ISPC2015

The 3rd International Symposium on Process Chemistry

July 13 Mon -15 Wed , 2015

Kyoto International Conference Center
KYOTO, JAPAN

Abstracts

J.S.P.C

The Japanese Society for Process Chemistry

Organizer
The Japanese Society for Process Chemistry
Support
The Society of Synthetic Organic Chemistry, Japan
The Kinki Chemical Society, Japan
The Society of Separation Process Engineers, Japan
The Chemical Daily Co.,Ltd.

女性研究者の
次世代型コンパクトロータリーエバポレータ

ロータリーエバポレータRC900

NEW

他社にない特長

- ワイヤレスリモートコントローラによる制御です。（バス温度、回転速度、ジャッキの自動昇降）
- 結露しやすい邪魔なホースをタワー内部に収納し、安全ですっきりとしたデザインです。
- ダイアフラムポンプメーカの長年の実績に基づく新型高品質の真空シールを採用
- フラスコ、ロータリージョイント コンデンサーの脱着が容易
- 停電時には試料フラスコが自動的に上がり、フラスコの過熱を防ぎます。
- コンパクトデザイン W487 x D447 x H823（ガラス部品を含む）
- 軽量設計　　質量：9kg

溶媒回収機能付き
真空ポンプシステム
SC920 + RC900

特長

- ワイヤレスリモートコントローラによる省エネ運転が可能です。
- 自動モードにより溶媒の沸点を自動で検知し突沸を防ぎます。溶媒のライブラリは不要です。
- 20L/minの排気速度と2hPa(mbar)の到達真空度によりロータリーエバポレータRC900の組合せで突沸を防ぎ高沸点の溶剤の回収に効果を発揮します。

株式会社ケー・エヌ・エフ・ジャパン
〒104-0033 東京都中央区新川 1-16-14
アクロス新川ビル　アネックス 3F
TEL: 03-3551-7931 FAX: 03-3551-7932
E-mail: info@knf.co.jp URL:http://www.knf.co.jp

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Dear Colleagues,

It is a great honor and pleasure for us to hold the Third International Symposium on Process Chemistry (ISPC 2015) in Kyoto during 13-15 July, 2015 under the auspices of the Japanese Society for Process Chemistry (JSPC) founded in 2001, just beginning of this century. JSPC mainly organizes summer and winter symposia in each year. Members of JSPC belong to pharmaceutical and chemical industries, manufacturers of pharmaceuticals intermediates, universities, and so on. The number of participants to such symposia is yearly increasing. Furthermore, the First and Second International Symposiums on Process Chemistry, ISPC 2008 and 2011, came to an end with great success with around 1,000 people participating. ISPC 2015 will include keynote lectures by top runners of process chemistry in the world, selected short oral presentations, poster presentations, and exhibitions. Mutual understanding among participants will be actively deepened in break of the lectures, welcome party, and banquet. We believe in the ultimate success of ISPC 2015 in association with all participants.

Kyoto is an ancient capital of Japan from year 794 until 1868 before the capital was moved to Tokyo. It has a reputation worldwide as Japanese most beautiful and traditional city, and you will find so many unparalleled collections of palaces, temples, and shrines. All participants will be able to enjoy these beautiful and historical world heritages and genuine Japanese cultures in addition to the process chemistry. Especially, Kyoto Gion Festival, the most traditional and beautiful event of Kyoto is being held during the same period. You can enjoy it.

Please enjoy the productive symposium together with spectacularly old-modern-flavored atmospheres of Kyoto. Thank you very much for your participation.

Kiyoshi Tomioka
Chairperson of the Third International Symposium on Process Chemistry (ISPC 2015)
President of the Japanese Society for Process Chemistry

Hironao Sajiki
Chairperson of the Program Committee

Organizing Committee

■ President of JSPC

Kiyoshi Tomioka (Doshisha Women's College of Liberal Arts)

■ Honorary President of JSPC

Takayuki Shioiri (Nagoya City Univ.)

■ Program Chair of ISPC

Hironao Sajiki (Gifu Pharm. Univ.)

■ Program Member

Takahiko Akiyama (Gakushuin Univ.)
Mitsunori Hashimoto (Consultant)
Hideo Hashimoto (Takeda)
Masahiro Ikeda (Daiichi Sankyo)
Takashi Inaba (Japan Tobacco)
Kunisuke Izawa (Hamari)
Koji Kagara (Ohara Pharm)
Toshihisa Kato (Ajinomoto)
Masahiro Kato (Chugai)
Taro Kiyoto (Toyama Chemical)
Toshiro Konoike (Osaka Synth. Chem. Labs)
Toshiaki Mase (Institute Molecular Science)
Norio Minami (Nard Chemicals)
Masaru Mitsuda (Kaneka)
Keiji Ohno (Wako)
Masahiro Ohshima (Mitsubishi Tanabe)
Minoru Okada (Astellas)
Osamu Onomura (Nagasaki Univ.)
Masakatsu Shibasaki (Microbial Chemistry Research Foundation)
Ichiro Shinkai (Consultant)
Kozo Shishido (Tokushima Univ.)
Shigeru Soda (Office Soda)
Kin-ichi Tadano (Keio Univ.)

Katsuya Tagami	(Eisai)
Kazuhiko Takahashi	(Sumitomo-Dainippon)
Osamu Yamada	(Nissan Chemical)

■ International Advisory Board

Tamin Braish	(Process Research, Pfizer Inc.)
Jingen Deng	(Sichuan Univ., China)
rancis Gerard Fang	(Eisai, USA)
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Sang-sup Jew	(Seoul National Univ., Korea)
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Roger Sheldon	(Delft Univ. Tech., The Netherland)
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Nobuyoshi Yasuda	(Merck, USA)

■ Local Committee

Kiyosei Takasu	(Kyoto Univ.)
Yasutomo Yamamoto	(Doshisha Woman's College of Liberal Arts)

To Participants of The 3rd International Symposium on Process Chemistry [ISPC 2015]

* 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.
* 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

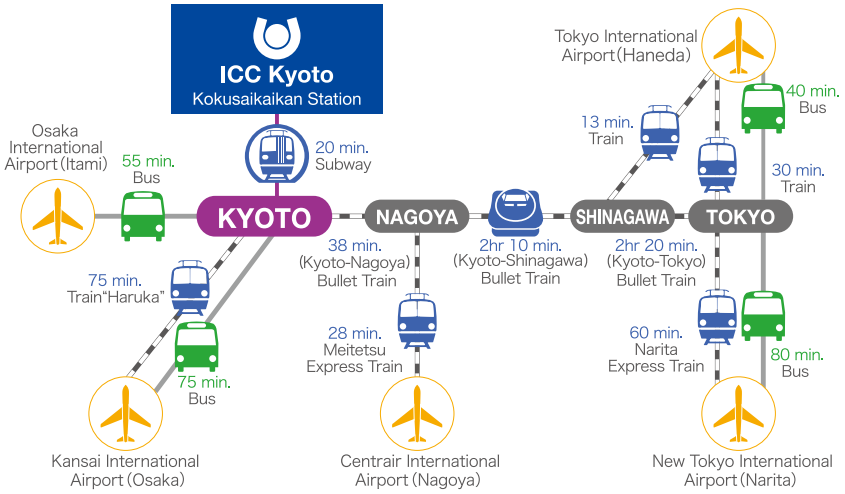
* The presentation codes 1P-xx and 2P-xx represent July 14 (Tuesday) and July 15 (Wednesday), respectively. The poster presentation is held at Annex Hall.
* Please put up all posters on the board from 9:00am to 2:50pm on July 14. Posters should be put up for two days (July 14 and 15), and please remove at the end of the poster session on July15. They are to be discarded when not removed.
* Oral presenters need to come to the front of the entrance of the Main Hall at the following times:

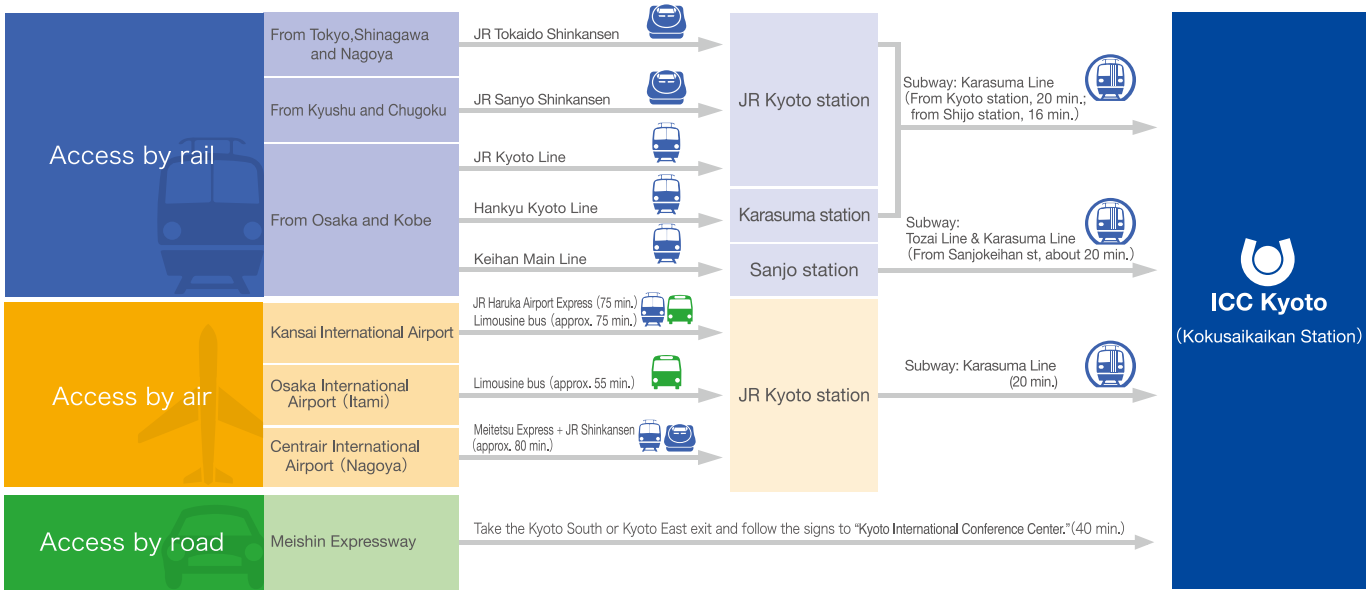
13:05 on July 14 12:35 on July 15

Access

Easy International Access

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

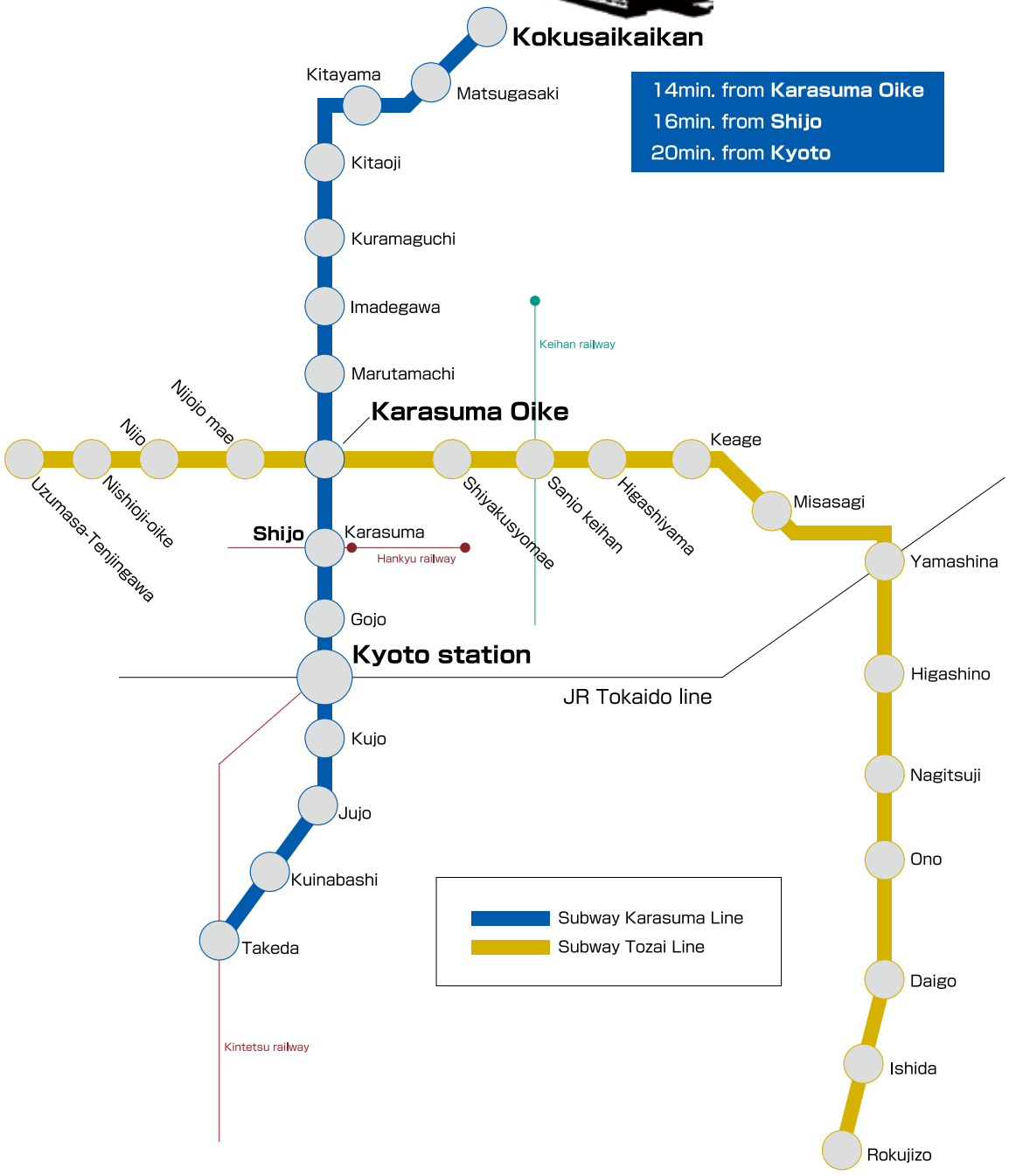




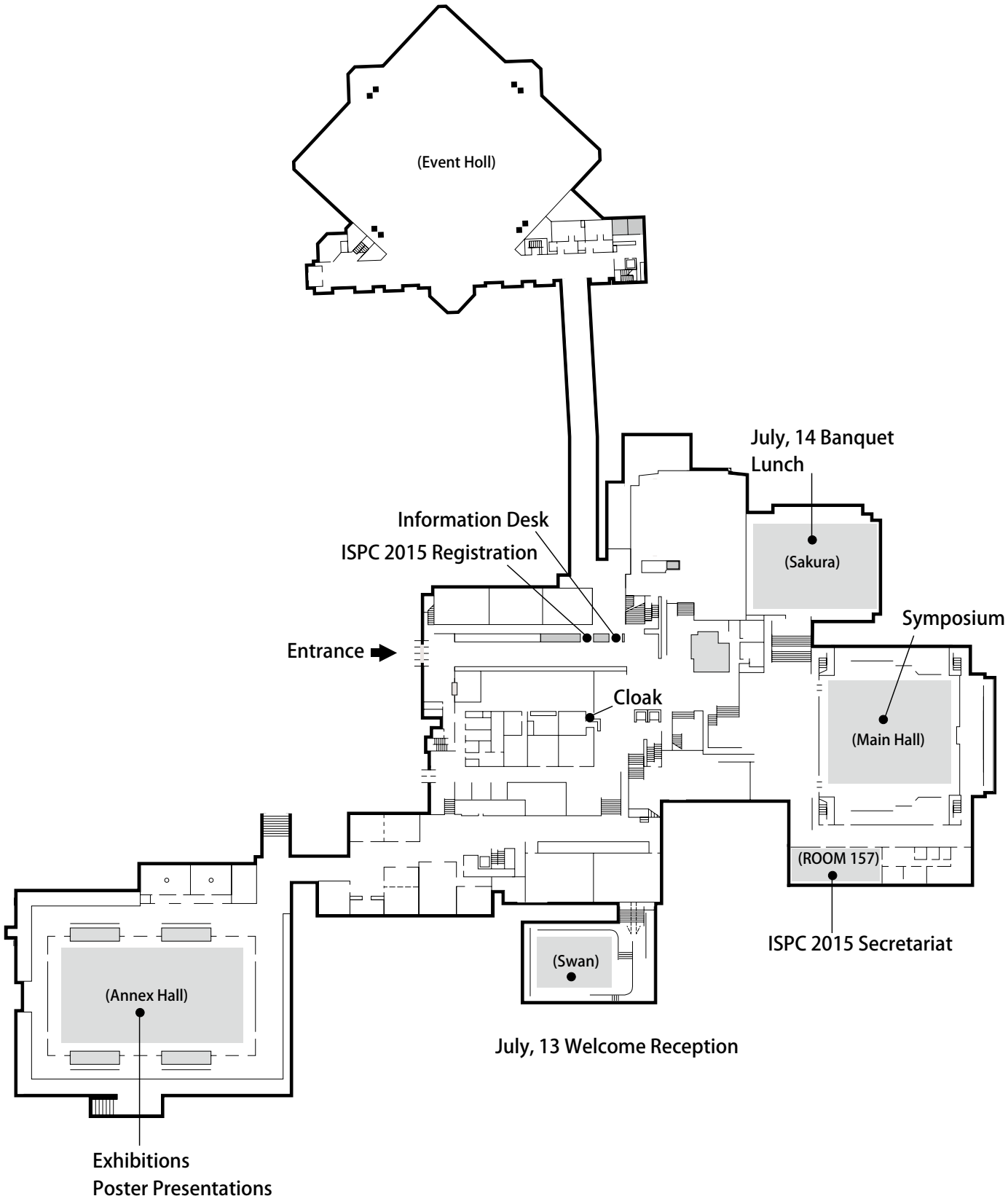
Subway Line

ICC Kyoto Subway Line

Kyoto International Conference Center



Floor Plan


(Event Holl)
July, 14 Banquet
Lunch
(Sakura)
Information Desk
ISPC 2015 Registration
Entrance
Symposium
Cloak
(Main Hall)
(ROOM 157)
ISPC 2015 Secretariat
(Swan)
July, 13 Welcome Reception
(Annex Hall)
Exhibitions
Poster Presentations

Poster Floor Layout

Annex Hall

POSTER SESSION

1P-01	2P-08	1P-09	2P-16	1P-17	2P-24	1P-25	2P-32	1P-33	2P-40	1P-41	2P-48	1P-49	2P-56	1P-57	2P-64
2P-01	1P-08	2P-09	1P-16	2P-17	1P-24	2P-25	1P-32	2P-33	1P-40	2P-41	1P-48	2P-49	1P-56	2P-57	
1P-02	2P-07	1P-10	2P-15	1P-18	2P-23	1P-26	2P-31	1P-34	2P-39	1P-42	2P-47	1P-50	2P-55	1P-58	2P-63
2P-02	1P-07	2P-10	1P-15	2P-18	1P-23	2P-26	1P-31	2P-34	1P-39	2P-42	1P-47	2P-50	1P-55	2P-58	1P-63
1P-03	2P-06	1P-11	2P-14	1P-19	2P-22	1P-27	2P-30	1P-35	2P-38	1P-43	2P-46	1P-51	2P-54	1P-59	2P-62
2P-03	1P-06	2P-11	1P-14	2P-19	1P-22	2P-27	1P-30	2P-35	1P-38	2P-43	1P-46	2P-51	1P-54	2P-59	1P-62
1P-04	2P-05	1P-12	2P-13	1P-20	2P-21	1P-28	2P-29	1P-36	2P-37	1P-44	2P-45	1P-52	2P-53	1P-60	2P-61
2P-04	1P-05	2P-12	1P-13	2P-20	1P-21	2P-28	1P-29	2P-36	1P-37	2P-44	1P-45	2P-52	1P-53	2P-60	1P-61

Drink Service

Resting place

Information

EXHIBITION

ENT ENT ENT ENT ENT

The 3rd International Symposium on Process Chemistry [ISPC 2015]

Program

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

July 13 (Mon)

15:30-17:00 **Registration**

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

July 14 (Tue)

8:30 **Registration**

9:00- 9:10 **Opening Remarks**

Kiyoshi Tomioka

(Chairman of ISPC 2015, Doshisha Woman's College of Liberal Arts., Japan)

9:10- 9:50 **Important Asymmetric and Catalytic Transformations for Drug**

K-1 **Development**

(Keynote Lecture) **Chris Senanayake** *(Boehringer Ingelheim Pharmaceuticals Inc., USA)*

Chair: Kazuhiko Takahashi *(Sumitomo Dainippon Pharma, Japan)*

9:50-10:30 **Understanding Reaction Kinetics for Optimization and Scale-up of API**

K-2 **Synthesis Steps**

(Keynote Lecture) **Steve Cropper** *(Scale-up Systems Ltd., Ireland)*

Chair: Yasuyuki Kita *(Ritsumeikan Univ., Japan)*

10:30-10:45 **Break**

10:45-11:25 **Application of Chiral Technologies in the Synthesis of Pharmaceutical**

K-3 **Intermediates**

(Keynote Lecture) **Vilas H. Dahanukar** *(Dr. Reddy's Laboratories Ltd., India)*

Chair: Kozo Shishido *(Tokushima Univ., Japan)*

11:25-12:05 **Helical Macromolecular Catalysts for Next-Generation Catalytic**

K-4 **Asymmetric Synthesis**

(Keynote Lecture) **Michinori Suginome** *(Kyoto University, Japan)*

Chair: Toshiro Konoike*(Osaka Synthetic Chemical Laboratories, Japan)*

12:05-13:00 **Lunch** *(Banquet Hall Sakura)*

13:00-13:25 **General Assembly of JSPC** *(in Japanese)*

13: 25-14:50 **Oral Presentation** *(10 min each)*

(1P-01, 1P-06, 1P-07, 1P-08, 1P-35, 1P-36, 1P-46, 1P-55)

Chair: Makoto Michida *(Daiichi Sankyo, Japan)*

Chair: Keiji Ohno (Wako, Japan)

14:50-15:50 **Poster Presentation (1P-01~1P-63) (Annex Hall)**

Chair: Yasumasa Hayashi *(Astellas, Japan)*

Chair: Osamu Yamada *(Nissan Chemical, Japan)*

15:55 -16:35 **Challenges in the Development of Processes for Chiral Drugs**

K-5 **Mukund Gurjar** *(Emcure, India)*

(Keynote Lecture) *Chair:* Kin-ichi Tadano *(Keio Univ., Japan)*

16:35-17:15 **Process Design with the End in Mind: Development of Omecamtiv**

K-6 **Mecarbil, a Novel Cardiac Myosin Activator**

(Keynote Lecture) **Shawn D. Walker** *(Amgen, Inc., USA)*

Chair: Hironao Sajiki (Gifu Pharm. Univ., Japan)

17:15-17:55 **Asymmetric Counteranion Directed Catalysis (ACDC): A General**

K-7 **Approach to Enantioselective Synthesis**

(Keynote Lecture) **Benjamin List** *(Max-Planck-Institut für Kohlenforschung, Germany)*

Chair: Takayuki Shioiri *(Nagoya City Univ., Japan)*

18:10-20:40 **Banquet** *(Banquet Hall Sakura)*

Welcome Address: Kiyoshi Tomioka

(President of JSPC, Doshisha Women's College of Liberal Arts, Japan)

July 15 (Wed)

9:00- 9:40 **Commercial Applications of Continuous Process in SK.**

K-8 **Jun-ku Park** *(SK Biotek Co., Ltd., Korea)*

(Keynote Lecture) *Chair:* Katsuya Tagami *(Eisai, Japan)*

9:40-10:20 **The Synthesis of Novel Pharmaceuticals**

K-9 **David M Tschaen** *(Merck, USA)*

(Keynote Lecture) *Chair:* Toshiaki Mase *(Institute Molecular Science, Japan)*

10:20 -10:35 **Break**

10:35 -11:15 **Dasotraline: From Laboratory to Commercial-Scale Manufacture**

K-10 **Robert Prytko, Charles Vandenbossche** *(Sunovion Pharmaceutical Inc., USA*)

(Keynote Lecture) *Chair:* Toshihisa Kato *(Ajinomoto, Japan)*

11:15-11:55 **Some Examples of Industrial Process Development Challenges**

K-11 **Stéphane Varray** *(Lonza AG,Switzerland)*

(Keynote Lecture) *Chair:* Minoru Okada *(Astellas, Japan)*

11:55-12:55 **Lunch** *(Banquet Hall Sakura)*

12:55-14:20 **Oral Presentation** *(10 min each)*

(2P-01, 2P-15, 2P-20, 2P-40, 2P-44, 2P-48, 2P-62, 2P-63

Chair: Takashi Inaba *(JT, Japan)*

Chair: Osamu Onomura *(Nagasaki Univ., Japan)*

14:20-15:20 **Poster Presentation (2P-01~2P-64)** *(Annex Hall)*

Chair: Taro Kiyoto *(Toyama Chemical, Japan)*

Chair: Norihiko Tanimoto *(Shionogi, Japan)*

15: 25-16:05 **Development of New Catalytic System for C-H Arylation and**

K-12 **Application to Synthesis of Pharmaceuticals**

(Keynote Lecture) **Masahiko Seki** *(API Corporation, Japan)*

Chair: Masahiro Ohshima *(Mitsubishi Tanabe, Japan)*

16:05-16:45 **Methodologies toward Efficient Synthesis of Chiral Natural Products**

K-13 **and Drugs**

(Keynote Lecture) **Wenjun Tang**

(Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China)

Chair: Masaru Mitsuda *(Kaneka, Japan)*

16:45-17:25 **A Few of My Favorite Rings: Catalytic Cycles Inspired by Macrocycles**

K-14 **Vy M. Dong** *(University of California, Irvine, USA)*

(Keynote Lecture) *Chair:* Takahiko Akiyama *(Gakushuin Univ., Japan)*

17:25-17:30 **Release of JSPC Awardees for Excellence 2015**

17:30-17:35 **Closing Remarks**

Toshiro Konoike *(Osaka Synthetic Chemical Laboratories, Japan)*

Poster Program

Poster Program

July 14 (Tue)

Oral Presentation 13:25-14:50 (Main Hall) ◆ Oral Presenter
Discussion 14:50-15:50 (Annex Hall)

1P-01 ◆ **Highly Practical New Methylenation Reagent for Aldehydes and Ketones**
Kaori Ando*, Takahisa Kobayashi, Nariaki Uchida (Gifu University, Japan)

1P-02 **Novel oxidation process for alcohols and sulfur compounds by sodium hypochloride pentahydrate($NaOCl \cdot 5H_2O$) crystals**
Tomohide Okada* (Nippon Light Metal, Japan) , Masayuki Kirihara (Shizuoka Institute of Science and Technology, Japan) , Yoshikazu Kimura (Iharanikkei Chemical Industry, Japan)

1P-03 **Enantioselective Synthesis of Optically Active Sultams Using *N*-Heteroarenesulfonyl Cinchona Alkaloid Amide Catalyst.**
Ayaka Toda*, Masahide Sano, Shuichi Nakamura
(Graduate School of Engineering, Nagoya Institute of Technology, Japan)

1P-04 **HasA Asymmetric Oxidation Catalysis from pea (*SanCat-R*)**
Hiroyuki Nagaoka* (Sanyo Foods, R & D, Japan)

1P-05 **Development of A Highly Active Iron Catalyst for Transesterification**
Rikiya Horikawa*, Chika Fujimoto, Ryo Yazaki, Takashi Ohshima (Kyushu University, Japan)

1P-06 ◆ **Enantioselective and Aerobic Oxidative Coupling of 2-Naphthol Derivatives Using Chiral Dinuclear Vanadium Complex in Water**
Makoto Sako*, Shinobu Takizawa, Yasushi Yoshida, Hiroaki Sasai (Osaka University, Japan)

1P-07 ◆ **Regio- and stereoselective synthesis of scaffolds for differentially all-carbon tetrasubstituted olefins**
Masataka Ide*, Tetsuo Iwasawa (Ryukoku University, Japan)

1P-08 ◆ **Process Research in NMR Tube**
Atsushi Akao*, Yumi Asai, Takashi Hasebe (Eisai Product Creation Systems, Japan)

1P-09 **Disiloxane Synthesis Based on Silicon-Hydrogen Bond Activation Using Platinum Group Metal on Carbon in Water and Heavy Water**
Yoshinari Sawama, Masahiro Masuda*, Ryosuke Nakatani, Shumma Nishimura, Kyoshiro Shibata, Tsuyoshi Yamada, Yasunari Monguchi, Hironao Sajiki
(Gifu Pharmaceutical University, Japan)

1P-10 **Palladium on carbon-catalyzed and chemoselective oxidation of aromatic acetals**
Yoshinari Sawama, Naoki Yasukawa*, Shota Asai, Yasunari Monguchi, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

1P-11 **Palladium-catalyzed synthesis of enol ethers by the direct alkoxylation of acrylic acids**
Koki Kunishima*, Tomohiro Hattori, Tohru Takahashi, Yuko Shishido, Yoshinari Sawama, Yasunari Monguchi, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

1P-12 **Nickel-Catalyzed Deuteration of Phenol Derivatives with Novel NHC Ligands**
Shota Kujirada*, Masami Kuriyama , Osamu Onomura
(Graduate School of Biomedical Sciences, Nagasaki University, Japan)

1P-13 **Selective deprotection of silyl ethers with SO_3H silica gel in the presence of acid-sensitive protecting group**
Hideaki Fujii*, Miki Kuwada, Saki Tajiri, Misaki Kanda, Mari Yanai, Kennosuke Itoh (Kitasato University, Japan), Mitsuhiro Kamimura (FUJI SILYSIA CHEMICAL, Japan)

1P-14 **Tautomerization of 5-Alkylidene-2-Oxazolidinone to 2-Oxazolone by Use of an N-Heterocyclic Carbene Catalyst**
Ken-ichi Fujita*, Hiroyuki Yasuda (National Institute of Advanced Industrial Science and Technology, Japan) , Junichi Sato (Ibaraki University, Japan)

1P-15 **Ethoxylation of *p*-Fluoronitrobenzene Using Phase-Transfer Catalysts by Microreactor Technology.**
Hajime Mori*, Akane Tsuchitani, Megumi Mori, Yoshie Tanaka
(Industrilal Technology Center of Wakayama Prefecture, Japan)

1P-16 **Study on Selective Synthesis of 1-Ethoxy-2,4-dinitrobenzene Under Phase-Transfer Conditions by Microreactor Technology**
Akane Tsuchitani*, Hajime Mori, Megumi Mori, Yoshie Tanaka
(Industrilal Technology Center of Wakayama Prefecture, Japan)

1P-17 **Considerations for the Validation of Quantitative NMR**
Takako Suematsu*(JEOL RESONANCE Inc., Japan), Shinji Nakao, Toru Miura, Shinya Takaoka, Yuko Yamada (Wako Pure Chemical Industries, Ltd., Japan)

1P-18 **Sodium Borohydride Reduction: A Sustainable PAT System for Safe Operation**
Yuki Hara*(Mettler-Toledo K.K., Japan), Dr. John O'Reilly, Frank Neville, Brian Coffey, Martin Cronin, Maria Lennonhe, Barry Reid, Andy McInerney
(Roche Pharmaceuticals, Cork Ireland)

1P-19 **EasySampler^{TM} 1210: Unattended, Representative Sampling**
Ryoichi Sugimoto*, Hiroki Takai, Yoshifumi Fujisawa, Yuki Hara
(Mettler-Toledo K.K., Jpana)

1P-20 **Development of a Practical and Scalable Synthesis of TRPA1 Receptor Activator, ASP7663**
Koji Kobayashi*, Ryoki Orii, Toshiyuki Sugimori, Takumi Takahashi, Atsushi Oohigashi, Minoru Okada (Process Chemistry Labs., Process Research, Astellas Pharma Inc., Japan)

1P-21 **Ligand-free Suzuki-Miyaura reaction of chloroarenes catalyzed by anion exchange resin-supported palladium**
Tomohiro Ichikawa*, Moeko Netsu, Tomohiro Hattori, Yoshinari Sawama, Yasunari Monguchi, Hironao Sajiki (Gifu Pharmaceutical University, Japan), Tomoteru Mizusaki (N.E. Chemcat Corporation, Japan)

1P-22 **Enantioselective Three-Component Synthesis of Propargylamines Accompanied by the Dehydration in Water**
Yoshichika Hara*, Mutsuyo Ohara, Shuichi Nakamura (Nagoya Institute of Technology, Japan)

1P-23 **Novel ESIPT fluorescent dyes with adjustable optical properties**
Kew-Yu Chen*, Hsing-Yang Tsai (Feng Chia University, Taiwan)

1P-24 **Protecting Group-Free Catalytic Synthesis of Sialic Acids**
Xiaofeng Wei*, Yohei Shimizu (The University of Tokyo, Japan), Motomu Kanai (The University of Tokyo; ERATO, Japan Science and Technology Agency, Kanai Life Science Catalysis Project, Japan)

1P-25 **Palladium-Catalyzed Three-Component Reaction of 3-(Pinacolatoboryl)ally Acetates, Aldehydes, and Organoboranes**
Yoshikazu Horino*, Ataru Aimono, Hitoshi Abe (University of Toyama, Japan)

1P-26 **Continuous multi-step synthesis of a benzofuran analogue under hidden brønsted acid catalysis using a microwave flow system**
Keiji Nakayama, Kazutoshi Ukai, Toshiyuki Tomoo, Yoshitaka Nakamura* (DAIICHI SANKYO CO., LTD., Japan)

1P-27 **Highly sensitive analytical method development for mutagenic impurities with the similar structures among them**
Nobuhiro Oba*, Mari Kayamori, Kazuki Shigemori, Meiko Tanaka, Miwako Asada, Kanako Kondo, Hiroaki Kataoka, Takashi Nihei, Jumpei Fujiyoshi, Tetsuhiro Yamamoto, Makoto Noguchi (Chemical Development Laboratories, CMC center, Takeda Pharmaceutical Company, Ltd., Japan)

1P-28 **Palladium-Catalyzed Three-Component Reaction of 3-(Tributylstannyl)ally Acetates, Aldehydes, and Organoboranes: A New Entry to Stereoselective Synthesis of *(E)-anti*-Homoallylic Alcohols**
Yoshikazu Horino, Miki Sugata*, Hitoshi Abe (University of Toyama, Japan)

1P-29 **Palladium-Catalyzed Multi-Component Reaction of 3-(Tributylstannyl)propargyl Acetates, Aldehydes, and Organoboranes**
Yoshikazu Horino, Ataru Aimono*, Hitoshi Abe (University of Toyama, Japan)

1P-30 **Efficient Gas-related Photo Reactions Using Micro- and Nanobubble Strategy Under Atmospheric Pressure**
Yuki Nishina*, Kohei Sato, Tetsuo Narumi, Naoharu Watanabe, Nobuyuki Mase (Shizuoka University, Japan)

1P-31 **Identification of Superior Organocatalysts Through High-Throughput Fluorescence-Based Screening**
Tsuguya Masuda*, Kohei Sato, Tetsuo Narumi, Naoharu Watanabe, Nobuyuki Mase (Shizuoka University, Japan)

1P-32 **Hydrolysis of Diazonium Salts Using Two-phase (CPME and Water)**
Toshihide Taniguchi*, Mitsutaka Imoto, Motonori Takeda (Seika Corporation, Japan), Takeo Nakai, Masatoshi Mihara, Toshiyuki Iwai, Takatoshi Ito, Takumi Mizuno (Osaka Municipal technical Research Institute, Japan), Akihiro Nomoto, Akiya Ogawa (Osaka PrefectureUniversity, Japan)

1P-33 **One-pot Transformation of Aliphatic Carboxylic Acids into *N*-Alkylsuccinimides**
Yuta Nakai*, Katsuhiko Moriyama, Hideo Togo (Graduate School of Science, Chiba Univ., Japan)

1P-34 **Homogeneous Ruthenium-Catalyzed Hydrogenation Using a Continuous Flow Reactor**
Naota Yokoyama*, Kiyoto Hori, Hideki Nara, Mitsuhiko Fujiwhara
(Takasago International Corporation, Japan)

1P-35 ◆ **Improvements in a Practical and Scalable Synthesis of Selective ALK Kinase Inhibitor ASP3026, Utilizing Readily Available Cyanuric Chloride as a Starting Material**
Kazuyoshi Obitsu*, Shun Hirasawa, Kazuhiro Takeguchi, Koji Kobayashi, Takahiro Akiba, Yuji Takahama, Ryoki Orii, Takumi Takahashi, Shigeru Ieda, Minoru Okada (Astellas Pharma Inc., Japan)

1P-36 ◆ **Root Cause Analysis of Uncontrollable Polymorph–Inhibition of a Trace Amount of Impurity in Selective ALK Inhibitor ASP3026–**
Yuji Takahama*, Kazuhiro Takeguchi, Kazuyoshi Obitsu, Norihiro Ueda, Ryoki Orii, Atsushi Ohigashi, Shigeru Ieda, Minoru Okada (Astellas Pharma Inc., Japan)

1P-37 **New Conceptual Diaryliodonium Salts for Metal-Free Arylation of Carboxylic Acids Giving Aryl Esters**
Toshifumi Dohi*, Kohei Sumida, Asami Kato, Kazuki Samura, Koji Morimoto, Yasuyuki Kita (Ritsumeikan University, Japan)

1P-38 **Chromatographic Separation of Stereoisomer Compounds**
Mari Hara Yasuda*, Shingo Andou, Masao Tamura (Mitsubishi Chemical Corporation, Japan), Tatsuma Fukumoto, Keiichi Uchibayashi (API Corporation, Japan), Zachary S. Breitbach, Daniel W. Armstrong (AZYP LLC, USA)

1P-39 **Performance Assessment of Cyclopentyl Methyl Ether (CPME): Application to Grignard Reactions**
Keisuke Shibukawa*, Araki Masuyama, Shoji Kobayashi
(Osaka Institute of Technology, Japan)

1P-40 **Efficient Synthesis of Chiral Diaminonitriles Using Chiral Bis(imidazoline)-Pd Catalysts**
Masaru Kondo*, Tomoki Nishi, Shuichi Nakamura (Nagoya Institute of Technology, Japan)

1P-41 **Conformational Studies of Symmetric Diesters**
Satomi Niwayama*(Muroran Institute of Technology, Japan, Texas Tech University, USA), Mai Kato, Yukiko Yamaguchi (Muroran Institute of Technology, Japan), Hanjoung Cho (Texas Tech University, USA)

1P-42 **Development of an Optimized Synthetic and Purification Process of S-2367 (Velneperit), a Novel Neuropeptide Y (NPY) Y5 Receptor Antagonist**
Shinichi Oda*, Kumiko Manaka, Kiyoshi Kakiya, Yasuyuki Hozumi, Yuki Fukui, Sohei Omura, Makoto Kurashita, Masanori Nishiwaki, Yoshiyuki Takeuchi and Hideyuki Kitamura (Shionogi & Co., Ltd, Japan)

1P-43 **Convenient and regioselective synthesis of biaryl compounds by heterogeneously catalyzed aerobic oxidative coupling**
Kenji Matsumoto*, Mitsuru Shindo (Institute for Materials Chemistry and Engineering, Kyushu University, Japan), Shohei Tachikawa, Shigenobu Fujimoto (Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Japan)

1P-44 **Application of Asymmetric Transfer Hydrogenation and H_2-Hydrogenation Catalyzed by Oxo-tethered Ruthenium(II) Complex**
Taichiro Touge*, Yamato Yuki, Hideo Shimizu, Hideki Nara, Mitsuhiko Fujiwhara
(Takasago International Corporation, Japan)

1P-45 **Process Intensification for the Continuous Flow Hydrogenation of Ethyl Nicotinate**
Takashi Ouchi* (Takeda Pharmaceutical Company Limited, Japan),
Claudio Battilocchio, Steven V. Ley (University of Cambridge, UK)

1P-46 ◆ **Total Synthesis of Prostaglandin E_1 Methyl Ester by Three One-pot Operations**
Yujiro Hayashi*, Shigenobu Umemiya (Tohoku University, Japan)

1P-47 **Studies of the peptide crystal form and its process development for commercial production**
Ryosuke Kunitani*, Aiko Hasegawa, Yoshinori Murata (Shionogi & Co., Ltd., Japan)

1P-48 **Total solution for the HPLC method development process by ChromSword software**
Kazuhide Konishi* , Sergey Galushko (ChromSword Japan Co., Ltd., Japan)

1P-49 **Study on Preparation of 5-Trifluoromethylated Pyrimidine Derivatives**
Takumi Kagawa*, Daiki Shigehiro, Kosuke Kawada (Tosoh F-tech, Inc., Japan)

1P-50 **Copper Complex Catalyzed Asymmetric Monosulfonylation of Glycerol**
Keisuke Miyamoto*, Masami Kuriyama, Osamu Onomura (Nagasaki University, Japan)

1P-51 **Intramolecular coupling method for stereo- and regio-controlled procyanidin synthesis**
Akiko Saito (Osaka Electro-communication University, Japan),
Noriyuki Nakajima* (Toyama Prefectural University, Japan)

1P-52 **A Novel Synthesis of α,α-Disubstituted α-Amino Acids by S_N2 Displacement at the Quaternary Carbon Center**
Kotaro Ishihara*, Hiromi Hamamoto, Masato Matsugi, Takayuki Shioiri
(Faculty of Agriculture, Meijo University, Japan)

1P-53 **Preparation of Unique Copper Complexes of Porphyrin and the Application to Photooxidation of Phenol Derivatives**
Yuko Takao*, Fukashi Matsumoto, Kazuyuki Moriwaki, Takumi Mizuno,
Toshinobu Ohno (Osaka Municipal Technical Research Institute, Japan),
Jun-ichiro Setsune (Kobe University, Japan)

1P-54 **New type of Silica Gel for Hydrophilic Interaction Chromatography (HILIC)**
Makoto Kawai*, Tomio Yamakoshi, Hirofumi Honda (Fuji Silysia Chemical Ltd., Japan)

1P-55 ◆ **Development of highly active iridium catalysts for reductive amination of carbonyl compounds**
Kouichi Tanaka*, Kunihiko Tsutsumi, Kunihiko Murata, Masahito Watanabe
(Kanto Chemical Co., Inc, Japan)

1P-56 **Reclamation of squid pen for the production of chitosanase and dye biosorbent by *Bacillus cereus***
Tzu-Wen Liang*, Bo-Chang Lo, San-Lang Wang (Tamkang University, Taiwan)

1P-57 **Ru-MACHO, 'Gentle' catalytic ester reduction and beyond**
Osamu Ogata*, Kiyoto Hori, Wataru Kuriyama, Kunimori Aoki, Hideki Nara
(Takasago International Corporation, Japan)

1P-58 **Cancelled**

1P-59 **Practical Asymmetric Hydrogenation of Sterically Congested Aromatic Ketones with Polysubstituents on Aromatic Rings**

Takeaki Katayama*, Kunihiko Murata, Kunihiko Tsutsumi (KANTO CHEMICAL Co., Inc., Japan), Noriyoshi Arai, Takanori Nanba, Takeshi Ohkuma (Hokkaido University, Japan)

1P-60 **Cycle Time Reduction for an Intermediate Crystallization Step Using a New Image-Based PAT Technique**

Hiroki Takai*, Des O'Grady, Terry Redman (Mettler-Toledo, Japan)

1P-61 **Synthetic Studies toward (+)-CJ-12,950 for the Stereochemical Assignment**

Yoshihito Oguma*, Takumi Yamagishi, Nozomi Yamamoto, Sho Shinoda, Kenji Sugimoto, Daishiro Minato, Yuji Matsuya (University of Toyama, Japan)

1P-62 **Trifluoromethylation using Fluoroform through Catalytic Amount of Phosphazene Base**

Satoshi Okusu*, Kazuki Hirano, Etsuko Tokunaga, Norio Shibata (Nagoya Institute of Technology, Japan)

1P-63 **Lonza MRT / Flow Technology Applied to Innovative Chemistry**

Dominique M.Roberge , Stéphane Varray*(Lonza AG, Switzerland), Daisuke Tanaka (Lonza Japan Ltd., Japan)

July15 (Wed)

Oral Presentation 12:55-14:20 (Main Hall) ◆ Oral Presenter
Discussion 14:20-15:20 (Annex Hall)

2P-01 ◆ **A robust and efficient process of the HCV protease inhibitor key intermediate**
Kohei Mori*, Narumi Kishimoto, Daisuke Moriyama, Akira Nishiyama, Masaru Mitsuda (Kaneka Coporation, Japan)

2P-02 **Nitroxyl Radical and Imide Dual Catalyzed NaOCl Oxidation of Alcohols and the Application to a Drug Candidate**
Naohiro Fukuda*, Tomomi Ikemoto (Takeda Pharmaceutical Company Limited, Japan)

2P-03 **Synthetic Study for Aristolochic Acids and its Derivatives**
Toshihide Maki*, Satoshi Mizuta (Nagasaki University, Japan), Paul Njihia Gichuhi (Technical University of Mombasa, Kenya), Malik Suliman Mohamed (University of Khartoum, Sudan)

2P-04 **Kinetic Resolution of Secondary Alcohols by Chiral Phosphoric Acid Catalyt**
Shingo Harada, Satoru Kuwano, Yousuke Yamaoka, Ken-ichi Yamada, Kiyosei Takasu* (Kyoto University, Japan)

2P-05 **Fermentation of squid pen for the production of tyrosinase inhibiors and insecticidal materials**
Chia-Hao Hsu*, San-Lang Wang (Tamkang University, Taiwan)

2P-06 **Recyclable and Recoverable Magnetic Nanoparticle-Supported Iodoarene Catalysts for Oxidation of 4-Alkoxyphenols to Quinones**
Ikumi Shimokawa*, Hisanori Nambu, Tomoya Fujiwara, Takayuki Yakura (Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Japan)

2P-07 **Microbial reclamation of squid pen and shrimp shell**
San-Lang Wang*, Tzu-Wen Liang (Department of Chemistry/Life Science Development Center, Tamkang University, Taiwan)

2P-08 **Development of acid-catalyzed alkylating reagents based on triazine chemistry**
Naoko Hayakawa*, Kohei Yamada, Hikaru Fujita, Masanori Kitamura, Munetaka Kunishima (Kanazawa University, Japan), Kazuma Yoshimura (NARD CHEMICALS, LTD., Japan)

2P-09 **One-Pot Transformation of Arenes into Aromatic Nitriles under Metal-Cyanide-Free Conditions**
Toshiyuki Tamura*, Katsuhiko Moriyama, Hideo Togo (Graduate School of Science, Chiba University, Japan)

2P-10 **Development of standard solutuions for qNMR**
Toru Miura*, Shinji Nakao, Yuko Yamada (Wako Pure Chemical Industries, Ltd., Japan), Takashi Ohtsuki, Atsuko Tada, Maiko Tahara, Naoki Sugimoto (National Institute of Health Science, Japan), Taichi Yamazaki, Takeshi Saito, Toshihide Ihara (National Metrology Institute of Japan), Takako Suematsu (JEOL Resonance Inc., Japan), Takaaki Horinouchi, Ryo Koike (Kao Corporation, Japan)

2P-11 **Revisiting Acetyl Group Technology: Lipase-catalyzed Regioselective Transformation of Polyphenols**
Kazuki Yashiro*, Susanta Mandal, Shun Hanamura, Kengo Hanaya, Mitsuru Shoji, Takeshi Sugai (Keio University, Japan)

2P-12 **Robust and Competitive Process Development of a Key Building Block for Anti-AIDS Drugs by Secondary Amine Catalyzed Enantio- and Diastereo-Selective Direct Cross Aldol Reaction**
Yumi Hayashi*, Toshiaki Aikawa, Hiroaki Okamoto, Yasuharu Shimasaki, Yosuke Tomioka, Takashi Miki, Masahiro Takeda, Tetsuya Ikemoto (Sumitomo Chemical Co., Ltd., Japan)

2P-13 **Synthesis of the GHI Fragment of Gymnocin-B**
Shota Kato*, Yoshinori Hadano, Takeo Sakai, Yuji Mori (Faculty of Pharmacy, Meijo University, Japan)

2P-14 **Addition Reactions to Isoquinolium Salts Catalyzed by Tetracyanocyclopentadienides**
Mai Hattori*, Akari Tada, Junpei Matsuoka, Takeo Sakai, Yuji Mori (Faculty of Pharmacy, Meijo University, Japan)

2P-15 ◆ **Highly Efficient and Chemoselective Aerobic Oxidation of Alcohols Using AZADO-Copper Catalysis**
Shota Nagasawa*, Yusuke Sasano, Naoki Kogure, Masatoshi Shibuya, Yoshiharu Iwabuchi (Graduate School of Pharmaceutical Sciences, Tohoku University, Japan)

2P-16 **Development of the Synthetic Process for the Naltrexamine Derivatives**
Masanori Murakami*, Takami Kanno, Tatsuya Fujita (Toray Industries, Inc., Japan)

2P-17 **Metal-free C(3)-H arylation of coumarins promoted by catalytic amounts of 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin**
Masahiro Kojima*, Kounosuke Oisaki, Motomu Kanai (The University of Tokyo, Japan)

2P-18 **Development of a Practical & Scalable Synthesis of Cyclic Oligopeptide AS1895286-00**
Ryoki Orii*, Hiroyoshi Matsubara, Minoru Okada (Astellas Pharma Inc., Japan)

2P-19 **Stereoselective Synthesis of *cis*-α,β-Unsaturated Sulfones Using New Peterson Reagents**
Tomohiro Wada*, Miho Okumura, Hiroshi Sumida, Kaori Ando (Gifu University, Japan)

2P-20 ◆ **Stereoselective Intramolecular Cross-aldol and Desymmetrization of Aliphatic Dials Enabled by Axially Chiral Aniline-type Catalyst**
Tomonori Baba, Ramesh Yella*, Yuya Tanaka, Satoru Yamamoto, Takumi Furuta, Takeo Kawabata (Institute for Chemical Research, Kyoto University, Japan)

2P-21 **Stereiselective Synthesis of *cis*-α,β-Unsaturated sulfonates Using New Peterson Reagents**
Kensuke Fujimoto*, Kaori Ando (Gifu University, Japan)

2P-22 **Syntheses of (1-propynyl)arenes: One-Pot Dephosphorylation and Sonogashira Coupling of Phosphorylpropyne**
Akihiro Orita, Kenta Shinohara*, Takanori Nishida, Lifeng Peng, Ryosuke Wada, Junzo Otera (Okayama University of Science, Japan)

2P-23 **Asymmetric Synthesis of 2-Substituted Dihydroquinolones by The Aza-Michael Reaction of *N*-Unprotected Amines**
Yuka Moriya*, Kodai Saito, Takahiko Akiyama (Gakushuin University, Japan)

2P-24 **One-pot synthesis of β,β-disubstituted α,β-unsaturated carbonyl compounds using sequential Ti-aldol addition to ketones and elimination**
Yasuhiko Ashikari*, Makoto Nakajima, Masaharu Sugiura (Kumamoto University, Japan)

2P-25 **Preparation of Optically Active Thioamides and Evaluation of Their Antibacterial Properties**
Yasutaka Shimotori*, Masayuki Hoshi, Ayana Aiki, Asami Morisawa
(Kitami Institute of Technology, Japan), Tetsuo Miyakoshi (Meiji University, Japan),
Taisei Kanamoto, Hideki Nakashima (St. Marianna University School of Medicine, Japan)

2P-26 **Syntheses of 1,3,6,8-Tetra-substituted Pyrenes and Steric Effect of Substituents on Their Photoluminescence**
Akihiro Orita, Takanori Nishida*, Feng Xu, Kenta Shinohara, Issei Kasuga,
Junzo Otera (Okayama University of Science, Japan)

2P-27 **Development of Novel Synthetic Methods of *N,Se*-Acetals by Highly Regioselective Hydroselenation of *N*-Vinyl Lactams**
Taichi Tamai*, Megumi Yoshikawa, Shinya Higashimae, Akiya Ogawa
(Osaka Prefecture University, Japan)

2P-28 **A Novel Approach to the Characterization of Pharmaceutical Drugs Within Processes using Morphologically Directed Raman Spectroscopy**
Cathryn Langley*, Daisuke Sasakura, Aiko Hayauchi, Deborah Huck-Jones
(Malvern Instruments, Japan & UK)

2P-29 **A Process Analytical Technology (PAT) Approach Using Online Mass Spectrometry to Evaluate Drying Process and Control Oxygen Generation**
Shoji Watanabe*, Atsushi Ueno, Takayuki Miyake (Sumitomo Dainippon Pharma Co., Ltd., Japan)

2P-30 **Organocatalytic site-selective acylation of polyol natural products**
Masanori Yanagi*, Yoshihiro Ueda, Takumi Furuta, Takeo Kawabata
(Institute for Chemical Research, Kyoto University, Japan)

2P-31 **An Investigation of Drug Crystallization Process by in-situ Particle Size Analysis using Mie Scattering Theory and Morphological Analysis.**
Fumiaki Sato*, Aiko Hayauchi, Cathryn Langley,
Daisuke Sasakura (Malvern Instruments, A division of Spectris Co., Ltd., Japan)

2P-32 **Expeditious Parallel Syntheses of All (*E*)- and (*Z*)-Zimeridines and Tamoxifens Utilizing (*E*)-, (*Z*)-Stereocomplementary Synthesis of Multi-Substituted α,β-Unsaturated Esters**
Yuichiro Ashida, Yuka Sato, Atsushi Honda, Hidefumi Nakatsuji*, Yoo Tanabe
(Kwansei Gakuin University, Japan)

2P-33 **Tertiary Amine Thiourea-Catalyzed Aldol Reaction of Aryl Methyl Ketones with Aryl Trifluoromethyl Ketones**
Léopold Mpaka Lutete*, Takashi Miyamoto, Tetsuya Ikemoto
(Sumitomo Chemical Co., Ltd., Japan)

2P-34 **Sulfenylation of Aromatic Compounds with *N*-Sulfenylbenzimidazoles in the Presence of Alkylating Agents**
Masao Shimizu, Shinji Tanaka, Wataru Ando (National Insititute of Advanced Industrial Science and Technology(AIST), Japan), Shin-ya Suzuki*, Norio Sakai(Tokyo University of Science, Japan)

2P-35 **Synthesis of pyrrolo[1,2-*b*][1,2]benzothiazin-10-one**
Masao Shimizu, Shinji Tanaka, Wataru Ando (National Institute of Advanced Industrial Science and Technology (AIST), Japan), Kotaro Masuda*, Daisuke Kato, Norio Sakai (Tokyo University of Science, Japan)

2P-36 **Selective Flow Synthesis of Methanofullerene Derivative PCBM Using Sulfur Ylide**
Takatoshi Ito*, Fukashi Matsumoto, Toshiyuki Iwai, Kazuyuki Moriwaki, Yuko Takao, Takumi Mizuno, Toshinobu Ohno (Osaka Municipal Technical Research Institute., Japan), Yuta Inoue, Tetsuo Iwasawa (Ryukoku University.,Japan)

2P-37 **Continuous flow synthesis of methanofullerene PCBM**
Toshiyuki Iwai*, Fukashi Matsumoto, Kazuyuki Moriwaki, Yuko Takao, Takatoshi Ito, Takumi Mizuno, Toshinobu Ohno (Osaka Municipal Technical Research Institute, Japan), Junki Murata, Tetsuo Iwasawa (Ryukoku University, Japan)

2P-38 **Synthesis of PHB-b-PLA Block Copolymer Useful as the Compatibilizer in PHB/PLA Blends**
Trong-Ming Don*, Kuo-Hua Liao, Yi-Hsun Liu (Tamkang University, Taiwan)

2P-39 **Sulfenylation of Aromatic Compounds with *N*-Sulfenylbenzimidazoles in the Presence of Acid**
Masao Shimizu*, Shinji Tanaka, Wataru Ando (National Institute of Advanced Industrial Science and Technology, Japan), Miki Nakao, Shin-ya Suzuki, Norio Sakai (Tokyo University of Science, Japan)

2P-40 ◆ **Single-pass flow reactions: only 20 seconds hydrogenation and Suzuki-Miyaura reaction**
Tomohiro Hattori*, Aya Tsubone, Takashi Ida, Yoshinari Sawama, Yasunari Monguchi, Hironao Sajiki (Gifu Pharmaceutical University, Japan)

2P-41 **Thermal hazard and evolved gases analyses on an acrylic acid runaway polymerization**
Michiya Fujita*, Atsumi Miyake (Yokohama National University, Japan), Yoshiaki Iizuka (PHA consulting Co.,Ltd., Japan)

2P-42 **Living Radical Polymerization of Styrene by ATRP Initiator Immobilized on Glass Surfaces**
Kohji Iwaida*, Shun Ichii, Yu Masui, Toshiyuki Kamei, Toyoshi Shimada (Dept. Chem. Eng., NNCT, Japan), Kazuyoshi Kanamori, Kazuki Nakanishi (Grad. Sch. Sci., Kyoto Univ., Japan)

2P-43 **Tris(pentafluorophenyl)borane-Catalyzed Organofunctionalization of Various Materials with Hydrosilane Derivatives**
Shun Ichii, Kohji Iwaida, Yu Masui*, Toshiyuki Kamei, Toyoshi Shimada (Dept. Chem. Eng., NNCT, Japan), Kazuyoshi Kanamori, Kazuki Nakanishi (Grad. Sch. Sci., Kyoto Univ., Japan)

2P-44 ◆ **Design and operation of microreactor for heterogeneously catalyzedprocess - Case study with direct synthesis of hydrogen peroxide**
Tomoya Inoue*, Ming Lu, Kenichiro Ohtaki, Hirotada Hirama (UMEMSME, AIST, Japan)

2P-45 **Purification of biopharmaceuticals using small particle polymer media**
Shinya Nozaki*, Kazuhiko Tokunaga, Yoshito Fukuda, Noriyuki Yasuda, Shouhei Ohara, Tadashi Adachi (Separation Materials Laboratories, R&D center, Mitsubishi Chemical Corporation, Japan)

2P-46 **Second Generation Syntheses of Benzyl Piperidine Derivatives: A Key Intermediate for the Preparation of SERT/5-HT_{1A} Dual Inhibitor**
Yuji Fujiwara*, Atsushi Ueno, Nobuyuki Ae, Katsunari Shimomae, Hidefumi Yoshinaga, Hideo Terauchi, Koji Fujimoto (Sumitomo Dainippon Pharma Co.,Ltd., Japan)

2P-47 **Withdraw 2P-47**

2P-48 ◆ **Asymmetric α-Fluorination of Amino Acid Derivatives via Memory of Chirality**
Koji Kasamatsu*, Tomoyuki Yoshimura, Takeo Kawabata
(Institute for Chemical Research, Kyoto University, Japan)

2P-49 **Enantioselective construction of all-carbon quaternary stereogenic centers via lipase-catalyzed dynamic kinetic resolution**
Koji Sugiyama, Shinji Kawanishi*, Yasuhiro Oki, Shuji Akai (Osaka University, Japan)

2P-50 **Challenge to Prediction of Secondary Nucleation Rate Generated by Crystal Collisions with Impeller Blade Based on Lagrangian Simulation of Crystal Motion**
Ryuta Misumi*, Kazuhiko Nishi, Meguru Kaminoyama (Yokohama National University, Japan)

2P-51 **Optimized Conditions for the Aerobic Alcohol Oxidation Using Nitroxyl Radical/Copper Catalysis**
Naoki Kogure*, Yusuke Sasano, Tomohiro Nishiyama, Shota Nagasawa, Yoshiharu Iwabuchi (Tohoku University, Japan)

2P-52 **Syntheses and Properties of Substituted Sondheimer-Wong Diynes**
Akihiro Orita*, Feng Xu, Takanori Nishida, Kenta Shinohara, Shinya Ohta, Katsutoshi Tomiyama, Junzo Otera (Okayama University of Science, Japan)

2P-53 **Development of Novel Reagents for Electrophilic SF_5-arylation**
Kohei Matsuzaki*, Kenta Okuyama, Prajwalita Das, Etsuko Tokunaga, Norio Shibata (Nagoya Institute of Technology, Japan)

2P-54 **A Catalytic Synthetic Approach to HSD-016 Through Enantioselective Trifluoromethylation**
Yoshimasa Yasuda*, Satoshi Okusu, Norio Shibata
(Nagoya Institute of Technology, Japan)

2P-55 **Preparation of PVDF Membrane for Membrane Distillation**
Tung-Wen Cheng*, Jhih-Wei Lin (Tamkang University, Taiwan)

2P-56 **Novel Synthesis of Arylalkynes via α-Azidotetrazoles from Cyanophosphates**
Hiroki Yoneyama*, Masahiro Numata, Kenji Uemura, Yoshihide Usami, Shinya Harusawa (Osaka University of Pharmaceutical Sciences, Japan)

2P-57 **Catalyst-controlled diastereoselective hetero-Diels-Alder reactions catalyzed by chiral dirhodium(II) carboxamidates**
Takuro Suzuki*, Shun Satake, Fumiya Tanada, Masahiro Anada, Shunichi Hashimoto (Faculty of Pharmaceutical Sciences, Hokkaido University, Japan), Shigeki Matsunaga (Faculty of Pharmaceutical Sciences, Hokkaido University, Japan) (ACT-C, JST, Japan)

2P-58 **Potential Utility of BenzP* Ligand for the Production of Chiral Pharmaceutical Ingredients**
Tsuneo Imamoto*, Yumi Horiuchi, Ken Tamura, Masashi Sugiya (Nippon Chemical Industrial Co., Ltd., Japan), Qiupeng Hu, Zhenfeng Zhang, Yangang Liu, Wanbin Zhang (Shanghai Jiao Tong University, China)

2P-59 **Catalytic Transoximation to Aldehydes**
Naoki Oishi*, Kengo Hyodo, Kingo Uchida (Ryukoku Univserity, Japan)

2P-60 **Catalytic Asymmetric Synthesis of Chiral Pharmaceutical Ingredients Using QuinioxP*-Rh Complexes**
Yumi Horiuchi*, Yosuke Takubo, Ken Tamura, Masashi Sugiya, Tsuneo Imamoto (Nippon Chemical Industrial Co., Ltd., Japan), Kunjiao Yu, Zhenfeng Zhang, Xiaohong Huo, Xingguang Wang, Delong Liu, Wanbin Zhang (Shanghai Jiao Tong University, China)

2P-61 **Indole Synthesis from 2-Aminochalcone via Rearrangement Reaction**
Tomohiro Maegawa*, Chiaki Ohta, Kazuma Fujimura, Mina Kato,Sho Hattori, Akira Nakamura, Yasuyoshi Miki (School of Pharmaceutical Sciences, Kinki University, Japan), Hiromi Hamamoto (Faculty of Agriculture, Meijo University, Japan)

2P-62 ◆ **iChemExplorer: A Powerful Tool for Catalyst Screening and Probing the Catalytic Cycle**
Mark B. Mitchell*, Michael D. Lopez (Reaction Analytics Inc., USA)

2P-63 ◆ **Continuous Flow Reactors: An Opportunity for the development of flexible & sustainable production processes**
Charlotte Wiles* (Chemtrix BV, Netherlands, The University of Hull UK)

2P-64 **Development of a High-Throughput Chiral Column using Ovomucoid Protein**
Kosuke Fukuzawa*, Hideyuki Otsuki, Takuya Ueda, Nobuya Mori (Shinwa Chemical Industries Ltd., Japan)

Keynote Speakers' Profile

K-1	Chris H. Senanayake (Boehringer Ingelheim Pharmaceuticals Inc., USA)
K-2	Steve Cropper (Scale-up Systems Ltd., Ireland)
K-3	Vilas H. Dahanukar (Dr. Reddy's Laboratories Ltd., India)
K-4	Michinori Suginome (Kyoto Univ., Japan)
K-5	Mukund Gurjar (Emcure, India)
K-6	Shawn D. Walker (Amgen, Inc., USA)
K-7	Benjamin List (Max-Planck-Institut für Kohlenforschung, Germany)
K-8	Jun-ku Park (SK Biopharmaceuticals, Korea)
K-9	David M Tschaen (Merck, USA)
K-10	Robert Prytko (Sunovion Pharmaceutical Inc. USA)
K-10	Charles Vandenbossche (Sunovion Pharmaceutical Inc. USA)
K-11	Stéphane Varray (Lonza AG, Switzerland)
K-12	Masahiko Seki (API Corporation, Japan)
K-13	Wenjun Tang (Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China)
K-14	Vy M. Dong (University of California, Irvine, USA)

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Chris Senanayake, Ph.D
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BIOGRAPHICAL SKETCH

Dr. Chris H. Senanayake was born in Sri Lanka and received a BS degree (First Class) in Sri Lanka. After coming to the United States, he completed his MS at Bowling Green State University with Professor Thomas Kinstle in synthetic chemistry. He obtained his Ph.D. under the guidance of Professor James H. Rigby at Wayne State University in 1987 where he worked on the total synthesis of complex natural products such as, ophiobolanes, and completed the first total synthesis of grosshemin in the guaianolide family. He then undertook a postdoctoral fellow with Professor Carl R. Johnson and worked on the total synthesis of polyol systems such as amphotericin B and compactin analogous, and the synthesis of C-nucleoside precursors.

In 1989, he joined the Department of Process Development at Dow Chemical Co. In 1990, he joined the Merck Process Research Group. After 6 years at Merck, he accepted a position at Sepracor, Inc. in 1996 where he was promoted to Executive Director of Chemical Process Research. In 2002, he joined Boehringer Ingelheim Pharmaceuticals. Currently, he is the Vice President of Chemical Development and leading a group of highly talented scientists, engineers, and administrative staff located in Ridgefield, CT.

Dr. Senanayake's research interests focus on the development of new asymmetric methods for the synthesis of bioactive molecules and heterocycles and on catalytic, enzymatic, and mechanistic studies. He has published and lectured in the area of practical asymmetric synthesis and many disciplines of organic chemistry how to develop drugs on an economical, greener and practical manner in large-scale operation for rapid development of drugs. He is the co-author > 350 papers, patents and applications, book chapters and review articles in many areas of synthetic organic chemistry, drug development and design of improved chemical entities.

Senanayake demonstrates the ability to define and optimize chemical research and development strategies and tactics. He is able to "connect the dots" between the purely scientific and commercial perspectives and set up creative and effective strategies for new and proprietary products in ways that build value for the organization and create a competitive advantage. He is an Editorial Advisory Board member of the Organic Process Research & Development Journal. In 2008, he was the chairperson of Stereochemistry Gordon Conference. In 2010, he received the prestigious Siegfried gold medal award for development of practical processes for APIs and Process Chemistry. In 2011, He was appointed as an editorial board member of the Advance Synthesis and Catalysis Journal. In 2012 He was appointed as an Advisory board member of the Asian Journal of Organic Chemistry. In 2013 he was appointed as a Board of Editors for Organic Syntheses.

K－2

Steve Cropper
Scale-up Systems, Ltd.

1994　BEng, Chemical Engineering, University of Bradford, UK
1994　Project Manager, Fluid Mixing Processes, BHR Group UK
2000　Sales Director, Performance Fluid Dynamics, Ireland
2008　Account Manager, MySQL, Ireland
2011　Business Development Manager, Scale-up Systems Ltd., Ireland
2012　Diploma in Sales Management, Smurfit, UCD, Ireland

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Vilas H. Dahanukar
Chief Scientist, Process R&D,
Dr. Reddy's Laboratories Ltd, India

Education:

1986 B. Pharm , Department of Chemical Technology, Bombay, India
1988 M. Pharm , Department of Chemical Technology, Bombay, India
1994 Ph.D., Medicinal Chemistry, Univeristy of Kansas, USA
1994 Postdoctoral Research Fellow, University of Minneapolis, USA
1996 Postdoctoral Research Fellow, University California, Irvine, USA

Career:

1996 Senior Scientist, Process R&D, Schering-Plough, New Jersey, USA
1998: Asscoiate Principal Scientist, Process R&D, Schering-Plough, New Jersey, USA
2000 Principal Scientist, Process R&D, Schering-Plough, New Jersey, USA
2002 Senior Principal Scientist, Process R&D, Schering-Plough, New Jersey, USA
2003 Director, Custom Pharmaceutical Serevices, Dr, Reddy's Laboratories Ltd, India
2004 Senior Director, Custom Pharmaceutical Serevices, Dr, Reddy's Laboratories Ltd
2008 Vice-President, Custom Pharmaceutical Serevices, Dr. Reddy's Laboratories Ltd
2014 Chief Scientist, Process R&D, Dr. Reddy's Laboratories Ltd, India

Awards:

1998: Schering-Plough Impact Award
2007: Dr. Reddy's Excellence Team Award for the Best Execution of External Customer Project
2013: Dr. Reddy's Chairman's Team Award for Internal Customer Delight
2014: Accepted as a Fellow of Royal Chemical Society

K－4

Michinori Suginome
Professor of Kyoto University

【Education, Career and Awards】

1988 B.S. Kyoto University, Department of Synthetic Chemistry, Faculty of Engineering

1993 Ph.D. Kyoto University, Department of Synthetic Chemistry, Graduate School of Engineering (Professor Yoshihiko Ito)

1993 Assistant Professor, Kyoto University, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering,

2002 Associate Professor, Kyoto University, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering,

2004 Professor, Kyoto University, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering,

1998-1999 Visiting Researcher, sabbatical leave to Massachusetts Institute of Technology, Department of Chemistry (Professor Gregory C. Fu)

1999 The Chemical Society of Japan Award for Young Chemist
2001 The Society of Silicon Chemistry Japan Award for Young Chemist
2005 Nagoya Silver Medal, Banyu Life Science Foundation International
2005 Mukaiyama Award, Society of Synthetic Organic Chemistry, Japan
2010 JSPS Prize, Japan Society for the Promotion of Science
2013 The Chemical Society of Japan Award for Creative Work
2015 The Humboldt Research Award, Humboldt Foundation

K－5

Mukund Gurjar

Chief Scientific Officer

1974	Master of Science
1977	Ph D (Nagpur)
1980	Ph D (London)
1980-82	Post Doctoral Fellow (Toronto)
1982-2007	CSIR National Chemical Laboratory, Pune & Indian Institute of Chemical Technology, Hyderabad
2007-present	Chief Scientific Officer and Member, Board of Directors

K– 6

Shawn D. Walker
Principal Scientist
Process Development, Amgen Inc., USA

1992–1995 B.Sc. (Chemistry), First Class Honors, McGill University, Canada
1995 Department of Medicinal Chemistry, Merck Frosst Inc., Canada
1996–2002 Ph.D. (Organic Chemistry), laboratory of Prof. Edward Piers, University of British Columbia, Canada
2002–2004 Post-Doctoral Fellow (Organometallic Chemistry), laboratory of Prof. Stephen L. Buchwald, Massachusetts Institute of Technology, USA
2004–2015 Department of Process Development, Amgen Inc., USA
2013 ACS Industrial Young Investigator Symposium

K– 7

Benjamin List
Professor and Director
Max-Planck-Institut fuer Kohlenforschung,
Muelheim an der Ruhr, Germany and
Honorary Professor, University of Cologne

Education / Career

1997 PhD, Frankfurt (J. Mulzer)
1997 Postdoc, The Scripps Research Institute, La Jolla, CA, USA (R. Lerner)
1999 Assistant Professor (Tenure Track), The Scripps Research Institute, La Jolla, CA, USA
2003 Group Leader (Tenured Associate Professor), Max-Planck-Institut fuer Kohlenforschung
2004 Honorary Professor University of Cologne, Germany
2005 Director (Full Professor) at the Max-Planck-Institut für Kohlenforschung, Department of Homogeneous Catalysis
2012 Managing Director of the Max-Planck-Institut für Kohlenforschung (2012-2014)

Awards

2000 Synthesis-Synlett Journal Award 2000, Germany
2003 Carl-Duisberg-Memorial Award 2003, Germany
2004 Dozentenstipendium of the Fonds der Chemischen Industrie, Germany
2004 Lieseberg Prize of the University of Heidelberg, Germany
2004 Degussa Prize for Chiral Chemistry 2004, Germany
2005 Scientific Member of the Max-Planck Society, Germany
2005 Novartis Young Investigator Award, USA-Switzerland
2005 AstraZeneca European Lecturer 2005, UK
2005 Society of Synthetic Chemistry, Japan: 2005 Lectureship Award
2005 Visiting Professorship, Gakushuin University, Tokyo, Japan
2006 100 Masterminds of Tomorrow, Germany
2006 JSPS Fellowship, Japan
2006 Wiechert Lectureship, FU-Berlin, Germany
2007 AstraZeneca Research Award in Organic Chemistry, UK
2007 Fonds der Chemischen Industrie Award, Germany
2007 OBC Lecture Award, UK
2008 Visiting Professorship, Sungkyunkwan University, Korea
2009 Honorary Lifetime Membership of the Israel Chemical Society
2009 Organic Reactions Lectureship, USA
2009 Boehringer-Ingelheim Lectureship, Canada
2009 Thomson Reuters Citation Laureate
2011 ERC-Advanced Grant and Boehringer-Ingelheim Lectureship, Harvard University, USA
2012 Otto-Bayer-Prize, Germany and Novartis Chemistry Lectureship Award 2012-2013
2013 Ruhrpreis, Mülheim, Germany
2013 Mukaiyama Award, Japan
2013 Horst-Pracejus-Prize, Germany
2013 Novartis Lectureship, UC Berkeley, USA
2013 Musher Memorial Lecture, Jerusalem, Israel
2014 Thomson Reuters Highly Cited Researcher Prize and Cope Scholar Award, USA
2015 Editor in Chief of Synlett (Thieme)

K- 8

Jun-Ku Park
CEO of SK biotek

【Education】

1993	Ph.D, Chemical Eng., Northwestern Univ., USA
1985	M.S, Chemical Eng., Yonsei Univ., Korea
1983	B.S, Chemical Eng., Yonsei Univ., Korea

【Career】

2015~	CEO of SK biotek
2010~ 2015	Head of CMS business
2006~ 2010	Plant Manager, CMS Plant
2002~ 2006	Continuous Process Development R&D, Corporate Research Center
1997~ 2002	Process R&D Engineer, Refining Plant R&D Center
1993~ 1996	Process Engineer, FCC Plant Start-up Team
1985~ 1988	Fine Chemical Biz development, R&D, Yukong Ltd. (SK's Former name)

K－9

David M. Tschaen, Ph.D.

Brief biography:

Dave received a B.S. degree in chemistry from Providence College in Providence, Rhode Island. He attended graduate school at the Pennsylvania State University and received a Ph.D. in chemistry under the mentorship of Professor Steven Weinreb. He joined Merck Research Labs in Rahway, New Jersey in 1984 in the department of Process Chemistry. He is currently, Director of Process Chemistry. Dave has co-authored >60 scientific publications and >30 patents.

K- 10

Robert Prytko, CPIP

Associate Director, Process Engineering, Sunovion R&D

1991 BSc with Distinction in Chemical Engineering, WPI

1992 Diploma, Heriot-Watt University

1993-2010 Sepracor R&D

2010-2015 Sunovion R&D

My career has spanned over 22 years at Sunovion Pharmaceuticals (formerly known as Sepracor). Over this time, I was involved with the development, scale-up and commercialization of the drug substance processes for Xopenex™ and Lunesta™. Recently, I pursued the Certified Pharmaceutical Industry Professional certification from the ISPE to advance my professional growth outside of my classical engineering training and experience.

Currently, I manage the scale-up of our development processes through our two state-of-the-art kilolabs, responsible for process hazard assessment, scalability and operations. I also lead the development of Dasotraline, responsible for project management, process development, optimization, technology transfer, manufacturing, trouble shooting and CMC regulatory.

K- 10

Charles Vandenbossche
Principal Research Chemist, Sunovion Pharmaceuticals Inc.

1994 B.A., Wayne State University (Detroit, Michigan)
1996 M.S., Wayne State University (Academic Advisor: Prof. James Rigby, Ph.D.)
1996 Sepracor Inc. (Marlborough, Massachusetts)
2010 Sunovion Pharmaceuticals Inc. (Marlborough, Massachusetts)
2009 A.C.S. Technical Achievement in Organic Chemistry Award

K- 11

Dr. Stéphane Varray
Head of Business development Chemical
Lonza Custom Development

My undergraduate study and master degree in chemistry were performed at Sciences and Technology University (Montpellier, France) in 1998. I completed my doctoral degree at the University of Montpellier in the field of ruthenium mediated metathesis applied to natural drug 2002. I participated to the Monbusho student exchange program in 2000 and stayed for 2 months at Nagoya University in the laboratory of Prof. M. Kitamura.
I joined Lonza in June 2002 after completing my PhD. I have been in charge of the development and manufacturing of Peptide and small molecule API for 5 years before moving to project management in the field of Peptide and antibody drug conjugates (ADC) in several leading positions. Since June 2013 I am now Business developer for the chemical development organization covering early clinical phase pipeline and manufacturing technologies including Flow/MRT, Peptide, Highly potent and cytotoxic.

K- 12

Masahiko Seki
Senior Research Manager
Process R&D Department
Healthcare Business Division II
API Corporation

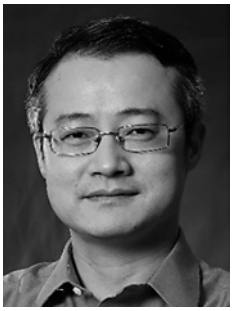
[Education, Career]
1982 M.S. from Kyoto University
1982 Mitsubishi Tanabe Pharma Corporation
1982 Medicinal Research Laboratory
1988 Ph.D. from Kyoto University
1993 Post Doc Research at Colorado State University (Prof. A. I. Meyers)
2000 Process Chemistry Research Laboratory
2004 Headquarters (Outsourcing, Procurement)
2011 API Corporation

[Award]
1993 The PSJ Kansai-Branch Award for Young Scientists
1997 1996 Incentive Award in Synthetic Organic Chemistry, Japan
2013 CPhI Pharma Award 2013
2014 Tetrahedron Synposium Best Poster Award　2014

K- 13

Professor Wenjun Tang

State Key Laboratory of Bio-Organic & Natural Products Chemistry,
Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, Shanghai 200032, China



Professor Wenjun Tang was born in 1974 in Zhejiang Province, China. He received his B. Eng. degree in 1995 from East China University of Sciences and Technology and his M.S degree in 1998 in Chemistry from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. He was awarded his Ph.D. in 2003 from The Pennsylvania State University. After two-year postdoctoral research at the Scripps Research Institute and six-year working experience as a process chemist at Boehringer Ingelheim Pharmaceuticals Inc, Connecticut, he took his current position as a research processer at Shanghai Institute of Organic Chemistry in 2011. He is also an adjunct professor at ShanghaiTech Univeristy and a PhD advisor at East China University of Sciences and Technology. Professor Tang has published over 50 research papers in internationally renowned chemistry journals and over 10 US or world patents. He is an awardee of 2012 national "Thousand Talents" youth program and 2009 President Award for individual excellence at Boehringer Ingelheim Pharmaceuticals Inc.

Recent Selected Publications:

1 Hu, N.;† Zhao, G.;† Zhang, Y.; Liu, X.; Li, G.; Tang, W.* *J. Am. Chem. Soc.* DOI: 10.1021/jacs.5b03760
2 Du, K.; Guo, P.; Chen, Y.; Cao, Z.; Tang, W* *Angew. Chem., Int. Ed.* **2015**, *54*, 3033.
3 Li, C.; Chen, T.; Xiao, G.; Li, B.; Tang, W* *Angew. Chem., Int. Ed.* **2015**, *54*, 3792
4 Fu, W.; Nie, M.; Wang, A.; Tang, W* *Angew. Chem., Int. Ed.* **2015**, *54*, 2520
5 Xu, G.; Zhao, Q.; Tang, W.* *Chin. J. Org. Chem.* **2014**, *34*, 1919
6 Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W.* *J. Am. Chem. Soc.* **2014**, *136*, 570
7 Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W.* *Angew. Chem., Int. Ed.* **2013**, *52*, 4235
8 Liu, G.; Xu, G.; Luo, R.; Tang, W* *Synlett*, **2013,** *24,* 2465
9 Tang, W.;* Capacci, A. G.; Wei, X. et al. *Angew. Chem., Int. Ed.* **2010**, *49*, 5879

K- 14

Vy Maria Dong
Professor of Chemistry at University of California, Irvine

【Education, Career and Awards】

1998 B.S. Chemistry, UC Irvine
2000 M.S. Chemistry, UC Berkeley
2004 Ph.D. Chemistry, California Institute of Technology
2006 Assistant Professor, University of Toronto
2010 Associate Professor, University of Toronto
2012 Full Professor, UC Irvine
2010 American Chemical Society Cope Scholar Award
2009 Alfred P. Sloan Research Fellowship
2013 Society of Synthetic Organic Chemistry, Japan Lectureship
2013 Japan Society for the Promotion of Science Fellowship
2015 Associate Editor at *Chemical Science*

Graphical Abstracts

Keynote Lecture

K-1

Important Asymmetric and Catalytic Transformations for Drug Development

Chris Senanayake

Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc. USA

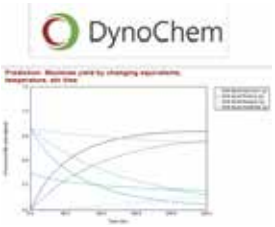
During the past two decades, my process research group is involved in the development of a truly efficient catalytic and asymmetric transformations for many drugs and drug candidates. Due to finding of effective asymmetric methodologies in a timely manner for important drug candidates, have provided many advantages to produce complex APIs in a rapidly for clinical development will be discussed.

K-2

Understanding Reaction Kinetics for Optimization and Scale-up of API Synthesis Steps

Steve Cropper*, Joe Hannon

Scale-up Systems Ltd.



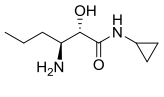
K-3

Application of the Chiral Technologies in Synthesis of Pharmaceutical Intermediates

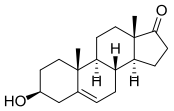
Vilas H. Dahanukar*[a], Christopher Cobley[b], Karen Holt[b], Jiwu Ruan[b], Sarah Warren[b], Anna Fryszkowska[b], Justine Peterson[b], Colin Dewar[b], Matthew Bycroft[b], Toni Fleming[b], Neil Triggs[b], Srikanth Sarat Chandra Gorantla[a], A. K. Srinivasan[a] & Rashid Abdul Rehman Khan[a]

[a]Dr. Reddy's Laboratories Ltd., Hyderabad 500090, India

[b]Chirotech Technology Center Ltd, Cambridge, UK



Telaprevir Intermediate



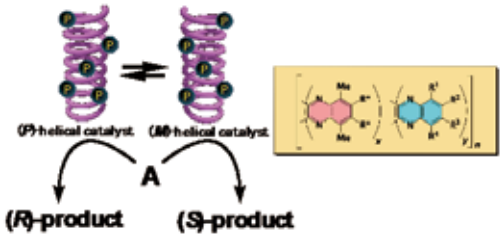
Abiraterine Acetate Intermediate

K-4

Helical Macromolecular Catalysts for Next-Generation Catalytic Asymmetric Synthesis

Michinori Suginome

Dept. of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University



K-5

Challenges in the Development of processes for Chiral Drugs

Mukund Gurjar

Research & Development, Emcure Pharmaceuticals Ltd.

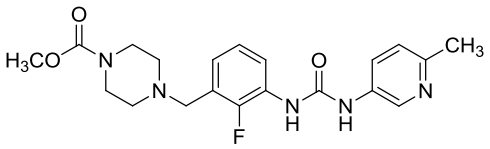
ITBT Park, Phase II, MIDC, Hinjwadi, Pune 411057, India

Mukund.Gurjar@emcure.co.in

K-6

Process Design with the End in Mind: Development of Omecamtiv Mecarbil, a Novel Cardiac Myosin Activator

Shawn D. Walker*
Department of Drug Substance Technologies, Amgen Inc.,
Thousand Oaks, California, USA 91320

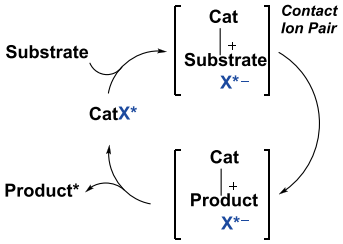


omecamtiv mecarbil

K-7

Asymmetric Counteranion Directed Catalysis (ACDC): A General Approach to Enantioselective Synthesis

List, Benjamin*
Max-Planck-Institute fuer Kohlenforschung,
Mülheim an der Ruhr, Germany



K-8

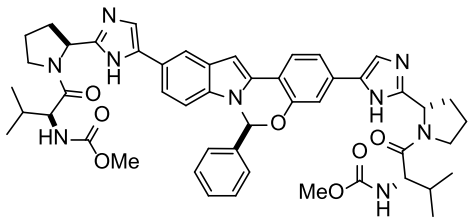
Commecial Application of Continuous Process in SK

Dr. Jun-Ku Park*
SK biotek

K-9

The Synthesis of Novel Pharmaceuticals

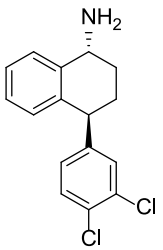
David M. Tschaen
Department of Process Chemistry
Merck Research Labs
Rahway, New Jersey 07065



K-10

Dasotraline: From Laboratory to Commercial-Scale Manufacture

Robert Prytko,* Kostas Saranteas, John Snoonian, Charles Vandenbossche*
Chemical Process Research & Development Dept., Sunovion Pharmaceuticals Inc.

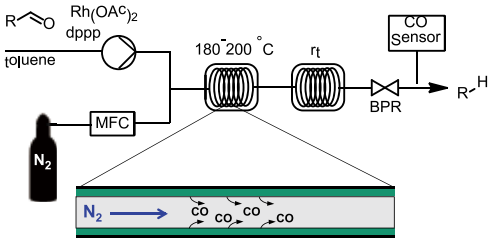


K-11

Some Examples of Industrial Process Development Challenges

Dominique Roberge, Conrad Roten, Bertin Zimmerman, Stéphane Varray

Chemical Development Org, Lonza Ltd.



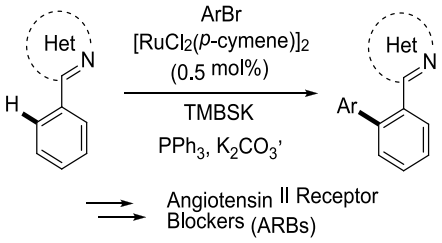
K-12

Development of New Catalytic System for C-H Arylation and Application to Synthesis of Pharmaceuticals

Masahiko Seki*

Process R&D Dept, Healthcare Business Div II

API Corporation,

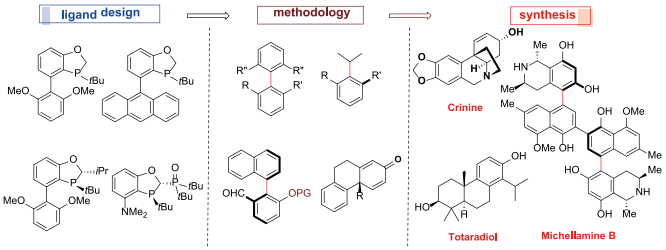


K-13

Methodologies toward Efficient Synthesis of Chiral Natural Products and Drugs

Wenjun Tang*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China

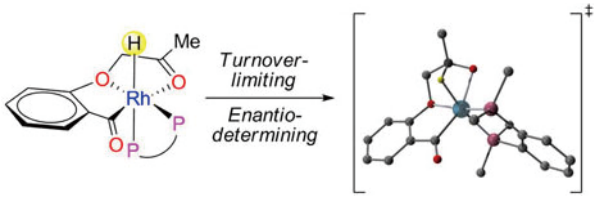


K-14

A Few of My Favorite Rings: Catalytic Cycles Inspired by Macrocycles

Vy Maria Dong*

Department of Chemistry, University of California Irvine

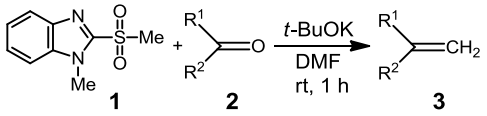


Poster Presentation
July 14 (Tue)

1P-01

Highly Practical New Methylenation Reagent for Aldehydes and Ketones

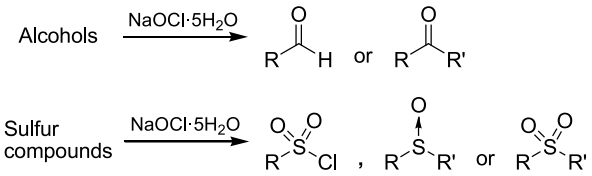
Kaori Ando,* Takahisa Kobayashi, Nariaki Uchida
Department of Chemistry and Biomolecular Science, Faculty of Engineering , Gifu University



1P-02

Novel oxidation process for alcohols and sulfur compounds by sodium hypochloride pentahydrate ($NaOCl{\cdot}5H_2O$) crystals

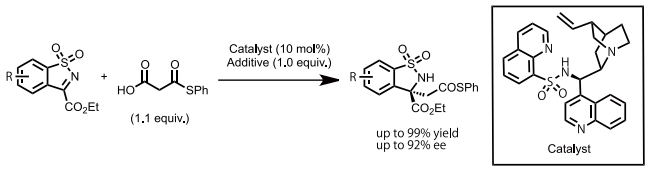
Tomohide Okada*[1)], Masayuki Kirihara[2)], Yoshikazu Kimura[3)]
[1)]Nippon Light Metal, Japan. [2)]Shizuoka Institute of Science and Technology, Japan. [3)]Iharanikkei Chemical Ind., Japan.



1P-03

Enantioselective Synthesis of Optically Active Sultams Using *N*-Heteroarenesulfonyl Cinchona Alkaloid Amide Catalyst.

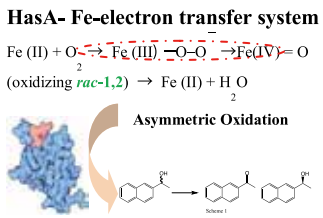
Ayaka Toda*, Masahide Sano, Shuichi Nakamura
Graduate School of Engineering, Nagoya Institute of Technology.



1P-04

HasA Asymmetric Oxidation Catalysis from Pea (*SanCat-R*)

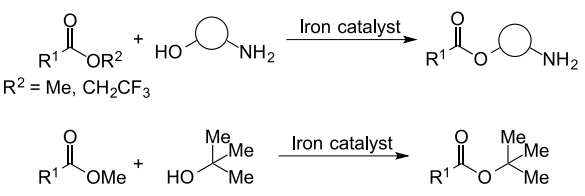
Hiroyuki Nagaoka*
Sanyo Shokuhin Co., Ltd. R & D



1P-05

Development of A Highly Active Iron Catalyst for transesterification

Rikiya Horikawa*, Chika Fujimoto, Ryo Yazaki, Takashi Ohshima
Graduate School of Pharmaceutical Sciences, Kyushu Univ.



1P-06

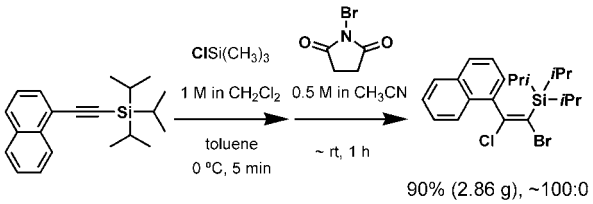
Enantioselective and Aerobic Oxidative Coupling of 2-Naphthol Derivatives Using Chiral Dinuclear Vanadium Complex in Water

Makoto Sako*, Shinobu Takizawa, Yasushi Yoshida, Hiroaki Sasai
The Institute of Scientific and Industrial Research (ISIR), Osaka University.

1P-07

Regio- and stereoselective synthesis of scaffolds for differentially all-carbon tetrasubstituted olefins

Masataka Ide,* Tetsuo Iwasawa
Ryukoku University

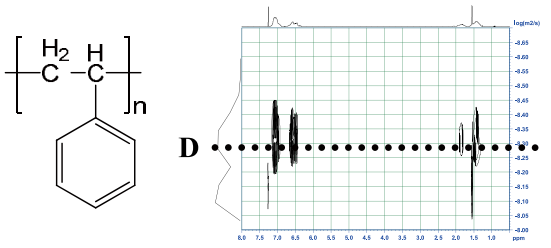


90% (2.86 g), ~100:0

1P-08

Process Research in NMR Tube

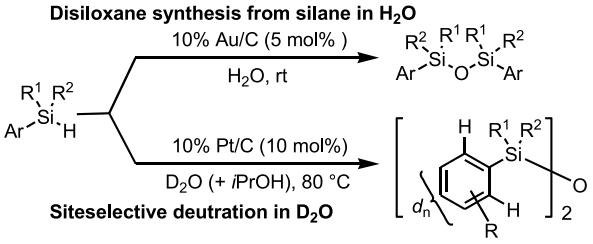
Atsushi Akao,* Yumi Asai and Takashi Hasebe
Analytical Research Laboratories, Eisai Product Creation Systems



1P-09

Disiloxane Synthesis Based on Silicon-Hydrogen Bond Activation Using Platinum Group Metal on Carbon in Water and Heavy water

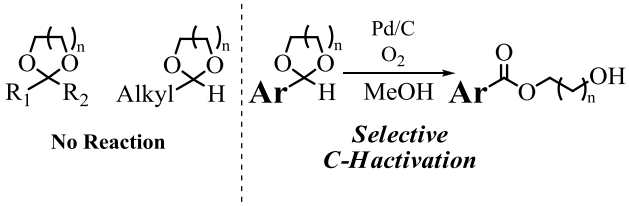
Yoshinari Sawama, Masahiro Masuda,* Ryosuke Nakatani, Shumma Nishimura, Kyoshiro Shibata, Tsuyoshi Yamada, Yasunari Monguchi, Hironao Sajiki
Gifu Pharmaceutical University



1P-10

Palladium on carbon-catalyzed and chemoselective oxidation of aromatic acetals

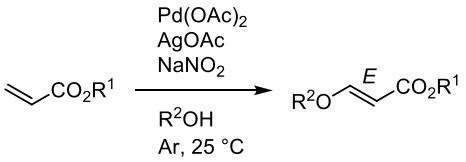
Yoshinari Sawama, Naoki Yasukawa*, Shota Asai, Yasunari Monguchi, Hironao Sajiki
Gifu Pharmaceutical University



1P-11

Palladium-catalyzed synthesis of enol ethers by the direct alkoxylation of acrylic acids

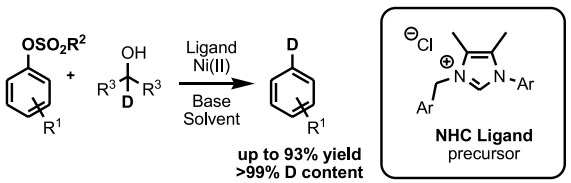
Koki Kunishima*, Tomohiro Hattori, Tohru Takahashi, Yuko Shishido, Yoshinari Sawama, Yasunari Monguchi, Hironao Sajiki
Laboratory of Organic Chemistry, Gifu Pharmaceutical University



1P-12

Nickel-Catalyzed Deuteration of Phenol Derivatives with Novel NHC Ligands

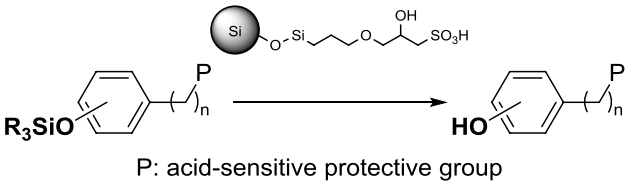
Shota Kujirada*, Masami Kuriyama, Osamu Onomura
Graduate School of Biomedical Sciences, Nagasaki University



1P-13

Selective deprotection of silyl ethers with SO_3H silica gel in the presence of acid-sensitive protecting group

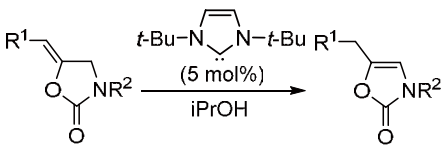
Hideaki Fujii[1,*], Miki Kuwada[1], Saki Tajiri[1], Misaki Kanda[1], Mari Yanai[1], Mitsuhiro Kamimura[2], Kennosuke Itoh[1]
[1] School of Pharmacy, Kitasato University and
[2] FUJISILYSIA CHEMICAL LTD.



1P-14

Tautomerization of 5-Alkylidene-2-Oxazolidinone to 2-Oxazolone by Use of an N-Heterocyclic Carbene Catalyst

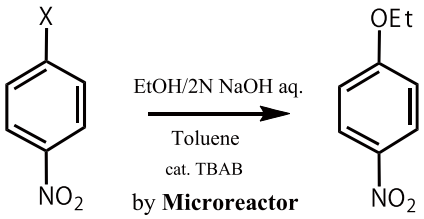
Ken-ichi Fujita,*[1] Junichi Sato,[2] Hiroyuki Yasuda[1,2]
[1]National Institute of Advanced Industrial Science and Technology (AIST)
[2]Graduate School of Science and Engineering, Ibaraki University



1P-15

Ethoxylation of p-Fluoronitrobenzene Using Phase-Transfer Catalysts by Microreactor Technology

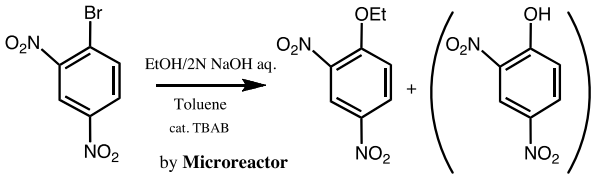
Hajime Mori*, Akane Tsuchitani, Megumi Mori, and Yoshie Tanaka
Industrial Technology Center of Wakayama Prefecture



1P-16

Study on Selective Synthesis of 1-Ethoxy-2.4-dinitrobenzene by Microreactor Technology

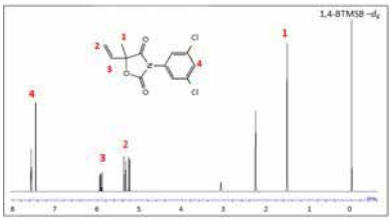
Akane Tsuchitani*, Hajime Mori, Megumi Mori, and Yoshie Tanaka
Industrial Technology Center of Wakayama Prefecture



1P-17

Considerations for the Validation of Quantitative NMR

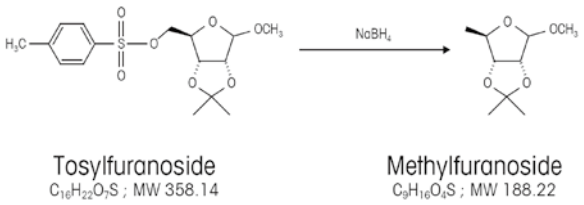
Takako Suematsu[1]*, Shinji Nakao[2], Toru Miura[2], Shinya Takaoka[2], Yuko Yamada[2]
[1]JEOL RSONANCE Inc., [2]Wako Pure Chemical, Industries Ltd.



1P-18

Sodium Borohydride Reduction:
A Sustainable PAT System for Safe Operationents

Yuki Hara*(Mettler-Toledo K.K.), Dr. John O'Reilly, Frank Neville, Brian Coffey, Martin Cronin, Maria Lennon, Barry Reid, Andy McInerney(Roche Pharmaceuticals)



1P-19

High Accuracy Sampling performance by EasySampler

Ryoichi Sugimoto, Hiroki Takai, Yoshifumi Fujisawa, Yuki Hara
AutoChem Team, Mettler-Toledo K.K.

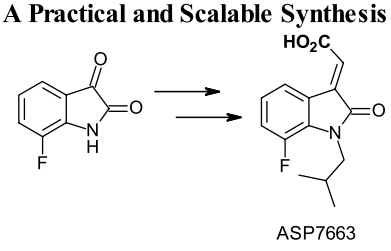
unit:%

stock concentration (mg/ml)	dilution factor	Manual		EasySampler	
		Accuracy	RSD	Accuracy	RSD
16.6	80	9.79	2.31	-1.53	0.35
31.5	160	9.15	0.42	-3.39	0.2
56.6	300	10.56	4.02	-3.41	0.66
89.7	450	9.86	1.13	-2.71	0.46

1P-20

Development of a Practical and Scalable Synthesis of TRPA1 Receptor Activator, ASP7663

Koji Kobayashi*, Ryoki Orii, Toshiyuki Sugimori, Takumi, Takahashi, Atsushi Oohigashi, Minoru Okada.
Process Chemistry Labs., Process Research, Astellas Pharma Inc.



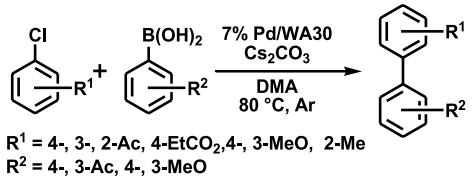
1P-21

Ligand-free Suzuki-Miyaura reaction of chloroarenes catalyzed by anion exchange resin-supported palladium

Tomohiro Ichikawa[a],* Moeko Netsu[a], Tomohiro Hattori[a], Tomoteru Mizusaki[b], Yoshinari Sawama[a], Yasunari Monguchi[a], and Hironao Sajiki[a]

[a] Laboratory of Organic Chemistry, Gifu Pharmaceutical University

[b] Chemical Catalysts R&D Department, Catalsyst Development Center, N.E. Chemcat Corporation



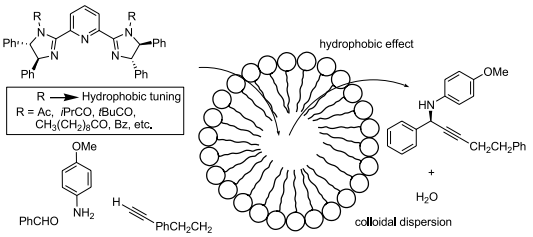
R^1 = 4-, 3-, 2-Ac, 4-$EtCO_2$,4-, 3-MeO, 2-Me
R^2 = 4-, 3-Ac, 4-, 3-MeO

1P-22

Enantioselective Three-Component Synthesis of Propargylamines Accompanied by the Dehydration in Water.

Yoshichika Hara*, Mutsuyo Ohara, Shuichi Nakamura

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



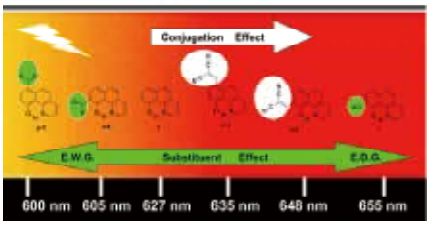
Three-component reaction in water using hydrophobic tunable chiral catalysts

1P-23

Novel ESIPT fluorescent dyes with adjustable optical properties

Kew-Yu Chen*, Hsing-Yang Tsai

Department of Chemical Engineering, Feng Chia University, 40724 Taichung, Taiwan



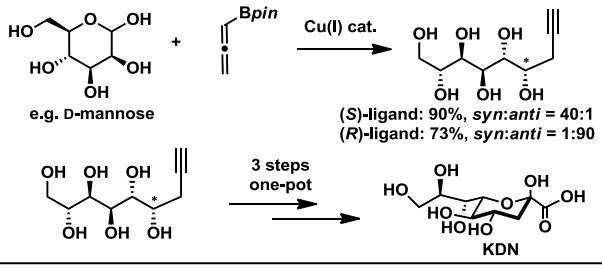
1P-24

Protecting Group-Free Catalytic Synthesis of Sialic Acids

Xiaofeng Wei[a]*, Yohei Shimizu[a], Motomu Kanai[a,b]

a. The University of Tokyo

b. ERATO, Japan Science and Technology Agency (JST)

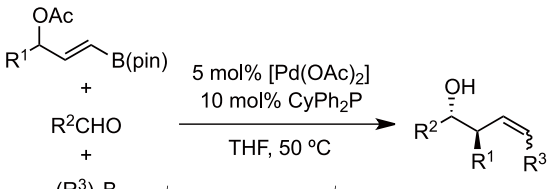


1P-25

Palladium-Catalysed Three-Componet Reaction of 3-(Pinacolatoboryl)ally Acetates, Aldehydes, and Organoboranes

Yoshikazu Horino,* Ataru Aimono, Hitoshi Abe

Department of Environmental Applied Chemistry, Faculty of Engineering, University of Toyama



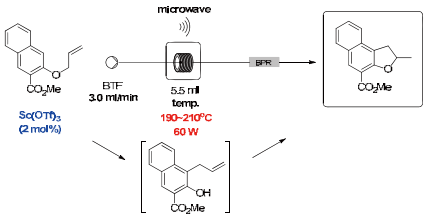
√ up to 90% yield √ up to >99/1 (*anti/syn*)
√ effficient chirality transfer

1P-26

Continuous multi-step synthesis of a benzofuran analogue under hidden brønsted acid catalysis using a microwave flow system:

Keiji Nakayama, Kazutoshi Ukai, Toshiyuki Tomoo and Yoshitaka Nakamura*

Process Technology Research Lab., DAIICHI SANKYO CO., LTD.

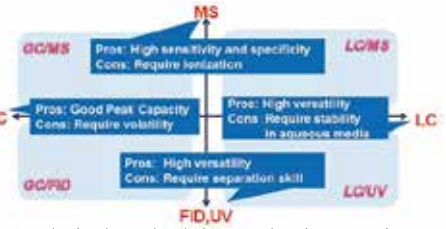


1P-27

Highly sensitive analytical method development for mutagenic impurities with the similar structures among them

Nobuhiro Oba*, Mari Kayamori, Kazuki Shigemori, Mieko Tanaka, Miwako Asada, Kanako Kondo, Takashi Nihei, Hiroaki Kataoka, Jumpei Fujiyoshi, Tetsuhiro Yamamoto, Makoto Noguchi

Chemical Development Laboratories, CMC Center, Takeda Pharmaceutical Company Limited.



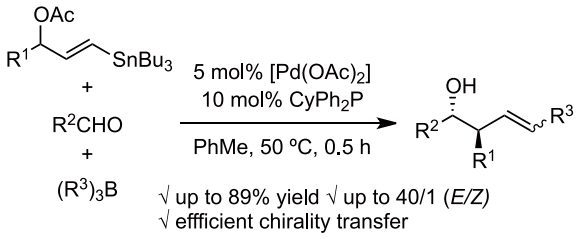
Analytical methodology selection matrix

1P-28

Palladium-Catalyzed Three-Component Reaction of 3-(Tributylstannyl)ally Acetates, Aldehydes, and Organoboranes: A New Entry to Stereoselective Synthesis of (*E*)-*anti*-Homoallylic Alcohols

Yoshikazu Horino,* Ataru Aimono, Hitoshi Abe

Department of Environmental Applied Chemistry, Faculty of Engineering, University of Toyama

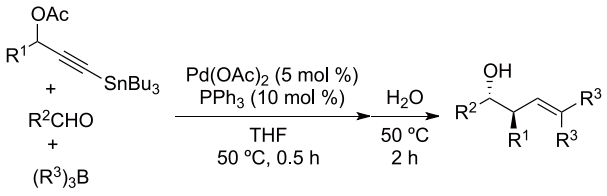


1P-29

Palladium-Catalyzed Multi-Component Reaction of 3-(Tributylstannyl)propargyl Acetates, Aldehydes, and Organoboranes

Yoshikazu Horino, Ataru Aimono*, Hitoshi Abe

Department of Environmental Applied Chemistry, Faculty of Engineering, University of Toyama

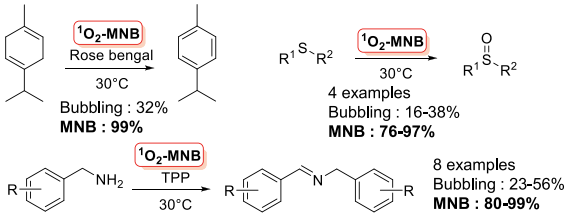


1P-30

Efficient Gas-related Photo Reactions Using Micro- and Nanobubble Strategy Under Atmospheric Pressure

Yuki Nishina*, Kohei Sato, Tetsuo Narumi, Naoharu Watanabe, Nobuyuki Mase

Graduate School of Integrated Science and Technology, Shizuoka University

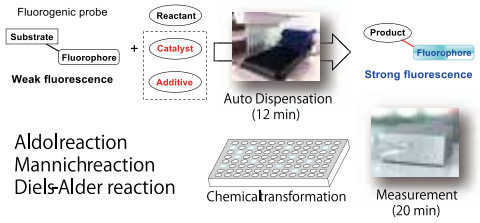


1P-31

Identification of Superior Organocatalysts Through High-Throughput Fluorescence-Based Screening

Tsuguya Masuda*, Kohei Sato, Tetsuo Narumi, Naoharu Watanabe, Nobuyuki Mase

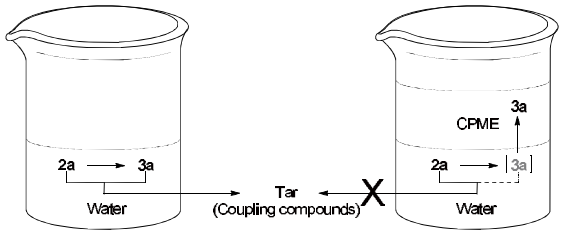
Graduate School of Integrated Science and Technology, Shizuoka University



1P-32

Hydrolysis of Diazonium Salts Using Two-phase System (CPME and Water)

Toshihide Taniguchi,* Mitsutaka Imoto, Motonori Takeda, Takeo Nakai, Masatoshi Mihara, Toshiyuki Iwai, Takatoshi Ito, Takumi Mizuno, Akihiro Nomoto, and Akiya Ogawa

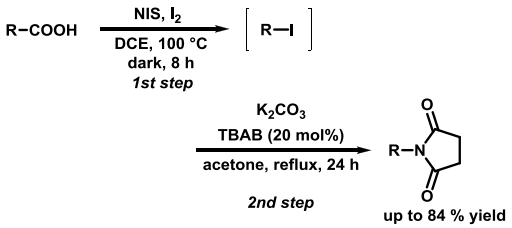


1P-33

One-pot Transformation of Aliphatic Carboxylic Acids into *N*-Alkylsuccinimides

Yuta NAKAI*, Katsuhiko MORIYAMA, Hideo TOGO

Graduate School of Science, Chiba University

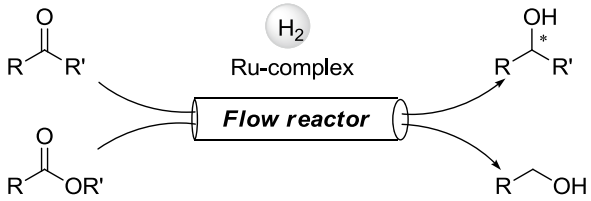


1P-34

Homogeneous Ruthenium-Catalyzed Hydrogenation Using a Continuous Flow Reactor

Naota Yokoyama,* Kiyoto Hori, Hideki Nara, Mitsuhiko Fujiwhara

Takasago International Corporation.

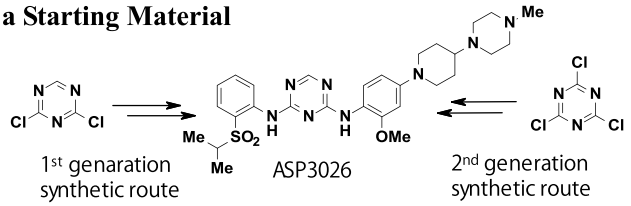


1P-35

Improvements in a Practical and Scalable Synthesis of Selective ALK Kinase Inhibitor ASP3026, Utilizing Readily Available Cyanuric Chloride as a Starting Material

Kazuyoshi Obitsu*, Shun Hirasawa, Kazuhiro Takeguchi, Koji Kobayashi, Takahiro Akiba, Yuji Takahama, Ryoki Orii, Takumi Takahashi, Shigeru Ieda, Minoru Okada.

Process Chemistry Laboratories, Astellas Pharma Inc.

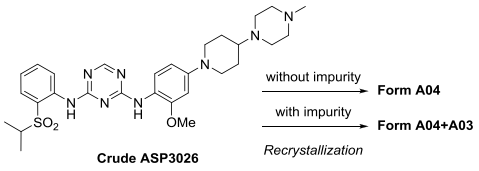


1P-36

Root Cause Analysis of Uncontrollable Polymorph –Inhibition of a Trace Amount of Impurity in Selective ALK Inhibitor ASP3026–

Yuji Takahama*, Kazuhiro Takeguchi, Kazuyoshi Obitsu, Norihiro Ueda, Ryoki Orii, Atsushi Ohigashi, Shigeru Ieda, Minoru Okada

Process Chemistry Laboratories, Astellas Pharma Inc.

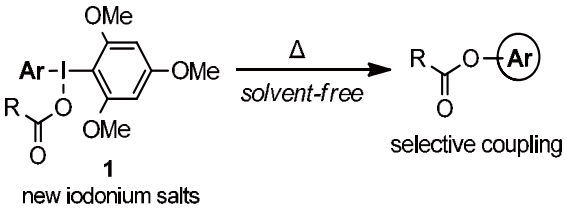


1P-37

New Conceptual Diaryliodonium Salts for Metal-Free Arylation of Carboxylic Acids Giving Aryl Esters

Toshifumi Dohi*, Kohei Sumida, Asami Kato, Kazuki Samura, Koji Morimoto, Yasuyuki Kita

Dept. of Pharmaceutical Sciences, Ritsumeikan University



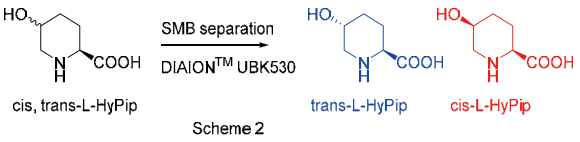
1P-38

Chromatographic Separation of Stereoisomer Compounds

M. Yasuda*[1], S. Ando[1], M. Tamura[1], T Fukumoto[2], K. Uchibayashi[2], D.W. Armstrong[3] Z. S. Breitbach [3]

1: Mitsubishi Chemical Corporation, 2: API Corporation

3: AZYP LLC



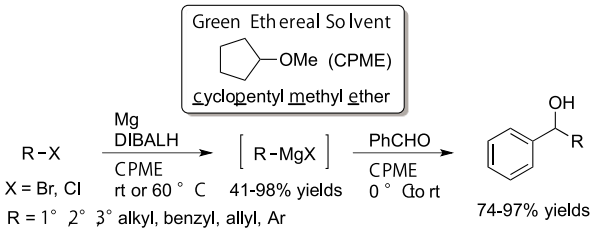
Scheme 2

1P-39

Performance Assessment of Cyclopentyl Methyl Ether (CPME): Application to Grignard Reactions

Keisuke Shibukawa*, Araki Masuyama, Shoji Kobayashi

Osaka Institute of Technology.

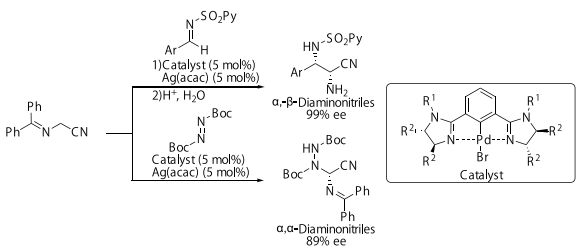


1P-40

Efficient Synthesis of Chiral Diaminonitriles Using Chiral Bis(imidazoline)-Pd Catalysts

Masaru Kondo*, Tomoki Nishi, Shuichi Nakamura

Nagoya Institute of Technology



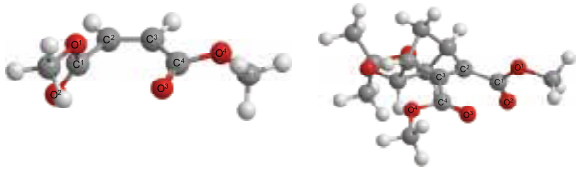
1P-41

Conformational Studies of Symmetric Diesters

Satomi Niwayama,[1,2]* Mai Kato,[1] Yukiko Yamaguchi,[1] Hanjoung Cho[2]

1. Muroran Institute of Technology, Japan

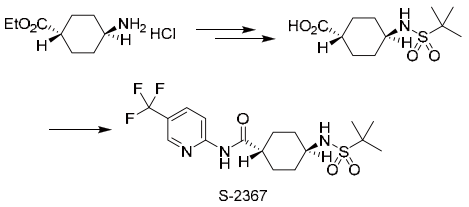
2. Texas Tech University, USA



1P-42

Development of an Optimized Synthetic and Purification Process of S-2367 (Velneperit), a Novel Neuropeptide Y (NPY) Y5 Receptor Antagonist

Shinichi Oda*, Kumiko Manaka, Kiyoshi Kakiya, Yasuyuki Hozumi, Yuki Fukui, Sohei Omura, Makoto Kurashita, Masanori Nishiwaki, Yoshiyuki Takeuchi and Hideyuki Kitamura Chem. Dev. Dept. Shionogi & Co., Ltd.

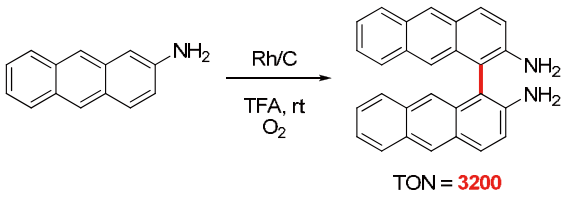


1P-43

Convenient and regioselective synthesis of biaryl compounds by heterogeneously catalyzed aerobic oxidative coupling

Kenji Matsumoto[1]*, Shohei Tachikawa[2], Shigenobu Fujimoto[2], Mitsuru, Shindo[1]

[1] IMCE, Kyushu University, [2] IEggS, Kyushu University

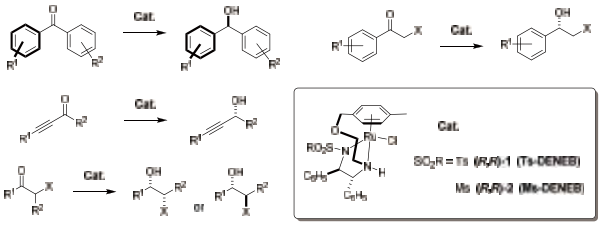


1P-44

Application of Asymmetric Transfer Hydrogenation and H_2-Hydrogenation Catalyzed by Oxo-tethered Ruthenium(II) Complex

Taichiro Touge,* Yamato Yuki, Hideki Nara, Mitsuhiko Fujiwhara

Takasago International Corporation, R&D Division.



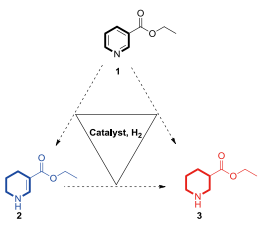
1P-45

Process Intensification for the Continuous Flow Hydrogenation of Ethyl Nicotinate

Takashi Ouchi*[§], Claudio Battilocchio[¶], Steven V. Ley[¶]

[§] Chemical Development Laboratories, CMC Center, Takeda Pharmaceutical Company Limited

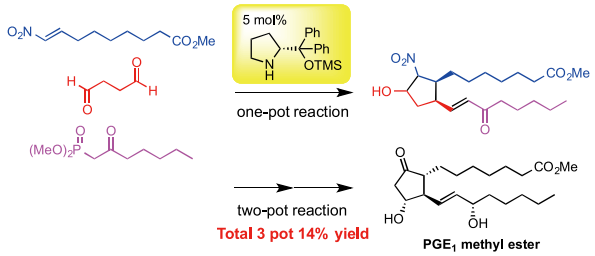
[¶] Innovative Technology Centre, Department of Chemistry, University of Cambridge



1P-46

Total Synthesis of Prostaglandin E_1 Methyl Ester by Three One-pot Operations

Yujiro Hayashi,* Shigenobu Umemiya
Graduate School of Science, Tohoku University



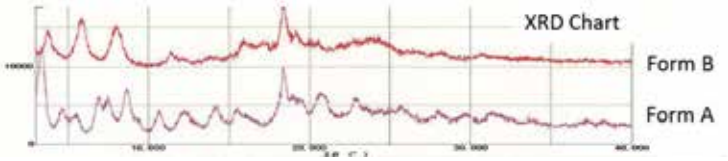
1P-47

STUDIES OF THE PEPTIDE CRYSTAL FORM AND ITS PROCESS DEVELOPMENT FOR COMMERCIAL PRODUCTION

Ryosuke Kunitani*, Aiko Hasegawa,
Yoshinori Murata

Chemical Development Center, CMC

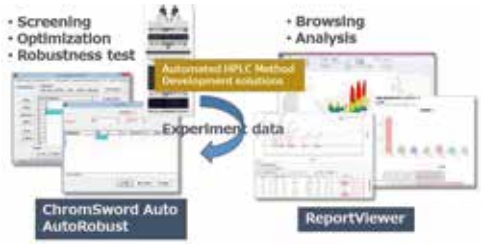
Development Laboratories, Shionogi & Co., Ltd.



1P-48

Total solution for the HPLC method development process by ChromSword software

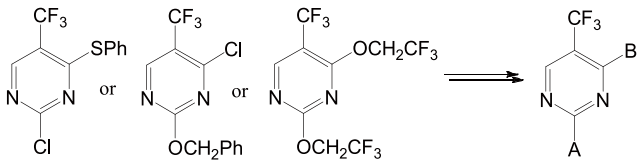
Kazuhide Konishi* Sergey Galushko
ChromSword Japan Co., Ltd.



1P-49

Study on Preparation of 5-Trifluoromethylated Pyrimidine Derivatives

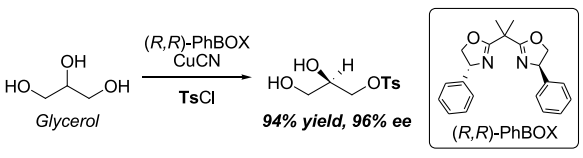
Takumi Kagawa*, Daiki Shigehiro, Kosuke Kawada
Research Laboratory, TOSOH F-TECH, inc.



