Development of Organocatalytic Functionalizations of C-H Bonds
（有機分子触媒を用いた **C-H** 結合官能基化反応の開発）
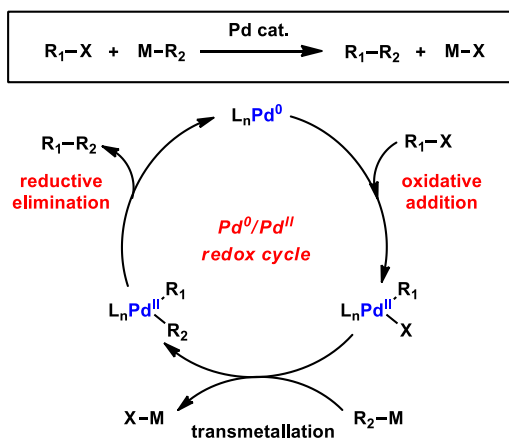
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Research background

　20th century has witnessed a substantial development of organometallic chemistry, not only in its basic understandings but also in its synthetic applications. As is evident from an example of Pd-catalyzed cross coupling reactions, redox behavior of transition metals is often indispensable for their catalytic activity (Figure 1). However, due to the rapid expansion of demands for metal resources along with industrialization and economic growth in the developing world, supply of transition metals is expected to be at risk. According to a survey by National Institute of Materials Science (NIMS), transition metals such as Mn, Fe, Co, Ni, Cu, Mo, Pd, Ag, W, Pt and Au are going to be running out within approximately 50 years. Therefore, in order to achieve sustainable development in the 21st century, novel alternative to metal catalysis is in high demand. In my Ph.D. course, I focused on two transition-metal-catalyzed C-H bond functionalization reactions, and developed two related organocatalytic transformations by utilizing organic compounds which facilitate redox processes. I believe that these **"redox organocatalysis"** would provide new prospects for the sustainable development of organic synthesis.

Figure 1. Pd as a redox mediator

(1) Metal-free C(3)-H arylation of coumarins promoted by catalytic amounts of 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin

　Coumarins represent desirable structural motif in synthetic drugs, natural products or probe molecules for chemical biology. A new functionalization method for coumarin skeleton would be hence beneficial, allowing facile access to its new derivatives. Cu-catalyzed Meerwein arylation is known as a classical method for C(3)-H arylation, but suffered from low yield (typically $< 50\%$).[1]

I anticipated that a metal-free porphyrin, which is a robust electron mediator in artificial photosynthesis,[2] could be a new organocatalyst for the one-electron mediated redox processes. Evaluation of porphyrin derivatives revealed that 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin **4e** worked as the most efficient catalyst for the metal-free Meerwein arylation (Figure 2). The reaction also proceeded under dark conditions, suggesting a thermal reaction pathway. Under the optimized conditions, the C-H arylated product **3a** was obtained in 63% yield. The reaction did not proceed in the presence of 10 mol% of *N,N*-diethylaniline, implying that the presence of porphyrin skeleton is indispensable.

Substrate scope study both on coumarin and aryl diazonium tetrafluoroborate revealed the high synthetic utility of the C-H arylation (Figure 3). Coumarins with

Figure 2. Evaluation of porphyrin derivatives

Figure 3. Metal-free C(3)-H arylation of coumarins by 4e

electron donating substituents (Me, OEt, OH, or NEt$_2$) afforded the product in good yield (61-78%). Unsubstituted, 4-methyl or 4-methoxy substituted aryl diazonium tetrafluoroborates were suitable for the transformation (70-78%), while aryl diazonium tetrafluoroborates with electron withdrawing substituents (halogen, ester, CF$_3$, or NO$_2$) afforded comparable yield (45-71%).

The one-electron redox of **4e** for the C-H arylation was supported by mechanistic studies. Radical detection experiments support the presence of aryl radical and benzyl radical intermediate in the reaction. In addition, an ICP analysis proved that contamination of metal impurities (Fe, Cu, Ti, Pd) in **4e** was below the detection limit. These results suggest that the present reaction is mediated by one-electron redox cycle of the porphyrin derivative (Figure 4).

