

## 論文の内容の要旨

### 論文題目 **Development of Organic Reactions through Nucleophilic Activation by Alkoxide**

(アルコキシドを用いた求核的活性化を経る有機合成反応の開発)

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#### **1. Introduction**

Metals generally receive electrons from a ligand into their vacant *d* orbital. By coordination of an anionic ligand to the metal complex, a metal complex is nucleophilically activated and the HOMO energy level of a metal complex is increased, resulting in an increase in electron density of the metal center and the ligands. Through this nucleophilic activation of a metal complex, two important reactivities can be induced. First, the metal center of the resulting complex has high nucleophilicity, resulting in the high reactivity toward electrophilic species. Second, ligands also have high nucleophilicity, resulting in the high reactivity of ligands toward electrophilic species and these sometimes dissociate from the metal complex. These reactivities are effective for difficult organic transformations such as reactions with low-reactive electrophiles under simple reaction conditions.

Nucleophilic activation is achieved by various nucleophiles, among these, an alkoxide is an important nucleophile for this purpose. An alkoxide is readily available anionic reagent and versatile structural tuning of the structure of an alkoxide and relatively lower reactivity of an alkoxide compared to the reactive organometallic reagents are good feature for nucleophilic activation of a metal complex to control the reactivity of the resulting metal complex.

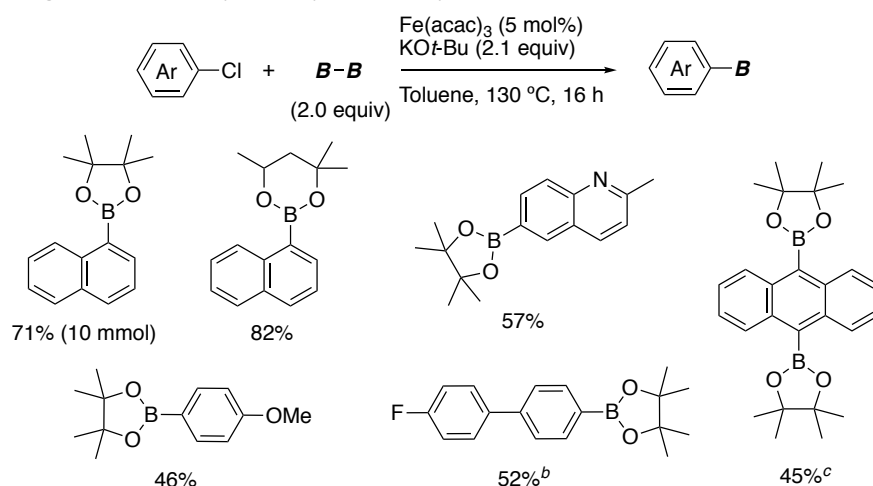
Recently, the concept of sustainability is important in modern organic synthesis. Therefore, achieving difficult organic transformations under simple reaction conditions is desirable. The goal of this thesis is to demonstrate the potential of nucleophilic activation of a metal complex with an alkoxide for difficult organic transformations under simple reaction conditions.

#### **2. Iron-Catalyzed Borylation of Aryl Chlorides.**

To develop synthetic methods for aryl or heteroarylboronic acid derivatives without reactive organometallic reagents is still important. Especially the use of inexpensive and readily available aryl chlorides as an electrophile has been only achieved by palladium, nickel and cobalt catalysis with tailored ligands and special additives because oxidative addition to aryl chlorides is difficult. To achieve this difficult transformation, I envisioned using the nucleophilic activation of an iron catalyst with an alkoxide. The key of reaction design is based on the two considerations: 1) Highly reductive iron-alkoxide complex can transfer electrons to an aryl

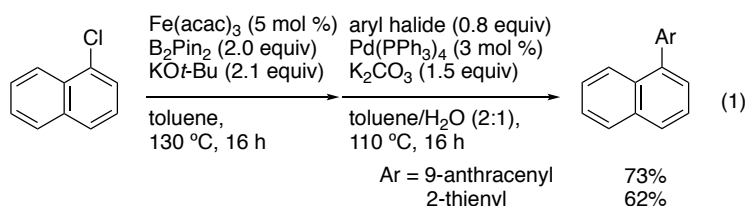
chloride to cleave the carbon-chloride bond. 2) An iron-alkoxide complex can generate an iron-boron complex with diboron reagents and it can react with an aryl anion or an aryl radical to give a borylated product. After extensive investigation, I found that the selection of an alkoxide is important for this transformation. The scope of this borylation reaction is showed in Figure 1. This

