ISPC 2019

The 4th International Symposium on Process Chemistry

July 24 Wed. – 26 Fri., 2019

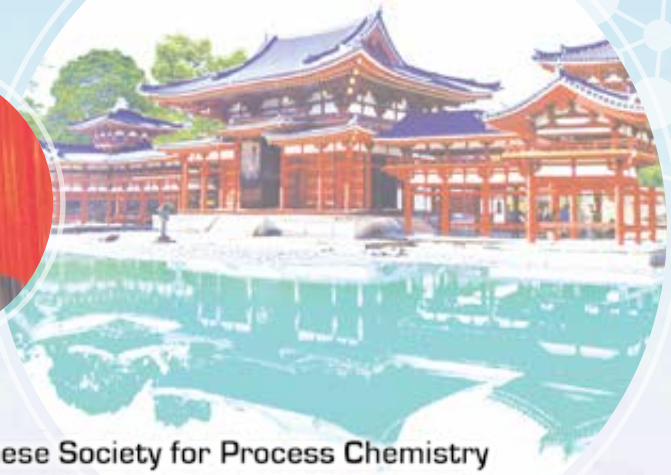
Kyoto, JAPAN

Kyoto International Conference Center

Abstracts

J.S.P.C

The Japanese Society for Process Chemistry



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The Japanese Society for Process Chemistry

Support
The Society of Synthetic Organic Chemistry, Japan
The Kinka Chemical Society, Japan
The Japan Society for Bioscience, Biotechnology, and Agrochemistry
The Society of Separation Process Engineers, Japan
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Dear Colleagues,

It is a great honor and pleasure for us to hold the fourth International Symposium on Process Chemistry (ISPC 2019) during July 24-26, 2019 in Kyoto under the auspices of the Japanese Society for Process Chemistry (JSPC).

JSPC was founded in 2001, just beginning of this century. It organizes summer and winter symposia ever year. Members of JSPC belong to pharmaceutical and chemical industries, manufacturers of pharmaceuticals intermediates, academics, and so on. More than 500 participants discuss process chemistry in the summer symposium every year.

Furthermore, JSPC already organized International Symposium on Process Chemistry (ISPC) in 2008, 2011, and 2015 in Kyoto, and total number of participants of the symposia has exceeded 2500. JSPC is planning to organize the 4th International Symposium on Process Chemistry (ISPC2019) in the summer of 2019 in Kyoto. Both industrial and academic chemists who are interested in process chemistry will be cordially invited to participate in the ISPC 2019 to present and discuss the recent progress of broad aspects of process chemistry.

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

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

Hironao Sajiki
President of the Japanese Society of Process Chemistry

Takahiko Akiyama
Chairperson of the Fourth International Symposium on Process Chemistry (ISPC 2019)

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Noriaki Murase (Taisho)
Keiji Ohno (FUJIFILM Wako Pure Chemical)
Masahiro Ohshima (Mitsubishi Tanabe)
Toshihiko Onoda (Daiichi Sankyo)
Osamu Onomura (Nagasaki Univ.)
Mikio Sasaki (Sumitomo Dainippon)

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To Participants of The 4th International Symposium on Process Chemistry [ISPC 2019]

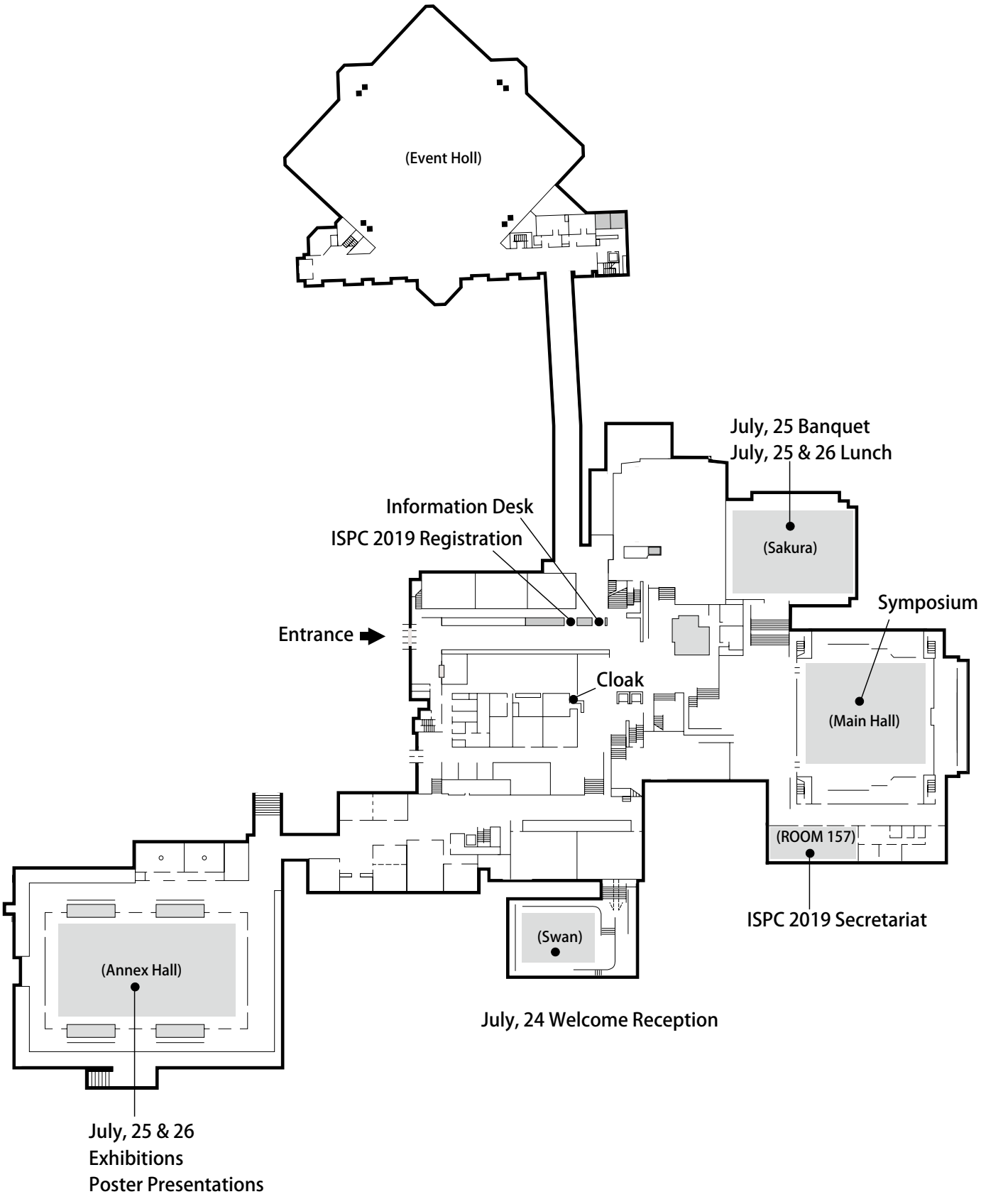
* Those who had registered in advance are advised to show to the receptionists before entering the venue the registration confirmations that we had previously mailed to them.
* Neither photographing nor videotaping is allowed at the symposium.
* Please set cell phones to silent mode.
* Light clothes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

To Poster Presenters

* The presentation codes 1P-xx and 2P-xx represent July 25 (Thursday) and July 26 (Friday), Respectively the poster presentation is held at Annex Hall.
* Please put up all poster on the board during 9:00 am and the end 2:40 pm on July 25. Posters should be put up for two days (July 25 and 26), and please remove at the end of the poster session on July 26. 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 25 12:45 on July 26

Floor Plan


(Event Holl)
July, 25 Banquet
July, 25 & 26 Lunch
(Sakura)
Information Desk
ISPC 2019 Registration
Entrance
Symposium
Cloak
(Main Hall)
(ROOM 157)
ISPC 2019 Secretariat
(Swan)
July, 24 Welcome Reception
(Annex Hall)
July, 25 & 26
Exhibitions
Poster Presentations

Poster/Exhibition Annex Hall

ポスターセッション
Poster Session

1P-01	2P-08	1P-09	2P-16	1P-17	2P-24	1P-25	2P-32	1P-33	2P-40
2P-01	1P-08	2P-09	1P-16	2P-17	1P-24	2P-25	1P-32	2P-33	1P-40
1P-02	2P-07	1P-10	2P-15	1P-18	2P-23	1P-26	2P-31	1P-34	2P-39
2P-02	1P-07	2P-10	1P-15	2P-18	1P-23	2P-26	1P-31	2P-34	1P-39
1P-03	2P-06	1P-11	2P-14	1P-19	2P-22	1P-27	2P-30	1P-35	2P-38
2P-03	1P-06	2P-11	1P-14	2P-19	1P-22	2P-27	1P-30	2P-35	1P-38
1P-04	2P-05	1P-12	2P-13	1P-20	2P-21	1P-28	2P-29	1P-36	2P-37
2P-04	1P-05	2P-12	1P-13	2P-20	1P-21	2P-28	1P-29	2P-36	1P-37

企業展示
Exhibition

		SPERA PHARMA, Inc./ スペラファーマ㈱	3	11 BRONKHORST JAPAN K.K./ ブロンコスト・ジャパン㈱	Umicore Japan KK/ ユミコアジャパン㈱	12	21 Agilent Technologies Japan, Ltd./ アジレントテクノロジー㈱	TACMINA CORPORATION/ ㈱ タクミナ	22	31 SCRUM Inc./ ㈱ スクラム	Kobe Steel, Ltd./ ㈱ 神戸製鋼所	32	41 YMC CO., LTD./ ㈱ ワイエムシィ	VACUUBRAND SCIENTIFIC JAPAN LTD./ ㈱ バキューブランド サイエンティフィック ジャパン	42	51 SEN LIGHTS Corporation/ セン特殊光源㈱
2 TOKYO CHEMICAL INDUSTRY CO.,LTD./ 東京化成工業㈱																			
		AJINO MOTO HEALTHY SU PPLY CO., INC./ 味の素ヘルシーサプライ㈱	4	10 PHT International Inc./ PHTインターナショナル㈱	WATANABE CHEMICAL INDUSTRIES, LTD./ 渡辺化学工業㈱	13	20 NEO CHEMICAL CO.,LTD./ ネオケミカル㈱	KANTO CHEMICAL CO.,INC./ 関東化学㈱	23	30 NIPPON PHARMACEUTICAL CHEMICALS CO.,LTD./ 日本理化学工業㈱	Sanofi K.K./ サノフィ㈱	33	40 HOKKO CHEMICAL INDUSTRY CO.,LTD./ 北興化学工業㈱	NAMIKI SHOJI CO., LTD./ ナミキ商事㈱	43	50 FUJIMOTO CHEMICALS CO.,LTD./ 藤本化学製品㈱
1 JULABO JAPAN Co., Ltd./ ユラボジャパン㈱																			
		Jubilant Biosys Limited	5	9 ORGANO CORPORATION/ オルガノ㈱	Nissei Corporation/ 日星産業㈱	14	19 BizComJapan,Inc./ ㈱ ビジコムジャパン	NARD CHEMICALS, Ltd./ ㈱ ナードケミカルズ	24	29 ATTO CO., LTD./ ATTO㈱	ERICA OPTICAL CO.,LTD./ ㈱ エリカ オプチカル	34	39 Evonik Japan Co.,Ltd./ エボニック ジャパン㈱	TOSOH FINECHEM CORPORATION/ 東ソー・ファインケム㈱	44	49 Apeiron Synthesis S.A.
		Mettler Toledo K.K./ メトラー・トレド㈱	6	8 Shigematsu & Co.,Ltd./ 重松貿易㈱	HIKAL/ ハイカルジャパン	15	18 DAICEL CORPORATION/ ㈱ ダイセル	UKIMA CHEMICAL CO.,LTD./ ㈱ 浮間化学研究所	25	28 ASAHI KASEI FINECHEM CO.,LTD./ 旭化成ファインケム㈱	FUJIFILM Wako Pure Chemical Corporation/ 富士フイルム和光純薬㈱	35	38 Central Glass Co.,Ltd./ セントラル硝子㈱	Fuji Pure Chemicals Co.,Ltd./ 富士純薬㈱	45	48 Hamari Chemicals, Ltd./ 浜理薬品工業㈱
				7 Asahi Lab Commerce, Inc./ ㈱ 朝日ラボ交易	IVIC Research Inc./ ㈱ アイビック・リサーチ	16	17 TOKYO RIKAKIKAI CO.,LTD./ 東京理化器械㈱	Syrris Japan Inc./ Syrris	26	27 Biotage Japan, LTD./ バイオタージ・ジャパン㈱	KNF Japan Co.,Ltd./ ㈱ ケー・エヌ・エフ・ジャパン	36	37 Shoko Science Co.,Ltd./ 昭光サイエンス㈱	DFC Co.,Ltd./ ㈱ DFC	46	47 PMT Corporation/ ㈱ PMT

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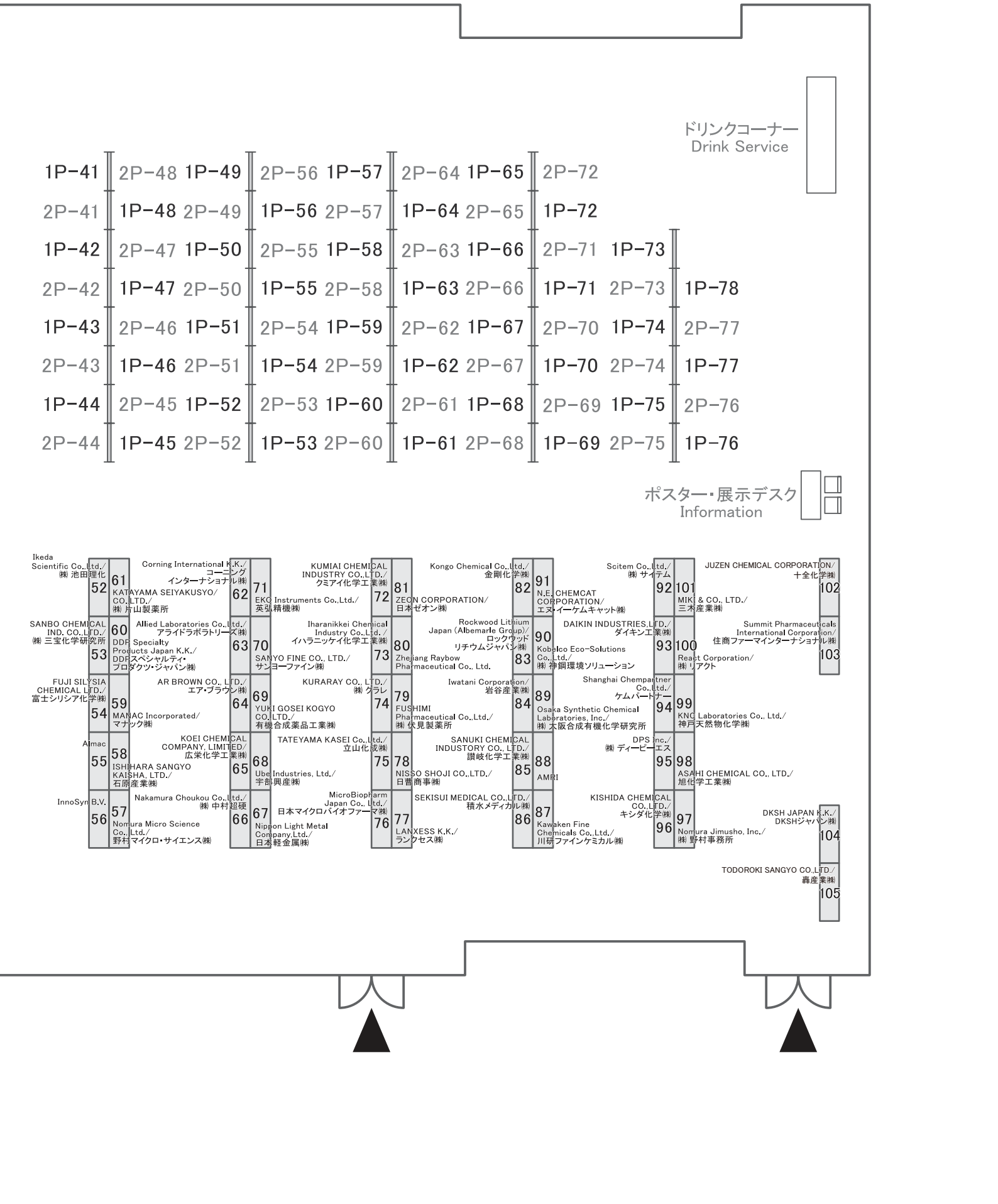
ドリンクコーナー
Drink Service
1P-41 2P-48 1P-49 2P-56 1P-57 2P-64 1P-65 2P-72
2P-41 1P-48 2P-49 1P-56 2P-57 1P-64 2P-65 1P-72
1P-42 2P-47 1P-50 2P-55 1P-58 2P-63 1P-66 2P-71 1P-73
2P-42 1P-47 2P-50 1P-55 2P-58 1P-63 2P-66 1P-71 2P-73 1P-78
1P-43 2P-46 1P-51 2P-54 1P-59 2P-62 1P-67 2P-70 1P-74 2P-77
2P-43 1P-46 2P-51 1P-54 2P-59 1P-62 2P-67 1P-70 2P-74 1P-77
1P-44 2P-45 1P-52 2P-53 1P-60 2P-61 1P-68 2P-69 1P-75 2P-76
2P-44 1P-45 2P-52 1P-53 2P-60 1P-61 2P-68 1P-69 2P-75 1P-76
ポスター・展示デスク
Information
Ikeda Scientific Co.,Ltd./ ㈱ 池田理化 52
61 Corning International K.K./ コーニング インターナショナル㈱
KATAYAMA SEIYAKUSYO/ CO.,LTD./ ㈱ 片山製薬所 62
71 EKO Instruments Co.,Ltd./ 英弘精機㈱
SANBO CHEMICAL IND. CO.,LTD./ ㈱ 三宝化学研究所 53
60 Allied Laboratories Co.,Ltd./ アライドラボラトリーズ㈱
DDP Specialty Products Japan K.K./ DDPスペシャルティ・プロダクツ・ジャパン㈱ 63
70 SANYO FINE CO., LTD./ サンヨーファイン㈱
FUJI SILYSIA CHEMICAL LTD./ 富士シリシア化学㈱ 54
59 AR BROWN CO., LTD./ エア・ブラウン㈱
MANAC Incorporated/ マナック㈱ 64
69 YUKI GOSEI KOGYO CO.,LTD./ 有機合成薬品工業㈱
Aimac 55
58 KOEI CHEMICAL COMPANY, LIMITED/ 広栄化学工業㈱
ISHIHARA SANGYO KAISHA, LTD./ 石原産業㈱ 65
68 Ube Industries, Ltd./ 宇部興産㈱
InnoSyn B.V. 56
57 Nakamura Choukou Co.,Ltd./ ㈱ 中村超硬
Nomura Micro Science Co.,Ltd./ 野村マイクロ・サイエンス㈱ 66
67 Nippon Light Metal Company,Ltd./ 日本軽金属㈱
KUMIAI CHEMICAL INDUSTRY CO.,LTD./ クミアイ化学工業㈱ 72
81 ZEON CORPORATION/ 日本ゼオン㈱
Iharanikkei Chemical Industry Co.,Ltd./ イハラニッケイ化学工業㈱ 73
80 Zhejiang Raybow Pharmaceutical Co., Ltd.
KURARAY CO., LTD./ ㈱ クラレ 74
79 FUSHIMI Pharmaceutical Co.,Ltd./ ㈱ 伏見製薬所
TATEYAMA KASEI Co.,Ltd./ 立山化成㈱ 75
78 NISSO SHOJI CO.,LTD./ 日曹商事㈱
MicroBiopharm Japan Co., Ltd./ 日本マイクロバイオファーマ㈱ 76
77 LANXESS K.K./ ランクセス㈱
Kongo Chemical Co.,Ltd./ 金剛化学㈱ 82
91 N.E.CHEMCAT CORPORATION/ エヌ・イーケムキャット㈱
Rockwood Lithium Japan (Albemarle Group)/ ロックウッド リチウムジャパン㈱ 83
90 Kobelco Eco-Solutions Co., Ltd./ ㈱ 神鋼環境ソリューション
Iwatani Corporation/ 岩谷産業㈱ 84
89 Osaka Synthetic Chemical Laboratories, Inc./ ㈱ 大阪合成有機化学研究所
SANUKI CHEMICAL INDUSTORY CO., LTD./ 讃岐化学工業㈱ 85
88 AMRI
SEKISUI MEDICAL CO.,LTD./ 積水メディカル㈱ 86
87 Kawaken Fine Chemicals Co.,Ltd./ 川研ファインケミカル㈱
Scitem Co.,Ltd./ ㈱ サイテム 92
101 MIKI & CO., LTD./ 三木産業㈱
DAIKIN INDUSTRIES,LTD./ ダイキン工業㈱ 93
100 React Corporation/ ㈱ リアクト
Shanghai Chempartner Co.,Ltd./ ケムパートナー 94
99 KNC Laboratories Co., Ltd./ 神戸天然物化学㈱
DPS Inc./ ㈱ ディーピーエス 95
98 ASAHI CHEMICAL CO., LTD./ 旭化学工業㈱
KISHIDA CHEMICAL CO.,LTD./ キシダ化学㈱ 96
97 Nomura Jimusho, Inc./ ㈱ 野村事務所
JUZEN CHEMICAL CORPORATION/ 十全化学㈱ 102
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DKSH JAPAN K.K./ DKSHジャパン㈱ 104
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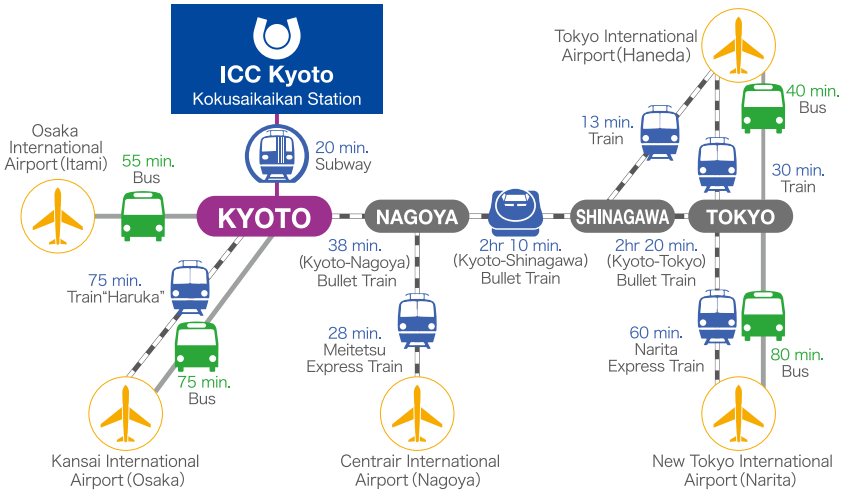
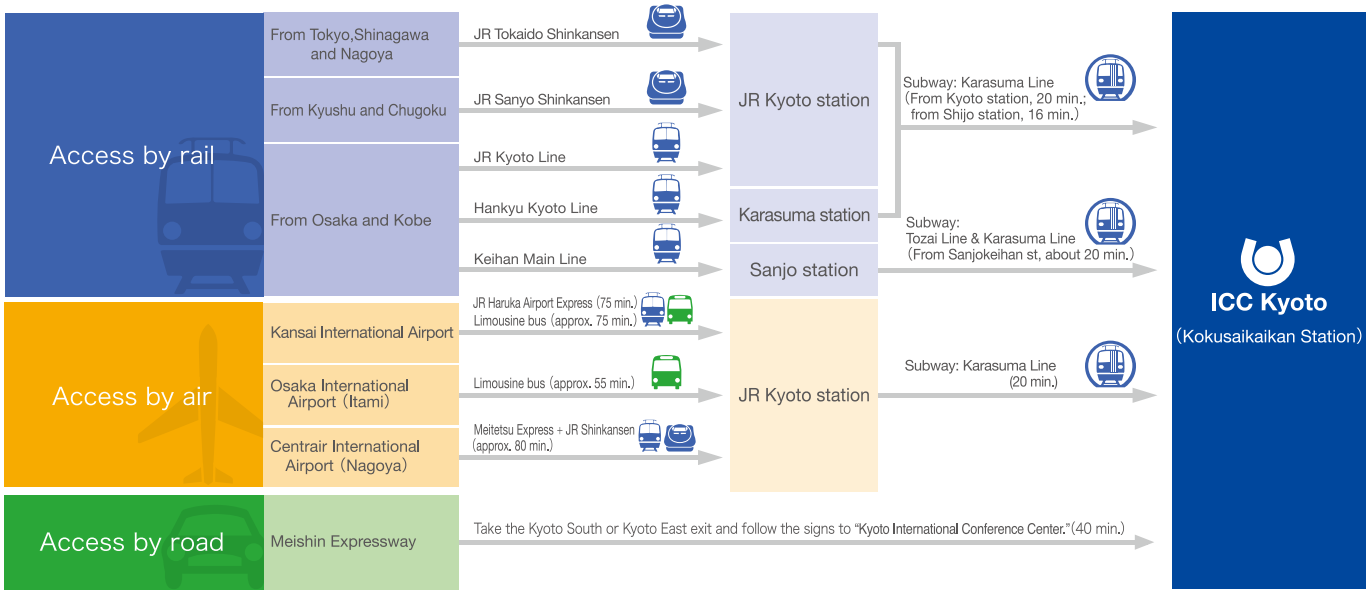
Access

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.

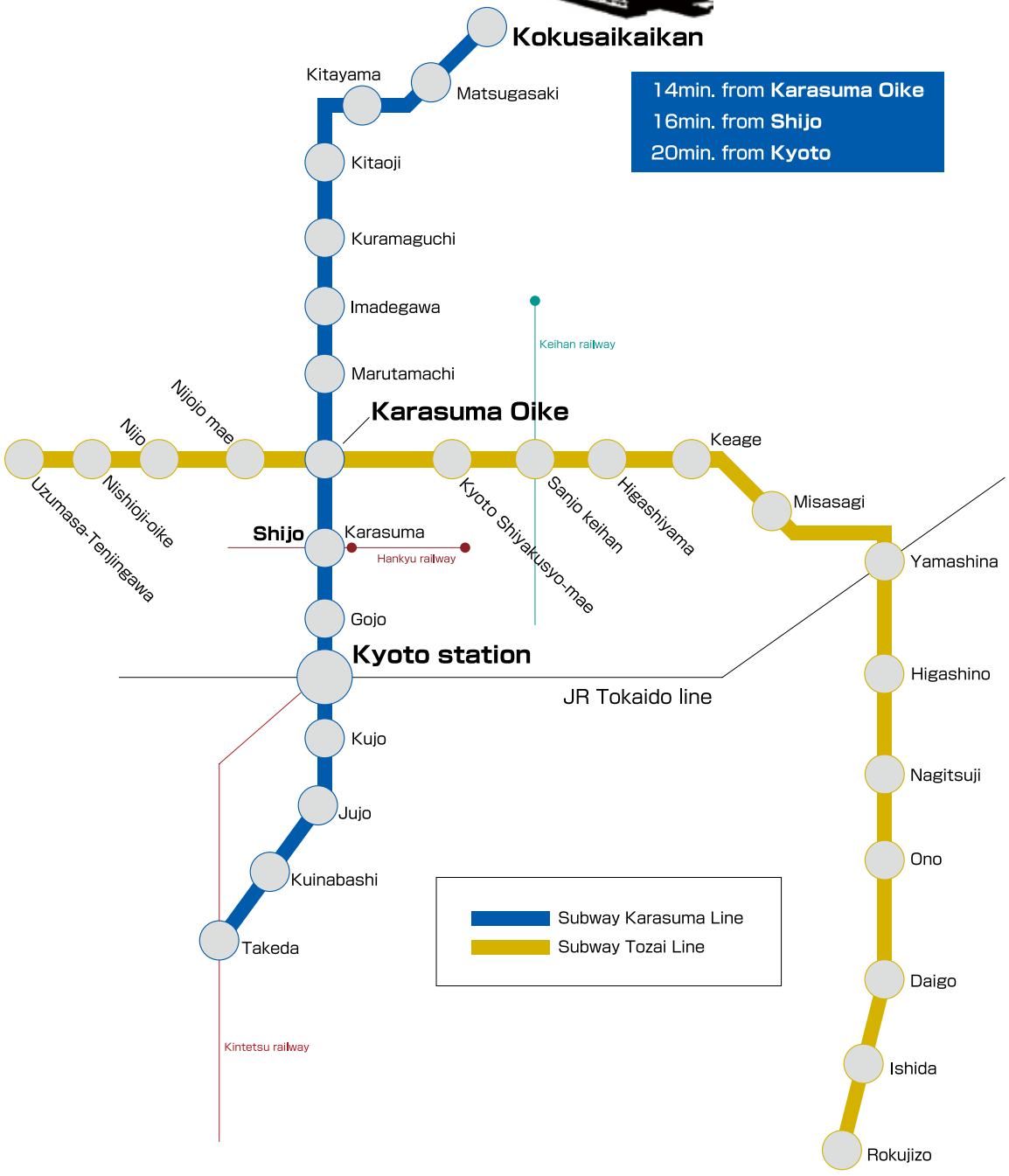




Subway Line

ICC Kyoto Subway Line

Kyoto International Conference Center



Program

The 4th International Symposium on Process Chemistry [ISPC 2019]

Program

July 24th (Wed)

16:30-17:00 **Registration**

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

July 25th (Thu)

8:30 **Registration**

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

Takahiko Akiyama

(Chairperson of ISPC 2019, Gakushuin University, Japan)

9:10- 9:50 **Nickel-Catalyzed Stereospecific Cross-Coupling and**

K-1 **Cross-Electrophile-Coupling Reactions**

(Keynote Lecture) **Elizabeth Jarvo** *(University of California, Irvine, USA)*

Chair : Osamu Onomura (Nagasaki University, Japan)

9:50-10:30 **Innovations in Synthetic Chemistry at MSD: Striving for the Ideal**

K-2 **Commercial Manufacturing Process**

(Keynote Lecture) **Kevin Campos** *(Merck, USA)*

Chair : Toshiaki Mase (Institute of Molecular Science, Japan)

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

10:45-11:25 **Oncology Drug Discovery Efforts in the Japanese Pharmaceutical**

K-3 **Company (Eisai Co., Ltd.) and My Next Challenge**

(Keynote Lecture) **Kentaro Yoshimatsu** *(The Pharmaceutical Society of Japan, Japan)*

Chair : Yasuhiro Shimada (FUJIFILM Wako Chemical, Japan)

11:25-12:05 **Simplifying Chemistry through Targeted Route Design: Snippets of**

K-4 **Early Stage Process Innovation for Newly Approved Anti-cancer Drugs**

(Keynote Lecture) **Srinivas Oruganti** *(Dr. Reddy's Institute of Life Sciences, India)*

Chair : Katsuya Tagami (Eisai, Japan)

12:05-13:10 **Lunch** *(Banquet Hall Sakura)*

13:10-13:25 **General Assembly of JSPC** *(in Japanese)*

13: 25-14:40 **Oral Presentation** *(10 min each)*

(1P-12,1P-16,1P-20,1P-27,1P-29,1P-51,1P-75)

Chair : Nobuyuki Mase (Shizuoka University, Japan)

14:40-15:50 **Poster Presentation (1P-01~1P-78)** *(Annex Hall)*

Chair : Takafumi Ohara (Shionogi, Japan)

15:55 -16:35 **The Importance of Process Chemistry**

K-5 **Kai Rossen** *(Lundbeck in Copenhagen, Denmark)*

(Keynote Lecture) *Chair : Shuji Akai (Osaka University, Japan)*

16:35-17:15 **Contribution from Pharmaceutical Process Chemistry to Green**

K-6 **Chemistry and Molecular Diversity**

(Keynote Lecture) **Hideya Mizufune** *(Spera Pharma, Inc., Japan)*

Chair : Toshihiko Onoda (Daiichi-Sankyo, Japan)

17:15-18:05 **Development and Applications of Selective Olefin Metathesis Catalysts**

PL-1 **Robert Grubbs** *(California Institute of Technology, USA)*

(Plenary Lecture) *Chair : Hironao Sajiki (Gifu Pharmaceutical University, Japan)*

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

Welcome Address: Hironao Sajiki

(President of JSPC: Gifu Pharmaceutical University, Japan)

Chair : Masahiro Ohshima (Tanabe Mitsubishi, Japan)

July 26th (Fri)

9:00- 9:40 **Peptide and Oligonucleotide Synthesis in Large Scale Using a Novel**

K-7 **Solution-Phase Approach AJIPHASE®**

(Keynote Lecture) **Daisuke Takahashi** *(Ajinomoto Co., Inc., Japan)*

Chair : Noriaki Murase (Taisho, Japan)

9:40-10:20 **Mighty Machines: Rapid and robust scaling of drug substance**

K-8 **processes in purpose-built reactors enabled by continuous**

(Keynote Lecture) **manufacturing technology**

Matthew Bio *(Snapdragon Chemistry, Inc., USA)*

Chair : Mikio Sasaki (Dainippon Sumitomo, Japan)

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

10:35 -11:15	**Synthetic Route Development for Manufacture of Venetoclax under**
K-9	**Expedited Timeline**
(Keynote Lecture)	**Yi-yin Ku** *(Abbvie Inc., USA)*
	Chair : Kaori Ando (Gifu University, Japan)
11:15-11:55	**Development of New Molecular Entities: Phase 1**
K-10	**Vikas Shirsath** *(Jubilant Chemsys Ltd., India)*
(Keynote Lecture)	*Chair : Shigeru Ieda (Astellas Pharma, Japan)*
11:55-13:05	**Lunch** *(Banquet Hall Sakura)*
13:05-14:20	**Oral Presentation** *(10 min each)*
	(2P-10,2P-15,2P-20,2P-21,2P-27,2P-50,2P-65)
	Chair : Takaaki Sato (Keio University, Japan)
14:20-15:30	**Poster Presentation (2P-01~2P-77)** *(Annex Hall)*
	Chair : Yoshifumi Hachisu (Daiichi Sankyo, Japan)
15: 35-16:15	**Review of Continuous Process in SK Biotek**
K-11	**Ryan Seongho Oh** *(Sk Biotek Co., Ltd., Korea)*
(Keynote Lecture)	*Chair : Masahiro Ohshima (Mitsubishi Tanabe, Japan)*
16:15-17:05	**Synthetic Strategies Based on Continuous-flow Methods**
PL-2	**Shu Kobayashi** *(The University of Tokyo, Japan)*
(Plenary Lecture)	*Chair : Takayuki Shioiri (Nagoya City University, Japan)*
17:05-17:10	**Release of JSPC Awardees for Excellence 2019**
17:10-17:15	**Closing Remarks**
	Kiyoshi Tomioka *(Kyoto University, Japan)*

Poster Program

Poster Program

July 25th (The)

Oral Presentation 13:25-14:40 (Main Hall) ◆ Oral Presenter
Discussion 14:40-15:50 (Annex Hall)

1P-01 **Sodium Hypochlorite Pentahydrate: Effective Oxidant for Organic Reactions**
Tomohide Okada*（Market Development Department, Chemicals Division, Nippon Light Metal Company, Ltd.）

1P-02 **Antidiabetic Materials Produced by *Paenibacillus* Fermentation**
San-Lang Wang* [1], Van Bon Nguyen [2]（[1] Department of Chemistry, Tamkang University, [2] Department of Science and Technology, Tay Nguyen University）

1P-03 **Synthesis and Characterization of Epoxies Using Self-Assembled Nanofibrillar as Scaffolds**
Wei-Chi Lai*, Ruey-Yi Hsia（Department of Chemical and Materials Engineering, Tamkang University）

1P-04 **One-Pot Preparation of 3-Arylpyrazoles and 3-Arylisoxazolines from Arenes**
Takahiro Yamamoto*, Hideo Togo（Graduate School of Science, Chiba University）

1P-05 **Advantages of Metal Ligand Complexes/Pre-Catalysts in Catalytic Reactions Compared to *in situ* Systems**
Yoshiaki Horiguchi*（Precious Metals Chemistry, Umicore Japan KK.）

1P-06 **One-Pot Transformation of Primary Alcohols into 3-Aryl- and 3-Alkylisoxazoles and- pyrazoles.**
Eiji Kobayashi*, Hideo Togo（Graduate School of Science, Chiba University）

1P-07 **Structure and Reactivity of Aromatic Radical Cations Generated by $FeCl_3$**
Takahiro Horibe*, Shuhei Ohmura, Kazuaki Ishihara（Graduate School of Engineering, Nagoya University）

1P-08 **Establishment of the Continuous Synthesis of Ceramide (D-*erythro*-CER[NDS]) *via* Oxo-Tethered Ruthenium Complex Catalyzed Asymmetric Transfer Hydrogenation using Pipe-Flow Reactor**
Masahiro Kuwana* [1,2], Taichiro Touge [1], Yasuhiro Komatsuki [1], Shigeru Tanaka [1], Hideki Nara [1], Kazuhiko Matsumura [1], Noboru Sayo [1], Yoshinobu Kashibuchi [2], Takao Saito [2]（[1] Corporate Research & Development Division, Takasago International Corporation, [2] Process Development Department, Takasago Chemical Corporation）

1P-09 **Highly Efficient Synthesis of Pyrrole-Imidazole Amide Sequence for Application to DNA-Binding Polyamides**
Takahiko Murata*, Shohei Yamamoto, Akira Nishiyama（Pharma & Supplemental Nutrition Solutions Vehicle, KANEKA CORPORATION）

1P-10 **Device Performance Improvement of Double-unit Air Gap Membrane Distillation Module for Seawater Desalination**

Chii-Dong Ho* [1], Luke Chen [2], Yu-An Chen [1], Chi-Hsiang Ni [1] ([1] Department of Chemical and Materials Engineering, Tamkang University, [2] Water Resources and Environmental Engineering Department, Tamkang University)

1P-11 ***anti*-Selective Catalytic Asymmetric Nitoaldol Reaction of α-Keto Esters: Intriguing Solvent Effect, Synthesis of APIs, and Flow Reaction**

Tomoya Karasawa* [1], Raphaël Oriez [2], Naoya Kumagai [2], Masakatsu Shibasaki [2] ([1] Process Research & Development Laboratories, Sumitomo Dainippon Pharma Co., Ltd., [2] Institute of Microbial Chemistry (BIKAKEN))

1P-12 ◆ **Development of New Catalytic Synthetic Methods of *N*-Unprotected Ketimines**

Hiroyuki Morimoto*, Yuta Kondo, Kazuhiro Morisaki, Tetsuya Kadota, Yoshinobu Hirazawa, Takashi Ohshima (Graduate School of Pharmaceutical Sciences, Kyushu University)

1P-13 **Safe and Scalable Aerobic Oxidation by 2-azaadamantan-2-ol (AZADOL)/NOx Catalysis: Large-Scale Preparation of Shi's Catalyst**

Yusuke Sasano [1], Hikaru Sato* [2], Shinsuke Tadokoro [2], Masami Kozawa [2], Yoshiharu Iwabuchi [1] ([1] Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, [2] Chemical Research Laboratory, Nissan Chemical Corporation)

1P-14 **Research on the Adsorptive Condition of Copper (II) Ion with the Use of Ephippia**

Azusa Oyama*, Saya Oikawa*, Nanami Kannno*, Noa Haneishi*, Kazunari Takahashi (Iwate Prefectural Mizusawa High School)

1P-15 **Efficient Synthesis of a 5α-Reductase Inhibitor, 3-(Tetrazol-5-yl)-3,5-pregnadien-20-one through Allylic Rearrangement of Cyanophosphates**

Shinya Harusawa*, Hiroki Yoneyama, Yoshihide Usami (Osaka University of Pharmaceutical Sciences)

1P-16 ◆ **Catalytic Transfer Hydration of Cyanohydrins to alpha-Hydroxyamides**

Tomoya Kanda, Asuka Naraoka, Hiroshi Naka* (Graduate School of Science and Research Center for Materials Science, Nagoya University)

1P-17 **Stereo-Defined Scaffold Strategy for Tamoxifens from (*E*)-1-Bromo-2-iodoalkenes.**

Yoshino Fujii*, Yuka Tamura, Nako Hashimoto, Naoki Endo, Tetsuo Iwasawa (Department of Materials Chemistry, Ryukoku University)

1P-18 **Crystallization Mechanisms Hiding Between Your Samples**

Mayu Nakatsukasa*, Des O'Grady (AutoChem Team, BU LAB Instruments, Mettler Toledo K.K.)

1P-19 **VARIOUS MANUFACTURING APPROACHES TO POORLY SOLUBLE PEPTIDES**

Go Shiino*, Aiko Hasegawa, Takaharu Matsuura, Shunsuke Ochi, Yoshinori Murata (API R&D Laboratory, CMC R&D Division, Shionogi & Co., Ltd.)

1P-20 ◆ **Development of an Efficient Manufacturing Process for E2212 toward Rapid Clinical Introduction**

Minetaka Isomura*, Taiju Nakamura, Katsuya Tagami (API Research Japan, Pharmaceutical Science & Technology CFU, Medicine Development Center, Eisai Co. Ltd.)

1P-21 **Asymmetric route to a chiral heterocyclic amine toward efficient manufacturing process**
Sayuri Hirano*, Masatoshi Yamada, Mitsuhisa Yamano（Chemical R&D Division, Spera Pharma, Inc.）

1P-22 **Aromatic Halogenation Using *N*-Halosuccinimide and PhSTMS or PhSSPh**
Yuuka Hirose, Mirai Yamazaki, Misa Nogata, Akira Nakamura, Tomohiro Maegawa*（Laboratory of Medicinal Chemistry, School of Pharmaceutical Sciences, Kindai University）

1P-23 **Stereospecific Synthesis of 1,5-Disubstituted Tetrazoles from Ketoximes via Beckmann Rearrangement Utilizing Diphenyl Phosphorazidate**
Kotaro Ishihara*, Yuki Kobayashi, Takayuki Shioiri, Masato Matsugi（Faculty of Agriculture, Meijo University）

1P-24 **Post-treatment Free Synthesis of Fairy Chemicals Using Fine Bubble and Flow Optimization Method**
Keiya Matsuo*, Kohei Sato, Tetsuo Narumi, Nobuyuki Mase（Applied Chemistry and Biochemical Engineering Course, Department of Engineering, Graduate School of Integrated Science and Technology, Shizuoka University）

1P-25 **Reaction Optimization Using Microwave-assisted Continuous Flow Reactor with In-line Analysis**
Takuya Kon*, Kohei Sato, Tetsuo Narumi, Kazuhiro Takeda, Nobuyuki Mase（Applied Chemistry and Biochemical Engineering Course, Department of Engineering, Graduate School of Integrated Science and Technology, Shizuoka University）

1P-26 **Synthesis of polymer-supported *cis*-2,4-disubstituted pyrrolidine derivatives and their application to asymmetric reactions**
Hidenori Ochiai* [1], Akira Nishiyama [1], Naoki Haraguchi [2], Shinichi Itsuno [2]（[1] Pharma & Supplemental Nutrition Solutions Vehicle, Kaneka Co., [2] Graduate School of Engineering, Toyohashi University of Technology）

1P-27 ◆ **Application of Macroporous Polystyrene-Triphenylphosphine Monolith to Palladium-Catalyzed Cross-Coupling Reaction in Flow System**
Hikaru Matsumoto* [1], Yu Hoshino [1], Tomohiro Iwai [2], Masaya Sawamura [2,3,] Yoshiko Miura [1]（[1] Department of Chemical Engineering, Kyushu University, [2] Department of Chemistry, Faculty of Science, Hokkaido University, [3] Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University）

1P-28 **Preparation of Oil-based Stable Sliver Nanoparticle Suspensions**
Trong-Ming Don*, Wen-Shan Yang, Tung-Wen Cheng（Department of Chemical and Materials Engineering, Tamkang University）

1P-29 ◆ **Design Space Success Stories: Reaction and Crystallization Processes**
Leela Christian-Tabak* [1], Hiroaki Tanaka [1], Haitao Zhang [2], Minoru Toshima [1], Mikio Sasaki [1]（[1] Technology Research and Development Divison, Process Research and Development Laboratories, Sumitomo Dainippon Pharma, [2] Chemical Process Research and Development, Sunovion Pharmaceuticals）

1P-30 **Process development of β—Lactamase inhibitor key intermediate**

Masato Murai* [1], Jun Takehara [2], Ryoma Miyake [3], Takanobu Iura [3], Hiroshi Kawabata [3]
([1] Process Research & Development Laboratory, Technology Division API Corporation, [2] Functional Organic Materials Laboratory, Fukuoka R&D Center, Mitsubishi Chemical Corporation, [3] Biotechnology Laboratory, Science & Innovation Center, Mitsubishi Chemical Corporation)

1P-31 **Nitrones with Benzylic Bromides, Zinc, and Isobutyl Nitrite**

Kei Yanai*, Hideo Togo (Graduate School of Science, Chiba University)

1P-32 **2-Amino-4-arylthiazoles through One-Pot Transformation of Alkylarenes with NBS and Thioureas**

Kaho Shibasaki*, Hideo Togo (Graduate School of Science, Chiba University)

1P-33 **Biocatalysts for Hydroxylation**

Hiroshi Kadono*, Taiki Nishioka (Strategic Research Planning Department, Research & Development Division, MicroBiopharm Japan Co., Ltd.)

1P-34 **Oxidative Construction of 2-Arylquinolines from β-Arylpropionitriles with Aryllithium and NIS through Iminyl Radical-mediated Cyclization**

Hiroki Naruto*, Hideo Togo (Graduate School of Science, Chiba University)

1P-35 **Novel and Practical Deprotection Method of *t*-Boc Group for Preparation of Cefcapene Pivoxil Hydrochloride Hydrate Using Formic Acid and Lithium Chloride**

Takanori Kurita*, Yoshiko Tanaka, Teruo Iizuka (Chemical Development, Production Technology Department, Shionogi Pharma Co., Ltd.)

1P-36 **The development for manufacturing process of methyl ester reduction with $LiBH_4$ prepared in-situ**

Takayuki Toyama*, Naoki Miyake, Yusuke Sato, Takanori Kurita (Chemical Development, Production Technology Department, Shionogi Pharma Co., Ltd.)

1P-37 **Continuous Flow Lipase-Catalyzed Dynamic Kinetic Resolution of Alcohols**

Koichi Higashio* [1], Satoko Katsuragi [1], Franziska Kühn [2], Niklas Adebar [2], Carmen Plass [2], Harald Gröger [2], Shuji Akai [1] ([1] Graduate School of Pharmaceutical Sciences, Osaka University, [2] Faculty of Chemistry, Bielefeld University)

1P-38 **Chemoselective demethylation of methoxypyridine**

Kosho Makino* [1], Yuki Tanaka [1], Yumi Hasegawa [2], Takahide Inoue [1], Koji Araki [2], Hidetsugu Tabata [2], Tetsuta Oshitari [2], Kiyomi Ito [3], Hideaki Natsugari [4], Hideyo Takahashi [1]
([1] Faculty of Pharmaceutical Sciences, Tokyo University of Science, [2] Faculty of Pharma Sciences, Teikyo University, [3] Research Institute of Pharmaceutical Sciences, Musashino University, [4] Faculty of Pharmaceutical Sciences, The University of Tokyo)

1P-39 **A Case Study of Theoretical Purge Factor for Mutagenic Impurity Management by Collaboration among 6 Pharmaceutical Companies**

Shinji Tamura* [1], Yasufumi Kawanaka [1], Yusuke Nagato [2], Kenichiro Sato* [3], Yosuke Mino [4], Takashi Watanabe [4], Muneki Kishida [5], Hiroki Ueoka [6], Yu Haranosono [6] ([1] Ono Pharmaceutical Co., Ltd., [2] Fujifilm Corporation, [3] Asahi Kasei Pharma Corporation, [4] Japan Tobacco Inc., [5] Mitsubishi Tanabe Pharma Corporation, [6] Senju Pharmaceutical Co., Ltd.)

1P-40 **Novel Preparation of Aromatic Nitriles from Aryl Bromides and Arenes via Imino-nitrogen-centered Radicals.**
Ko Uchida*, Hideo Togo（Graduate School of Science, Chiba University）

1P-41 **Pd/Cu-catalyzed Anti-Markovnikov Oxidation of Aliphatic Alkenes to Terminal Acetals**
Saki Komori*, Yoshiko Yamaguchi, Yasutaka Kataoka, Yasuyuki Ura（Department of Chemistry, Biology, and Environmental Science, Faculty of Science, Nara Women's University）

1P-42 **Heterogeneous Metal Catalyzed Aerobic Dehydrogenative Biaryl Coupling of Aniline Derivatives**
Kenji Matsumoto*, Satoshi Takeda, Yasunori Toubaru, Tsukasa Hirokane, Masahiro Yoshida（Faculty of Pharmaceutical Sciences, Tokushima Bunri University）

1P-43 **PAT: Optimize Processes From Liquids to Solids**
Yoichi Yamasaki*, Wittkamp Brian, Stephan Woods（AutoChem Business Unit, Mettler-Toledo）

1P-44 **Palladium and Niobic Acid on Carbons-Catalyzed Facile Hydrogenative Deprotection of *N*-Benzyl Groups**
Yuta Yamamoto* [1], Kazuho Ban [1], Yukio Takagi [2], Masatoshi Yoshimura [2], Yoshinari Sawama [1], Hironao Sajiki [1]（[1] Laboratory of Organic Chemistry, Gifu Pharmaceutical University, [2] Catalyst Development Center, N. E. Chemcat Corporation）

1P-45 **Pt/C-catalyzed oxidative annulation of diols to lactones**
Ryoya Takakura*, Kazuho Ban, Hironao Sajiki, Yoshinari Sawama（Gifu Pharmaceutical University）

1P-46 **Aromatic Aldehyde-Selective Functionalization via Pyridinium Salt Intermediates**
Takahiro Kawajiri* [1], Hiromichi Fujioka [2], Hironao Sajiki [1], Yoshinari Sawama [1]（[1] Laboratory of Organic Chemistry, Gifu Pharmaceutical University, [2] Graduate School of Pharmaceutical Sciences, Osaka University）

1P-47 **Chiral Macrocyclic Lithium Binaphtholate Catalysts for Enantioselective Addition of Lithium Acetylides to Ketones**
Manabu Hatano*, Kenji Yamashita, Kazuaki Ishihara（Graduate School of Engineering, Nagoya University）

1P-48 **Generation of ynolates via double deprotonation of 2,6-di-*tert*-butylphenol esters**
Jun Sun* [2], Toshiya Yoshiiwa [2], Takayuki Iwata [1], Mitsuru Shindo [1]（[1] Institute for Materials Chemistry and Engineering, Kyushu University, [2] Interdisciplinary Graduate School of Engineering Sciences, Kyushu University）

1P-49 **Synthetic Studies of Libraries of Polymers from Half-esters Obtained by Practical Selective Monohydrolysis of Symmetric Diesters**
Satomi Niwayama*, Jianjun Shi（Graduate School of Engineering, Muroran Institute of Technology）

1P-50 **Pd/Cu-catalyzed Aerobic Anti-Markovnikov Oxidation of Vinylarenes to Aldehydes and Terminal Acetals**
Yasuyuki Ura*, Sonoe Nakaoka, Yuka Murakami, Satoko Matsumura, Ruriko Sato, Wakana Yokotani, Yasutaka Kataoka（Department of Chemistry, Biology, and Environmental Science, Faculty of Science, Nara Women's University）

1P-51 ◆ **Biocatalytic Process Design – Challenges and Solutions**
Stefan Mix*, Gareth Brown, Iain Miskelly（Department of Biocatalysis and Isotope Chemistry, Almac Group）

1P-52 **Hydrosilane-Promoted Facile Deprotection of *tert*-Butyl Groups in Esters, Ethers, Carbonates, and Carbamates**
Zhenzhong Zhang*, Takuya Ikeda, Yukihiro Motoyama（Department of Advanced Science and Technology, Toyota Technological Institute）

1P-53 **Synthesis of 7-Deazaguanosine Derivatives via Glycosylation**
Koki Nakano*, Natsuhisa Oka, Akane Fukuta, Ayumi Mori, Kaori Ando（Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University）

1P-54 **Stereoselective Synthesis of Furanosyl Sulfones and Their Application to Julia-Kocienski Reaction**
Kanna Suzuki*, Natsuhisa Oka, Ayumi Mori, Kaori Ando（Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University）

1P-55 **One-Step Synthesis of Cyclopentene Derivatives from Julia-Kocienski Reagents Derived from Nucleosides**
Minami Furuzawa*, Natsuhisa Oka, Mayuka Kanda, Kaori Ando（Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University）

1P-56 **Selective Synthesis of Azoxybenzenes from Nitrobenzenes by Photoreduction with Flow Microreactors**
Akira Fujii*, Yasuhiro Nishiyama, Hajime Mori（Industrial Technology Center of Wakayama Prefecture）

1P-57 **Highly efficient synthesis of aromatic α-keto acids from acetophenones using nitrosylsulfuric acid as an oxidant**
Tadafumi Matsunaga*, Yasuhiro Kataoka, Shun Tanimura, Masato Kawamura（Health and Crop Sciences Research Laboratory, Sumitomo Chemical Co., Ltd.）

1P-58 **Palladium-catalyzed deoxygenative deuteration of aryl nonaflates**
Masami Kuriyama*, Kotaro Tsukuda, Hirotoshi Kiba, Tetsuro Morimoto, Kosuke Yamamoto, Osamu Onomura（Graduate School of Biomedical Sciences, Nagasaki University）

1P-59 **Efficient Synthetic Study of Multi-functionalized Biheteroaromatics by Suzuki Coupling**
Masahiro Hamada*, Ryota Fujimoto, Noriyuki Nakajima（Department of Pharmaceutical Engineering and Biotechnology Research Center, Toyama Prefectural University）

1P-60 **Precise Control of the Mutagenic Impurity Production by Flow Synthesis**
Masahiro Hosoya*, Takahiro Oshima, Yuki Masuda, Masashi Tanaka, Noriyuki Kurose（API R&D Laboratory, CMC R&D Division, Shionogi & Co., Ltd.）

1P-61 **Selective Synthesis of Benzofuran Isomers Using Rearrangement Reaction of Hydroxychalcone and the Application to Synthesis of Natural Product**
Yuichiro Ikegami*, Fei Rao, Akira Imamiya, Akira Nakamura, Tomohiro Maegawa（School of Pharmaceutical Sciences, Kindai University）

1P-62 **New Deprotection Method of PMB Protective Group of Alcohols Using Weak Acid in CF_3CH_2OH and Remarkable Acceleration of Deprotection of PMB Protected 4-phenylbutanol.**

Yugo Kotera*, Misa Matsumura, Hiroko Kawasaki, Norihiko Yamagami, Akira Nakamura, Tomohiro Maegawa（School of Pharmaceutical Sciences, Kindai University）

1P-63 **Design of Novel Halogen Bonding Donors with SF_5 and SO_2CF_3 Functional Groups on Iodobenzenes**

Yuji Sumii*, Kenta Sasaki, Norio Shibata（Department of Life and Applied Chemistry, Nagoya Institute of Technology）

1P-64 **Quick and Continuous Synthesis of Methyl Cinnamates Using a Flow-microwave Applicator**

Hiroki Yoneyama*, Naoki Oka, Megumi Yoshii, Shinya Harusawa, Yoshihide Usami（Osaka University of Pharmaceutical Sciences）

1P-65 **Utilization of Naturally Occurring Glycosylated Forms for the Synthesis of Flavonoids**

Takeshi Sugai*, Ryuji Tsunekawa, Kazuki Kurahayashi, Rie Fujita, Kengo Hanaya, Shuhei Higashibayashi（Department of Pharmaceutical Sciences, Keio University）

1P-66 **^{13}C NMR Spectroscopic Studies of Intra-and Intermolecular Interactions of Amino Acids and Dipeptide Derivatives in Solutions**

Yoshikazu Hiraga [1], Ryosuke Hoshide* [1], Satomi Niwayama [2]（[1] Graduate School of Science and Technology, Hiroshima Institute of Technology, [2] Graduate School of Engineering, Muroran Institute of Technology）

1P-67 **Simple Nucleophiles of Acetamide Equivalents: BENAC-K, PM-BENAC-K, and 2,4-DM-BENAC-K**

Yumika Koike*, Atsunori Hira, Toshiki Tatematsu, Takeo Sakai, Yuji Mori（Faculty of Pharmacy, Meijo University）

1P-68 **Three subjects in *Organic Syntheses*: Simple, useful, but hitherto inaccessible building blocks**

Yuichiro Ashida*, Takeshi Tsutsumi, Satomi Kajimoto, Hiroshi Nishikado, Hidefumi Nakatsuji, Yoo Tanabe（Determent of Chemistry, School of Science and Technology, Kwansei Gakuin University）

1P-69 **Thermal hazard analysis of self accelerating decomposition via acid production of dimethyl sulfoxide (DMSO)**

Yuto Koizumi* [1], Yu-ichiro Izato [1], Atsumi Miyake [1], Yoshikuni Deguchi [2], Masafumi Kono [3]（[1] Yokohama National University, [2] Kaneka Corporation, [3] Nippon Refine Corporation）

1P-70 ***In situ* analysis of liquid phase oxidation of nitric acid/formic acid mixtures using thermal and raman spectroscopic analyses**

Mahoko Ando*, Michiya Fujita, Yu-ichiro Izato, Atsumi Miyake（Yokohama National University）

1P-71 **Efficient Removal of Nitrate Ions Through Calcium Alginate Membrane Immobilizing Activated Carbon Particles as Adsorbents**

Keita Kashima* [1], Kota Teshima [1], Masahide Hagiri [2], Masanao Imai [3]（[1] Department of Materials Chemistry and Bioengineering, National Institute of Technology, Oyama College, [2] Department of Materials Chemistry and Bioengineering, National Institute of Technology, Fukushima College, [3] Graduate School of Bioresource Sciences, Nihon University）

1P-72 **Molecular Separation of Sugars via Calcium Alginate Membrane with Polysaccharide Network Precisely Controlled Polymeric Structure**

Kaito Yoshida* [1], Keita Kashima [1], Masanao Imai [2] ([1] Department of Materials Chemistry and Bioengineering, National Institute of Technology, Oyama College, [2] Graduate School of Bioresource Sciences, Nihon University)

1P-73 **Preparation and Characterization of Biocompatible Chitin/Chitosan Membrane Prepared through an Acetylation Process of Glucosamine Units**

Haruki Koya* [1], Keita Kashima [1], Masanao Imai [2] ([1] Department of Materials Chemistry and Bioengineering, National Institute of Technology, Oyama College, [2] Graduate School of Bioresource Sciences, Nihon University)

1P-74 **Effect of Monomer Composition on the Laccase/O_2-Catalyzed Oxidation of Aniline and *p*-Aminodiphenylamine in the Presence of Anionic Vesicles**

Tomoyuki Fujisaki* [1], Keita Kashima [1], Peter Walde [2] ([1] Department of Materials Chemistry and Bioengineering, National Institute of Technology, Oyama College, [2] Department of Materials, ETH Zurich)

1P-75 ◆ **Application of Highly Efficient Chiral Spiro Catalysts In the Synthesis of Key Chiral Intermediates of APIs**

Yuanqiang Li*, Guoliang Zhu, Pucha Yan (R&D, CDMO unit, Zhejiang Raybow Pharmaceutical Co. Ltd./ Zhejiang Jiuzhou Pharmaceutical Co., Ltd.)

1P-76 **Metal-Free Asymmetric Synthesis of Dihydroquinoxalinones and 4-Imidazolidinones from α-Amino Acid Precursors via Dehydrogenative N-H/C-H Coupling**

Kyalo Stephen Kanyiva* [1], Masashi Horiuchi [2], Marina Tane [2], Takanori Shibata [2] ([1] Global Center of Science and Engineering, Advanced School of Science and Engineering, Waseda University, [2] Department of Chemistry and Biochemistry, Advanced School of Science and Engineering, Waseda University)

1P-77 **COF Derived N,P Co-Doped Carbon as a Metal-Free Catalyst for Highly Efficient Oxygen Reduction Reaction**

Chao Yang*, Shinya Maenosono (School of Materials Science, Japan Advanced Institute of Science and Technology)

1P-78 **Preparation of 1,3-Substituted Pyrroles under Basic Conditions**

Kwesi Prah Thomford*, Zheyang Zhou, Yasunori Kama, Keita Kimura, Toshihide Maki (Graduate School of Biomedical Sciences, Nagasaki University)

July26th (Fri)

Oral Presentation 13:05-14:20 (Main Hall) ◆ Oral Presenter
Discussion 14:20-15:30 (Annex Hall)

2P-01 **Ligand-Free Kumada Coupling Catalyzed by Iron(II) Nanoparticle**
Yuki Wada* [1], Toshiki Akiyama [1], Tetsuo Honma [2], Yusuke Tamenori [2], Hiromichi Fujioka [1], Yoshihiro Sato [3], Mitsuhiro Arisawa [1]（[1] Graduate School of Pharmaceutical Sciences, Osaka University, [2] Japan Synchrotron Radiation Research Institute, [3] Faculty of Pharmaceutical Sciences, Hokkaido University）

2P-02 **Heterogeneous Palladium on Titania-Catalyzed Ligand-Free Suzuki–Miyaura Coupling of Aryl Chlorides**
Hayato Masuda* [1], Tsuyoshi Yamada [1], Kwihwan Park [1], Takumu Tachikawa [1], Tomohiro Ichikawa [1], Masatoshi Yoshimura [2], Yukio Takagi [2], Yoshinari Sawama [1], Hironao Sajiki [1]（[1] Laboratory of Organic Chemistry, Gifu Pharmaceutical University, [2] Catalysts Development Center, N.E.Chemcat Corporation）

2P-03 **Enantioselective Friedel-Crafts Alkylation Reaction of 4,7-Dihydroindole to Trifluoromethylated *N*-H Ketimines by Means of Chiral Phosphoric Acid**
Riku Suzuki*, Masaru Yoshida, Masamichi Miyagawa, Takahiko Akiyama（Department of Chemistry, Faculty of Science, Gakushuin University）

2P-04 **AJIPHASE®: Practical Oligonucleotide Synthesis Achieved by Solution Phase Approach**
Taisuke Ichimaru*, Kunihiro Hirai, Satoshi Inoue, Takuya Hamagaki, Takayuki Hamada, Daisuke Takahashi（Research Institute For Bioscience Products & Fine Chemicals, AJINOMOTO Co., Inc.）

2P-05 **Ion-Pair Extraction of Ammoniums Using Tetracyanocyclopentadienides**
Miho Ito*, Naotaka Noda, Chisato Fujimoto, Takeo Sakai, Yuji Mori（Faculty of Pharmacy, Meijo University）

2P-06 **Ultrafast enantiomeric separations using 1.6μm chiral column “CHIRALPAK U series”**
Daisuke Fukuda*, Takafumi Onishi, Ryota Hamasaki, Atsushi Ohnishi（Life Science Development Center, CPI Company, DAICEL Corporation）

2P-07 **Orthogonal selectivity controlled by organic bases in arylation for 2-pyridones with diaryliodonium salts**
Yusuke Abe*, Natsumi Hanazawa, Shinpei Ono, Masami Kuriyama, Kosuke Yamamoto, Osamu Onomura（Graduate School of Biomedical Sciences, Nagasaki University）

2P-08 **Total syntheses of all six chiral natural pyrethrins from available synthetic pyrethroids, directing for process chemistry: accurate determination of the physical properties and insecticidal activities**
Momoyo Kawamoto*, Yuichiro Ashida, Noritada Matsuo, Yoo Tanabe（Department of Chemistry, School of Science and Technology, Kwansei Gakuin University）

2P-09 **Process Development for Large-scale Synthesis of Baloxavir marboxil (Xofluza®)**
Nobuaki Fukui* [1], Setsuya Shibahara [1], Toshikatsu Maki [1], Tomohiro Fukuda [1], Kosuke Anan [2], Takayuki Tsuritani [1] ([1] API R&D Laboratory, CMC R&D Division, Shionogi & Co., Ltd., [2] Shionogi Pharmaceutical Research Center, Shionogi & Co., Ltd.)

2P-10 ◆ **Deacetylative Amination of Acetyl Arenes and Alkanes under Transition-Metal-Free Conditions**
Kengo Hyodo* [1], Genna Hasegawa [2], Kingo Uchida [2] ([1] Department of Chemistry, School of Science and Engineering, Kindai University, [2] Department of Materials Chemistry, Faculty of Science and Technology, Ryukoku University)

2P-11 **Application of the Palladium-loaded Monolithic Ion Exchange Resin to a Continuous Flow Processing**
Shinji Nakamura* [1], Hitoshi Takada [1], Tsuyoshi Yamada [2], Yoshinari Sawama [2], Hironao Sajiki [2] ([1] Functional Material Development Department, R&D Center, Organo Co., [2] Laboratory of Organic Chemistry, Gifu Pharmaceutical University)

2P-12 **Development of Boronic Ester-Mediated Ligand-Directed Protein Acylation**
Christopher Adamson*, Kenzo Yamatsugu, Motomu Kanai (Department of Pharmaceutical Sciences, University of Tokyo)

2P-13 **C-H γ,γ,γ-Trifluoroalkylation of Quinolines via Visible-light-induced Sequential Radical Additions**
Yuhei Kumagai*, Nanami Murakami, Futa Kamiyama, Ryo Tanaka, Tatsuhiko Yoshino, Masahiro Kojima, Shigeki Matsunaga (Faculty of Pharmaceutical Sciences, Hokkaido University)

2P-14 **Chlorocarbonysulfenyl chlorides: A unique bifunctional electrophilic reagent for the syntheses of heterocyclic compounds, directing for process chemistry**
Masatoshi Kakuno*, Shotaro Izawa, Taichi Takemoto, Yoo Tanabe (Department of Chemistry, School of Science and Technology, Kwansei Gakuin Univ.)

2P-15 ◆ **The Catalytic Synthesis of Cyclic Amines from Lactams using Ru-MACHO Family**
Osamu Ogata* [1], Hideki Nara [1], Kazuhiko Matsumura [1], Yoshihito Kayaki [2] ([1] Takasago International Corporation, [2] Tokyo Institute of Technology)

2P-16 **Catalytic asymmetric Mukaiyama aldol addition using 1,3-bis(siloxy)diene promoted by a $Ti(OiPr)_4$ / (*S*)-BINOL catalyst, directed for process chemistry**
Takeshi Tsutsumi, Mizuki Moriyama*, Yoo Tanabe (Determent of Chemistry, School of Science and Technology, Kwansei Gakuin University)

2P-17 **Catalytic oxidation reaction for synthesis of triarylmethane blue dyes**
Tomoya Okada* [1], Akihiro Nomoto [1], Yuki Yamamoto [1], Mika Yamamoto [1], Michio Ueshima [1], Akiya Ogawa [1], Tamotsu Nishigahana [2], Keiji Itoh [2], Gohei Kobata [2] ([1] Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, [2] Kobata Sangyo Co., Ltd.)

2P-18 **Synthesis of α-*exo*-Methylene Ketones from α,α-Disubstituted Allyl Alcohols by Electrochemical Oxidative Migration**
Kosuke Yamamoto*, Naoto Kikuchi, Tohru Hamamizu, Hirofumi Yoshimatsu, Masami Kuriyama, Yosuke Demizu, Osamu Onomura (Graduate School of Biomedical Sciences, Nagasaki University)

2P-19 **Metal-free Oxidative Synthesis of Imine Derivatives Catalyzed by Salicylic Acid**
Akihiro Nomoto*, Chun Ping Dong, Shintaro Kodama, Michio Ueshima, Akiya Ogawa
（Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University）

2P-20 ◆ **Autocatalytic Decomposition of Dimethyl Sulfoxide (DMSO)**
Yoshikuni Deguchi* [1], Masafumi Kono [2], Yuto Koizumi [3], Yu-ichiro Izato [3], Atsumi Miyake [3]
（[1] Kaneka Corporation, [2] Nippon Refine Co. Ltd., [3] Yokohama National University）

2P-21 ◆ **Development of Vanadium-catalyzed Organic Reactions in Water**
Makoto Sako* [1], Nadine Zumbrägel [2], Tomohiro Takiishi [1], Lukas Schober [2], Harald Gröger [2], Shinobu Takizawa [1], Hiroaki Sasai [1]（[1] The Institute of Scientific and Industrial Research (ISIR), Osaka University, [2] Department of Chemistry, Bielefeld University）

2P-22 **AI-Assisted Optimization for Synthesis of Spirooxindole Analogues via Enantioselctive Domino Reaction in Flow System**
H. D. P. Wathsala*, Masaru Kondo, Makoto Sako, Yutaro Hanatani, Satoshi Hara, Kazunori Ishikawa, Takayuki Takaai, Takashi Washio, Shinobu Takizawa, Hiroaki Sasai
（The Institute of Scientific and Industrial Research (ISIR), Osaka University）

2P-23 **Development of Composite Materials Comprised of Porphyrin Dyes and Nanocarbons : Effect of Preparation Methods**
Yuko Takao*, Kazuyuki Moriwaki, Takumi Mizuno, Toshinobu Ohno（Organic Materials Research Division, Osaka Municipal Technical Research Institute）

2P-24 **Benzylisoquinoline alkaloids production by bacteria for drug discovery**
Akira Nakagawa*, Hiromichi Minami（Research Institute for Bioresources and Biotechnology, Ishikawa Prefectural University）

2P-25 **Synthesis of tofogliflozin as an SGLT2 inhibitor *via* intramolecular cycloaddition**
Masatoshi Murakata, Akira Kawase*, Nobuaki Kimura, Takuma Ikeda, Masahiro Nagase, Masatoshi Koizumi, Kazuaki Kuwata, Kenji Maeda, Hitoshi Shimizu（API Process Development Department, Chugai Pharmaceutical Co., Ltd.）

2P-26 **Strong Base-Catalyzed Hydroamination of Aminoalkenes**
Yasutomo Yamamoto*, Maki Terashita, Mio Yamanoue, Masako Yukawa, Akari Miyawaki, Kiyoshi Tomioka（Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts）

2P-27 ◆ **Rapid and Practical Synthesis of Fluoren-9-ones Using a Carbon Monoxide Surrogate**
Hideyuki Konishi*, Suguru Futamata, Xi Wang, Kei Manabe（School of Pharmaceutical Sciences, University of Shizuoka）

2P-28 **Activation of Nucleophilic Aromatic Substitution Reaction by Using Silyl Amide Reagent**
Takashi Shigeta* [1], Shiho Suzuki [1], Nanomi Murata [2], Yuka Gonno [2], Minoru Ozeki [2], Ikuo Kawasaki [2], Masahiro Egi [1]（[1] School of Food and Nutritional Sciences, University of Shizuoka, [2] Graduate School of Pharmaceutical Sciences, Mukogawa Women's University）

2P-29 **Chemoselective Transformations of Aromatic Methoxymethyl Ethers Using Trialkylsilyl Triflate and 2,2'-Bipyridyl**
Mizushi Yanagihara*, Reiya Ohta, Kenichi Murai, Mitsuhiro Arisawa, Hiromichi Fujioka
（Graduate School of Pharmaceutical Sciences, Osaka University）

2P-30 **Acceptor-controlled Transfer Dehydration of Amides to Nitriles**

Asuka Naraoka*, Hiroyuki Okabe, Takahiro Isogawa, Shunsuke Oishi, Hiroshi Naka（Graduate School of Science, Institute of Transformative Bio-Molecules (WPI-ITbM), and Research Center for Materials Science, Nagoya University）

2P-31 **Hydroperoxide-Mediated Chemoselective, Decarboxylative Acylation of Amine.**

Takeshi Nanjo, Natsuki Kato*, Xuan Zhang, Yoshiji Takemoto（Graduate School of Pharmaceutical Sciences, Kyoto University）

2P-32 **Polymorphic Solubility Ratio of Pharmaceutical Drugs in Various Solvents**

Yoshihiro Takebayashi*, Kiwamu Sue, Takeshi Furuya, Satoshi Yoda（Research Institute for Chemical Process Technology, AIST）

2P-33 **Development of Palladium Phosphine Complexes for the Practical Cross-Coupling Reactions**

Yosuke Imanaka*, Shinji Ueno（Numazu Chemical Catalysts Group, Chemical Catalysts R&D Dept., Catalysts Development Center, N.E.Chemcat Corporation）

2P-34 **Development of a Synthetic Process for K-8986, an H1-receptor Antagonist**

Tomoaki Fukuda* [1,2], Takeaki Hara [1], Shinji Ina [1], Tetsuhiro Nemoto [2], Takeshi Oshima [1]
（[1] Tokyo New Drug Research Laboratories, Pharmaceutical Division, Kowa Co., LTD.,
[2] Graduate School of Pharmaceutical Sciences, Chiba University）

2P-35 **Development of *gem*-Diboronic Acids as Dehydrative Peptide Synthesis Catalysts**

Kenichi Michigami*, Tatsuhiko Sakaguchi, Yoshiji Takemoto（Graduate School of Pharmaceutical Sciences, Kyoto University）

2P-36 **A Bulky P-Chiral Phosphine Ligand (BulkyP*): Synthesis and Application in Rh-Catalyzed Asymmetric Hydrogenation**

Yuuki Sawatsugawa*, Ken Tamura, Natsuhiro Sano, Tsuneo Imamoto（Specialty Products R&D Department, Nippon Chemical Industrial Co., Ltd.）

2P-37 **Gas-Liquid Flow Synthesis Using Monolithic Catalysts**

Yusuke Saito* [1], Tomohito Mizukami [1], Yushi Nakamura [2], Nobuyuki Mase [2]
（[1] Cataler Corporation, [2] Shizuoka University）

2P-38 **Quality by Design (QbD) Approach by Automated Robustness Study to Develop the Design Space**

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

2P-39 **High Quality Peptide APIs from Sophisticated One-Pot Peptide Synthesis AJIPHASE®**

Tatsuji Inomata*, Takayoshi Torii, Shin Muronoi, Ryotaro Nakaya, Daisuke Takahashi（Research Institute for Bioscience Products and Fine Chemicals, AJINOMOTO Co., Inc.）

2P-40 **Platinum on Carbon Bead-Catalyzed Continuous-Flow Dehydrogenation of 2-Propanol under Microwave-Irradiation**

Tomohiro Ichikawa [1], Takumu Tachikawa* [1], Tomohiro Matsuo [1], Wataru Teranisihi [1], Tsuyoshi Yamada [1], Yoshinari Sawama [1], Yasunari Monguchi [2], Hironao Sajiki [1]（[1] Laboratory of Organic Chemistry, Gifu Pharmaceutical University, [2] Laboratory of Organic Chemistry, Daiichi University of Pharmacy）

2P-41 **Characterization of chiral column by analyzed of column screening result**

Takunori Ueda*, Masahiro Miyamoto, Ryota Hamasaki, Atsushi Ohnishi（Life Science Development center, CPI Company, DAICEL Corporation）

2P-42 **Asymmetric cross-aldol reaction of aldehydes via organocatalyst**
Yujiro Hayashi*, Kaito Nagai（Department of Chemistry, Graduate School of Science, Tohoku University）

2P-43 **Atomeconomical Approach to Allylsilanes through Iridium-Catalyzed Hydrosilylation of Allenes**
Ichino Takeuchi*, Shoko Samoto, Yasuyuki Ura, Yasutaka Kataoka（Department of Chemistry, Biology, and Environmental Science, Faculty of Science, Nara Women's University）

2P-44 **Stable Triazinone-Based Reagent for *O-p*-Methoxybenzylation under Mild Heating Conditions**
Hikaru Fujita* [1],Hiromitsu Terasaki [1],Satoshi Kakuyama [1],Kazuhito Hioki [2],Munetaka Kunishima [1]（[1] Faculty of Pharmaceutical Sciences Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University, [2] Faculty of Pharmaceutical Sciences, Kobe Gakuin University）

2P-45 **Catalytic Regioselective Ring Opening of Epoxides by Unprotected Amines**
Yuse Kuriyama*, Yusuke Sasano, Shogo Matsui, Akihito Noguchi, Yoshihiko Hoshino, Shun-ichiro Uesugi, Yoshiharu Iwabuchi（Graduate School of Pharmaceutical Sciences, Tohoku University）

2P-46 **Transition Metal-Free One-pot Synthesis of 3-Benzo[*b*]thienyl Thioethers via Benzo[*b*]thiophenone**
Nanae Habara*, Koichi Mitsudo, Seiji Suga（Division of Applied Chemistry, Graduate School of Natural Science and Technology, Okayama University）

2P-47 **Risks from Rising Temperature**
Yoshifumi Fujisawa*, Urs Groth, Fabio Visentin（AutoChem team, BU LAB Instruments, Mettler-Toledo K.K.）

2P-48 **Mechanistic Analysis in Lithiation-Methylation Reaction of Trifluorobenzoic Acid**
Yuya Orito*, Guy C. Lloyd-Jones（Process Technology Research Laboratories, Pharmaceutical Technology Division, Daiichi-Sankyo Co., Ltd.）

2P-49 **The Enhanced Enantio-recognition of Chiral Acylazolium in Kinetic Resolution of Chiral Secondary Alcohol by Carboxylate Additive**
Ken-ichi Yamada*, Yinli Wang, Satoru Kuwano, Tsubasa Inokuma, Yousuke Yamaoka, Kiyosei Takasu（Graduate School of Pharmaceutical Sciences, Tokushima University）

2P-50 ◆ **Synthetic Route Scouting and Process Development of Dolutegravir Sodium**
Tatsuro Yasukata*, Yasunori Aoyama（API R&D Laboratory, CMC R&D Division, Shionogi & Co., Ltd.）

2P-51 **Modernize Synthesis**
Naomi Fukuda*（AutoChem Team, BU LAB Instruments, Mettler Toledo K.K.）

2P-52 **Photoctalytic N-Methylation of Amino Acids with Methanol**
Ivven Huang*, Yuna Morioka, Susumu Saito, Hiroshi Naka（Graduate School of Science and Research Center for Materials Science, Nagoya University）

2P-53 **Platinum on carbon-bead-catalyzed energetically efficient, continuous hydrogen production method from methylcyclohexane enhanced by the microwave irradiation**

Tomohiro Ichikawa* [1], Tomohiro Matsuo [1], Takumu Tachikawa [1], Tsuyoshi Yamada [1], Takeo Yoshimura [2], Masatoshi Yoshimura [3], Yukio Takagi [3], Yoshinari Sawama [1], Jun-ichi Sugiyama [4], Yasunari Monguchi [1,5], Hironao Sajiki [1]（[1] Laboratory of Organic Chemistry, Gifu Pharmaceutical University, [2] SAIDA FDS Incorporated, [3] Catalyst Development, N.E.Chemcat Corporation, [4] National Institute of Advanced Industrial Science and Technology, [5] Laboratory of Organic Chemistry, Daiichi University of Pharmacy）

2P-54 **One-pot Preparation of α,β-Unsaturated Aldehydes by Julia-Kocienski Reaction and Hydrolysis**

Haruka Watanabe*, Zhu Xiaoxian, Kaori Ando（Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University）

2P-55 **Enhanced Development and Control of Continuous Processes Using Real-Time In Situ FTIR － What's Happening in Your Flow Chemistry?**

Yuki Hara*, Brian Wittkamp（LAB Instruments Business Unit, Mettler-Toledo）

2P-56 **Expansion of Substrate Scope of Nitroxyl Radical/Copper-Catalyzed Aerobic Alcohol Oxidation**

Yusuke Sasano, Ryota Sasaki*, Koki Kasabata, Naoki Kogure, Shota Nagasawa, Yoshiharu Iwabuchi（Graduate School of Pharmaceutical Sciences, Tohoku University）

2P-57 **Palladium-Catalyzed Reaction of Silyl-Substituted Allyl Acetates with Water Proceeding through 1,2-Shift of a Substituent on Silyl Group**

Yoshikazu Horino, Mayo Ishibashi*, Kosuke Nakasai, Hitoshi Abe（Graduate School of Science and Engineering, University of Toyama）

2P-58 **Scale-up Synthesis of Icatibant using Molecular Hiving Technology**

Daisuke Kubo* [1], Kazuaki Kanai [1], Rino Araki [1], Yu Ito [1], Natsumi Iwanaga [1], Kousuke Suzuki [1], Hideaki Suzuki [1], Ichiro Shima [1], Takashi Yamasaki [1], Yohei Okada [2], Hidehiro Kamiya [2], Kazuhiro Chiba [2]（[1] JITSUBO Co., Ltd., Life Science Research Center, [2] Tokyo University of Agriculture and Technology）

2P-59 **One-pot Preparation of Julia-Kocienski Sulfides and Sulfones from Alcohols**

Kaori Ando*, Junichiro Hattori（Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University）

2P-60 **Rapid Removal and Release ability of DualPore Metal Scavenger in High Flow System**

Riichi Miyamoto* [1], Hong-zhi Bai [1], Makoto Tsujisaka [2], Yoshiki Sohrin [2]（[1] DPS Inc., [2] Institute for Chemical Research, Kyoto University）

2P-61 **Synthesis of Aryl and Heteroaryl Tetrafluoro-λ^6-sulfanyl Chlorides**

Kiyoteru Niina* [1], Ibrayim Saidalimu [1], Yumeng Liang [1], Kazuhiro Tanagawa [1], Norimichi Saito [2], Norio Shibata [1]（[1] Department of Nanopharmaceutical Sciences and Department of Life Science and Applied Chemistry Nagoya Institute of Technology, [2] Pharmaceutical Division, Ube Industries, Ltd.）

2P-62 **Ab initio modeling for Michael addition reaction of acrylic acid**

Michiya Fujita* [1], Yu-ichiro Izato [1], Atsumi Miyake [2]（[1] Graduate School of Environment and information Sciences, [2] Institute of Advanced Sciences, /Yokohama National University）

2P-63 **Attractive reaction yield on hydrolysis of phospholipid by immobilized phospholipase A1 with hydrophobic porous carrier**

Yusuke Hayakawa* [1], Ryoichi Nakayama [2], Norikazu Namiki [2], Masanao Imai [1]（[1] Course in Bioresource Utilization Sciences, Graduate School of Bioresource Sciences, Nihon University, [2] Department of Environmental Chemistry & Chemical Engineering, School of Advanced Engineering, Kogakuin University）

2P-64 **Catalyst-free Decarboxylatiave functionalization of Lithium Pyridylacetate**

Ryouta Kawanishi*, Lacksany Phongphane, Kosuke Nakada, Seiji Iwasa, Kazutaka Shibatomi（Department of Applied Chemistry and Life Science, Toyohashi University of Technology）

2P-65 ◆ **Synthetic Strategy for Process Optimization of a PDE10A Inhibitor Consisting of Pyrazolopyrimidine and Quinoxaline as Key Units**

Takafumi Yamagami*, Noriaki Moriyama, Eiji Toyofuku, Hideki Horiuchi, Shinichi Izumoto, Ryo Kobayashi（Mitsubishi Tanabe Pharma Corporation）

2P-66 **Nucleophilic C2-arylation of quinolines using diaryliodonium salts**

Tatsuya Sugiyama*, Kosuke Yamamoto, Masami Kuriyama, Osamu Onomura（Graduate School of Biomedical Sciences, Nagasaki University）

2P-67 **Preparation of Diaryl Ether Using Ullmann Reaction and Its Application to Ellagitannin Synthesis**

Haruka Imai*, Kazuma Shioe, Yoshiyasu Kato, Daichi Ogura, Yoshikazu Horino, Hitoshi Abe（Graduate School of Innovative Life Science, University of Toyama）

2P-68 **Investigation of Purity Determination of Hygroscopic Compound using qNMR**

Hiroo Sugawara*, Toru Miura, Yoshiaki Iwamoto（Functional Materials Research Laboratories, FUJIFILM Wako Pure Chemical Corporation.）

2P-69 **Regioselective Formylation of Pyrrole Derivatives with Crystalline Vilsmeier reagent**

Takuya Warashina*, Daisuke Matsuura, Yoshikazu Kimura（Research & Development department, Iharanikkei Chemical Industry Co., Ltd.）

2P-70 **Development of multi-functional NHC catalysts bearing pyridine moiety: Application to catalytic asymmetric reactions**

Takahiro Soeta*, Yuichi Hatanaka, So Mizuno, Yutaka Ukaji（Division of Material Chemistry, Graduate School of Natural Science and Technology, Kanazawa University）

2P-71 **Synthesis of Ethynyl Benziodoxolone (EBX)−Acetonitrile Complex and Reaction with Sulfonamide**

Daisuke Shimbo*, Masaharu Yudasaka, Norihiro Tada, Eiji Yamaguchi, Akichika Itoh（Gifu Pharmaceutical University）

2P-72 **Divergent and scalable synthesis of β-amino acid analogues by catalytic enantioselective addition of glyoxylate cyanohydrin to imines**

Xuan Zhang, Yusuke Tokuhiro*, Takeshi Nanjo, Yoshiji Takemoto（Graduate School of Pharmaceutical Sciences, Kyoto University）

2P-73 **Developmental Research of Ynamides Synthesis Method Using Copper Catalyst and Hypervalent Iodine Compounds**

Ryogo Takai*, Norihiro Tada, Eiji Yamaguchi, Akichika Itoh（Gifu Pharmaceutical Univercity）

2P-74 **Synthetic Study of Total Synthesis of Sigillin A**

Yousuke Yamaoka*, Takamori Nakayama, Syota Kawai, Hiroshi Takikawa, Kiyosei Takasu
（Graduate School and Faculty of Pharmaceutical Sciences, Kyoto University）

2P-75 **KHMDS-Promoted Enolate–Olefin Metathesis**

Kiyosei Takasu, Kazuma Sugimoto*, Shun Fujimura, Ken-ichi Yamada, Hiroshi Takikawa, Yousuke Yamaoka（Graduate School of Pharmaceutical Sciences, Kyoto University）

2P-76 **Assessment of 4-Methyltetrahydropyran (4-MeTHP) as an Organic Reaction Solvent**

Tomoki Tamura*, Takashi Kawakami, Saki Yoshimoto, Araki Masuyama, Shoji Kobayashi
（Graduate School of Engineering, Osaka Institute of Technology）

2P-77 **Preparation of carboxymethyl cellulose, calcium alginate and chitosan membrane involved with mechanical strength**

Tomohiro Nakata*, Masanao Imai（Course in Bioresource Utilization Sciences, Graduate School of Bioresource Sciences, Nihon University）

Plenary Speakers' Profile
Keynote Speakers' Profile

PL-1	Robert Grubbs (California Institute of Technology, USA)
PL-2	Shu Kobayashi (The University of Tokyo, Japan)
K-1	Elizabeth Jarvo (University of California, Irvine, USA)
K-2	Kevin R. Campos (Merck, Sharpe, & Dohme Corp., USA)
K-3	Kentaro Yoshimatsu (The Pharmaceutical Society of Japan, Japan)
K-4	Srinivas Oruganti (Dr. Reddy's Institute of Life Sciences, India)
K-5	Kai Rossen (Lundbeck A/S, Copenhagen, Denmark)
K-6	Hideya Mizufune (Spera Pharma Inc., Japan)
K-7	Daisuke Takahashi (Ajinomoto Co., Inc., Japan)
K-8	Matthew M. Bio (Snapdragon Chemistry, Inc., USA)
K-9	Yi-Yin Ku (Abbvie Inc., USA)
K-10	Vikas Shirsath (Jubilant Chemsys Limited, India)
K-11	Ryan Seongho Oh (SK Biotek Co., Ltd., Korea)

PL- 1

Robert Grubbs
The Victor and Elizabeth Atkins Professor of Chemistry,
Division of Chemistry and Engineering,
California Institute of Technology

【Education and Career】

1963_B.S. Chemistry, University of Florida, Gainesville, Florida
1965 M.S. Chemistry, University of Florida, Gainesville, Florida
1968 Ph.D. Chemistry, Columbia University, New York
1968 NIH Postdoctoral Fellow in Chemistry, Stanford University
1969 Assistant Professor, Michigan State University, East Lansing, Michigan
1973 Associate Professor, Michigan State University, East Lansing, Michigan
1978 Full Professor, California Institute of Technology

【Fellowships and Awards】

1988 ACS National Award in Organometallic Chemistry
1995 ACS Award in Polymer Chemistry
1997 The Nagoya Gold Medal of Organic Chemistry
2000 Benjamin Franklin Medal in Chemistry (The Franklin Institute)
2000 ACS Herman F. Mark Polymer Chemistry Award
2001 ACS Herbert C. Brown Award for Creative Research in Synthetic Methods
2002 Arthur C. Cope Award
2003 ACS Award for Creative Research in Homogenous or Heterogeneous Catalysis
2003 Tetrahedron Prize for Creativity in Organic Chemistry
2005 Nobel Prize in Chemistry for 2005, Royal Swedish Academy of Sciences
2005 Honorary Fellow of the Royal Society of Chemistry
2006 Golden Plate Award, Academy of Achievement
2009 ACS Award for Creative Invention
2009 Fellow of the American Chemical Society
2011 ACS Roger Adams Award in Organic Chemistry
2013 National Academy of Inventors
2015 National Academy of Engineering
2015 Chinese Academy of Sciences
2017 George A. Olah Award in Hydrocarbon or Petroleum Chemistry

PL- 2

Shū Kobayashi

Professor, The University of Tokyo

【EDUCATION】

1983 B. Sc. ; The University of Tokyo (Professor T. Mukaiyama)

1988 Ph. D.; The University of Tokyo (Professor T. Mukaiyama)

【ACADEMIC CAREER】

1987 Assistant Professor; Science University of Tokyo (SUT)

1991 Lecturer; Science University of Tokyo (SUT)

1992 Associate Professor; Science University of Tokyo (SUT)

1998 Full Professor; Graduate School of Pharmaceutical Sciences, The University of Tokyo

2002 ERATO Investigator (JST, 2003-2008)

2007 Full Professor; Department of Chemistry, School of Science, The University of Tokyo

【MAJOR AWARDS】

1991 The Chemical Society of Japan Award for Young Chemists

1997 Springer Award in Organometallic Chemistry (OMCOS Award)

2000 Novartis Chemistry Lectureship

2001 IBM Science Award

2002 Organic Reactions Lecturer

Nagoya Silver Medal

Fellow of the Royal Society of Chemistry

2005 Mitsui Chemical Catalysis Science Award

JSPS Prize

2006 Arthur C. Cope Scholar Awards

C.S. Hamilton Award

2007 Merck-Cambridge Lecturer Award

2013 Humboldt Research Award

Green Chemistry Minister of Education Award

2015 Fellow of American Association for the Advancement of Science (AAAS)

2016 Toray Science and Technology Prize

2019 The Chemical Society of Japan Award

K– 1

Elizabeth Jarvo

Professor, University of California, Irvine

2017 Novartis Chemistry Lectureship
2017 UCI Chancellor's Faculty Fellow
2015 Japan Society for Promotion of Science (JSPS) Fellowship
2014 ACS Women in Chemistry Committee Rising Star Award
2010 Thieme Chemistry Journal Award
2009 UC Irvine School of Physical Sciences "Outstanding Contributions to Undergraduate Education" Award
2008 NSF-CAREER Award
2006 ACS-PRF Type G Award
2005 Lilly New Faculty Award
2005 Amgen New Faculty Award

K- 2

Dr. Kevin R. Campos
Associate Vice President
Merck, Sharpe, & Dohme Corp.

