The 5th International Symposium on Process Chemistry

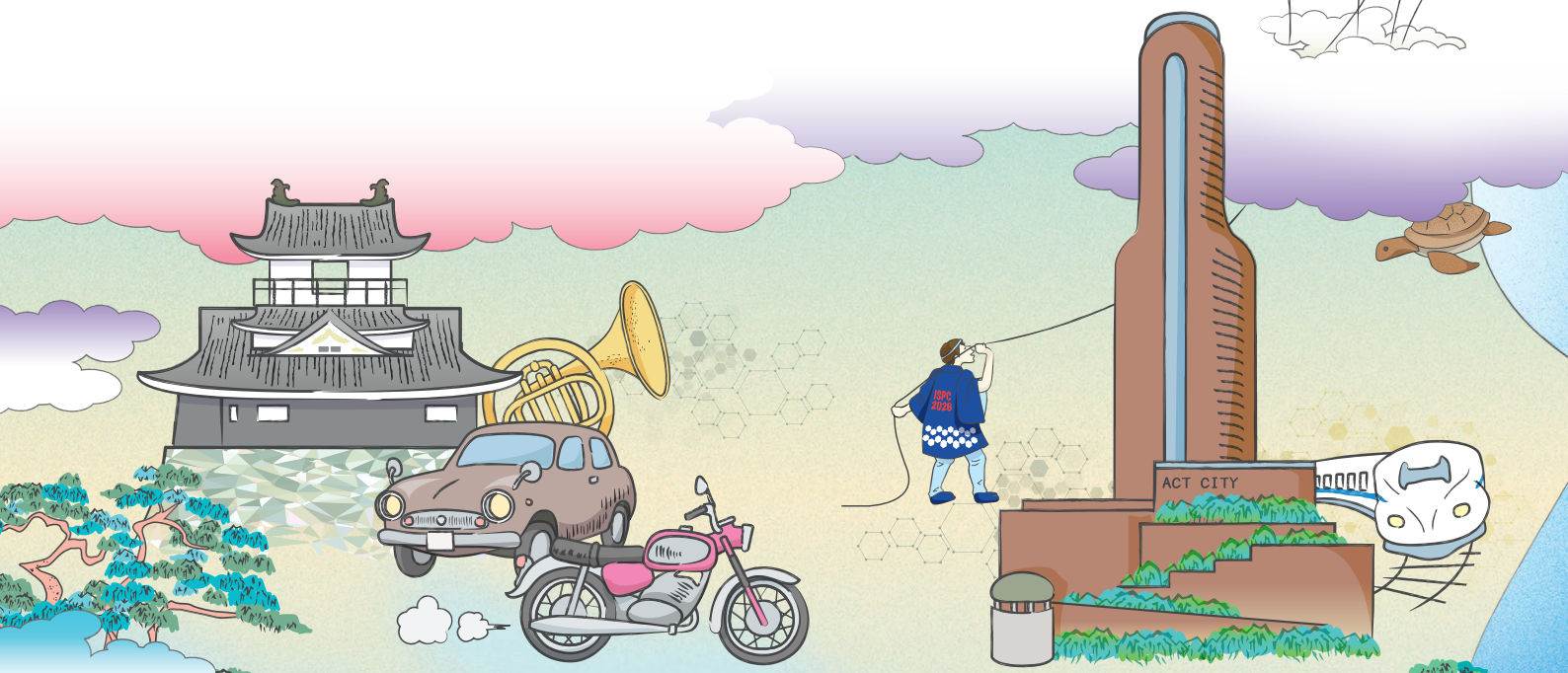
ISPC 2026

July 1 (Wed.) → 3 (Fri.), 2026

Hamamatsu, JAPAN

ACTCITY Hamamatsu

Abstracts



J.S.P.C

Japanese Society for Process Chemistry

Organizer

The Japanese Society for Process Chemistry

Support

The Society of Synthetic Organic Chemistry, Japan / Kinka Chemical Society, Japan /
The Society of Separation Process Engineers, Japan / Chem-Station /
Ichimura Foundation for New Technology / Hamamatsu & Lake Hamana Tourism Bureau /
Shizuoka University / Shizuoka University Research Institute of Green Science and Technology

EasyMax 102i Released!

有機合成や晶析のプロセス最適化

メトラー・トレド

ロングセラー EasyMax102 の

新モデル EasyMax 102i 登場! 新しくなったポイントとは?

- 有機合成の主な操作（温調や攪拌、試薬添加）を自動化
- 使いやすい機能はそのままに、新しくカメラ搭載。リアクタの中をリアルタイム表示
- pHセンサーとEasyMax 102i は追加ユニット不要で直接接続、3点校正が追加
- OPCUA による外部制御も可能

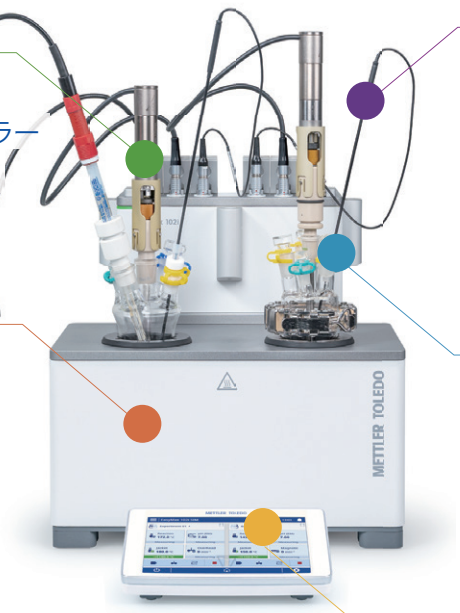
Stirring

メカニカル攪拌
マグネチックスターラー
ハイトルクモーター

Observation

HD カメラ搭載により
イベントを逃さず記録





EasyMax 102i
製品ページはこちら

Temperature

-40℃ ～ +180℃

Dosing

容量
重量試薬添加

Sampling

手動サンプリング
EasySampler
PAT との連携

展示ブースに実機を展示中！ 現地にてお待ちしております！

メトラー・トレド株式会社　ラボインスツルメンツ事業部　オートケムチーム
〒110-0008 東京都台東区池之端 2-9-7 池之端日殖ビル 6F
Email: support.jp@mt.com　電話 : 03-5815-5515（受付時間 平日 9:00~12:00、13:00~17:45）

METTLER TOLEDO

The 5th International Symposium on Process Chemistry

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Dear Colleagues,

It is our great pleasure and privilege to invite you to attend the International Symposium on Process Chemistry (ISPC 2026), taking place from July 1–3, 2026 in Hamamatsu, Shizuoka, under the auspices of the Japanese Society for Process Chemistry (JSPC).

Since its founding in 2000, JSPC has hosted annual summer and winter symposia, bringing together professionals and researchers from pharmaceutical and chemical industries, manufacturers of pharmaceutical intermediates, academic institutions, and beyond. Each summer, more than 700 participants gather to exchange insights and advance the field of process chemistry. In addition, building on the success of previous four international symposia (ISPC) held in 2008, 2011, 2015, and 2019 — with total attendance surpassing 3,000 — we are proud to host the 5th ISPC in Hamamatsu in 2026.

This international symposium serves as a dynamic platform for leading researchers from both industry and academia to share cutting-edge developments, foster innovation, and strengthen global collaboration in process chemistry.

We warmly welcome all chemists with an interest in process chemistry to join us at ISPC 2026, where you'll have the opportunity to present your work, engage in meaningful discussions, and explore a wide range of topics shaping the future of the field.

Hamamatsu, nestled between Tokyo and Osaka in western Shizuoka Prefecture, is a lively coastal city renowned as both the "City of Music" and the "City of Instruments." It is home to globally recognized manufacturers of musical instruments, automobiles, and motorcycles, and offers a rich cultural experience. Visitors can enjoy the serene beauty of Lake Hamana, savor local delicacies such as Hamamatsu-style gyoza and grilled eel, and explore historical and cultural landmarks including Hamamatsu Castle and the Hamamatsu Museum of Musical Instruments. With convenient access via the Tokaido Shinkansen and a welcoming atmosphere, Hamamatsu promises a memorable experience for all attendees.

We look forward to welcoming you to Hamamatsu and to an inspiring and engaging ISPC 2026.

Takahiko Akiyama
President of JSPC

Shuji Akai
Chairperson of ISPC 2026

Organizing Committee

■ President of JSPC

Takahiko Akiyama	(Gakushuin Univ.)

■ Chairperson of ISPC 2026

Shuji Akai	(Univ. Osaka)

■ Program Committee

Shuji Akai	(Univ. Osaka)
Takahiko Akiyama	(Gakushuin Univ.)
Yasunori Aoyama	(Shionogi)
Yujiro Hayashi	(Tohoku Univ.)
Akio Kayano	(Eisai)
Nobuyuki Mase	(Shizuoka Univ.)
Noriaki Murase	(Taisho Pharmaceutical)
Hideya Mizufune	(JITSUBO)
Takashi Ohshima	(Kyushu Univ.)
Hironao Sajiki	(Aichi Institute Technology)

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Keiichi Aritomo	(Mitsubishi Tanabe Pharma)
Nobuhisa Fukuda	(Sumitomo Pharma)
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Toshiaki Mase	(Univ. Tokyo)
Kazuhiko Matsumura	(TAKASAGO INTERNATIONAL)
Norikazu Miyoshi	(Tokushima Univ.)

Kazuo Nagasawa	(Tokyo Univ. Agriculture Technology)
Noriyuki Nakajima	(Toyama Prefectural Univ.)
Atsushi Ohigashi	(Astellas Pharma)
Shoji Onogi	(JAPAN TOBACCO)
Kazutaka Seki	(FUJIFILM Wako Pure Chemical)
Takayuki Shioiri	(Nagoya City Univ.)
Shigeru Soda	(Office Well SODA)
Misato Takashima	(ASAHI KASEI PHARMA)
Kiyosei Takasu	(Kyoto Univ.)
Masaru Takayanagi	(AJINOMOTO)
Yuki Takeuchi	(KYOWA PHARMA CHEMICAL)
Kiyoshi Tomioka	(Kyoto Univ.)
Masakazu Wakayama	(Daiichi Sankyo)
Hiroaki Yasukouchi	(KANEKA)

■ International Advisory Board

Matthew Bio	(Cambrex, USA)
Yi Hsiao	(Createrna, China)
Michael J. Krische	(Univ. Texas, Austin, USA)
Benjamin List	(Max-Planck-Institut für Kohlenforschung, Germany)
Kevin Maloney	(Merck, USA)
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Srinivas Oruganti	(Dr. Reddy's Institute of Life Sciences, India)
Chris Senanayake	(TCG GreenChem, USA)
Wenjun Tang	(Shanghai Institute of Organic Chemistry, China)

■ Local Committee

Nobuyuki Mase	(Shizuoka Univ.)
Shuichi Nakamura	(Nagoya Institute Technology)
Tetsuo Narumi	(Shizuoka Univ.)
Kohei Sato	(Shizuoka Univ.)

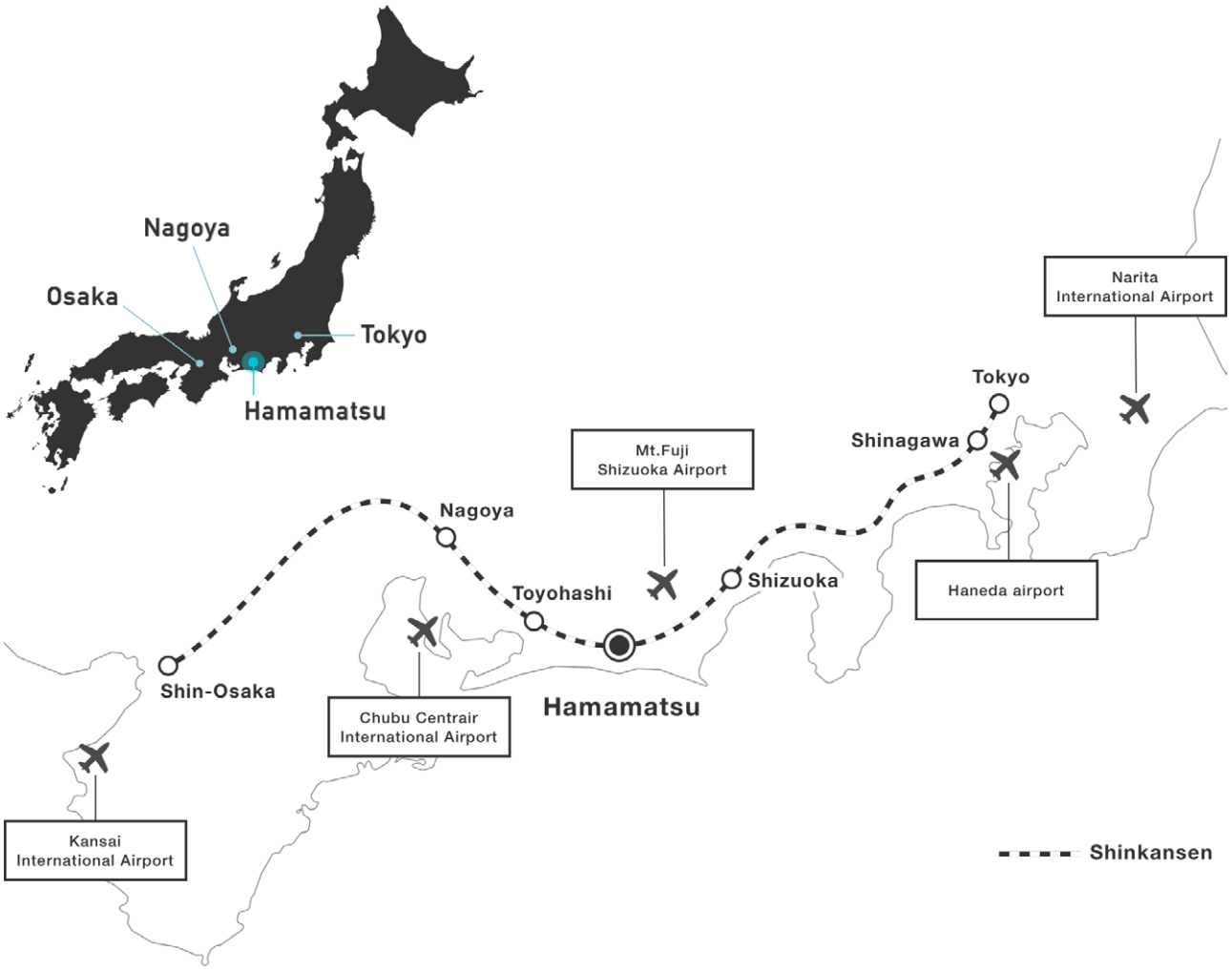
To Participants of The 5th International Symposium on Process Chemistry [ISPC 2026]

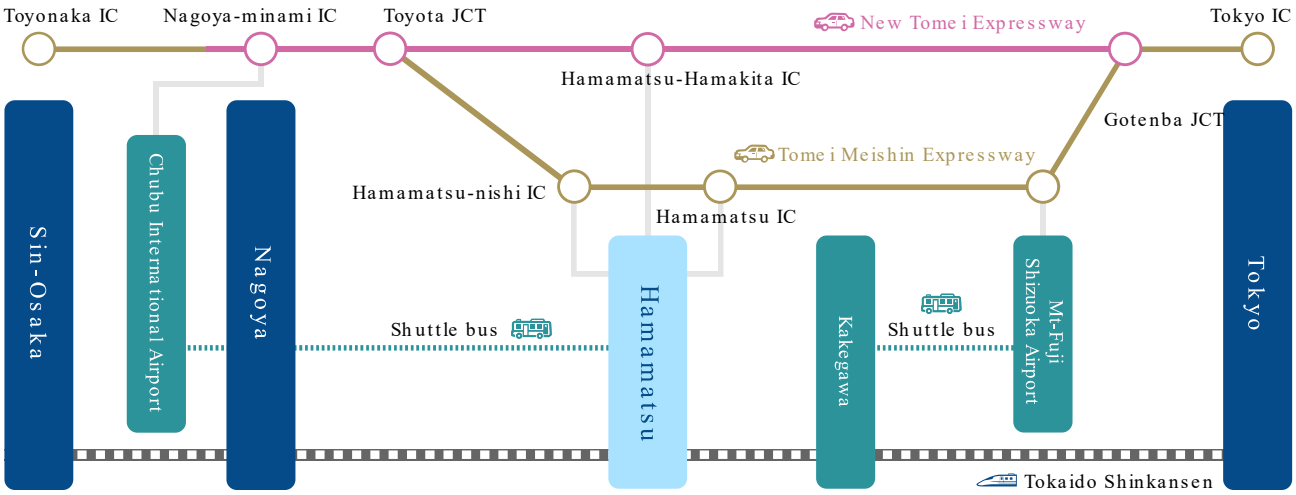
* Photographing and videotaping are not permitted during the symposium.
* Please set your mobile phones to silent mode.
* Light clothing is recommended for the symposium.
* A cloakroom is available.

To Poster Presenters

* The presentation codes 1P-xx and 2P-xx correspond to poster sessions on July 2nd (Thursday) and July 3rd (Friday), respectively. The poster presentations will be held in the Exhibition Hall.
* Presenters on both July 2nd and 3rd are requested to post their posters on the designated board between 10:00 a.m. and 11:00 a.m. on July 2nd. All posters should remain displayed for both days and must be removed at the end of the poster session on July 3rd. Posters that are not removed will be discarded.

Access





※ Participating Shops in the “Hamamatsu Downtown Omotenashi Passport” Program

The registration desk will be located in front of the Main Hall and will remain open throughout the symposium, from July 1st to 3rd.

Welcome Reception (July 1st.)
※from July 1st, renamed ANA Crowne Plaza Hamamatsu

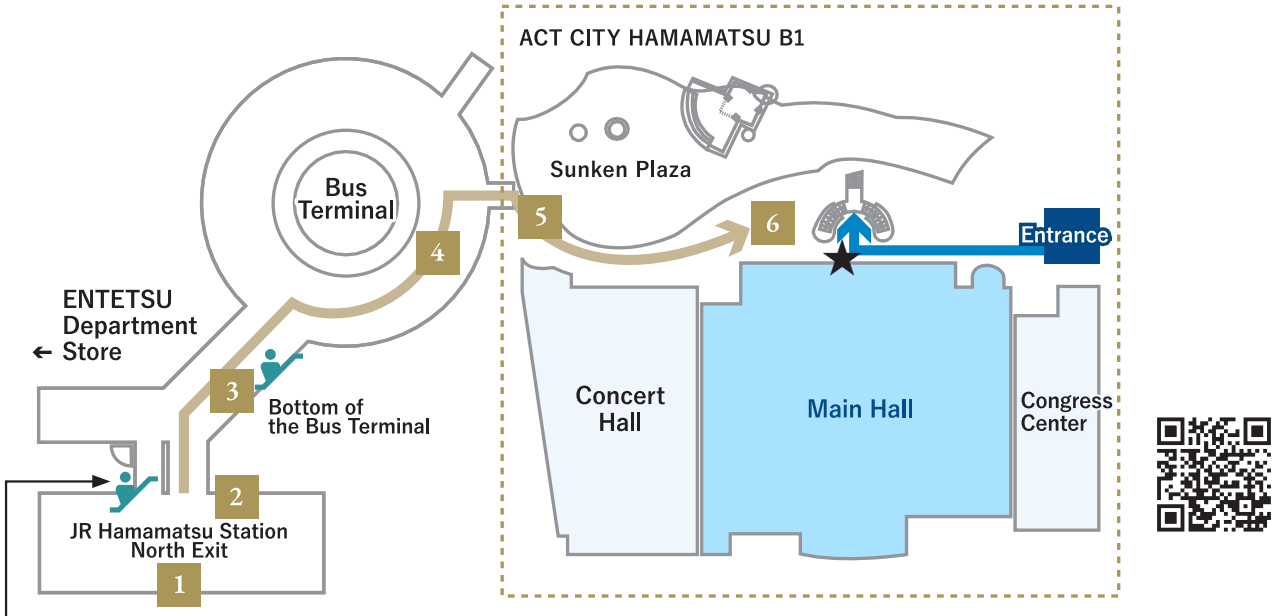


A-zone：Main Hall
Concert Hall
Congress Center
B-zone：ACT TOWER
C-zone：Exhibition and Event Hall
D-zone：Seminar & Exchange Center

Route A is recommended for accessing the Main Hall, where the opening remarks and invited lectures will be held.
Route B is recommended if you wish to go directly to the Exhibition and Event Hall, where the poster presentations and exhibitions will take place.
★ indicates the registration area.

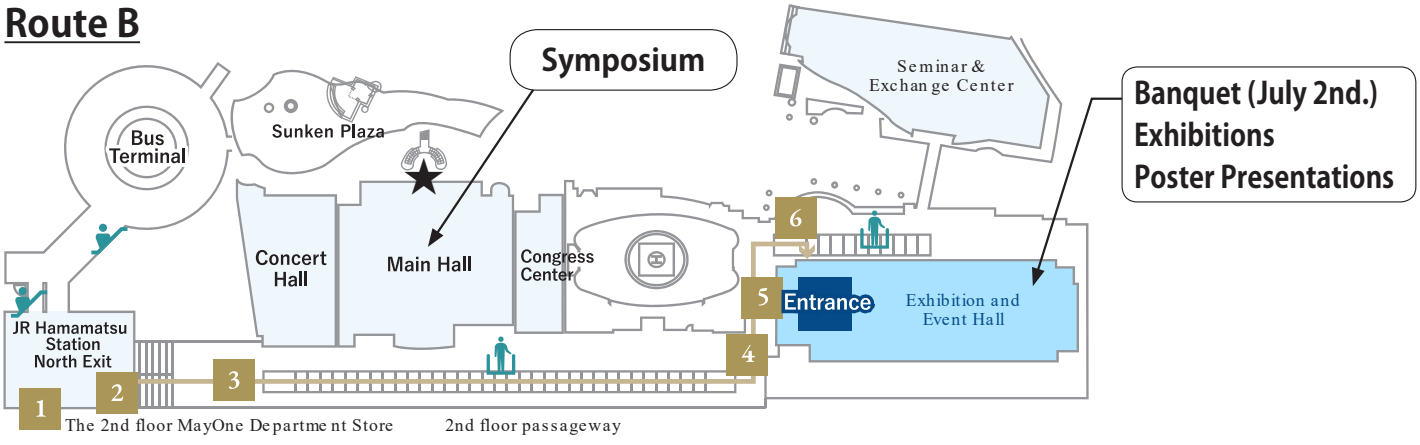
Route A

From Hamamatsu Station　From ACTTower



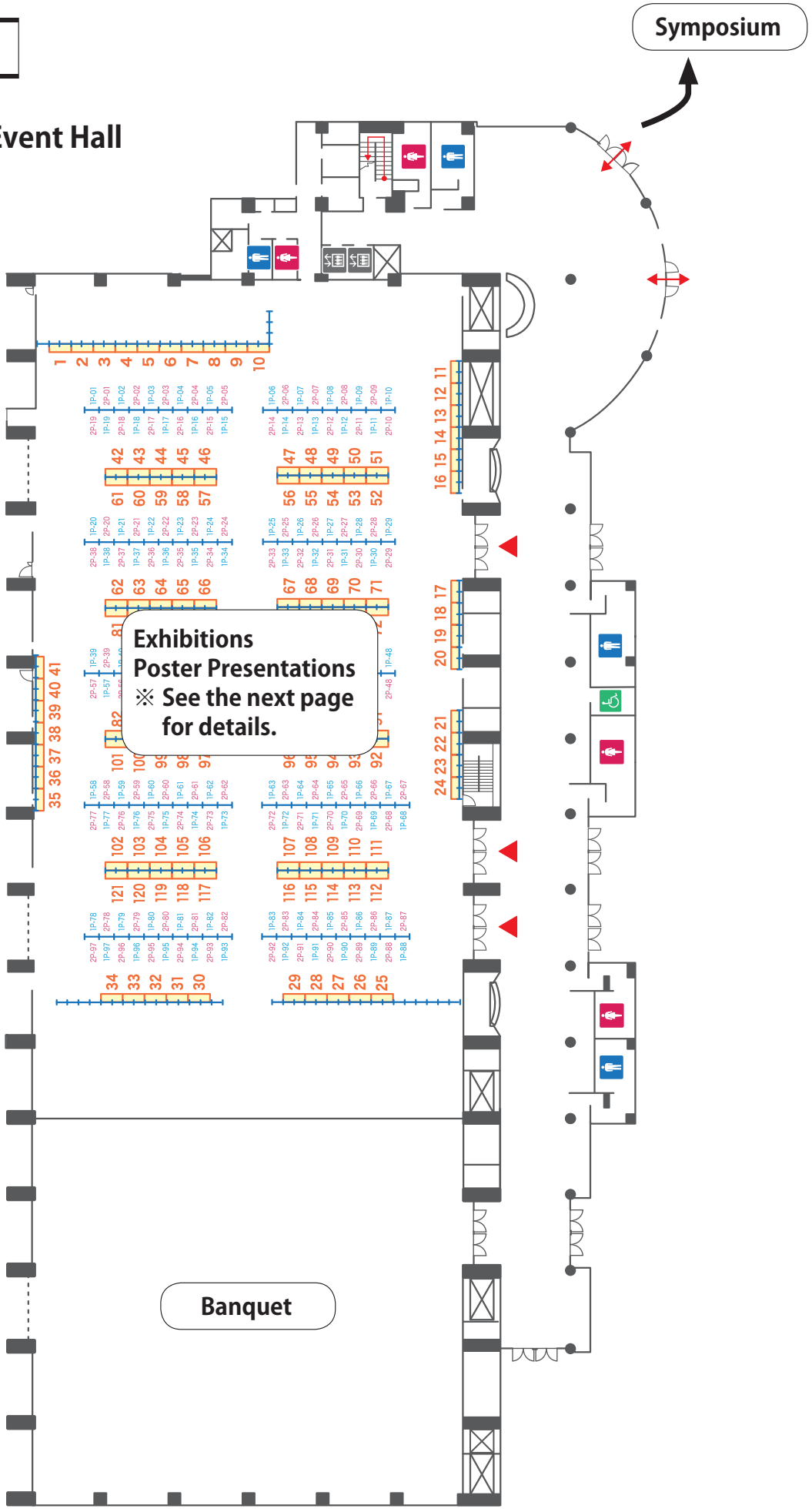
Take the escalator down to the first basement level (B1).

Route B



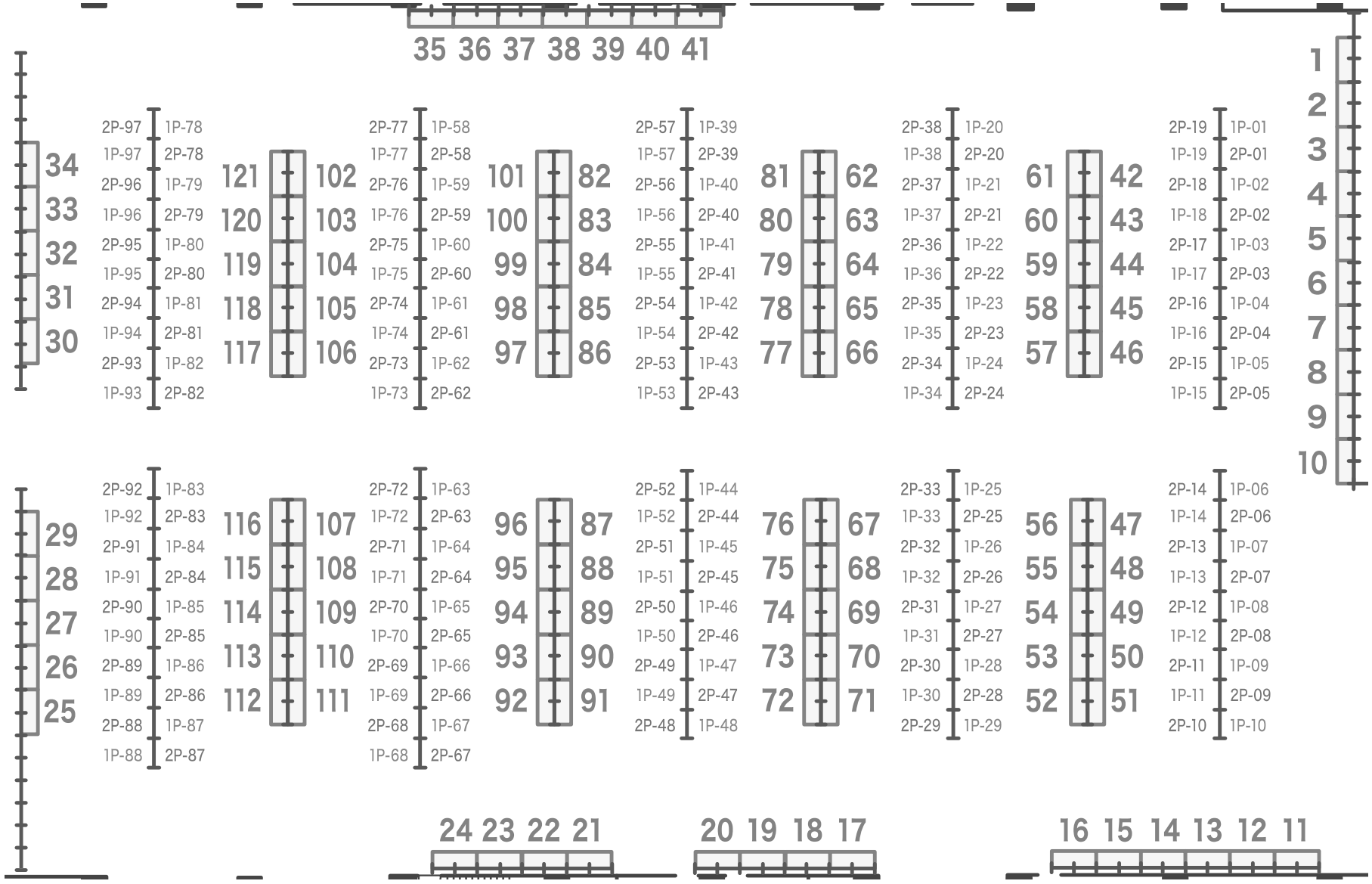
Floor Plan

Exhibition and Event Hall



Exhibitions and Poster Presentations

※The numbers below represent booth numbers and presentation codes (1P-xx and 2P-xx).



List of Exhibitors and booth number

A	106	Advion Interchim Scientific Co., Ltd.
	5	AGC Inc.
	19	Agilent Technologies Japan, Ltd.
	108	AR BROWN CO.,LTD.
	51	Asahi Glassplant Inc.
	109	Asahi Kasei Corporation
	112	Asahi Lab Commerce, Inc.
	54	Ascensus Specialties
	36	Asymchem Japan Co., Ltd.
	95	ATTO Co., Ltd.
B	70・71	BeatSensing Co., Ltd.
	82	Biotage Japan, Ltd.
	107	Bronkhorst Japan
C	76	CATALER CORPORATION
	26	ChromaJean Co., Ltd.
	83	ChromSword Co., Ltd.
	1	Chugai Pharmaceutical Co., Ltd.
D	68	DAICEL CORPORATION
	47	DFC Co.,Ltd.
	44	DKSH Japan K.K.
E	10	EBARA CORPORATION
	46	Endress+Hauser Japan Co., Ltd.
	31	EUROAPI Japan G.K.
F	74	FUJI SILYSIA CHEMICAL LTD.
	15・16	FUJIFILM Wako Pure Chemical Corporation
	9	FUJIMOTO CHEMICALS CO., LTD.
	4	Fukuzyu Pharmaceutical Co.,Ltd.
	80	FUSHIMI Pharmaceutical Co.,Ltd.
G	77	GL Sciences Inc.
H	18	Hikal Limited
	103	Hodogaya Chemical Co.,Ltd.
	72	HOKKO CHEMICAL INDUSTRY CO., LTD.
I	113	i Chemical Lab. Corporation
	117	iFactory inc.
	29	IKA Japan K.K.
	25	IKEDA SCIENTIFIC Co., Ltd.
	88	INABATA & Co.,LTD.
	91	IWAKI CO.,LTD.
J	90	Jiuzhou Pharma Labo Co., Ltd.
K	43	KANEKA CORPORATION
	45	KANTO CHEMICAL Co., INC.
	65	Kawaken Fine Chemicals Co.,Ltd.
	92	KNC Laboratories Co.,Ltd.
	97	KNF Japan Co., Ltd.
	94	KOEI CHEMICAL COMPANY, LIMITED
	78	KUMIAI CHEMICAL INDUSTRY CO.,LTD.
	118	KURARAY CO.,LTD.
	8	KYOWA PHARMA CHEMICAL CO., LTD.
M	96	MAK ENGINEERING CORPORATION
	79	MANAC Incorporated
	116	MATSUBO Corporation
	49	MECHANOCROSS CO.,Ltd.
	23・24	METTLER-TOLEDO K.K.
	50	MiChS Co., Ltd.
	59	MIKI & CO., LTD.
	7	Milestone General K.K.
	39	Mitsubishi Corporation
	11	MP Bio Japan K.K.
	67	MSH Systems, Inc.
N	85	N.E. CHEMCAT CORPORATION
	114	Naiki Shoji Co.,LTD.
	48	NARD Institute, Ltd.
	40	NEO CHEMICAL Co.,LTD.
	6	Neuland Laboratories K.K.
	2	NGK Corporation
	63	Nippoh Chemicals Co.,Ltd.
	38	Nippon Pharmaceutical Chemicals Co.,Ltd.
	81	Nippon Science Core Co.
	55	Nisso Shoji Co.,Ltd.
	53	Nomura Jimusho, Inc.
O	32	OSAKA YUKA INDUSTRY LTD.
P	12	Patheon by Thermo Fisher Scientific
	14	PharmaBlock Sciences
	102	PHT International Inc.
	27	PHYSIO MCKINA Co., Ltd.
	13	PI Japan Co., Ltd.
	17	PROCOS S.P.A.
R	20	RADWAG Japan
	34	Rockwood Lithium Japan K.K.
S	75	Sagami Chemical Research Institute
	98	SANCAL IND.CO.,LTD.
	58	Sankyo Kasei Co., Ltd.
	56	Sanshin Metal Working Co., Ltd.
	105	Sanuki Chemical Industry Co.,Ltd.
	100	SANYO FINE CO.,Ltd.
	119	Sanyu Chemical Co.,Ltd.
	61	Schrödinger K.K.
	42	SCHWALBEL CO.,LTD.
	110・111	SCRUM Inc.
	84	Sekisui Medical Co., Ltd.
	66	Shimadzu Corporation
	64	Shinritsu Chemical Co.,Ltd
	115	Sigma-Aldrich Japan G.K.
	21	Society of Synthetic Organic Chemistry, Japan
	89	Soneas Chemicals
	69	SPERA PHARMA, Inc.
	3	Sumika Technoservice Corporation
	60	SUMITOMO CHEMICAL Co., Ltd.
	104	Summit Pharmaceuticals International Corporation
	37	Swagelok Japan
T	62	TACMINA
	99	TAPI Japan Ltd.
	120	TATEYAMA KASEI CO., LTD.
	41	TECHNO ALPHA CO.,LTD
	22	The Chemical Society of Japan / Oxford University Press
	87	Thermo Fisher Scientific Life Technologies Japan Ltd.
	35	TLV CO., LTD.
	52	Tokyo Chemical Industry Co., Ltd.
	30	Tokyo Instruments, Inc.
	57	TOYOBO MC Corporation
U	28	UBE
	33	UKIMA CHEMICAL Co.,Ltd.
V	101	VACUUBRAND SCIENTIFIC JAPAN Co.,Ltd.
W	73	Wuxi AppTec Japan, Co., Ltd.
Y	86	Yamato Scientific Co.,Ltd.
	121	YMC CO., LTD.
	93	YUKI GOSEI KOGYO CO., LTD.

Program

The 5th International Symposium on Process Chemistry [ISPC 2026]

Program

July 1st. (Wed)

Act City Hamamatsu – Main Hall

16:30-17:00	**Registration**
17:00-19:00	**Welcome Reception (Hotel Crown Palais Hamamatsu)**
	※ from July 1st, renamed ANA Crowne Plaza Hamamatsu

July 2nd. (Thu)

Act City Hamamatsu – Main Hall

8:20	**Registration**
8:50-9:00	**Opening Remarks**
	Shuji Akai *(Chairperson of ISPC 2026, The University of Osaka, Japan)*
9:00-9:40	**Beyond the Paradigm: Liquid-Phase Synthesis of *N*-Alkyl-Rich Cyclic**
K-1	**Peptides from the First Scale-Up manufacturing**
(Keynote Lecture)	**Hiroshi Iwamura** *(Chugai Pharmaceutical, Japan)*
	Chair : Misato Takashima (Asahi Kasei Therapeutics, Japan)
9:40-10:20	**Development of Efficient Catalytic Flow Process: Stratergies and**
K-2	**Insights for Pharmaceutical Applications**
(Keynote Lecture)	**Eunpyo Hong** *(SK Pharmteco SM Asia, Korea)*
	Chair : Hirotsugu Usutani (Ono Pharmaceutical, Japan)
10:20-10:50	**Coffee Break**
10:50-11:30	**Using Data Science and Machine Learning in Synthetic Process**
K-3	**Optimization**
(Keynote Lecture)	**Matthew S. Sigman** *(University of Utah, USA)*
	Chair : Yusuke Sasano (Tohoku University, Japan)

11:30-12:10	**From Molecule to Medicine: Innovatorl–CDMO Synergy in Modern Drug**
K-4	**Development**
(Keynote Lecture)	**Cheng Yi Chen** *(Asymchem Laboratories (Tianjin), China)*
	Chair : Nobuaki Fukui (Shionogi, Japan)
12:10-13:30	**Lunch**
13:30-15:00	**Poster Presentation (Exhibition and Event Hall)**
15:00-15:20	**Coffee Break**
15:20-16:00	**Innovations in SHIONOGI Process Chemistry Scalable Manufacturing**
K-5	**Strategies for COVID-19 Antivirals**
(Keynote Lecture)	**Takahiro Kawajiri** *(Shionogi, Japan)*
	Chair : Takamasa Tanaka (Astellas Pharma, Japan)
16:00-16:40	**ENABLING COMPLEX INTERMEDIATE AND API SYNTHESES AT**
K-6	**SCALE WITH ENGINEERED ENZYMES.**
(Keynote Lecture)	**David A. Entwistle** *(Codexis, USA)*
	Chair : Keisuke Suzuki (Daiichi Sankyo, Japan)
16:40-17:20	**Ligand Development for Cu-Catalyzed Arylation of Nucleophiles**
K-7	**Dawei Ma** *(Shanghai Institute of Organic Chemistry, China)*
(Keynote Lecture)	*Chair : Sobi Asako (Riken, Japan)*
17:45-20:00	**Banquet (Exhibition and Event Hall, Block No.3)**
	Welcome Address: Takahiko Akiyama
	(President of JSPC: Gakushuin University, Japan)
	Chair : Nobuyuki Mase (Shizuoka University, Japan)

July 3rd. (Fri)

Act City Hamamatsu – Main Hall

8:30-9:00	**Registration**
9:00-9:40	**Enabling Technologies to Drive the MSD Portfolio**
K-8	**Rebecca T. Ruck** *(MSD, USA)*
(Keynote Lecture)	*Chair : Shio Komiya (Chugai Pharmaceutical, Japan)*
9:40-10:20	**Development and Demonstration of an Automated Continuous**
K-9	**Manufacturing System for Fine Chemicals Using Taylor–Couette**
(Keynote Lecture)	**Crystallization**
	Joji Tsurumoto *(iFactory, Japan)*
	Chair : Yuto Mifune (Tanabe Pharma, Japan)

10:20-10:50	**Coffee Break**
10:50-11:30	**Scaling Electrochemistry: From Lab Curiosities to Continuous**
K-10	**Processes**
(Keynote Lecture)	**Thomas Wirth** *(Cardiff University, UK)*
	Chair : Akihiro Ogura (Keio University, Japan)
11:30-12:10	**Continuous Flow Chemistry Enabled by 3D-Printed Metal Reactors:**
K-11	**From Development to Industrial Implementation including Bayesian**
(Keynote Lecture)	**Optimization**
	Daniel Mink *(InnoSyn BV, The Netherlands)*
	Chair : Kazutaka Seki (FUJIFILM Wako Pure Chemical, Japan)
12:10-12:30	**General Assembly of JSPC**
12:30-13:30	**Lunch**
13:30-15:00	**Poster Presentation (Exhibition and Event Hall)**
15:00-15:20	**Coffee Break**
15:20-16:00	**Process Chemistry Realisation for Neglected Tropical Diseases (NTDs):**
K-12	**Enabling Affordable and High-Quality Medicines for Patient Benefit**
(Keynote Lecture)	**Anil Shahaji Khile** *(Eisai Pharmaceuticals India, India)*
	Chair : Nobuhisa Fukuda (Sumitomo Pharma, Japan)
16:00-16:40	**Bis(trimethylsilyl)amine as a Versatile Ammonia Equivalent: Catalytic**
K-13	**Direct Synthesis of *N*-Unsubstituted Ketimines, Primary Amides, and**
(Keynote Lecture)	**Nitriles**
	Takashi Ohshima *(Kyushu University, Japan)*
	Chair : Munenori Inoue (Sagami Chemical Research Institute, Japan)
16:40-16:45	**Announcement of the 2026 ISPC Award Winners**
17:00	**Closing Remarks**
	Noriaki Murase *(Vice President of JSPC: Taisho Pharmaceutical, Japan)*

Poster Program

Poster Program

July 2nd. (The)

Discussion 13:30-15:00 (Exhibition and Event Hall)

1P-01 **Development of Two Complementary Epimerization-Resistant Fragment Coupling Reactions for Highly Convergent Synthesis of *N*-Alkyl-Rich Peptides**
Shio Komiya*, Takumi Matsumoto, Kohei Fujii, Hiroshi Iwamura, Kenji Maeda（API Process Development Department, Chugai Pharmaceutical Co., Ltd.）

1P-02 **Development of Solid-Phase Synthesis Method for N-Methyl Rich Peptides**
Junichi Shiina* [1], Hirotaka Ejima [1], Manabu Wadamoto [1], Kotaro Iwasaki [2]（[1] Discovery Chemistry Dept., Chugai Pharmaceutical Co., Ltd., [2] API Process Development Dept., Chugai Pharmaceutical Co., Ltd.）

1P-03 **Rapid Extraction of Acid-Labile Compounds into an Aqueous Phase Using a Mixer-Settler under Continuous Flow Conditions**
Masahiro Hosoya*, Kengo Inoue（API R&D Laboratory, Pharmaceutical Technology Research Division, Shionogi & Co., Ltd.）

1P-04 **Practical Synthesis of Both Enantiomers of Trichostatin A**
Takeo Fukuda*, Shinya Sasayama, Toshiharu Takeuchi, Kyohei Kawano, Kenta Suzuki（Tokyo Chemical Industry Co., Ltd.）

1P-05 **The Role of NO and NO_2 in *N*-Nitroso Compounds Formation in API and Formulation**
Takuma Onai*, Ryota Nomura, Hideyuki Sogo, Misako Iwazawa, Tomohiro Kaku, Osamu Uchikawa（Towa Pharmaceutical Co., Ltd.）

1P-06 **Development of a novel practical aryne precursor: *o*-triazenylarylboronic acid**
Motoki Ito*（Meiji Pharmaceutical University）

1P-07 **Spirobipyridine Ligands as a Unique Platform for Molecular Recognition and Reaction Control through Noncovalent Interactions**
Sobi Asako*, Laurean Ilies（RIKEN Center for Sustainable Resource Science）

1P-08 **Review on the use of additives for reduciton of amides using $NaBH_4$**
Mitsuhiko Izawa*（Advanced Sciences Department, Nomura Jimusho, Inc.）

1P-09 **Accessible and Automated GUI-Driven Discovery of Drug Degradation Mechanisms**
Pavel A. Dub*（Schrödinger, Inc., San Diego, CA, USA）

1P-10 **Development of a Packed-Bed Continuous Flow Process for Pharmaceuticals with Integrated Crystallization**
Kwihwan Kobayashi*（Catalytic Chemistry Research Institute, National Institute of Advanced Industrial Science and Technology）

1P-11 **Efficient Synthesis of Cyclo(-RGDfK) Using a Microflow Reactor**
Naoto Yamasaki* [1], Mina Kim [1], Kana Miyamoto [1], Yuma Otake [2], Kyohei Adachi [2], Daisuke Kubo [2], Shinichiro Fuse [1]（[1] Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, [2] Innovation Center, Marketing Headquarters, Yokogawa Electric Corporation）

1P-12 **Application of Continuous Flow Technology to Halogenation Reactions at AGC**
Kohei Azami*, Takuma Hirata, Yu Takeuchi（Technology General Division Innovative Technology Laboratories, AGC Inc.）

1P-13 **Process Development of Aromatic Amino Acids Aimed at Accelerating Mid-Size Molecule Drug Discovery**
Manabu Wadamoto, Atsuya Shimizu*（Discovery Chemistry Dept., Research Div., Chugai Pharmaceutical Co., Ltd.）

1P-14 **A novel flow device for one-step ionic liquid synthesis**
Junpei Takayanagi* [1], Masanori Motokawa [1], Kyo Miyaki [1], Yu Muto [1], Ryutaro Ohira [1], Ryota Asano [2], Hiroaki Kanayama [2], Shin-Ichi Ohira [3]（[1] GL Sciences Inc., [2] Sunactis Co., Ltd., [3] Department of Chemistry, Kumamoto University）

1P-15 **Practical Amide Condensation of Carboxylic Acids with Amines Using *N*-(Trifluoromethanesulfonyl)imidazole**
Takeshi Yamada* [1], Kotoha Nagasaki [1], Aika Nakashima [1], Isao Morita [1], Kogaku Kimura [2], Ren Tomita [2], Katsuhiko Akiyama [2], Manabu Hatano [1]（[1] Faculty of Pharmaceutical Sciences, Kobe Pharmaceutical University, [2] Fundamental Chemical Research Center, Central Glass Co., Ltd.）

1P-16 **On-line Monitoring of Flow Synthesis Reactions Using Nexera FV**
Ayano Tanabe*, Makoto Ogaito, Katsumasa Sakamoto（Shimadzu Corporation）

1P-17 **N-terminal Free Dipeptide Mediated Oligopeptide Synthesis from Unprotected Amino Acids and Amino Acid *t*-Butyl Esters Using Trimethoxysilane**
Alex Boateng*, Tomohiro Hattori, Hisashi Yamamoto（Peptide Research Center, Chubu University）

1P-18 **Second-Generation Process: A Sustainable Route to Alectinib's Indole Core**
Mami Yamaguchi*, Hiroshi Iwamura, Kenji Maeda（API Process Development Department, Chugai Pharmaceutical Co., Ltd.）

1P-19 **Tamsulosin-Dimeric Impurity: Identification and Elucidation of Its Formation Mechanism, Leading to the Efficient Manufacturing Process of the API**
Tatsunori Sato*, Sadayuki Maeda, Tetsuya Kawashima, Daijiro Hayashi, Hiroki Moriwaki, Kanji Meguro（Hamari Chemicals, Ltd.）

1P-20 **DFT Calculation-Assisted Virtual Screening to Refine Chiral Phosphoric Acid-Catalyzed Allylboration**
Shigenobu Umemiya*, Takumi Hirata, Masahiro Terada（Graduate School of Science Tohoku University）

1P-21 **Synthesis of Indoles via Aza-oxa-Cope Rearrangement**
Tomoki Uchida, Daiki Oka, Ryosuke Saito, Tomomi Ohtsuka, Yusuke Miyazawa, Ken-ichi Takao, Akihiro Ogura*（Keio University）

1P-22 **Unified Asymmetric Synthesis of Trichodermamides A–F: The Power of Gas-Liquid Two-Phase Flow Photo-Oxidation**
Atsushi Kimishima*, Yujin Takeshita, Kazumi Ikegami, Rei Nagata, Masayoshi Arai（Graduate School of Pharmaceutical Sciences, The University of Osaka）

1P-23 **Enabling the Scale-up of Synthesis Involving Safety Risk and Intermediates Stability Problems**
Naoki Omori* [1], Mo Jia [2], Hongwei Yang [2]（[1] WuXi AppTec Japan, [2] WuXi STA）

1P-24 **Development of Polymeric Iridium-Catalyzed C–H Borylation of Arenes under Batch and Continuous Flow Conditions**
Zhenzhong Zhang*, Aya Ohno, Yoichi M. A. Yamada（RIKEN Center for Sustainable Resource Science）

1P-25 **Peptide-based Rotaxanes Assembled via Square-Planar Palladium Coordination**

Yasuhito Koyama*, Takuma Shinoda, Chouma Kurihashi, Akio Miyazato, Issey Osaka, Kouji Yamamoto, Masahiro Hamada, Noriyuki Nakajima（Department of Pharmaceutical Engineering, Toyama Prefectural University）

1P-26 **Membrane-based non-thermal dehydration for pharmaceutical manufacturing processes**

Takahiro Osaki* [1], Takahiro Baba [1], Yoshiki Kawai [1], Yuji Katayama [1], Masato Mikawa [1], Tatsushi Murase [2], Mikimoto Katsukawa [2], Yuji Kawakami [2]（[1] Corporate Research & Development, Asahi Kasei Corporation, [2] Chemical Process R&D, CMC & Production, Ono Pharmaceutical Co., Ltd.）

1P-27 **From Process Fingerprints to Scalable Insight: Enabling Lab-to-Plant Crystallization with ParticleTrack™**

Maiko Kurisaki*, Shuxin Cong（AuotoChem Team, BU LAB Instruments, Mettler Toledo K.K.）

1P-28 **Development of Pd-supported Nonwoven Fabric *via* Graft Polymerization and Its Application to Ligand-free Suzuki-Miyaura Coupling**

Makoto Komatsu* [1], Hiroaki Harakawa [1], Takashi Ikawa [2], Hironao Sajiki [3]（[1] Ebara Corporation, [2] Gifu Pharmaceutical University, [3] Aichi Institute of Technology）

1P-29 **Carboxylated Amine–Boranes as Boryl Radical Precursors**

Naoki Yasukawa* [1], Shuichi Nakamura [1], Leonori Daniele [2]（[1] Graduate School of Engineering, Nagoya Institute of Technology, [2] Institute of Organic Chemistry, RWTH Aachen University）

1P-30 **Safe and Scalable Method for Quench of Triethylsilane in Dapagliflozin Propanediol Monohydrate Production**

Nanami Kamiyama*, Komori Kenta, Moe Sato, Koto Noguchi, Shigenobu Nishiguchi（API Process Research Department, API Business Division, Towa Pharmaceutical Co., Ltd.）

1P-31 **Crystallization Process Development in Mixed Solvent Systems to Improve Filterability of Poorly Soluble Pharmaceutical Intermediates**

Hisaaki Onoue*, Hiroshi Iwamura（API Process Development Department, Chugai Pharmaceutical Co., Ltd.）

1P-32 **Enantioconvergent Alkylation for the Construction of Chiral Quaternary Carbon Centers and Control of $C(sp^3)$–$C(sp^2)$ Bond Rotation**

Muhammad Sohail*, Fujie Tanaka（Okinawa Institute of Science and Technology Graduate University）

1P-33 **Development of Green and Sustainable Strategies for Peptide Synthesis**

Isai Ramakrishna*, Tomohiro Hattori, Hisashi Yamamoto（Peptide Research Center, Chubu University）

1P-34 **Development of a Practical Synthesis for the Amphiphilic Phospholipid Polymer PMBZU30-100**

Takeshi Nakaya* [1], Yoshimine Fujii [2], Ikuko Ariga [2], Fumiya Takahashi [1]（[1] Process Technology Research Laboratories, Daiichi Sankyo Co., Ltd., [2] Smart Research Laboratories II, Daiichi Sankyo Co., Ltd.）

1P-35 **Nucleophilic Acyl Substitution Reaction of Hydroxylamine Catalyzed by Basic Metal Salts**

Katsuko Shirai*, Ryuichi Shirai（Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts）

1P-36 **Determination of the Epimerizable Chiral Center of Pladienolide D under Acidic Stress Conditions Using ^{18}O-Labeled Water**

Nao Shibuguchi*, Yumi Asai, Masaharu Gotoda, Takashi Hasebe（Analytical Research Laboratory, Eisai Co., Ltd.）

1P-37 **Development of Organic Synthesis Experimental Information Utilization System Integrating Knowledge Graphs and Generative AI**
Toshiharu Morishita* [1], Haruka Hori [1], Masafumi Tsuyuki* [2], Shotaro Agatsuma [2], Ryota Noma [3]
([1] Pharmaceutical Technology Division, Chugai Pharmaceutical Co., Ltd., [2] Research & Development Group, Hitachi, Ltd., [3] Pharmaceutical Systems Division, Hitachi, Ltd.)

1P-38 **Materials for Improving Oligonucleotide Synthesis**
Yoshiyuki Hari*, Kazuki Yamamoto, Ryotaro Yamashita, Yuta Ito, Yasufumi Fuchi (Faculty of Pharmaceutical Sciences, Tokushima Bunri University)

1P-39 **Expanded Applicability of Our State-of-the-Art Purification Technology to Development-Stage Scales**
Chie Kushibe [1], Miho Tamura [2], Shio Komiya [2], Naokazu Kumura [1], Tadafumi Horisaki [1], Tsuneaki Kaneko [1], Katsuhiko Miwa* [1] ([1] ChromaJean Co., Ltd., [2] Chugai Pharmaceutical Co., Ltd.)

1P-40 **Evaluation of Precious Metal Catalyst Activities for Stepwise Oxidation of Alcohols to Carboxylic Acids Using Hydrogen Peroxide**
Toshihiko Sakai* [1], Eiichi Nakai [2], Yukiko Okamoto [2], Junki Nagakubo [1], Tomoteru Mizusaki [1], Koichiro Masuda [2] ([1] R&D Center, N.E. Chemcat Corp., [2] Catalytic Chemistry Research Institute, National Institute of Advanced Industrial Science and Technology (AIST))

1P-41 **Divergent Synthesis of Thio-Substituted Chiral Cyclopentenes via a Domino Reaction of Sugar-Derived Wittig Reagents**
Natsuhisa Oka* [1,2,3], Yusaku Ito [1], Shoma Horiki [1] ([1] Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University, [2] iGCORE, Gifu University, [3] COMIT, Gifu University)

1P-42 **Scale-Up Study and Challenges in Flow Hydrogenation Reactions**
Kenichi Kon*, Keisuke Morisaki (Kawaken Fine Chemicals Co., Ltd.)

1P-43 **Application of Hybrid Mechanistic and Machine Learning Models to Crystallization Process Optimization**
Rei Otsuka* (Department of Process Chemistry, CMC Headquarters, Otsuka Pharmaceutical Co., Ltd.)

1P-44 **Implementing a Fully Automated High-Throughput Experimentation System for Process Research Acceleration**
Yuma Otake* (Process Technology Research Laboratories, Technology Development Supervisory Department, Technology Division, Daiichi Sankyo Co., Ltd.)

1P-45 **Synthesis of imine derivatives via a diazo-free reductive O-H/N-H bond insertion reaction**
Norihiko Takeda*, Ryoya Maeda, Tomoki Miyashita, Takahiro Yamada, Masafumi Ueda (Kobe Pharmaceutical University)

1P-46 **Polymorphism Control in Industrial Process Development for the Metastable Crystal Form of Linagliptin**
Koto Noguchi*, Koya Shoji, Tomoki Isogai, Nobuyoshi Doi, Shigenobu Nishiguchi (API Process Research Department I, API Business Division, Towa Pharmaceutical Co., Ltd.)

1P-47 **Palladium-Catalyzed Deoxygenative Deuteration with Aryl and Heteroaryl Nonaflates as Effective Coupling Partners**
Masami Kuriyama* [1], Reo Wakiyama [1], Kotaro Tsukuda [1], Tetsuro Morimoto [1], Kosuke Yamamoto [1], Yosuke Demizu [2], Osamu Onomura [1] ([1] Nagasaki University, [2] National Institute of Health Sciences)

1P-48 **Pincer-Nickel-Catalyzed Enantioselective Addition of Acetonitrile to Ketimines**
Akira Saito, Asim Kumar Ghosh*, Masakatsu Shibasaki（Institute of Microbial Chemistry（BIKAKEN））

1P-49 **Evaluation of Sampling Device Performance and Integration in Online HPLC Process Monitoring**
Keiko Hayashi*, Miu Miyashita（Agilent Technologies Japan, Ltd.）

1P-50 **Efficient Asymmetric Synthesis of *N*-Alkyl-α-Amino Acids by Using a Chiral Iridium Catalyst**
Kenya Yabushita*[1], Noriyuki Utsumi[1], Yoshihito Kayaki[2], Shigeki Kuwata[3]（[1] Central Research Laboratory, Technology & Development Division, Kanto Chemical Co., Inc., [2] Department of Chemical Science and Engineering, School of Materials and Chemical Technology, [3] Department of Applied Chemistry, College of Life Sciences, Ritsumeikan University）

1P-51 **Process Development of a Chemoenzymatic Route to an *N*-Methylprolinol Derivative**
Toru Watanabe*, Hidenori Ochiai, Koji Machida（Bio-Pharma Research Laboratories, KANEKA CORPORATION）

1P-52 **AI-Driven Optimization of Solvent Swap Distillation: Integrating Machine Learning Video Imaging for Automated, Scalable, and Sustainable Chemical Processing**
Yoshifumi Fujisawa*, Fabio Visentin, Dan Hallow, Nina Taherimakhsousi（Mettler-Toledo K.K.）

1P-53 **Maximize Reaction Insight via Data-Rich Experiments and Intelligent Analytics**
Naomi Fukuda*[1], Brian Wittkamp[2]（[1] Mettler-Toledo K.K, Japan, [2] Mettler-Toledo International）

1P-54 **Calculation and Verification of Mixing and Heat Transfer Parameters in Stirred Tank Reactors for Process Development and Scale-up**
Hisayoshi Hamada* Sanket Salgaonkar, Steve Cropper（Mettler Toledo Autochem.）

1P-55 **Quantitative Analysis of Clinical Proteome by Nano LC-nano-ESI-SRM-MS with the Use of Stable Isotope-labeled and Unlabeled Iodoacetanilides**
Sadamu Kurono, Satomi Niwayama*（FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan）

1P-56S **Absolute Asymmetric Synthesis of Cyclic Aminals by Dynamic Crystallization**
Oji Kuwabara*[1], Takeshi Oishi[2], Shogo Fujiki[1], Takaaki Sato[1]（[1] Department of Applied Chemistry, Keio University, [2] School of medicine, Keio University）

1P-57S **Diastereo- and Enantioselective Allenylation of Imines with Propargyl Nitriles Assisted by Machine Learning**
Kosei Miyake*[1], Ayane Saiganji[1], Seika Kimura[1], Yusuke Oyamada[1], Shintaro Yamasaki[1], Naoki Yasukawa[1], Yu Inatsu[1], Ichiro Takeuchi[2], Shuichi Nakamura[1]（[1] Graduate School of Engineering, Nagoya Institute of Technology, [2] Graduate School of Engineering, Nagoya University）

1P-58S **Reductive Nucleophilic Addition to Morpholine Amides for Polyketide Synthesis**
Shogo Aoki*, Hiroaki Makita, Masato Kitamura, Shota Iiyama, Misaki Sugiyama, Kouki Mizutani, Toshitaka Okamura, Shogo Fujiki, Takaaki Sato（Department pf Applied Chemistry, Keio University）

1P-59S **Design of Phosphine-Heteroarenesulfonamide Ligands as Dinuclear Silver Catalysts for Enantioselective Construction of Unnatural Amino Acid**
So Nakamura*, Yuka Iizuka, Sayuri Okazima, Shuichi Nakamura（Graduate School of Engineering, Nagoya Institute of Technology）

1P-60S **Ir-Catalyzed Reductive Formation of Nitrones Enabling Asymmetric Total Synthesis of Indolizidine Alkaloids**
Yuma Honda*, Sora Iwamoto, Toshitaka Okamura, Shogo Fujiki, Takaaki Sato（Department of Applied Chemistry, Faculty of Science and Technology, Keio University）

1P-61S **General Synthetic Approach to Various Natural Products Using Dynamic Enantioselective Crystallization**

Yuta Shimotani* [1], Hayama Kojima [1], Takeshi Oishi [2], Shogo Fujiki [1], Takaaki Sato [1] ([1] Faculty of Science and Technology, Keio University, [2] School of Medicine, Keio University)

1P-62S **Practical Direct Azidomethylation Methods for the Synthesis of *N*-and *S*-Azidomethyl Compounds**

Ryoga Sawahata* [1], Yuga Takagi [2], Yoshiaki Kitamura [1,2,3,4] ([1] United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University, [2] Faculty of Engineering, Gifu University, [3] Graduate School of Natural Science and Technology, Gifu University, [4] Center for One Medicine Innovative Translational Research (COMIT), Gifu University)

1P-63S **Radical Transformations of Acidic Compounds Enabled by Ketone Photocatalysis**

Hayate Sano* [1], Yuki Goto [1], Hiroki Hayashi [2], Kenji Yamashita [1], Yoshitaka Hamashima[1] ([1] Grad. Sch. Pharm. Sci., University of Shizuoka, [2] Research Center for Materials Science, Nagoya University)

1P-64S **A Strategy for Access to Natural Product-Inspired Poly(cyclic ether) Architectures via ADMET Polymerization**

Suzuka Oda*, Mako Yunbe, Noriyuki Nakajima, Masahiro Hamada, Yasuhito Koyama (Department of Pharmaceutical Engineering and Biotechnology Research Center, Toyama Prefectural University)

1P-65S **Platinum-Group-Metal-on-Carbon Catalyzed Dehydration of Tertiary Alcohols and its Application to the One-Pot Synthesis of Aromatics**

Yuto Suganuma*, Shuki Oyama, Shuji Akai and Yoshinari Sawama (Graduate School of Pharmaceutical Sciences, The University of Osaka)

1P-66S **Gold(I)-Catalyzed Allylation of Ethynyl Cyclic Carbonates with Allylsilanes**

Momoka Ikeda*, Yoshikazu Horino (Chitose Institute of Science and Technology, Japan)

1P-67S **Dye-Sensitized Upconversion Nanoparticles with Enhanced Aqueous Luminescence**

Hengde Li*, Haitao Liu, and Angelo H. ALL (Hong Kong Baptist University)

1P-68S **Synthetic Studies on Fluorous Mixture Synthesis of Emericellamide A and Its Stereoisomers**

Tsubasa Hamano*, Yuzuki Mizogiwa, Takayuki Shioiri, Masato Matsugi (Graduate School of Agriculture, Meijo University)

1P-69S **Concise Synthesis of *cis*-Xanthophylls and Investigation of Their Photoisomerization**

Yuki Okura*, Rintaro Murakami, Kazuhiro J. Fujimoto, Takeshi Yanai, Shinichiro Fuse, Naoto Yamasaki (Grad. Sch. Pharm. Sci., Nagoya University, Institute of Transformative Bio-Molecules, Nagoya University)

1P-70S **Synthesis of Vinylidenecyclopropanes via Copper-Catalyzed Cyclopropanation of Vinyl Arenes**

Yuta Shimoji*, Yoshikazu Horino (Chitose Institute of Science and Technology, Japan)

1P-71S **Deuterated Alkylation Reagents Based on Sulfonium Salts as Cation and Radical Sources**

Sota Yoshimura*, Kazuho Ban, Shuji Akai, Yoshinari Sawama (Graduate School of Pharmaceutical Sciences, The University of Osaka)

1P-72S **Development of Crystalline Dihaloacetylene and Trihaloethylene Equivalents**

Takuto Naito*, Norihiro Tada, Akichika Itoh (Gifu Pharmaceutical University)

1P-73S **Continuous-Flow Semi-Hydrogenation of Nitroarenes to *N*-Aryl Hydroxylamines**
Naoya Sakurada* [1], Chie Morishige [1], Tomohiro Ichikawa [1], Takashi Shigeta [1], Hironao Sajiki [1,2], Takashi Ikawa [1] ([1] Laboratory of Advanced Chemistry, Gifu Pharmaceutical University, [2] Faculty of Engineering, Department of Applied Chemistry)

1P-74S **Pt/C-Catalyzed Deuteration of Polycyclic Aromatic Hydrocarbons with Suppressed Ring Hydrogenation**
Sae Tomoto* [1], Naoya Sakurada [1], Tomohiro Ichikawa [1], Takashi Shigeta [1], Hironao Sajiki [1,2], Takashi Ikawa [1] ([1] Laboratory of Advanced Chemistry, Gifu Pharmaceutical University, [2] Faculty of Engineering, Department of Applied Chemistry, Aichi Institute of Technology)

1P-75S **Chiral Hypobromite-catalyzed Enantioselective Dearomative Azidation of (Hetero)arenols**
Sho Akagawa*, Yasuo Tsukimori, Takaharu Morino, Muhammet Uyanik, Kazuaki Ishihara (Graduate School of Engineering, Nagoya University)

1P-76S **Dehydrative Amidation of Aromatic Carboxylic Acids with Amines Catalyzed by Carbazole-Based Diboronic Acid Anhydride**
Yuta Fujii*, Ota Koyama, Liu Xiaodong, Ryuichi Nishiyori, Naoyuki Shimada (Department of Chemistry, Nihon University)

1P-77S **Continuous-Flow Pd/C-Catalyzed Conversion of Azides to Nitriles**
Naoya Sakurada [1], Hikaru Naito* [1], Takanori Kitazono [1], Seiya Ootori [1], Tomohiro Ichikawa [1], Takashi Shigeta [1], Tsuyoshi Yamada [2], Hironao Sajiki [1,3], Takashi Ikawa [1] ([1] Gifu Pharm. Univ., Daigakunishi, Gifu, [2] Grad. Sch. Med. and Pharm. Sci., Univ. of Toyama)

1P-78S **Bismethoxybinaphthyl as an Organic Photoredox Catalyst: Functions and Applications**
Tomohisa Yamaguchi*, Masanori Tayu, Kakeru Matsukuma, Masahiro Noji, Satoshi Hayashi, Sayaka Ohrui, Nozomi Saito (Meiji Pharmaceutical University)

1P-79S **Gold(III)-catalyzed decarboxylative/dehydrative coupling of 2-hydroxy-1-naphthoic acid in water**
Kazuma Kondo*, Shoko Kikkawa, Hidemasa Hikawa, Isao Azumaya (Faculty of Pharmaceutical Sciences, Toho University)

1P-80S **Oxidative Fluorination of β-Ketoamides using Guanidinium Hypoiodite Catalysts**
Toma Osawa* [1,2], Hayate Ishizuka [1], Dominique Cahard [2], Kazuo Nagasawa [1] ([1] Graduate School of Engineering, Tokyo University of Agriculture and Technology, [2] CNRS-UMR 6064 CARMeN, Normandy University)

1P-81S **Site-Selective Hydroxylation of the CD-Ring of Vitamin D Metabolites by P450 BM3 Variants**
Sota Yoshimura* [1], Ryota Sakamoto [1,2], Mirei Morita [1], Rino Tsutsumi [1], Yuki Okamoto [3], Kaori Yasuda [3], Toshiyuki Sakaki [3], Kazuo Nagasawa [1] ([1] Graduate School of Engineering, Tokyo University of Agriculture and Technology, [2] Department of Life Science and Biotechnology, National Institute of Advanced Industrial Science and Technology (AIST), [3] Faculty of Engineering, Toyama Prefectural University)

1P-82S **A Universal Resin Catalyst for the Selective Monoacylation of Structurally Diverse Diols**
Keigo Sonokawa* [1], Hiroyuki Miyamura [2], Kiyosei Takasu [1], Yusuke Kuroda [1,3] ([1] Graduate School of Pharmaceutical Sciences, Kyoto University, [2]Catalytic Chemistry Research Institute, National Institute of Advanced Industrial Science and Technology (AIST), [3] The HAKUBI Center for Advanced Research, Kyoto University)

1P-83S **Development of Novel Thiourea Photocatalysts and Its Application to Reductive Transformations of α-Chloroamides**
Honoka Nagahara*, Kei Arai, Takumi Haraguchi, Hiromichi Egami, Yoshitaka Hamashima (School of Pharmaceutical Sciences, University of Shizuoka)

1P-84S **Synthesis of 1,5-diazocinone through sequential nucleophilic addition/skeletal remodelling of cyclic ureas**
Kaito Sakamoto*, Norihiko Takeda, Suzuna Ichioka, Takahiro Yamada, Masafumi Ueda（Kobe Pharmaceutical University）

1P-85S **Enantioselective Bromocyclization of Difluoroalkenes and Benzofuran Enabled by Concerted Lewis/Bronsted Base Catalysis with Chiral Bisphosiphine Oxide**
Yuki Nakahara* [1], Ryo Hirokawa [1], Shotaro Uchida [1], Makoto Inai [1,2], Kenji Yamashita [1], Yoshitaka Hamashima [1]（[1] Graduate Division of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan, [2] Faculty of Global Interdisciplinary Science and Innovation, Shizuoka University, Shizuoka, Japan）

1P-86S **Fine Bubble Organic Chemistry: Multi-Stacked Mixer for Gas-Involved Organic Reactions and Degassing**
Keishin Sakamoto*, Kohei Sato, Tetsuo Narumi, Nobuyuki Mase（Graduate School of Integrated Science and Technology, Shizuoka University）

1P-87S **Green Manufacturing: Development of a Continuous Process for Fairy Chemicals**
Kotaro Yuguchi*, Kohei Sato, Tetsuo Narumi, Nobuyuki Mase（Graduate School of Integrated Science and Technology, Shizuoka University）

1P-88S **Green Flow Chemistry: a Slurry Flow System Incorporating an Archimedean Screw**
Haruka Satsukawa*, Kohei Sato, Tetsuo Narumi, Nobuyuki Mase（Graduate School of Integrated Science and Technology, Shizuoka University）

1P-89S **Improving the accuracy of liquid film thickness measurement using a laser focus displacement meter**
Kanata Iwazaki*, Yuki Mizushima（Graduate School of Integrated Science and Technology, Shizuoka University）

1P-90S **Design and Synthesis of Novel Phase-transfer Catalyst Inspired by Cinchona Alkaloids**
Midori Kawasaki, Hinako Iwamoto*, Kenji Yatsuzuka, Katsuko Shirai, Ryuichi Shirai（Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts）

1P-91S **Dye Separation by Polymer Films based on Discotic Liquid Crystal with Photopolymerizable Cinnamate Groups**
Tsukasa Ohno*, Mikio Yasutake, Takuji Hirose, Koichi Kodama（Graduate School of Science and Engineering, Saitama University）

1P-92S **Enantioselective [2,3]-Wittig Rearrangement of Allyl Picolyl Ethers Enabled by Chiral Lithium Amides**
Midori Kawasaki, Chifumi Yumoto*, Yurika Otsubo, Kenji Yatsuzuka, Katsuko Shirai, Ryuichi Shirai（Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts）

1P-93S **Direct Real-Time Data Acquisition and Analysis for Flow Synthesis**
Aki Kohyama, Kanata Ishihara*, Kota Suzuki, Kiyosei Takasu（Graduate School of Pharmaceutical Sciences, Kyoto University）

1P-94S **Racemizing 3-aryl-3-hydroxy-2-oxindoles in a Pickering emulsion under acid catalysis and its application to dynamic kinetic resolution**
Jihoon Moon*, Shuji Akai, Yoshinari Sawama, Kyohei Kanomata（Graduate School of Pharmaceutical Sciences, The University of Osaka）

1P-95S **Continuous Flow Preparation of Methyl Vinyl Ketone from 4-Hydroxy-2-butanone with Heterogeneous Acid Catalyst**

Mamoru Hyodo* [a,b], Takahide Fukuyama [b,c], Masahiro Hosoya [d] ([a] Organization for Research Promotion, Osaka Metropolitan University, [b] MiChS Co., Ltd., [c] Department of Chemistry, Osaka Metropolitan University, [d] API R&D Laboratory, Pharmaceutical Technology Research Division, Shionogi & Co., Ltd.)

1P-96S **Synthesis and reactivity of α-Sulfonium Enones**

Shunsuke Nakamura*, Rikuto Chiba, Kanako Yazaki, Motoki Ito, Kazuhiro Higuchi, Shigeo Sugiyama (Meiji Pharmaceutical University)

1P-97S **Divergent Synthesis of Artoserichalcone A Derivatives and *In Silico* Lead Optimization for Antimalarial Drug Discovery**

M. Fadli* [1], Hilkatul Ilmi [2,3], Lidya Tumewu [2,3], Ervan Yudha [4], Aty Widyawaruyanti [2,3], Natsuhisa Oka [1,5,6] ([1] Department of Engineering Science, Graduate School of Engineering, Gifu University, [2] Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, [3] Natural Product Medicine Research and Development, Institute of Tropical Disease, Universitas Airlangga, [4] Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Gadjah Mada, [5] Institute for Glyco-core Research (iGCORE), Gifu University, [6] Center for One Medicine Innovative Translational Research (COMIT), Institute for Advanced Study, Gifu University)

July 3rd. (Fri)

Discussion 13:30-15:00 (Exhibition and Event Hall)

2P-01 **Effective Crystallization Process Development**
Airi Saito*, Charlie Rabinowitz, Cong Shuxin（AuotoChem Team, BU LAB Instruments, Mettler Toledo K.K.）

2P-02 **Study on the Partial Reduction of Esters with High Reduction Potentials Using a Flow Reactor**
Yuki Kobayashi*, Takahiro Yoshikawa（Kongo Chemical Co., Ltd.）

2P-03 **Computational Chemistry-Guided Industrial Process Development**
Tomohiro Kikuchi*, Taiju Nakamura, Masayuki Omori, Taichi Abe（API Research Lab. Japan, Eisai Co., Ltd.）

2P-04 **Development of the Commercial Manufacturing Process for Bilastine**
Seitaro Koshino*, Wang Weiqi, Masahiro Takeda, Yamato Taniguchi, Akihide Matsumoto（Advanced Medical Solutions Research Laboratory, Sumitomo Chemical Co., Ltd.）

2P-05 **Comparative Study of Pt and Pd Catalysts in Flow Hydrogenation Reactions Using a Computational Science Approach**
Keisuke Matsumura*, Hiroaki Harakawa（Ebara Corporation）

2P-06 **Study on the Development of an Online Reaction Vessel Monitoring System Using an HPLC Platform**
Hiromasa Iboshi*, Chua Chee keong（Innovation Centre, Shimadzu Asia Pacific Pte. Ltd.）

2P-07 **DirectInject-LC: Real-time Analysis by HPLC for Reaction Monitoring**
Makoto Ogaito*, Tomohiro Shagawa, Kyoko Watanabe（Shimadzu Corporation）
Yusuke Sato, Junliang Liu, Lars Yunker, Shad Grunert, Paloma Prieto, Jason E. Hein（Telescope Innovations）

2P-08 **Pd-catalyzed dehydrogenative coupling of 2,3-diaminopyridines and alcohols in water**
Hidemasa Hikawa*, Masakazu Kobayashi, Nanoka Kobori, Shoko Kikkawa, Isao Azumaya（Faculty of Pharmaceutical Sciences, Toho University）

2P-09 **ReactRaman: Real-time data yields comprehensive kinetic and mechanistic insight across diverse chemistries**
Kanako Hatanaka*[1], Brian Wittkamp[2]（[1] Mettler-Toledo K.K, Japan, [2] Mettler-Toledo International）

2P-10 **From Laboratory to Manufacturing: Development and Implementation of a Continuous Flow Process for a Pharmaceutical Intermediate (Part-1; Route Development and Introduction of Continuous Flow Chemistry)**
Yusei Takamatsu*, Hiro Sugiyama, Kousuke Komenoi（Chemical & Biological Technology Labs., Astellas Pharma Inc.）

2P-11 **From Laboratory to Manufacturing: Development and Implementation of a Continuous Flow Process for a Pharmaceutical Intermediate (Part-2; Scale-Up and Operational Experience in Manufacturing)**
Hiro Sugiyama*[1], Yusei Takamatsu[1], Kousuke Komenoi[1], Hiroaki Yasukouchi[2], Koji Machida[2], Takahiko Murata[2]（[1] Chemical & Biological Technology Labs., Astellas Pharma Inc., [2] KANEKA CORPORATION）

2P-12 **Practical Reduction of Nitroarenes to Anilines Using NaBH4 and Commercial CuO**
Tomoya Hagio*, Honoka Teraji*, Yuki Hirose, Junpei Ohtaka, Yoshinori Kohmura（Chemical & Biological Technology Labs., Astellas Pharma Inc.）

2P-13 **Automation-Enabled Process Development and Kinetic Modelling for PAR Determination**
A. Lena*, M. Donnola, B. Luchetta, L. Marinoni, A. Barozza, J. Roletto（PROCOS S.P.A., CBC GROUP）

2P-14 **The Value of Reaction Calorimetry**
Ryoma Tanaka*, Urs Groth（Mettler-Toledo K.K.）

2P-15 **Chiral Bronsted Acid Catalyzed Asymmetric Allylation Reaction with Sterically Hindered Aldehydes**
Shigenobu Umemiya, Sotaro Osaka, Naoya Shinagawa, Takumi Hirata, Masahiro Terada*（Graduate School of Science, Tohoku University）

2P-16 **Development of a Scalable and Practical Total Synthesis for Pladienolide D**
Jun Niijima* [1], Naoki Yoneda [1], Nobuaki Sato [1], Norio Murai [1], Yuki Karouji [1], Isao Ohashi [1], Yusuke Nakatani [1], Tsubasa Nakaue [1], Kazuki Kobayashi [1], Takeo Sasaki [1], Minetaka Isomura [1], Taro Yamashita [2], Yoko Ito [2], Takashi Hasebe [2], A.Desinghu [3], Chiranjeevi Terli [3], G Ramarao [3], B.Phanibhushan kumar [3], Subrahmanyam Medicherla [3], Subba Reddy A [3], A.V.V. Prasad [3], Anil Varma Alluri [3], B.V. Sasidhar [3], Ravi Kumar T [3], Anil S. Khile [3], Taichi Abe [1]（[1] API Research Japan, Pharmaceutical Science & Technology, DHBL, Eisai Co., Ltd., [2] Analytical Research, Pharmaceutical Science & Technology, DHBL, Eisai Co., Ltd., [3] Pharmaceutical Science & Technology, DHBL, Eisai Pharmaceuticals India Private Limited.）

2P-17 **Eco-friendly Manufacture of Ezetimibe: Impurity control and Sustainability**
V S Sureshbabu Chillara*, Narendra Kumar Tripathy, Sharadsrikar Venkatesan Kotturi（Neuland Laboratories Ltd., Research & Development Centre）

2P-18 **DirectInject-LC: a New PAT Platform with HPLC**
Yuki Sawatsugawa*, Brian Wittkamp（Mettler-Toledo K.K.）

2P-19 **Automated Preparation of Calibration Standards Using an HPLC Autosampler for Reproducible Quantitative Analysis**
Miu Miyashita*, Keiko Hayashi, Riho Noda（Agilent Technologies Ltd.）

2P-20 **High-Efficiency Continuous Extraction Technology Based on SMCR®**
Teppei Moroyama*, Haruna Ariki（Kobelco Eco-Solutions Co.Ltd.）

2P-21 **Practical Synthesis and Commercialization of Chiral Fmoc-Serine Derivatives via Copper Catalyzed Direct Asymmetric Aldol Reaction**
Hisashi Takada* [1], Toshihumi Takeuchi [1], Seiji Nukui [2], Takumi Watanabe [1], Masakatsu Shibasaki [1]（[1] Institute of Microbiral Chemistry, [2] Funakoshi Co., Ltd.）

2P-22 **Continuous-Flow Syntheses of 1,2-Diols from Alkenes Using Titanium Silicalite-1 Catalyst Column with Hydrogen Peroxide**
Yoshihiro Kon* [1], Takuya Nakashima [1], Shun-ya Onozawa [1], Sh. Kobayashi[1,2]（[1] Catalytic Chemistry Research Institute, National Institute of Advanced Industrial Science and Technology (AIST), [2] Department of Chemistry, School of Science, The University of Tokyo）

2P-23 **Heterogeneous Cobalt-Catalyzed Thiol Synthesis from Alkenes and Carbonyl Compounds Using Elemental Sulfur and Hydrogen as Simple Reagents**
Eiji Yamamoto* [a], Weixin Qi [a], Xu Ke [a], Haruno Murayama [a], Takashi Kamachi [b], Akina Yoshizawa [a], Akihiro Nakayama [a], Matsueda Hironobu [c], Makoto Tokunaga[a]（[a] Department of Chemistry, Graduate School of Science, Kyushu University, [b] Department of Life, Environment and Applied Chemistry, [c] Processing Technical Group 3, DIC Corporation）

2P-24 **N-Heterocycle Synthesis *via* TfOH-Mediated Iodocarbocyclization with Iodoarenes**
Kosuke Yamamoto* [1], Izumi Nakayama [1], Kentaro Higa [2], Masami Kuriyama [1], Osamu Onomura[1]
([1] Graduate School of Biomedical Sciences, Nagasaki University, [2] School of Pharmaceutical Sciences, Nagasaki University)

2P-25 **Automated Multi-Sampling Flow Reactor for Efficient Kinetic Analysis**
Yoshihiro Takebayashi*, Takehiro Yamaki, Sho Kataoka (Research Institute for Chemical Process Technology, AIST)

2P-26 **Thiobenzoic Acid-Catalyzed Regioselective Functionalization of Allylamines via Hydrogen Atom Transfer under Visible Light Irradiation**
Kaich Watanabe, Masashi Fujita, Riku Osanai, Kenji Yamamashita, Hiromichi Egami, Yoshitaka Hamashima* (School of Pharmaceutical Sciences, University of Shizuoka)

2P-27 **Integration & Intelligence Enabling Green Chemistry at PharmaBlock**
Yuqing Lu*, Gang Sheng (PharmaBlock Research Institute. PharmaBlock Sciences (Nanjing), Inc.)

2P-28 **Crystal Structure Elucidation of Ephemeral Metastable Polymorphs by 3D ED/MicroED Appearing During Crystallization Process**
Keiyo Nakai* [1], Kuniyoshi Miki [1], Takashi Kikuchi [2], Masaki Hattori [1], Kazuki Harada [1], Rina Konishi [1], Kayoko Hata [1], Chisato Okahashi [1], Mitsuhisa Yamano [1] ([1] SPERA PHARMA, Inc. Osaka R&D Center, [2] Rigaku Corporation)

2P-29 **Enantioselective Synthesis of α-Monofluorinated α-Amino Acid Derivatives and Their Application to α-Monofluorinated Peptides**
Riko Genka, Hikaru Oshimo, Hisanori Arakaki, Genta Koja, Kanami Sugiyama, Tomohiro Agou, Hirofumi Sato, Masahiro Higashi, Satoru Arimitsu* (Department of Chemistry, Biology, and Marine Science, University of the Ryukyus)

2P-30 **Computationally Guided Reaction Development for the Construction of Valuable Molecular Scaffolds from Small Molecules**
Tsuyoshi Mita*, Satoshi Maeda (Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University)

2P-31 **Data-Driven Multiparameter Optimization for Efficient Screening of Reaction Conditions in Flow and Electrochemical Synthesis**
Mohamed S. H. Salem*, Masaru Kondo, Shinobu Takizawa (SANKEN, The University of Osaka)

2P-32 **PIPAc: towards flow chemistry and artificial intelligence powered API production**
Sylvain Guizzetti*, Guillaume Bentzinger, Philippe Steinsoultz, Elena Salvadeo, Alizee Brouillard, Bogdan Penkovsky, Alejandro Bara Estaun (Novalix)

2P-33 **High-Speed C–H Halogenation and Alkylation Using a Diagonal Photoflow Reactor (LX-1) Combined with a High-Power UV-LED**
Yusuke Takahashi*, Mamoru Hyodo, Ilhyong Ryu, Takahide Fukuyama (Smart Chemistry Laboratory, MiChS Co., Ltd.)

2P-34 **Camphorsultam-Assisted Stereoselective Synthesis of *P*-Chiral Phosphonate Diesters**
Yasutomo Yamamoto* [1], Sakura Nakai [1], Tomoe Ishiura [1], Yurika Kambara [1], Ayase Matsumoto [1], Hideyasu China [1], Kenji Watanabe [1], Junpei Matsuoka [2] ([1] Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, [2] School of Pharmaceutical Sciences, Kindai University)

2P-35 **The Convergence of Three Novel Downstream Technologies: One Breakthrough in Peptide and Oligonucleotide API Manufacturing**

Shunsuke Ochi * [1], Kenta Saito [1], Yuta Hiroyama [1], Takayuki Morimoto [1], Ryosuke Kunitani [1], Yoshitaka Nemoto [1], Yusuke Kishi [2], Takashi Fujisawa [2], Tomoharu Maeseto [2], Masato Mikawa [3], Yuji Katayama [3], Yuki Suga [3], Mayuko Mouri [4], Eigo Muto [4], Kiyotaka Takimoto [4]（[1] R&D Department., PeptiStar Inc., [2] Kobelco Eco-Solutions Co.,Ltd., [3] Asahi Kasei Corporation, [4] YMC CO., LTD.）

2P-36 **Bioinspired Chemical Transformations of Grayanotoxin III to Kalmanol, *seco*-Rhodomollone, Rhodomolleins XXIII and XXIV**

Shoji Kobayashi*, Taiga Tsuruyama, Hinata Togo（Osaka Institute of Technology）

2P-37 **Advancing Flow Chemistry Implementation: Pilot-Scale Demonstration of Continuous Production and Scale-Up of Organolithium Flow Reactions**

Yusuke Kimuro, Shota Kawakami, Masashi Sugimoto*, Kyosuke Matsushita, Yuta Kobayashi（Juzen Chemical Corporation）

2P-38 **Development of the Efficient Purification Process for Tirzepatide Using Twin-Column Continuous Chromatography**

Kosuke Kawai*, Narumi Kobayashi, Jun Kawasaki, Munehiro Shoda, Kiyotaka Takimoto（YMC Co., Ltd.）

2P-39 **Self-Driving Optimization of Organic Reactions via Machine Learning and Automation**

Munenori Inoue*, Takuya Yamagata, Kazushi Hayashi（Sagami Chemical Research Institute）

2P-40 **Improving the efficiency of Ir type borylations and the development of [Ir(COE)2(Me2Bpy)Cl]**

Antonio Zanotti-Gerosa, Daniel Arnold, Douglas Hartline, Aaron Bloomfield, Sanita Taylor, Charley Tougard, Eric Slack*（Johnson Matthey）

2P-41 **From Soluble to Solubilizing Tag: Highly Efficient Liquid-Phase Peptide Synthesis Using Oleyl Tag**

Sota Adachi*, Shingo Shinjo-Nagahara, Yoshikazu Kitano, Yohei Okada（Tokyo University of Agriculture and Technology）

2P-42 **Practical Synthesis of Sulfonyl Cyanides from Sodium Sulfinates Using KCN and NaOCl·$5H_2O$**

Masaru Kondo*, Atsushi Baba, Yutaro Nakamura, Ryo Takita（School of Pharmaceutical Sciences, University of Shizuoka）

2P-43 **Reversal and Control of the Intrinsic Reactivity of Carbonyl Groups via Chemoselective TMSCl-Mediated In Situ Protection**

Hirendra Nath Dhara*, Muthu Karuppasamy, Mohamed S. H. Salem, Shinobu Takizawa, Hiromichi Fujioka（SANKEN, The University of Osaka）

2P-44 **Binaphthyl-type Chiral Borinic Acid Catalyst for Enantioselective Reactions**

Yuta Chikashige [1], Kazuhiro Higashi [1], Shinsuke Komagawa [1], Tsunayoshi Takehara [2], Takeyuki Suzuki [2], Atsuhi Nakayama [1], Mitsuhiro Arisawa [1], Makoto Sako * [1,2],（[1] Graduate School of Pharmaceutical Sciences, The University of Osaka, [2] Comprehensive Analysis Center, SANKEN, The University of Osaka）

2P-45 **Development of a Chemical Upcycling Process from Perchloroethylene by Photoactivated Chlorine Dioxide Treatment**

Nozomi Takao, Minami Fukuhara, Genta Taniguchi, Maiko Moriguchi, Shohei Ohno, Yuki Itabashi, Kei Ohkubo, Tsuyoshi Inoue, Haruyasu Asahara*（Graduate School of Pharmaceutical Sciences, The University of Osaka）

2P-46 **Thermal Control in Flow Synthesis Enabled by Silicon-Infiltrated High-Thermal-Conductivity Si–SiC Cartridges**

Takayuki Kanetake* [1], Taigo Tamagushi [1], Kosuke Niwa [1], Naoya Sakurada [2], Hikaru Naito [2], Tomohiro Ichikawa [2], Takashi Shigeta [2], Hironao Sajiki [2,3], Takashi Ikawa [2] ([1] NGK Corporation, [2] Laboratory of Advanced Chemistry, Gifu Pharmaceutical University, [3] Department of Applied Chemistry, Aichi Institute of Technology)

2P-47 **Reductive Deuteration of Carbonyl Compounds Using D_2O as a Deuterium Source Enabled by a Tin Oxide-Supported Pt-Ir Catalyst**

Alastair N. Herron* [1], Kosuke Nakajima [1], Heeyoel Baek [2], Shunsuke Yukitani [2], Takao Osako [2], Hiroshi Naka [1] ([1] Graduate School of Pharmaceutical Sciences, Kyoto University, [2] Mitsui Kinzoku Co. Ltd.)

2P-48 **Electrochemical Peptide Synthetic Process Aiming for Greener Production**

Shingo Shinjo-Nagahara*, Yohei Okada, Yoshikazu Kitano, Kazuhiro Chiba (Tokyo University of Agriculture and Technology)

2P-49 **Crystallization-Based Approach to Continuous Manufacturing: A Case Study of Acetaminophen Production**

Tetsuya Yamamoto* [1], Koichiro Masuda [1], Kwihwan Kobayashi [1], Hidekazu Sano [1], Aiichiro Nagaki [2], Akira Yada [1] ([1] Catalytic Chemistry Research Institute, National Institute of Advanced Industrial Science and Technology, [2] Department of Chemistry, Faculty of Science, Hokkaido University)

2P-50 **An Automated HTE Platform for Systematic Reaction Space Exploration in Early-Stage Process Development**

Yuta Sumii* [1], Mikio Ishihara [1], Takashi Shimizu [1], Katsunori Seki [1], Hiroyuki Yamashita [2], Kazuki Mukumoto[2] ([1] Astellas Pharma Inc., [2] SHIMADZU CORPORATION)

2P-51 **Solvent-Minimal and Epimerization-Suppressed Mechanochemical Synthesis of Peptide Thiocarboxylic Acid**

Kounosuke Oisaki, Hiroshi Igarashi, Koki Fujimura*, Masahiro Hayashi, Masato Nakano (CCRI/FoodMed-OIL, National Institute of Advanced Industrial Science and Technology (AIST))

2P-52 **Nitrosamine Risk Evaluation in Drug Substance: Development of a Nitrite Ion Analytical Method in High-Chloride Matrices**

Shohei Takayasu*, Kenichiro Sato, Takahiro Yamaguchi, Misato Takashima (CMC Department, Pharmaceuticals Research Center, Asahi Kasei Therapeutics Corp.)

2P-53 **Mild Liquid-Phase Sulfurization of P(III) Compounds Using Sodium Tetrasulfide**

Kazuki Yoshioka *[1,2], Ken-Ichiro Sotowa [1] ([1] Department of Chemical Engineering, Kyoto University, [2] Mitsuichemicals INC Kyoto University)

2P-54 **Eosin Y-catalyzed Cyclization: Syntheses of 6-Membered Sulfones**

Akihiro Orita*, Akira Iwakura, Shion Matsunaga, Yasuhiro Okuda (Department of Applied Chemistry, Okayama University of Science.)

2P-55 **Traceless electrogenerated acid-catalyzed dehydroxylative arylation for the synthesis of tri- and diarylmethane derivatives**

Tsuyoshi Yamada*, Tatsuki Ono, Yuka Abe, Masaru Tanioka, Yuji Matsuya (Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama)

2P-56S **Direct Approach towards Synthesis of Dihydroisoquinoline from Ketones *via* Bischler-Napieralski Type Reaction**

Kota Fujimori*, Masanori Inoue, Genichiro Nakae, Kengo Hyodo (School of Science and Engineering, Kindai University)

2P-57S **Selective Reductive Alkylation of Amines Using Nitriles under Continuous-Flow Conditions**

Naoya Sakurada [1], Masayuki Saito* [1], Mana Kumazawa [1], Eisho Shimizu [1], Tomohiro Ichikawa [1], Takashi Shigeta [1], Hironao Sajiki [1,2], Takashi Ikawa [1] ([1] Gifu Pharmaceutical University, [2] Aichi Institute of Technology)

2P-58S **Flow Synthesis of (–)-(α)-Kainic Acid**

Sosuke Takaki* [1], Atsuji Tajima [2], Kiichi Hirayama [1], Nobuyuki Mase [3], Kazuhiro Takeda [3], Takashi Ohshima [1] ([1] Graduate school of Pharmaceutical Sciences, Kyushu University, [2] Faculty of Pharmaceutical Sciences, Kyushu University, [3] Graduate school of Engineering, Shizuoka University)

2P-59S **Cross-Linked Random Polymer Enables Catalytic Diol Mono-Silylation**

Yusuke Kuroda [1, 2], Takumi Nasuno* [1], Kiyosei Takasu [1] ([1] Graduate School of Pharmaceutical Sciences, Kyoto University, [2] The HAKUBI Center for Advanced Research, Kyoto University)

2P-60S **A Green Process for the Synthesis of Amine-3HF Complexes via Cation Exchange between KF and Amberlyst 15DRY**

Haruka Homma*, Masahide Yamada, Toshiki Tajima (Graduate School of Engineering and Science, Shibaura Institute of Technology)

2P-61S **3'-Fluorinated Thalidomide Derivatives: Stereoselective Synthesis and CRBN Binding Properties**

Hisanori Arakaki*, Satoru Arimitsu (Department of Chemistry, Biology, and Marine Science, University of the Ryukyus)

2P-62S **A Co-solvent System to Reduce the Process Mass Index in Ullmann-type Biaryl Synthesis**

Sae Tomoto [1], Yuto Maki* [1], Takashi Shigeta [1], Hironao Sajiki [1,2], Tomohiro Ichikawa [1], Takashi Ikawa [1] ([1] Laboratory of Advanced Chemistry, Gifu Pharmaceutical University, [2] Faculty of Engineering, Department of Applied Chemistry, Aichi Institute of Technology)

2P-63S **Development of a Fiber-optic Interferometric Spectral Probe (FISP) for simultaneous measurement of bubble size and lamella thickness in foam**

Higen Mizushima* [1], Ryota Tanioka [1], Shimpei Saito [2], Kohei Sato [1], Yuki Mizushima [1] ([1] Graduate School of Integrated Science and Technology, Shizuoka University, [2] Research Institute for Energy Efficient Technologies, National Institute of Advanced Industrial Science and Technology (AIST))

2P-64S **Development of a Chemical Upcycling Process from Perchloroethylene by Photoactivated Chlorine Dioxide Treatment**

Genta Taniguchi*, Shohei Ohno, Yuki Itabashi, Tsuyoshi Inoue, Kei Ohkubo, Haruyasu Asahara (Graduate School of Pharmaceutical Sciences, The University of Osaka)

2P-65S **Direct Thickness Measurement in Wavy Liquid-Film Flow via Optical Waveguide Film**

Shota Ando*, Yuki Mizushima (Graduate School of Integrated Science and Technology, Shizuoka University)

2P-66S **Development of a synthetic method for a highly oxidized D ring in *cis*–CD–fused steroid skeletons**

Fumino Kitamura*, Masaru Tanioka, Tsuyoshi Yamada, Yuji Matsuya (Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Japan)

2P-67S **A Fiber-Optic-Mediated Reactor System for Thermal Control and Scalable Synthesis in Photocatalytic Cascade Annulation**

Kuo-Chun Chiu*, Ruo-Ya Huang, Yung-Wei Chen, and Chih-Chien Chu (Department of Medical Applied Chemistry, Chung Shan Medical University)

2P-68S **Gram-Scale Synthesis of the Opioid Alkaloid Mitragynine**

Yuki Shimizu*, Suzuka Yoshioka, Mariko Kitajima, Hayato Ishikawa（Laboratory of Natural Products and Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Chiba University）

2P-69S **Intramolecular Hydroamidation of Alkene Using Alkali Metal Bases and Cyclic Polyethers**

Mana Kawakami * [a], Junpei Matsuoka [a], Yasutomo Yamamoto [b], Tomohiro Maegawa [a]（[a] School of Pharmaceutical Sciences, Kindai University, [b] Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts）

2P-70S **Development of chloromethyl esterification reaction of carboxylic acids and methods for introducing of nitrate esters**

Haato Tsuda*, Junpei Matsuoka, Hiroki Yao, Natsumi Kuraoka, Tomohiro Maegawa（School of Pharmaceutical Sciences, Kindai University）

2P-71S **Three-Step Synthesis of Glycan-Asparagine Conjugates from Unprotected Sugars**

Junya Akeno* [1,2], Kiyosei Takasu [1], Kounosuke Oisaki [2], Norihisa Fukaya [2], Yoshihiro Ueda [2]（[1] Graduate School of Pharmaceutical Sciences, Kyoto University, [2] National Institute of Advanced Industrial Science and Technology）

2P-72S **Ester Reduction in Toluene by All-at-Once Addition of $NaBH_4$ and Alcohol Activator**

Reito Endo*, Mayu Ishida, Toshinobu Korenaga（Graduate School of Arts and Sciences, Iwate University）

2P-73S **Development of a Synthetic Method for Multisubstituted Cubanes using Aluminum Halaide σ–Complexes**

Hinata Mimaki*, Masaru Tanioka, Tsuyoshi Yamada, Yuji Matsuya（School of Pharmacy and Pharmaceutical Sciences, University of Toyama）

2P-74S **Development of electrodeprotection reaction of acetals under neutral conditions and its application to one-pot sequential transformation**

Yuka Abe* [1], Tsuyoshi Yamada [1], Tatsuki Ono [1], Masaru Tanioka [1], Takashi Ikawa [2], Hironao Sajiki [3], Yuji Matsuya [1]（[1] Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, [2] Laboratory of Advanced Chemistry, Gifu Pharmaceutical University, [3] Faculty of Engineering Development of Applied Chemistry, Aichi Institute of Technology）

2P-75S **Development of a Mild and Efficient Flow-Based Method for the Generation of *o*-Quinodimethane**

Tomoki Iwama*, Tsuyoshi Yamada, Masaru Tanioka, Yuji Matsuya（Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama）

2P-76S **Synthetic Studies of Callophycoic Acid A**

Kotaro Taniguchi*, Akihiro Ogura, Ken-ichi Takao（Department of Applied Chemistry, Keio University）

2P-77S **Controlled Tetradeuteration of Straight-Chain Fatty Acids**

Nonoka Hori* [1], Kotaro Hama [2], Ayako Watanabe [3], Koko Imai [1], Masaru Kondo [1], Kohei Watanabe [3], Yuko Fujiwara [2], Kazuaki Yokoyama [2], Shigeo Murata [3], Ryo Takita [1]（[1] School of Pharmaceutical Sciences, University of Shizuoka, [2] Faculty of Pharmaceutical Sciences, Teikyo University, [3] Graduate School of Pharmaceutical Sciences, The University of Tokyo）

2P-78S **Enantioselective Friedel-Crafts Alkylation Reaction of Pyrrole with β-Trifluoromethyl-β-alkynyl Nitroalkenes Catalyzed by Chiral BINOL Metal Phosphate**

Reina Baba*, Yuki Kaneko, Tatsuhiro Uchikura, Takahiko Akiyama（Department of Chemistry, Gakushuin University）

2P-79S **Enantioselective Visible-Light-Driven Radical Addition Reactions to Imines Using Chiral Phosphoric acid/photoinduced HAT dual catalysis**

Ryoji Ikeda*, Tatsuhiro Uchikura, Takahiko Akiyama（Department of Chemistry, Gakushuin University）

2P-80S **Catalytic Decarboxylative Cyanation for ^{13}C-Labeled Fatty Acids**

Yutaro Nakamura*, Atsushi Baba, Masaru Kondo, Ryo Takita（School of Pharmaceutical Sciences, University of Shizuoka）

2P-81S **Thermophysical Property Estimation of Multicomponent Mixtures Using Mixture Descriptors and Machine Learning**

Keisuke Ikeda*, Atushi Hatoyama, Yuya Murakami（Faculty of Engineering, Shizuoka University）

2P-82S **Synthesis of Fused Amines Bearing Tetrasubstituted Carbons via the Gold-Catalyzed Cyclization–3-aza-Cope–Mannich Cascade**

Miku Akahori*, Kaito Tozuka, Haruka Katayama, Ayame Taki, Ryu Tadano, Takeo Sakai（Faculty of Pharmacy, Meijo University）

2P-83S **Liquid-Phase Peptide Synthesis Utilizing Magnetic Liquid-Liquid Extraction**

Jun Karasawa* [1], Shohei Yamashita [1], Tomoyuki Taguchi [2], Sho Yoshida [2], Naoko Nishida [2], Shinji Nishida [2], Osamu Matsumoto [3], Hirofumi Kuroda [3], Masashi Kambara [3], Yohei Okada [1]（[1] Tokyo Univ. Agric. & Technol., [2] Chiyoda Corporation, [3] Chiyoda U-Tech Co., Ltd.）

2P-84S **Continuous-Flow Oxidation of Alcohols to Carboxylic Acids Using Molecular Oxygen and a Ternary Pd/C–Pt/C–Ru/C Catalyst System**

Yiyue Yao* [a], Mamoru Hyodo [b,c], Yusuke Takahashi [b,c], Kinryo Cho [d], Takahide Fukuyama [a], Ilhyong Ryu [b,e],（[a] Department of Chemistry, Osaka Metropolitan University, [b] Organization for Research Promotion, Osaka Metropolitan University, [c] Smart Chemistry Laboratory, MiChS Co., Ltd., [d] Green Chemical Inc., [e] Department of Applied Chemistry, National Yang Ming Chiao Tung University）

2P-85S **Investigation of Divergent Methodology to Synthesize Amino Acid-Incorporated Isoindolinones and Their Analogs from Mushrooms of the Genus *Hericium***

Audreyana Ariella*, Shoji Kobayashi（Osaka Institute of Technology）

2P-86S **Halogenation-triggered *endo*-to-*exo* carbonyl transformation of hydroxycoumarin**

Yusuke Yoto* [a], Osuke Shioya [a], Yusei Matsumoto [a], Kotaro Kikushima [a], Hideyasu China [b], Toshifumi Dohi [a]（[a] College of Pharmaceutical Sciences, Ritsumeikan University, [b] Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts）

2P-87S **Tunable Chemoselective Hydrogenation Using a Palladium Catalyst Supported on Nonwoven Fabric (Pd/NF)**

Hikaru Okubo* [1], Hitoshi Abe [1], Hiroaki Harakawa [2]（[1] Graduate School of Science and Engineering, University of Toyama, [2] Ebara Corporation）

2P-88S **Solid-Supported Photosensitizers for Highly Selective *E* → *Z* Photoisomerization of Oximes**

Mayuko Suga*, Ryusei Takada, Kayo Nakamura, Hidetsugu Tabata, Tetsuta Oshitari, Hideaki Natsugari, Hideyo Takahashi（Faculty of Pharmaceutical Sciences, Tokyo University of Science）

2P-89S **Synthesis of Stable 2-Tetrazene Radical Cation Salts and Exploration of Their Oxidation Catalytic Activity**

Shu Saito* [a], Yusuke Sasano [a], Ayari Oshiro [a], Shintaro Kitahata [a], Yasuyuki Araki [b], Eunsang Kwon [c], Yoshiharu Iwabuchi [a]（[a] Graduate School of Pharmaceutical Sciences, [b] Institute of Multidisciplinary Research for Advanced Materials (IMRAM), [c] Graduate School of Science, Tohoku University）

2P-90S **Soluble, Scalable, and Stable: Green Production of Peptides Enabled by "Ether Tags"**
Hana Haraguchi*, Sota Adachi, Shingo Shinjo-Nagahara, Yoshikazu Kitano, Yohei Okada（Tokyo University of Agriculture and Technology）

2P-91S **Aerobic Oxidative Peptide Synthesis Using Nitroxyl Radical/Copper Catalysis**
Riki Yamakawa*, Shuhei Akutsu, Shota Nagasawa, Yusuke Sasano, Yoshiharu Iwabuchi（Graduate School of Pharmaceutical Sciences, Tohoku University）

2P-92S **Mechanochemical Methanation of Carbonates Over a Ni/Al Alloy**
Naoya Ito*, Naoya Sakurada, Tatsunori Iwamura, Tomohiro Ichikawa, Takashi Shigeta, Takashi Ikawa, Hironao Sajiki（Laboratory of Advanced Chemistry and Next Generation Energy Chemistry Joint Research Laboratory, Gifu Pharmaceutical University, Aichi Institute of Technology）

2P-93S **Development of SNAr reactions for the synthesis of carbazoles**
Rui Ishikawa*, Takashi Shigeta, Tomohiro Ichikawa, Takashi Ikawa（Laboratory of Advanced Chemistry, Gifu Pharmaceutical University, Gifu Pharmaceutical University）

2P-94S **Biomimetic Straightforward Conversion of Ergosterol to Gargalol C and Strophasterol A: Chemical Demonstration of Putative Biosynthetic Pathways**
Yui Kanda*, Shoji Kobayashi（Osaka Institute of Technology）

2P-95S **Synthesis of chiral spiro compounds by decarboxylative intramolecular aldol reaction**
Akito Teraoka*, Kazutaka Shibatomi（Department of Applied Chemistry and Life Science, Toyohashi University of Technology）

2P-96S **Organocatalytic Aerobic Oxidative Monodealkylation of *tert*-Amines to *sec*-Amines**
Shuhei Akutsu*, Yusuke Sasano, Haruki Shimabayashi, Ryota Sasaki, Yoshiharu Iwabuchi（Graduate School of Pharmaceutical Sciences, Tohoku University）

2P-97S **Development of a Shrimp Shell-Derived Copper-Catalyzed Solid-Phase Oxidation System for Phenolics**
Mizuki Matsui*, Kousuke Asano, Hiromi Hamamoto（Faculty of Agriculture, Meijo University）

Keynote Speakers' Profile

K-1	Hiroshi Iwamura (Chugai Pharmaceutical, Japan)
K-2	Eunpyo Hong (SK pharmteco SM Asia, South Korea)
K-3	Matthew S. Sigman (University of Utah, USA)
K-4	Cheng Yi Chen (Asymchem Laboratories (Tianjin), China)
K-5	Takahiro Kawajiri (SHIONOGI, Japan)
K-6	David Entwistle (Codexis, USA)
K-7	Dawei Ma (Shanghai Institute of Organic Chemistry, China)
K-8	Rebecca T. Ruck (MSD, USA)
K-9	Joji Tsurumoto (iFactory, Japan)
K-10	Thomas Wirth (Cardiff University, UK)
K-11	Daniel Mink (InnoSyn BV, The Netherlands)
K-12	Anil S. Khile (Eisai Pharmaceuticals India, India)
K-13	Takashi Ohshima (Kyushu University, Japan)

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Hiroshi Iwamura, Ph.D.