**Figure 1. Iron-catalyzed borylation of aryl chlorides<sup>a</sup>**



<sup>a</sup>The reaction was performed on 0.4 mmol scale. <sup>b</sup>Reaction temperature is 150 °C. <sup>c</sup>3.0 equiv of B<sub>2</sub>Pin<sub>2</sub> and 3.3 equiv of LiOt-Bu were used.

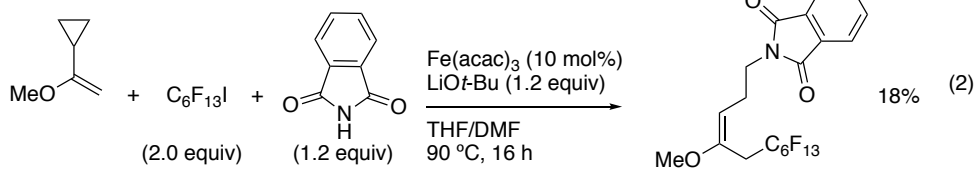
transformation can be carried out on 10 mmol scale. The reaction with a heteroaromatic chloride gave the borylated product in moderate yield. A simple aryl chloride gave the desired borylated product in lower yield. Two-fold borylation took place with 3.3 equiv of lithium *tert*-butoxide and 3.0 equiv of a diboron reagent to give the diborylated compound in moderate yield. The resulting aryl boronate underwent in one-pot cross-coupling reaction in the presence of a palladium catalyst (Eq. 1). I propose two possible catalytic cycles based on several previous reports. In both cases, nucleophilic activation of an iron catalyst is important to achieve carbon-chloride bond cleavage.



### 3. Iron-Mediated Carboamination and Carboalkoxylation of Alkenes with Perfluoroalkyl Halides

Carbofunctionalization of an alkene is an efficient method for rapid construction of two new bonds via 1,2-addition to an alkene. Among these reactions, carboalkoxylation and carboamination of an alkene is a direct method to create a carbon-nitrogen or a carbon-oxygen bond, concomitantly with a carbon-carbon bond. Although many intramolecular reactions have been reported to synthesize cyclic amines or ethers, intermolecular reaction is still underdeveloped because controlling the selectivity and reactivity to suppress the several side reactions is difficult. To achieve this three-component reaction, I conceived an idea on using the nucleophilic activation of an iron catalyst. Reaction design is shown below: An electron-rich iron alkoxide complex reduces an organic halide to give an alkyl radical and a halide anion, followed by addition to an alkene. If the resulting intermediate can be trapped with nucleophiles, three-component coupling is plausible. Based on this reaction design, I performed several preliminary experiments and found three-component coupling of functionalized alkenes, perfluoroalkyl halides and amines or phenols in the presence of an iron salt (Figure 2). In the presence of an electron-withdrawing group on nucleophiles, reaction efficiency was decreased and starting material was

recovered. Reactive functional groups such as bromide, nitro, amine and amide group could be tolerated. Imidazole could be utilized as a nucleophile. Trifluoromethylation could be achieved in the presence of a slightly large amount of trifluoromethyl iodide. Carboalkoxylation also occurred by changing the nucleophiles to phenols from amines. To obtain the mechanistic insight, two experiments were conducted and these suggested a radical mediated mechanism: first, addition of TEMPO completely retarded the reaction and second, a radical clock experiment gave the ring-opening product (Eq. 2). Based on these