1P-50

Copper Complex Catalyzed Asymmetric Monosulfonylation of Glycerol

Keisuke Miyamoto*, Masami Kuriyama, Osamu Onomura
Graduate School of Biomedical Sciences, Nagasaki University



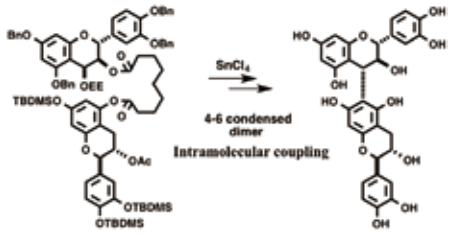
1P-51

Intramolecular coupling method for stereo- and regio-controlled procyanidin synthesis

Akiko Saito,[1,2] and Noriyuki Nakajima[3]*

[1,2] Osaka Electro-communication University and

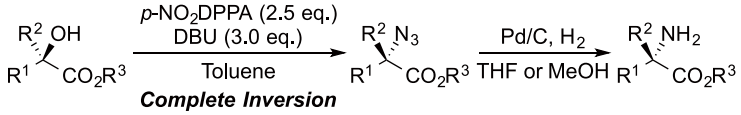
[3]Toyama Prefectural University



1P-52

A Novel Synthesis of α,α-Disubstituted α-Amino Acids by S_N2 Displacement at the Quaternary Carbon Center

Kotaro Ishihara,* Hiromi Hamamoto
Masato Matsugi, Takayuki Shioiri
Faculty of Agriculture, Meijo University, Japan

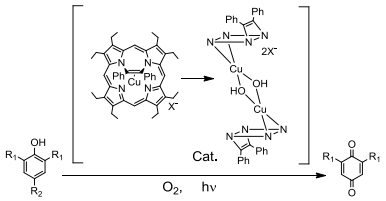


1P-53

Preparation of Unique Copper Complexes of Porphyrin and the Application to Photooxidation of Phenol Derivatives

Yuko Takao*[1], Fukashi Matsumoto[1], Kazuyuki Moriwaki [1], Takumi Mizuno [1], Toshinobu Ohno [1], Jun-ichiro Setsune[2]

[1]Osaka Municipal Technical Research Institute, [2]Kobe University



1P-54

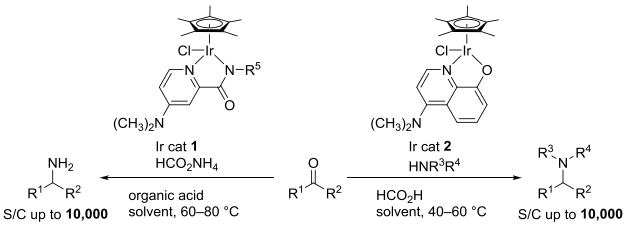
New type of Silica Gel for Hydrophilic Interaction Chromatography (HILIC)

Makoto Kawai*, Tomio Yamakoshi, Hirofumi Honda
Team Mirai Group, Fuji Silysia Chemical Ltd.

1P-55

Development of highly active iridium catalysts for reductive amination of carbonyl compounds

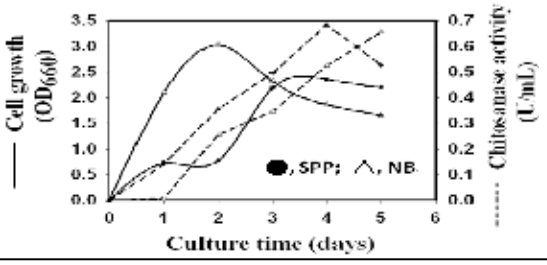
Kouichi Tanaka*, Kunihiko Tsutsumi, Kunihiko Murata, Masahito Watanabe
Central Research Laboratory, Kanto Chemical Co., Inc.



1P-56

Reclamation of squid pen for the production of chitosanase and dye biosorbent by *Bacillus cereus*

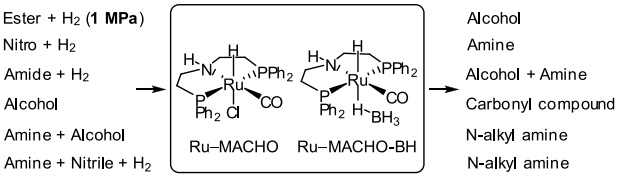
Tzu-Wen Liang*, San-Lang Wang
Life Science Development Center/ Department of Chemistry, Tamkang University, Taiwan



1P-57

Ru-MACHO, 'Gentle' catalytic ester reduction and beyond

Osamu Ogata*, Kiyoto Hori, Wataru Kuriyama, Kunimori Aoki, Hideki Nara
Takasago International Corporation



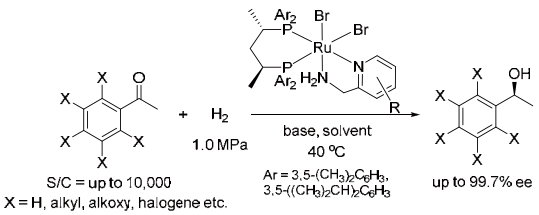
1P-58

Cancelled

1P-59

Practical Asymmetric Hydrogenation of Sterically Congested Aromatic ketones with Polysubstitutents on Aromatic rings

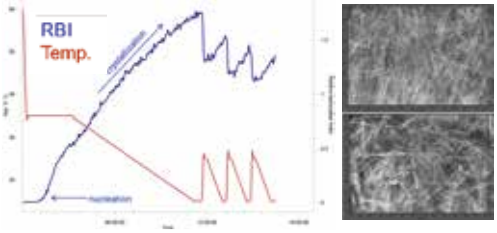
Takeaki Katayama[a], Noriyoshi Arai[b], Takanori Nanba[b], Kunihiko Murata[a], Kunihiko Tsutsumi[a], Takeshi Ohkuma[b]
[a] Central Research Laboratory, KANTO CHEMICAL Co., Inc.
[b] Division of Chemical Process Engineering and FCC, Faculty of Engineering, Hokkaido University



1P-60

Cycle Time Reduction for an Intermediate Crystallization Step Using a New Image-Based PAT Technique

Hiroki Takai*, Des O'Grady, Terry Redman
AutoChem Team, Mettler-Toledo K.K.

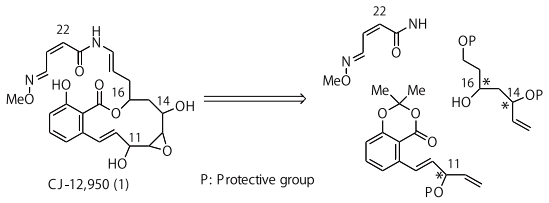


1P-61

Synthetic Studies toward (+)-CJ-12,950 for the Stereochemical Assignment

Yoshihito Oguma,* Takumi Yamagishi, Nozomi Yamamoto, Sho Shinoda, Kenji Sugimoto, Daishiro Minato, Yuji Matsuya

Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama

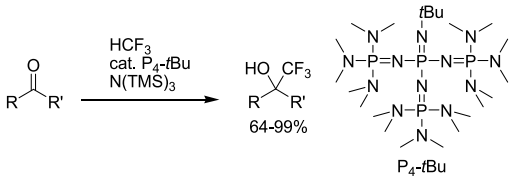


1P-62

Trifluoromethylation using Fluoroform through Catalytic Amount of Phosphazene Base

Satoshi Okusu*, Kazuki Hirano, Etsuko Tokunaga, Norio Shibata

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



1P-63

Lonza MRT / Flow technology applied to innovative chemistry

Dominique M. Roberge, Stephane Varray*, Daisuke Tanaka
Pharma and Biotech, Lonza AG / Lonza Japan Ltd

Lonza

FlowPlate™ MicroReactor

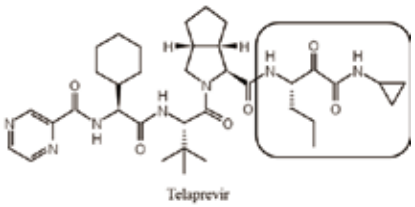
Lonza is developing and utilizing microreactors applicable for large-scale manufacturing of pharmaceuticals under GMP. The use of microreactors and mini plant systems enable the control of hazardous and demanding reactions which are difficult in ordinal batch reaction. The concept is embedded in the design of the “Factory of Tomorrow” at our plant in Switzerland.

Poster Presentation
July 15 (Wed)

2P-01

A robust and efficient process of the HCV protease inhibitor key intermediate

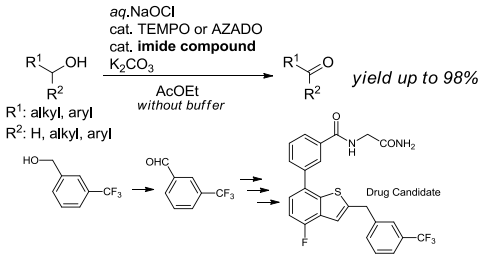
Kohei Mori,* Narumi Kishimoto, Daisuke Moriyama, Akira Nishiyama, Masaru Mitsuda
QOL Division, Kaneka Corporation



2P-02

Nitroxyl Radical and Imide Dual Catalyzed NaOCl Oxidation of Alcohols and the Application to a Drug Candidate

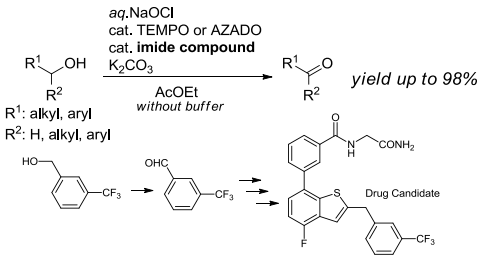
Naohiro Fukuda*, Tomomi Ikemoto
Chemical Development Laboratories, CMC Center, Takeda Pharmaceutical Company Limited



2P-03

Nitroxyl Radical and Imide Dual Catalyzed NaOCl Oxidation of Alcohols and the Application to a Drug Candidate

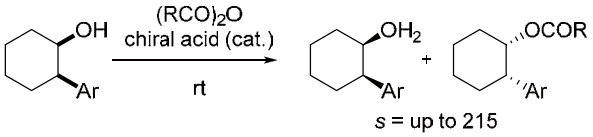
Naohiro Fukuda*, Tomomi Ikemoto
Chemical Development Laboratories, CMC Center, Takeda Pharmaceutical Company Limited



2P-04

Kinetic Resolution of Secondary Alcohols by Chiral Phosphoric Acid Catalyt

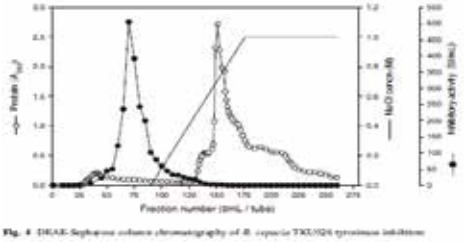
Shingo Harada, Satoru Kuwano, Yousuke Yamaoka, Ken-ichi Yamada, Kiyosei Takasu*
Grad. School of Pharm. Sci., Kyoto University



2P-05

DEAE-Sepharose column chromatography of B. cepacia TKU026 tyrosinase inhibitors

Chia-Hao Hsu* & San-Lang Wang
Department of Chemistry.,Tamkang University,Taiwan

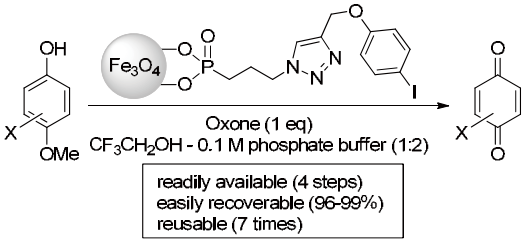


2P-06

Recyclable and Recoverable Magnetic Nanoparticle-Supported Iodoarene Catalysts for Oxidation of 4-Alkoxyphenols to Quinones

Ikumi Shimokawa,* Hisanori Nambu, Tomoya Fujiwara, Takayuki Yakura

Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama

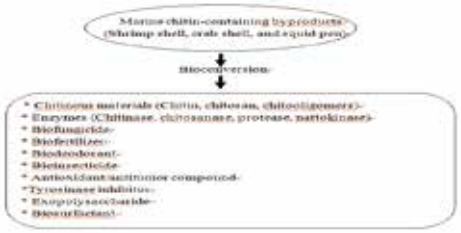


2P-07

Microbial reclamation of squid pen and shrimp shell

San-Lang Wang*, Tzu-Wen Liang

Life Science Development Center/ Department of Chemistry, Tamkang University, Taiwan

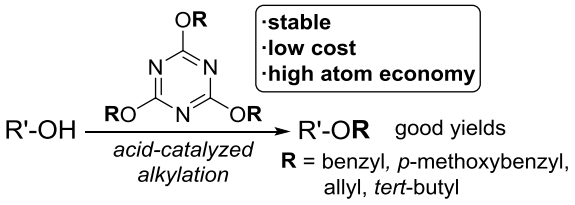


2P-08

Development of acid-catalyzed alkylating reagents based on triazine chemistry

Naoko Hayakawa[1], Kohei Yamada[1], Hikaru Fujita[1], Masanori Kitamura[1], Kazuma Yoshimura[2], Munetaka Kunishima[1]*

[1]Faculty of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University, [2]Process Development, NARD CHEMICALS, LTD.

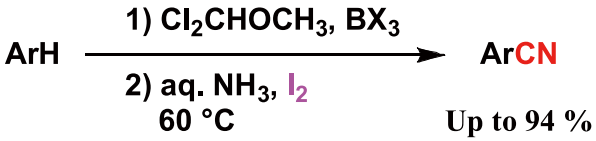


2P-09

One-Pot Transformation of Arenes into Aromatic Nitriles under Metal-Cyanide-Free Conditions

Toshiyuki TAMURA*, Katsuhiko MORIYAMA, Hideo TOGO

Graduate School of Science, Chiba University



2P-10

Development of quantity Analytical Standard by Using qNMR

Toru Miura[1]*, Taichi Yamazaki[3], Takashi Ohtsuki[2], Takako Suematsu[4], Takaaki Horinouchi[5], Takeshi Saito[3], Toshihide Ihara[3], Atsuko Tada[2], Maiko Tahara[2], Shinji Nakao[1], Yuko Yamada[1], Ryo Koike[5] and Naoki Sugimoto[2]

[1]Wako Pure Chemical Industries,Ltd. [2]National Institute of Health Science (NIHS)

[3]National Metrology Institute of Japan (NMIJ) [4]JEOL RESONANCE Inc.

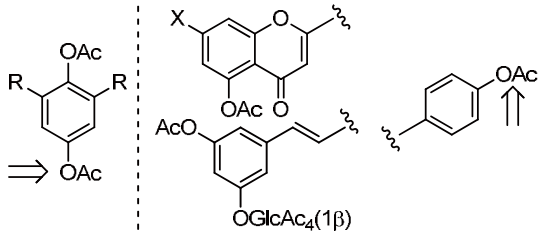
[5]Kao Corporation

$$p_x = \frac{S_a}{S_s}\frac{N_s}{N_a}\frac{m_s}{m_x}\frac{Mw_a}{Mw_s}p_s$$

2P-11

Revisiting Acetyl Group Technology: Lipase-catalyzed Regioselective Transformation of Polyphenols

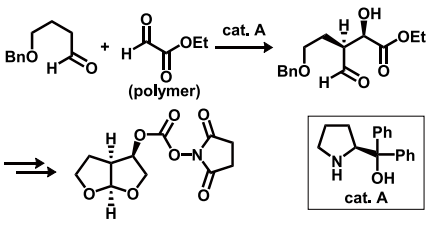
Kazuki Yashiro,* Susanta Mandal, Shun Hanamura, Kengo Hanaya, Mitsuru Shoji, Takeshi Sugai
Department of Pharmaceutical Science, Keio University



2P-12

Robust and Competitive Process Development of a Key Building Block for Anti-AIDS Drugs by Secondary Amine Catalyzed Enantio- and Diastereo-Selective Direct Cross Aldol Reaction

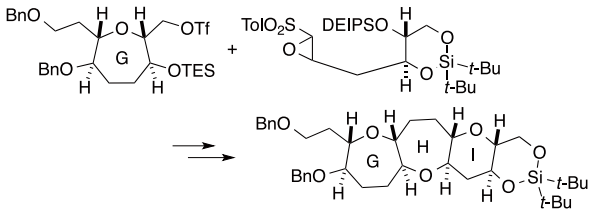
Yumi Hayashi,* Toshiaki Aikawa, Hiroaki Okamoto, Yasuharu Shimasaki, Yosuke Tomioka, Takashi Miki, Masahiro Takeda, Tetsuya Ikemoto
Health & Crop Sciences Research Laboratory, Sumitomo Chemical Co., Ltd.



2P-13

Synthesis of the GHI fragment of Gymnocin-B

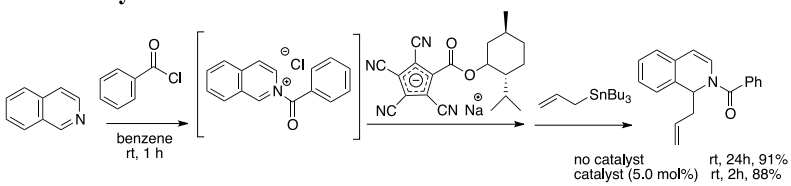
Shota Kato*, Yoshinori Hadano, Takeo Sakai, Yuji Mori
Faculty of Pharmacy, Meijo University



2P-14

Addition Reaction to Isoquinolium Salts Catalyzed by Tetracyanocyclopentadienids

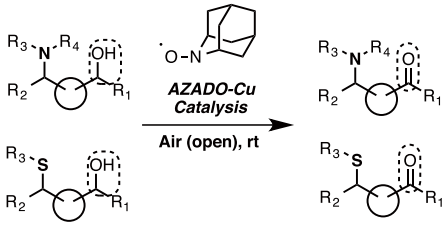
Mai Hattori*, Akari Tada, Junpei Matsuoka, Takeo Sakai, Yuji Mori
Faculty of Pharmacy, Meijo University



2P-15

Highly Efficient and Chemoselective Aerobic Oxidation of Alcohols Using AZADO-Copper Catalysis

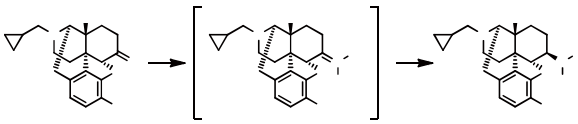
Shota Nagasawa,* Yusuke Sasano, Naoki Kogure, Shibuya Masatoshi, Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University



2P-16

Development of the Synthetic Process for the Naltrexamine Derivatives.

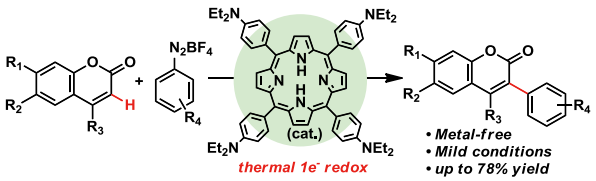
Masanori Murakami*, Takami Kanno, Tatsuya Fujita.
Pharmaceutical Research Laboratories, Chemistry Research Laboratory, Toray Industries, Inc.



2P-17

Metal-free C(3)-H arylation of coumarins promoted by catalytic amounts of 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin

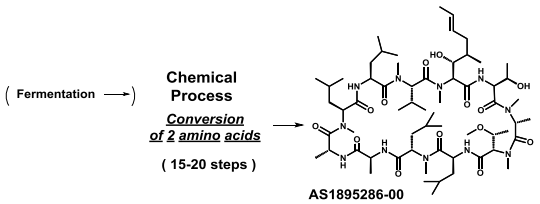
Masahiro Kojima,* Kounosuke Oisaki, Motomu Kanai
The University of Tokyo



2P-18

Development of a Practical & Scalable Synthesis of Cyclic Oligopeptide AS1895286-00

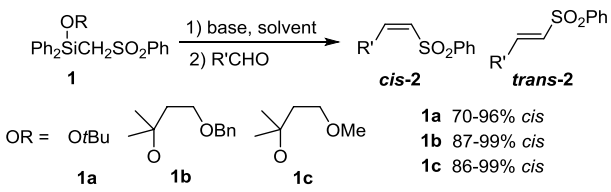
Ryoki Orii*, Hiroyoshi Matsubara, Minoru Okada
Process Chemistry Labs., Astellas Pharma Inc..



2P-19

Stereoselective Synthesis of *cis*-α,β-Unsaturated Sulfones Using New Peterson Reagents

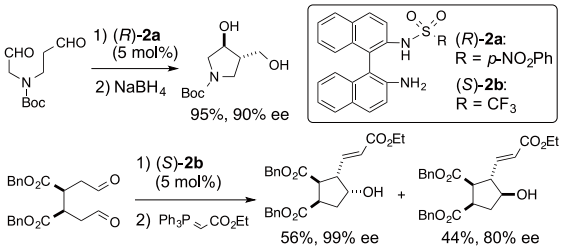
Tomohiro Wada *, Miho Okumura, Hiroshi Sumida, Kaori Ando
Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University



2P-20

Stereoselective Intramolecular Cross-aldol and Desymmetrization of Aliphatic Dials Enabled by Axially Chiral Aniline-type Catalyst

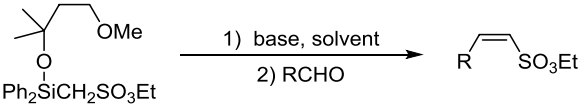
Tomonori Baba, Ramesh Yella*, Yuya Tanaka, Satoru Yamamoto, Takumi Furuta, Takeo Kawabata
Institute for Chemical Research, Kyoto University, Uji, Kyoto, 611-0011, Japan



2P-21

Stereoselective Synthesis of *cis*-α,β-Unsaturated sulfonates Using New Peterson Reagents

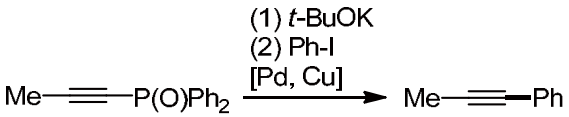
Kensuke Fujimoto*, Kaori Ando
Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University



2P-22

Syntheses of (1-Propynyl)arenes: One-Pot Dephosphorylation and Sonogashira Coupling of Phosphorylpropyne

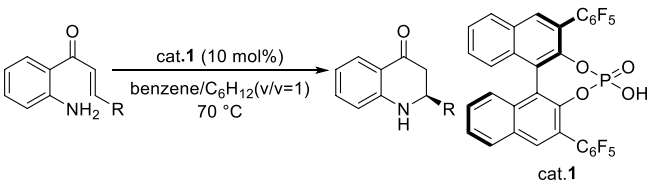
Akihiro Orita, Kenta Shinohara*, Takanori Nishida, Lifeng Peng, Ryosuke Wada, Junzo Otera
Okayama University of Science



2P-23

Asymmetric Synthesis of 2-Substituted Dihydroquinolones by the Aza-Michael Reaction of *N*-Unprotected Amines

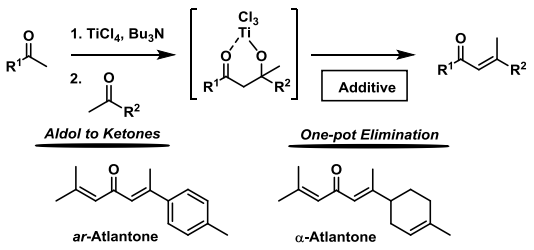
Yuka Moriya,* Kodai Saito, Takahiko Akiyama,
Chemical Department of Chemistry, Gakushuin University.



2P-24

One-pot synthesis of β,β-disubstituted α,β-unsaturated carbonyl compounds using sequential Ti-aldol addition to ketones and elimination

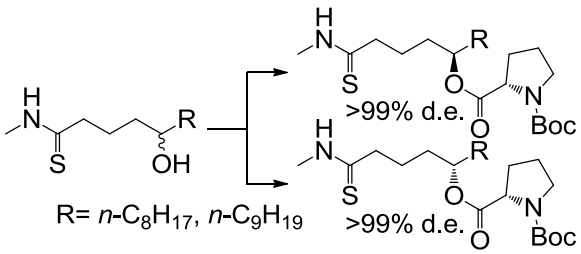
Yasuhiko Ashikari,* Makoto Nakajima, Masaharu Sugiura
Graduate School of Pharmaceutical Sciences, Kumamoto University



2P-25

Preparation of Optically Active Thioamides and Evaluation of Their Antibacterial Properties

Yasutaka Shimotori,* Masayuki Hoshi, Tetsuo Miyakoshi, Taisei Kanamoto, Hideki Nakashima
Dept. Biotech. Environ. Chem., Kitami Inst. Tech.

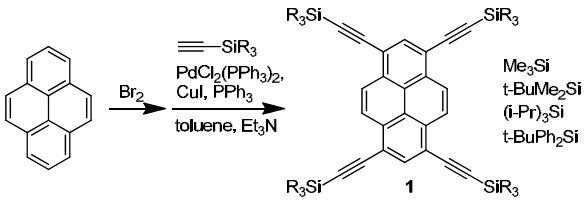


2P-26

Syntheses of 1,3,6,8-Tetra-substituted Pyrenes and Steric Effect of Substituents on Their Photoluminescence

Akihiro Orita, Takanori Nishida*, Feng Xu, Kenta Shinohara, Issei Kasuga, Junzo Oter

Okayama University of Science

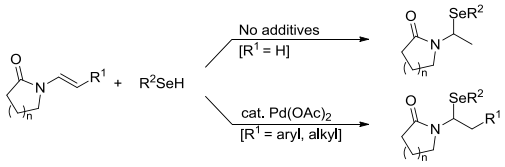


2P-27

Development of Novel Synthetic Methods of *N,Se*-Acetals by Highly Regioselective Hydroselenation of *N*-Vinyl Lactams

Taichi Tamai*, Megumi Yoshikawa, Shinya Higashimae, Akiya Ogawa

Graduate School of Engineering, Osaka Prefecture University

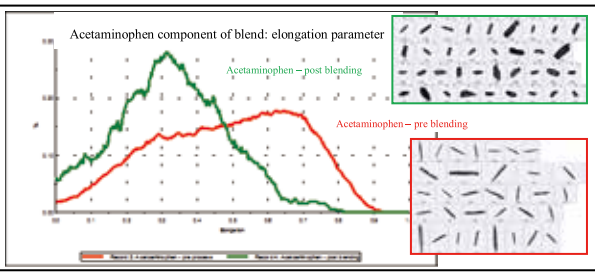


2P-28

A Novel Approach to the Characterization of Pharmaceutical Drugs Within Processes using Morphologically Directed Raman Spectroscopy

Cathryn Langley*, Daisuke Sasakura, Aiko Hayauchi and Deborah Huck-Jones

Malvern Instruments (a division of Spectris Co., Ltd.)

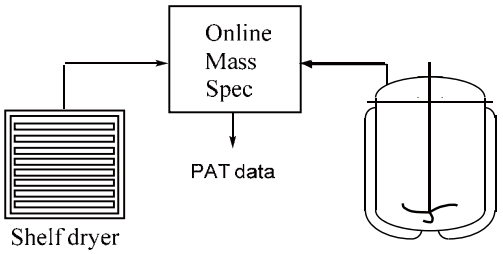


2P-29

A Process Analytical Technology (PAT) Approach Using Online Mass Spectrometry to Evaluate Drying Process and Control Oxygen Generation

Shoji Watanabe*, Atsushi Ueno, Takayuki Miyake

Sumitomo Dainippon Pharma Co., Ltd.

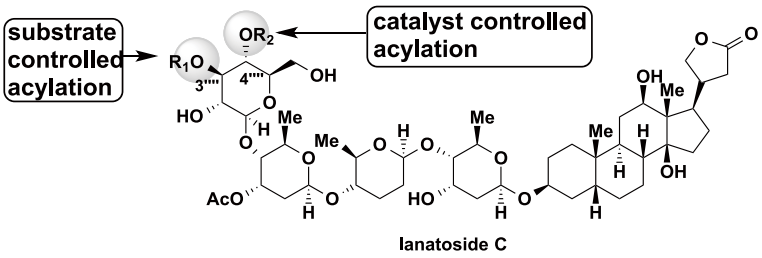


2P-30

Organocatalytic site-selective acylation of polyol natural products

Masanori Yanagi * ,Yoshihiro Ueda, Takumi Furuta, Takeo Kawabata

Institute for Chemical Research, Kyoto University

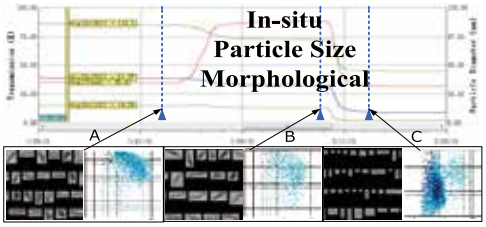


2P-31

An investigation of drug crystallization process by in-situ particle size and morphological analysis.

Fumiaki Sato*, Aiko Hayauchi , Cathryn Langley, Daisuke Sasakura

Malvern Instruments A division of Spectris Co., Ltd.

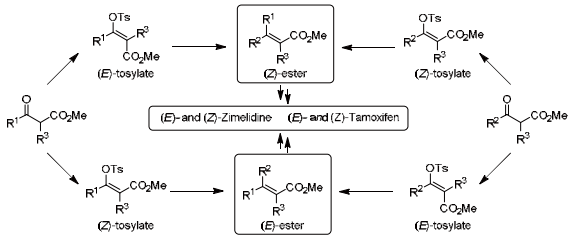


2P-32

Expeditious Parallel Syntheses of All (*E*)- and (*Z*)-Zimeridines and Tamoxifens Utilizing (*E*)-, (*Z*)-Stereocomplementary Synthesis of Multi-substituted α,β-Unsaturated Esters

Yuichiro Ashida, Yuka Sato, Atsushi Honda, Hidefumi Nakatsuji,* Yoo Tanabe*

Kwansei Gakuin University



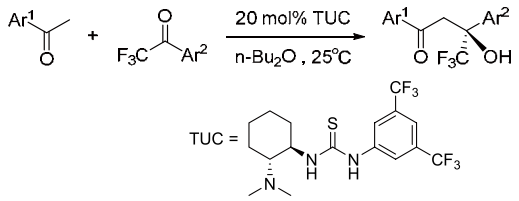
2P-33

Tertiary Amine Thiourea-Catalyzed Aldol Reaction of Aryl Methyl Ketones with Aryl Trifluoromethyl Ketones

Léopold Mpaka Lutete,* Takashi Miyamoto, Tetsuya Ikemoto

Health and Crop Sciences Research Laboratory

Sumitomo Chemical Co.,Ltd.

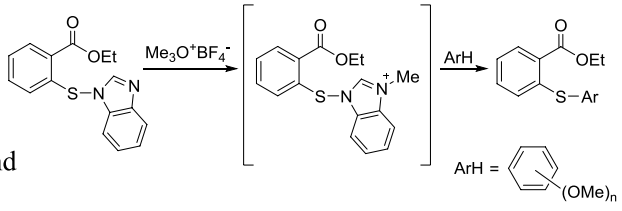


2P-34

Sulfenylation of Aromatic Compounds with *N*-Sulfenylbenzimidazoles in the Presence of Alkylating Agents

Masao Shimizu[1)], Shin-ya Suzuki*[2)], Shinji Tanaka[1)], Wataru Ando[1)], Norio Sakai[2)]

[1)]National Institute of Advanced Industrial Science and Technology (AIST); [2)]Tokyo University of Science.

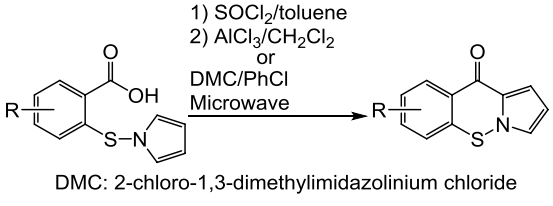


2P-35

Synthesis of pyrrolo[1,2-*b*][1,2]benzothiazin-10-one

Masao Shimizu[1)], Kotaro Masuda*[2)], Daisuke Kato[2)], Shinji Tanaka[1)], Wataru Ando[1)], Norio Sakai[2)]

1)National Institute of Advanced Industrial Science and Technology (AIST); 2)Tokyo University of Science

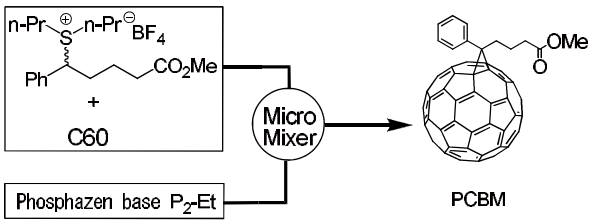


DMC: 2-chloro-1,3-dimethylimidazolinium chloride

2P-36

Selective Flow Synthesis of Methanofullerene Derivative PCBM Using Sulfur Ylide

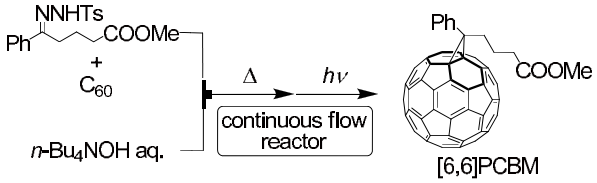
Takatoshi Ito*, Fukashi Matsumoto, Toshiyuki Iwai, Kazuyuki Moriwaki, Yuko Takao, Takumi Mizuno, Toshinobu Ohno (Osaka Municipal Technical Research Ins.), Yuta Inoue, Tetsuo Iwasawa (Ryukoku Univ.)



2P-37

Continuous flow synthesis of methanofullerene PCBM

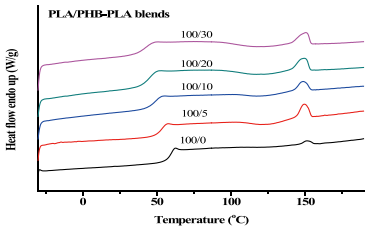
Toshiyuki Iwai*[1], Junki Murata[2], Tetsuo Iwasawa[2], Fukashi Matsumoto[1], Kazuyuki Moriwaki[1], Yuko Takao[1], Takatoshi Ito[1], Takumi Mizuno[1], Toshinobu Ohno[1]
[1] Osaka Municipal Technical Research Institute
[2] Faculty of Science and Technology, Ryukoku University



2P-38

Synthesis of PHB-b-PLA Block Copolymer Useful as the Compatibilizer in PHB/PLA Blends

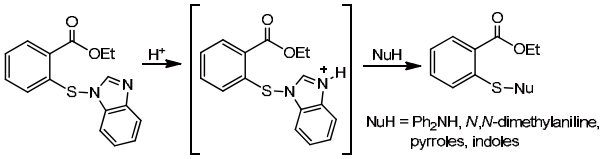
Trong-Ming Don*, Kuo-Hua Liao, Yi-Hsun Liu
Department of Chemical and Materials Engineering, Tamkang University.



2P-39

Sulfenylation of Aromatic Compounds with *N*-Sulfenylbenzimidazoles in the Presence of Acid

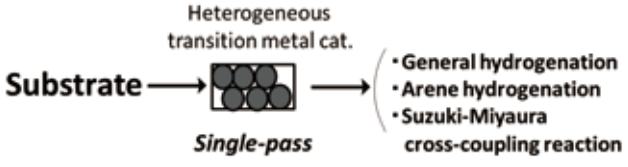
Masao Shimizu,*[1)] Miki Nakao,[2)] Shin-ya Suzuki,[2)] Shinji Tanaka,[1)] Wataru Ando,[1)] Norio Sakai[2)]
1)National Institute of Advanced Industrial Science and Technology (AIST); 2)Tokyo University of Science.



2P-40

Single-pass flow reactions: only 20 seconds hydrogenation and Suzuki-Miyaura reaction

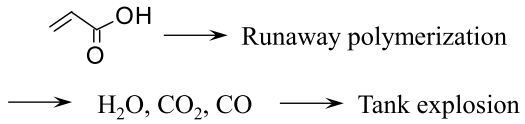
Tomohiro Hattori *, Aya Tsubone, Takashi Ida, Yoshinari Sawama, Yasunari Monguchi, Hironao Sajiki
Gifu Pharmaceutical University.



2P-41

Thermal hazard and evolved gases analyses on an acrylic acid runaway polymerization

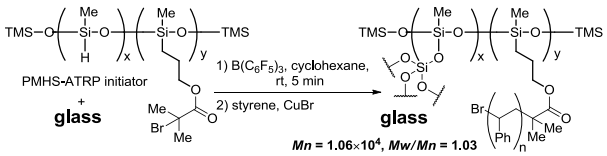
Michiya Fujita*[1], Yoshiaki Iizuka[2], Atsumi Miyake[1]
[1]Yokohama National University
[2]PHA consulting Co., Ltd.



2P-42

Living Radical Polymerization of Styrene by ATRP Initiator Immobilized on Glass Surfaces

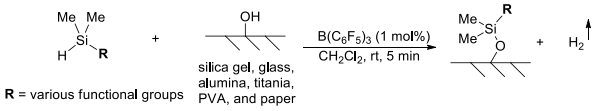
Kohji Iwaida*[†], Shun Ichii[†], Yu Masui[†], Kazuyoshi Kanamori[‡], Toshiyuki Kamei[†], Kazuki Nakanishi[‡], Toyoshi Shimada[†]
[†]Department of Chemical Engineering, Nara National College of Technology and [‡]Department of Chemistry, Graduate School of Science, Kyoto University



2P-43

Tris(pentafluorophenyl)borane-Catalyzed Organofunctionalization of Various Materials with Hydrosilane Derivatives

Shun Ichii[†], Kohji Iwaida[†], Yu Masui*[†], Kazuyoshi Kanamori[‡], Toshiyuki Kamei[†], Kazuki Nakanishi[‡], Toyoshi Shimada[†]
[†]Department of Chemical Engineering, Nara National College of Technology and [‡]Department of Chemistry, Graduate School of Science, Kyoto University



2P-44

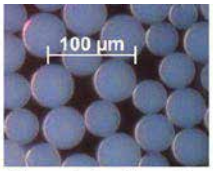
Design and operation of microreactor for heterogeneously catalyzedprocess

Tomoya Inoue*, Ming Lu, Kenichiro Ohtaki, and Hirotada Hirama
UMEMSME, AIST.

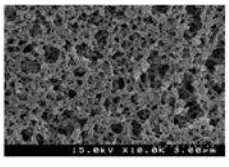
2P-45

Purification of biopharmaceuticals using small particle polymer media

Shinya Nozaki,* Kazuhiko Tokunaga, Yoshito Fukuda, Noriyuki Yasuda, Shouhei Ohara, Tadashi Adachi
Separation Materials Lab., Mitsubishi Chemical Corp.



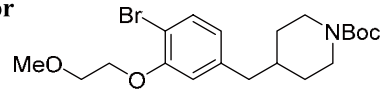
Microscopic view of the particles


SEM view of the surface of the particle

2P-46

Second Generation Syntheses of Benzyl Piperidine Derivatives: A Key Intermediate for the Preparation of SERT/5-HT$_{1A}$ Dual Inhibitor

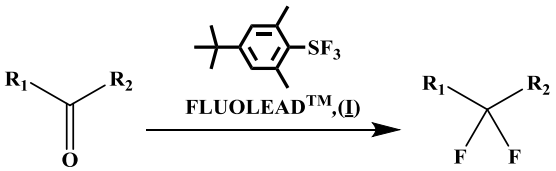
Yuji Fujiwara*, Atsushi Ueno, Nobuyuki Ae, Katsunari Shimomae, Hidefumi Yoshinaga, Hideo Terauchi, Koji Fujimoto
Process Chemistry R&D Laboratories, Sumitomo Dainippon Pharma Co., Ltd.



2P-47

4-tert-Butyl-2,6-dimethylphenylsulfur trifluoride, FLUOLEAD^{TM}: A new, widely applicable fluorinating agent with high stability and ease of handling

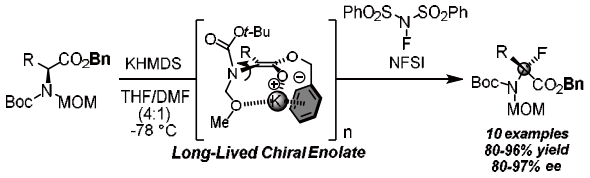
Norimichi Saito*, Junichi Chika
Pharmaceutical Division*, Organic Chemistry Research Laboratory, Ube Industries, Ltd.



2P-48

Asymmetric a-Fluorination of Amino Acid Derivatives via Memory of Chirality

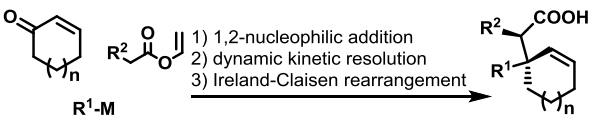
Koji Kasamatsu,* Tomoyuki Yoshimura, Takeo Kawabata
Institute for Chemical Research, Kyoto University



2P-49

Enantioselective construction of all-carbon quaternary stereogenic centers via lipase-catalyzed dynamic kinetic resolution

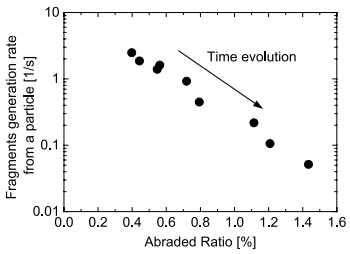
Koji Sugiyama, Shinji Kawanishi,* Yasuhiro Oki, Shuji Akai
Graduate School of Pharmaceutical Sciences, Osaka University



2P-50

Challenge to Prediction of Secondary Nucleation Rate Generated by Crystal Collisions with Impeller Blade Based on Lagrangian Simulation of Crystal Motion

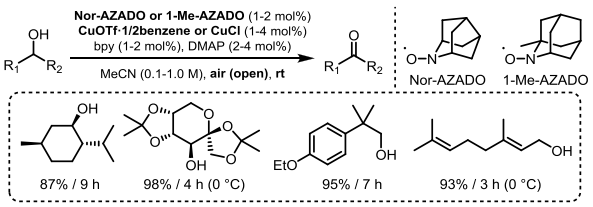
Ryuta Misumi,* Kazuhiko Nishi, Meguru Kaminoyama
Yokohama National University



2P-51

Optimized Conditions for the Aerobic Alcohol Oxidation Using Nitroxyl Radical/Copper Catalysis

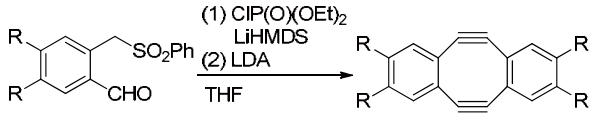
Naoki Kogure*, Yusuke Sasano, Tomohiro Nishiyama, Shota Nagasawa, Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University



2P-52

Syntheses and Properties of Substituted Sondheimer-Wong Diynes

Akihiro Orita*, Feng Xu, Takanori Nishida, Kenta Shinohara, Shinya Ohta, Katsutoshi Tomiyama, Junzo Otera
Okayama University of Science



2P-53

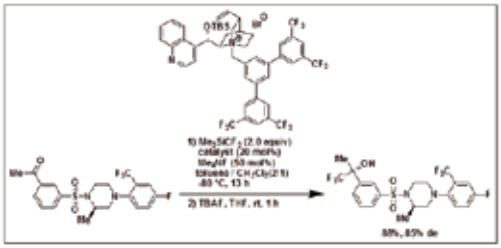
Development of Novel Reagents for Electrophilic SF_5-arylation

Kohei Matsuzaki*, Kenta Okuyama, Prajwalita Das, Etsuko Tokunaga, Norio Shibata
Nagoya Institute of Technology

2P-54

A Catalytic Synthetic Approach to HSD-016 Through Enantioselective Trifluoromethylation

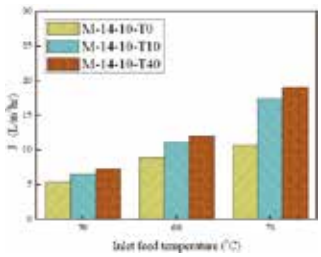
Yoshimasa Yasuda*, Satoshi Okusu, Norio Shibata
Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology



2P-55

Preparationo of PVDF Membrane for Membrane Distillation

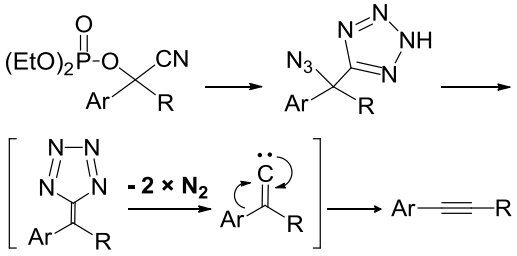
Tung-Wen Cheng*, Jhih-Wei Lin
Department of Chemical and Materials Engineering
Tamkang University



2P-56

Novel Synthesis of Arylalkynes via α-Aazidotetrazoles from Cyanophosphates

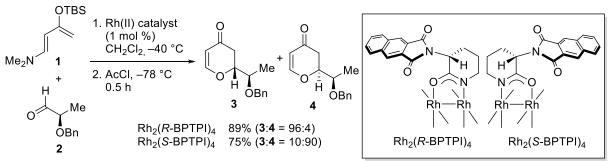
Hiroki Yoneyama,* Masahiro Numata, Kenji Uemura, Yoshihide Usami, Shinya Harusawa.
Osaka University of Pharmaceutical Sciences.



2P-57

Catalyst-controlled diastereoselective hetero-Diels-Alder reactions catalyzed by chiral dirhodium(II) chiral carboxamidates

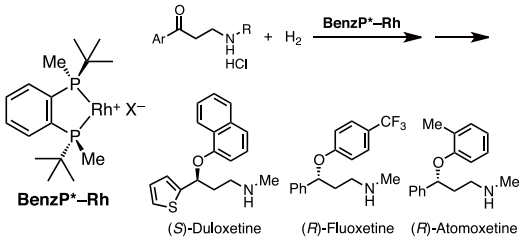
Takuro Suzuki,*[1] Shun Satake,[1] Fumiya Tanada,[1] Masahiro Anada,[1] Shigeki Matsunaga,[1,2] Shunichi Hashimoto[1]
[1]Faculty of Pharmaceutical Sciences, Hokkaido University,
[2]ACT-C, JST



2P-58

Potential Utility of BenzP* Ligand for the Production of Chiral Pharmaceutical Ingredients

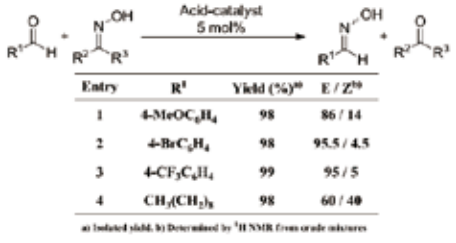
Tsuneo Imamoto,* Yumi Horiuchi, Ken Tamura, Masashi Sugiya
Nippon Chemical Industrial Co., Ltd.
Qiupeng Hu, Zhenfeng Zhang, Yangang Liu, Wanbin Zhang
Shanghai Jiao Tong University



2P-59

Catalytic Transoximation to Aldehydes

Naoki Oishi,* Kengo Hyodo, Kingo Uchida
Gra. Sch. Sci. Tech., Ryukoku Univ.



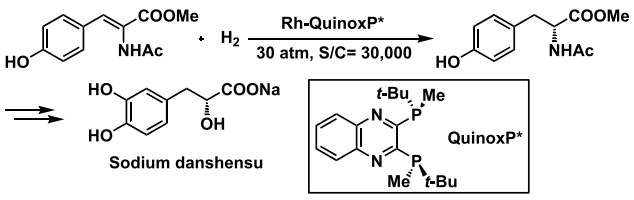
Entry	R^1	Yield (%)[a]	E / Z[b]
1	4-$MeOC_6H_4$	98	86 / 14
2	4-BrC_6H_4	98	95.5 / 4.5
3	4-$CF_3C_6H_4$	99	95 / 5
4	$CH_3(CH_2)_8$	98	60 / 40

[a] Isolated yield. [b] Determined by ^{1}H NMR from crude mixtures

2P-60

Catalytic Asymmetric Synthesis of Chiral Pharmaceutical Ingredients Using QuinoxP*-Rh Complexes

Yumi Horiuchi*, Yosuke Takubo, Ken Tamura, Masashi Sugiya, Tsuneo Imamoto (Nippon Chemical Industrial Co., Ltd.)Kunjiao Yu, Zhenfeng Zhang, Xiaohong Huo, Xingguang Wang, Delong Liu, Wanbin Zhang (Shanghai Jiao Tong University)

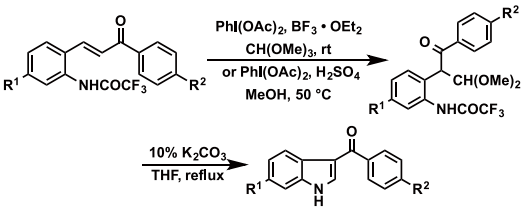


2P-61

Indole Synthesis from 2-Aminochalcone via Rearrangement Reaction

Tomohiro Maegawa[a]*, Chiaki Ohta[a], Kazuma Fujimura[a], Mina Kato[a], Sho Hattori[a], Akira Nakamura[a], Yasuyoshi Miki[a], Hiromi, Hamamoto[b]

[a]Kinki University, [b]Meijo University



2P-62

iChemExplorer: A Powerful Tool for Catalyst Screening and Probing the Catalytic Cycle

Mark B. Mitchell,* Michael D. Lopez

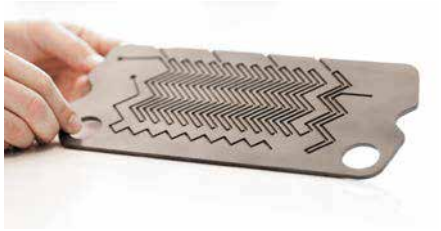
Reaction Analytics Inc.

2P-63

Continuous Flow Reactors: An Opportunity for the Development of Flexible & Sustainable Production Processes

Charlotte Wiles*

Chemtrix BV, The Netherlands

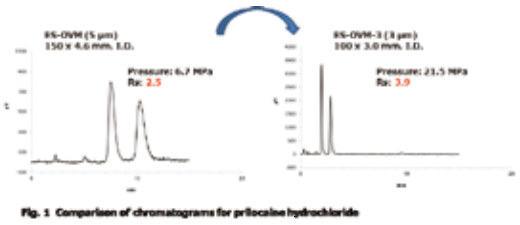


2P-64

Development of a High-Throughput Chiral Column using Ovomucoid Protein

Kosuke Fukuzawa,* Hideyuki Otsuki, Takuya Ueda, Nobuya Mori

LC Group, Shinwa Chemical Industries Ltd.



Abstracts

Keynote Lectures

K-1 ~ K-14

July 14 & 15

K- 1 （Keynote Lecture）

Important Asymmetric and Catalytic Transformations for Drug Development

Chris Senanayake, Ph.D
Vice President, Chemical Development

Department of Chemical Development

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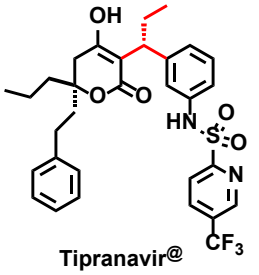
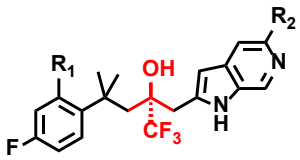
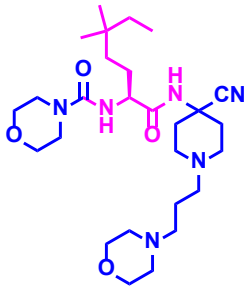
During the past two decades, my process research group is involved in the development of a truly efficient, reliable, greener and economically viable catalytic and asymmetric transformations for many drugs and drug candidates. Due to finding of effective asymmetric methodologies in a timely manner for important drug candidates, have provided many advantages to produce complex APIs in a rapidly for clinical development. This lecture will be centered on several highlights of these methods for the synthesis of important drug candidates.



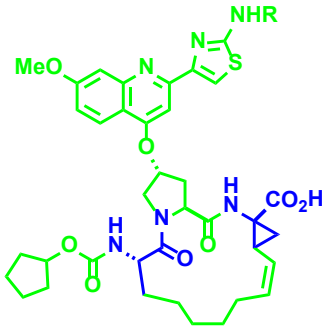
Tipranavir®



Glucocorticoid Agonists



Cathepsin S inhibitor



HCV Protease Inhibitor

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K- 2 （Keynote Lecture）

Understanding Reaction Kinetics for Optimization and Scale-up of API Synthesis Steps

Steve Cropper*, Joe Hannon

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Mechanistic understanding of the kinetics of the main steps of API synthesis reactions is an approach that is being increasingly applied by pharmaceutical companies in late stage development. It is increasingly recognized that a fundamental understanding of the relative rates of the main reaction steps that form products, intermediates and by-products can be invaluable in developing robust, scalable processes.

The Arrhenius equation is a simple, but remarkably accurate, formula for the temperature dependence of the reaction rate constant, and therefore, rate of a chemical reaction[1,2,3]. The equation gives the dependence of the rate constant k of chemical reactions on the temperature T (in absolute temperature kelvins) and activation energy Ea, as shown below:

$$k(T) = k_0 \exp\left(-\frac{Ea}{RT}\right)$$

where k_0 is the pre-exponential factor and R is the Universal gas constant.

The equation was first proposed in 1884 by the Dutch chemist J.H. van't Hoff and was given physical justification and interpretation in 1889 by the Swedish chemist Svante Arrhenius. Arrhenius argued that for reactants to transform into products, they must first acquire a minimum amount of energy, called activation energy Ea. At an absolute temperature T, the fraction of molecules that have a kinetic energy greater than Ea can be calculated from the Maxwell-Boltzmann distribution of statistical mechanics, and turns out to be proportional to exp(-Ea/RT). The concept of activation energy explains the exponential nature of the relationship between temperature and rates. For instance the rule-of-thumb "the rate of a reaction will double every 10 degrees centigrade" is an exponential relationship.

Modern laboratory analysis equipment and Process Analytical Technology (PAT) approaches enable scientists to follow the course of a reaction, not just to take end-point data. By following the key species profiles, a mechanistic kinetic model of the main reaction steps can be achieved. Understanding the interaction of substrate and reagent concentrations and operating conditions on the relative speeds of the reaction steps that form products, intermediates and by-products enables an optimized robust and scalable reaction to be developed. A number of software tools are available to assist scientists in fitting reaction kinetics to experimental data. This presentation features cases that used the DynoChem[4] software.

An example of identifying a reaction pathway during the synthesis of Moxifloxacin and the process optimization considering the reaction kinetics is described by Dr Reddy's Laboratories Ltd[5]. Data from seven individual runs were taken, and reaction schemes proposed prior to using software to fit reaction kinetics to the hypothesized reaction schemes. Having obtained a mechanistically and statistically sound fit it was understood that the reaction pathway of the Nucleophilic substitution reaction, where formation of product and impurities are in parallel, was due to the reaction of base

with the substrate and intermediate. An experimental screening program of different bases was therefore undertaken. These screening results indicated that DIPEA, a sterically hindered base, affords product with minimum percentage of impurities. The conversion of product increased from 77.5 to 88.89% and impurities were significantly reduced through this mechanistic insight obtained and confirmed by modeling of the reaction kinetics.

GlaxoSmithKline[6] describe an approach to apply classical Design of Experiment (DoE) approach, while simultaneously building up a descriptive kinetic model of the chemistry for a S_N2 displacement step between the 1,2,4-triazol-3-yl-halide derivative and variously substituted azabicyclo[3.1/0]hexanes. The kinetic model provided important information on the intrinsic nature of the process and computer simulation identified reaction conditions outside the Design Space previously investigated by the DoE that predicted a 9% enhancement of the solution yield. Experimentation in the laboratory confirmed good agreement (within 1% molar) between the simulation data and the experimental data.

Bristol-Myers Squibb Co. [7] detail an approach for using a mechanistic kinetic model as part of a QbD methodology that predicts the rates of the desired primary reaction that forms the final intermediate and the undesired reaction that generates an impurity for guidance in the selection of a Design Space. Having regressed and validated reaction rates and apparent activation energies at the laboratory scale, the mechanistic predictive model was then used to guide the selection of a Design Space by verifying model predictions against five manufacturing-scale batches.

PLIVA[8] demonstrate how this approach can also be applied to a heterogeneous Enantioselective hydrogenation reaction. By combining kinetics of the reactions with heat and mass transfer, quality specifications of the API such as enantiomeric purity and impurity levels can be described across the process space through modeling. This process space was defined through target specifications and known practical operating conditions on scale-up and plant control capabilities, enabling right-first-time scale-up to be achieved as part of their Quality-by-Design approach via a mechanistic modeling, with validation of the model provided by pilot plant trials.

These examples typify the benefits of modeling reaction kinetics to develop an enhanced understanding of the mechanism for process development and scale-up of both homogeneous and heterogeneous reaction steps. Additionally, a mechanistic model of this type can be used to explore transient conditions that are inaccessible to an empirical model for which only the exact process used in the DoE experiments are accessible for predictions. And there is the ability to run numerous simulations very quickly, vastly reducing the resources required compared to an experimental approach changing one variable at a time or a statistical process model. Furthermore, this approach can underpin design of continuous processes; an example of kinetic simulation in flow chemistry is given by Mannheim University of Applied Sciences[9].

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[3] "Modeling of Chemical Kinetics and Reactor Design" Gulf Professional Publishing 2001
[4] DynoChem software from Scale-up Systems Ltd. www.scale-up.com
[5] Chemistry & Biology Interface, 2012, 2, 5, 303-313
[6] Organic Process Research & Development 2010, 14, 1364-1372
[7] J Pharm Innov (2010) 5:193-203
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[9] Org. Process Res. Dev., 2014, 18 (11), 1535-1544

K- 3 （Keynote Lecture）

Application of Chiral Technologies in the Synthesis of Pharmaceutical Intermediates

Vilas H. Dahanukar*[a], Christopher Cobley[b], Karen Holt[b], Jiwu Ruan[b], Sarah Warren[b], Anna Fryszkowska[b], Justine Peterson[b], Colin Dewar[b], Matthew Bycroft[b], Toni Fleming[b], Neil Triggs[b], Srikanth Sarat Chandra Gorantla[a], A. K. Srinivasan[a] & Rashid Abdul Rehman Khan[a]

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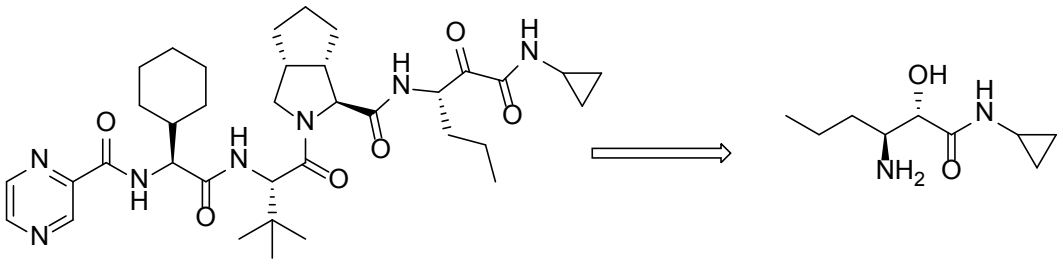
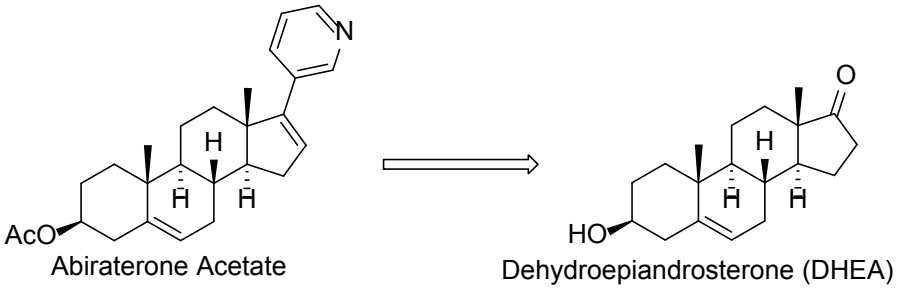
Various chiral technologies in the domain of chemocatalysis and biocatalysis are gaining acceptance in innovator and generic pharmaceutical industries. In chemocatalysis, asymmetric hydrogenation is widely used in reduction of prochiral C=O, C=C and C=N bonds to introduce chirality in molecules.[1] In biocatalysis area the use of lipase and alcohol dehdyrogenases have now became common place.[2] We present two case studies which demonstrate the application of asymmetric hydrogenation and alcohol dehydrogenases in synthesis of chiral intermediates.

Telaprevir (Incivek) was the first protease inhibitor drug that was introduced to treat hepatitis C. Telaprevir inhibits NS3 4A serine protease and has been indicated for use against hepatitis C genotype[3] and it is used in combination with peginterferon alfa and ribavirin. We have developed the synthesis of a norvaline chiral amino alcohol[4] using dynamic kinetic asymmetric hydrogenation[5] of ethyl 2-chloro-3-keto-hexanoate as the key asymmetric step.



Telaprevir (2*S*,3*S*)-3-amino-*N*-cyclopropyl-2-hydroxyhexanamide

Abiraterone acetate (Zytiga) is a drug used in combination with Prednisone to treat metastatic castration resistant prostate cancer.[6] The key steroidal fragment of Abiraterone is dehydroepidandrosterone (DHEA) acetate.[7] The current routes for DHEA acetate are based on steroids derived from yam. The soyabean derived 4-androstene-3,17-dione is a more sustainable starting material for the manufacturing of various steroidal intermediates.



Abiraterone Acetate Dehydroepiandrosterone (DHEA)

We have developed a three step chemoenzymatic process for the synthesis of DHEA acetate from 4–androstene-3,17-dione, incorporating a highly stereo- and regio-selective reduction of the C-3 carbonyl group using an alcohol dehydrogenase.

References:

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K- 4 （Keynote Lecture）

Helical Macromolecular Catalysts for Next-Generation Catalytic Asymmetric Synthesis

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Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan
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Much effort has been devoted to the development of new high-performance catalysts for asymmetric catalysis. Such new catalysts are expected to exhibit not only high enantioselectivity, but also high catalytic activity, recoverability, and reusability. Exploration of such high-performance catalysts unequivocally leads to the development of "green processes" in asymmetric synthesis. Furthermore, recent interest is focused on the creation of new concept and molecular design for "next-generation catalysts", which are endowed with remarkable characteristics in addition to the general but classical requirements including high enantioselectivity. Dynamic chirality can be one of such non-classical characteristics required for the next-generation catalysts, possibly allowing switch of enantioselection and amplification of chirality in catalytic asymmetric synthesis. The former allows synthetic organic chemist to obtain both enantiomers from a single chiral catalyst, while the latter permits production of highly enantiopure material even using poorly enantioenriched chemicals.

In this presentation are discussed new helical-poly(quinoxaline-2,3-diyl)-based chiral ligands **PQXphos**, which show high enantioselectivities (>95% ee for three different reactions), high reusability (up to 8-time reuse), and higher catalyst activity than do the corresponding low-molecular-weight chiral ligands in several different asymmetric reactions.[1-4] In addition, the polymer backbone underwent perfect switch of helical chirality by the effect of solvent.[5-7] This feature could be successfully applied to new catalytic systems in which either enantiomer can be produced with high enantioselectivities from a single chiral ligand, whose helical chirality is easily switchable.[2-4,7-10]

References

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K－５（Keynote Lecture）

Challenges in the Development of processes for Chiral Drugs

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Chiral drugs have made unprecedented impact on pharmaceutical industries particularly since US FDA published the guidelines in 1995. In these laboratories, we have constantly pursuing ‘chiral switch’ protocol to introduce known racemic drugs into their corresponding chiral versions with pronounced therapeutic values and lesser side effects. The success story is the introduction, for the first time, of *S*-amlodipine besilate which undoubtedly has better bioactivity with half the dose and lesser side effects particularly related to peripheral edema. Today S-amlodipine besilate is sold by Emcure in more than 33 countries worldwide. Some aspects of chiral chemistry related to synthesis of chiral switches will be described.

In addition, process chemistry on other chiral drug molecules will also be undertaken. For instance, process optimization of new chemical entities (NCE) of anti-asthmatic drug candidates will form the basic premise of my presentation.

K-６（Keynote Lecture）

Process Design with the End in Mind: Development of Omecamtiv Mecarbil, a Novel Cardiac Myosin Activator

Shawn D. Walker*, Sheng Cui, Steven Mennen, Alan Allgeier, Charles Bernard, Seb Caille, Andrew Clausen, Richard Crockett, Margaret M. Faul, Karl B. Hansen, Kelly Hu, Tony King, Neil Langille, Robert Larsen, Melody Mak-Jurkauskas, Henry Morrison, Karthik Nagapudi, Kumar Ranganathan, Steven Shaw, Tiffany Thiel, John Tucker, Justin Tvetan, Fang Wang, Jacqueline C. S. Woo, Jamie Zigterman

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Omecamtiv mecarbil (AMG 423) is a first-in-class direct activator of cardiac myosin, the motor protein that causes cardiac contraction. By enhancing the ability of the myosin molecule to strongly bind actin, the drug increases the duration of contraction and cardiac output. It has been evaluated as a potential treatment for heart failure in both intravenous and oral formulations with the potential to establish a continuum of care for patients in both in-hospital and outpatient settings. This presentation will describe the design of a robust synthetic process to prepare omecamtiv mecarbil and highlight the challenges and opportunities at the drug substance/drug product interface. This includes a convergent synthesis of the unsymmetrical urea core of the target from stable precursors, as well as engineering drug substance particle properties to aid drug product performance across formulations. The presentation will also include key elements of the control strategy for potential genotoxic impurities and highlight the use of PAT tools to increase process knowledge and guide chemical development.

K- 7 （Keynote Lecture）

Asymmetric Counteranion Directed Catalysis (ACDC): A General Approach to Enantioselective Synthesis

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Most chemical reactions proceed via charged intermediates or transition states. Such “polar reactions” can be influenced by the counterion, especially if conducted in organic solvents, where ion pairs are inefficiently separated by the solvent. Although asymmetric catalytic transformations involving anionic intermediates with chiral, cationic catalysts have been realized, analogous versions of inverted polarity with reasonable enantioselectivity, despite attempts, only recently became a reality. In my lecture I will present the development of this concept, which is termed asymmetric counteranion-directed catalysis (ACDC) and illustrate its generality with examples from organocatalysis, transition metal catalysis, and Lewis acid catalysis.

K-８（Keynote Lecture）

Commercial Applications of Continuous Process in SK

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In this presentation, actual scale-up experience and commercial examples of applying continuous process for the production of pharmaceutical products in SK biotek will be introduced.

SK biotek has been supplying pharmaceutical products to global pharmaceutical companies, which were produced by using continuous process, since early 2000. SK biotek's continuous process development for pharmaceutical products was initiated about 20 years ago, based on the experience and know-how accumulated through the 50 years of experience of operating petrochemical and refining plant which is SK group's major business area. Most petrochemical products are produced by using continuous process and this technology was extended to pharmaceutical area. SK's continuous process covers wide range of applications in pharmaceutical products manufacturing; continuous reactions using micro-reactor (or static mixer), catalytic reaction in a fixed bed packed with heterogeneous catalyst, distillation and extraction, etc. Each class of application will be introduced as follows:

First, static mixer (or micro reactor) application examples for fast exothermic and hazardous chemistry will be presented. Those examples will include low temperature organometallic reactions (using organo lithium, organo-hydride and Grignard reagent, etc.), azide reactions (such as Curtius rearrangement etc.), oxidation reactions using high concentration hydrogen peroxide and reactions using explosives such as tetrazole and nitro compounds and so on. Advantages of using continuous process for each case will be discussed.

Secondly, fixed bed catalytic application for high pressure hydrogenation, high temperature dehydrogenation, acid/base catalysed reaction and other catalytic reactions will also be presented. Fixed bed catalyst is usually more efficient than that of batch, easy to recover the catalyst, higher turnover, selective, and easy to work up (no need to separate catalyst from the product). Also fixed bed reactors can handle extreme conditions, such as high pressure to 300 atm and high temperature to 600^{o}C, which can accommodate exotic reactions that conventional batch reactors cannot handle. SK has unique position to produce custom made in-house fixed bed catalyst for specific application, by manipulating catalyst loading, pore size, shape and metal combinations, etc.

Third, our typical strategy or procedure of developing continuous process from lab to commercial plant in SK will also be introduced.

At the end of the talk, our practical experience of operating continuous process in commercial plant will be shared. This will include the handling of clogging problem and regulatory (GMP) aspects such as critical parameter control, traceability, cleaning validation, etc.

K－９（Keynote Lecture）

The Synthesis of Novel Pharmaceuticals

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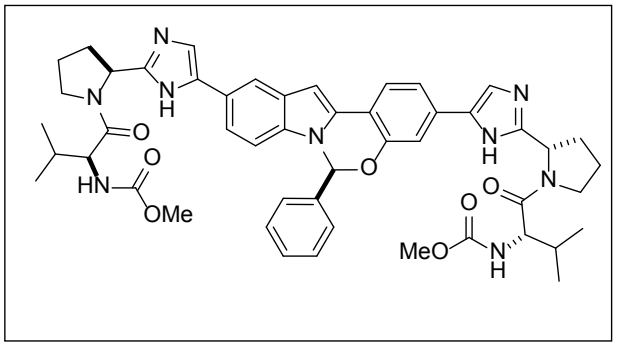
The synthesis of novel pharmaceuticals which are actively under development within Merck Research Labs will be presented. An overview of the strategy and approach to the process development of synthetic routes for the manufacturing of pharmaceuticals will be discussed, as well as some of the key factors which are considered during the design and development of the synthetic routes. Critical attributes of the route, such as the efficiency, robustness, operational safety, freedom of operation, and the environmental impact of the process will be highlighted. A few examples of new drug candidates which are currently in clinical trials will be presented. The development of a novel asymmetric synthesis of compound **1** (MK-8742), which is actively being investigated for the treatment of HCV, will be described. The development of an efficient approach to the synthesis of compound **2** (MK-8228), which is being studied for the treatment of CMV, will also be discussed.



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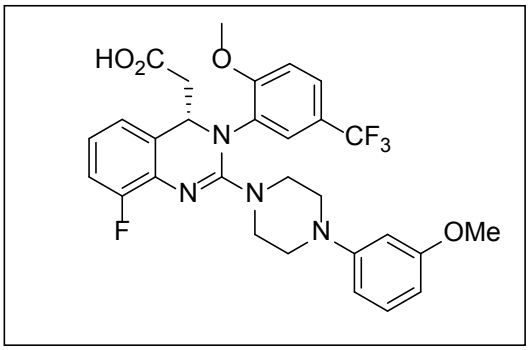

2

Dasotraline: From Laboratory to Commercial-Scale Manufacture

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The catalytic asymmetric hydrogenation approach continues to play an important role for the synthesis of chiral amines due to the ease of performing the reaction and the multitude of highly stereoselective asymmetric ligands now commercially available. However, significant chemistry challenges still must be overcome beyond mere catalyst selection before considering this methodology for commercial manufacture. For instance, despite the tremendous progress made in the area of catalyst design, only a few practical methods currently exist which allow one to easily access the required *N*-acetyl enamide starting materials on multi-kilogram scale. Likewise, even fewer practical methods currently exist that offer a solution to the difficult deprotection problem one is often faced with, if the chiral amine is ultimately the desired product. This presentation will highlight the manufacture of one of our late-stage clinical candidates (i.e., Dasotraline) on multi-kilogram scale using an efficient three-step catalytic asymmetric hydrogenation process that we have developed in-house. The presentation will demonstrate a QbD approach for mapping the design space and the critical process parameters of the hydrogenation reaction. It will also demonstrate the use of PAT tools in both laboratory and manufacturing settings leading to enhanced process understanding, improved cycle time and reduced manufacturing cost.

K-11 （Keynote Lecture）

Some Examples of Industrial Process Development Challenges

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Lonza is a world leader in custom development and manufacturing serving the pharmaceutical industry and Biotech. Our research and development organization has supported for more than 40 years clinical and commercial API supply using a broad technology toolbox and an innovative culture. The pharmaceutical market is evolving very rapidly and Lonza R&D has been able to adapt its chemical network and expertise to:

- strengthening regulatory requirement,
- fast moving innovative and licensing biotech landscape and
- Innovative drug at the edge of biology and chemistry.

Lonza has developed and enhance its core chemical technology with cutting edge capability like highly potent and cytotoxic containment and know-how, Bioconjugate complex supply management and continuous technology like Flow chemistry and micro reactor.

The Keynote will aim to demonstrate with several practical examples the main progress in the pharmaceutical development and manufacturing field which have been implemented in order to answer those few key challenges.

One of the examples will deal with flow chemistry:

Reactions within the pharmaceutical industry are usually conducted batch or semi-batch wise and would potentially economically and environmentally benefit from continuous flow and intensification via miniaturization. Moreover, process development and scale-up would be facilitated by the adoption of continuous flow reactors in the initial stages of molecule discovery and synthesis.

A methodology is introduced to select reactor type (Plate, Coil, or CSTR) and size based on the reaction kinetics/hazards and phases involved. The reactor design is also discussed in terms of operating conditions, including flow patterns, when optimizing product yields in a reaction network. Importantly, not all reactions benefit from continuous flow or miniaturization and thus process intensification should be implemented modularly as reactor geometry and operating conditions invariably affect transport-reaction kinetics interactions and their relative time scales.

K-12 (Keynote Lecture)

Development of New Catalytic System for C-H Arylation and Application to Synthesis of Pharmaceuticals

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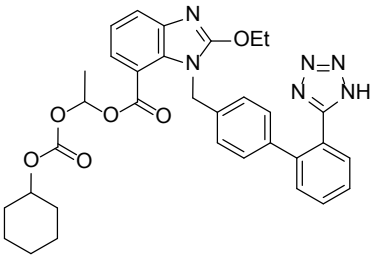
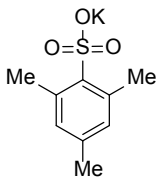
Angiotensin II receptor blockers (ARBs) exemplified by Candesartan Cilexetil (**1a**) has received a keen interest as antihypertensive due to high efficacy and safety. Annual amount of the active pharmaceutical ingredients of ARBs is reported to be >800MT in Japan. However, previous synthetic methods required stoichiometric amount of expensive and/or hazardous organometallic compounds. To address the challenge, we developed a novel synthesis of ARBs by means of C-H arylation to produce the biphenyl tetrazole unit in a highly atom economical manner. In this presentation, the author talks about a very efficient catalytic system for C-H arylation which contains Potassium 2, 4, 6-trimethylbenzenesulfonate (TMBSK) as a cocatalyst and the application to a practical synthesis of **1a**.

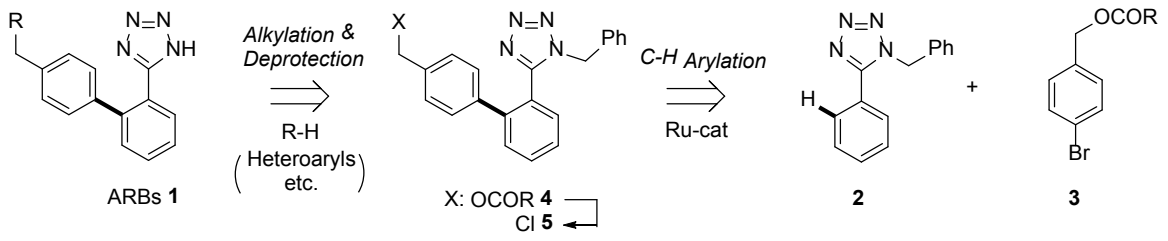


Candesartan Cilexetil (**1a**)



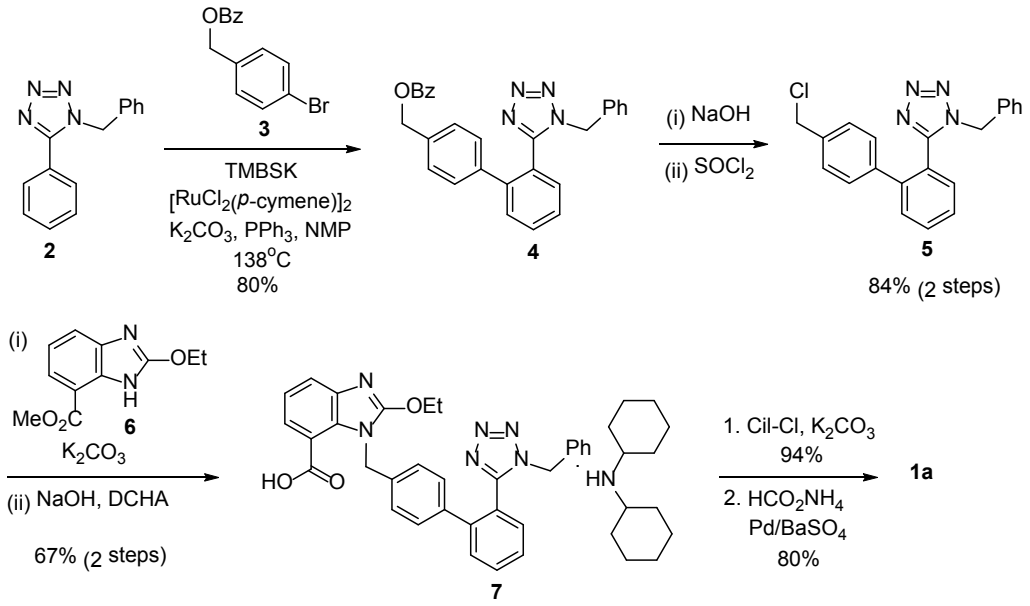
TMBSK

ARBs (**1**) carry biphenyl tetrazole unit as a common structure. The author came up with an idea to produce the key structural motif through C-H arylation. The C-H bond α to the tetrazole group in 1-benzyl-5-phenyl-1*H*-tetrazole (**2**) is supposed to be activated through chelation of Ru which permits C-H arylation of **2** with aryl bromide **3**. The resulting biphenyl derivative **4** might readily be converted to chloride **5** which, upon coupling with various functionalized fragments (R-H) followed by deprotection, would provide **1** in very short steps and in highly convergent manner.



Based on the strategy, the author developed a novel synthetic method ARBs through C-H arylation.[1-5] However, lack of reproducibility was observed for >100g scale synthesis and seriously retarded further development. To address the challenge, the author searched for a better catalytic system having a new cocatalyst to ensure robustness of the C-H arylation and finally discovered a highly efficient protocol employing a novel cocatalyst (Potassium 2, 4, 6-trimethylbenzenesulfonate: TMBSK).[6-12]

As an application of the present methodology, the author explored a new process for Candesartan Cilexetil (**1a**) and accomplished an innovative manufacturing method of **1a** through C-H arylation of **2** with **3**.[13]



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(13). This work has been chosen as "*Best Innovation in Process Development*" at CPhI Worldwide 2013 in Frankfurt and "*Best Poster Award*" at 15th Tetrahedron Symposium (6/22-28, London).

Methodologies toward Efficient Synthesis of Chiral Natural Products and Drugs

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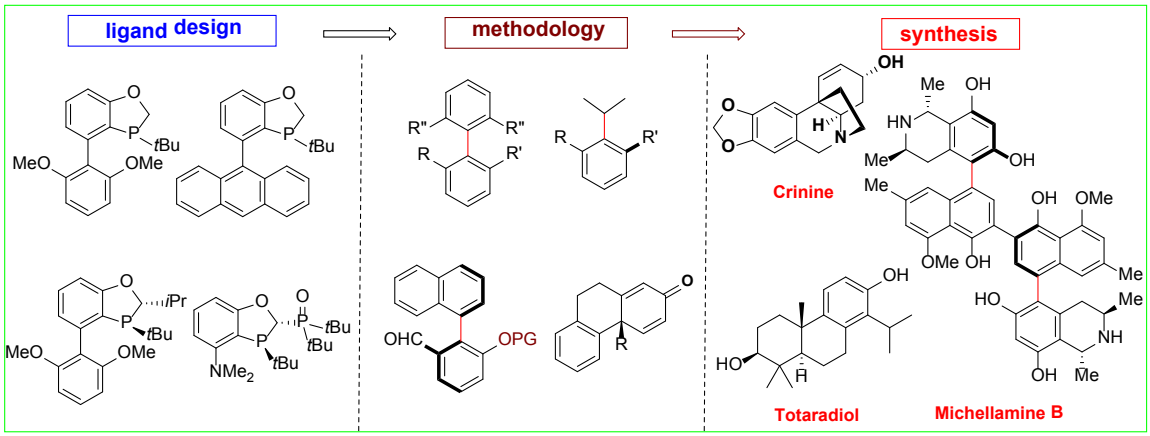
Development of efficient asymmetric catalytic methods for the synthesis of chiral natural products and drugs remains a significant challenge. Our research program is mainly focusing on exploring practical and efficient transition-metal catalyzed asymmetric transformations and their applications in syntheses of natural products and drugs. Using a series of genuinely designed P-chiral ligands as tools,[1] we have developed a few highly efficient asymmetric hydrogenation,[2] cyclization,[3] and cross-coupling[4] methodologies. The development of sterically hindered,[4a-c] functionalized, asymmetric aryl-aryl,[4d] and intramolecular dearomative cross-couplings[3b] will be mainly discussed in this presentation. Their applications in efficient syntheses of chiral biaryl natural products, terpenes, steroids, and alkaloids will be addressed.



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K- 14 （Keynote Lecture）

A Few of My Favorite Rings: Catalytic Cycles Inspired by Macrocycles.

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Erythromycin and ciclosporin represent macrocycles found in nature that challenge us due to their structural complexity and medicinal relevance. Inspired by these natural motifs, our laboratory has focused on developing synthetic methods based on transition metal-catalysis. In particular, we have focused on designing variants of hydroacylation, a strategy whereby an aldehyde C–H bond is added across an unsaturated functional group (e.g., olefins, alkynes, ketones). Our goal is to access transformations that are chemo-, stereo-, and regioselective. Building on these studies, we have recently extended our efforts to include related methods for making C–O, C–C, and C–N bonds through the coupling of two simple functional groups with high atom economy. Progress towards developing enantioselective hydroaminations, carboacylations, and cycloisomerizations will also be described.

Abstracts

Poster Presentation

1 P-01 ～ 1P-63

July 14

1P-01

Highly Practical New Methylenation Reagent for Aldehyds and Ketones

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The synthesis of alkenes from carbonyl compounds is one of the most fundamental reactions in organic synthesis. Since terminal alkene structures are frequently observed in natural products and are often used as the substrates for many synthetic reactions, their preparation has been studied intensively. Many methylenation reagents were developed by Wittig, Peterson, Jonson, Tebbe, and others. The Julia-Kocienski reactions (one-pot Julia olefination) are a very efficient tool for direct alkene synthesis via metallated heteroarylsulfones with carbonyl compounds.[1] Now we would like to introduce a practical methylenation reaction using a new Julia-type reagent, benzo-fused imidazolyl sulfone **1**.[2]

The dimethylation of cheap 2-mercaptobenzimidazole **2** gave a quantitative yield of **3** (Scheme 1). The oxidation of **3** with oxone gave **1** in 92% yield. Since the Julia-Kocienski reactions are generally more efficient when the Barbier-type procedure was used, a solution of **1** was treated with base in the presence of either aldehyde or ketone. The methylenation was first carried out with **2a** (Table 1). When 1.3 eq of NaHMDS was added to a THF solution of **1** and **2a** at -78 °C and the mixture was gradually warmed to room temperature, 42% yield of **3a** was obtained. LiHMDS and KHMDS was less effective and the use of DMF as solvent increased the yield to 79% and 88% yield was obtained with NaHMDS (1.7 eq). More practical conditions for the methylenation of **2a** were further studied. When the DMF solution of **1** and **2a** was treated with *t*-BuOK (1.7 eq) at room temperature, **3a** was obtained in 58% yield. Increasing the quantity of *t*-BuOK (3 eq) and **1** (1.2 eq) gave **3a** in 92% yield (Method A). This procedure is more economical and practical and the reaction proceeded in 1 h at room temperature. To establish scalability, the reaction was also run at the 5 mmol scale to give **3a** in 93% yield.

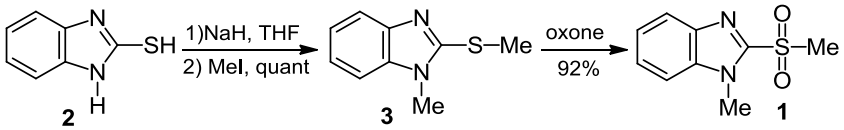
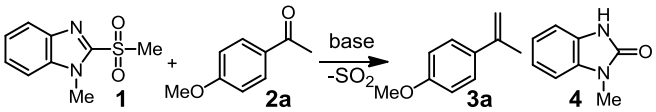


Table 1 Methylenation of **2a** with **1**[a]



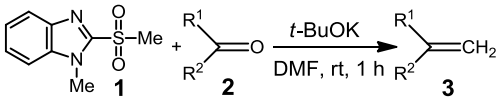
entry	base (eq)	solvent	conditions	yield%
1	NaHMDS (1.3)	THF	-78 °C to rt	42
2	LiHMDS (1.3)	THF	-78 °C to rt	21
3	NaHMDS (1.3)	DME	-55 °C to rt	54
4	KHMDS (1.3)	DME	-55 °C to rt	25
5	NaHMDS (1.3)	DMF	-55 °C to rt	79
6	NaHMDS (1.7)	DMF	-55 °C to rt	88
7	*t*-BuOK (1.7)	DMF	rt, 5 h	58
8	*t*-BuOK (2.5)	DMF	rt, 1.5 h	79
9[b]	*t*-BuOK (3.0)	DMF	rt, 1 h	92
10[b,c]	*t*-BuOK (3.0)	DMF	rt, 1 h	93

a) 0.3 mmol of **1** and 0.3 mmol of **2a** were used.
b) 1.2 eq of **1** was used. c) 5 mmol scale.

The methylenation of **1** with a variety of ketones and aldehydes were performed using *t*-BuOK (Table 2). The methylenation of **2b**

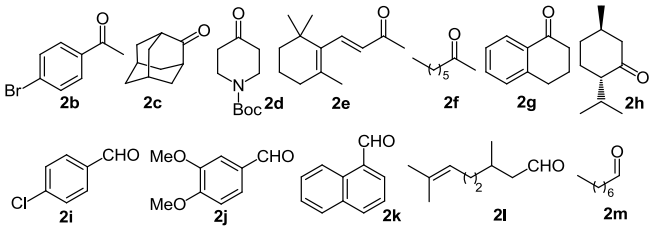
using 4 eq of *t*-BuOK gave **3b** in 95% yield. The reactions of aliphatic ketones were also efficient and not only **2c**, **2d**, and **2f** but also α,β-unsaturated ketone **2e** were transformed to the corresponding alkenes in 91-99% yield. Although the Wittig reagent, $CH_3P(C_6H_5)_3Br$ is the most often used methylenation reagent, problems occur in separation of triphenylphosphine oxide (FW 278) from the products in a large scale. In our reaction, the anion derived from **1** and base reacts with **2** to give the alkoxide **A**, from which nucleophilic addition to the benzimidazole part occurs to give **B**. Terminal alkene **3** would be formed by Smiles rearrangement along with **C** and SO_2. Since we could not detect any gas babble even in the 5 mmol scale reaction, SO_2 probably reacts with *t*-BuOK to form *t*-$BuOSO_2K$. After aqueous work-up with aq NH_4Cl, **3** and **4** were obtained. The by-product **4** (FW 148) is a small molecule and was easily removed from the reaction mixture by either filtration or column chromatography. When the reaction mixture was washed with 1 M NaOH, the usual work-up gave almost pure **3c**. The alkene **3c** was obtained in 96% yield after column chromatography. This method greatly simplifies purification of the product alkenes. The reaction of aliphatic ketone **2d** and aldehyde **2i** and **2l** were performed in the same way. For the reaction of aldehydes, 2.6 eq of *t*-BuOK is enough except for some improvement of yields were observed for **2i** and **2k** by using 3.0 eq of *t*-BuOK. Although it was reported that treatment of α-tetralone **2g** with methylenetriphenylphosphorane gave its enolate instead of leading to any alkene product, the reaction of **1** with **2g** gave **3g** in 77% yield. Furthermore, we tested the reaction of **1a** with sterically hindered (-)-menthone **2h**, which gave 59% yield of **3h** along with the recovered **2h** (39%) and trace amount of **1**. These results show that **1** decomposes slowly in the presence of *t*-BuOK in DMF and the yield of alkene **3h** was just moderate because of the low reactivity of sterically hindered **2h**.

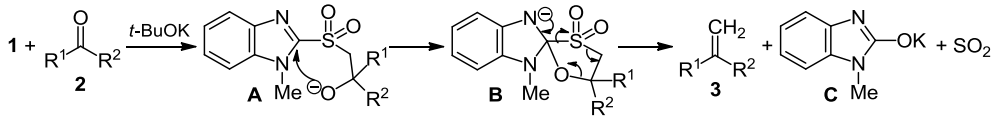
Table 2 Methylenation by *t*-BuOK[a]



entry	2	*t*-BuOK(eq)	1(eq)	yield%
1	**2b**	4.0	1.3	95
2[b]	**2c**	3.0	1.2	96
3[b]	**2d**	3.0	1.2	99
4	**2e**	3.5	1.2	91
5[c]	**2f**	3.0	1.2	91
6	**2g**	3.0	1.5	77
7	**2h**	3.0	1.2	59
8[b]	**2i**	3.0	1.1	93
9	**2j**	2.6	1.2	92
10	**2k**	3.0	1.1	91
11[b]	**2l**	2.6	1.1	97
12[c,d]	**2m**	2.6	1.5	74

a) 0.3 mmol of **2** was used. b) by basic aqueous work-up. c) NMR yield was determined by using methyl benzoate as an internal standard. d) 30 min.





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1) (a) Blakemore, P. A.; Cole, W. J.; Kocienski, P. J. Morley, A. *Synlett* **1998**, 26. (b) Kocienski, P. J.; Bell. A.; Blakemore, P. R. *Synlett* **2000**, 365.

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1P-02

Novel oxidation process for alcohols and sulfur compounds by sodium hypochloride pentahydrate ($NaOCl·5H_2O$) crystals

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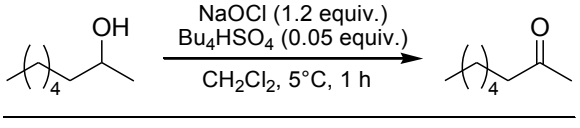
We have recently developed a new manufacturing process for sodium hypochlorite pentahydrate ($NaOCl·5H_2O$) crystals[1], whose use in chemical reaction has several notable features over conventional 13% aqueous sodium hypochlorite: (1) the available chlorine content is about 42%, (2) the pH upon solution is around 11-12, since the crystals contain small quantities of sodium hydroxide and sodium chloride, (3) the crystals are stable for 1 year below 7 ºC, and (4) easy weighable for being accurate equivalents. Nowadays, $NaOCl·5H_2O$ is commercial available from several companies in Japan.[2] Sodium hypochlorite is less danger for the handling and environmentally benign reagent because the wastes are water and NaCl after use.

We would like to report here several specific oxidations by $NaOCl·5H_2O$.

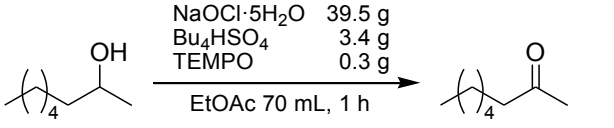
1) Oxidation of alcohols catalyzed by TEMPO[3]

Although oxidation of alcohols using a conventional sodium hypochlorite aqueous solution catalyzed by nitroxyl radicals represented by TEMPO[4] and AZADO[5] seems to be both economic and environmental friendly methods, it has several disadvantages as follows: (1) oxidation of bulky secondary alcohols with TEMPO is a low yield, (2) oxidation of alcohols with the AZADO can be achieved in good yield, but the preparation of which catalyst involves multi-steps, (3) reaction with around 10% concentration of aqueous NaOCl is poor volume efficiency, (4) in order to proceed the oxidation efficiently, it is necessary to be adjusted to pH 8~9.

We first examined oxidation of 2-octanol catalyzed by TEMPO or 1-Me-AZADO in dichloromethane. No pH adjustment was treated in all cases. 2-Octanone was obtained in good yields using $NaOCl·5H_2O$, while it was very low yield with conventional NaOCl solution.



TEMPO (0.01~0.005 equiv.)	$NaOCl·5H_2O$	97~99%
TEMPO (0.01 equiv.)	NaOCl aq.	1%
1-Me-AZADO (0.01equiv.)	$NaOCl·5H_2O$	100%
1-Me-AZADO (0.01 equiv.)	NaOCl aq.	14%

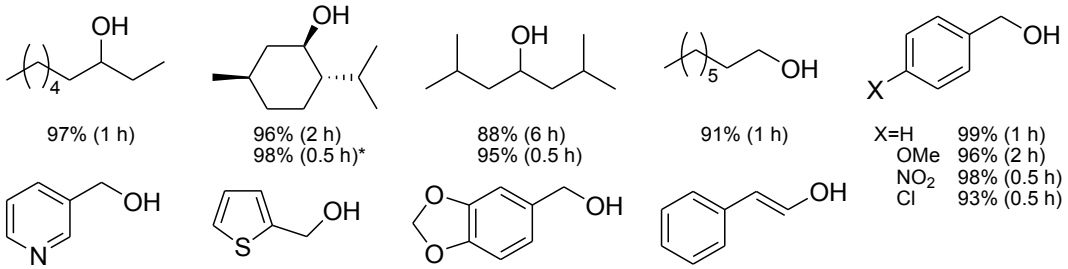


23 g (Y=90%)
b.p. 130°C/ 26 kPa

Preparative example using $NaOCl·5H_2O$

Example for the several tens gram scale oxidation with $NaOCl·5H_2O$ was demonstrated in ethyl acetate. 2-Octanone was isolated in 90% yield after distillation.

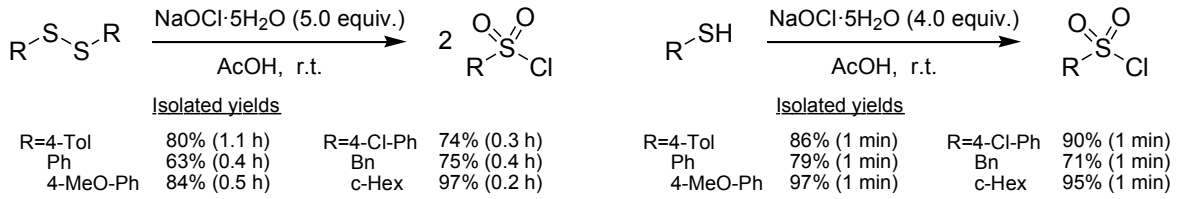
Next, we attempted the oxidations of several primary and secondary alcohols in this system of TEMPO (0.01equiv)-Bu_4NHSO_4 (0.05 equiv)-$NaOCl{\cdot}5H_2O$ crystals (1.2~1.6 equiv). Bulky secondary alcohols were oxidized to the corresponding ketones and primary alcohols afforded aldehydes in good yield, employed by inexpensive TEMPO without pH adjustment.



* 1-Me-AZADO was used instead of TEMPO

2) Preparation of sulfonyl chlorides from disulfides or thiols[6)]

Disulfides or thiols with $NaOCl{\cdot}5H_2O$ crystals in acetic acid gave the corresponding sulfonyl chlorides in high yields. Though the reactions were found to be proceeded in similar yields using conventional 12% aqueous NaOCl, synthetic advantages with $NaOCl{\cdot}5H_2O$ are a volume efficiency, stable oxidant for long period and easy weighable, and so on.



Isolated yields

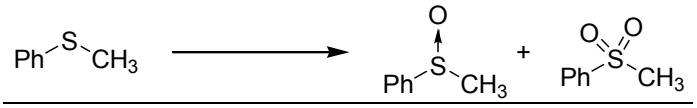
R=4-Tol	80% (1.1 h)	R=4-Cl-Ph	74% (0.3 h)
Ph	63% (0.4 h)	Bn	75% (0.4 h)
4-MeO-Ph	84% (0.5 h)	c-Hex	97% (0.2 h)

Isolated yields

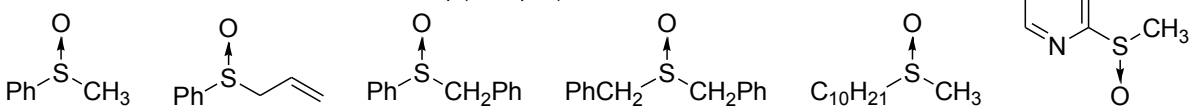
R=4-Tol	86% (1 min)	R=4-Cl-Ph	90% (1 min)
Ph	79% (1 min)	Bn	71% (1 min)
4-MeO-Ph	97% (1 min)	c-Hex	95% (1 min)

3) Selective oxidations of sulfides to sulfoxides and sulfones

Several sulfides were treated with $NaOCl{\cdot}5H_2O$ (1.1 equiv) in aqueous CH_3CN gave selectively the corresponding sulfoxides in high yield. When the oxidations with $NaOCl{\cdot}5H_2O$ (2.4 equiv) were performed in toluene-water heterogeneous solvents, the corresponding sulfones were given in high yields, selectively.



CH_3CN-H_2O, r.t.	$NaOCl{\cdot}5H_2O$ (1.1 equiv., pH 11)	98%	2%
	12% NaOCl aq. (1.1 equiv.,pH 13)	79%	16%
Toluene-H_2O, r.t.	$NaOCl{\cdot}5H_2O$ (2.4 equiv.)	—	99%
	12% NaOCl aq. (2.4 equiv.)	1%	1%



98% (18 min) 86% (8 min) 86% (7 min) 89% (10 min) 100% (9 min) 84% (23 min)

References: 1) T. Asawa *et. al*. Japanese Patent 4211130 (2008) 2) $NaOCl{\cdot}5H_2O$ is commercially available from Wako Pure Chemical Industries, Tokyo chemical industry, and Junsei Chemical Co. Large quantity of $NaOCl{\cdot}5H_2O$ can be directly supplied by Nippon Light Metal Company.

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1P-03

Enantioselective Synthesis of Optically Active Sultams Using *N*-Heteroarenesulfonyl Cinchona Alkaloid Amide Catalyst.

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Optically active sultams are an important class of synthetic targets because they often exhibit a broad range of biological activities. Therefore, expanding the scope of catalytic enantioselective synthesis of chiral sultams would be highly desirable. One of the simple ways to construct chiral sultams having quaternary carbon center is nucleophilic reaction to cyclic ketimines derived from saccharins. However, the enantioselective reaction to ketimines is not an easy task due to their low reactivity and difficulty of their enantiofacial control. On the other hand, we recently reported the first enantioselective decarboxylative Mannich-type reaction of malonic acid half thioesters (MAHTs) with ketimines derived from isatins using our original chiral *N*-heteroarenesulfonyl cinchona alkaloid amide catalysts.[1-3]

Herein, our ongoing interest was extended to the enantioselective decarboxylative addition of MAHTs to ketimines derived from saccharins using our original bifunctional organocatalyst. The reaction using *p*-toluene-, 1-naphthalene-, 2-pyridine- or 2-thiophenesulfonylated cinchona alkaloid amide catalysts gave the product in high yield but with lower enantioselectivity than that obtained from the reaction using 8-quinolinenesulfonyl cinchona alkaloid amide catalyst. Furthermore, the addition of protic reagent as an additive, such as hexafluoro-2-propanol or *p*-nitrophenol, afforded the product with high enantioselectivity. With these optimized conditions, the reaction of a series of ketimines derived from saccharins using *N*-heteroarenesulfonylated cinchona alkaloid amide catalysts in the presence of *p*-nitrophenol was examined, and various substituted ketimines derived from saccharins afforded products in good yield with high enantioselectivity.

In conclusion, we have developed a highly enantioselective decarboxylative addition of MAHT to ketimines derived from saccharine using 8-quinolinenesulfonylated cinchona alkaloid amide catalysts. To our knowledge, this is the first example of enantioselective Mannich-type reaction to ketimines derived from saccharins. [4]

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3. N. Hara, R. Tamura, Y. Funahashi, S. Nakamura, *Org. Let*. **2011**, *13*, 1662–1665.
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1P- 04

HasA Asymmetric Oxidation Catalysis from Pea (*SanCat-R*)

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In the past decade, the use of biomaterials as plant catalytic systems incorporating redox cofactors for asymmetric oxidation reactions has been investigated. In particular, the redox protein eluted from pea protein (PP) encapsulated with calcium alginate gel (PP gel) is available for synthesis. Specifically, membrane-bound enzymes (ME) are activated by a buffered glycine reaction solution (pH 9.0–10.0). Eluted from encapsulated PP, under aeration, ME can be applied to turnover kinetic resolutions; e.g., ME may synthesize *S*-(+)-**1** (*S*-naproxen precursor) utilizing a glutaraldehyde (GA)/a PEG (4000)-coated ME. An iron electron-transfer system may be incorporated as an oxygen driven-catalytic system for asymmetric oxidation. The species' exact nature engaged in the key reaction is demonstrated to be consistent with that of a heme-binding protein. An N-terminal sequence comparison also provides 93% similarity with a 20.853 kDa hemophore HasApf gene product [*Pseudomonas fluorescens* Pf-5]. Therefore, these features are regenerated by successive asymmetric catalytic events using an incorporated iron electron-transfer system in the presence of oxygen. However, a HasApf gene would be identified through the application of asymmetric oxidation, because no BLAST-hit exemplifying the gene was determined due to broad acquisition by PP.

The scope of this study is to clarify all the species engaged in the HasA biocatalytic oxidation sequence, eluted from encapsulated pea protein (PP) under aeration. The ESR spectrum appears at the g = 4.3 signals because of the intermediate spin (S = 5/2 and 3/2) in oxoferryl-Fe(IV) = O and/or a redoxin. FTIR experiments provide values 950 to 1250 cm^{-1} for the metal-bound sulfinate S–O vibrations. This indicates that the PP-HasA may be coordinated to Cys, not His/Tyr, and suggests that it can perform successive asymmetric catalytic events via an incorporated iron electron-transfer system. The asymmetric oxidation activity is attributed to a HasA that is native to the PP due to the broad acquisition by PP from commensal bacteria-*P. fluorescens PF-5*. The use of a raw biomaterial as a HasA-catalytic system for asymmetric oxidation is an important novelty, despite the apparent difficulties in working with pure dehydrogenase enzymatic/redox-cofactor systems for biotransformation. The new catalysis (i.e., *SanCat-R*) has placed on the market- Wako code No. 351-34213 (5g).

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1P-05

Development of A Highly Active Iron Catalyst for Transesterification

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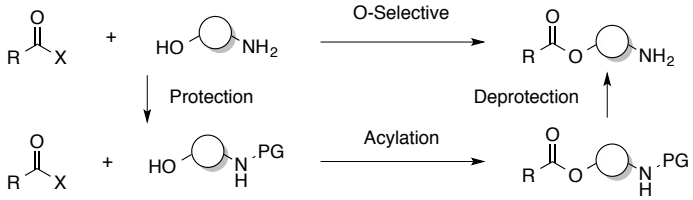
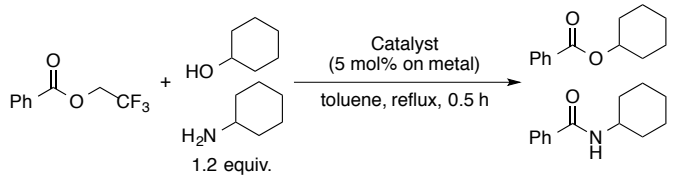
Ester and amide are ubiquitous functional groups in natural product and synthetic organic compounds. These important classes of compounds are generally prepared by condensation of carboxylic acid or treatment of highly reactive acylating reagent with alcohols or amines. As the innate nucleophilicity of amines is much greater than that of alcohols, the amines are preferentially acylated to give the corresponding amide even in the presence of the alcohols. On the other hand, chemoselective *O*-acylation is formidable task over *N*-acylation. Therefore, a stepwise protection-deprotection process is commonly adopted for the synthesis of amino esters. However, in terms of step- and atom economy, skipping protection-deprotection process is highly desirable. The ideal method is a direct conversion of alcohols to ester in the presence of amines in a catalytic manner (Scheme 1). Recently, chemoselective *O*-acylation of alcohol in the presence of the amines were reported including our zinc cluster catalysts.[1] However, there are only a few acylation using highly reactive activated esters or sterically congested tertiary alcohols.[2] Herein we report an iron catalyst-controlled chemoselective acylation of alcohols using activated esters in the presence of amines, and transesterification of tertiary butyl alcohol.

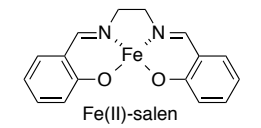


Scheme 1. Chemoselective*O*-Acylation of Amino Alcohols

Iron is among the most abundant and nontoxic metal and iron catalysis instead of precise metal have been emerged in cross coupling reaction. Although transesterification is fundamental and well investigated reaction, only limited numbers of iron catalyzed transesterification were reported and iron catalyst-controlled chemoselective reaction of alcohols over amines is unexplored.[3] We first evaluated the activity of various iron salts for chemoselective *O*-acylation using 2,2,2-trifluoroethyl ester as an activated ester in the presence of structurally similar amines (Table 1). While iron(II) chloride and iron(III) chloride showed moderate selectivity (Entries 1 and 2), iron(II) acetylacetonate and iron(III)



Entry	Catalyst	Yield (O)	Yield (N)	O/N
1	$FeCl_2$	73%	11%	6.6/1
2	$FeCl_3$	64%	9%	7.1/1
3	$Fe(acac)_2$	66%	6%	11.0/1
4	$Fe(acac)_3$	77%	3%	>20/1
5	Fe(II)-salen	90%	trace	>20/1
6	Fe(III)-salen	97%	trace	>20/1


Fe(II)-salen

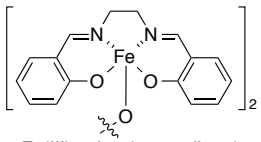
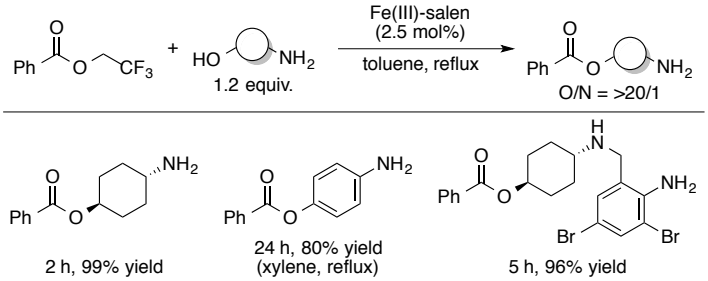

Fe(III)-salen (μ-oxo dimer)

Table 1. Screening of Iron Catalyst

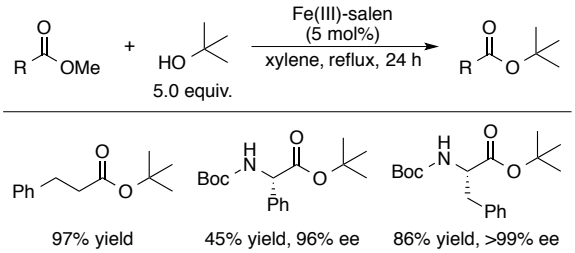
acetylacetonate afforded the product in high selectivity (Entries 3 and 4). Extensive ligand screening revealed that iron(II)- and iron(III)-salen complex showed excellent yield and selectivity (Entries 5 and 6).

With the optimized iron(III) catalyst in hand, we next examined the scope of amino alcohols (Scheme 2). Variety of simple amino alcohols could be acylated chemoselectively to afford corresponding amino ester. It is noteworthy that attenuate nucleophilic aminophenol was applicable to the iron catalysis. Moreover iron(III) complex was applied to the reaction of pharmaceuticals, thus highlighting high functional group compatibility of present iron catalysis. Iron catalyzed chemoselective transesterification was not confined to activated ester. Under analogous conditions, various methyl esters were successfully transformed into corresponding amino esters (not shown).



Scheme 2. Chemoselective Acylation of Amino Alcohols

The high activity of the present iron(III) complex prompted us to investigate transesterification of sterically congested tertiary alcohols. After slight modification of the reaction conditions, the corresponding tertiary butyl ester was obtained in high yield (Scheme 3). To the best of our knowledge, this is the first example of tertiary butyl ester formation through transesterification of tertiary butyl alcohol with methyl ester. To show the usefulness of the iron catalyzed butyl ester formation, we investigated tertiary butyl ester synthesis using chiral amino acid methyl ester. Although slight loss of enantiomeric excess was observed using phenylglycine, desired tertiary butyl ester was obtained in high yield without loss of enantiomeric excess using phenylalanine.



Scheme 3. Tertiary Butyl Ester Formation

In conclusion, we developed chemoselective *O*-acylation using activated ester in the presence of amines and transesterification of tertiary butyl alcohol. Further studies on improving reactivity and elucidation precise reaction mechanism are in progress.

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1P- 06

Enantioselective and Aerobic Oxidative Coupling of 2-Naphthol Derivatives Using Chiral Dinuclear Vanadium Complex in Water

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Water is a much safer reaction medium compared to toxic and/or flammable organic solvents, making aqueous processes environmentally benign methodologies. To date, a number of efficient, metal-catalyzed reactions and organocatalyzed reactions in water have been reported. In 2015, Adão and Pessoa's group reported the enantioselective oxidative coupling of 2-naphthol using amino acid-derived Cu(II) catalysts in $EtOH/H_2O$ to provide 1,1'-bi-2-naphthol (BINOL) (up to 33% yield, 44% ee).[1] We previously developed the dinuclear vanadium(V) complex (R_a,*S*,*S*)-**1** (Figure 1), which can catalyze the oxidative coupling of 2-naphthols through a dual activation mechanism.[2] Since (R_a,*S*,*S*)-**1** is stable in hydrophilic, polar solvents such as MeOH and EtOH in air, we envisioned that, in water, the chiral dinuclear vanadium(V) complex could promote the oxidative coupling of 2-naphthols to give BINOLs in high yields and high enantioselectivities.

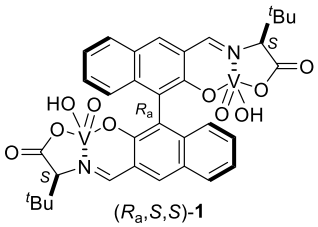
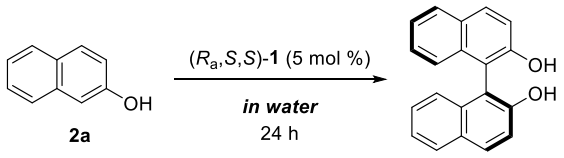


Figure 1. Dinuclear vanadium(V) complex (R_a,*S*,*S*)-**1**

Initially, the optimization of the reaction conditions for the oxidative coupling of 2-naphthol (**2a**) was performed with (R_a,*S*,*S*)-**1** (5 mol %) in water (Table 1). We previously reported that the oxidative coupling of **2a** in the presence of 5 mol % (R_a,*S*,*S*)-**1** in CH_2Cl_2 under air at 30 °C afforded (*S*)-BINOL (**3a**) in quantitative yield with 90% ee (entry 9).[2] In contrast, either no reaction or low conversion was observed in aqueous media, most likely due to the low solubility of 2-naphthol in water (entries 1 and 2). Although a catalytic amount of surfactants was added (entries 3–5), almost no improvement of either the chemical yield or enantioselectivity was observed. When the temperature was raised to 50 °C, **3a** was isolated in 91% yield with 80% ee (entry 6), but over 90 °C, the product's ee drastically decreased due to decomposition of the complex (entry 7). Based on these results, efficient dual activation of 2-naphthol using (R_a,*S*,*S*)-**1** in water requires a temperature of at least 50 °C to promote a single electron transfer from 2-naphthol to the catalyst.[2]

Table 1. Optimization of reaction conditions for the oxidative coupling of 2-naphthol (**2a**) in water

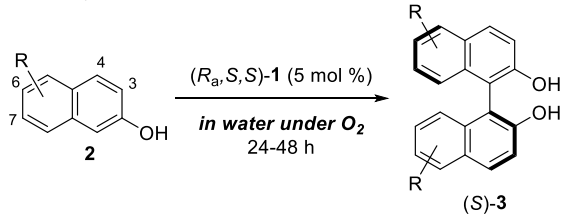


Entry	Air or O_2	Temp. (°C)	Additive (5 mol %)	Yield (%)[a]	Ee (%)[b]
1	Air	30	None	NR	—
2	O_2	30	None	11	Rac.
3	O_2	30	SDS	9	Rac.
4	O_2	30	TBAB	5	17
5	O_2	30	Triton X-100	26	25
6	O_2	50	None	92 (91)[c]	80
7	O_2	90	None	>99	66
8[d]	O_2	50	None	NR	—
9[e]	Air	30	None	quant	90

[a] ^{1}H NMR yield, 1,3,5-trimethoxybenzene was used as an internal standard. [b] Determined by HPLC. [c] Isolated yield. [d] Without (R_a,*S*,*S*)-**1**. [e] In CH_2Cl_2.[2]

To elucidate the applicability of the oxidative coupling using the vanadium complex in water, various 2-naphthol derivatives were examined (Table 2). 2-Naphthols bearing electron-donating or withdrawing groups such as MOM-O, MEM-O, CH_2=$CHCH_2O$, Br, MeO, Me, or Ph, at the C7, C6, or C4 position underwent the coupling reaction to produce corresponding BINOL derivatives **3b**–**3i** in good yields with high enantioselectivities (entries 2–9). 3-MeO-2-naphthol (**2j**) was also converted to coupling product **3j** in good yield with moderate enantioselectivity (entry 10).

Table 2. Oxidative coupling of 2-naphthol derivatives catalyzed by dinuclear vanadium complex in water



Entry	Substrate, R	Temp. (°C)	Yield (%)[a]	Ee (%)[b]
1	**2a**, H	50	**3a**, 91	80
2	**2b**, 7-OMOM	50	**3b**, 78	83
3	**2c**, 7-OMEM	50	**3c**, 65	63
4	**2d**, 7-OCH_2CHCH_2	50	**3d**, 78	85
5	**2e**, 7-Br	70	**3e**, 85	73
6	**2f**, 7-OMe	50	**3f**, 87	94
7	**2g**, 6-OMe	70	**3g**, 95	63
8	**2h**, 6-Me	70	**3h**, 89	77
9	**2i**, 4-Ph	70	**3i**, 82	85
10	**2j**, 3-OMe	70	**3j**, 69	44

[a]Isolated yield. [b]Determined by HPLC.

In an effort to clarify whether racemization of the products occurs, optically active 7,7'-dimethoxy-substituted BINOL **3f** (94% ee (*S*)) or 6,6'-dimethoxy-substituted BINOL **3g** (81% ee (*S*)) was stirred in water at 70 °C under the coupling conditions (100 mol % 2-naphthol (**2a**) and 5 mol % (R_a,*S*,*S*)-**1**. After 24 h, the dimethoxy-substituted BINOLs were recovered in 93% ee for (*S*)-**3f** and 77% ee for (*S*)-**3g**. Under the optimal reaction conditions in water, the ee of **3f** and **3g** decreased slightly. However, using $ClCH_2CH_2Cl$ as the reaction solvent instead of water resulted in decreasing ee (**3f**: from 94% ee (*S*) to 74% ee (*S*); **3g**: from 81% ee (*S*) to 11% ee (*R*)). It should be noted that in water, racemization of BINOLs is significantly suppressed as compared to organic solvent.[3]

To prove the utility of the present methodology, the oxidative coupling of **2** on a gram scale was examined. The reaction using 1.2 g of **2a** or **2f** in the presence of 5 mol % (R_a,*S*,*S*)-**1** allowed the formation of (*S*)-**3a** in 83% yield with 77% ee and (*S*)-**3f** in 63% yield with 94% ee, respectively.

In conclusion, we have developed the first example of a highly efficient and enantioselective oxidative coupling of 2-naphthol derivatives in water catalyzed by a chiral dinuclear vanadium(V) complex. In water, (R_a,*S*,*S*)-**1** maintained high catalytic activity for the coupling reaction to produce BINOLs in high yields with up to 94% ee. In water, almost no racemization of BINOLs was observed at 70 °C.[4]

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1P-07

Regio- and stereoselective synthesis of scaffolds for differentially all-carbon tetrasubstituted olefins

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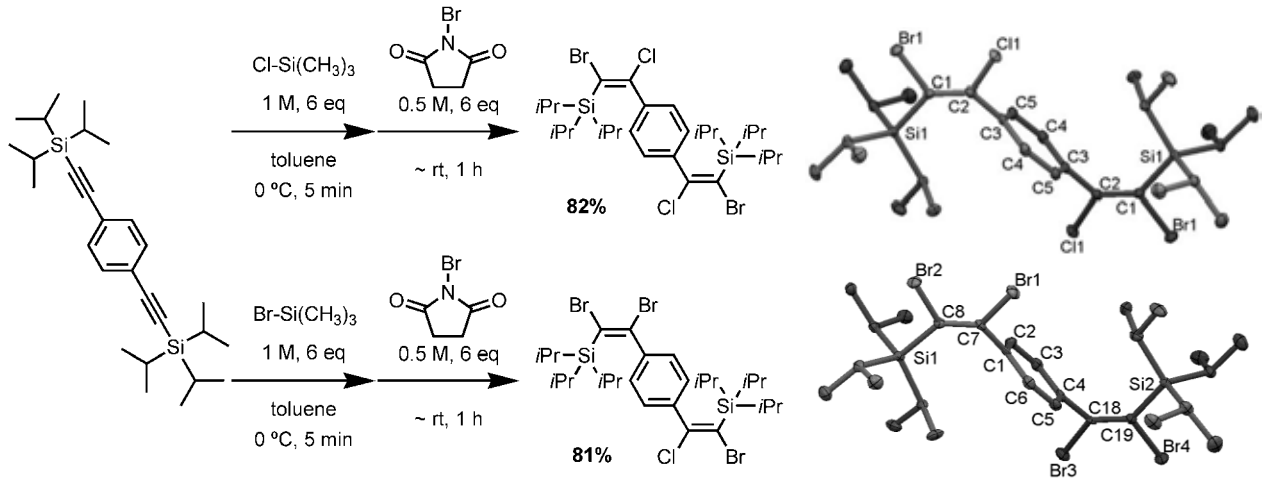
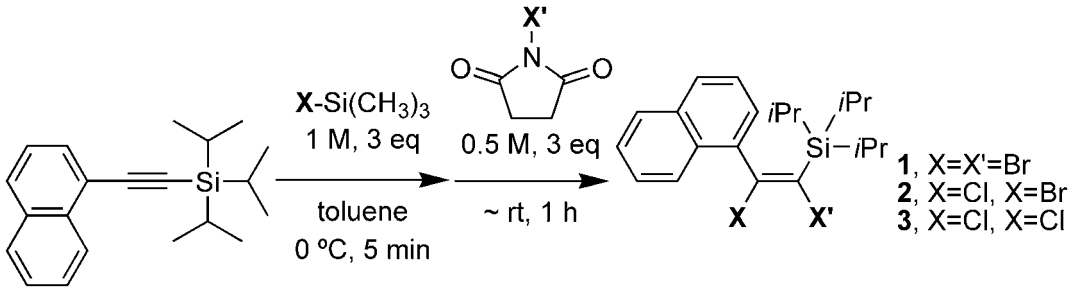
Regio- and stereoselective synthesis of differentially all-carbon tetrasubstituted olefins is significant issue in organic synthesis[1]; and the template strategy is one way to the olefins.[2,3] From the synthetic point of view, vicinal dihaloalkenyl silanes are good scaffolds because they have three tunable elements at vinyl positions. Despite the utility of vicinal dihaloalkenyl silanes, their synthetic availability still remains a challenge due to the inherent difficulty in regio- and stereoselective bis-halogenation of the corresponding silyl ethynylarenes. Employment of commercially available halogens is one way, but the halogens are occasionally unpleasant to work with. Particularly, bromine monochloride (BrCl) is typically gaseous (b.p. 5 ºC) and hygroscopic under an atmospheric air, which is apt to cause trouble to chemists in handling of reactions, purification, and safety. Herein we report the simple protocol enables an efficient regio- and stereoselective bis-halogenations of silyl ethynylarenes (**Scheme1**) .[4,5] The *in situ* BrCl was readily prepared by reaction of chlorotrimethylsilane with *N*-bromosuccinimide, which then perfectly added to the triple bond in a *syn*-mode. The high-yielding transformations formed each olefin as a perfectly single isomer, which occurred at 0 ºC ~ room temperature in just 1 h. In addition, the reaction system has significance to generate BrCl *in situ* formally, because toxic BrCl is handling-difficult in bench experiments owing to its low boiling point of 5 ºC. Thus, the methods achieved the selective bis-halogenation of silyl ethynylarenes, and provide a potentially synthetic scaffold for synthesis of differentially all-carbon tetrasubstituted olefins.



Scheme 1. Regio- and stereoselective bis-halogenations of triisopropylsilyl ethynylarenes

Screenings of different patterns of halogen source (TMSX/NX'S; X, X' = I, Br, Cl) were tested (**Table 1**). For entry 8, the combination of TMSCl/NBS afforded the desired Br–Cl adduct **2**; on the other hand, for entry 4, the employment of TMSBr and NCS did not afford the desired **2** but strangely gave bisbrominated **1** in 97% yield.

Table 1. Effect of pairing of TMSX/NX'S on silyl ethynylarenes



Entry	TMSX	NX'S	Product	Yield (%)	Recovered starting alkyne (%)
1	TMSI	NIS	-	0	~100
2	TMSI	NBS	**1**	78	15
3	TMSI	NCS	-[a]	26	73
4	TMSBr	NIS	**1**	97	0
5	TMSBr	NBS	**1**	85	0
6	TMSBr	NCS	**1**	71	0
7	TMSCl	NIS	-[a]	63	26
8	TMSCl	NBS	**2**	95	0
9	TMSCl	NCS	**3**	75	2
10	TMSI	-	-	0	-[b]
11	TMSBr	-	-	0	~100
12	TMSCl	-	-	0	~100
13	-	NIS	-	0	~100
14	-	NBS	-	0	~100
15	-	NCS	-	0	~100

[a] The reasonable Cl-I adduct was found in ^{1}H NMR spectra, but too labile to keep in pure form. [b] Multi spots on TLC were observed.

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1P-08

Process Research in NMR Tube

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In pharmaceutical development, it is highly important to supply suitable drug substance for clinical trial in timely manner. Quality control of the drug substance is a key for the development in the process of works, but unexpected impurities are sometimes found in the manufacturing processes. To investigate the root cause of impurity contamination, structural analysis for the impurity is required. If the impurity is a foreign material (ex. polymer or something), it will be very hard to do structural analysis, due to simple and broad signals in ^{1}H-NMR and undetectability in mass spectrometry. In this case, DOSY (Diffusion Ordered NMR Spectroscopy) can provide a solution. By measuring a diffusion coefficient, it will allow getting additional structural information of the impurity.

DOSY is a NMR method for measuring self-diffusion coefficients in a solution. Diffusion NMR (=DOSY) experiments resolve different compounds spectroscopically in a mixture based on their differing diffusion coefficients, depending on the size and shape of the molecules. In recent literature,[1] the molecular weight of unknown compound can be estimated by the diffusion coefficient.

The drag force f of the fluid on a sphere is written in Stokes' law as follows;[2]

$$f = 6\pi\eta_0 v r_H \qquad (1)$$

η_0 is the fluid viscosity, v is the velocity of the sphere relative to the fluid, and r_H is the Stokes radius. The relationship between the diffusion coefficient D and the drag force f is written in Stokes-Einstein equation as follows;[3]

$$D = (kT)/(f/v) = (kT)/6\pi\eta_0 r_H \qquad (2)$$

This equation can be transformed to the equation for the molecular weight M as follows;[1]

$$M = (4\pi r_M^3 \rho N_A)/3 \qquad (3)$$

r_M is the hydrodynamic radius. r_M can be empirically approximated to r_H. ρ is the fluid density and N_A is the Avogadro constant. DOSY experiment affords the diffusion coefficient D, by which the Stokes radius r_H can be calculated by the fluid viscosity η_0. By substitution of this rH and the fluid density ρ for the equation (3), the molecular weight M can be estimated. These experiment and calculation allows us getting the estimated molecular weight of such the polymeric contaminant.