Head of API Process Development Department, Chemical Process

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【Education and Career】

Hiroshi Iwamura, Ph.D., is Head of the API Process Development Department at Chugai Pharmaceutical Co., Ltd., where he leads chemical process R&D. With more than 30 years of experience in the pharmaceutical industry, he has developed expertise in API manufacturing, quality control strategy, pharmaceutical regulatory science, technology development, and project management.

Before joining Chugai Pharmaceutical Co., Ltd. in 2010, Dr. Iwamura served as a process chemist at Mitsubishi Tanabe Pharma Corporation (now Tanabe Pharma Corporation) from 1994 to 2010. He earned his M.S. in Pharmaceutical Sciences from Hokkaido University in 1994 and his Ph.D. in Science from Kyoto University in 2006 under the supervision of Professors Tamio Hayashi and Donna G. Blackmond, focusing on reaction kinetics analysis.

K－2



Eunpyo Hong

Principal Researcher,
Small Molecule Asia (SK biotek),
SK pharmteco

【Education and Career】

2010 B.S. Chemical Engineering, University of Seoul, Seoul, South Korea

2015 Ph.D. Chemical Engineering, University of Seoul, Seoul, South Korea (Integrated M.S.–Ph.D)

2015 Postdoctoral Researcher, Chungbuk National University, Chungju, South Korea

2015–2016 Senior Researcher, Heesung Metal Co., Incheon, South Korea

2016–2018 Invited Professor, Chungbuk National University, Chungju, South Korea

2018–Present SK pharmteco Small Molecule Asia (SK biotek), Daejeon, South Korea

2026–Present Principal Researcher

2020–2026 Senior Researcher

2018–2020 Junior Researcher

【Fellowships and Awards】

2014 Best Paper Award, University of Seoul

2021 Employee of the Year, SK biotek

2022 Outstanding Group Award (Catalyst Group), SK biotek

K－3



Matthew Sigman

Distinguished Professor of Chemistry
Department of Chemistry
University of Utah

【Education and Career】

1992 B.S. Chemistry, Sonoma State University, California
1996 Ph.D., Organometallic Chemistry, Washington State University
1996 – 1999 NIH Postdoctoral Fellow in Chemistry, Harvard University
1999 – 2004 Assistant Professor of Chemistry, University of Utah
2004 – 2008 Associate Professor of Chemistry, University of Utah
2008 – 2016 Professor of Chemistry, University of Utah
2016 – present Distinguished Professor of Chemistry, University of Utah
2019 – 2024 Chair, Department of Chemistry, University of Utah

【Fellowships and Awards】

2004 Camille and Henry Dreyfus Teacher Scholar Award
2004 Pfizer Award for Creativity in Organic Chemistry
2010 Arthur C. Cope Scholar Award
2012 Elected Fellow of the American Association for the Advancement of Science
2017 ACS Award for Creative Work in Synthetic Organic Chemistry
2018 Alexander von Humboldt Foundation Research Award
2022 University of Utah Distinguished Teaching Award
2025 University of Utah Distinguished Mentor Award
2026 Elected Member of the American Academy of Arts and Sciences

K－4



Cheng Yi Chen, PhD

Chief Technology Officer
Asymchem Laboratories

Dr. Cheng Yi Chen is a distinguished leader in chemical process development with over three decades of experience across at some of the most prominent names in the pharmaceutical industry, including Bristol Myers Squibb, Mirati Therapeutics, and Janssen Pharmaceutical Companies of Johnson & Johnson. In his current role as Chief Technology Officer at Asymchem Group, Dr. Chen oversees the development and manufacturing of all small molecule drug substance and drug products. His extensive expertise spans across R&D leadership, CMC strategy, GMP compliance, regulatory interactions, and global supply chain management, making him a pivotal figure in advancing pharmaceutical innovation from new molecular entities (NMEs) to commercialization.

Dr. Chen's impact is further evidenced by his significant contributions to the commercial launch of multiple oncology drug substances, including the breakthrough drug *adagrasib* (MRTX849). His leadership in developing cost-effective and sustainable manufacturing processes for small molecules has resulted in successful filing of multiple INDs and NDAs, reinforcing his reputation as a leading authority in chemical process development. With a proven record of building high-performing teams, Dr. Chen has consistently driven innovation in drug development, contributing to the successful market entry of numerous pharmaceutical products.

Beyond his industry leadership, Dr. Chen is a prolific contributor to the scientific community. He has authored more than 120 publications and patents and delivered over 80 invited presentations at prestigious conferences worldwide. His ability to bridge the gap between scientific research and regulatory requirements has been instrumental in accelerating development timelines for life-saving therapies, further solidifying his influence on the advancement of modern medicine.

Dr. Chen holds a PhD from the Ohio State University, where he completed the first total synthesis of *dl-Stenine* under the guidance of Professor David J. Hart. His career achievements have been recognized with numerous awards, including the CEO Special Recognition Award at Mirati Therapeutics and the prestigious Edward J. Grabowski Award for Excellence in Process Research at Merck.

K－5



Takahiro Kawajiri
API R&D Laboratory,
Pharmaceutical Technology Research Division,
Shionogi & Co., Ltd.

【Education and Career】

2010－2016	B.S. at Gifu Pharmaceutical University (Prof. Hironao Sajiki)
2016－2020	Ph.D. at Gifu Pharmaceutical University (Prof. Hironao Sajiki)
2020－present	Shionogi & Co., Ltd.

During the above

2018	Visiting student at Scripps Research (Prof. Ryan A. Shenvi)
2024	Visiting Researcher at Okayama University (Prof. Seiji Suga)
2025－2026	Associated Researcher at Yale University (Prof. Seth B. Herzon)

【Fellowships】

2016－2017	Sasakawa Scientific Research Grant
2017－2020	JSPS Research Fellow (DC1)

【Awards】

2017	Sasakawa Science Research Encouragement Prize Sasakawa Scientific Research Grant from The Japan Science Society
2026	Chemical & Environmental Technology Award The Kinka Chemical Society

K-6



David Entwistle

Codexis, USA

David is a synthetic organic chemist who obtained his Ph.D in 1994 under Prof. Steve Ley FRS. After two post-doctoral positions focused on synthetic organic methodologies and total synthesis David began his industrial career in 1998 at Pfizer Process Chemistry, UK, working on many early to mid-clinical phase APIs.

In 2012 David joined Codexis where he led the process chemistry department for eleven years. He has conceived and had oversight of many diverse enzyme screening and engineering projects across pharma other enzyme applications. Several of these programs have culminated in implemented commercial processes at the client's sites. In late 2025 David joined Codexis' Client Technical Services as Senior Director.

K－7



Dawei Ma

Shanghai Institute of Organic Chemistry,
Chinese Aacdemy of Sciences

Dr. Dawei Ma received his PhD in 1989 from Shanghai Institute of Organic Chemistry (SIOC), and did his postdoctoral studies at the University of Pittsburgh and Mayo Clinic. He returned to SIOC in 1994, and was appointed as research professor in 1995. From 2001 to 2010 he was the director of State Key laboratory of Bioorganic and Natural Products. He also served as a deputy director of SIOC from 2011 to 2019. He is presently the chairman of scientific committee of SIOC and a chaired professor of Southern University of Science and Technology. His research interests currently focus on the development of new synthetic methodologies, the total synthesis of complex natural products and their SAR and action mode studies, as well as the discovery of small modulators for target proteins and special biological processes. He has received numerous scientific awards, which include Nien-Chu C. Yang Memorial Lectureship Award (2016), Arthur C. Cope Scholars Award (2018), Future Science Prize-Physical Sciences (2018), Outstanding Science and Technology Achievement Prize of Chinese Academy of Sciences (2019) and Yao-Zeng Huang Award on Organometallic Chemistry (2021).

K－8



Rebecca T. Ruck

Associate Vice President, MSD

DSCS Digital Technologies

【Education and Career】

1998 A.B. Chemistry, Princeton Unviersity, Princeton, New Jersey

2003 Ph.D. Chemistry, Harvard University, Cambridge, Massachusetts

2003 NIH Postdoctoral Fellow in Chemistry, University of California-Berkeley

2005 Senior Scientist, MSD Process R&D, Rahway, NJ USA

2012 Director, MSD Process R&D, Rahway, NJ USA

2018 Executive Director, MSD Process R&D, Rahway, NJ USA

2022 Associate Vice President, MSD Process R&D, Rahway, NJ USA

2026 Associate Vice President, MSD DSCS Digital Technologies, Rahway, NJ USA

【Fellowships and Awards】

2014 ACS Division of Organic Chemistry Young Investigator Award

2016 ACS Women Chemists Committee Rising Star

2017 EPA Green Chemistry Greener Synthetic Pathways Team Award: letermovir

2018 ACS Award for Encouraging Women into Careers in the Chemical Sciences

2020 EPA Green Chemistry Greener Reaction Conditions Team Award: ProTide Synthesis

2020 ACS Fellow

2021 EPA Green Chemistry Greener Synthetic Pathways Team Award: gefapixant citrate

K-9



Joji Tsurumoto
Director, CTO
iFactory inc.

【Education and Career】

2004 B.S. Pharmaceutical Sciences, Nagasaki University, Japan
2006 M.S. Pharmaceutical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Japan
2006 Research Scientist, Pharmaceutical Research Division, Tanabe Seiyaku Co., Ltd.
2018 Deputy Senior Research Scientist, Process Research Department, Supply Chain Management Division, Mitsubishi Tanabe Pharma Corporation
2019 Senior Engineer, Technology Development Department, Kakegawa Plant, Takasago Chemical Co., Ltd.
2020 Manager, Technology Development Department, Kakegawa Plant, Takasago Chemical Co., Ltd.
2023 Chief Field Engineer, iFactory inc.
2024 General Manager, Business Development Center, Business Development Division, iFactory inc.
2025 Director & CTO, iFactory inc.

【Fellowships and Awards】

2022 The 4th Japan Open Innovation Prize, Minister of Economy, Trade and Industry Award
2023 The 15th Engineering Encouragement Special Award, Engineering Advancement Association of Japan

K-10



Thomas Wirth
Cardiff University

【Education and Career】
1992 Ph.D. Chemistry, Technische Universität Berlin, Germany
1992 JSPS Postdoctoral Fellow, Kyoto University
1994 Habilitation, Universität Basel, Switzerland
2000 Full Professor, Cardiff University, United Kingdom

【Fellowships and Awards】
1992 scholarship from the Japan Society for the Promotion of Science (JSPS)
1994 Liebig stipend (Fonds der Chemischen Industrie)
2000 Werner Prize from the New Swiss Chemical Society
2010 Fellow of the Royal Society of Chemistry (FRSC)
2013 JSPS London Furusato award
2016 Wolfson Research Merit Award (Royal Society)
2016 Elected fellow of The Learned Society of Wales
2016 Bader award (Royal Society of Chemistry)
2017 Distinguished Visiting Project Professor at Kyoto University, Japan
2023 Adjunct Professor, IISER Bhopal, India

K-11



Daniel Mink

CEO InnoSyn BV

Geleen, The Netherlands

【Education and Career】

1989 B.S. Chemistry, Johannes Gutenberg University of Mainz, Germany

1992 M.S. Chemistry, NSERC, University of New Brunswick, Canada

1996 Ph.D. Chemistry, NSERC, University of New Brunswick, Canada

1998 NSERC Postdoctoral Fellow in Chemistry, MIT and Scripps Research Institute

1998 Scientist DSM Research, The Netherlands

2000 Senior Scientist DSM Research, The Netherlands

2002 Principal Scientist DSM Research, The Netherlands

2010 Corporate Scientist, Head Life Science Chemistry DSM Research, The Netherlands

2017 CEO InnoSyn BV, The Netherlands

K-12



Anil Shahaji Khile

Senior Director & Deputy Head,
Pharmaceutical Science & Technology,
Deep Human Biology Learning,
Eisai Pharmaceuticals India Private Limited

【Education and Career]

1993 B.S. Chemistry, University of Pune, Maharashtra State, India
1993 M.Sc. Chemistry, University of Pune, Maharashtra State, India
2018 Ph.D. Chemistry, Rayalaseema University, Andhra Pradesh, India
1995 Sun Pharmaceuticals Limited (India)
1997 Merck India Limited (India)
2004 Glenmark Pharmaceuticals Limited (India)
2006 Actavis Pharma Development Centre Pvt. Limited (India)
2011 Eisai Pharmaceuticals India Private Limited (India)

【Fellowships and Awards】

Recipient of;

2004 Managing Director Award for Development of UVA/UVB Sun Protectors
2010 Awardee for achieving the successful Commercialisation of Cholesterol-Lowering Agent
2016 Special Award for Novel Program Approach and Progression Scheme Supports Speed to Clinic
2023 Drug Discovery of Novel Antifilarial Drug Candidates Chemistry Biology Interface Horizon Prize: Rita and John Cornforth Award by Royal Society of Chemistry

K－１３



Takashi Ohshima

Distinguished Professor
Graduate School of Pharmaceutical Sciences,
Kyushu University

【Education and Career】

1991 B.S. Pharmaceutical Sciences, The University of Tokyo, Japan
1993 M.S. Pharmaceutical Sciences, The University of Tokyo, Japan
1996 Ph.D. The University of Tokyo, Japan
1996 Otsuka Pharmaceutical Co., Japan
1997 Postdoctoral fellow, The Scripps Research Institute, USA
1999 Assistant Professor, The University of Tokyo, Japan
2005 Associate Professor, Osaka University
2010 Full Professor, Kyushu University
2021 Distinguished Professor, Kyushu University

【Fellowships and Awards】

1993 JSPS Research Fellow
2000 The Society of Synthetic Organic Chemistry, Japan, Fujisawa Award in Synthetic Organic Chemistry
2004 The Pharmaceutical Society of Japan Award for Young Scientists
2008 The Japanese Society for Process Chemistry Award for Excellence
2010 Green Sustainable Chemistry Award with MEXT Award
2012 Asian Core Program Lectureship Award (2012 China, 2013 Korea, 2015 Singapore, 2016 Taiwan, 2017 Singapore, 2018 China, 2024 Taiwan)
2014 The Pharmaceutical Society of Japan Award for Divisional Scientific Promotions
2014 The Japanese Society for Process Chemistry Award for Excellence
2016 The Japanese Society for Process Chemistry Award for Excellence
2017 ISPAC 2017 Lecture Award
2018 The Society of Synthetic Organic Chemistry, Japan, Nissan Chemical Industries Award for Novel Reaction and Method
2020 Organic Process Research & Development Highlights from the Literature Awarded for the year of 2020
2023 BCSJ (Bull. Chem. Soc. Jpn.) Award
2024 NAGASE Science Technology Foundation Award

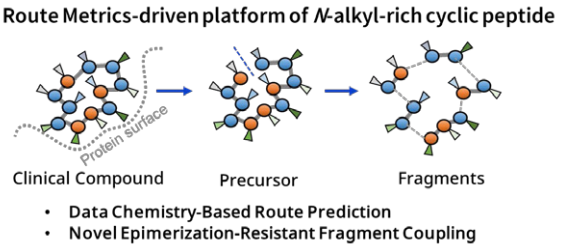
Graphical Abstracts

Keynote Lectures

K-1

Beyond the Paradigm:
Liquid-Phase Synthesis of *N*-Alkyl-Rich Cyclic Peptide from the First Scale-Up Manufacturing

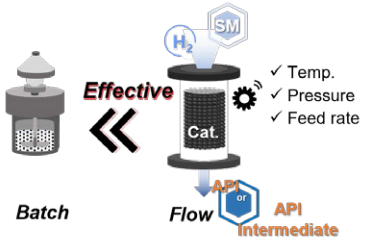
Hiroshi Iwamura,*
API Process Development Dept., Chugai Pharmaceutical Co., Ltd.



K-2

Development of Efficient Catalytic Flow Process: Stratergies and Insights for Pharmaceutical Applications

Eunpyo Hong,* Ryan Seongho Oh
Small Molecule Asia (SK biotek), SK pharmteco



K-3

Using Data Science and Machine Learning in Synthetic Process Optimization

Matthew S. Sigman
Department of Chemistry
University of Utah, Salt Lake City, UT (USA)

K-4

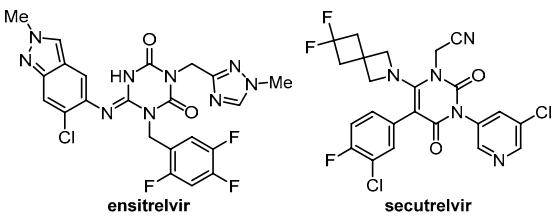
From Molecule to Medicine: Innovator–CDMO Synergy in Modern Drug Development

Cheng Yi Chen
Asymchem Laboratories (Tianjin), China

K-5

Innovations in SHIONOGI Process Chemistry Scalable Manufacturing Strategies for COVID-19 Antivirals

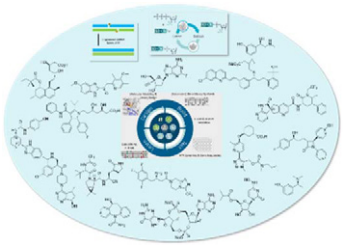
Takahiro Kawajiri
API R&D Laboratory, Shionogi & Co., Ltd.



K-6

ENABLING COMPLEX INTERMEDIATE AND API SYNTHESES AT SCALE WITH ENGINEERED ENZYMES.

Dr. David A. Entwistle
Codexis Inc, Redwood City, CA, USA



K-7

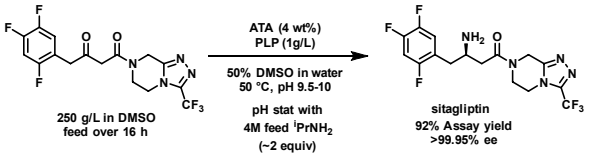
Ligand Development for Cu-Catalyzed Arylation of Nucleophiles

Dawei Ma
Shanghai Institute of Organic Chemistry, Chinese Aacdemy of Sciences.

K-8

Enabling Technologies to Drive the MSD Portfolio

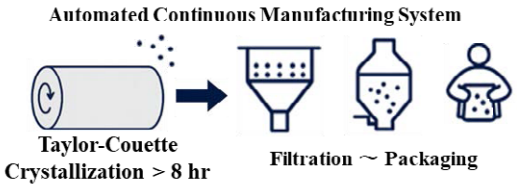
Rebecca T. Ruck*
MSD Development Sciences & Clinical Supply



K-9

Development and Demonstration of an Automated Continuous Manufacturing System for Fine Chemicals Using Taylor–Couette Crystallization

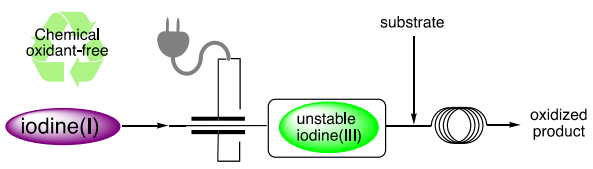
Joji Tsurumoto *, Nobuyoshi Doi, Takao Saito
iFactory inc.



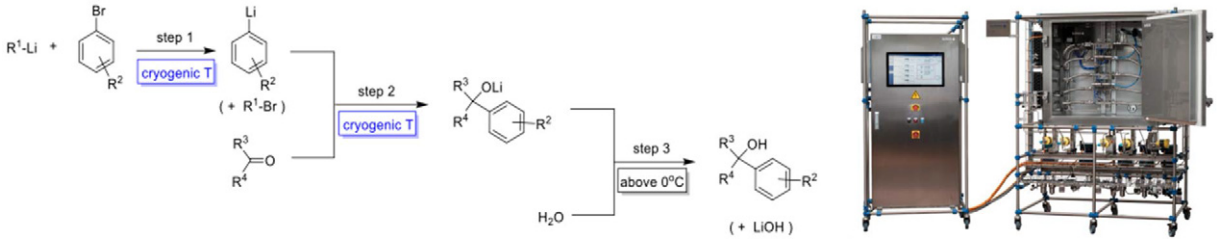
K-10

Scaling Electrochemistry: From Lab Curiosities to Continuous Processes

Thomas Wirth*
School of Chemistry, Cardiff University
Cardiff, CF10 3AT, United Kingdom



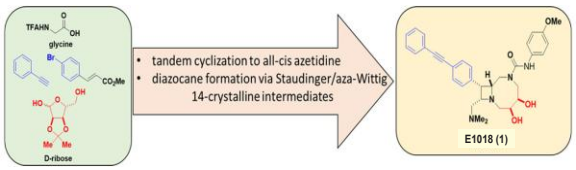
K-11



K-12

Process Chemistry Realisation for Neglected Tropical Diseases (NTDs): Enabling Affordable and High-Quality Medicines for Patient Benefit

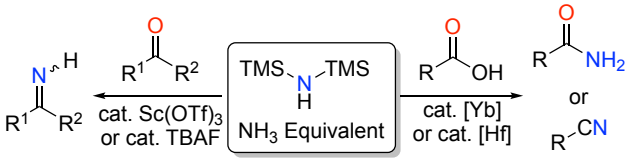
Anil Shahaji Khile,* Pharmaceutical Science & Technology, Deep Human Biology Learning, Eisai Pharmaceuticals India Private Limited



K-13

Bis(trimethylsilyl)amine as a Versatile Ammonia Equivalent: Catalytic Direct Synthesis of N-Unsubstituted Ketimines, Primary Amides, and Nitriles

Takashi OHSHIMA*
Graduate School of Pharmaceutical Sciences, Kyushu University



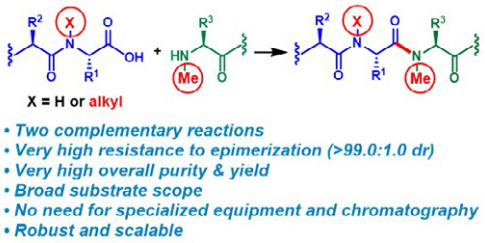
Poster Presentation
July 2nd. (Thu.)

1P-01

Development of Two Complementary Epimerization-Resistant Fragment Coupling Reactions for Highly Convergent Synthesis of *N*-Alkyl-Rich Peptides

Shio Komiya,* Takumi Matsumoto, Kohei Fujii, Hiroshi Iwamura, Kenji Maeda

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



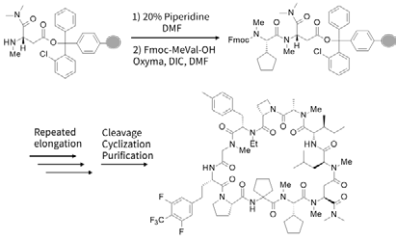
1P-02

Development of Solid-Phase Synthesis Method for N-Methyl Rich Peptides

Junichi Shiina,* Hirotaka Ejima, Manabu Wadamoto, Kotaro Iwasaki

Discovery Chemistry Dept., API Process Development Dept.

Chugai Pharmaceutical. Co.,Ltd.

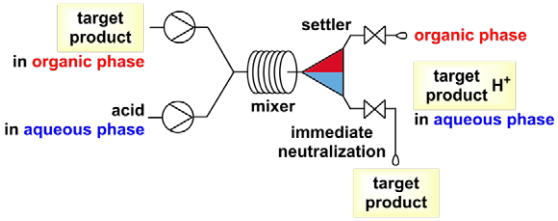


1P-03

Rapid Extraction of Acid-Labile Compounds into an Aqueous Phase Using a Mixer-Settler under Continuous Flow Conditions

Masahiro Hosoya,* Kengo Inoue

API R&D Laboratory, Shionogi & Co., Ltd.

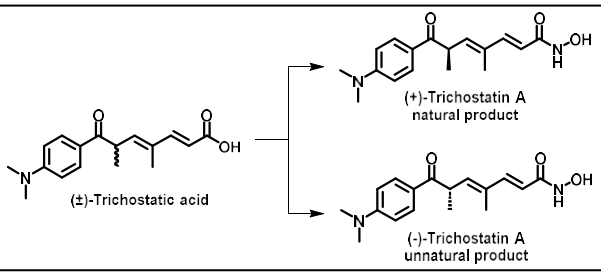


1P-04

Practical Synthesis of Both Enantiomers of Trichostatin A

Takeo Fukuda*, Shinya Sasayama, Toshiharu Takeuchi, Kyohei Kawano, Kenta Suzuki

Tokyo Chemical Industry Co., Ltd.

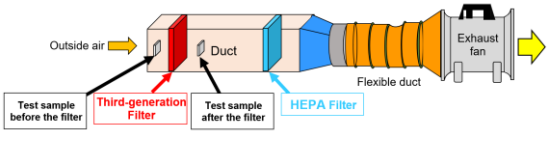


1P-05

The Role of NO and NO_2 in *N* -Nitroso Compounds Formation in API and Formulation

Takuma Onai*, Tomohiro Kaku, Ryota Nomura , Hideyuki Sogo, Misako Iwazawa and Osamu Uchikawa

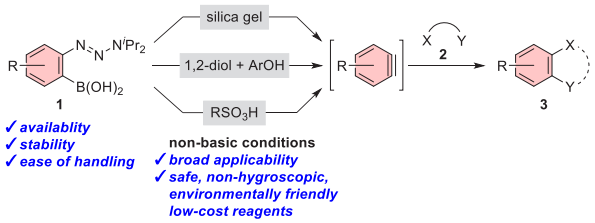
Towa Pharmaceutical Co., Ltd.



1P-06

Development of a novel practical aryne precursor: *o*-triazenylarylboronic acid

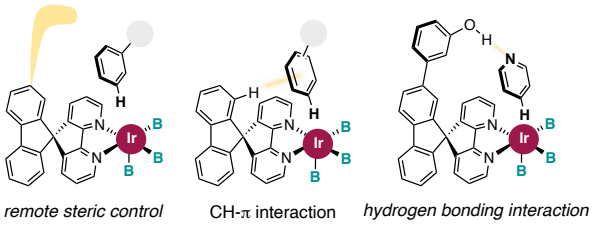
Motoki Ito*
Meiji Pharmaceutical University



1P-07

Spirobipyridine Ligands as a Unique Platform for Molecular Recognition and Reaction Control through Noncovalent Interactions

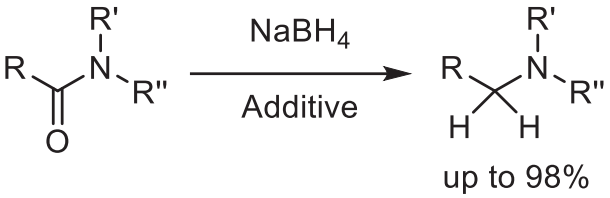
Sobi Asako,* Laurean Ilies
RIKEN Center for Sustainable Resource Science



1P-08

Review on the use of additives for reduciton of amides using $NaBH_4$

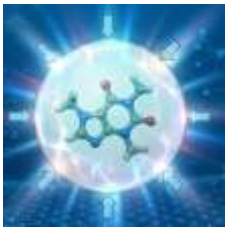
Mitsuhiko Izawa*
Advanced Sciences Department, Nomura Jimusho, Inc.



1P-09

Accessible and Automated GUI-Driven Discovery of Drug Degradation Mechanisms

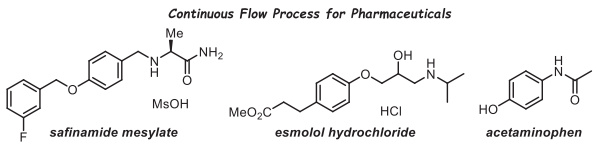
Pavel A. Dub*, Schrödinger, Inc., San Diego, CA, USA



1P-10

Development of a Packed-Bed Continuous Flow Process for Pharmaceuticals with Integrated Crystallization

Kwihwan Kobayashi*
Catalytic Chemistry Research Institute, National Institute of Advanced Industrial Science and Technology (AIST)



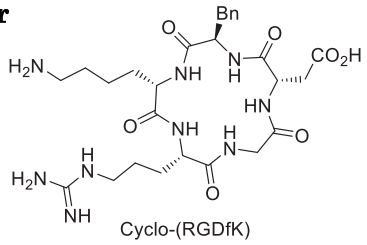
1P-11

An Efficient Synthesis of Cyclo(-RGDfK) Using Microflow Reactor

Naoto Yamasaki,[1]* Mina Kim,[1] Kana Miyamoto,[1] Yuma Otake,[2] Kyohei Adachi,[2] Daisuke Kubo,[2] Shinichiro Fuse[1]

[1]Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University

[2]Innovation Center, Marketing Headquarters, Yokogawa Electric Corporation



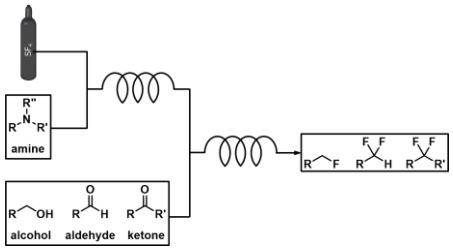
Cyclo-(RGDfK)

1P-12

Application of Continuous Flow Technology to Halogenation Reactions at AGC

Kohei Azami,* Takuma Hirata, Yu Takeuchi

Technology General Division Innovative Technology Laboratories, AGC Inc.

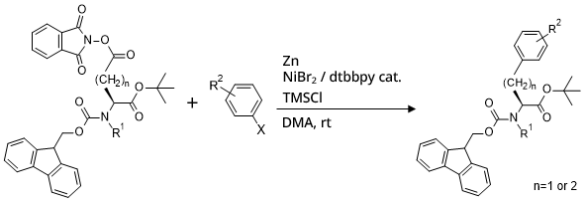


1P-13

Process Development of Aromatic Amino Acids Aimed at Accelerating Mid Size Molecule Drug Discovery

Manabu Wadamoto, Atsuya Shimizu*

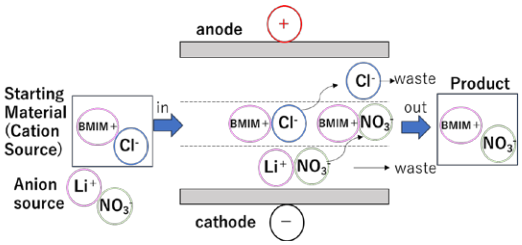
Discovery Chemistry Dept., Chugai Pharmaceutical Co., Ltd.



1P-14

A novel flow device for one-step ionic liquid synthesis

Junpei Takayanagi[1]*, Masanori Motokawa[1], Kyo Miyaki[1], Yu Muto[1], Ryutaro Ohira[1], Ryota Asano[2], Hiroaki Kanayama[2], Shin-Ichi Ohira[3] [1]GL Sciences Inc.,[2]Sunactis Co.,Ltd. [3]KumamotoUniversity

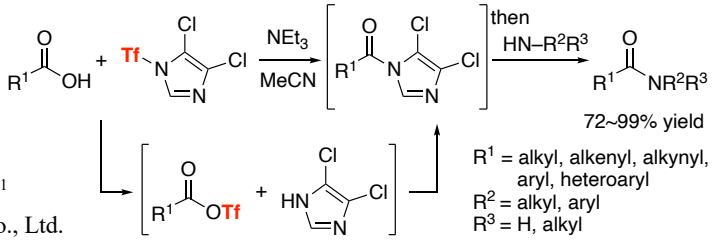


1P-15

Practical Amide Condensation of Carboxylic Acids with Amines Using *N*-(Trifluoromethanesulfonyl)imidazole

Takeshi Yamada,[1]* Kotoha Nagasaki,[1] Aika Nakashima,[1] Isao Morita,[1] Kogaku Kimura,[2] Ren Tomita,[2] Katsuhiko Akiyama,[2] Manabu Hatano[1]

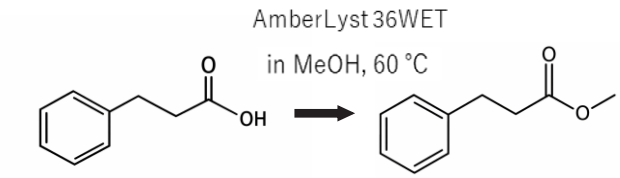
[1]Kobe Pharmaceutical University, [2]Central Glass Co., Ltd.



1P-16

On-line Monitoring of Flow Synthesis Reactions Using Nexera FV

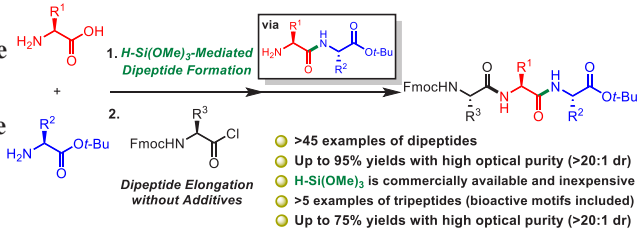
Ayano Tanabe, * Makoto Ogaito, Katsumasa Sakamoto
Shimadzu Corporation.



1P-17

N-terminal Free Dipeptide Mediated Oligopeptide Synthesis from Unprotected Amino Acids and Amino Acid *t*-Butyl esters Using Trimethoxysilane

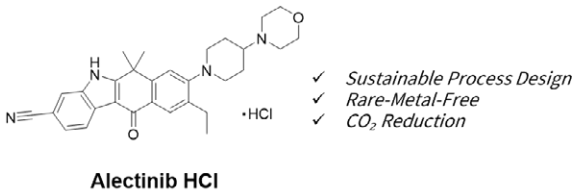
Alex Boateng,* Tomohiro Hattori, Hisashi Yamamoto
Peptide Research Center, Chubu University.



1P-18

Second-Generation Process:
A Sustainable Route to Alectinib's Indole Core

Mami Yamaguchi*, Hiroshi Iwamura, Kenji Maeda
API Process Development Department,
Chugai Pharmaceutical Co., Ltd.

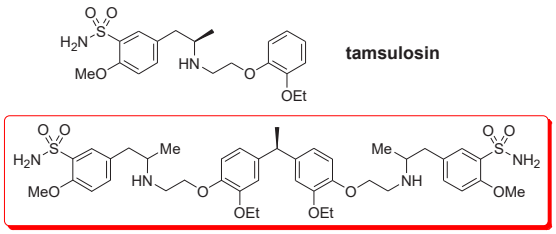


Alectinib HCl

1P-19

Tamsulosin-Dimeric Impurity: Identification and Elucidation of Its Formation Mechanism, Leading to the Efficient Manufacturing Process of the API

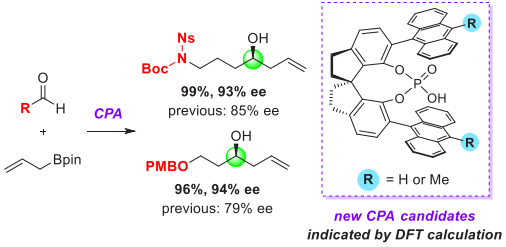
Tatsunori Sato,* Sadayuki Maeda, Tetsuya Kawashima,
Daijiro Hayashi, Hiroki Moriwaki, Kanji Meguro
Hamari Chemicals, Ltd.



1P-20

DFT Calculation-Assisted Virtual Screening to Refine Chiral Phosphoric Acid-Catalyzed Allylboration

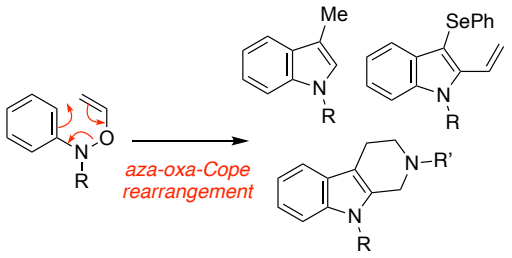
Shigenobu Umemiya,* Takumi Hirata, Masahiro Terada
Graduate School of Science Tohoku University



1P-21

Synthesis of Indoles via Aza-oxa-Cope Rearrangement

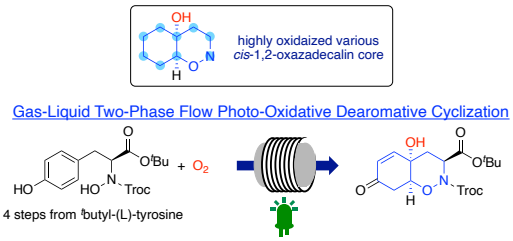
Tomoki Uchida, Daiki Oka, Ryosuke Saito, Tomomi Ohtsuka,
Yusuke Miyazawa, Ken-ichi Takao, Akihiro Ogura*
Keio University



1P-22

Unified Asymmetric Synthesis of Trichodermamides A–F: The Power of Gas-Liquid Two-Phase Flow Photo-Oxidation

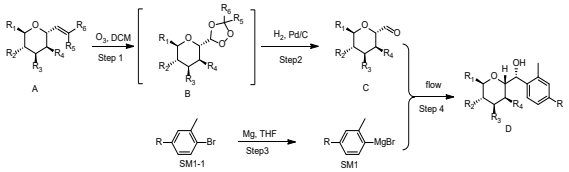
Atsushi Kimishima,* Yujin Takeshita, Kazumi Ikegami
Rei Nagata, Masayoshi Arai
Graduate School of Pharmaceutical Sciences, The University of Osaka



1P-23

Enabling the Scale-up of Synthesis Involving Safety Risk and Intermediates Stability Problems

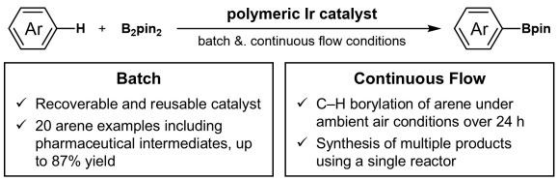
Naoki Omori[1*], Mo Jia[2], Hongwei Yang[2]
[1] WuXi AppTec Japan, [2] WuXi STA



1P-24

Development of Polymeric Iridium-Catalyzed C–H Borylation of Arenes under Batch and Continuous Flow Conditions

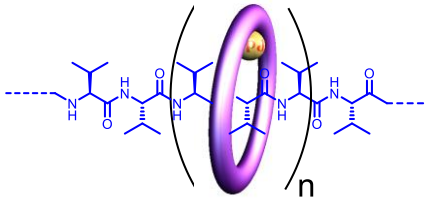
Zhenzhong Zhang,* Aya Ohno, Yoichi M. A. Yamada
RIKEN Center for Sustainable Resource Science



1P-25

Peptide-based Rotaxanes Assembled via Square-Planar Palladium Coordination

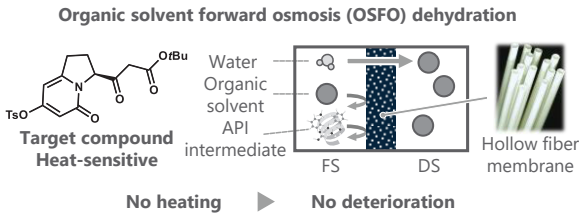
Yasuhito Koyama,* T. Shinoda, C. Kurihashi, A. Miyazato,
I. Osaka, K. Yamamoto, M. Hamada, N. Nakajima
Dept. of Pharm. Eng., Toyama Prefectural University.



1P-26

Membrane-based non-thermal dehydration for pharmaceutical manufacturing processes

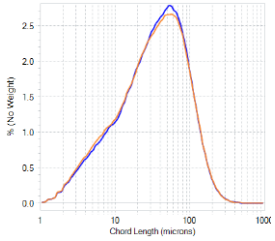
Takahiro Osaki[1]*, Takahiro Baba[1], Yoshiki Kawai[1], Yuji Katayama[1], Masato Mikawa[1], Tatsushi Murase[2], Mikimoto Katsukawa[2], Yuji Kawakami[2]
[1]Asahi Kasei Corporation, [2]Ono Pharmaceutical Co., Ltd.



1P-27

From Process Fingerprints to Scalable Insight: Enabling Lab-to-Plant Crystallization with ParticleTrack™

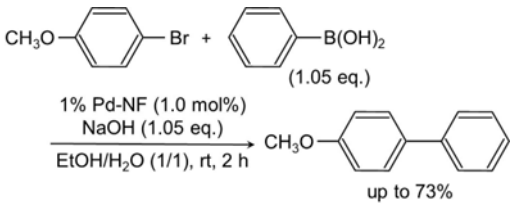
Maiko Kurisaki,* Shuxin Cong
AuotoChem Team, BU LAB Inst., Mettler Toledo K.K.



1P-28

Development of Pd-supported Nonwoven Fabric *via* Graft Polymerization and Its Application to Ligand-free Suzuki-Miyaura Coupling

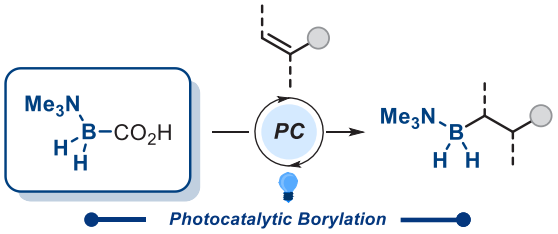
Makoto Komatsu[1]*, Hiroaki Harakawa[1], Takashi Ikawa[2], Hironao Sajiki[3]
[1]Ebara Corporation, [2]Gifu Pharmaceutical University
[3]Aich Institute of Technology



1P-29

Carboxylated Amine–Boranes as Boryl Radical Precursors

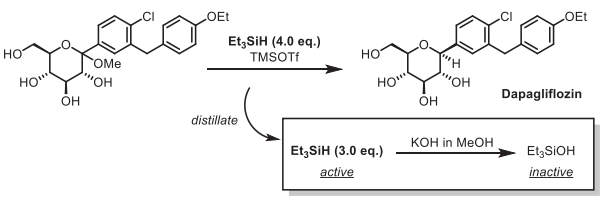
Naoki Yasukawa,[1]* Shuichi Nakamura,[1] Leonori Daniele[2]
[1] Nagoya Institute of Technology
[2] RWTH Aachen University



1P-30

Safe and Scalable Method for Deactivating Triethylsilane in Dapagliflozin Propanediol Monohydrate Production

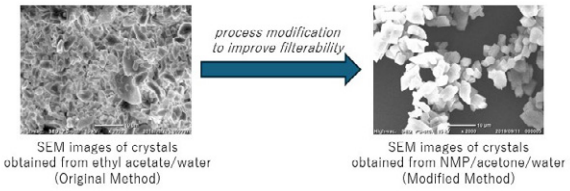
Nanami Kamiyama,* Komori Kenta, Moe Sato, Koto Noguchi, Shigenobu Nishiguchi
API Process Research Department, API Business Division, Towa Pharmaceutical Co., Ltd.



1P-31

Crystallization Process Development in Mixed Solvent Systems to Improve Filterability of Poorly Soluble Pharmaceutical Intermediates

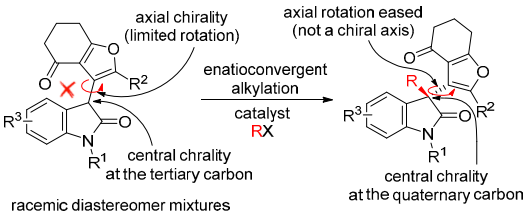
Hisaaki Onoue,* Hiroshi Iwamura
Chugai Pharmaceutical Co., Ltd



1P-32

Enantioconvergent Alkylation for the Construction of Chiral Quaternary Carbon Centers and Control of C(sp³)–C(sp²) Bond Rotation

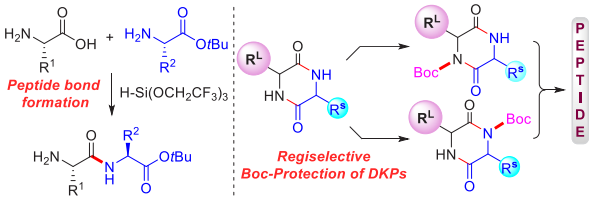
Muhammad Sohail,* Fujie Tanaka
Okinawa Institute of Science and Technology Graduate University



1P-33

Development of Green and Sustainable Strategies for Peptide Synthesis

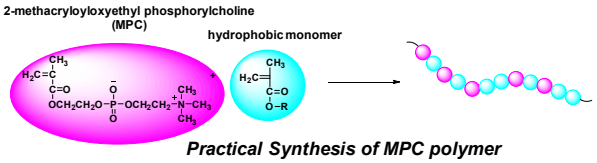
Isai Ramakrishna, * Tomohiro Hattori, Hisashi Yamamoto
Peptide Research Center, Chubu University.



1P-34

Development of a Practical Synthesis for the Amphiphilic Phospholipid Polymer PMBZU30-100

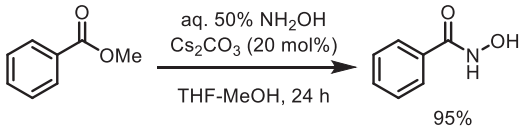
Takeshi Nakaya*, Yoshimine Fujii, Ikuko Ariga,
Fumiya Takahashi
Daiichi Sankyo Co., Ltd.



1P-35

Nucleophilic Acyl Substitution Reaction of Hydroxylamine Catalyzed by Basic Metal Salts

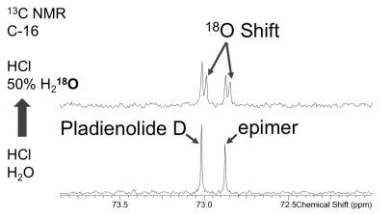
Katsuko Shirai,* Ryuichi Shirai
Faculty of Pharmaceutical Sciences
Doshisha Women's College of Liberal Arts



1P-36

Determination of the Epimerizable Chiral Center of Pladienolide D under Acidic Stress Conditions Using ^{18}O-Labeled Water

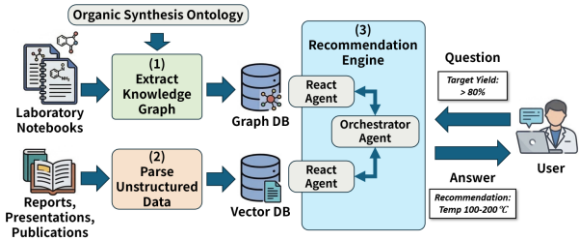
Nao Shibuguchi*, Yumi Asai, Masaharu Gotoda, Takashi Hasebe
Analytical Research Laboratory, Eisai Co., Ltd.



1P-37

Development of Organic Synthesis Experimental Information Utilization System Integrating Knowledge Graphs and Generative AI

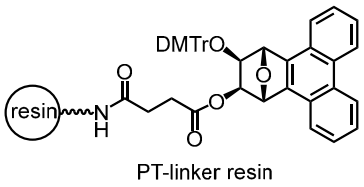
Toshiharu Morishita[1]*, Haruka Hori[1],
Masafumi Tsuyuki[2]*, Shotaro Agatsuma[2], Ryota Noma[2]
[1]Chugai Pharmaceutical Co., Ltd., [2]Hitachi, Ltd.



1P-38

Materials for Improving Oligonucleotide Synthesis

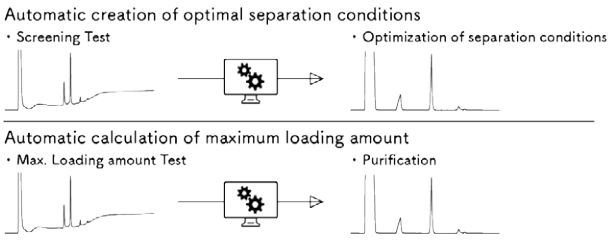
Yoshiyuki Hari,* Kazuki Yamamoto, Ryotaro Yamashita, Yuta Ito, Yasufumi Fuchi
Faculty of Pharmaceutical Sciences, Tokushima Bunri University



1P-39

Expanded Applicability of Our State-of-the-Art Purification Technology to Development-Stage Scales

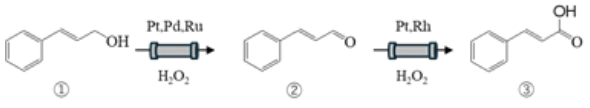
Chie Kushibe[1], Miho Tamura[2], Shio Komiya[2], Naokazu Kumura[1], Tadafumi Horisaki[1], Tsuneaki Kaneko[1], and Katsuhiko Miwa[1]*
(1. ChromaJean Co., Ltd., 2. Chugai Pharmaceutical Co., Ltd.)



1P-40

Precious Metal-Catalyzed Selective Oxidation of Alcohols to Aldehydes and Carboxylic Acids

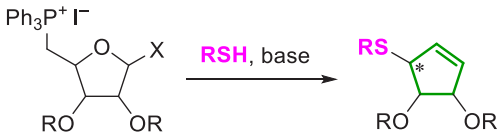
Toshihiko Sakai*[1], Eiichi Nakai[2], Yukiko Okamoto[2], Junki Nagakubo[1], Tomoteru Mizusaki[1], Koichiro Masuda[2]
[1]N.E. Chemcat Corp. [2]National Institute of Advanced Industrial Science and Technology (AIST)



1P-41

Divergent Synthesis of Thio-Substituted Chiral Cyclopentenes via a Domino Reaction of Sugar-Derived Wittig Reagents

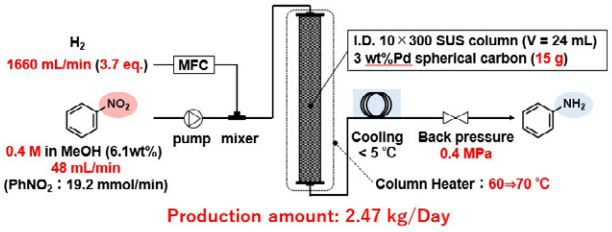
Natsuhisa Oka[1,2,3]*, Yusaku Ito[1], Shoma Horiki[1]
[1]Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University
[2]iGCORE, Gifu University [3]COMIT, Gifu University



1P-42

Scale-Up Study and Challenges in Flow Hydrogenation Reactions

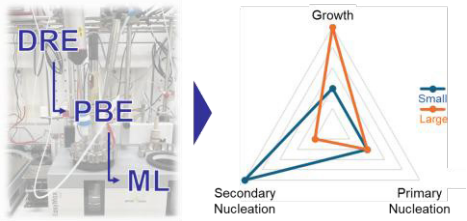
Kenichi Kon,* Keisuke Morisaki
Kawaken Fine Chemicals Co., Ltd.



1P-43

Application of Hybrid Mechanistic and Machine Learning Models to Crystallization Process Optimization

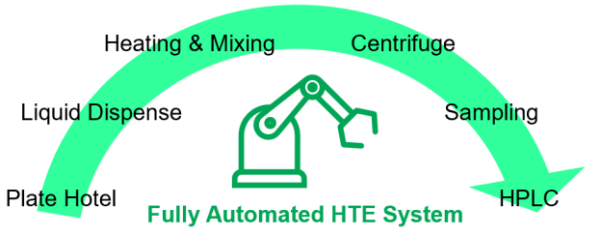
Rei Otsuka*
Department of Process Chemistry, CMC Headquarters, Otsuka Pharmaceutical Co., Ltd.



1P-44

Implementing a Fully Automated High-Throughput Experimentation System for Process Research Acceleration

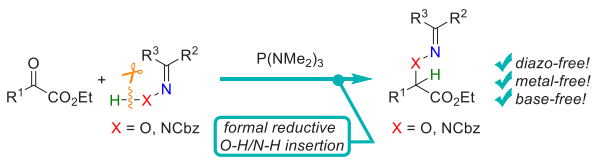
Yuma Otake*
Process Technology Research Laboratories,
Daiichi Sankyo Co., Ltd.



1P-45

Synthesis of imine derivatives via a diazo-free reductive O-H/N-H bond insertion reaction

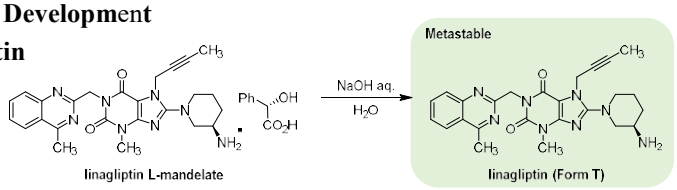
Norihiko Takeda,* Ryouya Maeda, Tomoki Miyashita, Takahiro Yamada, Masafumi Ueda
Kobe Pharmaceutical University



1P-46

Polymorphism Control in Industrial Process Development for the Metastable Crystal Form of Linagliptin

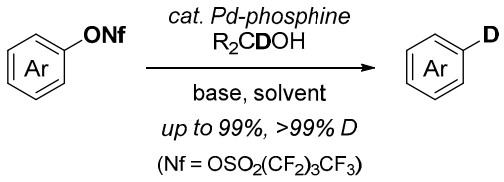
Koto Noguchi,* Koya Shoji, Tomoki Isogai,
Nobuyoshi Doi, Shigenobu Nishiguchi
Towa Pharmaceutical Co., Ltd.



1P-47

Palladium-Catalyzed Deoxygenative Deuteration with Aryl and Heteroaryl Nonaflates as Effective Coupling Partners

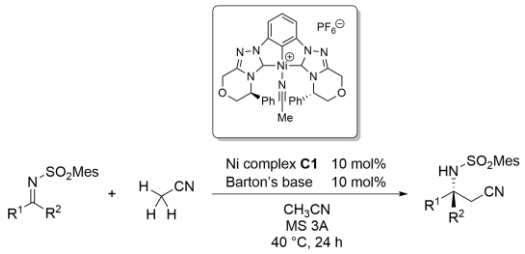
Masami Kuriyama,*[1] Reo Wakiyama,[1] Kotaro Tsukuda,[1]
Tetsuro Morimoto,[1] Kosuke Yamamoto,[1] Yosuke Demizu,[2]
Osamu Onomura[1]
[1] Nagasaki University, [2] National Institute of Health Sciences



1P-48

Pincer-Nickel-Catalyzed Enantioselective Addition of Acetonitrile to Ketimines

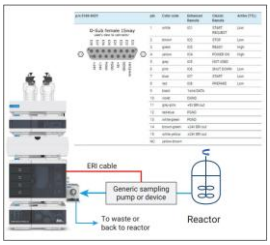
Akira Saito, Asim Kumar Ghosh*, and Masakatsu Shibasaki
Institute of Microbial Chemistry (BIKAKEN), Tokyo



1P-49

Evaluation of Sampling Device Performance and Integration in Online HPLC Process Monitoring

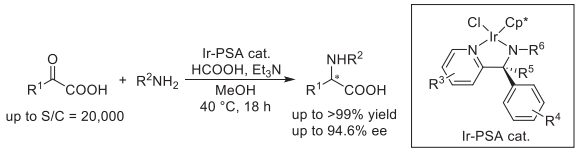
Keiko Hayashi*, Miu Miyashita
Agilent Technologies Japan, Ltd.



1P-50

Efficient Asymmetric Synthesis of *N*-Alkyl-α-Amino Acids by Using a Chiral Iridium Catalyst

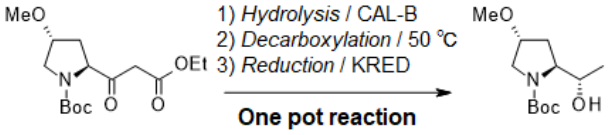
Kenya Yabushita,[1]* Noriyuki Utsumi,[1] Yoshihito Kayaki,[2]
Shigeki Kuwata[3]
[1]Kanto Chemical Co., Inc. [2]Institute of Science Tokyo
[3]Ritsumeikan University



1P-51

Process Development of a Chemoenzymatic Route to an *N* Methylprolinol Derivative

Toru Watanabe*, Hidenori Ochiai, Koji Machida
Bio-Pharma Research Laboratories,
KANEKA CORPORATION

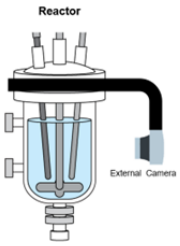


Total yield: 85.4%, Diastereomeric purity: >99.9%

1P-52

AI-Driven Optimization of Solvent Swap Distillation: Integrating Machine Learning Video Imaging for Automated, Scalable, and Sustainable Chemical Processing

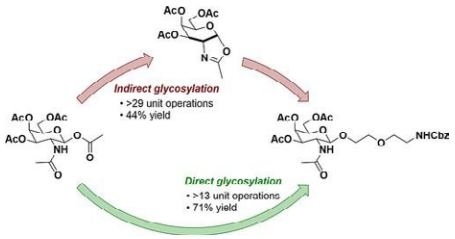
Yoshifumi Fujisawa*, Fabio Visentin, Dan Hallow, Nina Taherimakhsousi
Mettler-Toledo K.K.



1P-53

Maximize Reaction Insight via Data Rich Experiments and Intelligent Analytics

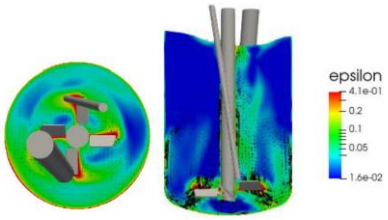
Naomi Fukuda*[1)], Brian Wittkamp[2)]
1) Mettler-Toledo K.K,Japan, 2) Mettler-Toledo International



1P-54

Calculation and Verification of Mixing and Heat Transfer Parameters in Stirred Tank Reactors for Process Development and Scale-up

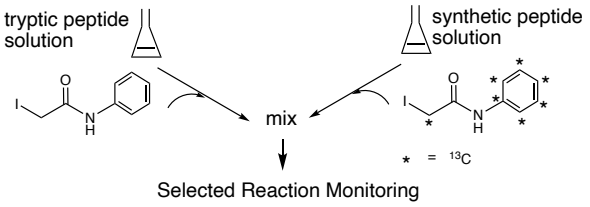
Hisayoshi Hamada* Sanket Salgaonkar, Steve Cropper,
Mettler Toledo



1P-55

Quantitative Analysis of Clinical Proteome by Nano LC-nano-ESI-SRM-MS with the Use of Stable Isotope-labeled and Unlabeled Iodoacetanilides

Sadamu Kurono, Satomi Niwayama*
FUJIFILM Wako Pure Chemical Corporation
Muroran Institute of Technology



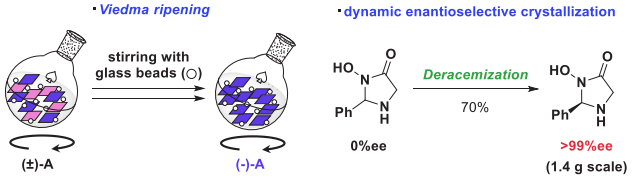
1P-56S

Absolute Asymmetric Synthesis of Cyclic Aminals via Dynamic Crystallization

Oji Kuwabara *,[1], Takeshi Oishi [2], Shogo Fujiki [1], Takaaki Sato [1]

[1] Department of Applied Chemistry, Keio University

[2] School of medicine, Keio University



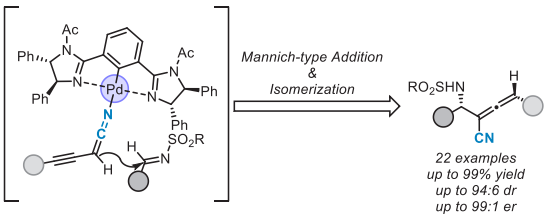
1P-57S

Diastereo- and Enantioselective Allenylation of Imines with Propargyl Nitriles Assisted by Machine Learning

Kosei Miyake,[1]* Ayane Saiganji,[1] Seika Kimura,[1] Yusuke Oyamada,[1] Shintaro Yamasaki,[1] Naoki Yasukawa,[1] Yu Inatsu,[1] Ichiro Takeuchi,[2] Shuichi Nakamura[1]

Nagoya Institute of Technology, Japan[1]

Nagoya University, Japan[2]

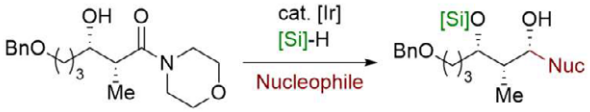


1P-58S

Reductive Nucleophilic Addition to Morpholine Amides for Polyketide Synthesis

Shogo Aoki*, Hiroaki Makita, Masato Kitamura, Shota Iiyama, Misaki Sugiyama, Kouki Mizutani, Toshitaka Okamura, Shogo Fujiki, Takaaki Sato

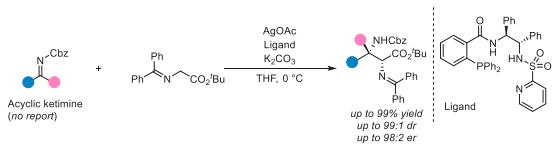
Department pf Applied Chemistry, Keio University



1P-59S

Design of Phosphine-Heteroarenesulfonamide Ligand as Dinuclear Silver Catalysts for Enantioselective Construction of Unnatural Amino Acid

So Nakamura,* Yuka Iizuka, Sayuri Okazima, Syuuiti Nakamura

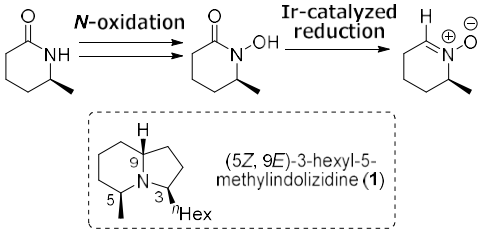


1P-60S

Ir-Catalyzed Reductive Formation of Nitrones Enabling Asymmetric Total Synthesis of Indolizidine Alkaloids

Yuma Honda,* Sora Iwamoto, Toshitaka Okamura, Shogo Fujiki, Takaaki Sato

Faculty of Science and Technology, Keio University.



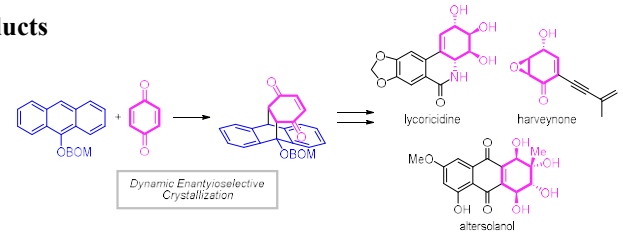
1P-61S

General Synthetic Approach to Various Natural Products Using Dynamic Enantioselective Crystallization

Yuta Shimotani,[1]* Hayama Kojima,[1] Takeshi Oishi,[2] Shogo Fujiki[1], Takaaki Sato[1]

[1]Faculty of Science and Technology, Keio University,

[2]School of Medicine, Keio University

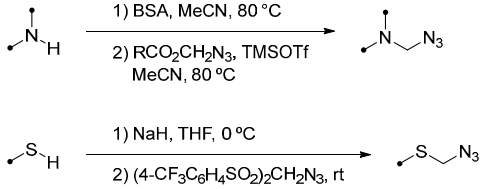


1P-62S

Practical Direct Azidomethylation Methods for the Synthesis of *N*- and *S*-Azidomethyl Compounds

Ryoga Sawahata,* Yuga Takagi, Yoshiaki Kitamura

Gifu University



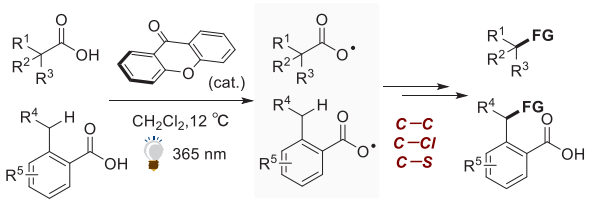
1P-63S

Radical Transformations of Acidic Compounds Enabled by Ketone Photocatalysis

Hayate Sano,*[1] Yuki Goto,[1] Hiroki Hayashi,[2] Kenji Yamashita,[1] Yoshitaka Hamashima[1]

[1]Grad. Sch. Pharm. Sci., University of Shizuoka

[2]Research Center for Materials Science, Nagoya University

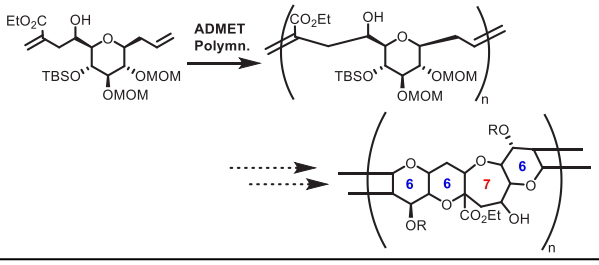


1P-64S

A Strategy for Access to Natural Product-Inspired Poly(cyclic ether) Architectures via ADMET Polymerization

Suzuka Oda,* Mako Yunbe, Noriyuki Nakajima, Masahiro Hamada, Yasuhito Koyama

Department of Pharmaceutical Engineering, Toyama Prefectural University



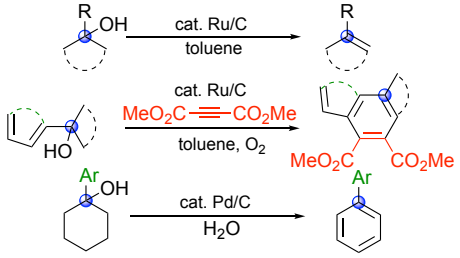
1P-65S

Platinum-Group-Metal-on-Carbon Catalyzed Dehydration of Tertiary Alcohols and its Application to the One-Pot Synthesis of Aromatics

Y. Suganuma, * S. Oyama, S. Akai and Y. Sawama

Graduate School of Pharmaceutical Sciences,

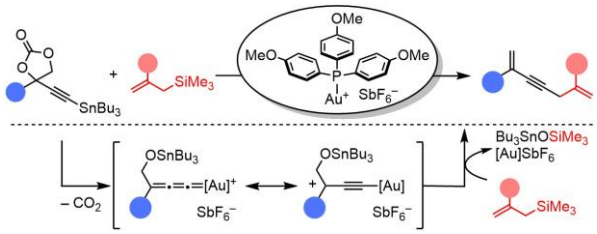
The University of Osaka



1P-66S

Gold(I)-Catalyzed Allylation of Ethynyl Cyclic Carbonates with Allylsilanes

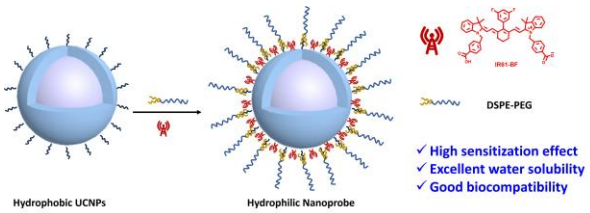
Momoka Ikeda,* Yoshikazu Horino
Chitose Institute of Science and Technology, Japan



1P-67S

Dye-Sensitized Upconversion Nanoparticles with Enhanced Aqueous Luminescence

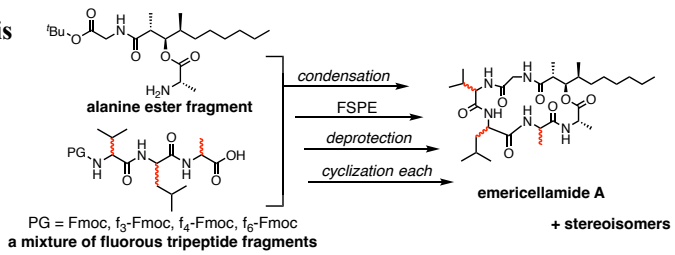
Hengde Li,* Haitao Liu, and Angelo H. ALL
Department of Chemistry, Hong Kong Baptist University.
Kowloon Tong, Hong Kong, China



1P-68S

Synthetic Studies on Fluorous Mixture Synthesis of Emericellamide A and Its Stereoisomers

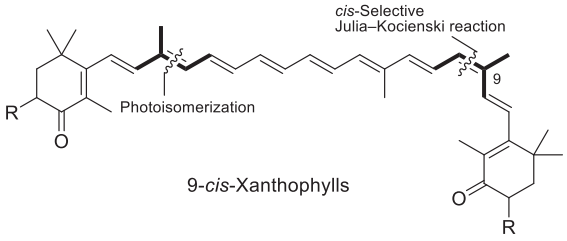
Tsubasa Hamano*, Yuzuki Mizogiwa
Takayuki Shioiri, Masato Matsugi
Graduate School of Agriculture, Meijo University



1P-69S

Concise Synthesis of 9-*cis*-Xanthophylls and Investigation of Their Photoisomerization

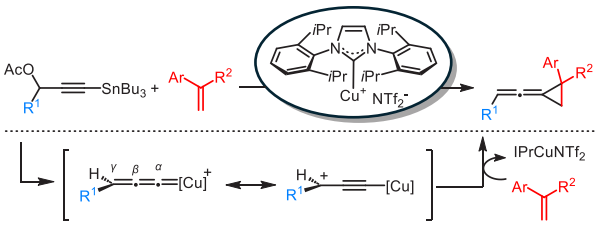
Yuki Okura,* Rintaro Murakami, Kazuhiro J. Fujimoto,
Takeshi Yanai, Shinichiro Fuse, Naoto Yamasaki
Grad. Sch. Pharm. Sci., Nagoya University
Institute of Transformative Bio-Molecules, Nagoya University



1P-70S

Synthesis of Vinylidenecyclopropanes via Copper-Catalyzed Cyclopropanation of Vinyl Arenes

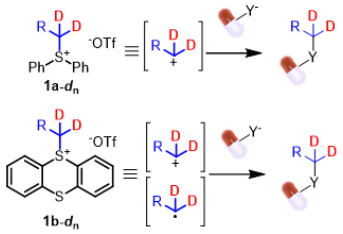
Yuta Shimoji,* Yoshikazu Horino
Chitose Institute of Science and Technology, Japan



1P-71S

Deuterated Alkylation Reagents Based on Sulfonium Salts as Cation and Radical Sources

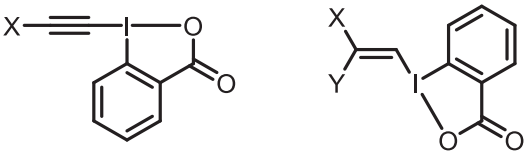
S. Yoshimura,* K. Ban, S. Akai, Y. Sawama.
Graduate School of Pharmaceutical Sciences,
The University of Osaka



1P-72S

Development of Crystalline Dihaloacetylene and Trihaloethylene Equivalents

Takuto Naito,* Norihiro Tada, Akichika Itoh
Gifu Pharmaceutical University

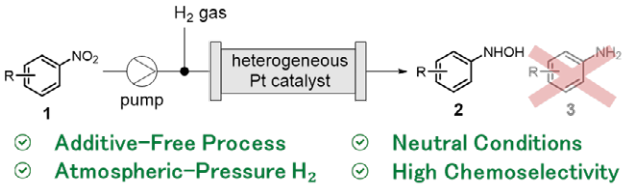


(X, Y = Halogen)

1P-73S

Continuous-Flow Semi-Hydrogenation of Nitroarenes to *N*-Aryl Hydroxylamines

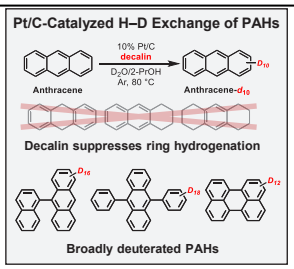
Naoya Sakurada*[1], Chie Morishige[1], Tomohiro Ichikawa[1], Takashi Shigeta[1], Hironao Sajiki[1,2], Takashi Ikawa[1]
[1] Gifu Pharmaceutical University, [2] Aichi Institute of Technology



1P-74S

Pt/C-Catalyzed Deuteration of Polycyclic Aromatic Hydrocarbons with Suppressed Ring Hydrogenation

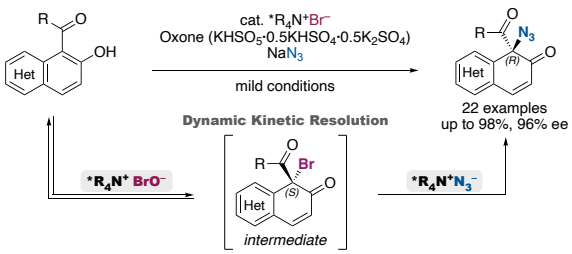
Naoya Sakurada[1], Sae Tomoto[1]*, Tomohiro Ichikawa[1], Takashi Shigeta[1], Hironao Sajiki[1,2], Takashi Ikawa[1]
[1]Gifu Pharmaceutical University, [2]Aichi Institute of Technology



1P-75S

Chiral Hypobromite-catalyzed Enantioselective Dearomative Azidation of (Hetero)arenols

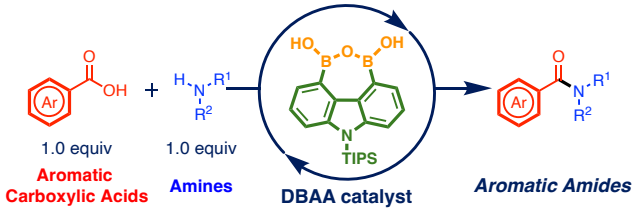
Sho Akagawa,* Yasuo Tsukimori, Takaharu Morino, Muhammet Uyanik, Kazuaki Ishihara
Graduate School of Engineering, Nagoya University



1P-76S

Dehydrative Amidation of Aromatic Carboxylic Acids with Amines Catalyzed by Carbazole-Based Diboronic Acid Anhydride

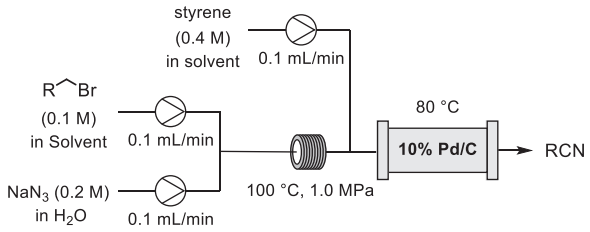
Yuta Fujii,* Ota Koyama, Liu Xiaodong, Ryuichi Nishiyori, Naoyuki Shimada
Department of Chemistry, Nihon University



1P-77S

Continuous-Flow Pd/C-Catalyzed Conversion of Azides to Nitriles

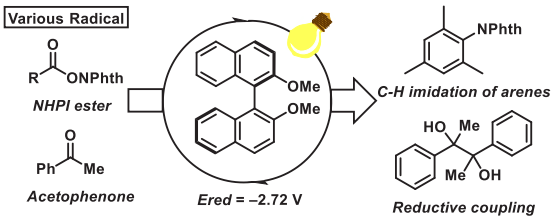
Naoya Sakurada,[1] Hikaru Naito,[1,*] Takanori Kitazono,[1] Seiya Ootori,[1] Tomohiro Ichikawa,[1] Takashi Shigeta,[1] Tsuyoshi Yamada,[2] Hironao Sajiki,[1,3] Takashi Ikawa[1]
1. Gifu Pharm. Univ., 2. Grad. Sch. Med. and Pharm. Sci., Univ. of Toyama, 3. Aichi Inst. of Tech.



1P-78S

Bismethoxybinaphthyl as an Organic Photoredox Catalyst: Functions and Applications

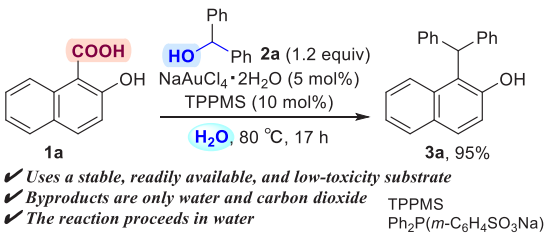
Tomohisa Yamaguchi, Masanori Tayu, Kakeru Matsukuma, Masahiro Noji, Satoshi Hayashi, Sayaka Ohrui and Nozomi Saito



1P-79S

Gold(III)-catalyzed decarboxylative/dehydrative coupling of 2-hydroxy-1-naphthoic acid in water

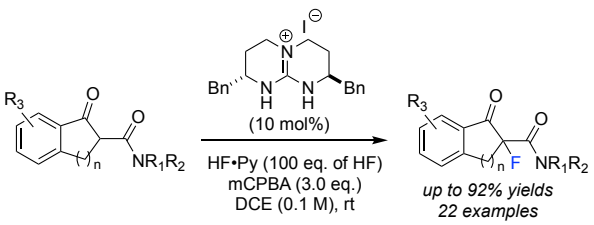
Kazuma Kondo,* Shoko Kikkawa, Hidemasa Hikawa, Isao Azumaya
Faculty of Pharmaceutical Sciences, Toho University



1P-80S

Oxidative Fluorination of β-Ketoamides using Guanidinium Hypoiodite Catalysts

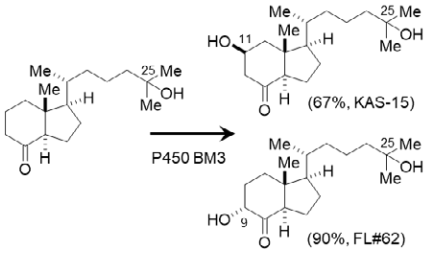
Toma Osawa,[1,2]* Hayate Ishizuka,[1] Dominique Cahard,[2] Kazuo Nagasawa[1]
[1] Graduate School of Engineering, Tokyo University of Agriculture and Technology, Japan
[2] CNRS-UMR 6064 CARMeN, Normandy University, France



1P-81S

Site-Selective Hydroxylation of the CD-Ring of Vitamin D Metabolites by P450 BM3 Variants

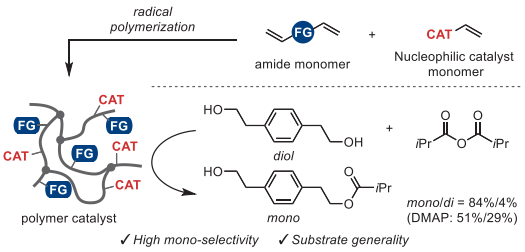
Sota Yoshimura,*[1] Ryota Sakamoto,[1,2] Mirei Morita,[1] Rino Tutsumi,[1] Yuki Okamoto,[3] Kaori Yasuda,[3] Toshiyuki Sasaki,[3] Kazuo Nagasawa[1]
[1]Tokyo University of Agriculture and Technology
[2]National Institute of Advanced Industrial Science and Technology
[3]Toyama Prefectural University



1P-82S

A Universal Resin Catalyst for the Selective Monoacylation of Structurally Diverse Diols

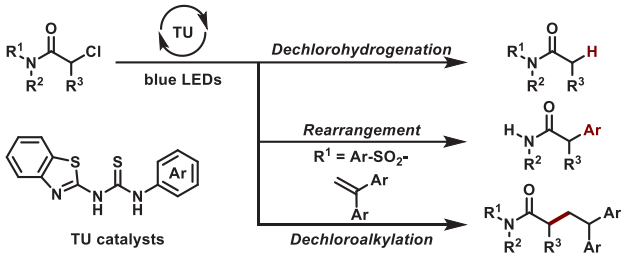
Keigo Sonokawa,[1]* Hiroyuki Miyamura,[2] Kiyosei Takasu,[1] Yusuke Kuroda[1,3]
[1]Graduate School of Pharmaceutical Sciences, Kyoto University
[2]Catalytic Chemistry Research Institute, National Institute of Advanced Industrial Science and Technology (AIST)
[3]The HAKUBI Center for Advanced Research, Kyoto University



1P-83S

Development of Novel Thiourea Photocatalysts and Its Application to Reductive Transformations of α-Chloroamides

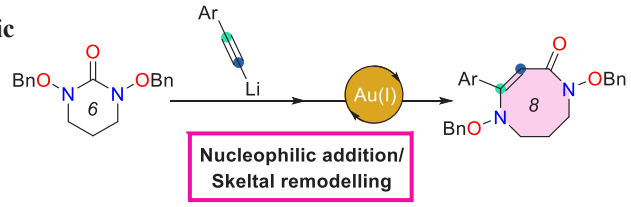
Honoka Nagahara,* Kei Arai, Takumi Haraguchi,
Hiromichi Egami, Yoshitaka Hamashima
School of Pharmaceutical Sciences, University of Shizuoka



1P-84S

Synthesis of 1,5-diazocinone through sequential nucleophilic addition/skeletal remodelling of cyclic ureas

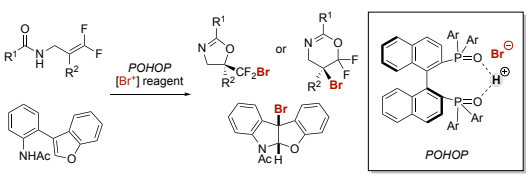
Kaito Sakamoto,* Norihiko Takeda, Suzuna Ichioka,
Takahiro Yamada, Masafumi Ueda
Kobe Pharmaceutical University



1P-85S

Enantioselective Bromocyclization of Difluoroalkenes and Benzofuran Enabled by Concerted Lewis/Brønsted Base Catalysis with Chiral Bisphosphine Oxide

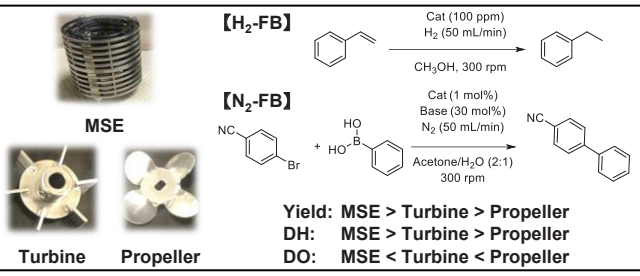
Yuki Nakahara,*[1] Ryo Hirokawa,[1] Shotaro Uchida,[1] Makoto Inai,[1, 2]
Kenji Yamashita,[1] Yoshitaka Hamashima[1]
[1]Graduate Division of Pharmaceutical Sciences, University of Shizuoka
[2]Faculty of Global Interdisciplinary Science and Innovation, Shizuoka University



1P-86S

Fine Bubble Organic Chemistry: Multi-Stacked Mixer for Gas-Involved Organic Reactions and Degassing

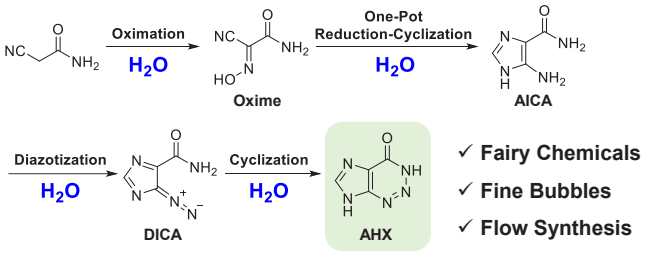
Keishin Sakamoto,* Kohei Sato,
Tetsuo Narumi, Nobuyuki Mase
Graduate School of Integrated Science and Technology,
Shizuoka University



1P-87S

Green Manufacturing: Development of a Continuous Process for Fairy Chemicals

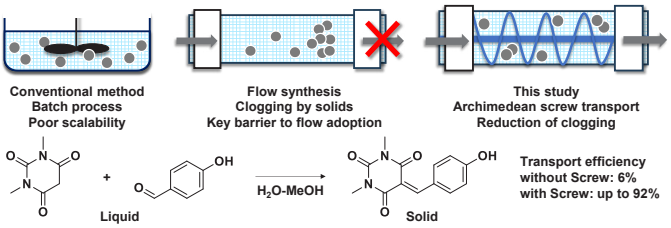
Kotaro Yuguchi,* Kohei Sato,
Tetsuo Narumi, Nobuyuki Mase
Graduate School of Integrated Science and Technology,
Shizuoka University



1P-88S

Green Flow Chemistry: a Slurry Flow System Incorporating an Archimedean Screw

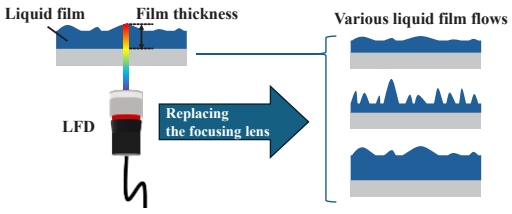
Haruka Satsukawa,* Kohei Sato,
Tetsuo Narumi, Nobuyuki Mase
Graduate School of Integrated Science and Technology,
Shizuoka University



1P-89S

Improving the accuracy of liquid film thickness measurement using a laser focus displacement meter

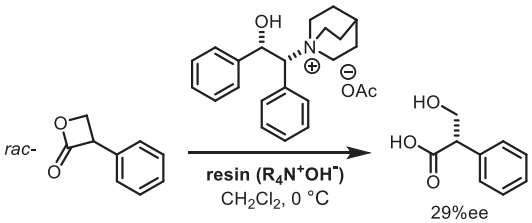
Kanata Iwazaki,* Yuki Mizushima
Graduate School of Integrated Science and Technology,
Shizuoka University



1P-90S

Design and Synthesis of Novel Phase-transfer Catalyst Inspired by Cinchona Alkaloids

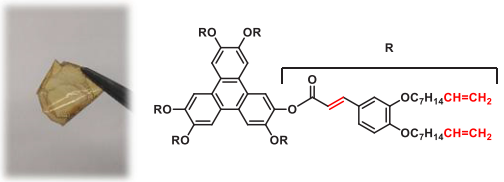
Midori Kawasaki, Hinako Iwamoto, Kenji Yatsuzuka,
Katsuko Shirai, Ryuichi Shirai
Faculty of Pharmaceutical Sciences
Doshisha Women's College of Liberal Arts



1P-91S

Dye Separation by Polymer Films based on Discotic liquid Crystal with Photopolymerizable Cinnamate Groups

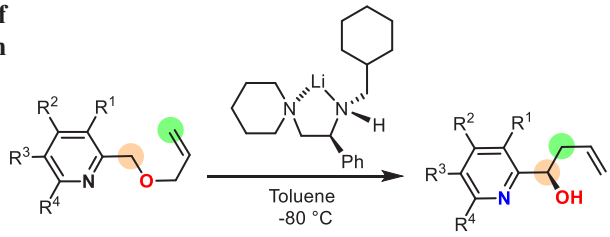
Tsukasa Ohno*, Mikio Yasutake, Takuji Hirose, Koichi Kodama
Graduate School of Science and Engineering, Saitama University



1P-92S

Enantioselective [2,3]-Wittig Rearrangement of Allyl Picolyl Ethers Enabled by Chiral Lithium Amides

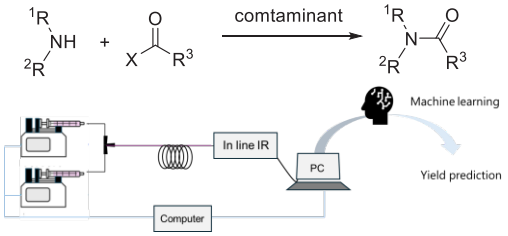
Midori Kawasaki, Chifumi Yumoto,* Yurika Otsubo, Kenji Yatsuzuka, Katsuko Shirai, Ryuichi Shirai
Faculty of Pharmaceutical Sciences,
Doshisha Women's College of Liberal Arts



1P-93S

Direct Real-Time Data Acquisition and Analysis for Flow Synthesis

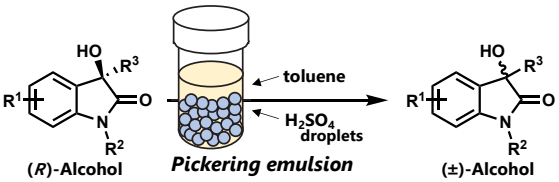
Aki Kohyama, Kanata Ishihara,* Kota Suzuki, Kiyosei Takasu
Graduate School of Pharmaceutical Sciences, Kyoto University



1P-94S

Racemizing 3-aryl-3-hydroxy-2-oxindoles in a Pickering emulsion under acid catalysis and its application to dynamic kinetic resolution

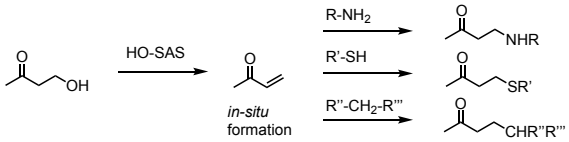
Jihoon Moon,* Shuji Akai, Yoshinari Sawama, Kyohei Kanomata
Graduate School of Pharmaceutical Sciences, The University of Osaka



1P-95S

Continuous Flow Preparation of Methyl Vinyl Ketone from 4-Hydroxy-2-butanone with Heterogeneous Acid Catalyst

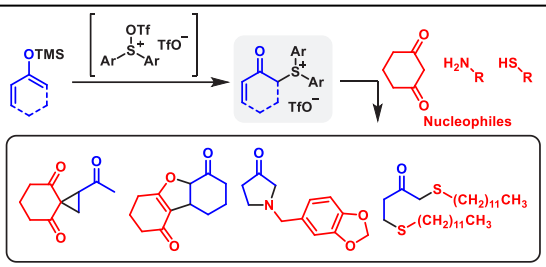
Mamoru Hyodo,*[a,b] Takahide Fukuyama,[b,c] Masahiro Hosoya[d]
[a]Organization for Research Promotion, Osaka Metropolitan University. [b]MiChS Co., Ltd. [c]Department of Chemistry, Osaka Metropolitan University. [d]API R&D Laboratory, Shionogi & Co., Ltd.



1P-96S

Synthesis and Reactivity of α-Sulfonium Enones

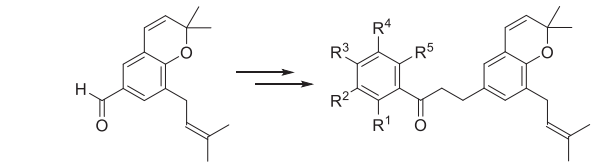
Shunsuke Nakamura,* Rikuto Chiba, Kanako Yazaki,
Motoki Ito, Kazuhiro Higuchi, and Shigeo Sugiyama
Meiji Pharmaceutical University



1P-97S

Divergent Synthesis of Artoserichalcone A Derivatives and *In Silico* Lead Optimization for Antimalarial Drug Discovery

M. Fadli[1]*, Hilkatul Ilmi[2], Lidya Tumewu[2], Ervan Yudha[3],
Aty Widyawaruyanti[2], Natsuhisa Oka[1]
[1]Gifu University [2]Universitas Airlangga
[3]Universitas Gadjah Mada.



key intermediate
(5 steps from 4-hydroxybenzaldehyde)

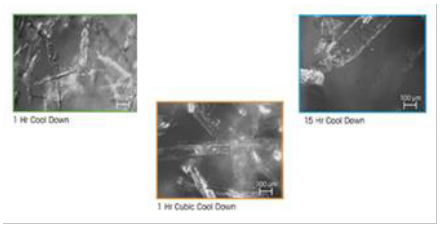
artoserichalcone A
and its derivatives

Poster Presentation
July 3rd. (Fri.)

2P-01

Effective Crystallization Process Development

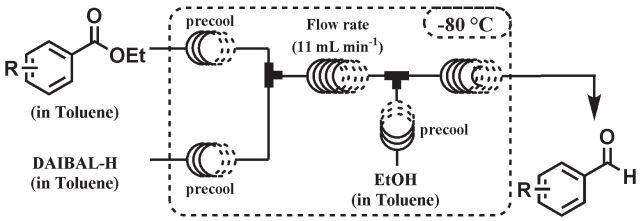
Airi Saito*, Charlie Rabinowitz, Cong Shuxin
AuotoChem Team, BU LAB Instruments, Mettler Toledo K.K.



2P-02

Study on the Partial Reduction of Esters with High Reduction Potentials Using a Flow Reactor

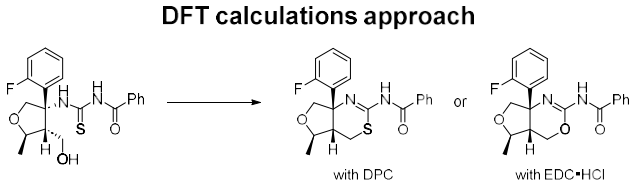
Yuki Kobayahsi,* Takahiro Yoshikawa
Kongo Chemical Co., Ltd.



2P-03

Computational Chemistry-Guided Industrial Process Development

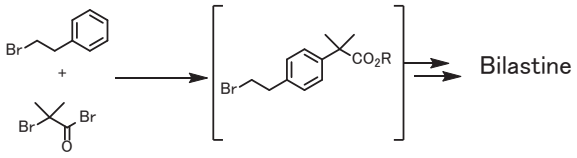
Tomohiro Kikuchi*, Taiju Nakamura, Masayuki Omori, Taichi Abe
API Research Lab. Japan, Eisai Co., Ltd.



2P-04

Development of the Commercial Manufacturing Process for Bilastine

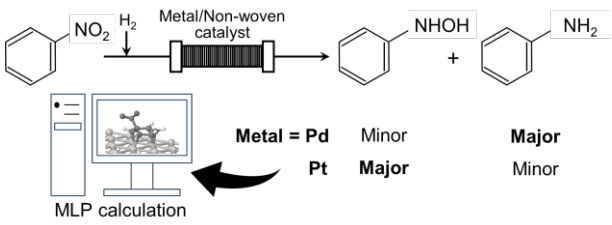
Seitaro Koshino* *et al.*
Advanced Medical Solutions Research Laboratory, Sumitomo Chemical Co., Ltd.



2P-05

Comparative Study of Pt and Pd Catalysts in Flow Hydrogenation Reactions Using a Computational Science Approach

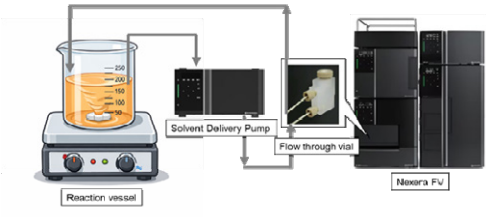
Keisuke Matsumura,* Hiroaki Harakawa
Ebara Corporation



2P-06

Study on the Development of an Online Reaction Vessel Monitoring System Using an HPLC Platform

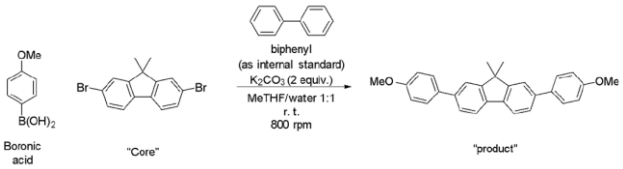
Hiromasa Iboshi*, Chua Chee keong
Innovation Centre, Shimadzu Asia Pacific Pte. Ltd.



2P-07

DirectInject-LC: Real-time Analysis by HPLC for Reaction Monitoring

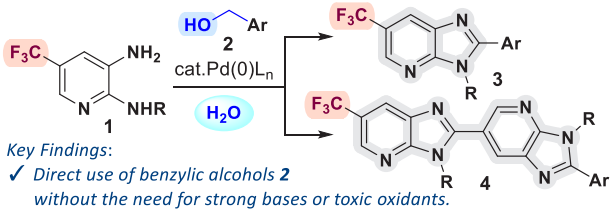
Makoto Ogaito*, Tomohiro Shagawa, Kyoko Watanabe (Shimadzu Corporation)
Yusuke Sato, Junliang Liu, Lars Yunker, Shad Grunert, Paloma Prieto, Jason E. Hein (Telescope Innovations)



2P-08

Pd-catalyzed dehydrogenative coupling of 2,3-diaminopyridines and alcohols in water

Hidemasa Hikawa,* Masakazu Kobayashi, Nanoka Kobori, Shoko Kikkawa, Isao Azumaya
Faculty of Pharmaceutical Sciences, Toho University



Key Findings:

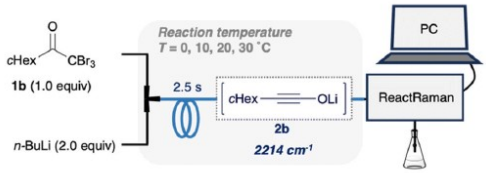
✓ *Direct use of benzylic alcohols* ***2*** *without the need for strong bases or toxic oxidants.*

✓ *Synthesis of biimidazopyridines via C–F bond cleavage of the* CF_3 *group.*

2P-09

ReactRaman: Real time data yields comprehensive kinetic and mechanistic insight across diverse chemistries

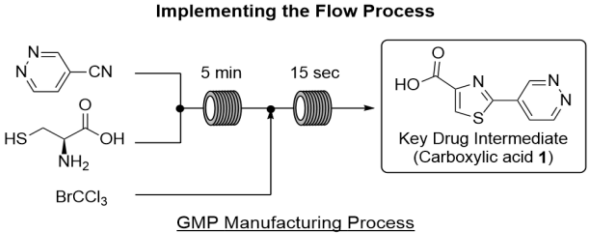
Kanako Hatanaka*[1)], Brian Wittkamp[2)]
1) Mettler-Toledo K.K,Japan, 2) Mettler-Toledo International



2P-10

From Laboratory to Manufacturing: Development and Implementation of a Continuous Flow Process for a Pharmaceutical Intermediate (Part-1; Route Development and Introduction of Continuous Flow Chemistry)

Yusei Takamatsu,* Hiro Sugiyama, Kousuke Komenoi
Chemical & Biological Technology Labs., Astellas Pharma Inc.

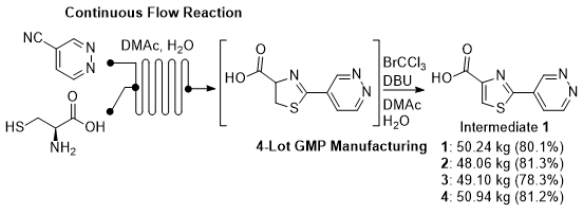


2P-11

From Laboratory to Manufacturing: Development and Implementation of a Continuous Flow Process for a Pharmaceutical Intermediate (Part-2; Scale-Up and Operational Experience in Manufacturing)

Hiro Sugiyama[1]*, Yusei Takamatsu[1], Kousuke Komenoi[1], Hiroaki Yasukouchi[2], Koji Machida[2], Takahiko Murata[2]

[1]Astellas Pharma Inc., [2]KANEKA CORPORATION

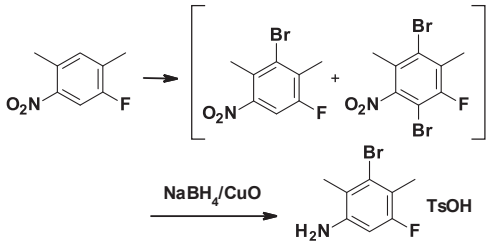


2P-12

Practical Reduction of Nitroarenes to Anilines Using NaBH4 and Commercial CuO

Tomoya Hagio*, Honoka Teraji*, Yuki Hirose, Junpei Ohtaka, Yoshinori Kohmura

Chemical & Biological Technology Labs., Astellas Pharma Inc.

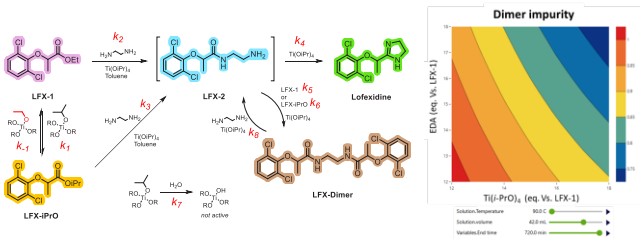


2P-13

Automation-Enabled Process Development and Kinetic Modelling for PAR Determination

A. Lena,* M. Donnola, B. Luchetta, L. Marinoni, A. Barozza, J. Roletto

PROCOS S.P.A., CBC GROUP

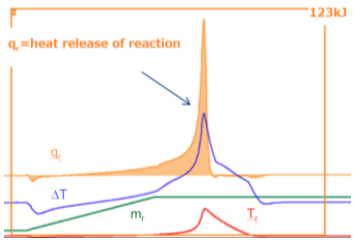


2P-14

The Value of Reaction Calorimetry

Ryoma Tanaka,* Urs Groth

Mettler-Toledo K.K.

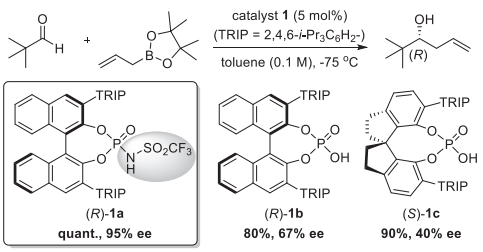


2P-15

Chiral Brønsted Acid Catalyzed Asymmetric Allylation Reaction with Sterically Hindered Aldehydes

Shigenobu Umemiya, Sotaro Osaka, Naoya Shinagawa, Takumi Hirata, Masahiro Terada*

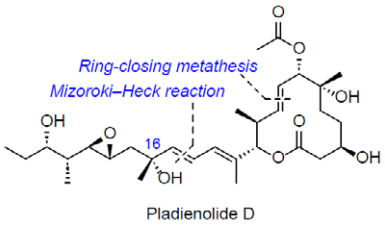
Graduate School of Science, Tohoku University



2P-16

Development of a Scalable and Practical Total Synthesis for Pladienolide D

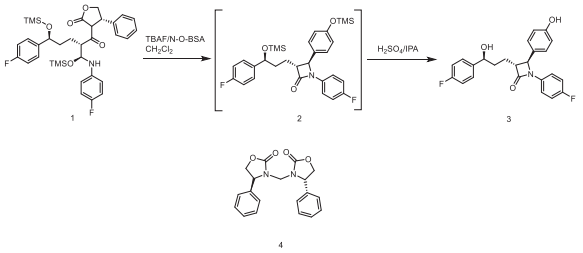
Jun Niijima,* et al.
API Research Japan, Pharmaceutical Science & Technology, DHBL, Eisai Co., Ltd.



2P-17

Eco-friendly Manufacture of Ezetimibe: Impurity control and Sustainability

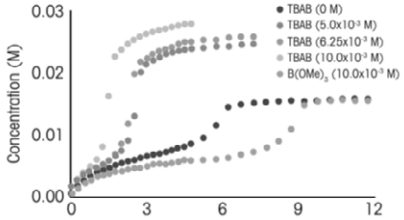
V S Sureshbabu Chillara,* Narendra Kumar Tripathy, Sharadsrikar Venkatesan Kotturi
Neuland Laboratories Ltd., Research & Development Centre, Bonthapally Village, Gummadidala Mandal, Sangareddy District, Telangana, India- 502313.



2P-18

DirectInject-LC: a New PAT Platform with HPLC

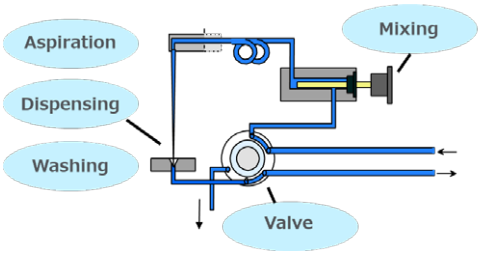
Yuki Sawatsugawa*, Brian Wittkamp
Mettler-Toledo K.K.



2P-19

Reproducibility of dilution using an LC autosampler

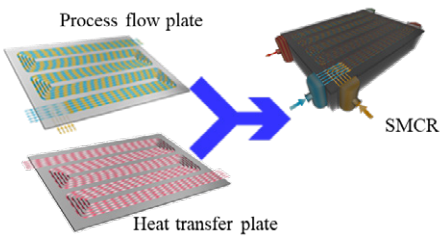
Miu Miyashita,* Keiko Hayashi, Riho Noda
Agilent Technologies Ltd.



2P-20

High-Efficiency Continuous Extraction Technology Based on SMCR®

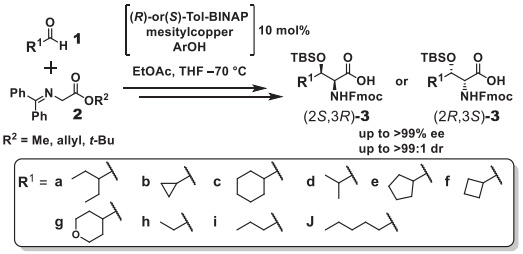
Teppei Moroyama*, Haruna Ariki
Kobelco Eco-Solutions Co., Ltd.



2P-21

Practical Synthesis and Commercialization of Chiral Fmoc-Serine Derivatives via Copper Catalyzed Direct Asymmetric Aldol Reaction

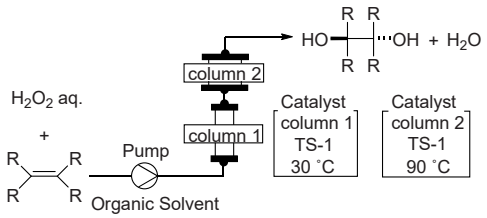
Hisashi Takada[1],* Toshihumi Takeuchi[1], Seiji Nukui[2], Takumi Watanabe[1], Masakatsu Shibasaki[1]
[1]Institute of Microbiral Chemistry
[2]Funakoshi Co., Ltd.



2P-22

Continuous-Flow Syntheses of 1,2-Diols from Alkenes Using Titanium Silicalite-1 Catalyst Column with Hydrogen Peroxide

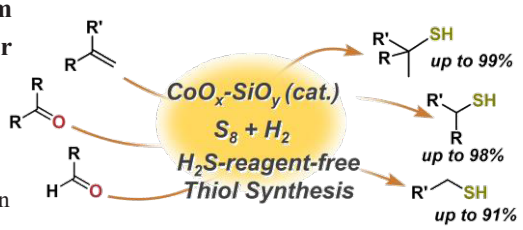
Yoshihiro Kon,[1,*] Takuya Nakashima,[1] Shun-ya Onozawa,[1] Shū Kobayashi[1,2]
[1] Catalytic Chemistry Research Institute, National Institute of Advanced Industrial Science and Technology (AIST).
[2] School of Science, The University of Tokyo.