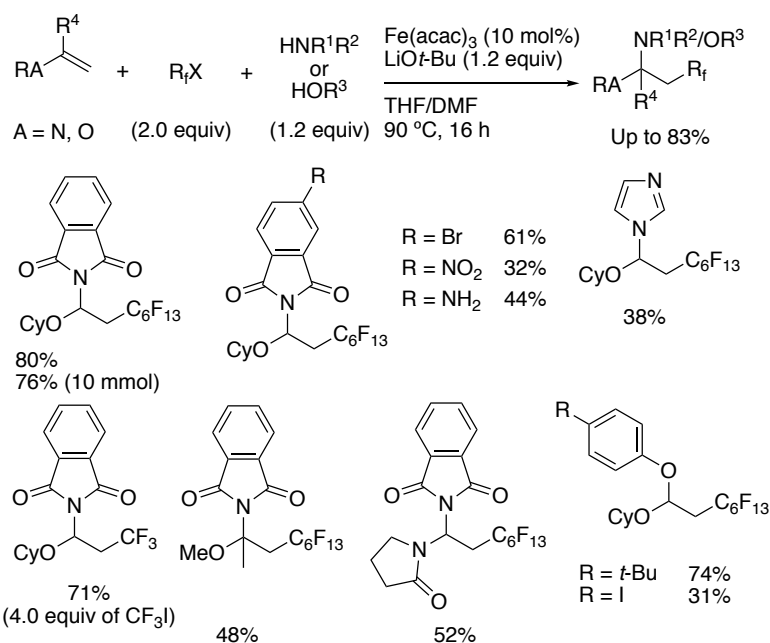


experimental results and previous reports, two possible mechanisms are proposed. In both cases, nucleophilic activation of an iron complex is important to generate perfluoroalkyl radical species.

#### 4. Silylation of Aryl Halides with Monoorganosilanes Activated by Lithium Alkoxide

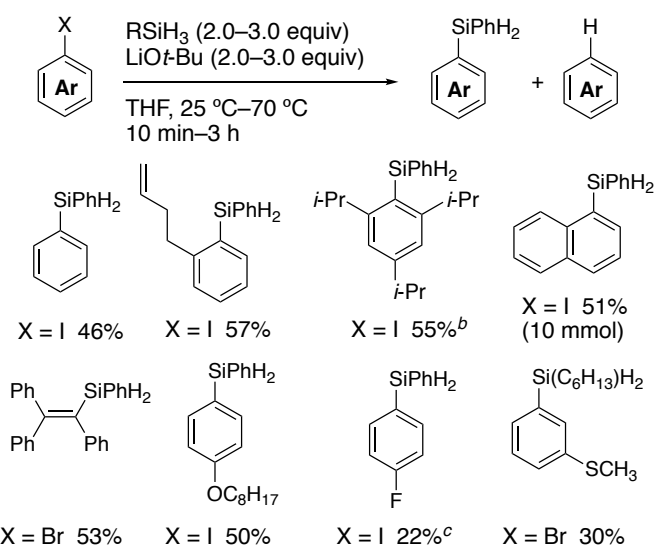
Diorganosilanes are important synthetic intermediates for the synthesis of organosilanes to be widely used in organic chemistry. There have been only limited synthetic routes to this class of compounds. The synthetic difficulty arises because of the high reactivity of monoorganosilanes and resulting diorganosilanes, which causes in many cases the disproportionation of silanes or formation of tri- or tetraorganosilanes via overreaction. In the initial reaction design to achieve silylation reaction, an iron salt, an alkoxide and a hydrosilane were used to utilize the nucleophilic activation. Finally, I

**Figure 2. Iron-mediated carboamination and carboalkoxylation of alkene<sup>a</sup>**



<sup>a</sup>The reaction was performed on 0.5 mmol scale.

**Figure 3. Silylation of aryl halides with monoorganosilanes<sup>a</sup>**



<sup>a</sup>Aryl iodide: 2.0 equiv of silane and 2.0 equiv of lithium *tert*-butoxide at 25 °C for 10 min. Aryl or alkenyl bromide: 3.0 equiv of silane and 3.0 equiv of lithium *tert*-butoxide at 70 °C for 3 h. <sup>b</sup>50 °C, 1 h.

