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研究課題名(和文) Iron-Catalyzed C-H Activation using Organoboron Compounds

研究課題名(英文) Iron-Catalyzed C-H Activation using Organoboron Compounds

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研究成果の概要(和文)：我々は新規有機鉄触媒種を用いた、効率的、選択的かつ汎用性の高いC-H結合活性化反応の開発に取り組んだ。C(sp²)-H活性化反応においては、配位子とマイルドな有機金属化合物を用いることで鉄の還元を防止し、高原子価鉄触媒による様々なカルボキシアミドと有機金属試薬や求電子剤との直接型カップリング反応を達成した。また、三座ホスフィン配位子を設計することによる、鉄触媒を用いたケトンやカルボン酸などのC-H活性化反応の開発に成功した。C(sp³)-H結合に対しては、有機鉄種のラジカル・有機金属の二重反応性を利用し、アルキルアレーンのガンマC-H結合を選択的に変換することに成功した。

研究成果の概要(英文)：We have developed new organoiron catalytic species for efficient, selective, and versatile C(sp²)-H and C(sp³)-H bond functionalization. For C(sp²)-H activation, we used stabilizing ligands and a mild organometallic reagent in order to prevent reduction of iron to a highly reactive and difficult to control low-valent state, and we achieved a high-valent organoiron species that catalyzes the reaction of various carboxamides with organometallic reagents or with electrophiles. We also developed a triphosphine ligand that enables the iron-catalyzed activation of a variety of weakly coordinating substrates such as ketones or carboxylic acids. For the cleavage of a C(sp³)-H bond, we used the dual radical/organometallic reactivity of organoiron to achieve the remote functionalization of the gamma C-H bond in alkylarenes with high regioselectivity.

研究分野：有機合成化学

キーワード：有機合成

様式 C-19、F-19-1、Z-19、CK-19 (共通)

1. 研究開始当初の背景

Transition-metal-catalyzed C–H bond activation followed by the creation of a new C–C or C–heteroatom bond has received much attention recently, because it enables a streamlined approach to the synthesis of complex organic molecules. To date, most of these reactions rely on second- or third-row transition metals (most notably Pd, Rh, Ru). There is much interest in the development of sustainable catalysis using first-row transition metals such as iron, which is abundant, inexpensive, and non-toxic. However, at the start of this project, the reported iron catalytic systems for C–H activation relied on a low-valent iron species generated in situ by the reduction of an iron salt with a Grignard or diorganozinc reagent; the reactivity of this species was difficult to control, and fast deactivation and side reactions resulted in low catalyst efficiency and poor versatility.

2. 研究の目的

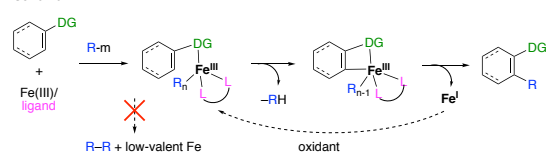
The purpose of the present research is to develop a new organoiron catalytic system and utilize it for efficient, selective, and versatile C(sp²)-H and C(sp³)-H bond functionalization.

3. 研究の方法

(1) Development of a high-valent organoiron species for catalytic C(sp²)-H activation

In order to solve the aforementioned problems of low-valent organoiron catalysis, I devised the strategy in Scheme 1: the use of stabilizing ligands and a mild organometallic reagent prevents reduction of iron to the difficult to control low-valent state, and a high-valent organoiron species catalyzes C–H activation with higher efficiency and versatility.

Scheme 1.

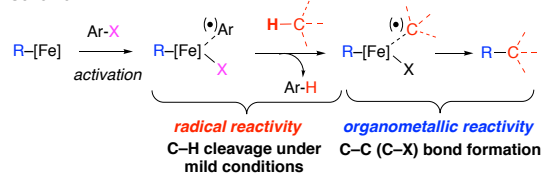


- ligand design: bidentate DG, diphosphine
- mild, less nucleophilic R-m (n = 1)

(2) Dual radical/organometallic reactivity of organoiron for catalytic C(sp³)-H activation

Because the cleavage of a C(sp³)-H bond by an organometallic complex is difficult, I envisioned a dual radical/organometallic strategy (Scheme 2): an organoiron species cleaves a C(sp³)-H bond in a radical manner under mild conditions, followed by creation of a new bond in an organometallic manner.

