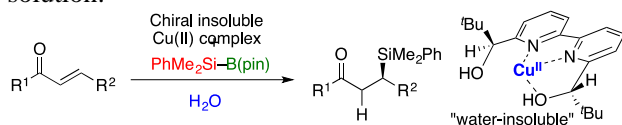


# SYNTHETIC ORGANIC CHEMISTRY

## Annual Research Highlights

### (1) An Insoluble Chiral Copper(II) Complex for Asymmetric Silyl Conjugate Addition

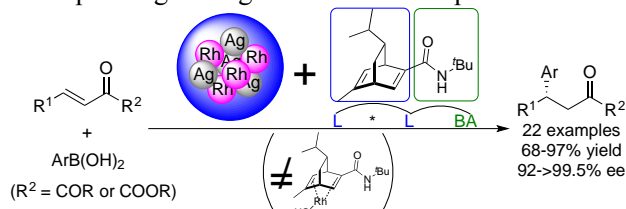
Needle-shaped purplish crystals were obtained from  $\text{Cu}(\text{acac})_2$  and a chiral bipyridine ligand. Although the crystals were not soluble, they nevertheless catalyzed asymmetric silyl conjugate addition of lipophilic substrates in water to achieve high yields and enantioselectivities. Indeed, the reactions proceeded efficiently only in water; they did not proceed well either in organic solvents or in mixed water/organic solvents in which the catalyst/substrates were soluble. This is in pronounced contrast to conventional organic reactions wherein the catalyst/substrates tend to be in solution.



**Scheme 1** Insoluble Chiral Copper(II)-catalyzed Enantioselective Silyl Conjugate-Addition Reactions in Water 1.(1)-25) *J. Am. Chem. Soc.*, **137**, 15422 (2015).

### (2) Chiral Rhodium/Silver Nanoparticle Systems as Heterogeneous Catalysts for Asymmetric 1,4-Addition of Arylboronic Acids

Chiral rhodium/silver nanoparticle systems were developed as novel heterogeneous chiral catalysts for the asymmetric 1,4-addition of arylboronic acids to  $\alpha,\beta$ -unsaturated carbonyl compounds. The reactions proceeded smoothly to afford the corresponding  $\beta$ -arylated products in high to excellent yields and outstanding enantioselectivities with wide substrate scope. Remarkably, the nanoparticle catalysts showed performance in terms of yield, enantioselectivity, and catalytic turnover that was superior to that of the corresponding homogeneous metal complexes.

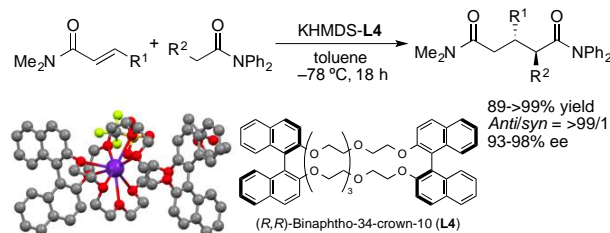


**Scheme 2** Chiral Rh/Ag Nanoparticle Systems for Asymmetric 1,4-Addition Reactions of Arylboronic Acids 1.(1)-10) *J. Am. Chem. Soc.*, **137**, 6616-6623 (2015).

### (3) Catalytic Asymmetric Direct-Type 1,4-Addition Reactions of Simple Amides

The development of catalytic asymmetric direct-type reactions of less-acidic carbonyl compounds such as amides and esters is a challenging theme in organic chemistry. We reported the asymmetric direct 1,4-addition reactions of simple amides with  $\alpha,\beta$ -unsaturated carbonyl compounds for

the first time by using a catalytic amount of a novel chiral catalyst consisting of a potassium base and a macrocyclic chiral crown ether. The desired 1,5-dicarbonyl compounds were obtained in high yields with excellent diastereo- and enantioselectivities.

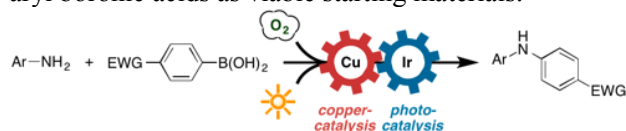


**Scheme 3** Catalytic Asymmetric Direct-type 1,4-Addition of Simple Amides

1.(1)-6) *J. Am. Chem. Soc.*, **137**, 4336 (2015).