2P-23

Heterogeneous Cobalt-Catalyzed Thiol Synthesis from Alkenes and Carbonyl Compounds Using Elemental Sulfur and Hydrogen as Simple Reagents

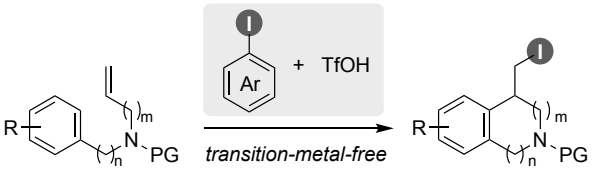
E. Yamamoto,*[,1] W. Qi,[1] X. Ke,[1] H. Murayama,[1] T. Kamachi,[2] A. Yoshizawa,[1] A. Nakayama,[1] H. Matsueda,[3] M. Tokunaga[1]
[1]Kyushu University, [2]Fukuoka Institute of Technology, [3]DIC Corporation



2P-24

N-Heterocycle Synthesis *via* TfOH-Mediated Iodocarbocyclization with Iodoarenes

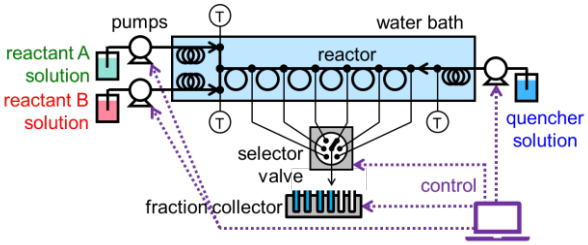
Kosuke Yamamoto,* Izumi Nakayama, Kentaro Higa, Masami Kuriyama, Osamu Onomura
Nagasaki University



2P-25

Automated Multi-Sampling Flow Reactor for Efficient Kinetic Analysis

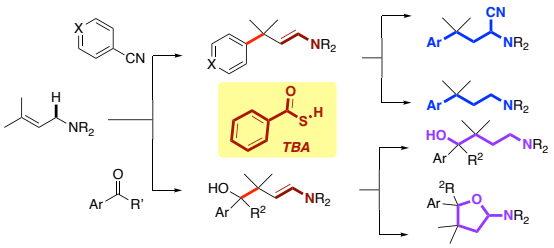
Yoshihiro Takebayashi,*
Takehiro Yamaki, Sho Kataoka
AIST



2P-26

Thiobenzoic Acid-Catalyzed Regioselective Functionalization of Allylamines via Hydrogen Atom Transfer under Visible Light Irradiation Kaich

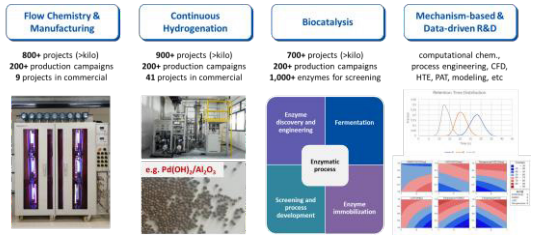
Watanabe, Masashi Fujita, Riku Osanai, Kenji Yamamashita, Hiromichi Egami, Yoshitaka Hamashima*
School of Pharmaceutical Sciences, University of Shizuoka



2P-27

Integration & Intelligence Enabling Green Chemistry at Pharmablock

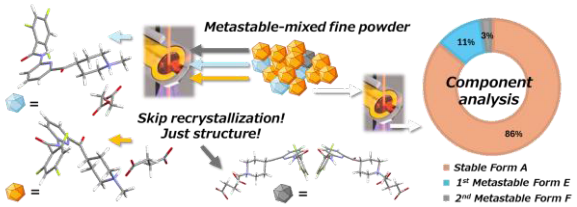
Yuqing Lu,* Gang Sheng
PharmaBlock Sciences (Nanjing), Inc.



2P-28

Crystal Structure Elucidation of Ephemeral Metastable Polymorphs by 3D ED/MicroED Appearing During Crystallization Process

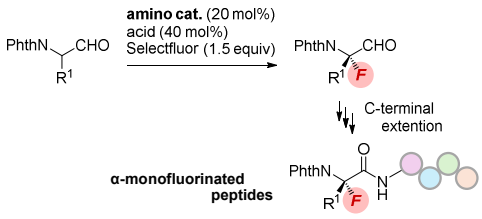
Keiyo Nakai,* [1]Kuniyoshi Miki, [2]Takashi Kikuchi, [1]Masaki Hattori, [1]Kazuki Harada, [1]Rina Konishi, [1]Kayoko Hata, [1]Chisato Okahashi, [1]Mitsuhisa Yamano [1]SPERA PHARMA, Inc. [2]Rigaku Corporation



2P-29

Enantioselective Synthesis of α-Monofluorinated α-Amino Acid Derivatives and Their Application to α-Monofluorinated Peptides

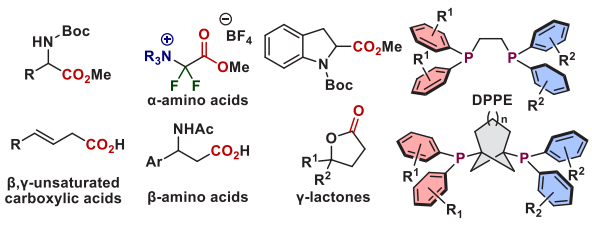
Riko Genka, Hikaru Oshimo, Hisanori Arakaki, Genta Koja, Kanami Sugiyama, Tomohiro Agou, Hirofumi Sato, Masahiro Higashi, Satoru Arimitsu*
Department of Chemistry, Biology, and Marine Science, University of the Ryukyus



2P-30

Computationally Guided Reaction Development for the Construction of Valuable Molecular Scaffolds from Small Molecules

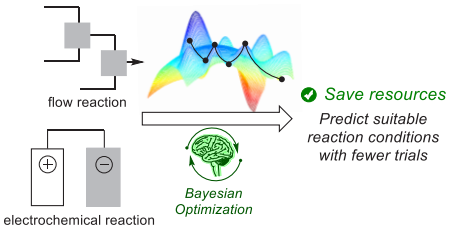
Tsuyoshi Mita,* Satoshi Maeda
WPI-ICReDD, Hokkaido University



2P-31

Data-Driven Multiparameter Optimization for Efficient Screening of Reaction Conditions in Flow and Electrochemical Synthesis

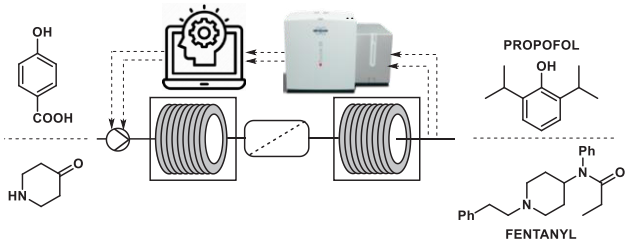
Mohamed S. H. Salem,* Masaru Kondo, Shinobu Takizawa
SANKEN, The University of Osaka, Japan.



2P-32

PIPAc: towards flow chemistry and artificial intelligence powered API production

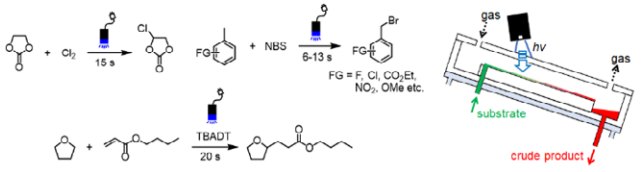
Sylvain Guizzetti,* Guillaume Bentzinger, Philippe Steinsoultz, Elena Salvadeo, Alizée Brouillard, Bogdan Penkovsky, Alejandro Bara Estaun
Novalix



2P-33

High-Speed C–H Halogenation and Alkylation Using a Diagonal Photoflow Reactor (LX-1) Combined with a High-Power UV-LED

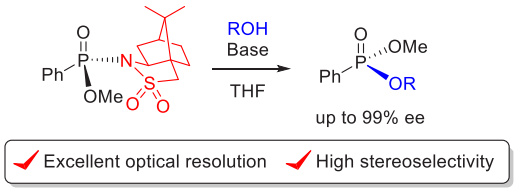
Yusuke Takahashi,* Mamoru Hyodo, Ilhyong Ryu, and Takahide Fukuyama
Smart Chemistry Laboratory, MiChS Co., Ltd.



2P-34

Camphorsultam-Assisted Stereoselective Synthesis of *P*-Chiral Phosphonate Diesters

Yasutomo Yamamoto[1],* Sakura Nakai[1], Tomoe Ishiura[1], Yurika Kambara[1], Ayase Matsumoto[1], Hideyasu China[1], Kenji Watanabe[1], Junpei Matsuoka[2]
[1] Doshisha Women's College of Liberal Arts [2] Kindai University



2P-35

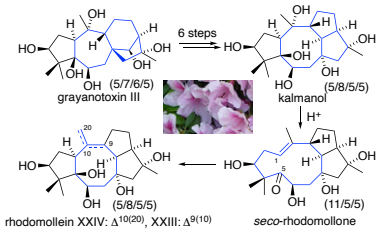
The Convergence of Three Novel Downstream Technologies: One Breakthrough in Peptide and Oligonucleotide API Manufacturing

Shunsuke Ochi 1,* Kenta Saito 1, Yuta Hiroyama 1, Takayuki Morimoto 1, Ryosuke Kunitani 1, Yoshitaka Nemoto 1, Yusuke Kishi 2, Takashi Fujisawa 2, Tomoharu Maeseto 2, Masato Mikawa 3, Yuji Katayama 3, Yuki Suga 3, Mayuko Mouri 4, Eigo Muto 4, Kiyotaka Takimoto 4
1 R&D Department., PeptiStar Inc., 2 Kobelco Eco-Solutions Co.,Ltd., 3 Asahi Kasei Corporation, 4 YMC CO., LTD.

2P-36

Bioinspired Chemical Transformations of Grayanotoxin III to Kalmanol, *seco*-Rhodomollone, Rhodomolleins XXIII and XXIV

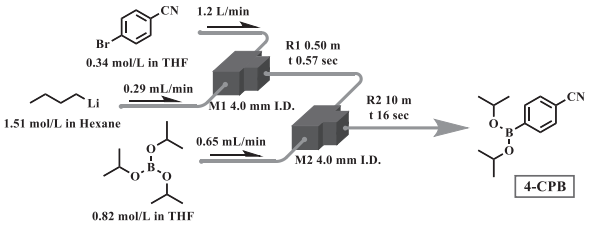
Shoji Kobayashi,* Taiga Tsuruyama, Hinata Togo
Osaka Institute of Technology



2P-37

Advancing Flow Chemistry Implementation: Pilot-Scale Demonstration of Continuous Production and Scale-Up of Organolithium Flow Reactions

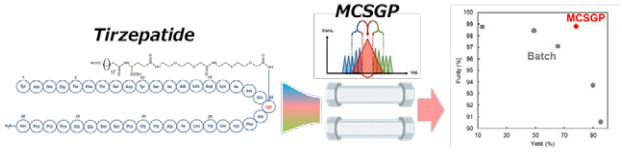
Yusuke Kimuro, Shota Kawakami, Masashi Sugimoto*, Kyosuke Matsushita, Yuta Kobayashi
Juzen Chemical Corporation



2P-38

Development of the Efficient Purification Process for Tirzepatide Using Twin-Column Continuous Chromatography

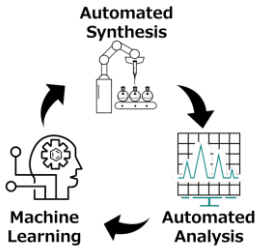
Kosuke Kawai,* Narumi Kobayashi, Jun Kawasaki, Munehiro Shoda, Kiyotaka Takimoto
YMC Co., Ltd.



2P-39

Self-Driving Optimization of Organic Reactions via Machine Learning and Automation

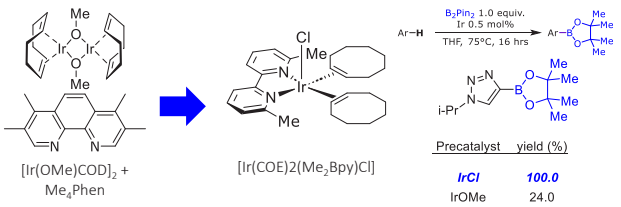
Munenori Inoue,* Takuya Yamagata, Kazushi Hayashi
Sagami Chemical Research Institute



2P-40

Improving the efficiency of Ir type borylations and the development of [Ir(COE)$_2$(Me2Bpy)Cl]

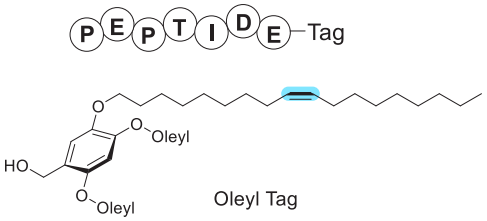
Antonio Zanotti-Gerosa, Daniel Arnold, Douglas Hartline, Aaron Bloomfield, Sanita Taylor, Charley Tougard and Eric Slack*
Johnson Matthey, 28 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire, CB4 0FP, United Kingdom



2P-41

From Soluble to Solubilizing Tag: Highly Efficient Liquid-Phase Peptide Synthesis Using Oleyl Tag

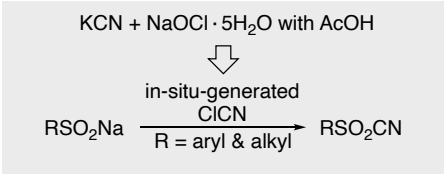
Sota Adachi,* Shingo Shinjo-Nagahara, Yoshikazu Kitano, Yohei Okada
Tokyo University of Agriculture and Technology



2P-42

Practical Synthesis of Sulfonyl Cyanides from Sodium Sulfinates Using KCN and NaOCl·5H$_2$O

Masaru Kondo,* Atsushi Baba, Yutaro Nakamura, Ryo Takita
School of Pharmaceutical Sciences, University of Shizuoka

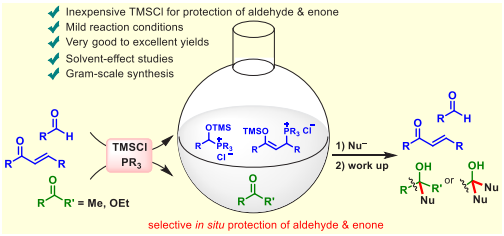


✓Mild reaction conditions ✓Gram-scale synthesis
✓^{13}C-labeled derivative

2P-43

Reversal and Control of the Intrinsic Reactivity of Carbonyl Groups via Chemoselective TMSCl-Mediated In Situ Protection

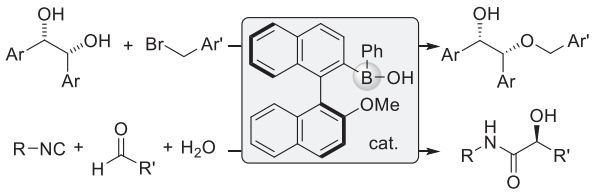
Hirendra Nath Dhara,* Muthu Karuppasamy, Mohamed S. H. Salem, Shinobu Takizawa, Hiromichi Fujioka
SANKEN, The University of Osaka, 8–1 Mihogaoka, Ibaraki-shi, Osaka 567–0047, Japan



2P-44

Binaphthyl-type Chiral Borinic Acid Catalyst for Enantioselective Reactions

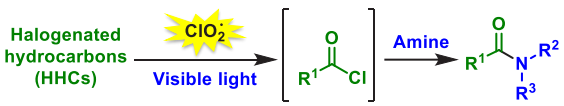
Yuta Chikashige[1], Kazuhiro Higashi[1], Shinsuke Komagawa[1], Tsunayoshi Takehara[2], Takeyuki Suzuki[2], Atsuhi Nakayama[1], Mitsuhiro Arisawa[1], Makoto Sako[1,2,*]
[1]Grad. Sch. Pharm. Sci., UOsaka [2]SANKEN, UOsaka



2P-45

Development of a Chemical Upcycling Process from Perchloroethylene by Photoactivated Chlorine Dioxide Treatment

Nozomi Takao, Minami Fukuhara, Genta Taniguchi, Maiko Moriguchi, Shohei Ohno, Yuki Itabashi, Kei Ohkubo, Tsuyoshi Inoue, Haruyasu Asahara*
Grad. Sch. Pharm. Sci., UOsaka

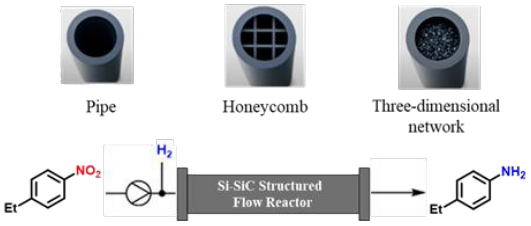


2P-46

Thermal Control in Flow Synthesis Enabled by Silicon-Infiltrated High-Thermal-Conductivity Si–SiC Cartridges

Takayuki Kanetake[1]*, Taigo Tamagushi[1], Kosuke Niwa[1], Naoya Sakurada[2], Hikaru Naito[2], Tomohiro Ichikawa[2], Takashi Shigeta[2], Hironao Sajiki[2,3], Takashi Ikawa[2]

[1]NGK Corp., [2]Gifu Pharm. Univ., [3]Aichi Inst. of Tech.

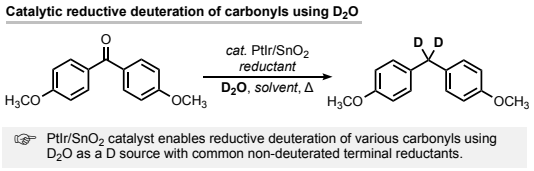


2P-47

Reductive Deuteration of Carbonyl Compounds Using D_2O as a Deuterium Source Enabled by a Tin Oxide-Supported Pt-Ir Catalyst

Alastair N. Herron,[1]* Kosuke Nakajima,[1] Heeyoel Baek,[2] Shunsuke Yukitani,[2] Takao Osako,[2] Hiroshi Naka[1]

[1] Graduate School of Pharmaceutical Sciences, Kyoto University. [2] Mitsui Kinzoku Co. Ltd.



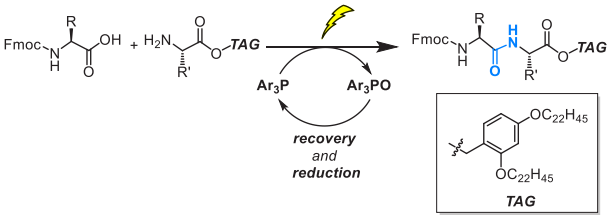
☞ $PtIr/SnO_2$ catalyst enables reductive deuteration of various carbonyls using D_2O as a D source with common non-deuterated terminal reductants.

2P-48

Electrochemical Peptide Synthetic Process Aiming for Greener Production

Shingo Shinjo-Nagahara,* Goki Hiratsuka, Yohei Okada, Yoshikazu Kitano, Kazuhiro Chiba

Tokyo University of Agriculture and Technology



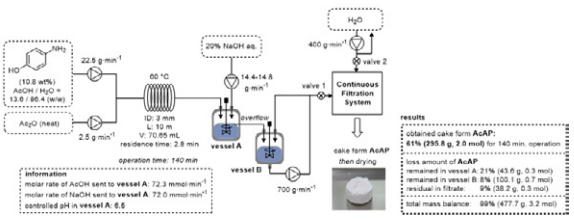
2P-49

Crystallization-Based Approach to Continuous Manufacturing: A Case Study of Acetaminophen Production

Tetsuya Yamamoto,[1]* Koichiro Masuda,[1] Kwihwan Kobayashi,[1] Hidekazu Sano,[1] Aiichiro Nagaki,[2] Akira Yada[1]

[1] Catalytic Chemistry Research Institute, AIST

[2] Department of Chemistry, Faculty of Science, Hokkaido University



2P-50

An Automated HTE Platform for Systematic Reaction Space Exploration in Early-Stage Process Development

Yuta Sumii,[1]* Mikio Ishihara,[1] Takashi Shimizu,[1] Katsunori Seki,[1] Hiroyuki Yamashita,[2] Kazuki Mukumoto[2]

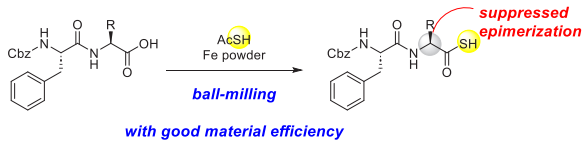
[1] Astellas Pharma Inc., [2] SHIMADZU CORPORATION



2P-51

Solvent-Minimal and Epimerization-Suppressed Mechanochemical Synthesis of Peptide Thiocarboxylic Acid

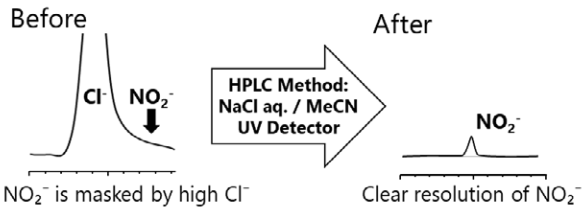
Kounosuke Oisaki, Hiroshi Igarashi, Koki Fujimura*, Masahiro Hayashi, Masato Nakano
CCRI/FoodMed-OIL, AIST



2P-52

Nitrosamine Risk Evaluation in Drug Substance: Development of a Nitrite Ion Analytical Method in High-Chloride Matrices

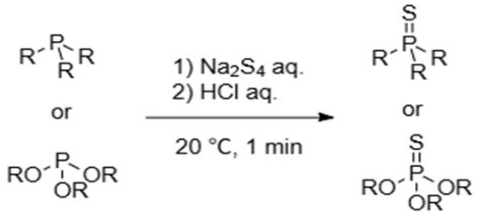
Shohei Takayasu*, Kenichiro Sato, Takahiro Yamaguchi, Misato Takashima
CMC Department, Pharmaceuticals Research Center, Asahi Kasei Therapeutics Corp.



2P-53

Mild Liquid-Phase Sulfurization of P(III) Compounds Using Sodium Tetrasulfide

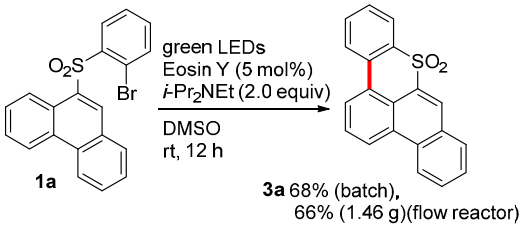
Kazuki Yoshioka [1,2]*, Ken-Ichiro Sotowa [1]
1 Department of Chemical Engineering, Kyoto University,
2 Mitsuichemicals INC



2P-54

Eosin Y-catalyzed Cyclization: Syntheses of 6-Membered Sulfones

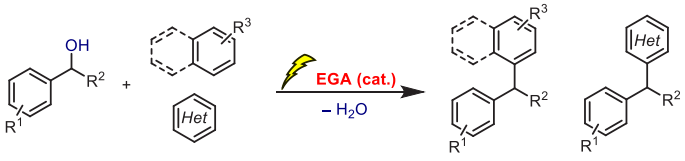
Akihiro Orita* Akira Iwakura, Shion Matsunaga, Yasuhiro Okuda
Okayama University of Science



2P-55

Traceless electrogenerated acid-catalyzed dehydroxylative arylation for the synthesis of tri- and diarylmethane derivatives

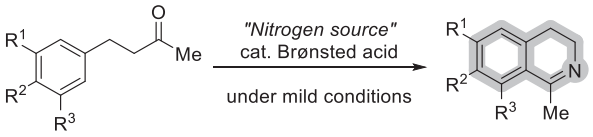
Tsuyoshi Yamada,* Tatsuki Ono, Yuka Abe, Masaru Tanioka, Yuji Matsuya
Grad. Sch. Med. and Pharm. Sci., Univ. of Toyama



2P-56S

Direct Approach towards Synthesis of Dihydroisoquinoline from Ketones *via* Bischler-Napieralski Type Reaction

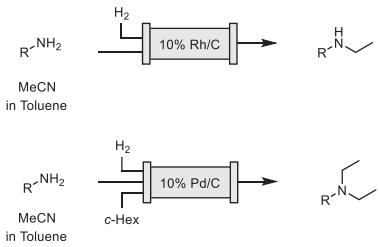
Kota Fujimori,* Masanori Inoue, Genichiro Nakae, Kengo Hyodo
School of Science and Engineering, Kindai University.



2P-57S

Selective Reductive Alkylation of Amines Using nitriles under Continuous-Flow Conditions

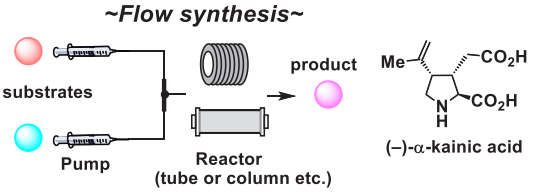
Naoya Sakurada[1], Masayuki Saito[1*], Mana Kumazawa[1], Eisho SHimizu[1], Tomohiro Ichikawa[1], Takashi Shigeta[1], Hirinao Sajiki[1,2],Takashi Ikawa[1]
Gifu Pharmaceutical University[1], Aichi Institute of Technology[2]



2P-58S

Flow Synthesis of (–)-(α)-Kainic Acid

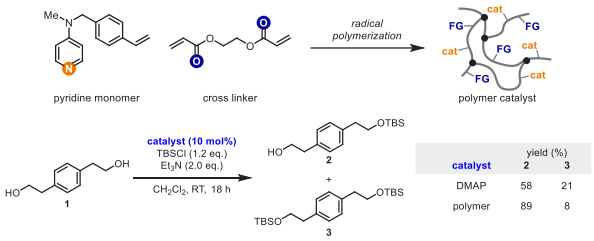
Sosuke Takaki,*[1] Atsuji Tajima,[2] Kiichi Hirayama,[1]
Nobuyuki Mase,[3] Kazuhiro Takeda,[3] Takashi Ohshima[1]
[1]Graduate school of Pharmaceutical Sciences, Kyushu University, [2]Faculty of Pharmaceutical Sciences, Kyushu University, [3]Graduate school of Engineering, Shizuoka University



2P-59S

Cross-Linked Random Polymer Enables Catalytic Diol Mono-Silylation

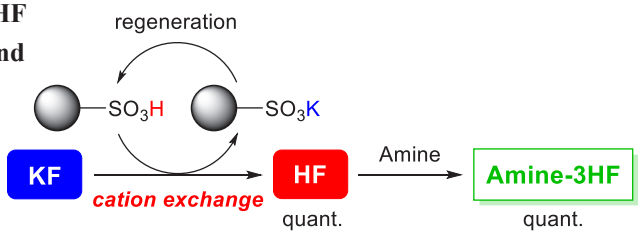
Yusuke Kuroda[1, 2], Takumi Nasuno[1]*, Kiyosei Takasu[1]
[1]Graduate School of Pharmaceutical Sciences, Kyoto University [2]The HAKUBI Center for Advanced Research, Kyoto University



2P-60S

A Green Process for the Synthesis of Amine-3HF Complexes via Cation Exchange between KF and Amberlyst 15DRY

Haruka Homma,* Masahide Yamada, Toshiki Tajima
Graduate School of Engineering and Science, Shibaura Institute of Technology

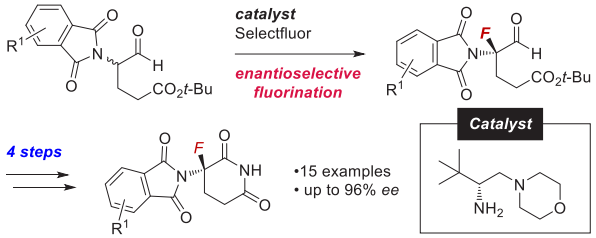


2P-61S

3'-Fluorinated Thalidomide Derivatives: Stereoselective Synthesis and CRBN Binding Properties

Hisanori Arakaki,* Satoru Arimitsu

Department of Chemistry, Biology, and Marine Science, University of the Ryukyus

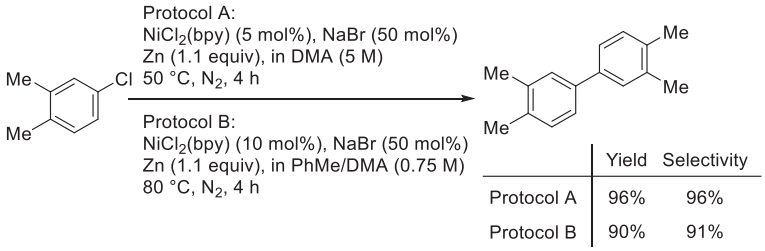


2P-62S

Co-solvent System to Reduce the Process Mass Index in Ullmann-type Biaryl Synthesis

Tomohiro Ichikawa[1], Sae Tomoto[1], Yuto Maki[1]*, Takashi Shigeta[1], Hironao Sajiki[2], Takashi Ikawa[1]

[1]Gifu Pharm. Univ. [2]Aichi Inst. of Tech.



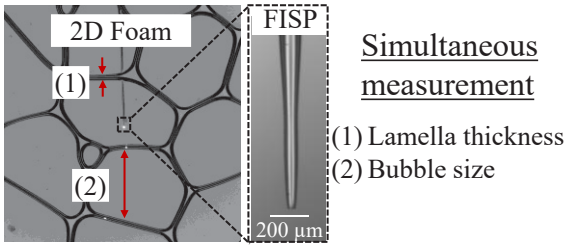
	Yield	Selectivity
Protocol A	96%	96%
Protocol B	90%	91%

2P-63S

Development of a Fiber-optic Interferometric Spectral Probe (FISP) for simultaneous measurement of bubble size and lamella thickness in foam

Higen Mizushima[1],* Ryota Tanioka[1], Shimpei Saito[2], Kohei Sato[1], Yuki Mizushima[1]

[1] Graduate School of Integrated Technology, Shizuoka University
[2] Research Institute for Energy Efficient Technologies, National Institute of Advanced Industrial Science and Technology (AIST)

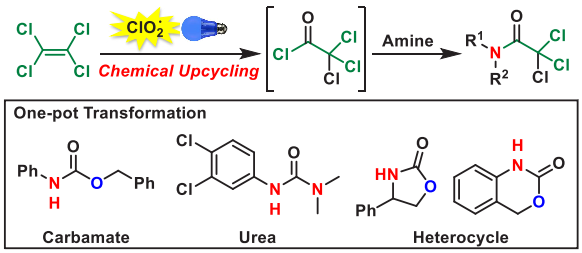


2P-64S

Development of a Chemical Upcycling Process from Perchloroethylene by Photoactivated Chlorine Dioxide Treatment

Genta Taniguchi,* Shohei Ohno, Yuki Itabashi, Tsuyoshi Inoue, Kei Ohkubo, Haruyasu Asahara

Graduate School of Pharmaceutical Sciences, The University of Osaka

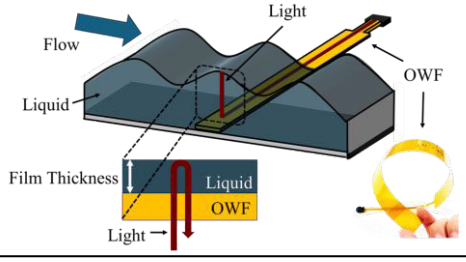


2P-65S

Direct Thickness Measurement in Wavy Liquid-Film Flow via Optical Waveguide Film

Shota Ando,* Yuki Mizushima,

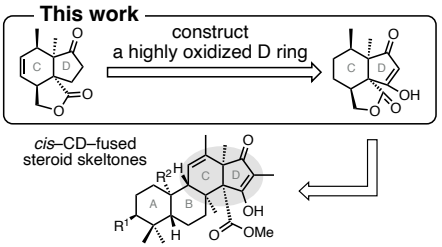
Graduate School of Integrated Science and Technology, Shizuoka University, Japan.



2P-66S

Development of a synthetic method for a highly oxidized D ring in *cis*–CD–fused steroid skeletons

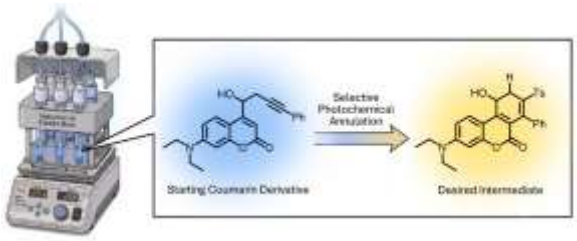
Fumino Kitamura,* Masaru Tanioka, Tsuyoshi Yamada, Yuji Matsuya
Graduate School of Medicine and Pharmaceutical Sciences,
University of Toyama



2P-67S

Fiber-Optic-Mediated Reactor System for Thermal Control and Scalable Synthesis in Photocatalytic Cascade Annulation

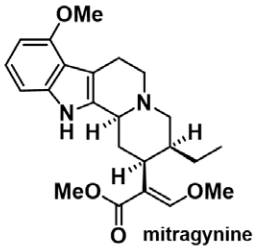
Kuo-Chun Chiu,* Ruo-Ya Huang, Yong-Wei Chen, Chih-Chien Chu
Department of Medical Applied Chemistry,
Chung Shan Medical University, Taichung, TAIWAN



2P-68S

Gram-Scale Synthesis of the Opioid Alkaloid Mitragynine

Yuki Shimizu,* Suzuka Yoshioka,
Mariko Kitajima, Hayato Ishikawa
Grad. Sch. Pharm. Sci. Chiba University

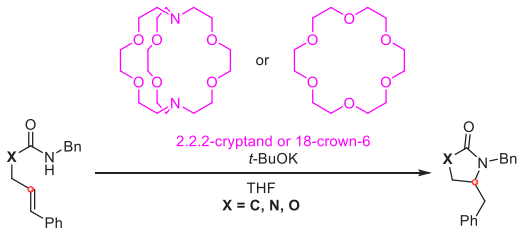


- ✓ ***1.5 g*** of mitragynine was prepared for *in vivo* exp.
- ✓ Total steps: **13**; overall yield: **13**%
- ✓ Only **6** column chromatographies, **single** recrystallization
- ✓ Chirality was introduced through an ***organocatalytic reaction***.

2P-69S

Intramolecular Hydroamidation of Alkene Using Alkali Metal Bases and Cyclic Polyethers

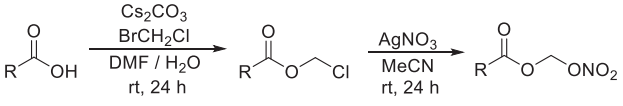
Mana Kawakami [1]*, Junpei Matsuoka [1]
Yasutomo Yamamoto [2], Tomohiro Maegawa [1]
1) Kindai University
2) Doshisha Women's College of Liberal Arts



2P-70S

Development of chloromethyl esterification reaction of carboxylic acids and methods for introducing of nitrate esters

Haato Tsuda*, Junpei Matsuoka, Hiroki Yao,
Natsumi Kuraoka, Tomohiro Maegawa
School of Pharmaceutical Sciences, Kindai University

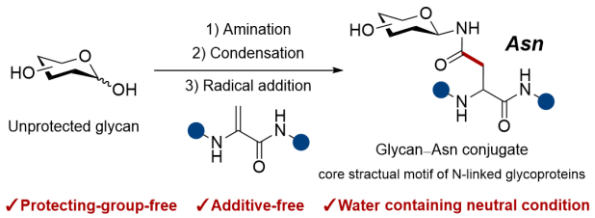


2P-71S

Three-Step Synthesis of Glycan-Asparagine Conjugates from Unprotected Sugars

Junya Akeno,*[1,2] Kiyosei Takasu,[1] Konosuke Oisaki,[2] Norihisa Fukaya,[2] Yoshihiro Ueda[2]

[1] Grad. Sch. Pharm. Sci., Kyoto Univ. [2]AIST.

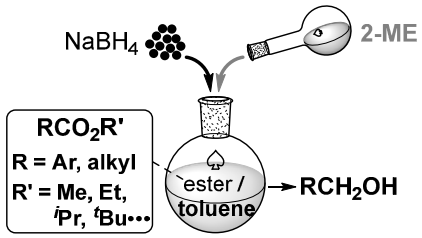


2P-72S

Ester Reduction in Toluene by All-at-Once Addition of $NaBH_4$ and Alcohol Activator

Reito Endo,* Mayu Ishida, Toshinobu Korenaga

Graduate School of Arts and Sciences, Iwate University

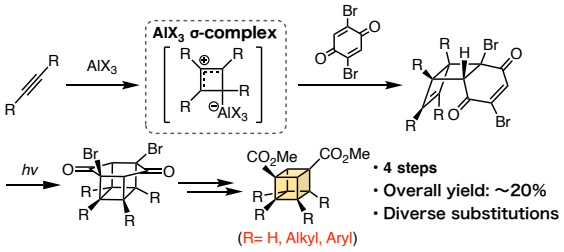


2P-73S

Development of a Synthetic Method for Multisubstituted Cubanes using Aluminum Halaide σ–Complexes

Hinata Mimaki, * Masaru Tanioka, Tsuyoshi Yamada, Yuji Matsuya

School of Pharmacy and Pharmaceutical Sciences, University of Toyama



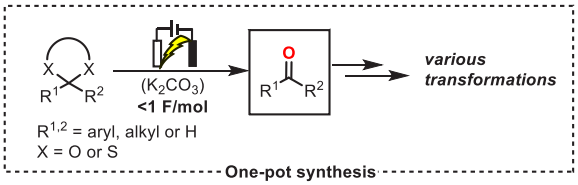
2P-74S

Development of electrodeprotection reaction of acetals under neutral conditions and its application to further one-pot transformation

Yuka Abe,*[1] Tsuyoshi Yamada,[1] Tatsuki Ono,[1] Masaru Tanioka,[1] Takashi Ikawa,[2] Hironao Sajiki,[3] Yuji Matsuya[1]

[1]Grad. Sch. Med. and Pharm. Sci., Univ. of Toyama

[2]Gifu Pharm. Univ. [3]Aichi Inst. of Tech.

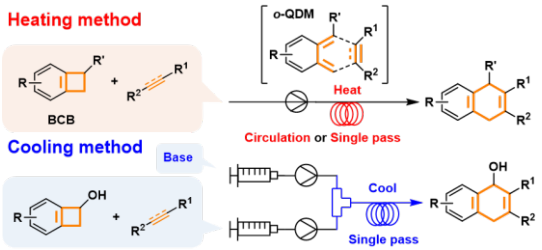


2P-75S

Development of a Mild and Efficient Flow-Based Method for the Generation of *o*-Quinodimethane

Tomoki Iwama,* Tsuyoshi Yamada, Masaru Tanioka, Yuji Matsuya

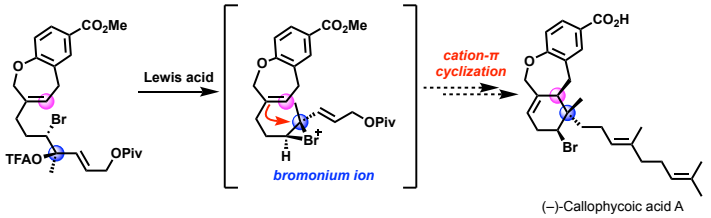
Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama



2P-76S

Synthetic Studies of Callophycoic Acid A

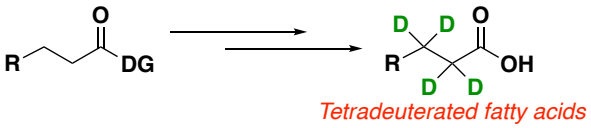
Kotaro Taniguchi,* Akihiro Ogura,
Ken-ichi Takao
Department of Applied Chemistry,
Keio University



2P-77S

Controlled Tetradeuteration of Straight-Chain Fatty Acids

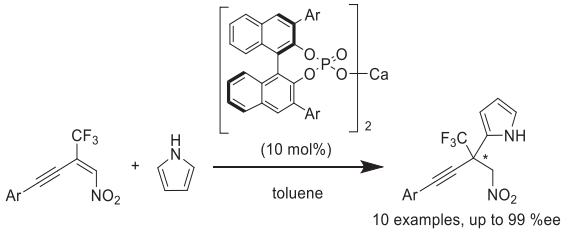
Nonoka Hori,*[1] Kotaro Hama,[2] Ayako Watanabe,[3] Koko Imai,[1] Masaru Kondo,[1] Kohei Watanabe,[3] Yuko Fujiwara,[2] Kazuaki Yokoyama,[2] Shigeo Murata,[3] Ryo Takita[1]
[1]Univ. of Shizuoka, [2]Teikyo Univ., [3]Univ. of Tokyo



2P-78S

Enantioselective Friedel-Crafts Alkylation Reaction of Pyrrole with β-Trifluoromethyl-β-alkynyl Nitro--alkenes Catalyzed by Chiral BINOL Metal Phosphate

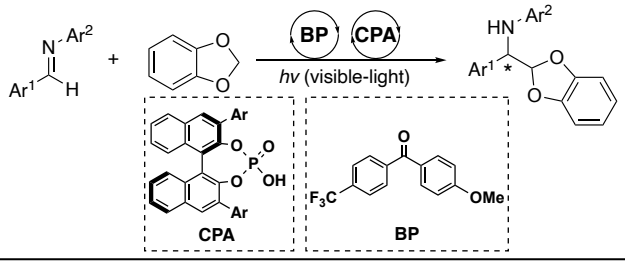
Reina Baba,* Yuki Kaneko, Tatsuhiro Uchikura,
Takahiko Akiyama
Department of Chemistry, Gakushuin University
1-5-1 Mejiro, Toshima-ku, Tokyo, 171-8588, Japan



2P-79S

Enantioselective Visible-Light-Driven Radical Addition Reactions to Imines Using Chiral Phosphoric acid/photoinduced HAT dual catalysis

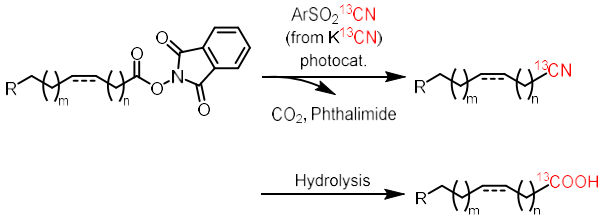
Ryoji Ikeda,* Tatsuhiro Uchikura, Takahiko Akiyama
Department of Chemistry, Gakushuin University



2P-80S

Catalytic Decarboxylative Cyanation for ^{13}C-Labeled Fatty Acids

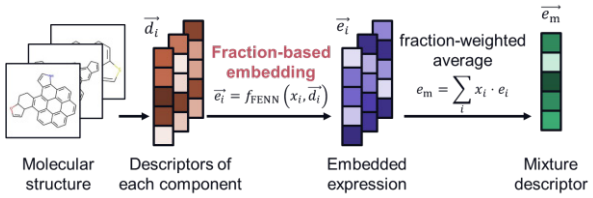
Yutaro Nakamura,* Atsushi Baba, Masaru Kondo,
Ryo Takita
School of Pharmaceutical Sciences, University of Shizuoka



2P-81S

Thermophysical Property Estimation of Multicomponent Mixtures Using Mixture Descriptors and Machine Learning

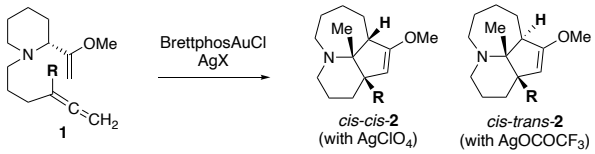
Keisuke Ikeda,* Atushi Hatoyama, Yuya Murakami
Faculty of Engineering, Shizuoka University



2P-82S

Synthesis of Fused Amines Bearing Tetrasubstituted Carbons via the Gold-Catalyzed Cyclization–3-aza-Cope–Mannich Cascade

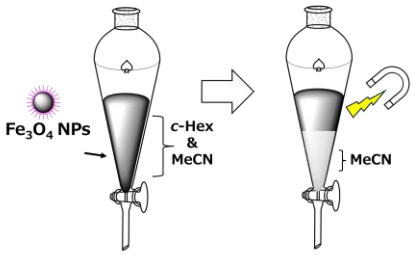
Miku Akahori,* Kaito Tozuka, Haruka Katayama, Ayame Taki, Ryu Tadano, Takeo Sakai
Faculty of Pharmacy, Meijo University



2P-83S

Liquid-Phase Peptide Synthesis Utilizing Magnetic Liquid-Liquid Extraction

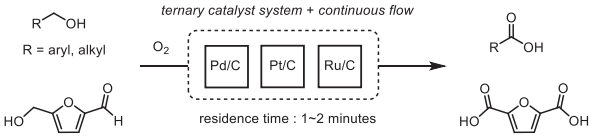
J. Karasawa,*[1] S. Yamashita,[1] T. Taguchi,[2] S. Yoshida,[2] N. Nishida,[2] S. Nishida,[2] O. Matsumoto,[3] H. Kuroda,[3] M. Kambara,[3] Y. Okada.[1]
[1]Tokyo Univ. Agric. & Technol., [2]Chiyoda Corporation,
[3]Chiyoda U-Tech Co., Ltd.



2P-84S

Continuous-Flow Oxidation of Alcohols to Carboxylic Acids Using Molecular Oxygen and a Ternary Pd/C-Pt/C-Ru/C Catalyst System

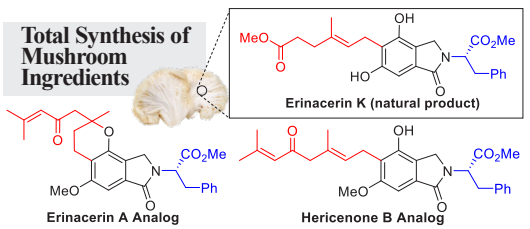
Yiyue Yao,*[a] Mamoru Hyodo,[b,c] Yusuke Takahashi,[b,c] Kinryo Cho,[d] Takahide Fukuyama,[a] Ilhyong Ryu[b,e]
[a]Department of Chemistry, Osaka Metropolitan. University.
[b]Organization for Research Promotion, Osaka Metropolitan University. [c]MiChS Co., Ltd.
[d]Green Chemical Inc. [e]Department of Applied Chemistry, National Yang Ming Chiao Tung University



2P-85S

Investigation of Divergent Methodology to Synthesize Amino Acid-Incorporated Isoindolinones and Their Analogs from Mushrooms of the Genus *Hericium*

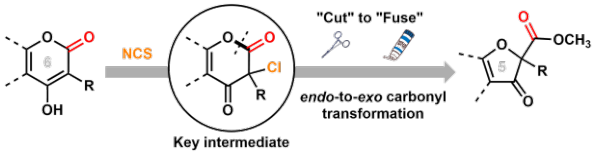
Audreyana Ariella,* Shoji Kobayashi
Graduate School of Engineering, Osaka Institute of Technology



2P-86S

Halogenation-triggered *endo*-to-*exo* carbonyl transformation of hydroxycoumarin

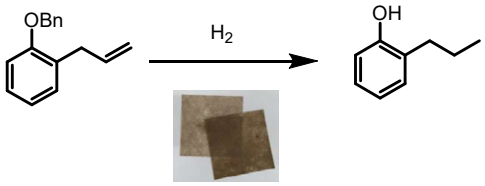
Yusuke Yoto,* Osuke Shioya, Yusei Matsumoto, Kotaro Kikushima, Hideyasu China, Toshifumi Dohi
College of Pharmaceutical Sciences, Ritsumeikan University.



2P-87S

Tunable Chemoselective Hydrogenation Using a Palladium Catalyst Supported on Nonwoven Fabric (Pd/NF)

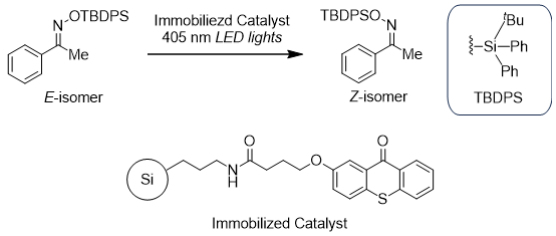
Hikaru Okubo,[1]* Hitoshi Abe,[1] Hiroaki Harakawa[2]
[1]Department of Applied Chemistry, University of Toyama
[2]Research Center, Ebara Corporation



2P-88S

Solid-Supported Photosensitizers for Highly Selective *E* → *Z* Photoisomerization of Oximes

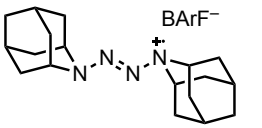
Mayuko Suga,* Ryusei Takada, Kayo Nakamura, Hidetsugu Tabata, Tetsuta Oshitari, Hideaki Natsugari, Hideyo Takahashi
Faculty of Pharmaceutical Sciences, Tokyo University of Science



2P-89S

Synthesis of Stable 2-Tetrazene Radical Cation Salts and Exploration of Their Oxidation Catalytic Activity

Shu Saito,[a,*] Yusuke Sasano,[a] Ayari Oshiro,[a] Shintaro Kitahata,[a]
Yasuyuki Araki,[b] Eunsang Kwon,[c] Yoshiharu Iwabuchi[a]
[a]Graduate School of Pharmaceutical Sciences, [b]Institute of Multidisciplinary Research for Advanced Materials (IMRAM), and [c]Graduate School of Science, Tohoku University



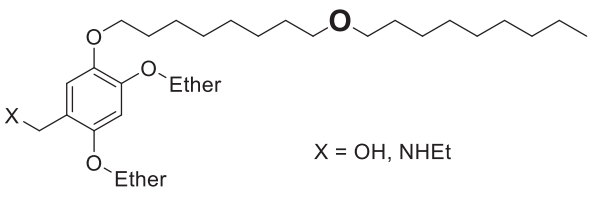
2-tetrazene radical cation salt

✔ **isolatable**
✔ **stable in air > 1 year**

2P-90S

Soluble, Scalable, and Stable: Green Production of Peptides Enabled by "Ether Tags"

Hana Haraguchi,* Sota Adachi, Shingo Shinjo-Nagahara, Yoshikazu Kitano, Yohei Okada
Tokyo University of Agriculture and Technology



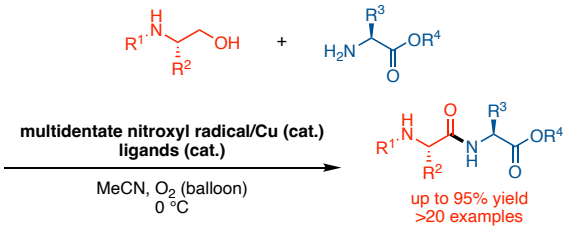
X = OH, NHEt

Ether tag

2P-91S

Aerobic Oxidative Peptide Synthesis Using Nitroxyl Radical/Copper Catalysis

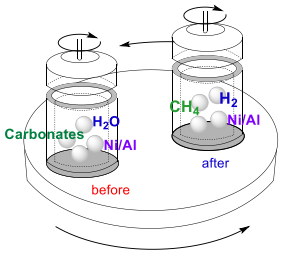
Riki Yamakawa,* Shuhei Akutsu, Shota Nagasawa, Yusuke Sasano, Yoshiharu Iwabuchi
Graduate School of Pharmaceutical Sciences, Tohoku University



2P-92S

Mechanochemical Methanation of Carbonates Over a Ni/Al Alloy

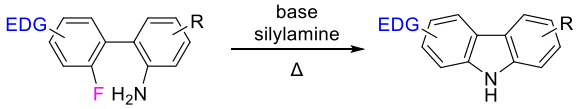
Naoya Ito,* Naoya Sakurada, Tatsunori Iwamura, Tomohiro Ichikawa, Takashi Shigeta, Takashi Ikawa, Hironao Sajiki
Gifu Pharmaceutical University, Aichi Institute of Technology



2P-93S

Development of Direct S_NAr reactions for the synthesis of carbazoles.

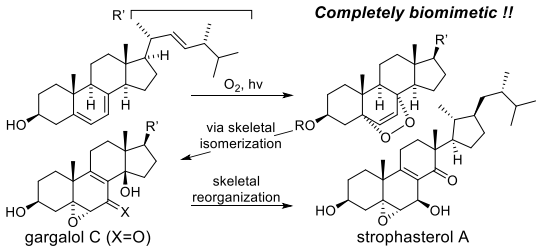
Rui Ishikawa,* Takashi Shigeta, Tomohiro Ichikawa, Takashi Ikawa
Gifu Pharmaceutical University



2P-94S

Biomimetic Straightforward Conversion of Ergosterol to Gargalol C and Strophasterol A: Chemical Demonstration of Putative Biosynthetic Pathways

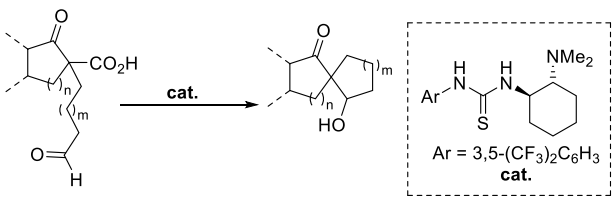
Yui Kanda,* Shoji Kobayashi
Osaka Institute of Technology



2P-95S

Synthesis of chiral spiro compounds by decarboxylative intramolecular aldol reaction

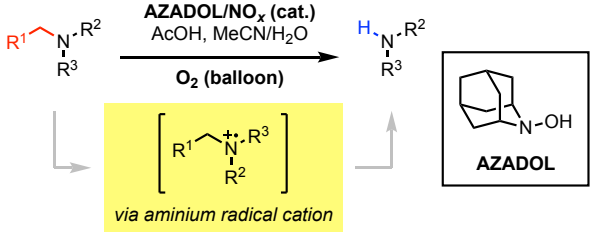
Akito Teraoka*, Kazutaka Shibatomi
Department of Applied Chemistry and Life Science, Toyohashi University of Technology



2P-96S

Organocatalytic Aerobic Oxidative Monodealkylation of *tert*-Amines to *sec*-Amines

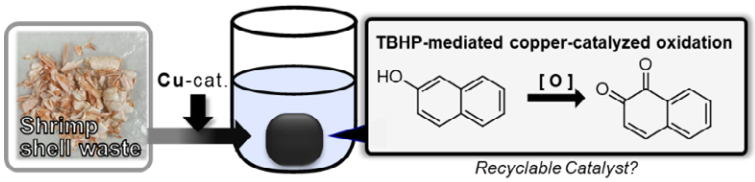
Shuhei Akutsu,* Yusuke Sasano, Haruki Shimabayashi, Ryota Sasaki, Yoshiharu Iwabuchi



2P-97S

Development of a Shrimp Shell-Derived Copper-Catalyzed Solid-Phase Oxidation System for Phenolics

Mizuki Matsui,* Kousuke Asano, Hiromi Hamamoto
Faculty of Agriculture, Meijo University



Abstracts

Keynote Lectures

K-1 ~ K-13

July 2nd. & 3rd.

K- 1（Keynote Lecture）

Beyond the Paradigm: Liquid-Phase Synthesis of *N*-Alkyl-Rich Cyclic Peptides from the First Scale-Up manufacturing

Hiroshi Iwamura
API Process Development Department, Chugai Pharmaceutical Co., Ltd.
5-5-1 Ukima, Kita-ku, Tokyo, 115-8543, Japan
Iwamura.Hiroshi89@chugai-pharm.co.jp

Cyclic peptides bearing *N*-alkyl amino acids are promising therapeutics because they can show oral absorption and access challenging intracellular targets.[1] LUNA18 (paluratide), for instance, was a potent clinical pan-RAS inhibitor.[2] Large-scale synthesis of *N*-alkyl-rich cyclic peptides remains difficult because steric hindrance lowers coupling reactivity and the peptides show limited stability under process conditions. We propose here a paradigm shift from conventional solid-phase peptide synthesis (SPPS) to liquid-phase peptide synthesis (LPPS) from the first scale-up manufacturing, representing a vital evolution in process chemistry.

1. The Current Paradigm and Its Limitations

The "Solid-Phase-First" strategy, commonly used for early clinical supply, needs specialized facilities and has a high environmental impact.[3] In the LUNA18 program, we found that SPPS also suffers intrinsic bottlenecks arising from the low reactivity and instability of *N*-alkyl-rich peptides.

2. Beyond the Paradigm: “Liquid-Phase-First” Strategy

To overcome the scale-up limitations on SPPS, we implemented the “Liquid-Phase-First” strategy from the early development phase.[4] A convergent two-fragment route comprising 24 telescoped transformations based on originally-developed liquid-phase peptide synthetic methodologies, followed by final crystallization, delivered over 2kg of LUNA18 in >30% overall yield with >98.5% purity by HPLC area (Figure 1). The shift from SPPS to LPPS also improved environmental performance, reducing process mass intensity (PMI) to approximately one sixth of the SPPS process.

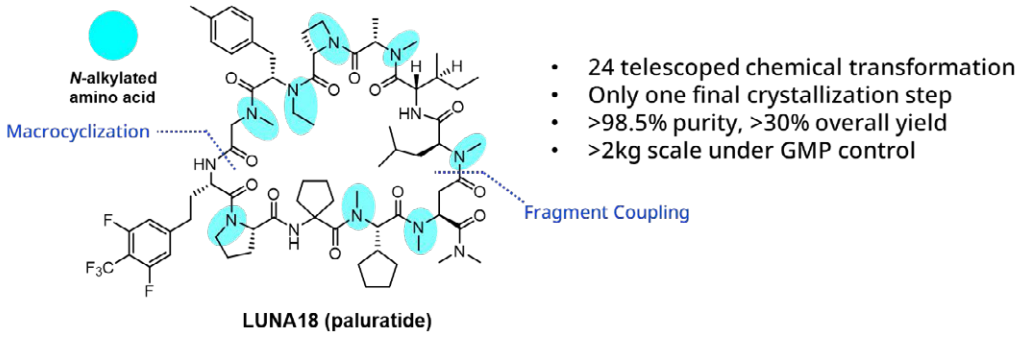


Figure 1. Overview of scale-up synthesis of LUNA18.

3. Route Metrics-Driven Platform: The Core Sustaining the New Paradigm

To support the rapidly expanding *N*-alkyl-rich cyclic peptide pipeline, we are transitioning from empirical route selection to a Route Metrics–driven platform that ensures the design and construction of efficient, highly convergent synthetic routes from the earliest stages of process development (Figure 2). The "Liquid-Phase-First" strategy is accelerated by the platform which is built on two novel technologies: data chemistry-based route prediction and novel epimerization-resistant fragment coupling methodologies.

· Data Chemistry-Based Route Prediction

We developed predictive models to evaluate various parameters governing synthetic efficiency and fragment stability, including the susceptibility to diketopiperazine (DKP) formation—a critical side reaction in peptide assembly. By integrating DFT calculations with kinetic experiments, the model links the primary peptide structure to reactivity, enabling risk-mitigating intermediate design and optimized route selection from the very outset of process development.

· Novel Epimerization-Resistant Fragment Coupling

To overcome the inherent low reactivity inherent in *N*-alkyl substrates, we developed two types of epimerization-resistant fragment coupling reactions. The methodologies are applicable to a broad scope of *N*-methylated substrates and provide superior stereochemical control, consistently achieving diastereomeric ratios exceeding >99.0:1.0 dr.[5] This approach significantly expands the synthetic utility of peptide coupling for these sterically hindered substrates.

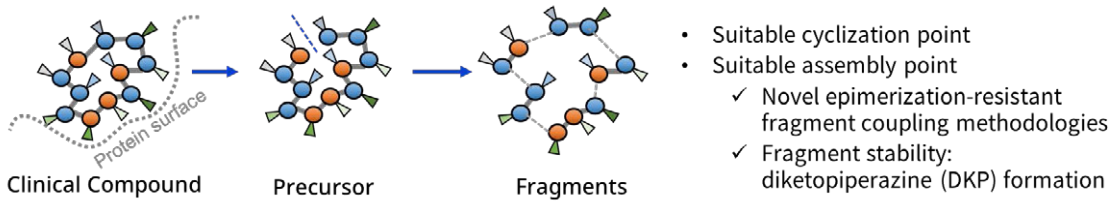


Figure 2. Route Metrics-driven platform of *N*-alkyl-rich cyclic peptide

The "Liquid-Phase-First" strategy is attained through Route Metrics-driven platform, which integrates rational route design with novel fragment coupling methodologies for *N*-alkyl substrates. We are confident that this strategy, by ensuring synthetic efficiency and scalability from the outset, will serve as a vital engine for agile development, delivering life-changing treatments to patients faster and more sustainably.

Reference

1) Ohta, A.; Tanada, M.; Shinohara, S. et al. *J. Am. Chem. Soc.* **2023**, *145*, 24035-24051.
2) Tanada, M.; Tamiya, M.; Matsuo, A. et al. *J. Am. Chem. Soc.* **2023**, *145*, 16610-16620.
3) Andersson, L.; Blomberg, L;, Flegel, M. et al. *Biopolymers*, **2000**, *55*, 227-250.
4) Hou, Z.; Komiya, S.; Iwasaki, K. et al. *Org. Process. Res. Dev.* **2025**, *11*, 2764-2782.
5) Komiya, S.; Matsumoto, T.; Fujii, K. et al. *J. Org. Chem.* ASAP, Apr. 24, **2026**, 91. https://doi.org/10.1021/acs.joc.6c00433

Development of Efficient Catalytic Flow Process: Stratergies and Insights for Pharmaceutical Applications

Eunpyo Hong,* Ryan Seongho Oh
Small Molecule Asia (SK biotek), SK pharmteco
325, Expo-ro, Yuseong-gu, Daejeon 34124, Korea
ephong@sk.com

Catalytic flow processes using fixed-bed reactors (FBRs) provide an efficient and scalable platform for pharmaceutical synthesis. At SK pharmteco, we integrate in-house catalyst design capabilities, catalytic flow reaction technology, and scale-up expertise to develop robust processes from laboratory to commercial production.

As a CDMO, rapid process development within a limited timeline is critical. To accelerate development, we employ strategic approaches, beginning with a proprietary catalyst library. Rather than maintaining catalysts simply in stock, we pre-design and characterize catalysts with diverse physicochemical properties, enabling rapid screening and efficient process optimization. In addition, we conduct preliminary case studies on compounds with diverse functional groups. These studies allow us not only to identify suitable catalysts for each reaction, but also to understand impurity profiles under various reaction conditions. This approach improves predictability and robustness during process development. Furthermore, in this study, we introduce representative examples of commercial projects and theoretical considerations for scale-up.

Based on our experience and theoretical background, we established practical design principles for catalyst selection and scale-up in FBR systems. These results demonstrate that integrated catalyst development and catalytic flow engineering provide a powerful and scalable solution for efficient pharmaceutical manufacturing.

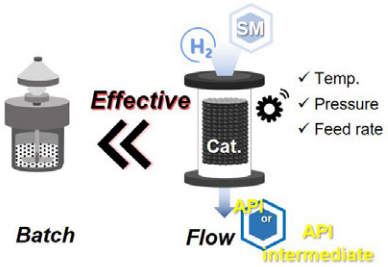


Figure 1. From Batch to Flow: Efficient and Scalable Catalytic Process in Fixed-Bed Reactors

References

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K- 3（Keynote Lecture）

Using Data Science and Machine Learning in Synthetic Process Optimization

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The optimization of reactions for organic synthesis can be challenging as the interplay between the catalyst structure, reaction conditions, and substrates involved is a complex multidimensional problem. This problem is magnified in Process Chemistry as the ultimate reaction must be scalable, safe, and highly efficient. We have developed several data science and machine learning tools that assist in designing the proper experiments and facilitating the optimization of catalysts. This lecture will outline how we have put into practice workflows that facilitate rapid reagent development and catalyst optimization with a focus on our collaborations with industry.

K- 4（Keynote Lecture）

From Molecule to Medicine: Innovator–CDMO Synergy in Modern Drug Development

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Abstract: The transition from a promising lead molecule to a life-saving medicine requires seamless integration of discovery, process development, and manufacturing. A critical challenge in this journey is translating discovery-scale chemistry into robust and scalable manufacturing processes. Experience spanning both large pharmaceutical innovators and oncology-focused biotechnology companies highlight how process chemistry serves as a key bridge between early discovery and clinical and commercial supply.

This keynote explores how close collaboration between innovator organizations and CDMO partners can accelerate the development and manufacture of new medicines. Selected case studies from oncology drug development will illustrate how integrated process strategy, combined with emerging technologies such as continuous flow chemistry, biocatalysis, electrochemistry, and photocatalysis, can enable safer, faster, and more sustainable drug production. Together, these examples highlight the importance of technical continuity and strong innovator–CDMO partnerships in navigating the path from molecule to medicine.

Innovations in SHIONOGI Process Chemistry
Scalable Manufacturing Strategies for COVID-19 Antivirals

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Infectious diseases not only threaten individual health but also profoundly disrupt social and economic activities. In an increasingly globalized world, newly emerging viruses can spread rapidly across the globe through human travel. The coronavirus disease 2019 (COVID-19) pandemic, which emerged in late 2019, remains shocked in our memory and has underscored the importance of preparation against infectious threats. As one of the leading pharmaceutical companies focused on infectious diseases, we engaged early in the development of COVID-19 therapeutics and have so far discovered two promising compounds. Here, we present the strategies, research and development for the manufacturing processes of both compounds.

The first is ensitrelvir (**1**, Figure 1), which received emergency authorization in Japan in 2022 and was granted full approval in 2024. **1** features a unique structure in which three (hetero)aromatic moieties are appended to a central 1,3,5-triazinone core. Considering this structure, a convergent synthetic strategy—namely, the stepwise introduction of the three (hetero)aromatic units onto the central triazinone scaffold—was considered to be rational and practical for a manufacturing process. Therefore, we aimed to establish this convergent route for manufacturing.

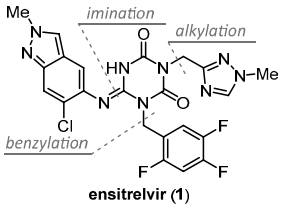
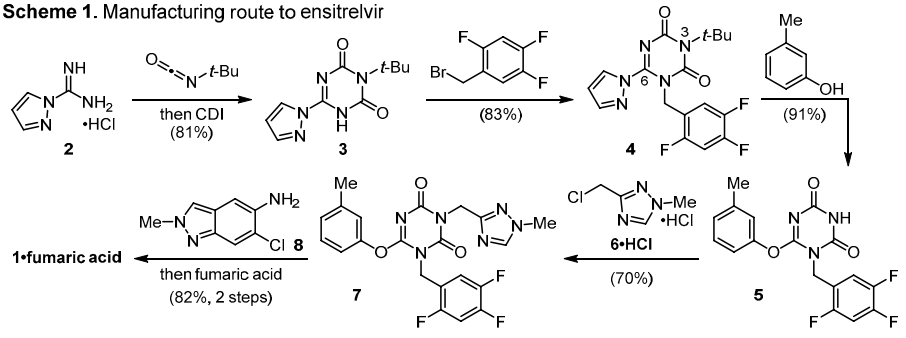


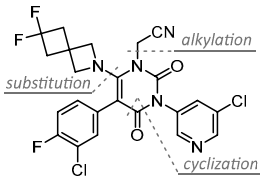
Figure 1. Chemical structure

A practical route to **1** was shown in Scheme 1. The key feature of this route was the strategic conversion of a pyrazolyl moiety to a cresolyl one (transformation of **4** to **5**). Although the pyrazolyl moiety originated from inexpensive, readily available precursor **2**, it suffered from poor stability to acids and bases and from low crystallinity, which complicate handling. Detailed investigations showed that deprotection at the 3-position and replacement of the pyrazolyl group at the 6-position of **4** proceed simultaneously in the presence of *meta*-cresol under the acidic condition, giving the corresponding cresolyl derivative **5**. This substitution markedly improved the stability and handleability of intermediates **5** and **7**. Furthermore, in the step for introduction of **8**, the cresolyl moiety worked as an effective leaving group, allowing conversion of **7** to **1** under mild condition. Practical manufacturing routes for heteroaromatic compounds **6**・**HCl** and **8** were also developed to ensure quality control and reduce costs.

Scheme 1. Manufacturing route to ensitrelvir



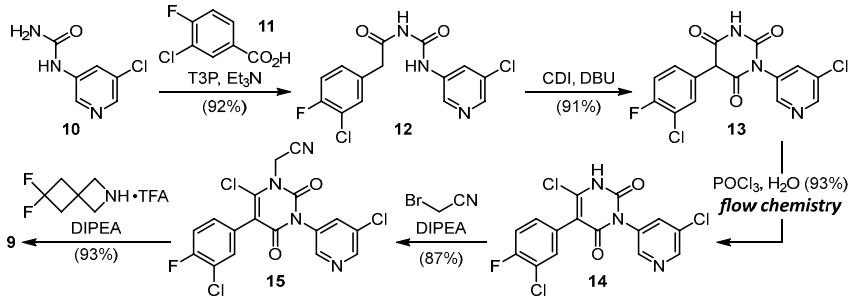
The second case study was the process development for secutrelvir, a next-generation COVID-19 therapeutic (**9**, Figure 2). In contrast to **1**, the central core of **9** consists of a barbiturate scaffold. To maximize efficiency, it was necessary to prepare a multi-functionalized barbiturate derivative that would allow the methyl cyano moiety and the azetidine core to be introduced at a later stage. The first innovation was the development of a novel method for constructing the central barbiturate scaffold. We conceived a stepwise methodology consisting of condensation of urea **10** with carboxylic acid **11** followed by a cyclization with an appropriate carbonyl source. The initial condensation proceeded smoothly only when using T3P as the coupling reagent, and the subsequent cyclization employed CDI as the carbonyl source, which together delivered the target **13**. This novel and unprecedented methodology could provide convenient access to highly substituted barbiturate scaffolds under mild conditions.



secutrelvir (**9**)

Figure 2. Chemical structure

Scheme 2. Manufacturing route to secutrelvir



Next challenge was improving reaction yield and efficiency for manufacturing **14**. We investigated chlorinating conditions in detail and found that a reactive intermediate ($HOPOCl_2$) generated by the combination of phosphorus oxychloride ($POCl_3$) with water strongly promoted the desired transformation. A kinetic study and mechanistic insights indicated that the dissolution of hydrogen chloride, a byproduct formed concomitantly with the $HOPOCl_2$, had a significant impact on the reaction rate. To control this parameter, continuous-flow chemistry was implemented for this step, generating $HOPOCl_2$ under elevated temperature and pressure within a confined flow channel and thereby creating a homogeneous reaction medium with a high dissolved HCl concentration. This approach stabilized the reaction rate and delivered a process with high reproducibility and efficiency. Finally, the yield of this step was increased from 77% to 93%.

In conclusion, we have developed practical processes of two promising compounds for scale-up production. In both manufacturing routes, all target compounds were isolated by crystallization, thereby entirely eliminating the need for column chromatography. Compared with the medicinal-stage synthesis, overall yields were substantially improved, rendering the processes practical for scalable implementation. Process mass intensity (PMI) was also reduced, reflecting a greener, more sustainable manufacturing approach. These innovations demonstrate the potential of our scalable, streamlined route to strengthen the supply chain for COVID-19 therapeutics.

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K- 6（Keynote Lecture）

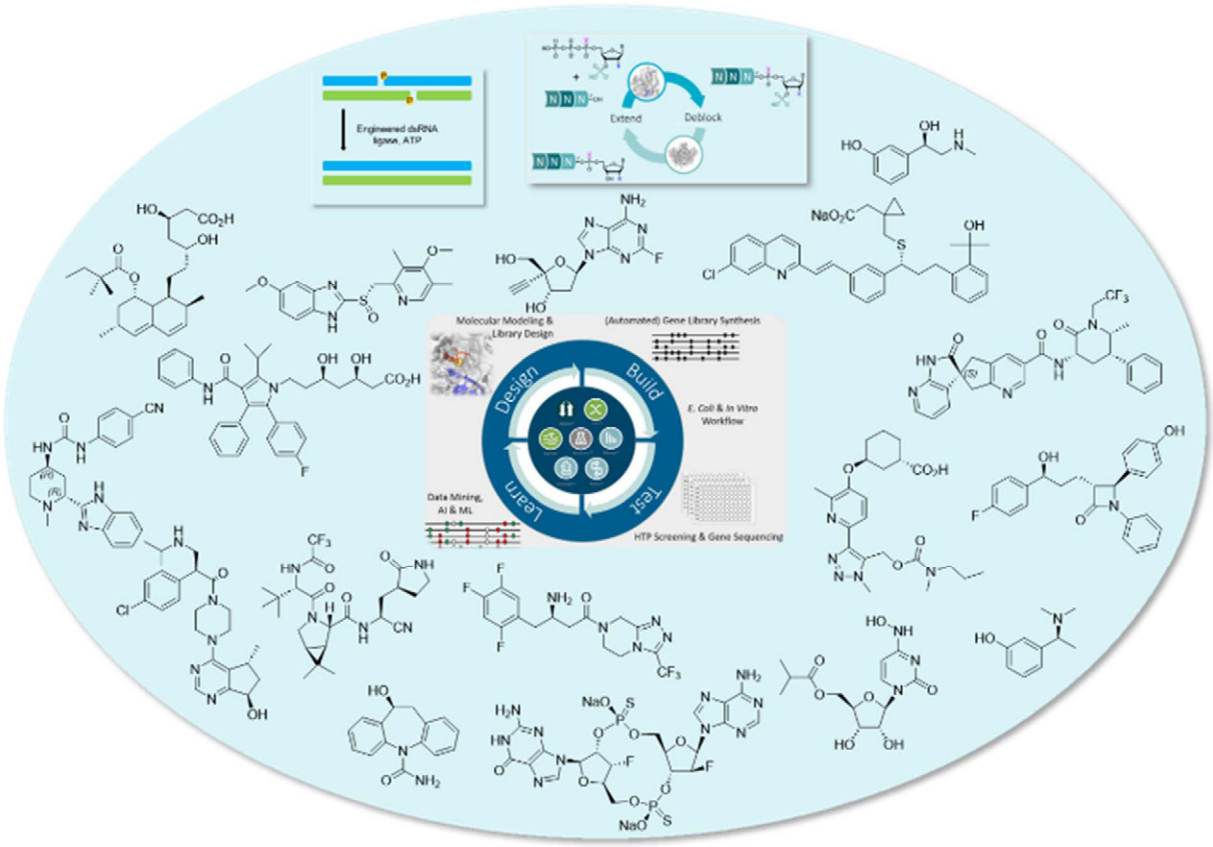
ENABLING COMPLEX INTERMEDIATE AND API SYNTHESES AT SCALE WITH ENGINEERED ENZYMES.

Dr. David A. Entwistle

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Codexis has been working with Pharmaceutical clients for over 24 years, helping them envision, develop and impliment advanced enzymatic solutions for syntheses of their intermediates and APIs. The presentation will showcase a selection of interemediate and API syntheses that have been scaled to kg scale and beyond, enabled by Codexis engineered enzymes (Scheme 1).

SCHEME 1. ENABLING COMPLEX INTERMEDIATE AND API SYNTHESES AT SCALE WITH ENGINEERED ENZYMES.

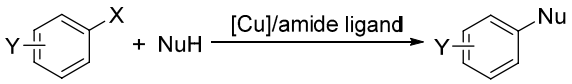


K- 7 (Keynote Lecture)

Ligand Development for Cu-Catalyzed Arylation of Nucleophiles

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Metal-catalyzed coupling reactions of aryl halides with nucleophiles are powerful tools for forming C–heteroatom and C–C bonds, representing one of the most frequently used transformations in the development of functional molecules such as pharmaceuticals, agrochemicals, and materials. Over the past two decades, significant progress has been made in ligand-promoted copper-catalyzed arylation of nucleophiles. Nevertheless, many challenges remain in this field. The most pressing issue is that less expensive aryl chlorides are generally inert under nearly all Cu/ligand-catalyzed coupling conditions. In addition, catalyst loadings are still high in most cases. Recently, we discovered that certain N,N'-diaryl, N-aryl-N'-alkyl, or N,N'-dialkyl substituted oxalamides, as well as heterocyclic amides, serve as highly effective ligands for copper-catalyzed nucleophile arylation. These ligands not only enable the coupling of (hetero)aryl chlorides with nucleophiles to proceed smoothly under relatively mild conditions, but also allow the coupling of aryl bromides and iodides to be performed at low catalyst loadings and reduced reaction temperatures. More importantly, the discovery of these ligands has enabled many previously less reactive nucleophiles to perform well, thereby greatly expanding the reaction scope. In this lecture, we wish to present these findings.

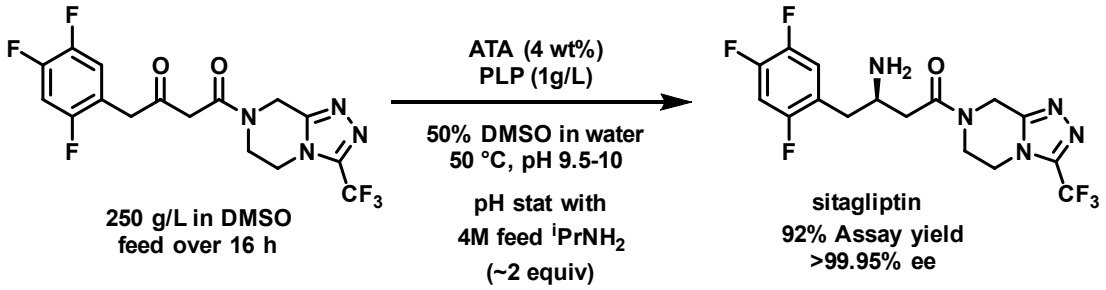


X = Cl, Br; Nu = amines, N-hetercycles, alcohols, phenols

Enabling Technologies to Drive the MSD Portfolio

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Biocatalysts can enable superior process routes that are impossible to access using chemical reagents and catalysts. Enzyme specificity and compatibility allow multiple enzymes to work together in cascade processes. Protein engineering enables a biocatalyst to be evolved from a natural starting point to an unnatural function. Investments in biocatalysis and protein engineering have transformed how we synthesize molecules at MSD. This presentation will focus on the evolution of our evolution capabilities and how we have progressed from single enzyme efforts to multi-enzyme incursions and from established enzyme-catalyzed transformations to novel bond disconnections. In turn, these innovations are seeing widespread use for complex pipeline problems and allowing MSD to bring critical medicines to patients worldwide.



Scheme 1. Sitagliptin synthesis

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Development and Demonstration of an Automated Continuous Manufacturing System for Fine Chemicals Using Taylor–Couette Crystallization

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The stable and sustainable supply of fine chemicals, represented by pharmaceuticals, has become an increasingly serious challenge in Japan in recent years. Japan's total population is projected to decline significantly from approximately 126 million in 2020 to about 87 million by 2070, accompanied by a marked decrease in the working-age population. In addition, many manufacturing processes for fine chemicals still rely heavily on manual operations, and structural labor shortages are expected to become even more pronounced. Furthermore, the risk of supply disruptions due to external factors such as international conflicts and natural disasters is increasing. Under these conditions, there is an urgent need to establish manufacturing facilities and develop process technologies that enable stable and continuous product supply.

In response to these challenges, we are developing a highly automated continuous manufacturing platform, termed iFactory, targeting fine chemicals including pharmaceuticals. The implementation of iFactory is expected to enhance the resilience of fine chemical supply by reducing dependence on human labor, enabling flexible adjustment of production rates in response to demand, and improving quality assurance. The core concept of iFactory is the reconfiguration of mobile, modular unit operation devices (iCubes) according to process requirements, which are integrally operated through an orchestration system. To date, continuous manufacturing systems have been developed at both laboratory scale (up to 0.3 kg/h) and commercial-scale demonstration level (up to 10 kg/h) (Figure 1).

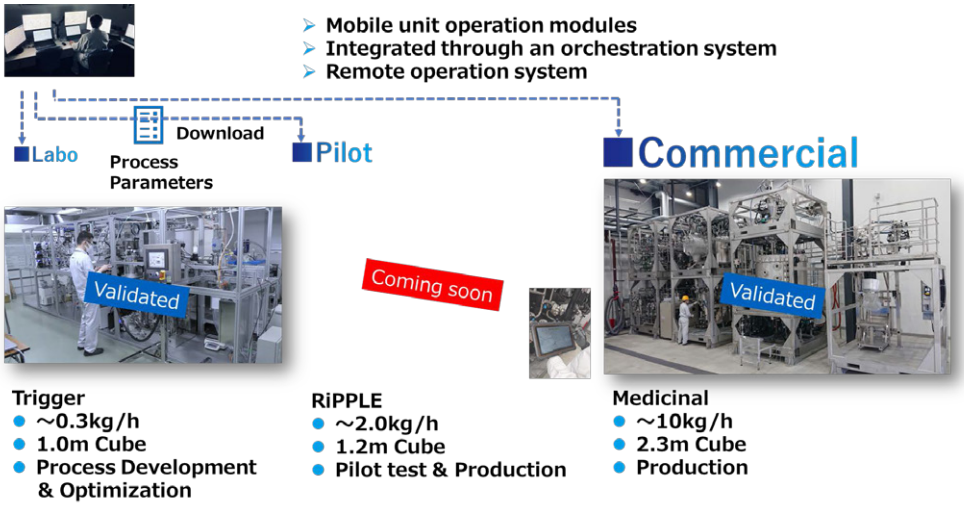


Figure 1. Concept and System Lineup of the iFactory Platform

Although numerous studies have been reported on continuous processing of homogeneous solutions, such as continuous reactions, there are relatively few examples addressing the continuous handling of process streams containing solids. We identified crystallization control as a critical factor for stabilizing downstream operations and focused our process development on a Taylor-Couette continuous crystallizer capable of precise temperature control under high-shear conditions (Figure 2). In 2023, as part of a NEDO-funded project, a commercial-scale demonstration was conducted using equipment installed at Takasago Chemical Corporation. Stable continuous production was achieved for more than 8 hours-corresponding to 490 times the mean residence time-yielding crystals with a unimodal particle size distribution and a D50 of 9 μm. Furthermore, by integrating subsequent continuous filtration, fluidized-bed drying, and continuous filling through the orchestration system and operating the process under fully automated conditions, we successfully manufactured 15.2 kg of product with quality equivalent to or superior to that of batch-produced material. No interruptions or cleaning operations were required during automated operation.

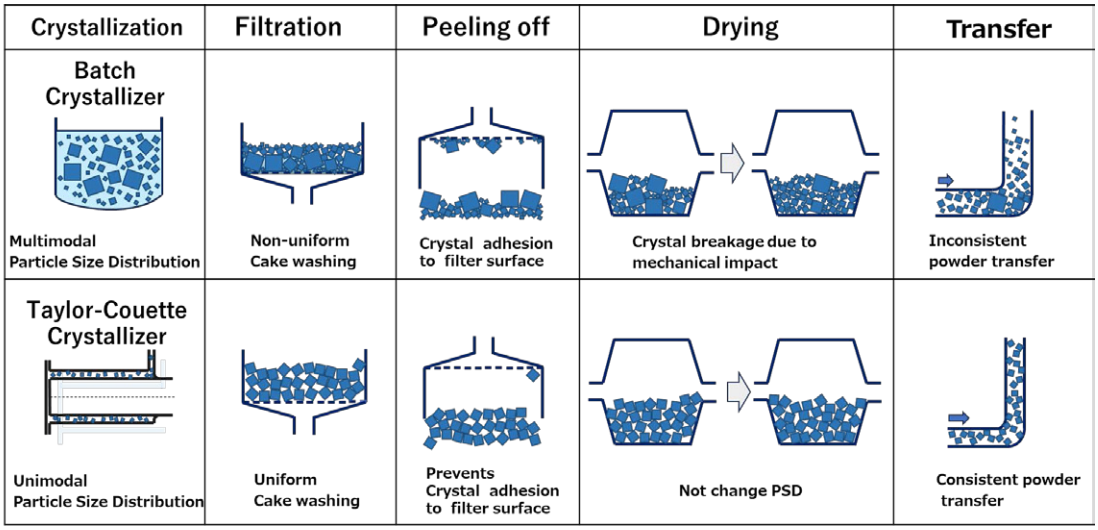


Figure 2. Effect of Crystallization PSD on Downstream Continuous Operations

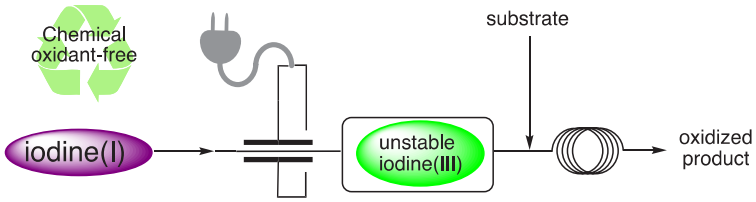
In addition, through a collaborative study with the National Institute of Advanced Industrial Science and Technology (AIST), stable operation for more than 7 hours was achieved even at laboratory scale, which imposes more stringent conditions due to narrower piping susceptible to clogging and greater sensitivity to disturbances. In this system, eight-unit operations, ranging from continuous extraction to crystal recovery, were connected and operated continuously.

Currently, development and standardization efforts are underway at the pilot scale (up to 2 kg/h). By adopting a standardized, scale-independent integrated modular configuration, smooth scale-up is expected without major changes to the overall process flow. Moreover, this presentation will also report the progress in developing a horizontal continuous reactor intended to serve as an alternative to conventional CSTRs, MSMPRs, and surge tanks.

Scaling Electrochemistry: From Lab Curiosities to Continuous Processes

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The advantages of increased mixing of biphasic reaction mixtures in flow offers great potential compared to conventional flask techniques. The development of a microreactor for electrochemistry including several applications to modern synthesis will be discussed.[1,2] The electrochemical generation of hypervalent iodine compounds using this technique will be highlighted (Scheme 1).[3,4,5] In addition to new flow electrochemical procedures, upscaling methods will demonstrate the versatility of such protocols also for pilot-scale operations.



Scheme 1. Electrochemical generation of iodine(III) reagents.

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K- 11（Keynote Lecture）

Continuous Flow Chemistry Enabled by 3D-Printed Metal Reactors: From Development to Industrial Implementation including Bayesian Optimization

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Continuous flow chemistry offers compelling advantages over conventional batch processing in terms of safety, scalability, heat and mass transfer, and process control. At InnoSyn B.V., flow chemistry has been developed and implemented as a core technology platform spanning early process development, piloting, and commercial manufacturing. This contribution presents an integrated overview of InnoSyn's continuous flow capabilities, with a particular focus on intensified 3D-printed metal reactor technologies and their application to challenging chemical transformations.

Advanced reactor design freedom enabled by laser powder bed fusion (selective laser melting) allows the fabrication of compact, seal-free metal flow reactors with near-ideal plug-flow behaviour, excellent heat transfer coefficients (up to ¥~8000 $W \cdot m^{-2} \cdot K^{-1}$), high surface-to-volume ratios, and operation across a wide temperature (−100 to +300 °C) and pressure range (up to >200 bar). Custom internal geometries, such as zigzag channels, induce secondary (Dean) flow, resulting in enhanced mixing, narrower residence time distributions, and improved reaction performance, at the expense of a manageable increase in pressure drop. The mechanical integrity and pressure resistance of these reactors have been experimentally validated, enabling safe operation even for highly exothermic and fast reactions.

A modular and automated skid concept ("Plug & Produce & Develop") integrates flow reactors with dosing, precooling, quenching, process monitoring, safeguarding, and data logging. This enables rapid transition from laboratory experiments to pilot scale and continuous kilogram-scale production. The approach is illustrated through multiple industrially relevant case studies, including low-temperature organometallic chemistry, selective DiBAl-H reductions, azide substitution reactions, aerobic oxidations, nitrations, polymerisations, and reactions followed by continuous crystallisation. In several examples, flow processing delivers markedly improved selectivity, higher productivity, and enhanced intrinsic safety compared to batch processing, while eliminating scale-up limitations associated with heat removal and mass transfer.

In addition to reaction engineering, InnoSyn's platform integrates Bayesian optimization, process safety analysis, continuous purification techniques, inline and PAT-enabled monitoring, and full pilot-to-plant implementation under appropriate regulatory frameworks (including PED-certified commercial reactors). Overall, this work demonstrates how tailored continuous flow reactor design, combined with modular process integration, enables robust and scalable manufacturing routes for complex and hazardous chemistries, supporting faster development timelines and reliable industrial deployment.

K- 12（Keynote Lecture）

Process Chemistry Realisation for Neglected Tropical Diseases (NTDs): Enabling Affordable and High-Quality Medicines for Patient Benefit

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Neglected tropical diseases (NTDs), including malaria, disproportionately affect vulnerable populations due to limited access to affordable and effective treatments. Addressing these challenges requires the development of medicines that are accessible, cost-effective, and suitable for deployment in resource-limited settings.

In this context, an efficient, robust, and scalable synthetic process was developed for the novel antimalarial drug candidate E1018 **(1)**, overcoming key limitations of the chromatography-intensive discovery route. The process development strategy emphasised early integration of stereochemical control, cost considerations, scalability, and reproducibility, along with comprehensive evaluation of process safety and hazard mitigation.

Key improvements include enhanced process mass intensity (PMI), stringent control of quality-critical attributes, and the development of crystalline intermediates enabling a chromatography-free manufacturing pathway suitable for large-scale production.

The developed route for compound **(1)** enables the construction of a structurally complex molecular scaffold containing five stereogenic centres. Key features of the synthesis include a diastereoselective glycine ester Claisen rearrangement, resolution through diastereomeric salt formation, and a highly diastereoselective iodolactonization. Molecular complexity is further enhanced through a novel tandem aziridine ring-opening and azetidine ring-closure sequence. Formation of the eight-membered diazocine ring is achieved via a tandem reductive amination–periodate cleavage–Staudinger–aza-Wittig reaction sequence on a sugar acetonide template, enabling efficient and controlled assembly of the core framework (Figure 1)[1].

This was established through in-depth mechanistic chemistry understanding, sound process engineering studies, scalability simulations, and rigorous evaluation of safety and operational hazards. Stringent quality control strategies were implemented, ensuring that all potential chiral isomers and individual impurities were controlled to below 0.10% using scientifically validated analytical methods. These studies enabled the successful translation of chemistry from the milligram scale to the

multi-kilogram scale with consistent quality and performance.

A more than sixty-fold increase in overall yield was achieved, resulting in an approximate 97% reduction in cost, along with significant improvement in Process Mass Intensity (PMI)[2] and a reduced environmental footprint. The resulting high-quality drug substance supports patient safety, broader access, improved treatment adherence, and sustainable deployment of antimalarial therapy.

This innovation was enabled through the effective application of the SECI (Socialization–Externalization–Combination–Internalization) knowledge-creation model,[3] highlighting the value of integrated scientific and process knowledge in advancing sustainable pharmaceutical manufacturing.

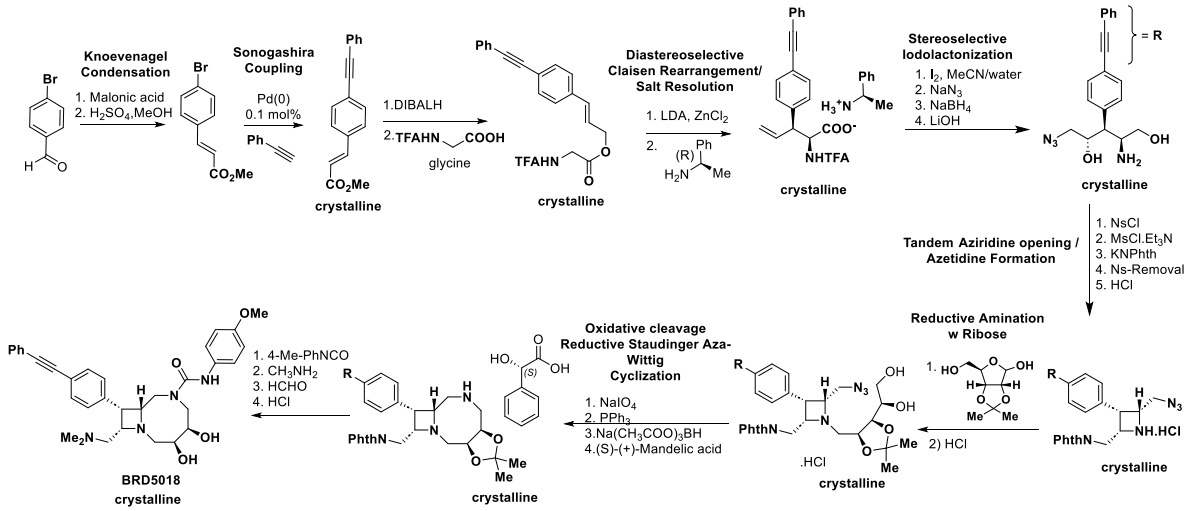


Figure 1: E1018 Drug Substance Synthesis Outline

Reference:

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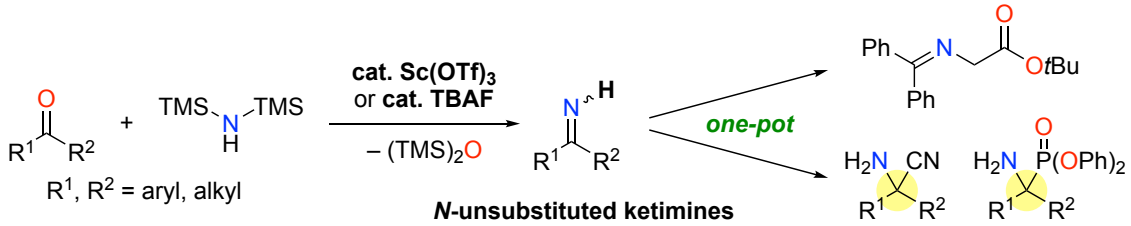
Bis(trimethylsilyl)amine as a Versatile Ammonia Equivalent: Catalytic Direct Synthesis of *N*-Unsubstituted Ketimines, Primary Amides, and Nitriles

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Ammonia (NH_3) is the most abundant and atom-economical nitrogen source available. Direct incorporation of NH_3 into organic molecules is therefore highly desirable from both synthetic and green chemistry perspectives. Our group has pursued this challenge through the development of transition-metal-catalyzed direct amination reactions using aqueous ammonia.[1)] Despite the conceptual elegance of direct NH_3 use, significant practical limitations remain: (i) gaseous NH_3 is toxic, corrosive, and hazardous to handle on scale; (ii) excess NH_3 can deactivate metal catalysts; and (iii) multi-step one-pot sequences are difficult. These challenges prompted us to explore bench-stable, easy-to-handle NH_3 surrogates compatible with Lewis acid catalysis and amenable to one-pot reaction sequences.

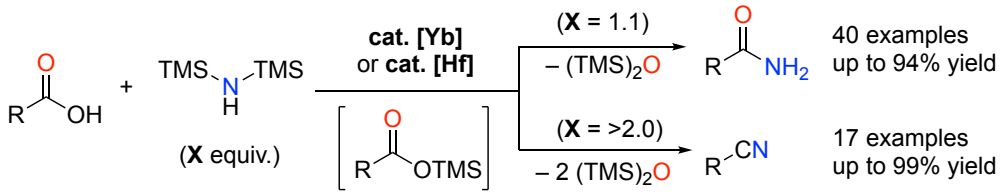
Bis(trimethylsilyl)amine (TMS_2NH, HMDS) is a commercially available, inexpensive, and widely used reagent in organic synthesis. HMDS offers several decisive advantages over NH_3 as a nitrogen source for Lewis acid-catalyzed reactions: (1) Irreversible reaction driven by a stable co-product: The sole by-product, hexamethyldisiloxane (TMS_2O, bp 101 °C), is chemically inert and is highly volatile. Its formation renders the overall transformation thermodynamically irreversible, eliminating the need for dehydrating agents such as molecular sieves. (2) Ideal for one-pot multi-step reactions: TMS_2O does not interfere with subsequently added reagents or catalysts. This unique property makes HMDS ideal for one-pot sequences without isolation of unstable intermediates. (3) Safe, scalable, and economical: HMDS is a liquid reagent (bp 127 °C) no pressurized vessels or specialized infrastructure required.

The first phase of our research focused on the synthesis of *N*-unprotected ketimines from ketones. Unlike traditional methods that require harsh conditions or toxic reagents, we developed a scandium(III) triflate-catalyzed protocol using HMDS;[2)] scale-up to 65 mmol (>10 g) was achieved with 0.20 mol% catalyst (E-factor = 1.3) (Scheme 1). The key to this success is the thermodynamic driving force provided by TMS_2O formation. TMS_2O is chemically stable and volatile enabls *one-pot reactions* such as the Strecker reaction and Mannich-type additions without isolation of unstable ketimine intermediates.



Scheme 1. Catalytic Synthesis of N-Unsubstituted Ketimines and Their Applications to One-Pot Reactions

Building on the ketimine work, we next extended the HMDS platform to carboxylic acids. Direct amidation of carboxylic acids with NH_3 is fundamentally hampered by the formation of thermodynamically stable ammonium carboxylate salts (RCOOH + NH_3 → $RCOO^-NH_4^+$). In contrast, HMDS reacts fast with carboxylic acids to form trimethylsilyl ester intermediates in situ, converting the carboxylic acid before NH_3 can form a salt; the liberated NH_3 then acts as the nitrogen nucleophile in the subsequent Lewis acid-catalyzed amidation, releasing TMS_2O as the sole by-product. Crucially, by adjusting only the equivalents of HMDS, the same catalyst/reagent system selectively delivers primary amides (x = 1.1 equiv.) or nitriles (x ≥2.0 equiv.) (Scheme 2).[3)]



Scheme 2. Catalytic Synthesis of N-Unsubstituted Ketimines and Their Applications to One-Pot Reactions

Primary amides: With $Yb(OTf)_3$ (3–5 mol%) or $Hf(OTf)_4$ (5 mol%) in THF at 40–90 °C, structurally diverse carboxylic acids—including halogenated, nitro, boronate ester, phosphate, and hydroxy-substituted substrates, as well as *N*-Boc-α-amino acids (without epimerization)—are converted efficiently. Gram-scale synthesis (20 mmol, 1.0 mol% catalyst) confirms industrial viability; product isolation by simple recrystallization exploits the easy removal of volatile TMS_2O.

Nitriles: At 2.4 equiv. HMDS and 100 °C, the primary amide intermediate undergoes further Lewis acid-mediated dehydration via bis-silylated amide and *N*,*O*-bis(trimethylsilyl)imidate intermediates (confirmed by HRMS), providing nitriles directly from carboxylic acids in one-pot.

Moreover, during systematic functional group evaluation using our original FGE kit,[4)] we discovered that replacing NH_3 with formamide derivatives in the HMDS-mediated system leads to an unprecedented three-component reaction yielding a new class of nitrogen-containing compounds. Further scope and mechanism are under active investigation.

We have established HMDS as a versatile and strategically superior ammonia surrogate in Lewis acid catalysis. The irreversibility conferred by TMS_2O formation, the absence of side reactions from this by-product, and the operational simplicity of the system collectively make the HMDS strategy a practical and broadly applicable tool in process-oriented organic synthesis.

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Abstracts

Poster Presentation

1 P-01 ～ 1 P-97S

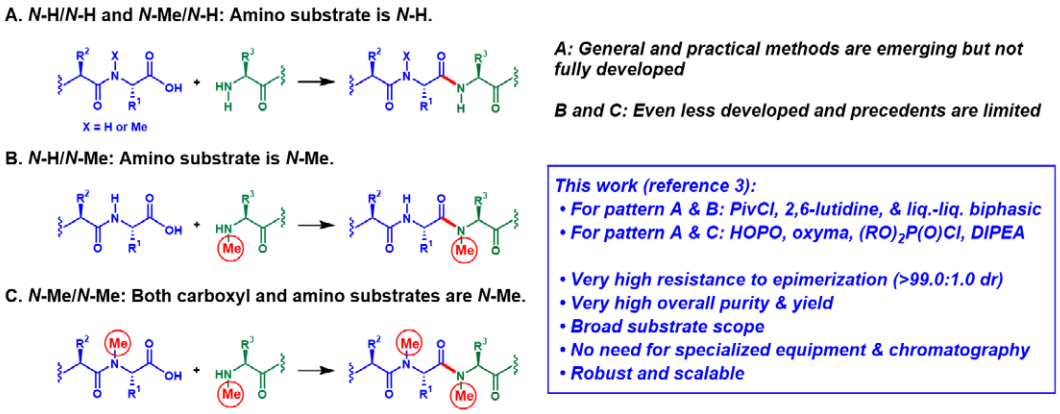
July 2nd.

1P-01

Development of Two Complementary Epimerization-Resistant Fragment Coupling Reactions for Highly Convergent Synthesis of *N*-Alkyl-Rich Peptides

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Cyclic peptides containing *N*-alkylated amino acids represent a promising therapeutic modality, offering access to intracellular targets previously considered "undruggable" and potential for oral administration.[1] The *N*-alkyl groups play important pharmacological roles by improving cell membrane permeability and metabolic stability. However, efficient synthesis of *N*-alkyl-rich peptides has been underdeveloped due to problems such as decreased reactivity and associated side reactions. Our pursuit of liquid-phase peptide synthesis (LPPS) over the past several years led to the scalable synthesis of LUNA18, a potent KRAS inhibitor.[2] Building on this foundation, we are currently developing **highly flexible and convergent LPPS strategies** designed to further improve synthetic efficiency with the advantages including reduced time, cost, PMI, and better quality control. Towards this goal, we have developed **two types of peptide fragment coupling reactions** that work effectively for diverse *N*-methylated substrates with exceptional resistance to epimer formation (>99.0:1.0 diastereomeric ratio) – a challenge that has proven difficult with established methods.[3] These two reactions have been found to work complementarily for the two different substrate patterns with distinct reactivity and selectivity. Together, they provide a significant breakthrough in the synthesis of *N*-alkyl-rich peptides.



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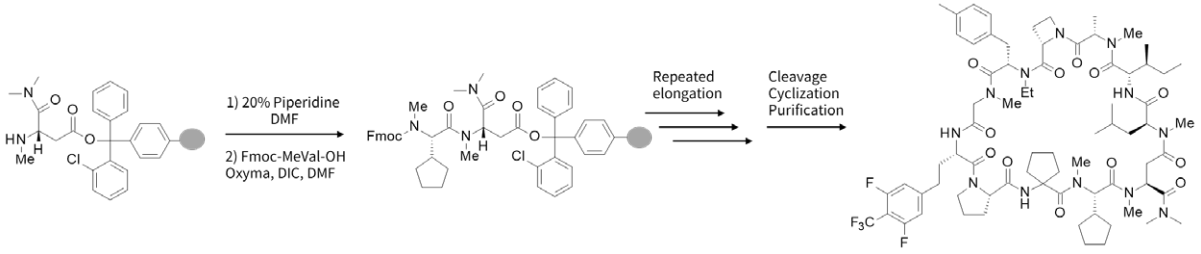
1P-02

Development of Solid-Phase Synthesis Method for N-Methyl Rich Peptides

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Chugai Pharmaceutical is advancing research on the development of orally bioavailable mid-size molecules. To improve oral absorption, a key structural feature of these compounds is the incorporation of numerous *N*-methyl amino acids within the molecule. In this study, we systematically investigated various synthetic challenges associated with the solid-phase synthesis of *N*-methyl-rich peptides and report herein the solutions we have identified.

Solid-phase peptide synthesis (SPPS) is a powerful approach for the rapid preparation of *N*-methyl-rich peptides. However, their synthesis remains challenging using conventional solid-phase synthesis methods, and three major synthetic issues that lead to decreased yield and purity have been identified. The first is premature cleavage from the resin. The second is the low reactivity in the amidation reaction between sterically hindered *N*-methyl amines and bulky carboxylic acids, and the consequent epimerization during coupling. The third is the formation of deletion peptides via diketopiperazine (DKP) elimination through a *cis*-amide intermediate[1]. To address these challenges, we systematically optimized the amidation conditions. Specifically, we screened various additives such as OxymaPure and coupling reagents such as DIC, and investigated the effect of reaction concentration, a parameter that has received little attention in solid-phase synthesis. As a result, we established a practical synthetic protocol that overcomes the major challenges in the synthesis of *N*-methyl-rich peptides[2]. This methodology is applicable to other *N*-methyl-rich peptides and is expected to provide valuable insights from an organic synthetic chemistry perspective.



