

論文の内容の要旨

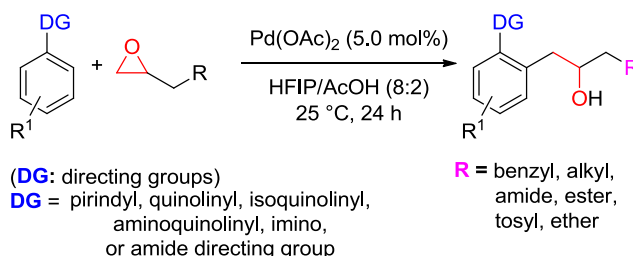
Development of Novel Synthetic Organic Reactions Directed Towards the Synthesis of Biologically Active Compounds

(生物活性化合物合成を志向した新規有機合成反応の開発)

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1. Palladium-Catalyzed Oxirane-Opening Reaction with Arenes via C-H Bond Activation¹⁾

In the past several decades, palladium-catalyzed C-H bond transformations have been developed dramatically. For example, coupling reactions of aromatic compounds with



First example of palladium-catalyzed C-H activation/coupling with strained ring

First example of using oxirane as a coupling partner in transition metal catalyzed intermolecular C-H transformation

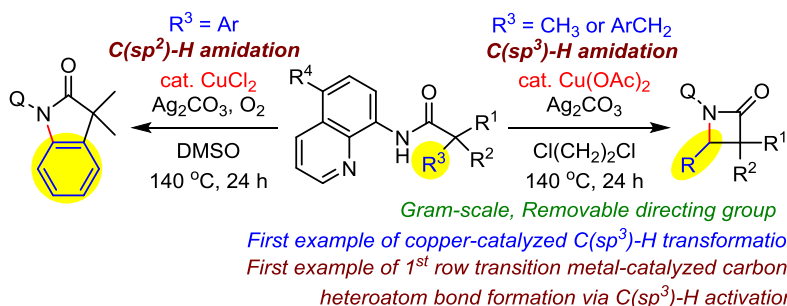
organohalides and organometallic reagents, insertion reactions of unsaturated molecules, such as acrylates, into a C-H bond of aromatic substrates, and introduction of heteroatom functionalities into aromatic compounds were reported. There is no report, however, about palladium-catalyzed coupling reaction between aromatic substrates and strained compounds via C-H bond activation.

I focused on oxiranes as a coupling partner because, to the best of my knowledge, there is no report on transition metal-catalyzed intermolecular direct C-H bond transformations using oxiranes as substrates. As a result of investigations, I succeeded to develop palladium-catalyzed C-H activation/C-C coupling reaction between arenes and oxiranes. The reaction proceeded at room temperature with high functional group tolerance, and the products were obtained in good to excellent yields, even in gram scale. By using *N*-methoxybenzamide as a substrate, I obtained 3-substituted isochroman-1-ones. The coupling reaction proceeded with

stereoretention. KIE experiments suggested that C–H bond activation is the rate-determining step.

2. Copper-Catalyzed Intramolecular C(sp³)-H and C(sp²)-H Amidation by Oxidative Cyclization²⁾

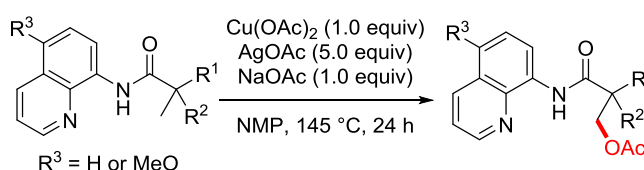
I developed the first example of copper-catalyzed intramolecular C(sp³)-H and C(sp²)-H amidation. The



reaction is also the first example of first row transition metal-catalyzed carbon-heteroatom bond formation. The reaction has broad substrate scope, and synthetically useful β-lactams were obtained from quinolyl amides in excellent yields, even in gram-scale. The reaction proceeded at a terminal methyl group as well as the internal benzylic position of an alkyl chain. By slightly modifying the reaction conditions, the reaction pathway switched to C(sp²)-H amidation for a specific substrate, and 2-indolinone was selectively produced in high yield. Since the quinolyl directing group could be removed by oxidation, this reaction must become a useful method to synthesize β-lactams and 2-indolinones.

3. Copper-Mediated C(sp³)-H and C(sp²)-H Acetoxylation³⁾

I developed the first example of a copper-mediated intermolecular acetoxylation via C(sp³)-H activation.



