



The 1st NCTU Conference on Advanced Organic Synthesis

Venue: Science Building II, Room 210
Department of Applied Chemistry, National Chiao Tung University
Date: December 17-18, 2018

Invited Speakers

- Prof. Masahiro Miura (Osaka University)
- Prof. Yoshito Tobe (National Chiao Tung University)
- Prof. Hiroaki Ohno (Kyoto University)
- Prof. Takahide Fukuyama (Osaka Prefecture University)
- Prof. Chih-Feng Huang (National Chung Hsing University)
- Prof. Mu-Jeng Cheng (National Cheng Kung University)



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December 17–18, 2018; Room 210, Science Building II, National Chiao Tung University

December 17 (Monday)

14:20 – 14:30 Chi-Shen Lee (Chairman of Applied Chemistry, NCTU) Opening Remark
Ilhyong Ryu (National Chiao Tung University)

Tutorial 1 *Transition Metal Catalysis as the Tool of Chemical Synthesis*

14:30 – 15:30 Masahiro Miura (Osaka University) Chair: Ilhyong Ryu

15:30 – 15:50 Coffee Break

Lecture 1 *Gold-catalyzed C-C Bond Formation and Its Application to Alkaloid Synthesis*

15:50 – 16:40 Hiroaki Ohno (Kyoto University) Chair: Yen-Ku Wu

Special Topic 1 *Applications of Quantum Mechanics to Study O-H Activation, Reductive Elimination, and Annulation*

16:40 – 17:20 Mu-Jeng Cheng (National Cheng Kung University) Chair: Yen-Ku Wu

18:00 – 20:00 Reception at Tsai-Yuan

December 18 (Tuesday)

10:00 – 12:00 Panel Discussion with Graduate Students Organized by Yi-Ching Lin

12:00 – 13:20 Lunch

Tutorial 2 *Supramolecular Chemistry on Surfaces: From On-Surface Chirality to Molecular Lithography*

13:30 – 14:30 Yoshito Tobe (National Chiao Tung University) Chair: Yen-Ju Cheng

Special Topic 2 *Synthesis of Functional Polyesters by Atom Transfer Radical Polyaddition and Polypiperidones by Multi-component Polymerization*

14:30 – 15:10 Chih-Feng Huang (National Chung Hsing University) Chair: Chia-Chih Chang

15:10 – 15:30 Coffee Break

Lecture 2 *Catalytic Cyclization of Aromatic Carboxylic Acids and Catalytic Reactions in Flow*

15:30 – 16:20 Takahide Fukuyama (Osaka Prefecture University) Chair: Kwok-Kong Mong

Lecture 3 *Development of Direct Aromatic Coupling Reactions by Transition Metal Catalysis*

16:20 – 17:10 Masahiro Miura (Osaka University) Chair: Chung-Ming Sun

17:10 – 17:20 Chung-Ming Sun Closing Remark

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Invited Lecturers



Prof. Masahiro Miura
(Osaka University)



Prof. Mu-Jeng Cheng
(NCKU)



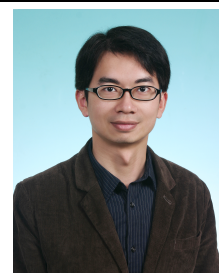
Prof. Hiroaki Ohno
(Kyoto University)



Prof. Yoshito Tobe
(NCTU)



Prof. Takahide Fukuyama
(Osaka Prefecture Univ.)



