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研究課題名(和文) Selective C-H Bond Transformations via Single-Electron Transfer Processes

研究課題名(英文) Selective C-H Bond Transformations via Single-Electron Transfer Processes

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研究成果の概要(和文)：有機合成化学では、単純な化学原料から結合生成反応により複雑な有機分子を構築する事が極めて重要である。本研究では、炭素-炭素結合や炭素-ヘテロ原子結合を生成させる持続可能な新手法と触媒の開発を目指した。我々は一電子移動過程を活用した、反応性の高い有機分子や金属種の生成を基本概念として用いた。この二年間の研究により、我々は効率的に結合生成反応を進行させる様々な新規触媒系の開発に成功した。例えば、アミノ酸誘導体を含むアミン類のC-Hクロスカップリングを選択的に誘発する手法を見出した。また、クリーンで持続可能なエネルギー源である可視光を利用した、種々のクロスカップリング反応の開発にも成功した。

研究成果の概要(英文)：The construction of complex organic molecules from simple chemical feedstocks through bond forming reactions is the essence of synthetic organic chemistry. Our research is focused on developing new methods and catalysts that can be used to produce carbon-carbon and carbon-heteroatom bonds in a sustainable manner. The basic concept we wish to utilize is the power of single-electron transfer processes to generate reactive organic and metal species. Over the past two years, we have developed several new catalyst systems that enabled efficient bond forming reactions. For example, we have found methods to selectively induce C-H cross-coupling reactions of amines, including amino acid derivatives. In addition, we have harnessed the visible light, as a clean sustainable source of energy, to mediate various types of cross-coupling reactions.

研究分野：有機化学

キーワード：single-electron transfer visible light C-H functionalization cross-coupling copper catalysis photocatalysis

1. 研究開始当初の背景

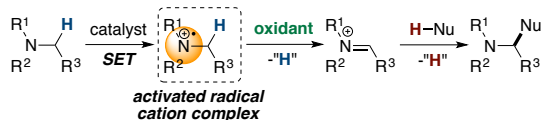
Synthetic organic chemistry is a fundamental science that is continuously evolving and improving in order to meet the constant demands posed by society for complex organic materials that improves the quality of our lives under efficient and cost-effective manner. As such, the development of efficient construction of carbon-carbon (C-C) bonds has occupied considerable time and effort of synthetic organic chemists. Recently, the use of simple C-H bonds as building blocks for cross-coupling reactions under oxidative conditions has emerged as an attractive and challenging goal (**Scheme 1**).

Scheme 1. Cross-dehydrogenative coupling reaction



The benefits of cross-dehydrogenative coupling (CDC) reactions lies in the fact that the direct use of C-H bonds has the potential to streamline synthetic approaches to complex organic molecules by eliminating the need for the preparation and isolation of activated substrates prior to the coupling event. In principle, the improvement in atom-economy, step-economy, and lower E factors ($\text{kg}_{\text{subproduct}}/\text{kg}_{\text{product}}$) of the cross-coupling reaction would result in lower cost and less waste. The challenges in CDC reactions are: (i) overcoming the low reactivity of C-H bonds; (ii) achieving site-selective functionalization; and (iii) finding mild, environmentally-friendly sacrificial oxidants. Despite these challenges, significant progress has been made in the area of oxidative cross-coupling reactions involving C-H bonds. The CDC reaction of the C-H bond adjacent to a nitrogen atom represents a remarkably effective strategy towards the realization of efficient C-C bond formation reactions (**Scheme 2**). The key mode of activation is the initial single-electron transfer (SET) process that generates the activated radical cation complex. Under oxidative conditions, this activated species is transformed into a reactive iminium ion intermediate that can be intercepted by a variety of nucleophiles to generate the desired C-C bond. Although numerous catalytic systems have been reported for the CDC reaction of tertiary amines, most systems relies on the use of N -aryl amines as substrates and peroxides as oxidants.

Scheme 2. Activation of α -hydrogen of amines via SET process



2. 研究の目的

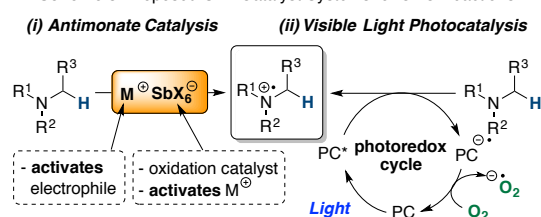
The purpose of this research is to develop new CDC reactions that can overcome the challenges faced in C-H cross-coupling reactions of amines,

such as the limited substrate scope and the need for strong oxidants. This will be achieved by inventing new catalysts.

3. 研究の方法

To achieve this goal, our initial plans are to investigate two different types of catalysts: (i) antimonate-based bifunctional metal complexes; and (ii) visible light photoredox catalysts (**Scheme 3**). In both cases, these new metal species are expected to facilitate the single-electron oxidation of the amine to generate the common reactive radical cationic intermediate.