Scheme 2.

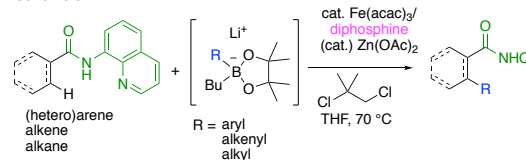


4. 研究成果

(1) Oxidative C–H functionalization of aromatic amides

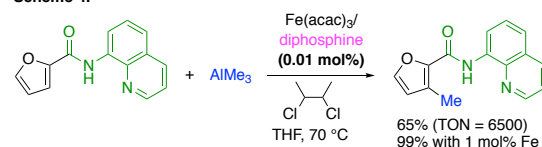
In order to prevent reduction and achieve the high-valent organoiron species described in Scheme 1, we found that the use of bidentate directing group, a diphosphine ligand, and a mild organoborate reagent is essential. Under these reaction conditions, a large variety of (hetero)arene-, alkene, and alkanecarboxamides reacted with aryl, alkenyl, and alkyl borates in high yield (Scheme 3, 発表論文 3, 11). The use of a zinc additive was essential to promote the difficult boron/iron transmetalation. Several mechanistic experiments confirmed the intermediacy of organoiron(III) species.

Scheme 3.



We also found that by using an even milder organoaluminum reagent, the methylation of carboxamides proceeded with high catalyst efficiency, surpassing precious metal catalysis (Scheme 4, 発表論文 9).

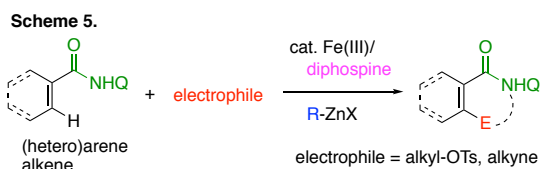
Scheme 4.



A similar strategy was used for the iron-catalyzed alkylation of carboxamides with alkylzinc halides, where β -hydride elimination of the alkyliron intermediate was largely suppressed (発表論文 10). These studies also inspired the development of a manganese-catalyzed C–H methylation reaction (発表論文 4).

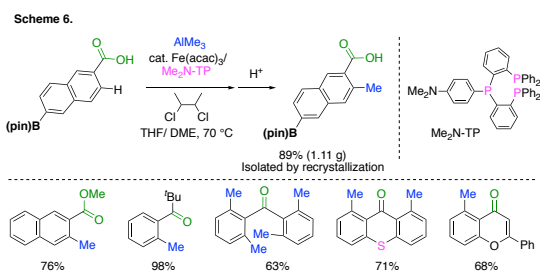
(2) Reaction of aromatic amides with electrophiles

By using the stabilizing ligands described in Scheme 1, the iron intermediate generated after C–H cleavage is stable enough to be reacted with electrophiles (Scheme 5). Thus, we developed the iron-catalyzed reaction of carboxamides with alkyl tosylates and halides (発表論文 12), and the cyclative reaction with alkynes (発表論文 1, 8).



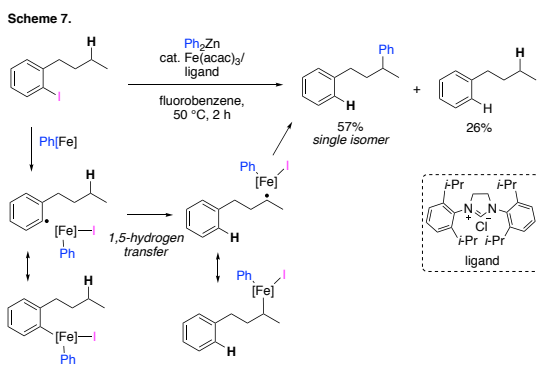
(3) C–H activation of weakly-coordinating aromatic substrates

The problem of the strategy depicted in Scheme 1 is the necessary use of a bidentate directing group, limiting the substrates to *N*-(8-quinolyl)carboxamides. In order to achieve a more general reaction, we designed a triphosphine ligand, which enabled the iron-catalyzed activation of a variety of weakly coordinating substrates such as ketones, carboxylic acids, esters, and amides (Scheme 6, 発表論文 7).