Prof. Chih-Feng Huang
(NCHU)

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Sun, Chung-Ming (co-chairman)
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Peng, Bo-Kai

Tobe, Yoshito
Cheng, Yen-Ju
Lin, Yi-Ching

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Transition Metal Catalysis as the Tool of Chemical Synthesis

Masahiro Miura

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Transition metal-catalyzed C-C and C-X (X = O, N, S etc.) bond formation reactions are highly important and indispensable in modern organic synthesis from both the academic and industrial points of view.¹⁻⁴ The transformation reactions involving cross-coupling, Mizoroki-Heck reaction, Heck carbonylation, and Sonogashira coupling as well as Ullmann-type coupling reactions have been widely used in the synthesis of pharmaceuticals, agrochemicals, and organic functional materials.⁵⁻⁷ In this conference, the practical and mechanistic aspects of the catalysis are briefly summarized by showing a number of industrial coupling reactions under consideration of atom- and step-economy.⁸ Then, the objectives of our own academic work based on the background will be described.⁹

- [1] T. J. Colacot, V. Sniekus *et al.*, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.
- [2] M. Beller *et al.*, *Cross Coupling Reactions* in “Applied Homogeneous Catalysis with Organometallic Reagents (3rd Ed), Wiley 2018, pp 411-464.
- [3] F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954-6971.
- [4] H.-U. Blaser *et al.*, *Adv. Synth. Catal.* **2004**, *346*, 1583-1598.
- [5] J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177-2250.
- [6] J. D. Hayler, D. K. Leahy, E. M. Simmons, *Organometallics* **2018**, *ASAP*, 10.1021/acs.organomet.8b00566.
- [7] G.-F. Yang *et al.*, *J. Agric. Food Chem.* **2018**, *66*, 8914-8934.
- [8] R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273-1283.
- [9] M. Miura, T. Satoh, K. Hirano, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751-761.



Brief CV: Masahiro Miura is a distinguished professor of the Department of Applied Chemistry, Osaka University of Japan. He studied chemistry at Osaka University and received his Ph.D. degree in 1983 (Prof. M. Nojima). After working in chemical industry for one and a half years, he started his academic career as assistant professor at Osaka University. He was promoted to associate professor in 1994 and to full professor in 2005. He also worked as a Humboldt fellow at Karlsruhe University of Germany (Prof. K. Griesbaum). His current research interests include transition-metal catalysis including C-H activation and the synthesis of functional aromatic molecules.

Gold-Catalyzed C-C bond Formation and Its Application to Alkaloid Synthesis

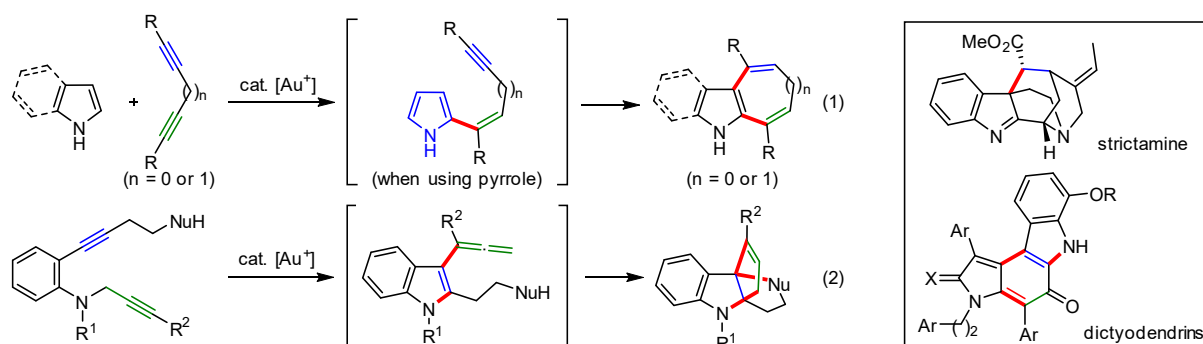
Hiroaki Ohno

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Cascade reactions have potential to rapidly increase molecular complexity in a single operation, allowing the utilization of reactive intermediates that are not stable enough for isolation. Homogenous gold catalysis is becoming a powerful tool for cascade reactions, especially based the activation of carbon-carbon triple bonds. Our group has been involved in the development of gold-catalyzed cascade cyclizations of alkynes for the direct construction of polycyclic heterocycles. In this talk, I would like to introduce our recent research progress in this area, including synthesis of 4,7-disubstituted indoles through formal [4 + 2] or [5 + 2] reactions between diynes and pyrroles (eq 1),^[1] synthesis of tetracyclic indolines via the rearrangement of a propargyl group (eq 2),^[2] and natural product syntheses based on gold-catalyzed cyclizations.^[3,4]



[1] (a) Matsuda, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Eur. J.* **2015**, *21*, 1463. (b) Hamada, N.; Yoshida, Y.; Oishi, S.; Ohno, H. *Org. Lett.* **2017**, *19*, 3875.

