0}C) the isomerization process was reversed.





(a) UV Spectrum of trans-PSADF; (b) Change of the absorption spectra of DMSO solutions of PSADF during trans-cis photoisomerization recorded at 0, 5, 10, 15, 20, 25, 30 min. and 25 °C; (c) Increasing of 280 nm peak recorded during trans-cis photoisomerization of PSADF.

An uncommon phenomenon was observed during the UV irradiation of the PSADF samples. The 280 nm band corresponding to the σ–π conjugation within polysilane varied following the isomerization state of the azo-segment and reached a maximum intensity when the azobenzene units were in the cis conformation. Due to the propylene bridge and shielding effect of the phenyl substituents, the azo segment is isolated from the polysilane conjugated chain and therefore the electronic influences are too week to explain this unexpected variation. In addition, if present, these electronic influences should affect especially the σ-electrons delocalized system within polysilane or the shape, position and intensity of the 332 nm band assigned to σ–σ* transitions remained unchanged durring irradiation. Therefore the origin of this phenomenon should be revealed by taking into account the conformational effect induced by the photoisomerization process. In polyphenylsilanes, the orbital mixing between delocalized σ highest occupied valence band (HOVB) state of the Si-skeleton and the π highest occupied molecular orbitals (HOMO) states of the phenyl groups causes the σ–π conjugation. The intensity of this orbital mixing (suggested by the black arrow) depends on the phenyl π HOMO orbitals position relative to the Si skeleton which in turn is dictated by the position and orientation of the aromatic rings. In our case, increasing of the UV 280 nm peak intensity proved that the azo- unit movement from trans to cis state induces local conformational disturbances which are responsible for a repositioning of the phenyls' molecular planes in a more favorable position for the σ–π orbitals mixing.

Because a variation of the σ–π conjugation intensity in polysilanes strongly affects the charge carriers mobility, PSADF could be used to obtain polymeric materials with photo-controlled opto-electronic properties.

1P-72

Microwave Assisted Hydrosilylation Processes

* Mihaela Simionescu, Gabriela Sacarescu, Liviu Sacarescu
Petru Poni Institute of Macromolecular Chemistry, Inorganic Polymers Dept.
Aleea Grigore Ghica Voda 41 A, 700487, Iasi, Romania
Ionel Mangalagiu
Al. I. Cuza University, Organic Chemistry Dept.
Bd. Carol No. 11, 700506, Iasi, Romania
msimionescu@icmpp.ro

The main advantage of using microwaves in organic synthesis is to dramatically shorten the reaction time. However, since the introduction of microwave assisted organic synthesis in 1986, there have been debates about what actually alters the rate outcome of the synthesis. Is it merely an effect of the thermal heat generated by the microwave or is it a kind of "specific microwave effect"?

The rate acceleration can be assigned to the solvent superheating induced by microwave irradiation. The heating rate for the solvents will increase during microwave heating, probably by limiting the formation of "boiling nuclei". This phenomenon is described as superheating and may result in the boiling points of solvents being raised up to 26°C above their conventional values. Superheating can lead to 10-15-fold reductions in reaction times for solution phase microwave assisted organic synthesis at atmospheric pressure, compared with traditional reflux conditions.

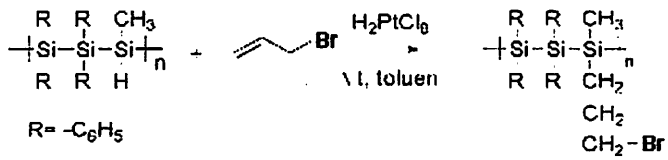
Strauss studied the kinetics of the Diels-Alder reaction between anthracene and diethyl maleate and found that the reaction rate is independent of the mode of heating by drawing the Arrhenius plot for both oil bath and microwave conditions. Therefore, he concluded that there is no non-thermal "specific microwave effect" in microwave-assisted organic synthesis. Even if there is this effect, it should appear to be less important than stated in earlier publications.

The simplest method for conducting microwave-assisted reactions involves irradiation of reactants in an open vessel. Such a method, termed "microwave-organic reaction enhancement (MORE)", was developed by Bose at al.. During the reaction, reactants are heated by microwave irradiation in polar, high-boiling solvent so that the temperature of reaction mixture does not reach the boiling point of a solvent. Despite the convenience, a disadvantage of the MORE technique consists in limitation to high-boiling polar solvents such as DMSO, DMF, *N*-methylmorpholine, diglyme, etc. The approach has been adapted to lower-boiling solvents (e.g., toluene), but it generates a potentially serious fire hazard. For reactions at reflux, domestic microwave ovens have been modified by making a shielded opening to prevent leakage, and through which the reaction vessel has been connected to a condenser.

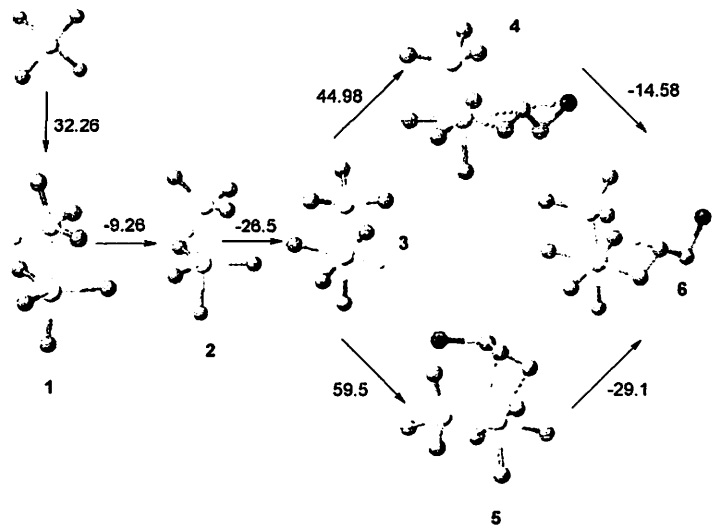
The effect of microwave irradiation on chemical reactions is generally evaluated by comparing the time needed to obtain a desired yield of final products with respect to conventional thermal heating. Research in the area of chemical synthesis has shown some potential advantages in the ability not only to drive

chemical reactions but to perform them in reduced time scale. In some cases the products exhibited properties that may not be possible using conventional thermal treatments.

The presence of the reactive Si-H groups in polyhydrosilanes allows obtaining of different polysilane structures with various functionalities through catalytic addition of unsaturated organic compounds. This work studies the effect of microwaves on such systems, using as a model of the catalytic addition of allyl bromide to reactive Si-H polysilanes.



The hydrosilylation reaction is carried out in the presence of a transition-metal catalyst, with platinum the most active catalyst. The accepted mechanism of platinum-catalyzed hydrosilylation is based on the intermediacy of platinum complexes. In particular regard to catalysis, microwave fields may have the effect of selectively activating the catalyst sites, an effect not possible by conventional heating.



The absence of the induction period, typical for the conventional method, leads to the conclusion that the microwave activating process takes place early in the first stage of the addition reaction leading to specific intermediate catalytic species characterized by high dipole moments. These species have a high microwave absorption capacity, therefore the reaction time is considerable reduced.

This new procedure has the advantage of shortening the reaction time from hours to minutes. Futhermore, the yields are much higher and the temperatures measured at the end of reactions are much lower than in conventional method. This fact allows a better protection of polysilane chemical structure which is often vulnerable in harsh conditions.

1P-73

Regioselective Diels–Alder Reactions of Silylbenzynes: Convergent Synthesis of Polysubstituted Biaryls

Sho-ichi Takayanagi,[1,*] Takashi Ikawa,[1] Yuki Morikawa,[1] Shinya Mohri,[1] Masaya Tsubakiyama,[1] Masahiro Egi,[1] Shuji Akai,[1] Yasufumi Wada,[2] Yasuyuki Kita[2,3]

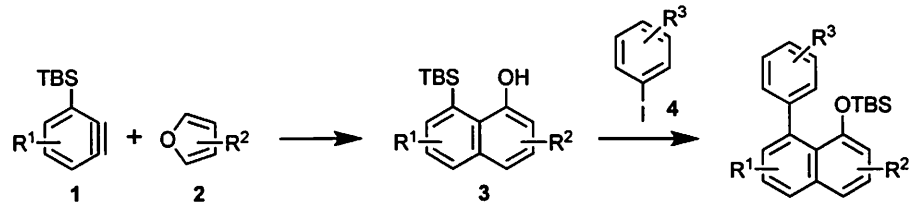
[1]School of Pharm. Sci., Univ. of Shizuoka, 52-1, Yada, Suruga-ku, Shizuoka, 422-8526, Japan

[2]Graduate School of Pharm. Sci., Osaka Univ., 1-6, Yamadaoka, Suita, Osaka, 565-0871, Japan

[3]School of Pharm. Sci., Ritsumeikan Univ., 1-1-1 Noji Higashi, Kusatsu, Shiga, 525-8577, Japan

akai@u-shizuoka-ken.ac.jp

Biaryls are ubiquitous moieties found in natural products, pharmaceuticals, polymers, sensors and ligands for transition-metal catalysts. A number of useful methods for the preparation of these compounds have been basically developed by the transition-metal-catalyzed cross-coupling of aryl halides with aryl metallic species, which include the Stille, Suzuki, Negishi, and Hiyama reactions. On the other hand, the multi-component assembly protocols have been appreciated as a powerful means for the preparation of molecular complexity and diversity, thereby being particularly adapted for combinatorial chemistry and diversity-oriented synthesis. As an approach towards this goal in the synthesis of the biaryls, we present at this symposium a novel preparation of the polysubstituted unsymmetrical biaryls **5** by assembling the following three components: the 3-*tert*-butyldimethylsilylbenzynes (3-TBS-benzynes) **1**, the furans **2** and the aryl iodides **4** (Scheme 1). Thus, this methodology involves the construction of the 8-TBS-1-naphthols **3** by the regioselective Diels–Alder reactions of **1** with **2** and the Hiyama cross-coupling of **3** and **4**.

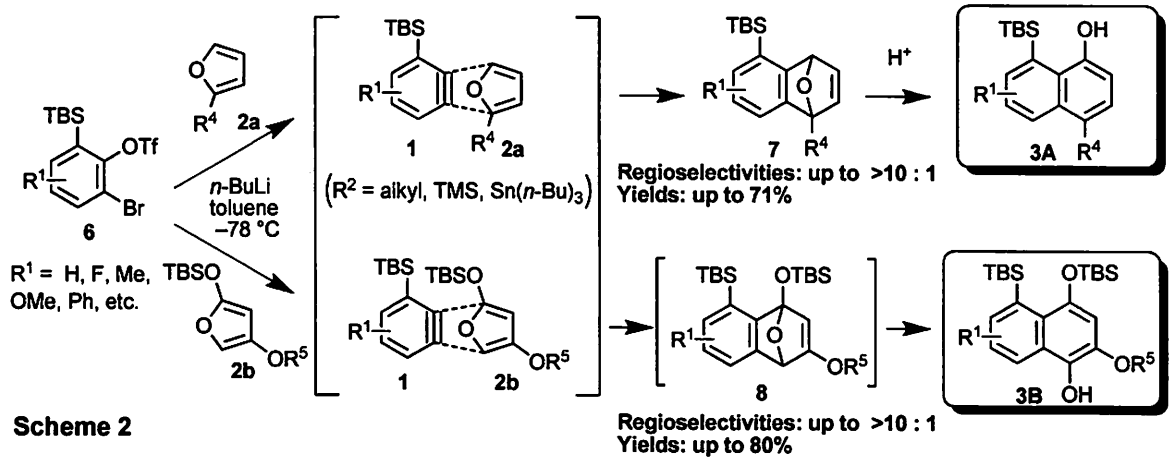


Scheme 1 Regioselective Diels-Alder Reaction Cross-Coupling Reaction

The Diels–Alder reactions of **1**, in situ generated by the treatment of the precursors **6** with *n*-BuLi at –78 °C, and the 2-alkylfurans **2a** in toluene gave the head-to-tail adducts **7** with high regioselectivities (up to >10:1). Similar reactions of **6** with the 2-silyl- and the 2-stannylfurans **2a** also provided **7** exclusively. The substituents R^1 on **1** were found not to affect the regioselectivities. Because the corresponding Diels–Alder reactions of the 3-phenyl- and the 3-*tert*-butylbenzyne with 2-*tert*-butylfuran **2a** gave two isomers with much lower regioselectivities, the excellent regioselectivities of the 3-silylbenzynes **1** cannot be explained by the simple steric hindrance of the silyl group. The TBS-adducts **7** were subjected to the acid-mediated regioselective cleavage of the epoxy ring to almost quantitatively give the 8-TBS-1-naphthols **3A** while retaining the TBS group intact (Scheme 2). Although a trimethylsilyl (TMS) group on the benzyne also worked as an effective directing group of the Diels–Alder reactions as did the TBS group,

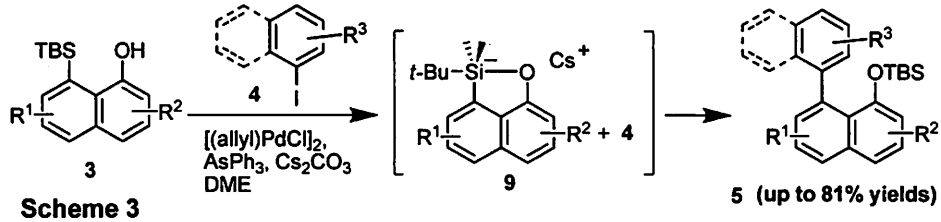
the TMS group on the cycloadducts was not stable enough during the acidic epoxy-ring opening.

Similar reactions of **1** with the 4-alkoxy-2-siloxyfurans **2b** directly gave the dihydroquinones **3B** with high regioselectivities (up to >10:1). **3B** is thought to be formed via the instantaneous epoxy-ring opening of the primary cycloadducts **8**, generated via the selective head-to-head Diels–Alder reactions of **1** with **2b**. (Scheme 2). These highly contrasting behaviors between **2a** and **2b** are very interesting, because such opposite regioselectivities arisen by the change of the substituents of furans have never been reported in the benzyne chemistry, to the best of our knowledge.



Scheme 2

Another highly intriguing, but difficult subject in this project, was the substitution of the TBS group on **3** with aryl groups. Although the usefulness of the Hiyama cross coupling reactions of arylsilanes has been widely appreciated, there is no precedent on the use of the robust TBS group. After intensive screening of palladium sources, ligands, bases and solvents, we finally found that the coupling reaction between **3** and the iodobenzene **4** was effected by using $[(allyl)PdCl]_2$, $AsPh_3$ and Cs_2CO_3 in 1,2-dimethoxyethane (DME) to provide the 8-phenyl-1-naphthyl TBS ether **5** in 77% yield. In like manner, moderate-to-good yields of **5** were obtained from both the electron-rich and the electron-poor phenyl iodides **4** and also from the 1-naphthyl iodide (Scheme 3). More noteworthy is that these reactions were achieved without using any fluoride activator. The fact that the TBS group was transferred to its oxygen neighbor during the reaction indicated the formation of the pentacoordinate silicates **9** as highly reactive intermediates.



Scheme 3

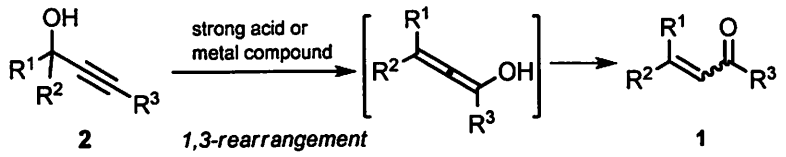
In summary, we have developed a novel convergent synthetic method of the biaryls **5** by assembling three components, i.e., the silylbenzynes **1**, the furans **2** and the aryl iodides **4**. This method features the consecutive use of the robust TBS group for two different purposes; viz., the silicon-directing Diels–Alder reaction of 3-TBS-benzynes **1** and the Hiyama coupling of the TBS-naphthols **3**.

1P-74

Mo-Au Combo Catalysis for Rapid 1,3-Rearrangement of Propargyl Alcohols into α,β-Unsaturated Carbonyl Compounds

Masahiro Egi, Noboru Fujiwara,* Yoshiko Yamaguchi, Shuji Akai
School of Pharmaceutical Sciences, University of Shizuoka
52-1, Yada, Suruga-ku, Shizuoka, 422-8526, Japan
akai@u-shizuoka-ken.ac.jp

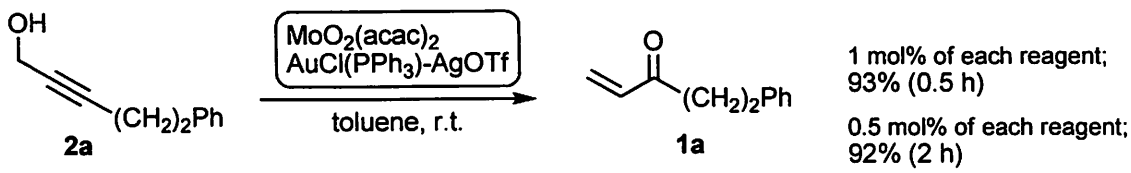
α,β-Unsaturated carbonyl compounds **1** are versatile intermediates for the synthesis of biologically active natural products, pharmaceuticals, agrochemicals, and other useful materials. One of the main methods to prepare such compounds is the 1,3-rearrangement of propargyl alcohols **2**, which is known as the Meyer–Schuster rearrangement (Scheme 1). Especially, due to its high atom economy, extensive efforts have been devoted to the development of efficient catalysts. Protic and Lewis acids have been widely utilized; however, they often showed low selectivities leading to poor yields. Such rearrangements were better catalyzed by transition metals, which usually required elevated temperature (>100 °C) or often produced side products.



Scheme 1

We present here a novel and practical method by the combined use of Mo, Au, and Ag compounds, which dramatically accelerates the 1,3-rearrangement even at room temperature and affords a diverse range of α,β-unsaturated carbonyl compounds in good to excellent yields.

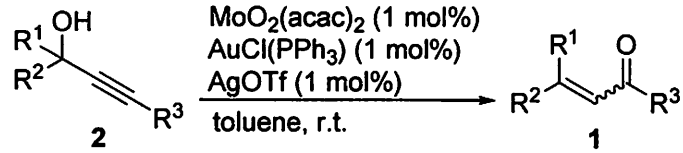
First, to develop a more effective catalytic system, a highly challenging primary propargyl alcohol **2a** was used as the substrate. No observable reaction occurred at room temperature in the presence of only the Mo, Au, or Ag catalyst, and all combination of two catalysts among them afforded no or poor yields of the desired compound **1a**. However, in stark contrast, the combination of 1 mol% each of Mo, Au, and Ag significantly enhanced the reaction to give **1a** in 93% yield (Scheme 2). Even in the case when the catalyst loading was reduced to 0.5 mol%, excellent yields were obtained, although a slightly longer reaction time was needed. We consider a synergetic mechanism in which a cationic Au catalyst, generated from $AuCl(PPh_3)$ and AgOTf, activates the acetylene bond, while $MoO_2(acac)_2$ isomerizes the propargyl alcohol via the rearrangement of an intermediate molybdate.



Scheme 2

Our protocol showed an excellent generality and provided good to excellent isolated yields of unsaturated ketones **1b-m** from primary, secondary, and tertiary propargyl alcohols **2b-m** (Table 1). The time required to reach completion was typically less than 1 h, while 3 h was sufficient for the less reactive tertiary substrates.

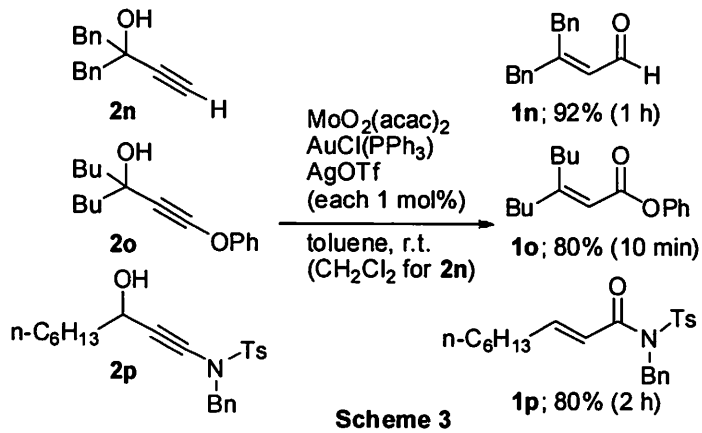
Table 1. Mo/Au/Ag catalyzed rearrangement of **2** to α,β-unstaturated ketones **1**



entry	propargyl alcohol **2**	R^1	R^2	R^3	reaction time (h)	isolated yield of **1** (%)	
1	**2b**	H	H	n-C_7H_{15}	0.5	**1b**	84
2 [a)]	**2b**	H	H	n-C_7H_{15}	1	**1b**	87
3	**2c**	H	H	Ph	1	**1c**	61
4	**2d**	H	Me	n-C_6H_{13}	0.25	**1d**	97
5	**2e**	H	$Ph(CH_2)_2$	n-C_4H_9	0.25	**1e**	94
6	**2f**	H	Ph	n-C_6H_{13}	0.5	**1f**	86
7	**2g**	H	Me	Ph	1	**1g**	88
8	**2h**	Me	Me	n-C_7H_{15}	0.5	**1h**	92
9	**2i**	Me	Me	Ph	2.5	**1i**	90
10	**2j**	Bn	Bn	Me	1.5	**1j**	91
11	**2k**	Me	t-C_4H_9	n-C_4H_9	3	**1k**	88
12	**2l**	Me	$Ph(CH_2)_2$	n-C_4H_9	2	**1l**	94
13	**2m**	$(CH_2)_5$		n-C_6H_{13}	1.5	**1m**	88

a) Mo:Au:Ag = 0.5:0.5:0.5 (mol%)

The developed method was also useful for the rearrangement of the propargyl alcohols **2n-p** bearing proton **2n**, oxygen **2o**, and nitrogen groups **2p** at the end of the acetylene functionality to give the α,β-unsaturated aldehyde **1n**, the phenyl ester **1o**, and the amide **1p**, respectively (Scheme 3). To the best of our knowledge, this is the first example of the 1,3-rearrangement of the *N*-alkynyl amide.



Scheme 3

In summary, we have disclosed that the combination of 1 mol% each of $MoO_2(acac)_2$, $AuCl(PPh_3)$, and AgOTf provides a highly powerful catalytic system for the rapid 1,3-rearrangement of propargyl alcohols. The reactions proceed at room temperature within 1 h in most cases to afford a variety of α,β-unsaturated carbonyl compounds in excellent yields. Especially, it is noteworthy that it is applicable to primary propargyl alcohols and *N*-alkynyl amides as the substrate.

1P-75

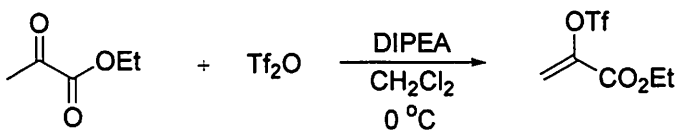
Radical Alkylations of Carbonyl Compounds

JinYoung Lee*, Misun Lee, Sunggak Kim

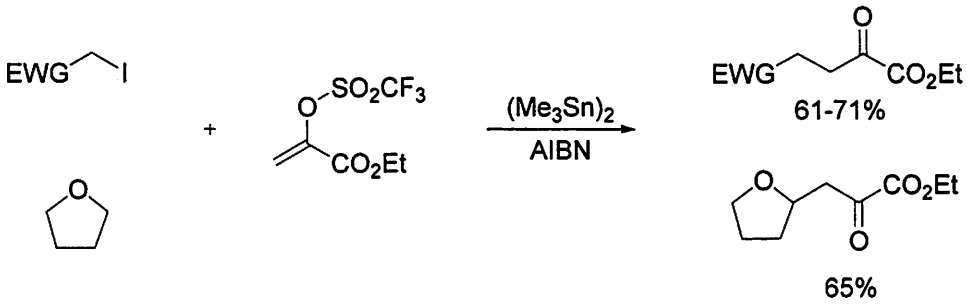
Center for Molecular Design & Synthesis and Department of Chemistry, School of Molecular Science (BK-21), KAIST, Daejeon 305-701, Korea

E-mail: skim @kaist.ac.kr

Free-radical alkylations are powerful tools for the formation of carbon-carbon bonds under mild conditions and are one of the most important and fundamental organic reactions. The trifluoromethyl sulfone(triflone) functional moiety is regarded as the strongest neutral electron-withdrawing group and is attractive in synthetic strategies involving sulfones. In spite of extensive development of trifluoromethyl radical, radical-mediated alkylations using trifluoromethyl radical have not been well investigated. Vinyl triflates are good radical acceptors to form carbon-carbon bonds throughout radical reactions. Vinyl triflates were easily prepared. Reaction of ethyl pyruvate with triflic anhydride and diisopropyl amine in dichloromethane gave vinyl triflate in moderate yield. When the radical reaction was carried out in the presence of hexamethylditin in benzene, the reaction proceeded cleanly, yielding α-ketoester compound in 61-71% yield. Also, radical alkylations of unactivated C-H bonds were studied.



(1)



(2)

Abstracts

Poster Presentation

2P-01 ～ 2P-74

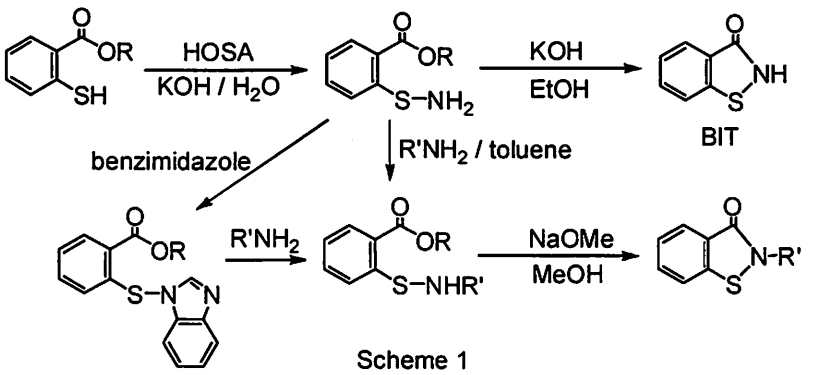
July 30

2P-01

Chlorine Gas Free Synthesis of Isothiazolo[5,4-*b*]pyridin-3-ones

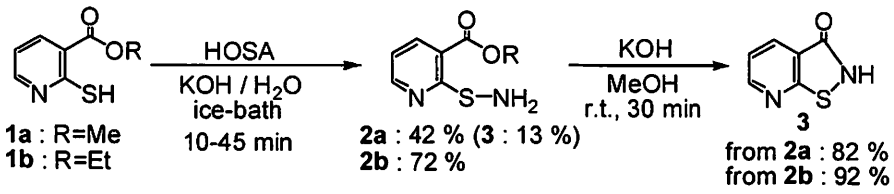
Masao Shimizu,*[,1] Yusuke Higuchi,[2] Takeo Konakahara[2]
[1]National Institute of Advanced Industrial Science and Technology (AIST),
1-1-1 Higashi, Tsukuba, Ibaraki, 305-8575, Japan
[2]Faculty of Science and Technology, Tokyo University of Science,
2641 Yamazaki, Noda, Chiba, 278-8510, Japan
m.shimizu@aist.go.jp

Isothiazolo[5,4-*b*]pyridine-3-one derivatives, which are aza-analogs of 1,2-benzisothiazolin-3-ones (BIT, industrial biocides), show bioactivities.[1)] These compounds were usually synthesized from the reaction of amines with sulfenyl chlorides prepared from chlorination of 2-mercaptonicotinates with chlorine gas. Since chlorine gas is toxic and corrosive, development of safe and convenient process of isothiazolo[5,4-*b*]pyridine-3-one syntheses is desired. In the previous papers, we reported the chlorine gas free synthesis of sulfenamides and 1,2-benzisothiazolin-3-ones[2)] (Scheme 1). In this presentation, we will report application of these synthetic methods to pyridine derivatives, and syntheses of pyridinesulfenamides and isothiazolo[5,4-*b*]pyridine-3-ones.



Scheme 1

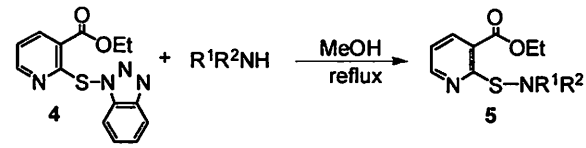
2-Mercaptonicotinic acid esters (1) were treated with aqueous potassium hydroxide solution of hydroxylamine-*O*-sulfonic acid (HOSA) for 10-45 min on an ice-bath to give 2-sulfenamoylnicotinates (2) as white precipitates. In the case of methyl 2-mercaptonicotinate (1a), the yield of sulfenamide (2a) was low due to higher solubility toward water and cyclization occurred to isolate isothiazolo[5,4-*b*]pyridine-3-one (3) from water solvent. Treatment of the pyridinesulfenamides (2) with potassium hydroxide in ethanol gave isothiazolo[5,4-*b*]pyridine-3-one (3) in high yields (Scheme 2).



Scheme 2

As we previously reported, amine exchange reactions on the sulfur atom occurred between 2-sulfenamoylbenzoates and various kinds of amines by heating in toluene and the corresponding *N*-substituted 2-sulfenamoylbenzoates were obtained.[2b] However, in the case of pyridinesulfenamides 2, amine exchange reactions did not occur with usual amines. Amines which had acidic protons such as benzotriazole and 1,2-benzisothiazolin-3-one only reacted with sulfenamides, and the corresponding *N*-sulfenylbenzotriazoles (4) and 1,2-benzisothiazolin-3-ones were obtained, respectively. These *N*-sulfenyl heterocycles reacted with various kinds of amines and *N*-substituted pyridinesulfenamides (5) were synthesized (Table 1). For *N*-monosubstituted sulfenamides, treatment of sodium methoxide in methanol under reflux afforded 2-substituted isothiazolo[5,4-*b*]pyridine-3-ones (6) in good yields (Table 2).

Table 1. Reaction of *N*-Sulfenylbenzotriazole (4) with Amines.

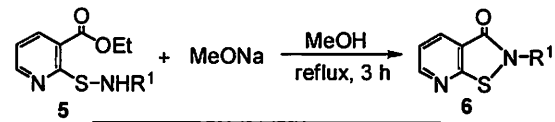


R^1	R^2	Time	Product	Yield (%)
Ph	H	4	**5a**	52
$PhCH_2$	H	5	**5b**	80
PhMeCH	H	4	**5c**	97
$PhMe_2C$	H	4[a]	**5d**	71
Et	Et	5[b]	**5e**	62
$-(CH_2)_4-$		5[b]	**5f**	86
$-(CH_2)_2O(CH_2)_2-$		4	**5g**	99
$-(CH_2)_2NMe(CH_2)_2-$		4	**5h**	96

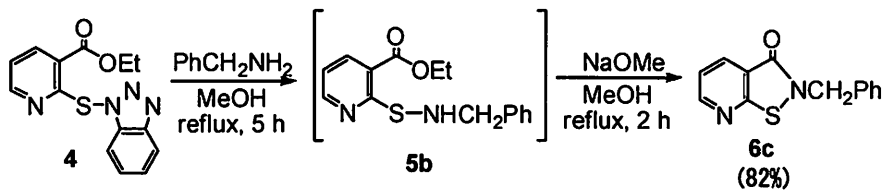
[a] Toluene, 100°C. [b] 80°C in sealed tube.

Since 5 was synthesized *N*-sulfenylbenzotriazole 4 and amines, it was possible that isothiazolo[5,4-*b*]pyridine-3-ones were prepared from the reaction of 4 with amine followed by treatment of base without isolation of sulfenamides 5 (Scheme 3).

Table 2. Synthesis of Isothiazolo[5,4-*b*]pyridine-3-ones (6).



R^1	Product	Yield (%)
Ph	**6a**	58
p-Tol	**6b**	84
$PhCH_2$	**6c**	82
$PhCH_2CH_2$	**6d**	96



Scheme 3

Reference

1) For examples, W. Malinka, *et al.*, *Farmaco*, **56**, 905 (2001); M. Pregnolato, *et al.*, *Farmaco*, **55**, 669 (2000); G. Pagani, *et al.*, *J. Med. Chem.*, **43**, 199 (2000).

2a) M, Shimizu, *et al.*, *Heterocycles*, **51**, 3005 (1999); b) *Heterocycles*, **60**, 1855 (2003); c) *Tetrahedron*, **62**, 2175 (2006).

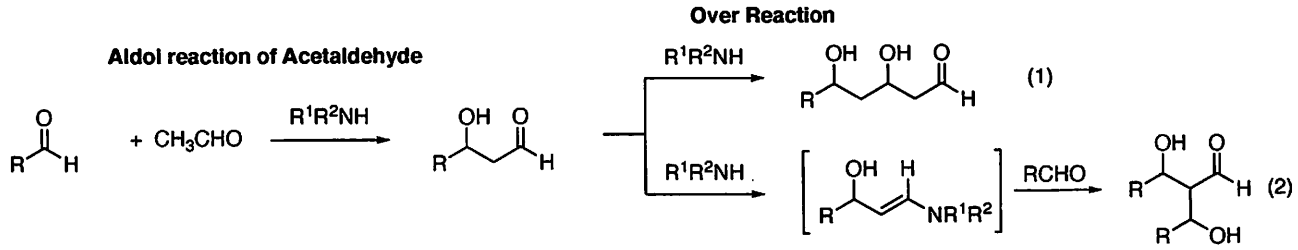
2P-02

The asymmetric reaction of acetaldehyde catalyzed by organocatalysis

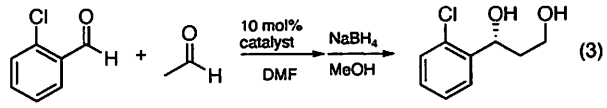
Yujiro Hayashi,* Takahiko Itoh, Seiji Aratake, Hayato Ishikawa
Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan
hayashi@ci.kagu.tus.ac.jp

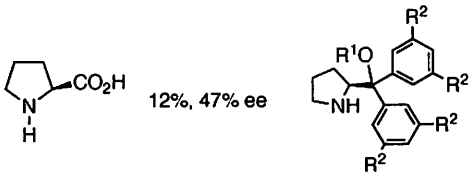
The aldol reaction is recognized to be one of the most important carbon-carbon bond forming processes in organic synthesis. Acetaldehyde, the simplest aldehyde, generates versatile β-hydroxy-α-unsubstituted aldehydes when it is employed as the nucleophilic component in this reaction. In spite of its synthetic importance, as far as we are aware there are no examples of a successful direct, enantioselective aldol reaction of this type.

Even among organocatalyst-mediated aldol reactions, there is no successful reaction of acetaldehyde in spite of the extensive research on this class of reactions in recent years. As the aldol product generated when acetaldehyde is employed would be α-unsubstituted, it is expected to act both as a reactive electrophile (Eq. 1) and nucleophile (Eq. 2). Thus, the suppression of over reactions is a difficult problem.



The aldol reaction of acetaldehyde with *o*-chlorobenzaldehyde was selected as a model (Eq. 3). The efficacy of various catalysts was examined first. Proline is known to be a suitable catalyst for the cross-aldol reactions of aldehyde/ketone and aldehyde/aldehyde. When proline was employed under several different conditions, hardly any cross-aldol product was obtained, and crotonaldehyde, generated by self-aldol reaction, followed by dehydration reaction, was formed. When trifluoromethyl substituted diarylprolinol **1** was employed, the cross-aldol product was generated in good yield and nearly optically pure. It should be noted that a diarylprolinol silyl ether, which has been developed independently by our[1] and Jørgensen's[2] groups, is not effective.

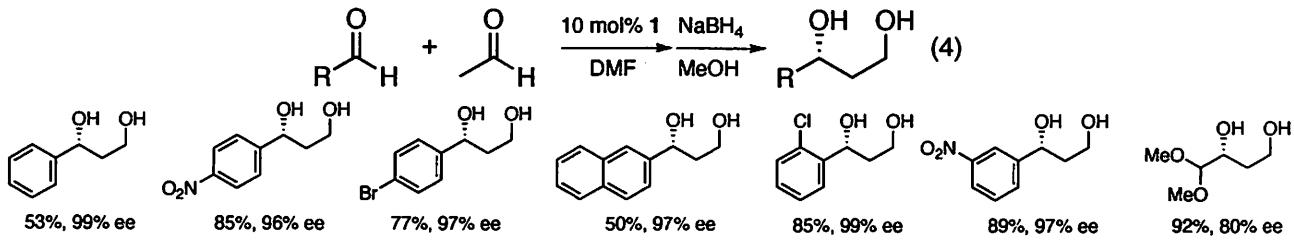




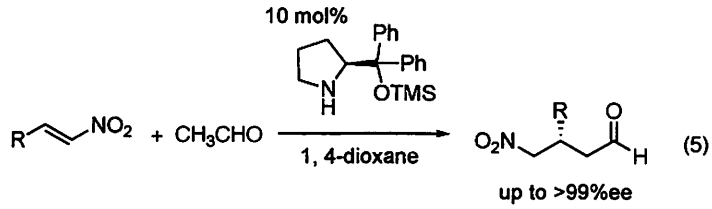
catalyst	R^1	R^2	Yield/%	ee/%
1	H	CF_3	85	99
2	TMS	CF_3	15	75
3	H	H	33	85
4	H	CH_3	11	78

The reaction proceeds efficiently with both electron-deficient aromatic aldehydes and olefinic aldehydes, affording the corresponding aldol products in good to excellent yield with excellent enantioselectivity. The reaction also proceeds with non-activated aldehydes such as benzaldehyde and 2-naphthaldehyde. Dimethoxyacetaldehyde was also a useful electrophilic aldehyde, and could be used as its commercially available aqueous solution, to afford a highly functionalized aldol. Notably excellent enantioselectivity was observed in most cases.

Though diarylprolinol silyl ether is widely used as an effective organocatalyst, the present reaction is a rare example of its precursor, diarylprolinol, acting as an outstanding catalyst, and a first example of the use of diarylprolinol in an enantioselective aldol reaction. The β-hydroxy-α-unsubstituted aldehydes generated are versatile synthetic intermediates, and are obtained with excellent enantioselectivity. Thus, the present aldol reaction of acetaldehyde is a synthetically useful process.[3]



Recently we also found that diphenylprolinol silyl ether is an effective catalyst in the Michael reaction of acetaldehyde with nitroalkene (Eq. 5).[4] With aryl-substituted nitroalkenes, both electron rich and electron deficient aryl groups could be successfully employed. Reaction occurred not only with aryl-substituted nitroalkenes but also with alkyl-substituted ones and nearly optically pure Michael adducts were obtained. As the obtained product, α-unsubstituted γ-nitro aldehyde, possesses useful functional groups, they are synthetically important chiral building blocks.



References

1) (a) Y. Hayashi *et al.*, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. (b) Y. Hayashi *et al.*, *Angew. Chem. Int. Ed.* **2006**, *45*, 6853. (c) Y. Hayashi *et al.*, *Angew. Chem. Int. Ed.* **2007**, *46*, 4922. (d) Y. Hayashi *et al.*, Y. *Org. Lett.* **2007**, *9*, 2859.

2) K. A. Jørgensen *et al.*, *Angew. Chem. Int. Ed.* **2005**, *44*, 794.

3) Y. Hayashi *et al.*, *Angew. Chem. Int. Ed.* **2008**, *47*, 2082.

4) Y. Hayashi *et al.*, *Angew. Chem. Int. Ed.* ASAP, DOI: 10.1002/anie.200801130.

2P-03

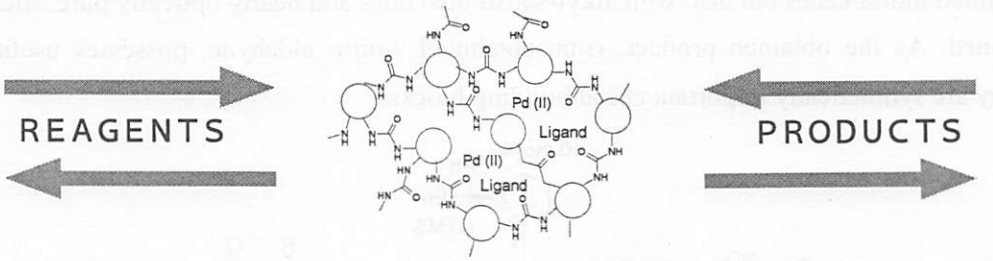
Overcoming The Issues Of Precious Metal Contamination Within Catalysed Reactions

David J. Evans,* Mohammed Nisar, Thomas E. O. Screen, Michael R. Pitts, Angus J. P. Stewart-Liddon
Reaxa Limited, PO Box 42, Hexagon Tower, Blackley, Manchester, M9 8ZS, UK
dave.evans@reaxa.com

Within the Pharmaceutical industry the specification to limits of residual metal contamination in drug substances and excipients is defined in European guidelines set out by the EMEA (2002 &2007)[1]. At present the acceptable concentration limits for platinum group metals Ru, Rh, Pd, Os, Ir & Pt are below 5 ppm for each individual metal. Other important metal catalyst residues such as Cu, Ni & Fe must achieve 10 – 20 ppm. Significantly for the Pharmaceutical sector, all new drug substances must comply with these guidelines immediately. In contrast all existing drugs must comply within 5 years.

In light of these specifications and the increased prevalence of precious metal catalysed reactions in the synthetic routes to new drug candidates there is a necessity to minimise metal release during synthetic processes. Taking into regard the recent rapid increases in platinum group metal prices the pharmaceutical industry is proactively implementing the conservation of metal catalysts. Strong economic drivers are forcing more effective metal use with minimal losses of metal value through individual chemical steps, deactivation and recovery of precious metals from process waste streams.

In face of these key processing challenges we have developed and commercialised a series of microencapsulated precious metal catalysts as a means of addressing the 'sustainability' agenda – namely easier, faster and cleaner chemistries. Pd(II) EnCat™ polyTPP incorporates palladium (II) acetate and bound polymeric-triphenyl phosphine ligand within a highly cross-linked microporous polyurea matrix. This heterogeneous catalyst successfully catalyses many C-C bong forming processes including Suzuki, Heck, Stille and Carbonylations. Separation of the microencapsulated heterogeneous catalyst from the product is achieved by simple filtration means. Furthermore, simple washing of the used catalyst allows highly economic recycling and reuse of the catalyst.[2]



Catalytic activity is retained yet the crude process stream contains very low ppm levels of precious metal contamination. In addition the benefit to using a bound polymeric TPP ligand facilitates a crude product containing low levels of TPP & TPP-oxide. In contrast the equivalent homogeneous reaction afford high levels of Pd contamination with very high levels of phosphine contamination (see Figure 1).

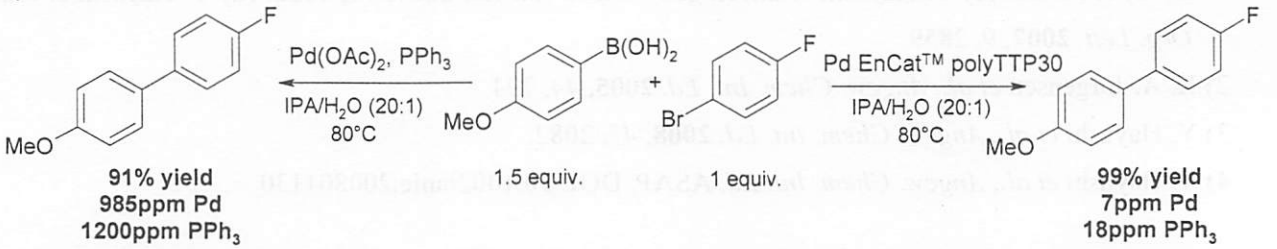


Figure 1: Example of Minimal Metal & Phosphine Contamination Using Pd(II) EnCat™ polyTPP Catalyst

In addition to use in classical batch processes the uniform spherical nature of Pd(II) EnCat™ polyTPP enables efficient translation to flow reaction processes[3]. The EnCat™ catalyst is stable to conventional heating and stirring whilst also demonstrating excellent reactivity under microwave conditions[4]. This was demonstrated in a microwave heated Sonogashira reaction (see Figure 2). Using Pd EnCat™ polyTPP30 the residual palladium was only 14 ppm in the crude. Simple treatment of this crude reaction mixture with QuadraPure™ TU scavenger resin at ambient temperature for 1hr quickly reduced the Pd & Cu content to <1ppm respectively by ICP analysis.

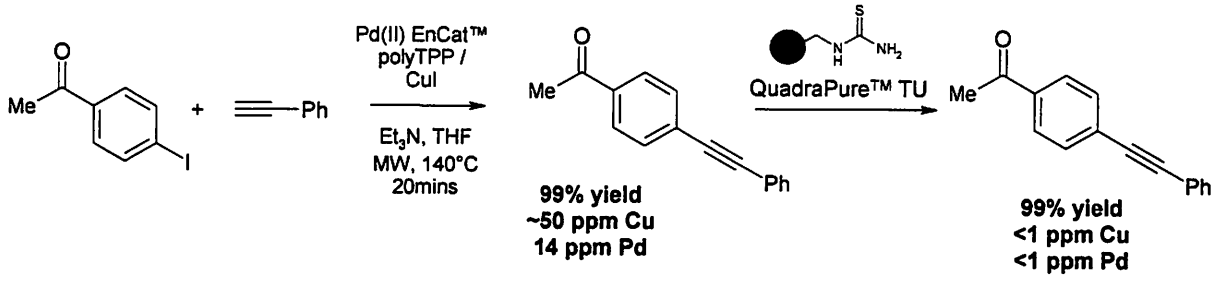


Figure 2: Using Pd(II) EnCat™ polyTPP Catalyst in Microwave mode

QuadraPure™ TU is a uniform, spherical macroporous based PS resin suitable for scavenging numerous metal species (in various oxidation states) from both organic and aqueous media. As the resin is supplied with supporting regulatory documentation the scavenger is highly suited for cGMP use. Equally, the QuadraPure™ scavenger range results in the efficient removal of metal contaminants from test reaction waste streams; either in batch or flow mode[5]. In this instance the use of scavengers in flow is further facilitated through their availability in pre-packed cartridges.

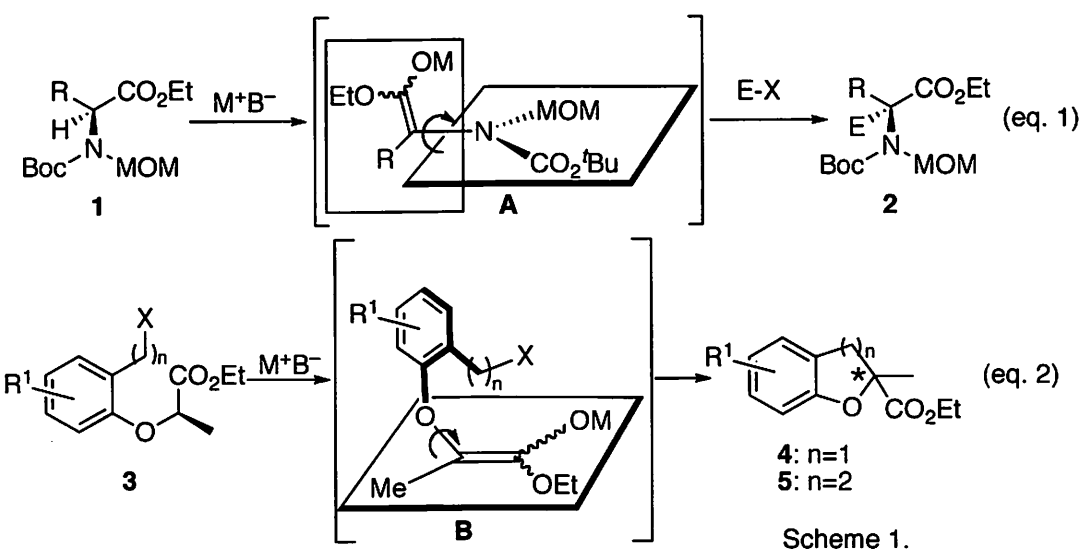
1. http://www.emea.europa.eu/pdfs/human/swp/444600.pdf
2. Ramarao, C.; Ley, S. V.; Smith, S. C.; Shirley, I. M.; DeAlmelda, N. *Chem. Commun.*, **2003**, 1132.
3. Santos, R. C. D.; Al-Duri, B.; Seville, J. P. K.; Smith, C. J.; Lee, C. K. Y.; Holmes, A. B.; McConvey, I. F. *Org. Process Res Dev.*, **2007**, *11*, 144-148.
4. Pitts, M. R. *Platinum Metals Review*, **2008**, *52*, 64.
5. Hinchcliffe, A.; Hughes, C.; Pears, D. A.; Pitts, M. R. *Org. Process Res Dev.*, **2007**, *11*, 477-481

2P-04

Asymmetric Synthesis of Dihydrobenzofurans and Chromans via Planar Chiral Enolates

*Tomoyuki Yoshimura, Keisuke Tomohara, Takeo Kawabata
Institute for Chemical Research, Kyoto University
Gokasho Uji 611-0011, JAPAN
tyoshimu@fos.kuicr.kyoto-u.ac.jp

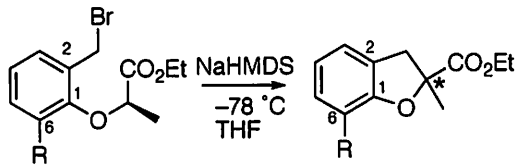
Chiral dihydrobenzofurans and chromans with tetrasubstituted carbon constitute an important part of numerous natural products and bioactive chromophores, such as silvestrol and vitamin E. Due to the continuous discovery of new natural products and the production of new derivatives of vitamin E, numerous asymmetric synthetic methods of chiral dihydrobenzofurans and chromans have been developed. We have developed asymmetric induction based on dynamic chirality of enolates generated from amino acid derivatives, where asymmetric inductions is assumed to occur via enolate intermediate **A** with a chiral C-N axis (memory of chirality) (scheme 1, eq. 1). Under these conditions, chiral α,α-disubstituted amino acid derivatives **2** are obtained from L-amino acid derivatives **1** without the aid of external chiral sources.[1] We then envisioned to apply this concept to the construction of chiral dihydrobenzofurans and chromans with tetrasubstituted carbon. The treatment of ester **3** which was prepared from inexpensive chiral ethyl lactate and phenol derivatives under Mitsunobu conditions with a base would give chiral dihydrobenzofuran **4** or chroman **5** via the enolate intermediate **B** (eq. 2). In contrast to the enolate **A**, enolate **B** has planar chirality whose racemization barrier is directly related to the rotational barrier of C-O bond. It is assumed that the expected enolate intermediate **B** would have a shorter half-life of racemization than that of the enolate **A** because of lower rotational barriers of C-O bonds than C-N bonds. In order to preserve the chirality of the enolate **B** during cyclization, various bases, solvents and substituents on an aromatic ring (R^1) were investigated.



Scheme 1.

We anticipated that the bulkiness of substituent at C(6) on the aromatic ring was responsible for the efficiency of asymmetric induction, so that substrates **6** (R=H), **7** (R=Me) and **8** (R=^{i}Pr) were subjected to five-membered ring cyclization (Table 1). Cyclization reaction was achieved by the treatment of them with NaHMDS in THF at −78 °C to give dihydrobenzofuran **10**, **11** and **12** in 61% yield and 0% ee, 66% yield and 82% ee, and 82% yield and 99% ee, respectively (Table 1, entries 1-3). The effects of bulkiness of C(6)-substituent on the asymmetric induction were crucial, as expected. Since it is possible to convert a TMS group on aromatic ring into hydrogen or other functional groups, cyclization of **9** was also examined to give **13** in 70% yield and 97% ee (entry 4).

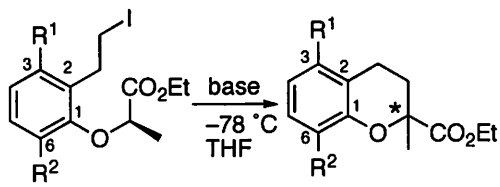
Table 1. Effect of C_6-substituent on five-membered ring cyclization



entry	R	substrate	product	yield (%)	ee (%)
1	H	**6**	**10**	61	0
2	Me	**7**	**11**	66	82
3	^{i}Pr	**8**	**12**	82	99
4	TMS	**9**	**13**	70	97

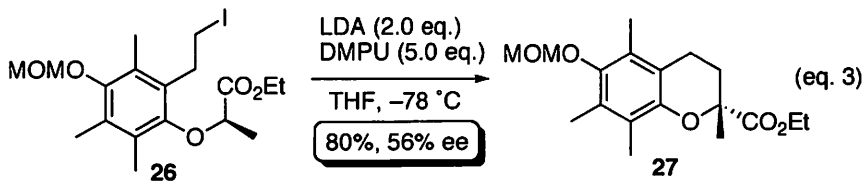
In contrast to five-membered ring cyclization, six-membered ring cyclization gave racemic chromans **18-20** irrespective of the bulkiness of substituent at C(6)(Table 2, entries 1-3). Because it was found that the cyclization of **26** gave **27** in 80% and 56% (eq. 3), we investigated the effects of other substituents on the aromatic ring. It was found that the substitutents both at C(6) (R^2) and C(3) (R^1) are critically involved in asymmetric induction (entries 4-6). The buttressing effect caused by the C(3)-substituent is assumed to be responsible for the faster rate of cyclization than that of recemization of the chiral enolate **B**. Unexpectedly, the substrate **19** having the bulkiest TMS substituent (entry 6) resulted in low enantioselectivity

Table 2. Effect of substituents on the aromatic ring on six-membered ring cyclization



entry	R^1, R^2	substrate	product	yield (%)	ee (%)
1	H, H	**14**	**20**	27	0
2	H, Me	**15**	**21**	40	0
3	H, ^{i}Pr	**16**	**22**	17	0
4	Me, Me	**17**	**23**	77	43
5	Me, ^{i}Pr	**18**	**24**	88	74
6	TMS, TMS	**19**	**25**	89	49[a]

a) Ee was determined after conversion of **25** into **20**.



References

1) Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D.; Moriyama, K. *J. Am. Chem. Soc.* **2006**, *128*, 15394; Kawabata, T; Fuji, K. *Topics in Stereochemistry,* Vol. 23; Denmark, S. E., Ed.; John Wiley & Sons: New York, **2003**, Chap. 3, 175.

2P-05

Studies Towards a Gram-Scale Synthesis of Spongistatin 1

Helmut Kraus,* Alejandro Diéguez-Vázquez, Matthew O'Brien, Yukihito Sumino, Takashi Tsunoda, Day-Shin Hsu and Steven V. Ley

University of Cambridge, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK

hk305@cam.ac.uk

The spongistatins comprise an important family of architecturally complex marine macrolides that display exceptional antitumour activities against a variety of cell types. Isolated independently by Pettit, Kitagawa and Fusetani in 1993,[1] the absolute stereochemistry remained unknown until proven by total synthesis in 1998.[2] All 9 members of the spongistatin family display remarkable growth inhibition characteristics against the US National Cancer Institute's panel of 60 human cell lines.[3] Spongistatin 1 (**1**) (Figure 1) was found to be the most active of the family with GI_{50} values between 0.025-0.035 nM and particular efficacy against cell lines derived from human melanoma.

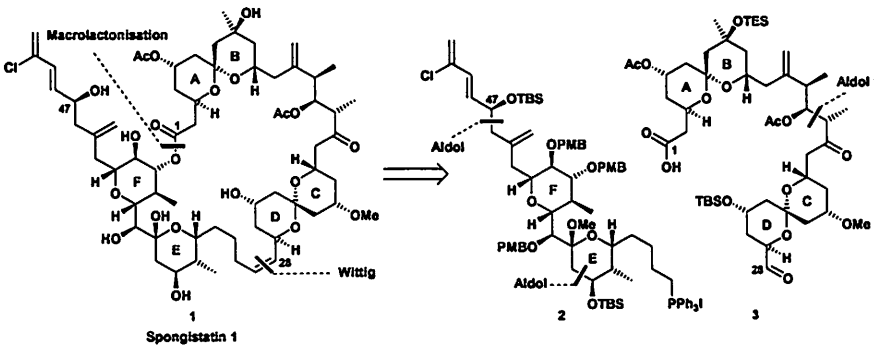


Figure 1. Retrosynthesis of Spongistatin 1 (**1**)

Natural supply of spongistatin 1 (**1**) is limited with very large quantities of sponge required to isolate milligram quantities of the natural product. Therefore, the isolation from natural sources on a sufficient scale to allow extensive biological studies is ecologically not justifiable. Furthermore, large-scale cultivations are currently not achievable, which leaves total synthesis as the only means to access this important molecule in sufficient quantities to enable further biological evaluations. Therefore, the goal of preparing spongistatin 1 (**1**) on a gram scale is considered a high priority.

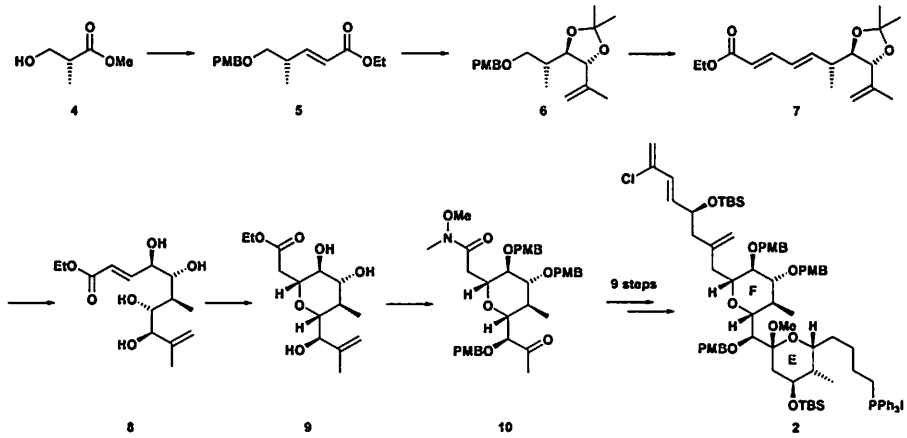
1 (a) G.R. Pettit, Z.A. Cichacz, F. Gao, C.L. Herald, M.R. Boyd, J.M. Schmidt and J.N.A. Hooper, *J. Org. Chem.*, 1993, **58**, 1302; (b) M. Kobayashi, S. Aoki, H. Sakai, K. Kawazoe, N. Kihara, T. Sasaki and I. Kitagawa, *Tetrahedron Lett.*, 1993, **34**, 2795; (c) N. Fusetani, K. Shinoda and S Matsunaga, *J. Am. Chem. Soc.*, 1993, **115**, 3977.

2 (a) D.A. Evans, P.J. Coleman and L.C. Dias, *Angew. Chem. Int. Ed.*, 1997, **36**, 2738; (b) J. Guo, K.J. Duffy, K.L. Stevens, P.I. Dalko, R.M. Roth, M.M. Hayward and Y. Kishi, *Angew. Chem. Int. Ed.*, 1998, **37**, 187.

3 (a) R. Bai, G.F. Taylor, Z.A. Cichacz, C.L. Herald, J.A. Kepler, G.R. Pettit and E. Hamel, *Biochemistry*, 1995, **34**, 9714; (b) R. Bai, Z.A. Cichacz, C.L. Herald, G.R. Pettit and E. Hamel, *Mol. Pharmacol.*, 1993, **44**, 757.

Its potent biological activity coupled with a complex molecular architecture has attracted great interest from the synthetic community, resulting in seven total syntheses including the Ley group's, published in 2005.[4] Current efforts in the Ley group laboratory are focussed on preparing quantities in excess of 1 g of spongistatin 1 (**1**). Considering the structural complexity of the molecule this poses a significant challenge. Alongside this key objective a further aspiration is to demonstrate that the Ley group synthesis is the most efficient route to date to achieve this ambitious goal. Although this is strongly believed to be true with regards to the C1-C28 fragment (**3**, Figure 1), the original synthesis of the C29-C51 fragment[5] (**2**, Scheme 1) highlighted the need for a more expedient route to access the quantities needed for a gram-scale synthesis of spongistatin 1. Therefore, a further aim is to implement a second generation synthesis towards the C29-C51 fragment (**2**). This will allow the efficient preparation of gram-quantities of this portion of the molecule en route to the total synthesis of the natural product.

The second generation route began with the assembly of enoate **5** from hydroxy ester **4** (Scheme 1) *via* a protection-DIBAL-Wittig sequence. Elaboration to the masked ketone **6** was then achieved under standard conditions. This sequence could be readily carried out on a large scale (100 mmol) and allowed substantial amounts of **6** (30 g batches) to be generated. Deprotection, oxidation and Horner-Wittig reaction yielded triene **7**, which underwent regio- and stereoselective dihydroxylation followed by acetonide deprotection to give tetraol **8**. An extensive trial of conditions for the oxy-Michael cyclisation revealed $Zn(OTf)_2$ in ethanol at 100 °C (sealed Schlenk tube) as optimal, affording the F ring fragment **9** in 88% isolated yield. Having successfully carried out this key strategic transformation, the tetrahydropyran unit was further elaborated *via* standard functional group interconversions to give intermediate **10**. At this stage the second-generation synthesis towards the EF fragment intercepts with the published route.[5] Thus, the fully protected F ring **10** will be further elaborated to the desired EF fragment **2**.



Scheme 1. Second Generation EF-Fragment (**2**) Synthesis

4 M. Ball, M.J. Gaunt, D.F. Hook, A.S. Jessiman, S. Kawahara, P. Orsini, A. Scolaro, A.C. Talbot, H.R. Tanner, S. Yamanoi S. V. Ley, *Angew. Chem. Int. Ed.*, 2005, **44**, 5433.

5 S. Kawahara, M.J. Gaunt, A. Scolaro, S. Yamanoi and S.V. Ley, *Synlett*, 2005, 2031.

2P-06

Enzymatic Resolution and Evaluation of Enantiomers of *cis*-5'-Hydroxythalidomide

Takeshi Yamamoto, * Masayuki Takashima, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology
Gokiso-cho, Showa-ku, Nagoya, 466-8555, Japan
nozshiba@nitech.ac.jp

Despite the notorious medical disaster caused by thalidomide (**1**), huge numbers of papers have been published about this drug since its formulation in 1956, because of its potential for treating a number of intractable diseases, such as leprosy, AIDS, and cancer. The pharmacological aspects of thalidomide and its derivatives have been frequently investigated; however, studies focusing on their enantioselective biological activities are limited due to the ease of racemization, as well as the lack of availability of the enantiomers. Therefore, the answer to the question of whether thalidomide is enantiospecifically teratogenic is still a matter of concern. Incidentally, the teratogenic properties of thalidomide appear to require prior biotransformation, and its anticancer activities have been attributed to the formation of metabolites. Therefore, much attention has recently been focused on the synthesis and biological activities of thalidomide metabolites (**Fig. 1**). *cis*-5'-Hydroxythalidomide (**2**), one of the major metabolites of thalidomide, is found to show enhanced inhibition of TNF-α production.

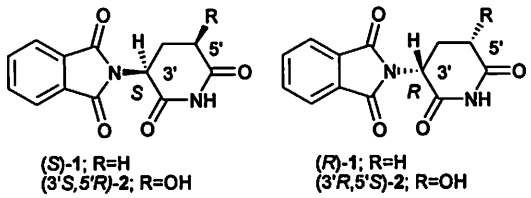
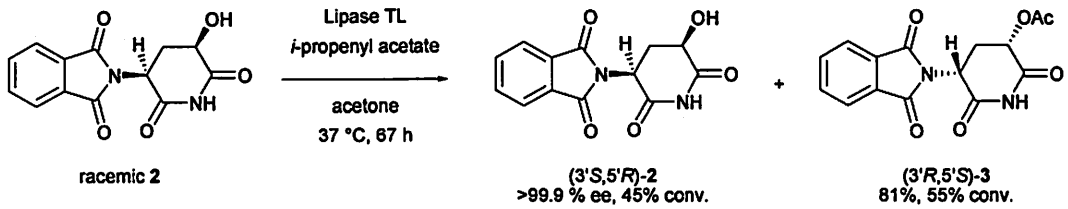


Fig. 1 Structures of (*S*)- and (*R*)-thalidomides (**1**) and their metabolites, (3'*S*,5'*R*)- and (3'*R*,5'*S*)-5'-hydroxythalidomides (**2**).

Enzymatic kinetic resolution of the racemic substrate should be the most practical and direct route for the preparation of enantiomeric **2**. Optimization of the reaction conditions identified lipase TL from *Pseudomonas stutzeri*, with isopropenyl acetate in acetone at 37 °C as the best combination for the enzymatic kinetic resolution of **2**. Enantiomerically pure (3'*S*,5'*R*)-**2** (>99.9% ee, 45% yield) and (3'*R*,5'*S*)-**3** (81% ee, 55% yield) were obtained with an *E* value of 70 (**Scheme 1**). (3'*R*,5'*S*)-**3** was easily converted to enantiomerically pure (3'*R*,5'*S*)-**2** (>99.9% ee) under refluxing in MeOH in the presence of TsOH followed by single recrystallization.



Scheme 1

We next investigated the stabilities of **1** and **2** toward racemization (epimerization) and hydrolysis (decay). Optically pure **1** and **2** were incubated at 37 °C and varying pH values, and monitored by HPLC. In the racemization study, **1** was racemized using all buffer solutions, the rate of racemization was rather quick in neutral and alkaline buffer solutions. On the other hand, under these conditions less than 12%

racemization of **2** was observed (**Fig. 2**) and no detectable epimerization from *cis*-**2** to its *trans*-isomer occurred. The effects of the pH dependent hydrolysis (decay) of **1** and **2** were essentially similar to each other in the range of pH 6–9 (**Fig. 3**).

Finally, preliminary enantioselective biological evaluation of **1** and **2** was investigated. Among the diverse biological activities of thalidomide that have been suggested, we were interested in anti-angiogenesis because it is hypothesized that the disruption of blood vessel formation in the fetal limb bud might be responsible for the teratogenicity of thalidomide. We found that racemic **1** and (*S*)-**1** blocked vascular sprout formation in high concentration, while (*R*)-**1**, racemic **2**, (3'*R*,5'*S*)-**2** and (3'*S*,5'*R*)-**2** failed to inhibit tube formation in this assay. These results are consistent with the traditional theory that the (*S*)-isomer of thalidomide is responsible for the teratogenicity

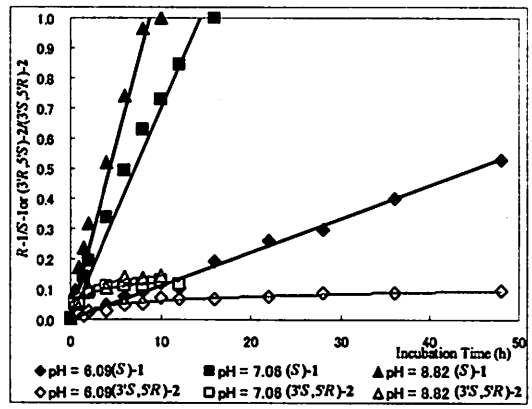


Fig. 2 Racemization study of (*S*)-**1** and racemization–epimerization study of (3'*S*,5'*R*)-**2**.

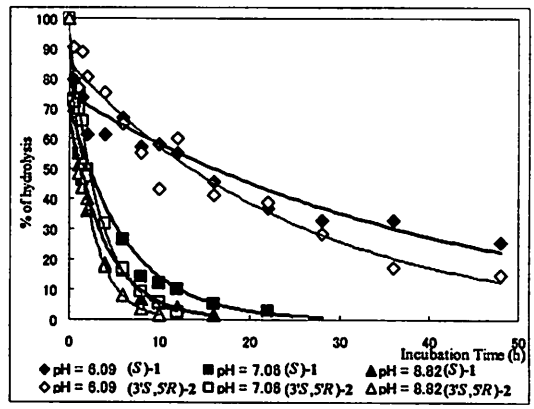


Fig. 3 Hydrolysis (decay) studies of (*S*)-**1** and (3'*S*,5'*R*)-**2**.

In summary, we have achieved the asymmetric synthesis of both enantiomers of the thalidomide metabolite **2** by enzymatic kinetic resolution catalyzed by lipase TL. The enantiomerically pure **2** shows resistance to racemization at physiological pH. A preliminary tube formation assay to assess the ability to inhibit angiogenesis suggests that racemic **1** and (*S*)-**1** is active and (*R*)-**1** and metabolites **2** failed to show anti-angiogenesis activity. Although this is a very preliminary experiment and more detailed biological evaluation is clearly required, the results are interesting because 1) metabolism is suggested to play amajor role in the teratogenicity of thalidomide, and 2) the anti-angiogenic activity of thalidomide correlates with the teratogenicity but not with the sedative or the mild immunosuppressive properties of thalidomide. Therefore, the teratogenicity of **2** could be dissociable. In addition, **2** possess TNF-α production-inhibitory activity. These experiments suggest that racemization-free enantomerically pure **2** would be effective for the treatment of diseases dependent on TNF-α production.

Acknowledgements

We thank Meito Sangyo Co., LTD, Novozymes Japan, Amano enzyme Inc. for their generous gift of enzymes, and Prof. H. Hara (Gifu Pharmaceutical Univ.) for anti-angiogenesis activity test.

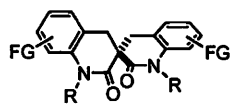
Yamamoto, T.; Shibata, N.; Takashima, M.; Nakamura, S.; Toru, T.; Matsunaga, N. and Hara, H. *Org. Biomol. Chem.* **2008**, *6*, 1540-1543.