Scheme 1. SPPS method for N-methyl rich peptides

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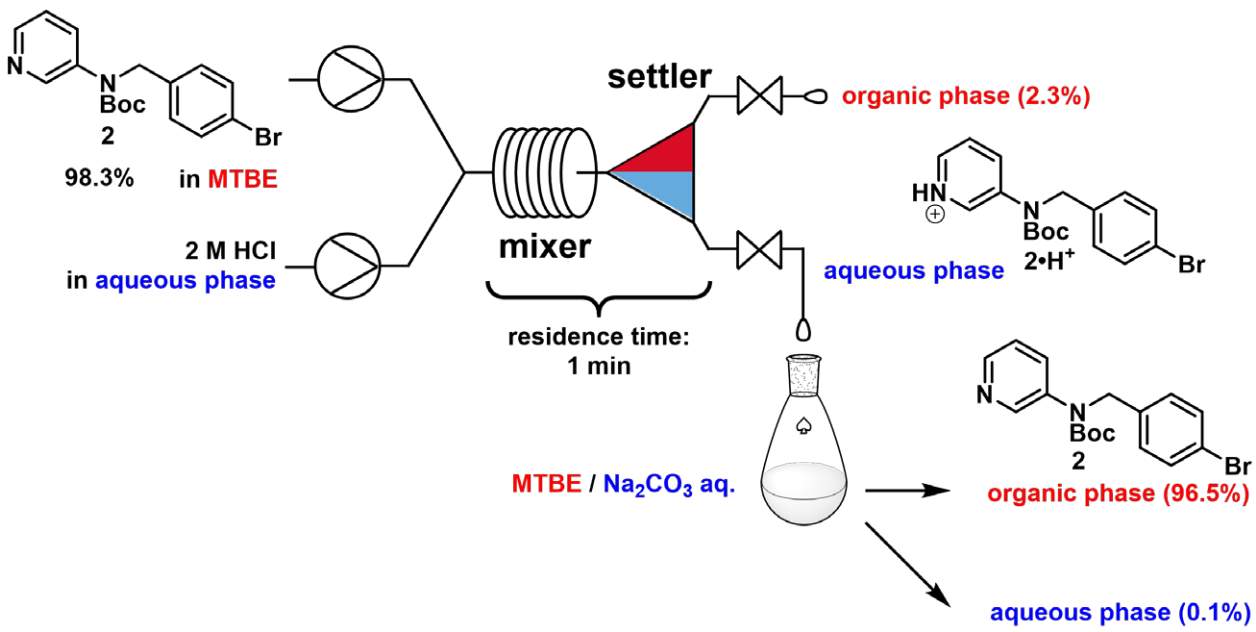
1P- 03

Rapid Extraction of Acid-Labile Compounds into an Aqueous Phase Using a Mixer-Settler under Continuous Flow Conditions

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Traditionally, basic compounds have been extracted into an aqueous phase under acidic conditions. However, basic compounds with a *tert*-butoxycarbonyl (Boc) protecting group are difficult to extract under acidic conditions because Boc-protected compounds are generally deprotected by acids and are labile in such environments.[1] The Boc group is widely used in organic synthesis to protect amino group. Being able to extract complex intermediates having the Boc group into an acidic aqueous phase can expand the options for purifying drug substances.

To address this issue, rapid extraction before decomposition is the simplest approach. Herein, we report the development of a rapid extraction method for 1 min using a mixer-settler, followed by an immediate neutralization protocol.[2]



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1P- 04

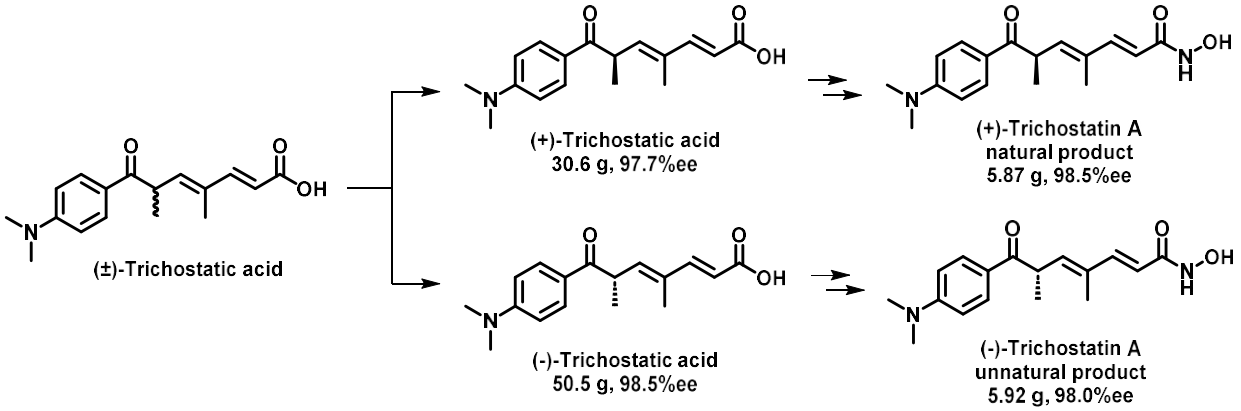
Practical Synthesis of Both Enantiomers of Trichostatin A

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Trichostatin A was discovered in 1976 by Tsuji and co-workers as a metabolite of a *Streptomyces* species and was originally reported as an antifungal antibiotic. Subsequently, it was identified as a potent inhibitor of histone deacetylases (HDACs) in mammalian cells and has since been widely used as a representative tool compound in epigenetics research. Even today, it occupies an important position as a benchmark compound in HDAC inhibitor research.

Although several synthetic approaches to trichostatin A have been reported, these studies were primarily focused on synthetic methodology, and reports describing process development aimed at stable supply on a practical scale have been limited. In this study, we focused on trichostatic acid as a key late-stage intermediate and established an optical resolution protocol. Repeated recrystallization of its cinchonidine salt afforded trichostatic acid with high optical purity (>96% ee). Furthermore, selective access to either enantiomer was achieved simply by changing the solvent, enabling a practical and scalable supply of both the natural and unnatural enantiomers on a multi-gram scale.

The ability to provide sufficient quantities of both enantiomers strengthens the research foundation for comparative biological studies and mechanistic investigations, and is expected to further support advances in related research fields.



Scheme 1. Scalable Preparation of Both Enantiomers of Trichostatin A

References

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1P- 05

The Role of NO and NO_2 in *N* -Nitroso Compounds Formation in API and Formulation

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We previously reported that trace nitrogen oxides (NOx) in the air promote nitrosation reactions during formulation processes, and that reducing NOx concentrations in formulation processes decreases nitrosamine content in pharmaceutical products.

Therefore, to identify the primary factor (reactive species) promoting nitrosation and implement more effective countermeasures, we evaluated the nitrosation potential of NO and NO_2, the main components of NOx, using two experimental systems.

Specifically, verification using a gas flow experimental system simulating a fluidized bed granulator and a duct experimental system equipped with Towa's third-generation filter revealed that NO_2 is the primary factor in both nitrosation reactions.

Based on these results, by implementing simplified countermeasures focused on NO_2 removal, we successfully obtained low-cost and long-lasting materials.

In this presentation, we will introduce the process that led us to conclude that NO_2 is the primary factor in the nitrosation reaction.

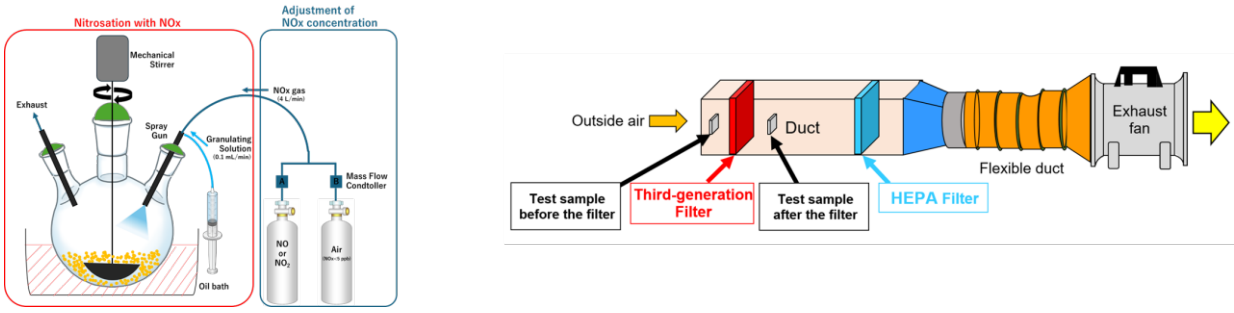


Figure 1. Gas flow model system designed to simulate a fluidized bed granulator (left) and Duct experimental system equipped with a third-generation filter (right) [1), 2)]

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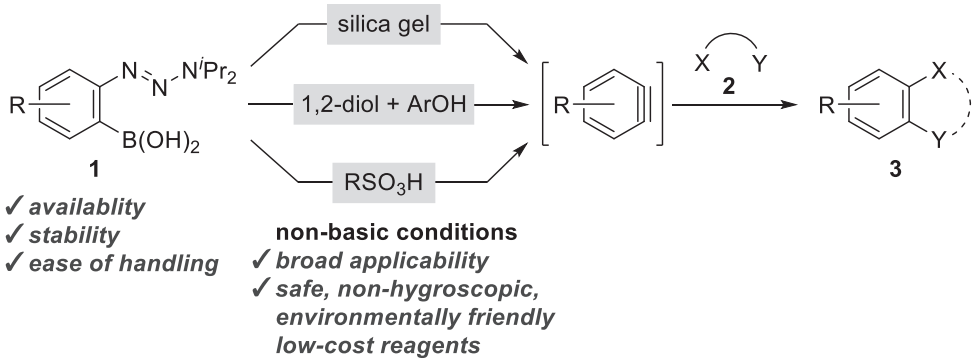
1P-06

Development of a novel practical aryne precursor: *o*-triazenylarylboronic acid

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Over the past few decades, a broad range of organic transformations involving arynes have been developed under basic conditions. A typical aryne precursor has two adjacent cleavable groups (LG^1 and LG^2) on its benzene ring. Leaving group LG^1 is activated by deprotonation, halogen–metal exchange, or the formation of an ate complex, thereby inducing the release of LG^2, which is characterized by a high leaving ability. In contrast, limited methods exist for generating arynes under non-basic conditions.

In this presentation, I will report the development of *o*-triazenylarylboronic acid **1** as a novel practical aryne precursor for generating arynes under neutral or acidic conditions.[1)] Compound **1** is readily available on gram-scale from the corresponding *o*-iodoanilines in two-steps, and is an easy-to-handle solid that can be stored in air at room temperature for over a year. Compound **1** generates an aryne upon activation by neutral silica gel,[1a,c)] by 1,2-diol and phenol,[1d)] or by Brønsted acid such as sulfonic acid.[1b)] These mild conditions complement the conventional basic conditions and are applicable to reactions involving various (hetero)arynes and arynophiles **2** with a broad range of functional groups. The salient advantages of precursor **1** include its availability, stability, ease of handling, broad applicability, and the exploitation of safe, non-hygroscopic, environmentally friendly, and low-cost reagents.



Scheme 1. Aryne Generation from *o*-Triazenylarylboronic Acid **1**

References

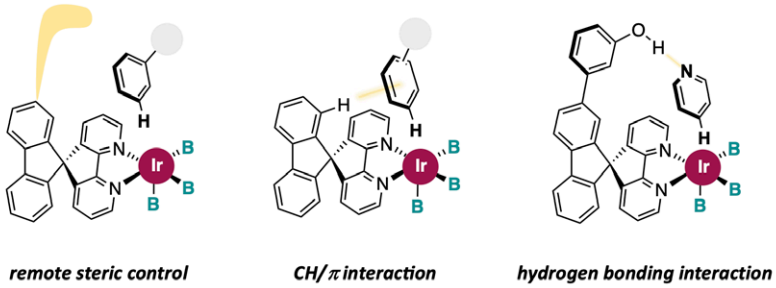
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1P- 07

Spirobipyridine Ligands as a Unique Platform for Molecular Recognition and Reaction Control through Noncovalent Interactions

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We present our recent efforts toward the development of efficient and selective catalytic systems based on spirobipyridine (**SpiroBpy**) ligands, three-dimensionally extended analogues of conventional planar bipyridines. Our initial design in this class is the conceptually novel ligand **SpiroBpy-Bpin**,[1] which sterically protects the most distal *para* site in addition to the *ortho* site, thereby enabling *meta*-selective C–H activation in iridium-catalyzed borylation. The rigid Bpin moiety attached to the **SpiroBpy** scaffold functions as a "remote steric roof", creating a molecular pocket that allows the substrate to approach the metal center preferentially in the *meta* orientation. More recently, unprecedented undirected *meta*-selective C–H silylation was achieved using a modified ligand, **Me$_2$-SpiroBpy-Bpin**.[2] Further investigations revealed that the iridium/**SpiroBpy** catalyst accelerates C–H borylation reactions.[3] A CH–π interaction between the ligand backbone and the arene substrate plays a key role in promoting this enhanced reactivity. In addition, we developed **SpiroBpy-OH** ligands bearing hydroxy groups as substrate-recognition units, enabling control over both selectivity and reactivity in the functionalization of pyridines and quinolines.[4] We anticipate that **SpiroBpy** derivatives, capable of recognizing substrates through noncovalent interactions, will serve as versatile ligands in transition-metal catalysis and provide solutions to challenges that remain difficult to address with conventional planar bipyridines.[5]



Scheme 1.

References

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1P-08

Review on the use of additives for reduciton of amides using $NaBH_4$

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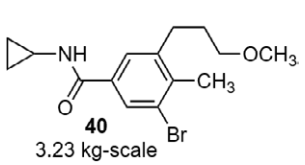
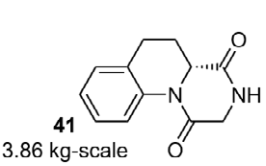
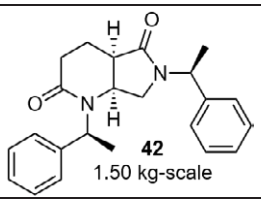
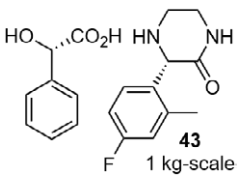
In most organic chemistry textbooks, $NaBH_4$ is introduced as a mild reducing agent, with its applicable substrates typically limited to aldehydes and ketones. However, various methods for reducing amides using $NaBH_4$ in conjunction with suitable additives have been reported[1]. Although some of these methods are attractive at the process scale, their recognition remains limited. Herein we present a literature-based review of $NaBH_4$, focusing on its reactivity in amide reduction, orthogonality, and the ease of work-up.

The active species in this case is typically diborane or its complexes. In this presentation, we will describe several methods for generating such species, as well as the reduction of amides to afford amines.

$BF_3{\cdot}OEt_2$ complex is a well-known Lewis acid reagent, which can act as an additive for the generation of the species[2]. However, during reaction completion or work-up, if BF_3 is converted into a species that no longer exhibits Lewis acidity, Diethyl ether—classified as a highly flammable substance—can be released. As a result, the risk of fire and explosion increases. In contrast, the species released from the $BF_3{\cdot}THF$ complex is THF, which does not lead to a comparable increase in such risks. Moreover, the $BF_3{\cdot}THF$ complex is industrially available on a large scale, and the METI (*Kashinhou*) number is granted. Results using $BF_3{\cdot}THF$ are shown in Table 1.

Results using other additives will also be presented in the poster.

Table 1. Reduction of Amides using $NaBH_4$ / $BF_3{\cdot}THF$

Substrate	 **40** 3.23 kg-scale	 **41** 3.86 kg-scale	 **42** 1.50 kg-scale	 **43** 1 kg-scale
Molar Ratio[a]	0.90	0.75	0.60	0.48
Yield[b]	89[c] (97.8%)	91 (85.4%)	98 (96%)	81.5 98.6% ee (95.6% <)
Ref.	(To be indicated on the poster)			

[a]$NaBH_4$/ $BF_3{\cdot}THF$. [b]Values in the parenthesis are HPLC purity. [c]Determined after Mesylation.

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1P-09

Accessible and Automated GUI-Driven Discovery of Drug Degradation Mechanisms

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Understanding drug degradation mechanisms is essential for assessing chemical stability, optimizing formulation strategies, and ensuring pharmaceutical safety. However, systematic exploration of degradation pathways remains challenging due to the complexity of competing reaction channels and the reliance on expert-driven, manual, hypothesis-driven studies, often guided by chemical intuition. Here, we present a user-accessible, GUI-enabled workflow based on nanoreactor molecular dynamics for automated discovery of drug degradation mechanisms. The approach enables non-expert users to initiate reaction discovery from a single drug structure through an intuitive interface, without requiring manual definition of reaction coordinates or prior mechanistic knowledge. Nanoreactor simulations generate unbiased molecular dynamics trajectories that sample kinetically accessible bond-breaking and bond-forming events, leading to automatic construction of reaction networks comprising degradation products, intermediates, and elementary steps. Post-processing of the generated networks enables identification of transition states and computation of free-energy profiles for competing degradation pathways. This allows systematic ranking of degradation routes in terms of kinetic accessibility and thermodynamic feasibility, capturing both expected and non-intuitive decomposition mechanisms. Overall, this GUI-driven nanoreactor framework transforms reaction discovery and degradation analysis into an accessible end-user workflow, enabling routine mechanistic studies of drug stability without reliance on manual quantum chemical expertise.[1]

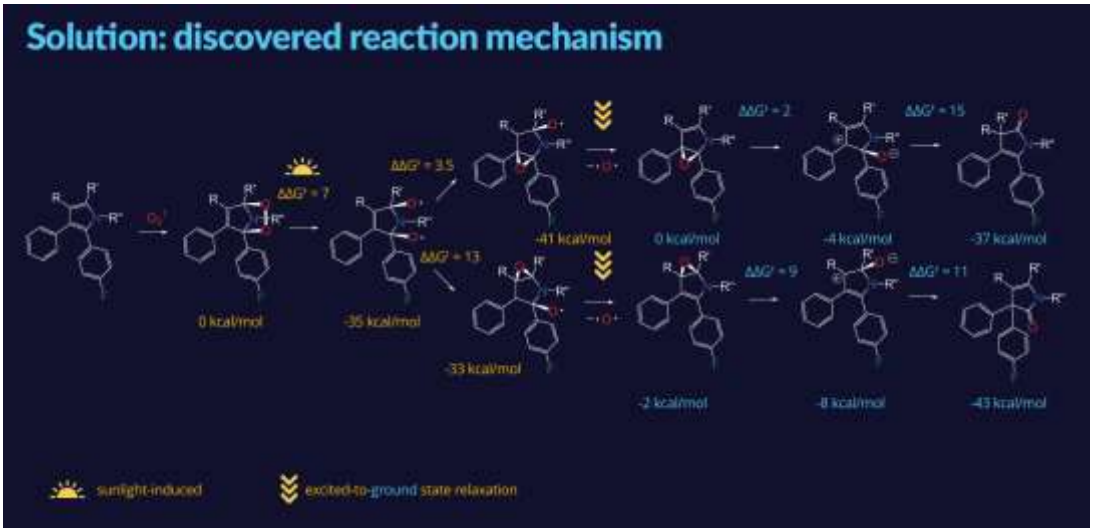


Figure 1. Discovered reaction mechanism for the oxidative degradation of atorvastatin.

References

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1P- 10

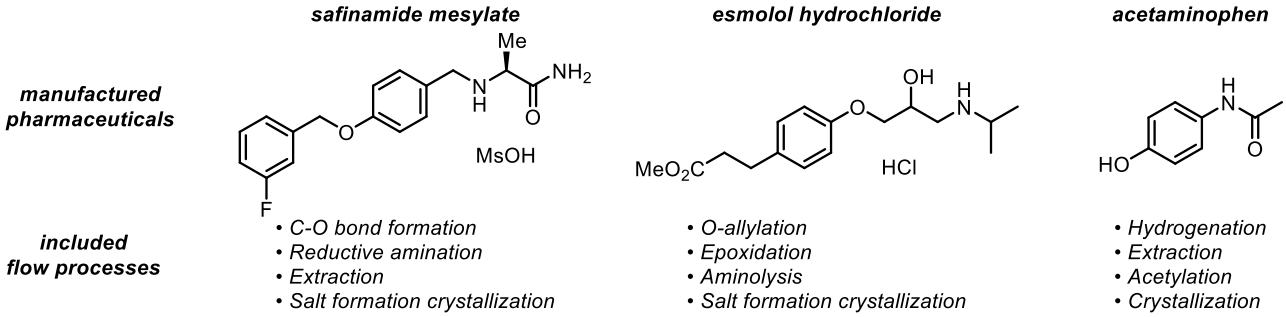
Development of a Packed-Bed Continuous Flow Process for Pharmaceuticals with Integrated Crystallization

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Continuous-flow methodologies offer advantages in reducing excess energy consumption and waste generation, and furthermore provide a viable solution to labor shortages associated with an aging society through automation. Therefore, the development of continuous manufacturing processes for finechemicals is of great importance. In continuous manufacturing of fine chemicals, not only the acquisition of the reaction mixture but also process design that anticipates subsequent purification steps is indispensable. Although numerous flow methodologies specialized for reaction development have been reported, processes that encompass continuous purification steps have seldom been described.

Silica gel column chromatography, which is commonly used in laboratory-scale purification, is disadvantageous in terms of time and cost and is difficult to implement in a continuous manner. In contrast, crystallization-based purification is superior in both efficiency and cost, and can be adapted to continuous operation through various methods. Thus, constructing continuous processes that incorporate crystallization is essential. Consequently, the development of continuous-flow methodologies that enable the integration of crystallization steps is highly significant.

In the present study, we developed continuous flow processes incorporating crystallization steps for (i) safinamide mesylate[1], a therapeutic agent for Parkinson's disease; (ii) esmolol hydrochloride[2], an antiarrhythmic drug; and (iii) acetaminophen[3], an antipyretic analgesic.



Scheme 1. Developed continuous flow process of pharmaceuticals.

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1P– 11

Efficient Synthesis of Cyclo(-RGDfK) Using a Microflow Reactor

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Shinichiro Fuse[1]

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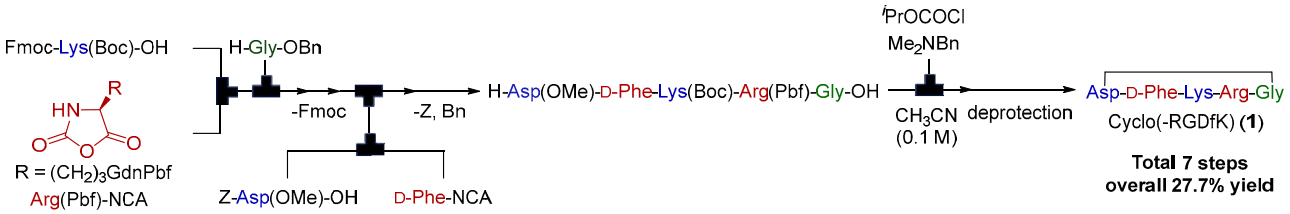
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Small cyclic peptides, consisting of fewer than seven amino acid residues, generally exhibit enhanced metabolic stability and improved membrane permeability compared to linear peptides. They display valuable biological activities and have emerged as important targets in modern drug discovery. However, their high yielding, low cost and scalable synthesis remains challenging, as current methods rely predominantly on solid-phase peptide synthesis, resulting in high production costs and large waste generation.

Herein, we report an efficient synthesis of cyclo(-RGDfK) (**1**), a high-affinity ligand for the integrin $\alpha_v\beta_3$ receptor, by integrating an α-amino acid *N*-carboxy anhydride (α-NCA)-based one-flow three-component coupling strategy[1] with rapid flow macrocyclization via a mixed carbonic anhydride intermediate[2] (Scheme 1). This approach reduces the number of peptide elongation steps (8–10 to 4) and shortens the total reaction time, enabling gram-scale preparation of the linear RGDfK precursor. The flow cyclization proceeds at concentrations over 50-fold higher than conventional batch conditions while suppressing dimerization, thereby improving productivity and reducing solvent consumption.

Mechanistic investigations revealed that precise control of water content in Boc-protected amino acid solutions is critical for improving reaction efficiency. In the case of Arg-containing substrates, suppression of guanidine nucleophilicity was shown to avoid undesired intramolecular cyclization. Inline IR analysis showed the pivotal role of NMI and $^{i}Pr_2NEt$ in the formation of the desired acyl NCA intermediate and revealed that excess base can induce the formation of undesired oxazolones. These results provide useful insights for the scaled-up synthesis of cyclo(-RGDfK) and related small cyclic peptides.[3]



Scheme 1. Synthetic route to cyclo(-RGDfK) (**1**) using a microflow reactor.

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1P- 12

Application of Continuous Flow Technology to Halogenation Reactions at AGC

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Flow chemistry has emerged as a next-generation technology for sustainable organic synthesis, offering advantages over batch processes in terms of reduced environmental impact, improved efficiency, and enhanced safety. In the pharmaceutical and fine chemical industries, the shift from batch to continuous manufacturing is accelerating, and AGC has initiated studies to apply flow chemistry to halogenation reactions, an area of longstanding expertise.

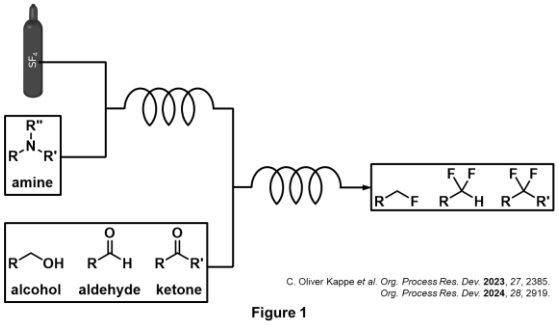


Figure 1

Among carbon–halogen bonds, the carbon–fluorine bond is especially important in medicinal chemistry, as it can modulate metabolic stability and pharmacological properties of drug candidates. Conventional fluorination reagents such as HF, F_2, SF_4, DAST, Deoxo-Fluor, and Fluolead^{TM}, however, face limitations in selectivity, cost, and safety. DAST is widely used in laboratories but is unstable and hazardous on scale. Continuous flow fluorination has therefore attracted attention as a safer and more productive approach. In 2023, Lonza and C. O. Kappe reported pioneering SF_4-mediated deoxyfluorination under flow conditions, inspiring further development. [1), 2)]

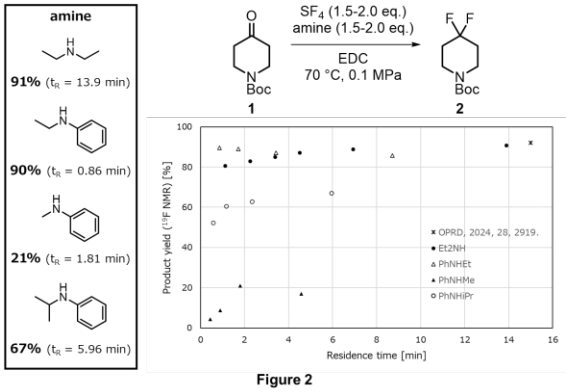


Figure 2

In this study, we applied SF_4-based deoxyfluorination to pharmaceutically relevant substrates. As a model, *N*-Boc-4-piperidone was converted to *N*-Boc-4,4-difluoropiperidine under flow conditions, with the results demonstrating both the critical influence of steric hindrance around the amine and the efficiency and scalability of this process.

In this presentation, we will report detailed results of SF_4-mediated deoxyfluorination under flow conditions, its application to pharmaceutical intermediates, and future perspectives for the implementation of flow synthesis technology at AGC.

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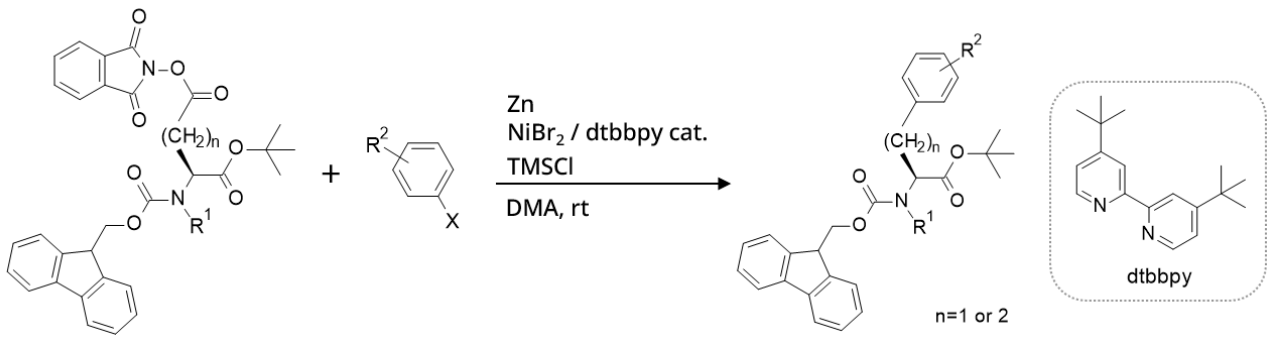
1P- 13

Process Development of Aromatic Amino Acids Aimed at Accelerating Mid-Size Molecule Drug Discovery

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Chugai Pharmaceutical Co., Ltd. has been focusing on mid-size molecule drugs with cyclic peptide structures as a solution to unmet medical needs that are difficult to address with existing modalities. To accelerate peptide drug discovery, two key elements are essential: a technological platform that enables the efficient synthesis of a large number of cyclic peptides, and synthetic methodologies capable of supplying diverse amino acid building blocks with high purity. For the former, solid-phase peptide synthesis (SPPS), which enables automated parallel synthesis, has been employed as an effective approach. In this study, recognizing that the purity of amino acid building blocks has a significant impact on the quality of cyclic peptides, we aimed to develop synthetic technologies to address the latter requirement.

In this presentation, we report a process development study on aromatic amino acids based on a coupling reaction using *N*-hydroxyphthalimide (NHPI) esters, originally reported by Weix and co-workers in 2016 [1]. This reaction forms new C(sp^2)–C(sp^3) bonds through a decarboxylative reductive coupling with aryl halides in the presence of zinc powder and a nickel catalyst. We investigated the applicability of this reaction to amino acid synthesis and demonstrated that a variety of phenylalanine and homophenylalanine derivatives can be synthesized. Furthermore, mechanistic studies enabled the identification of a robust and scalable synthetic process that affords aromatic amino acids with high purity. We will present the results of various optimization studies and their application to large-scale synthesis [2].



Scheme 1. Synthesis of aromatic amino acids via decarboxylative reductive coupling

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1P- 14

A novel flow device for one-step ionic liquid synthesis

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Ionic liquids (ILs) have attracted considerable attention due to their unique physicochemical properties, including high boiling points, thermal and electrochemical stability, low vapor pressure, and flame retardancy. As a result, they have been widely investigated for applications in electrochemistry, as solvents, in catalysis, and in biochemistry. Since trace impurities such as metal halides can significantly affect these properties(1), reproducible synthesis with high purity is essential. In particular, precise control of ionic composition is crucial, as the physicochemical properties of ILs strongly depend on the specific combinations of constituent cations and anions. In this study, we developed a novel flow synthesis device for ILs based on electrodialysis (ED) using an Ion Transfer Device (ITD) technology, which enables controlled ion exchange and flexible design of ion pairs while suppressing byproduct formation (2). As illustrated in Figure 1, an aqueous [BMIM]Cl solution is introduced as the cation source, while a $LiNO_3$ solution serves as the anion source. Under an applied electric field between the anode and cathode, chloride ions (Cl^-) migrate out of the main stream and are removed as waste, whereas nitrate ions (NO_3^-) are selectively introduced into the stream. Consequently, $BMIM^+$ cations are paired with NO_3^- anions, enabling the continuous formation of [BMIM][NO_3] in the product stream. Using this system, chloride ions were successfully replaced with nitrate ions with high conversion efficiency. These results demonstrate the potential of this method for the one-step synthesis of ILs with controlled composition and high reproducibility. Furthermore, we will present the synthesis of other ILs, including [BMIM][HCOO], and [BMIM][OAc].

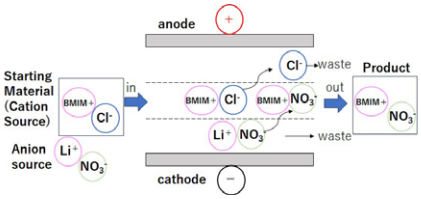


Fig.1 Schematic diagram of ITD ([BMIM]NO_3 synthesis)

Reference

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1P– 15

Practical Amide Condensation of Carboxylic Acids with Amines Using *N*-(Trifluoromethanesulfonyl)imidazole

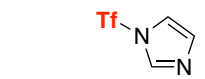
Takeshi Yamada,[1]* Kotoha Nagasaki,[1] Aika Nakashima,[1] Isao Morita,[1] Kogaku Kimura,[2] Ren Tomita,[2] Katsuhiko Akiyama,[2] Manabu Hatano[1]

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Amide bonds are a ubiquitous structural motif in pharmaceuticals and functional molecules. Despite the extensive research conducted on the catalytic dehydration condensation of carboxylic acids and amines, these catalytic methods often require harsh conditions and/or exhibit a limited substrate scope. Consequently, the development of practical and broadly applicable condensation reagents remains highly desirable.

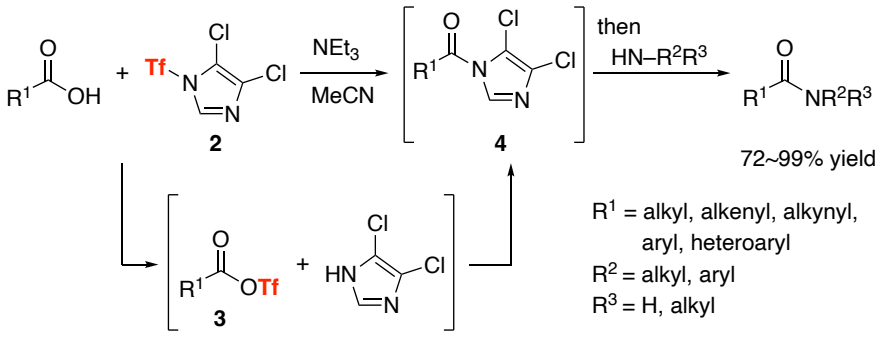
Our research focuses on *N*-(trifluoromethanesulfonyl)imidazole (Tf-imidazole **1**) as a safe, easy-to-handle, and mild triflation reagent, that is an alternative to common trifluoromethanesulfonic anhydride (Tf_2O) (**Figure 1**). In the preceding report,[1] a highly chemoselective triflation of phenols with **1** was demonstrated prior to the competitive amino groups. Herein, we report a practical amidation method using **1** as a mild condensation reagent (**Scheme 1**). Under the optimized reaction conditions using Tf-4,5-Cl_2-imidazole **2**, a variety of alkyl, aryl, and heteroaryl carboxylic acids could be used, and the corresponding amides were obtained in good yields. Remarkably, sterically demanding substrates such as 1-adamantanecarboxylic acid could be used successfully. Moreover, arylamines, primary- and secondary-alkylamines were compatible with this reaction. Mechanistic studies indicate that the reaction would proceed via an acylimidazole intermediate **4**, which is generated from an initially formed mixed acid anhydride **3**. Further details will be presented at this meeting.



1 (Tf = CF_3SO_2)

- Non-fuming and non-corrosive
- Stable at room temperature
- Mild triflation reagent

Figure 1. Tf-imidazole **1**.



Scheme 1. Amide condensation using Tf-4,5-Cl_2-imidazole **2**.

References

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1P- 16

On-line Monitoring of Flow Synthesis Reactions Using Nexera FV

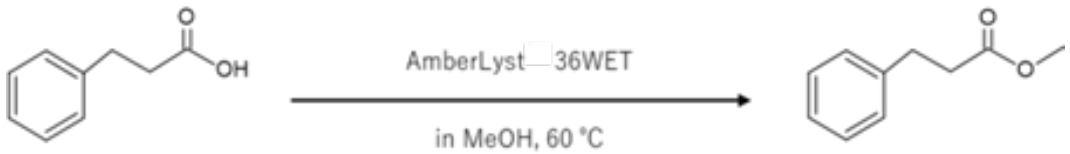
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On-line monitoring of flow synthesis reactions using Nexera FV was investigated with a model esterification reaction. Esterification of 3-phenylpropionic acid with methanol under acidic conditions was selected as the demonstration reaction. Amberlyst™ 36WET, a strong acid catalyst, was packed into a reaction column and heated to 60 °C, while the reaction solution was continuously delivered at a flow rate of 0.1 mL/min.

Nexera FV, an HPLC system equipped with a flow through vial, was connected directly to the flow synthesis system, enabling automated sampling and direct injection of the reaction solution into the HPLC. Analytical batches, sampling intervals, and reporting were controlled using LabSolutions™ FV software. Reaction monitoring was conducted from 20 to 960 minutes after the start of pumping.

As a result, phenylpropionic acid and the esterified product were clearly separated and detected. The ester product was obtained with a stable purity of 95–96% after 120 minutes under the investigated conditions. Trend plots automatically generated by the multi-data reporting function enabled real-time visualization of reactant consumption and product formation.

These results demonstrate that Nexera FV provides a reliable and efficient solution for on-line monitoring of flow synthesis reactions, contributing to improved efficiency, reduced manual workload, and enhanced process control in continuous manufacturing.



Reantant Product

Scheme 1. Esterification reaction of phenylpropionic acid

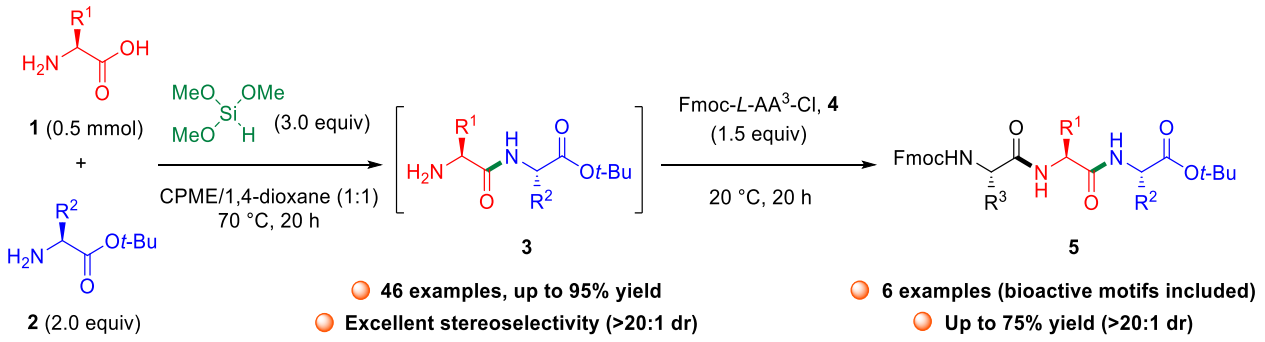
N-terminal Free Dipeptide Mediated Oligopeptide Synthesis from Unprotected Amino Acids and Amino Acid *t*-Butyl Esters Using Trimethoxysilane

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Peptides have gained massive interest over the years as important medium-size molecules in high demand in the global space of therapeutics. For decades, they have been prepared using the conventional protocol which requires multiple protection−deprotection steps, stoichiometric amounts of coupling reagents and additives, and large volumes of solvent.[1] This has resulted in some drawbacks like low atom economy and waste generation which hamper the goals of attaining green chemistry and sustainability.

It is therefore incumbent on organic chemists to combat this problem with a more favourable alternative for peptide synthesis thus the direct formation of peptide bonds using unprotected amino acids serves to be a great avenue for that. This strategy is however plagued with issues such as the low solubility of the unprotected amino acids in organic solvents, polymerization, racemization and other unwanted side reactions. To curb these limitations, we developed new methods for direct peptide bond formation[2,3] one of which involves using trimethoxysilane[2], an inexpensive and commercially available reagent.

Trimethoxysilane facilitates the solubilization of the unprotected amino acids in organic solvents, transient protection of the amine group, and the activation of carboxylic acids for coupling simultaneously. This method represents a one-pot strategy for the synthesis of N-terminal free dipeptides **3** from unprotected amino acids as electrophiles **1** and amino acid *tert*-butyl esters as nucleophiles **2** at 70 °C for 20 h in moderate to good yields (up to 95% yields) with high stereoselectivities (>20:1 dr). The strategy has a broad substrate scope compatibility (including unnatural and racemization prone amino acids). To explore the synthetic utilities, it was applied in the synthesis of tripeptides **5** including bioactive motifs of some therapeutically relevant peptide sequences hence vindicating its potential in oligopeptide synthesis.



Scheme 1. Trimethoxysilane-Mediated N-terminal Free Dipeptide Bond Formation and Application in Oligopeptide Synthesis

References

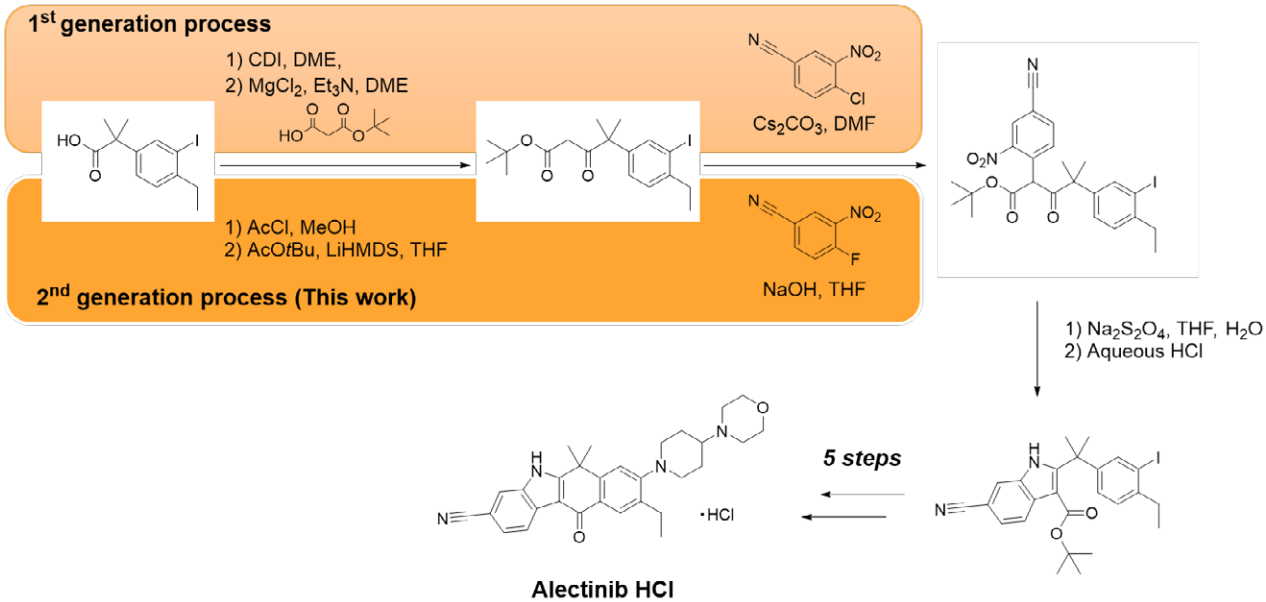
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1P- 18

Second-Generation Process: A Sustainable Route to Alectinib's Indole Core

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Alectinib (Alecensa®)[1] is a potent oral ALK inhibitor whose indole-fused tetracyclic scaffold necessitates a robust manufacturing process. The FIH route enabled multi-kilogram production of the indole core.
Building on this foundation, a second-generation process was deliberately designed from the outset with the objectives of reducing environmental impact and ensuring supply stability through the avoidance of rare metals. In this sustainability-driven process design, critical transformations were redesigned to avoid REACH-restricted solvents and rare earth elements, without compromising high conversion and product quality[2].
With this sustainability-driven approach, we successfully developed a second-generation, scalable process that demonstrates improved robustness and a reduced carbon footprint, achieving a quantified, calculation-based reduction in CO_2 emissions.
The poster highlights the underlying process design and optimization studies and the final quantified reduction in CO_2 emissions.



Scheme 1. Comparison of 1st generation process and 2nd generation process of Alectinib HCl

References

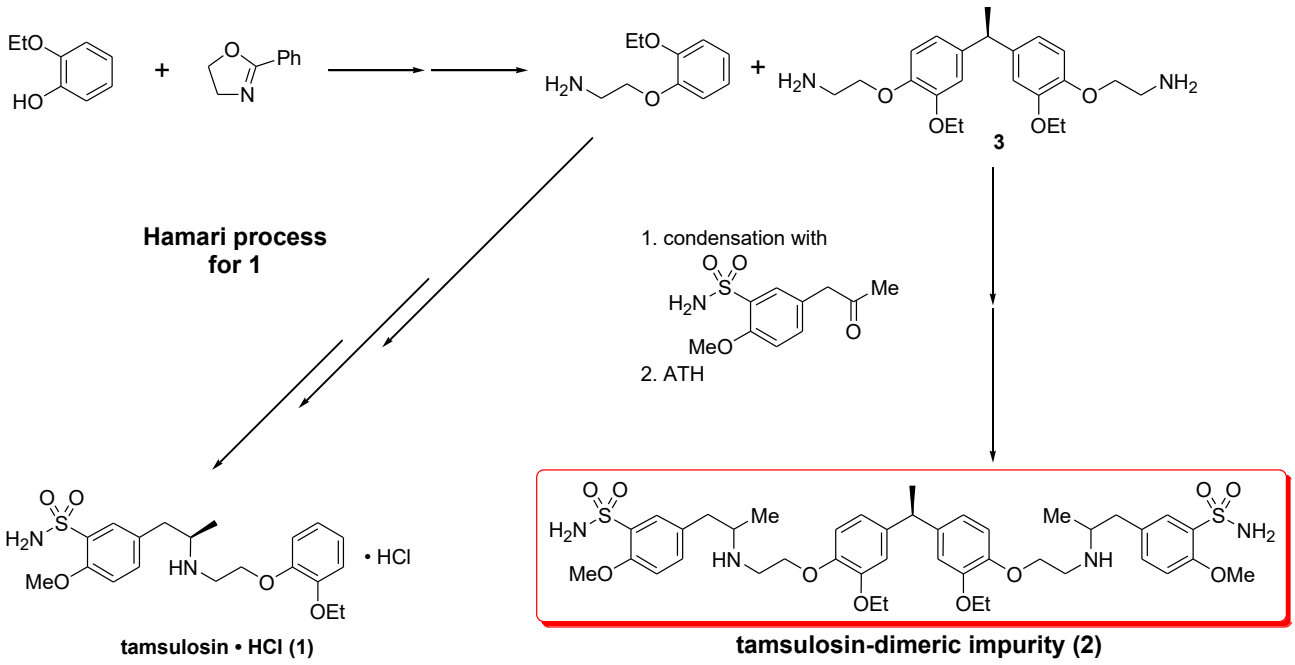
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1P- 19

Tamsulosin-Dimeric Impurity: Identification and Elucidation of Its Formation Mechanism, Leading to the Efficient Manufacturing Process of the API

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The tamsulosin-dimeric impurity (**2**) was detected in the related substance analysis of the intermediate obtained at the stage after asymmetric transfer hydrogenation (ATH) followed by optical resolution in our manufacturing process for tamsulosin hydrochloride (**1**).[1] It was found to be crucial to the quality of the API and impacted the overall yield of the process. This impurity was identified based on NMR and ESI-MS analysis. The root cause of the impurity (**2**) was clarified by isolation of its precursor diamine (**3**) and the mechanism for the formation of **2** was proposed, thus establishing the control strategy to suppress the formation of **2**. Finally, it was successfully implemented in the kilogram-scale manufacturing, leading to a dramatic increase in yield (*ca*. 23%) of the intermediate en route to the API.



References

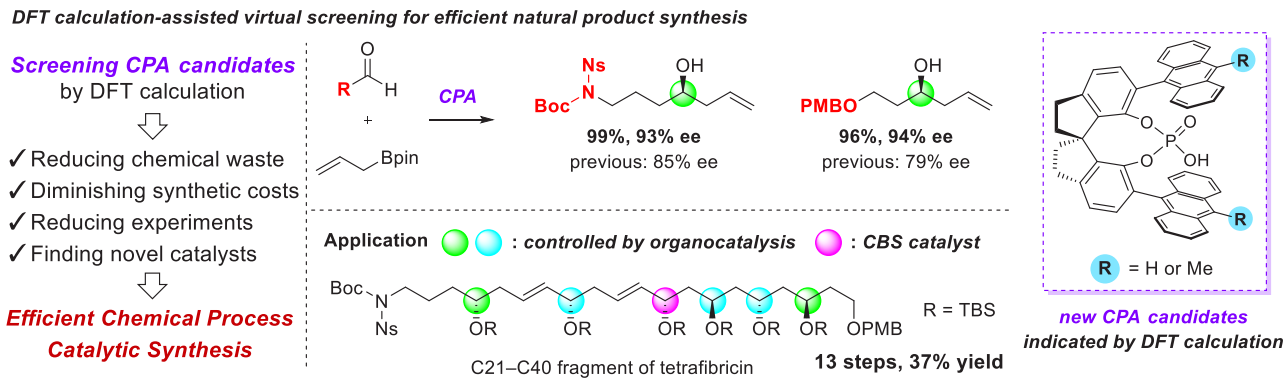
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1P– 20

DFT Calculation-Assisted Virtual Screening to Refine Chiral Phosphoric Acid-Catalyzed Allylboration

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The development of asymmetric reactions for the total synthesis of natural products often requires extensive trial-and-error approaches owing to the complexity of substrates. During our synthetic studies of tetrafibricin, a highly potent fibrinogen receptor antagonist, we encountered an issue with key enantioselective allylboration reactions in which the previously optimized CPA catalysts proved ineffective (Scheme 1).[1] We envisioned that a DFT calculation-assisted virtual screening approach could efficiently identify previously undiscovered optimal catalysts for such challenging systems. We performed virtual catalyst screening using DFT calculations for a system in which high enantioselectivity was not achievable with conventional CPAs. Our calculations revealed that a SPINOL-derived CPA having 9-anthryl or 9-anthryl-10-methyl groups, which have been largely unexplored in allylboration reactions, could exhibit excellent enantioselectivity. The discovery of these catalysts led to the efficient catalytic construction of all six stereogenic centers within the tetrafibricin C21–C40 fragment in a highly stereoselective manner. Moreover, our synthetic route enabled us to incorporate catalytic reactions into 7 of the 13 steps (LLS), reducing chemical waste and the use of expensive chiral sources. We demonstrated a DFT calculation-assisted virtual screening strategy that significantly streamlines this process, transitioning from an empirical to a more rational approach.[2]



Scheme 1. Concept of DFT Calculation-Assisted Virtual Screening of CPA catalyst

References

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1P- 21

Synthesis of Indoles via Aza-oxa-Cope Rearrangement

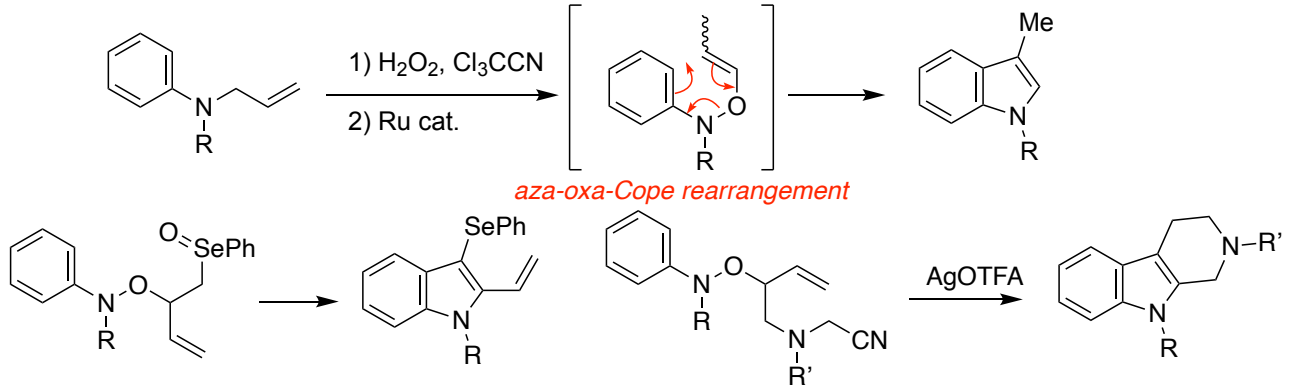
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Indole is a heterocycle contained in many pharmaceuticals and agrochemicals. Since many of reported indole syntheses involve excess amount of inorganic byproducts or harsh conditions, mild indole synthesis with low environmental impact is needed for the sustainable future.

We focused on aza-oxa-Cope rearrangement for indole synthesis. Allylaniline was oxidized with trichloroacetonitrile and hydrogen peroxideand following [2,3]-Meisenheimer rearrangement afforded allyloxyaniline. Subsequently, the compound was treated with ruthenium catalyst, which generated vinyloxyaniline by isomerization, and following aza-oxa-Cope rearrangement provided 3-methylindole. This sequence required no aqueous workup, because only neutral byproducts are generated.

To further prove the utility of aza-oxa-Cope rearrangement, allyloxyaniline with selenoxide moiety was heated. Selenoxide elimination afforded vinyloxyaniline, which underwent aza-oxa-Cope rearrangement to generate indole core. Finally, selenylation by selenenic acid afforded selenelated vinylindole.

The strategy was extended to tetrahydrocarboline synthesis, by silver-mediated extrusion of cyano group, followed by aza-Cope/aza-oxa-Cope rearrangement to provide the indole core. Finally, Pictet-Spengler reaction closed the 6-membered ring to afford tetrahydrocarboline skeleton.



Scheme 1. Indole synthesis via aza-oxa-Cope rearrangement

References

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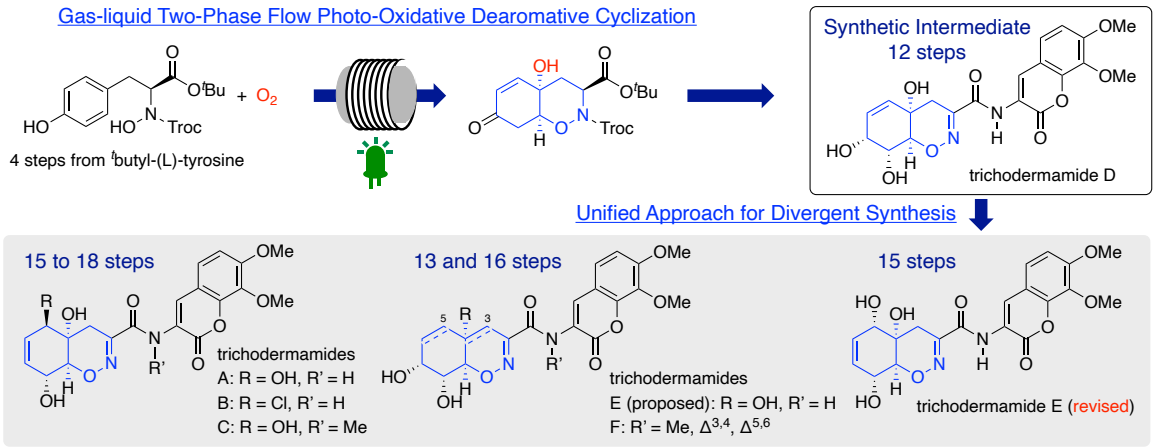
1P– 22

Unified Asymmetric Synthesis of Trichodermamides A–F: The Power of Gas-Liquid Two-Phase Flow Photo-Oxidation

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Natural products bearing the structurally diverse and highly oxidized *cis*-1,2-oxazadecalin frameworks exhibit pronounced bioactivities, including antiproliferative, anti-inflammatory, and antimicrobial activities. Although this class of molecules has attracted substantial interest from both synthetic and biological perspectives, in-depth biological investigations have been hampered by their limited availability from natural sources and the lack of reliable asymmetric methods for constructing the core framework. Namely, the unified construction of highly and diversely oxidized oxazadecalin skeletons in a site- and stereoselective manner remains a considerable challenge.

In this presentation, a new oxidative dearomative cyclization of an *N*-hydroxy tyrosine derivative for the construction of an enantioenriched *cis*-oxazadecalin framework and its application to the unified asymmetric synthesis of trichodermamides A–F will be discussed. Central to our approach was a gas-liquid two-phase flow photo-oxidative dearomative cyclization, enabling the direct construction of the *cis*-1,2-oxazadecalin enone. A subsequent diastereoselective Rubottom-type oxidation/1,2-reduction one-pot process effectively furnished the highly oxidized *cis*-1,2-oxazadecalin core. This strategy enabled gram-scale access to trichodermamide D, facilitating the late-stage divergent synthesis of a panel of trichodermamides.



Scheme 1. Gas-Liquid Two-Phase Flow Photo-Oxidative Dearomative Cyclization Enables Unified Asymmetric Synthesis of Trichodermamides A–F

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Enabling the Scale-up of Synthesis Involving Safety Risk and Intermediates Stability Problems

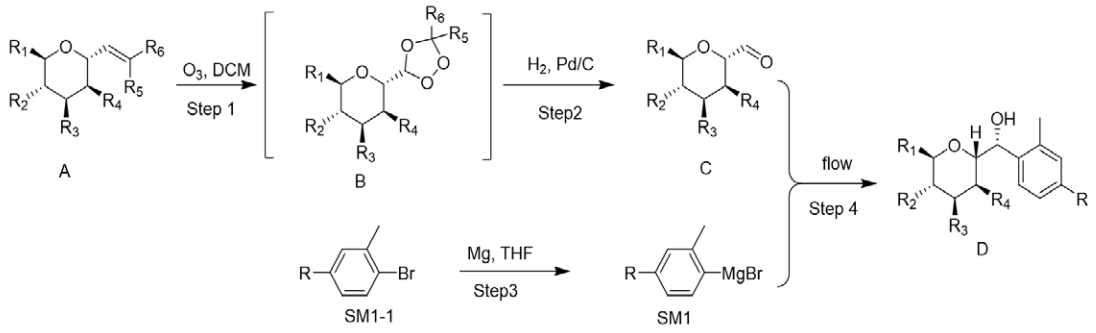
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Pharmaceutical development is a highly competitive field. In Early phase, the rapid delivery of active pharmaceutical ingredients (APIs) enables our clients to accelerate subsequent clinical trials, thereby gaining a competitive edge.

To achieve a high speed for the delivery of early-stage projects, WuXi STA has established an integrated, one-stop platform of enabling technologies that encompasses high-throughput chemo catalysis/ biocatalysis screening, enzyme evolution, flow chemistry, crystallization and preparative separation. This presentation highlights the key enabling features of different technologies and exemplifies our approach to accelerate API delivery via integrating different enabling technologies with real implementation cases.

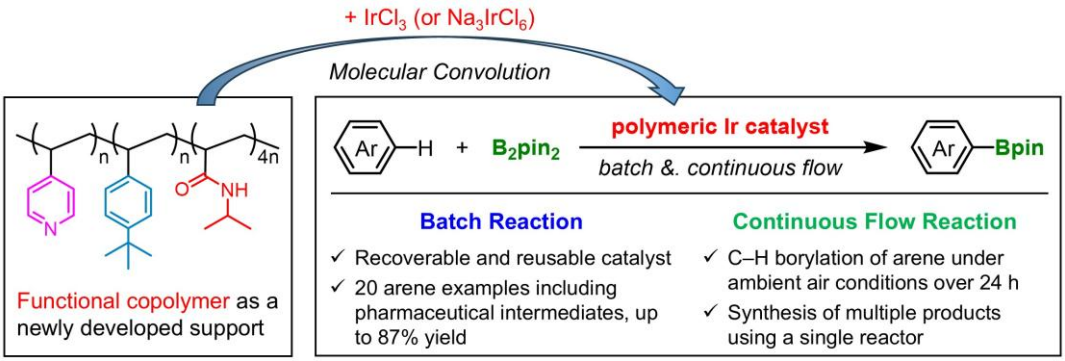


1P- 24

Development of Polymeric Iridium-Catalyzed C–H Borylation of Arenes under Batch and Continuous Flow Conditions

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Arylboronates are crucial intermediates in the synthesis of pharmaceuticals and functional materials. Direct C–H bond borylation of readily available arenes is considered an efficient one-step process for producing arylboronates. However, this process typically relies on sensitive homogeneous catalysts, such as iridium(I) complexes, which require inert gas protection, limiting both catalyst recycling and the broader industrial-scale applications of this method. In this study, we built on our previous molecular convolution method[1] to develop a series of insoluble, pyridine-containing polymeric iridium catalysts. These catalysts facilitate C–H borylation under both batch and continuous flow conditions.[2] A ternary copolymer, synthesized from 4-vinylpyridine, 4-*tert*-butylstyrene, and *N*-isopropylacrylamide, effectively immobilized and stabilized the iridium species, resulting in a polymeric iridium catalyst that promoted the batch C–H borylation of 20 different arenes with yields of up to 87%. Notably, packing the catalyst into a column-type reactor enabled the continuous flow synthesis of borylated products under ambient air conditions, producing multiple compounds in a single reactor over 42 h. XAFS analysis revealed partial reduction of the Ir(III) precursor during catalyst preparation and in situ during the borylation reaction. This study provides a practical approach for designing immobilized iridium catalysts, advancing the scalable application of C–H borylation reactions.



Scheme 1. Polymeric Ir catalyst for C–H borylation under batch and continuous flow conditions

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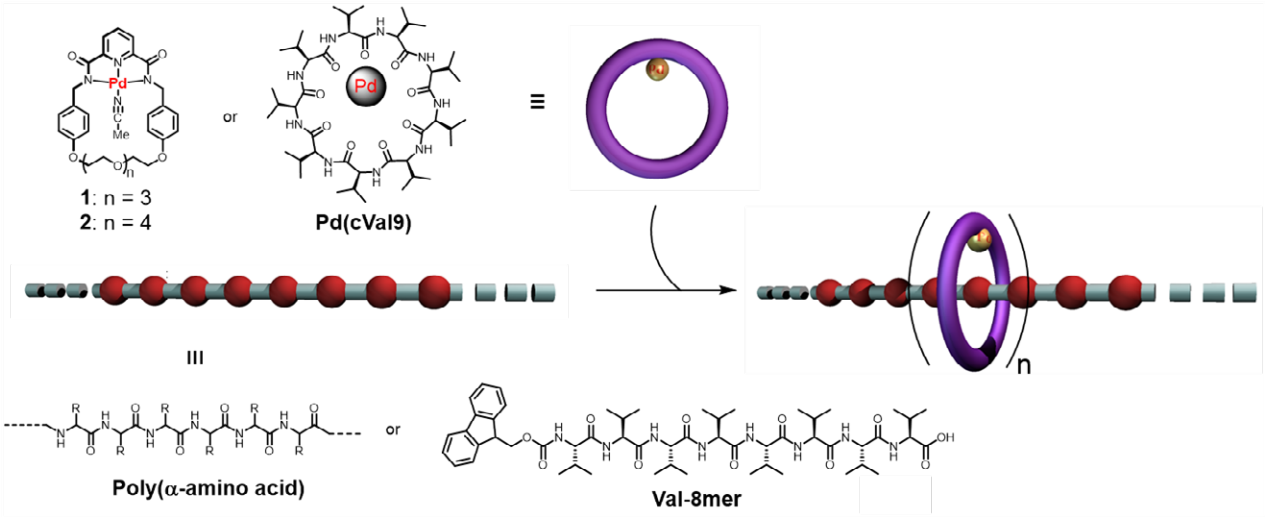
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Peptide-based Rotaxanes Assembled via Square-Planar Palladium Coordination

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1. Interlocked peptide molecules exhibit peptidase resistance as well as enzyme inhibitory activity, making them promising candidates for peptide-based drugs. Lasso peptides possess a [1]rotaxane structure, in which a peptide chain threads through the inner cavity of a cyclic peptide moiety. However, constructing such peptide-based interlocked structures remains highly challenging, and the total chemical synthesis of natural lasso peptides has not yet been achieved. Here, we aim to develop a synthetic method for peptide-based rotaxanes using a metal-template strategy.

2. A macrocyclic complex or cyclic peptide bearing a Pd(II) ion was employed to examine the threading of Poly(α-amino acid) in DMSO. Pseudorotaxane formation was evaluated by characteristic ^{1}H NMR shifts and DOSY measurements, and was confirmed by ESI-MS. Titration and variable-temperature NMR experiments were also investigated to elucidate the dynamic behavior of the rotaxanation process. These results demonstrate the feasibility of creating lasso-peptide-like architectures via metal-templated rotaxanation, providing a new strategy for the synthesis of both natural and artificial lasso peptides.



Scheme 1. Pd(II) Ion-assisted Rotaxanation to Afford Peptide-based Rotaxanes.

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1P- 26

Membrane-based non-thermal dehydration for pharmaceutical manufacturing processes

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Dehydration of organic solvents is commonly required in pharmaceutical manufacturing processes for anhydrous reactions and crystallization steps. This step has traditionally relied on distillation with heating. However, even mild heating can negatively affect heat-sensitive compounds, causing degradation or the formation of impurities. As a result, non-thermal dehydration methods are essential to obtain high-purity active pharmaceutical ingredients (APIs).

Asahi Kasei has developed an organic solvent forward osmosis (OSFO) membrane system based on hollow-fiber membrane technology. When a feed solution (FS) containing the APIs contacts a draw solution (DS) with high osmotic pressure across the OSFO membrane, an osmotic pressure difference is generated between the FS and DS. This osmotic pressure difference drives the transfer of water from the FS to DS. Therefore, the OSFO membrane system makes it possible to dehydrate organic solvents under mild conditions, which can be the new tool for the pharmaceutical manufacturing processes.

In order to demonstrate the potential of the OSFO membrane system, we evaluated the applicability of this system in collaboration with Ono Pharmaceutical Co., Ltd. In the process, dehydration is required before crystallization. However, the target compound is heat-sensitive and decomposed at 45 °C. The OSFO membrane system was applied for this process and successfully reduced the water content from 2 wt% to 0.3 wt% at 25 °C without any significant decomposition. This result demonstrated the applicability of OSFO membrane system to actual API manufacturing processes.

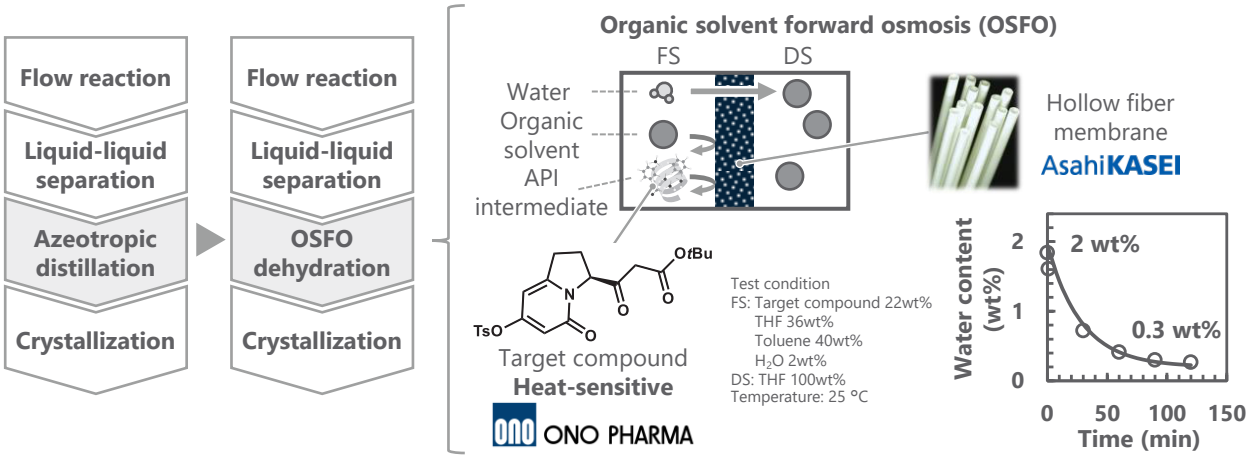


Fig 1. OSFO dehydration application for API manufacturing process at Ono Pharmaceutical Co.

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From Process Fingerprints to Scalable Insight: Enabling Lab-to-Plant Crystallization with ParticleTrack™

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Crystallization scale-up remains a critical challenge in pharmaceutical and fine chemical manufacturing due to the complex interactions between thermodynamics, kinetics, and mixing. Differences between laboratory and plant environments often lead to variability in particle size distribution, impacting yield, product quality, and downstream processing efficiency. This poster presents a lab-to-plant strategy using ParticleTrack™ with FBRM® technology to create a continuous, data-driven bridge across development, scale-up, and manufacturing.

Process Analytical Technology (PAT) enables real-time measurement of critical quality attributes during processing, replacing reliance on offline sampling and delayed analysis. In early development, ParticleTrack™ provides in situ monitoring of particle size and count through chord length distribution (CLD), allowing rapid understanding of nucleation, growth, agglomeration, and breakage mechanisms. This accelerates identification of critical process parameters and supports robust crystallization process design, improving yield, throughput, and reproducibility.

A major barrier in scale-up is the disconnect between laboratory and plant data, often resulting in fragmented datasets and limited knowledge transfer. By maintaining consistent measurement principles across scales, ParticleTrack™ enables the development of a process fingerprint—distribution or trend-based signatures that define expected process behavior. These fingerprints allow direct comparison of lab and plant performance, enabling rapid validation of scale-up success and immediate identification of deviations.

In manufacturing, real-time particle monitoring enhances process robustness by detecting disturbances such as secondary nucleation, polymorphic transitions, or mixing limitations as they occur. This enables faster root cause analysis and corrective action, reducing batch failures and variability. Industrial case studies demonstrate tangible benefits, including yield improvement, cycle time reduction, and elimination of downstream bottlenecks such as filtration and drying limitations.

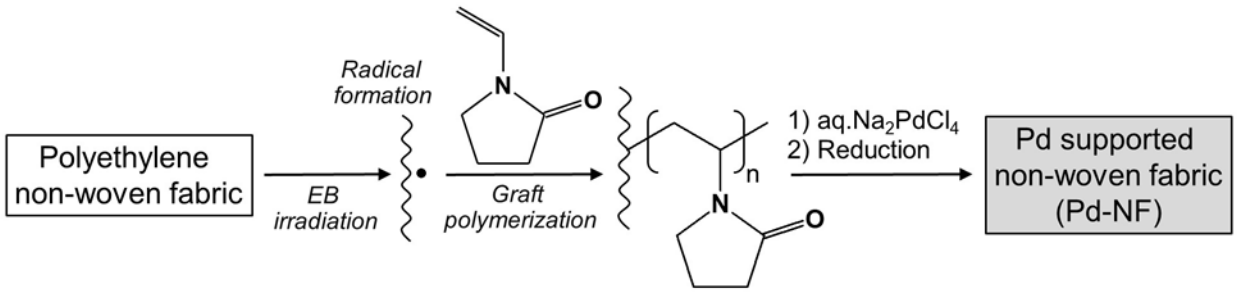
By transforming particle measurement into a continuous and scalable data stream, ParticleTrack™ establishes a digital thread from lab to plant, reducing scale-up risk and ensuring consistent product quality throughout the process lifecycle.

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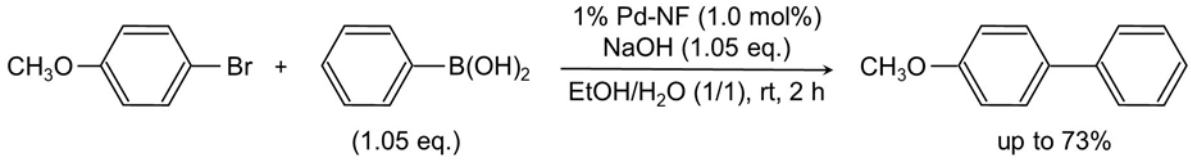
Development of Pd-supported Nonwoven Fabric *via* Graft Polymerization and Its Application to Ligand-free Suzuki-Miyaura Coupling

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Reaction processes employing heterogeneous catalysts are expected to become increasingly important in the future, particularly with respect to reducing environmental burdens. As a catalyst well-suited for this purpose, we have developed a palladium catalyst (Pd-NF) with a nonwoven fabric support. After graft polymerization of *N*-vinyl-2-pyrrolidone onto a polyethylene nonwoven fabric by radiation-induced graft polymerization, palladium nanoparticles were immobilized. Polyvinylpyrrolidone (PVP) is well known as a protective agent that suppresses the aggregation of metal nanoparticles during their formation.[1)]



Our previous investigations have focused on the flow hydrogenation reactions of olefins and nitro compounds using Pd-supported nonwoven fabric (Pd-NF),[2)] and confirmed that it exhibits lower pressure drop and easier flow compared to conventional Pd catalysts, and that target compounds can be obtained in high yields even with smaller net amounts of Pd. In this report, we describe in detail a mild, highly efficient, and ligand-free Suzuki–Miyaura coupling reaction[3)] using this catalyst material (Pd-NF).



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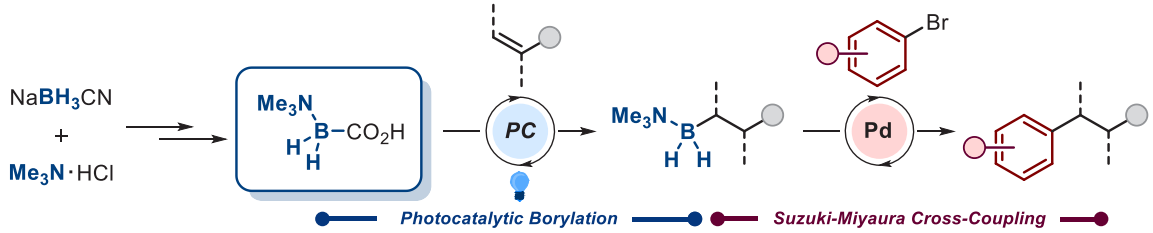
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Carboxylated Amine–Boranes as Boryl Radical Precursors

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Owing to advances in photocatalysis, radicals have become well-utilized in synthetic chemistry, enabling the development of novel methodologies. This trend has primarily focused on C-, N-, and O-centered radicals, whereas B-centered radicals have remained largely underexplored. Although amine-ligated boryl radicals were pioneered by Roberts in the 1980s, their application in modern synthesis has remained limited due to the high oxidation potential and strong B–H bond dissociation energy of simple precursors such as trimethylamine borane (Me_3NBH_3). To address these limitations, we developed an alternative boryl radical generation strategy featuring a carboxylated amine–borane ($Me_3NBH_2CO_2H$) that serves as a boryl radical precursor via photoredox oxidation and decarboxylation. Furthermore, the resulting amine-ligated boryl radicals were successfully applied to a range of photocatalytic radical borylation reactions.

Most importantly, this carboxylated amine–borane is readily accessible in two steps from commercially available $NaBH_3CN$ and $Me_3N{\cdot}HCl$ and can be prepared on a >10 g scale. Moreover, amine-ligated boryl radicals generated from this compound under photocatalytic conditions readily react with styrenes, imines, polyfluoroarenes, and cyanoarenes *via* radical–polar crossover or radical–radical coupling pathways. A wide range of electron-deficient radical acceptors are well tolerated, highlighting the broad scope of substrates. Furthermore, the resulting sp^3- and sp^2-organoboron compounds are stable solids and serve directly as coupling partners in Suzuki–Miyaura cross-coupling without protodeboronation. This work offers a complementary platform to conventional methods and expands the toolbox for organoboron synthesis and applications, contributing to both synthetic and process chemistry.



Scheme. Photocatalytic Generation and Application of Amine-Ligated Boryl Radicals

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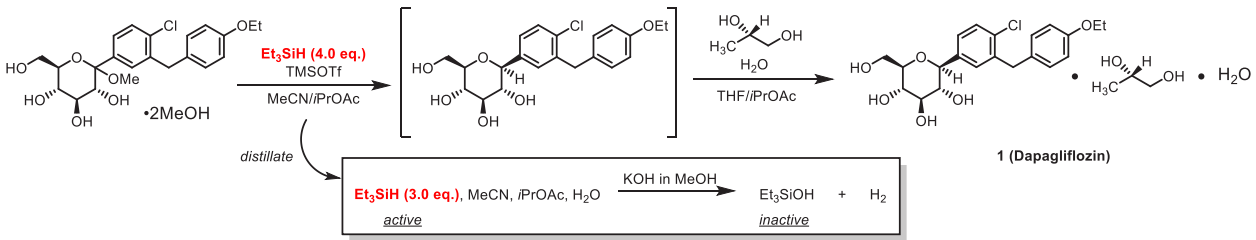
Safe and Scalable Method for Quench of Triethylsilane in Dapagliflozin Propanediol Monohydrate Production

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For the manufacture of active pharmaceutical ingredients, the development of safe treatment technologies for wastes and spent reagents discharged from the manufacturing process, in addition to the optimization of synthetic routes, is extremely important. In the production of dapagliflozin propanediol monohydrate (**1**), an excess of triethylsilane (Et_3SiH) was used as a reducing agent. Since Et_3SiH is flammable and highly reactive, any residual Et_3SiH should be quenched and safely disposed of. However, to our knowledge, no reports describe an efficient and safe pilot-scale quenching method for Et_3SiH. We present a safe pilot-scale procedure for treating Et_3SiH along with the associated safety measures.

During the manufacture of compound **1**, residual Et_3SiH was removed in the distillate after concentrating the reaction mixture under reduced pressure. The distillate primarily consisted of unreacted Et_3SiH, the reaction solvents MeCN and *i*PrOAc, and entrained water. In the case of acid treatment (Lewis or Brønsted acids), Et_3SiH was not sufficiently quenched under these conditions. In contrast, Et_3SiH was quantitatively quenched by replacing the acid with a base and by selecting an organic solvent to ensure a homogeneous basic solution.

Because the quench of Et_3SiH by KOH in MeOH produced a significant exotherm and hydrogen gas evolution, a risk of explosion due to runaway reaction was assessed to enable safe scale-up. First, the exotherm was quantified by reaction calorimetry to determine the heat-release profile, and the reaction was controlled by appropriately setting the addition rate of KOH solution based on those results. Second, to address the risk of explosion caused by combustible hydrogen gas, nitrogen purging at an appropriate flow rate kept the reactor headspace oxygen concentration below the limiting oxygen concentration (5.0%) for hydrogen gas. These measures enabled the quench of Et_3SiH on the pilot scale, reducing the residual Et_3SiH to below 0.01 wt% by processing 10 kg. We believe these findings contribute to fostering a safety culture in pharmaceutical manufacturing and the broader chemical industry.



Scheme 1. Synthesis of **1** and quench of Et_3SiH

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Crystallization Process Development in Mixed Solvent Systems to Improve Filterability of Poorly Soluble Pharmaceutical Intermediates

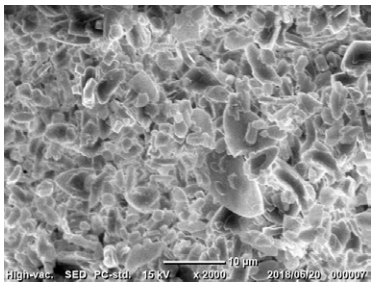
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PCO371 (MW 636) , a parathyroid hormone type 1 receptor (PTHR1) agonist, has been developed as an oral therapeutic agent for hypoparathyroidism. The precursor of PCO371, Compound A, was isolated and purified by crystallization[1]. However, large-scale manufacturing encountered **significant productivity issues**, as filtration required **over 30 hours**. Consequently, we initiated an investigation to enhance filterability and improve overall productivity for further scale-up.

For synthesis of Compound A, the reaction was carried out in NMP, followed by liquid-liquid extraction with ethyl acetate/water. Crystals were subsequently obtained in a biphasic system by adding water to the organic layer. Because the solubility of Compound A in ethyl acetate is extremely low (1.5 mg/mL), crystallization proceeded under a highly supersaturated state. This resulted in small, thin plate-like crystals (Figure 1, left), which were identified as the primary cause of poor filterability.

To address these issues, we aimed to **control the degree of supersaturation** to obtain larger and thicker crystals. The following factors were systematically evaluated: (1) solvent system, (2) addition rate of the antisolvent, (3) seeding, and (4) temperature. Solvent system evaluations revealed that the addition of MeCN prior to water addition enabled effective control of supersaturation.

Further optimization, incorporating seed crystal addition and an aging process under heating, successfully increased the particle size and improved the crystal habit (Figure 1, right). As a result, **the filtration time at the laboratory scale was reduced to one-fifth** of the original method. This significant enhancement in filterability was successfully reproduced in manufacturing at the several tens of kilograms scale.



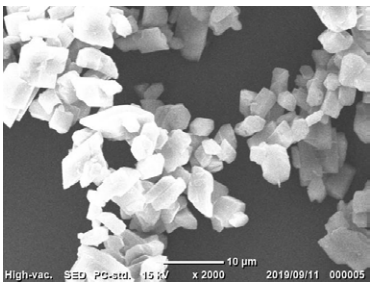


Figure 1. SEM Images of Obtained Crystals
Left: obtained from ethyl acetate/water (original method)
Right: obtained from NMP/acetone/water (Modified Method)

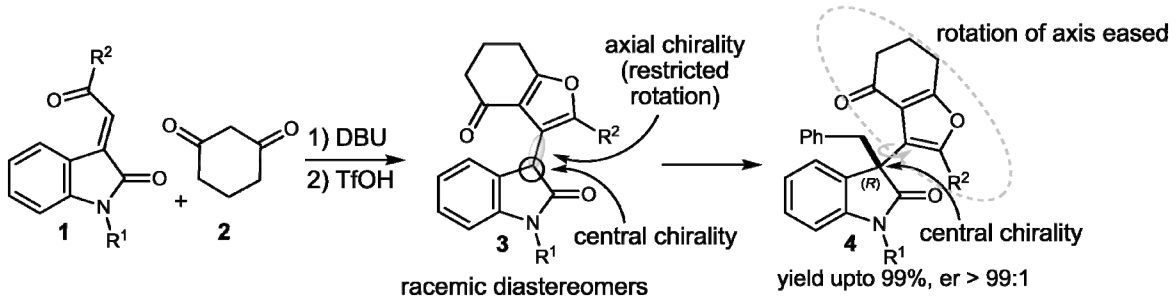
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Enantioconvergent Alkylation for the Construction of Chiral Quaternary Carbon Centers and Control of C(sp^3)-C(sp^2) Bond Rotation

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Conformational dynamics, including axis rotations, are often important during interactions between target proteins and bioactive small molecules that function as inhibitors, antagonists, or agonists. In this poster, we will present catalytic enantioconvergent alkylation reactions that transform racemic dihydrobenzofuranone-functionalized oxindole diastereomers involving central and axial chiralities into highly enantioenriched products possessing chiral quaternary carbon centers and flexibly rotating C(sp^3)-C(sp^2) bonds. These reactions achieve the construction of the product with high enantioselectivity (up to er 99:1) via a dynamic kinetic asymmetric transformation. In the products, rotational restriction around the C(sp^3)-C(sp^2) bond is eased, allowing the conformational flexibilities. Variable-temperature NMR analyses of the products confirm that alkylation lowers rotational barriers. We demonstrated that the rotation of the bond between a central chiral carbon center and a dihydrobenzofuranone can be tuned by selection of either a tertiary carbon bearing a hydrogen or a quaternary carbon at the central chiral center. The products have the benefits of a central chiral center and a flexibly rotatable bond, which can facilitate interactions with other molecules (Scheme 1).



Scheme 1. Enantioconvergent Alkylation

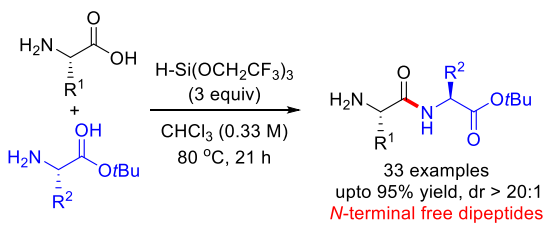
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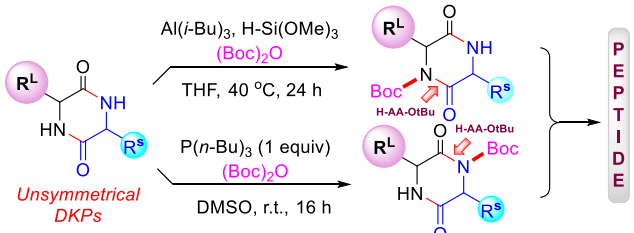
Development of Green and Sustainable Strategies for Peptide Synthesis

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Growing pharmaceutical interest in peptide therapeutics has exposed critical limitations of conventional synthesis approaches. Conventional methods suffer from poor atom economy, reliance on coupling reagents, complex protecting-group strategies, and excessive solvent use, thereby undermining scalability, sustainability, and cost-efficiency[1]. To address these challenges, our group focuses on developing non-conventional peptide synthesis methodologies. In this symposium, we present two recently developed strategies aimed at improving synthetic accessibility and meeting the demands of the peptide industry. Recently, we developed tris(2,2,2-trifluoroethoxy)silane as a cost-effective, sustainable, and efficient single reagent for synthesizing *N*-terminal free peptides from unprotected amino acids, with amino acid *tert*-butyl esters[2]. This reagent produces a series of *N*-terminal free peptides in good yields with excellent optical purity (Scheme 1). DKP is generally recognized as a by-product frequently found in peptide synthesis. To make effective use of this product, we identified Mono-Boc DKP as a suitable precursor for reagent-free peptide elongation, enabling a two-amino-acid chain extension in a single step in 2022[3]. However, synthetic methods for Mono-Boc DKPs remain underdeveloped. Therefore, we developed a selective protection strategy for the amide NH of DKP using triisobutylaluminum[4] or tributylphosphine[5], enabling access to desired Mono-Boc DKPs (Scheme 2). Notably, selectivity can be tuned by choosing between triisobutylaluminum and tributylphosphine, based on the target Mono-Boc DKP. Furthermore, the Mono-Boc-DKPs could serve as substrates for oligopeptide synthesis without the need for any reagents.



Scheme 1: H-Si(OCH$_2$CF$_3$)$_3$ Mediated Peptide Synthesis



Scheme 2: Regioselective Boc Protection of Amide N-H of DKP

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1P- 34

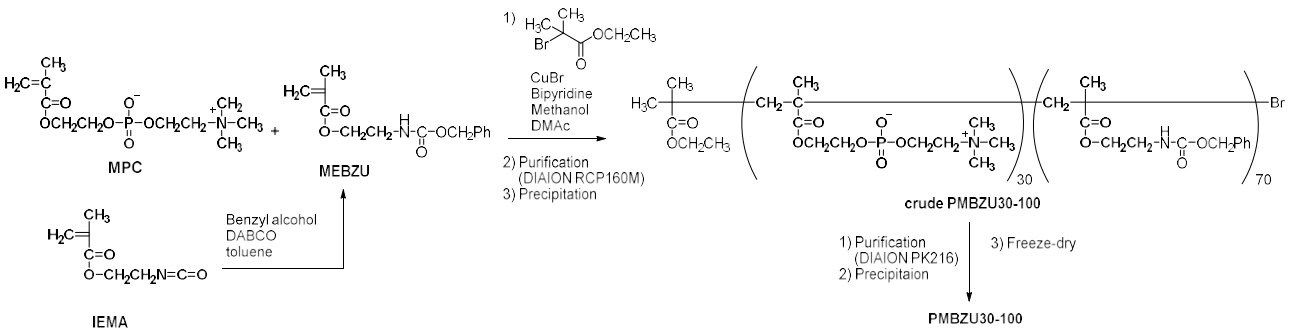
Development of a Practical Synthesis for the Amphiphilic Phospholipid Polymer PMBZU30-100

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Solid dispersions have been regarded as a promising formulation technique to enhance bioavailability of drug candidates by improving their solubility. Yoshie and co-workers reported the design and synthesis of amphiphilic 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymers, showing that PMBZU30-100 could be a potential carrier for solid dispersions. However, its synthesis had challenges in quality control and scalability. Herein, we report a practical synthesis of PMBZU30-100 to facilitate its large-scale supply.

The random-type copolymer PMBZU30-100 was synthesized by atom transfer radical polymerization using MPC as a hydrophilic monomer and 2-methacryloyloxyethyl benzylurethane (MEBZU) as a hydrophobic monomer prepared from 2-isocyanatoethyl methacrylate (IEMA) and benzyl alcohol. During the reaction optimization, we found that the relative reaction rates of the two monomers in the polymerization were significantly affected by the solvent system. By using MeOH/DMAc (1:1) as the optimal solvent, we successfully balanced their reaction rates, enabling the synthesis of polymers with a more uniform sequence distribution. Moreover, the improved purification method using adsorption with a cation exchange resin for the removal of the hydrophilic monomer and the copper catalyst resulted in much easier scale-up of the synthesis, compared with the previous method using dialysis with a semipermeable membrane. In this presentation, we will report on the details of the synthetic process and the mechanistic investigation into the origin of the different reactivity ratios of the monomers with the aid of DFT calculations.

Scheme 1. Synthetic route of PMBZU30-100



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1P- 35

Nucleophilic Acyl Substitution Reaction of Hydroxylamine Catalyzed by Basic Metal Salts

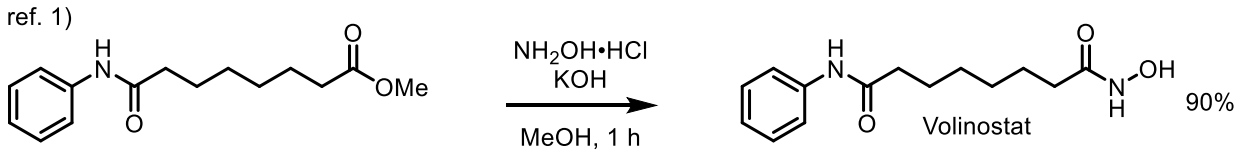
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Hydroxamic acid is important as a zinc ion binding group of histone deacetylase (HDAC) inhibitors such as Volinostat (SAHA).[1] It can be easily synthesized by hydroxylaminolysis of methyl esters with NH_2OH in the presence of KOH. An improved method involving the addition of KCN (0.2 equivalents) via a cyanoketone intermediate has also been reported.[2] While certain reaction acceleration can be expected due to the good leaving ability of the cyano group, KCN is also a strongly basic salt (pH 11, 0.1 mol/L), so the possibility of a base-catalyzed reaction mechanism similar to that of KOH cannot be ruled out.

In this study, metal carbonates such as Li_2CO_3, Na_2CO_3, K_2CO_3 and Cs_2CO_3, exhibiting similar basicity to KCN, were employed to clarify how they affect the rate of hydroxylaminolysis.

Methyl benzoate was subjected to hydroxylaminolysis using 50% NH_2OH aqueous solution in methanol-THF (1:1) in the presence of metal carbonates. The results showed that the reaction proceeded most rapidly in the presence of Cs_2CO_3 (95%), with the yield decreasing in the order of K_2CO_3 (47%), Na_2CO_3 (31%), and Li_2CO_3 (11%). The negative charges on the nitrogen and oxygen atoms and the positive charges on the metal ions of hydroxylamine metal alkoxides (trihydrates) in water was calculated by density functional theory (DFT) calculations.

In conclusion, metal ions with larger ionic radii tend to form more "naked" and highly nucleophilic anions of hydroxylamine.



Mulliken charge of $NH_2O^-M^+(H_2O)_3$

metal	N	$O^{\ominus}$	$M^{\oplus}$
Li	-0.577	-0.695	+0.270
Na	-0.580	-0.707	+0.411
K	-0.620	-0.708	+0.340
Cs	-0.626	-0.832	+0.823

ωB97X-D, 6-31G*

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1P- 36

Determination of the Epimerizable Chiral Center of Pladienolide D under Acidic Stress Conditions Using ^{18}O-Labeled Water

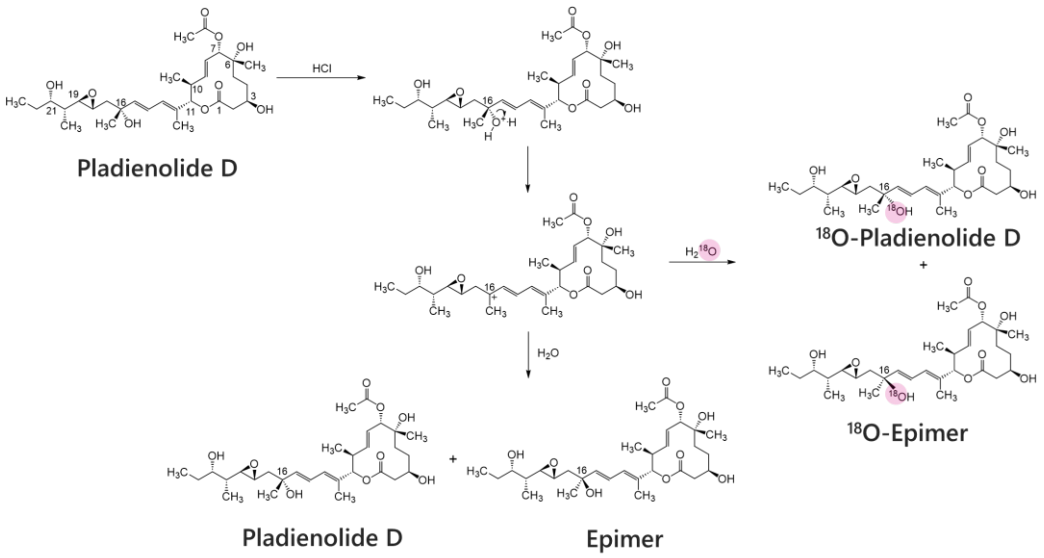
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In the early stage of CMC development, forced degradation studies are performed to elucidate degradation pathways, identify potential impurities, and support process and analytical development of drug substances.

Pladienolide D is isolated from a culture broth of *Streptomyces platensis* Mer-11107 and inhibits the growth of a variety of cancer cell lines in vitro with low nanomolar IC_{50} values. Previous studies have suggested the possibility of epimerization at C16, especially under acidic conditions. However, this has not been experimentally confirmed due to the flexibility of the side chain.

Based on the proposed mechanism of isomerization (Scheme 1), experiments using ^{18}O-labeled water were conducted to enable identification of the epimerizable chiral center using NMR.

Carbons bonded to ^{18}O generally exhibit chemical shifts a few hertz upfield relative to those bonded to ^{16}O[1]. The proposed mechanism predicts that an isotope shift should be observed only for the C16 carbon signal. Further details will be presented in the poster.



Scheme 1. Proposed Mechanism of Isomerization

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1P- 37

Development of Organic Synthesis Experimental Information Utilization System Integrating Knowledge Graphs and Generative AI

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In chemical pharmaceutical process development, researchers spend considerable time gathering and integrating information to optimize experimental conditions and accelerate decision-making[1]. Conventional keyword-based retrieval systems fail to capture the complex semantic relationships among chemical entities, reaction conditions, and experimental outcomes[2], and standard RAG approaches struggle with complex inter-document reasoning that requires integrating knowledge across multiple sources. To address these limitations, this study presents a novel organic synthesis experimental information utilization system integrating knowledge graphs and generative AI technologies.

As shown in Figure 1, the system consists of three core components: (1) a graph database construction module that automatically extracts knowledge graphs from semi-structured data (laboratory notebooks) using a specialized organic synthesis ontology, (2) a vector database construction module that parses unstructured data (reports, presentations, and publications), and (3) an experimental condition recommendation engine that provides context-aware suggestions by integrating search results from both databases. Built on a collaborative multi-agent architecture utilizing ReAct agents, the system features accurate graph database searches via Text-to-Query conversion. Furthermore, it enables advanced cross-domain retrieval through its "DeepResearch" function, seamlessly iterating between reasoning and querying across both databases to answer user questions.

Validation experiments demonstrated knowledge graph extraction accuracy exceeding 95% with response times of several seconds to tens of seconds, receiving consistently positive feedback from end users. The system significantly enhances efficiency in information retrieval, summarization, and experimental condition proposals, ultimately allowing researchers to focus on higher-level creative thinking and innovation.

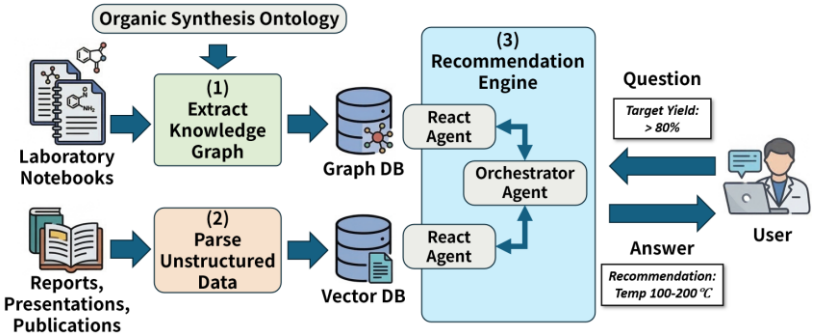


Figure 1. Multi-Agent AI System for Organic Synthesis

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1P- 38

Materials for Improving Oligonucleotide Synthesis

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Oligonucleotides (ONs) are generally synthesized by solid-phase process using phosphoramidite chemistry. Surface-modified resins by universal linker are mainly used as solid phase and the synthesis repeats the following four steps: deprotection, coupling, capping, and oxidation. After reaching the desired ON length, all-protecting groups and resins are removed, and the ONs are obtained via HPLC purification. As a research theme of our group, development of novel methodologies and materials for ON synthesis has been conducted. In this presentation, we report phenanthrene-type universal linker (PT-linker)[1] as solid phase, and cyclic phosphoramidite (EDCP)[2] as a capping reagent (Figure 1).

High hydrophobicity and molar absorption coefficient of PT-linker facilitate the separation and purification of desired ONs. A combination of PT-linker with alkyl phosphoramidites of nucleosides[3] can make basic treatment used after ON synthesis on an automated ON synthesizer milder and shorter. Meanwhile, EDCP is crystalline solid, shows high solubility against MeCN, and has higher capping ability than common capping reagents.

The above results suggest that these materials allow us to suppress by-products and facilitate purification of desired ONs.

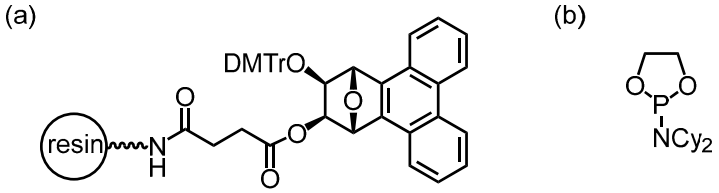


Figure 1. (a) PT-linker resin and (b) EDCP.

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1P- 39

Expanded Applicability of Our State-of-the-Art Purification Technology to Development-Stage Scales

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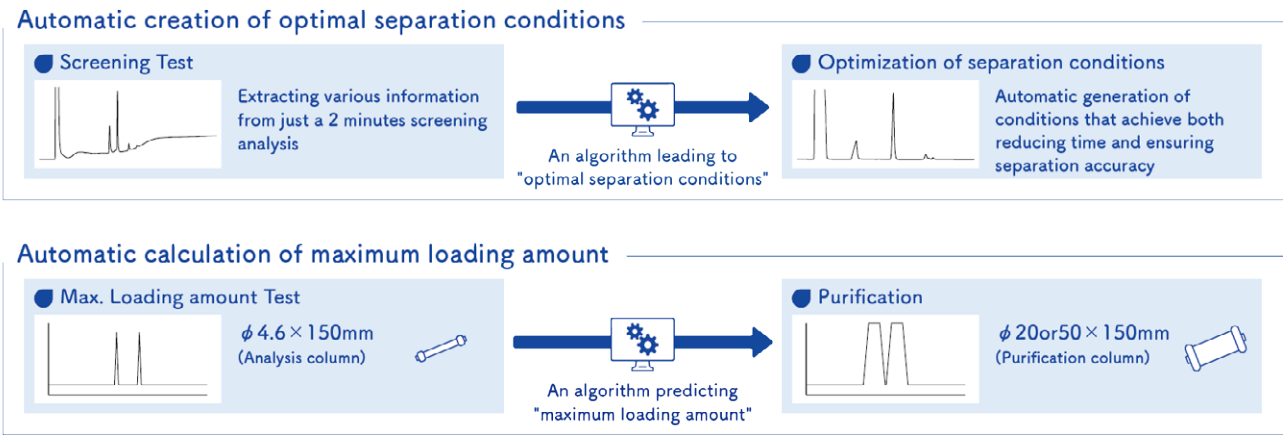
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For peptide purification, liquid chromatography is crucial in both the discovery and development stages, and traditional purification methods are highly labor-intensive. ChromaJean has already demonstrated that our state-of-the-art purification technology for the discovery-stage peptides can significantly reduce time, cost, and labor intensity at several pharmaceutical companies and CROs.

To expand the applicability, ChromaJean carried out collaborative development with Chugai Pharmaceutical Co., Ltd. In this presentation, we present the establishment of both the optimal separation conditions and the maximum loading amount for the purification of development-stage peptides at the 1 g and 10 g scales, based solely on screening results and a simple maximum-loading test. Furthermore, purification performed under these conditions yielded the target peptides with a purity of at least 95% and a recovery rate of at least 60%, confirming that the technology has sufficient practical applicability.

In general, as the amount of crude peptide increases, it becomes more challenging to create preparative conditions based on results obtained at the analytical-column scale. We addressed this challenge by ensuring predictive accuracy through a single additional analysis and automated data processing.

As a result, trial and error is no longer required for peptide purification. This technology is also expected to support further scale-up.



1P- 40

Evaluation of Precious Metal Catalyst Activities for Stepwise Oxidation of Alcohols to Carboxylic Acids Using Hydrogen Peroxide

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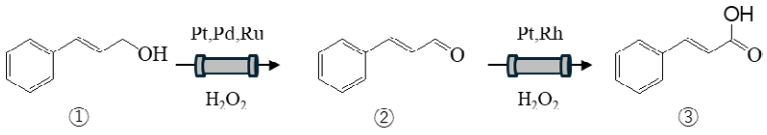
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Selective oxidation of alcohols to their corresponding carbonyl compounds is an important process in organic synthesis. In particular, α,β-unsaturated aldehydes are widely used as fragrance ingredients, whereas α,β-unsaturated carboxylic acids are essential intermediates in the pharmaceutical industry.

Recently, the selective oxidation of (*E*)-cinnamyl alcohol to (*E*)-cinnamaldehyde or (*E*)-cinnamic acid in a flow reactor system using a Pt black catalyst and hydrogen peroxide (H_2O_2) has been reported.[1)2)] This flow-based oxidation process has attracted attention as a green oxidation reaction, since H_2O_2 is used as the oxidant and only water is produced as a byproduct. The report showed that product selectivity can be switched by controlling the flow rate and reaction temperature, which leads to our interest in mechanism-based control of the oxidation of alcohols with H_2O_2 over precious metal catalysts.

In this study, we investigated the reaction characteristics over various carbon-supported precious metal catalysts. As a result, Pt/C exhibited high catalytic activity for both the oxidation of alcohols to aldehydes and the subsequent oxidation of aldehydes to carboxylic acids. In contrast, Pd/C and Ru/C showed activity only for the oxidation of alcohols to aldehydes, whereas Rh/C exhibited activity exclusively for the oxidation of aldehydes to carboxylic acids. These results demonstrate the distinct differences in reaction selectivity among precious metal catalysts and provide valuable insights for the design of stepwise alcohol oxidation processes.



Scheme 1. Precious metal–catalyzed oxidation

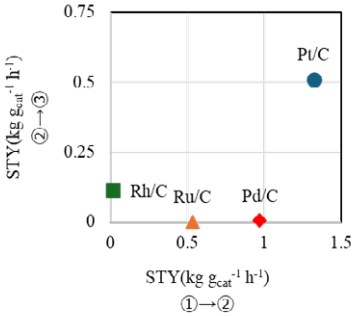


Figure 1. Catalyst activity

Acknowledgment

This presentation is based on results obtained from a project,JPNP19004, commissioned by the New Energy and Industrial Technology Development Organization (NEDO).

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1P– 41

Divergent Synthesis of Thio-Substituted Chiral Cyclopentenes via a Domino Reaction of Sugar-Derived Wittig Reagents

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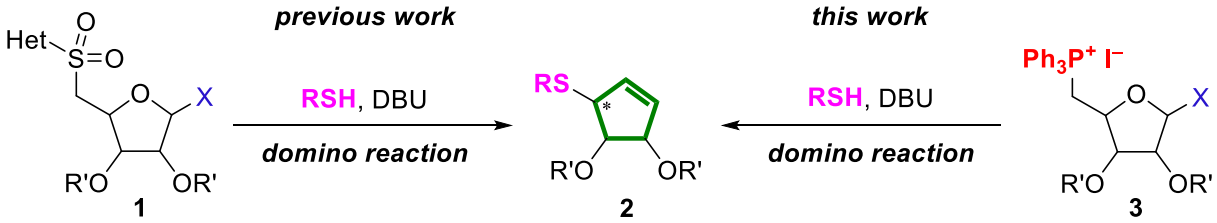
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Optically active, polysubstituted cyclopentenes are structural motifs found in many biologically active molecules and serve as versatile synthetic intermediates for optically active, polysubstituted cyclopentanes. One of the major approaches to these cyclopentenes involves the use of sugars as starting materials. For example, sugars can be transformed into diene intermediates, followed by ring-closing metathesis to afford cyclopentenes. However, these methods often suffer from multistep sequences, limited structural diversity from a single starting material, and the requirement for expensive transition-metal catalysts.[1]

We have previously reported a domino reaction of sugar-derived Julia–Kocienski sulfones **1**, triggered by base treatment in the presence of sulfur nucleophiles, which affords cyclopentenes bearing nucleophile-derived substituents with high *cis*-selectivity.[2,3] However, the scope of sulfur nucleophiles was limited to electron-deficient heteroaryl thiols and thiocarboxylic acids. More nucleophilic thiols led to decomposition via nucleophilic attack on the heteroaryl sulfone moiety of **1**.

Herein, we report that sugar-derived Wittig reagents **2** can be converted into optically active cyclopentenes **3** via a similar domino reaction with sulfur nucleophiles. Notably, thiols that cause decomposition of **1** can be employed in this system, enabling the introduction of a wide variety of sulfur substituents into the cyclopentene framework. Thus, the domino reaction of sugar-derived Wittig reagents **2** with thiols enables a divergent synthesis of sulfur-substituted, optically active cyclopentenes from a single precursor, and is expected to be useful for the exploration of biologically active molecules.



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1P- 42

Scale-Up Study and Challenges in Flow Hydrogenation Reactions

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Flow synthesis is a continuous production technology in which raw materials are supplied through mesochannels to carry out chemical reactions. Owing to its high safety and efficiency, it has attracted considerable attention. However, scaling up flow synthesis for industrial applications remains challenging because of channel blockage, optimization of reaction conditions, and changes in mixing and heat transfer behavior. In addition, stable operation and consistent product quality must be ensured. This study summarizes these challenges and discusses future directions toward industrial implementation.

As part of a scale-up study aimed at practical application, we focused on pressure loss and optimization of reaction conditions. The target reaction was the hydrogenation of nitro groups to amines using a column reactor packed with an in-house-developed 3 wt% Pd spherical carbon catalyst.

