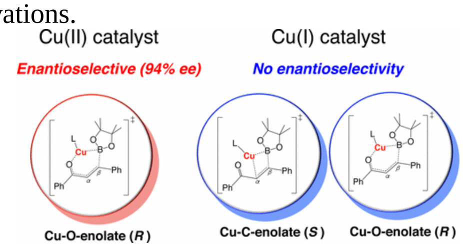
SYNTHETIC ORGANIC CHEMISTRY

Annual Research Highlights

(1) Mechanistic study of copper-catalyzed enantio-selective boron conjugate addition

A mechanistic survey on the chiral Cu-catalyzed enantioselective boron conjugate addition reaction using DFT and AFIR calculation methods was carried out. The theoretical calculation for the analogous chiral bipyridine–Cu^{II} catalyst indicated that only the transition state (TS) leading to Cu^{II}-O-enolate contributed to the reaction. The TSs leading to the *R* and *S* forms of Cu^{II}-O-enolates were energetically well separated, with the *R* form being of lower energy, which is consistent with experimental observations.

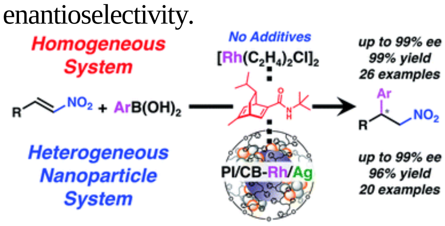


Scheme 1 Calculated transition states of the chiral Cu-catalyzed conjugate addition

1.(1)-9) *ACS Catal.* **7**, 5370 (2017).

(2) Development of asymmetric 1,4-addition reactions of arylboronic acids with nitroalkenes using chiral Rh catalysts

Asymmetric 1,4-addition reactions of arylboronic acids with nitroalkenes catalyzed by a rhodium complex with a chiral diene bearing a tertiary butyl amide moiety were developed. Just 0.1 mol% of the chiral rhodium complex could catalyze the reactions and gave the desired products in high yields with excellent enantioselectivities. The homogeneous catalyst thus developed could be converted to a reusable heterogeneous metal nanoparticle system using the same chiral ligand as a chiral modifier, which was immobilized using a polystyrene-derived polymer with cross-linking moieties, maintaining the same level of enantioselectivity.

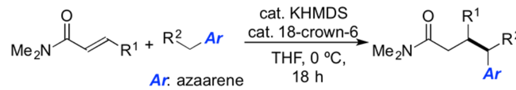


Scheme 2 Asymmetric 1,4-additions to nitroalkenes with arylboronic acids

1.(1)-12) *Chem. Sci.* **8**, 8362 (2017).

(3) Catalytic direct-type 1,4-addition reactions of alkylazaarenes

1,4-Addition reactions of alkylazaarenes catalyzed by strong Brønsted bases have been developed for the first time. The desired reactions with α,β-unsaturated amides proceeded under mild reaction conditions to give the 1,4-adducts in high yields. An asymmetric variant of this reaction was also found to be feasible.

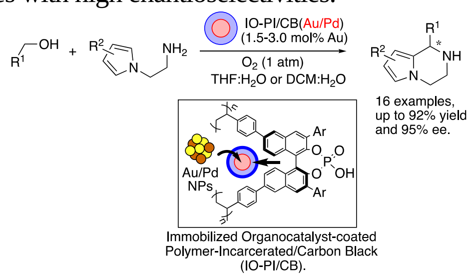


Scheme 3 Catalytic direct-type 1,4-addition reactions of alkylazaarenes

1.(1)-4) *Angew. Chem. Int . Ed.* **56**, 4520 (2017).

(4) Development of sequential aerobic oxidations and intramolecular asymmetric aza-Friedel–Crafts reactions

A new class of chiral bifunctional heterogeneous materials composed of Au/Pd nanoparticles and chiral phosphoric acids as active orthogonal catalysts was prepared. It was found that this heterogeneous catalyst was capable of facilitating the sequential aerobic oxidation-asymmetric intramolecular aza-Friedel–Crafts reaction between benzyl alcohols and *N*-aminoethyl-pyrroles with high enantioselectivities.