2P-07

Enantioselective Synthesis of Spirobilactams via the Intramolecular Double Buchwald-Hartwig Reaction

* Kazuhiro Takenaka, Noriyuki Itoh, Hiroaki Sasai
The Institute of Scientific and Industrial Research, Osaka University
Mihogaoka, Ibaraki, Osaka, 567-0047, Japan
sasai@sanken.osaka-u.ac.jp

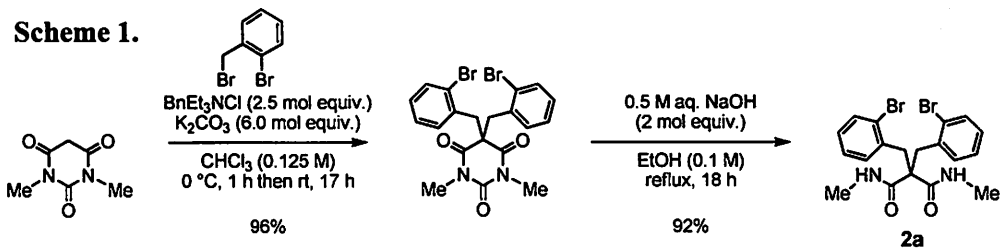
C_2-symmetric spiranes bearing stable axial chirality are promising structures for functional substances because they contain an entirely rigid spiro backbone which creates an effective asymmetric environment.[1] Although such chiral spiro compounds exhibit unique properties,[2] their applications to asymmetric synthesis have received relatively little attention. Apparently, a major drawback is the low availability of their enantiomerically pure forms, which could be obtained by a tedious resolution of racemates through fractional crystallization or chromatography. A catalytic asymmetric synthesis of C_2-symmetric spiro compounds would therefore provides highly practical method for their preparation.[3] Herein we report enantioselective synthesis of C_2-symmetric spirobilactams **1**[4] via the palladium/chiral phosphine-catalyzed Buchwald-Hartwig amidation.



1

As a key precursor of the desired spirobilactams **1**, 2,2-bis(2-bromobenzyl)-*N,N'*-dimethylmalonamide (**2a**) was designed and readily prepared from commercially available substrates. Thus, dialkylation of *N,N'*-dimethylbarbituric acid with 2-bromobenzyl bromide under phase transfer catalysis conditions, followed by hydrolytic ring-opening reaction gave the precursor **2a** in 88% yield (2 steps) as shown in Scheme 1.

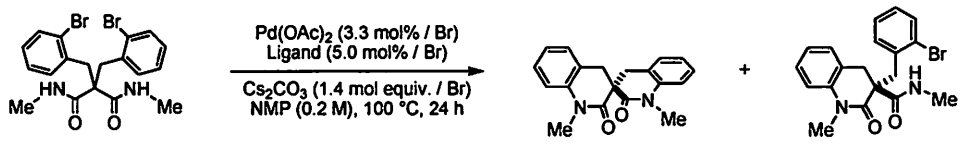
Scheme 1.



With the precursor **2a** in hand, we examined whether a Pd-catalyzed asymmetric intramolecular double cyclization would be indeed operative.[5] We were consequently pleased to find a quantitative formation of the spirobilactam **1a** with a moderate selectivity. Thus, treatment of **2a** with a catalytic amount of $Pd(OAc)_2$ (3.3 mol%/Br) and (*S*)-BINAP (5.0 mol%/Br) and an excess amount of Cs_2CO_3 (1.4 mol equiv./Br) as base in NMP (*N*-methyl-2-pyrrolidone) at 100 °C afforded **1a** in 99% yield with 55% ee (Table 1, run 1). This result prompted us to explore an efficient chiral ligand (Table 1). (*S*)-Tol-BINAP having 4-methylphenyl substituents on the phosphorus atoms in place of the phenyl groups of (*S*)-BINAP furnished a comparable result (run 2). Other axially chiral ligands, however, caused a lowering of the selectivity and/or the chemical yield (runs 3-6). Although a ferrocene-based chiral phosphine exhibited a

high catalytic activity, no enantioselectivity was observed (run 7). Other chiral ligands including a nitrogen-coordinating ligand, (*R,R*)-^{t}Bu-BOX, found to be ineffective (runs 8-10). Background reaction proceeded appreciably to give **1a** and the intermediate **1a'** in 19% and 66% yield, respectively (run 11).

Table 1. Ligand Screening[a]



Run	Ligand	Yield of **1a** / %[b] (Ee of **1a** / %)[c]	Yield of **1a'** / %[b] (Ee of **1a'** / %)[c]
1	(*S*)-BINAP	99 (55)	0 (−)
2	(*S*)-Tol-BINAP	97 (37)	0 (−)
3	(*R*)-MeO-BIPHEP	98 (26)	0 (−)
4	(*R*)-SEGPHOS	96 (14)	0 (−)
5	(*R*)-MeO-MOP	69 (*rac*)	25 (*rac*)
6	(*R*)-QUINAP	57 (*rac*)	38 (*rac*)
7	(*R*)-(*S*)-JOSIPHOS	99 (*rac*)	0 (−)
8	(*R*)-DIOP	53 (*rac*)	42 (*rac*)
9	(*R*)-^{i}Pr-PHOX	35 (*rac*)	60 (*rac*)
10	(*R,R*)-^{t}Bu-BOX	3 (*rac*)	68 (*rac*)
11	none	19 (−)	66 (−)

[a] The reaction was performed in NMP (0.5 mL) at 100 °C using **2a** (0.100 mmol), $Pd(OAc)_2$ (6.6 μmol), ligand (10 μmol), and Cs_2CO_3 (0.280 mmol). [b] Determined by ^{1}H NMR. [c] Determined by HPLC on a Chiralpak IB column.

After the extensive optimization of reaction conditions, the enantioselectivity of **1a** was improved to be 70% ee [$Pd(OAc)_2$ (3.3 mol%/Br), (*S*)-BINAP (6.7 mol%/Br), K_3PO_4 (1.4 mol equiv./Br) in DMPU (*N,N'*-dimethylpropylene urea, 0.4 M) at 100 °C]. It is noteworthy that **1a** was obtained in 87% overall yield from the starting material, *N,N'*-dimethylbarbituric acid, without chromatographic purification.

In summary, we have developed an asymmetric intramolecular double Buchwald-Hartwig amidation leading to optically active spirobilactams. We believe that our approach may open a new way to the practical synthesis of C_2-symmetric spiranes. Further studies on improvement of the enantioselectivity, the reaction mechanism, and synthetic utility of the products are currently in progress.

References and Notes

1 For a review, see: Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, ASAP.

2 We have been investigating the utility of C_2-symmetric spiranes, see: (a) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907. (b) Patil, M. L.; Rao, C. V. L.; Takizawa, S.; Takenaka, K.; Onitsuka, K.; Sasai, H. *Tetrahedron* **2007**, *63*, 12702.

3 (a) Takahashi, M.; Tanaka, M.; Sakamoto, E.; Imai, M.; Matsui, A.; Funakoshi, K.; Sakai, K.; Suemune, H. *Tetrahedron. Lett.* **2000**, *41*, 7879. (b) Tanaka, M.; Takahashi, M.; Sakamoto, E.; Imai, M.; Matsui, A.; Fujio, M.; Funakoshi, K.; Sakai, K.; Suemune, H. *Tetrahedron* **2001**, *57*, 1197. (c) Takahashi, T.; Tsutsui, H.; Tamura, M.; Kitagaki, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2001**, 1604. (d) Wada, A.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2007**, *9*, 1295.

4 Several racemic spirobilactams have been already reported, see: (a) Choi, H.-J.; Park, Y. J.; Kim, M. G.; Park, Y. S.; *J. Heterocyclic. Chem.* **2000**, *37*, 1305. (b) Choi, H.-J.; Park, Y. S.; Kim, M. G.; Park, Y. J.; Yoon, N. S.; Bell, T. W. *Tetrahedron* **2006**, *62*, 8696.

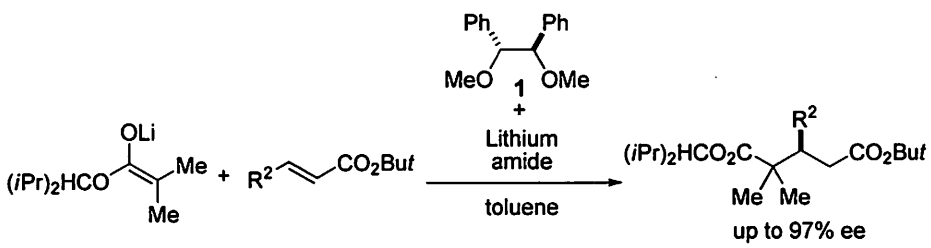
5 For a Pd-catalyzed cyclization of secondary amides, see: Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35.

2P-08

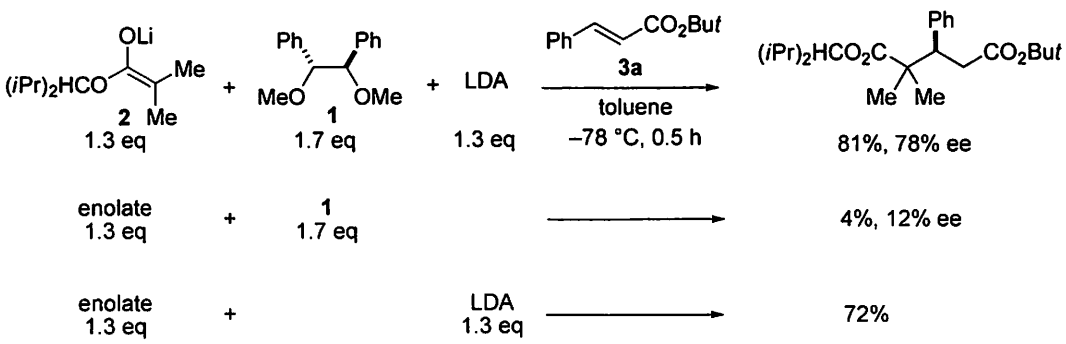
A ternary complex reagent for an asymmetric conjugate Michael addition of lithium ester enolates with enoates

Yasutomo Yamamoto,* Hirokazu Suziki, Yorinobu Yasuda, and Kiyoshi Tomioka
Graduate School of Pharmaceutical Sciences, Kyoto University,
Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
tomioka@pharm.kyoto-u.ac.jp

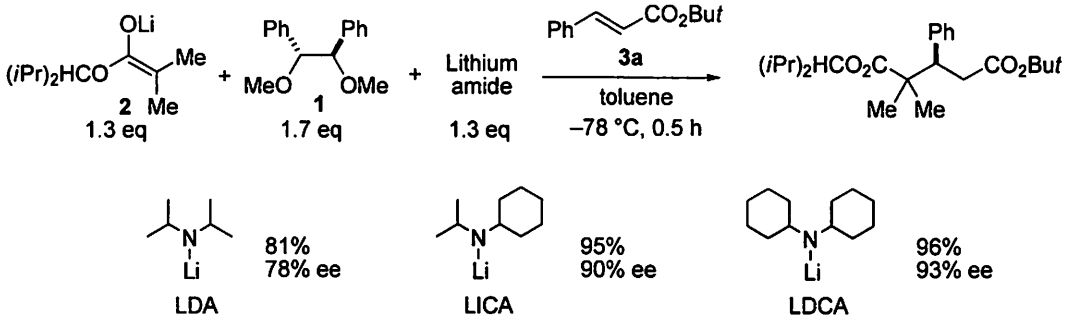
The activation of nucleophilic reagents has been the major challenge of organic chemistry. Lewis basic chiral ethereal or amino molecules are used as external ligands for generation of active nucleophiles in asymmetric reaction. We have developed a variety of chiral organic ligands for the activation of organometallics. Among these organoligands a chiral diether **1** has been shown to catalyze an asymmetric Mannich reaction of lithium ester enolate with imines by forming a ternary complex reagent which comprised lithium enolate-**1**-lithium amide. [1] Since the successful enantioselective asymmetric Michael reactions of lithium enolates are quite limited in number, we applied the ternary complex reagent into the Michael reaction of lithium ester enolates with unactivated simple enoates. We describe herein the highly enantioselective Michael reaction of a ternary complex reagent of a lithium ester enolate with enoates affording the Michael adducts in high enantioselectivity of up to 97% ee.



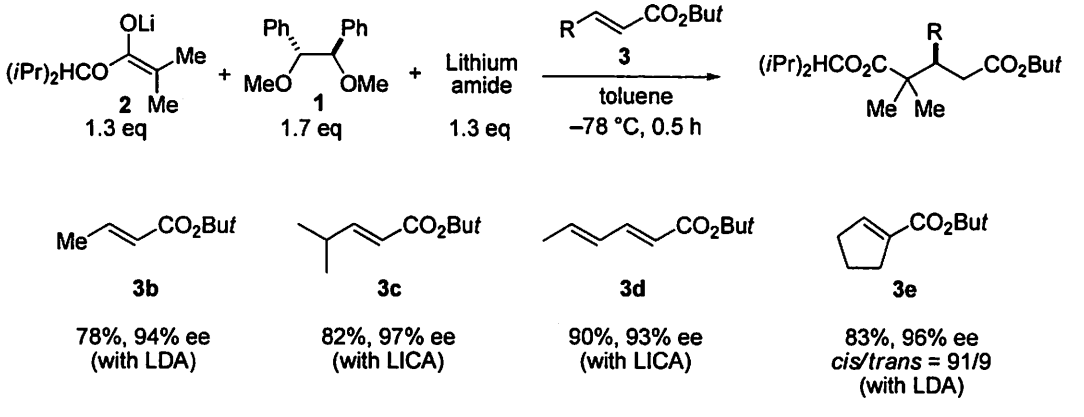
The higher reactivity of a ternary complex of lithium enolate became apparent from the reaction with cinnamate **3a** at –78 °C for 0.5 h to give Michael adduct with 78% ee in 81% yield. The absence of LDA resulted in the poorer reactivity to give 4% yield of adduct with 12% ee. A LDA assisted lithium enolate was also of powerful to give racemic Michael adduct in 72% yield.



The selection of a lithium amide was also found to be critical for the realization of high enantioselectivity. In the reaction with cinnamate **3a**, a ternary complex of lithium enolate **2-1**-LDA gave Michael adduct with 78% ee as above, while lithium isopropylcyclohexylamide (LICA) and dicyclohexylamide (LDCA)-mediated reaction realized higher selectivity of up to 93% ee.



The promisingly high reactivity of the ternary complex of the lithium enolate was also confirmed by the reaction with various enoates. Crotonate **3b** and 4-mehtyl-2-pentenoate **3c** were good reaction partners to afford their corresponding Michael adducts with 94% ee and 97% ee, respectively. The Michael addition with α,β,γ,δ-unsaturated ester **3d** was 1,4-selective to give adduct with 93% ee in 90% yield. Cyclic enoate **3e** was also compatible to afford the product with 96% ee.



We also carried out the NMR study of ternary complex reagent by using ^{6}Li-^{15}N doubly labeled LDA. ^{6}Li NMR of ternary complex reagent showed two set of doublet peaks, which indicate the incorporation of lithium amide to lithium enolate **2**-ligand **1** complex as shown in figure 1.

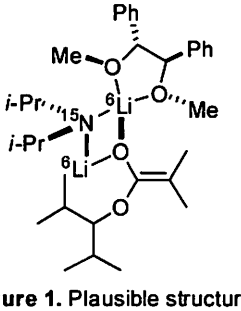


Figure 1. Plausible structure of ternary complex reagent

References

1) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061.

2P-09

Synthesis and spectroscopic properties of novel azo dyes derived from phthalimide

*Oh Tak Kwon, Hyun Yung Lee, Jae Hong Choi, Wilson Jung[⊠]
Department of Textile System Engineering, Kyungpook National University, 1370 Sankyuk-dong, Buk-gu, Daegu 702-701, Korea
bbmj2002@naver.com
[⊠]Eastwell Co. Ltd., 315, 1-Ma Shihwa-Kongdan, Shiheung-City, Kyunggi-Do, Korea

ABSTRACT

The series of azo dyes derived from phthalimide were prepared and characterized. The constitutions of new compounds were confirmed by the GC-MASS, ^{1}H NMR spectra and elemental analysis. The relationships between the structure of dyes and their absorption properties were investigated. The theoretical characteristics of electronic transition states were also studied by PPP-MO method.

INTRODUCTION

The demand for environmentally friendly dyes of high wet fastness on polyester is increasing [1]. To respond such requirement, novel azo dyes were prepared and characterized their spectroscopic properties.

EXPERIMENTAL

General information

The absorption spectra were measured in DMF on a Evolution 300 UV-Visible Spectrophotometer (England, Thermo). ChemBrain was used to calculate UV/Vis. spectrum based on a modified PPP SCF-CI-MO model.

Synthesis of dye 1-2

Sodium nitrite (0.14g) was added gradually to 2ml of conc. H_2SO_4 with stirring. The solution was cooled and 4ml of 1:5 mixed acid (1 part by volume propionic acid to 5 parts by volume acetic acid) was added below 15℃. 4-Amino-*N*-benzylphthalimide (0.50g, 0.002mole) was added to this mixture, then followed by addition of 4ml of 1:5 mixed acid below 5℃. The reaction mixture was stirred at 0-5℃ for 2 hr. The corresponding couplers (0.002mole) were dissolved in 20ml of 1:5 mixed acid.

The relevant couplers for dye 1 and dye 2 are followed,

N,N-Diethylaniline (Dye 1), 3-(*N,N*-Diethylamino)acetanilide (Dye 2)

Diazonium solution prepared was then added dropwise to coupler solution below 10℃. The pH of coupling mixture was maintained by the addition of ammonium acetate and allowed to stand for 1hr. The product was precipitated by the addition of water, then collected by filtration, washed with water and dried in dry-oven.

Synthesis of dye 3-4

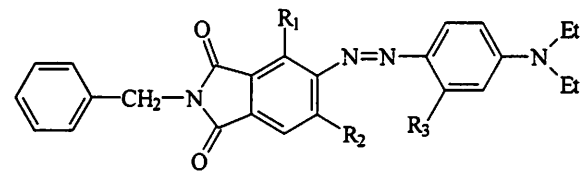
4-amino-3,5-dibromo-*N*-benzylphthalimide (0.82g, 0.002mole) was diazotized and coupled with 0.002 mole of each of the corresponding couplers as described in synthesis of dye 1-2.

The relevant couplers for dye 3 and dye 4 are followed,

N,N-Diethylaniline (Dye 3), 3-(*N,N*-Diethylamino)acetanilide (Dye 4)

Table 1 Chemical structure of synthesized dye 1-4.

Dye	R^1	R^2	R^3
1	H	H	H
2	H	H	$NHCOCH_3$
3	Br	Br	H
4	Br	Br	$NHCOCH_3$



RESULTS

Comparison of the observed absorption maximum with the calculated value

Table 2 λ_{max} and ε_{max} values of dye 1-4.

Dye	λ_{max} (nm)		ε_{max}
	Exp.	Calc.	(DMF)
1	494	491	38609
2	512	513	40615
3	441	491	44653
4	473	511	28105

The observed λ_{max} values and the calculated results are shown in Table 2. The PPP-MO method predicts λ_{max} accurately for dye 1-2. However, the presence of dibromo group resulted unacceptable predictions for dye 3-4.

CONCLUSIONS

4 kinds of disperse dyes have been synthesized in 54~81% yield. Their absorption maxima ranged in 441~512nm with ε_{max} values of 28,000~44,000.

REFERENCES

[1] Koh J, Greaves AJ, Kim JP; *Dyes and Pigments*, **56**, p69-81 (2003).

2P-10

Synthesis of alkali-clearable phthalimidyl dyes and their colorimetric properties

Hyun Young Lee, Jae Hong Choi, Jeong Min Jeon, Wilson Jung[c]
Department of Textile System Engineering, Kyungpook National University, 1370 Sankyuk-dong, Buk-gu, Daegu 702-701, Korea
mnm007@naver.com
[c]Eastwell Co. Ltd., 315, 1-Ma Shihwa-Kongdan, Shiheung-City, Kyunggi-Do, Korea

ABSTRACT

In this study, 9 azo disperse dyes based on phthalimide were synthesized including their precursors. The chemical structures of the dyes and the corresponding precursors were analyzed by the GC-MASS, ^{1}H NMR spectra and elemental analysis. The dye ability on PET, such as step dyeing and build-up properties, and color fastness were examined using conventional exhaust dyeing procedures these indicated their excellent wash and rubbing fastness.

INTRODUCTION

In recent wash fastness has been becoming as an important requirement of disperse dyes, moreover test standards have been also changed more and more strictly. Therefore the improved wash fastness of disperse dye should be of interest. In this study 9 phthalimide azo dyes were synthesized including their intermediates, followed by corresponding dyeing and color fastness tests.

EXPERIMENTAL

Nine phthalimide azo disperse dyes and corresponding precursors were synthesized through 5 steps. Their chemical structure were analyzed by the GC-MASS, ^{1}H NMR spectra and elemental analysis.[1)2)3)]

Both regular PET and micro fiber PET were dyed using synthesized dyes by the dyeing program, shown in Figure 1. After R/C and heat setting, some color fastness, such as wash, rubbing, light, were tested. Exhaustion yields were calculated from UV-Vis. absorbance data of the initial dyes and the residual dyes contained in dyeing solutions. M&S C4A and AATCC 16 methods were used for wash and light fastness test, respectively.

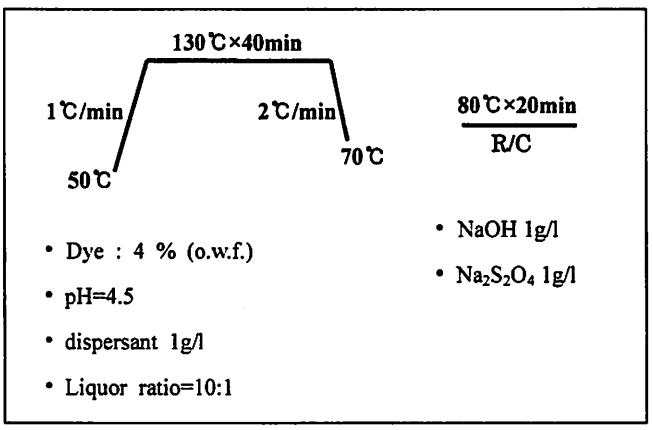
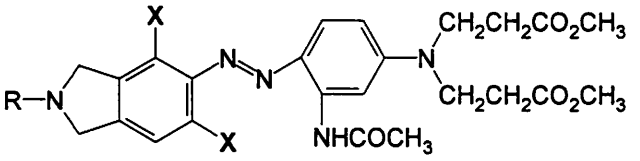


Figure 1 Dyeing program of PET fabric

RESULTS

The structure of synthesized dyes and their absorption maxima are shown in Figure 2. Exhaustion yields and fastness results of 9 disperse dyes on regular PET and micro fiber PET are given in Table 1 and Table 2, respectively. Dye 1, 3, 4 and 6 showed high Exhaustion Yield above 90% except dye 2, 5. All samples

show excellent wash and rubbing fastness over 3 grade. The light fastness of dye 3 and dye 6 shows higher result than all dyes.



Dye	R	X	λ_{max}(nm)	ε_{max}	Exhaustion yields(%)
Dye 1	$CH_3(CH_3CH_2)CH$	H	508	49440	87.04
Dye 2	$CH_3CH_2CH_2CH_2$	H	510	66360	67.90
Dye 3	$CH_3(CH_3CH_2)CH$	Br	471	33090	73.55
Dye 4	$CH_3CH_2CH_2CH_2$	Br	509	27890	78.41
Dye 5	$CH_3(CH_3CH_2)CH$	CN	602	38650	65.66
Dye 6	$CH_3CH_2CH_2CH_2$	CN	566	28400	75.10

Figure 2 The structure of synthesized dyes and their UV-absorbance and exhaustion yield

Table 2 Results of fastness tests for dyed PET and microfiber PET

Dye	Regular PET			Microfiber PET		
	Wash fastness	Rubbing fastness		Wash fastness	Rubbing fastness	
		Dry	Wet		Dry	Wet
Dye 1	3-4	4-5	3-4	3	4	3-4
Dye 2	4-5	4	4	4	4	3-4
Dye 3	4	4-5	4-5	3	4-5	4-5
Dye 4	3-4	4	4	3-4	4	4-5
Dye 5	4	4	4	3	4	3-4
Dye 6	3-4	4-5	4-5	3-4	4	4

CONCLUSIONS

Exhaustion yield of synthesized dyes are about 70% and their wash and rubbing fastness show over 3 grade. Dye 3 and dye 6 also show comparatively higher light fastness.

REFERENCES

[1] J.S. Koh, J.P. Kim, *Dyes and Pigments*, **37**, No.3, p.265-272 (1998).

[2] X. Collin, J.M. Robert, *Eur. J. Med. Chem.*, **36**, p.639-649 (2001).

[3] J.H. Choi, Dept. of Colour Chemistry and Dyeing, Leeds University, Ph.D. Thesis (1995).

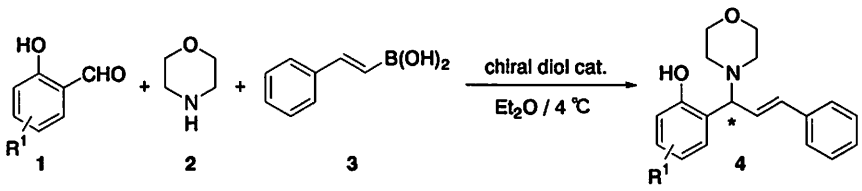
2P-11

Catalytic Enantioselective Petasis Reaction

Naoto Inakoshi,*[1)] Eric N. Jacobsen
Department of Chemistry and Chemical Biology, Harvard University
12 Oxford Street, Cambridge, MA 02138, USA
Inakoshi.Naoto@mm.mt-pharma.co.jp

Multicomponent reaction (MCR)[2)], in which three or more components react in one step to afford complex structure in an efficient manner, is one of the most attractive research area in modern organic synthesis. Due to this advantage, MCR possibly acts as a powerful tool in the pharmaceutical, agrochemical, and fine chemical industries in both of the library synthesis at the discovery stage and the large-scale synthesis at the development stage. Furthermore, its asymmetric variant is to be especially desirable for the syntheses of biologically active compounds.

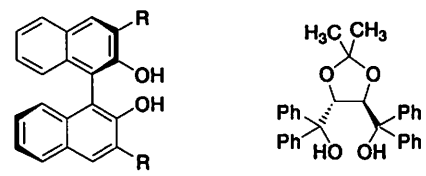
Among MCRs, Petasis reaction[3)], three-component reaction of carbonyl compound, amine, and boronic acid, is an attractive approach for the synthesis of chiral amine derivatives due to its mild reaction conditions and the availability of a variety of boronic acids. Herein, we would like to describe highly enantioselective Petasis reaction of salicylaldehyde derivatives **1** catalyzed by chiral diol (Eq. 1).



(1)

As a result of catalyst screening, chiral binaphthol derivative **5a** (Figure 1) was found out as a promising hit. With 10 mol% loading of the catalyst in Et_2O the allylamine product **4a** (R^1=H) was obtained in 84% ee. Catalyst optimization study clarified that the substituents on the phenyl rings at 3,3'-positions are influential in the enantioselectivity. Catalyst **5b** containing electron-withdrawing groups gave the highest ee (88% ee), while sterically hindered **5c** afforded the product in almost racemic form. TADDOL **6** resulted in no significant ee. The adjacent hydroxyl group to aldehyde plays an essential role in this catalytic process. No coupling product was obtained in the reaction of either 4-hydroxybenzaldehyde or 2-methoxybenzaldehyde. From the practical point of view, it should be emphasized that the 1:1:1 ratio of the starting materials realized very good yields.

Figure 1



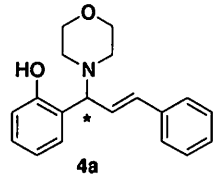
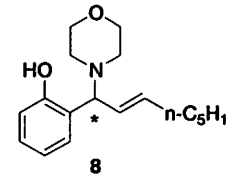
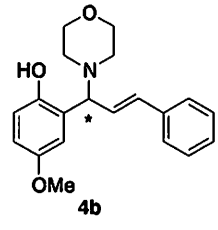
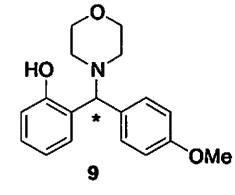
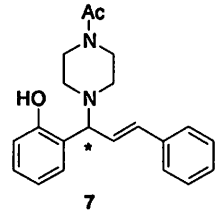
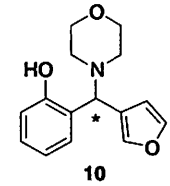
5a (R=C_6H_5)
5b (R=3,5-$(CF_3)_2$-C_6H_3)
5c (R=2,4,6-(i-C_3H_7)$_3$-C_6H_2)

6

Through the optimization of other reaction parameters and experimental procedure, the enantioselectivity was improved to 91% ee (Table 1, entry 1).

The substrate scope was summarized in Table 1. A wide variety of allylamine products were obtained in good yields together with high enantioselectivities (entries 1-4). With respect to the boronic acid component, aryl- and heteroarylboronic acids participated in the reaction as well as 2-substituted vinylboronic acids (entries 5 and 6).

Table 1. Enantioselective Petasis reaction[a]

entry	product	yield, %	ee, %	entry	product	yield, %	ee, %
1	 4a	92	91	4	 8	77	84
2	 4b	81	91	5	 9	85	98
3	 7	83	89	6	 10	61	99

a Reaction conditions: catalyst **5b** (10 mol%) / Et_2O / 4 ℃.

In summary, we have described highly enantioselective Petasis reaction of salicylaldehyde derivatives catalyzed by chiral binaphthol. The reaction proceeds smoothly under the mild conditions without excessive amounts of any starting materials. Details of the substrate scope study will be presented at the poster session.

References and notes

1) Current Address: Process Chemistry Research Department, CMC Research Center, Mitsubishi Tanabe Pharma Corporation. 14 Sunayama, Kamisu, Ibaraki 314-0255, Japan.
2) Zhu, J., Bienayme, H., Eds. *Multicomponent Reactions*, Wiley-VCH: Weinheim, 2005.
3) (a) First report: Petasis, N. A.; Akiritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583. (b) Petasis, N. A.; Zabianov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (c) Achiral Petasis reaction of salicylaldehyde: Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *34*, 539.

2P-12

Enantioselective Conjugate Addition of Hydrazines to α,β -Unsaturated Imides. Synthesis of Chiral Pyrazolidinones

Takahiro Soeta[A]*, Mukund P. Sibi[B]

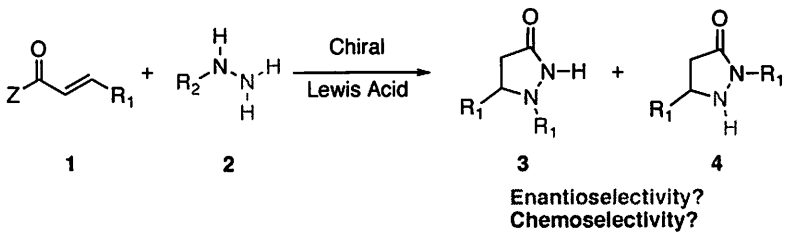
[A]Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa, 920-1192

[B]Department of Chemistry, North Dakota State University, Fargo, ND, 58105

soeta@cacheibm.s.kanazawa-u.ac.jp

Enantioselective conjugate addition of heteroatom nucleophiles to electron-poor acceptors continues to attract attention from the synthetic community. The addition of bisnucleophilic donors such as hydroxylamines and hydrazines provide direct access to pharmaceutically relevant heterocycles. Literature suggests that enantioselective conjugate addition of N-monosubstituted hydroxylamines should proceed with good enantioselectivity since there is a clear differentiation of nucleophilicity between the two donor atoms. While diastereoselective addition of chiral hydrazines with achiral acceptors and *vice versa* have been reported in the literature there are no reported examples of the enantioselective variant.

Furthermore, enantiomerically enriched pyrazolizinones can serve as versatile chiral building blocks. Only one example for the synthesis of chiral pyrazolidinones has been reported albeit utilizing a kinetic resolution to install the requisite stereogenicity. Herein, we report the straightforward asymmetric synthesis of chiral 3-pyrazolidinones with high enantioselectivity and in good yield via Lewis acid catalyzed chemo- and enantioselective addition of hydrazines to α,β-unsaturated imides (Scheme 1). In addition, we have demonstrated that the conjugate addition proceeds with high chemoselectivity using bisnucleophilic hydrazine donors (formation of **3** over **4**, Scheme 1), thus providing direct access to chiral pyrazolizinones.



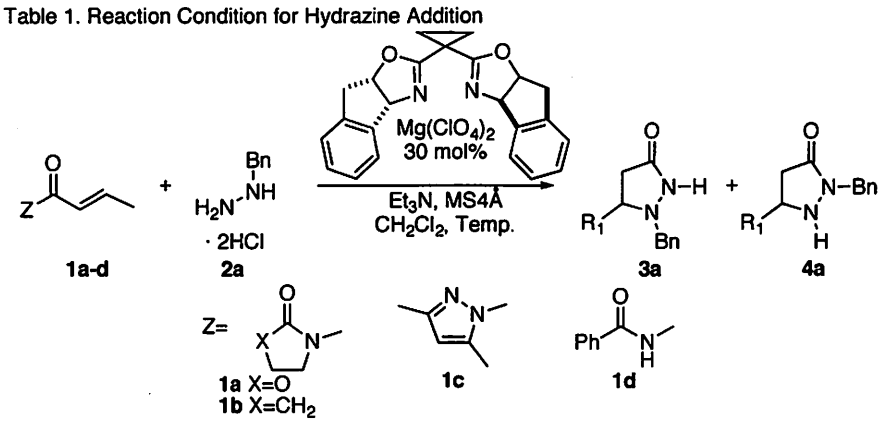
Scheme 1. Enantioselective Conjugate Addition of Hydrazines to α,β-Unsaturated Carbonyl Compounds.

We first sought to identify conditions that would allow for selective conjugate addition of hydrazines. We examined the addition of monosubstituted hydrazine, benzylhydrazine to acylated oxazololidinone **1a** in the presence of a chiral Lewis acid derived from **5** and magnesium salt (Table 1). In these reactions, after conjugate addition, the achiral template is cleaved resulting in the formation of the pyrazolidinone products. Magnesium iodide, triflates and triflimides gave approximately a 1:1 mixture of **3a** and **4a** in good overall yield, however with low enantioselectivity (6-20% ee). In contrast, magnesium perchlorate

proved to be a more viable Lewis acid and led to improved enantioselectivity for both isomers (entry 1).

Next, we investigated the achiral template on the substrates. A standard set of conditions was invoked to better evaluate the template. These conditions involved the application of the chiral Lewis acid prepared from **5** with magnesium perchlorate, benzylhydraine, trethylamine, and molecular sieves. Replacing the oxazolidinone template (**1a**) with that of a pyrrolidinone (**1b**) or dimethyl pyrazole (**1c**) did not lead to improved selectivity (entry 2,3). In contrast, utilization of an imide template, benzimide **1d**, afforded high levels of selectivity for major isomer at room temperature (entry 4). At lower temperatures significant improvement in both the chemoselectivity and enantioselectivity was observed (entry 5,6). It is interesting to note that at lower temperature the reaction is better able to discriminate between the nucleophilicity of the hydrazine nitrogens. Thus, the more nucleophilic and bulky nitrogen adds selectivity to the β-carbon. As can be expected, lower temperature also provides improved enantioselectivity. Other structural changes to the imide template did not provide improved enantioselectivity.

Table 1. Reaction Condition for Hydrazine Addition



Entry	Substrate	Temp. °C	Yield %	3a/4a	3a ee %	4a ee %
1	**1a**	room temp	92	45:55	55	56
2	**1b**	room temp	84	69:31	67	52
3	**1c**	room temp	93	70:30	58	55
4	**1d**	room temp	86	59:41	69	47
5	**1d**	−30	87	92:8	79	40
6	**1d**	−50	92	98:2	84	52

Having secured a highly selective method for conjugate hydrazine addition we explored the scope of the substrates and the reagents. Changing methyl substituent in **1e** to an ethyl, isopropyl, or phenyl group on the β-carbon gave the corresponding products in similar yields and selectivity. Furthermore, reaction of methyl and isopropyl hydrazines proceeded with high selectivity providing the corresponding products with 99% ee. These results demonstrate that the conjugate addition reaction of hydrazines to α,β-unsaturated imides is conducive to a variety of reagents and substrates.

In conclusion, we have developed a novel enantioselective method for the preparation of pyrazolizinones in a highly enantioselective fashion. Further investigation of these products as both chiral auxiliaries and ligand is ongoing in our laboratory.

2P-13

The study of in-situ monitoring to radical polymerization process using by fiber mid infrared spectroscopy.

Daisuke Sasakura,* Kazuo Osaki, Tsuyoshi Miura
Application Division ,Bruker Optics K.K.
1-6 ,Taito 1-chome, Taito-ku, Tokyo 110-0016,Japan
daisuke sasakura@bruker-optics.jp

1.Introduction

The radical polymerization has old history, and it is used many industrially. Especially this reaction is more clean compare to Olganometarics polymerization, and, more easy to control reaction. And so, radical reaction is notice from point view of the kinetics science, reaction mechanism of the organic chemistry and industrial reaction method.

The other hand, mid Infrared spectrometry (MIR) is well known to use for organic structural study. Because, MIR region is indicated to specific absorption indicated to organic substance. It is so called "Finger print spectrum". However, it was limited to application to in the laboratory. That reason comes from light property of MIR region. At first, in typically, process monitoring is need to the fiber probe measurement. However, MIR light region is not available Quartz and Grass fiber. In previous, chalcogenide was fiber using at probe application. However that material was very breakable, low through put, and narrow transmittance range. Therefore, it was difficult to use for real process monitoring by MIR, however, in recently, new type of fiber was developed for this probe application. This fiber name is PIR fiber. In the second reason, MIR region is high absorption against any organic compounds and water. This meaning, it is too difficult to measurement at transmittance. However, in recently, ATR (attenuated total refection) is available at such kind of probe application. It is big break thorough for process application.

This study will be suggested to process monitoring of radical polymerization under the "Finger print spectrum" and using by "ATR-PIR fiber probe".

2.PIR Fiber probe

The PIR fiber is made from AgClBrI solid solution. The production methods for crystalline silver halide fibers differ fundamentally from those used for fabrication of silica fibers. Core clad silver halide fibers are manufactured by direct or inverse hot extrusion of a composed bullet under compressed condition. Optimized parameter for the fiber extrusion combined with special crystal preparation technologies lead to a significant increase in fiber quality. Optical losses, in former times especially caused by micro voids, silver clusters, colloids and residual impurities are minimized by new technologies. These technologies start from ultra pure silver halide single crystalline material offering nowadays best optical and mechanical properties for polycrystalline silver halide fibers. These silver halide fibers show significantly better mechanical properties than the often-used brittle chalcogenide glass fibers. They are more flexible and non-brittle to even liquid nitrogen temperature. Although the theoretical estimations of minimum

fundamental optical losses in silver halides are 0.4 to 0.04 dB/km lower than in current silica glass fibers, the nowadays crystalline silver halide material show real optical losses some order of magnitude higher but less than 1 dB/m in the wavelength range from 4μm to 18μm, excellent for use with fiber length up to a few meters. (Standard fiber length is 1.5 m; whereas fiber lengths up to 4.5 m are available.)

2.ATR (attenuated total refection)

ATR (attenuated total refection) is a very common technique for infrared spectroscopy. First mentioned by N.J. Harrick in 1960 the success of the technique was limited until the 1990ties. This innovative technique is limited by its use in the sample compartment of the spectrometer and therefore the sample itself has to be placed into the spectrometer. Light guiding fibers are the solution to handle probe heads flexible and to run the measurement even in a laboratory reaction bulb. The two-reflection diamond ATR probe head with the excellent performance of MIR-silver halide fibers.

3.Instrument and Parameter.

MIR spectrometer was MATRIX-MF (Bruker Optics K.K. MIR fiber probe system) used. The detector was narrow band liquid nitrogen cooled MCT. The resolution was $4cm^{-1}$, scan time was 16scan.

4.Reaction measurement.

$CHCl_3$ as reaction solvent 50wt/%, styrene as monomer 50wt/%, AIBN as initiator 0.1wt/%, into the short flask. The reaction was in 55C. The measurement cycle was 30sec/1spectrum.Total measurement time was 5.9 hour, total number of spectrum was 700 spectrum. It was shown at Fig.1 as result, that result was subtraction of the initial time of spectrum from total result of spectrum. At $1389cm^{-1}$ (↑) was strongly noticed in this result.

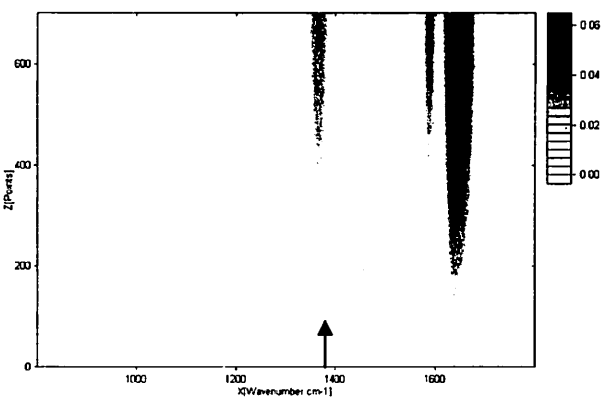


Fig.1 The 2D plot of spectrum of monitoring

This band assign to CH2- of symmetry strutting Alkenes in Styrene. It was shown that plot of Integration vs Time in Fig.2.

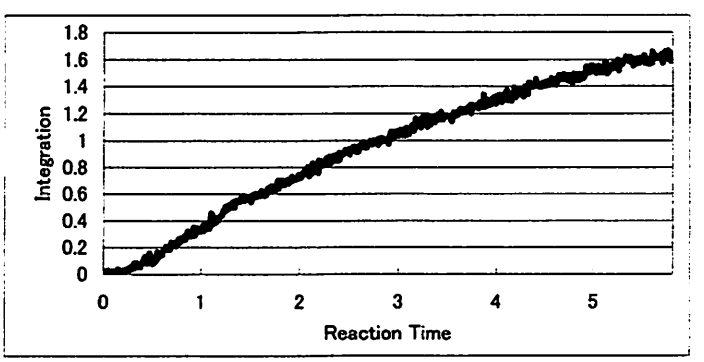


Fig.2 Trace plot of $1389cm^{-1}$

2P-14

Catalytic asymmetric hydrogenation using environment conscious new BINAP polymer

Yoshinori Takamatsu,[1]* Gakuto Goshima,[1] Naomi Takenaka,[1] Kenji Toribatake,[2] Hiroshi Shibaguchi,[2] Toyohiro Nagano,[2] Toyoshi Shimada[2]

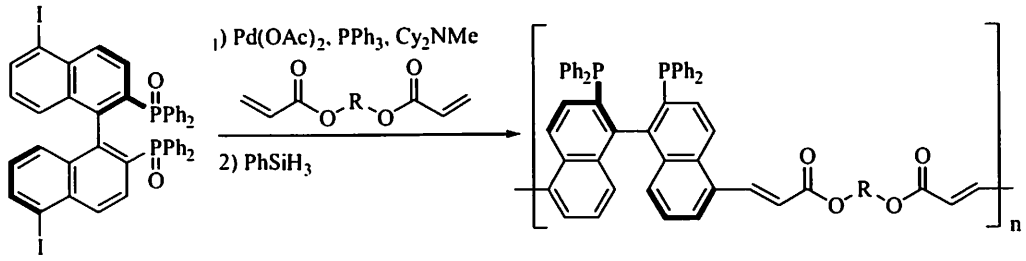
[1] Kyoeisha Chemical Co.,Ltd. Nara Laboratory. 2-5, 5-chome, Saikujo-cho, Nara 630-8453, Japan
y_takamatsu@kyoeisha.co.jp

[2] Nara National College of Technology. 22, Yata-cho, Yamatokoriyama, Nara 639-1080, Japan
shimada@chem.nara-k.ac.jp

Enantioselective catalysis has become an essential part in the production of chiral fine chemicals. The BINAP-Ru complex is quite a useful catalyst which shows high turn over number and excellent enantioselectivity in asymmetric hydrogenations of enamide, α,β-unsaturated carboxylic acid, and β-keto esters.[1] Recently, heterogenization of the BINAP ligand has attracted considerable attention,[2] which may provide a solution to the problem of separation and recycling of this precious chiral ligand. However, further developmental efforts are needed before the reaction can be practiced on a manufacturing scale because of difficult derivatization of BINAP with several steps and high cost.[3] Here we report the facile preparation of polymer BINAP ligand and its successful use for the ruthenium-catalyzed asymmetric hydrogenation of itaconic acid and methyl acetoacetate.

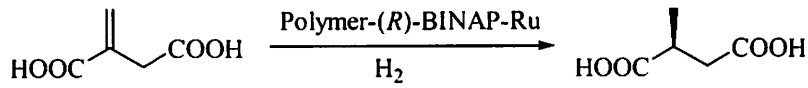
The synthetic pathway to the polymer-BINAP is straightforward as shown in Scheme 1. Mizoroki-Heck reaction of 5,5`-diiodoBINAP dioxide[4] with bifunctional acrylates gave the desired BINAP dioxide polymer and successive reduction with phenyl silane afforded BINAP polymer.

Scheme 1.



Ru-BINAP polymer complex obtained by the treatment of polymer BINAP with $Ru(cod)(h^3\text{-}(CH_2)_2CHCH_3)_2$ was successfully used for catalytic asymmetric hydrogenation to give the corresponding hydrogenated product of 91% ee in quantitive yield and reused for seven times of hydrogenation with high activity and enantioselectivity (Table 1). These enantiomeric excesses (up to 91% ee) are significantly higher than that (56% ee) of previously reported same reaction.[3]

Table1. Recycling and Reuse of Polymer-(*R*)-BINAP-Ru Catalyst for Asymmetric Hydrogenation of Itaconic acid.[a]

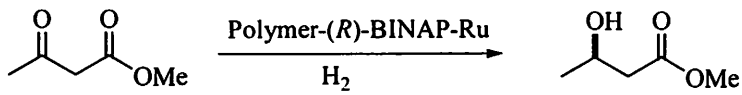


run	1	2	3	4	5	6	7
ee (%)[b]	91	89	89	87	86	85	81
yield (%)[c]	100	97	98	98	96	93	99

[a] The hydrogenation was carried out in 0.5M solution of itaconic acid (0.31mmol) in THF/EtOH under 3 atm of hydrogen at 50 ℃ in the presence of 2 mol% catalyst. [b] Determined by GC analysis of dimethyl methylsuccinate using Chiraldex G-TA(30 m × 0.25 mm) column. [c] Isolated yield.

The BINAP-polymer has been applied to the catalytic asymmetric hydrogenation of methyl acetoacetate, and the results are summarized in Table 2. Excellent ees of *β*-hydroxyester were obtained, although third run showed slight decrease of yield.

Table 2. Recycling and Reuse of Polymer-(*R*)-BINAP-Ru Catalyst for Asymmetric Hydrogenation of Methyl Acetoacetate.[a]



run	1	2	3
ee (%)[b]	95	97	95
yield (%)[c]	100	98	86

[a] The hydrogenation was carried out in 1.0 M solution of Methyl Acetoacetate in MeOH/Acetone under 15 atm of hydrogen at 70 ℃ in the presence of 2 mol% catalyst. [b] Determined by GC analysis using Chiraldex G-TA (30 m × 0.25 mm) column. [c] Isolated yield.

In summary, BINAP-polymer for practical use was easily prepared starting from commercially available BINAP. Ru complex with the resulting polymer exhibited versatile use in the asymmetric hydrogenation of C=C, and C=O bonds and showed excellent asymmetric induction abilities. Furthermore, the reuse with BINAP-polymer will find wide application in transition-metal-catalyzed asymmetric reactions even in industrial-scale synthesis.

References

1) Noyori, R. Angew. Chem. Int. Ed. **2002**, *41*, 2008.
2) (a) Fujii, A.; Sodeoka, M. Tetrahedron Lett. **1999**, *40*, 8011. (b) Otomaru, Y.; Senda, T.; Hayashi, T. Org. Lett. **2004**, *6*, 3357. (c) Fan, Q. H.; Ren, C. Y.; Yeung, C. H.; Hu, W. H.; Chan, A. S. C. J. Am. Chem. Soc. **1999**, *121*, 7407.
3) Bayston, D. J.; Fraser, J. L..; Ashton, M. R..; Baxter, A. D.; Polywka, M. E. C.; Moses, E. J. Org. Chem. **1998**, *63*, 3137.
4) Shimada, T.; Suda, M.; Nagano, T.; Kakiuchi, K. *J. Org. Chem.* **2005**, *70*, 10178.

2P-15

Improving the enantioselectivity of *Candida atarctica* lipase B for kinetic resolution of butyl tetrahydrofuran-2-carboxylate

* Sojung Park, Suhyun Jung, Seongsoon Park
249-1 Dongsung-dong 3-ga, Sungbuk-gu,Seoul 136-742, Korea
Sojung-letter@hanmail.net

Preparation of enantiomerically pure compounds is one of the most active fields is synthetic chemistry because chirality is a key factor in the efficiency of therapeutic agents. And production of single enanriomers of chiral intermediates has become increasingly important in pharmaceutical industry. The enzymatic catalysis has advanced an alternative tool for the synthesis of enantiopure compounds because enzymes have remarkable chemo-, regio-, and stereo selectivity and high catalytic efficiency.

Candida antartica lipase B is an efficient catalyst for preparation of enantiopure compounds via kinetic resolution. CAL-B belongs to the α/β hydrolase fold family with a conserved catalytic triad consisting of Ser, His, Asp/Glu. CAL-B is used in many industrial applications because of its high enantioselectivity, wild-range of substrates, thermal stability, and stability in organic solvents. It has proven to be a particularly useful biocatalyst with good stability and activity that catalyze a diverse range of reactions.

Enantiopure tetrahydrofuran-2-carboxylic acid is an important intermediate as well as a building block in the pharmaceutical industry and research. The (R)-Tetrahydrofuran-2-carboxylic acid was first incorporated into a penem skeleton to give rise to furopenem, which is a clinically efficent non-natural β-lactam antibiotic. Kinetic resolution could be one of the methods to produce the enantiopure tetrahydrofuran-2-carboxylic acid. Biocatalyst can be used to resolve tetrahydrofuran-2-carboxylic acid. However, most biocatalysts including CAL-B have low enantioselectivity toward butyl tetfahydrofuran-2-catboxylate.

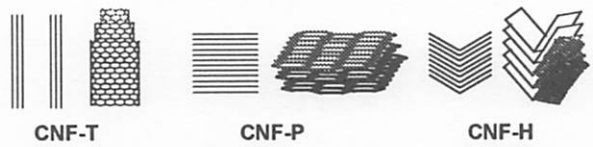
In this study, we present improving the enantioselecitivity of CAL-B for kinetic resolution of butyl tetrahydrofuran-2-carboxylate by rational design. We have designed to construct a favorable interaction via hydrogen bonding between a residue and one of the enantiomers. For this, we have selected two residues D134 and V190. The D134 residue was selected to introduce an amino acid for providing an hydrogen bonding and the V190 residue for creating space to accept the side chain of the introduced residue. We introduced Lys, Asn, and Gln instead of D134 and Gly instead of V190. The produced double mutant enzymes, such as D134K/V190G, D134N/V190G, and D134Q/V190G, were tested for the resolution of tetrahydrofuran-2-carboxylic acid.

2P-16

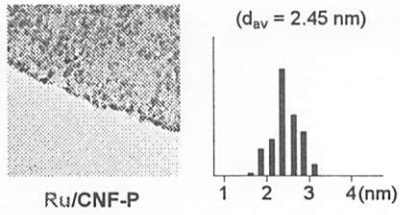
Carbon Nanofiber-Supported Metal Nanoparticles as Efficient Catalysts for Hydrogenation Reactions

Yukihiro Motoyama,* Mikihiro Takasaki, Kenji Higashi, Keita Tsuji, Hideo Nagashima
Institute for Materials Chemistry and Engineering,
Graduate School of Engineering Sciences, Kyushu University
6-1, Kasuga-koen, Kasuga, Fukuoka 816-8580, Japan
motoyama@cm.kyushu-u.ac.jp

Transition metal-immobilized materials are widely used as heterogeneous catalysts for the production of chemicals in both laboratory and industrial scales. Activated carbon (AC) has been the support of choice for metal anchoring, however, there still remain drawbacks which should be improved; e.g. less-reproducibility for the catalyst performances and the deactivation of the catalyst by sintering and/or leaching of the metallic species. These drawbacks can be attributed to ill-controlled structures of AC having a variety of surface and pore structures. In this sense, carbon nanofibers (CNFs) are potentially attractive solid supports for the heterogeneous catalysts since they have nano-level-controlled surface structures. The CNFs are classified into three types: graphite layers are parpendicular (platelet: CNF-P), parallel (tubular: CNF-T), and stacked obliquely (herringbone: CNF-H). Of particular interest is the high content of the reactive "nano-size edge" sites of the CNF-P and CNF-H, which is expected to interact with nano-size metal and contributes to the stabilization of the nanoparticles on the surface. We wish to report here a method for the transition metal nanoparticles on the CNFs (M/CNFs) [M = Ru, Pd, Pt] using zero-valent organometallic precursors. The catalytic properties in the hydrogenations are also presented.



The Ru/CNFs were readily prepared by thermal decomposition of $Ru_3(CO)_{12}$ in refluxing toluene in the presence of CNFs. Preparation of Pt and Pd/CNFs was achieved successfully by the reaction of $Pt(dba)_2$ or $Pd_2(dba)_3{\bullet}CHCl_3$ with CNFs in toluene. The location of Ru nanoparticles is attributed to the fine structures of CNFs: on the edge of the graphite layers (CNF-P), in the tubes and on the surface (CNF-T), and between the layers and on the surface (CNF-H). The Ru content was constant in several samples of Ru/CNF-P (1.6–1.7 wt %), however, that of the Ru/CNF-H and Ru/CNF-T was not very reproducible (1.1–3.8 wt % for Ru/CNF-T and 1.1–1.6 wt % for Ru/CNF-H). On the CNF-P, small and spheroidal species (d = 2.5 ± 1 nm) homogeneously dispersed selectively on the edge of the graphite layers. In sharp contrast, TEM images of the other Ru/CNFs showed that a majority of particles was in the size range of 2–4 nm; however, some large Ru masses (10 < d < 150 nm) were observed to coexist. The Pt and Pd particles could be highly dispersed on the surface in all cases with particle size range of 1–3 nm for Pt and 3–7 nm for Pd.

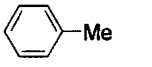
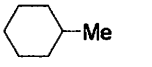
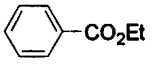
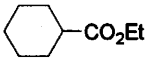
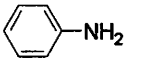
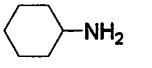
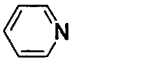
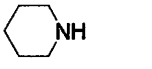
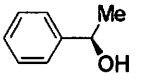
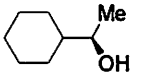
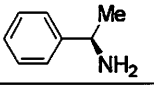
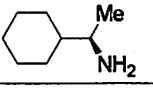


Among these M/CNFs, the Ru/CNF-P catalyst showed high catalytic efficiency for the functionalized benzene derivatives with excellent chemoselectivity. The TOFs are often comparable to the Pd/SiO_2-immobilized Rh complex, which is the most efficient catalyst reported by Anigelici et al., and even higher in some cases. In the reduction of benzoate, neither hydrogenolysis product nor the product formed from the reduction of the carbonyl group was detected. Similarly, the optically active (*R*)-1-phenylethyl alcohol is a good substrate to check the possible epimerization and hydrogenolysis of the benzylic C–O bond during the hydrogenation; however, exclusive formation of (*R*)-1-cyclohexylethyl alcohol (>99% ee) in quantitative yield completely ruled out this possibility.

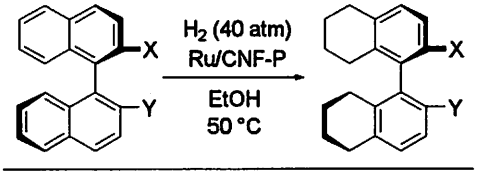
The Ru/CNF-P catalyst was also useful for production of derivatives of 5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyls (H_8-binaphthyls). In all cases, the partial hydrogenation proceeds at 50–100 °C to afford the corresponding H_8-product in almost quantitative yield without loss of optical purity. The reduction of ester function was not observed under these conditions. It is noteworthy that the present procedure is useful for the production of oily binaphthyls, in which optical purity of the partially racemized product cannot be improved by recrystallization. Optically pure H_8-BINOL-MOM_2 is a typical compound of such oily binaphthyls, which can be effectively synthesized by this method in high yield.

Pt/CNF-P was effective in the chemoselective hydrogenation of functionalized nitroarenes to the corresponding substituted anilines. Hydrogenation of halogenated nitrobenzene derivatives were achieved with high chemoselectivity with Pt/CNF-P by adding *n*-octylamine (10 mol % for halonitrobenzene). Nitro-selective reduction of other nitroarenes having carbonyl and benzyloxy groups proceeded even in the absence of *n*-octylamine.

Ru/CNF-P-catalyzed reduction of various arenes

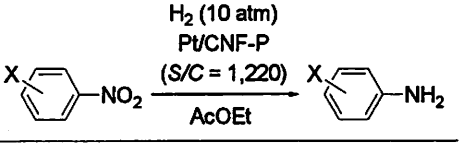
substrate	product	TON [TOF]
		35,800 [14,300]
		8,500 [1,700]
		13,900 [600]
		13,400 [560]
		5,300 [1,750]
		9,300 [390]

TON = mol (substrate)/mol (Ru); TOF = TON/h.



substrate	*S/C*	time (h)	yield (%)
X, Y = OH	300	7	>95
	1,400	48	>95
X = OH, Y = OPiv	300	7	>95
X, Y = OMe*	300	7	>95
X, Y = OMOM	300	7	>95
X, Y = NH_2*	150	24	83

* At 100 °C.



substrate	conditions	selectivity (%)
X = *p*-Cl*	rt, 2 h	> 99.9
m-Cl*	rt, 2 h	99.9
o-Cl*	rt, 4 h	> 98
p-Br*	rt, 4 h	99.8
p-I	50 °C, 4 h	97.0
CO_2Et	rt, 4 h	> 99.9
COMe	rt, 4 h	> 99.9
OBn	rt, 4 h	> 99.9

* 10 mol% of *n*-$C_8H_{17}NH_2$ was added.

References:

(1) *Chem. Lett.* **2006**, *35*, 876. (2) *Chem. Asian J.* **2007**, *2*, 1524. (3) *J. Org. Chem.* **2007**, *72*, 10291. (4) *Org. Lett.* **2008**, *10*, 1601.

2P-17

The Polymer-Supported Dirhodium(II) Catalyst for Asymmetric Intramolecular C–H Insertion Reactions

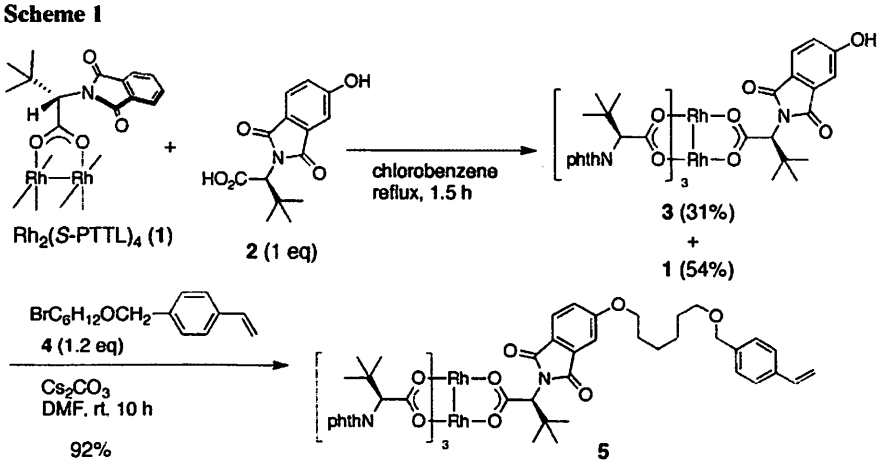
Koji Takeda,* Tadashi Ohara, Masahiro Anada, Hisanori Nambu, Shunichi Hashimoto
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812 (Japan)
hsmt@pharm.hokudai.ac.jp

The development of catalytic enantioselective C–C bond forming reactions has been a subject of intensive investigation in the field of synthetic organic chemistry. Among a variety of transition metal complexes used to catalyze a broad spectrum of transformations of α-diazocarbonyl compounds, chiral dirhodium (II) complexes have distinguished themselves as superior catalyst in C–H insertion that form C–C bonds in which a new stereogenic center is created at an unactivated carbon atom.[1]

Despite the potential of chiral dirhodium(II) catalysts, one of the fundamental problems for their industrial application is the need for efficient catalyst recovery and recycling, which arises from the relativity large quantity of very expensive catalyst (1 mol %) usually needed for these reactions. In this connection, there have already been some successful attempts to immobilize chiral dirhodium(II) complexes on solid supports through covalent linkages[2] or monocoordination to one of axial position of the catalyst.[3] Although these immobilized catalysts display similar high enantioselectivities to their homogeneous counterparts in some selected reactions, a major challenge in terms of catalyst activity, selectivity, recyclability and leaching still remains.

Independent of these strategies, our design for an effective immobilization of Rh_2(*S*-PTTL)$_4$ (**1**)[4] is based on the preparation of the monomer containing dirhodium(II) catalyst followed by copolymerization with styrene and cross-linker. Toward this goal, we selected *N*-4-hydroxyphtaloyl-*S*-*tert*-leucine (**2**) as a replaceable ligand. Treatment of the ligand with Rh_2(*S*-PTTL)$_4$ (**1**) in refluxing chlorobenzene gave an equilibrium mixture of the desired dirhodium(II) complex (**3**) and Rh_2(*S*-PTTL)$_4$ (**1**), which were readily separable by silica gel chromatography (Scheme 1). The desired complex was alkylated with the bromide (**4**) carrying a terminal styryl group to form the monomer (**5**) in high yield.

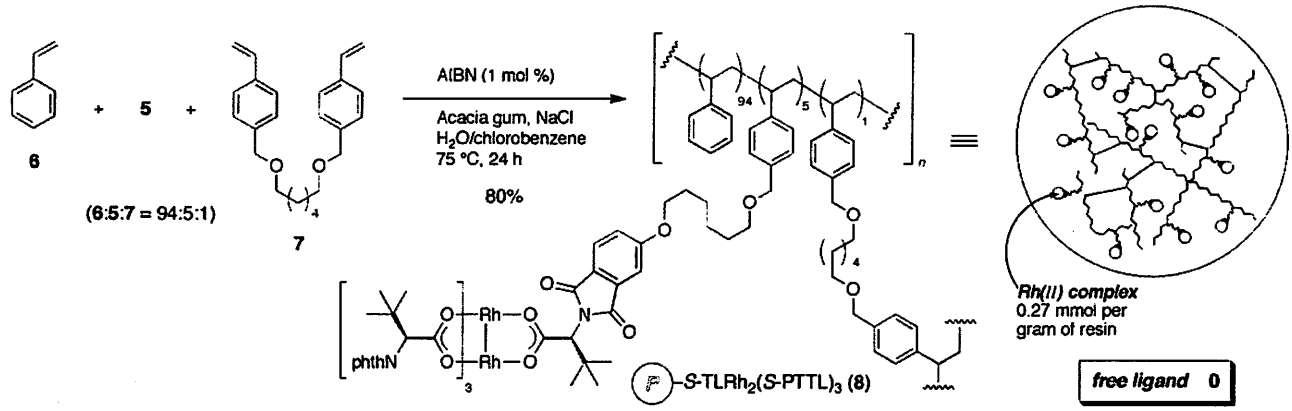
Scheme 1



Copolymerization of the monomer **5** with styrene **6** and 1,6-bis(4-vinylbenzyloxy)hexane (**7**) as a cross-linker in aqueous suspension in the presence of AIBN proceeded smoothly at 75 °C to give the

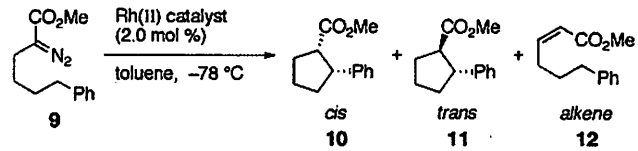
insoluble polymer-supported $Rh_2(S\text{-PTTL})_4$ **8** in high yield (Scheme 2).[5] Catalyst loading was determined from % rhodium and nitrogen elemental analyses (0.27 mmol of Rh_2/g of resin).

Scheme 2



We evaluated the polymer-supported $Rh_2(S\text{-PTTL})_4$ **8** using the intramolecular C–H insertion of diazoester **9** (Table 1).[6] Gratifyingly, the reaction with the use of 2 mol % of the polymer-supported $Rh_2(S\text{-PTTL})_4$ **8** that swells well in toluene proceeded smoothly at –78 °C to provide *cis*-2-phenylcyclopentane-1-carboxylate (**10**) in 94% ee, with no evidence of alkene formation. This result indicates that the present method of immobilization has only a mimimal effect on the chiral environment around the immobilized catalyst. Although the polymer-supported $Rh_2(S\text{-PTTL})_4$ **8** displayed lower reactivity relative to the homogeneous $Rh_2(S\text{-PTTL})_4$ (**1**), the robust polymer catalyst could be recycled at –78 °C twenty times with virtually no drop in yield or selectivity.[7]

Table 1. Enantioselective C–H Insertion Reaction of α-Phenyldiazoacetate



entry	Rh(II) catalyst	cycle	time [h]	yield[a] [%] (10:11:12)[b]	cis ee[c] [%]
1[d]	$Rh_2(S\text{-PTTL})_4$	–	0.5	85 (>99: – : –)	95
2	**8**	1	4	85 (>99: – : –)	94
3	**8**	5	4	84 (>99: – : –)	95
4	**8**	10	4	83 (>99: – : –)	95
5	**8**	20	4	81 (>99: – : –)	94

[a] Combined yield. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by HPLC. [d] *Adv. Synth. Catal.* **2005**, *347*, 1483. 1 mol % of $Rh_2(S\text{-PTTL})_4$ was used.

References

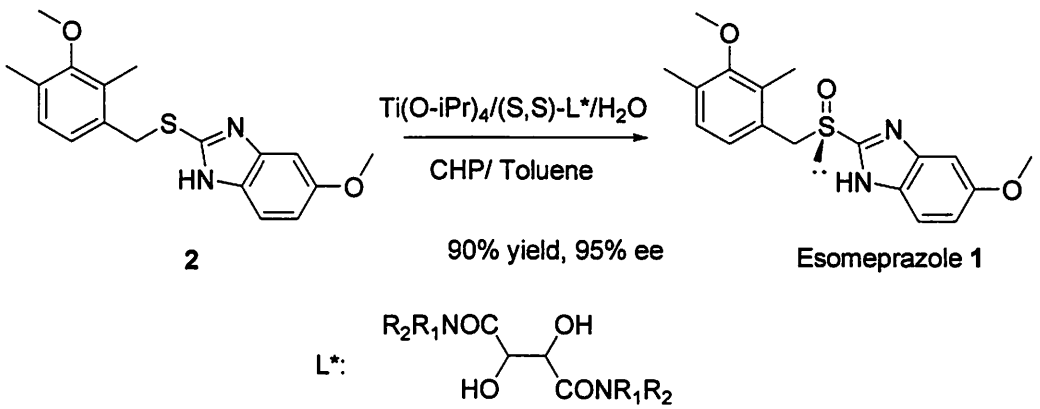
1. Doyle, M. P.; McKervey, M. A.; Ye, T. *Mordern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley&Sons: New York, 1998.
2. a) Doyle, M. P.; Timmons, D. J.; Tumonis, J. S.; Gau, H.-M.; Blossey, E. C. *Organometallics* **2002**, *21*, 1747. b) Doyle, M. P.; Yan, M. *Org. Lett.* **2003**, *5*, 561.
3. a) Nagashima, T.; Davies, H. M. L. *Org. Lett.* **2002**, *4*, 1989. b) Davies, H. M. L.; Walji, A. M. *Org. Lett.* **2003**, *5*, 479. c) Davies, H. M. L.; Walji, A. M.; Nagashima, T. *J. Am. Chem. Soc.* **2004**, *126*, 4271. d) Davies, H. M. L.; Walji, A. M. *Org. Lett.* **2005**, *7*, 2941.
4. Tsutsui, H.; Abe, T.; Nakamura, S.; Anada, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2005**, *53*, 1366.
5. Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329.
6. Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483.
7. International application No.: PCT/JP2007/062379

2P-18

Novel Asymmetric Catalytic Oxidation Approach to Esomeprazole

Jian Liao,* Tian Tian, Jin Zhu, Jingen Deng*
National Engineering Research Center of Chiral Drugs and Key Laboratory of Asymmetric Synthesis & Chirotechnology of Sichuan Province, Chengdu Insititute of Organic Chemistry, Chinese Academy of Sciences
Chengdu, 610041, P. R. China
jliao10@cioc.ac.cn, jgdeng@cioc.ac.cn

Esomeprazole **1**, (S)-5-methoxy-2{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfin- yl}-1H-benzimidazole, is the first proton-pump inhibitor (PPI) developed as a single isomer for the gastric acid secretion treatment[1] and has several billion US dollars per year global maketing. It is very important to develop an effective method to prepare esomeprazole in a garge scale. We developed a resolution approachs for this target, but 50% thoeritic yield is the limitation[2]. Unge et al disclosed an symmetric oxidation of prochiral sulfide **2** by titanium-mediated oxidation with cumene hydroperoxide (CHP) in the presence of (S,S)-diethyl tartrate and a nescessary amine such as diisopropylethylamine, 92% conversion and 94% ee were obtained. However, sulfone is unavoidable and ligand, (S,S)-diethyl tartrate, is unrecoverabe according to the procedure[3]. Jiang et al provided another oxidation system which dosn't need amine and ligand is recoverable, but the ligand synthesis is expensive way[4].
Herein, we present a novel asymmetric catalytic oxidation approach to the preparation of esomeprazole. Although the chiral ligands, such as diamides which derivated from tartaric acid, demonstrated very poor enantioselectivity in the oxidation of sulfides[5]. In our system, excellent results (up to 90% yield and 95% ee) were achived when (S,S)-diamide tartrates were utilized as ligand. This novel oxidation system also presents several other very important advantages like amine is not nescessary and no sulfone was observed in the oxidation.



Reference:

1. P. Lindberg; A. Brandstrom; B. Wallmark; H. Mattsson; L. Rikner; K. Hoffman *J. Med. Res. Rev.* **1990**, *10*, 1.
2. J. Deng; Y. Chi; F. Fu; X. Cui; K. Yu; J. Zhu; Y. Jiang *Tetrahedron: Asymmetry* **2000**, *11*, 1729.
3. H. Cotton; T. Elebring; M. Larsson; L. Li; H. Sorensen; S. Unge *Tetrahedron: Asymmetry* **2000**, *11*, 3819.