Polystyrene is a synthetic resin produced by the polymerization of styrene. It is widely employed in the pharmaceutical industry as rigid containers, disposable tools and foamed impact absorbing materials. Polystyrene can potentially contaminate pharmaceutical drugs because it is a very versatile material. If drugs are contaminated by polystyrene, its structural analysis will be very difficult, because the signals in ^{1}H-NMR is broad and the ion in mass spectrometry is not detectable.

Here, we would like to present that an approach for the structural analysis of an unexpected foreign material (such as polystyrene) by using DOSY and other NMR measurements, and will contribute to process research.

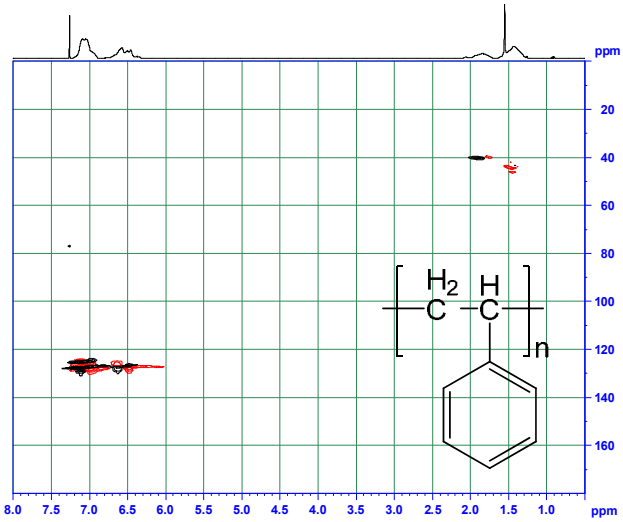

Figure 1 HSQC spectrum of polystyrene

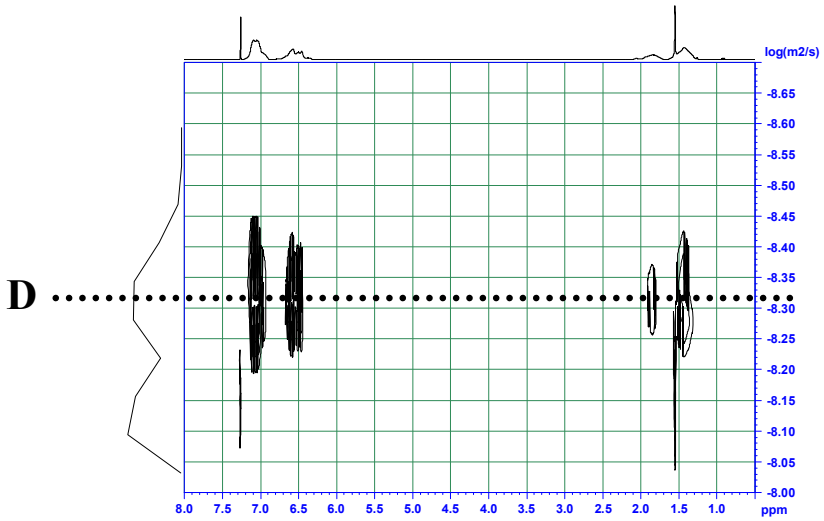

Figure 2 DOSY of polystyrene

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1P-09

Disiloxane Synthesis Based on Silicon-Hydrogen Bond Activation Using Platinum Group Metal on Carbon in Water and Heavy Water

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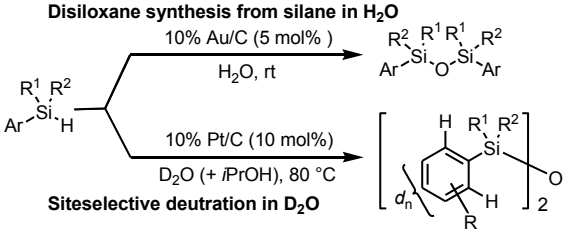
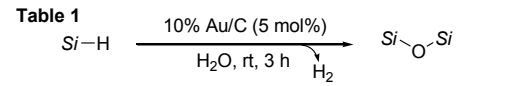
Siloxane possessing silicon-oxygen linkage is an important core of the functional materials, such as liquid crystals, thermosets, and bioactive compounds. Furthermore, aryl or vinyl-substituted disiloxanes can be Hiyama type coupling partners in organic synthetic chemistry. The transformation of hydrosilanes to disiloxanes is a straightforward synthetic method, and the direct disiloxane synthesis based on the $InBr_3$-catalyzed air oxidation of hydrosilanes[1] and the homogeneous Rh and Re catalytic methods using H_2O as the green solvent and oxidant were also developed.[2] We newly developed the heterogeneous Au/C-catalyzed direct synthesis of disiloxanes starting from hydrosilanes in water, and the unprecedented and regioselective Pt/C-catalyzed deuteration of aromatic nuclei of aryl-substituted disiloxanes generated by the oxidative coupling of hydrosilanes in deuterium oxide (D_2O, heavy water) (Scheme 1).

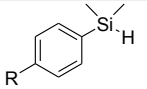
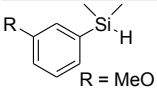
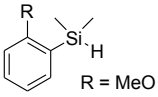
Scheme 1
Disiloxane synthesis from silane in H_2O



The oxidative coupling of hydrosilanes using H_2O in the presence of Au/C (5 mol%) effectively proceeded at room temperature under atmospheric argon within 3 h to give the corresponding disiloxanes in excellent yields (Table 1). Although Pt/C and Pd/C were also effective as catalysis, the yields were slightly lower than that using Au/C. Various aryldimethylsilanes could be applied for the Au/C-catalyzed direct synthesis of disiloxanes in H_2O. 4-MeO, Me, F, Br and CF_3-phenyl-substituted silanes were effectively transformed into the corresponding disiloxanes in excellent yields (Table 1, left column). Although hydrogen gas should be generated during the reaction process, TBS ether and alkyne moieties within the molecule could remain without their hydrogenation (Table 1, left column). Additionally, 3- or 2-MeO and F-phenyl-substituted silanes also underwent the Au/C-catalyzed oxidation in H_2O to give the disiloxanes (Table 1, right column). Furthermore, dihydromethylphenylsilane underwent the continuous oxidative coupling of the hydrosilane moieties to mainly

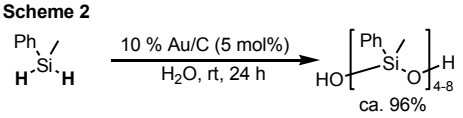
Table 1



Substrate	Yield (%)	Substrate	Yield (%)
			
R = OMe	>99	R = MeO	97
Me	>99	F	94[a]
F	97		
Br	92	R = MeO	97
CF_3	87	F	92
CH_2OTBS	91		
C≡CPh	82		

a) 6 h

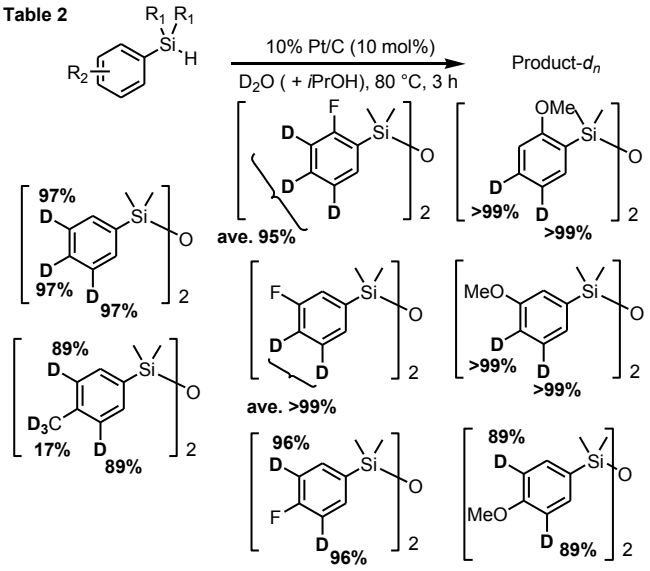
Scheme 2



give a mixture between tetramer to octamer (Scheme 2).

Meanwhile, deuterium-labeled compounds are widely utilized in various fields, such as analytical studies and material chemistry (e.g., fiber optics and heavy drugs). We have previously developed the mild and platinum group metal on carbon-catalyzed multi-deuteration methods of arenes using D_2O under atmospheric hydrogen as an activating agent of the heterogeneous metal surface.[3] We also revealed that the platinum group metal on carbon effectively catalyzed the dehydrogenation of secondary and primary alcohols to generate corresponding carbonyl products and hydrogen gas,[4] and *in situ*-genarated hydrogen derived from *i*-PrOH was utilized for the multi deuteration of aromatic nuclei as a catalyst activator.[5] Therefore, we presumed that the deuteration of arene nuclei of aryl-substituted disiloxane could proceeded in D_2O instead of H_2O based upon the activation of the catalyst by hydrogen generated during the transformation of hydrosilane to disiloxane. It is noteworthy that the use of Pt/C in D_2O/*i*-PrOH at 80 °C effectively catalyzed the oxidative disiloxane synthesis together with the regioselective deuteration on the arene nuclei at *meta*- and *para*-positions of the Ar-Si bond (Table 2). Various arylsilanes bearing fluoro- or methoxy group at the *ortho*-, *meta*- or *para* position of the aromatic ring could effectively proceed to give the corresponding deuterium-labeled disiloxanes with high D efficiencies and regioselectivities (Table 2).

Table 2



In the present reactions, heterogeneous catalysts could be reused without metal-leaching and only hydrogen was generated as a byproduct. Because the production method of hydrogen as an energy source from organosilanes is important and the diaryltetramethyldisiloxanes are good coupling reagents for the Hiyama-type reaction, the present methods are expected to contribute to various research fields.

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1P- 10

Palladium on carbon-catalyzed and chemoselective oxidation of aromatic acetals

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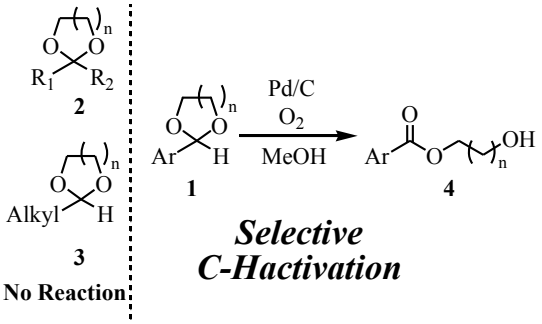
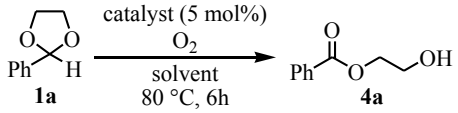
Acetals and ketals are generally utilized as protecting groups of aldehydes and ketones, and transformed to various functionalities in several steps including an acid-catalyzed deprotection process. Meanwhile, the direct oxidation of acetals into the corresponding ester derivatives was accomplished using the stoichiometric oxidants [e.g., Phenyliodine diacetate (PIDA)[1] and 2-iodoxybenzoic acid (IBX)[2]). Under these reaction conditions, aromatic cyclic acetals (**1**) as well as aliphatic cyclic acetals (**2**) were equally oxidized to the corresponding hydroxyalkyl esters (such as **4**) (Scheme 1), and acid-labile ketals may be deprotected to ketones due to acids generated during the oxidation process. The chemoselective transformations of acetals in the presence of ketals were solely acheived by the specific formation of pyridinium-type salts derived form acetals using the combination of the stoichometric pyridine derivatives (e.g., 2,6-lutidine and 2,4,6-collidine) and triethylsilyltriflate (TESOTf).[3,4] We have newly developed the chemoselective oxidation method of aromatic cyclic acetals (**1**) in the presence of aliphatic cyclic acetals (**2**) or ketals (**3**) by the heterogenesous Pd/C-catalyzed conditions under atomospheric oxygen (Scheme 1).

Scheme 1. Pd/C-catalyzed chemoselective oxidation of aromatic acetal under oxygen



First of all, we have examined the catalyst and solvent efficiencies in the oxidation of 5-membered cyclic acetal derived from benzaldehyde (**1a**) using the 5 mol% of catalyst under oxygen at 80 ˚C for 6 h (Table 1). The desired benzoic acid hydroxyethyl ester (**4a**) was obtained by the use of 10% Pd/C and Pt/C in MeOH in high yields (entries 1 and 2), while 10% Rh/C, Ru/C and Au/C were inefficient (entries 3-5). *i*-PrOH and THF were inadequate solvents for the Pd/C-catalyzed oxidation, and the reaction in H_2O gave benzoic acid resulting from the hydrolysis of **4a**. Therefore, Pd/C and MeOH were chosen as the optimal catalyst and solvent.

Table 1. Catalyst and solvent efficiencies

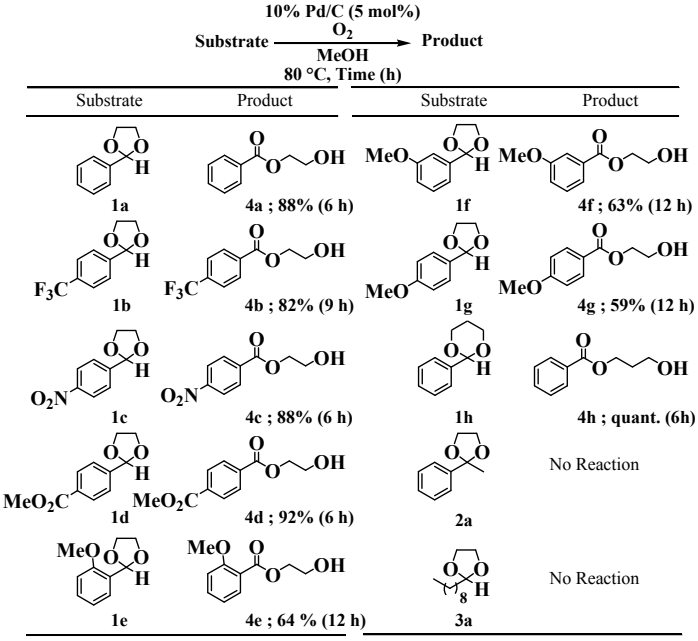


1a **4a**

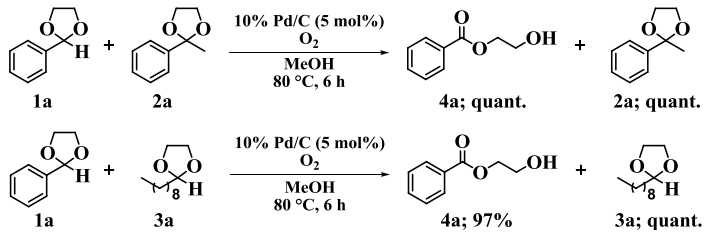
entry	catalyst	solvent	Yield (%) SM	Yield (%) Product
1	10% Pd/C	MeOH	0	88
2	10% Pt/C	MeOH	0	70
3	10% Rh/C	MeOH	16	0
4	10% Ru/C	MeOH	2	0
5	10% Au/C	MeOH	3	4
6	10% Pd/C	H_2O	0	0 [74][a]
7	10% Pd/C	*i*-PrOH	53	37
8	10% Pd/C	THF	45	43

[a] Benzoic acid was obtained.

Table 2. Scope of substrates



Scheme 2. Chemoselective oxidation of aromatic acetals



Pd/C-catalyzed oxidation in MeOH under oxygen could be applied to the various aromatic cyclic acetals, such as the electron-withdrawing CF_3 (**1b**), NO_2 (**1c**) and CO_2Me (**1d**) as well as the electron-donating MeO (**1e-g**)-substituted aromatic 5-membered cyclic acetals and 6-membered cyclic acetals (**1h**), to provide the corresponding ester derivatives (**4b-h**) (Table 2). On the other hand, the aliphatic acetals (**2a**) and ketal (**3a**) never underwent the oxidation and the unchanged starting materials were completely recovered. Encouraged by these selectivities, the chemoselective oxidation between aromatic cyclic acetals (**1a**) and aliphatic cyclic acetal (**2**) or ketal (**3**) derivatives was next examined (Scheme 2). The Pd/C-catalyzed oxidation of **1a** in the presence of **2a** chemoselectively proceeded to give the desirabled ester (**4a**) in 97% yield and the unreacted **2a** was quantitatively recovered. Furthermore, **1a** could be quantitatively converted into **4a** without any transformation of **3a**.

In conslusion, we have developed the first catalytic and chemoselective transformation method of aromatic cyclic acetals into the corresponding hydroxyalkyl ester derivatives in the presence of aliphatic cyclic acetals or ketals. Oxygen is a clean oxidant to be converted into water and heterogenesou Pd/C catalyst could be easily removed by the simple filtration. The present mild, neuteral and chemoselective oxidation of aromatic cyclic acetals can provide a novel synthetic route.

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1P- 11

Palladium-catalyzed synthesis of enol ethers by the direct alkoxylation of acrylic acids

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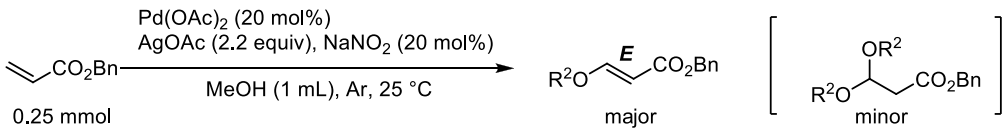
Enol ethers have been employed as synthetic intermediates aimed at the synthesis of heterocycles, such as isoxazole,[1] quinolinone,[2] furan,[3] and pyridine.[3] Some enol ethers also have significant biological activities, such as antitumor activity based on the inhibition of human DNA topoisomerase II.[4]

3-Alkoxyacrylic acid derivatives could be synthesized by a conjugate addition of alcohols to alkynes of the monosubstituted alkynoic acid derivatives as geometric mixtures of *E* and *Z* isomers.[5] Jiang et al.[6] reported that terminal alkenes of alkyl acrylates, acrylonitrile, and acrolein could react with methanol in supercritical carbon dioxide under 10 MPa of oxygen in the presence of $PdCl_2$ as a catalyst together with an oxidizing reagent, such as polystyrene-supported benzoquinone, to afford the corresponding dimethyl acetal as the major product, which would be generated by the conjugated addition of methanol to the intially obtained methyl enol ether. Therefore, a general, practical, and selective method for the generation of enol ethers from alkenes is highly demanded.

Scheme 1 Optimized reaction conditions on the methoxylation of benzyl acrylate.

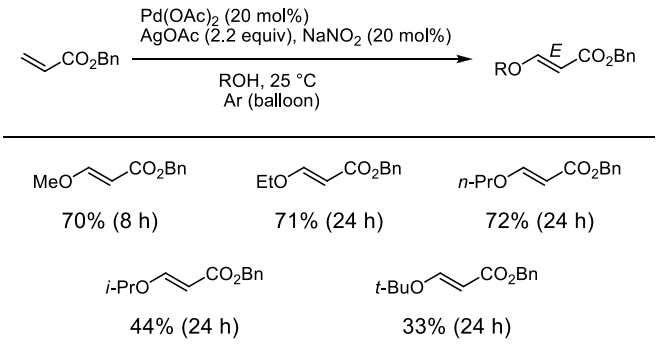


In the initial investigation of our methoxylation of benzyl acrylate using methanol in the presence of catalytic amount of $Pd(OAc)_2$, the reaction efficiency was found to be highly depended on the lot number of $Pd(OAc)_2$. Commercial $Pd(OAc)_2$ is generally prepared by the oxidation of palladium metal using nitric acid as an oxidizing agent in acetic acid. We then assumed that the different reactivity in the present methoxylation would be derived from the contamination of a small amount of nitrite ion. Use of catalytic amounts of sodium nitrite together with $Pd(OAc)_2$ was finally revealed to be effective in the presence of silver acetate (2.2 equiv) to afford the corresponding enol ether in good yield at room temperature after detail optimization of the reaction conditions, including catalysts, oxidizing reagents, additives, and temperature (Scheme 1). We then investigated the generality of this palladium-catalyzed alkoxylation at the terminal alkene of benzyl acrylate with various alcohols. As shown in Scheme 2, the primary, secondary, and tertiary alcohols could react with benzyl acrylate; especially primary alcohols, such as

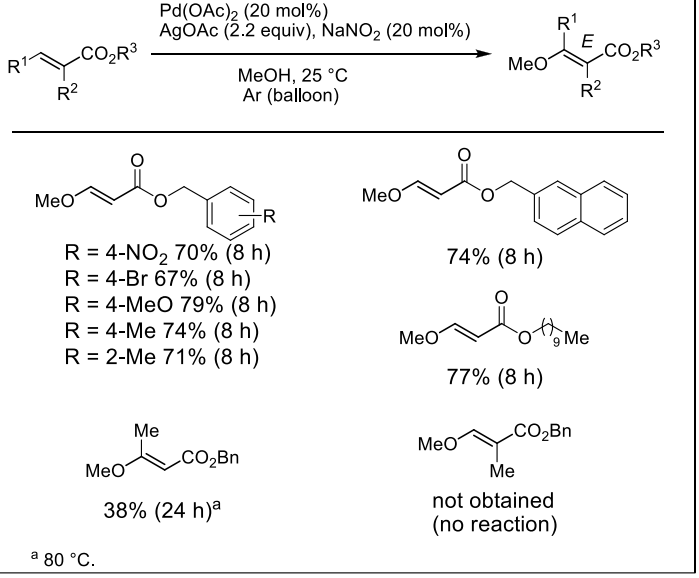
methanol, ethanol, and *n*-propanol, were good alkoxylating reagents to give the corresponding enol ethers in good yields, while secondary or tertialy alcohols, such as *i*-propanol and *t*-butanol, gave relatively low yields due to the steric hinderance.

The palladium-catalyzed methoxylation of the alkene moiety of various acrylates was summarized in Scheme 3. Both electron-donating and electron-withdrawing functionalities substituented on the aromatic ring of benzyl acrylate were tolerant under the conditions, and never affected the reaction progress. Both 2-naphthylmethyl and decyl acrylates were also applicable, leading to a good formation of the corresponding enol ethers. Furthermore, the methylation of benzyl crotonate as an internal alkene selectively gave the desired trisubstituted *E*-alkene in 38% yield by heating at 80 °C. On the other hand, benzyl α-methylated acrylate, benzyl methacrylate, was never reacted under the present alkoxylation conditions.

Scheme 2 $Pd(OAc)_2$-catalyzed alkoxylation of benzy acrylate with various alcohols.



Scheme 3 $Pd(OAc)_2$-catalyzed methoxylation of various acrylates.



[a] 80 °C.

In summary, we have developed a mild and efficient method for the synthesis of enol ethers based on the palladium-catalyzed direct alkoxylation of the terminal alkene of acrylates with various alcohols. Since the present reaction proceeds in a complete *E*-selective manner and no special equipments were required, the protocol will be of practical use in both academia and industry.

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1P- 12

Nickel-Catalyzed Deuteration of Phenol Derivatives with Novel NHC Ligands

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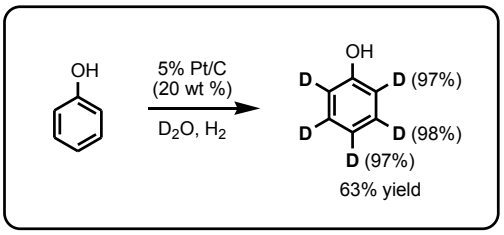
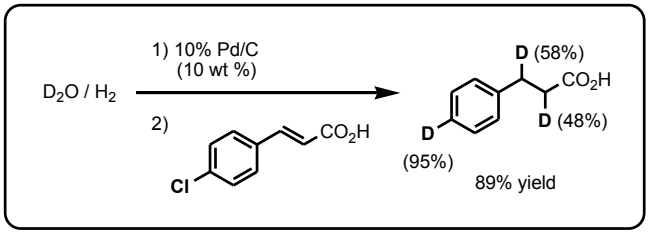
Deuterium is known to be useful as a labeled element for pharmacokinetic analysis. In recent years, it has attracted much attention that the introduction of deuterium into pharmaceutical agents is effective in controlling the bioactivities or drug interactions.[1] Although H/D exchange reactions have been reported as efficient deuteration methods of aryl/heteroaryl groups, there are problems in the control of reaction points and D contents. (Scheme 1).[2a] On the other hand, as a relatively advantageous method to control the reaction points, Cl/D exchange reactions are known (Scheme 2).[2b] But these methods have a problem in chemoselectivity. In addition, a deuterium source is required amount of solvent in most of these cases.

Scheme 1

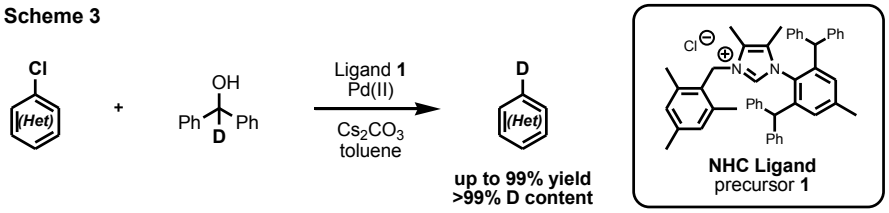


Scheme 2



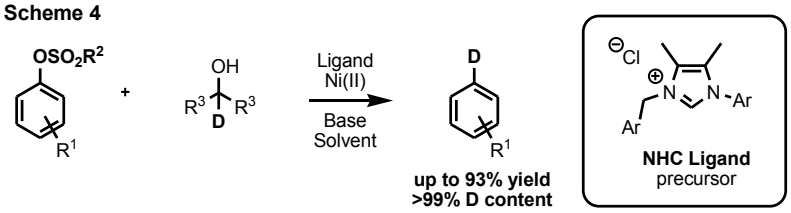
In our laboratory, we have recently developed the *palladium*-catalyzed deuterodechlorination of aryl/heteroaryl chlorides with high substrate tolerance and excellent D contents (Scheme 3).[3]

Scheme 3



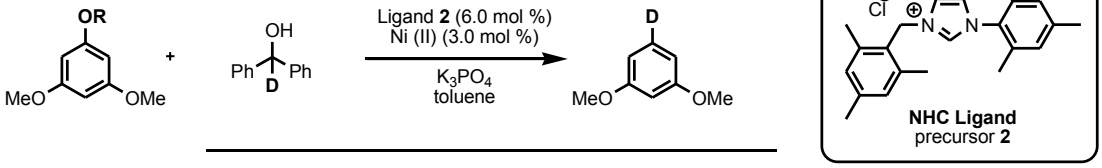
Phenol is a cheap raw material for medicines or dyestuffs, and it is possible to easily obtain a variety of derivatives. Also, aryl sulfonates can be easily synthesized from inexpensive phenols and sulfonyl chlorides. To the best of our knowledge, there are no examples of transition-metal-catalyzed deuterodesulfonation of aryl/heteroaryl sulfonates. Then, we successfully realized the efficient *nickel*-catalyzed deuterodesulfonation of aryl sulfonates with α-deuteriobenzhydrol as a deuterium source using an inexpensive and readily synthesized carbene ligand precursors (Scheme 4). This method made it possible to selectively and efficiently deuterate aryl sulfonates by using a catalytic reduction through the β-hydrogen elimination.

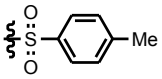
Scheme 4



First, we screened leaving groups using 3,5-dimethoxy sulfonates (mesylate, tosylate, and dimethyl sulfamate) and α-deuteriobenzhydrol as a deuterium source (Table 1). As a result, aryl dimethyl sulfametes gave the best yields and D contents (entry 3).

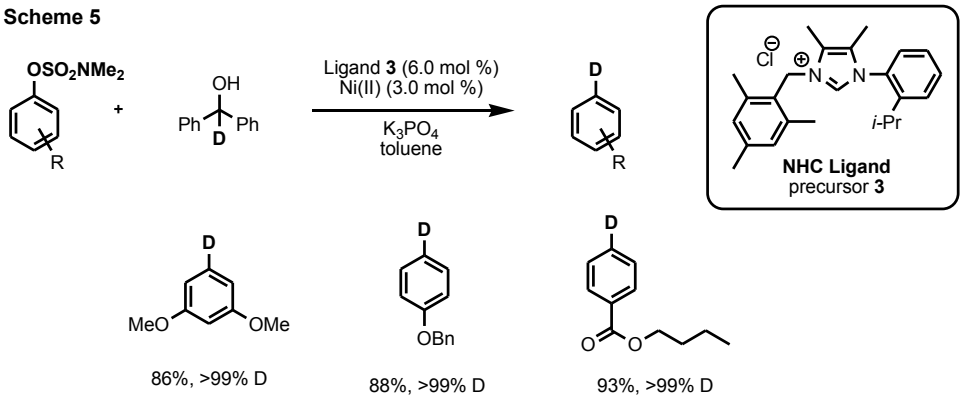
Table 1



entry	R	yield (%)	D content (%)
1		43	99
2		71	>99
3		75	>99

After screening NHC ligands, we examined the scope of substrates using ligand **3** (Scheme 5). Electron-rich and electron-deficient aryl dimethyl sulfamates afforded the desired products in high yields and D contents.

Scheme 5



In this presentation, we will report optimization of reaction conditions and the scope of substrates in detail.

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1P- 13

Selective deprotection of silyl ethers with SO_3H silica gel in the presence of acid-sensitive protecting group

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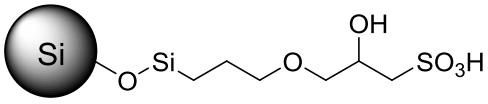
For a few decades, solid-supported reagents have widely been used in the organic synthesis.[1,2] The utility of the solid-supported reagents is expected to lower the waste product and to provide efficient and environmentally benign process. Indeed, solid catalysts can be easily separated from the reaction products by simple filtration and be recyclable. We recently reported desilylation reaction of aryl or alkyl silyl ethers using a silica gel whose surface was modified alkylsulfonic acid groups (SO_3H Silica gel) (Fig. 1).[3] The SO_3H silica gel is applicable to the desilylation reactions of various derivatives: alkaloid, sugar, and nucleoside derivatives with silyloxy group.[3,4] The feature of the procedure is that the crude filtrate (crude product) contained no silyl residues, which indicating that this is a column-less deprotection procedure. In this poster presentation, we report that selective desilylation reaction in the presence of acid-sensitive protective groups using the SO_3H silica gel.



Shape: spherical
Pore size: 7 nm
Particle size: 100 μm
SO_3H content: 0.46 mmol/g

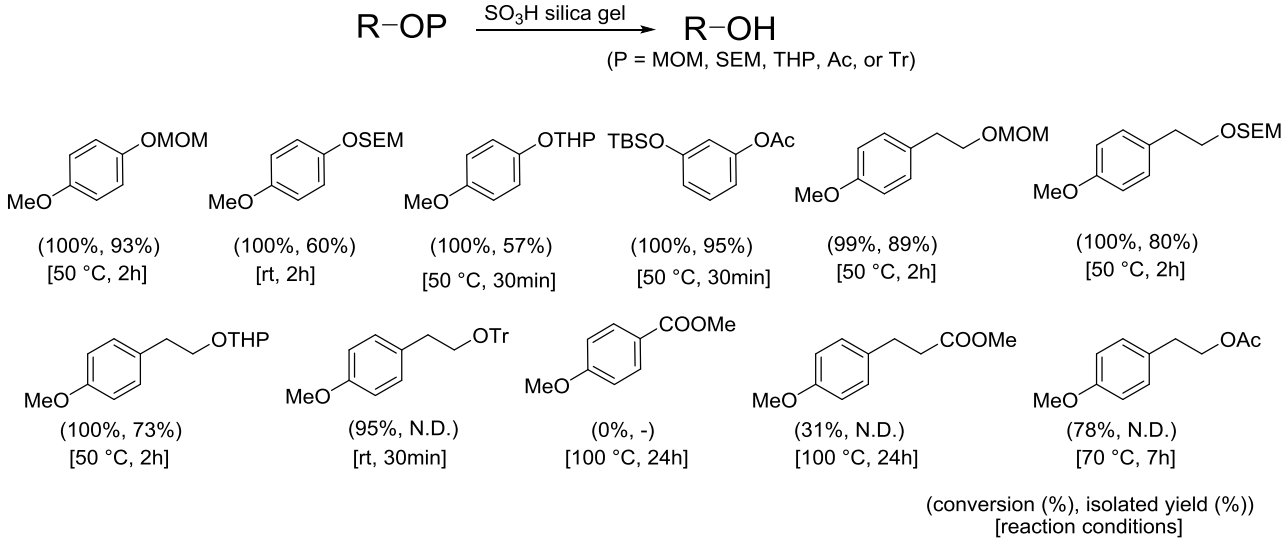
Figure 1. Structure of SO_3H Silica gel and its specification.

Deprotection reaction of acid-sensitive protective groups

At first, we attempted the deprotection reaction of some acid-sensitive protective groups (MOM, SEM, THP, Ac, or Tr groups) using the SO_3H silica gel. The MOM, SEM, THP, or Tr ethers were readily cleaved under the reaction conditions (Scheme 1). It is noteworthy that no silyl residues were observed in the crude product concerning SEM ether. Although aryl acetate was labile under the reaction conditions, alkyl acetate was resistant to the reaction conditions. Methyl esters hardly reacted under the reaction conditions.

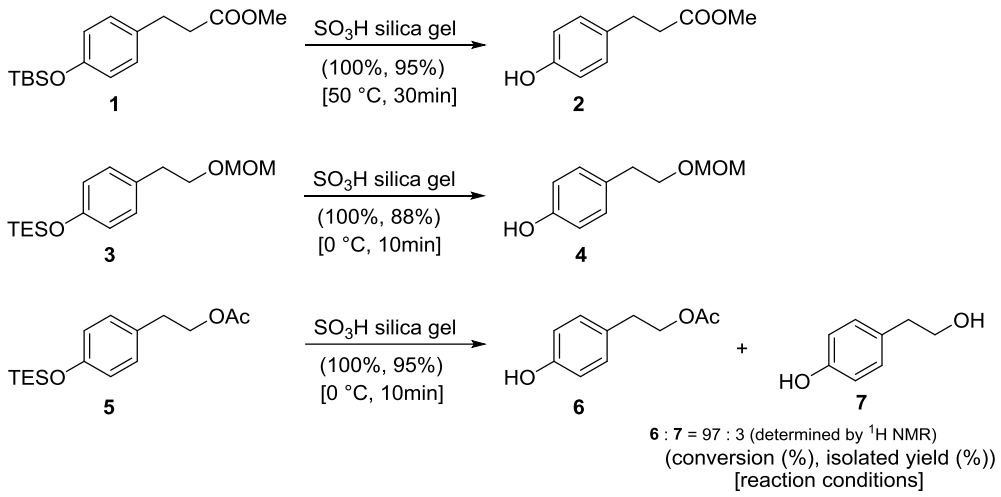
Selective desilylation reaction in the presence of acid-sensitive protective group

We next examined the reactivities of the acid-sensitive protective groups under the reaction conditions (rt, 10min) and found that a methyl ester was inert. Although about 20% amount of acetate was cleaved, a pivalate was inert. A MOM ether unexpectedly survived. Therefore, we chose methyl ester, acetate, pivalate, and MOM ether as the acid-sensitive protective groups (Scheme 2). The TBS group in methyl ester **1** was selectively deprotected. With respect to acetate and MOM ether, selective cleavage of the TBS



Scheme 1. Reactivities of acid-sensitive protective groups under reaction conditions

ether bond was hardly accomplished. However, selective deprotection of the TES group in MOM ether **3** proceeded. The treatment of acetate **5** provided almost selectively desilylated product **6**.



Scheme 2. Selective desilylation in the presence of acid-sensitive protective group

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1P- 14

Tautomerization of 5-Alkylidene-2-Oxazolidinone to 2-Oxazolone by Use of an N-Heterocyclic Carbene Catalyst

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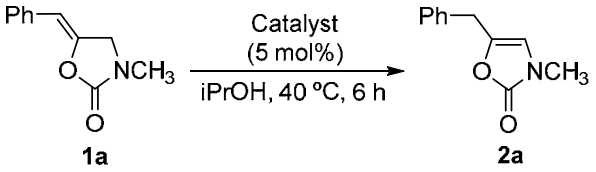
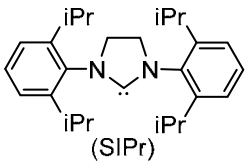
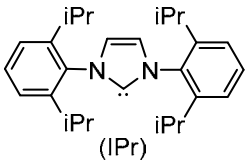
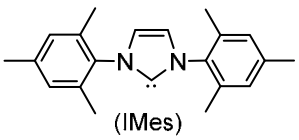
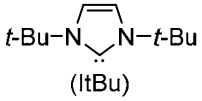
2-Oxazolones are heterocyclic compounds that perform an important role in the synthesis of several organic molecules, including amino alcohols, peptides, and polyfunctional compounds. Previous reports described several methods of synthesizing 2-oxazolones by the condensation of carbonyl groups, but these methods required strongly acidic or basic conditions. Recently, the transition-metal-catalyzed approach has emerged as a powerful method of preparing 2-oxazolones. However, to our knowledge, organocatalysts have not been used to prepare 2-oxazolones.

N-heterocyclic carbenes (NHCs) as organocatalysts has attracted increasing attention because of the rapid development of general synthetic methods and their potential for the wide applications in the field of catalytic organic syntheses. This is because their unique electronic and steric properties can be finely tuned by varying their substituent patterns. We report herein the NHC-catalyzed tautomerization of 5-alkylidene-2-oxazolidinone to 2-oxazolone.[1] Namely, through the use of an organocatalyst NHC, 2-oxazolone was easily afforded by the tautomerization of the corresponding 5-alkylidene-2-oxazolidinone, which was prepared by the carboxylative cyclization of a propargylic amine with CO_2.[2]

We have examined the tautomerization of 5-alkylidene-2-oxazolidinone **1a** to 2-oxazolone **2a** through the use of various NHCs as catalysts, according to Table 1. Stirring of a 2-propanol solution of 5-alkylidene-2-oxazolidinone **1a** at 40

Table 1. Tautomerization of the 5-Alkylidene-2-Oxazolidinone to 2-Oxazolone by Use of Various NHCs as Catalysts.



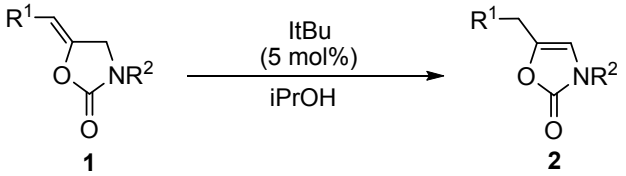
Entry	Catalyst	Yield (%)[a]	Recovery of **1a** (%)[a]
1	 (SIPr)	2	96
2	 (IPr)	31	62
3	 (IMes)	59	35
4	 (ItBu)	78	16

[a] Determined by ^{1}H NMR

ºC for 6 h under an argon atmosphere using 5 mol% of an NHC catalyst produced 2-oxazolone **2a** through the tautomerization of **1a** in all cases. Moreover, it was found that 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (IPr) afforded a much higher chemical yield of **2a** than 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene (SIPr) (Table 1, entries 1 and 2). The optimization of the substituent on nitrogen in the imidazolylidene ring revealed that 1,3-di-*t*-butylimidazol-2-ylidene (ItBu) was the most effective catalyst for the tautomerization of **1a** to provide 2-oxazolone **2a** in a 78% chemical yield (Table 1, entry 4).

We subsequently performed the tautomerization of various 5-alkylidene-2-oxazolidinones **1** by employing 5 mol% of ItBu, as shown in Table 2. By the introduction of a methoxy group at the phenyl group in R^1, the tautomerization proceeded slowly even at 80 ºC to afford the corresponding 2-oxazolone **2b** in a 48% chemical yield (Table 2, entry 2). Also, the introduction of a methyl group at the phenyl group in R^1 promoted the tautomerization at 80 ºC to afford **2c** in a 70% chemical yield (Table 2, entry 3). In contrast, introducing a cyano or a trifluoromethyl group at the phenyl group in R^1 enhanced the reactivity to complete the tautomerization of **1d** or **1e** at 40 ºC within 0.5 h, with excellent chemical yields in both cases (Table 2, entries 4 and 5). These results suggested that an electron-withdrawing group at the phenyl group in R^1 accelerated the tautomerization of **1**. On the other hand, 5-ethylidene-2-oxazolidinone **1g**, which had a methyl group in R^1, was converted even at room temperature to various products, but the corresponding 2-oxazolone **2g** could not be identified (Table 2, entry 7).

Table 2. Tautomerization of Various 5-Alkylidene-2-Oxazolidinones **1**.



1 **2**

Entry	R^1	R^2		Temp. (ºC)	Time (h)	Yield (%)[a]	Recovery of **1** (%)[a]
1	C_6H_5	CH_3	**a**	40	24	91	0
2[b]	4-$CH_3OC_6H_4$	CH_3	**b**	80	48	48	13
3[b]	4-$CH_3C_6H_4$	CH_3	**c**	80	48	70	3
4	4-CNC_6H_4	CH_3	**d**	40	0.5	99	1
5	4-$CF_3C_6H_4$	CH_3	**e**	40	0.5	100	0
6[b]	C_6H_5	$C_6H_5CH_2$	**f**	80	48	60	29
7	CH_3	$C_6H_5CH_2$	**g**	r.t.	51	-	0

[a] Determined by ^{1}H NMR. [b] Carried out in a sealed autoclave.

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1) Fujita, K.; Sato, J.; Yasuda, H. *Synlett*, **2015**, *26*, 1106–1110.

2) Fujita, K.; Sato, J.; Inoue, K.; Tsuchimoto, T.; Yasuda, H. *Tetrahedron Lett.* **2014**, *55*, 3013–3016.

1P- 15

Ethoxylation of *p*-Fluoronitrobenzene Using Phase-Transfer Catalysts by Microreactor Technology

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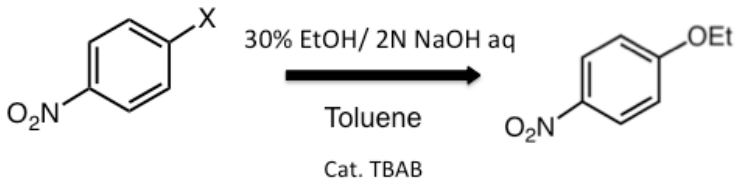
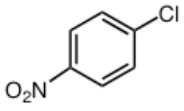
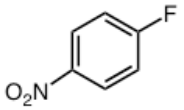
Microreactor is one of the promising technologies for the efficient synthesis of fine chemicals. It is well known that microreacter technology gives some advantages such as fast mixing, fine control of temperature and reaction time and safety, and a lot of applications for organic synthesis have been reported so far.[1)]

4-Nitrophenetol (Ethoxy-4-nitrobenzene) is an important starting material for various fine chemicals and is usually synthesized from 4-halogenonitrobenzene, ethanol and aqueous alkali hydroxide, using phase-transfer catalysts.[2)] In this symposium, we will report the study on synthesis of 4-nitrophenetol by microreactor technology.

Ethoxylation of 4-halogenonitorobenzene was carried out using tetrabutylammnonium bromide (TBAB) as a phase-transfer catalyst and the results of batch reaction were summarized at Table 1. 4-Chloronitrobenzene was sluggish for substitution reaction and 4-nitrophenetol was obtained in only 21% yield, after 72hrs

Table 1 Results of Ethoxylation of 4-Halogenonitrobenzene at Batch Conditions



Run	Substrate	Reaction condition	Yield
1		60°C, 6h	7 %
2		60°C, 72h	21 %
3		60°C, 2h	86 %
4		60°C, 4h	>99 %

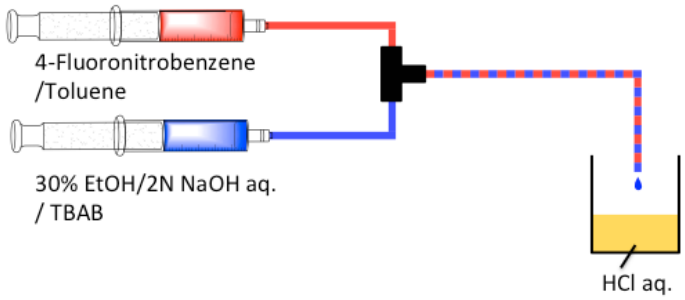
(Run 2). On the other hand, reaction of 4-fluoronitrobenzene smoothly proceeded and gave the ethoxylated product in excellent yield (Run 4). From the above results, we adopted 4-fluoronitrobenzene as a suitable substrate for microreactor reaction.

The reaction using microreactor was carried out at the apparatus as shown at Figure 1. Organic and aqueous solutions were separately pumped by syringe pump and each solution was mixed at T-shaped connector. Reaction tube (3 m) was immersed in water bath and reaction temperature was controlled by bath temperature.

Figure 1 Apparatus of Flow Reaction System

The results of microreactor reaction were summarized at Table 2. The segment flow was observed at each reaction conditions. The reaction using the 0.75 mm diameter tube gave better results and the good results were obtained at slower flow rate (Run 5 and 7).

Table 2 Results of Ethoxylation of 4-Fluoronitrobenzene using microreactor



Run	Diameter [mm]	Temperature [℃]	Flow rate [mL/h]	Yield (Conv.) [%]
1	0.25	60	0.5	17
2			2	5
3		80	0.5	29
4			2	10
5	0.75	60	0.5	80
6			2	26
7		80	0.5	96
8			2	31

Reference

1) Protasova, L.N., Bulut, M., Ormerod, D., Buekenhoudt, A., Berton, J., Stevens, C. V., *Org. Process. Res. Dev.*, **2013**, *17*, 760.

2) Wang. M.-L.; Rajendran, V., *Ultrasonics Sonochemistry*, **2007**, *14*, 368.

1P－16

Study on Selective Synthesis of 1-Ethoxy-2,4-dinitrobenzene Under Phase-Transfer Conditions by Microreactor Technology

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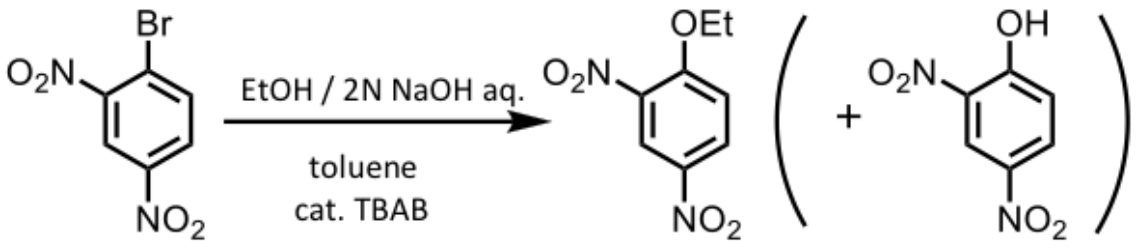
Microreactor is one of the promising technologies for the efficient synthesis of fine chemicals. It is well known that microreacter technology gives some advantages such as fast mixing, fine control of temperature and reaction time and safety, and a lot of applications for organic synthesis have been reported so far.[1)]

Nucleophilic aromatic substitution is an important reaction for the synthesis of various fine chemicals and is usually carried out in polar organic solvent. Although two phases reaction consisted of non-polar organic solvents and aqueous solution is a promising from easy separation, cost of organic solvent and so on, the longer reaction time, due to the sluggishness of mixing is undesirable. We studied the synthesis of 1-ethoxy-2,4-dinitrobenzene from 1-bromo-2,4-dinitrobenzene as a one of the typical nucleophilic aromatic substitution, under phase-transfer conditions and also investigated the possibility of selective synthesis of 1-ethoxy-2,4-dinitrobenzene by microreactor technology.

Batch reaction was carried out using tetrabutylammonium (TBAB) as a phase-transfer catalyst (Scheme 1), and we obtained 2,4-dinitrophenol (10%) as a by-product, in addition to the target compound (80%).



Scheme 1 Reaction of 1-Bromo-2,4-dinitrobenene with Ethanol

The reaction using microreactor was carried out at the apparatus as shown at Figure 1. Organic and aqueous solutions were separately pumped by syringe pump and each solution was mixed at T-shaped connector. Reaction tube (5 m) was immersed in water bath and reaction temperature was controlled by bath temperature.

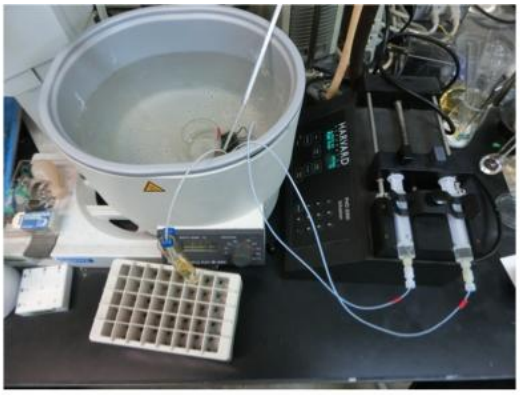
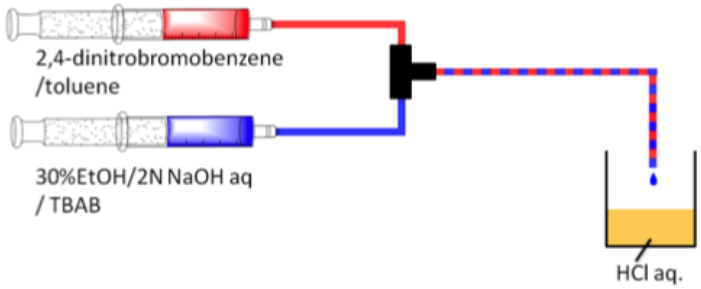


Figure 1 Apparatus of Flow Reaction System

The results of microreactor reaction were summarized at Table 2. The segment flow was observed at each reaction conditions. Although the reaction using the 0.75 mm diameter tube gave better results (Run 5 and 8), excellent selectivity of target compound was not observed. In this symposium, we will report the optimized conditions of the synthesis of 1-ethoxy-2,4-dinitrobenzene in detail.

Table 2 Results of Ethoxylation of 1-Bromo-2,4-dinitrobenzene using microreactor



Run	Diameter [mm]	Temperature [°C]	Flow rate [ml/h]	Yield [%]	Yield [%] (2,4-Dinitrophenol)
1	0.25	40	2	52	2
2			5	29	1
3		60	2	76	11
4			5	60	6
5	0.75	40	5	67	4
6			10	49	2
7		60	5	80	15
8			10	69	9

Reference

1) a) Protasova, L.N., Bulut, M., Ormerod, D., Buekenhoudt, A., Berton, J., Stevens, C. V., *Org. Process. Res. Dev.*, **2013**, *17*, 760. b) Mason, B. P.; Price, K.E., Steinbacher, J. L., Bogdan, A. R., McQuade, D. T., *Chem. Rev.*, **2007**, *107*, 2300.

1P- 17

Considerations for the Validation of Quantitative NMR

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<Introduction>

NMR spectroscopy is one of the methods essential for the structural elucidation of organic compounds. In addition, it exhibits accurate quantitative performance. Quantitative NMR (qNMR) has been attracting considerable attention in several fields, as it provides accurate quantitative information without the requirement of reference compounds that are the same as the analyte. Moreover, qNMR with SI (Le Système International d'Unités, International System of Units) traceability is permissible by using an appropriate protocol. Hence, qNMR can be applied for the evaluation of reference materials. [1] In fact, qNMR is categorized as an analysis method by Japan's regulatory standard such as the Japanese Pharmacopoeia.[2] As the result, currently, qNMR has been increasing applied to quality control.

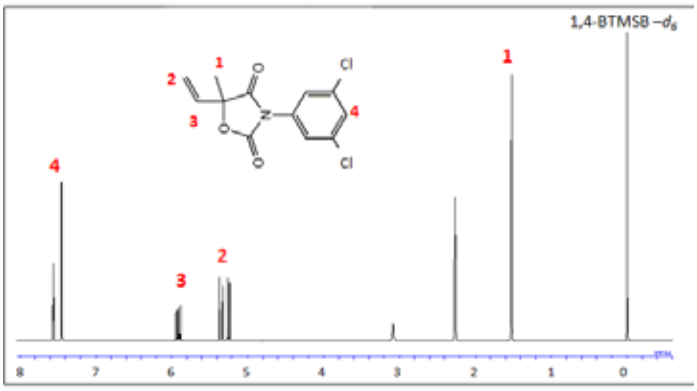
To ensure the reliability of assay results, it is necessary to validate an analytical method, and some studies have already been published in this regard.[3, 4] Maniara et al. have reported validation results of qNMR. [5] In their study, the accuracy, linearity, selectivity, limits of detection, limits of quantitation and robustness of parameters were evaluated, demonstrating the validity of the method; the results indicated that qNMR is capable of accurate quantitative analysis and is equivalent to chromatography in this regard. Nevertheless, the quality of assay results obtained is affected by several factors. When conducting assays using analytical instruments, among other factors, the most fundamental factor is the qualification of the instrument. Hence, we investigate the validation of the instrument for qNMR herein.

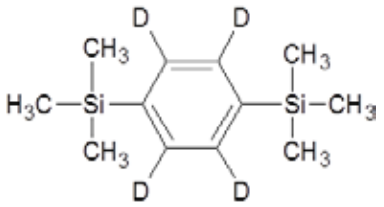
<Qualification of the NMR instrument>

When installing or conducting periodic inspection of an NMR instrument, specifications such as 90° pulse width, sensitivity, and resolution are typically confirmed. [6,7] For example, for ^{1}H-NMR measurements, sensitivity checks are typically performed using 0.1% ethyl benzene in a chloroform-d_1 solution, and resolution checks are performed using 1% or 3% chloroform in an acetone-d_6 solution. In other words, if the results of these tests meet the specifications, the performance of NMR instrument is qualified. However, for quantitative analysis, precision or repeatability under the applied measurement conditions needs to be evaluated to ensure the reliability of quantitative values. Accordingly, these performance checks correspond to the validation of the instrument for qNMR. In addition, this validation is applied to a daily performance check. Therefore, we conducted a performance check by using an analytical sample for qNMR qualification.

< Analytical sample for qNMR qualification >

For quantification an analytical sample prepared using vinclozolin and 1,4-bis-(trimethylsilyl) benzene-d_6 (1,4-BTMSB–d_6) as the analyte and reference material, respectively, was accurately weighed and dissolved in dimethyl sulfoxide -d_6. Fig.1 shows the ^{1}H-NMR spectrum of this analytical sample.





1,4-BTMSB- d_6

Wako Pure Chemical Industries, Ltd.

Fig1. ^{1}H-NMR spectrum of the analytical sample for qNMR qualification

A stability test was also performed using this analytical sample. The results confirmed the presence of vinclozolin and 1,4-BTMSB-d_6 in the analytical sample solution.

<Performance check for qNMR qualification>

Procedures for performing NMR quantification typically include 1) verification of the measurement file, 2) verification of the analytical sample and 3) verification of the results. The results are established the confirmation of the integral value of the molecules, as well as purity and repeatability. These procedures are in accordance with the suitability test for a system or the concept of management of instrument performance in the Japanese Pharmacopoeia.[2, 8] In this presentation, I would like to discuss the method to evaluate these criteria in detail.

<Reference>

1) T. Ihara, T. Saito, N. Sugimoto, *Synthesiology*, 2009, 2, 12-22
2) Japanese Pharmacopoeia, 16th Edition, Supplement II, announced and enforced on February 28, 2014
3) F.Malz, H.Jancke, *J.Pharm Biomed Anal.*2005,38,813-823
4) *Eurolab Technical Report* , No.1 / 2014, Guide to NMR Method Development and Validation
5) G. Maniara, K,Rajamoorthi, S.Rajan, G.W.Stockton, *Analytical Chemistry,* 1998, 70,4921-4928
6) *ASTM* , E2977-14, Standard Practice for Measuring and Reporting Performance of Fourier-Transform Nuclear Magnetic Resonance (FT-NMR) Spectrometers for Liquid Samples
7) *USP37,* NF32 , 2014 , Vol.1, <761> Nuclear Magnetic Resonance Spectroscopy
8) *Japanese Pharmacopoeial Forum*, 2014, 23 ,4, 606-610,726-728

1P- 18

Sodium Borohydride Reduction: A Sustainable PAT System for Safe Operation

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Roche Ireland implements a Process Analytical Technology (PAT) application of in situ mid-infrared probe based technology for the safe operation of a sodium borohydride reduction reaction. Methylfuranoside is a starting material in the synthesis of the anticancer drug, Xeloda®. It is manufactured on large scale in Roche Ireland. The manufacture of the methylfuranoside involves a hazardous reduction of the thermally labile tosylfuranoside with sodium borohydride reagent as shown in **Figure 1**. The reaction is carried out near 80 °C with hydrogen gas evolution, foaming and the precipitation of tosylate salts. The sodium borohydride is converted to a borohydridetriethylamine complex during the reaction.

The original manufacturing process required the isolation and drying of the tosylfuranoside prior to the reduction reaction (Double Isolation process). This isolation, drying, off-loading and recharging was extremely labor intensive, leading to reduced capacity. A major process improvement to eliminate the isolation was developed in-house and tested on full production scale.

The new single isolation process worked well giving acceptable quality product. Unexpectedly, a heat spike in the process – the main process safety control measure, proved to be small and unreliable and sometimes absent altogether. The lack of a reliable heat-spike in the new process is related to the levels of isopropanol solvent entering the reaction with the undried tosylfuranoside. After risk assessment it was decided that an alternative risk mitigation solution was required before the new process could be used.

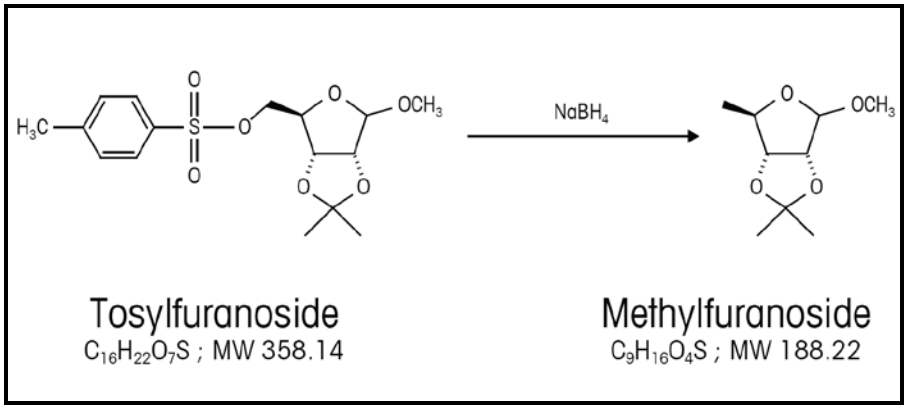

Figure 1. Reaction scheme

In-situ FTIR (ReactIR™) had been used in the laboratory to investigate the original process. The reaction of the sodium borohydride could be followed in great detail using inline Mid-IR without interference from the evolved gas, foaming and precipitated sodium tosylate (**Figure 2**). At manufacturing scale, in-process mid-IR was investigated for use as a possible process safety risk mitigation technology. The business case was proven and accepted. A strategy and system for the sodium borohydride reduction of tosylfuranoside was developed in collaboration with METTLER TOLEDO to use their latest process Mid-IR (ReactIR™ 45P). Extensive risk assessments, FMEA, HAZOP, LOPA etc. were carried out to ensure the revised process would deliver the product safely. The Mid-IR system was installed in October 2012 and has been operating continuously and successfully (**Figure 3**).

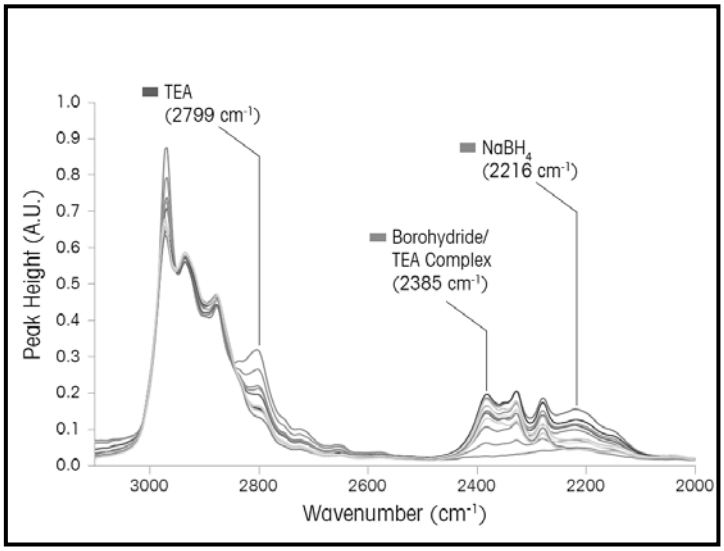

Figure 2. Mid-IR spectra

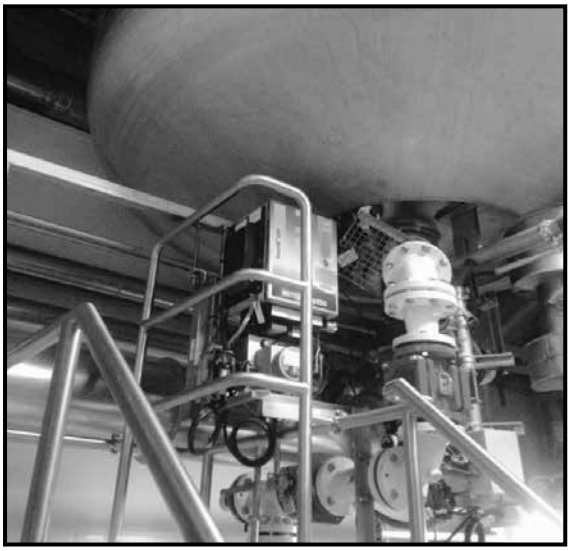

Figure 3. Installation of the ReactIR45P at the plant

Since introduction of the QC-PAT in November 2012 (batch 60), over 200 successful batches have been completed with zero failed batches. The new process led to the following improvements:

- 8 % Yield increase
- 15 % reduction in material used
- 25 % reduction in equipment
- 40 % reduction in manual operations
- € 60,000 reduction in energy costs per campaign
- 14 % improvement in reliability
- Elimination of site safety risk by:
  - ◊ removal of drying step
  - ◊ eliminating physical QC sample
  - ◊ reducing exposure risk to a hazardous material

This Presentation is based on a White Paper by John O'Riley of Roche Ireland called "Process FTIR For Safe Operation of Sodium Borohydride Reduction."

1P- 19

EasySampler™ 1210 : Unattended, Representative Smapling

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Sampling chemical reactions for offline analysis to determine reaction progress or impurity profiles is standard practice. However, the sampling process is not always a precise operation and can be challenging with reactions at elevated temperatures or reactions where a slurry exists. Delays in quenching can lead to variable results and inaccuracies in the analytical information gained.

EasySampler was designed to eliminate these challenges by providing an automated and robust inline method of taking representative samples from reactions, even at extreme conditions. In the poster presentation, we will provide some technical data and present how EasySampler get over those sampling difficulties.

Representative Samples

The unique patented probe enables the capture and immediate quenching of reaction samples. Immediate sample quenching provides a sample representative of the reaction at the time of sampling. This is particularly advantageous for monitoring low temperature and air-sensitive chemistry.

Unattended 24/7

At the touch of a button, samples are taken, quenched, diluted to a user-specified concentration and transferred to vials, ready for offline analysis. For unattended reaction sampling, a sample sequence can be programmed for continued sampling operations, day or night.

Heterogeneous Reactions

Sampling reactions with precision is challenging, especially for slurry reactions. EasySampler captures reaction samples, including the solids, into a pocket of fixed volume. Solids dissolution begins immediately, with the quench and dilution steps, delivering a dissolved sample to gain precise and accurate analytical data.

User Safety

EasySampler fully automates the sampling process, eliminating manual handling of liquids. This reduces risks and improves operator safety, especially with highly toxic chemistry, dangerous reactions at elevated temperatures, and other hazardous reaction conditions.

1P- 20

Development of a Practical and Scalable Synthesis of TRPA1 Receptor Activator, ASP7663

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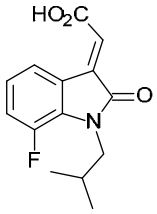
ASP7663 (**1**) was invented by Astellas Pharma Inc. as a potent TRPA1 activator for treatment of IBS-C. The initial medicinal synthetic route of **1** is shown in Scheme 1.

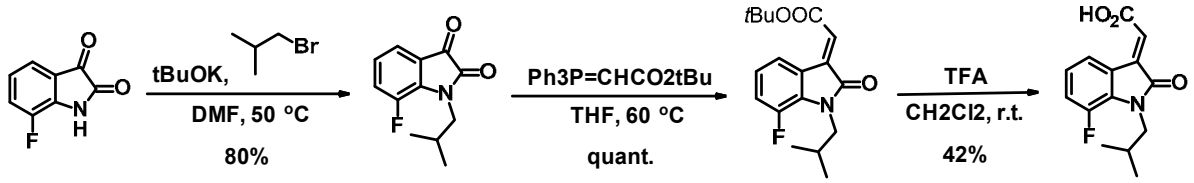


ASP7663 (1)

In the medicinal route, there was no critical issue, however we had to resolve some minor issues to establish a practical and scalable synthetic procedure. 1) Wittig reaction in Step 2 produces $Ph_3P=O$ which is difficult to be purged. 2) In Step 3, CH_2Cl_2 that is one of Class 2 solvents in the ICH guideline is used for the saponification of *t*Bu ester. Finally, as a result of our close investigation, Honner-Emmons reaction replaced the Wittig reaction and HCOOH/Acetone was chosen instead of TFA/CH_2Cl_2.

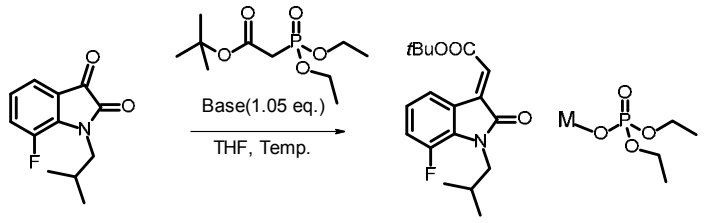
1) Change to Honner-Emmons reaction from Wittig reaction

Scheme 1 Medicinal Route



2 **3** **4** **ASP7663 (1)**

Table 1



3 4

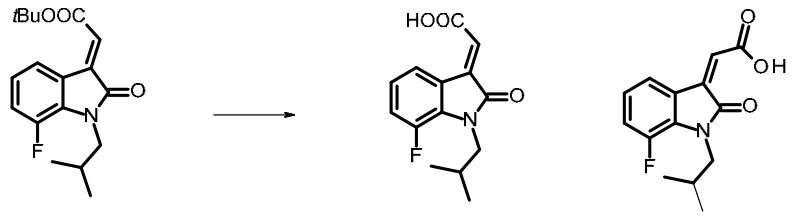
Entry	Base	Temp. (°C)	Results
1	*t* BuOK	rt	decomposed
2	*t* BuOK	0 to rt	complex mixture
3	DBU + LiCl	60	complex mixture
4	DBU + LiCl	0 to rt to 60	complex mixture
5	DBU + LiCl	0	complex mixture
6	DBU + LiCl	-15	54.9%
7*	DBU + LiCl (1.1 eq.)	-20	66.5%
8*	DIPEA + LiCl (1.1 eq.)	-20	71.2%
* Phospolic ester (1.1 eq,) was used.			

To avoid the formation of $Ph_3P=O$, Honner-Emmons reaction which can produce water soluble phospolic acid was investigated. Namely, that enables us to remove the phospholic acid by water washing. As shown in Table 1, some kinds of base, solvent and additive were examined. When *t*BuOK was used, serious decomposition of the product was observed. On the other hand, when a combination of DBU and LiCl was applied at temperatures of over 0 °C, the target compound was certainly detected, though it gave complex mixtures as well. The

preliminary result encouraged us to try lower temperatures and the product was obtained by 54.9% at -15 °C. Furthermore, when 1.1 eq. of phosphate, DBU and LiCl were used, the yield increased up to 66.5%. Finally DIPEA gave the best results at a yield of 71.2%, which was adopted to the 1st scale up synthesis.

2) Alternative solvent of TFA/CH_2Cl_2

Table 2

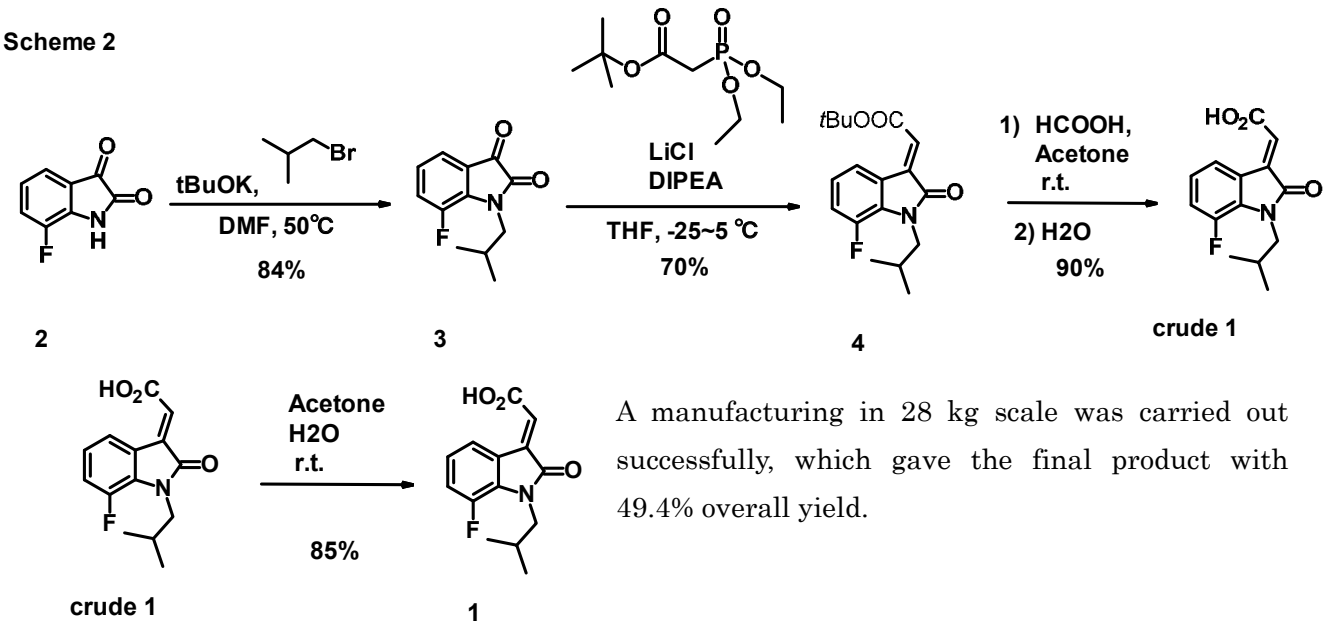


4 5 Byproduct 6

Entry	Acid	Solvent	Temp. (°C)	Yield (%)	Bypro
1	HBr(5 eq.)	CH3CN	rt	84.1	HPLC: 1.2A%
2	HBr(1 eq.)	CH3CN	rt	63.2	HPLC: Detected
3	HBr(10 eq.)	HCOOH	50	79.4	HPLC: 35.7A%
4	cHCl (20 V)		rt	96.8	ND
5	HCOOH (20 V)		50	97.0	HPLC: 26.0%
6	HCOOH (20 V)		rt	90.5	ND
7	HCOOH (18 V)	Acetone (2 V)	rt	94.4	HPLC: 0.1%

To avoid using one of Class 2 solvent CH_2Cl_2, several combinations of acid and solvent were tried (Table 2). When HBr was used as acid, byprodct (**6**), a geometric isomer of (**5**) was detected. After close investigation, it was found that conc HCl or HCOOH can proceed the saponification smoothly with no geometric isomerization. However, since the *t*Bu ester (**4**) showed low solubility in conc HCl, HCOOH was finally chosen as both of acid and solvent. In addition, the low fluidity of the reaction mixture with HOOH was mitigated by an addition of acetone. In conclusion, this optimized condition was adopted to scale up syntheses and the final synthetic route is shown in Scheme 2.

Scheme 2



A manufacturing in 28 kg scale was carried out successfully, which gave the final product with 49.4% overall yield.

1P- 21

Ligand-free Suzuki-Miyaura reaction of chloroarenes catalyzed by anion exchange resin-supported palladium

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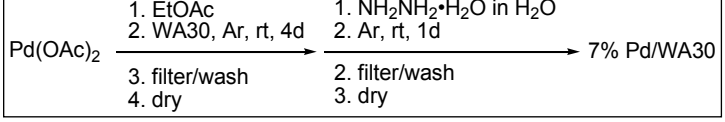
Suzuki-Miyaura reaction, which involves the palladium-catalyzed cross-coupling reaction between aryl halides and arylboronic acids, produces biaryl skeletons that are often included as partial structures in functional materials such as pharmaceuticals, natural products, and liquid-crystal materials. Recently, the methods using heterogeneous palladium-catalysts, which function without dissolving in the reaction media, in the absence of expensive or/and toxic ligands, have been under intense study due to environmental, reusable, economical, and metal contamination-free viewpoints. Although we have developed the ligand-free Suzuki-Miyaura reaction of aryl bromides and iodides using palladium on carbon or palladium on synthetic adsorbent as a catalyst[1], such protocols could not be applied to the coupling reaction of aryl chlorides because of their low reactivity. An application of aryl chlorides to the cross-coupling reaction is highly demanded especially in the field of process chemistry for their good availability and low cost.

Several solid-immobilized palladium catalysts have been employed for Suzuki-Miyaura reaction using chloroarenes[2,3]. However, almost all palladium catalysts on the functionalized polymers should be prepared starting from the polymer supports. The use of commercially available polymers possessing functional groups as a support should be a solution due to their secure quality and constant supply based on the industrial strict regulation.

We have developed a novel palladium catalyst immobilized on *tertiary*-amino-(*N,N*-dimethylaminoalkyl-)substituted polystyrene-divinylbenzene-based polymer (weakly basic anion exchange resin), DIAION WA30 (WA30, Mitsubishi Chemical Corporation).

7% Pd/WA30 was prepared by a consecutive adsorption–reduction method, thus palladium (II) ions were embedded on a colorless WA30 by only its gentle stirring in a palladium acetate solution in EtOAc, and then the resulting reddish (palladium (II)-adsorbed) WA30 was treated with hydrazine in H_2O to afford the black spherical Pd/WA30. The palladium content was determined to be 7 wt% by the atomic absorption analysis of the residual palladium species in the collected EtOAc and H_2O solutions as the filtrate and washings (Scheme 1).

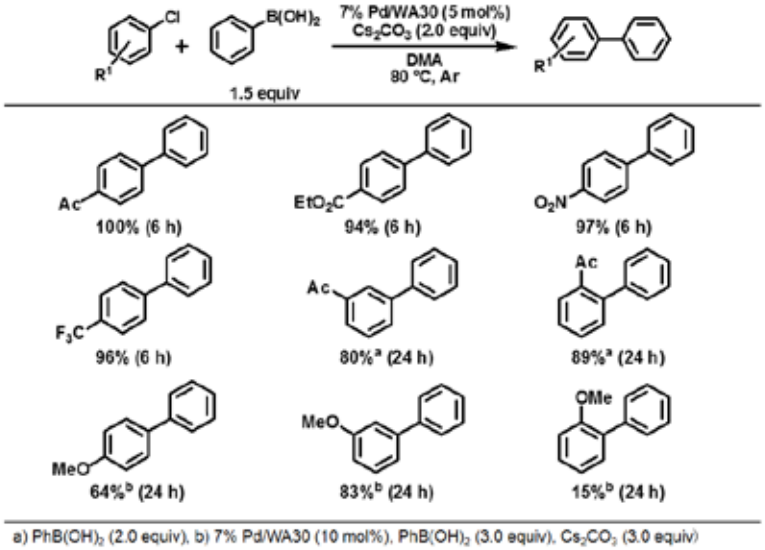
Scheme 1 : Preparation of 7% Pd/WA30



The reaction conditions of 7% Pd/WA30-catalyzed coupling of aryl chloride were optimized using 4'-chloroacetophenone and phenylboronic acid (1.5 equiv) as substrate. The reaction was completed in the presence of 5 mol% of 7% Pd/WA30 and Cs_2CO_3 (2.0 equiv) in *N,N*-dimethylacetamide (DMA) at 80 °C within 6 h to give the desired 4-acetylbiphenyl in quantitatively yield. Aryl chlorides bearing an electron-withdrawing

group, such as Ac, EtO_2C, NO_2, and CF_3 groups, on the aromatic ring efficiently reacted with phenylboronic acid (1.5–2.0 equiv) regardless of the substitution pattern to give the corresponding biaryls in excellent yields. The phenylation of chloroanisoles, which have an electron-donating methoxy group on their aromatic nucleus, also proceeded except for the case of the sterically-hindered *ortho*-substituted isomer (Table 1).

Table 1. Suzuki-Miyaura reaction between various chloroarenes and phenylboronic acids.

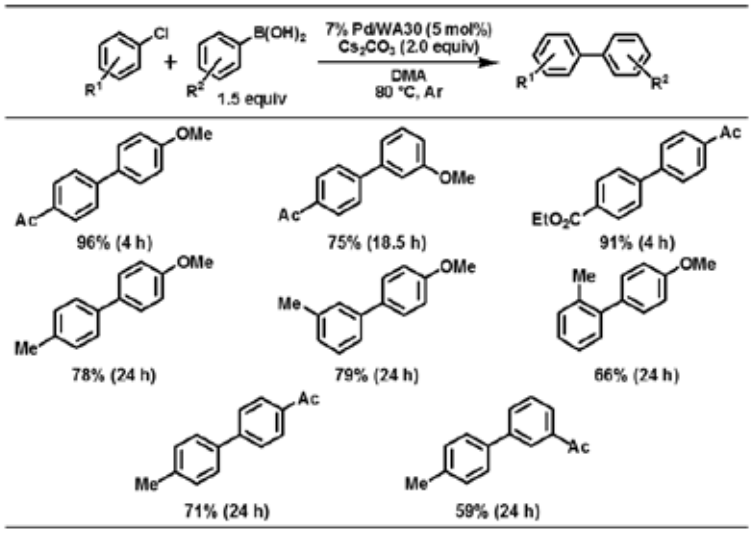


a) $PhB(OH)_2$ (2.0 equiv), b) 7% Pd/WA30 (10 mol%), $PhB(OH)_2$ (3.0 equiv), Cs_2CO_3 (3.0 equiv)

Various arylboronic acids, bearing either an electron-donating or -withdrawing substituent on the aromatic ring, were found to be good coupling reagents for the reaction with aryl chlorides. Even from the unfavorable combination of coupling partners, electron-sufficient chloroarene and electron-deficient arylboronic acid, the desired biaryl was obtained in a good yield (Table 2).

Furthermore, the cross-coupling reaction of 4'-chloroacetophenone with phenylboronic acid could be achieved with 3.8 mmol-scale, and no palladium species were detected in the reaction mixture by the inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis after removal (filtratin) of 7% Pd/WA30.

Table 2. Suzuki-Miyaura reaction between various chloroarenes and arylboronic acids.



In conclusion, we have developed a highly active heterogeneous palladium catalyst supported on a commercially-available weakly basic ion-exchange resin, DIAION WA30 (7% Pd/WA30). 7% Pd/WA30 quite efficiently catalyzed the Suzuki–Miyaura reaction between aryl chlorides and arylboronic acids without any ligands. The palladium leaching-free nature is a distinctive feature of the 7% Pd/WA30.

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1P- 22

Enantioselective Three-Component Synthesis of Propargylamines Accompanied by the Dehydration in Water.

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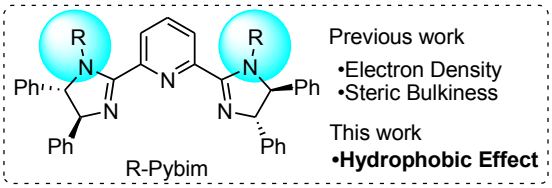
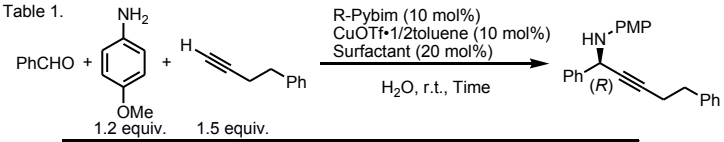
Optically active propargylamines are important synthetic intermediates for the preparation of various natural products and biologically compounds. Therefore, development of environmentally friendly synthetic process of these component is highly desired. Three-component reaction of aldehydes, amines and alkynes in water is one of the most attractive approach for the synthesis of optically active propargylamines. However, it is difficult to proceed the reaction because of low solubility and equilibrium to produce water. The best result for this type of reaction was reported by Li and co-workers, in which an enantioselective one-pot reaction of aldehyde, amine and phenylacetylene using a pybox-Cu(I) catalyst in water gave products in moderate to good yield but with lower enantioselectivities than that using organic solvents.[1] Furthermore, there is no report on the enantioselective synthesis of optically active propargylamines in water using alkyl-substituted alkynes.[2]



On the other hand, we recently developed three-component synthesis of optically active propargylamines from aldehydes, amines and aliphatic alkynes in organic solvents catalyzed by bis(imidazoline)-Cu(I) catalysts as highly electric or steric tunable chiral catalyst.[3] Herein, we examined the direct three-component reaction of aldehydes, amines, and aliphatic alkynes in water by using chiral bis(imidazoline) catalyst as highly hydrophobic tunable chiral catalysts.[4]

We first examined the reaction of benzaldehyde, *p*-anisidine, and 4-phenyl-1-butyne as an aliphatic alkyne using 10 mol% of chiral bis(imidazoline) Lewis acid catalysts in water. The results are shown in Table 1. The reaction using 10 mol% of *N*-benzoyl 1,3-bis(imidazolin-2-ly)pyridine (*N*-Bz-pybim)-CuOTf·1/2toluene complex gave product in low yield with moderate enantioselectivity (entry 1). During the reaction process, the reactants could not be insoluble in water. The reaction using SDS improved the yield

Table 1.



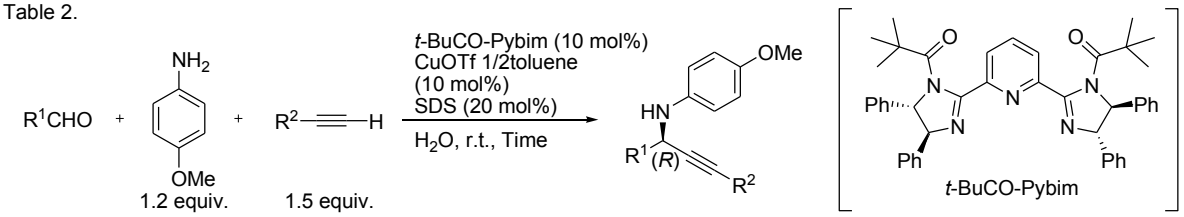
Entry	R	Surfactant	Time [h]	Yield [%]	Ee [%]
1	Bz	-	84	1	45
2	Bz	SDS	48	41	88
3	Ts	SDS	48	12	43
4	Ac	SDS	48	63	95
5	$CH_3(CH_2)_8CO$	SDS	48	37	93
6	*i*PrCO	SDS	48	89	94
7	*t*BuCO	SDS	18	99	98
8	*t*BuCO	Sodium laurate	18	0	-
9	*t*BuCO	CTAB	18	0	-
10	*t*BuCO	TritonX-100	18	17	98
11[a]	*t*BuCO	SDS	48	87	98
12[b]	*t*BuCO	SDS	72	73	96

[a] Tap water was used instead of purewater.
[b] Seawater was used instead of purewater.

and enantioselectivity of the product (entry 1 vs. 2). Optimization experiment for the fine-tuning of various substituents on nitrogen atom in imidazolines was carried out, the pivaloyl group was found to be the best substituent to give the product in high yield with high enantioselectivity (entries 2-7). Other anionic, cationic and neutral surfactants, such as sodium laurate, cetyltrimethylammonium bromide (CTAB), and polyoxyethylene *p*-(1,1,3,3-tetramethylbutyl)phenyl ether (Triton-X100), did not afford good results (entries 7-10). Finally, we tried the reaction using tap water and seawater instead of pure water because it is attracted as easily-available and environmentally friendly reaction media. In these aqueous solutions, the reaction proceeded well, giving product in high yield with high enantioselectivity (entries 11-12).

Under the optimized reaction conditions, the results of the reaction condition with a variety of aldehydes and alkyne are summarized in table 2. The reaction of various substituted alkynes with benzaldehyde afforded products in high yields with high enantioselectivity (entries 1–12). In the reaction with phenylacetylene, both electron-rich and -poor aldehydes performed well, giving the desired products with 86–99% ee (entries 13–19). The yield was excellent in most cases. In the reaction with cyclohexanecarboxaldehyde, the desired product was obtained in good yield with high enantioselectivity (entry 20), whereas the reaction in CH_2Cl_2 by using *N*-Bz-pybim-CuOTf·1/2toluene complex gave product in 13% yield with 72% ee.

Table 2.



Entry	Aldehyde [R^1]	Alkyne [R^2]	Time [h]	Yield [%]	Ee [%]
1	Ph	CH_2CH_2Ph	18	99	98
2	Ph	$CH_2CH_2CH_3$	36	80	97
3	Ph	$(CH_2)_3CH_3$	48	93	97
4	Ph	$(CH_2)_5CH_3$	24	87	99
5	Ph	$(CH_2)_7CH_3$	48	93	97
6[a]	Ph	cyclopropyl	96	90	95
7	Ph	cyclopentyl	66	91	95
8	Ph	cyclohexyl	66	76	98
9	Ph	CH_2CH_2Br	66	62	98
10	Ph	CH_2CH_2OH	72	77	96
11	Ph	$C(CH_3)_2OH$	72	60	90
12	Ph	Ph	48	99	98

Entry	Aldehyde [R^1]	Alkyne [R^2]	Time [h]	Yield [%]	Ee [%]
13	2-$MeOC_6H_4$	CH_2CH_2Ph	24	85	90
14	2-ClC_6H_4	CH_2CH_2Ph	24	95	98
15	3-$MeOC_6H_4$	CH_2CH_2Ph	24	86	99
16	3-ClC_6H_4	CH_2CH_2Ph	48	80	99
17	4-$MeOC_6H_4$	CH_2CH_2Ph	72	67	86
18[b]	4-ClC_6H_4	CH_2CH_2Ph	48	80	98
19	1-Naphthyl	CH_2CH_2Ph	96	91	92
20	Cyclohexyl	CH_2CH_2Ph	46	66	98

[a] Alkyne (3.0 equiv) was used. [b] Reaction was carried out at 40 ℃.

References

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1P- 23

Novel ESIPT fluorescent dyes with adjustable optical properties

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Abstract: Based on the design and synthesis of 10-hydroxybenzo[*h*]quinoline (**3**) derivatives, we demonstrate a prototypical system to investigate both substituent and conjugation effects on excited-state intramolecular proton transfer emission through a combination of experimental and theoretical studies. On the one hand, adding an electron-withdrawing substituent at the phenol ring in **3** results in a decrease of HOMO, and hence, an increase in the energy gap of the keto-tautomer emission (***o*-4** and ***p*-4**). An opposite effect is observed when an electron-donating substituent is added (**1**). On the other hand, the elongation of the p-conjugation length by the installed 2-methylenemalononitrile group (***o*-2** and ***p*-2**) induces further π-electron delocalization, and thus a smaller emission energy gap. Time-dependent density functional theory calculations on these proton transfer dyes are reported in order to rationalize their electronic structure and optical properties.

1P- 24

Protecting Group-Free Catalytic Synthesis of Sialic Acids

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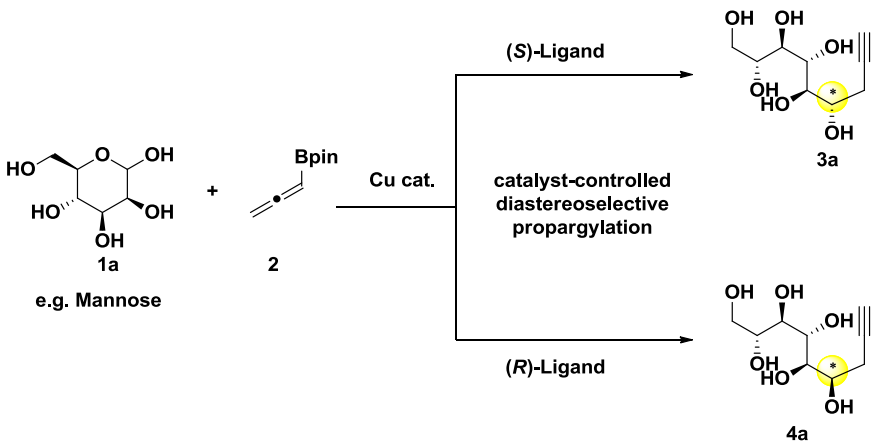
Sialic acids represent one of the most important constituents of glycoconjugates in biological system. Thus, rapid and scalable supply and broadening the structural diversity of sialic acids are an urgent demand in the current glycochemistry and glycobiology. Despite significant improvement on synthetic efficiency during past decades, there are still several points to be overcome: limited scope, unsatisfactory yield and scalability. Moreover, the flexibility in structural and stereochemical alternation are limited.

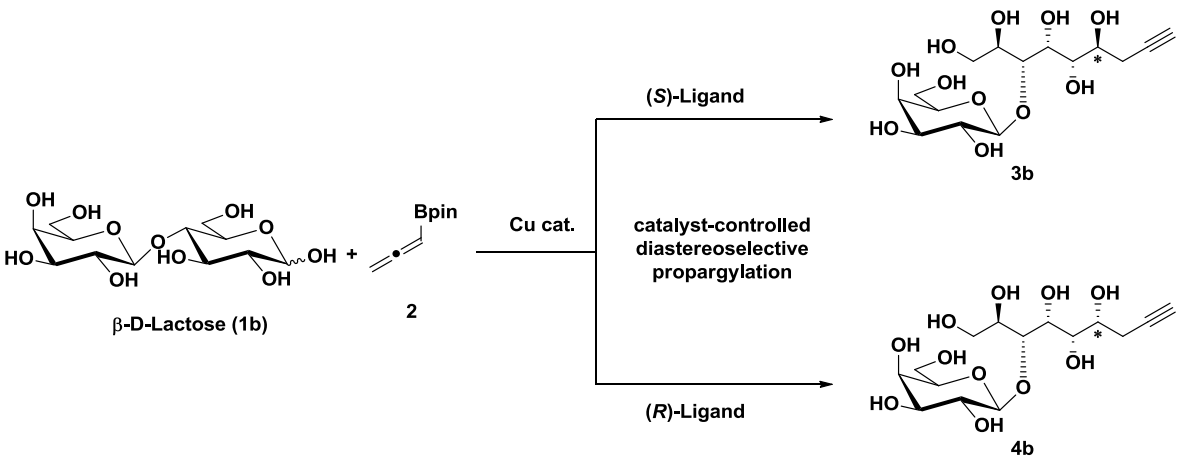
To realize efficient and scalable synthesis of wide variety of natural and unnatural sialic acid derivatives, we developed a catalyst-controlled stereodivergent C-C bond forming reactions of unprotected aldoses for the first time. A combination of a copper (I) catalyst and a chiral diphosphine ligand realized high level of stereoselectivity in a propargylation of various unprotected aldoses (13 examples) (Scheme 1).

Scheme 1. Stereodivergent synthesis of sialic acid derivatives.



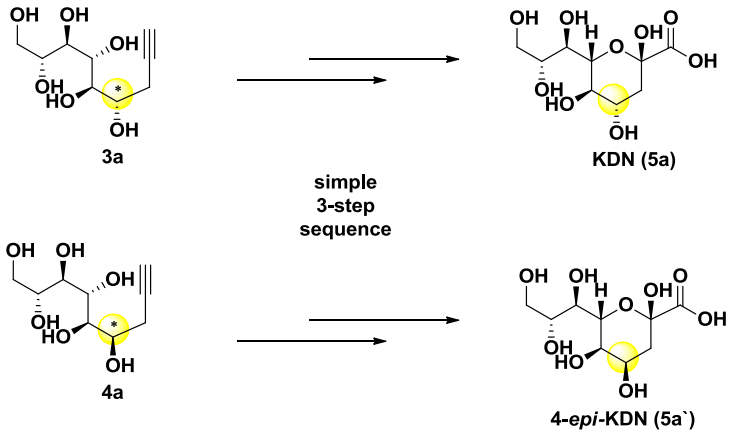
Notably, the reaction was also applicable to a disaccharide (Scheme 2). The reaction with β-D-lactose proceeded smoothly under the standard conditions for monosaccharide to give the corresponding target molecules **3b** and **4b** in good yield and excellent diastereoselectivity. The outstanding stereo-control ability and the tolerance to multiple free hydroxy groups made the developed reaction a general method for the concise synthesis of polyol-containing terminal alkyne modules.

Scheme 2. Stereodivergent propargylation of β-D-lactose.



The obtained products could be converted to sialic acid derivatives through simple three-step sequence. The established sequence was applicable to variety of unprotected aldoses (Scheme 3). Thus we can rapidly access various natural and unnatural sialic acid derivatives by combining the catalyst-controlled stereodivergent propargylation of unprotected aldoses and following three-step simple operation.

Scheme 3. Stereodivergent synthesis of sialic acid derivatives.



In conclusion, we have developed a catalytic stereodivergent propargylation of unprotected aldoses. The diastereoselectivity was completely controlled by our catalyst system even in the presence of complex chiral environment with multiple hydroxy groups. The propargylation products could be transformed to sialic acid derivatives by following simple three-step sequence. This synthetic method offers general and straightforward access to the synthesis of various sialic acid derivatives which can be a useful tool for further biological function elucidation.

1P- 25

Palladium-Catalysed Three-Componet Reaction of 3-(Pinacolatoboryl)ally Acetates, Aldehydes, and Organoboranes

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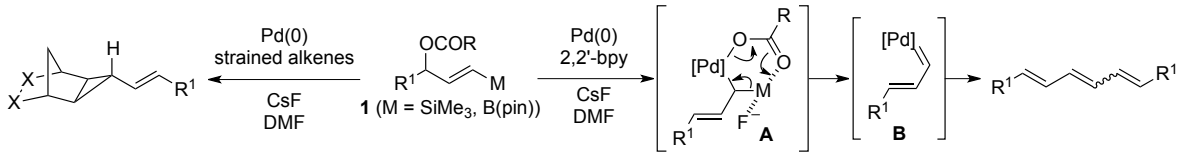
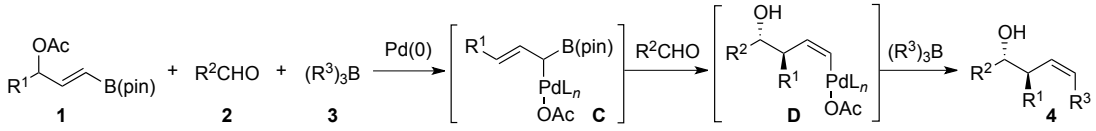
Organo-*gem*-sp^3-hetero bimetallic reagents have appeared to enhance the synthetic application of C–C bond forming reactions and opened the facile synthetic route to many molecular constructions in single-step reactions. In general, these methods require more than the stoichiometric amount of metal reagents and additional steps to install two different types of metal at geminal positions in advance. Moreover, most of the C–C bond forming reactions are limited to nucleophilic reaction. In our recent studies, we demonstrated the distinct reactivities of allylic *gem*-palladium/metalloid intermediates that could serve as C3 units in reactions other than allylation reactions. For example, we have reported the stereoselective cyclopropanation of strained alkenes by the palladium-catalyzed reaction of **1** (Scheme 1). Furthermore, a palladium-stabilized vinylcarbene intermediate **B** was formed from **A**, and it can be used in the carbene dimerization. Herein, we report that palladium-catalyzed three-component reaction of 3-(pinacolatoboryl)allyl acetates, aldehydes, and organoboranes.

Scheme 1.

Previous Work



This Work



Under optimized reaction conditions, the scope of various aldehydes was examined (Table 1). The reaction of **1a** and triethylborane with electron-rich aromatic aldehydes and electron-deficient aromatic aldehydes gave **4aa**–**4ad**, respectively, in good to high yields with high levels of diastereoselectivity and complete alkene stereocontrol. Notably, 4-hydroxybenzaldehyde was utilized without prior protection of the hydroxyl group although 3.6 equivalents of Et_3B were required to achieve satisfactory reaction progress. Furthermore, the present reaction was also effective for the heterocyclic aldehydes, such as pyridyl-, and furyl-substituted heterocyclic aldehydes, giving **4af** and **4ag** in good yields. Furthermore, not only aromatic aldehydes but also aliphatic aldehydes participated in the present reaction to afford the corresponding products **4ah** and **4ai** in good yields. To further demonstrate the scope of the present

reaction, substituents at the C1 position of **1** were surveyed under optimized reaction condition (Table 2). It was found that reaction proceeded smoothly irrespective of the electronic nature of substituent on the aromatic ring to give **4ba**–**4ha** in good yields with high diastereoselectivity and complete alkene stereocontrol. With respect to the isopropyl-substituted substrate **1i**, the reaction proceeded smoothly to provide **4ia** in moderate yield and the *β*-hydride elimination product of **1i** was obtained in 25% yield.

Table 1. Three-Component Reaction of 1a, 2, and Et_3B

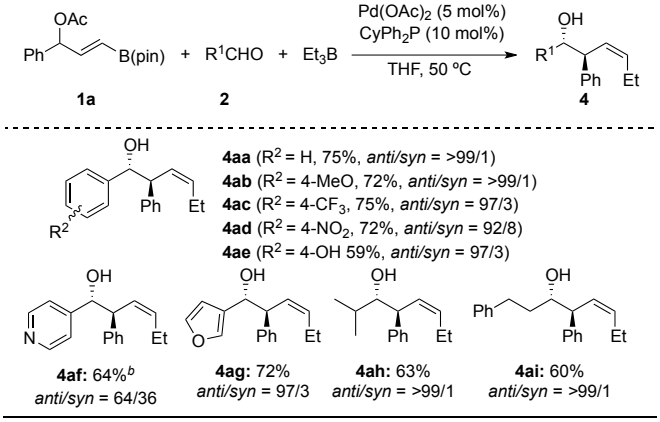
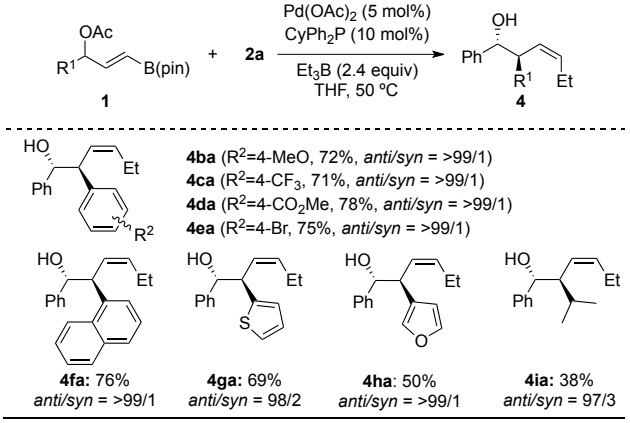
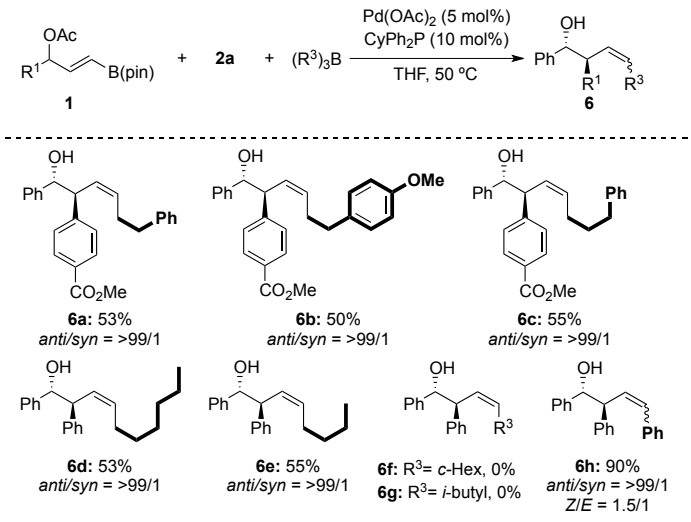


Table 2. Substrate Screening



Subsequently, we then performed reaction of **1** with **2a** and various organoboranes to demonstrate the generality of the coupling reaction (Table 3). The scope with respect to the tri-*n*-alkylboranes was demonstrated to be fairly broad. For example, tri-*n*-alkylboranes prepared from styrene, 4-methoxystyrene, allylbenzene, and 1-hexene with BH_3•SMe_2 complex nicely participated in the coupling reaction to give **6a**–**6d**, respectively, in good yields with excellent stereoselectivity. In addition, a commercially available tri-*n*-butylborane also underwent cross coupling reaction to afford **6e** in 55% yield. On the other hand, the present reaction did not proceed with tri-*sec*-alkylboranes, however, the use of Ph_3B provided the desired product **6h** in high yield as a mixture of (*E*)- and (*Z*)-isomers.

Table 3. Reactions with Various Organoboranes



In summary, we have developed a palladium-catalyzed three-component coupling reaction that provides access to a wide variety of (*Z*)-*anti*-homoallylic alcohols from easily accessible and stable 3-(pinacolatoboryl)allyl acetates, aldehydes, and organoboranes. Interestingly, the palladium complex and allylboronates function cooperatively in this process. This outstanding reactivity of allylic *gem*-palladium/boryl intermediates promises to serve as a powerful strategy for the development of η^3-allylpalladium-mediated transformations.

1P- 26

Continuous multi-step synthesis of a benzofuran analogue under hidden brønsted acid catalysis using a microwave flow system

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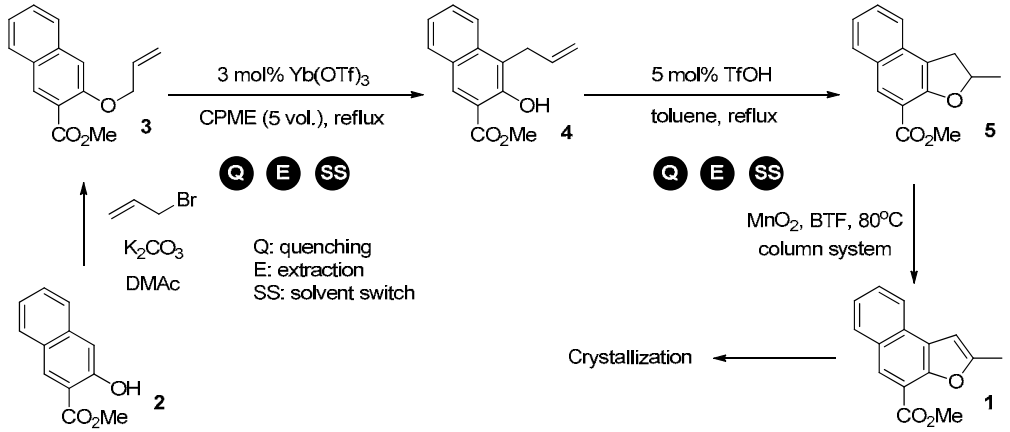
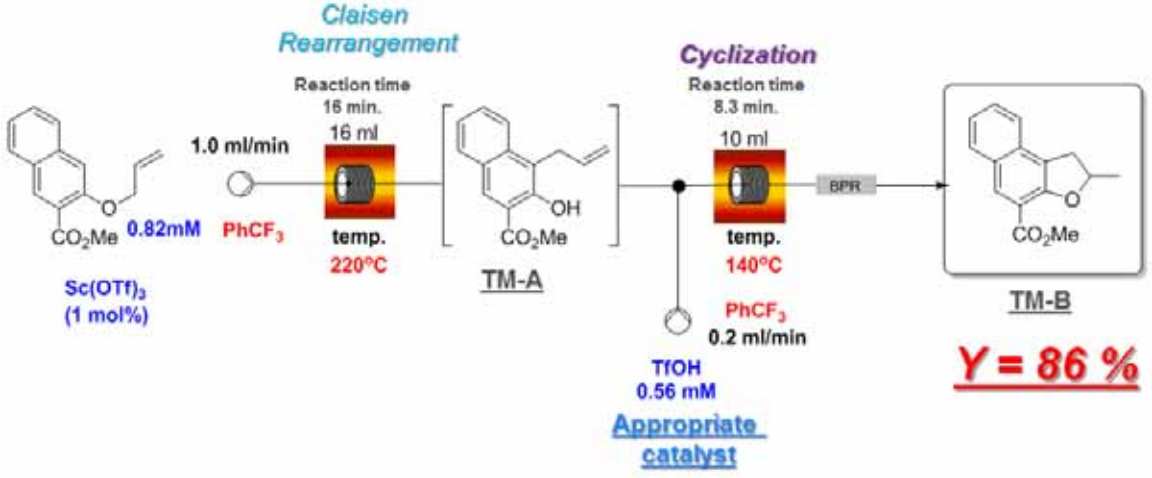
In traditional batch-mode synthesis, chemical researchers usually treat each reaction step in isolation. For instance, a chemical reaction is monitored by TLC or HPLC, quenched after reaction completion, worked up (e.g. extraction, filtration, or concentration), purified (e.g. chromatography or crystallization) in a stepwise manner, and then, the obtained product is moved forward to the next step after analysis of its structure and quality. For industrial manufacture, these "piled-up" operations sometimes have a significant impact onto the processing cost and lead time. By contrast, "multistep continuous-flow synthesis" has high potential to decrease such tedious operations including work-up or purification, and it can ultimately produce a desired product in high efficiency with lower cost, shorter lead time and smaller facility than traditional batch-systems. Because of these potential advantages, "multistep continuous-flow synthesis" has recently attracted much attentions by both chemists and engineers in academic and industry fields, and some useful and efficient continuous-flow systems have been developed recently as an emerging technology.

Here we report one example for "multistep continuous synthesis" using a flow reactor system, where a benzofuran analog **1** was planned to be synthesized according to the below scheme. First, we focus on the continuous reaction to obtain compound **5** from **3**. In our initial attempt by batch-system, compound **5** was prepared in a good yield in a two-step sequence, however, it required multiple work-up operations including quenching, extraction, and solvent switching at each step to obtain the target compound **5** in good yield with high purity.

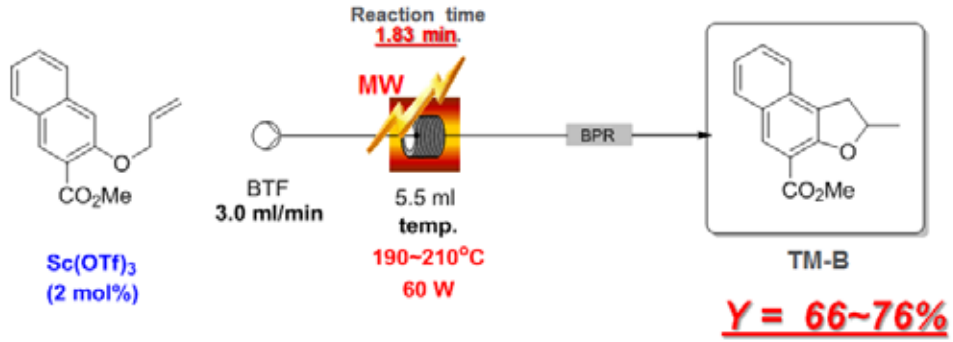


With this preliminary result at hand, we set up a flow system for two-reaction sequence as shown below. A mixture of **3** and $Sc(OTf)_3$ catalyst in benzotrifluoride (BTF) was introduced into the first flow

reactor at 220°C, and then, the resultant solution was subjected to the second flow reactor at 140°C after introducing a BTF solution of TfOH as an additional flow. It was found that the flow system efficiently gave compound **4** in 86% yield within a much shorter total reaction time in 2 steps than batch-system.



In the course of our initial research using the above flow-system, we found that the Claisen rearrangement with $Sc(OTf)_3$ catalyst at high temperature also gave the cyclized product **4** in a modest yield, although $Sc(OTf)_3$ catalyst was not very effective for the cyclization in batch-system. This observation suggested that a catalytic amount of TfOH, which is effective for the cyclization, would be generated in-situ as a "hidden catalyst"[1] by decomposition of $Sc(OTf)_3$ at high temperature. Based on this clue, we set up a continuous system using a microwave-flow reactor for synthesis of **4** as shown below. After optimization of the reaction conditions, it was revealed that the microwave-flow reactor system was very effective to provide the desired product **4** in a high-throughput manner (reaction time is less than 2 minutes), where TfOH would be generated in-situ as a "hidden brønsted acid catalyst" to promote the cyclization reaction immediately after $Sc(OTf)_3$-catalyzed Claisen rearrangement in a single flow-reactor. Our further challenges toward continuous-flow synthesis of benzofuran **1** including allylation and oxidation steps will be also discussed at our poster presentation.



Reference:

1) Dang T.T.; Boeck G.; Hintermann L. *J. Org. Chem*. **2011**, *76*, 9353.

Acknowledgement:

The authors thank SAIDA FDS. CO., LTD for their support in use of the microwave-flow system.

1P- 27

Highly sensitive analytical method development for mutagenic impurities with the similar structures among them

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Last year, ICH M7 reached Step 4 of the ICH process. The guideline requires to control mutagenic impurities (MIs) in drug substances (DS) and drug products (DP) at or below trace levels (e.g. ppm), and also to establish control strategy. It is challenging for analytical chemists, since highly sensitive analytical methods are officially required to confirm residual MIs for regulatory filing. In this presentation, our analytical method development for MIs will be presented as a case study.

During the course of our API process R&D, some potential MIs (PMIs) were considered by the risk assessment on the manufacturing process including all of the intermediates, reagents, and specified/potential impurities in the intermediates and the DS. These PMIs consist of compounds which are Ames positive, with alert structure on *in-silico* analysis, or known as mutagens.

In order to develop highly sensitive analytical methods for PMIs, HPLC (UPLC)/MS/MS, GC/MS, LC/UV or Head-space/GC/FID are generally selected by considering their physical and chemical properties (e.g. stability, volatility and ionization ability) and also each analytical method capability, as shown in Fig 1.

For our case studies, UPLC/MS/MS method was selected to achieve the limit of quantifications (LOQ) of 0.5 ppm for 5 PMIs with the quite similar structures among them. The method has effectively separated and evaluated the 5 PMIs at a time (Fig 2). After extensive optimization of the method to overcome the matrix effect, adequate spike recovery was obtained (Ave. 100.3%, RSD 1.31%). As a result, highly sensitive analytical methods to evaluate all PMIs in the manufacturing process have been established. The analytical results demonstrated that all PMIs were not detected in the DS above the LOQ and adequately controlled by the manufacturing process.

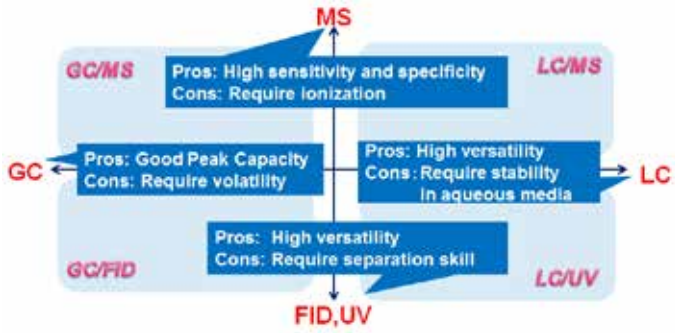

Fig 1: Analytical methodology selection matrix

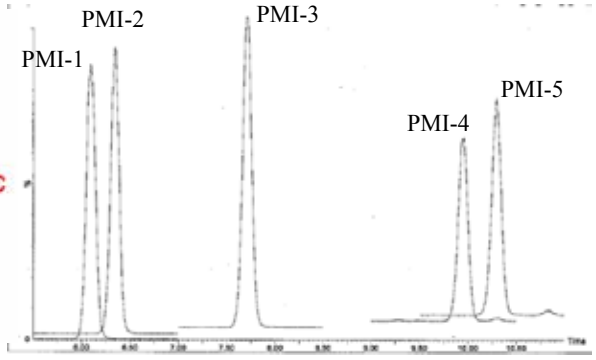

Fig 2: UPLC/MS/MS chromatogram for PMIs

1P- 28

Palladium-Catalyzed Three-Component Reaction of 3-(Tributylstannyl)ally Acetates, Aldehydes, and Organoboranes: A New Entry to Stereoselective Synthesis of (*E*)-*anti*-Homoallylic Alcohols

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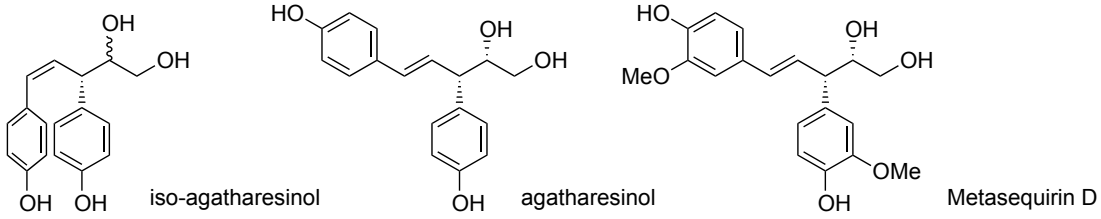
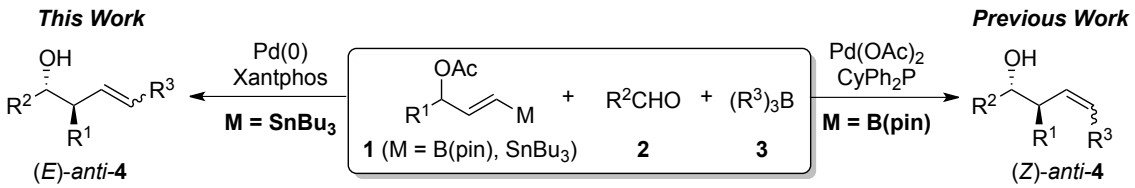
Allylation of carbonyl compounds with α,γ-substituted allyl metal and allyl metalloid reagents are synthetically useful for C-C bond formation reaction since use of such reagents allow easy access to the natural compounds such as iso-agatharesinol, agatharesinol, and metasequirin D.



Although stereochemically defined such reagents are supposed to make a significant contribution for efficient stereoselective transformations, however, synthetically difficult preparation of (*E*)- and (*Z*)-α,γ-substituted allyl metal and allyl metalloid reagents are unavoidable in order to achieve such reactions. So far, there exist a method for the stereocontrolled synthesis of α,γ-substituted allyl boronates and their subsequent reactions with aldehydes, which occur with almost complete selectivity over the three elements of stereogenicity created. However, there still has been no report on the catalytic methods. We previously reported the palladium catalyzed three-component reaction of 3-borylallyl acetates, aldehydes, and organoboranes to give (*Z*)-*anti*-homoallylic alcohols stereoselectively. This reaction proceeds thorough an allylation of aldehydes with allylic *gem*-palladium/boryl intermediates via a closed transition state by σ -allylpalladium followed by a coupling reaction of vinylpalladium and organoboranes, and this method is an alternative to allylation of aldehydes with (*E*)-α,γ-substituted allyl boronates.

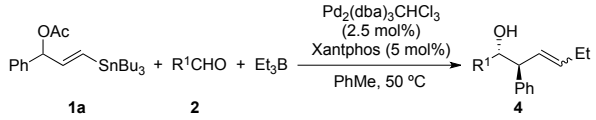
Scheme 1.



Initially we optimized reaction condition and found the reaction of **1a**, benzaldehyde (2.4 equiv.), and Et_3B (2.4 equiv.) in presence of 2.5 mol% of $Pd_2(dba)_3CHCl_3$, 5 mol% of Xantphos in toluene at 50 °C gave **4a** in good yield with high alkene stereocontrol (77%, *E/Z* = 11/1). Under optimized reaction conditions, the scope of various aldehydes was examined and revealed that using electron-rich aromatic aldehydes gave

with moderate alkene stereocontrol. On the other hand, in the case of electron-deficient aromatic aldehyde, a reasonable level of alkene stereocontrol was observed. To further demonstrate the scope of the present reaction, substituents at the C1 position of **1** were surveyed under optimized reaction condition (Table 2). It was found that reaction proceeded smoothly irrespective of the electronic nature of substituent on the aromatic ring to give **4j**–**4p** in good yields with moderate to good complete alkene stereocontrol.

Table 1. Three-Component Reaction of 1a, 2, and Et_3B



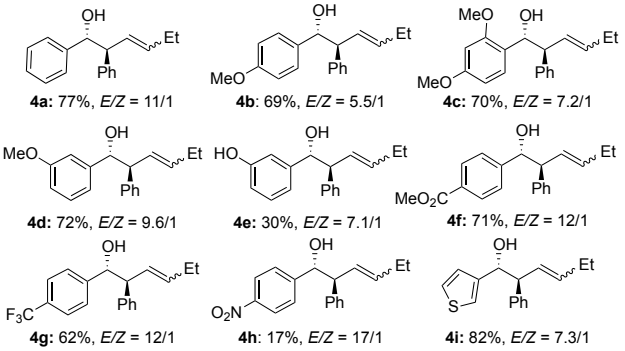
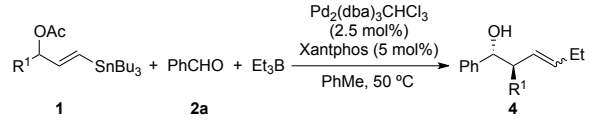
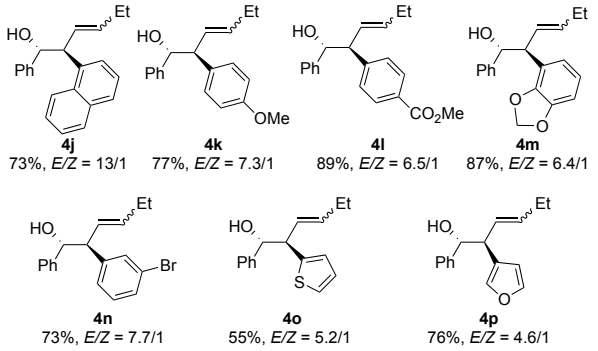


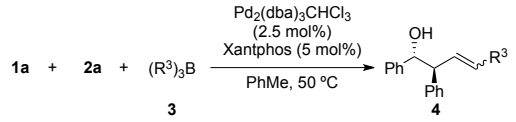
Table 2. Substrate Screening

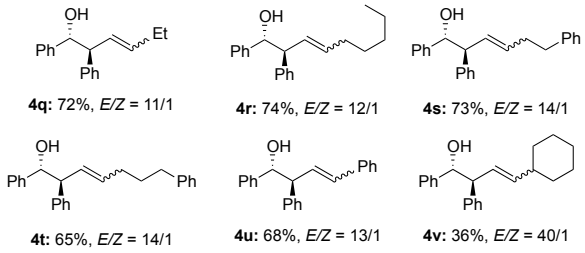




Subsequently, we performed the reaction with various tri-*n*-alkylboranes. It was found that reaction of **1a** with **2a** and various organoboranes to demonstrate the generality of the coupling reaction (Table 3). The scope with respect to the tri-*n*-alkylboranes was demonstrated to be fairly broad. For example, tri-*n*-alkylboranes prepared from 1-hexene, styrene, and allylbenzene with BH_3•SMe_2 complex nicely participated in the coupling reaction to give **4g**–**4t**, respectively, in good yields with high alkene stereocontrol. Furthermore, the present reactions also proceed with Ph_3B to provide the desired product **4u** in good yield. On the other hand, the use of tri-cyclohexylborane took part in the coupling reaction to afford **4v** in moderate yield.

Table 3. Reactions with Various Organoboranes





In summary, we have developed a palladium-catalyzed three-component coupling reaction that provides access to a wide variety of (*E*)-*anti*-homoallylic alcohols from easily accessible 3-(stannyl)allyl acetates, aldehydes, and organoboranes. This outstanding reactivity of allylic *gem*-palladium/stannyl intermediates promises to serve as a powerful strategy for the development of η^3-allylpalladium-mediated transformations.

1P- 29

Palladium-Catalyzed Multi-Component Reaction of 3-(Tributylstannyl)propargyl Acetates, Aldehydes, and Organoboranes

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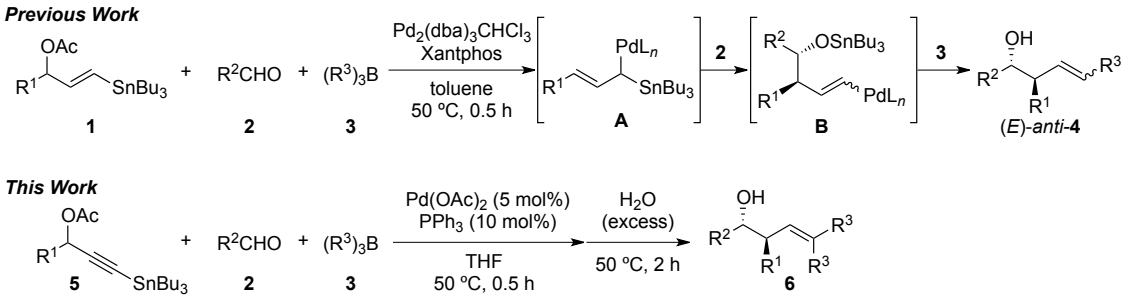
3190 Gofuku, Toyama, 930-8555, Japan
horino@eng.u-toyama.ac.jp

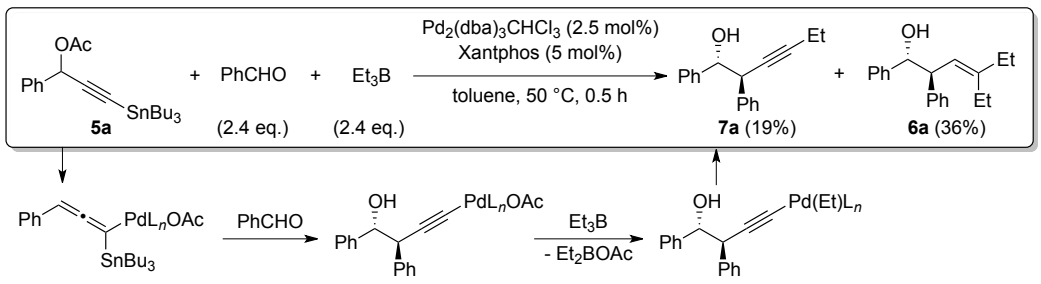
Combining several transformations into a single synthetic operation increases the efficiency of organic synthesis since such strategies have the potential to minimize the number of synthetic steps. Use of in situ generated organo-*gem*-heterobimetallic intermediates that enable to undergo two different types of C-C bond forming reaction in a consecutive fashion is one approach for tandem reaction. Recently, we have developed the palladium-catalyzed three-component reaction of 3-stannyl-substituted allyl acetates, aldehydes, and organoboranes to provide access to a wide variety of (*E*)-*anti*-homoallylic alcohols **4**, wherein allylic *gem*-palladium/stannyl intermediates **A** undergo nucleophilic allylation of aldehydes and the subsequent a coupling reaction of vinylpalladium **B** and organoboranes (Scheme 1). Herein, we report the palladium-catalyzed multi-component reaction of 3-stannyl-substituted propargyl acetates **5**, aldehydes, and organoboranes that provides homoallylic alcohols **6**.