### (4) Visible-Light-Mediated Chan-Lam Coupling Reactions

The copper(II)-catalyzed aerobic oxidative coupling reaction between aryl boronic acids and aniline derivatives (Chan-Lam coupling) was found to be improved significantly under visible-light-mediated photoredox catalysis. The substrate scope of this reaction was expanded to include electron-deficient aryl boronic acids as viable starting materials.

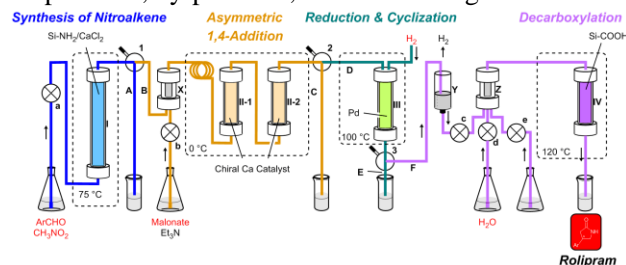


**Scheme 5** Visible-Light-Mediated Chan-Lam Coupling Reactions

1.(1)-7) *Angew. Chem. Int. Ed.*, **54**, 6587 (2015).

### (5) Multistep Continuous Flow Synthesis of (R)- and (S)-Rolipram Using Heterogeneous Catalysts

We reported the continuous-flow synthesis of drugs using only columns packed with heterogeneous catalysts. Commercially available starting materials were successively passed through four columns containing achiral and chiral heterogeneous catalysts to produce (R)-rolipram, an anti-inflammatory drug and one of the family of  $\gamma$ -aminobutyric acid (GABA) derivatives without the isolation of any intermediates and without the separation of any catalysts, co-products, by-products, and excess reagents.

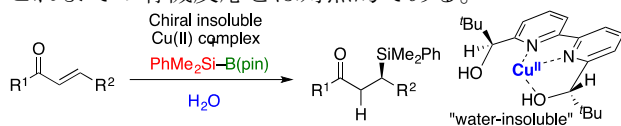


**Scheme 6** Multistep Continuous Flow Synthesis of Rolipram 1.(1)-5) *Nature*, **520**, 329-332 (2015).

研究ハイライト

(1) 不溶性キラル銅(II)触媒を用いるケイ素の不斉 1,4-付加反応

Cu(acac)<sub>2</sub> とキラルピピリジン配位子から調製される針状の紫色結晶が、ケイ素化合物の  $\alpha$ ,  $\beta$ -不飽和カルボニル化合物への触媒的共役付加反応を高収率、高立体選択的に促進することを見出した。この触媒はそれ自身や反応基質が溶解する有機溶媒や水と有機溶媒の混合溶媒では機能しない一方で、それ自身が水に不溶であるにも関わらず、水中でのみ目的の反応を効率的に促進した。この触媒の機能は、これまでの有機反応とは対照的である。

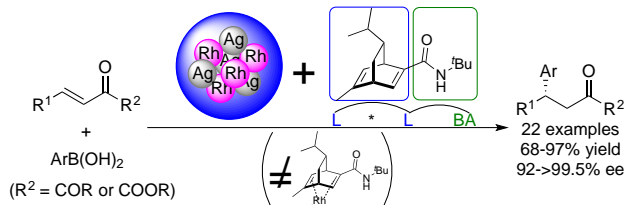


式1 不溶性キラル銅(II)触媒を用いるシリル化合物の水中での不斉共役付加反応

1.(1)-25) *J. Am. Chem. Soc.*, **137**, 15422 (2015).

(2) キラルロジウム/銀ナノ粒子を用いるアリールホウ素化合物の触媒的不斉 1,4-付加反応

アリールホウ素化合物の触媒的不斉 1,4-付加反応において有効に機能するキラルロジウム/銀ナノ粒子触媒を開発した。この反応は、目的の  $\beta$ -アリール付加体を高収率・高エナンチオ選択性で与え、また幅広い種類の基質に適用可能であった。本不均一系キラルロジウム/銀ナノ粒子触媒は、収率や不斉収率、触媒回転数において、対応する均一系キラルロジウム触媒をいずれも凌駕するものであった。

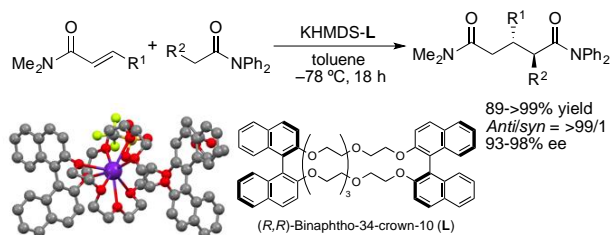


式2 キラルロジウム/銀ナノ粒子触媒を用いるアリールホウ素化合物の不斉 1,4-付加反応

1.(1)-10) *J. Am. Chem. Soc.*, **137**, 6616-6623 (2015).