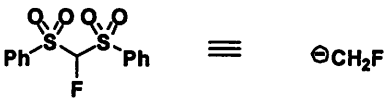
4. B. Jiang; X. Zhao; J. Dong; W. Wang; *patent*, DE102005061720.
5. P. Pitchen; E. Duiiach; M. Deshmukh; H. B. Kagan *J. Am. Chem. Soc.* **1984**, *106*, 8188.

2P-19

Enantioselective Michael Addition Reaction using FBSM

Tatsuya Furukawa*, Satoshi Mizuta, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya, 466-8555, Japan
nozshiba@nitech.ac.jp

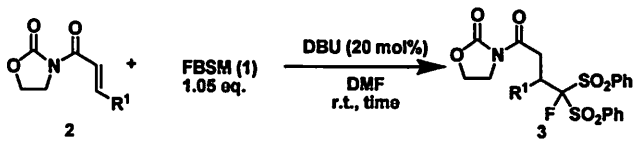
The development of efficient methodologies for the enantiocontrolled synthesis of fluorine-containing organic molecules has attracted much attention, particularly in the field of medicinal chemistry and material science. The current state-of art in asymmetric catalysis by the use of organocatalysts or ligand-metal complexes allows accessing the chiral fluoro-organic compounds with ease in high enantiocontrol. However, most of the recent innovations in this field are based on the enantioselective "electrophilic fluorination" reactions represented by the works of Togni, Sodeoka, Cahard, Jorgensen, MacMillan, Barbas, us and others for examples.[1] In comparison, the studies for the enantioselective "nucleophilic fluoromethylation" reactions still present a challenge.[2] In 2006, we disclosed 1-fluorobis(phenylsulfonyl)methane (FBSM, **1**, Figure 1) to be a synthetic equivalent of a fluoromethide species under the Tsuji-Trost allylic alkylation conditions, which provided the first palladium-catalyzed asymmetric allylic monofluoromethylation reaction with high enantiocontrol.[3a] Recently, we also demonstrated the potentiality of FBSM as a nucleophile for the enantioselective Mannich-type reaction in the presence of ammonium salts of cinchona alkaloids. Chiral, non-racemic α-monofluoromethylamines of biological interests were synthesized in high yields with excellent enantioselectivities.[3b] On the basis of this concept using FBSM as a synthetic equivalent of a fluoromethide species, we report herein an unprecedented, base-catalyzed Michael-type mono-fluoromethylation reaction to α,β-unsaturated ketones, aldehydes and esters. This reaction showed broad substrate generality and afforded formal 1,4-adducts regioselectively with high yields. Asymmetric version of this reaction was also examined.



FBSM: 1-Fluorobis(phenylsulfonyl)methane

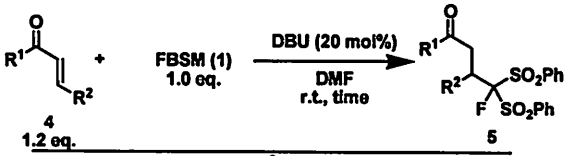
Figure 1

Table 1. Michael Addition of Oxazolidinone



entry	R^1	time (h)	yield (%)
1	Me	6	93
2	Et	4	86
3	Propyl	4	89

Table 2. Michael Addition of Aldehydes and Esters



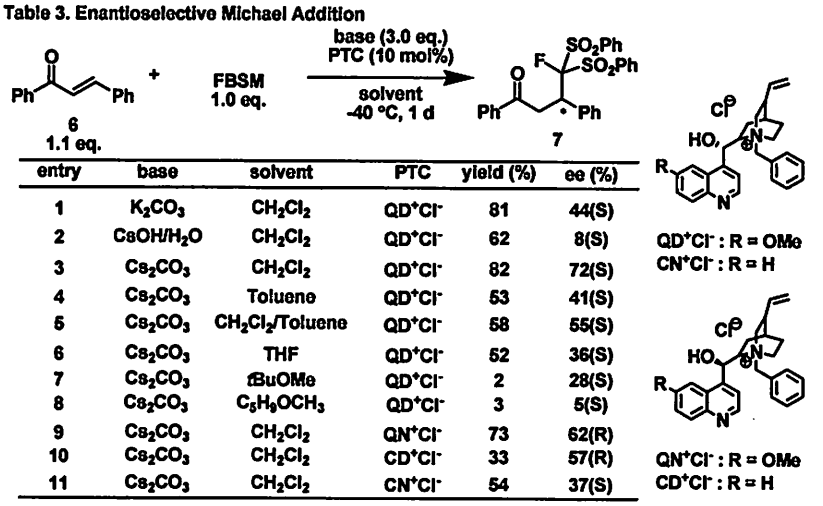
entry	R^1	R^2	time (h)	yield (%)
1	H	Me	6	74
2	H	Et	2	68
3[a]	EtO	Me	36	93
4[a]	EtO	Et	36	91

[a]Performed with 50 °C.

In an initial experiment, the regioselective nucleophilic 1,4-addition of FBSM to oxazolidinone **2** was investigated. After screening of the catalysts and solvents, the condition of 20 mol% of DBU in DMF at room temperature was found to be suitable for the Michael-addition of FBSM to afford the corresponding 1,4-adducts of oxazolidinone **3** in good to high yields (Table 1). We next turned our attention to the Michael-type addition of FBSM to α,β-unsaturated aldehydes and esters to show the further synthetic utility of the reaction. As can be seen in the Table 2, the corresponding β-fluorobis(phenylsulfonyl)methyl carbonyl compounds **5** were produced in high yields (Table 2).

Finally, we briefly attempted the enantioselective Michael-type addition of FBSM to chalcone (**6**) in the presence of a catalytic amount of phase transfer catalysts. Using FBSM (**1**), K_2CO_3 and a catalytic amount of *N*-benzylquinidinium chloride (QD^+Cl^-) in CH_2Cl_2 at –40 °C, chalcone was converted to the corresponding adduct in 81% yield with 44% ee (Table 3, entry 1). The enantioselectivity was improved to 72% ee when the reaction was performed in the presence of Cs_2CO_3 (entry 3). Solvents also had a considerable effect on the enantioselectivity, but the results were not improved (entries 4—8). A considerable difference in asymmetric induction was noticed between ammonium salts derived from quinine, quinidine, cinchonine, and cinchonidine, and quinidine was the most effective (entries 9—11). Despite promising results, this methodology is at a very preliminary stage of development. In particular, an efficient chiral ammonium salts remains to be designed. To our knowledge this is the first example of enantioselective Michael-type mono-fluoromethylation reaction.

Table 3. Enantioselective Michael Addition



entry	base	solvent	PTC	yield (%)	ee (%)
1	K_2CO_3	CH_2Cl_2	QD^+Cl^-	81	44(S)
2	CsOH/H_2O	CH_2Cl_2	QD^+Cl^-	62	8(S)
3	Cs_2CO_3	CH_2Cl_2	QD^+Cl^-	82	72(S)
4	Cs_2CO_3	Toluene	QD^+Cl^-	53	41(S)
5	Cs_2CO_3	CH_2Cl_2/Toluene	QD^+Cl^-	58	55(S)
6	Cs_2CO_3	THF	QD^+Cl^-	52	36(S)
7	Cs_2CO_3	*t*BuOMe	QD^+Cl^-	2	28(S)
8	Cs_2CO_3	$C_5H_9OCH_3$	QD^+Cl^-	3	5(S)
9	Cs_2CO_3	CH_2Cl_2	QN^+Cl^-	73	62(R)
10	Cs_2CO_3	CH_2Cl_2	CD^+Cl^-	33	57(R)
11	Cs_2CO_3	CH_2Cl_2	CN^+Cl^-	54	37(S)

References

[1] Selected reviews and papers: (a) H. Ibrahim, A. Togni, *Chem. Comm.* **2004**, 1147; (b) Y. Hamashima, M. Sodeoka, *Synlett*, **2006**, *10*, 1467; (c) J. –A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119; (d) M. Marigo, D. Fielenbach, A. Braunton, A. Kjarsgaard, K. A. Jørgensen, *Angew, Chem, Int, Ed*, **2005**, *44*, 3703; (e) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc*, **2005**, *127*, 8826; (f) D. D. Steiner, N. mase, C. F. Barbas, *Angew, Chem, Int, Ed*, **2005**, *44*, 3706; (g) N. Shibata, *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 14.

[2] N. Shibata, S. Mizuta, T. Toru, *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 215; J. –A. Ma, D. Cahard, *J. Fluorine Chem.* **2007**, *128*, 975.

[3] (a) T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura, T. Toru, *Angew. Chem., Int, Ed*, **2006**, *45*, 4973; (b) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, T. Toru, *J. Am. Chem, Soc*, **2007**, *129*, 6394

2P-20

Enantioselective Synthesis of (*R*)-Convolutamydine A using Novel Organocatalyst Having Heteroarylsulfonyl Group

Noriyuki Hara,* Hiroki Nakashima, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Graduate School of Engineering Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)

Convolutamydine A is an alkaloid that was isolated from the Floridian marine bryozoan *Amathia convoluta* by Kamano and co-workers in 1995. (*R*)-Convolutamydine A exhibited a potent inhibitory activity on the differentiation of HL-60 human promyelocytic leukaemia cells at 0.1-25 μg/mL. Recently, several groups have reported the enantioselective synthesis of (*R*)-convolutamydine A using chiral organocatalysts, however, unsolved problems include high catalyst loading the use of organocatalysts derived from unnatural α-amino acids to prepare (*R*)-convolutamydine A. In general, organocatalytic aldol reactions to ketones as acceptors generally need a high catalyst loading (at least 10 mol%) of organocatalysts, although there are many reports in the enantioselective aldol reactions to aldehydes using low catalyst loading of organocatalysts. To overcome the difficulty for the enantioselective synthesis of (*R*)-convolutamydine A, we designed novel natural L-proline-based sulfonimide organocatalysts (Figure 1). The fundamental concept of the catalyst design is based on controlling the structure of the transition state using intramolecular hydrogen bonding between N-H in the sulfonimide and heteroaryl group.

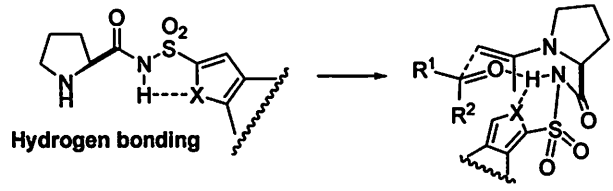


Figure 1.

We first examined the reaction of 4,6-dibromoisatin **1a** with acetone using sulfonimides **2a-h** as organocatalysts. The reaction was carried out using 10 mol% of organocatalysts **2a-h** and 10 equivalents of H_2O in acetone (200 eq.) at room temperature. The results are shown in Table 1.

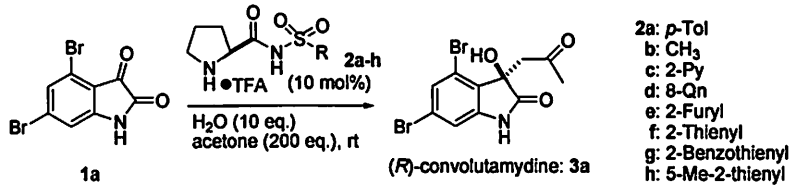


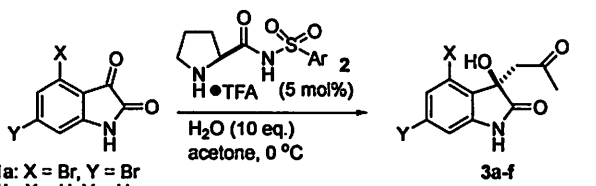
Table 1.

run	catalyst (mol%)	R	Reaction Time (h)	Yield (%)	Ee[a] (%)	run	catalyst (mol%)	R	Reaction Time (h)	Yield (%)	Ee[a] (%)
1	2a (10)	*p*-Tol	1	85	86	8	2h (10)	5-Me-2-thienyl	2	81	87
2	2b (10)	CH_3	13	83	51	9[b]	2f (10)	2-Thienyl	16	88	96
3	2c (10)	2-Py	3	86	80	10[c]	2f (10)	2-Thienyl	42	83	97
4	2d (10)	8-Qn	4	91	66	11[b]	2f (5)	2-Thienyl	9	99	95
5	2e (10)	2-Furyl	2	84	88	12[b]	2f (2)	2-Thienyl	23	98	95
6	2f (10)	2-Thienyl	7	92	92	13	2f (0.5)	2-Thienyl	170	49	91
7	2g (10)	2-Benzothienyl	7	95	92	14[d]	2f (5)	2-Thienyl	2.5	99	78

[a] Ee was determined by chiral HPLC analysis. [b] Reaction at 0 °C. [c] Reaction at -20 °C. [d] Without water.

The reaction using sulfonimide **2a** having a *p*-tolylsulfonyl group proceeded rapidly to give (*R*)-convolutamydine A (**3a**) in good yield with 86% ee, although the reaction using methylsulfonimide **2b** showed lower enantioselectivity (entries 1 and 2). Optimization of the arylsulfonyl group in sulfonimides was carried out, we found that efficient organocatalysts for the reaction of **1a** with acetone were *N*-(2-thienylsulfonyl)prolinamide **2f** and *N*-(2-benzothienylsulfonyl)prolinamide **2g** (entries 6 and 7). Since the preparation of prolinamide **2f** is easier than that of **2g**, we decided to study systematically the asymmetric performance of **2f**. The lower temperature improved the enantioselectivity of the reaction using **2f**, although the reactivity eventually became lower (entries 9 and 10). Catalyst loading can be reduced to 2 mol% of **2f** without loss of enantioselectivity (entries 11, 12). Although reactivity is reduced, the reaction using 0.5 mol% of **2f** at room temperature gave **3a** without loss of enantioselectivity (entries 6 vs 13). To the best of our knowledge, this result represents the lowest catalyst loading reported to date for direct aldol reaction to a ketone as an electrophile.

We next examined the preparation of various convolutamydine A derivatives **3a-f** using organocatalyst **2f**. The reaction of various substituted isatins using 10 mol% of **2f** are shown in Table 2. Although the reaction of unsubstituted isatin **1b** with acetone gave the product **3b** in excellent yield but with low enantioselectivity, the reaction of *N*-benzyl isatin using **2d** afforded **3b** with good enantioselectivity (entries 2 and 3). The reaction with 4,6-dichloro-, 4,6-diiode-4,6-dimethyl, and 4-bromoisatins **1c-f** gave the products **3c-f** with high enantioselectivity (entries 4-7). Enantiomerically pure convolutamydine A derivatives were easily obtainable by single recrystallization from hexane/ethyl acetate.



1a: X = Br, Y = Br
1b: X = H, Y = H
1c: X = Cl, Y = Cl
1d: X = I, Y = I
1e: X = CH_3, , Y = CH_3
1f: X = Br, Y = H

Table 2.

Entry	Isatin	catalyst	Reaction Time (h)	Yield (%)	Ee[a] (%)
1	1a	2f	9	99	95 (*R*) (>99)[b]
2	1b	2f	8	99	3 (*S*)
3[c]	1b	2d	14	50[d]	77
4	1c	2f	20	91	93 (98)[b]
5	1d	2f	24	>99	97 (>99)[b]
6[e]	1e	2f	40	61	91 (>99)[b]
7	1f	2f	22	93	97 (>99)[b]

[a] Ee was determined by HPLC analysis. [b] Ee inparentheses is that obtained after single recrystallization. [c] The reaction was carried out using *N*-benzylated isatin at roomtemperature. [d] *N*-Benzylated product was obtained. [e] 5 mol% of 2e was used. [f] The reaction was carried out at room temperature.

We found that the *N*-(2-thienylsulfonyl)prolinamide **2e** works as an efficient organocatalyst. Various convolutamydine A derivatives were obtained with high enantioselectivity with 0.5 mol% of **2e**. To our knowledge, this is the lowest catalyst loading in the aldol reaction of acetone to ketones to give the product with high enantioselectivity.

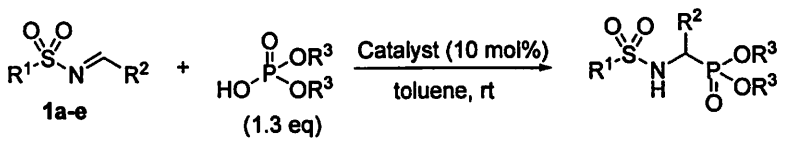
2P-21

Organocatalytic Enantioselective Hydrophosphonylation of Sulfonylimines Having Heteroarylsulfonyl Group

Akiko Yamamura,* Hiroki Nakashima, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Graduate School of Engineering, Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555, Japan
snakamur@nitech.ac.jp

Optically active α-amino phosphonic acids and their derivatives have been proved to be useful building blocks for the preparation of pharmaceutical targets, such as the antibacterial agent alafosfalin, anti-HIV agents, inhibitors of enzymes and peptidic materials having unique structural properties. The diastereoselective addition of phosphite derivatives to chiral imines and chiral Lewis acid-catalyzed enantioselective addition of phosphites to imines have been extensively investigated, whereas only a few studies exist of the organocatalytic enantioselective hydrophosphonylations of imines. Recently, we have reported enantioselective reactions using bifunctional coordinative heteroarylsulfonyl groups to control the conformations and reactivities by chelation with chiral Lewis acids. Herein, we report the first organocatalytic enantiocomplementary hydrophosphonylation of sulfonylimines catalyzed by commercially available cinchona alkaloids.

The enantioselective hydrophosphonylation reaction of various sulfonylimines with diethyl phosphite (1.5 equiv.) was carried out using 10 mol% of a variety of cinchona alkaloids as organocatalysts. Performing optimization experiments with various reaction conditions, the reaction with hydroquinine and hydroquinidine was found to afford both enantiomers of products with good enantioselectivity. The catalyst loading could be reduced to 5 mol% in the case of quinine.



1a: R^1= *p*-$MeOC_6H_4$
1b: R^1= 2-$PyCH_2$
1c: R^1= $PhSO_2$
1d: R^1= 2-$PySO_2$
1e: R^1= 6-Me-2-$PySO_2$

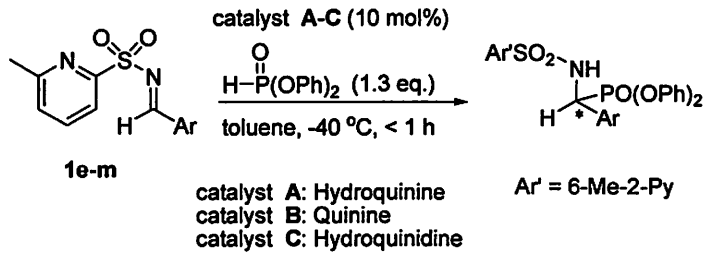
R^2 = Ph

1	Catalyst	R^3	Yield (%)	Ee[a] (%)
1a	Quinine	Et	0	-
1b	Quinine	Et	0	-
1c	Quinine	Et	68[b]	49
1d	Quinine	Et	98	65 (*S*)
1e	Quinine	Et	98	64 (*S*)
1e[c]	Quinine	Ph	> 99	92 (*S*)
1e[c]	Quinidine	Ph	> 99	88 (*R*)

1	Catalyst	R^3	Yield (%)	Ee[a] (%)
1e[c]	Hydroquinine	Ph	> 99	91 (*S*)
1e[c]	Hydroquinidine	Ph	> 99	92 (*R*)
1e[c]	$(DHQD)_2AQN$	Ph	98	40 (*S*)
1e[d]	Hydroquinine	Ph	98	97 (*S*)
1e[d]	Hydroquinidine	Ph	95	98 (*R*)
1e[c,e]	Quinine	Ph	> 99	92 (*S*)
1e[c,f]	Quinine	Ph	> 99	92 (*S*)

[a] Ee was determined by the HPLC analysis. [b] Conversion yield. [c] The reaction was carried out at -40 °C for 1 h. [d] The reaction was carried out at -78 °C for 1 h. [e] Quinine (5 mol%) was used. [f] Under an aerobic condition.

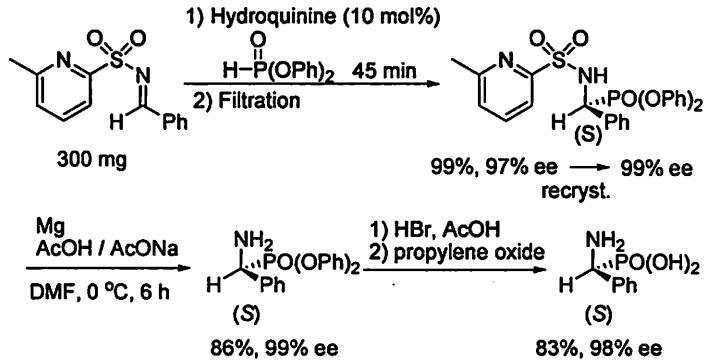
A series of sulfonylimines derived from aromatic aldehydes were all proved to be excellent substrates with respect to enantioselectivity and chemical yield using quinine, hydroquinine or hydroquinidine. Enantiomerically pure sulfonamides were easily obtainable by single recrystallization.



Ar	Cat.	Yield (%)	Ee (%)[a]	Ar	Cat.	Yield (%)	Ee (%)[a]
Ph	A[b]	98	97 (99)	Ph	C[b]	95	−98 (−99)
p-Tolyl	A[b]	> 99	92 (99)	*p*-Tolyl	C	> 99	−89 (−97)
p-$MeOC_6H_4$	A[b]	> 99	94 (98)	*p*-$MeOC_6H_4$	C[b]	> 99	−93 (−92)
o-$MeOC_6H_4$	A[b]	> 99	85 (96)	*o*-$MeOC_6H_4$	C[b]	> 99	−91 (−98)
m-$MeOC_6H_4$	B	> 99	81 (83)	*m*-$MeOC_6H_4$	C	> 99	−89 (−93)
p-ClC_6H_4	A[b]	> 99	87 (98)	*p*-ClC_6H_4	C[b]	> 99	−86 (−99)
1-Naphthyl	A[b]	> 99	82 (97)	1-Naphthyl	C[b]	> 99	−91 (−99)
2-Naphthyl	B	> 99	92 (95)	2-Naphthyl	B	> 99	−92 (−96)
trance-Cinnamyl	B	> 99	85 (92)	*trance*-Cinnamyl	B	> 99	−82 (−92)

[a] Ee obtained after single recrystallization from hexane/ethyl acetate is shown in parenthesis.
[b] The reaction was carried out at -78 °C for 5-6 h.

Larger scale synthesis starting with 300 mg of 6-methyl-2-Pyridylsulfonylimine also gave 97% ee and 99% yield by simple filtration without purification. Recrystallization of the crude, followed by desulfonation afforded the optically pure α-amino phosphonate, which was converted to the optically pure α-amino phosphonic acid.



We found that the heteroarylsulfonyl group works as a good activating group of the imino group in hydrophosphonylation. The first organocatalytic highly enantiocomplementary hydrophosphonylation of *N*-(heteroarylsulfonyl)imines was achieved using a catalytic amount of commercially available organocatalysts. The 6-methyl-2-pyridylsulfonyl group was shown to be an easily removable, efficient protective group, having notable properties such as high chiral inducibility and activation of the imino group toward the addition of nucleophiles.

S. Nakamura, H. Nakashima, A. Yamamura, N. Shibata, T. Toru *Adv. Synth. Catal.* **2008** in press.

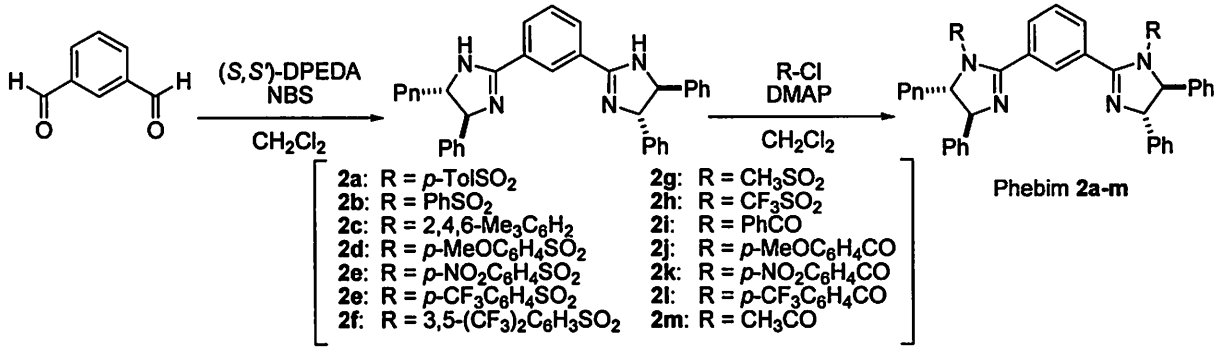
2P-22

A Novel C_2-Symmetric Chiral Bis(imidazoline) Ligands: Highly Enantioselective Friedel-Crafts Alkylation of Indoles with Ethyl 3,3,3-Trifluoropyruvate

Yuko Nakamura,* Kotaro Tsuji, Kengo Hyodo, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Graduate School of Engineering, Nagoya Institute of Technology
Gokiso, Syowa-ku, Nagoya, 466-8555, Japan
snakamur@nitech.ac.jp

The development of asymmetric catalysts has been extensively studied over the last decade. Certainly, one of the privileged classes of chiral ligands is the bis(oxazoline) framework, which consists of two *N,O*-containing five-membered rings coordinating to a metal cation. Fine tuning of the electron density and the steric bulkiness of the oxazoline ring remain to be solved. The highly tunable construction of bis(imidazoline) ligands would overcome this limitation and realize better matching of chiral ligands, metal ions, and substrates other than bis(oxazoline)s, and thus achieve excellent catalytic performance.

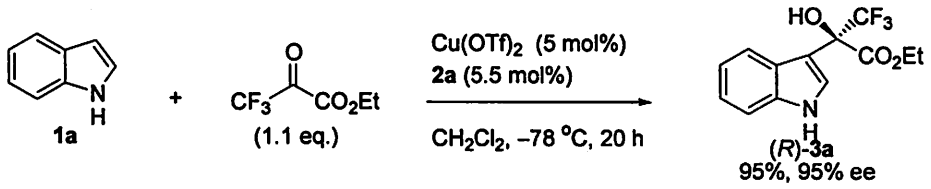
Various novel bis(imidazoline) ligands were prepared by the reaction of benzene-1,3-dicarbaldehyde, chiral 1,2-diphenylethylenediamine, and NBS as an oxidant giving phenylenebis(imidazoline) (phebim), followed by sulfonylation and acylation (Scheme 1).



Scheme 1

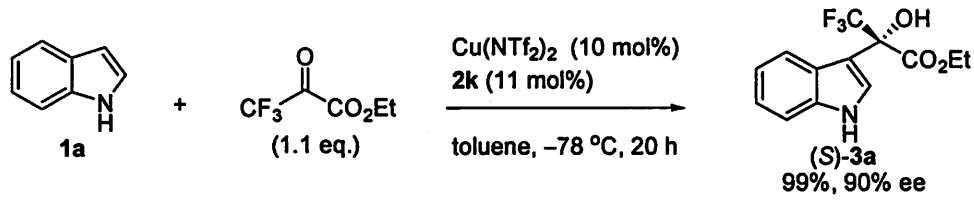
We chose Friedel-Crafts alkylation of indole derivatives as a benchmark reaction using phebim, since the synthesis of indole derivatives has captured much attention in organic chemistry for many decades.

The F-C alkylation of indole with ethyl 3,3,3-trifluoropyruvate using chiral Lewis acids prepared from $Cu(OTf)_2$ and *N-p*-tolylsulfonyl phebim **2a** gave (*R*)-**3a** in high yield with 95% ee (Scheme 2). The catalyst loading can be reduced up to 0.5 mol% without a significant decrease in yield and enantioselectivity.



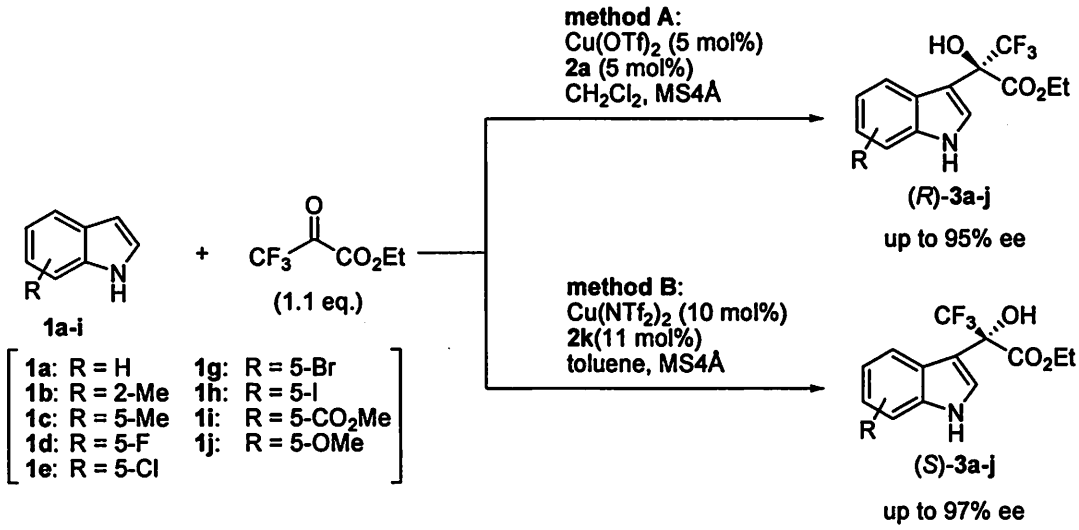
Scheme 2

Interestingly, the reaction using *N*-benzoyl phebim **2i** and $Cu(NTf_2)_2$ in toluene afforded (*S*)-**3a** having a stereochemistry opposite that obtained in the reaction using phebim **2a** and $Cu(OTf)_2$. Fine tuning of the substitution of phebim was carried out and *N*-*p*-nitrobenzoyl phebim **2k** was found to be very efficient (Scheme 3).



Scheme 3

We next examined the reaction with various indoles using two catalytic systems, method A; **2a**-$Cu(OTf)_2$ and method B; **2k**-$Cu(NTf_2)_2$ (Scheme 4). Results indicate that (*R*)- and (*S*)-**3a-j** can be obtained in high yield with good to high enantioselectivity by the respective method and that enantiocomplementary synthesis is generally quite applicable.



Scheme 4

We propose the dual activation transition state for the reaction of indole and Ethyl 3,3,3-trifluoropyruvate by two imidazoline rings in the presence of phebim-$Cu(OTf)_2$ (Figure 1).

Further experiments are in progress to study the scope of this process and the potential application of phebim to other reactions.

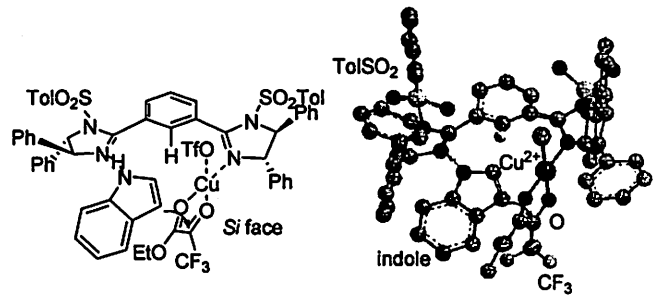


Figure 1

S. Nakamura, K. Hyodo, Y. Nakamura, N. Shibata, T. Toru *Adv. Synth. Catal.* **2008** in press.

2P-23

Chemoselective hydrogenation of nitro functionalities in the presence of olefins using Os/C-catalyst

Mutsumi Sato,[1]* Keiji Oono,[1] Yasunari Monguchi,[2] Tomohiro Maegawa,[2] Hironao Sajiki[2]
[1] Reagent Research Laboratories, Wako Pure Chemical Industries, Ltd.,
Matoba, Kawagoe, Saitama, 350-1101, Japan
[2] Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University,
Mitahora-higashi, Gifu, 502-8585, Japan

sato.mutsumi@wako-chem.co.jp

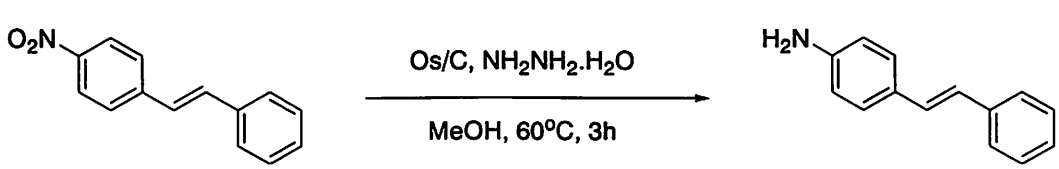
A combination of osmium carbon catalyst (Os/C) and hydrazine shows efficient chemoselectivity in hydrogenation of nitro functionalities in the presence of olefins that are readily reduced under carbon-supported transition metal-catalyzed hydrogenation conditions. These results reinforce the utility of amino styrene derivatives in synthetic chemistry, especially as raw materials of liquid crystal alignment layers and pharmaceutical intermediates.

1) Background

Amino styrene derivatives have been successfully and widely used as raw materials of liquid crystal alignment layer. Chemoselective reduction of nitro functionalities in the presence of olefin is a convenient method for the synthesis of amino styrene derivatives. The reduction is usually achieved using Fe as a reducing agent. Although the reaction requires excess amount of Fe, which is quite difficult to remove from the reaction mixture.[1] On the other hand, hydrogenation using metal carbon is one of the most useful methods, due to its easy separation from the reaction mixture and reusability. However, it is extremely difficult to accomplish the chemoselective catalytic hydrogenation of nitro functionalities due to the high catalyst activity. Selective catalytic hydrogenation of α, β-unsaturated aldehydes to unsaturated alcohols in the presence Os/C has been reported by Rylander and Steele[2] while the method has limitations with regard to generality [substrate applicability, high pressure (750-1000 psig) and so on].

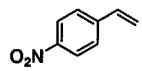
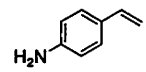
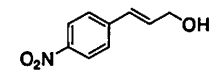
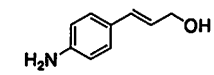
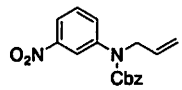
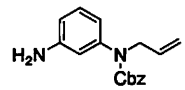
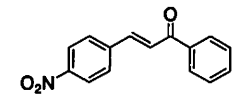
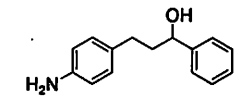
2) Chemoselective hydrogenation of nitrostilbene to aminostilbene with Os/C

Recently, we found the Os/C-catalyzed chemoselective hydrogenation of nitrostilbene to aminostilbene and the best result was obtained at 60°C using $NH_2NH_2.H_2O$ as a reducing reagent.



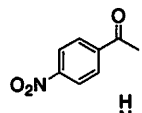
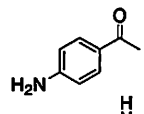
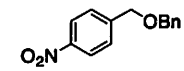
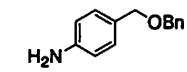
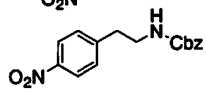
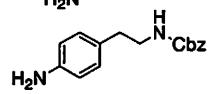
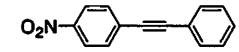
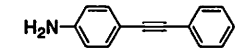
3) Chemoselective reduction of various nitro substrates bearing olefins

In the exploration of the scope of Os/C, the present reduction system was successfully applied to a variety of nitro compounds in the presence of olefins within the molecule.

entry	substrate	product	yield(%)	entry	substrate	product	yield(%)
1			94	3			97
2			97	4			88

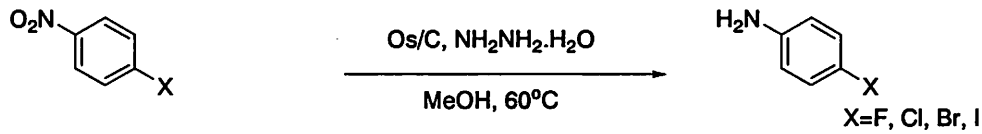
4) Chemoselective reduction of various nitro substrates bearing other reducible functionalities

The present chemoselective hydrogenation of the nitro functionality was also applied to substrates possessing aromatic ketones, *N*-Cbz protective groups, benzyl ethers and acetylenes without any undesirable over-reduction.

entry	substrate	product	yield(%)	entry	substrate	product	yield(%)
1			92	3			99
2			88	4			96

5) Chemoselective reduction of halogenated-nitrobenzenes

It is well known that aromatic halides are easily reduced under hydrogenation conditions. Chemoselective hydrogenation of nitro groups in distinction from aromatic halides remains to be a great challenge. The nitro groups of halogenated nitrobenzene derivatives were chemoselectively hydrogenated under the present reaction conditions with no change of the coexisting aromatic halide functionalities.



6) Conclusion

We have found an Os/C-catalyzed chemoselective hydrogenation method of nitro functionalities in the presence of olefins, aromatic ketones, acetylenes, benzyl ethers, aromatic halides and *N*-Cbz protective groups. It can be applied to the synthesis of raw material of liquid crystal alignment layer, and pharmaceutical intermediates.

1. A. J. Béchamp, *Ann. Chim. Phys.* **42**(3), 186 (1854)
2. Paul N. Rylander, Duane R. Steele, *Tetrahedron Lett.*, **20**, 1579 (1969)

2P-24

Preparation method of Pd/C(en) catalyst in water

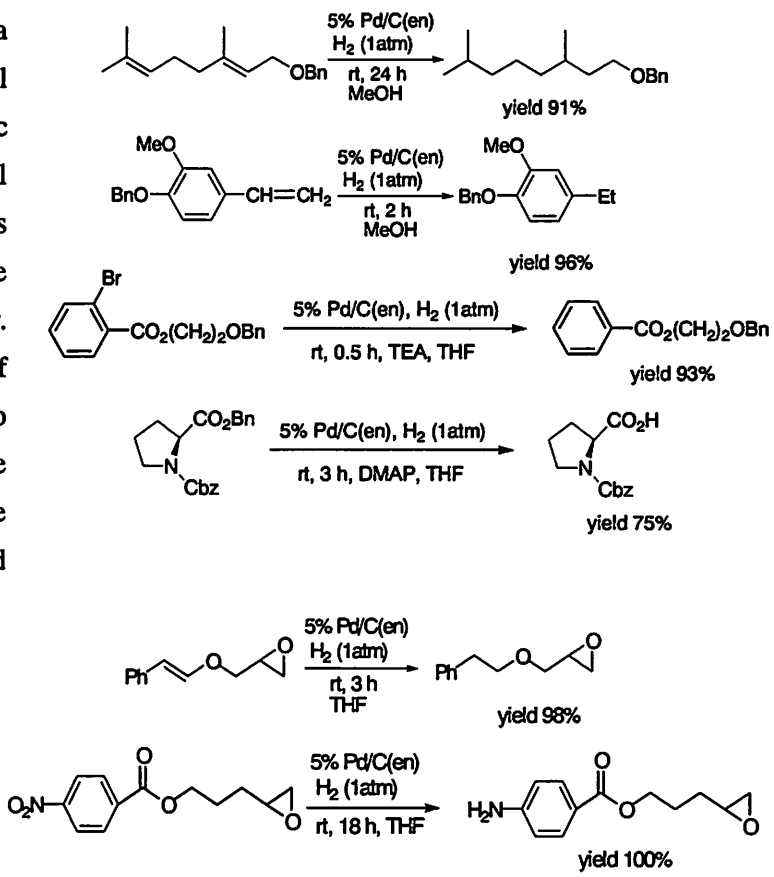
Keiji Oono,[1]* Mutsumi Sato,[1] Yasunari Monguchi,[2] Tomohiro Maegawa,[2] Hironao Sajiki[2]
[1] Reagent Research Laboratories, Wako Pure Chemical Industries, Ltd.,
Matoba, Kawagoe, Saitama, 350-1101, Japan
[2] Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University,
Mitahora-higashi, Gifu, 502-8585, Japan

oono.keiji@wako-chem.co.jp

A practical and efficient preparation method of the palladium-activated carbon ethylenediamine (en) complex [Pd/C(en)] possessing following advantages; the use of water as a solvent and the reduction of the usage of ethylenediamine, has been developed. The isolable complex catalyst, Pd/C(en) catalyzed chemoselective hydrogenation among a wide variety of reducible functionalities distinguishing *O*-benzyl, *N*-Cbz and *O*-TBDMS protective groups, aromatic nitriles, benzyl alcohols and epoxides. The present improved process is applicable to a large-scale preparation of Pd/C(en).

Catalytic hydrogenation using a heterogeneous catalyst has been a useful and widely applicable method in synthetic chemistry. Pd/C is one of the most useful heterogeneous catalysts, because of its stability, ease of separation from the reaction mixture, and recyclability. However, the great catalyst activity of Pd/C makes it extremely difficult to accomplish the chemoselective hydrogenation among reducible functionalities. We have recently reported several chemoselective hydrogenation methods using Pd/C(en)[1].

Pd/C(en) chemoselectively catalyzed the hydrogenation of a wide variety of reducible functionalities distinguishing *O*-benzyl, *N*-Cbz and *O*-TBDMS protective groups, aromatic nitriles,



Scheme 1

benzyl alcohols and epoxides (Scheme 1) [2]. The difference of the catalyst activity toward hydrogenation between Pd/C and Pd/C(en) is shown in Figure 1.

We report herein a practical and scalable preparation method of Pd/C(en). Although the use of large excess amount of ethylenediamine (70 equiv) and methanol as a solvent has been essential for the preparation of Pd/C(en), the present method successfully reduced the usage of ethylenediamine from 70 equiv to 1.1 equiv in aqueous media (Scheme 2). The method could safely applied to the kg-scale preparation of Pd/C(en) without any problems. Pd/C(en) prepared by the present method is also applicable as a chemoselective hydrogenation catalyst for benzyl esters, aromatic ketones, halides, alkenes, alkynes and azides, aromatic *N*-Cbz protecting groups in the presence of other reducible functional groups as well as conventional Pd/C(en) prepared in methanol.

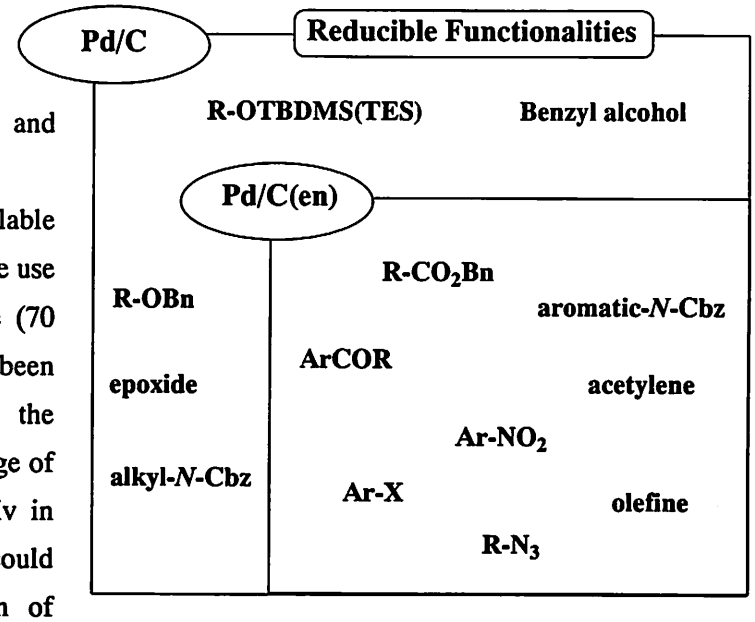
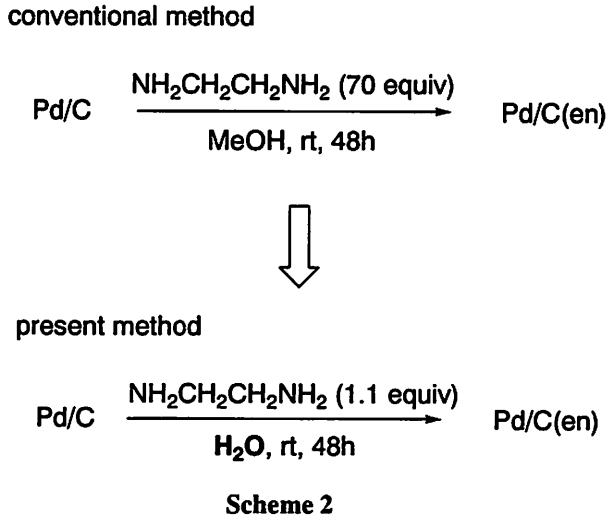


Figure 1 **Comparison of reducible functions by Pd/C and Pd/C(en)**



Scheme 2

Conclusion

The present environmentally-benign process using nearly-equimolar amount of ethylenediamine in water is safely applicable to the large-scale preparation of Pd/C(en).

References

1) (a) H. Sajiki, K. Hirota: *J. Syn. Org. Chem., Japan,* **59**, 109 (2001). ; (b) H. Sajiki, K. Hirota: *Organic Square (Wako),* **12**, 1, (2004). ; K. Oono, H. Sajiki: *Organic Square (Wako),* **22**, 2, (2008).

2) (a) H. Sajiki, K. Hattori, K. Hirota: *J. Org. Chem.*, **63**, 7990 (1998). ; (b) K. Hattori, H. Sajiki, K. Hirota: *Tetrahedron*, **56**, 8433 (2000). ; (c) H. Sajiki, K. Hattori, K. Hirota: *Chem. Eur. J.*, **6**, 2200 (2000). ; (d) K. Hattori, H. Sajiki, K. Hirota: *Tetrahedron Lett.*, **41**, 5711 (2000). ; (e) H. Sajiki, K. Hattori, K. Hirota: *J. Chem. Soc., Perkin Trans. 1*, 4043 (1998). ; (f) H. Sajiki, K. Hattori, K. Hirota: *Chem. Commun.*, 1041 (1999). ; g) K. Hattori, H. Sajiki, K. Hirota: *Tetrahedron*, **57**, 4817 (2001). ; h) T. Maegawa, Y. Fujita, A. Sakurai, A. Akashi, M. Sato, K. Oono, H. Sajiki: *Chem. Pharm. Bull.*, **55**, 837 (2007).

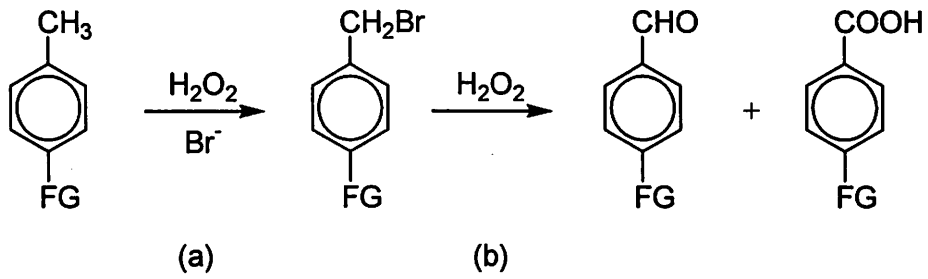
2P-25

Solvent Effect on Oxidation of Alkylbenzene Using Hydrogen Peroxide

Takeo Nakai,* Toshiyuki Iwai, Masatoshi Mihara, Takatoshi Ito, Takumi Mizuno
Osaka Municipal Technical Research Institute
1-6-50, Morinomiya, Joto-ku, Osaka 536-8553, Japan
nakai@omtri.city.osaka.jp

The introduction of carbonyl group at the benzylic position from the corresponding alkylbenzenes is an important transformation in organic synthesis. Aromatic carbonyl compounds are valuable materials for manufacture of specialty chemicals in pharmaceuticals and industrial materials. Innumerable methods have been studied on the oxidation of alkylbenzenes to corresponding ketones or carboxylic acids. In these oxidation reactions, stoichiometric or excess heavy-metal oxidants are used or severe condition (high-temperature and high-pressure) is demanded usually. These reactions are not environmental friendly because of massive toxic co-products and high energy consumption. Last decades, the significance to develop new oxidation method based on green & sustainable chemistry is augmenting. Oxygen and hydrogen peroxide are ideal oxidants from point in green & sustainable chemistry on account of no toxic co-product (co-product is only water) and high atom efficiency. We attempted to develop mild and simple system for oxidation of alkylbenzenes to corresponding aromatic carbonyl compounds using hydrogen peroxide as oxidant.

These are reported that combination of hydrogen peroxide and hydrogen bromide is good for replacement of benzyl C-H by bromine,[1] and combination of hydrogen peroxide and potassium bromide oxidize benzyl halide easily.[2] We expected that the similarity between these conditions may enable to perform oxidation of benzylic position, if these reactions work continuously in one-pot.



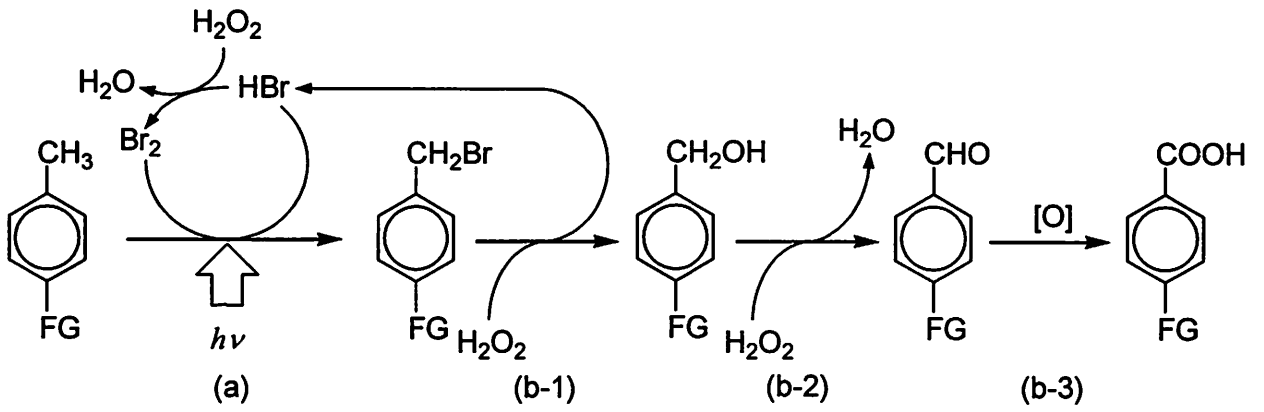
In this system, this is anticipated that the choice of solvent is most important factor. The reason is difference of suitable solvent for each step (a) and (b). The first half step (a) (bromination of benzyl) is carried out in biphasic (water-nonaqueous) solvent and latter half step (b) (oxidation) is carried out in aqueous solvent generally.

Results of experiments with various solvents were summarized in table. Acetone, 2-butanone and acetonitrile were not suitable solvent for this reaction system, starting material was recovered (Entry 5-7).

Entry	Solvent	Yield %		
		Bromide	Aldehyde	Carboxylic acid
1	*t*-BuOH	33.5	14.5	11.1
2	AcOH	49.1	4.6	3.4
3	AcOEt	37.2	7.9	1.2
4	AcOMe	43.3	Trace	-
5	CH_3CN	-	-	-
6	CH_3COCH_3	-	-	-
7	$CH_3COC_2H_5$	-	-	-

Reaction condition: Alkylbenzene (2 mmol); Solvent (10ml); 48% HBr aq (120μl); 30% H_2O_2 aq (35μl × 20); Temperature: 60℃; hν: 30W (incandescent lamp).

In solvent of acetic acid, ethyl acetate and methyl acetate, bromination reaction (a) was proceeded smoothly, but hydrolysis of benzyl bromide (b-1) was very slow, only a few oxidation product was obtained (Entry 2-4). The better solvent for this oxidation system was *t*-butyl alcohol. In this solvent, hydrolysis (b-1) was more easily than other cases (Entry 1). Even now hydrolysis was bottleneck in any solvent, so we examined the effects of addition of waters. We confirmed that addition of water affected not only acceleration of hydrolysis (b-1) but also selectivity of main product.



Reference

1. Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra J. *Tetrahedron Lett.* 2006, 47, 7245-7247.

2. Tang, J.; Zhu, J.; Shen Z.; Zhang Y. *Tetrahedron Lett.* 2007, 48, 1919-1921.

2P-26

Cinchona Alkaloid-catalyzed Asymmetric Aldol-type Reactions Using Trifluoropyruvates

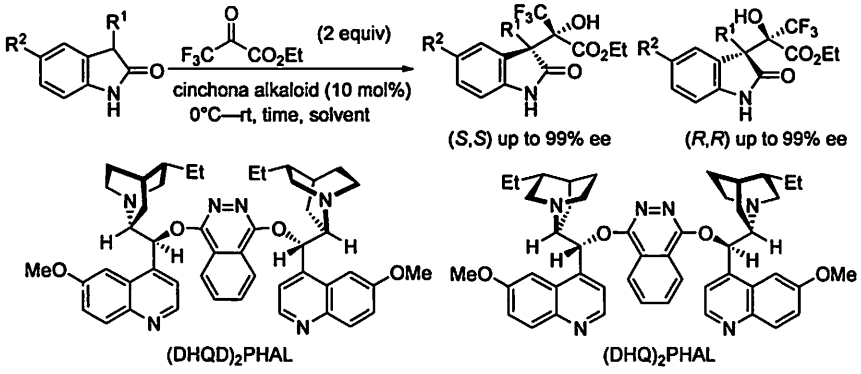
Shinichi Ogawa*, Hiroyuki Fujimoto, Norihito Iida, Shuichi Nakamura, Norio Shibata, Takeshi Toru
Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology
Gokiso-cho, Showa-ku, Nagoya, 466-8555, Japan,
17515004@stn.nitech.ac.jp

Heterocycles containing a trifluoromethyl group are a major contributor in agricultural and medicinal chemistry. Thus the development of a simple and flexible method to generate a trifluoromethylated heterocyclic system has received much attention.

We considered that the incorporation of a tertiary α-trifluoromethyl alcohol stereocenter, represented by $CF_3C^*(OH)R^1R^2$, into heterocycles could provide a novel drug candidate, with the unique properties of the tertiary α-trifluoromethyl alcohols contributing to new biological activities. As a first step, we became interested in the development of general methods leading to oxindoles having a tertiary α-trifluoromethyl alcohol moiety with a chiral environment.

Oxindoles with a quaternary stereogenic center, especially spiro-oxindoles, are of potential medicinal interest owing to the unique biological activities of natural products and man-made compounds that contain such systems.

We describe herein highly enantioselective synthesis of oxindoles with two continuous asymmetric tetrasubstituted carbons containing a tertiary α-trifluoromethyl alcohol center, resulting from an asymmetric *direct* oxindole-aldol condensation with ethyl 3,3,3-trifluoropyruvate(ETFP) catalyzed by cinchona alkaloids. Both enantiomeric products (*S,S*) and (*R,R*) adducts are selectively accessible in high yields with up to 99% ee, using pseudoenantiomeric cinchona alkaloids (**Figure**).[1)]



Figure

Trifluoropyruvate is one of the most versatile building blocks for the synthesis of chiral trifluoromethylated compounds. Several reports have appeared concerning the enantioselective nucleophilic addition to trifluoropyruvate in the Friedel-Crafts reaction, aldol reaction, Henry reaction, and the carbonyl-ene reaction catalyzed by chiral Lewis acids, cinchona alkaloids, or prolines.

However, there are no data available using oxindoles as nucleophiles for the corresponding asymmetric addition reactions.

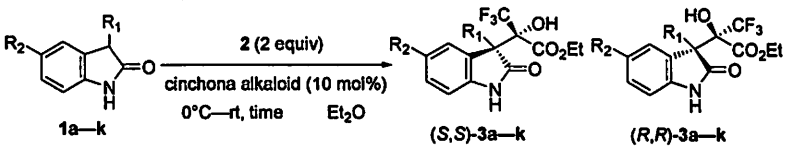
So, we attempted the enantioselective oxindole-aldol reaction of 3-methyl-2-oxindole with ETFP as the beginning of our work.

Catalyst screening using commercially available *bis*-cinchona alkaloids indicated that the oxindole-aldol reaction proceeds smoothly to yield the desired (*S,S*) adducts in excellent yield, with high diastereoselectivity and very high enantioselectivity, especially when the reaction was carried out in the presence of $(DHQD)_2PHAL$ (Run 1, 99% yield, 90/10 dr, 95% ee). In the presence of pseudoenantiomeric $(DHQ)_2PHAL$, the reaction proceeded to give the opposite enantiomer of the aldol product (*R,R*) (Run 9, 99% yield, 88/12 dr, 94% ee).(See table below.)

The result of screening was showed in table below. This methodology served as a facile approach for the preparation of a range of trifluoromethylated oxindoles containing two chiral centers in excellent enantiomeric excesses up to 99% ee and high diastereoselectivities up to 97/3.

Synthesis of both enantiomers of the products was accomplished with high yields and enantioselectivities by appropriate selection of the cinchona alkaloids $(DHQD)_2PHAL$ for (*S,S*) adducts (Run 1—8), $(DHQ)_2PHAL$ for (*R,R*) adducts(Run 9—16). Reducing the amount of the catalyst to 5 mol % gave slightly lower selectivities (Run 17).

The relative and absolute stereochemistry of (*R,R*)-**3d** was determined by X-ray crystallographic analysis. The separation of diastereomers was done by recrystallization. The stereochemistry of other oxindoles **3** was assigned tentatively analogy.



In conclusion, we have developed the first organocatalytic enantioselective direct oxindole-aldol reaction with trifluoropyruvate using cinchona alkaloids. Employing suitable pseudoenantiomeric cinchona alkaloids as catalysts, both enantiomers of trifluoromethylated oxindoles, with two continuous asymmetric tetrasubstituted carbon centers, are selectively obtained in one step. The CF_3 group of the pyruvate is essential to the success of the reaction. In the poster session, proposed reaction mechanism and application of this methodology will be shown.

	1	R^1	R^2	time (h)	yield (%)	dr	ee (%)
1[a]	1a	Me	H	16	99	90/10	95
2[a]	1b	Et	H	18	90	94/6	95
3[a]	1c	Bn	H	9	97	89/11	96
4[a]	1d	4-BrBn	H	21	93	86/14	92
5[a]	1e	4-ClBn	H	8	99	90/10	98
6[a]	1f	4-MeOBn	H	12	89	89/11	99
7[a]	1g	Et	Me	32	94	92/8	95
8[a]	1h	Bn	Me	3	75	85/15	95
9[b]	1a	Me	H	19	99	88/12	94
10[b]	1b	Et	H	23	99	88/12	99
11[b]	1c	Bn	H	3	95	95/5	98
12[b]	1d	4-BrBn	H	10	90	97/3	98
13[b]	1e	4-ClBn	H	3	99	94/6	99
14[b]	1f	4-MeOBn	H	3	81	94/6	97
15[b]	1g	Et	Me	23	97	95/5	90
16[b]	1h	Bn	Me	3	78	92/8	95
17[b,j]	1a	Me	H	26	98	92/8	88

[a] $(DHQD)_2PHAL$ was used as the catalyst.[b] $(DHQ)_2PHAL$ was used as the catalyst.

1) Shinichi Ogawa, Norio Shibata, Junji Inagaki, Shuichi Nakamura, Takeshi Toru, Motoo Shiro *Angew. Chem. Int. Ed.* **2007**, *46*, 8666 –8669.

2P-27

Ring-Opening Reaction of α- and β-Pinene in Hot, Compressed Water without Any Additive

Tomomi Kawahara[1]*, Toshiyuki Sato[2], Akiko Kawai-Nakamura[2], Kiwamu Sue[3], Hiizu Iwamura[2], Toshihiko Hiaki[1, 2]

[1)] College of Industrial Technology, Nihon University
1-2-1 Izumi-cho, Narashino, Chiba 275-8575, Japan

[2)] Advanced Research Institute for the Science and Humanities, Nihon University
12-5 Goban-cho, Chiyoda-ku, Tokyo 102-8251, Japan

[3)] Nanotechnology Research Institute, National Institute of Advanced Industrial Science and Technology
Tsukuba Central 5, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan

t5hiaki@cit.nihon-u.ac.jp

Introduction

It is highly important for sustainable development of our society to utilize waste biomass effectively[1)]. Some of the methods employ strongly acidic or basic conditions and biotechnology that are not necessarily to the environment. We became interested in developing a chemical process in near supercritical water that has a low dielectric constant, increased solubility for organic compounds, and an increased ion product. Our attention was paid to pinenes contained in the liquid waste of the kraft paper industry. In contrast to the acid catalyzed treatment of the bicyclic hydrocarbons, we studied its ring-opening in hot, compressed water without addition of any catalyst.

Experiment

We performed batch reactor experiments in 1/2 inch stainless steel tube. These reactors consisted of two caps which provided a 10 mL reactor volume. To 3.574 g of pure water in the reactors was added 0.2705 g of α or β-pinene (100:1 molar ratio). The mixture was flushed with argon unless otherwise stated at 250, 300 and 400 °C in a salt bath preheated at give temperature. Reaction time was 1~30 min. After prescribed time, the reaction mixture was collected, extracted with dietyl ether, and analyzed. Qualitative analyzed by the gas chromatography/mass spectrometry method with a Simadzu Corporation GC-2010, connected with GCMS-QP2010, and quantitative analyzed by the gas chromatography spectrometry method with a Simadzu Corporation GC-2010

Results and discussion

The main product from α-pinene and β-pinene was found to be limonene. The GC-MS spectral of main product and authentic sample of limonene.

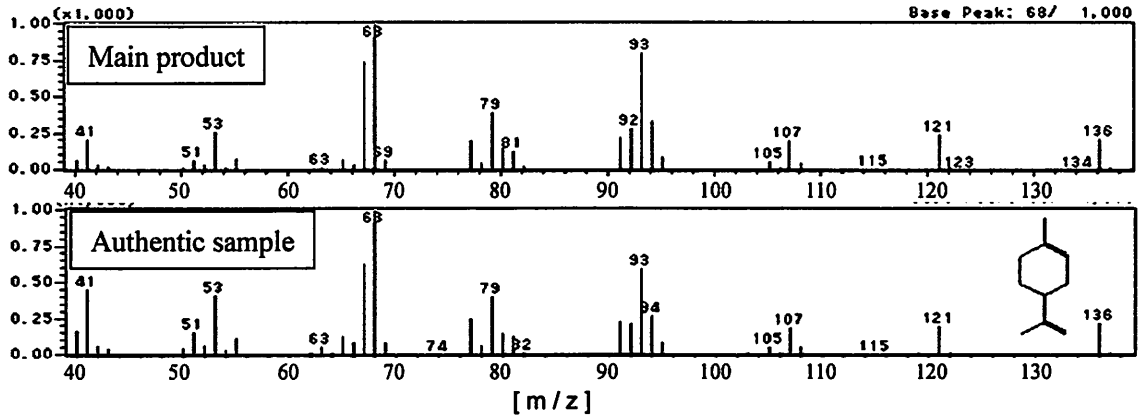


Fig.1 GC-MS spectrum of reaction product

As a result, we have understood a main product is a limonene. The conversion of the starting material was almost 100 % after 1 min at 400°C, and 3 min 300°C. The conversion was ca.40 % after 30 min at 250°C. Fig.2 show the time dependence of the yield of limonene from α-pinene. Limonene was obtained in hot, compressed water and maximum yield was ca. 70 % at 300°C for 20 min and 400°C for 1 min. The yield decreased somewhat with time. The yield of limonene was lower at 250°C and 19 % after 30 min.

When the reaction mixture was not flushed with argon, the limonene yield of ca. 70 % at 400°C for 1 min decreased rapidly with time to 41 %. At its expense, cymene was formed and its yield reached ca. 23 % at 400°C for 30 min (Fig.3). suggesting that the air is responsible for the dehydrogenation reaction. It is concluded that limonene and cymene can be selectively synthesized by controlling the reaction of α-pinene in high temperature high-pressure water by controlling amount of oxygen.

The behavior of β-pinene was similar but some difference was noted between the isomeric bicyclic hydrocarbons.

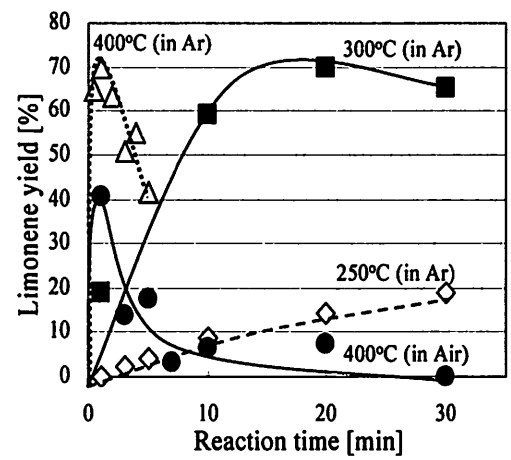


Fig.2 Yield at each reaction time

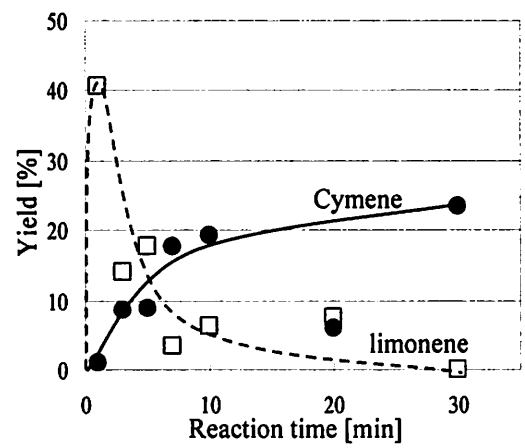


Fig.3 Yield at each reaction time (400 °C, 30 MPa, in Air)

References

[1] T. M. *aida et al ./ J.of Supercritical Fluids* 42 (2007)110-119

2P-28

Synthesis of Polyacenequinones in Hot, Compressed Water in the Absence of Added Catalysts

Takenori Sawada[1]*, Toshiyuki Sato[2], Akiko Kawai-Nakamura[2], Kiwamu Sue[3],
Hiizu Iwamura[2], Toshihiko Hiaki[1,2]
[1)] College of Industrial Technology, Nihon University
1-2-1 Izumi-cho, Narashino, Chiba 275-8575, Japan
[2)] Advanced Research Institute for the Science and Humanities, Nihon University
12-5 Goban-cho, Chiyoda-ku, Tokyo 102-8251, Japan
[3)] Nanotechnology Research Institute, National Institute of Advanced Industrial Science and Technology
Tsukuba Central 5, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan
t5hiaki@cit.nihon-u.ac.jp

[Introduction]

Many organic reactions are carried out by the action of acid or base catalysts in organic solvents that burden the environment with necessary work-up processes. We noted that water near the supercritical conditions has a low dielectric constant, increased solubility for small organic compounds, and an increased ion product, thereby facilitating various organic reactions such as aldol condensations without added catalysts.[1)] In this study we found that the aldol condensation of *o*-phthalaldehyde and 1,4-cyclohexanedione in a 2:1 molar ratio in near-supercritical water led to the formation of 6,13-pentacenequinone which was otherwise obtained by using a base catalyst in an EtOH.[2)]

6,13-pentacenequinone is a precursor of pentacene that serves as raw materials for solar battery and organic electroluminescence display. Accordingly the demand for 6,13-pentacenequinone is expected to increase in the future. For these reasons we investigated systematically this synthesis in high-temperature and pressure water without added catalyst.

[Experimentals]

We performed batch reactor experiments in 1/2 inch stainless steel Swagelok tubes fittings. These reactors consisted of two caps, which provided 10 cm^3 reactor volume. Reactions were carried out at 400, 370, 250, 240 and 230 ℃. To this reactor were added 3.574 g of water , which were expected to give a pressure of 30 MPa at 400 ℃. *o*-Phthalaldehyde , 1,4-cyclohexanedione were added to make molar ratios of 1 : 0.5 : 50～400 for *o*-phthalaldehyde : 1,4-cyclohexanedione : water.

The reactor containing the starting materials was immersed in a salt bath preheated at a given temperature and reaction was started. Reaction time was 1~30 min. After the reacting period, the reactor was removed from the salt bath and submerged in room-temperature water. Qualitative analysis of reaction products was carried out by a Shimadzu Corporation mass spectrometer. Quantitative analysis of the solid and liquid products obtained were carried out by Shimadzu Corporation HPLC and gas chromatography. The columns were Agilent technologys DB-5MS and Shimadzu Corporation Shim-Pack-ODS.

[Results and Discussion]

Figure 1 shows an example of the mass spectral analysis of the reaction products. The spectrum of the reaction product was in good agreement with an authentic sample of 6,13-pentacenequinone, demonstrating its identity.

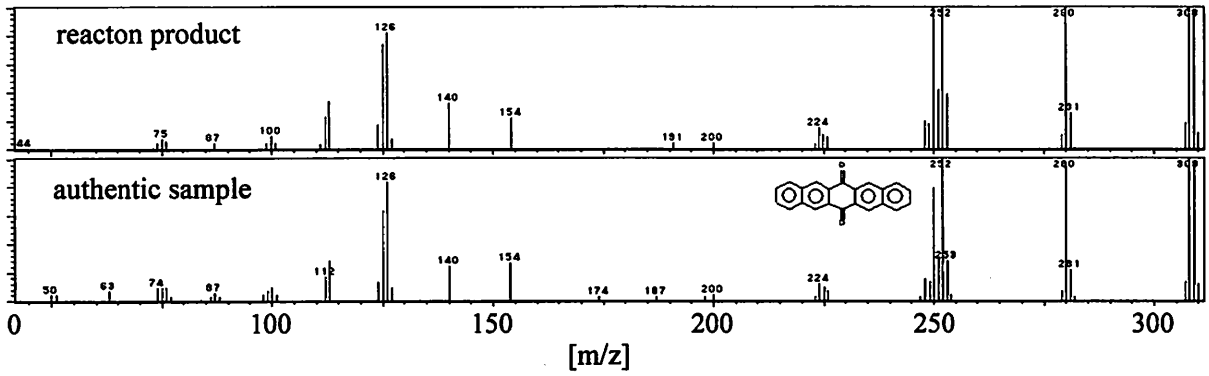


Fig.1 GC/MS spectrum of reaction product and authentic sample

Time-dependent changes of the yields of 6,13-pentacenequinone at each reaction temperature are given in Figure 2. The yield of 6,13-pentacenequinone first increased with time and eventually leveled off independent of the reaction temperature.