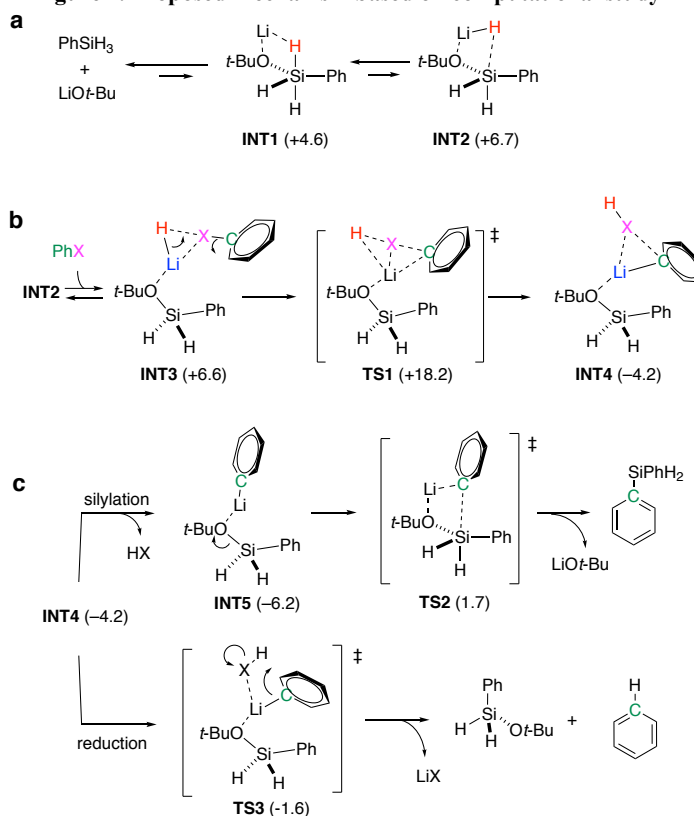
<sup>c</sup><sup>19</sup>F NMR yield.

found silylation of aryl halides with monoorganosilanes proceeded without an iron salt. Based on the related reports, I hypothesized that nucleophilic activation of a hydrosilane is important step to achieve this intriguing transformation. With this hypothesis, effect of base and solvent were examined and strong dependence on both of them was observed.

Reaction scope is shown in Figure 3. Iodobenzene gave the silylated product in 46% yield. An alkene-containing aryl iodide did not give the cyclized product. Although increasing the reaction temperature and prolonging the reaction time is necessary, the reaction proceeded in the presence of ortho-substitution. This reaction could be scaled up at least 10 mmol scale. A specific alkenyl bromide gave the product in moderate yield. The electron-rich aryl iodide gave the product in higher yield compared to the electron-poor aryl iodide. Finally, alkylsilane also could be used for this silylation reaction. To clarify the reaction mechanism of this intriguing reaction,

several experiments and theoretical study were carried out. Through this study several possible reaction mechanism was denied and finally, reaction mechanism was proposed based on the theoretical study (Figure 4). First step is generation of a silicate via nucleophilic activation of a hydrosilane and the hydride ligand attached to the silicon atom is dissociated from the silicon atom (a). This **INT2** can react with aryl halides to give an aryl anion and a hydrogen halide via halide abstraction (b). Then the aryl anion reacts with in situ-generated silyl alkoxide to give diorganosilane through **TS2**, or it reacts with in situ-generated hydrogen halide through **TS3** to give dehalogenated product (c). Based on this proposed mechanism, several experimental results can be explained. In this case, nucleophilic activation is important step to generate reactive hydride from stable two reagents to achieve this intriguing reactivity.

**Figure 4. Proposed mechanism based on computational study**



## 5. Conclusion

In conclusion, three organic transformations were developed utilizing nucleophilic activation of a metal complex using an alkoxide. Nucleophilic activation induces high nucleophilicity of the metal center and the ligands. By utilizing high nucleophilicity of the metal center, iron-catalyzed borylation of aryl chlorides and iron-mediated carboamination and carboalkoxylation of alkene were developed under simple reaction condition. By utilizing high nucleophilicity of ligands, silylation of aryl halides was developed without a transition metal. These study offer a unique and a new insight into utilization of nucleophilic activation of a metal complex for difficult organic transformations under simple reaction condition.