(3) 単純アミドの直接的触媒的不斉 1,4-付加反応の開発

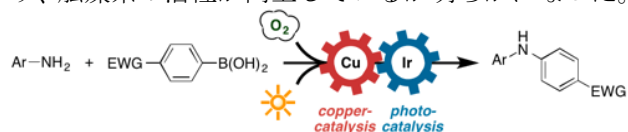
単純なアミドやエステルのような低酸性カルボニル化合物は、塩基触媒による直接的不斉反応に適用することがこれまで非常に困難であるとされてきた。今回、当研究室は単純アミドの  $\alpha$ ,  $\beta$ -不飽和アミドへの直接的触媒的不斉 1,4-付加反応を世界に先駆けて開発した。この反応にはカリウムアミドと光学活性大環状クラウンエーテルからなる強塩基触媒が効果的であり、目的とする 1,5-ジカルボニル化合物が高収率、高エナンチオ選択的に得られた。



式3 単純アミドの直接的触媒的不斉 1,4-付加反応  
1.(1)-6) *J. Am. Chem. Soc.*, **137**, 4336 (2015).

(4) 可視光照射促進型 Chan-Lam カップリング反応の開発

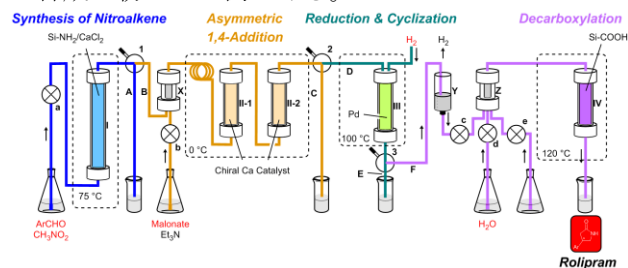
銅触媒によるアリールホウ素化合物とアニリン誘導体の空気酸化的カップリング反応 (Chan-Lam カップリング反応) が、可視光照射下で光酸化還元触媒を用いることで、大幅に促進されることを見出した。本反応条件では、これまで困難であった電子不足のアリールホウ素化合物も有意に反応することがわかり、触媒系の活性が向上しているが明らかになった。



式5 可視光照射促進型 Chan-Lam カップリング反応  
1.(1)-7) *Angew. Chem. Int. Ed.*, **54**, 6587 (2015).

(5) 不均一系触媒を活用する (R)-および (S)-ロリプラムの多段階連続フロー全合成

従来のバッチ法ではなく、連続フロー法を用いる医薬品合成は、効率性、安全性、環境調和性等から理想的な方法論であると言える。今回、抗炎症薬であるロリプラムの光学活性体を連続フロー法のみを用いて合成した。キラルカルシウム触媒を充填したカラムを含む4本の新たに開発した不均一系触媒を充填したカラムを用い、市販の原料を順次カラムに通すだけで、高純度のロリプラムを得ることができた。本合成は、4本のカラムを用い不斉炭素-炭素結合生成反応を含む8段階の反応を一挙に行うものであり、不均一系触媒のみを用いる医薬品の連続フロー合成の初めての例である。



式6 光学活性ロリプラムの多段階連続フロー全合成  
1.(1)-5) *Nature*, **520**, 329-332 (2015).