Scheme 3. Proposed SET Catalyst Systems for CDC Reactions



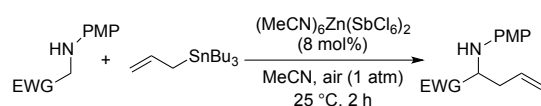
4. 研究成果

During the funding period, several cross-coupling reactions mediated catalysts that can facilitate SET processes were developed and are described below.

① Zinc(II) Antimonate-Catalyzed Oxidative Allylation of Glycine Derivatives

The C-H functionalization of glycine derivatives is one method of accessing various types of unnatural amino acids. To achieve this goal, we developed a bifunctional zinc antimonate catalyst that could facilitate the C-H allylation PMP-protected glycine esters and amides (**Scheme 4**). It was found that the antimonate anion enabled the aerobic oxidation of the amine to generate the imine intermediate, while the zinc played the role of a Lewis acid to catalyze the allylation reaction. In addition, we were able to demonstrate that this catalyst could be used to selectively functionalize the C-H bond adjacent to the PMP-protected nitrogen atom in a dipeptide substrate.

Scheme 4. Zn(SbCl₆)₂-Catalyzed Oxidative Allylation of Glycines

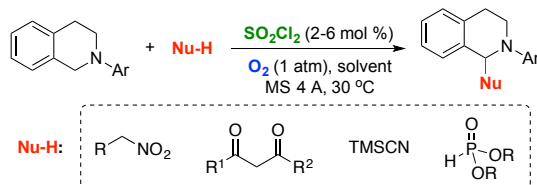


② Metal-Free Aerobic CDC Reactions of N -Aryl Tetrahydroisoquinolines

In order to understand the origin of the catalytic ability of antimonate anion (SbCl_6^-) for CDC reactions, we considered the possibility that it may act as a reservoir for the true catalyst, SbCl_5 . Since this is a well-known strong oxidant and an excellent electrophilic chlorinating reagent, we hypothesized that metal-free aerobic CDC

reactions of tertiary amines could be realized by using catalytic amounts of organic electrophilic halogenating reagents. Based on this consideration, we found that sulfuryl chloride (SO_2Cl_2) could act as an excellent catalyst that activated various *N*-aryl tetrahydroisoquinolines for CDC reactions with different types of pronucleophiles (**Scheme 5**). Although the exact mechanism has not been elucidated, based on control studies, we believe that the reaction occurs through a radical-initiated autoxidation mechanism. This catalyst system represents one of the most efficient and Green C-H functionalization reaction to date since only a catalytic amount of an inexpensive reagent is needed and the decomposition products of this catalyst can be easily removed by evaporation or aqueous work-up.

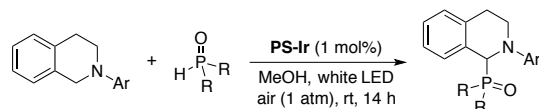
Scheme 5. SO_2Cl_2 -Catalyzed CDC Reactions of Tertiary Amines



③ Polymer-Supported Photocatalysts for CDC Reactions of *N*-Aryl Tetrahydroisoquinolines

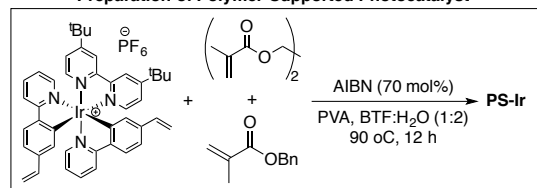
The use of sunlight as a renewable and clean source of energy to facilitate organic transformation represents a new frontier for environmentally sustainable organic chemistry. Recently, various types of metal polypyridyl complexes have been investigated as visible light photocatalysts for many types of organic reactions, including CDC reactions. Since many of these photocatalysts are expensive and toxic, the immobilization of these metal complexes to solid supports would lead to more safe and cost-effective reactions. With this in mind, we developed a new polymer-supported photocatalyst by using a well-established radical polymerization method and evaluated its effectiveness by using the CDC reaction as a case study (**Scheme 6**).

Scheme 6. Polymer-Supported Ir-Based Photocatalyst CDC Reactions



PS-Ir: Polymer-supported Ir photocatalyst

Preparation of Polymer-Supported Photocatalyst



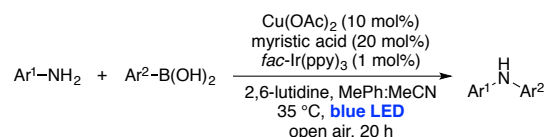
It was found that the polymer-supported photocatalyst enabled the CDC reaction to occur

in excellent yields and the catalyst could be recovered and reused up to five times without significant loss in yield and catalyst leaching.