Kevin Campos received a B.S. degree in Chemistry from Virginia Tech in 1993. In 1999, he obtained his PhD from Harvard University under the guidance of Professor David A. Evans. Upon completing his doctoral studies, he joined the Department of Process Research and Development at Merck as a Senior Research Chemist. Over the last 18 years, taking several leadership roles of functions in the US and the UK, Kevin has established himself as a leader in both drug discovery and development. In 2007, he was the recipient of the ACS Young Industrial Investigator's Award, and in 2008, he was the recipient of the Marcy Garb Award for Education and Training at MSD. Kevin is internationally recognized as author/co-inventor on over 75 publications, presentations and product patents. He is currently Associate Vice President and Head of Small Molecule Process Research and Development at MSD, where his team enables the MSD pipeline, from pre-clinical development to commercialization, through excellence in synthetic chemistry. Under his leadership, several novel therapies have been successfully launched, including ZEPATIER™, PREVYMIS™, PIFELTRO™, and ZERBAXA™. His team was recently recognized with the US EPA Presidential Green Chemistry Challenge Award for innovations in synthetic chemistry and process development applied to the commercial manufacturing process for PREVYMIS™, and the ACS Green Chemistry Award for the commercial manufacturing process of PIFELTRO™. Dr. Campos and his team recently published article in Science highlighting the power of innovations in synthetic chemistry to accelerate drug invention, development and commercialization.

K－3

Kentaro Yoshimatsu
Executive Director, The Pharmaceutical Society of Japan

【Education, Career and Awards】

1978–1972 Pharmaceutical Sciences, Tokyo University
1991 Doctor of Pharmaceutical Sciences, Tokyo University

1978 Eisai Co. Ltd,
1978 - 1984 Immunology & Inflammatory area
1984 - 1990 Biologics area
1987 - 2003 Oncology area
2003 - 2011 R&D Executive
2003 - 2005 R&D Head, Executive Officer
2006 - 2009 R&D Head, Managing Executive Officer
2009 - 2011, 9 Chief Scientific Officer, Managing Executive Officer
2010, 11 - 2011, 9 H3 Biomedicine Inc., Cambridge (US), President
2011, 9 Retired from senior position due to health reason, Senior scientific advisor
2018, 2 Left Eisai

2018, 2 - RIN Institute Inc. (President in 2018, 6)
3 - Board of Director, Anaeropharmascience Co. Ltd.
Scientific Advisor, K-Pharma Inc.
4 - Executive Director, The Pharmaceutical Society of Japan

2012 - Program Officer, The Program for Intractable Disease Research utilizing Disease-specific iPS, AMED

2013 Award for Drug Discovery Science, The Pharmaceutical Society of Japan

K－4

Srinivas Oruganti
Director, Dr. Reddy's Institute of Life Sciences

1998 Masters in Chemistry, Sri Sathya Sai Institute of Higher Learning, India
2004 Ph.D (Organic Chemistry), Indian Institute of Science, Bangalore, India
2006 La Ligue Contre Le Cancer Fellow, Centre De Biophysique Moleculaire, Orleans, France
2007 Senior Scientist, GVK-Biosciences, Hyderabad, India
2009 Senior Research Scientist, Sai Advantium, Hyderabad, India
2010 Head - Process Research & Innovation, Dr.Reddy's Institute of Life Sciences
2016 Deputy Director, Dr.Reddy's Institute of Life Sciences
2018 Director, Dr.Reddy's Institute of Life Sciences

K－5

Kai Rossen
Editor-in-Chief Organic Process Research & Development
And Vice President, Process Chemistry, Lundbeck A/S,
Copenhagen, Denmark

Education and Career

1982　Master of Science, Organometallic Chemistry, UNC Chapel Hill
1983　Diplom Chemiker Theoretical Chemistry, University Duesseldorf
1987　Ph.D. Cornell University, Organic Chemistry (Prof. Ganem)
1987 until 1990　Bayer AG, Leverkusen, Germany
1990 until 2000　Department of Process Chemistry, Merck & Co, Rahway, USA
2000 until 2005　Exclusive Synthesis, Degussa AG, Hanau, Germany
2005 until 2017　Process Research, Sanofi, Frankfurt, Germany
From 2017　Process Chemistry, Lundbeck A/S, Copenhagen
From 2015　Editor-in-Chief, ACS, Organic Process Research & Development

K－6

Hideya Mizufune, PhD
Division Head, Chemical R&D
Spera Pharma Inc.

【Education, Career and Awards】

1988　Graduated from Department of Applied Chemistry, Faculty of Engineering, Himeji Institute Technology

1990　Graduated from Division of Process Engineering, Graduate School of Engineering, Osaka University

1990　Joined Takeda Chemical Industries (currently Takeda Pharmaceutical Company) as a process chemist

1997　Promoted to Principal Scientist for Chemical Development Laboratories at Takeda

2001-2002　Visiting scientist for Professor Victor Snieckus in Queens University, Kingston Canada

2007　Promoted to Associate Director for Chemical Development Laboratories at Takeda

2008　Earned PhD degree from Division of Molecular Material Science, Graduate School of Science, Osaka City University

2012-2017　Served as the Director for Chemical Development Laboratories (later Process Chemistry) at Takeda

Jul 2017　Joined Sepra Pharma Inc, a spun-out company from Takeda, as the division head for contract process chemistry business.

K– 7

Daisuke Takahashi
Senior principal researcher of AJINOMOTO Co., Inc.

【Biography of Presenter】

He graduated Nihon University and earned Ph.D degree in 2012 from Gifu pharmaceutical University. After joining AJINOMOTO Co., Inc., He worked as a process chemist in amino acids, nucleosides and heterocyclic chemistry fields. He published on more than 10 scientific papers and 40 of patents so far. He commenced to research regarding peptide chemistry in 2005 and is originator of AJIPHASE® technology which combines both strong points of solid-phase and liquid-phase chemistry for peptide and oligonucleotide. He earned the International Symposium on Process Chemistry award in 2011. He is currently working on oligonucleotide and peptide chemistry as a leader of R&D in AJINOMOTO.

K－8

Matthew M. Bio, PhD
President & CEO Snapdragon Chemistry, Inc.

Dr. Matthew Bio is President & CEO at Snapdragon Chemistry. Matthew began his career in chemistry more than 20 years ago developing continuous processes for the manufacture and purification of acrylates at the former Rohm & Haas company. Matthew then moved to Columbia University and earned a PhD in Chemistry. Upon graduating, Matthew returned to industry as a process development chemist at Merck Research Laboratories. In 2006 Matthew moved to Amgen where he was Director of Process Development. At Amgen, Matthew led the development of both batch and continuous processes for clinical candidates and drove innovation in technologies for the manufacture of synthetic – biologic hybrid molecules. In 2015, Matthew joined Snapdragon Chemistry, Inc., a contract development firm specialized in the design of continuous manufacturing technology. Throughout his career, Matthew has been involved in the development of more than 50 clinical candidates and the launch of three new drugs to the market. He is author or inventor on more than 30 peer reviewed publications and patents and numerous regulatory filings. Matthew is driven by a passion for the development of new technologies in organic synthesis to enable safer, more efficient processes and providing access to new chemical architectures.

K－9

Yi-Yin Ku
Senior Research Fellow, Abbvie

Education and Career

1988 Ph.D. in Organic Chemistry, UIC, Chicago
1989 Scientist, Abbott
1992 Senior Scientist, Abbott
1996 Research Investigator, Group Leader, Abbott
1998 Associate Research Fellow, Abbott
2001 Senior Group Leader, Abbott
2007 Research Fellow, Abbott
2013 Research Fellow, Abbvie
2014 Senior Research Fellow, Abbvie - now

Awards and Accomplishments

1992 The Scientist of the Year Award, CAPD, Abbott
1989 The Chairman Award, CAPD, Abbott
1996 The Robert Stein Award, CAPD, Abbott
2007 The R&D President Award, PRD, Abbott
2008 The R&D President Award, PRD, Abbott
2009 The R&D President Award, PRD, Abbott
2012 The first Abbott Women in Science Innovation Award
2013 The company's Outstanding Research Team Award, Abbvie
2014 The R&D President Award, PRD, Abbvie
2016 The R&D President Award, PRD, Abbvie
2016 The company's highest honor Chairman Award
2019 The R&D President Award, PRD, Abbvie

- 43 peer-reviewed publications and book chapters
- 50 conference presentations with 35 as invited speaker
- 33 granted and pending U. S. patents
- Expert adviser to TB-Alliance
- Consultant for the DNDi (Drug for Neglected Diseases Initiative)

K- 10

Vikas Shirsath
Jubilant Chemsys Limited

【Education, Career and Awards】

1993 B. Pharm, NDMVP's College of Pharmacy, Poona University
1995 M. Pharm, L M College of Pharmacy, Gujarat University
2000 Ph. D. , L M College of Pharmacy, Gujarat University
2004 PG Diploma in Patent Law, NALSAR, Hyderabad
2000 Associate Research Scientist, Medicinal Chemistry, Zydus Research Centre, Ahmedabad
2002 Deputy GM, Medicinal Chemistry and Drug Discovery, Suven Life Sciences Ltd., Hyderabad
2006 Chief Scientific Officer, Oxygen Healthcare Private Ltd., Ahmedabad
2011 Chief Scientific Officer, Piramal Discovery Solutions, Ahmedabad
2012 Internal Consultant, Piramal Enterprise Limited, Chennai
2013 Associate VP, Jubilant Chemsys
2017 Senior VP and Global Head, Chemistry Operations, Jubilant Drug Discovery and Development Solutions (Jubilant Chemsys Ltd and Jubilant Biosys Ltd)

K- 11

Ryan Seongho Oh
Vice President, Head of Process R&D, SK Biotek

【Education, Career and Awards】

1991 B.S./ Chemistry, Yonsei University, Korea

1993 M.S./ Organic Chemistry, Yonsei University, Korea
Thesis Title: Synthetic Study on Liposidomycin B

1993 – 2000 New Drug Discovery, LG Chemical Ltd, Korea
Research Area: New beta-Lactam Antibiotics, MRSA Inhibition, Thrombin Inhibitor, Process Development for Clinical Study Candidates

2005 Ph.D./ Organic Chemistry, Texas A&M University, TX, USA
Thesis: Optimization and Extensions of the Nucleophile Catalyzed Aldol-Lactonization (NCAL) Process for Bicyclic beta-Lactone Synthesis

2007 Post-Doctoral Research, Johns Hopkins University, MD, USA
Research Area: Synthesis of Orally Active, Antimalarial, Anticancer, Artemisinin-Derived Trioxane Analogs

2007 Staff Scientist, Biocatalysis & Chemical Development, Codexis, CA, USA

2013 Principal Scientist, Process R&D, SK Biotek, Korea

2017 Vice President, Head of Process R&D, SK Biotek, Korea
Lead Cross Functional Teams of Process Chemists, Analytical Chemists, and Engineers providing API Related Production Process through Batch and Continuous Ways

Graphical Abstracts

Plenary Lectures
Keynote Lectures

PL-1

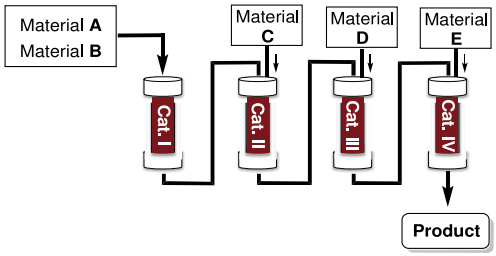
Development and Applications of Selective Olefin Metathesis Catalysts

Robert Grubbs*
Division of Chemistry and Engineering, California Institute of Technology

PL-2

Synthetic Strategies Based on Continuous-flow Methods

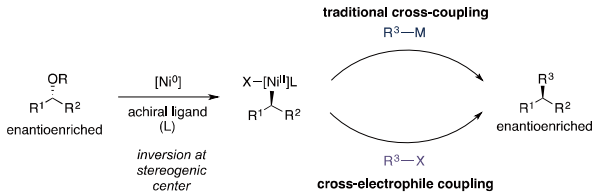
Shū Kobayashi *
Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan



K-1

Nickel-Catalyzed Stereospecific Cross-Coupling and Cross-Electrophile Coupling Reactions

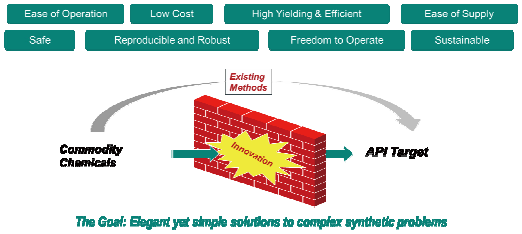
Elizabeth R. Jarvo*
University of California, Irvine



K-2

Innovations in Synthetic Chemistry at MSD: Striving for the Ideal Commercial Manufacturing Process

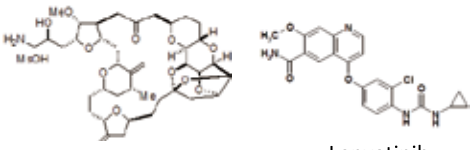
Kevin R. Campos*
Process Research, Merck Sharp & Dohme Corp.
Kenilworth, NJ, 07065, USA



K-3

Oncology drug discovery efforts in the Japanese pharmaceutical company (Eisai Co., Ltd.) and My next challenge

Kentaro Yoshimatsu
Executive Director, The Pharmaceutical Society of Japan

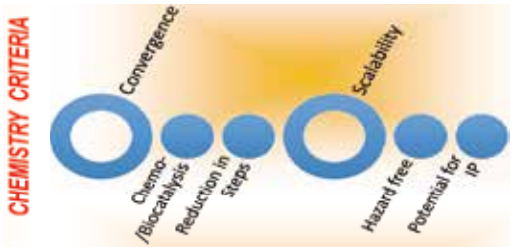


K-4

Simplifying chemistry through targeted route design: snippets of early stage process innovation for newly approved anti-cancer drugs

Srinivas Oruganti*

Center for Process Research and Innovation, Dr. Reddy's Institute of Life Sciences



K-5

The Importance of Process Chemistry

Kai Rossen

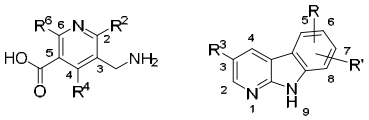
Organic Process Research & Development, American Chemical Society and Process Chemistry, Lundbeck A/S, Copenhagen,,Denmark.

K-6

Contribution from Pharmaceutical Process Chemistry to Green Chemistry and Molecular Diversity

Hideya Mizufune

Chemical R&D Division, Spera Pharma Inc.



K-7

Peptide and Oligonucleotide Synthesis in Large Scale Using a Novel Solution Phase Approach AJIPHASE®

Daisuke Takahashi

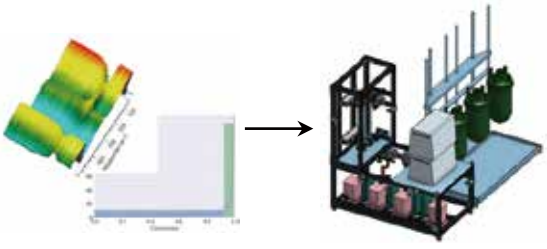
Research Institute for Bioscience products & Fine chemicals, AJINOMOTO Co., Inc.

K-8

Mighty Machines: Rapid and robust scaling of drug substance processes in purpose-built reactors enabled by continuous manufacturing technology

Matthew M. Bio*

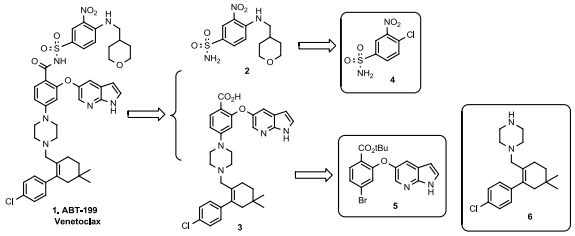
Snapdragon Chemistry, Inc.



K-9

Synthetic Route Development for Manufacture of Venetoclax under Expedited Timeline

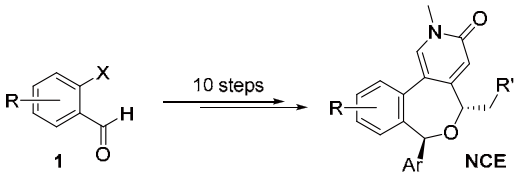
Yi-Yin Ku*
Process Chemistry, Research and Development,
Abbvie, United State



K-10

Development of New Molecular Entities: Phase 1

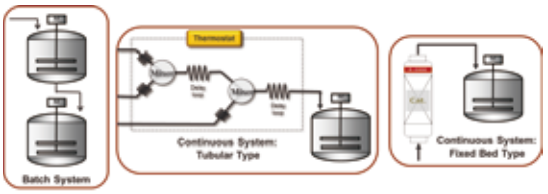
Vikas Shirsath
Jubilant Chemsys Ltd, B-34, Sector 58,
Noida 201301, INDIA



K-11

Review of Continuous Procss in SK Biotek

Ryan Seongho Oh
Process R&D Center, SK Biotek Co., Ltd., Korea

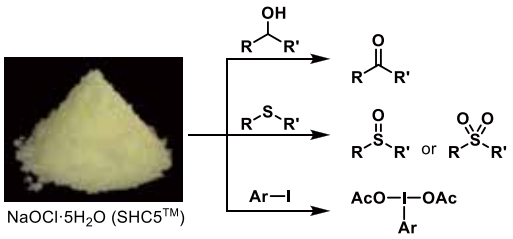


Poster Presentation
July 25 (Thu)

1P-01

Sodium Hypochlorite Pentahydrate: Effective Oxidant for Organic Reactions

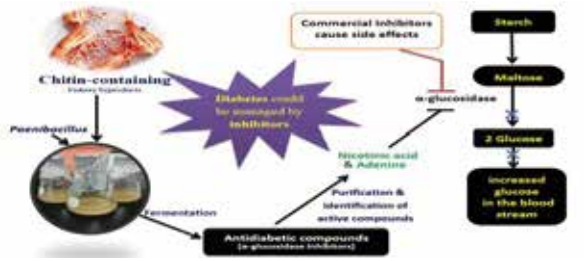
Tomohide Okada*
Market Development Department, Chemicals Division, Nippon Light Metal Co., Ltd.



1P-02

Antidiabetic Materials Produced by *Paenibacillus* Fermentation

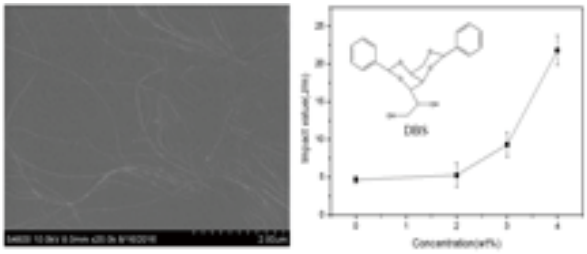
San-Lang Wang*, Van Bon Nguyen
Chemistry Department, Tamkang University



1P-03

Synthesis and Characterization of Epoxies Using Self-Assembled Nanofibrillar as Scaffolds

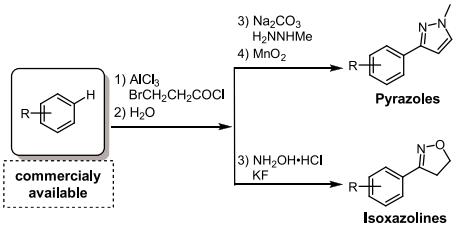
Wei-Chi Lai,* Ruey-Yi Hsia
Department of Chemical and Materials Engineering, Tamkang University, Tamsui, Taipei 25137, Taiwan.



1P-04

One-Pot Preparation of 3-Arylpyrazoles and 3-Arylisoxazolines from Arene

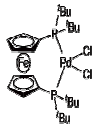
*Takahiro Yamamoto, Hideo Togo
Graduate School of Science, Chiba University



1P-05

Advantages of Metal Ligand Complexes/Pre-Catalysts in Catalytic Reactions Compared to *in situ* Systems

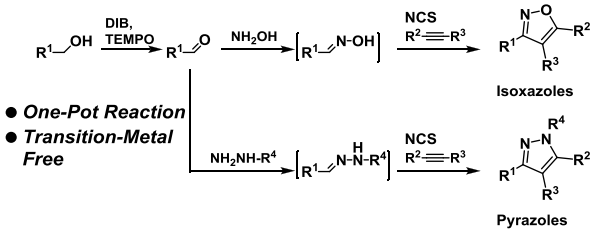
Yoshiaki Horiguchi*
Precious Metals Chemistry, Umicore Japan KK

In situ	ML-complex (Metal-Ligand-complex)
Pd_2dba_3 + dtbpf	

1P-06

One-Pot Transformation of Primary Alcohols into 3-Aryl-and 3-AlkylIsoxazoles and Pyrazoles.

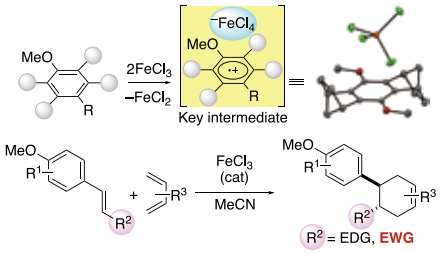
Eiji Kobayashi *, Hideo Togo
Graduate School of Science, Chiba University.



1P-07

Structure and Reactivity of Aromatic Radical Cations Generated by $FeCl_3$

Takahiro Horibe*, Shuhei Ohmura, Kazuaki Ishihara
Graduate School of Engineering, Nagoya University.

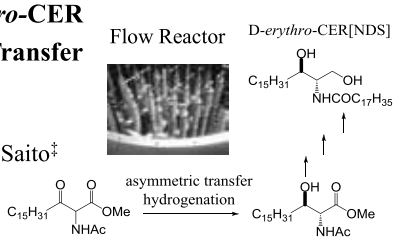


1P-08

Establishment of the Continuous Synthesis of Ceramide (D-*erythro*-CER NDS]) *via* Oxo-Tethered Ruthenium Complex Catalyzed Asymmetric Transfer Hydrogenation using Pipe-Flow Reactor

Masahiro Kuwana,*[,†,‡] Taichiro Touge,[†] Yasuhiro Komatsuki,[†] Shigeru Tanaka,[†] Hideki Nara,[†] Kazuhiko Matsumura,[†] Noboru Sayo,[†] Yoshinobu Kashibuchi,[‡] Takao Saito[‡]

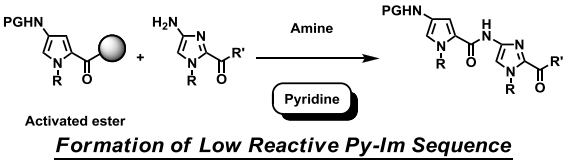
[†] Corporate Research & Development Division, Takasago International Corporation
[‡] Process Development Department, Takasago Chemical Corporation



1P-09

Highly Efficient Synthesis of Pyrrole-Imidazole Amide Sequence for Application to DNA-Binding Polyamides

Takahiko Murata,* Shohei Yamamoto, Akira Nishiyama
Pharma & Supplemental Nutrition Solutions Vehicle,
KANEKA CORPORATION

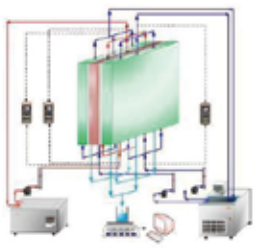


Formation of Low Reactive Py-Im Sequence

1P-10

Device Performance Improvement of Double-unit Air Gap Membrane Distillation Module for Seawater Desalination

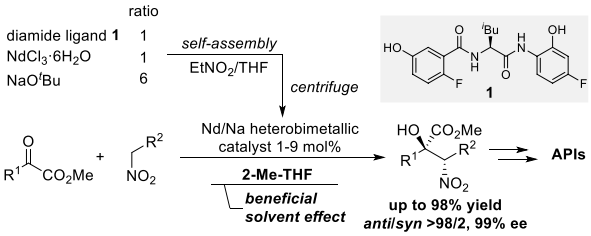
Chii-Dong Ho*[,a], Luke Chen[b], Yu-An Chen[a] and Chi-Hsiang Ni[a]
[a]Department of Chemical and Materials Engineering, Tamkang University, Taiwan
[b]Water Resources and Environmental Engineering Department, Tamkang University, Taiwan



1P-11

anti-Selective Catalytic Asymmetric Nitoaldol Reaction of α-Keto Esters: Intriguing Solvent Effect, Synthesis of APIs, and Flow Reaction

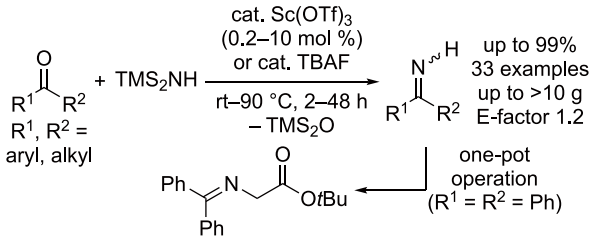
Tomoya Karasawa,*[1] Raphaël Oriez,[2] Naoya Kumagai,[2] Masakatsu Shibasaki[2]; [1] Sumitomo Dainippon Pharma, [2] Institute of Microbial Chemistry (BIKAKEN)



1P-12

Development of New Catalytic Synthetic Methods of _N_-Unprotected Ketimines

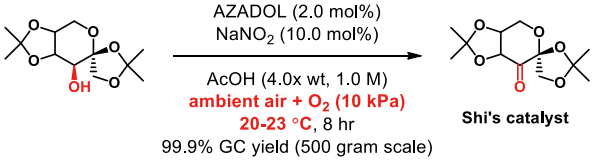
Hiroyuki Morimoto*, Yuta Kondo, Kazuhiro Morisaki, Tetsuya Kadota, Yoshinobu Hirazawa, Takashi Ohshima
Grad. School of Pharm. Sci., Kyushu University, Japan



1P-13

Safe and Scalable Aerobic Oxidation by 2-azaazamantane-2-ol(AZADOL)/NOx Catalysis: Large-Scale Preparation of Shi's Catalyst

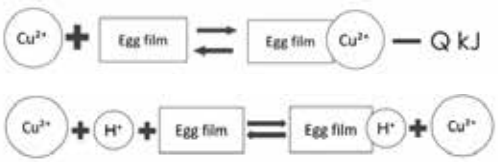
Yusuke Sasano[1], Hikaru Sato[2]*, Shinsuke Tadokoro[2], Masami Kozawa[2], Yoshiharu Iwabuchi[1]
1. Graduate School of Pharmaceutical Sciences, Tohoku University.
2. Chemical Research Laboratory, Nissan Chemical Corporation.



1P-14

The Research on the Adsorptive Condition of Copper (Ⅱ) ion with the Use of Ephippia

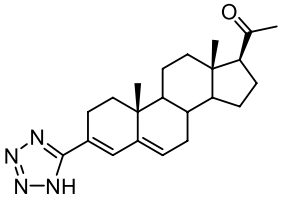
Azusa Oyama*, Saya Oikawa*, Nanami Kannno*, Noa Haneishi*, Kazunari Takahashi
Iwate Prefectural Mizusawa High School



1P-15

Efficient Synthesis of a 5α-Reductase Inhibitor, 3-(Tetrazol-5-yl)-3,5-pregnadien-20-one through Allylic Rearrangement of Cyanophosphates

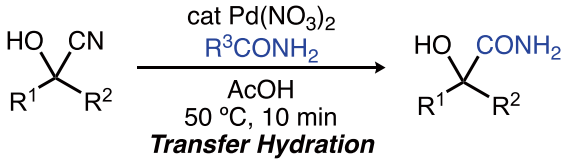
Shinya Harusawa*, Hiroki Yoneyama, Yoshihide Usami
Osaka University of Pharmaceutical Sciences



1P-16

Catalytic Transfer Hydration of Cyanohydrins to alpha-Hydroxyamides

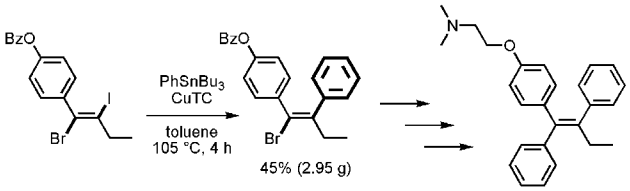
Tomoya Kanda, Asuka Naraoka, Hiroshi Naka*
Grad. Sch. Sci. and RCMS, Nagoya University



1P-17

Stereo-Defined Scaffold Strategy for Tamoxifens from (*E*)-1-Bromo-2-iodoalkenes.

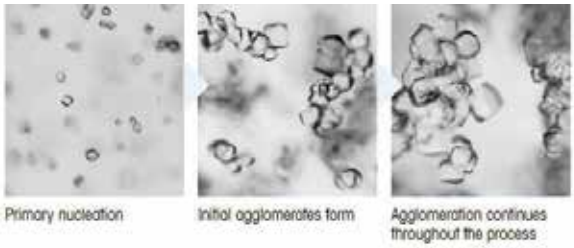
Yoshino Fujii*, Yuka Tamura, Nako Hashimoto, Naoki Endo, Tetsuo Iwasawa (Ryukoku University, Japan)



1P-18

Seven Crystallization Mechanisms Hiding Between Your Samples

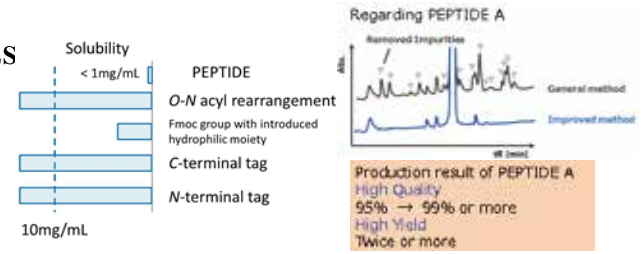
Mayu Nakatsukasa, Des O'Grady PhD
Mettler Toledo K.K.



1P-19

VARIOUS MANUFACTURING APPROACHES TO POORLY SOLUBLE PEPTIDES

Go Shiino*, Aiko Hasegawa, Takaharu Matsuura, Shunsuke Ochi, and Yoshinori Murata
API R&D Lab., CMC R&D Div., Shionogi & Co., Ltd.

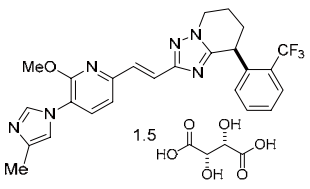


1P-20

Development of an Efficient Manufacturing Process for E2212 toward Rapid Clinical Introduction

Minetaka Isomura, * Taiju Nakamura, Katsuya Tagami

API Research Japan, Pharmaceutical Science & Technology
CFU, Medicine Development Center, Eisai Co. Ltd.



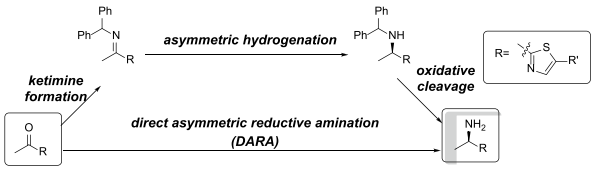
E2212

- Route Finding
- Optimization
- Flow-Mediated Photo-Isomerization

1P-21

Asymmetric route to a chiral heterocyclic amine toward efficient manufacturing process

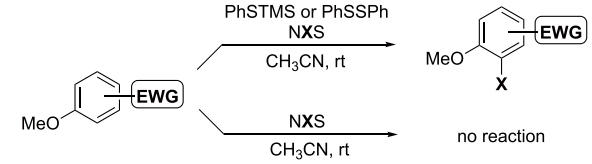
Sayuri Hirano,* Masatoshi Yamada, Mitsuhisa Yamano
Chemical R&D Division, Spera Pharma, Inc.



1P-22

Aromatic Halogenation Using *N*-Halosuccinimide and PhSTMS or PhSSPh

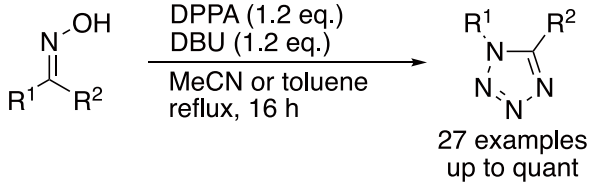
Yuuka Hirose, Mirai Yamazaki, Misa, Nogata, Akira Nakamura, Tomohiro Maegawa*
School of Pharmaceutical Sciences, Kindai University



1P-23

Stereospecific Synthesis of 1,5-Disubstituted Tetrazoles from Ketoximes via Beckmann Rearrangement Utilizing Diphenyl Phosphorazidate

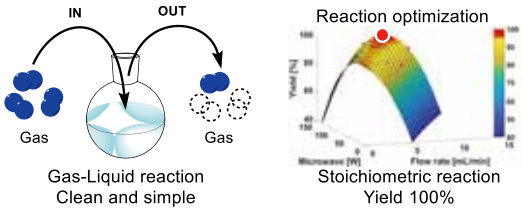
Kotaro Ishihara*, Yuki Kobayashi, Takayuki Shioiri, Masato Matsugi
(Meijo University, Japan)



1P-24

Post-treatment Free Synthesis of Fairy Chemicals Using Fine Bubble and Flow Optimization Method

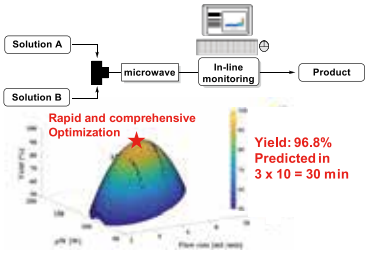
Keiya Matsuo*, Kohei Sato, Tetsuo Narumi, Nobuyuki Mase
Applied Chemistry and Biochemical Engineering Course,
Department of Engineering, Graduate School of
Integrated Science and Technology, Shizuoka University



1P-25

Reaction Optimization Using Microwave-Assisted Continuous Flow Reactor with In-Line Analysis

Takuya Kon*, Kohei Sato, Tetsuo Narumi, Kazuhiro Takeda, Nobuyuki Mase
Applied Chemistry and Biochemical Engineering Course,
Department of Engineering, Graduate School of
Integrated Science and Technology, Shizuoka University

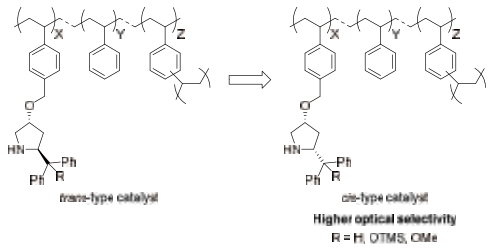


1P-26

Synthesis of polymer-supported *cis*-2,4-disubstituted pyrrolidine derivatives and their application to asymmetric reactions

Hidenori Ochiai[1,*], Akira Nishiyama[1], Naoki Haraguchi[2], Shinichi Itsuno[2]

[1]Kaneka Co. [2]Toyohashi University of Technology

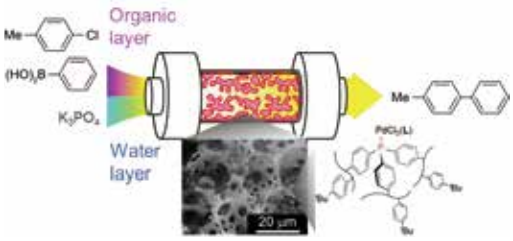


1P-27

Application of Macroporous Polystyrene-Triphenyl phosphine Monolith to Palladium-Catalyzed Cross-Coupling Reaction in Flow System

Hikaru Matsumoto*,[1] Yu Hoshino, [1] Tomohiro Iwai,[2] Masaya Sawamura,[2,3] Yoshiko Miura[1]

[1]Kyushu University, [2]Hokkaido University, [3]WPI-ICReDD

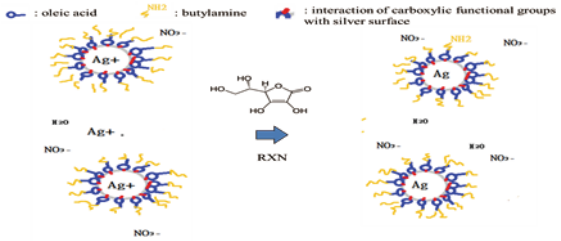


1P-28

Preparation of Oil-based Stable Sliver Nanoparticle Suspensions

Trong-Ming Don*, Wen-Shan Yang, Tung-Wen Cheng

Department of Chemical and Materials Engineering, Tamkang University, New Taipei City, Taiwan



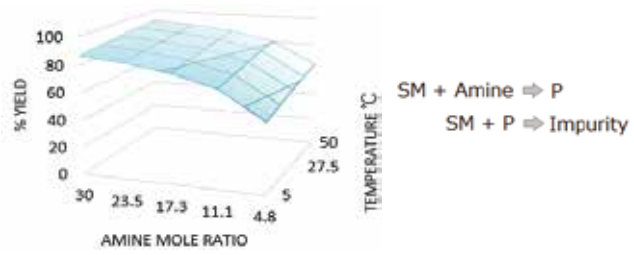
1P-29

Design Space Success Stories: Reaction and Crystallization Processes

Leela Christian-Tabak*[1], Hiroaki Tanaka[1], Haitao Zhang[2], Minoru Toshima[1], Mikio Sasaki[1]

[1]Process R&D Laboratories, Sumitomo Dainippon Pharma

[2]Chemical Process R&D, Sunovion Pharmaceuticals

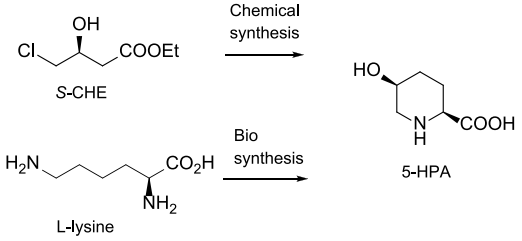


1P-30

Process development of β—Lactamase inhibitor key intermediate

Masato Murai,*[1] Jun Takehara[2], Ryoma Miyake[2], Takanobu Iura[2] Hiroshi Kawabata[2]

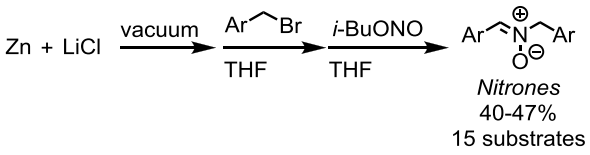
[1] API Corporation, [2] Mitsubishi Chemical Corporation



1P-31

Nitrones with Benzylic Bromides, Zinc, and Isobutyl Nitrite

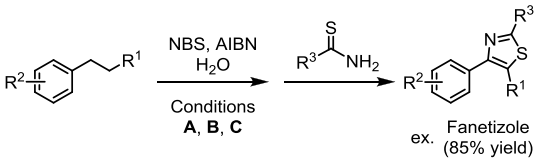
Kei Yanai*, Hideo Togo
Graduate School of Science and Engineering, Chiba University



1P-32

2-Amino-4-arylthiazoles through One-Pot Transformation of Alkylarenes with NBS and Thioureas

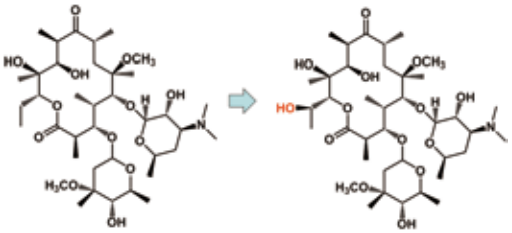
Kaho Shibasaki*, Hideo Togo
Graduate School of Science and Engineering, Chiba University



1P-33

Biocatalysts for Hydroxylation

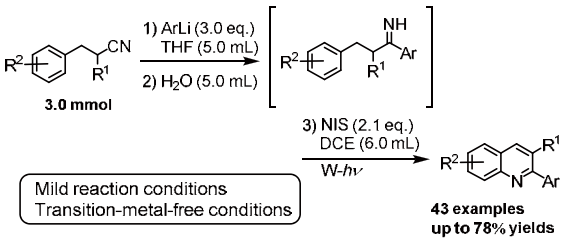
Hiroshi Kadono,* , Taiki Nishioka
MicroBiopharm Japan Co., Ltd.



1P-34

Oxidative Construction of 2-Arylquinolines from β-Arylpropionitriles through Iminyl Radical-mediated Cyclization

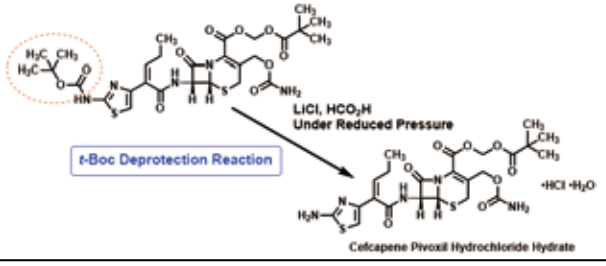
Hiroki Naruto*, Hideo Togo
Graduate School of Science and Engineering, Chiba University



1P-35

Novel and Practical Deprotection Method of *t*-Boc Group for Preparation of Cefcapene Pivoxil Hydrochloride Hydrate Using Formic Acid and Lithium Chloride

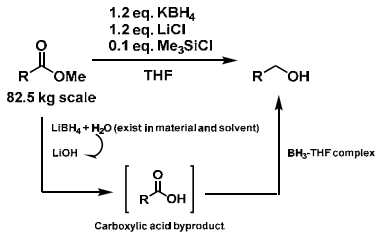
Takanori Kurita*, Yoshiko Tanaka, Teruo Iizuka
Shionogi Pharma Co., Ltd.



1P-36

The development for manufacturing process of methyl ester reduction with $LiBH_4$ prepared in-situ

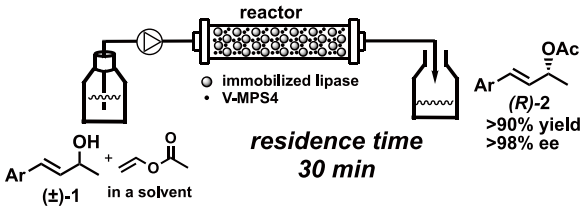
Takayuki Toyama*, Naoki Miyake, Yusuke Sato, Takanori Kurita
Chemical Development, Production Technology Department,
Shionogi Pharma Co., Ltd.



1P-37

Continuous Flow Lipase-Catalyzed Dynamic Kinetic Resolution of Alcohols

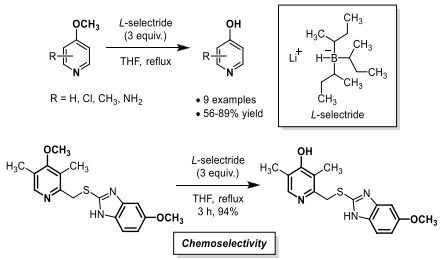
Koichi Higashio*[1], Satoko Katsuragi[1], Franziska Kühn[2],
Niklas Adebar[2], Carmen Plass[2], Harald Gröger[2], Shuji Akai[1]
[1]Graduate School of Pharmaceutical Sciences, Osaka University,
[2]Faculty of Chemistry, Bielefeld University



1P-38

Chemoselective demethylation of methoxypyridine

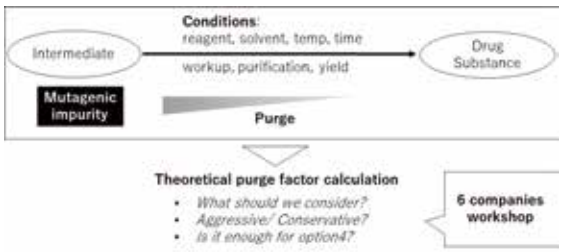
Kosho Makino,*[a] Yuki Tanaka,[a] Yumi Hasegawa,[b] Takahide Inoue,[a] Koji Araki,[b] Hidetsugu Tabata,[b] Tetsuta Oshitari,[b] Kiyomi Ito,[c] Hideaki Natsugari,[d] Hideyo Takahashi[a]
[a]Tokyo University of Science, [b]Teikyo University,
[c]Musashino University, [d]The University of Tokyo



1P-39

A Case Study of Theoretical Purge Factor for Mutagenic Impurity Management by Collaboration among 6 Pharmaceutical Companies

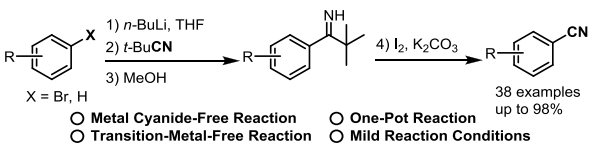
Shinji Tamura[1]*, Kenichiro Sato[2]*, *et al.*
[1]Ono Pharmaceutical Co., Ltd., [2]Asahi Kasei Pharma Corp.



1P-40

Novel Preparation of Aromatic Nitriles from Aryl Bromides and Arenes via Imino-nitrogen-centered Radicals

Ko Uchida,* Hideo Togo
Graduate School of Science, Chiba University.

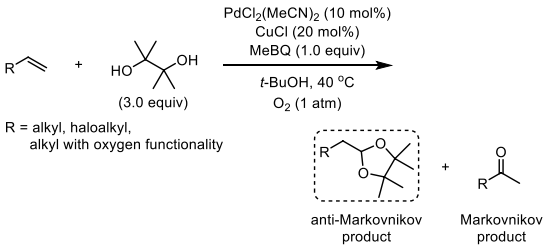


1P-41

Pd/Cu-catalyzed Anti-Markovnikov Oxidation of Aliphatic Alkenes to Terminal Acetals

Saki Komori*, Yoshiko Yamaguchi, Yasutaka Kataoka, Yasuyuki Ura

Faculty of Science, Nara Women's University

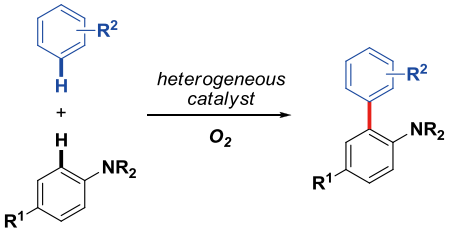


1P-42

Heterogeneous Metal Catalyzed Aerobic Dehydrogenative Biaryl Coupling of Aniline Derivatives

Kenji Matsumoto*, Satoshi Takeda, Yasunori Toubaru, Tsukasa Hirokane, Masahiro Yoshida

Faculty of Pharmaceutical Sciences, Tokushima Bunri University

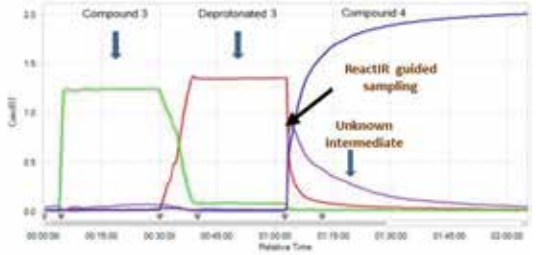


1P-43

PAT: Optimize Processes From Liquids to Solids

Yoichi Yamasaki*, Wittkamp Brian, Stephan Woods

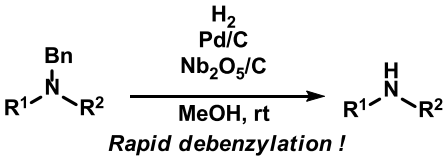
AutoChem Business Unit, Mettler-Toledo



1P-44

Palladium and Niobic Acid on Carbons-Catalyzed Facile Hydrogenative Deprotection of *N*-Benzyl Groups

Yuta Yamamoto,[1*] Kazuho Ban,[1] Yukio Takagi,[2]
Masatoshi Yoshimura,[2] Yoshinari Sawama,[1] Hironao Sajiki[1]
[1]Gifu Pharmaceutical University [2]N. E. Chemcat Corporation



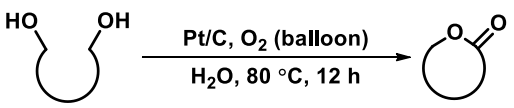
Nb_2O_5/C (Niobic acid on activated carbon)
Easily preparable, heterogeneous, reusable

1P-45

Pt/C-catalyzed oxidative annulation of diols to lactones

Ryoya Takakura*, Kazuho Ban, Hironao Sajiki, Yoshinari Sawama

Gifu Pharmaceutical University



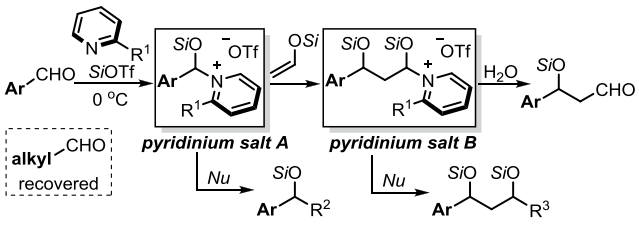
- ***Heterogeneous catalyst***
- ***Green solvent***
- ***Clean oxidant***

1P-46

Aromatic Aldehyde-Selective Functionalization via Pyridinium Salt Intermediates

Takahiro Kawajiri*, Hiromichi Fujioka, Hironao Sajiki and Yoshinari Sawama

Gifu Pharmaceutical University

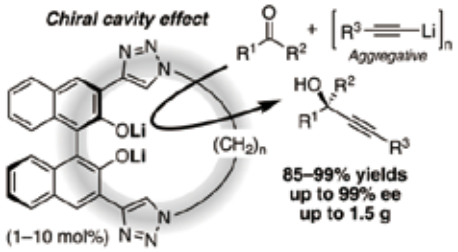


1P-47

Chiral Macrocyclic Lithium Binaphtholate Catalysts for Enantioselective Addition of Lithium Acetylides to Ketones

Manabu Hatano*, Kenji Yamashita, Kazuaki Ishihara

Graduate School of Engineering, Nagoya University

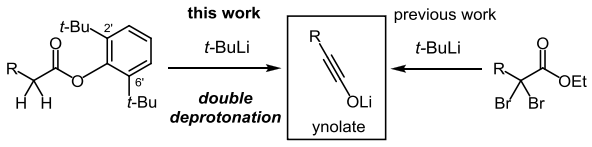


1P-48

Generation of ynolates via double deprotonation of 2,6-di-*tert*-butylphenol esters

Jun Sun,[*,2] Toshiya Yoshiiwa,[2] Takayuki Iwata,[1] Mitsuru Shindo[1]

[1]IMCE, [2]Interdiscip. Grad. Sch. Eng. Sci., Kyushu Univ.

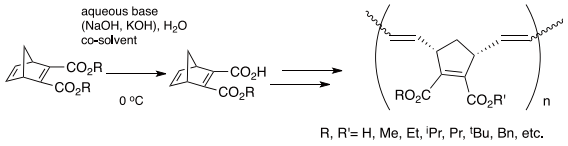


1P-49

Synthetic Studies of Libraries of Polymers from Half-esters Obtained by Practical Selective Monohydrolysis of Symmetric Diesters

Satomi Niwayama,* Jianjun Shi

Graduate School of Engineering, Muroran Institute of Technology

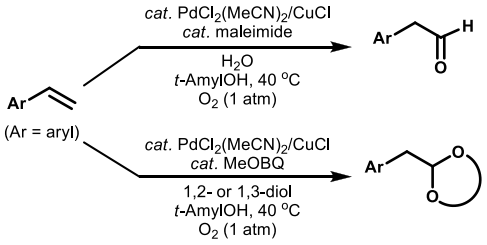


1P-50

Pd/Cu-catalyzed Aerobic Anti-Markovnikov Oxidation of Vinylarenes to Aldehydes and Terminal Acetals

Yasuyuki Ura*, Sonoe Nakaoka, Yuka Murakami, Satoko Matsumura, Ruriko Sato, Wakana Yokotani, Yasutaka Kataoka

Faculty of Science, Nara Women's University

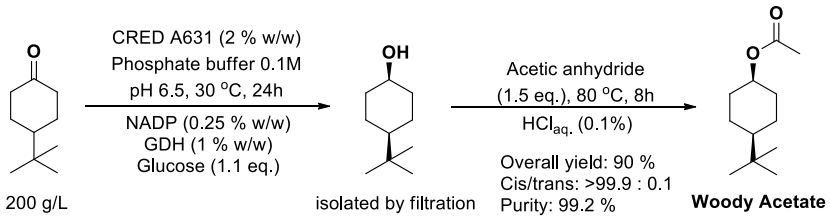


1P-51

Biocatalytic Process Design – Challenges and Solutions

Stefan Mix*, Gareth Brown, Iain Miskelly

Department of Biocatalysis and Isotope Chemistry, Almac Group

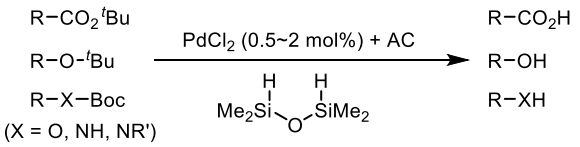


1P-52

Hydrosilane-Promoted Facile Deprotection of *tert*-Butyl Groups in Esters, Ethers, Carbonates, and Carbamates

Zhenzhong Zhang,* Takuya Ikeda, Yukihiro Motoyama

Adv. Sci. Tec. Dept., Toyota Tech. Inst.

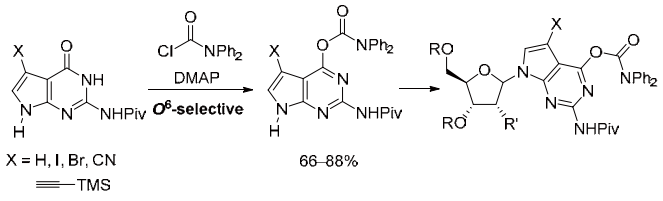


1P-53

Synthesis of 7-Deazaguanosine Derivatives via Glycosylation

Koki Nakano*, Natsuhisa Oka, Akane Fukuta, Ayumi Mori, Kaori Ando

Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University

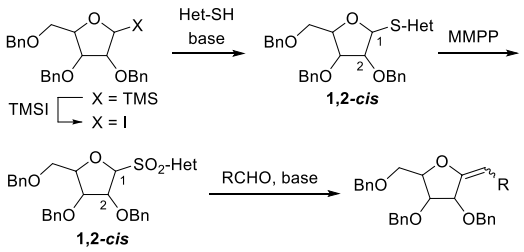


1P-54

Stereoselective Synthesis of Furanosyl Sulfones and Their Application to Julia-Kocienski Reaction

Kanna Suzuki*, Natsuhisa Oka, Ayumi Mori, Kaori Ando

Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University

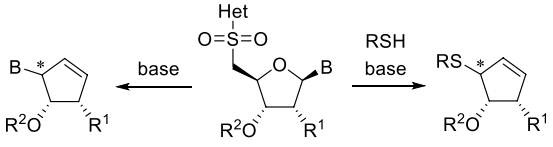


1P-55

One-Step Synthesis of Cyclopentene Derivatives from Julia-Kocienski Reagents Derived from Nucleosides

Minami Furuzawa*, Natsuhisa Oka, Mayuka Kanda, Kaori Ando

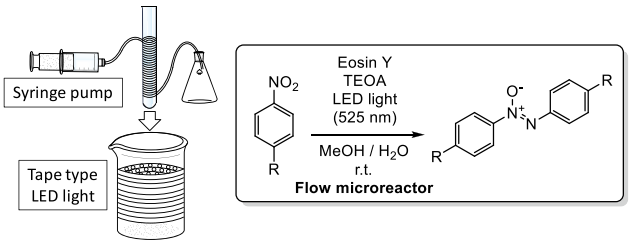
Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University



1P-56

Selective Synthesis of Azoxybenzenes from Nitrobenzenes by Photoreduction with Flow Microreactors

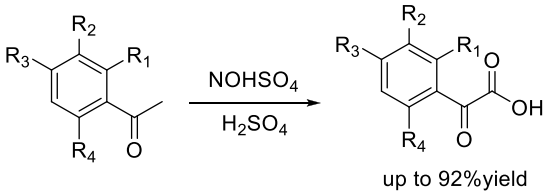
Akira Fujii*, Yasuhiro Nishiyama, Hajime Mori
Industrial Technology Center of Wakayama Prefecture



1P-57

Highly efficient synthesis of aromatic α-keto acids from acetophenones using nitrosylsulfuric acid as an oxidant

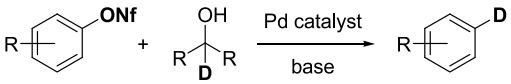
Tadafumi Matsunaga*, Yasuhiro Kataoka, Shun Tanimura, Masato Kawamura.
Health and Crop Sciences Research Laboratory, Sumitomo Chemical Co., Ltd.



1P-58

Palladium-catalyzed deoxygenative deuteration of aryl nonaflates

Masami Kuriyama*, Kotaro Tsukuda, Hirotoshi Kiba, Tetsuro Morimoto, Kosuke Yamamoto, Osamu Onomura
Nagasaki University

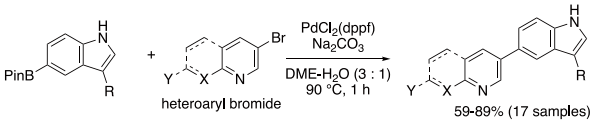


- *stable and readily-synthesized nonaflates*
- *a broad scope of substrates*
- *precisely-controlled deuterium incorporation*

1P-59

Efficient Synthetic Study of Multi-functionalized Biheteroaromatics by Suzuki Coupling

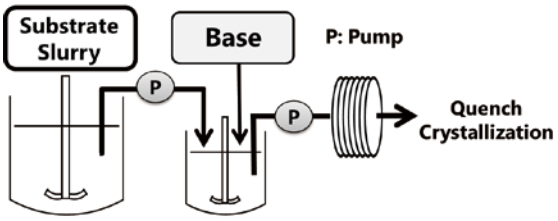
Masahiro Hamada*, Ryota Fujimoto, Noriyuki Nakajima
Department of Pharmaceutical Engineering and Biotechnology Research Center, Toyama Prefectural University



1P-60

Precise Control of the Mutagenic Impurity Production by Flow Synthesis

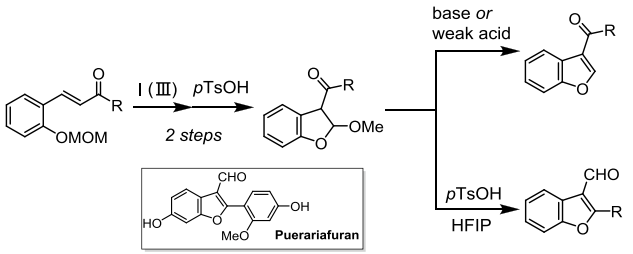
Masahiro Hosoya*, Takahiro Oshima, Yuki Masuda, Masashi Tanaka, Noriyuki Kurose
API R&D Lab., CMC R&D Div., Shionogi & Co., Ltd.



1P-61

Selective Synthesis of Benzofuran Isomers Using Rearrangement Reaction of Hydroxychalcone and the Application to Synthesis Natural Product

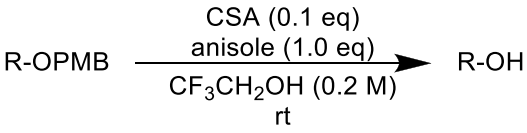
Yuichiro Ikegami*, Fei Rao, Akira Imamiya,
Akira Nakamura, Tomohiro Maegawa
School of Pharmaceutical Science, Kindai University



1P-62

New Deprotection Method of PMB Protective Group of Alcohols Using Weak Acid in CF_3CH_2OH and Remarkable Acceleration of Deprotection of PMB Protected 4-phenylbutanol.

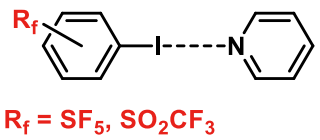
Yugo Kotera*, Misa Matsumura, Hiroko Kawasaki, Norihiko Yamagami, Akira Nakamura, Tomohiro Maegawa
School of Pharmaceutical Sciences, Kindai University



1P-63

Design of Novel Halogen Bonding Donors with SF_5 and SO_2CF_3 Functional Groups on Iodobenzenes

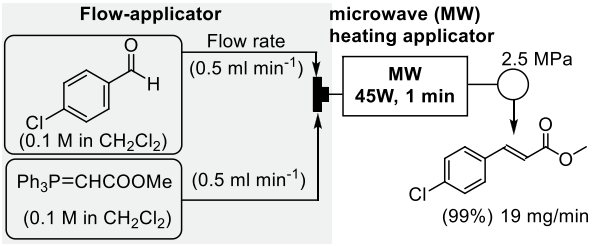
Yuji Sumii,* Kenta Sasaki, Norio Shibata
Department of Life and Applied Chemistry, Nagoya Institute of Technology



1P-64

Quick and Continuous Synthesis of Methyl Cinnamates Using a Flow-microwave Applicator

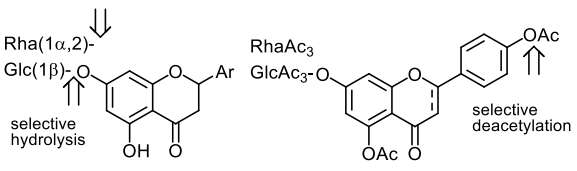
Hiroki Yoneyama*, Naoki Oka, Megumi Yoshii, Shinya Harusawa, Yoshihide Usami
Osaka University of Pharmaceutical Sciences.



1P-65

Utilization of Naturally Occurring Glycosylated Forms for the Synthesis of Flavonoids

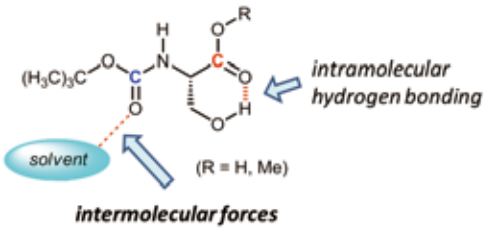
Takeshi Sugai*, Ryuji Tsunekawa, Kazuki Kurahayashi, Rie Fujita, Kengo Hanaya, Shuhei Higashibayashi
Department of Pharmaceutical Sciences, Keio University



1P-66

^{13}C NMR Spectroscopic Studies of Intra- and Intermolecular Interactions of Amino Acids and Dipeptide Derivatives in Solutions

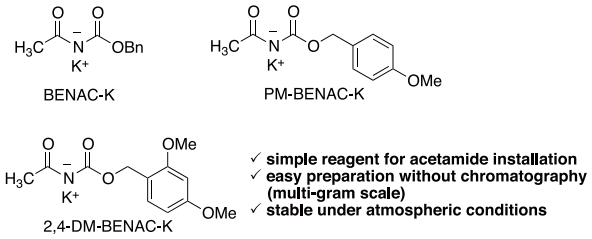
Yoshikazu Hiraga[1], Ryosuke Hoshide[1,*], Satomi Niwayama[2]
[1] Hiroshima Institute of Technology, [2] Muroran Institute of Technology



1P-67

Simple Nucleophiles of Acetamide Equivalents: BENAC-K, PM-BENAC-K, 2,4-DM-BENAC-K

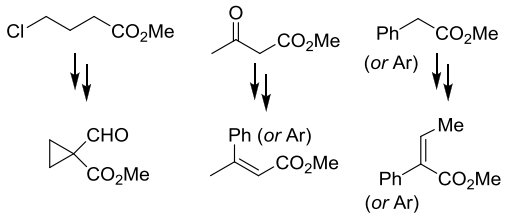
Yumika Koike*, Atsunori Hira, Toshiki Tatematsu, Takeo Sakai, Yuji Mori
Facluty of Pharmacy, Meijo University



1P-68

Three subjects in *Organic Syntheses*: Simple, useful, but hitherto inaccessible building blocks

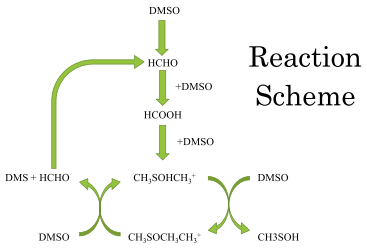
Yuichro Ashida,* Takeshi Tsutsumi, Satomi Kajimoto, Hiroshi Nishikado, Hidefumi Nakatsuji, Yoo Tanabe*
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University



1P-69

Thermal hazard analysis of self accelerating decomposition via acid production of dimethyl sulfoxide (DMSO)

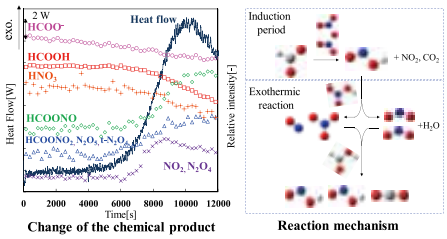
Yuto Koizumi[1]*, Yu-ichiro Izato[1], Atsumi Miyake[1]
Yoshikuni Deguchi[2], Masafumi Kono[3]
1Yokohama National University, 2Kaneka Corporation
3Nippon Refine Corporation



1P-70

***In situ* analysis of liquid phase oxidation of nitric acid/formic acid mixtures using thermal and raman spectroscopic acalyses**

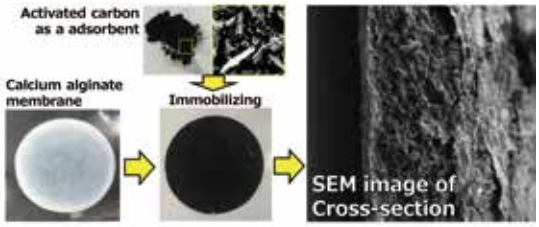
Mahoko Ando, Michiya Fujita, Yu-ichiro Izato, Atsumi Miyake*
*Yokohama National University



1P-71

Efficient Removal of Nitrate Ions Through Calcium Alginate Membrane Immobilizing Activated Carbon Particles as Adsorbents

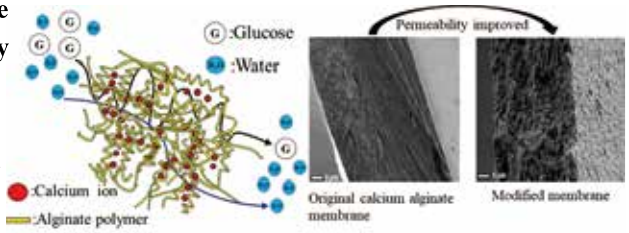
Keita Kashima,[1]* Kota Teshima[1], Masahide Hagiri[2], Masanao Imai[3]
[1] Dept. of Materials Chemistry and Bioengineering, NIT Oyama
[2] Dept. of Applied Chemistry and Biochemistry, NIT Fukushima
[3] Graduate School of Bioresource Sciences, Nihon University



1P-72

Molecular Separation of Sugars via Calcium Alginate Membrane with Polysaccharide Network Precisely Controlled Polymeric Structure

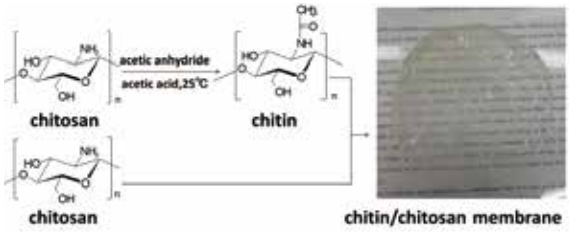
Kaito Yosida[1*], Keita Kashima[1], Masanao Imai[2]
[1]Dept. of Materials Chemistry and Bioengineering, NIT, Oyama
[2]Graduate School of Bioresource Sciences, Nihon University



1P-73

Preparation and Characterization of Biocompatible Chitin/Chitosan Membrane Prepared through an Acetylation Process of Glucosamine Units

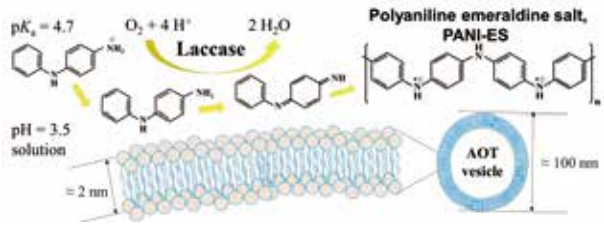
Haruki Koya*[1], Keita Kashima [1], Masanao Imai [2]
[1] Dept. of Materials Chemistry and Bioengineering, NIT Oyama
[2] Graduate School of Bioresource Sciences, Nihon Univ.



1P-74

Effect of Monomer Composition on the Laccase/O_2-Catalyzed Oxidation of Aniline and *p*-Aminodiphenylamine in the Presence of Anionic Vesicles

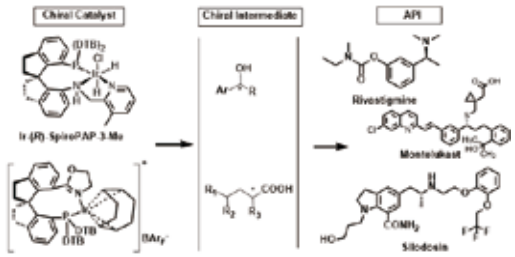
Tomoyuki Fujisaki[1]*, Keita Kashima[1], Peter Walde[2]
Dept. of Materials Chemistry and Bioengineering, NIT, Oyama
Dept. of Materials, ETH Zurich



1P-75

Application of Highly Efficient Chiral Spiro Catalysts In the Synthesis of Key Chiral Intermediates of APIs

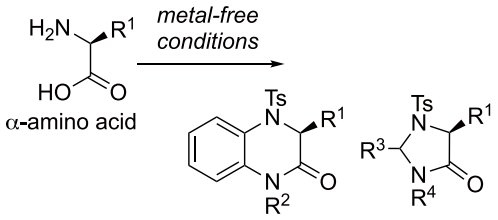
Yuanqiang Li*, Guoliang Zhu, Pucha Yan
R&D, CDMO unit, Zhejiang Raybow Pharmaceutical Co. Ltd., Taizhou, China



1P-76

Metal-Free Asymmetric Synthesis of Dihydroquinoxalinones and 4-Imidazolidinones from α -Amino Acid Precursors via Dehydrogenative N-H/C-H Coupling

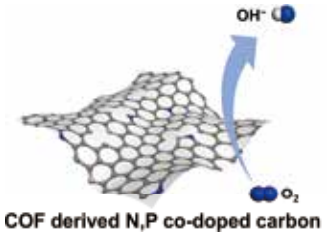
K. S. Kanyiva,* M. Horiuchi, M. Tane, T. Shibata
Advanced School of Sci. and Eng., Waseda University



1P-77

COF Derived N,P Co-Doped Carbon as a Metal-Free Catalyst for Highly Efficient Oxygen Reduction Reaction

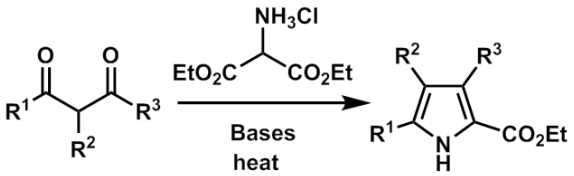
Chao Yang,* Shinya Maenosono
Japan Advanced Institute of Science and Technology



1P-78

Preparation of 1,3-Substituted Pyrroles under Basic Conditions

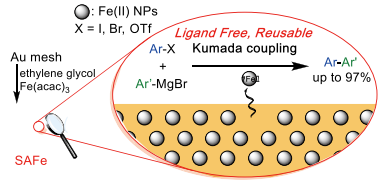
Kwesi Prah Thomford*, Zheyang Zhou, Yasunori Kama, Keita Kimura, Toshihide Maki
Graduate School of Biomedical Sciences, Nagasaki University.



Poster Presentation
July 26 (Fri)

2P-01

Ligand-Free Kumada Coupling Catalyzed by Iron(II) Nanoparticle



Yuki Wada,*[a] Toshiki Akiyama,[a] Tetsuo Honma,[b] Yusuke Tamenori,[b] Hiromichi Fujioka,[a] Yoshihiro Sato,[c] Mitsuhiro Arisawa[a]

[a]Graduate School of Pharmaceutical Sciences, Osaka University

[b]Japan Synchrotron Radiation Research Institute

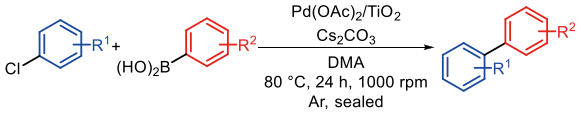
[c]Faculty of Pharmaceutical Sciences, Hokkaido University

2P-02

Heterogeneous palladium on titania-catalyzed ligand-free Suzuki–Miyaura coupling of aryl chlorides

Hayato Masuda[1]*, Tsuyoshi Yamada[1], Kwihwan Park[1], Takumu Tachikawa[1], Tomohiro Ichikawa[1], Masatoshi Yoshimura[2], Yukio Takagi[2], Yoshinari Sawama[1], and Hironao Sajiki[1]

[1]Gifu Pharmaceutical University, Japan, [2]Catalysts Development Center, N.E.Chemcat Corporation, Japan

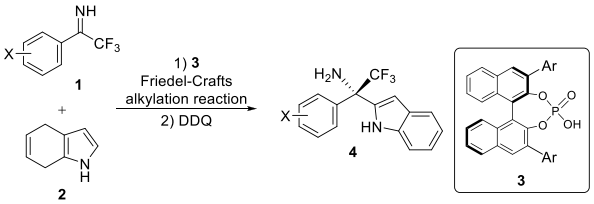


2P-03

Enantioselective Friedel-Crafts Alkylation Reaction of 4,7-Dihydroindole to Trifluoromethylated N-H Ketimines by Means of Chiral Phosphoric Acid

Riku Suzuki*, Masaru Yoshida, Masamichi Miyagawa, Takahiko Akiyama

Department of Chemistry, Faculty of Science, Gakushuin University

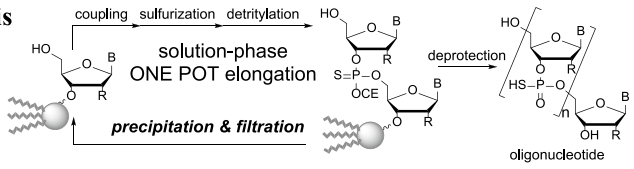


2P-04

AJIPHASE®: Practical Oligonucleotide Synthesis Achieved by Solution Phase Approach

Taisuke Ichimaru*, Kunihiro Hirai, Satoshi Inoue, Takuya Hamagaki, Takayuki Hamada, Daisuke Takahashi

AJINOMOTO Co., Inc.

