Academic Program [Oral A] | 15. Organic Chemistry -Aliphatic and Alicyclic Compounds, and New Synthetic Technology- : Oral A

Thu. Mar 27, 2025 9:00 AM - 11:40 AM JST | Thu. Mar 27, 2025 12:00 AM - 2:40 AM UTC
[F]2401(2401, Bldg. 2, Area 4 [4F])

[[F]2401-2am] 15. Organic Chemistry -Aliphatic and Alicyclic Compounds, and New Synthetic Technology-

Chair: Yosuke Ashikari, Masaharu Ueno

Japanese
9:00 AM - 9:10 AM JST | 12:00 AM - 12:10 AM UTC
[[F]2401-2am-01]

Generation and flow in-line analysis of formylated-aryllithium equivalent

〇Moe Adachi[1], Ryuhei Kikuchi[1], Hiroki Soutome[1,2], Aiichiro Nagaki[1] (1. Department of Chemistry, Faculty of Science, Hokkaido University, 2. AGC Inc.)

Japanese
9:10 AM - 9:20 AM JST | 12:10 AM - 12:20 AM UTC
[[F]2401-2am-02]

Unsymmetrical Carbonylation of Dibromoarenes Using Dianionic Organolithium Species

〇Ryuhei Kikuchi[1], Moe Adachi[1], Hiroki Soutome[1,2], Aiichiro Nagaki[1] (1. Department of Chemistry, Faculty of Science, 2. AGC Inc.)

Japanese
9:20 AM - 9:30 AM JST | 12:20 AM - 12:30 AM UTC
[[F]2401-2am-03]

Selectivity control in competitive parallel and sequential organolithium reactions by flowmicro coexisting method

〇masatomo iwata[1], Yosuke Ashikari[2], Aiichiro Nagaki[2] (1. Hokkaido Univ. graduate school of chemical sciences and engineering, 2. Hokkaido Univ. Graduate School of Science)

English
9:30 AM - 9:40 AM JST | 12:30 AM - 12:40 AM UTC
[[F]2401-2am-04]

Development of Highly Stable Continuous-Flow Hydrogenation and Reductive Alkylation System Using Etched Silicon Powder-Supported Palladium Catalyst

〇Eman Soliman[1,2], Zhenzhong Zhang[1], Heeyoel Baek[1], Yoichi M. A. Yamada[1,2] (1. RIKEN CSRS, 2. Saitama University, Faculty of Science and Engineering)

Japanese
9:40 AM - 9:50 AM JST | 12:40 AM - 12:50 AM UTC
[[F]2401-2am-05]

Study on Olefin-Selective Catalytic Hydrogenation Reactions using Continuous Flow Synthesis

〇Miku Tashima[1], Norikazu Miyoshi[1], Masaharu Ueno[1] (1. Graduate School of Science and Technology, Tokushima University)

English
9:50 AM - 10:00 AM JST | 12:50 AM - 1:00 AM UTC
[[F]2401-2am-06]

Fast Reductive Transformation Reactions Enabled by Highly Active Monolithic Polymer-Supported Catalysts

○Xianzhu Zhong[1], Kazuhiro Okamoto[1], Aiichiro Nagaki[1] (1. Department of Chemistry, Faculty of Science, Hokkaido University)

🏷 Japanese
10:00 AM - 10:10 AM JST | 1:00 AM - 1:10 AM UTC
[[F]2401-2am-07]

Development of chemoselective aerobic oxidation enabled by flow reaction system

○Kyoko Mandai[1,2], Kazuhiro Okamoto[1], Hiroki Mandai[2], Aiichiro Nagaki[1] (1. Department of Chemistry Faculty of Science, Hokkaido University, 2. Department of Pharmacy, Faculty of Pharmacy, Gifu University of Medical Science)

10:10 AM - 10:30 AM JST | 1:10 AM - 1:30 AM UTC

Break

🏷 Japanese
10:30 AM - 10:40 AM JST | 1:30 AM - 1:40 AM UTC
[[F]2401-2am-08]

Development of Polymer-supported Triarylmethyl Cations for Photocatalytic Reactions

○Kazumichi Maeda[1], Tomoya Hisada[1], Yasuhiro Yamashita[1], Shu Kobayashi[1] (1. The University of Tokyo)

🏷 Japanese
10:40 AM - 10:50 AM JST | 1:40 AM - 1:50 AM UTC
[[F]2401-2am-09]

Polymer Mechanochemistry in Wet Bead Milling

○Yuho Kinbara[1,2], Haruro Ishitani[2], Shū Kobayashi[2] (1. Mitsuichemicals Inc., 2. The University of Tokyo)

🏷 Japanese
10:50 AM - 11:00 AM JST | 1:50 AM - 2:00 AM UTC
[[F]2401-2am-10]

Solid-State Béchamp Reduction Using Mechanochemistry and Its Application to Synthesis of Boacalid

○Asahi Nagao[1], Kubota Koji[1,2], Hajime Ito[1,2] (1. Graduate School of Engineering, Hokkaido University, 2. WPI-ICReDD, Hokkaido University)

🏷 Japanese
11:00 AM - 11:10 AM JST | 2:00 AM - 2:10 AM UTC
[[F]2401-2am-11]

Mechanochemistry-Directed Ligand Design Enabling Highly Efficient Solid-State Palladium-Catalyzed Conjugate Arylation

○Hina Shoji[1], Keisuke Kondo[1], Koji Kubota[1,2], Hajime Ito[1,2] (1. Graduate School of Engineering, Hokkaido University, 2. WPI-ICReDD, Hokkaido University)

🏷 Japanese
11:10 AM - 11:20 AM JST | 2:10 AM - 2:20 AM UTC
[[F]2401-2am-12]

Deprotection of benzyl group by mechanochemical Birch reduction with sodium metal

○NAOKI SHIZUKUISHI[1], Keisuke Kondo[1], Koji Kubota[1,2], Hajime Ito[1,2] (1. Graduate School of Engineering, Hokkaido University, 2. WPI-ICReDD, Hokkaido University)

🏷 Japanese
11:20 AM - 11:30 AM JST | 2:20 AM - 2:30 AM UTC

[[F]2401-2am-13]

Mechanochemistry-enabled transformation of *N*-sulfinyl imines to nitriles

○Tetsu Makino[1], Koji Kubota[1,2], Hajime Ito[1,2] (1. Graduate School of Engineering, Hokkaido University, 2. WPI-ICReDD, Hokkaido University)

