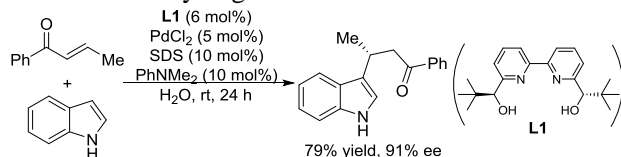


SYNTHETIC ORGANIC CHEMISTRY

Annual Research Highlights

(1) Development of palladium catalyzed asymmetric C-H bond functionalization of indoles in water

We found that a chiral palladium (II) complex composed of a 2,2'-bipyridine ligand **L1** catalyzed the C-H bond functionalization reaction of indoles in water with high enantioselectivity using an anionic surfactant. Both the noble metal catalyst and the micelle catalyst are indispensable in this system, and new reactivity in water due to a synergistic effect can be realized.

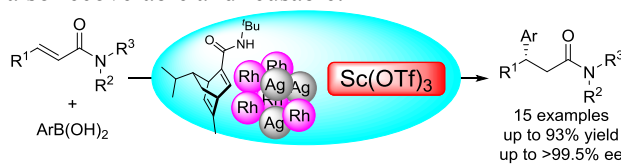


Scheme 1 Chiral Pd(II) catalyzed asymmetric C-H bond functionalization of indoles in water

1.(1)-10) *ACS Sustainable Chem. Eng.* **4**, 6101 (2016).

(2) Development of asymmetric 1,4-addition reaction by cooperative catalytic system of chiral Rh/Ag nanoparticles and Lewis acid catalyst

Asymmetric 1,4-addition reactions of aryl boron compounds to unsaturated amides were difficult reactions, since the reactivity of electrophiles was relatively low. We found that a cooperative catalyst system composed of a chiral Rh/Ag nanoparticle catalyst and Sc(OTf)₃ as a Lewis acid catalyst effectively functioned for these reactions. This system gave the desired β -aryl adducts in high yields and high enantioselectivities and was applicable to a wide variety of substrates. The nanoparticle catalyst was also recoverable and reusable.



Chiral NP / Lewis acid Cooperative Catalysis

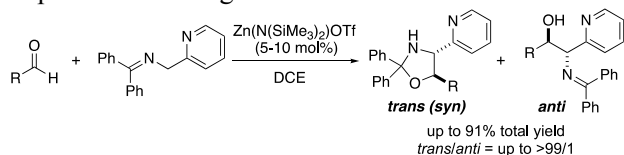
Scheme 2 Asymmetric 1,4-addition to α,β -unsaturated amides by chiral Rh/Ag nanoparticles and Lewis acids

1.(1)-4) *Angew. Chem. Int. Ed.* **55**, 8058 (2016).

(3) Aldol type reaction of 2-picolyamine with Schiff base by zinc amide hybrid catalyst

Zn(N(SiMe₃)₂)OTf, which is a Lewis acid / metal amide hybrid catalyst using zinc, effectively functioned in aldol type reactions of 2-picolyamine Schiff base with aldehydes. In these reactions, Zn(OTf)₂ having stronger Lewis acidity or Zn(N(SiMe₃)₂)₂ having stronger basicity did not work at all and only the hybrid catalyst system in which the Lewis acidity of the catalyst was controlled was effective. We have found that *trans*-*N,O*-acetal adducts, which is equivalent to *syn*-aldol adducts, were obtained

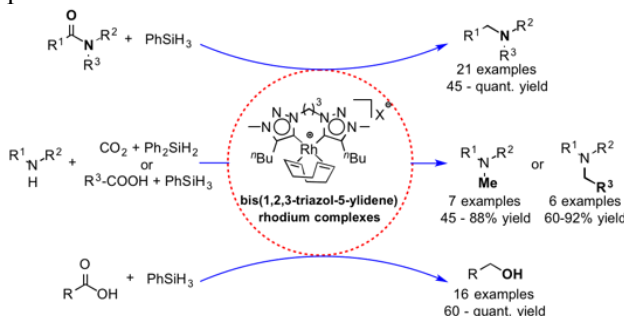
as products with high selectivities.