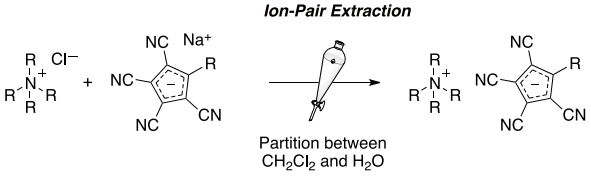


2P-05

Ion-Pair Extraction of Ammoniums Using Tetracyanocyclopentadienides

Miho Ito*, Naotaka Noda, Chisato Fujimoto, Takeo Sakai, Yuji Mori

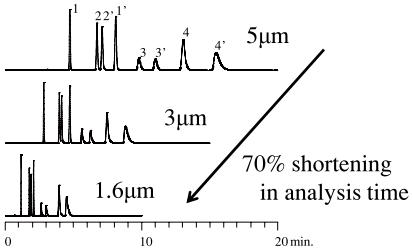
Faculty of Pharmacy, Meijo University



2P-06

Ultrafast enantiomeric separations using 1.6μm chiral column "CHIRALPAK U series"

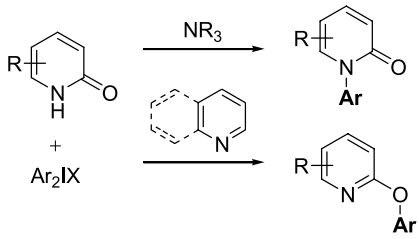
Daisuke Fukuda*, Takafumi Onishi, Ryota Hamasaki, Atsushi Ohnishi
Life Science Development Center, CPI Company, DAICEL Corporation



2P-07

Orthogonal selectivity controlled by organic bases in arylation for 2-pyridones with diaryliodonium salts

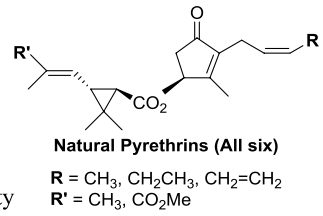
Yusuke Abe*, Natsumi Hanazawa, Shinpei Ono,
Masami Kuriyama, Kosuke Yamamoto, Osamu Onomura
Graduate School of Biomedical Sciences, Nagasaki University



2P-08

Total syntheses of all six chiral natural pyrethrins from available synthetic pyrethroids, directing for process chemistry: accurate determination of the physical properties and insecticidal activities

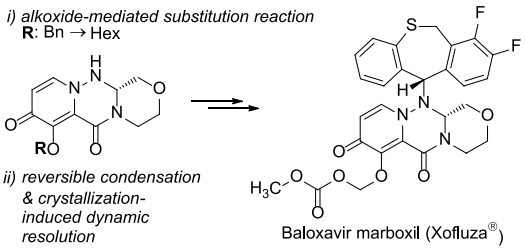
Momoyo Kawamoto*, Yuichiro Ashida, Noritada Matsuo, Yoo Tanabe
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University



2P-09

Process Development for Large-scale Synthesis of Baloxavir marboxil (Xofluza®)

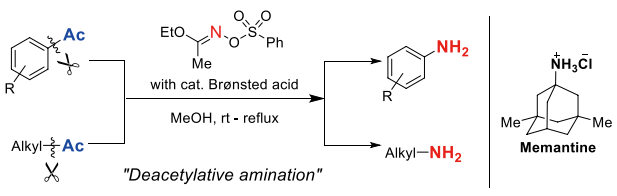
Nobuaki Fukui*, Setsuya Shibahara, Toshikatsu Maki, Tomohiro Fukuda, Kosuke Anan, Takayuki Tsuritani
API R&D Lab., CMC R&D Div., Shionogi & Co., Ltd.



2P-10

Deacetylative Amination of Acetyl Arenes and Alkanes under Transition-Metal-Free Conditions

Kengo Hyodo,[1,*] Genna Hasegawa,[2] Kingo Uchida[2]
[1]School of Science and Engineering, Kindai University
[2]Faculty of Science and Technology, Ryukoku University

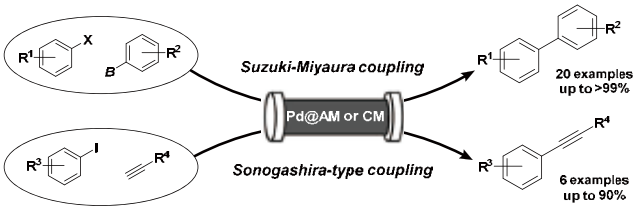


2P-11

Application of the Palladium-loaded Monolithic Ion Exchange Resin as the Immobilized Catalyst in Continuous Processing

Shinji Nakamura[1]*, Hitoshi Takada[1], Tsuyoshi Yamada[2], Yoshinari Sawama[2], Hironao Sajiki[2]

[1]Organo Co., [2]Gifu Pharmaceutical University

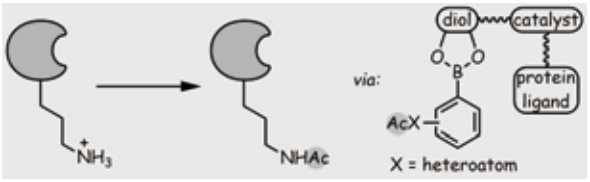


2P-12

Development of Boronic Ester-Mediated Ligand Directed Protein Acylation

Christopher Adamson,* Kenzo Yamatsugu, Motomu Kanai

Department of Pharmaceutical Sciences, University of Tokyo

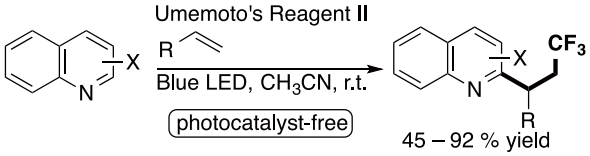


2P-13

C-H γγγ-Trifluoroalkylation of Quinolines via Visible-light-induced Sequential Radical Additions

Yuhei Kumagai,* Nanami Murakami, Futa Kamiyama, Ryo Tanaka, Tatsuhiko Yoshino, Masahiro Kojima, Shigeki Matsunaga

Faculty of Pharmaceutical Sciences, Hokkaido University

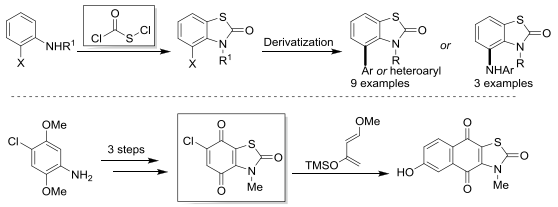


2P-14

Chlorocarbonysulfenyl chlorides: A unique bifunctional electrophilic reagent for the syntheses of heterocyclic compounds, directing for process chemistry

Masatoshi Kakuno*, Shotaro Izawa, Taichi Takemoto, Yoo Tanabe

Department of Chemistry, School of Science and Technology, Kwansei Gakuin University



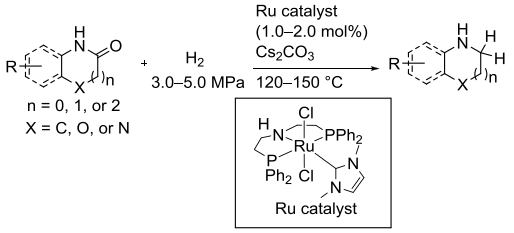
2P-15

The Catalytic Synthesis of Cyclic Amines from Lactams using Ru-MACHO Family

Osamu Ogata,[a]* Hideki Nara,[a] Kazuhiko Matsumura,[a] Yoshihito Kayaki[b]

[a]Takasago International Corporation

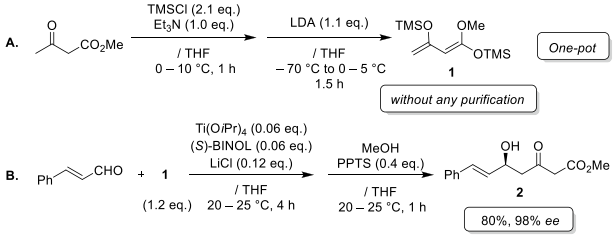
[b]Tokyo Institute of Technology



2P-16

Catalytic asymmetric Mukaiyama aldol addition using 1,3-bis(siloxy)diene promoted by a Ti(OiPr)$_4$ / (*S*)-BINOL catalyst, directed for process chemistry

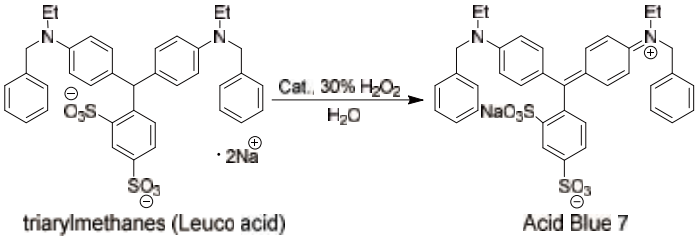
Takeshi Tsutsumi, Mizuki Moriyama*, Yoo Tanabe
Determent of Chemistry, School of Science and Technology, Kwansei Gakuin University



2P-17

Catalytic oxidation reaction for synthesis of triarylmethane blue dyes

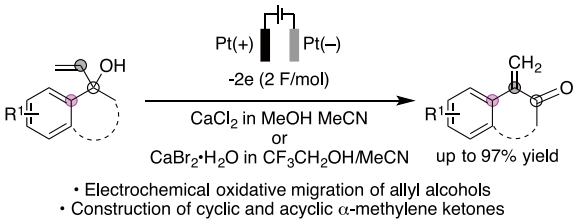
Tomoya Okada[1]*, Akihiro Nomoto[1], Yuki Yamamoto[1], Mika Yamamoto[1], Michio Ueshima[1], Akiya Ogawa[1], Tamotsu Nishigahana[2], Keiji Itoh[2], Gohei Kobata[2]
[1]Osaka Prefecture University
[2]Kobata Sangyo Co., Ltd.



2P-18

Synthesis of α -*exo*-Methylene Ketones from α,α-Disubstituted Allyl Alcohols by Electrochemical Oxidative Migration

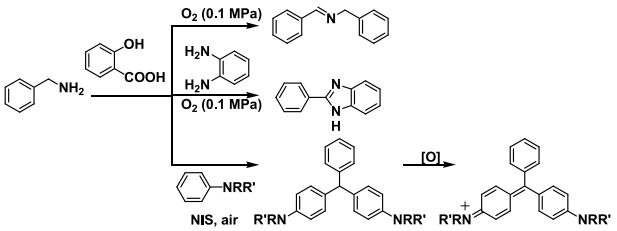
Kosuke Yamamoto*, Naoto Kikuchi, Tohru Hamamizu, Hirofumi Yoshimatsu, Masami Kuriyama, Yosuke Demizu, Osamu Onomura (Nagasaki University)



2P-19

Metal-free Oxidative Synthesis of Imine Derivatives Catalyzed by Salicylic Acid

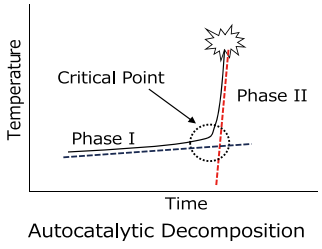
Akihiro Nomoto,* Chun Ping Dong, Shintaro Kodama, Michio Ueshima, Akiya Ogawa
Osaka Prefecture University



2P-20

Autocatalytic Decomposition of Dimethyl Sulfoxide (DMSO)

Yoshikuni Deguchi*, Masafumi Kono, Yuto Koizumi, Yu-ichiro Izato, Atsumi Miyake
Yokohama National University, 79-5 Tokiwadai, Hodogaya-ku, Yokohama 240-8501, Japan

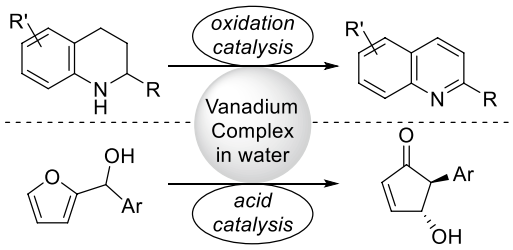


2P-21

Development of Vanadium-catalyzed Organic Reactions in Water

Makoto Sako,[1,*] Nadine Zumbrägel,[2] Tomohiro Takiishi,[1] Lukas Schober,[2] Harald Gröger,[2] Shinobu Takizawa,[1] Hiroaki Sasai[1]

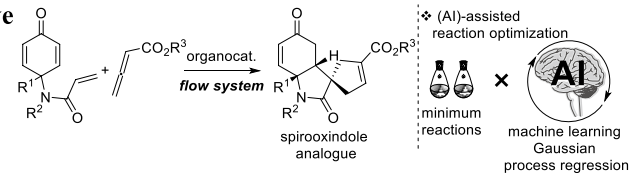
[1]ISIR, Osaka University [2]Bielefeld University, Germany



2P-22

AI-Assisted Optimization for Synthesis of Spirooxindole Analogues via Enantioselective Domino Reaction in Flow system

H. D. P. Wathsala, M. Kondo, M. Sako, Y. Hanatani, K. Ishikawa, S. Hara, T. Takaai, T. Washio, S. Takizawa, H. Sasai, ISIR, Osaka University

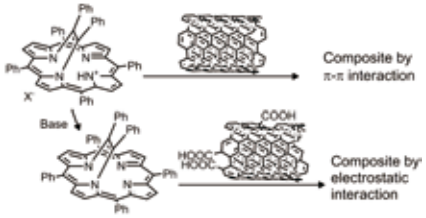


2P-23

Development of Composite Materials Comprised of Porphyrin Dyes and Nanocarbons : Effect of Preparation Methods

Yuko Takao*, Kazuyuki Moriwaki , Takumi Mizuno ,Toshinobu Ohno

Research Division of Organic Materials, Osaka Research Institute of Industrial Science and Technology

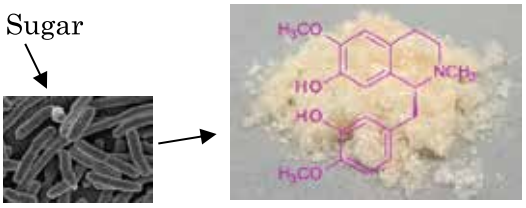


2P-24

Benzylisoquinoline alkaloids production by bacteria for drug discovery

Akira Nakagawa*, Hiromichi Minami

Research Institute for Bioresources and Biotechnology, Ishikawa Prefectural University

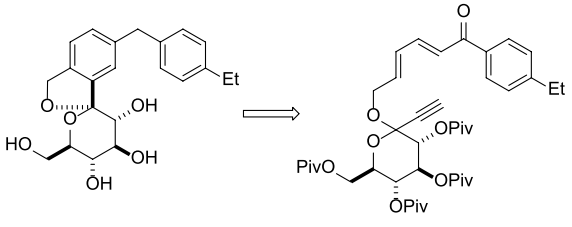


2P-25

Synthesis of tofogliflozin as an SGLT2 inhibitor *via* intramolecular cycloaddition

Masatoshi Murakata, Akira Kawase, Nobuaki Kimura, Takuma Ikeda, Masahiro Nagase, Masatoshi Koizumi, Kazuaki Kuwata, Kenji Maeda, Hitoshi Shimizu

API Process Development Department,
Chugai Pharmaceutical Co., Ltd.

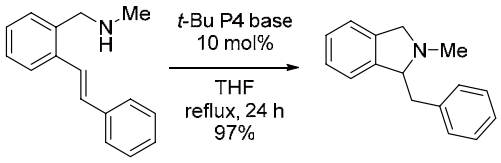


2P-26

Strong Base-Catalyzed Hydroamination of Aminoalkenes

Yasutomo Yamamoto*, Maki Terashita, Mio Yamanoue, Masako Yukawa, Akari Miyawaki, Kiyoshi Tomioka

Doshisha Women's College of Liberal Arts

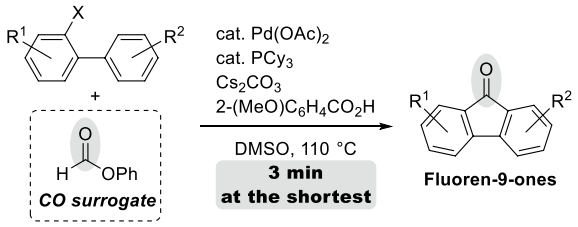


2P-27

Rapid and Practical Synthesis of Fluoren-9-ones Using a Carbon Monoxide Surrogate

Hideyuki Konishi,* Suguru Futamata, Xi Wang, Kei Manabe

School of Pharmaceutical Sciences, University of Shizuoka



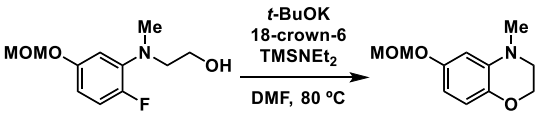
2P-28

Activation of Nucleophilic Aromatic Substitution Reaction by Using Silyl Amide Reagent

Takashi Shigeta[1]*, Shiho Suzuki[1], Nanomi Murata[2], Yuka Gonno[2], Minoru Ozeki[2], Ikuo Kawasaki[2], Masahiro Egi[1]

[1] School of Food and Nutritional Sciences, University of Shizuoka;

[2] Graduate School of Pharmaceutical Sciences, Mukogawa Women's University

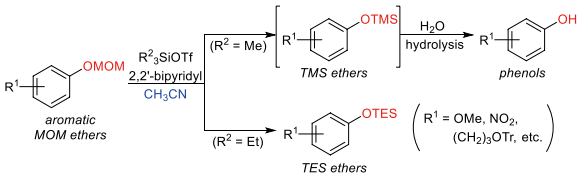


2P-29

Chemoselective Transformations of Aromatic Methoxymethyl Ethers Using Trialkylsilyl Triflate and 2,2'-Bipyridyl

Mizushi Yanagihara*, Reiya Ohta, Kenichi Murai, Mitsuhiro Arisawa, and Hiromichi Fujioka

Graduate School of Pharmaceutical Sciences, Osaka University

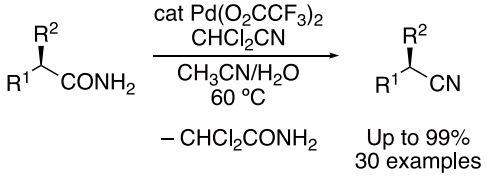


2P-30

Acceptor-controlled Transfer Dehydration of Amides to Nitriles

Asuka Naraoka,* Hiroyuki Okabe, Takahiro Isogawa, Shunsuke Oishi, Hiroshi Naka

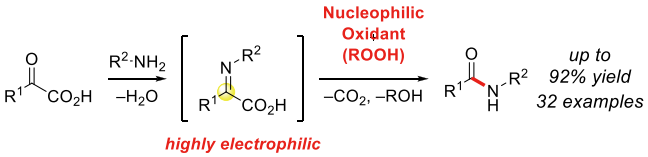
Grad. Sch. Sci.; WPI-ITbM; RCMS, Nagoya University



2P-31

Hydroperoxide-Mediated Chemoselective, Decarboxylative Acylation of Amine.

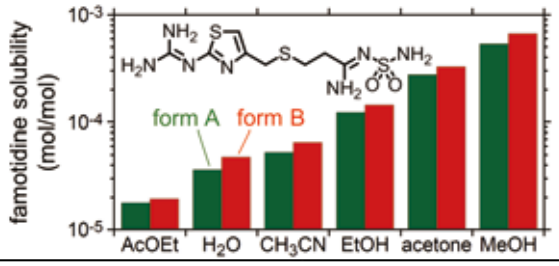
Takeshi Nanjo, Natsuki Kato,* Xuan Zhang, Yoshiji Takemoto
Graduate School of Pharmaceutical Sciences, Kyoto University,



2P-32

Polymorphic Solubility Ratio of Pharmaceutical Drugs in Various Solvents

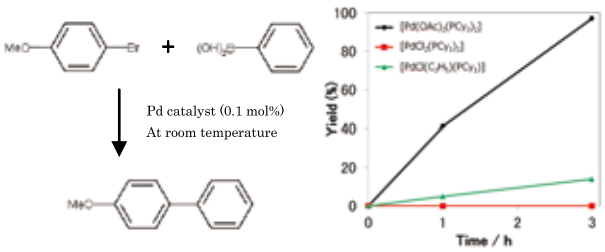
Yoshihiro Takebayashi,* Kiwamu Sue, Takeshi Furuya, Satoshi Yoda
Research Institute for Chemical Process Technology, AIST



2P-33

Development of Palladium Phosphine Complexes for the Practical Cross-Coupling Reactions

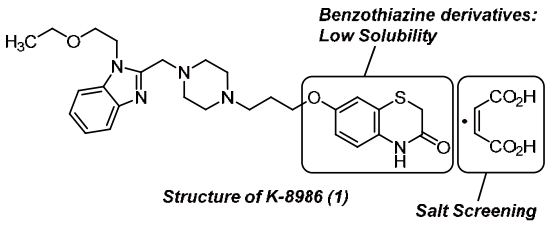
Yosuke Imanaka,* Shinji Ueno
Chemical Catalysts R&D Dept., Catalysts Development Center, N.E.Chemcat Corporation



2P-34

Development of a Synthetic Process for K-8986, an H1-receptor Antagonist

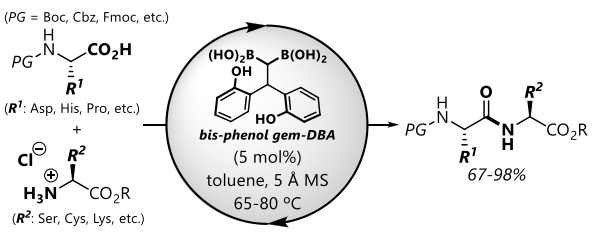
Tomoaki Fukuda[1,2]*, Takeaki Hara[1], Shinji Ina[1], Tetsuhiro Nemoto[2], and Takeshi Oshima[1]
[1]Kowa Co., LTD., [2]Chiba University



2P-35

Development of *gem*-Diboronic Acids as Dehydrative Peptide Synthesis Catalysts

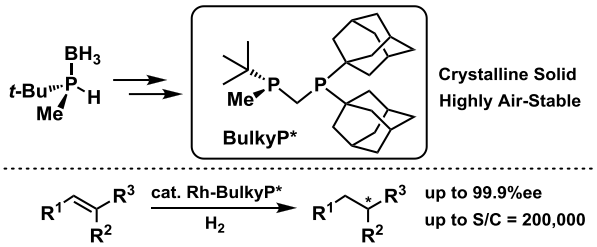
Kenichi Michigami*, Tatsuhiko Sakaguchi, Yoshiji Takemoto (Graduate School of Pharmaceutical Sciences, Kyoto University)



2P-36

A Bulky P-Chiral Phosphine Ligand (BulkyP*): Synthesis and Application in Rh-Catalyzed Asymmetric Hydrogenation

Yuuki Sawatsugawa,* Ken Tamura, Natsuhiro Sano, Tsuneo Imamoto
Nippon Chemical Industrial Co., Ltd.



2P-37

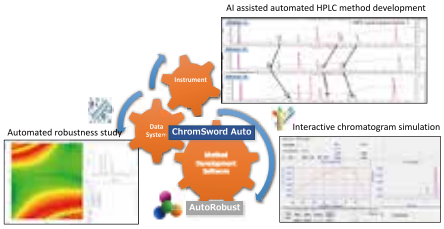
Gas-Liquid Flow Synthesis Using Monolithic Catalysts

Yusuke Saito [a,*], Tomohito Mizukami [a], Yushi Nakamura [b], Nobuyuki Mase [b]
[a] Cataler Corporation, [b] Shizuoka University

2P-38

Quality by Design (QbD) Approach by Automated Robustness Study to Develop the Design Space

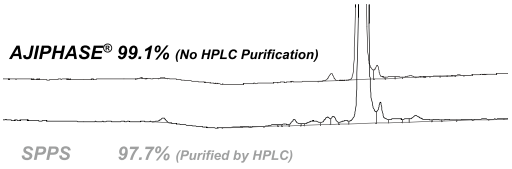
Kazuhide Konishi* Sergey Galushko
ChromSword Japan Co., Ltd.



2P-39

High Quality Peptide APIs from Sophisticated One-Pot Peptide Synthesis AJIPHASE®

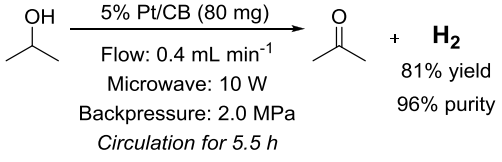
Tatsuji Inomata,* Takayoshi Torii, Shin Muronoi, Ryotaro Nakaya, Daisuke Takahashi
Research Institute for Bioscience Products and Fine Chemicals
AJINOMOTO CO., INC.



2P-40

Platinum on Carbon Bead-Catalyzed Continuous-Flow Dehydrogenation of 2-Propanol under Microwave-Irradiation

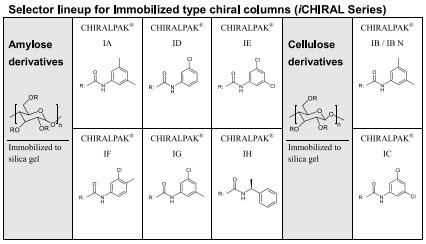
Tomohiro Ichikawa[1], Takumu Tachikawa*[1], Tomohiro Matsuo[1], Wataru Teranishi[1], Tsuyoshi Yamada[1], Yoshinari Sawama[1], Yasunari Monguchi[2], Hironao Sajiki[1].
[1]Laboratory of Organic Chemistry, Gifu Pharmaceutical University
[2]Laboratory of Organic Chemistry, Daiichi university of Pharmacy



2P-41

Characterization of chiral column by analyzed of column screening result

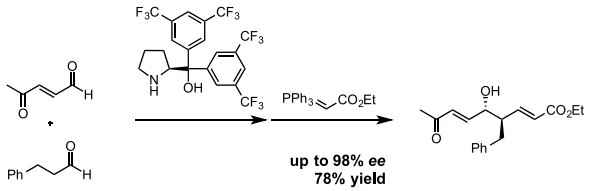
Takunori Ueda*, Masahiro Miyamoto, Ryota Hamasaki, Atsushi Ohnishi
Life Science Development center, CPI Company, DAICEL Corporation



2P-42

Asymmetric cross-aldol reaction of aldehydes via organocatalyst

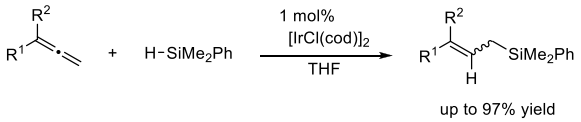
Yujiro Hayashi,* Kaito Nagai
Department of Chemistry, Graduate School of Science
Tohoku University



2P-43

Atomeconomical Approach to Allylsilanes through Iridium-Catalyzed Hydrosilylation of Allenes

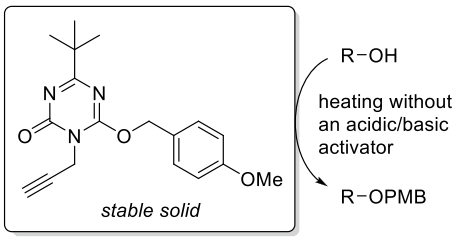
Ichino Takeuchi,* Shoko Samoto, Yasuyuki Ura, Yasutaka Kataoka
Faculty of Science, Nara Women's University



2P-44

Stable Triazinone-Based Reagent for *O*-*p*-Methoxybenzylation under Mild Heating Conditions

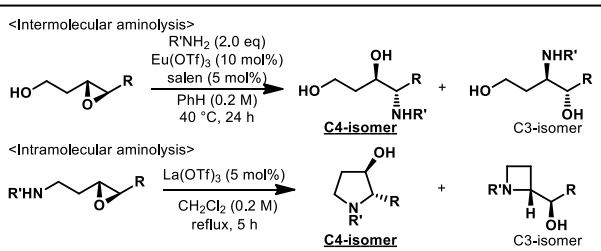
Hikaru Fujita*,[1] Hiromitsu Terasaki,[1] Satoshi Kakuyama,[1] Kazuhito Hioki,[2] and Munetaka Kunishima[1]
[1]Faculty of Pharmaceutical Sciences Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University
[2]Faculty of Pharmaceutical Sciences, Kobe Gakuin University



2P-45

Catalytic Regioselective Ring Opening of Epoxides by Unprotected Amines

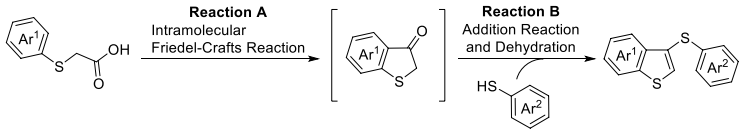
Yuse Kuriyama,* Yusuke Sasano, Shogo Matsui, Akihito Noguchi, Yoshihiko Hoshino, Shun-ichiro Uesugi, Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University



2P-46

Transition Metal-Free One-pot Synthesis of 3-Benzo[*b*]thienyl Thioethers via Benzo[*b*]thiophenone

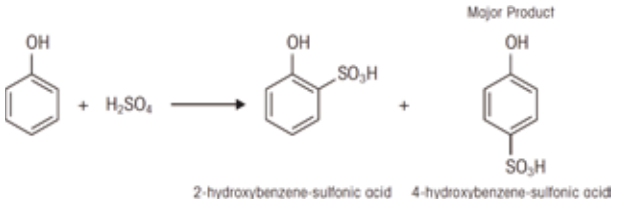
Nanae Habara*, Koichi Mitsudo, Seiji Suga
Graduate School of Natural Science and Technology, Okayama University



2P-47

Risks from Rising Temperature

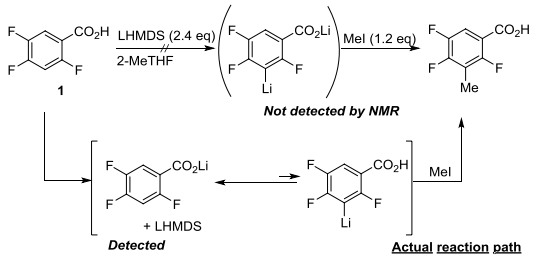
Yoshifumi Fujisawa*, Urs Groth, Fabio Visentin
AutoChem team, BU LAB Instruments,
Mettler-Toledo K.K.



2P-48

Mechanistic Analysis in Lithiation-Methylation Reaction of Trifluorobenzoic Acid

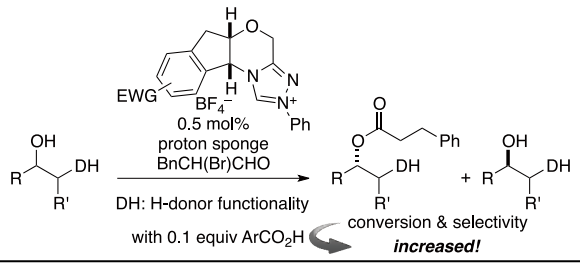
Yuya Orito*, Guy C. Lloyd-Jones
Process Thechnology Research Laboratories,
Daiichi-Sankyo Co., Ltd., and
School of Chemistry, The University of Edinburgh



2P-49

The Enhanced Enantio-recognition of Chiral Acyl-azolium in Kinetic Resolution of Chiral Secondary Alcohol by Carboxylate Additive

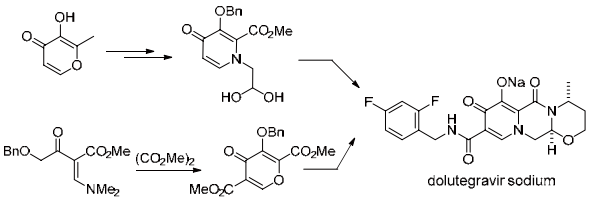
Ken-ichi Yamada*, Yinli Wang, Satoru Kuwano,
Tsubasa Inokuma, Yousuke Yamaoka, Kiyosei Takasu
Tokushima University



2P-50

Synthetic Route Scouting and Process Development of Dolutegravir Sodium

Tatsuro Yasukata,* Yasunori Aoyama
API R&D Lab., CMC R&D Div., Shionogi & Co., Ltd.



2P-51

Modernize Synthesis

Naomi Fukuda*

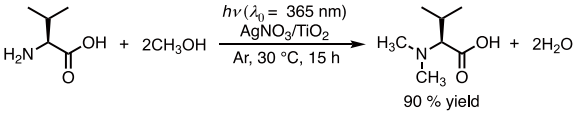
AutoChem Team, BU LAB Instruments, Mettler Toledo K.K.

2P-52

Photocatalytic N-Methylation of Amino Acids with Methanol

Ivven Huang,* Yuna Morioka, Susumu Saito, Hiroshi Naka

Grad. Sch. Sci. and RCMS, Nagoya University

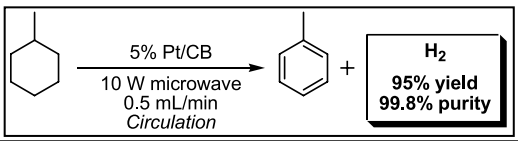


2P-53

Platinum on carbon-bead-catalyzed energetically efficient, continuous hydrogen production method from methylcyclohexane enhanced by the microwave irradiation

Tomohiro Ichikawa,*[a] Tomohiro Matsuo,[a] Takumu Tachikawa,[a] Tsuyoshi Yamada,[a] Takeo Yoshimura,[b] Masatoshi Yoshimura,[c] Yukio Takgai,[c] Yoshinari Sawama,[a] Jun-ichi Sugiyama,[d] Yasunari Monguchi,[a,e] Hironao Sajiki[a]

[a] Laboratory of Organic Chemistry, Gifu Pharmaceutical University
[b] SAIDA FDS Incorporated
[c] Catalyst Development, N.E. Chemcat Corporation, Japan
[d] National Institute of Advanced Industrial Science and Technology,
[e] Laboratory of Organic Chemistry, Daiichi University of Pharmacy



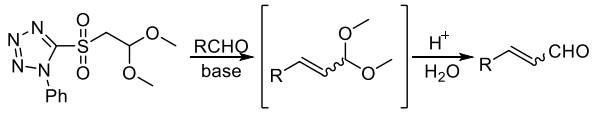
2P-54

One-pot preparation of α,β-unsaturated aldehydes by Julia-Kocienski reaction and hydrolysis

Haruka Watanabe,* Zhu Xiaoxian, and Kaori Ando

Department of Chemistry and Biomolecular Science,

Faculty of Engineering, Gifu University

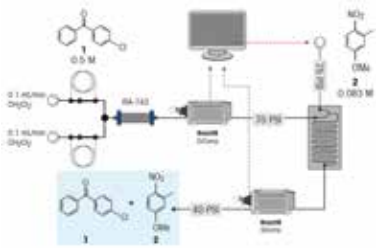


2P-55

Enhanced Development and Control of Continuous Processes Using Real-Time In Situ FTIR – What's Happening in Your Flow Chemistry?

Yuki Hara*, Brian Wittkamp

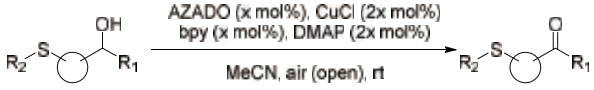
LAB Instruments Business Unit, Mettler-Toledo



2P-56

Expansion of Substrate Scope of Nitroxyl Radical/Copper-Catalyzed Aerobic Alcohol Oxidation

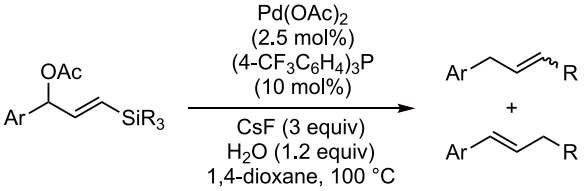
Yusuke Sasano, Ryota Sasaki*, Koki Kasabata, Naoki Kogure, Shota Nagasawa, and Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University



2P-57

Palladium-Catalyzed Reaction of Silyl-Substituted Allyl Acetates with Water Proceeding through 1,2-Shift of a Substituent on Silyl Group

Yoshikazu Horino, Mayo Ishibashi*, Kosuke Nakasai, Hitoshi Abe
Graduate School of Science and Engineering, University of Toyama



■ Approximate order of migratory aptitude:
C≡CPh > Ph > Me

2P-58

Scale-up Synthesis of Icatibant using Molecular Hiving Technology

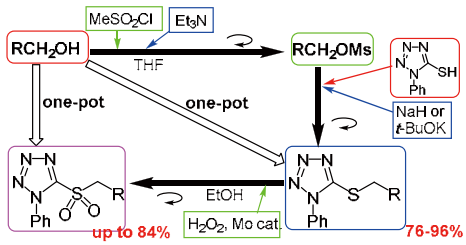
Daisuke Kubo*[1], Kazuaki Kanai[1], Rino Araki[1], Yu Ito[1], Natsumi Iwanaga[1], Kousuke Suzuki[1], Hideaki Suzuki[1], Ichiro Shima[1], Takashi Yamasaki[1], Yohei Okada[2], Hidehiro Kamiya[2], Kazuhiro Chiba[2]

[1]JITSUBO Co., Ltd., [2]Tokyo University of Agriculture and Technology

2P-59

One-pot Preparation of Julia-Kocienski Sulfides and Sulfones from Alcohols

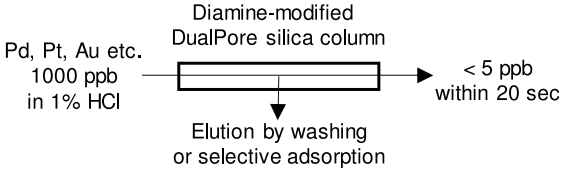
Kaori Ando,* Junichiro Hattori
Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University



2P-60

Rapid Removal and Release ability of DualPore Metal Scavenger in High Flow System

Riichi Miyamoto,* Hong-zhi Bai, Makoto Tsujisaka, and Yoshiki Sohrin
DPS Inc. & Kyoto University

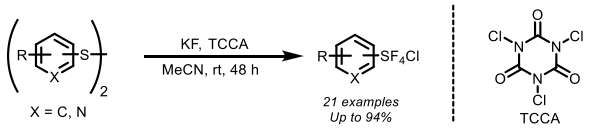


2P-61

Synthesis of Aryl and Heteroaryl Tetrafluoro-λ⁶-sulfanyl Chlorides

Kiyoteru Niina,[1]* Ibrayim Saidalimu,[1] Yumeng Liang,[1] Kazuhiro Tanagawa,[1] Norimichi Saito,[2] and Norio Shibata[1]

[1]Nagoya Institute of Technology [2]Ube Industries, Ltd.

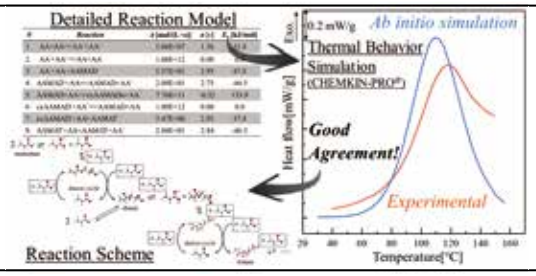


2P-62

Ab initio modeling for Michael addition reaction of acrylic acid

Michiya Fujita, Yu-ichiro Izato, Atsumi Miyake

Yokohama National University

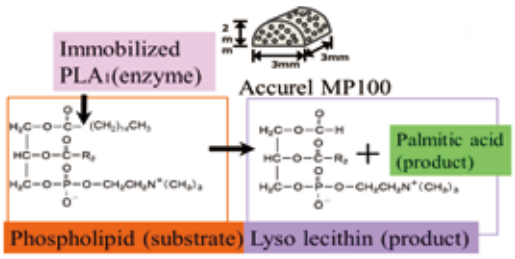


2P-63

Attractive reaction yield on hydrolysis of phospholipid by immobilized phospholipase A1 with hydrophobic porous carrier

Yusuke Hayakawa*[1] , Ryoichi Nakayama[2] , Norikazu Namiki[2], Masanao Imai[1]

[1] Nihon University,Japan [2] Kogakuin University,Japan

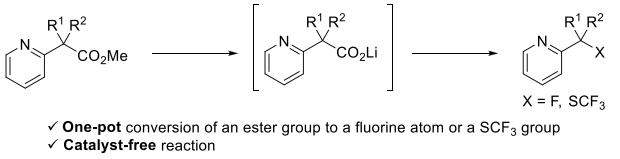


2P-64

Catalyst-free Decarboxylative Functionalization of Lithium Pyridylacetate

Ryouta Kawanishi,* Lacksany Phongphane, Kosuke Nakada, Seiji Iwasa, Kazutaka Shibatomi

Toyohashi University of Technology

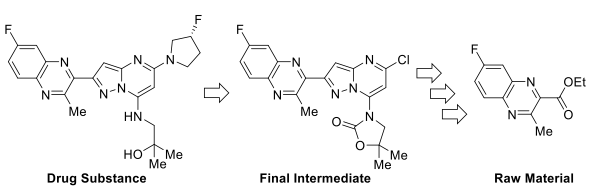


2P-65

Synthetic Strategy for Process Optimization of a PDE10A Inhibitor Consisting of Pyrazolopyrimidine and Quinoxaline as Key Units

Takafumi Yamagami*, Noriaki Moriyama, Eiji Toyofuku, Hideki Horiuchi, Shinichi Izumoto, Ryo Kobayashi

Mitsubishi Tanabe Pharma Corporation

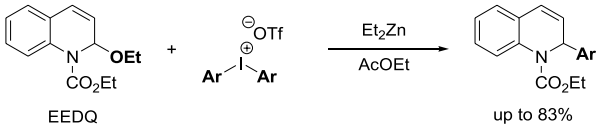


2P-66

Nucleophilic C2-arylation of quinolines using diaryliodonium salts

Tatsuya Sugiyama*, Kosuke Yamamoto, Masami Kuriyama, Osamu Onomura

Graduate School of Biomedical Sciences, Nagasaki University



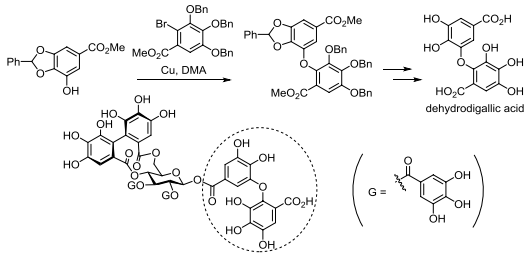
EEDQ up to 83%

2P-67

Preparation of Diaryl Ether Using Ullmann Reaction and Its Application to Ellagitannin Synthesis

Haruka Imai*, Kazuma Shioe, Yoshiyasu Kato, Daichi Ogura, Yoshikazu Horino, Hitoshi Abe

Graduate School of Innovative Life Science, University of Toyama



2P-68

Investigation of Purity Determination of Hygroscopic Compound using qNMR

Hiroo Sugawara*, Toru Miura and Yoshiaki Iwamoto

Functional Materials Research Laboratories, FUJIFILM Wako Pure Chemical Corporation.

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

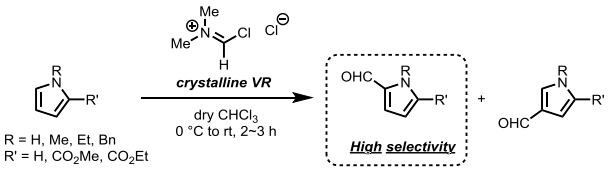
2P-69

Regioselective Formylation of Pyrrole Derivatives with Crystalline Vilsmeier reagent

Takuya Warashina*, Daisuke Matsuura, Yoshikazu Kimura

Research & Development department,

Iharanikkei Chemical Industry Co., Ltd..



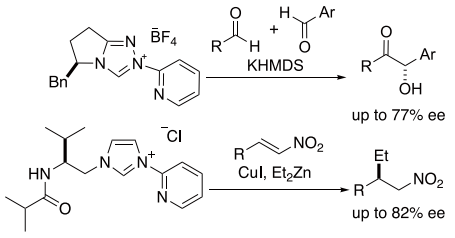
R = H, Me, Et, Bn
R' = H, CO_2Me, CO_2Et

2P-70

Development of multi-functional NHC catalysts bearing pyridine moiety: Application to catalytic asymmetric reactions

Takahiro Soeta*, Yuichi Hatanaka, So MIzuno, Yutaka Ukaji

Graduate School of Natural Science and Technology, Kanazawa University

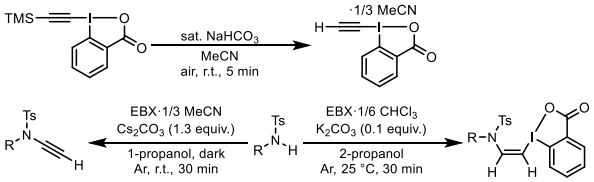


2P-71

Synthesis of Ethynyl Benziodoxolone (EBX)–Acetonitrile Complex and Reaction with Sulfonamide

Daisuke Shimbo*, Masaharu Yudasaka, Norihiro Tada, Eiji Yamaguchi, Akichika Itoh

Gifu Pharmaceutical University, Japan

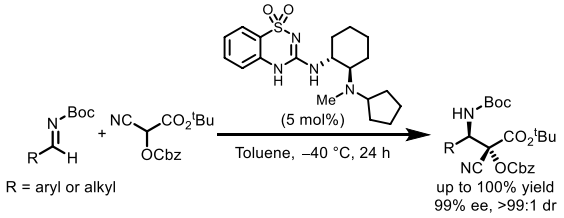


2P-72

Divergent and scalable synthesis of β-amino acid analogues by catalytic enantioselective addition of glyoxylate cyanohydrin to imines

Xuan Zhang, Yusuke Tokuhiro*, Takeshi Nanjo, Yoshiji Takemoto

Graduate School of Pharmaceutical Sciences, Kyoto University

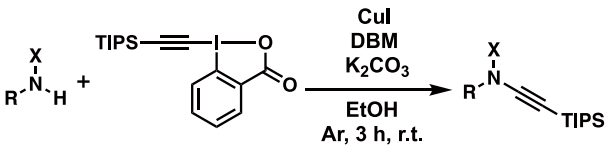


2P-73

Developmental Research of Ynamides Synthesis Method Using Copper Catalyst and Hypervalent Iodine Compounds

Ryogo Takai,* Norihiro Tada, Eiji Yamaguchi, Akichika Itoh

Gifu Pharmaceutical Univercity, Japan

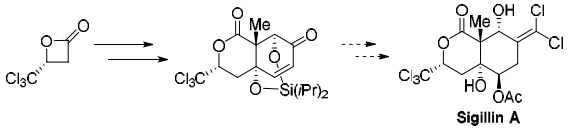


2P-74

Synthetic Study of Total Synthesis of Sigillin A

Yousuke Yamaoka,* Takamori Nakayama, Syota Kawai, Hiroshi Takikawa, Kiyosei Takasu

Kyoto University

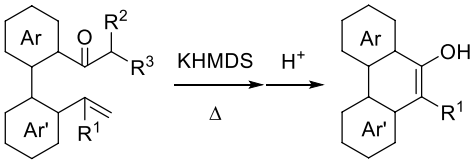


2P-75

KHMDS-Promoted Enolate–Olefin Metathesis

Kiyosei Takasu, Kazuma Sugimoto,* Shun Fujimura, Ken-ichi Yamada, Hiroshi Takikawa, Yousuke Yamaoka

Graduate School of Pharmaceutical Sciences, Kyoto University

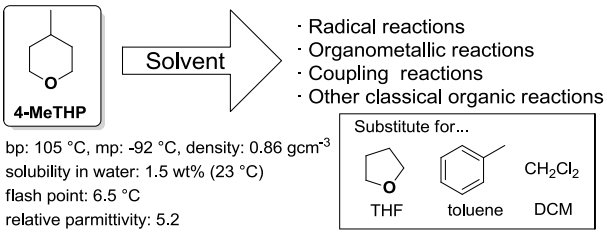


2P-76

Assessment of 4-Methyltetrahydropyran (4-MeTHP) as an Organic Reaction Solvent

Tomoki Tamura,* Takashi Kawakami, Saki Yoshimoto, Araki Masuyama, Shoji Kobayashi

Osaka Institute of Technology

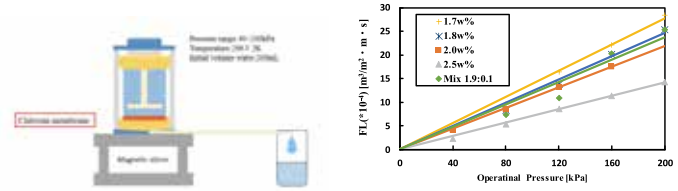


2P-77

Preparation of carboxymethyl cellulose, calcium alginate and chitosan membrane involved with mechanical strength

Tomohiro Nakata* Masanao Imai

Nihon University, Japan.



Abstracts

Plenary Lectures

PL-1 ~ PL-2

Keynote Lectures

K-1 ~ K-11

July 25 & 26

PL- 1 （Plenary Lecture）

Development and Applications of Selective Olefin Metathesis Catalysts

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Development and application of selective olefin metathesis catalysts will be discussed.

PL- 2 （Plenary Lecture）

Synthetic Strategies Based on Continuous-flow Methods

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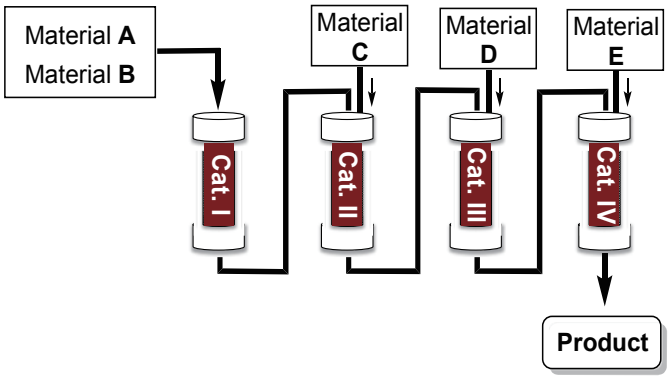
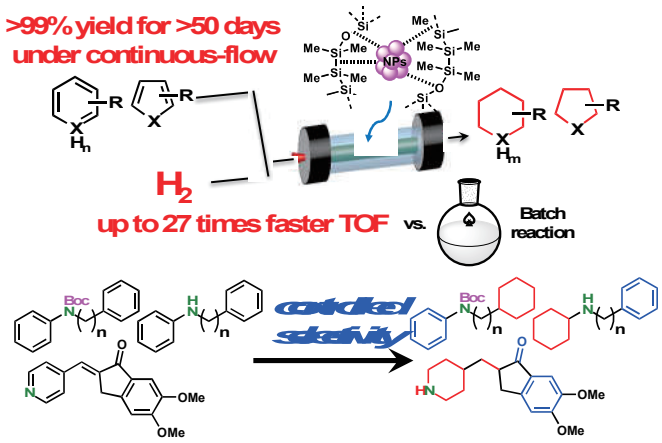
As a synthetic method, flow processes have several advantages over batch in terms of environmental compatibility, efficiency, and safety. Wastes derived from work-up processes can be minimized or omitted altogether by performing organic transformations in flow. Equipments for chemical manufacturing can be designed to be smaller, which would enable significant savings in space and costs. In addition, the differences between batch and flow reactors, which are the large surface to volume ratios and the rapid mixing/quenching of reagents, should make chemical productions safer and more efficient. While continuous-flow practices have been adopted in the petrochemical and bulk chemical industries, its application in fine chemical production is limited. It was believed that synthesis by flow methods could be applicable for the production of simple gasses such as ammonia, but was difficult to apply to the preparation of complex molecules such as active pharmaceutical ingredients (APIs). This lecture will discuss recent advances in organic synthesis enabled by continuous-flow methods. In particular, the development of heterogeneous catalysts in multi-step continuous-flow reactions (sequential-flow reactions) for the synthesis of complex organic molecules will be highlighted.

The ideal synthesis of fine chemicals is shown in the figure (below). In this sequential-flow synthesis, materials are successively flowed into columns with heterogeneous catalysts, which are connected accordingly based on synthetic strategies. Ideally, no separation and purification are conducted before the final stage.

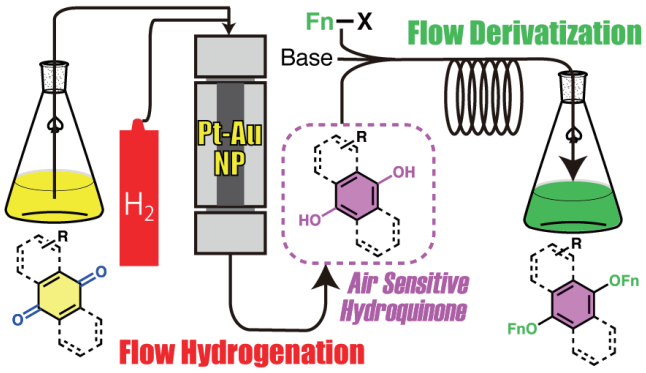


To attain this goal, we have been developing continuous flow atom-economical organic transformations, especially addition and condensation reactions, catalyzed by heterogeneous catalysts. An example is hydrogenation of arenes, which is an important reaction for the synthesis of

functional molecules such as APIs and other biologically active compounds. We have developed heterogeneous Rh-Pt bimetallic nanoparticle catalysts for the hydrogenation of arenes with inexpensive polysilane as support. The catalysts could be used in continuous-flow systems with high performance under mild conditions and showed wide substrate generality. The product could be obtained by simply passing the substrate and 1 atm H_2 through a column packed with the catalyst. Remarkably, much higher catalytic performance was observed in the flow system than in the batch system, and extremely strong durability under continuous-flow conditions was demonstrated (>50 days continuous run; turnover number $>10^6$).



Another example is selective hydrogenation of quinones to hydroquinones using Pt-Au bimetallic nanoparticle catalysts immobilized on dimethyl polysilane (Pt-Au/(DMPSi-Al_2O_3)). High reactivity, selectivity, and robustness of the catalysts were confirmed under continuous-flow conditions. Various direct derivatizations of quinones, such as methylation, acetylation, trifluoromethanesulfonylation, methacrylation and benzoylation were successfully performed under sequential continuous-flow conditions to afford the desired products in good to excellent yields. Especially, air-sensitive hydroquinones, such as anthrahydroquinones and naphthohydroquinones, could be successfully generated and derivatized under closed sequential continuous-flow conditions without decomposition.



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Nickel-Catalyzed Stereospecific Cross-Coupling and Cross-Electrophile Coupling Reactions

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Transition metal-catalyzed cross-coupling reactions have revolutionized the synthesis of natural products and medicinal agents and provided rapid synthetic access to a diverse range of molecules for biological testing. Important challenges remain, however, particularly in reactions that form C–C bonds between sp^3 hybridized carbons. We are developing methods for stereospecific alkyl-alkyl cross coupling and cross-electrophile coupling reactions, where transposition of stereochemical information from the electrophilic starting material to the product occurs. Stereospecific intramolecular reductive cross-electrophile coupling reactions for synthesis of *cis*- and *trans*-substituted cyclopropanes, as well as annulation reactions, will be described. Application of these methods in synthesis of known bioactive compounds and in discovery of compounds that exhibit selective anti-cancer activity will also be reported.

K- 2 （Keynote Lecture）

Innovations in Synthetic Chemistry at MSD: Striving for the Ideal Commercial Manufacturing Process

Kevin R. Campos*
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At MSD, we believe that innovation in synthetic chemistry is pivotal to our goal to invent, develop, and commercialize important new medicines “better and faster” than ever before. While there appears to have been a trend over the last decade toward viewing synthetic chemistry as a mature science, our experience and intent is completely opposite to this. At, MSD we see massive opportunity for innovation and impact in synthetic chemistry, and this is central to our mission in Process Research & Development: to launch every new product, regardless of molecular complexity, with the best conceivable chemistry, converting easily sourced commodity materials into the active pharmaceutical ingredient with a chemical synthesis that is lowest cost, easiest to run, safe, efficient, and environmentally sustainable. This presentation describes our strategy to achieve this goal, using a recent example from our labs.

K- 3 （Keynote Lecture）

Oncology drug discovery efforts in the Japanese pharmaceutical company (Eisai Co., Ltd.) and My next challenge

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1. Oncology drug discovery efforts in 1987 - 2002

Eisai entered the oncology research area in 1987 after the oen-year discussion at the special committee, and I was one of the initial 8 members of oncology research group. The recommendation of the special committee was that the oncology research should be initiated to perform the derivative research to improve the existing oncology drugs such as 5-FU, platinum and others, which were mainstream of oncology research at that time. The leader of the oncology research group did not follow the recommendation and set the goal “novel mechanism of action, novel structure, prominent in vivo anti-tumor activity” and “create good oncology drug which is believed to be used for our families”. The oncology research at Andover research site of US Eisai was also initiated and the both groups competitively performed the oncology research based on the strength of each group, and the technology and knowledges were exchanged.

Nine interesting development candidate molecules were created by Tsukuba and Andover group in 1987 - 2002 (the period before I left the front-line of oncology research due to the promotion) and seven molecules entered clinical trials, and two molecules (eribulin: halichondrin B analogue created in Andover and lenvatinib created in Tsukuba: 4-[3-chloro-4-(cyclopropylcarbamoylamino)phenoxy]-7-methoxy-quinoline-6-carboxamide) were successfully launched and seven molecules were discontinued during the pre-clinical and clinical development. Anti-mitotic sulfonamide (the 1st created molecule, (N-(2-((4-hydroxyphenyl)amino)- 3-pyridinyl)-4-methoxybenzenesulfonamide, E7010), G1 phase-targeting sulfonamide (N-(3-chloro-7-indolyl)-1,4-benzenedisulfonamide, E7070), carbazole-type topoisomerase II inhibitor ([12,13-dihydro-5-[2-(dimethylamino)ethyl] -4H-benzo[*c*]pyrimido[5,6,1-jk]carbazole-4,6,10(5H,11H)- trione hydrochloride], ER-37328), peptide mimetic farnesyltransferase inhibitor for ras protein (ER-51785), sulfonamide angiogenesis inhibitor (*N*-(3-Cyano-4-methyl-1*H*-indol-7-yl)-3-cyanobenzene-sulfonamide, E78720), splicing modulator pladienolide B analog from fermentation (semi-synthetic pladienolide analog, E7107), an analogue of the sponge-derived anti-microtubule tripeptide hemiasterlin (E7974). ER-51785 was jointly created by Andover and Tsukuba. Lenvatinib, E7010, E7070, ER-37328, T7820 and E7107 were created at Tsukuba. Eribulin and E7974 were created at Andover.

Success rate was approx. 20% after the selection of development candidate and approx. 28% after clinical introduction (higher than industry average: 9.6%).

2. Utilization of knowledge and technology accumulated though the past efforts

The target molecule of E7107 was identified as splicing factor SF3B1 during the pre-clinical development.

However, the relationship between SF3B1essential for eukaryote RNA splicing and cancer specificity of splicing modulator E7107 was unclear, though E7107 killed cancer cells preferentially compared with normal cells. The mutation of SF3B1 was recently reported in hematological malignancies and new molecule (H3-8800, orally active pladienolide derivative) targeting SF3B1 has been developed at H3 Biomedicine (Eisai subsidiary company in US) and in clinical development.

The target molecules of E7070 and E7820 had not been identified for long time despite great efforts. The anti-tumor profile of both sulfonamide compounds showed some similarity, and the overlap of target molecules were suggested. Very recently it was found that both compounds inhibited tumor growth by promoting the degradation of splicing factors via DCAF15 E3 ligase. These results have been utilized to initiate the creation of new molecules effective against high DAF15 expression hematological malignancies.

Liposomal formulation of eribulin was created by utilizing liposomal formulation technology and knowledge, and is expected to show better efficacy by EPR (enhanced permeability and retention) effect in tumor tissue. It is reported that preliminary evidence of clinical activity in solid tumors was observed.

Eribulin has been proved its efficacy and safety in clinic. Its highly potent cytotoxicity and water-soluble physicochemical property led to the application of eribulin to payload of antibody drug conjugate. MORAb-202 (farletuzumab-[Mal-PEG2-Val-Cit-PAB-eribulin]) was created though the combination between Andover-originated eribulin and Morphotek (Eisai subsidiary company in US)-originated farletuzumab. MORAb-202 entered Phase 1 trial and the result will be reported at this ASCO in June.

The MOA studies to understand the unique survival benefit of eribulin in Phase 3 clinical trials showed the effect of improvement of tumor microenvironment by eribulin. Eisai research team decided to create more complexed molecule, the entire structure of halichondrins (eribulin is right hand of halichondrin B). E7130 was created as the next generation of eribulin and in clinical development.

Finally, I would like to tell you that the combination with immune checkpoint inhibitor, anti-PD-1 Ab, greatly enhanced the clinical usefulness and commercial value of lenvatinib, but no one knew those opportunity when the discovery research was initiated the drug discovery research of lenvatinib.

Even the successful molecules had been encountered the difficulty for the continuation of the development, and more importantly the experiences of development failure could be utilized for the next molecules.

3. My next challenge

I left Eisai in 2018 after 40 years R&D works and joined the small bio-venture company developing antibody drug candidates in oncology. The business environment of the small bio-ventures in Japan is not easy in terms of fund raising and collaboration/partnering with domestic and global pharmaceutical companies. The dairy work, however, is exciting and challenging for me with less bureaucratic work. Two novel antibody (Ab) molecules, naked Ab and Ab-drug conjugate (ADC), are in pre-clinical development. Anti-TMEM-180 Ab has been developed against TMEM-180 overexpressed colorectal cancer and other cancers. Anti-insoluble fibrin-ADC has been developed against anti-insoluble fibrin produced by the destruction of tumor vasculature by tumor invasion in tumor stroma. I hope that my experiences in my past drug discovery and development will be utilized to create more effective and safer drugs.

K- 4 （Keynote Lecture）

Simplifying chemistry through targeted route design: snippets of early stage process innovation for newly approved anti-cancer drugs

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Bringing an active pharmaceutical ingredient to market as a generic drug involves neither just copying nor mere demonstration of the innovator's route of synthesis. Innovation in chemical process development plays a pivotal role in the development of any generic API and offers a strategic vantage point to any pharmaceutical company in its efforts to carve out a niche for itself in ever challenging generic drug market. It is however important to recognize that on the wide and holistic canvas of a generic API development, an innovative and sustainable chemical process is rarely the one that requires a global re-structuring of the known synthetic route or a brute force inclusion of an exotic chemical transformation. Indeed, an efficient synthetic route to an API evolves through a continuous process of incremental improvement and gradual simplification of the existing chemical processes to the API and related intermediates. It is this paradigm that has always formed the basis for our ideation and proof-of-concept demonstration of novel synthetic routes to even complex APIs.[1]

Our route selection process places emphasis on satisfying seven key concepts: (i) the need for the route to be convergent, (ii) having as many chemo-/biocatalytic steps in the reaction sequence as possible, (iii) an overall reduction in the number of steps as compared to the existing synthetic routes to the API, (iv) ensuring that the chemical transformations envisaged are robust and scalable, (v) making a conscious effort to avoid using reagents, solvents and reaction conditions that are known to be hazardous, (vi) patentability and (vii) adherence to the twelve principles of green chemistry in general.[2] The manner in which these criteria have helped us to develop novel multi-gram syntheses of various drug candidates, APIs and advanced API intermediates will be illustrated through specific case studies on the synthesis of such newly approved anti-cancer drugs as Ceritinib[3], Idelalisib[4] and Ruxolitinib[5].

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K-５（Keynote Lecture）

The Importance of Process Chemistry

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Process chemistry is not often recognized as a field of its own, even though it is central to the pharmaceutical and agrochemical industry.

Process chemistry is turning the promises of drug treatments and availability of food into a reality and Process Chemistry is thus undoubtedly critically important for the benefit of society. It functions in the context of many different scientific fields, from organic synthesis to catalysis and biocatalysis to synthetic biology and makes use of any technology and engineering tool available to achieve its goal of safe, environmentally benign synthesis of valuable organic compounds, such as lifesaving medicines.

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K- 6 （Keynote Lecture）

Contribution from Pharmaceutical Process Chemistry to Green Chemistry and Molecular Diversity

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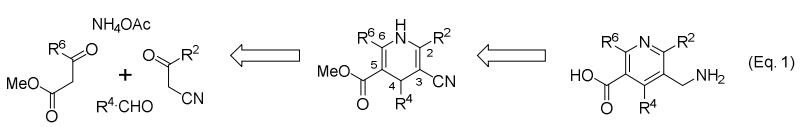
The objective of pharmaceutical process chemistry is to support preclinical, clinical R&Ds and commercial manufacturing by developing an efficient chemical process for a drug candidate. The expectation for synthetic process to be developed is quality assurance, robustness, convenience & safety, cost-effectiveness, and environmental friendliness. To establish such an ideal chemical process, pharmaceutical process chemists need to focus on one selected drug candidate and consider its distinctive chemical structure which is a key to solve process chemistry challenges.

As the green chemistry aspect, process chemistry efforts include reduction of waste materials by step/atom economy manner, pursuing selective reactions to avoid by-products, and utilization of safe/environmentally friendly reactions. In addition, an efficient synthetic method by process chemists contributes to molecular diversity which is a platform to effectively find new multiple chemical compounds. In this lecture, two selected examples on pharmaceutical process chemistry with the both aspects will be discussed.[1,2]

In the first topic, process chemistry on an antidiabetic drug candidate bearing a five-substituted pyridine core and a hydrophilic amino acid moiety will be presented.[1] The original medicinal synthesis required a stepwise construction to the dihydropyridine intermediate and a protective group for the amino group to isolate the saponified product with the carboxylic acid moiety. During the process chemistry efforts, an efficient synthetic route for the candidate has been developed, employing a multicomponent reaction (MCR) to the dihydropyridine intermediate and a direct saponification method to the amino acid moiety without a protective group (Eq. 1). The newly developed process contributed dramatically to step/atom economy, reducing the synthetic steps and waste materials. In addition, the MCR to the dihydropyridine has been extended to a versatile synthetic method for preparing various 3-cyanodihydropyridine derivatives bearing bulky substituents at the 2-position and relatively small substituents at the 6-position.

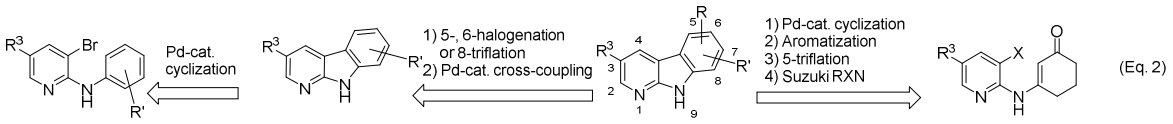


(Eq. 1)

As the second topic for contribution from process chemistry to green chemistry and molecular diversity, α-carboline-based drug candidates will be discussed.[2] α-carboline is a tricyclic heterocycle bearing pyridine and indole rings. This heterocyclic system is relatively uncommon in nature but a few of natural products have been identified, represented by Grossularine 1&2 as marine natural products with anticancer activities. In addition, the tricyclic system has been paid attention as a template to explore a kinase

inhibitor, especially for oncology area for the recent decade. Among various synthetic methods for the ring system, Graebe-Ullmann synthesis and an intramolecular S_NAr reaction using fluorine atom as the leaving group have been often employed as the conventional and medicinal chemistry syntheses. However, the former method required a high-temperature reaction to break the benzotriazole precursor and was suffered from a lack of regioselectivity for the cyclization. The later one involved a process chemistry challenge to use a complex and expensive starting material and included a drawback on atom economy regarding the functionalization of the ring system. In addition, the both methods had a limitation to effectively introduce multiple substituents into the benzene ring.

Under these circumstances, the presenter and the co-researchers have developed the following three new strategies; 1) a Pd-catalyzed direct C-H arylation method for the α-carboline from the *N*-aryl-2-amino-3-bromopyridine derived from 2-amino-3-bromopyridine, 2) a selective halogenation of the α-carbolines prepared by the direct C-H arylation, and a subsequent Pd-catalyzed cross-coupling reaction, 3) a Pd-catalyzed cyclization of the enamine intermediate derived from 2-amino-3-bromopyridine and 1,3-cyclohexanedione, followed by aromatization and Suzuki coupling reaction *via* the corresponding triflate (Eq. 2). By these methods, efficient synthetic sequences from commercially available starting materials to multiple drug candidates have been developed in order to support the corresponding development programs. Furthermore, the newly developed synthetic strategies have contributed to achieving the process chemistry goals (*e.g.* safety and atom-economy of the process, highly regioselective annulation/derivatization) as well as molecular diversity with various substituents on the benzene ring that had not been explored by the previous synthetic approaches.



(Eq. 2)

Acknowledgment

The topics to be presented were conducted as process R&D activities at Takeda Pharmaceutical Company. The presenter sincerely appreciates many collaborations with co-researchers in the company and Spera Pharma which is a spun-out company from Takeda.

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Peptide and Oligonucleotide Synthesis in Large Scale Using a Novel Solution-Phase Approach AJIPHASE®

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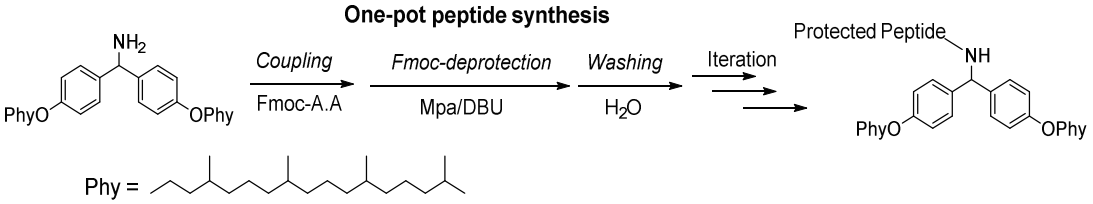
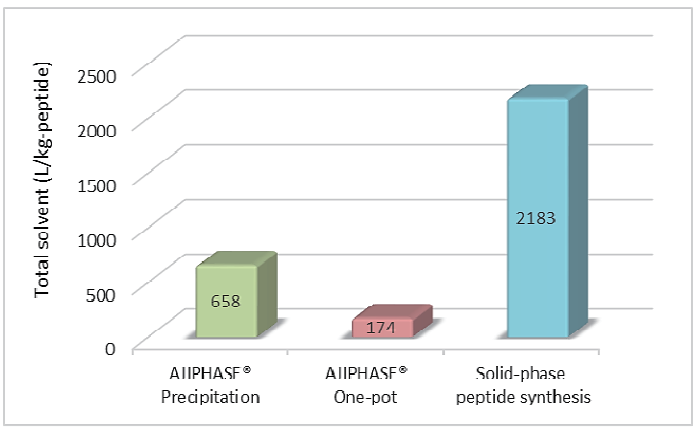
Recently, the number of peptide and oligonucleotide drugs in development has significantly increased in the world. Most of peptide and oligonucleotide are synthesized by solid-phase approach. However, more practical manufacturing method has been strongly required for the future development and demand. We have initially developed AJIPHASE® technology for peptide synthesis as a novel solution based method by using an anchor compounds having long aliphatic chains as a protecting group at the C-terminal of a peptide. This method retains the advantages of both solid-phase and liquid- phase peptide synthesis. The efficacy of AJIPHASE® has been demonstrated by the successful synthesis of various peptides in high yield and high purity even at large scale.

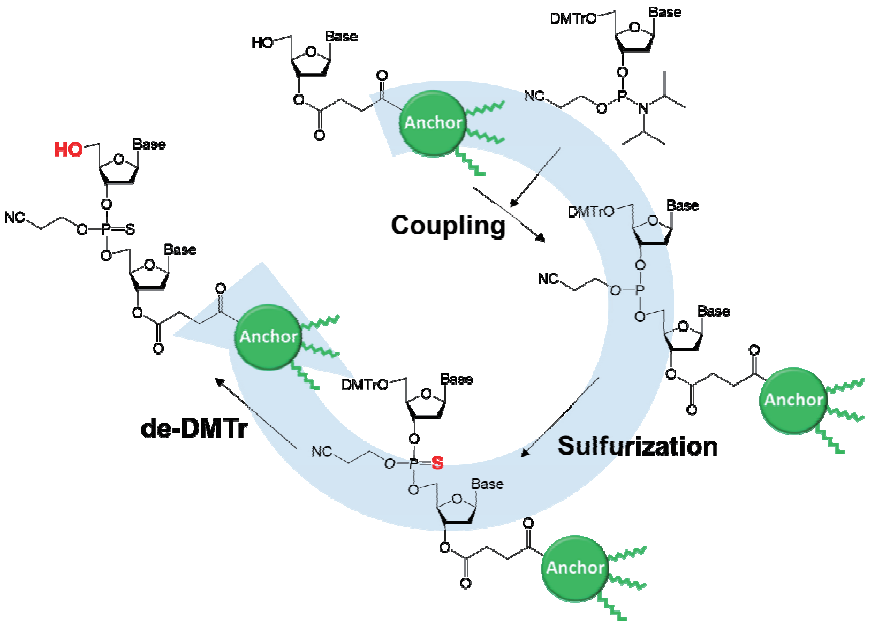


Furthermore we developed an evolved AJIPHASE® method using solvent extraction instead of precipitation for isolation. The continuous one-pot synthesis without isolation can be realized in peptide elongation only by solvent extraction using new type of the anchor compound having branched chains and using new Fmoc deprotection system. We demonstrated that the synthesis of a 20 mer peptide was successfully achieved by this AJIPHASE® one-pot method. The method can significantly shorten the operation time and reduce the solvent consumption, compared with solid-phase synthesis.

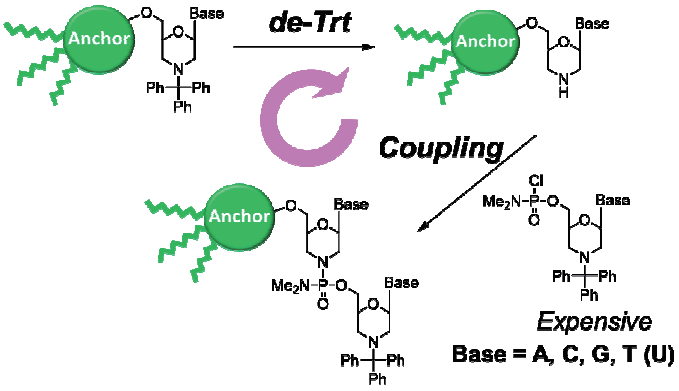


Next we have applied the AJIPHASE® technology to oligonucleotide synthesis. Several liquid phase technologies for the synthesis of oligonucleotides have been reported in the literature, however most of them are suitable only for short nucleotides

in small quantities. We have developed a practical manufacturing method for long chain oligonucleotides by a “telescope” elongation system and several reaction manners. The method can synthesize various types of oligonucleotides with high purity on a large scale.



In the synthesis of PMO (Phosphoroamidate Morpholino Oligomer) which is an important oligonucleotide analogue, the developed AJIPHASE® protocol showed big advantages regarding monomer consumption and purity of the obtained crude PMO, compared to the common solid-phase synthesis.



We have already demonstrated that the AJIPHASE® chain elongation technologies mentioned above can produce peptides and oligonucleotides even at large scale for clinical development. In this presentation, the method and process development will be described in detail.

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K－８（Keynote Lecture）

Mighty Machines: Rapid and robust scaling of drug substance processes in purpose-built reactors enabled by continuous manufacturing technology

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Continuous manufacturing (CM) technology creates new opportunities for efficient, single-cycle process development. The complexity of continuous manufacturing systems and the challenges of translating lab results to production are a significant barrier to the use of CM technology. Snapdragon has developed a CM lab development platform that accurately models production-scale systems enabling right-first-time scale-up. An iterative refinement approach of reaction and reactor is able to rapidly deliver production-ready manufacturing machines with product quality control built into the design of the reactor. Delivery of both process technology and the production hardware ensures successful manufacturing.

K-９（Keynote Lecture）

Synthetic Route Development for Manufacture of Venetoclax under Expedited Timeline

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Venetoclax[1] (ABT-199), the first small molecule BCL-2 selective inhibitor, obtained accelerated approval from the U.S. Food and Drug Administration (FDA) in April 2016 for treating relapsed/refractory chronic lymphocytic leukemia (CLL) patients with the 17p deletion genetic mutation. Venetoclax is currently being investigated in a number of other indications. Recently, in June 2018, it obtained FDA approval for treating patients who have received at least one prior therapy [2] with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion in combination with rituximab.

The first-generation synthesis adapted from the medicinal chemistry route was rapidly developed to produce multi-kilogram quantities of venetoclax, allowing early development of this promising drug candidate to move forward without delay. However, this route was not amendable for routing large scale manufacturing as it involved several significant concerns: (1) low overall yield and throughput resulting in high cost of drug substance, (2) involved a poor regioselective reaction with sensitive scale dependency resulting in poor process robustness, and (3) included a syrup type of Regulatory Starting Material [3] which required column purification complicating its isolation and the removal of mutagenic and carcinogenic impurities generated from the process.

The redesigned convergent synthetic route for venetoclax was development under expedited timeline which allowed the Process Chemistry only ten months to develop an alternate synthesis to produce the primary stability batches [4]. The new synthesis features a Buchwald-Hartwig amination to construct the core ester, it successfully addressed the chemistry challenges associated with the first-generation route and improved the process convergence, more than doubled the overall yield and significantly improved the manufacturing robustness.

This presentation will discuss in detail the discovery and development of the new synthesis and several notable process chemistry innovations that enabled successful implementation of the new synthesis for routing large scale manufacture. Timely developing this new synthesis not only resulted in significant cost saving for manufacturing of the drug substance; but also enabled accelerated regulatory approval of venetoclax and supported the increased demand for the drug substance.

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K- 10 （Keynote Lecture）

Development of New Molecular Entities: Phase 1

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Jubilant Drug Discovery and Development Solutions (Jubilant Chemsys & Biosys) are actively involved in both discovery and development of new molecular entities while collaborating with drug discovery companies around the world. Our conventional clients were pharmaceutical companies which are capable developing their process optimization and manufacture in house. However, there is an increasing number of biotechs which are backed with venture capital funds but have almost no laboratory and manufacturing facilities, and/or even in house scientists nowadays. We generally start collaboration with such biotechs which are innovative and dynamic but lack in house resources to do various drug discovery programs. Along with discovery of drug candidates, we often facilitate development programs in need for IND.

The required development for preclinical and Phase 1, is “quick scale-up”. However, medicinal chemistry routes are generally not suitable for scale-up in terms of yield, scale, work-up, reagents used, and production costs. Our chemistry experts empowered with a large synthetic toolbox and years of knowledge do a thorough route scouting and develop the route further for larger scale synthesis. The process team follows strictly the principles of green chemistry while designing and improving the scheme. Process engineers ensure that the methods are safe and scalable with fewer operations.

My presentation will include an in-house discovery and development of a BRD4 inhibitor.[1] Key chemistry around the molecule especially the generation of chiral biaryl carbinol and diastereomeric oxa-Michael reaction will be discussed. While working on the product development, we focused on applying the principles of green chemistry to minimize co-generation of waste. There were challenges as the scaffold contained fused tricycle with an oxepino ring having two chiral centers. The medicinal chemistry involved racemic synthesis thereby generating four stereoisomers which were later separated by chiral SFC. We developed an asymmetric route to a challenging biaryl methanol with a chiral purity (94%). The optical purity was further enriched during the process with very high de and ee (99.99%). Overall chemical yield was also improved 11 folds.

Case studies from medicinal chemistry to Phase 1 from some client programs will also be introduced.

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K- 11 （Keynote Lecture）

Review of Continuous Process in SK Biotek

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Recently, there has been increasing interest in the continuous process in the pharmaceutical area from drug product process to drug substance production. The continuous process offers more efficient scale-up, improved safety, and environmentally friendly process as compared to the classic batch process. As such, the application of continuous process has extensively increased for many new reactions these days. However, the main challenge is to develop and implement commercial process from R&D scale results.

The continuous process developed by SK Biotek utilizes our expertise in the industrial refinery process accumulated over 50 years such as automated & closed manufacturing system, chemical conversion, catalytic process, and purification. Among the new and innovated discoveries we achieved, two of the main development pathways such as continuous tubular reactions (Static mixer type) and continuous catalytic reactions (Fixed bed type) will be discussed. For continuous tubular reactions, organometallic reactions (Cryogenic process required in batch mode) and hazardous reactions (Azide chemistry and hydrogen peroxide chemistry) will be discussed from R&D development to commercial stage. In-house capability of new catalyst design and production delivered new opportunities of continuous catalytic reactions such as selective nitro hydrogenation, Rosenmund reduction, lactam reduction, and reductive debromination successfully.

Our progress in integrated continuous process will also be described briefly as various approaches are under development.

Abstracts

Poster Presentation

1 P-01 ～ 1P-78

July 25

1P-01

Sodium Hypochlorite Pentahydrate: Effective Oxidant for Organic Reactions

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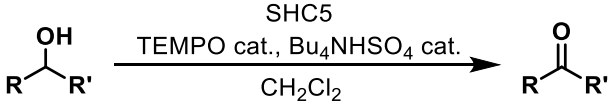
We have developed manufacturing process for sodium hypochlorite pentahydrate ($NaOCl \cdot 5H_2O$, SHC5™). This crystalline SHC5 has notable features over conventional bleach: (1) the available chlorine concentration is about 42% and more than 3 times higher than conventional bleach, (2) SHC5 indicates high activity due to its low pH, and (3) SHC5 is stable under 7 °C. Since SHC5 has these properties, SHC5 shows good performance in organic reactions. We would like to report here several specific oxidations by SHC5.[1)]

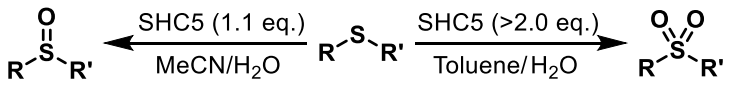
1) Oxidation of alcohols[2)]

The oxidation of primary and secondary alcohols using SHC5 in Cl_2Cl_2 in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and tetrabutylammonium hydrogen sulfate as catalysts without pH adjustment proceeded smoothly to give corresponding carbonyl compounds in high yields whereas the reaction with conventional bleach needed longer reaction time, giving poor yields. Sterically hindered alcohol such as menthol was also oxidized with SHC5 under the same condition. The results from Hirashita's group using this oxidant revealed that MeCN was optimal solvent for the alcohol oxidation which proceeded without any catalysts or additives in high yields although the substrates were limited to secondary, benzylic and allylic alcohols.[3)]



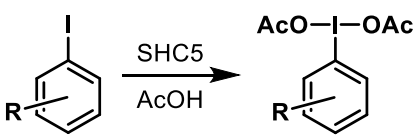
2) Oxidation of sulfur compounds[4)]

The sulfur compounds were also effectively oxidized to the corresponding sulfoxides or sulfones. In this case, no catalysts were required, but solvent selection was essential for selective oxidation. The sulfoxides could be obtained selectively by using $MeCN/H_2O$ as solvents, while the reaction in toluene gave sulfones selectively.



3) Oxidation of Iodoarenes[5)]

SHC5 could be used for the preparation of diacetoxyiodo arenes. The optimized conditions were widely applicable not only to electron-deficient but also to electron-rich iodoarenes. The methods were superior and efficient over existing methods in terms of safety, cost and simplicity of the operation.



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1P-02

Antidiabetic Materials Produced by *Paenibacillus* Fermentation

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Over 90% of diabetes mellitus (DM) cases are type 2. The use of alpha-glucosidase inhibitors (aGI), such as acarbose, miglitol, and voglibose has been reported in regard to the treatment of type 2 diabetes. These remedies entailed some problematic side effects, such as diarrhea, flatulence, and abdominal discomfort. Therefore, there is an interest in discovering new natural sources of aGI.