Scheme 1.



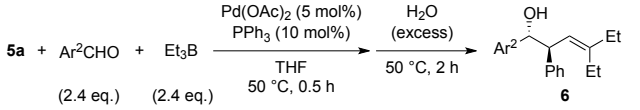
Initially we examined the reaction of **5a**, benzaldehyde (2.4 equiv.), and Et_3B (2.4 equiv.) in presence of 2.5 mol% of $Pd_2(dba)_3CHCl_3$, 5 mol% of Xantphos in toluene at 50 °C (Scheme 2). Interestingly, unexpected product **6a** was obtained as a major product along with an expected homopropargylic alcohol **7a** as a minor product.

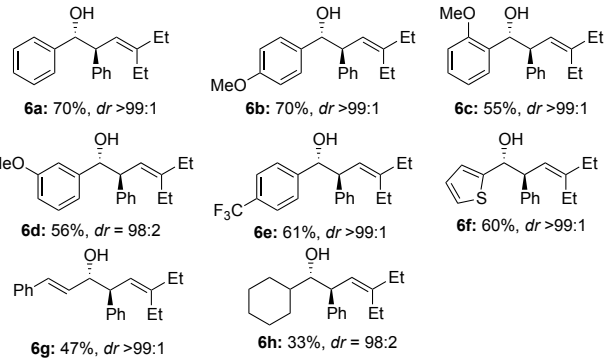
Scheme 2.



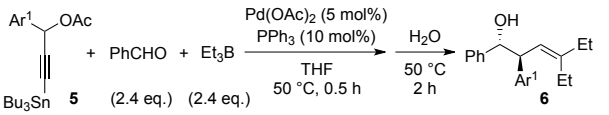
After several attempts, we found that the chemical yield of **6a** was increased if the reaction mixture was treated with H_2O after consumption of **5a** under the optimal reaction conditions (Scheme 3). The scope of various aldehydes was examined. The electron-rich aromatic aldehydes and electron-deficient aromatic aldehydes gave **6b**–**6e** in good yields with high levels of diastereoselectivity. In addition, use of 2-thienylaldehyde also participated in the present reaction to provide **6f** in 60% yield. On the other hand, reactions with aliphatic aldehydes were rather difficult, and **6g** and **6h** were obtained in moderate yields, respectively. To further demonstrate the scope of the present reaction, substituents at the C1 position of **5** were surveyed under optimized reaction condition (Scheme 4). It was found that reaction proceeded dependently on the electronic nature of substituent on the aromatic ring to give **6i**–**6m** in moderate to good yields, respectively, with high diastereoselectivity.

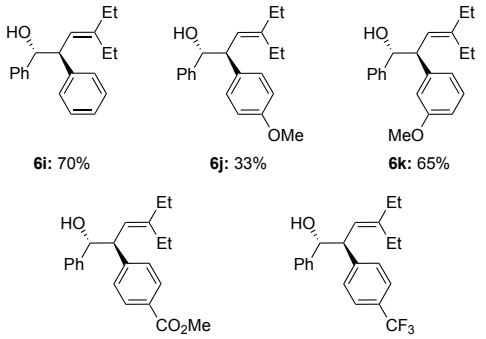
Schcme 3. Multi-Component Reaction of 1a, 2, and Et_3B





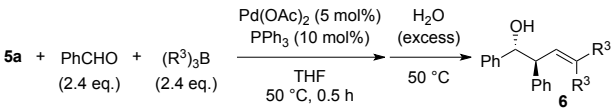
Scheme 4. Substrate Screening

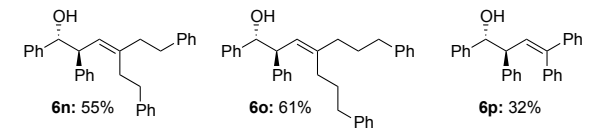


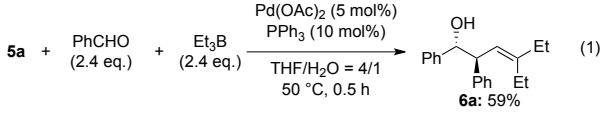


Subsequently, we then performed reaction of **5a** with benzaldehyde and various organoboranes to demonstrate the generality of the coupling reaction (Scheme 5). The reaction of tri-*n*-alkylboranes prepared from styrene and allylbenzene with BH_3•SMe_2 complex nicely participated in the coupling reaction to give **6n** and **6o**, respectively, in good yields. On the other hand, a commercially available tri-*n*-butylborane also underwent cross coupling reaction to afford **6p** in 32% yield. Interestingly, present reaction can be performed in the presence of H_2O, and **6a** was obtained in 59% yield (eqn. 1).

Schcme 5. Reactions with Various Organoboranes







In summary, we demonstrated the utility of *gem*-allenylpalladium/stannyl intermediates in the synthesis of 1,2-*anti*-disubstituted homoallylic alcohols with excellent diastereoselectivities.

1P- 30

Efficient Gas-related Photo Reactions Using Micro- and Nanobubble Strategy Under Atmospheric Pressure

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Micro- and nanobubbles (MNB) are defined as bubbles of less than 50 μm in diameter. They possess characteristic properties that are distinct from those of common cm- and mm-bubbles. For example, microbubbles exhibit excellent gas-dissolution abilities because of their larger gas/liquid interfacial areas, as well as longer stagnation due to their low buoyancy. Focusing on these properties, we applied MNB to gas-related multiphase chemical reactions, which are clean and simple reaction systems because reactive gases are easily removed from the reaction mixture to isolate the products. However, the conventional gas-related multiphase reactions require high pressure, high temperature, and vigorous stirring conditions to increase reaction yields. We have recently developed a new experimental methodology using MNB for gas-related multiphase reactions in organic synthesis under room temperature, atmospheric pressure, and in the absence of vigorous mechanical stirring conditions. In order to further develop this methodology, we applied the MNB method to conventional photo gas-liquid reactions that generally require external irradiation and autoclaving (Figure 1).

We tried photo oxidation with singlet molecular oxygen using the photo MNB method under atmospheric pressure and room temperature. Photo oxygenation by use of singlet oxygen, which is formed *via* energy-transfer from an excited dye molecule, is known to be a cleaner and greener method to furnish oxygenated products. Moreover, generated active species in photo reactions are readily controlled

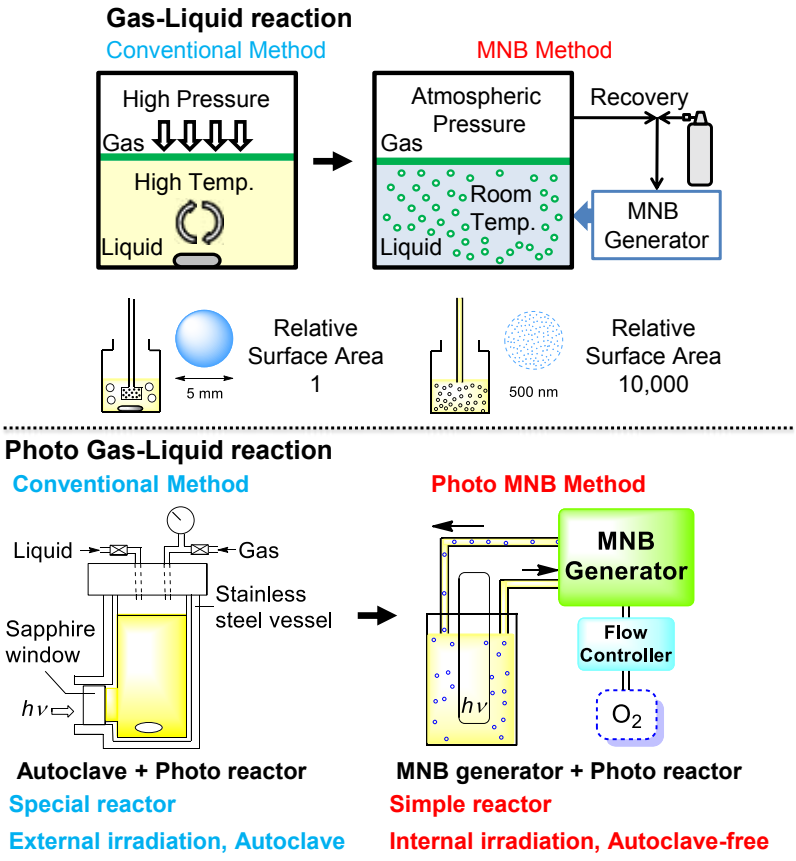
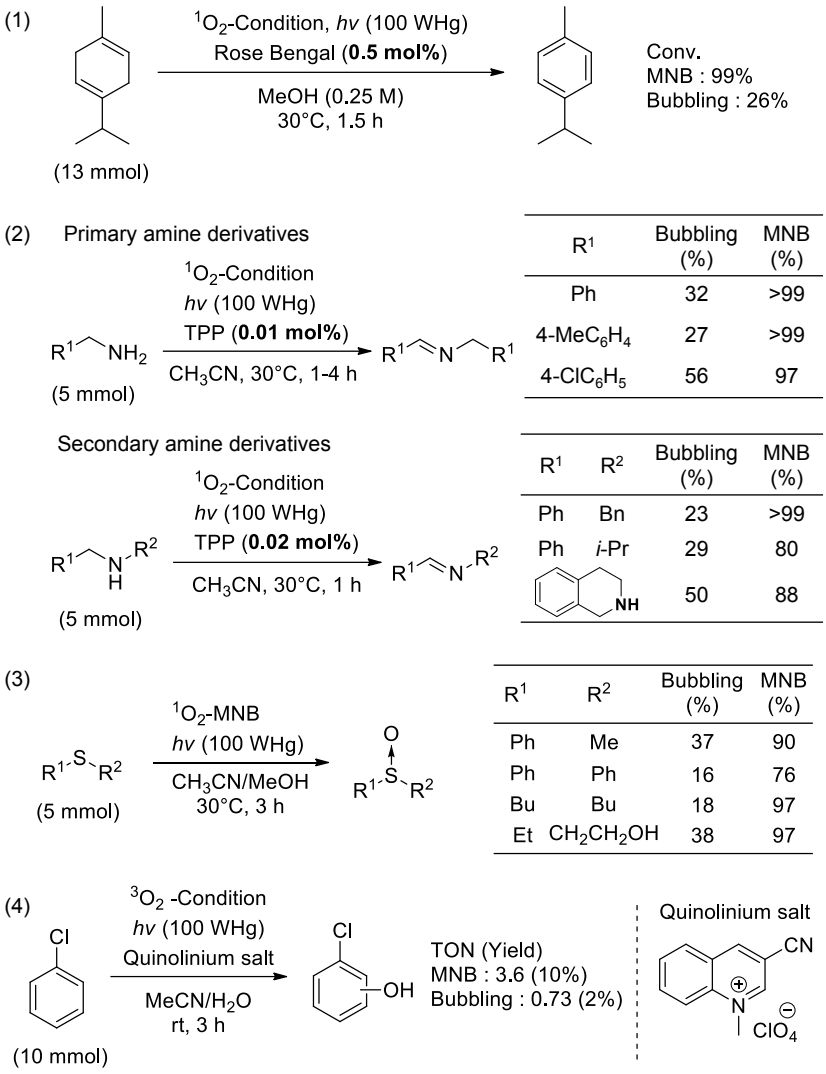


Figure 1. Comparison between conventional and MNB methods

by turning a light ON/OFF. At first, we examined oxidative dehydrogenations of γ-terpinene (Scheme 1-1), which, in the presence of a small amount of rose bengal (0.5 mol%) as a sensitizer, resulted in high yields of *p*-cymene in shorter reaction times compared to conventional bubbling or balloon conditions. We then investigated oxidative imine homo-coupling, affording excellent yields with only 10 ppm TPP (5,10,15,20-tetraphenylporphine) as sensitizer under MNB condition (Scheme 1-2). Not only primary, but also secondary amines can be applied to this reaction system. Moreover, we studied oxidative addition reactions of sulfides to sulfoxides (Scheme 1-3). Although sensitizers are generally needed to generate singlet oxygen, quantitative sulfoxides without formation of sulfones were obtained in the absence of sensitizer (Scheme 1-3). Evaporation of the reaction mixture directly gave the desired product. Consequently, we have disclosed the advantage of the photo MNB method under atmospheric pressure with simple reactor. In addition, direct oxygenation of arenes to phenols using homogeneous photo-organocatalyst was investigated. In the case of MNB condition, TON (turnover number) indicated that the quinolinium salt can work in a catalytic cycle probably due to the higher oxygen concentrations.



R^1	Bubbling (%)	MNB (%)
Ph	32	>99
4-MeC_6H_4	27	>99
4-ClC_6H_5	56	97

R^1	R^2	Bubbling (%)	MNB (%)
Ph	Bn	23	>99
Ph	*i*-Pr	29	80
		50	88

R^1	R^2	Bubbling (%)	MNB (%)
Ph	Me	37	90
Ph	Ph	16	76
Bu	Bu	18	97
Et	CH_2CH_2OH	38	97

Scheme 1. Photo gas-liquid reaction using oxygen : (1) Oxidative dehydrogenation of γ-terpinene, (2) Oxidative imine coupling, (3) Oxidation of sulfide, (4) Phenols synthesis with photo-organocatalyst

We have achieved a significant improvement in the gas-related photo reactions with the environmentally-friendly MNB-based technique. We believe that this new methodology is an important contribution to general gas-related photo reactions with simple, safe, autoclave-free, and green protocols under atmospheric pressure.

Reference) *Chem. Commun.* 2086 (2011); *Synlett* 2225 (2013); Patent application number: 2011-158551, 2012-140292, 2013-152163, and 2014-46542.

1P- 31

Identification of Superior Organocatalysts Through High-Throughput Fluorescence-Based Screening

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Development and identification of highly reactive catalysts are required to improve productivity and safety for a green sustainable society. Unfortunately, conventional manual methods to identify catalysts are often labor intensive, time-consuming, and expensive. However, methods for monitoring the reaction progress of chemical transformations through an increase in fluorescence intensity are useful for screening of catalysts and reaction conditions, as well as the characterization of catalysis on a small scale (Figure 1). Herein, we report the synthesis and the use of fluorogenic aldehydes, imines, and enals bearing arylethynyl groups that are suitable for monitoring the enamine/iminium-based organocatalytic C–C bond-forming reactions, such as aldol, Mannich, and Diels-Alder reactions in DMSO.

Fluorescence properties of aromatic carbonyl compounds are generally complex and often difficult to predict. Many aromatic aldehydes and ketones have a low-lying n-π* excited state and thus exhibit low fluorescence quantum yields due to intersystem crossing. Therefore, we considered anthracene, naphthalene, and benzene derivatives bearing carbonyl functional groups as candidate fluorogenic sensors. Indeed, the fluorescence intensity ratios of aldols to aldehydes were greater than 300 times. Based on the above observations, we investigated a novel screening method for aldol and Mannich reactions in enamine catalysis by using aldehyde and imine

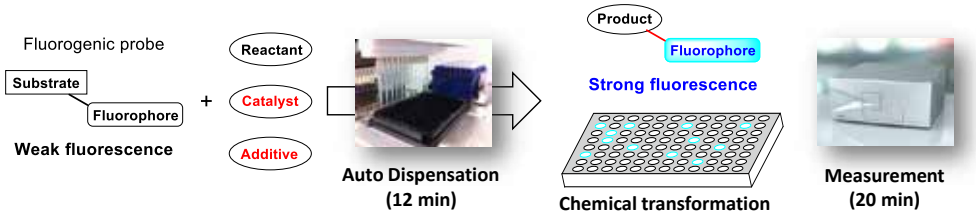

Figure 1. Method of fluorescence screening

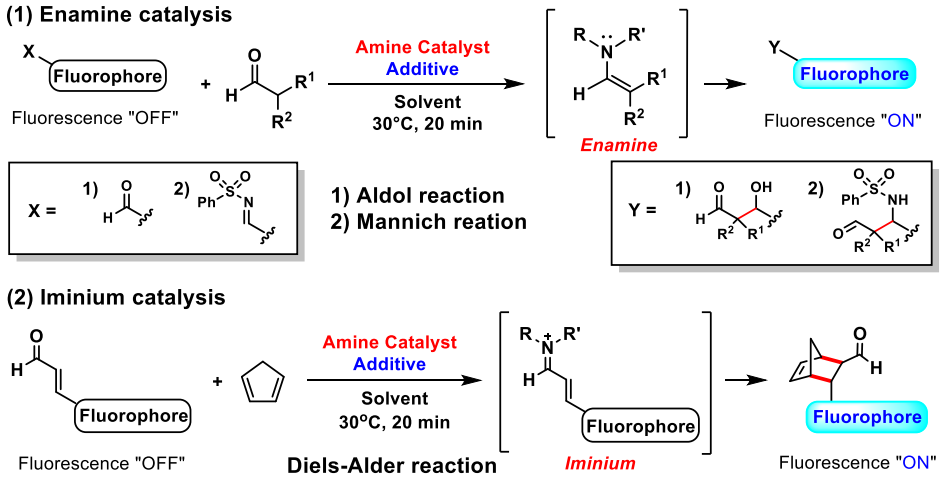

Figure 2. OFF-ON fluorogenic sensor for enamine / iminium catalyst screening

sensors (Figure 2-1). Furthermore, we applied this system to identify superior catalysis in Diels-Alder reaction via iminium catalysis using the enal sensor (Figure 2-2).

We first screened organocatalysts and reaction conditions in quaternary carbon-containing aldol reactions. We identified a superior combination of acid-base organocatalyst, such as pyrrolidine and 5-hydroxyisophtalic acid, according to fluorescence screening and model reactions using *p*-nitrobenzaldehyde (Figure 3). This result suggests that the fluorescence assay system is useful for the rapid identification of superior aldol catalysts and reaction conditions.

We then focused on the Mannich reaction, which is one of the most predominantly used reaction for the formation of C-C bonds. The results of fluorescence screening and model reaction showed fine correlation. As a consequence, we identified the combination of pyrrolidine and trimesic acid as a superior organocatalyst in enamine-based Mannich reaction.

Finally, we applied the fluorogenic screening method to iminium-based Diels-Alder reaction, which is useful for the formation of the six-membered ring in modern synthetic organic chemistry and is widely used in natural product synthesis. We found that the combination of ethylenediamine and citric acid showed the most effective iminium catalytic activities among over thousand tests.

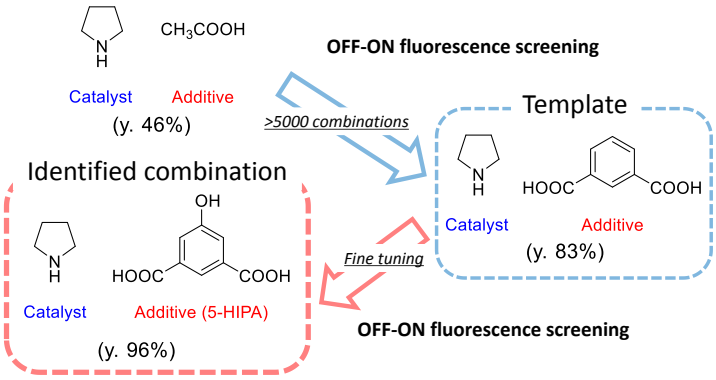

Figure 3. Fine tuning of enamine catalyst for aldol reactions

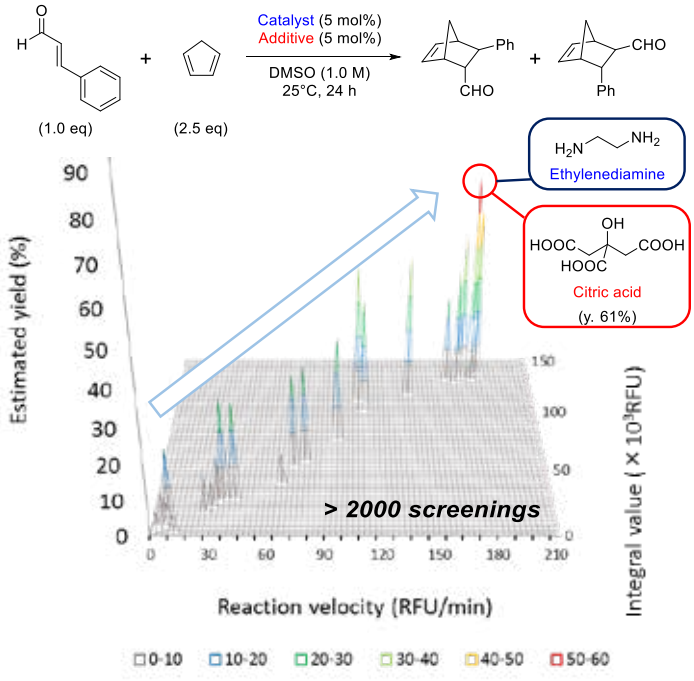

Figure 4. Fluorescence screening in Diels-Alder reactions

In conclusion, we have developed fluorogenic sensors that can be used for monitoring various organocatalytic enamine/iminium formations through increased fluorescence. The utility of the fluorogenic sensors was demonstrated in monitoring the catalytic progress of aldol, Mannich, and Diels-Alder reactions. As a result, we identified the superior combinations of amine catalyst and acid additive from libraries in both enamine and iminium catalysis.

References: *Tetrahedron Lett.* 4306 (2013), 1946 (2014)

1P- 32

Hydrolysis of Diazonium Salts Using Two-phase System (CPME and Water)

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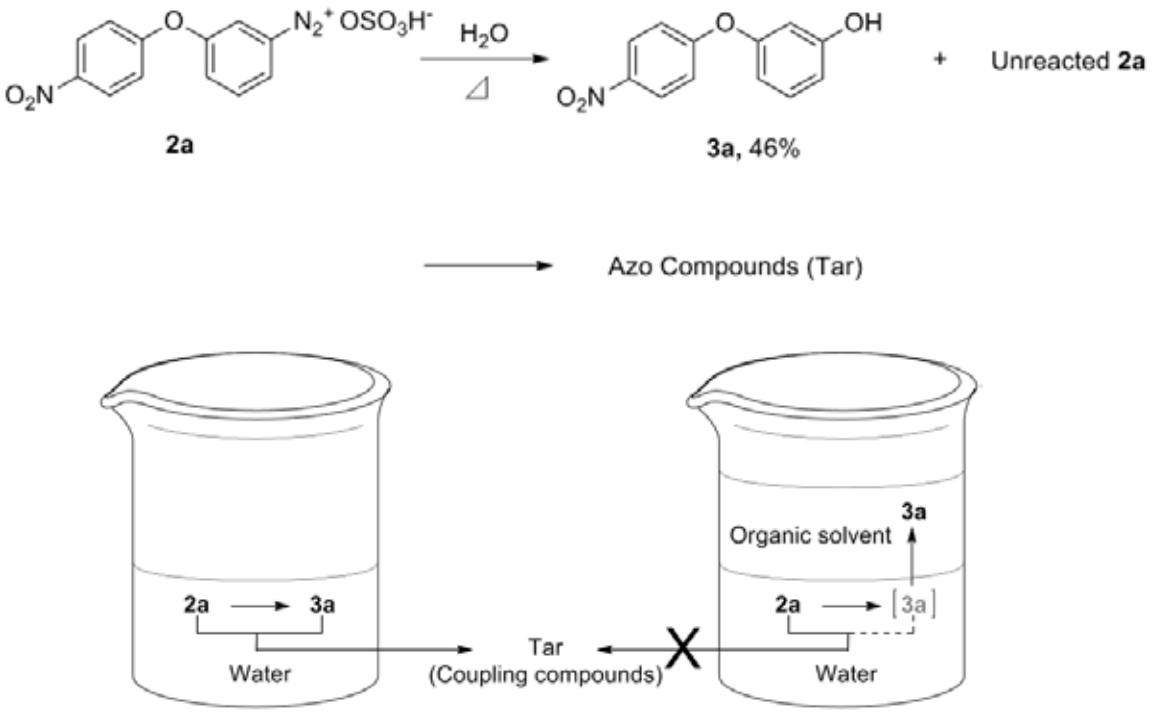
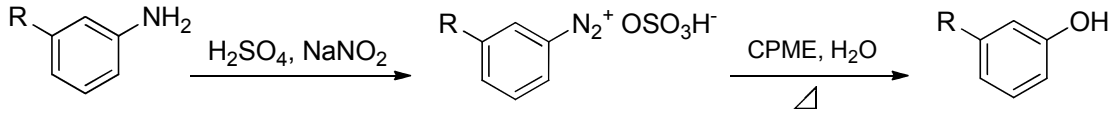
In our project concerning the production of a raw material for functional plastics (polyimide resin), 3-(4-aminophenoxy)phenol and 3-(4-nitrophenoxy)phenol (**3a**) are very significant compounds.
Generally, the synthesis of *m*-substituted phenols is difficult, because phenol has ortho/para-directing ability due to the electron-donating hydroxyl group. For ortho- and para-functionalization of phenols, many methodologies are well known. However, this strong directing effect prevents the selective direct functionalization of phenols at the meta position.
To develop a safe, simple, low-cost, and high-yielding synthetic method, the synthesis of **3a** using the hydrolysis of diazonium salt **2a** prepared from 3-(4-nitrophenoxy)aniline (**1a**) was examined. However, the classical reactions written in textbooks are not always practical and industrially feasible. In such reaction systems, large amounts of tar are formed during the reaction, making the establishment of suitable experimental manipulation difficult.

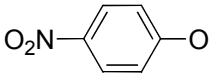
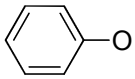
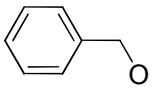


To solve this problem, the use of a two-phase system comprising a mixture of an organic solvent and water was envisioned. After intensive examinations of the hydrolysis of **2a** prepared from **1a** in a variety of two-phase systems, we herein report the surprising effect of a two-phase system consisting of cyclopentyl methyl ether (CPME) and water. To the best of our knowledge, this is the first example of the hydrolysis of diazonium salts using a two-phase system (CPME and water).

Table Synthesis of *m*-Substituted Phenols (**3a-j**) in the Two-Phase System (CPME and Water)



1a-j **2a-j** **3a-j**

Entry	*R*	*Product*	*Yield, %*[a]	*Method*
1		**3a**	96	A
2		**3b**	95	B
3		**3c**	64	B
4	*i*-Pr	**3d**	96	B
5	Me	**3e**	93	B
6	MeO	**3f**	91	B
7	Ac	**3g**	92	B
8	NO_2	**3h**	56, 75[b]	B
9	CF_3	**3i**	94	A
10	COOH	**3j**	98	A

[a] Isolated yields. [b] Co-solvent is pseudocumene.

From the viewpoint of practical and industrial production of a variety of phenols **3**, the present method is very noteworthy because of the use of easily available and cheap reagents and solvents, and mild reaction conditions.

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One-pot Transformation of Aliphatic Carboxylic Acids into *N*-Alkylsuccinimides

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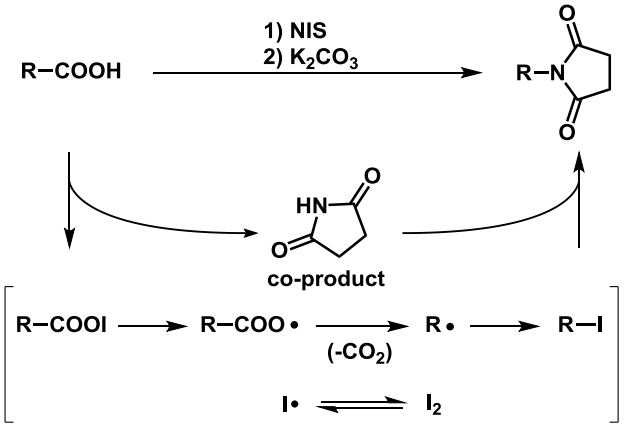
[Introduction]

Aliphatic carboxylic acids are easily available and inexpensive, since they exist as important parts of glycerol esters in vegetable oils and animal fats. Therefore, the functional group transformations of aliphatic carboxylic acids are very important. Especially, functional transformation via radical decarboxylative pathway is attractive. However, these reported methods relied upon precious transition-metal catalysts or high temperature. Decarboxylative functionalization of carboxylic acids using the Hunsdiecker reaction and the Barton decarboxylation is well known. However, one-pot decarboxylative C-N bond formation is scarcely studied. Here, we would like report for decarboxylative C-N bond formation from aliphatic carboxylic acids in one-pot manner under transition-metal-free condition with NIS. On the other hand, *N*-alkylimides are important compounds, which have been known as their pharmacological properties such as anti-inflammatory and analgesic properties. They are also useful intermediates in organic synthesis, especially for preparation of primary amines. So, we have focused on the value of succinimides produced as co-product and found that they could be converted into the corresponding *N*-alkylsuccinimides in one-pot manner via radical decarboxylative iodination with NIS, followed by the *N*-alkylation of succinimides formed as shown in Scheme 1.

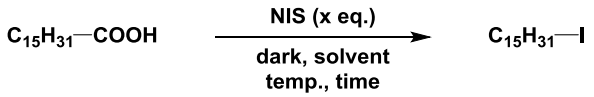


Scheme 1. Plausible Reaction Mechanism

[Results and Discussion]

First, optimized reaction conditions for the conversion of hexadecanoic acid into 1-iodopentadecane with NIS in DCE at 80 °C were achieved as shown in Table 1.

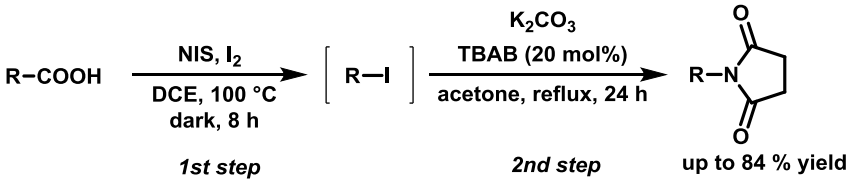
Table 1. Optimization for Reaction Conditions



entry	x	solvent	temp. (°C)	time (h)	yield (%)
1	1.2	DCE (0.5 M)	80	2	19 (78)[a]
2[b]	1.2	DCE (0.5 M)	80	2	11 (84)[a]
3[c]	1.2	DCE (0.5 M)	80	2	N.R.
4	3.0	DCE (0.5 M)	100	4	51 (43)[a]
5	3.0	DCE (0.1 M)	100	6	89 (9)[a]
6	3.0	DCE (0.1 M)	100	12	92
7[d]	3.0	DCE (0.1 M)	100	12	96
8	3.0	CCl_4 (0.1 M)	80	12	76 (18)[a]
9	3.0	toluene (0.1 M)	100	12	89 (5)[a]
10	3.0	MeCN (0.1 M)	100	24	46 (48)[a]
11	3.0	propionitrile (0.1 M)	110	24	44 (46)[a]

[a] Recovery of starting material. [b] K_2CO_3 (10 mol%) was added.
[c] $TsOH•H_2O$ (10 mol%) was added. [d] I_2 (1.0 eq.) was added.

Based on these results, various aliphatic carboxylic acids with NIS in the presence of I_2 in DCE at 100 °C, followed by the reaction with succinimides formed in situ were carried to provide the corresponding *N*-alkylsuccinimides in moderate to good yields. The present reaction is a one-pot transformation of aliphatic carboxylic acids into *N*-alkylsuccinimides using less expensive reagents under transition-metal-free conditions.



Scheme 2. One-pot Synthesis of *N*-Alkylsuccinimides from Carboxylic Acids with NIS

Now, we have achieved direct conversion of aliphatic carboxylic acids into *N*-alkylsuccinimides. However, NIS is expensive as halogenating reagents. So, we have aimed to further improvements, and used NCS/NaI instead of NIS.

As a result of various investigations, the corresponding *N*-alkylsuccinimides was obtained in moderate to good yields in one-pot manner. This reaction has the same features as the method using NIS.

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Homogeneous Ruthenium-Catalyzed Hydrogenation Using a Continuous Flow Reactor

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Continuous flow technology has been developed in the chemical, agrichemical and pharmaceutical industry for the efficient, safe and environmentally benign process. Compared to heterogeneous catalyst, homogeneous one promises stable production in flow mode because the catalytic activity and selectivity do not change during the reaction. This feature is important especially for the production in GMP environment. We investigated homogeneous ruthenium complex catalyzed (1) asymmetric hydrogenation, (2) direct asymmetric reductive amination and (3) reduction of optically active ester using a 350 mL tube reactor.

(1) Asymmetric hydrogenation of hydroxyacetone[1)]

Asymmetric hydrogenation of hydroxyacetone catalyzed by $[NH_2Me_2][\{RuCl[(R)\text{-segphos}]\}_2(\mu\text{-}Cl)_3]$ was performed in flow mode. All starting materials were pre-mixed and the substrate mixture was combined with hydrogen gas prior to feed into the tube reactor (Figure 1). The reaction proceeded smoothly at the early stage, highly diluted condition (5–6 h).

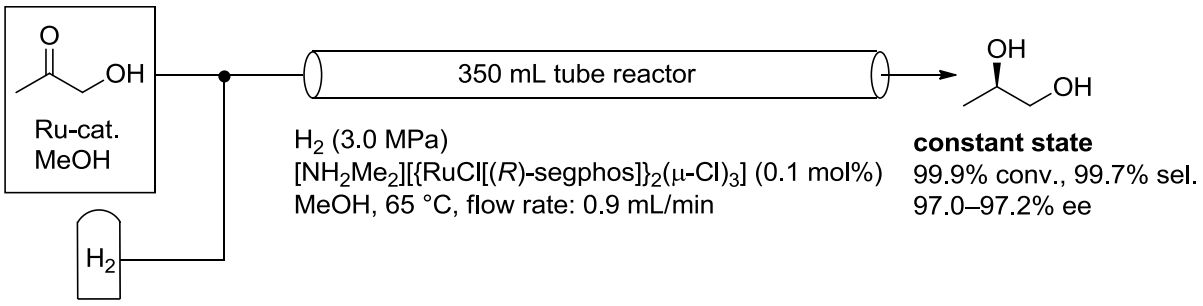

Figure 1. Asymmetric hydrogenation of hydroxyacetone using a 350 mL tube reactor.

Figure 2 shows the result of the continuous asymmetric hydrogenation using a tube reactor. At constant state, (*R*)-1,2-propanediol was eluted in 99.9% conv. with 97.0–97.2% ee.

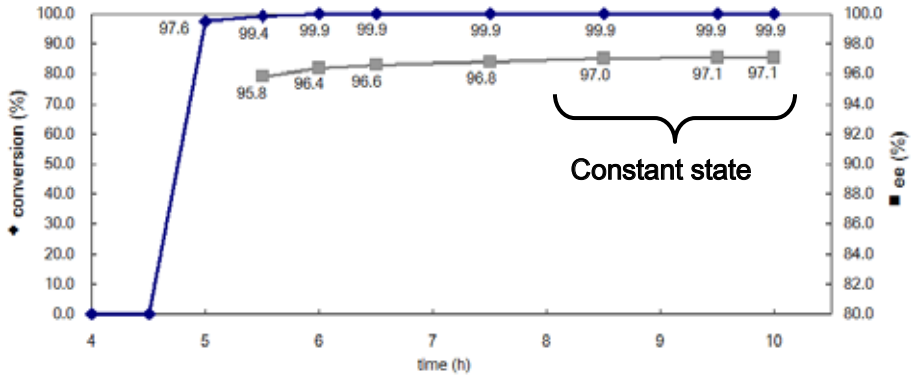

Figure 2. Conversion and ee (%) vs. time (h) curve.

2) Direct asymmetric reductive amination of methyl acetoacetate[2)]

Direct asymmetric reductive amination using ammonium salt was also applicable to the continuous flow process. In this system, the substrate solution (methyl acetoacetate and ammonium acetate in MeOH) and precatalyst solution ($[NH_2Me_2][\{RuCl[(S)\text{-dm-segphos}]\}_2(\mu\text{-}Cl)_3]$ in MeOH) were separated and mixed just before feeding into the tube reactor. At constant state, β-amino acid derivative was eluted in 96.0% yield with 94.0% ee.

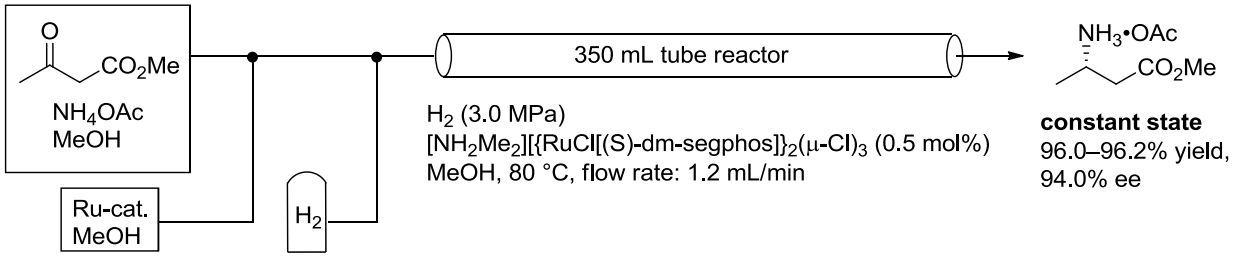

Figure 3. Direct asymmetric reductive amination of methyl acetoacetate using a 350 mL tube reactor.

3) Reduction of optically active esters[3)]

Ester group could be reduced to corresponding alcohol with PNP-Ru complex (Ru-MACHO) in a flow mode. The reduction of D-pantolactone proceeded smoothly at mild conditions and corresponding triol was eluted in 99.5% conversion at constant state. The optical purity was maintained during the reaction (Δ% ee: < 1%). Noncyclic esters were also applicable to the flow mode.

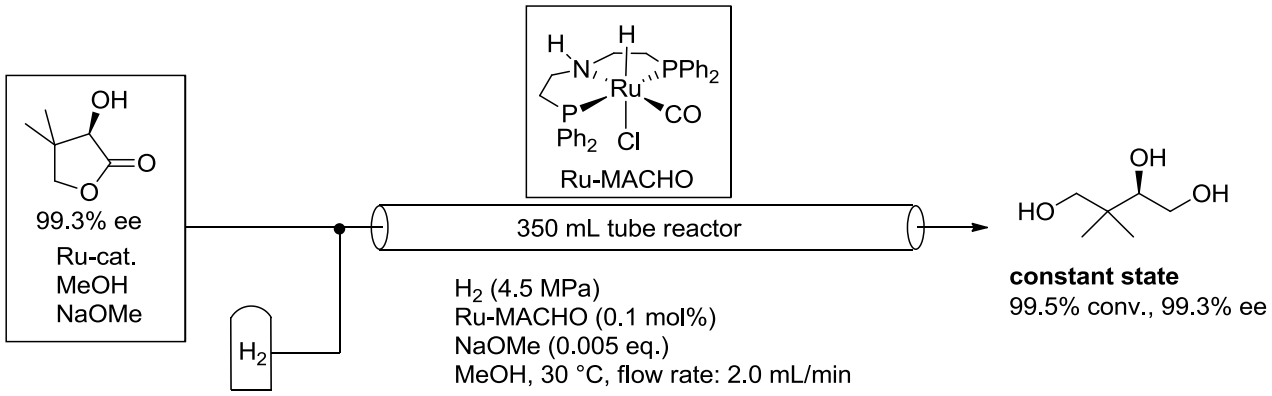

Figure 4. Reduction of optically active ester using a 350 mL tube reactor.

References

1) Takao Saito, Tohru Yokozawa, Takero Ishizaki, Takashi Moroi, Noboru Sayo, Takashi Miura, Hidenori Kumobayashi, *Adv. Syn. Catal.*, **2001**, *343*, 264–267. 2) Kazuhiko Matsumura, Xiaoyong Zhang, Kiyoto Hori, Toshiyuki Murayama, Tadamasa Ohmiya, Hideo Shimizu, Takao Saito, Noboru Sayo, *Org. Process Res. Dev.*, **2011**, *15*, 1130–1137. 3) Wataru Kuriyama, Takaji Matsumoto, Osamu Ogata, Yasunori Ino, Kunimori Aoki, Shigeru Tanaka, Kenya Ishida, Tohru Kobayashi, Noboru Sayo, Takao Saito, *Org. Process Res. Dev.* **2012**, *16*, 166–171.

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Improvements in a Practical and Scalable Synthesis of Selective ALK Kinase Inhibitor ASP3026, Utilizing Readily Available Cyanuric Chloride as a Starting Material

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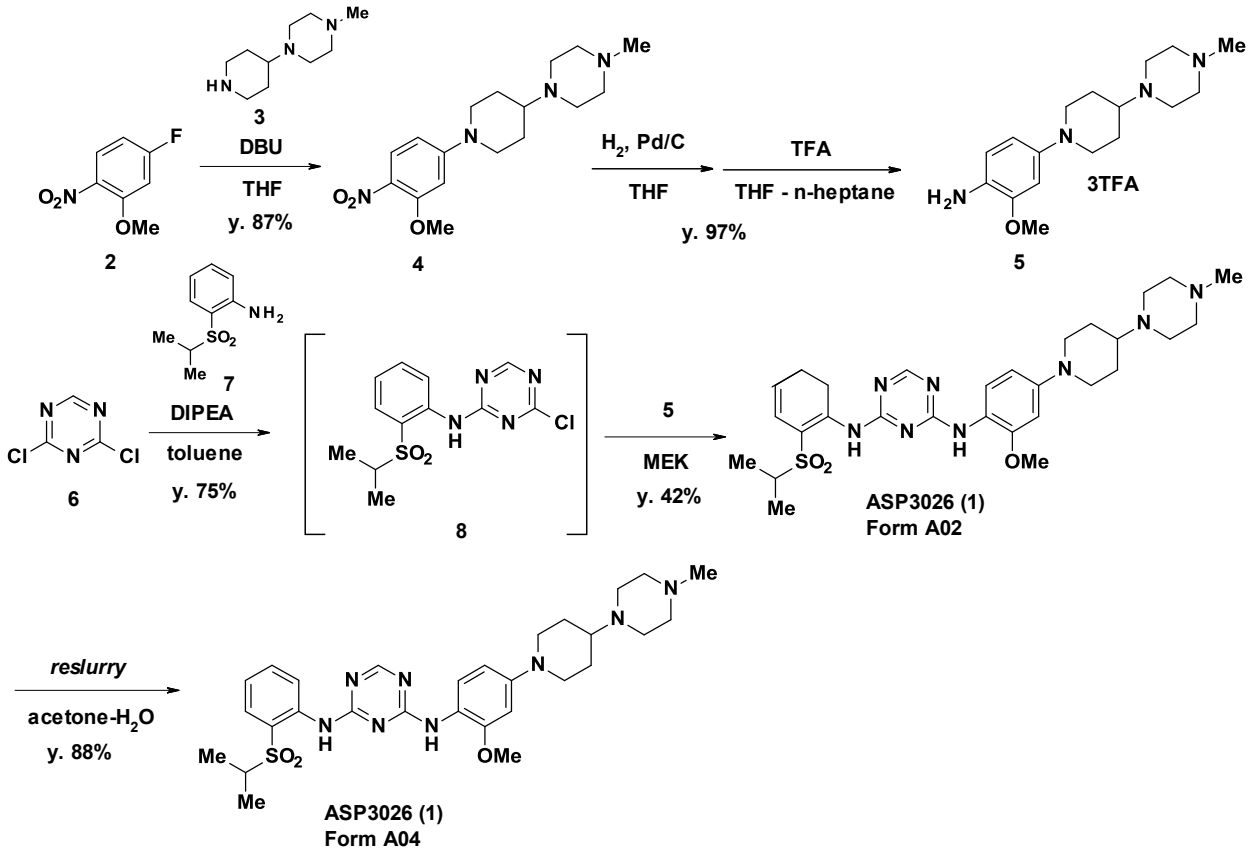
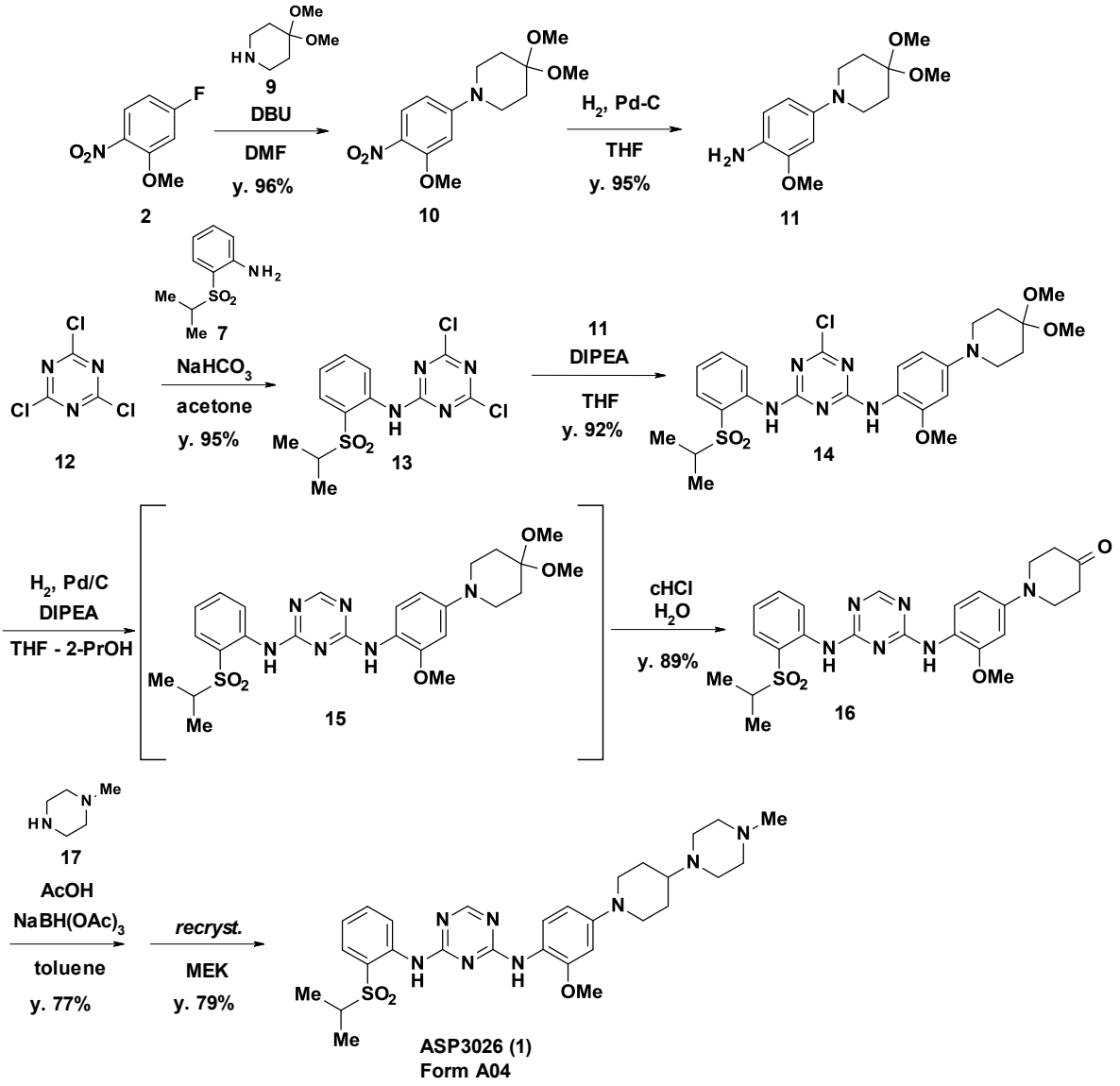
ASP3026 (**1**) is the novel candidate for EML4-ALK kinase inhibitor. In early development stage, ASP3026 (**1**) had been manufactured along 1st generation synthetic route[1] (Scheme 1). In this process, however, there are three critical drawbacks should be overcome to accomplish the further scale-up synthesis as described below.

1. 2,4-dichloro-1,3,5-triazine (**6**) is expensive and has low availability for industrial scale.
2. The aniline **5** is unstable.
3. The yield in nucleophilic substitution reaction (S_NAr) is unacceptably low.



Scheme 1. 1st generation synthetic route

From these reasons, we have established new synthetic route featured by utilizing cheap and readily available cyanuric chloride[2)] (Scheme 2). By this improvement, manufacturing cost has been reduced to approximately half in comparison with 1st generation synthetic route. Along this method, 250 kg of high quality ASP3026 has been produced stably.



Scheme 2. 2nd generation synthetic route

References

1) (a) Takeguchi, K. *Bunri Gijutsu*, **2011**, *41*, 354. (b) Hirasawa, S. *et al*. *Abstracts of 2012 Summer Symposium of the Japanese Society of Process Chemistry*, **2012**. (c) Takeguchi, K. *Bunri Gijutsu*, **2014**, *44*, 8.

2) WO2012102393 A1 (Astellas Pharma Inc.).

1P- 36

Root Cause Analysis of Uncontrollable Polymorph –Inhibition of a Trace Amount of Impurity in Selective ALK Inhibitor ASP3026–

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ASP3026 is a candidate compound of selective ALK inhibitor invented by Astellas Pharma Inc. One of the most important points for its solid manufacturing is the polymorphic control for the following reasons; 1) ASP3026 has 6 anhydrous polymorphs (Form A01, A02, A03, A04, A05 and A06) and hydrates.[1,2] 2) The difference of thermodynamic stability between the most stable Form A04 (desired polymorph) and metastable Form A03 is considerably small. Moreover, it is difficult to convert Form A03 to Form A04 by solvent-mediated polymorphic transformation (SMPT) once a concomitant polymorph of Form A04/A03 is obtained.

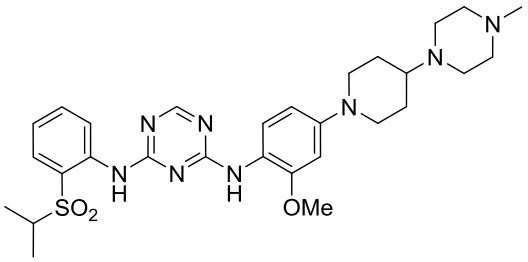


Fig 1. ASP3026 (**1**)

We have already established 1st and 2nd generation synthetic route of ASP3026.[2,3] In the 1st synthetic route, the desired Form A04 was obtained reproducibly by SMPT of crude ASP3026 (Form A02) in aqueous acetone solution as we reported previously.[4] On the contrary, in the 2nd generation, since crude ASP3026 was obtained as a concomitant polymorph of Form A02/A04/A06 with poor reproducibility, recrystallization was adopted instead of the SMPT process. However, the recrystallized crystals from the manufactured crude ASP3026 contained 15% of Form A03, whereas pure Form A04 was successfully obtained from another crude ASP3026 prepared in the lab (Fig. 2).

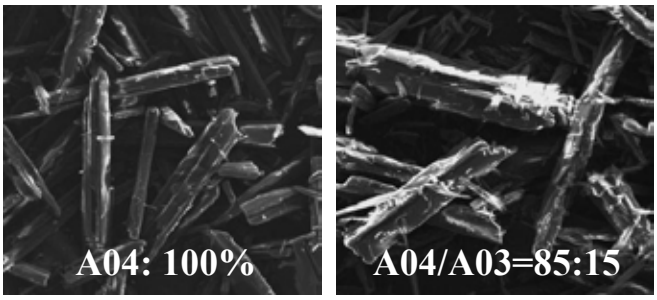
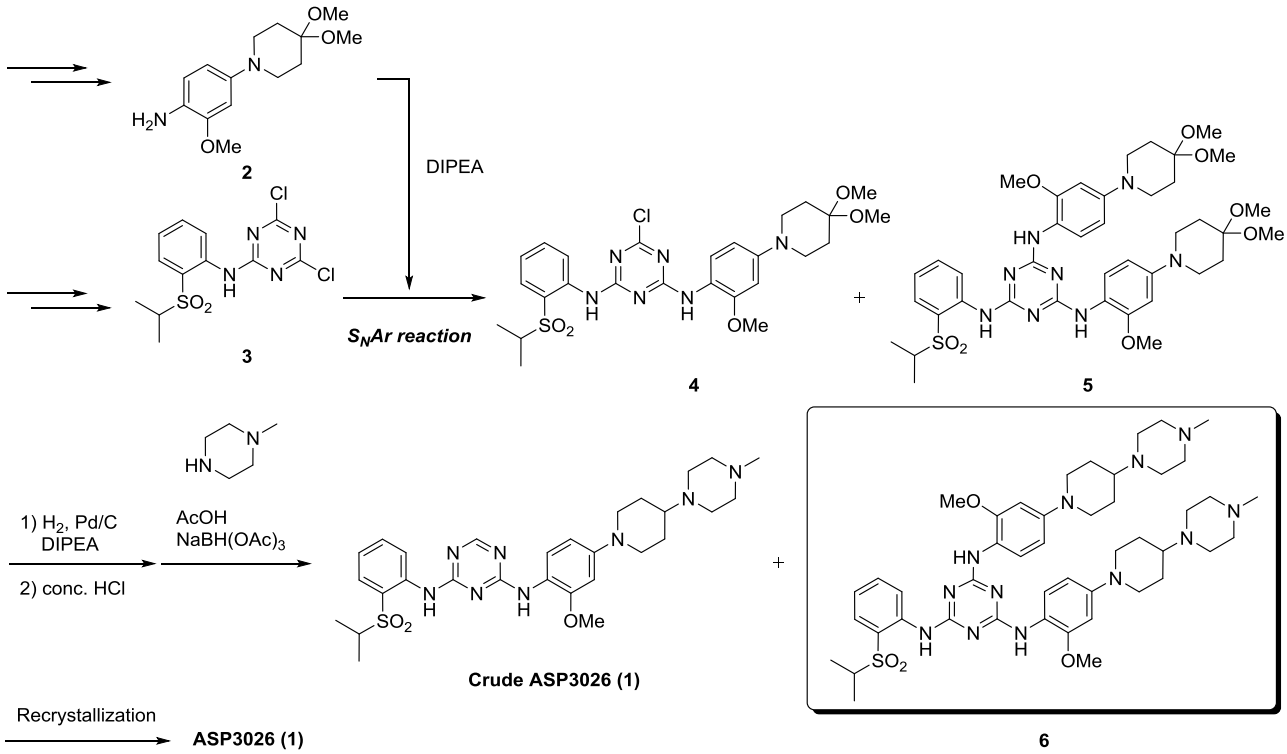


Fig 2. SEM images of ASP3026 (x500)

After close investigation, a treatment with activated charcoal during the recrystallization turned out to be effective to enhance the ratio of Form A04. With this procedure, 250 kg of ASP3026 (Form A04) had been manufactured. However in consequence, we ended up facing new issues such as decrease of the yield due to adsorption of the material on activated charcoal, generation of new impurities and coloration of ASP3026 caused by oxygen-charcoal oxidation. Therefore, a drastic improvement was strongly required in the recrystallization step.

From the fact that the ratio of Form A04 was improved when activated charcoal treatment was introduced, we presumed that some impurities could inhibit the polymorphic control of ASP3026. As a result of further investigation, it was found that trisubstituted byproduct **6** has a negative impact on the polymorphic control.



Scheme 1. Generation of the related substance **6**

Table 1. Condition screening of S_NAr reaction toward inhibition of **5**

Entry	**2** (equiv.)	Temp. (°C)	Time (h)	**4** (area%)	**5** (area%)
1 (Mfg.)	1.05	25	3	97.4	0.21[a]
2	0.95	25	3	97.7	0.04
3	0.95	0	3	97.5	**0.01**
4	0.95	-10	3	97.5	**ND**

[a] In manufacturing, **5** was further increased to 0.40% during overnight storage after reaction.

As shown in Table 1, byproduct **5**, a precursor of **6** was effectively inhibited by reducing the equivalent of aniline derivative **2** under a lower reaction temperature (-10 °C) in the S_NAr reaction. The crude ASP3026 prepared with this new protocol gave pure Form A04 without charcoal treatment in the final recrystallization step. In consequence, this improvement made it possible to conduct robust polymorphic control of ASP3026 in the 2nd generation synthetic route.

[1] PCT Int. Appl. WO 2011145548 A1, Astellas Pharma Inc. (2011). [2] PCT Int. Appl. WO 2012102393 A1, Astellas Pharma Inc. (2012). [3] Obitsu, K. *et al*. *Abstracts of ISPC 15 The Third International Symposium on Process Chemistry*, **2015**. [4] (a) Takeguchi, K. *Bunri Gijutsu*, **2011**, *41*, 354. (b) Hirasawa, S. *et al*. *Abstracts of 2012 Summer Symposium of the Japanese Society of Process Chemistry*, **2012**. (c) Takeguchi, K. *Bunri Gijutsu*, **2014**, *44*, 8.

1P- 37

New Conceptual Diaryliodonium Salts for Metal-Free Arylation of Carboxylic Acids Giving Aryl Esters

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The diaryliodonium salts (Figure 1), which take a T-shaped form of an iodine atom with two bound aryl moieties and a ligand (X), have been used in organic synthesis as versatile arylating agents and for other applications, such as active bactericides, photoacid generators (PAG) for cationic polymerization processes, etc.[1] Utilizing the excellent leaving nature as more stable monovalent iodoarene moieties, nucleophilic substitutions with organometallic reagents or enolates under basic conditions as well as transition-metal catalyzed couplings have thus been established for the use of the salts in organic synthesis.

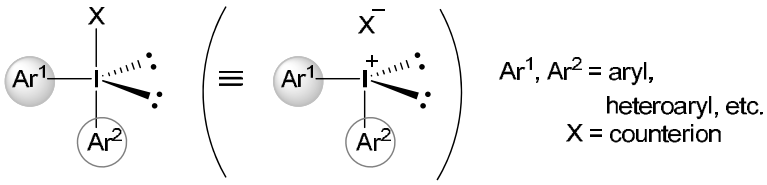


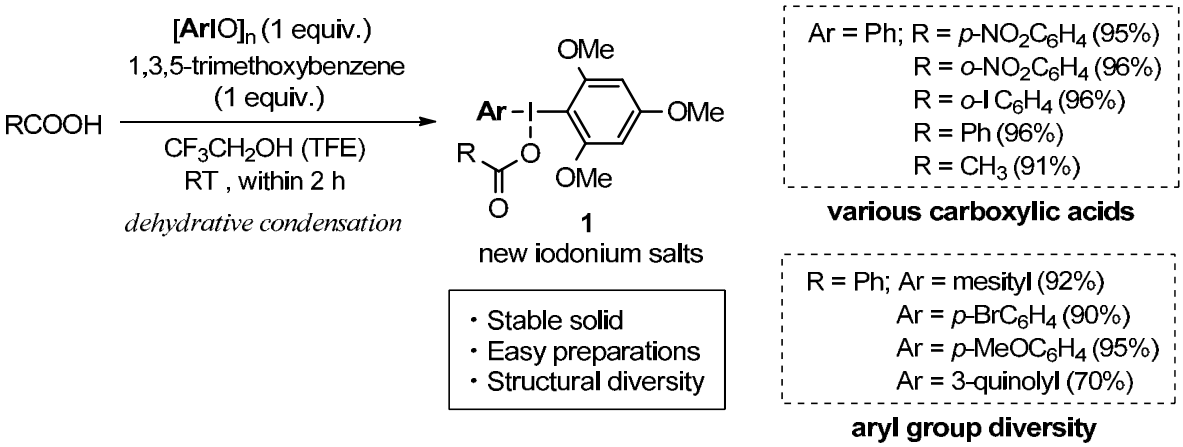
Figure 1. Structural discription of diaryliodonium(III) salts.

Recently, Olofsson's research group has been contributing to significant improvement of the metal-free nucleophilic substitutions for the diaryliodonium salts by further optimizing the reaction conditions. The investigations regarding the base, solvent, temperature, and reaction time have defined the conditions as the use of potassium *tert*-butoxide in refluxing toluene for the arylation of carboxylic acids, which enabled efficient and practical metal-free arylations giving aryl esters.[2] However, the method still has limitations, such as the requirement of base, and sometimes accompanied problems in the product yields and aryl selectivities for low nucleophilic carboxylic acids and unsymmetrical diaryliodonium salts having two different aryl groups.

Herein, we have developed a more efficient arylation of carboxylic acids meeting green chemistry by utilizing new conceptual diaryliodonium salts.

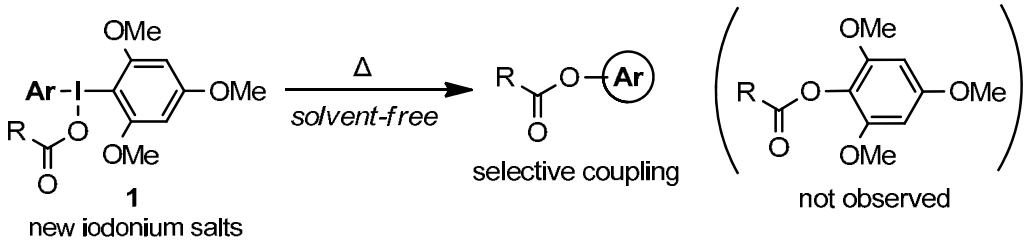
[Synthesis of New Iodonium Carboxylate Salts] We have recently developed a direct dehydrative approach toward various diaryliodonium salts proceeding in the fluoroalcohols with alkoxy benzenes as applicable substrates.[3] Using fluoroalcohols would enhance the electrophilicity of the iodine atom, and in a greener strategy, the new iodonium salts **1** having variable organo-carboxylate ligands can be readily formed without any external activator and prefunctionalization of the arene rings. Indeed, the organocarboxylates can be introduced as an anionic ligand by treating with corresponding carboxylic acids during the preparations (Scheme 1). Except for

non-crystalline salts carrying high molecular weight carboxylates, the pure compounds can be obtained by filtration of the precipitates, which are generally air- and moisture-stable solids capable of long-time storage.



Scheme 1. Direct dehydrative synthesis of diaryliodonium(III) organocarboxylate salts.

[Metal-Free Arylations of Carboxylic Acids] By utilizing the new diaryliodonium salts designed in our laboratory, the efficient metal-free arylation of carboxylic acids has occurred upon heating without base and solvent, giving aryl esters in extreme high yields within short reaction times (Scheme 2). In comparison, the reactions are more efficient, especially for low nucleophilic carboxylic acids, such as *p*-nitrobenzoic acid, that were unsatisfactory as substrates in known intermolecular coupling methods using ordinary diaryliodonium salts.[2] Remarkably, the arylations usually proceeded with perfect chemo-selectivities for non-alkoxy aryl groups. The transition metal-free conditions are compatible with substrates having a range of functional groups including free alcohols, and thus the method can yield complex highly hydroxylated aryl esters hard to obtain by other usual esterification protocols.



Scheme 2. Highly efficient metal-free arylation of carboxylic acids.

[References] 1) For reviews, see: (a) E. A. Merritt, B. Olofsson, *Angew. Chem., Int. Ed.* **2009**, *48*, 9052; (b) M. S. Yusubov, A.V. Maskaev, V. V. Zhdankin, *ARKIVOC* **2011**, *1*, 370; (c) P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123. 2) (a) T. B. Petersen, R. Khan, B. Olofsson, *Org. Lett.* **2011**, *13*, 3462; (b) N. Jalalian, T. B. Petersen, B. Olofsson, *Chem.-Eur. J.* **2012**, *18*, 14140. 3) (a) T. Dohi, M. Ito, K. Morimoto, Y. Minamitsuji, N. Takenaga, Y. Kita, *Chem. Commun.* **2007**, 4152; (b) T. Dohi, N. Yamaoka, Y. Kita, *Tetrahedron*, **2010**, *66*, 5775.

1P- 38

Chromatographic Separation of Stereoisomer Compounds

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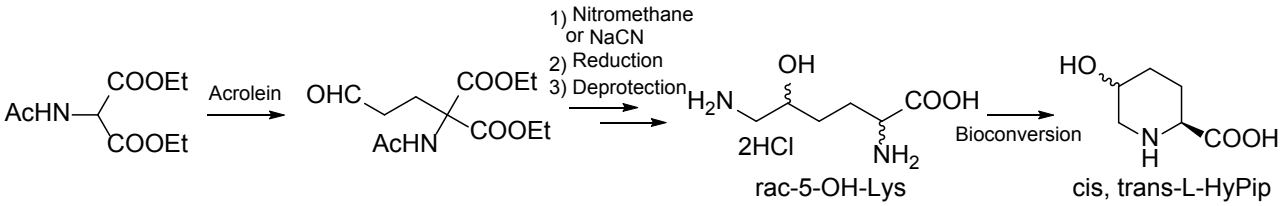
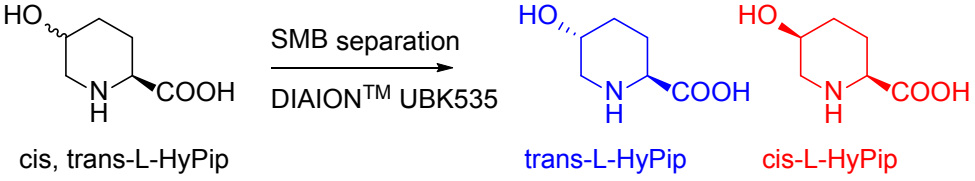
Ion exchange resins and synthetic adsorbents have been used for various pharmaceutical manufacturing processes; such as desalting, impurity removal by chromatographic process, condensation by selective adsorption from natural extract or fermentation broth, enzyme immobilization, in-situ solid phase adsorption during fermentation, and continuous flow reaction as a catalyst.

The demand of chromatographic process is getting increased due to complexity of current active pharmaceutical ingredients (API) structure. Even with recent improved catalyst, stereoisomer impurities are produced in organic chemical processes as by-products. As new tools for diastereomer separation, we studied applicability of ion exchange resins and synthetic adsorbents.

L-Hydroxypipecolic acid (Fig. 1) (L-HyPip) is one of promising hydroxy amino acids valuable as building blocks for organic synthesis of various pharmaceuticals. We prepared L-HyPip by combination of chemical synthesis and bioconversion process described in scheme 1. But the product was mixture of cis and trans-L-HyPip. We screened the suitable separation media and found calcium form of cation exchange resin, DIAION™ UBK535 has excellent performance for diastereomer separation. After optimization separation conditions, we performed simulation study for 4 bed simulated moving bed chromatography process (SMB) with pulse data (Fig 1). As a calculation result (Fig 2, Table 1), we found >98% d.e. of each cis and trans-L-HyPip would be obtained by SMB system.



Scheme 1



Scheme 2

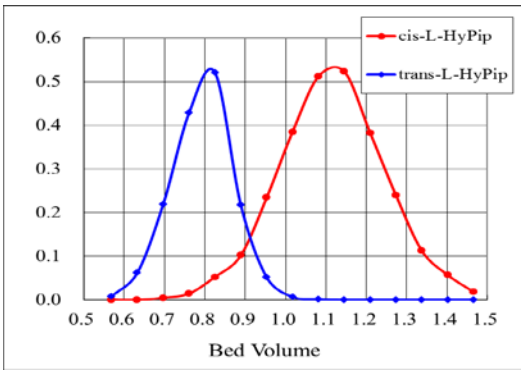


Fig 1 Pulse Data

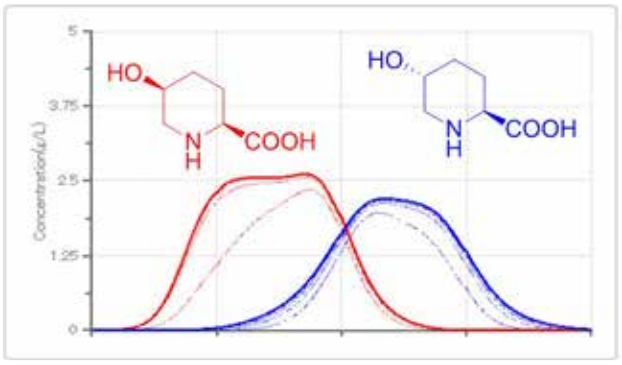


Fig 2 Simulation Result of SMB

	Feed	P-fra.	R-fra.	R-Rec.	M. B.
cis-L-HyP	59.70%	99.33%	0.93%	0.63%	100.00%
trans-L-HyPip	40.30%	0.67%	99.07%	98.92%	99.91%
Total	6.70g/L	1.25g/L	1.80g/L	40.24%	99.96%

Table 1 Simulation Result of SMB

We also studied separation of stereoisomer of various APIs. For amygdalin and its epimer neo-amygdalin (Fig 3) separated well with MCI GEL™ CHP20/C04 comparing C18 silica gel (Fig 4). More examples will be shown in the poster.

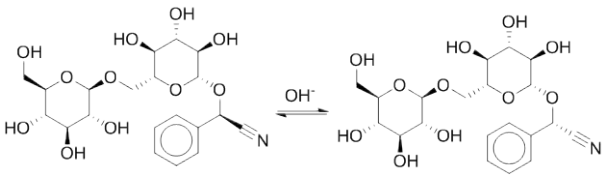


Fig 3 Amygdalin and neo-Amygdalin

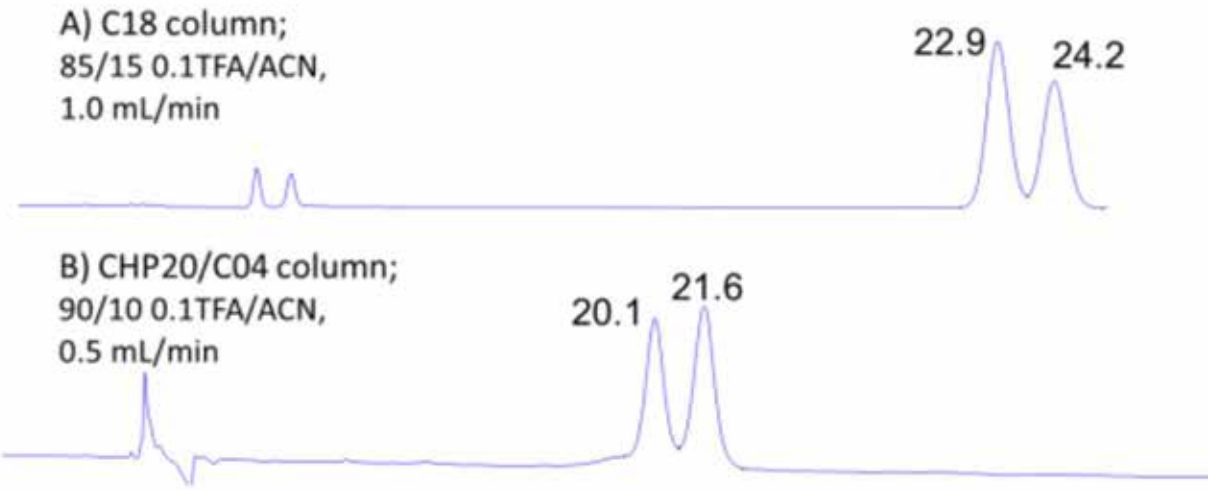


Fig 4 Chromatogram of amygdalin and neo-amygdalin

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Performance Assessment of Cyclopentyl Methyl Ether (CPME): Application to Grignard Reactions

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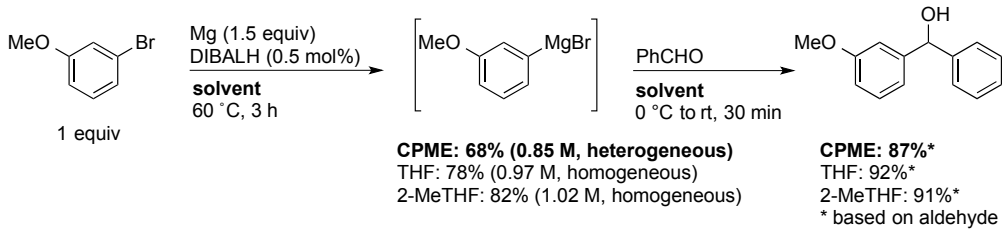
Grignard reaction is one of the most important organic reactions because a carbon-carbon bond is readily constructed by the simple operation. The most commonly used organic solvents for Grignard reactions are diethyl ether (Et_2O) and THF; in fact, a number of commercial Grignard reagents are available in either of these solvents. However, such an ordinary solvent system is not desired for use in the manufacturing process of chemical products in the plant scale, because of some disadvantages regarding safety, health, and environmental aspects. 2-Methyltetrahydrofran (2-MeTHF) emerged as an alternative Grignard reaction solvent but it is still expensive and their scopes are ambiguous. Recently, we reported that cyclopentyl methyl ether (CPME), developed by *ZEON CORPORATION*, could be a good alternate of the conventional solvent in a variety of radical reactions involving radical additions, radical deoxygenations, radical cyclizations, and radical-containing multi-step reactions.[1] These prospective results led us to examine more application of CPME to organic reactions. We herein report a first comprehensive study of Grignard reactions with CPME as a reaction solvent.

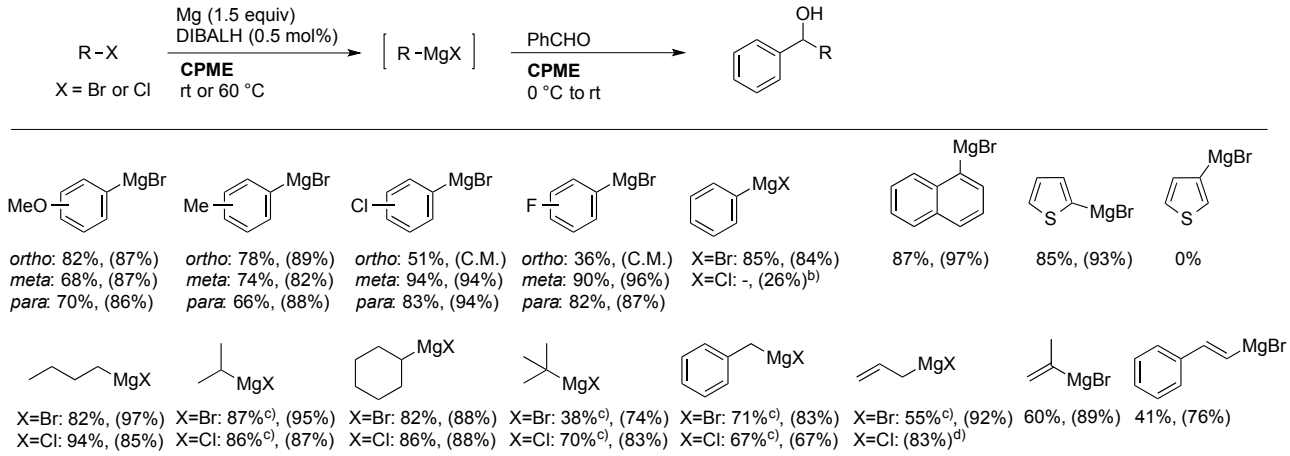
The research commenced with preparation of the Grignard reagent with 3-bromoanisole as a representative substrate (Scheme 1). While the initiation did not take place at room temperature even in the presence of an activator of magnesium, gentle heating of the reaction mixture at 60 °C during the addition of aryl bromide led to the formation of the Grignard reagent. Diisobutylaluminum hydride (DIBALH) turned out to be the most suitable activator of magnesium as compared to iodine, 1,2-dibromoethane, and other hydride reductants. The optimal concentration for the formation of the Grignard reagent was around 1 M while deep color emulsion settled down on the bottom of the flask. While the Grignard reagent in CPME was heterogeneous, subsequent addition reaction with benzaldehyde proceeded in 87% yield. The yield was in comparable with those obtained with other ethereal solvents.

Scheme 1. The Grignard reaction of 3-bromoanisole in different ethereal solvents



With optimal conditions in hand, we explored substrate scope to evaluate the performance of CPME in formation and the reaction of a variety of Grignard reagents. The results clearly showed that a number of Grignard reagents could be prepared in CPME in acceptable yields (Scheme 2). It is noteworthy that some of the Grignard reagents were obtained as homogeneous solutions while the relationship between the substrate structures and the solution states was ambiguous. We also succeeded in alkyl chloride Grignard reactions and obtained colorless heterogeneous Grignard reagent solutions. Some of the Grignard reagents were stored in a refrigerator for several months without drop of the concentration. CPME used in the Grignard reaction was efficiently recovered and reused repeatedly.

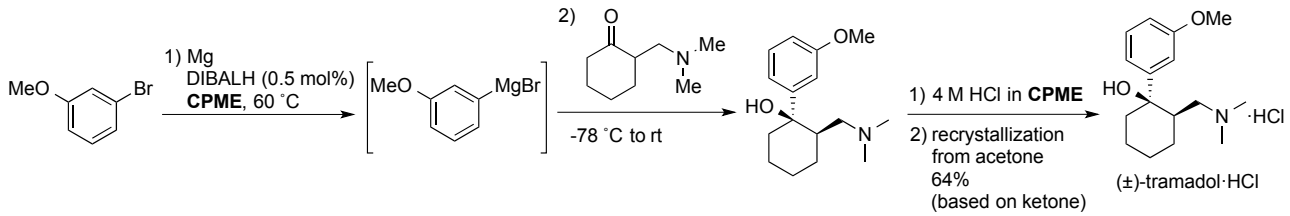
Scheme 2. Substrate scope of the Grignard reactions in CPME[a)]



a) The former yields refer to the formation stage of the Griganard reagents, while the yields in parentheses refer to the addition stage of the Griganrd reagents. C.M. = complex mixture. b) 5 mol% of DIBALH was used. Initiation was carried out at 90 °C for 20 h. c) Initiation was carried out at room temperature. d) Aryl bromide and benzaldehyde were added simultaneously to the activated magnesium solution.

Finally, we applied the Grignard reaction with the CPME solvent to the synthesis of tramadol hydrochloride, an analgesic agent now being used in over a hundred countries (Scheme 3). Diastereoselectivity was satisfactory and subsequent crystallization afforded tramadol hydrochloride in 64% isolated yield. This investigation provides one of the "green" processes of tramadol synthesis.

Scheme 3. Synthesis of tramadol hydrochloride



[1] Kobayashi, S.; Kuroda, H.; Ohtsuka, Y.; Kashihara, T.; Masuyama, A.; Watanabe, K. *Tetrahedron* **2013**, *69*, 2251-2259.

1P- 40

Efficient Synthesis of Chiral Diaminonitriles Using Chiral Bis(imidazoline)-Pd Catalysts

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Optically active α,β-diaminonitriles and their derivatives are chiral building blocks for the synthesis of natural products. They are also important structural motifs in biologically active compounds such as saframycin A, phthalascidin and aspeverin (Figure 1).

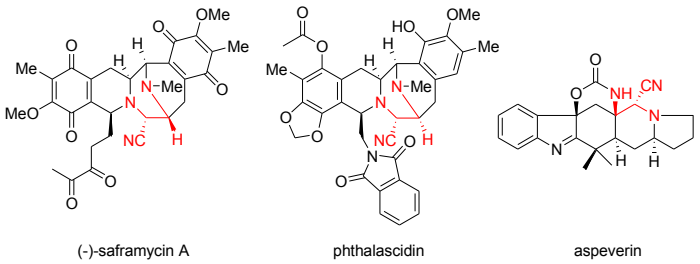
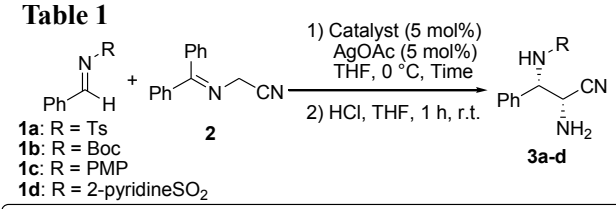


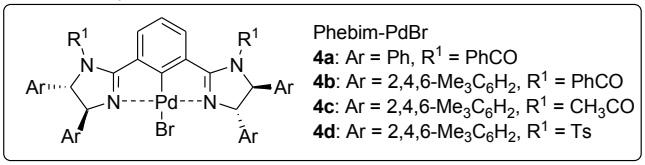
Figure 1. Biologically active α,β-diaminonitriles

Therefore, asymmetric synthesis of α,β-diaminonitriles is important. One of the efficient synthetic methods for the preparation of α,β-diaminonitriles is catalytic enantioselective nucleophilic addition of α-aminoacetonitriles with imines.[1] However, the generation of α-cyano carbanion is difficult due to the low acidity of α-proton in α-aminoacetonitriles. In general, strong bases are used for the generation of α-cyanocarbanion, epimerization and side reactions occurred under harsh reaction conditions. Therefore, the development of the generation of α-cyano carbanion without using strong bases is necessary for the catalytic enantioselective synthesis of α,β-diaminonitriles. *N*-Alkylidene acetonitriles are useful nucleophiles because of the easy generation of α-cyano carbanion under mild reaction conditions. Recently, we developed an efficient and specific activating method for nitrile compounds by using palladium pincer complexes with 1,3-bis(imidazolin-2-yl) benzene (Phebim) ligand.[2]

Herein, we developed highly enantio- and diastereoselective reaction of *N*-alkylidene aminoacetonitriles with imines using Phebim-PdBr catalysts. We first examined the reaction of α-aminoacetonitriles **2** (1.2 equiv.) with various imines **1a-d** (1.0 equiv.) using 5 mol% Phebim-PdBr **4a-d** and AgOAc at 0 °C (Table 1). The reaction of **2** with **1a** using **4a**-AgOAc gave the product **3a** in good yield with moderate

Table 1





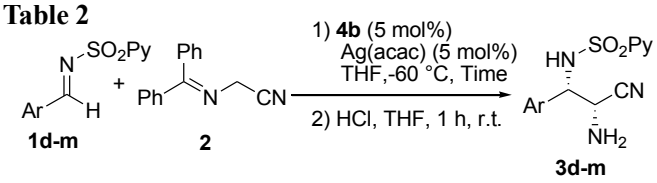
Entry	1	Cat.	Time [h]	Yield [%]	Dr[a] (*syn*:*anti*)	Ee (*syn*) [%]
1	**1a**	**4a**	12	88	75:25	9
2	**1a**	**4b**	72	82	78:22	94
3	**1a**	**4c**	72	81	73:27	94
4	**1a**	**4d**	72	65	66:34	4
5	**1b**	**4b**	72	69	63:37	75
6	**1c**	**4b**	72	-	-	-
7	**1d**	**4b**	72	86	86:14	99
8[b]	**1d**	**4b**	72	86	92: 8	99
9[b,c]	**1d**	**4b**	24	89	95: 5	99

[a] Diastereomer ratio was determined by ^{1}H NMR analysis.
[b] The reaction was carried out using **2** (2.0 equiv.) and Ag(acac) instead of AgOAc at -60 °C. [c] TMSOH (20 mol%) was added.

syn-selectivity but with low enantioselectivity (entry 1). To improve enantio- and diastereoselectivity, we optimized structure of catalysts **4**. Catalyst **4b** afforded the product with good diastereoselectivity and high enantioselectivity (entry 2). We next examined activating group of imines (entries 4-7). As a result, 2-pyridinesulfonyl imines **1d** improved reactivity and stereoselectivity (entry 7). We also optimized other reaction conditions, the reaction of **1d** with **2** using **4b**-Ag(acac) at -60 °C gave product **3d** in good yield with excellent stereoselectivity (entry 8). The addition of 20 mol% of trimethylsilylalcohol (TMSOH) slightly improved the yield and diastereoselectivity of the product (entry 9).

With the optimized reaction condition, the reaction of various imines **1d-m** with **2** was examined (Table 2). Imines **1d-g** carrying either electron-donating or -withdrawing substituents gave products **3d-g** in good yield with high enantioselectivity (entries 1-4). The reaction of naphthylimines **1h,i** also gave products **3h,i** with high enantioselectivity (entries 5 and 6). Imines **1j-m** having furyl or thienyl groups as heteroaryl groups, also afforded products **3j-m** in high yield with good diastereo- and enantioselectivity, although it is difficult to coordinate the metal catalyst with **2** selectively in the presence of heteroatoms (entries 7-10).

Table 2



Entry	1	Ar	3	Time [h]	Yield [%]	Dr (*syn*: *anti*)	Ee (*syn*) [%]
1[a]	**1d**	Ph	**3d**	24	89	95: 5	99
2[b]	**1e**	4-$MeOC_6H_4$	**3e**	72	73	91: 9	99
3[a]	**1f**	4-ClC_6H_4	**3f**	72	83	77:23	99
4	**1g**	3-ClC_6H_4	**3g**	72	86	72:28	99
5[a]	**1h**	1-naphthyl	**3h**	72	84	99: 1	99
6[b]	**1i**	2-naphthyl	**3i**	72	82	81:19	99
7[b]	**1j**	2-furyl	**3j**	24	73	89:11	99
8[b]	**1k**	3-furyl	**3k**	60	71	85:15	99
9	**1l**	2-thienyl	**3l**	96	86	92: 8	99
10[a]	**1m**	3-thienyl	**3m**	54	95	97: 3	99

[a] TMSOH (20 mol%) was added. [b] At -30 °C.

Furthermore α,α-diaminonitriles and their derivatives are also important compounds as chiral building blocks for biologically active compounds such as devacade and BRL36650 (Figure 3). The reaction of di-*tert*-butyl azodicarboxylate with **2** using **4b**-Ag(acac) gave α,α-diaminonitriles in good yield with good enantioselectivity (Scheme 1).[3]

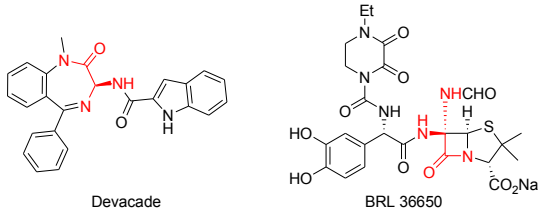
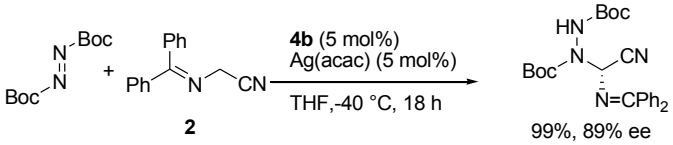


Figure 3. Biologically active α,α-diaminonitrile derivatives



Scheme 1. Enantioselective amination of **2**

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1P-41

Conformational Studies of Symmetric Diesters

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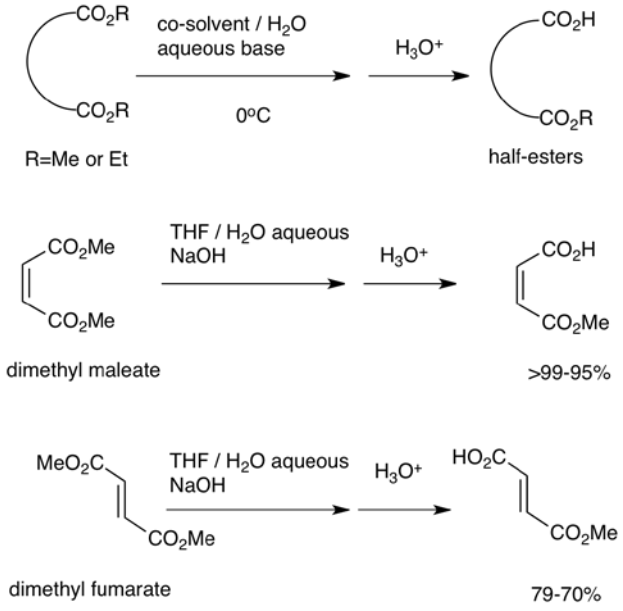
Ester groups are among the most important functional groups in organic synthesis, and symmetric or non-symmetric diesters have been utilized as starting materials in a variety of well-known reactions. We have also reported practical selective monohydrolysis reactions of symmetric diesters, producing half-esters from symmetric diesters under environmentally benign conditions in high yields.[1] However, few systematic structural studies are reported for symmetric diesters.

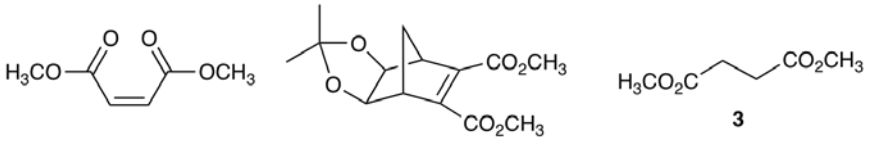
In general, reactions of acyclic molecules tend to show low stereoselectivity due to their conformational flexibility. However, when two carbonyl groups are located in close proximity, electrostatic interaction between the two carbonyl groups becomes possible. Such interactions are sometimes proposed in compounds with two carbonyl groups, and thus play an important role in controlling the selectivity of organic reactions. We previously observed that dimethyl maleate showed higher selectivity than dimethyl fumarate in the above selective monohydrolysis of symmetric diesters (Scheme 1).[1] Since dimethyl fumarate and dimethyl maleate are the stereoisomers of each other, we assumed that the geometry of the starting symmetric diesters is an important factor in distinguishing the two identical ester groups at the initial stage of the reaction.



It is also reported that dialkyl maleates are less reactive than dialkyl fumarates toward some reactions such as Diels-Alder reactions[2] and AIBN-initiated oxidation reactions.[3] Some

differences in the rate of polymerization for dialkyl maleates and dialkyl fumarates are also reported.[4]

Here we performed theoretical studies in order to examine conformation of symmetric diesters, dimethyl maleate, **1**, dimethyl 5,6-isopropylidenedioxybicyclo [2.2.1]hepta-2-ene-2,3-dicarboxylate, **2**, and dimethyl succinate, **3**, at the density functional theory (DFT) and Møller-Plesset pertubation theory (MP2) levels.[5]



1 **2** **3**

In dimethyl maleate, **1**, and dimethyl 5,6-isopropylidenedioxybicyclo[2.2.1] hepta-2-ene-2,3-dicarboxylate, **2**, it was found that the structures wherein one of the carbonyl groups is oriented near-perpendicular with respect to the C=C bond and the other carbonyl group is oriented near-parallel with respect to the C=C bond have the lowest energies both at the B3LYP/6-31G(d)//B3LYP/6-31G(d) and B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p) levels. A bonding interaction between the oxygen of the carbonyl group near-parallel to the C=C bond and the carbon of the other carbonyl group was also found in these structures at both the levels. This tendency is in good agreement with the X-ray crystal structures of **2**. On the other hand, a linear symmetric diester, dimethyl succinate, **3**, showed different results depending on the theory levels, but in the *gauche* conformation, a bonding interaction between the carbonyl oxygens and the carbonyl carbons was also found. These results suggest the existence of the n->π* interaction between the two carbonyl groups, which has recently been proposed for elucidation of the folding of proteins or peptides, or isomerism in peptoids.[6] It is likely that such non-covalent interaction can also exist in various organic molecules with more than one carbonyl group and may contribute to the enhancement of selectivities or reactivities in various organic reactions.

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1P-42

Development of an Optimized Synthetic and Purification Process of S-2367 (Velneperit), a Novel Neuropeptide Y (NPY) Y5 Receptor Antagonist

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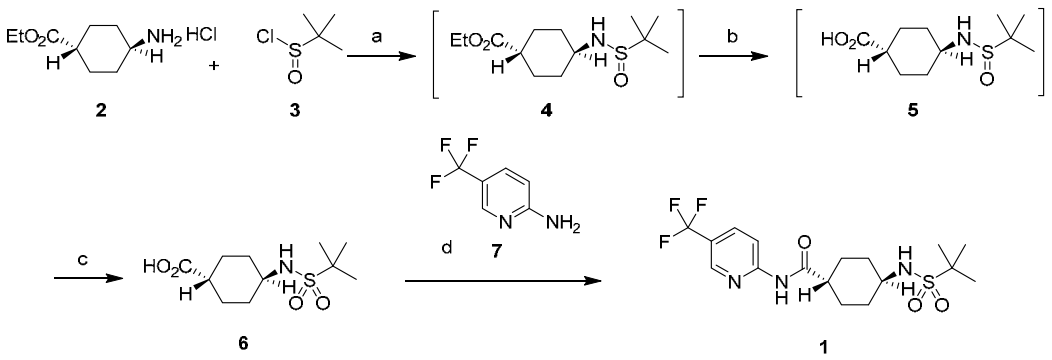
In this poster we would like to discuss process development of a novel NPY Y5 antagonist S-2367 (Velneperit) (**1**), which suggests its potential as a promising anti-obesity drug.

ⅰ) Synthetic route

We developed a simple synthetic route using *trans*-1-ethoxycarbonyl-4-aminocyclohexane hydrochloride salt (**2**) as a starting material. The process was efficient from the viewpoint of the number of reactions, yield, throughput and EHS (environment, health and safety) (Scheme 1).

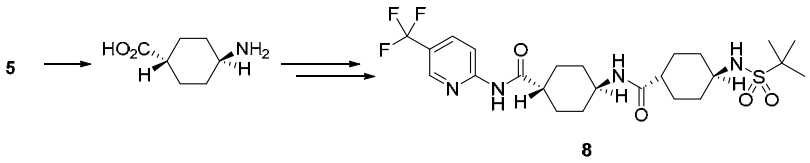


Reagents and conditions: (a) Et_3N, toluene, H_2O (b) NaOH (c) H_2O_2, $Na_2WO_4 \cdot 2H_2O$ cat., H_2O, 95% (3 steps) (d) $SOCl_2$, DMF cat., toluene→**7**, pyridine, recrystallization using acetone, water, 95% (2 steps)

Sheme1. An optimized synthetic route of S-2367

ⅱ) Control of impurity **5** using pH acceleration effect on Na_2WO_4/H_2O_2 oxidation

The key step of the process was oxidation of **5** using $H_2O_2/Na_2WO_4 \cdot 2H_2O$ cat. because residual **5** in the intermediate **6** was quantitatively converted to the impurity **8** with low removal rate in the following steps (Scheme 2). As a result of investigation, we found the interesting new knowledge that the oxidation reaction in the weakly basic condition of pH 9.0-9.5 was faster than that in nearly neutral condition. It was useful to control residual **5** in **6**.



Sheme2. Fate of impurity **5** in intermediate **6**

iii) Optimization and trouble shooting of recrystallization of **1** using acetone/water

To reduce the bottleneck volume, the solvent dissolving crude **1** during the recrystallization was changed from 100% acetone to 95v/v% acetone/water. However, an unexpected quality deviation occurred in the pilot manufacturing; **6** content in **1** was over the upper limit. The cause was presumed to be acidic hydrolysis of **1** during recrystallization step. After finding it, we developed two reliable purification processes. The first was slurry washing of crude **1** through solvent-mediated polymorphic transformation. Enclosed acid could be removed efficiently by the process and it prevented acidic hydrolysis. The second was salt formation of **6** and rational building of the recrystallization procedure based on solubility. The removal rate of **6** varied from 36% to 73% in the flask experiments probably due to possible weak interaction of acid **6** with the basic pyridyl group of **1**. The salt formation could prevent this (Figure 1). The precipitation point of **1** (form I) was set at 80v/v% acetone/water in which the solubility of sodium salt of **6** was sufficiently large (Figure 2). By the tricks the removal rate of **6** was dramatically improved.

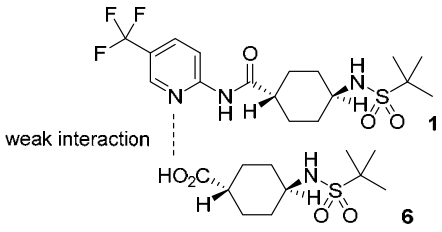


Figure 1. Possible interaction of **1** and **6**

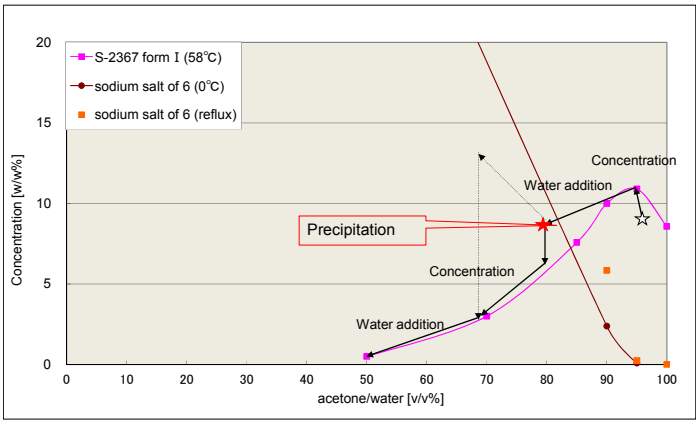


Figure 2. Concentration transition of the recrystallization

Reference.

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1P- 43

Convenient and regioselective synthesis of biaryl compounds by heterogeneously catalyzed aerobic oxidative coupling

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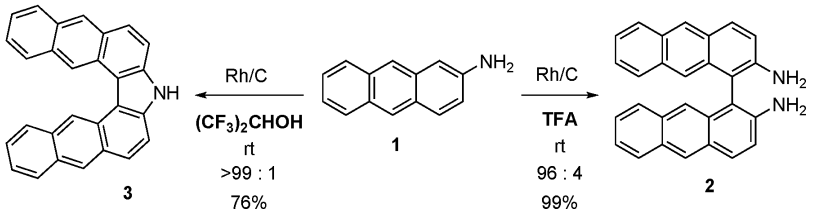
The direct carbon–carbon bond formation between two aromatic C–H bonds using C–H activation methodology has gained significant attention. Thus, the oxidative coupling of arenes is simple and desirable method for the preparation of the biaryl compounds from the viewpoint of improved atom economy. Although the oxidative coupling of naphthols using homogeneous and heterogeneous metal catalysts has been well studied, the oxidative coupling of aryl amines to provide 1,1′-biaryl-2,2′-diamines, such as BINAMs, remains largely unexplored. Because aryl amines are easily oxidized, generating many side products, this type of oxidative reaction is usually uncontrollable. The use of heterogeneous catalysts gives several advantages including the ease of catalyst recovery and recycling and also the reduced metal contamination in the products. However, to our knowledge, there are no examples of oxidative coupling of aryl amines using heterogeneous metal catalysts.

Recently, we reported the heterogeneous rhodium catalyzed oxidative coupling of aryl amines under aerobic conditions to provide biaryl diamines in high yields (Scheme 1).[1] When trifluoroacetic acid (TFA) was used as a solvent for aerobic oxidative coupling of 2-aminoanthracene (**1**), the homo-coupling reaction proceeded successfully at room temperature in the presence of 2 mol% Rh/C to afford the dimer **2** in quantitative yield. We also found that the solvent had a strong influence on the yield of the dimer as well as the selectivity. When hexafluoroisopropanol (HFIP) was used as a solvent, the homo-coupling reaction followed by the cyclization proceeded to afford the carbazole **3** in excellent yield. Here, the scopes and limitations as well as the aerobic intramolecular oxidative coupling will be presented.

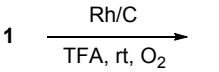


Scheme 1 Heterogeneous Rh/C catalyzed aerobic oxidative coupling of 1

To investigate the catalytic activity, lowering the catalyst loading of Rh/C to 0.10 mol% resulted in 79% yield of the dimer **2** under oxygen atmosphere (Table 1). At even lower loading of 0.025 mol%, the dimer **2** was obtained in 80% yield, and the heterogeneous Rh/C catalyst showed the excellent catalytic activity with

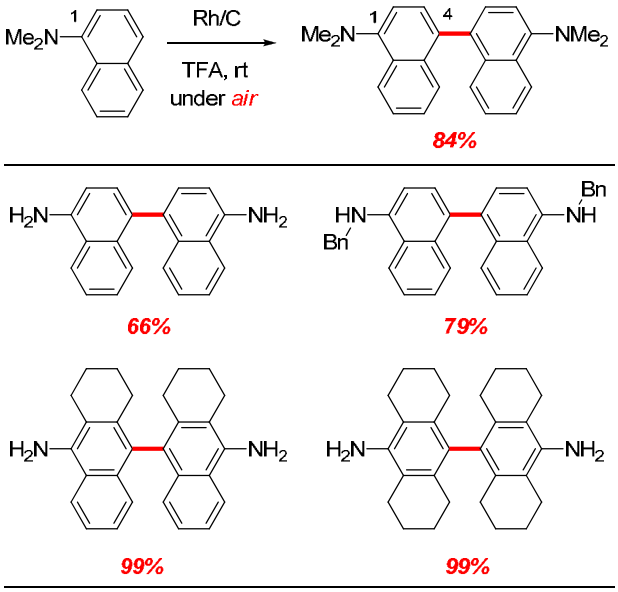
a turnover number (TON) of 3200. The recyclability of Rh/C was also examined in the aerobic oxidative coupling of 2-aminoanthracene (**1**). Rh/C was able to be recycled 7 times affording 86% yields of the product **2** in the mean without any loss of reactivity.

Table 1 Lowering of the Rh/C loading



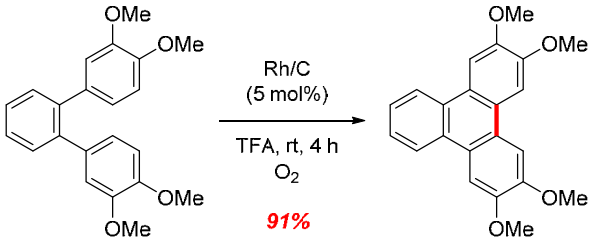
entry	Rh/C (mol%)	Yield	TON
1	2.0	99%	49
2	0.10	79%	790
3	0.025	80%	3200

We examined the scopes and limitations for Rh/C catalyzed oxidative coupling reactions of aryl amines (Scheme 2). Interestingly, *N,N*-dimethyl-1-aminonaphthalene underwent C–C bond formation at 4-position, generating the dimer in 84% yield. The reactions using 1-aminonaphthalene and the *N*-benzyl substituted derivative also proceeded to give the dimers in 66% and 79%, respectively. The octahydroanthracene derivative, which is not a fused aromatic compound, also dimerized to afford the corresponding product in quantitative yield. Thus, the anthracene derivatives as well as naphthalene and aniline derivatives underwent oxidative coupling to furnish the corresponding dimers in good yields.



Scheme 2 The scopes of catalytic oxidative coupling

The versatility of the Rh/C−acid system for the oxidative coupling is further demonstrated by the aerobic intramolecular oxidative coupling of *o*-terphenyl **4** (Scheme 3). Thus, a reaction of **4** in TFA was conducted in the presence of 5 mol% Rh/C under oxygen atmosphere to afford triphenylene **5** in excellent yield. It is noteworthy that the Rh/C−acid system was effective for intramolecular as well as intermolecular aryl-aryl bond formations.



Scheme 3 The intramolecular oxidative coupling

In conclusion, we developed the heterogeneous rhodium-catalyzed oxidative coupling reaction to prepare biaryl compounds. We demonstrate that the acidic solvent has a strong influence on the yield and selectivity of the products. The current synthetic strategies for aryl–aryl bond formation provide greener alternatives to previously reported methods, and involve heterogeneous catalysts, fewer steps, and milder conditions.

Reference

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1P－44

Application of Asymmetric Transfer Hydrogenation and H_2-Hydrogenation Catalyzed by Oxo-tethered Ruthenium(II) Complex

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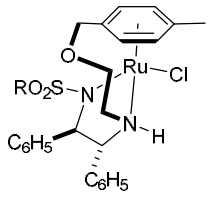
Asymmetric transfer hydrogenation and H_2-hydrogenation of ketones is one of the most sophisticated chiral multiplication methods. We previously reported oxo-tethered Ru(II) complexs **(*R*,*R*)-1** and **(*R*,*R*)-2**, which showed excellent catalytic performance in reduction of acetophenone-type compounds.
Currently, **(*R*,*R*)-1** and **(*R*,*R*)-2 (DENEB series)** is manufactured at multi-KG scale in Takasago and applied to synthesis of pharmaceutical intermediates.

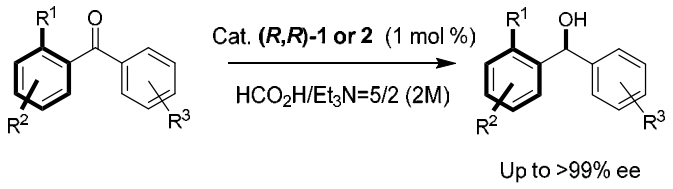
In this study, we expanded the substrate scope to various types of functionalized ketonic compounds. With fine tuning of reaction conditions (hydrogen sources, solvent, temperature …), **(*R*,*R*)-1** or **(*R*,*R*)-2** exhibited high catalytic performances and gave the optically pure alcohol with high yield.



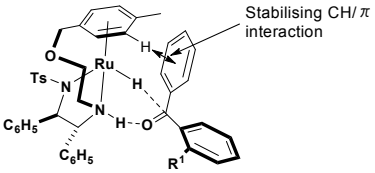
SO_2R = Ts **(*R*,*R*)-1 (Ts-DENEB)**

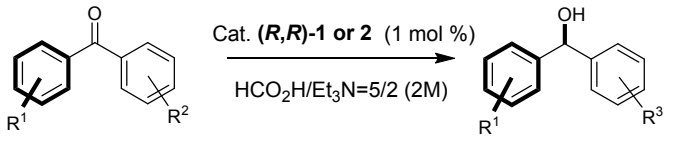
Ms **(*R*,*R*)-2 (Ms-DENEB)**

1. Asymmetric Transfer Hydrogenation of Aryl-Aryl-ketones

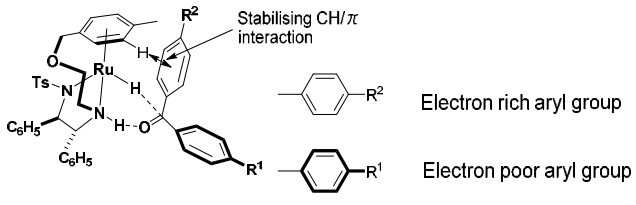


Up to >99% ee



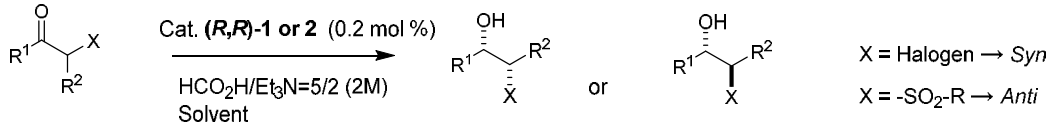


Up to 93% ee



Asymmetric transfer hydrogenation of Aryl-Aryl ketones smoothly proceeded and afforded corresponding alcohol with high enantioselectivity. In this reaction, **(*R*,*R*)-1** or **(*R*,*R*)-2** distinguished two benzene rings by the differences in steric and/or electronic features.

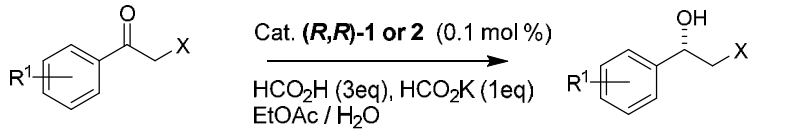
2. Asymmetric Transfer Hydrogenation of α-Functionalized Ketones *via* Dynamic Kinetic Resolution System



Up to >99% de, >99% ee

Asymmetric transfer hydrogenation of α-functionalized ketones such as α-haloketones or α-sulfonated ketones successfully controlled the two stereo-centers via dynamic kinetic resolution with perfect diastereoselectivity and enantioselectivity.

3. Asymmetric Transfer Hydrogenation of α-Haloketones



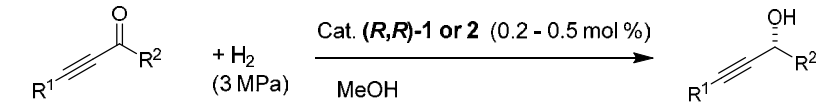
(X = Cl, Br)

High chemo-selectivity

Up to 96% ee

Asymmetric transfer hydrogenation of α-chloro or α-bromo-ketones worked well when we used HCO_2H/HCO_2K system as reducing agent. The obtained halohydrins can be derived to various synthetically useful compounds.

4. Asymmetric H_2-Hydrogenation of Alkynyl Ketones



(R^1= TMS, TBS, Ph)

Up to 99% ee

Asymmetric hydrogenation of alkynyl ketones by hydrogen gas proceeded with mild condition and provided α-Alkynyl alcohol with high enantioselectivity. In addition to TBS or Ph, TMS group, which is much more sensitive to acid or base condition could tolerate the hydrogenation.

Reference)

T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki, T. Ikariya

J. Am. Chem. Soc., **2011**, *133*, 14960.

1P- 45

Process Intensification for the Continuous Flow Hydrogenation of Ethyl Nicotinate

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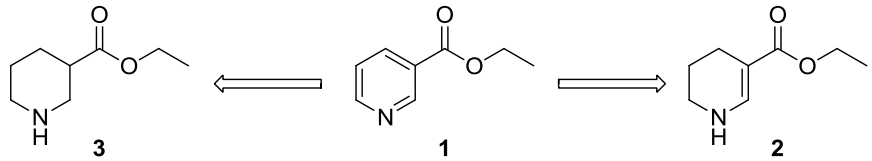
A particular challenge that has not yet been fully met is how to move rapidly and safely, to scale up reactions in research laboratories, from mgs to kgs. It is precisely under these circumstances where new tools can significantly assist the process. Indeed, by definition, process intensification is the "strategy for making dramatic reductions in the size of a chemical plant so as to reach a given production objective". [1] Accordingly, this approach can involve shrinking the size of individual pieces of equipment or cutting the number of unit operations or devices required. In addition, interest in greater sustainability through more selective processes, often under heterogeneous conditions, has become heightened. Nevertheless, working with and scaling up of hydrogen gas reactions brings with it well recognized issues (*i.e.* safety assessment, mixing and H_2 solubility) despite the importance of this reductive process in fine chemical manufacture. One such process, involving precious metal catalyzed hydrogenation of substituted pyridines, is of interest due to the importance of the functionalized piperidine products as intermediates in the preparation of many biologically active molecules. Here we report a process intensification study for the selective, partial and full hydrogenation of ethyl nicotinate (Scheme 1) using a trickle bed reactor for meso-flow transformations.



Scheme 1. Products obtained from partial (**2**) and full (**3**) hydrogenation of ethyl nicotinate (**1**)

Partial hydrogenation process

Partial reduction of ethyl nicotinate was conducted using a trickle bed reactor, HEL FlowCAT (Figure 1). Use of the usual wet Pd/C with glass beads (which are often used to prevent catalyst packing) failed due to blockage by catalyst packing. So some samples of granulated Pd catalyst[2] were evaluated in the reaction for comparison, and it was found that 5% Pd/Al_2O_3 with a particle size of 0.1-0.25 mm was the most active catalyst

Figure 1. Picture of HEL FlowCAT reactor (left: column reactor; right: whole system).

for the reaction, among the 4 catalysts used having different supports and particle sizes. After screening different parameters such as concentration, flow rate, temperature and pressure, using **RC2** (Reactor Column 2,Figure 2), the concentration could be increased to 0.8 M and the flow rate adjusted to 7.0 mL min^{-1} to obtain a throughput of 1219 g/d with complete consumption of the starting material (Scheme 2).

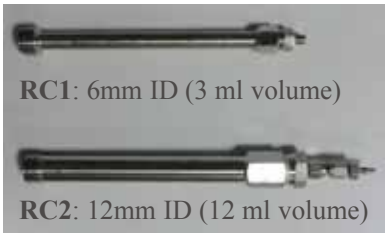
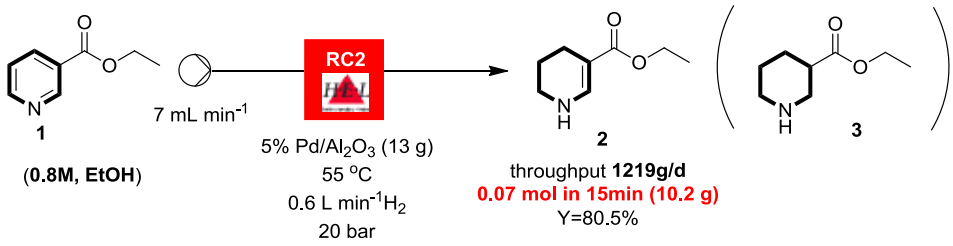


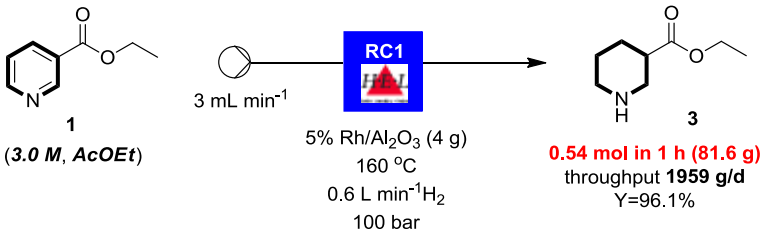
Figure 2. Used column reactor



Scheme 2

Full hydrogenation process

In order to achieve the full hydrogenation of **1** to **3** we followed a similar optimization approach. Under the optimized conditions (catalyst, solvent, temperature, pressure, concentration and flow rate), we were able to continuously produce 81.6 g of material using **RC1** in just 1h, which equates to 1959 g/d throughput of material (Scheme 3). The continuous flow approach represents a huge advantage as it enables a sequence of troublesome operations to be eliminated or greatly simplified (*i.e.* filtration of catalyst, washing procedure).



Scheme 3

In conclusion, we report a study for a specific process intensification program for hydrogenation reactions that can be carried out in a research laboratory environment.[3)] Use of flow technologies allowed operation at high pressure and temperature, which enabled the use of high substrate concentrations and high flow rates. This provided very high throughput from a bench top reactor, with potential throughput for multi-kilo scale purposes using extended time manifolds.

<References>

1) Stankiewicz, A.; Moulijn, J. A. *Ind. Eng. Chem. Res.* **2002**, *41*, 1920–1924. 2) The catalysts were kindly provided by Johnson & Matthey. 3) Ouchi, T.; Battilocchio, C.; Hawkins, J. M.; Ley, S. V. *Org. Process Res. Dev.* **2014**, *18*, 1560-1566.

1P- 46

Total Synthesis of Prostaglandin E_1 Methyl Ester by Three One-pot Operations

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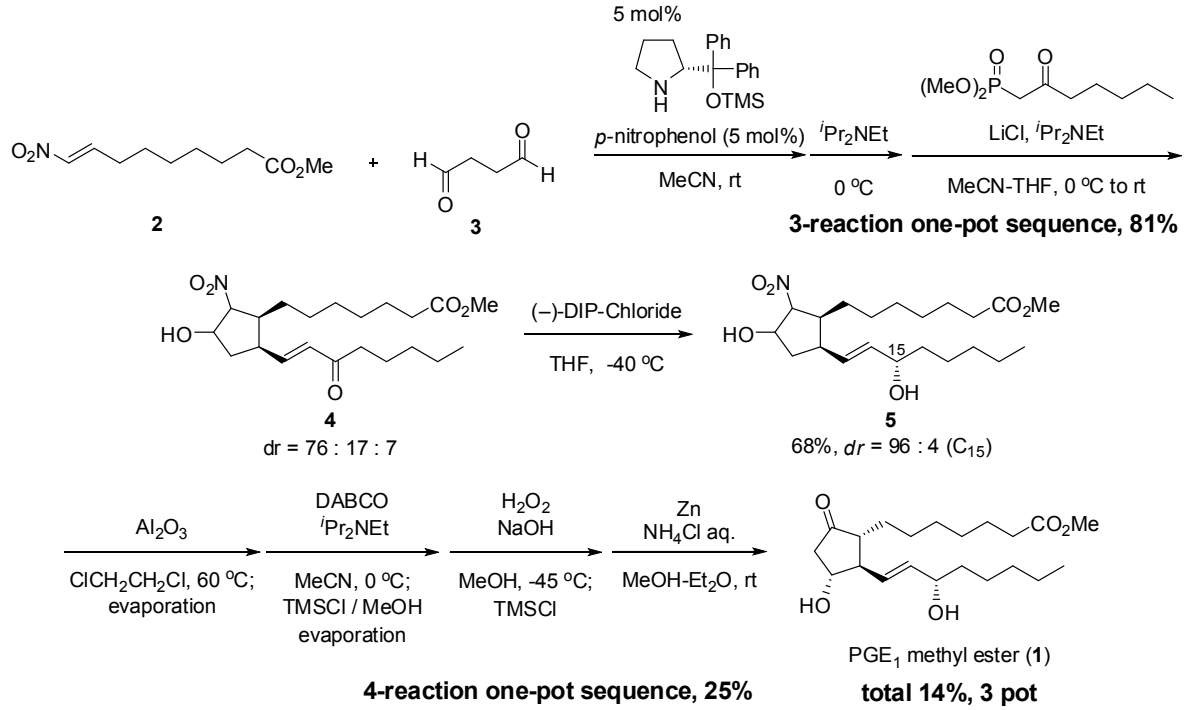
Prostaglandins (PG) regulate a broad range of physiological processes and some of their derivatives are used as effective drugs. As previous syntheses have required many steps, it is a synthetic challenge to prepare PGs and its derivatives in short steps and by a sustainable manner.

Asymmetric Michael reaction of nitroalkene **2** with succinaldehyde (**3**) successfully proceeded by using diphenylprolinol silyl ether.[1] Successive intramolecular Henry reaction and Horner–Wadsworth–Emmons reaction were carried out in one-pot to furnish enone **4**, containing all the necessary carbon atoms, in good yield with good diastereoselectivity and excellent enantioselectivity. The diastereoselective reduction of **4** afforded allyl alcohol **5** in moderate yield with high diastereoselectivity. The transformation from **5** to **1** including a newly developed oxidative Nef reaction[2] can be performed in a single vessel in 25% yield over four steps. This synthesis requires only three one-pot operations. The total yield of PGE_1 methyl ester (**1**) from nitroalkene **2** is 14%.[3] We will also describe our new findings about oxidative Nef reaction.



References

[1] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

[2] S. Umemiya, K. Nishino, I. Sato, Y. Hayashi, *Chem. Eur. J.* **2014**, *20*, 15753.

[3] Y. Hayashi, S. Umemiya, *Angew. Chem. Int. Ed.* **2013**, *52*, 3450.

1P- 47

STUDIES OF THE PEPTIDE CRYSTAL FORM AND ITS PROCESS DEVELOPMENT FOR COMMERCIAL PRODUCTION

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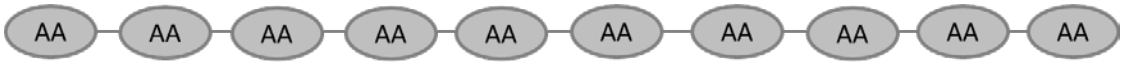
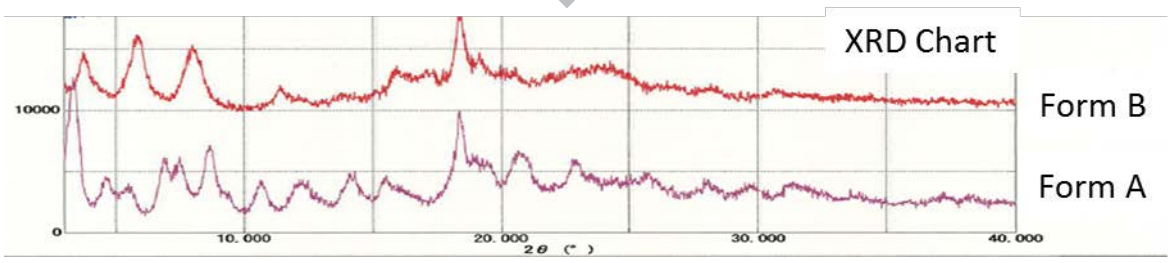
The physical stability of active pharmaceutical ingredient (API) is one of the key factors in developing pharmaceutical product. Generally speaking, crystal is physically more stable than amorphousness. However, it is difficult to crystallize peptides, especially small-sized peptides which consist of 9-11 amino acid residues. It has been generally conceived that for a protein keeping stable 3D structures, it has to possess at least 30～50 amino acid residues [1]. Therefore, we have to handle small-seized peptides as amorphousness in many cases. Unfortunately, amorphousness often shows physical instability or difficult handling and it causes the quality issues of API or manufacturing scale-up issues.

As a result of various examinations, we succeeded in crystallization of our target-peptide and found two polymorphisms (Form A and B) [2]. We also found that Form A was physically more stable than amorphousness, and we selected Form A as polymorphism of API. Next we tried to manufacture Form A and we developed the manufacturing strategy to obtain it constantly, including transformation from Form B to Form A. Finally, more than 100g of peptide in Form A was manufactured, using our controlled transformation strategies, under GMP (Good Manufacturing Practice) condition.

In the poster session, we will show you more detailed information about the selection methods of Polymorph and key factors to affect the transformation rate.

AA: Amino acid　small-sized peptide　could be crystallized !





[1] Honda, S., Akiba, T., Kato, S. Y., Sawada, Y., Sekijima, M., Ishimura, M., Ooishi, A., Watanabe, H., Odahara, T., Harata, K. (2008) *J. Am. Chem. Soc.*, ***130*** (46), 15327–15331

[2] Kunitani, R.; Hasegawa, A. Patent pending

1P-48

Total solution for the HPLC method development process by ChromSword software

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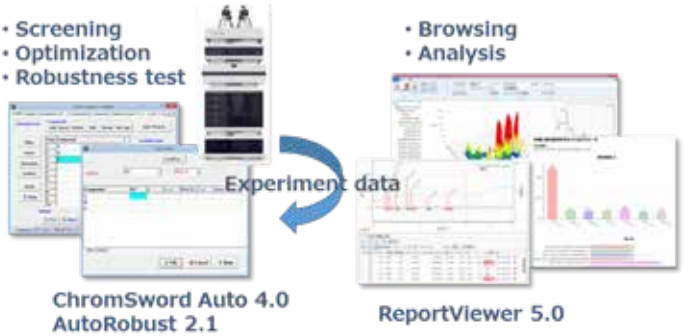
The method development by using HPLC and LC/MS is one of important steps for various research and development processes in pharmaceutical, chemical, food, agricultural and environmental fields. Especially for the process chemistry in pharmaceutical industries, the HPLC method development is a critical step to increase productivity and to improve chemical quality under regulations as QC and QA requirement. In this process, it is a tremendous need to rapidly develop the chromatographic condition by HPLC toward the next drug manufacturing process to detect and analysis chemical impurities in each step. Recently, since the preparation and synthesis of active pharmaceutical ingredients (API) are shifting to the Asian countries, more strict regulations should be applied to API. Therefore, from the point of pharmaceutical QC and QA, the importance of the exact and repaid method development could be increased in the pharmaceutical industries.

ChromSword Auto have been developed as an innovative software product to support the method development in HPLC/LCMS chromatography for more than twenty years. AutoRobust and ReportViewer could also be used to the support for evaluation of robustness of HPLC method and browsing HPLC experiments respectively. Some pharmaceutical scientists had published the efficient examples for the method development using ChromSword Auto in comparison with conventional manual methods.[1), 2)] In this presentation, we would like to introduce of the renewed chromatographic data browsing tool, ReportViewer 5.0 and reaffirm ChormSword Auto and AutoRobust as a set of total solution software for automated method development.