In summary, I have developed the first organocatalytic *sp^2* C-H arylation of coumarins using metal-free porphyrin. The mild reaction conditions and high functional group tolerance provide access to versatile coumarin derivatives, making the method superior to previously reported Meerwein-type
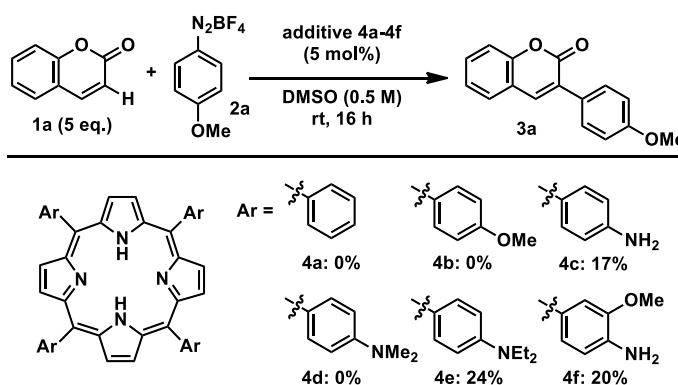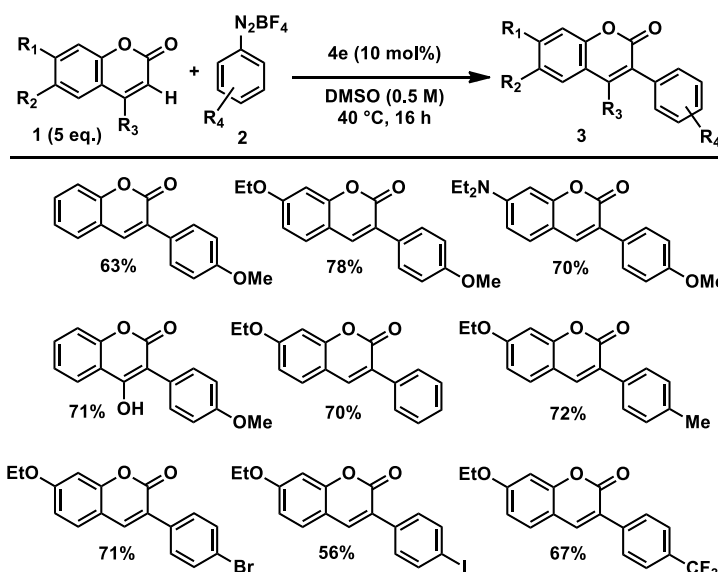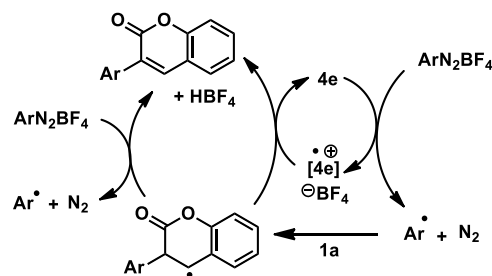
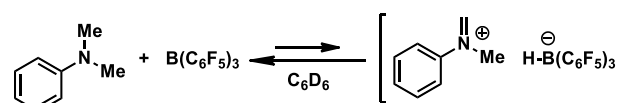**Figure 4. Plausible catalytic cycle**

arylations.[3]

(2) Tris(pentafluorophenyl)borane-catalyzed acceptorless dehydrogenation of N-heterocycles

Nitrogen containing heteroarenes are ubiquitous in pharmaceuticals, natural products, or synthetic materials. One desirable method for their synthesis is dehydrogenation of corresponding saturated N-heterocycles via sp^3 C-H functionalization. Among all, catalytic acceptorless dehydrogenation is attractive, because no external reagent is necessary and valuable molecular hydrogen is expelled during the desaturation. However, such catalytic systems are not widely appreciated in synthetic manipulations due to high cost, toxicity, and limited substrate generality of the conventional Ir catalysts.[4]
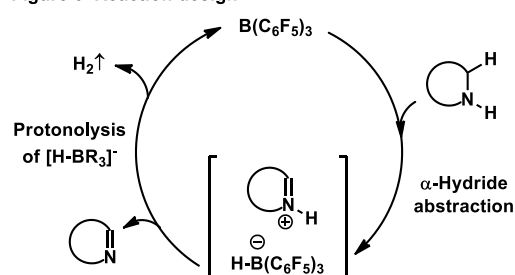
As a candidate for a synthetically benign catalyst, I focused on the chemistry of electrophilic organoboranes. In 2002, Basset reported that tris(pentafluorophenyl)borane abstracts hydride from α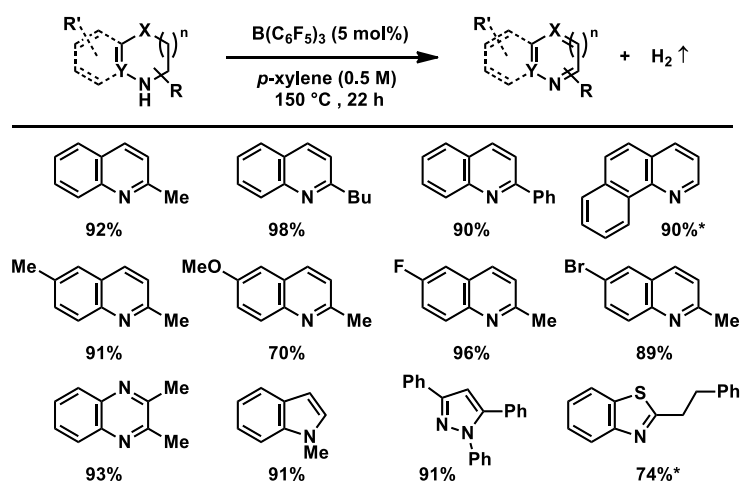-sp^3 C-H bond of *N,N*-dialkylaniline, and reversibly forms iminium-borohydride complex (Figure 5).[5] Based on this discovery, I hypothesized that catalytic acceptorless dehydrogenation of N-heterocycles should be possible in a scheme shown in Figure 6. First, α-hydride abstraction from sp^3 C-H bond of amines by electrophilic organoborane forms iminium-borohydride complex. Subsequent