Many strains of *Paenibacillus* have been reported to use chitinous materials as the sole C/N (carbon/nitrogen) source for producing exopolysaccharides. Chitin-containing fishery byproduct such as shrimp shells and crab shells have been efficiently recycled *via* microbial fermentation to produce chitinolytic enzymes, and have also been used as the sole C/N source for the screening of aGI-producing bacterial strains.

Our previous studies revealed that *Paenibacillus* sp. TKU042, a bacterium isolated from Taiwanese soil, secreted acarbose-comparable aGI in the fermented nutrient broth.

In this study, six kinds of chitin-containing materials were used as the C/N source for aGI production by *Paenibacillus* sp. TKU042; other chitinolytic bacteria strains of *Paenibacillus* species were tested for aGI productivity.

The effect of protein supplement and some cultivation parameters on the aGI productivity and the specific inhibition of *Paenibacillus* sp. TKU042 aGI were also investigated. Herein, the IC_{50} and maximum activity were estimated and compared with those of fermented nutrient broth and acarbose.

1P-03

Synthesis and Characterization of Epoxies Using Self-Assembled Nanofibrillar as Scaffolds

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The easy preparation and enhanced characterization of novel epoxies using self-assembled 1,3:2,4-dibenzylidene sorbitol (DBS) organogels as scaffolds were discussed in this study. DBS is a butterfly-shaped amphiphile with two hydrophilic hydroxyl groups and two hydrophobic phenyl groups. It is derived from the sugar alcohol D-glucitol. DBS and its derivatives are widely used as nucleating agents in certain crystalline polymers, such as polyethylene and polypropylene, to improve the crystallization rates and optical properties. Recently, DBS and its derivatives were observed to exhibit self-assembly behaviors in a variety of organic solvents and liquid polymers at very low concentrations to form the organogels.12-15 The DBS organogels were the result of the formation of 3-D nanofibrillar networks. The diameters of these nanofibrils ranged from 1 μm to 10 nm, as observed by electron microscopy, depending on the solvent polarity and DBS amounts. DBS organogels can be used in many applications, such as battery electrolytes, drug-delivery systems, cosmetic products and template techniques. In our previous study, in addition to the synthesis of porous polymers prepared using self-assembled templates formed by organogels, we kept these templates within polymers. The physical cross-linked DBS networks consisting of nanofibrils in a polystyrene (PS) matrix acted as the reinforcing materials. The thermal and mechanical properties of PS improved by the addition of DBS. In addition, DBS and its derivatives were also observed to be added in certain thermoplastic polymers by melt blending to enhance the mechanical properties. In this study, DBS organogels were used as self-assembled nanofibrillar scaffolds in the thermosetting polymers. DBS organogels, due to the DBS network structures consisting of nanofibrils, were used for the reinforcement of epoxies. For DBS/DGEBA organogels (before curing), electron microscopy results showed that there were DBS nanofibrils measuring from 10 nm to 20 nm in diameter. The diameters of DBS nanofibrils were not affected by the change of DBS amounts; however, the amount of the nanofibrils, as well as the cross-linked density increased with the increase of DBS contents, leading to the increase in G', as determined by the rheological measurement. When the thermal curing agent was added to the DBS/DGEBA gel, the synthesis (curing) of the epoxies was performed at 70 °C for 3 hours. The curing time was not influenced by the change of DBS amounts. The DBS did not interfere or participate in the reaction. After curing, the DBS nanofibrillar structures were still present within the epoxies. The hardness and toughness of these epoxies were significantly enhanced by the presence of the DBS networks. In addition, the glass transition and thermal degradation temperatures of the epoxies were significantly improved by the addition of the DBS.

1P- 04

One-Pot Preparation of 3-Arylpyrazoles and 3-Arylisoxazolines from Arenes

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[Introduction]

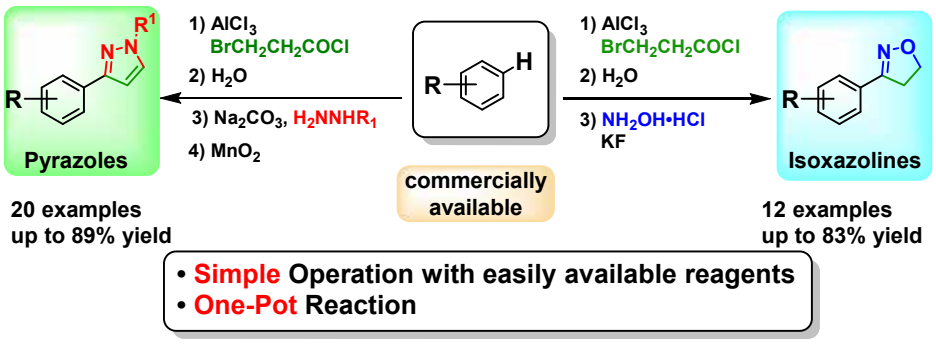
Pyrazoles and isoxazolines, nitrogen-containing heteroaromatics, exhibit a wide range of biological activities and therefore, they are important units containing in many medicines, such as antibacterial drugs, anti-inflammatory drugs and anthelmintics.

Here, we found that 3-arylpyrazoles could be synthesized in one pot by the Friedel-Crafts acylation of arenes with 3-bromopropionyl chloride and $AlCl_3$, followed by the reaction with NH_2NHCH_3 and subsequent oxidation with MnO_2. In addition, we also found that isoxazolines could be synthesized in one pot by the same method with arenes, ß-bromopropionyl chloride and $AlCl_3$, followed by the reaction with NH_2OH and KF.

[Results]

First, the reaction conditions were optimized with cumene, ß-bromopropionyl chloride, and $AlCl_3$ in CH_2Cl_2 at 0°C. Next, NH_2NHCH_3 and Na_2CO_3 were added to the mixture to carry out the formation of hydrazone and *5-exo-tet* cyclization, followed by oxidation with MnO_2 to obtain 3-(4'-isopropyl)phenylpyrazole in good yield.

The same treatment of cumene, ß-bromopropionyl chloride, and $AlCl_3$ in CH_2Cl_2 at 0°C, followed by the treatment with $NH_2OH \cdot HCl$ and KF gave 3-(4'-isopropyl)phenylisoxazoline through the formation of oxime and *5-exo-tet* cyclization in good yield. Other arenes could be also used to gave the corresponding 3-arylpyrazoles and 3-arylisoxazolines. These reactions are one-pot synthesis in which the purification process is simplified with the commercially available reagents has advantages of cost reduction and less wastes.



1P-05

Advantages of Metal Ligand Complexes/Pre-Catalysts in Catalytic Reactions Compared to *in situ* Systems

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In the last decades, precious metals based homogeneous catalyst usage in industries increased more and more, especially asymmetric hydrogenation, cross-coupling reaction, metathesis are getting frequently used. Among them, for both asymmetric hydrogenation and cross-coupling reaction, *in-situ* preparation methods of the catalysts were developed from early decades and still are being used as the majority even though *in-situ* prepared catalyst systems may often retain potential risks like incomplete formation of intended complexes, formation of unknown complex mixtures, and so on, leading to lower conversions/yields, undesired side reactions. On the other hands, nowadays, definite trends to use metal ligand complexes/pre-catalysts are coming to utilize these classes of well-defined catalysts as reliable and effective catalysts which form the desired active complexes rapidly and quantitatively in the reaction conditions. Thus, providing process chemists very convenient and robust solutions to use the above mentioned versatile technologies to develop valuable processes in practice. In this presentation, more detailed advantages of metal ligand complexes/pre-catalysts in comparison to *in situ* systems will be described.

1P- 06

One-Pot Transformation of Primary Alcohols into 3-Aryl- and 3-Alkylisoxazoles and- pyrazoles.

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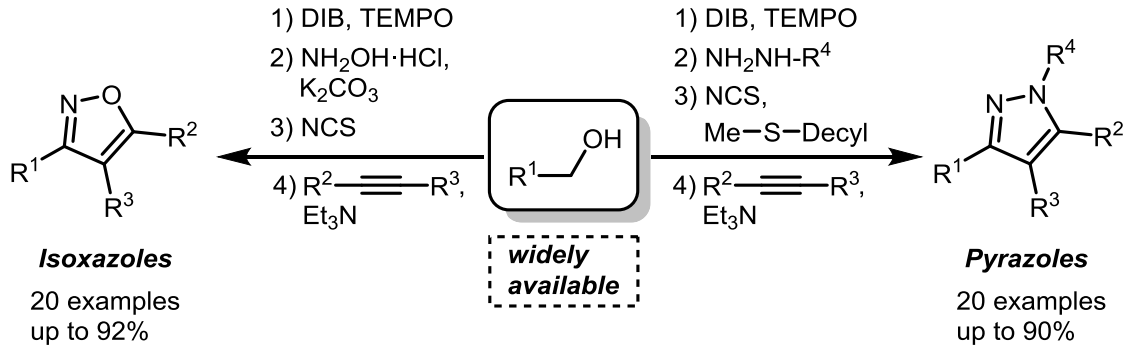
[Introduction]

Nitrogen-containing heteroaromatics, such as isoxazoles and pyrazoles, are important units, especially for pharmaceuticals and agrochemicals due to their broad range of biological activities. Among them, isoxazoles and pyrazoles are one of the most important nitrogen-containing five-membered heteroaromaceutics and serve as units or cores of some pharmaceuticals and agrochemicals. We developed the transition-metal-free and one-pot transformation of widely available primary alcohols into 3-aryl -and 3-alkylisoxazoles, and 3-aryl- and-3-alkylpyrazoles, respectively.

[Results]

3-Aryl- and 3-alkylisoxazoles could be obtained efficiently from primary alcohols by the successive treatment with DIB in the presence of TEMPO, hydroxylamine, and then NCS, followed by the reaction with alkynes in the presence of Et_3N. 3-Aryl- and 3-alkyl-1-phenylpyrazoles could be also obtained efficiently from primary alcohols by the successive treatment with DIB in the presence of TEMPO, phenylhydrazine, and then NCS in the presence of decyl methyl sulfide, followed by the reaction with alkynes in the presence of Et_3N. The chlorine atom derived from NCS plays an important role in the formation of 1,3-dipolar precursors, nitrile *N*-oxides and nitrilimines, from oximes and hydrazones, respectively. These methods are applicable also to aliphatic primary alcohols. Furthermore, these obtained isoxazoles and pyrazoles could be smoothly transformed into various isoxazoles and pyrazoles derivatives.



·One-Pot Reaction

·Transition-Metal Free

1P-07

Structure and Reactivity of Aromatic Radical Cations Generated by $FeCl_3$

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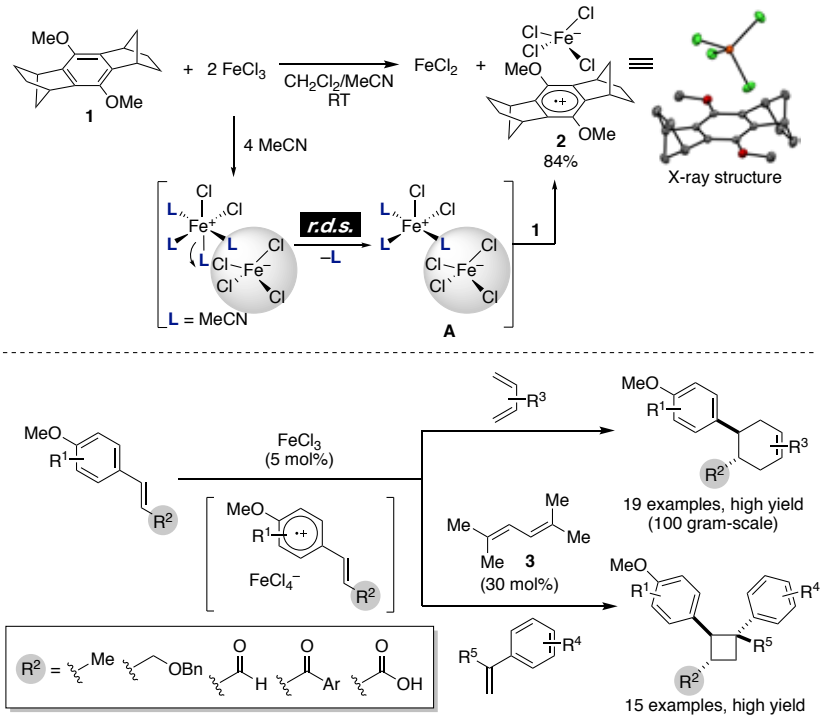
Aromatic radical cation is a labile intermediate that appears in various one-electron oxidation reactions.[1] Despite the utility of such reactions, the structural characterization of radical cations has been challenging because of their high reactivities and short lifetimes.[2] For examples, aromatic radical cation generated by $FeCl_3$ have been postulated as a key intermediate for $FeCl_3$-promoted oxidative coupling reaction. However, there have been no reports on the isolation of aromatic radical cations generated by $FeCl_3$. Here, we isolated a stable radical cation **2** generated from $FeCl_3$ with sterically-congested arene **1**.[3] The X-ray crystal structure of **2** reveals an ion pair of $FeCl_4^-$ with $\mathbf{1}^{\bullet+}$. The mechanism of the generation of **2** was elucidated by kinetic studies, which suggests the oxidation of **1** by the true oxidant **A**. With the oxidant **A** and the aromatic radical cation identified, we developed two radical cation cycloadditions initiated by $FeCl_3$. When anetholes with dienes were used in the presence of 5 mol% of $FeCl_3$, [4 + 2] cycloadducts were obtained. In contrast, when anetholes with styrenes were used in the presence of 5 mol% of $FeCl_3$ and 30 mol% of diene **3**, [2 + 2] cycloadducts were obtained. Both [4 + 2] cycloaddition and [2 + 2] cycloaddition with a broad substrate scope were achieved. Whereas electron-deficient anetholes are scarcely used in the conventional [4 + 2]- and [2 + 2]-cycloadditions, electron-deficient anetholes were tolerable in both cycloadditions under our reaction conditions. Moreover, a 100g-scale reaction was demonstrated with the use of 1 mol% of $FeCl_3$ as a simple and a highly active initiator.



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1P- 08

Establishment of the Continuous Synthesis of Ceramide (D-*erythro*-CER[NDS]) *via* Oxo-Tethered Ruthenium Complex Catalyzed Asymmetric Transfer Hydrogenation using Pipe-Flow Reactor

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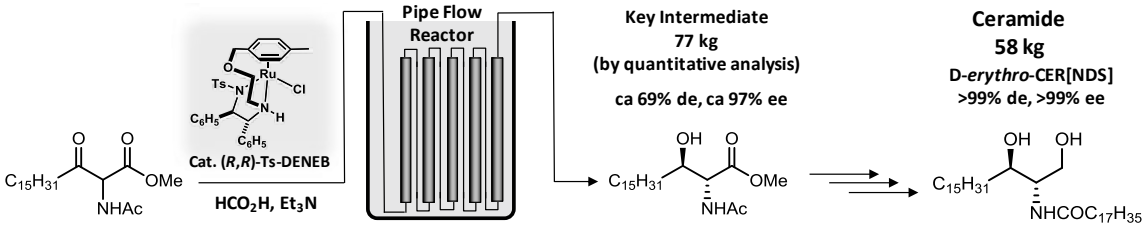
The optically active ceramide *N*-((2*S*,3*R*)-1,3-dihydroxyoctadecan-2-yl) stearamide (D-*erythro*-CER [NDS]) plays a critical role for the barrier function of mammalian skin. We have established the synthesis of this compound that has a continuous asymmetric transfer hydrogenation as a key-reaction.[1]



The asymmetric transfer hydrogenation of α-amido-β-keto ester catalyzed by oxo-tethered Ru complexes ((*R*,*R*)-Ts-DENEB) gave the key intermediate on *erythro*-selective *via* dynamic kinetic resolution. We applied it to continuous reaction by the pipe flow reactor (Vertical Pipes-in-Series Reactor) that fabricated from many stainless-steel pipes connected by smaller diameter jumper tubes. This pipe flow reactor is advantageous in safety and cost for the continuous reactions with the gas generation.

We have run this ceramide synthesis on a production scale for the evaluation. The continuous asymmetric transfer hydrogenation in the 100 L vertical pipes-in-series reactor were very consistent across 36 h and the conversion reached 98.9%. It gave 77.4 kg of the key-intermediate in 96% of yield with 69% de and 97% ee. We also tried to produce materials with continuous reactions in subsequent steps, then 58 kg of the target D-*erythro*-CER[NDS] was obtained with perfect selectivity (>99% de, >99% ee).

100 L Vertical Pipes-in-series Reactor

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1P-09

Highly Efficient Synthesis of Pyrrole-Imidazole Amide Sequence for Application to DNA-Binding Polyamides

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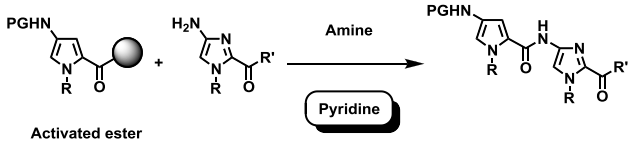
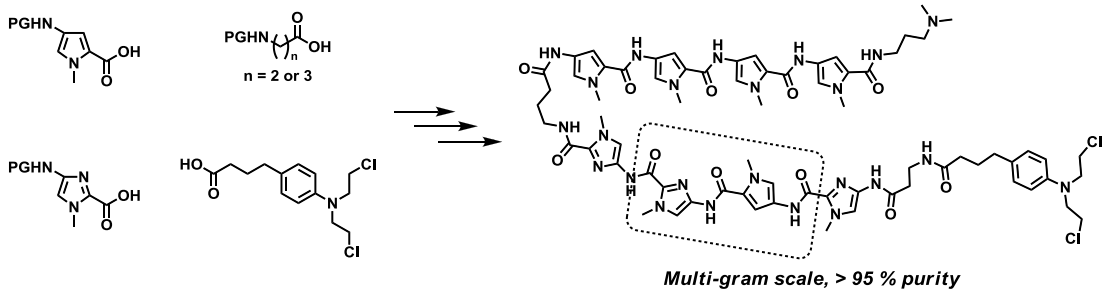
Pyrrole-imidazole polyamides (PIPs) are cell-permeable DNA-binding ligands which can be designed to recognize specific base sequences in the minor groove of DNA.[1] The essential components of PIPs are N-methylpyrrole amino acid (Py) and N-methylimidazole amino acid (Im), but the preparation of Py-Im sequence has difficulty due to the coupling of electron-rich electrophile (Py) with electron-poor nucleophile (Im). To overcome this problem, it was necessary to use uncommon starting materials,[2] highly activating reagents,[3] or heating condition in some cases despite of thermal lability of nucleophile.[4] In this time, we have developed highly efficient condensation condition to obtain the Py-Im sequence with appropriate activated ester, amine and solvent. This method can be applied not only to dimer synthesis but also elongation reaction by monomer or polyamide fragments. Eventually, we have manufactured 10-mer of PIP[5] which has the sequence of Py-Im on gram-scale using our manner. We would like to discuss the detail and utility of this method in our poster presentation.

Formation of Low Reactive Py-Im Sequence



Application to Preparation of PIP on Gram Scale



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1P-10

Device Performance Improvement of Double-unit Air Gap Membrane Distillation Module for Seawater Desalination

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The modeling equations for predicting distillate flux in a double-unit air gap membrane distillation (AGMD) module with inserting corrugated carbon-fiber open slots acting as an eddy promoter were developed theoretically and experimentally. The design of a more compact double-unit device implementing carbon-fiber open slots could not only increase the membrane stability for preventing from vibration but also enhance the pure water productivity due to decreasing temperature polarization effect for desalination applications. A considerable permeate flux enhancement was achieved as compared to that of the device with an empty channel. The correlated expression of Nusselt number with inserting corrugated carbon-fiber open slots was formulated and regressed with the use of experimental data, and thus, the prediction of the heat transfer coefficient of the double-unit AGMD module was obtained. The effects of volumetric flow rate and fluid inlet temperature on the permeate flux were also delineated with considering the power consumption increment due to increasing the turbulent intensity by inserting corrugated carbon-fiber open slots. The good agreement between the experimental results and theoretical predictions was accomplished within acceptable accuracy.

Keywords: Air gap membrane distillation, Double-unit, Permeate flux, Carbon-fiber spacers, Temperature polarization.

1P- 11

anti-Selective Catalytic Asymmetric Nitoaldol Reaction of α-Keto Esters: Intriguing Solvent Effect, Synthesis of APIs, and Flow Reaction

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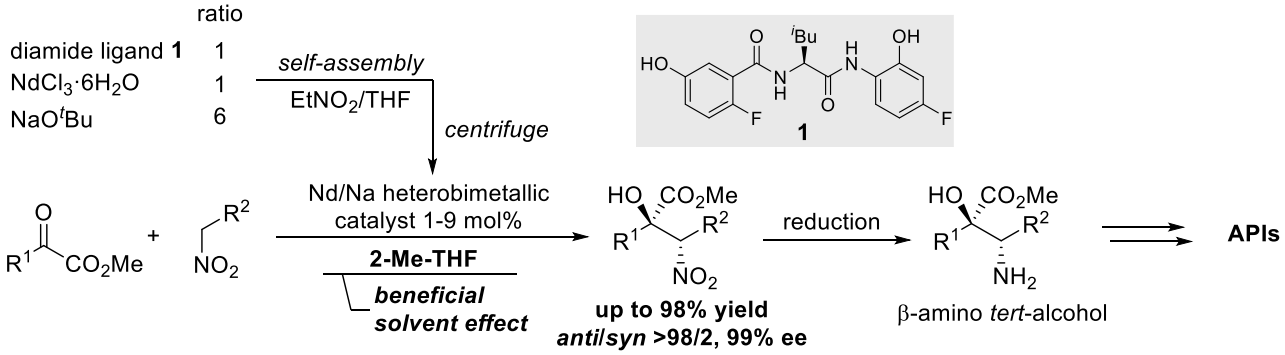
The nitroaldol reaction is a synthetically advantageous carbon−carbon bond-forming reaction that produces β-nitroalcohols from readily available starting materials under mild proton transfer conditions with perfect atom economy. In particular, catalytic asymmetric variants offer streamlined access to chiral building blocks, such as β-aminoalcohols which are privileged structural motifs in pharmaceuticals. Our laboratory has established *anti*-selective catalytic asymmetric nitroaldol reaction of aldehydes using heterogeneous heterobimetallic catalyst prepared from inexpensive $NdCl_3 \cdot 6H_2O$, NaO^tBu and a chiral diamide ligand **1** by self-assembly via simple mixing.

We report that the Nd/Na heterobimetallic system could be applied to the *anti*-selective catalytic asymmetric nitroaldol reaction of α-keto esters. In this reaction, β-nitro *tert*-alcohols could be obtained with high stereoselectivity and broad substrate generality, and a significant beneficial solvent effect of 2-Me-THF was observed. Detailed studies reveal that the Nd/Na heterobimetallic catalyst recognized the chirality of 2-Me-THF and the interaction between the catalyst and one enantiomer of 2-Me-THF resulted in a positive effect in selectivity and reaction rate.

The Nd/Na heterobimetallic system was compatible with a flow-reaction platform, and the enantioriched products could be converted to antifungal agents efinaconazole and albaconazole, confirming the synthetic utility of this asymmetic reaction.



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1P- 12

Development of New Catalytic Synthetic Methods of *N*-Unprotected Ketimines

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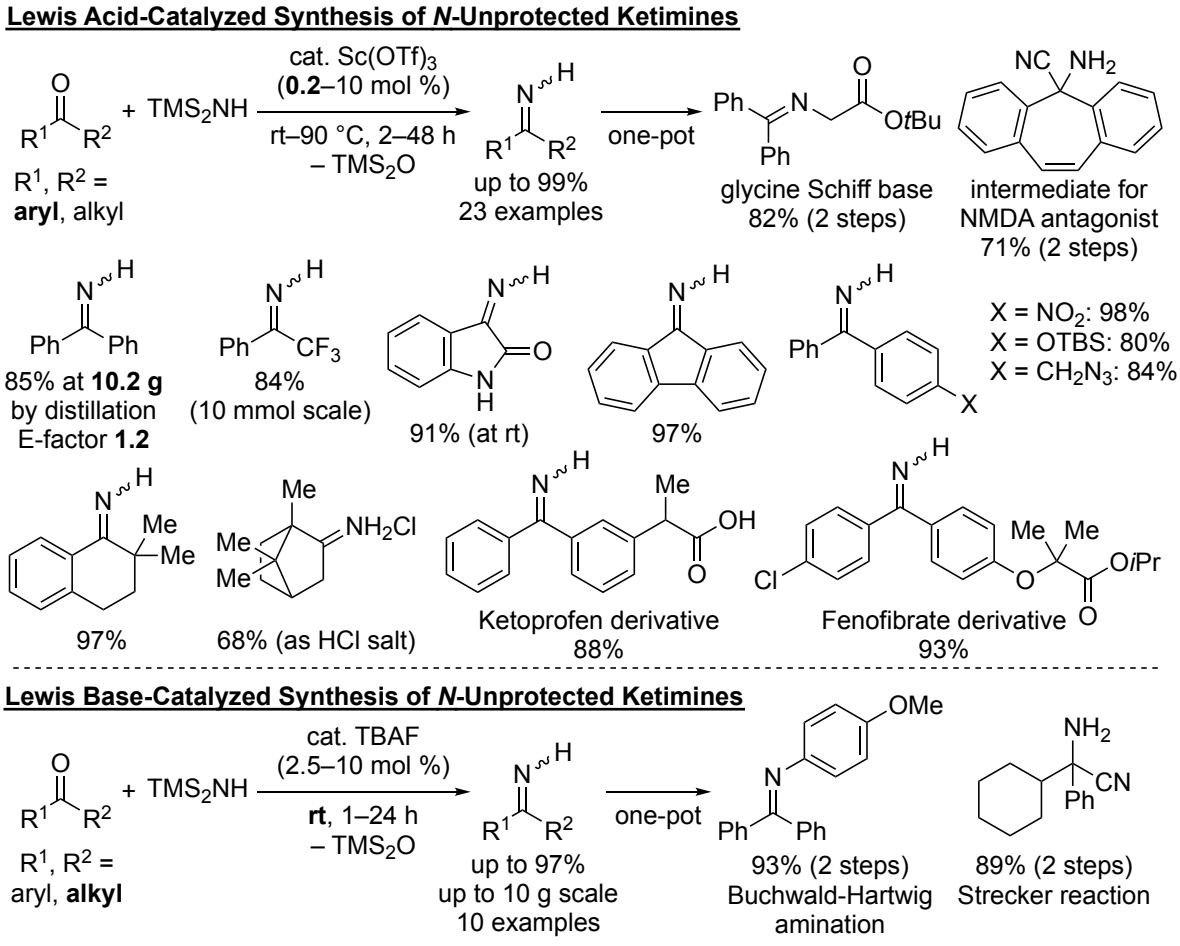
N-Unprotected ketimines are useful compounds and intermediates for the synthesis of various biologically active amines and amino acids,[1] but their synthesis generally requires conventional synthetic methods with stoichiometric amounts of metal reagents. Herein we report new catalytic methods for synthesizing *N*-unprotected ketimines.[2] The use of bis(trimethylsilyl)amine as a nitrogen source and appropriate Lewis acid or base catalysts is key to effectively promoting the reactions even in decagram scales and with much broader functional group tolerance. Application to the one-pot synthesis of valuable compounds via *N*-unprotected ketimines is also demonstrated.



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1P- 13

Safe and Scalable Aerobic Oxidation by 2-azaadamantan-2-ol (AZADOL)/NO*x* Catalysis: Large-Scale Preparation of Shi's Catalyst

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Catalytic aerobic oxidation has been regarded as an ideal method because its bulk oxidant, molecular oxygen, is abundant and its byproduct is only water. We have developed highly efficient aerobic oxidation of alcohols catalyzed by 2-azaadamantane-*N*-oxyl (AZADO) and a NOx source.[1] With our firm belief in the facile operation and wide substrate scope of the AZADO/NOx system for aerobic alcohol oxidation, we sought to apply this reaction to the large-scale synthesis of a useful compound in a conventional batch reaction. We envisaged that 2-azaadamantan-2-ol (AZADOL), a hydroxylamine variant of AZADO, is a reasonable source of an AZADO-type catalyst for large-scale applications because of its good availability.

Herein we develop a safe and scalable method for aerobic alcohol oxidation by AZADOL/NOx catalysis in a batch reactor. During the optimization of the reaction conditions, we found that ideal catalytic amounts of AZADOL and $NaNO_2$ was crucial for achieving quantitative conversion. Thermal analysis of the reaction demonstrated the safety of the reaction, which is ensured by controlling the reaction temperature to be below the flash point of acetic acid. The robustness of the developed method was demonstrated by a 500 g scale oxidation of diacetone fructose (**1**) into Shi's catalyst **2** for asymmetric epoxidation.

Because the reaction proceeds under mild conditions (almost ambient temperature and pressure), it is expected to show a broad substrate applicability similar to that of other aerobic alcohol oxidation.

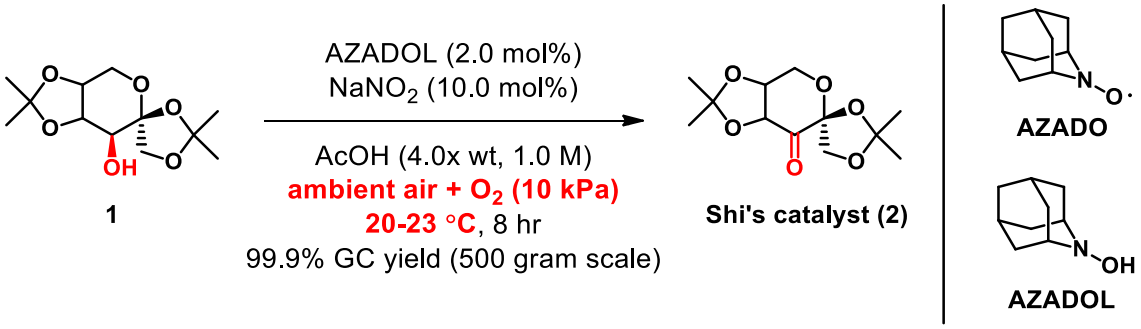

Fig.1 Aerobic alcohol oxidation of **1** to Shi's catalyst (**2**) by AZADOL/NOx catalysis.

Reference

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1P－14

Research on the Adsorptive Condition of Copper (II) Ion with the Use of Ephippia

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On annual, humans consume about two million seventy tons of eggs. People usually use only egg yolks and albumins to cook. In the other words, most egg films and egg shells are not used and are thrown away.
It was thought that the egg films have some available properties. When literature was revealed, it was found that egg films can adsorb metal ions. However, the conditions required for egg film to easily absorb metal ions was not well-explained. The purpose of this research is to investigate the condition is better adsorb the copper (Ⅱ) ion to egg films.
Method of this research is following. The solutions were adjusted the solutions using hydrochloric acid and 0.5g of the dried egg films was added to 50mL of the copper (Ⅱ) sulfate water solutions. The solution was stirred with a thermostat. The copper (Ⅱ) sulfate water solutions were percolated to remove the egg film. The concentration of the copper (Ⅱ) ion removed from the egg films was measured with a spectrophotometer. The adsorptive amount was calculated using the difference in the concentration before adsorption and the concentration after adsorption.
Three things were found from the experiments. First, when the concentration of the copper (Ⅱ) sulfate water solution was high, the adsorptive amount of the copper (Ⅱ) ion increased. Second, when the temperature of the copper (Ⅱ) sulfate water solution was high, the adsorptive amount of the copper (Ⅱ) ion increased. Third, when the pH of the copper (Ⅱ) sulfate water solutions was low, the adsorptive amount of the copper (Ⅱ) ion decreased.
This experiment was conducted by adding a constant amount of the egg film to a large amount of the copper (Ⅱ) ion. Assuming that the adsorptive reaction of the copper (Ⅱ) ion is an irreversible reaction, the adsorptive amount must be constant. But the adsorptive amount wasn't constant, and it was found that the adsorptive amount is influenced by concentration, temperature, and pH. That is why it was thought that the adsorption of the copper (Ⅱ)ion is a reversible reaction.
A new experiment was tried to prove that the adsorption of the copper (Ⅱ) ion is a reversible reaction, The experimental method is as follows. It was adjusted to the condition of the copper (Ⅱ) ion adsorb easily that the aqueous solutions temperature and pH. And the copper (Ⅱ) ion was adsorbed to the egg films. Next, the solutions were adjusted for the condition in which that the copper (Ⅱ) ion adsorb difficulty. Then the concentration of the copper (Ⅱ) ion before and after the adjustment of the conditions was measured. This result illustrated that the copper (Ⅱ)ion is adsorbed to egg films once, however, when the conditions are changed, the copper (Ⅱ) ion is desorbed from the egg films. From the above, it turned out that the reaction about the copper (Ⅱ) ion adsorption with the egg films is a reversible reaction.
The future tasks are following. First, whether the copper (Ⅱ) ion adsorptive reaction is an endothermic will be checked in another way. Second, metal ions other than the copper(Ⅱ) ion will be investigated to determine if they have properties similar to those of the copper(Ⅱ) ion.

1P- 15

Efficient Synthesis of a 5α-Reductase Inhibitor, 3-(Tetrazol-5-yl)-3,5-pregnadien-20-one through Allylic Rearrangement of Cyanophosphates

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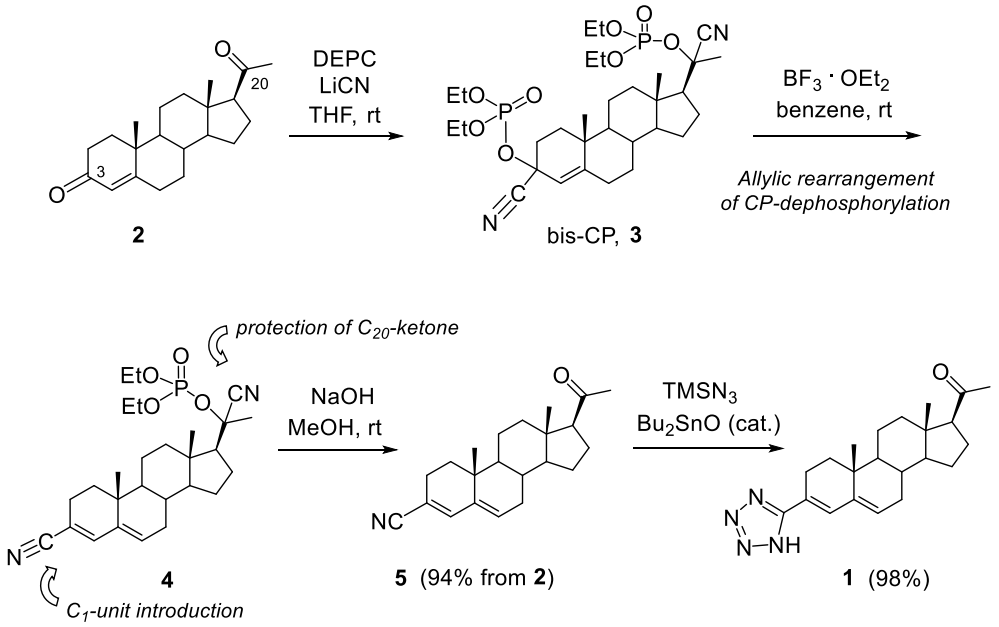
The most commonly used 5α-reductase (5AR) inhibitor in benign prostatic hyperplasia (BPH) treatment is finasteride, which was the first 5AR inhibitor approved in the U.S. for the treatment of BPH. However, its limited activity and side effects have prompted the development of new 5AR inhibitors. Kumar and co-workers recently reported a series of steroidal tetrazole derivatives; 3-(tetrazol-5-yl)-3,5-pregnadien-20-one (TzPD**, 1**) showed the most potent 5AR-2 inhibition with an IC_{50} of 15.6 nM, while that of clinically used drug finasteride is 40 nM.[1]

Meanwhile, α-cyanophosphates (CPs)[2] have been widely utilized as synthetic intermediates in organic synthesis,[2] in which we reported that CPs derived from α,β-unsaturated ketones were transformed into diene nitriles via a $BF_3{\cdot}OEt_2$-catalyzed allylic rearrangement. We now describe the efficient and practical synthesis of TzPD **1** from pregnene-3,20-dione (**2**) in 92% overall yield in four steps using allylic rearrangement of CP **3**.[3]



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1P- 16

Catalytic Transfer Hydration of Cyanohydrins to alpha-Hydroxyamides

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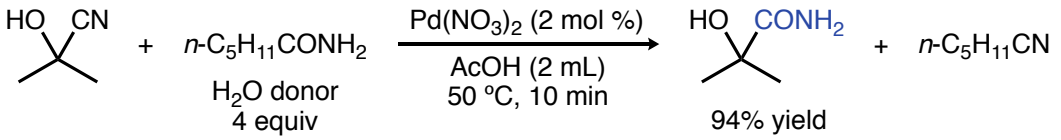
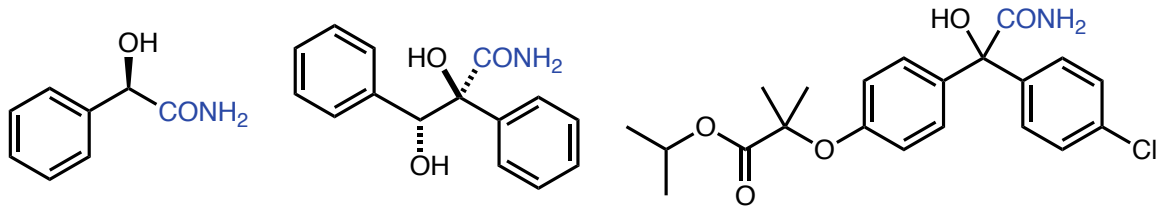
The catalytic hydration of cyanohydrins is one of the most important reactions in both laboratory and industrial synthesis.[1] Cyanohydrins are readily available through cyanation of aldehydes or ketones. Further, α-hydroxyamide substructures are found in various bioactive compounds, and are easily convertible to α-hydroxyl esters, α-hydroxycarboxylic acids, and acrylic analogs. Despite the high utility of metal catalysts for nitrile hydration, however, the hydration of cyanohydrins by homogeneous catalysts is not straightforward. We here report a palladium(II)-catalyzed transfer hydration of cyanohydrins to α-hydroxylamides by using carboxamides as water donors. This method enables selective hydration of various aldehyde- and ketone-derived cyanohydrins to afford the corresponding amides under mild conditions.[2]

For example, the catalytic transfer hydration of acetone cyanohydrin (1.0 mmol) at 50 °C for 10 min using *n*-hexanamide (4 equiv), $Pd(NO_3)_2$ (2 mol %), and acetic acid (2 mL) gave the corresponding amide in 94% isolated yield. The rapid and efficient catalytic conversion of acetone cyanohydrin was unprecedented, and the calculated turnover frequency (TOF) of 280 h^{-1} is more than 10 times larger as compared with those reported for the hydration of acetone cyanohydrin. The presentation will cover the development, scope, and mechanism of this transfer catalysis.



Representative products:



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1P- 17

Stereo-Defined Scaffold Strategy for Tamoxifens from (*E*)-1-Bromo-2-iodoalkenes.

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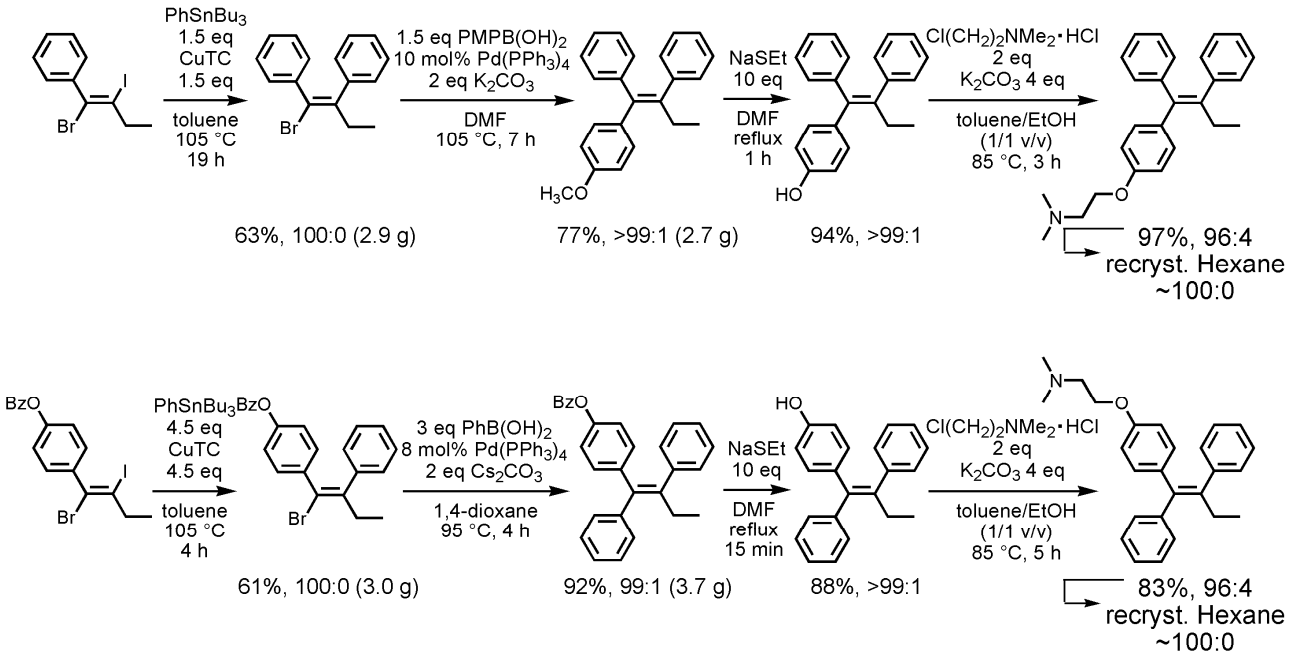
Efficient regio- and stereoselective synthesis of biological active Tamoxifen analogues still remains a grand challenge, because the tetra-substituted olefins have inherently steric hindrance of eclipsing geometries around the carbon-carbon double bonds[1, 2]. Herein we present chemo-selective activation reactions of (*E*)-1-bromo-2-iodoalkenes: the iodine atom of the scaffold selectively undertook CuTC-mediated cross-coupling reactions with tributylphenyltin, suppressing side-production of alkynes which are terribly caused by *β*-halogen elimination reactions in (*E*)-1-bromo-2-iodoalkenes. The stereochemistry of the double bond is fully retained in the activation of the vinylic bromine, deprotection, and alkylation steps: thus it enables us to singly construct (*E*)- and (*Z*)-Tamoxifen (**Scheme 1**), and the template strategy would provide a general entry of Tamoxifen analogues syntheses[3].



Scheme 1. Stereo-defined template-syntheses of (*E*)- and (*Z*)-Tamoxifens.

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1P- 18

Crystallization Mechanisms Hiding Between Your Samples

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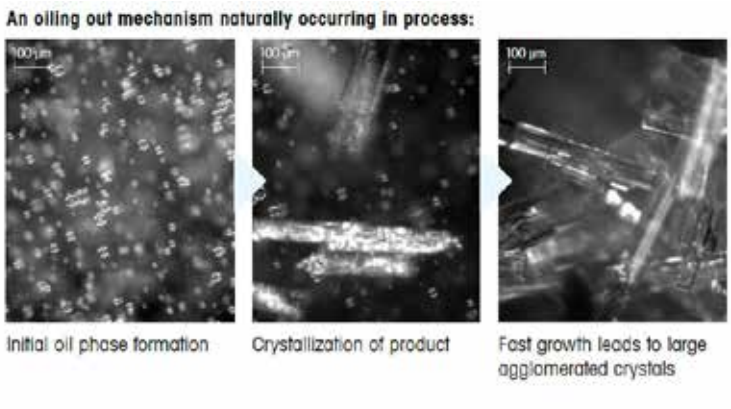
The design of a successful crystallization process depends on choosing process parameters that will produce crystals of the required purity and yield, that can be isolated, filtered, and dried easily. Process parameters such as cooling rate, solvent composition, and agitation rate directly impact crystallization behavior. Scientists are tasked with understanding how these parameters will influence the outcome of the crystallization process. Often, process parameters for crystallization are chosen based on previous experience, and the outcome is determined by careful analysis of offline analytical data, such as particle size analysis, XRPD, or microscopy. This approach is common, but neglects to consider that crystallization occurs through a sequence of interdependent mechanisms which all contribute to the final outcome, and are each uniquely influenced by the choice of process parameters.

Crystal nucleation and growth, phase separation, breakage, agglomeration, and polymorph transformations can occur separately, but also simultaneously, and are influenced by process parameters in unique ways. This convolution of mechanisms can mask the true role process parameters play in determining the outcome of a crystallization process, and make crystallization process design a particular challenge for scientists. In the absence of mechanistic understanding for crystallization processes, scientists must often rely on trial-and-error to adjust process parameters and optimize yield, purity, and particle size. This can be a time-consuming task and is one that rarely delivers crystals that can be isolated, filtered, and dried in a facile manner.

ParticleView, an in-situ video microscope, visualizes crystals and crystallization mechanisms directly within process without the need for sampling. In-situ images enable scientists to quickly uncover root causes for undesired particle behavior and remove trial-and-error approaches by allowing fact based decisions to expedite process development.



1P- 19

VARIOUS MANUFACTURING APPROACHES TO POORLY SOLUBLE PEPTIDES

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In recent years, expectations for medium molecular like peptides are increasing as next-generation drug modalities. In peptide manufacturing, controlling the quality of API is one of the most important points. Purification of column chromatography is usually needed to reach the requested quality. However, regarding poorly soluble peptides, column purification is not able to be selected at all.
Recently, some groups have reported several approaches to prepare poorly soluble peptides [1].
To improve the peptide solubility, we have attempted the following approaches.

1. *O-N* acyl rearrangement
2. Utilization of modified Fmoc protecting group with introduced hydrophilic moieties
3. *C*-terminal tag methods
4. *N*-terminal tag methods

In this poster session, we would like to show our results on solubility data obtained by the 4 types of solubility improvement approaches. In addition, in the case of using *O-N* acyl rearrangement, we will introduce that the improvement of solubility has achieved dramatic improvement of quality and yield on the production scale.

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1P- 20

Development of an Efficient Manufacturing Process for E2212 toward Rapid Clinical Introduction

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Process studies of E2212, an orally bioavailable γ-secretase modulator developed as an agent for the treatment of Alzheimer's disease, are described: especially an efforts to enable the fastest clinical introduction through the fastest supply of API required for an early stage of the drug development such as toxicological evaluation and clinical studies.

SELECTION OF MANUFACTURING ROUTE:

Comprehensive route finding studies conducted to identify an optimal manufacturing process are presented. After evaluation of a chiral synthetic route and a racemic approach coupled with the chiral salt-based resolution and enantiomer recovery processes, the racemic approach was selected for further development.

OPTIMIZATION OF CONDENSATION AND CYCLIZATION STEP:

Through careful selection of a base and temperature for a key cyclocondensation process, the various reaction pathways leading to side products could be suppressed and the highly selective formation of the desired racemate could be achieved in excellent isolated yield and quality control. The overall process is mild, operationally simple, robust and was successfully scaled-up to hundred kilogram scale production, contributing to the rapid delivery of GMP drug substance.

PHOTO-ISOMERIZATION OF OLEFIN USING FLOW SYSTEM:

Preparation of drug substance containing Z-isomer was achieved for the preclinical safety studies. The photo-mediated isomerization of the internal olefin was readily scaled-up to multi-hundred liter scale with excellent reproducibility by applying a rapid (within one minute), single-path flow irradiation system. A sufficient quantity of the Z-isomer could be rapidly prepared which is difficult to achieve by using a traditional batch reaction system.

1P- 21

Asymmetric route to a chiral heterocyclic amine toward efficient manufacturing process

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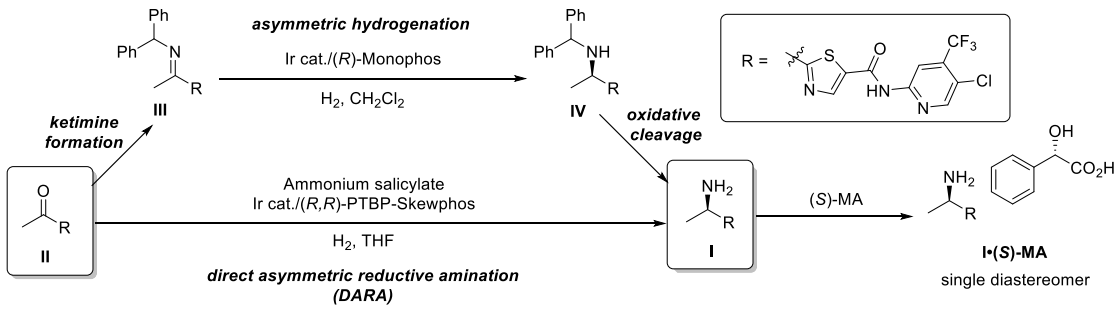
Asymmetric reaction is a pivotal technology that efficiently produces chiral compounds with high yield. Several asymmetric reactions that provide a primary chiral amine have been reported so far, but they have not been versatile especially when the target compound is highly functionalized and has a coordination site to a metal catalyst that deactivates its catalytic activity.

We have developed two asymmetric routes to a primary amine (**I**) that contains many coordination sites such as pyridine, thiazole, and an amide moiety.[1)] The first generation includes iridium-catalyzed asymmetric hydrogenation of a ketimine (**III**) that possesses a diphenylmethyl moiety. The diphenylmethyl moiety proved to be quite important to provide the corresponding amine (**IV**) with high enantiomeric excess and make the reaction proceed with low catalyst loading. The diphenylmethyl moiety was easily cleaved under the oxidative conditions to afford the chiral amine (**I**). The total yield was dramatically improved from the conventional optical resolution by ca. 40%. The second generation applied direct asymmetric reductive amination (DARA) of the ketone (**II**). DARA is the powerful approach for the synthesis of chiral primary amine, but there have been a few examples for DARA of aryl methyl ketone reported just in 2018. After careful screening of the catalyst, we finally found that the combination of iridium(I) with (*R,R*)-skewphos in the presence of ammonium salicylate was essential to afford the corresponding amine **I** with excellent yield and high enantioselectivity. Using the transformation chiral amine **I** was obtained as the salt with (*S*)-mandelic acid in 67% yield as a single stereoisomer starting from ketone **II**. Thus, the DARA of ketone **II** enables us to produce the chiral amine **I** in a single operation. To the best of our knowledge, this is the first example of DARA of highly functionalized 2-thiazolyl methyl ketone.

Both routes were successfully applied to the manufacturing of **I** in a large scale, that shows the robustness of these new asymmetric processes.



1) WO2018220533 A2

1P- 22

Aromatic Halogenation Using *N*-Halosuccinimide and PhSTMS or PhSSPh

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Aryl bromides are known as some of the most efficient substrates for transition-metal catalyzed cross-coupling reaction. A number of methods for aromatic bromination using NBS with activating reagents including Lewis acids and Lewis bases have been reported. However, many of reported methods examined the bromination of reactive (electron-rich) arenes such as phenol and aniline derivatives. Conversely, we have reported mild conversion method of methylene acetals using a combination of *N*-bromosuccinimide (NBS) and phenylthiotrimethylsilane (PhSTMS). This reaction seems to involve the bromination of the methylene acetal moiety. We therefore hypothesized that the combination of these reagents would effectively brominate aromatic compounds under mild conditions. The reaction proceeded using PhSTMS and NBS in CH_3CN at room temperature affording methyl 3-bromo-4-methoxybenzoate in 95% yield. Surprisingly, no reaction was observed in the absence of PhSTMS. Note, however, that sulfur compounds activate NBS even under oxidative conditions. The substrate scope indicated in Fig 1.[1)] In addition, sulfur compound can be replaced with PhSSPh (Fig. 2),[1)] which is less expensive than PhSTMS and, being a solid, is easier to handle. PhSSPh also exhibits less of the malodor associated with sulfur. This reaction is applicable to a chlorination using PhSTMS or PhSSPh and *N*-chlorosuccinimide (NCS).

Figure 1

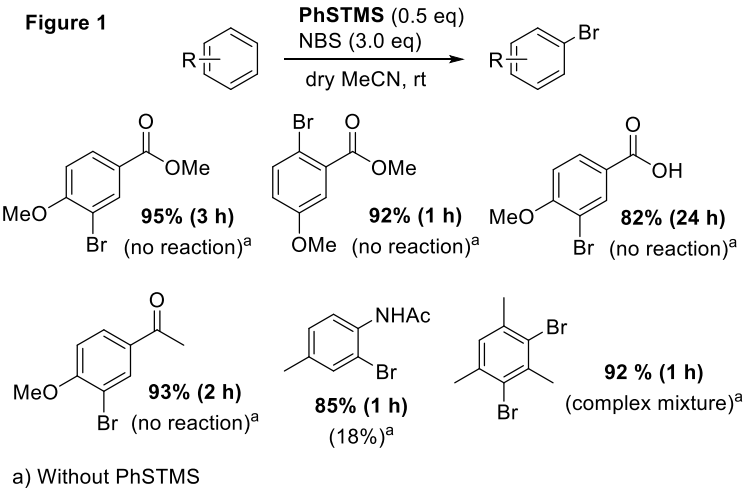
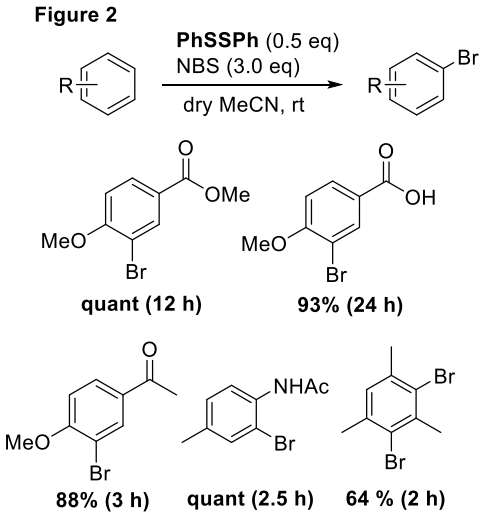


Figure 2



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1P- 23

Stereospecific Synthesis of 1,5-Disubstituted Tetrazoles from Ketoximes via Beckmann Rearrangement Utilizing Diphenyl Phosphorazidate

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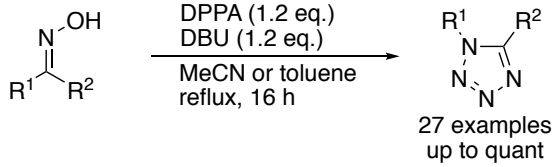
Tetrazoles are an important class of synthetic heterocyclic compounds, and have been attracting increasing attention due to their wide range of applications in various scientific fields. Among the tetrazole family, 1,5-disubstituted tetrazoles have been known to exhibit biological activity, such as cardiazol and cilostazol.

Methods for synthesis of 1,5-disubstituted tetrazoles from ketoxime esters *via* Beckmann rearrangement[1] or ketones *via* Schmidt rearrangement[2] have been reported. However, the application of these reactions require the use of toxic and explosive reagents.

On the other hand, diphenyl phosphorazidate (DPPA) is an azidating reagent suppressed explosibility due to the stabilization by conjugation with the phosphorus atom. Recently, we have reported the synthesis of 5-substitured 1*H*-tetrazoles from aldoximes utilized DPPA as both activator and azide source.[3] Therefore, 1,5-disubstitited tetrazoles could be synthesized from ketoximes if a Beckmann-type rearrangement proceeded by activation and azidation with DPPA.

First of all, we investigated whether the synthesis of a tetrazole *via* Beckmann rearrangement with DPPA was viable using acetophenone oxime as a model substrate. As a result, the desired product was obtained in good yield by using DPPA in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Various ketoximes were easily converted into the corresponding tetrazoles. No ketoxime isomerization occurred during the reaction, and rearrangement occurred stereospecifically with only the migration of *trans*-group. The advantages of this method include operational simplicity and increased safety as toxic or explosive azide reagents can be avoided.[4]



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1P- 24

Post-treatment Free Synthesis of Fairy Chemicals Using Fine Bubble and Flow Optimization Method

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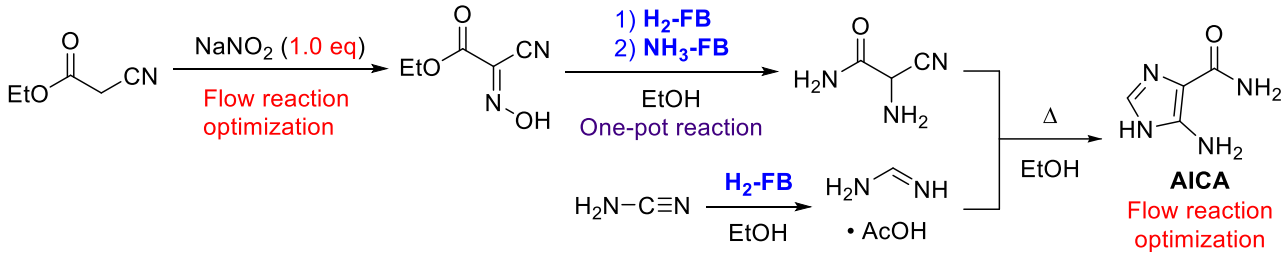
From a green sustainable chemistry (GSC) perspective, shifting from a batch process to a flow process that can reduce waste and save energy is desired.[1] Reducing the number of post-treatment steps enables practical multi-step synthesis in the flow method. The reaction involving the gas phase is a clean and simple initiated by simply injection of a gas, which can be stopped by removing the gas to save time for the post-treatment. In the present study, we report investigated improving the reaction efficiency by utilizing the fine bubbles (FB) by taking advantage of its excellent dispersibility and gas solubility in liquid reaction medium. In addition, we could conduct continuous reaction and post-treatment free reaction by identifying the reaction condition in the stoichiometric reaction to give the desired product in quantitative yield. We have previously developed a 9+4+1 method that combines design of experiments (DoE) and curved surface approximation using flow reactor.[2] Here, a new synthetic method of 5-aminoimidazole-4-carboxamide (AICA), which is an important intermediate of fairy compounds showing plant growth regulation,[3] was developed using FB method and flow reaction optimization method. As a result of applying the 9+4+1 method in the stoichiometric oximation, reaction conditions with a yield of 95% were identified in 14 experiments (180 min). Moreover, the H_2-FB hydrogenation reaction of the obtained oxime followed by the NH_3-FB amidation reaction of the ester could be carried out in a one-pot operation by readily changing the gas from H_2 to NH_3. Finally, AICA synthesis was achieved by H_2-FB hydrogenation reaction of cyano-group of cyanamide to imine and subsequent coupling reaction between amide and imine. All reactions except oximation were carried out in ethanol. Although a continuous process has not been achieved for all steps, a new synthetic scheme reported here has been established that significantly reduces the number of post-treatment steps.



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1P- 25

Reaction Optimization Using Microwave-assisted Continuous Flow Reactor with In-line Analysis

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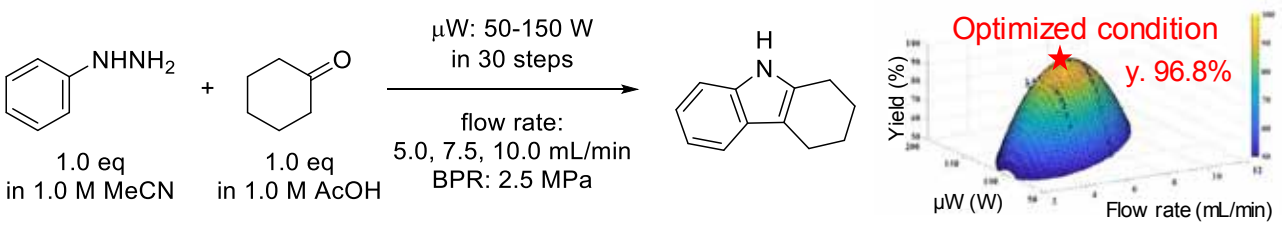
In order to develop new and/or non-industrialized chemical reactions in the laboratory, it is necessary to embrace the concept of green sustainable chemistry. It can improve waste, safety, time, energy, and cost. To solve these problems, various parameters in the chemical reaction need to be optimized. Although various reaction optimization methods have been developed, they have required a large number of experiments and a lot of time. Therefore, the 9+4+1 method[1] was developed by combining microwave-assisted continuous flow reactor and the design of experiments (DoE). By this method, the optimized reaction conditions were successfully determined in a total of 14 experiments (14 × 10 minutes = 140 min). However, the 9+4+1 method has the problem that reagents are consumed wastefully until the reaction reaches a steady state. In this report, the yield under continuous changing temperature condition by the gradient heating method was calculated by in-line analysis using near infrared (NIR) detector for aiming to develop a quick and easy optimization method in non-steady state.

A total of three experiments in the optimization of the Fischer-Indole synthesis predicted a reaction condition of 95.4% yield with a reaction time of only 30 minutes. When the actual reaction was carried out under the predicted conditions, a yield of 96.8% was obtained, and we found that our method can predict accurately. Furthermore, even in the case of the acetylation reaction of *tert*-butyl alcohol, which produces by-products such as isobutene, conditions of a yield of 68.0% are predicted, and a yield of 57.5% was actually obtained under the predicted reaction conditions. The combination of gradient heating with microwave-assisted continuous flow reactor and in-line analysis enabled the acquisition of comprehensive data. As a result, the optimization time and the number of experiments were significantly reduced compared to the conventional method. In the past, it was common to optimize for each reaction, but it can be optimized rapidly for each substrate now.



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1P- 26

Synthesis of polymer-supported *cis*-2,4-disubstituted pyrrolidine derivatives and their application to asymmetric reactions

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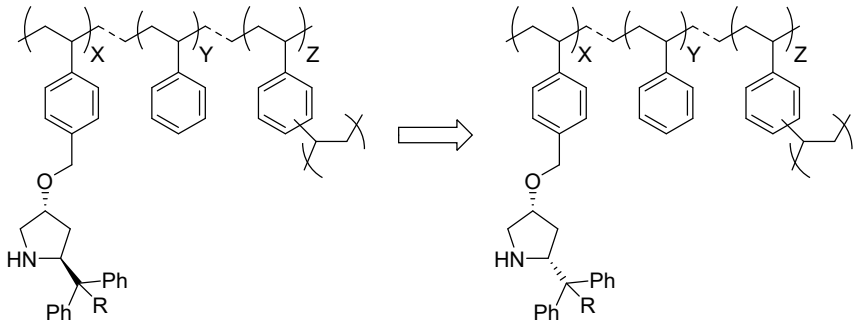
Organocatalyst has attracted much attention because of its chemical stability, environmental-friendliness, and high cost efficiency compared to organometallic catalyst. Particularly, polymer-supported organocatalyst is industrially attractive due to its easy separation from reaction mixtures and has been well investigated.

On the other hand, multi-substituted pyrrolidine catalysts derived from proline derivatives have been frequently used for asymmetric synthesis, and some of them were extended to polymer-supported catalysts. However, only *trans*-2,4-disubsstituted pyrrolidine catalysts were used for polymer-supported asymmetric catalysts probably because *trans*-4-hydroxyproline derivatives are easily available.

At this point, we envisioned that polymer-supported *cis*-2,4-disubstituted pyrrolidine catalysts which can be derived from *cis*-4-hydroxyproline would provide higher optical selectivity for asymmetric reactions than *trans*-2,4-disubstituted pyrrolidine catalysts because of their enhanced face selectivity caused by substituents on the same face of pyrrolidine ring.

Base on this hypothesis, we have synthesized new type of *cis*-2,4-disubstituted pyrrolidine catalysts from *cis*-4-hydroxyproline derivatives and applied them to some asymmetric reactions for investigation of optical yield. As a result, *cis*-2,4-disubstituted pyrrolidine catalysts gave higher enantioselectivity than *trans*-catalysts as we expected.

In this conference, the syntheses of *cis*-2,4-disubstituted pyrrolidine catalysts and their applications to asymmetric reactions will be provided.



trans-type catalyst

cis-type catalyst

Higher optical selectivity

R = H, OTMS, OMe

1P- 27

Application of Macroporous Polystyrene-Triphenylphosphine Monolith to Palladium-Catalyzed Cross-Coupling Reaction in Flow System

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Flow syntheses for production of fine chemicals have attracted much attention in laboratory or industrial application. The flow system has advantages over batch system in respects of cost- or energy-efficiency, safety, and automation. Transition-metal-catalyzed cross-coupling reactions are strong tools for production of active pharmaceutical ingredients with high reaction efficiency, selectivity, and energy saving. The increased demand for industrial-scale production of fine chemicals has motivated the development of flow cross-coupling reaction. In addition, using immobilized metal catalyst for the flow synthesis is desired to facilitate separation, purification, and recovery processes. Particularly, transformation of inactive and inexpensive aryl chlorides under flow condition are highly desirable but have been rarely reported.

Typically, flow cross-coupling reactions require careful design of reactor because of inorganic base reagents and salt byproducts. The inorganic components insoluble in organic solvent cause serious issues of clogging in the reactor. One general solution is to use solvent system which solubilize both organic and inorganic compounds. Some reports have demonstrated that use of organic/water biphasic solvent is beneficial for complete solubility of all the components and efficient cross-coupling reaction. We postulated three-keys to achieve challenging flow cross-coupling reaction: 1) organic/water solvent, 2) immobilized catalyst, 3) efficient mixing; but never demonstrated experimentally yet.

Herein, we first report an application of macroporous polystyrene-triphenylphosphine monolith (**M-PS-TPP**) to palladium (Pd)-catalyzed Suzuki-Miyaura cross-coupling reaction in flow system. The **M-PS-TPP** was synthesized by copolymerization of three-fold cross-linking triphenylphosphine, divinylbenzene, and *p-tert*-butylstyrene. The macroporous structure of **M-PS-TPP** was fabricated during the polymerization processes. The **M-PS-TPP** had characteristic window and void structure with the pore sizes of 2–5 and 10–20 μm. Pd-loaded **M-PS-TPP** column was applied to flow Suzuki-Miyaura cross-coupling reaction between 4-chlorotoluene and phenylboronic acid in THF/water biphasic media containing K_3PO_4. Tuning the column length and residence time achieved efficient mixing and high production efficiency in the reaction.

1P- 28

Preparation of Oil-based Stable Sliver Nanoparticle Suspensions

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In this study, we focused on how to development an oil-based stable suspension of conductive ink, to enhance the attachment of ink onto the substrate, and to seek the best conditions for printing quality. Furthermore, the stability mechanism and related applications were studied in detail, such as the use of prepared dispersion solution to produce a conductive film, and further to obtain a conductive pattern. First, silver nitrate was used as the metal precursor and ascorbic acid was added as the reducing agent with the addition of the surfactant and the protective agent. Through a series of formulations, we developed the oil-based conductive ink, whose suspension could maintain stable more than one year with no obvious precipitates. The ink was coated onto a glass slide via drop-casting method and subjected to sintering at 250 °C, the resulting conductive film had a sheet resistance of lower than 0.6 Ω/sq. Moreover, we also prepared the conductive pattern with a resistance of 3 Ω via desktop dispensing robot.

1P- 29

Design Space Success Stories: Reaction and Crystallization Processes

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When discrete reaction conditions (solvents, reagents, etc.) have been fixed, optimization of continuous variables (temperatures, times, concentrations) remains. One-variable-at-a-time experiments give only a vague picture of the effects of each paramter. A design space clearly delineates best, acceptable, and failure operating ranges, and it can provide surprising process insights.

In this presentation, we report two design space successes:

1.) Design spaces of a fed-batch reaction with a mixing-sensitive undesirable side reaction.

A design space of the yield with respect to temperature and amine reagent mole ratio revealed that excess amine (which was used to suppress the side reaction) was beneficial only to a limit, after which it became harmful. Another design space of the temperature and mixing time delineated the operating range in which the mixing sensitive, undesirable side reaction would become favored.

These results were generated by simulation. Kinetic data on the main and side reactions were gathered, a kinetic model was created, and simulations of the reaction and of the vessel mixing conditions were conducted.

2.) Design space of a crystallization, with the aim of controlling particle size.

A design space of temperature and anti-solvent addition time revealed that a crystallization was unaffected by these parameters within the ranges tested; the crystallization stably produced the desired crystal size.

This design space was generated by performing experiments at 1-L scale.

1P- 30

Process development of β—Lactamase inhibitor key intermediate

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Unnatural amino acids have become increasingly important as a pharmaceutical intermediate. We have been focusing on its development in recent years, and this poster shows one of the results.

5-Hydroxypiperidine-2-carboxylic acid (5-HPA) can be commonly used for β-lactamase inhibitors such as Avibactam, Relebactam, and Nacubactam. Due to the importance as a key intermediate, we have started on the synthetic study of 5-HPA in two ways.

Firstly, we have established a synthetic route to 5-HPA with a chiral pool method starting with commercially available ethyl (*S*)-4-chloro-3-hydroxybutyrate (*S*-CHE). Although compound 1 was an isomeric mixture, we found out an efficient method to give compound 2 *via* concomitant epimerization of the undesired 25% trans-isomer (Fig.1), following acid treatment gave 5-HPA.

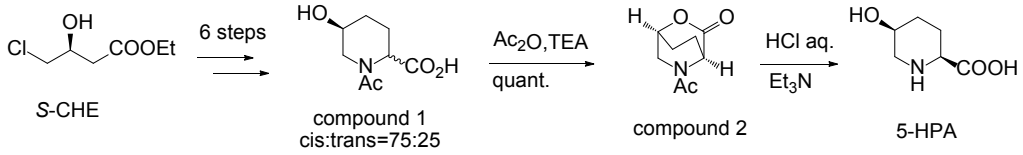

Fig.1 Synthetic process of 5-HPA utilizing isomerization.

Then, we turned our attention to an enzymatic approach to develop a simpler process. In order to reduce production steps, we have established a novel one-pot enzymatic process utilizing enzymatic cyclization and hydroxylation. This process makes it possible to use inexpensive natural amino acid, L-lysine, as a starting material and we succeeded to develop an efficient process with the combinations of several enzymes (Fig.2).

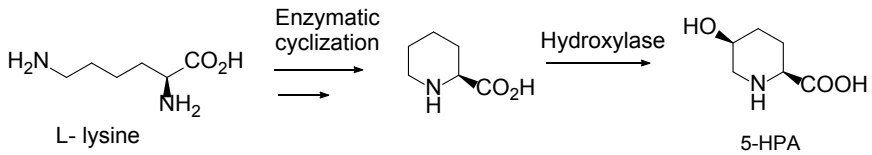

Fig.2 One-pot enzymatic process of 5-HPA from L-lysine

We are convinced that our chemical and enzymatic technology can be applied to other unnatural-hydroxylated amino acids.

1P- 31

Nitrones with Benzylic Bromides, Zinc, and Isobutyl Nitrite

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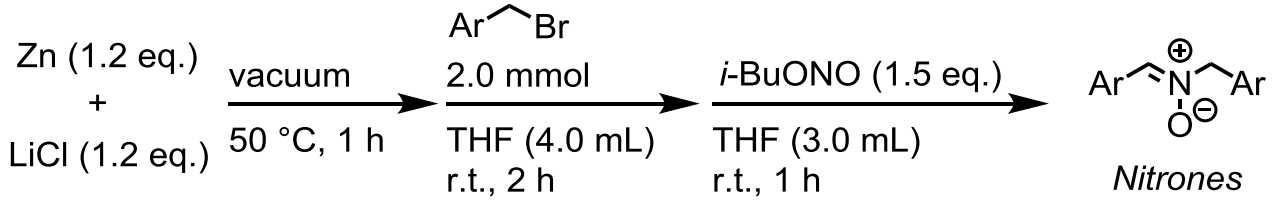
[Introduction]

Nitrones are useful and versatile intermediates for preparation of nitrogen-containing compounds, *i.e.*, addition to nitrones by organometallic reagents, 1,3-dipolar cycloaddition to alkynes, *etc*. As conventional nitrone syntheses, oxidation of *N,N*-dialkylhydroxylamines, oxidation of secondary amines, and reaction of *N*-alkylhydroxylamines with aldehydes have been used. However, these synthetic methods require the use of *N,N*-dialkylhydroxylamines and *N,N*-alkylhydroxylamines which are not easy to prepare, transition metals, or explosive hypervalent iodine. Here, we found simple preparation method of nitrones from benzylic bromides by the treatment with zinc and lithium chloride, followed by the reaction with isobutyl nitrite.

[Result]

After drying of a mixture of zinc and lithium chloride under reduced pressure at 50 °C., an organozinc bromide was prepared by the addition of a benzylic bromide in THF. Then, isobutyl nitrite was added to the solution of organozinc bromide, to form nitrone in a moderate yield. We also studied derivatization of nitrones obtained by this reaction, such as formation of isoxazoline through 1,3-dipolar cycloaddition reaction with alkyne, and reaction with benzyne.



Scheme. Preparation of Nitrones

[Reference]

K. Yanai, H. Togo, *Tetrahedron*, *75*. in press

1P- 32

2-Amino-4-arylthiazoles through One-Pot Transformation of Alkylarenes with NBS and Thioureas

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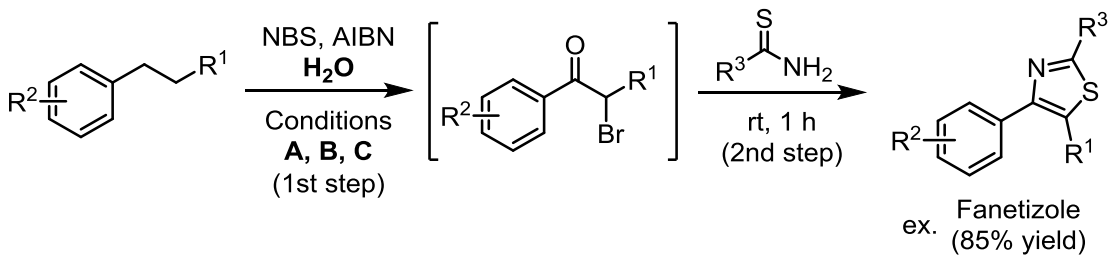
[Introduction]

Thiazole is one of representative nitrogen-containing heteroaromatics contained in pharmaceuticals and natural products. Today, they are usually synthesized from α-haloketones prepared beforehand from ketones, and thioamides, and some of them required toxic transition metals, such as Cu, Pd, etc. Here, we found the direct preparation of thiazoles in good yields from alkylarenes, which are easily available and inexpensive, with thioamides for the first time. The key step of the present one-pot synthesis is the transformation of alkylarenes into α-bromoketones selectively, and it was accomplished by simply employing water as an additive in the Wohl-Ziegler reaction, which doesn't include any expensive or harmful transition metals.

[Results]

First, the reaction conditions were optimized for the substrates (*i.e.*, R^2 = H), the α-bromoketone which was an intermediate could be obtained in high yield by reacting with the brominating agent NBS and the radical initiator AIBN in a mixture of AcOEt/H_2O at 60 °C. Next, the reaction conditions were readjusted to the substrates bearing electron-withdrawing groups (*i.e.*, R^2 = *p*-CO_2Me), a mixture of MeCN/H_2O at 80 °C was the best for benzylic oxidation. And finally, the reaction conditions were readjusted for the substrates bearing electron-donating groups (*i.e.*, R^2 = *p*-OMe), and the best results were obtained under the irradiation conditions with a tungusten lamp in a mixture of $(EtO)_2CO/H_2O$ at 30-40 °C.

Thus, the reactivity for the transformation depends on the electron density of aromatic rings of alkylarenes. However, by using the optimized three reaction conditions various thiazoles were directly synthesized from alkylarenes bearing a broad range of substituents via α-bromoketones in situ. Moreover, Fanetizole, an immunomodulatory drug, was prepared immediately and cheaply with the present method.



[References]

(1) K. Shibasaki, H. Togo, *Eur. J. Org. Chem.* **2019**, *14*, 2520.
(2) S. Shimokawa, Y. Kawagoe, K. Moriyama, and H. Togo, *Org. Lett.* **2016**, *18*, 784.

1P-33

Biocatalysts for Hydroxylation

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Cytochrome P450 monooxygenases (P450s) constitute a gene superfamily that widely exist in nature; most of living organisms, from microorganisms to humans, and play important roles in biosynthetic and xenobiotic pathways by catalyzing different reactions, including hydroxylation reaction. Due to its reaction specificity, P450s are capable of catalyzing regio- and stereo-specific hydroxylation reactions even which are difficult to achieve by chemical reactions.

Here we present our P450 library and the practical example of its application.
In Microbiopharm Japan's P450 library (MBJ P450 library), various types of microbial cytochrome P450 genes were cloned and co-expressed with electron transport cofactor genes of camA and camB in *E.coli*. In order to maximize hydroxylation efficiency of P450s, the MBJ P450 library was given stepwise improvement: the first improvement was made by improvement of *E.coli* cell to increase intracellular uptake efficiency of substrate, and also by optimization of electron transfer system. The second improvement made to MBJ P450 library was the establishment of mutant sub-library with superior enzymes that has higher enzymatic activity with better selectivity. These improvements allow to construct the strains being feasible for industrial use in short period of time.

Application of MBJ P450 library adds values to the compound itself and/or production processes. As one of the examples, we present the bioconversion from clarithromycin to 14-OH-clarithromycin, in which productivity of the target compound was increased significantly. At first, we selected from MBJ P450 library the P450 enzyme which are able to convert clarithromycin into 14-OH-clarithromycin. However, due to the broad substrate specificity of the selected enzyme, by-products such as 15-OH and N-demethylated clarithromycin were formed, resulting in low yields of 14-OH clarithromycin, the target compounds. In order to reduce the production of by-products, we constructed the mutated sub-library of the selected enzyme. Screening results of the constructed sub-library showed increased the 14-OH clarithromycin yield as well as reduced production of by-products.

1P- 34

Oxidative Construction of 2-Arylquinolines from *β*-Arylpropionitriles with Aryllithium and NIS through Iminyl Radical-mediated Cyclization

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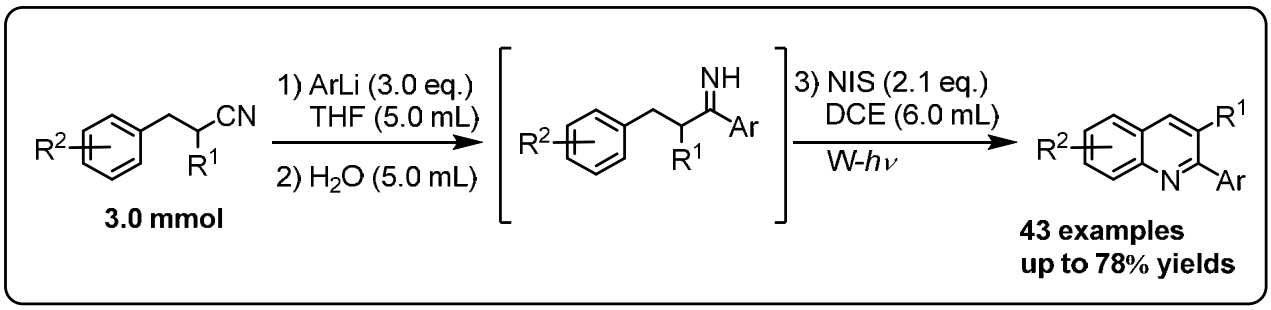
[Introduction]

Quinolines, one of the typical nitrogen-containing heteroaromatics, are known as important units in pharmaceuticals and functional materials due to their broad range of biological activities and functional abilities. Today, there are many established methods for the preparation of quinoline skeletons as name reactions, such as the Skraup quinoline synthesis with anilines and acrolein, the Knorr quinoline synthesis with acetoacetanilides. However, most of those synthetic methods require harsh reaction conditions or transition metals. So, still simple and efficient synthetic method have been required, due to the importance of quinolines. Here, we have succeeded in novel and efficient preparation of quinoline derivatives from β-arylpropionitriles with aryllithium through formation of imines and *N*-iodo imine with iodine reagents, via cyclization onto the aromatic ring by imino-nitrogen-mediated cyclization.

[Results]

To a solution of β-arylpropionitrile (3.0 mmol) in THF was added ArLi at -10 °C. The obtained mixture was stirred for 30 min at –10 °C under argon atmosphere and then with water to form imine. Then, the imine was treated with *N*-iodosuccinimide (NIS) in 1,2-dichloroethane under irradiation with a tungsten lamp (300 W) at the range of 35 °C ~40 °C to give 2-arylquinoline in moderate yield. Using this method, various 2-arylquinolines were obtained in good to moderate yields.



1P- 35

Novel and Practical Deprotection Method of *t*-Boc Group for Preparation of Cefcapene Pivoxil Hydrochloride Hydrate Using Formic Acid and Lithium Chloride

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Cefcapene Pivoxil Hydrochloride Hydrate (CFPN-PI) is drug substance of Flomox®, which is one of 3rd generation cephem antibiotics and it is isolated as hydrochloride salt and hydrate.

The final step for producing CFPN-PI in current commercial manufacture is deprotection reaction of *tert*-butoxycarbonyl (*t*-Boc) group. The reaction efficiently proceeds using $TiCl_4$ as a Lewis acid in dichloromethane, and only small amount of impurities are by-produced. On the other hand, the following several negative points have been remained yet.

- Quantitative amount of $Ti(OH)_4$ is by-produced by quenching after the reaction, and it is removed by extraction to aqueous layer. Hence, *Complicated Sub-Processes* are needed to recover $Ti(OH)_4$ as TiO_2.
- Dichloromethane is *NOT* environment-friendly solvent.

The study for developing novel deprotection method of *t*-Boc group for producing CFPN-PI started with that kind of background. We focused to establish using the combination of mineral acid or organic acid and additive from the point of view of simplification of manufacturing process and cost.

At first, we studied effect of acid using solvent amount of several acids. From the results, formic acid (HCO_2H) was found most suitable acid. We also evaluated effect of additives using HCO_2H solvent system. Addition of alkyl-metal halides except for NaCl and KCl promoted deprotection reaction of *t*-Boc group. NaI, KI and LiI have a concern about work-up for free I_2, and hydrobromate of product may contaminate in the cases of using NaBr and LiBr. Therefore, we selected LiCl as an additive for the reaction.

During process development, the amount of one impurity (Impurity A) was found more than 0.15% (based on identification threshold by ICH Q3A) in the crystal of CFPN-PI. Impurity A is formed by the reaction of CFPN-PI and *t*-butyl cation which is by-produced during deprotection reaction *in situ*. We tried to improve reaction method to reduce by-produced amount of impurity A since Impurity A is hardly removed by crystallization. We planned to reduce *t*-butyl cation *in situ* by discharging isobutene and *t*-BuCl outside continuously. We found that the reaction under reduced pressure was effective to reduce by-produced amount of Impurity A, and Impurity A was able to be controlled by not more than 0.15% in CFPN-PI.