Early reaction time, 6,13- pentacenequinone yield has increased with reaction temperature. At reaction temperature of 250 ℃ and reaction time of 1min, the conversion was too low to determine the yield of 6,13-pentacenequinone. But 6,13-pentacenequinone yield has increased withreaction time ,and yield of 20 % was obtained at reactiontime of 20 min . It was investigated that water wasobtained for maximum self-dissociation constant at 250 ℃.

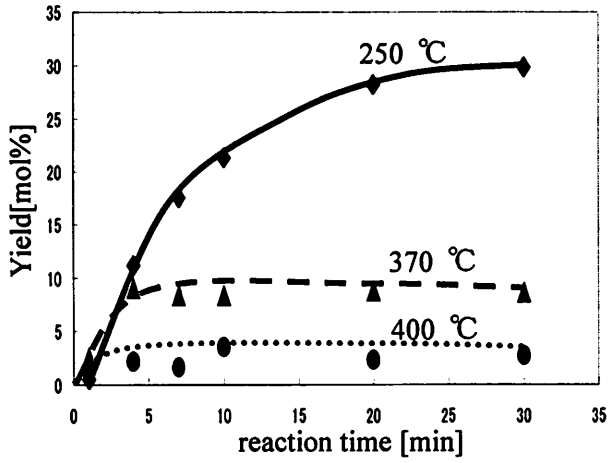


Fig.2 yield at each reaction time

In figure 3 are given the effects of the amount of water on the relative moler concentration of the starting materials at the product at 250 ℃ , and maximum yield of 80 % was obtained at the water to *o*-Phthalaldehyde molar ratio of 400:1. It followed from these observation that catalysis of water was responsible for this reaction.

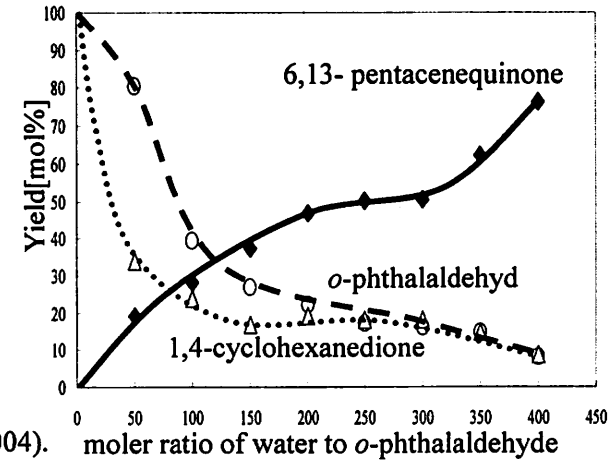


Fig.3 yield of molar rate change

[References]

1) C. M. Comisar, P. E. Savage, Green Chem., 6, 227 (2004).

2) V. Bruckner, A. Karczag, K. Kormendy, M. Meszaros and J. Tomasz, Tetrahedron Lett., 1, 5 (1960).

2P-29

Pd-perovskite applied to catalytic organic reaction

Mitsuhiro Yamada,[a,*] Hiroyuki Morikawa,[a] Junzo Nokami,[a] Yoshiki Hayakawa,[b]
Kimiyoshi Kaneko,[b] Shun-ichi Murahashi[a]
[a]Faculty of Engenieering, Okayama University of Science, 1-1, Ridai-cho, Okayama, 700-0005, Japan
[b]Hokko Chemical Industry Co., Ltd., 4-4-20, Nihonbashihonseki-cho, Chuo-ku, Tokyo, 103-8341, Japan
e-mail: nogami@dac.ous.ac.jp

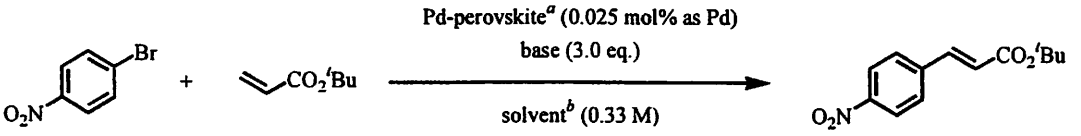
In recent years a large number of palladium-catalyzed syntheses for complex synthetic building blocks and also for structurally simple industrially important intermediate products have been found and further developed. Commercially available palladium compounds in the presence of different ligands were often used as catalysts. However, the quality of the used catalysts is generally not sufficient for industrial demands.

On the other hand, Perovskite-based palladium catalyst ($LaFe_{0.57}Co_{0.38}Pd_{0.05}O_3$), being high activity during long-term for use in automotive emissions control,[1] has been employed for Suzuki-Miyaura coupling[2] and more recently for Ullmann and Sonogashira reactions.[3]

We report here a few results of our recent investgation on Pd-perovskite-catalyzed C-C bond formation reaction using catalytic amount of Pd-perovskite, $LaFe_{0.95}Pd_{0.05}O_3$.

First, we tried Pd-perovskite-catalyzed Mizoroki-Heck reaction and discovered that a reaction condition using methyl cellsolve (MC) and sodium acetate gave the best result (entry 6, Table 1).

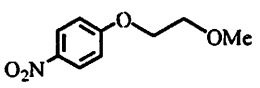
Table 1. Optimization of condition for Pd-perovskite catalyzed Mizoroki-Heck reaction.



1a (1 mmol) 2a (1.5 eq.) 3a

entry	base	solvent[b]	yield (%)[c]
1	NaOAc	ethylene glycol	trace
2	NaOAc	PEG-300	77
3	NaOAc	diglyme	N.R.
4	NaOAc	diglyme/H_2O(1/1)	87
5	NaOAc	H_2O	8
6	NaOAc	MC	99
7	NaOAc	MC/H_2O (1/1)	71
8	HCO_2Na	MC	76
9	K_2CO_3	MC	N.D.[d]
10	$^nBu_3N$	MC	N.R.

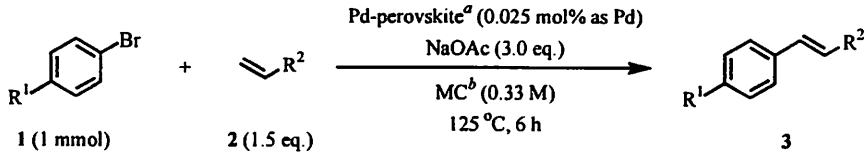
[a] Pd perovskite; $LaFe_{0.95}Pd_{0.05}O_3$. [b] MC; methyl cellsolve (2-methoxyethanol), PEG-300; polyethylene glycol 300 (average molecular weight = 300).
[c] Isolated yield. [d] Byproduct 4 was obtained in 44% yield.



4

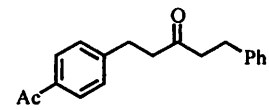
Aryl bromides having electron-withdrawing substituent, **1a,b**, gave the coupling products **3** quantitatively, although aryl bromides having electron-donating substituent did not give a satisfactory result (Table 2).

Table 2. Pd-perovskite catalyzed Mizoroki-Heck reaction.



entry		R^1		R^2	yield (%)[c]
1	**1a**	$-NO_2$	**2a**	$-CO_2{}^tBu$	99
2	**1a**	$-NO_2$	**2b**	-Ph	98
3	**1b**	-Ac	**2a**	$-CO_2{}^tBu$	86
4	**1b**	-Ac	**2b**	-Ph	92
5[d]	**1b**	-Ac	**2c**	$-C(OH)(CH_2)_2Ph$	35[e]
6	**1c**	-OMe	**2a**	$-CO_2{}^tBu$	5
7	**1d**	-H	**2a**	$-CO_2{}^tBu$	trace

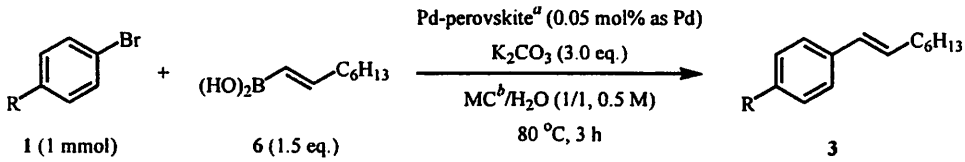
[a] Pd perovskite; $LaFe_{0.95}Pd_{0.05}O_3$.
[b] MC ; methyl cellsolve (2-methoxyethanol). [c] Isolated yield.
[d] 5 mol% of Pd-perovskite (0.25 mol% as Pd) was used.
[e] Byproduct **5** was obtained in 51% yield.



5

In the Pd-perovskite-catalyzed coupling reaction of aryl bromides with alkenylboronic acid **6**, the desired Suzuki-Miyaura coupling products were obtained in good yield for aryl bromides having electron-donating substituents as well as aryl bromide having electron-withdrawing substituents (Table 3).

Table 3. Pd-perovskite-catalyzed coupling reaction of aryl bromides with alkenylboronic acid.



entry		R	yield (%)[c]
1	**1a**	$-NO_2$	99
2	**1c**	-OMe	75
3	**1d**	-H	74

[a] Pd perovskite; $LaFe_{0.95}Pd_{0.05}O_3$. [b] MC ; methyl cellsolve (2-methoxyethanol).
[c] Isolated yield.

References

(1) Nishiyama, Y.; Mizuki, J.; Akao, T.; Tanaka, H.; Uenishi, M.; Kimura, M.; Okamoto, T.; Hamada, N. *Nature* **2002**, *418*, 164.

(2) Smith, M. D.; Stepan, A. F.; Ramarao, C.; Brennan, P. E.; Ley, S. V. *Chem. Commun.* **2003**, 2652.

(3) Lohmann, S.; Andrews, S. P.; Burke, B. J.; Smith, M. D.; Attfield, J. P.; Tanaka, H.; Kaneko, K.; Ley, S. V. *Synlett* **2005**, 1291.

2P-30

Optimization of Crystallization Experiments Using In-Process Particle Size Characterization: Lasenetec and PVM

Eric Hukkanen,* Benjamin Smith

Mettler-Toledo Autochem, Inc.

14833 NE 87th Street, Redmond, WA 98052, USA

eric.hukkanen@mt.com

Crystallization from solution is a widely applied unit operation for solids liquid separation and purification, with particular importance in both the pharmaceutical and bulk chemical industries. Typically, for an industrial crystallization, the size and shape of the crystals are very important process parameters. Product quality and efficacy are often contingent on adequate control of particle size and shape in the crystallizer. In addition, the characteristics of the material produced in the crystallizer can have a significant influence on subsequent downstream processing operations such as filtration, drying, milling, blending, granulation and tabletting. Lasentec and PVM have been successfully implemented for in-process particle size characterization in crystallization development and control from lab to production. Lasentec is a precise and sensitive measurement for quantifying the particle number, particle dimension, and particle shape. PVM is a probe-based high resolution imaging

system that enables the scientist to visualize the particle or droplet system as it naturally exists.

This presentation will focus on the implementation of PVM for the process understanding, development, and optimization of crystallization unit operations. Case studies that will be presented include detection of phase separation, polymorph conversion, and understanding particle agglomeration/aggregation mechanisms.

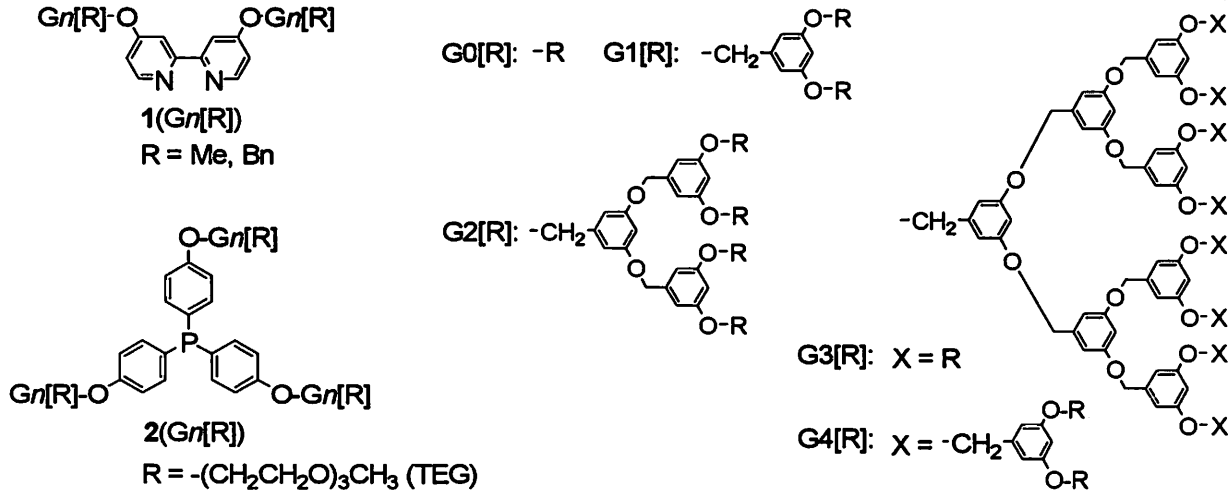
2P-31

Efficient Catalytic Process Using Dendritic Catalyst

Ken-ichi Fujita,* Takahito Muraki, Masato Kujime
National Institute of Advanced Industrial Science and Technology (AIST)
AIST Tsukuba Central 5, 1-1-1, Higashi, Tsukuba, Ibaraki, 305-8565, Japan
k.fujita@aist.go.jp

The development of a recyclable catalyst has been required from the perspectives of green chemistry. One of the most certain methods of recycling a catalytic metal is its immobilization on a macromolecular ligand.

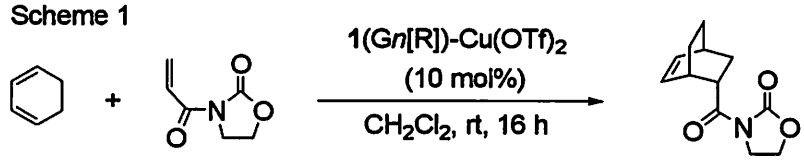
Dendrimers are fascinating macromolecules due to their unique physical and chemical properties, which are caused by their well-defined hyperbranched framework. Metallodendrimers, with catalytic sites immobilized within the dendrimer, are particularly useful as synthetic catalysts not only because of their unique reactivity and fair solubility but also because of their recyclability by reprecipitation or by nanofiltration (membrane separation) based on their nano-order size. We wish to report herein the unique catalytic activity of dendritic catalyst and their easy recycling by reprecipitation or by nanofiltration.



By performing Diels–Alder reaction using 10 mol% of various-generation dendritic Lewis acid catalysts 1(G*n*[R])-Cu(OTf)$_2$, the chemical yield of an adduct was enhanced by increasing the generation of the dendritic Cu(OTf)$_2$ catalyst. This relationship between the generation of the dendritic catalyst and the chemical yield is one of the positive dendritic effects (Scheme 1).[1]

Next, we examined the recycling of the dendritic catalyst in Diels–Alder reactions with 10 mol% of the 1(G*n*[Me])-Cu(OTf)$_2$ catalyst. After the reaction had proceeded for 30 min, the reaction mixture was poured into hexane and was stirred to precipitate the dendritic catalyst 1(G*n*[Me])-Cu(OTf)$_2$, which was collected by filtration and was subsequently reused. Both the second- and the third-generation dendritic Cu(OTf)$_2$ catalysts could be used 5 times without deactivation (Scheme 2).[2]

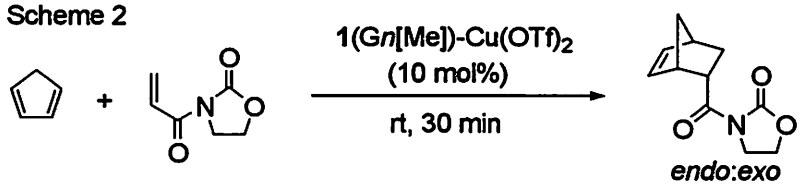
Scheme 1



R	Gn	Yield (%)
Me	G1	5
	G2	56
	G3	80

R	Gn	Yield (%)
Bn	G1	77
	G2	87
	G3	94

Scheme 2



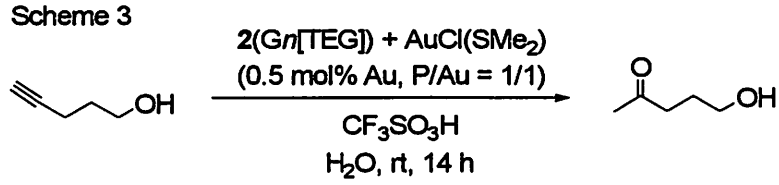
endo:*exo*
9:1

Gn	Yield (%)					
	Recycle	—	1st[a)]	2nd	3rd	4th
G2[b)]		88	98	99	95	88
G3[c)]		94	94	99	99	99

a) Number of recycle b) Carried out in CH_2Cl_2
c) Carried out in toluene

By performing hydration reaction of alkynes using 0.5 mol% of various-generation dendritic phosphine-gold catalysts (2(G*n*[TEG])+AuCl(SMe_2)), the corresponding hydration products were obtained in fair yields in all generations. Especially, in the case of using 2(G4[TEG]), the corresponding dendritic phosphine-gold catalyst was recovered by nanofiltration and was subsequently reused. The fourth-generation dendritic catalyst could be used four times without deactivation (Scheme 3).

Scheme 3



	G1	G2	G3	G4	G4	G4	G4
Yield (%)	93	89	86	89	90	93	91
					Recycle 1st	2nd	3rd

Reference

1) K. Fujita, T. Muraki, H. Hattori, T. Sakakura, *Tetrahedron Lett.*, 47, 4831–4834 (2006).

2) T. Muraki, K. Fujita, M.Kujime, *J. Org. Chem.*, 72, 7863–7870 (2007).

2P-32

Process Development of MCP-1 R antagonist TEI-E00526

Hiroaki Makino,*[1] Asahi Kawana[2], Yoshinori Satou[1] and Takumi Takeyasu[1]

1. Pharmaceutical Products Research Laboratories, Teijin Pharma Limited
2-1, Hinode-cho, Iwakuni, Yamaguchi, 740-8511, Japan

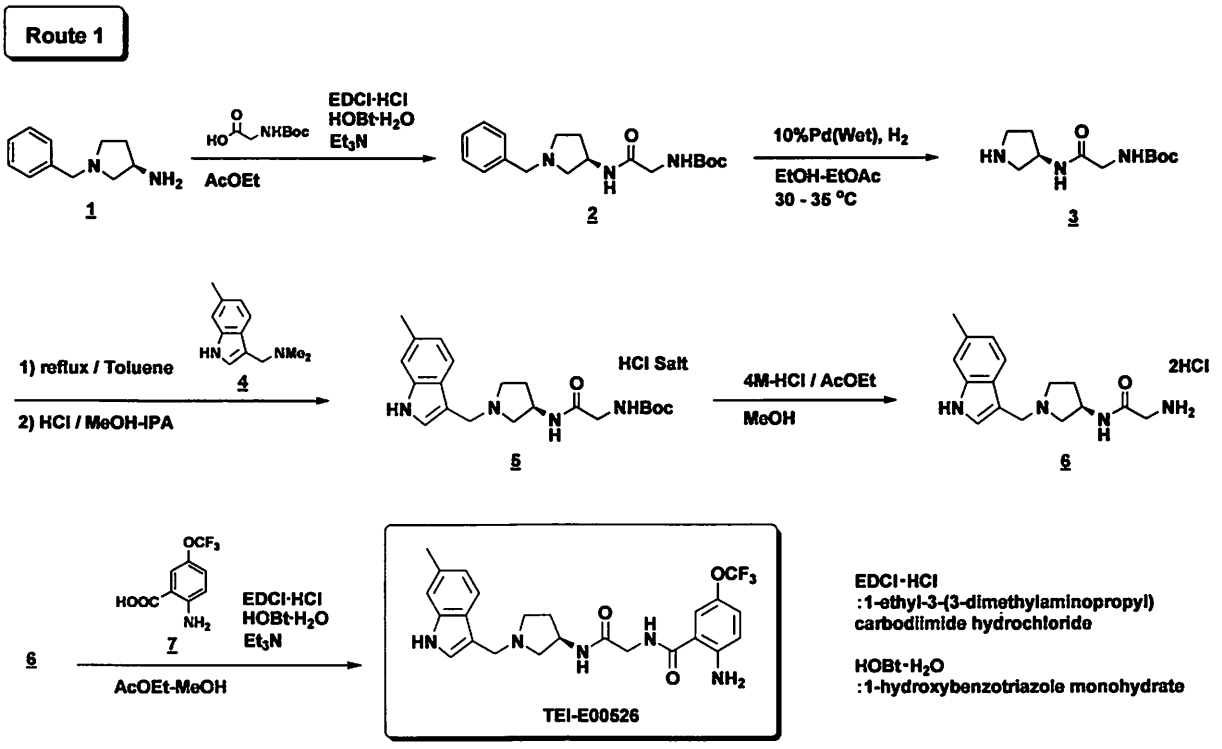
2. Pharmaceutical Discovery Research Laboratories 1, Medicinal Chemistry Research Department 1, Teijin Pharma Limited
4-3-2, Asahigaoka, Hino, Tokyo, 191-8512, Japan

h.makino@teijin.co.jp

The TEI-E00526 of our developing active ingredient has been discovered as a highly active compound having a MCP-1 receptor antagonist activity. It has been widely known that a MCP-1, a kind of chemokines induces various inflammatory symptoms when it binds to the receptor. In this respect, we may expect that the TEI-E00526 will be a good candidate as a therapeutic drug for inflammatory diseases thanks to its MCP-1 receptor antagonism.

We have initiated to design the manufacturing process of the TEI-E00526.

At the early process design in the drug discovery stage, a column purification procedure was required at each synthesis step from the intermediate to the final drug substance. However, we have succeeded in dispensing with the column purification procedure by forming a hydrochloride salt (5) of each intermediate and by purifying the hydrochloride salt under crystallization. Considering that the TEI-E00526 is liable to decompose in a hot solution, instead of a conventional crystallization procedure, we apply the crystallization process where a target compound is crystallized while the hydrochloride salt solution is neutralized with an adding alkaline solution. Moreover, we have succeeded in dispensing with the isolation process by using a common solvent over the entire reaction steps. (Route 1)

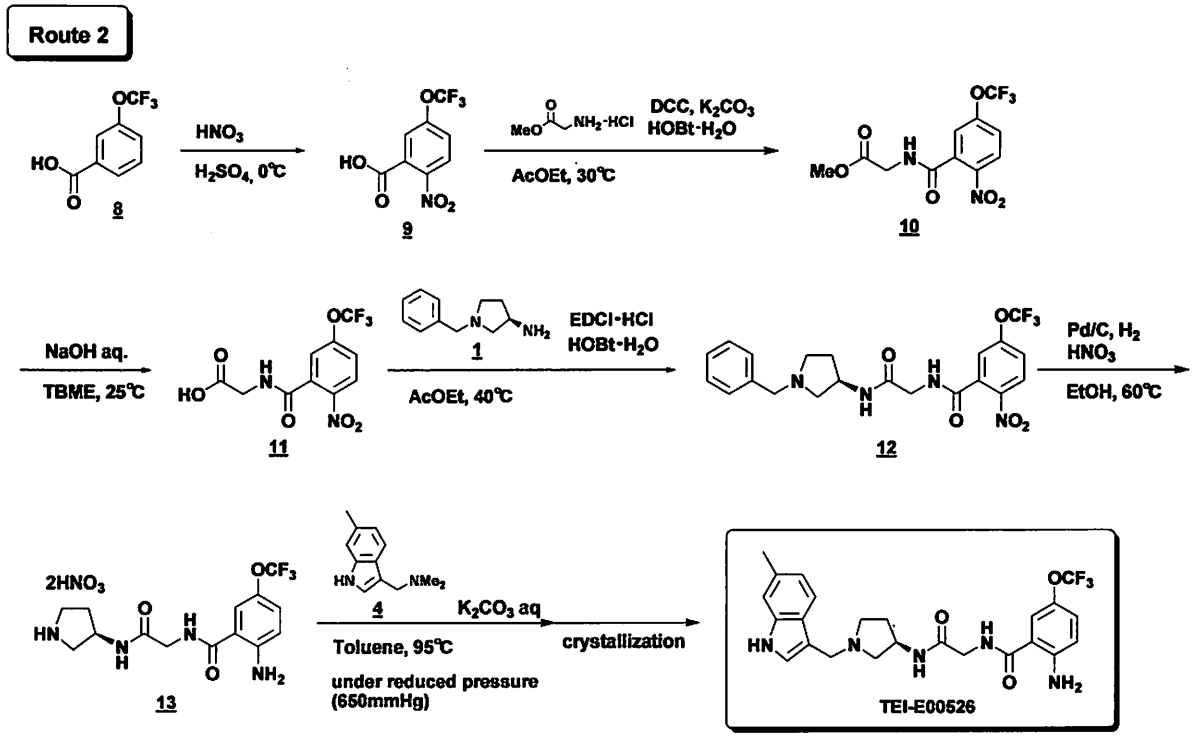


In the course of our process development, we encountered the following problems: expensive 2-amino-5-trifluoromethoxybenzoic acid (7) was needed for this process, and traces of many impurities probably attributed to the condensation agent {1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride} or the reaction auxiliary agent (1-hydroxybenzotriazole monohydrate), which were used at the reaction processes, were contaminated into the final drug substance bulk. To solve the above problems, we challenged the improvement of the reaction process for the drug substance.

Firstly, we have established the synthesis route (Route 2) at which inexpensive 3-trifluoromethoxybenzoic acid (8) is used as the starting material. Because the expensive materials (1) and (4) are used at the latter steps of the synthesis route, we can expect a cost benefit with this synthesis route. Besides, due to the high crystallization potency of the intermediates (10) and (12) having nitro-groups, the recrystallization procedure can be performed effectively and thus high quality intermediates are produced in this synthesis route.

At the hydrogenation reaction between the intermediates (12) and (13) where deprotection and nitro-reduction were performed, several kinds of impurities were generated. To reduce such impurities we examined to add appropriate substances such as palladium-carbon, acid etc, and finally reached the applicable reaction conditions.

For the coupling reaction between the intermediates (13) and (4), which is the final synthesis step, we have established the reaction conditions under which any reagents that may potentially remain in the final bulk are excluded.



Based on the above studies, we have established the several 100-g scale synthesis route for the TEI-E00526 bulk to such a level that the total yield is 65% and purity is 98.8%. We have confirmed, through a several kg-scale run, that there was no specific problem in the operation performance and safety of this synthesis process.

2P-33

New Syntheses of Diaryl Ketones and Diaryl 1,2-Diketones: Nucleophilic Aroylation with Arylaldehydes by *N*-Heterocyclic Carbene Catalysis

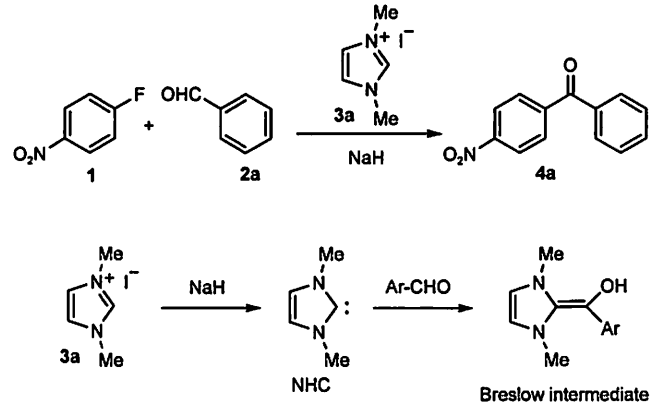
*Yumiko Suzuki, Shinya Ota, Yoshinori Fukuta, Abu Bakar Md., Takashi Tanoi, Masayuki Sato
School of Pharmaceutical Sciences, University of Shizuoka
52-1 Yada, Suruga-ku, Shizuoka, 422-8526, Japan
suzuyumi@u-shizuoka-ken.ac.jp

N-heterocyclic carbenes (NHCs) play an important role as organocatalysts in a number of reactions.[1,2] Besides the widely known benzoin condensation and Stetter reaction, the use of the NHCs as organocatalysts has recently been extended to a variety of reactions such as transesterification/amidation, living ring-opening polymerization, and homoenolate reaction.

We have employed the NHCs as catalysts for the nucleophilic substitution of electron-deficient haloheteroarenes, *N*-phenylimidoyl chlorides, and fluorobenzenes bearing electron-withdrawing groups.[3] In this substitution, the halogen substituents of these compounds are replaced by aroyl groups originating from aldehydes to afford keto compounds. We found the reaction is a useful tool for the syntheses of diaryl ketones and diaryl 1,2-diketones.

1. Synthesis of diaryl ketones

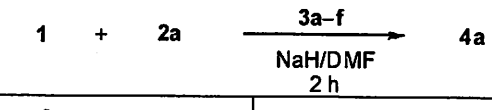
The nucleophilic aryolation of **1** with benzaldehyde **2a** using the NHC derived from **3a** affords 4-nitrobenzophenone **4a** (Scheme 1).[4] It is considered that the reaction pathway includes the "Breslow intermediate,"[1] as in the benzoin and Stetter reactions.



Scheme 1. Nucleophilic aroylation of 4-fluoronitrobenzene **1**.

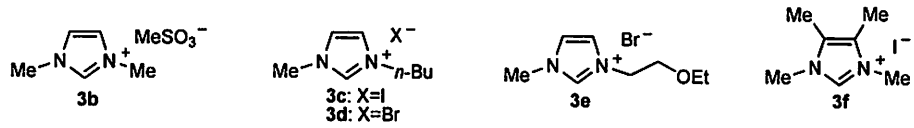
We have examined the aroylation of fluorobenzenes using imidazolium salts with various substituents as NHC precursors in order to improve the yields and reduce catalyst loading. The reaction of **1** with **2a** was carried out using 30 mol% of **3a** as the NHC precursor and sodium hydride at −15°C up to room temperature in DMF (Table 1, entry 1). The NHC was generated in situ and catalyzed the reaction to afford **4a** in 66% yield. The reactions using the other imidazolium salts **3b–f** were also examined under the same reaction conditions (entries 2–6). It was expected that the electron-donating effect of the methyl groups at C-4 and C-5 of imidazol-2-ylidene would increase the nucleophilicity of the carbene center and accelerate the reaction. In fact, the reaction in the presence of the NHC derived from 1,3,4,5-tetramethylimidazolium iodide **3f** yielded **4a** quantitatively (entry 6). When the catalyst loading was decreased to 10 mol%, the reaction using **3f** proceeded in 81% product yield (entry 7). Even with 1 mol% of **3f**, the product yield did not drop significantly and **4a** was obtained in 79% yield under the same condition (entry 8).

Table 1. Benzoylation of **1** using **3a–f** as NHC precursors.



entry	cat. (mol%)	condition[a]	yield (%)	entry	cat. (mol%)	condition[a]	yield (%)
1	**3a** (30)	A	66	5	**3e** (30)	A	75
2	**3b** (30)	A	45	6	**3f** (30)	A	quant.
3	**3c** (30)	A	70	7	**3f** (10)	B	81
4	**3d** (30)	A	76	8	**3f** (1)	B	79

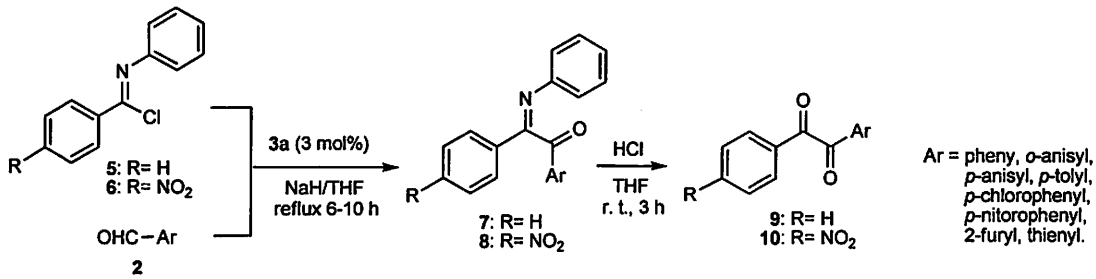
[a]A: –15°C to r. t. B: –15°C, 10 min and then to –5 to 0°C.



2. Synthesis of diaryl 1,2-diketones

Diaryl 1,2-diketones are very important intermediates since they serve as building blocks for the syntheses of biologically active biaryl heterocyclic compounds. The synthesis of diaryl 1,2-diketones **9,10** was examined through NHC-catalyzed aroylation of *N*-arylbenzimidoyl chlorides **5,6** with aromatic aldehydes **2**, followed by the hydrolysis of the products.

Chlorides **5,6** were synthesized from the corresponding benzanilides. The aroylation of **5,6** with **2** was carried out using 3 mol% of **3a** in refluxing THF to afford α-ketoimines **7,8** in good yields (74–91%). The treatment of **7,8** with 10% HCl yielded diaryl 1,2-diketones, in most cases, quantitatively.



In summary, we have demonstrated that the NHC-catalyzed aroylation is useful for the synthesis of diaryl ketones and diaryl 1,2-diketones. The NHC derived from 1,3,4,5-tetramethylimidazolium iodide exhibited a high catalytic activity for the aroylation of fluorobenzens.

References

1. *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, 2006.
2. Enders, D.; Niemeier O.; Henseler A. *Chem. Rev.* **2007**, *107*, 5606–5655.
3. Suzuki, Y. *J. Syn. Org. Chem. Jpn.* **2008**, *66*, 377–386.
4. Suzuki, Y.; Toyota, T.; Imada, F.; Sato, M.; Miyashita, A. *Chem. Commun.* **2003**, 1314–1315.
5. Suzuki, Y.; Ota, S.; Fukuta, Y.; Ueda, Y.; Sato, M. *J. Org. Chem.* **2008**, *73*, 2420–2423.

2P-34

Development of micro chemical process by intensive controls of exlplosive atmosphere

*Tomoya Inoue, [+]Yoshikuni Kikutani, Satoshi Hamakawa, [+]Kazuma Mawatari,
Fujio Mizukami, and [+,++]Takehiko Kitamori
Research Center for Compact Chemical Process, AIST
[+]Micro Chemistry Group, KAST
[++]Graduate School of Engineering, The University of Tokyo
4-2-1, Nigatake Miyagino-Ku, Sendai, Miyagi 983-8551, Japan
inoue-tomoya@aist.go.jp

Recently, efforts in process miniaturization and microreaction technology has shown opportunity for conducting chemical processes with potential danger safely - such as direct fluorination with gas phase fluorine, ozonolysis, synthesis of intermediates of explosives, as well as gas phase hydrogen oxidation reaction. These safety characteristics of micro fabricated reactor can be attributed to rapid heat dissipation by the factor of 100, preventing the generation of hot spot during reaction, owing to higher surface to volume ratio compared with conventional reactors. Also, microstructure inside the reactor helps generate high interfacial area between gas and liquid, which promotes mass transfer.

The author had demonstrated the eligibility of microreactor technology by hydrogen peroxide synthesis via direct combination between hydrogen and oxygen. This reaction is multiphase reaction among the reactant gases, the reaction solution and catalyst. The application of the microreactor technology was so advantageous that the explosive reaction between hydrogen and oxygen did not occur even using the explosive content, as well as coexistence of palladium catalyst that could ignite the explosion (Figure 1). We regard that the nature of this technology, such as rapid heat dissipation and the suppression of radical propagation reaction in the explosive hydrogen oxygen mixture, worked beneficially in conducting the reaction safely. The author also successfully analyzed the reactor performance for the efficiency estimation of mass transfer from gas to liquid. The overall mass transfer coefficient ($K_l a_i$) for hydrogen was estimated to be 3.8, which shows more efficient mass transfer compared with conventional reactor technologies.[1]

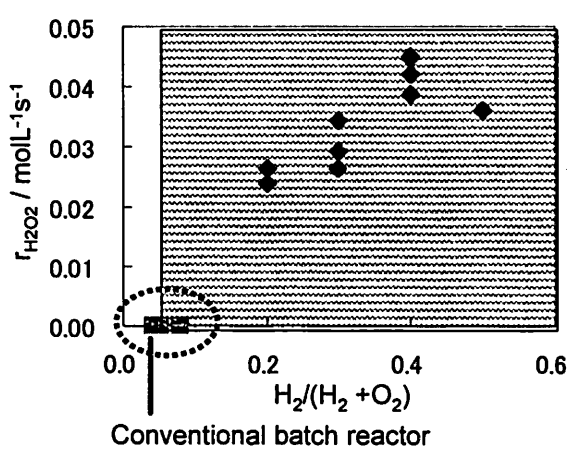


Figure 1. Comparison of the reactor performance between the microreactor and conventional batch reactor. The enhancement of productivity by the microreactor can be attributed to higher hydrogen content and efficient mass transfer.

Based on these results, we conducted the reaction by glass fabricated reactors. As it is transparent, flow regime inside the reactor can be easily monitored during the reaction, which is crucial for the reactor performance. Also glass as the reactor material has been proved by the fine chemical processes, as a good example by Lonza's c-SSP process.[2] Microchannels were fabricated by the combination of chemical etching (Institute for Micro Technology (IMT), Japan) and mechanical machining. Chemical etching was suitable for channel fabrication less than 100 micrometer width, while mechanical machining is suitable for larger channels with more than 200 micrometer width. Once microchannels as well as inlet/outlet holes were fabricated on glass wafers (30mm width X 70mm length X 0.7mm depth), each wafer was thermally bonded (IMT). Catalyst was loaded into the channel (600 micrometer width X 300 micrometer depth) by slurry. The overview of the reactor is shown in Figure 2.

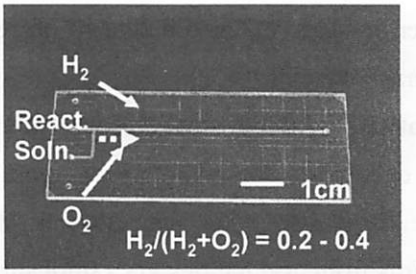


Figure 2. The reactor used for the H_2-O_2 reaction in the explosive condition

We found that the gap of channel size is crucial for the reactor design, especially for validating proper gas – liquid distribution into the reactor. When gas channel was more than 100 micrometer width, the flow regime was unstable because of the crosstalk between gas and liquid dispensing channels, causing pulsing flow into the catalyst bed. The crosstalk between the gas – liquid dispensing channel was significantly improved when the width of gas inlet channel became 50 micrometer (depth of the channel became 25 micrometer because of the geometrical characteristics of wet etching). As the both of gas and liquid flows are pressure driven, we regard that the difference of pressure drop by gas and liquid is responsible for this crosstalk issue.[3] Gas channels should be narrow enough in order to compensate the pressure drop difference between gas and liquid channel.

We could successfully achieve the hydrogen peroxide concentration more than 2 wt% as the preliminary results, while it was around less than 0.2 wt% in the previous results. The advantages of the microreactor technology based process as well as the results of productivity intensification will be disclosed on site.

Acknowledgement

This research project is supported by the Grant for Industrial Technology Research (Project ID: 07A31002a), NEDO (The New Energy and Industrial Technology Development Organization), Japan.

References

1 T. Inoue, M. A. Schmidt, and K. F. Jensen, *Ind. Eng. Chem. Res.* **46,** 1153 (2007).

2 D. M. Roberge, N. Bieler, and M. Thalmann, *PharmaChem.* **June,** 15 (2006).

3 Y. Wada, M. A. Schmidt, and K. F. Jensen, *Ind. Eng. Chem. Res.* **45,** 8036 (2006).

2P-35

Synthesis of Benzazoles

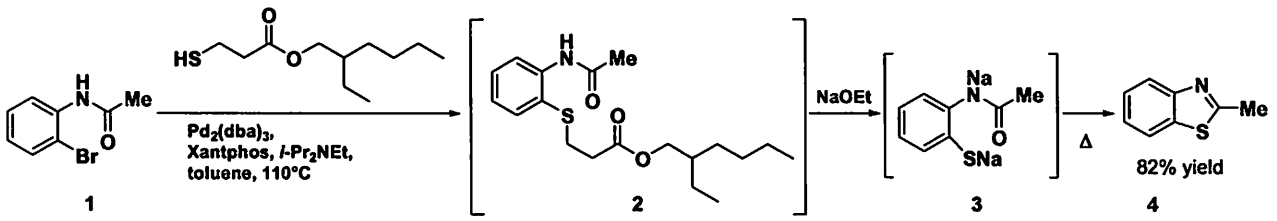
Yuhei Yamamoto,* Takahiro Itoh, Toshiaki Mase,
Process Research Preclinical Development, Banyu Pharmaceutical Co., Ltd
3 Okubo, Tsukuba, Ibaraki, 300-2611, Japan
yuhei_yamamoto@merck..com

Substituted benzazole is a structural motif that is seen in many pharmaceutically and biologically interesting molecules. Although the widespread interest in benzazole-containing structures has prompted extensive studies for their synthesis, practical synthetic methods to access this class of molecules are rather limited. In this poster session, we would like to present our recent findings on practical synthesis of benzothiazoles and benzimidazoles.

A Novel Practical Synthesis of Benzothiazoles via Pd-Catalyzed Thiol Cross-Coupling[1]

Recently, we have developed the Pd-catalyzed cross-coupling reaction of aryl bromide/triflates and alkyl/aryl thiols. We have also been interested in developing protocols that would allow for the preparations of aryl thiols from aryl halides via a thiol surrogate. In the initial study for the preparation of sulfide, we carried out the reaction of 2'-bromoacetanilide **1** with a very inexpensive and odorless 2-ethylhexyl 3-mercaptopropionate as a thiol surrogate catalyzed by $Pd_2(dba)_3$/Xantphos to afford the corresponding sulfide **2** (Scheme 1). The resulting sulfide **2** was treated with NaOEt at room temperature to afford the corresponding sodium thiolate **3** followed by heating at reflux to form 2-methylbenzothiazole **4** in 82% yield via intramolecular condensation.

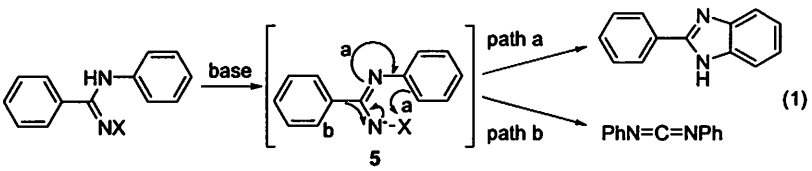
Scheme 1.



Various 2-bromobenzanilides was converted into the corresponding benzothiazoles in good yields *via* Pd-catalyzed C-S bond formation followed by deprotection and the condensation. The yields of C-S bond formation did not depend on the substrates; however, the yields and the conditions of the intramolecular condensation depended on the substrates. The substrates possessing an electron-deficient or neutral carbonyl group of amides rapidly cyclized under basic conditions at reflux temperature. When the amide was electron rich, on the other hand, the yield of the condensation under basic conditions was quite low. The basic condensations of some anilides possessing electron-withdrawing groups on the benzene ring were also sluggish. Unlike the basic conditions, the acidic conditions were more effective (shorter reaction time and higher yield). It was found that trifluoroacetic acid (TFA) was the best reagent. Details would be discussed on the poster session.

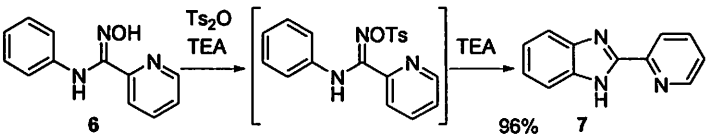
Synthesis of substituted benzimidazoles via tosylation of N-aryl amidoxime[2]

The most commonly used starting materials to synthesize benzimidazoles are *ortho*-aminoanilines, and these amines are either condensed with carboxylic acids (or their synthetic equivalents), or reacted with aldehydes in the presence of an oxidant. Recent publications have synthesized these moieties *via* transition metal catalyzed amination of *ortho*-haloaniline derivatives as the key reaction. The main drawback of these procedures is the requirement of *ortho*-substituted anilines, and thereby limits the diversity of the available starting materials. We became interested in developing a practical and effective pathway to benzimidazoles which does not rely on substituted anilines. We were particularly interested in the reaction involving nitrene precursor intermediate **5** (Eq. 1). It is reported that two modes of reaction can be envisioned for the intermediate **5**. Firstly, cyclo-a-elimination which gives the desired benzimidazole (path a), and secondly, rearrangement leading to the carbodiimide (path b), and the mode of the reaction (path a vs. path b) is influenced by the leaving group on the amidine nitrogen. In order to get further insights this relationship, we envisioned that *N*-aryl amidoximes are excellent substrates since the hydroxy group of the amidoxime could be easily modified. *N*-aryl amidoximes can readily be prepared by reaction of aniline with either imidoyl cholorides or with nitrile oxides.



(1)

We started our investigation using *N*-hydroxy-*N'*-phenyl-2-pyridinecarboximidamide **6** as the starting material, which was obtained in 92% yield by the reaction of aniline and *N*-hydroxy-2-pyridinecarboximidoyl chloride in the presence of TEA. The hydroxy group of the amidoxime was converted to several leaving groups *in situ*, and subsequent reaction to yield the benzimidazole proceeded without further treatment. Among the conditions we investigated, tosylation with Ts_2O in the presence of triethylamine was the best, and gave the product in 96% yield.



References

1. Itoh, T.; Mase, T., *Org. Lett.* **2007**, *9*, 3687–3689.

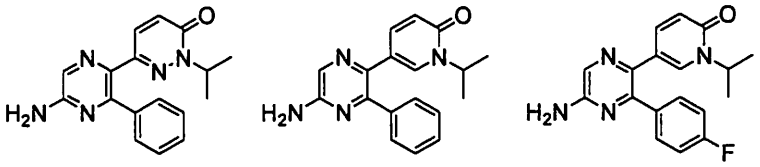
2. Yamamoto, Y.; Tsuritani, T.; Mase, T. *Tetraheron Lett.*, **2008**, *49*, 876–878.

2P-36

Rapid Parallel Development for Three Adenosine A1/A2a Receptor Antagonists

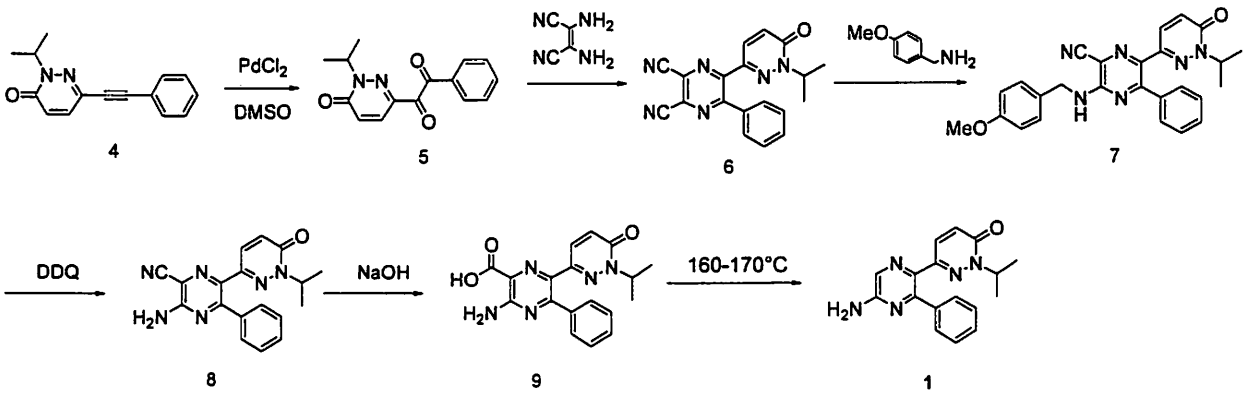
Ryoki Orii,* Hiroyoshi Matsubara, Takashi Kikuchi, Norio Hashimoto, Shunsuke Goto
Process Chemistry Laboratories, Astellas Pharma Inc.,
160-2, Akahama, Takahagi-shi, Ibaraki, 318-0002, Japan
ryoki.orii@jp.astellas.com

Compounds **1**~**3**, the adenosine A1/A2a receptor antagonists, are chosen for the development. For the selection of the best candidate, kgs amount of each compound was necessary in a short period to have a long term toxic study. First, considering the structural similarity of **2** and **3**, we concluded to adopt their medicinal divergent route for the first sample manufacturing. On the other hand, we had invented a new DAPA (2,3-diaminopropionic acid hydrobromide) route for **1**, which is applicable to future commercialization. As a result of these rapid parallel process developments, three compounds became available very quickly. At the second stage, we developed a new DAPA route for **2** and **3**. We will present the effectiveness of these approaches at the early stage of process development.

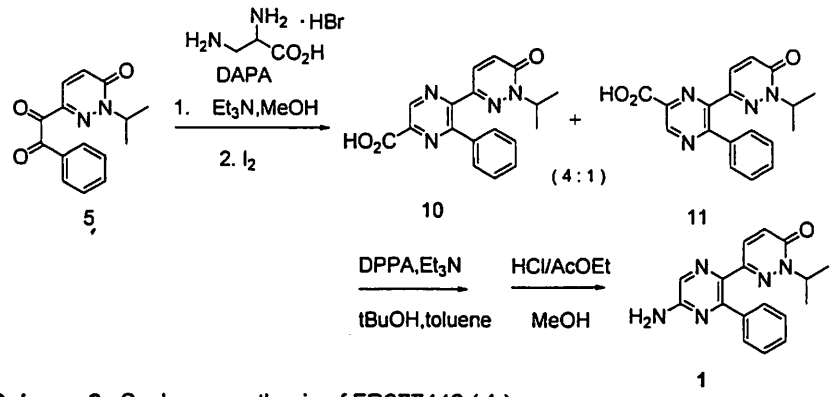


FR277446 (**1**) FR294063 (**2**) FR295854 (**3**)

The medicinal chemistry synthesis of compound **1** was 6 steps and summarized in Scheme 1. In the third step, hydrogen cyanide was evolved. The use of DDQ and high temperature decarboxylation were other issues. Various attempts were tried, and a new synthesis via pyrazine formation using DAPA was found and summarized in Scheme 2. Though the isomer ratio was 4:1, we invented a highly efficient separation procedure based on the difference of pH dependent solubility profile of two compounds.

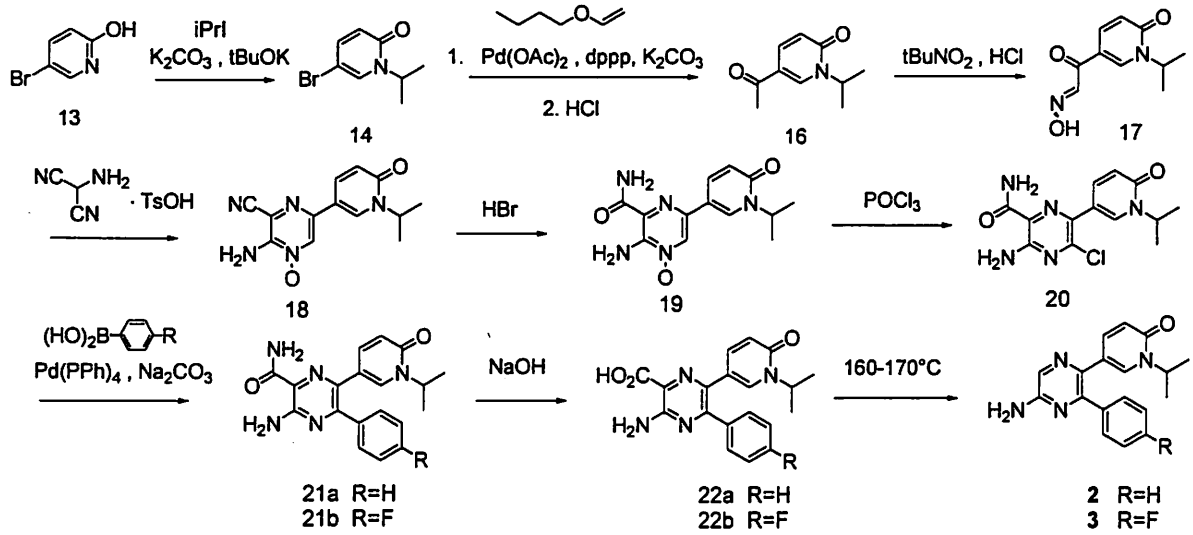


Scheme 1. Medicinal chemistry synthesis of FR277446 (**1**)

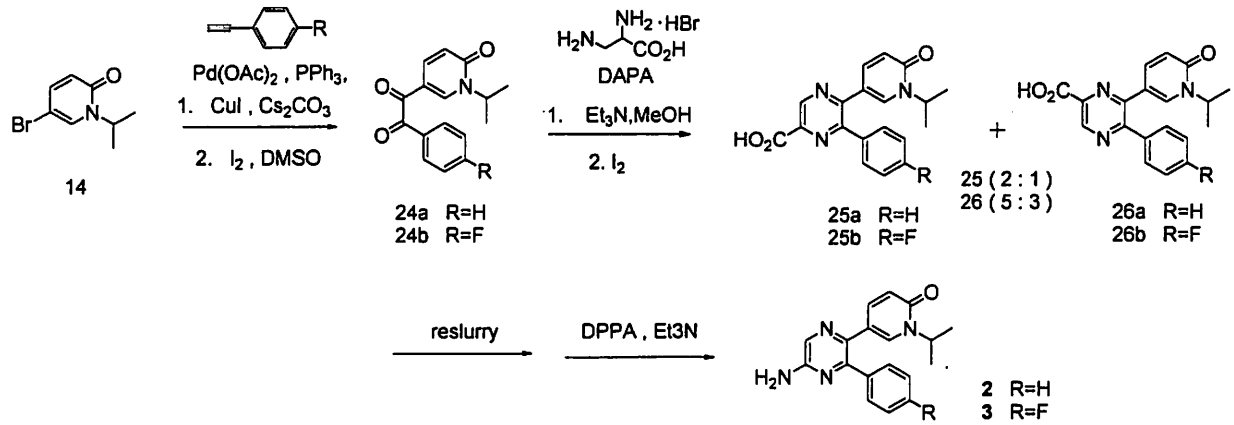


Scheme 2. Scale-up synthesis of FR277446 (**1**)

For compound **2** and **3**, we have chosen divergent medicinal route for the first scale-up, because it could deliver two compounds from a common intermediate quickly (Scheme 3). The medicinal route suffered from several problems from a view point of industrial manufacturing. So, we tried to apply the new DAPA route for the synthesis of these compounds. Though the selectivity of the two isomers needed further optimization, we developed a practical chromatography-free process in a very short period (Scheme 4).



Scheme 3. Medicinal chemistry synthesis of FR294063 (**2**) and FR295854 (**3**)



Scheme 4. Scale-up synthesis of FR294063 (**2**) and FR295854 (**3**)

2P-37

Process Intensification Assisted by Zeolite Membranes

*Tomoya Inoue, Takako Nagase, Yasuhisa Hasegawa, Yoshimichi Kiyozumi
Satoshi Hamakawa, +Toshikazu Nishide, and Fujio Mizukami
Research Center for Compact Chemical Process, AIST
+Graduate School of Engineering, Nihon University
4-2-1, Nigatake Miyagino-Ku, Sendai, Miyagi 983-8551, Japan
inoue-tomoya@aist.go.jp

Water removal process often plays an important role among organic chemical processes, and pervaporation (PV) by organic and/or inorganic membranes is attracting attentions as an alternative of distillation, especially handling azeotropes. Chemoselective performance is mandatory for separating azeotrope, and zeolite membranes have been proved to be capable for dehydration from lower alcohols compared with polymer membranes. Still, chemical stability should be intensified for extensive use of zeolite membranes among chemical processes, especially acid tolerance as well as hydrothermal stability for long term operation.[1-3]

Recently, we succeeded in preparing hydrophilic zeolite membrane (CHA, MER and PHI) with acid tolerance, so that we could conduct dehydration reactions assisted by pervaporation via these zeolite membranes. The membranes we prepared were based on Merlinoite (MER, Si/Al = 2.34), Phillipsite (PHI, Si/Al = 2.34) and Chabazite (CHA, Si/Al = 2.34). All were prepared in our laboratory by secondary zeolite crystalline growth on mullite tubings. We investigated pervaporation performances of these zeolite membranes and dehydrative condensation reactions with acid catalysts. PV performances as well as condensation reactions were conducted below 323 K.[4-6]

Table 1 shows the comparison of PV performance among zeolite membranes for equimolar mixture of ester condensation reaction solution at 313 K. CHA membrane and MER membrane exhibited excellent dehydration properties for both flux and water selectivity among these membranes. PHI membrane also showed good dehydration property, and its development will be updated in our presentation.

Table 1 PV performance of zeolite membranes at 313 K

Membrane species	total initial flux(kg m^{-2} h^{-1})	Separation factor α
CHA*	0.383	500
MER*	0.178	1800
PHI*	0.131	24
MER**	0.211	25

*Initial feed content was equimolar mixture of acetic acid, ethyl acetate, ethanol and water. Separation factor α was defined as (water content in the permeate / organic content in the permeate) / (water content

in the feed / organic content in the feed). **Initial feed content was equimolar mixture of methanol and water.

Figure 1 shows the reaction profile in the batch reactors. PV by CHA membranes promoted methyl acetate yield, whose effect became visible from 6 - 8 hours after the reaction started, and the ester yield reached 98 %, exceeding the equilibrium yield by nearly 25 %. Conventionally, methyl acetate has been produced by Eastman Process, in which reactive distillation removes methyl acetate out of the reaction system. In this case, the product should be volatile enough compared with reactants (methanol and acetic acid) and other product (water), which limits the availability of reactive distillation process for other methyl ester syntheses. On the contrary, PV aided process removes water from the reaction system, which validates the wide range availability compared with conventional reactive distillation process. At the same time, it should be noted that acid tolerant hydrophilic zeolite membranes are strongly favored for this process. As we discussed in PV performances of zeolite membranes, some zeolite membranes, such as our CHA and/or MER based membranes, exhibit excellent permselectivity of water even from water-methanol mixture. Such selectivity is hard to achieve for polymer based conventional membranes.

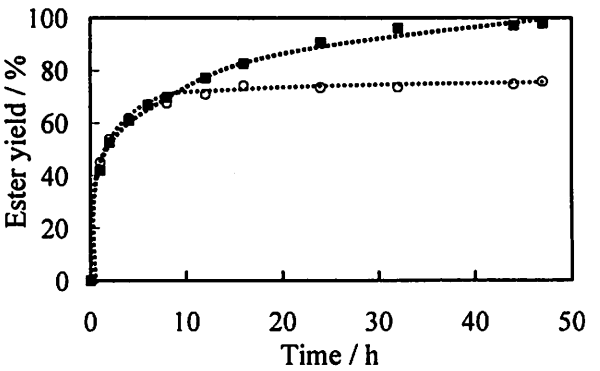


Figure 1. PV assisted stoichiometric ester condensation reaction between methanol and acetic acid at 313 K. PV was conducted using CHA membrane. Blank test (non-PV) was also conducted (○), with the same condition except PV.

Acknowledgement

This research project is partly supported by the Grants-in-Aid for Scientific Research (Scientific Research (C) Project ID: 20560709), JSPS (Japan Society for the Promotion of Science), Japan.

References

1 X. Feng, and R. Y. M. Huang, *Ind. Eng. Chem. Res.* **36**, 1048 (1997).

2 T. C. Bowen, R. D. Noble, and J. L. Falconer, *J. Membrane Sci.* **245**, 1 (2004).

3 K. Tanaka, R. Yoshikawa, C. Ying, H. Kita, and K.-i. Okamoto, *Chem. Eng.Sci.* **57**, 1577 (2002).

4 T. Nagase, Y. Kiyozumi, Y. Hasegawa, and F. Mizukami, *Clay Sci.* **12**, (Suppl. 2), 100 (2005).

5 T. Inoue, T. Nagase, Y. Hasegawa, Y. Kiyozomi, K. Sato, K. Kobayashi, M. Nishioka, S. Hamakawa, and F. Mizukami, *Chem. Lett.* **35**, 76-77 (2006).

6 T. Inoue, Y. Hasegawa, T. Nagase, Y. Kiyozumi, S. Hamakawa, and F. Mizukami, in *Proc. MRS (Vol. 894)*, 2005; p. 211.

7 T. Inoue, T. Nagase, Y. Hasegawa, Y. Kiyozumi, K. Sato, M. Nishioka, S. Hamakawa, and F. Mizukami, *Ind. Eng. Chem. Res.* 46, 3743 (2007).

2P-38

Development of Polymer Incarcerated Osmium Catalyst

Yasunori Tsuchiya[2]*, Ryo Akiyama[2], Hidekazu Oyamada[2], Shū Kobayashi[1,2]

The Univ. of Tokyo[1] ; ERATO, JST[2]

3-1, Hongo 7-chome, Bunkyo-ku, Tokyo, 113-0033, Japan

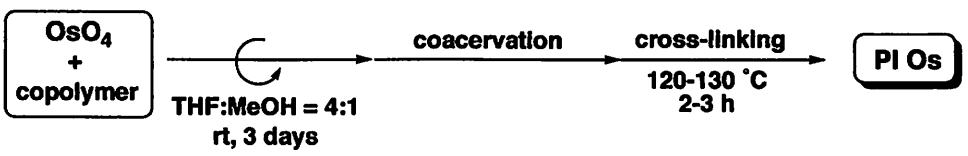
shu_kobayashi@chem.s.u-tokyo.ac.jp

In 1998, we reported the dihydroxylation of various alkenes using polystyrene- microencapsulated (PS-MC) Os catalyst with *N*-methylmorpholine *N*-oxide (NMO) as the cooxidant in H_2O/acetone/CH_3CN (1:1:1).[1] Since initial attempts to utilize PS-MC Os for asymmetric dihydroxylation were unsatisfactory, the acryronitrile-butadiene-polystyrene (ABS) polymer was found to be effective.[2] Next, we indicated to use $K_3Fe(CN)_6$ as a cooxidant, since NMO require slow addition of the substrate to prevent the second catalytic cycle leading to low enantioselectivity.[3] We found the poly[4-(phenoxyethoxymethyl)styrene-co-styrene] (PEM) and cross-linked polystyrene (PSresin, cross-linked by 1 mol% 1,4-divinylbenzene) was effective as the polymer support.[4] Asymmetric dihydroxylation of various alkenes using PEM-MC Os or PSresin-MC Os, bis-cinchona alkaloid as a ligand, and $K_3Fe(CN)_6$ as a cooxidant in water in the presence of Triton® X-405 were afforded the desired diols in good yields with high enantiomeric excess. However, in these catalysts, enantioselectivity of the products were sometimes lower than that of the report by Sharpless *et al.*[5]

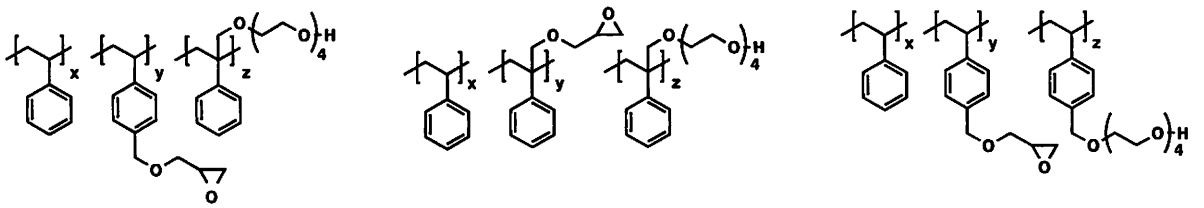
On the other hand, recently we developed a novel method "the polymer incarcerated (PI) method" for immobilization of metal catalysts using epoxide-containing copolymer, which is based on micro-encapsulation and cross-linking, and successful in immobilizing highly active, metal-based catalysts.[6]

In this time, we synthesized polymer incarcerated osmium (PI Os) catalyst and this system applied to practical asymmetric synthesis of camptothecin.[7] PI Os was prepared from copolymer (***Fig. 1***) and OsO_4 in a THF/MeOH system as shown in ***Scheme 1***.

Scheme 1. Synthesis of PI Os Catalyst.



We examined asymmetric dihydroxylation of styrene (2 mmol scale) using PI_1 ~ PI_3 Os catalysts. The reaction were carried out using PI_1 ~ PI_3 Os, $(DHQD)_2PHAL$ (5 mol% each), $K_3Fe(CN)_6$ as cooxidant, K_2CO_3 in H_2O/alcohol solvent (***Table 1***). Especially, the combination with PI_1 and IPA/H_2O afforded desired diol in 82% yield with 97% *ee*, and was reused three times without leaching of Os and loss of catalytic activity (2nd: 81% yield, 97% *ee*, 3rd: 81% yield, 97% *ee*).



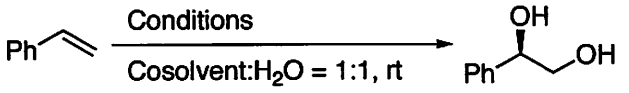
PI_1 Os (100% yield) (x/y/z =85/11/4)

PI_2 Os (48% yield) (x/y/z = 91/6/3)

PI_3 Os (94% yield) (x/y/z = 89/5/6)

Fig 1. PI Os Catalysts.

Table 1. Asymmetric Dihydroxylation of Styrene Using PI Os Catalyst.



Entry	Cat.	Time (h)	Cosolvent	Yield[a] [ee][b] (Leaching[c]) (%)
1	PI_1	12	*t*-BuOH	77 [97] (2)
2	PI_2	12	*t*-BuOH	91 [97] (8)
3	PI_3	12	*t*-BuOH	80 [97] (6)
4	PI_1	6	IPA	82 [97] (ND), 81 [97] (ND)[d], 81 [97] (ND)[e]
5	PI_2	6	IPA	87 [97] (6)
6	PI_3	6	IPA	77 [97] (2)

Conditions; $(DHQD)_2PHAL$ (5 mol%), PI Os (5 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.); [a] Isolated yield. [b] Determined chiral HPLC analysis.[c] Determined by X-ray fluorescent (XRF) analysis, ND = <1%. [d] 2nd run. [e] 3rd run.

At the poster presentation, we will demonstrate practical asymmetric dihydroxylation of camptothecin key intermediate.

【References】

1. (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985-2986. (b) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094-6095. (c) Kobayashi, S.; Akiyama, R. *Chem. Commun.* **2003**, 449-460.
2. Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229-11230.
3. Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* **2001**, *3*, 2649-2652.
4. (a) Ishida, T.; Akiyama, R.; Kobayashi, S. *Adv. Synth. Cat.* **2003**, *345*, 576-579. (b) Ishida, T.; Akiyama, R.; Kobayshi, S. *Adv. Synth. Cat.* **2005**, *347*, 1189-1192.
5. For reviews on asymmetric dihydroxylation, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric synthesis*, 2nd edn. ; Ojima, I., Ed.; Wiley-VCH, Weinheim, 2000, pp 357-398.
6. Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412-3413.
7. For reviews on camptothecin and it's derivatives, see: (a) Du, W. *Tetrahedron* **2003**, *59*, 8649-8687. (b) Wall, M. E.; Wani, M. C. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: Sna Diego, CA, 1998; Vol. 50, Chapter 13, pp 509-520. (c) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047-1065.

2P-39

Basic Study on Separation by Mild Adsorption in Supercritical CO_2

Kazuyukli Chihara,* Mai Hikita, Taichi Wada and Ryota Suzuki
Department of Industrial Chemistry , Meiji university,
1-1- 1 Higashi-mita, Tama-ku, Kawasaki, 214-8571,Japan
chihara@isc.meiji.ac jp

1. Abstract

Adsorption of aromatic organics on activated carbon, MSC and siliceous Y-type zeolite in supercritical CO_2 fluid were measured, using a super critical fluid chromatograph. Chromatographic columns were assumed to be packed beds of spherical particles of adsorbents having bidispersed pore structure. Moment analyses of pulse response of aromatic organics were performed to get the apparent adsorption equilibrium constant, K* from the retention time of response peaks and the mass transfer steps with diffusivity in micro pore from second central moment of response peaks. Futher, comparison of these adsorption properties of F400, MSC and PQ-USY was tried.

2. Introduction

Separation by mild adsorption in supercritical CO_2 might be suitable for separation or purification of medical compounds or medicines. Recovery after separation might be also feasible, because CO_2 would be vaporized easily.

Many organics shows moderate adsorption on activated carbon, MSC (molecular sieving carbon) and high silica zeolite in supercritical CO_2 fluid[1)2)3)4)5)]. It is rather easy to change their adsorbability by changing temperature or pressure of supercritical CO_2 fluid, because of the change of solubility and competitive adsorption of CO_2. And of course, high diffusivity in supercritical CO_2 fluid is one of the advantages. There is a potential application to some separation processes, using adsorption operation in supercritical CO_2 fluid[6)]. Then, fundamental information on adsorption equilibrium and adsorption dynamics in supercritical CO_2 fluid are required for designing such processes.

However, there seems to be different affinity to various organics for their adsorbability in supercritical CO_2 fluid[1)2)3)].

In this study, adsorption of aromatic organics on activated carbon (FILTRASORB 400, Calgon Co.), MSC (Takeda chemicals) and siliceous Y-type zeolite (USY by PQ Co.) in supercritical CO_2 fluid were measured, using a super critical fluid (SCP) chromatograph. Recently, a good analytical apparatus, so-called supercritical fluid chromatograph was commercialized (JASCO Co.). Chromatographic columns were assumed to be packed beds of spherical of adsorbents having bidispersed pore structure with a size distribution of the microparticles. Moment analyses of pulse response of aromatic organics were performed to get the apparent adsorption equilibrium contact, K* from the retention time of response peaks and the mass transfer steps with diffusivity in micro pore from second central moment of response peaks. Futher, comparison of these adsorption properties of F400, MSC and PQ-USY was tried.

Here, we didn't account for the competitive adsorption of CO_2, though the phenomena is co-adsorption in principle. This co-adsorption problem needs investigation in the future. There is difficulties for separating the effect of solubility change and adsorbability change. At this moment, adsorption of aromatic organics are compared and discussed with temperature and pressure or density of CO_2, as condition parameters. However, in practical sense, there found some differences between these adsorbents.

3.Comparison between adsorbents

Fig.4-a and b shows relation K* vs D/a^2 for various aromatic compounds on PQ-USY, F-400 and MSC. Both PQ-USY and F-400 or MSC have inverse relation in K* vs D/a^2. This relation is quite understandable.

Both figures includes hydrophilic and hydrophobic compounds. Both PQ-USY and F-400 or MSC are though to be hydrophobic adsorbent. F-400 or MSC shows affinity for hydrophobic compounds. Though PQ-USY shows affinity for hydrophilic compounds with some special selectivity. That means some special function group may contribute to the affinity.

