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Development of Greener Synthetic Routes to Functionalize Heteroarenes

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論文題名　：Development of Greener Synthetic Routes to Functionalize Heteroarenes (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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論文審査の結果の要旨

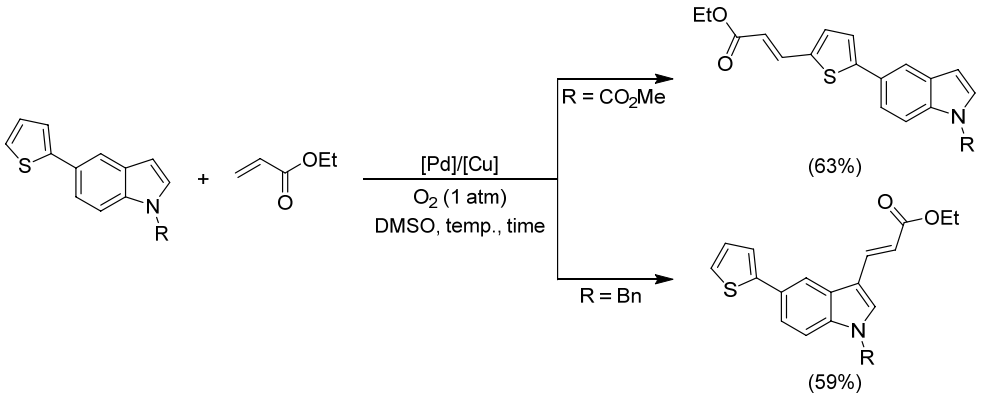
下記に示すように、論文提出者は(1)Pd 触媒による穏和な条件における化学選択的酸化的 Heck 反応の開発と医薬品の Late-Stage 官能基化への応用、(2)ボロン酸触媒による三成分連結反応の開発に成功しており、創薬化学にも応用可能な有用な合成法を提示したと言える。以上のことから、本学位請求論文は博士（創薬科学）の学位に値すると判断した。

[Introduction] Heteroaromatic compounds have been known to be the most important structural units, found in many biologically active compounds. 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. In this scope of study, I paid attention to work on mild oxidative Heck reaction to derivatize heteroaromatic substrates (Chapter 2). Catalytic generation of H_2O_2 was only side product from this reaction. I also have studied multicomponent reaction of heteroarenes catalyzed be aryl boronic acid which could proceed at mild temperature and produced water as soul byproduct (Chapter 3).

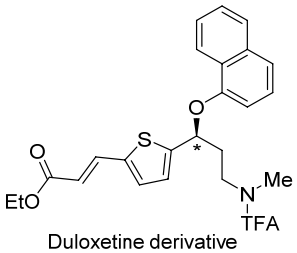
[1] Development of Mild and Selective Oxidative Heck Reaction to Derivatize Complex Molecules and Reactivity Study of Heteroarenes

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. 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).

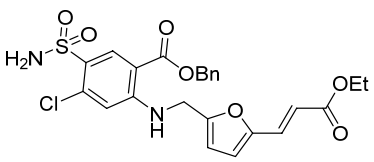
Scheme 1. Tuning Reactivity between Thiophene and Indole in a Single Molecule



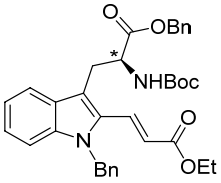
Then, this methodology was successfully applied to the late-stage C-H functionalization (LCHF) of acid sensitive chiral drug duloxetine, as well as several complex natural and medicinal compounds containing various heteroarenes.



Duloxetine derivative
88%; 99.9% ee



Furosemide derivative
57%

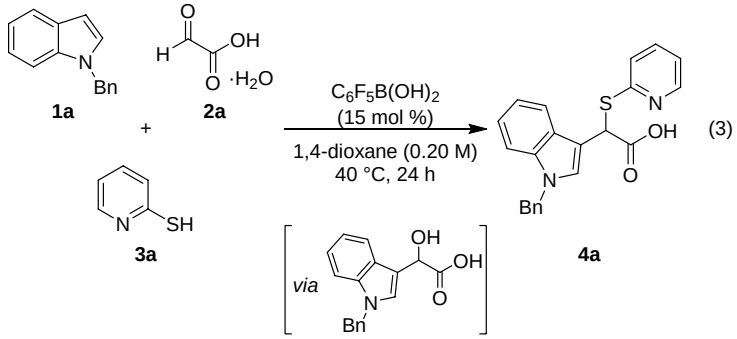


Tryptophan derivative
73%; 98.7% ee

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

Boronic acid mediated esterification or amidation of α-hydroxycarboxylic acids have been known to proceed via cyclic intermediate (eq. 1). In chapter 3, I reported boronic acid-accelerated substitution of α-hydroxy group of carboxylic acids in a multicomponent reaction (eq. 2).

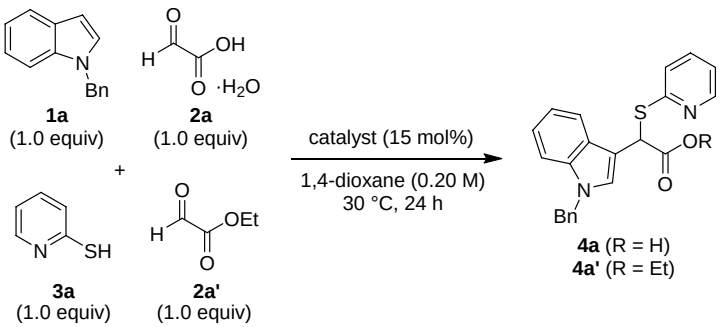
I have optimized the reaction condition with *N*-benzylindole, glyoxylic acid monohydrate and 2-mercaptopyridine by using pentafluorophenylboronic acid catalyst in 1,4-dioxane solvent and under mild reaction temperature (eq. 3). With the optimized condition in hand, I examined the substrate scope with various substituents on both indoles and thiols. I also achieved the construction of quaternary carbon centre adjacent to carboxylic acid group by using pyruvic acid and phenyl glyoxylic acid.



(3)

Further chemoselective activation of glyoxylic acid over its corresponding ester was demonstrated (Scheme 2). 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 2. 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