Reaction conditions were optimized using a column with an inner diameter (I.D.) of 5 mm and a length of 50 mm (1 mL). Under conditions using a 5 M substrate solution in methanol, stable continuous operation for 24 hours was achieved. The process was then scaled up to a column with an I.D. of 10 mm and a length of 300 mm (24 mL), corresponding to a 24-fold increase in substrate throughput. Under these conditions, heat generated by the reaction made temperature control difficult.

To mitigate heat generation, the substrate concentration was reduced to 0.4 M. Although this alleviated the thermal issue, new challenges arose, including increased pressure loss and hydrogen supply instability due to the higher solution flow rate. By adjusting the heater temperature and optimizing operating conditions, stable continuous operation for 27 hours was achieved using the I.D. 10 mm × 300 mm column. Under these optimized conditions, complete nitro group conversion and an average amine yield of 96% were maintained, achieving a production rate of 2.47 kg/day.

These results demonstrate that the 3 wt% Pd spherical carbon catalyst exhibits low pressure loss and excellent durability, and that stepwise scale-up of flow hydrogenation is feasible with appropriate concentration control and thermal management. The findings provide valuable insights for designing continuous production processes aimed at further scale-up.

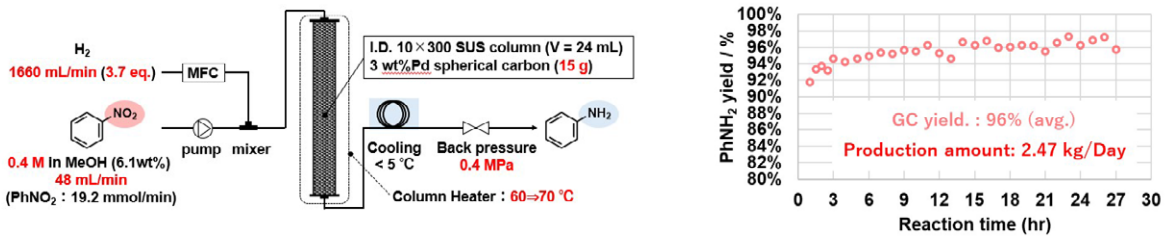


Fig. 1 Reaction conditions and evaluation results

1P-43

Application of Hybrid Mechanistic and Machine Learning Models to Crystallization Process Optimization

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Crystal particle size is a critical quality attribute in active pharmaceutical ingredient (API) manufacturing, strongly influencing processability and formulation performance. Although crystallization is widely used for particle size control, nucleation and growth behaviors are inherently stochastic and nonlinear, and process conditions are often determined empirically, requiring extensive experimentation and posing challenges for reproducibility and process understanding [1,2].

In this study, focusing on API cooling crystallization, we established an integrated experimental workflow for non-empirical process optimization by combining data-rich experimentation (DRE) using an automated synthesis platform and process analytical technologies (PAT; EasyViewer 100, ReactIR 702L, and ReactRaman 802L) with a population balance model (PBM), and applied the model to experimental design and design space exploration.

To support crystallization process optimization, solubility curves and an inline solution concentration monitoring model (g/kg) were developed using a polythermal method with EasyViewer 100 and ReactIR 702L, while crystal form changes were monitored in parallel using ReactRaman 802L due to polymorphism. A concentration prediction model was constructed from IR spectra using partial least squares (PLS) regression, with solute concentrations calculated from theoretical solubility curves and initial charge conditions as response variables.

Desaturation experiments were then performed to independently evaluate the crystal growth rate, a key parameter for particle size control. After complete dissolution, the solution was cooled to a supersaturation ratio of S = 1.2, followed by the addition of seed crystals (50% of the initial charge) and stirring for 1 hour. Based on the growth rate data, four additional experiments under varied conditions were conducted to identify primary and secondary nucleation parameters, which were fitted using the PBM. Model validation under three additional conditions confirmed the reproducibility of crystal particle size predictions.

A highly accurate PAT-based solubility prediction model was developed, and compound-specific growth and nucleation parameters were identified; these results, together with extensive in silico experiments over a wide range of operating conditions using the PBM, will be presented.

References

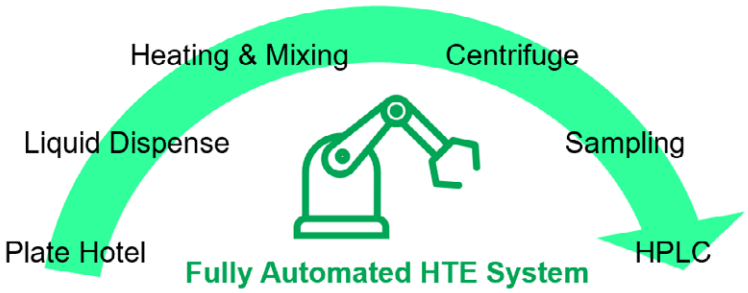
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Implementing a Fully Automated High-Throughput Experimentation System for Process Research Acceleration

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As therapeutic modalities continue to diversify and grow in complexity, process chemists are increasingly expected to deliver robust processes that satisfy the SELECT criteria[1] — Safety, Environment, Legal, Economy, Control, and Throughput — even in the face of mounting constraints on time and human resources. In this context, high-throughput experimentation (HTE)[2] has emerged as a powerful enabler, allowing process chemists to rapidly explore and optimize reaction parameters in a parallel fashion and generate data-rich insights. The incorporation of automation into HTE further amplifies these advantages, enhancing experimental reproducibility while simultaneously reducing human effort and error.

Against this background, we have developed an automated system capable of executing a sequence of HTE activities without manual intervention. The system integrates a liquid handler, an HPLC unit, a plate storage hotel, and a centrifuge, connected via a robotic arm. This configuration enables the seamless, fully automated execution of workflows — including plate retrieval from a plate hotel, liquid dispensing, heating and mixing, centrifugation, sample preparation, and HPLC data acquisition. In the poster presentation, we will provide a detailed description of the system and representative case studies including solubility study and salt screening.



References

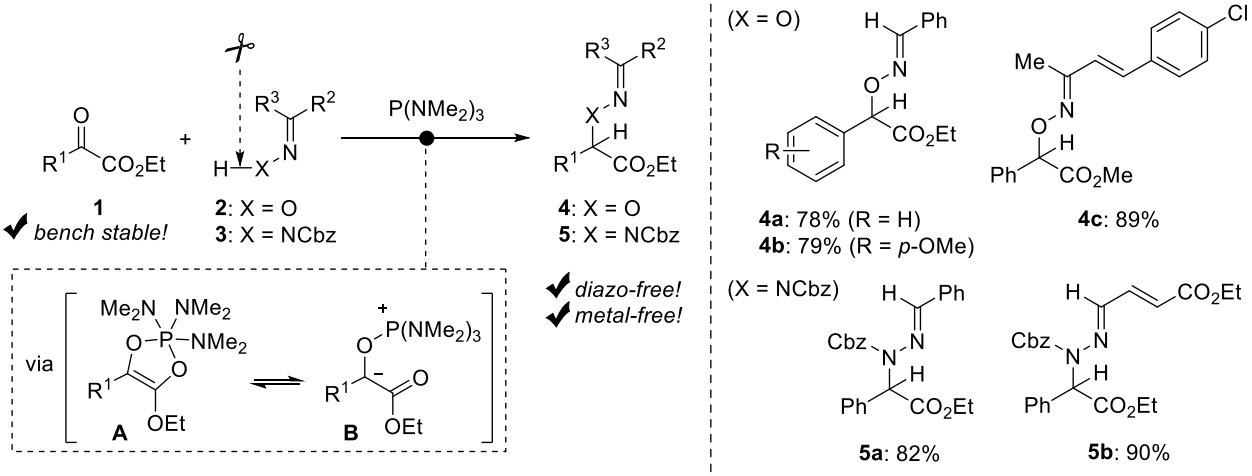
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Synthesis of imine derivatives via a diazo-free reductive O-H/N-H bond insertion reaction

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X–H bond insertion reactions (X = C, N, O, S, Si) are valuable transformations, wherein C1 units such as carbenes, carbenoids, and their surrogates can be incorporated into X–H bonds to form X–C–H bond. Although a variety of X–H bond insertion reactions have been developed so far, most of them have used diazo compounds as carbene equivalent precursors. Furthermore, efficient conversion required the use of (i) transition metal catalysts, (ii) thermal conditions or (iii) blue LED irradiations. Therefore, safety considerations still necessitate the development of efficient, diazo- and transition-metal-free X–H bond insertion reactions.

Herein, we present diazo-free O–H/N–H bond insertion of an oxime/hydrazone with a bench-stable α-ketoester for the synthesis of oxime ethers/hydrazones. The reaction of Kukhtin-Ramirez Adduct (KRA: **A** or **B**), which can be *in situ* formed from α-ketoester **1** and $P(NMe_2)_3$, with oxime **2**/acylhydrazone **3** afforded corresponding O–H/N–H insertion products. The protocol features a broad substrate scope and good functional group tolerance, providing oxime ethers **4** or multisubstituted hydrazones **5** in moderate to excellent yields.[1,2]



Scheme 1. A non-diazo approach to imine derivatives

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1P- 46

Polymorphism Control in Industrial Process Development for the Metastable Crystal Form of Linagliptin

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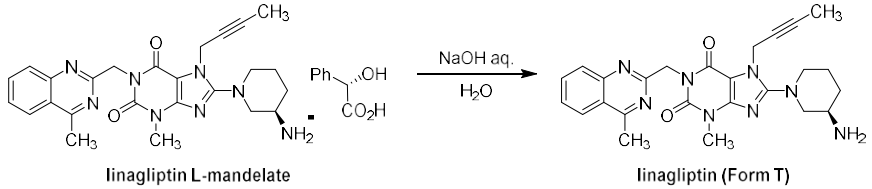
Since polymorphism affects physicochemical properties such as solubility, chemical stability, and crystal shape, the control of crystal transition is extremely important in pharmaceutical development. Obtaining metastable crystals with high reproducibility is particularly challenging due to their high tendency to transition to stable crystals. Therefore, in the scale-up manufacturing of a metastable form, precisely setting process parameters such as crystallization temperature and stirring speed in advance is essential.

To ensure a stable supply of pharmaceuticals, we have initiated the in-house manufacturing of linagliptin, an antidiabetic drug. In this presentation, we report the development of a robust manufacturing process for form T, which is a metastable crystal form of linagliptin. With reference to the patent,[1)] we adopted the route via linagliptin L-mandelate as an intermediate. In the initial studies, low-crystallinity form T or mixed crystals consisting of the form T and another crystal form as a hydrate polymorph were obtained. To prepare high-crystallinity form T, the effects of each process parameter on crystal polymorphism were experimentally examined. Furthermore, a highly reproducible manufacturing method suitable for scale-up was developed by utilizing chemical engineering calculations.

As a result, temperature was the most important factor controlling crystalline polymorphism with a narrow tolerance range. In addition, stirring speed was also found to be an important parameter that could significantly influence the final polymorphic form.

The manufacturing process, developed by appropriately setting these critical parameters, was implemented at the pilot scale to validate the scale-up, successfully producing 5.7 kg of high-crystallinity form T.

This research is expected to contribute to ensuring a stable supply of pharmaceuticals and to the development of polymorphism control technology.



Scheme 1. Process development of linagliptin form T

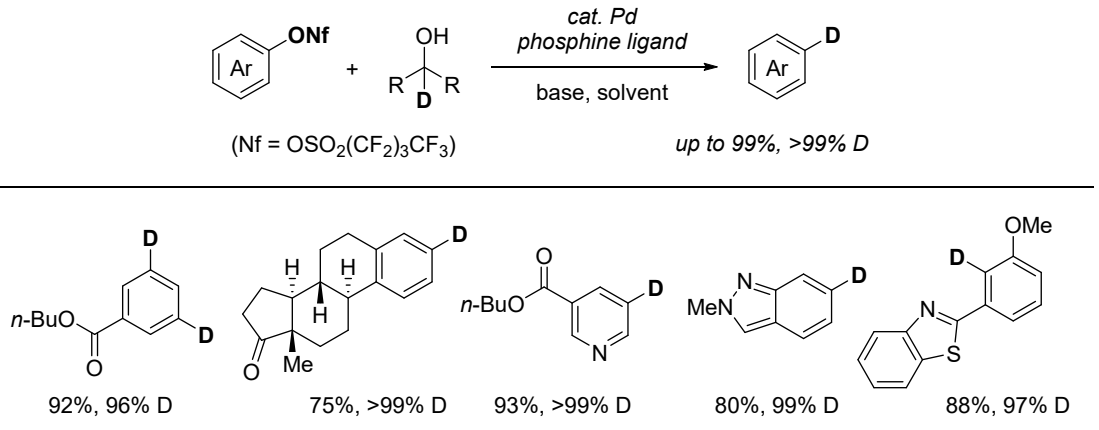
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Palladium-Catalyzed Deoxygenative Deuteration with Aryl and Heteroaryl Nonaflates as Effective Coupling Partners

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Deuterated compounds are highly important in pharmaceutical development as the incorporation of deuterium into bioactive molecules provides an effective means of controlling their properties through isotope effects.[1] For example, deutetrabenazine (Austedo) was approved as the first deuterated drug in the United States, and deuteration has attracted considerable attention as a powerful methodology in drug discovery. Aromatic moieties are known to be key substructures in pharmaceutical agents, and deuterodefunctionalization has emerged as an effective transformation. In particular, deoxygenative deuteration is highly promising because of the broad availability and structural diversity of phenolic precursors.[2] Aryl nonaflates (ArONf = $ArOSO_2(CF_2)_3CF_3$) are known as an attractive alternative to aryl triflates owing to their superior hydrolytic stability and comparable reactivity. To the best of our knowledge, no catalytic deoxygenative deuteration of aryl nonaflates has been reported. Herein, we report the palladium-catalyzed deoxygenative deuteration with aryl and heteroaryl nonaflates (Scheme 1). This process accepted a diverse range of substrates, giving desired products in high yields with excellent deuterium incorporation. Furthermore, a successful gram-scale reaction demonstrated the promising scalability and utility of this methodology.



Scheme 1. Pd-catalyzed deoxygenative deuteration of aryl and heteroaryl nonaflates

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1P– 48

Pincer-Nickel-Catalyzed Enantioselective Addition of Acetonitrile to Ketimines

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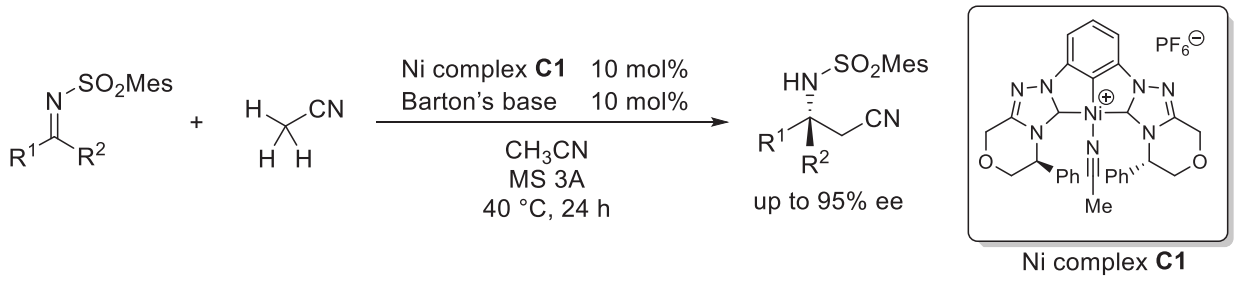
The cyano (–CN) functionality plays a pivotal role in synthetic organic chemistry as a versatile synthon for the preparation of amines and carboxylic acid derivatives. In view of the acute toxicity associated with cyanide, readily available acetonitrile has long been pursued as a safer alternative pronucleophile for the synthesis of cyano-containing chiral building blocks.[1]

Chiral α-tertiary amine frameworks are common in many biologically active molecules, prompting extensive research into their synthesis.[2,3] Although chiral α-trialkyl amines are structurally most diverse and synthetically most important among α-tertiary amines, catalytic asymmetric methods toward these chiral amines remain extremely limited. Here, we report a new method for the catalytic asymmetric synthesis of chiral α-tertiary amines, which was realized by Ni pincer complex catalyzed reaction of nonactivated ketimines with acetonitrile.

After systematic screening of the Ni–pincer catalyst, solvent, and base, optimal conditions were established using Ni complex **C1** (10 mol%) and Barton's base (10 mol%) in CH_3CN at 40 °C for 24 h, delivering the acetonitrile adduct in excellent yield with high enantioselectivity.

This protocol demonstrates broad substrate tolerance toward various ketimines, enabling the synthesis of structurally diverse chiral α-tertiary amines.

The practicality of the method was confirmed by gram-scale synthesis and subsequent diversification of the nitrile functionality into primary amines, amides, esters, and aldehydes.



Scheme 1. Pincer-Nickel-Catalyzed Enantioselective Addition of Acetonitrile to Ketimines

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1P- 49

Evaluation of Sampling Device Performance and Integration in Online HPLC Process Monitoring

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Abstract

Process monitoring using high-performance liquid chromatography (HPLC) is an effective approach for understanding and controlling chemical reaction processes. Online monitoring requires reliable and timely sample transfer from a batch reactor to the analytical system, with the sampling devices tailored to the samples and the reactors.

In this study, near real-time sample delivery from a batch reactor to an online LC system is demonstrated using an aldol reaction as a model system. Four different sampling and delivery devices—an isocratic pump, a piston pump, a peristaltic pump and a programmable syringe pump—are evaluated and compared with the performance for online process monitoring.

In addition, the ability to generate trigger signals and to control pumping and sampling devices is essential for orchestrating the complete sampling workflow. We demonstrate the generation of trigger signals from the online LC system to control external sampling devices, enabling automated and synchronized sample transfer and analysis.

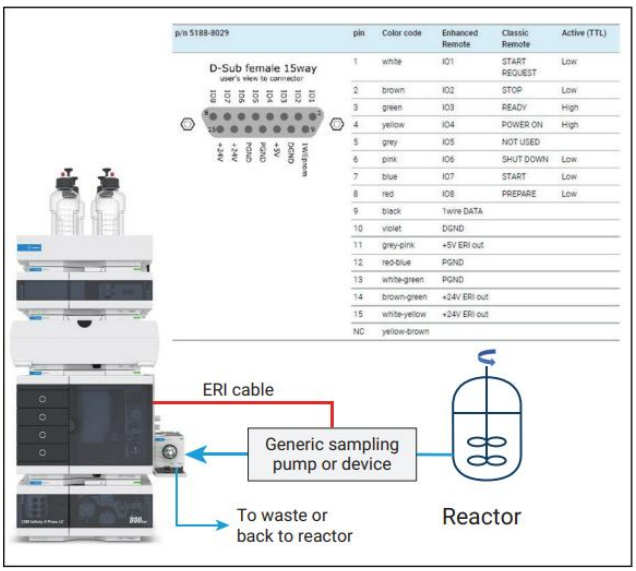


Fig 1. Schematic of physical and electrical connections between the reactor and the online HPLC for process monitoring

1P- 50

Efficient Asymmetric Synthesis of *N*-Alkyl-α-Amino Acids by Using a Chiral Iridium Catalyst

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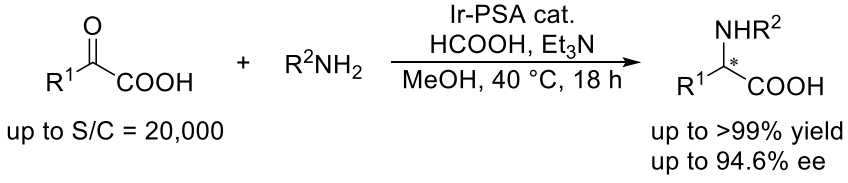
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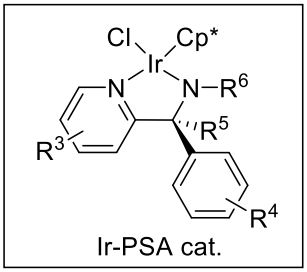
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Peptide-based therapeutics have attracted increasing attention. In particular, peptides containing chiral *N*-alkyl-α-amino acids exhibit increased hydrophobicity, leading to improved membrane permeability. Meanwhile, *N*-alkylation also enhances resistance to proteolytic degradation, thereby improving *in vivo* stability. Therefore, *N*-alkyl-α-amino acids are important structural motifs. However, existing synthetic methods still suffer from limitations in efficiency and applicability. We have previously reported the diastereoselective synthesis of unnatural amino acids via catalytic reductive amination of α-keto acids with chiral amino alcohols.[1)] In this study, we developed a direct asymmetric reductive amination of α-keto acids with primary alkyl amines using a chiral iridium catalyst for the synthesis of *N*-alkyl-α-amino acids.

Under transfer hydrogenation conditions using a formic acid/triethylamine system, the reductive amination of phenylpyruvic acid with methylamine in methanol using (*S*)-Ir-PSA cat. afforded (*S*)-*N*-methylphenylalanine in 83% yield with 84% ee. Optimization of the reaction conditions allowed the synthesis of various *N*-alkyl-α-amino acids in a single step with high enantioselectivity, achieving a substrate-to-catalyst molar ratio (S/C) of up to 20,000. After derivatization to the Cbz- and Fmoc-forms, the desired products were isolated with more than 99% ee. These results demonstrate the practical utility of this method for preparing protected *N*-alkyl-α-amino acid building blocks for peptide and medicinal chemistry applications.





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1P-51

Process Development of a Chemoenzymatic Route to an *N*-Methylprolinol Derivative

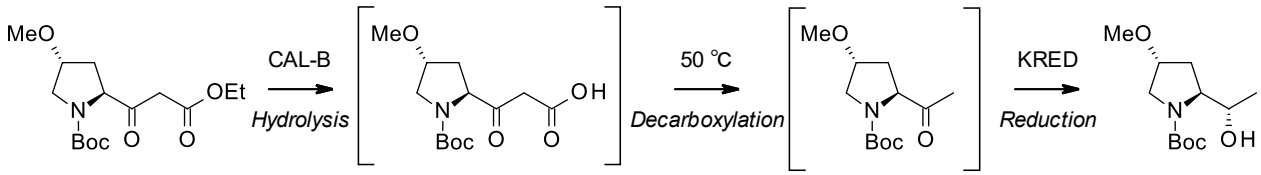
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The development of safe, robust, and scalable processes is a central challenge in the industrial synthesis of chiral pharmaceutical intermediates. We report an integrated chemoenzymatic synthetic route for the kilogram-scale preparation of an *N*-methylprolinol derivative, a key intermediate for KRAS inhibitor candidates.

The overall process combines conventional organic synthesis with a one-pot enzymatic transformation as a key step. A chemically synthesized β-keto ester was converted into the corresponding *N*-methylprolinol derivative in aqueous media through sequential enzymatic hydrolysis, decarboxylation, and stereoselective reduction in one-pot. Hydrolysis catalyzed by Candida antarctica lipase B (CAL-B) proceeded under mild, near-neutral conditions, effectively suppressing epimerization at the α-carbon. Controlled thermal treatment enabled decarboxylation in the same vessel, generating the corresponding methyl ketone intermediate. Subsequent stereoselective reduction was achieved using a keto-reductase (KRED) identified through enzyme screening, affording the desired alcohol with excellent diastereoselectivity.

The high mutual compatibility of CAL-B and the selected KRED enabled a true one-pot biotransformation, minimizing unit operations, solvent consumption while simplifying the overall process. Downstream chemical steps were redesigned to replace hazardous reagents with safer alternatives. The final product was isolated as a crystalline tartrate salt with high chemical purity and high stereoselectivity.

The chemoenzymatic process described herein enabled the kilogram-scale preparation of the target *N*-methylprolinol derivative through a one-pot transformation, delivering high stereochemical purity and improved process safety.



Scheme 1. One-pot biotransformation of a β-keto ester

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AI-Driven Optimization of Solvent Swap Distillation: Integrating Machine Learning Video Imaging for Automated, Scalable, and Sustainable Chemical Processing

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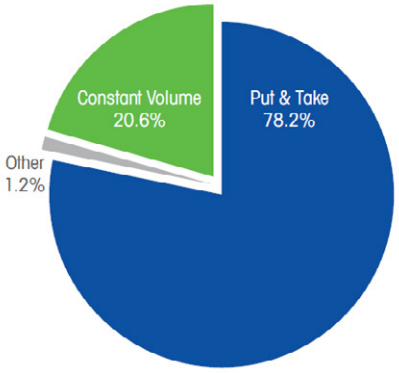
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Solvent swap distillation is a fundamental operation in chemical manufacturing, enabling the replacement of solvents to improve downstream processes such as reactions, extractions, and crystallizations. This work presents a comprehensive workflow integrating vapor-liquid equilibrium modeling, dynamic simulations, and automated experiments to design robust, efficient, and sustainable solvent swap operations using video imaging ML model. The approach ensures high data quality, scalable process development, and unattended operation modes, addressing common scale-up challenges and advancing sustainable chemical manufacturing.

Solvent swap distillation modifies solvent composition by introducing a replacement solvent while distilling off the original. Two common operating modes exist: (a) "put and take," where liquid volume transitions between two set points by adding and removing solvents in stages, and (b) "constant volume," maintaining steady liquid volume by continuous replacement solvent addition as original solvent evaporates. The mode selection influences fresh solvent quantity and energy efficiency. Process conditions impact significantly the distillation performance therefore, vapor-liquid equilibrium (VLE) models aid solvent selection and process design by predicting phase behavior, azeotropes, and boiling points. Dynamic modeling using Dynochem software and experimental data using Synthesis platform from Mettler Toledo AutoChem ensure optimal simulation results to be use to design the Lab to Plant scale-up process.



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1P- 53

Maximize Reaction Insight via Data-Rich Experiments and Intelligent Analytics

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Deep understanding of reaction chemistry is advanced by the synergistic integration of data-rich experimentation and sophisticated data reduction methodologies. The following examples demonstrate how chemists and engineers are leveraging the METTLER TOLEDO process analytical technology (PAT) portfolio and complementary tools to extract maximum insight from every experiment.

1. O'Sullivan et al. apply ReactIR, EasyMax, and Dynochem in a new route for the synthesis of N-acetylgalactosamine (GalNAc) ligand clusters (Fig. 1).[1)]
2. Qin et al. describe a novel modification to an EasySampler probe that enables true on-line analysis of a flow photocatalysis reaction using DirectInject-LC.[2)]
3. Argulo et al. use Dynamic Response Surface Methodology to understand a crystallization process performed in an Optimax synthesis workstation equipped with ReactIR and EasySampler technology.[3)]

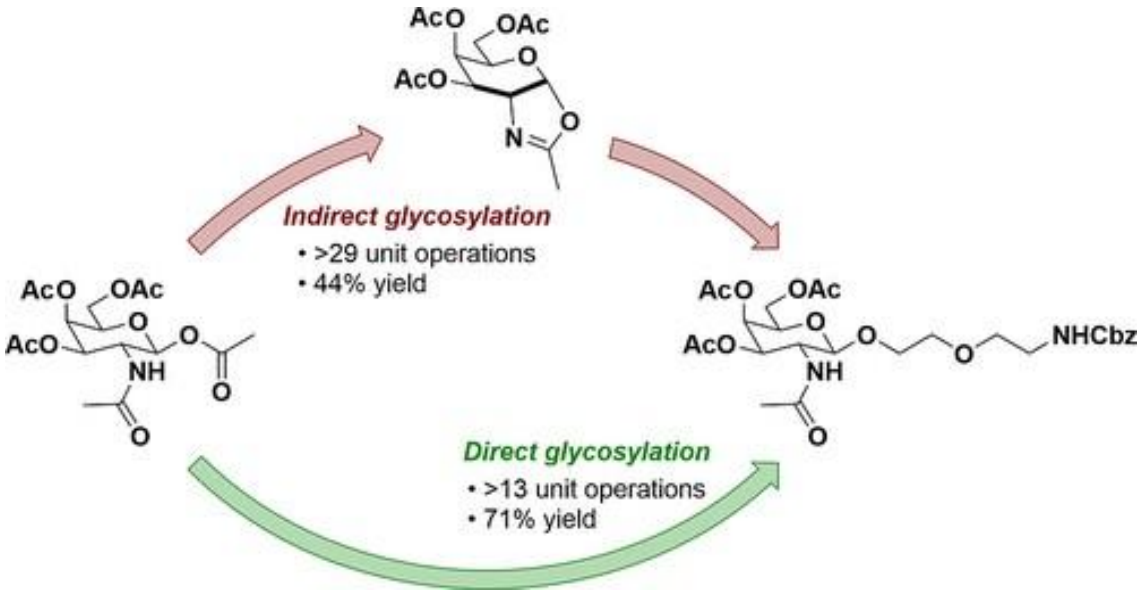


Figure 1. A one-pot glycosylation process developed to reduce unit operations and in-process controls.

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1P-54

Calculation and Verification of Mixing and Heat Transfer Parameters in Stirred Tank Reactors for Process Development and Scale-up

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The rates of physical parameters related to mixing and heat transfer are a function of the details of the equipment set-up and operating conditions and thus can vary significantly between stirred tank reactors of different design and scale[1]. If these physical parameters are not adequately designed for on changing scale, or moving between reactors of similar scale but different design and operation, then factors such as reaction yield, productivity, crystal size distribution and even the intrinsic safety of the operation could be at risk. Mixing and heat transfer calculations are most quickly and easily done via correlations that account for the main physical parameters and operating conditions, however verification is required to ensure validity and improve the accuracy of these approaches, this can be done experimentally or via alternative methodologies.

In this work we look at a combination of experimental work, first principles modeling and verification via measurements on scale to underpin empirical approaches for right-first-time scale-up of processes where mixing and heat transfer parameters can substantially affect performance.

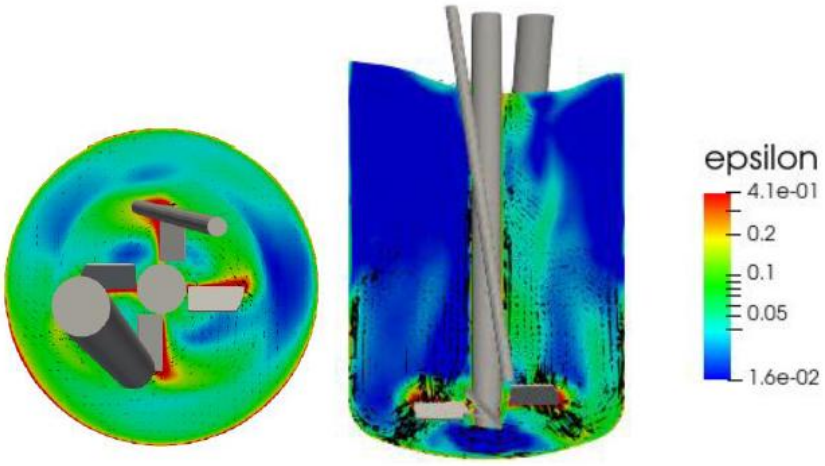


Figure 1. Local energy dissipation rates in a laboratory scale reactor calculated using computational fluid dynamics

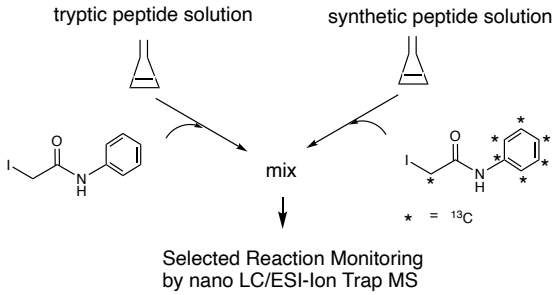
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1P- 55

Quantitative Analysis of Clinical Proteome by Nano LC-nano-ESI-SRM-MS with the Use of Stable Isotope-labeled and Unlabeled Iodoacetanilides

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Proteomics plays an important role in the comprehensive analysis of protein expression patterns under certain physiological conditions. Quantitative analysis of proteins is thus essential for proteomics. We have been developing our methodology for quantitative analysis of proteins by a combination of stable isotope-labeled and unlabeled modification of specific amino acid residues by small organic molecules followed by mass spectrometry. We previously demonstrated that the Selected Reaction Monitoring (SRM) by modifying cysteine residues with ^{13}C-labeled or -unlabeled iodoacetanilide (IAA)[1] followed by nano LC-nano-ESI-SRM-MS analysis is effective for absolute quantification of commercial proteins[2] and candidate proteins for breast cancer biomarkers from nipple discharge (ND) of breast cancer patients.[3]
A custom-synthesized significant peptide in catalase was reacted with IAA or $^{13}C_7$-IAA at cysteine. A standard curve was prepared from five IAA-modified peptide solutions with different concentrations and a constant concentration of the $^{13}C_7$-IAA-modified peptide. The standard curve based on the results of five mixtures showed high correlation. Next, absolute quantification of catalase, a candidate for the breast cancer protein biomarker, of unknown concentration was attempted. Ten catalase solutions obtained from ten breast cancer patients were reacted with IAA and digested with trypsin, followed by being mixed with 100 fmol/μL of $^{13}C_7$-IAA-modified peptide. The result showed a similar trend with the sandwich ELISA results of catalase in ND. Thus, this SRM technique was found useful for quantitative analysis of proteins without antibodies.



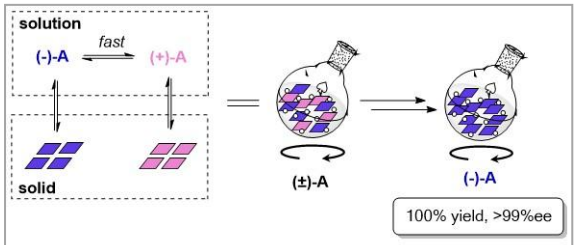
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Absolute Asymmetric Synthesis of Cyclic Aminals by Dynamic Crystallization

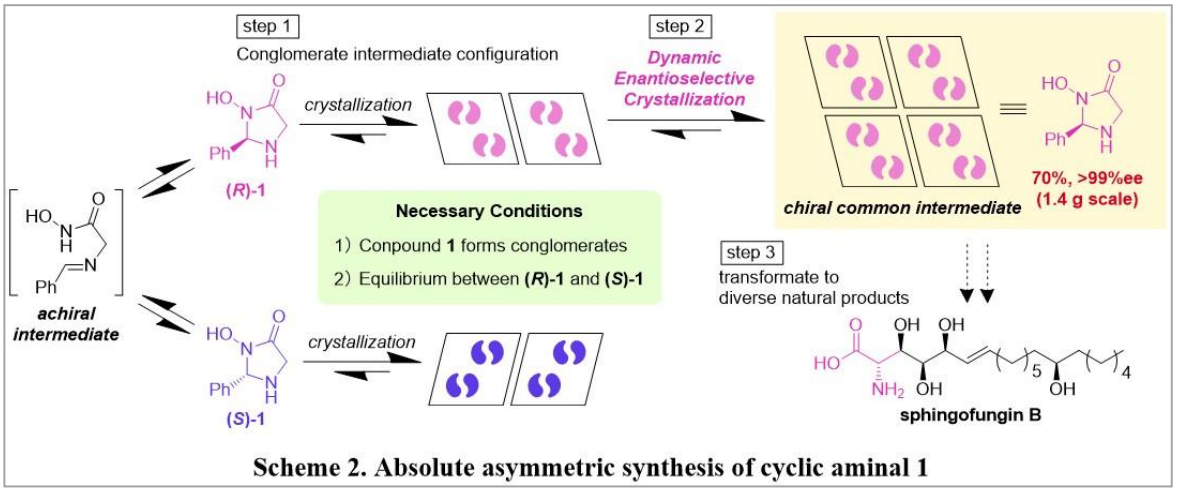
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Crystals produced from a racemic compound in solution are known to be classified into racemic crystals and conglomerates. While racemic crystals consist of a pair of both enantiomers, conglomerates contain a single enantiomer in each individual crystal, although they are racemic overall. If compound A forms conglomerates, dynamic crystallization of racemic compound **A** gives enantiopure crystals in theoretically 100% yield through a symmetry breaking event (deracemization) and asymmetric amplification under facile racemization process without addition of any chiral source. However, practical examples of dynamic enantioselective crystallization are limited because very few compounds crystallize as conglomerates.



Scheme 1. Dynamic enantioselective crystallization

To address this limitation, our group have been exploring a new synthetic strategy utilizing dynamic enantioselective crystallization of a conglomerate common intermediate, which can be converted to versatile chiral products. In this study, we developed dynamic asymmetric crystallization of cyclic aminal **1** as a common chiral intermediate for synthesis of various α-amino acid motifs such as sphingofungin B. A suspension of racemic compound **1** and an alcoholic solvent was vigiously stirred with glass beads, affording cyclic aminal **1** in 70% yield with 99% ee.



Scheme 2. Absolute asymmetric synthesis of cyclic aminal 1

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Diastereo- and Enantioselective Allenylation of Imines with Propargyl Nitriles Assisted by Machine Learning

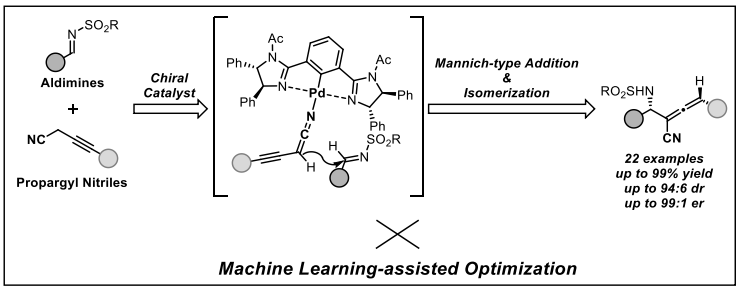
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Chiral homoallenylamines are valuable intermediates for the synthesis of bioactive molecules and versatile building blocks for further transformations. One of the most straightforward approaches to these compounds is the asymmetric allenylation of imines. In 2013, Maruoka and co-workers reported the first enantioselective synthesis of axially chiral homoallenylamines using a phase-transfer catalyst.[1)] Then, in 2022, Yin and co-workers reported an enantioselective synthesis of trisubstituted chiral homoallenylamines via an alkynylogous Mannich reaction of propargyl pyrazoleamides. This transformation proceeds through a copper(I)–phosphine catalytic system involving an allenyl–copper intermediate and exhibits high γ-selectivity.[2)] Inspired by these previous works, we hypothesized propargylic nitriles could serve as promising precursors for allene synthesis, and the reaction with imines could afford novel chiral homoallenylamines. To address this challenge, machine learning was employed as a complementary tool for efficient exploration of the multidimensional parameter space. A strategy combining Gaussian process regression (GPR) and Bayesian optimization was used to guide condition selection.

Herein, we developed novel synthetic method for chiral homoallenylamines (**Scheme 1**). In this method, the cyano group played a dual role in facilitating nucleophile activation and controlling regio- and stereoselectivity via a ketenimide-type intermediate, thereby enabling the simultaneous construction of central and axial chirality in homoallenylamines. In addition, machine learning of reaction conditions improved selectivity. Moreover, the reaction exhibits a broad substrate scope, affording a variety of chiral homoallenylamines in high yields with high diastereo- and enantioselectivities (up to 99% yield, 94:6 dr, 99:1 er). Furthermore, the origin of the stereoselectivity and assumed reaction mechanism were elucidated by computational analyses.

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Scheme 1. Overview of this study

Reductive Nucleophilic Addition to Morpholine Amides for Polyketide Synthesis

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Polyketides are a group of natural products accounting for approximately 20% of low molecular weight drugs. Most polyketide drugs are supplied by either cultivation or semi-synthesis. Chemical synthesis has been expected as an alternative method to supply polyketide drugs. Even with modern organic synthesis, however, the current synthesis is not efficient enough to supply polyketides drugs due to their complexity.

One of the structural features of polyketides is their repeating carbon units composed of alcohol and methyl groups. Conventionally, installation of polyketide carbon units required three steps: 1) protection of alcohols, 2) reduction of ester equivalents, and 3) aldol reaction. Thus, the total synthesis requires an enormous number of reaction steps through multiple iterations of this cycle. To address this challenge, we developed an iridium-catalyzed reductive nucleophilic addition to morpholine amides.

Morpholine amide **2** was prepared from aldehyde **1** by Roush's asymmetric aldol reaction.[1] Addition of an iridium catalyst and a silane reducing agent to **2** initiated dehydrogenative silylation of the secondary alcohol and hydrosilylation of the amide carbonyl, generating *N,O*-acetal **3**. While addition of a crotylation agent gave homoallyl alcohol **5** via *N,O*-acetal **2** in a one pot process, use of DMF, TBABr and the ylide to **3** provided unsaturated amide **6**.[2]

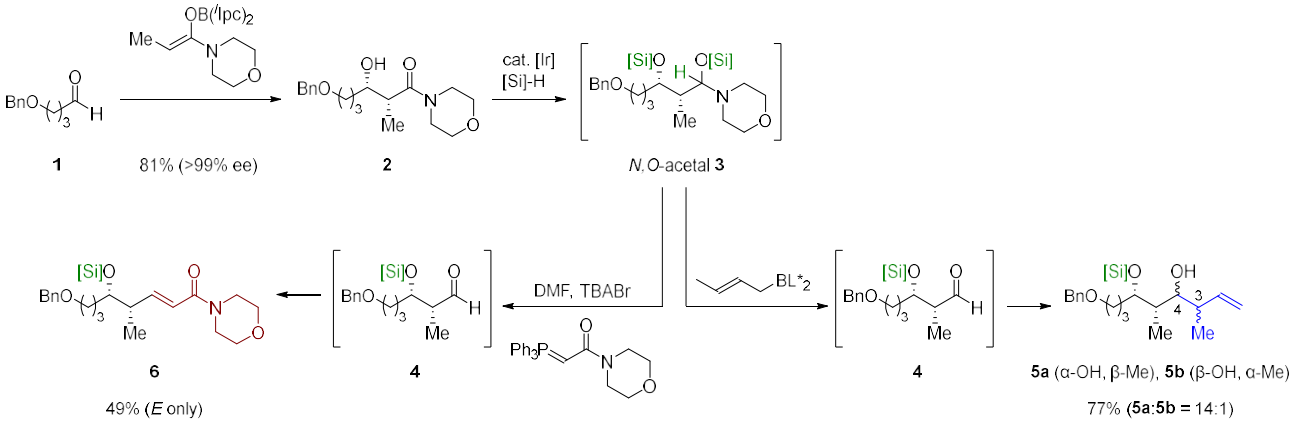


Figure 1. Reductive nucleophilic addition to morpholine amides

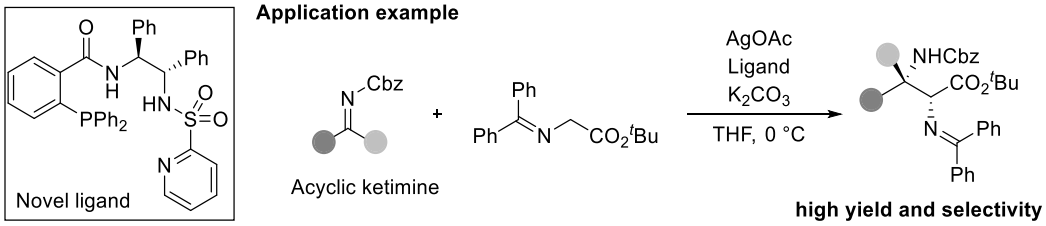
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Design of Phosphine-Heteroarenesulfonamide Ligands as Dinuclear Silver Catalysts for Enantioselective Construction of Unnatural Amino Acid

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The design of new asymmetric catalyst systems represents a fundamental strategy to access the valuable chiral molecules, including natural products and pharmaceuticals. Among previously developed chiral catalysts, phosphine ligands have enabled a broad range of asymmetric syntheses. Incorporation of the 2-(diphenylphosphino)benzoic acid framework into a chiral diamine backbone has become an important strategy in chiral ligand design. For example, Trost ligands[1] and Dixon ligands[2] are highly valued as extremely versatile chiral ligands for single-metal catalysis and have been widely applied in asymmetric and total synthesis. Recently, we designed and developed a dinuclear metal ligand bearing a phosphine-heteroarensulfonamide. Comprehensive mechanistic studies combining global reaction route mapping (GRRM), artificial force-induced reaction (AFIR), and density functional theory calculations revealed a cooperative bimetallic transition-state architecture responsible for the observed stereocontrol. These findings establish a new design principle for asymmetric catalysis based on homodinuclear activation and highlight the potential of dinuclear silver catalysis for the construction of complex chiral molecules.

As a result, a first enantioselective Mannich-type reaction between glycinate Schiff base and acyclic ketiminoester was achieved, affording α,β-diamino acid derivatives bearing tetrasubstituted chiral carbon centers in excellent yields and enantioselectivities (up to 99% yield, 99:1 dr and 98:2 er) (**Scheme 1**).[3]



Scheme 1. Overview of this study

References

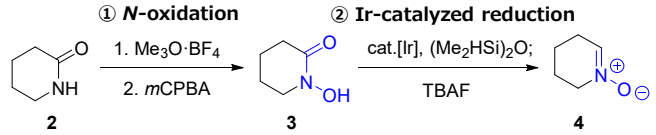
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Ir-Catalyzed Reductive Formation of Nitrones Enabling Asymmetric Total Synthesis of Indolizidine Alkaloids

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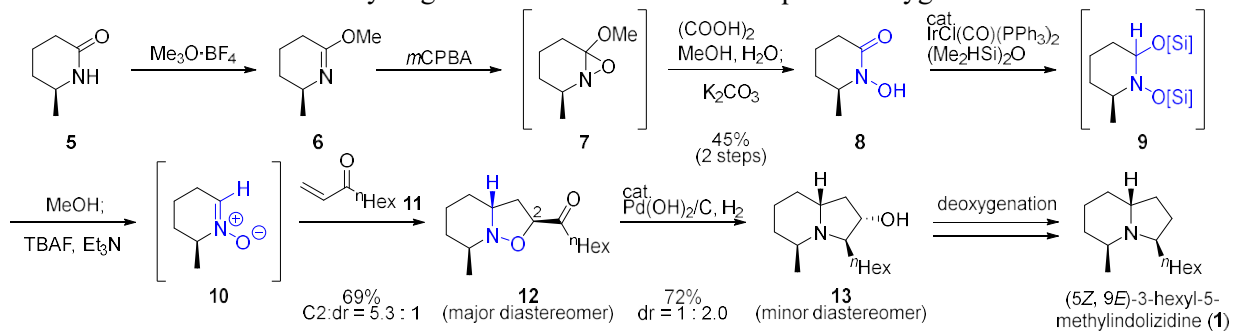
Nitrones are widely applied as 1,3-dipoles in various reactions, such as [3+2] cycloaddition with alkenes and Kinugawa reaction. Due to the synthetic utility of nitrones, they serve as practical intermediates for alkaloid natural products. Therefore, numerous synthetic routes to nitrones have been developed. However, the efficient methods for accessing chiral nitrones have been exclusively limited.

Our laboratory has developed a two-stage strategy for the formation of nitrones from lactams (Scheme 1). This protocol involves *N*-oxidation of lactam **2**[1], followed by the Ir-catalyzed reduction of *N*-hydroxylactam **3**[2]. This method can be applied for chiral lactams affording nitrones without loss of their chirality. This time, we report the asymmetric total synthesis of 3-hexyl-5-methylindolizidine (**1**) enabled by this reductive formation of nitrones.



Scheme 1. Iridium-catalyzed reductive formation of nitrones

The synthesis commenced with *N*-oxidation of commercially available chiral lactam **5** (Scheme 2). Methylation of **5** with Meerwein's reagent provided imidate **6**, which was oxidized with *m*CPBA to give oxaziridine **7**. *In-situ* generated **7** was converted to *N*-hydroxylactam **8** by the treatment with oxalic acid in H_2O/MeOH, followed by the addition of K_2CO_3. The Ir-catalyzed reduction of *N*-hydroxylactam **8** with $(Me_2HSi)_2O$ afforded *N,O*-acetal **9**. Exposure of **9** to TBAF led to decomposition of the *N,O*-acetal to generate nitrone **10**, which underwent a [3+2] cycloaddition with enone **11** in a one-pot process to furnish isoxazolidine **12**. Finally, the total synthesis of 3-hexyl-5-methylindolizidine (**1**) was accomplished through the formation of the indolizidine skeleton under hydrogenation conditions and subsequent deoxygenation of **13**.



Scheme 2. Total synthesis of (5*Z*, 9*E*)-3-hexyl-5-methylindolizidine (**1**)

References

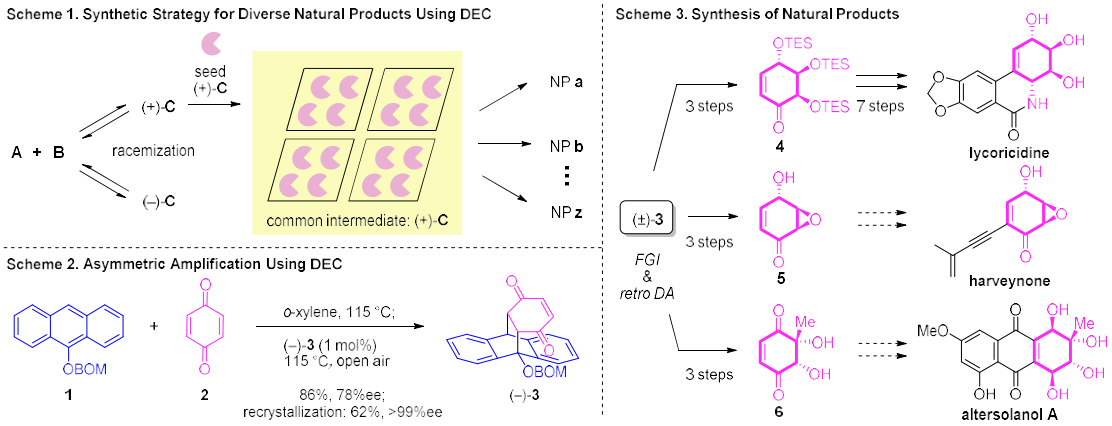
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General Synthetic Approach to Various Natural Products Using Dynamic Enantioselective Crystallization

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In general, crystallization of racemic compounds provides racemic crystals, However, certain racemic compounds are known to produce conglomerate crystals, in which each crystal is composed of a single enantiomer, although it is racemic overall. Dynamic enantioselective crystallization (DEC) provides enantiopure compounds from racemic compounds if the compounds form conglomerate crystals under an equilibrium reaction in solution.[1,2] When seed crystals of (+)-**C** are added under equilibrium conditions, (+)-**C** is preferentially crystalized as the reaction proceeds in theoretically 100% yield (Scheme 1). However, practical applications of this method remain limited because a target compound rarely forms a conglomerate crystal. In this presentation, we developed a new synthetic strategy, in which protected quinone **3** was synthesized by DEC as a common intermediate to gain access to a variety of natural products.

After Heating a suspension of anthracene derivative **1**, *p*-benzoquinone **2** and *o*-xylene at 115 °C, addition of seed crystal (−)-**3**, induced asymmetric amplification through dynamic crystallization, affording (−)-**3** in 86% yield with 78%ee. Subsequent recrystallization provided (−)-**3** in 62% yield with 99%ee (Scheme 2). To demonstrate the synthetic utility of protected quinone **3**, transformation of (±)-**3** to natural products was investigated (Scheme 3). Stereo- and regioselective transformations of **3** and retro-Diels–Alder reaction furnished cyclohexanones **4-6**. Further derivatization enabled the total synthesis of lycoricidine.



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Practical Direct Azidomethylation Methods for the Synthesis of *N*- and *S*-Azidomethyl Compounds

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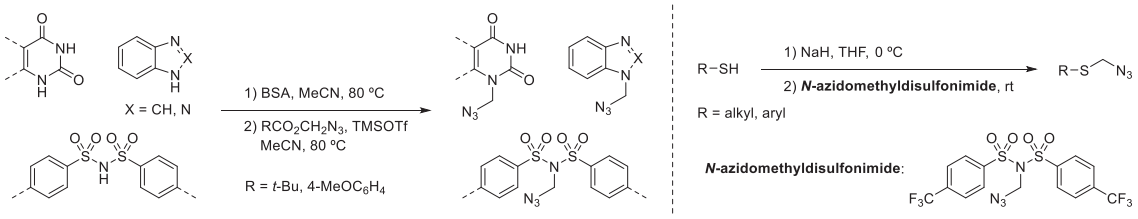
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Organic azides are versatile building blocks in synthetic chemistry because they can be readily transformed into a variety of functional groups, such as amino and amido groups, as well as *N*-heterocycles. Azido compounds also serve as key intermediates for accessing bioactive and functional molecules through copper-catalyzed azide–alkyne 1,3-cycloadditions or Staudinger ligations.

Traditionally, azidomethyl compounds have been synthesized through multistep sequences involving halomethylation. We recently discovered that azidomethylation occurs at the N1 position of thymine when silylated thymine is treated with an azidomethyl ester at 80 ºC in the presence of trimethylsilyl triflate (TMSOTf).[1)] In the proposed mechanism for this reaction, the azidomethyl ester reacts with TMSOTf to generate an azidomethylium ion, which then serves as the active azidomethylating species. This method enables the direct installation of an azidomethyl group onto nitrogen atoms in amines, including nucleobases, benzazoles, and bis(arene)sulfonimides.

Building on the fact that disulfonimides are excellent leaving groups, we further found that *N*-azidomethyldisulfonimides can be directly used to synthesize azidomethyl sulfides.[2)] This reaction proceeds under mild conditions and is applicable to a variety of aliphatic and aromatic thiols, affording the corresponding azidomethyl sulfides in good yields.

In this presentation, we report the details of these two azidomethylation reactions.



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Radical Transformations of Acidic Compounds Enabled by Ketone Photocatalysis

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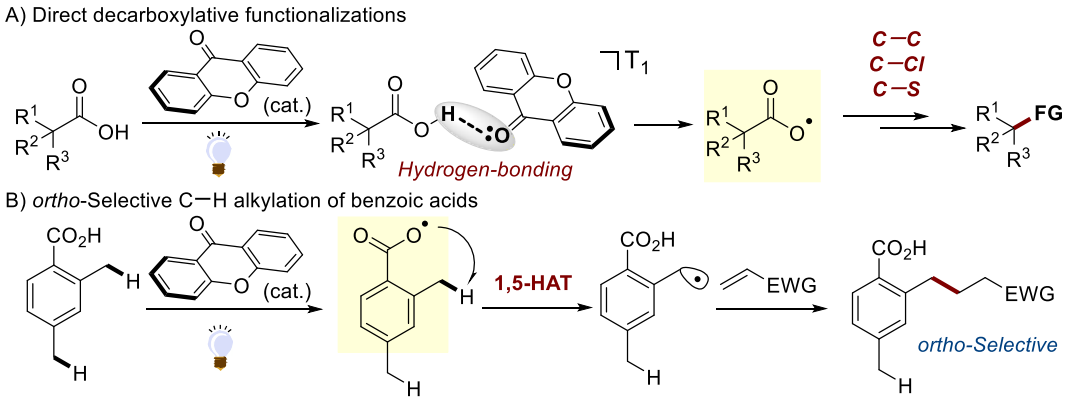
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Carboxyl radicals are among the most useful open-shell species that can undergo a diverse array of valuable transformations.[1] While various catalytic methods for generating carboxyl radicals have been developed to date, they generally require stoichiometric amounts of reagents, transition-metal catalysts, or prefunctionalized redox-active esters. Herein, we present a novel photoactivated-ketone-catalyzed direct generation of carboxyl radicals via hydrogen atom transfer (HAT) from the O–H bond of carboxylic acids.[2] Owing to a hydrogen-bonding interaction between ketone and the acids, the selective O–H bond cleavage has been achieved.

This chemoselective O–H HAT enabled the decarboxylative functionalization of aliphatic carboxylic acids (Scheme A). The ketone photocatalysis for selective O–H activation was also applicable to benzoic acid derivatives, and the corresponding benzoyloxy radicals could be prepared without difficulty (Scheme B). Thus-formed benzoyloxy radicals selectively cleave the benzylic C(sp^3)–H bonds at the *ortho*-position through a 1,5-HAT mechanism. The resulting benzyl radicals then undergo a Giese-type addition to electron-deficient alkenes, providing the desired alkylated products. In the presentation, we will present detailed mechanistic studies and substrate generalities.



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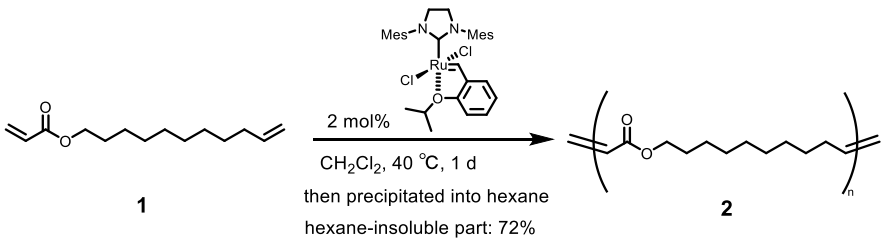
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A Strategy for Access to Natural Product-Inspired Poly(cyclic ether) Architectures via ADMET Polymerization

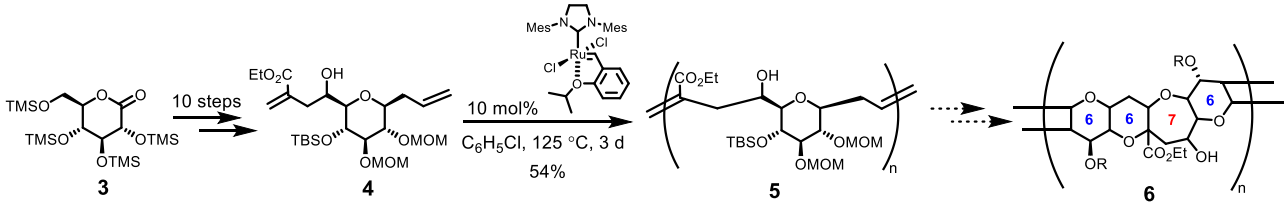
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Poly(cyclic ether)s are neurotoxins that strongly bind to ion channels on cell membranes, enhancing ion permeability into cells. Since the 1990s, extensive efforts have been devoted to the synthesis of natural poly(cyclic ether)s.[1] However, due to their structural complexity, the synthesis of their derivatives remains challenging, and their functions as organic materials have not yet been evaluated. In this study, we aimed to develop a new synthetic strategy for natural product-inspired poly(cyclic ether)s consisting of 6/6/7/6-tetracyclic ether as a repeating sequence.

Prior to the synthesis of poly(cyclic ether)s, we reproduced a reported ADMET polymerization.[2] Polymerization of **1** proceeded via selective metathesis between the terminal olefin and the enone, affording **2** with a well-defined primary structure (**Scheme 1**). Monomer **4** was synthesized from **3** via 10 steps. ADMET polymerization of **4** was carried out to afford glycopolymer **5** (**Scheme 2**). The scope of polymerization conditions and the attempts for access to **6** will also be reported.



Scheme 1. Model reaction of ADMET polymerization.



Scheme 2. Synthesis of sequence-regulated glycopolymer **5** as a precursor of poly(cyclic ether) **6**.

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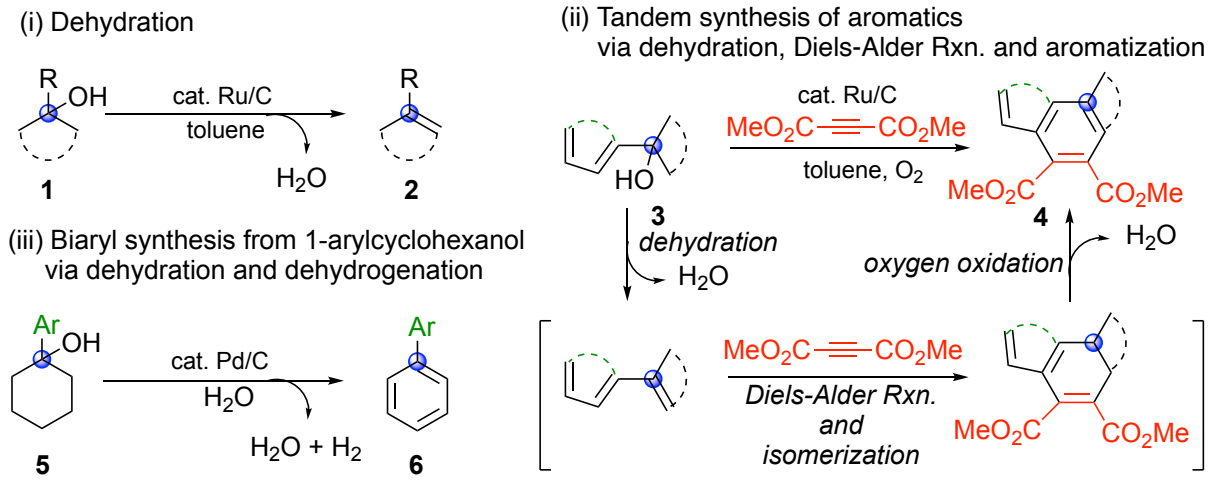
Platinum-Group-Metal-on-Carbon Catalyzed Dehydration of Tertiary Alcohols and its Application to the One-Pot Synthesis of Aromatics

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Catalytic dehydration of alcohols remains a challenge in organic synthesis, and olefin products (**2**) are important synthetic precursors because of their high reactivity. Platinum-group-metal-on-carbon catalysts (such as Ru/C and Pd/C) are commercially available and widely utilized as heterogeneous, green, and sustainable catalysts in various organic reactions. However, examples of their application to the catalytic dehydration of alcohols have not been reported. We developed the Ru/C-catalyzed dehydration of *tertiary*- (*tert*-) alcohols (**1**) in toluene under thermal conditions.[1] Since the dehydration of alcohols is typically carried out using acid catalysts, it is difficult to apply this method to compounds containing acid-sensitive functional groups. In contrast, the present method using Ru/C can be applied to compounds containing acid-sensitive silyl protecting groups or acetals. Ru/C also potentially exhibits oxidative activity. Therefore, a tandem reaction involving the Ru/C-catalyzed dehydration of *tert*-benzylic alcohols (**3**), a Diels-Alder reaction, and subsequent oxygen oxidation can be carried out to afford highly functionalized aromatic products (**4**).[1] Additionally, a one-pot synthesis of biaryls (**6**) from 1-arylcyclohexanols as *tert*-alcohol substrates (**5**) was successfully developed via Pd/C-catalyzed dehydration and subsequent dehydrogenation in H_2O.[1] These green and sustainable synthetic approaches based on novel heterogeneous dehydration methodologies are valuable for the construction of diverse functional materials.



References

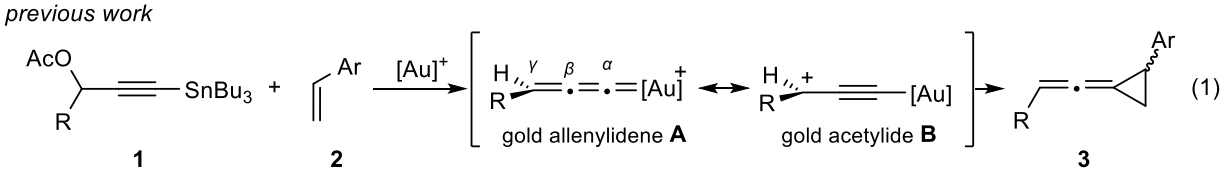
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Gold(I)-Catalyzed Allylation of Ethynyl Cyclic Carbonates with Allylsilanes

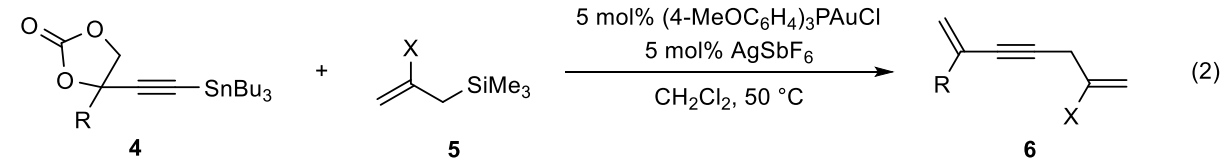
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Gold carbene-mediated catalytic reactions enable diverse transformations. While numerous catalytic reactions involving gold alkylidene and vinylidene complexes have been reported, catalytic carbon–carbon bond-forming reactions via gold allenylidene complexes remain limited.[1–3] We previously reported that the gold(I)-catalyzed reaction of tributylstannyl-substituted propargyl ester **1** with vinyl arene **2** affords vinylidenecyclopropane derivative **3** (eq 1).[2] Mechanistic studies revealed that the vinyl arene reacts at the α-carbon of gold acetylide **B**, a resonance form of gold allenylidene **A**. In this study, we report a new carbon–carbon bond-forming reaction via intermediates **A** or **B**. The reaction of ethynyl cyclic carbonate **4** with allylsilane **5** affords compound **6**, bearing both conjugated enyne and 1,4-enyne frameworks (eq 2).

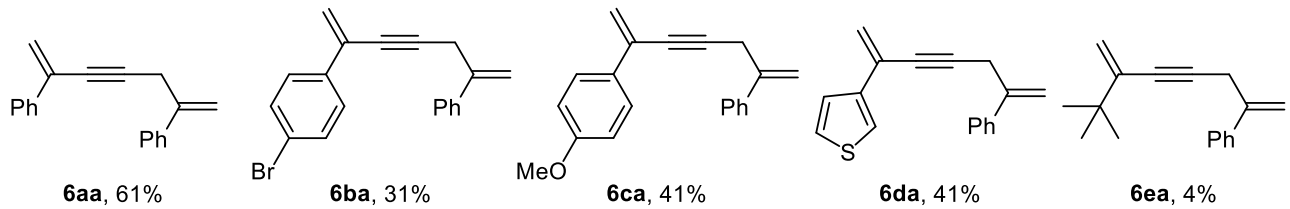
previous work



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The scope of substituent R in substrate **4** was investigated using β-phenylallyltrimethylsilane under 5 mol% (4-MeOC$_6$H$_4$)$_3$PAuCl/AgSbF$_6$. Substrates **4a–c**, bearing phenyl or electron-donating/electron-withdrawing group-substituted phenyl groups, afforded the desired products **6aa–ca** in moderate yields (Scheme 1). The thienyl-substituted substrate **4d** gave the desired product in moderate yield, whereas alkyl-substituted substrate **4e** gave only trace amounts of **6ea**. Further studies on allylsilanes and the reaction mechanism will be presented.



Scheme 1. Substrate Scope

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1P-67S

Dye-Sensitized Upconversion Nanoparticles with Enhanced Aqueous Luminescence

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Abstract

Upconversion nanoparticles (UCNPs) represent an advanced class of nanomaterials capable of converting low-energy near-infrared (NIR) light into high-energy visible light through a nonlinear optical process. However, a major limitation of UCNPs is their relatively low absorption cross-section in the NIR spectrum, which significantly limits their upconversion efficiency. Cyanine derivatives are widely utilized as organic dyes for dye-sensitized UCNPs due to their high absorption cross-section and broad absorption spectra, which significantly enhance upconversion luminescence (UCL) under NIR excitation. Additionally, surface functionalization techniques can achieve high signal-to-noise ratio, enabling exceptional spatial resolution for bio-imaging. The objective of our project is to develop a heptamethylcyanine derivative (IR61-BF) for dye-sensitized UCNPs to enhance luminescence efficiency in aqueous environments. This is accomplished by introducing a difluorobenzene moiety into the cyanine structure. Rare-earth-doped UCNPs with a core-shell structure ($NaYF_4$:YbTm@$NaYF_4$:YbNd) were synthesized via a high-temperature thermal decomposition method, in which Nd^{3+} ions function as efficient sensitizers for 808 nm NIR excitation. To further improve upconversion efficiency, the molecular structure of the NIR dye IR61 was optimized. Incorporation of a difluorinated phenyl group into the cyanine backbone significantly increased the fluorescence quantum yield and strengthened the dye-sensitization effect on UCNPs. Subsequently, the UCNPs were coated with an amphiphilic ligand (DSPE-PEG) and IR61-BF was incorporated into the hydrophobic interfacial region, resulting in a remarkable 167.1-fold enhancement of upconversion luminescence in the aqueous phase. The biocompatibility of the resulting nanoprobes was evaluated using NSC34, Neuro2a, and C6 glioma cells. Their potential for retrograde intra-neuronal delivery was validated using a microfluidic cortical neuron model, in which axonal and somatic compartments were separated by microchambers and microchannels. Neuronal imaging experiments confirmed the capability of the synthesized nanoprobes for retrograde neuronal transport, providing a controlled *in vitro* platform for studying mechanisms such as neurotrophin transport and retrograde viral infection. Overall, we demonstrated that the newly synthesized heptamethine cyanine derivative IR61-BF shows exceptional sensitization efficiency for UCNPs, particularly in aqueous solutions, through the incorporation of a difluorobenzene group.

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1P-68S

Synthetic Studies on Fluorous Mixture Synthesis of Emericellamide A and Its Stereoisomers

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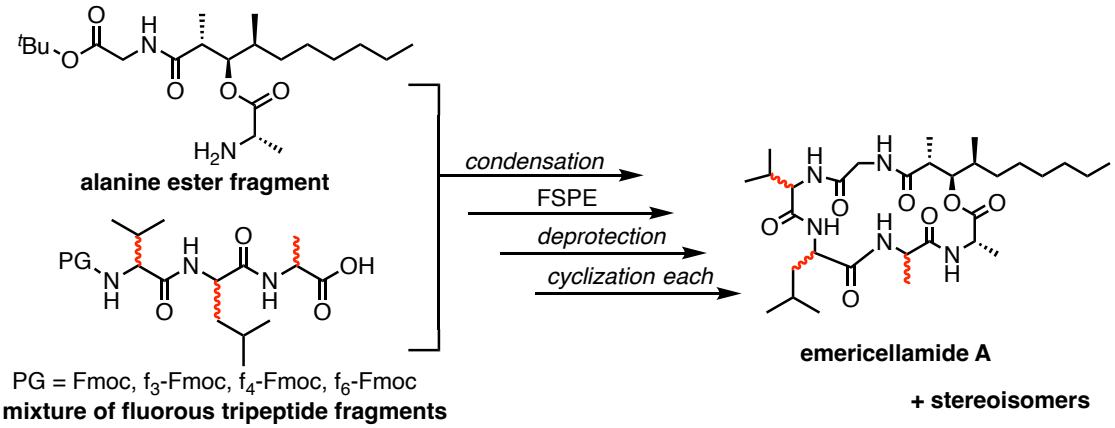
Emericellamide A is a cyclic depsipeptide isolated from marine microorganisms that exhibits antibacterial activity against methicillin-resistant *Staphylococcus aureus* and cytotoxicity against human colorectal cancer cell lines.[1] However, a comprehensive synthesis of its stereoisomers has not yet been achieved, and their biological activities remain unclear.

We aim to accomplish the simultaneous synthesis of emericellamide A and its stereoisomers by fluorous mixture synthesis (FMS) using fluorous Fmoc (f-Fmoc) reagents developed in our laboratory as encoding reagents.[2]

As part of this study, we synthesized the alanine ester fragment and a mixture of eight fluorous tripeptide fragments, both of which are key constituents of emericellamide A and its stereoisomers.

The tripeptide mixture will next be coupled with the alanine ester fragment, and the resulting products will be separated and identified based on their fluorine content by fluorous solid-phase extraction (FSPE).[3] Cyclization of each product will then enable the simultaneous synthesis of several stereoisomers.

In this presentation, we describe the synthetic studies toward emericellamide A using non-fluorous model substrates, as well as the synthesis of a mixture of fluorous tripeptides, which serve as key intermediates in FMS. This strategy provides an efficient approach to access stereoisomers in a single synthetic sequence.



Strategy of Fluorous Mixture Synthesis of Emericellamide A and Its Stereoisomers

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Concise Synthesis of *cis*-Xanthophylls and Investigation of Their Photoisomerization

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Xanthophylls, including astaxanthin (AST) and canthaxanthin (CNT), exhibit high reactive oxygen species (ROS) scavenging activity. In particular, AST has been reported to possess more than 54-fold higher ROS scavenging activity than β-carotene,[1] highlighting its potential in pharmaceutical applications. However, all-*trans* AST and CNT, which contain extended polyene structures, are poorly soluble and thus suffer from low bioavailability. Recently, *cis*-xanthophylls, in which part of the polyene chain adopts a *cis* geometry, have attracted increasing attention. These compounds exhibit 2–4-fold higher ROS scavenging activity than their all-*trans* counterparts. Moreover, the addition of *cis*-isomers to all-*trans* xanthophyll, significantly improves solubility and enhances intestinal absorption.[2] Despite these promising properties, *cis*-xanthophylls are present only in trace amounts in nature. Accordingly, we aimed to develop a highly selective and general synthetic method for *cis*-xanthophylls and to elucidate their structure–function relationships.

A major challenge in accessing *cis*-xanthophylls is the construction of trisubstituted double bonds with *cis* selectivity. To address this issue, we designed a synthetic route featuring a *cis*-selective Julia–Kocienski reaction[3] as a key step and achieved the total synthesis of 9,9'-*cis*-CNT (**1**) and 9,9'-*cis*-AST (**2**), which are extremely difficult to obtain from natural sources.[4] Furthermore, we discovered a selective photoisomerization that converts **1** and **2** into the corresponding 9-*cis*-CNT (**3**) and 9-*cis*-AST (**4**) (Scheme 1). In this presentation, we report the practical synthesis of 9,9'-*cis*- and 9-*cis*-xanthophylls and their key intermediates, along with a detailed investigation of their photoisomerization mechanism.

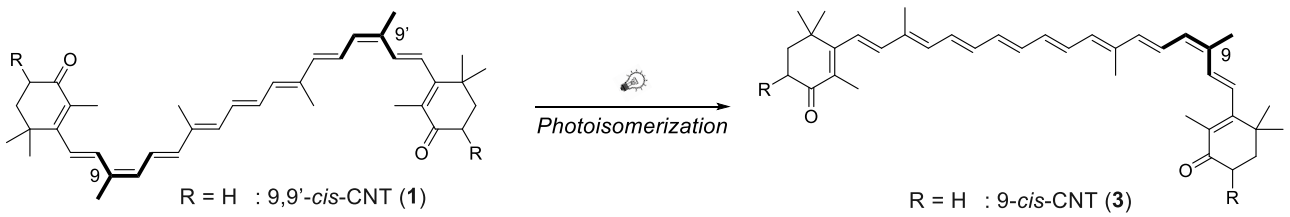


Figure 1. Structures of 9-*cis*-xantphylls

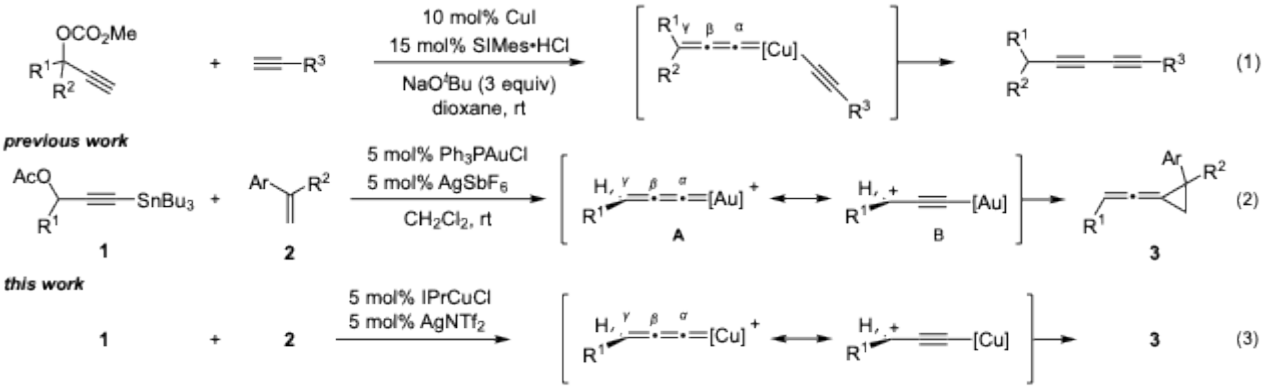
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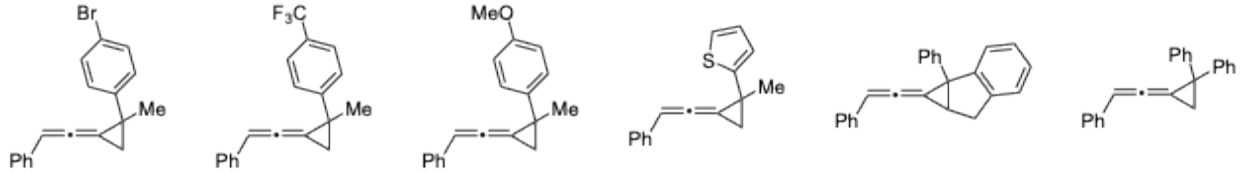
Synthesis of Vinylidenecyclopropanes via Copper-Catalyzed Cyclopropanation of Vinyl Arenes

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Catalytic reactions involving copper allenylidene species, or its resonance form, copper acetylide species, have been extensively studied,[1] and most studies have focused on propargylic substitution. In contrast, catalytic C–C bond-forming reactions at the α-position of copper allenylidene species remain limited (eqn 1).[2] We previously reported that the gold(I)-catalyzed cyclopropanation of vinyl arene **2** with tributylstannyl-substituted propargyl ester **1** afforded vinylidenecyclopropane derivative **3** (eqn 2).[3] Mechanistic studies revealed that the reaction proceeds via gold acetylide species **B**, a resonance form of gold allenylidene species **A**. Herein, we report a copper-catalyzed cyclopropanation of **2** proceeding via copper allenylidene species, or their resonance forms, copper acetylide species, to afford **3** with a broader substrate scope than the corresponding gold-catalyzed reaction (eqn 3).



The scope of **2** was investigated using **1** in the presence of IPrCuCl/AgNTf$_2$.Vinyl arenes bearing either electron-withdrawing or electron-donating substituents at the para-position of the phenyl ring, as well as heteroaryl-substituted substrates, underwent the cyclopropanation reaction to afford the corresponding products **3aa**–**ad** in good yields. In addition, the reactions of 3-phenylindene and 1,1-diphenylethylene proceeded smoothly to furnish products **3ae** and **3af** in high yields. Further studies on the substrate scope of **1** and the reaction mechanism will also be presented.



Scheme 1. Vinyl Arene Scope

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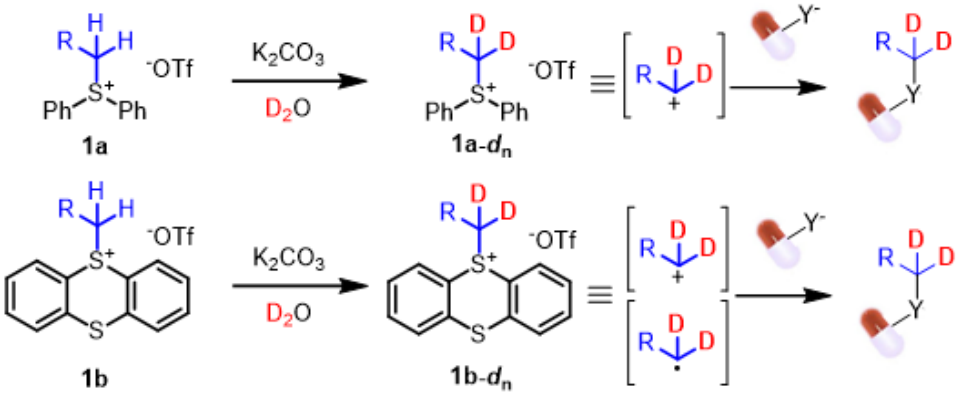
Deuterated Alkylation Reagents Based on Sulfonium Salts as Cation and Radical Sources

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Deuterated drugs (heavy drugs) have recently attracted considerable attention as a new modality in small-molecule therapeutics, because replacing C–H bonds with more stable C–D bonds at metabolically labile positions can improve pharmacokinetic properties. However, the limited diversity of deuteration sites in approved deuterated pharmaceuticals remains a challenge in drug discovery. This is because there is still a lack of inexpensive, versatile, and site-selective approaches for the flexible introduction of deuterium.[1] Therefore, the development of inexpensive and versatile deuteration is highly desirable.

Recently, we have developed d_n (deuterated)-alkylated sulfonium salts (**1a-*d*$_n$**, **1b-*d*$_n$**), which were easily prepared by site-selective deuteration (H/D exchange reaction) with D_2O of the corresponding alkyl sulfonium salts (**1a**, **1b**), as deuterated alkylation reagents. [2),3)] These reagents act as electrophilic d_n-alkylating reagents (cation sources) and provide the deuterated products with high D contents and high regioselectivities. Additionally, **1b-*d*$_n$** served as radical sources under photo-induced reaction conditions using Ir photocatalyst or bases.

We successfully established a novel concept to diversify deuterium drug discovery using d_n-alkylation reagents (**1a-*d*$_n$**, **1b-*d*$_n$**) with excellent D contents and perfect site-selectivity, which were easily prepared by the H/D exchange reaction of the corresponding hydrogen form using D_2O. This novel synthesis method is expected to contribute to the discovery of deuterium drugs in the future.



Scheme 1. Deuterated sulfonium salts as cation and radical sources.

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1P- 72S

Development of Crystalline Dihaloacetylene and Trihaloethylene Equivalents

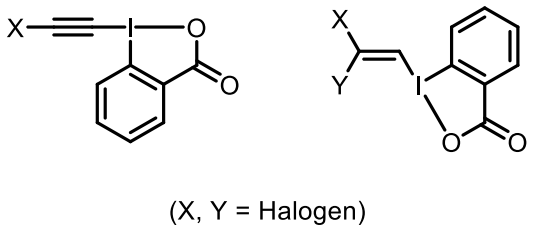
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【Background/Objective】

Hypervalent iodine compounds have become indispensable reagents in organic synthesis because of their unique reactivity arising from highly polarized 3-center-4-electron bonds. Our group has previously developed a variety of ethynylbenziodoxolones (EBXs) and demonstrated their utility in the ethynylation and diynylation of sulfonamides[1]. Although many EBX derivatives bearing diverse substituents have been reported, β-halogenated EBXs have remained largely unexplored. Because dihaloacetylenes are generally highly volatile and difficult to handle, stable β-halogenated EBXs could serve as practical dihaloacetylene equivalents. In this study, we investigated the synthesis of EBXs bearing a halogen atom at the β-position and their conversion into β-dihalogenated vinylbenziodoxolones (VBXs).

【Methods/Results】

β-Halogenated EBXs and their precursors, β-haloiodonium salts, were successfully synthesized as stable crystalline compounds. Treatment of these species with pyridine hydrohalide salts afforded the corresponding dihalogenated VBXs. In particular, the use of pyridine hydrochloride or pyridine hydrobromide enabled stereoselective access to chloro- and bromo-substituted dihalogenated VBXs. The structure of (*E*)-Br-Cl-VBX was unambiguously confirmed by X-ray crystallographic analysis.



(X, Y = Halogen)

Scheme 1. Newly synthesized β-halogenated EBXs and dihalogenated VBXs

References

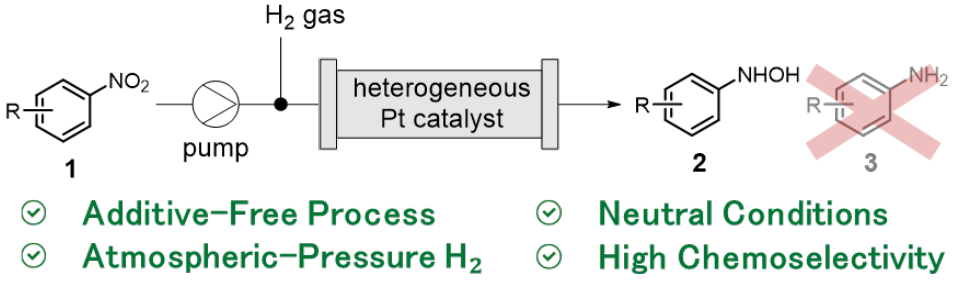
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Continuous-Flow Semi-Hydrogenation of Nitroarenes to *N*-Aryl Hydroxylamines

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N-Aryl hydroxylamines are valuable intermediates in the synthesis of pharmaceuticals, agrochemicals, and functional materials. However, their selective synthesis is challenging because they are intermediates in the reduction of nitro compounds and are readily over-reduced to anilines or converted into azo and azoxy byproducts via nitroso intermediates. Conventional stepwise methods often require stoichiometric reductants, while reported Pt-catalyzed hydrogenations frequently rely on additives such as DMSO and amine bases or on high-pressure hydrogen conditions, thereby complicating workup, hindering solvent recovery, and making the process less straightforward.[1–3] To address these limitations, we investigated a continuous-flow partial reduction process using a heterogeneous Pt catalyst. Catalyst cartridges in flow systems allow precise control of residence time, temperature, and gas–liquid–solid contact, and are therefore advantageous for suppressing over-reduction in consecutive hydrogenation processes.

By controlling the activity of a heterogeneous Pt catalyst solely through reaction parameters, we established an additive-free continuous-flow synthesis of *N*-aryl hydroxylamines. When solutions of nitrobenzene derivatives **1** were passed together with hydrogen gas through a Pt-packed catalyst cartridge, the corresponding hydroxylamines **2** were obtained in high yields, while over-reduced anilines **3** were formed only in trace amounts. Under the optimized conditions, the turnover frequency (TOF) exceeded 25 h^{-1}, and the reaction proceeded stably under atmospheric pressure and neutral conditions. Because this method does not require DMSO or amine additives, it may simplify downstream processing, lower purification costs, and avoid risks associated with additive residues. In addition, reduced waste generation and fewer separation steps enhance its utility from a green chemistry perspective. Overall, this method provides a promising continuous-flow platform for the on-demand and stable supply of valuable yet unstable *N*-aryl hydroxylamines.



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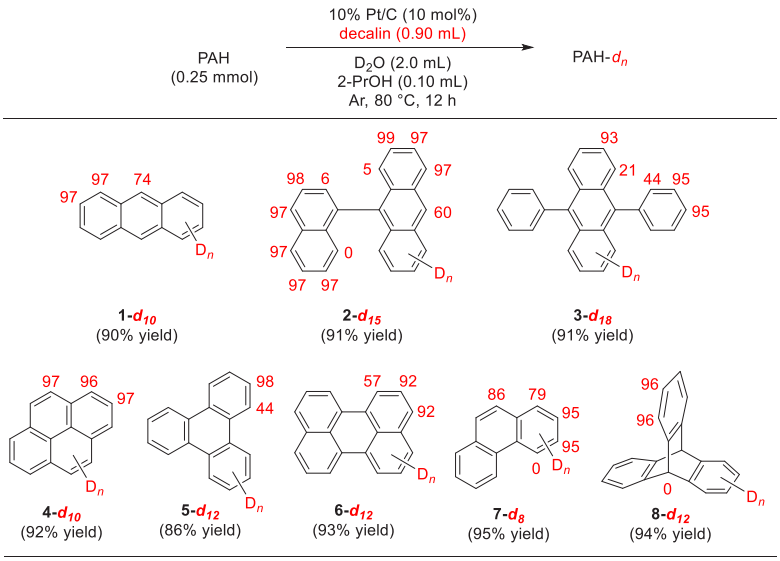
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Pt/C-Catalyzed Deuteration of Polycyclic Aromatic Hydrocarbons with Suppressed Ring Hydrogenation

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Polycyclic aromatic hydrocarbons (PAHs) are important π-conjugated scaffolds widely used in organic electronic materials. While replacing C–H bonds with C–D bonds is an effective strategy to enhance the photophysical properties and operational stability of these materials, achieving high deuterium incorporation in PAHs that are prone to hydrogenation without inducing concomitant ring hydrogenation remains a significant challenge.

Herein, we report a practical and highly selective Pt/C-catalyzed hydrogen–deuterium (H–D) exchange protocol for PAHs. The reaction utilizes inexpensive deuterium oxide (D_2O) as the deuterium source in the presence of 2-propanol under mild conditions. Through systematic additive screening, decalin was identified as a key additive. The use of decalin effectively suppressed undesired partial hydrogenation of the aromatic core while facilitating efficient H–D exchange. Under the optimized conditions (10% Pt/C, 80 °C, 12 h), anthracene (**1**) underwent H–D exchange to afford **1**-d_{10} with up to 97% deuterium incorporation. Furthermore, this method demonstrated broad substrate scope: a range of fused PAHs, including 9-(1-naphthyl)anthracene (**2**-d_{15}), 9,10-diphenylanthracene (**3**-d_{10}), pyrene (**4**-d_{10}), triphenylene (**5**-d_{12}), perylene (**6**-d_{12}), phenanthrene (**7**-d_{10}), and triptycene (**8**-d_{12}), were successfully converted into their deuterated analogues in good to excellent isolated yields with negligible ring hydrogenation. This operationally simple approach provides practical access to highly deuterated PAHs, facilitating future materials-oriented investigations and isotopic-labeling applications.



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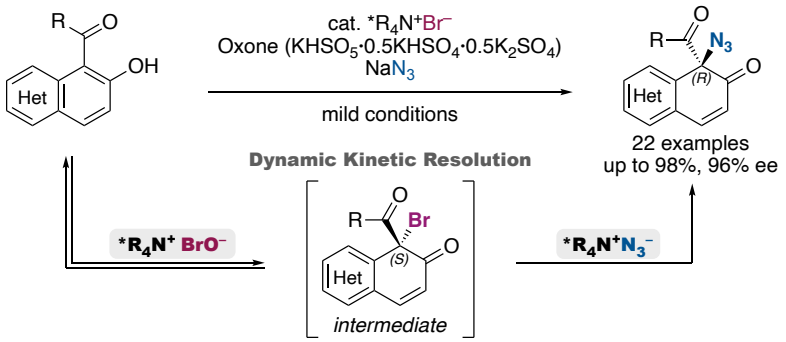
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Chiral Hypobromite-catalyzed Enantioselective Dearomative Azidation of (Hetero)arenols

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Dearomatization of arenols is a powerful strategy for the rapid construction of complex three-dimensional molecular frameworks bearing quaternary stereocenters from readily available planar aromatic precursors. Among the resulting products, nitrogen-containing cyclohexadienone derivatives are particularly attractive because of their relevance to medicinally important molecules. Conventional enantioselective dearomative amination methods typically rely on azodicarboxylates, which suffer from poor atom economy due to bulky protecting groups and require harsh reductive conditions for N–N bond cleavage. To address these limitations, we focused on the azido group as a versatile single nitrogen unit equivalent with superior atom economy and broad synthetic utility.

Despite its synthetic potential, enantioselective dearomative azidation remains underdeveloped and has been limited to a single example requiring transition-metal catalysis in combination with preprepared, potentially explosive hypervalent iodine reagents, with the substrate scope restricted to simple 2-naphthols.[1] In contrast, we previously reported an oxidative dearomative azidation of electron-rich arenols using hypoiodite catalysts generated *in situ* from the corresponding quaternary ammonium iodides with hydrogen peroxide as an oxidant.[2] Building on this work, we herein report a more effective catalytic system based on ammonium bromides[3] in place of iodides, using oxone as an oxidant and NaN_3 as an inexpensive and relatively safe azide source. This hypobromite catalysis enables the dearomative azidation of electron-deficient arenols and heteroarenols, which are expected to be challenging substrates for the previously reported transition metal catalyzed method.[1] By employing a chiral quaternary ammonium bromide catalyst, we achieved the first organocatalytic highly enantioselective dearomative azidation of (hetero)arenols. Mechanistic studies suggest that the reaction proceeds through dynamic kinetic resolution of a dearomatized brominated intermediate. In addition, a slow addition protocol improved the reaction efficiency, resulting in shorter reaction times and higher enantioselectivity.[4]



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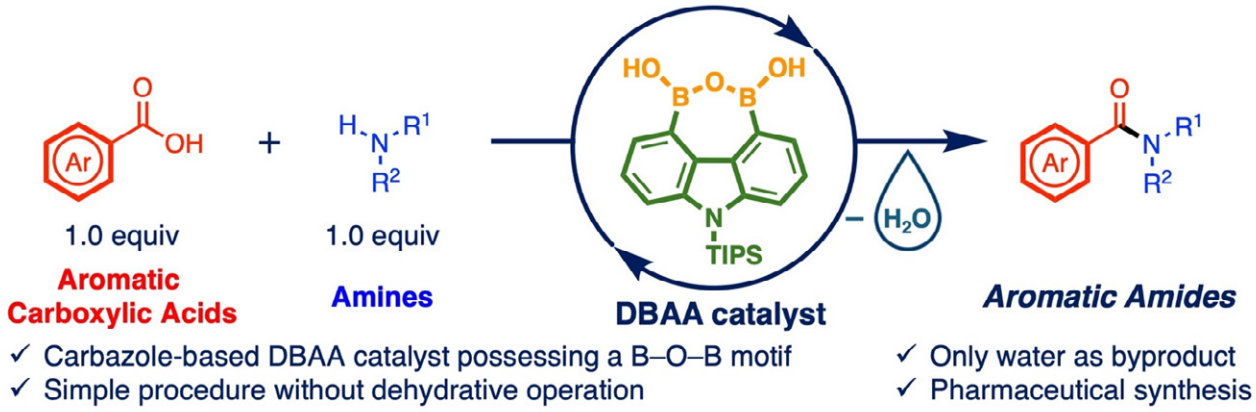
Dehydrative Amidation of Aromatic Carboxylic Acids with Amines Catalyzed by Carbazole-Based Diboronic Acid Anhydride

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Amides are important chemical linkages found in many natural products and pharmaceuticals. Therefore, the development of efficient synthetic methodologies for amide bond formation is essential. [1] Conventional methods for amide synthesis rely on the condensation reaction between carboxylic acids with amines using condensation reagents. However, these protocols require stoichiometric amounts of reagents, resulting in tedious workup and purification procedures. In contrast, the most ideal methodology is catalytic dehydrative amidation, in which water is generated as the only byproduct.

We have previously reported diboronic acid anhydride (DBAA),[1] characterized by a B–O–B motif, as an efficient catalyst for the direct dehydrative amidation of *α*-/*β*-hydroxycarboxylic acids[2] or *β*-hydroxy-*α*-amino acids.[3] Notably, this procedure does not require additional dehydrative operations, such as the adding of dehydrating agents.

In this work, we successfully developed a dehydrative amidation of less-reactive aromatic carboxylic acids with amines utilizing carbazole-based DBAA without rigorous dehydrative operations. (Scheme 1). Furthermore, this catalytic amidation is applicable to the efficient synthesis of pharmaceutically important amide-containing compounds.



Scheme 1. Catalytic Dehydrative Amidation of Aromatic Carboxylic Acids with Amines

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Continuous-Flow Pd/C-Catalyzed Conversion of Azides to Nitriles

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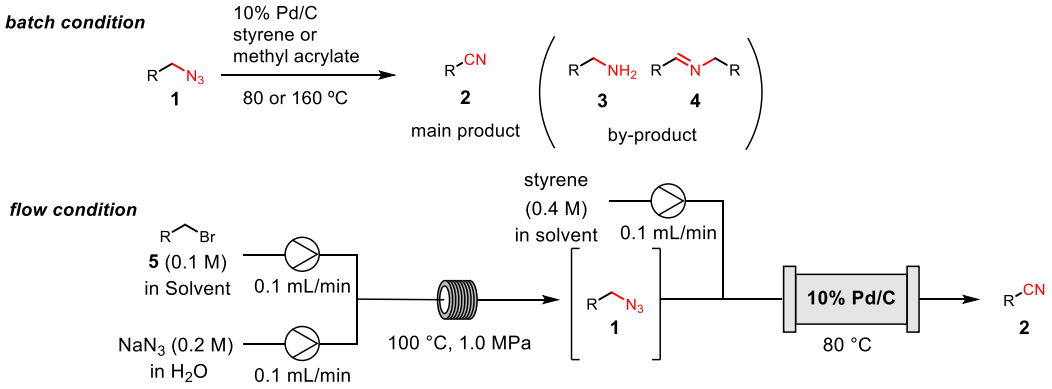
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Nitriles are versatile synthetic precursors and valuable structural motifs in pharmaceuticals and other bioactive molecules. However, classical nitrile synthesis using metal cyanides poses significant concerns regarding toxicity and handling, thereby creating a demand for alternative methods.[1)] We discovered that, under Pd/C catalysis, organic azides can be converted into nitriles via concomitant denitrogenation and dehydrogenation. Based on this finding, we developed this methodology and extended it to flow chemistry.

Initially, under batch conditions, heating substrate **1** in the presence of 10% Pd/C afforded nitrile **2**, along with byproducts such as amine **3** and imine **4**. The addition of hydrogen acceptors (e.g., methyl acrylate and styrene) suppressed these side reactions and improved the yield of the desired nitrile. In terms of substrate scope, both benzylic and aliphatic azides were efficiently converted into the corresponding nitriles in good yields, with good functional-group tolerance. The reaction was translated into a continuous-flow system using a 10% Pd/C-packed catalyst cartridge, integrating the in-line azidation of bromides with the subsequent nitrile-forming step. This setup minimizes the accumulation of potentially explosive azide intermediates, thereby enhancing process safety. The method proceeds under mild, neutral conditions and offers good scalability and operational safety, making it a useful cyanide-free approach to nitrile synthesis.



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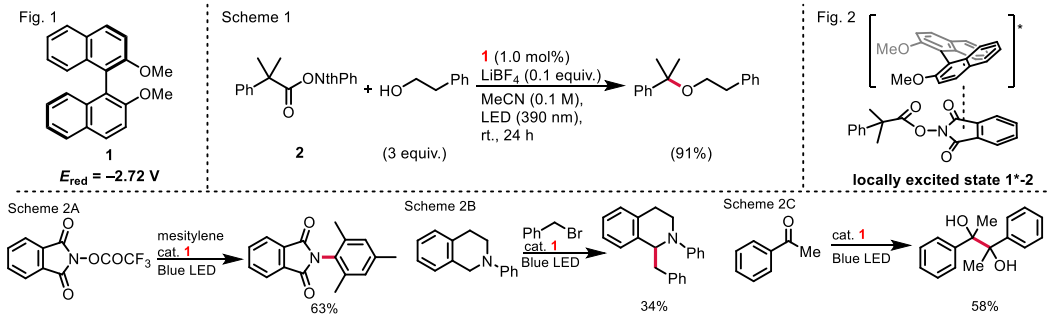
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Bismethoxybinaphthyl as an Organic Photoredox Catalyst: Functions and Applications

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The growing interest in photoredox catalysis attracted during organic synthesis, has led to the development of a wide range of transformations. In addition to ruthenium and iridium complexes, organic catalysts such as acridinium salts have gained increasing interest because of that their high redox potential under photoirradiation In this study, methoxyarenes were found to act as photoredox catalysts. Detailed investigations revealed that bismethoxybinaphthyl **1** (Fig. 1) functions as a catalyst with strong reducing power, the details of this study are reported herein.[1)]

In a photoredox-reaction[2)] where phthalimide ester **2** served as a radical precursor for alcohol condensation, irradiation at 390 nm with **1** as a catalyst afforded the desired ether in 91% yield (Scheme 1). Spectroscopic investigations revealed that electron transfer proceeded via a locally excited state**1*-2** generated by **1*** and **2** (Fig. 2). Further, the reduction potential of **1*** was estimated to be –2.72 V (vs. SCE), confirming that it possesses stronger reducing power than that using typical photoredox catalysts. Subsequently, various photoredox reactions were performed using **1** as the catalyst, including C–H imidation (Scheme 2A)[3)], C–H benzylation (Scheme 2B)[4)], and coupling by the reduction of carbonyl groups (Scheme 2C)[5)].



References

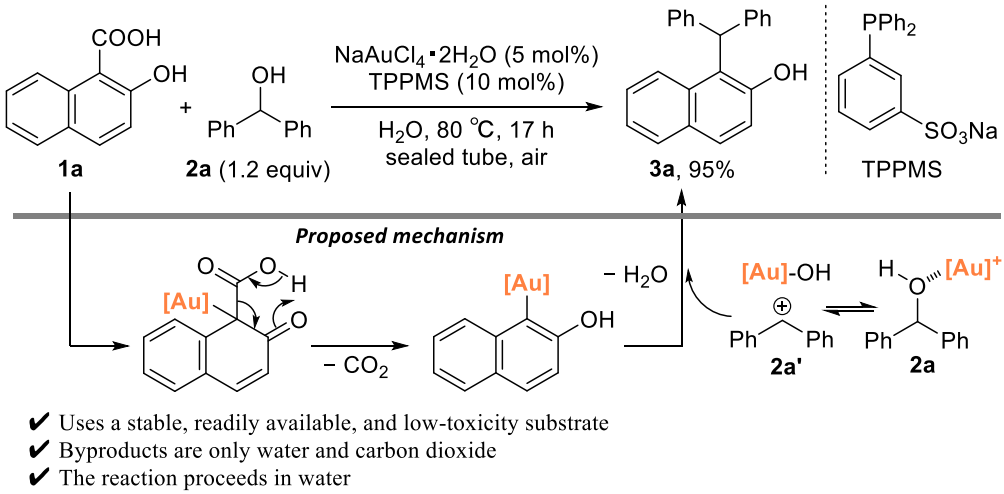
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Gold(III)-catalyzed decarboxylative/dehydrative coupling of 2-hydroxy-1-naphthoic acid in water

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Transition metal–catalyzed decarboxylative transformations provide a powerful methodology for C–C bond formation. To date, numerous decarboxylative couplings of alkyl carboxylic acids with aryl halides involving the elimination of carbon dioxide have been reported. Consequently, carboxylic acids are increasingly recognized as atom-economical alternatives to traditional coupling partners such as organometallic compounds in synthetic organic chemistry. Despite these advances, there are very few examples of decarboxylative/dehydrative coupling reactions in which carboxylic acids and alcohols react directly.[1,2)]

Herein, we present a strategy for a catalytic decarboxylative and dehydrative coupling reaction in water. The combination of a gold(III) catalyst and a water-soluble TPPMS ligand demonstrates high catalytic activity toward the direct coupling of 2-hydroxy-1-naphthoic acid, a salicylic acid derivative, with benzhydrols, enabling straightforward and rapid access to the corresponding benzylated products. Notably, this tandem reaction proceeds efficiently in water and generates only water and carbon dioxide as byproducts.



✔ Uses a stable, readily available, and low-toxicity substrate
✔ Byproducts are only water and carbon dioxide
✔ The reaction proceeds in water

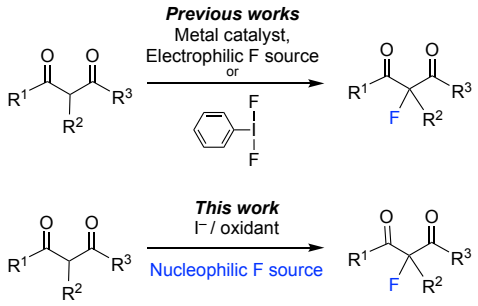
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Oxidative Fluorination of β-Ketoamides using Guanidinium Hypoiodite Catalysts

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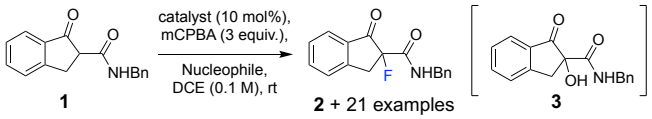
The development of organofluorine compounds has exerted a transformative influence on various fields. Despite this progress, the construction of quaternary carbon centers bearing a fluorine atom remains a formidable challenge in organic synthesis. In addition, conventional mono-fluorination reactions predominantly rely on electrophilic fluorinating reagents in the presence of metal catalysts or metal-free hypervalent aryl iodine reagents (Scheme).[1)] The use of aryl iodides introduces extra atoms that are often discarded as waste, reducing the atom economy for this reaction. Our group has previously reported oxidative coupling reactions with various nucleophiles and substrates mediated by hypoiodite (IO^-), generated in situ from iodide anion and alkyl preoxide.[2)] Building on these reports, we have carried out the oxidative fluorination reaction of 1,3-dicarbonyl compounds with nucleophilic fluorinating reagents mediated by hypoiodite.



Scheme. Previous and the present work

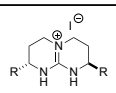
The oxidative fluorination of β-ketoamide **1** was investigated (Table). When NaF or $Et_3N{\cdot}3HF$ as fluoride sources were used with *m*CPBA as an oxidant in the presence of guanidinium catalyst **4**, only the hydroxylated side-product **3** was obtained (entries 1-2). In contrast, when HF·Py was employed as the fluoride source, the desired product **2** was obtained in 70% NMR yields (entry 3). Further optimization of the reaction conditions led to a significant improvement. Under the conditions with 100 equivalents of HF·Py in the presence of guanidinium catalyst **5**, the desired fluorinated product **2** was isolated in 92% yield (entry 5). Substrate scope and mechanistic suggestions will be detailed in my presentation.

Table. Investigation of oxidative fluorination of **1**



Entry	Nucleophile (eq.)	Cat.	Result	
			Yield (%)	2:3
1	NaF (35)	**4**	**3**	
2	$Et_3N{\cdot}3HF$ (35 eq. of HF)	**4**	**1, 3**	
3	HF·Py (35 eq. of HF)	**4**	(70%)[b]	5.8:1
4	HF·Py (100 eq. of HF)	**4**	68%[a] (72%)[b]	5.8:1
5	HF·Py (100 eq. of HF)	**5**	92%[a]	13:1

[a] isolated yields, [b] ^{19}F NMR yields



4 : R = H
5 : R = Bn

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Site-Selective Hydroxylation of the CD-Ring of Vitamin D Metabolites by P450 BM3 Variants

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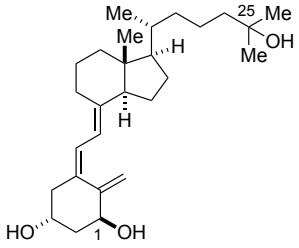
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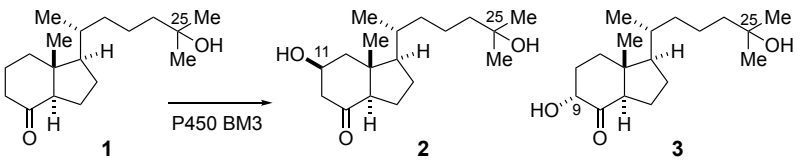
Vitamin D is metabolized in vivo to 1α,25-dihydroxyvitamin D (1,25D), which binds to the vitamin D receptor (VDR) and exhibits diverse biological activities related to bone, muscle, and immune function. In recent years, the other metabolites of 1,25D also have been found to display unique biological activities, and the identification of their target proteins has become an important issue for elucidating their mechanisms of action.