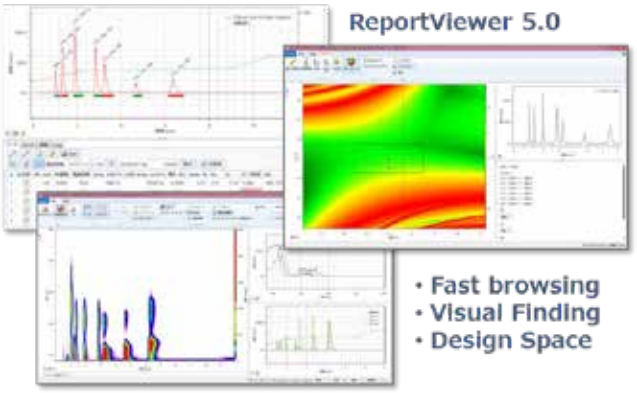


[Method]

Seven compounds, which included API and three pairs of isomers in a reaction mixture, were used as test samples for the method development. HPLC instruments, column and solvent condition were Agilent 1200 series HPLC with an 8 ports switching valve and a multi-wavelength detector (MWD), Chromolith SpeedROD RP18e and acetonitrile/water respectively. Using ChromSword Auto 4.0, HPLC conditions were fully optimized after screening different factors, such as columns, solvents, buffers and temperatures. After finishing the method development process by ChromSword Auto, the robustness test experiments were carried by AutoRobust 2.1. All data were seamlessly browsed and reanalyzed on ReportViewer 5.0.

[Results]

The HPLC various conditions were easily and quickly screened by ChromSword Auto to determine the best columns, solvents and buffer combinations. Using the result parameters of screening test, repaid and fine optimization was carried out by ChromSword Auto to find out the best HPLC condition for fine separation of each peak. The result of fine optimization could be tested for its robustness by AutoRobust in accordance with Quality by Design (QbD) principles. ReportViewer could help us to understand the result of all experiments by fast browsing and visual data finding, and from the experiment results, the expected chromatogram could be easily simulated for building up the next experiment conditions by the new design space of ReportViewer 5.0.



Based on these studies, for the purities separation in process chemistry, a set of ChromSword software could be powerful total solution tools to facilitate the method development process. ChromSword Auto is able to develop new methods or to brush up existing HPLC conditions fully automatically to reduce the method development time. AutoRobust and ReportViewer can also efficiently assist the robustness test and data analysis seamlessly with ChromSword Auto. All procedure and steps in the method development should be constructed and reported for the former review regarding QbD requirements. In this presentation, more detailed information and results will be discussed.

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1) Elizabeth F. Hewitt et al., Journal of Chromatography A, 1107 (2006) 79-87
2) Kang Ping Xiao et al., Journal of Chromatography A, 1163 (2007) 145-156

1P- 49

Study on Preparation of 5-Trifluoromethylated Pyrimidine Derivatives

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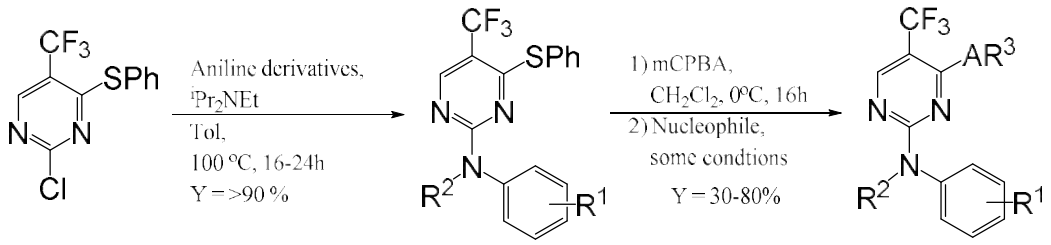
The 5-(trifluoromethyl)pyrimidine ring is often a key raw subunit in a number of new pharmaceutical products. Historically, 2,4-dichloro-5-trifluoromethyl pyrimidine (CFP) has been used as a raw material for introducing the different substituent at the 2- and 4- positions. However, because of the low regioselectivity of the CFP to the nucleophile, the desired product is often obtained with only low yield. So we have investigated 2-chloro-4-phenylthio-5-(trifluoromethyl)pyrimidine (4PSCFP), 2-benzyloxy-4-chloro-5- (trifluoromethyl)pyrimidine (2BNOCFP) and 2,4-bis(2,2,2-trifluoroethoxy)-5-(trifluoromethyl) pyrimidine (TFEFP) as potential reagents for regioselective subsitituion at the 2-position or the 4-position on pyrimidine ring. 4PSCFP, 2BNOCFP and TFEFP were easily prepared from CFP with thiophenol, benzylalcohol or 2,2,2-trifluoroethanol.

1. Reaction of 4PSCFP

4PSCFP reacts with amines at 2-position on pyrimidine ring in high yield. The 2-position substututed 4PSCFP was then oxidized with mCPBA to the sulfoxide. The 2-position substituted 4PSCFP sulfoxide can then react at the 4-position with either amines or alcohols to give a variety of regioselective di-substituted pyrimidine derivatives in moderate to high yield.



(1) 4PSCFP

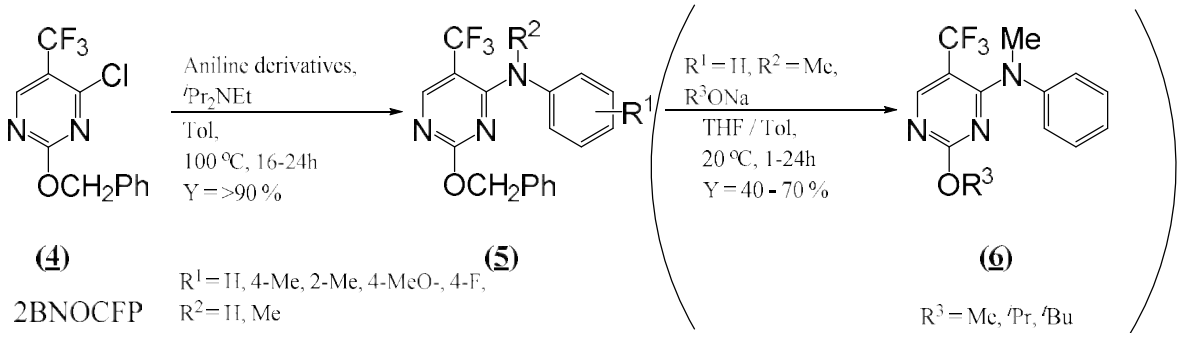
(2) R^1=H, 4-Me, 2-Me, 4-F, R^2=H, Me

(3) AR^3=4-Me-PhNH, 4-MeO-PhNH, 4-F-PhNH, PhN(Me), MeO, EtO, iPrO, tBuO

2. Reaction of 2BNOCFP

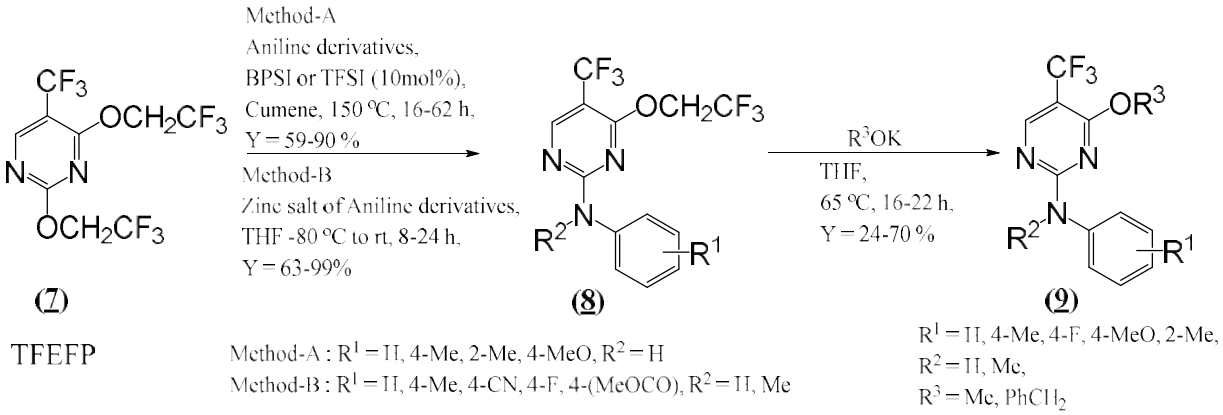
2BNOCFP reacts with amines at 4-position on pyrimidine ring in high yield. The 4-position substituted 2BNOCFP by *N*-methylaniline can then react at the 2-position with alcohols to give regioselective di-substituted pyrimidine derivatives in moderate to high yield. But in the case of the substitution reaction of 4-position substituted 2BNOCFP by primary amine such as aniline or 4-position substituted aniline derivatives, the target product was not found. 4-position substituted 2BNOCFP by primary amine such as

aniline or 4-position substituted aniline derivatives can derive to the 2-chloro derivative through the debenzylosidation with hydrogen in a presence of Pd/C catalyst followed by the chlorination of the 2-positon with Vilsmeier reagent in moderate yield.



3. Reaction of TFEFP

In a presence of acid catalyst such as benzenesulfonylimide (BPSI) or trifluoromethanesulfonylimide (TFSI), TFEFP **7** was reacted with some aniline derivatives which were substituted by electron donating groups such as methyl group or methoxy group to be obtained the 2-position substituted product **8** in high yield and high regioselectivity (Method-A). In the case of using zinc salt of aniline, TFEFP **7** was reacted to be obtained product **8**, which is 2-positon substituted TFEFP **7** by aniline in high yield and high regioselectivity (Method-B). This reaction could be applied to the introduction of electron-donating or electron-withdrawing group substituted aniline derivatives to TFEFP **7**. 2-Position substituted compounds **8** could be reacted with some metal alkoxides to be prepared 4-position subustituted product of **9** with alkoxy group. This reaction was promoted in the case of using potassium primary alkoxides.



1P-50

Copper Complex Catalyzed Asymmetric Monosulfonylation of Glycerol

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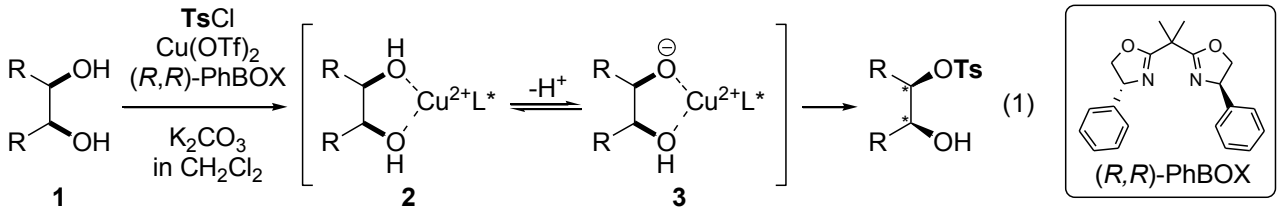
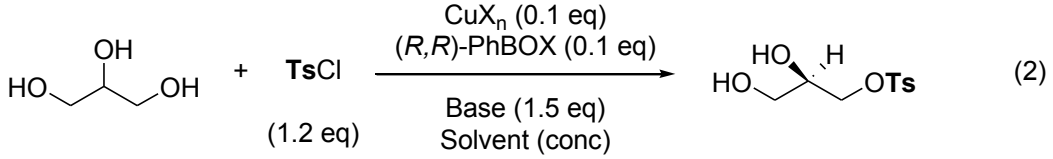
Desymmetric monosulfonylation of glycerol provides an important C3 chiral building block for bioactive compounds and pharmaceuticals. Otherwise, glycerol is a major byproduct of biodiesel fuel production, recent spread of biodiesel fuel causes excess of glycerol, valuable use of glycerol is desired.

Some nonenzymatic asymmetric desymmetrization of glycerol derivatives have been reported but they are limited to benzoylation. We have reported that chiral Cu catalyst ($Cu(OTf)_2$ and (*R,R*)-PhBOX) promotes the asymmetric sulfonylation of *meso*-*vic*-diols (eq 1).[1] In this scheme, coordination of hydroxyl groups of diol **1** to Cu(II)-complex generates activated intermediate **2**, which is easily deprotonated by the base to afford the corresponding alkoxy anion **3**. Anion **3** is sulfonylated, therefore second sulfonylation does not proceed.

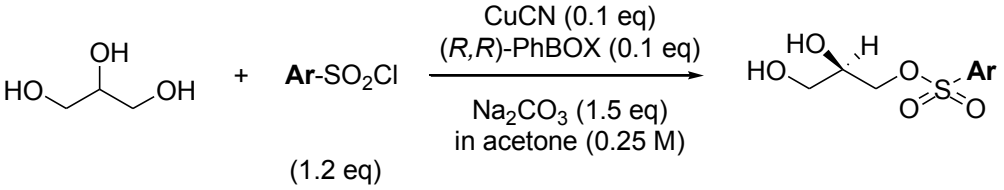


We apply this reaction condition to glycerol to develop the asymmetric desymmetrization of glycerol but both yield and enantioselectivity were low (13% yield, 9% ee). Accordingly, we screened reaction conditions. Cu(I) were suitable for this conversion, the best result was given in a case of using CuCN or CuI as a copper salt, Na_2CO_3 as a base and acetone as a solvent (eq 2). It afforded desired monosulfonylated product in excellent yield and enantioselectivity.[2]

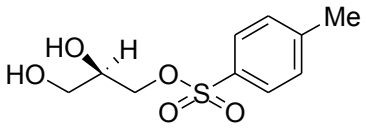


entry	CuX_n	Base	Solvent	conc (M)	yield (%)	ee (%)
1	$Cu(OTf)_2$	K_2CO_3	CH_3CN	0.125	62	65
2	$Cu(OTf)_2$	Na_2CO_3	CH_3CN	0.125	96	84
3	CuI	Na_2CO_3	CH_3CN	0.125	82	92
4	CuCN	Na_2CO_3	CH_3CN	0.125	83	90
5	CuCN	Na_2CO_3	CH_3CN	0.25	82	90
6	CuCN	Na_2CO_3	acetone	0.25	94	96
7	CuCN	Na_2CO_3	acetone	1.00	90	90

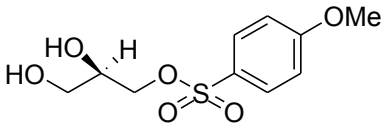
With the optimized condition, we examined the effect of the substituent on the benzene ring of the sulfonylation reagent (eq 3). A diverse array of sulfonylation reagent bearing electron–donating or –withdrawing or sterically hindered group substituted benzene rings gave different results but *p*-CH_3 gave the best yield and enantioselectivity. Electron-donating group didn't have significant effect for both yield and enantioselectivity. However, when the benzene ring has electron-withdrawing group, it reduced conversion and enantioselectivity.



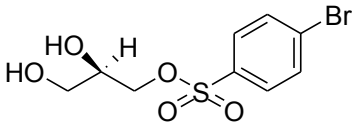
(3)



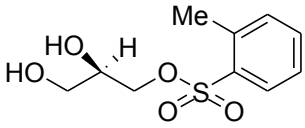
94% yield
96% ee



76% yield
94% ee

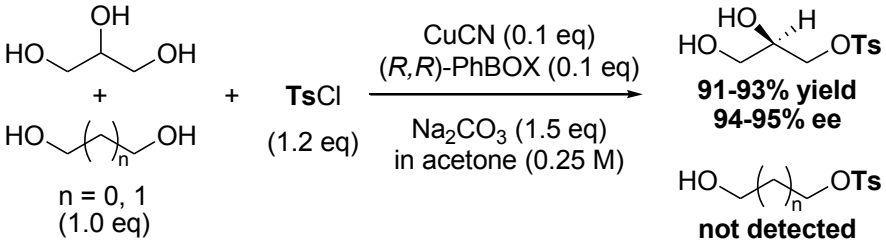


83% yield
89% ee



93% yield
82% ee

This catalytic system has high chemoselectivity of glycerol, in the case of performing the reaction by adding a compound similar structure to glycerol in the optimized condition, only glycerol was monosulfonylated and kept high yield and enantioselectivity (eq 4).



(4)

We present the details of reaction condition screening, effects of various sulfonylation reagents, chemoselectivity and mechanism of enantioselectivity appearance at the venue.

References

1) Demizu, Y.; Matsumoto, K.; Onomura, O.; Matsumura, O. *Tetrahedron Lett*. **2007**, *48*, 7605-7609

2) Onomura, O.; Takemoto, Y.; Miyamoto, K.; Ito, M. PCT/JP2014/077862

1P－51

Intramolecular coupling method for stereo- and regio-controlled procyanidin synthesis

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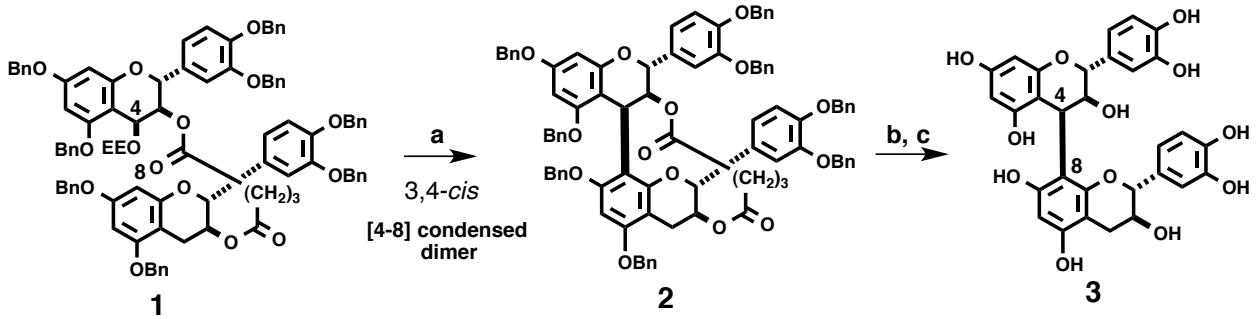
Proanthocyanidins, are known as condensed tannins and/or oligomeric flavonoids, are included in many edible plants and show interesting various biological activity such as powerful antioxidant activity, free-radical-scavenging activity anti-tumor promoting activities. Scientific investigations of proanthocyanidines have become increasingly important because of the various strong biological activities of these substances.

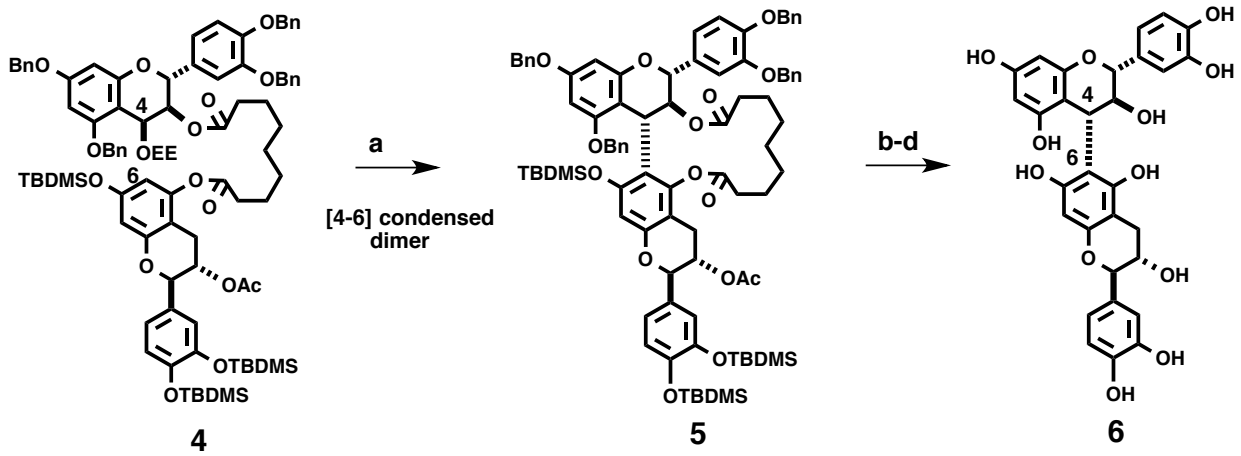
We studied the TMSOTf-catalyzed intramolecular condensation for catechin and epicatechin units. A potential electrophile and a nucleophile were connected with diester linkers and TMSOTf-catalyzed condensation of [4-8] condensed 3,4-*cis* dimer was examined (**Scheme 1**). TMSOTf-catalyzed intermolecular catechin and catechin coupling gave 3,4-*trans* products, on the other hand, the intramolecular condensation of glutaryl diester (**1**) afforded reversed 3,4-*cis* product (**2**). This intramolecular condensation method can solve the difficulty of stereoselective proanthocyanidin synthesis, especially for minor constituents found in nature, such as 3,4-*cis* oligomers. The condensed product (**2**) was transformed into the natural 3,4-*cis* (+)-catechin-(4ß→8)-(+)-catechin dimer (**3**).[1]



Reagents and conditions: a) TMSOTf, CH_2Cl_2,-20°C, 98%. b) K_2CO_3, MeOH, 77% c) DIBAL-H, CH_2Cl_2, 100%.

Scheme 1. Synthesis of 3,4-*cis* (+)-catechin-(4ß→8)-(+)-catechin dimer

We next examined intramolecular coupling method for the stereoselective synthesis of [4-6] condensed procyanidin dimer (**Scheme 2**). $SnCl_4$-Catalyzed intramolecular condensation of di-azelaic acid ester (**4**), C9 dicarboxylic acid ester, at −20 °C proceeded smoothly to give [4-6] condensed catechin dimer (**5**) in 72% yield. Compound (**5**) was finally converted into 3,4-*tras*-(+)-catechin-(4α→6)-(+)-catechin dimer, procyanidin B6 (**6**), by using DIBAL reduction, TBDMS groups deprotection and $Pd(OH)_2$-catalyzed hydrogenolysis in 85% and 65% yield, respectively. The regioselective synthesis of procyanidin B6 was achieved, despite the suitability of the C9-long linker being unclear for this cyclization reaction.



Reagents and conditions: a) $SnCl_4$, CH_2Cl_2,-20°C, 72%.b) DIBAL-H, CH_2Cl_2, 66%. c) TBAF, AcOH, THF, 85% d) $Pd(OH)_2$/C, H_2, THF/MeOH/H_2O (20/1/1), 65%.

Scheme 2. Synthesis of 3,4-*tras*-(+)-catechin-(4α→6)-(+)-catechin dimer

Here, we report on the simple stereoselective synthesis of 3,4-*cis* (+)-catechin-(4ß→8)-(+)-catechin dimer (**3**) and 3,4-*tras*-(+)-catechin-(4α→6)-(+)-catechin dimer, procyanidin B6 (**6**), by using the intramolecular condensation reaction without any modification of 8-position.

Reference

1. Saito A.; Nakajima, N.; Tanaka, A.; Ubukata, M. *Tetrahedron Lett.*, **2003**, *44*, 5449-5452.

1P- 52

A Novel Synthesis of α,α-Disubstituted α-Amino Acids by S_N2 Displacement at the Quaternary Carbon Center

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<Introduction>

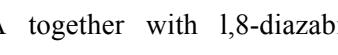
Substitution by the S_N2 mechanism proceeds by the attack of the nucleophile to the reactant from the back side of the leaving group, while simultaneously displacing the leaving group. Therefore, S_N2 reaction is susceptible to the effect of steric hindrance. Generally it does not occur at quaternary carbon atoms, because the nucleophile does not attack from the back of sterically hindered reaction centers. However, only a few examples have been reported on the conversion of sterically hindered tertiary alcohols to azides by using phenyl diphenylphosphinite and $TMSN_3$,[1] and the Mitsunobu reaction with HN_3.[2] These azidation reactions will proceed through an S_N2 mechanism. The application of these reactions is, however, neither convenient nor necessarily safe owing to the use of highly toxic and explosive azide sources.

On the other hand, bis(*p*-nitrophenyl) phosphorazidate (*p*-NO_2DPPA),[3] an azidating agent, is suppressed explosibility due to stabilization by the function of the phosphorus atom. Previously, they were applied to the azidation of primary and secondary alcohols, in which the reactions proceed via an S_N2 mechanism and afford azides with inversion of their stereochemistries.[4] There are no reports dealing with the application to tertiary alcohols to date. Thus, the application of *p*-NO_2DPPA to the azidation of tertiary alcohols would be appreciated. Therefore, the user-friendly and safe method was investigated to develop the direct conversion of tertiary alcohols into azides. Furthermore, we attempted to apply this method to synthesize α,α-disubstituted α-amino esters or amino acids, because the azides were easily converted to the amines by catalytic hydrogenation.

<Experiments and Results>

We initially explored the azidation of racemic methyl atrolactate as a model substrate using *p*-NO_2DPPA together with l,8-diazabicyclo [5.4.0]undec-7-ene (DBU) in toluene (**Table 1**). Optimization of the reaction conditions was performed through the investigation of various equivalents of reagents. Then yields were improved as increasing the quantities of *p*-NO_2DPPA. The reaction could proceed smoothly by using a slight excess of DBU, while the use of a large excess of DBU was revealed to lower the yield. Subsequently, the reaction condition was further optimized by the investigating various solvents and DPPA instead of *p*-NO_2DPPA. The use of THF as a solvent lowers the yield compared with toluene, while desired azide was not obtained in DMF.

Table 1. Optimization of the reaction conditions



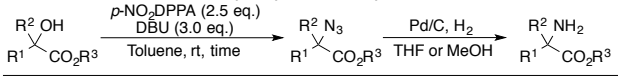
entry	*p*-NO_2DPPA (eq.)	DBU (eq.)	Solvent	yield (%)
1	1.2	1.2	Toluene	19
2	1.2	1.5	Toluene	44
3	1.5	2.0	Toluene	59
4	1.5	2.5	Toluene	52
5	1.5	3.0	Toluene	47
6	2.0	2.0	Toluene	46
7	2.0	2.5	Toluene	77
8	2.0	3.0	Toluene	67
9	2.0	5.0	Toluene	48
10	2.5	3.0	Toluene	96
11	2.5	3.5	Toluene	94
12	2.5	4.0	Toluene	65
13	2.5	3.0	THF	68 [a]
14	2.5	3.0	DMF	trace
15 [b]	2.5	3.0	Toluene	13

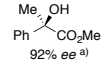
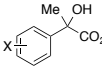
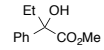
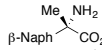
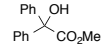
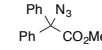
a) Determined by ^{1}H NMR. b) DPPA was used instead of *p*-NO_2DPPA.

On the other hand, the use of DPPA afforded desired azide in low yield owing to low reactivity compared with *p*-NO_2DPPA.

Encouraged by these results, we extended this reaction to a variety of α-hydroxy esters (**Table 2**). Benzylic and aliphatic alcohols gave the desired azides in high to moderate yields. Similarly, the reaction of heteroaromatic and cyclic alcohols proceeded to afford the corresponding azides in moderate yield. However, the azidation of more sterically hindered alcohols were unsuccessful. The hydroxy succinate ester also did not undergo the azidation since an elimination reaction occurred. Chiral alcohols were converted into the corresponding azides with inversion of configuration without loss of enantiomeric purity. Further, these azides could be smoothly converted to α,α-disubstituted α-amino esters or α-amino acids by catalytic hydrogenation.

Table 2. Azidation of various α-hydroxy esters and synthesis of α,α-disubstituted α-amino acids



entry	alcohol	azide	time (h)	yield (%)	amine	yield (%)
1	 92% *ee* [a]		16	98	 92% *ee* [a]	84
2			16	X= *p*-Me 97 [c] *p*-F 95 [c] *o*-F 93 [c]		X= *p*-Me 88 *p*-F 82 *o*-F 75
3			72	12[c]	-	-
4	 81% *ee* [a]		16	93	 81% *ee* [a]	82
5			3	55		65
6			36	75		91
7			72	71		84
8	 72% *ee* [a]		16	82 [c]	 72% *ee* [a]	68
9			16	84 [c]		80
10			16	77		79
11			16	69		99
12			60	nd	-	-
13	 43% *ee* [a]	 43% *ee* [b]	72	63		98
14			72	62		96
15			16	nd [d]	-	-

a) Enantiomeric excess was determined by HPLC analysis. b) Enantiomeric excess was determined by HPLC analysis after converting the azide to 1,4-disubstituted 1,2,3-triazole. c) Determined by ^{1}H NMR. d) Elimination reaction was observed.

Incidentally, the substrate scope of the azidation was investigated with a variety of structurally diverse alcohols with respect of substituent groups in the neighborhood of the hydroxyl group (**Table 3**). The alcohols with other substituent groups did not afford the corresponding azides. Only α-hydroxy esters gave desired azides in high yield.

Table 3. Azidation of tertiary alcohols

entry	R^1	R^2	Solvent	time (h)	yield (%)
1	Me	CO_2Me	Toluene	16	96
2	Me	$COCH_3$	Toluene	16	nd
3	Me	$CONH_2$	THF	16	nd
4	Me	CN	Toluene	16	nd
5	Me	Et	Toluene	72	9
6	Me	CF_3	Toluene	60	nd
7	Ph	Ph	Toluene	16	5

<Conclusion>

We have developed the novel method for the S_N2 azidation on quaternary carbon atoms by using *p*-NO_2DPPA. Chiral α-hydroxy esters were directly converted into the corresponding chiral azides with inversion of configuration without loss of enantiomeric purity. Several α,α-disubstituted α-amino esters or amino acids were prepared through the conversion of azides to the corresponding amines by catalytic hydrogenation.[5]

<References>

1. (a) Mukaiyama, T.; Kuroda, K.; Maruyama, Y.; Hayashi, Y. *Chem. Lett.* **2008**, *37*, 1072. (b) Mukaiyama, T.; Kuroda, K.; Maruyama, Y. *Heterocycles* **2010**, *80*, 63.
2. Green, J. E.; Bender, D. M.; Jackson, S.; O'Donnell, M. J.; McCarthy, J. M. *Org. Lett.* **2009**, *11*, 807.
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Preparation of Unique Copper Complexes of Porphyrin and the Application to Photooxidation of Phenol Derivatives

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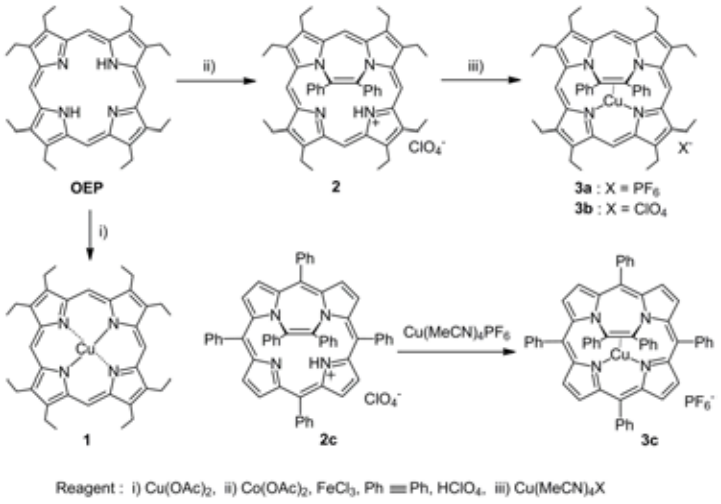
Oxidation of phenol derivatives is of interest because of various industrial applications of the oxidized products in such as pharmaceuticals and dye intermediates, and also from a view of the wastewater treatment of chlorinated or *p*-alkylated phenols. Among several methods, photooxidation method using oxygen from air and visible light having the largest energy density in solar radiation as unlimited natural resources is regarded as a friendly process for environment. Further, immobilizations of photosensitizers on solid supports have been studied to increase utility of the photosensitizers. For the purpose, porphyrin derivatives are candidates of excellent photosensitizer, and several efforts have been made to develop effective photooxidations.[1)] We have already reported the properties and application of unique μ-(dihydroxo)dipalladium(II) complex with N^{21},N^{22}-etheno porphyrin ligand that can be used as a photosensitizer in oxidation of phenol derivatives.[2)] Here we report the preparation and structure of the copper complexes with the N^{21},N^{22}-etheno bridged porphyrin ligands, application of the complex as a photosensitizer in oxidation of phenol derivatives, and further the behavior and effect of the complex as a photocatalyst in heterogeneous reaction.[3)]

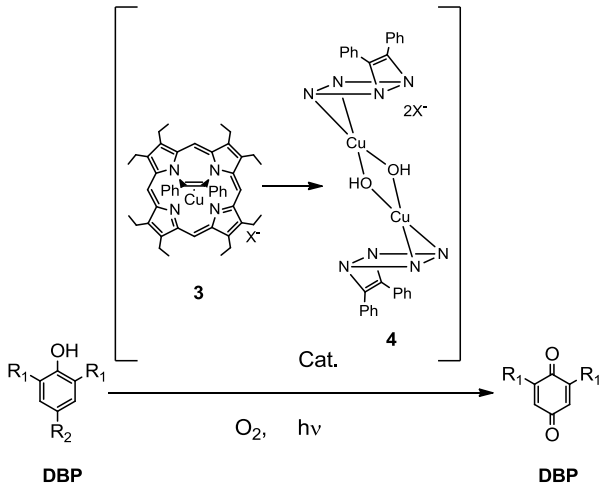
N^{21},N^{22}-(PhC=CPh)(OEP)$HClO_4$ (**2**) was allowed to react with $[Cu(I)(CH_3CN)_4]PF_6$ (5 equiv.) in dichloromethane at room temperature under argon for 1 day to afford N^{21},N^{22}-(PhC=CPh)(OEP)Cu(I)PF_6 (**3a**), and other complexes were prepared similarly as shown in Scheme 1.

When an acetonitrile solution (3 mM) of 2,6-di-*tert*-butylphenol (DBP) containing **3a** (0.3 mM) was irradiated with visible light by a xenon lamp (350 nm < λ < 800 nm) for 90 min under air,



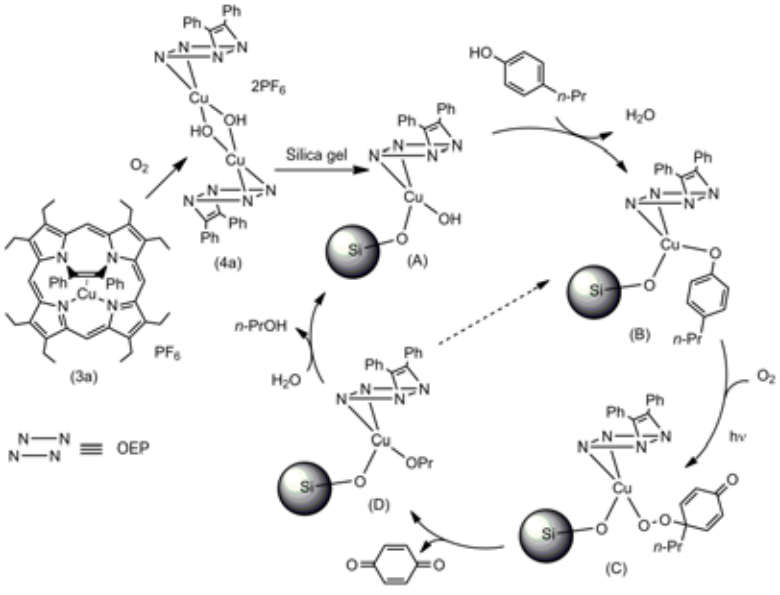
Scheme 1. Preparation of copper(I) complexes with porphyrin or N^{21},N^{22}-(diphenyletheno) bridged porphyrin derivatives

2,6-di-*tert*-butyl-1,4-benzoquinone (DBQ) was formed selectively as an initial oxidized product (80%). The UV-Vis spectrum of **3** was changed to the pattern of **4** through photoirradiation without phenols in acetonitrile to indicate that Cu(I) complex of N^{21},N^{22}-bridged porphyrin was oxidized to di(μ-hydroxo)dicopper(II) complex under aerobic condition (Scheme 2). So this photooxidation of DBP was considered to be promoted by the di(μ-hydroxo)dicopper(II) complex formed in the photoreaction system spontaneously.



Scheme 2. Generation of active species from bidentate porphyrin Cu complex in photooxidation system

Further, to study the photocatalytic activity in heterogeneous reaction, the photosensitizers were immobilized on silica gel as a support to make composite photocatalysts. The photooxidation of *p*-*n*-propylphenol (PNPP) in aqueous solution (1.5 mM) containing the composite of **3a** proceeded faster than that in the case of **2**. It is considered that **3a** was immediately oxidized to (hydroxo)copper(II) complex when adsorbed on the support, and the complex played a role of active species from the beginning in the heterogeneous photoreaction. This heterogeneous reaction is speculated to depend on the catalytic mechanism mainly (Scheme 3), though singlet oxygen may contribute. The high adsorptive ability and photostability seemed to increase catalytic activity. Moreover the used photocatalyst of **3a** could be recovered easily and re-used with little inactivation after 3 recycles. Thus the copper complexes reported here promoted photooxidation of phenol derivatives with visible light in both of homogeneous and heterogeneous system in which the (hydroxo)Cu(II) complexes with N^{21},N^{22}-etheno bridged porphyrin played a role of the key species.



Scheme 3. Plausible mechanism for the heterogeneous photooxidation

1) Nagai, K.; Yasuda, Y.; Abe, T. Jpn. Kokai Tokkyo 2010, JP 2010119996 A.
2) Takao Y.; Ohno T.; Moriwaki K.; Matsumoto F.; Setsune J. *J. Porphyrins Phthalocyanines* 2010, 14, 64
3) Takao Y.; Matsumoto F.; Moriwaki K.; Mizuno T.; Ohno T.; Setsune J. *J. Porphyrins Phthalocyanines* in press.

1P－54

New type of Silica Gel for Hydrophilic Interaction Chromatography (HILIC)

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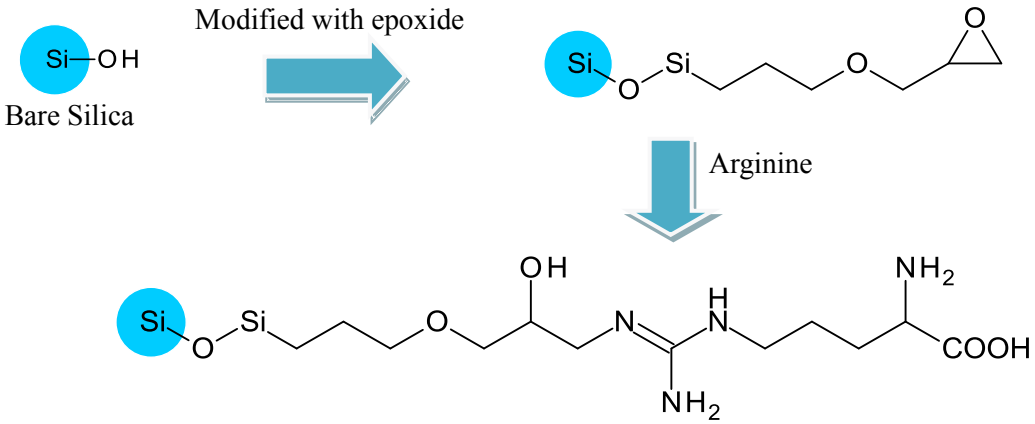
New type of silica gel has been synthesized by chemical bond with arginine (ARG silica). Chromatographic separation properties were compared with three types of silica gels such as NH silica, DIOL silica, and bare silica. ARG silica was expected as a new type of media for the separation of hydrophilic compounds such as nucleobases and puline bases.

1. Synthesis of argnine silica (ARG silica)

At first, bare silica (Shape = Spherical, Specific surface area = 300 m^2/g, Particle size = 30 μ m , Pore size = 10 nm) was modified with epoxide group by using silane coupling agents. Then ARG silica was obtained by reacting with arginine to the epoxy delivatized silica.



Scheme1. Synthesis of ARG silica

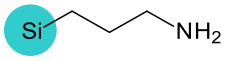
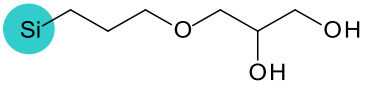
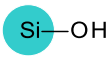
2. Separation properties of hydrophilic compounds

ARG silica, NH silica, DIOL silica and bare silica compared the separation of hydrophilic compounds (Table1). Those four types of silica were made from the same bare silica and packed cartridges column.

(Chromatography conditions)

Column size : ϕ 28 mm × 100 mm
Column volume : 60 ml
Mobile phase : 90 vol% Acetonitorile / water (Fig.1)
80 vol% Acetonitorile / water (Fig.2)
Flow rate : 30 ml/min
Detector : UV254 nm

Table1. Structure of silica compared with ARG silica

Type	Structure
NH	
DIOL	
Bare Silica	

2-1 Separation properties of nucleobases

Fig.1 shows the separation of three kinds of nucleobases by using four types of silica. ARG silica and bare silica performed to separate with the all nucleobases, and ARG silica had a strong selectivity of the nucleobases and the retention time was more than two times of bare silica. ARG silica is effective for the separation of nucleobases.

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2-2 Separation properties of puline bases

Fig.2 shows the separation of four kinds of puline bases by using four types of silica. ARG silica performed to separate with the all puline bases. ARG silica is effective for the separation of puline bases.

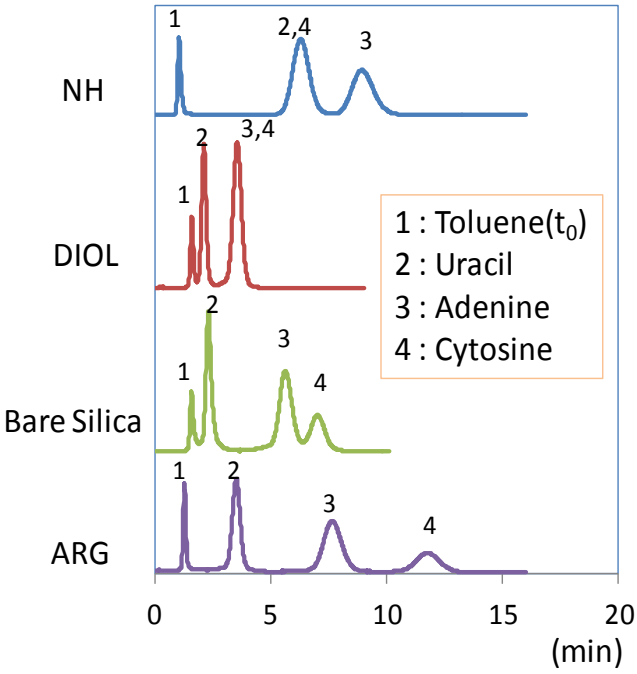

Fig.1 Chromatogram of nucleobases separation of by four types of silica
(Mobile phase: 90 vol% Acetonitrile / water)

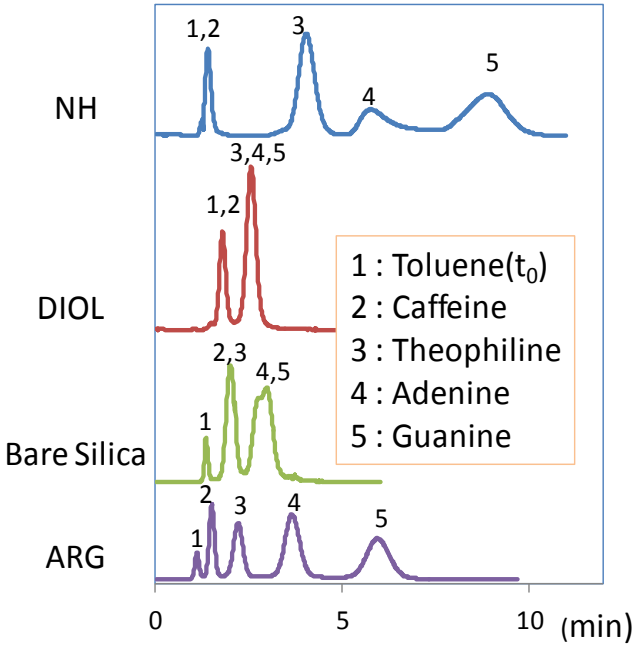

Fig.2 Chromatogram of puline bases separation by four types of silica
(Mobile phase: 80 vol% Acetonitrile/water)

Summary

ARG silica shows a strong selectivity of hydrophilic compounds such as nucleobases and puline bases.

1P- 55

Development of highly active iridium catalysts for reductive amination of carbonyl compounds

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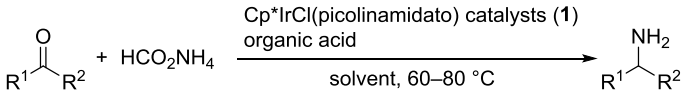
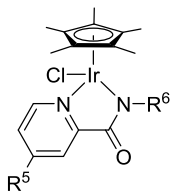
We found out practical reductive amination catalysts for synthesis of primary, secondary, and tertiary amines under moderate reaction conditions. This time, we have developed iridium catalysts with much higher activity. For example, reductive amination of aromatic ketones with ammonium formate gives corresponding primary amines in high yield, even when S/C (substrate-to-catalyst molar ratio) is over 10,000.

Amine compounds are useful compounds used in a wide range of applications such as pharmaceuticals, agricultural materials, functionalized materials, and starting materials for resins. Reductive amination of carbonyl compounds is known as one of the effective method for the preparation of amines without isolation of imine, or enamine intermediates. So far, several reagents such as $NaBH_3CN$, $NaBH(OAc)_3$, and pyridine-borane were investigated as the reductive amination reagents, but they have some problems such as toxicity, wastes, and explosiveness. In the case of hydrogenation reaction using heterogeneous catalysts such as Pd/C, and sponge metal, pressure bottle is required, and there are cases where functional groups such as a cyano, nitro, and halogen group can not be tolerated. We found that Cp*IrCl(picolinamidato) catalyst (**1a**) and Cp*IrCl(quinolinolato) catalyst (**2a**) have a high catalytic activity for transfer hydrogenative reductive amination using formic acid or formate as a hydrogen source (Scheme 1).[1,2] These catalysts are applicable to alkyl, aryl and heteroaryl ketones, leading to corresponding amines. Notably, cyano, nitro, and halogen groups in aromatic rings can be tolerated. Since these reactions utilize ammonium formate or formic acid as a hydrogen source, these reactions can be conducted with a conventional flask in a laboratory without special equipment such as a pressure bottle.

Scheme 1

■ Primary amine synthesis

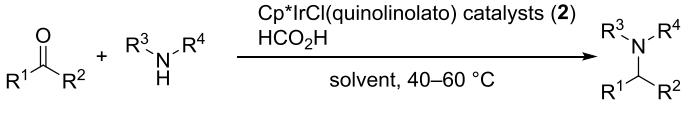


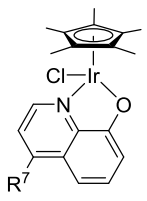


1a: R^5 = H, R^6 = 4-$N(CH_3)_2$-C_6H_4
1b: R^5 = $N(CH_3)_2$, R^6 = H
1c: R^5 = $N(CH_3)_2$, R^6 = 4-$N(CH_3)_2$-C_6H_4

Cp*IrCl(picolinamidato) catalysts, **1a–1c**

■ Secondary and tertiary amine synthesis



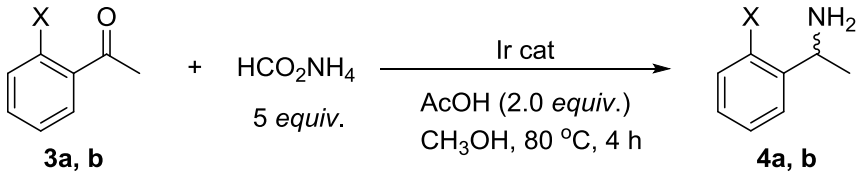


2a: R^7 = H
2b: R^7 = $N(CH_3)_2$

Cp*IrCl(quinolinolato) catalysts, **2a–2b**

This time, we have developed these iridium catalysts in order to increase the catalytic activity. For example, catalyst (**1c**) has much higher catalytic activity by introduction of dimethylamino group on the pyridine ring of picolinamidato catalyst.[3] Acetophenone (**3a**) reacts with ammonium formate at S/C of 10,000 to afford 1-phenylethylamine (**4a**) in 90% yield (Scheme 2). Even though sterically bulky substrate (**3b**) having bromo group adjacent to carbonyl group reacts with less bulky catalyst (**1b**), leading to 1-(2-bromophenyl)ethylamine (**4b**) in 85% yield (Scheme 2).

Scheme 2



3a, b
a: X = H
b: X = Br

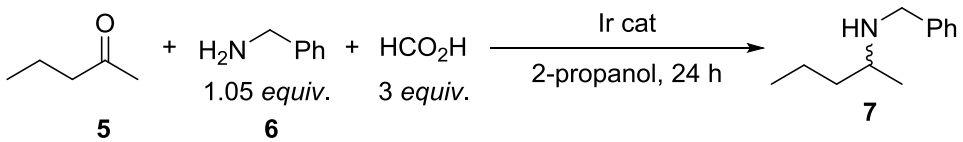
4a, b

entry	ketone	Ir cat	S/C	conv. (%)[a]	yield (%)[a]
1	**3a**	**1a**	10,000	88	55
2	**3a**	**1b**	10,000	76	31
3	**3a**	**1c**	10,000	>99	90
4	**3b**	**1a**	2,000	51	18
5	**3b**	**1b**	2,000	>99	85
6	**3b**	**1c**	2,000	96	69

[a] Determined by ^{1}H NMR using an internal standard.

In a synthesis of secondary amine, the use of modified iridium catalyst (**2b**) is helpful to achieve high activity. 2-pentanone (**5**) reacts with benzylamine (**6**) at S/C of 10,000 to afford *N*-benzylpentan-2-amine (**7**) in 92% yield (Scheme 3).

Scheme 3



5 **6** **7**

entry	Ir cat	S/C	temp (°C)	yield (%)[a]
1	**2a**	3,000	40	63
2	**2b**	3,000	40	97
3	**2b**	10,000	40	51
4	**2b**	10,000	60	73
5[b]	**2b**	10,000	60	92

[a] Determined by ^{1}H NMR using an internal standard.
[b] 1.2 equiv. of **6** was used.

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1) Kanto Chemical Co., Inc. Japan patent JP2010-235604A.
2) Watanabe, M.; Tanaka, K.; Murata, K. *Abstract JSPC summer symposium* **2012**, 128.
3) Watanabe, M.; Tanaka, K.; Tsutsumi, K.; Murata, K. *Abstract JSPC summer symposium* **2014**, 146.

1P-56

Reclamation of squid pen for the production of chitosanase and dye biosorbent by *Bacillus cereus*

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The aim of this work is to produce chitosanase by fermenting from squid pen, and recover fermented squid pen for dye removal by adsorption. One chitosanase induced from squid pen powder (SPP)-containing medium by *Bacillus cereus* TKU034 was purified with high purification fold (441) and high yield of activity recovery (50.9%) by ammonium sulfate precipitation and combined column chromatography. The SDS-PAGE results show its molecular mass is around 43 kDa. The TKU034 chitosanase used for the chitooligomers preparation was studied. The enzyme products revealed that the chitosanase could degrade chitosan with various degrees of polymerization, ranging from 3 to 9, and the chitosanase in an endolytic manner. Besides, the fermented SPP was recovered and displayed a better adsorption rate (up to 99.5%) for the disperse dyes (red, yellow, blue and black) than the water-soluble food colorants, Allura Red AC (R40) and Tartrazne (Y4). FT-IR analysis proved that the adsorption of the dyes onto fermented SPP adsorbents was a physical adsorption. Results also showed that fermented SPP was favourable adsorbers and could be employed as low-cost alternatives for dye removal in wastewater treatment.

1P- 57

Ru-MACHO, 'Gentle' catalytic ester reduction and beyond

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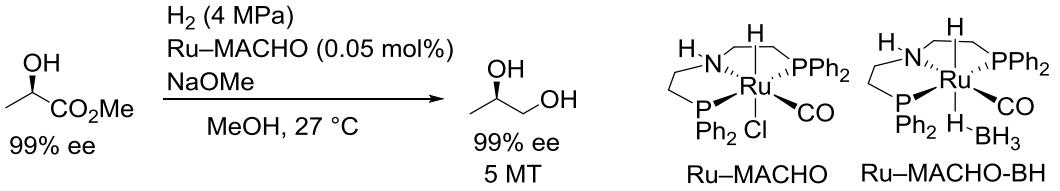
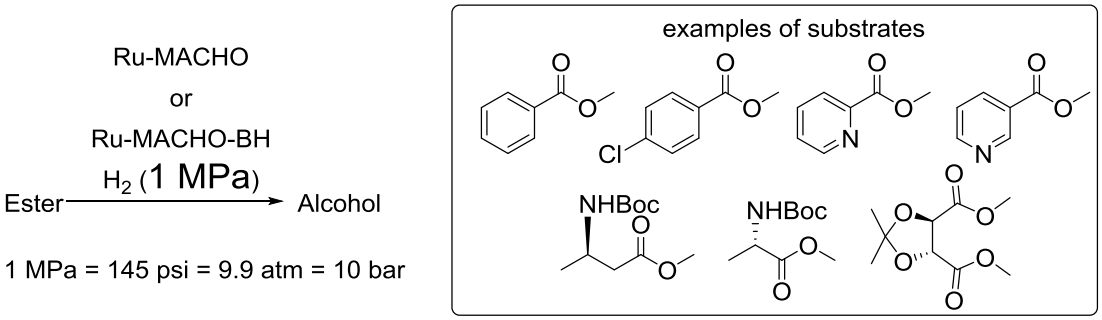
In recent years, manufacturing processes which achieve low waste, safe and easier operations are highly demanded from a viewpoint of environment and safety concern. Catalytic reactions are one of the solutions for this purpose. Stoichiometric reactions accompany considerable amount of waste, which require additional operations in order to eliminate waste. Catalytic reactions, which require tiny amount of reagents, achieve low waste and safe manufacture.

Ester Reduction is the case which is required to replace from stoichiometric reaction to catalytic one. Conventionally, esters have been reduced using a stoichiometric amount of hydride reagents. While this method has been reliable on laboratory scale, a large amount of waste and hazardous work-up made the process problematic on manufacturing scale. We previously reported Ru-MACHO for hydrogenation of esters to alcohols[1]. Ru-MACHO was powerful catalyst and enabled to reduce esters without generating a large amount of waste and dangerous operations. For example, 5 MT of 1,2-propanediol was manufactured from methyl lactate by hydrogenation using Ru-MACHO without losing optical purity, accompanying only a small amount of distillation residue as by-product. We also developed Ru-MACHO-BH for hydrogenation under neutral conditions. This catalyst enabled hydrogenation without strong bases, and base sensitive esters could be hydrogenated to the corresponding alcohols without racemization or decomposition.



Ru-MACHO and Ru-MACHO-BH showed excellent performance in ester reduction at 4 MPa, we then explored a protocol tolerable at lower hydrogen pressure, which could provide more flexibility in equipment / facilities.

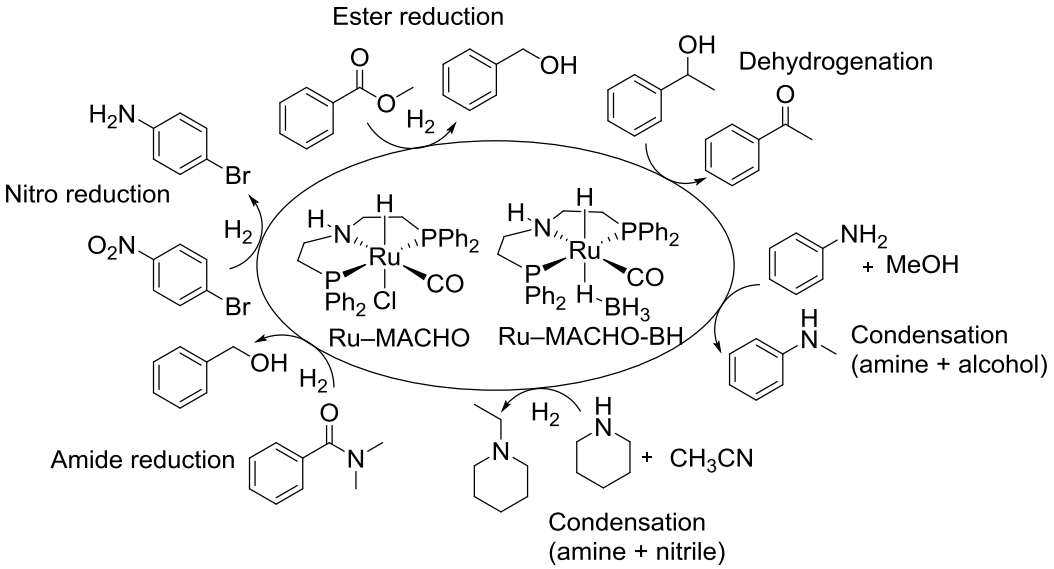
Herein, we introduced hydrogenation of esters under lower hydrogen pressure. By applying suitable solvent to each substrate, hydrogenation of esters under 1 MPa of hydrogen pressure could proceed. Ru-MACHO-BH could be used under 1 MPa of hydrogen pressure, too. Hence various kinds of esters could be hydrogenated under low hydrogen pressure. Detailed reaction conditions and examples of substrates will be discussed in this symposium.



We also applied Ru-MACHO and Ru-MACHO-BH to other catalytic reactions. As a result of the study, we succeeded in developing several reactions using Ru-MACHO and Ru-MACHO-BH.

New applications of Ru-MACHO and Ru-MACHO-BH are described below.

- Dehydrogenation of alcohols to carbonyl compounds, which could avoid explosive oxidizing reagents such as peroxides.
- Condensation between alcohols and amines using the borrowing hydrogen methodology, which did not need mutagenic alkyl halides.
- Condensation between nitriles and amines, which did not need mutagenic alkyl halides.
- Amide reduction to alcohols and amines, which had been difficult due to low reactivity of amides.
- Nitro reduction to amines with high chemoselectivity.



Details will be discussed in this symposium.

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1) W. Kuriyama, T. Matsumoto, O. Ogata, Y. Ino, K. Aoki, S. Tanaka, K. Ishida, T. Kobayashi, N. Sayo, T. Saito, *Org. Process Res. Dev.* **2012**, *16*, 166-171

1P-58

Cancelled

Cancelled

1P- 59

Practical Asymmetric Hydrogenation of Sterically Congested Aromatic Ketones with Polysubstituents on Aromatic Rings

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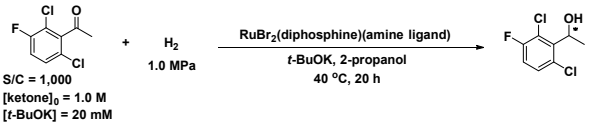
The asymmetric hydrogenation of a variety of ketones with diphosphine/diamine-Ru complex proceeds smoothly with high enantioselectivity.[1] Although optically active alcohols with polysubstituents on aromatic rings are useful compounds, only a few asymmetric hydrogenation method for obtaining these compounds have been reported.[2] In case of (*S*)-1-(2,6-dichloro-3-fluorophenyl)ethanol, which is a key building block of XALKOLI® (crizotinib), the anticancer drug, developed by Pfizer, has been prepared by optical resolution using pig liver esterase or asymmetric reduction catalyzed by an engineered ketoreductase.[3]

We have already reported asymmetric hydrogenation of tertiary alkyl ketones like a pinacolone by using Ru complex having 2-(aminomethyl)pyridine (PICA) as diamine ligand.[4] We report here that this diphosphine/PICA-Ru complex effectively catalyzes enantioselective hydrogenation of ketones having polysubstituents on the aromatic rings.

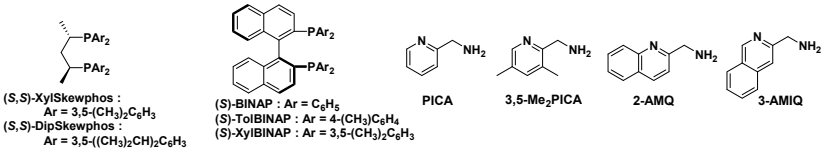
Although for the hydrogenation of 2',6'-dichloro-3'-fluoroacetophenone, XylSkewphos/diamine-Ru(II) (XylSkewphos = 2,4-bis(di-3,5-xylylphosphino)pentane) or BINAP/diamine-Ru(II) complex having optically active diamine ligand such as DAIPEN or DPEN showed poor reactivity and enantioselectivity, XylSkewphos/PICA-Ru(II) complex gave better result of 99% yield and 94.0% ee (S/C = 1000). Skewphos type ligands are the better choices, as TolBINAP/PICA-Ru(II) complex gave almost racemic alcohol. Enantioselectivity was improved by introducing substituents into the PICA ligand, and the PICA ligands which were introduced substituents more than two in particular showed high enantioselectivity. Enantioselectivity of 98.5% was obtained by XylSkewphos/3,5-Me_2PICA-Ru(II) catalyst. DipSkewphos (2,4-bis(di-3,5-diisopropyl phenylphosphino)pentane) resulted in improvement of the enantioselectivity. Thus 98.8% ee of the product was obtained with $RuBr_2$[(*S*,*S*)-dipskewphos](3-amiq) (Scheme 1). These substituted Skewphos/PICA-Ru(II) complexes are applicable to the asymmetric hydrogenation of a series of sterically congested aromatic ketones having polysubstituents on the aromatic rings (Scheme 2). The reaction of some sterically hindered ketones proceeded smoothly; 2',6'-dichloroacetophenone (>99% yield, 98.7% ee), 2',6'-dimethoxyacetophenone (>99% yield, 99.5% ee), 2',4',6'-trimethylacetophenone (>99% yield, 98.0% ee). Pentasubstituted acetophenone was hydrogenated in high enantioselectivity but with

low reactivity. 1',2',3',4',5'-Pentafluoroacetophenone was converted to the alcohol in 29% yield with 94.4% ee (S/C = 300). The noteworthy is that 1',2',3',4',5'-pentamethylacetophenone could not be reduced even with $NaBH_4$, but the reaction proceeded smoothly with $RuBr_2$[(*S*,*S*)-dipskewphos](3-amiq) leading to the chiral alcohol in 98% yield with 98.1% ee. This is the first case of asymmetric hydrogenation of these pentasubstituted acetophenones progressed in high enantioselectivity to our knowledge.

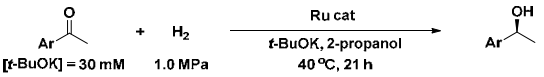
Scheme 1



entry	Diphosphine	amine ligand	yield (%)	ee (%)	config.
1	(*S*)-BINAP	(*S*,*S*)-DPEN	21	15.3	*R*
2	(*S*)-XylBINAP	(S)-DAIPEN	9	19.0	*S*
3	(*S*)-TolBINAP	PICA	99	3.4	*R*
4	(*S*,*S*)-XylSkewphos	(*S*,*S*)-DPEN	28	26.7	*R*
5	(*S*,*S*)-XylSkewphos	PICA	>99	94.0	*S*
6	(*S*,*S*)-XylSkewphos	3,5-Me_2PICA	>99	98.5	*S*
7	(*S*,*S*)-XylSkewphos	2-AMQ	>99	96.3	*S*
8	(*S*,*S*)-XylSkewphos	3-AMIQ	>99	98.2	*S*
9	(*S*,*S*)-DipSkewphos	3,5-Me_2PICA	>99	98.5	*S*
10	(*S*,*S*)-DipSkewphos	3-AMIQ	>99	98.9	*S*



Scheme 2



Ru cat \ Ar	S/C = 2,000 [ketone]0 = 2.0 M	S/C = 2,000 [ketone]0 = 1.0 M	S/C = 2,000 [ketone]0 = 2.0 M	S/C = 200 [ketone]0 = 1.0 M	S/C = 300 [ketone]0 = 2.0 M
$RuBr_2$[(*S*,*S*)-dipskewphos](3-amiq)	>99% yield 98.7% ee	>99% yield 99.5% ee	>99% yield 98.0% ee	98% yield 98.1% ee	29% yield 94.4% ee
$RuBr_2$[(*S*,*S*)-dipskewphos](3,5-Me_2pica)	>99% yield 98.5% ee	>99% yield 99.5% ee	>99% yield 96.3% ee	96% yield 97.4% ee	14% yield 92.7% ee
$RuBr_2$[(*S*,*S*)-xylskewphos](3,5-Me_2pica)	>99% yield 98.2% ee	>99% yield 99.5% ee	>99% yield 95.8% ee	94% yield 93.2% ee	57% yield 86.3% ee

〔*Reference*〕

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1P- 60

Cycle Time Reduction for an Intermediate Crystallization Step Using a New Image-Based PAT Technique

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Controlling crystal size, shape and concentration is critical during the development and manufacture of high value chemicals in order to ensure product quality as well as efficient processing. Crystallization processes are typically poorly understood, particularly early in the development cycle where complex phenomena such as phase separation, unexpected polymorphic transformations and excessive secondary nucleation can extend development time and cost. Intermediate crystallization steps are particularly prone to poor process understanding and once scaled up can represent a major component of overall process cycle time due to unnecessary hold times and difficult filtration and washing steps caused by inconsistent crystals size and shape distributions.

Offline microscopy and inline turbidity measurements may be used by scientists to develop better process understanding of crystallization steps, however offline measurements are not typically reliable for delicate crystals that can change during sampling and turbidity measurements are generally insensitive in systems where crystal size, shape and concentration are changing simultaneously.

It is with these challenges in mind that a new, probe-based, PAT technique has been developed that combines high resolution real time microscopy with an image-based process trend that indicates how crystal size, shape and concentration is changing in real time. Real time microscopy allows scientists to directly observe crystals and associated crystallization mechanisms, such as nucleation growth, phase separation or habit shifts, in process without the need for sampling. Relative Backscatter Index (RBI) is a process trend that uses information from every image collected to indicate how crystal size, shape and concentration is changing under dynamic process conditions. The combination of real time microscopy and RBI in a single probe-based PAT technique allows crystallization processes to be routinely understood using a simple method.

In this study RBI and real time microscopy are applied to reduce the cycle time of an intermediate crystallization step by 60% while maintain the same crystal size and shape distribution. In addition, a self-seeding step was implemented that removed the need for seed addition during manufacturing. Finally solubility and MSZW curves were developed for the intermediate compound using a dynamic and automated method that relies on RBI to accurately determine clear and cloud points.

1P-61

Synthetic Studies toward (+)-CJ-12,950 for the Stereochemical Assignment

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CJ-12,950 (**1**), a direct inducer of low density lipoprotein (LDL) receptor gene, was isolated from the zygomycete *Mortierella verticillata* ATCC 42662 in 1998 by Dekker and co-workers and was identified as a 12-membered macrolactone possessing an unusual oxime side chain (Figure 1).[1] While the novel biological activity, the relative and absolute configurations of stereogenic centers were not completely elucidated at that time. Thus, we started the synthetic studies of the possible diastereomers of CJ-12,950 *via* a highly convergent approach for its stereochemical assignment by a comparison of their spectral data with those of natural CJ-12,950.

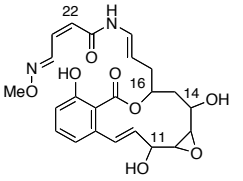
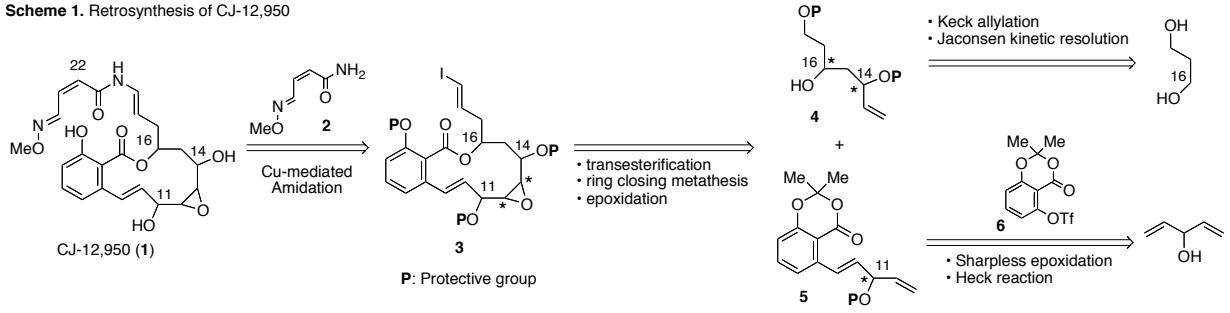


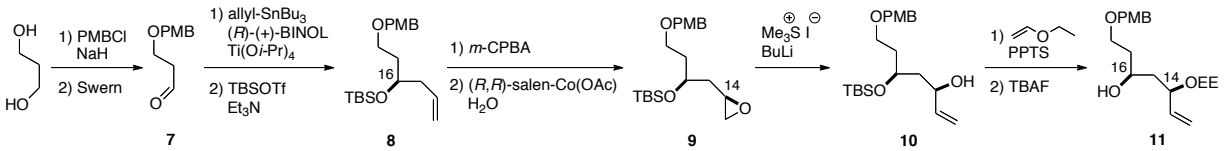
Figure 1. Structure of CJ-12,950 (**1**)

We planned a convergent synthetic route accessible to possible diastereomers from commercially available propane diol and divinylcarbinol utilizing reliable asymmetric inductions (Scheme 1). CJ-12,950 would be furnished by Cu-mediated amidation reaction of the macrolactone **3** with enamide side chain **2**. The macrolactone **3** was disconnected into the optically active secondary alcohol **4** and the aromatic fragment **5**. Two stereogenic centers in fragment **4** would be stereoselectively constructed via Keck asymmetric allylation of aldehyde and Jacobsen hydrolytic kinetic resolution of epoxides. On the other hand, allylic chiral center in **5** must be established by Sharpless asymmetric epoxidation of commercial divinylcarbinol.

Scheme 1. Retrosynthesis of CJ-12,950



Scheme 2. Preparation of Optically Active Fragment **11**

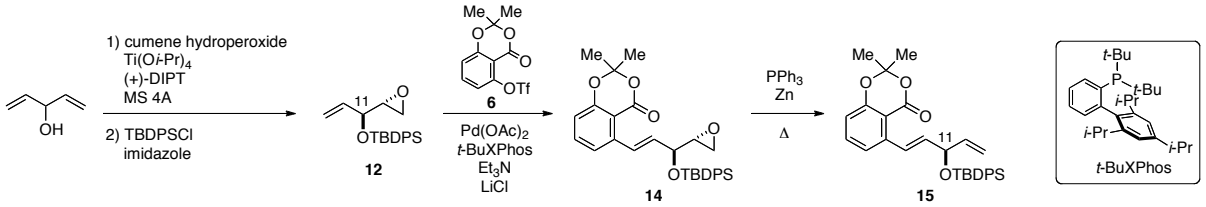


Starting with 1,3-propanediol, the aldehyde **7** was prepared by PMB protection followed by Swern oxidation (Scheme 2). Asymmetric induction on C16 position was achieved by Keck allylation protocol (89 %ee) and Jacobsen kinetic resolution of racemic epoxides derived from **8**[2] afforded **9**. The allylic

alcohol moiety in **10**[3] was established by the exposure of **9** to excess dimethylsulfonium methylide. After protection of allylic alcohol as ethoxyethyl ether, desilylation gave desired fragment **11**.

Aromatic fragment **15** could be prepared in four steps starting from divinylcarbinol. According to the literature method,[4] Sharpless asymmetric epoxidation of divinylcarbinol followed by silylation of hydroxyl group furnished optically active **12**. Heck reaction of **12** with triflate **6**[5] in the presence of *t*-BuXPhos afforded **14**, which was deoxygenated with PPh_3/Zn into requisite aromatic fragment **15** (98 %ee).

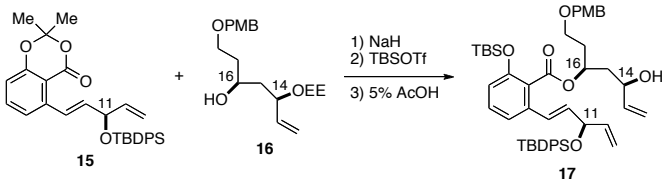
Scheme 3. Preparation of Optically Active Aromatic Fragment **15**



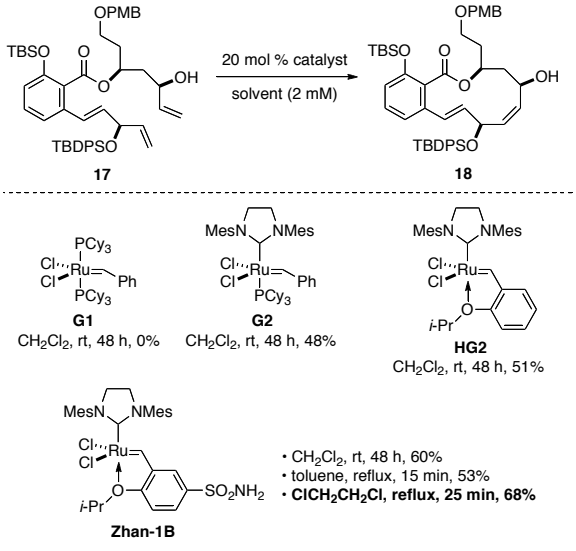
With optically active fragments in hand, we assembled them by transesterification reaction and RCM reaction of triene **17** was examined after silylation of phenolic hydroxyl group and subsequent cleavage of ethoxyethyl ether (Schemes 4 and 5). While Grubbs catalysts **G1** did not catalyze the desired metathesis reaction, **G2** was found to afford the macrolactone **18** in moderate yield. **HG2** slightly improved the yield and finally, recently developed **Zhan-1B** gratifyingly gave the lactone **18** up to 68%.

Epoxidation of **18** fortunately afforded a sole diastereomer and the key iodo olefin **20** was obtained *via* four-step sequence including Takai-Utimoto reaction. Now we are in effort on the endgame of the synthesis, Cu-mediated amidation reaction (Scheme 6).

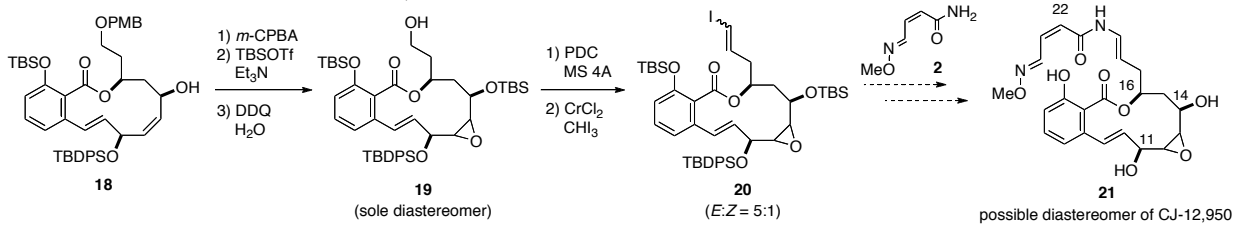
Scheme 4. Assembly of the Fragments



Scheme 5. Ring Closing Metathesis



Scheme 6. Toward the Possible Diastereomer of CJ-12,950



[References] (1) Dekker, K. A.; Aiello, R. K.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14. (2) Rajesh, K.; Suresh, V.; Selvam, J. J. P.; Rao, C. B.; Venkateswarlu, Y. *Hel. Chim. Acta* **2009**, *92*, 1866. (3) Dubey, A.; Kauloorkar, S. V.; Kumar, P. *Tetrahedron* **2010**, *66*, 3159. (4) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. (5) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071.

1P-62

Trifluoromethylation using Fluoroform through Catalytic Amount of Phosphazene Base

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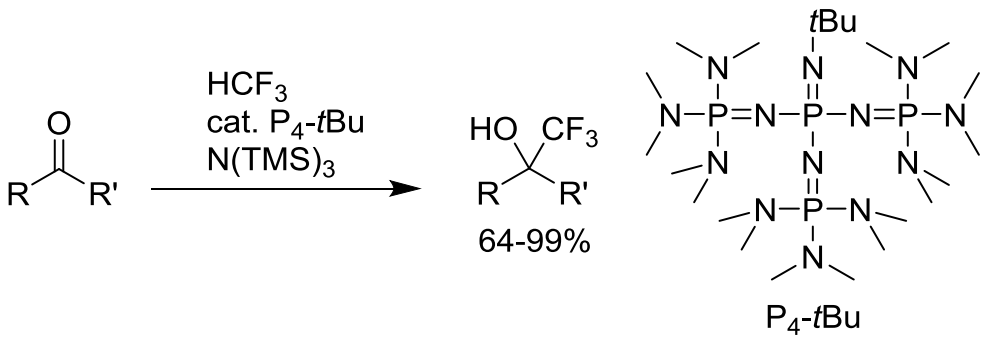
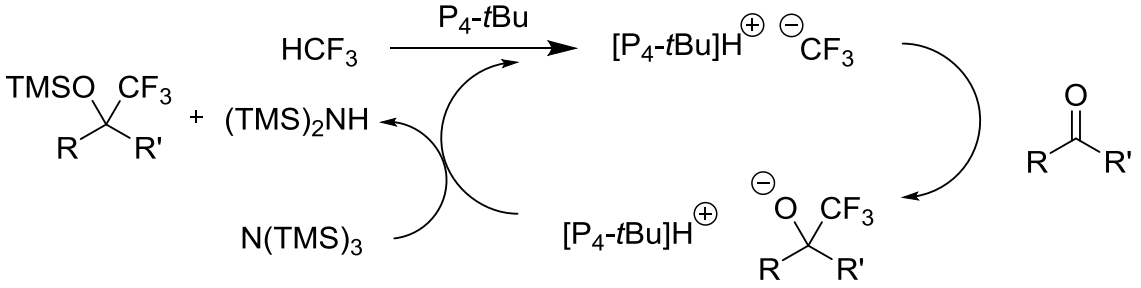
Organofluorine compounds play an important role in the search of new pharmaceuticals, agrochemicals, and advanced materials. In particular, the trifluoromethyl (CF_3) group including fluorinated functional groups has attracted much attention recently, since the CF_3-substituted compounds constitute a particular class with specific properties, such as the high lipophilicity provided by this group. Thus, the trifluoromethylated variants of biologically active molecules making it an interesting moiety with respect to the design of bioactive molecules, which might be potential candidates in the future-drug market. Among a variety of methods for this goal, the nucleophilic trifluoromethylation of carbonyl compounds such as ketones using a Ruppert–Prakash reagent is absolutely the most rightful and well-explored strategy. In spite of the straightforward, convenient, and versatile method, this reagent is less than ideal. Ruppert–Prakash reagent has two demerits: expensiveness for its preparation and the fact that it is mostly prepared from the ozone-depleting bromotrifluoromethane (CF_3Br) as the hazardous environment. In this context, fluoroform is a side product in the manufacture of Teflon, and is ozone-friendly, nontoxic, cheap, and available in large quantities. Despite its attractive characters, the trifluoromethylation reaction using fluoroform has been years of problem in organofluorine chemistry.

Recently, we were able to use a sterically demanding organic superbase P_4-*t*Bu to generate a stabilized trifluoromethyl anion that will undergo nucleophilic addition to aromatic aldehydes, ketones and disulphide[1]. However, our strategy had big program that this reaction need a stoichiometric amount of P_4-*t*Bu. This phosphazene base is very expensive and it is inconvenient to try asymmetric trifluoromethylation using fluoroform and the chiral phosphazene base. In 2000, Langlois and coworkers reported the trifluoromethylation to the ketones using fluoroform, $N(TMS)_3$ and a catalytic amount of fluorine source[2]. This reaction could be carried out in DMF and no reaction carried out in THF. However, our reaction using P_4-*t*Bu could be carried out in THF. So, we think that P_4-*t*Bu was reduced when our condition collaborated with Langlois's condition. We developed for the first time the trifluoromethylation of ketones through the catalytic amount of P_4-*t*Bu and the use of fluoroform. A series of ketones with a variety of substituents at their aromatic rings, such as methoxy and chloro, heteroaromatic ring and alkyl-substituted ketones were nicely converted to the corresponding α-trifluoromethyl alcohols in good yields. The new and epoch-making methodology provides a convenient route for efficient trifluoromethylation.



Based on these results, we hypothesized the reaction mechanism. First, the deprotonation of fluoroform with P_4-*t*Bu is initiated and the naked CF_3 anion is generated. In case of ketones, the naked CF_3 anion react with ketones to provide α-trifluoromethyl alkoxides and these alkoxides desilylate $N(TMS)_3$. Because the desilylation $N(TMS)_3$ is very strong base, it can deprotonate fluoroform.



Reference

[1] H. Kawai, Z. Yuan, E. Tokunaga, N. Shibata, *Org. Biomol. Chem.* **2013**, *11*, 1446-1450.

[2] S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848-8856.

1P- 63

Lonza MRT / Flow Technology Applied to Innovative Chemistry

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The key concept behind the utilization of flow is to achieve extreme process intensification. The intensification process enables inherently safer conditions that lead to the development of new processes, so-called "Flash Chemistry," that could otherwise never be performed under batch conditions. In a microreactor it is possible to perform highly energetic reactions, work with unstable intermediates, employ more reactive reagents, and use more active catalysts that enable new, out-of-the-box chemistry. In addition, the workspaces can be designed for high temperature and high pressures reactions; a new domain for a typical organic chemist. A microreactor will be at the heart of flow processes to control the "Flash Reaction" but will be implemented in parallel with other flow unit operations such as liquid-liquid extraction, distillation and crystallization. The outcome will lead to highly intensified mini-plant approaches that will be the basis of the "Factory of Tomorrow." The ultimate results of the initiative are more sustainable, greener, and economical processes for producing a wide range of pharmaceuticals.

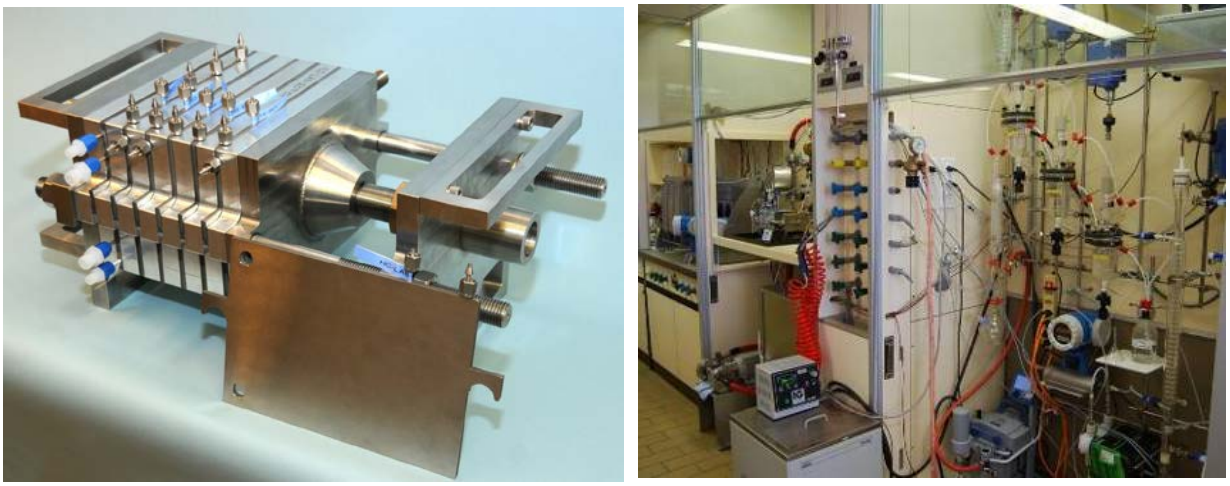

Figure 1. Lonza FlowPlate™ MicroReactor and integration in a MiniPlant System.

Abstracts

Poster Presentation

2P-01 ～ 2P-64

July 15

2P-01

A robust and efficient process of HCV protease inhibitor key intermediate

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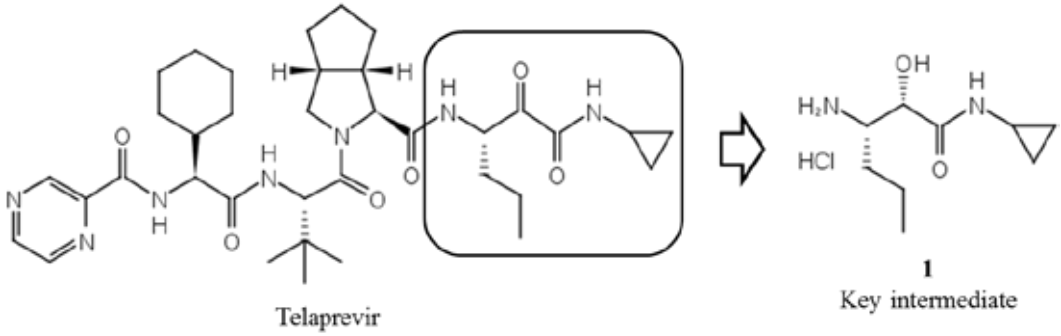
Hepatitis C, one of the worst widespread diseases in the world, causes both acute and chronic liver complications on the virus carriers. A hypodermic injection of pegylated INF-α used to be the standard treatment for hepatitis C infection for a decade. Recently oral administrable small molecular antivirals such as HCV NS3-NS4A protease inhibitor were developed and used for hepatitis C chemotherapy instead or combined with INF-α injection.

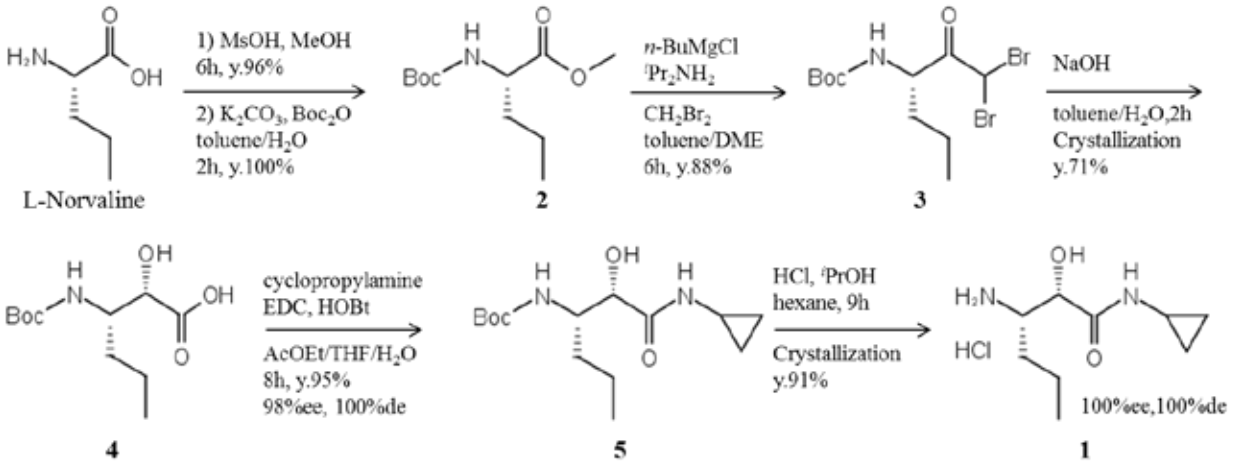
We have started on synthetic study of N-Cyclopropyl-3S-amino-2S-hydroxyhexanamide (Compound 1) as a key intermediate of Telaprevir, one of the pioneer HCV protease inhibitors, to develop a robust and efficient process for large scale commercial production.



Scheme 1. Chemical structure of Telaprevir and its key intermediate

First, we have developed a synthetic route to the Compound 1 utilized with a chiral pool method starting from L-Norvaline with the object of developing a scalable process swiftly (Scheme 1). Protected L-Norvaline (Compound 2) was reacted with dibromomethane anion to carry out functionalized one carbon extension. An alkaline hydrolysis followed by proton migration of Compound 3 afforded a desired diastereomer of Compound 4 predominantly (100%de, 98%ee). After amidation, Boc deprotection and crystallized purification, high quality Compound 1 HCl salt was obtained in 51% overall yield based on L-Norvaline.

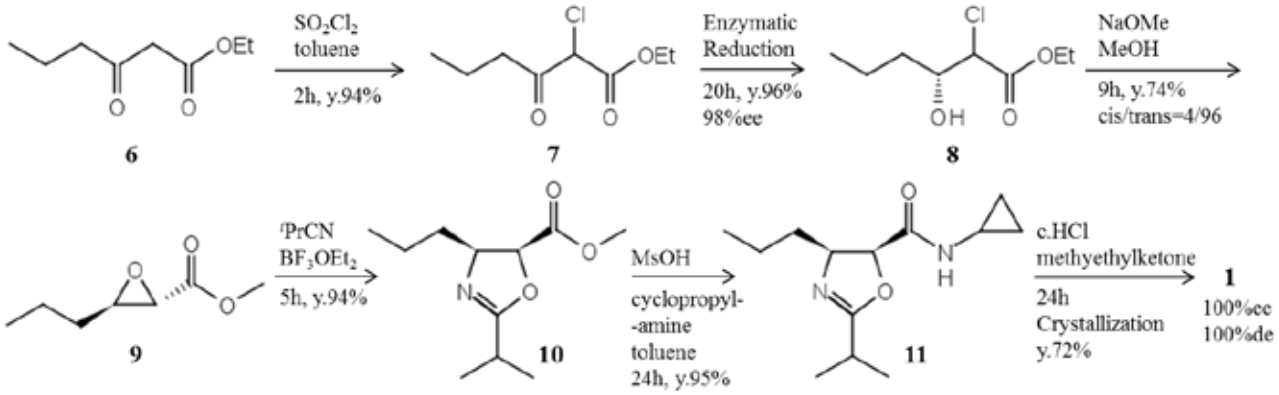
While we had been able to conduct commercial scale production of compound 1, the total efficiency utilizing this process was not enough satisfactory.



Scheme 2. Synthetic route of 1st generation process

We changed our interest to the development of another robust and economic process and finally developed a new route including asymmetric enzymatic reduction followed by Ritter type reaction in order to construct two carbon chiral centers with anti-configuration (Scheme 3). We chose Compound 6 as a commercially available starting material which contained all carbon atoms required for the target molecule carbon chain. After chlorination of compound 6, Compound 7 was converted to compound 8 by utilizing highly enantioselective enzymatic reduction (96%yield, 98%ee). A base treatment of Compound 8 with sodium methoxide promoted epimerization, epoxidation and transesterification to afford Compound 9 in a single step. In order to introduce an amino group at 3-position stereoselectively, we applied Ritter type reaction to the epoxide compound 9. Reaction of Compound 9 and isobutyronitrile proceeded to give an amino alcohol equivalent Compound 10. We also discovered a direct amidation method from Compound 10 to 11 with acid catalyst. High quality Compound 1 HCl salt crystal was produced applied with reactive crystallization by hydrolysis of Compound 11 with hydrochloric acid.

In this way, we succeeded to develop a novel and highly enamtio and diastereoselective process to the Telaprevir key intermediate from cheap starting material in high overall yield (43%), in which the only one isolation was included at the last step.



Scheme 3. Synthetic route of 2nd generation Process

2P- 02

Nitroxyl Radical and Imide Dual Catalyzed NaOCl Oxidation of Alcohols and the Application to a Drug Candidate

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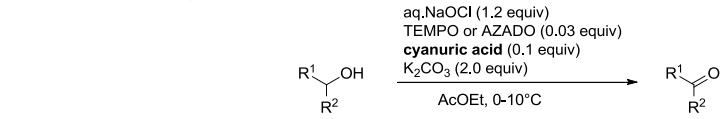
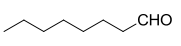
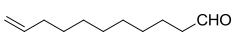
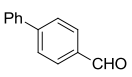
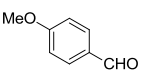
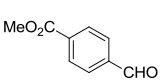
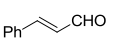
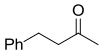
[Oxidation of Alcohols]

Since the selective oxidation of alcohols to the corresponding carbonyl compounds is one of the most significant and widely used transformations in synthetic organic chemistry, a number of useful methods have been developed. Among them, metal catalyzed systems using co-oxidants such as oxygen have recently attracted much attention due to the growing environmental requirement. However, trace metal contamination of products is especially a concern for pharmaceutical manufacturing. Meanwhile, the oxidation of alcohols by oxoammonium salts has also become a widely used non-metallic oxidation system. More commonly, alcohol oxidations using nitroxyl radical such as TEMPO and 2-azaadamantane *N*-oxyl (AZADO) are conducted in catalytic systems. Although these methods are useful in terms of the mild reaction conditions, some drawbacks remain from the viewpoints of scale-up synthesis such as safety, productivity and waste. To solve these issues, we have established a novel and practical alcohol oxidation system.

We examined the oxidation of a variety of primary and secondary alcohols with 1.2 equivalents of NaOCl in ethyl acetate and the presence of K_2CO_3, 3 mol% of nitroxyl radical and 10 mol% of cyanuric acid as an imide catalyst at 0-10°C (Table 1). As a result, aliphatic alcohols were oxidized to give the corresponding aldehydes in high yield even when the substrates had double bond which often suffers from chlorination. A wide range of benzylic alcohols bearing electron-withdrawing group or electron-donating group were also readily oxidized to give the corresponding benzaldehydes in high yield. Although the oxidation of

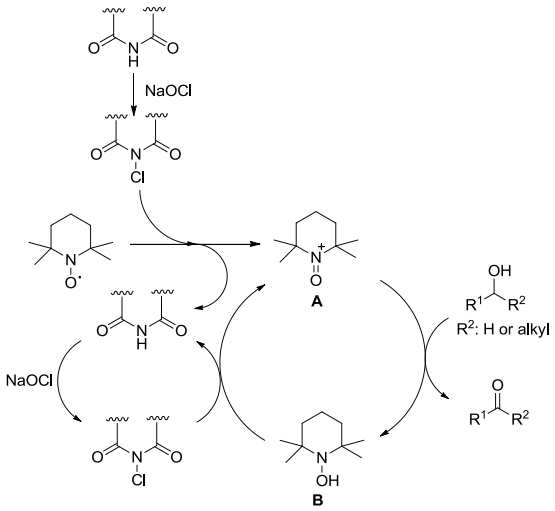
Table 1. Dual catalytic oxidation of alcohols



 91% (TEMPO, 4 h) 90% (TEMPO, 1 h)[a]	 90% (TEMPO, 4 h)	 97% (TEMPO, 8 h) 98% (TEMPO, 1 h)[a]	 89% (TEMPO, 3 h)
 86% (TEMPO, 3 h)	 88% (TEMPO, 7 h) 90% (AZADO, 2 h)	 95% (TEMPO, 6 h) 93% (TEMPO, 1 h)[a]	 56% (TEMPO, 6 h) 96% (AZADO, 3 h) 92% (AZADO, 1 h)[a]

a) Without K_2CO_3

secondary alcohol, 4-phenyl-2-butanol, with TEMPO did not obtain the corresponding ketone in sufficient yield, the oxidation went to completion within 3 hours when using AZADO, to afford the corresponding ketones in excellent yield. Furthermore, the reaction without K_2CO_3 was completed by dropwise addition of NaOCl with the reaction mixture remaining at >pH 7. A plausible catalytic dual redox cycle in the case of using TEMPO is postulated as shown in Scheme 1. NaOCl first reacts with the imide catalyst in the aqueous layer to produce *N*-chloroimide, which transfers to the organic layer. Then, the reaction of TEMPO with the resulting *N*-chloroimide affords the oxoammonium salt **A**. This salt reacts with alcohol to give the corresponding aldehyde or ketone and generates the hydroxylamine **B**, which is oxidized by *N*-chloroimide to regenerate the oxoammonium salt **A**.

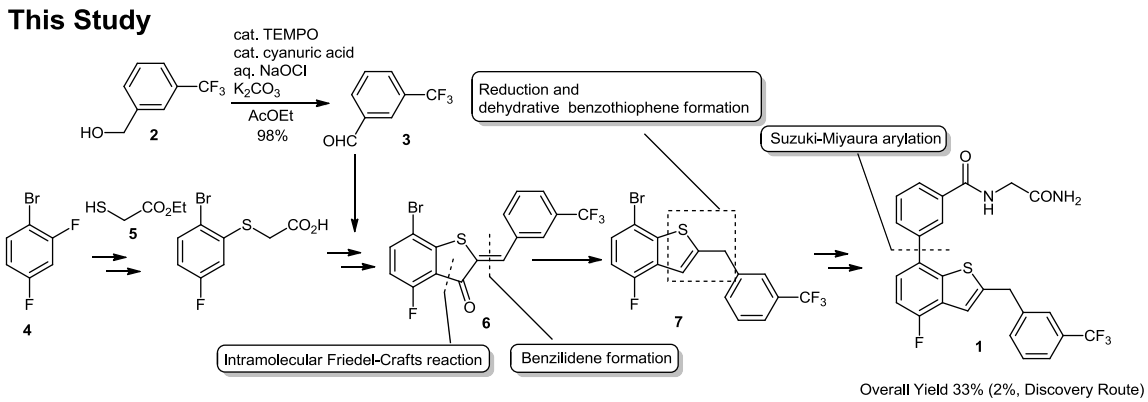


Scheme 1. Plaucible catalytic cycle

Since this reaction system is practical and does not require tedious operations such as preparing buffer solution or pH adjustment, it is thought to be applicable to scale-up synthesis.

[Process development of GPR52 agonist 1 by utilizing developed alcohol oxidation]

We have established a scalable and facile synthesis of GPR52 agonist **1** by utilizing a novel alcohol oxidation system mentioned above. 3-Trifluoromethylbenzylalcohol **2** was readily oxidized to give the corresponding aldehyde **3** as a synthetic intermediate in 98% yield. Hemithioindigo **6** was obtained by a regioselective sulfenylation of **4** with ethyl thioglycolate **5** and a subsequent benzilidene formation with **3**. **6** was directly converted to benzothiophene **7** by $NaBH_4$ reduction followed by H_2SO_4 dehydration. After that, **1** was finally afforded via Suzuki-Miyaura arylation followed by an amidation. This synthesis proceeds in ten chemical transformations with effective telescopic operations and four isolations of synthetic intermediates. The overall yield was dramatically improved to 33% from 2% in discovery synthesis.



Scheme 2. Synthesis of GPR52 agonist **1**

2P-03

Synthetic Study for Aristolochic Acids and its Derivatives

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Aristolochic acids (AA I, AA II) are plant alkaloid found in *Aristolochiaceae* which have been used as herbal traditional medicine. The compounds, however, are recognized as nephrotoxicity for human and their mutagenic property. Many mechanistic studies revealed that its *N*-hydroxamine metabolites form adducts with adenosine and guanosine (Figure 1). It has unique nitrated alkaloids. Also the mechanism seems quite unusual to form adduct with adenosine via metabolic activation.

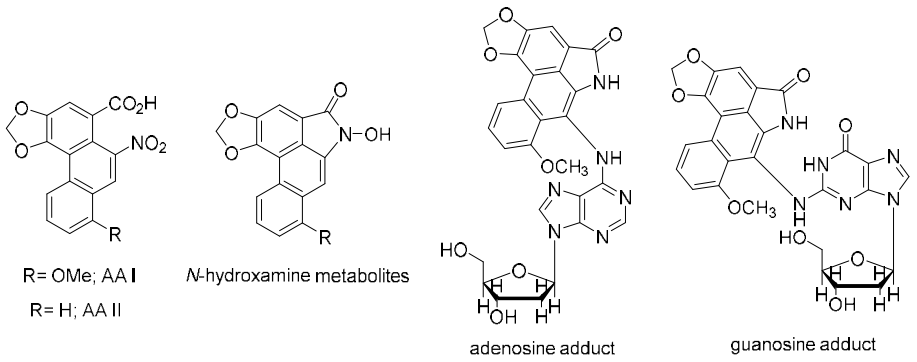
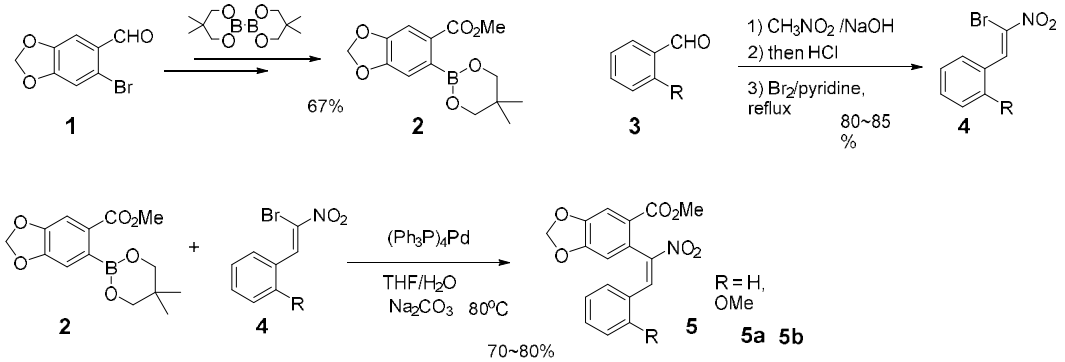


Figure 1

Although the compounds are commercially available and also possible to extract from natural resources, synthesis of many related compounds may contribute to understand this group of coupons.[1)] Thus we started synthetic study for Aristrochic acids and its derivatives.

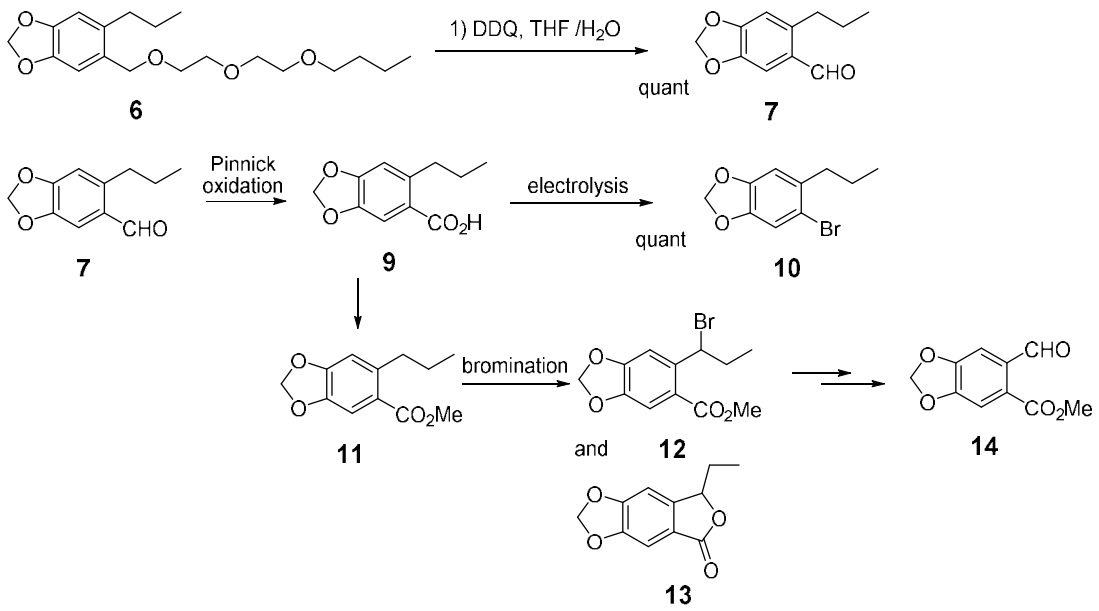


Scheme 2

Initial trial started with Suzuki coupling of **2** and **4** which were readily prepared from compound **1** and **3** respectively. The obtained compound **5a** and **5b** are interesting analog for AA I and II, which have stilbene

structure instead of phenanthrene. However, the compounds **5a** an **5b** did not afford cyclized AA I and II under several reaction conditions (photo reaction, oxidative condition, *etc.*).

Then we examined synthetic route from piperonyl butoxide **6** which is abundantly available from commercial source. The oxidative functionalization expected to lead efficient key compounds.



Scheme 3

Oxidaton of **6** with DDQ in THF/H_2O system afforded aldehyde **7** in quantitative yield. Then Pinnick oxidation of aldehyde **7** afforded carboxylic acid. The acid **9** was converted into bromide **10** by electrochemical bromination in quantitative yield. While esterified compound **11** was subjected to the electrolysis at room temperature, and bromide **12** was obtained in moderate yield with small amount of lactone **13**. When the NBS/benzoyl peroxide in CCl_4 system (standard bromination condition) was applied to the reaction the lactone **13** was main product. This may be due to higher temperature required to initiate radical reaction. The brominated compound **12** was readily converted into the aldehyde **14** which is key compound for total synthesis of AAI and II which was reported in very recently by Johnson *et al.*[2)]

We had run many reactions on these compounds. We shall discuss about conversion efficiency and nature of these group of substances from the view point of process chemistry.

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2) S. Attaluri, C.R.Iden, R.R.Bonala,F.Johnson *Chem.Res. Toxicol.* **2014**, 27, 1236-1242.

2P- 04

Kinetic Resolution of Secondary Alcohols by Chiral Phosphoric Acid Catalyt

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Of the many methods available to separate enantiomeric constituents from racemic materials, kinetic resolution offers distinct advantages, especially when a chiral catalyst is involved. Kinetic resolution separates enantiomers via unequal reaction rates of the enantiomers in a racemate. Optically pure substances are obtained by modulating the degree of conversion, even if the enantioselectivity of the reaction is low. Kinetic resolution of racemic alcohols by esterification is an important process in synthetic chemistry, and many artificial catalysts as well as enzymatic methods have been developed for this purpose. Their catalytic mechanisms are classified into two types: (1) enhancement of the nucleophilicity of alcohols as a metal alkoxide bearing a chiral ligand (Fig. 1, *class a*) and (2) in situ generation of chiral acylating reagents by nucleophilic chiral organocatalysts (Fig. 1, *class b*). As a new mechanistic class, we expect that a chiral Brønsted acid will activate the acylating agent by hydrogen bonding and simultaneously discriminate the enantiomers of alcohols (Fig. 1, *class c*). Herein we report the first kinetic resolution of secondary alcohols via chiral phosphoric acid-catalyzed acylation. This methodology provides effective access to optically pure alcohols, especially 2-arylcycloalkanols, which are structural motifs of biologically significant compounds, such as lycorine, epicatechin, PF-998,425, and L-733,060 .

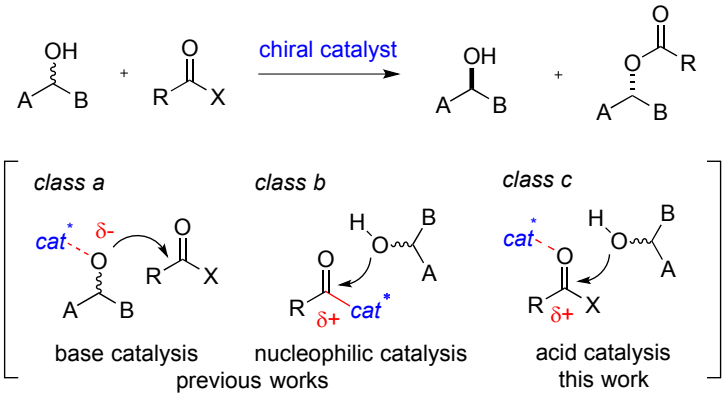

Figure 1. Activation and Enantiomer-Discrimination Modes in Acylation-based Kinetic Resolution of Secondary Alcohol.

(±)-*Cis*-2-arylcyclohexanol **1** was treated with isobutyric anhydride (**2**) in the presence of a catalytic amount of BINOL-derived phosphoric acid **3**, which was developed by Terada's and Akiyama's groups, in

chloroform at room temperature. After 48 h, enantiomerically enriched ester **4** was obtained along with the recovered starting material **1** with high enantiomeric excess. The *s* value was calculated to be 24. After further screening of the catalyst and reaction conditions, *s* value was finally increased to more than 200 even at room temperature (Figure 2). Details including substrate scope and mechanistic study will be discussed in the presentation.

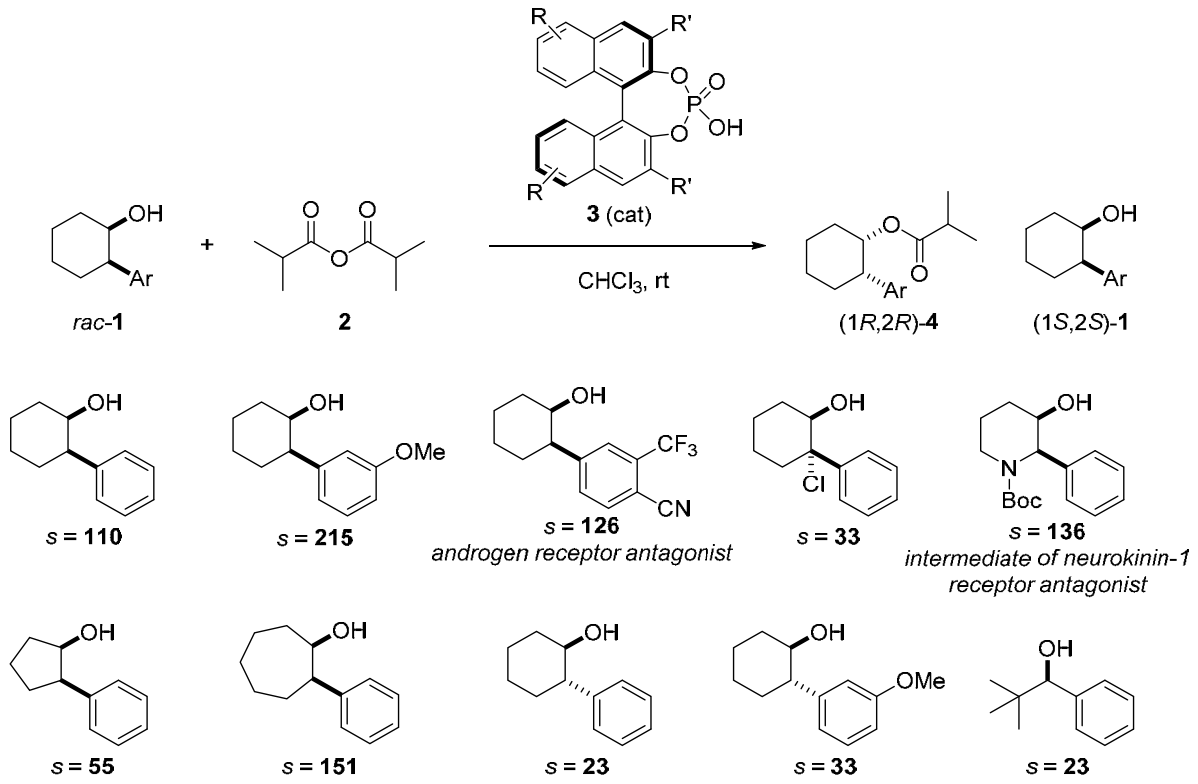

Figure 2. Kinetic resolution of racemic alcohols by phosphoric acid **3** (5 mol%).

Ref) Chiral Phosphoric Acid-Catalyzed Kinetic Resolution of Secondary Alcohols, Harada, S.; Kuwano, S.; Yamaoka, Y.; Yamada, K.; Takasu, K. *Angew. Chem. Int. Ed.* **2013**, 52, 10227-10230.

2P-05

Fermentation of squid pen for the production of tyrosinase inhibiors and insecticidal materials

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Tyrosinase (EC 1.14.18.1) is a multifunctional copper-containing enzyme that is widely distributed in fungi, plants, and animals and is responsible for melanin biosynthesis , as well as the browning reaction in fruits, vegetables or seafood , and human skin pigmentation abnormalities. In addition, tyrosinase is also an important enzyme in the process of insect moulting . Melanogenesis can be controlled by tyrosinase inhibition or by blocking the maturation processes of tyrosinase and its related proteins .

In this study , We use microorganisms fermentation of squid pen for the production of tyrosinase inhibiors and insecticidal materials.

Reports of tyrosinase inhibitors from microorganisms are rare. A tyrosinase inhibitor and insecticidal materials-producing bacterium, strain TKU026, was isolated from Taiwanese soil and identified as *Burkholderia cepacia.* Among the tested chitin-containing materials, squid pen best enhanced the production of tyrosinase inhibitors and insecticidal materials. The tyrosinase inhibitory activity (5,000 U/mL) and insecticidal activity (81 %) against Drosophila larvae was maximised after cultivation on 1 % squid pen-containing medium for 3 days. The tyrosinase inhibitory activity persisted even when the culture was treated with acidic or alkaline conditions of pH 3 or 11. The activities of both tyrosinase inhibitors and insecticide remained at 100 %, even after treatment at 100 _C for 30 min. The culture supernatant after 3 days of cultivation also showed antifungal activity against *Aspergillus fumigatus* and *Fusarium oxysporum* with maximal activities of 100 and 80 %, respectively, but no antibacterial activity against *Escherichia coli* was observed. The tyrosinase inhibitors were assumed to be polyphenolic compounds according to the results of chromatography.

2P- 06

Recyclable and Recoverable Magnetic Nanoparticle-Supported Iodoarene Catalysts for Oxidation of 4-Alkoxyphenols to Quinones

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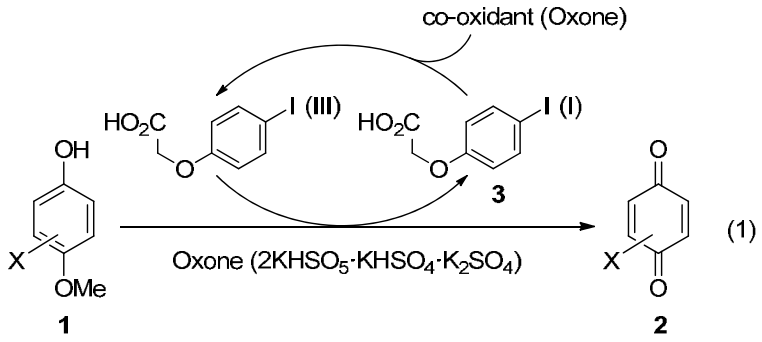
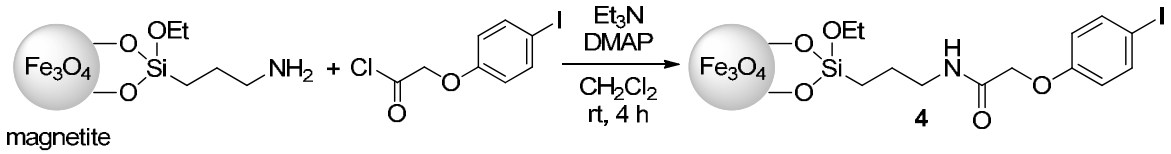
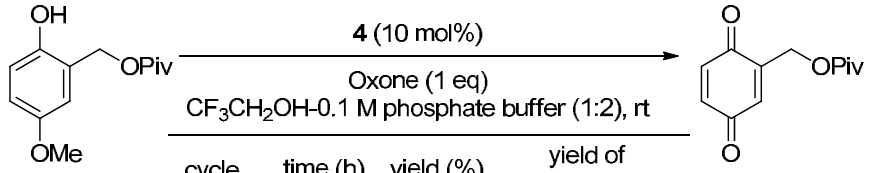
Hypervalent iodine compounds have been used extensively in recent organic synthesis because of their low toxicity, ready availability and easy handling. For the oxidation reaction, however, stoichiometric amounts of iodine reagents are usually required and produce equimolar amounts of organic iodine waste. Moreover, these reagents are very expensive and some of them are potentially explosive. A promising solution to these problems is a catalytic version of hypervalent iodine oxidation, in which only a catalytic amount of cheap and safe iodoarene is used. We recently developed a catalytic hypervalent iodine oxidation of 4-alkoxyphenols **1** to *p*-quinones **2** using a catalytic amount of 4-iodophenoxyacetic acid **3** with Oxone as a co-oxidant (eq. 1).[1] As a part of our study of the development of organocatalysts with great industrial potential, we herein report recyclable and recoverable magnetic nanoparticle-supported iodoarene catalysts **4** and **5**, which can be used for the oxidation of phenols **1** to *p*-quinones **2**.



Magnetic nanoparticles were chosen as the core support because of their simple synthesis, high reactivity, and easy recovery from the reaction.[2] We first synthesized silica-coated magnetite nanoparticles-supported iodoarene **4** by reaction of magnetite-supported 3-aminopropane,[3] derived from magnetite (Fe_3O_4) and 3-amiopropyltriethoxysilane, with 4-iodophenoxyacetyl chloride (Scheme 1). The oxidation of 2-pivaloyloxymethyl-4-methoxyphenols (**1a**) using 10 mol% of catalyst **4** in the presence of Oxone (1 eq) in CF_3CH_2OH−0.1 M phosphate buffer (1:2) gave the corresponding *p*-quinones **2a** in 91% yield. The catalyst **4** was readily recovered by the use of an external magnet (98% yield). This is the first example of a magnetic nanoparticle-supported iodoarene catalyst. However, the recovered catalyst **4** could be recycled only 3 times because cleavage of the silyloxy bonds would occur under the acidic conditions in the presence of Oxone.

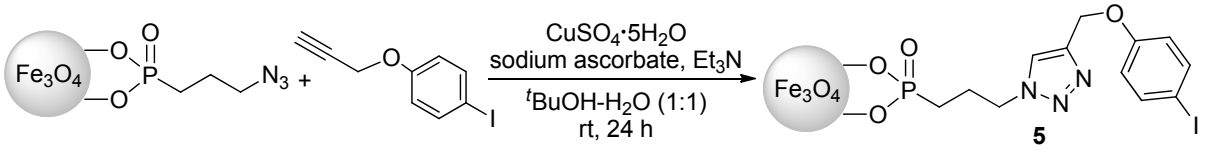


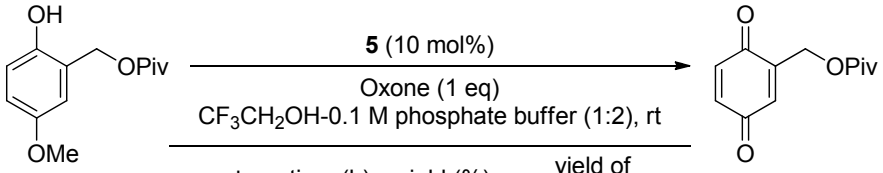


cycle	time (h)	yield (%)	yield of recov. cat. (%)
1	2	91	98
2	4	91	100
3	8	91	100
4	24	80	100

Scheme 1

We next examined the synthesis of the phosphonic acid-coated magnetic nanoparticles catalyst **5** because the phosphonic acid-coated particles remain stable under the highly acidic oxidizing conditions.[2] The catalyst **5** was prepared by Cu-catalyzed cycloaddition of magnetite-supported 3-azidepropyl-phosphonate[4] with 1-iodo-4-(prop-2-ynyloxy)benzene (Scheme 2). The oxidation of **1a** using 10 mol% of catalyst **5** under the same conditions gave **2a** in 80% yield. As had been expected, the recovered catalyst **5** could be recycled up to 7 times.





recycle	time (h)	yield (%)	yield of recov. cat. (%)
1	4	80	98
2	4	81	97
3	5.5	80	98
7	15	78	96
8	24	71	96

Scheme 2

References

1. (a) Yakura T., Tian Y., Yamauchi Y., Omoto M., Konishi T., *Chem. Pharm. Bull.*, **57**, 252–256 (2009).
(b) Yakura T., Omoto M., Yamauchi Y., Tian Y., Ozono A., *Tetrahedron*, **66**, 5833–5840 (2010).
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3. Fujita K., Umeki S., Yasuda H., *Synlett*, **24**, 947–950 (2013).
4. Chouhan G., Wang D., Alper H., *Chem. Commun.*, 4809–4811 (2007).

2P-07

Microbial reclamation of squid pen and shrimp shell

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Byproducts generated in high levels by marine processes have been recognized for their value as recyclable or reclaimable waste. Among the marine byproducts, shrimp shell, crab shell, and squid pen have the highest chitin content. The chemical treatments of these chitin-containing byproducts for preparing chitin and chitosan create waste disposal problems because neutralization and detoxification of the discharged wastewater are necessary. Therefore, the cost of chitin and chitosan preparations was far higher than those of their raw materials, marine chitin-containing byproducts. Chitin and chitosan have been widely used as the major carbon source of bacteria for producing chitinolytic enzymes. In 1997, the bifunctional chitinase/lysozymes from *Pseudomonas aeruginosa* K-187 using shrimp and crab shell as the sole carbon/nitrogen (C/N) source had first been reported. Thereafter, the use of squid pen as the only C/N source for producing enzymes and bioactive materials had also been studied. The utilization of shellfish chitin waste as the sole C/N source not only solves environmental problems, it decreases the production costs for microbial conversion. This review summarizes our recent research of microbial reclamation of these marine byproducts for producing enzymes and bioactive materials; the characterization and applications of these products were also studied.

2P- 08

Development of acid-catalyzed alkylating reagents based on triazine chemistry

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Background Benzyl 2,2,2-trichloroacetimidate (BTCAI) is a frequently used acid-catalyzed benzylating reagent[1)]. However, BTCAI is not convenient for routine use because of its instability and cost. Therefore, the development of a new acid-catalyzed benzylating reagent that can overcome these drawbacks is desired.

Concept for design of new reagents: For the development of a new acid-catalyzed benzylating reagent by exploiting the characteristics of imidate, we conceived the idea that the formal trimerization of the smallest unit of benzyl imidate leads to 2,4,6-tris(benzyloxy)-1,3,5-triazine (**TriBOT**[2)], Figure 1). It can be considered as the smallest benzyl imidate structure without any attachment. The π-electron deficient triazine ring of **TriBOT** would function as an electron-withdrawing group corresponding to the trichloromethyl group of BTCAI, which will enhance the reactivity of the leaving group. Moreover, the atom economy of **TriBOT** is better than that of BTCAI. The specific features of **TriBOT** are summarized in Table 1.

Figure 1. Design of TriBOT

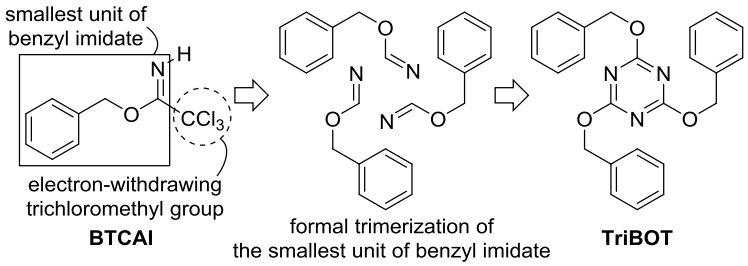


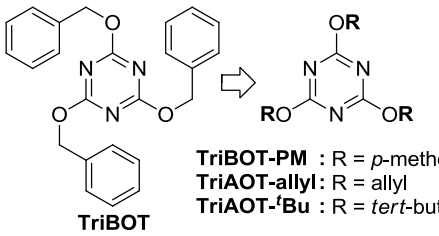
Table 1. Comparison with BTCAI

	BTCAI	TriBOT
stability	sensitive to moisture and heat	stable in the air
form	liquid	crystalline solid
leaving group (per benzyl group)	C_2HCl_3NO (MW: 161.4)	CNO (MW: 42)

In this presentation, we will report various triazine-based alkylating reagents; a *p*-methoxybenzylating reagent **TriBOT-PM**[3)]; an allylating reagent **TriAOT-allyl**; and a *tert*-butylating reagent **TriAOT-^{t}Bu**, as well as **TriBOT**.