Figure 5. α-Hydride abstraction of amines by B(C$_6$F$_5$)$_3$[5)]

Figure 6. Reaction design

protonolysis of the borohydride releases the desaturated amine and molecular hydrogen, regenerating the organoborane catalyst.

Gratifyingly, catalytic acceptorless dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline proceeded in 92% yield with 5 mol% of tris(pentafluorophenyl)borane (Figure 7). Release of hydrogen gas was also confirmed with a dual reactions experiment. Under relevant conditions, 2- or 8-substituted 1,2,3,4-tetrahydroquinolines were desaturated in good to excellent yield (67%-quant.). Other N-heterocycles such as tetrahydroquinoxalines, indolines, pyrazolines, and benzothiazolines were dehydrogenated in modest to excellent yield (45-93%). It is noteworthy that the borane catalyst exhibited higher reactivity for benzothiazoline compared to the [Cp*Ir(2-hydroxypyridine)] catalyst.[4] This result implies that the borane catalysis is uniquely tolerant to sulfur functionalities compared to metal

Figure 7. Borane-catalyzed acceptorless dehydrogenation of N-heterocycles

* 10 mol% of B(C$_6$F$_5$)$_3$ was used.

catalyzed counterparts.

The borane-catalyzed dehydrogenation was successfully applied to the transition-metal-free synthesis of a functional molecule (Figure 8). The heterobiaryl A, a synthetic intermediate for the O_2 probe, was previously synthesized by Pd-catalyzed Suzuki coupling. However, risk of contamination with toxic Pd should be avoided considering its biological applications. Following the method by Miyata,[6] the respective tetrahydroquinoline was prepared in

Figure 8. Transition-metal-free synthesis of a heterobiaryl

mitochondria-targeted O_2 probe

78% yield. Then, the metal-free catalytic dehydrogenation afforded the heterobiaryl in quantitative yield.

In summary, I have developed the first metal-free catalytic acceptorless dehydrogenation of N-heterocycles. As the borane catalyst is readily accessible and exhibits unprecedented chemoselectivity for a broader range of N-heterocycles, it offers explicit advantages relative to transition metal catalyzed reactions.[7] Application of the method to other sp^3 C-H functionalizations is currently in progress.

References

(1) Meerwein, H.; Buchner, E.; van Emster, K. *J. Prakt. Chem.* **1939**, *152*, 237. (2) Gust, D.; Moore, T. A.; Moore, A. L. *Acc. Chem. Res.* **2009**, *42*, 1890. (3) Kojima, M.; Oisaki, K.; Kanai, M. *Chem. Commun.* **2015**, *51*, 9718. (4) Yamaguchi, R.; Ikeda, C.; Takahashi, Y.; Fujita, K. *J. Am. Chem. Soc.* **2009**, *131*, 8410. (5) Millot, N.; Santini, C.C.; Fenet, B.; Basset, J. M. *Eur. J. Inorg. Chem.* **2002**, 3328. (6) Ueda, M.; Kawai, S.; Hayashi, M.; Naito, T.; Miyata, O. *J. Org. Chem.* **2010**, *75*, 914. (7) a) Kojima, M.; Kanai, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 12224; b) Maier, A. F. G.; Tussing, S.; Schneider, T.; Flörke, U.; Qu, Z.-W.; Grimme, S.; Paradies, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 12219.