[2] Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 7862.

[3] Nishiyama, D.; Ohara, A.; Chiba, H.; Kumagai, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2016**, *18*, 1670.

[4] (a) Matsuoka, J.; Matsuda, Y.; Kawada, Y.; Oishi, S.; Ohno, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 7444. (b) Kawada, Y.; Ohmura, S.; Uchiyama, M.; Suzuki, T.; Ohno, H. *et al. Chem. Sci.* **2018**, *9*, 8416.



Hiroaki Ohno was born in 1973. He graduated with a B.Sc. in Pharmaceutical Sciences from Kyoto University in 1996. After his doctoral work at the same university under the direction of Prof. Toshiro Ibuka, he joined the group of Prof. Tetsuaki Tanaka at Osaka University as a Research Associate in 1999. He accepted a position as Associate Professor of Kyoto University (Prof. Nobutaka Fujii's group) in 2005. In 2014, he was appointed as a full professor to the Graduate School of Pharmaceutical Sciences, Kyoto University.

Applications of Quantum Mechanics to Study O-H Activation, Reductive Elimination, and Annulation

Mu-Jeng Cheng

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Quantum mechanics (QM) has become a powerful tool for exploring chemical reactions, and, in some cases, even to allow us to design novel molecules with desired functions. In the past two years, we have used QM to investigate the reactions that our collaborators discovered. The reactions include (a) water O-H activation by vanadium complexes, (b) C_{sp}³-H trifluoromethylation through reductive elimination using copper complexes, (c) oxidative annulation of arylglyoxal with alkyne promoted by iron complexes, and (d) (4+3)-annulations of 2-alkenyl-1-alkynylbenzenes with anthranils promoted by gold complexes. In this seminar, I will talk about the puzzles that we encountered when studying those system, and how we used QM to provide more insights into those systems.

[1] Yan, J.-A.; Yang, Z.-K.; Chen, Y.-S.; Chang, Y.-H.; Lyu, C.-L.; Luo, C.-G.; Cheng, M. J.;* Hsu, H.-F.* "Activation of O-H and C-O Bonds in Water and Methanol by a Vanadium-bound Thiyl Radical" *Chem. Eur. J.* **2018**, 24, 15190.

[2] Paeth, M.; Carson, W.; Luo, J.-H.; Tierney, D.; Cao, Z.; Cheng, M. J.;* Liu, W.* "Copper Mediated Trifluoromethylation of Benzylic Csp³ -H Bonds" *Chem. Eur. J.* **2018**, 24, 11559.

[3] Hung, C.-H.; Gandeepan, P.; Cheng, L.-C.; Chen, L.-Y.; Cheng, M. J.;* Cheng, C.-H.* "Experimental and Theoretical Studies on Iron-Promoted Oxidative Annulation of Arylglyoxal with Alkyne: Unusual Addition and Migration on the Aryl Ring" *J. Am. Chem. Soc.* **2017**, 139, 17015.

[4] Singh, R. R.; Skaria, M.; Chen, L.-Y.; Cheng, M. J.;* Liu, R.-S.* "Gold-catalyzed (4+3)-Annulations of 2-Alkenyl-1-Alkynylbenzenes with Anthranils with Alkyne-Dependent Chemoselectivity: Skeletal Rearrangement versus Non-Rearrangement" *Chem. Sci.* **2019** in press.