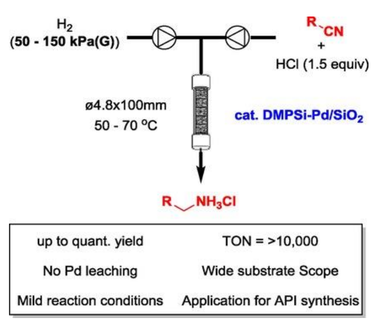


Scheme 4 Sequential aerobic oxidations and intramolecular asymmetric aza-Friedel–Crafts reactions

1.(1)-1) *Chem. Sci.* **8**, 1356 (2017).

(5) Selective hydrogenation of nitriles catalyzed by a polysilane/SiO_2-supported palladium catalyst under continuous-flow conditions

Hydrogenation of nitriles to primary amines with heterogeneous catalysts under liquid-phase continuous-flow conditions was investigated. Newly developed polysilane/SiO_2-supported Pd was found to be an effective catalyst, and various nitriles were converted into primary amine salts in almost quantitative yields under mild reaction conditions. Lifetime experiments showed that this catalyst remained active for more than 300 h ($TON \geq 10\,000$) without loss of selectivity and no metal leaching from the catalyst occurred.



Scheme 5 Selective hydrogenation of nitriles to primary amines under continuous-flow conditions

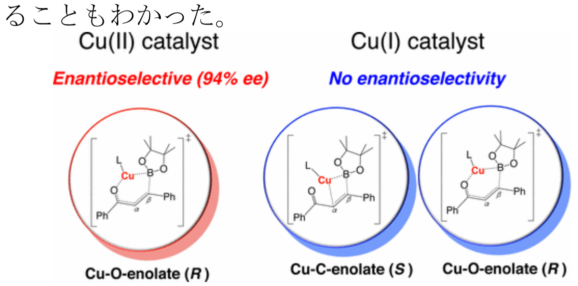
1.(1)-3) *Chem. Open.* **6**, 211 (2017).

有機合成化学研究室

研究ハイライト

⑴ 銅触媒を用いるホウ素の不斉 1,4−付加反応の反応機構解明

銅触媒を用いるホウ素の不斉 1,4-付加反応の反応機構について、DFT 法と AFIR 法を用いて理論計算を行なったところ、高エナンチオ選択性の発現に Cu(II)のエノラート種が機能することが非常に重要であることがわかり、得られた R 体のエナンチオマーが優位に得られるという予測も実験結果と良い整合性が取れることがわかった。一方で、Cu(I)種を有する中間体ではエナンチオ選択性の発現が困難であることもわかった。

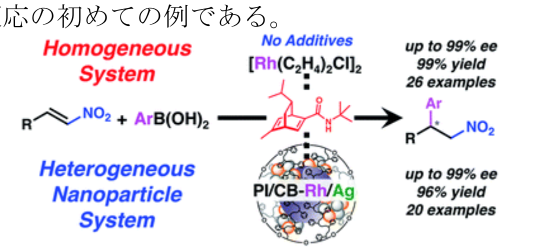


式１　キラル銅触媒を用いる不斉 1, 4-付加反応の反応遷移状態

1.(1)-9) *ACS Catal.* **7**, 5370 (2017).

⑵キラルロジウム触媒を用いるアリールホウ素化合物のニトロアルケンへの不斉 1,4−付加反応の開発

均一系ロジウム触媒と *tert*-ブチルアミド基を有するキラルジエンを不斉配位子として用いたアリールホウ素化合物のニトロアルケンへの不斉 1,4-付加反応を開発した。この触媒は 0.1 mol%の触媒量でも高反応性および高エナンチオ選択性を示した。さらに、不均一系触媒への展開の検討も行い、キラルナノ粒子触媒系に適用することにより、高いエナンチオ選択性を実現した。本系は不均一系触媒を用いるアリールホウ素化合物のニトロアルケンへの不斉 1,4-付加反応の初めての例である。

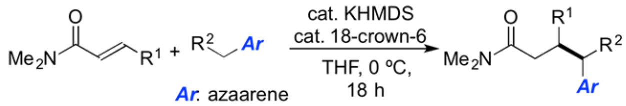


式２　キラルロジウム触媒を用いるアリールホウ素化合物のニトロアルケンへの不斉 1, 4-付加反応

1.(1)-12) *Chem. Sci.* **8**, 8362 (2017).