## 1. 原著論文

### (1) Refereed Journals

- 1) Lithium *tert*-Butoxide-mediated Carboxylation Reactions of Unprotected Indoles and Pyrroles with Carbon Dioxide, W.-J. Yoo, T. V. Q. Nguyen, M. G. Capdevila, S. Kobayashi, *Heterocycles*, **90**, 1196-1204 (2015).
- 2) Toward Chemistry-Based Design of the Simplest Metalloenzyme-Like Catalyst That Works Efficiently in Water, T. Kitanosono, S. Kobayashi, *Chem. Asian J.*, **10**, 133-138 (2015).
- 3) Simple Homopolymer-Incarcerated Gold Nanoclusters Prepared by Self-Assembled Encapsulation with Aluminum Reagents as Crosslinkers: Catalysts for Aerobic Oxidation Reactions, T. Yasukawa, H. Miyamura, S. Kobayashi, *Chem. Lett.*, **44**, 50-52 (2015).
- 4) Synergistic Cascade Catalysis by Metal Nanoparticles and Lewis Acids in Hydrogen Autotransfer, G. C. Y. Choo, H. Miyamura, S. Kobayashi, *Chem. Sci.*, **6**, 1719-1727 (2015).
- 5) Multistep Continuous Flow Synthesis of (*R*)- and (*S*)- Rolipram Using Heterogeneous Catalysts, T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature*, **520**, 329-332 (2015).
- 6) Catalytic Asymmetric Direct-type 1,4-Addition Reactions of Simple Amides, H. Suzuki, I. Sato, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.*, **137**, 4336-4339 (2015).
- 7) Visible Light-Mediated Chan-Lam Coupling Reactions of Arylboronic Acids and Aniline Derivatives, W.-J. Yoo, T. Tsukamoto, S. Kobayashi, *Angew. Chem. Int. Ed.*, **54**, 6587-6590 (2015).
- 8) Calcium-catalyzed Asymmetric Synthesis of 3-Tetrasubstituted Oxindoles: Efficient Construction of Adjacent Quaternary and Tertiary Chiral Centers, S. Shimizu, T. Tsubogo, P. Xu, S. Kobayashi, *Org. Lett.*, **17**, 2006-2009 (2015).
- 9) Size of Gold Nanoparticles Driving Selective Amide Synthesis through Aerobic Condensation of Aldehydes and Amines, H. Miyamura, H. Min, J.-F. Soulé, S. Kobayashi, *Angew. Chem. Int. Ed.*, **54**, 7564-7567 (2015).
- 10) Chiral Metal Nanoparticle Systems as Heterogeneous Catalysts beyond Homogeneous Metal Complex Catalysts for Asymmetric Addition of Arylboronic Acids to  $\alpha,\beta$ -Unsaturated Carbonyl Compounds, T. Yasukawa, A. Suzuki, H. Miyamura, K. Nishino, S. Kobayashi, *J. Am. Chem. Soc.*, **137**, 6616-6623 (2015).
- 11) Zinc Bis[bis(trimethylsilyl)amide] as an Efficient Lewis Acid/Brønsted Base Cooperative Catalyst for the Direct Alkynylation of Nitrones, Y. Saito, Y. Yamashita, S. Kobayashi, *Chem. Lett.*, **44**, 976-977 (2015).
- 12) Catalytic Asymmetric 1,4-Addition Reactions of Simple Alkyl nitriles, Y. Yamashita, I. Sato, H. Suzuki, S. Kobayashi, *Chem. Asia J.*, **10**, 2143-2146 (2015).
- 13) Cu(II)-Based strategy for catalytic enantioselective  $\beta$ -borylation of  $\alpha,\beta$ -unsaturated acceptors, L. Zhu, T. Kitanosono, P. Xu and S. Kobayashi, *Chem. Commun.*, **51**, 11685-11688 (2015).

