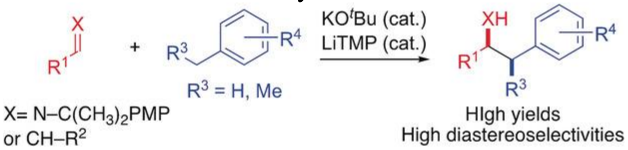
SYNTHETIC ORGANIC CHEMISTRY

Annual Research Highlights

(1) Catalytic addition reactions of alkylarenes with imines and alkenes

Catalytic addition reactions of weakly acidic nonactivated alkylarenes such as toluene were achieved by a strongly basic mixed catalyst. Addition reactions with imines and alkenes proceeded smoothly under proton-transfer conditions to afford the desired products in good to high yields. An asymmetric addition reaction of an alkylarene was also feasible.

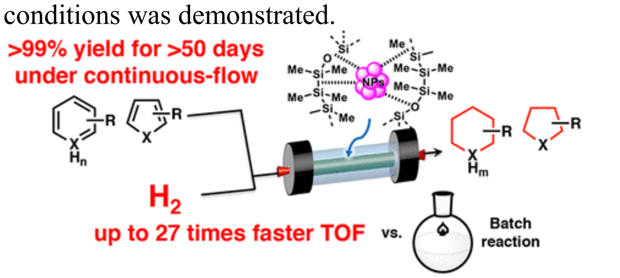


Scheme 1 Strong Brønsted-base-catalyzed addition of alkylarenes with imines and alkenes

1.(1)-6) *Angew. Chem. Int. Ed.* **57**, 6896 (2018).

(2) Polysilane-immobilized Rh–Pt bimetallic nanoparticles as powerful arene hydrogenation catalysts

Heterogeneous Rh-Pt bimetallic nanoparticle catalysts were developed for the hydrogenation of arenes with inexpensive polysilane as support. The catalysts could be used in both batch and continuous-flow systems with high performance under mild conditions and showed wide substrate generality. Remarkably, much higher catalytic performance was observed in the flow system than in the batch system, and extremely strong durability under continuous-flow conditions was demonstrated.

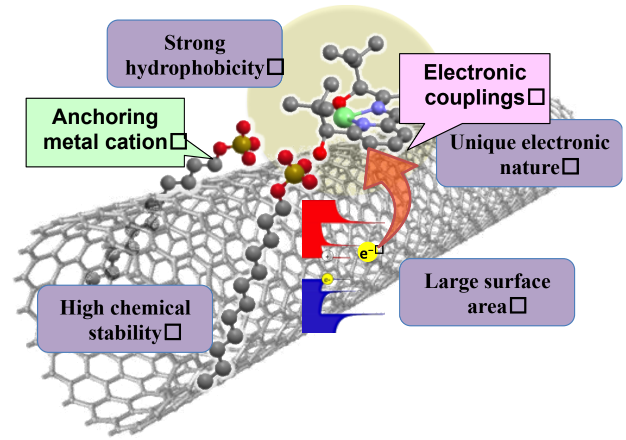


Scheme 2 Arene hydrogenation using hydrogen gas under continuous-flow conditions

1.(1)-7) *J. Am. Chem. Soc.* **140**, 11325 (2018).

(3) Chiral Lewis acids integrated with single-walled carbon nanotubes for asymmetric catalysis in water

We demonstrated that single-walled carbon nanotubes (SWNTs) could similarly render simple nickel catalysts effective in water. Integration of the nickel ions with chiral ligands and surfactants at the nanotube surface produces a highly enantioselective catalyst for nitrone formation from aldoximes and unsaturated ketones with long-term stability. Spectroscopy suggested that SWNTs enhanced electron density at the nickel center as well as provided a hydrophobic milieu.

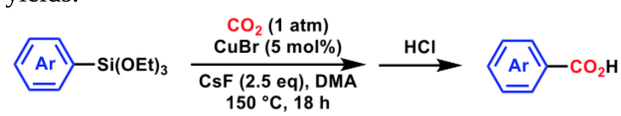


Scheme 3 Schematic image of Lewis acid–SWNT–integrated catalysts

1.(1)-13) *Science* **362**, 311 (2018).