In conclusion, we established novel and practical deprotection method for *t*-Boc group using combination of LiCl and HCO_2H. Complicated work-ups and sub-processes are *NOT* needed in the method. Manufacturing cost is expected to be reduced and yield is expected to be increased compared with current process.

1P- 36

The development for manufacturing process of methyl ester reduction with $LiBH_4$ prepared in-situ

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Lithium borohydride ($LiBH_4$) is generally used for ester reduction to obtain alcohols. And sodium borohydride ($NaBH_4$) can also be used for same purpose. However, in most of the cases, reduction of esters with $NaBH_4$ needs activation. During activation, the reaction is generally exothermic and intensive hydrogen gas generation occurs, and difficult to control them. That's why $LiBH_4$ is much better to reduce esters from process chemistry point of view.

In our scale up study of methyl ester reduction with $LiBH_4$, we encountered three big issues.

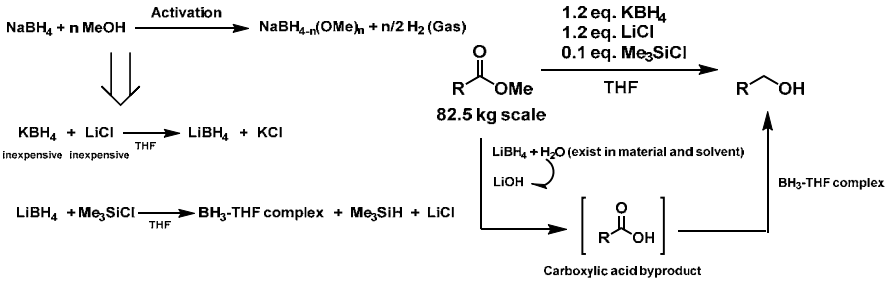
1. $LiBH_4$ is somewhat expensive to use in industrial scale, so we have to prepare it by ourselves from inexpensive reagents.
2. We have no analytical measurement for $LiBH_4$ when it is prepared from inexpensive reagents.
3. Hydrolysis side reaction occurs by small amount of water, which exists in the raw materials and solvent, this carboxylic acid byproduct is contaminated in desired product.

Regarding $LiBH_4$ reagent cost: $LiBH_4$ can be generated from potassium borohydride (KBH_4) and lithium chloride (LiCl), these reagents are inexpensive. This procedure can reduce purchasing cost of reagents.

Regarding analytical measurement for generation rate of $LiBH_4$: At first, we used React-IR to conduct qualitative confirmation. However, React-IR can't confirm generation rate of $LiBH_4$ quantitatively, so we developed new quantitative analytical method by using reaction between *p*-anisaldehyde and $LiBH_4$ which is generated from KBH_4 and LiCl. This method can determinate the generation rate of $LiBH_4$ indirectly.

Regarding carboxylic acid: Although many attempts were conducted to prevent hydrolysis of methyl ester and remove the byproduct during crystallization and by using activated carbon filter, all attempts were failed. So, we changed a strategy for controlling the byproduct and tried to covert carboxylic acid byproduct to desired alcohol. After our investigation, the byproduct can be reduced by pre-addition of catalytic amount of chlorotrimethylsilane (TMSCl) in the reaction mixture. TMSCl is known to react with LiBH4 and produce borane-THF complex. And this borane-THF complex converted the carboxylic acid by-product to desired alcohol.

Finally, we established manufacturing process of ester reduction and succeeded this reaction in our commercial production (82.5 kg scale).



1P- 37

Continuous Flow Lipase-Catalyzed Dynamic Kinetic Resolution of Alcohols

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Recently we have developed dynamic kinetic resolution (DKR) of racemic secondary alcohols by the combined use of a commercial immobilized lipase and an immobilized racemization catalyst, V-MPS, in a batch reactor to produce optically pure esters in more than 90% yields.[1] V-MPS, in which oxovanadium species are covalently bound on the inner surface of mesoporous silica (MPS), catalyzes the racemization by bonding with the hydroxyl group of the alcohols through formation of a cation intermediate **A** followed by recombination. In this symposium, we will present applications of this method to a continuous flow system, which has attracted increasing attention as a new production process.

First, we tried continuous flow lipase-catalyzed DKR of secondary alcohols (±)-**1** using a reactor packed with the lipase used for the batch process and V-MPS4. The continuous flow DKR has caused a problem of formation of a by-product, dimer ether **3**, formed by the reaction of **A** with **1** (Figure 1). We have extensively examined the reaction conditions, such as the flow rate and amounts and ratio of two catalysts, to succeed in producing optically pure esters (*R*)-**2** in >90% yields. Advantages of this flow method over the traditional batch process contain shorter reaction time (residence time: around 30 min; batch reactions: 12-24 h) and easy workup—simple concentration of the eluent produces the products (*R*)-**2** because an excess amount of vinyl acetate is distilled off with the solvent.

The details will be presented on poster.

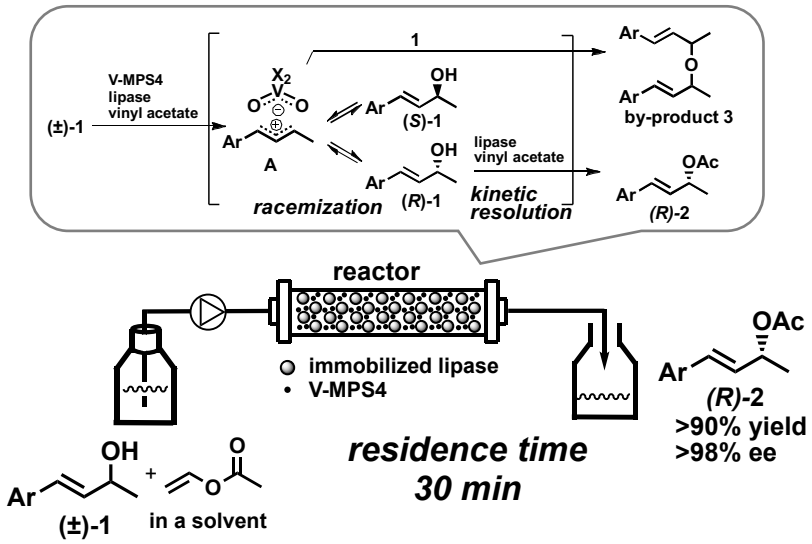

Figure 1. Continuous flow lipase-catalyzed dynamic kinetic resolution of (±)-**1**.

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1P- 38

Chemoselective demethylation of methoxypyridine

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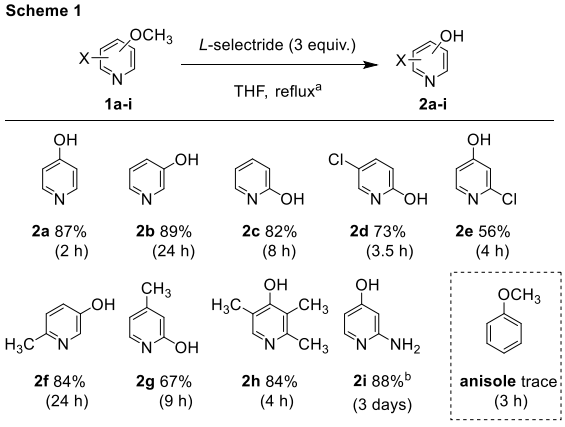
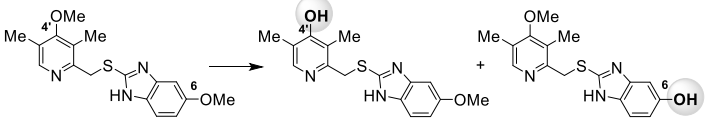
Methyl ether is considered to be the most useful and effective protective group for phenols in synthetic chemistry because of a tolerance to a variety of reaction conditions. We found a chemoselective demethylation for various methoxy pyridines. Treatment of 4-methoxypyridine with *L*-selectride in THF for 2 hours at reflux temperature afforded 4-hydroxypyridine in good yield, while no reaction occurred to anisole (Scheme 1)[1]. Intriguingly, the position of the -OCH_3 group has a profound influence on the reactivity for demethylation, and the reaction was completed in 2 h for **2a**, while 24 h was needed for **2b**. Other methoxypyridines, irrespective of their electronic nature (electron-rich/electron-poor), furnished the corresponding demethylated compounds **2d**–**2i** in 56–84% yields. The utility of our method was demonstrated by the efficient synthesis of the metabolites of anti-ulcer agent, omeprazole (**3**-**5**). A chemoselective demethylation at the site of 3,5-dimethyl-4-methoxypyridine in the presence of 4-methoxybenzimidazole was achieved (Table 1). We anticipate this method would be useful to prepare biologically active heterocyclic compounds.

Scheme 1



a) Reaction times are shown in parentheses. b) 6 equiv. of *L*-selectride were used.

Table 1



Entry	Reagents	Equiv.	Solvent	Temp.	Time	**4** (%)	**5** (%)
1	*L*-selectride	3	THF	reflux	3 h	94	–
2	BBr_3	2.5	CH_2Cl_2	0 °C	12 h	–	79

1) K. Makino, Y. Hasegawa, T. Inoue, K. Araki, H. Tabata, T. Oshitari, K. Ito, H. Natsugari, H. Takahashi. *Synlett* **2019**, *30,* 951－954.

1P- 39

A Case Study of Theoretical Purge Factor for Mutagenic Impurity Management by Collaboration among 6 Pharmaceutical Companies

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ICH M7 guideline provides the framework of the assessment and control of mutagenic impurities (MIs) for pharmaceuticals to limit potential carcinogenic risk. According to ICH M7 guideline, “A control strategy that relies on process controls in lieu of analytical testing can be appropriate if the process chemistry and process parameters that impact levels of mutagenic impurities are understood and the risk of an impurity residing in the final drug substance above the acceptable limit is determined to be negligible. In many cases justification of this control approach based on scientific principles alone is sufficient. Elements of a scientific risk assessment can be used to justify an option 4 approach”. A scientific risk assessment can be justified by theoretical purge factor (TPF).

TPF of a mutagenic impurity (MI) is calculated from its physicochemical properties such as reactivity, solubility, volatility, and physical processes. However, there is no clear guidance to calculate TPF, so the calculation depends on the knowledge and/or policy of each company or scientist; as the result, the scores of TPF could be different. Six pharmaceutical companies consisted of a small close workshop in order to practice TPF calculation in a case study.

We discussed 4 potential impurities in a publicly disclosed synthetic route of Atovaquone and each company determined their TPFs; however, the values were different up to 1000 times. Especially, opinions about solubility and physical process scores were divided whereas reactivity scores were roughly consistent with each other. In addition, there were pros and cons of the multiplication of the same kinds of factor in a single step. As the outcome of the case study, we suggest the member’s recommended approach to calculate TPF.

1P- 40

Novel Preparation of Aromatic Nitriles from Aryl Bromides and Arenes via Imino-nitrogen-centered Radicals.

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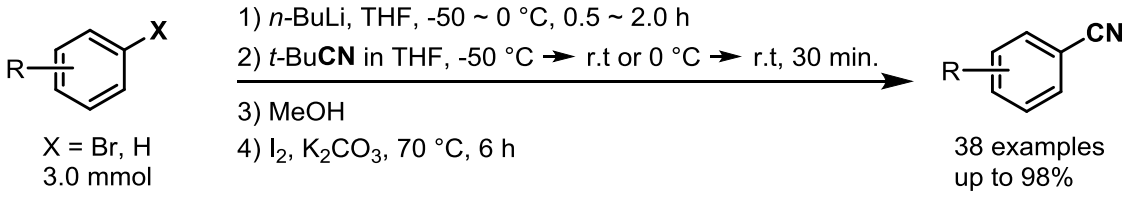
[Introduction]

Aromatic nitriles are widely used for medicines, agrochemicals, and functional materials, such as liquid crystals. Additionally, since the nitrile group can be easily converted into other functional groups, such as carboxylic acid, amide, amine, and tetrazole, aromatic nitriles are important compounds from the viewpoint of organic synthesis. However, most of those synthetic methods require toxic or expensive transition metals, or metal cyanides. Here, we have established one-pot preparation of aromatic nitriles from aryl bromides and arenes via imino-radical *β*-elimination through formation of imines and *N*-iodoimines with iodine reagents.

[Results]

Treatment of aryl bromides or arenes with *n*-BuLi, and then pivalonitrile, followed by the reaction with MeOH and then molecular iodine in the presence of K_2CO_3 under warming conditions gave the corresponding aromatic nitriles in good yields, respectively. By using the present methods, aromatic nitriles could be obtained effectively in one pot from various aryl bromides and arenes under metal-cyanide-free and transition-metal-free conditions.



- **Metal Cyanide-Free Reaction**
- **Transition-Metal-Free Reaction**
- **One-Pot Reaction**
- **Mild Reaction Conditions**

Scheme . Preparation of Aromatic Nitriles.

1P－41

Pd/Cu-catalyzed Anti-Markovnikov Oxidation of Aliphatic Alkenes to Terminal Acetals

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Realization of anti-Markovnikov selectivity in Wacker-type oxidation and related reactions from terminal alkenes is challenging. As for acetal formations, alkenes with electron-deficient groups, alkenes with O, N, or S directing groups, 1,5-dienes, and vinylarenes are known to afford terminal acetals preferentially by reactions with alcohols or diols; however, unbiased aliphatic terminal alkenes still remain as difficult substrates. Here we report the Pd/Cu-catalyzed anti-Markovnikov oxidation of aliphatic terminal alkenes to terminal acetals under mild reaction conditions.[1] The key features include: (i) slow addition of alkenes, which suppresses isomerization of terminal alkenes into internal alkenes, (ii) addition of electron-deficient cyclic alkenes as auxiliary ligands, which enhance catalytic activity and anti-Markovnikov selectivity, and (iii) halogen groups in alkenes, which operate as directing groups, affording high selectivity.

1-Octene and pinacol were treated with $PdCl_2(MeCN)_2$ (10 mol%) and CuCl (20 mol%) in *t*-BuOH under 1 atm of O_2 at 40 °C for 8 h. Under these conditions, the terminal acetal was formed only 8% along with 2- and 3-octanones in 25% total yield. 2-Octenes were also observed (39%). When slow addition of 1-octene (over 7 h) was performed, formation of 2-octenes was suppressed (19%) and the yield of the terminal acetal and anti-Markovnikov selectivity were both increased (34% and 55%). The effect of electron-deficient cyclic alkenes as additives (1.0 eq) was then examined, because they operate as ligands to increase the catalytic activity in the Pd-catalyzed aerobic anti-Markovnikov Wacker-type oxidation[2] and acetalization[3] of vinylarenes. Among the additives examined, methyl-*p*-benzoquinone (MeBQ) afforded a best result (53% yield of the terminal acetal and 61% selectivity).

The optimized reaction conditions were applied to various aliphatic alkenes. When 4,4-dimethyl-1-pentene was used as a substrate, the terminal acetal was obtained in 73% yield with 86% anti-Markovnikov selectivity. 4-Bromo-1-butene afforded high yield of the terminal acetal (84%) with high selectivity (97%). In this case, slow addition of the alkene was not necessary because the isomerization of alkene did not compete. These results suggest that the halogen substituent would operate as a directing group, albeit they are regarded as weakly coordinating ligands in general. Alkenes with oxygen functional groups were also applicable to afford good yield of the corresponding terminal acetals with good to high selectivity.

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1P-42

Heterogeneous Metal Catalyzed Aerobic Dehydrogenative Biaryl Coupling of Aniline Derivatives

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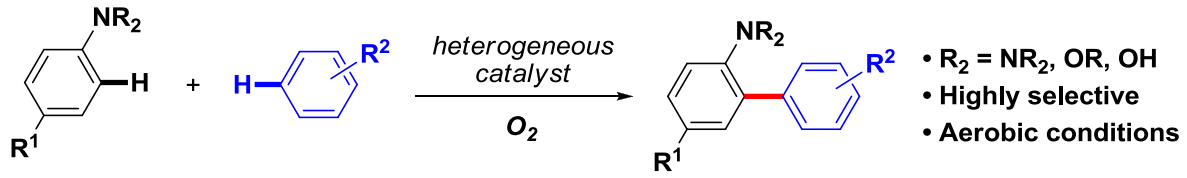
Biaryl compounds are important fundamental skeleton in natural products, pharmaceuticals, and material sciences. Particularly, axially chiral biaryls, such as BINOL, BINAP, and BINAM, are known as the most successful ligands in asymmetric catalysis and have already been studied in details. For the access to the biaryl compounds, selective direct oxidative homo- and cross-coupling of naphthols and phenols has received tremendous attention within the past decade because of the atom and step economy. However, the direct oxidative biaryl coupling of aryl amines is largely limited because aryl amines are easily oxidized and thus generate many side products. Oxidative homo-coupling of naphthylamines with the stoichiometric amounts of copper salts have been reported but the yields of the produced biaryls were generally moderate or poor. Furthermore, only few examples of oxidative coupling of aryl amines using heterogeneous catalysts have been reported. Thus, the development of novel and powerful synthetic strategies of 2-aminobiaryl is strongly needed.

Recently, we have found that the commercially available heterogeneous rhodium catalyst can function as an excellent catalyst for the aerobic oxidation reactions and developed heterogeneously catalyzed homo-coupling as well as the selective cross-coupling of naphthylamines to provide symmetrical and nonsymmetrical 2-aminobiaryls in high yields.[1] However, the oxidative cross-coupling between two arenes with similar chemical properties, such as aniline-aniline coupling, are still difficult and thus only limited success has been reported until recently. Herein, we demonstrate the first catalytic oxidative dehydrogenative aniline−aniline cross-coupling with heterogeneous catalyst under mild aerobic conditions. Various electron rich arenes can be selectively coupled to provide 2-aminobiaryls in excellent yields.



Reference

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1P- 43

PAT: Optimize Processes From Liquids to Solids

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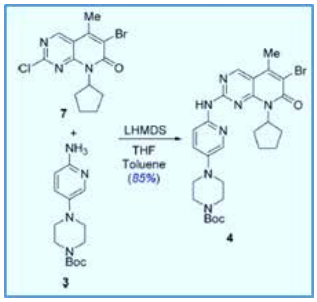
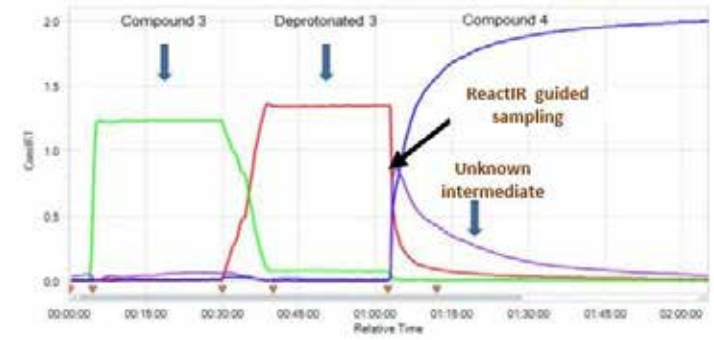
It has been a main practice in the Chemical industry for several years now to utilize PAT technologies and more recently has become increasingly adopted within the Pharmaceutical industry. Through the use of "in-process", in-situ analytical tools, scientists are gaining greater insight into their chemistry faster and on a wider scope than ever before. ReactIR and Raman are two good examples of PAT technologies that are proving to be valuable to process development, product quality and safety by the depth of real time information they provide independent of traditional offline methods.

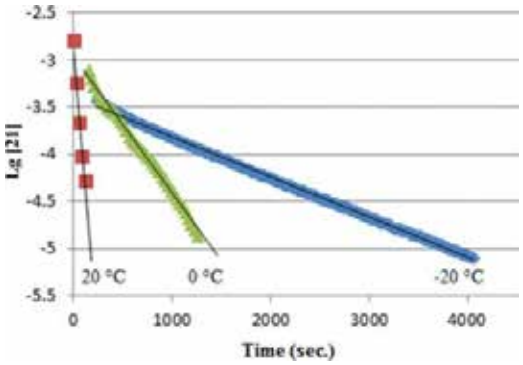
<u>In situ & automated analytics isolate important intermediate, and provide insight into reaction mechanism</u>

In-situ ReactIR monitoring provided some insight into the reaction mechanism based on the reaction progression. Deprotonation of aminopyridine (3) was instantaneous upon addition of LiHMDS. Subsequent addition of (7) resulted in the formation of a small amount of desired product (4) and a larger amount of an intermediate that slowly converted to the desired product (4). Using a METTLER TOLEDO EasySampler probe. We were able to capture samples containing this intermediate, the pyridinium salt





A series of experiments at −20 °C, 0 °C, and 20 °C were performed, and the data were exported to iC Kinetics software for kinetic modeling.
The kinetic simulation confirmed that the decay of 21 (the imino form of the intermediate) was first order conversion of (21) to the desired product was through an intramolecular rearrangement



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1P- 44

Palladium and Niobic Acid on Carbons-Catalyzed Facile Hydrogenative Deprotection of *N*-Benzyl Groups

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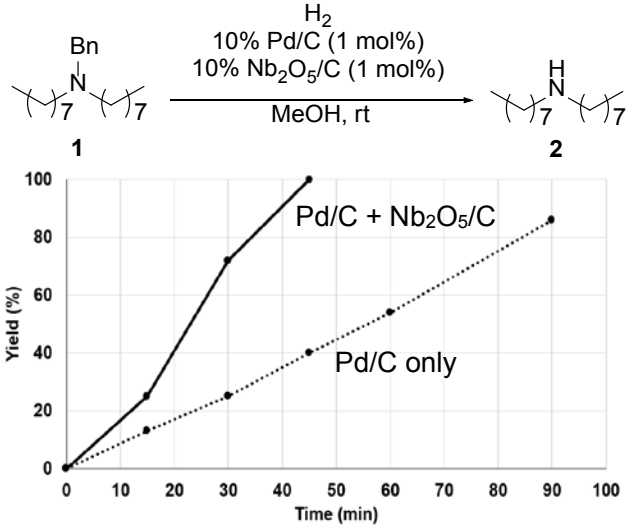
The protecting group is crucially important in the efficient syntheses of the target molecules. Benzyl (Bn) group is often utilized as a protecting group of amine functionalities, and the deprotection of *N*-benzyl protected amines can be achieved by the use of palladium on activated carbon (Pd/C)-catalyzed hydrogenative conditions. Although the acidic conditions in the presence of hydrochloric acid or acetic acid were reported to accelerate the reaction rate, the neutralization process was required to regenerate the desired amine products.[1,2] By the way, niobic acid (Nb_2O_5) possessing Brønsted as well as Lewis acidity attracts much attention as an acidic solid catalyst.[3] We have newly developed an easy preparation method of Nb_2O_5 on activated carbon (Nb_2O_5/C), which effectively facilitates the Pd/C-catalyzed hydrogenative deprotection of an *N*-benzyl group to provide the corresponding deprotected amine.

Figure 1



The effect of the addition of Nb_2O_5/C in Pd/C-catalyzed hydrogenative deprotection of *N*-benzyl dioctylamine (**1**) is shown in Figure 1. The deprotection of **1** progressed slowly by the independent use of 1 mol% of Pd/C, however, the deprotection was incomplete even in 90 min (Figure 1, dotted line). Meanwhile, the addition of Nb_2O_5/C (1 mol%) significantly accelerated the Pd/C-catalyzed deprotection of **1**, and **2** was obtained in quantitative yield within 45 min (solid line). It is noteworthy that an analytically pure product (**2**) was obtained by only simple filtration.

N-benzyloxycarbonyl (Cbz) and *O*-Bn protecting groups were also effectively and quickly deprotected under Pd/C and Nb_2O_5/C-catalyzed hydrogenative conditions.

The present method is useful from the viewpoint of green and process chemistry due to the ease of preparation, reusable property, and promoting effect toward the Pd/C-catalyzed hydrogenative deprotection of benzyl type protecting groups of Nb_2O_5/C.

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1P- 45

Pt/C-catalyzed oxidative annulation of diols to lactones

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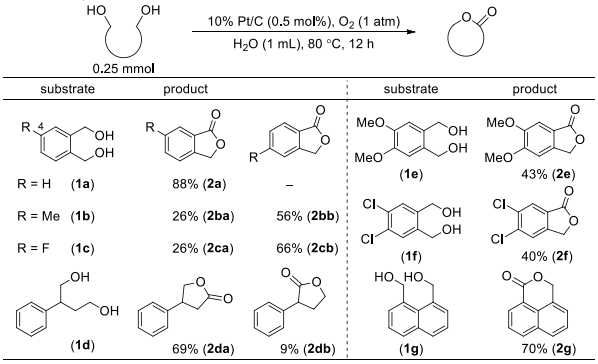
Lactones are essential frameworks in organic, pharmaceutical and industrial chemistries. Among the versatile lactone syntheses, the oxidative lactonization of easily-available diol as substrates are also eagerly investigated. Notably, the lactonization of diols using atmospheric O_2 as an oxidant in the presence of transition metal catalysts are of value in terms of the viewpoint of atom economy and green sustainability because the only by-product is water.

Although various homogeneous and heterogeneous catalytic methods have been reported for the effective lactonization, ~~the~~ organic solvents were required to facilitate the desired lactonization. We have already established the oxidation of primary and secondary alcohols catalyzed by ruthenium on carbon in toluene under an oxygen atmosphere.[1] Herein we newly report platinum on carbon (Pt/C)-catalyzed oxidative lactonization of diols using molecular oxygen as a green oxidant in water to provide the corresponding lactones.

Table 1: Scope of substrate



The desired lactonization was carried out in the presence of 10% Pt/C (0.5 mol%) in water under atmospheric O_2 at 80 °C for 12 h, and the scope of substrates is shown in Table 1. 1,2-Benzenedimethanol (**1a**) was effectively converted to phthalide (**2a**) in 88%.

1,2-Benzenedimethanol derivatives (**1b** and **1c**) bearing a substituent at the 4-position of the aromatic nuclei underwent the lactonization to phthalide derivatives (**2b** and **2c**) as isomeric mixtures.

The lactonization of 2-phenyl-1,4-butanediol (**1d**) gave the corresponding γ-butyrolactones as an 88:12 mixture of isomers (**2da** and **2db**) in good yield under optimized conditions.

4,5-Dimethoxy and dichloro 1,2-benzenedimethanol derivatives (**1e** and **1f**) were also transformed to phthalide s (**2e** and **2f**). 1,8-Bis(hydroxymethyl)naphthalene (**1g**) was smoothly converted to 1,8-naphthalide bearing a six-membered lactone moiety (**2g**)

We have accomplished the efficient oxidative lactonization of a variety of diols using the heterogeneous Pt/C in aqueous media under an atmosphere of oxygen at 80 °C. The present catalytic method using molecular oxygen in water is valuable from the viewpoint of green sustainability and atom-efficiency.

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1P- 46

Aromatic Aldehyde-Selective Functionalization via Pyridinium Salt Intermediates

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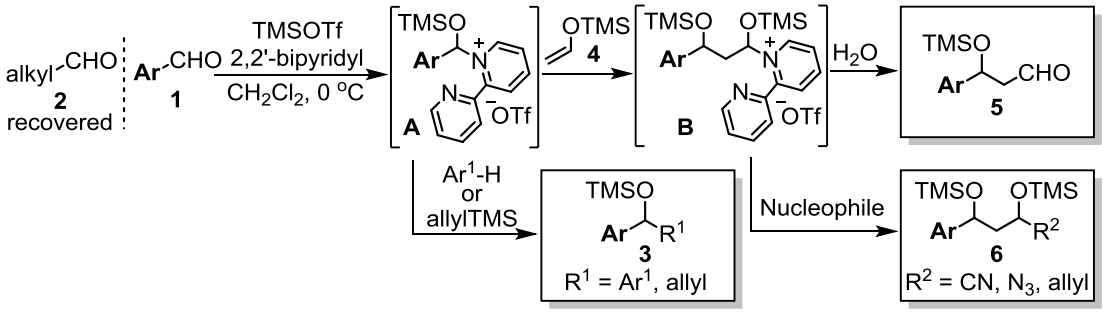
Aldehydes are widely utilized as reactive electrophiles toward carbon nucleophiles to form carbon-carbon bonds in organic synthesis. However, it is still challenging to accomplish the perfect chemoselectivity between aromatic and aliphatic aldehydes. Herein, we demonstrate an aromatic aldehyde-selective nucleophilic functionalization using silyl triflate and a pyridine derivative via the pyridinium-type salt intermediates.[1,2)]

The pyridinium-type salt intermediate (**A**), generated from aromatic aldehydes (**1**) in the presence of 2,2'-bipyridyl and TMSOTf, efficiently reacted with electron-rich arene (Ar^1-H) or allyl silane to give the corresponding benzyl silyl ether (**3**). Although aliphatic aldehydes (**2**) might also be transformed to the corresponding pyridinium-type salt intermediates, the complete recovery of **2** was observed due to low reactivity toward arenes or allylsilanes as nucleophiles. When using TMS enol ether (**4**) derived from acetaldehyde as a nucleophile, the aromatic aldehyde (**1**)-selective aldol addition effectively proceeded via two types of pyridinium salt intermediates (**A** and **B**). The reactive pyridinium salt intermediate (**A**) derived from the aromatic aldehyde (**1**) was converted into the less reactive pyridinium salt intermediate (**B**) based on an aliphatic aldehyde. Then, **B** was smoothly transformed to the desired *β*-siloxy aldehyde (**5**) after aqueous work up. Meanwhile, the sequential addition using a variety of nucleophiles, such as TMSCN, $TMSN_3$, and allyl-Bpin, gave the highly-functionalized compounds (**6**) in a one-pot manner. The present unprecedented and chemoselective functionalizations are useful to diversify the synthetic strategies for target organic molecules.



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1P-47

Chiral Macrocyclic Lithium Binaphtholate Catalysts for Enantioselective Addition of Lithium Acetylides to Ketones

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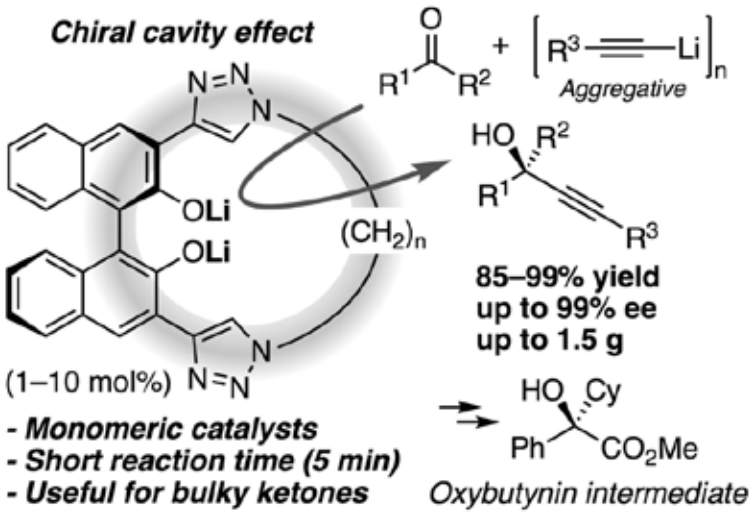
Optically active propargyl alcohols are versatile chiral building blocks in asymmetric synthesis, and are used as intermediates of natural products and pharmaceuticals. The key alkynyl moiety can be easily transformed, and the corresponding alkenes, alkanes, allenes, hydroxy ketones, etc. are provided. In particular, catalytic enantioselctive alkynyl addition to carbonyl compounds is useful synthesizing optically active both 2°- and 3°-propargyl alcohols. Traditionally, zinc acetylides have been used for this purpose in the presence of chiral BINOLs often with the use of Ti(O*i*-Pr)$_4$. Moreover, recently, terminal alkynes have been directly used in the presence of chiral transition metal catalysts. These excellent methods using nucleophilic acetylides *in situ* are effective for aldehydes, α-keto esters, and trifluoromethyl ketones, since these substrates are highly reactive. In contrast, sterically hindered and much less reactive simple ketones are still challenging substrates. To use low-reactive simple ketones, highly reactive lithium acetylides, unlike much less nucleophilic other metal acetylides, might be attractive. However, the inherent oligomerization of lithium acetylides and Li(I) catalysts often prevent the desired reactions. If active monomeric Li(I) catalysts should be used exclusively without a loss of catalytic activity, great improvements in both substrate scope and reaction efficiency, such as catalyst loading, reaction time, and scalable synthesis, might be achieved.

In the present study, chiral BINOL ligands, of which the 3,3'-positions are linked to be a macrocycle around the active Li(I)-centers, were synthesized. From a viewpoint of simple molecular design and atom economy, the $(CH_2)_n$-tethered half-helical macrocyclic structure without introducing sterically bulky substituents is greatly attractive to avoid aggregation of catalysts and reagents. Remarkably, the chiral macrocyclic Li(I) catalysts showed extremely high catalytic activity in the enantioselective addition of lithium acetylides to a variety of simple and bulky ketones, and the desired optically active 3°-propargyl alcohols were obtained within 5 min. A gram-scale synthesis for an intermediate of oxybutynin was also demonstrated by using 1 mol% of catalyst. To help understanding this practical catalysis, correlation of the macrocyclic structure to catalytic activity and possible transition states were also considered.



1P- 48

Generation of ynolates via double deprotonation of 2,6-di-*tert*-butylphenol esters

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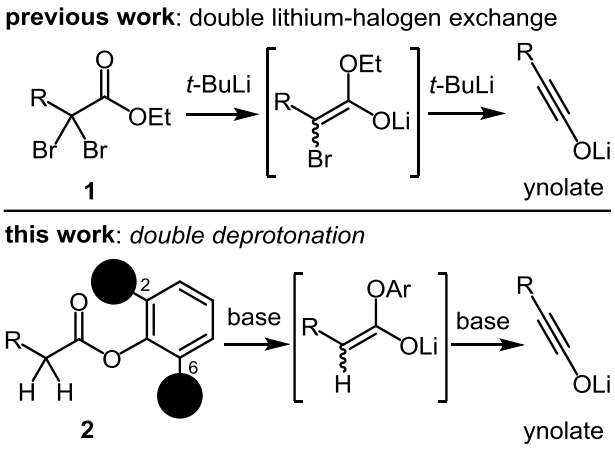
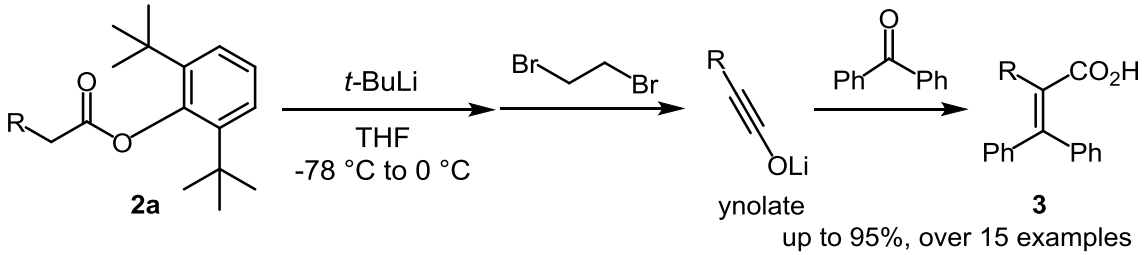
Ynolates, which have a C-C triple bond in place of the C-C double bond in enolates, have been shown to efficiently react with carbonyl compounds such as ketones to provide multi-substituted olefins.[1] We reported a method for generation of ynolates by double lithium-halogen exchange reaction of α,α-dibromoesters **1**.[2] Although this method efficiently provides various ynolates, the multi-step preparation of **1** is needed in advance (Scheme 1). In order to develop a more convenient method to generate ynolates, herein, double deprotonation of 2,6-disubstituted phenol esters **2** was investigated.



2,6-Disubstituted phenol esters **2** was selected as a promising precursor because of its sterically hinderance to prevent base from attacking to the carbonyl group. After screening several 2,6-disubstituted phenol esters, 2,6-di-*tert*-butylphenol ester **2a** was found to efficiently give the corresponding ynolate. We then optimized the reaction conditions using **2a** as the precursor. As a result, we found the conditions where ester **2a** was treated with *tert*-butyllithium at -78 °C, followed by warm up to 0 °C, and then 1,2-dibromoethane was added for deactivation of the unreacted *tert*-butyllithium to efficiently provide the ynolate. The yield of the ynolate were evaluated by those of the olefination product **3** reacted with benzophenone. This method provided over 15 kinds of ynolate, some of which are difficult to be generated by our previous method. In the presentation, we will show the details of this method in addition to its mechanistic investigation and its synthetic application to other ynolate-initiated reactions.[3]



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1P- 49

Synthetic Studies of Libraries of Polymers from Half-esters Obtained by Practical Selective Monohydrolysis of Symmetric Diesters

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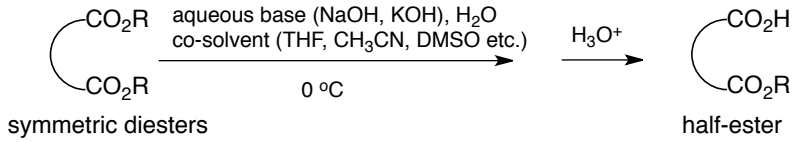
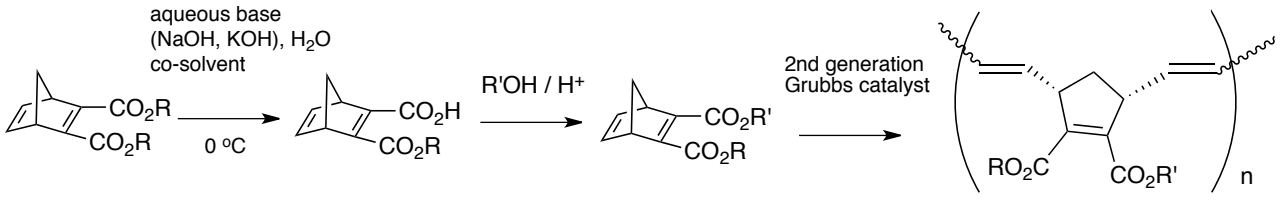
Half-esters are versatile building blocks in organic synthesis, and are typically applied to the synthesis of pharmaceuticals, natural products, and polymers. We previously reported highly efficient and practical selective monohydrolysis reactions, which produce the corresponding half-esters in high yields.[1]



In particular, diesters having the norbornadiene (bicycle[2.2.1]hept-2,5-diene) skeleton afforded the corresponding half-esters in near quantitative yields. Norbornadiene derivatives are known to effectively undergo ring-opening metathesis polymerization (ROMP) reactions because of the ring strain. Therefore, here we applied such half-esters as well as the starting symmetric diesters to the synthesis of a library of polymers. The polymers thus produced should have cyclopentene backbones, which are expected to exhibit stiffer and hence more stable properties than the corresponding linear backbones.

The starting symmetric diesters with the norbornadiene skeleton were obtained by the Diels-Alder reaction of cyclopentadiene and dialkyl diacetylenedicarboxylic acid. These symmetric diesters are converted to the corresponding half-esters by the selective monohydrolysis we reported previously in high yields. Half-esters thus obtained were first converted to various kinds of non-symmetric diesters by esterification of the carboxyl group in the presence of the corresponding alcohol and a Lewis acid. These non-symmetric and symmetric diesters were subjected to the ring-opening metathesis polymerization (ROMP) with the use of the ruthenium-based 2nd generation Grubbs catalyst.



R, R'= H, Me, Et, ^{i}Pr, Pr, ^{t}Bu, Bn, etc.

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1P- 50

Pd/Cu-catalyzed Aerobic Anti-Markovnikov Oxidation of Vinylarenes to Aldehydes and Terminal Acetals

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Arylacetaldehydes are frequently used as synthetic building blocks for natural products, such as alkaloids and bisabolane sesquiterpenes, and biologically active compounds. Oxidation of vinylarenes using molecular oxygen is a simple and atom-efficient method to synthesize the arylacetaldehydes. Pd-catalyzed Wacker-type oxidation is a candidate for achieving such a transformation. However, the Wacker-type oxidation of terminal alkenes generally follows Markovnikov's rule to afford methyl ketones. Here we report the selective anti-Markovnikov Wacker-type oxidation of various vinylarenes to arylacetaldehydes using a $PdCl_2(MeCN)_2$/CuCl catalyst system in the presence of a catalytic amount of maleimide, which is an electron-deficient cyclic alkene, under 1 atm of O_2 and mild reaction conditions.[1] A bulky tertiary alcohol, *t*-AmylOH, which was used as a solvent, attacks to the terminal carbon of the vinylarenes coordinated to Pd, affording high anti-Markovnikov selectivity due to the steric hindrance. Maleimide would coordinate to either Pd or Cu (in a Pd-Cu bimetallic complex) to facilitate the nucleophilic attack of *t*-AmylOH to the coordinated vinylarenes and the reducing step from Pd(II) to Pd(0), and stabilize the Pd(0) species to suppress the decomposition.

Direct synthesis of acetals from alkenes and alcohols is a useful method which formally involves two steps, i.e. oxidation of alkenes to aldehydes or ketones and their protection. Markovnikov selectivity is mainly observed in the Pd-catalyzed acetalization of alkenes to afford internal acetals. Considering that the formation of arylacetaldehydes from vinylarenes is rare, the accessible aerobic synthesis of the corresponding terminal acetals can be an attractive alternative. By using similar reaction conditions as the abovementioned anti-Markovnikov Wacker-type oxidation, i.e. a $PdCl_2(MeCN)_2$/CuCl/MeOBQ (methoxy-*p*-benzoquinone) catalyst system, *t*-AmylOH as a solvent and 1 atm of O_2, we developed a synthesis of terminal acetals from various vinylarenes and pinacol.[2] Ethylene glycol, 1,3-propanediol and 2,2-dimethyl-1,3-propanediol were also applicable instead of pinacol. Kinetic experiments indicated that MeOBQ operates as a ligand for either Pd or Cu to accelerate the reaction efficiently.

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1P-51

Biocatalytic Process Design – Challenges and Solutions

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Biocatalytic synthetic methods have received much attention in recent years across the pharmaceutical and fine chemical industry. Enzymes often offer unique advantages over other chemical methods such as superior chemo- and stereoselectivity, and generally mild conditions. The recent strong rise of biocatalysis has been facilitated by advances in molecular biology and bioinformatics, enabling ever more rapid and competitive access to an increasing variety of biocatalysts from all enzyme classes.

Productivity and competitiveness of a biocatalytic manufacturing process are inextricably linked to three factors: (a) the intrinsic catalytic properties of the enzyme(s), (b) the fermentation process used for generating bulk enzyme, and (c) the design of the chemical process unlocking the full catalytic potential of the enzyme. Almac have developed extensive expertise with all three areas, as is illustrated by some of its most productive keto- and imine reductase application examples: the syntheses of cis-Woody acetate, a fragrance material, of a nicotine-analogue as pharmaceutical building block, and of UDCA, a generic API.

All three cases have in common that an advanced manufacturing process was required to deliver on ambitious targets for catalyst cost contribution and product price. The presentation illustrates how careful selection of the enzyme, optimization of the fermentation process, and chemical process design minimizing catalyst deactivation, were integrated to open the way to high catalytic turnover in a very green and highly productive manufacturing process.

1P- 52

Hydrosilane-Promoted Facile Deprotection of *tert*-Butyl Groups in Esters, Ethers, Carbonates, and Carbamates

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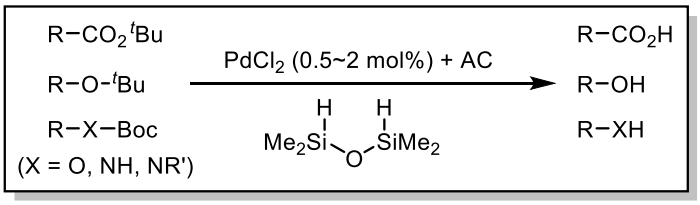
The *tert*-butyl substituent (*t*-Bu), which possesses prominent stability under a variety of reaction conditions, is widely applied as one of the most powerful protecting groups for alcohols and carboxylic acids. However, the harsh conditions are commonly required to cleave the C–O bond of *tert*-butoxy moiety (deprotection) by using strong Brønsted or Lewis acids.

In 2010, Nagashima and co-workers reported the first catalytic method for C–O bond cleavage of *tert*-butoxy moiety (O-*t*-Bu) by using ($\mu^3,\eta^2,\eta^3,\eta^5$-acenaphthylene)$Ru_3(CO)_7$ complex and Me_2PhSiH.[1] In that report, heterolytic cleavage of the Si–H bond of hydrosilane is induced by the triruthenium cluster to form an ionic intermediates, then the Lewis acidic $[Si]^+$ species interacts with carbonyl or ether oxygen atom followed by deprotonation of the *t*-Bu group by the $[Ru_3–H]^-$ species resulting in the formation of silyl ester, isobutene, and hydrogen gas. This catalytic system is attractive because the procedure is simple and reaction proceeds under neutral conditions, but the preparation of triruthenium cluster complex is unavoidable. In addition, this system is not compatible towards a compound having other ester groups in a molecule because they are reduced under reaction conditions to afford the corresponding silyl ethers.

Our group recently reported the catalytic silane-reduction of carbonyl compounds using commercially available palladium on carbon (Pd/C) as a catalyst. During the studies, we became aware of the gas evolution and formation of silyl esters and isobutene as a by-product in the Pd-catalyzed reaction of *tert*-butyl esters with hydrosilanes.[2] In this work, we developed a simple process for the Pd-catalyzed cleavage reaction of C–O bond of O-*t*-Bu groups leading to the facile deprotection of *tert*-butyl esters, *tert*-butyl ethers, *O*-Boc, and *N*-Boc derivatives under mild conditions. The addition of activated carbon (AC) was found to be crucial for the present silane-induced deprotection. It is of practical importance that inexpensive $PdCl_2$ and 1,1,3,3-tetramethyldisiloxane (TMDS) can be used, and the present procedure can be scaled up to a gram-quantity reaction.[3]



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1P- 53

Synthesis of 7-Deazaguanosine Derivatives via Glycosylation

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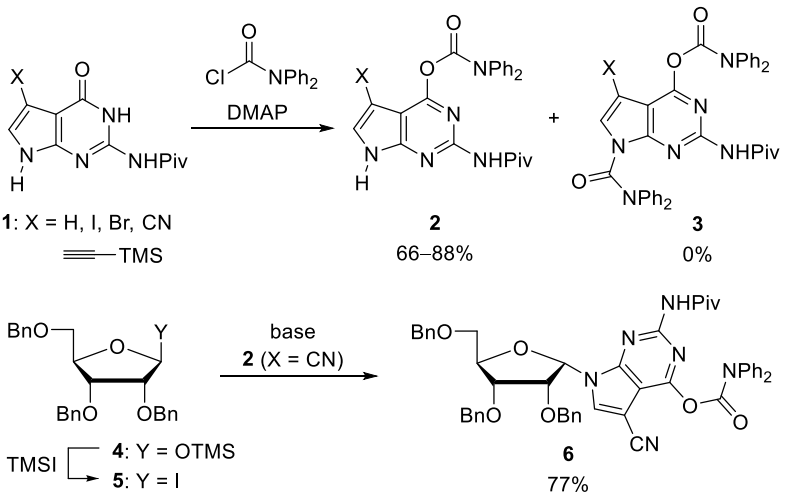
7-Deazaguanosines are present in nature as antibiotics produced by bacteria and hypermodified nucleosides in tRNA. Many kinds of non-natural 7-deazaguanosine derivatives have also been developed for their potential applications such as therapeutic agents and fluorescent probes. Chemical synthesis of 7-deazaguanosines is generally carried out via glycosylation of appropriately protected 7-deazaguanine derivatives. Therefore, regioselective protection of 7-deazaguanines and highly stereoselective glycosylation of the protected 7-deazaguanines are important factors for an efficient synthesis of 7-deazaguanosine derivatives. Herein we describe a new regioselective O^6-diphenylcarbamoylation reaction using DPC-Cl and DMAP and application of the resultant protected 7-deazaguanines to a stereoselective synthesis of 7-deazaguanosine derivatives.

We investigated the reaction of N^2-pivaloyl-7-deazaguanines **1** with *N*,*N*-diphenylcarbamoyl chloride (DPC-Cl) and found that only the desired O^6-DPC-N^2-pivaloyl-7-deazaguanines **2** was generated when the reaction was conducted using DMAP as a base. Generation of undesired O^6,N^9-bis-DPC-byproduct **3** was not observed. O^6-DPC-N^2-pivaloyl-7-deazaguanines **2** with various 7-substituents such as halo, cyano, and trimethysilylethynyl groups were obtained in good yield with complete regioselectivity.

Then we studied the synthesis of 7-deazaguanosine derivatives via glycosylation reaction using O^6-DPC-N^2-pivaloyl-7-deazaguanines **2**. We have reported the synthesis of 7-cyano-7-deazaguanosine via a β-selective ribofuranosylation.[1] In this study, we synthesized the α-anomer of 7-cyano-7-deazaguanosine (**6**) by an α-selective glycosylation of **2** using a ribofuranosyl iodide as a glycosyl donor[2] in 77% yield. The results obtained with other 7-deazaguanines will be presented in detail.



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1P- 54

Stereoselective Synthesis of Furanosyl Sulfones and Their Application to Julia-Kocienski Reaction

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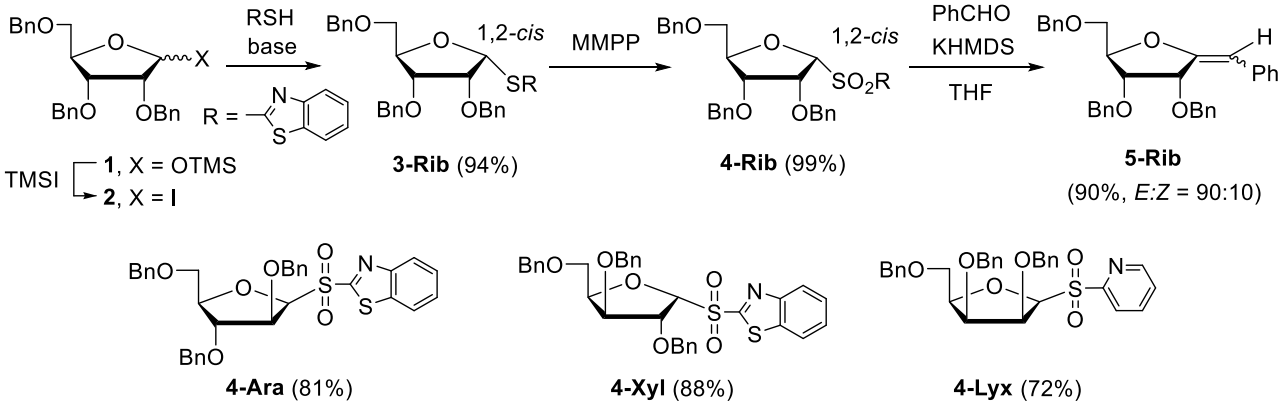
Furanosyl sulfones are useful as synthetic intermediates of a wide range of furanoside derivatives. However, studies on the stereoselective synthesis of furanosyl sulfones, especially 1,2-*cis*-isomers, are rather limited, even though their properties are significantly affected by the anomeric configuration. We have recently reported a highly 1,2-*cis*-selective ribofuranosylation reaction of thiols using ribofuranosyl iodides as glycosyl doners.[1] In this study, we extended this reaction to arabino-, xylo-, and lyxofuranoses. The resultant 1,2-*cis*-furanosyl sulfides were then used for the synthesis of 1,2-*cis*-furanosyl sulfones. In addition, we studied the synthesis of *exo*-glycals, which are also useful synthetic intermediates of various furanoside derivatives, by applying the 1,2-*cis*-furanosyl sulfones to Julia-Kocienski reaction with aldehydes.

1-*O*-TMS-ribofuranose **1** was converted into a ribofuranosyl iodide **2** and used as a glycosyl donor for the 1,2-*cis*-selective ribofuranosylation of 2-mercaptobenzothiazole. The reaction gave 1,2-*cis*-ribofuranosyl sulfide **3-Rib** in 94% yield with high 1,2-*cis*-selectivity. The sulfide **3-Rib** was used to synthesize 1,2-*cis*-ribofuranosyl sulfone **4-Rib** by oxidation with magnesium monoperoxyphthalate hexahydrate (MMPP). According to this procedure, we synthesized **4-Ara**, **4-Xyl**, and **4-Lyx** from arabinose, xylose, and lyxose, respectively, as stereopure 1,2-*cis*-isomers. Finally, we applied the resultant sulfones to Julia-Kocienki reaction for the synthesis of *exo*-glycals. An *exo*-glycal **5-Rib** was obtained from **4-Rib** and benzaldehyde in 90% yield with 90% *E*-selectivity. Results obtained with other aldehydes and furanosyl sulfones will be reported in detail.



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1P- 55

One-Step Synthesis of Cyclopentene Derivatives from Julia-Kocienski Reagents Derived from Nucleosides

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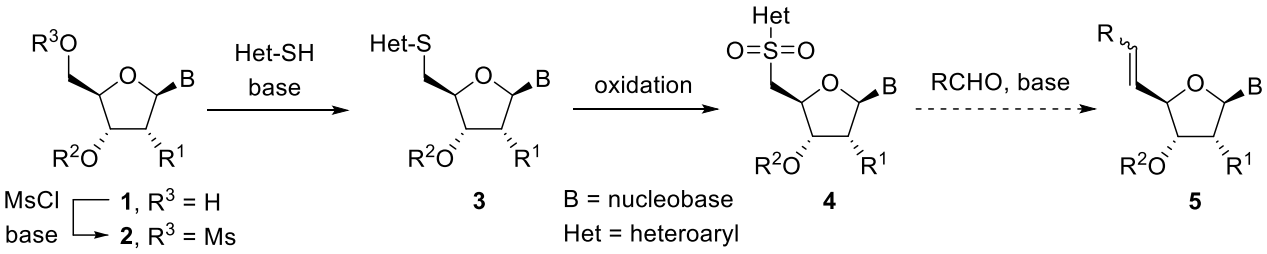
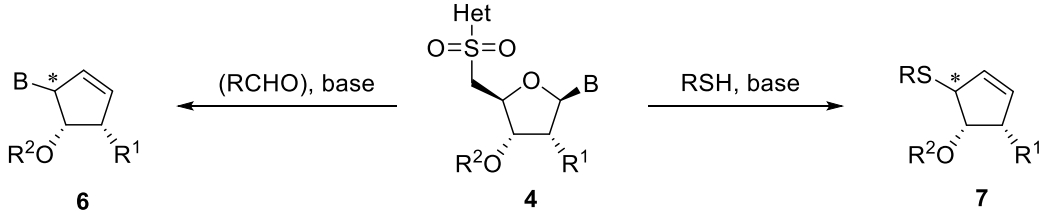
Julia-Kocienski reaction is a powerful tool for the synthesis of alkenes. It is often used for the synthesis of complex natural products. We synthesized 5′-deoxy-5′-heteroarylsulfonylnucleosides **4**, a new type of Julia-Kocienski reagents, from nucleosides **1** according to Scheme 1, and allowed to react with an aldehyde in the presence of a base, in expectation that 5′-alkylidene-5′-deoxynucleosides **5** would be obtained. However, the reaction unexpectedly afforded cyclopentene nucleoside derivatives **6** (Scheme 2, left). This transformation is considered to proceed via the α-deprotonation of the heteroarylsulfone, elimination of the nucleobase and concomitant formation of a formyl group, the Michael addition of the resultant nucleobase to the α,β-unsaturated sulfone, and intramolecular Julia-Kocienski reaction. The reaction proceeded as well in the absence of an aldehyde. This unique reaction should be useful for the synthesis of carbocyclic nucleosides, many of which are known to have antibiotic or antiviral activities, such as neplanocin A, aristeromycin, carbovir, and abacavir.

In addition to the synthesis of cyclopentene nucleoside derivatives **6**, the Julia-Kocienski reagents **4** afforded cyclopentene derivatives **7** when they were reacted with a base and a thiol (Scheme 2, right), indicating that the nucleobase moiety can be replaced by a nucleophile. We expect that this reaction will be useful for the synthesis of various chiral cyclopentene derivatives.



Scheme 1. Synthesis of Julia-Kocienski reagents **4** and attempted Julia-Kocienski reaction with aldehydes.



Scheme 2. One-step synthesis of cyclopentene derivatives **6** and **7** from Julia-Kocienski reagents **4**.

1P- 56

Selective Synthesis of Azoxybenzenes from Nitrobenzenes by Photoreduction with Flow Microreactors

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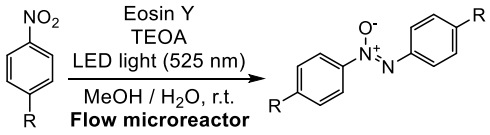
Hydrogenation of nitrobenzenes is an important reaction to provide the intermediates for various applications in industry. However, when nitrobenzenes have some reducible groups, the product selectivity should be poor. Recently, it was reported that an efficient and selective photocatalytic reduction of nitrobenzenes to provide anilines with green LED light irradiation at room temperature [1]. However, despite of the attractive reaction from viewpoint of green chemistry, long-time photoirradiation was required because of the low efficient light transmission of the reaction solution in batch systems. On the other hand, flow microreactors have many advantages for the photoreaction such as the efficient light irradiation because of the narrow reaction channels[2,3].

In this work, we carried out the above photoreductions of nitrobenzene in a microreactor in order to shorten the reaction time (Scheme 1). As the results, nitrobenzenes were smoothly converted for 4 h photoirradiation and azoxybenzenes were obtained as main products instead of anilines. These results suggest that the condensation of nitrosobenzenes and *N*-phenylhydroxylamines, which are the intermediates in the hydrogenation of nitrobenzenes, smoothly proceeded in the microreactor. In addition, the flow rate significantly affected the chemical yield of azoxybenzene (Figure 1). Under higher flow rate conditions, azoxybenzene was obtained in good yield. In contrast, at lower flow rate and no flow conditions, azoxybenzene was hardly obtained although nitrobenzene was smoothly converted for 4 h photoirradiation. Moreover, some intermediates were observed in addition to azoxybenzene under their conditions. This result suggests that the condensation reaction smoothly proceeded by the stirring caused by higher flow rate.



Scheme 1. Photoreduction of nitrobenzenes with flow microreactor.

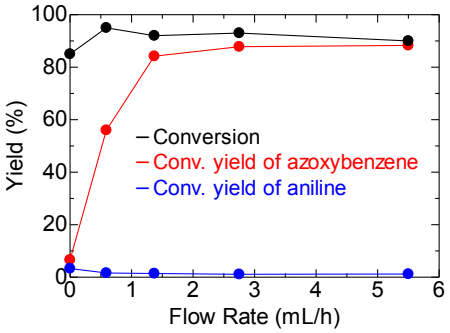


Figure 1. Photoreduction for 4 h at several flow rates.

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1P-57

Highly efficient synthesis of aromatic α-keto acids from acetophenones using nitrosylsulfuric acid as an oxidant

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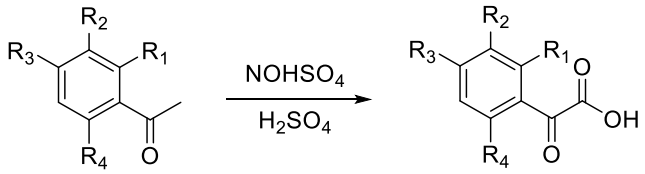
α-Keto acids have been widely used as useful intermediates for synthesis of pharmaceuticals and agrochemicals. Selective oxidation reaction of acetophenones is one of the most convenient approach to them. A major drawback of this approach is low reaction selectivity, which is due to severe reaction conditions that lead to undesirable carboxylic acid. Therefore, there has been a strong demand for an efficient oxidant which affords α-keto acids selectively.

Threre are few successful exaples that can be used in commercial process. It was reported that acetophenone was oxidized to give benzoylformic acid with SeO_2[1]. Although the reaction proceeded under mild conditions in high yield, this method suffers from highly toxic Se-containing wastes.

We have investigated selective oxidation reaction of acetophenones using nitrosylsulfuric acid as an oxidant. Nitrosylsulfuric acid is known as an inexpensive nitrosating reagent and commercially available as a sulfuric acid solution, which is a product of the lead chamber process for producing sulfuric acid. The oxidation reaction of acetophenones proceeded at 40～50 °C to give corresponding α-keto acids in good to moderate yield. The reaction yield showed a good correlation with Hammet σ value of the substituents.



R_1	R_2	R_3	R_4	%Yield[a]
F	H	H	F	92
H	H	CH_3	H	75
H	H	H	H	83
Cl	H	H	H	57

[a]Determined by LC analysis.

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Palladium-catalyzed deoxygenative deuteration of aryl nonaflates

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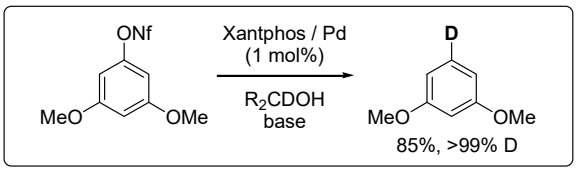
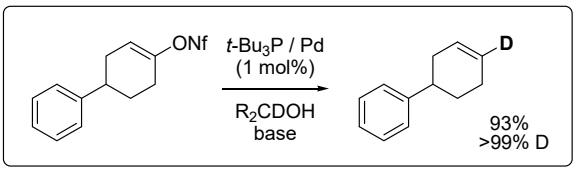
Increasing interest has been recently focused on site-specific incorporation of deuterium into pharmaceutical molecules owing to its beneficial effects to improve their therapeutic profiles on the basis of isotopic effects.[1] However, catalytic deoxygenative deuteration for phenol derivatives is quite rare despite their lower cost and easy availability.[2] Aryl nonaflates (ArONf = $ArOSO_2(CF_2)_3CF_3$) are known as an attractive alternative to aryl triflates because this type of reagent has similar reactivity to aryl triflates and higher stability toward hydrolysis. To the best of our knowledge, no catalytic deoxygenative deuteration of aryl nonaflates has been reported.

Scheme 1

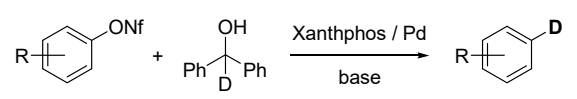


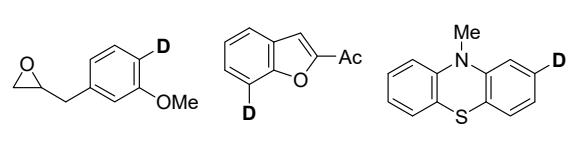
Scheme 2



In the optimization of reaction conditions, we found that Pd/xantphos system was effective in the catalytic deoxygenative deuteration of aryl nonaflates (Scheme 1). On the other hand, the deuterium incorporation into alkenes with alkenyl nonaflates proceeded efficiently in the presence of Pd-P*t*Bu_3 catalyst (Scheme 2). As well as heteroaryl structures, an aryl compound with an easily-reduced epoxy group were tolerated to give high yields and excellent deuteration degrees (Scheme 3). Furthermore, a variety of alkenyl nonaflates proved to be suitable substrates in this precisely-controlled deuteration process (Scheme 4).

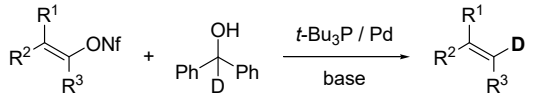
Scheme 3

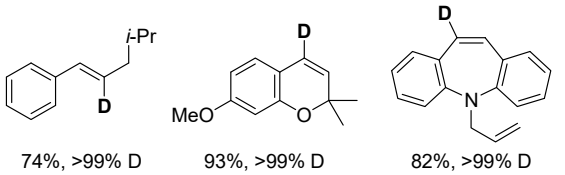




91%, >99% D | 91%, >99% D | 91%, >99% D

Scheme 4





74%, >99% D | 93%, >99% D | 82%, >99% D

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2) Kuriyama, M.; Kujirada, S.; Tsukuda, K.; Onomura, O. *Adv. Synth. Catal.* **2017**, *359*, 1043-1048.

1P- 59

Efficient Synthetic Study of Multi-functionalized Biheteroaromatics by Suzuki Coupling

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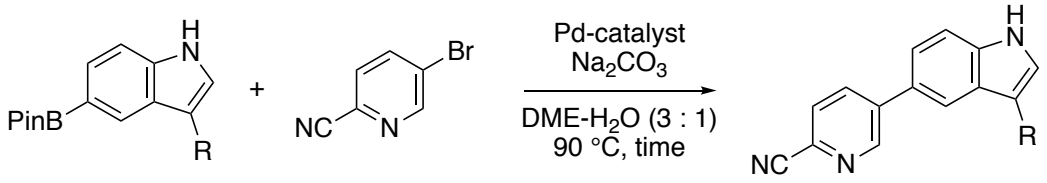
Biheteroaromatics is very important structure as one of basic skeletons for bio-active compounds. Palladium-catalyzed Suzuki-Miyaura cross coupling is widely used for the synthesis of these compounds. A non-functionalized indolyl borate was reacted with a non-functionalized heteroaryl halide to give the corresponding biheteroaromatics in high yield. If the functionalized heteroaryl halide was used, the chemical yield was often tended to decrease. In general, the bio-active compounds having biheteroaromatics skeleton is highly functionalized, it is difficult to functionalize with regio- and chemo-selectivity on the biheteroaromatics. Herein, we report about the efficient synthesis of the functionalized heteroaromatics using Suzuki coupling.

Non-functionalized 5-borylindole (**1a**) was reacted with 5-bromo-2-cyanopyridine (**2**) in the presence of 6 mol% of $Pd(PPh_3)_4$ and 5 equiv. of Na_2CO_3 in the mixed solvent of DME and water to give the corresponding pyridylindole (**3a**) in 81% yield (**Table 1**, Entry 1). On the other hands, 3-ethoxycarbonyl-5-borylindole (**1b**) was used as a substrate, the product yield was decreased (**Table 1**, Entry 2). In this case, the decomposition of substrate and products was observed on TLC. At last we accomplished to get the desired product in high yield using 10 mol% of $PdCl_2(dppf)$ as a catalyst and 3 equiv. of Na_2CO_3 as a base in DME-water (3 : 1) (**Table 1**, Entry 4). Furthermore, we applied to use other heteroaryl bromides, and found that the corresponding products were given in good yield.



1a (R = H)
1b (R = CO_2Et)

2

3a (R = H)
3b (R = CO_2Et)

Table 1: Modification of Suzuki coupling conditions.

Entry	Substrate	Pd-catalyst (mol%)	Na_2CO_3 (eq)	Time (h)	Product (%)
1	**1a**	$Pd(PPh_3)_4$ (6)	5.0	2.5	81 (**3a**)
2	**1b**	$Pd(PPh_3)_4$ (6)	5.0	2.5	43 (**3b**)
3	**1b**	$PdCl_2(dppf)$ (6)	5.0	2.5	51 (**3b**)
4	**1b**	$PdCl_2(dppf)$ (10)	3.0	1.0	70 (**3b**)

1P- 60

Precise Control of the Mutagenic Impurity Production by Flow Synthesis

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In manufacturing of drug substances, flow synthesis has advantages of precise temperature adjustment, fast mixing, and precise residence time. These advantages have the potential to improve the quality and yield of drug substances.

In our target step, the previous study revealed that amount of a mutagenic impurity was increasing with the operating time throughout the whole process, which consists of reaction, quench and crystallization. We applied flow synthesis to the whole process and accomplished the precise control of the mutagenic impurity production by precise residence time. In this study, the following 3 points are emphasized.

1) In this reaction, starting material has low solubility in various commercially available solvents, and we needed to handle slurry in flow synthesis. Therefore, we combined Continuous Stirred Tank Reactor (CSTR) and Plug Flow Reactor (PFR) to enable continuous and stable flow of starting material slurry.

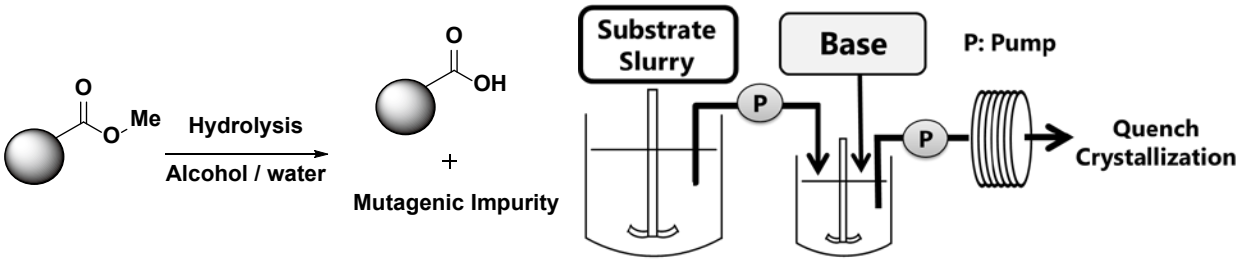

Figure 1. Flow system of hydrolysis reaction that combined CSTR and PFR

2) During this reaction, we combined HPLC analysis with in situ Fourier Transform Infrared Spectroscopy (FTIR) analysis to monitor the reaction rate. We evaluated quantitative performance of in situ FTIR and demonstrated that in situ FTIR had a strong correlation with HPLC quantitatively. This result shows the possibility that in situ FTIR analysis could be applied to an in-line monitoring tool to control the reaction rate.

3) We also applied flow synthesis to quench and crystallization process, and the continuous crystallization with wet-milling drastically shortened the crystallization aging time. This result led to the decrease of mutagenic impurity regardless of production scale and establishment of the total application of flow synthesis in this step.

In the poster presentation, the technical details about the topics described above and the effectiveness of flow synthesis to manufacturing of drug substances will be discussed.

1P-61

Selective Synthesis of Benzofuran Isomers Using Rearrangement Reaction of Hydroxychalcone and the Application to Synthesis of Natural Product

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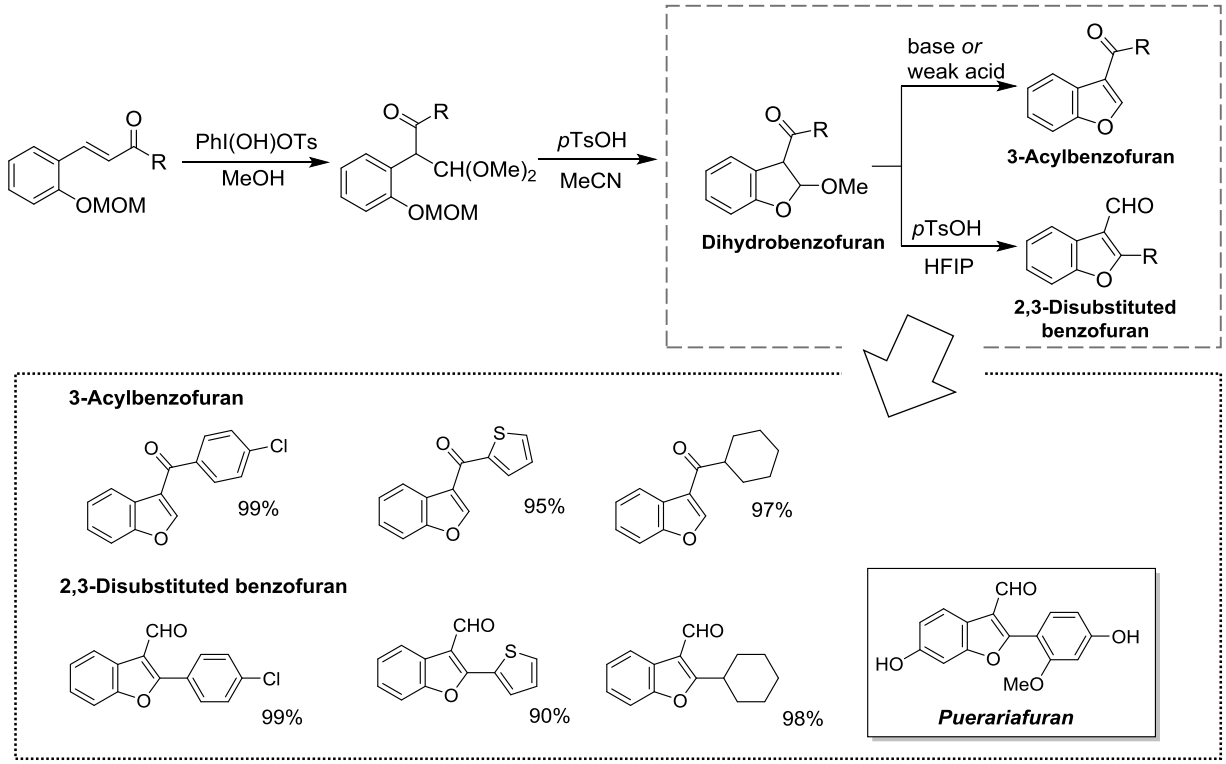
Benzofurans are a class of very important heterocyclic compound found in natural products and pharmaceutically active compounds. A general synthetic approach for 3-acylbenzofurans is the acylation of benzofurans using Friedel-Crafts-type reactions. However, the direct acylation of benzofurans results in moderate yields due to the lack of regioselectivity at C2 and C3 position. We have developed the synthetic methods of heterocycle compounds via rearrangement reaction of the chalcones by using hypervalent iodine reagent, and recently 3-acylindoles were synthesized from 2-aminochalcones in one-pot procedure [1]. For the application of this method, we next examined the synthesis of 3-acylbenzofurans from 2-hydroxychalcones. As a result different from the previous indole synthesis, the intermediate, dihydrobenzofurans, were isolated in good yield and could be selectively converted to two benzofuran isomers. Under the basic or weak acidic conditions, the corresponding 3-acylbenzofurans were obtained. On the other hand, 2,3-disubstituted benzofurans were generated with *p*TsOH in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). A variety of dihydrobenzofurans prepared from 2-hydroxyochalcones were successfully converted into their corresponding 3-acyl- and 2,3-disubstitutedbenzofuran isomers in high yields, respectively. This method is also applicable to the synthesis of natural product, Puerariafuran.



Reference:
1. *Org. Biomol. Chem.,* **2017**, *15*, 6702-6705

1P-62

New Deprotection Method of PMB Protective Group of Alcohols Using Weak Acid in CF_3CH_2OH and Remarkable Acceleration of Deprotection of PMB Protected 4-phenylbutanol.

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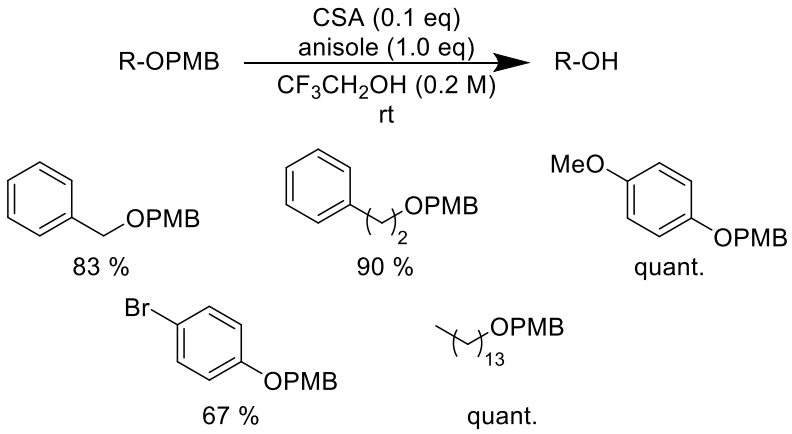
p-Methoxybenzyl (PMB) group is one of the useful protective group for alcohols. Generally, deprotection reactions were conducted DDQ and acids. However, heating and strongly acid conditions were usually necessary for them. We have developed reactions using combination of the fluorous solvents and hypervalent iodine reagents. We herein report a new deprotection of PMB group under mild conditions using 10-camphorsulfonic acid (CSA) as a relatively weak acid with anisole (1.0 eq) in CF_3CH_2OH. This reaction proceeded using catalytic amount (0.1 eq) of CSA at room temperature giving the corresponding alcohols in high yields.



During the study of this deprotection, we found that the deprotection of PMB protected 4-phenylbutanol was significantly accelerated compared with similar alcohols such as 3-phenylpropanol. We speculated that the number of the carbon and aromatic ring is very important in acceleration of such reaction. To reveal the involvement of aromatic ring, we investigated various substituents on aromatic ring and conducted the calculation using a molecular dynamics method.

1P- 63

Design of Novel Halogen Bonding Donors with SF_5 and SO_2CF_3 Functional Groups on Iodobenzenes

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Halogen bonding refers to the noncovalent interactions between an electrophilic region associated with a halogen atom of a molecule (donor) and lone pair associated with a Lewis basic moiety of a molecule (acceptor). The strength of halogen bonding is comparatively weak with reversible formation; thus the design of halogen bonding donors with suitable efficiency is crucial for the success of the research projects. Currently, perfluorinated aromatic iodides are one of the well-explored halogen bonding donors. However, the multiple fluorinated substitutions of aromatic iodides profoundly restrict to the design of novel halogen bonding aromatic iodides with desired properties. In this context, we became interested in sulfur-containing fluoro-functional groups, pentafluorosulfanyl (SF_5) and trifluoromethanesulfonyl (SO_2CF_3). They show reliable electron-withdrawing property (SF_5: $\sigma_m = 0.61$, $\sigma_p = 0.68$ and SO_2CF_3: $\sigma_m = 0.83$, $\sigma_p = 0.96$), which could be efficient enough to induce halogen bonding in the aromatic iodides even with a single substitution of aromatic ring (Fig. 1). We herein disclose the studies of halogen bonding between SF_5- and SO_2CF_3-substituted iodobenzenes (SF_5-C_6H_4-I, CF_3SO_2-C_6H_4-I) and tetra *n*-butyl ammonium chloride (TBAC, halogen bonding accepter).

Fig. 1 Halogen bonding between Rf-C_6H_4-I and pyridine

The synthesis of SF_5-C_6H_4-I and CF_3SO_2-C_6H_4-I was achieved according to our previous reports.[1] The ^{13}C NMR titration experiments of SF_5-C_6H_4-I and CF_3SO_2-C_6H_4-I in the presence of TBAC were carried out in $CDCl_3$. The chemical shifts of original carbon were gradually shifted with the addition of the TBAC, which highly indicates the formation of halogen bonding between Rf-C_6H_4-I and Cl^- (Fig. 2).

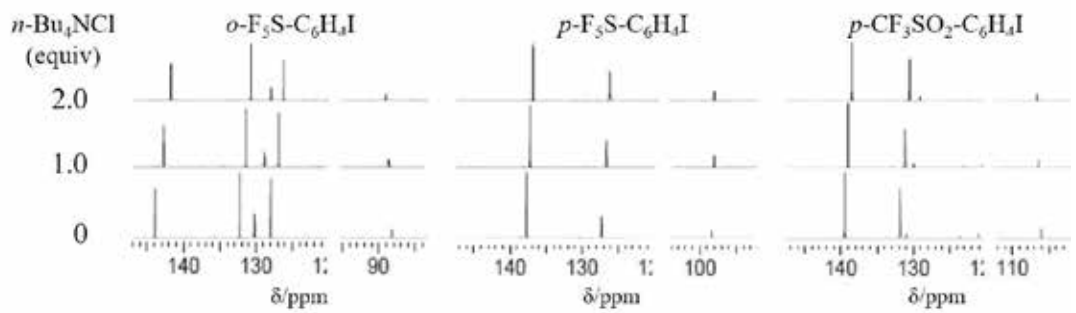

Fig. 2 ^{13}C NMR titration experiments of *o*-, *p*-SF_5- and *p*- CF_3SO_2-C_6H_4-I with TBAC in $CDCl_3$.

Reverences

1. a) Shibata, N. *et al*., *Org. Lett.* **2015**, *17*, 3038−3041, b) Shibata, N. *et al*., *Beilstein J. Org. Chem.* **2018**, *14*, 364−372, c) Das, P.; Shibata, N. *J. Org. Chem.* **2017**, *82*, 11915−11924.

1P- 64

Quick and Continuous Synthesis of Methyl Cinnamates Using a Flow-microwave Applicator

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In cases of the reactions using standard microwave (MW)-heating applicators, toluene or dichloromethane are rarely used as solvents owing to their low MW-energy absorbabilities. Meanwhile, the MW-heating applicator of SAIDA.FDS Ltd. may easily use toluene or dichloromethane as solvents, because it becomes possible to irradiate only the optimal wavelength for each solvent which can absorb most effective energy by a special polarizing plate. In addition, it allows instantaneous heating and cooling of the reaction system.

We herein describe quick and continuous synthesis of methyl cinnamates using Wittig olefination with flow-MW applicator (FMA) equipped with flow and MW-heating applicators, as outlined below.

