論文内容の要旨

論文題目:**Iron-Catalyzed Functionalization of Amides through Directed C(sp^2)–H Bond Activation**

(鉄触媒によるsp^2炭素−水素結合の直接活性化を経たアミドの官能基化反応の開発)

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1. Introduction

Cross-coupling reactions through cleavage of unactivated carbon–hydrogen (C–H) bonds is the most efficient strategy to create new chemical bonds, because of its step and atom economy. In this context, transition-metal-catalyzed directed activation of arenes and alkenes has great potential to develop into a methodology largely applicable in academia and industry, because it provides site-selective functionalization of C–H bonds under mild reaction conditions.

Since a pioneering report of a catalytic reaction in 1993, a variety of transformations based on directed C–H activation have been accomplished using various transition metals, mostly late-transition metals that are typically expensive, their complexes are air-unstable and their strong toxicity imposes strict regulation of the permissible leaching amount into the final product. Therefore replacement of such metals to inexpensive, non-toxic metals has been highly desired.

Iron is the most abundant and inexpensive transition metal, and therefore development of such transformations using iron has attracted much attention. During the past 10 years, our laboratory has disclosed unique reactivity of iron catalysis in combination with an organometallic base, and developed C(sp^2)–H bond activation reactions. Despite of these progresses, the scope of these reactions are limited because of side-reactions, which are mostly derived from reactive “low-valent” iron species that generates through over-reduction of iron by the organometallic base.

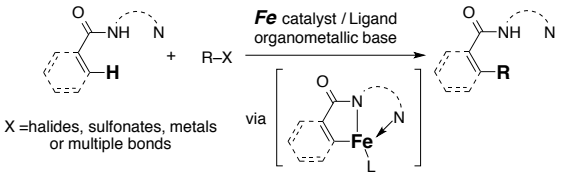


Figure 1. Bidentate directing group for stabilization of the organoiron intermediate

I hypothesized that if the directing group would possess another coordinating heteroatom, the

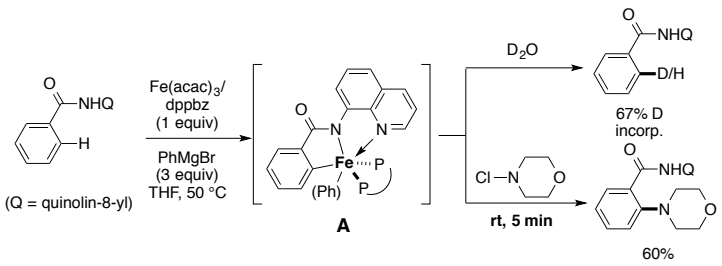
over-reduction of iron would be suppressed due to occupation of the coordination site of iron, which would result in stabilization of the organoiron intermediate with an appropriate ligand (Figure 1). During my Ph.D. studies, I have discovered several cross-coupling reactions based on iron-catalyzed directed C–H bond activation of arenes and alkenes possessing *N*-(quinolin-8-yl)amide as a bidentate directing group.

2. *Ortho*-amination of carboxamides with *N*-chloroamines

Direct amination of arene C–H bonds often suffers from slow reductive elimination due to high electronegativity of the nitrogen atom, therefore such reactions typically competes with homo-coupling of arenes, requires harsh reaction conditions or usage of strong and toxic oxidants. When the project had started, the C–H amination reactions were mostly limited to intramolecular reactions with late-transition metals, and therefore it remained as a challenging topic. Considered from these backgrounds, I selected *ortho*-amination of amides as an initial target reaction to be achieved.