🏷 Japanese

11:30 AM - 11:40 AM JST | 2:30 AM - 2:40 AM UTC

[[F]2401-2am-14]

Development of Mechanochemical Rieke Method

○Yamato Fukuzawa[1], Kouji Kubota[1,2], Hajime Ito[1,2] (1. Graduate School of Engineering, Hokkaido University, 2. WPI-ICReDD, Hokkaido University)

ホルミル基を有する有機リチウム種等価体の発生とフローインライン IR 法による観測

（北大院理 [1]・AGC 株式会社 [2]）○足立 萌衣 [1]、菊池 竜平 [1]、早乙女 広樹 [1,2]、永木 愛一郎 [1]

Generation and flow in-line analysis of formylated-aryllithium equivalent

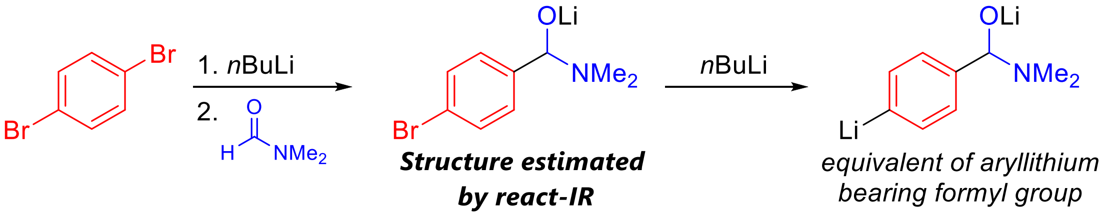
([1]*Department of Chemistry, Faculty of Science, Hokkaido University*, [2]*AGC Inc.*) ○Moe Adachi[1], Ryuhei Kikuchi[1], Hiroki Soutome[1,2], Aiichiro Nagaki[1]

Organolithium species generally have a low compatibility with electrophilic functional groups. With flow microreactors, we have successfully generated and reacted a range of short-lived aryllithium species. However, organolithium species bearing highly electrophilic substituents such as formyl groups are still difficult to generate, rendering conventional flow synthesis methods ineffective for these compounds. Inspired by the concept of Weinreb amides, we hypothesized that lithium alkoxide moieties, formed by a reaction of aryllithium species with DMF, could serve as “masked formyl groups” and thus act as equivalents of formyl-functionalized aryllithium species. Inline IR analysis of the reaction between mono-lithiated dibromoarenes with DMF suggested the formation of chemical species containing an anionic formyl-equivalent moiety. These intermediates could be lithiated to generate organolithium species bearing formyl-equivalent groups.

Keywords : flow microreactor; in-line IR; Formyl groups

有機リチウム種は様々な有機合成反応に活用されるが、求電子性官能基の許容性が低い。我々は反応時間をミリ秒スケールで精密に制御可能なフローマイクロリアクターを活用し、種々の短寿命アリールリチウム種の発生と反応を達成している。しかし求電子性が極めて高いホルミル基などの置換基を有する有機リチウム種は発生させることすら困難であり、これまでのフロー合成法では対応できない。

最近我々は、求電子性官能基のアニオンマスク化によるジブロモアレーン類の二官能基化に取り組んでいる [1]。今回、ワインレブアミドに着想を得て、アリールリチウム種と DMF の反応により生じる、リチウムアルコキシド部位を「マスクされたホルミル基」として扱うことにより、ホルミル基を有するアリールリチウム種の等価体として合成利用可能と考え、検討を行った。ジブロモアレーン類のモノリチオ化により生じたアリールリチウム種と DMF との反応をインライン IR により分析したところ、アニオン性のホルミル基等価部位を有する化学種が発生していることが示唆された。本化学種は更なるリチオ化が可能であり、すなわちホルミル基の等価部位を有する有機リチウム種の発生が可能であった。



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[1] Ashikari, Y.; Kawaguchi, T.; Mandai, K.; Aizawa, Y.; Nagaki, A. *J. Am. Chem. Soc.* **2020**, *142*, 17039; Ichinari, D.; Ashikari, Y.; Mandai, K.; Aizawa, Y.; Yoshida, J.; Nagaki, A. *Angew. Chem. Int. Ed.* **2020**, *59*, 1567.

ジアニオン型有機リチウム種を用いたジブロモアレーン類の非対称カルボニル基導入法の開発

（北大院理[1]・AGC 株式会社[2]）○菊池竜平[1]・足立萌衣[1]・早乙女広樹[1,2]・永木愛一郎[1]

Unsymmetrical Carbonylation of Dibromoarenes Using Dianionic Organolithium Species

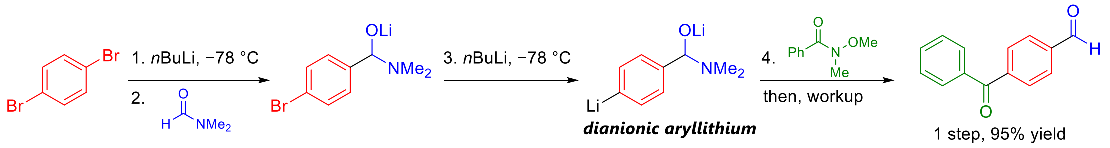
([1]*Department of Chemistry, Faculty of Science, Hokkaido University*, [2]*AGC Inc.*) ○Ryuhei Kikuchi,[1] Moe Adachi,[1] Hiroki Soutome,[1,2] Aiichiro Nagaki[1]

The introduction of carbonyl groups into aromatic compounds is exemplified by the carbonylation of aryllithium species with Weinreb amides. However, the generation of aryllithium species bearing highly electrophilic functional groups such as formyl groups is extremely challenging. As a result, conventional methods require the use of protecting groups, making it impossible to introduce multiple carbonyl groups in a single step. Recently, we discovered that the reaction between organolithium species and DMF produces intermediates containing an anionic equivalent of formyl groups.

In this presentation, we report the generation and reactions of dianionic aryllithium species formed through the monolithiation of dibromoarenes followed by reaction with DMF to yield an anionic intermediate, which is then further lithiated. By leveraging this method, we achieved one-pot, high-yield synthesis of aromatic compounds bearing asymmetric carbonyl groups, which previously required multi-step reactions in conventional methods.