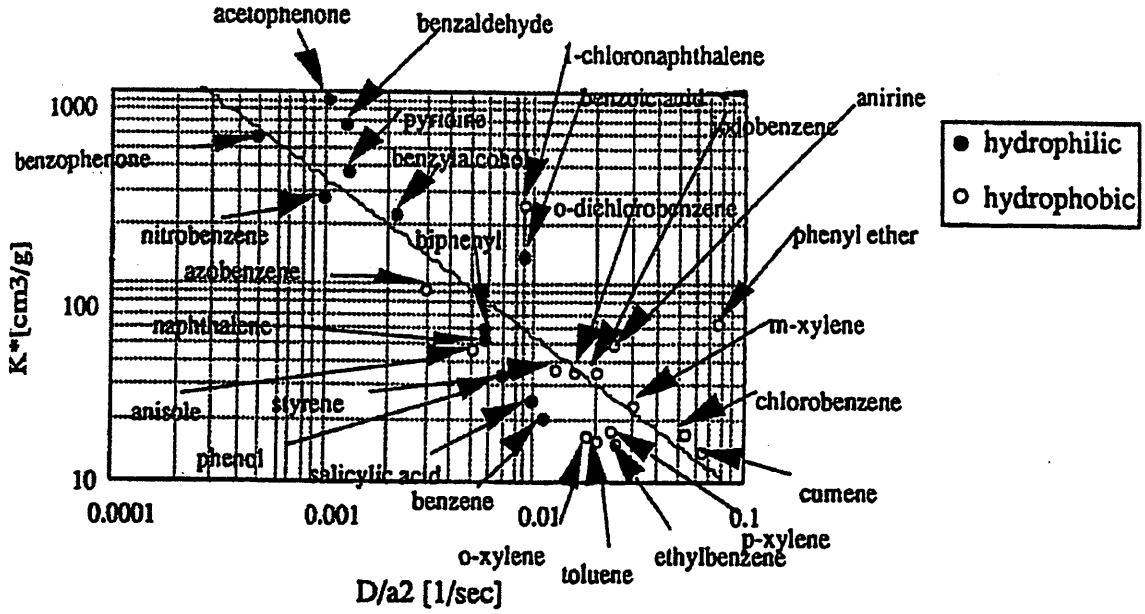


Fig.4-a Relation of K and D/a2 on PQ-USY*

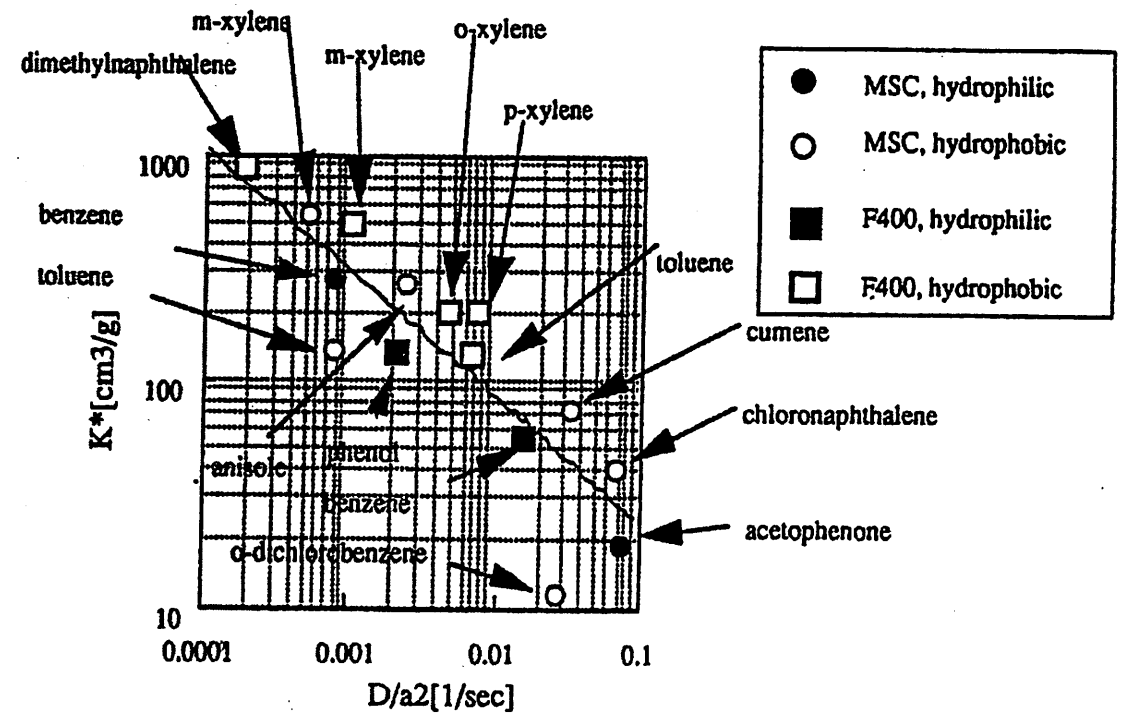


Fig.4-b Relation of K and D/a2 on F400 and MSC*

4. Conclusion

The adsorption equilibrium constants, K*, and micropore diffusivity, D, for various aromatic compounds in supercritical CO_2 fluid were evaluated by chromatographic measurement and moment analysis, between 313 and 353 K and between 15.0 and 25.0 MPa. The comparison of F-400, MSC and PQ-USY was done as adsorbents.

All of F-400, MSC and PQ-USY adsorbents shows rather high adsorbability with measurable adsorption rate in super critical CO_2 fluid. However the affinity of each adsorbents is slightly different. It need for optimizing some separation process to select adsorbents. This paper shows some tendency of affinity for aromatic compounds.

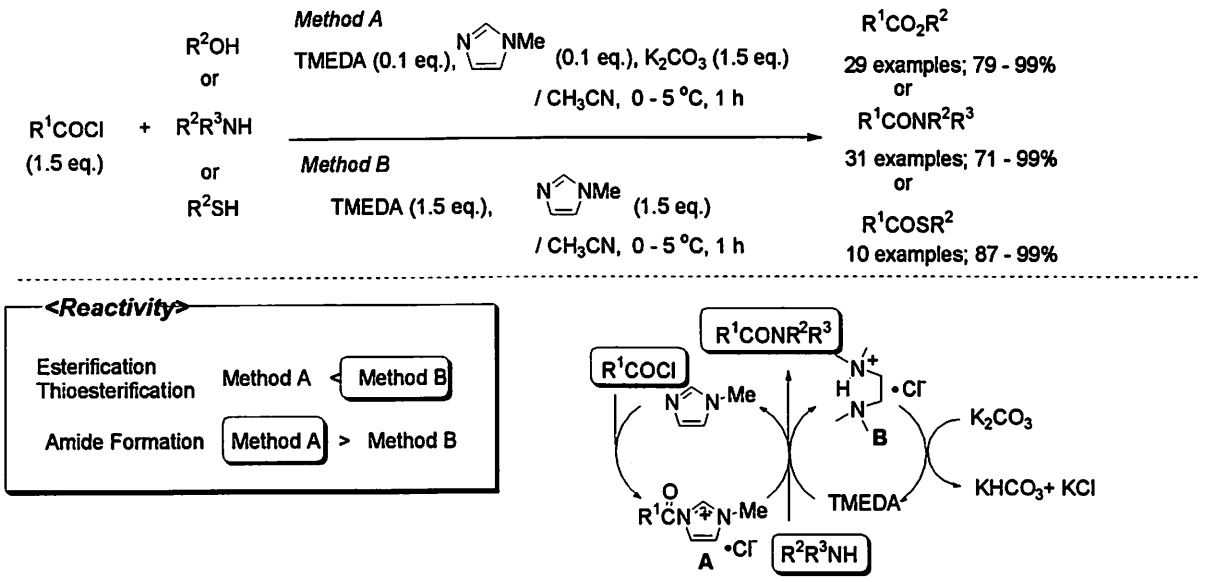
2P-40

Mild, powerful, and robust acylations utilizing *N*-methylimidazole (NMI) - amine combined catalyst (joint action of amines)

Hidefumi Nakatsuji,* Mami Morimoto, Kanako Ueno and Yoo Tanabe
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University,
2-1 Gakuen, Sanda, Hyogo 669-1337, Japan
tanabe@kwansei.ac.jp

Acylations are the most frequently-used reactions in organic synthesis and process chemistry. We present here efficient acylations promoted by the combined catalytic base, *N*-methylimidazole (NMI) and amines (joint action of amines).

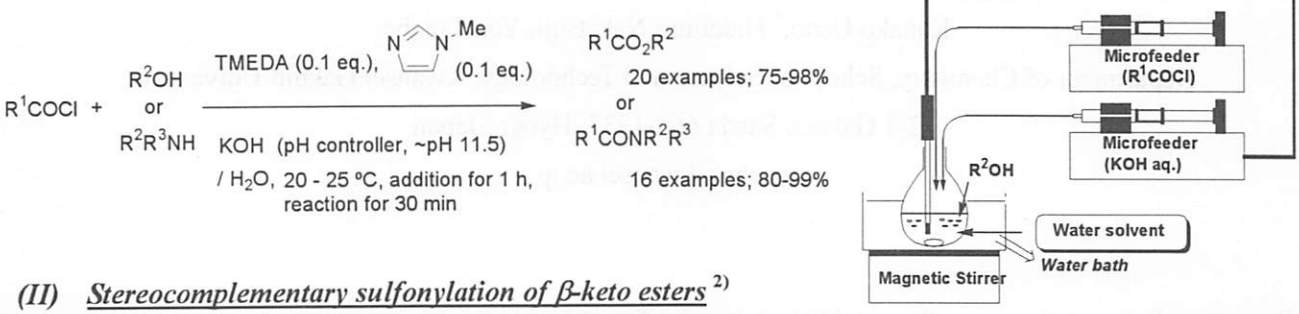
(I) Esterifications and amide-formations [1)]



Synergistically active combined amines, NMI and *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) mildly and powerfully promote esterification, amide formation, thioesterification between acid chlorides and alcohols, amines, thiols, respectively. Highly reactive acylimidazolium intermediates **A** (^{1}H NMR chart is depicted below) play a key roll for the present reactions. Method A uses catalytic NMI and TMEDA with 1 equiv of K_2CO_3, whereas Method B uses each 1 equiv of NMI and TMEDA. A striking feature is that Method B was superior to Method A for esterification and thioesterification, whereas cost-effective Method A was superior to Method A for amide formation with regarad to the reactivity. Amide formation proceeded smoothly even for less nucleophilic and stereocongested amines such as 2,6-dichloroaniline compared with the conventional methods.

This protocol was successful extended to an efficient water solvent method for esterification and amide formation between acid chlorides and alcohols (or amines), wherein combining catalytic amines, NMI and TMEDA exhibited remarkable synergistic activity. The present Schotten-Baumann-type reaction was

performed by maintaining the pH at around 11.5 using a pH controller to prevent the decomposition of acid chlorides and/or esters and to facilitate the condensation.

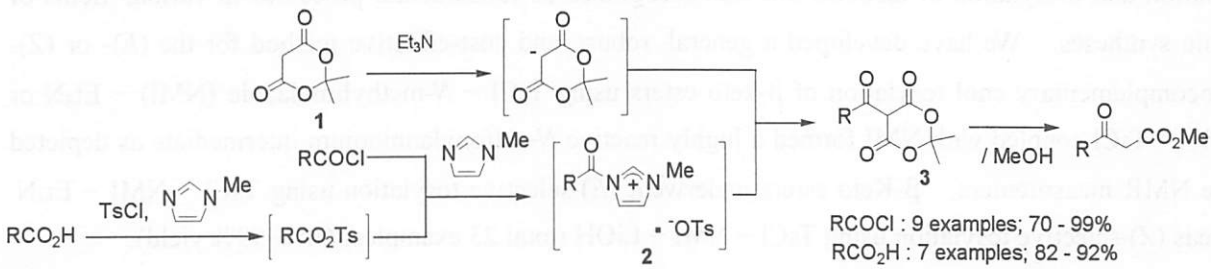


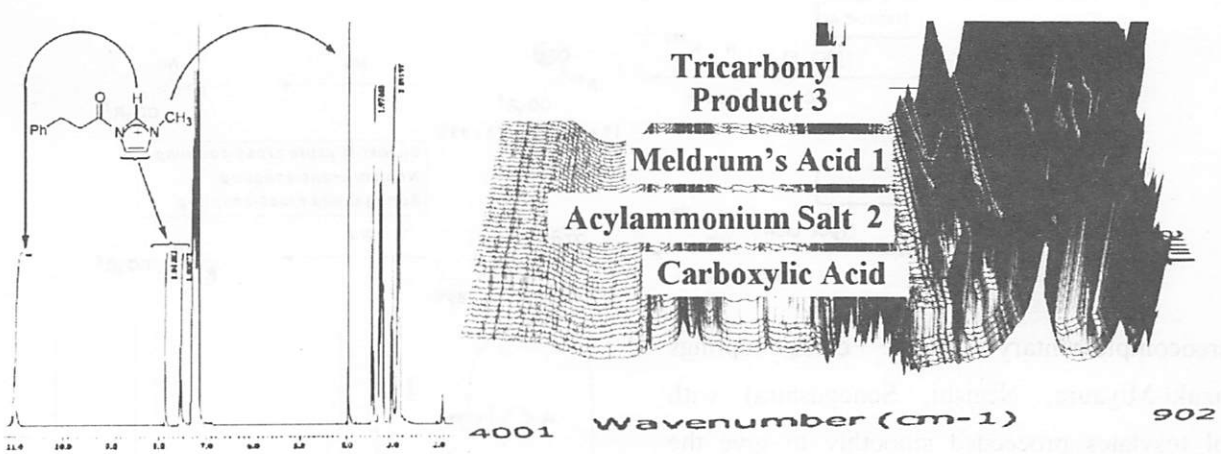
(II) ***Stereocomplementary sulfonylation of β-keto esters*** [2)]

Using TsCl – NMI – Et_3N, β-keto esters underwent (*E*)-selective tosylation and using TsCl – NMI – LiOH (*Z*)-selective tosylation. Stereoretentive Negishi and Sonogashira couplings using enol tosylates proceeded successfully to give trisubstituted α,β-unsaturated esters.

(III) ***C-Acylation of Meldrum's Acid*** [3)]

Meldrum's acid (**1**) underwent *C*-acylation with activated acylammonium intermediates **2** derived from RCOCl or RCO_2Ts [4)] to successfully give tricarbonyl product **3**. Methanolysis of the **3** smoothly proceed to give methyl β-ketocarboxylates in good yield. ^{1}H NMR and React IR monitoring studies strongly support the existence of acylimidazolium intermediates **2**.





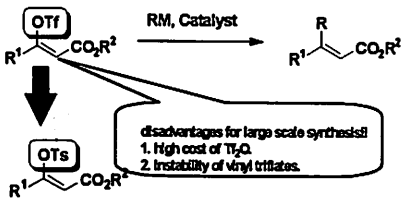
1) (a) Nakatsuji, H.; Morimoto, M.; Misaki, T.; Tanabe, Y. *Tetrahedron* **2007**, *50*, 12071. (b) Nakatsuji, H.; Morita, J.; Misaki, T.; Tanabe, Y. *Adv. Synth. Catal.* **2006**, *348*, 2057. 2) Nakatsuji, H.; Ueno, K.; Misaki, T.; Tanabe, Y. *Org. Lett.* ASAP. See presentation poster 2P-41. 3) Unpublished. 4) Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, 1209. **Commentary Article**.

2P-41

Highly stereocomplementary method for the preparation of tri-substituted olefins and its application to 2-arylcarbapenem synthesis

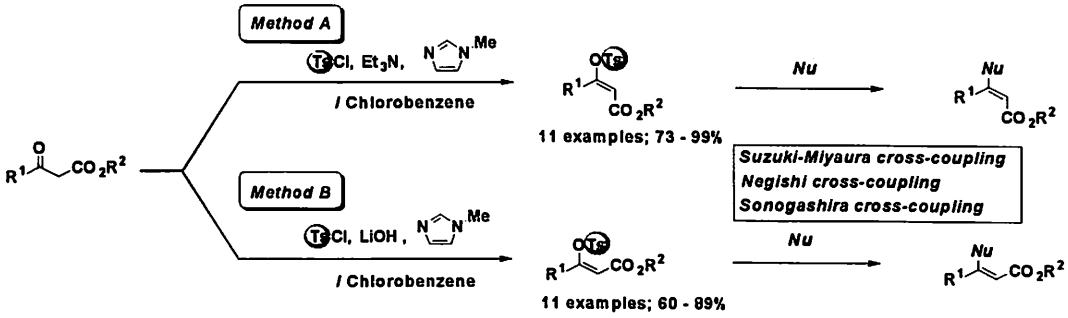
Kanako Ueno,* Hidefumi Nakatsuji, Yoo Tanabe
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University
2-1 Gakuen Sanda 669-1337, Hyogo, Japan
tanabe@kwansei.ac.jp

Cross-coupling reactions are the established avenue for organic syntheses. Enol triflates are generally used for this purpose, however, there are two problems of instability and high cost in view of the process chemistry. This disadvantage frequently resists a large-scale synthesis of pharmacueticals. The alternation of enol triflates for enol tosylates is considered to be one of the significant goal.



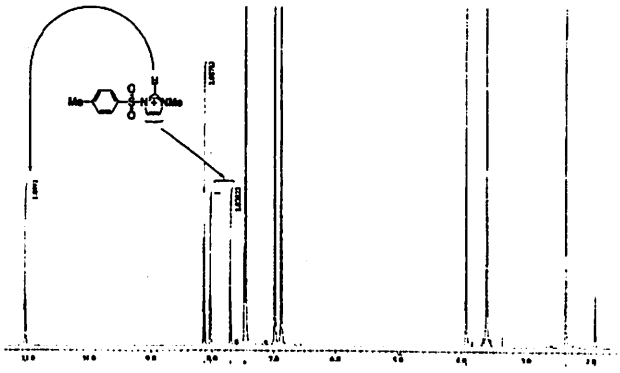
(I) Stereocomplementary sulfonylation of β-keto esters and application to cross-coupling reactions

Tosylation and mesylation of alcohols are well recognized as fundamental processes in various fields of organic syntheses. We have developed a general, robust, and cost-effective method for the (*E*)- or (*Z*)-stereocomplementary enol tosylation of β-keto esters using TsCl – *N*-methylimidazole (NMI) – Et_3N or LiOH[1]. TsCl coupled with NMI formed a highly reactive *N*-sulfonylanmonium intermediate as depicted in the NMR measurement. β-Keto esters underwent (*E*)-selective tosylation using TsCl – NMI – Et_3N, whereas (*Z*)-selective tosylation using TsCl – NMI – LiOH (total 23 examples; 60%–99% yield).

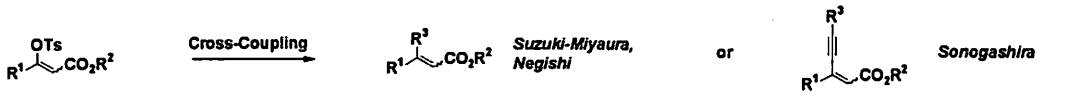


Stereocomplementary cross-couplings (Suzuki-Miyaura, Negishi, Sonogashira) with enol tosylates proceeded smoothly to give the corresponding trisubstituted α,β-unsaturated esters with nearly complete stereoretention.

We have been pointing out that NMI is superior to DMAP for acylation reactions with regard to



reactivity, cost, and toxicity [NMI (rat LD_{50}, oral, 1130 mg/kg) and DMAP (56 mg/kg)]. The present method provides a new avenue for practical and stereocontrolled preparation of trisubstituted olefins.



Suzuki-Miyaura (20 examples ; 54 - 95%)

R^1	R^2		R^3	Yield / %
Me	Me	(E)	Ph	90
		(Z)		95
Me	Me	(E)		89
		(Z)		86
	Me	(E)	Ph	72
		(Z)		54
	Me	(E)	Ph	83
		(Z)		88

Negishi (20 examples; 74 - 95%)

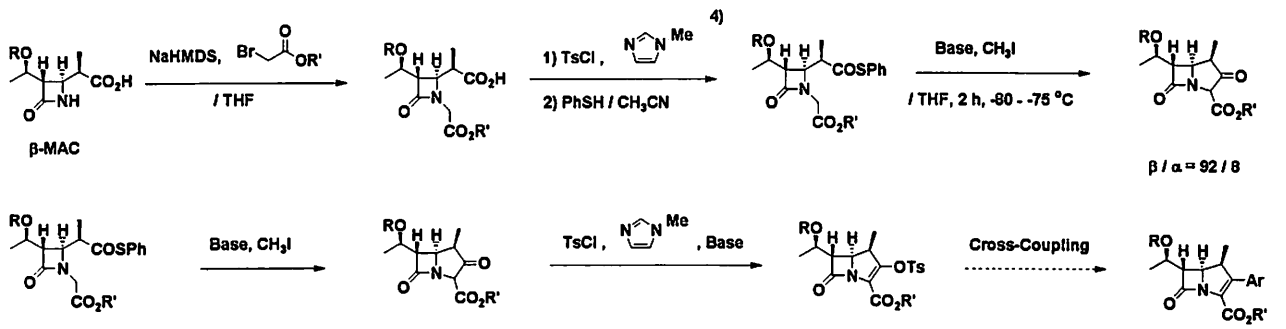
R^1	R^2		R^3	Yield / %
Me	Me	(E)	Ph	84
		(Z)		94
Me	Me	(E)		85
		(Z)		87
	Me	(E)	Ph	92
		(Z)		74
	Me	(E)	Ph	75
		(Z)		83

Sonogashira (18 examples; 70 - 97%)

R^1	R^2		R^3	Yield / %
Me	Me	(E)	Ph	91
		(Z)		84
	Me	(E)	Ph	84
		(Z)		70
	Me	(E)	Ph	88
		(Z)		76

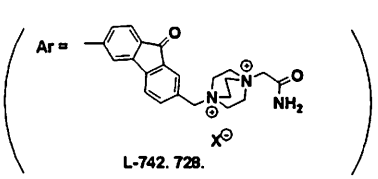
(II) Application to 2-arylcarbapenem synthesis

The Merck process group disclosed *anti*-MRSA active 2-aryl-1-β-methyl carbapenems such as L-742,728. The key step of the synthesis utilizes a cross-coupling of the enol triflate intermediate with aryl metals. As an extension of the aforementioned method, we planned an alternative route for the synthesis of 2-aryl-1-β-methyl carbapenems utilizing enol tosylates. The β-ketoester precursor (β / α = 92 / 8) was prepared by the reported method as outlined below.[3] The key enol tosylation was successfully performed using TsCl – NMI – Et_3N or $^iPr_2NEt$. The cross coupling is now under investigation.



R	R'	Base	Yield / %
TBS	Allyl	NaHMDS	78
	PNB	LiHMDS	54

R	R'	Base	Yield / %
TBS	Allyl	$^iPr_2NEt$	83
	PNB	Et_3N	86



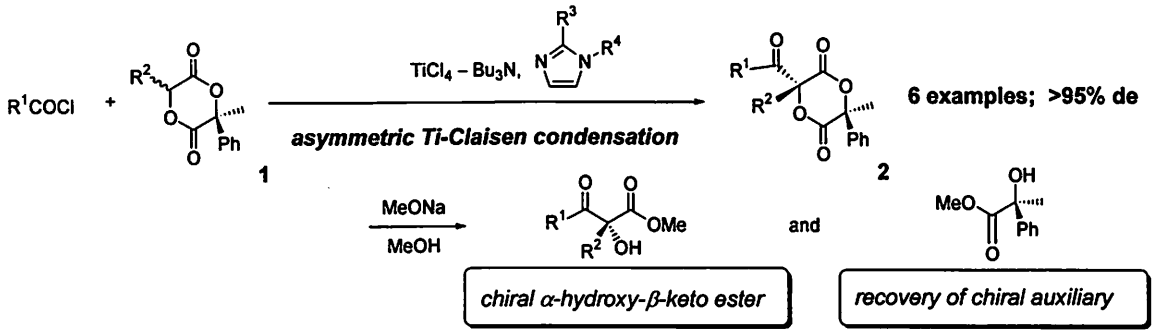
1) Nakatsuji, H.; Ueno, K.; Misaki, T.; Tanabe, Y. *Org. Lett.* ASAP.
2) Yasuda, N.; Mark A, Huffman.; Paul J. Reider, *et al. J. Org. Chem.* **1998**, *63*, 5438.
3) Seki, M.; Kondo, K.; Iwasaki, T. *J. Chem., Perkin Trans. 1*, **1996**, 2851.
4) Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, *345*, 1209.

2P-42

Development of asymmetric Ti-Claisen condensation directed for process chemistry: application to asymmetric total syntheses of two natural products

Ryohei Nagase,* Mikiko Sugi, Yumiko Oguni, Tomonori Misaki, Yoo Tanabe
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University,
2-1 Gakuen Sanda, Hyogo 669-1337, Japan
tanabe@kwansei.ac.jp

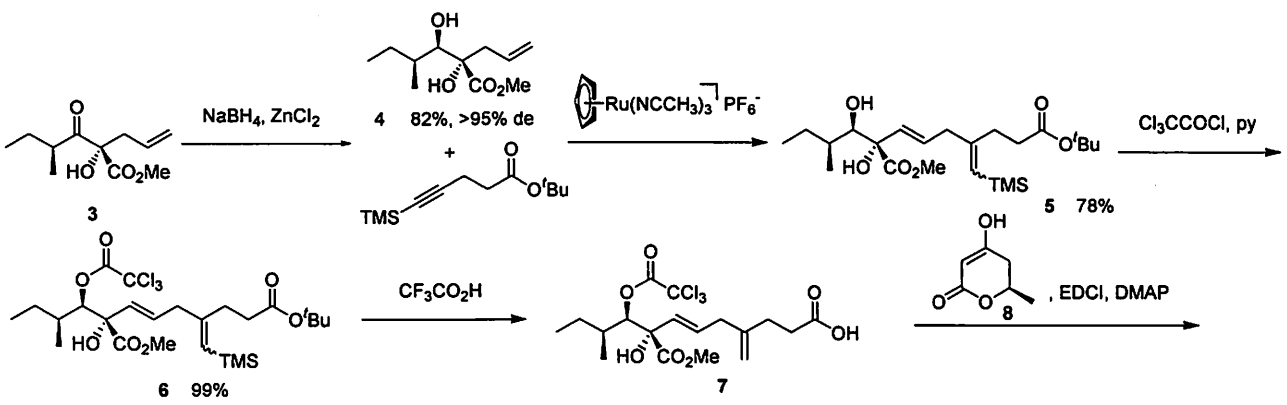
The Claisen condensation is recognized as a fundamental and useful C-C bond forming reaction for obtaining various β-keto esters in organic synthesis. Our longstanding interest in mild and powerful Ti- (or Zr-) *crossed*-Claisen condensation,[1] and relevant aldol and Mannich reactions,[2] led us to extend it toward the *asymmetric* Ti-Claisen condensation. The present method utilized readily available chiral template, 1,4-dioxolane-2,5-diones **1**, which underwent a *crossed* Ti-Claisen condensation to give the acylated product **2** with high diastereoselectivity (>95%; all 6 examples). Methanolysis of **2** proceeded smoothly to give chiral α-hydroxy-β-keto esters with nearly complete recovery of chiral auxiliary.

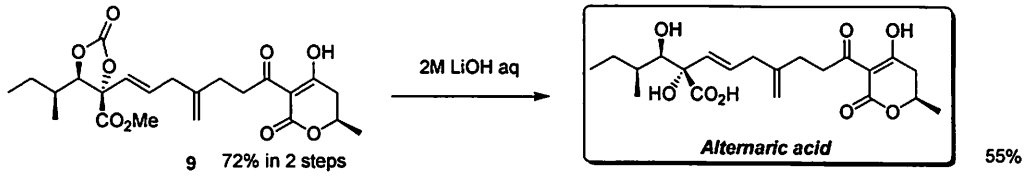


With this result in hand, we achieved efficient asymmetric total syntheses of a couple of biologically active natural products, alternaric acid and (-)-azaspirene, which have contiguous acyclic and cyclic stereogenic centers, respectively.

1. Asymmetric total synthesis of alternaric acid.[3]

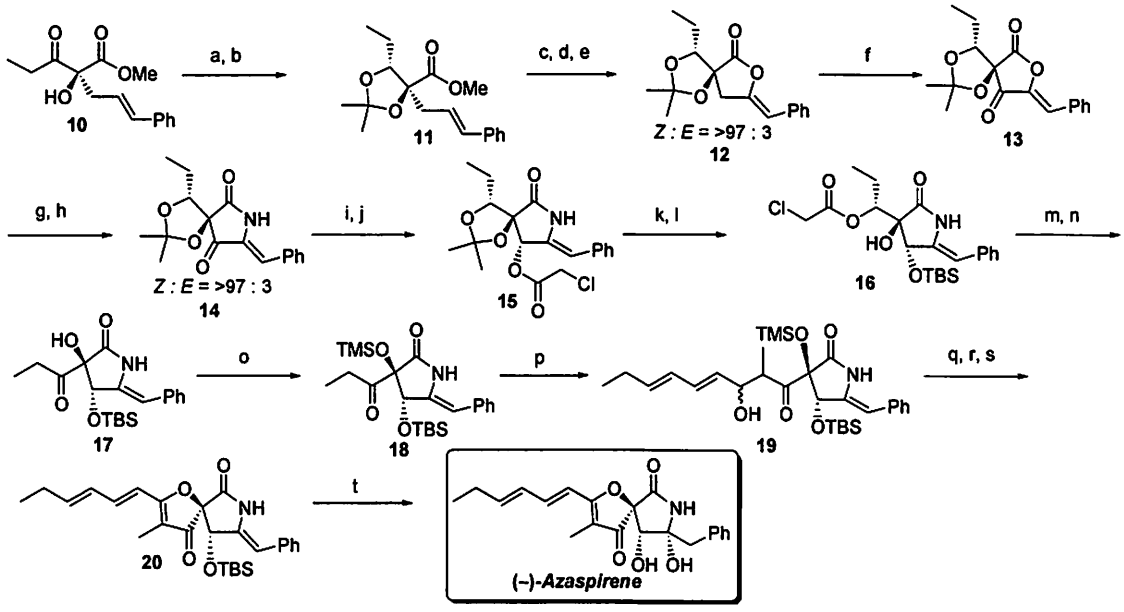
Chiral α-hydroxy-β-keto ester **3**, obtained by asymmetric Ti-Claisen condensation, was reduced diastereoselectively using $NaBH_4 - ZnCl_2$ to give diol **4**. An alkene-alkyne coupling between **4** and ^{t}Bu 5-(TMS)-4-pentynoate using Ru catalyst produced ester **5**.[4] Successive protection of **5** using Cl_3CCOCl – Py, and protodesilylation and ^{t}Bu removal using CF_3CO_2H group, gave acid **7**. *C*-acylation of **7** with chiral dihydropyranone **8**, followed by hydrolysis, provided alternaric acid (9 steps and 16% overall yield).





2. Asymmetric synthesis of (-)-Azaspirene.[5]

Stereoselective reduction of chiral α-hydroxy-β-keto ester **10**, followed by actetonide protection, gave ester **11**. Successive hydrolysis of **11**, iodo-lactonization, and elimination of HI using DBU, produced lactone **12**. Allylic oxidation of **12** using Se_2O, followed by NH_3 treatment and PPTS dehydration provided **14**. Convex-face reduction using $NaBH(OAc)_3$, followed by $ClCH_2CO$- protection of hydroxyl group, provided chloroacetate **15**. Successive deprotection of acetonide of **15** and regioselective TBS protection of the secondary -OH gave **16** through 1,3-rearrangement of $ClCH_2CO$-gorup. Deprotection of $ClCH_2CO$-, the Dess-Martin oxidation, follwed by TMS-protection produced the key intermediate **18**. Direct Ti-aldol addition using **18** could introduce the side chain. Deprotection of TMS of the adduct **19**, followed by the Dess-Martin oxidation and acid-treatment, constructed the desired spiro ring of **20**. Finally, deprotection of TBS group with $PhCO_2H$ – TBAF reagents afforded (-)-azaspirene (24 steps and 2.3% overall yield).



Reagents and Conditions: (a) $NaBH_4$, $ZnCl_2$. (b) 2,2-Dimethoxypropane, H^+ (81% 2 steps). (c) 5 M KOH aq/MeOH. (d) I_2, $BnEt_3N^+Cl^-$, sat. $NaHCO_3$ aq. (e) DBU, Ac_2O (64% 3 steps). (f) SeO_2 / Dioxane. (g) NH_3 / ^iPrOH. (h) PPTS. (77% 3 steps). (i) $NaBH(OAc)_3$. (98%) (j) $(ClCH_2CO)_2O$, DMAP, Et_3N. (94%) (k) TFA/H_2O. (94%) (l) TBSOTf-2,6-lutidine. (91%) (m) 2-Aminophenol, NaHMDS. (n) Dess-Martin Oxidation. (80% 2 steps) (o) BSA, $PyH^+ \cdot {}^-OTf$. (97%) (p) $TiCl_4$-Bu_3N, *E,E*-2,4-Heptadienal. (46%) (q) HF-Pyridine (88%). (r) Dess-Martin Oxidation. (s) $TsOH \cdot H_2O$ (54% 2 steps). (t) TBAF - $PhCO_2H$ (70%)

References

(1) a) Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1988**, *62*, 1917. b) Tanabe, Y.; Hamasaki, R.; Funakoshi, S. *Chem. Commun.* **2001**, 1674. c) Misaki, T.; Nagase, R. Matsumoto, K. Tanabe, Y. *J. Am. Chem. Soc.* **2005**, *127*, 2854.

(2) a) Nagase, R.; Matsumoto, N.; Tanabe, Y. *et al. Org. Biomol. Chem.* **2007**, *5*, 151. b) Funatomi, T.; Nakazawa, S.; Tanabe, Y. *et al. Chem. Commun.* **2008**, 771.

(3) a) Tabuchi, H.; Hashimoto, T. *et al. J. Org. Chem.* **1994**, *59*, 4749. b) Trost, B. M. *et al. J. Am. Chem. Soc.* **1998**, *120*, 9228.

(4) Trost, B. M. *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 6630.

(5) a) Hayashi, Y; Shoji, M. *et al. J. Am. Chem. Soc.* **2002**, *124*, 12078. b) Tadano, K. *et al. Bull. Chem. Soc. Jpn.* **2004**, *77*, 1703.

2P-43

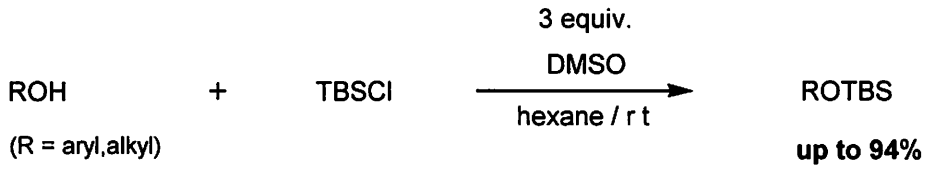
Catalyst-free Efficient Reactions in DMSO

Tomoko Kakinuma,* Ryoichi Chiba, Katsuyuki Iwanami, Masaru Aoyagi, Takeshi Oriyama
Department of Chemistry, Faculty of Science, Ibaraki Univ.
2-1-1, Bunkyo, Mito, Ibaraki 310-8512, Japan
tor@mx.ibaraki.ac.jp

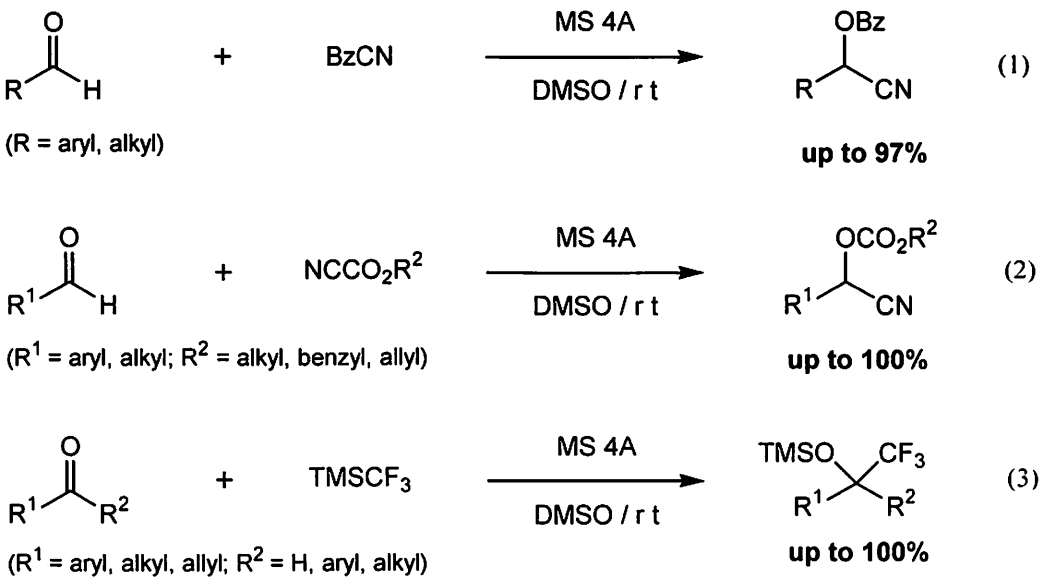
The continuous discovery of new and efficient catalytic reactions is one of the key steps in the development of simpler and cheaper syntheses of complex organic molecules. Furthermore, a catalyst-free reaction is more significant and attractive in synthetic organic chemistry from the viewpoint of environmentally friendly chemistry. Recent efforts in our laboratory have focussed on the catalyst-free efficient reactions in dimethyl sulfoxide (DMSO).

Silyl ethers are the most popular and promising protecting groups for hydroxyl function in synthetic organic chemistry. Silyl ethers are commonly obtained by the reaction of the parent alcohols with the corresponding trialkylsilyl halide in the presence of stoichiometric amounts of a base. We discovered that various silyl ethers were prepared by the silylation of alcohols in DMSO-hexane without catalyst[1] (**Scheme 1**). And furthermore, we have found that (1) cyanobenzoylation of aldehydes,[2] (2) cyanocarbonation of aldehydes,[3] and (3) trifluoromethylation of carbonyl compounds[4] were proceeded very smoothly in DMSO without catalyst (**Scheme 2**).

Scheme 1. The silylation of alcohols in DMSO

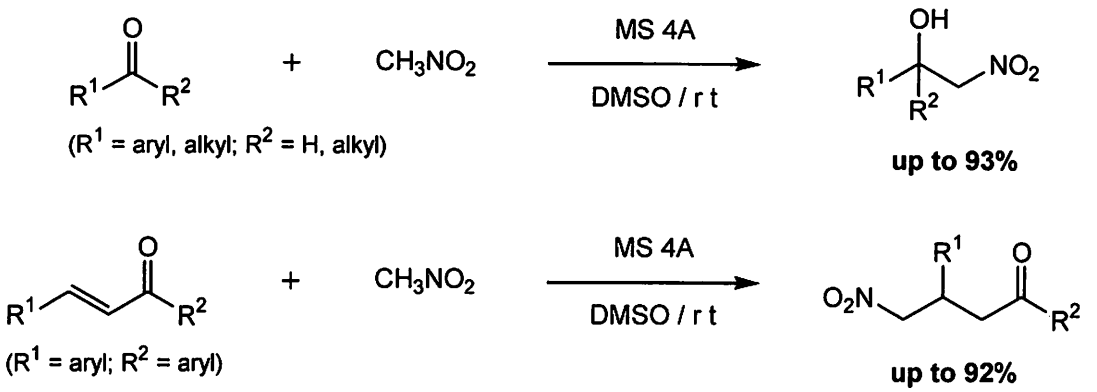


Scheme 2. Ctatlyst-free carbon-carbon bond forming reactions in DMSO



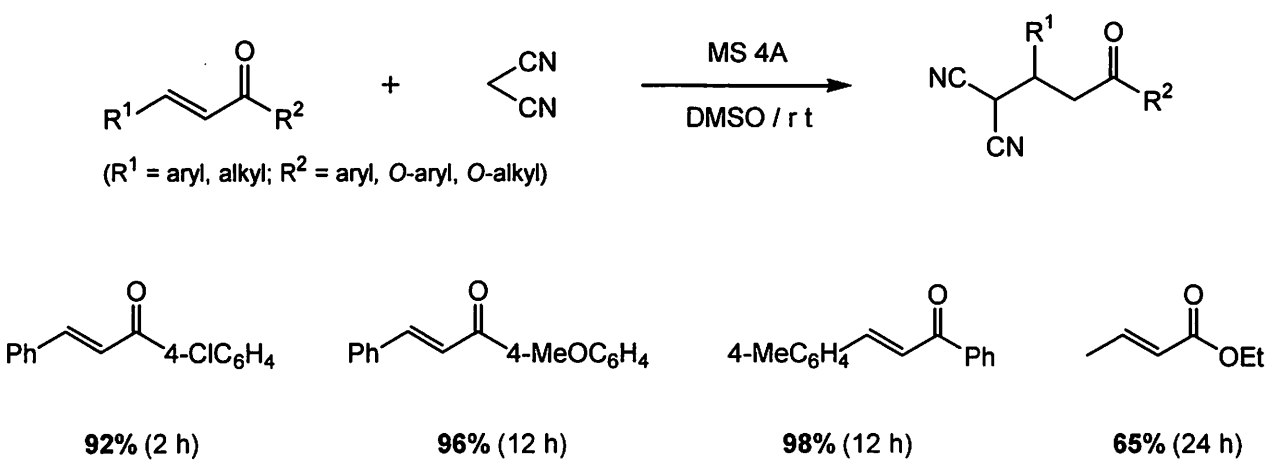
Recently, we have reported that Henry reaction of various carbonyl compounds with nitroalkanes was achieved to give the corresponding β-nitroalcohol in DMSO without a base catalyst.[5] Moreover, 1,4-addition of nitroalkane to α,β-unsaturated ketones was also performed in DMSO (**Scheme 3**).

Scheme 3. Henry reaction in DMSO



Latest our investigation is Michael addition of active methylene compounds to α,β-unsaturated carbonyl compounds. Michael addition of malononitrile to enones also proceeded smoothly to afford the corresponding 1,4-adduct in the presence of MS 4A in DMSO (**Scheme 4**).

Scheme 4. Michael addition to enones in DMSO



These reactions shown here are experimental convenient and very attractive from the standpoints of green chemistry, because the atom economy is extremely high to consume almost all reagents under mild reaction conditions.

1) T. Watahiki, M. Matsuzaki, T. Oriyama, *Green Chemistry*, **5**, 82, (2003).
2) T. Watahiki, S. Ohba, T. Oriyama, *Org. Lett.*, **5**, 2679 (2003).
3) K. Iwanami, Y. Hinakubo, T. Oriyama, *Tetrahedron Lett.*, **46**, 5881 (2005).
4) K. Iwanami, T. Oriyama, *Synlett*, **2006**, 112.
5) T. Oriyama, M. Aoyagi, K. Iwanami, *Chem. Lett.*, **36**, 612 (2007).

2P-44

$BF_3 \cdot THP$-promoted [3+2]Cycloaddition of *N*-Tosylaziridines with Nitriles

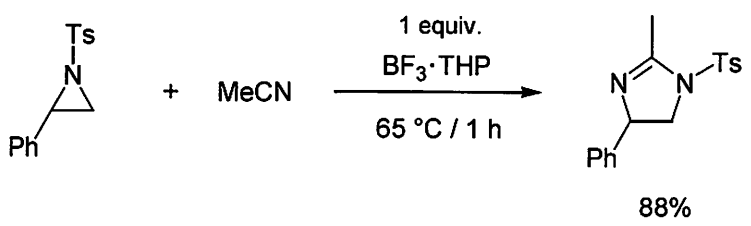
Hitomi Urai,[1]* Ryoichi Chiba,[1] Hiroshi Yasuda,[2] Yoshihiko Maeda,[2] Takeshi Oriyama[1]
Department of Chemistry, Faculty of Science, Ibaraki Univ.,[1] Corporate R&D Center, Showa Denko K. K.[2]
2-1-1, Bunkyo, Mito, Ibaraki 310-8512, Japan[1]
5-1, Ogimachi, Kawasaki, Kanagawa 210-0867, Japan[2]
tor@mx.ibaraki.ac.jp

[3+2]Cycloaddition of aziridines with dipolarophiles provides a very useful and convenient approach to the synthesis of nitrogen-containing five-membered heterocycles, a class of compounds that has found extensive use as building blocks for total syntheses of various natural products. When nitriles are used as a dipolarophile for [3+2]cycloaddition of aziridines, imidazolines can be obtained. Imidazolines are versatile intermediates for designing molecules with pharmacological activities such as anticancer, antitumor, and antihyperglycemic activities. In addition, they have been used as a chiral auxiliary and an organocatalyst for asymmetric synthesis.

There are several reports concerning [3+2]cycloaddition of aziridines with nitriles promoted by Lewis acid such as $BF_3 \cdot Et_2O$,[1)] $Sc(OTf)_3$,[2)] and $Cu(OTf)_2$.[3)] However these methods suffered from lower yields, the employment of moisture sensitive Lewis acid, and limited generality of substrates. On the other hand, $BF_3 \cdot THP$ has never been utilized as a Lewis acid for synthetic organic reactions.

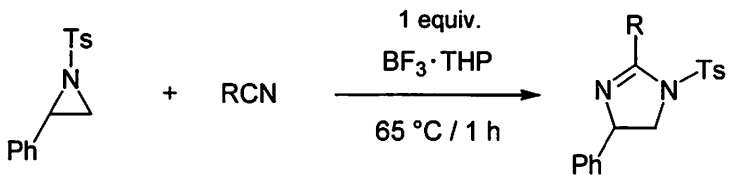
First, we examined the reaction of 2-phenyl-*N*-tosylaziridine as a model compound with acetonitrile catalyzed by $BF_3 \cdot THP$. The corresponding imidazoline was obtained as a single regioisomer in good yield under the influence of $BF_3 \cdot THP$. So we screened the optimal reaction conditions for this [3+2]cycloaddition of aziridines. And we found that the reaction of 2-phenyl-*N*-tosylaziridine with acetonitrile catalyzed by 1 equiv. of $BF_3 \cdot THP$ proceeded smoothly at 65 °C (Scheme 1).

Scheme 1. [3+2] Cycloaddition of 2-phenyl-*N*-tosylaziridine with acetonitrile.



Next, the reaction of 2-phenyl-*N*-tosylaziridine was conducted with various nitriles (Table 1). The reaction proceeded most effectively with aliphatic acetonitrile or aromatic benzonitrile.

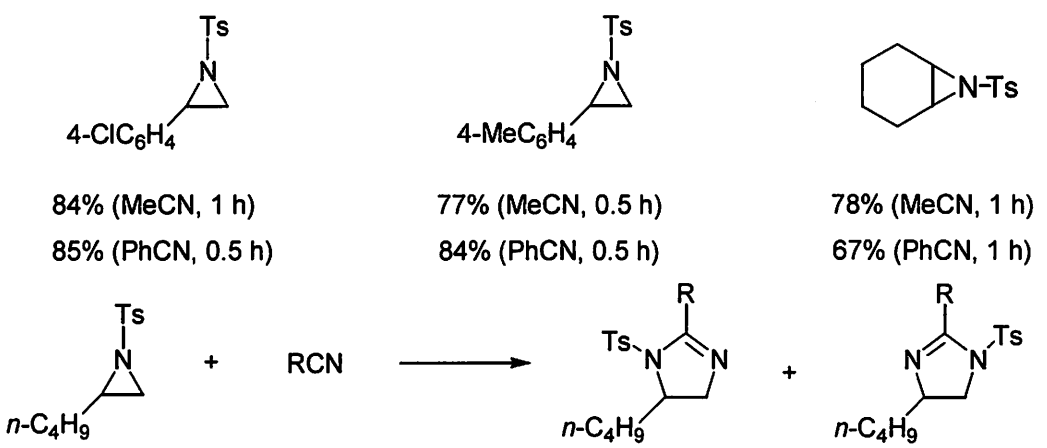
Table 1. [3+2] Cycloaddition of 2-phenyl-*N*-tosylaziridine with various nitriles.



RCN	Yield / %	RCN	Yield / %
MeCN	88	PhCN	82
EtCN	80	4-ClC_6H_4CN	71
^{t}BuCN	73	4-MeC_6H_4CN	78

Finally, we tested the scope of the [3+2]cycloaddition of various *N*-tosylaziridines with acetonitrile or benzonitrile as a dipolarophile (Table 2). Various substituted *N*-tosylaziridines reacted smoothly with acetonitrile or benzonitrile to produce a wide range of imidazoline derivatives in good yields. In the case of 2-*n*-butyl-*N*-tosylaziridine, the corresponding two regioisomers were obtained using acetonitrile or benzonitrile as dipolarophiles. Moreover, it is noteworthy that this reaction could be carried out under open air and in large scale similarly.

Table 2. [3+2] Cycloaddition of various *N*-tosylaziridines with nitriles.



55%	73	:	27	(R = Me, 1 h)
52%	83	:	17	(R = Ph, 1 h)

In conclusion, we have described a simple and efficient method for the synthesis of substituted imidazolines using 1 equiv. of BF_3·THP via [3+2]cycloaddition of aziridines with nitriles. BF_3·THP is found to be a very promising Lewis acid and very easy to be handled.

References

1) B. A. B. Prasad, G. Pandey, V. K. Singh, *Tetrahedron Lett.*, **2004**, *45*, 1137.
2) J. Wu, X. Sun, H. -G. Xia, *Tetrahedron Lett.*, **2006**, *47*, 1509.
3) M. K. Ghorai, K. Ghosh, K. Das, *Tetrahedron Lett.*, **2006**, *47*, 5399.

2P-45

Attractive role of sugar ester W/O microemulsion phase on lipid hydrolysis by lipase to provide highest reactivity

*Aki Uehara, Masanao Imai, Isao Suzuki
Course in Bioresource Utilization Sciences, Graduate School of Bioresource Sciences,
Nihon University, 1866 Kameino, Fujisawa, Kanagawa-pref., 252-8510, Japan
*gr96025u@st.brs.nihon-u.ac.jp

1. Introduction

Analysis of the favorable reaction condition will make a significant contribution of W/O microemulsion techniques to apply to enzyme reactions in the food and pharmaceutical industries. The physicochemical characterization of the W/O microemulsion droplets is major factor for determining lipase reactivity [1]. The aim of this study is to investigated the attractive role of sugar ester W/O microemulsion phase on lipid hydrolysis by *Candida rugosa* lipase to provide highest reactivity. The hydrophobicity of the microemulsion droplet and the fluidity of the micro interface with a focus on higher reaction performance reactivity were evaluated from fluorometric analysises. The favorable reaction condition was demonstrated.

2. Materials and Methods

The sugar ester, DK-ester-F-110 was employed as an amphiphile, defined as a mixture of sucrose esters of fatty acids whose components are stearic acid and palmitic acid. The DK-ester-F-110 (average MW=703, Lot. No.349519) was provided by Dai-ichi Kogyo Seiyaku Ltd. (Kyoto, Japan). The organic phase of the W/O microemulsion was composed of 2,2,4-trimethylpentane (isooctane) as a main solvent, and ethanol and 1-butanol as co-solvents. The aqueous phase was 200mM acetate buffer solution (pH 7.2). The molar ratio of water to amphiphile in the organic phase, W_{soln} (≡[mol-H_2O_{soln}]/[mol-amphiphile]) indicated the water content in the W/O microemulsion organic phase. The solubilized water mole ([mol-H_2O_{soln}]) was measured by Karl-Fischer titration (MKA-210, Kyoto Electronics, Kyoto, Japan).

The enzymatic reactivity of the lipase, *Candida rugosa* (1410 U/mg, Sigma-Aldrich Co. (Steinheim, Germany)) in that system was determined by the initial reaction rate of hydrolysis of triolein. The increase in oleic acid was measured according to the Lowry-Tinsley colorimetric method [2].

The hydrophobicity of the water pool was determined by the change in fluorescence wavelength of Coumarin 343 (MP Biochemicals Inc., Eschwege, Germany), which was dissolved in the inside water pool. The wavelength at which the maximum fluorescence strength appeared was shifted to a longer wavelength range as the water pool became more hydrophilic. The excitation wavelength was 435nm and the fluorescence wavelengths were 435 to 600nm, as determined by a preliminary experiment with a fluorescence photometer (HITACHI F-7000).

The fluidity of the micro interface was determined by the change in fluorescence anisotropy indicated by

TMA-DPH (1,6-Diphenyl-1,3,5-hexatriene-4'- trimethylammonium tosylate, Fluka, Steinheim, Switzerland). The excitation wavelength of 356nm and the fluorescence wavelength of 432nm were employed as measuring conditions, as determined by a preliminary experiment with a fluorescence photometer (HITACHI F-7000) with an automatic polarization device (HITACHI 5J 0-0116).

3. Results and Discussion

The initial reaction rate by *Candida rugosa* lipase strongly depended on the water content (Fig.1). Lipase reactivity increased with the water content and leveled off at its maximum value. The maximum reaction rate of 1-butanol system was similar with that of ethanol system. The hydrophobicity of the micro water pool considerably depended on the solubilized water content (Fig.2). The fluidity of the micro interface did not depend on the solubilized water content. Thus, the initial reaction rate acutely depended on the hydrophobicity of the micro water pool. The wavelength of Coumarin 343 apprearing the maximum initial reaction rate was obtained in the limited range of 450 to 460nm, in the all systems.

It was suggested that the physicochemical characteristics of the emulsion droplet strongly affected the enzyme reactivity and, the high reactivity was decided by the fluidity of the micro interface.

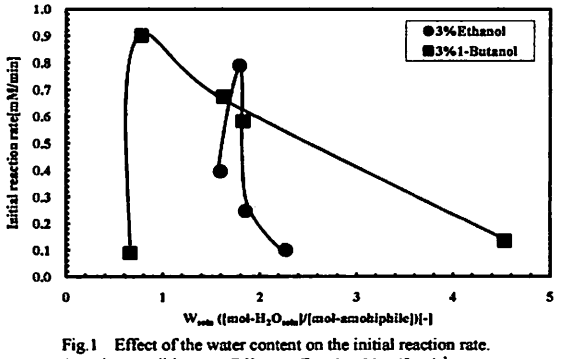


Fig.1 Effect of the water content on the initial reaction rate. Reaction condition was DK-ester-F-110 = 20g·(ℓ_{org})$^{-1}$, Lipase=5mg/50ml, Temperature = 310K,

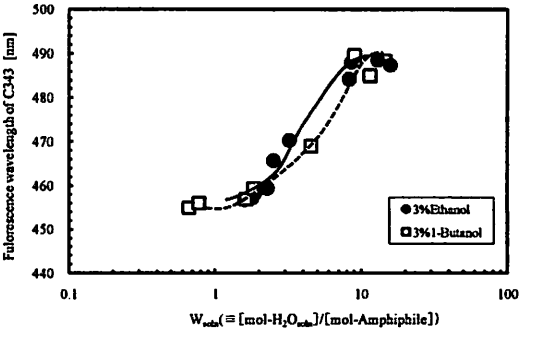


Fig.2 Effect of the water content on the hydrophilicity of the micro water pool, evaluated by Coumarin 343. The red shift on the ordinate means an elevation of the hydrophilicity.

4. Conclusion

The W/O microemulsion system was prepared by mixing sugar ester, DK-ester-F-110 with alcohol as co-solvents. The hydrophobicity of the water pool and the fluidity of the micro interface were analyzed with relation to the reactivity of *Candida rugosa* lipases in lipid hydrolysis.

The reaction condition provided high reactivity of hydrolysis appeared at the specific limited range, satisfied both the hydrophobicity of water pool and the fluidity of micro interface.

Acknowledgement

Sugar ester was kindly provided by Dai-ichi Kogyo Seiyaku Ltd (Kyoto, Japan).

Reference

[1] Uehara, A., M. Imai and I, Suzuki (2008) *Colloids and Surfaces A: Physicochem. Eng. Aspects* (in press)

[2] Lowry, R. R. and I. J. Tinsley (1976) *J. Am. Oil Chem. Soc.*, 53: 470-472

2P-46

Production of Biodiesel from Algal Oil Using Microwave-based Transesterification Process

Ching-An Peng*, Guen-Yen Chen, Wen-Yi Tsai
Department of Chemical Engineering, National Taiwan University
No. 1, Sec. 4, Roosevelt Road, Taipei 10617, Taiwan
chinganpeng@ntu.edu.tw

Microalgae are microscopic single-cell aquatic plants with the potential to produce large quantities of lipids that are well suited for use in biodiesel production. Microalgae can be grown in arid and semi-arid regions with poor soil quality, with a per hectare yield estimated to be many times greater than that of even tropical oilseeds. Algae can also grow in saline water, such as water from polluted aquifers or the ocean, which has few competing uses in agriculture, forestry, industry or municipalities. Algae feedstock received early attention from the US National Renewable Energy Laboratory in the 1980s, and interest in them has recently resurged based on their potential for cultivation near power plants. The primary nutrient for growing microalgae is carbon dioxide, creating an opportunity for developing integrated systems that produce oil-rich microalgae that feed on the emissions of coal, petroleum and natural gas power plants.

The demand of renewable combustible derived from vegetable oils increased in the last years, and has led to the development of a number of processes for transesterification of oils with methanol or ethanol, involving acidic and or basic catalysis. Recently, some papers showing the advantages of microwave irradiated transesterification methods have been published in the literature. However, to the best of our knowledge, microwave irradiation to perform the transesterification of algal oil with methanol or ethanol has not yet described.

Transesterification reaction is employed to convert triglycerides to fatty acid methyl esters which is simply a process of displacement of an alcohol group from an ester by another alcohol. Transesterification can be performed via catalytic or non-catalytic reaction using different heating systems. An alternative heating system "microwave irradiation" has been used in transesterification reactions in recent years. When the reaction is carried out under microwaves, transesterification is efficiently accelerated in a short reaction time. As a result, a drastic reduction in the quantity of by-products and a short separation time are obtained. Microwave-assisted extraction is also known as a popular extraction technology. It carries the advantage of being a simple device and has a wide area of application, high extraction efficiency, good reproducibility, and low consumption of organic solvents and time as well as low environmental pollution.

In this study, effect of microwave heating system on the yield and quality of biodiesel obtained by the transesterification of algal oil was investigated. Quality of biodiesel samples was also compared according to catalyst types. Experiments were carried out in the presence of two different alkali catalysts which are

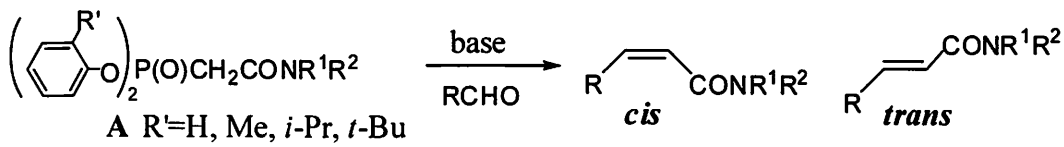
sodium hydroxide and potassium hydroxide. Effects of various reaction parameters such as catalyst ratio, reaction temperature and time were investigated. Mono-, di- and triglyceride content of biodiesel were determined by gas chromatography analysis. Yield and purity (ester content) percentages of biodiesel were specified in weight. The results indicated that microwave heating has effectively increased the biodiesel yield and decreased the reaction time.

2P-47

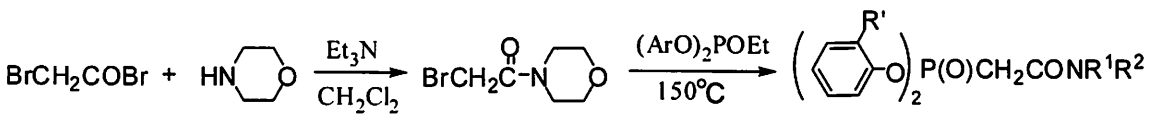
Highly cis-Selective Synthesis of α,β-Unsaturated Amides by Horner-Wadsworth-Emmons Reaction

Kaori Ando,* Yuko Tarumi
Department of Chemistry, Faculty of Engineering, Gifu University
Yanagido, Gifu 501-1193, Japan
ando@apchem.gifu-u.ac.jp

Cis-α,β-Unsaturated amides are not only useful building blocks in organic synthesis but also the important parts of biologically active natural products such as oximidines, salicylihalamides, and crocacins. Although it is rather easy to obtain the thermodynamically favored *trans* isomers, there are only a limited number of methods for preparing the *cis* isomers. We reported the Horner-Wadsworth-Emmons (HWE) reagents, (diphenylphosphono)acetamides **A** (R'=H) react with a variety of aldehydes to give the corresponding *cis*-α,β-unsaturated amides in moderate to high *cis* selectivity (75-98% *cis*).[1] After that, Deslongchamps et al. reported the reaction of $(CF_3CH_2O)_2P(O)CH_2CON(Me)OMe$ **1** with octanal gave more than 20:1 *cis* selectivity.[2] However, Kojima et al. separately prepared **1** and performed the HWE reaction of **1** with RCHO (R=$PhCH_2CH_2$, *c*-Hexyl, $PhMe_2C$) to get the α,β-unsaturated amides in 85:15, 68:32, and 43:57 selectivity, respectively.[3] Since the more general and practical method is desirable, we decided to improve our reagents. During the course of our study on the *cis* selective HWE ester reagents, we found *ortho*-substituted phenyl reagents showed the higher *cis* selectivity.[4] Here we wish to report our new reagents, (diarylphosphono)acetamides **A** containing *ortho*-substituent react with several types of aldehydes to give *cis*-α,β-unsaturated amides in high selectivity.



The morpholine amide reagents **2a-c** were prepared by the Arbusov reaction of $(ArO)_2POEt$ and the bromoacetamide in 64-72% yields. The results of the HWE reaction of **2a-c** with aldehydes were

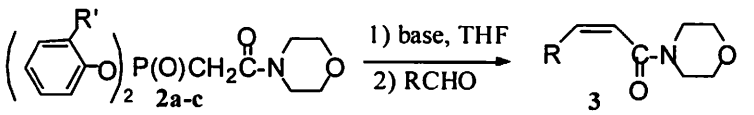


2a: R'=Me, **2b**: R'=*i*-Pr, **2c**: R'=*t*-Bu

summarized in Table 1. Treating **2a** with NaH in the presence of 2-ethylhexanal at 0 ℃ gave the olefin **3** in 83:17 *cis*-selectivity (entry1). The reagent **2b** also gave **3** in 82:18 *cis*-selectivity and in 99% in the same condition (entry 2). The selectivity was improved by treating **2a** with NaH at -78 ℃ and allowing the mixture to warm to 0 ℃ (89:11 selectivity) (entry 3). Furthermore, **2c** gave 94:6 *cis*-selectivity even at 0 ℃ and 95:5 selectivity at lower temperature (entries 4-6). Thus the selectivity is highest with the

biggest *t*-Bu substituted reagent **2c** (R': H < Me ≅ *i*-Pr < *t*-Bu). Using *t*-BuOK and NaI as base, *n*-octanal gave *cis*-olefin in 95% selectivity. Cyclohexanecarboxaldehyde, pivalaldehyde, 2-*E*-hexenal, and benzaldehyde gave 94-98% selectivity using *t*-BuOK (entries 8-11). We also prepared the Weinreb amide reagent **4** and dimethylamide reagent **5** in 52% and 83% yield. The results of the HWE reaction of **4** and **5** are given in Table 2. When **4** was treated with *t*-BuOK and benzaldehyde at -78 ℃ and allowing the mixture to warm to 0 ℃, 96% *cis* selectivity was obtained in 94% yield. For the aliphatic aldehydes, high *cis* selectivity was also obtained (89-95%). Only the reaction with α,β-unsaturated aldehyde, 2*E*-hexenal gave moderate selectivity (82:18). These results can be favorably compared with the results of the corresponding diphenyl reagent (75-81% *cis*). The reactions of **5** are more *cis*-selective and 90-99% selectivity was obtained irrespective of the type of aldehydes, that is, aromatic, aliphatic, and α,β-unsaturated aldehydes. The *cis*:*trans* ratios of the α,β-unsaturated amides were determined by integrating the vinyl proton signals in the 400 MHz ^{1}H NMR spectra. These assignments were confirmed by NOE experiments.

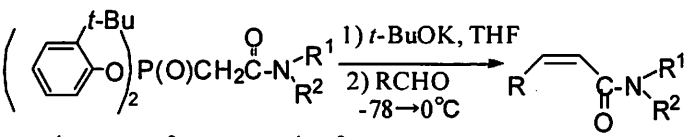
Table 1 The HWE reaction of **2** with aldehydes



Entry	reagent	RCHO	base	conditions	yield	*cis*:*trans*
1	**2a**	2-Et-hexanal	NaH	0℃	94	83:17
2	**2b**	2-Et-hexanal	NaH	0℃	99	82:18
3	**2a**	2-Et-hexanal	NaH	-78→0℃	92	89:11
4	**2c**	2-Et-hexanal	NaH	0℃	78	94:6
5	**2c**	2-Et-hexanal	NaH	-78→0℃	87	95:5
6	**2c**	2-Et-hexanal	*t*-BuOK*	-78→0℃	91	95:5
7	**2c**	*n*-octanal	*t*-BuOK*	-78→0℃	84	95:5
8	**2c**	*c*-HexylCHO	*t*-BuOK	-78→0℃	97	94:6
9	**2c**	*t*-BuCHO	*t*-BuOK	-78→0℃	87	96:4
10	**2c**	2*E*-hexenal	*t*-BuOK	-78→0℃	98	94:6
11	**2c**	PhCHO	*t*-BuOK	-78℃	82	98:2

* NaI (3 eq)

Table 2 The HWE reaction of **4** and **5**



4: R^1=OMe, R^2=Me **5**: R^1=R^2=Me

	reagent **4**		reagent **5**	
RCHO	yield	*cis*:*trans*	yield	*cis*:*trans*
n-octanal	92	90:10	93	97:3
2-Et-hexanal	96	94:6	100	94:6
c-HexylCHO	95	89:11	94	90:10
t-BuCHO	75	95:5	68	95:5
2*E*-hexenal	86	82:18	87	95:5
PhCHO	94	96:4	94	99:1
p-ClPhCHO			97	99:1

In summary, the HWE reaction described above provides a direct route to a wide range of *cis*-α,β-unsaturated amides in high selectivity. Furthermore, the yields are generally almost quantitative.

References

1) K. Ando, *Synlett*, **2001**, 1272.

2) S. Fortin, F. Dupont, P. Deslongchamps, *J. Org. Chem.*, **2002**, *67*, 5437.

3) S. Kojima, T. Hidaka, A. Yamakawa, *Chem. Lett.*, **2005**, *34*, 470.

4) K. Ando, *J. Org. Chem.*, **1997**, *62*, 1934-1939.

2P-48

Cinchona Alkaloids/TMAF Combination-Catalyzed Nucleophilic Enantioselective Trifluoromethylation of Aryl Ketones

Hiroyuki Kawai,* Satoshi Mizuta, Surendar Akiti, Hiroyuki Fujimoto, Shuichi Nakamura, Norio Shibata, Takeshi Toru

Graduate School of Engineering, Nagoya Institute of Technology

Gokiso, Showa-ku, Nagoya 466-8555, Japan

nozshiba@nitech.ac.jp

Tetrasubstituted α-trifluoromethyl aryl alcohol have extensively provided important building blocks in the design of drug candidates. Among a variety of approaches available for the synthesis of the α-trifluoromethyl aryl alcohols, enantioselective nucleophilic trifluoromethylation of aryl ketones using the Ruppert-Prakash reagent, (trifluoromethyl)trimethylsilane, Me_3SiCF_3, is surely the most straightforward operation for construction of the corresponding chiral molecules. However, chiral auxiliary based diastereoselective trifluoromethylation is still the most widely applied approach in the field with enantioselective catalysis remaining a big challenge.

We recently found 1-fluorobis(phenylsulfonyl)methane (FBSM) to be a synthetic equivalent of a fluoromethide species under the catalytic enantioselective monofluoromethylation reaction of in situ generated prochiral imines with FBSM in the presence of a chiral phase transfer catalyst. In connection with our studies on the development of a new methodology for asymmetric synthesis, herein we disclose the highly enantioselective trifluoromethylation of aryl ketones with Me_3SiCF_3 catalyzed by a combination of ammonium bromides of cinchona alkaloids and tetramethylammonium fluoride (TMAF). Our approach is especially attractive because nonfluorinated prochiral substrates can be directly transformed to chiral trifluoromethylated aryl alcohols with tetrasubstituted carbon centers, with unprecedentedly high enantioselectivities (up to 94% ee), using readily available chiral ammonium bromides of cinchona alkaloids and TMAF (Figure 1).

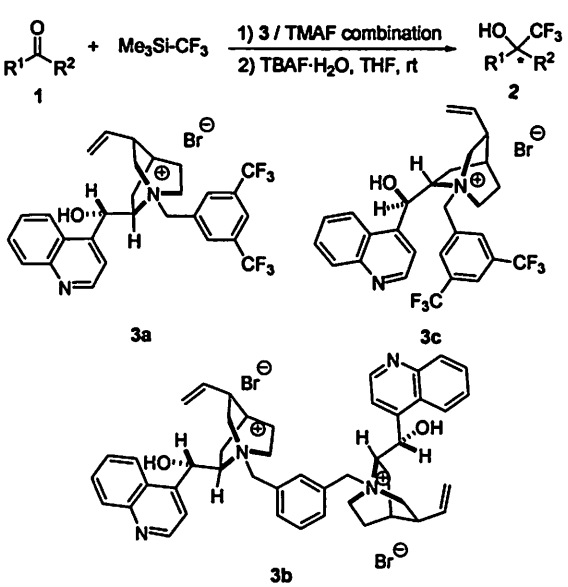


Figure 1.

We started our investigation with the reaction of methyl 2-naphthyl ketone (**1a**) with Me_3SiCF_3 and screened a broad range of additives as combination catalysts with the chiral ammonium bromide (Table 1). First, a catalytic amount of $KF/2H_2O$ was added to a mixture of **1a** and 2.0 equiv of Me_3SiCF_3 in toluene in the presence of a catalytic amount of *N*-3,5-bis(trifluoromethyl)benzylcinchoninium bromide (**3a**) at -40 °C.