- 14) Effective Formylation of Amines with Carbon Dioxide and Diphenylsilane Catalyzed by Chelating bis(tzNHC) Rhodium Complexes, T. V. Nguyen, W.-J. Yoo and S. Kobayashi, *Angew. Chem. Int. Ed.*, **54**, 9209-9212 (2015).
- 15) Self-Assembled Nanocomposite Organic Polymers with Aluminum and Scandium as Heterogeneous Water-Compatible Lewis Acid Catalysts, H. Miyamura, A. Sonoyama, D. Hayrapetyan and S. Kobayashi, *Angew. Chem. Int. Ed.*, **54**, 10559-10563 (2015).
- 16) Integrated Process of Aerobic Oxidation-Olefination-Asymmetric C-C Bond Formation Catalyzed by Robust Heterogeneous Gold/Palladium and Chirally Modified Rhodium Nanoparticles, H. Miyamura, A. Suzuki, T. Yasukawa and S. Kobayashi, *Adv. Synth. Catal.*, **357**, 3815-3819 (2015).
- 17) Visible Light-Mediated Ullmann-Type C-N Coupling Reactions of Carbazole Derivatives and Aryl Iodides, W.-J. Yoo, T. Tsukamoto and S. Kobayashi, *Org. Lett.*, **17**, 3640-3642 (2015).
- 18) The Combined Use of Cationic Palladium(II) with a Surfactant for the C-H Functionalization of Indoles and Pyrroles in Water, T. Kitanosono, M. Miyo and S. Kobayashi, *Tetrahedron*, **71**, 7739-7744 (2015).
- 19) The Mechanism of Iron(II)-catalyzed Asymmetric Mukaiyama Aldol Reaction in Aqueous Media: Density Functional Theory and Artificial Force-Induced Reaction Study, W.M.C. Sameera, M. Hatanaka, T. Kitanosono, S. Kobayashi, K. Morokuma, *J. Am. Chem. Soc.*, **137**, 11085-11094 (2015).
- 20) Cellulose-Supported Chiral Rh Nanoparticles as Sustainable Heterogeneous Catalysts for Asymmetric Carbon-Carbon Bond-Forming Reactions, T. Yasukawa H. Miyamura and S. Kobayashi, *Chem. Sci.*, **6**, 6224-6229 (2015).
- 21) Chiral Cu(II)-Catalyzed Enantioselective  $\beta$ -Borylation of  $\alpha,\beta$ -Unsaturated Nitriles in Water, L. Zhu, T. Kitanosono, P. Xu and S. Kobayashi, *Beil. J. Org. Chem.*, **11**, 2007-2011 (2015).
- 22) Powerful Continuous-Flow Hydrogenation by Using Poly(dimethyl)silane-Supported Palladium Catalysts, S. Kobayashi, M. Okumura, Y. Akatsuka, H. Miyamura, M. Ueno, H. Oyamada, *ChemCatChem*, **7**, 4025-4029 (2015).
- 23) Catalytic Asymmetric *endo*-Selective [3+2] Cycloaddition Reactions of Schiff Bases of  $\alpha$ -Aminophosphonates with Olefins Using Chiral Metal Amides, *Chem. Commun.*, **51**, 17064-17067 (2015).
- 24) Zinc Amide Catalyzed Regioselective Allenylation and Propargylation of Ketones with Allenyl Boronate, Y. Yamashita, Y. Cui, P. Xie and S. Kobayashi, *Org. Lett.*, **17**, 6042-6045 (2015).
- 25) An Insoluble Copper(II) Acetylacetonate-Chiral Bipyridine Complex that Catalyzes Asymmetric Silyl Conjugate Addition in Water, T. Kitanosono, L. Zhu, C. Liu, P. Xu, and S. Kobayashi, *J. Am. Chem. Soc.*, **137**, 15422-15425 (2015).

## 2. 総説・解説

- 1) "Chiral Alkaline Earth Metal Complexes in Asymmetric Catalysis", Y. Yamashita, T. Tsubogo, S. Kobayashi, *Topics in Organometallic Chemistry*, 1-25 (2015).
- 2) "Hafnium Trifluoromethanesulfonate [Hf(OTf)<sub>4</sub>] as a Unique Lewis Acid in Organic Synthesis," H. Ishitani, H. Suzuki, Y. Saito, Y. Yamashita, S. Kobayashi, *Eur. J. Org. Chem.*, **25**, 5485–5499 (2015).

#### 4. その他

- 1) 毎日新聞、2015年4月16日、「医薬品効率的に合成」
- 2) 日本経済新聞、2015年4月16日、「原料流すだけ医薬品を合成」
- 3) 日刊工業新聞、2015年4月16日、「複雑な化合物連続合成」
- 4) 科学新聞、2015年5月1日、「医薬品などの新合成法開発」
- 5) 日刊工業新聞（コラム）、2015年5月15日、「化合物連続自動合成」
- 6) JST NEWS、2015年6月号、「環境にやさしい医薬品合成で国際競争に勝つ」
- 7) 読売新聞夕刊、2015年8月13日、「無駄省き、環境に優しい化学」