芳香族化合物へのカルボニル基導入では、例えばアリールリチウム種とワインレブアミドによるカルボニル化が知られている。しかしホルミル基など求電子性官能基を持ったアリールリチウム種の発生が極めて困難なため、この方法で複数のカルボニル基を導入することはできず、保護基の導入が必要である。一方、最近我々は、有機リチウム種とDMF との反応により生じる中間体がアニオン性のホルミル基等価部位を有することを見出した[1]。

本講演ではこの特徴を活用したジアニオン種の発生と求電子剤との反応について発表する。すなわち、ジブロモアレーン類のモノリチオ化およびDMF との反応により発生させたアニオン性ブロモアレーン中間体に対し、再度リチオ化反応を行うことでジアニオン型のアリールリチウム種を発生させた。このアリールリチウム種はワインレブアミドなどの種々の求電子剤との反応が可能であり、ホルミル基を損なわずにカルボニル基の導入が可能であった。本手法を活用し、従来法では多段階反応が必要であった非対称なカルボニル基を有する芳香族化合物合成をワンポットかつ高収率で達成した。



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[1] 足立萌衣、菊池竜平、早乙女広樹、永木愛一郎　2025 日本化学会第 105 年会

フローマイクロ共存法を用いた有機リチウム反応における競争的並行および逐次反応制御

（北大院総合 [1]・北大院理 [2]）○岩田 真朋 [1]・芦刈 洋祐 [2]・永木 愛一郎 [2]
Selectivity control in competitive parallel and sequential organolithium reactions by flowmicro coexisting method ([1]*Graduate School of Chemical Sciences and Engineering, Hokkaido Univ.,* [2]*Faculty of Science, Hokkaido Univ.*) ○Masatomo Iwata,[1] Yosuke Ashikari,[2] Aiichiro Nagaki[2]

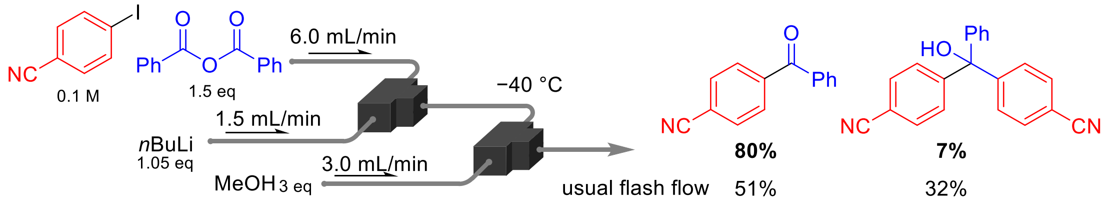
The reaction of highly reactive chemical species such as organolithiums can be controlled by employing flow microriactors.[1] We have recently studied flash co-existing chemistry where unstable organolithiums are generated and reacted in the presence of multiple electrophilic functional groups. We herein report that this methodology can control not only competitive parallel reactions but also competitive sequential reactions such as the reaction between organolithiums and acid anhydride.

Using a flow microreactor, a solution of 4-iodobenzonitrile and benzoic anhydride was mixed with *n*-butyllithium at −40 °C, affording the desired compound, 4-cyanobenzophenone in a high yield. This indicates that flash co-existing method prevents the over-reaction of the organolithiums with the product.

Keywords : Flow microreactor; Coexisting reaction; Competitive parallel reaction; Competitive sequential reaction; Acid anhydride

フローマイクロリアクターは有機リチウム種のような高反応性化学種を用いた高化学選択的反応が可能である [1]。最近我々は、フローマイクロリアクターの高化学選択性を活用した共存フラッシュケミストリー法を活用し、複数の求電子剤が共存する条件における有機リチウム反応に取り組んでいる [2]。今回、本手法により競争的並行反応に加えて競争的逐次反応を制御できることを見出した。

4-ヨードベンゾニトリルと安息香酸無水物の混合溶液をフローマイクロリアクター中、−40 °C で *n*-ブチルリチウムと混合したところ、目的物である 4-シアノベンゾフェノンが高収率で得られた。一方、同様の反応を従来の非共存フロー法で行ったところアルコール体が多く得られた。すなわち共存フラッシュケミストリー法の活用により、アリールリチウム種と安息香酸無水物との反応における過剰反応が抑制可能であることが示唆された。



1. Nagaki, A.; Imai, K.; Ishiuchi, S.; Yoshida, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 1914.
2. 岩田真朋, 芦刈洋祐, 永木愛一郎 日本化学会第 104 春季年会（2024）, E1143-3pm-04.

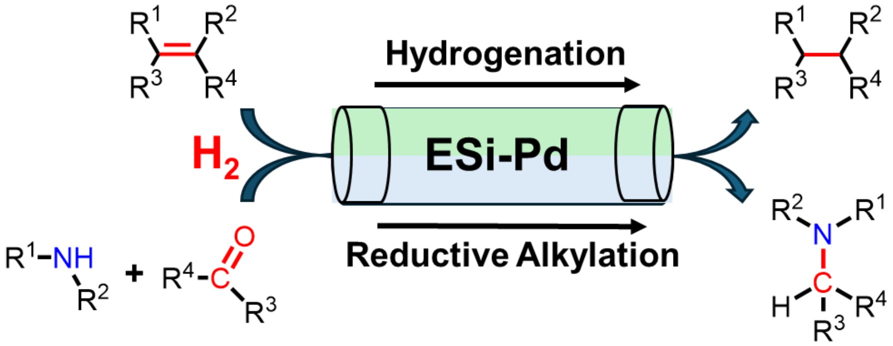
Development of Continuous-Flow Hydrogenation and Reductive Alkylation Using Highly Stable Etched Silicon Powder- Supported Palladium Catalyst

([1]*RIKEN Center for Sustainable Resource Science*, [2]*Graduate School of Science and Engineering, Saitama University*) ○Eman Soliman,[1,2] Zhenzhong Zhang,[1] Heeyoel Baek,[1] Yoichi M. A. Yamada[1,2]

Keywords: Flow Chemistry; Heterogeneous Catalyst; Reductive Alkylation; Hydrogenation; Palladium Nanoparticles

Development of solid-supported metal nanoparticle catalysts for continuous-flow organic transformation is important for modern synthetic organic chemistry. However, overcoming their deactivation owing to leaching and aggregation remains a challenge. Our team previously developed robust silicon nanostructure-supported metal nanoparticle catalysts for organic reactions.[1] Here, a more durable etched Si powder-supported palladium catalyst (ESi-Pd) was developed for continuous-flow hydrogenation of alkenes and reductive alkylation of amines.