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2. Postdoctoral Researcher, University of California at Berkeley, College of Chemistry, Berkeley, CA, USA
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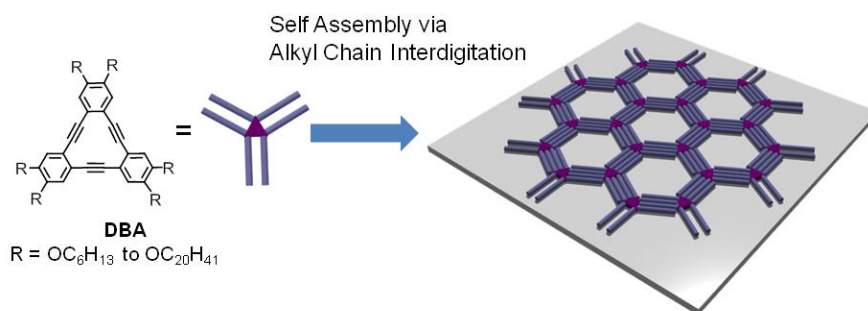
Supramolecular Chemistry on Surfaces: From On-Surface Chirality to Molecular Lithography

Yoshito Tobe

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Because of huge demand to control matters in nanometer scale in nanoscience/technology related to molecular scale electronics and tailor-made catalysis, supramolecular chemistry on surfaces has advanced significantly during the last few decades, thanks to the advances in microscope technology which made it possible to *visualize* molecules adsorbed on surfaces. Among the various types of molecular self-assemblies, porous networks have attracted a great deal of interest in view of potential applications in the above-mentioned technologies and fundamental principle such as crystallization. For more than a decade we have studied on-surface self-assembly at the liquid/solid interface of a series of triangle building blocks, alkoxy-substituted dehydro[12]annulenes (DBAs), which form honeycomb type porous network and exhibit remarkable adaptability thank to their versatility in synthetic modifications. These include (i) pore size control by alkyl chain length,^[1] (ii) parity effect on assembly, (iii) induction and reversion of supramolecular chirality,^[2,3] (iv) chemical modification of the pore interior for selective co-adsorption of guest molecules. Our recent efforts are focused on epitaxial multilayer formation and the use of we non-covalent molecular networks as masks for periodical surface modification. After general introduction, the lecture will focus on the on-surface chirality control via different mechanisms and periodical surface modification using the networks as removable masks directed toward molecular lithography.



[1] Tahara, K.; De Feyter, S. Tobe, Y. et al. *J. Am. Chem. Soc.* **2006**, *128*, 16613.

[2] Tahara, K.; De Feyter, S. Tobe, Y. et al. *Nat. Chem.* **2011**, *3*, 714.

[3] Tahara, K.; De Feyter, S. Tobe, Y. et al. *Nat. Chem.* **2016**, *8*, 711.



Dr. Eng. Osaka University (1979), Assistant Professor, Osaka University (1979), Visiting Professor, The University of Chicago (1986-1987), Associate Professor, Osaka University (1992), Professor (1998), Professor Emeritus, Osaka University (2017), Chair Professor, National Chiao Tung University (2018).

Chemical Society Award of Japan for Young Chemists (1985), The Chemical Society of Japan Award (2015), The Nozoe Lecturer (2017), The Society of Physical Organic Chemistry Japan Award (2018).

Synthesis of Functional Polyesters by Atom Transfer Radical Polyaddition and Polypiperidones by Multi-component Polymerization

Chih-Feng HUANG

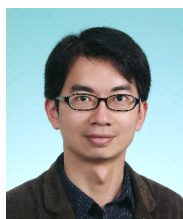
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Abstract

In the first part,^[1] two AB-type inimers (4-vinylbenzyl 2-bromo-2-isobutyrate (VBBiB) and 4-vinylbenzyl 2-bromo-2-phenylacetate (VBBPA)) were synthesized and used to obtain novel aliphatic polyesters through atom transfer radical polyaddition (ATRPA). We then modified the novel aliphatic polyesters to produce polymer brushes with different hydrophilic/hydrophobic ratios. In the second part, we aim at designing a novel multi-component polymerizations (MCPs)^[2] through three-component Mannich-type reaction to efficiently synthesize a library of novel polypiperidones (PPds). Several di-functional aldehydes (X component) and various ketones (Y component) were used as a monomers to synthesis PPds by simply mixing of X and Y monomers through different combinations in the presences of NH₄OAc (C component) concurrently. This new MCP fulfills the direction of green chemistry.