(4) Copper-catalyzed carboxylation of aryl- and alkenyltrialkoxysilanes

The use of CuBr as a catalyst, in conjunction with CsF as an activator, enabled a wide range of aryl- and alkenyltrialkoxysilanes to undergo carboxylation at 150 °C under atmospheric pressure of CO_2, affording the corresponding carboxylic acids in good to high yields.

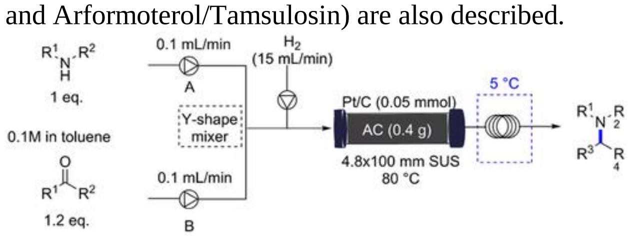


Scheme 4 Copper-catalyzed carboxylation process with arylsilanes under atmospheric pressure of CO_2

1.(1)-1) *Asian J. Org. Chem.* **7**, 116 (2018).

(5) Direct reductive amination of carbonyl compounds with H_2 using heterogeneous catalysts in continuous-flow

A general continuous-flow procedure was developed for direct reductive amination of secondary and primary amines with aldehydes and ketones by using hydrogen gas and commercially available Pt/C as a heterogeneous catalyst. In addition to exhibiting an excellent functional group tolerance, this method allows the fast formation of C−N bonds without production of any hazardous chemical waste. Applications to the synthesis of key intermediates toward active pharmaceutical ingredients (Donepezil and Arformoterol/Tamsulosin) are also described.



Scheme 5 Continuous-flow procedure for reductive amination

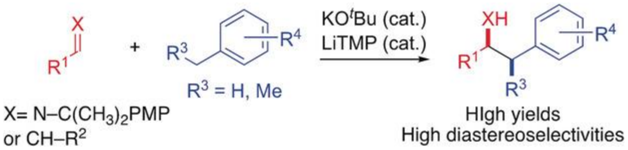
1.(1)-14) *Adv. Synth. Catal.*, **360**, 4699 (2018).

有機合成化学研究室

研究ハイライト

(1) イミン及びアルケン類に対するアルキルアレンの付加反応

トルエンなどのアルキルアレンは極めて低酸性な求核前駆体であるが、超強塩基ハイブリッド触媒系を用いることにより、イミンやアルケン類に対する付加反応が円滑に進行することを見出した。不斉反応への展開も可能である。

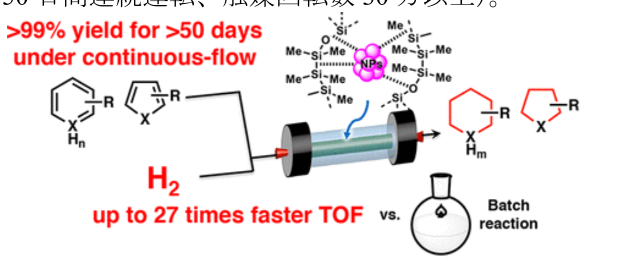


式１　超強塩基条件下での触媒的なアルキルアレン変換反応

1.(1)-6) *Angew. Chem. Int. Ed.* **57**, 6896 (2018).

(2) ポリシラン固定化 Rh/Pt ナノ粒子触媒を用いる芳香族化合物の水素化

安価なポリシランを担体として用いた、不均一ロジウム-白金二元金属ナノ粒子触媒を開発し、芳香環類の水素化反応に適用した。この触媒は、温和な条件下で機能し、バッチ法および連続フロー法の両方で、幅広い種類の基質に対して使用可能であった。連続フロー法では、触媒を充填したカラムに、基質と常圧水素を流すことによって生成物を得ることができ、従来のバッチ法よりもはるかに高い触媒性能が観察され、また非常に強い耐久性が実証された（>50 日間連続運転、触媒回転数 30 万以上）。

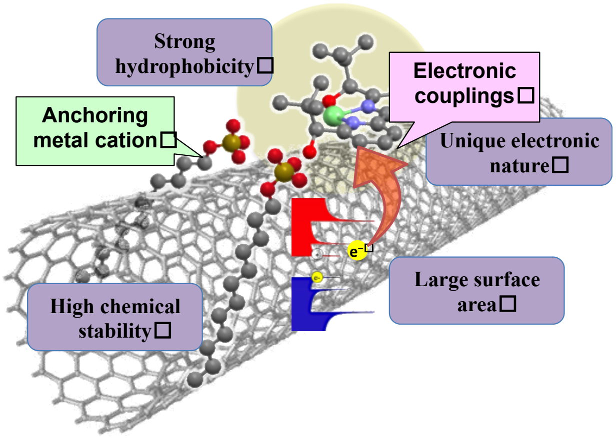


式２　ロジウム―白金ナノ粒子触媒による連続フロー条件下での芳香環水素化反応

1.(1)-7) *J. Am. Chem. Soc.* **140**, 11325 (2018).

