アカデミックプログラム［Ｂ講演］｜15. 有機化学—脂肪族・脂環式化合物，新反応技術：口頭Ｂ講演

2025年3月27日(木) 13:00 ~ 15:20 [F]2403(第4学舎 2号館 [4階] 2403)

[[F]2403-2pm] 15. 有機化学—脂肪族・脂環式化合物，新反応技術

座長：山口 潤一郎、村上 翔

英語

13:00 ~ 13:20

[[F]2403-2pm-01]

多次元データ中の疎な領域の解析によるデヒドロアミノエステルへの光ラジカル反応の条件最適化

〇田上 湖都[1]、伊藤 貴之[1]、矢島 知子[1] (1. お茶の水女子大学)

英語

13:20 ~ 13:40

[[F]2403-2pm-02]

可視光触媒によるチロシン修飾のための生体適合型臭素化剤BODNの開発

〇吉田 楽人[1]、堀 雄一郎[2]、浦口 大輔[1]、浅野 圭佑[1] (1. 北大触媒研、2. 九大院理)

英語

13:40 ~ 14:00

[[F]2403-2pm-03]

α-アンモニオラジカルを鍵活性種とする第４級アンモニウム塩の変換

〇木之下 拓海[1]、榊原 陽太[1]、村上 慧[1] (1. 関西学院大学)

14:00 ~ 14:20

休憩

日本語

14:20 ~ 14:40

[[F]2403-2pm-04]

高効率的廃棄物フリー炭素—炭素結合生成反応の開発研究

〇山下 恭弘[1]、久田 智也[1]、小林 修[1] (1. 東京大学)

英語

14:40 ~ 15:00

[[F]2403-2pm-05]

塩基アシスト型光酸化還元触媒/コバルト触媒協働系によるDATを起点とした不活性アルケンの還元的多重水素化反応

〇鈴木 晶彦[1,2]、東田 皓介[2]、吉野 達彦[3]、松永 茂樹[1,2] (1. 北大院薬、2. 京大院理、3. 京大白眉センター)

英語

15:00 ~ 15:20

[[F]2403-2pm-06]

イミンアニオン型Smiles転位によるオルトヒドロキシフェニルケチミン合成とその応用

〇神野 峻輝[1]、高須賀(川崎) 智子[1]、森 啓二[1] (1. 東京農工大学大学院)

多次元データ中の疎な領域の解析によるデヒドロアミノエステルへの光ラジカル反応の条件最適化

（お茶女大院理）○田上 湖都・伊藤 貴之・矢島 知子

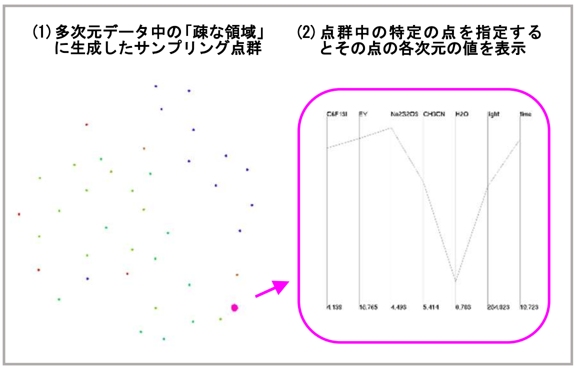
Reaction optimization for photo-induced radical reaction of dehydroamino esters through analysis of sparse regions in multidimensional data

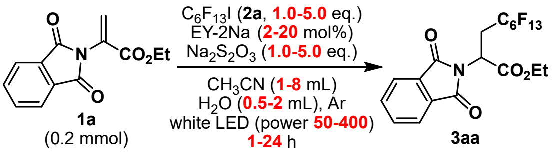
(*Department of Chemistry, Ochanomizu University*) ○Koto Tagami, Takayuki Itoh, Tomoko Yajima

In recent years, reaction optimizations that combine information science with organic chemistry has been attracting attention. One efficient way to reduce the number of experiments is to visualize untried experimental settings among multidimensional parameters and select reaction conditions that are likely to produce good results based on the experimenter's own experience. In this presentation, we propose a method to visualize "sparse regions" by placing a large number of sampling points in low-density regions in multidimensional space. We applied this method to the optimization of reaction conditions for the photo-induced radical hydro-perfluoroalkylation reaction of dehydroamino esters.