ESi-Pd exhibited high stability and catalytic activity. Thus, continuous flow hydrogenation of various alkenes afforded the corresponding alkanes up to quantitative yield. Especially the hydrogenation of stilbene provided 1,2-diphenylethane quantitatively for 30 d consecutively. Moreover, the flow system was applied to a continuous-flow reductive alkylation of primary and secondary amines with aldehydes or ketones. This flow system was also applied to the synthesis of valuable compounds of (-)-menthol and donepezil.



(1) Accounts, see: (a) H. Baek, Y. M. A. Yamada, *Synlett* **2023**, *34*, 1739. (b) Y. M. A. Yamada, *Chem. Pharm. Bull.* **2017**, *65*, 805. Examples, see: (c) H. Baek, T. Sato, Y. Uozumi, Y. M. A. Yamada, *Eur. J. Inorg. Chem.* **2021**, 708. (d) T. Sato, Y. Uozumi, Y. M. A. Yamada, *ACS Omega.* **2020**, *5*, 26938. (e) Y. M. A. Yamada, H. Baek, T. Sato, A. Nakao, Y. Uozumi, Comms. Chem. **2020**, *3*, 81. (f) H. Baek, K. Kashimura, T. Fujii, S. Fujikawa, S. Tsubaki, Y. Wada, Y. Uozumi, and Y. M. A. Yamada, *ACS Catal.* **2020**, *10*, 2148. (g) Y. M. A. Yamada, Y. Yuyama, T. Sato, S. Fujikawa, Y. Uozumi, *Angew. Chem. Int. Ed.* **2014**, *53*, 127.

反応連続フロー合成によるオレフィン選択的接触水素化反応の検討

（徳島大院理工）○田島 美来・三好 徳好・上野 雅晴

Study on Olefin-Selective Catalytic Hydrogenation Reactions Using Continuous Flow Synthesis

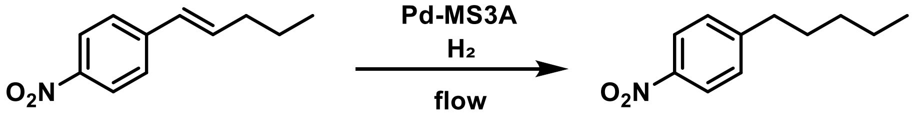
(*Graduate School of Science and Technology, Tokushima University*) ○Miku Tashima, Norikazu Miyoshi, Masaharu Ueno

HPCB-5 developed in our laboratory functions as an inhibitor of the ceramide transport protein, and we are conducting synthetic research aimed at mass supply for drug discovery and development. However, there were problems concerning selectivity and reproducibility in the olefin-selective catalytic hydrogenation reaction with substrates coexisting with nitro groups and olefins, which is necessary in the synthetic process. In recent years, heterogeneous palladium catalysts with reduced activity have been developed, enabling selective reduction of functional groups. On the other hand, it is difficult to control reaction conditions in large scale reactions due to technical problems, and there are issues related to selectivity and reproducibility. We investigated the reaction conditions for the continuous flow synthesis, which could precisely control the reaction. We have now succeeded in selective synthesis on a decagram scale, and will report on the details in this presentation.

Keywords : Continuous-flow; Green chemistry; Selective hydrogenation; Olefin; Decagram scale

当研究室で開発された HPCB-5 はセラミドを輸送するタンパク質の阻害剤として機能し、創薬開発に向けて大量供給を志向した合成研究を行っている1)。しかし合成過程においてニトロ基及びオレフィンが共存する基質でのオレフィン選択的接触水素化反応を行う必要があった。近年では、活性を低下させた不均一系パラジウム触媒が開発され官能基選択的な還元が可能となっている2)。一方、大スケールの反応においては技術的な問題から反応条件のコントロールが困難であり、選択性や再現性に関する課題があった。

そこで本研究では、連続フロー合成を用い精密な反応制御が可能と考え反応条件の検討を行った。現在デカグラムスケールでの選択的な合成に成功しており、講演ではその詳細を報告する。



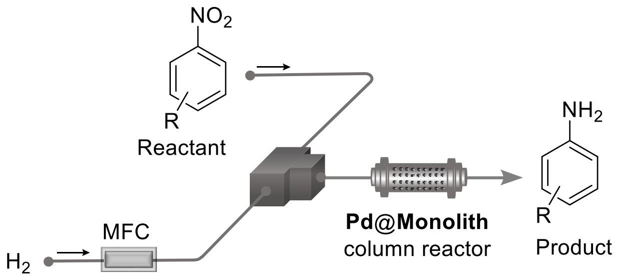
high selectivity

1) N. Nakano, M. Ueno, S. Sakai, D. Egawa, S. Kawasaki, K. Kumagai, M. Suzuki, K. Hanada, S. Kobayashi, *Communications. Chemistry*, **2019**, 2, Articlenumber:20;
2) T. Takahashi, M. Yoshimura, H. Suzuka, T. Maegawa, Y. Sawama, Y. Monguchi, H.Sajiki*,* *Tetrahedron Lett*., **2012**, *68,* 8293

Fast Reductive Transformation Reactions Enabled by Highly Active Monolithic Polymer-Supported Catalysts

([1]*Department of Chemistry, Faculty of Science, Hokkaido University*)
○Xianzhu Zhong[1], Kazuhiro Okamoto[1], Aiichiro Nagaki[1]

Keywords: Monolithic polymers; Palladium catalyst; Hydrogenation



Heterogeneous catalysts play a pivotal role in catalytic chemistry due to their unique advantages, however, their lower catalytic activity, resulting in slower reaction rates, has limited their application in processes demanding rapid and efficient synthesis. To address this limitation, this study introduces a novel approach combining the development of highly active heterogeneous catalysts with a methodology to control "reaction time and space." [1]

Monolithic polymers were engineered as high-surface-area supports with tailored active sites for immobilizing transition metals.[2] By screening various precursor monomers with functional groups and optimizing synthesis conditions, monoliths with different degrees of cross-linking, pore sizes, and surface areas were prepared. These modified monoliths were then combined with palladium to fabricate the Pd@monolith catalyst.

Using the Pd@monolith catalyst, a column reactor was designed for the reductive transformation of nitro compounds via a flow reaction system. Hydrogen, as the reducing agent, was delivered through a microflow controller, enabling precise regulation of reaction parameters such as time and temperature to maximize reaction efficiency. Unlike conventional batch reactions, flow reactions allowed for rapid reactant reduction within seconds and facilitated easy replacement of the catalytic column, enabling efficient screening of optimal catalysts for a variety of reactants.

