Development of Greener Synthetic Routes to Functionalize Heteroarenes

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(官能基化ヘテロアレーンの環境調和的合成法の開発)

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【Introduction】

Heteroaromatic compounds have been known to be the most important structural units, found in many biologically active compounds.[1] Thiophene, furan and indole are most common heterocyclic scaffolds, which are widely used in synthesizing many pharmaceutical and medicinal compounds and to design various drug candidates. Thus it is of high interest to the organic chemists to functionalize such heteroarenes. In chapter 1, several literature reports have been described to make use of versatile synthetic routes for the catalytic functionalization of heteroarenes. In most cases, however, quantitative formation of waste product has been observed, which could be problematic for the development of environmentally benign synthetic methods.

【Contents】

1. Development of Mild and Selective Oxidative Heck Reaction to Derivatize Complex Molecules and Reactivity Study of Heteroarenes

【Purpose】

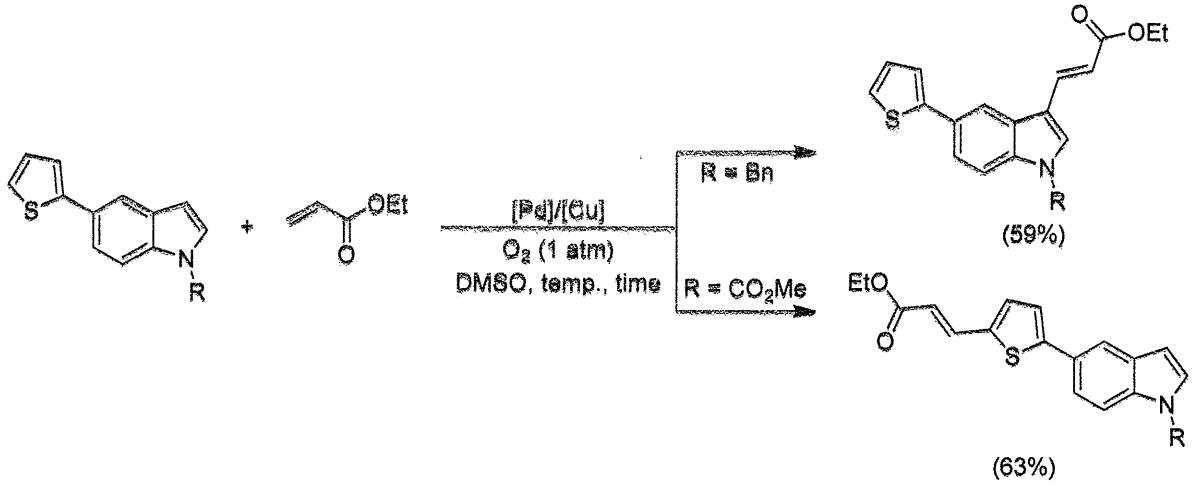
In this scope of study, I paid attention to work on mild oxidative Heck reaction to derivatize heteroaromatic substrates. In chapter 2, an oxidative Mizoroki-Heck reaction was examined that could proceed under mild and neutral condition without using a stoichiometric amount of the metal oxidant.[2] Catalytically generated H_2O_2 was only side product from this reaction and could be easily removed without any complex work up procedure. Thus successful development of environment friendly synthetics route was achieved.

【Method and Result】

After basic trials, the catalytic combination of $Pd(OAc)_2$ and $Cu(OAc)_2$ in the presence of molecular oxygen was found beneficial to promote the desired reaction. I studied the competitive reactivity of several electron-rich arenes and heteroarenes under the optimized reaction condition, where olefination proceeded selectively at the thienyl group over other electron rich arenes. Moreover, the reactivity of thienyl and indolyl groups in single molecules could be tuned by

changing protecting groups of indole (Scheme 1).

Scheme 1. Tuning Reactivity between Thiophene and Indole in a Single Molecule



Then, this methodology was successfully applied to the late-stage C-H functionalization (LCHF) of acid sensitive chiral drug duloxetine, as well as several complex natural and medicinal compounds containing various heteroarenes (Figure 1).