Keywords : Reaction Optimization; Multidimensional Data Analysis; Visualization; Dehydroamino Esters; Photo-Induced Radical Reaction

反応条件探索での実験回数削減のために、有機化学に情報科学を組み合わせることが注目されている[1]。特に、複数変数の同時探索において未実施の実験条件を可視化し、実験者が自らの経験則と照らし合わせて良好な結果が得られそうな設定を選択することができれば、効率の良い反応条件探索が可能となる。我々は、多次元空間における低密度領域に多数のサンプリング点を配置することで「疎な領域」を可視化する手法を開発した[2]。今回、この手法をデヒドロアミノエステルへの光ラジカルヒドロペルフルオロアルキル化反応の条件最適化に適用した。





α-エチルフタルイミドアクリレート (**1a**、0.2 mmol) に対してヨウ化ペルフルオロヘキシルを **1.0–5.0** 当量、エオシン Y-2Na を **2–20** mol%、チオ硫酸ナトリウムを **1.0–5.0** 当量、アセトニトリルを **1–8** mL、水を **0.5–2** mL、白色 LED の照射強度を **50–400**、反応時間を **1–24** 時間に設定し、これら 7 つのパラメーターの同時探索と最適化を試みた。

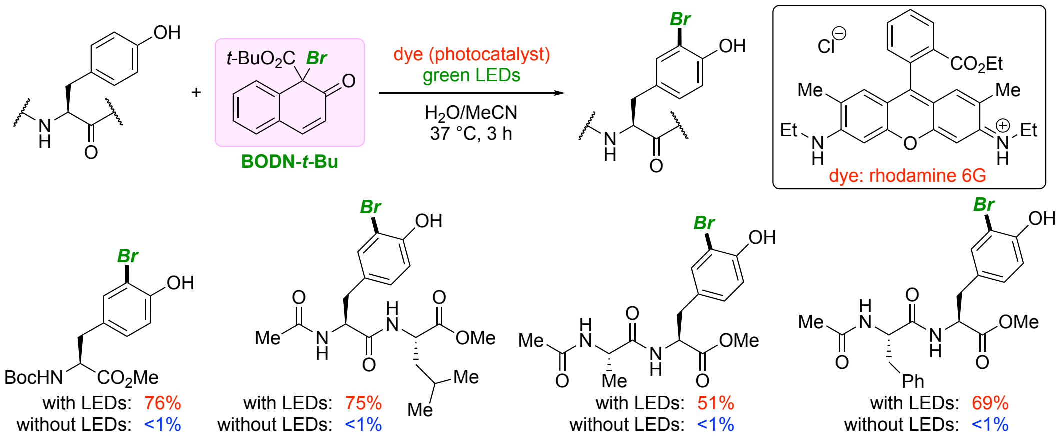
1) K. Tagami, M. Kondo, S. Takizawa, N. Mase, T. Yajima, *J. Fluorine Chem*, **2024**, 276, 110294.
2) 伊藤貴之、田上湖都、矢島知子、李国政、第 32 回インタラクティブシステムとソフトウェアに関するワークショップ(WISS)、3-A12、**2024**.

BODNs as Biocompatible Brominating Reagents for Visible-Light Photocatalytic Tyrosine Modification

([1]*Institute for Catalysis, Hokkaido University*, [2]*Department of Chemistry, Faculty of Science, Kyusyu University*, [3]*List Sustainable Digital Transformation Catalyst Collaboration Research Platform, Institute for Chemical Reaction Design and Discovery (ICReDD List-PF), Hokkaido University*) ○Rakuto Yoshida,[1] Yuichiro Hori,[2] Daisuke Uraguchi,[1,3] Keisuke Asano[1]

Keywords: Brominating Reagent; Visible Light Photocatalysis; Tyrosine Modification; Biocompatibility

Photocatalytic labeling of amino acid side chains in proteins is crucial for understanding significant biomolecular communications. However, amino acid residues with limited surface exposure, such as tyrosine, exhibit lower reactivity, resulting in decreased sensitivity in mass analyses of labeled molecules despite their biological importance. The bromo group serves as a sensitive mass tag that is valuable for analyzing complex macromolecules due to the relative abundance of bromine isotopes. However, biocompatible methodologies for photocatalytic bromination remain underdeveloped due to the lack of a brominating reagent, reactions of which can be catalytically controlled under biocompatible conditions. In this study, we investigated the photochemical reactivity of 1-bromo-2-oxo-1,2-dihydronaphthalene-1-carboxylates (BODNs).[1] These compounds remain stable in the dark under physiological conditions but become activated as brominating reagents under visible light irradiation in the presence of a catalyst during tyrosine modification. Photocatalytic reactions offer advantages such as the use of less invasive light with a longer wavelength as compared to non-catalytic reactions and the spatiotemporal control of bromination. In our reaction system, the fluorescent dyes commonly utilized in bioimaging probes serve as photocatalysts. This characteristic facilitates the applications of BODNs as chemical biology tools enabling the installation of attractive labeling tags on tyrosine-containing peptides and proteins.