However, even after 1 day of stirring, the reaction did not proceed (entry 1). The reaction was then attempted using a more soluble fluoride source, $TBAH_2F_3$, in toluene/dichloromethane at -40 °C. We were encouraged to find that trifluoromethylated adduct **2a** was formed in 83% yield with 25% ee (entry 2). This preliminary result encouraged us to investigate other combinations in an attempt to improve enantioselectivity. After screening several additives (TBAT, LiOAc, TBAF, TEAF), we found that the tetramethylammonium fluoride (TMAF) combination in toluene/dichloromethane at -40 °C affected the enantioselective trifluoromethylation of **1a** to furnish **2a** in 65% yield with 70% ee (entry 7). These results clearly indicate the combined effect of the additives and chiral ammonium bromide on the enantioselectivity. When the reaction was performed in toluene/dichloromethane (2:1) at -80 °C, the best result was achieved with the catalyst combination of **3a** (10 mol %) and TMAF (20 mol %) (98% and 87% ee, run 10). It is interesting to note that biscinchoninium derivative **3b** was found to be equally effective. The CF_3 adduct was obtained in 87% yield with 85% ee when the reaction was carried out using a combination of **3b** with TMAF (10 mol %) in toluene/dichloromethane (2:1) at -60 °C (entry11). The antipode of **2a** was obtained by using the pseudoenantiomeric *N*-3,5-bis(trifluoromethyl)benzylcinchonidinium bromide (**3c**) in 70% yield with 77% ee (entry 12).

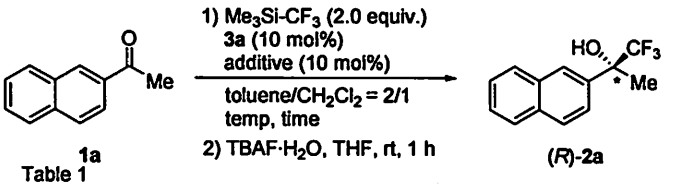
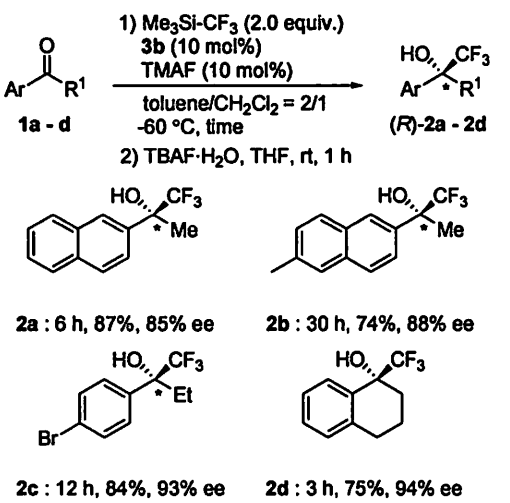


Table 1

entry	additive[a]	temp (°C)	time (h)	yield (%)	ee (%)
1	$KF/2H_2O$	-40	24	NR	-
2	$TBAH_2F_3$	-40	2	83	25
3	TBAT	-40	2	89	18
4	LiOAc	-40	2	99	19
5	$TBAF/H_2O$	-40	2	94	22
6	$TEAF/H_2O$	-40	2	38	66
7	TMAF	-40	8	65	70
8	TMAF	-60	2	65	81
9	TMAF	-80	2	53	80
10[b]	TMAF	-80	12	98	87
11[c]	TMAF	-60	6	87	85
12[d]	TMAF	-60	3	70	77

[a] $TBAH_2F_3$, tetrabutyl ammonium dihydrogen trifluoride; TBAT, tetrabutylammonium triphenyldifluorosilicate; TBAF, tetrabutylammonium fluoride; TEAF, tetraethylammonium fluoride. [b] 20 mol % of TMAF was used. [c] Catalyst **3b** was used instead of **3a**. [d] Catalyst **3c** was used instead of **3a**.

With conditions optimized, the scope of our trifluoromethylation reaction using the chiral ammonium bromide/TMAF catalyst was investigated in terms of substrates (Scheme 1). We found that our **3b**/TMAF combination is an extremely general catalyst for the asymmetric trifluoromethylation reaction of a broad range of alkyl aryl and cyclic ketones. It should be mentioned that cyclic ketones gave high enantioselectivities (up to 94% ee). The results are quite impressive because these chiral cyclic α-trifluoromethylated alcohols with a quaternary carbon center are difficult to prepare by other methodologies.



Scheme 1

Scale-up of hydrogenation reactions in continuous processes

*Laszlo Urge, Zsolt Otvos, Attila Wootsch, Eszter Varga, Ferenc Darvas
ThalesNano Inc.
Zahony u 7, Budapest, H-1031, Hungary
laszlo.urge@thalesnano.com

The difficulties involved with scaling-up reactions from laboratory to process scale are well known. The processes for producing desired compounds in industrial scale - which have previously been synthesized successfully in lab-scale - are often difficult and complicated, with several expensive and time-consuming steps. Chemical processes usually originate on small scale in the laboratory and their development is normally carried out by conducting the reactions on successively larger scale, through pilot plant stages, before transferring to full size production plants. Failure to scale up properly and to take appropriate precautions may lead to the loss of process control, resulting in runaway exothermic reactions and /or generation or release of toxic materials. The hazard of runaway reactions and over-pressurized conditions are the two major concerns during the scale-up processes, and besides them other problems, such as dust and vapor explosions inside the vessels, fires caused by the overfilling of vessels, auto-ignition of flammable vapors and inadequate mixing of reactants and solvents may occur, too. Consequently, when target compounds are identified and prepared for transfer to production, the synthetic route frequently requires re-optimization.

In order to shorten the time between identifying a target compound and scaling-up the reaction a flow hydrogenation system, called the H-Cube Midi™ (Figure 1.), has been designed.

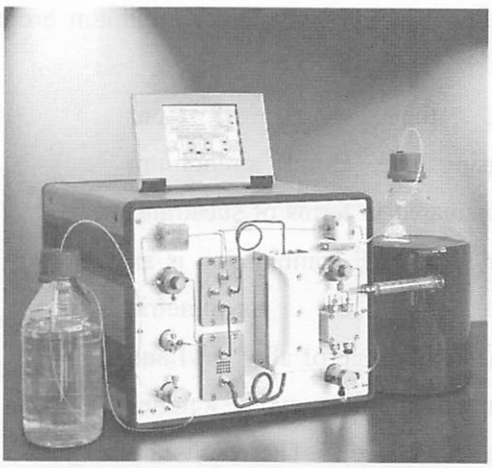


Figure 1.: The H-Cube Midi™ equipment

The system works in the same way as the H-Cube®, but is designed with a higher throughput. Up to 5 mol compound in a day can be processed, through higher hydrogen production and a larger, fixed bed cartridge system. Users can directly apply the optimized temperature and pressure identified on the small scale H-Cube® to the larger scale system, nevertheless, the temperature parameter of the H-Cube Midi™ system and maximum flow rate can be set up to 150 °C and 25 mL/min, respectively. If minor adjustments to parameters need to be performed, they can be adjusted on the fly. This method significantly reduces the scale-up optimization time from weeks or months to hours.

From reactions that have been performed on H-Cube Midi™ the scaled-up hydrogenation of quinoxaline is demonstrated (Figure 2.).

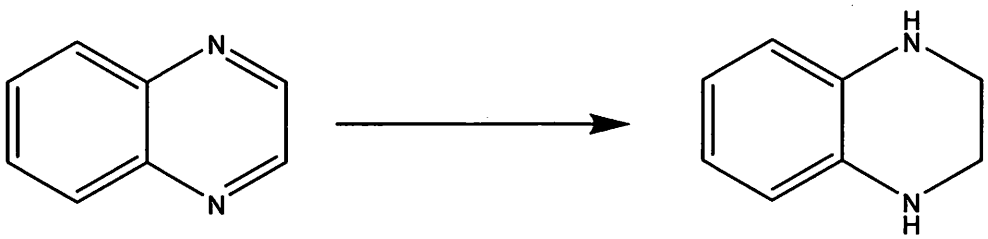


Figure 2.: Hydrogenation of Quinoxaline

The reaction mentioned above was successfully carried out previously in H-Cube® system with 100% conversion at 70 °C, 70 bar hydrogen pressure and 1 mL/min flow rate over Raney-Ni catalyst; however this reaction carried out in batch-type reactor resulted in only 5% conversion. The reaction performed in H-Cube Midi™ gave the same result, namely, the outstanding conversion. However, due to the increased capacity of the system, the estimated daily product of the tetrahydro-quinoxaline is in the 100 grams scale, which result in a two orders of magnitude increase in the capacity achieved in H-Cube®.

The H-Cube Midi™ has been managed to increase upon the throughput of the original H-Cube® significantly while maintaining the safety benefits. The use of microreactor flow technology allows reactions to be scaled up without the hazards of batch scale-up, such as the lack of precise temperature control. The technology allows the possibility to scale-up reactions, which may not have been possible before. It was proven with several examples that working with H-Cube Midi™ reactor several 100 grams per day of hydrogenated products can be synthesized safely and effectively.

2P-50

Synthesis of PVDF-g-PMMA by atom transfer radical polymerization

*Dar-Jong Lin, Liao-Ping Cheng, Chun-Liang Lin, Chang-Li Lin
Department of Chemical and Materials Engineering, Tamkang University, Tamsui 25137, Taiwan
djlin@mail.tku.edu.tw/ Fax:+886-2-26209887
NSC 96-2221-E-032-029-MY3

Introduction. Among the methods of chemical modification of Poly(vinylidene fluoride) (PVDF), there were usually plasma-activation, γ-ray or electron beam irradiation, and ozone treatment. These are suitable on the solid sample surface except γ-ray which usually causes degradation of polymer.

In this research we used different method of chemical modifications, which is Atom Transfer Radical Polymerization (ATRP). ATRP, which is one of the living radical polymerizations, proceeds in solution where all the PVDF molecules in the reaction medium are concerned. In 1995 years, Matyjaszewski and Sawamoto et al. [1-3] used the Cu and Ru metallic catalysts to control the condition of radical in polymerization where normally alkyl halides were utilized as initiator. The catalyst induced the halide atom transferred onto metal, and the alkyl halides form the activated radical site. The radical together with the metallic catalyst constitute ensemble, in certain sense, an activated complex of which the equilibrium exists between active and de-active states. The mechanism of activation and de-activation equilibrium can then permit each initiated site to propagate with a similar rate of polymerization, giving in consequence products of very narrow polydispersity as is often the case for living polymers.

In recent year, Mayes et al. [4] succeeded in using secondary fluorine of PVDF as the macroinitiator to directly graft *tert*-butyl methacrylate onto PVDF by way of ATRP. The PtBMA side chains were hydrolyzed to PMAA afterwards.

Our present work proved to graft directly PMMA side chains onto PVDF with a kinetic behavior following ATRP mechanism in spite of the competence of side reaction due to thermal self-initiation. The increment of molecular mass and graft ratio were determined by static light scattering and spectrometric methods respectively. Furthermore the intramolecular interaction between different constituent chains within the graft copolymer in solution was found to be so important that the molecule shrank remarkably. This novel discovery invokes very much attention in our future study of application with such graft copolymers.

Methods. Solvent dimethylformamide (DMF) and monomer methyl methacrylate (MMA) were purged with argon gas before use. The atom transfer catalyst cuprous chloride (CuCl, 0.096 g) accompanied with ligand molecule 4,4-dimethyl 2,2-dipyridyl (DMDP, 0.480 g) were then prepared in solution with purified DMF (135 ml) and maintained under argon atmosphere in reactor flask. Poly(vinylidene fluoride) (PVDF, 9.37 g) as macro-initiator was also dissolved in purified DMF (135 ml) at 90 °C and then introduced into the reactor. Finally MMA (40g) was added in the reaction medium and the polymerization was allowed to proceed for 8 hours. The raw product was precipitated into a large volume of water/methanol (1/9) mixture and then washed by methanol twice. It was finally dried under vacuum overnight at 80 °C. The raw product of reaction was composed of PVDF-g-PMMA graft copolymer through ATRP and PMMA homopolymer due to thermal self-initiated polymerization. The latter was removed by Soxhlet extractor in toluene for 18 hours. The residual graft-copolymer was recovered by vacuum oven drying overnight at 80 °C after washing in isopropanol twice.

IR samples films were prepared by casting a dilute polymer solution on PTFE plates followed by vacuum drying. The instrument setting was as follows: signal-averaged 32 scans at a resolution of 4 cm^{-1} with a Nicolet Magna-IR Spectrometer 550. NMR ^1H spectra of PVDF, PMMA and the graft copolymers in deuterated acetone solution were performed using a BRUKER AVANCE 600 MHz spectrometer. Gel permeation chromatography (GPC) was conducted at 40°C in NMP at a flow rate of 1 ml/min, using Waters 1515 HPLC pump system equipped with Waters Styragel®HT5 column and Waters 2414 differential refractometer. The intrinsic viscosity of copolymers were measured by capillary viscometer (Ubbelohde viscometers model: OB) in thermostat water bath at 30°C. The hydrodynamic diameters of grafted polymers at the concentration of 5mg/ml in NMP were determined by the Zetasizer Nano ZS system (Malvern Instruments, UK). The measurements for the average of weight molecular weight of copolymers were performed on a multi-angle static light scattering instrument DAWN HELEOS 8 (Waytt, USA).

Structure Characterization. The structure of graft copolymer was firstly determined by IR analysis. As shown in Fig. 1, the comparison of IR spectra between PVDF and PMMA clearly shows the characteristic signal of carboxyl group C=O (1729 cm^{-1}) of PMMA and that of methylene CH_2 (881 cm^{-1}) of PVDF. These two signals respectively permit us to well distinguish one constituent polymer chain from another. The structural constituents of graft copolymer are thus revealed by the spectrum (c) in which two characteristic signals are present.

In Fig. 2, the NMR ^1H spectrum of PVDF at 2.334 ppm and 2.91 ppm is found for methylene CH_2, which respectively represent head-to-head (hh) and head-to-tail (ht) configuration. In the case of PMMA the α-methyl (α-CH_3), methylene (CH_2) and methoxy (O-CH_3) are found in the regions around 0.84 to 1.03 ppm, 1.85 to 1.95 ppm and 3.604 ppm respectively. The spectrum (c) reveals all the corresponding aforementioned signals, indicating then PMMA chains attached onto the backbones of PVDF.

Kinetics. From the weighing data of raw product, calculation of total conversion of monomer MMA with respect to reaction time is shown in Fig. 3. Also figured is the graft conversion, which was determined by quantitative calibration method based on IR spectra analysis of the aforementioned characteristic peak. The linear growth of graft conversion implies that the normal mechanism of ATRP kinetic may be proposed. This would be approved in the following sections of hydrodynamic properties and molecular weight study.

The difference between these two curves reveals the part of conversion due to the thermal self-initiated polymerization of MMA. It is found that the reaction rate of ATRP is much slower than that of thermal self-initiated polymerization which gives rise to PMMA homopolymer. The future study will be dedicated to the suppression of such side reaction from thermal self-initiation and at the same time to maintain the ATRP reaction as maximum as possible.

Hydrodynamic Properties. The kinetic study of ATRP with respect to reaction time permitted us to synthesize PVDF-g-PMMA copolymers of different graft ratio. Four copolymers (G1-G4) and unmodified PVDF (G0) were selected for investigation of fundamental physical properties in solution state. Table 1 summarizes the intrinsic viscosity [η] and hydrodynamic diameter d_H of them. It reveals the fact that the values of intrinsic viscosity of graft copolymers (G1-G4) are all smaller than PVDF (G0). This means that even though the mass of molecules becomes larger through the grafting of additional PMMA chains on to the PVDF backbone, their effective coil excluded volume in solution decreases instead, and ,extraordinarily, larger the mass is, smaller the volume.

Such unexpected results were further confirmed by the measurement of hydrodynamic diameter using dynamic light scattering, that is, hydrodynamic diameter d_H actually decreases in spite of the increase of molecular mass. The diminution of molecular volume may be interpreted as the effect of intra-molecular interaction between different constituent chains within the graft copolymer molecule. It had been observed that the blend of PVDF and PMMA showed very good compatibility between these two constituent polymers, and the existing interaction assigned mainly due to the polar effect could be approved through IR spectrum. Likewise, it is thus believed that the interaction force of between PVDF chain segments and PMMA ones is more important than that of between PVDF, or PMMA, and solvent molecules.

Molecular Weight. The absolute weight average molecular weight ($\overline{M}_w$) was obtained from Zimm plot of static light scattering analysis. Table 2 summarizing the molecular weights of the selected samples indicates the weight increments of graft copolymers relative to PVDF (G0). The molecular weight increases gradually from sample G1 to G4 as is anticipated from IR analysis. Theoretically these increments should be equal to graft ratio determined from IR quantitative calibration. The consistency of these two experimental data appears quite well on considering the limit of accuracy in each method.

The confirmation of both molecular weight increment and the kinetic data shown in Fig. 1 reveals the fact that in the present study the ATRP mechanism works normally well as predicted, even though it is competed by the side reaction of thermal self-initiation of MMA.

Conclusion. PVDF has been chemically modified polymer by ATRP polymerization using cuprous chloride as catalyst. The reaction product included graft copolymer and homopolymer, where the latter constitutes more and the graft ratio of the former obtained in this work is around 0.2 at most. Hydrodynamic diameters of graft copolymers were smaller than PVDF, and they diminish with the increasing graft ratio. Apparently, polar interaction between PVDF and PMMA constituent chains turns out to be more important than that between polymer chains and solvent molecules. In this research, the fact that both the variation of graft ratio and molecular weight increment follows the reaction kinetics confirms good ATRP mechanism of which terminal reaction was normally absent.

References:

[1] Wang, J.-S.; Matyjaszewski, K. *Macromolecules* **1995**, *28*, 7901- 7910.

[2] Wang, J.-S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614- 5615.

[3] Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1995**, *28*, 1721-1723.

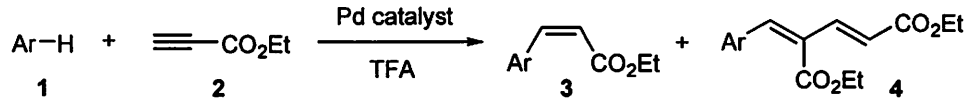
[4] Hester, J. F.; Banerjee, P.; Won, Y.-Y.; Akthakul, A.; Acar, M. H.; Mayes, A. M., *Macromolecules* **2002**, *35*, 7652-7661.

2P-51

Effect of Ligands on Pd-Catalyzed Hydroarylation of Ethyl Propiolate

Tsugio Kitamura,* Juzo Oyamada
Department of Chemistry and Applied Chemistry, Faculty of Science and Engineering, Saga University
Honjo-machi, Saga 840-8502, Japan
kitamura@cc.saga-u.ac.jp

Direct functionalization of C-H bonds is an attractive reaction because it is a powerful and straightforward method for transformation of organic compounds.[1] Previously, we reported that $Pd(OAc)_2$ catalyzed the hydroarylation of alkynes with simple arenes in the presence of trifluoroacetic acid (TFA), affording *cis*-aryl substituted alkenes.[2] In this reaction, ethyl propiolate (**2**) afforded a small amount of arylbutadiene derivatives **4** although the main products were usual hydroarylation products, ethyl cinnamates **3** (eq. 1).[2b]



(eq. 1)

During the course of our study on the hydroarylation of alkynes, we found that arylbutadienes **4** were formed selectively when a palladium complex with a bidentate phosphine ligand, $Pd(dppe)(OAc)_2$ (dppe = 1,2-bis(diphenylphosphino)ethane), was used as a catalyst. Here, we report Pd-catalyzed functionalization of arenes with ethyl propiolate leading to selective formation of arylbutadienes.

First, we investigated the reaction of mesitylene (**1a**) with **2** in the presence of $Pd(dppe)(OAc)_2$ as a catalyst. The reaction afforded **4a** as a major product along with a small amount of cinnamate **3a**. Optimization of the reaction conditions revealed that an amount of **1a** affected the selectivity of the products (Table 1, Entries 1-4).

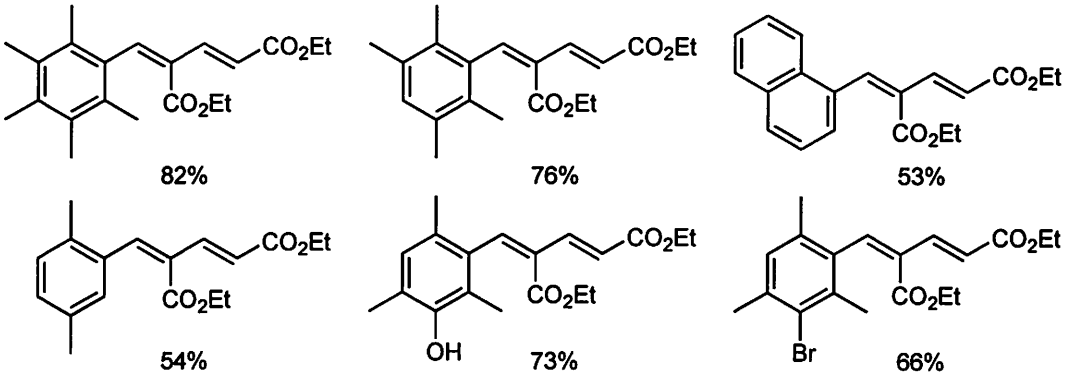
Table 1. Optimization of Reaction Conditions[a]

Entry	**1a**/mmol	**2**/mmol	GC yields / %[b]		
			3a	**4a**	**5a**[c]
1	3	2	17	83	0
2	2	2	17	83	0
3	1	2	7	68	4
4	1	3	0	25	2
5	2	2[d]	16	83	0
6	2	2[e]	9	91	0

[a] Reaction conditions: $Pd(dppe)(OAc)_2$ (0.005 mmol), **1a**, **2** and TFA (1 mL) at 30°C for 5 h. [b] The yields based on **2**. [c] Diethyl (2*Z*,2'*Z*)-3,3'-(2,4,6-trimethylbenzene-1,3-diyl)bisprop-2-enoate (**5a**). [d] TFA (0.5 mL) and CH_2Cl_2 (0.5 mL). [e] TFA (0.25 mL) and CH_2Cl_2 (0.75 mL).

An excess amount of **1a** prevented the products from the further reaction, resulting in higher yields. An amount of TFA also affected the selectivity of **4a** (Entries 5 and 6). A less amount of TFA is favorable for selective formation of **4a** although TFA is essential for the reaction. As a result, **4a** was obtained in 91% yield along with 9% of **3a**.

This reaction is also applicable to other arenes, such as pentamethylbenzene, 1,2,4,5-tetramethylbenzene, naphthalene, *p*-xylene, 2,4,6-trimethylphenol and 2-bromomesitylene. The results will be presented in detail.



References

(1) (a) Kakiuchi, F.; Murai, S. In *Topics in Organometallic Chemistry*; Murai, S., Ed.; Springer, **1999**. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (c) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1698. (d) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047. (e) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437. (f) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (g) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (h) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (i) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(2) (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252.

2P-52

Tetrabutylammonium Fluoride-Induced Dehydrobromination of Vinyl Bromides to Terminal Acetylenes

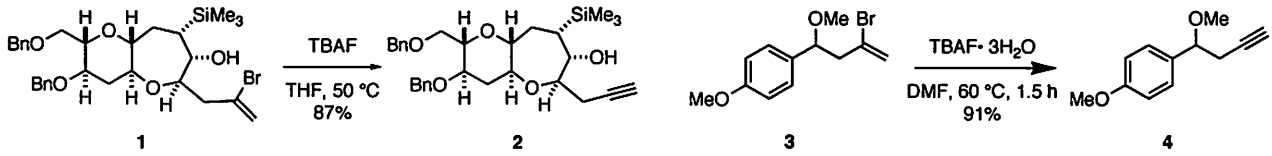
Masaru Okutani and *Yuji Mori

Faculty of Pharmacy, Meijo University, 150 Yagotoyama, Tempakuku-ku, Nagoya 468-8503, Japan

mori@ccmfs.meijo-u.ac.jp

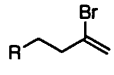
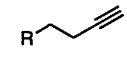
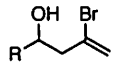
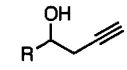
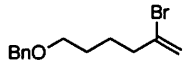
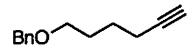
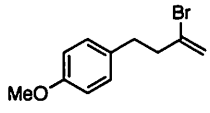
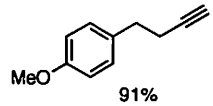
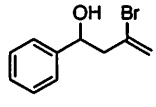
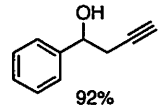
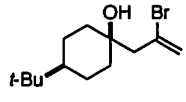
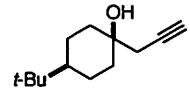
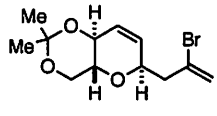
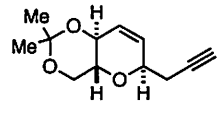
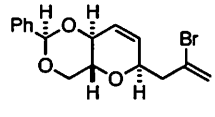
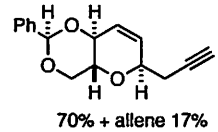
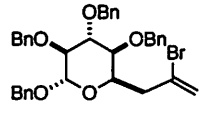
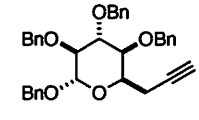
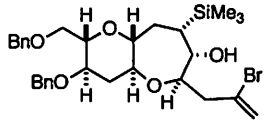
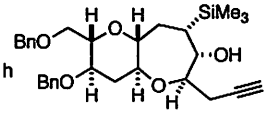
Terminal acetylenes are an important functional group and widely used in organic synthesis. Recent progress with transition metal-catalyzed carbon-carbon coupling reactions such as Sonogashira coupling reactions, Pauson-Khand reactions, and metatheses has also proven the importance of terminal acetylenes. Dehydrobromination of vinyl bromides is a simple method for the preparation of terminal acetylenes, and many procedures have been reported: $NaNH_2$ in liquid NH_3, KO*t*-Bu in THF, NaOMe in DMSO, NaH in DMSO or DMF, LDA in THF, KH in THF, DBU in THF, *n*-BuLi in Et_2O, and *t*-BuLi in pentane-Et_2O. The common disadvantages of these methods are the requirement of a strong base and anhydrous reaction conditions due to the low acidity of olefinic protons. It is therefore useful to find a new method that can tolerate moisture or water.

During the course of our synthetic studies of polycyclic ethers, we discovered an unexpected reaction of vinyl bromide **1** with tetrabutylammonium fluoride (TBAF) in THF. The reaction product obtained was the dehydrobromination product **2** instead of the desired desilylation compound. Considering that the commercially available TBAF (1 M in THF) contains approximately 5% water,[1] the acetylene formation in the presence of water is quite interesting and stimulated us to investigate the dehydrobromination of vinyl bromides with TBAF.



Treatment of **3** with 1.0 equiv of TBAF (1 M in THF) in THF at 60 °C resulted in the reaction conversion to only a 44% value after 25 h. No reaction was observed with the halogenated solvent CH_2Cl_2 or a polar protic solvent such as MeOH. DMF was found to be an acceptable solvent, qualitatively as good and better than THF in terms of reaction times. Acetonitrile was found to be inferior when compared to THF. In the reaction with DMF, TBAF·$3H_2O$ was selected as the reagent because it is readily available as a stable salt. Increasing the quantity of TBAF improved the conversion yield. Five equivalents of TBAF·$3H_2O$ were needed to

Table 1. Dehydrobromination of vinyl bromides with TBAF (5.0 equiv) in DMF at 60 °C.

Entry	Substrate	Time	Product IsolatedYield (%)
1	 R = C_9H_{19}	4 h	 93%
2	 R = C_9H_{19}	3 h	 95%
3		2 h	 90%
4		1.5 h	 91%
5		3 h	 92%
6		3 h	 82%
7		3 h	 78% + allene 9%
8		3 h	 70% + allene 17%
9		4.5 h	 77% + allene 11%
10		2 h	 92%

complete the reaction at 60 °C in a few hours. Other fluoride salts such as CsF and KF were shown to be ineffective for this dehydrobromination.

Next, we extended the optimized dehydrobromination conditions to various vinyl bromides: the results are represented in Table 1. The reaction is quite general and many substances tolerate the optimized reaction conditions, giving products in good to high yields. Vinyl bromides containing a hydroxy group were also found to give the corresponding acetylenes in good yields (entries 2, 5, and 6). It is notable that only trace amounts (< 2%) of allenic products were detected in the experiments listed in entries 2, 5 and 6, whereas large amounts (9–17%) of allene derivatives were formed in the dehydrobromination of the vinyl bromides derived from glucose (entries 7–9).[2]

In conclusion, TBAF was found to be an efficient and mild base in the dehydrobromination of vinyl bromides to terminal acetylenes. The reaction can be carried out by using TBAF·$3H_2O$ in DMF, and the water tolerance and the absence of metal salts make this method attractive. This procedure provides a reasonable alternative to other methods that require strong bases and anhydrous conditions.

References

1. TBAF (1 M in THF) was purchased from Aldrich. (a) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216–3219. (b) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112–2114.
2. Okutani, M.; Mori, Y. *Tetrahedron Lett.* **2007**, *48*, 6856–6859.

2P-53

AZADOs : Highly Active Oxidation Catalysts for Alcohols -Discovery and Characterization-

*Masaki Tomizawa[1], Masatoshi Shibuya[1], Yusuke Sasano[1], Iwao Suzuki[1], Fabio Pichierri[2] and Yoshiharu Iwabuchi[1]

[1] Graduate School of Pharmaceutical Sciences, Tohoku University

[2] Graduate School of Engineering, Tohoku University

6-3, Aoba-yama, Aoba-ku, Sendai, 980-8578, Japan

iwabuchi@mail.pharm.tohoku.ac.jp

The oxidation of primary and secondary alcohols to the corresponding aldehydes (or carboxylic acids) or ketones is a fundamental and important transformation in modern organic synthesis. Stable organic nitroxyl radicals as represented by TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) have been used extensively to catalyze the oxidation of a number of alcohol substrates employing environmentally benign co-oxidants such as bleach (NaOCl) or $PhI(OAc)_2$ [a] (Figure 1). Although TEMPO oxidation is better known as a method for selective oxidation of primary alcohols to the corresponding aldehydes, the TEMPO-based method is not very efficient for the oxidation of structurally hindered secondary alcohols. The origin of this feature is the structure of TEMPO, which has four methyl groups adjacent to the catalytic center. We then designed 2-azaadamantane *N*-oxyl (AZADO) and 1-Me-AZADO, a structurally less hindered class of nitroxyl radical, and revealed their excellent catalytic activity for oxidation of a variety of alcohols (Figure 2, Table 1).[b] It was envisioned that the α-hydrogen flanked by the nitroxyl group of AZADO would resist participating in the well-known disproportionation reaction to give a nitrone and a hydroxylamine because of Bredt's rule and, therefore, should allow facile access of various alcohols to the catalytically active center, enabling them to proceed to subsequent oxidation events.

Figure 1. The proposed mechanism of TEMPO oxidation

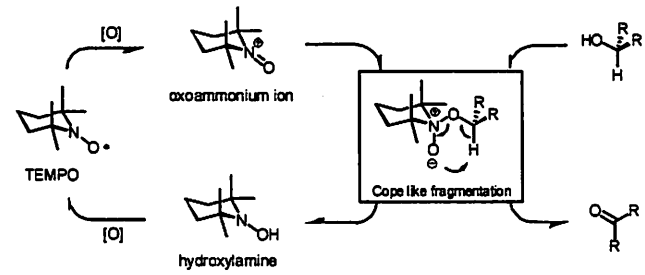


Figure 2. Our design for oxoammonium salts : AZADO⁺

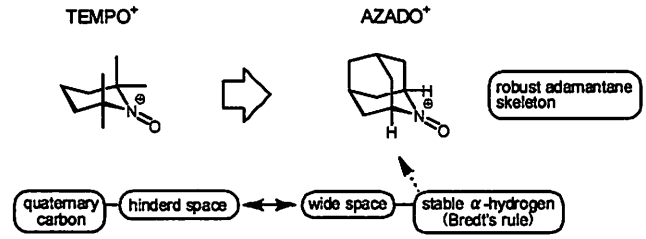
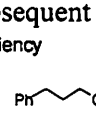
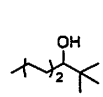
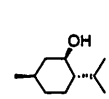
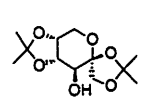
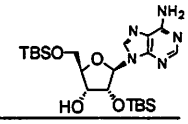


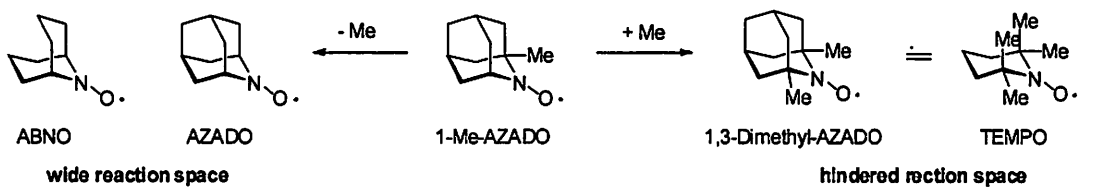
Table 1. Comparison of catalytic efficiency

					
TEMPO	23% [a]	15%	5%	8%	12%[c]
AZADO	---	92%	94%	97%	99%[d]
1-Me-AZADO	91%[b]	93%	95%	99%	100%[d]

general conditions : nitroxylradical (1 mol%), NaOCl (1.5 eq.), KBr (0.1 eq.), aq. $NaHCO_3$-CH_2Cl_2, 0 °C, 20 min
catalyst loading : (a) 0.01 mol%, (b) 0.003 mol%
conditions : (c) : cat. 5 mol%, $PhI(OAc)_2$ 330 mol%, CH_2Cl_2, (d) : cat. 5 mol%, $PhI(OAc)_2$ 150 mol%, CH_2Cl_2

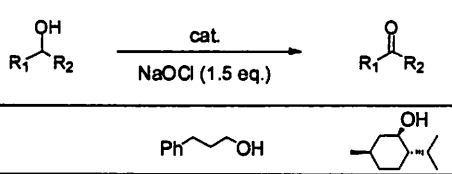
To verify our assumptions, we synthesized bridgehead nitroxyl radicals including 1,3-dimethyl-AZADO and 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO) and evaluated their catalytic activities for the oxidation of alcohols in detail (Figure 3).

Figure 3. Bridgehead nitroxyl radicals



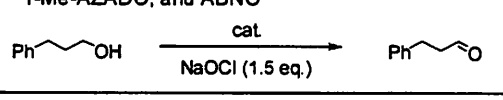
[1,3-dimethyl-AZADO] : In case of the oxidation of a primary alcohol, 1,3-dimethyl-AZADO exhibits a same activity as AZADO and 1-MeAZADO. On the other hand, similar to TEMPO, it does not efficiently oxidize sterically demanded alcohols, showing a remarkable difference from AZADO and 1-Me-AZADO (Table 2). [ABNO] : Although ABNO shows behavior similar to AZADO and 1-MeAZADO for the oxidation of sterically demanding alcohols, its catalytic efficiency is slightly decreased compared with that of 1-Me-AZADO (Table 3). Based on our experimental results, we concluded that an α-methyl group flanking the nitroxyl group affects reactivity for the oxidation of sterically hindered alcohols and the azaadamantane skeleton contributes to the high turnover of the catalyst.

Table 2. Comparison of catalytic efficiency



ABNO	90%	94%
AZADO	89%	94%
1-Me-AZADO	91%	95%
1,3-Dimethyl-AZADO	92%	trace
TEMPO	90%	trace

Table 3. Comparison of catalytic efficiency between TEMPO, 1-Me-AZADO, and ABNO



entry	mol%	TEMPO	1-Me-AZADO	ABNO
1	1	91%	89%	94%
2	0.1	88%	90%	88%
3	0.01	23%	91%	85%
4	0.003	—	81%	41%

Furthermore, electorochemical experiments were also conducted to gain insight of the correlation between electrometric properties and reactivities of the AZADO family. We also carried out DFT calculations on the AZADO family and found a relationship between SOMO energy and $E^{o'}$ values. Details will be discussed in this symposium.

References)

a) de Nooy, A. E.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153.

b) Shibuya, M; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

2P-54

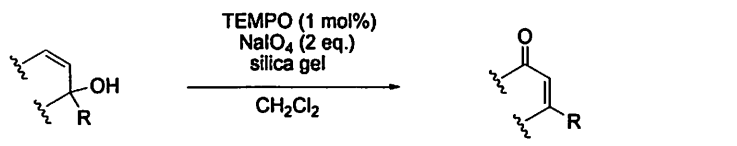
New Application of Oxoammonium Salt-based Catalysts

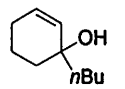
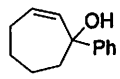
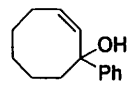
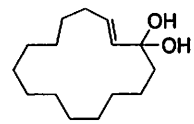
*Masatoshi Shibuya, Takahisa Sato, Masaki Tomizawa, Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University.
6-3, Aoba-yama, Aoba-ku, Sendai, 980-8578, Japan
iwabuchi@mail.pharm.tohoku.ac.jp

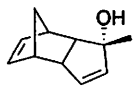
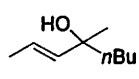
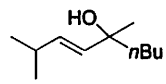
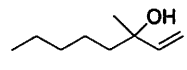
Oxidation employing the redox system of the nitroxy radical/oxoammonium ion has become popular because the method offer environmentally benign processes for laboratory scale synthesis as well as for industrial synthesis. Expanding the scope of oxoammonium ion-based oxidation is, therefore, promising for sustainable development. We present two new oxidation methods using oxoammonium salts-based catalysts.

1) Catalytic oxidative 1,3-rearrangement of tertiary allylic alcohols

The oxidative rearrangement of tertiary allylic alcohols to β-substituted α, β-unsaturated ketones is a useful transformation in synthetic chemistry. Oxochromium(IV)-based reagents have been exclusively used since the report in the mid-70s that PCC, PDC, and Collins reagent are effective for this transformation. From the viewpoint of green sustainable chemistry, we had explored the alternative method.[1] As a result, we developed methods using stoichiometric amounts of $TEMPO^+BF_4^-$ and $TEMPO^+SbF_6^-$.[2] Quite recently, we have developed catalytic methods using catalytic amount of TEMPO with $NaIO_4/SiO_2$ as the co-oxidant. This catalytic method requires only 1 mol% TEMPO. Various tertiary alcohols ranging from medium-sized to macrocyclic substrates as well as acyclic substrates effectively undergo the oxidative rearrangement.



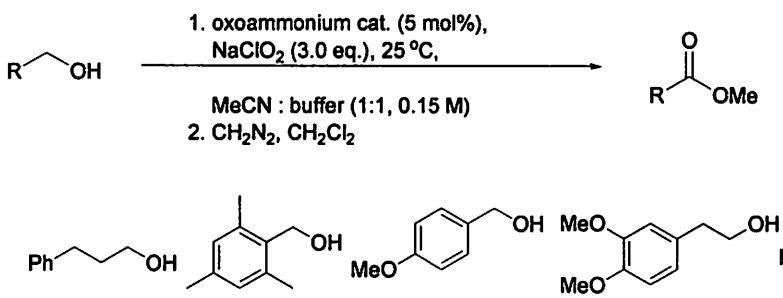
substrate				
yield time	92% (2 h)	94% (8 h)	92% (14 h)	92% (24 h)

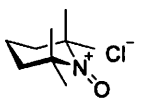
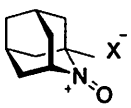
substrate				
yield time	81% (12 h)	84% (15 h)	76% (20 h)	0% (24h)

2) One-pot oxidation of primary alcohols to carboxylic acids

One-pot oxidation of primary alcohols to carboxylic acids is also an important reaction in organic synthesis. Since relatively few good general reactions are available for this process, a two-step method involving Swern oxidation or Dess-Martin oxidation followed by oxidation of the resulting aldehyde by the Kraus-Pinnick reaction are often applied. The development of a good general one-pot oxidation should increase efficiency in organic synthesis. We sought methods using AZADOs which we have reported as more aggressive organocatalysts than TEMPO for alcohol oxidation.[3]

The Merck method employing cat.TEMPO/cat.NaClO/$NaClO_2$ is known as the most effective method for this transformation.[4] However, this method has some limitations; it is not applicable to substrates having electron-rich aromatic moieties and the careful, slow addition of $NaClO_2$/NaClO is required. We found that a simple procedure using catalytic amounts of oxoammonium salts and $NaClO_2$ is effective as a one-pot oxidation for various primary alcohols including substrates having an electron-rich aromatic ring which fail to oxidize under Merck condition. Me-AZADO$^+$ gave better results than TEMPO$^+$, although the differences in reactivity are modest.



		98% (0.5 h)	100% (9.5 h)	100%* (37.5 h)	64% (7 h)	89%** (19 h)
	X = Cl	98% (0.5 h)	98% (7 h)	92%* (23.5 h)	92% (0.2h)	92%** (19 h)
	X = BF_4	93 % (0.5 h)	98% (7 h)	97%* (26 h)		81%** (19 h)

* 5 eq. of $NaClO_2$ was used.

** 20 mol% of catalyst and 5 eq. of $NaClO_2$ were used

1) Shibuya, M.; Ito, S.; Takahashi, M.; Iwabuchi, Y. *Org. Lett.* **2004**, *6*, 4303.

2) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Org. Chem.* **2008**, *in press*.

3) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

4) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.

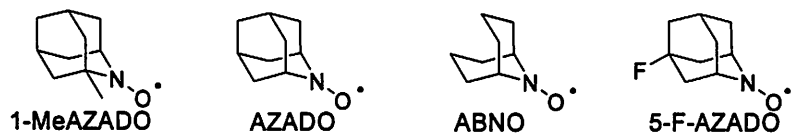
2P-55

Aerobic Oxidation of Alcohols using AZADOs

*Yuji Osada, Masatoshi Shibuya, Masaki Tomizawa, Yusuke Sasano, Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University.
6-3, Aoba-yama, Aoba-ku, Sendai, 980-8578, Japan
iwabuchi@mail.pharm.tohoku.ac.jp

Catalytic oxidation systems of that make use of molecular oxygen as the terminal oxidant have received great attention for economic as well as environmental benefits.[1] However, many of these methods require a rather expensive or toxic transition-metal, and/or high temperature, and/or high pressure. Recently transition-metal-free methods for oxidation of alcohols using stable nitroxyl free radicals (2,2,6,6,-tetramethyl-piperidyl-1-oxyl, TEMPO) have been developed, as exemplified by the TEMPO/ halogen source/$NaNO_2$ oxidation system.[2] However, many of these systems still require high temperature and/or high pressure and halogen-containing solvent, and substrate applicability is limited. We recently reported azaadamantane-*N*-oxyl (AZADO) derivatives (Figure 1) as more aggressive variants of TEMPO.[3] We explored the applicability of AZADOs in the aerobic oxidation of alcohols and found AZADOs/ $NaNO_2$/AcOH/O_2 (balloon) a promising aerobic oxidation system.

Figure 1. AZADOs

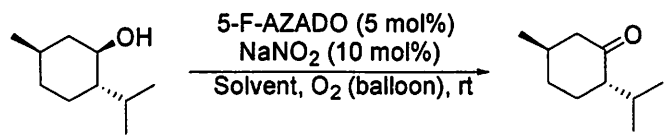


The catalytic system developed offers transition-metal free, halogen free, room temperature oxidation of alcohols.

Our investigation began with the screening of co-catalysts and solvents that link redox cycles between AZADOs and molecular oxygen using menthol as the substrate. After considerable experimentation, we found AcOH afford superior performance for the AZADOs/$NaNO_2$/O_2 system CH_2Cl_2 (Table 1).

Next, we screened catalytic efficiency of AZADOs using 2-hydroxycyclohexyl benzoylester (**1**) as a substrate, for which the TEMPO-based system failed to oxidize (Table 2, Entry 1). Even 1-Me-AZADO, which exhibited satisfactory performance with the same substrate under conventional conditions using NaOCl or $PhI(OAc)_2$, resulted low yield (Entry 2). AZADO and ABNO showed

Table 1.



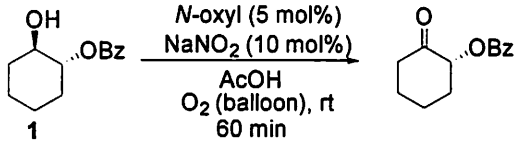
Entry	Sovent	Time (h)	Yield (%)	Note
1	CH_2Cl_2	24	0	NR
2	AcOH	2	92	

[a] All yields refer to pure, isolated products.

improved reactivity (Entries 3 and 4). To our delight, 5-F-AZADO showed a remarkable reactivity and afforded satisfactory yields.

We then explored the substrate applicability to the 5-F-AZADO/$NaNO_2$/O_2/AcOH system. This oxidation system accepted a variety of alcohols to give the corresponding carbonyl compounds (Table 2). It is important to note that this system allowed conversion of quinuclidinol to quinuclidinone, which is difficult to obtain cleanly by other methods.

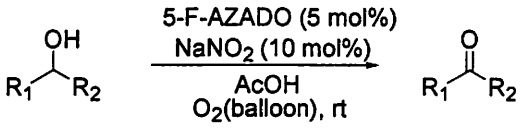
Table 2

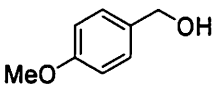
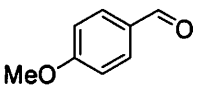
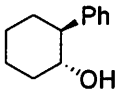
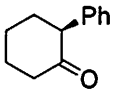
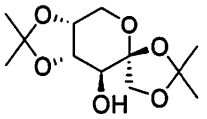
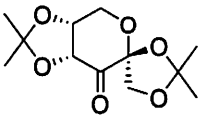
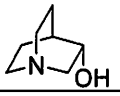
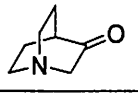


Entry	N-oxyl	[a] Conversion (%) 30 min	[a] Conversion (%) 60 min	[b] Yield (%)
1	TEMPO	< 1	< 1	trace
2	1-Me-AZADO	11	26	27
3	AZADO	63	72	76
4	ABNO	65	74	78
5	5-F-AZADO	> 99	100	99

[a] Conversions are based on GC analyses with area normalization.
[b] All yields refer to pure, isolated products.

Table 3



Entry	Substrate	Product	Time (h)	[a] Yield (%)	Note
1			1	92	
2			1	90	
3			1	97	
4			1	80	Using $NaNO_2$ (30 mol%)

[a] All yields refer to pure, isolated products.

[Reference]

1) M. J. Schultz; M. S. Sigman. *Tetrahedron* **2006**, 62, 8227.

2) X. Wang; R. Liu; Y. Jin; X. Liang. *Chem. Eur. J.* **2008**, 14, 2679

3) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, 128, 8412

2P-56

Practical Synthesis of Highly Efficient Organocatalysts for Oxidation of Alcohols: AZADO, 1-Me-AZADO and ABNO

*Yusuke Sasano, Masatoshi Shibuya, Masaki Tomizawa, Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University
6-3, Aoba-yama, Aoba-ku, Sendai, 980-8578, Japan
iwabuchi@mail.pharm.tohoku.ac.jp

Oxidation of alcohols to obtain ketones, aldehydes or carboxylic acids is a fundamental transformation in organic chemistry. The recent global demand for alleviating environmental stress has spurred much effort directed toward the development of green oxidation processes that fulfill the requirements for practical applications. Nitroxyl-radical catalyzed oxidation methods, for example, TEMPO-oxidation, have attracted attention in many areas of synthetic organic chemistry because they enable the use of various safe bulk oxidants, thereby also enabling the safe and extremely efficient oxidation of alcohols with considerable operational simplicity.

In this update, we report practical syntheses of highly efficient nitroxyl radical catalysts developed by us, 2-azaadamantane *N*-oxyl (AZADO, **1**), 1-Me-AZADO (**2**), and 9-aza-bicyclo[3,3,1] nonane *N*-oxyl (ABNO, **3**).

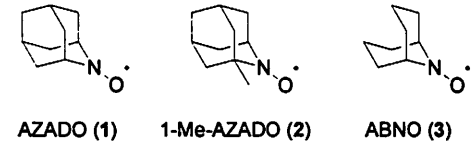
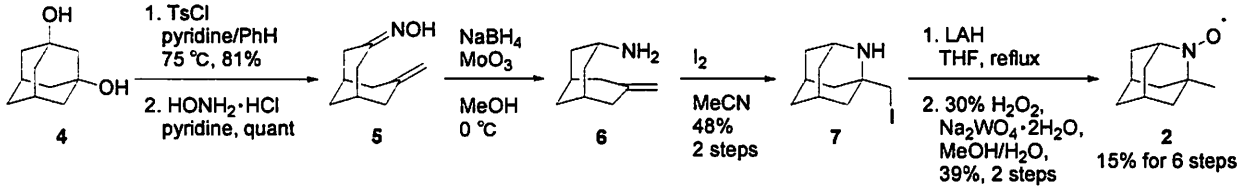


Figure 1

1) Practical synthesis of 1-Me-AZADO

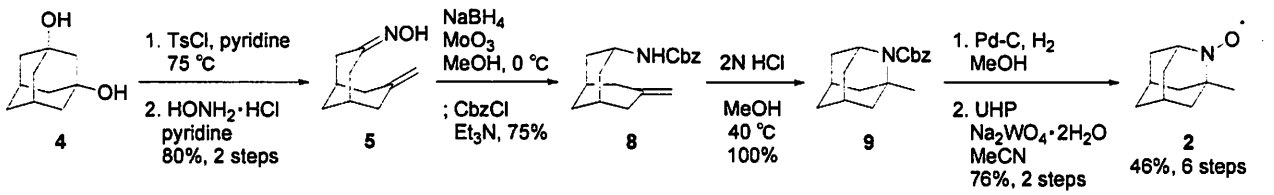
The first-generation synthesis of 1-Me-AZADO (**2**) gave 15% overall yield for 6 steps staring from 1,3-adamantanediol (**4**) (**Scheme 1**).[1]



Scheme 1: First-generation synthesis of 1-Me-AZADO (**2**)

The most significant problem in the synthesis was difficulty in purification of amine **6** because it is both highly polar and volatile.

To overcome this problem, we developed a second-generation synthesis of 1-Me-AZADO (**2**) (**Scheme 2**). The problem of purification of the amine was solved by its *in situ* protection with the Cbz group. Additionally, treatment of carbamate **8** with 2N HCl led to the intramolecular hydroamination. Removal of the Cbz protecting group from **9** and following oxidation afforded 1-Me-AZADO (**2**) in 46% overall yield for 6 steps.

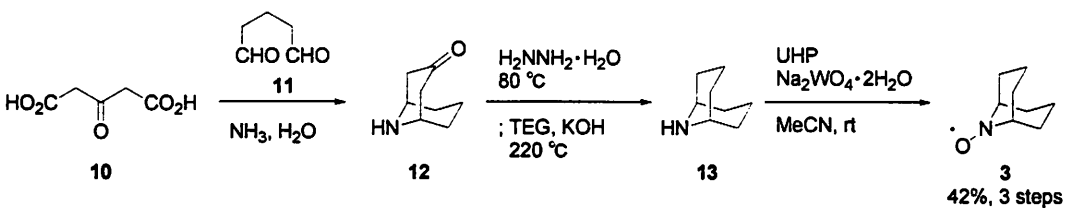


Scheme 2: Second-generation synthesis of 1-Me-AZADO (**2**)

2) Practical synthesis of ABNO

We synthesized bicyclic catalysts, such as ABNO (**3**), to study of structure and reactivity-correlations (SAR) of nitroxyl radicals. ABNO (**3**) exhibited efficient activity rivaling that of 1-Me-AZADO (**2**).

We thus embarked on developing a practical synthetic method for ABNO (**3**) (**Scheme 3**). ABNO (**3**) was prepared in 42% overall yield for 3 steps including one chromatographic purification. A double Mannich reaction of acetonedicarboxylic acid (**10**), glutaraldehyde (**11**), and ammonia (from aqueous ammonia) afforded keto-amine **12**. Application of a Wolff-Kishner reduction to **12** delivered 9-aza-bicyclo[3,3,1] nonane (**13**). Finally, oxidation of amine **13** afforded ABNO (**3**).



Scheme 3: Practical synthesis of ABNO (**3**)

3) Practical synthesis of AZADO

Since AZADO (**1**) was established as the best nitroxyl radical catalyst from SAR studies of AZADOs and ABNOs, we developed a practical preparative method for AZADO (**1**). AZADO (**1**) was more stable than ABNO (**3**) and gave higher reaction rates than 1-Me-AZADO (**2**).

We recently achieved a 4-step synthesis of AZADO (**1**) from commercially available 2-adamantanone. The details will be disclosed in the poster session.

1) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

2P-57

Oxidative degradation analysis of organic ethers

Arata Kimura[1*], Hayato Kitoh[1], Atsumi Miyake[1] and Kiyoshi Watanabe[2]
[1] Yokohama National University
79-7, Tokiwadai, Hodogaya-ku, Yokohama 240-8501, Japan
[2] Zeon Corporation
1-6-2, Marunouchi, Chiyoda-ku, Tokyo 100-8246, Japan
Corresponding author : d06tf013@ynu.ac.jp

1. Introduction

Organic ethers are widely used as a solvent for synthesis reaction and its hazardous peroxides are formed by an autoxidation in air is well known. Cyclopentylmethylether (CPME), which is a newly developed ethereal solvent and has a high tolerance of a formation of peroxide, is expected to be an alternative solvent to conventional solvent such as tetrahydrofuran (THF).

In this study, to investigate the thermal hazard of CPME by autoxidation, accelerated stability test was performed at 20 and 60°C and thermal and infrared spectroscopic analyses were carried out and the experimental data was compared with those of THF.

2. Experimental

THF and CPME without an antioxidant which were pressurized with 0.99MPa of O_2 in SUS316 closed vessel (shown in Fig.1) were stored at 20 or 60°C. The material was sampled at adequate interval time and the thermal and spectroscopic analyses were carried out by using differential scanning calorimetry (DSC) and infrared spectroscopy (FT-IR) respectively.

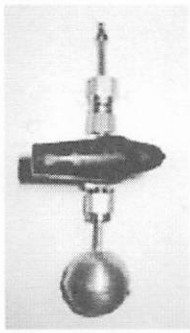


Fig.1
Caption of vessel

3. Results and discussions

3.1 Thermal analysis

Fig.2 shows the DSC profiles of THF as functions of storing time at 20, 40 and 60°C. The heat of reaction of exothermic peak increased with the increase of storing time at 20 or 40°C. Since THF peroxides decompose exothermically at about 80°C, the accumulation of them took place in the storage at 20 or 40°C. On the other hand, THF peroxides were not accumulated significantly at 60°C, because the decomposition rate of THF peroxides depends on temperature and produced THF peroxides decomposed immediately at 60°C.

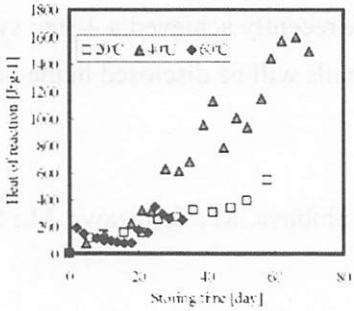


Fig.2
DSC profiles of THF

The heat of reaction of CPME as a function of storing time is shown in Fig.3. The heat of reaction of exothermic peak

increased with the increase of storing time at each temperature and the rate of increase of the heat of reaction depended on the storing temperature. Comparing with THF, the maximum heat of reaction of CPME was much lower than that of THF. It was shown that CPME has a lower thermal hazard by autoxidation than THF.

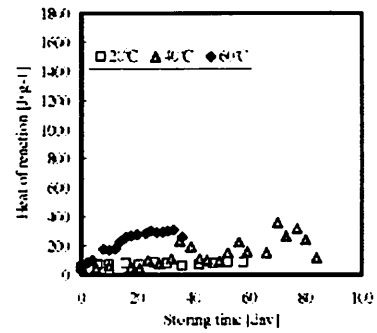


Fig.3
DSC profiles of CPME

3.2 Infrared spectroscopic analysis

Fig.4 shows the comparison of FT-IR spectra of THF at several temperature. Since the OO-H stretch peaks at 3330cm^{-1} appeared at 20 and 40°C, the formation of peroxides was considered. On the other hand, the peak at 3330cm^{-1} weakened and the absorption of C=O stretch at 1720cm^{-1} and 1765cm^{-1} were confirmed at 60°C. γ-butyrolactone and succinic acid are produced by the decomposition of THF peroxides [1]. It was shown that THF peroxides formed at each temperature and the decomposition of the produced peroxides proceeded at 60°C.

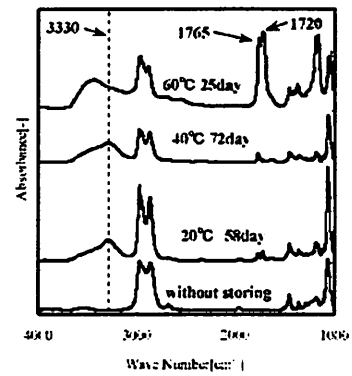


Fig.4
FT-IR spectra of THF

From the comparison of FT-IR spectra at several temperature with samples without storing shown in Fig.5, FT-IR spectra of CPME did not show a significant change between storing samples at 20 or 40°C and without storing. Since the weak peak of O-H at around 3400cm^{-1} and the peak of C=O stretch at 1740cm^{-1} appeared at 60°C, cyclopenthanol and cyclopenthanone as the decomposition products of the CPME peroxides were considered.

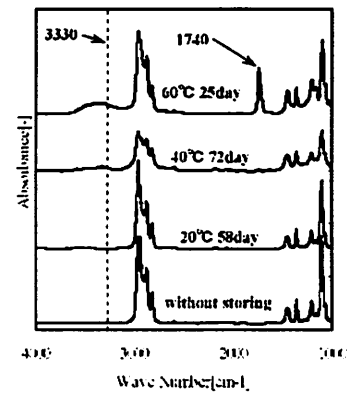


Fig.5
FT-IR spectra of CPME

4. Conclusions

From the results of accelerated stability tests and thermal and spectroscopic analyses, it was found that CPME has a higher tolerance of the formation of peroxides than THF and a potential of alternative solvent. THF is easily oxidized and THF peroxides are produced at ambient temperature. While, CPME is a relatively stable and an accumulation of its peroxides does not take place at ambient temperature.

5. Reference

[1]A.Miyake, K.Nagasawa, K.Watanabe, Proc. 12th International Symposium on Loss Prevention and Safety Promotion in the Process Industries. (2007)

2P-58

A mild preparation of substituted indolizines and indole from simple aromatic precursors using (trimethylsilyl)diazomethane

Liusheng Zhu, Marc Vimolratana, Sean P. Brown,* Julio C. Medina
Amgen Inc., 1120 Veterans Boulevard, South San Francisco, CA 94080, United States
sebrown@amgen.com

The indolizine ring system is an important heterocycle commonly used by medicinal chemists in their drug-design efforts. Indolizine-derived compounds have been reported to be L-type calcium channel blockers, leukotriene synthesis inhibitors, histamine H3 receptor antagonists, 5-HT1A receptor ligands, and phosphodiesterase V inhibitors.

Currently, several condensation reactions, 1,3-dipolar cycloadditions, and 1,5-dipolar cyclizations are known to facilitate the formation of these heterocyles. Perhaps the most widely utilized method is the Tschitschibabin synthesis, in which a quaternary pyridinium halide, resulting from the reaction of a 2-substituted pyridine with an α-halo carbonyl compound, undergoes intramolecular condensation to deliver an indolizine product. Unfortunately, many classical methods for indolizinine construction, such as the Tschitschibabin reaction, require elevated temperatures and/or extended reaction times and, thus, may not be compatible with some functionality. Here, we report a mild synthesis of substituted indolizines from readily available 2-(pyridin-2-yl)acetyl derivatives using (trimethylsilyl)diazomethane.

Typical reaction conditions involve treatment of a 0.1 M solution of the 2-(pyridin-2-yl)acetyl substrate (1 equiv.) with (trimethylsilyl)diazomethane (1.2 equiv.) at room temperature in a vial open to air. Aprotic solvents of different polarities, such as CH_2Cl_2, CH_3CN, THF, DMF, and DMSO, and protic solvents, such as MeOH, EtOH and *i*-PrOH, were examined. In general, the reactions were clean, and no products other than unreacted starting material were identified. It was noted that protic solvents were significantly preferred over aprotic solvents and that the reaction was fastest in MeOH.

In light of the mild conditions and operational simplicity of our indolizine synthesis, we sought to extend the described protocol to the preparation of other heterocycles. Having noted both the presence and proximity of nucleophilic and electrophilic moieties in the 2-(pyridin-2-yl)acetyl derivatives discussed above, we hypothesized that similarly disposed bifunctional molecules might also prove amenable substrates for heterocycle formation. We were, thus, pleased to discover that 2-aminobenzaldehyde, a bifunctional substrate, could be converted to indole in moderate yield. While the rate of indole formation was slower than that typically observed for the indolizine derivatives described in this letter, efficient conversion was achieved at 60 °C using 4 equivalents of (trimethylsilyl)diazomethane and 2 equivalents of Cs_2CO_3 as an alkaline additive. The utility of this method for the synthesis of functionalized indoles is currently under investigation and will be reported in due course.

In conclusion, we have developed a mild and convenient method for the synthesis of substituted indolizines from readily available 2-(pyridin-2-yl)acetyl derivatives using (trimethylsilyl)diazomethane in

moderate to good yields (41-84%). We have further demonstrated that this reaction can be applied to the synthesis of indole from 2-aminobenzaldehyde and are currently evaluating the feasibility of this synthetic construct for the preparation of substituted indoles and other heterocycles.

2P-59

Non-degraded expression and one-step purification of yeast ALD6 enzyme in *E. coli*

Wei-Jyh Shiah, Yu-Chun Chen, *Ming-Kai Chern
Graduate Institute of Life Sciences, Tamkang University, Taiwan
151 Ying-chun Road, Tamsui, Taipei County, 25137, Taiwan
mkchern@mail.tku.edu.tw

...

Abstract

The ALD6p of *Saccharomyces cerevisiae* has been overexpressed in *E. coli* strain. The protein was predominantly insoluble when the expression was induced by isopropyl β-D-thiogalactopyranoside (IPTG) in the host cells grown at either 37 or 30 °C. When the expression was induced at 30 °C using lactose as the inducer, however, the percentage of insoluble form was lessened by 6.1 fold. However, the purified protein ends up with two bands as shown on SDS-polyacrylamide gel electrophoresis (SDS-PAGE), the major one being of correct molecular size, the other being smaller by ~ 1.3 kDa. Apparently, the recombinant protein was subjected to degradation under the conditions used.

To solve this problem, we reasoned that degradation may be due to improper folding of the protein of which the exposed hydrophobic site was prone to the attack of cellular proteases. The improper folding may in turn result from the higher than the physiological rate of biosynthesis of proteins. Therefore, we managed to reduce the temperature for induction in order to decrease the biosynthetic rate. Thus we first induced the expression of ALD6p at 18 °C and found that the smaller fragment on SDS-PAGE did disappear as expected. However, the total amount of ALD6p also decreased, which is disadvantageous to purification. Therefore, we raised the induction temperature up to 25 °C, and found the highest temperature to prevent degradation is 24 °C. We finally adopted 24 °C as the induction temperature.

We then carried out purification in two chromatography steps, first on Q Sepharose™ Fast Flow ion exchanger and followed by Blue Sepharose™ 6 Fast Flow affinity column. To our surprise, ALD6p from both steps exhibited single band on SDS-PAGE, indicating that one-step purification might be achieved on Q Sepharose™ Fast Flow. We then confirmed the homogeneity by comparing the specific activity of ALD6p from individual step. They are 6.350 ± 1.125 μmol/(min × mg) and 6.672 ± 1.688 μmol/(min × mg) for ALD6p from Q Sepharose and Blue Sepharose, respectively, indicating that both have comparable specific activities, confirming the accomplishment of one-step purification on the Q Sepharose step.

Materials

E. coli strain used for overexpression was BL21(DE3) (Novagen). Isopropyl β-D-thiogalactopyranoside (IPTG) was from MDBio. Lactose was from Takayama. Q Sepharose™ Fast Flow and Blue Sepharose™ 6 Fast Flow were from GE Healthcare. Salt gradient was generated on Low Pressure Gradientor LPG-100 (EYELA). Spectrophotometer was constructed using a deuterium light source (ORIEL) and a CCD array (BRC111A, BWTEK). β-nicotinamide adenine dinucleotide phosphate ($NADP^-$) and bovine serum albumin (BSA) were from MP Biochemicals. Coomassie Brilliant Blue R-250

and G-250 were from WS Simpson. Propionaldehyde was from SHOWA. Mid-range protein molecular weight markers were from GeneMark

Expression system

Full-length open reading frame of *ALD6* gene was cloned and inserted at the restriction sites *NdeI/SpeI* of pET 43.1c (Novagen). The construct is designated as pET43-ALD6. Standard chemical methods were performed for transformation of competent *E. coli* cells.

Induction and overexpression

E. coli containing the expression vector pET43-ALD6 was grown in 50 mL LB medium in a 250 mL flask on a shaker of 175 rpm for induction with IPTG at 37 °C or 30 °C or with lactose at 18 to 30 °C . Cells were first grown to 0.6 O.D. at 600 nm prior to the addition of inducer. For induction with IPTG, 0.4 mM (final) was used. For induction with lactose, 0.5% (w/v) (final) was used.

Cell breaking and crude protein extraction

All operations following harvest of cells were done at 4 °C. 200 mL of culture was centrifuged at 2,720 × g for 30 min. The cell pellet was resuspended in 5 mL of lysis buffer (50 mM Tris-Cl, pH 6.8, containing 1 mM EDTA, 6 mM 2-mercaptoethanol, 10% glycerol, and 1 mM PMSF). *E. coli* cells were broken on ice with a Branson sonicator Digital Sonifier® 250 D equipped with a 1/8-inch microtip. Each 6-second cycle contained one-second pulse of 28% amplitude with a five-second break on ice. A total of sixty minutes of sonication was carried out. The lysate was then centrifuged to remove debris with the supernatant saved for purification.

Purification on Q Sepharose

Buffers used were buffer A: 50 mM Tri-Cl, pH 7.6, 1 mM EDTA, 6 mM 2-mercaptoethanol, 10% glycerol, 50 mM NaCl, and buffer B: buffer A containing 1 M NaCl. A Q Sepharose column of 1.6 cm diameter and 30 mL bed volume was equilibrated and washed with buffer A after sample loading. ALD6p was eluted with a gradient from 0% to 100% of buffer B in 100 mL. The active fractions were collected for protein determination, electrophoresis, and enzyme assays.

Purification on Blue Sepharose

The active fractions from Q Sepharose step were pooled and applied to a Blue Sepharose column of 2 mL bed volume, equilibrated with buffer C: 50 mM phosphate buffer, pH7.4 containing 10% glycerol. After wash with 5 mL buffer C the protein was eluted with buffer C containing 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9 M NaCl stepwise. Fro each step, 1 mL of NaCl containg buffer was applied.

Protein and enzyme assays

Protein concentration was determined by the microassay method of Bradford using BSA as the standard. All enzyme activities were assayed at 25 °C in 60 mM sodium phosphate, pH 7.4, containing 0.6 mM propionaldehyde, 2 mM $NADP^-$, and 20 mM $MgCl_2$. The real-time absorbance at 340 nm was followed for the formation of NADPH. Molar activity was calculated using an extinction coefficient of 6.22 $mM^{-1}cm^{-1}$.

2P-60

Reusable chaperone-conjugated magnetic nanobeads in production of a functionally active biocatalyst

*Suhyun Jung and Seongsoon Park
Department of Chemistry, Sungshin Women's University, Seoul 136-742, Korea
sswu98@hanmail.net

B. cepacia lipase (*Burkholderia cepacia* lipase, old name: *Pseudomonas cep*acia lipase) is one of the most widely used enzymes in academic and industrial areas because of their high stability in organic media and at high temperature as well as high stereo- and regio-selectivity. Overexpression of a lipase in *Escherichia coli* (*E. coli*) benefits researchers because *E. coli* grows fast and is easy to handle. However, many lipases are poorly expressed with function in *E. coli* and often form inclusion bodies to be needed in vitro refolding by its molecular chaperone. Recently, Schmid and coworkers presented overexpression of *B. cepacia* lipase in *E. coli* and reported that the enzyme needs to be refolded after being expressed because of inclusion body formation. The near-stoichiometric amount of a specific molecular chaperone is required for refolding *B. cepacia* lipase, although a chaperone catalyzes folding of a protein. This requires much effort in producing the functional *B. cepacia* lipase because additional expression of the chaperone is necessary and another separation step may be required after refolding the enzyme. Thus, recycling the chaperone may be useful for decreasing the efforts in production of the functional *B. cepacia* lipase.

Immobilization of a chaperone is required for recycling. Proteins can be immobilized on supporting materials by physical adsorption using hydrophobic interactions or by covalent attachment. In immobilization of a chaperone, choosing a material as a supporter is an important step because the functionality of a protein strongly depends on the supporting materials. Currently nano-sized particles or nanoporous materials are widely studied in material research area and have been used for bio-applications, such as nucleic acid detachment, protein separation, and immobilization of enzymes, because their large surface area creates many interesting phenomena. However, not all materials can be used for immobilization of proteins. For example, inorganic nanoparticles may not be suitable for physical absorption of proteins because there is no hydrophobic interaction available. Physically absorbed proteins onto polymeric nanoparticles would not work in aqueous media because the proteins could be diffused out from the particles. We have considered the following conditions to choose suitable materials for immobilization of a chaperone: 1) proper immobilization methods available, 2) stability in reaction media, and 3) easiness of recovery for reuse.

The refolding process of an enzyme should be performed in aqueous media. Thus, covalent attachment of a chaperone on supporting materials is required. We chose polymer-coated magnetic nanobeads as a supporting material because the nanobeads are stable in aqueous media and easy to recover by simple centrifuge or magnetic field. In addition, the chaperone can be covalently conjugated to the nanobeads by a simple chemical treatment.