Scheme 3 Aldol type reactions by zinc amide hybrid catalyst
1.(1)-9) *Chem. Asian J.* **11**, 2372 (2016).

(4) Hydrosilylation reactions with chelating bidentate NHC ligand-Rh complex

The *N*-heterocyclic carbene (NHC)-Rh complex was used as a catalyst for the hydrosilylation reaction, but its application range was limited to highly reactive substrates. We developed a Rh complex catalyst prepared from a chelating bidentate NHC ligand. We have found that by using this catalyst, various reactions such as reductive methylation of amine using carbon dioxide, reduction of amide and carboxylic acid, carboxylic acid reductive alkylation of amines, etc., proceeded under mild conditions.

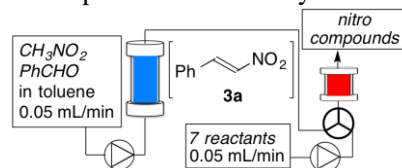


Scheme 4 Hydrosilylation reactions with chelating bidentate NHC ligand-Rh complex

1.(1)-1) *Adv. Synth. Catal.* **358**, 452 (2016).

(5) Synthesis of nitro compounds by multistep continuous flow with heterogeneous catalyst

By using a column packed with amino group-modified silica and CaCl₂ as a catalyst, a continuous flow synthesis of nitrostyrene derivatives from aromatic aldehydes and nitromethane was developed. Following this flow synthesis, flow synthesis of seven kinds of organic nitro compounds in two steps was performed by connecting columns packed with heterogeneous acid, base, organic molecular catalyst, etc. and supplying new raw materials. Furthermore, it was revealed that three-step continuous flow reaction also proceeded by connecting another column packed with a catalyst.



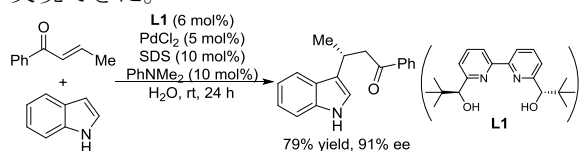
Scheme 5 Synthesis of nitro compounds by multistep continuous flow

1.(1)-2) *Org. Lett.*, **18**, 1346 (2016).

研究ハイライト

(1)パラジウム触媒によるインドール類の水中不斉 C-H 結合官能基化反応の開発

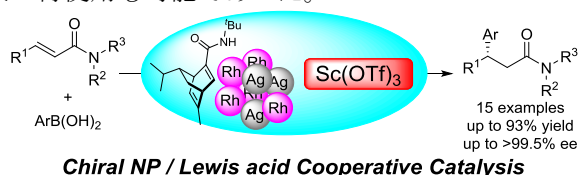
2,2'-ビピリジン配位子 L1 からなるキラルパラジウム(II)錯体が、アニオン性界面活性剤を用いることで、水中でのインドール類の C-H 結合官能基化反応を、高いエナンチオ選択性で触媒することを見出した。本系は、貴金属触媒とミセル触媒の両方が必要不可欠であり、相乗的な効果による水中での新たな反応性が実現できた。



式1 キラルパラジウム(II)触媒を用いるインドール類の水中での不斉 C-H 結合官能基化反応
1.(1)-10) *ACS Sustainable Chem. Eng.* **4**, 6101 (2016).

(2)キラルロジウム/銀ナノ粒子とルイス酸触媒の協働触媒系による不斉 1,4-付加反応の開発

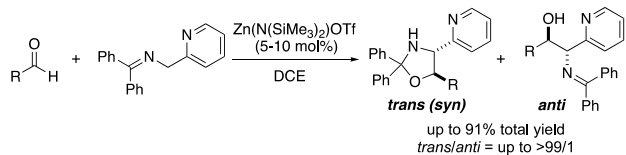
アリールホウ素化合物の不飽和アミド類への不斉 1,4-付加反応は、求電子剤の反応性が比較的 low、困難な反応であった。今回、キラルロジウム/銀ナノ粒子触媒とルイス酸触媒である Sc(OTf)₃ からなる協働触媒系が有効に機能することを見出した。この反応は、目的の β-アリール付加体を高収率・高エナンチオ選択性で与え、また幅広い種類の基質に適用可能であった。本キラルロジウム/銀ナノ粒子触媒は、回収・再使用も可能であった。



式2 キラルロジウム/銀ナノ粒子とルイス酸触媒によるアリールボロン酸類の不飽和アミド類への不斉 1,4-付加反応
1.(1)-4) *Angew. Chem. Int. Ed.* **55**, 8058 (2016).