1) Yoshida, R.; Hori, Y.; Uraguchi, D.; Asano, K. *Chem. Commun.* **2024**, *60*, 12381.

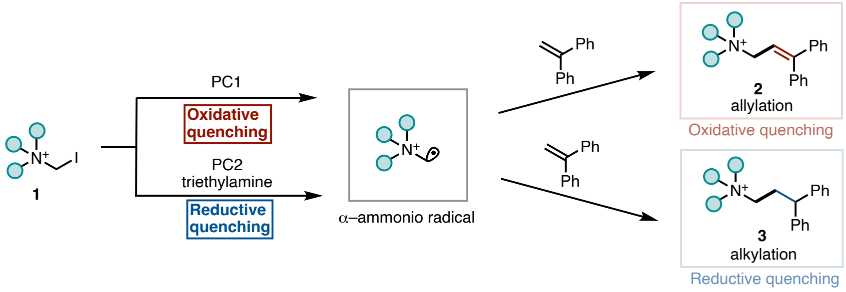
Diversification of ammonium salts via α-ammonio radical

(*Graduate Department of Chemistry, School of Science and Engineering, Kwansei Gakuin University*)
○Takumi Kinoshita, Yota Sakakibara, Kei Murakami

Keywords: photoredox catalyst; radical; ammonium salt; deuteration; salinity-tolerance

Nitrogen-containing compounds, especially quaternary ammonium salts, are ubiquitous in various high-value materials, such as pharmaceuticals, agrochemicals, and catalysts. However, the preparation of these compounds is limited to the reactions of tertiary amines. If ammonium salts can be converted into other ammonium salts, the discovery of novel classes of potential bioactive molecules can be accelerated. Herein, we report new synthetic methods for the preparation of these compounds through diversification of quaternary ammonium salts.1) The key active species in our reactions is the distonic α-ammonio radical, which is generated via photoredox catalysis (PC). Notably, we achieved the generation of α-ammonio radical by two different mechanisms of PC: oxidative quenching and reductive quenching.

Two types of radical generation mechanisms allowed us to control products of reactions between ammonium salt **1** and olefins. Under oxidative quenching conditions, ammonium salt **1** is direct one electron reduced by PC, and allylation occurs to afford product **2**. On the other hand, under reductive quenching conditions, triethylamine is one electron oxidized by PC, and generated radical abstracts iodine atom from ammonium salt **1**, thus, this condition produces alkylation product **3**.2) These two types of products are produced efficiently with high selectivity. This procedure was applied to the derivatization of bioactive quaternary ammonium salts and tertiary amines, spiro-cyclic ammonium salts, and the identification of salinity-tolerance-conferring molecules.



1) Kinoshita T.; Sakakibara, Y.; Hirano, T.; Murakami K. *Chem* in press. DOI:10.1016/j.chempr.2024.11.004
2) Constantin, T.; Leonori, D. *et al. Science* **2020**, 367, 1021–1026.

高効率的廃棄物フリー炭素―炭素結合生成反応の開発研究

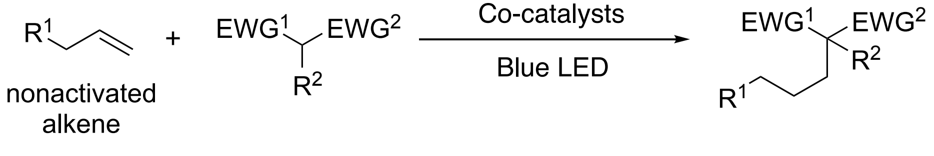
(東大院理) ○山下恭弘・久田智也・小林 修

Development of Highly Efficient and Waste-free Carbon–Carbon Bond Forming Reactions (School of Science, The Univ. of Tokyo) ○ Yasuhiro YAMASHITA, Tomoya HISADA, Shū KOBAYASHI

In modern society, the transition of the chemical industry to environmentally friendly synthetic methods is crucial for addressing global environmental issues. We are currently focusing on the development of efficient and waste-minimizing carbon–carbon bond forming reactions, which are essential for constructing the fundamental frameworks of organic compounds. Addition-type alkylation reactions using alkenes as electrophiles at the α-position of carbonyl compounds are important in organic synthesis from the viewpoint of atom economy. However, reactions utilizing nonactivated alkenes such as 1-decene, which lack electron-withdrawing groups (EWGs), have been extremely challenging due to their low electrophilicity. Recently, we have successfully achieved the alkylation of active methylene compounds with nonactivated alkenes under blue light irradiation by using a small amount of the organophotocatalyst 4CzIPN and a metal thiophenoxide catalyst. This reaction represents one of the most practical and ideal alkylation reactions. However, further expansion of the substrate scope and improvement in reactivity are desirable. This presentation will focus on our recent developments of new catalytic systems to promote this reaction.