This system also demonstrated high chemoselectivity and catalytic activity in the reductive transformation of challenging compounds with high steric hindrance, high polarity, or low solubility. By intricately controlling conditions such as temperature, reactant flow rate, and column length, this approach successfully overcame traditional limitations of heterogeneous catalysts, paving the way for broader applications in efficient and selective chemical transformations.

1) a) Vogt, C., Weckhuysen, B.M., *Nat. Rev. Chem.* ***2022**,* 6, 89. b) Timothy N. et al., *Chem. Sci.*, **2023**,14, 4230. 2) Miura, Y, et al., *Polymers* ***2022**, 14*, 5123.

フロー反応場が可能にする化学選択的空気酸化反応の開発

([1]北大院理、[2]岐阜医療科学大薬) ○萬代 恭子[1,2]、岡本 和紘[1]、萬代 大樹[2]、永木 愛一郎[1]

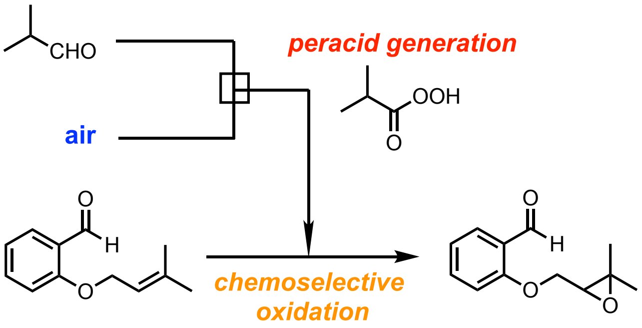
Development of chemoselective aerobic oxidation enabled by flow reaction system

([1]*Department of Chemistry Faculty of Science, Hokkaido University*, [2]*Department of Pharmacy, Faculty of Pharmacy, Gifu University of Medical Science*) ○Kyoko Mandai[1,2], Kazuhiro Okamoto[1], Hiroki Mandai[2], Aiichiro Nagaki[1]

Development of the reactions using air as the sole oxidant source is important in view of low cost, low environmental impact, and safe operation. Oxidation with air, however, are not practically viable when it is performed in a conventional batch reactor due to the low efficiency for gas–liquid mixing. Using our previously reported flow aerobic oxidation system, which was established for epoxidation of cyclohexene, the substrate with two oxidizable functional groups could not be oxidized efficiently because of internal generation of an active oxidizing agent. Based on the plausible reaction mechanism, we developed the flow system, consisting of the first part of peracid generation from isobutyraldehyde and air, and the latter part of subsequent oxidation of the substrate, to find the functional substrate was oxidized chemoselectively in controlled manner.

Keywords : aerobic oxidation; flow reactor; chemoselective oxidation

空気を酸化剤源として用いる反応の開発は、コスト削減、低環境負荷、安全性の観点から重要である。しかし、従来のバッチ型反応において実用的なレベルで空気を酸化剤源として利用することは気液混合の効率が低いため困難である。発表者らは、シクロヘキセンとイソブチルアルデヒドが共存する溶液と空気をフローリアクターで反応させることで、高速かつ高生産性の空気エポキシ化反応を開発している。[1]この反応システムにおいて基質適用範囲の拡大を目指し検討を開始したが、アルデヒドとプレニロキシ基をベンゼン環上に有する基質とイソブチルアルデヒドとの共存状態では基質の酸化反応が効率よく進行しなかった。そこで、推定反応機構に基づき、本研究では、フローリアクター内でイソブチルアルデヒドと空気から活性な過酸を効率よく発生させた後に基質の酸化反応に用いるという基質非共存条件下で関連する反応を段階的に行うことで、官能基選択的に酸化できることを見出したので報告する。



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高分子固定化トリアリールメチルカチオンの開発と光触媒反応への応用

(東大院理) ○前田一統・久田智也・山下恭弘・小林　修

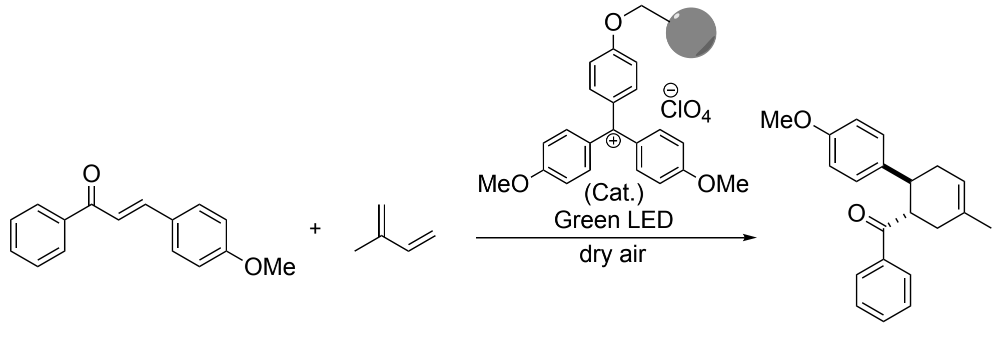
Development of Polymer-supported Triarylmethyl Cations for Photocatalytic Reactions

(School of Science, The Univ. of Tokyo) ○ Kazumichi MAEDA, Tomoya HISADA, Yasuhiro YAMASHITA, Shū KOBAYASHI

Photoreactions have attracted much attention as environmentally friendly reactions, and the immobilization of photocatalysts is important to achieve efficient photoreactions. In our previous research, we found that triarylmethyl cations promoted radical-induced [4+2] cycloaddition reactions in high yields with high regio- and diastereoselectivity. In this study, we investigated the immobilization of triarylmethyl cations on polymethacrylate, which is highly light permeable, for continuous-flow reactions. After examining polymer structures and counter anions, we found that the radical-induced [4+2] cycloaddition reaction proceeded with high yields and selectivity under optimal conditions. Also, the high catalyst activity was maintained after the 6th run in recovery and reuse experiments. Furthermore, by performing reactivation with perchloric acid, the catalyst activity was successfully recovered. In addition, the application to a continuous-flow reaction was also investigated. This presentation will report the details of these investigations.