(3) 単層カーボンナノチューブを用いた水中で働く不斉触媒の高機能化

単層カーボンナノチューブ(SWNT)の疎水的な表面環境、またその特異な電子特性を反応場に組み込むことで、不斉触媒の高機能化を実現した。SWNT はチューブ間の相互作用によって束状になる性質のため、相互作用の弱いカチオン性ルイス酸触媒と組み合わせることは難しい。そこでルイス酸－界面活性剤一体型触媒を用い、高度分散状態を作り出す新規複合触媒の設計を試みた。SWNT 表面に吸着されたルイス酸－界面活性剤一体型触媒分子が特異な反応場を形成し、高収率、高選択性を以てニトロン類の触媒的不斉合成が達成された。

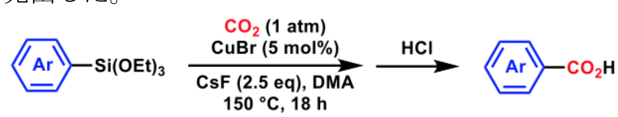


式３　不斉ルイス酸－SWNT 複合触媒

1.(1)-13) *Science* **362**, 311 (2018).

(4) 銅(I)触媒を用いた二酸化炭素によるトリアルコキシシラン類のカルボキシル化反応

二酸化炭素を求電子剤として用いる炭素−炭素結合生成反応を目指し、臭化銅(I)及びフッ化セシウム存在下、芳香族及びアルケニルトリアルコキシシランが常圧の二酸化炭素雰囲気下にカルボキシル化を受けて対応するカルボン酸を高収率で与えることを見出した。

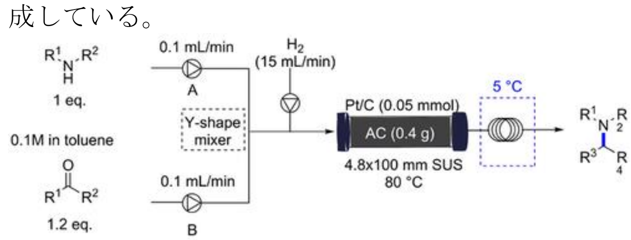


式４　二酸化炭素雰囲気下でのトリアルコキシシラン類のカルボニル化反応

1.(1)-1) *Asian J. Org. Chem.* **7**, 116 (2018).

(5) 不均一系触媒を用いたフロー法による還元的アミノ化

水素ガスと市販の Pt/C を使用することにより、アルデヒド及びケトンと第二級および第一級アミンとの直接還元アミノ化のための普遍的なフロー法を確立した。本手法は、優れた官能基耐性を示すことに加え、有害な化学廃棄物を生成することなく、迅速な結合生成を可能にすることを特徴とする。上市されている医薬品(ドネペジルやアルホルモテロール/タムスロシン)合成に繋がる重要な中間体合成を達成している。



式５フロー法による水素ガスを用いた還元的アミノ化反応

1.(1)-14) *Adv. Synth. Catal.,* **360**, 4699 (2018).