Keywords: Photoalkylation reaction; Organophotocatalyst; Carbonyl compound; Alkene; Visible light

現代社会において、化学産業が環境調和型の合成手法へと転換することは、地球環境問題の解決に向けて不可欠である。近年、我々は、反応時に発生する廃棄物を極力抑制する、有用な有機合成反応の開発に取り組んでおり、特に有機化合物の基本骨格を構築する炭素-炭素結合生成反応に焦点を当てている。カルボニル化合物の α 位で、アルケンを求電子剤として用いる付加型のアルキル化反応は、副生成物を生じないため、原子効率の観点から重要な反応である。しかし、電子求引基 (EWG) を持たない 1-デセンなどの不活性アルケンを用いた反応は、その低い求電子性のために、これまで非常に困難であった。最近、我々は、有機光触媒 4CzIPN と金属チオフェノキシド触媒を少量用いることで、不活性アルケンによる活性メチレン化合物などのアルキル化反応を、青色光照射下で実現することに成功した。この反応は、実用性の面からも理想的なアルキル化反応の一つと言える。しかし、基質適用範囲の拡大や反応性のさらなる向上が望まれる。本講演では、この反応を促進する新たな触媒系の開発に焦点を当て、最近の研究成果について報告する。



1) Yamashita, Y.; Kobayashi, S. *et al. J. Am. Chem. Soc.* **2023**, *145*, 23160.

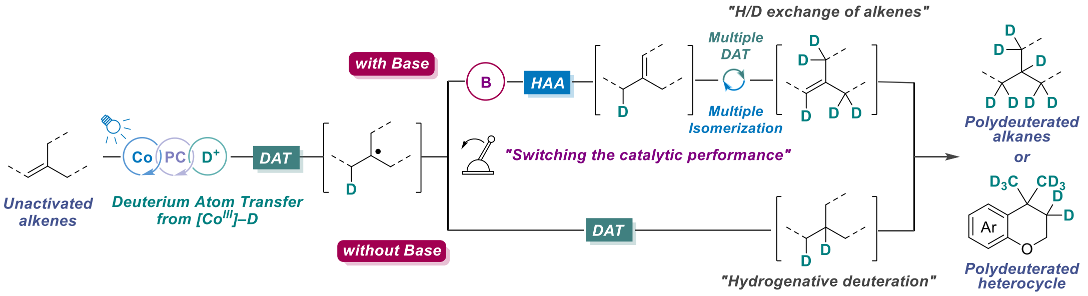
Multiple Deuterium Atom Transfer Perdeuteration of Unactivated Alkenes under Base-Assisted Cobalt/Photoredox Dual Catalysis

([1]*Graduate School of Pharmaceutical Sciences, Hokkaido University*, [2]*Graduate School of Science, Kyoto University,* [3]*The Hakubi Center for Advanced Research, Kyoto University*)
○Akihiko Suzuki,[1,2] Kosuke Higashida,[2] Tatsuhiko Yoshino,[2,3] Shigeki Matsunaga,[1,2]

Keywords: Deuteration, Late-stage functionalization, Cobalt catalysis, Photocatalysis

Recently, deuterium-labeled compounds have garnered increasing attention in drug discovery for their strategic potential to modify ADME properties.[1] Given this background, the development of new deuterium-labeling methodologies has witnessed significant advances in modern synthetic organic chemistry, but it remains difficult to construct polydeuterated aliphatic moieties at a late-stage.[2] To address this challenge, we propose leveraging our previously reported deuterium atom transfer (DAT) deuteration method[3] to synthesize inert polydeuterated alkanes from diverse alkenes.

In this study, we have newly developed the stepwise or one-pot perdeuteration of unactivated alkenes via multiple hydrogen atom abstraction (HAA) and multiple deuterium atom transfer (DAT) under base-assisted cobalt/photoredox dual catalysis.[4] The addition of a suitable base plays a key role in controlling two competing pathways—"H/D exchange" and "hydrogenative deuteration" of alkenes—by switching the catalytic performance of the cobalt/photoredox dual catalyst system. This radical mechanism-based approach enables the synthesis of various polydeuterated tertiary alkanes with high functional group tolerance, providing a complementary method to the pioneering hydrogenative perdeuteration reported by Milstein and co-workers[5]. Additionally, this method provides access to complex deuterium-labeled compounds, including polydeuterated amino acid and dipeptide derivatives, as well as pharmaceutical analogs. The presentation will also cover reaction mechanism analysis, details of the one-pot procedure, and several practical applications.