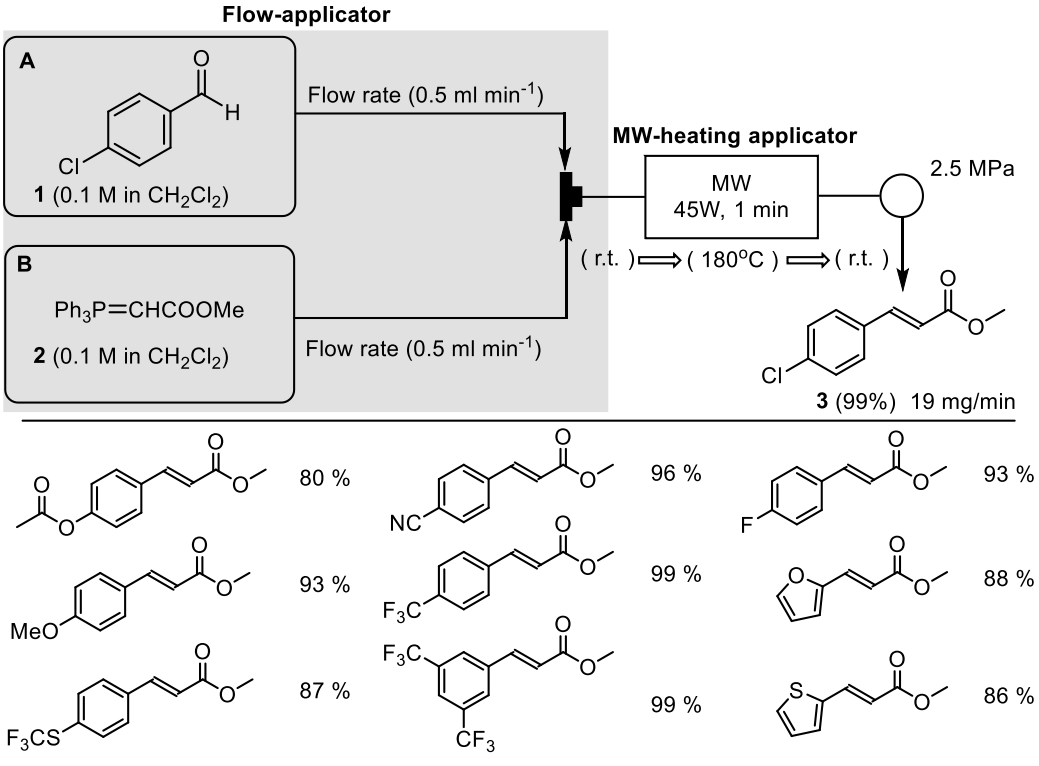
FMA configuration

Solution A: 0.1M solution of 4-chlorobenzaldehyde (**1**) in CH_2Cl_2

Solution B: 0.1 M solution of methyl phosphoranylidene (**2**) in CH_2Cl_2

Reactor tube: spiral glass tube (1 mL internal volume)

Flow rate: 0.5 mL / min; **Back pressure**: 2.5 MPa; **MW irradiate**: 45 W



1P-65

Utilization of Naturally Occurring Glycosylated Forms for the Synthesis of Flavonoids

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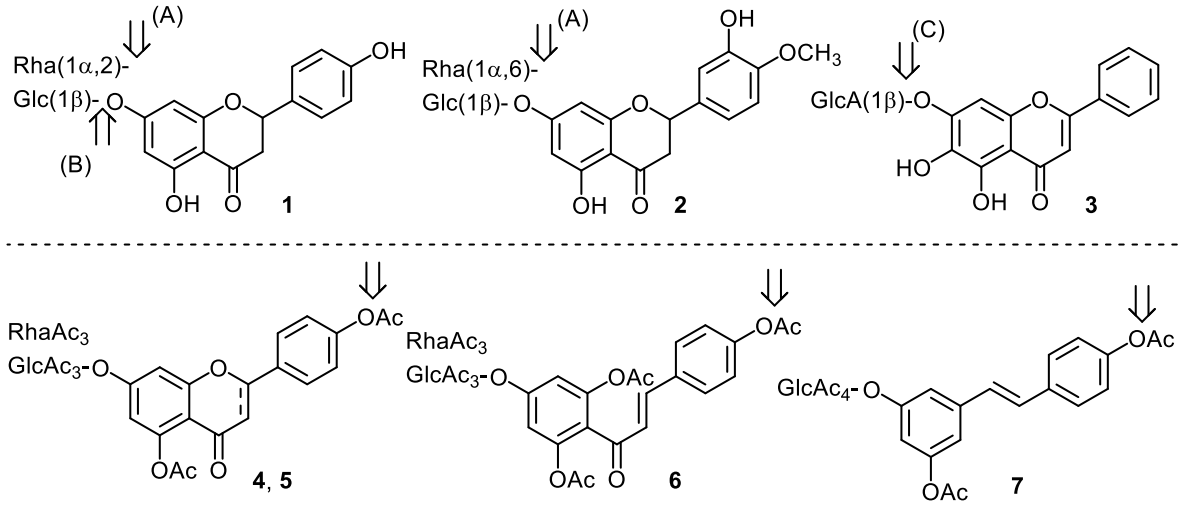
Flavonoids and related polyhydroxy aromatics are representative secondary metabolites with plant origin. However, the availability of aglycones are not always high. In contrast, several corresponding glycosylated forms are industrially produced. We developed practical routes from naturally abundant corresponding glycosylated forms in the synthesis of the physiological active compounds.

In this poster, first, we present the examples in the partial acidic hydrolysis of bonds (A) in naringin (**1**)[1] and hesperidin (**2**)[2] to give monoglycosides. The hydrolysis was catalyzed with non-volatile sulfuric acid in aqueous conditions at high temperature in a steam sterilizer. Prolonged reactions under more acidic conditions, further hydrolysis of bond (B) in **1** proceeded to give the aglycone.[1] In the case of the hydrolysis of obstinate glucronide (C) in baicalin (**3**),[3] more harsh reaction conditions were required.



Peracetylated forms of glycosylated forms are easily prepared. Lipase-catalyzed deacetylation occurs chemo- and site-selectively, on sterically least hindered phenolic acetates over many acetates located on glycosyl side chains. Examples on flavanone (**4**),[4] flavone (**5**),[5] chalcone (**6**),[6] and related stilbenoid (**7**)[5] are presented.

1) Kurahayashi, *et al*., *Biosci. Biotechnol. Biochem.* **2018**, *82*, 1463; 2) Tsunekawa, *et al*., *ChemBioChem* **2019**, *20*, 210; 3) Fujita, *et al*., *Heterocycles* **2018**, *97*, 1165; 4) Kobayashi, *et al*., *J. Mol. Catal. B: Enz.* **2013**, *92*, 14; 5) Hanamura, *et al*., *J. Mol. Catal. B: Enz.* **2016**, *128*, 19; 6) Tsunekawa, *et al*., *Biosci. Biotechnol. Biochem.* **2018**, *82*, 1316.

1P-66

^{13}C NMR Spectroscopic Studies of Intra- and Intermolecular Interactions of Amino Acids and Dipeptide Derivatives in Solutions

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It is well known that compounds having polar functional groups, such as a carbonyl group and a hydroxyl group, can form aggregates by inter- or intramolecular forces such as hydrogen bonding and dipolar-dipolar interaction in a solution. For measurement of such forces, we recently reported that the chemical shifts of the carbonyl carbons in ^{13}C NMR have good correlation with an empirical parameter for solvent polarities, E_T^N, depending on the structures.[1] For example, by ^{13}C NMR spectroscopic studies of half-esters having a carboalkoxy group and a carboxyl group in the same molecule and their derivatives, we previously demonstrated that intramolecular hydrogen bonding has especially notable effects in the chemical shifts of the carbonyls due to the reduced electron densities of the carbon atoms, leading to downfield shifts. In this study, ^{13}C NMR chemical shifts were monitored for evaluation of the interaction between *N*-Boc protected amino acids (*N*-Boc-alanine, *N*-Boc-serine, *N*-Boc-proline) and dipeptide derivatives (*N*-Boc-Pro-Ala-COOMe, *N*-Boc-Pro-Ser-COOMe, *N*-Boc-Ala-Pro-COOMe, *N*-Boc-Ser-Pro-COOMe, *N*-Boc-Pro-Pro-COOMe) and various solvents with different polarities.

We found that for *N*-Boc-protected amino acids having a small aliphatic functional group (alanine), more prominent downfield shifts with increase of a solvent polarity parameter were observed for the ^{13}C NMR chemical shifts of the carbonyl carbons in the carboxyl group and in the Boc group. On the other hand, the *N*-Boc-protected amino acids and the dipeptides having a large functional group (proline) showed slight down-field shifts for the carbonyl carbon in the *N*-Boc group with the increase of the solvent polarity due to the bulkiness and the amide bond. In particular, with *N*-Boc-Pro-Pro-COOMe, the carbonyl carbons in the peptide bond and in the amide bond in the Boc group were hardly affected by the solvent polarity due to the bulkiness.

On the other hand, for *N*-Boc protected amino acids and dipeptide having a hydroxyl group as polar functional group (serine), the ^{13}C NMR chemical shifts of the carbonyl carbons in the carboxyl group (COOH or COOMe) were almost constant regardless of the polarity of the solvent, perhaps due to the 6-menbered intramolecular hydrogen bonding, and therefore the carbonyl carbons of the carboxyl groups were not affected by the polarity of the solvent. This tendency is consistent with that observed in the half-esters described above.

1) Y. Hiraga, S. Chaki, S. Niwayama, *Tetrahedron Lett.*, **2017**, *58*, 4677-4681.

1P- 67

Simple Nucleophiles of Acetamide Equivalents: BENAC-K, PM-BENAC-K, and 2,4-DM-BENAC-K

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The *N*-alkylacetamide is an important structural motif present in a variety of pharmaceutical compounds and natural products. Alkyl halides and alkyl sulfonates are good precursors for *N*-alkylacetamides. While, installation of the *N*-acetamide functional group is typically performed through a three-step conversion of azidation–reduction–acetylation. Thus, development of easy and safe procedures is an important objective for the efficient synthesis of *N*-alkylacetamides. We herein report three simple reagents for *N*-acetamide installation: benzyl acetylcarbamate potassium salt (BENAC-K), *p*-methoxybenzyl acetylcarbamate potassium salt (PM-BENAC-K), and 2,4-dimethoxybenzyl acetylcarbamate potassium salt (2,4-DM-BENAC-K). All of BENAC-Ks were easily prepared on a multi-gram scale without resorting to chromatography. They are stable and easily handled under atmospheric conditions (Figure 1).

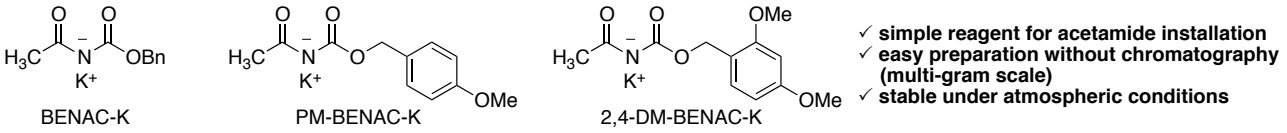
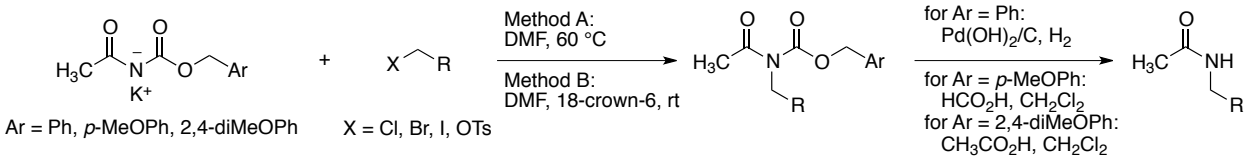


Figure 1. BENAC-K, PM-BENAC-K, and 2,4-DM-BENAC-K

The *N*-acetamide installation to alkyl halides or alkyl sulfonates was carried out in two steps involving a substitution reaction using BENAC-Ks and demasking of the aryloxymethylcarbonyl group. The substitution reactions were carried out in DMF at 60 °C (Method A), or at room temperature in the presence of 18-crown-6 (Method B). Demasking of the benzyloxycarbonyl group was achieved by hydrogenation. The *p*-methoxybenzylcarbonyl group was removed by the treatment with formic acid. A milder acid such as acetic acid was available for the deprotection of the 2,4-dimethoxybenzylcarbonyl group.



Scheme 1. *N*-alkylacetamide synthesis using BENAC-K, PM-BENAC-K, and 2,4-DM-BENAC-K

1P- 68

Three subjects in *Organic Syntheses*: Simple, useful, but hitherto inaccessible building blocks

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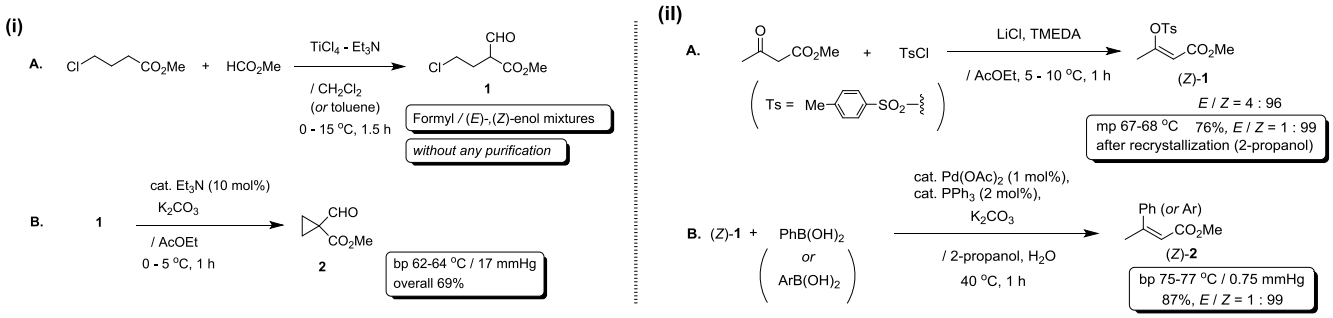
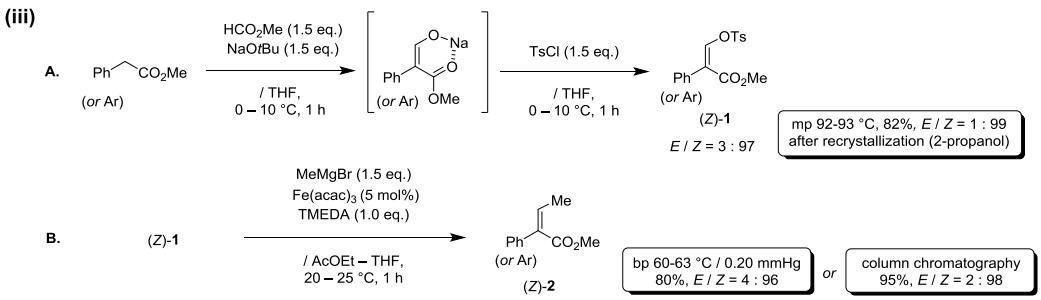
We would like to present the titled studies.

(i) Synthesis of Methyl 1-Formylcyclopropanecarboxylate utilizing Ti-Claisen Condensation, *Org. Synth.* **2016**, *93*, 286-305. Commercially available: M3045 (Tokyo Chemical Industry)

(ii) (*Z*)-Enol *p*-Tosylate Derived from Methyl Acetoacetate: A Useful Cross-coupling Partner for the Synthesis of Methyl (*Z*)-3-Phenyl (or Aryl)-2-butenoate, *Org. Synth.* **2017**, *94*, 93-108. Commercially available: M3043 (Tokyo Chemical Industry)

(iii) Stereoretentive Iron-catalyzed Cross-coupling of an Enol Tosylate with MeMgBr, *Org. Synth*. **2018**, *95*, 403-424. It will be commercially available (Sigma-Aldrich; October, 2019).





(iv) "Catalytic Asymmetric Mukaiyama Aldol Addition using 1,3-Bis(siloxy)diene Promoted by a Ti(O*i*Pr)$_4$ / (*S*)-BINOL / LiCl Catalyst," This is a forthcoming (fourth) article and is dedicated to the late professor Teruaki Mukaiyama.

1P-69

Thermal hazard analysis of self accelerating decomposition via acid production of dimethyl sulfoxide (DMSO)

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Dimethyl sulfoxide (DMSO) is widely used in chemical industries, because of its high dissolving ability and low toxicity [1]. It is well-known that DMSO is highly stable at temperatures below 150 °C. On the other hand, DMSO has high energy enough to cause explosion and several accidents in laboratories and chemical processes have been reported [2]. Previous studies reported that the decomposition of DMSO was autocatalytic. Autocatalytic reaction is hazardous because of decomposition product acts as a catalyst and the apparent reaction rate does not increase. After that sudden heat evolution and unexpected initiation happen due to catalyst gradually accumulated. Therefore, it is important to obtain information regarding autocatalysis and to understand how we can handle DMSO safety.

Our previous study declared that a fraction of DMSO decompose to several acids such as formic acid (HCOOH), sulfuric acid and acetic acid [3]. To reveal the condition of sudden heat evolution, it is necessary to declare detailed mechanism of decomposition of DMSO and that of acid generation. The purpose of this study is to get better understanding of decomposition mechanism of DMSO. First, we carried out thermal analysis using Calvet calorimeter (C80). After that the reaction pathways were built based on previous studies [3,4] and C80 result. A detailed chemical kinetics model was constructed based on quantum chemical calculations. Optimized structures for reactants, products, and transition states were obtained at the M06-2X/6-311++G(d,p)/SCRF=(smd,solvent=DMSO) level of theory, and the total electron energies of these structures were calculated at the G4 level of theory.

C80 result showed that induction period become shorter as concentration of HCOOH increase. Potential energy surface estimated that the reaction pathway of dimethyl sulfide generation via proton adduct of DMSO and $CH_3SOCH_3CH_3^+$ has lower activation energy than other pathways. This pathway generates formaldehyde (HCHO) and parts of HCHO is oxidized to form HCOOH.

[1] Gaylord Chemical Corporation. TECHNICAL BULLENTIN REACTION SOLVENT DIMETHYL SULFOXIDE (DMSO).
[2] Lam TT, Vickey T, Tuma L. Thermal hazards and safe scale-up of reactions containing dimethyl sulfoxide. J. Therm. Anal. Calorim., 85, 25-30 (2006)
[3] Y. Deguchi et al., Abstract of 12th Euro. Symp. Therm. Anal. Calorim., 420 (2018)
[4] Head D. L. et al., the thermal decomposition of DMSO, Tetrahedron Let., 16, 1405-1408 (1973)

1P-70

In situ analysis of liquid phase oxidation of nitric acid/formic acid mixtures using thermal and raman spectroscopic analyses

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An autocatalytic reaction is a chemical reaction whose product acts as a catalyst [1]. In general, the rate of the reaction increases rapidly as the concentration of the auto-catalytic product increases [2]. An obvious reaction occurs rapidly after an induction period in which the reaction proceeds slowly. In such a reaction, it is difficult to anticipate when the obvious reaction initiates using thermal analysis because no remarkable thermal behavior can be observed during the induction period. If the autocatalytic reaction is an exothermic reaction, the rapid reaction can cause runaway reaction and explosion. Therefore, it is necessary to reveal the concentration conditions to begin the exothermic reaction because the reaction progresses depending on the concentration of the auto-catalytic compound. It is important to elucidate the reaction mechanism to identify the auto-catalytic product and clarify the composition change in the system. The purpose of this study is to obtain a better understanding of the autocatalytic reaction mechanism. The autocatalytic reaction includes some unstable auto-catalytic compounds, so it should conduct *in situ* analysis. It is effective in elucidation of the reaction mechanism to use thermal and spectroscopic analyses which can obtain simultaneously the thermal behavior and the change of the chemical products with time.

We have chosen the oxidation of formic acid and nitric acid, which is a strong oxidizer, as an example of autocatalytic reaction. It is not clear how the rapid exothermic reaction initiates after the induction period and how the oxidation reaction leads autocatalytic thermal runaway and gas generation [3, 4]. We conducted thermal analysis and *in situ* raman spectrometry to obtain simultaneously the thermal behavior and the change of the chemical products with time. We analyzed the oxidation reaction mechanism in the induction period and exothermic reaction separately.

The results showed that there is a new reaction pathway against the previous studies. In the induction period, the new reaction pathway is thought to be below; nitrous acid was formed via a reaction of nitrogen oxide with $HCOO^-$ in the induction period. After that, NO_2 and N_2O_4 were formed via a reaction of nitric acid and nitrous acid in the exothermic reaction. In addition, the exothermic reaction proceeded via the formation of $HCOONO_2$. The exothermic reaction mechanism is thought to be as follow; a molecule of nitrous acid is consumed in the first step of the exothermic reaction, while two molecules of nitrous acid are generated in the second step via the formation of $HCOONO_2$.

[1] S. Liu et al., Thermochimica Acta, 605, 68-76(2015)
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1P- 71

Efficient Removal of Nitrate Ions Through Calcium Alginate Membrane Immobilizing Activated Carbon Particles as Adsorbents

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The stable calcium alginate membrane immobilizing activated carbon particles as adsorbents was successfully prepared and its removal ability for nitrate ions in aqueous phase was investigated. The biopolymer membrane which immobilizes adsorbent particles exerts high adsorption ability in combination with molecular screening ability [1].

A mixture consisted of 1 wt% sodium alginate, 5 wt% polyethylene glycol (PEG, Mn = 1000 Da), and 2 wt% activated carbon particles was cast on a circular membrane mold. The cast solution was dried at room temperature (T = 25˚C) for 6 days. The dried membrane was immersed in 0.1 M aqueous calcium chloride solution to cross-link alginate polymer. The formed membrane was washed to remove PEG from the membrane with 100 mL of distilled water at 60 ˚C in a shaking bath. Using prepared membrane, isothermal adsorption in a batch process and removal test in a continuous membrane permeation process were carried out for evaluating removal ability of nitrate ions.

The prepared membrane was observed using Field Emission Scanning Electron Microscopy (FE-SEM). Stably immobilizing activated carbons inside the membrane as well as on the surface was confirmed. From the isothermal adsorption of nitrate ions, the membrane immobilizing activated carbon showed the higher adsorbed amount in equilibrium state in comparison with the membrane without activated carbon. In the removal test in membrane permeation process, the total adsorbed amount of nitrate ions was higher than the adsorption in batch process (Fig. 1). The adsorption ability of activated carbon performed in collaboration with molecular screening ability originating from polymeric network of calcium alginate. The membrane has a potential to serve purification of water recourses polluted by nitrate ions such as well water.

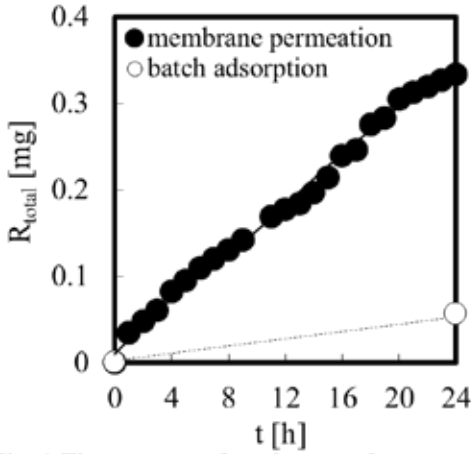

Fig. 1 Time course of total removal amount of nitrate ions (R_{total}). T = 25˚C.

Reference [1] Fujisaki, T. et al., *Chemical Engineering & Technology* **42** (2019) 910-917.

1P- 72

Molecular Separation of Sugars via Calcium Alginate Membrane with Polysaccharide Network Precisely Controlled Polymeric Structure

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Highly efficient separation of sugars is important technique for the fields of biochemistry and food industries. A molecular separation membrane prepared from calcium alginate known as a biopolymer is capable of separating the molecular size of monosaccharide and oligosaccharides by molecular screening ability [1]. This study demonstrates the nano-structural modification of calcium alginate membranes using oligoethylene glycol (oligoEG, Mn = 200 Da) for improvement of solvent permeability.

A casting solution consisted of 10 g L^{-1} sodium alginate and 0 to 10 g L^{-1} oligoEG was placed in a glass-made Petri dish (φ 90 mm), and then, it was dried at 303 K for 48 h in an electrical drying chamber. The dried membrane was immersed in 20 mL of 1 M aqueous calcium chloride solution to cross-link alginate polymer for 40 min. The formed calcium alginate membrane was washed for removing oligoEG with 100 mL of distilled water at 333 K for 30 min repeated twice within a shaking bath. A 10 mM glucose solution was permeated through the membrane using a membrane holder (KST-90-UH, ADVANTEC) with nitrogen gas (⊿P = 300 kPa). The mass of glucose solution permeated through the membrane with time was measured by electrical balance and was converted to permeated volume using density.

From FE-SEM observation, the specific pores were not observed in all the membrane, however, clear differences were occurred. The membrane prepared with oligoEG has a rougher structure than the membrane without oligoEG. In the permeation of glucose solution, the permeated flux was remarkably improved with an increase in concentration of the added/removed oligoEG during membrane preparation. In contrast, the rejection of glucose was almost constant. The results indicate oligoEG modification develops the volume of mass transfer channel in similar size with glucose molecule.

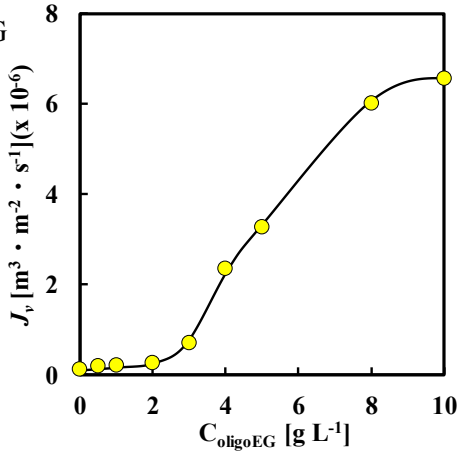

Fig. 1 Effect of the added/removed concentration of oligoEG ($C_{oligoEG}$) on the permeation flux of glucose aqueous solution (J_V)

The nano-structural modification of calcium alginate membrane with addition/removal of oligoEG for the improvement of solvent permeability was successfully achieved. The membrane is expected to exert high performance on the sugars purification.

Reference [1] Kashima, K. et al., *Food and Bioproducts Processing,* **102** (2017) 213-221.

1P- 73

Preparation and Characterization of Biocompatible Chitin/Chitosan Membrane Prepared through an Acetylation Process of Glucosamine Units

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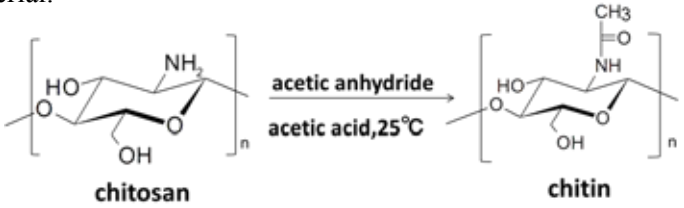
A biocompatible membrane consisted of two type biopolymer chain which were chitosan (β-(1→4)-linked D-glucosamine) and chitin (β-(1→4)-linked D-acetylglucosamine) converted from chitosan through an acetylation process was successfully prepared. Chitin and chitosan are well known as typical biological polymers produced from the external skelton of crustaceans, such as club and shrimp. The chitosan membrane has sufficient mechanical properties for practical use [1].

Three grams of chitosan powder (SIGMA-ALDRICH) was dissolved in 297 g of 10 vol% acetic acid aqueous solution. A 500 μL potion of acetic anhydride was gently added in the chitosan solution for acetylation of glucosamine units in chitosan (Scheme 1). The acetylated solution was frozen in liquid nitrogen and complately dried under high vacuum (< 25 Pa) for obtaining chitin fiber. Twenty grams of cast solution which is composed of 1 wt% chitosan and 0.2 wt% chitin in 10 wt% acetic acid solution was placed in glass Petri dish with diameter 90 mm. The cast solution was dried at 60 ˚C for 12 h, and then the dried membrane was obtained. The dried membrane was immersed in 4 wt% NaOH aqueous solution to deprotonate amino groups in polymer chains for insolubilization of the membrane. In addition, the membrane consisted of only chitosan polymer was prepared in same way for comparison of membrane characteristics.

Both chitosan membrane and chitin/chitosan membrane had not only good stability in water but also flat and smooth surface (Fig. 1). The chitosan membrane showed a more transparency than chitin/chitosan hybrid membrane. The mechanical properties of membranes were evaluated from tengile measurement using a tension testing apparatus (AGS-X, SHIMADZU). The chitin/chitosan hybrid membrane exerted higher maximum strength and higher maximum strain than the chitosan membrane. The chitin/chitosan membarne developed in this study has an applicative capability as an environmentally‐friendly film material.



Scheme 1 Acetylation of chitosan

Fig. 1 The chitin/chitosan membrane

Reference [1] Fujisaki, T. et al., *Chemical Engineering & Technology* **42** (2019) 910-917.

1P- 74

Effect of Monomer Composition on the Laccase/O_2-Catalyzed Oxidation of Aniline and *p*-Aminodiphenylamine in the Presence of Anionic Vesicles

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1. Intruduction

The enzymatic synthesis of the electroconductive emeraldine salt form of polyaniline (PANI-ES) from aniline, PADPA or their mixtures – catalyzed by *Trametes versicolor* laccase (TvL)/O_2 – in the presence of anionic vesicles from sodium bis(2-ethylhexyl) sulfosuccinate (AOT) as reaction templates was investigated. This enzymatic oxidation was carried out at room temperature in a phosphate solution of pH = 3.5. [1] This process is environmentally friendlier than the traditional chemical synthesis of PANI-ES, which occurs at strongly acidic conditions and a strong chemical oxidant.

2. Methods

The reactions were carried in 50 mL Schott glass bottles by adding the different reaction components (10 mL total volume): pH = 3.5 solution (0.1 M NaH_2PO_4 + H_3PO_4), AOT vesicle suspension, substrate solution (consisting of aniline, PADPA or their mixtures), laccase solution. The concentration of AOT was 1.5 mM and [laccase] = 0.207 μg/mL. The total aniline unit concentration was kept constant at 2.0 mM to allow comparison with the reaction containing only PADPA at 1.0 mM (aniline – 2.0, 1.8, 1.6, 1.4 … mM + PADPA – 0.0, 0.1, 0.2, 0.3 … mM). The reaction mixtures were withdrawn and analyzed with a UV-vis spectrophotometer (UV mini-1240, SHIMADZU) at desired times (t = 24 h).

3. Results and Discussion

The formation of PANI-ES-type products (with their characteristic absorption bands around 1000 nm, A_{1000}) was confirmed in the reactions with PADPA or aniline/PADPA mixtures. In the reaction of aniline only, the reaction rate was very slow and the main absorption band was around 730 nm. The reaction with PADPA only and with the mixture of aniline:PADPA = 3:7 showed a high value of A_{1000}. However, the formation of undesired phenazine core units (with their characteristic absorption bands around 600 nm, A_{600}) was observed in all reaction mixtures. The products obtained with the mixture of aniline:PADPA = 6:4 showed the highest value of A_{1000}/A_{600}, indicative for best PANI-ES quality within the mixtures tested.

4. Conclusion

All reaction mixtures consisting of aniline and PADPA yielded products with typical emeraldine color, which is characteristic for PANI-ES. Optimal compositions of aniline:PADPA were found to be 6:4 or 3:7.

Reference

[1] Kashima, K. et al., *ACS Omega*, **4** (2), 2931–2947, 2019.

1P- 75

Application of Highly Efficient Chiral Spiro Catalysts In the Synthesis of Key Chiral Intermediates of APIs

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The transition metal catalyzed asymmetric hydrogenation has proved to be an efficient and economically feasible method for preparing chiral compounds. A type of iridium catalysts with chiral tridentate spiro ligands, SpiroPAPs, an unique type of ligands, have proved to be extremely efficient for the asymmetric hydrogenation of ketones to chiral alcohols, while the other type of Ir-chiral catalyst as Ir-SIPHOXs show highly efficiency and selectivity for the asymmetric hydrogenation of α,β-unsaturated carboxylic acids with very high turnover numbers, and high turnover frequencies. Our research program has been focusing on the application of Ir-SpiroPAPs and Ir-SIPHOXs in the asymmetric hydrogenation reaction, which enable efficient process development of chiral key pharmaceutical intermediates and APIs. Several successful cases are reported on industrial scale, such as Rivastigmine, Montelukast, Crizotinib, and Silodosin etc.

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1P- 76

Metal-Free Asymmetric Synthesis of Dihydroquinoxalinones and 4-Imidazolidinones from α-Amino Acid Precursors via Dehydrogenative N-H/C-H Coupling

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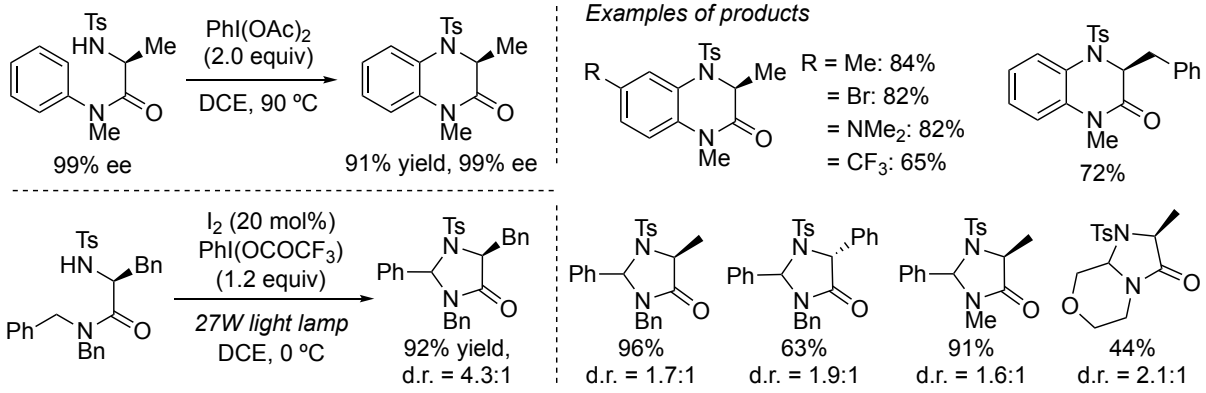
Dehydrogenative N-H/C-H coupling represents a promising strategy for the formation of C-N bonds in terms of atom- and step-economy. It is mainly realized using stoichiometric or catalytic transition metals, but their toxicity, cost and difficult purification from the target products have driven the development of alternative methods. In this respect, metal-free dehydrogenative coupling is attractive in terms of greenness and cost-efficiency. On the other hand, α-amino acids are inexpensive and readily available feedstocks widely used in synthetic organic chemistry to provide chiral pool for the asymmetric synthesis of drugs and natural products.

We established a method for the asymmetric synthesis of dihydroquinoxalinones via intramolecular N-H/C(sp^2)-H coupling using hypervalent iodine.[1] The starting materials were prepared from α-amino acids and aniline derivatives. The reaction tolerates various functional groups to afford multisubstituted dihydroquinoxalinones in moderate to high yields. We also described an efficient method for the asymmetric synthesis of 4-imidazolidinones via an iodine-catalyzed intramolecular N-H/C(sp^3)-H coupling of amides prepared from α-amino acids and alkylamines.[2] The N-H/C(sp^3)-H coupling proceeded under visible light irradiation to afford a variety of 4-imidazolidonones under mild reaction conditions in moderate to excellent yields. Importantly, the chirality of the amino acid was retained in the desired product without loss of enantiomeric excess.



References: (1) Kanyiva, S. K.; Horiuchi, M.; Shibata, T. *Eur. J. Org. Chem.* **2018**, 1067. (2) Kanyiva, S. K.; Tane, M.; Shibata, T. *Submitted for publication*.

1P- 77

COF Derived N,P Co-Doped Carbon as a Metal-Free Catalyst for Highly Efficient Oxygen Reduction Reaction

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The oxygen reduction reaction (ORR) are the heart of many renewable energy storage and conversion technologies such as fuel cells and water electrolysis. Noble metals like Pt and their alloys are revealed as one of the most efficient electrocatalysts for ORR. However, their high cost, supply scarcity, and poor durability constraint the practical application. Designing and synthesizing noble-metal-free electrocatalysts are highly impending to promote the development and usage of renewable energy and devices.

Metal-free carbon nanomaterials as electrocatalysts have been paid much attention in the field of energy conversion and storages including ORR due to their low cost, abundant resources, good conductivity, and excellent stability. Doping and co-doping carbon nanomaterials with heteroatoms such as B, O, N, P, and S are demonstrated a rational route to tune and modify the surface and electronic properties of carbon nanomaterials. Graphene, carbon nanotubes, biomass, ion liquids, graphdiyne, and metal-organic frameworks are common precursors to fabricate these doped and co-doped metal-free carbon electrocatalysts. Nevertheless, to the best of our knowledge, COF-derived carbons as electrocatalysts have rarely been discussed and not truly reported to date.

Herein, N, P co-doped carbon *via* direct carbonization and phosphorization of 2D COF exhibits a robust and superior ORR performance with the half-wave potential (0.81 V vs. RHE), high limiting current density (5.7 mA cm^{-2}), low Tafel slope (72 mV $decade^{-1}$), and methanol tolerance to commercial Pt/C.

1P- 78

Preparation of 1,3-Substituted Pyrroles under Basic Conditions

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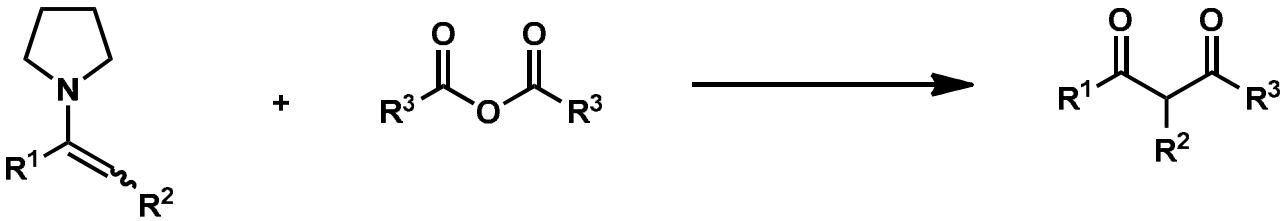
Substituted pyrroles are frequently found in natural compounds which would be good resources for bioactive materials. Also they are essential material for fluorescent dyes. Although a variety of synthetic method has been developed so far, new simple and reliable preparation methods are still needed. Since the pyrrole ring is electron rich, metal catalyzed coupling reactions afforded pour results in many cases. So we investigated pyrrole synthesis via reaction between 1,3-dicarbonyl compounds and aminomalonate under basic conditions.

Scheme 1 reaction between 1,3-dicarbonyl compounds and aminomalonate

Some conditions (base, solvent, reaction temperature) and procedure were examined. Initial imine formation seems decide final position of substituent and largely relayed on nature of the subsutituents (R^1 to R^3 in Scheme 1). The rage yields were 30~85% and strongly influenced by pattern of the substiturents. Starting 1,3-dicarbonyl compound were prepared by condensation between acid anhydrides and enamines effectively.



Scheme 2 Condensation reaction between enamine and acid anhydrides

To understand the mechanism, i) keto- enol tautomerism, ii) enamine formation, iii) cyclization have been accessed and characterized by spectroscopic method (Ramann, NMR *etc.*).
We are going to discuss about the mechanism and the scopes and limitation on the reaction.

References

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Abstracts

Poster Presentation

2 P-01 ～ 2 P-77

July 26

2P-01

Ligand-Free Kumada Coupling Catalyzed by Iron(II) Nanoparticle

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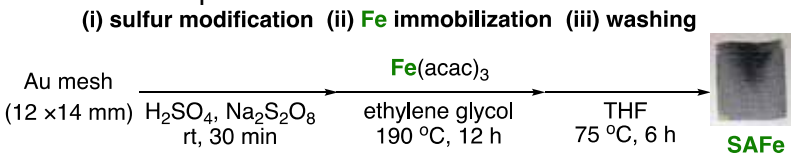
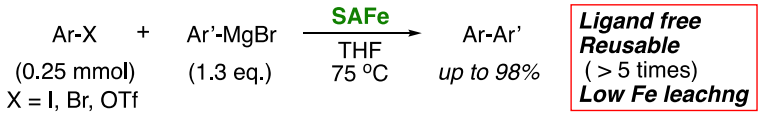
Biaryls constitute core structural units for an enormous range of functional molecules, including medicine.[1] They are easily synthesized by transition metal-catalyzed cross-coupling, such as Kumada coupling. We previously developed a sulfur-modified Au-supported Pd nanoparticle (NPs) catalyst (SAPd) and used it to catalyze Suzuki-Miyaura coupling, Buchwald-Hartwig coupling, C-H functionalization without ligands.[2] However, recyclable and non-palladium catalysts, like iron, for ligand-free Kumada coupling has not been developed very well, although iron catalyst is an ideal transition metal catalyst which is relatively safe and abundant on the earth. To solve this problem, here we developed a conceptually and methodological novel iron(II) NPs catalyst, sulfur-modified Au-supported Fe catalyst (SAFe) and applied to Kumada coupling under ligand-free conditions.

SAFe is easily prepared *via* three-step procedures; (i) sulfur modification, (ii) Fe(II) NPs immobilization and (iii) washing (**Scheme 1**) . SAFe is useful for liquid-phase combinatorial synthesis, because SAFe repeatedly catalyzed ligand-free Kumada coupling of aryl halides, including heterocyclic aryl bromides with trace amount of iron leaching (**Scheme 2**). It can be used for the reaction with various kinds of substituted aryl compounds in highly reliable yields. The structure and chemical composition of SAFe were investigated spectroscopically and microscopically. As the result, iron immobilized on SAFe were Fe(II) NPs (ca. 3 nm) by X-ray absorption near-edge structure (XANES) and transition electron microscopy (TEM) analysis. In the poster presentation, we will report the result of screening of substrates including aryl iodides, aryl bromides, aryl triflates and aryl Grignard reagents, and the characterization of SAFe.[3]

Scheme 1. Preparation of SAFe



Scheme 2. SAFe catalyzed lgand-free Kumada coupling



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3. *ACS Appl. Nano Mater.* **2018**, *1*, 6950.

2P- 02

Heterogeneous Palladium on Titania-Catalyzed Ligand-Free Suzuki–Miyaura Coupling of Aryl Chlorides

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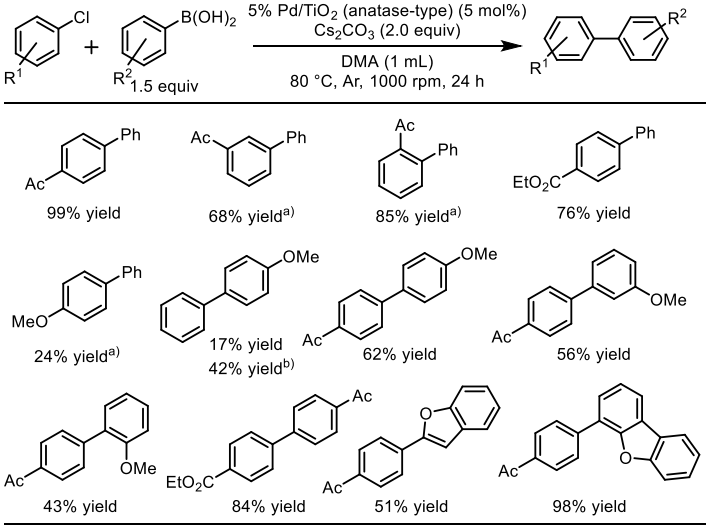
Palladium (Pd)-catalyzed Suzuki–Miyaura coupling is one of the useful synthetic methods to construct biaryl derivatives as partial structures of various pharmaceuticals and functional materials. Especially, heterogeneous Pd-catalyzed Suzuki–Miyaura coupling reactions have been attracted attention as environmentally-friendly, metal contamination-free, and cost-effective methods. Although some specific ingenuity is necessary due to the low reactivity of the carbon-chloride bond, it is preferable to use aryl chlorides as more versatile and inexpensive substrates compared to aryl iodides and bromides.

We have prepared various heterogeneous Pd catalysts supported on anatase-, rutile-, and brookite-type titania (TiO_2) and applied these catalysts to the ligand-free Suzuki-Miyaura cross-coupling of aryl chlorides. The heterogeneous Pd on anatase-type titanium oxide [Pd/TiO_2 (anatase-type)] catalyst without reduction process during the preparation indicated the highest catalyst activity and various aryl chlorides could be coupled with arylboronic acids including heteroarylboronic acids in moderate to excellent yield [5 mol% of 5% Pd/TiO_2 (anatase-type) and 2 equiv of cesium carbonate (Cs_2CO_3) in DMA at 80 ℃ for 24 h at 1000 rpm, Table 1]. Although aryl chlorides possessing an electron donating group on the aromatic ring was less reactive for the coupling reaction, the coupling of aryl bromides possessing an electron donating group on the aromatic ring with phenylboronic acid smoothly proceeded to give 4-methoxylbiphenyl in high yield (Scheme 1).

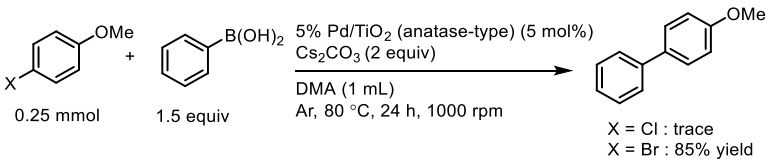
Table 1. Scope of substrates.



a) Phenylboronic acid (2.0 equiv), 5% Pd/TiO_2 (10 mol%) and Cs_2CO_3 (3.0 equiv) were used.
b) KO^{t}Bu (2.0 equiv) was used instead of Cs_2CO_3.

The anatase-type TiO_2-supported Pd [5% Pd/TiO_2 (anatase-type)] catalyzed ligand-free Suzuki–Miyaura coupling reaction would be expected to use in various chemistry fields as an inexpensive and environmentally-friendly reaction.

Scheme 1. Palladium on titania-catalyzed ligand-free Suzuki–Miyaura coupling of aryl chlorides



2P- 03

Enantioselective Friedel-Crafts Alkylation Reaction of 4,7-Dihydroindole to Trifluoromethylated *N*-H Ketimines by Means of Chiral Phosphoric Acid

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Mejiro, Toshima-ku, Tokyo 171-8588, Japan
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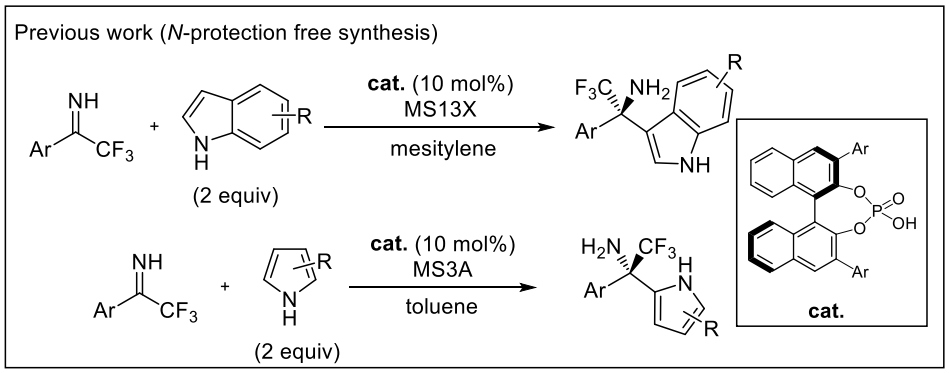
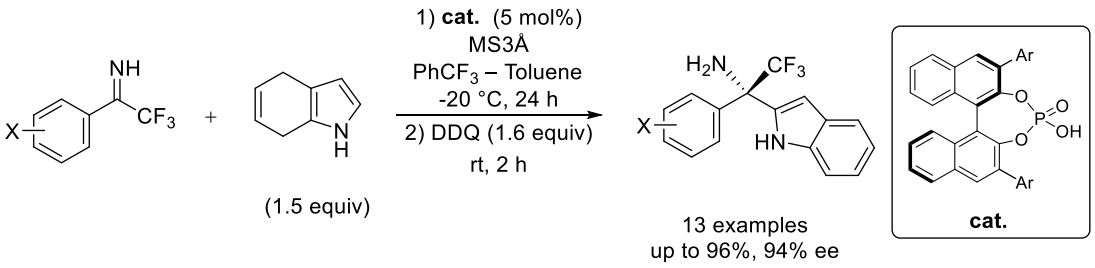


Chiral amines having stereogenic center at the α-carbon are found in various pharmaceuticals and natural products. α-Trifluoromethylated amines, in particular, have attracted much attention because of their intriguing biological activity.

Enantioselective Friedel-Crafts alkylation reaction of trifluoromethyl ketimines is known to give α-trifluoromethylated chiral amines. Trifluoromethyl *N*-H ketimines are relatively stable because of electron-withdrawing nature of the trifluoromethyl group, and have been utilized for the synthesis of α-trifluoromethylated chiral primary amines. We have already reported an enantioselective Friedel-Crafts alkylation reaction of indoles and pyrroles with *N*-unprotected trifluoromethylated ketimines to provide chiral trifluoromethylated primary amines.[1)]



We have found that Friedel-Crafts alkylation reaction of *N*-H trifluoromethyl ketimine with 4,7-dihydroindole by means of chiral phosphoric acid and subsequent DDQ oxidation furnished 2-substituted chiral indole derivatives in good yields and with high ee without protecting the nitrogen atom.

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2P- 04

AJIPHASE®: Practical Oligonucleotide Synthesis Achieved by Solution Phase Approach

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Oligonucleotide therapeutics have been developed as potential drugs for various diseases. The successes of approved drugs such as eteplirsen, nusinersen, patisiran, and the encouraging clinical trial results suggest that large quantities of synthetic oligonucleotide will be required within several years. A solid-phase approach is commonly used as a synthetic method for oligonucleotides. However, this method has scale-up limitation due to the requirement of special equipment, large excess of reagents and materials. From this point of view, a practical solution-phase approach has been required to overcome these issues.

We have already developed a unique and efficient solution-phase peptide synthesis method, the AJIPHASE® technology, that comprises repeated reactions and isolations by precipitation[1-2]. This technology uses a soluble anchor molecule with long chain alkyl groups as a protecting group for the C-terminus instead of resin. This methodology has an advantage of carrying out reactions under homogeneous condition to give high purity products in high yields.

In this work, we challenged applying the AJIPHASE® technology to DNA/RNA oligonucleotide synthesis in order to establish a practical and robust process. Fundamentally, oligonucleotide synthesis using phosphoramidite chemistry is composed of three steps: coupling, oxidation/sulfurization and removal of DMT group. In solid-phase synthesis, washing processes to remove all excess of reagents are included after every reaction step. To pursue a practical solution-phase synthesis, we first attempted an establishment of the one-pot elongation process by skipping two isolation steps after coupling and oxidation steps. After much research on alternatives to the isolation process, we achieved the one-pot process by using appropriate reagents to quench the excess activated monomer and scavenge several reactive side-products. Next, we tried to improve the purity of the oligonucleotide. Several unknown impurities were initially observed in the synthesized oligonucleotides. However, as AJIPHASE® can directly analyze the oligonucleotide by HPLC and LC/MS unlike solid-phase synthesis, a substantial improvement of the purity was achieved by suppressing some impurities as well as elucidation of the reaction mechanism. Finally, we confirmed that the improved process could apply into various types of oligonucleotides. These results provided a conclusive proof that the AJIPHASE® technology is a practical and robust synthetic method.

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[2] Takahashi, D.; Inomata, T; Fukui, T. *Angew. Chem.* **2017**, 27, (56), 7803

2P- 05

Ion-Pair Extraction of Ammoniums Using Tetracyanocyclopentadienides

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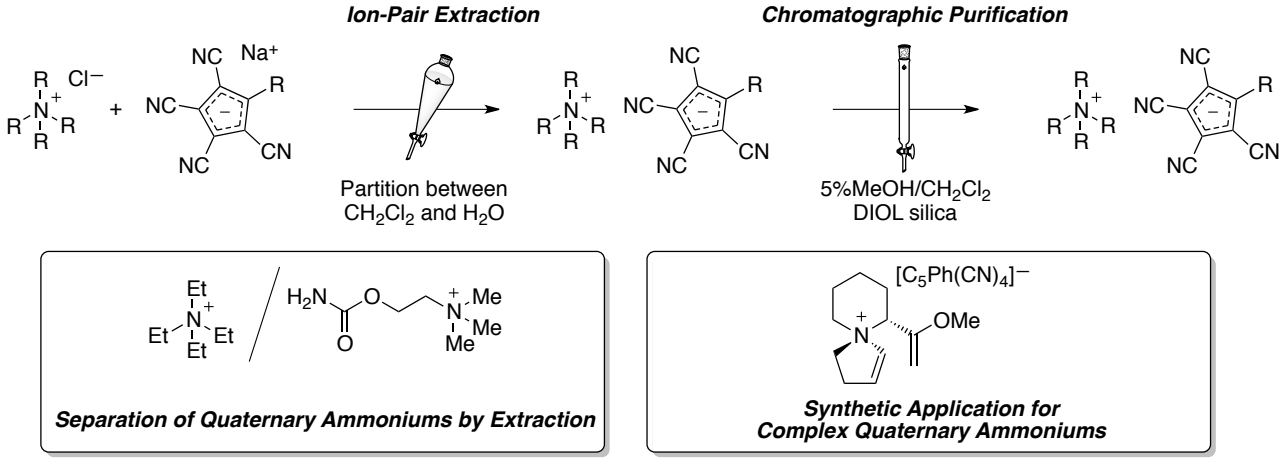
Quaternary ammonium salts play important roles in many sciences involving biological and organic chemistry. Despite of their significance, quaternary ammoniums are typically difficult in handling because they cannot be isolated as a salt-free form. We herein report an easy isolation method for quaternary ammonium cations by ion-pair extraction using tetracyanocyclopentadienide (TCCP). In the presence of sodium TCCP, ammonium cations formed an ion pair with TCCP, which was extracted with CH_2Cl_2 in good extraction yield with high purity. The scope investigation of ammonium salts and TCCP salts disclosed that the range of extractable ammonium cations was strongly correlated to lipophilicity of TCCP salts. Thus, separation of tetraethylammonium and carbachol cations was achieved by the ion-pair extraction using two TCCPs with different lipophilicity. We also established the conditions of chromatographic purification of ion pairs using a DIOL silica gel and MeOH-CH_2Cl_2 as the eluent. The ion-pair extraction with TCCPs also applied in the synthesis of a complex spiro quaternary vinylammonium salt that is a precursor of the novel 3-aza-Cope–Mannich reactions.



Sakai, T.; Noda, N.; Fujimoto, C.; Ito, M.; Takeuchi, H.; Nishiwaki, M.; Mori, Y. *Org. Lett.* **2019,** *21,* 3081–3085.

2P-06

Ultrafast enantiomeric separations using 1.6μm chiral column "CHIRALPAK U series"

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During recent years, high-speed analysis has been required in ODS column field and UHPLC system using sub-2μm columns has spread world-wide. Also chiral chromatographers have the same request and high performance sub-2μm chiral columns were awaited.

In 2016, we succeeded in developing the first sub-2μm chiral columns named as "CHIRALPAK® U series" in the world. These columns show higher theoretical plate number and good van Deemter curve as expected from their smaller particle size (1.6μm). By using smaller particle size and down sized column tube, CHIRALPAK® IA-U shows up to 70% shortening in analysis time with keeping in the almost same resolution. Needless to mention, these 1.6μm columns contribute to rapid method development of chiral separation.

In this poster, at first, we introduce the performances of "CHIRALPAK® U series" and next, show the examples of the chiral column screening protocol and rapid method development using them.

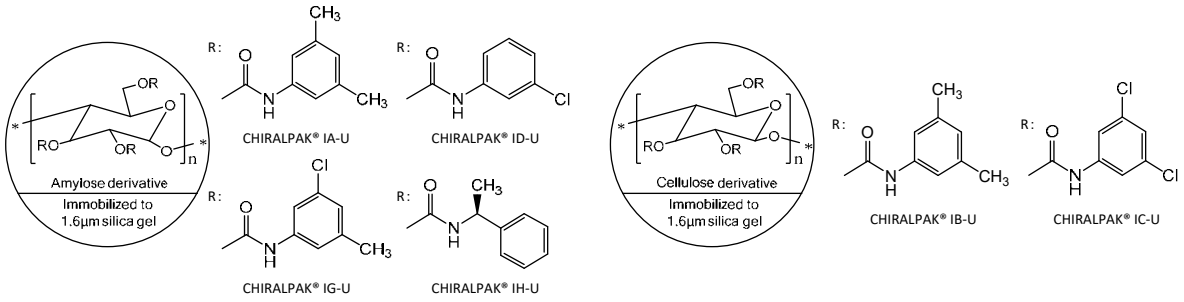

Figure 1. Chiral selectors of CHIRALPAK® U series

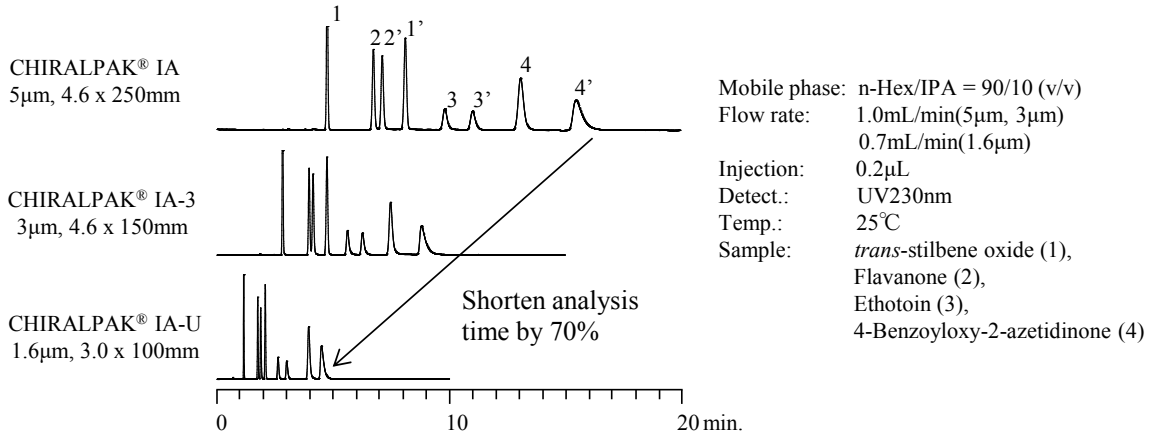

Figure 2. Reduction of analysis time by using CHIRALPAK® U series

2P- 07

Orthogonal selectivity controlled by organic bases in arylation for 2-pyridones with diaryliodonium salts

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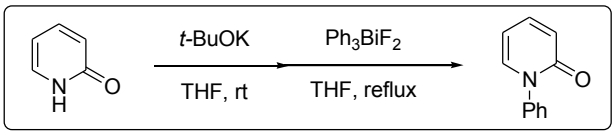
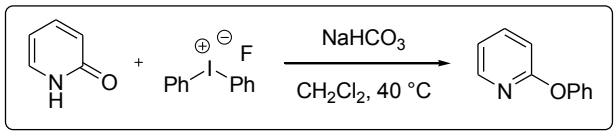
Chemoselective arylation of pyridones are important because the corresponding arylated products are known as key substructures of pharmaceutical molecules. While transition metal-catalyzed N-arylation and O-arylation of 2-pyridones has been actively pursued, metal-free selective arylation methods for 2-pyridones are rare. In these metal-free processes, a high level of chemoselectivity was achieved, but better accessibility to the arylating agents are desired (Schemes 1 and 2).

Scheme 1. *N*-arylation[1)]

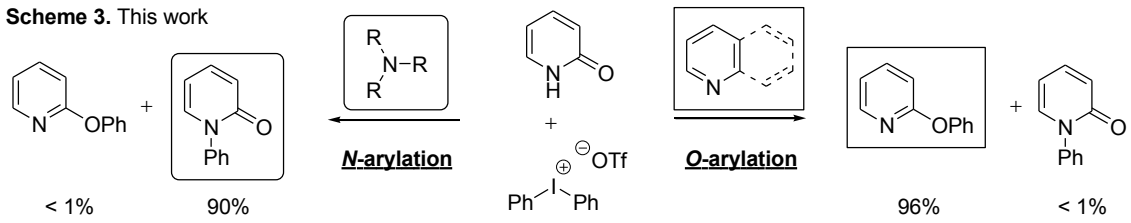


Scheme 2. *O*-arylation[2)]



In the screening of bases in the selective arylation of 2-pyridones with easily-synthesized diphenyliodonium triflates, the orthogonal chemoselectivity was observed depending on the kind of organic bases (Scheme 3). The selective N-arylation of 2-pyridones was achieved with tertiary amines, while pyridine-type bases proved to be suitable for the O-arylation reaction. In both cases, desired arylated products were obtained with excellent chemoselectivities.

Scheme 3. This work



Subsequently, influence of varying pyridones and diaryliodonium triflates was examined, and we found that steric and electronic influences did not give significant decrease in yield and selectivity. In addition, investigation on the reaction mechanism was conducted, the results and findings will be given in the poster presentation.

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2P- 08

Total syntheses of all six chiral natural pyrethrins from available synthetic pyrethroids, directing for process chemistry: accurate determination of the physical properties and insecticidal activities

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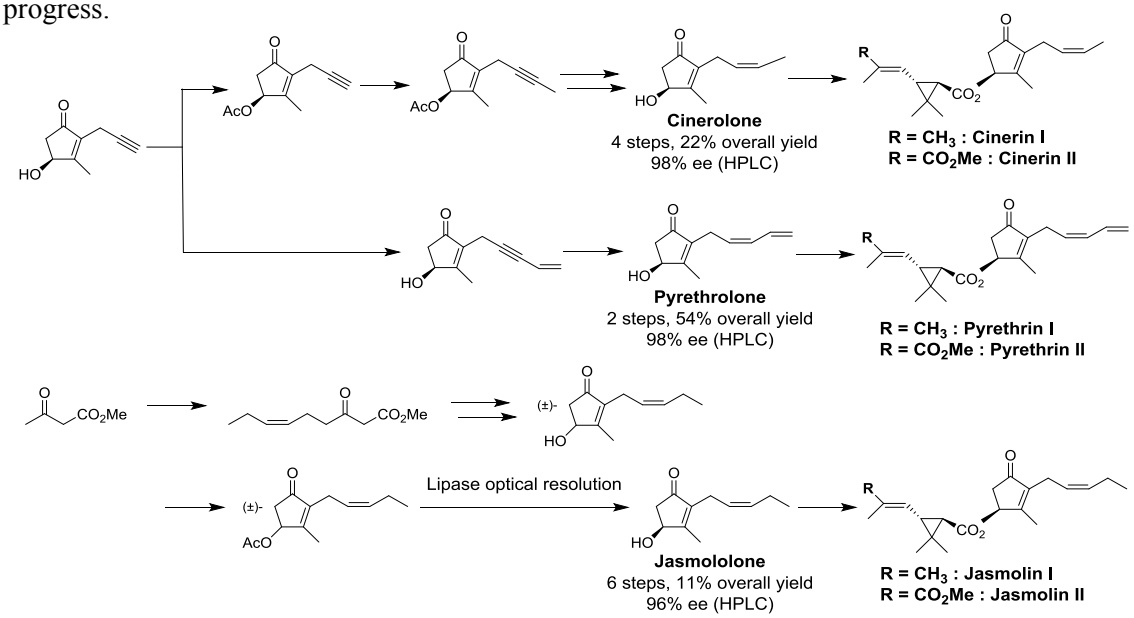
Natural pyrethrin families are well-recognized lead origins of a variety of synthetic pyrethroid insecticides. The flowers of pyrethrums (*Tanacetum cinerariifolium*) produce pyrethrins, which are composed of six different esters: two (1*R*,3*R*)-*trans*-chrysanthemic acids and three (*S*)-4-hydroxy-3-methylcyclopent-2-en-1-ones.[1] Despite its significance, contrary to general brief, accurate physical properties of all the six esters have not been confirmed to date, due to resemblance of the structure. We envisaged the confirmation of this issue with the aid of chemical synthesis. Three alcohol segments in natural pyrethrins with high optical purity were successfully synthesized utilizing Sonogashira cross-coupling[2] and optical resolution methods using Lipase as the crucial steps.[3,4] Esterification of the obtained chiral alcohols with chiral chrysanthemic acids were performed by TsCl / NMI / *i*Pr_2Et reagent.[5] Insecticidal activity against the common mosquito (*Culex pipiens pallens*) was assessed for all six natural pyrethrins and the results of structure-activity relationship would be firstly disclosed. Syntheses of all four enantiomers of cinerine I composed of the antipodal chrysanthemic acid and the alcohol are now under progress.



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2P- 09

Process Development for Large-scale Synthesis of Baloxavir marboxil (Xofluza®)

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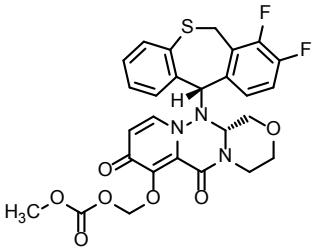
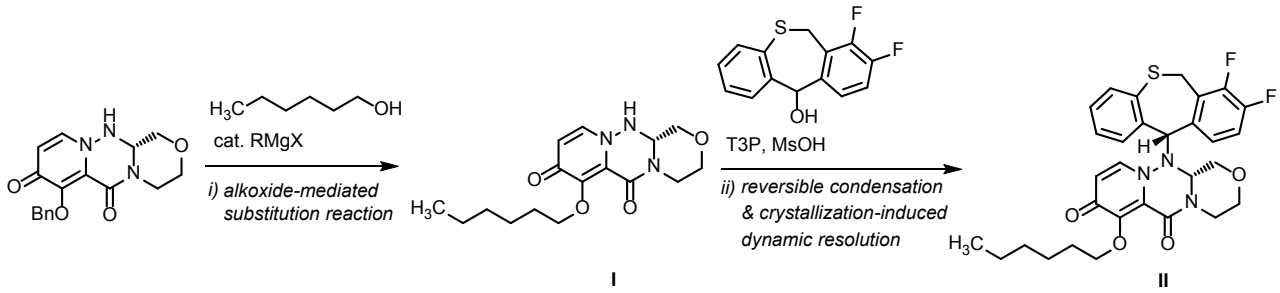
Baloxavir marboxil (trade name Xofluza®) is a new influenza (flu) antiviral drug discovered and developed in Shionogi, which was approved in February 2018, under SAKIGAKE designation system by Pharmaceuticals and Medical Devices Agency (PMDA), and in October 2018, by the U.S. Food and Drug Administration (FDA). Baloxavir marboxil exploits as a cap-dependent endonuclease inhibitor, a new mechanism of action, so that it works differently than the other conventional flu antiviral drugs, which are neuraminidase inhibitors.



Baloxavir marboxil (Xofluza®)

The medicinal chemistry synthesis for this active pharmaceutical ingredient could be improved aiming to its commercial manufacturing in terms of reliable quality control, cost reduction, and avoiding harmful reagents. Herein we report process development for large-scale synthesis. The new practical synthetic route includes the following highlighted steps; i) magnesium alkoxide-mediated substitution reaction to prepare an intermediate **I** without loss of optical purity, and ii) diastereoselective preparation of an intermediate **II** via the reversible condensation reaction with crystallization-induced dynamic resolution.



We revealed that the hexyl group on intermediate **I** played an important role to establish high diastereomer ratio and yield of the condensation product **II** at the later step. The usage of catalytic amount of a Grignard reagent in 1-hexanol enabled us to generate the corresponding alkoxide reagent that switches the protecting group on the enol moiety to give intermediate **I** at the former step. The detail data obtained through our investigation will be disclosed in the presentation.

2P- 10

Deacetylative Amination of Acetyl Arenes and Alkanes under Transition-Metal-Free Conditions

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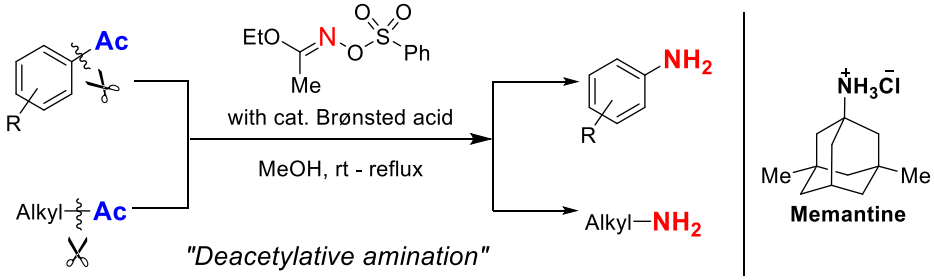
Primary amines are important compounds found in pharmaceuticals, natural products, polymers, and textiles. Aromatic primary amines have been synthesized using various approaches such as Bechamp reduction and Pd-catalyzed Buchwald-Hartwig coupling, Chan-Lam amination, electrophilic amination, C-H amination. However, these reactions often require the use of costly transition metals and designer ligands, and can involve a tedious process to remove trace metal impurities, especially when applied to the synthesis of drugs. Therefore, transition-metal-free aromatic amination reactions are so attractive.

This work demonstrates that an acetyl group can act as a substrate for transition-metal-free amination using the method we developed.[1)] Acetyl arene, which is commercially available or easily prepared by Friedel-Crafts acylation, could be transformed into an aromatic primary amine without the use of a metal catalyst and organometallic reagents. However, the process required multiple steps, such as oximation and Beckmann rearrangement, hydrolysis or Schmidt reaction, and hydrolysis. Therefore, the lack of a straightforward synthesis involving a functional transformation from acetyl to amino group is not recognized widely compared to those involving nitrobenzene and halogenated arenes.

To dissolve the problem, we achieved the direct synthesis of aromatic primary amines from acetyl arene catalyzed by a Brønsted acid *via* domino transoximation/Beckmann rearrangement/Pinner reactions. The methodology accommodated the synthesis of aliphatic primary amines from acetyl alkanes. Thus, this deacetylative amination was expanded to synthesize pharmaceuticals, memantine (anti-Alzheimer's drug), baclofen (CNS depressant) such as γ-aminobutyric acid (GABA) and rolipram (selective PDE IV inhibitor). This is the first synthetic report demonstrating a simple transformation from acetyl arene/alkane to aromatic/aliphatic primary amine without requiring a transition metal with ligands or organometallic reagents.



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2P- 11

Application of the Palladium-loaded Monolithic Ion Exchange Resin to a Continuous Flow Processing

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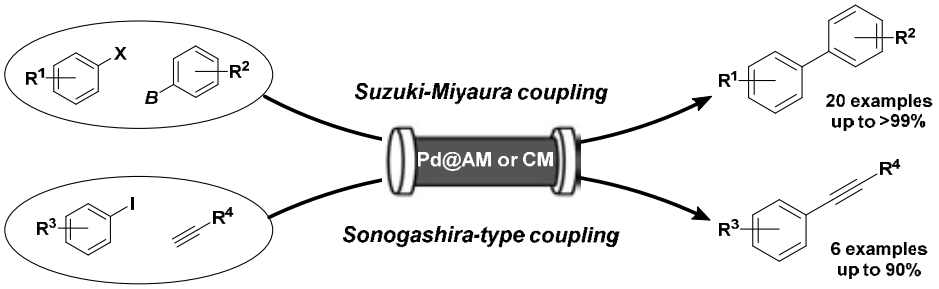
The most of functionalized compounds, such as pharmaceuticals, agrichemicals, organic EL materials have been generally produced by the system which the product is manufactured in a large vessel (batch chemistry system) in industry. The batch chemistry system has advantage in the cost of the equipment and so on; however this system also has several safety and environmental problems. Therefore, it is desired to convert the batch chemistry system to "flow chemistry system" which the chemical reaction is run in the flow stream in the tube and the product is allowed to obtain in continuously. In particular, the development of the metal catalyzed coupling reactions is expected, it is essential for the improvement of the green and sustainable flow chemistry system to develop the metal immobilized catalyst.

Meanwhile, we developed the palladium catalyst immobilized on monolithic polystyrene-DVB polymer bearing strongly acidic cation exchange function (Pd@CM) and basic anion exchange function (Pd@AM),[1-4] which are allowed to apply to the coupling reactions under batch chemistry system.[3] In this report, we demonstrated to apply the Pd@CM and Pd@AM to coupling reactions under flow chemistry system. Furthermore, we found that the catalytic activity was increased by exchanging the anion species of Pd@AM.

The substrate solution was passed through a column packed with Pd@CM or Pd@AM (φ4.6×30 mm) at 80 ˚C by a diaphragm pump. The reactions were carried out with about 30 seconds of residence time in Pd@CM or Pd@AM, the product was quantitatively obtained in some substrate.



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2P-12

Development of Boronic Ester-Mediated Ligand-Directed Protein Acylation

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Ligand-directed catalysis has emerged as a promising method for covalent modification of proteins within living cells. However, it is currently challenging to generate an effective concentration of reactive intermediate while still using mild and bio-compatible conditions. In other words, a large excess of electrophilic reagent may be required. The resulting off-target reactivity impedes further development of ligand-directed catalysis as a chemical biology tool or therapeutic strategy.
A potential solution involves the use of a bio-orthogonal Lewis acid/base interaction. This interaction should permit generation of a reactive intermediate while using less forcing conditions. I will present development of a boronic ester-mediated system for ligand-directed protein acylation.

2P- 13

C-H γ,γ,γ-Trifluoroalkylation of Quinolines via Visible-light-induced Sequential Radical Additions

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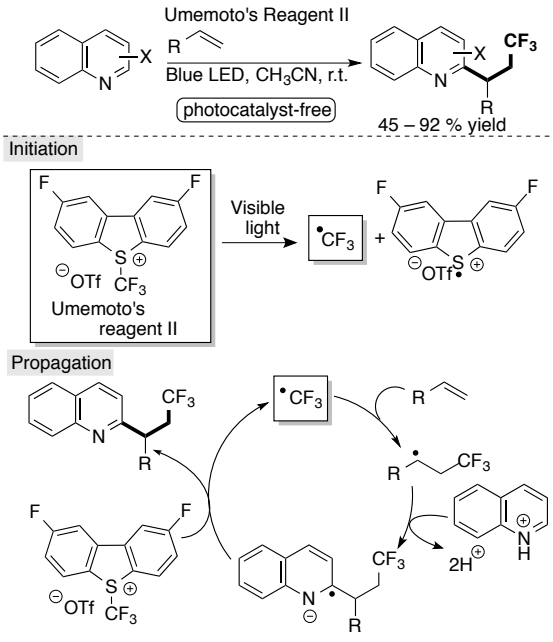
Fluoroalkyl groups have been intensively employed to improve the bioactivity and pharmacodynamics of drug lead compounds. Among these, γ,γ,γ-trifluoroalkyl group, which has three C-F bonds at the terminal position of a linear alkyl chain, is useful to prevent metabolic C-H oxidation by cytochrome P450 at the terminal position of alkyl chain and prolong *in vivo* activity of such lead compounds. In addition, enhancement of bioactivity of these compounds can be expected by additional interactions with target proteins and improved lipophilicity. Despite these advantages, a synthetic method to introduce γ,γ,γ-trifluoroalkyl group to electron-deficient N-heteroaromatics, a prevalence in medicinal chemistry, has been limited. For example, the report by MacMillan requires preparation of the respective γ,γ,γ-trifluoroalcohols and is not feasible for constructing a large compound library[1]. We planned visible-light-induced sequential radical additions with easily available trifluoromethyl radical source, alkene, and quinoline to achieve C-H γ,γ,γ-trifluoroalkylations of quinolines with a broad substrate scope.

After considerable experimentation, we were pleased to obtain the C(2)-H or C(4)-H γ,γ,γ-trifluoroalkylated quinolines in 45-92% yield with Umemoto's reagent II, which is easily available trifluoromethylating reagent, alkene, and quinoline under blue light irradiation at room temperature. Variety of alkenes can be employed in this condition, and quinolines that have electron-withdrawing group gave good result. Furthermore, C-H γ,γ,γ-trifluoroalkylated products derived from 2-chloroquinoline serve as versatile intermediates for further transformations. Thus, this C-H γ,γ,γ-trifluoroalkylation reaction allows construction of novel nitrogen-containing heterocycle library and provides versatile intermediates for the synthesis of bioactive compounds[2].



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2P- 14

Chlorocarbonysulfenyl chlorides: A unique bifunctional electrophilic reagent for the syntheses of heterocyclic compounds, directing for process chemistry

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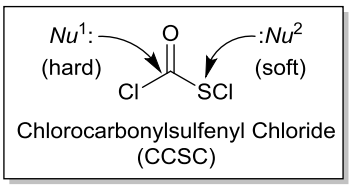
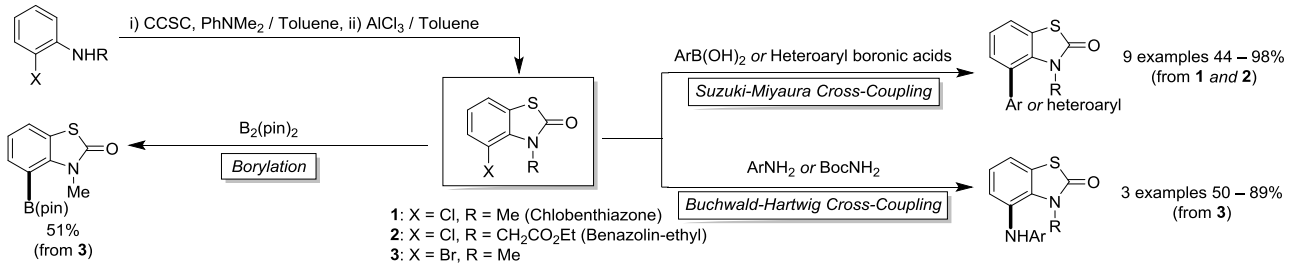
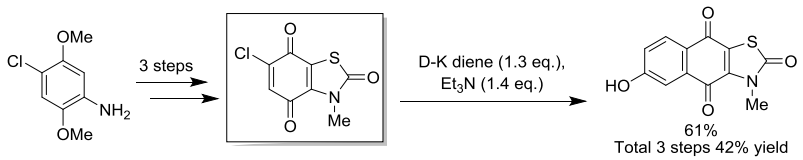


Chlorocarbonylsulfenyl chlorides [ClC(=O)SCl: abbreviated CCSC] is a unique, commercially available bifunctional electrophilic reagent, for the construction of 5 for *S,N*-containing heterocyclic compounds ($Cl_3CSCl + H_2O \rightarrow ClC(=O)SCl$; >100 g preparation available).[1,2] In particular, 2(3*H*)-Benzothiazol-2-ones are these representative benzologue heterocycles that are incorporated in various pharmaceuticals and agrochemicals. Among them, *N*(3)- and 4-disubstituted 2(3*H*)-benzothiazol-2-ones are noteworthy due to their synthetic difficulty, compared with the other *N*(3)- and 5- or 6-disubstituted 2(3*H*)-benzothiazol-2-ones; construction of the stereocongested structure with three contiguous substituents in requires a specific synthetic approach.

Chlobenthiazone[3] (a fungicide against rice blast disease), Benazolin-ethyl[4] (a selective herbicide), and the 4-bromo analogue were prepared by the reported straightforward method utilizing cyclo-condensation of the corresponding *N*-alkylanilines with CCSC.[5] Here, we present derivatizations of these two agrochemicals utilizing Suzuki-Miyaura cross-couplings (9 examples; 44-98% yield), Buchwald-Hartwig cross-couplings (3 examples; 50-89% yield),[6] and borylation (51% yield).[7] In addition, a concise synthesis of the key chloro-type quinone segment in natural mevashuntin[8,9] with a unique 2(3*H*)-benzothiazol-2-one skeleton was successfully performed using Danishefsky-Kitahara diene (three short steps, 61% overall yield).





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2P- 15

The Catalytic Synthesis of Cyclic Amines from Lactams using Ru-MACHO Family

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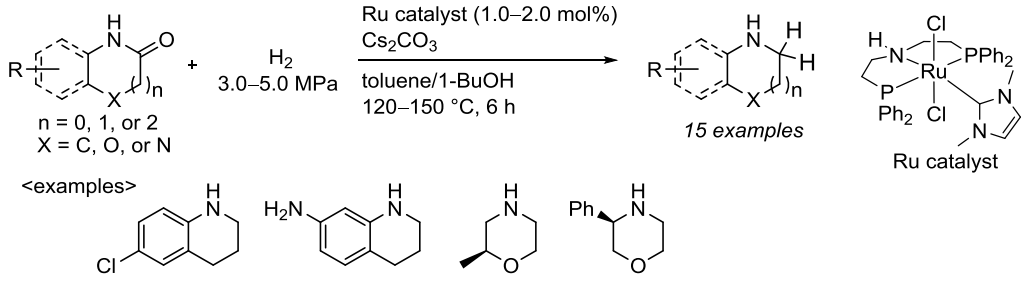
Reduction of amides to amines without stoichiometric hydride reagents, such as $LiAlH_4$, boranes, and silanes, has attracted great attention from a viewpoint of environmental and safety concern. Catalytic deoxygenative hydrogenation of amides with hydrogen gas is an ideal approach to overcome these issues; however, attempts of reduction of amides often afforded divided amines and alcohols instead of the desired deoxygenated products. Recently, the metal-triphos systems were reported to selectively hydrogenate amides to the deoxygenated amines, albeit with necessity of addition of Brϕnsted or Lewis acid. Hence catalytic deoxygenative hydrogenation of amides without acidic additives is desired.

Herein, we report our catalysts, Ru-MACHO family,[1] transform lactams to the corresponding cyclic amines with hydrogen gas. This process consists of (1) the ring opening hydrogenolysis of lactams to aminoalcohols, (2) dehydrogenative ring closing coupling of the transient aminoalcohols to generate imines, and (3) hydrogenation of imines to give the desired cyclic amines.

This method enabled simple and safe operation, and wide range of functional group tolerance under non-acidic conditions. Various lactams were reduced with hydrogen gas (3.0–5.0 MPa) at a temperature range of 120–150 °C with 1.0–2.0 mol% of catalysts in the presence of Cs_2CO_3. Furthermore, the stereochemical integrity was maintained under this transformation. For example, optically pure morpholines which have been demanded as chiral building blocks for pharmaceutical and biological agents were obtained from easily available lactams without losing their optical purity.

Detailed will be discussed in this symposium.



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2P- 16

Catalytic asymmetric Mukaiyama aldol addition using 1,3-bis(siloxy)diene promoted by a Ti(OiPr)$_4$ / (*S*)-BINOL catalyst, directed for process chemistry

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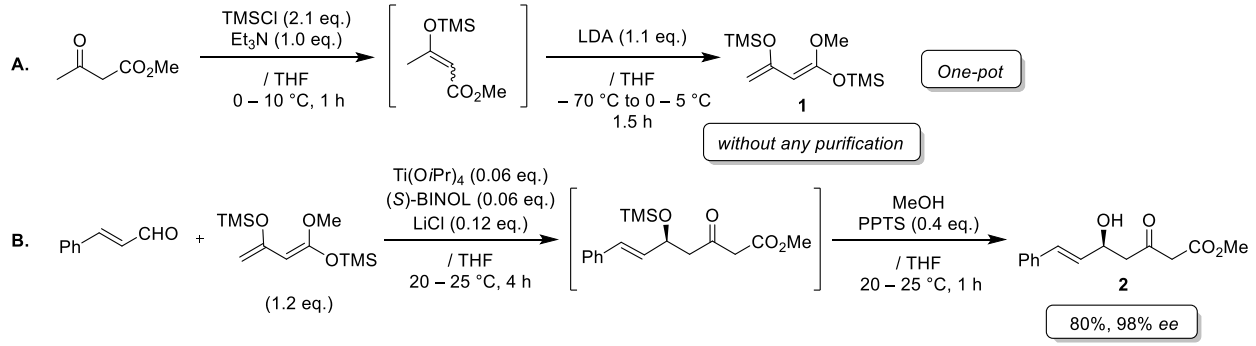
Catalytic asymmetric Mukaiyama aldol additions are well-recognized superb synthetic tools for constructing acyclic chiral β-hydroxycarbonyl compounds due to their reliable utility and efficiency.[1] 1,3-Bis(TMSO)-dienes **1** (so-called, Chan's diene) serve not only as dianion equivalents of methyl acetoacetates, but also as various building blocks, as mentioned by Chan's report.[2] Chiral 5-hydroxy-3-oxocarboxylic ester **2** was synthesized utilizing the Mukaiyama-type catalytic asymmetric addition of **1**, which was obtained by one-pot procedure.