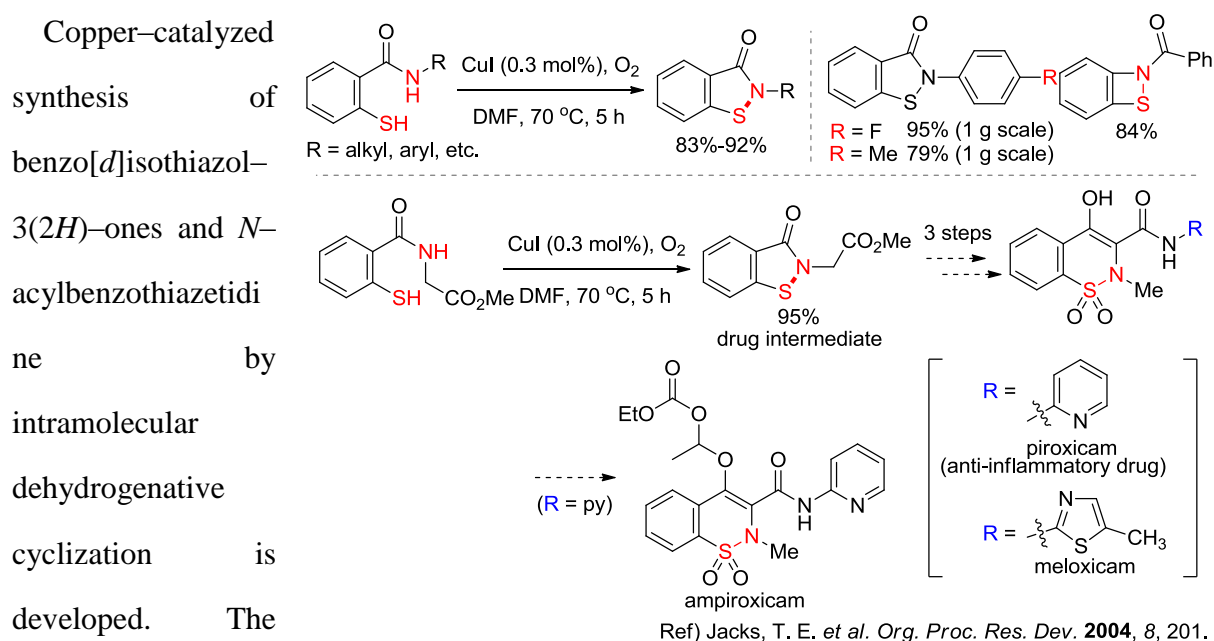
First Example of First Row Transition Metal-Mediated C(sp³)-H Acetoxylation
The reaction absolutely proceeded at the methyl group.

This reaction is also the first-row transition metal-mediated intermolecular

carbon-heteroatom bond formation. The reaction absolutely proceeded at the β-methyl group. The steric effect played an important role in the distribution of the products. This reaction has high functional group tolerance, and the reaction proceeded in excellent yield, even in gram-scale, for a complicated compound. The directing group can be removed by oxidation using a

5-methoxyquinolyl group as a directing group. This acetoxylation can be applied to a complex molecule, which will lead to late-stage functionalization. Deuterium labeling experiments suggested that the C(sp³)-H bond activation step is not the rate-determining step, which is different from copper-catalyzed intramolecular C(sp³)-H amidation. Aromatic C(sp²)-H acetoxylation also proceeded under the similar reaction conditions.

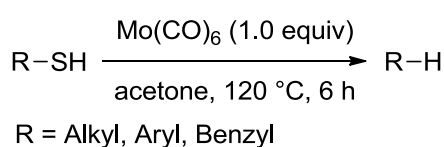
4. Copper-Catalyzed Intramolecular N-S Bond Formation⁴⁾



reaction proceeded under oxygen atmosphere with 0.3% CuI, and without any additives. In this reaction, a new nitrogen-sulfur (N-S) bond is formed by N-H/S-H coupling. The present reaction has high functional group tolerance and gives products in gram scale. This method promotes double cyclization, allowing for synthesis of a drug intermediate, which can be used to synthesize anti-inflammatory drugs.

5. Molybdenum-Mediated Desulfurization of Thiols and Disulfides⁵⁾

Mo(CO)₆-mediated desulfurization of thiols and disulfides was realized. In this reaction, the mercapto groups of aryl, benzyl, and primary and secondary alkyl



thiols; and S–S single bonds of disulfides could be removed. This reaction has high functional group tolerance. In addition, the desulfurization reaction was not affected by steric hindrance. The results of the reactions in acetone-*d*₆ suggested that the hydrogen sources in thiol and disulfide desulfurization were the hydrogen atom(s) of an SH group and acetone (solvent), respectively, and the desulfurization reaction proceeded via the formation of an organomolybdenum species.

References:

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