☑ *Mild conditions, Bulky alkenes, Late-stage, 34 examples*

1) Di Martino, R. M. C.; Maxwell, B. D.; Pirali, T. *Nat. Rev. Drug Discov.* **2023**, *22*, 562.
2) Kopf, S.; Bourriquen, F.; Li, W.; Neumann, H.; Junge, K.; Beller, M. *Chem. Rev.* **2022**, *122*, 6634.
3) Suzuki, A.; Kojima, M.; Matsunaga, S. *et al. Angew. Chem. Int. Ed.* **2023**, *62*, e202214433.
4) Suzuki, A.; Higashida, K.; Yoshino, T.; Matsunaga, S. *Under revision*.
5) Luo, J.; Lu, L.; Montag, M.; Liang, Y.; Milstein, D. *Nat. Chem.* **2023**, *15*, 1384.

Access to *ortho*-Hydroxyphenyl Ketimines via Imine Anion-Mediated Smiles Rearrangement and its Application

(*Graduate School of Engineering*, *Tokyo University of Agriculture and Technology*) ○Shunki Jinno, Tomoko Kawasaki-Takasuka, Keiji Mori

Keywords: *Smiles Rearrangement; Nucleophilic Aromatic Substitution; Imine Synthesis*

The imine structure is one of the most important structural motifs, which is found in numerous useful organic molecules such as ligands, biologically active molecules, and so on. Recently, we developed a novel synthetic method to the target structure via imine-anion mediated Smiles rearrangement.[1] The reaction has two characteristics: (1) easy modification of substituents on imino-carbon atom, and (2) access to *ortho*-hydroxyphenyl ketimines, whose effective synthetic approach is limited. This synthetic strategy can lead to various ketimines with bulky mesityl group, or even 9-anthryl one on imino-carbon atom. Products are also notable because these are quite tough to form by conventional condensation reaction between ketones and amines. Another intriguing feature is that reacting the bulky nucleophiles such as anthryl-, and 1-naphthyl-lithium enables a rearrangement of aryl rings such as electron-rich aryl groups and sterically hindered one, unsuited groups for $\mathrm{S_NAr}$-type reactions.[2] Obtained ketimines are good synthetic platform, and they could be transformed into a nitrogen-containing polycyclic aromatic compounds by Lewis acid-catalyzed photo-induced electrocyclic reaction.

Ketimine synthesis via imine anion-mediated Smiles rearrangement

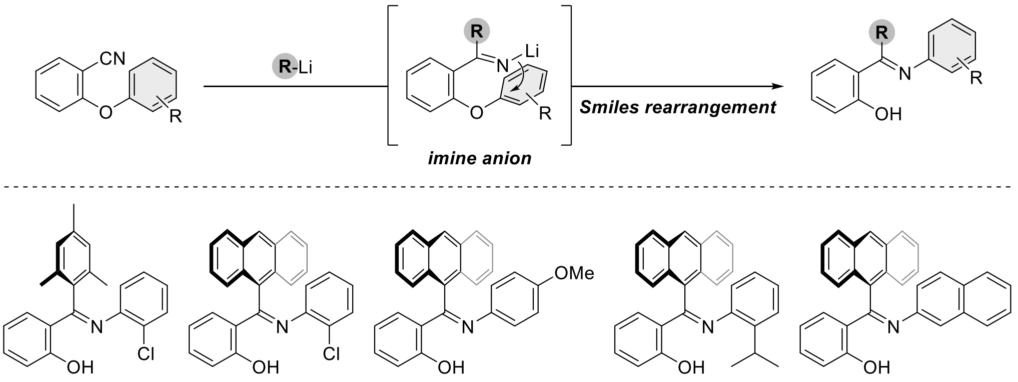
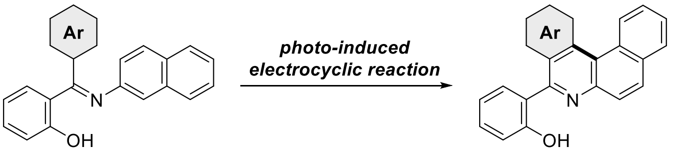


Photo-induced electrocyclic reacion for the formation of N-doped PAHs



1) Jinno, S.; Senoo, T.; Mori, K. *Org. Lett.* **2022**, *24*, 4140.
2) Jinno, S.; Kawasaki-Takasuka, T.; Mori, K. *Synlett* **2024**, *35*, 1565.