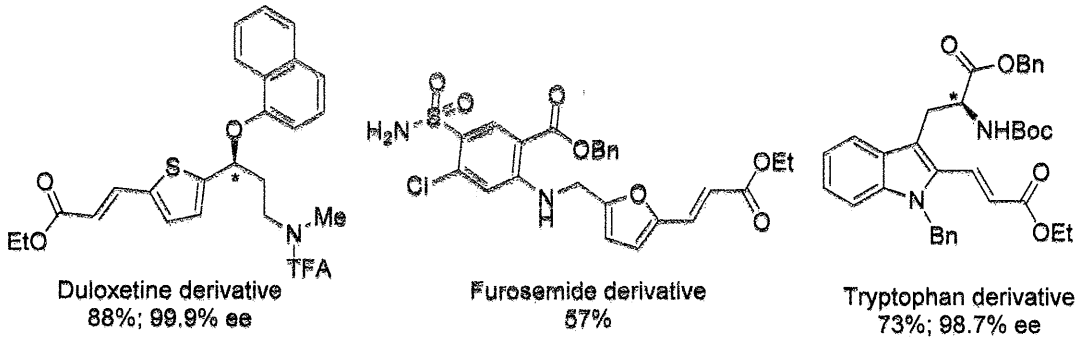


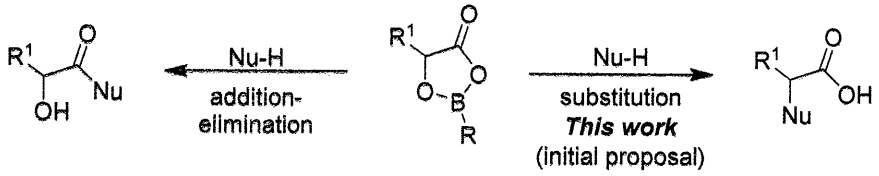
Figure 1. Application of LCHF to Functionalize Bioactive Complex Molecules

2. Boronic Acid-Accelerated Multicomponent Reactions for the Synthesis of α-Substituted Indole-3-acetic Acids

【Purpose】

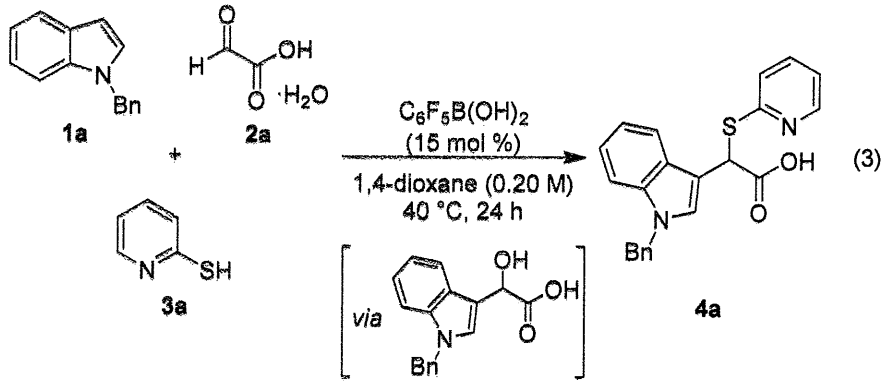
Boronic and boric acid-catalyzed transformations of carboxylic acids are well documented in literature.[3] In case of α-hydroxycarboxylic acids, boronic acid mediated esterification or amidation have been known to proceed *via* cyclic intermediate (eq. 1).[4] In chapter 3, I reported boronic acid-accelerated substitution of α-hydroxy group of carboxylic acids (eq. 2) in a

multicomponent reaction of heteroarenes, which could proceed at mild temperature and produced water as soul byproduct.[5]