Keywords: Heterogeneous catalyst; Organocatalyst; Cycloaddition; Photooxidation-reduction catalyst; Continuous-flow synthesis

光反応は、環境に優しい反応として注目されており、それらを促進する光触媒の固定化は、効率的な光反応を実現するために重要である。我々はこれまでに、トリアリールメチルカチオンが、可視光照射下でラジカル誘導型［4+2］環化反応を高収率、高選択的に進行させることを見出している。本研究では、この触媒の連続フロー反応への応用を志向し、光透過性が高いポリメタクリレートを担体として用いたトリアリールメチルカチオンの固定化を試みた。高分子構造やカウンターアニオン種などの諸条件を検討した結果、最適条件下でラジカル誘導型［4+2］環化反応を高収率、高位置選択的に進行させることを見出した。また、この触媒は、高収率を維持したまま少なくとも 6 回、回収・再使用することが可能であり、さらに、過塩素酸を用いた再活性化を行うことで、触媒活性を回復させることに成功した。さらに、連続フロー反応への応用も検討した。本講演では、これらの検討の詳細について報告する。



湿式ビーズミル装置におけるポリマーメカノケミストリー

（*三井化学株式会社*[1]・*東大院理*[2]・*東大院GSC社会連携講座*[3]）
○金原悠帆[1,2]・石谷暖郎[3]・小林修[2,3]

Polymer Mechanochemistry in Wet Bead Milling

(Mitsuichemicals Inc.[1], School of Science[2] and GSC Social Cooperation Laboratory[3], The Univ. of Tokyo)
○Yuho KINBARA[1,2], Haruro ISHITANI[3], Shū KOBAYASHI[2,3]

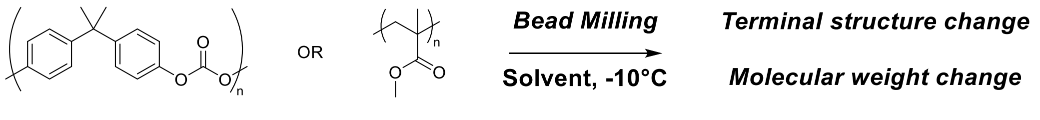
In mechanochemistry, where mechanical stress and force are used for molecular transformation, specific chemical phenomena on insoluble compounds occur such as reactions or molecular weight changes. Recently, various reactions have been reported using dry mechanochemistry, but wet mechanochemical achievable in bead milling performed in solvents, has not been sufficiently investigated. In this study, we focused on the molecular weight change of polymers by bead milling and attempted to apply wet mechanochemistry toward chemical recycling method for polymers.[1]

For polycarbonate, each solvent gave different molecular weight changes, but there was no correlation between the molecular weight and the yield of their depolymerization reaction. Similarly, for polymethyl methacrylate, different molecular weight changes were observed depending on the solvent, and the results of TG analysis confirmed a decrease in pyrolysis temperature due to lower molecular weight. A discussion of each result using mass spectrometry and solvent parameters will be reported.

Keywords *: Bead Mill, Mechanochemistry, Molecular weight control, Polymer, Chemical Recycling*

機械的応力を分子変換に利用するメカノケミストリーでは、難溶性化合物の反応や分子量変化等の特異な化学現象が起こる。近年では乾式メカノケミストリーでの分子変換が報告されているが、溶媒中で行われるビーズミルでの湿式メカノケミカル現象については十分な調査がなされていない。本研究ではポリマーのケミカルリサイクルへの適用を目的として、ビーズミルによる湿式メカノケミストリーが分子量変化に与える効果を検討した[1]。

ポリカーボネートを用いた検討では、溶媒ごとに異なる分子量変化を与えるが、分子量と解重合反応の収率に相関は見られなかった。ポリメタクリル酸メチルを処理した場合も同様に、選択する溶媒により異なる分子量変化が確認されたことに加え、TG 分析の結果では低分子量化による熱分解温度の低下を確認した。各結果について質量分析や溶媒パラメータを用いた考察を報告する。



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メカノケミカル法による固体 Béchamp 還元反応の開発とボスカリドの全工程メカノケミカル合成への応用

(北大院工 [1]・北大 WPI-ICReDD[2]) ○長尾 旭飛 [1]・久保田 浩司 [1,2]・伊藤 肇 [1,2]

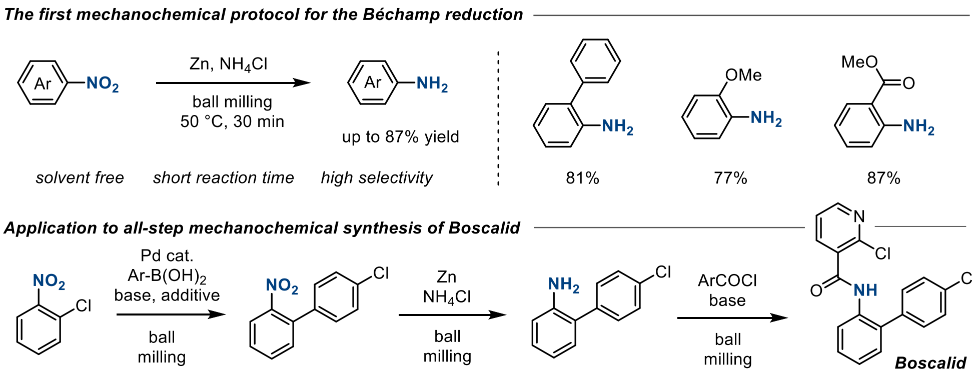
Solid-State Béchamp Reduction Using Mechanochemistry and Its Application to Synthesis of Boscalid.

([1]*Graduate School of Engineering, Hokkaido University,* [2]*WPI ICReDD, Hokkaido University*) ○Asahi Nagao[1], Koji Kubota[1,2], Hajime Ito[1,2]

The Béchamp reduction is a well-known method for reducing nitroarenes to aromatic amines using zero-valent metals. However, conventional approaches face challenges such as the requirement for large volumes of solvent, high temperatures, and prolonged reaction times.[1] In this study, we successfully developed a mechanochemical protocol for the Béchamp reduction using inexpensive Zn metal as a reductant. Notably, this newly developed solid-state protocol does not require an organic solvent, and all synthetic operations can be performed under ambient conditions. This reaction is considerably faster than previous solution-based reactions, and most nitroarenes were reduced within 30 min. Furthermore, we utilized this method to achieve the mechanochemical synthesis of Boscalid, which is widely used as a pesticide, showcasing its practical applicability.