Herein, we present preparation of polymer-coated magnetic nanobeads and conjugation of a molecular chaperone on the nanobeads. The stoichiometric amount of chaperone was required to obtain the near-maximum hydrolysis activity of the refolded *B. cepacia* lipase. The larger amount of the nanobeads did not significantly improve the hydrolysis activity, although the refolded enzyme by the half amount of the beads showed only 6% hydrolysis activity. The time course for refolding process showed that there is no significant increase of the hydrolytic activity of the refolded *B. cepacia* lipase after 24 hours.

We have attempted to reuse the chaperone-conjugated magnetic nanobeads up to five times and measured the hydrolytic activity of the refolded *B. cepacia* lipase at each round. The hydrolytic activities at each round were similar. The refolding activity of the chaperone-conjugated nanobeads still remained above 95% after five-time reuse. These results indicated that the chaperone conjugated magnetic beads are suitable for refolding the denatured *B. cepacia* lipase and reusable.

2P-61

Development and application of odorless thiol reagents

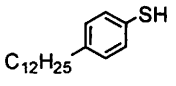
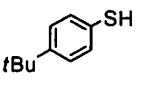
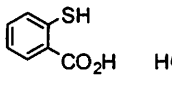
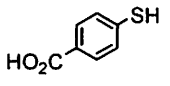
Manabu Matoba,* Tetsuya Kajimoto, Manabu Node
Department of Pharmaceutical Manufacturing Chemistry, 21st COE, Kyoto Phamaceutical University.
1 Shichono-cho, Misasagi, Yamasina-ku, Kyouto, 607-8414, Japan
node@mb.kyoto-phu.ac.jp

2-Nitrobenzenesulfonyl (*o*-nosyl) and 4-nitrobenzenesulfonyl group (*p*-nosyl) have been used for both the protection and activation of amino groups because of facile cleavability under mild conditions. Because nosyl groups remain intact under the conditions to cleave *N*-carboalkoxy protecting groups and possess selective cleavability with thiols, the use of the nosyl groups has been widely used in organic synthesis. 2-Mercaptoethanol, benzenethiol, and α-mercaptoacetic acid have been employed as thiols to date; however, the malodorous stench on handling the thiols would degrade the benefits of nosyl groups.

In the beginning, nosylamide **1** was chosen as the substrates for denosylation reactions. Among many odorless or faint-smelling thiols, *n*-dodecanethiol (**2**) was first employed to cleave the nosyl group from **1** using lithium hydroxide as a base. As expected, the reactions proceeded smoothly at room temperature to give the desired product **3** in good yield (Table 1, entry 1). Moreover, the substrates **1** was subjected to a reaction where either an odorless or faint-smelling aromatic thiol, *i.e.*, *p*-dodecylbenzenethiol (**4**) or *p-tert*-butylbenzenethiol (**5**) was used instead of **2** and lithium hydroxide was replaced with a weaker base, potassium carbonate (Table 1, entry 2, 3). However, the separation of products **3** from a workup residue containing *o*-nitrophenyl *p*-alkylphenyl sulfides required tedious chromatographic procedure. Therefore, *o*-mercaptobenzoic acid (**6**) was employed to remove the resulting sulfide facilely by extraction with alkaline aqueous solution and organic solvent. Finally, *p*-mercaptobenzoic acid (**7**), having a less hindered mercapto group than **6**, was tested as the deprotection agent. The reaction afforded excellent results in the case of substrates at a lower temperature (40℃) than those using **6** as a reagent to cleave the nosyl group (Table 1, entries 5).

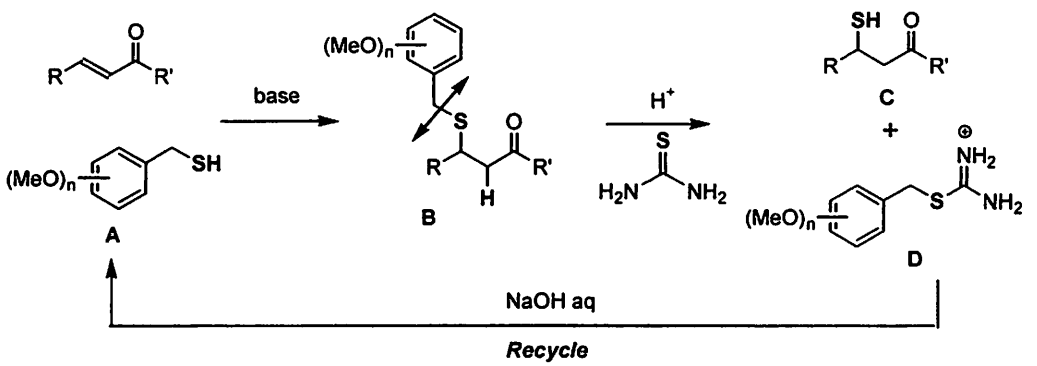
Table 1. Denosylation with odorless thiols

1 → **3**

Entry	1	2	3	4	5
Thiol and Condition	$C_{12}H_{25}SH$ **2**, (2.0 eq) $LiOH{\cdot}H_2O$ (2.0eq) r.t., 4hr	 **4**, (1.2 eq) K_2CO_3 (3.0eq) r.t., 4hr	 **5**, (1.2 eq) K_2CO_3 (3.0eq) r.t., 5hr	 **6**, (2.0 eq) K_2CO_3 (4.0eq) 60°C, 12 hr	 **7**, (2.0 eq) K_2CO_3 (4.0eq) 40°C, 12 hr
Yield (%)	94	95	96	94	91

Next, we developed a new method utilizing novel polymethoxy benzyl mercaptan A as an odorless equivalent of hydrogen sulfide as shown scheme 1. Namely, if Michael adduct B derived from α,β-unsaturated carbonyl compound and A is treated with thiourea under acidic conditions, we will obtain thiol C, a formal Michael adduct of hydrogen sulfide to the α,β-unsaturated carbonyl compound. Moreover, isothiouronium salt D, which is a side-product obtained on debenzylation, would be converted by alkaline hydrolysis to A (Scheme 1).

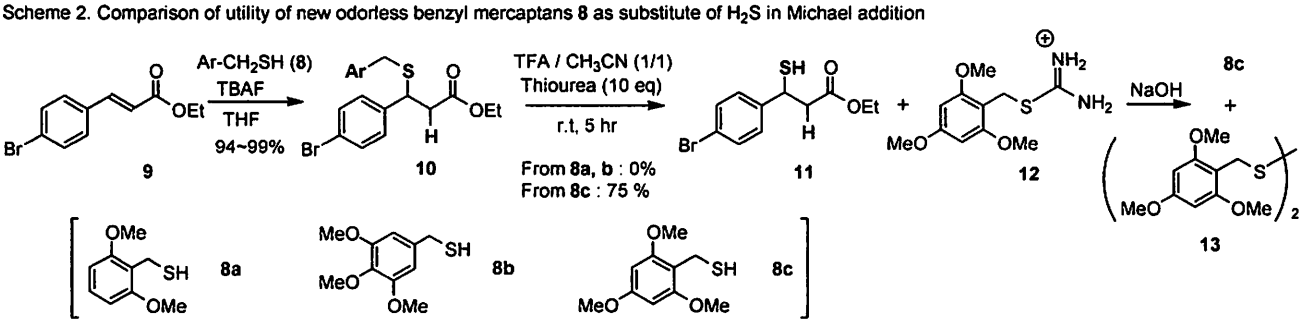
Scheme 1. Strategy of new odorless benzyl mercaptan



We first prepared a few benzyl mercaptans (8a-c) which had two or three methoxy groups and studied Michael addition reaction of 8 and debenzylation of 10 with trifluoroacetic acid. Interestingly, the Michael addition resulted in excellent yields (94–99%), while debenzylation of the Michael adducts of **8a** and **8b** with thiourea and trifluoroacetic acid in acetonitrile did not give the β-mercapto ester **11** at all (Scheme 2). Only the debenzylation of **10c** under the same conditions yielded the desired product **11** in a good yield.

Moreover, 2,4,6-trimethoxybenzyl isothiouronium salt **12**, which is a side-product obtained on debenzylation, could be converted to **8c** and its disulfide **13** by alkaline hydrolysis. The disulfide **13** could be reduced to **8c** with $LiAlH_4$.

Scheme 2. Comparison of utility of new odorless benzyl mercaptans 8 as substitute of H_2S in Michael addition



Reference

Matoba, M.; Kajimoto, T.; Node, M. *Synthetic Commun.* 2008, 1194-1200.

Matoba, M.; Kajimoto, T.; Node, M. *Synlett* 2007, 1930-1934.

2P-62

Deveropment of Selective C-N bond Cleavage Reaction Using *N*-Halosuccinimides

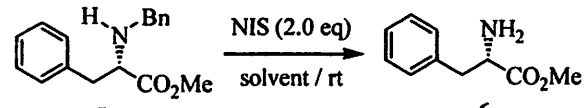
Tsunefumi Watanabe,* Noboru Hayama, Takahiro Katoh, Minoru Ozeki, Tetsuya Kajimoto, Manabu Node
Department of Pharmaceutical Manufucturing Chemistry, Kyoto Pharmaceutical University,
Misasagi, Yamashina-ku, Kyoto 607-8414, Japan
node@mb.kyoto-phu.ac.jp

β-Amino acid moieties are often responsible to express biological and pharmacological activities in a huge number of naturally occurring compounds. Recently we have developed a novel stereoselective Michael additions of a chiral amine to α,β-unsaturated esters as an practical methods to synthesize the chiral β-amino acid units. Herein, a facile method to cleave the chiral auxiliaries on the amino group was indispensable to convert the Michael adducts to free β-amino acids. Taking advantage of the oxidative property of NIS (*N*-iodosuccinimide), we succeeded in the removal of a chiral alkyl group from the amino group of the Michael adducts by using NIS (2 eq.) as an oxidative agent.

On the basis of these background, we applied the method to *N*-dealkylation reaction of *N*-alkylated amino acid derivatives. The details of the reactions would like to be reported here.

First, *N*-benzyl-L-phenylalanine methyl ester (**5a**) was chosen as a substrate of secondary amine and tried *N*-debenzylation with NIS in various solvents (Table 1). When CH_2Cl_2 or DMF was used as a solvent, *N*-debenzylated product (**6**) was obtained in a moderate yield (Table 1, entry 1, 2). The reaction in acetonitrile gave the desired product in good yield (Table 1, entry 3).

Table 1. Optimization of solvents in dealkylation of secondary amine.

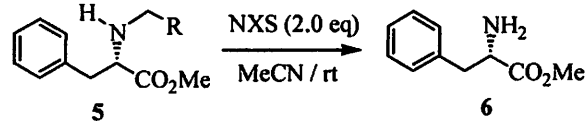


5a **6**

Entry	Solvent	Time (h)	Yield (%)
1	CH_2Cl_2	24	53
2	DMF	6	48
3	MeCN	7	93

Next, *N*-dealkylation of various derivatives of *N*-benzyl-L-phenylalanine methyl ester was attained (Table 2). Almost all reactions smoothly proceeded and gave primary amines **6** (Table 2, entry 1-4). It is noteworthy that mesityl group, which can not be easily cleaved by catalytic hydrogenation, was cleaved in good yield (Table 2, entry 5). On the other hand, C-N cleavage reactions with NBS (*N*-bromosuccinimide) instead of NIS, also afforded *N*-debenzylated products in good yields and shorter reaction time (1-2h). Meanwhile, neither the reactions with NBS nor NIS cleaved the C-N

Table 2. Dealkylation of *N*-alkyl-L-phenylalanine methyl esters.



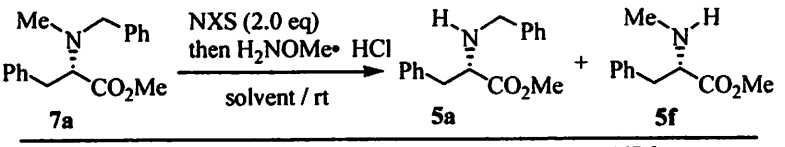
5 **6**

Entry		R	NBS		NIS	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	a	Ph	1	81	7	93
2	b	4-MeO-Ph	1	94	4	83
3	c	4-Cl-Ph	1	73	15	80
4	d	4-NO_2-Ph	1	65	6	87
5	e	Mesityl	1	80	6	78
6	f	H	-	0	-	0

bond in the case where substrate carried an *N*-methyl group instead of an *N*-benzyl group (Table 2, entry 6).

Furthermore, we investigated applicability of the reaction toward tertiary amines. First, *N*-benzyl-*N*-methyl-L-phenylalanine methyl ester **7a** was used as a substrate and the reactions with either NBS or NIS in various solvents were attempted (Table 3). The reaction performed in DMF gave the debenzylated product **5f** as a major product either NIS or NBS was utilized as a oxidative agent (59 %, 27 %, respectively) (Table 3, entry 1). Surprisingly, the reaction with NIS attained in acetonitrile afforded the *N*-demethylated product **5a** (83 %) accompanied with a small amount of the debenzylated product **5f** (14 %) (Table 3, entry 2). On the other hand, the reaction with NBS in acetonitorile gave the *N*-debenzylated product **5f** (52 %) and a small amount of the *N*-demethylated product **5a** (21 %) (Table 3, entry 2). The reaction attained with NIS in dichloromethane yielded both demethylated product **5a** (59 %) and debenzylated product **5f** (26 %), while **5f** (32 %) was given as a major product in a reaction where NBS was employed instead of NIS (Table 3, entry 3). In these reactions, addition of *O*-methylhydroxylamine hydrochloride was effective.[1]

Table 3. Optimization of solvent in dealkylation of tertiary amine.

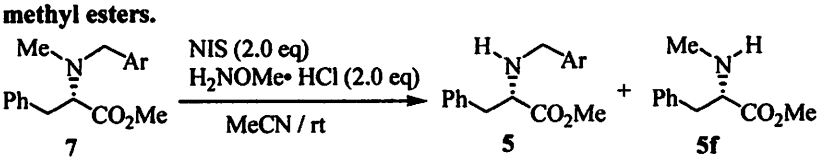


Entry	Solvent	NIS Time (h)	NIS Yield (%) 5a	NIS Yield (%) 5f	NBS Time (h)	NBS Yield (%) 5a	NBS Yield (%) 5f
1	DMF	2.5	5	59	2	15	27
2	MeCN	2.5	83	14	3	21	52
3	CH_2Cl_2	3.5[a]	59	26	2.5	9	32

[a] NIS (3.0 eq) was employed

Next, we tried to generalize the selectivity in the demethylation of various tertialy amines by using the NIS / acetonitrile system to afford secondary amines **5**. (Table 4). All reactions proceeded through the selective C-N bond oxidation (1-2 h) and gave *N*-benzylated secondary amines **5** as major product in good yields (Table 4, entry 1-5).[2] On the basis of these results, it seems that the functional groups on the aromatic ring would not affect both reactivity and selectivity.

Table 4. Selective dealkylation of *N*-benzyl-*N*-methyl-L-phenylalanine methyl esters.



Entry		Ar	Time (h)		Yield (%) 5	Yield (%) 5f
1	a	Ph	2.5	**5a**	83	14
2	b	4-MeO-Ph	2.5	**5b**	79	6
3	c	4-Cl-Ph	2.5	**5c**	87	10
4	d	4-NO_2-Ph	3.5	**5d**	73	14
5	e	Mesityl	3	**5e**	83	-

Further application of the method and the reaction mechanism will be discussed.

References.

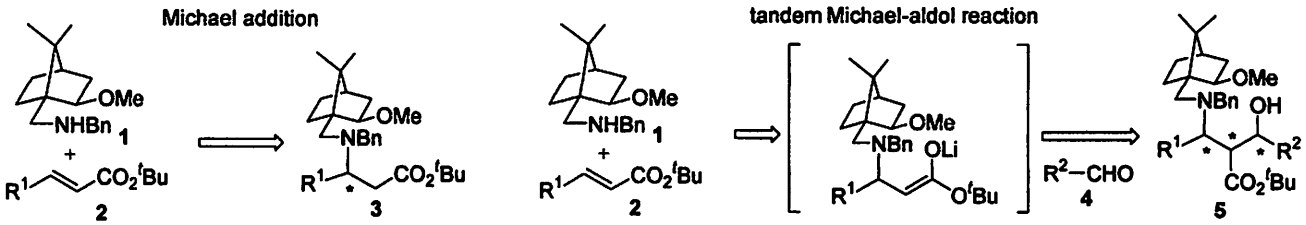
1. Tomioka, K. *et al. Tetrahedron* **2006**, *62*, 8351-8359.
2. Node, M. *et al. Tetrahedron Lett.* **2008**, *49*, 598-600.

2P-63

Construction of Three Contiguous Stereogenic Centers *via* Asymmetric Michael Addition Using Chiral Amino Ether as a Chiral Reagent

Shunsuke Ochi,* Minoru Ozeki, Takahiro Katoh, Tetsuya Kajimoto and Manabu Node
Department of Pharmaceutical Manufacturing Chemistry, 21st COE, Kyoto Phamaceutical University.
1 Shichono-cho, Misasagi, Yamasina-ku, Kyouto, 607-8414, Japan
node@mb.kyoto-phu.ac.jp

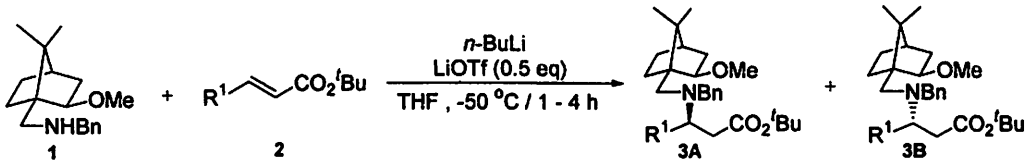
Asymmetric Michael addition of amines to α,β-unsaturated esters are very promising because they afford units of β-amino acids that are a part of a number of naturally occurring bioactive compounds. Recently, we have investigated the Michael addition reaction of a chiral amino ether (1) to α,β-unsaturated esters as a Michael acceptor. Here, we report the asymmetric Michael addition to a variety of α,β-unsaturated ester (2) and the stereoselective construction of three contiguous stereogenic centers through a tandem Michael-aldol reaction.



1. Asymmetric Michael addition to α,β-unsaturated esters.

Asymmetric Michael addition of several substrates was examined as shown in Table 1.

Table 1. Asymmetric Michael Addition Using Chiral Amino Ether



entry	R	no additive		additive (LiOTf)	
		yield (%)	3A : 3B[a)]	yield (%)	3A : 3B[a)]
1	Ph	90	93 : 7	99[b)]	94 : 6
2	4-Cl-Ph	80	91 : 9	91[b)]	94 : 6
3	4-MeO-Ph	90	94 : 6	97	96 : 4
4	4-Me-Ph	83	91 : 9	80	94 : 6
5	*n*-Pr	83	91 : 9	95	91 : 9
6	*n*-Hex	83	90 : 10	81	94 : 6
7	*i*-Pr	90	>99 : 1	95	93 : 7
8	*c*-Hex	99	>99 : 1	92	>99 : 1

a) The ratio was determined by 1H-NMR analysis b) The reaction was carried at -78°C

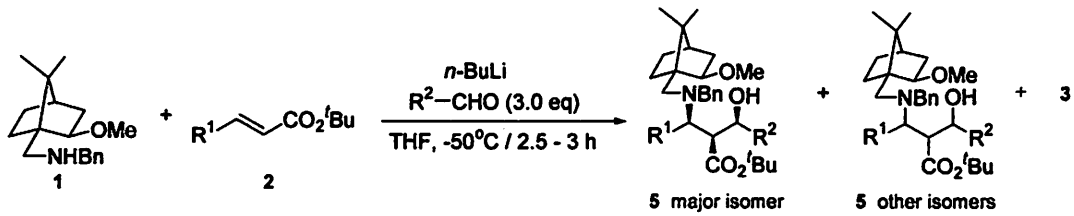
Aromatic α,β-unsaturated esters, regardless of electron-donating and –withdrawing substituents, gave the Michael adduct in high yield with high diastereoselectivity (Table 1, entry 1 to 4). Aliphatic α,β-unsaturated esters,

which have primary alkyl substituents such as *n*-Pr, provided the adducts in good yield and diastereoselectivity (entry 5,6). The substrates having secondary alkyl substituent such as *i*-Pr and *c*-Hex gave the products in high yield with high diastereoselectivity (entry 7,8). Moreover, we investigated effects of additive(Lithium triflate) in the reaction. Although the remarkable effect was not observed in the case of aliphatic α,β-unsaturated esters, the reaction of aromatic α,β-unsaturated esters showed improved chemical yield and diastereoselectivity.

2. Application to a Tandem Michael-aldol reaction

Next, we investigated the tandem Michael-aldol reaction, in which the enolate intermediate allow to react with aldehyde for aimed to construction of three contiguous stereogenic centers.

Table 2. Construction of Three Contiguous Stereogenic Centers via Tandem Michael-aldol Reaction

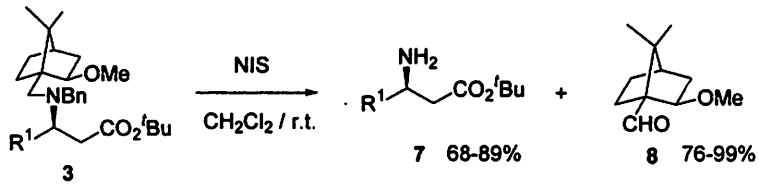


entry	R^1	R^2	5 yield (%)	5 major isomer : other isomers [a)]	3 yield (%)
1	Ph	Ph	77	89 : 11	13
2	4Cl-Ph	Ph	54	88 : 12	24
3	4Me-Ph	Ph	82	88 : 12	11
4	4MeO-Ph	Ph	69	89 : 11	17
5	Ph	4Cl-Ph	60	85 : 15	15
6	Ph	4Me-Ph	73	85 : 15	14
7	Ph	4MeO-Ph	87	89 : 11	1
8	Ph	*i*-Pr	93	90 : 10	2
9	Ph	*c*-Hex	84	76 : 24	20
10	Ph	*n*-Pen	80	84 : 16	18

a) The ratio was determined by 1H-NMR analysis

We first investigated tandem reaction with benzaldehyde as electrophile, and the results are 77% yield with high diastereoselectivity (89 :11). Then, we applied this reaction to a variety of α,β-unsaturated esters and aldehydes. Almost all of the substrates and electrophiles gave the products in good yield and diastereoselectivity.

In addition, the chiral auxiliary linked to the amino group in the Michael adducts (**3**) was facilely removed and converted to β-aminoesters (**7**) and aldehydes (**8**) by reaction with *N*-iodosucinimide. Moreover, this aldehyde can be reclaimed to the chiral amine (**1**) by reductive amination with benzylamine. Now we are investigating the application of this reaction to tandem Michael-aldol products (**5**).



2P-64

Adsorption Kinetic of Three Particle Size Chitosan

Feng-Chin Wu,*[1] Pin-Hsueh Wu[2], Ru-Ling Tseng[2]

[1] *Department of Chemical Engineering, National United University, Miao-Li 360, Taiwan*

[2] *Department of Safety, Health and Environmental Engineering, National United University*

E-mail address: wfc@nuu.edu.tw

The shells (from lobster)were first immersed in 5 wt. % NaOH for 18 h to remove proteins (solid shells / solutions = 10% w / w) and in 10 wt. % HCl for 18 h to remove all mineral materials (mainly, $CaCO_3$). The resulting insoluble solid is the so-called chitin. The chitin (40g) was deacetylated in 50 wt.% NaOH (800g) at 90℃ for 3 h. The final particle type of chitosan were filtered and washed with deionized water. They were dried at 50℃ in a vacuum for 12 h.The kinetics and mechanism of adsorption of a commercial reaction red dye (RR222) from water on three chitosan particles (dp: 0.25-0.42, 0.42-0.59, and 0.59-0.84 mm) were studied at 30℃. Three simplified kinetic models including a pseudo-second-order, an intraparticle diffusion model, and Elovich equation were tested. It was shown all adsorption could be fitted to Elovich equation.

In reactions involving the chemisorption of gases on a solid surface without desorption of the products, the rate decrease with time due to an increase in surface coverage. One of the most useful models for describing such activated chemisorption is the Elovich equation [1].

$$dq_t / dt = a\exp(-bq_t) \qquad (1)$$

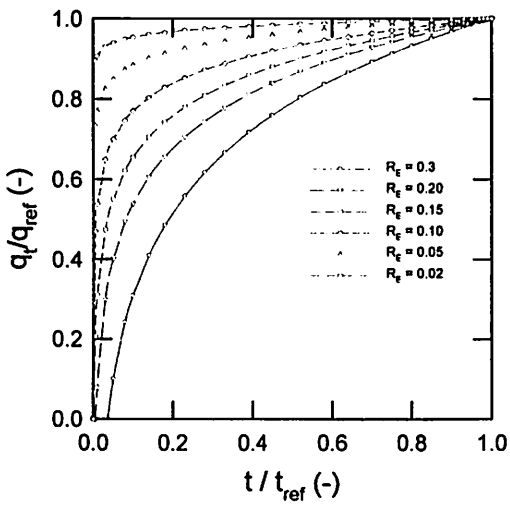


Fig. 1 Adsorption characteristic curves of dimensionless Elovich equation

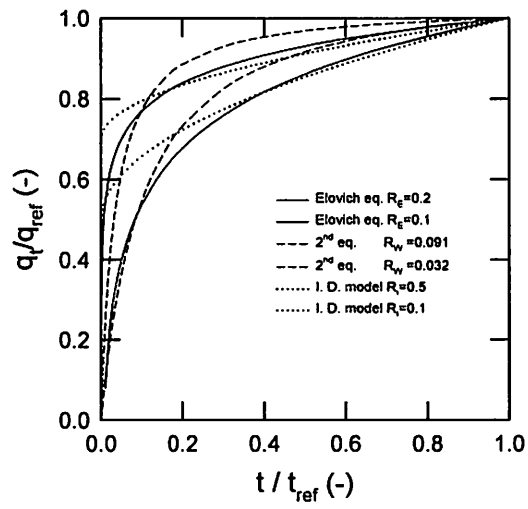


Fig. 2 Dimensionless Elovich equation, intraparticle diffusion model, and pseudo-second-order equation of adsorption characteristic curve

where a and b are constants during any experiment. The constant, a, is regarded as the initial rate because (dq_t/dt) approaches a when q_t approaches 0.

Given that $q_t = q_t$ at $t = t$ and $q_t = 0$ at $t = 0$, the integrated form of Eq. (1) is

$$q_t = (1/b)\ln(t + t_0) - (1/b)\ln t_0 \qquad (2)$$

where $t_0 = 1/ab$. If t is much larger than t_0, Eq. (2) can be simplified as

$$q_t = (1/b)\ln(ab) + (1/b)\ln t \qquad (3)$$

The validity of Eq. (3) is checked by the linear plot of q_t versus ln t.

TABLE 1 Kinetic parameters and mead deviations for mean deviations for the adsorption of RR222 on chitosan

Dp	Elovich eq.						
	a (mg/g min)	b (g/mg)	t_0 (min)	q_{ref} (mg/g)	R_E (-)	r^2	MD (mg/g)
0.59	12.32	0.0467	1.74	119	0.180	0.996	1.596
0.42	16.43	0.0388	1.57	147	0.175	0.995	2.241
0.25	25.38	0.0345	1.14	174	0.167	0.998	1.400

$$q_t = (1/b)\ln(ab) + (1/b)\ln t \qquad (4)$$

$$q_{ref} = (1/b)\ln(ab) + (1/b)\ln t_{ref} \qquad (5)$$

$$(q_t/q_{ref}) = (1/q_{ref}b)\ln(t/t_{ref}) + 1 \qquad (6)$$

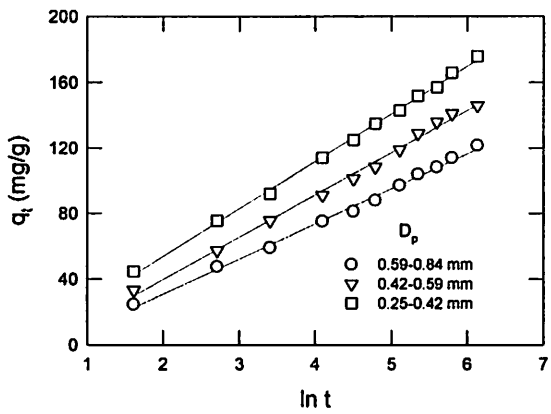


Fig.3Test three particle sizes of chitosansadsorption of RR222 by Elovich equation,

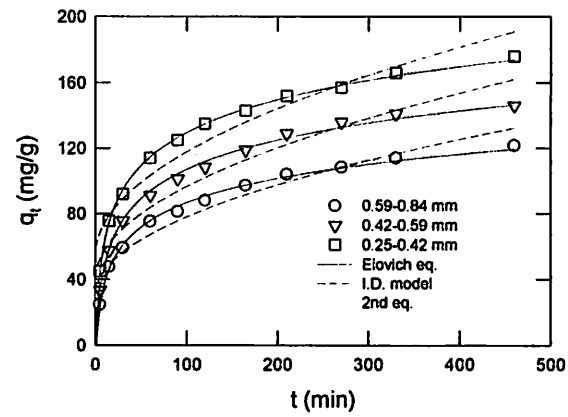


Fig. 4 Compare of three kinetic model equation for three particle sizes of chitosans adsorption of RR222

Conclusions

Both pseudo second-order equation and intraparticle diffusion model cannot successfully confirm the mechanism. The Elovich equation was well fitted to the experimental data. Adsorption characteristics curves can be employed to describe the adsorption kinetic behavior of various adsorbates on the adsorbent, and can facilitate a more accurate inference in adsorbent selection for engineering practice.

Acknowledgement

This work was supported in part by a grant of the National Science Council, Taiwan (NSC 95-2221-E-239-022).

References

Elovich S.Y., Zhabrova, G.M., Zh. Fiz. Khim. 13(1939)1762.

R.S. Juang, R.L. Tseng, F.C. Wu, S.H. Lee, Adsorption behavior of reactive dyes from aqueous solutions on chitosan, J. Chem. Tech. Biotechnol. 70 (1997) 391-399

2P-65

Adsorption Kinetic of Chitosan from Three Source

Ru-Ling Tseng,*[1] Pin-Hsueh Wu[1], Feng-Chin Wu[2]

[1] *Department of Safety, Health and Environmental Engineering, National United University*

[2] *Department of Chemical Engineering, National United University, Miao-Li 360, Taiwan*

E-mail address: trl@nuu.edu.tw

In this work, the chitosans were prepared from three fishery wastes (prawn, lobster, and crab shells). The shells were first immersed in 5 wt. % NaOH for 18 h to remove proteins (solid shells / solutions = 10% w / w) and in 10 wt. % HCl for 18 h to remove all mineral materials (mainly, $CaCO_3$). The resulting insoluble solid is the so-called chitin. The chitin (40g) was deacetylated in 50 wt.% NaOH (800g) at 90℃ for 3 h. The final particle type of chitosan were filtered and washed with deionized water. They were dried at 50℃ in a vacuum for 12 h and finally sieved in the size range 16-30 mesh for further processing. The kinetics and mechanism of adsorption of a commercial reaction red dye (RR222) from water on three chitosan sources were studied at 30℃. Three simplified kinetic models including a pseudo-second-order, an intraparticle diffusion model, and Elovich equation were tested. It was shown their adsorption could be fitted to Elovich equation.

Table 1 Adsorption kinetic curve parameter (R_E) and adsorption behavior of Elovich equation

R_E (-)	Approaching level	Zone
$R_E>0.3$	Slow approaching	I
$0.3>R_E>0.15$	Mild approaching	II
$0.15>R_E>0.05$	Rapid approaching	III
$R_E<0.05$	Abrupt approaching	IV

Table2 Physical properties of chitosan prepared from fishery wastes

	Degree of deacetylation %	Molar mass
Chitosan 1 (prawn)	80.9	7.93×10^5
Chitosan 2 (lobster)	76.3	7.97×10^5
Chitosan 3 (crab)	77.9	7.44×10^5

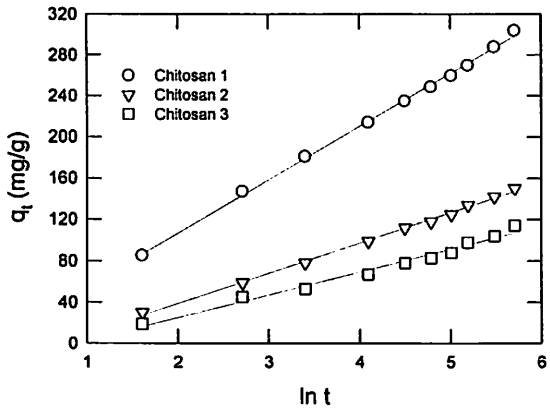


Fig.1Test three particle sizes of chitosansadsorption of RR222 by Elovich equation

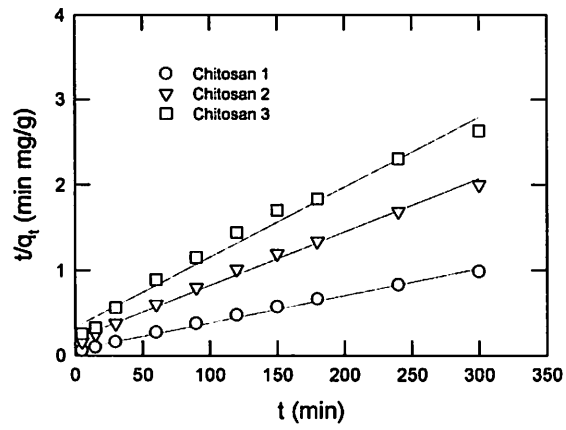


Fig.2Test three particle sizes of chitosansadsorption of RR222 by psudo-second-order equation

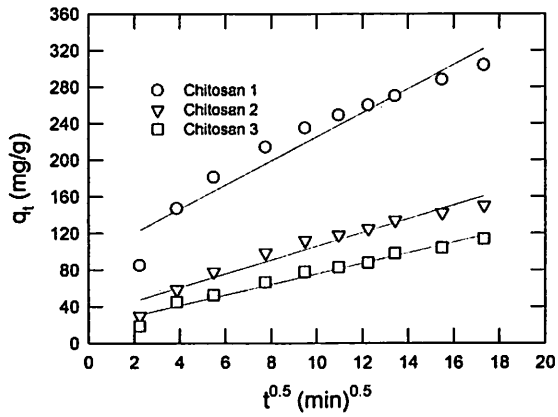


Fig.3Test three particle sizes of chitosansadsorption of RR222 by intrapartcle diffusion model

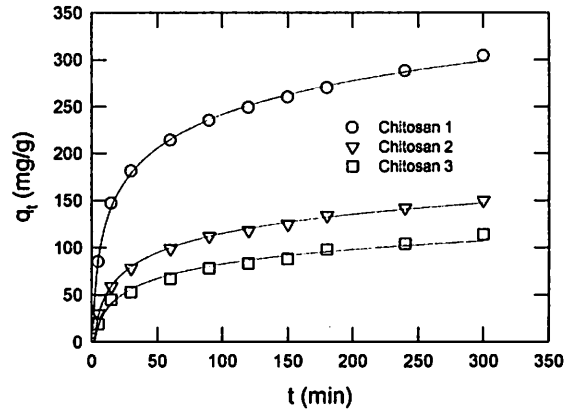


Fig. 4 Elovich equation for three particle sizes of chitosans adsorption of RR222

TABLE 3 Kinetic parameters and mead deviations for mean deviations for the adsorption of RR222 on chitosan

	Elovich eq.							2nd eq.		I.D.	
	a (mg/g min)	*b* (g/mg)	t_0 (min)	q_{ref} (mg/g)	R_E (-)	r^2	*MD* (mg/g)	r^2	*MD* (mg/g)	r^2	*MD* (mg/g)
Chtosan 1	54.96	0.0193	1.061	299	0.173	0.998	2.265	0.994	13.57	0.932	13.39
Chtosan 2	14.95	0.0342	0.511	147	0.199	0.997	1.634	0.993	5.184	0.945	7.000
Chtosan 3	9.384	0.0453	0.425	107	0.206	0.981	3.525	0.983	5.473	0.967	4.134

Conclusions

The chitosans prepared from the three wastes, the prawn shell chitosan has a higher capacity for RR222 than the lobster and crab shells by a factor 2.03 and 2.79. All kinetic data can well fitted by the Elovich equation..

Acknowledgement

This work was supported in part by a grant of the National Science Council, Taiwan (NSC 95-2221-E-239-022).

References

Elovich S.Y., Zhabrova, G.M., Zh. Fiz. Khim. 13(1939)1762.

Cerofolini, G. F., Re, N., Extracting the energy distribution functions of heterogeneous surfaces from their desorption kinetics. J. Colloid Interface Sci. 174 (1995) 428-440.

R.S. Juang, R.L. Tseng, F.C. Wu, S.H. Lee, Adsorption behavior of reactive dyes from aqueous solutions on chitosan, J. Chem. Tech. Biotechnol. 70 (1997) 391-399

R.S. Juang, R.L. Tseng, F.C. Wu, S.J. Lin Use of chitin and chitosan in lobster shell wastes for color removal from aqueous solutions", J. Environ. Sci. Health A 31 (1996) 325-338

M.Y. Chang, R.L. Tseng, F.C. Wu, Relationship between the preparation conditions of chitosan and its adsorption ability, Journal of the Chinese Agricultural Chemical Society, 36 (1998) 293-299.

2P-66

Bioconversion of aromatic compounds using *Escherichia coli* expressing cytochrome P450

Toshihiko Otomatsu,[a]* Liming Bai [a], Naoya Fujita [a], Kazutoshi Shindo [b], Norihiko Misawa [c]
[a]KNC Bio Research Center, Technology Development Dept., KNC Laboratories Co., Ltd.
1-1, murodani 1-chome, Nishi-ku, Kobe, 651-2241, Japan
t_otomatsu@kncweb.co.jp
[b]Department of Food and Nutrition, Japan Women's University
[c]Marine Biotechnology Institute (Present address: Central Laboratories for Frontier Technology, Kirin Holdings Co., Ltd.)

Cytochromes P450 compose the largest superfamily of heme-containing enzymes and are distributed in a wide range of organisms from bacteria to plants or mammals. P450s catalyze a large diversity of monooxiganation reactions on a variety of hydrophobic low-molecular-weight compounds. These reactions contain not only hydroxylation reactions but also other redox reactions such as epoxidation of alkenes, dealkylation of compounds including *O*- or *N*-alkyl groups, sulfoxylation, *N*-hydroxylation, oxidative cleavage of C-C bond, oxidative dehaloganation, oxidative aryl coupling, and NO synthesis. The P450s that animals or plants possess are involved in the activation of hormones or the degradation of hydrophobic pharmaceuticals and agrichemicals. The P450s derived from bacteria are involved in the biosynthesis of secondary metabolites such as antibiotics, or the degradation of alkanes and aromatic compounds, while many of their functions are unknown.

Cytochromes P450 are classified in 4 groups based on the difference in their electron-transfer manners (Fig. 1)[1]. The P450s originated in mitochondria and bacteria mostly belong to Class I. The P450s of this class function as a monooxigenase by transferring electrons from NADP(H) to their P450 proteins containing heme iron as an active center. This electron transfer is performed by way of a ferredoxin and a ferredoxin reductase (called as a redox partner). It is however difficult to display the catalytic activity of a P450 belonging to class I, since the incompatibility between its P450 protein and a redox partner often occurs. Therefore, when gene sequence of a novel P450 was found out, it is necessary to reconstitute the catalytic activity of the P450 by using the redox partner that is able to transfer an electron to the P450 protein. Cytochrome P450RhF that was found in *Rhodococcus* sp. NCIMB 9784 belongs to Class IV. This P450RhF included a redox partner consisting of a ferredoxin reductase (FMN) and a ferredoxin (FeS) by way of linker sequence in the single polypeptide chain (Fig. 1)[1]. We have succeeded in constructing a functional expression vector pRED in *E. coli* by using the terminal region of the redox partner and the linker region of P450RhF, which contains a cloning region for a foreign P450 gene[2].

Cytochromes P450 belonging to CYP153 family have been isolated from several bacteria with alkane-assimilating ability, although the function has not been reported until recently due to the difficulties of the display of the function. We have succeeded in functionally expressing the CYP153A13 (Balk) gene with vector pRED in *E. coli* for the first time[2]. This P450 gene was isolated from marine bacterium

Alcanivorax borkumensis SK12 that is able to grow on alkanes as the only carbon source. We have revealed that CYP153A13 hydroxylates the terminal region of alkanes with carbon number of 6 to 8 [2), 3)]. Furthermore, we analyzed the catalytic functions of CYP153, and have revealed that CYP153A13 (Balk) is capable of mediating diverse conversions toward a variety of aromatic compounds (Table 1). The bioconversion reactions, to be concrete, are hydroxylation of aromatic rings, hydroxylation of alkyl groups bound to aromatic rings, deetherification, and oxidative aryl coupling.

These reactions will allow us the creation of novel compounds which are useful for a drug discovery , the preparation of metabolites, the process developments, and their industrial productions.

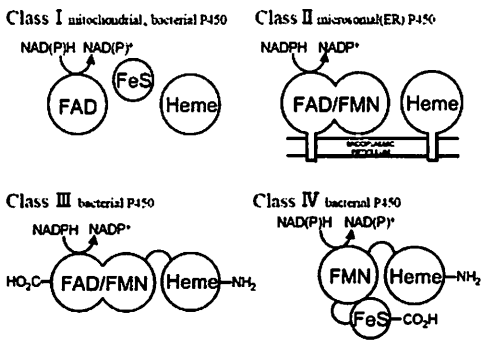


Fig. 1. Class of P450

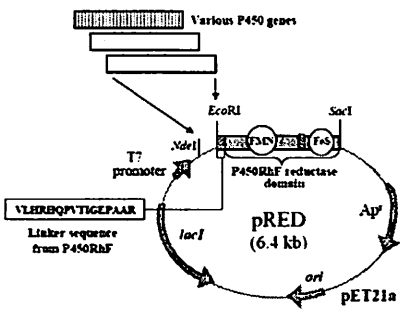
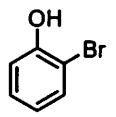
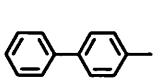
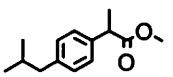
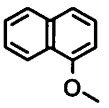
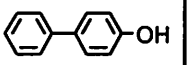
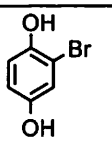
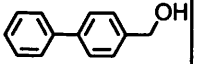
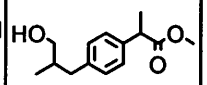
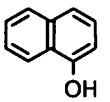
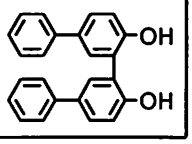


Fig. 2. Structure of vector pRED

Table 1. Examples of bioconversion of various aromatic compounds

Substrates					
Products					

Acknowledgement

This work was supported by New Energy and Industrial Technology Development Organization (NEDO).

References

1) G. A. Roberts, G. Grogan, A Greter, S. L. Flitsch, N. J. Turner, *J. Bacteriol.*, **184**, 3898-3908 (2002)

2) M. Nodate, M. Kubota, N. Misawa, *Appl. Microbiol. Biotechnol.*, **71**, 455-462 (2006)

3) M. Kubota, M. Nodate, M. Yasumoto-Hirose, T. Uchiyama, O. Kagami, Y. Shizuri, N. Misawa, *Biosci. Biotechnol. Biochem.*, **69**, 2421-2430 (2005)

2P-67

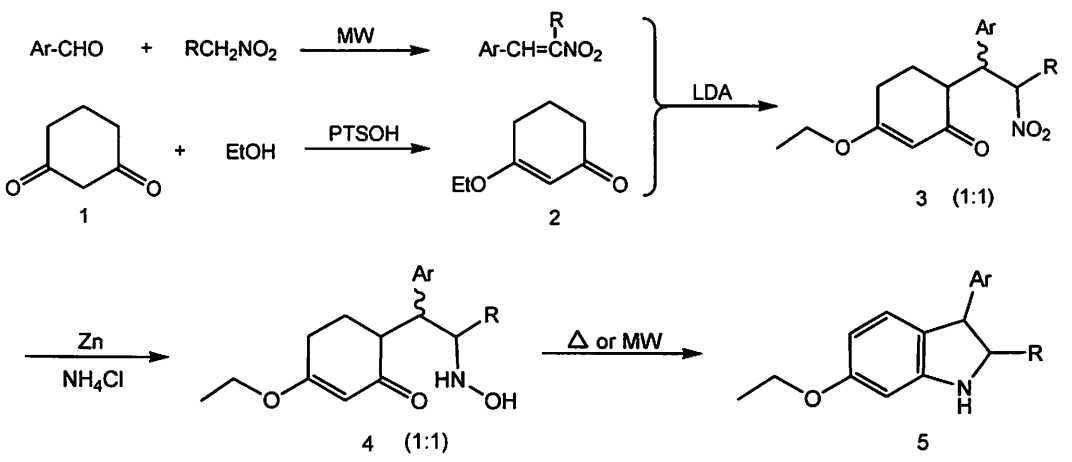
Synthesis of indole derivatives under microwave conditions

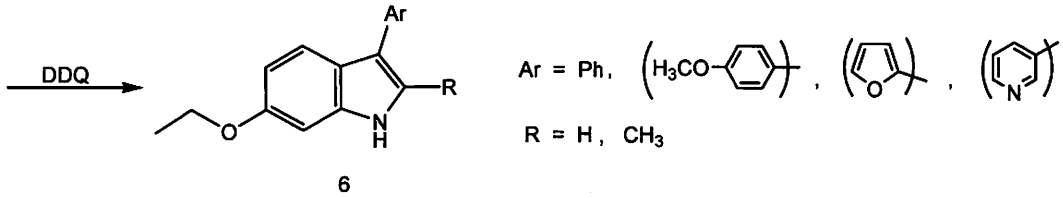
Li-Jian Ma, Zhen-Wu Mei, Tomoyo Kusuyama, and Tsutomu Inokuchi*
Department of Medicinal and Bioengineering Science, The Graduate School of Natural Science and Technology, Okayama University, Tsushima-naka, Okayama, 700-8530, Japan
inokuchi@cc.okayama-u.ac.jp

Over the past 20 years, microwave irradiation has become a powerful method to perform challenging reactions in shorter time with higher yields and purity. In fact, microwaves offer a number of advantages over conventional heating, such as non-contact heating, energy transfer instead of heat transfer, material selective and volumetric heating, fast start-up and stopping, and last but not least a reverse thermal effect, in which heat starts to build up from the interior of the material body.

The indole ring system is probably the most widespread heterocycle in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents. For over a hundred years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed.

To date, although a variety of classical methods have been achieved, these methods employ aromatic nucleus as starting materials, and the examples of indole synthesis from aliphatic starting materials are limited. Accordingly, we developed an efficient method for the construction of indoles that involved a facile cyclization of reduced nitro group and cyclohexenyl ketone group. And as the most important and efficient method, microwave irradiation was used at the first and the key steps of our synthesis route (**Scheme 1**).

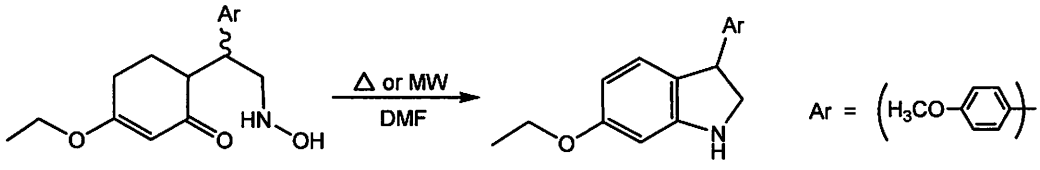




Scheme 1 Synthesis route of indole derivatives

The enolate from **2** with LDA was used for a Michael addition with nitroalkenes to afford **3** with the ratio about one to one of diastereomers. After being reduced with zinc powder and ammonium chloride, the reaction stopped at the stage of compound **4**. And the two diastereomers of **4** can be isolated easily with liquid chromatographer. Then, microwave irradiation was used in the cyclization of the next step and the result of the microwave reaction was compared with that reaction under conventional heating. In addition, we also surveyed the cyclization with or without catalysts (**Table 1**). After that, the cyclization product compound **5** was oxidated by DDQ to afford the goal compound of indole derivatives.

Table 1 Comparison of microwave irradiation and conventional heating



isomer 1 or 2

reaction of isomer 1:

entry	methods	catalysts	time (min)	yield (%)
1	Δ (~155 °C)	x	4 x 60	14.9
2	MW (500 W)	x	30	28.4
3	MW (500 W)	PPTS	15	66.9
4	MW (500 W)	$Yb(OTf)_3$	6	81.8

MW: Microwave, 500W, RT to ~160 °C

From the key step of our synthesis route we know, the reaction by heating only also can achieve the cyclization. But it need long reaction time and yield is very low. Microwave irradiation can shorten the reaction time and improve the yield. And after the addition of catalysts to MW reaction, a good result can be achieved only in seconds.

2P-68

High-performance method of TEMPO-oxidation of alcohols

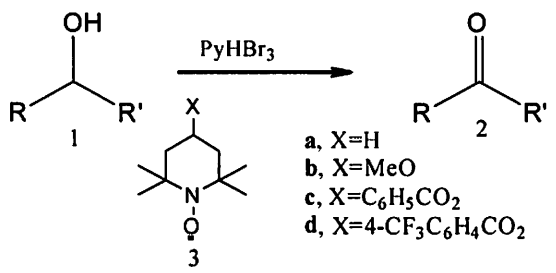
Zhen-Wu Mei[1], Li-Jian Ma[1], Hiroyuki Kawafuchi[2], and Tsutomu Inokuchi[1*]

[1] Department of Medicinal and Bioengineering Science, The Graduate School of Natural Science and Technology, Okayama University, Tsushima-naka, Okayama, 700-8530, Japan

[2] Toyama National College of Technology, Hongo-machi, Toyama, 939-8630, Japan

inokuchi@cc.okayama-u.ac.jp

TEMPO oxidation by using inexpensive reagents is promising methodology at the point of process chemical view. We examined the use of pyridinium hydrobromide perbromide (Py•HBr•Br_2) as a co-oxidant, since this commercially available and stable reagent is relatively less expensive, and more advantageously polymer supported Py•HBr•Br_2 is now available, though its oxidizing ability is not well characterized until now.



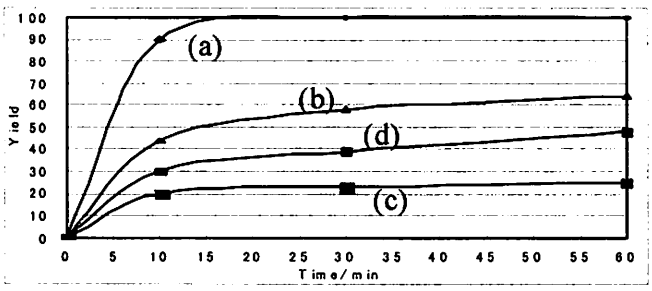


Figure 1. Time-conversion curves for oxidation of **1a** to **2a** under the condition of different amounts of **3c** with $PyHBr_3$(1.5 equiv.) at 0-4 °C.

Symbols are as follows: **3c**, 10mol% (a); **3c**, 1.0mol% (b); **3c**, no addition (c); **3c**, (10mol%)-Bu_4NBr_3 (d).

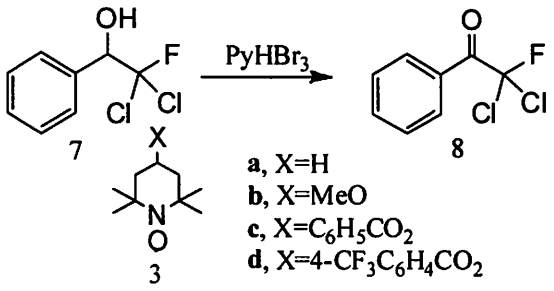
Data points were obtained by GC analyses.

We firstly examined the reactivity of Py•HBr•Br_2 as a co-oxidant in the TEMPO-mediated catalytic oxidation of secondary alcohols. As shown in Figure 1, the reaction of 2-undecanol (**1a**, R = C_9H_{19}, R' = CH_3) with a mixture of 4-BzOTEMPO (**3c**, X = $C_6H_5CO_2$, 10 mol%) and Py•HBr_3 (1.5 equivalent) in a CH_2Cl_2-aqueous $NaHCO_3$ system completes within 15 min to form the corresponding 2-undecanone (**2a**, R = C_9H_{19}, R' = CH_3) in 99%, selectivity. The amount of **3c** can be reduced to 1 mol% for this conversion (b), though the reaction becomes somewhat sluggish. The oxidation of **1a** to **2a**, which is presumably due to oxidizing ability of Py•HBr•Br_2, was observed in the reaction system that lacks the presence of **3c** (c), though being of no synthetic potential. Noteworthy is that, as shown in (d), the oxidation of **1a** to **2a** by the combination of **3c** and R_4NBr_3as co-oxidant proceeds much slower compared with Py•HBr_3.

Merit of Py•HBr•Br_2 as a co-oxidant lies in its easy extension to the polymer supported derivative, poly(4-vinyl) Py•HBr•Br_2, which is commercially available. Thus, we examined the use of this polymer-supported reagent as a co-oxidant for the TEMPO (**3c**)-mediated oxidation of secondary alcohols to produce the ketones and the results are shown in Table 1. Almost similar results as that with Py•HBr•Br_2 are obtained with this supported reagent, which were performed by quantitative recovery of the solid

pyridine support only by filtration.

Next, effect of the appendage on TEMPOs is examined by dictating the time-course of the conversion of **7a** (Ar = C_6H_5) to **8a** (Ar = C_6H_5) by changing kind of substituent at the C-4 position. As shown in Figure 2, the oxidation of **7a** is fairly facilitated by appendage of an arenecarboxyl group on TEMPO, compared with the TEMPO bearing no appendage. Among them, the most favorable conversion was attained with the 4-(4-trifluoromethylbenzoyl)-substituted **3d**. Similar enhancement in the conversion was also observed in the oxidation of 2-octanol, being classified as electron-rich alcohol compared with 2,2-dichloro-2-fluroethyl derivatives, in which the best conversion was attained with **3d**.



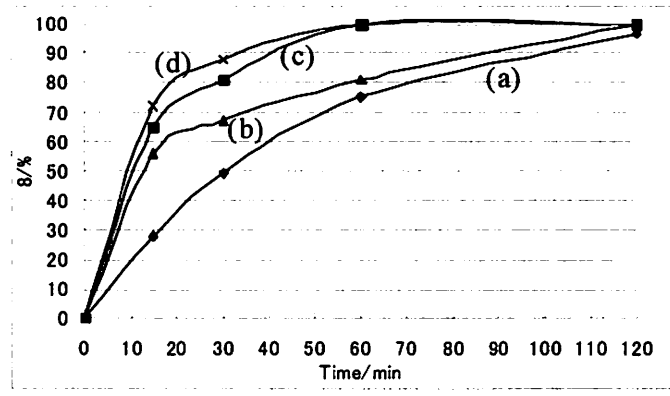
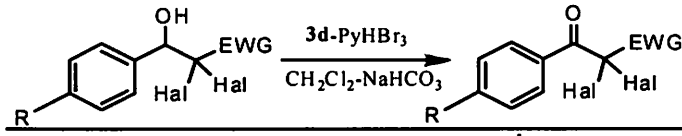
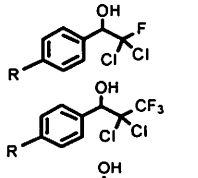
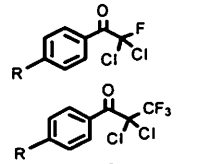
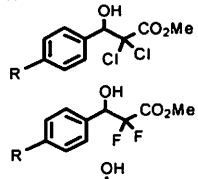
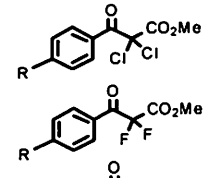


Figure 2. Time-conversion curves for oxidation of **7a** to **8a** under the condition of various TEMPOs of **3** with $PyHBr_3$(1.5 equiv.) at room temperature.
Symbols are as follows: **3a**, (a); **3b**, (b); **3c**, (c) ;**3d**, (d).
Data points were obtained by GC analyses.

Based on these results, we next attempted the oxidation of carbinol with an electron-withdrawing group. As shown in Table 3, the dichlorofluoro and dichlorotrifluoromethyl, dichlorocarboxy alcohols are cleanly oxidized under the conditions developed above.



alcohol	product	yield[b](%)
		R=H, 91% R=OMe, 94% R=Cl, 92% R=Me, 93%
		R=H, 69% R=OMe, 86%
		R=H, 79% R=Br, 78%
		R=H, 80% R=OMe, 72%
		R=H, 80%

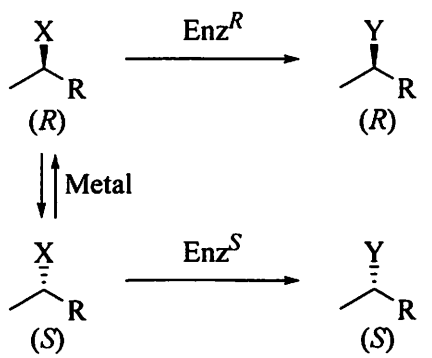
a, The condition is **3d**(0.1equiv), $PyHBr_3$(1.5equiv),CH_2Cl_2(6ml),$NaHCO_3$(12ml).
b, Isolated yield based on isolated products.

2P-69

Dynamic Kinetic Resolution of 1,2-Diarylethanols by Lipase-Ruthenium Cocatalysis

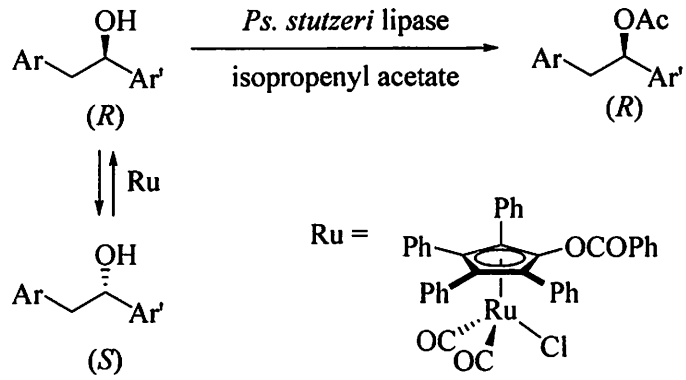
*Sol Kim, Yun Kyung Choi, Yunwoong Kim, Cheolwoo Kim, Jaiwook Park, Mahn-Joo Kim
Department of Chemistry, Pohang University of Science and Technology (POSTECH),
San 31 Hyojadong, Pohang 790-784, Korea
sol@postech.ac.kr

Transforming racemic molecules to single enantiomers is one of active research areas in organic synthesis. The development of methods for the synthesis of chiral compounds is important particularly in pharmaceutical industry. From our point of view, dynamic kinetic resolution (DKR) is one of the most promising methodologies to prepare optically pure enantiomers. In the past decade, we and others have applied enzyme-metal cocatalyst systems to the DKR (Scheme 1).[1] We herein wish to present a recent development in this area, DKR of racemic 1,2-diarythanol by lipase-ruthenium cocatalysis.



Scheme 1. Dynamic kinetic resolution by enzyme-metal combinations

Optically pure 1,2-diarylethanols are pharmaceutically interesting as a result of the great potential of combretastatin and analogues as anti-cancer agents.[2] We conducted enzyme-screening experiments and found that *Pseudomonas stutzeri* lipase (PSL; trade name, lipase TL) is highly enantioselective toward 1,2-diarylethanols. We therefore combined PSL with a Ru complex as the catalysts for the DKR of 1,2-diarylethanols (Scheme 2). Sixteen 1,2-diarylethanols have been efficiently transformed via the lipase-Ru catalyzed DKR to their acetyl derivatives with good yields (95-97%) and high enantiomeric excesses (96-99%).



Scheme 2. DKR of 1,2-diarylethanols by PSL-Ru combinations

References

[1] Reviews, (a) Kim, M.-J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578-587. (b) Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247-3262. (c) Kim, M.-J.; Ahn, Y.; Park, J. *Bull. Kor. Chem. Soc.* **2005**, *26*, 515-522.

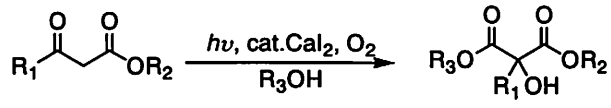
[2] (a) Petit, G. R.; Cragg, G. M.; Herald, D. L.; Schmidt, J. M.; Lohavanijaya, P. *Can. J. Chem.* **1982**, *60*, 1374-1376. (b) Petit, G. R.; Singh, S. B.; Cragg, G. M. *J. Org. Chem.* **1985**, *50*, 3404-3406. (c) Ramacciotti, A.; Fiaschi, R.; Napolitano, E. *Tetrahedron: Asymmetry* **1996**, *7*, 1101-1104. (d) Cirla, A.; Mann, J. *Nat. Prod. Rep.* **2003**, *20*, 558-564.

2P-70

New One-Pot Synthesis of Malonic Acid Derivatives

Akichika Itoh,* Norihiro Tada, Hiroki Nakayama, Naohiko Kanai
Gifu Pharmaceutical University
5-6-1, Mitahora-higashi, Gifu, 502-8585, Japan
itoha@gifu-pu.ac.jp

Malonic acid derivatives, especially hydroxymalonic acid derivatives, have been used as starting materials or key intermediates for the synthesis of biologically active products. Many synthetic efforts have already been devoted to the practical access of the hydroxymalonic acid derivatives, and the prevalent way is oxidation of the corresponding malonic acid derivatives with various oxidants; however these reactions involve problems, such as low yield or the necessity of over stoichiometric amount or environmental high impact catalyst. With this background in mind, we have studied the aerobic photo-oxidation in the presence of iodo sources, [1] and found that α-nonsubstituted-β-keto esters effectively produced 2-hydroxy-2-alkyl- or 2-hydroxy-2-arylmalonate esters by one step through tandem reaction of oxidation-rearrangement in the presence of cat. CaI_2 under VIS irradiation (eq. 1).



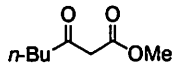
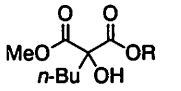
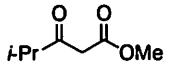
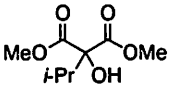
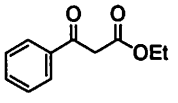
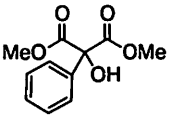
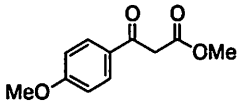
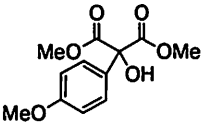
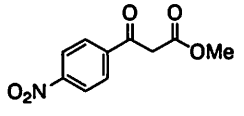
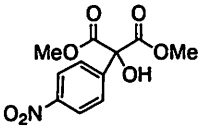
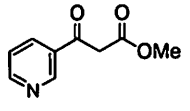
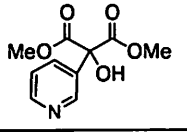
(1)

Table 1 shows the results for this transformation of a variety of β-keto esters to the corresponding hydroxymalonate esters under our optimized reaction conditions. The reaction of methyl 3-oxoheptanoate gave the corresponding 2-butyl-2-hydroxymalonate ester, which possess an ester group derived from solvent, in high yield (entries 1-3). This reaction was applicable for 3-aryl-3-oxopropanoate esters, including heterocyclic moiety, and gave the corresponding aryl-substituted malonate esters in good yields. These results show that an electron-donating group accelerates and an electron-withdrawing group retards this reaction (entries 5-8).

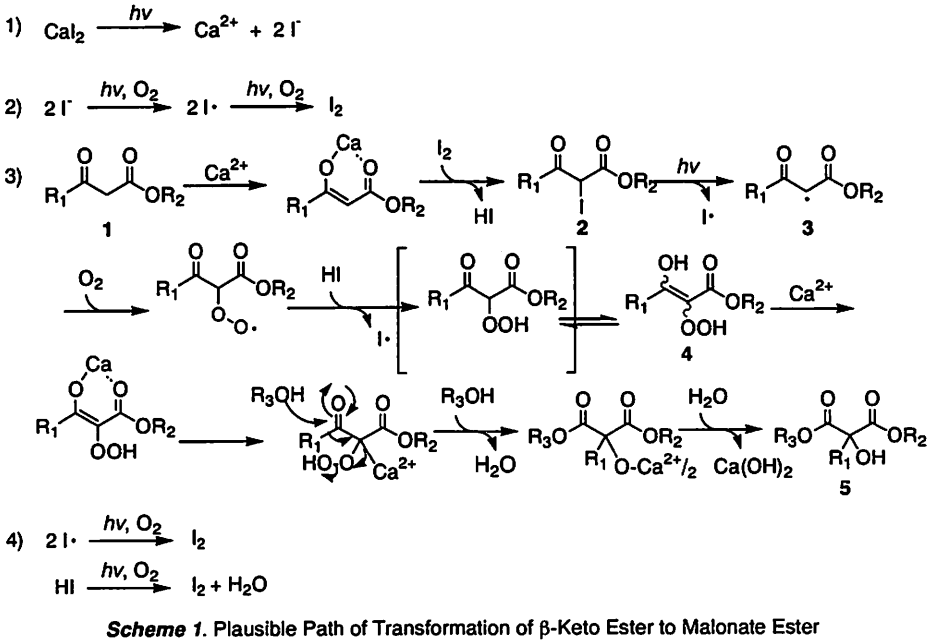
Scheme 1 shows the plausible path, which is postulated by considering all of the results we have, and the necessity of continuous irradiation, catalytic amount of CaI_2 and molecular oxygen. β-Keto ester **1** reacts with iodine, which is formed from CaI_2, to afford α-iodo-β-keto ester **2**, which produce radical species **3** under photo-irradiation. The resulting species **3** traps molecular oxygen to afford hydroperoxide **4**, which reacts with Ca^{2+} and alcohol to give 2-hydroxy-2-alkyl- or 2-hydroxy-2-arylmalonate ester **5**. Iodo radical and hydrogen iodide, formed in situ, are oxidized to iodine again under aerobic photo-oxidation condition.

This is the first successful report of one-pot synthesis of hydroxymalonate esters from β-keto esters. In this conference, we also show more data and the results of study of reaction conditions and of the mechanism of this novel reaction.

Table 1. Transformation of β-Keto Esters to Malonate Esters [a]

Entry	Substrate	Solvent	Product	Yield (%) [b]
1		MeOH	 R = Me	85
2		EtOH	R = Et	80
3		i-PrOH	R = *i*-Pr	71
4		MeOH		78
5		MeOH		72 [c]
6		MeOH		88
7		MeOH		57 [d, e]
8		MeOH		70

[a] Reaction conditions: substrate (0.3 mmol) and catalyst (0.2 equiv.) in solvent (5 mL) was irrradiated with fluorescent lamp for 10 h in an oxygen atmosphere. [b] All yields are for pure, isolated products. [c] The reaction was carried out in the presence of CaI_2 (0.5 equiv.). [d] The reaction was carried out for 24h. [e] Methyl 4-Nitrobenzoate was also obtained in 17%.



Scheme 1. Plausible Path of Transformation of β-Keto Ester to Malonate Ester

References

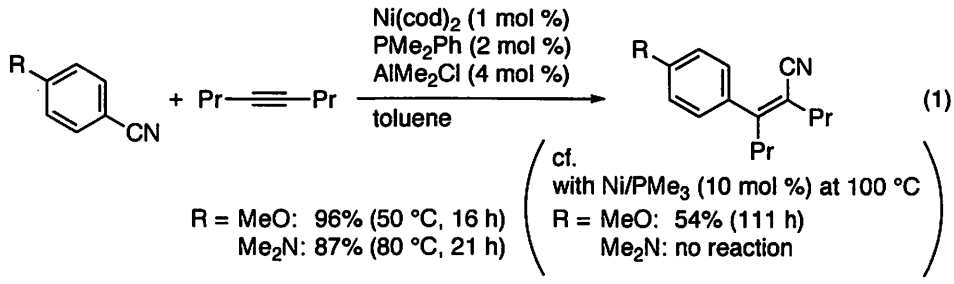
1) H. Nakayama, A. Itoh, *Chem. Pharm. Bull.* **2006**, *54*, 1620; H. Nakayama, A. Itoh, *Tetrahedron Lett.* **2007**, *48*, 1131; H. Nakayama, A. Itoh, *Synlett.* **2008**, *5*, 675; H. Nakayama, A. Itoh, *Tetrahedron Lett.* **2008**, *49*, 2792.

2P-71

Nickel/Lewis Acid-catalyzed Carbocyanation Reaction of Unsaturated Compounds

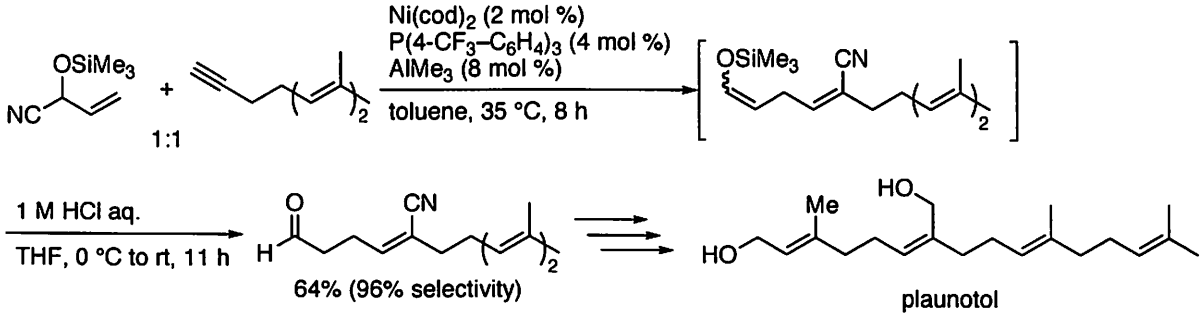
Yoshiaki Nakao,* Akira Yada, Shiro Ebata, Yasuhiro Hirata, Tomoya Yukawa, Tamejiro Hiyama
Department of Material Chemistry, Graduate School of Engineering, Kyoto University
Katsura, Nishikyo-ku, Kyoto, 615-8510, Japan
yoshiakinakao@npc05.mbox.media.kyoto-u.ac.jp

Stereoselective synthesis of polysubstituted alkenes has been a major subject in organic synthesis. We have demonstrated the carbocyanation reaction of alkynes as a new entry to stereochemically well-defined and atom economical protocol for the synthesis of tri- or disubstituted acrylonitriles, versatile synthetic intermediates for polysubsituted alkenes.[1] We recently reported a dramatic effect of Lewis Acid (LA) catalysts on the nickel-catalyzed carbocyanation of alkynes.[2] For examples, the addition reaction of 4-methoxybenzonitrile across 4-octyne is significantly accererated in the presence of $AlMe_2Cl$ as a LA catalyst to give the corresponding arylcyanation product in over 90% yields in an exclusive *cis*-fashion (Eq. 1).