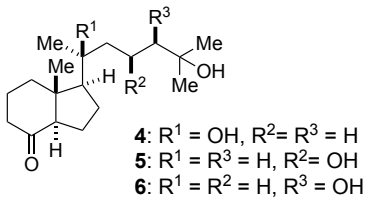


Structure of 1,25 D

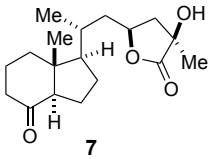
In this study, with the aim of readily generating chemical probes for mechanistic studies of these metabolites, we investigated the direct hydroxylation-based modification of the CD-ring of representative vitamin D metabolites using cytochrome P450 enzymes.

First, compound **1** was subjected to screening with wild-type (WT) CYP102A1 (P450 BM3) and six of its variants. As a result, the KSA-15 variant[1)] promoted hydroxylation selectively at the 11β-position, affording the hydroxylated **2** in 67% yield. In contrast, the FL#62 variant[2)] catalyzed selective hydroxylation at the 9α-position, providing the product **3** in 93% yield. We then extended this study to the CD-rings of other vitamin D metabolites **4**–**7**. In all cases examined, KSA-15 selectively hydroxylated the 11β-position, whereas FL#62 selectively hydroxylated the 9α-position in 40–87% yields.





4: R^1 = OH, R^2= R^3 = H
5: R^1 = R^3 = H, R^2= OH
6: R^1 = R^2 = H, R^3 = OH



7

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A Universal Resin Catalyst for the Selective Monoacylation of Structurally Diverse Diols

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The development of catalysts for the monoacylation of diols that exhibit both high chemoselectivity and broad substrate generality remains a formidable challenge in organic synthesis.[1,2] To address this challenge, we sought to exploit an underexplored feature of random polymers. Specifically, we designed a polymer catalyst incorporating 4-aminopyridine-based catalytic units (CAT) and amide-based functional groups (FG) capable of hydrogen bonding interactions with hydroxyl groups (Figure 1A). We hypothesized that the hydrogen bonding interaction would direct one hydroxyl group of the diol toward the acylpyridinium species, thereby promoting highly selective monoacylation (Figure 1B). Furthermore, the random distribution of these functional groups on the polymer surface—a hallmark of radical polymerization—enables the catalyst to accommodate structurally diverse substrates. Indeed, our catalyst exhibited broad substrate generality and provided the monoacylated products in high yields.[3] To demonstrate its practical utility, the catalyst was implemented in a continuous-flow system using a column packed with a catalyst-Celite mixture (Figure 1C). This presentation will detail the reaction optimization, substrate scope, and mechanistic insights.

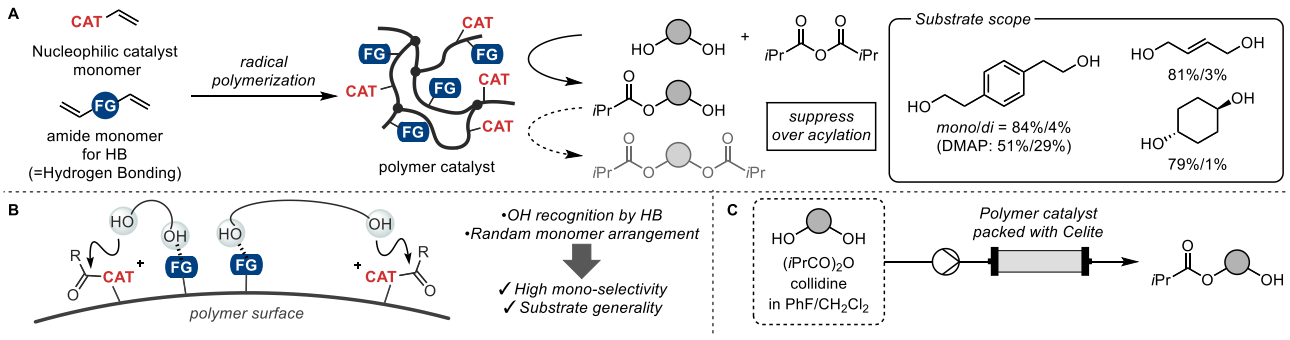


Figure 1. (A) Our strategy exploiting a random heteropolymer. (B) The working hypothesis for polymer catalysis with broad substrate adaptability. (C) Continuous flow process with our polymer catalyst.

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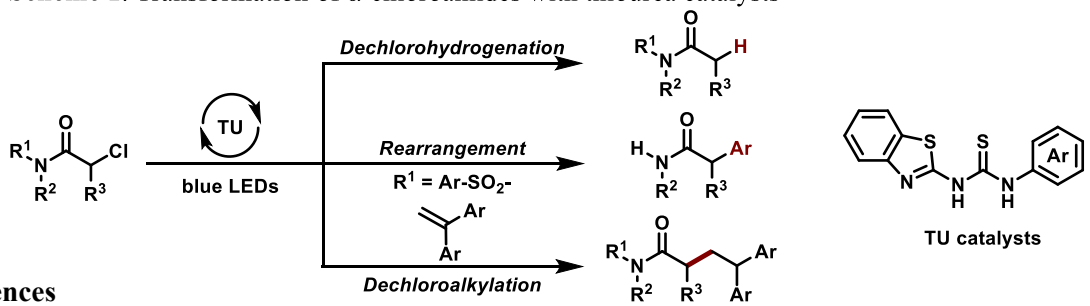
Development of Novel Thiourea Photocatalysts and Its Application to Reductive Transformations of α-Chloroamides

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Since photoreactions enable unique transformations that are difficult to achieve under thermal reaction conditions and have become readily accessible with the development of photoreactors, photo-catalytic radical reactions have regained significant attentions in organic synthesis. Accordingly, new photocatalysts, including organo-photocatalysts capable of utilizing visible light, have been developed. During our research project on photocatalysis of thiobenzoic acid, we hypothesized that the thiocarbonyl unit is an essential structural element for its photocatalytic activity. In this context, we anticipated that thiourea, which is readily tunable and capable of capturing and activating substrates through hydrogen bonding owing to the photoacid function, could act as a photoredox catalyst.

To confirm our working hypothesis, we initially examined the dechlorination of α-chloroamides using commercially available Schreiner's thiourea under ultra-violet irradiation. Although the catalytic activity was modest, thiourea was found to function as a photoredox catalyst. Encouraged by the preliminary result, we decided to develop new thiourea-based photocatalysts, which can act under visible-light irradiation. As a result of screening of thioureas, the thiourea bearing the benzothiazole unit was found to absorb visible-light and to catalyze the dechlorination of α-chloroamides in good to high yields (Scheme 1). In addition, we found that the thiourea photocatalyst promotes the reductive C–C bond formation of α-chloroamide with diarylethenes, as well as the reductive rearrangement of *N*-alkyl-*N*-arylsulfonyl-α-chloroamides. In this presentation, we will discuss the details regarding the structure and reactivity of thiourea photocatalysts, along with the above-mentioned photoreactions.

Scheme 1. Transformation of α-chloroamides with thiourea catalysts



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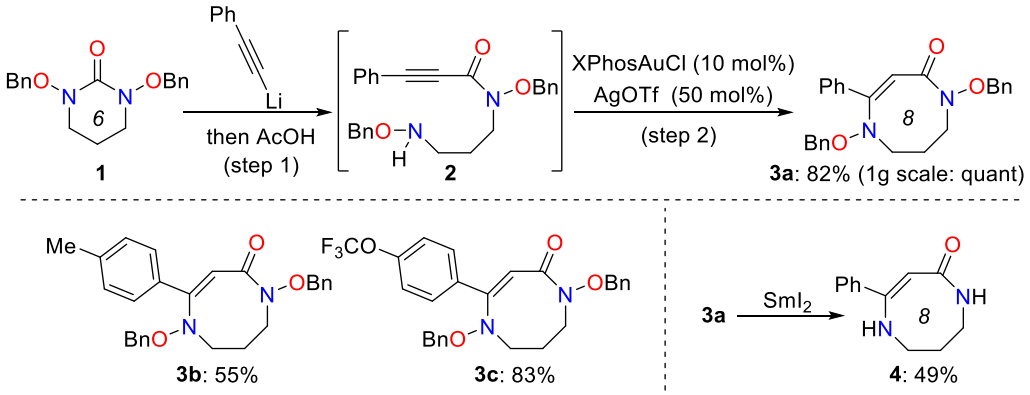
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Synthesis of 1,5-diazocinone through sequential nucleophilic addition/skeletal remodelling of cyclic ureas

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1,5-Diazocinones are important heterocyclic skeletons found in a variety of bioactive compounds. Numerous synthetic methods for benzene fused 1,5-diazocinones have been reported, while methods for non-fused analogues remain limited. Therefore, the development of new synthetic approaches to non-fused 1,5-diazocinones is highly desirable. Recently, we have focused on *N*-alkoxylactams bearing a halogen at the α-position and have developed sequential reactions triggered by nucleophilic addition to the carbonyl group.[1,2] To extend the synthetic utility of our lactam chemistry, we designed *N*-alkoxycyclic urea. We envisioned that the reaction of a cyclic urea with an alkynyl organometallic reagent followed by treatment with a gold(I) catalyst would enable a formal ring-expansion reaction, providing to the synthesis of 1,5-diazocinone.

The reaction of cyclic urea **1** with phenylethynyl lithium followed by quenching with acetic acid to afford intermediate **2** via nucleophilic addition. Subsequent treatment with a catalytic amount of XPhosAuCl in the presence of AgOTf provided 1,5-diazocinone **3a** in 82% yield. Next, we investigated arylethynyl lithium bearing electron-donating or electron-withdrawing groups on the benzene ring. As a result, the corresponding products **3b** and **3c** were obtained. Furthermore, 1,5-diazocinone **3a** can be converted to **4** by the cleavage of N-O bond. Further substrate scope and other transformations will be presented.



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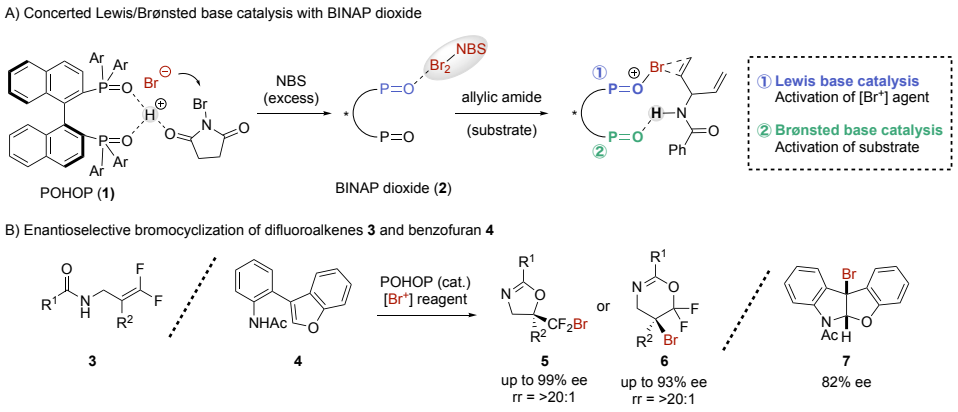
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Enantioselective Bromocyclization of Difluoroalkenes and Benzofuran Enabled by Concerted Lewis/Brønsted Base Catalysis with Chiral Bisphosiphine Oxide

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We recently revealed that a chiral proton-bridged bisphosphine oxide complex, POHOP **1**, is a key catalyst precursor for the asymmetric bromocyclization of allylic amides.[1] It reacts with *N*-bromosuccinimide (NBS) to afford BINAP dioxide (**2**) and molecular bromine (Br_2) simultaneously. The resulting **2** serves as a bifunctional catalyst, acting as both a Lewis base to form a chiral brominating agent, and also as a Brønsted base for activation of the substrate (Fig A).

Herein, we present an enantioselective bromocyclization of difluoroalkenes **3**[2] and benzofuran **4** utilizing the above-mentioned catalytic system. Owing to the simultaneous activation of both the brominating reagent and substrate, the cyclization of less reactive **3** and **4** undergoes smoothly even at low temperature. Notably, the solvent, catalyst structure, and brominating reagent greatly affect the enantioselectivity and, in the case of **3**, the regioselectivity. Consequently, highly enantioenriched oxazolines **5** and oxazines **6** bearing a tetrasubstituted difluoromethylated stereocenter,[3] as well as benzofuroindoline **7**, a unique motif found in diazonamide A and azonazine, were obtained (Fig B). Furthermore, a gram-scale synthesis was demonstrated with 1 mol % of the catalyst, highlighting the practical utility of the present catalysis.



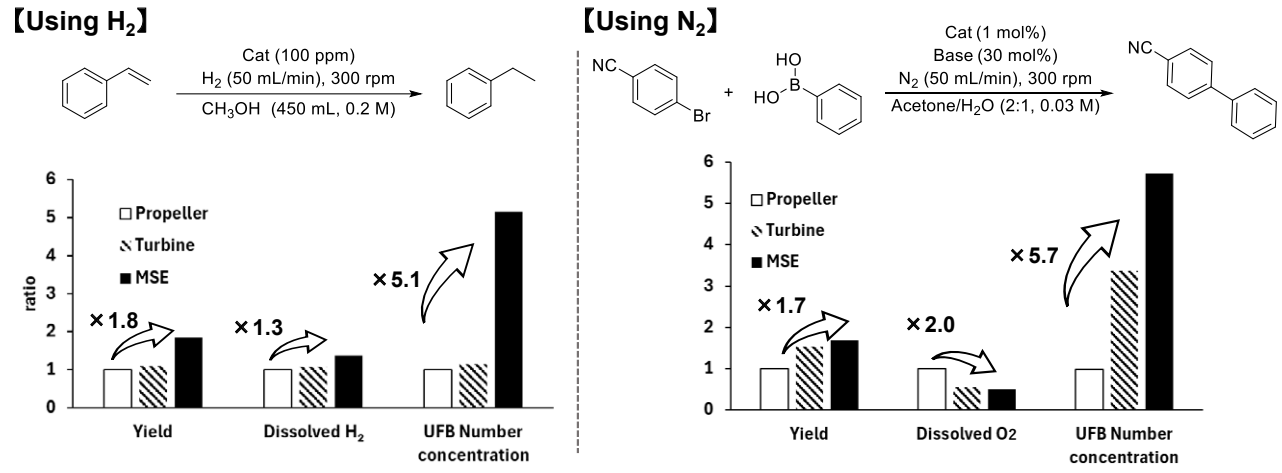
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Fine Bubble Organic Chemistry: Multi-Stacked Mixer for Gas-Involved Organic Reactions and Degassing

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In gas-involved reactions in organic synthesis, such as hydrogenation and degassing, inefficient gas–liquid mass transfer is a major factor limiting reaction rate and yield. Conventional fine bubble (FB) generation methods, including porous membrane, and pressurized dissolution/depressurization methods, have mainly been applied to flow systems, and their application to ambient-pressure batch reaction systems remains challenging.[1)] In this study, we employed a multi-stacked element (MSE) impeller in ambient-pressure batch systems to continuously generate FBs with diameters below 100 μm directly in the reactor, thereby enhancing both gas dissolution and degassing (removal of dissolved oxygen). Quantitative analysis of dissolved hydrogen concentration and the concentration of ultrafine bubbles (UFBs) generated during hydrogen supply revealed that the MSE impeller increased the dissolved hydrogen concentration by 1.3-fold and the UFB number concentration by 5.1-fold compared with conventional impellers. In the hydrogenation of styrene, the MSE impeller improved reaction efficiency by 1.8-fold. Since dissolved hydrogen concentration and yield did not show a simple proportional relationship, bubble generation itself was suggested to contribute to enhanced reactivity. In the Suzuki–Miyaura cross-coupling reaction requiring degassing, the MSE impeller also increased the yield by 1.7-fold. These results demonstrate that FB-assisted gas supply and degassing are effective under ambient-pressure batch conditions.



Scheme 1. Enhanced efficiency in hydrogenation and Suzuki–Miyaura coupling

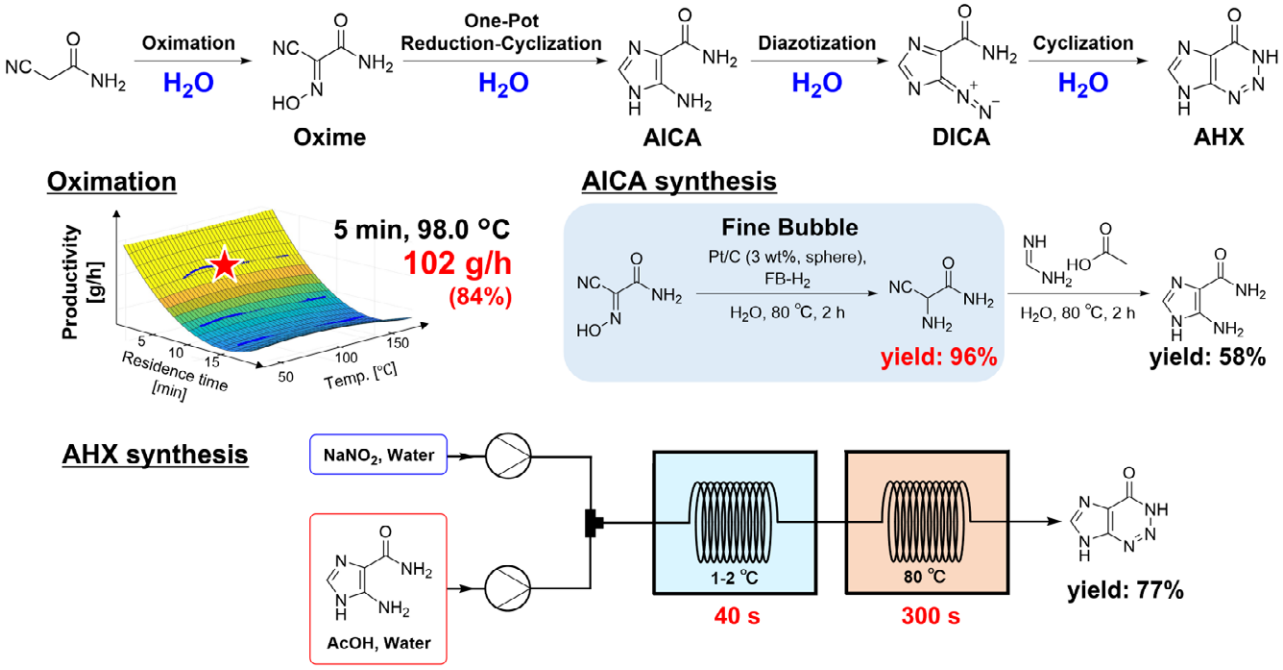
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Green Manufacturing: Development of a Continuous Process for Fairy Chemicals

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Fairy chemicals, including 2-azahypoxanthine (AHX), are bioactive compounds produced by fungi and have been reported to act as plant growth regulators, potentially reducing reliance on agrochemicals. To enable their stable supply, we developed a continuous-flow synthesis of AHX as a second-generation process. In the first step, oximation of 2-cyanoacetamide was optimized using a gradient-based method, allowing rapid screening of ~200 conditions within 60 min. The reaction achieved a maximum yield of 86% and a productivity of 102 g/h, corresponding to a 130-fold increase over the batch process. In the second step, reduction and cyclization to AICA were performed using hydrogen supplied via fine bubbles. Using water as the solvent improved the reaction outcome, giving an isolated yield of 96%, whereas only 64% conversion was obtained in methanol. In the third step, a continuous-flow system integrating diazotization and intramolecular cyclization was established. Optimization of reaction parameters shortened the diazotization time by 22-fold, affording AHX in 77% yield (HPLC) without solvent exchange. The pK_a of AHX was determined to be 6.64 using a flow-based method, enabling efficient crystallization under acidic conditions (pH ≤ 5) with an isolated yield of 44%.



Scheme 1. Optimization of reaction conditions for each step in AHX synthesis

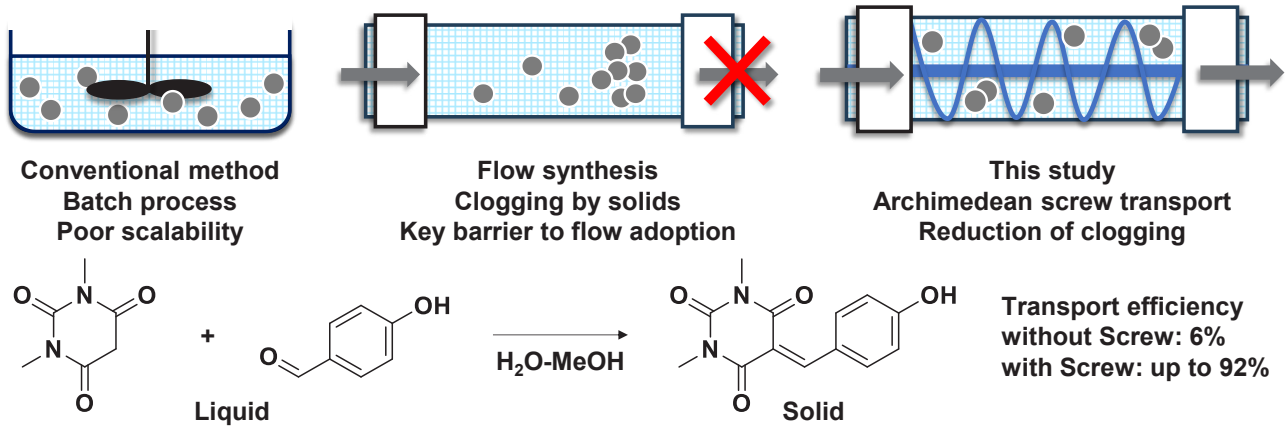
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Green Flow Chemistry: a Slurry Flow System Incorporating an Archimedean Screw

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Continuous-flow synthesis is a promising approach for improving the safety, efficiency, and scalability of organic reactions. However, its application to slurry systems remains limited because suspended solids often lead to sedimentation, adhesion to channel walls, and clogging.[1)] To address these challenges, we developed a slurry-flow device incorporating an Archimedean screw, which enables mechanical solid conveyance and stable transport under continuous-flow conditions. The transport behavior of solid–liquid mixtures was first evaluated using solid beads of different particle sizes and densities. Smaller and less dense particles exhibited higher transport efficiency, suggesting that the system is suitable for the slurry transport of common organic solids over a range of operating conditions. The device was then applied to a precipitation system based on NaCl crystallization induced by differences in solubility. Screw rotation successfully prevented clogging and improved the recovery of precipitated solids from 27% to 82%. The utility of the device was further demonstrated in organic reactions accompanied by solid formation. In an aqueous Knoevenagel reaction, screw rotation improved the recovery of the solid product from 6% to 92% under continuous-flow conditions. The system was also applicable to an amidation reaction involving solid formation, where both clogging suppression and improved product recovery were observed. These results demonstrate that the Archimedean screw-based slurry-flow strategy is effective for continuous heterogeneous synthesis involving precipitation and solid formation, and that it provides a practical platform for handling solid-forming reactions in flow.



Scheme 1. Challenges in Slurry Synthesis and Solution Strategy

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Improving the accuracy of liquid film thickness measurement using a laser focus displacement meter

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Liquid film flow is observed in various chemical industrial fields. Film thickness directly affects the heat and mass transfer coefficients across the gas-liquid interface; for instance, in absorption towers[1], CO_2 is captured into the liquid phase through the gas-liquid interface of the liquid film. If the liquid film becomes too thin and breaks, the effective absorption surface area decreases, leading to a significant drop in efficiency. Therefore, accurately measuring liquid film thickness is a vital challenge in process chemistry.

In this study, we propose the laser focus displacement (LFD)[2] method (Figure 1). This method uses chromatic aberration of the focusing lens, where different wavelengths focus at different depths. By obtaining the color spectrum of the reflection at the layered interfaces, we can non-invasively measure their thickness with wavelength-order precision without a "z-scan." Figure 2 shows the chromatic aberration of different focusing lenses, i.e., applicable thickness range. According to this, we can easily adjust the thickness range and resolution only by replacing the focusing lens. We will discuss the applicability of LFD to various liquid film flows.

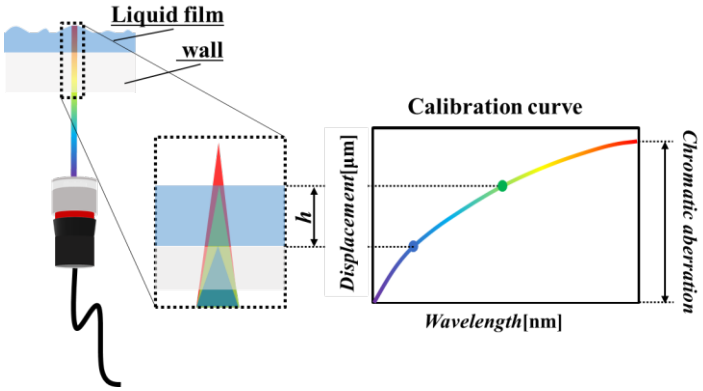


Figure 1. Schematic diagram of liquid film measurement using LFD

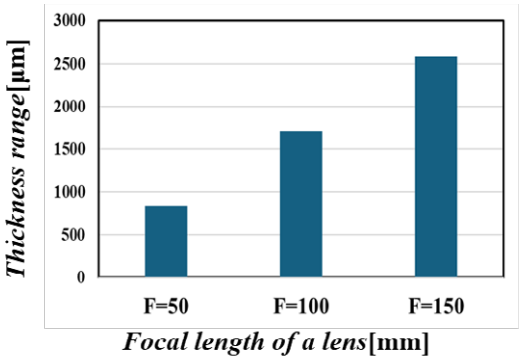


Figure 2. Relationship between Focal Length and Chromatic Aberration

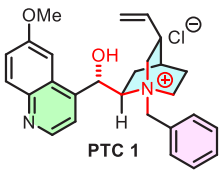
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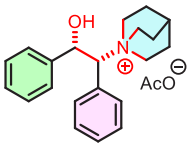
Design and Synthesis of Novel Phase-transfer Catalyst Inspired by Cinchona Alkaloids

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We have been studied the hydrolytic dynamic kinetic resolution of racemic tropic acid β-lactone using chiral phase-transfer catalysts (PTC 1) derived from cinchona alkaloids.[1] However, since these catalysts are derived from natural resources, there are limitations to further structural development. Because masking the OH group of the phase-transfer catalyst by *O*-alkylation completely eliminates the enantioselectivity, we planned to develop a novel quinuclidium ion class phase-transfer catalysts inspired by the Cinchona alkaloids, having free OH group as hydrogen bond donor.

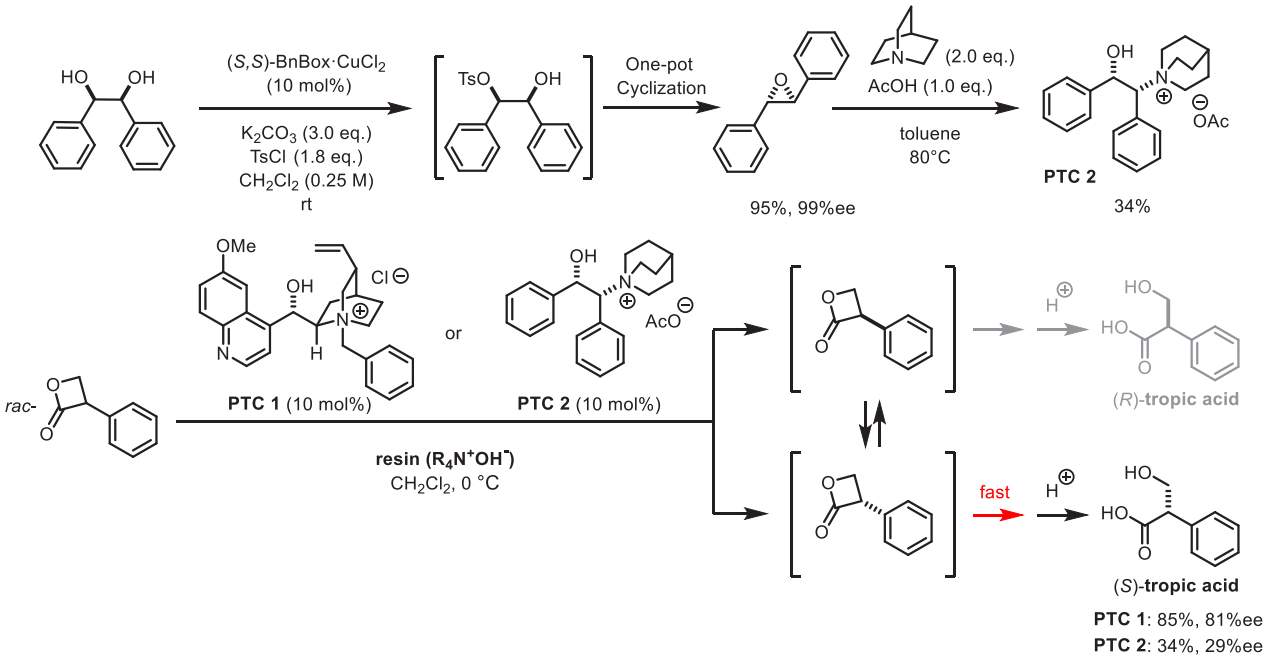


PTC 1



PTC 2

Recently, we have achieved a one-pot synthesis of stilbene oxide *via* the asymmetric sulfonylation of *meso*-hydrobenzoin catalyzed by a chiral bisoxazoline (Box)-$CuCl_2$ complex, followed by an intramolecular cyclization.[2] The nucleophilic ring-opening of chiral stilbene oxide by quinuclidine gave core structure of the novel phase-transfer catalyst (PTC 2). The hydrolytic dynamic kinetic resolution of racemic tropic acid β-lactone using this catalyst was not very high, but the encouraged results were obtained. We believe that increasing the size of the aromatic ring could improve enantioselectivity.



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Dye Separation by Polymer Films based on Discotic Liquid Crystal with Photopolymerizable Cinnamate Groups

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Nanoporous materials are essential in separation technology because of simple and energy-efficient operation compared with other methods. Organic nanoporous materials recognize target molecules through molecular size and electrostatic interactions; therefore, controlling both the pore size and chemical environment inside the pores is crucial.

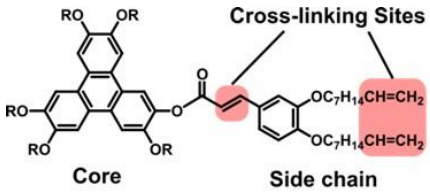


Figure 1. Structure of **TPCV**.

As one approach to address this control, application of columnar structures formed by thermotropic discotic liquid crystalline molecules (DLCs) has attracted considerable attention. We developed DLCs with photopolymerizable cinnamate groups and terminal vinyl groups (TPCV)(Figure 1).[1,2] After formation of a columnar structure, the structure can be fixed by cross-linking these reactive groups (Figure 2). Subsequently, chemical removal of the cores of TPCV yields a porous film whose pores originate from the removed cores.

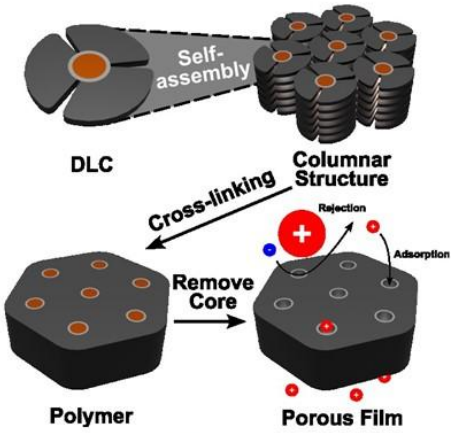


Figure 2. Schematic illustration of preparation of porous film with **DLC**.

TPCV formed a hexagonal columnar structure. A TPCV polymer film was obtained by UV irradiation under N_2 atmosphere at room temperature, where the columnar structure was fixed through [2 + 2] cycloaddition reaction and thiol-ene reaction in the presence of a photo-radical initiator and a cross-linker. The IR absorption peak derived from the terminal vinyl groups at 909 cm^{-1} disappeared, and the intensity of the original C=O absorption peak at 1725 cm^{-1} decreased, while the peak at 1762 cm^{-1} increased. The TPCV polymer film was hydrolyzed to remove triphenylene cores to give self-standing TPCV porous film. The film was expected to possess pores originating from the removed triphenylene cores, with a pore size of approximately 1nm. In addition, there are carboxy groups on the pore surface. When the porous film was soaked in a solution of two cationic dyes with different molecular sizes, the film selectively adsorbed the smaller cationic dye.

References

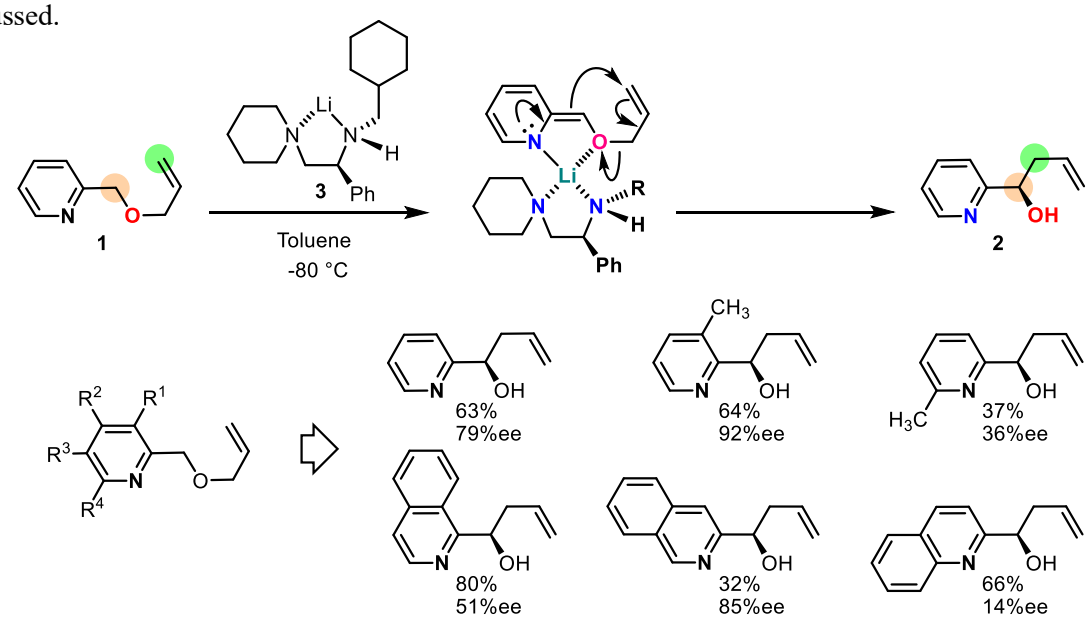
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Enantioselective [2,3]-Wittig Rearrangement of Allyl Picolyl Ethers Enabled by Chiral Lithium Amides

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Pyridines are found in many pharmaceuticals, pesticides, and asymmetric ligands, making the development of methodologies for constructing asymmetry on carbon atoms adjacent to the pyridine ring extremely important. In 1956, Suzuki reported the synthesis of 2-pyridine alkanol (**2**) via the Wittig rearrangement of 2-allyloxymethylpyridine (**1**), [1]. In 2023, we reported the enantioselective [2,3]-Wittig rearrangement of α-allyloxycarboxylic acid using chiral lithium amides. [2] In this study, we aimed to expand the scope of chiral lithium amide chemistry for the enantioselective [2,3]-Wittig rearrangement of **1**. [3]

Deprotonation of **1** by chiral lithium amide **3** prepared from 1.4 equivalents of chiral amine and n-BuLi in toluene at -80°C produced the rearranged products in 79%ee. The position of substituents on the pyridine ring significantly affects the enantioselectivity; the optical yield was as high as 92%ee for the 3-methyl substituted analogue, while it decreased to 36%ee for the 6-methyl analogue. The asymmetric yield was improved up to 95%ee when the reaction of **1** was carried out in the presence of TMSCl. In this presentation, detailed study of this asymmetric transformation, including solvent effect, scope of the substrates, transition state analysis, will be discussed.



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1P-093S

Direct Real-Time Data Acquisition and Analysis for Flow Synthesis

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Organic synthesis has advanced through the accumulation of reaction data reported in the literature. However, existing experimental datasets often suffer from limited reproducibility, a lack of negative results, and variability in experimental conditions. These limitations lead to bias and incompleteness to the available data.

In recent years, artificial intelligence (AI) and machine learning (ML) have been increasingly adopted for the analysis of chemical data. Among various types of chemical data, full spectrum IR data enables high-throughput and comprehensive analysis, thereby providing large datasets for AI within a short time. For example, ML-based quantification of substrate concentrations using full-spectrum IR data has been reported.[1] However, such approaches typically depend on spectral preprocessing, and direct analysis of raw full-spectrum IR data remains underexplored.

Herein, we present an integrated platform that consists of automated flow synthesis, in-line IR analysis, and machine learning to achieve high-throughput acquisition of high-quality reaction data with minimized bias. This system enables real-time monitoring and analysis of chemical reaction. As a model system, the acylation of amines in the presence of impurities was investigated (Fig. 1). We further demonstrated automated control of the flow system and in-line IR monitoring and report the development of a machine-learning regression model for predicting reaction yields directly from full-spectrum IR data.

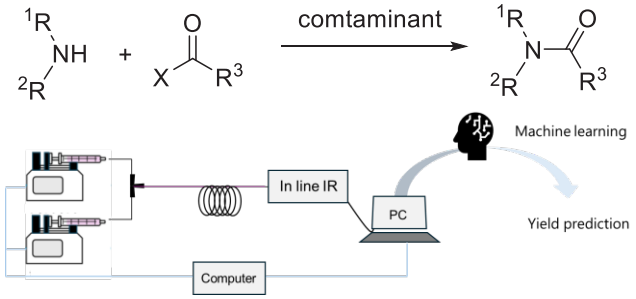


Fig. 1. Flow system for amine acylation

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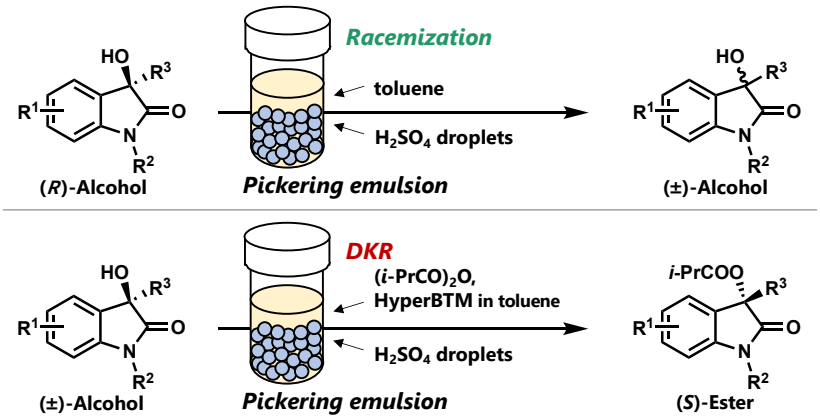
Racemizing 3-aryl-3-hydroxy-2-oxindoles in a Pickering emulsion under acid catalysis and its application to dynamic kinetic resolution

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Dynamic kinetic resolution (DKR) combines kinetic resolution (KR) and rapid racemization of the starting materials in a one-pot system to obtain optically active compounds from racemic mixtures in quantitative yields.[1] However, the application of DKR to tertiary alcohols is still under development and has been limited to few specific substrates.[2] This limitation arises from the lack of racemization methodologies for tertiary alcohols that are compatible with KR.

To address this challenge, we embarked on the development of a racemization method for tertiary alcohols that satisfies two essential requirements: (1) no substrate degradation, and (2) high compatibility with KR. Therefore, we envisioned that performing the racemization in an aqueous sulfuric acid phase within an oil/water biphasic system would overcome these two challenges.

In this poster, we describe a compartmentalization strategy using a Pickering emulsion that proved effective for the racemization of 3-aryl-3-hydroxy-2-oxindoles, isatin-derived tertiary alcohols, along with its subsequent application to DKR (**Scheme 1**).[3]



Scheme 1. H_2SO_4-catalyzed Racemization and DKR of tertiary alcohols

References

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1P- 95S

Continuous Flow Preparation of Methyl Vinyl Ketone from 4-Hydroxy-2-butanone with Heterogeneous Acid Catalyst

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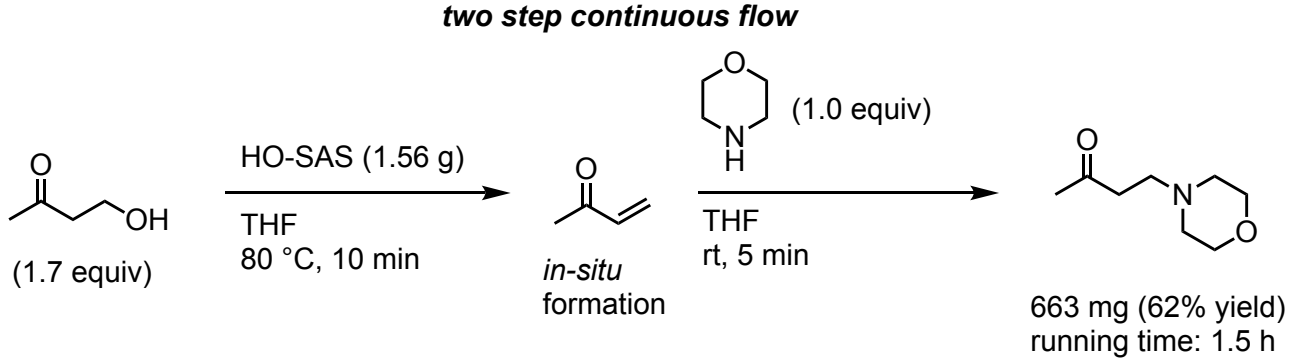
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− Methyl vinyl ketone (MVK) is an important building block for the synthesis of pharmaceuticals, polymers, and specialty chemicals. MVK can be synthesized via the dehydration of 4-hydroxy-2-butanone (4-HB). However, due to its high reactivity and toxicity, it must typically be prepared immediately prior to use under controlled safety conditions and stabilized with inhibitors to prevent spontaneous polymerization. To overcome these limitations, we focused on developing a methodology in which MVK is generated *in-situ* from 4-HB via acid-catalyzed dehydration and subsequently utilized without isolation.

− We applied a continuous flow approach for the preparation of MVK, which offers a safe and user-friendly alternative. Continuous flow chemistry operates within a closed system, eliminating the risk of exposure to MVK and allowing for direct downstream use without the need for storage. For the dehydration of 4-HB, we employed HO-SAS, a sulfonic acid-functionalized silica bearing a β-hydroxy group. After optimizing the reaction conditions (e.g. temperature, residence time and catalyst loading), the established protocol was applied to a two-step continuous flow Michael addition of N-, C-, and S-nucleophiles (**Scheme 1**). During the flow experiment, no pressure fluctuations were observed, and the liquid feeding was stable, enabling continuous operation for over one hour. This method represents a safe and practical approach for the preparation and use of MVK.



Scheme 1. Continuous flow synthesis of 4-morpholino-2-butanone through *in-situ* MVK preparation

Synthesis and reactivity of α-Sulfonium Enones

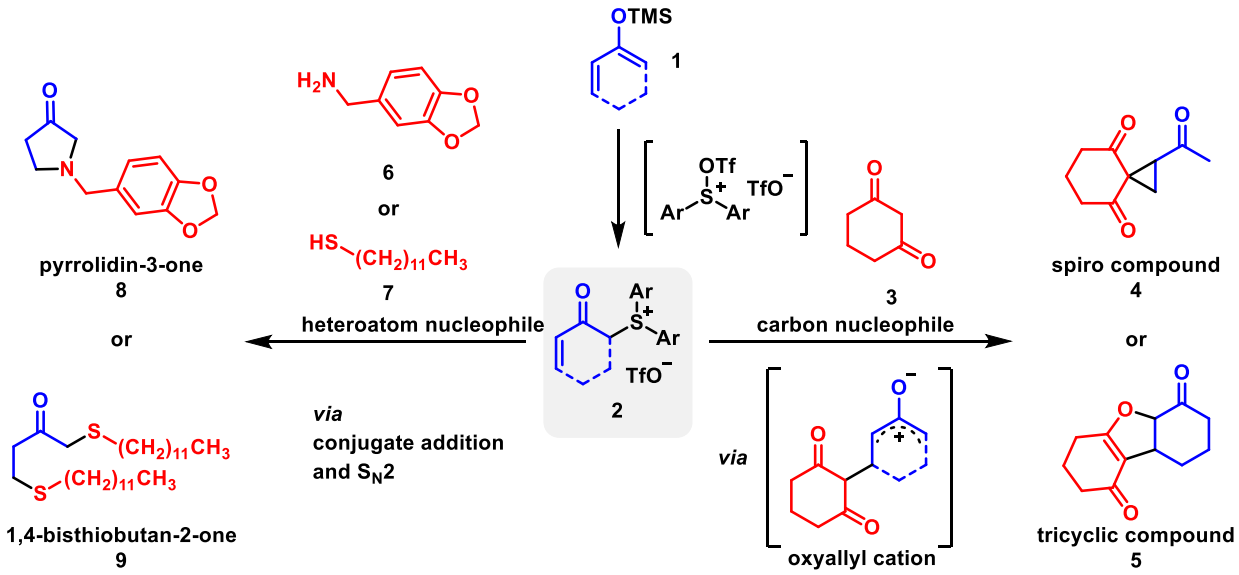
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Sulfonium salts, featuring a positively charged tetravalent sulfur atom, possess diverse reactivities and are versatile and valuable chemical species. Specifically, certain alkylsulfonium salts play a crucial role in biological processes and serve as key scaffolds in pharmaceuticals. Conventionally, these salts have been synthesized from sulfides and electrophiles. In contrast, our laboratory has developed a novel approach using diaryl sulfoxides and nucleophilic alkylating agents.[1,2] This complementary method enables access to highly novel alkylsulfonium derivatives. In this study, we extended this methodology by employing siloxydiene **1** as a nucleophile to achieve the synthesis of a novel sulfonium enones as salt. As a result, several types of α-sulfonium enones **2** were successfully synthesized. Upon investigating their reactivity, the reaction of **2** with cyclohexane-1,3-dione (**3**) as a carbon nucleophile afforded spirocyclic compound **4** or tricyclic compound **5** via 1,4-addition followed by the formation of an oxyallyl cation intermediate. On the other hand, the use of heteroatom nucleophiles, such as piperonylamine (**6**) and 1-dodecanethiol (**7**), produced pyrrolidin-3-one **8** and 1,4-bisthiobutan-2-one **9**, respectively, through a sequence of 1,4-addition and S_N2 substitution.



Scheme 1. **Reactivity of α-Sulfonium Enones**

References

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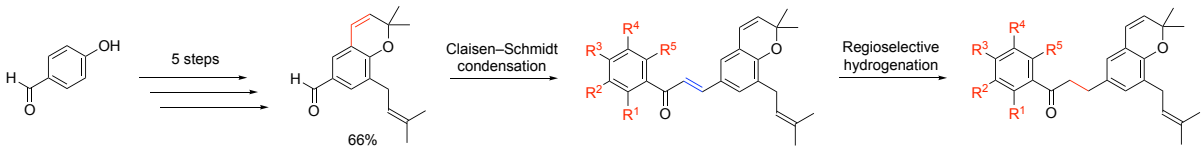
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Divergent Synthesis of Artoserichalcone A Derivatives and *In Silico* Lead Optimization for Antimalarial Drug Discovery

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The emergence of drug-resistant *Plasmodium falciparum* necessitates the development of novel antimalarial chemotypes supported by efficient and scalable research strategies. In this study, we report an integrated workflow combining synthetic chemistry and computational modeling to investigate the antimalarial potential of artoserichalcone A[1] and its derivatives. A robust total synthesis of artoserichalcone A and structurally diversified analogs was established. The synthesis route features a key bond-forming transformation, including a microwave-assisted rearrangement, a base-catalyzed Claisen–Schmidt condensation, and regioselective hydrogenation that efficiently constructs the chalcone-based molecular framework, thereby enabling systematic structure–activity relationship (SAR) studies. Complementary *in silico* studies include molecular docking, molecular dynamics simulations, and ADMET prediction to elucidate molecular interactions and pharmacokinetic properties. These *in silico* approaches accelerate lead prioritization and provide mechanistic insight into antimalarial activity. This interdisciplinary framework establishes a scalable platform for antimalarial drug discovery. The integration of synthesis and predictive modeling is expected to deliver novel lead compounds effective against resistant malaria strains.



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Abstracts

Poster Presentation

2P-01 ～ 2P-97S

July 3rd.

2P- 01

Effective Crystallization Process Development

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In this poster the fundamentals of crystallization will be introduced and common-sense guidelines for the design of a high-quality crystallization process will be presented. Using case studies and references from industry and academia, key crystallization topics such as solubility and supersaturation will be explained with examples of how each can be utilized to make informed decisions regarding effective crystallization process development. Regardless of method chosen to crystallize product, a common feature is starting with a saturated solution. Solubility curves are commonly used to illustrate the relationship between solubility, temperature and solvent type and reveal the theoretical yield for a given crystallization process. Once an appropriate solvent is chosen, the solubility curve becomes a critical tool for the development of an effective crystallization process.

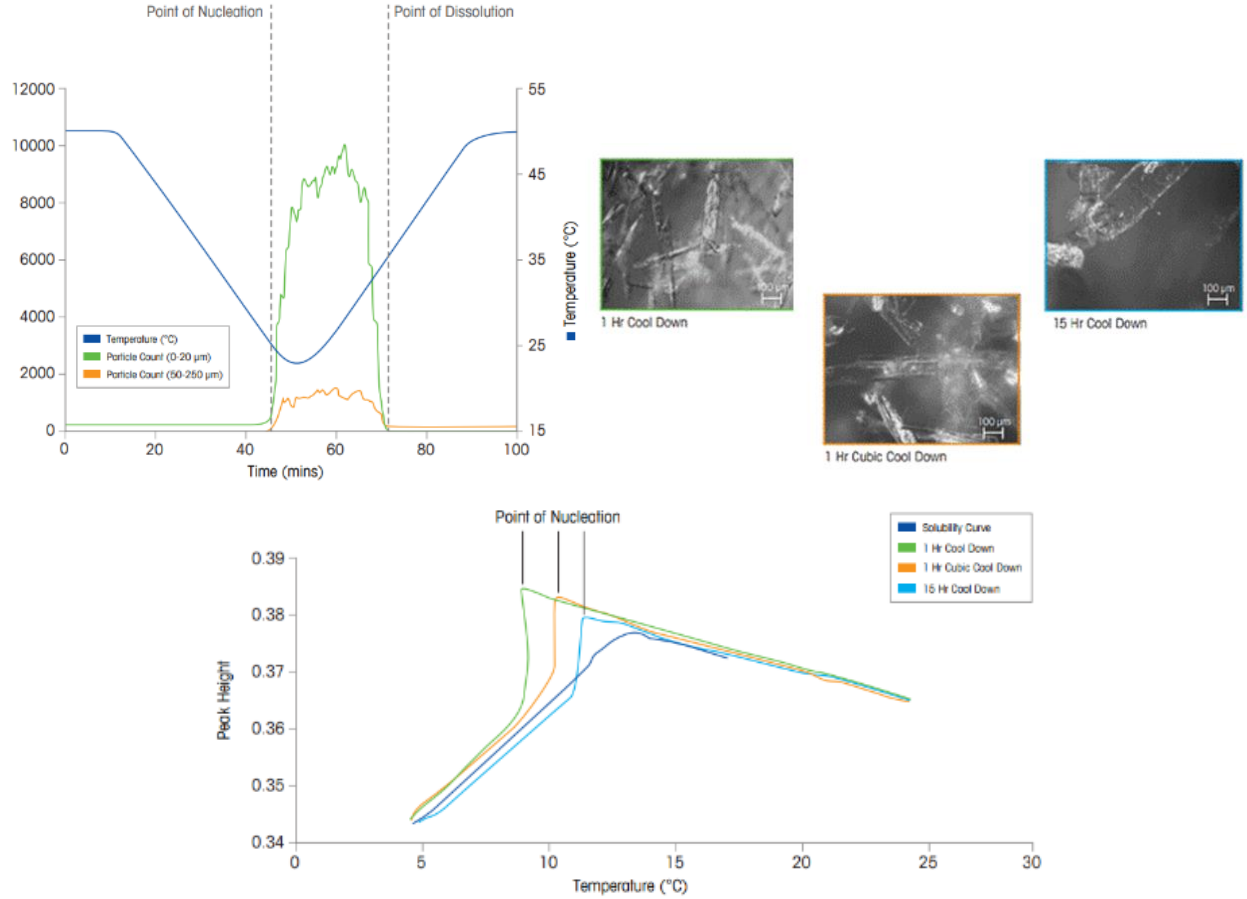


Figure 1: Points of nucleation and dissolution during cooling and heating. Temperature vs. peak height for three experiments with different cooling profiles

2P- 02

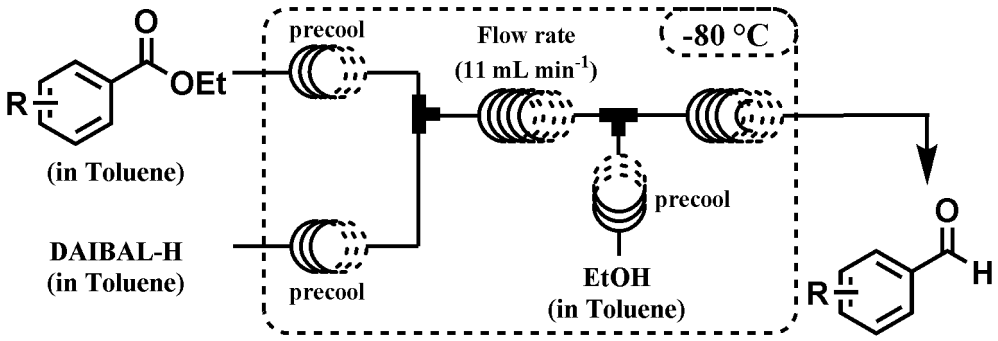
Study on the Partial Reduction of Esters with High Reduction Potentials Using a Flow Reactor

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Stepwise synthetic approaches are essential for constructing complex molecules, and aldehydes are therefore highly valuable as key intermediates because they can be converted into various functional groups. Although aldehydes can be synthesized through various methods, such as the oxidation of alcohols and the reduction of nitriles, a pathway via esters followed by their direct reduction is particularly valuable for the synthesis of fine chemicals and pharmaceuticals, as carboxylic acids are abundant in nature and a wide variety of their derivatives are commercially available.

However, the method of directly synthesizing aldehydes from highly reducible molecules using inexpensive DIBAL-H faces challenges in commercial implementation because the resulting aldehydes are often over-reduced, leading to the formation of alcohols. For example, in the partial reduction of ethyl benzoate, although An et al. were unable to obtain the desired product even using the flow synthesis method with DIBAL-H, they succeeded in synthesizing it by changing the reducing agent to sodium diisobutyl-*t*-butoxyaluminum hydride [1], and Doi et al. succeeded in synthesizing it by switching a flow reactor to a microreactor [2].

In this study, with the aim of developing practically applicable methods, we explored the partial reduction of aromatic esters with a high reduction potential, including ethyl benzoate, using a flow synthesis method that combines a T-shaped mixer with an inner diameter of 1 mm and a coil.



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2P- 03

Computational Chemistry-Guided Industrial Process Development

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In industrial process development, rapid decision-making based on limited experimental data is often required under stringent development timelines. However, when process development proceeds without sufficient chemical understanding of reaction mechanisms and molecular behavior, issues such as poor reproducibility on scale-up and latent safety risks may arise. In this context, computational chemistry offers an opportunity to deepen chemical understanding and guide process development.

In this study, density functional theory (DFT) calculations were performed for therapeutic candidates for Alzheimer's disease, E2212 [1] and E2609 [2] (**Figure 1**). Especially, by focusing on reaction selectivity, experimental results were verified. For E2212, it was examined whether DFT calculations could enable rationalization of experimentally observed distribution of multiple byproducts and their corresponding intermediates. On the other hand, for E2609, the effect of different condensation reagents on O/S selectivity in a cyclization reaction was investigated.

Furthermore, as a step toward computational chemistry-driven process development, DFT calculations using a model compound were performed to predict the onset temperature of exothermic decomposition. In the presentation, we will also discuss the prediction accuracy and the scope of applicability, and would appreciate feedback and suggestions.

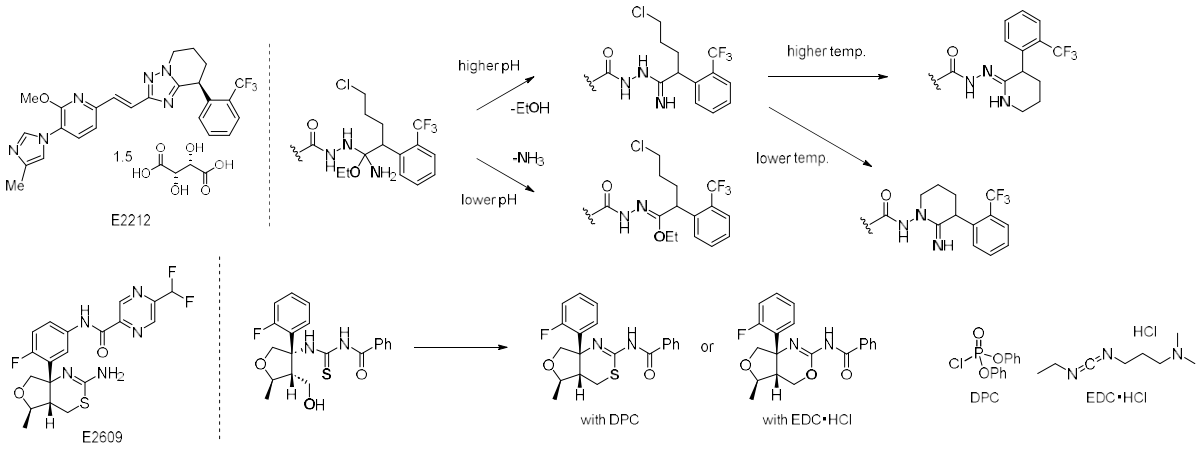


Figure 1. the structure of E2212 and E2609 and experimental results

References

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2P- 04

Development of the Commercial Manufacturing Process for Bilastine

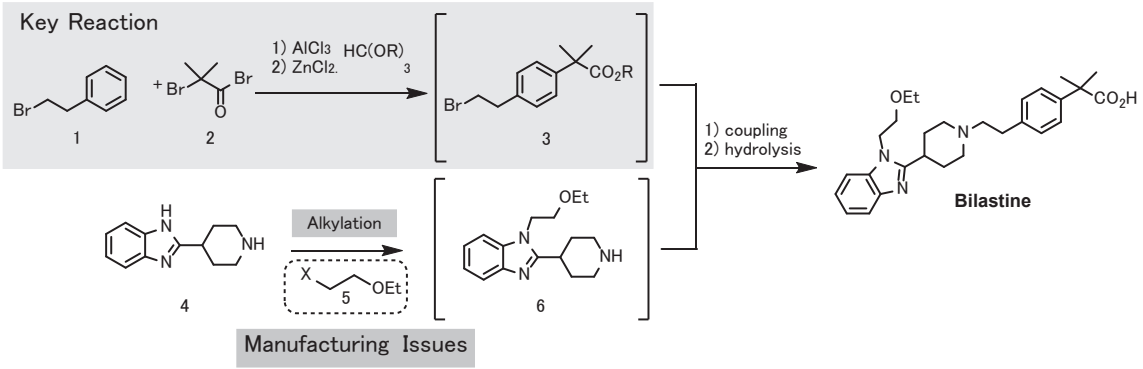
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In recent years, disruptions in the pharmaceutical supply chain have become an important societal concern, and shortages have at times delayed patient access to high-demand medicines. Ensuring a stable supply of active pharmaceutical ingredients (APIs), thereby contributing to patient care, is an important role forAPI manufacturers.

Bilastine is a second-generation H1 antihistamine indicated for allergic rhinitis (AR) and chronic urticaria (CU). Owing to its established clinical efficacy, demand for bilastine has been increasing, and substantial demand is also anticipated for generic bilastine.

To support a reliable market supply of generic bilastine, we developed a proprietary manufacturing process suitable for industrial-scale production. A key challenge was to establish an efficient synthesis of intermediate **3**. We found that reacting alkyl bromide **1** with acid halide **2** at low temperature in the presence of $AlCl_3$, followed by heating in the presence of $ZnCl_2$ and $HC(OR)_3$, then affords Intermediate **3** in high yield with excellent selectivity. Subsequently, bilastine was obtained in high yield and excellent quality (HPLC area% ≧99.8%; largest single impurity ≦0.07 area%) by alkylation of intermediate **4** with alkyl reagent **5**, coupling with intermediate **3**, and hydrolysis.[1)]

After establishing the process, we conducted pilot-scale manufacturing and then performed trial runs at commercial scale; however, during the trial runs, incomplete conversion was observed in the alkylation of intermediate **4**, prompting a detailed reinvestigation. In this presentation, we report the results of these investigations and the insights gained.



Scheme 1. Synthetic route to bilastine

References

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2P- 05

Comparative Study of Pt and Pd Catalysts in Flow Hydrogenation Reactions Using a Computational Science Approach

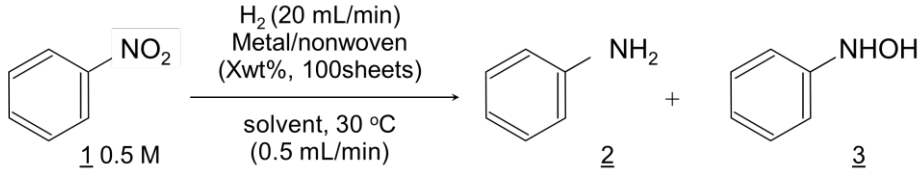
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Platinum-group metals, such as Pt and Pd, are widely used as catalysts for the hydrogenation of organic compounds. In recent years, global demand for these precious metals has been increasing, while their supply remains persistently constrained, raising concerns about a further tightening of the supply–demand balance.[1] Therefore, there is a strong need to develop catalyst materials that maintain high catalytic activity while significantly reducing precious metal loading.

We have developed metal catalysts in which Pd and Pt nanoparticles are immobilized on polyethylene (PE) nonwoven fabrics functionalized with poly(N-vinyl-2-pyrrolidone) (PVP) introduced via radiation-induced graft polymerization. We have previously reported that these catalysts exhibit high catalytic activity in flow hydrogenation reactions.[2,3]

In this study, we investigated the flow hydrogenation of nitroarenes using our developed catalysts. revealing defferences in reactivity and product selectivity between Pt- and Pd-based catalysts (Table 1). To elucidate the origin of these differences, reaction pathway exploration of hydrogenation on Pd and Pt catalysts was performed using machine learning interatomic potential (MLIP). The results revealed that the reaction pathways differ between Pt and Pd.

Table 1. flow hydrogenation of nitrobenzene



1 0.5 M　　2　　3

entry	Metal(X)	solvent	conversion(%)	selectivity(%) 2	3
1	Pd(1)	MeOH	>99	>99	<1
2	Pd(1)	*i*-PrOH	36	84	16
3	Pt(0.4)	MeOH	99	79	21
4	Pt(0.4)	*i*-PrOH	17	29	71

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2P- 06

Study on the Development of an Online Reaction Vessel Monitoring System Using an HPLC Platform

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In process chemistry, scaling up reaction from laboratory to production scales and maintaining stable process operation are major challenges. To optimize reaction conditions, ensure product quality, and improve equipment utilization, real-time monitoring of reaction behavior is essential. One such method is online reaction monitoring. That enables continuous tracking of reaction rates and product profiles, which aids scale-up prediction, early detection of process deviations, and development of robust control strategies.

Conventional approaches typically rely on periodic manual sampling followed by GC or HPLC analysis. However, manual sampling for long-running reaction is time-consuming, labor-intensive, and costly, and is susceptible to human error such as missing sampling points.

Therefore, in order to automate this time-consuming process of sampling reaction solutions from the reactor, we developed an online monitoring system that integrates Nexera FV and Solvent-Delivery Pump (Fig. 1). Nexera FV is an HPLC platform equipped with an autosampler and flow through vials to support online analysis. In this study, the reaction mixture in the reaction vessel was circulated using an HPLC pump and was sampled via flow through vials.

As a model experiment for system evaluation, we selected the alkyl levulination reaction of levulinic acid and monitored both starting materials and products. Levulinic acid is an important biomass-derived intermediate, and ethyl levulinate, produced by its alkylation, have potential applications, including as a pharmaceutical intermediate, fragrance, and cosmetic ingredient. In this study, we analyzed the changes in ethyl levulinate and levulinic acid over time using Nexera FV and evaluated them using trend plots.

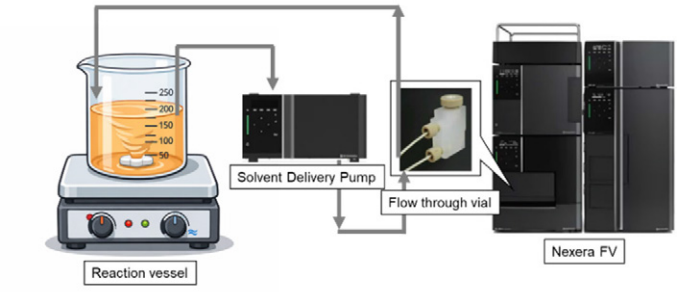


Fig. 1 Online reaction vessel monitoring system

References

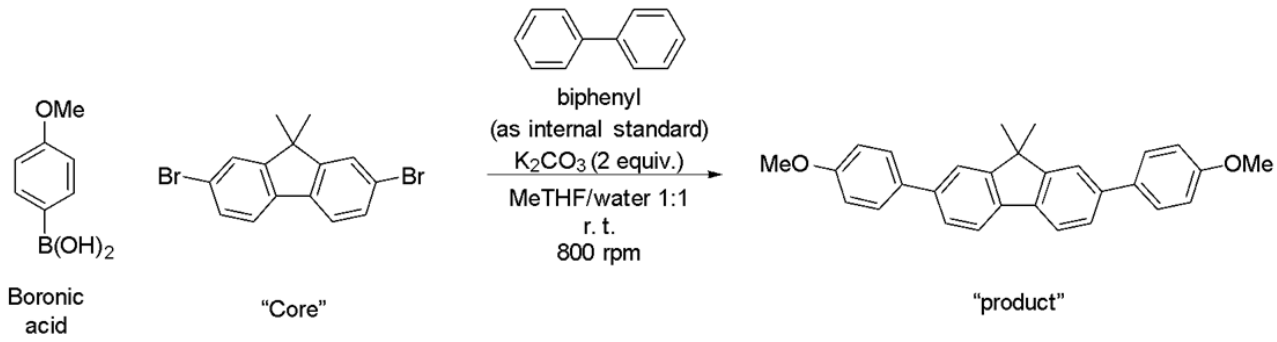
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2P- 07

DirectInject-LC: Real-time Analysis by HPLC for Reaction Monitoring

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Shimadzu Corporation
Yusuke Sato, Junliang Liu, Lars Yunker, Shad Grunert, Paloma Prieto, Jason E. Hein
Telescope Innovations

An online HPLC platform integrating the DirectInject-LC™ system has been developed for automated, real-time reaction monitoring. The system enables continuous and reproducible sampling across homogeneous, liquid/liquid, liquid/solid, and triphasic heterogeneous reaction media. Unlike conventional online HPLC sampling methods, which often suffer from clogging, inconsistent sampling, and limited functionality in complex systems, DirectInject-LC enables rapid inline mixing, precise automated dilution (up to >30,000-fold), and direct injection onto the HPLC within minutes of sampling. Optional filtration attachments allow reliable analysis of slurry and liquid/solid reactions without instrument fouling, with sampling intervals as short as three minutes.
Coupling DirectInject-LC with Shimadzu Nexera™ HPLC systems enables orthogonal UV/DAD and MS detection, providing comprehensive real-time reaction profiles. Automated calibration and signal normalization support accurate kinetic monitoring of reactants, intermediates, and products. This integrated platform enhances reaction understanding and offers a robust process analytical technology solution for both laboratory and process development applications.



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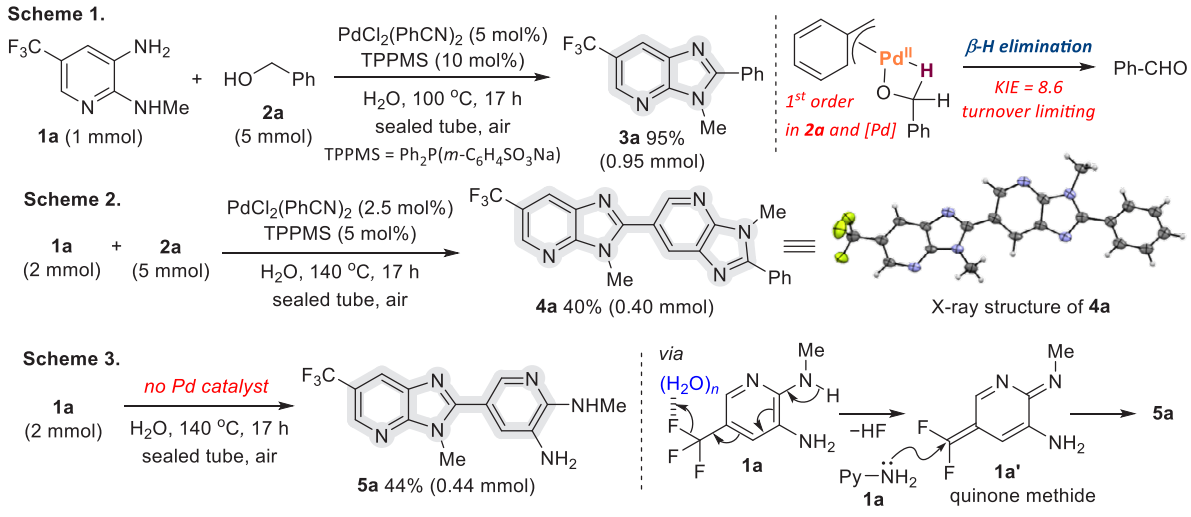
2P- 08

Pd-catalyzed dehydrogenative coupling of 2,3-diaminopyridines and alcohols in water

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Imidazo[4,5-*b*]pyridines are an important class of nitrogen-containing heterocycles consisting of an imidazole ring fused to a pyridine moiety. They can be regarded as isosteric analogues of purine and benzimidazole frameworks. Typically, these heterocycles are prepared through a cyclocondensation/aromatization cascade of 2,3-diaminopyridines with prefunctionalized coupling partners such as aldehydes. Therefore, the direct use of benzyl alcohols in place of aldehydes represents an attractive, step- and atom-economical strategy for constructing these heterocycles.

Herein, we report a dehydrogenative coupling utilizing readily available benzylic alcohols for the construction of 6-trifluoromethylated imidazo[4,5-*b*]pyridines in water (Scheme 1). Mechanistic studies suggest this cascade reaction involves an initial catalytic dehydrogenation of benzyl alcohols **2** followed by the cyclocondensation of 2,3-diaminopyridines **1** with *in situ* generated aldehydes, allowing rapid access to the desired imidazopyridines **3**. Notably, this practical method also enables direct construction of biimidazopyridine **4a** from amine **1a** and alcohol **2a** *via* a one-pot protocol (Scheme 2). When only amine **1a** was heated in water, the homocoupling product **5a** was formed in 44% yield (Scheme 3). These results suggest that the reaction sequence consists of C-F bond cleavage of **1a** and the nucleophilic addition of another amine **1a** to the *in situ* generated quinone methide **1a'**, leading to the corresponding homocoupling product **5a**.



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ReactRaman: Real-time data yields comprehensive kinetic and mechanistic insight across diverse chemistries

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ReactRaman spectroscopy provides in depth understanding of reaction kinetics, mechanisms and molecular structure in an ever-expanding range of applications. Whether exploring novel synthesis routes, developing green chemistry and sustainable processes or gaining insight into producing advanced engineered materials, the real-time reaction data from ReactRaman spectroscopy is invaluable. The following three examples showcase the breadth and power of ReactRaman technology:

1. Kohyama et al. optimize the reaction conditions in a flow method to produce lithium ynolate anions for the synthesis of functionalized cyclobutenes (Fig.1).[1)]
2. Stager et al. improve the efficiency of four major steps in industrial solid phase peptides synthesis (SPPS) processes (Fig.2).[2)]
3. Chen et al. track key reaction species in solid and liquid phases in a synthesis for perovskite energetic materials (PEMs) (Fig. 3).[3)]

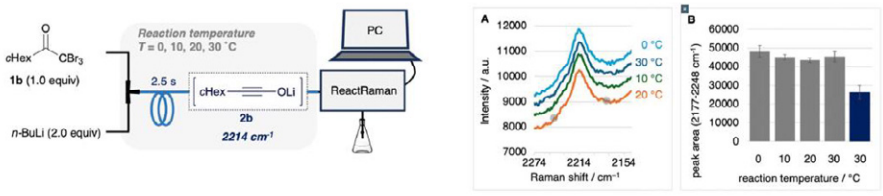


Figure 1. In-line Raman analysis of **2b.** A: Observed Raman spectra, B: peak area (2177–2248 cm^{-1}).

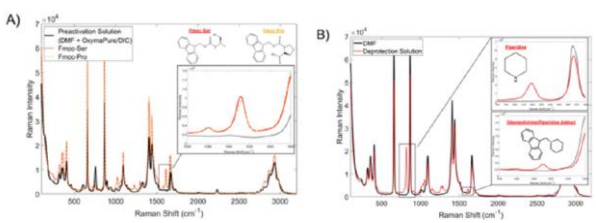


Figure 2. Reference spectra for species of interest during SPPS

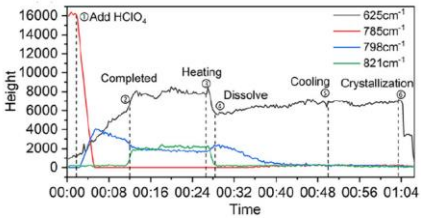


Figure3. Trends of characteristic peaks

References

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2P- 10

From Laboratory to Manufacturing: Development and Implementation of a Continuous Flow Process for a Pharmaceutical Intermediate (Part-1; Route Development and Introduction of Continuous Flow Chemistry)

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Carboxylic acid **1** is a key synthetic intermediate for a drug candidate under development at Astellas Pharma Inc., critical to both quality and cost. The original medicinal route relied on a Stille cross-coupling reaction, which was applied to scale-up production for initial clinical supply; however, several limitations were identified. Specifically, installation of the tin substituent required BuLi-mediated deprotonation under cryogenic conditions. In addition, the use of highly toxic Sn- and Pd- based reagents resulted in significant purification burdens and low overall yield.

As a result, a new synthetic route was identified, consisting of cyclization of pyridazine-4-carbonitrile with L-cysteine, followed by oxidative aromatization to afford carboxylic acid **1** in a one-pot manner. This improved route eliminated the need for cryogenic conditions and heavy metal reagents, and provided a higher yield compared with the original process. During scale-up evaluation, however, multiple challenges were identified, such as purity loss due to formation of L-cystine and prolonged mixing with the oxidant further resulted in intermediate decomposition, yield loss, and product coloration.

To address this issue, a flow-based approach was investigated to enable precise control of mixing time. An optimized flow process enabled improved yield and product quality compared with the batch process. The developed flow process has been implemented for GMP manufacturing. Operational experience and scale-up considerations will be presented separately (Part-2).

	1st Gen. Pilot	2nd Gen. Lab.	**2nd Gen. Pilot**
System	Batch	Batch	**Flow**
Yield	32%	59%	**81%**
PMI	438	NA	**35**
Cost	100	NA	**49***

* Relative cost (1st Gen = 100)

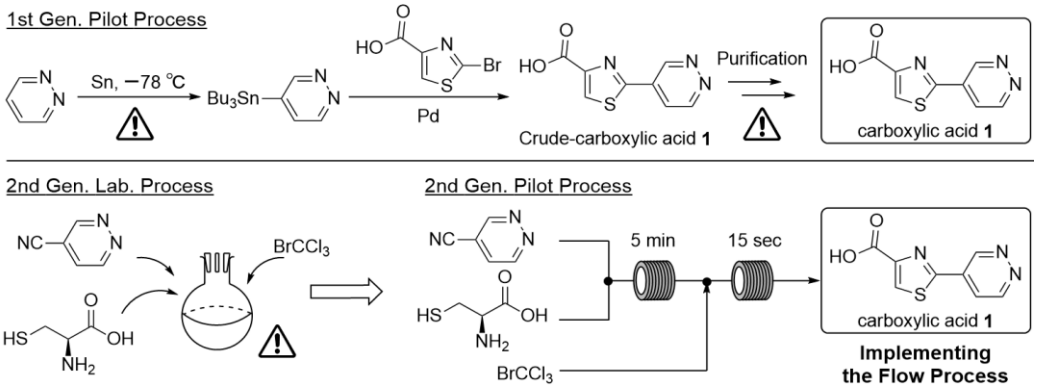


Figure 1. Evolution of the synthetic route and introduction of continuous flow chemistry

2P- 11

From Laboratory to Manufacturing: Development and Implementation of a Continuous Flow Process for a Pharmaceutical Intermediate (Part-2; Scale-Up and Operational Experience in Manufacturing)

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Following the establishment of an improved synthetic route and flow process reported in Part 1, this study describes scale-up studies and GMP manufacturing (50 kg scale) of a pharmaceutical intermediate **1**.

Figure 1 shows the reaction scheme and an overview of the continuous flow manufacturing setup. Based on QRA and scale-up studies, reaction and operating conditions were optimized to enable stable continuous operation at manufacturing scale, and appropriate monitoring parameters were established for diversion control. During GMP manufacturing, unexpected issues that had not been observed at laboratory scale became apparent, highlighting differences between laboratory studies and actual manufacturing environments. The main challenges were product coloration and clogging, both of which affected product quality and productivity. Product coloration was improved through optimization of temperature control, while clogging due to precipitation of cystine was mitigated by revising the reaction condition and washing process. By stepwise review and adjustment of manufacturing and operating conditions across successive production lots, process robustness was improved and stable manufacturing was achieved.

In this presentation, we report the challenges encountered throughout the transition from scale-up studies to GMP flow manufacturing, and share practical insights gained through an integrated approach combining process chemistry and chemical engineering to achieve robust pharmaceutical manufacturing.

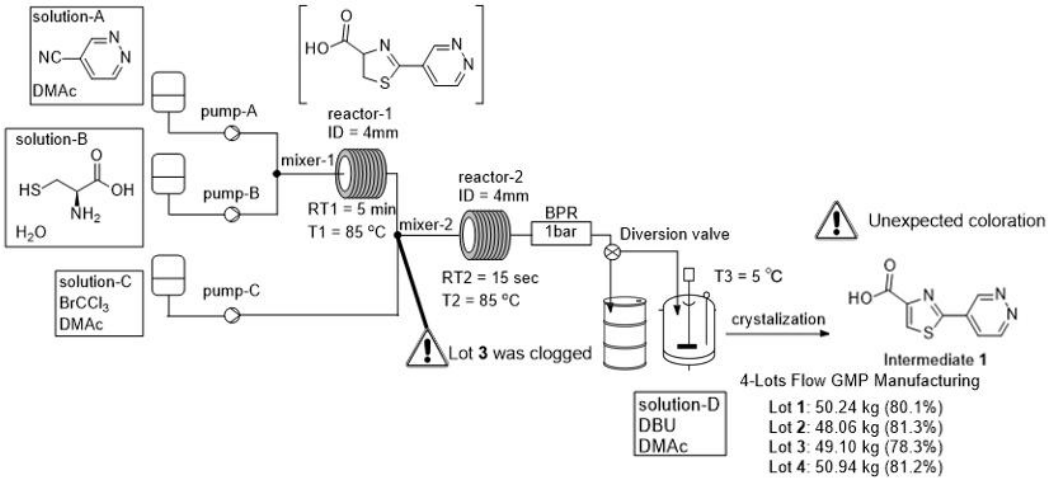


Figure 1. schematic overview of the continuous flow manufacturing setup.

2P- 12

Practical Reduction of Nitroarenes to Anilines Using $NaBH_4$ and Commercial CuO

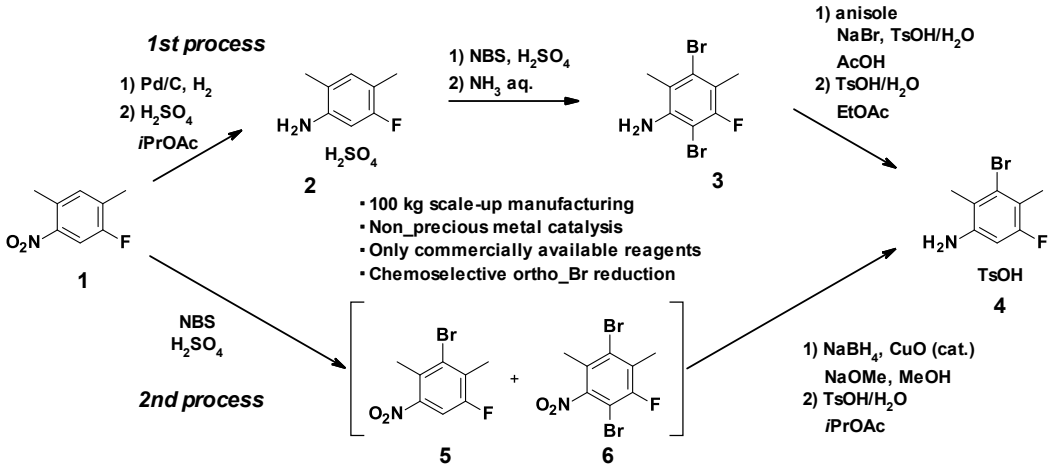
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Precious metals such as Pd face challenges due to their limited availability and price volatility. Consequently, replacing them with more abundant ubiquitous metals has become an important objective. The use of less toxic metals is advantageous from a safety perspective in pharmaceutical manufacturing.

Cu is an abundant and inexpensive metal that is widely used in organic synthesis. In 2020, it was reported that nitrobenzene can be reduced using CuO and ammonia borane complex (BH_3-NH_3, AB) [1]; however, this system proved unsuitable for scale-up because of thermal safety issues associated with AB. During process development of aniline (**4**), we found that nitrobenzene could be readily reduced using a combination of commercially available CuO and $NaBH_4$, a more practical reductant (**Scheme 1**). Compared with catalytic hydrogenation using Pd/C, this $NaBH_4$/CuO (BC) reduction system does not require precious metals, high-pressure hydrogenation, or specialized equipment, thereby reducing operational complexity.

Interestingly, this reaction was found to chemoselectively reduce the *ortho*-bromine substituent. Therefore, the desired aniline **4** was efficiently obtained by direct reduction of the brominated mixture (**5** and **6**). Using this method, manufacturing was successfully conducted on the 100 kg scale, eliminating one reaction step and two isolation steps, and avoiding the use of Pd/C and harsh debromination condition, thereby improving process sustainability. In this poster session, we report the application of this method to other substrates and the results of scale-up studies.

Scheme 1. Process Development of Synthesis of Aniline *via* $NaBH_4$/CuO Reduction.



References

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2P- 13

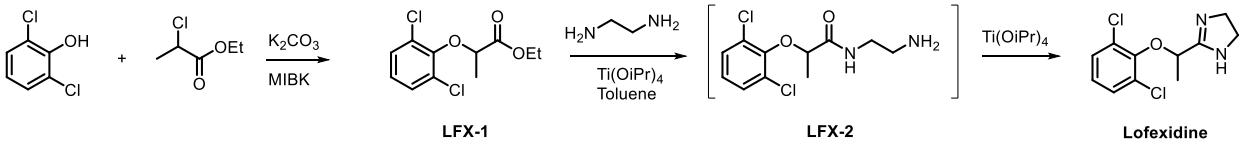
Automation-Enabled Process Development and Kinetic Modelling for PAR Determination

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Automated screening and optimization platforms equipped with representative reactor geometries (e.g., Chemspeed) offer a powerful approach to accelerate early-stage process development by enabling rapid experimentation, improved data quality, and enhanced reproducibility. These systems support efficient exploration of process variables and facilitate the identification of critical trends with reduced material consumption and development timelines.

Kinetic Modelling - based on reaction rate laws and temperature dependence described by the Arrhenius equation - provides a mechanistic understanding of reaction pathways, impurity formation, and system behavior over time, ultimately allowing the definition of multivariate Proven Acceptable Ranges (PARs) by exploiting the full potential of a mechanism-based predictive model.

Automation-enabled optimization, combined with kinetic modelling, supported the successful development and fine-tuning of the final step in the synthesis of Lofexidine, leading to the establishment of robust proven acceptable ranges (PARs).



Scheme 1. Synthesis of Lofexidine



Figure 1. Chemspeed Robotic Automation

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2P- 14

The Value of Reaction Calorimetry

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The development of new compounds and their subsequent scale-up to manufacturing requires a comprehensive understanding of the chemical route, process parameters, and safety considerations. Early identification of critical conditions facilitates efficient process adjustment, design, and implementation. Experimental findings may necessitate alternative synthetic routes, underscoring the importance of obtaining accurate information early to reduce time and resource expenditure and accelerate chemical workflows.

Traditional development tools are often inadequate to meet modern requirements, prompting the need for advanced technologies and procedures tailored to current needs. Reaction calorimetry plays a pivotal role in this context by providing essential calorimetric data that guide the safe transfer of reactions from laboratory to plant scale.

This technique supplies fundamental insights for each step of the chemical development workflow, enabling risk assessment, scalability evaluation, and identification of critical process parameters. Furthermore, reaction calorimetry detects issues related to heat and mass transfer, mixing efficiency, and unexpected behaviors such as viscosity changes, precipitation, fouling, and reagent accumulation. These insights allow for real-time optimization of temperature, stirring, and dosing profiles, making scalability challenges visible and quantifiable.

In summary, integrating reaction calorimetry into chemical process development enhances safety, efficiency, and scalability, addressing the limitations of traditional methods and meeting the demands of modern chemical manufacturing.

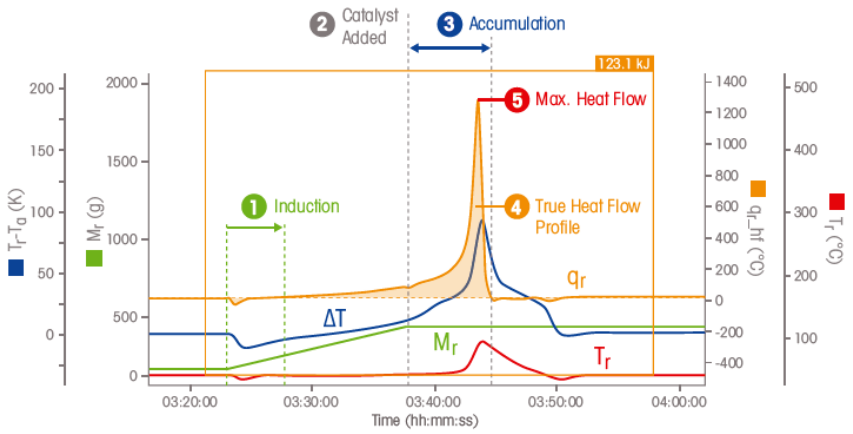


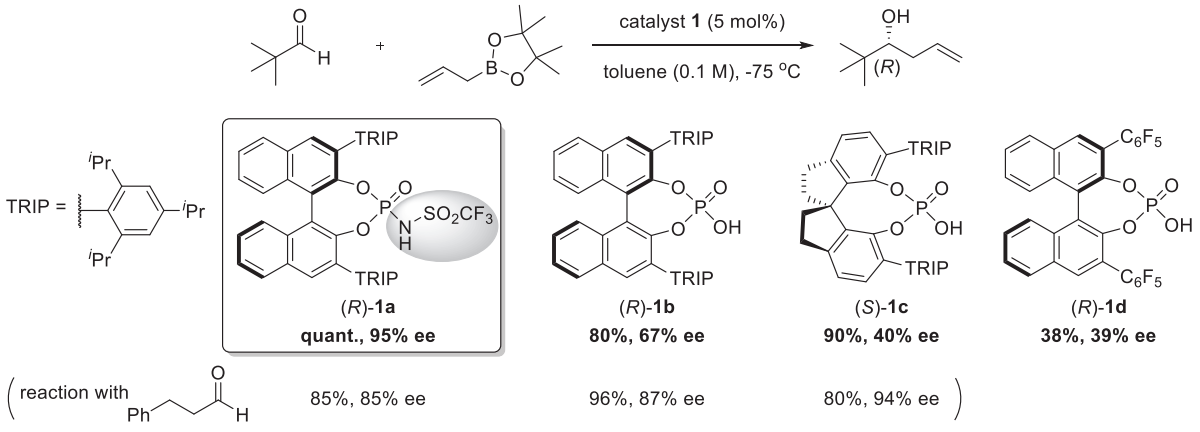
Figure 1. heat release pattern of the reaction

2P- 15

Chiral Brønsted Acid Catalyzed Asymmetric Allylation Reaction with Sterically Hindered Aldehydes

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Chiral phosphoric acids (CPAs) are privileged chiral Brønsted acid catalysts for highly efficient enantioselective allylboration of aldehydes.[1] However, conventional CPA-catalyzed allylboration is not suitable for sterically hindered aldehydes, limiting access to enantioenriched secondary alcohols bearing quaternary carbon centers—key motifs in biologically active natural products. To address this issue, we employed a chiral phosphoramide catalyst for the allylation and crotylation of allylboronic acid pinacol ester. This system utilizes multiple hydrogen-bonding interactions between the catalyst and substrates, enabling efficient enantioselective allylboration of both sterically hindered and less hindered aldehydes via an "interaction strategy."[2] In contrast, conventional CPAs, which were useful for less sterically hindered aldehydes, were ineffective for these reactions, affording low enantioselectivities. Computational studies revealed that the most stable transition state is stabilized by weak attractive interactions between the phosphoramide and the substrates. Notably, non-classical hydrogen bonds (O···H–C and F···H–C) play a key role in controlling enantioselectivity. The method was also applied to the total synthesis of natural products.[3]



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2P- 16

Development of a Scalable and Practical Total Synthesis for Pladienolide D

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Pladienolides are a family of 12-membered macrolides with potent anticancer activity, originally isolated from *Streptomyces platensis* Mer-11107. Subsequent studies revealed that they bind to splicing factor 3b (SF3b), thereby inducing cell-cycle arrest at the G1 and G2/M phases. Among the pladienolides (A–G), pladienolide D exhibits particularly strong *in vivo* anticancer activity. Based on these findings, two novel splicing modulators, E7107 and H3B-8800, were advanced to phase I clinical trials by Eisai.

To date, the active pharmaceutical ingredients (APIs) of these compounds have been manufactured via semi-synthesis from fermentation-derived pladienolide D. However, its supply is severely limited because of high production costs and the need for HPLC purification to achieve adequate purity. These issues represent significant obstacles to large-scale manufacturing for clinical and commercial use.

To address these limitations and enable future commercial production, we undertook comprehensive, process-oriented studies into the total synthesis of pladienolide D, aiming to establish a scalable and efficient manufacturing process. As a result, we developed a 17-step longest linear sequence (LLS) incorporating several key transformations: stereoselective construction of the C-16 stereocenter using an L-(+)-lactic acid-derived chiral source, 12-membered macrolactonization via ring-closing metathesis (RCM), and late-stage coupling of the core with the side chain through a Mizoroki–Heck reaction.

Ultimately, a scalable total synthesis of pladienolide D was established from inexpensive starting materials, providing a practical manufacturing platform for future clinical and commercial supply.

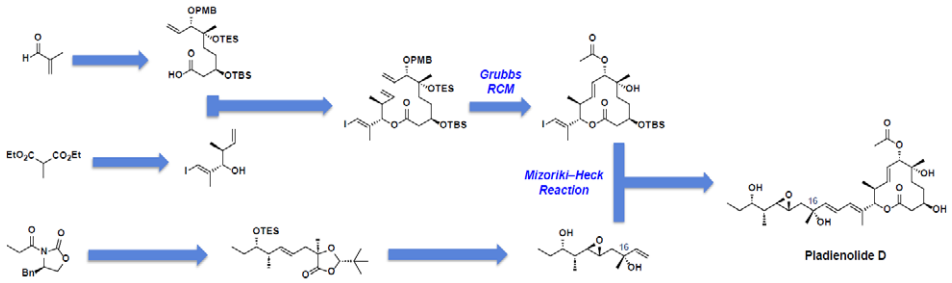


Figure 1. Overview of the Scalable and Practical Total Synthesis for Pladienolide D

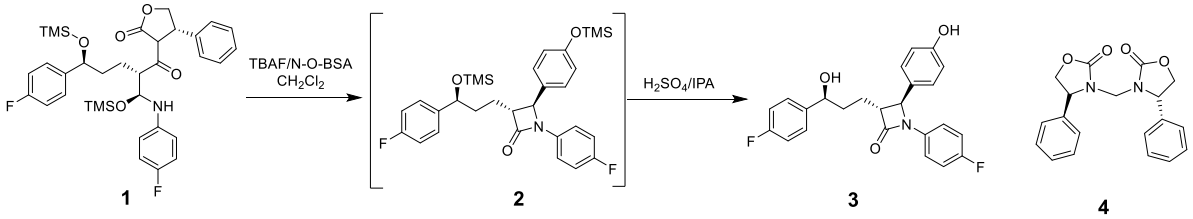
2P- 17

Eco-friendly Manufacture of Ezetimibe: Impurity control and Sustainability

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Ezetimibe is an USFDA approved drug to control elevated blood cholesterol levels. It is also approved in combinations with statins in select high-risk persons to whom low-density lipoprotein goals cannot be achieved by maximally tolerated statin alone.[1]

The Neuland manufacturing process of Ezetimibe (**3**) involves the cyclization of Intermediate (**2**) using TBAF/ N-O-BSA, followed by the acid mediated de-silylation (Scheme-1).



Scheme 1: Synthesis of Ezetimibe

The above process results in the formation of an impurity, Oxazolidinone dimer (**4**), due to the use of dichloromethane (DCM) as a solvent during the reaction and workup procedures. The control of this impurity as per ICH guidelines in Ezetimibe presents several challenges, needing several purifications using excess solvents.

The Neuland approach presents a "*greener and leaner*" framework to the last stage of the manufacturing process. The successful replacement of DCM (ICH: Class-2 solvent) with a Class-3 solvent, not only resulted in making the process environment friendly but also eliminated the formation of the process impurity. The poster details the benefits and advantages of the adopted approach.

Reference:

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2P- 18

DirectInject-LC: a New PAT Platform with HPLC

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DirectInject-LC is a new PAT platform that effectively addresses the common issues associated with acquiring real-time measurements on chemical reactions using liquid chromatography (HPLC). The applications demonstrated in this poster reflect the breadth and capability of DirectInject-LC to provide time-course analysis of complex chemistry via HPLC.

In application 1, Shi et al. demonstrate the effect of halide salts on reactions rates in Suzuki–Miyaura a cross-coupling reaction performed under homogeneous aprotic conditions.

In application 2, Deem et al. use DirectInject-LC technology to provide mechanistic insights for the synthesis of asymmetric SpiroOMeTAD derivatives.

In application 3, Kukor et al use EasySampler with DirectInject-LC technology and chiral chromatography to enable control over a continuous crystallization to obtain large yields of an enantiopure compound.

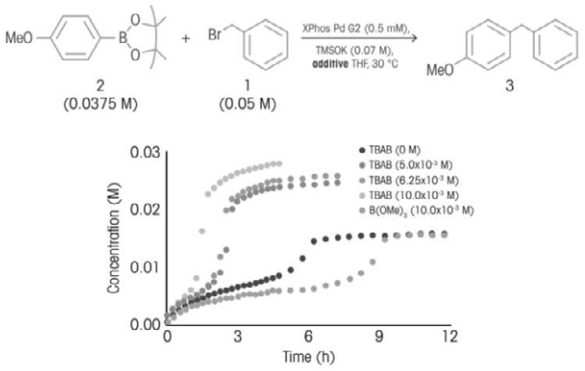




Figure 1. Tetrabutylammonium bromide added to the SMC reaction

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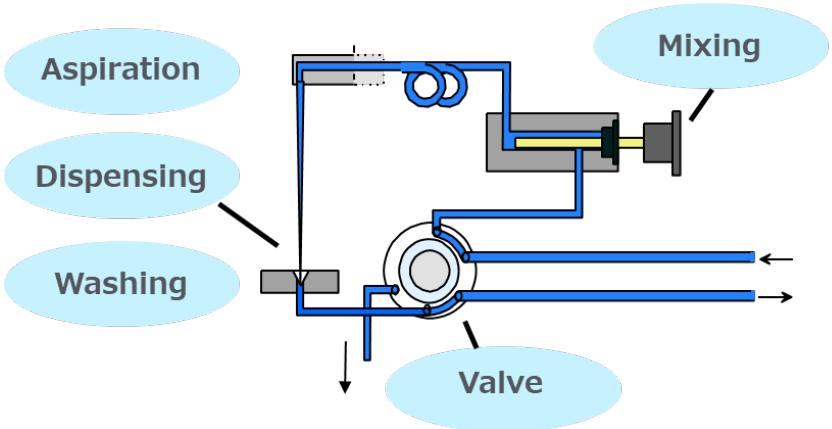
Automated Preparation of Calibration Standards Using an HPLC Autosampler for Reproducible Quantitative Analysis

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Reproducible preparation of calibration standards is essential for quantitative HPLC analysis. However, manual dilution procedures are often time-consuming and subject to operator-dependent variability. In this study, the reproducibility of stepwise dilution using an LC autosampler was evaluated with the Agilent Infinity III LC system. This approach enables fully automated dilution and injection without additional devices or complicated pretreatment.

A caffeine standard solution was used as a stock solution, and serial dilutions were automatically prepared by programmed aspiration, dispensing, and mixing using the autosampler injector program. The prepared dilution samples were repeatedly analyzed to valuate dilution reproducibility and calibration performance.

Excellent reproducibility of peak areas was obtained at each concentration level, and the resulting calibration curves showed high linearity with coefficients of determination exceeding 0.999. These results demonstrate that autosampler-based dilution provides reliable calibration data while reducing manual operations. From a routine analytical and quality control perspective in process development and manufacturing environment, this approach represents a practical and effective strategy for improving analytical efficiency, data reproducibility, and robustness of quantitative HPLC analysis.



Scheme 1. InjectorProgram

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2P- 20

High-Efficiency Continuous Extraction Technology Based on SMCR®

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In recent years, there has been a shift from batch production to continuous flow production, and microflow synthesis methods using channels with diameters of only a few millimeters have attracted considerable attention. Although microflow synthesis is expected to become more widely adopted in the future, conventional microflow reactors have limited throughput and are therefore currently restricted to laboratory-scale experiments and small-scale production.

The SMCR (Stacked Multi-Channel Reactor) is a reactor designed for high-throughput processing by arranging numerous fine channels in parallel. This poster presents a method for improving the efficiency of batch production by leveraging the excellent heat transfer and extraction performance of the SMCR.

In solvent extraction processes, a slug flow is formed in which the continuous phase and dispersed phase flow alternately. Internal circulation within each slug continuously renews the liquid–liquid interface, resulting in a significant enhancement in extraction efficiency. In addition, this flow regime offers several advantages, including suppression of emulsion formation due to the increased specific interfacial area and the application of gentle shear forces.

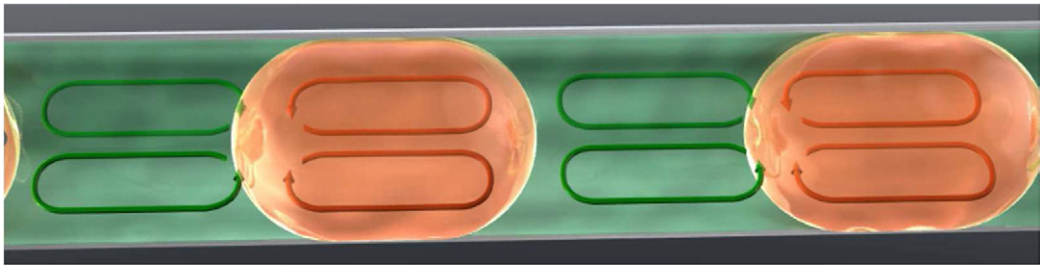


Fig. 1 Formation of slug flow in the SMCR channel

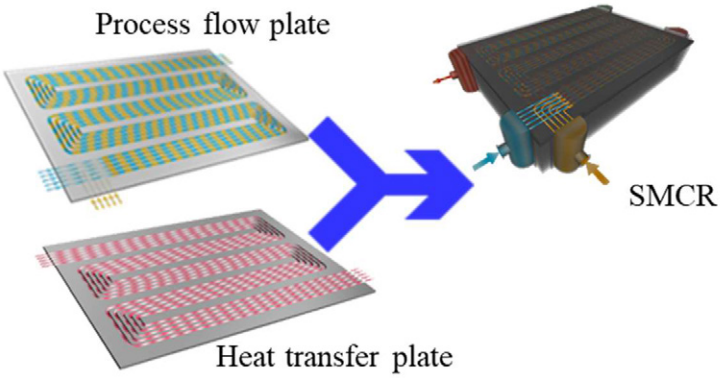


Fig. 2 Stacked plate structure of the SMCR

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Practical Synthesis and Commercialization of Chiral Fmoc-Serine Derivatives via Copper Catalyzed Direct Asymmetric Aldol Reaction

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Optically active β-hydroxy-α-amino acids, particularly serine derivatives, are highly valuable chiral building blocks for the discovery of peptide-based drugs. However, the availability of these Fmoc-protected derivatives with diverse functional groups on the side chain remains limited. We have previously developed a highly stereoselective direct catalytic asymmetric aldol reaction to prepare β-hydroxy-α-amino esters.[1)] In this study, we applied this core method to establish a practical and scalable synthetic route for a variety of Fmoc-serine derivatives, in collaboration with Funakoshi Co., Ltd. While the initial asymmetric aldol reaction requires precise control of reaction conditions, the subsequent functional group transformations and Fmoc protection follow conventional and robust procedures, allowing for the reliable synthesis of the diverse derivatives. Through this approach, we successfully synthesized 19 different Fmoc-serine derivatives, all exhibiting high purity (>95%) and excellent optical purity (>95% ee). This scalable process enables the stable supply of these complex chiral building blocks as commercial reagents, which is expected to significantly accelerate drug discovery research.

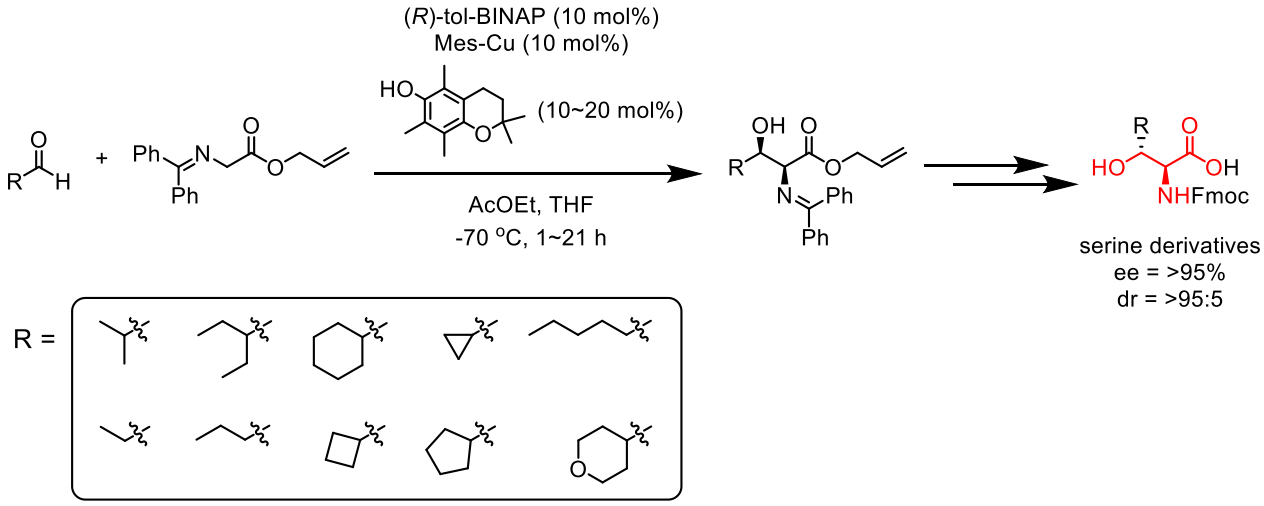


Figure 1. Copper Catalytic Direct Asymmetric Aldol Reaction and Derivatization of Serine Derivatives

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2P- 22

Continuous-Flow Syntheses of 1,2-Diols from Alkenes Using Titanium Silicalite-1 Catalyst Column with Hydrogen Peroxide

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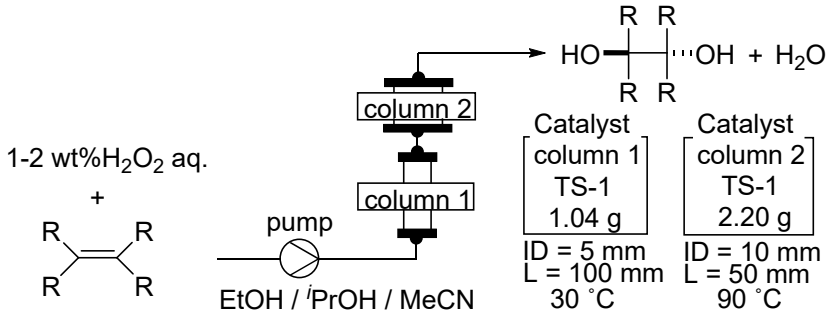
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Vicinal diol is known as a useful chemical used in moisturisers and pharmaceuticals. When synthesis of *anti*-1,2-diol from the corresponding alkene *via* an oxidation reaction, a two-step process involving epoxidation followed by hydration is required. In the industrial synthesis, hydrogen peroxide (H_2O_2) and carboxylic acids are frequently used in the epoxidation process, and strong acids are used in hydration reactions; however, such acids should be discharged because of a significant environmental impact.