⑶アルキルアザアレンの触媒的 1,4−付加反応の開発

強塩基触媒を用いるアルキルアザアレンの α, β -不飽和アミドへの 1,4-付加反応を開発した。本反応は温和な条件で進行し目的物を高収率にて与えた。さらに、本反応の不斉合成反応への展開も可能なことを明らかにした。

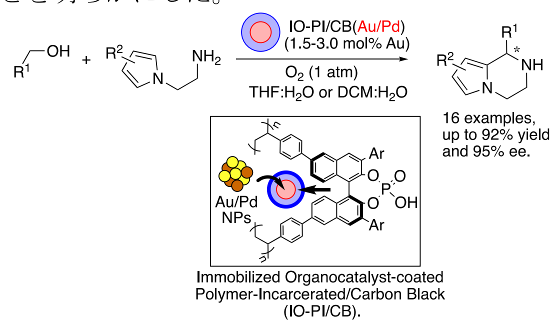


式３　アルキルアザアレンの触媒的 1, 4-付加反応

1.(1)-4) *Angew. Chem. Int . Ed.* **56**, 4520 (2017).

⑷ 固定化不斉触媒を用いる連続的酸素酸化＆不斉分子内アザ Friedel−Crafts 反応の開発

Au/Pd ナノ粒子と固定化キラルリン酸触媒からなる不均一系二機能性不斉触媒を開発し、アルコールの酸素酸化とそれに続く分子内不斉アザ Friedel-Crafts 反応の連続反応に適用した。検討の結果、ベンジルアルコールと N-アミノエチルピロールとの連続反応が高いエナンチオ選択性で進行することを明らかにした。

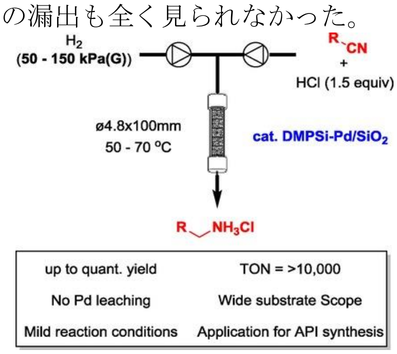


式４　Au/Pd ナノ粒子−固定化キラルリン酸触媒を用いる連続的酸素酸化&不斉分子内アザ Friedel-Crafts 反応

1.(1)-1) *Chem. Sci.* **8**, 1356 (2017).

⑸ 連続フロー反応によるニトリルの選択的水素化反応

不均一系触媒を用いる連続フロー条件下でのニトリルの一級アミンへの水素化反応を開発した。ポリシラン-シリカゲル担持パラジウム触媒を用いることにより、様々なニトリルを温和な条件下ほぼ定量的に対応する一級アミンに変換することができた。この触媒系は 300 時間触媒活性を失うことなく機能し、触媒の漏出も全く見られなかった。



式５　連続フロー条件下でのニトリルの一級アミンへの選択的水素化反応

1.(1)-3) *Chem. Open.* **6**, 211 (2017).

1. 原著論文

(1) Refereed Journals

1) Integration of Aerobic Oxidation and Intramolecular Asymmetric Aza-Friedel–Crafts Reactions with a Chiral Bifunctional Heterogeneous Catalyst, H.-G. Cheng, J. Miguelez, H. Miyamura, W.-J. Yoo, S. Kobayashi, *Chem. Sci.*, **8**, 1356-1359 (2017).