Keywords : Mechanochemistry; Ball mill; Amine synthesis; Zinc; Nitro group

Béchamp 還元は 0 価金属を用いてニトロ基を還元する手法であり、芳香族アミンの代表的な合成法である。しかし、この既存の反応条件の多くは有機溶媒が必要である上、高温条件や反応時間が長い等の実用面での課題があった。本研究では、メカノケミカル法による安価な亜鉛金属を還元剤として用いた Béchamp 還元反応の開発に成功した [1]。本反応は有機溶媒を用いる必要がなく、すべての実験操作は空気下で実施可能である。また、この反応は従来の溶液条件での Béchamp 還元よりも非常に速く、多くの基質に対して 30 分以内で反応が完結した。さらに、本手法を活用することで、農薬として広く用いられるボスカリドの全工程メカノケミカル合成を達成し、本反応の合成化学的な有用性が示された。



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メカノケミカル合成を指向した触媒設計に基づくパラジウム触媒による固体共役アリール化反応の開発

（北大院工[1]・北大 WPI-ICReDD[2]）○庄司 陽菜[1]・近藤 恵祐[1]・久保田 浩司[1,2]・伊藤 肇[1,2]

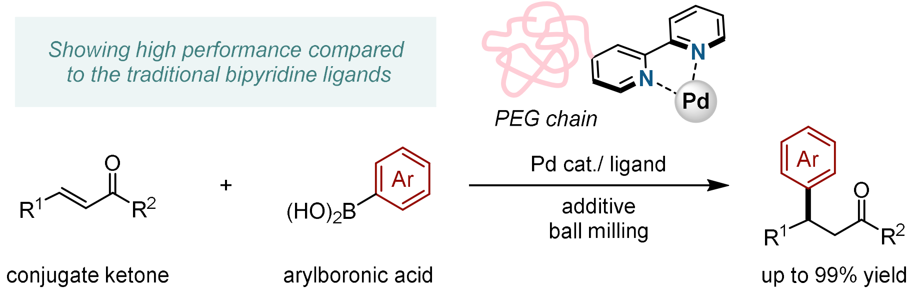
Mechanochemistry-Directed Ligand Design Enabling Highly Efficient Solid-State Palladium-Catalyzed Conjugate Arylation

([1]*Graduate School of Engineering, Hokkaido University*, [2]*WPI-ICReDD, Hokkaido University*) ○Hina Shoji,[1] Keisuke Kondo,[1] Koji Kubota,[1,2] Hajime Ito[1,2]

In our previous study, we found that phosphine ligands bearing poly(ethylene)glycol (PEG) chains were capable of promoting highly efficient mechanochemical palladium-catalyzed Suzuki–Miyaura cross-coupling reactions under mild conditions.1) In this study, motivated by this success, we developed a highly efficient mechanochemical conjugate arylation reaction catalyzed by palladium by designing novel bipyridine ligands with PEG chains. Traditional bipyridine ligands, which were used in the solution-based conjugate addition, showed poor catalytic activities under mechanochemical conditions. In contrast, the newly developed PEGylated bipyridine ligand facilitated the mechanochemical conjugate addition to give the desired arylated products in excellent yield. This mechanochemical arylation was fast and required only 60 min to complete the reactions for most substrates.

Keywords : Mechanochemistry; Conjugate Addition; Ball Mill; Palladium; Bipyridine Ligand

当研究室では以前、ポリエチレングリコール(PEG)鎖を導入したホスフィン配位子を用いることで、パラジウム触媒を用いたメカノケミカル鈴木-宮浦クロスカップリング反応が温和な条件下で効率良く進行することを報告した1)。本研究では、このメカノケミカル条件を指向した配位子設計に基づき、ビピリジン配位子に PEG 鎖を導入した新しい配位子を開発することによって、高効率なパラジウム触媒によるメカノケミカル共役アリール化反応の開発に成功した。従来の溶液条件で用いられているビピリジン配位子は、メカノケミカル条件において低い活性を示した。一方、新たに開発した PEG 型ビピリジン配位子を用いると、反応効率が大幅に向上することを見出した。本メカノケミカル反応は非常に速く、ほとんどの基質において 60 分で反応が完結した。



Ligand design enabling new mechanochemical reaction development

1) T. Seo, K. Kubota, H. Ito, *J. Am. Chem. Soc.* **2023**, *145*, 6823–6837.

メカノケミカル法によるバーチ還元型ベンジル脱保護反応

（北大院工 [1]・北大 WPI-ICReDD[2]）○雫石 尚輝 [1]・近藤 恵祐 [1]・久保田 浩司 [1,2]・伊藤 肇 [1,2]

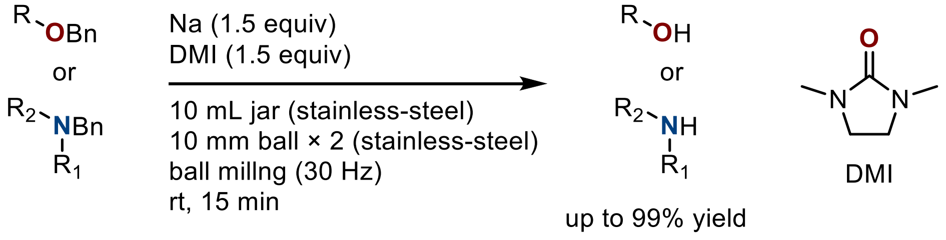
Deprotection of benzyl group by mechanochemical Birch reduction with sodium metal

([1]*Graduate School of Engineering, Hokkaido University*, [2]*WPI-ICReDD, Hokkaido University*)
○Naoki Shizukuishi,[1] Keisuke Kondo,[1] Koji Kubota,[1,2] Hajime Ito[1,2]

The benzyl group as well as its derivatives are widely adopted as protecting groups in organic synthesis. The Birch reduction has been widely used for deprotection of the benzyl groups, but traditional solution-based conditions often require a large excess amount of alkali metals, highly dehydrated conditions with relatively complex reaction set-ups, and large quantities of dry bulk solvents. Our group previously reported a mechanochemical protocol using ball milling for extremely fast Birch reduction using alkali metals under solvent-less, ambient conditions.[1,2] In this study, we developed a highly efficient debenzylation of alcohols and amines using an almost stoichiometric amount of sodium lump under solvent-less mechanochemical conditions. Notably, these reactions are rapid (within minutes) and generate the desired products in high yield at room temperature. Importantly, all synthetic operations can be carried out in air without special precautions against moisture and temperature control.