④ Visible Light-Mediated Chan-Lam Coupling Reactions

Based on our experiences with using visible light photocatalysts to activate organic substrates via SET processes, we considered the possibility of utilizing these photocatalysts to modulate the oxidation states of transition metal catalysts. Based on this idea, we examined the productive merger between copper catalysis and photocatalysis to facilitate various types of C-N cross-coupling reactions. A well-known C-N bond forming process is the Chan-Lam coupling reaction, which the reaction between heteroatom nucleophiles and aryl boronic acids under oxidative conditions. Some of the major drawbacks of this reaction are: (i) the need to use (sub)stoichiometric amounts of copper; and (ii) limited substrate scope. We found that by introducing a visible light photocatalyst, some of these limitations could be solved (**Scheme 7**).

Scheme 7. Visible Light Mediated Chan-Lam Coupling Reaction

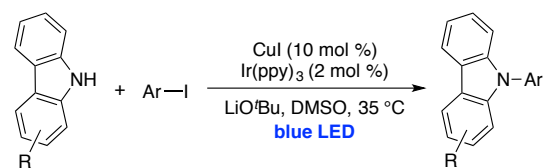


Visible light photocatalyst expands the substrate scope!

⑤ Visible Light-Mediated C-N Ullmann-Type Coupling Reactions

Continuing our efforts to expand upon the concept of combining copper catalysis with photocatalysis to perform challenging C-N cross-coupling reactions, we examined the coupling reaction between amines and aryl iodides. Typically, these C-N Ullmann-type reactions require harsh reaction conditions to generate the desired C-N bond. However, we found that by combining a simple copper salt with $\text{Ir}(\text{ppy})_3$ as a photocatalyst, the C-N Ullmann-type coupling reaction can be performed at room temperature (**Scheme 8**). While we were able to demonstrate the importance of combining the two catalysts, we also found that the reaction is limited to carbazole derivative and further investigations to improve the reaction is on-going.

Scheme 8. Visible Light Mediated C-N Ullmann-Type Reaction



5. 主な発表論文等

(研究代表者、研究分担者及び連携研究者に

は下線)

[雑誌論文] (計 5 件)

- ① "Visible Light-Mediated Ullmann-Type C-N Coupling Reactions of Carbazole Derivatives and Aryl Iodides" Woo-Jin Yoo, Tatsuhiro Tsukamoto, Shū Kobayashi, *Organic Letters*, **2015**, 17, 3640-3642. DOI: 10.1021/acs.orglett.5b01645. (peer-reviewed)
- ② "Visible Light-Mediated Chan-Lam Coupling Reactions of Arylboronic Acids and Aniline Derivatives", Woo-Jin Yoo, Tatsuhiro Tsukamoto, Shū Kobayashi, *Angewandte Chemie International Edition*, **2015**, 54, 5487-6590. DOI: 10.1002/anie.201500074. (peer-reviewed)
- ③ "Zinc(II) Hexachloroantimonate-Catalyzed Oxidative Allylation of Glycine Derivatives" Woo-Jin Yoo, Arata Tanoue, Shū Kobayashi, *Asian Journal of Organic Chemistry*, **2014**, 3, 1066-1069. DOI: 10.1002/ajoc.201402108. (peer-reviewed)
- ④ "Sulfuryl Chloride as an Efficient Initiator for the Metal-Free Aerobic Cross-Dehydrogenative Coupling Reaction of Tertiary Amines" Arata Tanoue, Woo-Jin Yoo, Shū Kobayashi, *Organic Letters*, **2014**, 16, 2346-2349. DOI: 10.1021/ol500661t. (peer-reviewed)
- ⑤ "Efficient Visible Light-Mediated Cross-Dehydrogenative Coupling Reactions of Tertiary Amines Catalyzed by a Polymer-Immobilized Iridium-Based Photocatalyst" Woo-Jin Yoo, Shū Kobayashi, *Green Chemistry*, **2014**, 16, 2438-2442. DOI: 10.1039/C4GC00058G. (peer-reviewed)

[学会発表] (計 2 件)

- ① "Visible Light-Mediated C-N Cross-Coupling Reactions Enabled by the Productive Merger of Copper and Photoredox Catalysis" Woo-Jin Yoo, Tatsuhiro Tsukamoto, Shū Kobayashi, *15th Tateshina Conference on Organic Chemistry*, Nagano, Japan, 2015.11.6-8. (poster)
- ② "Visible Light-Mediated C-N Cross-Coupling Reactions Enabled by the Productive Merger of Copper and Photoredox Catalysis" Woo-Jin Yoo, Tatsuhiro Tsukamoto, Shū Kobayashi, *18th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis*, Sitges, Spain, 2015.6.28-7.2. (poster)

[その他]

研究室ホームページ

<http://www.chem.s.u-tokyo.ac.jp/users/synorg/index.html>

6. 研究組織

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