Our method comprises two steps: (i) A novel one-pot dienol bistrimethylsylilation of methyl acetoacetate using Et_3N / LDA / TMSCl as the reagent (step A) and (ii) A mild catalytic asymmetric Mukaiyama aldol addition using Ti(OiPr)$_4$ / (*S*)-BINOL / LiCl (Soriente–Scettri–Yang catalyst), based primarily on the reported protocol (Step B).[3,4] Both procedures of the two-step reaction are accessible and user-friendly to produce the desired aldol adducts with excellent enantiomeric purity[5,6] The original and conventional method necessitated the isolation of monosilylated intermediate, followed by a second silylation step to afford 1,3-bis(TMSO)diene.[3,4] Notably, the present procedure has clear advantages that sequential silylations were conducted in a "one-pot procedure" (pot-economical) using bench-top handling reagents to produce **1** without any purification[7]. This strategy will contribute to the construction of useful chiral synthetic blocks for poly-oxy natural products, statin drugs, etc.



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2P- 17

Catalytic oxidation reaction for synthesis of triarylmethane blue dyes

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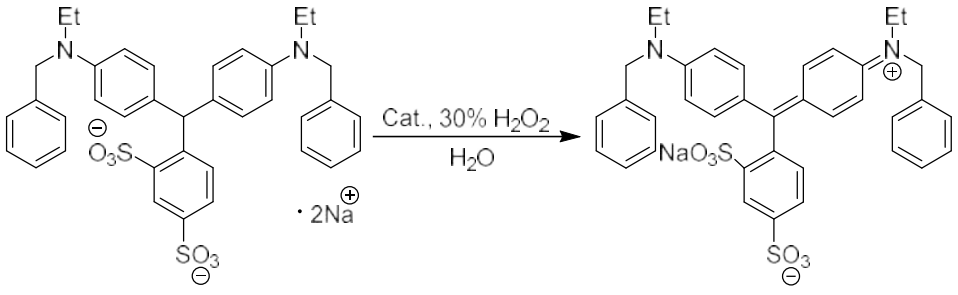
Oxidation reaction is one of the most important processes in organic synthesis and industrial chemistry. Traditionally, stoichiometric amounts of heavy metal reagents have been used for the oxidation. From the viewpoint of green chemistry, development of eco-friendly oxidation processes has attracted much attention. In our laboratory, we have developed a novel catalytic system for oxidation of various amines[1–2], and reported synthesis of triarylmethanes from benzylamines via oxidative C–N bond cleavage and subsequent double C–C bond formations[3]. Furthermore, these obtained triarylmethanes were converted into a series of triarylmethane blue dyes by oxidation. In this study, we investigated a new catalytic oxidation reaction for synthesis of triarylmethane blue dyes (Acid Blue 7) without using harmful substances and found that the oxidation reaction was carried out using heteropolyacid and copper as catalysts[4]. In this reaction, hydrogen peroxide, which produces only water, acted as an oxidizing agent efficiently.



triarylmethanes (Leuco acid) Acid Blue 7

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2P- 18

Synthesis of α-*exo*-Methylene Ketones from α,α-Disubstituted Allyl Alcohols by Electrochemical Oxidative Migration

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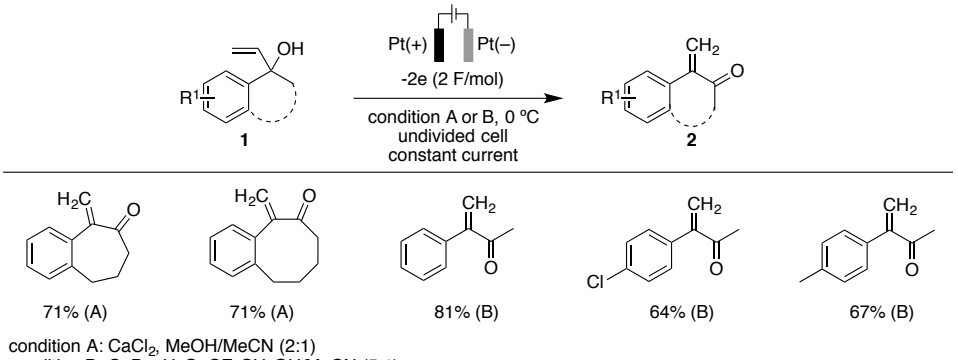
α-*exo*-Methylene ketone groups have been utilized for versatile building blocks in organic synthesis and also found in many natural products and biologically active compounds. Oxidative migration of α,α-disubstituted allyl alcohols would be one of the promising method for the preparation of α-*exo*-methylene compounds, since starting alcohols are easily prepared by reacting vinyl Grignard reagent with the corresponding ketones. Reported methods based on this approach, however, required the use of stoichiometric amount of organic oxidants or heavy metal oxidants.[1] Therefore, more environmental-friendly approaches for the synthesis of α-*exo*-methylene compounds are highly desired.

We herein report the facile synthesis of α-*exo*-methylene ketone **2** from allyl alcohols **1** under electrochemical conditions.[2] The reaction was carried out in an undivided cell with a Pt anode and a Pt cathode under constant current condition in the presence of $CaCl_2$ or $CaBr_2$•H_2O as a halogen mediator. Electrochemically generated halogen cation effectively promoted the oxidative migration reaction of **1**, and subsequent dehydrohalogenation provided the desired product **2** in good to excellent yields. Under the optimized conditions, cyclic and acyclic alcohols were successfully transformed into the corresponding migration products. Moreover, α-*exo*-methylene ketones bearing an aliphatic group on the α-position of the carbonyl group were obtained by electrochemical oxidative migration followed by DBU-mediated dehydrohalogenation in a one-pot manner.



condition A: $CaCl_2$, MeOH/MeCN (2:1)
condition B: $CaBr_2$•H_2O, CF_3CH_2OH/MeCN (5:1)

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2P- 19

Metal-free Oxidative Synthesis of Imine Derivatives Catalyzed by Salicylic Acid

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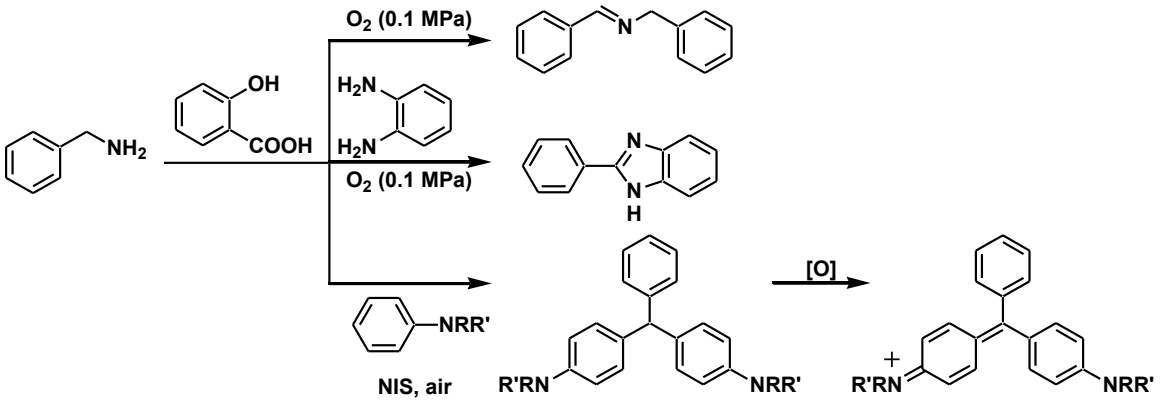
Catalytic oxidation reactions of organic compounds with the aid of molecular oxygen as the primary oxidant have attracted much attention. Recently, we have developed the efficient oxidation process catalyzed by vanadium complexes with pressurized molecular oxygen, and applying our method to atmospheric oxidation, direct conversion of benzylamines to imines proceeded efficiently.[1]

However, in modern chemical industry, catalytic oxidation without any metal catalysts is strongly desired, thus we also try to investigate the metal-free oxidative synthesis of imines. In the former catalytic oxidation, 3-hydroxypicolinic acid (H_2hpic) or its analogues were used as ligands for oxovanadium complexes, so we decided to use phenols or benzoic acids as organic catalysts. When salicylic acid was used as oxidation reaction, it functioned as an efficient organocatalyst for the oxidation of benzylamines to imines under an oxygen atmosphere. This amine oxidation could also be applied to the synthesis of nitrogen-containing heterocycles such as benzimidazole derivatives.[2]

Furthermore, in the presence of salicylic acid derivative as a co-oxidant and *N*-iodosuccinimide (NIS) as an oxidant, benzylamines can be condensed with *N*,*N*-dimethylanilines to yield 4,4'-diaminotriarylmethanes (DTMs) under open-air condition. This method provides the first reported synthesis of DTMs from benzylamines via oxidative C–N bond cleavage and subsequent double C–C bond formations. The obtained DTMs, were easily converted into a series of blue dyes with chloranil.[3]



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2P- 20

Autocatalytic Decomposition of Dimethyl Sulfoxide (DMSO)

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Dimethyl Sulfoxide (DMSO) is a member of the aprotic dipole solvents and DMSO has superior dissolving ability, water miscibility and relatively high boiling point as do all group members. However, unlike others, DMSO has a low level of biological toxicity; this may be the reason why it is preferably used as a solvent for hard to dissolve chemicals such as pharmaceutical products, polymeric materials, resins, several inorganic salts and so on.

Despite of wide use in industries, thermal runaway phenomena associated with DMSO decomposition has been reported [1,2]. Many chemicals such as organic and inorganic acids, acid halides, acid anhydrides, strong bases, organic halides, oxidizing agents and so on are advised not to mix with DMSO. On the contrary, DMSO itself is moderately stable at temperatures below 140°C [3]. Based on the incident report, typical runaway reactions were prone to take place in recycling process such as evaporation and distillation. Some literatures indicated DMSO decomposition was autocatalytic, but details of autocatalyst and autocatalytic reactions were not described so far [4].

The primary objective of our project is to understand the DMSO decomposition comprehensively to construct safe plant and operation protocol. In our previous study, several acids were found to be generated and accumulated during the thermal treatment of DMSO in nitrogen atmosphere [5,6]. Isothermal heating of DMSO resulted in a runaway reaction at near boiling temperature without any foreign promoters [6]. It was noted addition of small portion of acids at the beginning of thermal treatment shortened the induction period [7]. By combining a series of investigations, it was proved acids generated *in situ* were the autocatalysts causing runaway reaction.

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2P- 21

Development of Vanadium-catalyzed Organic Reactions in Water

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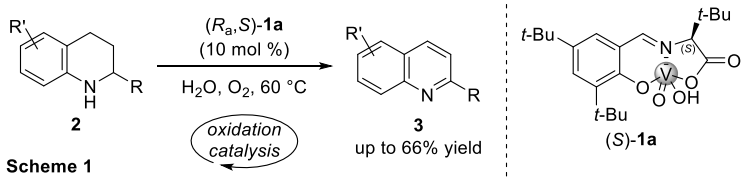
Water is a much safer reaction medium compared to toxic and/or flammable organic solvents. In 2015, we achieved an enantioselective oxidative coupling of 2-naphthols in water using a water-resistant chiral oxovanadium catalyst.[1] Herein, we report our recent research progress on the development of environmentally benign vanadium-catalyzed organic reactions in aqueous medium; dehydrogenation of *N*-heterocycles and *oxa*-Piancatelli reaction. In these reactions, the vanadium complex works as an oxidation or acid catalyst.[2]

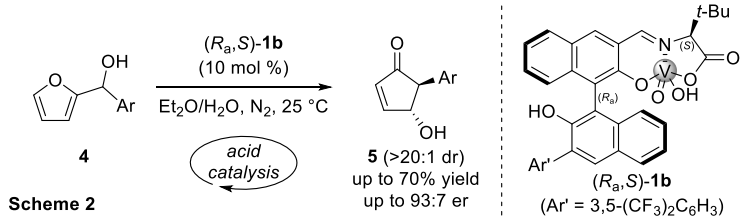
1) Dehydrogenation of *N*-heterocycles[3]



Scheme 1

Nitrogen-containing aromatic compounds play an important role in natural products and medicines. Treatment of tetrahydroquinolines **2** with the vanadium catalyst (*S*)-**1a** in water under O_2 at 60 °C allowed the dehydrogenation to afford quinoline derivatives **3** in good yields. The present method can also be used for the dehydrogenation of tetrahydroquinoxalines and 9,10-dihydroacridine.

2) Asymmetric *oxa*-Piancatelli reaction



Scheme 2

4-Hydroxy-2-cyclopentenones **5** have received a great deal of interest by organic chemists since it works as a useful building block in various natural product syntheses. The vanadium catalyst (R_a,*S*)-**1b** efficiently promoted the reaction of furfuryl alcohols **4** to provide the desired product **5** in good yields with enantiomeric ratio of up to 93:7 and diastereomeric ratio exceeding 20:1 (**Scheme 2**).

In this presentation, Pictet–Spengler reaction/dehydrogenative aromatization sequence using the vanadium complex as an oxidation and acid catalyst will also be discussed.

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2P- 22

AI-Assisted Optimization for Synthesis of Spirooxindole Analogues via Enantioselctive Domino Reaction in Flow System

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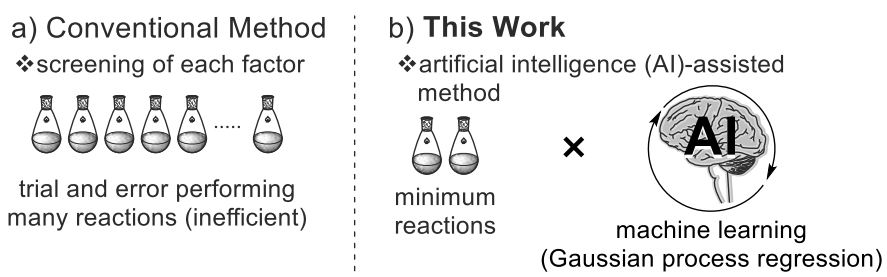
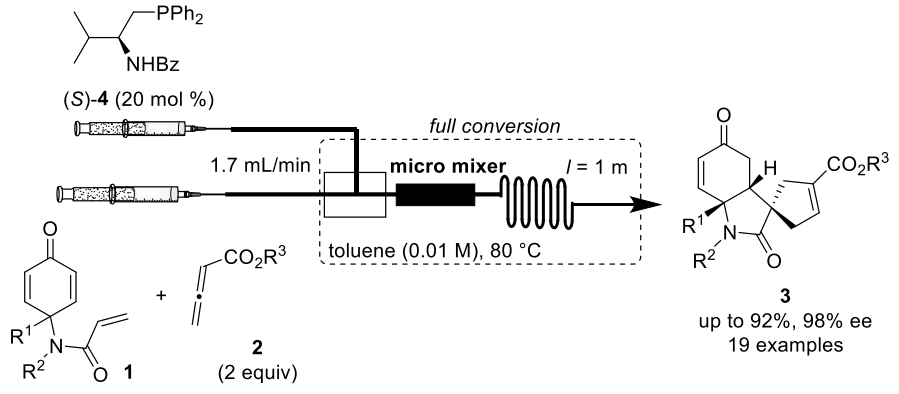


In the development of new synthetic reactions, the optimization of reaction conditions is a crucial and unavoidable process. However, the conventional optimization methods are time-consuming and high cost. Therefore, an efficient and rapid reaction screening strategy has been of significant interest to the process community. Herein, we report a highly atom-economical enantioselective organocatalyzed Rauhut-Currier[1]/[3+2] annulation sequence of dienone **1** and allenoate **2** by using flow system and Artificial Intelligence (AI)-assisted reaction optimization.

The optimal conditions in the flow system were predicted through minimum reaction screening (approximately 10 experimental data) of multiple parameters (temperature, substrate amount, and flow rate) with machine learning Gaussian process regression (GPR).[2] Under the AI-suggested conditions, organocatalyst (*S*)-**4** promoted this enantioselective sequential reaction to afford fully functionalized chiral spirooxindole analogues in up to 92% yield with 98% ee as a single diastereomer within one minute.[3]



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2P- 23

Development of Composite Materials Comprised of Porphyrin Dyes and Nanocarbons : Effect of Preparation Methods

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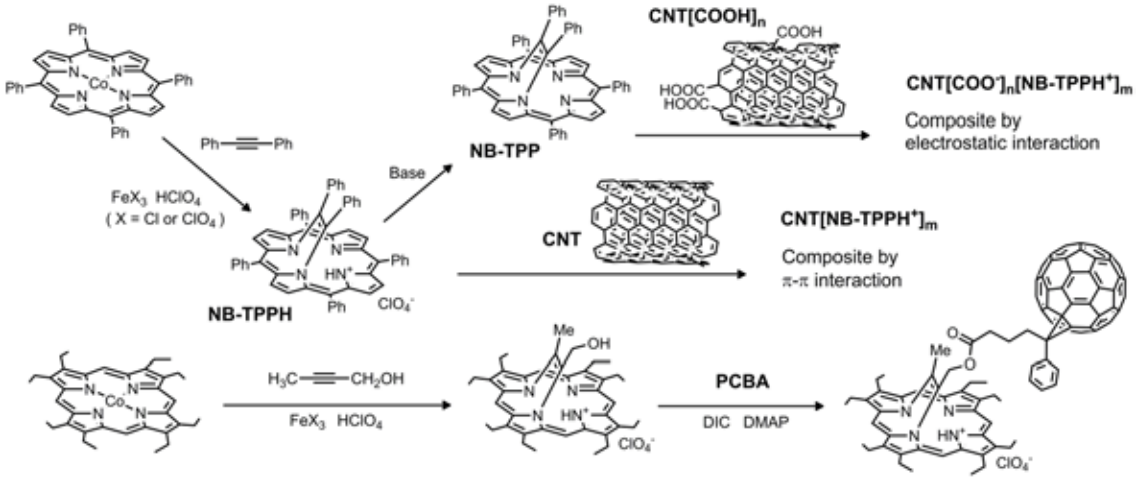
Functionalization of nanocarbon materials with dyes is an important way to develop new materials in several fields, such as organic solar cells, optoelectronic materials, sensors and so on.[1,2] Unique optical properties of dyes with high light-absorption efficiency are expected to be combined with electrical properties of nanocarbons with delocalized π-electron system. Herein, composite materials of porphyrin derivatives and carbon nanotubes (CNTs) or a fullerene derivative are developed. Three preparing methods by means of π-π interaction, electrostatic interaction and covalent bond are studied.

Since used monoprotonated porphyrin derivatives exist in cationic form stably due to *N*,*N'*-etheno bridge substituent,[3] NB-TPPH was treated with base. Then a mixture of formed free base porphyrin (NB-TPP) and carboxylated CNT was sonicated in THF leading to the generation of composite based on electrostatic interaction accompanied by H^+ transfer. In the case of functionalization via π-π interaction, pristine CNT was added to a THF solution of NB-TPPH, and the suspension was sonicated at room temperature followed by filtration and washing to obtain the composite. The functionalization based on covalent bonding was performed by ester condensation of hydroxyl group in the bridge moiety of the porphyrin derivative and carboxylated CNT. The ester condensation with phenyl-C_{61}-butyric acid (PCBA) has also afforded dyads of the porphyrin derivatives and a fullerene. The stability and properties of these composite materials will be reported.



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2P- 24

Benzylisoquinoline alkaloids production by bacteria for drug discovery

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Benzylisoquinoline alkaloids (BIAs) include up to 2500 species which have various biological activities. Morphine is the most famous BIA and have been used as an analgesic since ancient era. In the present day, morphine like compounds, opiates are widely used against strong and persistent pains. Berberine is known as an antidiarrheal drug and contained in oriental herbs such as *Phellodendron amurense* and *Coptis japonica*. Furthermore, because berberine can regulate glucose metabolisms of human, berberine is sometimes subscribed for diabetes patients. Glaucine is classified as an aporphine alkaloid, a subfamily of BIA, and have been found to have bronchodilator, anti-inflammatory and anticancer activities. Besides these effects, glaucine also has anti-cellulite activity, therefore it is formulated in cosmetics and beauty cream. Other than these famous BIAs, rare and unknown BIAs also would be useful for human life.

BIAs can be obtained from plant extract, but cultivation of plants are not costly-feasible. Although many methods of BIA production by chemical synthesis have been developed, that has not been put to practical use yet, due to its chirality problems.

As an alternative way to produce BIAs, microbial production has been studied for a decade. For supplying costly-feasible BIAs, we have studied to construct the BIA production system using bacteria, *Escherichia coli*. We succeeded to produce three major groups of BIA, protoberberine, morphinan and aporphine alkaloids from a simple sugar glucose.

In this presentation, we would like to discuss how to construct the BIA producing *E. coli* and prospects for practical production of BIAs.

2P- 25

Synthesis of tofogliflozin as an SGLT2 inhibitor *via* intramolecular cycloaddition

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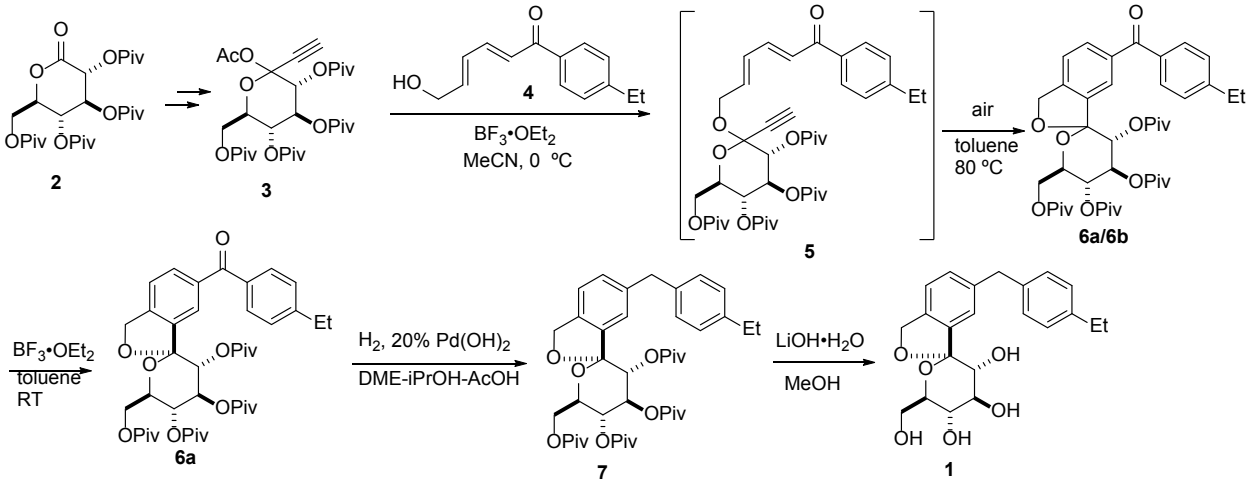
Tofogliflozin (**1**) is a spirocyclic *C*-arylgycoside which acts as a sodium glucose cotransporter 2 (SGLT2) inhibitor for the treatment of diabetes. Several synthetic routes to **1** have recently been reported in the literature. In these reports, halogen-metal exchange reaction has been used to form a *C*-Glycosidic bond between an aromatic ring and a sugar moiety. We sought an alternative route and focused our attention on [4+2] cycloaddition reaction to synthesize **1**. While intramolecular [4+2] reactions between a diene and yne moiety have been demonstrated, little is known about cyclization by use of dienone compounds to form a dihydroisobenzofuran skelton. Herein we describe the synthesis of **1** *via* [4+2] cyclization of a dienone-yne compound.

Lactone **2** was subjected to 1,2-addition by lithium trimethylsilylacetylide in the presence of tetramethylethylenediamine (TMEDA), and the resulting alkoxide was trapped by acetic anhydride. Trimethylsilyl group was removed to give **3**. The glycosylation of **3** with dienylmethyl alcohol **4** was carried out by use of boron trifluoride etherate ($BF_3 \cdot OEt_2$) to afford diene-yne **5** as an anomeric mixture. [4+2] Cyclization of **5** was accomplished in toluene at 80 °C under aerobic conditions, and air oxidation afforded aromatic compounds **6a** and **6b** as an anomeric mixture. Conversion of **6b** to **6a** proceeded smoothly by treatment with $BF_3 \cdot OEt_2$ in toluene at room temperature. The telescoping process of the glycosylation and successive [4+2] cyclization-isomerization was successfully demonstrated: **6a** was obtained in 52% isolated yield (after recrystallization) from **3**. The hydrogenolysis of **6a** by use of $Pd(OH)_2$ followed by hydrolysis afforded the desired compound **1**.



2P- 26

Strong Base-Catalyzed Hydroamination of Aminoalkenes

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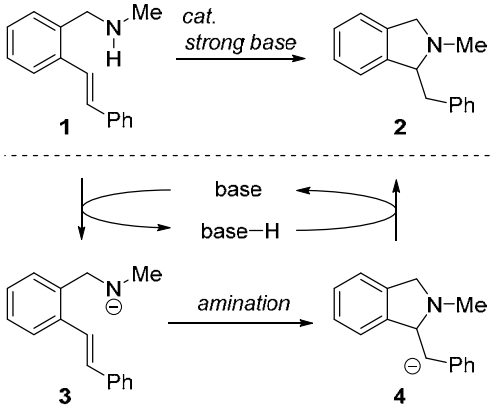
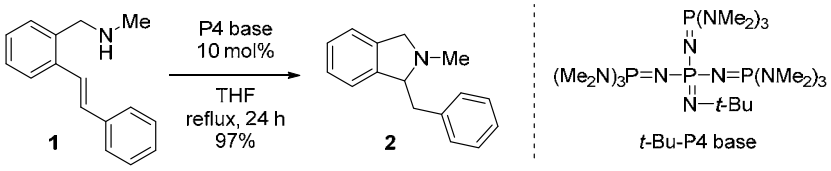
The addition reaction of nitrogen nucleophiles with a carbon–carbon multiple bond (i.e., hydroamination) is a very powerful carbon–nitrogen bond forming reaction. An intramolecular version of the amination reaction is an effective process for the synthesis of nitrogen-containing heterocycles. The intramolecular hydroaminatin reaction can be catalyzed by a strong base such as lithium amide; thus, deprotonation of an aminoalkene **1** by a base yields amide anion **3** and base–H, and the following addition reaction with intramolecular olefin gives carbanion **4**. Finally, protonation of **4** by base–H affords cyclized product **2** and a base, which can catalyze the reaction.[1] This cyclization process was effective for the synthesis of isoquinoline alkaloids.[2]



We report herein that phosphazene P4 base, strong organic base of pK_{BH+} 42.1,[3] catalyzed the hydroamination of aminoalkene **1**. This cyclizatoin was highly 5-*exo* selective to afford **2** as a sole product.



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2P- 27

Rapid and Practical Synthesis of Fluoren-9-ones Using a Carbon Monoxide Surrogate

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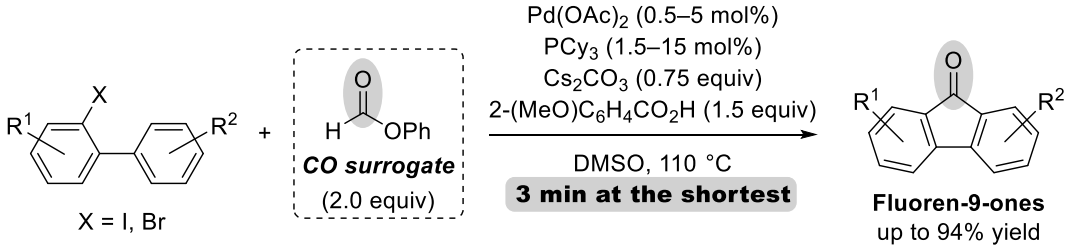
Carbon monoxide (CO) surrogates have been paid much attention because they could be utilized in organic reactions instead of using toxic and difficult-to-handle CO gas, which provided highly safe and practical synthetic methods.[1] We have developed formic acid derivatives as novel CO surrogates and various carbonylative reactions using the surrogates.[2]

We tried to apply phenyl formate as our unique CO surrogate to the synthesis of fluoren-9-ones, an important class of compounds widely used in material sciences and biological research, via a Pd-catalyzed carbonylation of 2-halogenated biphenyls.[3] After the optimization of the reaction conditions, the desired fluonen-9-ones could be obtained from both 2-iodo- and 2-bromobiphenyls in high yields. The appropriate choice of the base was revealed to be important for smooth promotion of the reaction. Especially, the combined use of cesium carbonate and *o*-anisic acid resulted in a remarkable rate enhancement, where the reaction completed within 3 min in some cases. This rapid reaction was successfully conducted in a normal round-bottom flask with an empty balloon without an external CO gas, and the reaction could be scaled up to gram-scale. Mechanistic studies indicated that the reaction proceeded via a concerted metalation-deprotonation step, and that the turnover-limiting step of the reaction was the C–H bond-cleaving step or the oxidative addition step, depending on the substrate used.

Since a variety of 2-halogenated biphenyls can be prepared by using standard coupling chemistry, this reaction has been established as an easy access to various fluoren-9-ones, with potential to be widely used due to high safety and practicality of the reaction.



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2P- 28

Activation of Nucleophilic Aromatic Substitution Reaction by Using Silyl Amide Reagent

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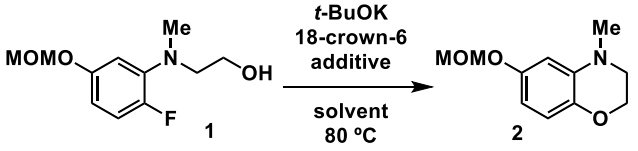
Multiple electron-donating groups substituted aromatic compounds, such as polyphenols or benzoxazinoids, exhibit a variety of bioactive properties. However, the synthesis of these compounds poses problems because of their high sensitivity to acid, base, light and oxidants [1]. For this reason, development of synthetic methods for electron rich aromatic compounds have been a fundamental challenge in organic chemistry.

Nucleophilic aromatic substitution (S_NAr) is one of the most useful strategies for the preparation of polysubstituted aromatic compounds. S_NAr reaction of fluorobenzene derivatives has been frequently utilized. Especially, electron-withdrawing groups substituted fluorobenzenes are valuable substrates for the syntheses of complex aromatic molecules. On the other hand, S_NAr reaction of multiple electron-donating groups substituted fluorobenzenes have scarcely been developed. The difficulty might come from low reactivity of reactants due to poor electrophilicity [2]. Recently, we have found that trimethylsilyldiethylamine ($TMSNEt_2$) shows the improvement on reactivity of reactants with electron-donating substituents. Herein, we report the study on the effect of $TMSNEt_2$ in the intramolecular S_NAr reaction.

We chose 2-[2-fluoro-5-(methoxymethoxy)phenyl](methyl)aminoethanol (**1**) as a standard substrate for the intramolecular S_NAr reaction and examined the conditions. The reaction of **1** with potassium *tert*-butoxide and 18-crown-6 in 1,4-dioxane at 80 ºC gave 1,4-benzoxazine **2** in 78% yield (**Table 1, entry 1**). With the addition of $TMSNEt_2$, the intramolecular S_NAr reaction of **1** afforded the 92% yield of **2** (**entry 2**). However, the reaction of **1** using $TMSNEt_2$ alone in 1,4-dioxane at 80 ºC didn't proceed at all. By changing the solvent to DMF, the reaction was almost completed within 6 hours and **2** was obtained in 86% yield (**entry 5**). Under this condition, side reaction has scarcely occurred. Our results have revealed that $TMSNEt_2$ accelerates the intramolecular S_NAr reaction (**entries 4 and 5**).

Further investigations of reaction mechanism and practical application are currently in progress.



entry	additive	solvent	time	yield
1	—	dioxane	36 h	78%
2	$TMSNEt_2$ (4 eq.)	dioxane	36 h	92%
3	$TMSNEt_2$ (4 eq.)	dioxane	6 h	26%
4	—	DMF	6 h	34%
5	$TMSNEt_2$ (4 eq.)	DMF	6 h	86%

Table 1 Investigation of reaction condition

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2P- 29

Chemoselective Transformations of Aromatic Methoxymethyl Ethers Using Trialkylsilyl Triflate and 2,2'-Bipyridyl

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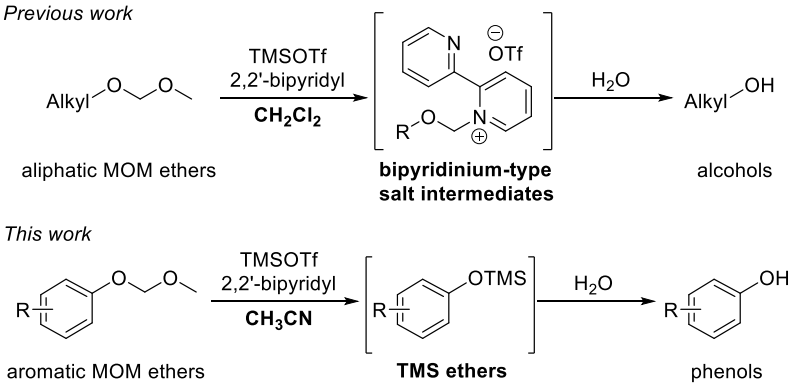
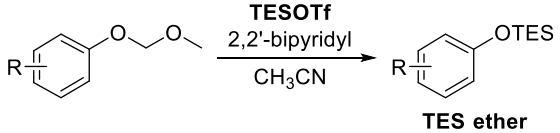
Methoxymethyl (MOM) group is widely used hydroxyl protecting group due to the resistance in strongly basic to weakly acidic conditions. Therefore, the deprotection of the MOM group generally needs strongly acidic conditions. Then, the substrates with acid-labile functional groups usually need other protective groups, whose deprotection doesn't need such acidic conditions. However, a development of new mild deprotection method of MOM ether, which doesn't affect the substrates having labile functional groups, can broaden the range of the use MOM group.

We have recently reported that aliphatic MOM ethers form bipyridinium salt intermediates upon treatment with trimethylsilyl triflate (TMSOTf) and 2,2'-bipyridyl in CH_2Cl_2 (Scheme 1, Previous work).[1] The intermediates susceptible to nucleophilic attack by H_2O which affords the corresponding deprotected products via hemiacetal intermediates. However, aromatic MOM ethers have reduced reactivity under the same conditions compared with that of aliphatic MOM ethers.

We then explored the reaction of aromatic MOM ethers with TMSOTf and 2,2'-bipyridyl in detail, and found the remarkable effect of CH_3CN as a reaction solvent and the reaction pathway of deprotection of aromatic MOM ethers is completely different from that of aliphatic ones (Scheme 1, This work). Also, this difference in reactivity also allowed us to develop an unprecedented conversion of an aromatic MOM ether directly to a TES ether (Scheme 2). [2]



Scheme 1. The reaction of MOM ether with TMSOTf and 2,2'-bioyridyl



Scheme 2. The reaction of aromatic MOM ethers with TESOTf and 2,2'-bipyridyl

References

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2P- 30

Acceptor-controlled Transfer Dehydration of Amides to Nitriles

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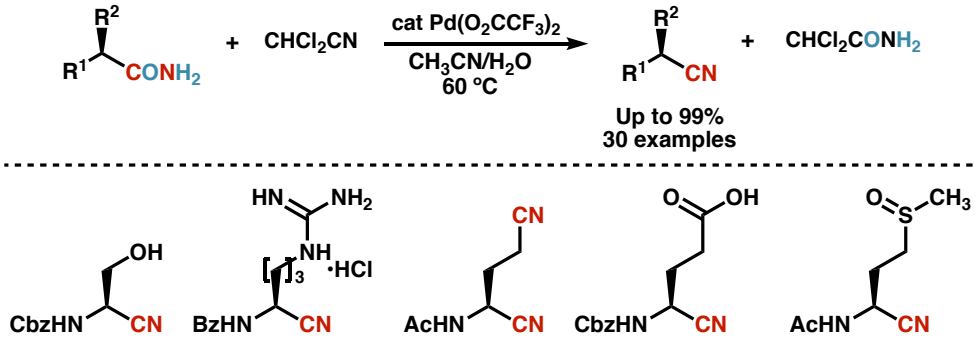
The cyano group is a privileged functionality broadly found in natural products and pharmaceuticals. The introduction of cyano groups into highly functionalized (bio)molecules is of great importance in synthetic chemistry. One of the most popular approaches has been the dehydration of primary amides ($RCONH_2$) to nitriles (RCN) by using dehydrating agents under harsh and anhydrous conditions. However, a general methodology for the dehydration of amides that is compatible with other nucleophilic or protic functionalities (*e.g.* carboxylic acids, water) has remained to be developed.

In this presentation, we report an efficient palladium(II)-catalyzed transfer dehydration of primary carboxamides to nitriles using dichloroacetonitrile as a water acceptor. Building on our recent work on the transfer hydration of cyanohydrins,[1] we screened electron-deficient nitriles as water acceptors and found that dichloroacetonitrile serves as an excellent water acceptor for the transfer dehydration of various amides under aqueous conditions.

This method is effective for the dehydration of a series of alpha-aminoamides derived from naturally abundant amino acids to corresponding nitriles without the loss of the chirality at the alpha-carbons and functional groups under mild, aqueous conditions. The excellent chemoselectivity of this reaction originates from high thermodynamic and kinetic reactivity of dichloroacetonitrile for the desired Pd-catalyzed transfer dehydration of amides as well as from its high stability towards undesired reactions with protic functional groups. Dipeptides and a cyclic peptide having primary amides in the side chain could be also dehydrated. The transfer dehydration protocol can be carried out on a gram-scale.[2]



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2P- 31

Hydroperoxide-Mediated Chemoselective, Decarboxylative Acylation of Amine.

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Development of efficient amidation reaction is still important area in organic synthesis due to the growing interest in peptide synthesis. In the course of investigations to find a different approach from a conventional dehydrative condensation reaction, we focused on decarboxylative condensation of α-ketoacids. α-Ketoacids are found in biochemical intermediates such as pyruvic acid and α-ketoglutaric acid which could be regarded as aldehyde equivalents by decarboxylation. This attractive functional group is also useful in synthetic organic chemistry considering α-ketoacids as acylanion equivalents by decarboxylative conversion. In recent years, Bode and coworkers realized a decarboxylative amidation using α-ketoacids and hydroxylamines as known as KAHA ligation which proceeds without any condensation reagents[1]. Moreover, Lan and Lei also reported a visible light mediated decarboxylative amidation with aniline[2]. Despite these brilliant preceding studies representing how useful α-ketoacids are as an acylating reagent, there is no report on high-yielding decarboxylative acylation of "normal" aliphatic amines. We envisioned that a highly electrophilic iminoacid derived from α-ketoacid and amine could smoothly react with nucleophilic oxidants such as hydroperoxide to provide corresponding amide. (Figure 1).

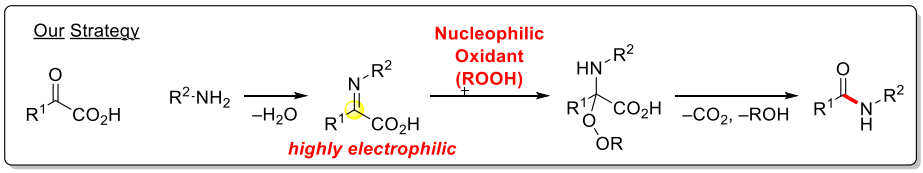

Figure 1. Strategy for Decarboxylative Amidation Mediated by Hydroperoxide.

On the basis of this strategy, we found that TBHP mediates decarboxylative acylation of both aliphatic and aromatic amine using α-ketoacids under mild condition. This reaction presents a unique chemoselectivity and a wide range of amides including peptide could be prepared in excellent yield.

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2P- 32

Polymorphic Solubility Ratio of Pharmaceutical Drugs in Various Solvents

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Most pharmaceutical drugs have several crystal polymorphs, i.e., solid phases with different crystal structures.[1-4] The polymorphs have different properties with each other, e.g., in the solubility, stability, and particle shape. The polymorphic difference affects not only the bioavailability but also the separation efficiency in the industrial processes. It is thus required in pharmaceutical industry to selectively crystalize a target polymorph with desirable property. Solubility data of the polymorphs are essential information for the selective crystallization. Here we measured the solubility of famotidine, a histamine H2 receptor antagonist having the two polymorphs, a stable form A and a metastable form B,[5] in various solvents to study how the solubility ratio between the polymorphs depends on the solvent species.

For the solubility measurement, a mixture of solvent and excess amount of famotidine was shaken for 2 h in a block bath shaker thermostated at 298.15 K and then was filtered through a hydrophilic PTFE membrane filter (0.2 μm pore) to obtain saturated solution. The saturated solution was analyzed with HPLC to determine the concentration of famotidine. The undissolved famotidine was dried under reduced pressure at room temperature to identify the crystal structure with powder X-ray diffraction. No solvent-mediated transformation between the polymorphs was observed in all the solvents tested.

For both polymorphs, the solubility increased in the order of ethyl acetate < water < acetonitrile < ethanol < acetone < methanol, as shown in the graphical abstract. In all the solvents, the solubility of form B was larger than that of form A. The solubility ratio B/A varied with the solvent from 1.09 to 1.32 in the order of ethyl acetate < ethanol < acetone < acetonitrile < methanol < water. The experimental solubility ratio was smaller than that estimated (1.48) thermodynamically from the melting temperature and the molar enthalpy of fusion for the polymorphs. In the presentation, we will discuss also the polymorphic solubility ratios of other pharmaceutical drugs, such as sulfathiazole and 6-methylprednisolone.

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2P- 33

Development of Palladium Phosphine Complexes for the Practical Cross-Coupling Reactions

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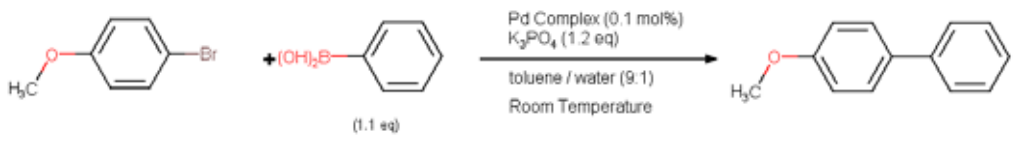
Palladium-catalyzed cross-coupling reactions are widely used for construction of carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds. A variety of ancillary ligands including phosphine ligands have been developed for these reactions. Tricyclohexylphosphine (PCy_3) is one of the good ancillary ligand due to its high electron-donation ability. However, air-sensitivity of PCy_3 prevents us from application of PCy_3 for the practical cross-coupling reactions in industrial processes. Use of air-stable palladium complexes containing PCy_3 ligand is required for reproducibility of catalysis and ease of handling. In this research, we prepared a series of palladium complexes containing one or two PCy_3 ligands, and evaluated their catalytic activity for the cross-coupling reactions were examined.

A series of palladium complexes ($[PdCl_2(PCy_3)_2]$, $[Pd(OAc)_2(PCy_3)_2]$, and $[PdCl(C_3H_5)(PCy_3)]$, respectively) were prepared by the reactions of PCy_3 ligand with palladium sources ($PdCl_2$, $Pd_3(OAc)_6$, and $[PdCl(C_3H_5)]_2$, respectively). These complexes have high stability, and can be stored under air at room temperature. The catalytic activity of these complexes for the Suzuki-Miyaura coupling reactions of 4-bromoanisole and phenylboronic acid at room temperature were examined. Although $[PdCl_2(PCy_3)_2]$ and $[PdCl(C_3H_5)(PCy_3)]$ showed low catalytic activity, the reaction using $[Pd(OAc)_2(PCy_3)_2]$ as a catalyst afforded the coupling product in quantitative yield. $[Pd(OAc)_2(PCy_3)_2]$ was also applied to the C-N coupling reaction of chlorobenzene and diphenylamine, affording the coupling product in 60% yield. As consequence, $[Pd(OAc)_2(PCy_3)_2]$ has been proven to be highly stable and good catalyst for both C-C and C-N coupling reactions.



Entry	Catalyst	Yield (%)
1	$[Pd(OAc)_2(PCy_3)_2]$	97
2	$[PdCl_2(PCy_3)_2]$	0
3	$[PdCl(C_3H_5)(PCy_3)]$	14

2P- 34

Development of a Synthetic Process for K-8986, an H1-receptor Antagonist

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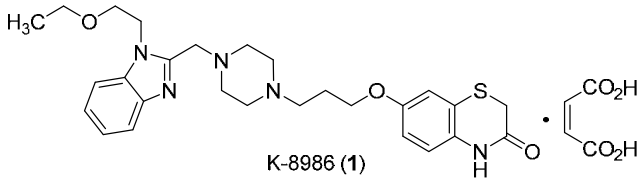
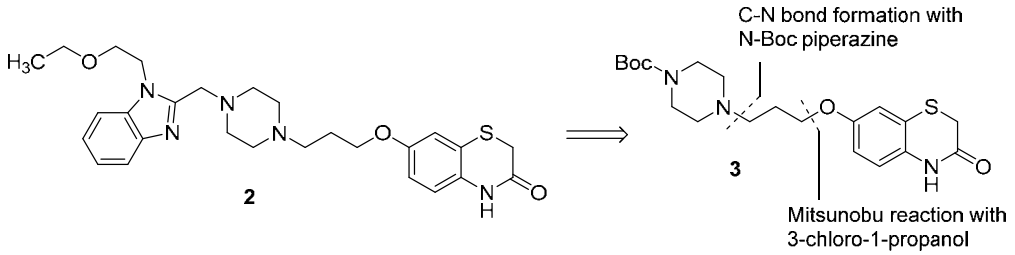
We developed a robust and scalable synthetic process for K-8986 (**1**). To solve the problems in terms of physicochemical properties of **2** (a free base unit of **1**), we have screened the suitable salt forms of the target. The monomaleate salt was the most suitable form for the API. To overcome challenges regarding the unremovable impurity caused by the carryover of piperazine in the medicinal chemistry route, we designed and developed a novel synthetic route.





This route furnished more opportunities to purify the synthetic intermediates after introduction of the piperazine unit. Both impurities and co-products in each step of the revised synthesis could be easily removed via filtration, leveraging the low solubility of benzothiazine derivatives. The newly established process was applied to the synthesis of **1** (the monomaleate salt of **2**) on a practical scale, achieving high purity and reproducibility.

Table. Results of Scale-Up Manufacturing of **1**.

yield		purity (HPLC area%)	melting point	quantitation of maleic acid
1.1 kg	67%	99.6%	149.0°C	18.4%
1.1 kg	69%	99.1%	148.6°C	18.4%
1.6 kg	73%	99.5%	149.8°C	18.3%
1.6 kg	72%	99.4%	149.8°C	18.3%

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2P- 35

Development of *gem*-Diboronic Acids as Dehydrative Peptide Synthesis Catalysts

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A general approach for amide synthesis is based on stoichiometric activation of carboxylic acid using coupling reagents to switch the low reactive carboxyl group to a highly versatile acyl donor. This reagent-driven methodology has thus become a fundamental reaction of organic chemistry, regardless of unavoidable generation of non-recyclable wastes. In sharp contrast, arylboronic acids have been realized as catalysts for dehydrative amidation, featuring the production of water as a theoretically sole side product. A detail investigation of substituent effects of aryl groups provided several criteria for high-performance catalysts.[1] Yet, simple boronic acids have confronted severe limitations on catalytic peptide synthesis in terms of catalyst turnover, protecting groups, and functional groups. The development of finely engineered catalysts is thus indispensable for efficient amidation of α-amino acids.[2] To this end, based on the recent mechanistic studies of boronic acid-catalyzed amidation,[3] we envisaged an efficient activation of carboxyl groups with a robust bidentate "B–C–B" bis-boron Lewis acids, leading us to develop "*gem*-diboronic acid (*gem*-DBA)" as a new class of organoboron catalysts for dehydrative peptide condensation.

After examination of *gem*-DBAs with different substituents on central carbon atom, we eventually revealed that a *gem*-DBA endowed with two phenol moieties, forming a *gem*-diboronic bis-half ester by *in situ* cyclocondensation, efficiently promoted dehydrative amidation of α-amino acids using α-amino esters as nucleophiles in the presence of 5 Å MS in toluene under heating conditions. Remarkably, a wide range of functional groups containing oxygen, nitrogen, and sulfur atoms were tolerated, and the nucleophiles can be employed as commercially available hydrochloride salts. Besides, common *N*-protecting groups for peptide ligation (Boc, Fmoc, etc.) were also applicable to the reaction, furnishing dipeptides in up to 98% yield without significant epimerization. The feasibility of catalytic oligopeptide synthesis was also demonstrated by coupling using dipeptide-derived acid electrophiles and amine nucleophiles. The initial mechanistic studies implied that a cyclized *gem*-diboronic bis-half ester can activate carboxylate rather than carboxylic acid itself, giving an intermediate containing two tetragonal boron atoms.

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2P- 36

A Bulky P-Chiral Phosphine Ligand (BulkyP*): Synthesis and Application in Rh-Catalyzed Asymmetric Hydrogenation

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Chiral phosphine ligands have played an important role in transition-metal-catalyzed asymmetric reactions. Although many useful chiral phosphine ligands have been reported so far, the development of more efficient and widely applicable ligands is still a vital research topic.

In 2004, Hoge and co-workers synthesized a three-hindered quadrant chiral ligand, di-*tert*-butyl-phosphino(*tert*-butylmethylphosphino)methane (Trichickenfootphos, TCFP)[1] and demonstrated its excellent enantioselectivity in Rh-catalyzed asymmetric hydrogenation. Despite its very high catalytic activity arising from four-membered chelate structures, TCFP has not yet been widely used in asymmetric catalysis, mainly because the ligand is air-sensitive oil and cannot be easily handled.

We have long studied synthesis and application of P-chiral phosphine ligands and developed air-stable chiral phosphine ligands such as QuinoxP*,[2] BenzP*,[2] 3H-QuinoxP*,[3] and BiphenylP*.[4] Based on the experiences, we intended to synthesize a new ligand that is structurally analogous as TCFP but air-stable solid and practically useful. Our new ligand, di(1-adamantyl)phosphino(*tert*-butylmethyl-phosphino)methane named BulkyP*, was prepared in good yield from enantiopure *tert*-butylmethyl-phosphine-borane in short steps without any chromatographic separation procedures. It is noted that BulkyP* is white crystalline solid and not oxidized on exposure to air at least for two days.

The catalytic activity of BulkyP* was examined in Rh-catalyzed asymmetric hydrogenation. Thus, the ligand was converted into a cationic four-membered rhodium complex, [Rh(BulkyP*)(cod)]SbF_6, and the catalyst was employed in the hydrogenation of more than 26 prochiral substrates of α- and β-dehydroamino acid derivatives, enamides, alkenyl esters, α,β-unsaturated phosphonates, and itaconic acid esters. In most cases, the hydrogenations proceeded smoothly in the presence of very low catalyst loading of up to 0.0005 mol% (S/C = 200,000) to afford the products with excellent enantioselectivities of up to 99.9%. These results in conjunction with the availability of both (*R*)- and (*S*)-enantiomer ligands indicate that BulkyP* is potentially useful in various catalytic asymmetric reactions, especially for the large-scale production of chiral active pharmaceutical ingredients.

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2P- 37

Gas-Liquid Flow Synthesis Using Monolithic Catalysts

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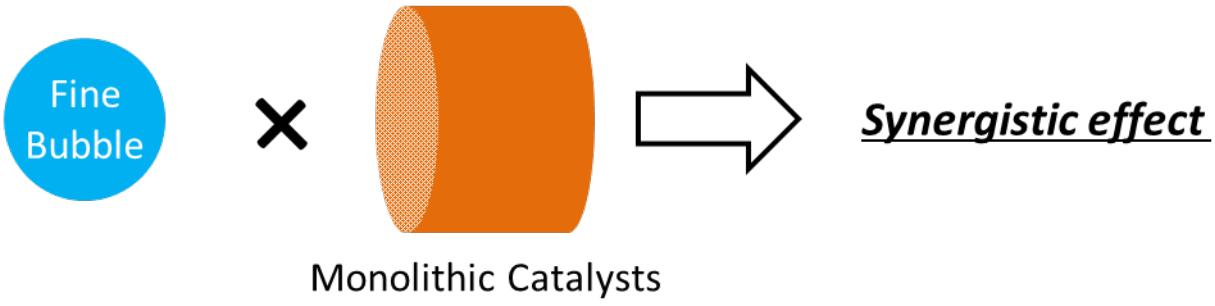
In flow synthesis, chemical reactions run in a restricted space. The main advantages of the flow method are accurate control of reaction time and temperature, saving energy and solvent, and high safety, which is the key points of Green Sustainable Chemistry. The use of solid catalysts offers more benefits, such as eliminating the need for a catalyst separation process, and reducing contamination by catalysts.[1]

Monolithic honeycomb catalysts are a kind of solid catalysts. One of their industrial usages is the purification of automotive exhaust gas. Honeycomb structure brings together lower pressure loss and high mixing frequency. Thus, honeycomb catalysts are more suitable for continuous production as compared to packing pellet or powder catalysts. Furthermore, the conditions for loading the monolith catalyst into the pipe are more reproducible and better in processability than the loading with the powder or pellets.

The gas-liquid multiphase reactions using honeycomb catalysts and fine bubbles (FBs) were carried out. FBs include microbubbles (<100 μm diameter) and ultra fine bubbles (<1 μm diameter). The use of FBs increases the reactive interface and improves the reaction efficiency. Furthermore, FBs have different properties from ordinary bubbles such as low rising speed, self-pressurizing effect, collapsing, all of which are beneficial for reactions using gas phase.[2]

To investigate the effects of catalyst shape (honeycomb vs. pellet) and FBs (with vs. without FBs) in the flow synthesis system, cross-conditional experiments were carried out. As a result, a strong synergetic effect was observed combining honeycomb catalysts and FBs.



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2P- 38

Quality by Design (QbD) Approach by Automated Robustness Study to Develop the Design Space

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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.

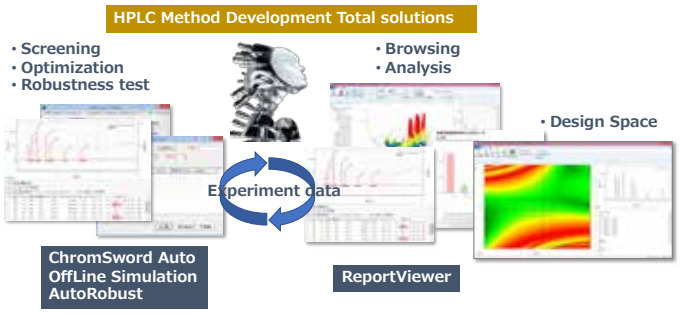
Recently, the procedure of HPLC method development based on Quality by Design, QbD approach is recognized to develop more robust HPLC condition in the manufacturing process in pharmaceutical industry. The HPLC method transfer based on QbD is important to analyze samples by different HPLCs. However, the QbD approach in the HPLC method development is required cumbersome process such as DOE experiments with various HPLC parameters, statistical analysis and design space development.

[Method]

Using ChromSword Auto, HPLC conditions were automatically optimized after screening different factors, such as columns, solvents, buffers and temperatures. The robustness test experiments were automatically carried by AutoRobust and ReportViewer to analyze the data of chromatogram and make the design space after finishing the method development process by ChromSword Auto

[Results]

The HPLC various conditions were automatically optimized by AI algorism of ChromSword Auto to find out the best HPLC condition for fine separation of each peak which directly controlled HPLC modules. The obtained chromatogram was simulated by OffLine to further improve the peak resolution which we wanted. The result of fine optimization could be tested for its robustness by AutoRobust in accordance with QbD principles. In this presentation, more detailed information and results will be discussed.



2P- 39

High Quality Peptide APIs from Sophisticated One-Pot Peptide Synthesis AJIPHASE®

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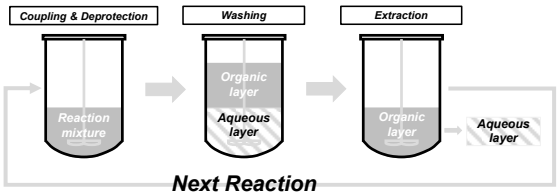
Previously, we have reported efficient peptide synthesis methodology. By combining the advantages of both solid-phase and solution-phase approach, we have developed an efficient peptide synthetic process;AJIPHASE®. This method is a solution-phase based one-pot peptide synthesis featuring liquid-liquid extraction, which allows skipping isolation of intermediates (Scheme 1). The new methodology has been successfully applied to large scale manufacturing of peptide API.



Scheme 1 AJIPHASE® one-pot process for peptides

The method is unique in many aspects. To name a few:

I. "Anchor" molecule on the *C*-terminal brings solubility and lipophilicity to the peptide intermediates and enables reactions and work-up in a homogeneous system (Figure 1).
II. Simple liquid-liquid washing is sufficient as work-up and elongations stages are connected seamlessly.
III. The simple work-up minimizes the material loss.
IV. The simple operation boosts up-scaling.
V. Being able to directly analyze the reaction system enables agile development of a robust process.

These characteristics lead to the manufacturing of high-quality peptide APIs. For instance, Bivalirudin and Degarelix have been obtained with over 80% LC purity as the crude products. More impressively, we have succeeded in manufacturing ≥99% purity API of an approximately 15 mer peptide drug candidate without any chromatographic purification (Figure 2). In the presentation, the details of AJIPHASE® technology will be described.

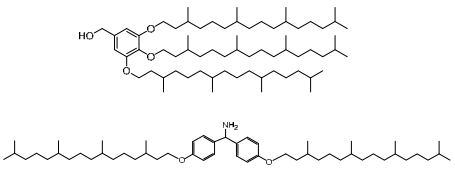


Figure 1 Anchor molecule

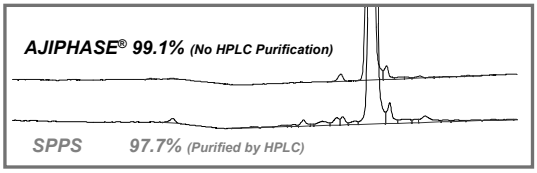


Figure 2 Comparison of peptide purity

2P- 40

Platinum on Carbon Bead-Catalyzed Continuous-Flow Dehydrogenation of 2-Propanol under Microwave-Irradiation

Tomohiro Ichikawa[1], Takumu Tachikawa*[1], Tomohiro Matsuo[1], Wataru Teranisihi[1], Tsuyoshi Yamada[1], Yoshinari Sawama[1], Yasunari Monguchi[2], Hironao Sajiki[1].
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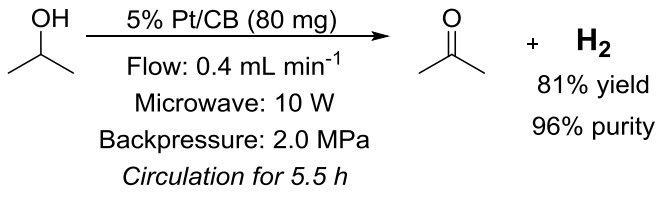
Hydrogen gas an as clean energy source has been attracted attention since it could mitigate the global climate crisis and a steam reforming of methane can practically produce hydrogen gas under harsh reaction conditions. Therefore, the developments of the energetically efficient method for hydrogen production and its practical usage are highly demanded. The studies for the hydrogen generation method from organic compounds, such as methylcyclohexane, and alcohols via dehydrogenative oxidation have been actively investigated. We have recently reported an efficient and continuous hydrogen production method using methylcyclohexane as a hydrogen carrier under carbon bead-supported Pt-catalyzed microwave heating conditions.[1)] We have newly developed a hydrogen production method using 2-propanol as a hydrogen source proceeding under a similar microwave mediated continuous flow reaction conditions.

2-propanol was transformed to acetone and high purity of hydrogen gas was produced in 81% yield under only 10W microwave irradiation during the circulation in the flow path equipped with a 5 wt% platinum on spherical carbon (5% Pt/CB)-packed cartridge (flow rate 0.4 mL/min and 2.0 MPa backpressure) in 96% purity by GC/TCD. A tiny amount of methane, propane, carbon dioxide and carbon monoxide derived from the decomposition of acetone were contaminated in the generated hydrogen gas. Selective and direct heating of carbon beads as catalyst support enabled by microwave irradiation and flow reaction system provided a new hydrogen generation method from 2-propanol as a cost-friendly and versatile hydrogen carrier.



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2P- 41

Characterization of chiral column by analyzed of column screening result

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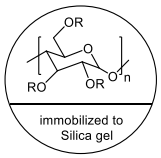
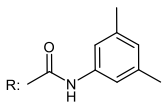
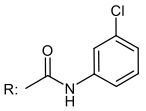
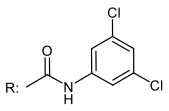
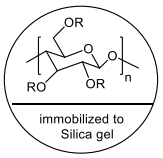
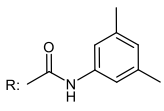
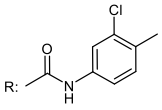
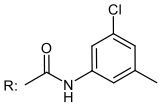
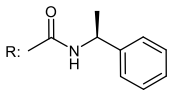
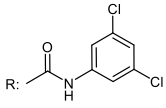
Chiral stationary phases (CSPs) based on polysaccharide derivatives are known to have high recognition abilities for a wide range of chiral compounds[1]. Therefore, these CSPs are widely used as methods for enantiomeric analysis and separation in variety fields.

The main chiral recognition mechanism of CSP is considered to be shape recognition. It was clarified by the calculation chemical approach using a model case that it is recognized by various interactions[2]. However, it is difficult to apply all chiral compounds because the separation mechanisms were not clarified in almost cases.

We have a production lineup of a number of chiral column varieties to accommodate the separation of various chiral compounds. A column screening is common method for searching the most suitable column. Also we have been providing a column screening service as one of the technical service in Japan. In this service, we receive a lot of racemic compound from customer and search the best column that can resolve.

In this presentation, we introduce the feature of each immobilized type CSPs (*i*CHIRAL series), that characterized by the analysis of the column screening results in recent years.

Table. The chiral selector structures of the immobilized type CSPs (*i*CHIRAL series).

Amylose derivatives 	CHIRALPAK® IA 	CHIRALPAK® ID 	CHIRALPAK® IE 	Cellulose derivatives 	CHIRALPAK® IB / IB N 
	CHIRALPAK® IF 	CHIRALPAK® IG 	CHIRALPAK® IH 		CHIRALPAK® IC 

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2P- 42

Asymmetric cross-aldol reaction of aldehydes via organocatalyst

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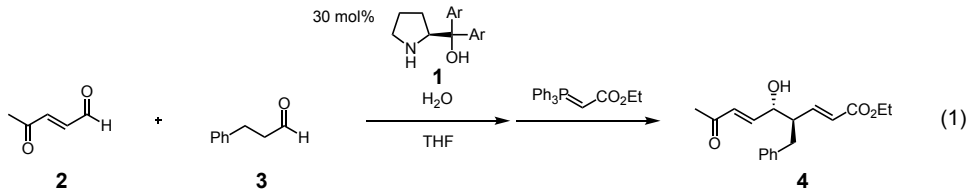
The aldol reaction is a key carbon-carbon bond forming reaction that is used to create the β-hydroxy carbonyl structural units, which are found in many natural products and drugs. Our group has developed trifluoromethyl-substituted diarylprolinol **1**[1] as an effective organocatalyst for the asymmetric cross-aldol reaction of two different aldehydes. Using this catalyst **1**, we accomplished cross-aldol reactions employing various electrophilic aldehydes such as ethyl glyoxylate, trifluoroacetaldehyde, chloral, dichloroacetaldehyde, chloroacetaldehyde, pivalaldehyde, glyoxal, formaldehyde, and alkynyl aldehyde. To expand the utility of this catalyst **1**, we further applied catalyst **1** to the aldol reaction of alkenyl aldehyde.

Firstly, we investigated the reaction of cinnamaldehyde and 3-phenylpropanal (**3**) in the presence of catalyst **1**, but the reaction did not proceed under several reaction conditions. We considered that the electrophilicity of cinnamaldehyde might be inadequate. Therefore, we employed a more electron deficient alkenyl aldehyde **2**. Aldol reaction of alkenyl aldehyde **2** with 3-phenylpropanal (**3**) proceeded in the presence of catalyst **1** and water, and it was completed within 48 hours to furnish an aldehyde that was directly subjected to Wittig reaction in one pot to give the product **4** in 56% overall yield from **2**. Although the aldol reaction proceeded under this condition, the reaction time was very long. From results of various optimizations, it was found that the addition of acetic acid shortens the reaction time to 19 hours. Further screening of the reaction temperature lead to the most suitable condition which gives the target material **4** in high yield with excellent enantioselectivity (eq. 1). The generality of the reaction and the role of acid will be presented in the poster.



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2P- 43

Atomeconomical Approach to Allylsilanes through Iridium-Catalyzed Hydrosilylation of Allenes

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A lot of methods for preparing allylsilanes have been reported so far for easy access to allylsilanes known as a valuable synthetic intermediate. Hydrosilylation of allenes is one of the atomeconomical approach to allylsilanes, but it is recognized that regio- and stereo-controlled transformation is much challenging due to the presence of sequentially linked double bond in the allenes.[1] Herein, we report recent our efforts on the iridium-catalyzed hydrosilylation, in which a readily available iridium(I) complex, $[IrCl(cod)]_2$ (cod = cyclooctadiene), acts as a highly active catalyst for the hydrosilylation of terminal allenes providing allylsilanes selectively.

After screening of various parameters of the hydrosilylation of disubstituted terminal allenes such as the substitutions of silanes, the reaction temperature, the iridium(I) complexes as a catalyst and the experimental procedure, we revealed that the addition of both phenyl methyl allene (0.40 mmol) and Me_2PhSiH (0.48 mmol) at one time to a THF solution (1.0 mL) of $[IrCl(cod)]_2$ (0.004 mmol) at 0 ˚C afforded 1-dimethylphenylsilyl-3-phenylbut-2-ene as an allylsilane in a 97% NMR yield as a mixture of stereoisomers (*Z*/*E* = 86/14). In the present iridium-catalyzed hydrosilylation, the isolation of the product is very simple and easy to operate: after the completion of the reaction, the mixture was filtered and then the purification by a short column chromatography afforded the allylsilane in a 87% isolated yield. This procedure was applied to the hydrosilylation of various *gem*-disubstituted terminal allenes. The substituents on the aromatic ring in the allenes had an insignificant effect on the yield of the allylsilanes and their stereoselectivities. Dialkyl-substituted terminal allene was also utilized in this system with no trouble at all. The steric hindrance of the substituents of allenes had a strong effect on the stereoselectivities of the products.

Our system presumably proceeds through the concerted Si-H oxidative addition and hydroiridation pathway in analogy with the molybdenum-catalyzed hydrosilylation of allenes by the Takai's group.[2] In addition to mechanistic observations, we also discuss on the large-scale preparation of allylsilanes by this hydrosilylation.

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2P- 44

Stable Triazinone-Based Reagent for *O*-*p*-Methoxybenzylation under Mild Heating Conditions

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The *p*-methoxybenzyl (PMB) group is one of the most useful protecting groups for alcohols. This group is commonly introduced with PMB chloride and NaH under basic conditions (Williamson ether synthesis) or with PMB 2,2,2-trichloroacetimidate under acidic conditions. However, these conditions would be not suitable for alcohols bearing acid- and base-labile functionalities. Furthermore, accidental decomposition of PMB chloride and PMB 2,2,2-trichloroacetimidate during storage is known to be problematic. For example, addition of a stabilizer (potassium or calcium carbonate) to PMB chloride is required to prevent autocatalytic production of HCl gas, which may cause overpressurization and rupture of containers. In this poster, we report a new, triazinone-based reagent **1** (Scheme 1, prepared from cyanuric chloride in 54% overall yield) for *O*-*p*-methoxybenzylation under mild heating conditions (50 °C).[1] Various alcohols were converted into the corresponding PMB ethers with **1** in the presence of $^{n}Bu_4NOTs$ in $MeNO_2$/1,4-dioxane (Figure 1). Other solvents such as MeCN and chlorobenzene can also be used for the reaction. High functional group tolerance is achieved because **1** does not require the addition of an acidic or basic activator. In contrast to its reactivity in solution, **1** is stable to storage in solid form: No decomposition was detected after it was stored at room temperature under open air for 20 days. Studies of the thermal behavior of **1** revealed that it decomposed to a rearranged product at around 115 °C without producing gas.

Scheme 1. Synthesis of the new *p*-methoxybenzylating reagent **1**.

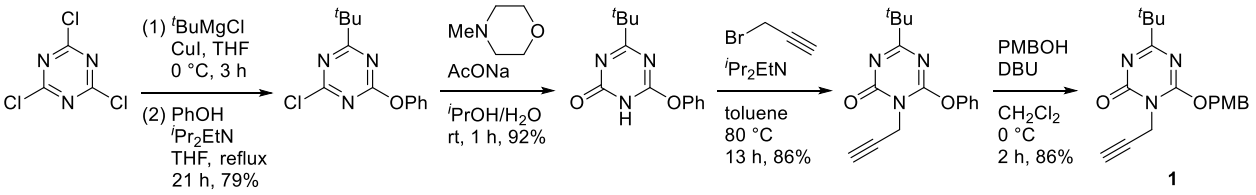
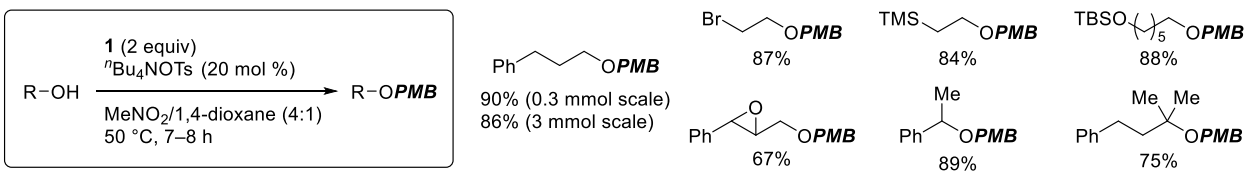


Figure 1. *O*-*p*-Methoxybenzylation of various alcohols with **1**.



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2P- 45

Catalytic Regioselective Ring Opening of Epoxides by Unprotected Amines

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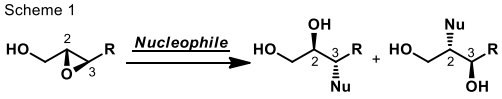
Scheme 1

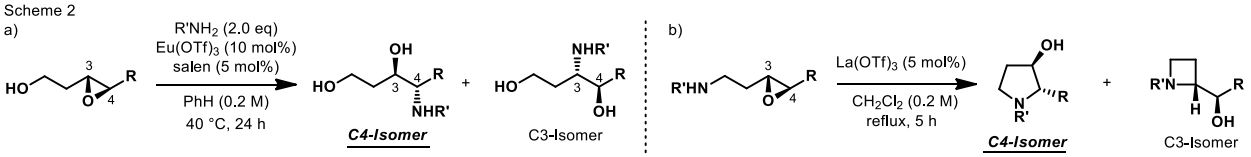


Many bioactive compounds have contiguous stereocenters consisting of polar functional groups. Catalytic methods that enable construction of such structural motifs are highly rewarding for the synthetic ventures. Regioselective ring opening reactions of 2,3-epoxy alcohols are useful reactions for synthesis of chiral diols, and have been studied actively since 1980's. In 2014, the first catalytic ring opening reaction of 2,3-epoxy alcohols using $W(OEt)_6$ was reported by Yamamoto and co-workers.[1] We also reported such reaction with catalytic amount of $Eu(OTf)_3$ in the same year.[2] On the other hand, regioselective ring opening reactions of 3,4-epoxy alcohols have rarely been investigated although highly enantioselective epoxidation of homoallylic alcohols into 3,4-epoxy alcohols has been reported. Regioselective aminolysis reactions of 3,4-epoxy alcohols with aliphatic amines are considered as powerful synthetic methods for the synthesis of nitrogen-containing chiral compounds (e.g. alkaroids). Such reaction has only been reported by Yamamoto and co-workers, using a Ni catalyst.[3] Here we report two types of catalytic regioselective ring opening reactions of epoxides by unprotected amines: one is intermolecular aminolysis of 3,4-epoxy alcohols by aliphatic amine nucleophiles, and the other is intramolecular aminolysis of 3,4-epoxy amines.

[Intermolecular aminolysis of 3,4-epoxy alcohols by aliphatic amine nucleophiles] During exploration of ligands for the $Eu(OTf)_3$ catalyst, it was found that salen is effective for improving regioselectivity of the intermolecular aminolysis (Scheme 2a). It is interesting that the Lewis acid catalyst worked in the presence of over-stoichiometric amounts of amine bases.

[Intramolecular aminolysis of 3,4-epoxy-1-amines] Screening of Lewis acid catalysts for the intramolecular aminolysis identified $La(OTf)_3$ as the best catalyst (Scheme 2b). This reaction features anti-Borldwin *5-endo-tet* cyclization.

Scheme 2



1) H. Yamamoto *et al. J. Am. Soc. Chem.* **2014**, *136*, 6888. 2) Y. Iwabuchi *et al. Org. Lett.* **2014**, *16*, 4408. 3) H. Yamamoto *et al. J. Am. Soc. Chem.* **2015**, *137*, 4308.

2P- 46

Transition Metal-Free One-pot Synthesis of 3-Benzo[*b*]thienyl Thioethers via Benzo[*b*]thiophenone

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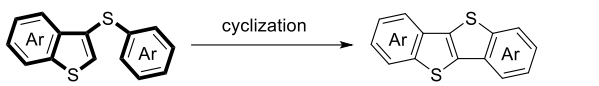
3-Benzo[*b*]thienyl thioethers are significant compounds in the field of pharmaceuticals because they are potent candidates for bioactive compounds, such as endothelin inhibitors[1] and thrombin inhibitors[2] (Scheme 1). They can also be used as precursors for π-expanded benzothienothiophene derivatives which are known as excellent semiconductors.[3] The conventional ways to synthesize 3-benzo[*b*]thienyl thioethers are transition metal-catalyzed cross-coupling reactions between 3-bromobenzo[*b*]thiophene and phenylthiol.[4] These reactions require the use of a transition metal-catalyst and a halogenated reagent. From environmental and economical point of view, transition metal and halogen-free synthesis of benzo[*b*]thienyl thioethers are quite attractive. Based on the perspective, we focus on benzo[*b*]thiophen-3-one (**2**) which can be derived from arylthioacetic acids by an intramolecular Friedel–Crafts cyclization (Scheme 2, Reaction A). We found that thus-obtained **2** can be converted to 3-benzo[*b*]thienyl thioethers (**1**) by an acid-catalyzed addition of arylthiols and subsequent dehydration (Reaction B).

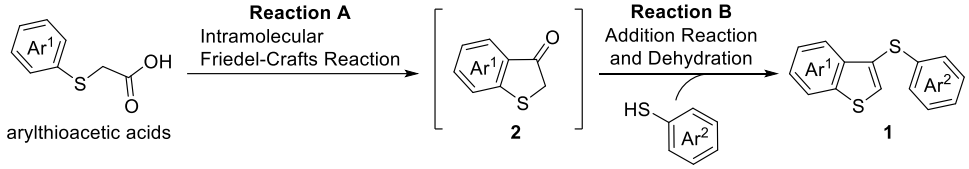
Scheme 1. 3-Benzo[*b*]thienyl Thioethers



3-Benzo[*b*]thienyl thioethers (1)
• biologically active

Benzothienothiophenes
• organic functional materials

Scheme 2. One-Pot Synthesis of 3-Benzo[*b*]thienyl Thioethers



These two reactions could be carried out in one-pot. We also achieved a telescoping synthesis of benzothienothiophene derivatives from arylthioacetic acids. The details of these reactions will be presented.

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2P- 47

Risks from Rising Temperature

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Many chemical processes are exotherm and release a defined amount of energy. If the energy released can't be removed instantaneously, the temperature will rise. Even those processes that are intended to be run isothermally will show a small deviation from the target temperature, which may have important implications on reaction kinetics and safety of the process. Temporary temperature changes are due to physical effects, and vary with the reactant addition rate, the heat release rate, the process dynamics, and the reactor vessel. Such behavior may also be caused by limitations of the temperature control or the heating and cooling capacity. This occurs when reactions are fast and strong and the heat release is larger than the heat removal capacity. When this happens, a defined amount of heat is accumulated temporarily, and released again over time. Consequently, the temperature changes initially, but returns to the defined target temperature at the end of the reaction. For any researcher involved in chemical process scale-up, understanding this temperature change, and the associated heat that is accumulated by the reaction, is critical to understand the safety of the process.

In order to truly understand the risks, the following three questions below must be addressed.
1. "Why and when does thermal accumulation occur?"
2. "Is accumulation important to consider, and how big is it?"
3. "What is the impact of an incorrect calculation of the accumulation?"

It will provide examples from both the lab and pilot plant which highlight methods to answer these questions and assess the implications of changing temperature regimes under which chemical reactions are carried out.

2P- 48

Mechanistic Analysis in Lithiation-Methylation Reaction of Trifluorobenzoic Acid

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2,4,5-Trifluorobenzoic acids are well-recognized as good starting material of fluoroquinolone antibiotics synthesis. To improve the antibacterial activity of the quinolone drug, the substituent on 3-position (i.e. 8-position on quinolone ring) is known to have a significant impact. Among various substituents introduced and evaluated, 3-methylated species have attracted many research interest according to its strong effect on activity. We previously reported this 3-methylation process in good yield and selectivity, employing iodomethane with LHMDS in MTHF condition to control the amount of residual non-methylated benzoic acid, which is very difficult to remove throughout following (>10 steps of) synthetic process. Although this process worked well in scale, we still had some mechanistic concern; cause of regioselectivity and ambiguity in temperature dependency. Especially, in this reaction 3-position is specifically methylated with no reaction at 6-position, which is rather supposed to be reactive based on ortho-lithiation mechanism. Thus we decided to investigate the detailed mechanisms of this lithiation-methylation reaction, and some unexpected results were obtained as follows.

At the first point, we set hypothesis that assumes contribution of some kind of semi-stable states like aggregation of lithiated species, but unfortunately no characteristic signal was obtained in any way neither by NMR nor IR. After further investigation, we successfully prepared the condition to run the reaction *in-situ* in proton NMR spectrometer and surprisingly it has been revealed, with added 2.4 equivalents of LHMDS, still all aromatic protons remained intact during 'lithiation step'. Furthermore, when iodomethane was added into this NMR tube, one of the proton signal quickly disappeared and afforded expected methylated product.

Next, we also tried to track the reaction indirectly by appropriate deuterium quenching. Again, we only obtained the signal of starting material and product during methylation without any signal related to lithiation in contrast to LDA case, in which reasonable amount of deuteration can be detected by the same quenching method.

Based on these results, we suspect the mechanism of this reaction might not be step-by-step type lithiation-methylation, but rather involve equilibrium between starting material and trace amount of lithiated species, and addition of iodomethane would shift the equilibrium toward product-side by consuming lithiated species. Details are discussed in poster.

2P- 49

The Enhanced Enantio-recognition of Chiral Acylazolium in Kinetic Resolution of Chiral Secondary Alcohol by Carboxylate Additive

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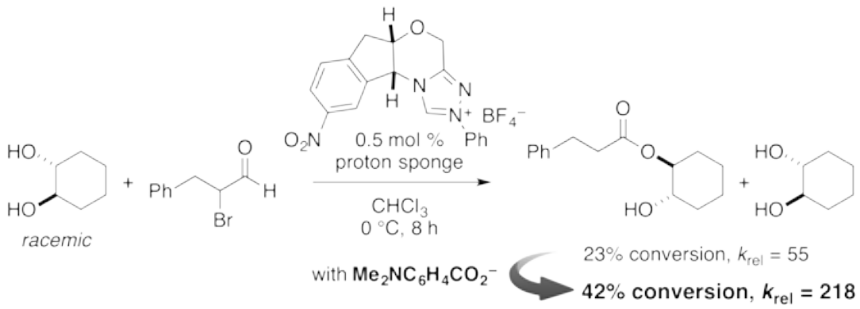
Kinetic resolution of racemic secondary alcohols via enantioselective acylation is an important method in synthetic chemistry.[1] Recently, we found that the rates and enantioselectivities of chiral NHC-catalyzed asymmetric acylation of alcohols bearing an adjacent H-bond donor functionality are remarkably enhanced in the presence of a carboxylate cocatalyst. The degree of the enhancement is correlated with the basicity of the utilized carboxylate. Using a cocatalyst and newly developed electron-deficient chiral NHC, kinetic resolution of 1,2-cyclohexanediol was achieved with high enantioselectivity (k_{rel} = 218) with low catalyst loading (0.5 mol %), while the significantly decreased selectivity (k_{rel} = 55) was observed in the absence of the cocatalyst (Scheme 1).[2] The methodology was also applicable to kinetic resolution of cyclic amino alcohols and α-hydroxy thioamides as well as desymmetrization of a *meso* compound.



Scheme 1. NHC–Carboxylate Catalyzed Kinetic Resolution of 1,2-Cyclohexanediol.

References

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2P- 50

Synthetic Route Scouting and Process Development of Dolutegravir Sodium

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Dolutegravir sodium, an inhibitor of HIV integrase, is a promising drug for the treatment of HIV infection and is being used worldwide. It has a highly functionalized tricyclic core structure, and thus many synthetic steps and chromatographic purification were required for its preparation in the medicinal chemistry stage, resulting difficulty for large-scale synthesis. We made exploration for improvement of the synthetic route, process development and manufacturing method for practical scale production, and successfully developed 2 practical synthetic methods for the preparation of dolutegravir sodium;

1. Synthetic Method Starting from Maltol

Synthetic method in medicinal chemistry stage includes numerous synthetic steps, in particular oxidation of starting material maltol, and subsequent functional group transformation. We investigated oxidation method of methyl moiety of maltol and successfully developed scalable oxidation process of maltol using aldol-type addition of protected maltol followed by oxidative cleavage of C-C double bond. Tricyclic core structure formation proceeded in high diastereoselectivity and introduction of amide moiety was successfully accomplished by palladium-catalyzed amidation of bromide using difluorobenzylamine under carbon monoxide atmosphere. The newly developed synthetic method gives quite high yield in each conversion step and enabled multikilogram scale manufacturing of dolutegravir sodium with high purity.

2. Synthetic Method via a Pyrone Diester Intermediate

Having developed preparative synthetic method for dolutegravir sodium, we continued an extensive research for more efficient synthetic method. We had an idea that an appropriately functionalized pyrone diester compound was a key intermediate for more efficient method, since pyrone diesters would be readily prepared from enamines and oxalates and can be easily converted into amides, leading to a more efficient method for the preparation of dolutegravir. After extensive exploration, the desired pyrone diesters were obtained from enamines and oxalates in good yield. The obtained pyrone diester was easily transformed into dolutegravir sodium in short synthetic steps via crystalline intermediates. The developed synthetic method has an advantage of efficacy that it has short synthetic steps along with each crystalline intermediate. Additionally, this method has no oxidation and cryogenic reaction, and also has a highly atom-efficient property as the waste from the process consists of only low molecular weight compounds (water, methanol, dimethylamine, toluene).