(3) 亜鉛アミドハイブリッド触媒による 2-ピコリルアミンのシッフ塩基とのアルドール型反応

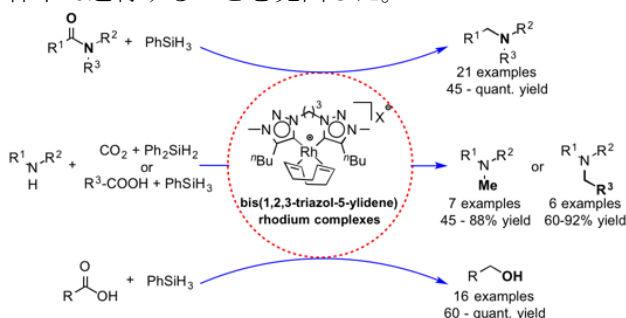
亜鉛を用いた、ルイス酸/金属アミドハイブリッド触媒である Zn(N(SiMe₃)₂)OTf が、2-ピコリルアミンのシッフ塩基とアルデヒドとのアルドール型反応において、有効に機能することを明らかにした。本反応ではよりルイス酸性の強い Zn(OTf)₂ や塩基性の強い Zn(N(SiMe₃)₂)₂ は全く機能せず、触媒のルイス酸性を調節した、ハイブリッド触媒系のみが有効であった。生成物として、*syn*-アルドール体の等価体である *trans*-*N,O*-アセタール体が高選択的に得られることを見いだした。



式3 亜鉛ハイブリッド触媒によるアルドール型反応
1.(1)-9) *Chem. Asian J.* **11**, 2372 (2016).

(4) キレート性二座 NHC 配位子-Rh 錯体によるヒドロシリル化反応

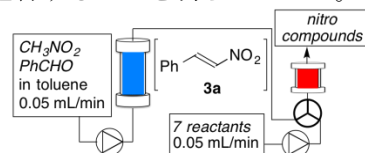
N-ヘテロサイクリックカルベン(NHC)-Rh 錯体はヒドロシリル化反応に効率的な触媒として使用されてきたが、その適用範囲は反応性の高い基質に限定されていた。今回、キレート性二座 NHC 配位子を用いた Rh 錯体触媒を開発し、これを用いることで、二酸化炭素を用いたアミンの還元的メチル化、アミドおよびカルボン酸の還元、カルボン酸を用いたアミンの還元的アルキル化など、種々の反応が温和な条件下で進行することを見出した。



式4 キレート性二座 NHC 配位子-Rh 錯体によるヒドロシリル化反応
1.(1)-1) *Adv. Synth. Catal.* **358**, 452 (2016).

(5) 不均一系触媒を用いた多段階連続フロー反応によるニトロ化合物の合成

芳香族アルデヒドとニトロメタンから、アミノ基修飾シリカと CaCl₂ を充填したカラムを触媒として用いることで、ニトロスチレン誘導体のフロー法による連続合成法を開発した。さらに、本フロー合成に引き続き、不均一系酸・塩基・有機分子触媒などを充填したカラムを連結し、新たな原料を供給することで、2段階での7種類の有機ニトロ化合物のフロー合成を行った。さらに、もう一つ触媒を充填したカラムを連結することにより、3段階の連続フロー反応も進行することを明らかにした。



式5 多段階連続フロー反応によるニトロ化合物の合成
1.(1)-2) *Org. Lett.*, **18**, 1346 (2016).