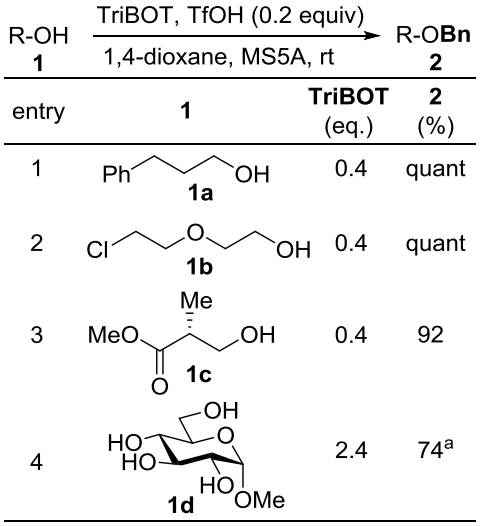
All the reagents could be easily synthesized from the corresponding inexpensive alcohols and cyanuric chloride in one step, and are nonhygroscopic materials without irritating or allergenic properties, and stable in the air at room temperature.

Figure 2. Triazine-based alkylating reagents



Benzylation using TriBOT[2] Reaction of **1a** with **TriBOT** (0.4 equiv) and TfOH (0.2 equiv) in 1,4-dioxane with MS5A (a dehydrating agent to remove residual moisture) at room temperature gave the corresponding benzyl ether in an excellent yield (Table 2, entry 1). Alkali-labile alcohols **1b** and **1c** were benzylated in excellent yields under the same conditions (entries 2 and 3). No racemization was observed during the reaction of **1c**. Importantly, the benzylation of highly polar methyl α-D-glucoside **1d** afforded corresponding tetrabenzylated derivative in 74% yield (entry 4).

Table 2

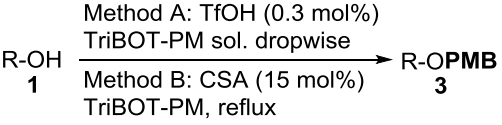


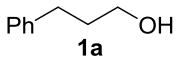
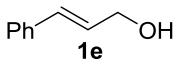
entry	1	TriBOT (eq.)	2 (%)
1	**1a**	0.4	quant
2	**1b**	0.4	quant
3	**1c**	0.4	92
4	**1d**	2.4	74[a]

a) TfOH (0.8 equiv) was used.

***p*-Methoxybenzylation using TriBOT-PM**[3] Two methods have been developed for the reaction: dropwise addition of a solution of **TriBOT-PM** (0.37 equiv) to a reaction mixture of an alcohol and 0.3 mol% of TfOH at room temperature (Method A), refluxing a mixture of an alcohol, an excess of **TriBOT-PM** (0.6 equiv) and (+)-10-camphorsulfonic acid (CSA) (Method B). The reaction of **1a** by Method A afforded the corresponding PMB ether **3a** in 94% yield (Table 3, entry 1). However, the reaction of cinnamyl alcohol **1e** resulted in 66% yield under the same conditions (entry 2). In the latter case, the reaction yield was improved to 85% by Method B. Therefore, Method A can be considered as a high-atom-economy and time-saving procedure, and Method B as a procedure under milder conditions for acid labile substrates.

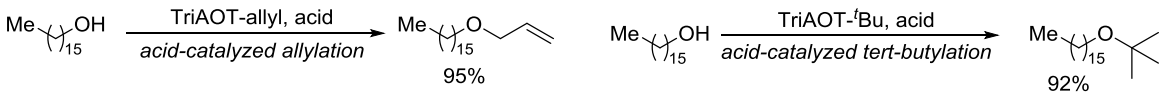
Table 3



entry	1	Method	3 (%)
1	 **1a**	A	94
2	 **1e**	A	66
3		B	85

Allylation using TriAOT-allyl and *tert*-butylation using TriAOT-^{t}Bu Allylation and *tert*-butylation of alcohols using **TriAOT-allyl** and **TriAOT-^{t}Bu** have been also found to proceed under similar conditions; the details of these reactions will be discussed (Scheme 1).

Scheme 1. Allylation using TriAOT-allyl and *tert*-butylation using TriAOT-^{t}Bu



Conclusion Based on the chemistry of π-electron deficient triazine, we have developed various acid-catalyzed alkylating reagents, which are superior to the conventional reagents with respect to atom economy, stability, and cost. These reagents can be used for the alkylation of various functionalized alcohols.

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2P- 09

One-Pot Transformation of Arenes into Aromatic Nitriles under Metal-Cyanide-Free Conditions

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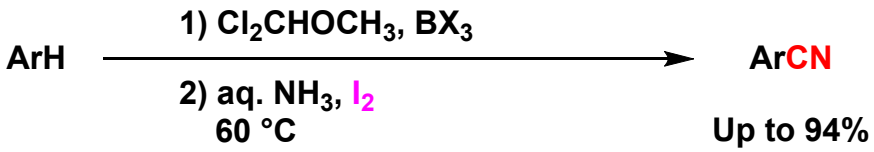
Introduction

Aromatic nitriles are some of the most important compounds for organic synthesis. They are intermediates in the synthesis of aromatic amides, carboxylic acids, amines, aldehydes, ketones, and nitrogen-containing heterocycles such as tetrazoles, imidazoles, oxazoles, thiazoles, and selenazoles. Moreover, some important pharmaceuticals are aromatic nitriles, and examples include Citalopram hydrobromide (treatment of alcohol dependency), Periciazine (antipsychotic drug), Fadrozole (oncolytic drug), Letrozole (breast cancer therapy), Bicalutamide (prostate cancer and breast cancer therapy), and Etravirine (anti-HIV). 4-Cyano-4′-pentylbiphenyl is one of the typical liquid-crystal materials. The most well-known methods for the preparation of aromatic nitriles include the dehydration of primary aromatic amides with $SOCl_2$, TsCl/pyridine, P_2O_5, $POCl_3$, $COCl_2$, or Ph_3P/CCl_4, and the Sandmeyer reaction, which requires aromatic diazonium halides and toxic CuCN. However, these reactions require toxic metal cyanides and/or expensive rare metals, such as Pd, and high temperatures. Electron-rich aromatics underwent a Vilsmeier–Haack reaction with $POCl_3$ and DMF, and this was followed by treatment with molecular iodine and aq. ammonia to give the aromatic nitriles in good yields. The reaction is very useful, because it can be used for the one-pot introduction of a cyano group into rather electron-rich arenes under mild reaction conditions, such as at room temperature or with warming temperature, without using metal cyanides. However, there are still disadvantages. However, there are still disadvantages. For example, the introduction of a cyano group into *m*-xylene, benzothiophene, or naphthalene is difficult, because the initial Vilsmeier–Haack reaction of those arenes with DMF and $POCl_3$ does not occur efficiently. Thus, we report a mild one-pot transformation of arenes into the corresponding aromatic nitriles by treatment with dichloromethyl methyl ether and boron reagent, followed by reaction with molecular iodine and aq. ammonia.

General Procedure

A solution of arene (1.0 mmol) in CH_2Cl_2 (3.0 mL) or $ClCH_2CH_2Cl$ (3.0 mL) was added to a solution of dichloromethyl methyl ether (1.2 equiv.) and Boron reagent (1.2 equiv.) in CH_2Cl_2 (1.0 mL) or $ClCH_2CH_2Cl$ (1.0 mL) at room temperature, and the mixture was stirred for 0.5–25 h at -50–40 °C, depending on the substrates. Then, NH_3 (28% aq.; 4.0 mL) and iodine (2.5 equiv.) were added to the reaction mixture, and the resulting mixture was stirred at 60 °C. The reaction mixture was quenched with satd. aq. Na_2SO_3 (10.0 mL). The mixture was extracted with AcOEt (3 × 20 mL), and then the combined organic extracts were dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by short column chromatography on silica gel to give the corresponding aromatic nitriles. This method could be used for semi-large scale preparation of aromatic nitriles from arenes.

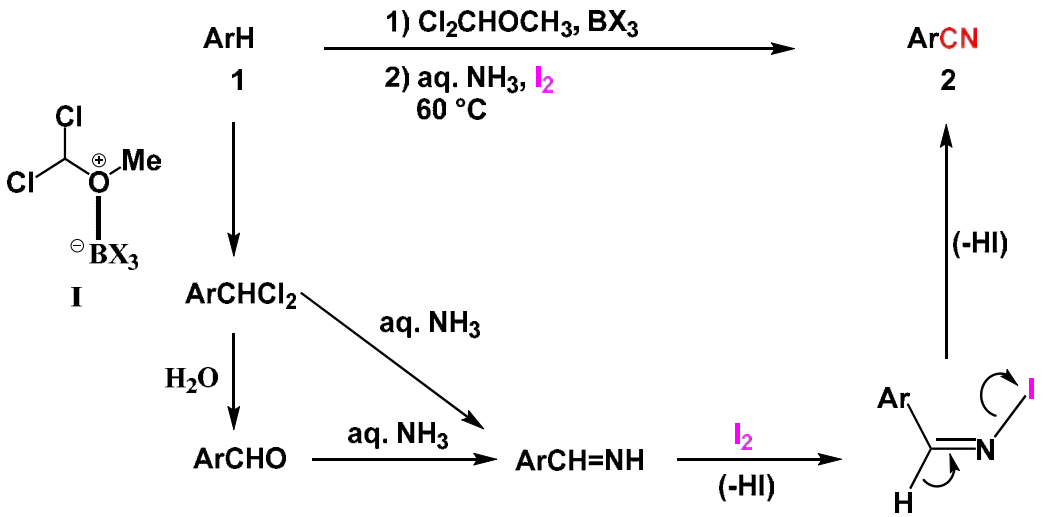
Scheme 1. **Introduction of Cyano Group into Arenes**



Possible Reaction Mechanism

The electrophilic species (I) formed from the reaction of dichloromethyl methyl ether with boron reagent reacts with aromatic ring by S_EAr pathway. The resulting (dichloromethyl) arene reacts with aq. ammonia to form an aromatic imine. Once the imine is formed, it smoothly reacts with molecular iodine to form the *N*-iodoimine. Subsequent elimination of HI takes place to give the aromatic nitrile.

Scheme 2. **Reaction Mechanism.**



Reference

T. Tamura, K. Moriyama, H. Togo. *Eur. J. Org. Chem,* 2023 (**2015**)

2P- 10

Development of standard solution for qNMR

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AQARI (Accurate QuAntitative NMR with Internal reference substance) has been recently applied to purity determination of the official analytical method such as the Japanese Pharmacopoeia and Japan's Specifications and Standards for Food Additives because of absolute purity determination method with traceability to the International System of Units (SI). A large number of reference materials for AQARI are being distributed in the commercial market by reagent makers. In addition, it has been reported that AQARI with standard solution was able to conduct absolute quantitation with accuracy of approximately less than or equal to 1% without using high-resolution[1)] However, standard solution suitable for AQARI with guaranteed concentration is not currently being distributed.

For this reason, we have developed standard solution suitable for AQARI named as DSS-d6 Standard Solution (500 mg/l Deuterium Oxide Solution) with SI- traceability and expanded uncertainty(Table1). This standard solution is suitable for AQARI because of having singlet signal around 0 ppm.

Table 1. Standard Solution for qNMR

Wako Cat. No.	Product Name	Grade	Pkg. Size
041-33641	DSS-d_6 Standard Solution (500mg/L D_2O)	for qNMR	1ml×5A

1) Taichi Yamazaki, Takeshi Ohtsuki, Toru Miura, Takako Suematsu Naoki Sugimoto et al., Bunsekikagaku, Vol. 63 (2014) No. 4 p. 323-329.

2P- 11

Revisiting Acetyl Group Technology: Lipase-catalyzed Regioselective Transformation of Polyphenols

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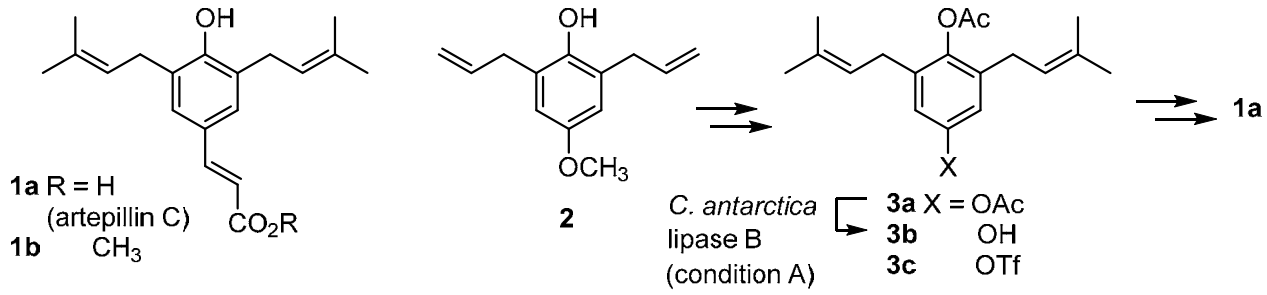
Development of synthetic approaches to physiologically active but less available polyphenols, starting from readily available starting materials, especially from naturally abundant resources, is industrially very important. Although acetyl protective groups are rather labile in polyphenols, the regioselective transformation under mild conditions enables a short-cut in synthetic routes. Herein we report several examples with an emphasis on lipase-catalyzed reactions as the key steps.

Artepillin C (**1a**), a diprenylated *p*-hydroxycinnamate was isolated from Brazilian propolis and exhibits antioxidative and antitumor activities. We planned the synthesis of **1a** from readily available 2,6-diallylphenol **2** [1]. Replacement of allyl groups with prenyl groups by Grubbs' technology and the subsequent transformation yielded diacetate **3a**. *Candida antarctica* lipase B (Novozym 435)-catalyzed transesterification in 2-propanol (condition A) at room temperature worked on only one acetyl group to produce **3b**. So far, it has been reported that such reaction predominantly occurred on sterically less hindered phenyl acetates [2]. Palladium-mediated alkenylation of triflate **3c** with methyl acrylate [3] afforded **1b**, and the following hydrolysis of ester protective groups efficiently provided **1a**.

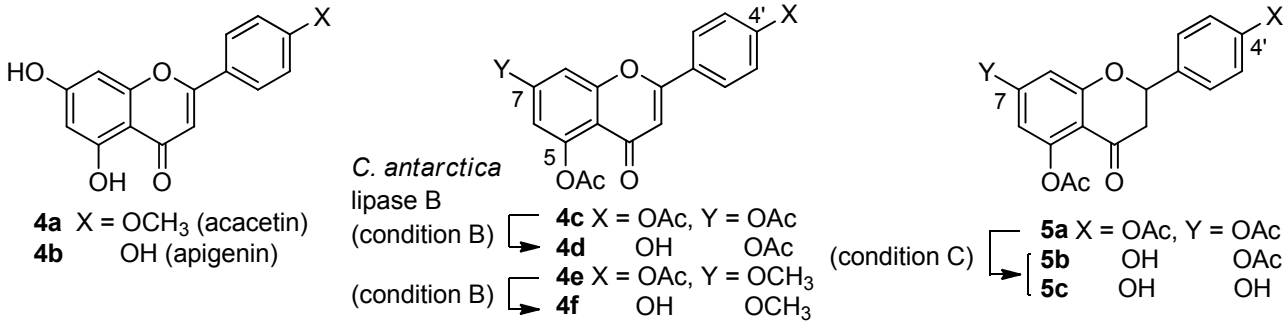


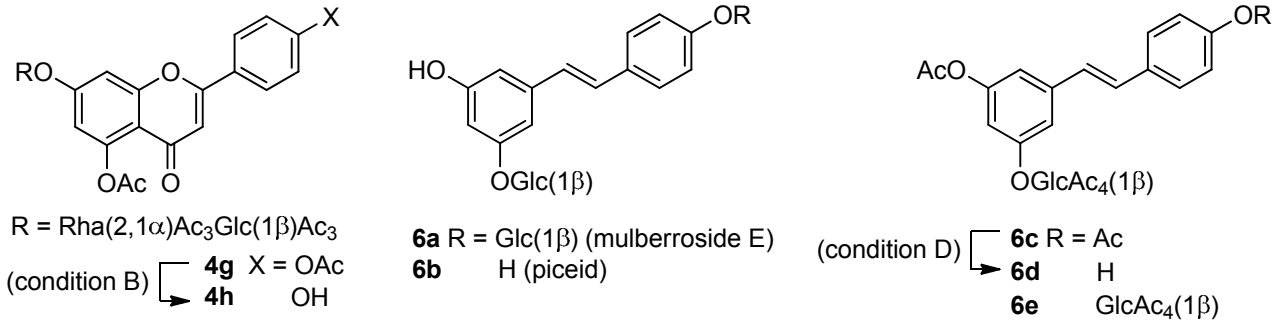
Acacetin (**4a**) has been reported to induce melanogenesis [4] and is expected for the treatment of grey hair. Apigenin triacetate (**4c**), which was prepared from rhoifolin **4g** via **4b**, was treated with *C. antarctica* lipase B with 2-propanol in THF at 22 °C (condition B). Deacetylation of C-4' acetate selectively proceeded, while leaving C-7 and C-5 acetates intact to give **4d**.

It was contrasting with the previous observation that only poor regioselectivity was shown between C-4' and C-7 acetates in closely related substrate **5a** by the same lipase with cyclopentanol in cyclopentyl methyl ether (condition C) to a mixture of **5b** and **5c** [5]. In the case of **4c** as substrate, even at elevated temperature as high as 65 °C in dioxane, the reaction almost stopped at the step of **4d**. Methylation of

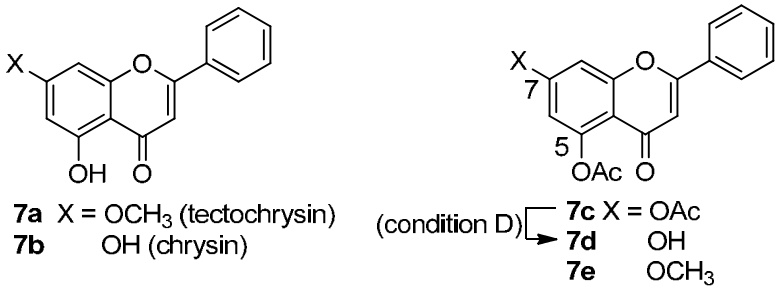
free C-4' hydroxy group resulted **4e**, diacetylated form of acacetin. The deacetylation of genkwanin acetate (**4e**) and rhoifolin octaacetate (**4g**) under condition B smoothly proceeded at C-4' to afford **4f** and **4h**, respectively.

Mulberroside E (**6a**) would be synthesized from piceid (**6b**) by using above-mentioned transesterification. When acetate **6c**, which was obtained by acetylation of **6b**, was treated with *Burkholderia cepacia* lipase (Amano PS-IM) and 2-propanol in THF at 22 °C, the reaction worked on only C-4' acetyl group to produce **6d** (condition D). Glycosylation of **6d** with a hydroxy group progressed efficiently to provide **6e**. Now the optimization of reaction conditions for hydrolysis of **6e** is under way.





Tectochrysin (**7a**) has been isolated from Nepalese propolis with inhibitory activity on melanogenesis [6]. Application of the lipase-catalyzed transesterification on diacetate (**7c**) of easily available chrysin (**7b**) under harsh conditions (D, cyclopentanol in dioxane, at 65 °C) resulted in **7d**, with deacetylation of C-7 acetate while leaving C-5 acetate intact. Methylation of free C-7 hydroxy group of **7d** furnished **7e**, which was followed by the deprotection to afford **7a**.



[1] *Yakugaku Zasshi* **1950**, *70*, 30. [2] *Tetrahedron Lett.* **2007**, *48*, 8334. [3] *J. Org. Chem*. **2002**, *67*, 2355. [4] *J. Nat. Med.* **2013**, *67*, 705. [5] *J. Mol. Catal. B: Enz.* **2013**, *92*, 14. [6] Abstract papers of the 60th annual meeting of the Japanese Society of Pharmacognosy, Sapporo, **2013**, p. 246.

2P- 12

Robust and Competitive Process Development of a Key Building Block for Anti-AIDS Drugs by Secondary Amine Catalyzed Enantio- and Diastereo-Selective Direct Cross Aldol Reaction

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A bis-tetrahydrofuranyl moiety has been utilized in the design of a number of potent HIV protease inhibitors. Much effort has been devoted to the synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro [2,3-*b*]furan-3-ol **7** or 1-({[(3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yloxy]carbonyl}oxy)pyrrolidine-2,5-dione **1**[1]. However, further improvement of the synthetic method and process is still required from an industrial point of view.

In our previous study[2], a practical method for the synthesis of **7** using a proline catalyzed enantio- and diastereo-selective direct cross aldol reaction as the key reaction was developed (Fig. 1). This method was successfully scaled up and proven to be environmentally benign. However, there was still room for improvement especially from an economical point of view. Benzyloxyacetaldehyde **10** is rather expensive because of its synthetic difficulty. More problematic is the moderate diastereoselectivity in the proline catalyzed aldol reaction, necessitating an additional redox process to obtain a single diastereomer.

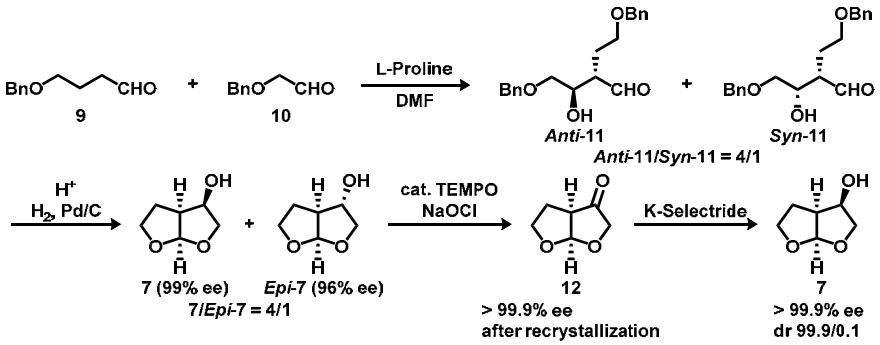

Fig. 1 Synthesis of 7 using a proline catatalyzed direct cross aldol reaction

In 2010, Hayashi's group reported a highly enantio- and diastereo-selective direct cross aldol reaction of polymeric ethyl glyoxylate with aldehydes using diaryl prolinol catalyst[3]. Ethyl glyoxylate is a relatively inexpensive aldehyde and easy to handle in its polymeric form, thus we regard this highly stereoselective reaction as a promising candidate for an efficient construction of stereocenters of **1**.

Herein, we report a robust and competitive synthetic method of **1** from an industrial point of view using the above mentioned asymmetric cross aldol reaction as the key step (Fig. 2). This efficient process has been developed based on the findings from our detailed investigation on the mechanism of each reaction, especially that of the key step.

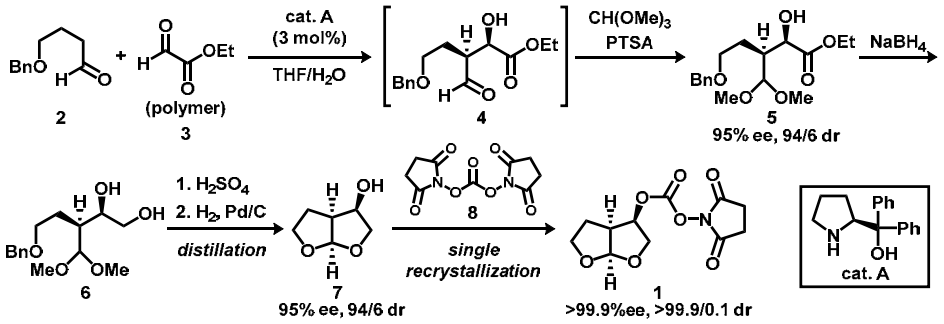

Fig. 2 Improved synthesis using diphenylprolinol catalyt as a key reaction

Ethyl glyoxylate **3** is commercially available in its polymeric form as a toluene solution. It is a great synthetic advantage of Hayashi's report that a commercially available polymeric ethyl glyoxylate can be directly used without pyrolysis for the aldol reaction. We found that the degree of polymerization of ethyl glyoxylate differs from its manufacturer and lots, which dramatically affected the reaction rate of this asymmetric aldol reaction. We also found that a small amount of glyoxylic acid is presented in commercial polymeric ethyl glyoxylate, which greatly influences the reaction rate and yield. These issues could constitute a significant handicap for a stable commercial production. Various studies indicated that stirring polymeric ethyl glyoxylate in toluene solution with water for an appropriate period before aldol reaction was very effective to ensure the reaction with great reproducibility.

In addition, we found the desired product **4** reacted with **cat. A** to give the corresponding adduct, which was inactive for the following acetalization. Intensive studies revealed that **4** could be recovered from this adduct by adding methanol to the reaction mixture.

Under the above mentioned optimized conditions, the desired product **5** could be surely obtained in around 85% yield from **2**, with 95% ee and 94/6 dr. Acetal **5** was successfully transformed to the final product **1** in a practical way, as shown in Fig. 2. Diol intermediate **6** was obtained by reduction of **5** with $NaBH_4$ in quantitative yield. Acetal exchange reaction followed by hydrogenation with Pd/C catalyst afforded crude **7** in around 95% yield over 2 steps. No purification was needed before the distillation of crude **7**. The condensation reaction of **7** with **8** afforded almost pure crystalline **1** (>99.9/0.1 dr, >99.9% ee) after single recrystallization.

In summary, we have developed a robust and competitive synthetic process of **1** compatible with industry using secondary amine catalyzed enantio- and diastereo-selective cross aldol reaction of polymeric ethyl glyoxylate with an aldehyde as the key reaction.

References

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

2) Ikemoto, T.; Y. Watanabe, Y; Tomokawa, J; Kawakami, T.; Uekita, Y.; Kurimoto, I. *Proceedings of the 1st International Symposium on Process Chemistry* **2008**, 92.

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2P- 13

Synthesis of the GHI Fragment of Gymnocin-B

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Gymnocin-B is a polycyclic ether marine toxin isolated from a red-tide dinoflagellate *Karenia mikimotoi*. The structure is characterized by 15 fused ether ring system, which is the second longest among the known marine polycyclic ethers. Although several synthetic studies were reported, total synthesis of this large molecule have not been achieved until now. We report herein the synthesis of the GHI fragment of Gymnocin-B using an oxiranyl anion convergent strategy.

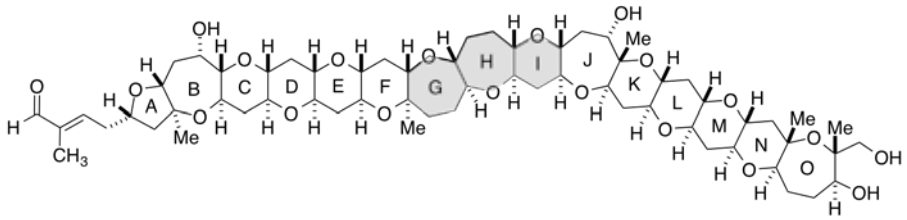
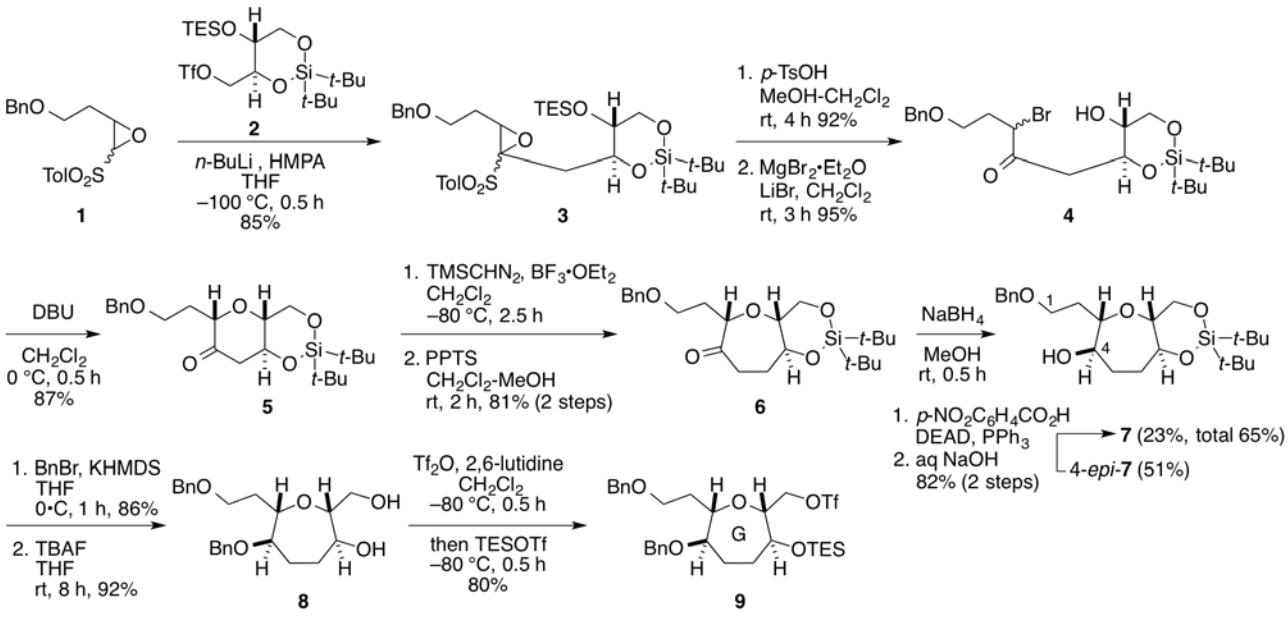


Figure 1. Gymnocin-B

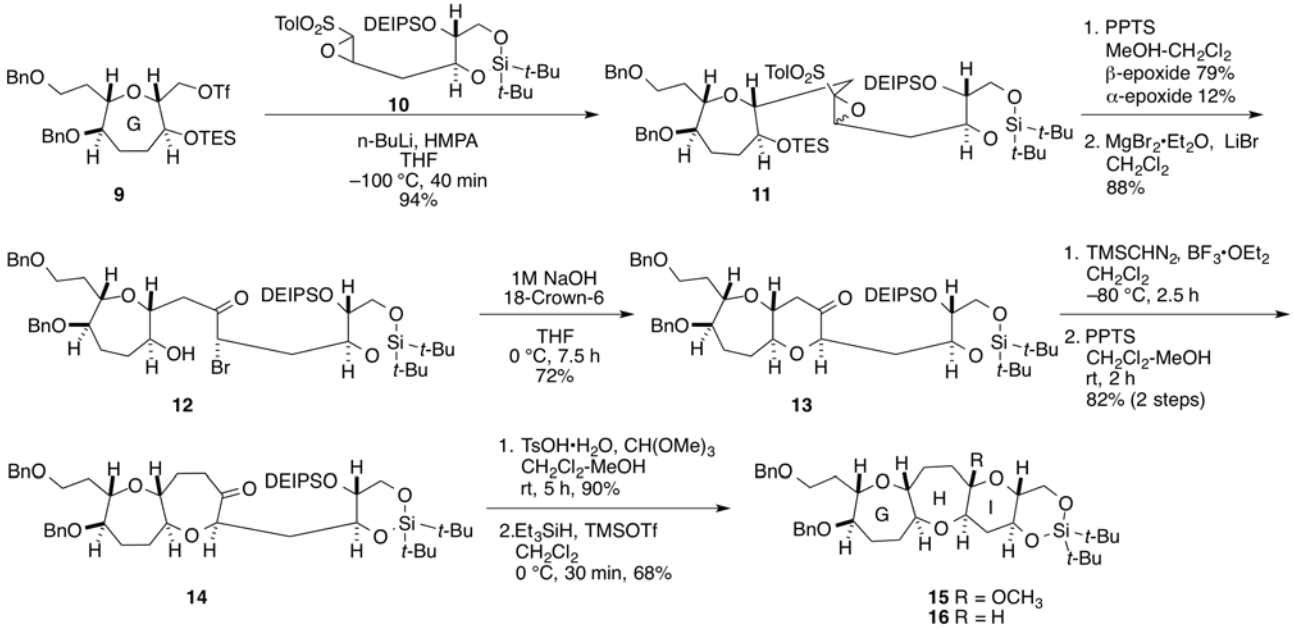
Synthesis of the G ring triflate **9** is shown in Scheme 1. Lithiation of epoxysulfone **1** with *n*-BuLi generated oxiranyl anion, which was alkylated *in situ* with triflate **2** at –100℃ to give the coupling product **3**. Removal of the TES group followed by epoxide-opening reaction with $MgBr_2$•OEt_2 afforded bromoketone **4**.



Scheme 1. Synthesis of the G ring triflate **9**

The DBU-mediated cycloetherification furnished the six-membered ketone **5** as a single diastereoisomer, which underwent the ring expansion with $TMSCHN_2$ in the presence of BF_3•OEt_2 to give the seven-membered ketone **6**. $NaBH_4$ reduction of ketone **6** afforded the desired secondary alcohol **7** in 23% yield along with the stereoisomer 4-*epi*-**7** in 51% yield. The undesired major isomer was inverted to **7** by the Mitsunobu reaction. Subsequent benzylation and removal of the silylene group afforded diol **8**, which was then converted to the G ring triflate **9** by a one-pot process of triflation and TES protection.

Oxiranyl anion coupling between the G ring triflate **9** and epoxysulfone **10** afforded product **11** in 94% yield (Sheme 2). After removal of the TES group, two diastereomers were separated by column chromatography. A bromoketone formation from the major β-epoxide with $MgBr_2$•OEt_2 was finished at –15 °C in 0.5 h, while the minor α-epoxide required higher temperature and longer reaction time (0 °C, 24 h). Interestingly, both diastereomers afforded the same bromoketone **12**, which would be a more thermodynamically stable than the other. Although the DBU-mediated cyclization resulted in a poor yield, cyclization of **12** with 1 M NaOH afforded the six-membered ketone **13** in good yield. The ketone **13** was then subjected to ring expansion reaction as described for **5** to give the seven-membered ketone **14**. Cleavage of the TBS group and the subsequent acetalization were carried out in one-pot to give methyl acetal **15**. Finally, reductive etherification of the methyl acetal with Et_3SiH/TMSOTf afforded the tricyclic GHI fragment **16** in good yield.



Scheme 2. Synthesis of the GHI fragment **16**

References

1) Sakai, T.; Sugimoto, A.; Mori, Y. *Org. Lett*. **2011**, *13*, 5850–5853.

2) Sakai, T.; Sugimoto, A.; Tatematsu, H.; Mori, Y. *J. Org. Chem*. **2012**, *77*, 11177–11191.

Addition Reaction to Isoquinolium Salts Catalyzed by Tetracyanocyclopentadienides

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Tetracyanocyclopentadienides ($C_5R(CN)_4^-$) are one of the superacid conjugate bases strongly stabilized by four cyano groups and aromaticity of Cp ring. These characteristic pentagonal anions have a substituent R which can be directly functionalized, while direct modification of representative superacid anions (ClO_4^-, $CF_3SO_3^-$, BF_4^-, PF_6^-, etc) are difficult. We previously disclosed that $C_5R(CN)_4$ salts could be synthesized from tetracyanothiophene and sulfones, and the synthetic method is efficient to prepare various salts.[1] As an application study, we herein report the $C_5R(CN)_4$-catalized addition reactions to isoquinolium salts.

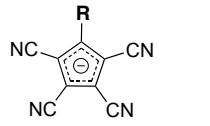
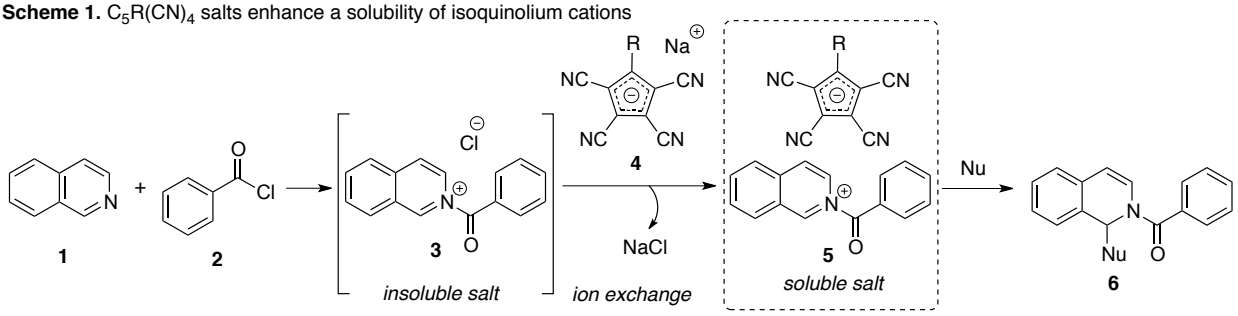


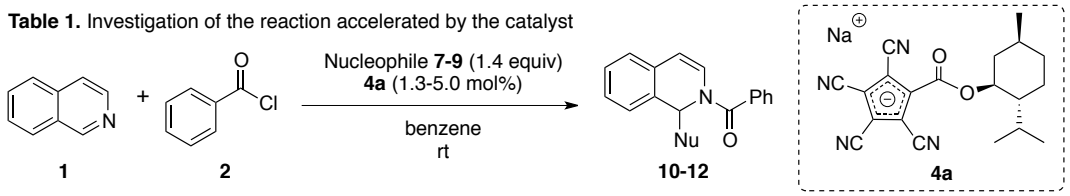
Figure1. $C_5R(CN)_4$ anion

Scheme 1. $C_5R(CN)_4$ salts enhance a solubility of isoquinolium cations



$C_5R(CN)_4$ salts are soluble in various organic solvents. We therefore hypothesized that $C_5R(CN)_4$ salts could enhance the solubility of cationic reactants through anion-exchange. In a non-polar solvent, isoquinoline **1** and benzoyl chloride **2** produce an insoluble isoquinolium chloride **3** (Scheme 1). Addition of catalytic amount of Na[$C_5R(CN)_4$] **4** promotes the anion-exchange between the chloride ion and the $C_5R(CN)_4$ anion to form a soluble isoquinolium•$C_5R(CN)_4$ salt **5**. The isoquinolinium salt **5** is expected to

Table 1. Investigation of the reaction accelerated by the catalyst

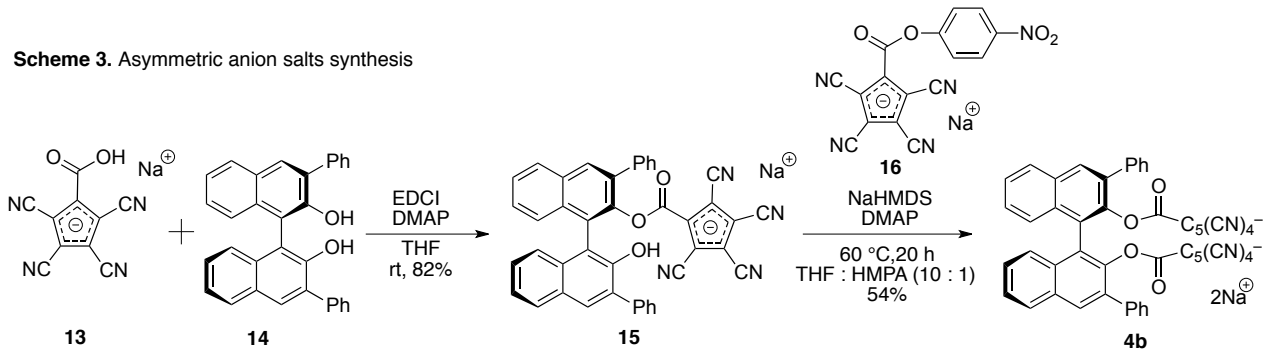


Entry	Nucleophile		4a	Time		Yield
1	$SnBu_3$	**7**	5.0 mol %	2 h	**10**	88%
2		**7**	–	24 h	**10**	91%
3	$OSiMe_3$	**8**	1.3 mol%	8 h	**11**	86% (dr = 55:45)
4		**8**	–	24 h	**11**	0%
5	OTBS	**9**	2.0 mol%	18 h	**12**	95%
6		**9**	–	27 h	**12**	0%

have a high reactivity toward various nucleophiles in addition reactions to produce product **6**. Superacid anions are advantageous for this reaction system because they have a very low nucleophilicity.

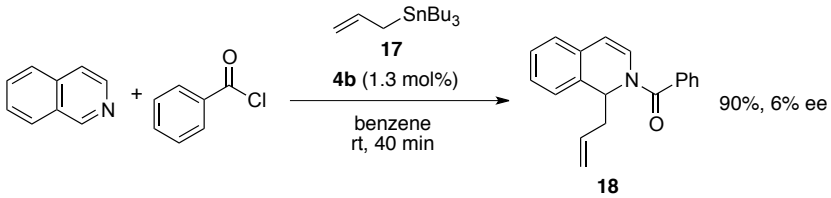
For the investigation of catalytic activity of **4**, we selected the menthoxy carbonyl derivative **4a** because it showed a high lipophilicity. A suspension of isoquinolium salt **3** in benzene was prepared *in situ* from **1** and **2**, and subsequent addition of 5 mol % of **4a** and allyl(tributyl)stannane **7** provided **10** as the sole product after 2 h (Table 1, entry 1). In the absence of **4a**, the reaction time was prolonged to 24 h (entry 2). When silyl enol ethers **8** and **9** were employed, the addition products **11** and **12** were obtained in good yields after 8-18 h with use of only 1.3-2.0 mol % of **4a** (entries 3 and 5). Silyl enol ether addition reactions did not proceed without the catalyst after 24 h (entries 4 and 6). In the case of allyl(trimethyl)silane, any addition product was not obtained because of its low reactivity. Instead, benzoic anhydride was obtained after quenching the reaction with aqueous sodium bicarbonate solution. The benzoate anion formed by alkaline hydrolysis of **2**, a weaker acid anion, was easily and quickly captured by **5** to give benzoic anhydride.

Scheme 3. Asymmetric anion salts synthesis



Since salt **4** proved to have a catalytic activity, our next attention was focused on the asymmetric reaction. Carboxylic acid **13** and 3,3'-diphenylBINOL **14** were subjected to the EDCI condensation to afford mono-ester **15** in good yield. The second esterification of the phenolic hydroxyl group was failed due to the steric congestion. Base-mediated acyl transfer reaction with *p*-nitorophenyl ester **16** provided chiral di-ester catalyst **4b** in good yield (Scheme 3). A preliminary examination of the asymmetric addition of **17** to a isoquinolium salt using 1.3 mol% of **4b** gave product **18** with 6% ee (Scheme 4). To obtain higher enantioselectivity, we are screening other chiral anions derived from **4**.

Scheme 4. Preliminary attempt for asymmetric reaction



Reference : 1) Sakai, T.; Seo, S.; Matsuoka, J.; Mori,Y. *J. Org. Chem.* **2013,** *78,* 10978-10985

2P- 15

Highly Efficient and Chemoselective Aerobic Oxidation of Alcohols Using AZADO-Copper Catalysis

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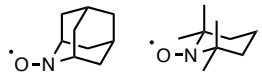
The oxidation of alcohols is a fundamental reaction in organic chemistry, and, therefore, numerous methods to effect this reaction have been developed. Nevertheless, it is still difficult to directly oxidize alcohols with "unprotected" amino groups (amino alcohols) into their corresponding amino carbonyl compounds owing to undesired reactions induced by electron-rich amino groups. Thus, there is no general method capable of oxidizing amino alcohols "chemoselectively" and the synthetic strategy that entails the oxidation of amino alcohols is considered to be very challenging or senseless. Additionally, it is also difficult to oxidize alcohols containing "oxidatively labile" functional groups such as sulfide, electron-rich aromatic ring (ex. *p*-methoxy benzyl group), tri-substituted alkene and selenide. These functional groups are converted into oxidatively high-order functional groups or damaged under the oxidative conditions. There is also no general method for oxidizing such an oxidatively labile alcohols "chemoselectively"

Figure: Nitroxyl radicals

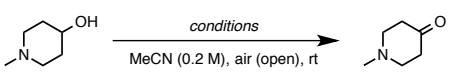


AZADO TEMPO

We have reported that 2-azaadamantane *N*-oxyl (AZADO) and its derivatives, which are sterically less hindered classes of nitroxyl radicals, exhibit a much higher catalytic activity than 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO, Figure)[1]. Furthermore, we also developed several AZADO-catalyzed alcohol oxidation conditions using mild and environmentally benign terminal oxidants, such as NO_x-O_2[2] and diisopropyl azodicarboxylate (DIAD).[3] Under the conditions we developed, various alcohols, including benzylic or aliphatic alcohols but also sugar- or nucleic-acid-derived alcohols can be oxidized cleanly to give the corresponding carbonyl compounds. Unfortunately, amino alcohols resisted to be oxidized under our conditions. Herein, we report a highly chemoselective aerobic oxidation of amino alcohols to amino carbonyl compounds catalyzed by AZADO and copper salt.[4] Furthermore, we found that sulfur-containing alcohols were oxidized chemoselectively without overoxidation of sulfur atom under the same reaction conditions.

We referred to Hoover and Stahl's recent report on a practical method of aerobic alcohol oxidation using TEMPO and CuOTf as catalysts.[5] Although Hoover and Stahl demonstrated that their reaction conditions have a wide functional group tolerance, they showed only one example of sulfur-containing alcohol. Furthermore, they did not examine the method to "unprotected" amino

Table 1: Optimization of the reaction conditions



entry	conditions	GC conversion / time
1	**TEMPO (5 mol%)**, CuOTf•1/2 benzene (5 mol%) bpy (5 mol%), *N*-methylimidazole (10 mol%) (Hoover and Stahl's original conditions)	25% / 24 h
2	**AZADO (1 mol%)**, CuOTf•1/2 benzene (3 mol%) bpy (3 mol%), *N*-methylimidazole (6 mol%)	80% / 24 h
3	AZADO (1 mol%), CuCl (3 mol%) bpy (3 mol%), DMAP (6 mol% **(optimized conditions)**	**100% / 2 h**

alcohols. In our preliminary experiment using AZADO for the oxidation of *N*-methyl-4-piperidinol using Hoover and Stahl's reaction conditions, we found that AZADO oxidized the alcohol chemoselectively to afford *N*-methyl-4-piperidinone in quantitative conversion (Table 1, entry 2), whereas TEMPO oxidized it with only 25% conversion (Table 1, entry 1)

Encouraged by the excellent reactivity and selectivity, we optimized the reaction conditions. After the screening for nitroxyl radicals, copper salts, ligands, additives and solvents, we finally determined the optimum conditions, namely, "AZADO (1–3 mol%), CuCl (3 mol%), bpy (3 mol%), DMAP (6 mol%), MeCN, air (open)" (Table 1, entry 3).

With the optimum reaction conditions in hand, we explored the substrate spectrum. Our result showed that various alcohols with *tert*- or *sec*- amine moieties were efficiently oxidized to give the corresponding amino carbonyl compounds. In addition, our reaction conditions also tolerated labile functional groups such as the *p*-methoxybenzyl groups under oxidative conditions. Note that alcohols with the primary or benzylic amine moiety were also oxidized chemoselectively without damaging these amino groups. Our method was applicable to highly functionalized amino alcohols that could not be oxidized efficiently by conventional alcohol oxidation methods (Table 2). We also found that oxidatively labile sulfur-containing alcohols oxidized chemoselectively in the same reaction condition (Table 3). Furthermore, our reaction conditions are applicable to the final step in the synthesis of natural alkaloids (Scheme).

Table 2: Substrate spectrum (amino alcohols)

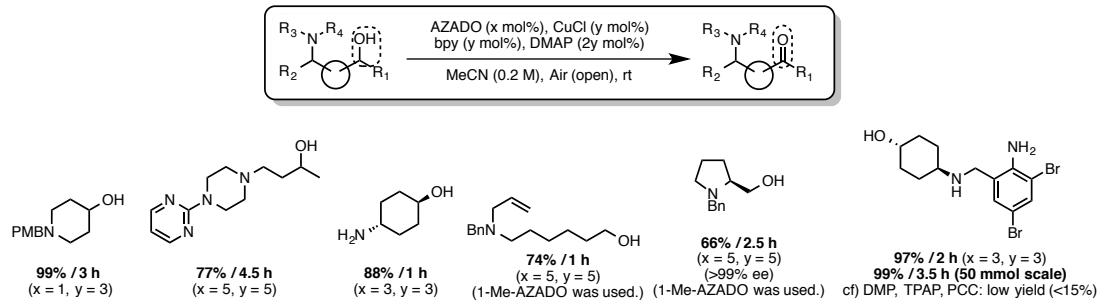
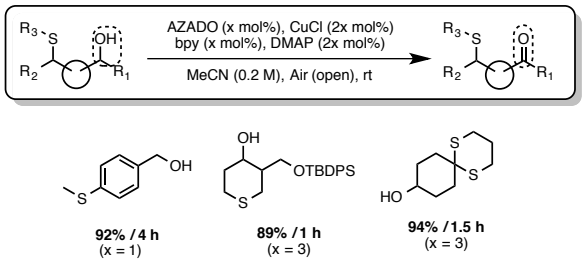
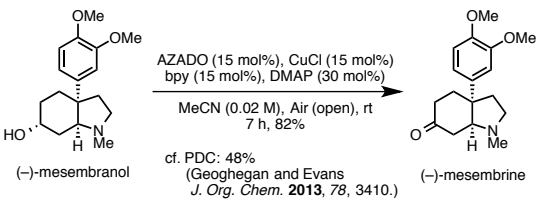


Table 3: Substrate spectrum (sulfur-containing alcohols)



Scheme :Application for natural alkaloid synthesis



References:

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2P- 16

Development of the Synthetic Process for the Naltrexamine Derivatives.

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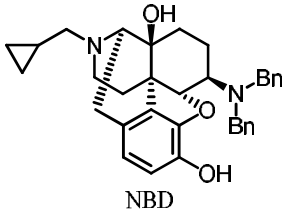
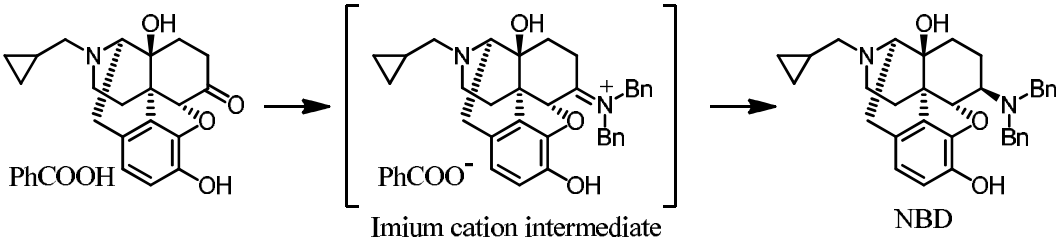
A practical symthesis of a Naltrexamine derivative, NBD, have been developed (Figure 1). NBD is the key intermediate in the synthesis of TRK-130, a novel opioid Ligand, as a new theraputic agent for overactive bladder.



NBD

Figure 1

The synthesis of NBD was performed via a reductive amination utilizing Naltrexone and Dibenzylamine. Reductive amination is one of the most practical and effective reactions to synthesize amines from ketones or aldehydes. In this reaction, the efficiency of the iminium cation formation is the most significant factor to obtain NBD in high yield, and that depends on the dehydration condition. We examined reaction conditions in detail, solvent effect, temperature, amount of the reagents and so on (table 1). Entry 5 is the best condition for the iminium cation formation.



Imium cation intermediate

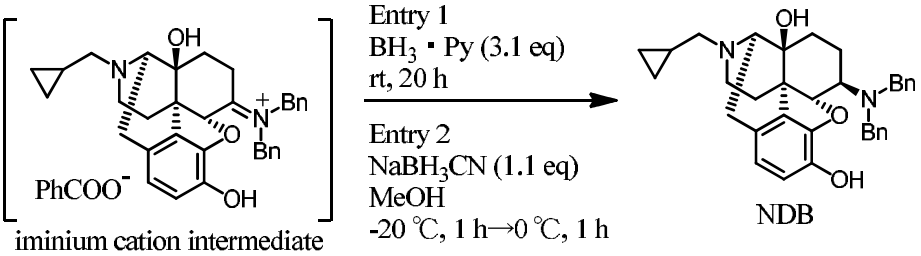
NBD

Entry No.	Toluene/THF	temp.(°C)	time (h)	Bn_2NH (eq.)	$PhCO_2H$ (eq.)	NTXB (%)	NDB (%)	by-product (%)
1	50/50	80~95	20	1.1	0	22.2	63.1	14.7
2	100	110	24	1.1	0	3.2	79.0	17.8
3	50/50	80~95	21	1.1	1.1	3.0	85.4	11.6
4	50/50	80~95	20	1.5	1.6	2.1	91.5	5.8
5	50/50	80~95	20	2.2	2.4	1.4	92.3	6.3

Table 1

In the scale-up experiments of this reaction, we observed the reaction time extension (from 10 g scale, 20 h to 250 g scale, 88 h) along with the increase of by-products. We thought the reaction time extension was caused by the lowered efficiency of the azeotropic dehydration by scale-up. Then, we utilized Triethyl orthoformate as a dehydrating agent. Using triethyl orthoformate, the reaction time extension was mot observed in the 250 g scale study.

Next, we examined the reducing agent to improve the steroselectivity and the isolate yield. Using sodium cyanoborohydride ($NaBH_3CN$) instead of borane-pyridine complex ($BH_3 \cdot Py$), steroselectivity and isolate yield were considerably improved (table 2).



Entry No.	β/α ratio	isolate yield (%)
1	86.8/13.2	77
2	98.4/1.6	88

Table 2

Futher details will be discussed at the poster session.

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Metal-free C(3)-H arylation of coumarins promoted by catalytic amounts of 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin

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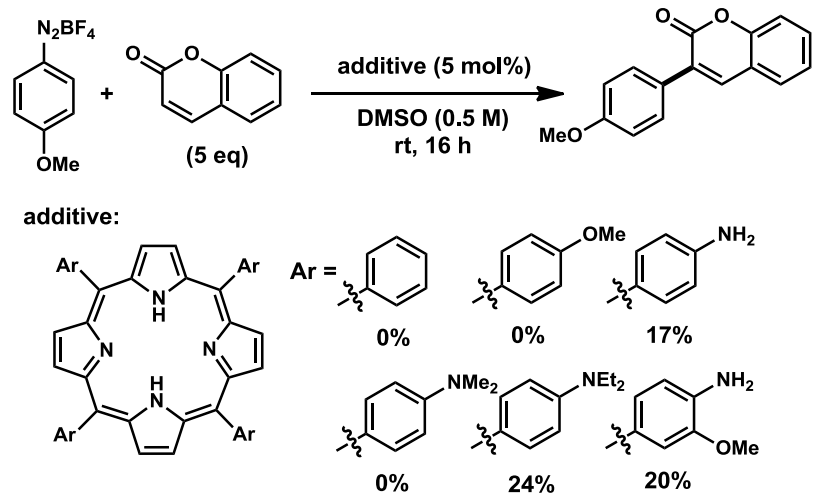
[Background]

Coumarins represent a highly desirable structural motif in medicinal chemistry, chemical biology, and materials chemistry. Considering their wide applications, a new synthetic method allowing for effective diversification of the coumarin motif would potentially contribute to various fields of chemical science. Direct catalytic C-H functionalization of coumarins presents a facile, atom efficient, and environmentally friendly option to extend existing coumarin libraries. However, palladium-catalyzed C(3)-H and C(4)-H arylations of coumarins required high temperatures or stoichiometric amount of heavy metal oxidants.

[Methods]

We focused on Meerwein-type C-H arylation of coumarins. In classical Meerwein arylation, transition metals catalyze aryl radical generation from aryl diazonium salt. However, yields were low to moderate and substrate scope of coumarins was not exhaustively examined. As a candidate for a more effective catalyst, metal-free porphyrins were examined. Metal-free porphyrins are known as robust one electron mediator in artificial photosynthetic systems and its one electron donating ability, in combination with the electron-accepting ability of their radical cations, should render these compounds ideal catalyst candidates for synthetic transformations involving redox processes.

Scheme 1. Evaluation of porphyrin derivatives

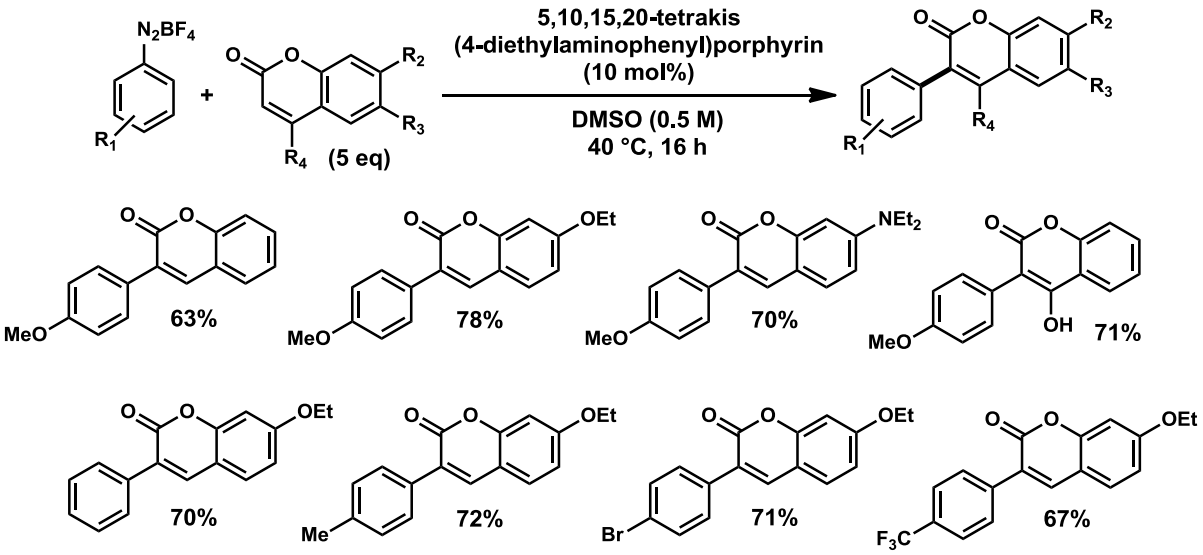


[Results and Discussions]

Initially, we investigated catalytic amounts of 5,10,15,20-tetrakisarylporphyrins, in order to assess their

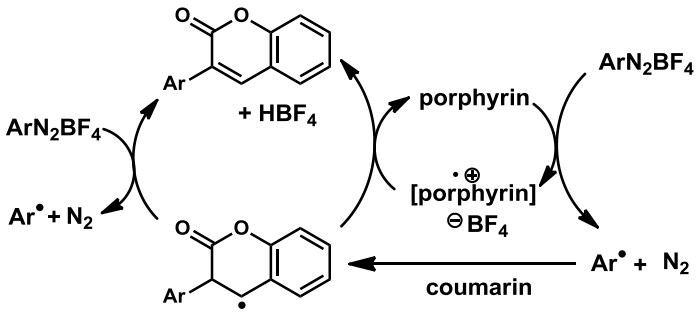
potential to promote the C(3)-H arylation of coumarins with 4-methoxybenzenediazonium tetrafluoroborate. Using 5,10,15,20-tetrakis(4-aminophenyl)porphyrin afforded the targeted coumarin in 17% yield and the highest yield was obtained from 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin (24%, Scheme 1), whereby the presence or absence of light did not affect the yield significantly, suggesting a thermal reaction pathway. Optimal reaction conditions were established as 10 mol% of the porphyrin and 40 °C. The optimized conditions produced broad substrate scope both on coumarin and aryl diazonium tetrafluoroborate (Table 1).

Table 1. Porphyrin-mediated C(3)-H arylation of coumarins



Preliminary mechanistic investigations supported the presence of the aryl diazonium-derived aryl radical intermediates and the coumarin-derived benzyl radical intermediates. An ICP analysis showed that the amount of metal contamination (Ti, Fe, Cu, Pd) in 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin was below the detection limit. These observations suggest that the present reaction is metal-free Meerwein arylation mediated by thermal one-electron redox cycle of the porphyrin derivatives (Scheme 2).[2]

Scheme 2. Plausible reaction mechanisms



[References]

1) a) D. P. Hari, B. König, *Angew. Chem. Int. Ed.,* 2013, **52**, 4734; b) C. S. Rondestvedt, *Org. React.,* 1976, **24**, 225.

2) M. Kojima, K. Oisaki, M. Kanai, *Chem. Commun.,* DOI: 10.1039/C5CC02349A.

2P- 18

Development of a Practical & Scalable Synthesis of Cyclic Oligopeptide AS1895286-00

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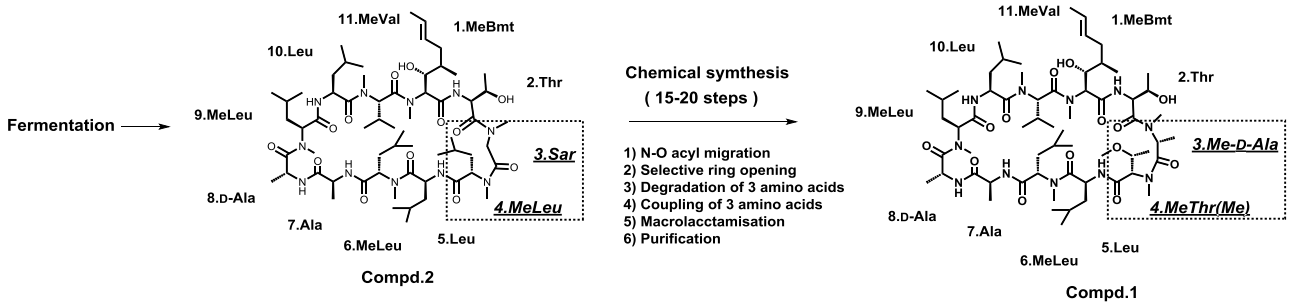
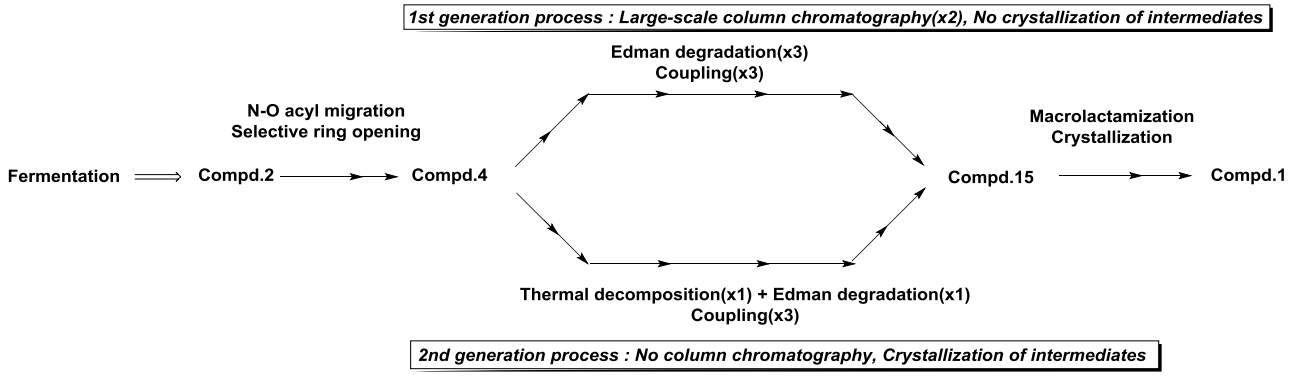
A cyclic oligopeptide AS1895286-00(Compd.1) is a candidate of anti HCV agent and contains 11 amino acids. The manufacturing process consists of 1 fermentation step and ca. 15-20 chemical synthesis steps. 2 amino acids (Sar and MeLeu) in Compd.2 are converted into Me-D-Ala and MeThr(Me) by chemical synthesis. A practical synthesis has been developed and supported multiple scale-up campaigns.

Scheme.1 Manufacturing process of AS1895286-00(Compd.1)



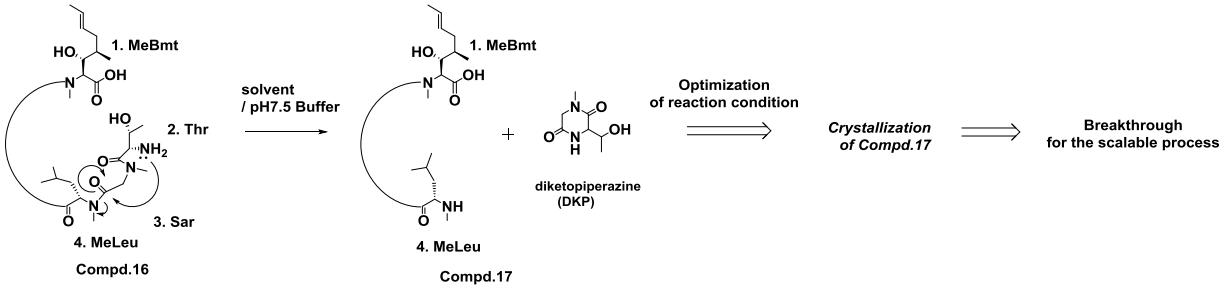
The 1st generation process contained twice large-scale column chromatography process because any intermediate did not crystallize. Purification process became the bottleneck for scale-up manufacturing. After supplying 835g of Compd.1 by the 1st generation process, the 2nd generation process has been investigated for further scale-up manufacturing.

Scheme 2 1st generation & 2nd generation process for AS1895286-00(Compd.1)



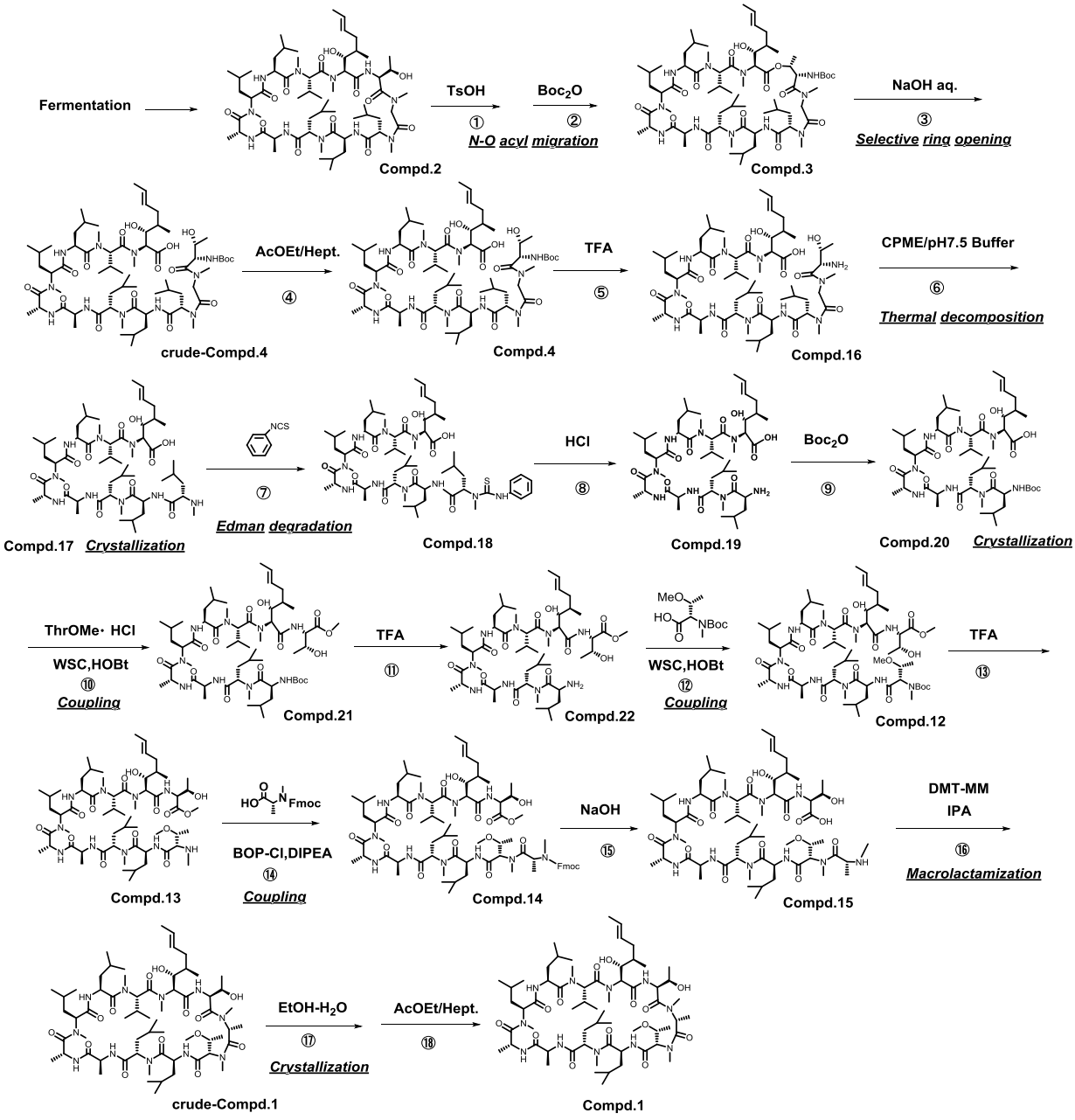
Many investigations (*e.g.,* selective ring opening, degradation of amino acids, scalable macrolactamization, crystallization process) have been conducted widely and thoroughly. With regard to chemical processes, thermal decomposition was a key of the 2nd process. By optimization of reaction solvents, the reaction rate was accelerated dramatically and the reaction product crystallized through work-up procedure. Crystallization of intermediates became a breakthrough for scalable process. As a result of introducing crystallization, the 2nd generation process does not involve any column chromatography.

Scheme 2 Thermal decomposition: Key process for the 2nd generation process



Overcoming many challenges and difficulties, scale-up manufacturing by the 2nd process has been achieved three times reproducibly and supplied 30kg of Compd.1.

Scheme 3 The 2nd generation process



Stereoselective Synthesis of *cis*-α,β-Unsaturated Sulfones Using New Peterson Reagents

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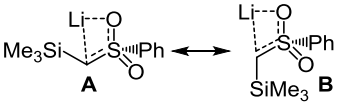
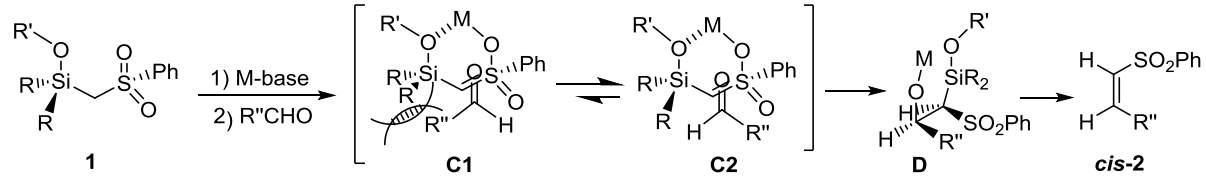
α,β-Unsaturated sulfones are useful substrates in stereo-specific reactions for the construction of chiral centers, such as the Michael reaction, epoxidation, and cycloaddition reactions. Therefore, the stereo-defined synthesis of carbon-carbon double bonds with high selectivity is critically important. Although it is rather easy to obtain the thermodynamically stable *trans*-α,β-unsaturated sulfones, there is no general method for the construction of *cis*-counterparts. It was reported the Peterson reagent, $Me_3SiCH_2SO_2Ph$ reacted with a variety of aldehydes to give α,β-unsaturated sulfones with generally 1:1 stereoselectivity.[1] The reason for this non-stereoselectivity seems to be the presence of two conformers **A** and **B** for the sulfone anions. Here we wish to report the *cis*-selective preparation of α,β-unsaturated sulfones by using new Peterson reagents, which have predominant conformers for the anions by chelation control.

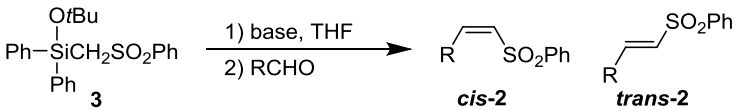


In order to fix the conformation of the sulfone anion, we introduced an alkyloxy group to the silicon atom (the reagent **1** in Scheme 1). When the anion derived from **1** reacts with aldehyde, there are two plausible transition structures **C1** and **C2**. Since the structure **C1** suffers from the steric repulsion between the R" group of aldehyde and the R group of the silicon atom, the reaction seems to occur via **C2** to give **D**, from which *cis*-α,β-unsaturated sulfone **2** would be obtained.



Scheme 1

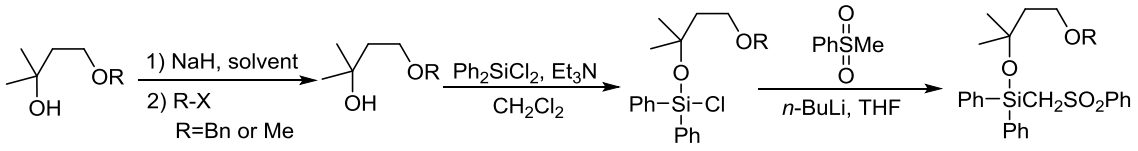
In order to test this working hypothesis, the *t*-BuO reagent **3** was prepared and the reaction of **3** with a variety of aldehydes was studied (Scheme 2). The Peterson reaction of **3** with aromatic aldehydes gave **2** in good yields with 86-92% *cis*-selectivity. Also, the reaction with α-branched aldehydes gave *cis*-**2** in good yields with excellent selectivity (94:6 to 96:4). However, the reactions with other types of aldehydes gave moderate *cis*-selectivity.



Scheme 2

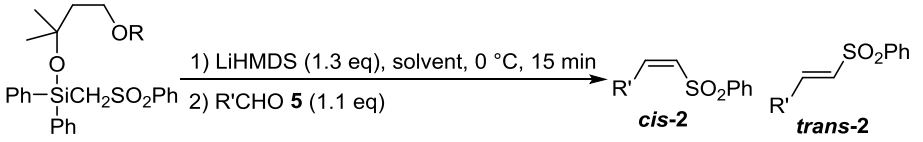
aromatic aldehydes 86-92% *cis*
aliphatic aldehydes 70-96% *cis*

Further improvement was attained by the introduction of the alkoxyalkyloxy group to the silicon atom. The reagents **4a** and **4b** were prepared as shown in Scheme 4 starting from 1,1-dimethylpropane-1,3-diol.



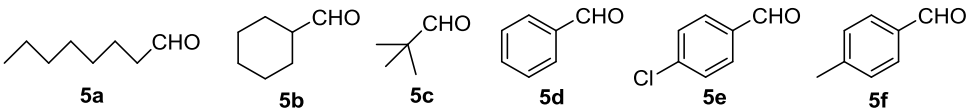
Scheme 3

When **4a** was treated with LiHMDS in CPME (cyclopentyl methyl ether) at 0 °C for 15 min followed by the reaction with *n*-octanal **5a** at -78 °C, *cis*-**2a** was obtained in 75% yield with 95:5 selectivity (entry 1 in Table). In order to see the effect of alkoxy group, RO, the same reaction was performed using **4b** to give *cis*-**2a** in 80% yield with 97:3 selectivity (entry 2). The reactions with cyclohexanecarbaldehyde **5b** were highly stereoselective even at 0 °C to give *cis*-**2b** with 99:1 selectivity from both **4a** and **4b**. The difference of the reactivity between **4a** and **4b** was found for the reaction with pivalaldehyde **5c**. Although the reaction of **4a** proceeded at 0 °C, the reaction of **4b** hardly proceeded at 0 °C. From both reactions, *cis*-**2c** was obtained in good yield with slightly lower selectivity (entries 3 and 4). The reaction with aromatic aldehydes **5d**-**5f** gave the corresponding α,β-unsaturated sulfones with high *cis*-selectivity in THF (entries 7-12). Further optimizations of the reaction conditions are in progress in our laboratory.



Table

entry	4	R'CHO 5	solvent	conditions	product	yield	*cis*:*trans*
1	**4a**	**5a**	CPME	-78 °C, 100 min	**2a**	75	95:5
2	**4b**	**5a**	CPME	-78 °C, 100 min	**2a**	80	97:3
3	**4a**	**5b**	CPME	0 °C, 100 min	**2b**	84	99:1
4	**4b**	**5b**	CPME	0 °C, 100 min	**2b**	91	99:1
5	**4a**	**5c**	CPME	0 °C, 100 min	**2c**	76	89:11
6	**4b**	**5c**	CPME	rt, 2 h	**2c**	92	86:14
7	**4a**	**5d**	THF	0 °C, 1 h	**2d**	68	92:8
8	**4b**	**5d**	THF	-78 °C, 1 h	**2d**	96	90:10
9	**4a**	**5e**	THF	0 °C, 2 h	**2e**	30	87:13
10	**4b**	**5e**	THF	-78 °C, 4 h	**2e**	82	86:14
11	**4a**	**5f**	THF	0 °C, 2 h	**2f**	91	91:9
12	**4b**	**5f**	THF	0 °C, 1 h	**2f**	92	90:10



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2P- 20

Stereoselective Intramolecular Cross-aldol and Desymmetrization of Aliphatic Dials Enabled by Axially Chiral Aniline-type Catalyst

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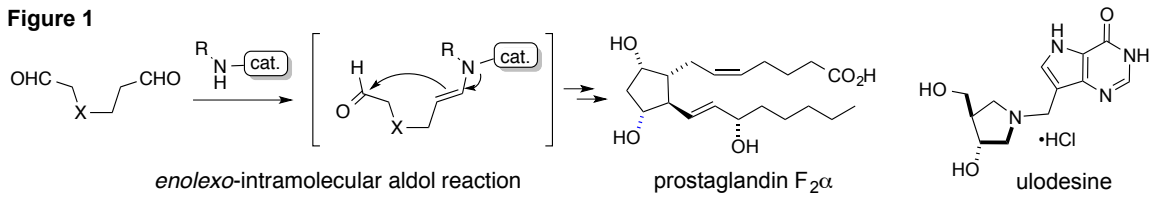
Chiral β-hydroxy and α,β-unsaturated carbonyl compounds are important building blocks for bioactive natural products and pharmaceuticals such as prostaglandins and nucleic acid medicines as shown in Figure 1. Catalytic asymmetric direct aldol reaction is an attractive C–C bond forming reaction as a synthetic tool for these bioactive compounds. Intramolecular aldol reactions were well known to catalyze by proline since 1970s. However, using L-proline as catalyst in particular, unsymmetric enolizable aliphatic dials, is difficult to control selectivity due to the formation of all possible regio- and stereoisomeric aldol products. Moreover, an *enolendo*-intramolecular direct aldol reaction is well documented in the literature. However, *an enolexo*-intramolecular direct aldol reaction as shown in Figure 1 is found to be limited and is potential transformation for the preparation of β-hydroxy carbonyl compounds.

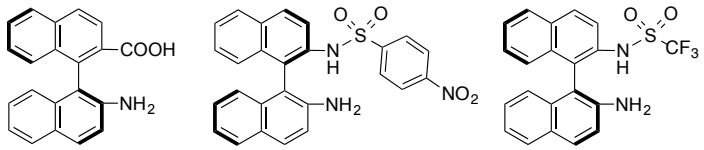
Figure 1



enolexo-intramolecular aldol reaction prostaglandin $F_{2}\alpha$ ulodesine

In our recent studies, we synthesized unnatural axially chiral amino acid derivatives bearing aniline-type amine (*S*)-**1** (Figure 2).[1] In this event, based on changing carboxyl group to sulfonamide moiety, aniline based acid-base catalysts (*R*)-**2a** and (*S*)-**2b** were prepared. We postulated that these catalysts are advantageous for regio- and stereoselective *enolexo*-intramolecular direct aldol reaction by virtue of the mild reactivity of their aniline-type amine. Based on our hypothesis, we tested intramolecular cross-aldol reaction of *N*-Ts 1,6-dial **3a** in the presence of catalyst (*R*)-**2a**.[2]

Figure 2

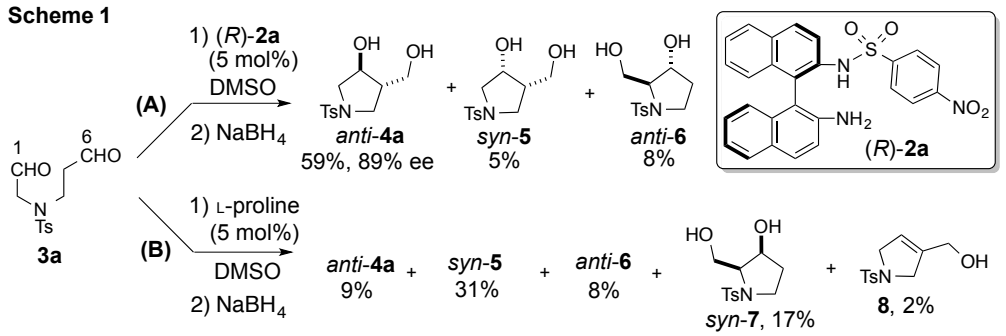


(*S*)-**1** (*R*)-**2a** (*S*)-**2b**

When dial **3a** treated with 5 mol% of L-proline and successive $NaBH_4$ reduction gave complex mixture of aldol products, *anti*-**4a** (9%), *syn*-**5** (31%) and *anti*-**6** (5%), *syn*-**7** (17%) {regioslelectivity, (**4a** + **5**) : (**6** + **7**) = 2 : 1} obtained from enamine intermediate of 6- and 1-formyl groups, respectively, with dehydrated product **8** (2%) (Scheme 1B). In sharp contrast, cat. (*R*)-**2a** discriminated the tiny difference between formyl groups in **3a** efficiently to give *anti*-**4a** (59%) as major product with 89% ee and minor products *syn*-**5** (5%) and *anti*-**6** (8%) with high regioselectivity {(**4a** +

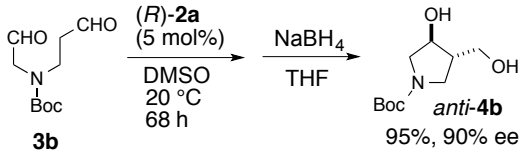
5) : **6** = 8 : 1}(Scheme 1A). The regioselectivity was found to increase by changing *N*-substituent of dial from *N*-Ts to *N*-Boc (Scheme 2). To the best of our knowledge, these results are the first successful examples for regio- and stereoselective direct *enolexo*-intramolecular aldol reaction.

Scheme 1



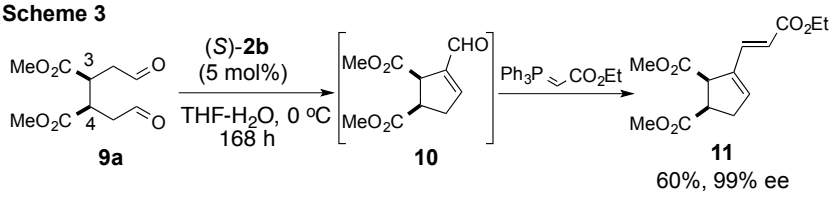
With above successful achievement using mild reactivity of aniline-type amino group of cat. (*R*)-**2a**, in efficient discrimination formyl groups, we further examined asymmetric desymmetrization of *meso*-3,4-disubstituted 1,6-dial **9a** through intramolecular aldol reaction (Scheme 3). The aldol reaction in the presence of cat. (*S*)-**2b** and successive Wittig olefination gave dehydrated product **11** with 99% ee in moderated yield (60%).

Scheme 2

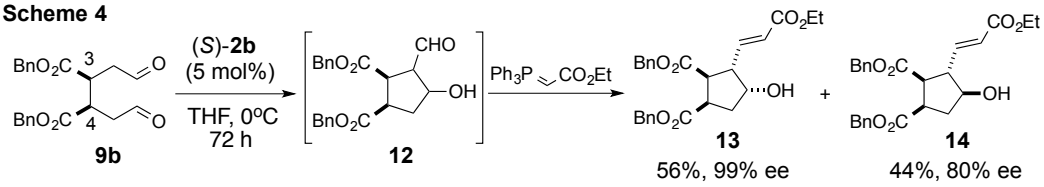


When the reaction condition was optimized using dial **9b** with THF as sole reaction solvent and minimized the reaction time to 74 h at 0 °C, aldol adducts **13** and **14** were obtained in excellent yield and enantioselectivity,

Scheme 3



Scheme 4



although the diastereoselectivity was found to be unsatisfactory (Scheme 4). Potentiality of this method to various substrates is under progress in our laboratory.

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1. (a) Furuta, T.; Yamamoto, J.; Kitamura, Y.; Hashimoto, A.; Masu, H.; Azumaya, I.; Kan, T.; Kawabata, T. *J. Org. Chem*., **2010**, *75*, 7010–7013. (b) Furuta, T.; Nikaido, M.; Yamamoto, J.; Kuribayashi, T.; Kawabata, T. *Synthesis,* **2013**, *45*, 1312–1318.
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2P- 21

Stereoselective Synthesis of *cis*-α,β-Unsaturated sulfonates Using New Peterson Reagents

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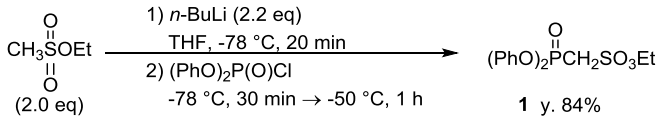
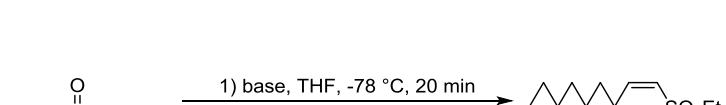
α,β-Unsaturated sulfones and sulfonates are useful substrates in stereospecific reactions for the construction of chiral centers, such as the Michael reaction, epoxidation, and cycloaddition reactions. Also some vinyl sulfones and sulfonates are known as cysteine protease inhibitors.[1] Therefore, the stereo-defined synthesis of carbon-carbon double bonds with high selectivity is critically important. Although it is rather easy to obtain the thermodynamically stable *trans*-α,β-unsaturated sulfonates, there is no general method for the construction of *cis*-counterparts. During the course of our study on the *cis*-selective Horner-Wadsworth-Emmons reaction, we found the reaction of $(ArO)_2P(O)CH_2CO_2Et$ with aldehydes gave *cis*-α,β-unsaturated esters highly selectively. In order to test this method for the synthesis of *cis*-α,β-unsaturated sulfonates, $(PhO)_2P(O)CH_2SO_3Et$ **1** was prepared from ethyl methanelsulfonate and diphenyl chlorophosphate (Scheme 1). The reaction of **1** with *n*-octanal was performed using a variety of base such as *n*-BuLi, NaHMDS, and KHMDS (Table 1). However, the reaction gave a mixture of *cis* and *trans*-α,β-unsaturated sulfonates **2a** with 40:60 to 53:47 ratios. For the C-C bond formation of the phosphonate anion and aldehyde, there are two plausible transition structures **A** and **B**. Since both structures suffer from the steric repulsion between the R group of aldehyde and either the phosphonate oxygen or sulfonate oxygen, the obtained low selectivity can be explained by this non-stereoselective C-C bond formation.



Scheme 1



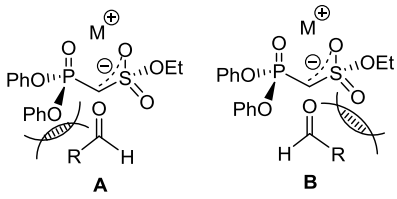


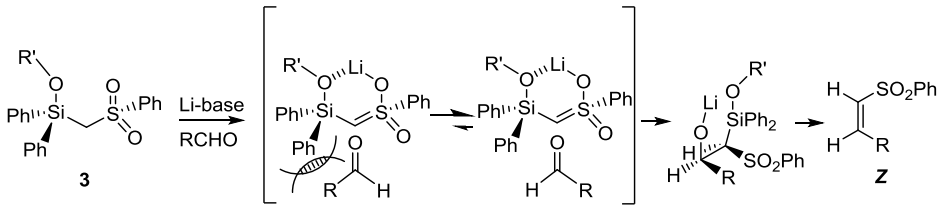
Table 1

entry	base (eq)	conditions	yield (%)	*cis:trans*
1	*n*-BuLi (1.1 eq)	-78 °C, 30 min, -78 °C → 0 °C, 1.5 h	89	50:50
2	NaHMDS (1.3 eq)	-78 °C, 4 h, -78 °C → 0 °C, 1.5 h	73	44:56
3	KHMDS (1.3 eq)	-78 °C, 1 h, -78 °C → 0 °C, 1.5 h	96	53:47
4[a]	KHMDS (1.3 eq)	0 °C, 30 min	88	40:60

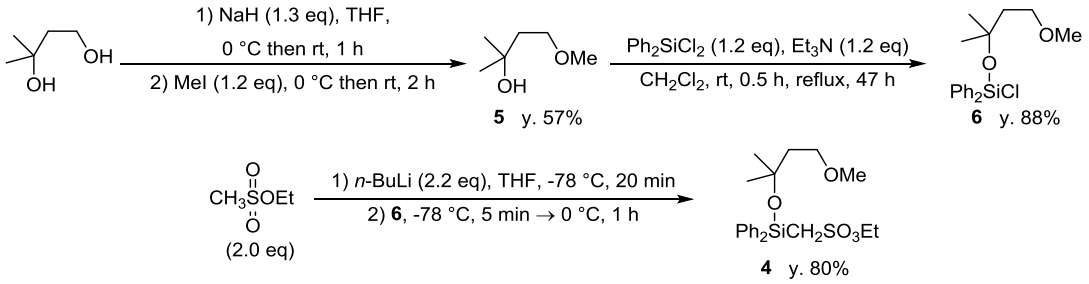
a: KHMDS was added at 0 °C.

Next, we planned the synthesis of *cis*-α,β-unsaturated sulfonates by the Peterson reaction. In our laboratory, the stereoselective synthesis of *cis*-α,β-unsaturated sulfones is studied using the Peterson reaction, where new reagents **3** were designed to fix the conformation of the sulfone anion as shown in

Scheme 2.[2] The reaction of **3** with a variety of aldehydes gave *cis*-α,β-unsaturated sulfones highly selectively. In this study, a new ethyl sulfonate reagent **4** was prepared and the reactions of **4** with a variety of aldehydes were studied. The preparation of **4** starting from 1,1-dimethylpropane-1,3-diol was shown in Scheme 3.



Scheme 2



Scheme 3

When the reagent **4** was treated with LiHMDS in CPME (cyclopentyl methyl ether) at 0 °C for 20 min and then aldehyde was added to the reaction mixture at 0 °C, α,β-unsaturated sulfonate **2** was obtained in 89% yield with 90:10 *cis*-selectivity (entry 1 in Table 2). The reactions of **4** with 2-methypentanal, cyclohexanecarbaldehyde, and pivalaldehyde were performed by the same way and *cis*-**2** was obtained in good yields (90-94%) with 91:9 to 98:2 ratios (entries 2-4). When the reaction of **4** with benzaldehyde was performed in the same way, **2** was obtained in 88% yield with reduced 86:14 selectivity (entry 5). When *n*-BuLi was used instead of LiHMDS at -78 °C, both the selectivity and the yield was improved (91:9 selectivity, 99% yield) (entry 6).

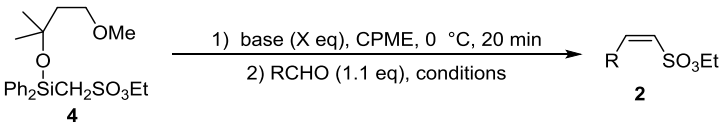


Table 2

entry	base (eq)	RCHO	conditions	yield (%)	*cis*:*trans*
1	LiHMDS (1.3 eq)	*n*-octanal	0 °C, 2 h	89	90:10
2	LiHMDS (1.3 eq)	2-methylpentanal	0 °C, 2 h	94	97:3
3	LiHMDS (1.3 eq)	*c*-HexCHO	0 °C, 2 h	90	98:2
4	LiHMDS (1.3 eq)	*t*-BuCHO	0 °C, 1 h	92	91:9
5	LiHMDS (1.3 eq)	PhCHO	0 °C, 1 h	88	86:14
6[a]	*n*-BuLi (1.1 eq)	PhCHO	-78 °C → 0 °C, 2,5 h	99	91:9

a: *n*-BuLi was added at -78 °C.

References

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2P- 22

Syntheses of (1-Propynyl)arenes: One-Pot Dephosphorylation and Sonogashira Coupling of Phosphorylpropyne

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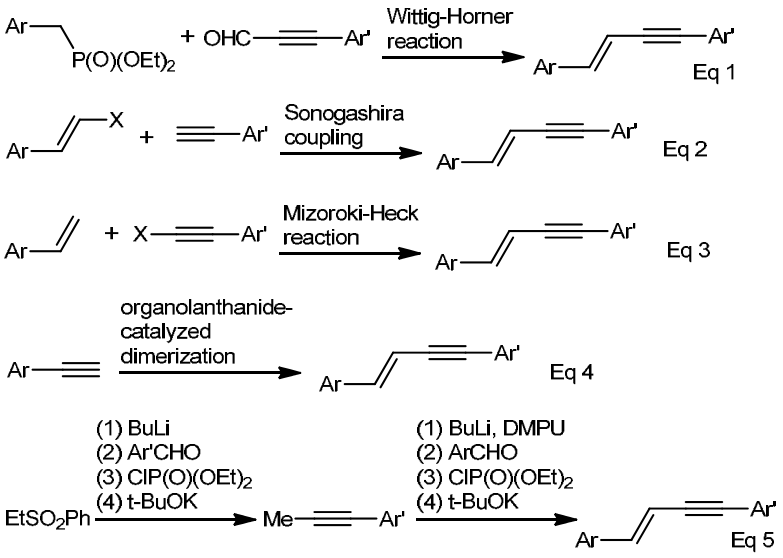
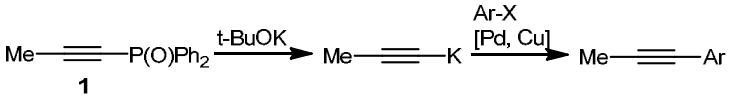
Great attention is paid to highly expanded π-systems because they can be used as organic materials such as light-emitting diodes (LEDs), field-effect transistors (FETs) and dye-sensitized solar cells (DSSCs). Although various π-expanded materials were developed, only few enyne motifs were explored as organic materials in spite of the high potentials as sensing fluorophore and as emitter of white light-emitting devices (WOLEDs).[1] For syntheses of the enyne motifs, several synthetic routes were reported; Wittig-Horner olefination of propynal (Eq 1 in Scheme 1), Sonogashira coupling of vinyl halide with terminal ethyne (Eq 2), Mizoroki-Heck reaction of propynyl halide with olefin (Eq 3) and organolanthanide-catalyzed dimerization of arylethyne (Eq 4). We are involved in syntheses of π-expanded acetylenic compounds such as phenyleneethynylenes and disclosed their physical properties as organic materials. In the course of our research, we developed one-pot synthesis of (1-propynyl)arenes by using ethylsulfone and arylaldehydes as starting compounds and one-pot transformation of (1-propynyl)arenes thus obtained to enyne derivatives (Eq 5).[2] Although (1-propynyl)arenes can be prepared by Sonogashira coupling of the corresponding aryl halides with propyne, propyne is difficult to handle because of the low boiling point (-23 °C). We have already reported that $Ph_2P(O)$-protected ethynes underwent dephosphorylation by treatment with t-BuOK, and the resulting acetylide could be subjected to transition metal-catalyzed coupling to give the desired coupling product.[3] By using this $Ph_2P(O)$-protection, we planned to utilize phosphorylpropyne **1** as a propyne equivalent: we envisioned the syntheses of (1-propynyl)arenes by consecutive t-BuOK-assisted dephosphorylation of **1** and Sonogashira coupling of the resulting



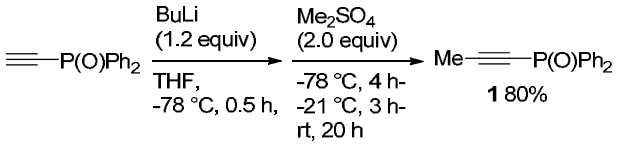
Scheme 1. Synthetic Routes of Enyne Motifs



Scheme 2. One-pot Synthesis of (1-Propynyl)arene from **1**

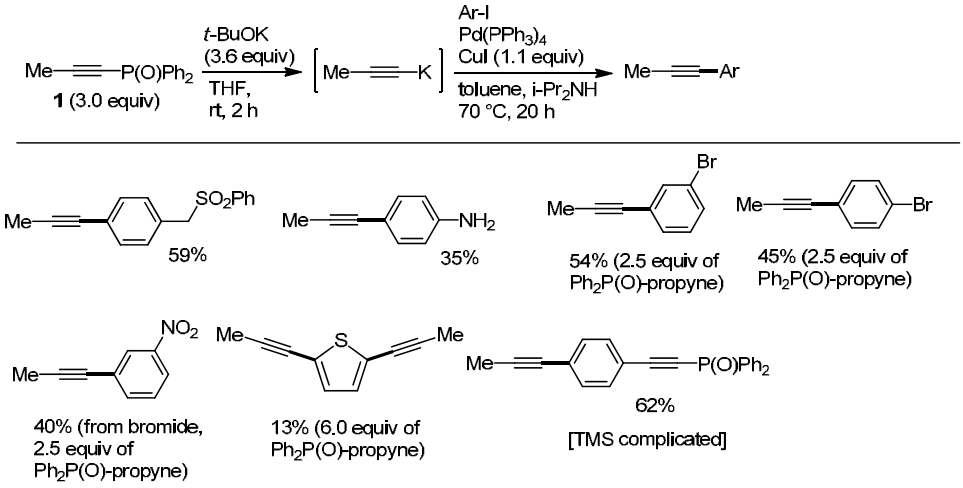
potassium acetylide with aryl halides (Scheme 2).

Phosphorylpropyne **1** was prepared by methylation of lithium salt derived from phosphorylethyne (Scheme 3). In this methylation, a combination of BuLi and Me_2SO_4 served best, and when other bases such as MeMgBr and LDA or other methylation reagent (methyl iodide) were used, chemical yield of **1** decreased remarkably.



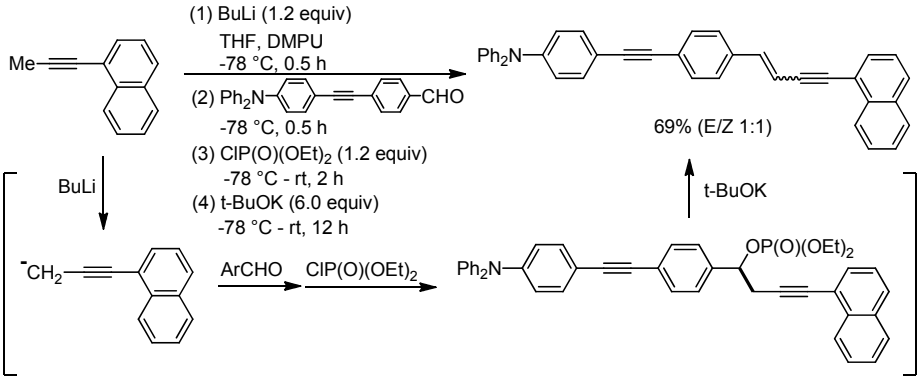
Scheme 3. Synthesis of phosphorylpropyne **1**

When **1** was treated with t-BuOK and successively subjected to Sonogashira coupling of aryl halides, the desired propynylation proceeded smoothly to afford the corresponding (1-propynyl)arenes (Scheme 4).



Scheme 4. One-pot Synthesis of (1-Propynyl)arenes from **1**

(1-Propynyl)arenes thus obtained were transformed to enyne through the preparation of propargyl anion, the addition to aldehyde, transformation of the alcohol to phosphate and elimination of phosphoric acid (Scheme 5).



Scheme 5. One-pot Synthesis of Enyne

1 (a) La Clair, J.J. *J. Am. Chem. Soc*. 1997, 119, 7676. (b) Brümmer, O.; La Clair, J.J.; Janda, K.D. *Org. Lett*. **1999**, *1*, 415.

2 An, D-L.; Zhang, Z.; Orita, A.; Mineyama, H.; Otera, J. *Synlett* **2007**, 1909.

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Asymmetric Synthesis of 2-Substituted Dihydroquinolones by The Aza-Michael Reaction of *N*-Unprotected Amines

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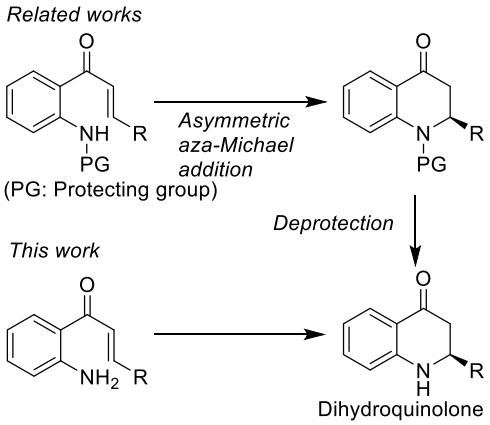
Organocatalyzed aza-Michael addition reaction has been extensively studied in recent years, and recognized as one of the most powerful tools to synthesize enantioenriched nitrogen-containing heterocycles. The key issue here is how to effect the cyclization in an efficient and stereocontrolled manner. To achieve the goal, removable activating group on nitrogen atom is frequently required for stereocontrol and increasing the acidity of hydrogen on nitrogen. Nevertheless, the development of a protecting group-free aza-Michael addition is highly desirable for streamlining synthesis.

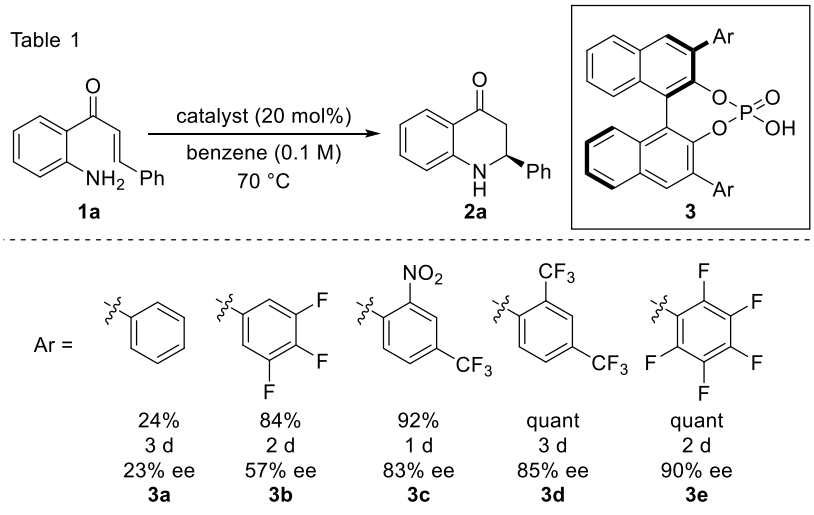
Scheme 1



2,3-Dihydroquinolone skeleton is a representative building block in medicinal chemistry. While enantioselective aza-Michael reaction is a useful method for the asymmetric synthesis of this skeleton, use of substrates bearing protecting group on nitrogen atom was necessary.[1] We have developed asymmetric synthesis of 2,3-dihydro-2-substituted 4-quinolones based on the protecting group free aza-Michael addition[2] by means of chiral phosphoric acid to give corresponding 2-aryl-2,3-dihydro-4-quinolones highly enantioselectively (Scheme 1).

At the outset, we treated **1a** with 20 mol% of **3a** in benzene at 70 °C for 3 d. Aza-Michael reaction proceeded to give **2a** in 24% with 23% ee. In order to improve the enantioselectivity, we screened the substituents at 3,3'-position and found that electron-withdrawing group improved both reactivity and enantioselectivity. The highest enantioselectivity was observed when 2,3,4,5,6-pentafluorophenyl group was introduced at the 3,3'-position (Table 1).

Table 1



We also screened solvents, and

found that aromatic solvents, such as benzene, toluene, and xylene, gave higher enantioselectivity. Furthermore, a mixture of benzene and cyclohexane (v:v = 1:1) gave **2a** in good yield and with the highest enantioselectivity.

It was found that the catalyst loading could be reduced to 10 mol% without compromising both chemical yield and enantioselectivity.

α,β-Unsaturated ketones bearing various kinds of substituents at β-position, such as aryl, heteroaryl, and alkyl groups were subjected to the optimized reaction conditions (**3e** (10 mol%), benzene : cyclohexane (v:v = 1:1) of 70 °C) to give **2** in up to 95% yield and 93% ee (Table 2).

Table 2

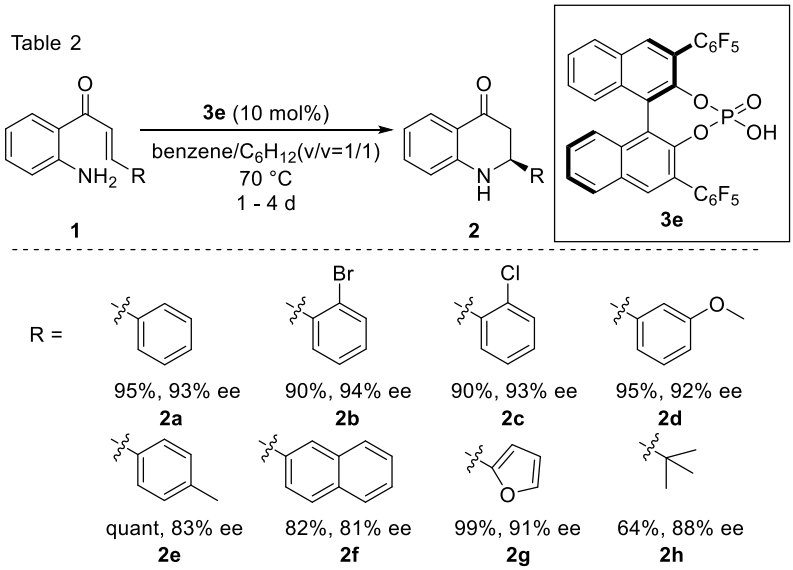
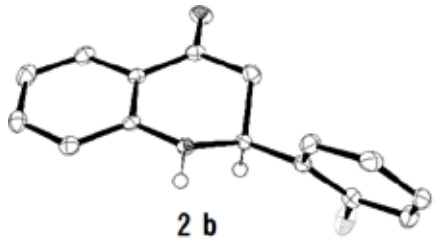


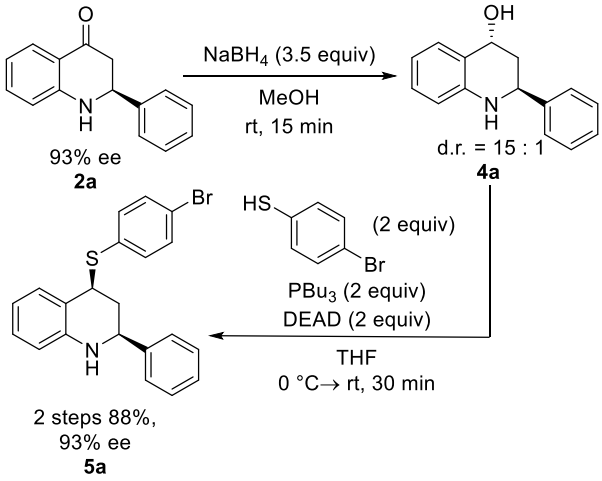
Figure 1



The absolute stereochemistry of **2b** was unambiguously determined to be *S* by single crystal X-ray analysis (Figure 1). Those of others were surmised by analogy.

We also investigated the derivatization of the product **2a**. Compound **2a** was treated with sodium borohydride, to yield alcohol **4a** with a high diastereomeric ratio by reducing the carbonyl group. Mitsunobu reaction led to the formation of sulfide **5a** (Scheme 3).

Scheme 3



In summary, we have succeeded in the enantioselective intramolecular aza-Michael addition reaction by means of chiral phosphoric acid. Corresponding dihydroquinolones were obtained highly enantioselectively. Salient feature of this reaction is that use of *N*-protecting group was obviated.

1. a) X. Liu, Y. Lu, *Org. Lett.* **2010**, 12, 5592-5595, b) S. Cheng, L. Zhao, S. Yua, *Adv. Synth. Catal,* **2014**, 356, 982-986, c) X. Xiao, X. Liu, S. Dong, Y. Cai, L. Lin, X. Feng, *Chem. Eur. J.* **2012**, 18, 15922–15926.
2. K. Kanagaraj, K. Pitchumani, *J. Org. Chem*. **2013**, 78, 744-751.

2P- 24

One-pot synthesis of β,β-disubstituted α,β-unsaturated carbonyl compounds using sequential Ti-aldol addition to ketones and elimination

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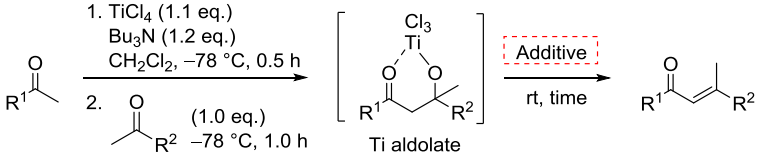
Introduction

β,β-Disubstituted α,β-unsaturated carbonyl compounds are useful starting materials for building tri- or tetrasubstituted asymmetric carbon center at the carbonyl β-position, which can be seen in natural products. In general, Horner-Wadsworth-Emmons reaction to ketones has been utilized for their synthesis. However, low *E*/*Z* selectivity is often observed and several reaction steps are required to further transform to unsaturated ketones. The aldol reaction to ketones as aldol acceptor and the subsequent elimination reaction may offer a short synthetic route to these unsaturated carbonyl compounds from readily available starting materials. However, this route has not yet been systematically studied. That is presumably because of low electrophilicity of ketones compared to aldehydes, concomitance of undesired cross-aldol and self-aldol reactions, and propensity of retroaldol reaction from the aldol intermediate. In one of the few examples, Tanabe *et al.* reported diastereoselective aldol addition to ketones using $TiCl_4$.[1] Elimination of an alolate to a muscone precursor was also reported. Here we report synthesis of β,β-disubstituted α,β-unsaturated carbonyl compounds utilizing Ti-aldol reaction and base-promoted elimination in a one-pot procedure.

Results and Discussion

Initially, we investigated the reaction of methyl isopropyl ketone as the aldol donor and acetophenone as the aldol acceptor (Table 1). The aldol step was performed with $TiCl_4$ and Bu_3N at –78 °C with slight modification of Tanabe's procedure; clean generation of the aldol product was confirmed by TLC analysis. However, when the temperature was increased to rt to facilitate the elimination, the desired enone was obtained only in 18% yield (entry 1). A large amount of acetophenone was

Table 1. Synthesis of β,β-disubstituted α,β-enones

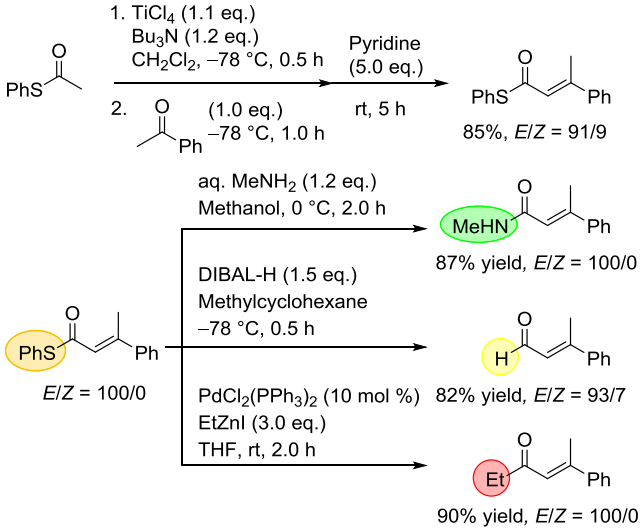


Entry	R^1	R^2	Additive (eq.)	Time (h)	Yield (%)	*E*/*Z*
1	^{i}Pr	Ph	none	20	18	97/3
2	^{i}Pr	Ph	DMF (5.0)	20	80	97/3
3	^{i}Pr	Ph	TMEDA (1.0)	20	72	97/3
4	^{i}Pr	Ph	Pyridine (5.0)	5.0	87	86/14
5	Ph	^{i}Pr	DMF (5.0)	24	45	86/14
6	Ph	^{i}Pr	TMEDA (1.0)	1.0	86	87/13
7	Ph	^{i}Pr	Pyridine (5.0)	2.0	73	88/12
8	Ph	Ph	DMF (5.0)	20	45	98/2
9	Ph	Ph	TMEDA (1.0)	2.0	64	97/3
10	Ph	Ph	Pyridine (5.0)	2.0	67	87/13
11	^{t}Bu	Ph	DMF (5.0)	20	38	98/2
12	^{t}Bu	Ph	TMEDA (1.0)	20	78	98/2
13	^{t}Bu	Ph	Pyridine (5.0)	1.0	87	82/18
14	^{i}Pr	^{t}Bu	Pyridine (5.0)	2.0	99	73/27

generated, which indicated progress of the retroaldol reaction. We reasoned that the Ti-enolate was regenerated because Ti strongly coordinated to the carbonyl oxygen atom in the Ti-aldolate intermediate. To cleave the coordinate bond, DMF (5 equiv.) was added as a ligand of titanium in the elimination step. As expected, the yield of the enone largely increased (entry 2). TMEDA (1 equiv.), which can bidentately coordinate to titanium, also afforded a good yield (entry 3). When pyridine (5 equiv.) was examined, significant rate enhancement was observed although the *E* selectivity was decreased (entry 4). It should also be noted that the titanium residue can be removed by simple filtration through a Celite pad without aqueous workup. A variety of aromatic and aliphatic ketones were found to be applicable in the one-pot reaction (entries 5-16). In most cases, pyridine resulted in a shorter reaction time and higher yield but lower *E* selectivity than DMF or TMEDA. Meanwhile, high *E*/*Z* selectivity (>95:5) was generally observed with DMF and TMEDA additives.

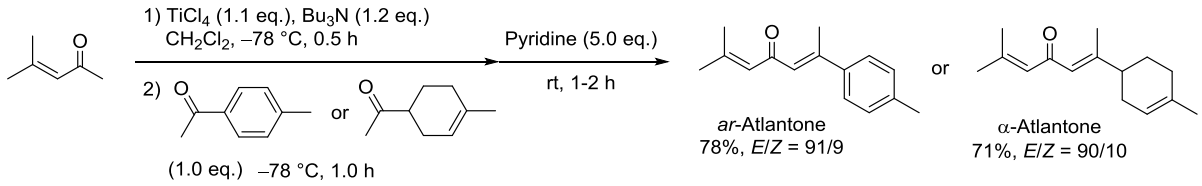
The reaction of *S*-phenyl thioacetate with acetophenone using pyridine in the elimination step afforded the desired unsaturated thioester in good yield with good *E* selectivity (Scheme 1). In addition, the thioester product could be transformed to the corresponding *N*-methyl amide, aldehyde, or ethyl ketone by treatment with $MeNH_2$, DIBAL-H, and EtZnI/palladium catalyst, respectively.

Scheme 1. Synthesis of β,β-disubstituted α,β-unsaturated thioester



The current method was also applied to the one-pot synthesis of simple natural products, *ar*-atlantone and α-atlantone (Scheme 2). The Ti-aldol reaction of mesityl oxide with the required ketones followed by elimination with pyridine provided *ar*-atlantone and α-atlantone in good yield and *E* selectivity.

Scheme 2. One-pot synthesis of atlantones



Conclusion

We have demonstrated a one-pot method to prepare β,β-disubstituted α,β-unsaturated carbonyl compounds. Extension of the substrate scope and further synthetic application are now in progress.

Reference

(1) (a) Y. Tanabe, N. Matsumoto, T. Higashi, T. Misaki, T. Itoh, M. Yamamoto, K. Mitarai, Y. Nishii, *Tetrahedron* **2002**, *58*, 8269. (b) R. Nagase, N. Matsumoto, K. Hosomi, T. Higashi, S. Funakoshi, T. Misaki, Y. Tanabe, *Org. Biomol. Chem.* **2007**, *5*, 151.

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Preparation of Optically Active Thioamides and Evaluation of Their Antibacterial Properties

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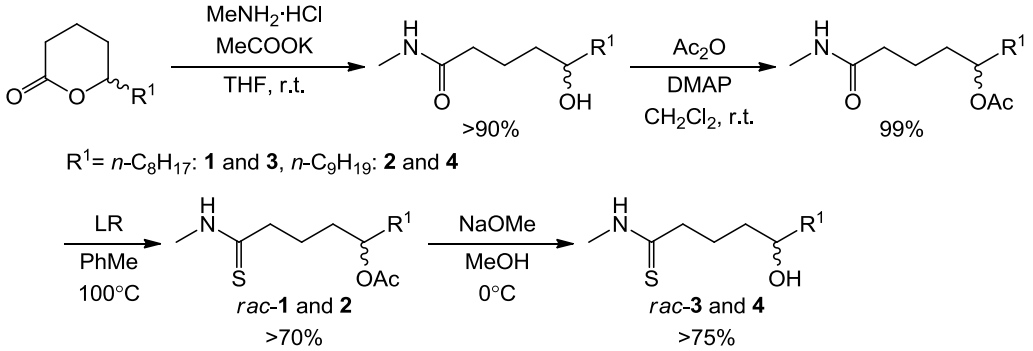
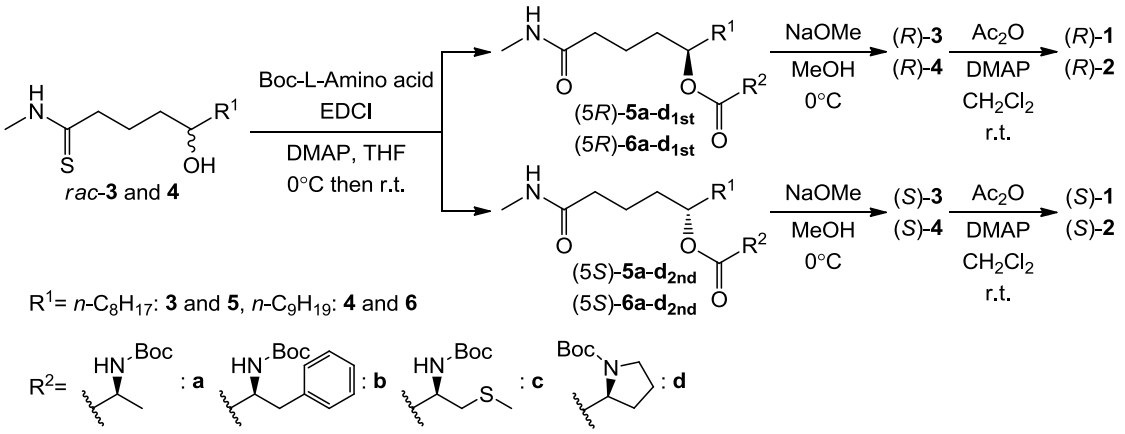
We have attempted to synthesize various optically active γ-, δ- and ε-lactones. The precursor such as *N*-methyl-5-acetoxyalkylamides for the preparation of optically active δ-lactones showed antibacterial activity against *Staphylococcus aureus* (MRSA and MSSA) and *Streptococcaceae pnumoniae*. Generally, it is known that different biological activities exhibit among each enantiomer in many case and thioamides have antibacterial activities potentially. It is expected that *N*-methyl-5-acetoxyalkylthioamides increases antibacterial activities compared with *N*-methyl-5-acetoxyalkylamides. Therefore, we attempted to synthesize various optically active thioamides and evaluated their antibacterial properties.

Racemic *N*-methyl-5-hydroxyalkanthioamides (*rac*-**3** and **4**) were prepared from δ-tri- or tetradecalactone (**Scheme 1**). Amidation of δ-tri- and tetradecalactone were subjected with methylamine hydrochloride, and subsequent acetylation was progressed quantitatively. Thionation with Lawesson's reagent gave racemic *N*-methyl-5-acetoxyalkanthioamides (*rac*-**1** and **2**), and alkaline hydrolysis afforded *rac*-**3** and **4**.



Scheme 1 Preparation of various thioamide from racemic δ-lactones

Optical resolution of *rac*-**3** and *rac*-**4** were performed by diastereomer method using amino acid derivatives as a resolving agent (**Scheme 2**, **Table 1**). We previously reported diastereomeric resolution using amino acid derivatives as a resolving agent, and these gave good results. Various Boc-L-amino acids also investigated in this paper.



Scheme 2 Diastereomeric resolution of *rac*-3a and *rac*-4a

All amino acids gave the corresponding diastereomer esters (**5a-d**), and the column separation of **1st** and **2nd** was comparatively easy. These **1st** and **2nd** were obtained quantitatively and had 99% diastereomeric excesses despite the difference of amino acids. Boc-L-proline showed the largest ΔRf, and **6d** was prepared using it. Both **6d** also obtained quantitatively and 99% diastereomeric excesses (Entry 5).

Table 1. Effect of amino acid derivatives on Rf value[1)]

Entry	R^2	Boc-L-amino acid	Product	Rf value[2)]		ΔRf	Yield [%] / *d.e.* [%][3)]	
				1st	2nd		1st	2nd
1	*n*-C_8H_{17}	Alanine	**5a**	0.24	0.15	0.09	50 / 99	48 / 99
2		Phenylalanine	**5b**	0.30	0.23	0.07	50 / 99	48 / 99
3		Methionine	**5c**	0.23	0.16	0.07	50 / 99	48 / 99
4		Proline	**5d**	0.28	0.15	0.13	43 / 99	44 / 99
5	*n*-C_9H_{19}	Proline	**6d**	0.24	0.13	0.11	46 / 99	47 / 99

1) *rac*-**3** and **4**: 1.0 mmol, Boc-L-amino acid: 2.0 mmol, EDCI: 2.0 mmol, DMAP: 1.0 mmol, 0°C, 2 h then r.t., 3 h

2) Measured from TLC analysis using *n*-hexane/EtOAc=3/1 as eluent.

3) Determined by ^{1}H NMR.

Antibacterial activities of optically active **1**-**4** were evaluated for MSSA (**Table 2**). **2** and **4** had *n*-C_9H_{19} at R^2 group had no activities. In contrast, all **1** and **3** exhibited high antibacterial activities, and **3** had higher activity than **1**. From these results, it was seemed that some degree of high polarity was required. Certain different activity showed among each enantiomer of **3**, and (5*R*)-**3** had the strongest activity.