We have developed a method for synthesizing vicinal diols in high yields using a flow reaction involving a column packed with a titanium silicalite-1 catalyst (TS-1) in the presence of aqueous 2% H_2O_2 solution without acids. By optimizing the reaction conditions to facilitate the first-stage epoxidation using low-concentration H_2O_2 and to allow the second-stage hydration reaction, which needs higher temperature with water, we synthesized vicinal diols in high yields in a retention time of ca. 5 min within the column.

The developed reaction showed good to excellent yields to synthesize various vicinal diols such as aliphatic diols and cyclic diols. Furthermore, we confirmed that vicinal diol was synthesized continuously for over 200 h with average yields of 91% by loading enough TS-1 catalyst onto the column.



Scheme 1. Continuous-flow syntheses of vicinal diols using TS-1 catalyst with H_2O_2

This presentation is based on results obtained from a project, JPNP19004, subsidized by the New Energy and Industrial Technology Development Organization (NEDO), Japan.

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2P- 23

Heterogeneous Cobalt-Catalyzed Thiol Synthesis from Alkenes and Carbonyl Compounds Using Elemental Sulfur and Hydrogen as Simple Reagents

Eiji Yamamoto,[a,*] Weixin Qi,[a] Xu Ke,[a] Haruno Murayama,[a] Takashi Kamachi,[b] Akina Yoshizawa,[a] Akihiro Nakayama,[a] Matsueda Hironobu,[c] Makoto Tokunaga[a]

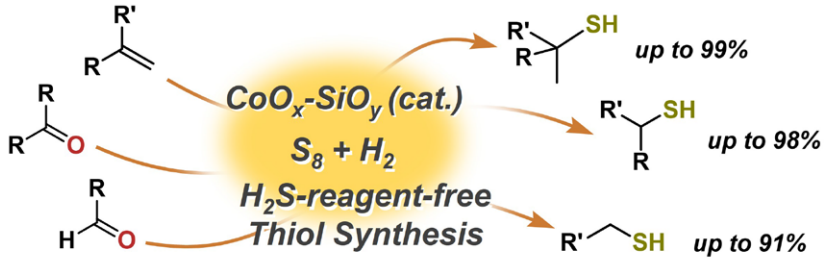
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Elemental sulfur and molecular hydrogen are among the most atom-efficient sulfurizing and reducing agents, respectively. However, their combined use in the catalytic synthesis of organosulfur compounds remains largely unexplored, and H_2S or related sulfur reagents have been used in the industrial synthesis despite its significant toxicity. While metal catalysts are typically employed for reactions involving molecular hydrogen, the progress of research in this area has been hindered, likely because sulfur-containing species often poison transition-metal catalysts. In this context, we have successfully developed a heterogeneous cobalt-catalyzed synthesis of dialkyl polysulfanes (RS_nR), which are widely used as extreme-pressure additives, from elemental sulfur, molecular hydrogen and alkenes. In addition, we observed thiols as byproducts in this catalytic system. Based on this observation, we envisioned that catalytic thiol synthesis would be achieved by using metal catalysts having strongly reducing activity. Investigations of alkenes and carbonyl substrates revealed that the corresponding thiols were obtained in good to high yields by using cobalt silicate (CoO_x-SiO_y) as a catalyst.



Scheme 1. H_2S-Reagent-Free Thiol Synthesis from Alkenes and Carbonyl Compounds

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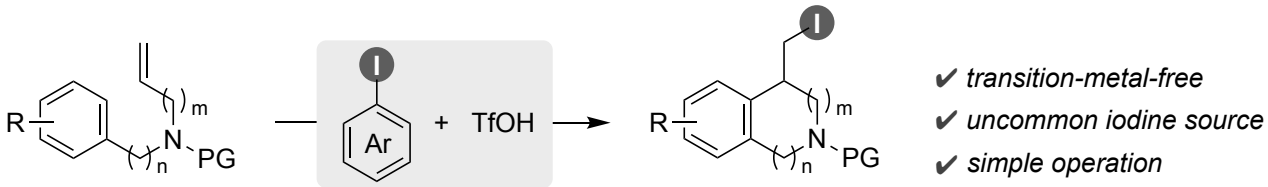
N-Heterocycle Synthesis *via* TfOH-Mediated Iodocarbocyclization with Iodoarenes

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Benzo-fused N-heterocycles are important skeletons for the development of novel drugs and pesticides. Friedel–Crafts-type iodocarbocyclization of alkenyl substrates would be an efficient method for constructing benzo-fused N-heterocycles with an iodine functionality.[1] Although several groups have been investigated the iodocarbocyclizations utilizing $(Py)_2IBF_4$ or *N*-iodo reagents,[2] the reported protocols mostly focused on the transformation of aniline-derived substrates. Thus, the development of synthetic methods suitable for other substrate classes would expand the structural diversity of the accessible scaffold, which would contribute to the progress of medicinal and agricultural chemistry.

Herein, we report a TfOH-mediated iodocarbocyclization of allylic and homoallylic sulfonamides utilizing iodoarenes as iodinating reagents.[3] Iodoarenes would provide a key electrophilic iodine species for iodocarbocyclization in the presence of TfOH. A variety of sulfonamides derived from benzylamines, phenethylamines, and anilines were transformed into the corresponding benzo-fused N-heterocycles in good to high yields under transition-metal-free conditions.



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Automated Multi-Sampling Flow Reactor for Efficient Kinetic Analysis

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Flow reactors have great advantages over batch reactors for kinetic analysis, such as rapid mixing, precise controls of reaction time and temperature, and ease of automation.[1)] However, in order to vary the reaction time, i.e., the residence time in the reactor tube, over a wide range, it is necessary to significantly change the flow rate. This may adversely affect mixing efficiency and temperature control. In addition, each change in the flow rate requires a long waiting time for the effluent to reach a new steady state, leading to a practical drawback. Alternatively, the residence time can be adjusted by changing the length of the reactor tube, but exchanging the reactor tube needs much effort.

In this study, we developed an automated flow reactor which has multiple sampling ports along the flow path to quench the reaction at a desired residence time simply by controlling a selector valve without changing the flow rate and reactor tube. A schematic diagram of the apparatus is shown in Fig. 1. Reactant solutions A and B are delivered by HPLC pumps at constant flow rates. The solutions are preheated in a water bath and then mixed to initiate the reaction. The reaction is quenched at a designated position by mixing with a quencher solution supplied by another HPLC pump at a constant flow rate. The effluent is sequentially collected by a fraction collector synchronized to the selector valve. At the symposium, we will present an application of this system to the kinetic analysis of acetaminophen synthesis from 4-aminophenol and acetic anhydride.

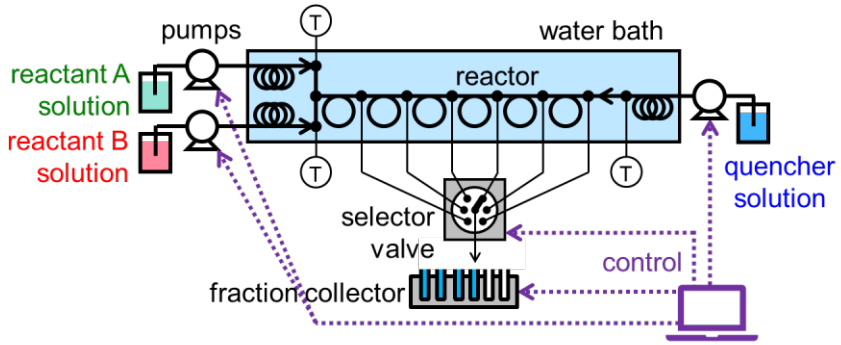


Fig 1. Schematic diagram of the automated multi-sampling flow reactor.

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Acknowledgement

This study is based on the results obtained from a project, JPNP23028, commissioned by the New Energy and Industrial Technology Development Organization (NEDO), Japan.

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Thiobenzoic Acid-Catalyzed Regioselective Functionalization of Allylamines via Hydrogen Atom Transfer under Visible Light Irradiation

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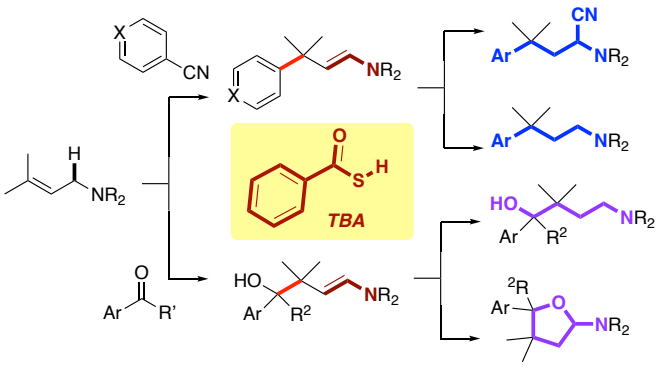
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Direct functionalization of C–H bonds has been long recognized to be step- and atom-economical. With recent advances in photochemistry, C–H functionalizations mediated by photoredox catalysts (PCs) have gained significant attention. Activation of the α-C–H bond of a nitrogen or oxygen atom is particularly important for further derivatization of bioactive compounds such pharmaceuticals and agrochemicals. In this context, we previously reported that thiobenzoic acid (TBA) can act as a dual-role PC mediating single electron transfer (SET) and hydrogen atom transfer (HAT), which is expected to avoid complication that may arise from the combined use of multiple catalysts, and catalyzes α-C–H coupling reactions of benzylamines, benzyl alcohols, and dihydroimidazole derivatives with either of cyanoarenes[1] or aromatic ketones.[2,3]

Encouraged by the previous success, we anticipated that allylic amines would also be a good C–H donor. Although the *N*-allylic C−H bond has a similar bond dissociation energy to the *N*-benzylic C−H bond, its C–H activation under photocatalytic conditions is extremely rare, because the higher reactivity of the allylamines and the enamine intermediates may potentially induce undesired redox-related side reactions. Nevertheless, we envisaged that the mild redox potential and HAT ability of TBA would enable the desired transformation to proceed efficiently. Actually, various allylamines underwent C−H coupling reactions with cyano(hetero)arene and arylketones, respectively, in high yield with excellent γ-regioselectivity.[4] In-situ-formed enamine intermediates are versatile intermediates, and thus appropriate set-up provided multiple kinds of potentially useful molecules, including 1,3-difunctionalized aminonitriles, 3-aryl-propylamines, and 1,4-amino alcohols, and 2-amino tetrahydrofurans. The details of the study including the reaction mechanism will be discussed.

This work: Unique transformations of allylamines initiated by Cα-H cleavage



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2P- 27

Integration & Intelligence Enabling Green Chemistry at PharmaBlock

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PharmaBlock integrates continuous flow chemistry, heterogeneous catalytic hydrogenation, biocatalysis, process analytical technology (PAT), automation, and digital intelligence to accelerate sustainable pharmaceutical manufacturing. Through the integration of advanced technology platforms and data-driven process development, safer, greener, and more efficient chemical processes can be rapidly translated from laboratory development to commercial manufacturing.

Key capabilities include continuous flow processing for hazardous and fast reactions, micro-packed bed hydrogenation for scalable catalytic transformations, biocatalysis for highly selective synthesis under mild conditions, and PAT-enabled real-time monitoring and control. Combined with high-throughput experimentation [1] and AI-assisted optimization, these technologies significantly improve process efficiency, product quality, and sustainability metrics.

PharmaBlock's green chemistry platforms have been successfully applied across discovery, development, and manufacturing projects, enabling reductions in solvent consumption, process mass intensity (PMI), energy usage, and overall manufacturing risk. These innovations were recognized with the 2023 and 2024 ACS Green Chemistry Awards.

This poster highlights PharmaBlock's integrated platform strategy and demonstrates how intelligent process technologies are enabling the next generation of sustainable pharmaceutical manufacturing.

Note: *PharmaBlock has been inspected by US FDA and PMDA.*

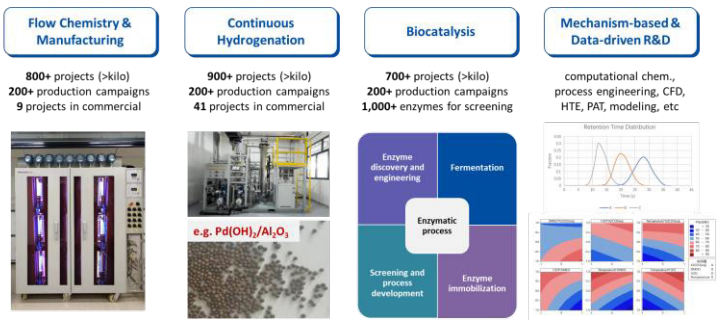


Figure 1. Core technology platforms at PharmaBlock PBRI supporting green and sustainable pharmaceutical manufacturing.

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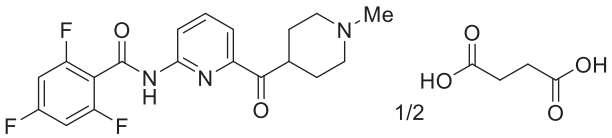
Crystal Structure Elucidation of Ephemeral Metastable Polymorphs by 3D ED/MicroED Appearing During Crystallization Process

[1]Keiyo Nakai,* [1]Kuniyoshi Miki, [2]Takashi Kikuchi, [1]Masaki Hattori, [1]Kazuki Harada, [1]Rina Konishi, [1]Kayoko Hata, [1]Chisato Okahashi, [1]Mitsuhisa Yamano

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Lasmiditan 0.5 succinate is a novel anti-migraine drug developed by Eli Lilly and Company. During the first attempt to prepare its commercial crystalline polymorph, Form A[1,2], in our laboratory, we unexpectedly encountered the formation of previously unreported metastable polymorphs, Forms E and F, coexisting with Form A. Initial efforts to obtain single crystals of these new polymorphs for structure determination were unsuccessful; crystallization from various solvents system consistently yielded only Form A. Further investigation revealed that Forms E and F are extremely short-lived and rapidly transform into the stable Form A within minutes in ethanol. Moreover, their (Form A, E, and F mixtures) reproducible preperation was strongly suppressed by dominant unintentional seeding effects arising from trace amounts of Form A present in the laboratory environment.



Scheme 1. Chemical structure of lasmiditan 0.5 succinate.

In this study, we first employed multi-point[3] 3D ED/MicroED[4-8] analysis to successfully characterize the polymorphic composition of the inseparable Form A, E and F mixture. Subsequently, by selecting high quality microcrystals, we achieved direct elucidation of all crystal structures present in the polymorphic mixture. Packing analyses of the resolved structures provided structural support for the experimentally (competitive slurry conversion method) observed thermodynamically stable hierarchy among the polymorphs. Furthermore, clustering analysis of lattice parameters enabled us to describe the bulk crystalline sample as a distribution of various unit-cell, thereby introducing a new analytical concept that allows direct observation of structural homogenization processes occurring during crystal growth.

References

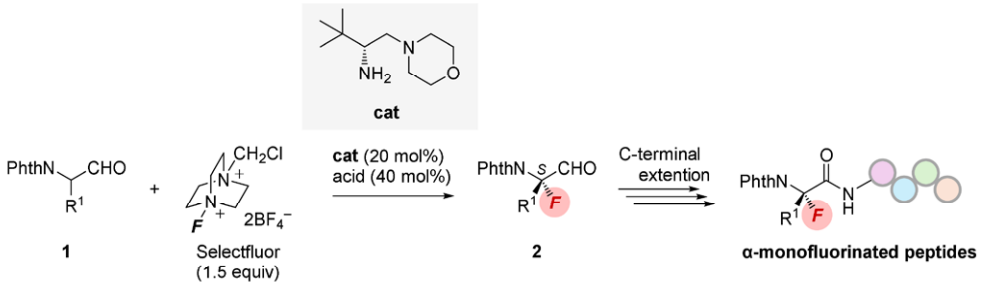
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Enantioselective Synthesis of α-Monofluorinated α-Amino Acid Derivatives and Their Application to α-Monofluorinated Peptides

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It is widely recognized that organofluorine compounds play an important role in medicinal chemistry. Among the myriad fluorinated bioactive compounds, fluorinated amino acids have attracted considerable attention as valuable building blocks for peptides and pharmaceuticals. Accordingly, many fluorinated amino acid analogues have been developed, including α-amino acids bearing fluorinated side chains at the β- and/or γ-positions.[1] In contrast, only a few synthetic methods for α-monofluorinated α-amino acids have been reported, and to date, no catalytic enantioselective synthesis has been described.[2]

First, we discuss the enantioselective fluorination of α-aminoaldehyde (1) using an organocatalyst. After screening the reaction conditions, a highly enantioselective fluorination at the α-position was successfully achieved using a primary amine catalyst (20 mol%) and Selectfluor (1.5 equiv) as the fluorinating reagent. Investigation of the substrate scope revealed that a wide variety of α-monofluorinated α-aminoaldehydes (2) could be obtained with good enantioselectivities (up to 97% ee). Furthermore, these fluorinated aldehydes could be oxidized to the corresponding carboxylic acids and subsequently converted into α-monofluorinated peptides. In this presentation, we also discuss the detailed synthesis and properties of α-monofluorinated peptides (Scheme 1).



Scheme 1. Outline of a presentation

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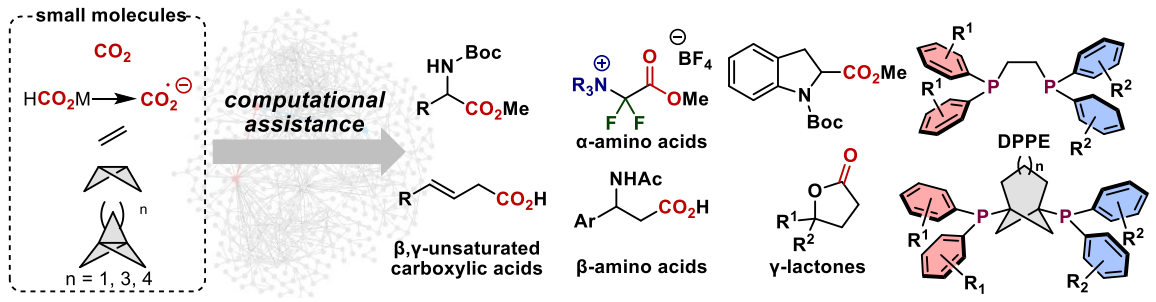
2P- 30

Computationally Guided Reaction Development for the Construction of Valuable Molecular Scaffolds from Small Molecules

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Our research group in WPI-ICReDD develops new synthetic reactions by integrating experimental organic chemistry with quantum chemical calculations. In particular, we use automated reaction-path search method (the AFIR method) to design, understand, and improve reactions that are difficult to discover by conventional trial-and-error approaches. Our recent studies focus on the use of carbon dioxide, ethylene, and strained molecules as simple and sustainable building blocks. Through computational analysis, we identify key intermediates, transition states, and hidden reaction pathways. These insights are then used to guide experimental reaction development. This approach may be useful for process chemistry. It can reduce unnecessary screening, clarify reaction mechanisms, and accelerate the optimization of synthetic routes. By combining computation and experiment, we aim to create a practical platform for molecular synthesis with higher efficiency and sustainability.

At WPI-ICReDD, we also promote industry–academia collaboration through **MANABIYA Industry** (https://www.icredd.hokudai.ac.jp/manabiya). In this program, researchers from companies can work with ICReDD scientists for approximately one year. They learn computational chemistry and reaction design while addressing their own research challenges. MANABIYA Industry provides an opportunity to connect advanced academic methods with real industrial problems. This poster presentation will introduce our recent reaction-development studies and discuss potential opportunities for collaboration.



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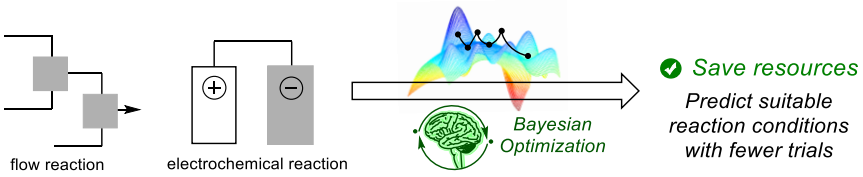
2P- 31

Data-Driven Multiparameter Optimization for Efficient Screening of Reaction Conditions in Flow and Electrochemical Synthesis

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Optimization of reaction conditions is a pivotal yet notoriously time- and resource-intensive process in organic synthesis. Traditional one-variable-at-a-time approaches fail to capture parameter interdependencies and are poorly suited to the multidimensional condition spaces. Bayesian optimization (BO) overcomes these limitations by iteratively proposing experiments that balance exploration of untested conditions and exploitation of high-performing ones, enabling rapid convergence to global optima from minimal data. Doyle and coworkers pioneered the application of BO to batch reaction optimization.[1] However, its application to electrochemical and flow syntheses, where parameters such as current, flow rate, and reactor type further expand the space and increase the complexity, has remained largely unexplored.[2]

Our group has developed BO-based multiparameter optimization strategies tailored to electrochemical and flow synthesis. In our first study, BO was applied to optimize five numerical parameters simultaneously in the electrochemical oxidative synthesis of α-ketiminophosphonates identifying optimal conditions in twelve experiments (71% yield).[3] In a second study, we employed categorical variables by developing an algorithm incorporating one-hot encoding, enabling simultaneous optimization of six parameters, including micromixer type, for the organocatalytic flow synthesis of functionalized biaryls, achieving 93% yield within fifteen experiments.[4] In materials science, we further applied BO to the electrochemical synthesis of a chiral double oxaza[7]dehydrohelicene through a complex domino anodic oxidation. By sequentially employing two acquisition functions—Lower Confidence Bound (LCB) to maximize exploration followed by Expected Improvement (EI) for exploitation—we quadrupled the yield within sixteen experiments.[5]



Bayesian optimization-driven screening of multiple parameters

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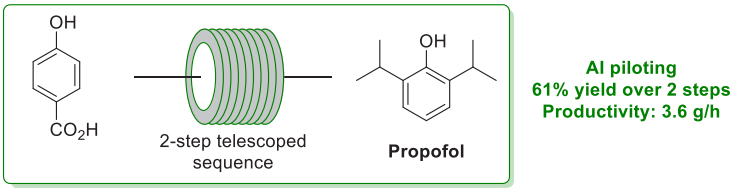
2P- 32

PIPAc: towards flow chemistry and artificial intelligence powered API production

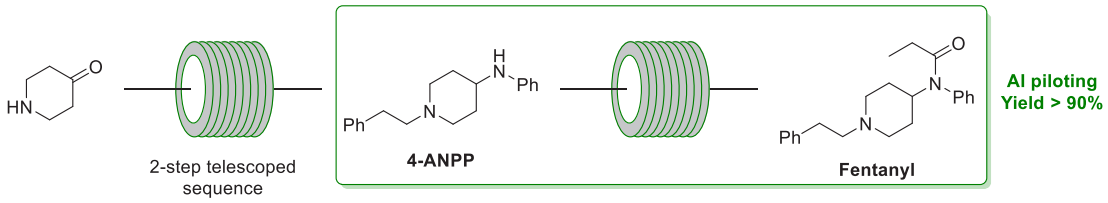
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The use of flow chemistry [1] and artificial intelligence[2] in the production of API has witnessed significant interest both from academia and industry over the last years. Propofol[3] and fentanyl[4] are standing as privileged target because they experience shortage during COVID-19 crisis and are on the WHO's list of essential medicine. The PIPAc project aim is to bring the first AI-powered autonomous industrial demonstrator for APIs manufacturing through the combination of continuous flow chemistry, artificial intelligence, and additive manufacturing. In this frame, we successfully:

1) developed a two-step sequence towards propofol including intermediate in-line work-up and implemented an AI-agent to pilot the process:



2) translated fentanyl synthesis under flow conditions. A 2-step sequence allows the synthesis of penultimate fentanyl intermediate 4-ANPP while the final stage is piloted by AI using in-line ^{1}H NMR:



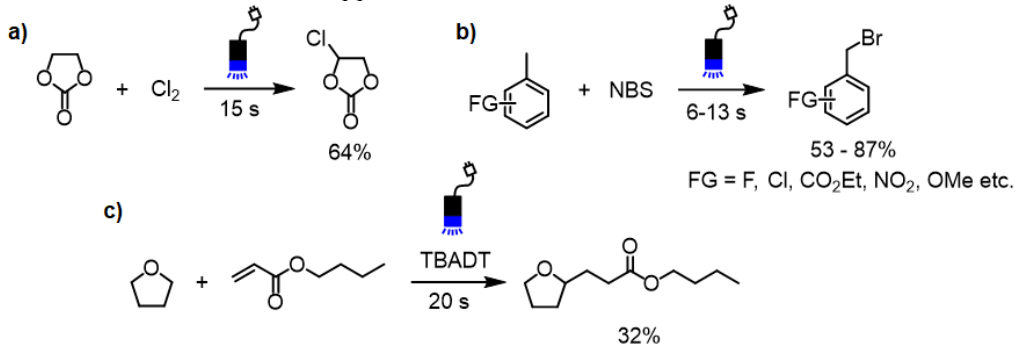
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High-Speed C–H Halogenation and Alkylation Using a Diagonal Photoflow Reactor (LX-1) Combined with a High-Power UV-LED

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Photochemical reactions have attracted considerable attention as environmentally benign and sustainable synthetic methodologies. However, conventional batch photoreactors suffer from limited light penetration and difficulties in scale-up. In this study, we investigated high-speed C–H functionalization reactions using a novel photoflow setup consisting of a diagonal photoflow reactor (MiChS LX-1) and a high-power UV-LED (365 nm: MiChS LED-s). The LX-1 reactor possesses sloped parallel channels that generate a thin liquid film, enabling efficient light irradiation. The system was applied to the C–H chlorination using chlorine gas. Chloroethylene carbonate, a precursor to vinylene carbonate, was obtained with a residence time of 15–30 s (Scheme 1a). Successful partial irradiation suggested that photoirradiation functions as the radical initiation step. Benzylic C–H bromination using N-bromosuccinimide (NBS) was examined. Various benzylic compounds were converted into the corresponding brominated products in good yields with residence times of only 6–13 s (Scheme 1b). The practical utility of this protocol was demonstrated by the gram-scale synthesis of ticlopidine by the photoflow benzylic C–H bromination of ortho-chlorotoluene. The photo flow set-up was tested for photocatalytic C-H alkylation. An acetonitrile solution of tetrahydrofuran and butyl acrylate were subjected to photocatalytic conditions using tetrabutylammonium decatungatate (TBADT, 1 mol%) in acetonitrile. As a result of carrying out the reaction, giving the addition product. These results demonstrate that the LX-1 reactor combined with a high-power UV-LED enables rapid and scalable photochemical C–H functionalization suitable for industrial applications.



Scheme 1. High-Speed C-H Functionalization Using LX-1 Combined with a High-Power UV-LED

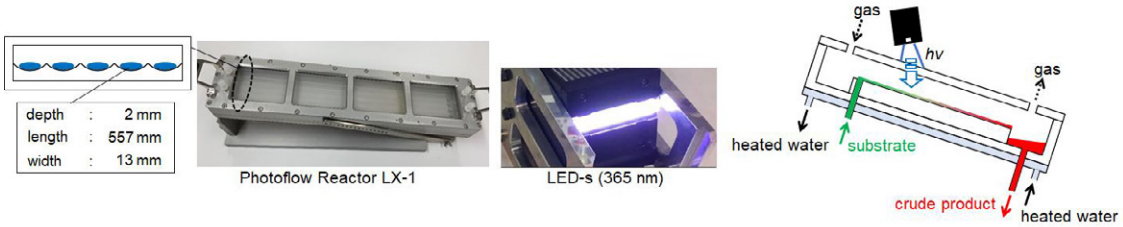


Figure 1. Photo Flow Setup.

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This work was carried out in collaboration with the Laboratory for Advanced Organic Synthesis at Osaka Metropolitan University.

2P- 34

Camphorsultam-Assisted Stereoselective Synthesis of *P*-Chiral Phosphonate Diesters

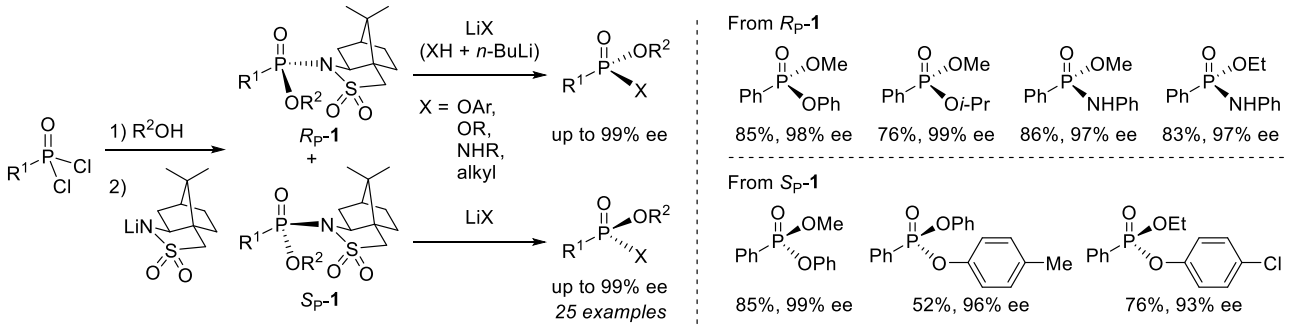
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P-Chiral organic compounds are important classes of biologically active organic molecules.[1] Optical resolution using a chiral auxiliary is a classical method that is highly reliable and practical for synthesizing chiral phosphorus compound with high optical purity. In this process, it is important to note the "dual roles" of the chiral auxiliary; one is the efficiency of the optical resolution and the other is the leaving ability in the following substitution reaction because the synthesis of *P*-chiral compounds usually requires that the chiral auxiliary be replaced with other functional groups. We planned to use a commercially available chiral sulfonamide of camphorsultam as a highly "reactive" auxiliary for synthesizing *P*-chiral compounds. Because of the low pK_a values of sulfonamides (pK_a~17.5), camphorsultam can serve as a good leaving group for the substitution with phenols as well as other nucleophiles, including aliphatic alcohols, amines, and carbon nucleophiles. Herein, we present the synthesis of *P*-chiral phosphorus compounds by an optical resolution-substitution process using camphorsultam (Scheme 1). The process can be applied to the synthesis of *P*-chiral phosphinic esters, phosphonamidates, and thiophosphonate diesters, demonstrating the versatility of phosphonamidates of camphorsultam for the synthesis of *P*-chiral phosphrus (V) compounds.[2]



Scheme 1. Camphorsultam-assisted stereoselective synthesis of *P*-chiral compounds.

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2P- 35

The Convergence of Three Novel Downstream Technologies: One Breakthrough in Peptide and Oligonucleotide API Manufacturing

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Peptide and oligonucleotide active pharmaceutical ingredients (APIs) are manufactured through four principal unit operations: synthesis, cleavage, purification, and lyophilization. Each operation requires rigorous quality control and continual reductions in raw-material costs and processing time to lower overall manufacturing expenses. Although upstream technologies such as synthesis have advanced, optimization of downstream operations - particularly purification and lyophilization - remains a major bottleneck. Peptistar, in collaboration with partner companies, is driving downstream innovation. This presentation focuses on purification, concentration, and lyophilization.

Purification is the critical step for impurity removal, but achieving both high purity and high recovery is often a trade-off that constrains cost reduction. Single-column purification typically improves impurity clearance at the expense of yield. By contrast, continuous purification using Contichrom® enables production of high-purity APIs while maintaining recovery. Validation with a model oligonucleotide demonstrated approximately a twofold increase in recovery and a substantial reduction in processing time through automation.

Concentration reduces the volume of the purified solution prior to lyophilization. Conventional options include tangential flow filtration (TFF) and vacuum concentration; TFF can suffer from organic-solvent incompatibility and membrane adsorption that reduce yield, while vacuum concentration can induce quality degradation and complicate control of physicochemical properties. Using Asahi Kasei Corporation’s membrane concentration system FO-MD, we achieved concentration with negligible quality deterioration and minimal changes in solution composition.

Lyophilization is commonly performed in shelf-type lyophilizer, which present challenges in cycle time and quality control. Using Kobelco Eco-Solutions Co.,Ltd.’s mixer-type lyophilizer, RHEOFREED®, and benchmarking against a shelf-type unit used in GMP production, we reduced lyophilization time by 74% and markedly lowered residual acetonitrile in the API.

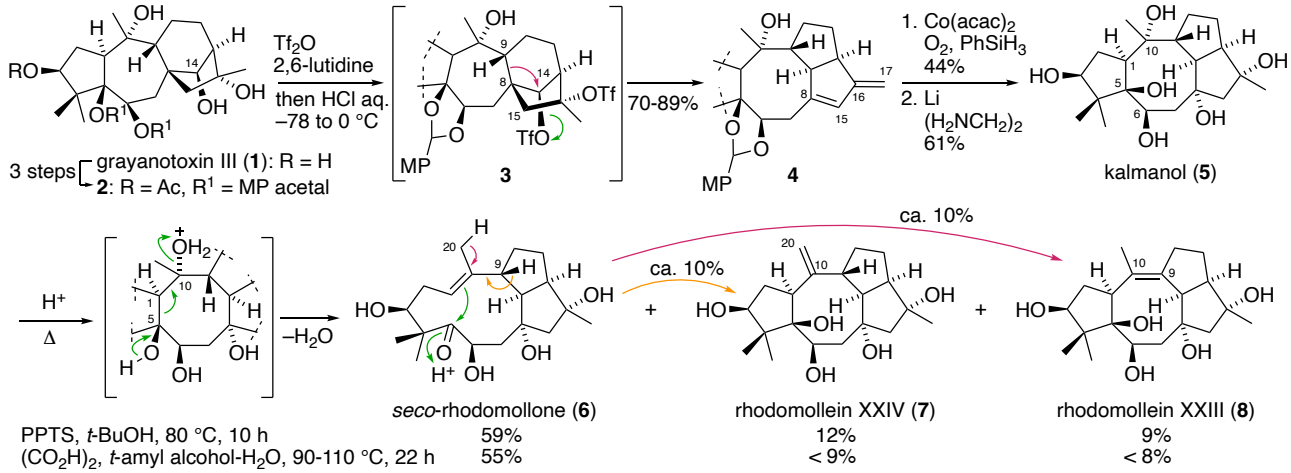
Adoption of these technologies yields clear advantages in both cost and quality control. Detailed experimental data and process parameters are presented on the poster.

Bioinspired Chemical Transformations of Grayanotoxin III to Kalmanol, *seco*-Rhodomollone, Rhodomolleins XXIII and XXIV

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Grayanoids are a group of diterpenoids specifically isolated from plants of the Ericaceae family. Since the first structure elucidation of grayanotoxin I (GTX I) and III (GTX III) in the 1960s, hundreds of grayanoids have been isolated, and their structures have been identified. Their highly complex, diverse, and congested ring structures, together with salient toxic and pharmacological activities, have made grayanoids fascinating research targets in the fields of toxicology, pharmacology, and chemical synthesis. Herein, we report the first chemical conversion of GTX III (**1**) into four kalmanes, namely kalmanol (**5**), *seco*-rhodomollone (**6**), rhodomollein XXIV (**7**), and rhodomollein XXIII (**8**) in accordance with their proposed biosynthetic hypotheses. This study not only showed a methodology to supply rare kalmanes in short synthetic steps from the relatively abundant natural GTX III (**1**), but also revealed their putative biosynthetic pathways.

The key skeletal rearrangement from the grayanane (**2**) to the kalmane framework (**4**) was achieved at low temperature by introducing triflate as the leaving group of the C14 hydroxyl group. Subsequent regio- and stereoselective hydration and global deprotection gave kalmanol (**5**) in a total of six steps from GTX III. Further conversion to *seco*-rhodomollone (**6**), rhodomollein XXIV (**7**), and XXIII (**8**) demonstrated the putative biosynthetic pathway of these natural products. The present findings establish the route to structurally complex and rare kalmane diterpenoids, which can serve as potential lead compounds for drug discovery, and advance the overall understanding of the biogenetic pathway of grayanoids.



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2P- 37

Advancing Flow Chemistry Implementation: Pilot-Scale Demonstration of Continuous Production and Scale-Up of Organolithium Flow Reactions

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Compared to batch-type reactions, flow-type reactions offer many advantages, such as high space efficiency, relatively easy scale-up, efficient heat transfer, the ability to handle unstable intermediates, and improved safety. Therefore, flow chemistry is attracting attention as a next-generation technology. We are also conducting research in this field to enable large-scale manufacturing using flow reactions, and we have recently introduced a pilot-scale liquid–liquid flash reactor.

To initiate this project, we selected a model reaction, as shown in Scheme 1, for the synthesis of diisopropyl (4-cyanophenyl) boronate (4-CPB), which is difficult to synthesize using conventional batch processes and highlights the advantages of flow chemistry for such transformations. This reaction involves transmetalation of 4-bromobenzonitrile with *n*-BuLi, followed by nucleophilic addition to triisopropyl borate. Prior to introducing the pilot-scale reactor, we had collected the necessary data to design a reactor approximately 200 times larger than our laboratory-scale reactor.

After introducing the pilot-scale reactor, 4-CPB was produced at pilot scale and compared with laboratory results. Comparable product quality required a lower jacket temperature (−40°C vs −25°C in the laboratory). Continuous liquid feeding was then evaluated down to −65°C, and stable operation for 8 hours was achieved without clogging, yielding a reaction mixture of consistent quality.

Scheme 1. The reaction scheme for 4-CPB production

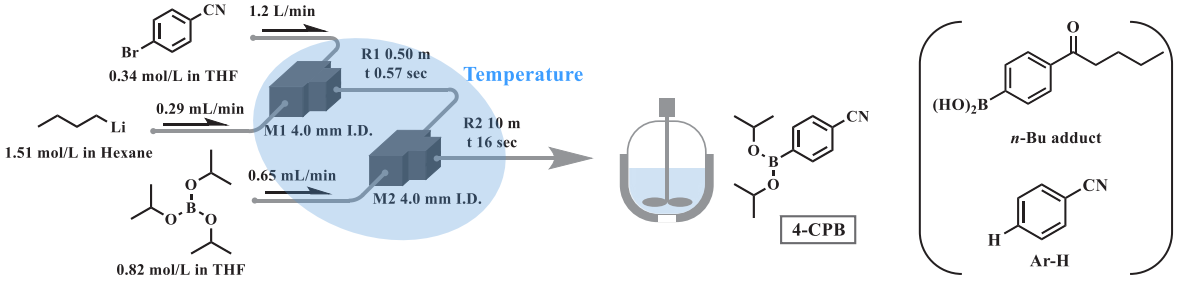


Table 1. Comparison of the reaction condition and the result

Operation System	Reactor i.d.	Flow Rate	Jacket Temp.	Operation Time (Volume)	Yield [%]	Ar-Br [%]	Ar-H [%]	*n*-Bu adduct [area% 254nm]
Lab PFR	1.0 mm	F1: 6.0 mL/min F2: 1.5 mL/min F3: 3.0 mL/min	−25° C	10 min (100 mL)	87.0	0.9	1.8	44040
Plant PFR	6.0 mm	F1: 1.20 L/min F2: 0.29 L/min F3: 0.65 L/min	−40° C	15 min (45 L)	88.5	0.9	1.7	45035

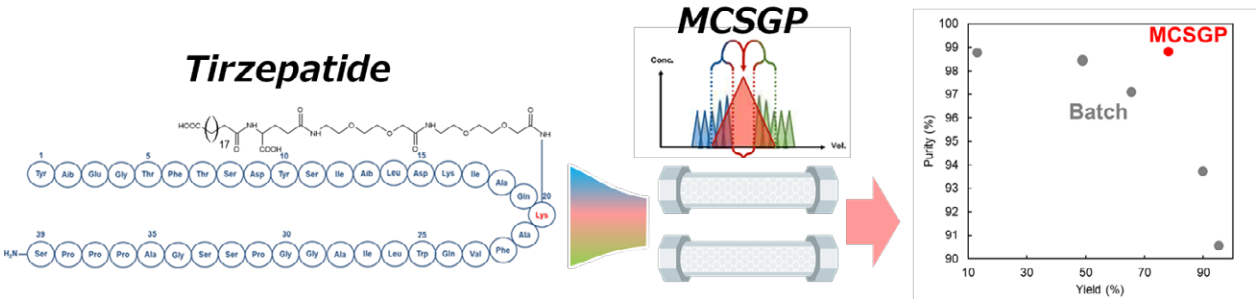
2P- 38

Development of the Efficient Purification Process for Tirzepatide Using Twin-Column Continuous Chromatography

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Peptides, such as GLP-1/GIP receptor agonists like tirzepatide, have attracted growing attention as emerging therapeutic modalities. These peptides are often characterized by increased size and structural complexity. However, their chemical synthesis tends to generate structurally similar impurities, posing challenges in terms of purification cost and extensive solvent consumption. In conventional batch purification, the trade-off between purity and yield is often unavoidable. To address this issue, MCSGP-AutoPeak (Multi-column Countercurrent Solvent Gradient Purification) has been developed.[1] MCSGP is a continuous chromatography process that integrats automated side-cut recycling and in-line dilution between two identical columns. In recent years, MCSGP has been increasingly applied to peptide purification, and its implementation in GMP manufacturing has also been reported.[2]

In this study, we first optimized the batch purification conditions of tirzepatide, including packing material, mobile-phase, loading amount, and retention factor. During this process, the newly developed packing material showed superior separation performance compared with conventional packing materials. Subsequently, the application of MCSGP enabled a higher yield while maintaining purity, compared with the conventional batch purification. Moreover, MCSGP exhibited superior performance in productivity and process mass intensity (PMI); therefore, its utility as a highly efficient purification process was demonstrated.



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2P- 39

Self-Driving Optimization of Organic Reactions via Machine Learning and Automation

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Reaction optimization has traditionally relied on expert knowledge and iterative trial-and-error processes, and therefore has required substantial time and effort. In recent years, advances in information science and automated technologies have significantly accelerated digitalization, automation, and materials informatics in the field of organic synthesis. To overcome the limitations of tedious trial-and-error procedures, considerable efforts have been devoted to the development of data-driven autonomous reaction optimization. In this context, our research institute has initiated the ***SaLA (Sagami Laboratory Automation) project***, an automation platform centered on an automated synthesis system, to enable data-driven autonomous optimization of organic reactions.

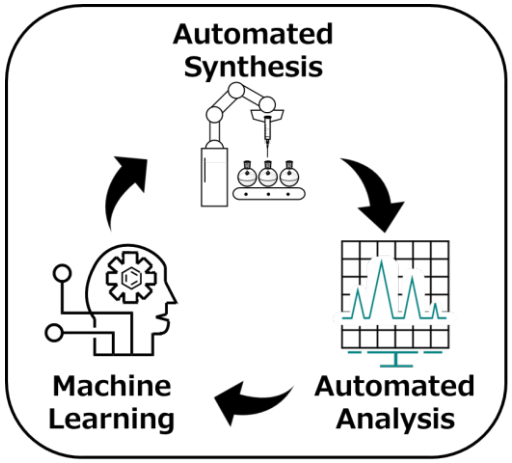


Figure 1 Autonomous Reaction Optimization

This closed-loop system generally comprises three key components: (1) an automated synthesis system (Swing XL, Chemspeed), (2) an automated HPLC analysis system (EXTREMA 4500, JASCO) for evaluating reaction outcomes (e.g., yield and selectivity), and (3) a machine learning (ML) module for generating experimental conditions. We have investigated the applicability of automated synthesis equipment to various reactions and developed an integrated system that connects synthesis and analytical instruments, thereby enabling full automation of the workflow from reaction execution to data acquisition. Furthermore, by incorporating machine learning, we have established a closed-loop system capable of autonomous optimization, in which the analysis of experimental results informs the selection of subsequent experimental conditions.

In this presentation, we report the configuration of the developed system and the results of its validation, including its application to the atuonomous closed-loop optimization to nucleophilic substitution reactions (e.g., Williamson ether synthesis, SNAr reactions).

2P- 40

Improving the efficiency of Ir type borylations and the development of [Ir(COE)2(Me2Bpy)Cl]

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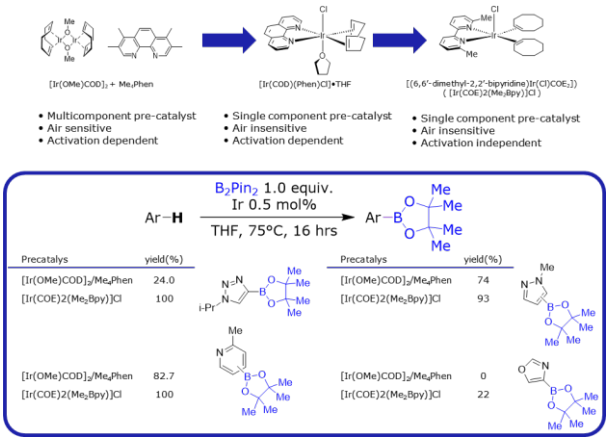
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Pharmaceutical innovation has profoundly impacted global health over the past century, driven by the discovery of biologically active compounds and the development of synthetic methodologies to access them. Foundational work by Barbier and Grignard established key principles of carbon–carbon bond formation through activation and coupling strategies, which continue to underpin modern catalysis. Contemporary catalytic systems extend these concepts beyond carbon, enabling the formation of bonds to nitrogen, phosphorus, and other heteroatoms essential for constructing complex molecular architectures.

Although such transformations are now routine, the generation of active catalytic species is often more complex than simplified reaction schemes suggest. Herein, we report Johnson Matthey's efforts toward the development of improved preactivated catalyst systems for pharmaceutical applications. In particular, we investigate activation pathways for classical iridium-based precatalysts used in C–H borylation and evaluate how these pathways influence the design of more efficient catalyst platforms for this important transformation.

This work provides new insights into catalyst formation, particularly in relation to bipyridine- and phenanthroline-based ligand systems. Furthermore, it has enabled the development of a novel class of complexes supported by cyclooctene ligands instead of cyclooctadiene ligands. These systems exhibit enhanced reactivity, improved solution stability, and eliminate the need for an additional activation step.



2P- 41

From Soluble to Solubilizing Tag: Highly Efficient Liquid-Phase Peptide Synthesis Using Oleyl Tag

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Liquid-phase peptide synthesis (LPPS) has attracted attention in process chemistry due to its scalability and ease of real-time monitoring. However, in the synthesis of hydrophobic or long-chain peptides, challenges include reduced reaction efficiency caused by intermediate aggregation and difficulties in purification. To address these issues, hydrophobic anchor (Tag) that controls the physical properties of peptides have been developed; however, conventional saturated alkyl tags have low solubility in organic solvents and are prone to causing intermediate aggregation as the peptide chain elongates. Previously, the introduction of branched structures or silyl groups has been reported as effective solutions to this solubility problem.[1]

In this study, we developed a hydrophobic carrier, the oleyl tag, which shifts the paradigm from conventional “soluble” tags to “solubilizing” tags through the introduction of an unsaturated chain. It was demonstrated that the unsaturated hydrocarbon chain of the oleyl tag exhibits excellent solubility to the peptide during elongation process and effectively suppresses aggregation, which causes a decrease in solubility. The high-solubility oleyl tag enabled synthesis under high-concentration conditions, up to 200 mM. Furthermore, we successfully synthesized long-chain peptides of up to 20 residues via linear synthesis and aggregation-prone peptides, obtaining the target products with high purity and high yield.

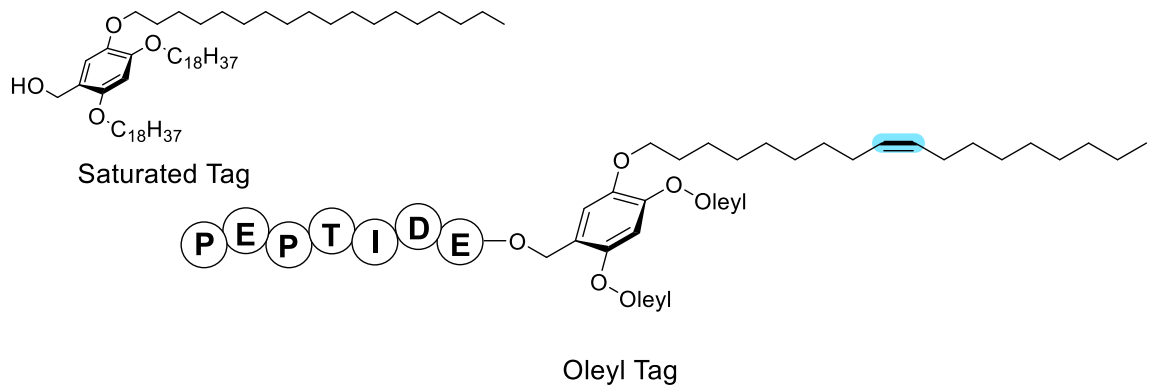


Figure 1. Introduction of unsaturated chain.

Reference

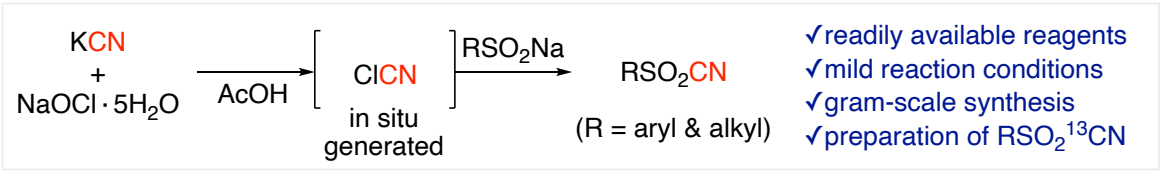
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Practical Synthesis of Sulfonyl Cyanides from Sodium Sulfinates Using KCN and NaOCl·5H₂O

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Sulfonyl cyanides (RSO_2CN) are versatile reagents in a wide range of chemical transformations, including electrophilic and radical-mediated cyanation, as well as sulfonylation.[1] However, *p*-toluenesulfonyl cyanide (TsCN) remains the only commercially available example, and systematic tuning of reactivity and selectivity through structural modification has been largely unexplored. Although several synthetic approaches to sulfonyl cyanides have been reported,[2] practical methods employing readily available reagents under mild conditions are still lacking. In this study, we report a practical synthesis of sulfonyl cyanides using inexpensive KCN as the cyanide source, enabling cost-effective preparation and straightforward access to ^{13}C-labeled derivatives ($RSO_2{}^{13}CN$) from $K^{13}CN$.

Initially, we found that nucleophilic substitution of sulfonyl halides (RSO_2X: X = F, Cl, Br) with KCN did not proceed, despite extensive screening of additives and solvents.[2a] We then turned our attention to a room-temperature approach using sodium sulfinates (RSO_2Na) and cyanogen chloride gas (ClCN),[2b] which is highly toxic gas (boiling point 13 °C) and thus poses significant safety concerns. We envisioned that *in situ* generation of ClCN from KCN at temperatures below its boiling point could mitigate the hazardous risk. Based on this concept, we developed a one-pot synthesis of sulfonyl cyanides from RSO_2Na using KCN and sodium hypochlorite pentahydrate ($NaOCl·5H_2O$) under mildly acidic conditions in an ice–water bath (Scheme 1).[3] In this reaction, a biphasic solvent system (AcOEt/H_2O) effectively suppressed undesired side reactions and enabled a broad substrate scope (R = alkyl, aryl). The protocol is also applicable to the preparation of ^{13}C-labeled derivatives and gram-scale synthesis.



Scheme 1. Practical synthesis of sulfonyl cyanides

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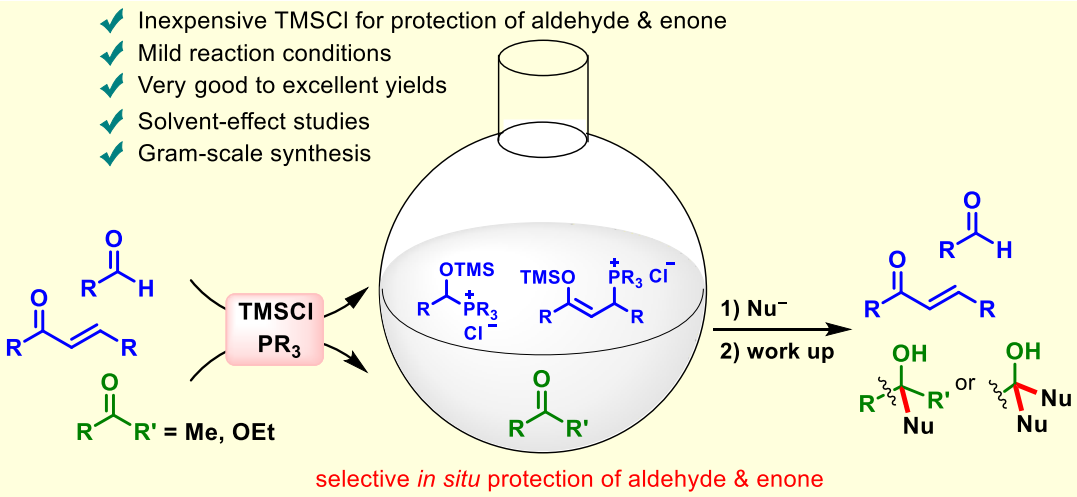
Reversal and Control of the Intrinsic Reactivity of Carbonyl Groups via Chemoselective TMSCl-Mediated In Situ Protection

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In recent years, we have developed in situ protection methods to reverse[1] or control[2] the intrinsic reactivity order of carbonyl groups. These methods previously used TMSOTf as the Lewis acid, which requires careful storage and handling. This time, we discovered a significant solvent effect and succeeded in using TMSCl, the most widely used and easy-to-handle TMS reagent. By combining PR_3 (R = Et, Bu) and TMSCl in a suitable solvent such as THF and DCM, we were able to selectively mask aldehydes in the presence of ketones and esters, as well as enones in the presence of ketones. This effectively reversed and controlled the original reactivity, and we succeeded in chemoselective nucleophilic transformation (reductions, alkylations) of ketone or ester functional groups in the presence of aldehydes, and of ketones in the presence of enones. The protocol is operationally simple, requires no specialized reagents, and exhibits broad functional group tolerance. Its robustness is highlighted by gram-scale reactions in 2-Me-THF, delivering the desired products in excellent yields.



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Binaphthyl-type Chiral Borinic Acid Catalyst for Enantioselective Reactions

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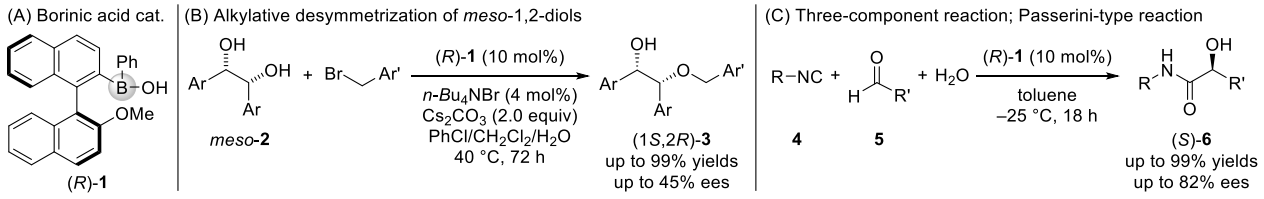
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Boron-containing catalysts have emerged as powerful tools in modern organic synthesis due to their unique reactivity and broad applicability. Although many asymmetric organoboron catalysts based on boranes, boronic acids, and borates have been reported,[1] asymmetric catalysis using borinic acids remains poorly developed.[2] Therefore, considering the catalytic utility of borinic acids,[3] the creation of new chiral borinic acid catalysts represents an important challenge. In this presentation, we would like to introduce our recent efforts to develop axially chiral borinic acid catalysts and to explore their synthetic applications.

A binaphthyl-type chiral borinic acid catalyst (*R*)-**1** was synthesized from (*S*)-BINOL, together with a library of related derivatives. These catalysts exhibit high stability toward moisture and oxygen, allowing practical handling. Their catalytic potential was first demonstrated in the enantioselective alkylative desymmetrization of *meso*-diols **2**, affording the corresponding products **3** with moderate enantioselectivity.[4a] We then applied the catalyst to a three-component Passerini-type reaction using isocyanides **4**, aldehydes **5**, and water. This method provides α-hydroxyamides **6** in good yields with up to 82% ee, including for aliphatic aldehydes.[4b] Overall, these results establish chiral borinic acids as robust and versatile organocatalysts and expand their utility to water-tolerant enantioselective processes.



Scheme 1. Design and catalytic applications of axially chiral borinic acid (*R*)-**1**.

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2P- 45

Development of a Chemical Upcycling Process from Perchloroethylene by Photoactivated Chlorine Dioxide Treatment

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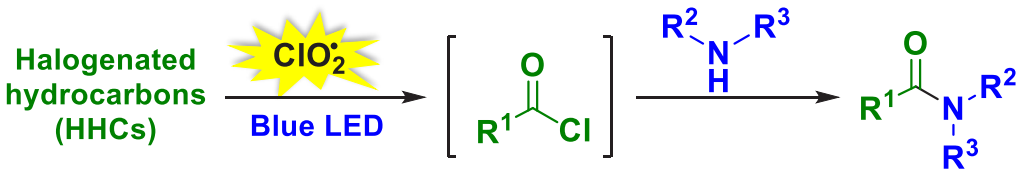
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Halogenated hydrocarbons are widely used in chemical industries as solvents, reagents, and intermediates; however, their disposal remains a significant environmental and process-chemistry challenge. Conventional degradation-based treatments often focus on detoxification, whereas the direct conversion of these compounds into valuable synthetic intermediates would provide a more attractive upcycling strategy. We have developed visible-light-induced transformations of halogenated hydrocarbons using photoactivated chlorine dioxide radical ($ClO_2^{\bullet}$) as a mild radical oxidant.

In our initial study, chloroform was oxygenated under visible-light irradiation in the presence of $ClO_2^{\bullet}$ to generate phosgene in situ, enabling the safe synthesis of carbamoyl chlorides from amines.[1] This strategy avoided the direct handling of phosgene and was further applicable to the synthesis of carbonates. We subsequently expanded this concept to the upcycling of various halogenated hydrocarbons under conditions using only stoichiometric amounts of the substrates.[2] In this system, visible-light-induced oxidation of halogenated hydrocarbons afforded the corresponding acyl chlorides in situ, which were directly trapped with amines to give a variety of amides, including pharmaceutically relevant structures.

Mechanistic studies, including photochemical quantum yield measurements and DFT calculations, suggest that chlorine-radical-mediated hydrogen-atom abstraction, oxygenation, and C–Cl bond cleavage are involved in the formation of reactive carbonyl intermediates. These studies demonstrate that photoactivated $ClO_2^{\bullet}$ provides a process-friendly strategy for the upcycling of halogenated hydrocarbons into valuable carbonylation and acylation equivalents under mild conditions.



Scheme 1. Visible-light-induced upcycling of halogenated hydrocarbons using photoactivated $ClO_2^{\bullet}$.

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2P- 46

Thermal Control in Flow Synthesis Enabled by Silicon-Infiltrated High-Thermal-Conductivity Si–SiC Cartridges

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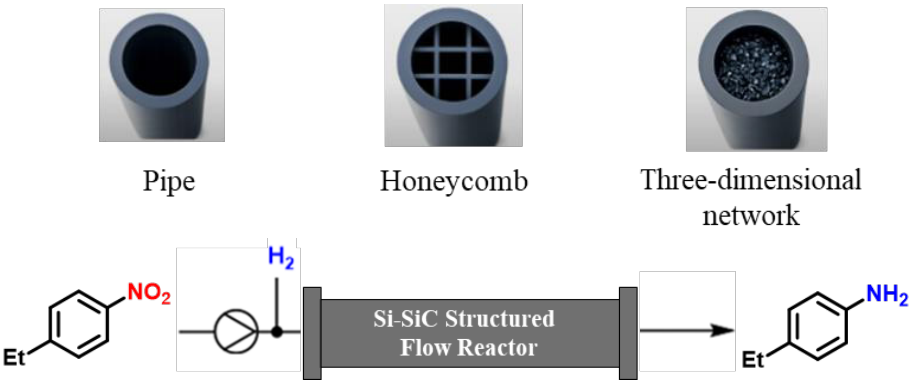
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In recent years, the adoption of flow synthesis has been expanding, particularly in the pharmaceutical and fine chemical industries. However, highly exothermic reactions cause reduced conversion, formation of by-products, and catalyst deactivation. These issues remain significant challenges to achieving stable continuous operation. In this study, we aimed to establish design guidelines for fixed-bed flow reactors suitable for highly exothermic reactions by investigating the heat removal characteristics and temperature distribution control performance of reactors made from highly thermally conductive ceramics.

First, CFD simulations were conducted to investigate the effects of internal structures on heat removal characteristics. Silicon-infiltrated silicon carbide (Si–SiC) was selected as the high-thermal-conductivity ceramic, and reactors with internal pipe, honeycomb, and three-dimensional network structures were fabricated as a prototype. The pipe-structured reactor showed a tendency to suppress the formation of by-products (Scheme 1). In addition, the honeycomb-structured reactor effectively suppressed temperature rise under solvent-free conditions, suggesting enhanced heat removal due to the internal structure. Three-dimensional network structure will also be reported. High-thermal-conductivity ceramics and optimized internal structures are key to reactor design for highly exothermic reactions and to the development of continuous synthesis processes.



Scheme 1. Si-SiC Structured Flow reactors

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Reductive Deuteration of Carbonyl Compounds Using D_2O as a Deuterium Source Enabled by a Tin Oxide-Supported Pt-Ir Catalyst

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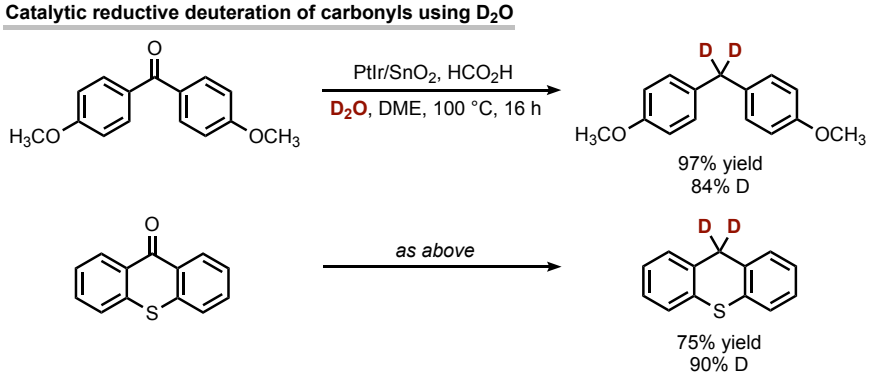
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Deuterated compounds are increasingly important in the pharmaceutical industry, both for the preparation of stable-isotope-labelled internal standards (SILS) and as active pharmaceutical ingredients, as demonstrated by the recent approvals of deucravacitinib (Sotyktu®) and deutetrabenazine (Austedo®). However, methods for the efficient and cost-effective preparation of deuterated compounds remain underdeveloped. The reductive deuteration of carbonyl compounds is typically accomplished using metal deuterides, such as $NaBD_4$ and $LiAlD_4$, which are expensive, present considerable safety hazards, and generate copious waste. In principle, catalytic reductive deuteration using D_2 is a greener reaction and generates less waste; however, D_2 gas is itself highly costly and requires special handling due to its flammability.

Considering these challenges, we herein report[1] the development of a reductive deuteration reaction of carbonyl compounds leading to the corresponding deuterated alkanes using D_2O as a low-cost deuterium source enabled by a tin oxide-supported platinum-iridium heterogeneous catalyst. A variety of non-deuterated terminal reductants, including H_2 gas, formic acid, and 2-propanol can be used, with deuterated products routinely isolated in over 90% yield with high deuterium incorporation. Preliminary mechanistic investigations of the system are also reported.



☞ New heterogeneous catalyst $PtIr/SnO_2$ enables the reductive deuteration of ketones using D_2O as a D source with common non-deuterated terminal reductants.

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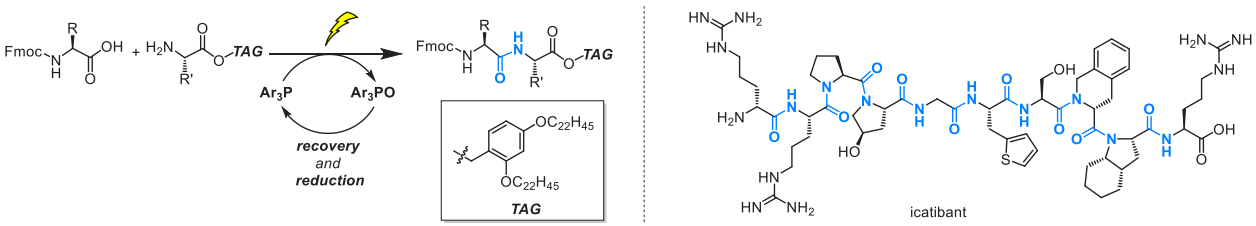
Electrochemical Peptide Synthetic Process Aiming for Greener Production

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Peptides have been gaining much attention as one of the promising candidates for medium molecular medicines. Some peptides have been approved as drugs and the number of peptide drugs is expected to increase. In this context, the development of a novel peptide synthetic process which enables the reduction of the amount of waste is recognized as an urgent issue. In conventional peptide synthesis, 3000-15,000 kg of waste is produced per 1 kg of peptide. One of the causes is byproducts from coupling reagent, which facilitate peptide bond formation. These reagents are used stoichiometrically every elongation step and the same amount of byproducts are accumulated as waste.

To address this issue, we are working on the development of electrochemical peptide synthesis using triaryl phosphines (Ar_3P) as recyclable coupling reagents. Anodically oxidized Ar_3P activates carboxylic acids and promotes peptide bond formations. Although triaryl phosphine oxides (Ar_3PO) are stoichiometrically generated, the reduction of Ar_3PO to Ar_3P has been achieved in various ways. Therefore, we envisioned that the development of the electrochemical peptide bond formations with broad substrate scope and a recovery method of Ar_3PO would prove that Ar_3P can be a recyclable coupling reagent.

Based on the strategy, we have developed electrochemical peptide synthesis employing Ph_3P (the 1st generation)[1], $(4\text{-}MeOC_6H_4)_3P$ (the 2nd generation)[2], and the combination of $(4\text{-}MeOC_6H_4)_3P$ and I^- (the 3rd generation)[3]. Exploiting soluble tag strategy, the recovery method of Ph_3PO and $(4\text{-}MeOC_6H_4)_3PO$ was established through the development of 1st generation and 2nd generation to show that Ar_3P is a promising recyclable coupling reagent. Furthermore, we have succeeded in broadening the substrate scope. The 3rd generation electrochemical peptide synthesis is applicable to highly sterically hindered amino acids such as α-aminoisobutylic acid (Aib) and *N*-methyl phenylalanine, and the synthesis of icatibant, a peptide drug for hereditary angioedema, was successfully synthesized.



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2P- 49

Crystallization-Based Approach to Continuous Manufacturing: A Case Study of Acetaminophen Production

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Continuous manufacturing has attracted considerable attention as a promising approach for on-demand and distributed production of pharmaceutical active ingredients (APIs). [1)] In this study, acetaminophen (AcAP) was selected as a model compound to develop a crystallization-based continuous process, enabling continuous manufacturing with integrated downstream operations. [2)]

First, solubility data of AcAP in various solvent systems were systematically evaluated, and cooling crystallization conditions were selected to achieve efficient crystal recovery. As a result, it was found that high crystal recovery and stable slurry formation could be achieved by simultaneously performing aqueous cooling crystallization and neutralization. Based on these crystallization requirements, continuous acetylation of 4-aminophenol was designed using a plug-flow reactor (PFR), and the reaction effluent was directly connected to the crystallization step. Furthermore, continuous filtration, fluidized-bed drying, and packaging processes were integrated with careful consideration of slurry handling, enabling continuous operation across all unit operations. The developed system was stably operated for approximately 5 hours without critical issues such as reactor blockage or process instability, and it was confirmed that the AcAP API produced during the operation satisfied the Japanese Pharmacopoeia content specification (≥98.0%). This study demonstrates that crystallization-based process design provides an effective strategy for integrating continuous-flow reactions with downstream solid-handling operations, and contributes to the development of practical and scalable continuous manufacturing technologies for pharmaceutical production.

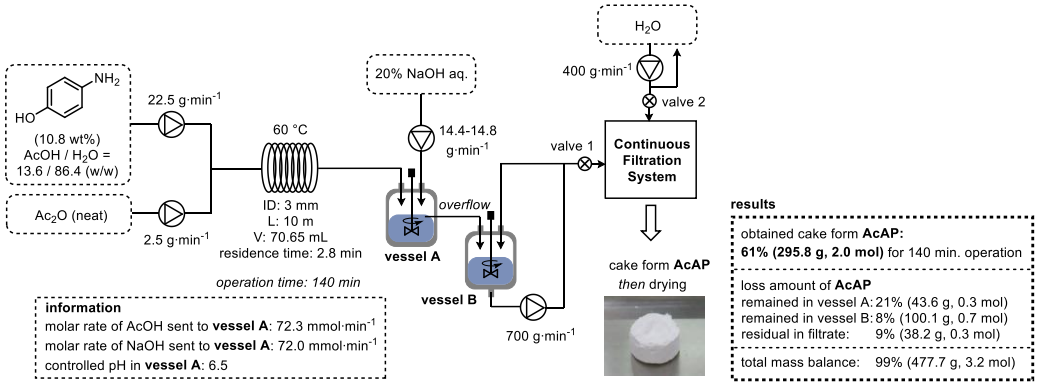


Figure 1. Continuous reaction-crystallization-filtration.

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2P- 50

An Automated HTE Platform for Systematic Reaction Space Exploration in Early-Stage Process Development

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Although high-throughput experimentation (HTE) is widely used in process chemistry, early-stage process development is often constrained by scarce intermediates, leading to fragmented data when defining a viable reaction space within a single screening campaign. We developed an automated Robotic-HTE platform to enable efficient, reproducible multi-condition reaction screening at very small scale.

Robotic-HTE performs reactions at the 5-mg scale in a 96-well glass-vial plate format under temperature-controlled conditions, with all modules integrated in a nitrogen-purged glovebox. The automated workflow combines validated HPLC-autosampler-based reagent dispensing (50 µL accuracy) with robotic plate transfer between modules. Automated sealing/peeling and capping/decapping ensure vial isolation during dispensing and solvent handling, thereby minimizing evaporation, contamination, and operator-dependent variability inherent to manual microscale experiments. Vacuum centrifugal concentration enables solvent removal or exchange without breaking containment. The system supports fully unattended operation of up to eight 96-well plates per day, corresponding to a throughput of approximately 2,000 experiments per week.

To enable high-throughput evaluation while minimizing solvent consumption and waste generation, screening campaigns are coupled with supercritical fluid chromatography–mass spectrometry (SFC-MS) as an external analytical platform. In parallel, a digital workflow was developed to transform how reaction design and data handling are performed across large reaction matrices. This digital transformation (DX) enables rapid design of experimental conditions mapped onto 96-well plate formats and automates post-run analytical data processing, visualization, and cross-condition comparison, thereby substantially reducing manual effort associated with high-throughput experimentation.

Overall, Robotic-HTE provides a practical framework for reproducible microscale reaction screening in early process development, including Ni-catalyzed Miyaura borylation (JSPC Summer Symposium 2025, Abstract Book, p. 198), expanding experimental coverage under strict sample constraints. The platform supports more informed early-stage decision making and helps improve robustness in downstream process development.



Figure 1. Robotic-HTE Hardware

Notes: This research was funded by Astella

2P- 51

Solvent-Minimal and Epimerization-Suppressed Mechanochemical Synthesis of Peptide Thiocarboxylic Acid

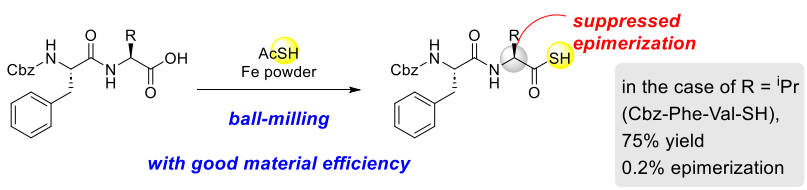
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Peptide synthesis has been fundamental to the production of pharmaceuticals, diagnostics, and functional materials. However, conventional solution-phase methodologies typically produces large amount of waste derived from organic solvents and excess reagents. Furthermore, epimerization at the activated C-terminus remains a persistent challenge, especially for sterically demanding or heteroatom-containing amino acids.

Thiocarboxylic acids have emerged as attractive intermediates for C-terminal activation due to their moderate reactivity and versatility.[1] In parallel, mechanochemical synthesis has gained increasing attention as a sustainable alternative that minimize solvent use and can suppress undesired epimerization.[2]

In this presentation, we introduce mechanochemical approach to the synthesis of peptide thiocarboxylic acids via ball-milling. Based on our previous solution-phase methodology,[3] we investigated the thiocarboxylation of sterically demanding dipeptide Cbz-Phe-Val-OH using thioacetic acid as a sulfur source under solvent-minimal conditions. In the presence of iron powder as an activator, the corresponding dipeptide thiocarboxylic acid Cbz-Phe-Val-SH was obtained in good yield (75%) and with greatly suppressed epimerization (0.2%). The developed ball-milling protocol was also applicable for various epimerization-prone dipeptides, affording the desired products in consistently good yields with low epimerization levels. In addition to stereochemical fidelity, significant reductions in process mass intensity (PMI), E-factor, and solvent consumption were achieved compared to conventional solution-based methods.

These results demonstrate that mechanochemical thiocarboxylation provides an efficient and sustainable strategy for peptide C-terminal activation, combining high material efficiency and stereochemical control.



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2P- 52

Nitrosamine Risk Evaluation in Drug Substance: Development of a Nitrite Ion Analytical Method in High-Chloride Matrices

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[Background and Objective] Risk management for nitrosamine (NA) impurities in pharmaceuticals is critically important, even at the clinical development stage. In this study, we evaluated the NA contamination risk in a drug substance at an early stage of development, focusing on potential sodium nitrite impurities in the raw materials. An initial risk assessment was conducted using theoretical purge factors (PFs) in accordance with the ICH M7 guideline. Under worst-case scenarios, the control limit of nitrite ions in the intermediate was estimated to be not more than 0.05 ppm. However, the high chloride concentration in the raw material precluded the use of standard ion chromatography with carbonate-based mobile phases. Significant interference from the chloride peak and the presence of system "dip" peaks hampered stable quantification at the target sensitivity**.** As a result, stable quantification at the required sensitivity was difficult.
In this presentation, we report on the development of a control strategy through the evaluation of measured PF for sodium nitrite based on spiking experiments, as well as a trace analytical method for nitrite ions in the presence of high concentrations of chloride ions using HPLC-UV with a sodium chloride (NaCl) aqueous solution as the mobile phase.
[Methods] Spiking experiments were conducted in processes where nitrite ion contamination was anticipated, and the control limit was redefined based on the measured PF. Simultaneously, to ensure sufficient specificity in the presence of high concentrations of chloride ions, a gradient HPLC-UV method (Column: TSKgel SuperIC-AZ) using an aqueous NaCl solution and acetonitrile as the mobile phase was developed.
[Results and Discussion] The spiking experiments confirmed the measured PF of 100 or greater. By incorporating this result, the control limit for nitrite ions was redefined to a scientifically justified level. In the optimization of the analytical method, the adoption of gradient elution using an aqueous NaCl solution achieved effective separation of nitrite ions, even in the presence of 0.75 mg/mL chloride ions. This method provided sufficient quantitative sensitivity relative to the redefined control limit. Application of the developed method confirmed that the nitrite ion content in the intermediate was below the redefined control limit.
[Conclusion] The revision of the control strategy using measured PF, combined with the development of a gradient HPLC-UV method using a NaCl mobile phase, enabled highly sensitive limit testing of nitrite ions in matrices containing high concentrations of chloride ions. This approach provides a practical and scientific framework for NA risk assessment of drug substances in early-stage development.

2P- 53

Mild Liquid-Phase Sulfurization of P(III) Compounds Using Sodium Tetrasulfide

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[Introduction]

Phosphorothioate (PS) structures are important motifs in oligonucleotide intermediates and functional materials, and practical sulfurization methods for P(III) compounds are highly desirable [1]. Organic sulfurizing reagents are widely used, but their cost and availability can be problematic [2]. Elemental sulfur is inexpensive, but its low solubility limits its use in liquid-phase processes [3]. In this study, sodium tetrasulfide (Na_2S_4) was investigated as an inexpensive inorganic sulfur source applicable to the sulfurization of P(III) compounds under liquid-phase conditions (Figure 1). Particular attention was paid to the pH-dependent equilibrium of polysulfide species and its influence on reactivity and operational stability [4].

[Results]

Na_2S_4 showed high reactivity toward representative P(III) compounds, affording the corresponding sulfurized products in high yields (>90%) from both phosphine-type and phosphite ester-type substrates. Comparison with elemental sulfur revealed no significant difference for phosphine-type substrates, whereas a clear difference was observed for phosphite ester-type substrates. While elemental sulfur was ineffective or less effective, Na_2S_4 afforded the desired products in high yields under mild conditions, likely because it supplies soluble sulfur species in the reaction system.

The reaction strongly depended on solution pH. High reactivity was obtained under near-neutral conditions, whereas deviation toward acidic conditions caused turbidity and solid formation. This behavior is attributed to the pH-dependent equilibrium and disproportionation of polysulfide species, which promote precipitation of elemental sulfur. Thus, pH is an important reaction factor governing sulfur speciation, reaction efficiency, and operational stability. These results demonstrate that Na_2S_4-mediated sulfurization is an effective liquid-phase method for P(III) compounds, especially phosphite ester-type substrates. Further studies toward process development are currently underway.

Figure 1. pH-guided sulfurization of P(III) compounds using sodium tetrasulfide.



Sulfurizing reagent	Cost	Ease of separation	Liquid-phase compatibility
Organic sulfurizing reagent	×	×	○
Elemental sulfur	○	○	×
Na_2S_4 (This work)	○	○	○

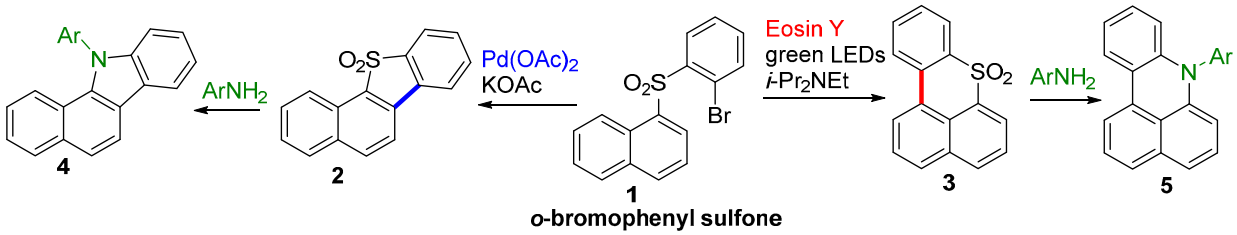
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Eosin Y-catalyzed Cyclization: Syntheses of 6-Membered Sulfones

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Nitrogen-doped polycyclic aromatic hydrocarbons (PAHs) have attracted considerable attention because of their applications as light-emitting and hole-transporting materials for organic electronic devices. In particular, carbazole- and acridine-based π-conjugated systems are promising photofunctional materials.

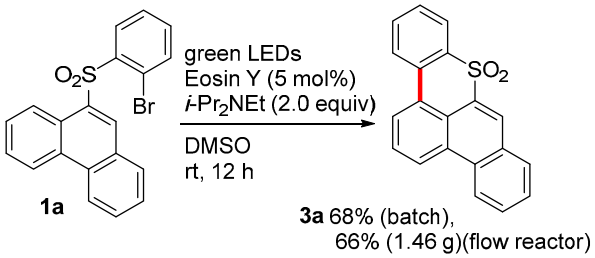
Recently, we developed a chemodivergent synthetic strategy for the selective synthesis of 5- and 6-membered cyclic amines from a common *ortho*-bromophenyl sulfone precursor (Scheme 1).[1] Catalyst-controlled annulation selectively transforms bromosulfone **1** into 5-membered sulfone **2** or 6-membered sulfone **3**, which are subsequently converted into π-expanded carbazole **4** and acridine derivatives **5** through desulfonylative amination.



Scheme 1. Chemodivergent Ring Annulation

In this presentation, we describe the Eosin Y-catalyzed photoredox cyclization of **1a** to **3a** under green LED irradiation using a flow microreactor. The photochemical annulation proceeded efficiently in a transparent tube reactor under continuous-flow conditions. Continuous operation for 100 h enabled gram-scale synthesis of **3a** in 66% yield (1.46 g) on a 7.0 mmol scale (Scheme 2).

Furthermore, the obtained cyclic sulfones were successfully transformed into the corresponding cyclic amines, providing various nitrogen-doped PAHs with characteristic optical properties.



Scheme 2. Eosin Y-catalyzed Photoredox Cyclization

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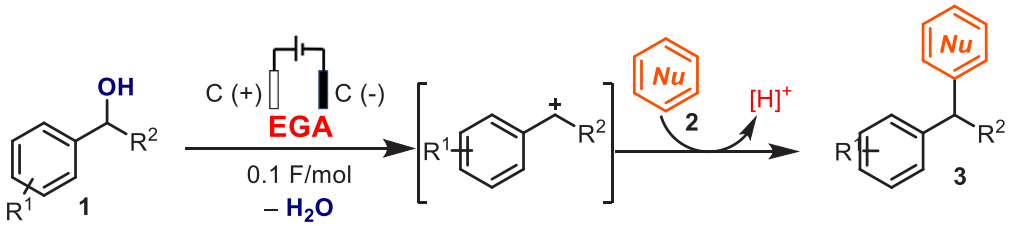
2P- 55

Traceless electrogenerated acid-catalyzed dehydroxylative arylation for the synthesis of tri- and diarylmethane derivatives

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Organic electrosynthesis (EOS) is a green synthetic approach, because electron transfer between an electrode and an organic molecule enables oxidation or reduction without the use of stoichiometric chemical oxidants or reductants.[1] It is also known that electrolysis of electrolyte solutions, such as lithium perchlorate ($LiClO_4$), can generate electrogenerated acid (EGA) in the reaction mixture.[1,2] Benzylic arylation reactions, typified by Friedel–Crafts type reactions, represent powerful tools for constructing triarylmethane and diarylmethane frameworks, which are frequently found as key structural motifs in functional materials and biologically active compounds. These compounds are generally synthesized by the reaction of benzylic alcohol derivatives with arenes under acidic conditions. However, the external addition of acids and neutralization treatment after completing the reaction are required. Furthermore, the hydroxy (OH) group on benzyl alcohol must be converted into a better leaving group prior to the reaction in case using less reactive arenes.[3]

We developed an EGA-catalyzed benzylic arylation reaction between benzylic alcohols and arenes using the OH group as a leaving group. When a nitromethane solution of a variety of benzylic alcohols (**1**) and arenes (**2**) was electrolyzed in the presence of $LiClO_4$, the dehydrative arylation of **1** proceeded with only 0.1 F mol^{-1} of electricity, affording the corresponding products **3** in high yields. EGA generated derived from $LiClO_4$ by passing a catalytic amount of electricity acts as a short-lived, traceless acid catalyst that efficiently activates the OH group of benzylic alcohols. Since the electro-assisted benzylic arylation reaction can reduce the neutralization treatment and generate only water as the sole byproduct, this method is expected to serve as a practical and environmentally benign electrochemical process for synthesizing triarylmethane and diarylmethane derivatives, minimizing both waste generation and energy consumption.



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Direct Approach towards Synthesis of Dihydroisoquinoline from Ketones *via* Bischler-Napieralski Type Reaction

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The 3,4-dihydroisoquinoline skeleton have been found in various bioactive compounds (Figure 1(a)).[1] The Bischler-Napieralski reaction have been well-known as a representative method for preparing 3,4-dihydroisoquinolines; in this reaction, the products are obtained from *β*-arylethylamides using $POCl_3$ (Figure 1(b)). The proposed reaction mechanism was considered that *nitrilium ion* was generated from *β*-arylethylamide under dehydration conditions, followed by an intramolecular electrophilic aromatic substitution to yield the 3,4-dihydroisoquinoline. In this process, the generation of the key *nitrilium ion* intermediate required harsh conditions or reagents to dehydrate the starting amide. In contrast, we have previously reported the direct synthesis of amides from ketones using oxime reagents that behave as equivalents of hydroxylamine derivatives.[2] The reaction was assumed to proceed *via* the generation of a *nitrilium ion* from the ketoxime through a Beckmann rearrangement, followed by trapping with water to yield the secondary amide. Based on these findings, we herein propose a different approach for the direct synthesis of dihydroisoquinoline from ketones *via* Bischler-Napieralski type mechanism (Figure 1(c)).

We attempted the reaction using arylethyl alkyl ketone and explored suitable nitrogen sources. As a result, the optimized reaction condition afforded the corresponding 3,4-dihydroisoquinoline in moderate to good yields under mild conditions. In this presentation, we discuss the reaction conditions and the mechanism.

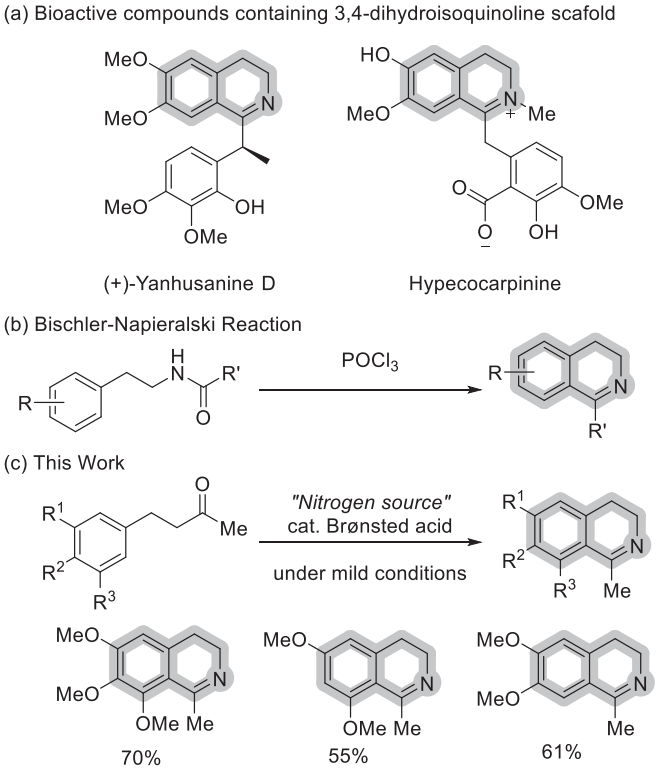


Figure 1. Utility and synthesis of 3,4-dihydroisoquinolines.

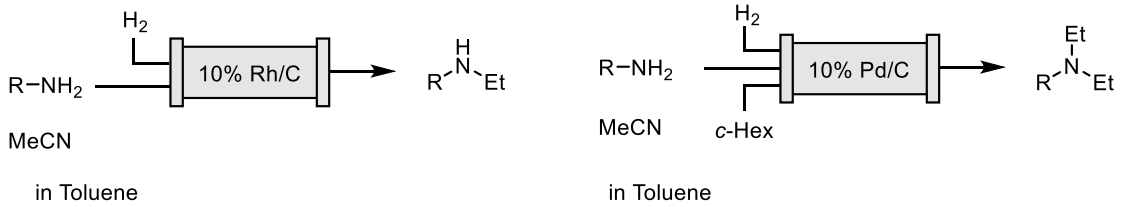
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Selective Reductive Alkylation of Amines Using Nitriles under Continuous-Flow Conditions

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Secondary and tertiary amines are important structural motifs in pharmaceuticals, agrochemicals, and functional materials. Conventional *N*-alkylation using alkyl halides is operationally simple, but often suffers from over-alkylation and salt formation, which reduce atom economy and complicate purification and scale-up. We previously developed a heterogeneous catalytic *N*-alkylation of primary amines using nitriles as alkylating agents, in which product selectivity is governed by the metal catalyst, with Rh/C selectively affording secondary amines and Pd/C favoring tertiary amines.[1)] Building on this concept, we developed a packed-bed continuous-flow method for the selective alkylation of amines using acetonitrile as a halogen-free alkylating agent. This selectivity was likewise governed by the choice of supported metal catalyst: Rh/C preferentially afforded secondary amines, whereas Pd/C promoted further alkylation to give tertiary amines in high yields. A mixed solution of amine substrates and acetonitrile was delivered and co-fed with H_2 through a catalyst cartridge packed with Celite-diluted catalyst at elevated temperature, enabling efficient reductive alkylation under continuous-flow conditions. The reactor showed stable performance for at least 12 h without loss of activity or selectivity. Compared with conventional batch processing, the flow protocol significantly enhanced reaction efficiency, providing a turnover frequency of 6.4 h^{-1} and a space-time yield of 640 kg L^{-1} h^{-1}. Because this method avoids alkyl halides and high-pressure operation, and generates only NH_3 as the by-product, it represents a safe, sustainable, and scalable approach to the selective synthesis of secondary and tertiary amines. The modular nature of the packed-bed reactor also highlights its potential for straightforward parallelization to kilogram-scale production.



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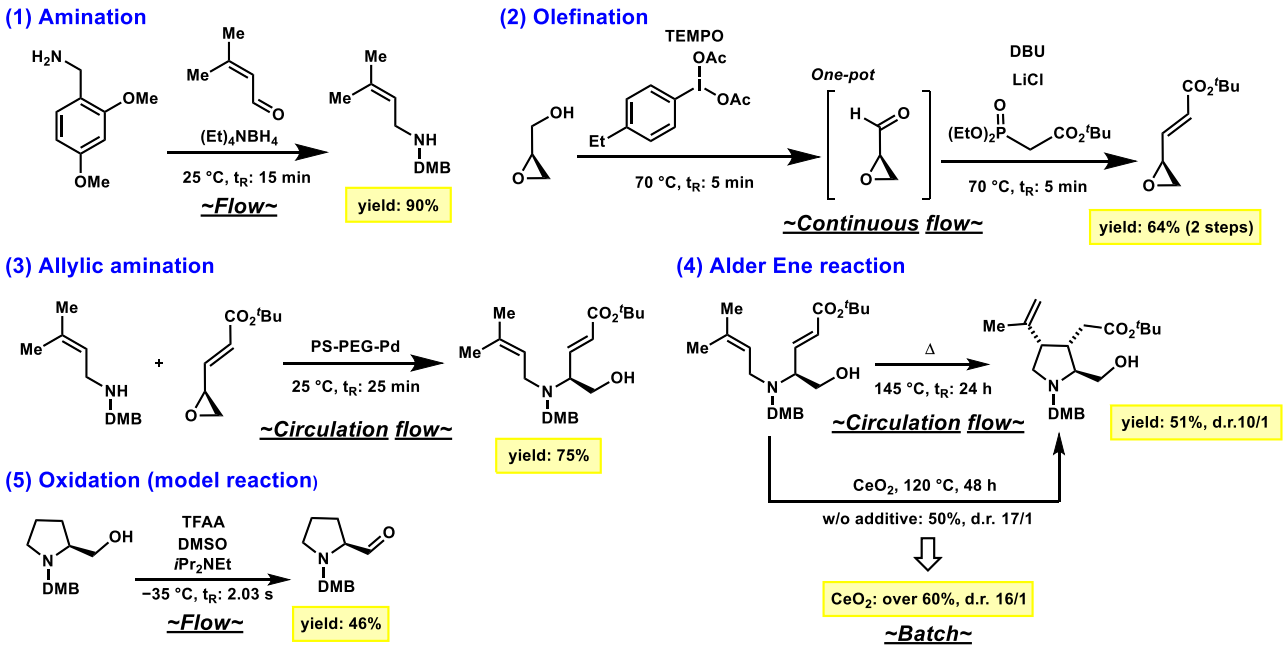
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Flow Synthesis of (–)-(α)-Kainic Acid

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(–)-(α)-Kainic acid is a naturally occurring pyrrolidine alkaloid isolated from the red alga Digenea simplex. Due to its potent neuroexcitatory activity and importance as a pharmacological tool for studying neurological disorders, demand for this compound has been steadily increasing.[1] Therefore, we previously developed a six-step total synthesis.[2] However, this synthesis method is limited to the gram scale, because conventional batch synthesis poses a challenge for large-volume supply due to the inherent limitations of batch process. To address this limitation, we explored the application of continuous flow synthesis for the efficient and scalable production of kainic acid.

We optimised the reaction conditions for four key steps: (1) amination, (2) oxidation reaction and subsequent olefination, (3) allyl amination, and (4) Alder-ene reaction. Flow synthesis conditions were successfully established for each step. Notably, in the Alder-ene reaction, the addition of cerium oxide improved the yield. In the fifth-step oxidation reaction, a moderate yield was obtained using a model substrate under conditions. We will mainly discuss details of the optimization of the reaction conditions and the future prospects of the synthesis plan.



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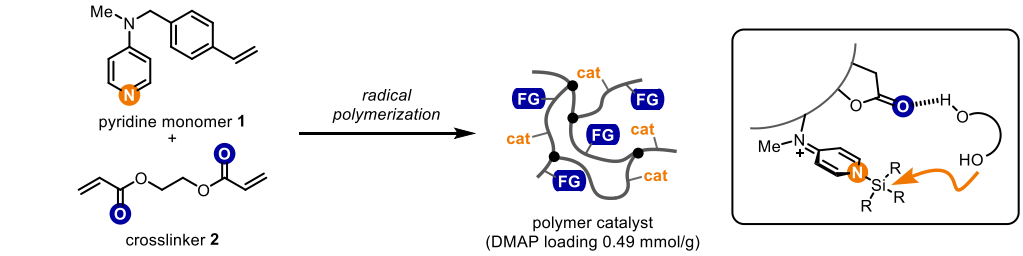
Cross-Linked Random Polymer Enables Catalytic Diol Mono-Silylation

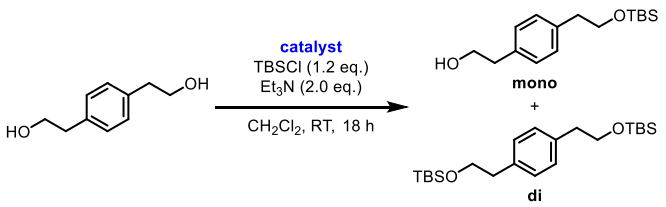
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Mono-silylation of diols is a fundamentally important transformation in organic synthesis; however, competing bis-silylation often leads to undesired di-silylated products. Although methods employing stoichiometric amounts of base have been reported [1)], developing a catalytic protocol[2) 3)] applicable to broad substrates remains challenging, especially in the case of long-chain diols. To address this issue, we focused on artificial polymers prepared via radical polymerization of monomers bearing a Lewis basic catalytic site (cat), responsible for promoting the silylation of alcohols[2)], and a functional group (FG) capable of hydrogen-bonding interaction of diols. These functional groups distributed on the polymer surface were envisioned to create a cooperative reaction environment that promotes selective mono-silylation of diols. After screening various monomers, a polymer catalyst derived from pyridine-containing monomer **1** and ester-based crosslinker **2** was identified as an effective catalyst, providing the mono-silylation product with significantly improved selectivity compared with DMAP. Details of the catalyst development and the substrate scope will be presented.





entry	catalyst	yield (%) mono	di
1	DMAP	58	21
2	polymer catalyst	89	8

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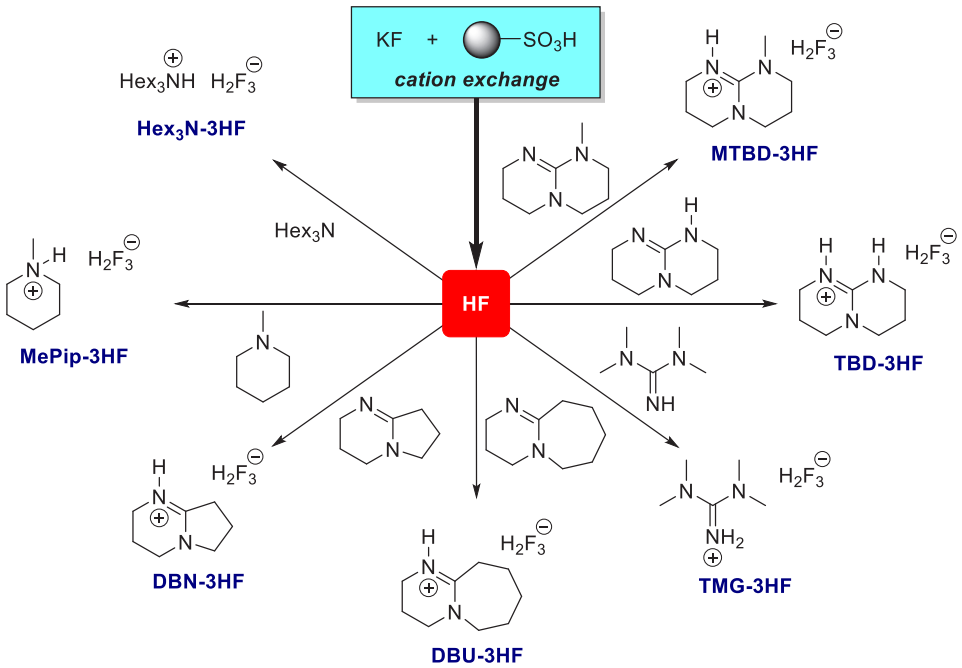
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A Green Process for the Synthesis of Amine-3HF Complexes via Cation Exchange between KF and Amberlyst 15DRY

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Hydrogen fluoride (HF) is a fundamental nucleophilic fluorinating reagent; however, its high toxicity, corrosiveness, and volatility pose significant handling challenges. While HF-amine complexes, such as Olah's reagent, offer safer alternatives, their preparation typically relies on hazardous HF gas. Conversely, potassium fluoride (KF) is safe and inexpensive but suffers from low solubility in organic solvents.

We previously demonstrated HF generation from KF via cation exchange with Amberlyst 15DRY in acetonitrile under reflux, though limitations remained regarding yield and its applicability to fluorination reactions. In the present study, we optimized the reaction conditions to achieve quantitative HF generation from KF through a safe and straightforward procedure. Using this method, we successfully synthesized a variety of HF-amine complexes (Scheme 1). Investigations into their reactivity in fluorination reactions are currently underway.



Scheme 1. Synthesis of various amine-3HF complexes based on the cation exchange reaction.

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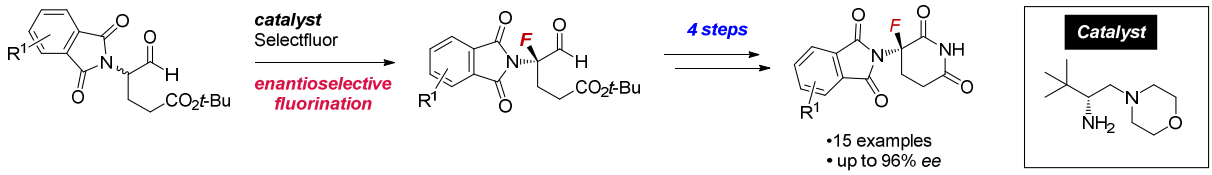
3'-Fluorinated Thalidomide Derivatives: Stereoselective Synthesis and CRBN Binding Properties

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Thalidomide was used as a sedative and hypnotic in the 1960s; however, its teratogenic effects soon became evident, leading to a devastating drug-related tragedy. In recent years, its pharmacological activities have been re-evaluated, and it has regained attention as a therapeutic agent for multiple myeloma. Furthermore, thalidomide has been utilized as a cereblon (CRBN) E3 ligase ligand in Proteolysis-Targeting Chimeras (PROTACs), further increasing its importance in medicinal chemistry.

It is well established that the (S)-enantiomer is primarily responsible for teratogenicity, whereas the (R)-enantiomer confers therapeutic effects. Recent studies have also revealed that the (S)-enantiomer exhibits higher affinity for CRBN. However, the stereogenic center readily undergoes racemization in vivo, making it difficult to eliminate undesired effects. To address this issue, 3′-fluorothalidomide was developed.[1,2] Incorporation of a C–F bond suppresses racemization while retaining pharmacological activity, and no teratogenicity has been observed.[3] Despite these advantages, only one example of its asymmetric synthesis has been reported, with limited enantioselectivity and substrate scope (88% ee, R^1 = H only).[2] Consequently, comprehensive structure–activity relationship (SAR) studies and applications toward PROTAC development remain unexplored.

In this presentation, we report a facile and highly enantioselective synthesis of 3′-fluorothalidomide via α-fluoro-α-amino aldehydes as key intermediates. This strategy enables the asymmetric synthesis of various 3-fluorinated thalidomide analogues (>90% ee, 15 examples; see Scheme 1).



Scheme 1. Asymmetric synthesis of 3'-fluorinated thalidomide

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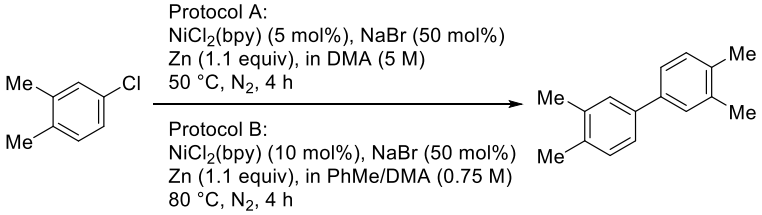
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A Co-solvent System to Reduce the Process Mass Index in Ullmann-type Biaryl Synthesis

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Process Mass Intensity (PMI) is an important metric for evaluating the industrial practicality of a manufacturing process, as this value inherently increases with higher solvent usage and waste generation.[1)] Classical Ni-catalyzed reductive homocoupling of aryl halides using powdered metal reductants has been studied for the synthesis of biaryls used in various functional materials, such as pharmaceuticals, thermostable polymers, and optical materials. Although the use of amide-based solvents [e.g., *N*,*N*-dimethylacetamide (DMA)] allows high-yield formation of target biaryls, their high boiling points and miscibility with water severely complicate separation and work-up. Furthermore, heating these solvents accelerates their degradation, significantly diminishing their recoverability and recyclability. This constitutes a major limitation in commercial-scale production, thereby resulting in an undesirably high PMI. To date, ball-milling reactions and micellar aqueous reactions have been reported as effective methods to reduce solvent consumption.[2)] However, ball milling requires specialized equipment, and micellar aqueous conditions are unlikely to be compatible with metal-reductant-mediated coupling systems, particularly for the Ullmann-type biaryl synthesis.

Herein, we report a practical strategy for reducing PMI using standard batch reactors, without relying on specialized reaction media or equipment. To reduce the amount of amide-based solvent while maintaining reaction selectivity, we investigated high-concentration conditions and the use of co-solvent systems. Under the optimal conditions for the homocoupling reaction of 4-chloro-*o*-xylene [using catalytic $NiCl_2$(bpy) with NaBr and Zn at 50 °C], the reaction proceeded at concentrations up to 5 M without significant loss of yield or selectivity. Notably, a PhMe/DMA co-solvent system (50:50) also afforded the desired product in 90% yield. We also demonstrate synthetically useful homocoupling products from aryl chlorides bearing electron-donating groups, which have traditionally been challenging substrates under these coupling conditions.



	Yield	Selectivity
Protocol A	96%	96%
Protocol B	90%	91%

Scheme 1. Solvent effect for homocoupling of aryl chloride

References

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Development of a Fiber-optic Interferometric Spectral Probe (FISP) for simultaneous measurement of bubble size and lamella thickness in foam

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Aqueous foams play a vital role in various fields, such as foam separation for the efficient recovery and removal of persistent pollutants like per- and polyfluoroalkyl substances (PFAS)[(1)]. In these processes, the efficiency directly relates to the internal foam structure, i.e., bubble size and lamella thickness.

To measure these two critical parameters simultaneously, we have developed the Fiber-optic Interferometric Spectral Probe, FISP (Fig. 1). The FISP integrates invasive gas-liquid phase detection based on refractive index differences[(2-4)] with non-invasive thickness measurement via interferometric spectroscopy[(5)] through a single optical fiber. To ensure reliable detection in dense foam, the probe features a microfabricated cone-shaped tip for signal sharpening. Validation experiments using a simulated lamella train as illustrated in Fig. 2 confirmed that bubble sizes were measured within 1% accuracy compared to visualization, while lamella thicknesses of approximately 10 μm were obtained simultaneously. We will discuss FISP's applicability to analyze foam measurement.