Keywords : Mechanochemistry, Ball Mill, Sodium, Debenzylation, Green Chemistry

ベンジル基およびその誘導体は有機合成における保護基として幅広く用いられている。バーチ還元反応は、ベンジル基の脱保護法として活用されているが、既存の溶液系条件では、基質に対して過剰量のアルカリ金属が必要となる場合が多い上、比較的複雑な反応セットアップおよび乾燥溶媒を用いた厳密な禁水条件が求められる。当研究室では以前、ボールミルによるメカノケミカル法を用いることで、バーチ還元反応が大幅に加速することを見出し、また省溶媒かつ空気下で実施可能なプロトコルの確立に成功した[1,2]。本研究ではこのメカノケミカル法を用いることで、基質に対して化学量論量の塊状ナトリウム金属による高効率なベンジル脱保護反応の開発に成功した。この反応は速やかに進行し、目的の脱ベンジル化体を高収率で与えた。特に、この条件では特別な水へのケアや温度制御などが不要であり、すべての実験操作は空気下で行うことができ、簡便に実施が可能であった。



1) Y. Gao, K. Kubota, H. Ito, *Angew. Chem. Int. Ed.* **2023**, *62*, e202217723.
2) K. Kondo, K. Kubota, H, Ito, *Chem. Sci.* **2024**, *15*,4452.

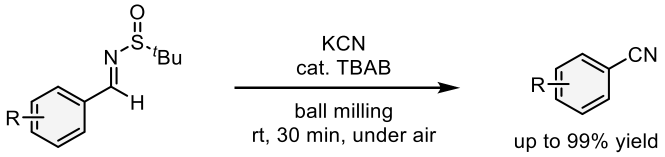
メカノケミカル法による *N*-スルフィニルイミンからニトリルへの変換反応

（北大院工 [1]・北大 WPI-ICReDD[2]）○牧野 哲 [1]・久保田 浩司 [1,2]・伊藤 肇 [1,2]
Mechanochemistry-enabled transformation of *N*-sulfinyl imines to nitriles ([1]*Graduate School of Engineering, Hokkaido University*, [2]*WPI-ICReDD, Hokkaido University*) ○Tetsu Makino,[1] Koji Kubota,[1,2] Hajime Ito[2]

Nitriles are important compounds found in pharmaceuticals and functional materials. One of their synthesis methods is the pyrolysis of *N*-sulfinyl imines that yields the corresponding nitriles. However, the conditions reported so far require considerably high temperatures and suffer from low functional group tolerance.[1–3] In this study, we found that *tert*-butanesulfinyl imines can be converted to corresponding nitriles under mild conditions at room temperature in the presence of potassium cyanide in DMSO. These reactions were rapid and completed within 30 min for most substrates. Furthermore, by employing a mechanochemical method[4,5] with a catalytic amount of tetrabutylammonium bromide (TBAB), this experimental procedure was simplified, eliminating the need for high-boiling point solvents in the reaction.

Keywords : Mechanochemistry; Ball mill; Solid-state reaction; Aldimine; Nitrile

ニトリルは、医薬品や機能性材料などに見られる重要な化合物である。その合成法のひとつに *N*-スルフィニルイミンの熱分解が知られているが、高温条件が必要であり、官能基許容性が低いという課題があった [1–3]。本研究では、*tert*-ブタンスルフィニルイミンを DMSO 溶媒中、シアン化カリウムと反応させることで、室温という穏和な条件で対応するニトリルに変換できることを見出した。本反応は速やかに進行し、ほとんどの基質に対して 30 分以内に完結した。さらに、ボールミルを用いたメカノケミカル法 [4,5] を本反応に適用したところ、触媒量のテトラブチルアンモニウムブロマイド (TBAB) を添加することで無溶媒条件での効率的なニトリル化も可能であることがわかった。この方法により、反応溶媒の削減や実験操作の簡便化を実現した。



✓ **mild conditions** ✓ **broad substrate scope**

✓ **solvent-free conditions** ✓ **simple operation under air**

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2) Mukade, T.; Dragoli, D. R.; Ellman, J. A. *J. Comb. Chem.* **2003**, *5*, 590.
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メカノケミストリーを用いた Rieke 法の開発

（北大院工[1]・北大 WPI-ICReDD[2]）○福澤 大和[1]・久保田 浩司[1,2]・伊藤 肇[1,2]

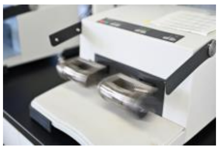
Development of Mechanochemical Rieke Method

([1]*Graduate School of Engineering, Hokkaido University*, [2]*WPI-ICReDD, Hokkaido University*)
○Yamato Fukuzawa,[1] Koji Kubota,[1,2] Hajime Ito[1,2]

The Rieke method is a practical protocol for producing highly reactive metal particles and has been widely used for the synthesis of a variety of organometallic compounds.[1-3] However, this method usually requires large amounts of toxic organic solvents, an inert gas atmosphere, and a strictly dehydrated environment, making the synthetic procedure very complicated. Our group has studied mechanochemical methods characterized by solvent-minimized conditions, short reaction time, and simple operation under air.[4-6] In this study, we attempted to overcome the drawbacks of the conventional Rieke method by developing a new, effective mechanochemical solid-state Rieke method. Details of the reaction conditions, surface observations of the metals through XPS analysis, and the application of the prepared active Rieke metals to organic synthesis will be discussed.

Rieke 法は、金属ハロゲン化物をアルカリ金属で還元することで高反応性金属パーティクルを発生させる方法であり、様々な有機金属化合物の合成に用いられてきた[1-3]。しかし、従来の条件では大量の有害な有機溶媒を用いる必要がある上、不活性ガス雰囲気や禁水環境が必須であり、煩雑な操作が求められる。当研究室では、ボールミルを用いたメカノケミカル反応について研究をしている。この方法は空気下で簡便に実施でき、溶媒使用量を最小限に抑制できるという特徴をもつ[4-6]。本研究では、従来の Rieke 法の欠点を克服することを目的に、ボールミルを用いたメカノケミカル合成法による新しい効率的な固体 Rieke 法の開発を検討した。本発表では、具体的な反応条件の検討結果や XPS 測定による金属表面の調査、および調製した活性金属の有機合成への応用の試みについて、詳細を報告する。

$$\mathrm{MX_n} + \text{alkali metal (Li, Na, K)} \xrightarrow[\text{ball milling}]{\text{additive}} \text{"Rieke M"}$$



- Solvent-minimized conditions
- Simple synthetic operation
- Short reaction time

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