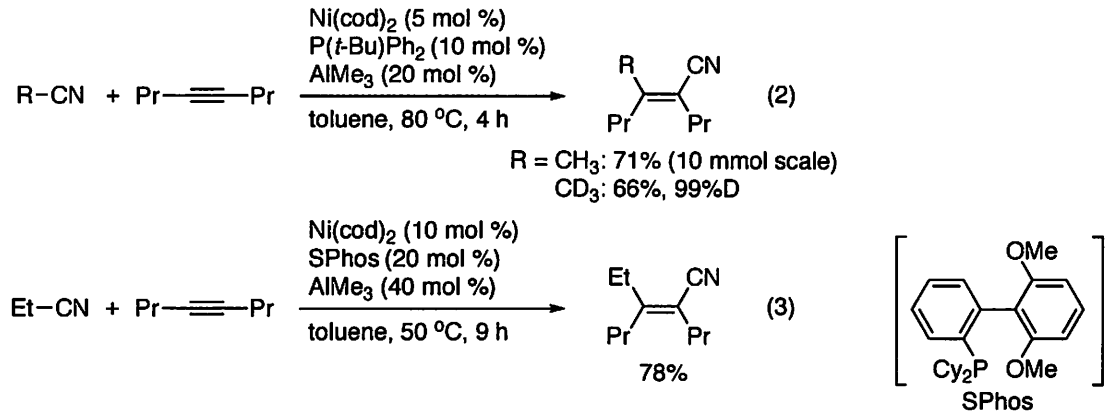
Nickel-catalyzed allylcyanation reaction[1c] of alkynes is also promoted in the presence of a LA catalyst. The addition of α-siloxylallyl cyanide across terminal alkynes proceeds in excellent stereo- and regioselectivities (Scheme 1). The transformation has been applied successfully to the stereoselective synthesis of plaunotol, an antibacterially active compound against *Helicobacter pylori*.

Scheme 1.



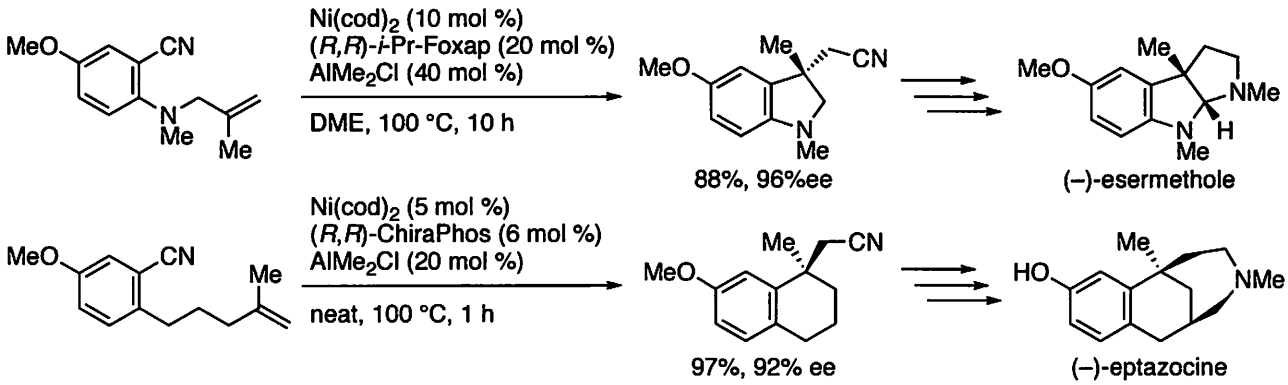
The Ni/LA catalyst allowed us to achieve even alkylcyanation of alkynes (Eqs. 2 and 3). For example, acetonitrile added across 4-octyne in the presence of $Ni(cod)_2$ (5 mol %), $PPh_2(t\text{-Bu})$ (10 mol %), and $AlMe_3$ (20 mol %) to give methylcyanation product in 71% yield with a 10 mmol scale. The fact that the

reaction of CH_3CN-d_3 gave the corresponding adduct of 99% deuteriation clearly showed that the methyl group is fully derived from acetonitrile and definitely never from $AlMe_3$. Propionitrile also underwent the reaction by using SPhos, a bulky ligand suppressing β-hydride elimination from an ethylnickel intermediate.



Enantioselective intramolecular arylcyanation of alkenes has been achieved with the binary catalysis (Scheme 2). The transformation represents a novel access to alkaloids having benzylic quaternary stereocenters such as (–)-esermethole and (–)-eptazocine.

Scheme 2.



More examples of the carbocyanation reaction as well as detailed mechanism of the reaction based on experimental and theoretical analyses will be discussed.

References

(1) (a) Y. Nakao, S. Oda, T. Hiyama, *J. Am. Chem. Soc.*, **126**, 13904–13905 (2004). (b) Y. Nakao, S. Oda, A. Yada, T. Hiyama, *Tetrahedron*, **62**, 7567–7568 (2006). (c) Y. Nakao, T. Yukawa, Y. Hirata, S. Oda, J. Satoh, T. Hiyama, *J. Am. Chem. Soc.*, **128**, 7116–7117 (2006).

(2) (a) Y. Nakao, A. Yada, S. Eabta, T. Hiyama, *J. Am. Chem. Soc.*, **129**, 2428–2429 (2007). (b) Y. Nakao, Y. Hirata, M. Tanaka, T. Hiyama, *Angew. Chem. Int. Ed.*, **47**, 385–387 (2008).

2P-72

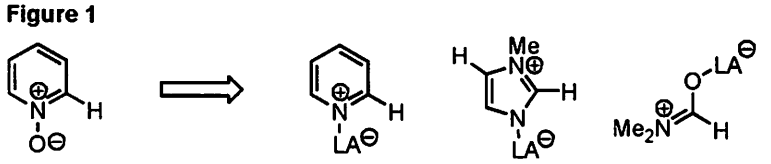
Nickel/Lewis Acid Catalyzed Hydroheteroarylation and Hydrocarbamoylation of Unsasutated Bonds

Kyalo Stephen Kanyiva,* Hiroaki Idei, Yoshiaki Nakao, Tamejiro Hiyama
Graduate School of Engineering, Department of Material Chemistry, Kyoto University, Kyoto 615-8510, Japan
stefhanoh@t06.mbox.media.kyoto-u.ac.jp

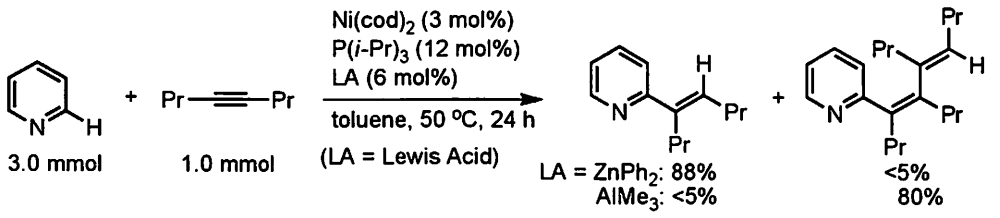
A central goal of organic synthesis is to develop and utilize efficient and atom-economical methods for construction of complex molecules from simple and readily available precursors. To this end, recently use of transition metal catalysts has become a hot research topic for direct introduction of a carbon chain to heteroaromatic rings. Pyridine derivatives are among the target heteroaromatics, but their functionalization has always been a problem owing to their low reactivity toward electrophilic substitution reactions such the Friedel–Crafts reaction due to electron-withdrawing nitrogen atom. The limited number of reported examples suffers from harsh reaction conditions of over 150 °C,[1] limited scope of substrates, [2] and requirement of directing groups including *N*-oxides.[3]

Recently we demonstrated the C–H activation of pyridine *N*-oxides using a nickel catalyst.[3b] Since the reactivity of nickel toward pyridine *N*-oxide is attributed to an electron deficient nitrogen that increases the acidity of C(2)-H bond, we envisioned that coordination of a Lewis acid (LA) catalyst to the nitrogen atom would generate the activated species *catalytically* in situ. Herein, we report that a combination of nickel and LA catalyst allows direct C-2 alkenylation and dienylaion of pyridines under mild conditions.[4] Moreover, the dual metal catalysis has been used effectively for activation of other nitrogen-substituted sp^2 C–H bonds of imidazoles and formamides (Figure. 1).

Figure 1



After surveying several combinations of catalyst precursors, we found that pyridine added across 4-octyne smoothly in the presence of $Ni(cod)_2$ (3 mol%), $P(i\text{-}Pr)_3$ (12 mol%), and $ZnPh_2$ as the LA catalyst at 50 °C to give a C-2 monoalkenylated pyridine in 88% isolated yield. On the other hand, use of $AlMe_3$, a stronger Lewis acid than $ZnMe_2$, gave a dienylated product almost exclusively (Eq. 1).

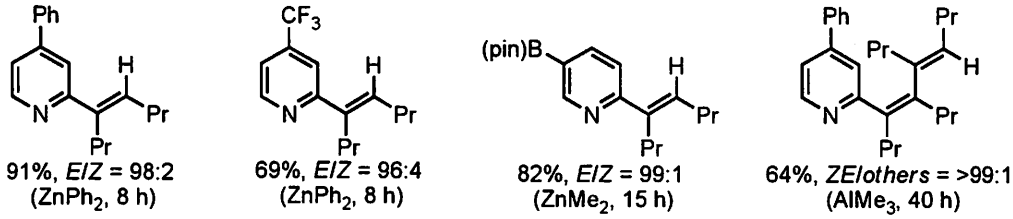


(1)

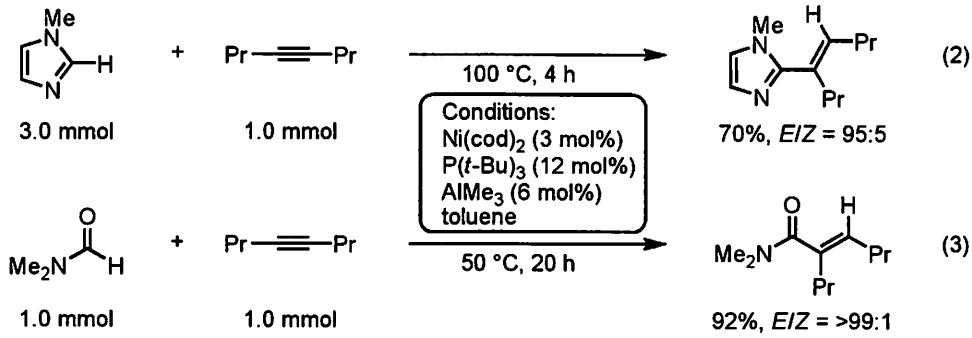
A range of substituted pyridine derivatives bearing electron-withdrawing and –donating groups tolerated the

reaction conditions to give the corresponding adducts in regio- and stereoselective manner (Figure 2).

Figure 2



For efficient hydroheteroarylation of imidazoles and hydrocarbamoylation of formamides, however, $AlMe_3$ was found to give the required adducts in yields better than $ZnMe_2$ (Eq. 2 and 3). Thus, the reaction of *N*-methylimidazole with 4-octyne resulted in excellent regioselective cleavage of the C(2)-H bond, affording the target adduct in high yield. An equimolar hydrocarbamoylation of 4-octyne with *N,N*-dimethylformamide under the same nickel-LA catalysis at 50 °C for 18 h proceeded smoothly without decarbonylation to afford an enamide in 92% yield. The limited number of reported hydrocarbamoylation reactions are performed under a CO atmosphere, at high temperatures or in the presence of a directing group.[5] The scope and mechanism of the dual metal catalysis, together with several transformations of the obtained adducts will be discussed.



References:

1. (a) E. J. Moore, W. R. Pretzer, T. J. O'Connell, J. Harris, L. LaBounty, L. Chou, and S. S. Grimmer, *J. Am. Chem. Soc.*, **114**, 5888 (1992). (b) M. Murakami and S. Hori, *J. Am. Chem. Soc.*, **125**, 4720 (2003). (c) J. C. Lewis, R. G. Bergman, and J. A. Ellman, *J. Am. Chem. Soc.*, **129**, 5332 (2007). (d) T. Kawashima, T. Takao, and H. Suzuki, *J. Am. Chem. Soc.*, **129**, 11006 (2007).
2. (a) R. F. Jordan and D. F. Taylor, *J. Am. Chem. Soc.*, **111**, 778 (1989). (b) S. Mukhopadhyay, G. Rothenberg, D. Gitis, M. Baidossi, D. E. Ponde, and Y. Sasson, *J. Chem. Soc., Perkin Trans.* **2**, 1809 (2000).
3. (a) L.-C. Campeau, S. Rousseaux, and K. Fagnou, *J. Am. Chem. Soc.*, **127**, 18020 (2005). (b) K. S. Kanyiva, Y. Nakao, and T. Hiyama, *Angew. Chem. Int. Ed.*, **46**, 8872 (2007).
4. Y. Nakao, K. S. Kanyiva, and T. Hiyama, *J. Am. Chem. Soc.*, **130**, 2448 (2008).
5. (a) Y. Tsuji, S. Yoshii, T. Ohsumi, T. Kondo, and Y. Watanabe, *J. Organomet. Chem.*, **331**, 379 (1987). (b) T. Kondo, T. Okada, and T. Mitsudo, *Organometallics*, **18**, 4123 (1999). (c) S. Ko, H. Han, and S. Chang, *Org. Lett.*, **5**, 2687 (2003). (d) Y. Kobayashi, H. Kamisaki, K. Yanada, R. Yanada, and Y. Takemoto, *Tetrahedron Lett.*, **46**, 7549 (2005).

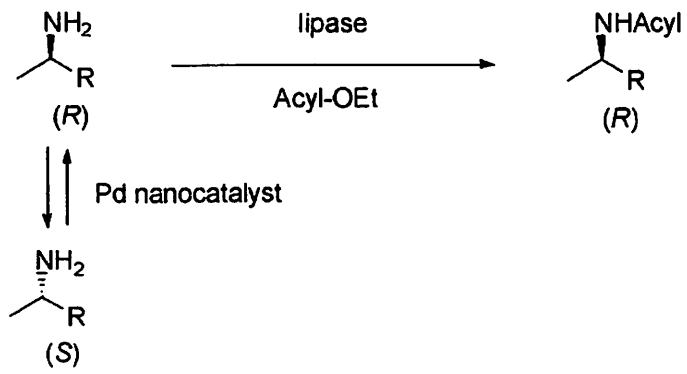
2P-73

Dynamic Kinetic Resolution of Primary Amines by Lipase-Palladium Cocatalysis

* Kiwon Han, Yoon Kyung Choi, Cheolwoo Kim, Jaiwook Park, Mahn-Joo Kim
Department of Chemistry, Pohang University of Science and Technology, San-31, Hyoja-dong, Nam-gu, Pohang, 790-784, Korea
tenor@postech.ac.kr

The complete transformation of a racemic mixture into a single enantiomer is one of challenging problems in chiral synthesis. Recently, a novel strategy has attracted great attention as a solution to this problem: *dynamic kinetic resolution (DKR) by the coupling of an enzymatic resolution with a metal–catalyzed racemization.*[1] Several groups including ours have developed enzyme–metal combinations as useful catalysts for such DKR and demonstrated that racemic substrates can be efficiently transformed by them into enantiomerically enriched products with high yields and excellent enantiomeric excesses, both approaching 100%.[2] Now a pair of complementary enzyme–metal combinations, lipase–Ru and subtilisin–Ru, is available for the DKR of a wide range of racemic secondary alcohols.[3] The (*R*)-selective DKR can be performed with the former while the (*S*)-selective DKR can be done with the latter. DKR of amines, however, is more challenging, and few practical procedures have been developed for such a DKR.

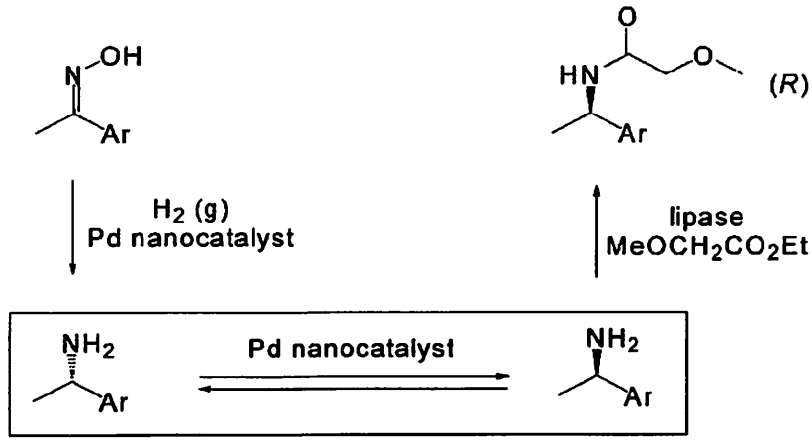
We have developed a practical procedure for the dynamic kinetic resolution (DKR) of primary benzylic and aliphatic amines (Scheme 1).[4] This procedure employs a palladium nanocatalyst as the racemization catalyst, a commercial lipase (CALB; trade name, Novozym-435) as the resolution catalyst, and ethyl acetate or ethyl methoxyacetate as the acyl donor. The Pd nanocatalyst, readily prepared as palladium nanoparticles entrapped in aluminum oxyhydroxide (Pd/AlO(OH)), displayed high activity and excellent stability even at 100 °C. The DKR of aliphatic amines has been performed at 100 °C with 12 mol% of Pd, while that of aromatic ones at 70 °C with 1 mol% of Pd. In all the cases, the amines have been efficiently resolved with good yields (85-99%) and high enantiomeric excesses (97-99%).



Scheme 1. DKR of primary amines by enzyme-metal combination

We have applied the method in the asymmetric reductive acylation of ketoximes (Scheme 2).[5] In

this case, Pd nanocatalyst acts as a dual catalyst for both hydrogenation of ketoximes and racemization of corresponding amines. Eight ketoximes have been efficiently transformed to the corresponding amides in good yields (83-92%) and high enantiomeric excesses (93-98%).



Scheme 2. Asymmetric reductive acylation of ketoximes by enzyme-metal cocatalysis

---

(1) Reviews: (a) Kim, M.–J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578–587. (b) Kim, M.–J.; Park, J.; Ahn, Y. In *Biocatalysis in the Pharmaceutical and Biotechnology Industries*; Patel, R. N., Ed.; CRC Press: Boca Raton, FL, 2006; pp 249–272.
(2) (a) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.–J.; Park, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2373–2376. (b) Kim, M.–J.; Chung, Y. I.; Choi, Y. K.; Lee, H. K.; Kim, D.; Park, J. *J. Am. Chem. Soc.* **2003**, *125*, 11494–11495. (c) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972-1977. (d) Martin–Matute, B.; Edin, M.; Bogar, K.; Bäckvall, J. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6535–6539. (e) Kim, N.; Ko, S.–B.; Kwon, M. S.; Kim, M.–J.; Park, J. *Org. Lett.* **2005**, *7*, 4523–4526. (f) Martin–Matute, B.; Edin, M.; Bogar, K.; Kaynak, F. B.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825.
(3) Kim, M.–J.; Kim, H. M.; Kim, D. H.; Park, J. *Green Chem.* **2004**, *6*, 471–474.
(4) Kim, M.–J.; Kim, W.–H.; Han, K.; Choi, Y. K.; Park, J. *Org. Lett.* **2007**, *9*, 1157–1159.
(5) Han, K.; Kim, M.–J.; Park, J. *J. Org. Chem.* **in press**.

2P-74

Micronization of Pharmaceutical Compounds by Supercritical Technology

Yen-Ming Chen[(1)], Yan-Ping Chen[*(1)], Muoi Tang[(2)]
(1) Department of Chemical Engineering, National Taiwan University
(2) Department of Chemical Engineering, Chinese Culture University
Taipei, Taiwan, ROC
ypchen@ntu.edu.tw

1. Introduction

Supercritical fluid technology has been extensively applied for various fields such as extraction, reaction, and material processing. Literature reviews have been presented for the application of supercritical fluid on the preparation of nanomaterials [1], green chemical synthesis [2] and processing of semiconductors [3]. Carbon dioxide is the most commonly used supercritical fluid because of its nontoxic, nonflammable properties, as well as its mild supercritical conditions. The supercritical technology has also been used for the production micronized pharmaceutical particles. Classification and selection of supercritical particle formation processes have been reviewed by several authors [4-6]. Micronization of pharmaceutical compounds can improve the dissolution rate of the active pharmaceutical ingredient (API). The results provide the advantages of high efficiency, low dosage requirement and avoiding possible side effects. In the supercritical particle formation methods, supercritical anti-solvent process (SAS) is the most commonly used technique. We have presented the SAS experimental results in a recent literature [7].

2. Experimental

The schematic diagram of the continuous SAS experimental apparatus is shown in Fig. 1. It consisted of three sections: carbon dioxide supply, solution supply, and the precipitator. A high flow rate HPLC pump (SSI, Prep 100) was used for CO_2 delivery, and another HPLC pump (SSI, series II) was employed for delivery of drug solution. The precipitator was a stainless steel tube with volume of 75mL, and it had stainless steel frits with different pore sizes (0.1 and 0.5 μm). The CO_2 flow rate was adjusted to about 4L/min by the micro-metering valve at the exit, and the pressure in the precipitator was controlled by a back pressure regulator (Tescom). The supercritical CO_2 was charged to the precipitator until the pressure and flow rate reached a steady state. The drug solution was then pumped into the precipitator through the nozzle (20cm long stainless tube with internal diameters of 127μm) at a specific flow rate. Upon contacting with the supercritical CO_2, the drug particles were formed due to the super-saturation of the solution. The residual solvent inside the precipitator was removed by the continuous flow of CO_2 before the particles were collected for further analyses. Particle morphology was examined by scanning electron microscope (SEM, JSM-6335FNT). Particle size and its distributions were determined using image analysis software Image-J.

3. Results and discussion

This study shows our typical experimental results for an API of deoxycholic acid (DCA, $C_{24}H_{40}O_4$). It was used in the human body for the emulsification of fats. The original mean particle size was about 30 μm, as shown in Fig. 2. After the SAS treatment (acetone as the solvent, operating temperature 308 K, operating pressure 100 bar), the particle size was reduced to less than 13 μm, as shown in Fig. 3. Fig. 4 shows that different micronization effects were obtained using various solvents in the SAS processes.

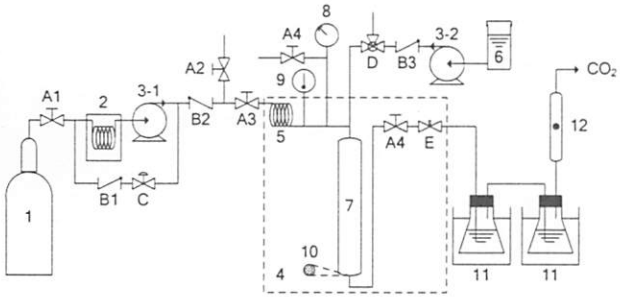


Figure 1 The SAS apparatus.

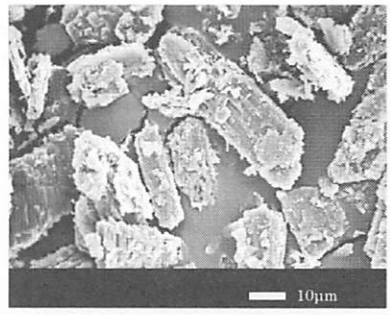


Figure 2 The SEM image of the original DCA.

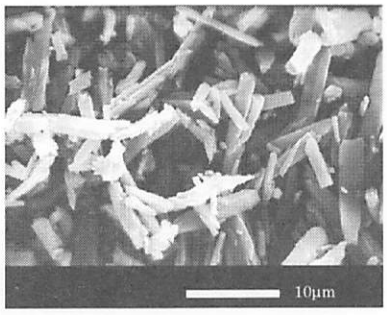


Figure 3 The SEM image of SAS treated DCA.

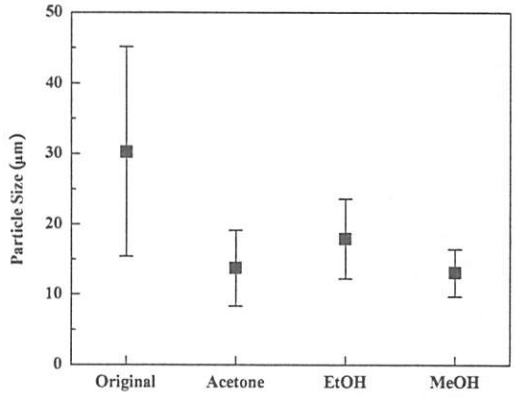


Figure 4 Comparison of micronized DCA using various solvents.

4. References:

[1] Reverchon, E. and Adami, R., J. Supercrit. Fluids, 37 (2006) 1-22.

[2] Beckman, E. J., J. Supercrit. Fluids, 28 (2004) 121-191.

[3] King, J. W. and Williams, L. L., Curr. Opin. Solid State Mater. Sci., 7 (2003) 413-424.

[4] Bahrami, M., Ranjbarian, S., J. Supercrit. Fluids, 40 (2007) 263-283.

[5] Perrut, M. and Clavier, J. Y., Ind. Eng. Chem. Res., 42 (2003) 6375-6383.

[6] Pasquali, I., Bettini, R. and Giordano, F., Eur. J. Pharm. Sci., 27 (2006) 299-310.

[7] Chang, Y. P., Tang, M. and Chen, Y. P., J. Materials Sci., 43 (2008) 2328-2335.

Author Index

Author Index

* Presenter

〔A〕

Abu Bakar Md. 2P-33
Aki Uehara* 2P-45
Akichika Itoh* 2P-70, 1P-29
Akiko Ido 1P-33
Akiko Kawai-Nakamura 2P-27, 2P-28
Akiko Yamamura* 2P-21
Akinori Mori 1P-26
Akira Akashi 1P-27
Akira Kume 1P-17
Akira Ogawa* 1P-34
Akira Yada 2P-71
Alejandro Diéguez-Vázquez 2P-05
Angus J. P. Stewart-Liddon 2P-03
Aniruddha B. Pandit* K-5
Arata Kimura* 2P-57
Arata Yanagisawa* 1P-03
Asahi Kawana 2P-32
Asayuki Kamatani* 1P-55
Atsumi Miyake 2P-57
Atsushi Kamata 1P-13
Atsusi Yamatodani 1P-02
Attila Wootsch 2P-49
Ayako Maki 1P-03
Ayako Tani 1P-09
Azusa Tsutsui* 1P-44

〔B〕

Benjamin Smith 2P-30
Brian M. Coleridge K-6

〔C〕

Chang-Li Lin 2P-50
Cheolwoo Kim 2P-69, 2P-73
Chihiro Kondo* 1P-25
Chii-Dong Ho* 1P-08
Ching-An Peng* 2P-46
Chun-Liang Lin 2P-50
Chun-Yuan Wang 1P-67

〔D〕

Daisuke Sasakura* 2P-13
Daisuke Shirakawa K-9
Dar-Jong Lin* 2P-50, 1P-57
David Haywood* K-13
David j Evans* 2P-03
Day-Shin Hsu 2P-05
Dong-Tsamn Lin 1P-57

〔E〕

Eiichiro Imai 1P-03
Elizabeth R. Burkhardt K-6
Eric J Hukkanen* 2P-30
Eric N. Jacobsen 2P-11
Eszter Varga 2P-49

〔F〕

Fabio Pichierri 2P-53
Feng-Chin Wu* 2P-64, 2P-65
Ferenc Darvas 2P-49
Fujio Mizukami 2P-34, 2P-37

〔G〕

Gabriela E Hitruc 1P-71
Gabriela Sacarescu* 1P-71, 1P-70, 1P-72
Gakuto Goshima 2P-14
Guen-Yen Chen 2P-46

〔H〕

Hanjoung Cho 1P-53
Haruyuki Ishii 1P-48
Hayato Hosino 1P-50
Hayato Ishikawa 2P-02
Hayato Kitoh 2P-57
Helmut Kraus* 2P-05
Hezhen Wang 1P-53
Hideaki Natsugari 1P-32
Hidefumi Nakatsuji* 2P-40, 2P-41
Hidehiro Sasakuma A-2

Hidekazu Oyamada 2P-38
Hideki Tatsumi 1P-21, 1P-68
Hideko Nagasawa 1P-14
Hideo Nagashima* A-2, 2P-16
Hideo Nemoto 1P-40, 1P-41
Hideo Nogusa A-3
Hideyo Takahashi 1P-32
Hiizu Iwamura 2P-27, 2P-28
Hikaru Tanaka 1P-21
Hiroaki Idei 2P-72
Hiroaki Makino* 2P-32
Hiroaki Okuno 1P-54
Hiroaki Sasai 2P-07
Hiroaki Yamamoto 1P-18
Hirokazu Suzuki 2P-08
Hirokazu Takagi K-9
Hiroki Nakagawa 1P-47
Hiroki Nakashima 2P-20, 2P-21
Hiroki Nakayama 1P-29, 2P-70
Hiroki Suzuki 1P-64
Hiroki Yoneyama 1P-02
Hiromi Hamamoto* 1P-32
Hironao Sajiki 1P-09, 1P-17, 1P-26
1P-27, 1P-33, 1P-42
1P-43, 1P-44, 1P-45
1P-46, 2P-23, 2P-24
Hironori Tsutsumi A-2
Hiroshi Iwamura 1P-11
Hiroshi Kuroda 1P-13
Hiroshi Naka 1P-61
Hiroshi Shibaguchi 2P-14
Hiroshi Umakoshi* 1P-49, 1P-48
Hiro□hi Yamazaki 1P-05
Hiroshi Yasuda* 1P-37, 2P-44
Hiroyoshi Matsubara 2P-36
Hiroyuki Fujimoto 2P-26, 2P-48
Hiroyuki Ishibashi 1P-35
Hiroyuki Kawafuchi 2P-68
Hiroyuki Kawai* 2P-48
Hiroyuki Morikawa 2P-29
Hisamitsu Nagase 1P-33
Hisanori Nambu 2P-17
Hisao Nemoto 1P-62
Hitomi Urai* 2P-44
Hongjun Zhang 1P-39
Hsu-Hsien Chang 1P-57
Hyun yung Lee* 2P-10, 2P-09

〔I〕

Isao Fujii 1P-36
Isao Kurimoto A-1
Isao Suzuki 2P-45
Iwao Chujo 1P-34
Iwao Suzuki 2P-53
Izumi Hirasawa* 1P-20

〔J〕

Jae hong Choi 2P-09, 2P-10
Jaiwook Park K-4, 2P-69, 2P-73
Jeong Min jeon 2P-10
Jian Liao* 2P-18
Jianchun Liao 1P-23
Jin Zhu* 2P-18
Jingen Deng 2P-18
JinYoung Lee* 1P-75
Jr-Wei Tu 1P-08
Julio C. Medina 2P-58
Junichi Tomokawa A-1
Junji Itoh 1P-59
Junpei Otaka 1P-05
Junzo Nokami 2P-29
Juzo Oyamada 2P-51

〔K〕

Kanako Ueno* 2P-41, 2P-40
Kanwal Ahmed 1P-41
Kaori Ando* 2P-47
Kaoru Nakamura 1P-52
Karl Matos* K-6
Katsuo Oda A-3
Katsutaka Yasue 1P-22
Katsuya Matsumoto 1P-22
Katsuyuki Iwanami 2P-43
Kazuaki Ishihara* K-3

Kazuhiko Watabe 1P-38
Kazuhiro Takenaka* 2P-07
Kazuhisa Sakakibara* 1P-50
Kazuishi Makino* 1P-66
Kazuma Mawatari 2P-34
Kazumi Kakugawa 1P-16
Kazumi Okuro 1P-38
Kazunori Nobuhara* 1P-07
Kazuo Osaki 2P-13
Kazuo Umezawa 1P-52
Kazushi Mashima 1P-31
Kazutake Hagiya* 1P-21
Kazutoshi Shindo 2P-66
Kazuyuki Chihara* 2P-39
Kei Manabe 1P-69
Keiichi Nishiyama 1P-48
Keiji Mori 1P-59, 1P-60
Keiji Oono* 2P-24, 2P-23
Keiko Inami 1P-52
Keisuke Miyamoto 1P-06
Keisuke Tomohara 2P-04
Keita Tsuji 2P-16
Keith Fagnou* K-10
Ken Furukawa 1P-13
Ken Suzuki 1P-30
Kengo Hyodo 2P-22
Kengo Morimoto 1P-49
Ken-ichi Fujita* 2P-31
Kenji Higashi 2P-16
Kenji Osumi* 1P-63
Kenji Toribatake 2P-14
Kenji Yatsuzuka 1P-62
Kiichiro Yaguchi* 1P-27
Kimiyoshi Kaneko 2P-29
Kiwamu Sue 2P-27, 2P-28
Kiwon Han* 2P-73
Kiyosei Takasu* 1P-24
Kiyoshi Ikeda* 1P-06
Kiyoshi Ikura 1P-18
Kiyoshi Tomioka 2P-08
Kiyoshi Watanabe* 1P-01, 1P-50, 2P-57
Kohei Fuchibe 1P-59
Kohei Fuchibe 1P-60
Kohtaro Goto 1P-63
Koichiro Nishimura 1P-03, 1P-34
Koji Kobayashi* 1P-61
Koji Takeda* 2P-17
Kotaro Tsuji 2P-22
Kouta Hatano 1P-02
Kyalo Stephen Kanyiva* 2P-72
Kyoji Ando 1P-03

〔L〕
Laszlo Urge* 2P-49
Le Quoc Tuan 1P-49
Liao-Ping Chang* 1P-57, 2P-50
Li-Jian Ma* 2P-67, 2P-68
Liming Bai 2P-66
Lisa Araki 1P-02
Liusheng Zhu 2P-58
Liviu Sacarescu* 1P-70, 1P-71, 1P-72

〔M〕
M. Christina White* K-2
Mahn-Joo Kim* K-4, 2P-69, 2P-73
Mai Hikita 2P-39
Makoto Kawai 1P-07
Makoto Sunagawa 1P-25
Mami Morimoto 2P-40
Mamoru Miyazawa 1P-13
Mamoru Mizuno 1P-63
Manabu Hamada* 1P-52
Manabu Kubota* 1P-13
Manabu Matoba* 2P-61
Manabu Node 2P-61, 2P-62, 2P-63
Marc Vimolratana 2P-58
Mark Butchko* K-12
Martin Karpf* K-1
Masahiro Anada* 1P-51, 2P-17
Masahiro Egi 1P-73, 1P-74
Masahiro Kudoh 1P-32
Masahiro Kurotani 1P-20
Masahiro Tanaka 1P-22
Masaki Kamiya 1P-62

Masaki Tomizawa* 2P-53, 2P-54, 2P-55
2P-56
Masanao Imai 2P-45
Masao Miyatake 1P-21
Masao Shimizu* 2P-01
Masaru Aoyagi 2P-43
Masaru Mitsuda* 1P-38
Masaru Okutani 2P-52
Masaru Sakaguchi 1P-66
Masashi Endo 1P-26
Masato Kujime 2P-31
Masatoshi Mihara* 1P-64, 1P-04, 2P-25
Masatoshi Shibuya* 2P-54, 2P-53, 2P-55
2P-56
Masatoshi Yoshimura* 1P-26
Masatsugu Kato 1P-09
Masaya Tsubakiyama 1P-73
Masayuki Sato 1P-06, 2P-33
Masayuki Takashima 2P-06
Matthew O'Brien 2P-05
Michael J. Krische* K-11
Michael R. Pitts 2P-03
Mifuyu Yasunaga 1P-02
Mihaela Simionescu* 1P-72, 1P-70, 1P-71
Mikihiro Takasaki 2P-16
Mikiko Sugi 2P-42
Ming-Kai Chern* 2P-59
Minoru Ozeki 2P-62, 2P-63
Minoru Ubukata 1P-22
Misun Lee 1P-75
Mitsuhiro Kamimura 1P-07
Mitsuhiro Yamada* 2P-29
Mohammed Nisar 2P-03
Motoko Hayashi* 1P-18
Mukund P. Sibi 2P-12
Muoi Tang 2P-74
Mutsumi Sato* 2P-23, 2P-24

〔N〕
Naohiko Kanai 2P-70
Naohiro Hashikawa 1P-18
Naohiro Oshima 1P-05
Naoki Kominami, 1P-20
Naomi Takenaka 2P-14
Naoto Inakoshi* 2P-11
Naoya Fujita 2P-66
Naoyuki Shimada 1P-51
Naoyuki Shimomura 1P-13
Nariaki Harada A-2
Noboru Fujiwara* 1P-74
Noboru Hayama 2P-62
Noboru Sayo 1P-30
Nobuo Kato 1P-25
Norihiko Misawa 2P-66
Norihiro Kimoto 1P-18
Norihiro Mizoshita 1P-47
Norihiro Tada 1P-29, 2P-70
Norihito Iida 2P-26
Noriko Koizumi 1P-34
Norio Hashimoto 2P-36
Norio Shibata 2P-06, 2P-19, 2P-20
2P-21, 2P-22, 2P-26
2P-48
Norio Tanaka 1P-28
Noriyuki Hara* 2P-20
Noriyuki Itoh 2P-07

〔O〕
Oh tak Kwon* 2P-09
Osamu Onomura 1P-10
Osamu Saku 1P-34

〔P〕
Pin-Hsueh Wu 2P-64, 2P-65

〔Q〕
Qing-Li Zhao 1P-41

〔R〕
Risa Maeda* 1P-54
Ru-Ling Tseng* 2P-65, 2P-64
Ryo Akiyama 2P-38
Ryohei Nagase* 2P-42
Ryoichi Chiba 1P-37, 2P-43, 2P-44

Ryoichi Kuboi 1P-48, 1P-49
Ryoki Orii* 2P-36
Ryota Suzuki 2P-39
Ryuji Orii 1P-07

〔S〕
San-Lang Wang* 1P-67
Satoko Sako 1P-44, 1P-46
Satomi Niwayama* 1P-53
Satoshi Hamakawa 2P-34, 2P-37
Satoshi Mizuta 2P-19, 2P-48
Satoshi Ueda* 1P-14
Sean P Brown* 2P-58
Seiichiro Ogawa 1P-52
Seiji Aratake 2P-02
Seongsoon Park 2P-15, 2P-60
Shen-Chen Tseng 1P-56
Shigeki Mori* 1P-17
Shigeki Nunomura 1P-36
Shin-ichi Hirashima* 1P-29
Shinichi Ogawa* 2P-26
Shin-ichiro Mohri 1P-03
Shinji Inagaki 1P-47
Shinji Ishihara* 1P-33
Shinobu Takao 1P-26
Shinya Harusawa * 1P-02
Shinya Mohri 1P-73
Shinya Ota 2P-33
Shiro Ebata 2P-71
Shiro Ikegami 1P-32
Sho-ichi Takayanagi* 1P-73
Shota Hashimoto 1P-43
Shu Kobayashi 2P-38
Shuichi Nakamura 2P-06, 2P-19, 2P-20
2P-21, 2P-22, 2P-26
2P-48
Shuji Akai 1P-73, 1P-74
Shunichi Hashimoto 1P-51, 2P-17
Shun-ichi Murahashi 2P-29
Shunpei Ishikawa* 1P-69
Shunsuke Goto 2P-36
Shunsuke Ochi* 2P-63

Sojung Park* 2P-15
Sol Kim* 2P-69
Sousuke Hara 1P-66
Steven V. Ley 2P-05
Sueo Wada 1P-33
Suhyun Jung* 2P-60, 2P-15
Sunao Mitsui 1P-68
Sunggak Kim 1P-75
Surendar Akiti 2P-48
Syang-Peng Rwei* 1P-15

〔T〕
Tadashi Ema 1P-65
Tadashi Ohara 2P-17
Taichi Akimoto* 1P-36
Taichi Wada 2P-39
Tai-Horng Young* 1P-12, 1P-57
Takafumi Matsuo 1P-22
Takahiko Akiyama 1P-59, 1P-60
Takahiko Itoh 2P-02
Takahiro Itoh 2P-35
Takahiro Katoh 2P-62, 2P-63
Takahiro Soeta* 2P-12
Takahiro Udzu 1P-44
Takahisa Sato 2P-54
Takahito Muraki 2P-31
Takako Inoue 1P-07
Takako Nagase 2P-37
Takanori Iwasaki 1P-31
Takanori Kawaguchi 1P-41
Takanori Kodera 1P-20
Takanori Kurita 1P-46
Takao Tani 1P-47
Takashi Fukuyama 1P-16
Takashi Ikawa 1P-17, 1P-73
Takashi Inaba* 1P-22
Takashi Kikuchi 2P-36
Takashi Kondo 1P-41
Takashi Naka* 1P-11
Takashi Ogo 1P-22
Takashi Ohshima* 1P-31
Takashi Okazoe* K-9

Takashi Sakai 1P-65
Takashi Sugimura 1P-21
Takashi Tanoi 2P-33
Takashi Tsunoda, 2P-05
Takatoshi Ito 1P-64, 2P-25
Takehiko Kawakami A-1
Takehiko Kitamori 2P-34
Takemasa Hida* A-3
Takenori Sawada* 2P-28
Takeo Kawabata 2P-04
Takeo Konakahara 2P-01
Takeo Nakai* 2P-25, 1P-04, 1P-64
Takeru Hasegawa 1P-47
Takeshi Oriyama 1P-37, 2P-43, 2P-44
Takeshi Sugai 1P-52
Takeshi Toru 2P-06, 2P-19, 2P-20
2P-21, 2P-22, 2P-48
2P-26
Takeshi Yamamoto* 2P-06
Takesi Sakamoto 1P-05
Takumi Mizuno* 1P-04, 1P-64, 2P-25
Takumi Takeyasu 2P-32
Takuya Washio 1P-51
Tamejiro Hiyama 2P-71, 2P-72
Tatsuya Furukawa* 2P-19
Tetsuhiro Nemoto* 1P-16
Tetsuro Watadani 1P-36
Tetsuya Ikemoto* A-1
Tetsuya Kajimoto 2P-61, 2P-62, 2P-63
Tetsuya Nezu 1P-03
Thomas E. O. Screen 2P-03
Tian Tian 2P-18
Tohru Kobayashi* 1P-30
Tohru Suzuki* 1P-60
Tohru Takahashi 1P-09
Tohru Tanaka 1P-24
Tomohiro Maegawa* 1P-09, 1P-17, 1P-26
1P-27, 1P-33, 1P-42
1P-43, 1P-44, 1P-45
1P-46, 2P-23, 2P-24
Tomohisa Utsunomiya 1P-28
Tomokazu Watanabe 1P-34
Tomoko Kakinuma* 2P-43
Tomomi Kawahara* 2P-27
Tomonori Misaki 2P-42
Tomoteru Mizusaki 1P-26
Tomoya Inoue* 2P-34, 2P-37
Tomoya Yukawa 2P-71
Tomoyo Kusuyama 2P-67
Tomoyuki Kawamura* 1P-62
Tomoyuki Ohkubo 1P-17
Tomoyuki Yoshimura* 2P-04
Toshiaki Masui A-3
Toshihiko Hiaki 2P-27, 2P-28
Toshihiko otomatsu* 2P-66
Toshikazu Nishide 2P-37
Toshinobu Ohno 1P-64
Toshinori Higashi 1P-52
Toshinori Shimanouchi* 1P-48, 1P-49
Toshiro Konoike* K-8
Thomas E. O. Screen 2P-03
Toshiyuki Sato 2P-27, 2P-28
Toshiyuki Iwai 1P-64, 2P-25
Tosiaki Mase 2P-35
Toyohiro Nagano 2P-14
Toyoshi Shimada* 1P-47, 2P-14
Trong-Ming Don* 1P-58
Tsai-Yi Huang 1P-67
Tsubasa Sakamoto* 1P-59
Tsugio Kitamura* 2P-51
Tsunefumi Watanabe* 2P-62
Tsutomu Inokuchi 2P-67, 2P-68
Tsutomu Katsuki* K-7
Tsutomu Matsumura 1P-34
Tsuyoshi Miura 2P-13
Tsuyoshi Taniguchi* 1P-35

〔V〕
Vu Thi Huong 1P-48

〔W〕
Wei-Chi Lai* 1P-56
Weihua He 1P-23
Wei-Jyh Shiah 2P-59

Wei-Wei Shun 1P-58
Wen-Yi Tsai 2P-46
Wilson Jung 2P-09, 2P-10

[Y]
Yandong Zhang 1P-39
Yan-Ping Chen* 2P-74
Yasufumi Wada 1P-73
Yasuhiro Hirata 2P-71
Yasuhiro Sakamoto 1P-21
Yasuhiro Sakurai* 1P-28
Yasuhiro Sato 1P-68
Yasuhiro Torisawa 1P-01
Yasuhisa Hasegawa 2P-37
Yasumasa Hamada 1P-66, 1P-16
Yasunari Monguchi* 1P-46, 1P-09, 1P-17
1P-26, 1P-27, 1P-33
1P-42, 1P-43, 1P-44
1P-45, 2P-23, 2P-24
Yasunari Takayasu 1P-11
Yasunori Tuchiya* 2P-38
Yasuo Kikugawa* 1P-05
Yasuo Shirai 1P-28
Yasuo Uekita A-1
Yasutomo Yamamoto* 2P-08
Yasuyoshi Miki 1P-32
Yasuyuki Kajimoto 1P-22
Yasuyuki Kita 1P-73
Yen-Ming Chen 2P-74
Yogesh Jorapur 1P-47
Yong Cai* 1P-39
Yongping Yu 1P-39
Yoo Tanabe 2P-40, 2P-41, 2P-42
Yoon Kyung Choi 2P-73
Yorinobu Yasuda 2P-08
Yoshiaki Horiguchi* 1P-19
Yoshiaki Kitamura 1P-44, 1P-46
Yoshiaki Nakao* 2P-71, 2P-72
Yoshifumi Maegawa 1P-47
Yoshiharu Iwabuchi 2P-53, 2P-54, 2P-55
2P-56
Yoshihiko Maeda 1P-37, 2P-44
Yoshihiro Tsutsumi* 1P-65
Yoshiji Takemoto 1P-24
Yoshikazu Hiraga 1P-53
Yoshiki Hayakawa 2P-29
Yoshiko Yamaguchi 1P-74
Yoshikuni Kikutani 2P-34
Yoshimichi Kiyozumi 2P-37
Yoshinori Fukuta 2P-33
Yoshinori Kondo 1P-61
Yoshinori Satou 2P-32
Yoshinori Takamatsu* 2P-14
Yoshio Ishino 1P-64
Yosuke Demizu 1P-10
Yosuke Watanabe A-1
Youhei Iwasaki* 1P-45
Youhei Koma 1P-66
Yu Ogawa 1P-24
Yu-Chun Chen 2P-59
Yuhei Yamamoto* 2P-35
Yuichi Kimoto 1P-13
Yuji Matsuya* 1P-41, 1P-40
Yuji Mori* 2P-52
Yuji Osada* 2P-55
Yujiro Hayashi* 2P-02
Yuki Fujita* 1P-43
Yuki Kubo* 1P-10
Yuki Morikawa 1P-73
Yukihiro Motoyama* 2P-16, A-2
Yukihito Sumino 2P-05
Yukio Takagi 1P-26
Yukio Takahashi 1P-36
Yuko Maruyama 1P-16
Yuko Nakamura* 2P-22
Yuko Tarumi 2P-47
Yumiko Oguni 2P-42
Yumiko Suzuki* 2P-33
Yun Kyung Choi 2P-69
Yunaqiang Li* 1P-23
Yunwoong Kim 2P-69
Yuriko Hirose 1P-63
Yusuke Higuchi 1P-25, 2P-01
Yusuke Maegawa 1P-31

Yusuke Sasano* 2P-56, 2P-53, 2P-55
Yuta Fujiwara* 1P-42, 1P-45
Yuta Kobayashi* 1P-40
Yuudai Watanabe 1P-51
Yuusaku Yokoyama 1P-54
Yuya Inagaki 1P-42

〔Z〕
Zhen-wu Mei* 2P-68, 2P-67
Zsolt Otvos 2P-49

Exhibition

July 29 & 30

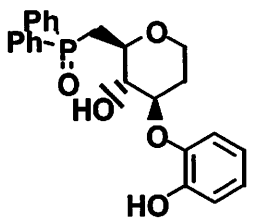
LIST OF EXHIBITORS

Company	URL
[A]	
Almac science	http://www.almacgroup.com/
ALPS Pharmaceutical Ind. Co., Ltd.	http://www.alps-pharm.co.jp
ANTHEM BIOSCIENCES PVT LIMITED	http://www.anthembio.com/
ASAHI GLASS CO., LTD	http://www.agc.co.jp
ASAHI KASEI FINECHEM CO., LTD.	http://www.asahikasei-fc.jp/
Asahi Spectra Co.,Ltd.	http://www.asahi-spectra.co.jp
[B]	
BASF Japan Ltd.	http:www.japan.basf.com
Biotage Japan, Ltd.	http://www.biotage.com
Bruker Optics K.K.	http://www.bruker-optics.jp/
[C]	
CBC Co.,Ltd.	http://www.cbc.co.jp
Central Glass Co., Ltd.	http://www.cgco.co.jp/
central scientiffic commerce,inc.	http://www.cscjp.co.jp
Chemetall Japan K.K.	http://www.chemetall.co.jp
ChemGenesis Incorporated	http://www.chemgenesis.com
Chiro-Technology res.&dev.Co.,Ltd.	http://www.chiro-technology.co.jp/
CHUKAN BUTSU LTD.	http://www.chukan.co.jp
CONFLEX Corporation	http://www.conflex.co.jp/
[D]	
DAICEL CHEMICAL INDUSTRIES,LTD.	http://www.daicelchiral.com/
DAIKIN□CHEMICALS□SALES,LTD.	http://www.daikin-dcs.co.jp/
DAISO CO.,LTD.	http://www.daiso.co.jp
[F]	
Fuji-Silysia Chemical LTD.	http://www.fuji-silysia.co.jp
Fushimi Pharmaceutical Co.,Ltd.	http://www.fushimi.co.jp/
[H]	
HACH ULTRA JAPAN	http://hachultra.jp
Hamari Chemicals, Ltd.	http://www.hamarichemicals.com
HODOGAYA CHEMICAL CO.,LTD.	http://www.hodogaya.co.jp

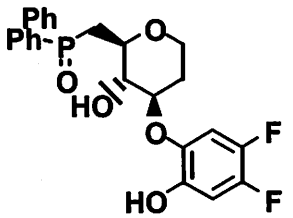
Company	URL
HULINKS, Inc.	http://www.hulinks.co.jp/
HYDRUS CHEMICAL, Inc.	http://www.hydrus.co.jp
[I]	
IHARA CHEMICAL INDUSTRY CO., LTD.	http://www.iharachem.co.jp/
Imtakt Corporation	http://www.imtakt.com
Institute of Microchemical Technology	http://www.i-mt.co.jp
[J]	
Japan Chemical edata Corporation	http://www.chem-edata.com
JEOL Ltd.	http://www.jeol.com/
Julabo Japan Co.,Ltd	http://www.julabo-japan.co.jp
Junsei Chemical Co.,Ltd.	http://www.junsei.co.jp
[K]	
KANTO CHEMICAL CO.,INC.	http://www.kanto.co.jp/english/index.html
KANTO DENKA KOGYO CO., LTD.	http://www.kantodenka.co.jp/
KNC Laboratories Co., Ltd.	http://www.kncweb.co.jp/
KOEI CHEMICAL COMPANY LIMITED	http://www.koeichem.com/
[M]	
MANAC Incorporated	http://www.manac-inc.co.jp/global/index.html
Mettler-Toledo.K.K.	http://japan.mt.com/autochem
Midori Book Store Co.,	http://www.midori-book.co.jp
Mitsubishi Corporation, Reaxa Limited	http://www.mitsubishicorp.com/jp/index.html
MITSUBISHI TANABE PHARMA CORPORATION	http://www.mt-pharma.co.jp/
MORITEX CORPORATION	http://www.moritex.co.jp
[N]	
N.E.Chemcat Corporation	http://www.ne-chemcat.co.jp/
NACALAI TESQUE,INC	http://www.nacalai.co.jp
Nagase & Co.,Ltd.	http://www.nagase.co.jp
NAMIKI SHOJI Co., Ltd.	http://www.namiki-s.co.jp
NARD CHEMICALS.Ltd.	http://www.nard.co.jp/group.html
New Japan Chemical Co.,Ltd.	http://www.nj-chem.co.jp
NICHIA CORPORATION	http://www.nichia.co.jp/
Nichia Pharmaceutical Industries Ltd.	http://nichia-yakuhin.com
Nihon SiberHegner K.K.	http://www.dksh.com

Company	URL
NIKKISO Co., Ltd.	http://www.microtrac.com/
NIPPON KAYAKU CO.,LTD	http://www.nipponkayaku.co.jp/
NIPPON SODA CO.,LTD.	http://www.nippon-soda.co.jp
NISSAN CHEMICAL INDUSTRIES, LTD.	http://www.nissanchem.co.jp
[O]	
OMRON Corporation	http://www.fa.omron.co.jp/
Optima Inc.	http://www.optimajp.com
[P]	
Pharmaron	http://www.pharmaron.com/
PI Japan, Ltd	http://www.piindustries.com/
Process Systems Enterprise Limited	http://www.psenterprise.com
[S]	
S.T. Japan,Inc.	http://www.stjapan.co.jp/
SAFC	http://www.safcglobal.com
Saltigo GmbH (LANXESS K.K.)	http://www.saltigo.com
Sapala Organics Pvt. Ltd.	httpwww.sapalaorganics.com
Shanghai ChemPartner Co., Ltd.	http://www.chempartner.cn
Shikoku Instrumentation CO.,LTD	http://www.yonkei.co.jp
SIBATA SCIENTIFIC TECHNOLOGY LTD.	http://www.sibata.co.jp/
SUGIYAMA-GEN CO.,LTD.,	http://www.sugiyama-gen.co.jp
SUMITOMO SEIKA CHEMICALS CO., LTD.	http://www.sumitomoseika.co.jp
Summit Pharmaceuticals International Corporation	http://www.summitpharma.co.jp
SyrrisJapan Inc.	http://www.syrris.com
[T]	
TAIYO NIPPON SANSO Corporation	http://www.tn-sanso.co.jp/en/
TAKASAGO INTERNATIONAL CORPORATION	http://www.takasago-i.co.jp
TATEYAMA KASEI CO.,LTD	http://www.tateyamakasei.com
TECHNIS Co., Ltd	http://www.technis.jp/
Thieme Publishing Group	http://www.thieme-connect.com
TOKYO CHEMICAL INDUSTRY CO.,LTD	http://www.tokyokasei.co.jp□
Tokyo Rikakikai Co.,Ltd.	http://www.eyela.co.jp
TORAY ENGINEERING Co., Ltd.	http://www.toray-eng.co.jp/
TOSOH FINECHEM CORPORATION	http://www.tosoh-finechem.com

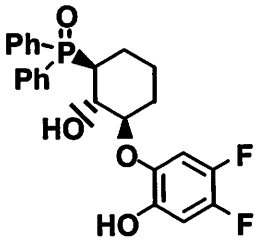
Chiral Ligands



GluCAPO

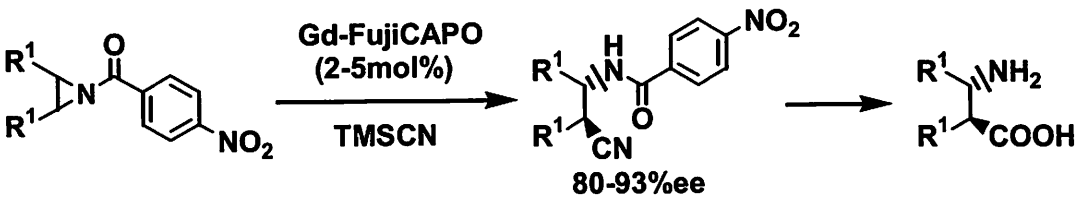


Glu(F2)CAPO

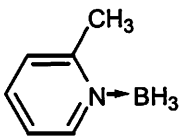


Fuji(F2)CAPO

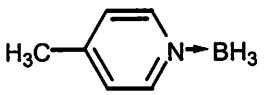
Catalytic Asymmetric Aziridine-Opening Reaction with Gd-Fuji(F2)CAPO Complex.



Picoline-Boranes

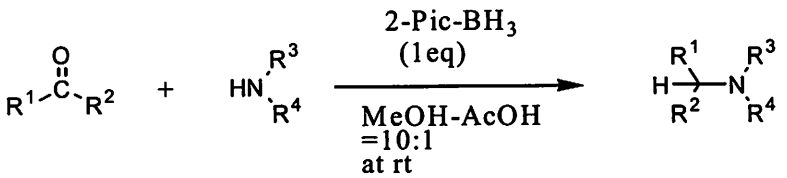


2-Picoline-Borane

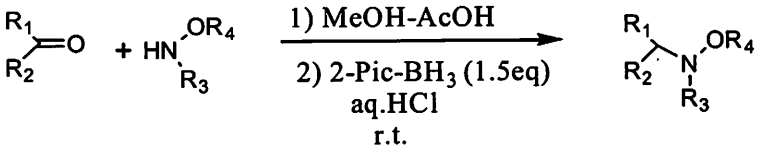


4-Picoline-Borane

The pressure vessel test(100-200℃) proves 2-Picoline-borane thermally stable.
Picoline-boranes are mild reducing agents suitable for reductive amination of aldehydes or ketones.



Kikugawa,Y. et al.,Tetrahedron, 2004, 60, 7899



The Japanese Society for Process Chemistry 2007 Summer Symposium 1P-30

Junsei Chemical Co.,Ltd. Sales Headquater.

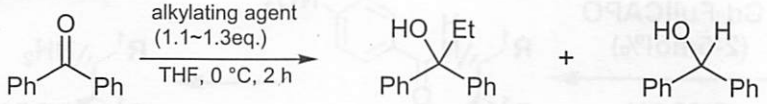
6-1, Ohmano-cho, Koshigaya-shi, Saitama, 343-0844, Japan

Phone: +81-48-988-3621 FAX: +81-48-988-8719 MAIL: shiyaku-t@junsei.co.jp

Highly Efficient Alkylating Agent

Ethylmagnesium Chloride (*ca.* 0.8mol/L in Tetrahydrofuran)
activated with Zinc Chloride (*ca.* 10mol%) 250g JPYen 12,000. **[E0778]**

Recently, Ishihara *et al.* discovered that tertiary alcohols are synthesized in high yields with minimum side reactions by the addition of a catalytic amount of zinc chloride to the Grignard reagents. They rationalized this observation by invoking the formation of highly active zinc-ate complexes $R_3ZnMgCl$ *in situ* in an efficient catalytic cycle. They have applied this method the alkylation of various ketones.

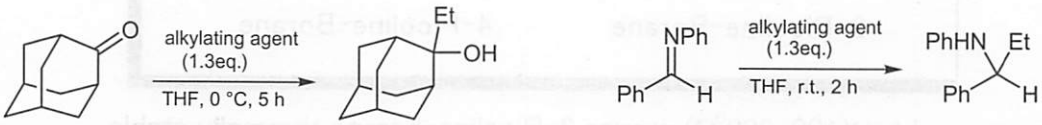


alkylating agent	tertialy alcohol [Y.(%)]	reduction product [Y.(%)]
EtMgCl	25	71
EtMgCl + $ZnCl_2$ (10mol%)	84	15

In the alkylation of 2-adamantanone, which is typically considered to be difficult since reduction occurs in preference to the desired alkylation when only Grignard reagents are used, the yield of desired product was improved greatly by using this protocol.

Furthermore, addition of lithium chloride increased the yields up to 81%. 2-Alkyl-2-adamantanol is a useful photoresist material, so it is anticipated that this method will be of great utility in various fields.

Furthermore, it was also reported that this reaction is applicable to the related, but much less reactive aldimines and that the addition reaction proceeds efficiently.



alkylating agent	Y.(%)
EtMgCl	29
EtMgCl + $ZnCl_2$ (10mol%)	58
EtMgCl + $ZnCl_2$ (10mol%) + LiCl	81

alkylating agent	Y.(%)
EtMgCl	41
EtMgCl + $ZnCl_2$ (10mol%)	81

In this way, the reactions mentioned above constitute simple and practical methods for the generation of tertiary alcohols, which can be performed under mild conditions, and which are also useful industrially. The original paper by Ishihara *et al.* qualified as the 1st "Most-Accessed Articles" in the category of communications for the *Journal of the American Chemical Society* (Web Edition) from July to September, 2006.

TCI is happy to make available the zinc chloride-activated Grignard reagent which is convenient to use for the above alkylation.

1) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.*, **2006**, *128*, 9998.
2) M. Hatano, S. Suzuki, K. Ishihara, *Kagaku*, **2007**, *62* (3), 16.

The new TCI catalog "Laboratory Chemicals 2008-2009" is available now. Request your free copy now!!

東京化成工業株式会社
Phone : 03-3241-0573
Fax : 03-3246-2094
E-mail : sales@tokyokasei.co.jp
Website : www.tokyokasei.co.jp

TOKYO CHEMICAL INDUSTRY CO., LTD.
Phone : +81-3-5640-8878
Fax : +81-3-5640-8902
E-mail : globalbusiness@tokyokasei.co.jp
Website : www.tci-asiapacific.com

TCI AMERICA
Phone : 800-423-8616 • 503-283-1681
Fax : 888-520-1075 • 503-283-1987
E-mail : sales@tciamerica.com
Website : www.tciamerica.com

TCI EUROPE N.V.
Phone : 00 800 46 73 86 67
+32 (0)3 735 07 00
Fax : +32 (0)3 735 07 01
E-mail : sales@tcieurope.eu
Website : www.tcieurope.eu

梯希爱(上海)化成工业发展有限公司
Phone : 021-6712-1388
Fax : 021-6712-1385
E-mail : sales@tcishanghai.com.cn
Website : www.tcishanghai.com.cn

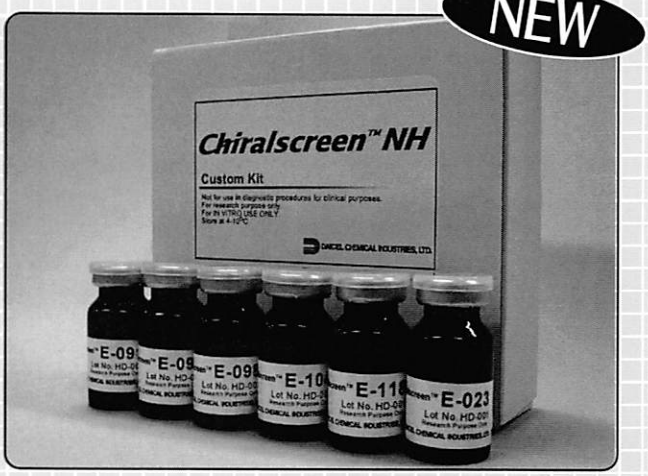
TCI Chemicals (India) Pvt. Ltd.
Phone : +91-44-4261 2444
Fax : +91-44-4261 1065

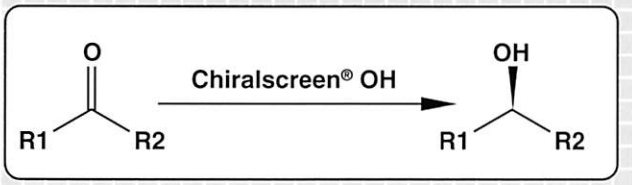
バイオ触媒

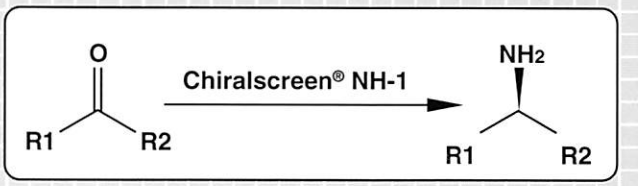
Chiralscreen™

NEW

NEW







バイオ触媒キット

- ❑ ***Chiralscreen® OH*** : 不斉還元バイオ触媒
- ❑ ***Chiralscreen® NH*** : キラルアミンバイオ触媒

短時間での評価が可能

- Chiralscreen®を使えば、反応の正否が一日以内に評価できます。
- また、弊社へのスクリーニング委託も可能です。

使 い 方 は 簡 単

- Chiralscreen®は、酵素反応が初めての方でも、簡単に使用できます。
- 使用するにあたって、特別な技術や知識は不要です。
- 反応は水系、常温常圧で進みます。（基質が水に完溶する必要はありません。有機溶媒添加も可）

スケールアップをサポート

- 1g以下や10gなど、少量のサンプル調整にも対応いたします。
- パイロットや商業製造のためのプロセスの最適化、および実機製造もお引き受けいたします。
- もちろん、お客様ご自身でのスケールアップも可能です。

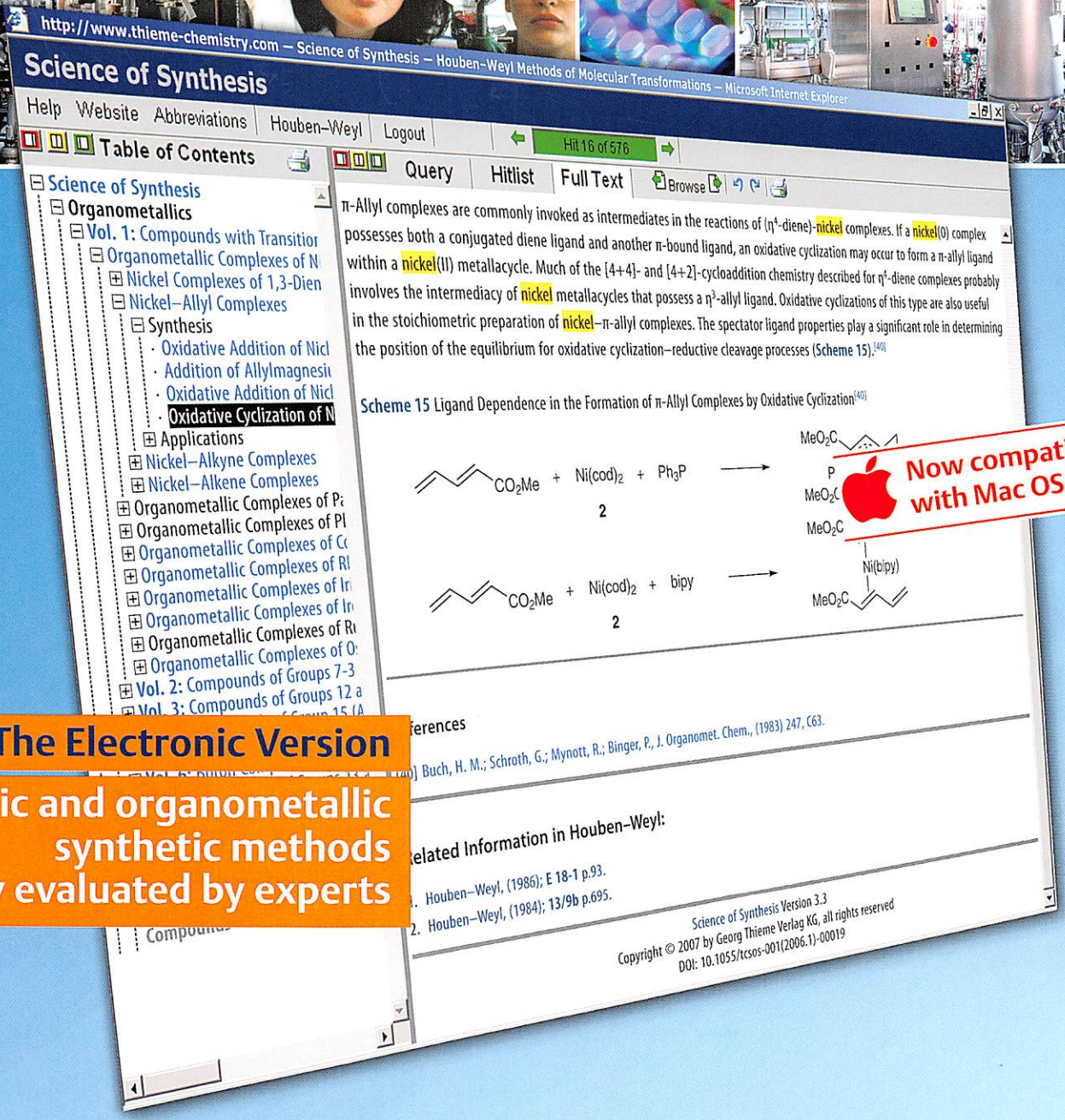
Innovation for Tomorrow
ダイセル化学工業株式会社
CPIカンパニー Chiral Pharmaceutical Ingredients

●東日本：〒108-8230 東京都港区港南2-18-1 JR品川イーストビル14F
TEL.03-6711-8221（直） FAX.03-6711-8228
●西日本：〒530-0001 大阪市北区梅田3-4-5 毎日インテシオ20F
TEL.06-6342-6161（直） FAX.06-6342-6168
●http://www.daicelchiral.com/ ●E-mail:biochem@daicel.co.jp

Science of Synthesis

Houben–Weyl Methods of Molecular Transformations®

The Electronic Version



The Electronic Version

Organic and organometallic synthetic methods critically evaluated by experts

For further information, please visit **www.thieme-chemistry.com**
or contact us at **marketing@thieme-chemistry.com**
Within Japan, please contact our distribution partner Bureau Hosoya at
brhosoya@poplar.ocn.ne.jp

Thieme