2) Lewis Acid-assisted Dirhodium(II)-catalyzed Ketone Hydroacylation, T. Yasukawa, S. Kobayashi, *Chem. Lett.*, **46**, 98-100 (2017).

3) Selective Hydrogenation of Nitriles to Primary Amines Catalyzed by a Polysilane/SiO_2-Supported Palladium Catalyst under Continuous-Flow Conditions, Y. Saito, H. Ishitani, M. Ueno, S. Kobayashi, *Chem. Open.*, **6**, 211-215 (2017).

4) Catalytic Direct-type 1,4-Addition Reactions of Alkylazaarenes, H. Suzuki, R. Igarashi, Y. Yamashita, S. Kobayashi, *Angew. Chem. Int. Ed.*, **56**, 4520-4524 (2017).

5) Catalytic Asymmetric Direct-type 1,4-Addition Reactions of Alkanesulfonamides, Y. Yamashita, R. Igarashi, H. Suzuki, S. Kobayashi, *Synlett*, **28**, 1287-1290 (2017).

6) Continuous-flow synthesis using a column reactor packed with heterogeneous catalysts: A convenient production of nitroolefinsby using amino-functionalized silicagel, H. Ishitani, Y. Furiya, S. Kobayashi, *Bioorg. Med. Chem*., **25**, 6229-6232 (2017).

7) Incorporation of Carbon Dioxide into Phthalides via Ligand-free Copper-Catalyzed Direct Carboxylation of Benzoxasiloles, T. V.Q. Nguyen, J. A. Rodríguez-Santamaría, W.-J. Yoo, S. Kobayashi, *Green Chem.*, **19**, 2501-2505 (2017).

8) A Polystyrene-Supported Phase-Transfer Catalyst for Asymmetric Michael Addition of Glycine-Derived Imines to *α,β*-Unsaturated Ketones, J. Miguélez, H. Miyamura, S. Kobayashi, *Adv. Synth. Catal*., **359**, 2897-2900 (2017).

9) Copper-Catalyzed Enantioselective Boron Conjugate Addition: DFT and AFIR Study on Different Selectivities of Cu(I) and Cu(II) Catalysts, M. Isegawa, W. M. C. Sameera, A. K. Sharma, T. Kitanosono, M. Kato, S. Kobayashi, K. Morokuma, *ACS Catal*., **7**, 5370-5380 (2017).

10) Catalytic Stereoselective 1,4-Addition Reactions Using CsF on Alumina as a Solid Base: Continuous-Flow Synthesis of Glutamic Acid Derivatives, P. Borah, Y. Yamashita, S. Kobayashi, *Angew. Chem. Int. Ed.*, **56**, 10330-10334 (2017).

11) Water as a catalytic switch in the oxidation of aryl alcohols by polymer incarcerated rhodium nanoparticles, J. O. Weston, H. Miyamura, T. Yasukawa, D. Sutarma, C. A. Baker, P. K. Singh, M. Bravo-Sanchez, N. Sano, P. J. Cumpson, Y. Ryabenkova, S. Kobayashi, M. Conte, *Catal. Sci. Technol.*, **7**, 3985-3998 (2017).

12) Rhodium-catalyzed Asymmetric 1,4-addition Reactions of Aryl Boronic Acids with Nitroalkenes: Reaction Mechanism and Development of Homogeneous and Heterogeneous Catalysts, H. Miyamura, K. Nishino, T. Yasukawa, S. Kobayashi, *Chem. Sci.*, **8**, 8362-8372 (2017).

13) Synthesis of (±)-Pregabalin by Utilizing a Three-Step Sequential-Flow System with Heterogeneous Catalysts, H. Ishitani, K. Kanai, Y. Saito, T. Tsubogo, S. Kobayashi, *Eur. J. Org. Chem.*, **2017**, 6491-6494 (2017).

3. 著書

1) Water-Compatible Chiral Lewis Acids, T. Kitanosono, S. Kobayashi, In Book *Chiral Lewis Acids in Organic Synthesis*, ed. by J. Mlynarski, Wiley-VCH, (2017), 299-344.