References:

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- [2] (a) Kreye, O.; Tóth, T.; Meier, M. A. R. *J. Am. Chem. Soc.* **2011**, *133*, 1790. (b) Xue, H.; Zhao, Y.; Yang, B.; Wei, Y.; Wang, Z.; Tao, L. *J. Am. Chem. Soc.* **2016**, *138*, 8690.



EDUCATION

- **Ph. D.** in Department of Applied Chemistry, Sep. 2000 ~ Apr. 2004, National Chiao Tung University (NCTU), Hsinchu city, Taiwan
- **M. S.** in Department of Chemical Engineering, Sep. 1998 ~ Jun. 2000, National Cheng Kung University (NCKU), Tainan city, Taiwan
- **B. S.** in Department of Chemical Engineering, Sep. 1994 ~ Jun. 1998, National Chung Hsing University (NCHU), Taichung city, Taiwan

WORK EXPERIENCE

- 02.2016~present, **Associate Professor**, Dep Chem Eng, NCHU
- 02.2012~01.2016, **Assistant Professor**, Dep Chem Eng, NCHU
- 10.2010~01.2012, **Researcher**, National Institute for Materials Science (NIMS), Biomaterial Center, Japan (under *Prof. Hisatoshi Kobayashi*)
- 08.2009~09.2010, **Postdoctoral Fellow**, Dep Appl Chem, Kanagawa Univ, JP (under *Prof. Tsutomu Yokozawa*)
- 12.2007~07.2009, **Postdoctoral Fellow**, Dep Chem, Carnegie Mellon University, USA (under *Prof. Krzysztof Matyjaszewski*)
- 01.2005~11.2007, **Postdoctoral Fellow**, Dep Appl Chem, NCTU (under *Prof. Feng-Chih Chang*)

Catalytic Cyclization of Aromatic Carboxylic Acids and Catalytic Reactions in Flow

Takahide Fukuyama

Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Japan

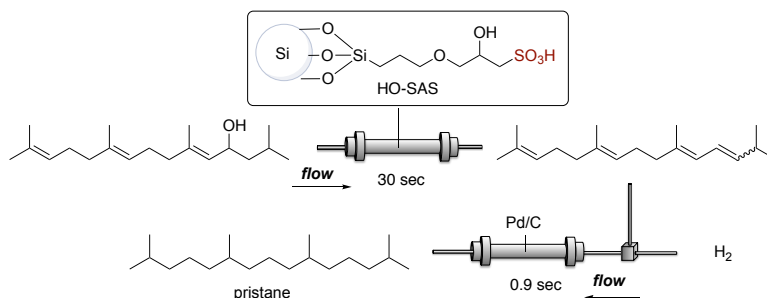
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Catalytic reactions play an important role in both laboratory and industrial scale synthesis. We have been interested in the development of new methodologies using transition metal catalysts and efficient catalytic processes using a flow reaction device.

Polycyclic aromatic compounds have attracted considerable attention as functional materials because the structures composed of plural aromatic rings exhibit specific light and electronic characteristics. In this paper, I will present our recent results on the rhodium-catalyzed cyclization reaction using aromatic carboxylic acids, which involves new synthetic methods for the synthesis of dibenzofurans,¹ fluorenones,² and perinaphthenones³ via decarbonylative C-H arylation of 2-aryloxybenzoic acids, C-H acylation of 2-arylbenzoic acids, and dehydrative annulation of 1-naphthoic acids with alkynes, respectively.