1. 原著論文

(1) Refereed Journals

- 1) Chelating Bis(1,2,3-triazol-5-ylidene) Rhodium Complexes: Versatile Catalysts for Hydrosilylation Reactions, T. V. Q. Nguyen, W.-J. Yoo, S. Kobayashi, *Adv. Synth. Catal.*, **358**, 452-458 (2016).
- 2) Synthesis of Nitro-Containing Compounds through Multistep Continuous Flow with Heterogeneous Catalysts, H. Ishitani, Y. Saito, T. Tsubogo, S. Kobayashi, *Org. Lett.*, **18**, 1346-1349 (2016).
- 3) Enantioselective Organometallic Catalysis in Flow, H. Ishitani, Y. Saito, S. Kobayashi, *Top. Organomet. Chem.*, **57**, 213-248 (2016).
- 4) Chiral Nanoparticles/Lewis Acids as Cooperative Catalysts for Asymmetric 1,4-Addition of Arylboronic Acids to α,β -Unsaturated Amides, T. Yasukawa, Y. Saito, H. Miyamura, S. Kobayashi, *Angew. Chem. Int. Ed.*, **55**, 8058-8061 (2016).
- 5) Asymmetric Arylation of Imines Catalyzed by Heterogeneous Chiral Rhodium Nanoparticles, T. Yasukawa, T. Kuremoto, H. Miyamura, S. Kobayashi, *Org. Lett.*, **18**, 2716-2718 (2016).
- 6) *N*-Heterocyclic Carbene Coordinated Heterogeneous Pd Nanoparticles as Catalysts for SuzukiMiyaura Coupling, H. Min, H. Miyamura, S. Kobayashi, *Chem. Lett.*, **45**, 837-839 (2016).
- 7) Development of Chiral Metal Amides as Highly Reactive Catalysts for Asymmetric [3+2] Cycloadditions, Y. Yamashita, S. Yoshimoto, M. J. Dutton, S. Kobayashi, *Beilstein J. Org. Chem.*, **12**, 1447-1452 (2016).
- 8) Catalytic Asymmetric Direct-type 1,4-Addition Reactions of Simple Esters, I. Sato, H. Suzuki, Y. Yamashita, S. Kobayashi, *Org. Chem. Front.*, **3**, 1241-1245 (2016).
- 9) Development of a Simple Adjustable Zinc Acid/Base Hybrid Catalyst for C-C and C-O Bond-Formation and C-C Bond-Cleavage Reactions, Y. Yamashita, K. Minami, Y. Saito, S. Kobayashi, *Chem. Asian J.*, **11**, 2372-2376 (2016).
- 10) Surfactant-Aided Chiral Palladium(II) Catalysis Exerted Exclusively in Water for the C-H Functionalization of Indoles, T. Kitanosono, M. Miyo, S. Kobayashi, *ACS Sustain. Chem. Eng.*, **4**, 6101-6106 (2016).
- 11) Upregulation of an Artificial Zymogen by Proteolysis, Z. Liu, V. Lebrun, T. Kitanosono, H. Mallin, V. Köhler, D. Häussinger, D. Hilvert, S. Kobayashi, T. R. Ward, *Angew. Chem. Int. Ed.*, **55**, 11587-11590 (2016).
- 12) Catalytic Hydrogenation of Aliphatic Nitro Compounds with Polysilane/Bone Charcoal-Supported Palladium Catalysts under Continuous-Flow Conditions, Y. Saito, H. Ishitani, S. Kobayashi, *Asian J. Org. Chem.*, **5**, 1124-1127 (2016).
- 13) Lewis Acid-Driven Reaction Pathways in Synergistic Cooperative Catalysis Over Gold/Palladium Bimetallic Nanoparticles for Hydrogen Autotransfer Reaction Between Amide and Alcohol, H. Miyamura, S. Isshiki, H. Min, S. Kobayashi, *Chinese J. Catal.*, **37**, 1662-1668 (2016).

- 14) Chiral Ligand-Modified Metal Nanoparticles as Unique Catalysts for Asymmetric CC Bond-Forming Reactions: How Are Active Species Generated?, T. Yasukawa, H. Miyamura, S. Kobayashi, *ACS Catal.*, **6**, 7979-7988 (2016).

2. 総説・解説

- 1) Flow “Fine” Synthesis: High Yielding and Selective Organic Synthesis by Flow Methods, S. Kobayashi, *Chem. Asian J.*, **11**, 425-436 (2016).

4. その他

- 1) Chemical Engineering News, 2016年1月11日, ”Insoluble Catalysts Works Wonders”