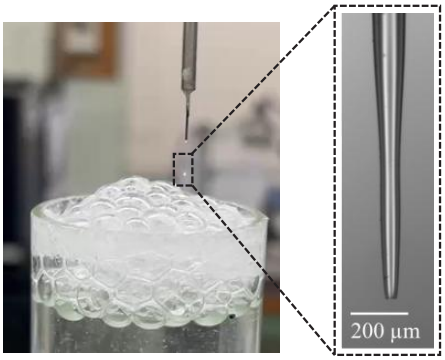


Fig. 1 Measuring foam bubbles with FISP

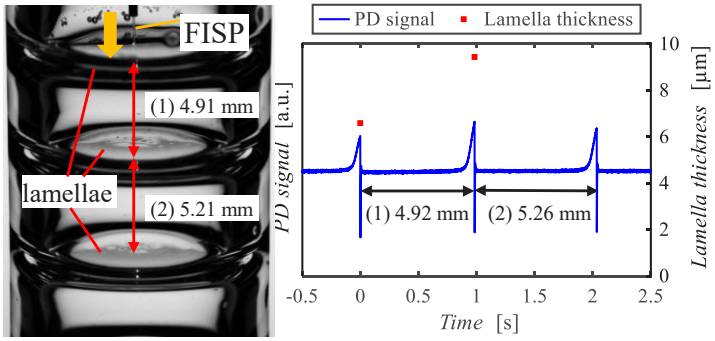


Fig. 2 Validation experiment and results

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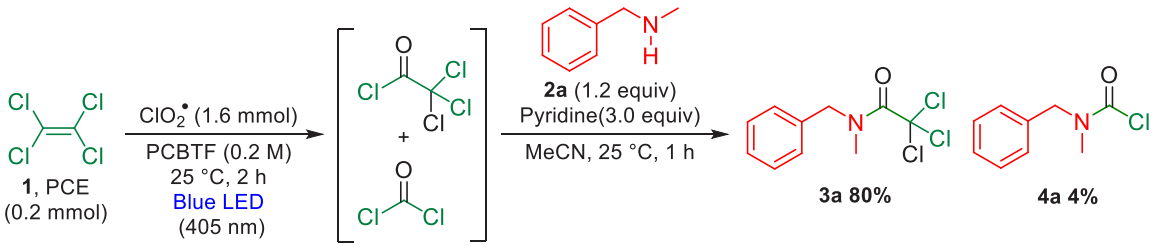
Development of a Chemical Upcycling Process from Perchloroethylene by Photoactivated Chlorine Dioxide Treatment

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Perchloroethylene (PCE) is a chlorinated solvent widely used in industrial processes such as dry cleaning and metal degreasing. Owing to its high stability and resistance to degradation, PCE persists in the environment, raising concerns about its potential mutagenicity and carcinogenicity. Nevertheless, PCE is still generated in various industrial processes. Accordingly, chemical upcycling technologies that convert PCE into valuable organic molecules represent a sustainable approach for reducing its environmental impact. Consequently, there is growing interest in the development of technologies that directly convert surplus PCE into useful products.

We have been developing oxidation reaction based on the photoactivation of chlorine dioxide ($ClO_2^{\bullet}$).[1] Under visible light irradiation $ClO_2^{\bullet}$ generates chlorine radicals and singlet oxygen, which can be harnessed for oxidative molecular transformations under mild conditions. In this study, we applied this reactivity to the chemical upcycling of PCE, achieving its conversion into trichloroacetyl chloride (TCAC) through chlorine radical addition and oxygen introduction, followed by transformation into useful products through reaction with heteronucleophiles.[2] (Scheme 1).

Here, we report the broad applicability of this transformation to various substrates, providing carbamates, ureas, and heterocyclic compounds as valuable products. We also discuss the reaction mechanism on the basis of experimental results and DFT calculations. Furthermore, we describe our ongoing efforts to improve the efficiency of this reaction using a flow system toward scalable process development.



Scheme 1. Transformation of Perchloroethylene by Photoactivated Chlorine Dioxide Treatment

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Direct Thickness Measurement in Wavy Liquid-Film Flow via Optical Waveguide Film

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In chemical manufacturing processes, thin “liquid film flows” of a few hundred microns play a crucial role in the efficient heat and mass transfer. For example, cleaning and drying of semiconductor wafers, inside absorbers and evaporators, and so on. However, measurement methods for the thickness of the liquid film in such actual equipment are quite limited. Therefore, direct and accurate thickness measurements are required to ensure stable equipment operation and product quality.

In this study, we introduce a method for measuring liquid film thickness using an “Optical Waveguide Film (OWF),” which forms an optical path within a 0.1 mm-thick polyimide film. The OWF is a very flexible device, making it easy to instrument the target area. Further, thanks to the OWF's high temporal resolution of up to 1 MHz and spatial resolution of 50 μm, it can directly detect rapid fluctuations in the wavy film thickness. The OWF detects the intensity of surface reflection at the gas-liquid interface as a signal and derives the film thickness based on a pre-acquired calibration curve. According to our experiment, the OWF can measure thicknesses ranging from 50 to 500 μm. We will discuss the limitations and applicability of this method.

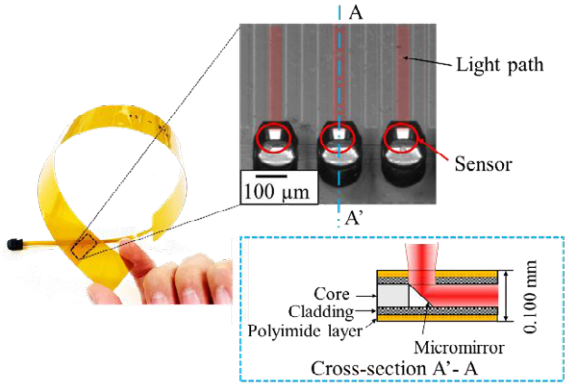


Figure 1. Structure of the OWF

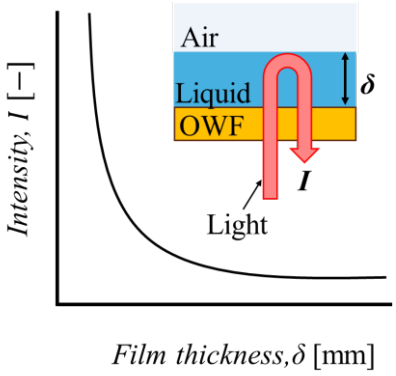


Figure 2. Relationship between liquid film thickness and reflected light intensity

References

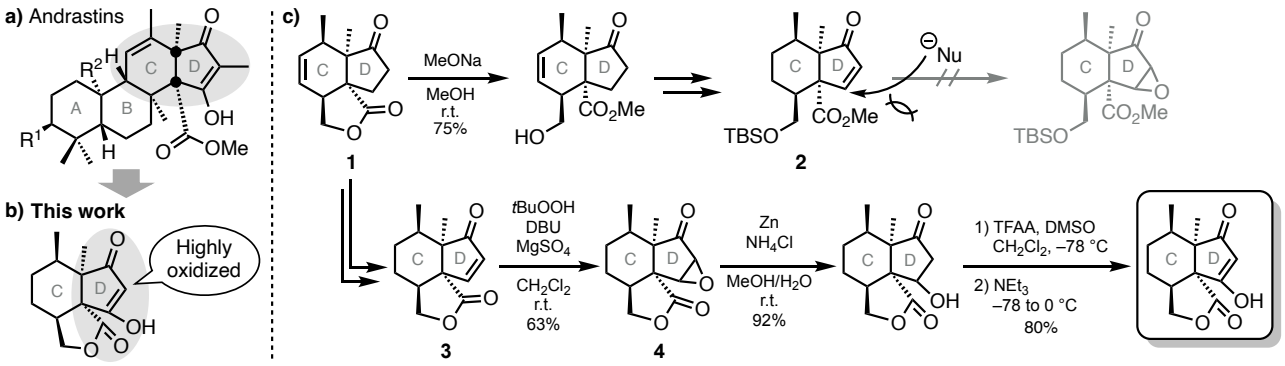
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Development of a synthetic method for a highly oxidized D ring in *cis*–CD–fused steroid skeletons

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Steroid CD ring structure can be classified into *trans*– and *cis*–fused types, and biologically active andrastins possess a *cis*–CD–fused steroid skeleton (Fig. a). Andrastins contain two quaternary carbon centers at the CD ring junction and a highly oxidized D ring moiety. Therefore, their synthesis is difficult, and there have been only a limited number of reported total synthesis examples. Our group has previously succeeded in constructing a *cis*–fused CD ring structure with two quaternary carbon centers via an intramolecular Diels-Alder reaction.[1)] In this study, toward the total synthesis of natural products possessing a *cis*–CD–fused steroid skeleton, we investigated an efficient strategy for the introduction of oxygen functionalities onto the D ring moiety (Fig. b).

Initially, we examined whether oxygen functionalities could be introduced after opening the lactone ring of **1** (Fig. c). The lactone moiety of CD ring derivative **1** was opened using NaOMe, and enone **2** was synthesized through several steps. Subsequently, an attempt was made to epoxidize enone **2**, but the reaction did not proceed at all due to steric hindrance around the reaction site. DFT calculations suggested that enone **3**, which retains the lactone ring, would have less steric hindrance around the D ring than enone **2**. Indeed, treatment of enone **3** with *t*BuOOH as an oxidant successfully afforded the desired epoxide **4**. Furthermore, reductive opening of the epoxide using zinc enabled the introduction of a hydroxy group onto the D ring. Finally, oxidation of the hydroxyl group under DMSO–TFAA conditions completed the construction of the desired highly oxidized D ring moiety.



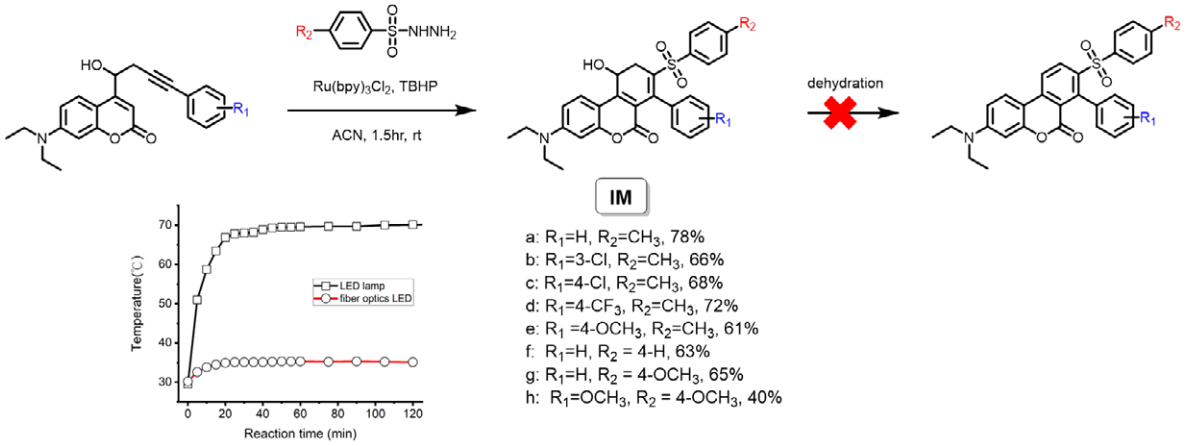
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A Fiber-Optic-Mediated Reactor System for Thermal Control and Scalable Synthesis in Photocatalytic Cascade Annulation

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Efficient photocatalytic radical cascade annulation was successfully employed to synthesize novel hydroxylated cyclohexene-fused coumarin intermediate (IM) and its dehydrated product benzo[c]coumarins. We found that a critical challenge identified in visible-light-driven systems is the heat accumulation from high-power LEDs, which triggers uncontrollable thermal dehydration, thereby undermining reaction selectivity and process robustness. Herein, we report a fiber-optic-based illumination strategy that decouples photon input from thermal energy, ensuring the selective formation of key intermediates for photocage applications. The resulting cyclohexene-fused coumarins enable fast, visible-light-triggered cargo release with a dual-signal self-reporting mechanism involving hypsochromic shift and fluorescence-off. To further demonstrate practical relevance, a home-built multi-channel parallel reactor with integrated fiber-optics was developed, facilitating the scalable and reproducible synthesis across the substrate scope. Compared to conventional batch photoreactors, the system provides superior thermal control and improves reproducibility. Notably, it serves as a practical alternative to flow chemistry for high-throughput applications, offering a more accessible strategy for parallel reaction screening and process optimization.



Scheme 1. Fiber-optical LED-driven photocatalytic cascade annulation for ring-fused coumarins

References

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Gram-Scale Synthesis of the Opioid Alkaloid Mitragynine

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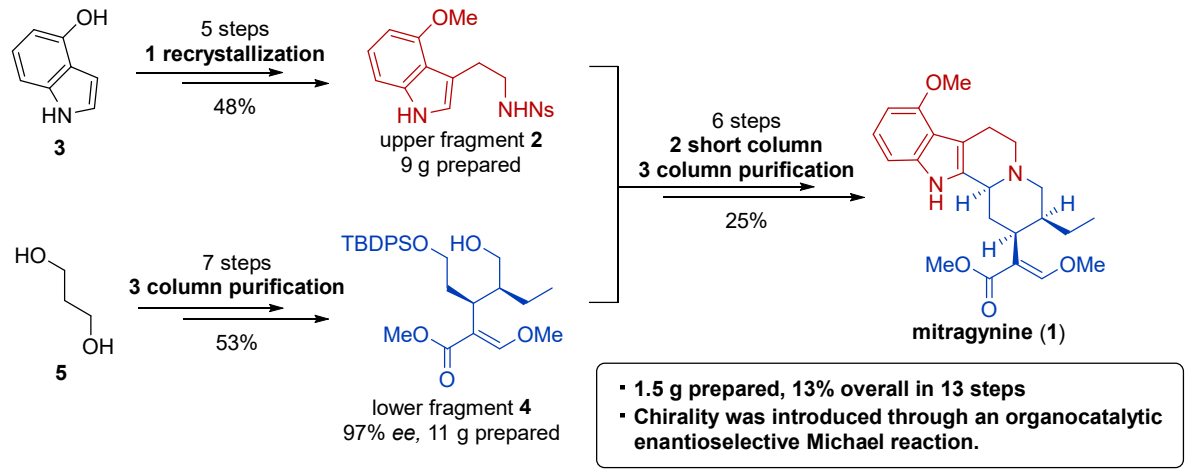
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Mitragynine (**1**), isolated from *Mitragyna speciosa*, and its derivatives exhibit potent μ-opioid receptor-mediated analgesic activity[1]. These alkaloids have attracted considerable attention as biased agonists with the potential to provide safer analgesics with reduced side effects[2]. Our group has previously investigated the structure–activity relationships of mitragynine (**1**)[3]. As part of this effort, we aimed to establish a gram-scale supply of **1** in order to conduct *in vivo* studies of the promising derivatives identified during our investigations.

The upper fragment **2** was synthesized from commercially available 4-hydroxyindole (**3**) in five steps with a single recrystallization, providing the product in 48% overall yield. Next, optically active lower fragment **4** was synthesized from commercially available 1,3-propanediol (**5**) in seven steps, including an organocatalytic enantioselective reaction, with only three column chromatographic purifications, affording the product in 53% overall yield and 97% *ee*.

With fragments **2** and **4** in hand, mitragynine (**1**) was prepared on gram scale in six steps, including a Mitsunobu coupling and a diastereoselective Pictet–Spengler reaction, to afford 1.5 g of the product in 25% overall yield. This sequence required only two short silica gel plug filtrations and three column chromatographic purifications. Overall, mitragynine (**1**) was synthesized in 13 steps from diol **5** in 13% overall yield.



Gram-scale total synthesis of mitragynine (**1**)

References

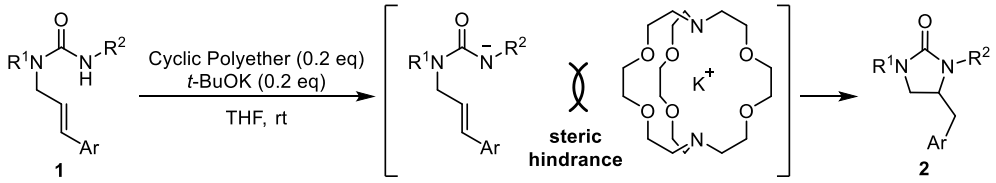
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Intramolecular Hydroamidation of Alkene Using Alkali Metal Bases and Cyclic Polyethers

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Intramolecular hydroamidation is one of the useful methods for synthesizing cyclic amides such as lactams, imidazolidinones, and oxazolidinones. We reported that imidazolidinone **2** can be obtained from urea-tethered alkene **1** using a catalytic amount of P4-base. [1] In this reaction, P4-base deprotonates the amide to generate the corresponding amidate anion. The resulting bulky phosphazenium counter-cation facilitates the formation of a loose ion pair, thereby enhancing the nucleophilicity of the amide. However, the high cost of P4-base limits its practical application. In this study, we focused on the combination of alkali metal bases and cyclic polyethers as a more cost-effective alternative since cyclic polyether are expected to form a bulky counter cation promoting the intramolecular hydroamidation (Scheme 1).

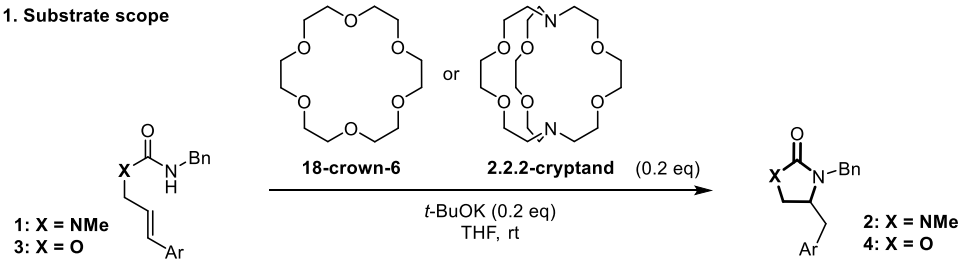
Scheme 1. This work: Intramolecular hydroamidation using alkali metal base and cyclic polyether

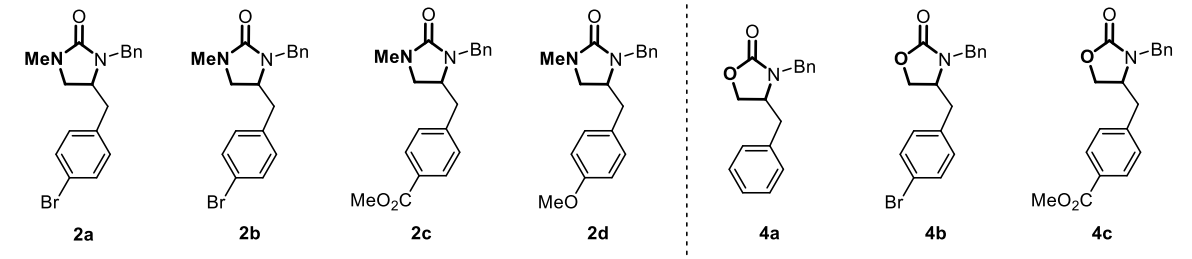


First, we examined various combination of alkali metal bases and cyclic ether using urea-containing alkene **1a** as a model substrate. As a result, a catalytic system of 18-crown-6 (18C6) and *t*-BuOK afforded the cyclized product **2a** in high yield in 5 min. We then investigated the substrate scope. The reactions of **1b** and **1c** bearing an electron-withdrawing group (Br and CO_2Me) at the para position gave the desired products **2b** and **2c** (98% yields). Although the methoxy group slightly lowered the yield and extended reaction times, the use of the more sterically demanding 2.2.2-cryptand (C222) afforded the imidazolidinone **2d** in good yield within a short time. Carbamate-tethered styrene was examined. The reaction proceeded successfully to provide the corresponding oxazolidinones **4a–c** in high yields (91-93%).

In this presentation, the detailed substrate scope and the reactivity of this reaction will be discussed.

Table 1. Substrate scope





2a	2b	2c	2d	4a	4b	4c
96% (18C6, 5 min)	98% (18C6, 5 min)	98% (18C6, 15 min)	60% (18C6, 24 h) 95% (C222, 10 min)	93% (18C6, 5 min)	91% (18C6, 5 min)	92% (18C6, 5 min)

Reference

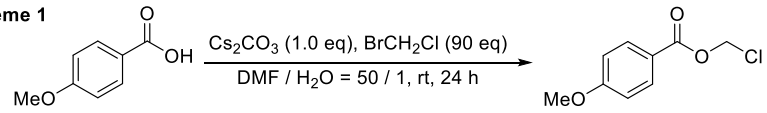
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Development of chloromethyl esterification reaction of carboxylic acids and methods for introducing of nitrate esters

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The nitrate ester is metabolized in the body to release nitric oxide, which dilates coronary blood vessels and the blood pressure-lowering effect. For example, nicorandil, composed of nitrate ester and nicotinamide, exhibits a potent blood pressure-lowering effect due to the synergistic effect of these components. Thus, incorporating nitrate esters into drugs with different mechanisms of action is expected to lead to the development of new pharmaceuticals. In this context, we focused on chloromethyl esters, as synthetic precursor for introducing nitrate esters into pharmaceuticals. As conventional methods for synthesizing chloromethyl esters from carboxylic acids, chloromethyl sulfate[1] and chloroiodomethane[2] have been used. However, these reports have several drawbacks, such as the high cost and instability of the reagents. To address these issues, we selected bromochloromethane ($BrCH_2Cl$) as an inexpensive and stable reagent. However, previous methods using $BrCH_2Cl$[3] required the corresponding carboxylate salt and had a narrow substrate scope, therefore we re-investigated the reaction conditions and found that the use of Cs_2CO_3 as the base promotes the chloromethyl esterification reaction to proceed in a one-pot reaction from carboxylic acid (Scheme 1).

Scheme 1

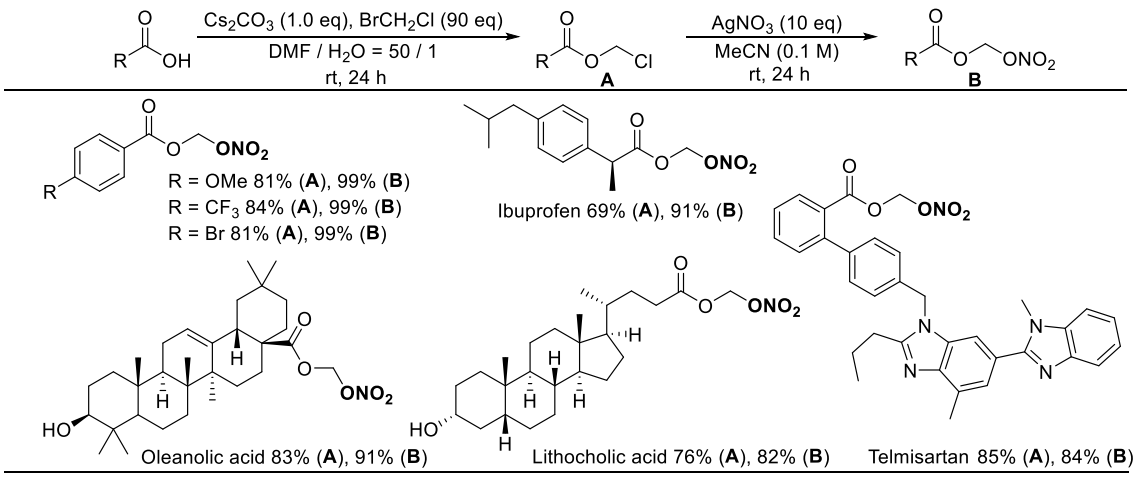


Next, we synthesized nitrate esters from the obtained chloromethyl esters. We found that the transformation of chloromethyl ester with silver nitrate proceeded smoothly at room temperature, affording the corresponding nitrate esters in high yield.

The optimized conditions were then applied to various carboxylic acids (Scheme 2). The reactions proceeded with various substitutes such as electron-withdrawing or -donating groups, giving the corresponding chloromethyl esters in good yields. Pharmaceuticals, complex natural products, and tertiary carboxylic acid were also smoothly converted, giving the corresponding chloromethyl esters in good yields. The subsequent conversion to nitrate esters proceeded in high yields.

In this presentation, we will discuss the optimization of these reactions, as well as details of substrate generality.

Scheme 2



Reference

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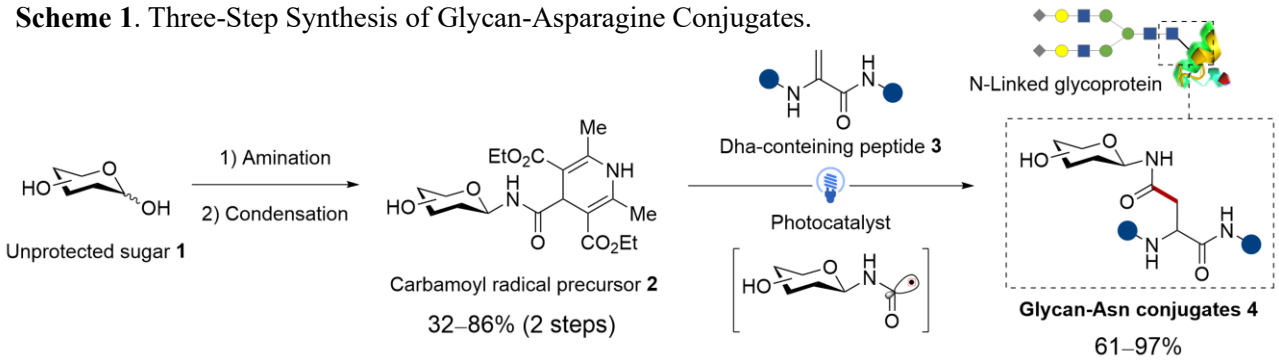
Three-Step Synthesis of Glycan-Asparagine Conjugates from Unprotected Sugars

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N-Linked glycoproteins, in which oligosaccharides are covalently attached to the nitrogen atom of asparagine (Asn) residues, play critical roles in protein folding, stability, and biological activity[1]. However, because glycoproteins exist as heterogeneous mixtures of glycoforms, the chemical synthesis of structurally homogeneous glycoproteins is essential for elucidating the effects of individual glycan structures on glycoprotein function. Conventionally, peptide elongation using glycosylated Asn derivatives as building blocks has been widely employed for the total synthesis of N-linked glycoproteins[2]. However, this approach requires multistep synthetic operations and is limited in the accessible protein size, making it unsuitable for the efficient construction of glycoprotein libraries bearing diverse glycan structures. In this study, we report a three-step synthesis of glycan–Asn linkages toward N-linked glycoproteins. The key step involves a Giese-type addition of an unprotected sugar-derived carbamoyl radical to dehydroalanine (Dha)-containing peptides under mild photoredox conditions.

The carbamoyl radical precursor **2** can be readily prepared from unprotected Sugar **1** via anomeric amination and condensation without the use of protecting groups. As referred to the work of carbamoyl radical generation from 1,4-dihydropyridine-3-carboxamide derivatives[3], visible-light irradiation of a mixture of compound **2**, Dha derivative **3**, and a photocatalyst afforded the desired Glycan–Asn conjugate **4** as expected. This method is applicable to complex oligosaccharides as well as biologically relevant peptides. Exhibition of broad photocatalyst and solvent compatibility, including aqueous buffered systems, highlighting its potential for future applications in site-selective protein modification.

Scheme 1. Three-Step Synthesis of Glycan-Asparagine Conjugates.



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Ester Reduction in Toluene by All-at-Once Addition of $NaBH_4$ and Alcohol Activator

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$LiAlH_4$ is a standard reagent for ester reduction, its high reactivity limits its use in process-scale synthesis, while $NaBH_4$, despite being a safer alternative, is generally ineffective for ester reduction. The $NaBH_4$ reduction system using a THF/MeOH mixed solvent reported by Soai[1] enabled ester reduction; however, the need for dropwise addition of MeOH during the reaction and its incompatibility with toluene, a solvent generally preferred over THF in process chemistry, limited its practicality for process-scale applications. In this study, we report an ester reduction with $NaBH_4$ in toluene that proceeds by all-at-once addition of 2-methoxyethanol (2-ME) as an activator, inspired by Red-Al, without the need for dropwise addition (Figure 1).

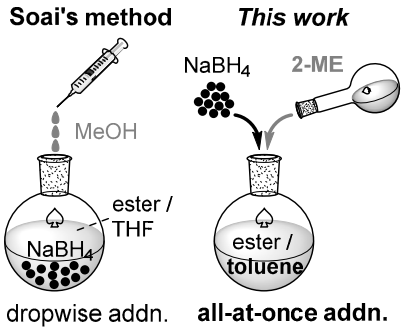
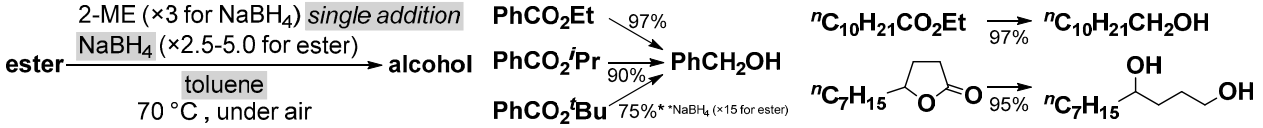


Figure 1.

To a solution of ethyl benzoate **1a** in toluene were added 4 molar equivalents of $NaBH_4$ and 12 molar equivalents of 2-ME (×3 for $NaBH_4$) in a single addition (all-at-once addition method), and the mixture was stirred at 70 °C for 2 h under air to give benzyl alcohol (**2a**) in 97% yield (Scheme 1). The reduction method was also effective for other esters. Even isopropyl and *tert*-butyl esters, which showed poor reactivity using the Soai's method, underwent reduction with increased amounts of the $NaBH_4$/2-ME.



Scheme 1. $NaBH_4$ reduction of esters in toluene using 2-ME by all-at-once addition method.

The highest activity was observed with the addition of three equivalents of 2-ME relative to $NaBH_4$, suggesting that $NaBH(OCH_2CH_2OCH_3)_3$ is the active species. DFT calculations revealed that coordination of Na^+ to the oxygen atoms of 2-methoxyethoxide enhanced solubility in toluene. Furthermore, the activation free energy for the reduction of **1a** using $NaBH(OCH_2CH_2OCH_3)_3$ was lower than that using $NaBH_4$ or $NaBH(OMe)_3$, the proposed active species in the Soai's method.

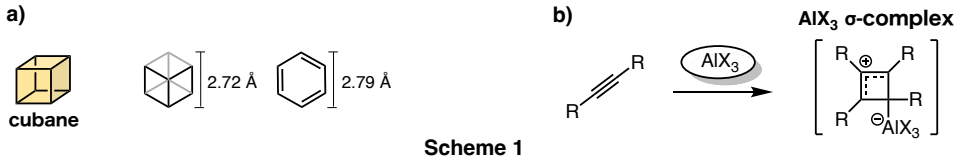
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Development of a Synthetic Method for Multisubstituted Cubanes using Aluminum Halaide σ–Complexes

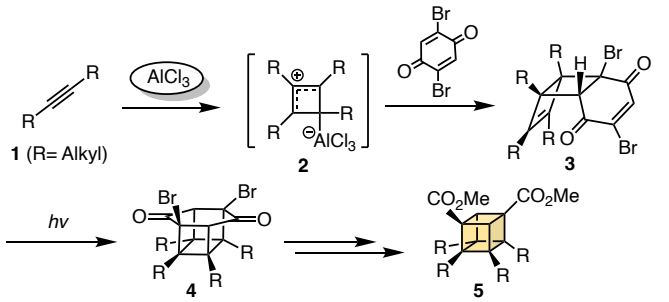
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Cubane possesses geometric similarity to the benzene rings (Scheme 1-a)[1] and is therefore expected to serve as bioisosteres of benzene rings in drug compounds[2]. Although several cubane synthetic methods have been reported, there are still some issues to be resolved such as multistep synthetic processes, the necessity of expensive reagents, and the limitation of acceptable substitutions. Therefore, we initiated a bottom-up cubane synthetic method that can introduce diverse substitutions from affordable reagents in fewer steps. As the kye synthetic elements, we used aluminum halide σ-complexes of cyclobutadienes (Scheme 1-b). This complex can be obtained in a one-step procedure from alkyne and aluminum halide[3].

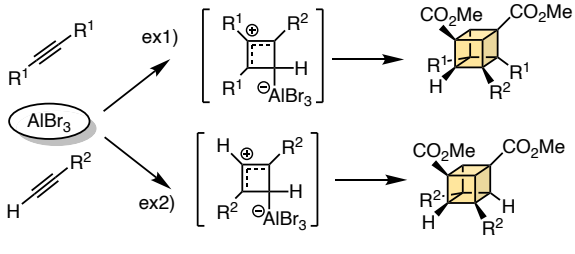


Scheme 1

The reaction of dialkyl-substituted alkyne **1** with aluminum chloride provided aluminum chloride σ-complexes **2** (Scheme 2). Inspired by MacMillan's protocol[2], this reaction mixture added to *p*-dibromo quinone to form tricyclic intermediate **3**, followed by photoirradiation to obtain **4**. Finally, Favorskii rearrangement and esterification provided cubane-1,3-diester **5** substituted with four alkyl groups. In addition, using aluminum bromide σ-complexes, it was able to synthesis cubane-1,3-diester which substituted with different numbers of alkyl groups or an allyl group (Scheme 3).



Scheme 2



Scheme 3

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Development of electrodeprotection reaction of acetals under neutral conditions and its application to one-pot sequential transformation

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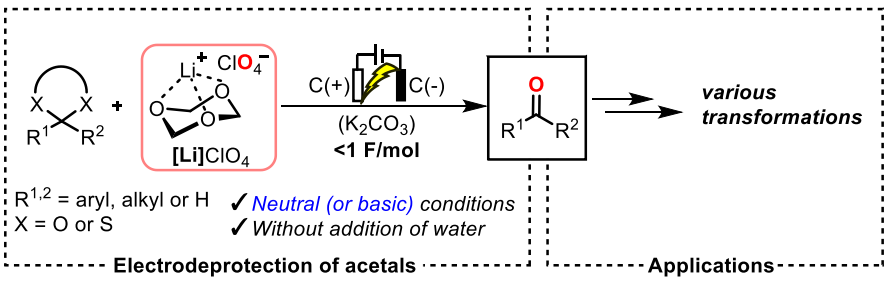
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Acetals serve as protecting groups in organic synthesis to temporarily deactivate carbonyl groups, thereby facilitating the selective transformation of the desired functional group. Thus acetal protection provides a critical platform for the synthesis of complex compounds during multistep syntheses. Since acetals generally undergo deprotection under acidic conditions with a Brønsted or Lewis acid in the presence of water serving as the carbonyl oxygen source, careful consideration is required for applying it to the substrate containing acid-sensitive functional groups. Although acetal deprotection under non-acidic conditions has been reported,[1] these methods require aqueous workup, and their applicability to aromatic acetals has not been enough investigated.

To address these issues, we have developed the electrodeprotection method for acetal, ketal, and dithioacetal derivatives that do not require the addition of water under neutral conditions (Figure 1).[2] The electrodeprotection process is efficiently performed with a lithium perchlorate ($LiClO_4$)–1,3,5-trioxane complex ([Li]ClO_4), which functions simultaneously as the electrolyte, carbonyl oxygen source, and acetal activator. Under the electrodeprotection conditions, aromatic and aliphatic acetals including dithioacetals, which are typically deprotected using hazardous and toxic reagent, were converted into their corresponding aldehydes and ketones in good to quantitative yields.

Furthermore, leveraging the advantages of this electrodeprotection methodology, we subjected *in situ*-prepared aldehydes to the Horner–Wadsworth–Emmons olefination in a one-pot process. The sequential electrodeprotection and olefination process can reduce operational costs and time, and solvent waste.[3] The details of the electrodeprotection reaction and its application to the one-pot sequential olefination reaction will be described in the presentation.

Figure 1. Electrodeprotection and its one-pot application



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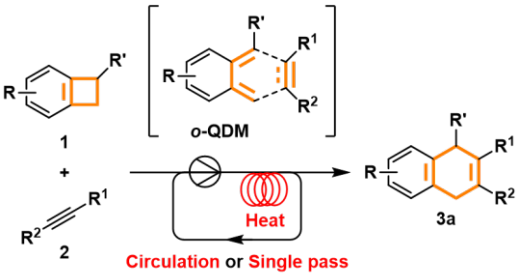
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Development of a Mild and Efficient Flow-Based Method for the Generation of *o*-Quinodimethane

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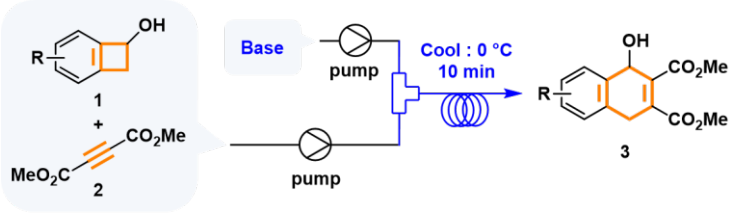
Benzocyclobutene (BCB) derivatives undergo thermal ring-opening reactions driven by the release of strain in the four-membered ring, yielding *o*-quinodimethane (*o*-QDM). Although *o*-QDM has been utilized as a highly reactive diene intermediate in natural product syntheses and reaction developments,[1), 2)] efficient methods for generation and utilization of *o*-QDM has been still challenges due to its instability. One continuous flow method for ring-opening of BCB has been reported, while supercritical conditions using specific flow apparatus are required.[3)] Therefore, the substrate generality and practicality still leave room for improvement. In this study, we aimed to develop a facile method for generating *o*-QDM from BCB under mild reaction conditions using a commonly available flow system.

After several investigations, we found that BCB substituted with a cyano group (CN) on the cyclobutene ring was transformed to *o*-QDM in moderate to high yield under circulation flow method at 140 °C, which could be react with various dienophiles bearing electron withdrawing groups during circulation flow (Scheme 1). BCB possessing an electron-donating oxygen functional group onto cyclobutene moiety exhibited high reactivity, and the ring-opening of BCB and the subsequent Diels–Alder reaction was completed within 10 minutes in a single pass manner. Furthermore, when benzocyclobutenol was used as the substrate, the reaction proceeded even at 0 °C by activating benzocyclobutenol using base (Scheme 2).



Scheme 1 : Heating conditions

We developed a method for the efficient continuous generation of *o*-QDM under practical flow conditions. With further refinement of this method, the reaction is expected to be utilized in a continuous synthesis of multi-substituted naphthalene derivatives as useful synthetic building blocks.



Scheme 2 : Cooling conditions

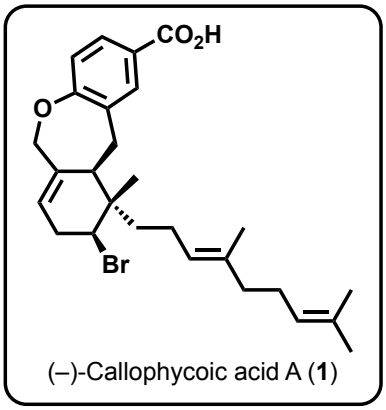
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Synthetic Studies of Callophycoic Acid A

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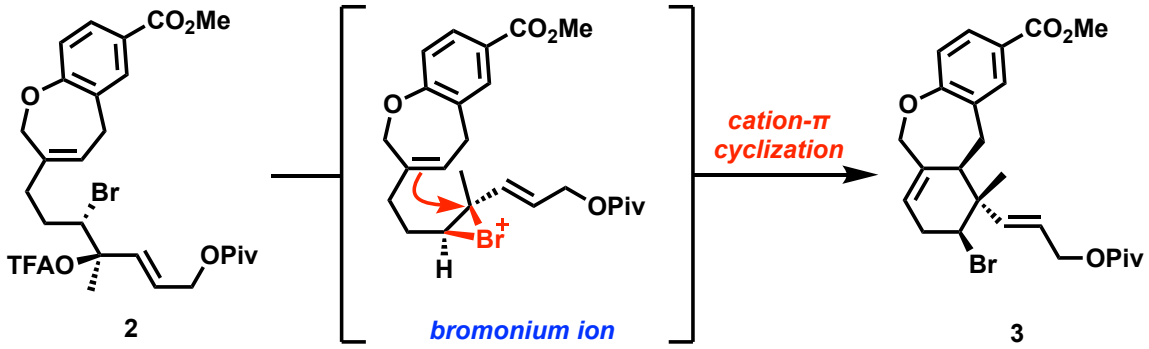
Callophycoic acid A (**1**) was isolated from extract of the Fijian red alga *Callophycus serratus*.[1] Structurally, this molecule is characterized by a hybrid framework composed of a diterpene and benzoic acid, as well as a brominated tricyclic skeleton containing three consecutive stereocenters, one of which is an all-carbon quaternary center. In addition, compound **1** has been reported to exhibit antibacterial activity against vancomycin-resistant *Enterococcus*, antimalarial activity, and cytotoxicity toward human cancer cells.[2] Based on this background, we investigated the total synthesis of **1**.



(–)-Callophycoic acid A (**1**)

Previous studies in our laboratory achieved the construction of the tricyclic carbon skeleton of **1** through radical cyclization and intramolecular etherification.[3] However, the introduction of the bromine substituent was unsuccessful due to severe steric hindrance encountered after the core ring formation.

To address this issue, we focused on a cation-π cyclization reaction, previously established in our laboratory, which enables the construction of a brominated cyclohexene ring via a bromonium ion intermediate. Using this reaction, we devised a synthetic strategy in which the upper segment was first constructed by coupling with aromatic unit and forming a seven-membered ring. Then, we aimed to synthesize compound **3**, featuring the callophycoic acid A skeleton, by performing the cation-π cyclization of substrate **2** via the bromonium ion intermediate.



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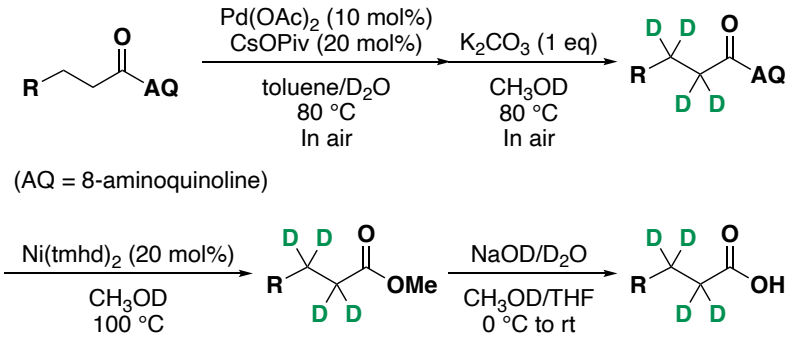
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Controlled Tetradeuteration of Straight-Chain Fatty Acids

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Recent advances in LC–MS/MS analysis have revealed that structurally diverse lipids and fatty acids are present in living organisms and exhibit a wide range of biological activities. Stable isotope-labeled probe molecules are indispensable for their quantitative analysis and for elucidating metabolic pathways. In this study, we developed a site- and number-selective deuteration process for straight-chain fatty acids. This methodology employs inexpensive deuterium sources and operationally simple procedures, enabling the selective introduction of four deuterium atoms at the α- and β-positions based on the carboxylic acid moiety. Specifically, fatty acid-derived 8-aminoquinoline amides were subjected to catalytic β-selective deuteration using D_2O as the deuterium source, followed by α-deuteration under basic conditions. The amide moiety was then converted into the corresponding methyl ester using a nickel catalyst and subsequently hydrolyzed to afford fatty acids in which the four hydrogen atoms at the α- and β-positions were highly selectively replaced with deuterium.

Building on this strategy, we have investigated the synthesis of labeled oxidized linoleic acids, which have been implicated in inflammatory diseases. The synthesized deuterated probes enable selective and comprehensive tracking of incorporation into phospholipids by monitoring product-ion mass shifts in LC–MS/MS analysis. These results will also be presented.



Scheme 1. Controlled tetradeuteration of straight-chain fatty acids

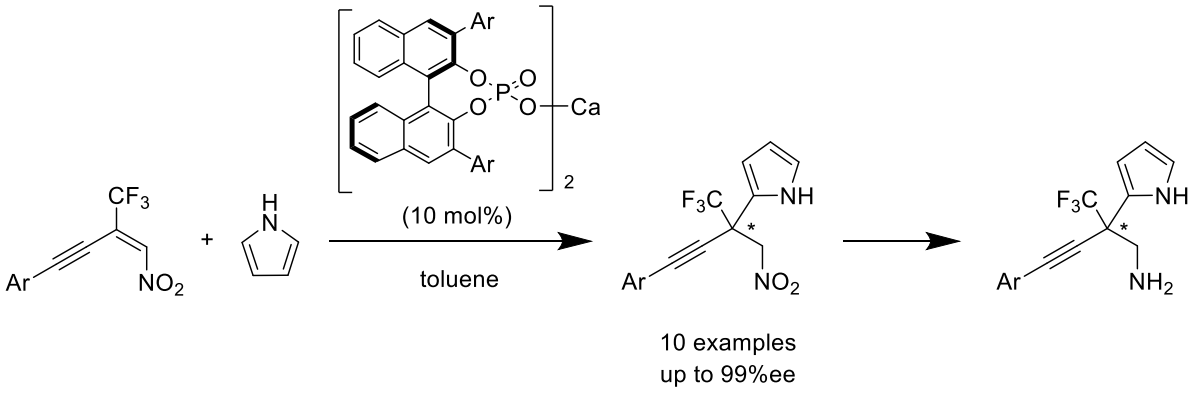
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Enantioselective Friedel-Crafts Alkylation Reaction of Pyrrole with β-Trifluoromethyl-β-alkynyl Nitroalkenes Catalyzed by Chiral BINOL Metal Phosphate

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Chiral amines bearing trifluoromethyl group at α or β position are essential intermediates in pharmaceutical sciences, owing to the unique biological activities imparted by the trifluoromethyl moiety. Consequently, the development of efficient methods for the asymmetric synthesis of trifluoromethylated amines remains a critical challenge in organic chemistry. We already reported Friedel-Crafts alkylation reaction of trifluoromethyl-substituted nitrostyrenes with indole,[1] pyrrole,[2] and transfer hydrogenation reaction[3] by means of chiral calcium phosphates. In this study, we developed a Friedel-Crafts alkylation reaction of β-alkynyl-β-trifluoromethyl nitroalkenes with pyrrole. Upon treatment of β-trifluoromethyl-β--alkynyl nitroalkene with pyrrole in the presence of a chiral calcium phosphate (10 mol%), Friedel-Crafts alkylation reaction proceeded smoothly to give pyrrole adduct in good yield with high enantioselectivity (Scheme). Selective reduction of the nitro moiety afforded chiral amines bearing a quaternary carbon center at the β-position. In addition to enabling the construction of fluorine-containing quaternary stereocenters, this catalytic asymmetric transformation offers significant potential for process chemistry applications.



Scheme. Friedel-Crafts Alkylation Reaction of Trifluoromethylated Nitroalkene by Chiral Metal Phosphate

References

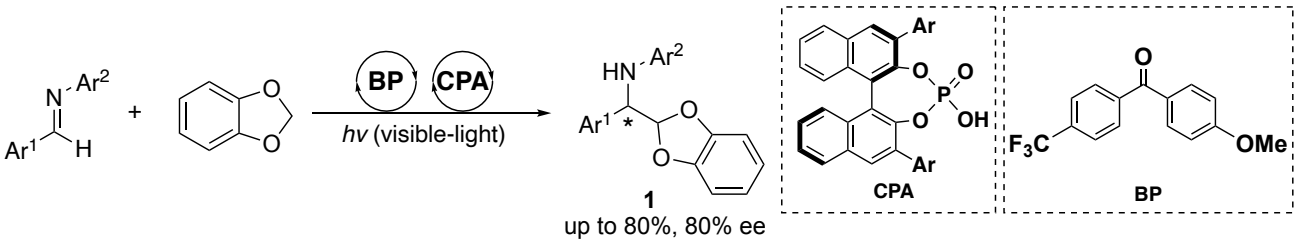
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Enantioselective Visible-Light-Driven Radical Addition Reactions to Imines Using Chiral Phosphoric acid/photoinduced HAT dual catalysis

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Chiral amines are prevalent in pharmaceuticals and agrochemicals, and intensive research is underway to develop efficient methods for their synthesis. Enantioselective radical addition reactions to prochiral imines using organocatalysts have attracted much attention in recent years, owing to its broad functional group tolerance and substrate versatility. We recently reported a visible-light-driven enantioselective radical addition reactions to imines catalyzed by chiral phosphoric acid, utilizing benzothiazoline derivatives as radical precursors.[1)] However, the generality of the adding radicals was limited. On the other hand, reactions involving the generation of alkyl radicals via photoinduced hydrogen atom transfer (HAT) catalysis have been extensively developed, facilitating the access to a diverse array of alkyl radical species. We hypothesized that combination of a photoinduced HAT catalyst and a chiral phosphoric acid would broaden the scope of enantioselective radical addition to imines.

In this study, we have developed visible-light-driven enantioselective alkyl radical addition reactions to imines using dual catalysis with a chiral phosphoric acid (CPA) and a photoinduced-HAT catalyst (**Scheme**). Irradiation of aldimines and 1,3-benzodioxole with 390 nm light in the presence of a benzophenone derivative (BP) and chiral phosphoric acid afforded the corresponding chiral amines **1** in high yields with high enantioselectivities.



Scheme. Radical Addition Reactions to Aldimines

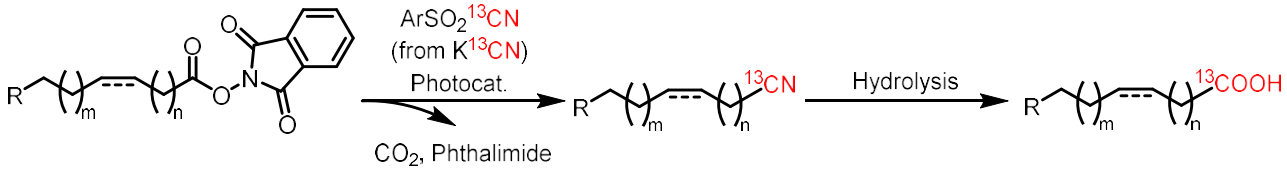
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Catalytic Decarboxylative Cyanation for ^{13}C-Labeled Fatty Acids

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Stable isotope labeling is indispensable for the quantification by LC-MS in studies of lipid and fatty acid (FA) metabolism. We previously developed a method for the controlled tetradeuteration of straight-chain FAs and applied them to the identification of acyltransferases.[1)] In the present study, we have investigated the efficient synthesis of ^{13}C-labeled fatty acids for biological applications, including metabolic analysis of β-oxidation. The decarboxylative cyanation–hydrolysis sequence enables very high ^{13}C isotopic enrichment. In this context, the decarboxylative ^{13}C isotope exchange processes of carboxylic acids using $^{13}CO_2$ proceed under equilibrium conditions, thereby inherently limiting the extent of ^{13}C incorporation.[2)] In addition, most reported decarboxylative cyanation methods have proven ineffective for primary alkyl carboxylic acids such as FAs. To achieve high ^{13}C-labeling efficiency with practical utility, we have developed an efficient organophotocatalytic decarboxylative cyanation of straight-chain FA derivatives. The key was the rational structural design of the cyanating reagents, namely sulfonyl cyanides ($ArSO_2CN$); whereas the use of commercially available TsCN resulted in poor efficiency and undesirable side reactions, including olefin isomerization with unsaturated substrates, the employment of tailored $ArSO_2CN$ offered enhanced reactivity while substantially suppressing side reactions. Building on our previously developed synthesis of $ArSO_2CN$ from KCN, structurally diverse ^{13}C-labeled $ArSO_2CN$ can be concisely prepared using readily available K^{13}CN as the ^{13}C source.[3)] Subsequent hydrolysis of the ^{13}C-labeled nitriles prepared from $ArSO_2{}^{13}CN$ furnished the corresponding ^{13}C-labeled FAs.[4)]



Scheme 1. Practical synthesis of ^{13}C-labeled fatty acids

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2P-81S

Thermophysical Property Estimation of Multicomponent Mixtures Using Mixture Descriptors and Machine Learning

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The viscosity of water–organic solvent systems is an important parameter in process engineering. However, the viscosity of these systems shows complex nonlinear behavior with respect to composition and temperature. Therefore, accurate prediction using simple ideal mixing rules or conventional semi-empirical models remains difficult[1]. In this study, we developed a neural-network-based property prediction model applicable even to highly non-ideal solutions by introducing composition-dependent mixture descriptors.

The viscosity of 10-component solvent mixtures consisting of water, DMA, acetonitrile, acetone, NMP, methanol, ethanol, 1-propanol, tert-butanol, and 1,2-butanediol was measured at 298.15 K. The training data consisted of 153 binary-system data points and 85 experimentally obtained data points for 10-component systems collected under conditions selected by active learning. Three types of machine learning models were constructed: a model without embedding (NN), a model that converts molecular descriptors into embedded representations (ENN), and a model that converts both molecular descriptors and composition information into embedded representations (FENN). The predictive performance of each model was evaluated by 10-fold cross-validation.

The predictive accuracies of the ideal mixing rule and the three machine learning models are shown in Fig. 1. As a result, the FENN model showed the lowest MSE value of 0.0306, which was less than half that obtained using the ideal mixing rule. Furthermore, to investigate the influence of input descriptors on the performance of the FENN model, five descriptors were tested in various combinations. Additionally, it was shown that an embedding dimension of 10 or fewer is sufficient, suggesting that the embedding process efficiently extracts the necessary information from the original descriptors.

These results suggest that the proposed method is a promising new approach for multicomponent property prediction, as it can simultaneously reduce the amount of required training data and may also be applicable to extrapolative prediction for mixtures containing previously unseen components.

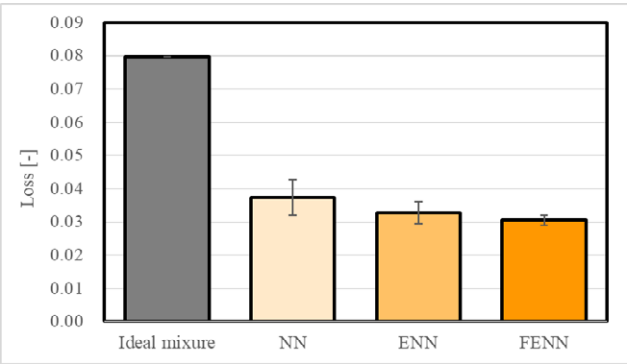


Figure 1. Comparison of the accuracy of each model

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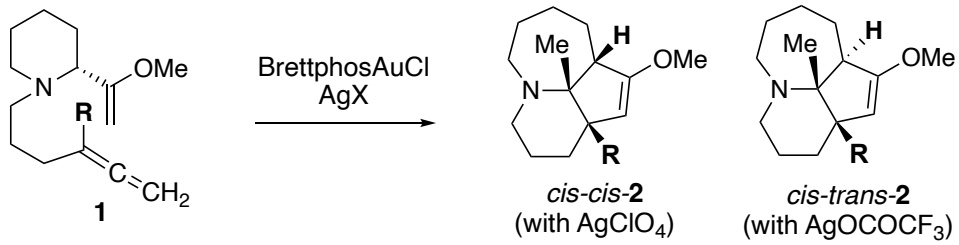
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Synthesis of Fused Amines Bearing Tetrasubstituted Carbons via the Gold-Catalyzed Cyclization–3-aza-Cope–Mannich Cascade

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Alkaloids are natural products with complex structures. They often contain fused ring systems, numerous stereogenic centers, and quaternary carbons, which have attracted the interest of synthetic chemists. This structural diversity is paralleled by a corresponding diversity in their biological activities, rendering alkaloids and pseudoalkaloids significant molecules for drug discovery. Therefore, the development of efficient synthetic methods for fused amines is important. The integration of multiple reactions in an experimental process greatly improves the synthetic efficiency. We previously reported the construction of fused amine skeletons through a cascade reaction involving the spirocyclization of aminoalkynes, 3-aza-Cope rearrangement, and transannular Mannich cyclization.[1-2] Herein, we report a new cascade reaction initiated by the spirocyclization of a tertiary amine onto an allene, providing fused cyclic amines bearing contiguous tetrasubstituted carbons.

Allenylalkyl cyclic amines **1** were treated with a cationic gold (I) catalyst generated *in situ* from BrettphosAuCl and silver salts. *Cis-cis*-**2** and *cis-trans*-**2** were diastereoselectively obtained depending on the choice of silver salts. Silver salts with weakly coordinating anions, such as $AgClO_4$, provided *cis-cis*-**2** exclusively. Meanwhile, $AgOCOCF_3$ stereospecifically furnished *cis-trans*-**2**. The reaction mechanism, as well as the scope and limitations of cyclic amines and allene substituents will be discussed in the symposium.



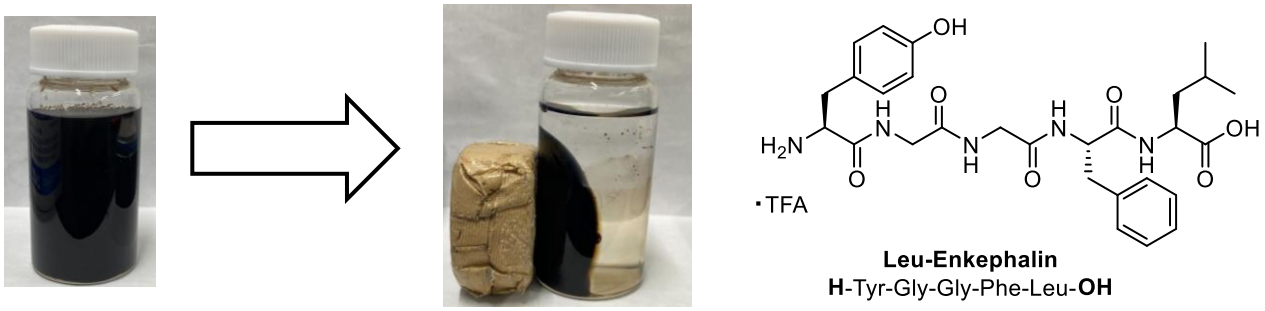
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Liquid-Phase Peptide Synthesis Utilizing Magnetic Liquid-Liquid Extraction

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Recently, as peptide drugs such as GLP-1 receptor agonists attract more attention, liquid-phase peptide synthesis (LPPS) is being studied as an alternative to the currently mainstream solid-phase peptide synthesis (SPPS) to meet the increasing demand for large-scale production. LPPS is expected to offer advantages over SPPS in terms of volumetric efficiency and reaction efficiency. As a core technology for LPPS, the use of hydrophobic soluble supports ("tags") has been widely investigated.[1] In tag-based synthesis, the target compound is typically recovered by precipitation and filtration. However, filter clogging can prevent efficient separation especially during large-scale synthesis. While liquid-liquid extraction has been studied as an alternative, it frequently faces challenges with emulsion formation depending on the peptide sequence, which hinders rapid phase separation. To address these issues, we present herein our work on magnetic liquid-liquid extraction. In a biphasic organic solvent system, we successfully resolved emulsions and achieved liquid-liquid extraction using magnetic force. The key strategy is dispersing hydrophobic iron oxide nanoparticles in the less-polar phase to form a magnetic fluid. This technology enables LPPS using only liquid-liquid extraction for purification during the elongation steps. As a proof of concept, the pentapeptide Leu-Enkephalin was obtained with a relatively good yield.



Scheme 1. Photographs of magnetic liquid-liquid extraction and chemical structure of Leu-Enkephalin.

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Continuous-Flow Oxidation of Alcohols to Carboxylic Acids Using Molecular Oxygen and a Ternary Pd/C–Pt/C–Ru/C Catalyst System

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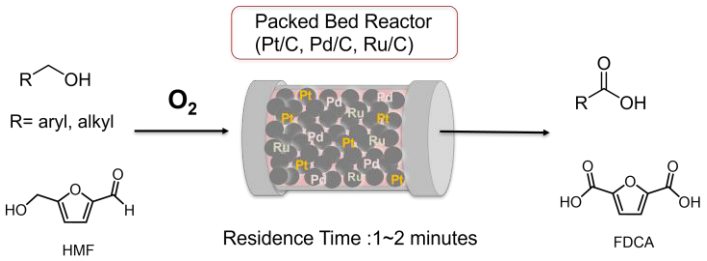
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An efficient and scalable continuous-flow process for the aerobic oxidation of primary alcohols to carboxylic acids is described (Scheme 1). Central to this methodology is a packed-bed continuous-flow reactor employing a ternary catalyst system composed of Pt/C, Pd/C, and Ru/C, which cooperatively promotes the complete oxidation sequence.[1] Molecular oxygen is used as the sole oxidant, generating water as the only by-product, thereby avoiding toxic stoichiometric oxidants and minimizing waste generation.

The packed-bed reactor, operated under gas–liquid slug-flow conditions, provides highly efficient oxygen mass transfer, continuous contact between substrates and catalysts, and effective heat dissipation. The utility of the system was demonstrated by the oxidation of biomass-derived 5-hydroxymethylfurfural (HMF) to 2,5-furandicarboxylic acid (FDCA), an important precursor for bioplastics, with a remarkably short residence time of only 1 min. Notably, the process maintained full catalytic activity for more than two weeks under continuous operation, demonstrating excellent long-term stability.

Furthermore, the method exhibits broad substrate scope, accommodating aromatic, heteroaromatic, and aliphatic primary alcohols in good to excellent yields. Overall, this study provides a practical, green, and scalable continuous-flow platform for the synthesis of carboxylic acids, highlighting its potential for sustainable chemical manufacturing.



Scheme 1. Continuous-Flow Oxidation of Primary Alcohols to Carboxylic Acids

Reference

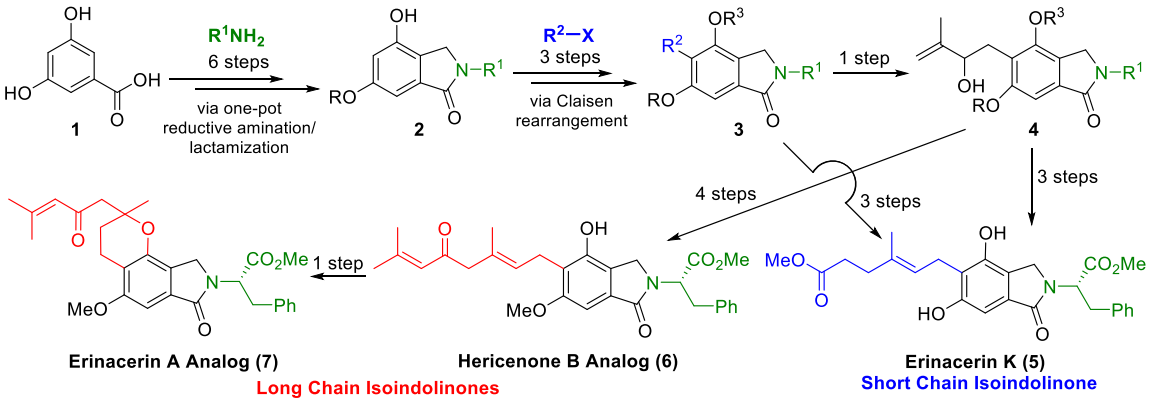
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Investigation of Divergent Methodology to Synthesize Amino Acid-Incorporated Isoindolinones and Their Analogs from Mushrooms of the Genus *Hericium*

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Edible mushrooms contain various bioactive secondary metabolites with notable health-promoting effects. In particular, secondary metabolites generated in the genus *Hericium* have been known to exhibit neuroprotective and neurite outgrowth-promoting activity, as well as the ability to stimulate nerve growth factor production, which are associated with potential anti-dementia effects.[1] These activities are partially attributed to the geranyl-resorcinol family, a structurally diverse class of natural products unique to the genus *Hericium*, with over 70 derivatives identified.[2] Among these, amino acid-incorporated isoindolinones have not yet been chemically synthesized, and their neuroprotective activities have not been evaluated. Herein, we report an efficient divergent synthetic strategy toward the unexplored amino acid-bound isoindolinones and related analogs for future structure–activity relationship (SAR) studies.

The synthesis features a one-pot reductive amination/lactamization between the resorcinol moiety and the amino acid component for rapid construction of the isoindolinone scaffold **2**, followed by a highly efficient Claisen rearrangement to introduce the side-chain anchor (R^2). Compared to the O→C rearrangement method being studied in parallel,[3] the present strategy provided the nitrogen-substituted isoindolinones on a practical scale. Subsequent diversification of the side-chain enabled access to both short-chain and long-chain isoindolinones, including the natural product, erinacerin K (**5**) in 12 or 13 steps, as well as analogs of hericenone B (**6**) and erinacerin A (**7**) in 14 and 15 steps from the inexpensive commercially available material **1**. Collectively, this divergent approach offers a versatile platform for the rapid construction of analog libraries for future biological evaluation and SAR studies on the effects of amino acid substituents and alkyl side chains for neuroprotective activity.



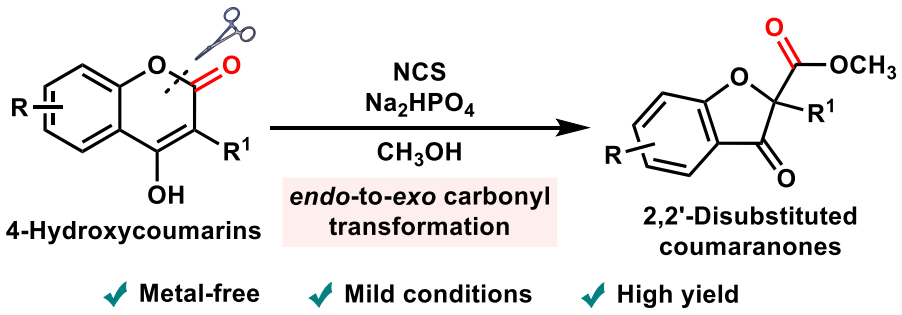
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Halogenation-triggered *endo*-to-*exo* carbonyl transformation of hydroxycoumarin

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The 3-coumaranone scaffold is recognized as a privileged structural motif in pharmaceuticals, agrochemicals, and dye molecules. In particular, coumaranones featuring a quaternary carbon center at the C2 position are important structural motifs frequently observed in biologically active compounds. However, their synthesis predominantly relies on transition-metal catalysis and often requires multistep preparation of the starting materials. Our research group has proposed a "cut-to-fuse strategy", which involves reconstructive heterocyclization of chain molecules generated by the halogenation of 1,3-diketones followed by solvolysis[1)], inspired by the halogenation-induced bond cleavage mechanism observed in the biosynthesis of halogenated compounds. Utilizing this strategy, 3-coumaranones with a quaternary carbon center were directly synthesized in high yields and with broad functional group tolerance by treating the abundantly available corresponding 4-hydroxycoumarins in methanol containing Na_2HPO_4 and *N*-chlorosuccinimide (NCS) under weak basic conditions at room temperature. The driving force behind this unique transformation is the transient introduction of a halogen, which facilitates ring-opening *via* alcoholysis and re-cyclization *via* intramolecular nucleophilic substitution, thereby enabling *endo*-to-*exo* carbonyl transformation. Interestingly, replacing methanol with ethyl acetate promoted a decarbonylative transformation, affording coumaranone with a tertiary C2 carbon center. These halogenation-triggered transformations were applicable to various cyclic β-keto esters, providing access to valuable molecular scaffolds.



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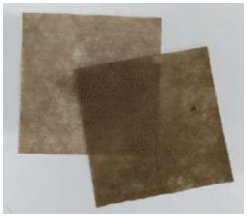
2P-87S

Tunable Chemoselective Hydrogenation Using a Palladium Catalyst Supported on Nonwoven Fabric (Pd/NF)

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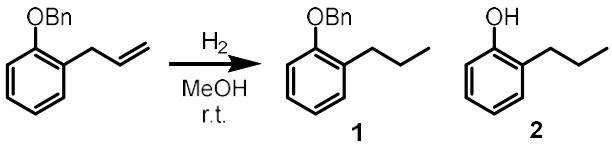


Catalytic hydrogenation is a key transformation in pharmaceutical and fine chemical manufacturing. Conventional palladium on carbon (Pd/C) is widely used, but its powder form presents challenges in operability, separation, and safety, including the risk of ignition during handling. To overcome these limitations, we investigated a palladium catalyst supported on a nonwoven fabric (Pd/NF) developed by Ebara Corporation.[1] Unlike powder catalysts, Pd/NF is handled as a flexible sheet, allowing simple mechanical recovery from the reaction mixture without filtration. This feature improves process operability and enables streamlined one-pot operations.

The catalytic activity and chemoselectivity of Pd/NF were evaluated using substrates bearing multiple reducible functional groups. Under neutral conditions, alkenes such as terminal alkenes and enones were selectively reduced, while benzyl groups remained intact. In contrast, Pd/C reduced both functionalities under similar conditions. Furthermore, the reactivity of Pd/NF was tunable depending on palladium loading: low Pd loading favored selective alkene reduction, whereas higher loading promoted reduction of multiple functional groups including benzyl groups (**Table**). Pd/NF showed excellent reusability and high activity over multiple cycles, highlighting its advantages in operability, safety, and process efficiency.

We will also discuss the applicability of Pd/NF to a wider variety of substrates and reaction conditions during the symposium.

Table. Tunable chemoselectivity with Pd/NF



entry	catalyst	yield (%)	
		1	**2**
1	5% Pd/C	87	1
2	1% Pd/NF	-	99
3	0.3% Pd/NF	99	-

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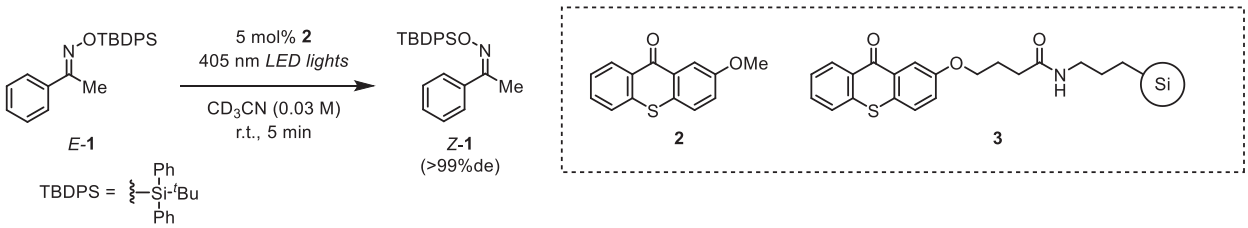
Solid-Supported Photosensitizers for Highly Selective *E* → *Z* Photoisomerization of Oximes

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Oximes are important intermediates in the synthesis of pharmaceuticals and functional polymers. In particular, the Beckmann rearrangement converting oximes to amides or lactams is widely used industrially. This reaction is known to provide products according to the stereochemistry of oxime. Therefore, controlling the *E/Z* stereochemistry of the starting oxime is essential for the Beckmann rearrangement. However, conventional synthetic methods typically yield either a mixture of *E*/*Z* isomers or the thermodynamically stable *E*-isomer only. Therefore, this study aimed to provide thermodynamically unfavorable *Z*-isomer in high yield and high purity by developing an *E* → *Z* photoisomerization reaction under mild conditions. Based on a 2021 report by Rovis and co-workers[1], we further pursued a more sustainable approach using our original solid-phase photocatalyst[2].

We found that *O*-protection is effective for promoting the photoisomerization of oximes. To improve the *E* → *Z* photoisomerization of *O*-protected oximes, we optimized both the oxime protecting group and the thioxanthone photosensitizer. A bulky protecting group in **1** enhanced the reaction rate, and thioxanthone **2** with a 2-methoxy group showed the highest activity. *E*-**1** was irradiated with 405 nm light in the presence of 5 mol% **2** in a CD_3CN solvent. The progress of the reaction was followed by measuring ^1H NMR spectra over time under irradiation with light. Under the optimized conditions, *Z*-**1** was obtained quantitatively with 99% de after 5 min of irradiation (Scheme 1). We then synthesized immobilized catalyst **3** derived from **2**. Immobilized catalyst **3** was reusable, enabling simplified purification.

Scheme 1. *E*-to-*Z* photoisomerization of *O*-Silyl Oximes



References

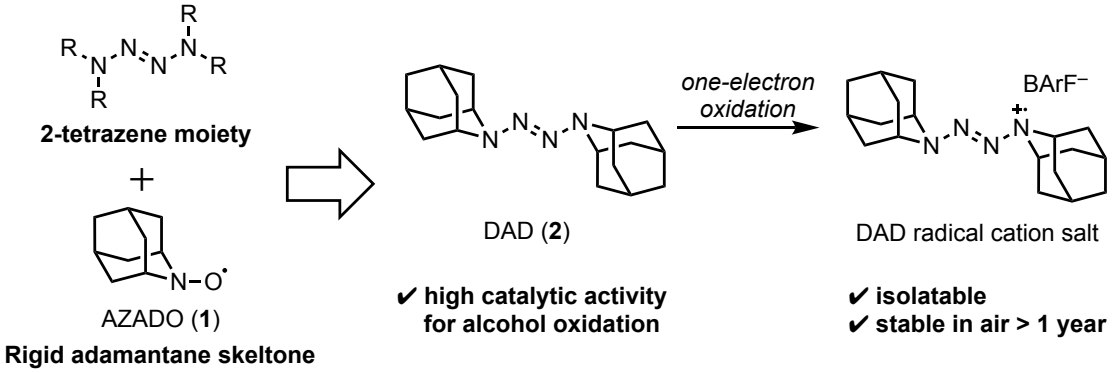
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Synthesis of Stable 2-Tetrazene Radical Cation Salts and Exploration of Their Oxidation Catalytic Activity

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2-Tetrazenes are compounds bearing a structural unit composed of four linearly connected nitrogen atoms. Although radical cations generated by one-electron oxidation of 2-tetrazenes have been observed by low-temperature ESR spectroscopy,[1] no tetrazene radical cation has been isolated and structurally characterized because of its instability. Our laboratory has previously reported that 2-azaadamantane *N*-oxyl (AZADO, **1**) exhibits high catalytic activity for alcohol oxidation. The rigid adamantane framework of AZADO (**1**) plays an important role in stabilizing the nitroxyl radical structure. Based on this background, we hypothesized that the radical cation generated by one-electron oxidation of the novel 2-tetrazene derivative 1,2-di(2-azaadamantan-2-yl)diazene (DAD, **2**) could be stably isolated.

DAD (**2**), synthesized from 2-azaadamantane in three steps, was oxidized with chlorine gas, and subsequent counteranion exchange to the BArF salt enabled the first successful isolation of a 2-tetrazene radical cation salt. The obtained salt was found to be stable for more than one year under ambient conditions. Furthermore, DAD (**2**) was found to exhibit two reversible redox processes, and its structure–redox property relationships were investigated through the synthesis and evaluation of DAD analogues with truncated adamantane frameworks or different functional groups. In addition, taking advantage of the reversible redox properties of DAD (**2**), it was applied as a catalyst for alcohol oxidation.[2]



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Soluble, Scalable, and Stable: Green Production of Peptides Enabled by "Ether Tags"

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Two major strategies for chemical peptide synthesis have been developed, including solid-phase (SPPS) and liquid-phase (LPPS) approaches. We have been focusing on LPPS due to its sustainability and scalability. In this method, both coupling and deprotection can be carried out in homogeneous liquid-phase and therefore highly pure peptide can be synthesized with smaller excess amount of reagent and solvent as compared to SPPS. Recently, solubilizing supports, “tags,” have been attracted attention to realize effective LPPS and various tags have been reported.[1]

The solubility of these tags affects reaction efficiency and the range of applicable solvents. Our conventional tags showed insufficient solubility, limiting both peptide sequences and solvents applicable to LPPS.[2] Although the “oleyl tag” previously developed in our group exhibited excellent solubility, its low stability caused by carbon–carbon double-bond isomerization remained problematic.

In this study, we developed “Ether tag” containing oxygen atoms. Introduction of ether structures into the alkyl chain was expected to achieve both high solubility and improved stability. Solubility evaluations revealed that the ether tag exhibited significantly higher solubility than our conventional tags. Using this ether tag, we succeeded in the synthesis of leuprorelin and leucine enkephalin in ethyl acetate, a green solvent, with high purity.

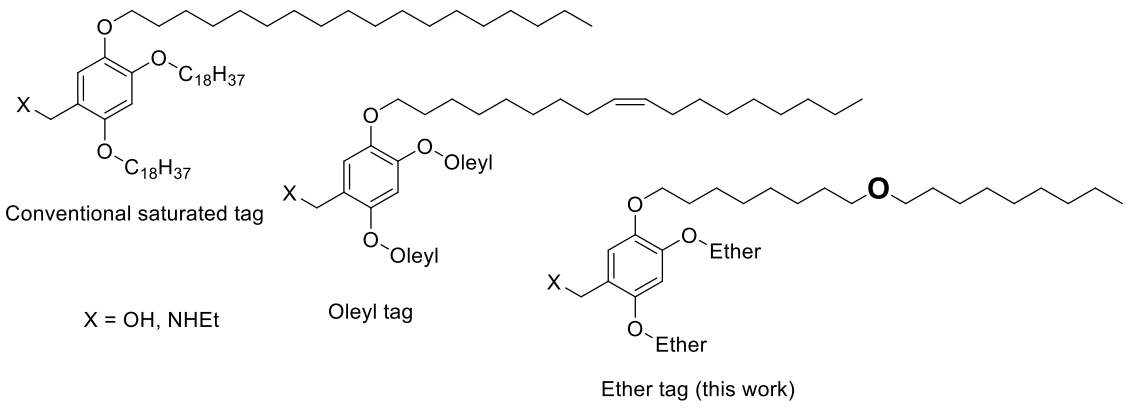


Figure 1. Comparison of tag structures

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Aerobic Oxidative Peptide Synthesis Using Nitroxyl Radical/Copper Catalysis

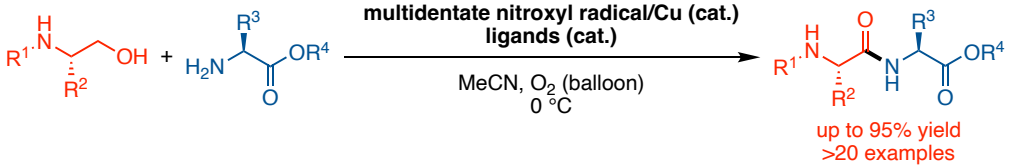
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Peptide bond formation is a fundamental transformation in the development of fine chemicals. Although conventional peptide synthesis using condensation reagents is reliable, it generates stoichiometric amounts of non-recyclable byproducts, raising environmental concerns. Accordingly, catalytic peptide synthesis has attracted increasing attention; however, efficient and environmentally compatible methods remain limited.

Oxidative amidation, which directly converts alcohols and amines into amides, represents an attractive strategy for amide bond formation. As the only example of oxidative amidation applied to peptide synthesis, Stahl et al. reported an aerobic oxidative amidation using a nitroxyl radical/copper catalytic system.[1] However, the desired dipeptide was obtained only in moderate yield, and the substrate scope remained very limited. This is presumably due to undesired coordination of amino alcohols, amino esters, and peptide products to the copper center, leading to catalyst deactivation.

Herein, we developed an aerobic oxidative peptide synthesis enabled by cooperative nitroxyl radical/copper catalysis. To suppress catalyst deactivation, we designed a multidentate nitroxyl radical catalyst bearing a coordinating functional group, which was expected to stabilize the nitroxyl radical/copper intermediate through multidentate coordination.

Optimization of the reaction conditions revealed that a bidentate nitroxyl radical catalyst exhibited high catalytic activity, enabling peptide bond formation in high yields (**Scheme 1**). The reaction was applicable to various dipeptides and tripeptides. Notably, no epimerization at the amino alcohol-derived stereogenic center was observed for a representative substrate. Furthermore, combining this reaction with *C*-terminal ester reduction established an *N*-to-*C* peptide elongation method, which was applied to the synthesis of a tetrapeptide and a physiologically active tripeptide.



Scheme 1. Aerobic Oxidative Peptide Synthesis Using Bidentate Nitroxyl Radical/Copper Catalysis

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2P-92S

Mechanochemical Methanation of Carbonates Over a Ni/Al Alloy

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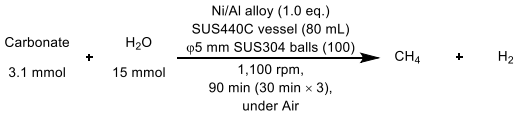
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Methanation of metal carbonates using mechano-energy and water as a reducing agent is a promising methodology from the viewpoint of process chemistry and carbon resource utilization. Carbonates are stable, safe, and easily handled carbon sources, but their direct conversion into valuable chemicals is generally difficult because they are thermodynamically more stable than CO_2. In this study, we developed a mechanochemical methanation system for various metal carbonates using Ni/Al alloy and H_2O as a hydrogen source.

Under ball-milling conditions, several metal carbonates, including $CaCO_3$, $MnCO_3$, and $CuCO_3$, were efficiently converted into CH_4. Notably, $CaCO_3$ was converted to CH_4 in near-quantitative yield under optimized conditions. This reaction proceeds without the direct use of gaseous H_2, and H_2O serves as the reducing agent. The use of mechanochemical energy enables the activation of highly stable carbonate species under relatively simple experimental conditions.

XRD and XPS analyses suggested that the Ni/Al alloy plays an important role in the reaction. In particular, Ni is considered to act as an active catalytic species for methanation, while Al may function as an oxygen acceptor, contributing to the maintenance of the active Ni surface during the reaction. These results indicate that mechano-energy can promote the reductive conversion of stable inorganic carbonates into methane.

This methodology provides a new approach for the utilization of metal carbonates as dense and safe carbon resources. Therefore, mechanochemical methanation of metal carbonates using H_2O as a reducing agent is expected to be a useful and sustainable process for carbon recycling and on-site methane production.



Entry	Carbonate	CH_4 Yield (%)[a)]	H_2 Yield (%)[a)]
1	$MgCO_3$	85	80
2	$CaCO_3$	>99	61
3	$FeCO_3$	76	79
4	$NiCO_3$	79	>99
5	$MnCO_3 \cdot nH_2O$	>99	57
6	$CuCO_3 \cdot Cu(OH)_2$	>99	78

a) Determined with GC-TCD

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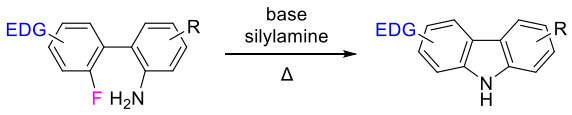
N. Ito *et al*, *Chem. Eng. J. Adv.*, doi: 10.1016/j.ceja.2026.101221

Development of S_NAr reactions for the synthesis of carbazoles

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Heteroaromatic frameworks are widely found in bioactive compounds, natural products, and organic light-emitting diodes (OLED). Given the utility of carbazole-containing scaffolds, numerous synthetic methods have been developed for carbazoles. Nucleophilic aromatic substitution (S_NAr) is a classical yet robust transformation that enables the replacement of halogen substituents on aromatic rings with nucleophiles. This reaction proceeds *via* a Meisenheimer intermediate generated by nucleophilic attack at the *ipso* carbon bearing the leaving group. Electron-withdrawing groups (EWGs) stabilize the intermediate, whereas electron-donating groups (EDGs) significantly destabilize it. Consequently, S_NAr reactions rarely occur with electron-rich aromatics. We previously reported an intramolecular S_NAr reaction employing trimethylsilyldiethylamine ($TMSNEt_2$), which enhances the reactivity of aromatic substrates bearing EDGs, such as methoxy groups.[1)] In this presentation, we report a new S_NAr reaction for the synthesis of carbazoles and *N*-heterotriangulenes bearing EDGs in the presence of silylamines.

To expand the scope of the S_NAr reaction to include carbazoles, various bases, silylamines, and solvents were screened using 2'-fluoro-5-methoxy-3'-methyl-[1,1'-biphenyl]-2-amine (**1a**) as a substrate. The reaction did not proceed in the presence of base alone at 120 °C for 24 h, likely due to the low acidity of the aniline N–H. However, the addition of silylamines afforded the corresponding carbazole **2a** in high yield. Furthermore, when terphenyl substrates were subjected to the optimized conditions, *N*-heterotriangulenes were obtained in good yield. Herein, we present the substrate scope, mechanistic considerations, and applications for the synthesis of *N*-heteroaromatic compounds (Scheme 1).



1 **2**

Scheme 1

References

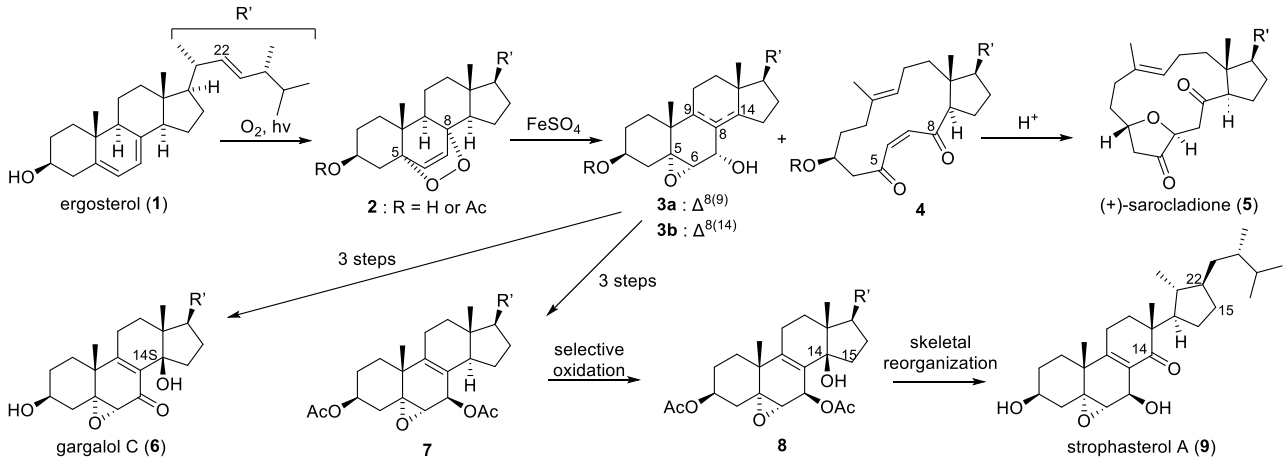
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Biomimetic Straightforward Conversion of Ergosterol to Gargalol C and Strophasterol A: Chemical Demonstration of Putative Biosynthetic Pathways

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Oxysterols are widely distributed in mushrooms and play pivotal roles in their life cycle. It is thought that the various health-promoting effects observed in mushrooms are partiallly attributed to oxysterols. Many oxysterols produced in fungi (mushrooms) are generated by oxidative metabolisms of ergosterol (**1**), via primary oxidation products such as ergosterol 5,8-peroxide (**2**). Recently our group reported biomimetic skeletal isomerization of **2** under iron-mediated conditions, providing 5,6-*α*-epoxy-7-ols (**3a**/**b**) and the ring-expanded conjugated 5,8-diketone (**4**).[1] The latter compound **4** was found to undergo skeletal reorganization to give (+)-sarocladione (**5**), a metabolite derived from deep-sea fungi, in high yield.[1] In the meanwhile, the former epoxyalcohol **3a**/**b** were converted into several oxysterols, leading not only to confirmation or revision of the chemical structures of mushroom ingredients but also to the discovery of novel sterol-based neuroprotective agents.[1] In this presentation, we will report further biomimetic transformation to more advanced oxysterols such as gargalol C (**6**)[2] and strophasterol A (**9**)[3]. This synthetic route is completely biomimetic and demostrates putative biosynthetic pathways of complex oxysterols from a chemcial viewpoint. Moreover, this synthetic approach poses an idea to expand the structural diversity of sterol-based oxidative metabolic products that can be used for drug discovery.

Overall biomimetic conversion



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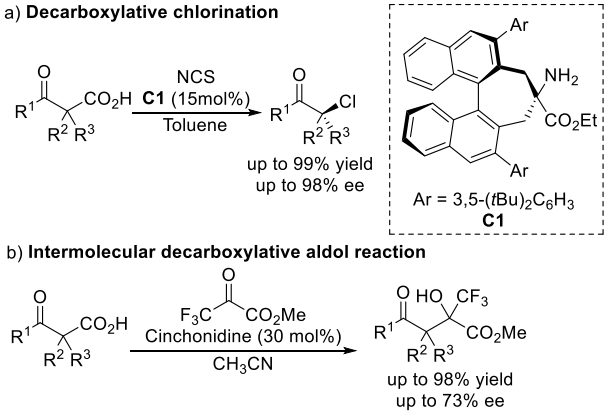
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Synthesis of chiral spiro compounds by decarboxylative intramolecular aldol reaction

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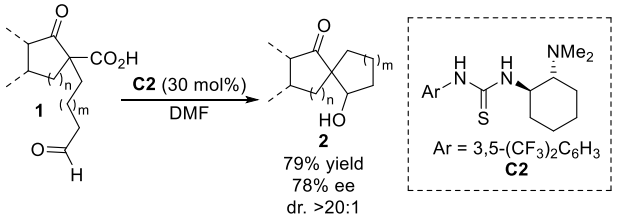
β-Keto carboxylic acids serve as enolate equivalents through decarboxylation, and thus they are known to be useful synthetic intermediates. There are many reports on decarboxylative functionalization of primary or secondary β-keto carboxylic acids. On the other hand, the reaction with tertiary β-keto carboxylic acids has rarely reported probably because their decarboxylative functionalization competes with undesired decarboxylative protonation and the desired pathway is unfavored due to steric hinderance of the substrate.

Our research group previously reported an enantioselective decarboxylative chlorination of tertiary β-keto carboxylic acids with *N*-chlorosuccinimide (NCS) (Scheme 1a)[1]. We also reported an enantioselective decarboxylative aldol reaction of tertiary β-keto carboxylic acids with trifluoropyruvates as the electrophile (Scheme 1b)[2]. These reactions proceeded smoothly supressing competeing protonation due to the use of highly reactive electrophiles.



Scheme 1. Previous work

In this study, we investigated the synthesis of spirocyclic compounds by decarboxylative intramolecular aldol reaction of tertiary β-keto carboxylic acids with a formyl group at the terminal of side chain. We envisaged that the intramolecular aldol reaction proceeds predominantly over undesired protonation. First, cyclic β-keto carboxylic acid **1** with a formyl group at the terminal of the side chain was prepared. Subjecting **1** to decarboxylative enantioselective intramolecular aldol reaction in the presence of chiral amine catalyst **C2** afforded the desired spiro compound **2** in 79% yield with 78% ee and >20:1 of dr (Scheme 2). We will discuss on the details of the reaction such as optimization of reaction conditions, substrate scope, and reaction mechanism.



Scheme 2. This work

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Organocatalytic Aerobic Oxidative Monodealkylation of *tert*-Amines to *sec*-Amines

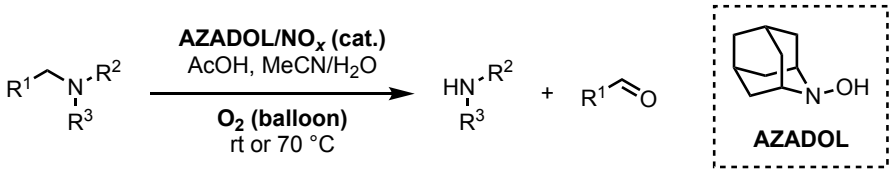
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Tertiary amines are ubiquitous structural motifs in pharmaceuticals and natural products, and their selective monodealkylation provides a direct and valuable strategy for late-stage modification. However, conventional approaches often require stoichiometric toxic reagents or multistep operations, while catalytic methods that combine high efficiency and broad substrate scope remain scarce.

Organic nitroxyl radicals, such as 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) and 2-azaadamantane *N*-oxyl (AZADO), exhibit unique redox properties and have been widely used as catalysts for alcohol oxidation. Recent advances have extended nitroxyl radical catalysis to oxidative transformations of nitrogen-containing substrates. However, nitroxyl radical-catalyzed oxidation of tertiary amines has remained largely unexplored.

In this context, Permentier et al. reported that the dealkylation of opiate-based tertiary amines could proceed using stoichiometric TEMPO under electrochemical oxidation conditions.[1] Inspired by this report, we aimed to establish a nitroxyl radical-catalyzed dealkylation method for tertiary amines. We envisioned that this transformation could be achieved by combining terminal oxidants originally developed for alcohol oxidation with highly active, less sterically hindered nitroxyl radicals, such as AZADO.

To this end, we developed a highly efficient aerobic oxidative monodealkylation of tertiary amines to secondary amines through AZADOL/NO_x cooperative catalysis (**Scheme 1**).[2] This method demonstrates excellent functional group tolerance and broad applicability to various substrates, including amino acid derivatives and complex alkaloids. Mechanistic analysis suggests that the reaction proceeds through aminium radical cations generated via one-electron oxidation of tertiary amines by oxoammonium species.



Scheme 1. Aerobic oxidative monodealkylation of *tert*-amines

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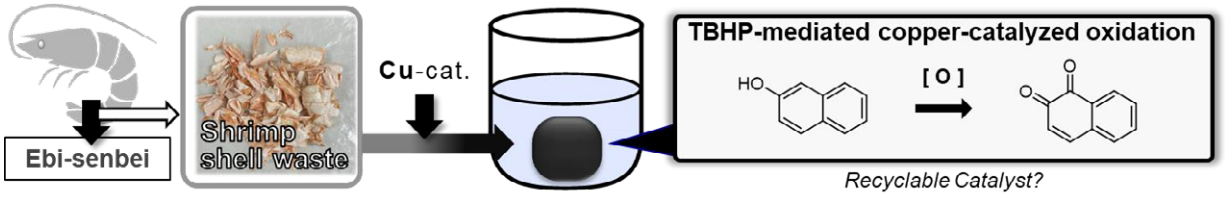
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Development of a Shrimp Shell-Derived Copper-Catalyzed Solid-Phase Oxidation System for Phenolics

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The Aichi region is one of Japan's major shrimp cracker (ebi-senbei)–producing areas. Large quantities of shrimp shells are generated as waste byproducts (30–50% of the raw materials) during the production of shrimp crackers, and their disposal has long posed a significant challenge for the industry. Recently, novel utilization strategies based on the properties of chitin, the main biopolymer in shrimp shells, and its derivative chitosan have been increasingly regarded as an attractive route for waste valorization.[1] Chitin and chitosan show excellent metal ion adsorption performance. They are considered promising materials for environmental remediation and resource recovery, and are expected to be applicable as catalyst supports.[2] On the other hand, copper catalysts are useful for oxidation reactions under mild conditions using safe co-oxidants. The development of recoverable and reusable heterogeneous copper catalysts supported on polymeric materials, including chitin, has attracted growing interest.[3] The present work focuses on the preparation of a shrimp shell-supported copper catalyst and the development of a recyclable phenol oxidation system with TBHP (*t*-BuOOH) as the co-oxidant.

Shrimp shells were washed with acetone to remove pigments and lipids, demineralized by treatment with dilute acid, and subsequently subjected to alkaline treatment to obtain chitin, which was further converted into chitosan by deacetylation under strongly alkaline conditions. Processed chitosan derived from shrimp shell waste produced during shrimp cracker manufacturing was employed as a support material, and copper salts were introduced in fluorinated alcohols[4] to afford a solid phase catalyst. The resulting solid phase catalyst exhibited recyclable catalytic activity in the TBHP oxidation of anisaldehyde to anisic acid. The catalytic system could be applied to phenolic oxidation reactions, such as the TBHP-mediated oxidation of 2-naphthol to 2-naphthoquinone and the oxidation of vanillic acid to methoxyquinone. The recovered catalyst could be reused in subsequent reactions. In this presentation, the details of the solid-phase catalyst preparation and optimization of the reaction system will be discussed.



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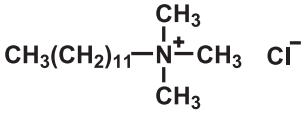
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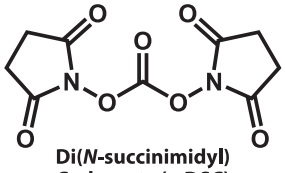
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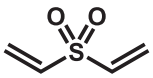
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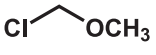
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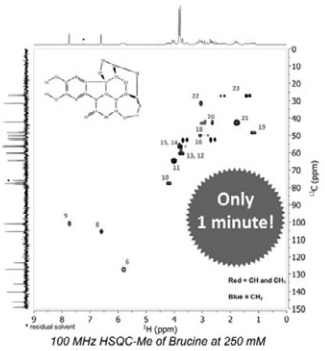
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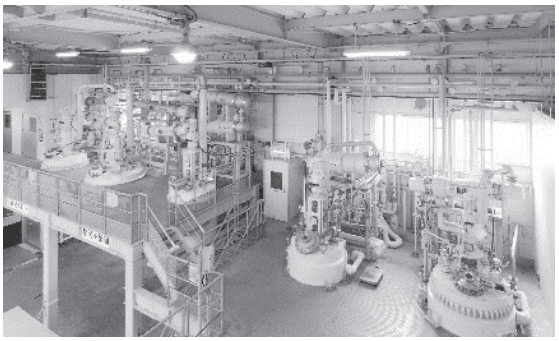
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KNC Laboratories Co., Ltd.

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HIKAL

High Potency Active PHARMACEUTICAL INGREDIENT (HPAPI) Laboratory



Safety & Specialized Tech

Containment Leadership

Fully operational infrastructure engineered to handle potent compounds up to OEB 5.

Integrated Lab

Dedicated 1,880 sq. ft. footprint in Pune with jacketed reactors with temp. ranging from -40°C to 160°C along with dedicated UPLC and GC-HS for analysis.

Advanced Modalities

Holistic development of potent components of ADC, PDC and Protacs and HPAPIs.

Scale Continuum

Seamless technical support for development and scaleup from milligram to 200g per batch.



Junjiro Sato

junjiro_sato@hikal.com | www.hikal.com



THINK CDMO
THINK PROCOS

CBC GROUP procos SPA

日本人常駐のイタリアのCDMO
治験薬から商用品、高活性、ペイロード、フロー、
自動実験などの多様な実績

- cGMP Small scale units : 25L ～ 2,500L reactors
- cGMP Large scale units : 2,500L ～ 12,000L reactors
- HPAPI units : up to OEL 1 ng/m^3 (OEB7)
- US-FDA, EU authority, PMDA, etc. inspected





Contacts:
sales@procos.it
shiraishi@procos.it
furumichi@procos.it

www.procos.it

HOKKO Chemical Industry CO., LTD



Our Manufacturing Site

Reactors

Glass Lining·····65(50～15,000L)
Stainless Steel·····46(200～15,000L)
Operating temperature: -10～150°C
Operating pressure: ～0.4MPa

Other facilities

Distillation facilities·····14
Double-cone rotating vacuum dryers···2









Main Products

Grignard reagents

Organophosphine compounds

Specialty Styrenes

Boron compounds

Metal alkoxides

Contact:

Hokko Chemical Industry Co., Ltd.
Fine Chemicals Marketing Department

Sumitomo Fudosan Nihonbashi Building
1-5-4, Nihonbashi Honcho, Chuo-Ku, Tokyo
103-8341, Japan
TEL : +81-3-3279-5142
FAX : +81-3-3279-3857

反応状態をリアルタイムモニタリング
成分・濃度計測、進捗管理用センサー

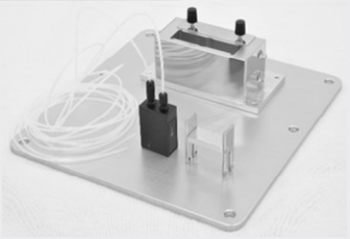


近赤外線式インライン分析計
コンパクトビートセンサー

ＢＳ-Ｆ１０００
ＢＳ-Ｆ１７００

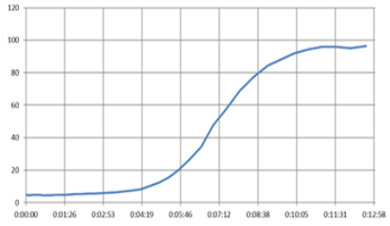
ＰＮＩＲ-Ｆ１７

フローセルプローブ



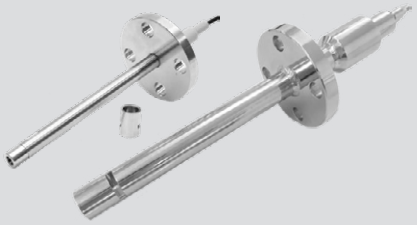
チューブ送液経路でリアルタイムモニタリング

フロー合成　アセチル化　事例



経時変化モニタリング

液浸プローブ

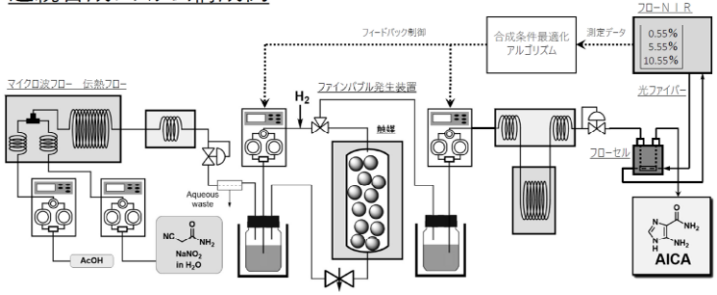


タンク・配管内でリアルタイムモニタリング

【特徴】

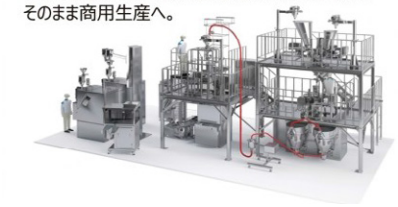
・水分濃度の高い液でも安定した測定が可能な
　近赤外線光方式
・同時に３成分のモニタリングが可能
・トレンド記憶や通信出力でフィードバック制御にも対応
・製薬会社等への多くの導入実績
・国内開発、生産のため迅速で安心できる対応
・用途に合わせて選択可能な多くのオプション測定プローブ
・多機能で高度なＰＬＳ検量線作成ソフトを標準付属

連続合成システム構成例



スケールアップという壁を、なくす。
CTS-MiGRA
連続生産システム

混合→造粒→乾燥→整粒→
打錠→コーティングを1ラインで連続処理。
PATによるリアルタイム品質管理で、ラボの処方を
そのまま商用生産へ。



粉粒体装置の総合メーカー
株式会社 パウレック

【本　　社】〒664-0837
兵庫県伊丹市北河原5-5-5
Tel:072-778-7301（代表）

【東京支店】〒101-0041
東京都千代田区神田須田町1丁目9
神田須田町プレイス6階
Tel:03-3518-5140（代表）

Beat Sensing co.,ltd.
近赤外線式インライン分析計
開発・設計・製造

株式会社 ビートセンシング
〒411-0917 静岡県駿東郡清水町徳倉1072-1

TEL : 055-933-0007
FAX : 055-933-0010

https://www.beatsensing.com
sales@beatsensing.com

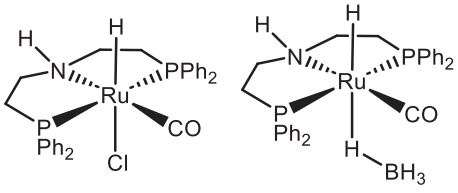
TAKASAGO's Catalysts

- High activity and selectivity enable "more economical" and "more green" processes.
- 80 catalysts from reagent scale* to commercial scale.
- 40 years of experience in catalyst development.

*Reagent scales are available from Strem Chemicals Inc., Sigma-Aldrich Co., and Tokyo Chemical Industry Co., Ltd.

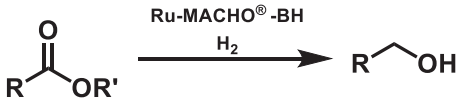
Hydrogenation Catalyst for Esters

Ru-MACHO® / Ru-MACHO®-BH



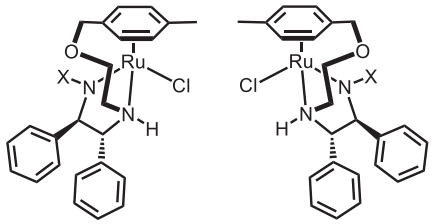
Ru-MACHO® **Ru-MACHO®-BH**

- Alternative to hydride reduction.
- High catalytic activity. (0.1~0.0025 mol% catalyst)
- Available under high temperature conditions. (~200 ℃)



Ketone-Selective - Asymmetric Hydrogen Transfer Catalyst

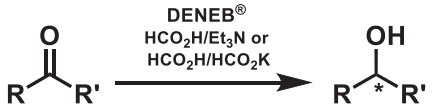
DENEB®



(*R,R*)-Ts-DENEB® **(*S,S*)-Ts-DENEB®** (X=Ts)

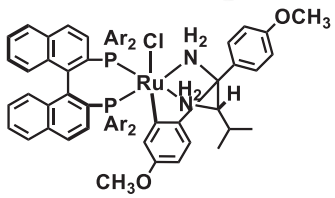
(*R,R*)-Ms-DENEB® **(*S,S*)-Ms-DENEB®** (X=Ms)

- High catalytic activity.
  - ✓Catalyst usage 0.0033 mol%~ (S/C=30,000~)
- High-pressure equipment not required.
- Stable in air and easy to handle.



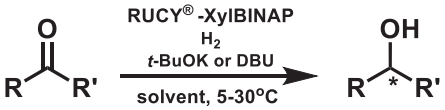
Ketone Selective - Fast Asymmetric Hydrogenation Catalyst

RUCY®-XylBINAP



(*R*)-RUCY®-XylBINAP
(*S*)-RUCY®-XylBINAP

- Extremely high catalytic activity with small amount.
  - ✓Catalyst usage 0.001~0.01 mol% (S/C=100,000~)
  - ✓TON = 35,000/min
- High-pressure equipment not required.



TAKASAGO

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Corporate Website
(Catalysts / Ligands)

https://www.takasago.com/en