1. 原著論文

(1) Refereed Journals

1) Copper-Catalyzed Carboxylation of Aryl- and Alkenyltrialkoxysilanes, T. V. Q. Nguyen, W-J Yoo, S. Kobayashi, *Asian J. Org. Chem*., **7**, 116-118 (2018).
2) Oxyfunctionalization of Active Methylene Compounds Using Sodium Chlorite in Water, T. Kitanosono, S. Tani, and S. Kobayashi, *Asian J. Org. Chem*., **7**, 350-354 (2018).
3) Catalytic Direct-type Addition Reactions of Alkylarenes with Imines and Alkenes, Y. Yamashita, H. Suzuki, I. Sato, T. Hirata, S. Kobayashi, *Chem. Eur. J*., **24**, 10-17 (2018).
4) Catalytic Addition Reactions of Alkylazaarenes to Vinylsilanes, Y. Yamashita, K. Minami, S. Kobayashi, *Chem. Lett*., **47**, 690-692 (2018).
5) Catalytic Alkylation Reactions of Weakly Acidic Carbonyl and Related Compounds Using Alkenes as Electrophiles, Y. Yamashita, R. Igarashi, H. Suzuki, S. Kobayashi, *Org. Biomol. Chem.*, **16**, 5969-5972 (2018).
6) Catalytic Direct-Type Addition Reactions of Alkylarenes with Imines and Alkenes, Y. Yamashita, H. Suzuki, I. Sato, T. Hirata, S. Kobayashi, *Angew. Chem. Int. Ed.*, **57**, 6896-6900 (2018).
7) Polysilane-Immobilized Rh–Pt Bimetallic Nanoparticles as Powerful Arene Hydrogenation Catalysts: Synthesis, Reactions under Batch and Flow Conditions and Reaction Mechanism, H. Miyamura, A. Suzuki, T. Yasukawa, S. Kobayashi, *J. Am. Chem. Soc.*, **140**, 11325-11334 (2018).
8) Development of N-Doped Carbon-Supported Cobalt/Copper Bimetallic Nanoparticle Catalysts for Aerobic Oxidative Esterifications Based on Polymer Incarceration Methods, T. Yasukawa, X. Yang, S. Kobayashi, *Org. Lett.*, **20**, 5172-5176 (2018).
9) Knoevenagel Condensation of Aldehydes and Ketones with Alkyl Nitriles Catalyzed by Strongly Basic Anion Exchange Resins under Continuous-Flow Conditions, H. Ishitani, Y. Saito, Y. Nakamura, W.-J. Yoo, S. Kobayash, *Asian J. Org. Chem.,* **7**, 2061–2064 (2018)
10) Chiral Calcium-Catalyzed Asymmetric Epoxidation Reactions Using Hydrogen Peroxide as the Terminal Oxidant, Y. Yamashita, J. A. Macor, S. Fushimi, T. Tsubogo, S. Kobayashi, *Chem. Pharm. Bull.*, **66**, 847-850 (2018).
11) Reactivity and properties of bis(chlorodifluoroacetyl) peroxide generated in situ from chlorodifluoroacetic anhydride for chlorodifluoromethylation reactions, S. Kawamura, C. J. Henderson, Y. Aoki, D. Sekine, S. Kobayashi, M. Sodeoka, *Chem. Commun*., **54**, 11276-11279 (2018).
12) A Convenient and Mild Cyclocondensation Using Water-soluble Aldehydes in Water, T. Kitanosono, S. M. Cho, S. Kobayashi, *Tetrahedron,* **74**, 7237-7241 (2018).
13) Chiral Lewis acids integrated with single-walled carbon nanotubes for asymmetric catalysis in water, T. Kitanosono, P. Xu, S. Kobayashi, *Science,* **362**, 311-315 (2018).

14) Direct reductive amination of carbonyl compounds with H_2 using heterogeneous catalysts in continuous flow as an alternative to *N*-alkylation with alkyl halides, B. Laroche, H. Ishitani, S. Kobayashi, *Adv. Synth. Catal.*, **360**, 4699-4704 (2018).

2. 総説・解説

1) Catalytic Organic Reactions in Water toward Sustainable Society, T. Kitanosono, K. Masuda, P. Xu, S. Kobayashi, *Chem. Rev.*, **118**, 679-746 (2018).
2) Catalytic Carbon–Carbon Bond-Forming Reactions of Weakly Acidic Carbon Pronucleophiles Using Strong Brønsted Bases as Catalysts, Y. Yamashita, S. Kobayashi, *Chem. Eur. J.*, **24**, 10-17 (2018).
3) Flow Fine Synthesis with Heterogeneous Catalysts, K. Masuda, T. Ichitsuka, N. Koumura, K. Sato, S. Kobayashi, *Tetrahedron*, **74**, 1705-1730 (2018).
4) Catalytic Enantioselective Aldol Reactions, Y. Yamashita, T. Yasukawa, W-J Yoo, T. Kitanosono, S. Kobayashi, *Chem. Soc. Rev.,* **47,** 4388-4480 (2018).

4. その他

1) Chem-Station スポットライトリサーチ, ”水素社会実現に向けた連続フロー合成法を新開発”