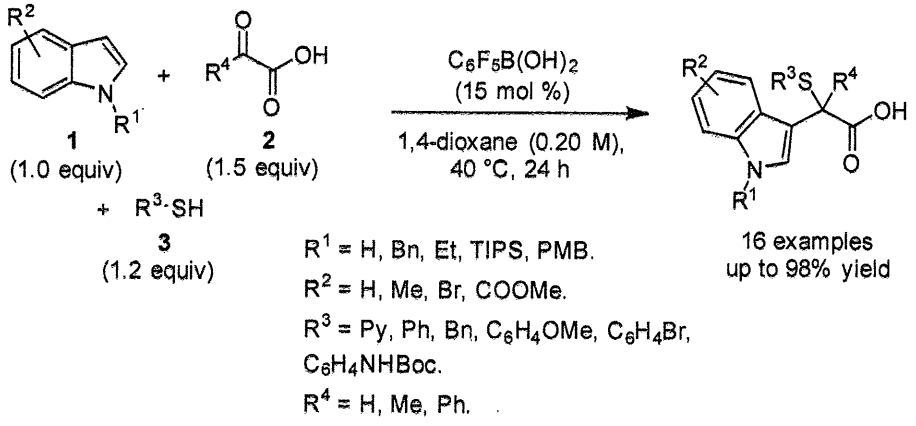
【Method and Result】

I have optimized the reaction condition with *N*-benzylindole, glyoxylic acid monohydrate and 2-mercaptopyridine by using pentafluorophenylboronic acid catalyst in 1,4-dioxane solvent and under mild reaction temperature (eq. 3).



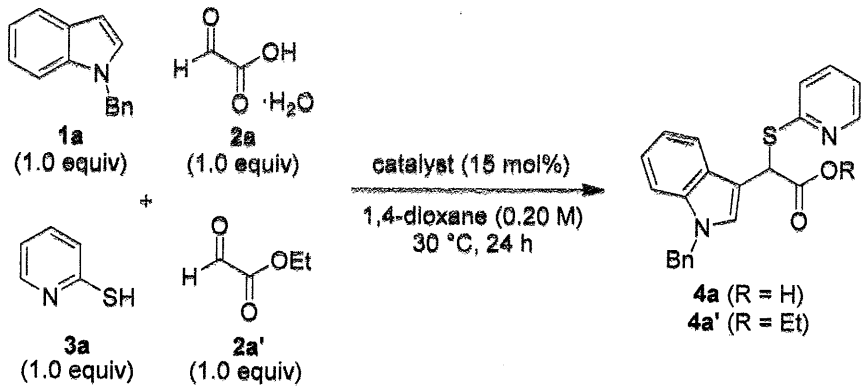
With the optimized condition in hand, I examined the substrate scope (Scheme 2). This reaction was well tolerated over various substituents on both indoles and thiols. I also achieved the construction of quaternary carbon center adjacent to carboxylic acid group by using pyruvic acid and phenyl glyoxylic acid.

Scheme 2. Substrate Scope for Indoles, Thiols and Glyoxylic Acids



Further chemoselective activation of glyoxylic acid over its corresponding ester was demonstrated (Scheme 3). Excellent Chemoselectivity was achieved with **4a** over **4a'** by using boronic acid catalyst, whereas rather strong acids (*p*-toluenesulfonic acid and phosphoric acid) promoted the reaction more slowly with reduced chemoselectivity.

Scheme 3. Chemoselective Reaction between Glyoxylic Acid and Its Ethyl Ester



catalyst	4a (%)	4a' (%)	4a/4a'
$C_6F_5B(OH)_2$	84	2	42/1
p-TsOH.H_2O	37	17	2.2/1
H_3PO_4 (1.0 equiv)	14	2	7/1

【References】

[1] For recent reviews, see: a) Martin, P.; Jesus, J.; Santos, S.; Raposo, L. R.; Roma-Rodrigues, C.; Baptista, P. V.; Fernandes, A. R. *Molecules* **2015**, *20*, 16852. b) El-salam, N. M. A.; Mostafa, M. S.; Ahmed, G. A.; Alothman, O. Y. *J. Chem.* **2013**, *2013*, 1.

[2] "Development of Oxidative Mizoroki-Heck Reaction for Late-Stage C–H Functionalization of Complex Molecules and Application to Pharmaceutical Studies." Watanabe, K.*; Das, A.*; Kimijima, T.; Yamashita, T.; Inoue, K.; Tsuda, M.; Ohshima, T. (Manuscript in Preparation, * equal contribution).

[3] For reviews see: a) Dimitrijević, E.; Taylor, M. S. *ACS Catal.* **2013**, *3*, 945. b) Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. *Chem. Soc. Rev.* **2014**, *43*, 2714.

[4] a) Yamashita, R.; Sakakura, A.; Ishihara, K. *Org. Lett.* **2013**, *15*, 3654. b) Houston, T. A.; Wilkinson, B. L.; Blanchfield, J. T. *Org. Lett.* **2004**, *6*, 679. c) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5047.

[5] "Boronic Acid-Accelerated Multicomponent Reactions for the Synthesis of α-Substituted Indole-3-acetic Acids." Das, A.; Watanabe, K.; Morimoto, H.; Ohshima, T. (Manuscript in Preparation).