Table 2. Comparison of antibacterial property for MSSA among each enantiomer

	1 and **2**			**3** and **4**		
Config.	*racemic*	5*R*	5*S*	*racemic*	5*R*	5*S*
n-C_8H_{17}	+++	+	+	++	+++	++
n-C_9H_{19}	-	-	+	-	-	-

*) +++: >10^5 decrease, ++: >10^3 decrease, +: >10 decrease, -: No great decrease

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Syntheses of 1,3,6,8-Tetra-substituted Pyrenes and Steric Effect of Substituents on Their Photoluminescence

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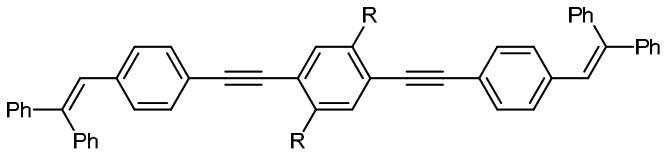
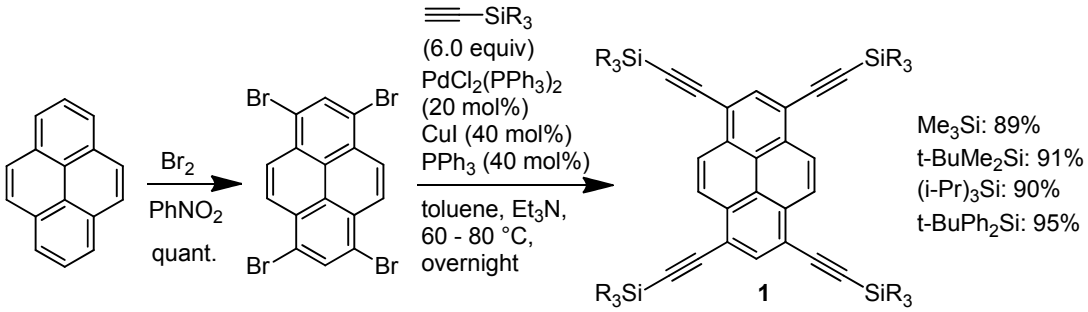
Great attention is paid to highly expanded π-systems because they can be used as organic materials such as light-emitting diodes (LEDs), field-effect transistors (FETs) and dye-sensitized solar cells (DSSCs). We have been involved in syntheses of phenyleneethynylenes and their application to organic materials. In the course of these researches, we found that bulky substituents of fluorophore played a pivotal role to enhance the photo- and electroluminescence[1] (Scheme 1). Pyrene has an expanded π-system, and it is expected that pyrene derivatives would serve as emitting materials. In general, pyrenes show photoluminescence in solution as anticipated, while it emitted only little fluorescence in the solid states because of their strong π–π interaction to result in the aggregation of the pyrenes. In order to realize strongly fluorescent pyrenes, we synthesized a series of 1,3,6,8-tetra(trialkylsilylethynyl)pyrenes **1** and evaluated the steric effect on their fluorescent properties in the solid state.



Scheme 1. Blue Emitting Material for Electroluminescence

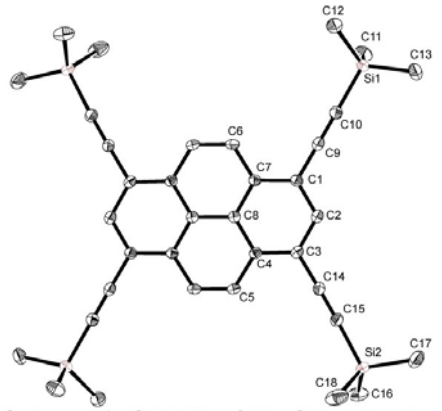
Tetra(trialkylsilylethynyl)pyrenes **1** were prepared from pyrene in two steps: tetrabromination and Sonogashira coupling of the tetrabromide with trialkylsilylethyne (Scheme 2). A series of tetra(silylethynyl)pyrenes **1** were purified by column chromatography followed by recrystallization. The structure of Me_3Si derivative was confirmed by single-crystal X-ray analysis (Scheme 3).



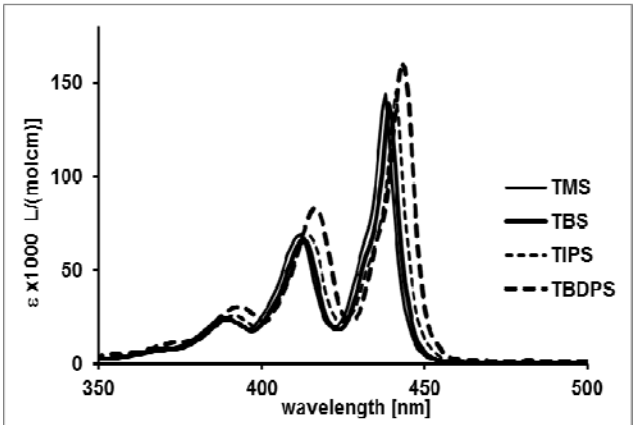
Scheme 2. Synthesis of Tetra(trialkylsilylethynyl)pyrenes

Having these derivatives in hand, optical properties such as UV-vis absorption and photoluminescence spectra were investigated. All the derivatives showed the large absorption bands at 430 nm in UV-vis

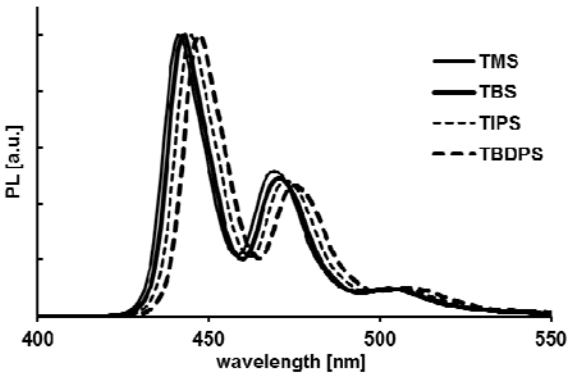
absorption (CH_2Cl_2, 1.0 x 10^{-4} mol/L) (Scheme 4) and strong emission at 433 nm in photoluminescence (CH_2Cl_2, 1.0 x 10^{-6} mol/L)(Φ_F > 0.90)(Scheme 5). The small Stokes shifts observed in the tetraethynylpyrenes **1** could be explained in terms of the small changes of their structures in the ground and the excited states. When the photoluminescence spectra of **1** were recorded in the solid states (Scheme 6), TMS and TBS derivatives exhibited emission at ca. 520 nm (Φ_F > 0.60), while TIPS and TBDPS derivatives did two emission bands around 480 nm and 515 nm (Φ_F > 0.20).



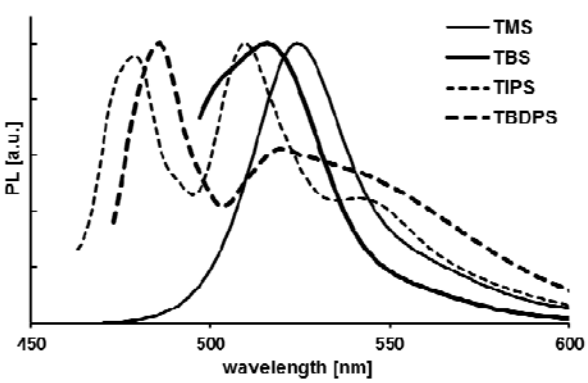
Scheme 3. ORTEP of Me_3Si Derivative



Scheme 4. UV-vis Absorption Spectra



Scheme 5. PL Spectra in CH_2Cl_2



Scheme 6. PL spectra in the solid state

Reference

1 Mao, G.; Orita, A.; Fenenko, L.; Yahiro, M.; Adachi, C.; Otera, J. *Mater. Chem. Phys*. **2009**, *115*, 378.

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Development of Novel Synthetic Methods of *N,Se*-Acetals by Highly Regioselective Hydroselenation of *N*-Vinyl Lactams

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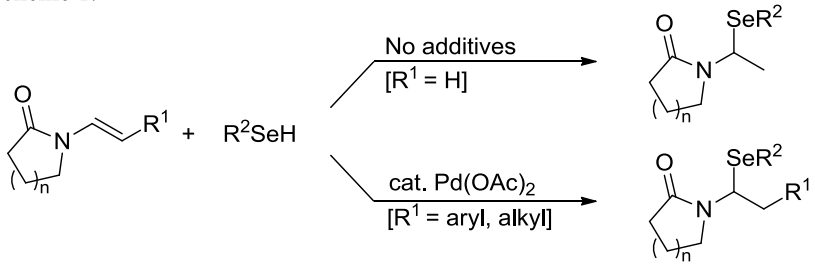
Many organoselenium compounds are used as functionalized molecules such as synthetic intermediates, bioactive compounds, and functional materials. One of the most useful synthetic methods of organoselenium compounds is addition reaction of selenols to unsaturated molecules. Although addition of selenols to alkynes has been established as acid- or base-assisted ionic reaction, radical reaction, and transition-metal-catalyzed reaction, corresponding addition to alkenes has serious drawbacks such as limitation of alkenes and difficulty in realizing transition-metal-catalyzed reactions.

Herein, we report highly regioselective hydroselenation of *N*-vinyl lactams with selenols, which affords corresponding Markovnikov adducts, *N*,*Se*-acetals, successfully. In the case of terminal *N*-vinyl lactams, Markovnikov-selective hydroselenation proceeds efficiently in the absence of any catalyst or additive based on the high acidity of selenols themselves. In contrast, such self-promoted hydroselenation of internal *N*-vinyl lactams occurs inefficiently. In the presence of palladium diacetate ($Pd(OAc)_2$), however, the desired hydroselenation of internal *N*-vinyl lactams proceeds well to afford Markovnikov adducts, successfully (Scheme 1).

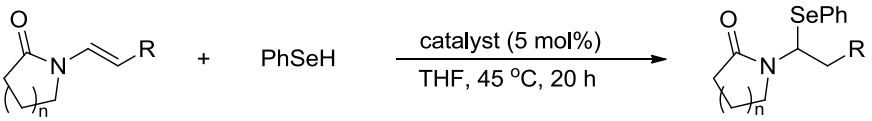
Scheme 1.

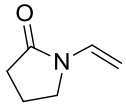
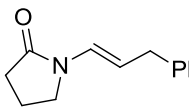
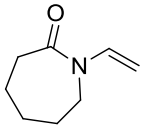
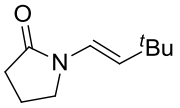
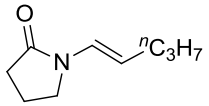
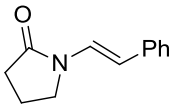


When the reaction of *N*-vinyl pyrolidone, as a manageable *N*-vinyl lactam, and benzeneselenol was conducted at 45 °C for 20 h with no additives, the Markovnikov-type hydroselanation product was obtained in 93% yield in regioselective fashion without formation of any byproduct (Table 1, entry 1). Next, the hydroselenation of several *N*-vinyl lactams was performed to examine the scope and limitation of this hydroselanation. In the case of *N*-vinyl caprolactam, the desired Markovnikov hydroselenation product was obtained in 57% yield (entry 2). In contrast, when the internal *N*-vinyl lactams were used for hydroselenation, the desired hydroselenation proceeded very ineffectively (entries 4, 6, 8, 10). Interestingly, it was revealed that $Pd(OAc)_2$ promoted the hydroselenation of internal *N*-vinyl lactams despite the generally known difficulty of the transition-metal-catalyzed reaction of internal alkenes with

organoselenium compounds. In particular, the yields of the hydroselenation products of *N*-vinyl caprolactam and internal *N*-vinyl lactams having t-butyl or phenyl group were dramatically improved (entries 3, 9, 11).

Table 1.

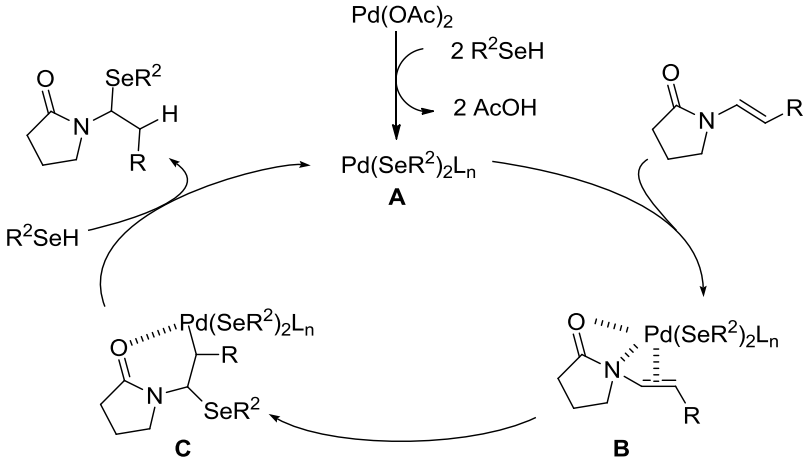


entry	substrate	catalyst	yield (%)[a]	entry	substrate	catalyst	yield (%)[a]
1		——	93	6		——	28
				7		$Pd(OAc)_2$	64
2		——	57	8		——	7
3		$Pd(OAc)_2$	92	9		$Pd(OAc)_2$	99
4		——	13	10		——	ND
5		$Pd(OAc)_2$	44	11		$Pd(OAc)_2$	99

[a] Determined by ^{1}H NMR

A plausible reaction pathway for the Pd-catalyzed hydroselenation of *N*-vinyl lactams is shown in Scheme 2. Firstly, the $Pd(OAc)_2$ catalyst reacts with selenols to form Pd-selenide complex **A**. Then, *N*-vinyl lactams coordinates to Pd-selenide complex **A**, providing Pd-selenide-alkene complex **B**, where heteroatoms might coordinate to the palladium, stabilizing the complex **B**. Subsequent selenopalladation generates palladium intermediate **C**. The following protonation of palladium intermediate **C** with selenol provides the Markovnikov hydroselenation product regioselectively, with regeneration of Pd-selenide complex **A**.

Scheme 2.



Reference

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2P- 28

A Novel Approach to the Characterization of Pharmaceutical Drugs Within Processes using Morphologically Directed Raman Spectroscopy

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1. Introduction

It is widely recognised that particle size and shape influences the macroscopic behaviour and physical characteristics of a material. Within the pharmaceutical industry, the importance of understanding particle properties and solid state characterisation of pharmaceutical formulations and their impact on the quality and safety of pharmaceutical products is highlighted in the International Conference on Harmonisation (ICH) Q9 document [1]. Knowledge of the size and shape parameters of the various components within a blend is of great importance in understanding and then controlling the behaviour of that blend. Specifically, the morphology of the active pharmaceutical ingredients (API) in oral solid dose administered drugs can have a profound impact on the ease with which the API is processed; the presence of additional fines or irregularly shaped particles can lead to a decreased flow rate and increased risk of adhesion to surfaces during the formulation process [2]. It also impacts the bioavailability since the size and shape of particles may influence the release of the compound in vivo [3] [4] [5]. Therefore, variations in these parameters can lead to unpredictable bioavailability and the potential for patients to receive either toxic or ineffective doses of a therapeutic agent.

In this study, we aim to investigate how the size and shape of individual components in a pharmaceutical blend could be monitored as it undergoes typical process steps. In addition we will assess the impact of these process steps on the different components within the blend. As Gamble et al. noted, in contrast to during API development, it is often assumed that the pre-formulated API properties are the same as the properties of the API in the final drug form [2]. Gamble and co-workers attributed this to the difficulties associated with accurately measuring the particle size of a single component within a multi-component sample. Here we present a novel technique, Morphologically Directed Raman Spectroscopy (MDRS), which can be used to chemically identify individual components within a blend and generate a morphological profile specific to each component. MDRS combines Automated Particle Image Analysis (APIA) with Raman spectroscopy. APIA uses sample dispersion and digital imaging technology, based on two dimensional images, to measure a statistically significant number of particles in terms of a wide range of morphological parameters. The integrated Raman spectrometer uses a laser to probe the molecular structure of the species of interest. The resultant scattering from the Raman active molecular vibrations is unique to that species, and generates a spectrum which allows it to be chemically identified. The combination of APIA with Raman spectroscopy is a powerful tool and this study will investigate the

capability of the MDRS technique to aid understanding of process behaviour in pharmaceutical manufacture.

2. Materials and Method

MDRS analyses were conducted on a Morphologi G3SE-ID instrument (Malvern Instruments, Worcestershire, UK.). A blend of ibuprofen, acetaminophen (as the APIs) and lactose (as the excipient) was used as the model blend.

3. Result and Discussion

The model blend was subjected to two process steps, a) tumble blending, simulated using a roller mixer, and b) milling, using an FT4 rheometer (Freeman Technology, Gloucestershire, UK) to simulate transmission through a powder feed system. Samples from before processing, after blending and after milling were measured by MDRS. Each measurement comprised of the dry dispersion of the sample using the integrated dispersion unit, followed by an automated morphological and Raman analysis of the dispersed sample. The components of interest were identified from their respective Raman spectral signatures and particle classes were established based on these parameters. The whole measurement and classification was automatically performed according to a Standard Operating Procedure (SOP). For each measurement the PSD and shape distribution of the APIs were generated. Consequently, the impact of the various processes on each component can be assessed from comparing the results from the different stages of the processing.

The information and knowledge generated from an MDRS study on the properties of pharmaceutical components during the formulation process will provide useful insight that may be used to direct API development and to assist in controlling the formulation process.

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2P- 29

A Process Analytical Technology (PAT) Approach Using Online Mass Spectrometry to Evaluate Drying Process and Control Oxygen Generation

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1. Real-time monitoring of the drying process

Online mass spectrometry is widely used for mole fraction measurements of multiple components in gas samples and is simple and easy to use. It offers a noninvasive and ideal method to measure the solvent concentration in the head space of a dryer and the trend line of solvent concentration indicates the end stage of drying.

In this study the drying progress of wet cakes containing various solvents were monitored with an online mass spectrometer and thermometers (Figure 1) at the drying cake.

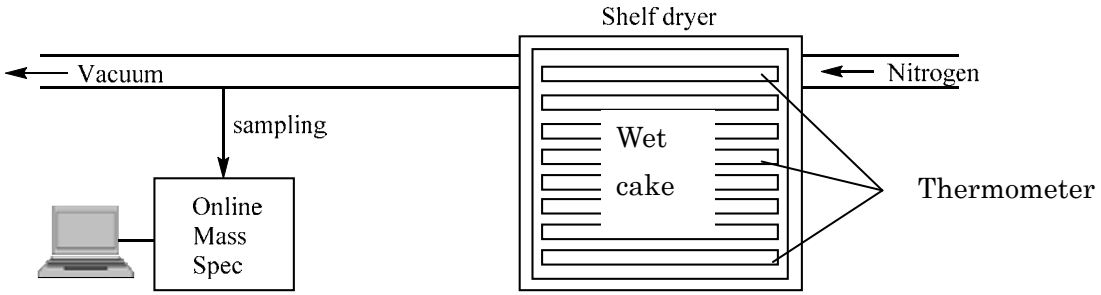
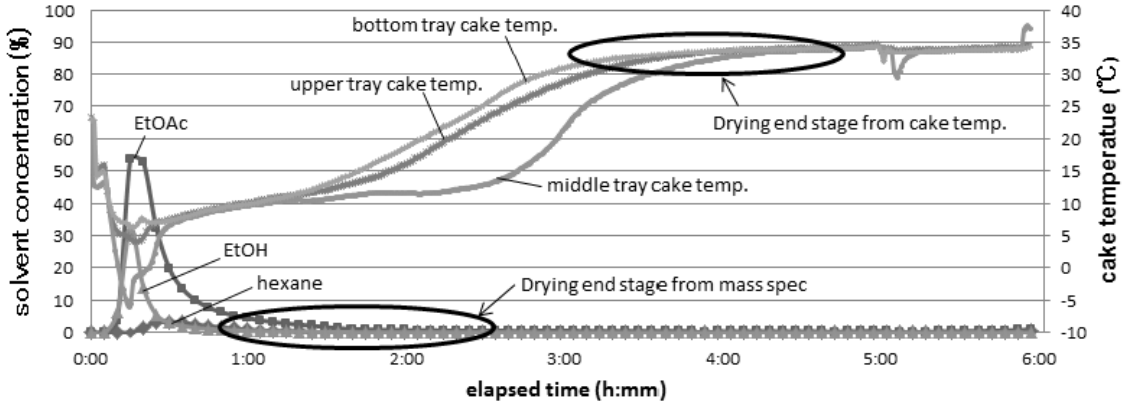


Figure 1. An online mass spectrometer connected to a pilot scale vacuum shelf dryer for real-time monitoring of drying.

Nitrogen was introduced into the dryer as a carrier gas. The obtained data is plotted in Figure 2.

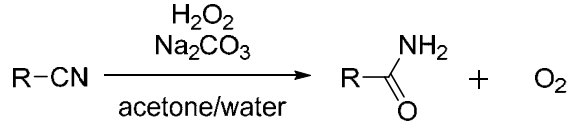
Figure 2. Real-time monitoring of drying



The drying end stage was indicated at 2 hours by the trend line of solvent concentrations, but cake temperature indicated only after 4 hours.

2. Real-time monitoring of oxygen generation

The hydration reaction of a nitrile to an amide with hydrogen peroxide as shown in Scheme 1 generates 1 mole ratio of oxygen as a by-product. In this case, oxygen concentration has to be kept under the limiting oxygen concentration for acetone (LOC: 11.5%). Oxygen concentration in the waste gas of the reaction was monitored by an online mass spec during hydrogen peroxide addition and aging (Figure 3).



nitrile 1 **amide 1**

Scheme 1. Hydration of a nitrile to an amide with hydrogen peroxide.

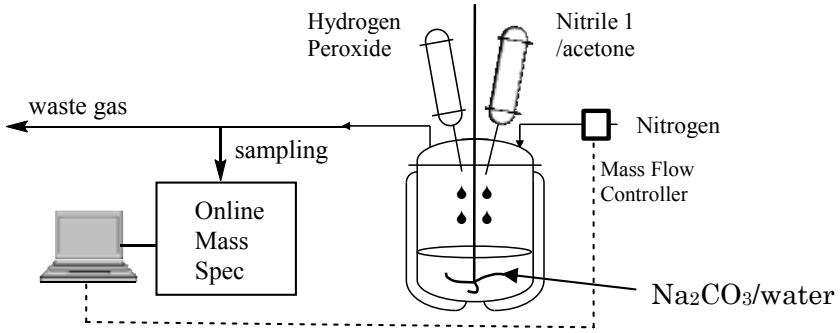
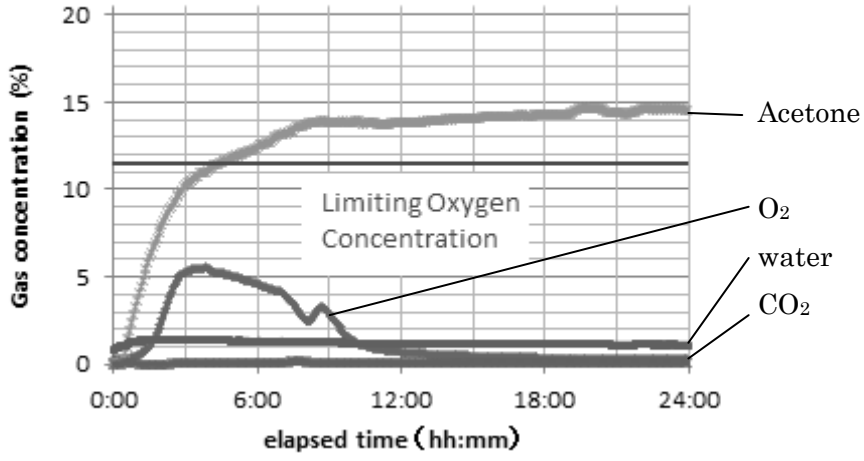


Figure 3. Real-time monitoring of oxygen evolution with an online mass spectrometer.

Nitrogen was introduced into the reactor as a carrier gas. The obtained data was plotted in Figure 4.

Figure 4. Real-time monitoring of Oxygen evolution



We confirmed that we can keep the oxygen concentration under the LOC by controlling the nitrogen flow rate and the hydrogen peroxide charging rate. In addition, acetone concentration in waste gas was simultaneously monitored. However, it was absolutely impossible to keep the acetone concentration under the lower flammable limit for acetone (LFL: 2.5%).

2P- 30

Organocatalytic site-selective acylation of polyol natural products

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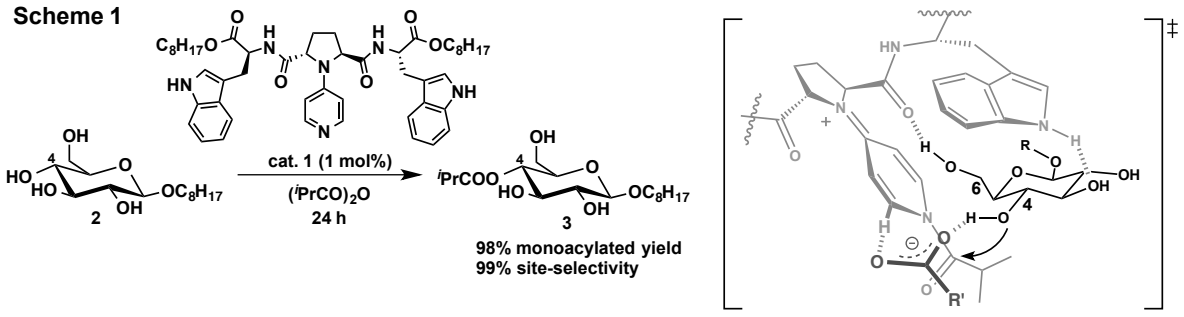
Introduction

Functionalization of natural products and pharmaceuticals is one of the most promising approaches to construct valuable library of bioactive molecules. Since bioactive molecules often possess multiple functional groups, direct and site-selective functionalization of them is an attractive approach to the structurally defined and diverse library in minimum steps. In contrast to the well-developed enzymatic process, non-enzymatic site-selective functionalization of the multifunctionalized molecules such as polyols has been a fundamental challenge in organic synthesis. We have developed an organocatalytic one-step procedure for the site-selective acylation of a secondary hydroxy group of glucoside **2** (Scheme 1). [1] A hypothetical transition state model via multiple H-bonding interaction was proposed to explain the unusually high reactivity of the secondary C(4)-OH in the presence of an otherwise more reactive primary C(6)-OH. Considering the high molecular-recognition-ability of catalyst **1**, we had envisioned and found that catalyst **1** could promote site-selective acylation of lanatoside C (**4**), clinically used cardiac glycoside, possessing eight free hydroxyl groups. [2] Moreover, in the course of our continuous efforts for site-selective functionalization of polyol natural products, we found that highly site-selective acylation of 10-deacetyl baccatin III (**5**), a key synthetic precursor of antitumor drug, paclitaxel.

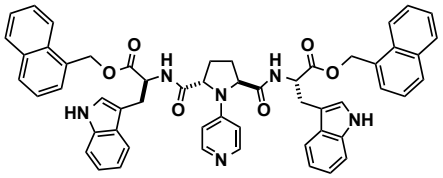


Results and Discussion

The regiochemical profile of acylation of **4** with an isobutylic anhydride was investigated in the presence of catalyst **6** (Figure 1), an ester analogue of catalyst **1**, and 4-dimethylaminopyridine (DMAP) (Scheme 2).

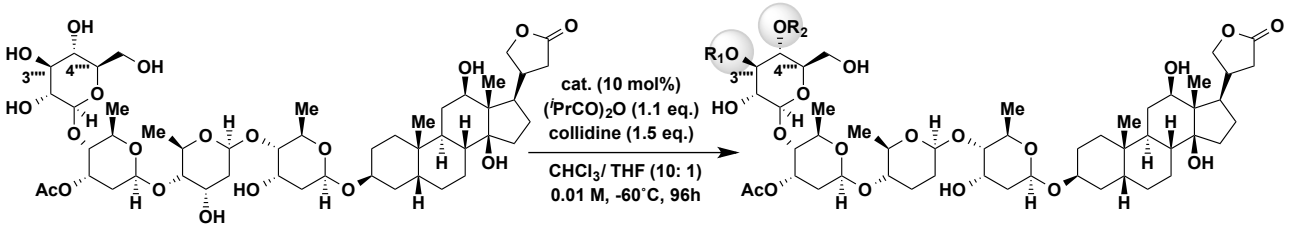
Treatment of **4** with isobutyric anhydride in the presence of 10 mol % of DMAP in $CHCl_3$/THF (9:1) at -60 °C for 96 h gave the C(3’’’’)-isobutyrate as the major acylate in 97% site-selectivity and 85% yield for monoacylation. This result indicates that C(3’’’’)-OH has the highest intrinsic reactivity among eight hydroxy groups of **4** in a $CHCl_3$/THF (9:1) solution, *i.e., substrate-controlled site-selectivity.* On the other hand, site-selective acylation at C(4’’’’)-OH was attained by catalyst **6** by overcoming the extraordinary high intrinsic reactivity of C(3’’’’)-OH in the solution, *i.e., catalyst-controlled site-selectivity*.

Figure 1



6

Scheme 2

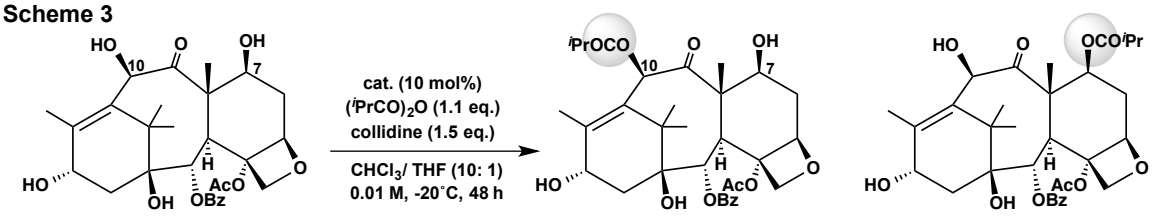


lanatoside C (4)

3''''-*O* selective acylation with DMAP : R_1=^{i}PrCO, R_2=H (97% selectivity)
4''''-O selective acylation with catalyst 6: R_1=H, R_2=^{i}PrCO (90% selectivity)

Next, we investigated the regiochemical profile of acylation of **5** (Scheme 3). Treatment of **5** with isobutyric anhydride in the presence of 10 mol % of DMAP in $CHCl_3$/THF (10:1) at -20 °C for 48 h gave the C(10)-isobutyrate as the major acylate in 62% site-selectivity and 95% yield for monoacylation. On the other hand, acylation of **5** by catalyst **1** gave the C(10)-isobutyrate as the major acylate in 93% site-selectivity and 87% yield for monoacylation. These results indicate that catalyst **1** amplified the high intrinsic reactivity of C(10)-OH.

Scheme 3



10-deacetylbaccatin III (5)

with DMAP (site-selectivity)	65%	35%
with catalyst 1 (site-selectitity)	93%	7%

References

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2P－31

An Investigation of Drug Crystallization Process by in-situ Particle Size Analysis using Mie Scattering Theory and Morphological Analysis.

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1. Introduction

The crystallization process is commonly used for pharmaceutical drug manufacture of active ingredients. The key important to control the product are investigation of the particle size distribution (PSD) and a detection of fluctuation of particle concentration. With regard to particle characteristics, such as particle size, shape and figure are widely recognized making up a material greatly influences its macroscopic behavior and physical characteristics. Notably issue of particle morphology , knowledge of the PSD gives verification of quality control processes based on solubility with a surface area effect such as that described by the Noyes-Whitney equation model.. In-situ real time PSD measurement and in-situ an automated particle image analysis (APIA) to observe particle morphology observation techniques will be suggested as a solid approach to monitor and control of the crystallization process behavior. The purpose of this study is a feasibility investigation of monitoring to a drug crystallization process using in-situ real-timed PSD and APIA..

2. Methodology In-situ real time PSD measurement by Mie Scattering Theory and APIA

Existing method of the in-situ monitoring of particle size measurement technique used in the crystallization process is a reflectance particle counting method (RPCM) such as focus beam reflectance measurement (FBRM) technology. RPCM is a count-based technique which means that the sizing results are provided by a number of particles measured within a chord length class. The advantages of RPCM are capability to a probe monitoring and possibility of non-dilution measurement. However, the drawbacks of RPCM are complicated to correlate with lab equipment due to be such as count based approach and only little possibilities for capability of the concentration estimation. A laser diffraction used by Mie scattering theory is most commonly approach to PSD investigation. This theory is measuring the angular variation in the intensity of light scattered as a laser beam passes through a dispersed particulate sample. Large particles scatter light at small angles relative to the laser beam and small particles scatter light at large angles. A The advantages of this methodology of implementation of in-situ real time monitoring are long history , Establishment support by ISO 13320 , possibility of concentration detection depend on Lambert-Beer’s theory and only few effort is needed to correlate with lab method. An automated particle image analysis (APIA) is possible to obtain the significant particle size and shape information by over than ten thousand numbers of particles projection images. The methodology of this technique is based on the

digital binary image processing technology from projection image picture of CCD camera pixels on microscope with flow technics. The determinations of particle size and shape parameter are calculated by the particle projection images by pixels. The most of the advantage of this method is not only possible to described numerical definition of particle analysis but also available to the diverse analysis by two dimensional correlations plot between shape parameter and particle size

3. Laboratory instrument

Ibuprofen was selected as a model drug which has an acid-base neutralization reaction. Particle size was measured using an on-line real-time laser diffraction particle sizing system (Insitec, Malvern Instruments Ltd.) using the Hydro SM dispersion unit. Shape analysis was measured by a flow particle imaging instrument (FPIA3000, Malvern Instruments Ltd.). Throughout the experiment, the stirring was kept steady and constant. 0.2g ibuprofen was added into the dispersion unit, and concentration and particle size distribution were stabilized, after which uniform dispersion was confirmed. Sodium Hydroxide (0.5mol) was added drop-wise at regular intervals and drop-wise Hydrochloric acid (0.5mol) was added in a neutralization reaction. Throughout this reaction in-situ monitoring of the concentration, the particle size distribution and particle imaging was conducted.

4. Result Conclusion

The size history is shown in Fig.1 which shows the average particle size and concentration changes over time. Dispersed particles of Ibuprofen in water were initially stabilized (Fig.1A). To this Sodium Hydroxide was added drop-wise. The reduction of concentration (increasing light transmittance Trans (%)) illustrates the reduction in the number of particles and the thinner shapes which would result in the solubility (Fig. 1B). If Hydrochloric acid was added instead, it shows a needle like crystal forming, this eventually brings about the effects of particle precipitation.(Fig. 1C).

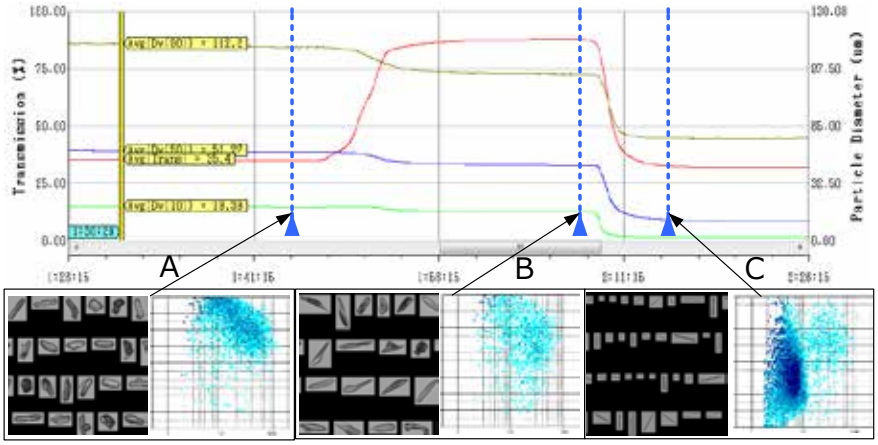

Fig.1 all of the result of a particle size distribution and particle shape

5. Conclusion

An online real time experimental system has been designed which is capable of monitoring the changes in particle size during the crystallization process. This can be coupled with imaging for increased understanding of the process.

2P- 32

Expeditious Parallel Syntheses of All (*E*)- and (*Z*)-Zimeridines and Tamoxifens Utilizing (*E*)-, (*Z*)-Stereocomplementary Synthesis of Multi-substituted α,β-Unsaturated Esters

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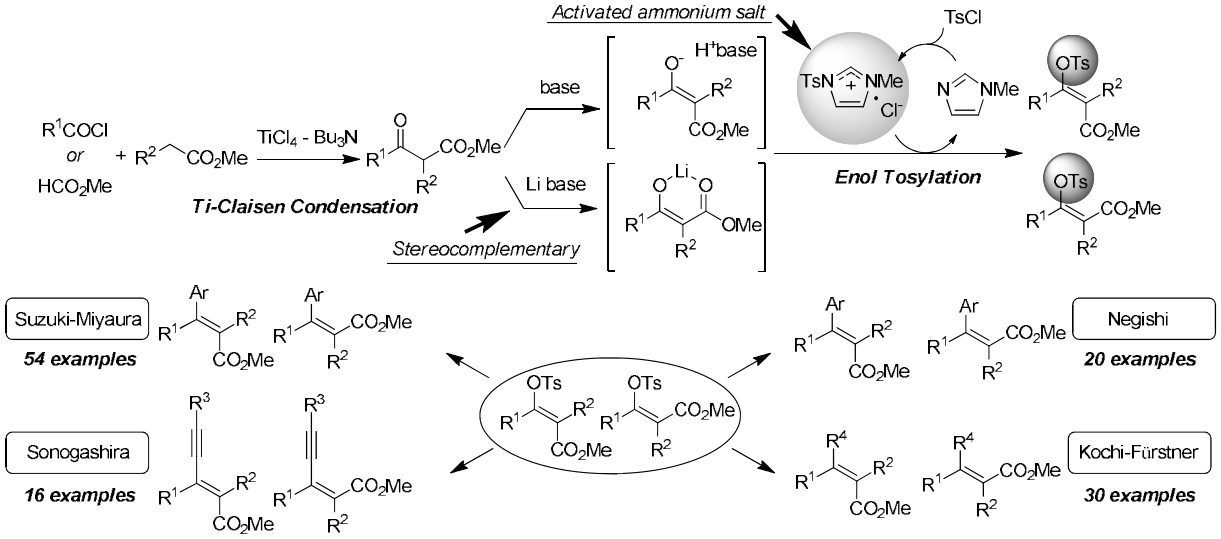
Stereocontrolled synthesis of ubiquitous (*E*)- and (*Z*)-α,β-unsaturated esters occupies a pivotal position in organic synthesis, especially for process chemistry. Nonetheless, (*E*)-, (*Z*)-stereocomplementary and parallel synthetic methods for "multi"-substituted α,β-unsaturated esters with high substrate-generality is extreamly limited due to its inherent complexity. We disclose here efficient syntheses of the titled pharmaceuticals utilizing the present accessible and sufficient substrate-general method.

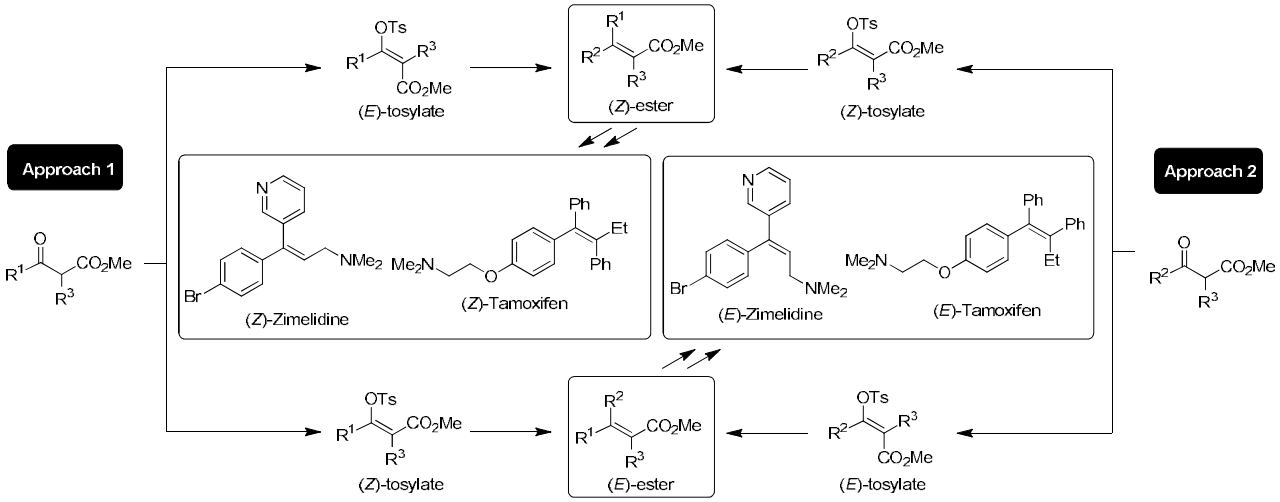
1. Strategy toward the (*E*)- and (*Z*)-stereocomplementary synthetic method for "multi"-substituted α,β-unsaturated esters

Our longstanding studies on mild, practical, and cost-effective condensation reactions reveal that *N*-methylimidazole (NMI) is a key potential activator for *O, N ,S*-acylations, sulfonylation, as well as *C*-acylations.[1,2] With these information taken into account, we achieved the titled synthetic method, which involves three highly substrate-general and robust reaction sequences; (i) Ti-crossed Claisen condensations producing a variety of β-ketoesters or α-formyl esters,[1,3] (ii) (*E*)- and (*Z*)-Stereocomplementary enol tosylations of these esters using TsCl−*N*-methylimidazole (NMI)−bases,[3] and (iii) a number of (**>100 examples**) (*E*)- and (*Z*)-stereoretentive cross-couplings (Negishi,[3a] Sonogashira,[3a] Suzuki-Miyaura,[3b] and Kochi-Fürstner Iron-catalyzed Grignard couplings[4]).



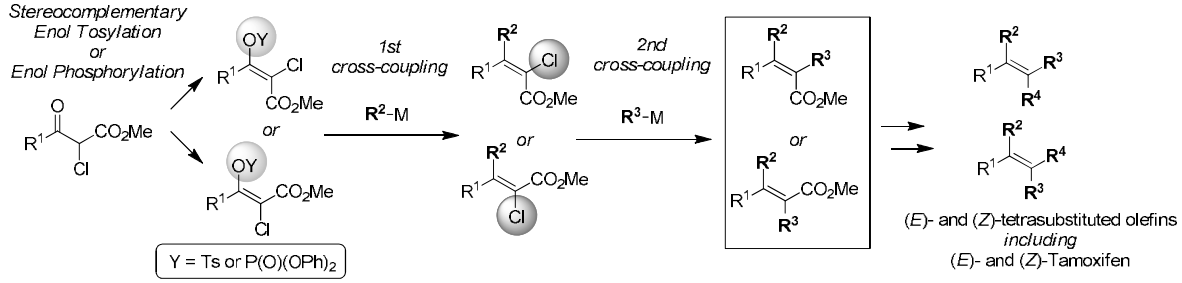
2. "Parallel" syntheses of all four (*E*)- and (*Z*)-Zimelidines and Tamoxifens

Utilizing the present method, syntheses of the titled pharmaceuticals, representative stereodefined olefin motifs, were successfully accomplished with *parallel approach*. The current issue utilizes highly substrate-general (*E*)- and (*Z*)-parallel preparative methods for stereodefined β,β-diaryl, α,β-diaryl,[5] and α,β,β-triaryl-α,β-unsaturated esters. The present dual-mode approach will enhance the versatility for process chemistry.



3. Sequential cross-coupling of α-chlorinated (*E*)- and (*Z*)-enol both tosylates and phosphonates

As a further extension, relevant method for readily accessible reaction sequence for the synthesis of "multi"-substituted (*E*)- and (*Z*)-α,β-unsaturated esters will be presented; (i) (*E*)- and (*Z*)-Stereocomplementary not only *enol tosylations* but also *phosphorylations* starting from available α-chloro-β-ketoesters (ii) First stereoretentive and site-selective cross-couplings of the α-chlorinated enol tosylates or phosphonates (iii) Second stereoretentive cross-couplings of the vinyl chlorides. To demonstrate the utility, an alternative stereocomplementary synthesis of (*E*)- and (*Z*)-Tamoxifens and that for other "multi"-substituted (*E*)- and (*Z*)-multi-substituted olefins are now under progress.



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Tertiary Amine Thiourea-Catalyzed Aldol Reaction of Aryl Methyl Ketones with Aryl Trifluoromethyl Ketones

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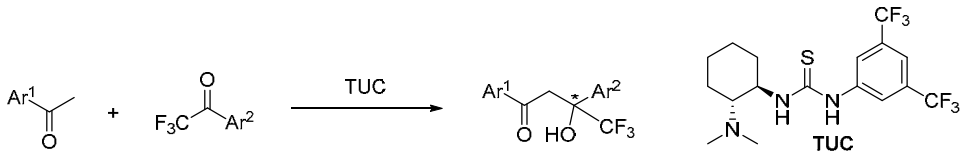
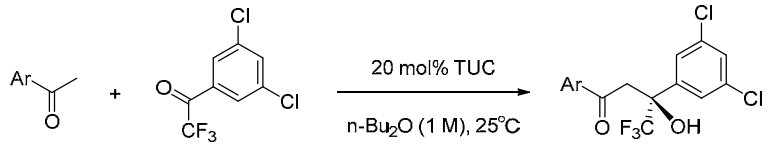
The cross aldol reaction of ketones with trifluoromethyl ketones is an essential tool for the synthesis of β-trifluoromethyl-β-hydroxy ketones. The latter are important intermediates in the pharmaceutical and agrochemical industry, and, therefore, their synthesis has received much attention in recent years. In 2005 Zhang and coworkers first reported the L-proline–catalyzed enantioselective aldol reaction of acetone with 2,2,2-trifluoromethyl aryl ketones, giving tertiary alcohol products with a moderate enantioselectivity of up to 64% ee.[1] Since then, a few other reports involving aliphatic ketones as donors and secondary amine catalysts have emerged. From a mechanistic point of view, in these transformations the catalyst activates the nucleophile via the formation of an enamine intermediate. To our knowledge, there has been no report of an organocatalytic enantioselective aldol reaction between trifluoromethyl ketones as acceptors and aromatic ketones as donors. Presumably, the scarcity of methods utilizing aryl ketones may be attributed to their well-known low ability to form enamine intermediates with secondary amine catalysts. Alternatively, in 2010 Zhao and coworkers reported the first example of enantioselective aldol reaction of ketones with isatin derivatives catalyzed by quinidine thiourea.[2] Assumingly, the tertiary amine deprotonates the nucleophile at α-position of the carbonyl to generate an enolate, which then reacts with the enolate acceptor to furnish the product. We anticipated that such a mechanism would circumvent the above mentioned low reactivity of aryl ketones and render them effective partners in an aldol event.
Herein, we report an enantioselective aldol reaction of aryl methyl ketones with aryl trifluoromethyl ketones catalyzed by a tertiary amine thiourea.



Scheme 1. Enantioselective addition of aryl methyl ketones to aryl trifluoromethyl ketones

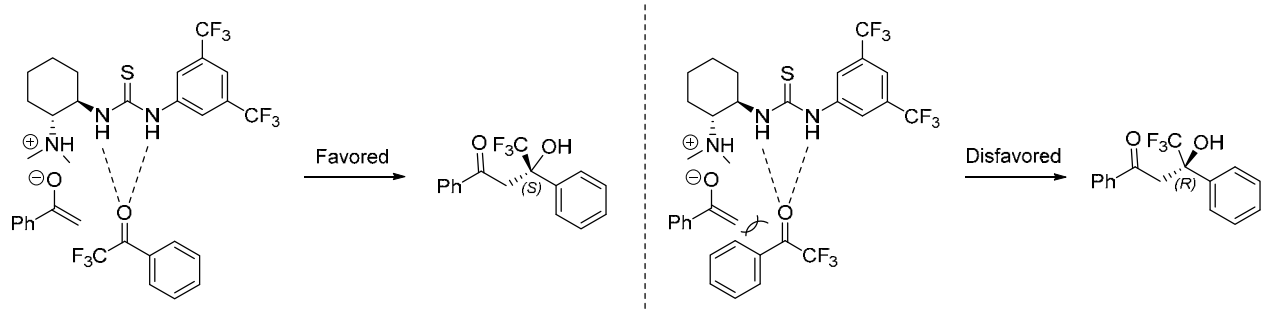
In our preliminary investigation acetophenone and 3',5'-dichloro-2,2,2-trifluoroacetophenone were chosen as reactants. Among a variety of tertiary amine thiourea catalysts tried, Takemoto thiourea (TUC) gave the best outcome in terms of reaction rate and enantioselectivity. Similarly, dibutyl ether was found to be the best solvent for the present transformation. Under our optimized conditions, the scope of the reaction was examined and the results are outlined in Table 1.

Table1. Enantioselective Addition of Aryl Methyl Ketones to 3',5'-Dichloro-2,2,2-trifluoroacetophenone



entry	Ar	time (h)	yield (%)	ee (%)
1	C_6H_5	48	96	76
2	4-NO_2-C_6H_4	24	93	52
3	4-CF_3-C_6H_4	24	95	69
4	2-naphthyl	48	94	75
5	4-MeO-C_6H_4	48	93	79
6	3,4,5-MeO-C_6H_4	48	70	89

The reaction of electron deficient nucleophiles gave the products in excellent yield with a moderate enantioselectivity within 24 h (Table 1, entries 2 & 3). Electron rich ketones required a longer time to furnish the products in good to excellent yield with a high level of enantioselectivity (Table 1, entries 4-6). On the other hand, the reaction of acetophenone with 2,2,2-trifluoroacetophenone proceeded to give the product in 58% yield with 75% ee after 6 days. The S configuration of the product was determined by comparison of its optical rotation with the value reported in the literature.[3] The assumed transition states shown in Scheme 2 are proposed to account for the enantioselectivity observed in this reaction.



Scheme 2. Assumed transition state for the reaction of acetophenone with 2,2,2-trifluoroacetophenone

In conclusion, we have developed an efficient aldol reaction of aryl methyl ketones with aryl trifluoromehyl ketones catalyzed by a tertiary amine thiourea. This method represents a complementary approach to the synthesis of optically active β-trifluoromethyl-β-hydroxy ketones, valuable intermediates in the pharmaceutical and agrochemical industry.

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Sulfenylation of Aromatic Compounds with *N*-Sulfenylbenzimidazoles in the Presence of Alkylating Agents

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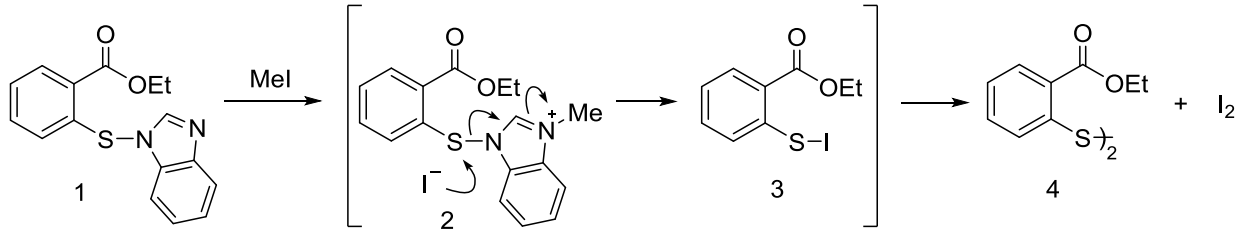
Sulfenylation, an introducing reaction of divalent sulfur atoms to molecules, is commonly carried out with sulfenyl chlorides to various nucleophiles. The sulfenyl chlorides are prepared from reaction of thiols or disulfides with chlorine gas, but chlorine gas is toxic and difficult to handle in laboratories. Therefore, development of a new sulfenylating agent has been desired.

We have developed *N*-sulfenylbenzimidazoles as sulfenylating agents. Since benzimidazolyl groups of the *N*-sulfenylbenzimidazoles worked as good leaving groups instead of chlorides in the sulfenyl chlorides, chlorine gas-free sulfenylation performed. *N*-Sulfenylbenzimidazoles reacted with various nucleophiles such as amines, amides, and thiols to yield the corresponding sulfenylated products. Furthermore, in the presence of acid, the benzimidazolyl group became more electron-deficient state by *N*-protonation, and changed better leaving group. However, these methods did not applied for relatively electron-deficient aromatic compounds. Therefore, we investigated to improve the leaving ability of the benzimidazolyl group by using alkylating agent. Since alkylation is an irreversible reaction being different from protonation, alkylation would more strongly activate leaving group than protonation.

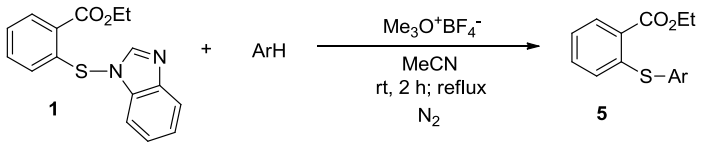
1,3,5-Trimethoxybenzene was treated with **1** in the presence of 10 equivalent amounts of iodomethane as a alkylating agent. As a result, the corresponding sulfenylated products were not obtained and disulfide (**4**) was quantitatively formed. Since the nucleophilicity of iodide ion was probably involved formation of the disulfide by way of a sulfenyl iodide intermediate **3** (Scheme 1), we tried another alkylating agent whose counter anion has no nucleophilicity.



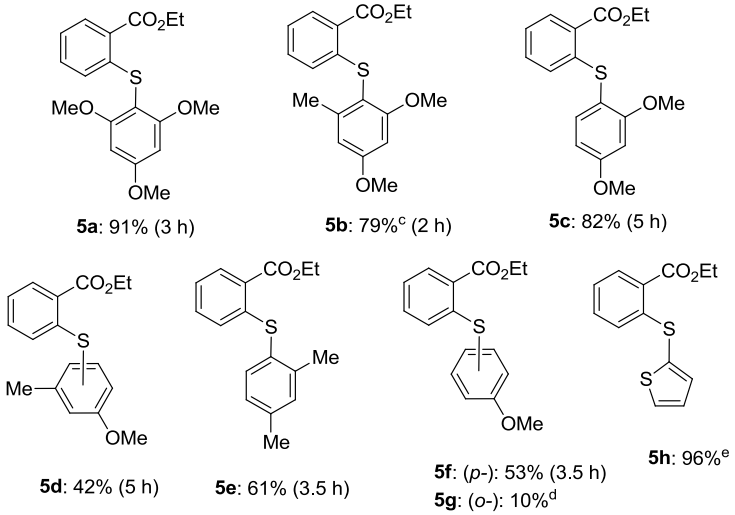
Scheme 1. Methylation of 1 with iodomethane.

When 1,3,5-trimethoxybenzene was treated with **1** in the presence of 2 equivalent amounts of trimethyloxonium tetrafluoroborate (Meerwein reagent) as an alkylating agent, the aimed product **5a** was obtained in 91% yield. This product had not formed without the methylating agent, or was synthesized in a low yield in the presence of 10-camphorsulfonic acid. Acetonitrile was a superior solvent for this sulfenylation. For various kind of aromatic compounds, sulfenylation with **1** in the presence of the Meerwein reagent occurred under the same reaction conditions (Table 1). Sterical hindered 1,3,5-trisubsituted benzenes were sulfenylated on the benzene rings in good yields. Treatment of less methoxy substituted benzenes with **1** also afforded sulfenylated benzenes. Especially, in the case of 1,3-dimethoxybenzene or thiophene, which failed to be sulfenylated with **1** even in the presence of acid, sulfenylated products were obtained. Furthermore, we succeeded in sulfenylation of *m*-xylene or anisole. Triethyloxonium tetrafluoroborate was also used as alkylating agents. Although addition of Meerwein reagents toward **1** activated sulfenylation, this method could not applied for substrates which have reactive substituents to Meerwein reagents, such as amino or hydroxyl groups.

Table 1. Sulfenylation to aromatic compounds[a]



Products and Yields[b]



[a] 1: 0.5 mmol; benzene derivatives: 0.75 mmol: $Me_3^+BF_4^-$: 1.0 mmol; MeCN: 20 mL.
[b] Isolated products. [c] rt, overnight; reflux. [d] NMR yield.
[e] Thiophene: 10 eq. ; rt, 2 h then 100 °C, 5 h; in sealed tube.

In summary, in the presence of Meerwein reagent, *N*-sulfenylbenzimidazole (**1**) was good sulfenylating reagent and proceeded sulfenylation of the benzene derivatives having electron-donating substituents.

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Synthesis of pyrrolo[1,2-*b*][1,2]benzothiazin-10-one

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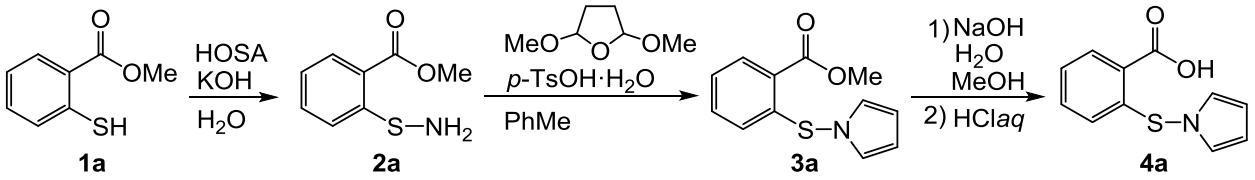
Sulfenamides have sulfur-nitrogen bonds in molucules. Some sulfenamide derivatives are important compounds from the point of bioactivity and synthetic intermediacy. Especially, there are many bioactive compounds in cyclic sulfenamide derivatives. It was reported that pyrrolo[1,2-*b*][1,2]benzothiazin-10-one, which has sulfenamide moiety in the ring, showed antimicrobial activity, but one synthetic method was reported and sole derivative was synthesized[1)]. According to the privious papers, we succeeded in the chlorine gas-free synthesis of various kinds of sulfenamide derivatives; usual sulfenamides were prepared by use of chlorine gas[2)]. Using this method, synthesis of various kinds of sulfur-nitrogen bond containing copmouds was easily performed. In this presentation, we will report synthesis of pyrrolo[1,2-*b*][1,2]benzothiazin-10-ones from sulfenamides by way of *N*-sulfenylpyrroles.

Methyl 2-sulfenamoylbenzoate (**2a**) was synthesize by the reaction of methyl thiosalicylate (**1a**) with hydroxylamine-*O*-sulfonic acid (HOSA) under basic conditions. Since pyrrole ring formation from amines or amide by the reaction with 2,5-dimethoxytetrahydrofuran was known as the Clauson-Kaas pyrrole synthesis, this synthetic method was applied to *N*-unsubstituted sulfenamide **2a**. As a result, *N*-sulfenylpyrrole derivative **3a** was obtained by the reaction of **2a** with 2,5-dimethoxytetrahydrofuran.

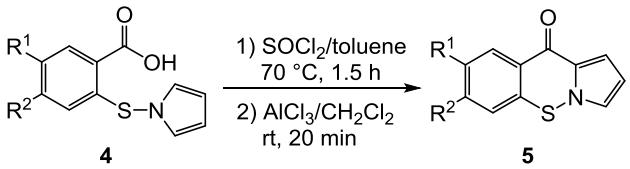
When *N*-sulfenyl *N*-heterocycles were treated with nucleophiles, heterocyclic groups worked as leaving groups and substitution reaction occurred on the sulfur atoms. Among the *N*-sulfenylheterocycles, *N*-sulfenylbenzimidazoles were operated as good sulfenylating reagents: amines and thiols were convered to sulfenamides and disulfides, respectively. However, the pyrrolyl group of *N*-sulfenylpyrrole **3a** did not leave by the reaction with nucleophiles such as primary amines or thiols, and the starting material was recovered. Atack by hydroxyl anion also did not occur at the sulfur atom but hydrolysis occurred at an ester moiety of a substituent. As a result, 2-(*N*-pyrrolylsulfenyl)benzoic acid (**4a**) was synthesized.



Scheme 1. Synthesis of *N*-pyrrolylsulfenylbenzoic acid (**4a**)

Using 2-(*N*-pyrrolylsulfenyl)benzoic acid **4a**, intramoleculary cyclization was investigated to synthesize pyrrolo[1,2-*b*][1,2]benzothiazin-10-ones. After chlorination of carboxlic acid **4a** with thionyl chloride, intramoleculary cyclization proceeded by treatment of the formed acid chloride with aluminum chloride to affrded the aimed pyrrolo[1,2-*b*][1,2]benzothiazin-10-one (**5a**). Using this reaction procedure, various kinds of substituted pyrrolo[1,2-*b*][1,2]benzothiazine ring were able to be synthesized (Table 1).

Table 1. Synthesis of **5** by way of acid chlorides

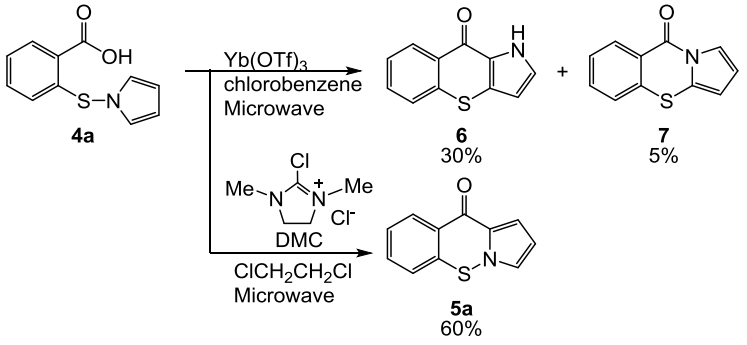


4 **5**

R^1	R^2	**5**	Yield[1)] (%)
H	H	**5a**	73
H	Me	**5b**	48
H	MeO	**5c**	45
F	H	**5d**	36

1) Isolated product.
Reaction conditions;
$SOCl_2$: 1 mL, toluene: 10 mL,
$AlCl_3$: 1.2 eq., CH_2Cl_2: 50 mL.

In recent years, direct cyclization of benzoic acid derivatives to heterocycles was reported. For example, thioxanthone derivatives were directly synthesized from 2-phenylthiobenzoic acid[3)]. Therefore, intramolecular cyclization of *N*-sulfenylpyrrole **4a** was initially tried in the presence of Lewis acids. When **4a** was heated at 165 °C under microwave irradiation in the presence of catalytic amount of $Yb(OTf)_3$, a main product was **6** along with its isomer **7** as a by-product. This result showed that the S-N bond in the *N*-pyrrolylsulfenylbenzoic acid **4a** was easily cleaved with Lewis acids, and rearrangement reaction occurred. Next, cyclization of **4** with dehydrating reagent was tried. Synthesis of **5a** was succeeded in the reaction of **4a** with 2-chloro-1,3-dimethylimidazolium chloride (DMC) as a dehydrating reagent under microwave irradiation conditions.



4a **6** 30% **7** 5% **5a** 60%

Scheme 2. Cyclization of *N*-sulfenylpyrrole **4a.**

It is concluded that the Clauson-Kaas reaction was applicable to sulfenamides to yield *N*-sulfenylpyrroles. After 2-(*N*-pyrrolesulfenyl)benzoates were hydrolyzed to the corresponding carboxylic acid, intramolecular cyclization was performed to afford pyrrolo[1,2-*b*][1,2]benzothiazin-10-ones.

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Selective Flow Synthesis of Methanofullerene Derivative PCBM Using Sulfur Ylide

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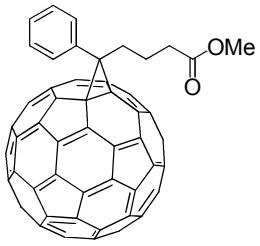
Bulk heterojunction (BHJ) organic solar cells are considered to be a promising alternative for a low-cost sustainable energy source. The excellent electron-accepting capabilities of fullerenes offer promise as materials for organic photovoltaics. In particular, since Sariciftci *et al.*[1] reported that a conversion efficiency of 2.5–3.0% could be achieved using a polymer solar cell based on a bulk heterojunction (BHJ) of poly[2-methoxy-5- (3',7'-dimethyloctyloxy)-1,4-phenylenevinylene] (MDMO-PPV) and methanofullerenes, typically [60]PCBM ([6,6]-phenyl-C_{61}-butyric acid methyl ester), the polymer/methanofullerene photovoltaic system has attracted a great deal of attention for its significant promise (Figure 1).

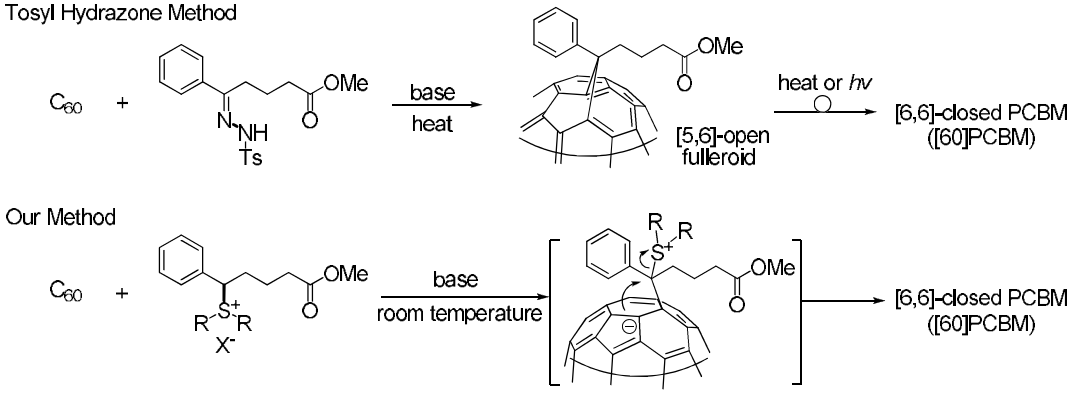


[60]PCBM

Figure 1

More recently, power conversion efficiencies of 8–10% have been achieved for solution-processed BHJ solar cells through the use of new conjugated polymer donor materials with PCBMs. Despite the use of these improved conjugated polymer donors, PCBMs are still considered the standard acceptors in organic photovoltaic systems. The development of scalable and efficient methods for the synthesis of PCBMs should be further investigated for the purpose of promoting their practical use.

However, PCBM preparative methods have been restricted to the few procedures by Hummelen and Wudl *et al.*[2] They originally cyclopropanated of C_{60} with 1-phenyl-1-(3-(methoxycarbonyl) propyl)diazomethane that was formed *in situ* through the base-induced decomposition of the sodium salt of methyl 4-benzoylbutyrate *p*-tosylhydrazone. This method always produces isomeric



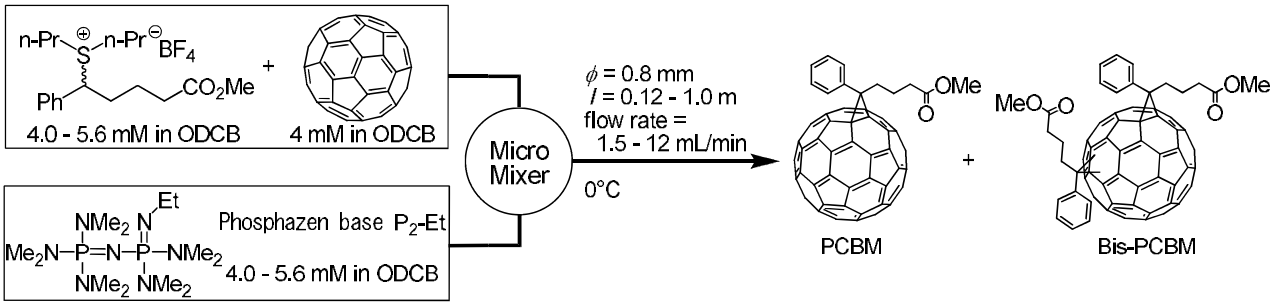
Scheme 1

intermediates (primarily the [5,6]-open fulleroids) as mono-adduct, and as well as bis-adduct (Bis[60]PCBM) which obtains as a by-product of the preparation of PCBM. Previously, we reported an alternative, one-pot, [6,6]-direct, mild, efficient synthesis of PCBMs with a semi-stabilized sulfur ylide generated *in situ* from the corresponding novel sulfonium salts (Scheme 1).[3] Although a mild synthesis for PCBMs using sulfur ylide was achieved, the problem of multi adduct formation still remained.

Recently, a wide variety of chemical reactions have been already carried out in micro flow syntheses offering selectivity control by suppression of by-product formation, which is mainly related to accurate temperature control, efficient mass transfer and mixing. In the course of our study, we report here selective micro flow synthesis of methanofullerene derivative PCBM using sulfur ylide.

When the T-shaped mixer was used, the selectivity was almost the same as the batch reactor. The use of the IMM mixer (channel width 40 μm) increased the selectivity. By increasing flow rate, PCBM was obtained in 70% yield (Table 1).

Table 1. Micro Flow Synthesis of PCBM Using IMM Mixer



entry	micro mixer	total flow rate (mL/min)	residence time (s)	PCBM (%)	Bis-PCBM (%)
1[a]	IMM	1.5	2.5	48	11
2[a]	IMM	3	2.5	54	11
3[a]	IMM	6	2.5	64	11
4[a]	IMM	12	2.5	65	10
5[b]	IMM	12	0.3	70	16

a) conditions : 4.8 mM of sulfonium salt and 4.8 mM of base were used.

b) conditions : 5.4 mM of sulfonium salt and 5.4 mM of base were used.

In conclusions, we demonstrated the selective flow synthesis to prepare PCBM for BHJ organic solar cells. Sulfur ylide intermediate, formed in situ through the organic base, quickly reacts with fullerenes to directly give the target methanofullerene in high yield.

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2P- 37

Continuous flow synthesis of methanofullerene PCBM

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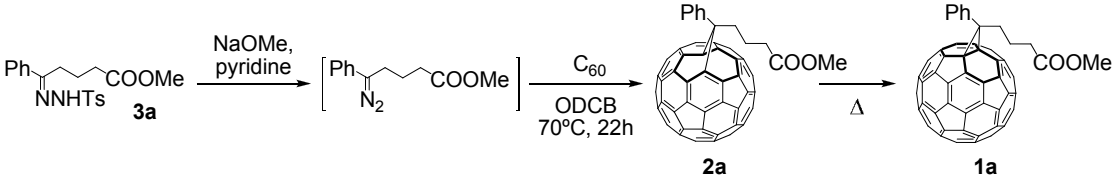
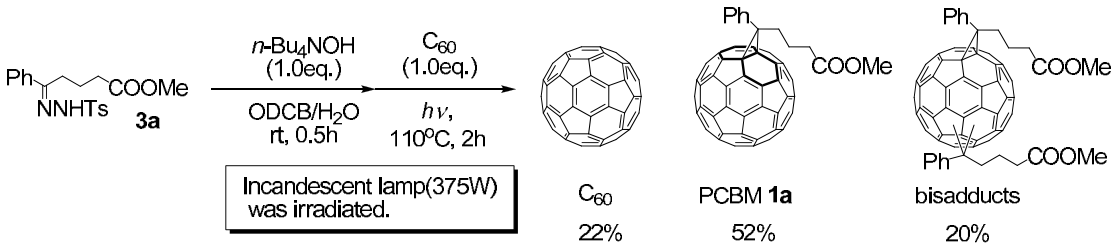
Organic thin film photovoltaics are a promising alternative to silicon-based solar cells owing to their considerable advantages, such as light weight, flexibility, and low fabrication cost. The power conversion efficiency of organic photovoltaics is still lower than that of silicon-based solar cells; however, numerous studies have achieved improvements in the performance of organic photovoltaics during the past decade. In spite of these developments, [6,6]PCBM **1a** is still widely recognized as a standard acceptor molecule, and numerous studies have continued to develop novel acceptor materials based on the modification of PCBM, including our previous work.[1]

Syntheses of [6,6]PCBM **1a** and its analogues are carried out following the procedure reported by Hummelen et al.[2] In their procedure, C_{60} reacts with tosylhydrazones **3a** in the presence of NaOMe in pyridine and *o*-dichlorobenzene (ODCB) to give derivative of [6,6]PCBM **1a** (Scheme 1). In general, this procedure is performed under severe anhydrous conditions and [6,6]PCBM **1a** is obtained in relatively low yield (~40%) together with unreacted C_{60} and higher adducts, such as bisadducts. This reaction is very sensitive to moisture; in our group, we have found the reproducibility of this method problematic, and also found that the selectivity and yield of PCBM depends on the degree of anhydrous conditions. To improve the selectivity for PCBM, excess amounts of C_{60} are sometimes used to prevent the formation of higher adducts. Additionally, during this procedure, open-cage [5,6]PCBM **2a** is obtained first and then converted to the thermally stable closed-cage [6,6]PCBM **1a** under thermal or photoirradiation conditions.[2] Recently, the synthesis of [6,6]PCBM derivatives via photoirradiation conditions has gained popularity, but the yields and selectivity of the PCBMs are still low. Separation of PCBM from the reaction mixture and purification are laborious and costly; therefore, a cost-effective and convenient preparation of PCBM is desired for practical use.



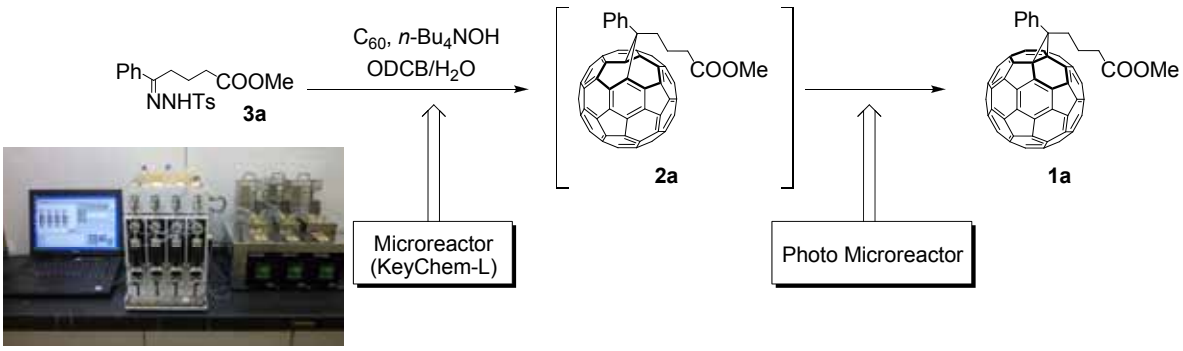
Scheme 1 Procedure of Hummelen et al.[2] for the synthesis of [6,6]PCBM **1a**

During our research on the development of fullerene derivatives for acceptor molecules in photovoltaics,[1] we have also focused on efficient, convenient, and cost-effective synthetic methods for PCBMs. After the reinvestigation of the procedure to generate the diazocompound from the corresponding tosylhydrazone **3a**, the aqueous quaternary ammonium hydroxide solution was found to be an appropriate base not only for the generation of the diazocompound but also for the reaction with fullerene. Now, we have developed a facile synthetic method of [6,6]PCBM **1a** with a good yield using an aqueous two-phase system in the presence of quaternary ammonium hydroxide under photoirradiation conditions (Scheme 2).[3] This aqueous two-phase system with quaternary ammonium hydroxide gave reproducible results and avoids the need for laborious anhydrous conditions and excess amount of reagents; however, there is still room to improve the yield and selectivity for the PCBM.



Scheme 2 Direct [6,6]PCBM **1a** synthesis under photoirradiation condition.

Microreactors afford efficient mixing and precise temperature and residence time control. That enables to improve the product yield and selectivity in some cases. Therefore, we have attempted using microreactors for this aqueous two-phase system to synthesize PCBM. When KeyChem-L (YMC Co., Ltd.) was used, the product yield and selectivity were comparable with batch process, but the product was predominantly open-cage fulleroid [5,6]PCBM **2a** owing to the lack of photoirradiation. Next, we have developed the continuous tandem flow system consisted of KeyChem-L as a heating reactor with the additional photo microreactor (Scheme 3). In this presentation, the detailed results of this system will be discussed.



Scheme 3 Continuous flow system for the synthesis of [6,6]PCBM **1a**.

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3) Iwai, T.; Matsumoto, F.; Hida, K.; Moriwaki, K.; Takao, Y.; Ito, T.; Mizuno, T.; Ohno, T. *Synlett*, **2015**, *26*, 960.

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Synthesis of PHB-b-PLA Block Copolymer Useful as the Compatibilizer in PHB/PLA Blends

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PLA is a biodegradable polymer derived from renewable resources, and it is considered as non-toxic for human and environment. PHB is produced from the fermentation of bacteria and is also an environmentally friendly biodegradable polymer. These two polymers can be used in biomedical engineering, tissue regeneration, the substrate of drug release and replacing commercial polymeric materials to reduce the impact on the environment. Yet, PLA and PHB are incompatible in all proportions. The purpose of this study is to synthesize PHB-b-PLA copolymer as a compatibilizer for the PHB/PLA blends and hopefully increasing their mechanical properties and toughness. First, PHB oligomers were produced by methanol alcoholysis of PHB at 100°C. The molecular weight measured from GPC decreased rapidly from the original 110 kDa to 15.3 kDa at 10 min, and after that it gradually decreased with time. After 2 h of degradation, the molecular weight was 2.25 kDa determined from NMR, which indicated this degraded PHB had 26 repeating units. Subsequently, this PHB_{26} oligomer was used to initiate the ring-opening polymerization of lactide using stannous octanoate ($Sn(Oct)_2$) as catalyst to produce PHB-b-PLA block copolymer. After 1 day of reaction at 140°C, a copolymer of PHB_{26}-b-PLA_{10} was synthesized. In order to investigate the miscibility of PHB/PLA blends, differential scanning calorimeter (DSC) was used to determine their thermal properties, especially glass transition temperature (T_g). It is known that if two polymers are immiscible, two T_gs would appear on the DSC curve which correspond to the respective T_gs of the two polymer components. However, if they are miscible, only one T_g lying between the two individual T_gs would be observed. If they are only partial miscible, two T_gs would still be observed but shift to each other on the DSC curve. The blends of PHB and PLA exhibited two T_gs, 2.0 and 58.7°C, exactly the same as those of pure components, indicating they are immiscible. Yet, the blends of PHB_{26}-b-PLA_{10} and PLA showed only one T_g which decreased with increasing the composition of PHB_{26}-b-PLA_{10}. This demonstrated the copolymer was miscible with PLA. Moreover, the T_g-composition relationship can be fitted very well with the Gordon-Taylor equation. Furthermore, tensile mechanical properties of the PHB_{26}-b-PLA_{10}/PLA blends were measured. The results showed that the copolymer could serve as plasticizer for the PLA in which tensile elongation increased with the addition of copolymer. The elongation at break could increase from 2.8% for the pure PLA to a large value of 328% for the blend at 30% PHB_{26}-b-PLA_{10}. Yet, both initial modulus and ultimate tensile strength decreased. We also investigate the blends of PHB and PLA by addition of PHB_{26}-b-PLA_{10} as the compatibilizer. It was found that the copolymer could increase the compatibility of PLA and PHB up to 10 wt.% PHB.

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Sulfenylation of Aromatic Compounds with *N*-Sulfenylbenzimidazoles in the Presence of Acid

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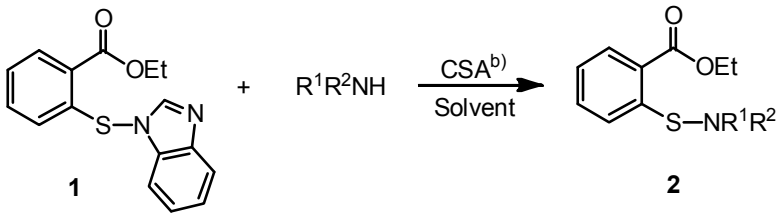
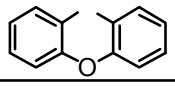
Introduction of sulfur substituents to organic compounds was an important process for synthesis of organosulfur compounds. Among these processes, sulfenylation was the reaction of introducing divalent sulfur atoms as substituents. Although sulfenyl chlorides were in general used as sulfenylating agents, they were unstable and were synthesized from the corresponding thiols or disulfides by using chlorine gas. Chlorine gas is toxic and difficult to handle in usual laboratories. Therefore, a new alternative method without using sulfenyl chlorides has been desired. In the previous paper, we have reported that *N*-sulfenylbenzimidazoles were good sulfenylating agents to various nucleophiles, such as nitrogen, sulfur, and carbon nucleophiles, to produce sulfenamides, disulfides, sulfides, respectively[1)]. Moreover, the *N*-sulfenylbenzimidazoles were prepared without using chlorine gas. However, there was limitation for sulfenylation with the *N*-sulfenylbenzimidazoles, and sterical hindered or weak nucleophiles could not be sulfenylated[2)].

A benzimidazolyl group was a good leaving group due to electron-deficiency of the heterocyclic ring. Since protonation of the benzimidazolyl group occurred on the nitrogen atoms by addition of acid, the group would become more electron-deficient state and change to better leaving group. Therefore, sulfenylation of *N*-sulfenylbenzimidazole (**1**) under acidic conditions was investigated (Table 1). When *N*-methylaniline was treated

Table 1. *N*-Sulfenylation to secondary amines[a)]



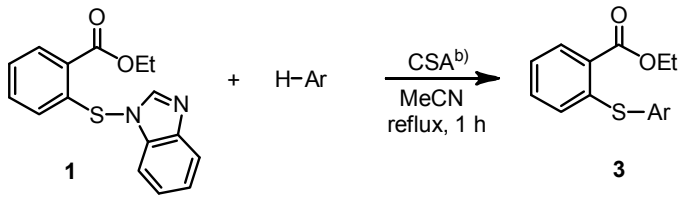
R^1	R^2	Solvent	Temp. (°C)	Time (h)	CSA (eq.)	**2**	Yield[c)] (%)
Me	Ph	Toluene	100	10	none	**2a**	29 [d)]
		Toluene	100	20	none		81 [d)]
		Toluene	100	2	1		76
		MeCN	reflux	2	1		74
Ph	Ph	Toluene	100	8	none	**2b**	0 [d)]
		Toluene	100	1	1		47
		MeCN	reflux	1	1		80
		MeCN	reflux	1	1	**2c**	90

a) **1**: 0.6 mmol; amine: 1.0 mmol; CSA: 0.6 mmol; solvent: 15 mL.
b) 10-Camphorsulfonic acid. c) Isolated product. d) See Ref. 2.

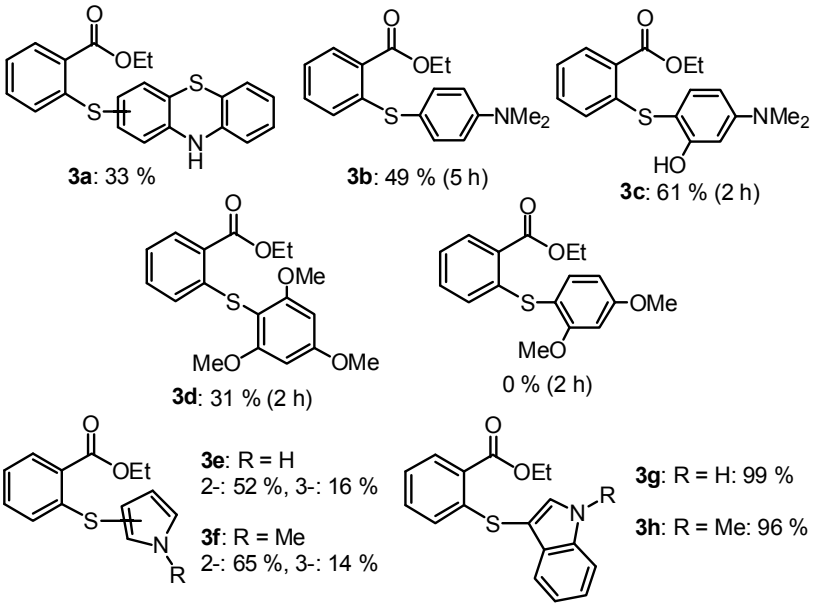
with **1** in the presence of one equivalent amount of 10-camphorsulfonic acid (CSA), *N*-sulfenyl-*N*-methylaniline (**2a**) was obtained in a good yield under milder reaction conditions than those reported previoulsly[2]. Although diphenylamine was not sulfenylated with **1** under previous reaction conditions, *N*,*N*-diphenylsulfenamide (**2b**) was obtained in good yield under this acidic conditions. One equivalent amount of acid was required for efficient sulfenylation.

As *N*-heterocycles, phenoxazine was *N*-sulfenylated to form *N*-sulfenylated phenoxazine (**2c**) in a good yield. However, in the reaction of phenothiazine, a *C*-sulfenylated product (**3a**) was obtained. In the same manner, electron rich aromatic compounds, such as *N*,*N*-dimethylaniline or 1,3,5-trimethoxybenzene, were allowed to react with *N*-sulfenylbenzimidazole (**1**), sulfenylation on the benzene ring occurred. However, 1,3-dimethoxybenzene was not sulfenylated even acidic conditions due to insufficient nucleophilicity. For pyrroles and indoles, sulfenylated products were obtained with the acidic sulfenylation in good yields (Table 2).

Table 2. *C*-Sulfenylation to aromatic compounds[a)]



Products and Yields[c)]



a) **1**: 0.6 mmol; amine: 1.0 mmol; CSA: 0.6 mmol; solvent: 15 mL.
b) 10-Camphorsulfonic acid. c) Isolated products.

In conclusion, *N*-sulfenylbenzimidazoles activated by one equivalent amount of acid were good sulfenylating reagents: *N*-sulfenylation for aniline derivatives and *C*-sulfenylation for electron rich benzene derivatives and heterocycles.

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2P- 40

Single-pass flow reactions: only 20 seconds hydrogenation and Suzuki-Miyaura reaction

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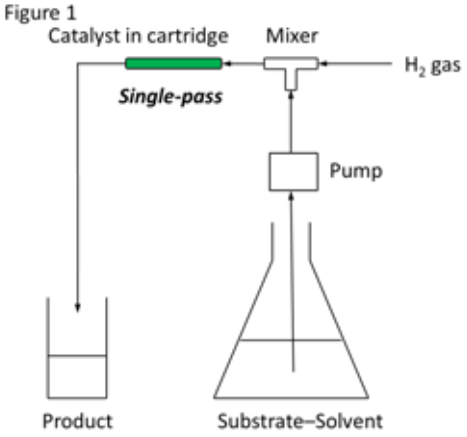
Figure 1

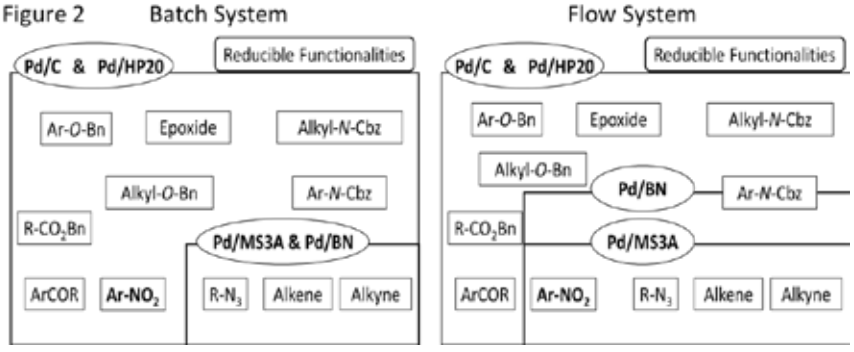


The continuous flow system is a technology that significantly achieves high reaction efficiency compared to the batch system in a flask or reaction vessel (Figure 1). The systems use an apparatus for delivering a substrate solution toward the cartridge filled with a solid catalyst. Since the channel in the catalyst cartridge for the passing of the substrate solution is narrow, the reaction efficiency should be enhanced based on the secure contact of the substrate with the catalyst, and reagents including hydrogen gas. The immobilized transition-metal catalyst, which has a risk of ignition under atmospheric conditions, is tightly enclosed in the cartridge, hence, the reactions should be carried out in safe. Furthermore, no operation for the removal of the metal residue from each reaction solution should be necessary, and the catalyst can be continuously used unless the degradation of the catalyst quality is observed.

In this symposium, three types of effective flow reactions, general hydrogenation, arene hydrogenation, and Suzuki-Miyaura reaction, which could be completed within only 20 seconds, are presented.

Hydrogenation using a variety of supported catalysts under continuous flow conditions have been applied to the reduction of various reducible functionalities[1], although no systematic evaluation of each catalyst for the hydrogenation of each functionality has ever been investigated due to a lot of variable parameters, such as solvent, concentration of the substrate solution, flow rate of the liquid, temperature, and hydrogen pressure. We have recently developed a variety of palladium catalysts immobilized on various supports, such as a synthetic adsorbent (DIAION HP20)[2], molecular sieves (MS3A and MS5A)[3], and boron nitride (BN)[4]. 10% Pd/HP20 has a quite high catalyst activity comparable to 10% Pd/C, while 0.5% Pd/MS3A and 0.3% Pd/BN are useful for the chemoselective hydrogenation of alkynes, alkenes, and azides in the presence of other reducible functionalities including nitro groups. In this symposium, we

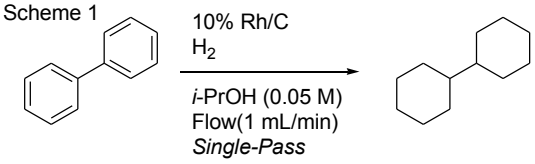
Figure 2



demonstrate a systematic study on the flow hydrogenation of a variety of reducible functional groups using 10% Pd/C, 10% Pd/HP20, 0.5% Pd/MS3A, and 0.3% Pd/BN as catalysts. When 10% Pd/C or 10% Pd/HP20 was used as a catalyst, the hydrogenation of various reducible functionalities was completed just within approximately 20 seconds during the single-pass process through the catalyst cartridge[5]. Specific chemoselectivies for the 0.5% Pd/MS3A or 0.3% Pd/BN-catalyzed flow hydrogenation system were also observed. Namely, nitro groups, which were tolerant under the batch hydrogenation conditions, could be reduced to the corresponding amines under the present flow conditions (Figure 2).

Saturated carbocyclic and heterocyclic skeletons are important basic structural units for functional materials. Since the functionalization of saturated cyclic compounds is quite difficult in comparison to that of aromatic compounds, the hydrogenation of arenes after the chemical modification on their rings should be expected to be a practical preparation method of functionalized saturated cyclic compounds. 10% Rh/C and 10% Ru/C are found to be effective catalysts for the hydrogenation of aromatic rings, affording a variety of saturated cyclic compounds in excellent yields under not only batch[6] but also flow[7] conditions. The arene hydrogenation was successfully completed during the single-pass of the reaction mixture to the catalyst cartridge (Scheme 1).

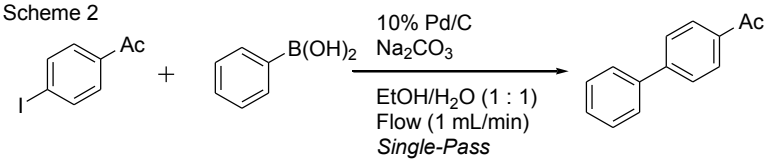
Scheme 1



The Pd-catalyzed Suzuki-Miyaura coupling reaction between aryl halides and arylboronic acids is one of the most useful methods for the construction of biaryl units. In our laboratory, an efficient batch-type ligand-free Pd/C-catalyzed Suzuki-Miyaura coupling reaction was developed; a variety of biaryls could be synthesized from aryl bromides and arylboronic acids in good to high yields at room temperature in the aqueous media[8]. Here, we demonstrate a continuously flow Pd/C-catalyzed Suzuki-Miyaura coupling reaction under the continuous flow system. Aryl iodides smoothly reacted with various arylboronic acids in a single-pass manner to give the corresponding biaryls in good yields (Scheme 2)[9].

It is a distinct feature of three flow reactions that we present in this symposium is that the completion of reactions requires only 20 seconds (single pass of the reaction solution through the catalyst cartridge).

Scheme 2



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2P-41

Thermal hazard and evolved gases analyses on an acrylic acid runaway polymerization

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Introduction

Acrylic acid (AA) is widely used as a feedstock of highly transparent and water absorptive polymer. On the other hand, AA is highly reactive towards runaway polymerization that has been causing many accidents. Polymerization is known as a reaction which generates dangerous amount of heat. When a runaway polymerization occurs, temperature rise immediately, and then internal pressure of the tank is generated by residual monomer vaporization and polymer thermal decomposition and the tank explosion occur. Therefore, to prevent AA tank explosion, it is necessary that not only thermal hazard but also pressure generation mechanism of runaway polymerization are clarified.

Thermal decomposition of AA polymer prepared by controlled polymerization produced H_2O, CO_2 and CO gases [1]. The accident investigation report [2] remarked that the boiling liquid expanding vapor explosion (BLEVE) of the AA tank was occurred. BLEVE is a vapor explosion caused by the rupture of a tank or vessel containing a pressurized liquid superheated. In terms of BLEVE, it has been known that H_2O is more dangerous than other liquids [3]. It is considered that an AA runaway polymerization produces water. Therefore, an AA runaway polymerization could enhance potential of BLEVE.

To obtain better understanding for pressure generating when AA undergoes a runaway polymerization, temperature and pressure profile were measured using Accelerating Rate Calorimeter (ARC). In addition, evolved gases analysis of AA polymer was conducted using thermogravimetry-mass spectroscopy (TG-MS).

Experimental

ARC has been used as the instrument which can evaluate reaction runaway hazards in adiabatic condition at chemical processes. It can measure self heat rate, pressure, pressure rate under adiabatic condition which is in the worst case to analyze and assess thermal hazard. ARC (TIAX) was used to confirm that an AA runaway polymerization generates accidental pressure. We added *p*-methoxyphenol (hydroquinone monomethyl ether: MQ), a radical inhibitor, to AA up to 2 mass% which is much higher than industrial suitable ratio to suppose an AA storage tank.

TG (Rigaku TG8120) coupled with a mass spectrometer (MS; Shimadzu QP-2010) was employed. The associated TG-MS data were acquired simultaneously to determine the thermal behavior of the AA polymer samples upon heating while evolved gases were analyzed. The samples were prepared by heating and spontaneous polymerization (110^{o}C, 3hrs in the atmosphere).

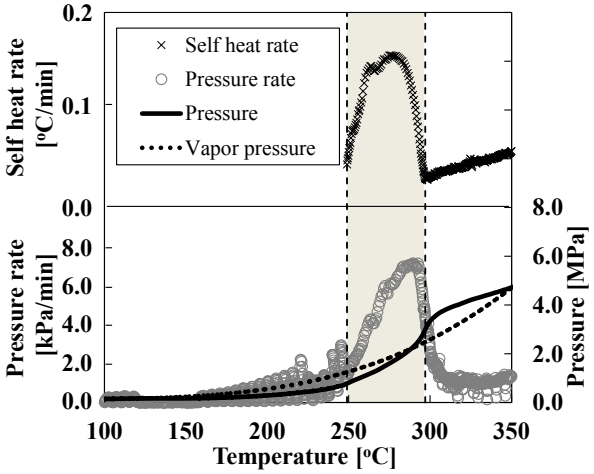

Fig.1 Pressure profile of AA containing MQ 2 mass% in ARC

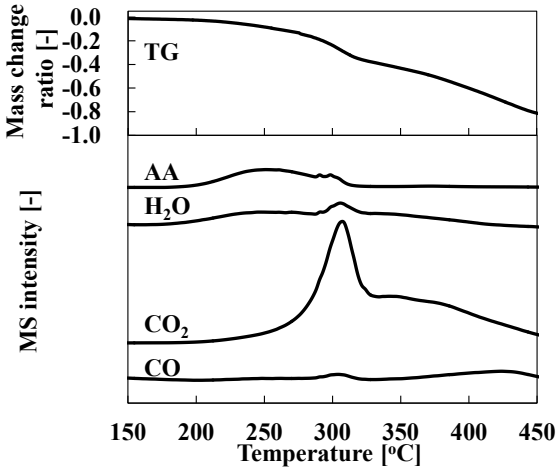

Fig.2 Evolved gases of an AA spontaneous polymer thermal decomposition in TG-MS

Results and discussion

Figure 1 shows a result of pressure profiles of AA containing MQ 2 mass% in ARC. The sample generated higher pressure than AA monomer's vapor pressure [4] from 290°C. That meant materials whose boiling point were lower than AA were produced. In comparison of the accident investigation report [2], the sample generated accidental pressure which could rupture a tank. Exotherm of the sample was detected from 249°C. The exothermic reaction was polymerization and pressure rate of the sample increased. Therefore, the AA polymer simultaneously decomposed to low molecules with polymerization.

Figure 2 shows a result of evolved gases of an AA spontaneous polymer thermal decomposition in TG-MS. The result indicated AA monomer vapor and H_2O generated, after that, CO_2 and CO evolved. The residue was 11% after the reaction. This result was similar to that of AA polymer prepared by controlled polymerization [1]. In consequence, AA containing excessive MQ ratio was polymerized spontaneously over 250°C and the polymer was decomposed to H_2O, CO_2 and CO gases in parallel with the polymerization. Therefore, an AA polymerization produce these vapor and gases which could enhance the potential and impact of BLEVE.

Summary

To clarify the causes of BLEVE induced by an AA runaway polymerization, pressure profile during the reaction progress was measured using ARC, thermal decomposition products were analyzed using TG-MS. From the ARC result, higher pressure than AA monomer's vapor pressure was observed. The result of TG-MS indicated the major products of AA polymer were H_2O, CO_2 and CO. These vapor and gases enhance the potential and impact of an AA tank BLEVE.

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2P- 42

Living Radical Polymerization of Styrene by ATRP Initiator Immobilized on Glass Surfaces

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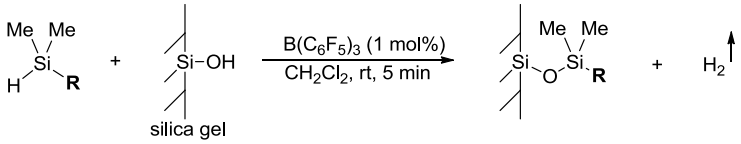
Organofunctionalization of silica gel via a covalent bonds using silane coupling agents such as halosilanes and alkoxysilanes is useful for preparation of organic-inorganic hybrid materials. However, it is difficult to purify their silane coupling agents by silica gel column chromatography due to the moisture sensitivity and high reactivity. Recently, we reported an alternative class of silane coupling agents, allylsilanes, which behave as the synthetic equivalent of alkoxysilane and have sufficiently low reactivity to allow purification using silica gel chromatography.[1] However, both high temperature and long reaction time are required for organofunctionalization of silica gel surface with allylsilanes. Very recently, we reported an effective surface functionalization of silica by Si-H activation of hydrosilanes catalyzed by tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) within 5 min at room temperature (Scheme 1).[2] Several kind of hydrosilane coupling agents were prepared starting from 3-chloropropyldimethylsilane and its Grignard

Scheme 1. Efficient organofunctionalization of silica with hydrosilanes



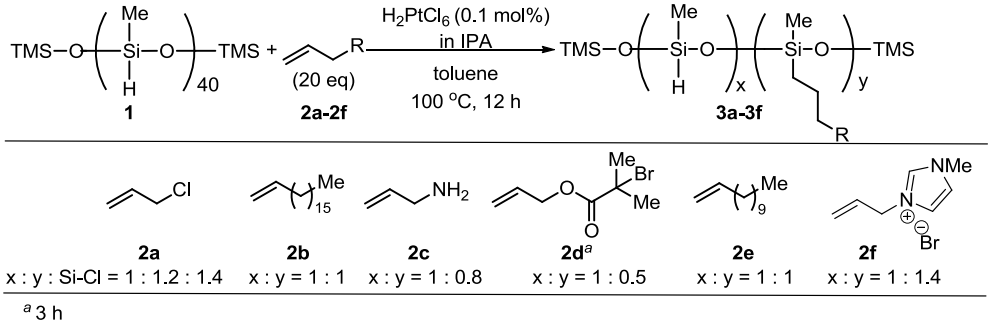
R = $CH_2CH_2CH_2Cl$, $CH_2CH_2CH_2Br$, $CH_2CH_2CH_2N_3$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NO_2$, $CH_2CH_2CH_2MgBr$, Ph, Bn, $CH_2CH_2CH_2COOH$, $CH_2CH_2CH_2COOEt$, $CH_2CH_2CH_2COPh$, $CH_2CH_2CH_2SH$, $CH_2CH_2CH_2OH$, $C_{12}H_{25}$, $C_{18}H_{37}$

reagent (Scheme 1). Herein we disclose a facile preparation method for a series of poly-hydrosilanes instead of mono-hydrosilanes starting from inexpensive polymethylhydrosiloxane (PMHS) and their applications to surface modification.

Initially, we examined the transformation of Si-H in PMHS to functional group by hydrosilylation with terminal alkenes. Although hydrosilylation with simple alkenes smoothly proceeded to give the corresponding PMHS derivatives having alkyl chains, allyl halides and terminated olefin esters reacted with Si-H to provide the desired product in poor yield. Our initial studies were focused on the screening of transition metal catalysts such as $[IrCl(cod)]_2$, $RhCl(PPh_3)_3$, $(^nBu_4N)_2[PtCl_6]$, $[PtCl_2(C_2H_4)]_2$, Karstedt's catalyst, and H_2PtCl_6, which are capable of hydrosilylation of PMHS. It was found that H_2PtCl_6 catalyst

controls the ratio of the number of introduced-functional groups and the number of unreacted-hydrosilyl groups, giving the desired PMHS derivatives (Scheme 2). Particularly, we focused on the preparation of a novel PMHS derivative **2d** acting as ATRP initiator. In result, PMHS derivative containing both 2-bromoisobutyroxysilyl and hydrosilyl groups (PMHS-ATRP) was successfully prepared via

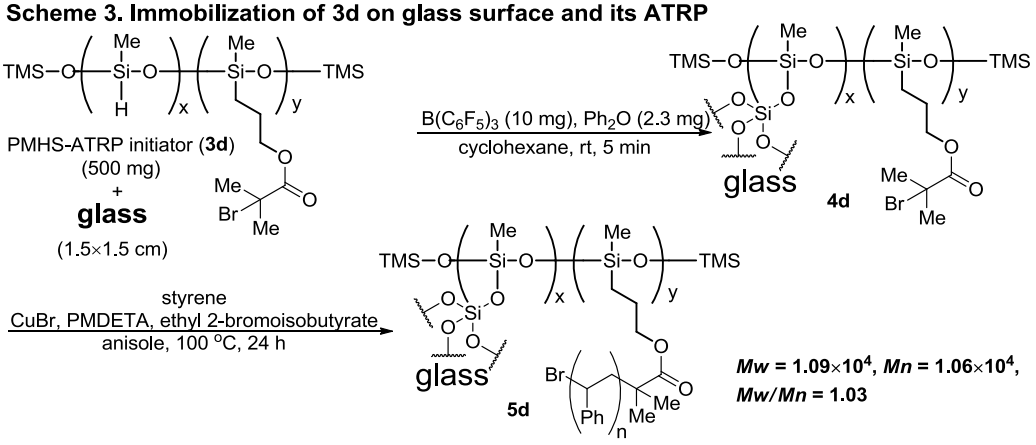
Scheme 2. Preparation of PMHS derivatives



[a] 3 h

hydrosilylation of allyl 2-bromoisobutyrate with PMHS in the presence of H_2PtCl_6, though the hydrosilylation of simple allyl ester like allyl acetate did not provide the desired PMHS derivatives. The resulting PMHS-ATRP was used for $B(C_6F_5)_3$-catalyzed immobilization on glass surface to give the desired functional glass. The living radical polymerization of styrene initiated on glass surface smoothly proceeded to give the expected polymer with *Mn* of 1.06×10^4 and *Mw/Mn* of 1.03.

Scheme 3. Immobilization of 3d on glass surface and its ATRP



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2P- 43

Tris(pentafluorophenyl)borane-Catalyzed Organofunctionalization of Various Materials with Hydrosilane Derivatives

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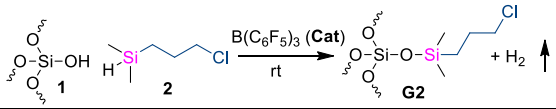
Grafting of an organic functional group to a silica surface via a covalent bond is the most reliable method of modification and functionalization of the silica surface. The covalent bond used for the binding is mostly the Si-O-Si bond, where one of the silicon atoms is on the silica surface and the other comes from organosilicon compounds, and the Si-O-Si bond is formed by the reaction of an Si-OH group on the silica gel surface with organosilicon compounds containing a leaving group of high reactivity on the silicon atom. The organosilicon compounds most commonly used are those containing an alkoxy leaving group. Unfortunately, these functional groups are so reactive toward hydrolysis that the silicon compounds cannot be handled under hydrolytic conditions or cannot be purified by silica gel chromatography. Recently, we have reported new conceptional allysilane derivatives acting as silane coupling agent or sol-gel precursor instead of conventional silane coupling agent such as alkoxy-, halo-, amino-, and acyloxysilanes. The allylsilanes can be purified by column chromatography and easily prepared their derivatives due to moisture stability. However, harsh conditions are required to immobilize them on silica gel surface. Herein, we report innovated method for surface modification of silica gel with dehydrogenation catalyzed by tris(pentafluorophenyl)borane ($B(C_6F_5)_3$). The new metal-free process is sufficiently completed at room temperature within five minutes and applicable to surface modification of inorganic oxides and polymer.

Initially, a benchmark reaction between amorphous mesoporous silica microparticles (MCM-41, **1**, specific surface area 850 $m^2\ g^{-1}$) and (3-chloropropyl)dimethylsilane (**2**) in the presence of $B(C_6F_5)_3$ catalyst (**Cat)** was performed under various conditions for optimization of the condition (Table 1). All the reactions were performed under the anhydrous condition by suspending 0.1 g of dry **1** in 3 mL of dichloromethane (DCM) containing 0.5 mmol of **2**. The addition of 5 mol % of **Cat** in the aforementioned reaction mixture leads to an intensive evolution of hydrogen, which terminates within a few minutes. The elemental analysis on the samples reacted for 60 min (**G2**, Entry 1, Table 1) and 5 min (**G2,** Entry 2, Table 1) shows almost identical loading of organics (1.68 and 1.65 mmol g^{-1}, respectively), indicating the completion of reaction within 5 min. Decreasing the **Cat** loading to 1 mol % (**G2**, Entry 3, Table 1) did not change the reaction rate and comparable (1.67 mmol g^{-1}) loading of organics was obtained within 5 min. Furthermore, the reaction proceeded without diminishing its rate in the absence of solvent (**G2**, Entry 4, Table 1), and can be

performed at even lower temperature (0 °C, **G2**, Entry 5, Table 1). It is noteworthy that in the absence of catalyst no detectable loading of organics was found even after 24 h (**G2**, Entry 6, Table 1).

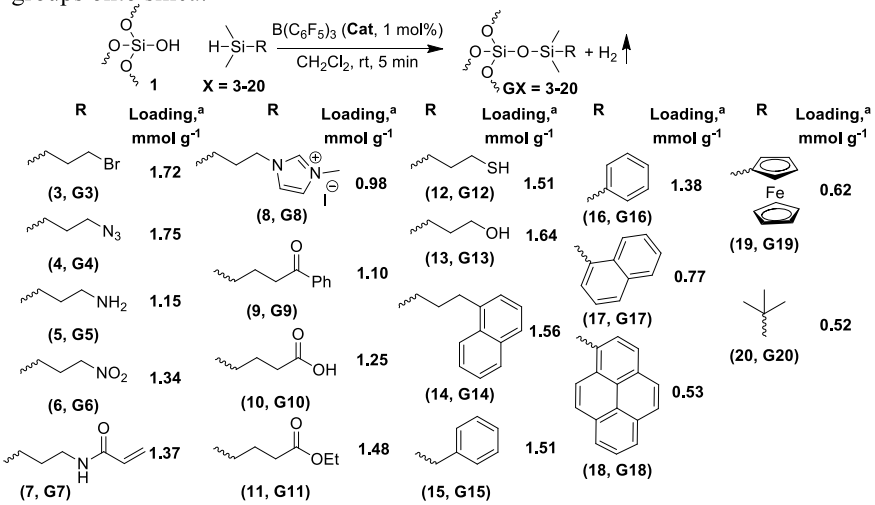
Table 1. Optimization of reaction conditions for immobilization of **2** on **1** at room temperature.



Entry	**Cat**, mol %	Solvent, mL	Time, min	Loading on **G2**, mmol g^{-1}
1	5.00	CH_2Cl_2, 3	60	1.68
2	5.00	CH_2Cl_2, 3	5	1.65
3	1.00	CH_2Cl_2, 3	5	1.67
4	1.00	N. A., 0	5	1.71
5	1.00	N. A., 0/ 0 °C	5	1.69
6	0.00	CH_2Cl_2, 3	1440	0.00

All the surface grafted products were purified by vigorous washing with dichloromethane and hexane, followed by drying under vacuum.

Figure 1. Catalytic immobilization of hydrosilanes containing various functional groups onto silica:



In order to extending the methodology, we have synthesized hydrosilanes bearing diverse functional groups using simple traditional synthetic methods. All the compounds after synthesis were purified by using conventional laboratory procedures like extraction and silica gel column chromatography, and were obtained with high yields and purity. Grafting of these functionalized hydrosilanes on **1** was performed using the same condition as Entry 3 (Table 1), and in all the cases, grafting was finished within 5 min irrespective of the functional groups on hydrosilanes. The loading efficiencies vary between 1.75 and 0.52 mmol g^{-1} depending on the functional groups (Figure 1). Furthermore, this grafting method was successfully used for modification on the surface of supports such as glass, alumina, titania, polyvinylalcohol (PVA), polyethylene terephthalate (PET) and cellulose.

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2P- 44

Design and operation of microreactor for heterogeneously catalyzedprocess - Case study with direct synthesis of hydrogen peroxide

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Microreactor technology has been developed more than two decades. It is contributing process intensification by increasing productivity, promoting safety, and expanding process window for which conventional process technology cannot afford. These reactors commercially available mainly support liquid-phase reactions, while those for multiphase reactions (such as gas-liquid, gas-liquid-solid) have been still limited; the reactor design should be optimized depending on the types of reactions, and we are applying current digital fabrication technologies to pursue such optimization.

In this presentation, we would like to show how we developed reactor for the direct synthesis of hydrogen peroxide. Hydrogen peroxide is currently produced by the anthraquinone process, through its redox cycle. Our target reaction is the direct synthesis from hydrogen and oxygen, which remains uncommercialized in spite of great effort among chemical process industry. This reaction is conducted as a three phase reaction, hydrogen and oxygen (gas) – water (liquid) – catalyst (solid) reaction, in which hydrogen and oxygen dissolved in water react over the catalyst to produce hydrogen peroxide. The inherent risk of explosion, and poor solubility of both hydrogen and oxygen into water has kept the process challenging.

Initially we demonstrated that the characteristics of microreactor, explosion prevention by microchannel, effective heat removal, and mass-transfer, fits well to conduct the direct synthesis of hydrogen peroxide by freeing hydrogen / oxygen ratio and mass transfer promotion (Fig. 1) [1]. Based on the result, we attempted to promote the reactor performance by controlling gas- and liquid flow by the reactor design.

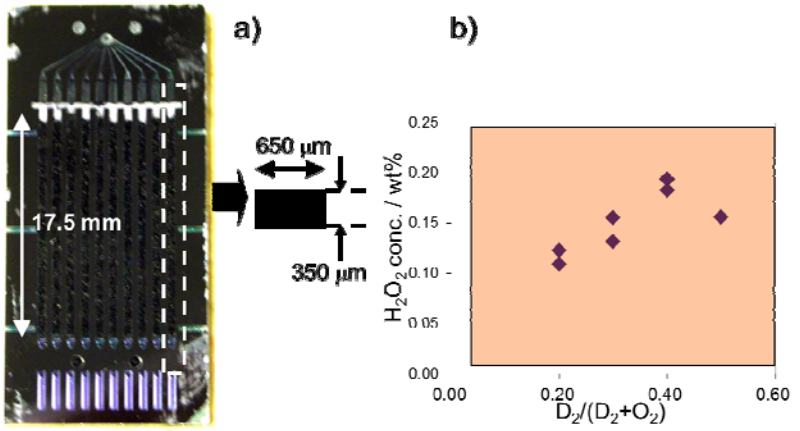

Fig. 1 Si microfabricated reactor for direct synthesis of hydrogen peroxide, in which catalyst was packed in 10 microchannels separately (a). and its performance for hydrogen peroxide production (b). All experimental data were taken within explosive region.

Fig. 2 shows the detailed structure of our glass fabricated microreactor with packed bed channels; the reactor consist of catalyst packed beds, two gas inlets (hydrogen and oxygen), one liquid inlet, and outlet.

Shallow channels fabricated by HF etching create reasonable pressure drops during the introduction of hydrogen and oxygen into each packed bed, while a series of bundle of shallow channels contribute to equal liquid distribution. Both contribute equal and steady gas- and liquid flow among each catalyst packed bed channel, realizing the productivity increase by scaling out instead of scaling up. It should be noted that such shallow channels are enabled by MEMS fabrication procedure over glass wafer; fabricating similar structure over metal still remains challenging. Such flow control system leads to the production of 10 wt % of hydrogen peroxide at room temperature (no extra cooling effort) and 1 MPa, much milder condition than past achievements disclosed in literatures. We were also successful for demonstrating parallel operation of microreactor based on the same principle. The throughput of 10 wt% hydrogen peroxide can achieve 10 kg/day, by multiplying single packed bed of ca. 10g/d of productivity [2, 3].

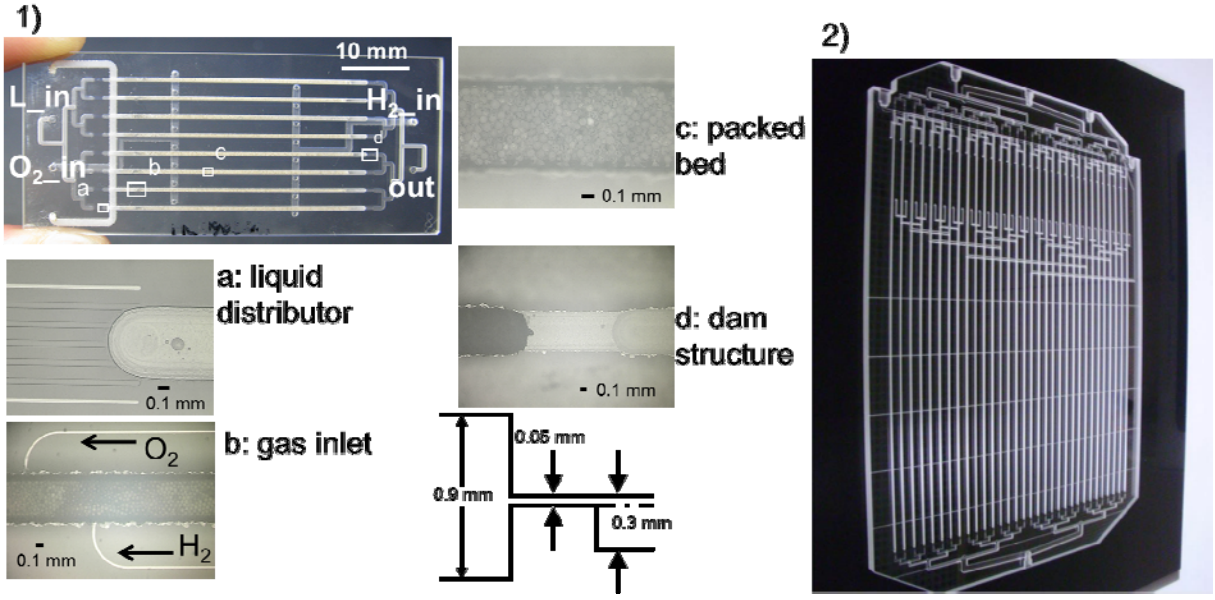

Fig. 2 1) Glass fabricated 8-parallel packed bed reactor (30mm X 70 mm) for hydrogen peroxide synthesis. Overall structure as well as detailed magnified structures (a – d) are shown. The throughput of 10 wt% hydrogen peroxide is 20 g/day. 2) 32-parallel packed bed reactor (120 mm X 180 mm) with the throughput of 0.5 kg/day.

Through this presentation, we show that microreactor technology can serve small scale “production”, based reactor optimization and scaling our effort supported by microfabrication technique. We hope that the reactor development promoted by digital fabrication, other than chemistry (reaction, catalyst…) development will be an option in conducting chemical process development.

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Purification of biopharmaceuticals using small particle polymer media

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Rapid development of high-yielding and robust manufacturing processes for biopharmaceuticals is an area of significant focus in the pharmaceutical landscape [1]. Monoclonal antibodies (mAb) have emerged as one of the most exciting therapeutic modalities. Monoclonal antibodies are commonly produced by cell culture, followed by downstream purification processes. As a titer of cell culture increased rapidly, there have been strong interests for a chromatography media with high throughput protein purification [2]. Affinity and ion-exchange chromatography are principal tools used for such purification processes, and the key factors to improve such productivity are a dynamic binding capacity and a selectivity of the chromatography media [3]. And these factors can be essentially controlled and optimized by carefully choosing adequate chromatography media with optimal size and a pore size.

Due to fairly rigid, spherical and totally porous particles, polymethacrylate beads are chosen. It is expected that mass transfer is relatively fast for smaller particle, as the column bed keeps durable at high flow rate [4]. In particular, affinity media MabSpeed™ and ion exchange media ChromSpeed™ series are used in this study. Average particle diameters of these media lie in the range of 30 to 60μm. ChromSpeed™ shows higher selectivity (Table 1, Fig. 1) and dynamic binding capacity (Fig. 2) compared to other commercial media. In addition, pressure drop has been measured and observed to be proportional to the process flow rate, indicating that the polymer media have sufficient physical strength [5].

In this presentation high dynamic binding capacities and high selectivity will be presented when they are applied for mAb purification. We also present dynamic binding capacities after repeated cleaning in place cycles with 0.1-0.5M NaOH to show that they will meet the demands of biopharmaceutical manufacturer.

	ChromSpeed™ S103	Agarose Based Media	Polymer Based Media
Base matirics	Polymethacrylate	Agarose	Polymethacrylate
SBC (mg-IgG/mL-resin)	143	144	143
Particle Size(μm)	60	90	75
Ion Exchange Capacity (meq/mL-resin)	0.09	0.12	0.16
Functionality	$-SO_3^-$	$-SO_3^-$	$-SO_3^-$

Table 1. Strong Cation Exchangers used in basic study.

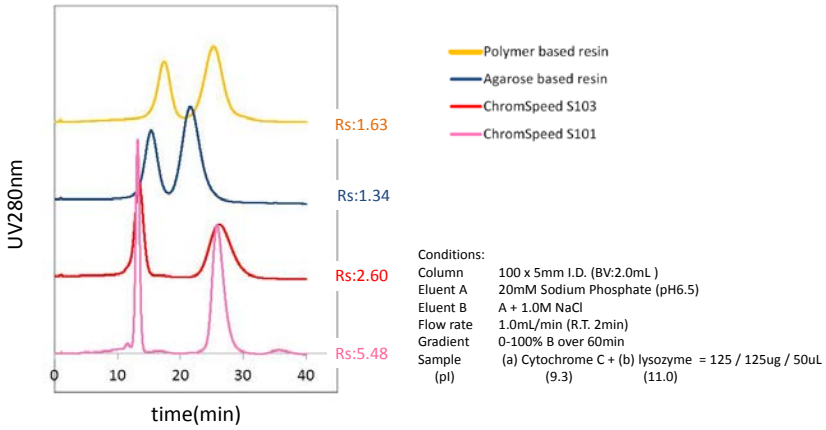

Fig.1 Selectivity

Column	5 x 100 mmH (BV:2.0mL)
Buffer	20mM Sodium Acetate (pH5.5)
Flow rate	200, 400, 600, 800 cm/h (R.T. 3.0, 1.5, 1.0, 0.75 min)
Sample	a) 1.0, b) 2.5, c) 10 mg/mL human IgG

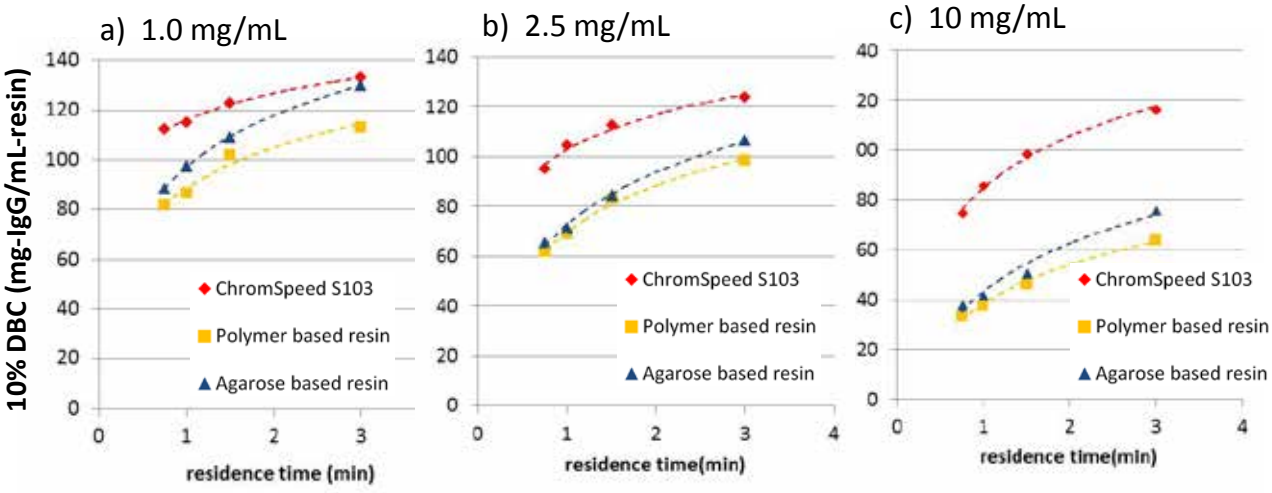

Fig. 2 High Binding Capacity for ChromSpeed™

References

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[4] S. Katsuo et al., poster presentation at SPICA 2014, Basel (2014)

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2P- 46

Second Generation Syntheses of Benzyl Piperidine Derivatives: A Key Intermediate for the Preparation of SERT/5-HT_{1A} Dual Inhibitor

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Hidefumi Yoshinaga[2], Hideo Terauchi[1], Koji Fujimoto[1]
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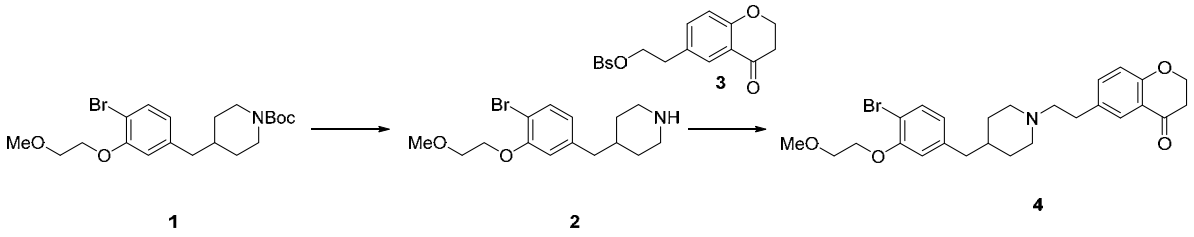
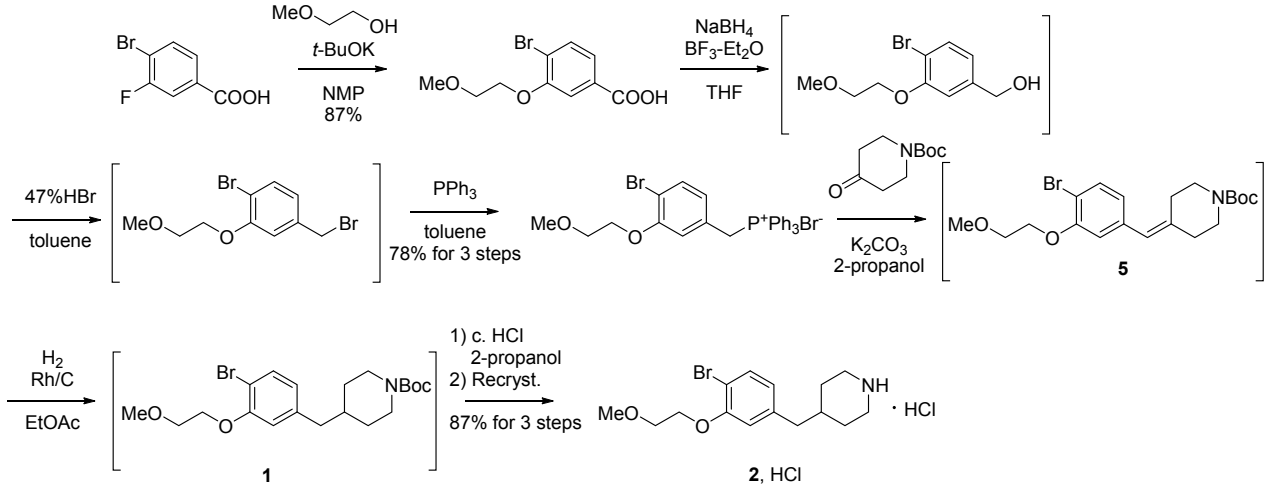
Second generation processes for benzyl piperidine compound **1,** an intermediate of SERT/5-HT_{1A} dual inhibitor **4** (scheme 1),[1] are described.