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2P－51

Modernize Synthesis

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1. The Limits of your Lab

   For most synthesis experiments, chemists and chemical engineers will focus on four specific actions: Heating and Cooling, Stirring, Dosing, Sampling. The traditional setup needed to conduct these activities largely relies on assemblies of glassware, hot plates, basic cooling devices, stirrers, and other peripherals. Conducting experiments using this type of equipment is limiting in six key areas.

2. A new way to run experiments

   Smart synthesis workstations , combined with unattended dosing and automated sampling, provide a simple and safe way to precisely control reaction parameters and obtain reaction information around the-clock. These workstations ensure recipe steps, experimental conditions, and analytical data are automatically recorded, making it easy to obtain valuable process knowledge. This means successful experiments can be repeated with one click, and experimental results can be shared easily with colleagues and archived for future use.

3. The modern synthesis lab

   Chemists are continually searching for innovative chemistry to develop breakthrough molecules and process conditions which enable safe and economically viable processes. Due to the increase in molecular complexity ,shorter time lines, and a tighter regulatory environment, new techniques are necessary to develop better chemistry and execute more successful experiments, while assuring efficient information and knowledge sharing within the organization. Demand for higher yield, increased safety, and optimized product quality means scientists need to be equipped with instrumentation that allows them to quickly investigate new conditions with minimal errors resulting in meaningful data and results to make informed decisions.

   In the modern synthesis laboratory, standardized chemistry workstations with integrated data management capabilities can replace round bottom flasks and other antiquated chemistry tools. These easy-to-use setups can execute parallel experiments exactly as the chemist intended while documenting results automatically. Process parameters, across a wide application range, can be controlled with exquisite precision for every single experiment, and the data generated can be distributed to a data management system automatically. Representative samples can be taken at regular intervals around-the-clock limiting information gaps and improving the personal safety of every chemist.

Figure1. EasyMax 102 with Dosing

2P- 52

Photoctalytic N-Methylation of Amino Acids with Methanol

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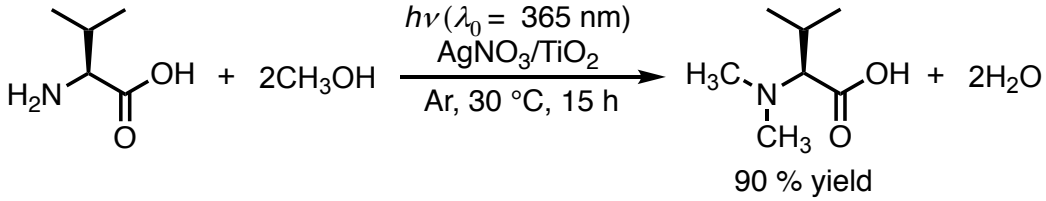
N-Methyl amino acid residues represent an important substructure in bioactive natural products, pharmaceuticals, and their synthetic intermediates. The N-methylation of amino acids using methanol as a methylating agent is one of the most straightforward methods for producing *N*-methyl amino acids with a minimal environmental impact. However, a general method for the methylation of various amino acids with methanol still remains a challenge.[1] To address this issue, we here report a photocatalytic method for the N-methylation of amino acids with methanol by extending our previous systems.[2,3]

As a typical example, the N,N-dimethylation of L-Valine with methanol smoothly proceeds in the presence of a silver nitrate-loaded titanium dioxide ($AgNO_3/TiO_2$) photocatalyst at 30 °C under 15-h light irradiation with UV-LEDs, producing the corresponding *N,N*-dimethylvaline in 90% yield (Scheme 1). This reaction produces water as a byproduct, which fits with the idea of green and sustainable chemistry.

Scheme 1



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2P- 53

Platinum on carbon-bead-catalyzed energetically efficient, continuous hydrogen production method from methylcyclohexane enhanced by the microwave irradiation

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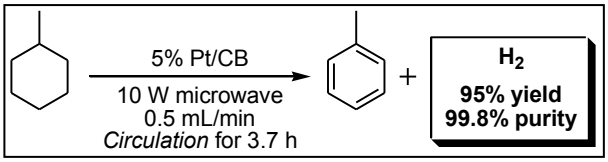
Hydrogen is gathering much attention as clean energy because only water is emitted as a by-product of combustion. A steam reforming of methane is one of the practical hydrogen production methods although it requires harsh reaction conditions. Catalytic dehydrogenation methods using readily available compounds, such as hydrocarbons, alcohols, etc., are noteworthy as CO_2-free hydrogen production methods. Methylcyclohexane (MCH) is prospective candidates as a liquid organic hydride since it can be regenerated by hydrogenation of toluene as a co-product of the catalytic dehydrogenation (hydrogen production) of MCH. Although the dehydrogenation of partially unsaturated alicyclic compounds relatively readily proceeds, the dehydrogenation of fully saturated hydrocarbons is a significant endothermic reaction and it requires harsh reaction conditions for the dehydrogenation progress. Although many researchers have actively researched for the development of effective catalysts and/or reaction devices for the dehydrogenation of MCH, high temperature, and pressure conditions are still required, and serious problems remain in terms of energy efficiency.

Recently, we have developed that the energetically efficient method for the dehydrogenation of MCH and other hydrocarbons by the use of a continuous flow reaction system equipped with a heterogeneous catalyst cartridge and microwave irradiation as a direct-heating source.[1]

The catalyst support, carbon-bead (CB), of 5 wt% Pt/CB (80 mg) in a quartz glass cartridge which was effectively and selectively heated by microwave irradiation enables the conversion of MCH to toluene during the circulation under 10 W microwave irradiation at 0.5 mL/min flow rate for 3.7 h. Hydrogen gas was obtained in 95% yield and 99.8% purity. The present system could be operated continuously for at least 12 h without loss of catalyst activity, and turnovers of 5% Pt / CB could reach over 670,000 times. This continuous reaction system could be also applied to the dehydrogenative aromatization of saturated hydrocarbons including hetero-alicyclic compounds. The combination of the flow reaction system and microwave irradiation extremely effectively facilitated the hydrogen production compared to the batch system.



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2P- 54

One-pot Preparation of α,β-Unsaturated Aldehydes by Julia-Kocienski Reaction and Hydrolysis

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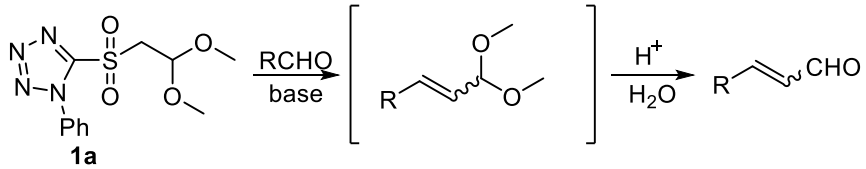
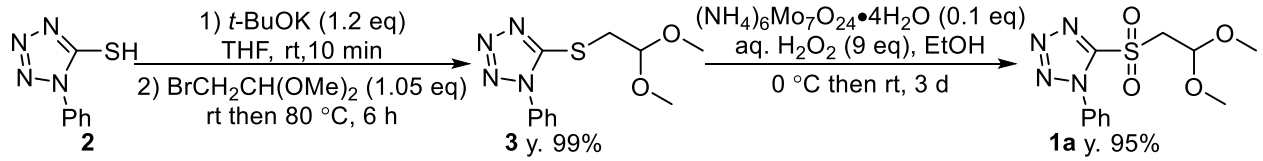
Stereoselective formation of carbon-carbon double bonds is important for the synthesis of bioactive compounds and the preparation of substrates for stereoselective reactions. Although the Wittig reaction of Ph_3P=CHCHO with aldehydes yields α,β-unsaturated aldehydes, the product aldehydes also react with the Wittig reagent, so the reaction usually gives a mixture. In this study, we prepared 2,2-dimethoxyethyl sulfone reagent **1a** and studied the Julia-Kocienski reaction of **1a** with aldehydes, which should give α,β-unsaturated aldehydes after acid hydrolysis (Scheme 1).

Scheme 1



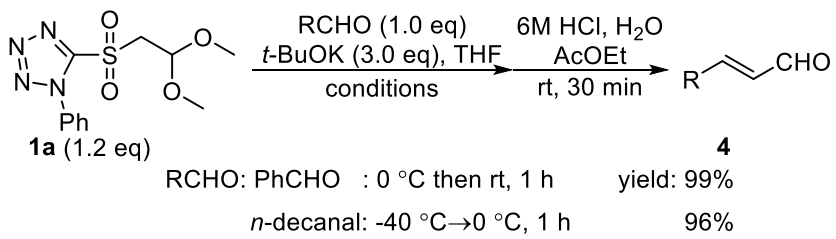
Reagent **1a** was obtained by the reaction of 5-mercapto-1-phenyl-1*H*-tetrazole **2** and 2,2-dimethoxyethyl bromide using *t*-BuOK in THF followed by oxidation with hydrogen peroxide in ethanol (Scheme 2).

Scheme 2



When a THF solution of **1a** and benzaldehyde was treated with *t*-BuOK for 1 h and then hydrolyzed by adding 6M HCl, *trans*-cinnamaldehyde was obtained in 99% yield. Since side reactions occurred in the Julia-Kocienski reaction of *n*-decanal, *t*-BuOK was added to a THF solution of **1a** and *n*-decanal at -40 ℃ and the reaction was allowed to warm to 0 ℃. After acid hydrolysis, *trans*-2-dodecanal was obtained in 96% yield (Scheme 3).

Scheme 3



2P- 55

Enhanced Development and Control of Continuous Processes Using Real-Time In Situ FTIR – What's Happening in Your Flow Chemistry?

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In the chemical development and manufacturing, improvements in product quality, yield, synthetic route, safety and overall time efficiency are key factors in driving chemists and engineers to seek alternative chemical development methods. Continuous flow reactor technologies provide the opportunity to address many of these issues as they allow for rapid testing, optimization, and scaling of chemical sequences. However, a common limiting factor with these methods relates to inline monitoring as it is important with respect to optimization and synchronized control of multi-step reactions. One of the most convenient and nondestructive methods for real-time inline monitoring is FTIR. Not only does this technique allow the formation of products and reactive intermediates to be monitored in real time but immediate reaction feedback is also possible on the effect of changing a process parameter which can lead to an improved understanding and a faster optimization of the flow process.

This presentation will discuss how this approach has been successfully used to monitor product streams and dispersion effects in a continuous flow reactor, and then use that information to successfully perform a multi-step synthesis, where a third reagent stream is stoichiometrically controlled based on the output of the first part of the reaction.

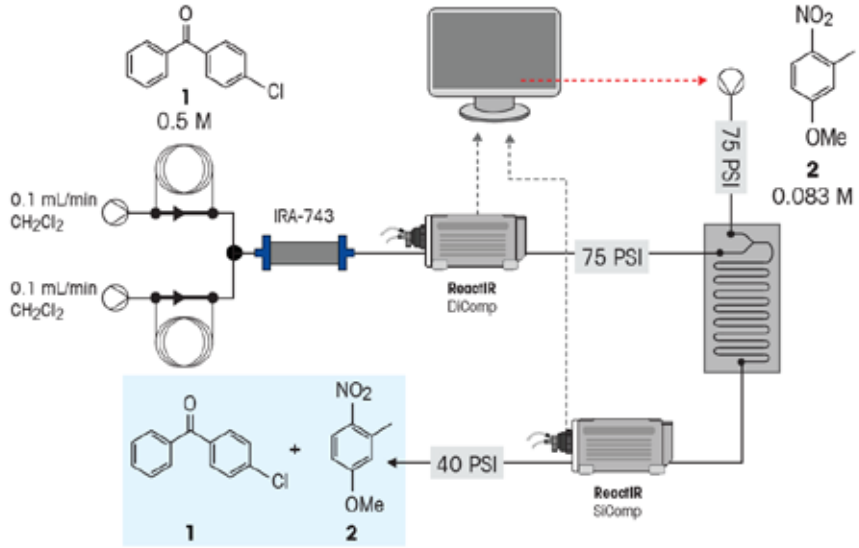

Figure 1. The experimental setup to prove that the dispersion curve of the1st reagent could be mapped by the IR and used to accurately dispense a 2nd reagent proportional to the concentration of the 1st reagent.

2P- 56

Expansion of Substrate Scope of Nitroxyl Radical/Copper-Catalyzed Aerobic Alcohol Oxidation

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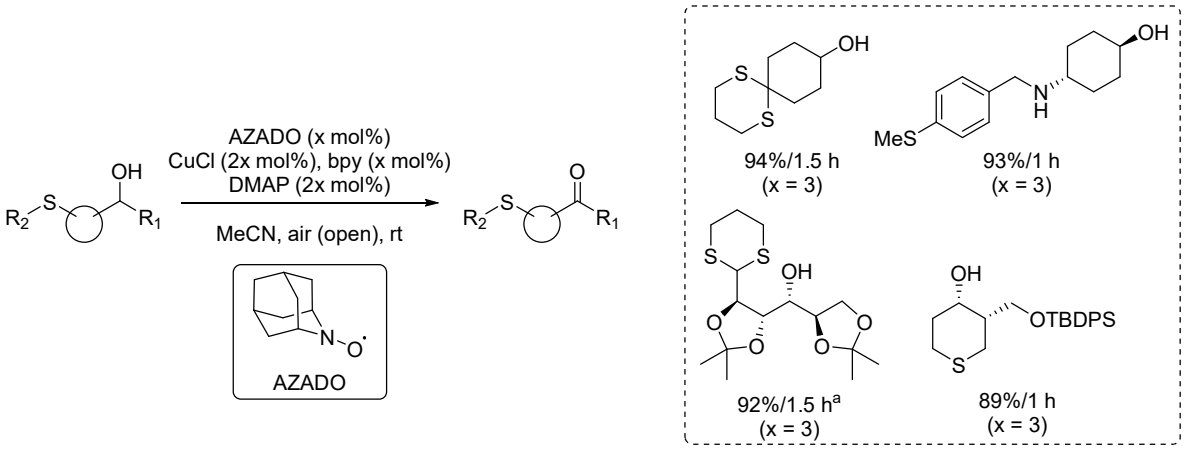
The oxidation of alcohols is one of the most useful reactions in organic synthesis. Therefore, it has been extensively investigated, and numerous methods have been developed. However, the oxidation of alcohols with electron-rich and oxidation-labile functional groups often causes problems. In our laboratory, a useful solution for the problem of the oxidation of amino alcohols has been developed. The cooperative catalysis of 2-azaadamantane *N*-oxyl (AZADO) and a copper salt efficiently catalyzed the chemoselective oxidation of unprotected amino alcohols into amino carbonyl compounds using molecular oxygen (O_2) in ambient air as the terminal oxidant.[1] We envisaged that the substrate scope of the alcohol oxidation using AZADO/copper-catalysis would be wide.

Here, we report the applicability of the aerobic alcohol oxidation catalyzed by AZADO/copper to alcohols containing divelent sulfur functional groups into the corresponding carbonyl compounds.[2]

In the poster presentation, we will present further application of the aerobic alcohol oxidation using AZADO/copper catalysis.



[a]The reaction was performed at 0 ºC.

[1] Y. Sasano, S. Nagasawa, M. Yamazaki, M. Shibuya, J. Park, and Y. Iwabuchi, *Angew. Chem. Int. Ed*., **2014**, *53*, 3236-3240.

[2] Y. Sasano, N. Kogure, S. Nagasawa, K. Kasabata, and Y. Iwabuchi, *Org. Lett.* **2018**, *20*, 6104-6107

2P- 57

Palladium-Catalyzed Reaction of Silyl-Substituted Allyl Acetates with Water Proceeding through 1,2-Shift of a Substituent on Silyl Group

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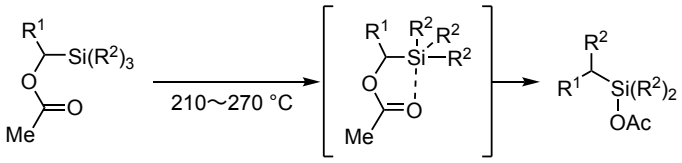
Thermal rearrangement of α-acetoxysilanes, in which there is exchange of the acetoxy group and the substituent on the silicon atom, is known to occur between 200 ˚C and 270 ˚C to give the corresponding silyl acetates (Scheme 1a).[1, 2] The reaction usually takes place with almost complete inversion of configuration, and shows good preference for phenyl over methyl migration. As synthetic routes to acylsilanes are limited, thermal rearrangements of α-acetoxysilanes have not yet reached a point where it is a practical and general synthetic methods. We report herein that palladium-catalyzed reaction organosilyl-substituted allyl acetates **1** and water that involves 1,2-migration of a substituent from a organosilyl group (Scheme 1b).

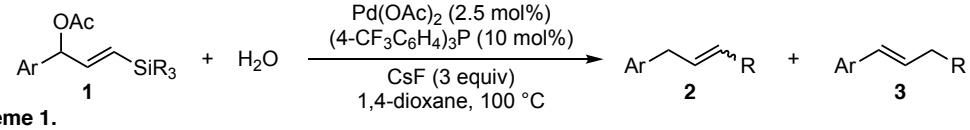
Previous work: Thermal Rearrangements of α-Acetoxysilanes (refs. 1 and 2)



(a)

■ Approximate order of migratory aptitude: H, C≡C > Ph > Me

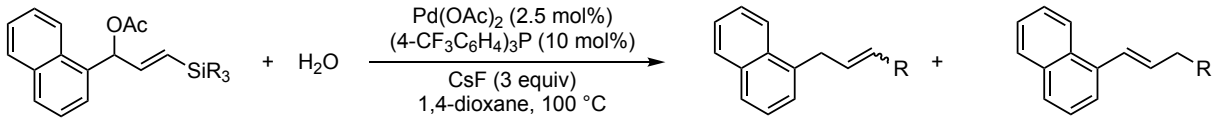
This work



(b)

Scheme 1.

The palladium-catalyzed reaction of organosilyl-substituted allyl acetates **1** and water in 1,4-dioxane at 100 °C induced previously unprecedented 1,2-migration of a substituent of organosilyl group (Scheme 2). The approximate order of migratory aptitude was found to be alkynyl group > phenyl group > alkyl group.



1a, R = Me
1b, R = Ph
1c, R = C≡CPh

■ Approximate order of migratory aptitude: C≡CPh > Ph > Me

2a, R = Me, 56%, *E*/*Z* = 1:7
2b, R = Ph, 48%, *E*/*Z* = 8:1
2c, R = C≡CPh, 7%, *E*/*Z* = 1:2

3a, R = Me, 17%, *E*/*Z* = >20:1
3b, R = Ph, 40%, *E*/*Z* = >20:1
3c, R = C≡CPh, 36%, *E*/*Z* = >20:1

Scheme 2. Scope of palladium-catalyzed reaction of organosilyl-substituted allyl acetates **1** and H_2O

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1 a) A. R. Bassindale, A. G. Brook, P. F. Jones, J. M. Lennon, *Can. J. Chem*. **1975**, *53*, 332. b) A. G. Brook, P. F. Jones, *J. Chem. Soc., Chem. Commun.* **1969**, 1324. c) M. T. Reek, N. Greif, *Angew. Chem., Int. Ed. Engl*. **1977**, *16*, 712. d) R. Tacke, Lange, H. *Chem. Ber.* **1983**, *116*, 3685.
2 a) J. D. Buynak, J. B. Strickland, T. Hurd, A. Phan, *J. Chem. Soc., Chem. Commun.* **1989**, 89. b) J. D. Buynak, J. B. Strickland, G. W. Lamb, D. Khasnis, S. Modi, D. Williams, H. Zhang, *J. Org. Chem.* **1991**, *56*, 7076.

2P- 58

Scale-up Synthesis of Icatibant using Molecular Hiving Technology

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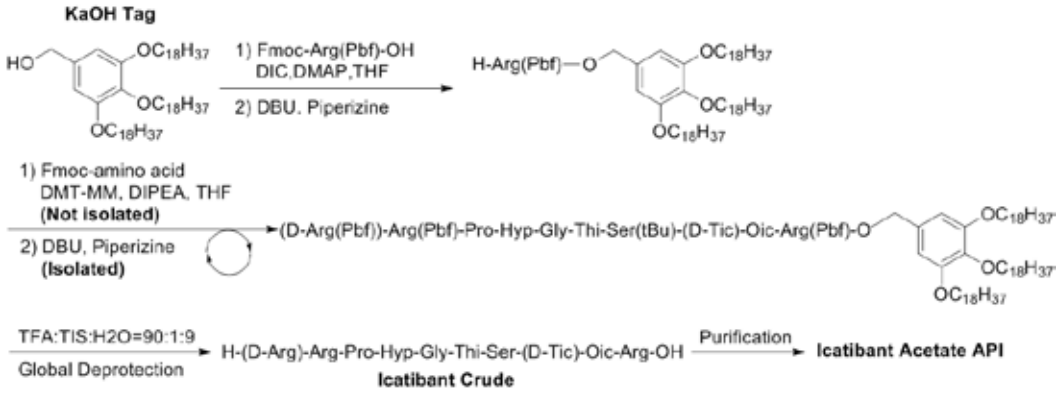
At present, the market of peptide API have been increasing, accordingly the high quality and low-cost peptide synthesis is becoming more demanding. We have been developing hydrophobic tag-assisted liquid phase peptide synthesis method (Molecular Hiving^{TM}) that combines the advantages of both conventional solid phase peptide synthesis (SPPS) and liquid phase peptide synthesis (LPPS).

Unlike conventional SPPS, reaction can be conducted under homogeneous solution by Molecular Hiving that results in enhancing reactivity. Therefore, it is no need to use excess amount of reagents and reaction time become shorter. Moreover, we can carry out in process control by HPLC in any step. By conducting IPC, we confirmed that impurities which is characteristic in SPPS can be controlled sufficiently. There is an advantage that each intermediates of consecutive reaction can be taken out as a solid and can confirm quality, however, the manufacturing time in pilot scale seems to be longer when conducting solidification at each step.

Herein, we will report we have applied this method to pilot scale production and have successfully established the procedure of 300g scale of crude manufacturing.



References

1) Y. Okada et al. *J.Org.Chem.* 2013, 78, 320-327

2) WO2007/034812, WO2007/122847

2P- 59

One-pot Preparation of Julia-Kocienski Sulfides and Sulfones from Alcohols

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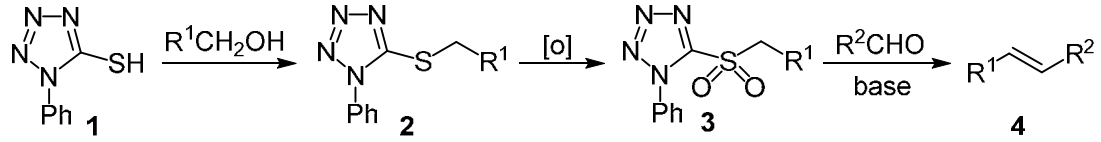
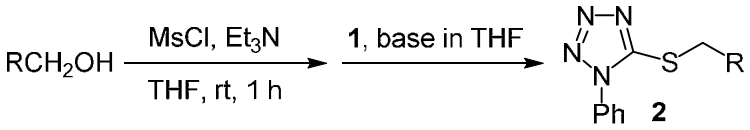
The Julia-Kocienski reaction is a very strong tool for the synthesis of *E*-alkenes from carbonyl compounds and heteroaryl sulfones such as **3**. When the sulfone reagents **3** are prepared from thiol **1** and alcohols, the corresponding sulfides **2** are generally prepared by Mitsunobu reaction using either DEAD or DIAD along with Ph_3P. However, both DEAD and DIAD are expensive and the byproducts (Ph_3P=O and $(NHCO_2R)_2$) are often difficult to be removed from the desired product. Since alcohols can be easily transformed to alkyl halides and sulfonates which can be used for alkylation of thiol, sulfides can be prepared by these two steps. Although these two reactions could be carried out in one-pot, there is no report for the one-pot procedure in the literature as far as we know. Therefore, we studied one-pot preparation of Julia-Kocienski sulfides and sulfones from alcohols and thiols. Herein, we would like to report our results.



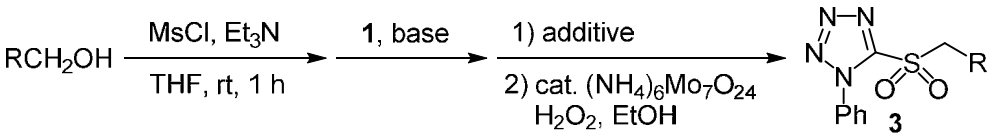
Scheme 1. Preparation of sulfones **3** and their Julia-Kocienski reaction

After alcohols were treated with methansulfonyl chloride and triethylamine in THF for 1 h, a mixture of thiol **1** and base in THF was added to the reaction as shown in Scheme 2. A variety of sulfides **2** were obtained in 76-96% yields (13 examples).



Scheme 2. One-pot preparation of sulfides **2** from alcohols

Furthermore, one-pot preparation of sulfones **3** was achieved by mesylation, alkylation of thiol **1**, adjustment of pH, and oxidation by H_2O_2 and ammonium molybdate in a same pot up to 84% yield (Scheme 3).



Scheme 3. One-pot preparation of sulfones **3** from alcohols

2P- 60

Rapid Removal and Release ability of DualPore Metal Scavenger in High Flow System

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Metal scavengers using DualPore silica beads are suitable to remove metal ions quickly to "0" ppm in a high flow system with an extremely low pressure. Recently, an actual example was reported on efficiently removal of leached palladium catalyst in C-C coupling reaction.[1] Here, adsorption selectivity of DualPore scavengers on other metal ions to remove in ppb order and their desorption characteristics are reported.
3 mL of aqueous solution in 1% hydrochloric acid containing 1000 ppb of each metal ion was flowed into a column of DualPore scavenger (0.7 mL). Depending on the ligand, the concentration of certain metal ions at the outlet of the column was less than the lower detection limit (< 5 ppb) by ICP-AES analysis, demonstrating 100% removal. Furthermore, some of adsorbed metal ions tended to be quantitatively eluted by washing the column with nitric acid, hydrochloric acid, and then thiourea solution in hydrochloric acid, suggesting the resistance to acid solvent as well as potentially repeated usage with regeneration (in Figure). The selectivity of the other transition metals will be reported on-site.

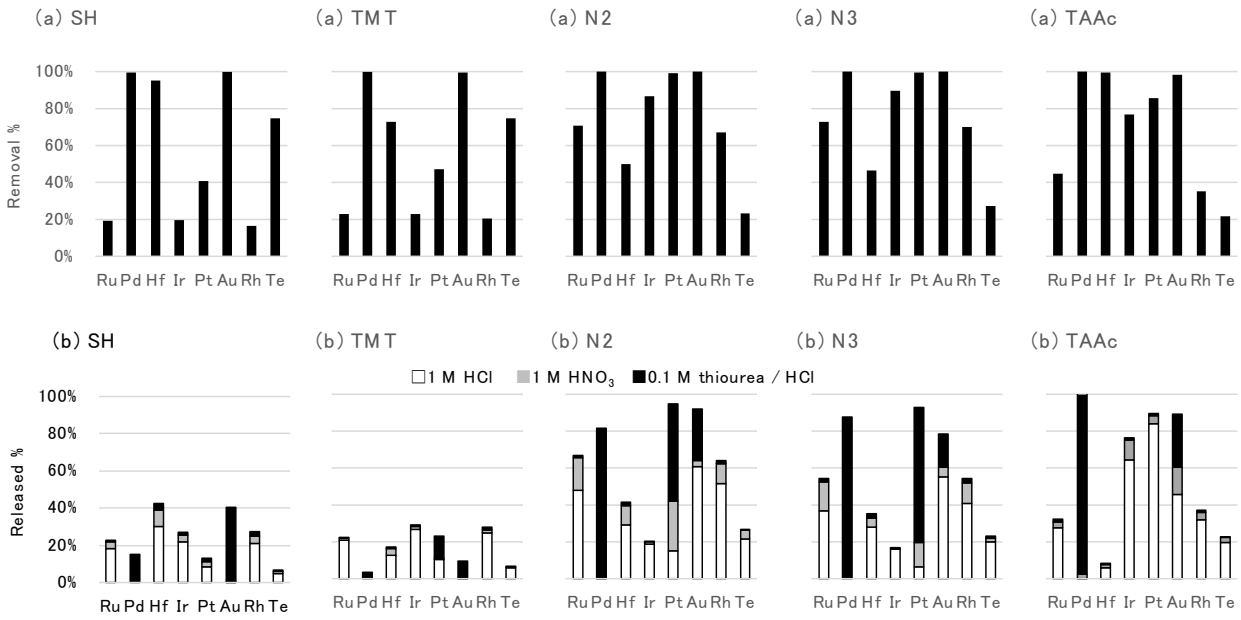

Fig. Removal ratio of metal ions from 1 ppm (a), and the accumulated released ratio (b). Ligand abbreviations; SH: mercaptopropyl, TMT: trimercaptotriazine, N2: ethylenediamine, N3: diethylenetriamine, and TAAc: ethylenediamine-triacetate.

1. T. Yamada, and H. Sajiki et al., *Org. Process Res. Dev.*, **2019**, *23*, 462-469.

2P-61

Synthesis of Aryl and Heteroaryl Tetrafluoro-λ^6-sulfanyl Chlorides

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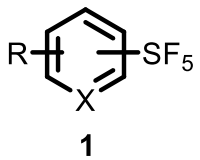
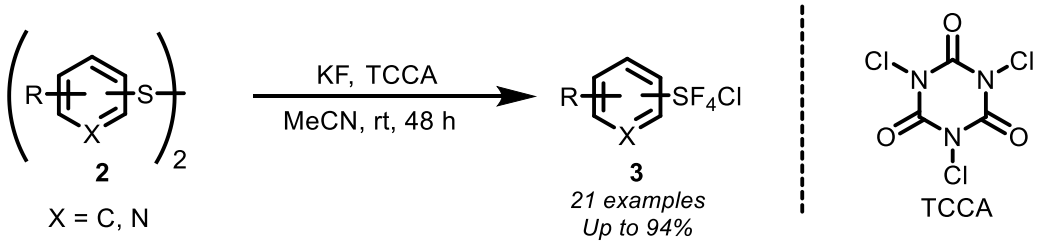
Pentafluorosulfanyl (SF_5) group has gained attention in recent years due to its combination of unique properties, including high chemical and thermal resistance, steric demand, electronegativity, and lipophilicity. The introduction of the SF_5 group into the candidates of specialty materials, agrochemicals, and pharmaceuticals would expect the real improvement of their fundamental properties. SF_5-substituted aryl and heteroaryl compounds ((Het)Ar-SF_5, **1**) can be synthesized from corresponding (Het)Ar disulfides **2** *via* tetrafluoro-λ^6-sulfanyl chlorides ((Het)Ar-SF_4Cl **3**) by oxidative chlorotetrafluorination with Cl_2/KF followed by Cl/F exchange reaction. Our group has disclosed a couple of efficient methods for the second step of Cl/F exchange reaction by using AgF, IF_5, and Ag_2CO_3, resulting in the synthesis of (Het)Ar-SF_5, **1** more easily.[1] While the first step of oxidative chlorotetrafluorination of **2** exhibits a broad substrate scope, the method requires corrosive gaseous Cl_2. Therefore, we have examined the alternative synthesis of **3** from diaryl disulfides **1** using shelf-stable chlorination reagents. After optimization of various chlorinating agents, we have found that the treatment of **2** with trichloroisocyanuric acid (TCCA) and KF in MeCN furnished **3** in moderate to good yields.[2]



1

X = C, N



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2P- 62

Ab initio modeling for Michael addition reaction of acrylic acid

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Thermal hazard of reactive chemicals shall be declared prior to scale-up considerations in process chemistry, and it is essential to gather thermal hazard information, such as reaction schemes, amount of energy release and chemical kinetics, which are called as hazardous reaction mechanisms in this article. Nowadays, hazardous reaction mechanisms of the reactive materials can be obtained with enough accuracy to due to the rapid growth of quantum chemical calculation techniques [1, 2]. The aim of this study is to obtain better understanding about reaction mechanisms of hazardous reactions.

In this study, we selected Michael addition reaction (MAR) of acrylic acid (AA) as a sample of hazardous reaction. This reaction is known to be a trigger of runaway polymerization [3], which causes equipment destruction and explosion or fire in chemical industries. To examine the reaction pathways of MAR based on ab initio calculations. The geometries of the reactants, products and transition states (TSs) were optimized at the M06-2X/6-311++G(d,p)/SCRF = (SMD, solvent=[AA]) level of theory using the Gaussian 09 program package. The energies of corresponding molecules were evaluated at the G4// M06-2X/ 6-311++G(d,p)/ SCRF=(SMD, solvent=[AA]) level of theory. Solvent effects were included by applying their self-consistent reaction field (SCRF) and solvent model density (SMD) options within program. The rate constant for reactions were calculated on the basis of transition state theory. The thermodynamic data were calculated from the partition function using statistical mechanics. These calculations were performed using the GPOP software package [4]. The detailed reaction model was developed in this study, which consists of carious kinetic parameters (a total of 9 reactions) and the thermodynamic data (for 8 species). To better understand the MAR process for AA, this model was employed to predict the MAR of AA in an adiabatic reactor at constant enthalpy and volume. These calculations were performed with the CHEMKIN-PRO software package.

To validate the detailed reaction model, the simulated heat flow curve was compared with the Calvet-type calorimeter C80 result in our previous study [5]. The simulated onset of MAR and the exothermic peak are in good agreement with the C80 results. Based on the model, it is considered that MAR of AA proceed accompanying with consumption and production-cycle of AA carboxylate anion (H_2C=CHCOO$^-$). To avoid unintended MAR of AA, addition of carboxylate anion scavenger is thought to be quite effective.

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2P-63

Attractive reaction yield on hydrolysis of phospholipid by immobilized phospholipase A1 with hydrophobic porous carrier

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Lysolecithin was anticipated a fictional component for human health produced from phospholipid. It has been widely applied in food, cosmetics and medical supplement. Supercritical carbon dioxide was expected safety solvent for industrial application. In this work, Immobilized phospholipase A_1 was applied for production of lysolecithin. Immobilization of phospholipase A1 was successfully carried out combination of adsorption and cross-linked using glutaraldehyde. Porous carrier (Accurel MP 100) was treated by methanol before adsorption of enzyme. Adsorbed amount was 20 folds higher than that of original Accurel particle. Optimal pH in adsorption was 6.5. Immobilized yield via cross linking by glutaraldehyde was 90%. Hydrolysis reaction was monitored by production of palmitic acid. The reaction was quickly initiated and the maximum initial reaction rate was appeared at the water amount of the organic phase 75μL. When 10 times repeated use performed, the reaction rate and the productivity of palmitic acid were kept 50% in the glutaraldehyde 6% used for immobilization.

2P- 64

Catalyst-free Decarboxylatiave functionalization of Lithium Pyridylacetate

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Pyridine backbone is an important substructure found in various biologically active compounds. Therefore, development of an efficient method to synthesis substituted pyridine is an important synthetic task. Fluorine-containing compounds are also important in medicinal chemistry because introducing fluorine atom(s) into biologically active compounds often improves their activity. It is known that β-oxocarboxylic acids easily release carbon dioxide to work as the enolate equivalent. This property can be attributed to resonance stabilization of the resulting enolate. Using this property, our research group previously reported highly enantioselective decarboxylative chlorination of tertiary β-ketocarboxylic acids with a chiral primary amine catalyst. Recently, we also reported the decarboxylative fluorination of β-ketocarboxylic acids under catalyst-free conditions. Based on these previous works, we envisaged that 2-pyridylacetic acids would occur decarboxylation in a manner similar to β-ketocarboxylic acids and treatment with electrophilic fluorinating reagent would realize the decarboxylative fluorination of 2-pyridylacetic acids.

First, we carried out the decarboxylative fluorination of 2-pyridylacetic acid with Selectfluor. As a result, we obtained the desired fluorinated product in 77% yield along with 18% of protonated product. While examining the reaction conditions, we found that decarboxylative fluorination of lithium 2-pyridylacetes yield fluorinated product in 90% yield without yielding protonated product. Furthermore, alkaline hydrolysis of methyl 2-pyridylacetates and subsequent decarboxylative fluorination could be performed in one-pot manner to afford the desired product in good yield, up to 99% yield.

Next, we examined the use of electrophilic trifluoromethylthiolation reagent in decarboxylative functionalization. After the screening of several trifluoromethylthiolation reagents, we found that the use of *N*-trifluoromethylthiobenzenesulfonimide worked efficiently in decarboxylative trifluoromethylthiolation of lithium 2-pyridylacetates to afford the desired product with up to 91% yield.

In conclusion, we developed the decarboxylative fluorination and trifluoromethylthiolation of lithium 2-pyridylacetates. Alkaline hydrolysis of methyl 2-pyridylacetates and subsequent decarboxylative functionalization could be performed in a one-pot manner. Formally, the method enables to convert a methyl ester function into a fluorine atom or a SCF_3 group in a one-pot manner.

2P- 65

Synthetic Strategy for Process Optimization of a PDE10A Inhibitor Consisting of Pyrazolopyrimidine and Quinoxaline as Key Units

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"What is your ultimate manufacturing process for a chemically synthesized drug substance?" Our answer is that the ultimate process does not only consistently produce drug substances with high quality, but also is productive using a synthetic route that can achieve the following three requirements at low cost. First, high quality materials (i.e., the amount of impurity is less than 0.05%) must be needed. Second, the reaction should be highly selective (i.e., the selectivity is >1000:1) and can suppress by-products. Third, the isolation step of drug substance can improve chemical and physical quality and do not require additional purification. However, it is not easy to achieve the above requirements with limited resources and time. While processes are optimized step by step toward the goal of commercial process from the early stage of development, the commercial process is far from the desired ultimate process. To achieve the ultimate process with limited resources and time by the commercial stage, the risk management of process development is important. In the commercial stage, it is important to pursue the process with low cost and high productivity, on the other hand, the consistent quality of drug substance is the most important and challenging issue regardless of the complexity of drug substance structure in the development stage. An initial pilot manufacturing using less commonly available raw materials and less robust methods, for example, in the early stages of development, may result in an unexpected contamination of impurities. The failure cannot be controlled by the quality of raw materials or reaction conditions, and causes not to provide timely supplies of drug substances. Therefore, in the early stages of development, the following items have high priorities, that is, the powerful tools for quality control, the determination of intermediates that can be crystallized to remove impurities effectively and efficiently, and the improvement for robustness of process to reduce the quality deterioration.

In this poster presentation, we will report on our synthetic strategy to establish the consistent quality of the promising candidate of a PDE10A inhibitor.[*1] We would like to share the information of the following items, that is, (i) the quality control of raw materials to prevent the contamination of unexpected impurities, (ii) optimization of reaction conditions to suppress by-products, and (iii) crystallized purification of intermediates to remove impurities in the drug substance step. In addition, we would like to present our future manufacturing method.

[*1] T. Yamagami, R. Kobayashi, N. Moriyama, H. Horiuchi, E. Toyofuku, Y. Kadoh, E. Kawanishi, S. Izumoto, H. Hiramatsu, T. Nanjo, M. Sugino, M. Utsugi, and Y. Moritani *Org. Process Res. Dev.* **2019,** *23,* 578.

2P- 66

Nucleophilic C2-arylation of quinolines using diaryliodonium salts

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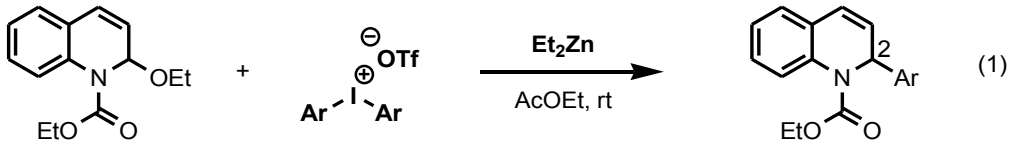
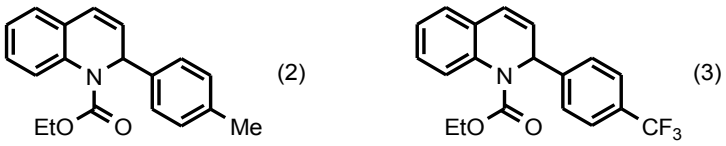
Quinoline skeletons are important scaffolds, which are found in many pharmaceuticals and biologically active compounds. Therefore, the development of regioselective functionalization of quinolines is highly desirable. 1-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinolines (EEDQs) have been considered as useful *N*-acylquinolinium precursors because of their availability and stability. Diaryliodonium salts, also named diaryl-λ^3-iodanes, serve as versatile electrophilic arylating agents with a variety of carbon and heteroatom nucleophiles under both metal-free and metal-catalyzed conditions. Originally, EEDQs should not react with diaryliodonium salts because both have the same nature as electrophilic reagent. On the contrary, we develop the reaction EEDQs undergo an addition reaction with diaryliodonium salts using diethylzinc (eq 1). The present reaction proceeded under mild conditions without any transition metal catalyst, affording C-2 arylated quinolines in good to high yield. We estimate that diethylzinc participate in umpolung of diaryliodonium salts



Under the optimized conditions, the substrate scope was investigated in symmetry diaryliodonium triflates. The benzene ring bearing electron-donating substituent at *para*-position such as CH_3 afforded the products in high yields (eq 2). Electron-withdrawing group didn't have significant effect for yields (eq 3).



We present the details of reaction condition screening, effect of various symmetrical and asymmetrical diaryliodonium triflates and selectivity for the arylation products.

2P-67

Preparation of Diaryl Ether Using Ullmann Reaction and Its Application to Ellagitannin Synthesis

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Synthesis of highly oxygenated diaryl ethers is difficult due to severe steric hindrance. Functionalized diaryl ethers are components of many ellagitannins, a family of polyphenolic compounds that exhibit various biological activities and are found in many higher plants. The synthesis of diaryl ethers is an important step in ellagitannin synthesis. In 1996, Feldman and co-workers constructed a highly functionalized diaryl ether and succeeded in the total synthesis of a simple ellagitannin[1]. Despite their pioneering work, the synthesis of other diaryl ethers remains difficult. In this study, we prepared dehydrodigallic acid and its derivative, which are generally found in natural ellagitannins, using the Ullmann reaction[2]. This method can be widely applied to the synthesis of multi-substituted diaryl ether compounds.

We investigated the preparation of diaryl ethers using the classical Ullmann reaction between phenol (**1**) and aryl bromide (**2**) in the presence of copper dust and DMA (Figure 1). Dehydrodigallic acid was successfully prepared from a diaryl ether derivative (**3**) using a two-step transformation. Isodehydrodigallic acid and valoneic acid dilactone were also synthesized using this method. Finally, we attempted total synthesis of an ellagitannin containing diaryl ether as a partial structure.

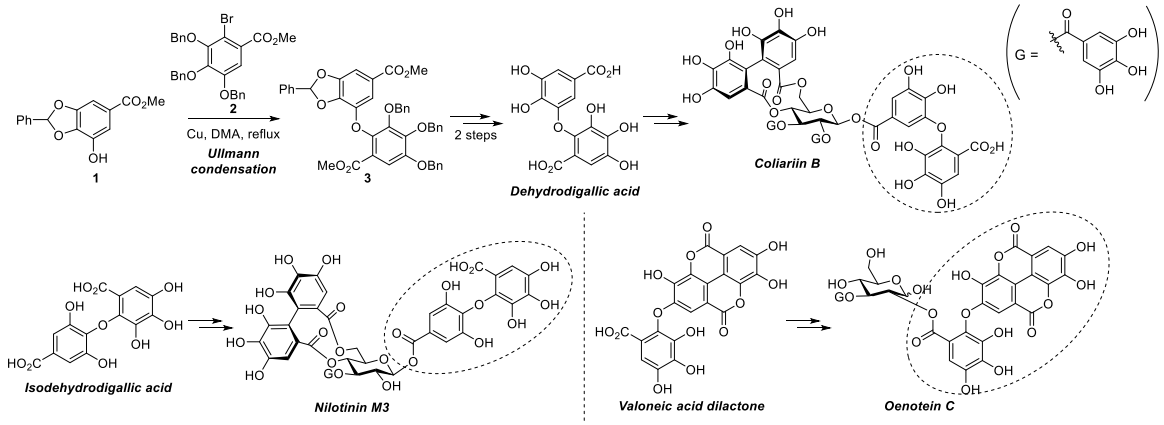

Figure 1.

1) Feldman K. S., Quideau S., Appel H. M., *J. Org. Chem.*, **61**, 6656-6665 (1996)
2) Shioe K., Ishikura S., Horino Y., Abe H., *Chem. Pharm., Bull.*, **61**, 1308-1314 (2013)

2P-68

Investigation of Purity Determination of Hygroscopic Compound using qNMR

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quantitative NMR (qNMR) is an innovative analytical technique that differs in principle from conventional chromatographic analysis by HPLC and GC. qNMR permits to efficiently obtain an absolute, precise, accurate and SI-traceable value by direct measurement, rather than resorting to the mass balance approach that requires quantification and subtraction of all sample impurities. qNMR is used as a compendial analytical method in Japanese Pharmacopoeia (JP), Japan's Specifications and Standards for Food Additives (JSSFD) and Japanese Industrial Standards (JIS). In this presentation, we discuss the application of this method to purity determination of [6]-Shogaol which is an active pharmaceutical ingredient included in Ginger, one of the prominent Kampo medicines. In sample preparation procedure, it is difficult to perform a price weighing due to its hygroscopic property and different moisture content according to ambient relative humidity. We carried out qNMR measurement in accordance with measurement conditions of JP except sample preparation. In sample preparation procedure, we performed weighing with ultra-micro balance in two controlled different humidity environments (high relative humidity: around 10%, low relative humidity: around 59%) and after mass equilibration by the high and low ambient relative humidity. As a result of the investigation, we could obtain accurate analytical values using qNMR corresponding to the high and low ambient relative humidity.

2P- 69

Regioselective Formylation of Pyrrole Derivatives with Crystalline Vilsmeier reagent

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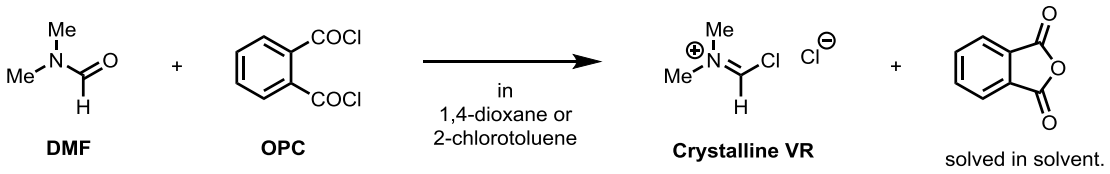
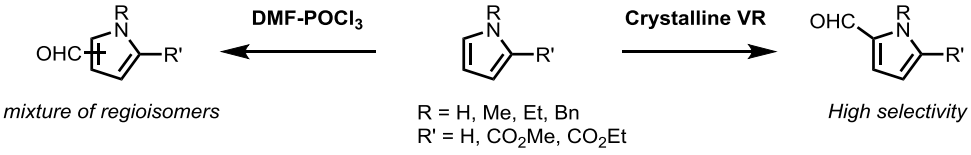
Direct introduction of the formyl group into the desired position of the aromatic nucleus is an important synthetic method because the aromatic aldehyde can be transformed to various functional groups in organic molecule. Direct formylation of aromatic compounds is routinely accomplished by using Vilsmeier-Haack reagent (VR). However, typical preparation methods of VR are a treatment of *N*,*N*'-dimethylformamide (DMF) with toxic chlorinating agents such as phosphoryl oxychloride, thionyl chloride and phosgene. In addition, this reagent often gives a mixture of differently substituted formylation products. In previous, we developed eco-friendly preparation of VR using phthaloyl dichloride (OPC) to avoid high toxic and environmental load chlorinating agents[1]. VR can be easily isolated as a solid form by filteration, and the crystalline VR can be used in a preferred solvent.



Scheme 1. Preparation of crystalline VR from DMF-OPC.

Pyrrole derivatives containing formyl group are known to be useful intermediates for pharmaceutical synthesis. Direct formylation into pyrrole rings by VR was examined, in which conventional method (DMF-$POCl_3$) gives a mixture of regioisomers of formyl pyrroles, whereas crystalline VR gave mostly a single regioisomer. For examples, although a treatment of ethyl pyrrole-2-carboxylate with DMF-$POCl_3$ afforded a mixture of 5-formyl and 4-formyl derivatives with 75/25, that reaction with crystalline VR gave ethyl 5-formylpyrrole-2-carboxylate with excellent selectivity: the regioselectivity in near perfect > 99.9/ < 0.1[2]. For another examples, formylations of 1-methyl, 1-ethyl, and 1-benzyl pyrrole with the crystalline VR resulted in α-isomer with higher regioselectivity.



Scheme 2. Synthesis of pyrrole derivatives with crystalline VR.

reference

1) Kimura, Y.; Matsuura, D.; Hanawa, T.; Kobayashi, Y., *Tetrahedron Lett.* **2012**, *53*, 1116. 2) Warashina, T.; Matsuura D.; Sengoku, T.; Takahashi, M.; Yoda, H.; Kimura, Y. *Org. Process Res. Dev.* **2019**, *23*, 614.

2P- 70

Development of multi-functional NHC catalysts bearing pyridine moiety: Application to catalytic asymmetric reactions

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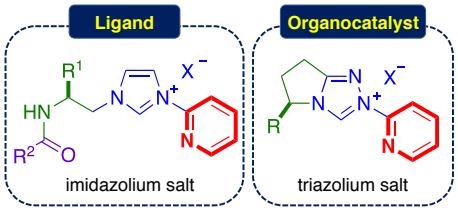
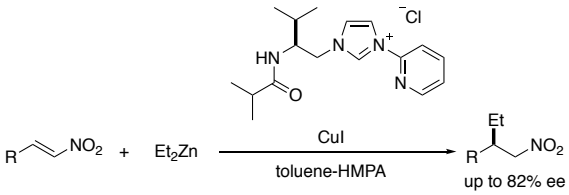
The application of *N*-heterocyclic carbenes (NHCs) in organic synthesis has dramatically increased since Bertrand, Arduengo and their coworkers reported the first stable nucleophilic carbene around 1990. NHCs have become extremely popular ligands in organometallic chemistry and many complexes incorporating NHCs have been used in synthetic methods. In addition, NHCs act as organocatalysts and the majority of these processes are initiated by nucleophilic attack of the carbene onto carbonyl groups present in organic substrates. Applications of chiral NHCs to catalytic asymmetric reactions have been reported, with good to excellent stereoselectivity. Here, amino acid-derived chiral imidazolium and triazolium salts, each bearing a pyridine ring, were developed as *N*-heterocyclic carbene catalysts.



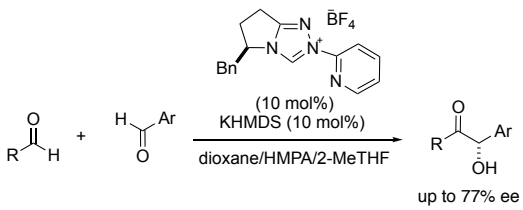
1) Chiral NHC ligands bearing a pyridine moiety in copper-catalyzed addition of diethylzinc to nitroalkenes

The use of chiral nitroalkanes as intermediates in synthetic reactions is due to the versatile functionality of the nitro group. As excellent Michael acceptors, nitroalkenes add to the range of functionalized nucleophiles. We have examined the 1,4-addition of dialkylzinc reagents to nitroalkenes catalyzed by a combination of CuI and amino acid-based chiral imidazolium salts containing a pyridine ring to give the corresponding chiral nitroalkanes. The advantages of this process include high yields, broad and complementary substrate scope, and good to high enantioselectivities.



2) Asymmetric cross-benzoin condensation promoted by a chiral triazolium precatalyst bearing a pyridine moiety

We have developed a cross-benzoin condensation reaction catalyzed by NHC prepared from chiral triazolium salts bearing a pyridine ring, giving α-hydroxy ketones with reasonable chemical yields and enantioselectivities.



2P- 71

Synthesis of Ethynyl Benziodoxolone (EBX)−Acetonitrile Complex and Reaction with Sulfonamide

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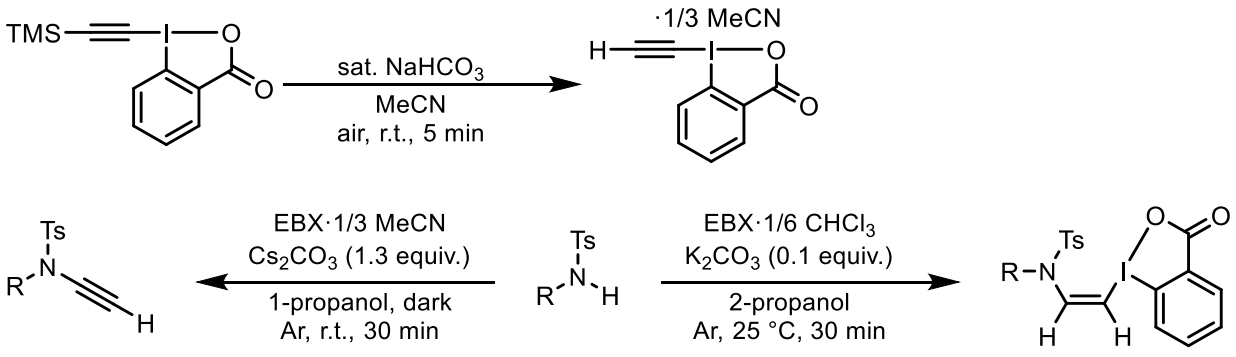
Alkyne is the simple two carbon source and is used for various reactions including dipolar cycloaddition such as click chemistry. However, when introducing alkyne directly, a transition metal catalyst is usually required. For that reason, a milder and metal free method of introducing alkyne is required. Recently, the direct introduction of alkyne using ethynyl benziodoxolone (EBX) has attracted attention. It was reported by Waser that EBX was synthesized by deprotecting silyl-protected EBX (TMS-EBX) in situ using fluoride etc and it has high reactivity as an electrophile.[1] However, isolation of EBX had not been reported because of the instability of EBX. Coordination of additional ligands through hypervalent bonding and secondary bonding has been used to modify the stability and reactivity of hypervalent iodine.

Therefore, we attempted the synthesis and isolation of EBX using coordination stabilization by acetonitrile. As a result, we succeeded in the synthesis and isolation of EBX-acetonitrile complex, and determined the detailed structure by single crystal X-ray structural analysis.[2] In addition, we performed *N*-ethynylation of sulfonamide using EBX and gave the desired product in up to 90% isolated yield. Furthermore, by tuning the reaction conditions, we succeeded in obtaining an amide adduct of EBX, β-amido vinylbenziodoxolones. Interestingly, this addition is *cis*-selective and the addition product can be used to introduce the *cis*-enamide into various compounds using cross coupling reactions.



1) González, D. F.; Brand, J. P.; Waser, J., *Chem. Eur. J.* **2010**, *16*, 9457-9461.
2) Yudasaka, M.; Shimbo, D.; Maruyama, T.; Tada, N.; Itoh, A. *Org. Lett.* **2019**, *21,* 1098-1102.

2P- 72

Divergent and scalable synthesis of β-amino acid analogues by catalytic enantioselective addition of glyoxylate cyanohydrin to imines

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β-Amino acid motif is an important non-proteinogenic amino acid, which can dramatically change a physical property and bioactivity of a peptide. In particular, α-keto/hydroxy-β-amino acid is an important structure found in many bioactive natural products and pharmaceuticals (Figure 1). In addition, α-keto-β-amino acid can be proceeded the decarboxylative condensation including KAHA ligation[1] developed by Bode and coworkers. For this reason, a catalytic and stereoselective transformation to rapidly afford a series of β-amino acids is demanded.

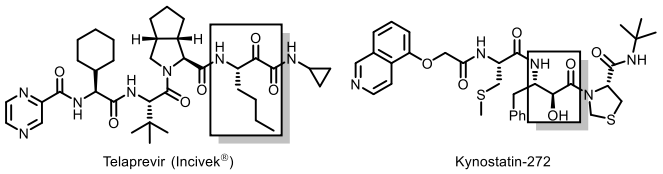
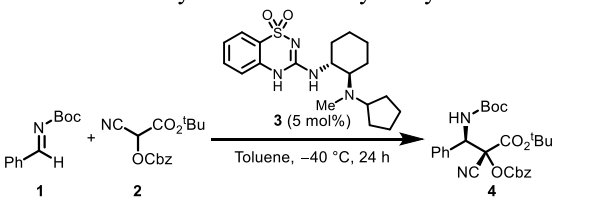


Figure 1. α-Keto/hydroxy-β-amino acid motif

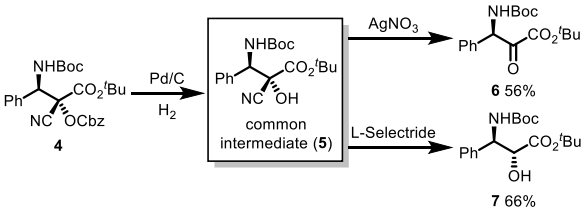
In order to establish a new method which allows divergent synthesis of α-keto/hydroxy-β-amino acids, we focused on glyoxylate cyanohydrin as a C_2 nucleophile, and envisioned that Mannich-type addition of cyanohydrin to imines afforded α-keto-β-amino acid equivalents. Based on this concept, we screened various bifunctional amino hydrogen-bond donor catalysts for the reaction of *N*-Boc imine **1** and cyanohydrin **2**. As a result, cyclopentyl group substituted aminobenzothiadiazine catalyst **3** provided the Mannich adduct **4** as an almost single stereoisomer, 93% yield, 97% ee, 31:1 dr (Scheme 1). In addition, this catalytic system is easily scalable, and the adduct **4** could be prepared in gram scale even with 1 mol% catalyst loading without a loss of yield and stereoselectivity.

Scheme 1. Catalytic addition of cyanohydrin to imine



Subsequently, we derivatized the Mannich adduct **4** to β-amino acid analogues (Scheme 2). The deprotection of Cbz group followed by treatment with aqueous silver nitrate provided β-amino-α-ketoester **6** in 56% yield over 2 steps. In addition, the reduction of intermediate **5** using L-Selectride provided *anti*-β-amino-α-hydroxyester **7** in 66% yield over 2 steps. In both cases, stereochemical information was maintained during the transformations. These results show that the Mannich-type addition could be applied for the efficient synthesis of a variety of chiral building blocks including useful bioactive compounds.

Scheme 2. Derivatization of the Mannich adduct



Reference : 1) Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1248.

2P- 73

Developmental Research of Ynamides Synthesis Method Using Copper Catalyst and Hypervalent Iodine Compounds

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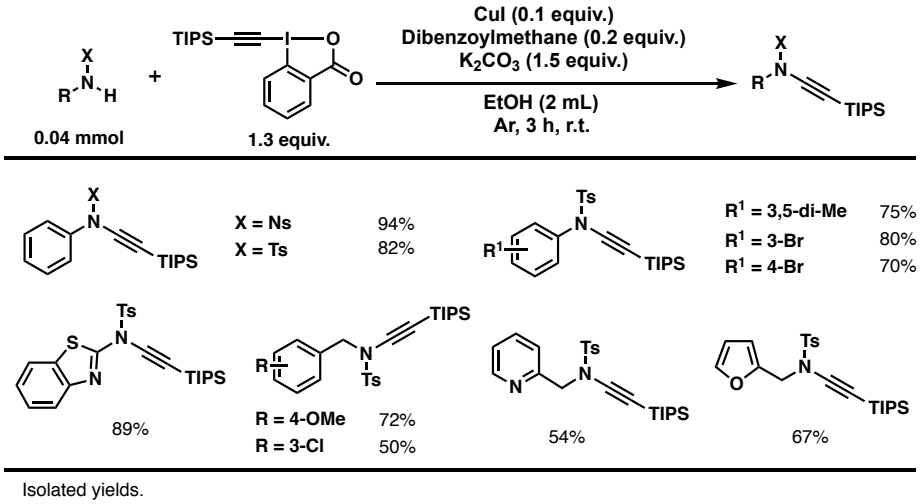
Ynamides are unique and synthetically valuable building blocks for organic synthesis and other fields because it has high reactivity and stability, which can be controlled by changing the protective group. The electron-donating ability of the ynamide nitrogen polarizes the triple bond, which allows the regioselective synthesis of complex products by having both nucleophilic and electrophilic carbon.

Ynamides have been usually synthesized by using amide and alkynyl bromides or terminal alkynes in the presence of a copper catalyst at high temperature. In addition, although dibromoalkenes and hypervalent iodine compounds have also been used for the synthesis of ynamides, they require strong bases. On the other hand, a combination of a hypervalent iodine compound and a copper catalyst has hardly been used.[1]

In the course of our study on the synthesis of ynamide from amino acid derivatives using cyclic hypervalent iodine, ethynyl benziodoxolone (EBX), at ambient temperature,[2] we aimed to develop the ynamide synthesis method under mild conditions by using alkynyl benziodoxolone and a copper catalyst.

As a result of the examination of reaction conditions using *N*-tosyl aniline and TIPS-EBX, ynamide was obtained in 82% yield at room temperature for 3 hours by using copper iodide as a copper catalyst, dibenzoylmethane as a ligand, and potassium carbonate as a base in dehydrated ethanol. The examination of reaction scope using sulfonamides revealed that it is applicable to a variety of substrates.



Isolated yields.

1) Tokimizu, Y.; Oishi, S.; Fujii,, N.; Ohno, H *Org. Lett.* **2014**, *16*, 3138−3141

2) Yudasaka, M.; Shimbo, D.; Maruyama, T.; Tada, N.; Itoh, A. *Org. Lett*. **2019**, *21*, 1098−1102.

2P- 74

Synthetic Study of Total Synthesis of Sigillin A

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Sigillins are unique polychlorinated natural products derived from polyketides, which were isolated from the snow flea *Ceratophysella sigillata* by Schulz in 2015.[1] The structure of sigillin A was confirmed by X-ray crystallographic analysis (Figure 1). Sigillin A possesses *trans*-fused octahydroisocoumarin skeleton decorated with five chlorine atoms. In addition, it has four consecutive stereocenters including two quaternary carbons. These structural features of sigillin A make us interested in its total synthesis.

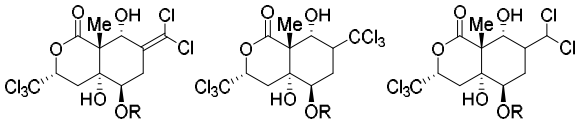
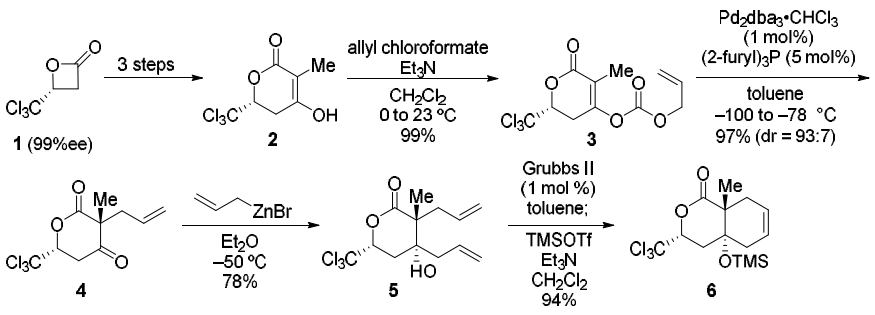


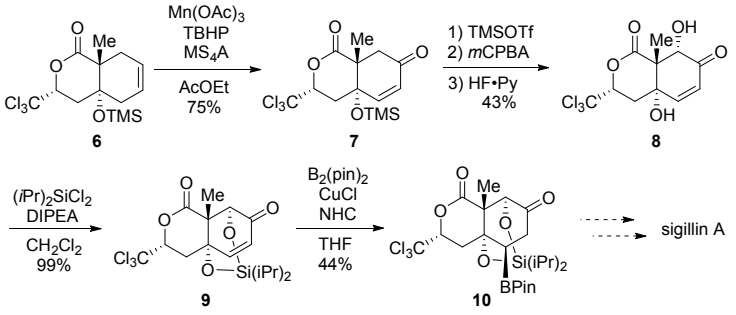
Figure 1. The sigillins

The synthesis of octahydroisocoumarin core was begun with known enantiopure β-lactone **1**. lactone **2** could be prepared from β-lactone **1** in three steps. After several investigations of electrophilic allylation of lactone **2**, allyl carbonate **3** could be used in the allylation to give compound **4** with high diastereoselectivity. Nucleophilic allylation of **4** followed by RCM and silyl protection afforded the carbon framework **6**.



Scheme 1. Synthesis of Octahydroisocoumarin Core

Mn-catalyzed allylic oxidation of **6** proceeded at an unexpected position to obtain enone **7**. Rubottom oxidation of **7** followed by deprotection gave diol **8** in moderate yield. Conjugate addition of boron pinacol ester to enone **9** was accomplished to give **10**, from which transformation into sigillin A is currently in progress.



Scheme 2. Toward the Synthesis of Sigilln A

Reference 1) Schulz, S. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 7698.

2P- 75

KHMDS-Promoted Enolate–Olefin Metathesis

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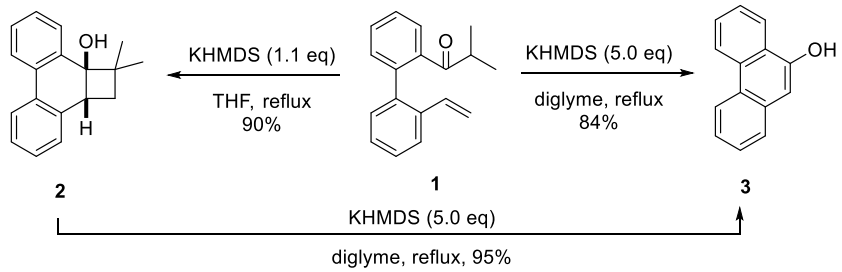
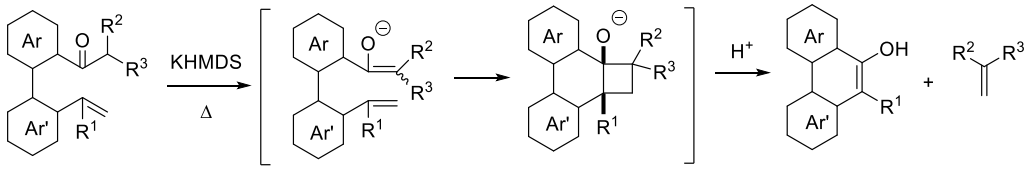
Olefin metathesis is a quite useful and powerful synthetic method which entails the redistribution of two alkenes by the scission and regeneration of carbon-carbon double bonds. Because of its synthetic utility and functional group tolerance the metathesis is often applied in the late stage of the synthesis. Since the development of the olefin metathesis, its related metathesis reactions such as enyne metathesis, carbonyl–ene metathesis have been investigated. In this paper, we wish to describe the new entry of the metathesis reaction, intramolecular enolate-olefin metathesis, giving polyaromatic hydrocarbons.

Recently, we have reported an intramolecular [2+2] cycloaddition promoted by potassium hexamethyldisilazide (KHMDS). When biaryl compounds **1** bearing acyl and vinyl moieties at the 2 and 2' positions, respectively, was treated with KHMDS in refluxing THF (bp 66 °C), polycyclic cyclobutanols **2** was obtained in 90% yield through stepwise 8-*endo*-trig–4-*exo*-trig anionic cyclization, which is formally an intramolecular [2+2] cycloaddition. We accidentally found that the same reaction of **1** in refluxing diglyme (bp 162 °C) afforded 9-phenanthrol **3** in 95%. Further study revealed that **3** was formed through retro [2+2] cycloaddition of **2**. Thus, we call this unique reaction "enolate-olefin metathesis" (Scheme 2). Gram-scale synthesis, substrate scope, mechanistic studies and synthetic application will be presented at the poster session.



Scheme 1. Reaction of biaryl **1** in the presence of KHMDS



Scheme 2. Reaction pathway of the enolate-olefin metathesis

[1] Nagamoto, Y.; Yamaoka, Y.; Fujimura, S.; Takemoto, Y.; Takasu, K. *Org. Lett.* **2014**, *16*, 1008–1011.

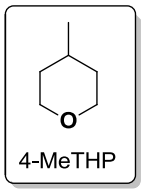
[2] Ogawa, N.; Yamaoka, Y.; Yamada, K.; Takasu, K. *Org. Lett.* **2017**, *19*, 3327–3330.

2P- 76

Assessment of 4-Methyltetrahydropyran (4-MeTHP) as an Organic Reaction Solvent

Tomoki Tamura,* Takashi Kawakami, Saki Yoshimoto, Araki Masuyama, Shoji Kobayashi
Graduate School of Engineering, Osaka Institute of Technology
5-16-1, Ohmiya, Asahi-ku, Osaka, 535-8585, Japan
m1m18507@st.oit.ac.jp

4-Methyltetrahydropyran (4-MeTHP) is hydrophobic cyclic ether expected as a reaction solvent alternative to conventional ethers, especially, in the process chemistry field. In this presentation, we report the wide applications of 4-MeTHP in various types of organic reactions. This study revealed that 4-MeTHP was a promising alternative to not only conventional ethers but also harmful dichloromethane (DCM).



bp: 105 °C
mp: -92 °C
density: 0.86 gcm-3
solubility in water: 1.5 wt% (23 °C)
flash point: 6.5 °C
ralative parmittivity: 5.2

The Grignard reaction is one of the most important organic reactions, however, many of the commercially available Grignard reagents are prepared in THF (difficult to recover) or Et_2O (flammable), which is not suitable for industrial usage. We showed that 4-MeTHP was compatible with the formation of unstable Grignard reagents such as propargyl- and *o*-chloromagnesium bromide, as well as phenylmagnesium chloride, all of which were difficult to prepare in CPME (Figure 1).

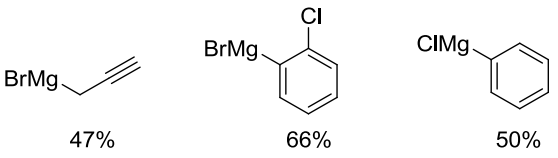
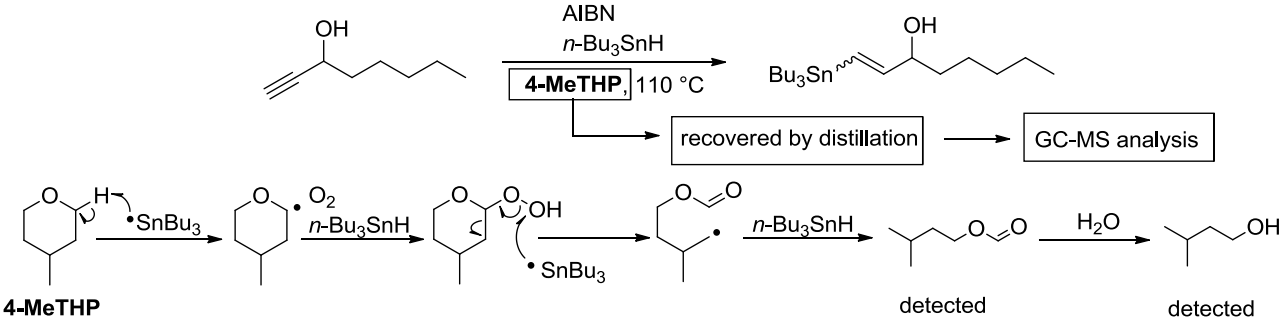


Figure 1. Grignard reagents difficult to prepare in CPME. Yields indicated are isolated yields of alcohol based on R-X after the reactions with benzaldehyde.

4-MeTHP also served as a solvent for a variety of organometallic coupling reactions, oxidation, reduction, epoxidation, esterification, amidation, halogen-metal exchange, conjugate addition, ring-closing metathesis and so on, although the certain Lewis acid-promoted reactions didn't proceed in 4-MeTHP. Under the radical conditions, 4-MeTHP was found more stable than 2-MeTHF, making the use of the former solvent more preferable. A minor but possible degradation pathway of 4-MeTHP under the radical addition conditions was elucidated on the basis of GC-MS analyses (Scheme 1).



Scheme 1. A possible degradation pathway of 4-MeTHP under the radical addition conditions.

2P- 77

Preparation of carboxymethyl cellulose, calcium alginate and chitosan membrane involved with mechanical strength

Tomohiro Nakata* and Masanao Imai

Course in Bioresource Utilization Sciences,
Graduate School of Bioresource Sciences, Nihon University
1866 Kameino, Fujisawa, Kanagawa-pref. 252-0880, Japan

Chitosan, calcium alginate and carboxymethyl cellulose-aluminum membrane were successfully prepared by desired casting methods, respectively. The membranes were water-insoluble and optically transparent to apply for practical use in water treatment. Mechanical strength of the membrane was evaluated by maximum stress and maximum elongation ratio at membrane rupture. The maximum stress of chitosan membrane was superior to other biopolymer membranes. Measured value of mechanical strength (Maximum stress and elongation ratio) was depended on the extension speed of sample piece of membrane. Measuring by high extension speed (60 mm / min) brought higher value of mechanical strength than that of low extension speed (10 mm / min). That was due to drying of membrane during measurement. Volumetric water permeation flux was linearly proportional to the pressure leaded on the membranes. Especially on chitosan membrane, the volumetric water permeation flux for that of lower concentration of casting solution was non-linearly increased with increasing pressure. Construction of water permeation channel in the chitosan membrane was depended on the chitosan concentration of casting solution. Effective diffusion coefficient of methyl orange (Mw 327) was decayed 10 fold with increasing chitosan solution from 1.0 to 3.0 wt%. Density of polymer networks in chitosan membranes significantly affected on the structure of mass transfer channel in the membrane. The chitosan membrane was anticipated as a molecular sieve for water soluble component.

Author Index

Author Index

*** Presenter**

〔H〕

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〔U〕

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The 4th International Symposium on Process Chemistry

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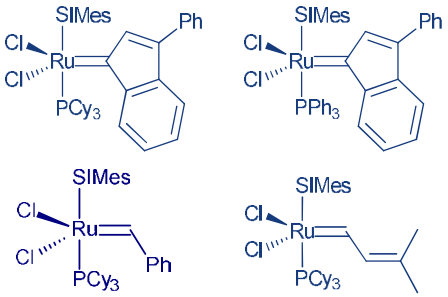

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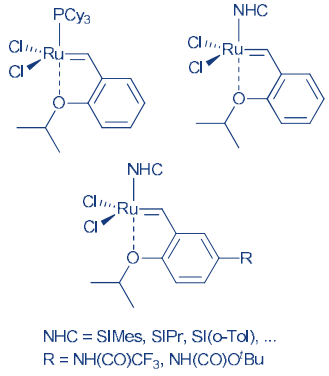

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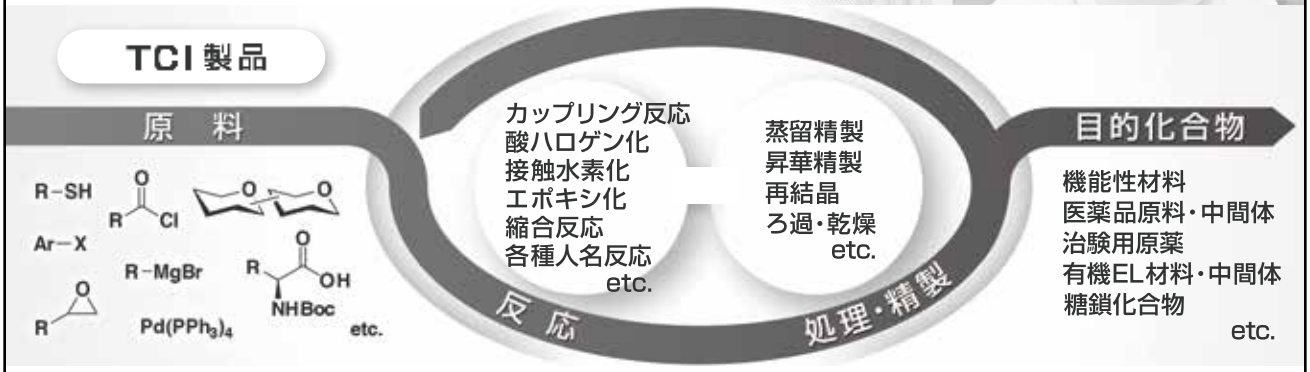

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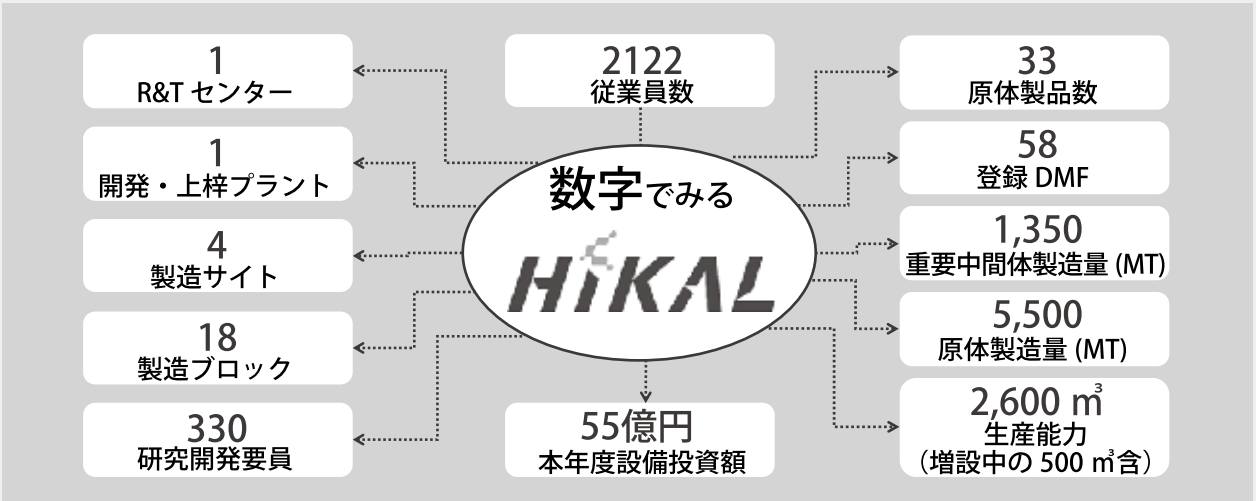

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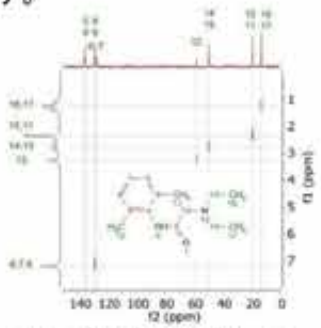

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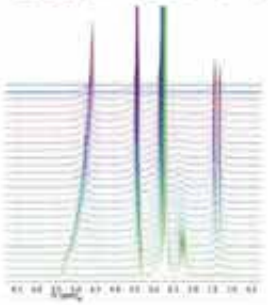

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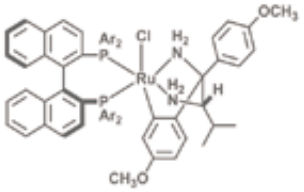
Powerful Tools for Your Smart and Practical Process

- Takasago catalysts help develop economical and eco-friendly processes
- Consistent quality from reagent scale to commercial scale*
- Based on over 30 years industrial commercial experience

*Reagent quantity is available from Strem Chemicals Inc., Sigma-Aldrich Co. LLC. and Tokyo Chemical Industry Co., LTD.

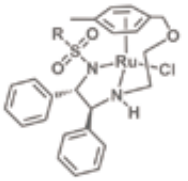
RUCY®

Asymmetric Hydrogenation of ketone



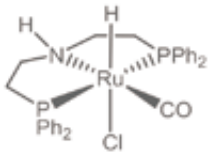
DENEB®

Asymmetric Transfer Hydrogenation of ketone



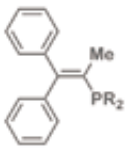
Ru-MACHO®

Ester Reduction



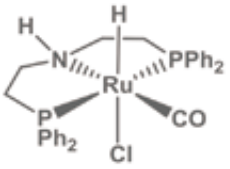
BRIDP®

Coupling Ligands

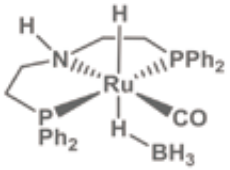


For more information, please search by "TAKASAGO CATALYST" ▶▶ TAKASAGO CATALYST

Ru-MACHO®／Ru-MACHO®-BH



Ru-MACHO®

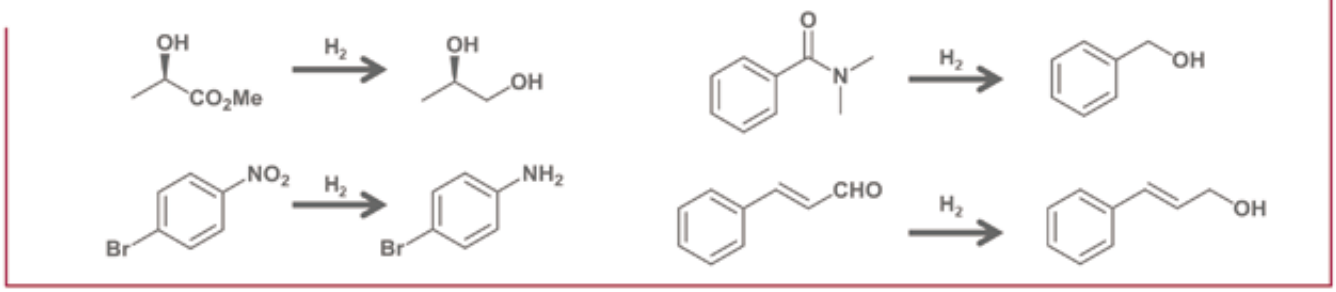


Ru-MACHO®-BH

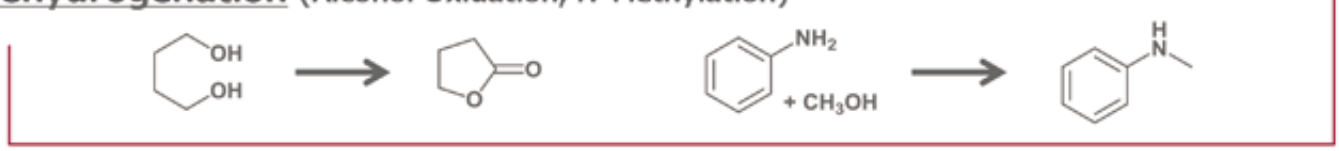
Robust, Safe, Efficient and Eco-Friendly

- Replacement of LAH and $NaBH_4$
- No metal hydride waste
- Low catalyst loading 0.1～0.0025 mol%
- Work even less than 1MPa of H_2 gas
- High heat stability (applicable over 200℃)

Hydrogenation (Ester, Nitro, Amide, Aldehyde, Nitrile)



Dehydrogenation (Alcohol Oxidation, *N*-Methylation)



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