This paper also focuses on recent advances in flow heterogeneous catalysis, which have been achieved in our group. Sulfonic acid-functionalized silica gel having hydroxyl group (HO-SAS) is quite useful for acid-catalyzed flow esterification of carboxylic acids⁴ and dehydration of allylic alcohols.⁵

As a useful application of the dehydration of allylic alcohols, one flow synthesis of pristane was successfully carried out by using a consecutive flow dehydration and hydrogenation (Scheme 1).⁵



Scheme 1. One Flow Synthesis of Pristane

[1] Maetani, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 2754.

[2] Fukuyama, T.; Maetani, S.; Miyagawa, K.; Ryu, I. *Org. Lett.* **2014**, *16*, 3216.

[3] Fukuyama, T.; Sugimori, T.; Maetani, S.; Ryu, I. *Org. Biomol. Chem.* **2018**, *16*, 7583.

[4] Furuta, A.; Fukuyama, T.; Ryu, I. *Bull. Chem. Soc. Jpn.* **2017**, *90*, 607.

[5] Furuta, A.; Hirobe, Y.; Fukuyama, T.; Ryu, I.; Manabe, Y.; Fukase, K. *Eur. J. Org. Chem.* **2017**, *2017*, 1365.



Takahide Fukuyama received his PhD in 1999 from Osaka University under the direction of Professor Shinji Murai. He spent 1999-2000 as a postdoctoral fellow of the JSPS at Okayama University of Science (Professor Junzo Otera). He was appointed as assistant professor at Osaka Prefecture University in 2000. He was promoted to lecturer in 2007 and to associate professor in 2010. He had the experience of working as visiting researcher at the University of Pierre and Marie Curie (2006). His current research includes carbonylation chemistry, catalytic reactions of carboxylic acids, and flow chemistry.

Development of Direct Aromatic Coupling Reactions by Transition Metal Catalysis

Masahiro Miura

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Transition metal-catalyzed aromatic cross-coupling reactions are highly useful for the construction of various organic fine chemicals including pharmaceuticals and organic functional materials. The conventional methods, however, usually require the pre-activation of aromatic substrates such as stoichiometric halogenation and metalation before the coupling event, which increases the steps leading to target molecules and yields inevitable salts as byproducts. In order to cope with these problems, catalytic C-H transformation reactions on aromatic substrates have been one of the most intensive subjects in the area of OMCOS for the last two decades. In this conference, our recent efforts for developing direct aromatic and heteroaromatic coupling reactions, especially under oxidative conditions by using a number of transition metals including palladium, rhodium, and copper as catalysts will be presented.^{1,2}

[1] Reviews: (a) M. Miura, T. Satoh, K. Hirano, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751-764. (b) K. Hirano, M. Miura, *Chem. Lett.* **2015**, *44*, 868-873.

[2] Latest publications: (a) Y. Itai, Y. Nishii, P. Stachelek, P. Data, Y. Takeda, S. Minakata, M. Miura, *J. Org. Chem.* **2018**, *83*, 10289-10302. (b) C. Kona, Y. Nishii, M. Miura, *Org. Lett.* **2018**, *20*, 4898-4901. (c) K. Nishimura, Y. Unoh, K. Hirano, M. Miura, *Chem. Eur. J.* **2018**, *24*, 13089-13092. (d) S. Xu, K. Takamatsu, K. Hirano, M. Miura, *Angew. Chem. Int. Ed.* **2018**, *57*, 11797-11801.



Brief CV: Masahiro Miura is a distinguished professor of the Department of Applied Chemistry, Osaka University of Japan. He studied chemistry at Osaka University and received his Ph.D. degree in 1983 (Prof. M. Nojima). After working in chemical industry for one and a half years, he started his academic career as assistant professor at Osaka University. He was promoted to associate professor in 1994 and to full professor in 2005. He also worked as a Humboldt fellow at Karlsruhe University of Germany (Prof. K. Griesbaum). His current research interests include transition-metal catalysis including C-H activation and the synthesis of functional aromatic molecules.

Chairmen

Ilhyong Ryu

Chung-Ming Sun

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