Scheme 1. Process to prepare **4**



Scheme 2. Synthetic route of **2** (hydrochloride) for early stage development



Although the first generation process (scheme 2) was successfully scaled up to 40 kg to deliver material for early clinical trials, the route needed to be improved for future material supply due to the following three problems:

[1] WO 2011016468 A1, WO2009099087 A1.

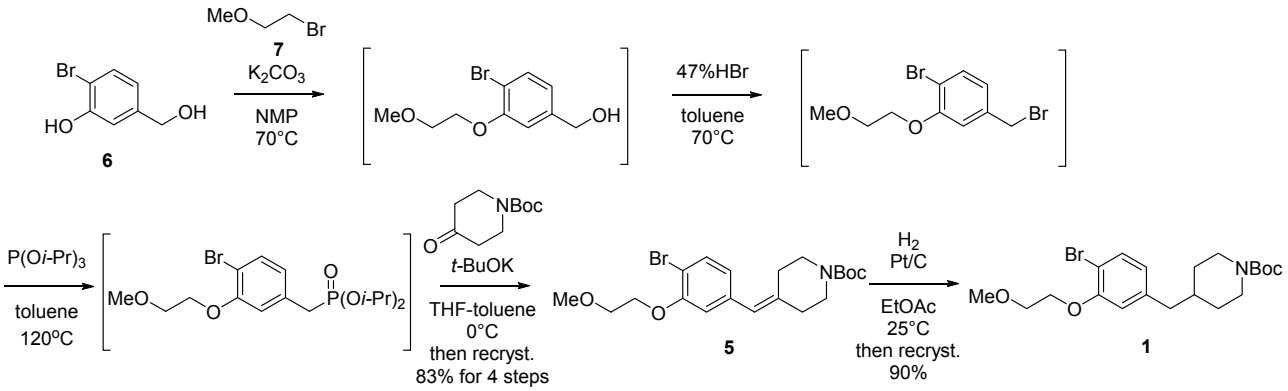
i. Hydrogen fluoride is formed at acidic workup in the first step.

ii. Silica gel column chromatography was needed to remove phosphine oxide after the Wittig reaction.

iii. 40 weight % (vs **5**) of expensive 10% Rh/C (50% wet) was needed for full conversion in the hydrogenation step.

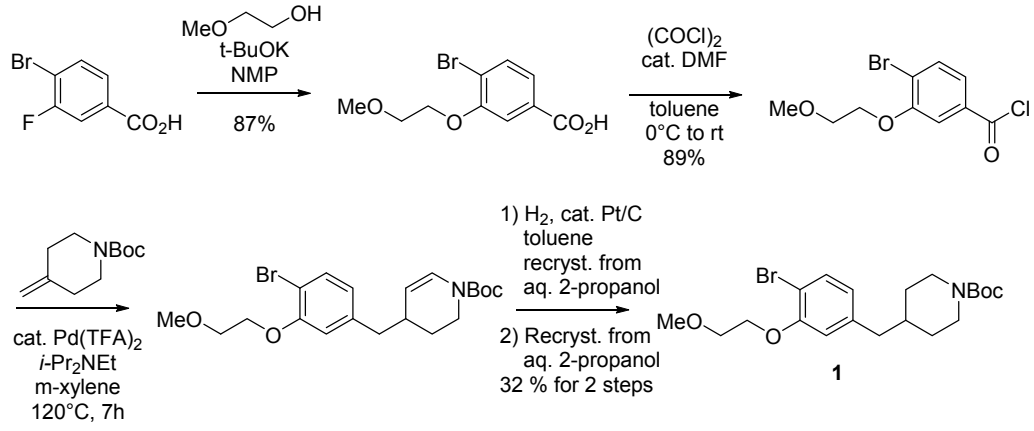
After extensive route scouting, we were able to establish the second generation process (scheme 3), which was demonstrated in 5 kg scale without an issue. The process highlights the Horner-Wadsworth-Emmons reaction with minimum side reaction, selective hydrogenation of a double bond in the presence of aryl bromide. Impurities in **1** were identified by LC-MS analysis and isolation by preparative HPLC. It was confirmed that the amount of these impurities could be reduced to acceptable level by limiting the quality of two starting materials **6** and **7**, thus established robust process.

Scheme 3. The second generation synthesis of compound **1**



Significant efforts for route scouting as well as potential future manufacturing methods (third generation synthesis, scheme 4) will also be discussed.

Scheme 4. Route to **1** via decarbonylative Heck reaction



Asymmetric α-Fluorination of Amino Acid Derivatives via Memory of Chirality

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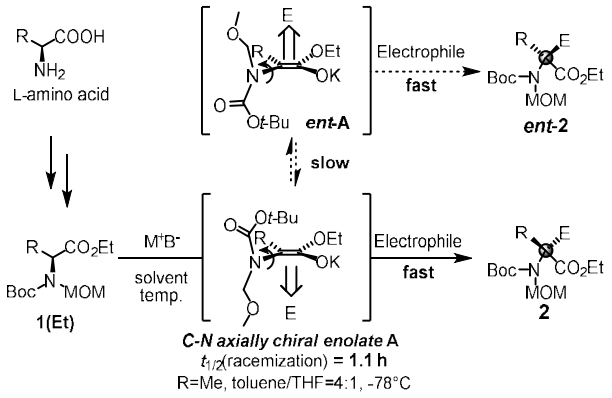
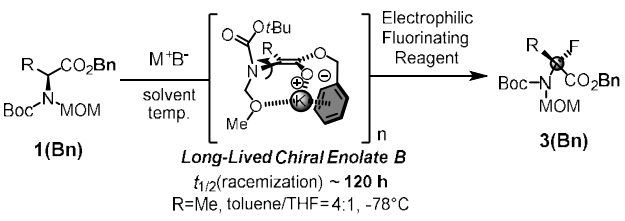
Fluorinated amino acids have attracted increasing interests as characteristic mimics of natural amino acids. Whereas preparation and application of α-amino acids with fluorinated side-chains has been well developed, only little has been known for α-fluoro α-amino acids. We describe here a new method for the asymmetric synthesis α-fluoro α-amino acids from naturally abundant α-amino acids.

We have developed asymmetric reactions that proceed via axially chiral enolate intermediates (Memory of Chirality, MOC).[1] This methodology provides a direct access to various α-functionalized amino acids from natural α-amino acid without any additional chiral sources (Scheme 1). Therefore, MOC strategy is suitable for large-scale preparation, and indeed utilized for kilogram-scale preparations of drug candidates.[2] The key player that enables this strategy is the intermediary axially chiral enolate, which, however, undergoes time-dependent racemization by themselves. Chiral enolate **A** generated from an alanine ethyl ester derivative are assumed not to be suitable for the relatively slow reaction processes, especially in intermolecular reactions including α-fluorination because of their relatively short half-life of racemization as observed in enolate **A** (R=Me, $t_{1/2}$=1.1 h). To overcome this limitation, we focused on exploring a method to elongate the life-time of the chiral enolate. We have previously found that aggregate structure of chiral enolate critically affected their half-lives of racemization.[3), 4)] Based on these backgrounds, we recently developed that chiral enolate **B** generated from alanine benzyl ester **1(Bn)** undergoes racemization with a half-life of about 120 hours (Scheme 2). Enolate **B** was assumed to be racemization-tolerant due to its tight aggregate structure involving intramolecular cation-π interaction between counter cation of the enolate and the phenyl ring of the ester moiety. Encouraged by these findings, we applied this phenomena to long-lived chiral enolates to asymmetric α-fluorination of amino acid derivatives.



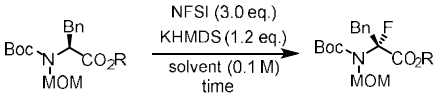
Scheme 1. Strategy of Memory of Chirality



Scheme 2. Asymmetric α-Fluroination of Amino Acid Derivatives via Long-Lived Chiral Enolate

Solvent effects in the reactions and the ester moiety of the substrate were investigated (Table 1). Treatment of phenylalanine benzyl ester derivative **1b(Bn)** with KHMDS and NFSI in THF/DMF (1:1) at -78 °C gave **3b(Bn)** in 96% yield and 82% ee. By decreasing the coordination ability of the solvent, enantioselectility of th asymmetric α-fluorination was increased up to 92% ee in THF/DMF (4:1) (entry 1-3). While use of ethyl ester **1b(Et)** as a substitute gave **3b(Et)** in 71% yield and 51% ee under the similar conditions, **3b(Et)** was obtained in 85% ee (5% yield) when the reaction was quenched after 10 min (entry 4, 5). These results indicate that enantioselectivity of this reaction largely relied on the life-time of chirality of the enolate intermediate.

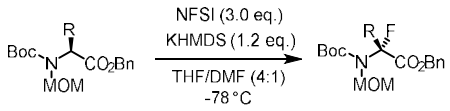
Table 1. Effects of solvent and ester moiety

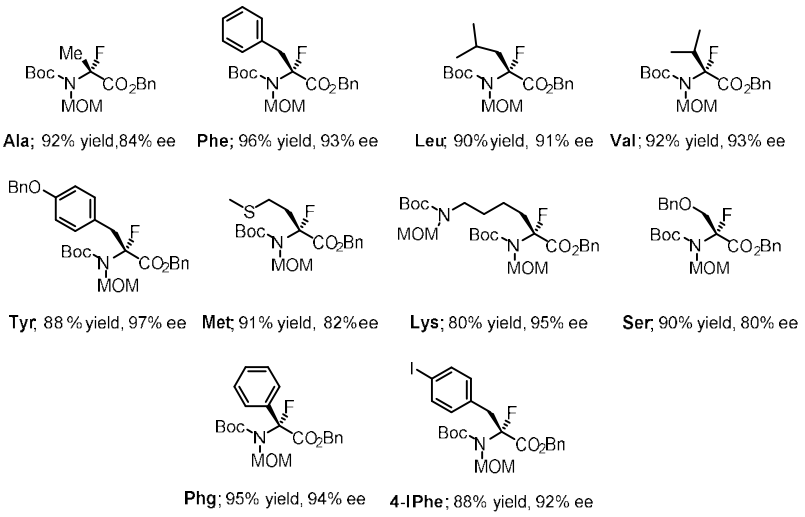


entry	R	solvent	Time	yield	ee
1	Bn	THF/DMF (1:1)	5 h	96	82
2	Bn	THF/DMF (2:1)	6 h	95	90
3	Bn	THF/DMF (4:1)	5 h	**96**	**92**
4	Et	THF/DMF (4:1)	5 h	71	51
5	Et	THF/DMF (4:1)	10 min	<5	85

Next, we explored the scope of this reaction (Table 2). Various α-fluorinated amino acid derivatives were obtained in high enantiomeric excess from the parent α-amino acids. The reaction proceeded in retention of the configuration, which was determined by X-ray crystallographic analysis of **4-I Phe** (Figure 2).

Table 2. Substrate Scope





Yield was given by ^{1}H-NMR analysis.

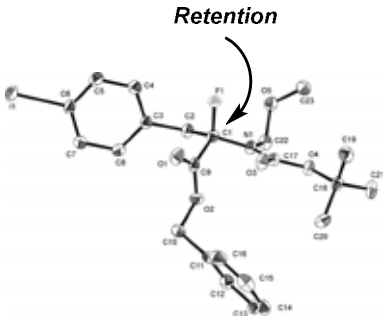


Figure 2. ORTEP of **4-I Phe**

References

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Enantioselective construction of all-carbon quaternary stereogenic centers via lipase-catalyzed dynamic kinetic resolution

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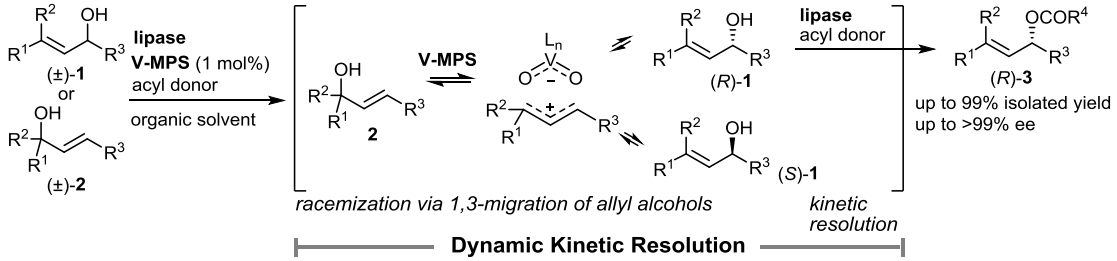
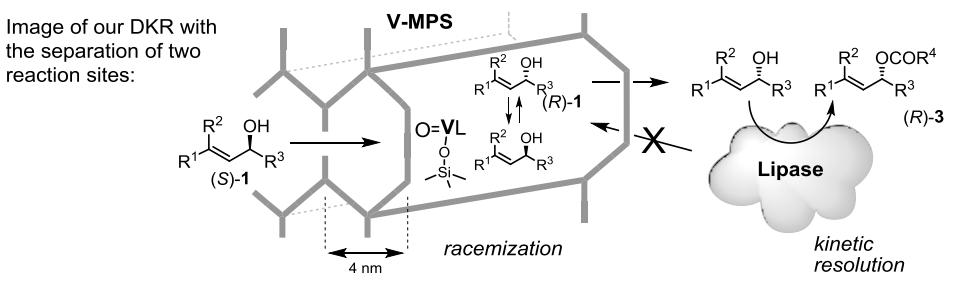
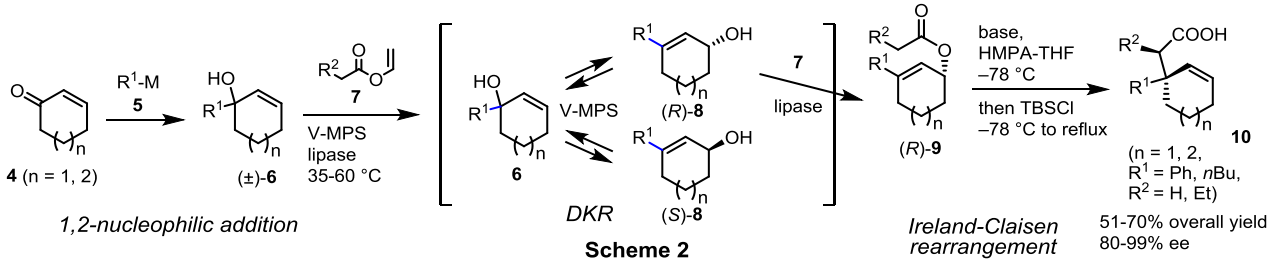
Introduction: Lipase-catalyzed kinetic resolution (KR) of racemic secondary alcohols has been widely employed for the production of optically active compounds because of its easy operation and excellent enantioselectivity. However, it can only achieve maximum yields of 50% of each enantiomer. To solve this problem, dynamic kinetic resolution (DKR) has been developed by combining the lipase-catalyzed KR and the racemization of less reactive enantiomers.[1] Very recently we have also developed new DKR of secondary allyl alcohols (±)-**1** using a combination of lipases and V-MPS, in which oxovanadium moieties were immobilized on the inside surface of mesoporous silica (MPS) with pores of 4 nm in diameter. In this DKR, lipase conducts kinetic resolution of (±)-**1**, while V-MPS catalyzes the racemization of the remaining less reactive enantiomer (*S*)-**1** to give optical active allyl esters (*R*)-**3** in up to >99% yield and >99% ee. The characteristic features of our DKR include the complete division of the racemization site and the KR site, which minimizes the interaction between the lipases and vanadium species, because lipases cannot enter the pores of MPS. In our DKR the racemization proceeds along with the 1,3-migration of the hydroxyl group of the substrates, (±)-**1** and (±)-**2**, and therefore, both (±)-**1** and (±)-**2** can be used as equivalent substrates to produce the same products (*R*)-**2**.[2] In this symposium, we present an application of our DKR to the enantioselective synthesis of all-carbon quaternary stereogenic centers **10** by the best use of the acyl moiety,[3] installed by DKR of tertiary alcohols (±)-**6**, for the Ireland–Claisen rearrangement.





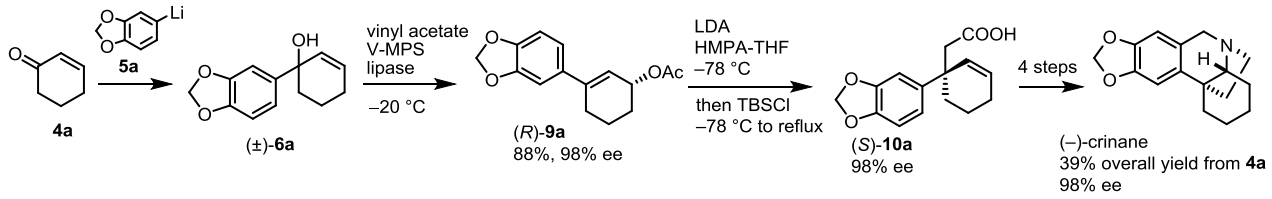
Scheme 1

Results and discussion: The tertiary alcohols (±)-**6**, available by the 1,2-nucleophilic addition of organometallic reagents **5** to cycloalkenones **4**, reacted with an acyl donor **7** possessing a variety of alkyl group R^2, V-MPS (1 mol%), and commercially available *C. antarctica* lipase B in organic solvents at 35–60 °C for 24–72 hours to provide allyl esters (*R*)-**9** in 81–99% yields and 80–99% ee. Then, (*R*)-**9** were converted into *O*-silyl ketene acetals, which were heated to conduct the Ireland–Claisen rearrangement to give the carboxylic acids **10**, bearing an all-carbon quaternary stereogenic center, after acidic work-up. The products **10** (80–99% ee) were isolated in 51–70% overall yields from **4** (Scheme 2).



Scheme 2

A typical application of the developed method was demonstrated by the asymmetric synthesis of (–)-crinane, a core structure of a range of natural alkaloids (Scheme 3). Although the first trial of DKR of (±)-**6a** under the standard conditions provided the ester (*R*)-**9a** with 89% ee, intensive examination of the reaction temperature and equivalents of the reagents achieved the production of (*R*)-**9a** with 98% ee. The Ireland–Claisen rearrangement of (*R*)-**9a** followed by 4-step chemical transformation completed the total synthesis of (–)-crinane with 98% ee (total 7 steps, 39% overall yield from **4a**).



Scheme 3

Conclusion: The above-mentioned method provides a novel asymmetric synthesis of all-carbon quaternary stereogenic centers through connecting three prochiral components, that is, conjugated enones, organometallic compounds, and acyl donors, by sequential 1,2-nucleophilic addition, dynamic kinetic resolution (DKR), and Ireland–Claisen rearrangement. This method also features the availability of various acyl groups for the lipase-catalyzed DKR and the high atom economy with production of fewer waste materials. The protective-group-free asymmetric total synthesis of (–)-crinane was achieved by utilizing the acyl group introduced by the DKR to construct its tricyclic framework, which demonstrates another synthetic advantage of our method.

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2P-50

Challenge to Prediction of Secondary Nucleation Rate Generated by Crystal Collisions with Impeller Blade Based on Lagrangian Simulation of Crystal Motion

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Prediction and control of secondary nucleation rate in a crystallizer is the important to control particle size distribution of crystal products. Crystal particle collisions in a crystallizer often induce particle abrasion, and subsequent secondary nucleation. Relation between crystal particle collision and secondary nucleation, however, have not been understood sufficiently. In this study, time evolution of size distribution of crystal attrition fragments generated by crystal collisions was measured in a stirred vessel using Potash Alum as a model crystal. In addition, particle collision velocity and frequency with impeller blade were evaluated based on Lagrangian simulation of crystal particle motion in a stirred vessel. Relation between crystal fragments generation rate and particle collision rate were discussed.

Time evolutions of number and size distribution of attrition fragments were measured using Potash Alum as a model crystal in anti-solvent[1]. Silicone oil whose solvency to Potash Alum is almost zero was chosen as solvent. A cylindrical stirred vessel filled with silicone oil was of 100 mm inner diameter and 100 mm liquid height. A six-blade, paddle type impeller of 50 mm diameter and 10 mm axial width was used. Impeller rotational speed n was set as 6, 8, 10 s^{-1}. Potash Alum particles of 350 – 400 microns were injected in the vessel initially, and then stirring was started soon. Number of parent crystals was 2000. Silicone oil contains parent crystals and generated fragments were sampled every 5 hours, and SEM pictures of them were taken. A MATLAB® based image analysis algorithm was implemented to quantify particle size and number of attrition fragments.

The time evolution of number of attrition fragments generated from 2000-parent crystal was evaluated. The number of attrition fragments increases rapidly with time. And then it saturates after about 40 hours regardless of impeller speed. Shape of cones of a parent crystal became roundly with stirring time, although surface of parent crystal did not change significantly. So, attrition fragments must be mainly generated from cones of a parent crystal. The relation between the generation rate of attrition fragments and change of shape of parent crystal were also clarified. Results show that both number of attrition fragments and abraded volume of parent crystal increase rapidly initially, and then saturate after about 40 hours. Generation rate of attrition fragments decreases with roundness of parent crystal cone, and is correlated with abraded ratio of a parent crystal.

Collision rate and collision velocity of a crystal particle with impeller blade were evaluated by Computational Fluid Dynamics (CFD) coupled with Lagrangian simulation of particle motion[2, 3]. The

form and dimensions of the vessel are set as same as the stirred vessel used in the crystal attrition experiments. Particle collision velocity is distributed from zero to 0.45 m s^{-1}, which is smaller than a half of impeller tip speed (= 0.94 m s^{-1} at n = 6 s^{-1}). And particle collision frequency of a particle of 375 microns with ρ = 1750 kg/m^3 which is equivalent to Potash Alum are about 1.5 per second.

The generation rate of crystal attrition fragments caused by a particle were calculated based on the CFD and attrition experiments results. Fig. 1 shows the relation between attrition fragment generation rate and crystal abraded ratio. The results show that two or three fragments are born from a particle per second initially, and then generation rate of attrition fragment decreases until about 1/100 as crystal cones are rounded.

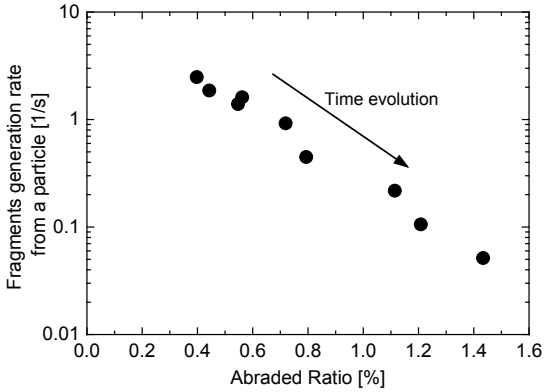

Fig. 1 Relation between attrition fragment generation rate and particle abraded ratio (n = 6 s^{-1}).

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2P- 51

Optimized Conditions for the Aerobic Alcohol Oxidation Using Nitroxyl Radical/Copper Catalysis

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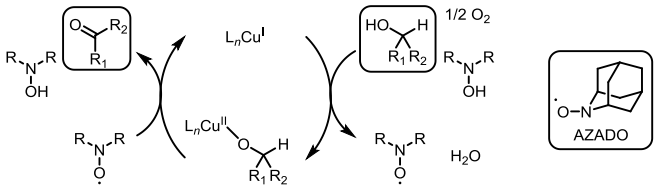
Aerobic oxidation is an ideal process for alcohol oxidation to give the corresponding carbonyl compound, the development of which has attracted attention in current process chemistry. Various methods enabling aerobic alcohol oxidation have been reported, most of which, however, require high temperature and/or high pressure, and are, therefore, limited their applicability to structurally simple substrates. Thus, the development of a practical aerobic oxidation method with broad applicability and high efficiency has been desired. In this symposium, we report the optimum conditions of AZADO/copper aerobic oxidation of alcohols, and that these conditions allow efficient oxidation of various alcohols in at or below room temperature.

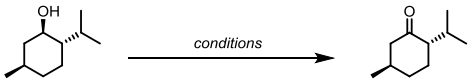
We have recently developed a highly active nitroxyl radical catalyst named 2-azaadamantane *N*-oxyl (AZADO) for the oxidation of alcohols.[1] In our recent report, AZADO/copper catalysis promoted the highly chemoselective aerobic oxidation of unprotected amino alcohols into amino carbonyl compounds under mild conditions.[2] The unprecedented, surprising chemoselectivity observed would be due to characteristic mechanism involving a copper-complex-type active species (Figure 1). With our ambition to expand the scope of AZADO/copper catalysis to not only unprotected amino alcohols but also other various alcohols including highly hindered and heteroatom-rich substrates, we embarked on this study.

Figure 1: Mechanism of the nitroxyl/copper catalysis



We began by optimizing the reaction conditions for the oxidation of menthol, which required elevated temperatures and an O_2 atmosphere under ABNO/copper catalysis, reported by Steves and Stahl (Table 1, entry 1).[3] Referring to this condition and optimization in detail, we found that the condition using AZADO, CuOTf, bpy, and DMAP in MeCN (1 M) oxidized menthol under air (open) with lower amounts of the catalysts (Table 1, entry 2). Furthermore, reaction time was shortened by using the least-hindered nitroxyl radical, namely, Nor-AZADO [4] (Table1, entry 3). Because CuCl, which has shown good activity for the oxidation of

Table 1: Optimization of the reaction conditions



entry	conditions	GC conv. / time
1	ABNO (1 mol%), Cu(MeCN)$_4$OTf (5 mol%) ^{MeO}bpy (5 mol%), *N*-methylimidazole (10 mol%) MeCN (0.1 M), O_2, 70 °C (Steves and Stahl's conditions)	89% / 1 h (isolated yield)
2	**AZADO** (1 mol%), CuOTf·1/2benzene (1 mol%) **bpy** (1 mol%), **DMAP** (2 mol%) MeCN (**1 M**), **air (open)**, **rt**	100% / 24 h
3	**Nor-AZADO** (1 mol%), CuOTf·1/2benzene (1 mol%) bpy (1 mol%), DMAP (2 mol%) MeCN (1 M), air (open), rt	100% / **6 h**
4	Nor-AZADO (1 mol%), **CuCl** (1 mol%) bpy (1 mol%), DMAP (2 mol%) MeCN (1 M), air (open), rt	64% / 6 h

amino alcohols, was not suitable for the oxidation of menthol, we found that adoption of a "matched" copper salt depending on the substrate structure is important for efficient oxidation (Table 1, entry 4).

Furthermore, during close examination of the reaction conditions using other several alcohols, we identified two distinct reaction conditions, the selection of which is roughly estimated by the presence or absence of coordinating groups in the substrate (Scheme 1).

Method A: If the substrate "does NOT contain" coordinating groups,

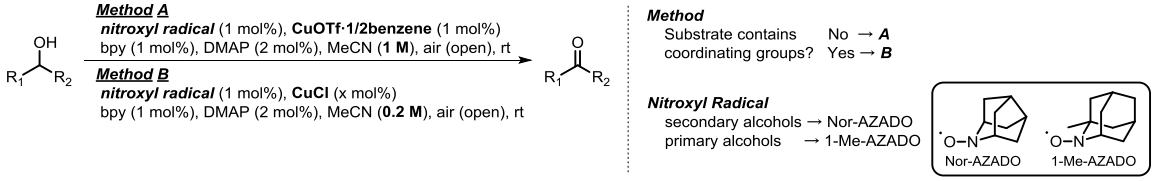
nitroxyl radical (1 mol%), CuOTf·1/2benzene (1 mol%), bpy (1 mol%), DMAP (2 mol%)
MeCN (1 M), air (open), rt;

Method B: If the substrate "contains" coordinating groups,

nitroxyl radical (1 mol%), CuCl (x mol%), bpy (1 mol%), DMAP (2 mol%)
MeCN (0.2 M), air (open), rt;

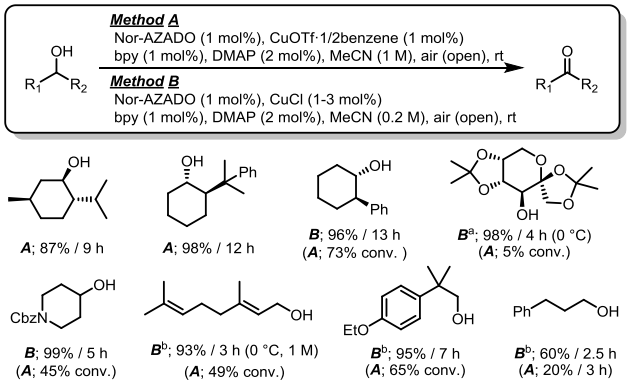
in which optimum nitroxyl radical depends on whether the substrate is a primary or secondary alcohol. Nor-AZADO should be used for secondary alcohols, especially sterically hindered substrates, whereas 1-Me-AZADO should be used for primary alcohols.

Scheme 1: Optimixed conditions



With sets of optimum conditions in hand, we applied them to examine the substrate scope (Table 2). Various alcohols, including highly hindered and heteroatom-rich substrates, were efficiently oxidized to give the corresponding carbonyl compounds under mild conditions by using optimum conditions with smaller amounts of catalysts.[5] Interestingly, AZADO/copper catalysis did not efficiently oxidize 3-phenylpropanol, because of deactivation of the catalyst. The detail will be discussed in this presentation.

Table 2: Substrate scope



[a] Nor-AZADO (2 mol%), CuCl (4 mol%), bpy (2 mol%), DMAP (4 mol%) was used.
[b] 1-Me-AZADO was used instead of Nor-AZADO.

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2P-52

Syntheses and Properties of Substituted Sondheimer-Wong Diynes

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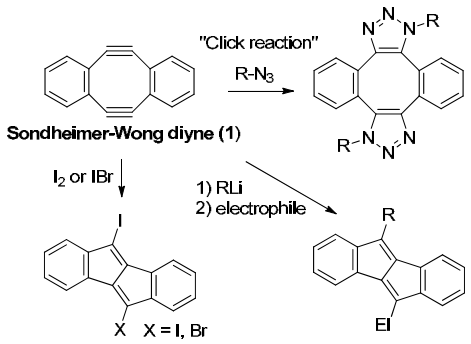
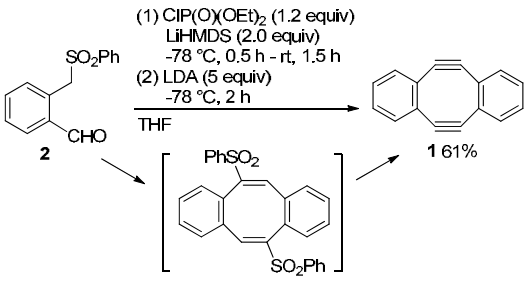
Arylalkynes attract a great attention because they have expanded π-systems and thus serve for organic optoelectronic materials such as light-emitting materials for electroluminescence (EL) and organic semiconductor materials. Arylalkynes undergo a variety of transformations in organic synthesis to give newly formed expanded π-systems. Terminal acetylenes undergo Sonogashira coupling with aryl halides to provide arylalkynes bearing more expanded π-systems. A cyclic arylalkyne, 5,6,11,12-tetradehydrodibenzo[a,e]cyclooctene (Sondheimer-Wong diyne, **1**)(Scheme 1), exhibits high reactivity because of its inherent strain energy. For instance, when **1** is treated with alkyl or arylazides, the desired click reaction of **1** with azide proceeds without Cu catalyst to give the corresponding triazoles (Scheme 1). Sondheimer-Wong diyne **1** serves as a precursor of 16π-anti-aromatic compound dibenzopentalene (Scheme 1).[1,2]



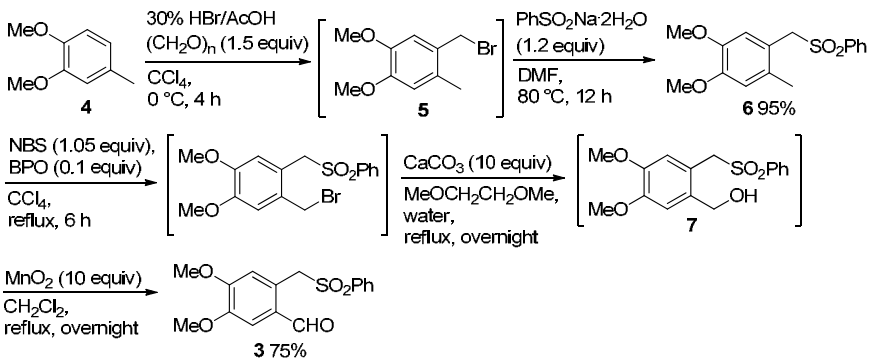
Scheme 1. Transformation of 1 to ditriazol and pentalenes

In 2002, we realized one-pot synthesis of **1** by taking advantage of double elimination protocol starting from formylbenzylsulfone **2** (Scheme 2).[3] In this synthesis, when a THF solution of **2** and diethyl chlorophosphate was treated with LiHMDS and LDA successively, **1** was obtained in 61% yield. In order to expand cyclic diyne chemistry and develop new π-systems such as pentalenes and triazoles, we applied our double elimination protocol to synthesis of substituted cyclic diynes. We repot herein preparation of substituted formylsulfones and their transformation to substituted cyclic diynes by taking advantage of our double elimination protocol. Dimethoxy-substitued formylsulfone **3** was prepared from commercially available 3,4-dimethoxytoluene **4** as shown in Scheme 3. When **4** was treated with paraformaldehyde in the presence of HBr and AcOH, bromomethylation proceeded regioselectively to give **5**, and treatment of **5** with $PhSO_2Na$ in DMF provided benzylsulfone **6** in 95% yield (for 2 steps). The sulfone **6** was transformed to hydroxybenzylsulfone **7** through bromination (NBS, BPO) and nucleophilic hydroxylation ($CaCO_3$, water).

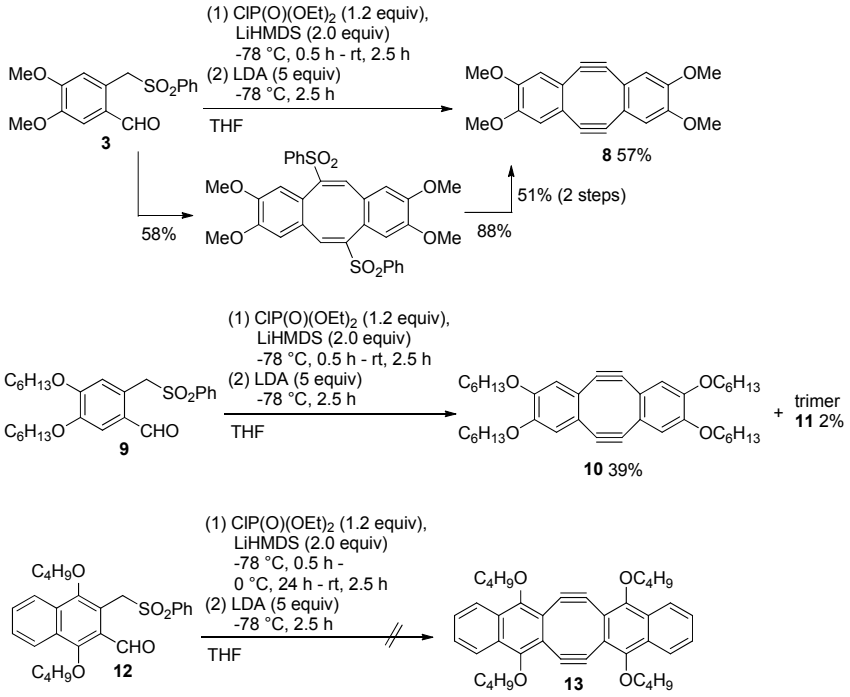


Scheme 2. One-pot Synthesis of Sondheimer-Wong diyne 1

Oxidation of the resulting benzyl alcohol **7** with MnO_2 gave the desired dimethoxyformylsulfone **3** in 75% yield (for 3 steps). Other formylsulfones were prepared in the similar procedures. When LiHMDS and LDA were added successively to a THF solution of **3** and diethyl chlorophosphate, tetramethoxy-substituted cyclic acetylene **8** was obtained in 57% yield after purification by column chromatography on silica gel (Scheme 4). A stepwise procedure for **8** proceeded smoothly as well to afford a similar result: 51% yield for two steps (58% x 88%). The cyclic acetylene **8** was a yellow powdery compound and poorly soluble in any organic solvents. Surprisingly, **8** was remarkably stable, and **8** could be kept at rt in the air over 6 months. Subjection of bis(hexyloxy)-substituted formylsulfone **9** to the one-pot double elimination protocol provided **10** and **11** in 39% and 2% yield, respectively. Tetra(hexyloxy)-substituted cyclic acetylene **10** exhibited higher solubility than **8** because of longer alkyl chains of **10**. When di(butoxy)-substituted sulfone **12** was used, the cyclization proceeded sluggishly, and **13** was not obtained.



Scheme 3. Synthesis of Sulfone 3



Scheme 4. Synthesis of Substituted Cyclic Diynes

References

1 Babu, G.; Orita, A.; Otera, J. *Chem. Lett*. **2008**, *37*, 1296.

2 Xu, F.; Peng, L.; Orita, A.; Otera, J. *Org. Lett.* **2012**, *14*, 3970.

3 Orita, A.; Hasegawa, D.; Nakano, T.; Otera, J. *Chem. Eur. J*. **2002**, *8*, 2000.

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Development of Novel Reagents for Electrophilic SF_5-arylation

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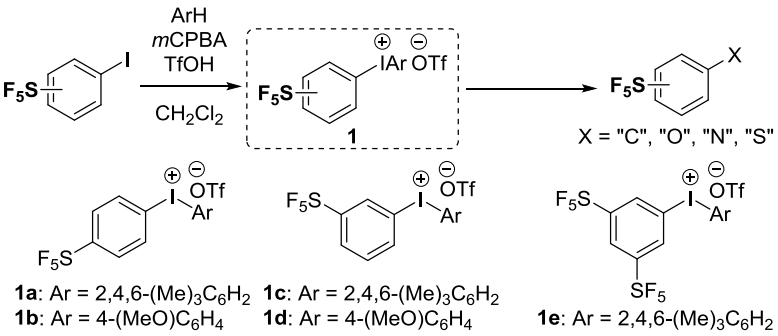
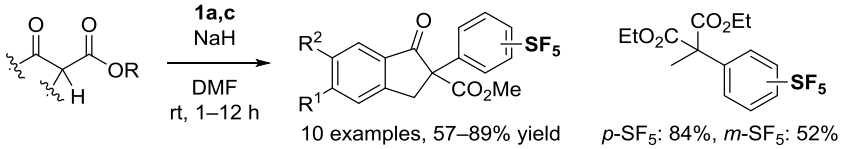
Pentafluorosulfanyl (SF_5)-substituted compounds have become targets as future materials in recent years due to their high lipophilicity and strong electron-withdrawing character. The direct construction of an SF_5 unit on benzene rings is possible from aryl disulfides using HF/Cl_2, AgF_2 or F_2 methodology. However, the methods are limited to simple SF_5-arenes and more effective and convenient methods are required. From our recent works on fluorinated hypervalent iodium compound,[1] we planned the development of regents based on diaryl-λ^3-iodanes (diaryliodonium salts) for the direct introduction of SF_5-containing aryl group.

For the initial work, synthesis of various SF_5-arylating reagents were investigated. According to reported practical method for the synthesis of diaryliodonium satls, SF_5 aryl iodide was successively transformed into *p*-, *m*-SF_5 diaryl-λ^3-iodanes reagents using ArH, *m*CPBA and TfOH at room temperature in one-pot (Scheme 1). Two types of dummy ligand such as 2,4,6-trimethyl benzene and 4-methoxy benzene were selected for the efficient transformation of various nucleophiles.



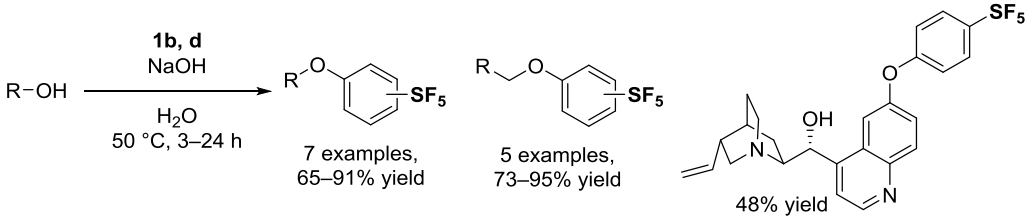
Scheme 1. Synthetic approach to SF_5-aryl compounds using reagents **1**

At the first attempt, we examined *p*- and *m*-SF_5-arylation reaction of cyclic β-ketoesters derived from indanones with our reagents in the presence of NaH in DMF (Scheme 2). Compared to the iodonium salt **1b** with anisole in the dummy part of the ligand, the reagent **1a** having a steric mesityl group was found to be preferred giving desired product in good yield (64% by **1b** *vs* 84% by **1a**). Both electron-donating and electron-withdrawing functional groups on the substrates are acceptable. Acyclic malonate was also reacted with **1a, c** under same reaction condition.



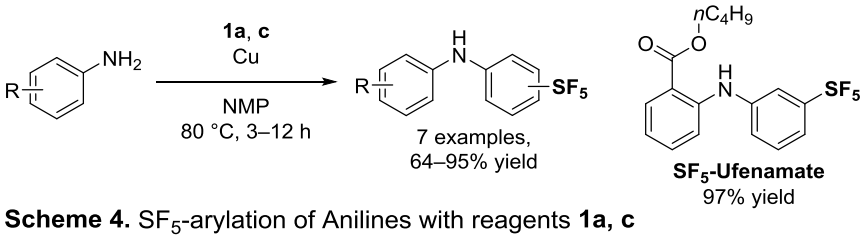
Scheme 2. SF_5-Arylation of 1,3-dicarbonyl compounds with reagents **1a,c**

Phenols and alcohols were next examined for SF_5-arylation by **1** (Scheme 3). It should be noted that reagent **1b** with anisole as a dummy ligand gave considerably better yields in most cases than **1a** under $NaOH/H_2O$ conditions. The reaction proceeded smoothly not only for phenols but also other oxygen nucleophiles such as naphthylmethanols, benzyl alcohol and cinnamyl alcohol using **1b** and **1d**. It is noteworthy that SF_5-arylation of the drug-like estrone derivative and cinchona alkaloid derivative progressed nicely to give desired products.



Scheme 3. SF_5-arylation of Phenols and Alcohols with reagents **1b, d**

We further expanded the scope of these reagents **1** for SF_5-arylation of aromatic amines. After considerable optimization of the reaction conditions, it was found that 10 mol% of Cu (0) at 80 °C in NMP allowed for the SF_5-arylation of anilines with **1**, providing desired products in good yields (Scheme 4). Both electron-donating and electron-withdrawing groups on the benzene ring were accepted and the position of their substituents, including the sterically demanding ortho position, had no effect on conversion yields. We succeeded in synthesizing a medicinally attractive SF_5-analogue of an anti-inflammatory agent, Ufenamate in 97% yield under the same condition.



Scheme 4. SF_5-arylation of Anilines with reagents **1a, c**

In conclusion, this study revealed SF_5-aryl-aryl-λ^3-iodanes **1** as effective reagents for electrophilic SF_5-arylation of 1,3-dicarbonyl compounds, phenols, alcohols, and anilines. A wide variety of SF_5-arylated compounds were obtained in the presence of a base or copper catalyst under mild conditions in good to high yields. We also have succeeded to react *N*-hydroxyphthalimide, carboxylic acid, sulfonic acid, and sulfonates with our reagents to furnish SF_5-arylated products. The reagents **1** were applicable for the late-stage functionalization of medicinally attractive molecules. Further studies on the potential of **1** and characterization by X-ray crystallographic analyses of **1** will be discussed in this poster presentation.

Reference

1) Matsuzaki, K.; Okuyama, K.; Tokunaga, E.; Shiro, M.; Shibata, N. *ChemistryOpen* **2014**, *3*, 233.

A Catalytic Synthetic Approach to HSD-016 Through Enantioselective Trifluoromethylation

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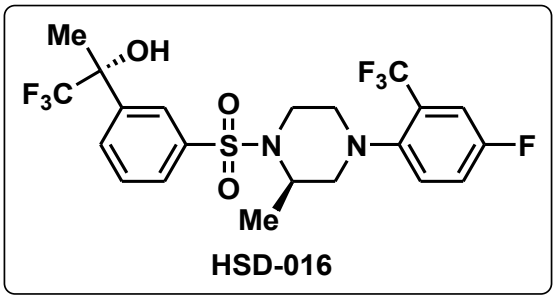
We demonstrated a metal-free catalytic process of HSD-016((R)-1,1,1-trifluoro-2-(3-((R)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-ylsulfonyl)phenyl)propan-2-ol) with 85% de.

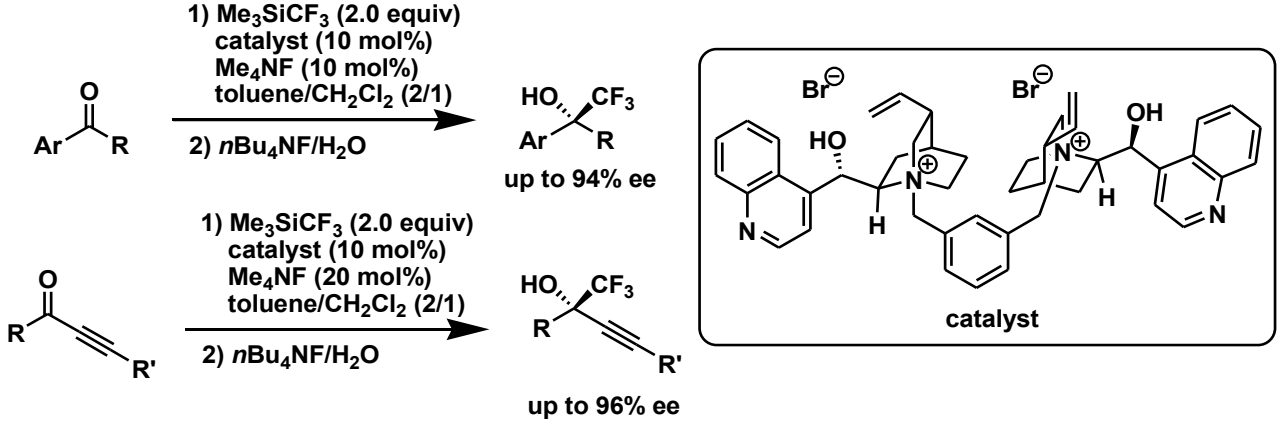
HSD-016 is an 11β-hydroxysteroid dehydrogenase type 1 inhibitor. It is an effective medicine for obesity and hyperglycemia. It is proceeded the clinical trial as anti-obesity agent.



HSD-016

HSD-016 has two trifluoromethyls on that structure. One trifluoromethyl is on the tertiary alcohol and another one is on the benzene. There is no synthesis of an asymmeric point at trifluoromethyl on the tertiary alcohol without enantioselective syntheses. It is important to introduce trifluoromethyl as late as possible because of its expensiveness.

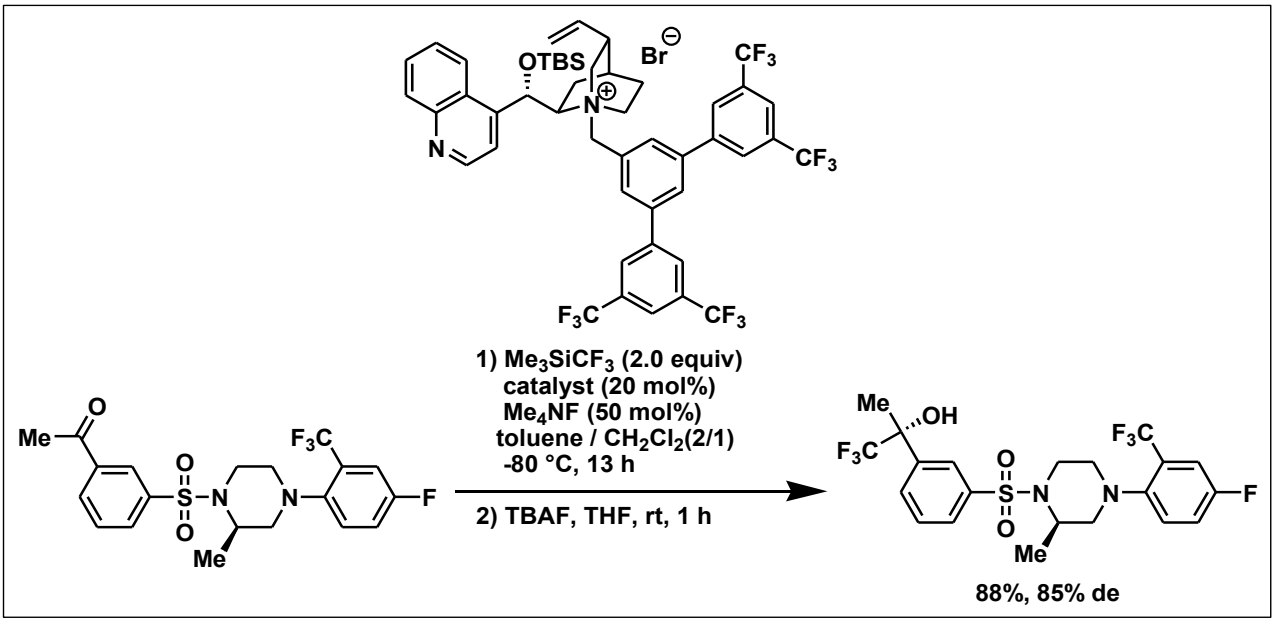
Our group has been engaged in the development of efficient methods for the enantioselective synthesis of fluoroorganic compounds over the last decade. Recently, we developed the first enantioselective trifluoromethylation of alkynyl ketones with Me_3SiCF_3 by employing an ammonium salt derived from cinchonine and Tetramethylazanium fluoride (TMAF) as a catalyst. We efficiently condensed a wide range of alkynyl ketones and Me_3SiCF_3 to provide trifluoromethylated propargyl alcohols having a quaternary carbon center in very high enantiomeric excess[1, 2].



That previous method was able to be applied to synthesis of HSD-016. We used the combination of a chiral quaternary ammonium salt and TMAF. They are cheap and stable. Thus, that combination is suited to the industrial process of manufacturing HSD-016.

Catalytic asymmetric synthesis of HSD-016 was achieved by an organocatalyzed enantioselective trifluoromethylation using Me_3SiCF_3 as a key reaction. We considered the shape of cinchona alkaloid-derived phase-transfer catalyst (PTC) and discovered the best one. The PTC modified with long chain silicon ethers and TMAF enabled the enantioselective trifluoromethylation for 1-(3-(((2R)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methyl-1-piperazinyl)-sulfonyl)phenyl)ethanone with high enantioselectivity.

Since our method is better efficiency than previous method, it would provide an alternative industrial manufacturing process of HSD-016.



1) N. Shibata et al. *Org. Lett.* **2007**, 9, 3707.

2) N. Shibata et al. *Org. Lett.* **2010**, 12, 5104.

2P- 55

Preparationo of PVDF Membrane for Membrane Distillation

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Membrane distillation (MD) is a thermal driven process that is a combination of membrane technology and distillation. The applications of MD include the production of ultrapure water from salt solutions, concentration of solutions, purification of wastewater, etc. In the process, two streams with different temperatures are separated by a hydrophobic membrane. The vapor molecules transport from the side of higher temperature through the micro-sized pores of membrane, and then condense at the cooler side as the collected permeate. The permeate side has various operation modes, thus MD can be divided into direct contact membrane distillation (DCMD), vacuum membrane distillation (VMD), sweeping gas membrane distillation (SGMD), and air gap membrane distillation (AGMD).

The performance of MD is mainly related to the membrane properties, operating parameters and the module design. The modified polyvinylidene fluoride (PVDF) membranes made from different compositions of coagulation bath were prepared and their performances in membrane distillation of saline water were also conducted in this work.

The dope solution of PVDF/TEP/Tween20 with 18/74.5/7.5 wt% was pumped through a spinneret, and then the fiber was immersed in a nonsolvent bath where the coagulation process occurred. The water/TEP ratios of coagulation bath were adjusted to forming the various morphologies of PVDF hollow fibers.

The DCMD experiments were conducted in this work. The feed solution was 3.5 wt% NaCl solution, and the operating parameters include feed temperature (50 – 70 ^{o}C), feed flow rate (0.1 – 0.4 l/min), and the temperature and flow rate of permeate side were kept at 17.5 ^{o}C and 0.4 l/min.

The experimental results of permeate fluxes show that the performance of modified membrane is better than the original membrane (T0, without TEP in coagulation bath), and the T40 (40 wt% TEP) is superior to T10 (10 wt% TEP). The results imply that the membrane performance in DCMD can be improved significantly by adding TEP concentration in the coagulation bath in preparation the PVDF membrane.

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Novel Synthesis of Arylalkynes via α-Aazidotetrazoles from Cyanophosphates

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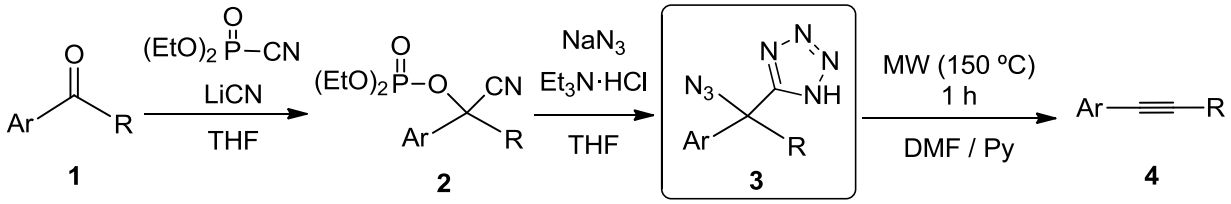
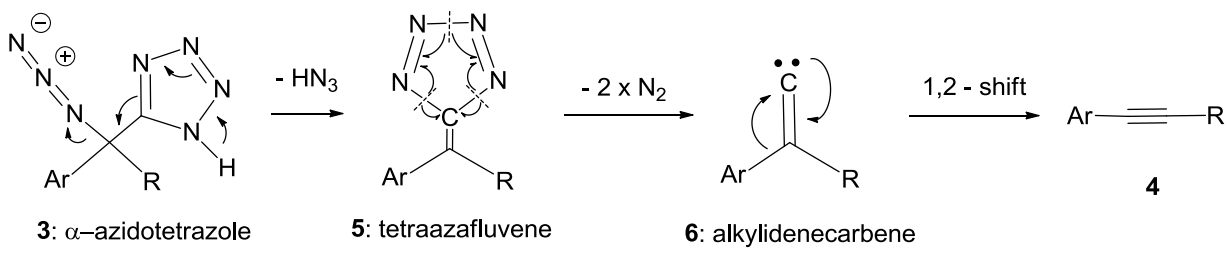
Benzlic cyanophosphates (**2**: CPs) are generally prepared by reaction of carbonyl compounds **1** with diethyl phosphorocyanidate (DEPC) in the presence of LiCN. To date, CPs have been employed as the versatile intermediates for C_1-unit introduction in organic synthesis. In this presentation, we newly describe that reaction of CPs **2** with NaN_3-Et_3N·HCl affords easily α-azidotetrazoles **3** (AT) which may lead to arylalkynes **4** under microwave (MW) conditions (Table 1). The convension of **3** into alkynes **4** might be explained by the plausible mechanism, as shown in Scheme 1: elimination of HN_3 from **3**, formation of tetraazafulvene **5**, eruption of nitrogen (2 x N_2) from **5**, generation of alkylidene carbene **6**, and 1,2-rearrangement of **6** (Scheme 1).

Table 1.

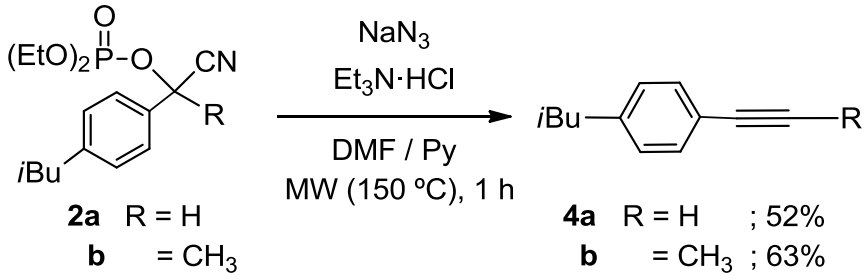


entry	Ar	R	yield (%) 2		3		4	
1	*i*Bu	H	**2a**	98	**3a**	81	**4a**	62
2	*i*Bu	CH_3	**2b**	99	**3b**	91	**4b**	76
3	Cl	CH_3	**2c**	99	**3c**	88	**4c**	65
4			**2d**	99	**3d**	54	**4d**	88



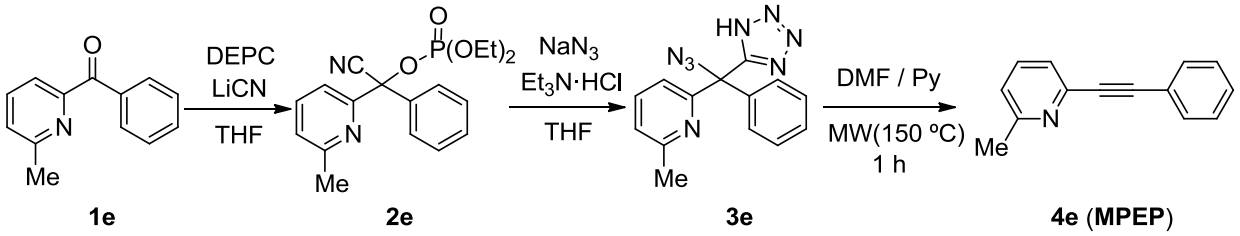
Scheme 1.

Alternatively, treatment of CPs **2** with NaN_3-$Et_3N{\cdot}HCl$ under MW irradiation provided directly alkynes **4** (Scheme 2).



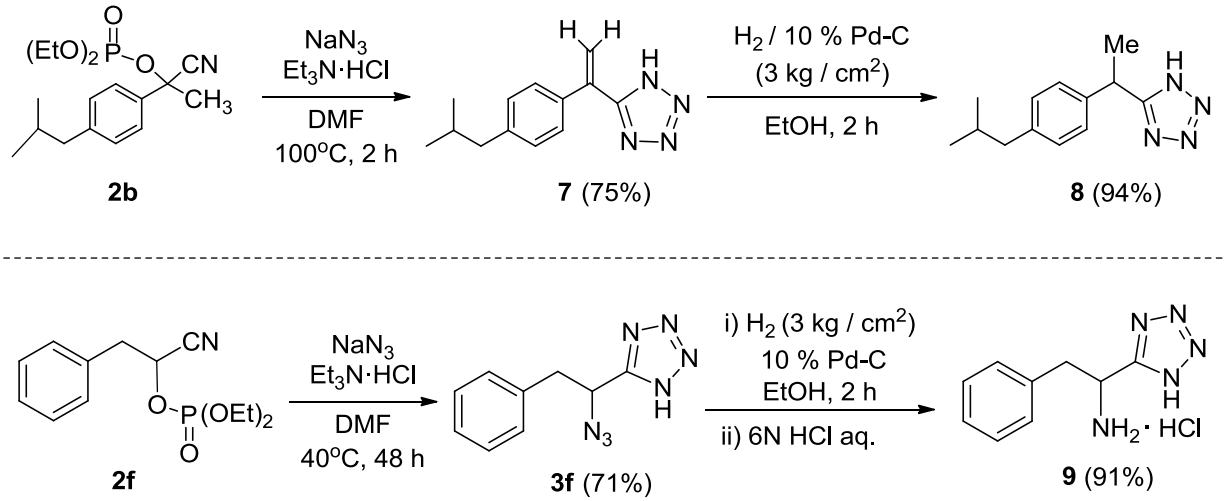
Scheme 2.

The novel alkyne synthesis via ATs **3** additionally afforded 2-methyl-6-(phenylethynyl)pyridine **4e** which is a mGluR5 antagonist (**MPEP**) (Scheme 3).



Scheme 3.

Further this study have revealed the two efficient synthesis of bioactive compounds: ibuprofen-tetrazole analogue **8** (2 fold analgetic activity of ibuprofen) via a vinyltetrazole **7** and tyrosine hydroxylase inhibitor **9** by catalytic reduction of AT **3f** (Scheme 4).



Scheme 4.

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Catalyst-controlled diastereoselective hetero-Diels-Alder reactions catalyzed by chiral dirhodium(II) carboxamidates

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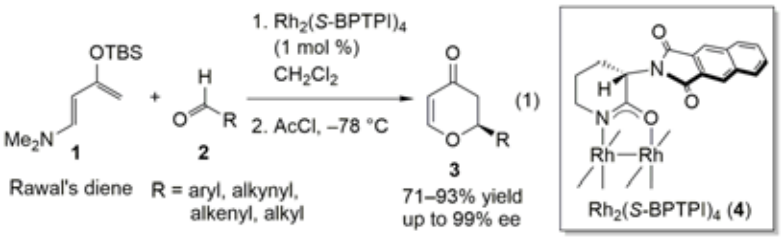
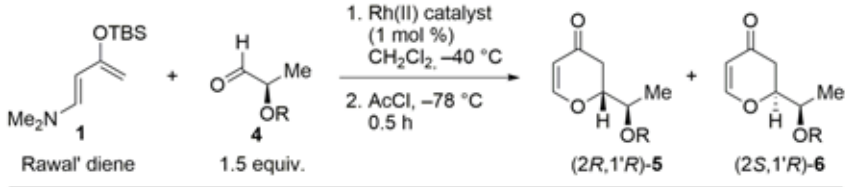
The asymmetric hetero-Diels–Alder (HDA) reaction between electron-rich dienes and aldehydes catalyzed by chiral Lewis acids represents one of the most straightforward methods for the construction of optically active six-membered oxygen-containing heterocycles.[1)] The cycloaddition of aldehydes bearing a stereogenic center is clearly of great importance in the application of the HDA reaction to synthesis. Despite the existence of a number of reports on substrate-controlled diastereoselective HDA reactions of chiral aldehydes, only few examples of chiral Lewis acid-controlled diastereoselective HDA reactions of chiral aldehydes have been reported.[2)]

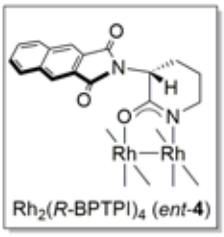
Recently, we reported that Rh_2(*S*-BPTPI)$_4$, a dirhodium(II) carboxamidate complex that incorporates (*S*)-3-(benzene-fused phthalimido)-2-piperidinonate as chiral bridging ligands, is a highly efficient Lewis acid catalyst for *endo*- and enantioselective HDA reactions of a diverse range of aldehydes with Danishefsky-type dienes and monooxygenated dienes as well as Rawal's diene.[3)] In the Rh_2(*S*-BPTPI)$_4$-catalyzed HDA reaction of Rawal's diene (**8**), the applicable aldehydes include not only aromatic, α,β-acetylenic, and α,β-olefinic aldehydes, but also sterically hindered aliphatic aldehydes that were less effective dienophiles when a Danishefsky-type diene was used (eq. 1).[3b,c)] As a part of our interest in further extending the utility of Rh_2(*S*-BPTPI)$_4$ and Rh_2(*R*-BPTPI)$_4$, we describe the catalyst-controlled diastereoselective HDA reaction between Rawal's diene and chiral aldehydes.

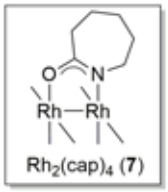


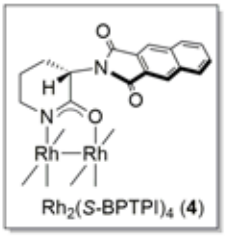
The HDA reaction between Rawal's diene (**1**) and TBS-protected (*R*)-lactaldehyde **4a** catalyzed by Rh_2(cap)$_4$ provided, after treatment with acetyl chloride, a mixture of dihydropyranone products (2*R*,1'*R*)-**5a** and (2*S*,1'*R*)-**6a** in 13% yield with a 52:48 diastereomeric ratio (dr) (Table 1, entry 1). This result, together with our previous findings,[3)] suggested that combinations of **4a**/Rh_2(*R*-BPTPI)$_4$ and **4a**/Rh_2(*S*-BPTPI)$_4$ should constitute matched and mismatched pairs, respectively. Indeed, Rh_2(*R*-BPTPI)$_4$ provided (2*R*,1'*R*)-**5a** in 73% yield with 96:4 dr (entry 2). On the other hand, however, Rh_2(*S*-BPTPI)$_4$ only led to a formation of (2*S*,1'*R*)-**5a** in 33% yield with 44:56 dr (entry 3). We then examined the HDA reaction with benzyl-protected (*R*)-lactaldehyde derivative **4b**. To our delight, even a mismatched pair

Table 1. HDA Reaction Catalyzed by Rh(II) Complexes between Rawal's Diene (**1**) and (*R*)-Lactaldehyde Derivatives **4**







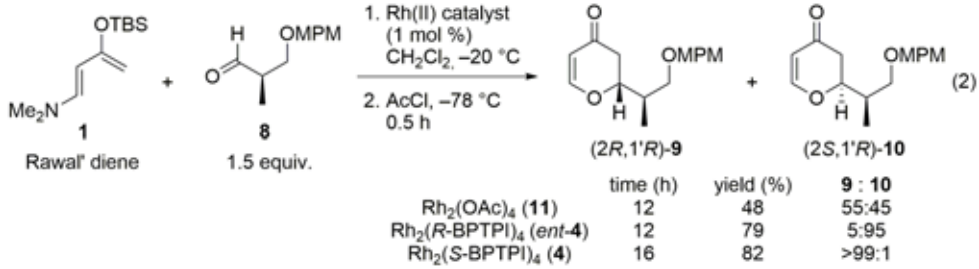


entry	R	4	Rh(II) catalyst	time (h)	5	6	yield (%)[a]	5 : 6
1	TBS	**4a**	Rh_2(cap)$_4$	16	**5a**	**6a**	13	52:48[b]
2	TBS	**4a**	Rh_2(*R*-BPTPI)$_4$	16	**5a**	**6a**	73	96:4[b]
3	TBS	**4a**	Rh_2(*S*-BPTPI)$_4$	16	**5a**	**6a**	33	44:56[b]
4	Bn	**4b**	Rh_2(cap)$_4$	14	**5b**	**6b**	22	51:49[c]
5	Bn	**4b**	Rh_2(*R*-BPTPI)$_4$	12	**5b**	**6b**	89	97:3[c]
6	Bn	**4b**	Rh_2(*S*-BPTPI)$_4$	12	**5b**	**6b**	75	12:88[c]

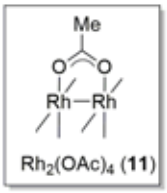
[a] Combined yield of A and B. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis.

using Rh_2(*S*-BPTPI)$_4$ was found to bring about a reversal in the inherent diastereoselection in this system to result in a ratio of 10:90 favoring **6b** (entry 6).

The HDA reaction between Rawal's diene (**1**) and (*R*)-2-methyl-3-hydroxypropanal derivative **8** using Rh_2(*S*-BPTPI)$_4$ and Rh_2(*R*-BPTPI)$_4$ (1 mol %) in dichloromethane at –20 °C also provided the dihydropyranone products (2*R*,1'*R*)-**9** and (2*S*,1'*R*)-**10** in a >99:1 dr (82% yield) and 5:95 dr (79% yield), respectively (eq. 2).



	time (h)	yield (%)	9 : 10
Rh_2(OAc)$_4$ (**11**)	12	48	55:45
Rh_2(*R*-BPTPI)$_4$ (*ent*-**4**)	12	79	5:95
Rh_2(*S*-BPTPI)$_4$ (**4**)	16	82	>99:1



Further application of this method to synthesis of polysubstituted oxygen-containing heterocycles is currently in progress.

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Potential Utility of BenzP* Ligand for the Production of Chiral Pharmaceutical Ingredients

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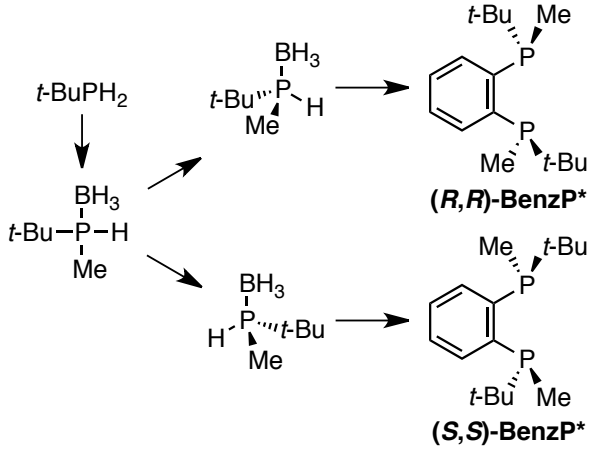
Optically active phosphine ligands have played a pivotal role in transition-metal-catalyzed asymmetric reactions. Though many efficient chiral phosphine ligands have been reported so far, the development of new ligands is still a vital research subject in the field of asymmetric catalysis. Here, we report synthesis of a structurally simple and rigid P-chiral phosphine ligand, 1,2-bis(*tert*-butylmethylphosphino)benzene (BenzP*), and its application in Rh-catalyzed asymmetric hydrogenation of prochiral alkenes and ketones. The potential utility of the ligand for the production of some chiral pharmaceutical ingredients is also presented.

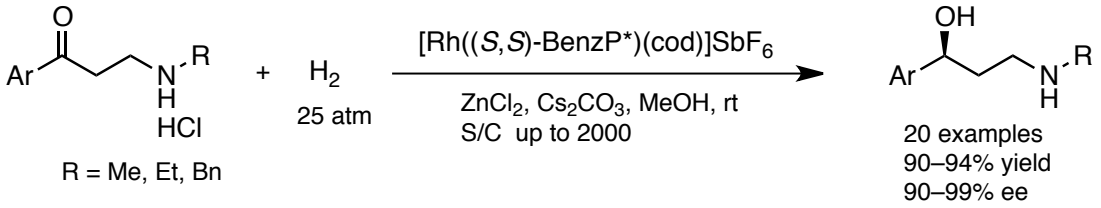
The both enantiomers of BenzP* were prepared from enantiomerically pure (*R*)- and (*S*)-*tert*-butylmethylphosphine–boranes which were produced on a large-scale from *tert*-butylphosphine.[1,2] The (*R*)- and (*S*)-BenzP* ligands are white crystalline solids and can be handled in air without any special precaution, and they are currently supplied from Nippon Chemical Industrial Co., Ltd. and Strem.



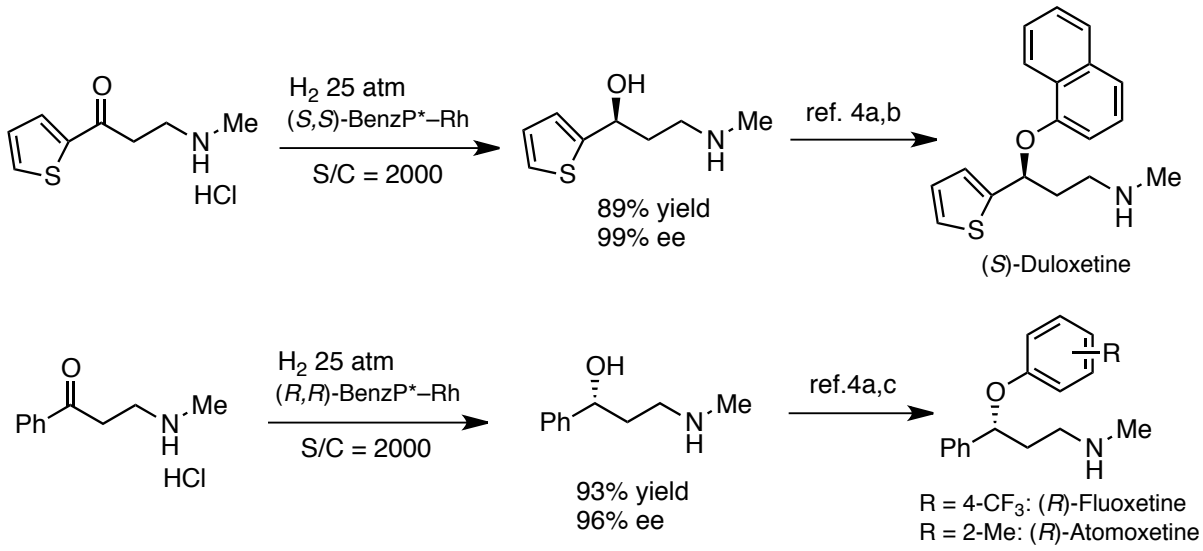
The practical utility of BenzP* in asymmetric catalysis was tested in Rh-catalyzed asymmetric hydrogenation of α- and β-dehydroamino acids and enamides. Very high catalytic activity and enantioselectivities of up to 99.9% were observed in most cases. The results indicate the high utility of the BenzP* for the production of some important pharmaceutical ingredients.[2]

Based on the results, we tried to extend the BenzP*-Rh-catalyzed asymmetric hydrogenation to the synthesis of chiral γ-secondary-amino alcohols from β-secondary-amino ketones, because this transformation is known to be notoriously difficult to be achieved. Our initial attempts were carried out by

using QuinoxP*, BisP*, MiniPHOS, and BenzP*, all of which were synthesized in our laboratory. Among these ligands, BenzP* afforded the highest enantioselectivity and chemical yield, though considerable amounts of by-products were produced. In order to suppress the formation of the by-products and to prevent the deactivation of the Rh-catalyst, we examined the effects of various additives, and found that zinc chloride promoted the hydrogenation most efficiently, affording the desired chiral γ-secondary-amino alcohols in high yields. Under the optimized conditions, many β-secondary-amino ketones were subjected to hydrogenation to give the corresponding products in high yields and excellent enantioselectivities of up to 99%.[3]



This asymmetric hydrogenation method was applied to the synthesis of three important drugs, (*S*)-duloxetine, (*R*)-fluoxetine, and (*R*)-atomoxetine. The intermediates γ-secondary-amino alcohols were prepared in high yields and with excellent enantioselectivities by the use of our catalyst system with an S/C of 2000.[3] The resulting amino alcohols can be readily etherified by the reported procedures to furnish the desired drugs.[4]



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Catalytic Transoximation to Aldehydes

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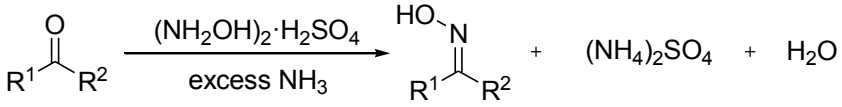
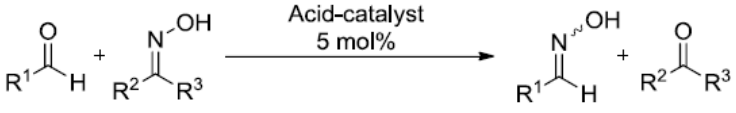
Hydroxylamine is known unstable, explosive and moisture sensitive compounds, which is difficult to handle as a substance. Therefore we usually treated as the salt form with inorganic acid, although in order to synthesize oximes, stoichiometric base is required and a large amount of inorganic salt generates after reaction. This salt becomes waste and sometimes occurs some problem in process chemistry (Scheme 1).



Scheme 1. General procedure for synthesis of oximes

In nature, oxime was known to produce via transoximation reaction by enzyme from which was obtained silkworm under mild conditions[1]. On the other hand, non-enzymatic catalytic transoximation is also much attractive methods, and those reaction from acetone oxime to aldehyde and ketone under acid conditions, have been already reported[2]. However these methods was required harsh conditions and stoichiometric acid. Therefore, we attempt catalytic transoximation to aldehydes under mild conditions and would like to propose the use of oxime as a hydroxylamine equivalent on safety process chemistry in this symposium.

Table 1. Catalytic transoximation to aldehydes



Entry	R^1	Yield (%)[a]	E / Z[b]
1	4-$MeOC_6H_4$	98	86 / 14
2	4-BrC_6H_4	98	95.5 / 4.5
3	4-$CF_3C_6H_4$	99	95 / 5
4	$CH_3(CH_2)_8$	98	60 / 40

a) Isolated yield. b) Determined by ^1H NMR from crude mixtures

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Catalytic Asymmetric Synthesis of Chiral Pharmaceutical Ingredients Using QuinoxP*-Rh Complexes

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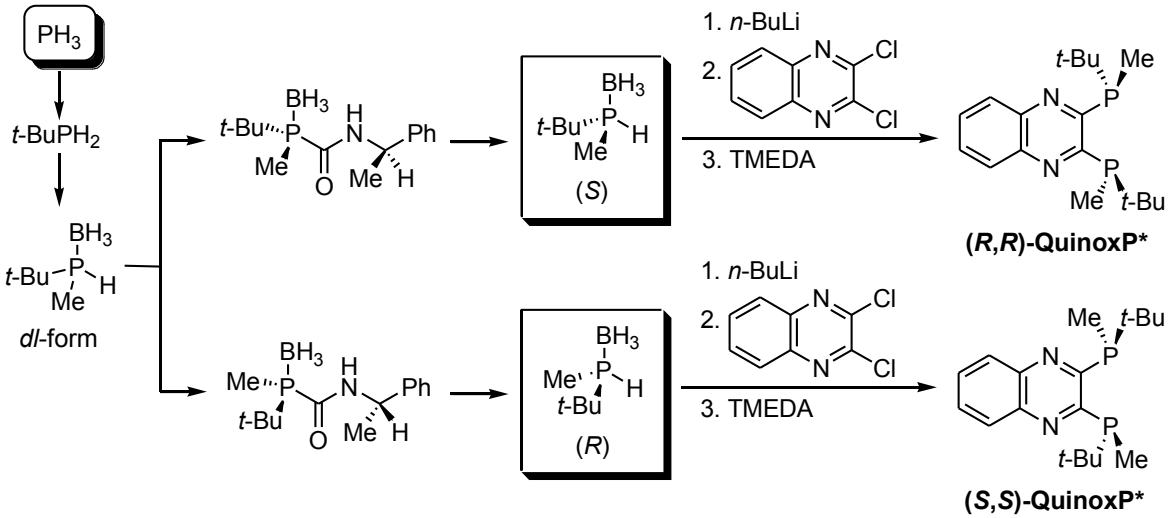
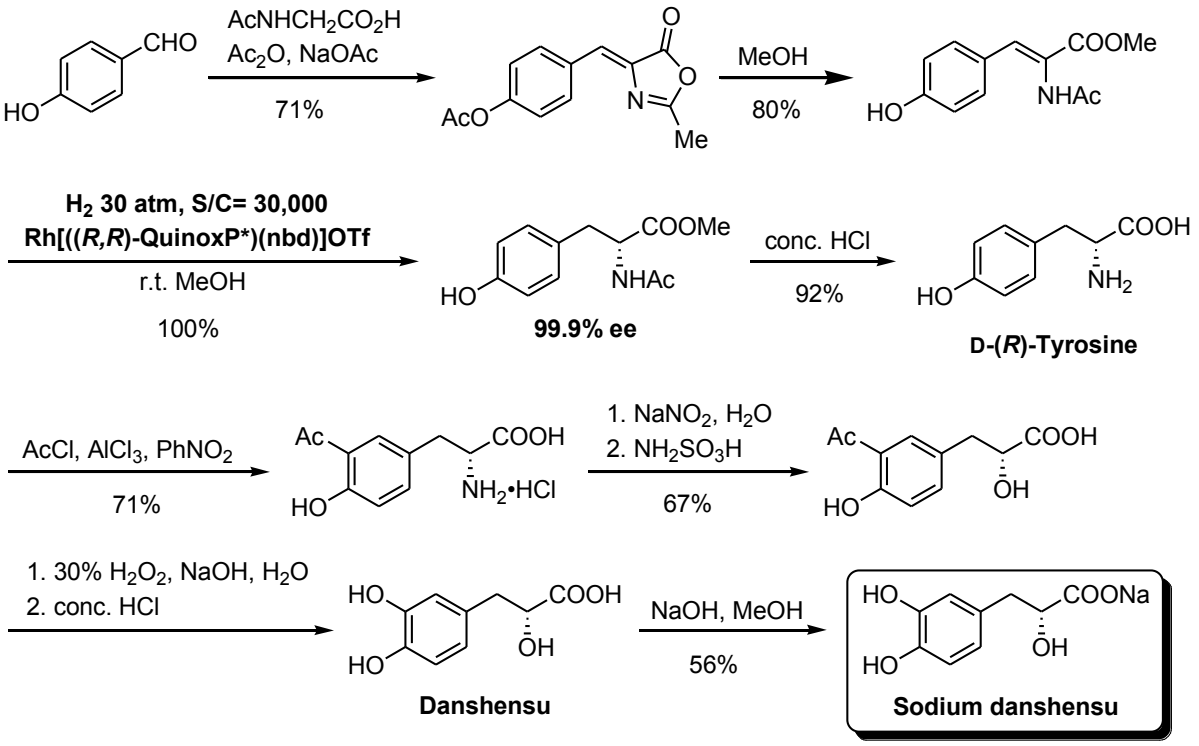
Since the development of an electron-rich P-chiral phosphine ligand, (*S*,*S*)-bis(*tert*-butylmethylphosphino) ethane (BisP*),[1] many analogous ligands bearing a bulky alkyl group and a small group at the same phosphorus atom have been reported so far. Among them, 2,3-bis(*tert*-butylmethylphosphino)quinoxaline (QuinoxP*) is known to be practically useful because of its air-stability and high to excellent enantioinduction ability in various catalytic asymmetric reactions including hydrogenation and C–C bond forming reactions.[2,3] Based on these facts, we recently established its large-scale preparation method using enantiopure (*S*)- and (*R*)-*tert*-butylmethylphosphine–boranes as the key intermediates.



Here, we report our recent study on the utilization of QuinoxP* ligand in the production of pharmaceutically important chiral compounds employing Rh-catalyzed asymmetric hydrogenation as a pivotal protocol. Our target compound is (*R*)-3-(3,4-dihydroxyphenyl)-2-hydroxypropanoic acid (Danshensu), which has been widely used for treatment of cardiovascular diseases. The overall reaction sequence is shown in the following scheme in which unnatural tyrosine is a key intermediate.



In order to obtain D-(*R*)-tyrosine in a practical scale, we used Rh-catalyzed asymmetric hydrogenation of a dehydroamino acid derivative prepared from inexpensive 4-hydroxybenzaldehyde. After various screening of the reaction conditions, we found that the hydrogenation proceeded smoothly under 30 atm hydrogen pressure with S/C = 30,000 in methanol to furnish the desired product in quantitative yield and 99.9% enantioselectivity. The product was converted to D-(*R*)-tyrosine in 92% yield without any racemization. Further transformation to danshensu and its sodium salt was accomplished by the modification of reported procedure.[4,5] It should be noted that all the intermediates were obtained in crystalline solids and separation procedures did not require chromatography, and hence this method is suitable for industrial production.[4]

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Indole Synthesis from 2-Aminochalcone via Rearrangement Reaction

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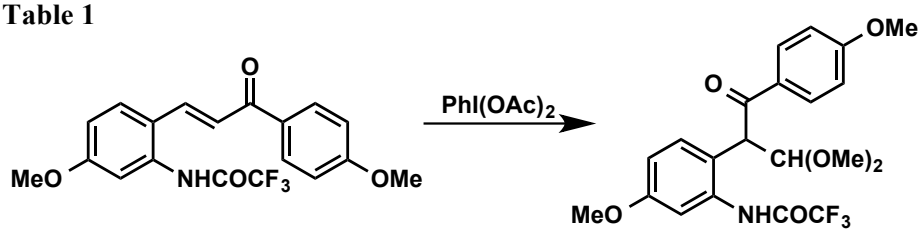
Indoles are important compounds not only as biological materials but also as bioactive compounds like natural products and pharmaceuticals. Many synthetic methods have been reported to date but the development of novel synthetic method for indole is still important. We have been interested in the reactivity of chalcone compounds and developed the flavonoid synthesis from chalcones.[1)] Then we planned the novel indole synthesis from 2-aminochalcone using hypervalent iodine reagent. Chalcone skeleton is known to react with hypervalent iodine reagent, $PhI(OAc)_2$ (phenyliodine diacetate), to afford the dimethylacetal as a rearranged product. We assumed that the introduction of amino group in one aromatic ring on appropriate position could lead cyclization to indole.

We first examined the rearrangement reaction of various *N*-protected-2-amino- 4,4'-dimethoxychalcone. The reaction of *N*-Ac or *N*-SO_2Ph chalcone with $PhI(OAc)_2$ and H_2SO_4 in MeOH did not afford the desired product. In the case of *N*-Cbz protection, the rearrangement reaction proceeded in good yield. Further optimization of reaction conditions, the use of $BF_3 \cdot Et_2O$ gave better result than the use of H_2SO_4. In addition, the change of solvent significantly affected the yield and the replacement of MeOH into $CH(OMe)_3$ resulted in the best yield (Table 1).

Table 1

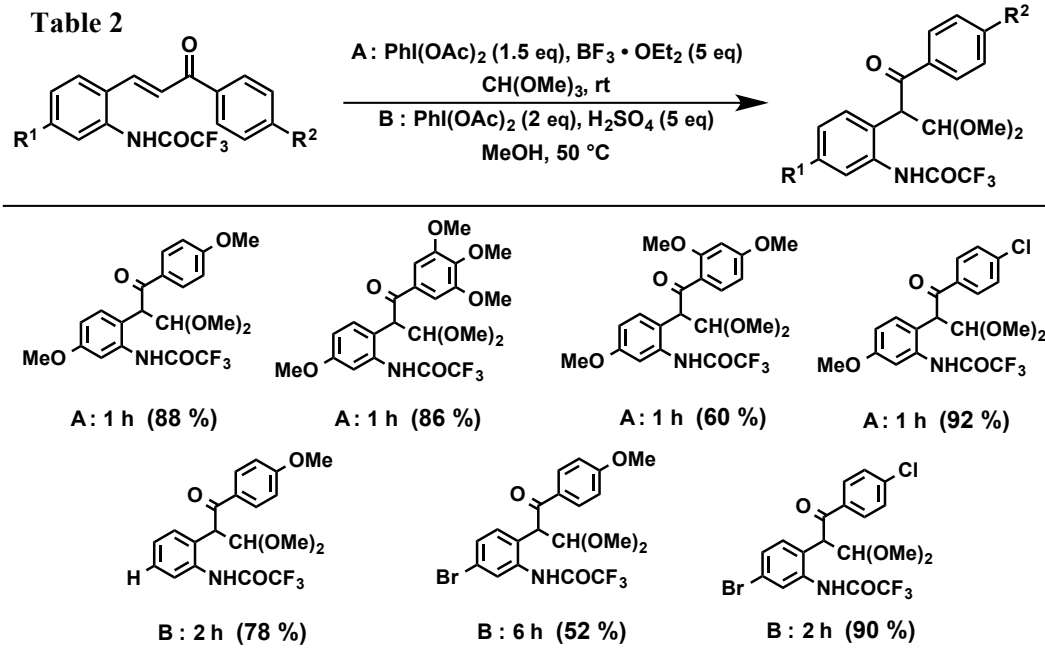


Entry	$PhI(OAc)_2$ (eq)	Acid (5 eq)	Solvent	Condition	Yield (%)	
1	1.2	H_2SO_4	MeOH	50 °C, 3 h	59	(32)
2	1.2	-	MeOH	50 °C, 24 h	-	(79)
3	1.2	TsOH	MeOH	50 °C, 24 h	-	(-)
4	2	H_2SO_4	MeOH	50 °C, 2 h	45	(9)
5	1.2	$BF_3 \cdot OEt_2$	MeOH	rt, 7 h	60	(26)
6	1.2	$BF_3 \cdot OEt_2$	$CH(OMe)_3$	rt, 2 h	84	(14)
7	1.5	$BF_3 \cdot OEt_2$	$CH(OMe)_3$	rt, 1 h	88	(-)

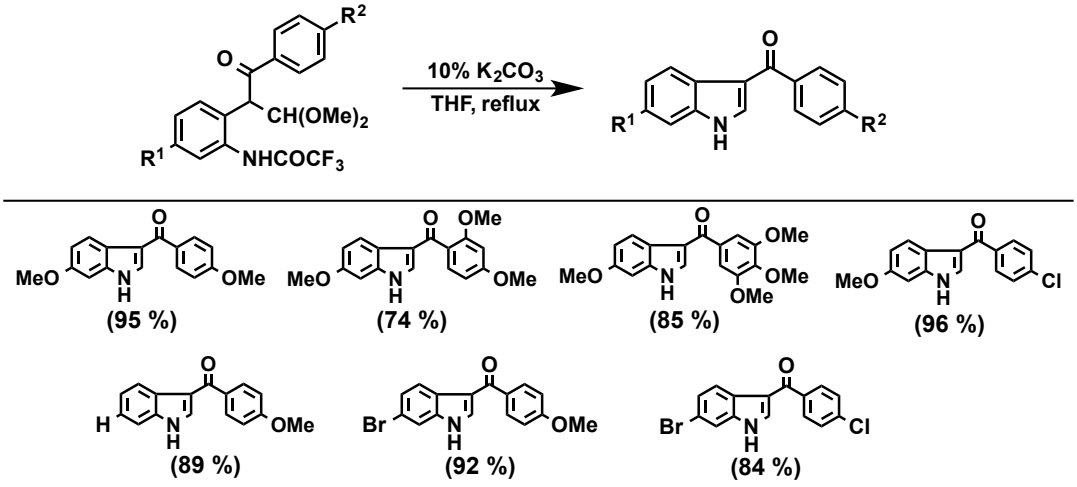
( ) : Recovered

The optimized conditions in hand, we conducted the rearrangement reaction using various substrates. The substrates bearing methoxy group on aromatic ring with amino group reacted under the conditions to give the corresponding rearranged acetal in good yield (Table 2). However, the non-substituted or Br substituted substrates afforded unsatisfied results under the conditions. Then we examined the reaction conditions and the use of H_2SO_4 instead of $BF_3 \cdot Et_2O$ afforded better result.

Table 2



Finally, we examined the indole formation under the basic conditions. The treatment of the rearranged substrate with 10% K_2CO_3 aq in THF afforded the desired indoles in good to high yields (Table 3).



Reference

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iChemExplorer: A Powerful Tool for Catalyst Screening and Probing the Catalytic Cycle

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Since its introduction in 2005 iChemExplorer has been shown to be an invaluable tool in the process chemist's arsenal by allowing reactions to be effected in parallel and at small scale directly on the Agilent HPLC auto-sampler. This has been crucially important in the area of catalyst screening and will be exemplified by drawing upon a number of published and pharmaceutically relevant examples. In particular the application of iChemExplorer in combination with diverse reagent selection and statistical experimental design will be discussed in such areas as cross coupling, green catalytic oxidation utilizing air as terminal oxidant, phase transfer catalysis and metal catalyzed rearrangements. In each case the use of the tool to identify effective catalyst-reagent combinations will be described.

iChemExplorer is also a powerful tool for collecting both qualitative and quantitative kinetic data for catalytic transformations and each of these cases will be addressed. At the qualitative level the visualization tools allow the chemist to quickly assess the relative effect of process changes upon the catalytic kinetics and will be described in the context of a Heck coupling.

For quantitative kinetics, iChemExplorer excels as a tool for readily collecting in parallel the kinetic profiles required to probe the catalytic cycle by means of Blackmond Reaction Progress Kinetic Analysis (RPKA) methodology (*Angew. Chem. Int.. Ed.,* **2005**, 44, 4302). This will be described for a novel and highly selective catalytic alkoxycarboxylation and furnishes the delineation of the rate limiting step and resting state of the catalytic cycle.

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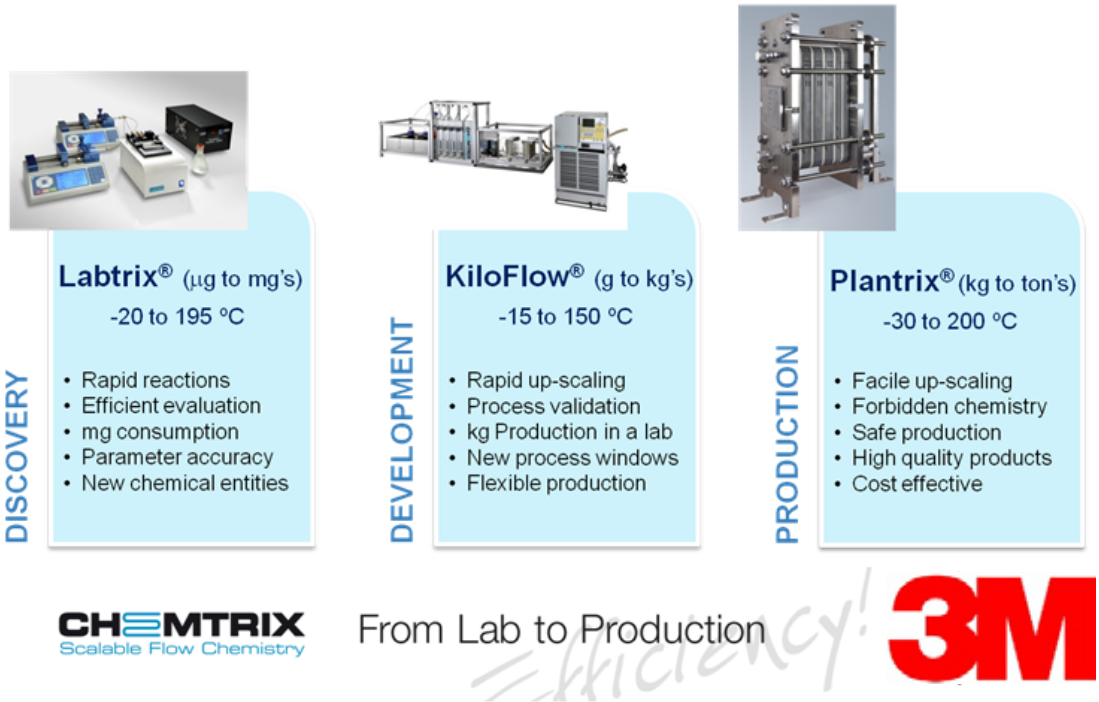
Title: Continuous Flow Reactors: An Opportunity for the development of flexible & sustainable production processes

Author: Dr Charlotte Wiles*, Chemtrix BV, The Netherlands

Abstract:

Whilst chemical engineers are trained to think of continuous processing as being an efficient route to the development of safe and controllable processes, synthetic chemists have received largely the same training for Centuries – which is based on the use of stirred reaction vessels. Consequently, within medicinal chemistry and development laboratories, focus is on the speed of compound preparation and not on the process or route employed to obtain the material. Looking to how reactions are conventionally performed they are often executed under non-ideal conditions in order to gain control over the process; this can include the use of large volumes of solvent, cryogenic conditions, the use of stoichiometric reagents and long dosing/reaction times. Subsequent product isolation is then time consuming and results in the generation of large quantities of waste. Time is then lost when a target is identified as the synthetic route must be redeveloped in order to be suitable for up-scaling to the target production quantities.

Compared to stirred vessels, flow reactors have significant processing advantages which include improved thermal management, enhanced mixing control and access to larger operating windows enabling the development of safe, efficient, robust and sustainable production processes – with benefits not only harnessed for the reaction steps, but also in cost and waste reduction when considering that increased product purities require less downstream processing. Applicable at both the lab and production scale, continuous flow reactor technology therefore has the ability to benefit both early stage researchers and process development chemists/engineers in the exploitation of sustainable synthetic processes.



The presentation will demonstrate through a selection of Customer case studies the advantages that can be leveraged through the use of continuous flow reactor technology including control of hazardous processes, small-footprint systems, low material consumption for process development and on-site local production – including examples of online analysis.

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Development of a High-Throughput Chiral Column using Ovomucoid Protein

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1. Introduction

Recently, while requirements with respect to high-throughput analyses of chiral compounds have been increasing, high-throughput columns employing protein chiral stationary phases (CSPs) are almost nonexistent. Consequently, we developed a high-throughput column utilizing a packing material with a small particle diameter. Additionally, ovomucoid columns have been successfully used as reverse phase chiral columns in separations of more than 170 enantiomers. From 70 to 80% of enantiomers can be separated using ovomucoid columns.

2. Experimental method

Ovomucoid protein was immobilized to aminopropylsilica via an N, N-disuccinimidyl carbonate coupling reaction to prepare OVM CSPs. As back pressure increases with decreases in packing material particle diameter, a packing method investigation was performed with the aim of improving pressure stability. We carried out a high-throughput investigation using different particle diameters and column sizes. Also, as examples of applications of this column, we performed analyses involving optical purity and linearity tests, etc. designed to obtain basic data, and separation and detection using an LC/MS system.

3. Results and observations

As shown in Fig. 1, on reducing the particle size from 5 μm to 3 μm and the column dimensions from 150 x 4.6 mm.I.D. to 100 x 3.0 mm.I.D. analysis times were reduced by approximately 1/4 while maintaining the same levels of resolution.

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* Presenter

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JSPC 2015 Winter Symposium

November 27 (Fri.), 2015
Nagai Memorial Hall, Tokushima University, Kuramoto Campus
Organizer: Kenichiro Sotowa (Tokushima University), Shinji Aki (Otsuka Pharmaceutical)

The 10 th Process Lounge

December 4 (Fri.) – 5 (Sat.), 2015
Yugawara Traning Center, Wako Pure Chemical Co., Ltd.
Organizer: Seiji Niwa (Ajinomoto)

The International Chemical Congress of Pacific Basin Societies [PACIFICHEM 2015]

December 15 (Tue.) – 20 (Sun.), 2015
Honolulu, Hawaii, USA
Organizer : Kiyoshi Tomioka, Robert M. Williams, Reuben Jih-Ru Hwu, Hironao Sajiki, Takayuki Shioiri, Nobuyoshi Yasuda

JSPC 2016 Summer Symposium

July 28 (Thu.) – 29 (Fri.), 2016
Nagoya Congress Center
Organizer: Hironao Sajiki (Gifu Pharmaceutical Univ.), Yoshihiko Hirose (Amano Enzyme)

ABSTRACTS of ISPC 2015
The 3rd International Symposium on Process Chemistry

■ **Published on** **June 23, 2015**

■ **Published by** **The Organizing Committee of ISPC 2015**
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URL：http://www.jspc-home.com/index.html

■ **Edited by** **The Chemical Daily Co., Ltd., Enterprise Division**
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Umicoreの高活性均一系貴金属触媒
（工業スケールでの製造販売・サンプル量も対応可）

umicore
Precious Metals
Chemistry

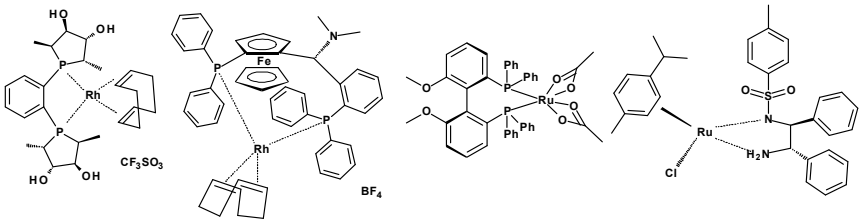
不斉水添用触媒

貴金属前駆体

$[Rh(COD)Cl]_2$, $[Rh(COD)_2]BF_4$, $[Rh(C_5Me_5)Cl_2]_2$, $[Rh(COD)_2]BARF$
$[Ru(p\text{-}cymene)Cl_2]_2$, $[Ru(p\text{-}cymene)I_2]_2$, $Ru(COD)(methylallyl)_2$
$[Ir(COD)Cl]_2$, $[Ir(COD)_2]BF_4$, $[Ir(COD)_2]BARF$, $[Ir(C_5Me_5)I_2]_2$

Metal ligand（ML）complex

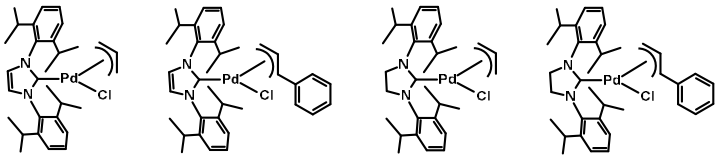
純粋な不斉配位子金属錯体：高不斉収率、高化学収率、高触媒回転率
ユーザーフレンドリーなIPモデル（IP使用料込み価格）、工業化向き



クロスカップリング用Pd触媒

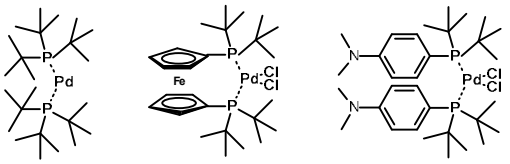
NHC-Pd触媒（Umicore CXシリーズ）

高活性、酸素に安定、多様な反応形式・基質に適用化、高触媒turnover
堅牢な反応プロセス、後処理・Pd残渣除去容易、工業化向き
有機合成化学協会誌, **67**, 653 (2009)



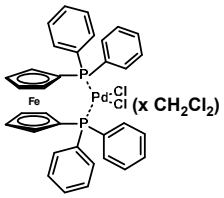
CX21　CX31　CX23　CX32

高活性Pd-リン錯体触媒



汎用Pd-リン錯体触媒

$Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(Po\text{-}Tol_3)_2Cl_2$,
$Pd(Pc\text{-}Hex_3)_2Cl_2$, $Pd(dppe)Cl_2$, $Pd(dppp)Cl_2$

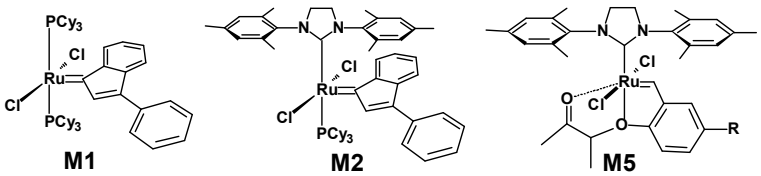


汎用Pd前駆体

$Pd(OAc)_2$, $Pd_2(dba)_3$x dba, $[Pd(allyl)Cl]_2$, $Pd(acac)_2$

メタセシス用触媒（Umicore Mシリーズ）

高活性、第一～第三世代＋α、多様な反応形式・基質に適用化
ユーザーフレンドリーなIPモデル（IP使用料込み価格）、工業化向き



M1　M2　M5

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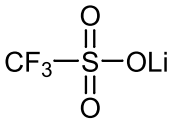
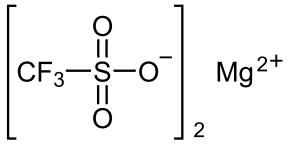
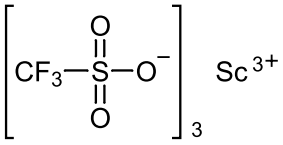
Metal Triflates



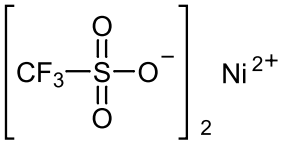
Lithium Triflate
25g JPY 6,600
[T1548]



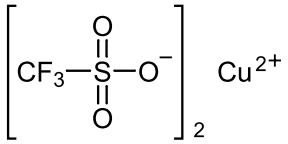
Magnesium Triflate
5g JPY 4,900 / 25g JPY 16,300
[T1304]



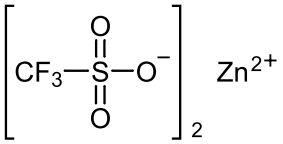
Scandium(III) Triflate
1g JPY 9,200 / 5g JPY 29,500
[T1663]



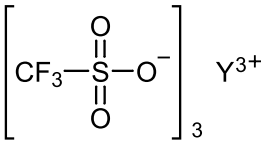
Nickel(II) Triflate
1g JPY 7,600 / 5g JPY 28,300
[N0861]



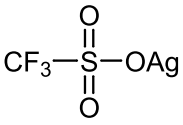
Copper(II) Triflate
5g JPY 6,200 / 25g JPY 19,100
[T1292]



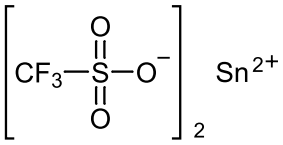
Zinc(II) Triflate
25g JPY 10,800
[T1294]



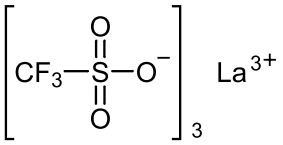
Yttrium(III) Triflate
5g JPY 7,700 / 25g JPY 25,700
[T1921]



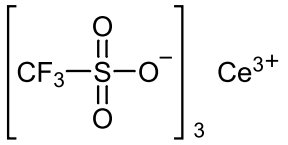
Silver Triflate
1g JPY 2,600 / 10g JPY 13,700 /
25g JPY 24,500
[T1331]



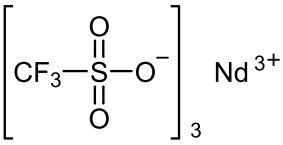
Tin(II) Triflate
1g JPY 5,900 / 5g JPY 17,600 /
25g JPY 61,400
[T1194]



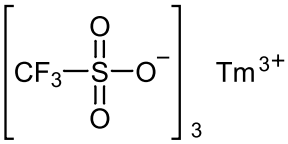
Lanthanum(III) Triflate
5g JPY 6,500 / 25g JPY 20,000
[T1293]



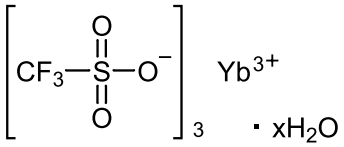
Cerium(III) Triflate
5g JPY 7,800 / 25g JPY 25,500
[T1918]



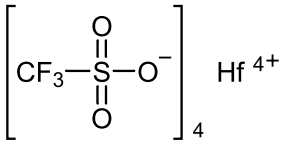
Neodymium(III) Triflate
5g JPY 5,100 / 25g JPY 17,000
[T1919]



Thulium(III) Triflate
5g JPY 10,400
[T1920]



Ytterbium(III) Triflate Hydrate
5g JPY 5,500 / 25g JPY 17,500
[T1610]



Hafnium(IV) Triflate
1g JPY 5,200 / 5g JPY 18,900
[T1708]

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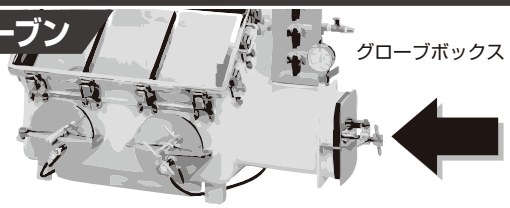
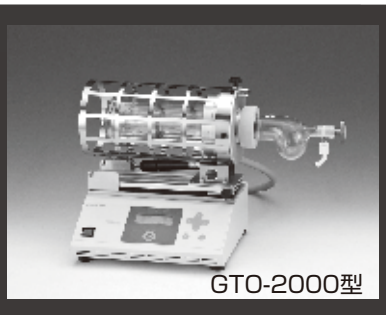


グローブボックス

GTO-200型

減圧乾燥後、そのまま グローブボックスへ IN!!

乾燥後、減圧状態のまま移動させることが可能です。
大気中の水分の吸着や酸素との反応を防げます。



GTO-2000型

ロータリーエバポレーター

ロータリーエバポレーター
SRE-M3型

ウォーターバスWB-16M型

三角トラップ

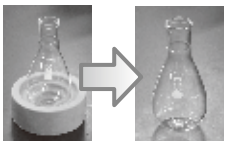
■液だまり防止により、濃縮・蒸留作業効率をUP！

使用例

平底なす形フラスコ

■自立型
■エバポレーターに使用可能
（190Pa30分間の減圧に対応）

作業例



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日本語、英語
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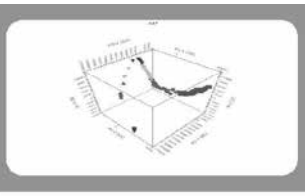
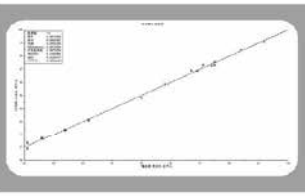
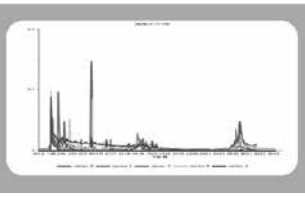


多次元スペクトルの低次元化
主成分分析: PCA
個々のスペクトル傾向の見える化



スペクトルの相関、定量解析
部分最小二乗回帰: PLSR
主成分回帰: PCR など
応答因子に対しての検量線を作成



混合スペクトルのピーク分離
多変量スペクトル分解: MCR
ソフトウェアクロマトグラフィー
結晶多形評価、不純物検出などに

試用版ソフトウェア請求、デモ依頼は弊社まで

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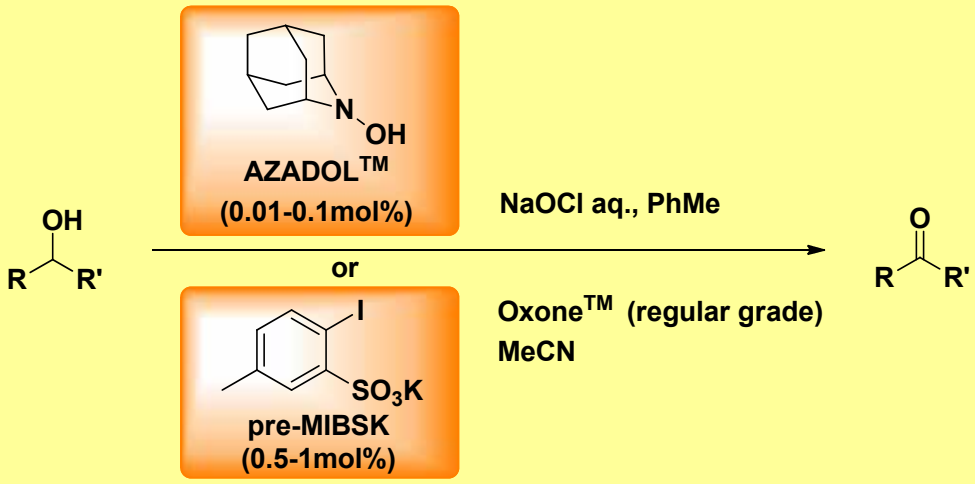
AZADOL™

and

pre-MIBSK



Advantages:

- High activity (Low catalytic amount)
- **AZADOL™** is able to oxidize bulky secondary alcohols.
- **Pre-MIBSK** is non-explosive and used as replacement of IBX.
- **AZADOL™** and **pre-MIBSK** are Ames negative.

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化学品情報のあらゆるニーズに応える

16615の化学商品

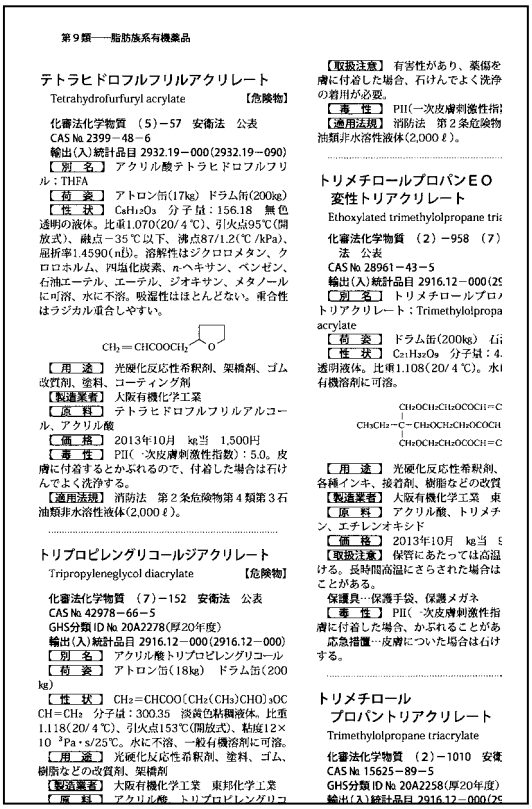
◆B5判・2,100頁 ◆定価：本体33,000円+税（送料込）◆2015年1月27日発売

2015年版の特色

- ●緊急時応急措置指針番号を収載
- ●化審法、安衛法番号、HSコード改正に対応
- ●GHS分類IDナンバー、CAS番号など充実
- ●毒性情報、改正法令等適用法規さらに拡充

《内容》

市場性の高い化学品を30類に分類し、各商品ごとに**英文名/化審法化学物質番号/労働安全衛生法番号/CASナンバー/GHS分類IDナンバー/輸出入統計品目番号/別名/概説/荷姿/性状/規格/用途/製造業者/原料/製法/最近の生産・輸出・輸入量/PRTR排出・移動量/価格/取扱注意/消火上の注意/保護具/毒・劇物の廃棄法/毒性/応急措置/輸送コード/緊急時応急措置指針番号/適用法規**の順に詳述してあります。輸送コードでは、**国連番号、IMDG、ICAO/IATA危険物質クラス、容器等級**が記載されています。2014年版より、緊急時応急措置指針番号を新たに収載しました。また、関連する各種法規の改正にも即応しています。本書で化学品の調査は完璧です。



第９類――脂肪族系有機薬品

テトラヒドロフルフリルアクリレート
Tetrahydrofurfuryl acrylate 【危険物】

化審法化学物質 （5）−57 安衛法 公表
CAS No. 2399−48−6
輸出(入)統計品目 2932.19−000(2932.19−090)
【別 名】 アクリル酸テトラヒドロフルフリル；THFA
【荷 姿】 アトロン缶(17kg) ドラム缶(200kg)
【性 状】 $C_8H_{12}O_3$ 分子量：156.18 無色透明の液体。比重1.070(20/4℃)、引火点95℃(開放式)、融点−35℃以下、沸点87/1.2(℃/kPa)、屈折率1.4590(nD)。溶解性はジクロロメタン、クロロホルム、四塩化炭素、n-ヘキサン、ベンゼン、石油エーテル、エーテル、ジオキサン、メタノールに可溶、水に不溶。吸湿性はほとんどない。重合性はラジカル重合しやすい。

【用 途】 光硬化反応性希釈剤、架橋剤、ゴム改質剤、塗料、コーティング剤
【製造業者】 大阪有機化学工業
【原 料】 テトラヒドロフルフリルアルコール、アクリル酸
【価 格】 2013年10月 kg当 1,500円
【毒 性】 PII(一次皮膚刺激性指数)：5.0。皮膚に付着するとかぶれるので、付着した場合は石けんでよく洗浄する。
【適用法規】 消防法 第２条危険物第４類第３石油類非水溶性液体(2,000ℓ)。

トリプロピレングリコールジアクリレート
Tripropyleneglycol diacrylate 【危険物】

化審法化学物質 （7）−152 安衛法 公表
CAS No. 42978−66−5
GHS分類 ID No. 20A2278(厚20年度)
輸出(入)統計品目 2916.12−000(2916.12−000)
【別 名】 アクリル酸トリプロピレングリコール
【荷 姿】 アトロン缶(18kg) ドラム缶(200kg)
【性 状】 $CH_2=CHCOO(CH_2(CH_3)CHO)_3OCH=CH_2$ 分子量：300.35 淡黄色粘調液体。比重1.118(20/4℃)、引火点153℃(開放式)、粘度12×10^{-3}Pa・s/25℃。水に不溶、一般有機溶剤に可溶。
【用 途】 光硬化反応性希釈剤、塗料、ゴム、樹脂などの改質剤、架橋剤
【製造業者】 大阪有機化学工業 東邦化学工業
【原 料】 アクリル酸 トリプロピレングリコ

【取扱注意】 有害性があり、薬傷を膚に付着した場合、石けんでよく洗浄の着用が必要。
【毒 性】 PII(一次皮膚刺激性指
【適用法規】 消防法 第２条危険物油類非水溶性液体(2,000ℓ)。

トリメチロールプロパンEO変性トリアクリレート
Ethoxylated trimethylolpropane tri
化審法化学物質 （2）−958 （7）法 公表
CAS No. 28961−43−5
輸出(入)統計品目 2916.12−000(29
【別 名】 トリメチロールプロトリアクリレート；Trimethylolpropa acrylate
【荷 姿】 ドラム缶(200kg) 石
【性 状】 $C_{21}H_{32}O_9$ 分子量：4. 透明液体。比重1.108(20/4℃)。水 有機溶剤に可溶。

【用 途】 光硬化反応性希釈剤、各種インキ、接着剤、樹脂などの改質
【製造業者】 大阪有機化学工業 東
【原 料】 アクリル酸、トリメチン、エチレンオキシド
【価 格】 2013年10月 kg当 5
【取扱注意】 保管にあたっては高温ける。長時間高温にさらされた場合はことがある。
保護具…保護手袋、保護メガネ
【毒 性】 PII(一次皮膚刺激性指膚に付着した場合、かぶれることがあ
応急措置…皮膚についた場合は石けする。

トリメチロールプロパントリアクリレート
Trimethylolpropane triacrylate
化審法化学物質 （2）−1010 安衛
CAS No. 15625−89−5
GHS分類 ID No. 20A2258(厚20年度)
輸出(入)統計品目 2916.12−000(29

（16514の化学商品〈2014年版〉内容見本）

16615の化学商品PDF

◆2015年2月発売
◆定価：本体33,000円＋税（送料込）

●ご注文、お問い合わせは、

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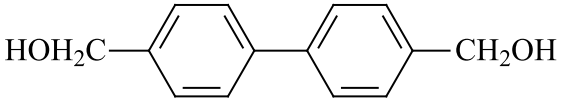
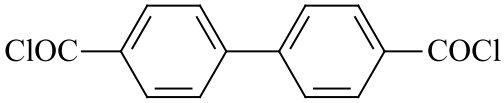
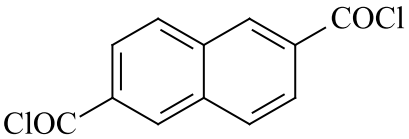
Fine-Chemical Products of NLM



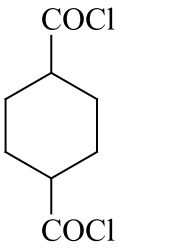
BPG [1667-12-5]

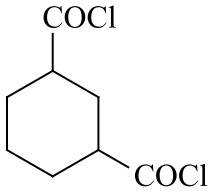


DPDOC [2351-37-3]



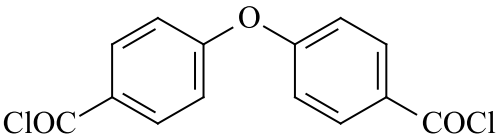
NADOC [2351-36-2]





13CHDC [27768-32-7]

14CHDC [13170-66-6]



OBBOC [7158-32-9]

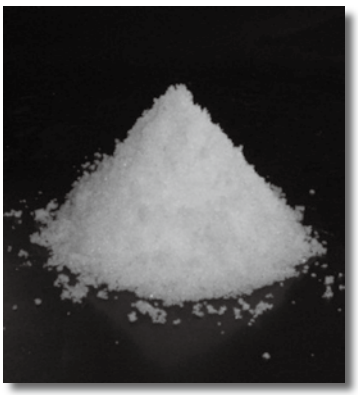
New Oxidizer/Sterilizer

Solid Sodium hypochlorite

Chemical Name : Sodium hypochlorite pentahydrate
次亜塩素酸ナトリウム５水塩

Chemical Formula : $NaClO \cdot 5H_2O$

CAS 10022-70-5　METI (1)-237



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Solid Yellowish-white crystal powder
High Volumetric capacity: 3.5 times
Desirable Concentrations: 0 – 42%

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Stable over 360 days in cold storage

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Barely contains any Bromic/Chloric acids
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☆ **New Oxidizer/Sterilizer**

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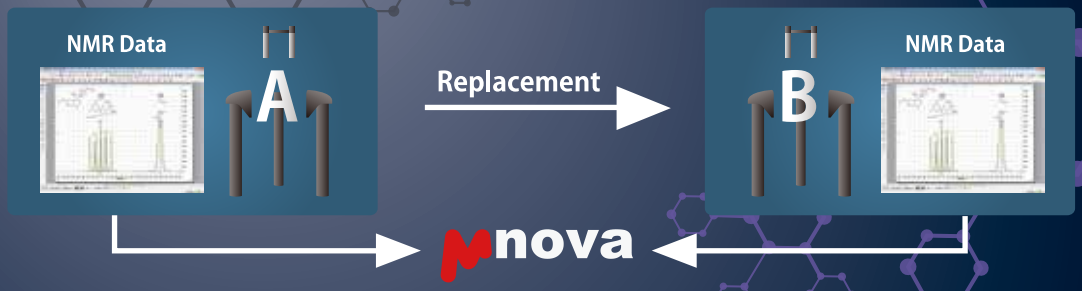

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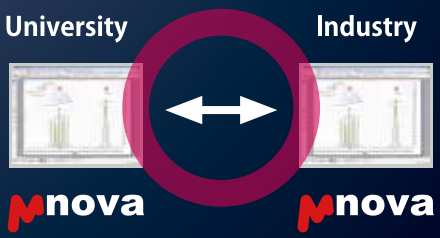

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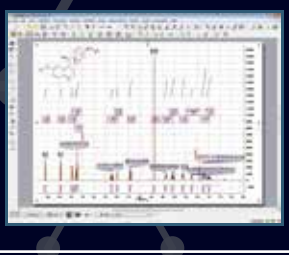

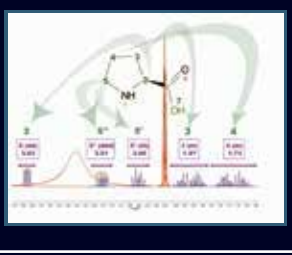

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