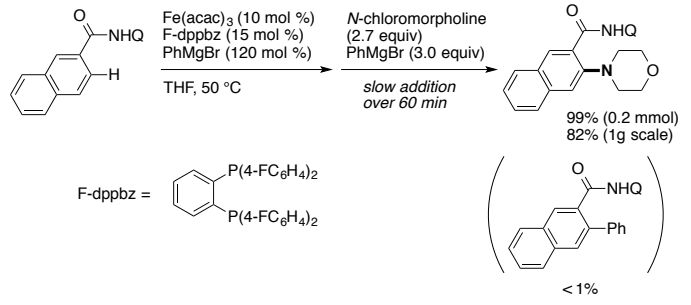
First, stoichiometric reactions were performed to confirm that the *ortho* C–H bond can be cleaved by iron/organometallic base. As depicted in Scheme 1 top, organoiron intermediate **A** was generated by treating *N*-(quinolin-8-yl)benzamide with a stoichiometric amount of $Fe(acac)_3$/1,2-bis(diphenylphosphino) benzene (dppbz) and 3 equiv of phenylmagnesium bromide (PhMgBr), which was indirectly confirmed by *ortho*-deuterium incorporation after quenching by D_2O. Then, I investigated the reactivity of **A** toward aminating reagents, expecting that the C–N bond would be formed after the reaction with an appropriate aminating reagent. As a result, addition of electrophilic nitrogen such as *N*-chloroamine was found to be effective; in the putative organoiron intermediate **A** was added freshly prepared *N*-chloromorpholine to afford *ortho*-aminated benzamide in 60% yield (Scheme 1, bottom). Thus, viability of *ortho*-amination under iron catalysis could be confirmed.

Scheme 1. Stoichiometric reactions with D_2O and chloroamine



After extensive investigations, amination with a catalytic amount of iron/diphosphine was achieved by slowly adding *N*-chloroamine and PhMgBr simultaneously, to give anthranilic acid derivatives in >90% yield in most cases (Scheme 2). Electron-withdrawing diphosphine ligand with conjugated backbone (F-dppbz) effectively suppresses side-reactions. Control experiments revealed that the reaction did not proceed with monodentate directing groups such as 2-pyridyl and pyrazolyl group, again demonstrating the importance of the bidentate directing group.

Scheme 2. Iron-catalyzed *ortho*-amination of amides using *N*-chloroamines

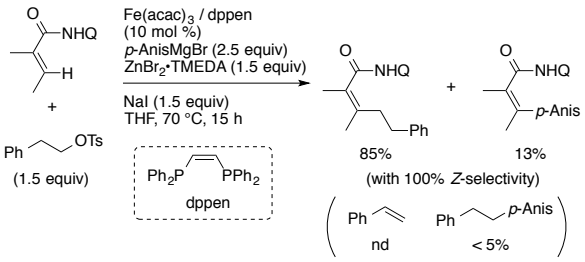


3. Alkylation of alkene- and areneamides with alkyl sulfonates and halides

Alkylation of aromatic and olefinic substrates via transition-metal-catalyzed cross-coupling had been considered to be difficult, because the alkyl-metal intermediate would be amenable to β-hydride elimination affording metal hydride species, which could induce side reactions such as reduction/isomerization of multiple bonds. Based on an initial finding of stoichiometric *ortho*-alkylation using alkyl halides, I started investigation on the C–H alkylation reaction with alkyl electrophiles using a catalytic amount of iron, and developed the first directed alkylation of C(sp^2)–H bonds with primary and challenging secondary alkyl tosylates and halides.

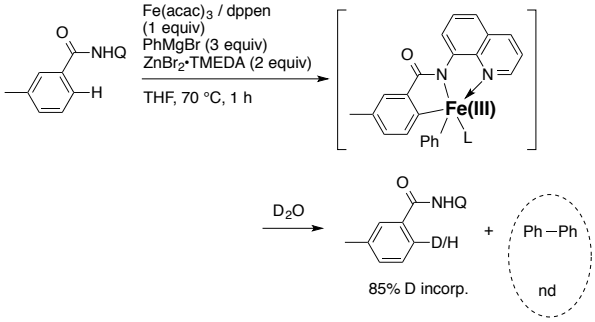
As shown in Scheme 3, β C–H bond of alkeneamides, as well as *ortho* C–H bond of benzamides, were successfully alkylated using alkyl tosylate as an alkyl electrophile, arylzinc halide as a base and sodium iodide as an additive, in the presence of $Fe(acac)_3$/*cis*-1,2-bis(diphenylphosphino)ethylene (dppen) as a catalyst. 100% *Z*-selective introduction of alkyl group was achieved, when alkeneamide was used as a substrate. Arylzinc halide base (ArZnX) was found to be crucial to suppress the competing homo- and cross-coupling reactions; diarylzinc base (Ar_2Zn) prefers to promote cross-coupling reaction with alkyl electrophiles. β-hydride eliminated alkene did not observed at all. Sodium iodide was found to improve the yield through *in situ* tosylate/iodide exchange, as confirmed by monitoring the reaction at early stage, but the reaction also proceeded well in its absence.