(4) Remote functionalization of a $C(\text{sp}^3)$ -H bond

Regioselective functionalization of a non-activated aliphatic C–H bond is a challenging task, because differentiation of C–H bonds having similar electronic and steric environments is very difficult. Based on the strategy depicted in Scheme 2, we achieved the iron-catalyzed phenylation of a remote γ -C–H bond in alkylarenes with high regioselectivity (Scheme 7, 発表論文 2). Mechanistic experiments suggested that an organoiron species transfers one electron to the aryl halide, and the resulting aryliron intermediate reacts in a radical manner and undergoes 1,5-hydrogen transfer to selectively cleave the γ -C–H bond.



5. 主な発表論文等

[雑誌論文] (計 15 件)

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② “Iron-Catalyzed Remote Arylation of Aliphatic C–H Bond via 1,5-Hydrogen Shift”, Bingwei Zhou, Hiroki Sato, Laurean Ilies, Eiichi Nakamura, *ACS Catal.* **2018**, 8, 8-11 (査読有) .

DOI: 10.1021/acscatal.7b03458

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④ “Manganese-Catalyzed Directed Methylation of $C(\text{sp}^2)$ -H Bonds at 25 °C with High Catalytic Turnover”, Takenari Sato, Takumi Yoshida, Hamad H. Al Mamari, Laurean Ilies, Eiichi Nakamura, *Org. Lett.* **2017**, 19, 5458-5461 (査読有) .

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DOI: 10.1021/acs.chemrev.6b00772

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⑩ “Iron-Catalyzed Directed Alkylation of Alkenes and Arenes with Alkylzinc Halides”, Laurean Ilies, Saki Ichikawa, Sobi Asako, Tatsuaki Matsubara, Eiichi Nakamura, *Adv. Synth. Catal.* **2015**, 357, 2175-2179 (査読有) . DOI: 10.1002/adsc.201500276

⑪ “Iron-Catalyzed C(sp²)-H Bond Functionalization with Organoboron Compounds”, Rui Shang, Laurean Ilies, Sobi Asako, Eiichi Nakamura, *J. Am. Chem. Soc.* **2014**, 136, 14349-14352 (査読有) . DOI: 10.1021/ja5070763

⑫ “Iron-Catalyzed Directed Alkylation of Aromatic and Olefinic Carboxamides with Primary and Secondary Alkyl Tosylates, Mesylates, and Halides”, Laurean Ilies, Tatsuaki Matsubara, Saki Ichikawa, Sobi Asako, Eiichi Nakamura, *J. Am. Chem. Soc.* **2014**, 136, 13126-13129 (査読有) . DOI: 10.1021/ja5066015

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② “C-H Activation Catalyzed by Earth Abundant Metals”, Laurean Ilies, The 9th OCARINA International Symposium, Osaka City University, Osaka, March 7-8, 2018 (招待講演) .

③ “Iron-Catalyzed C-H Bond Activation”, Laurean Ilies, The 67th Conference of Japan Society of Coordination Chemistry, Hokkaido University, Hokkaido, September 16-18, 2017 (招待講演) .

④ “Iron-Catalyzed C-H Bond Activation of Simple Substrates”, Laurean Ilies, International Symposium on Pure & Applied Chemistry 2017, Ho Chi Minh, Vietnam, June 8-10, 2017 (招待講演) .

⑤ “Iron-Catalyzed C-H Bond Activation”, Laurean Ilies, The 5th Keio Organic Chemistry Young Chemists Symposium, Keio University, Tokyo, April 22, 2017 (招待講演) .

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[図書] (計 1 件)

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6. 研究組織

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