Scheme 3. Iron-catalyzed β-alkylation of alkeneamides with alkyl tosylates



When the reaction was performed by using arylzinc halide as a base, stoichiometric reactions suggested that the reaction proceeds through an organoiron(III) species (Scheme 4). That is, after quenching the stoichiometric reaction by D_2O, biphenyl was not observed at all, with 85% of *ortho*-deuterium incorporation. Because homo-coupling of the organometallic reagent is only the way for iron to be reduced, this result clearly indicates that unusual organoiron(III) species should be involved in the reaction, and that might be a reason for the unique reactivity. Further usage of such a mild base for iron(III)-catalyzed C–H functionalization with electrophiles will find further development of this chemistry.

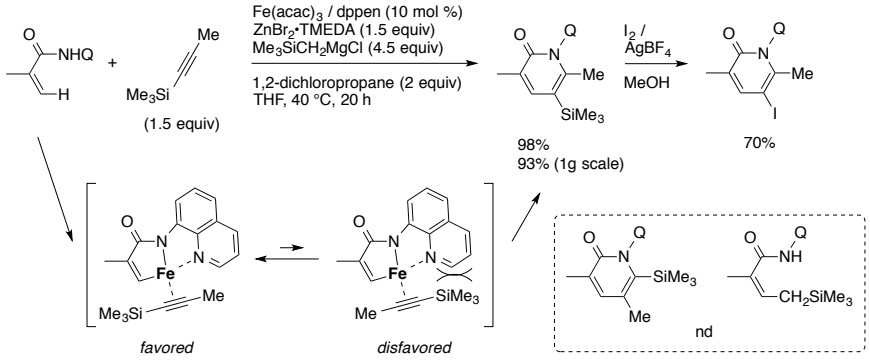
Scheme 4. Stoichiometric reaction with arylzinc halide as a base



No reduction of iron was observed

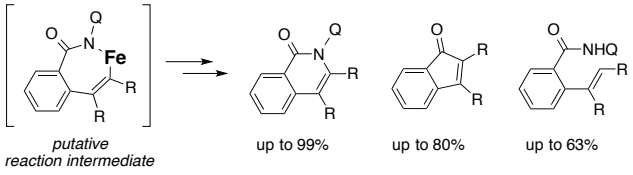
4. Regiocontrolled synthesis of 2-pyridones through coupling of amides with unsymmetrical alkynes

Scheme 5. Iron-catalyzed oxidative coupling of amides with alkynes affording 2-pyridones



Through development of organoiron(III)-catalyzed reactions through C–H bond activation, I found the oxidative coupling of alkeneamides with alkynes affording 2-pyridones proceeded with high regioselectivity under mild reaction conditions, when unsymmetric alkynes were used (Scheme 5). Origin of the regioselectivity can be ascribed to small atomic radius of iron, which might be sensitively affected by sterics in alkyne insertion step. That is, size of substituents of amides and alkynes seems to determine the selectivity; mixture of regioisomers was obtained when *β*-methylated alkeneamide was used. Sterically congested silylmethylzinc base was found to be the best, in the sense that side reactions such as oxidative coupling of amides and organometallic bases were suppressed. Thus, I could firstly demonstrate 2-pyridone syntheses through coupling of amides with alkynes with perfect regioselectivity.

Scheme 6. Product-selectivity from alkenyl-metal intermediate



The reactivity of putative alkenyl-metal intermediate from benzamide and alkyne can be controlled by additive/base, and different products were obtained depending on the reaction conditions. Thus, I obtained isoquinolones, indenones, and alkenylated amides in good yield (Scheme 6), which highlights the high reactivity and utility of iron complexes for organic synthesis.

5. Conclusion

During the Ph.D. course study, I have developed a series of reactions based on directed C–H bond activation of amides possessing bidentate auxiliary. Through development of these reactions, unique reactivity of iron catalysis, some of which surpasses those of late-transition metals, has been disclosed. These reactions are not only scientifically interesting but also synthetically useful, because in most cases the directing group can be easily converted to carboxylic acids by hydrolysis. Overall, these transformations may achieve streamlined synthesis of fine chemicals with inexpensive reagents, and provide guidelines for the future design of iron-catalyzed reactions.