論文の内容の要旨

論文題目　Iron-Based Aromatic C–H Bond Functionalization with Electrophiles

(鉄と求電子剤を用いた芳香族炭素－水素結合の官能基化)

氏名　浅子　壮美

1. Introduction

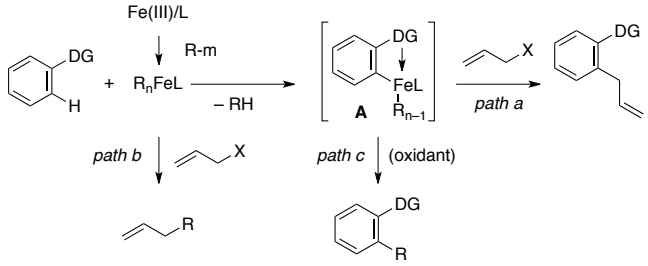
With numerous urgent issues such as the energy crisis, resource depletion, and environmental problems to address, modern organic synthesis should aim towards maximizing reaction efficiency and sustainability. To this end, transition metal-catalyzed C–H bond functionalization has recently received much attention as a potential strategy for solving these problems because it avoids the requirement for preactivation of one or even both of the coupling partners. However, most of these reactions require rare and toxic transition metal catalysts and typically harsh reaction conditions, which is incompatible with the concept of sustainability. On the other hand, we have been interested in sustainable synthetic methodologies using iron as a ubiquitous and benign catalyst and have reported a series of iron-catalyzed sp^2 and sp^3 C–H bond arylation reactions with a nucleophilic coupling partner. While these reactions are the first and still the only catalytic examples of iron-based directed C–H bond functionalization, the coupling partner was limited to nucleophilic aryl donors. Considering the rapid growth in the 2nd and 3rd row transition-metal-catalyzed C–H bond functionalization reactions which now enable introduction of almost every type of coupling partner and find practical applications, the introduction of various types of functional groups using iron would be highly desirable and further expand the utility of iron as a sustainable catalyst for the functionalization of C–H bonds. During my Ph.D. course, I achieved an unprecedented iron-based directed aromatic C–H bond functionalization using electrophilic coupling partners and developed catalytic allylation and stoichiometric C–H bond functionalization reactions.

2. Iron-Catalyzed Aromatic C–H Bond Functionalization with Allylic Electrophile

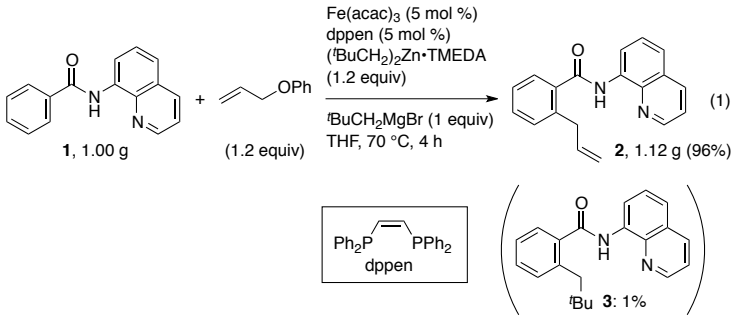
Derivatives of allylbenzene are a structural motif in numerous natural products and biologically active compounds and are also versatile intermediates in synthesis that can be transformed into various functional molecules. The Lewis acid-promoted Friedel–Crafts-type allylation of a simple arene is a classical and straightforward method to synthesize allylarenes. However, the reaction is limited to electron-rich arenes and it often produces a mixture of regioisomers and overallylated products. Transition-metal-catalyzed directed C–H bond allylation has been recently developed to achieve broader scope and superior regioselectivity, but these reactions typically require a precious metal catalyst and/or harsh reaction conditions. Herein, I have developed an iron-catalyzed ortho allylation of arenes with allyl phenyl ether that takes place in *γ*-selective manner under mild conditions. Notably, this is the first demonstration that iron-catalyzed directed C–H bond activation can be followed by reaction of the putative chelated iron intermediate with an electrophile.

2.1. Iron-Catalyzed Directed Allylation of Aromatic Carboxamides

Scheme 1.



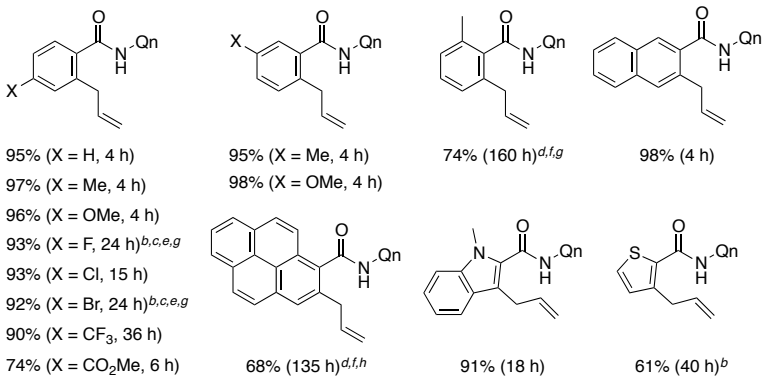
The reaction was designed based on the following two considerations (Scheme 1, path a): 1) an organoiron species cleaves the ortho C–H bond of an arene possessing a directing group under mild conditions, and 2) the resulting iron intermediate **A** may react with an allylic electrophile. In order to achieve this scenario, two potential competing reactions must be overcome: the cross-coupling of the organometallic reagent (R-m) with the allyl electrophile (path b), and the decomposition of the iron intermediate through oxidant-induced reductive elimination (path c). After extensive experimentation, I found that the choice of directing group and organometallic reagent is crucial to selectively promote the allylation reaction (path a). Thus, *N*-(quinolin-8-yl)benzamide (**1**, 1.00 g, 4.03 mmol) reacted with allyl phenyl ether (1.2 equiv) in the presence of $Fe(acac)_3$ (5 mol %), *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 5 mol %), $ZnCl_2$•TMEDA (1.2 equiv), and *t*-$BuCH_2MgBr$ (3.4 equiv) to give the ortho-allylated product **2** in 96% yield after 4 h at 70 °C (eq 1). Ortho-neopentylated product **3** (path c) was obtained in a trace amount (1%), and 0.15 equiv of allyl ether was recovered. The reaction with 1.0 equiv of allyl phenyl ether gave **2** in 89% yield. Among 3.4 equiv of *t*-$BuCH_2MgBr$, 1 equiv is consumed to deprotonate the amide proton and the other 2.4 equiv forms 1.2 equiv of $(t\text{-}BuCH_2)_2Zn$. The use of the corresponding monoalkylzinc halide instead of $(t\text{-}BuCH_2)_2Zn$ largely decreased the yield. Arenes possessing a different directing group such as *N*-methylbenzamide, 2-phenylpyridine, arylimine, and 1-phenylpyrazole gave no product under these conditions. When organozinc reagents such as Ph_2Zn or Me_2Zn were used instead of the neopentyl reagent, **2** was obtained in a trace amount and paths b and c were dominant.



The scope of the allylation reaction is illustrated in Table 1. The reaction with carboxamides bearing an electron-donating or electron-withdrawing substituent at the para position proceeded smoothly to give the corresponding ortho-allylated product in good yields, while the latter needed longer reaction time. Functional groups

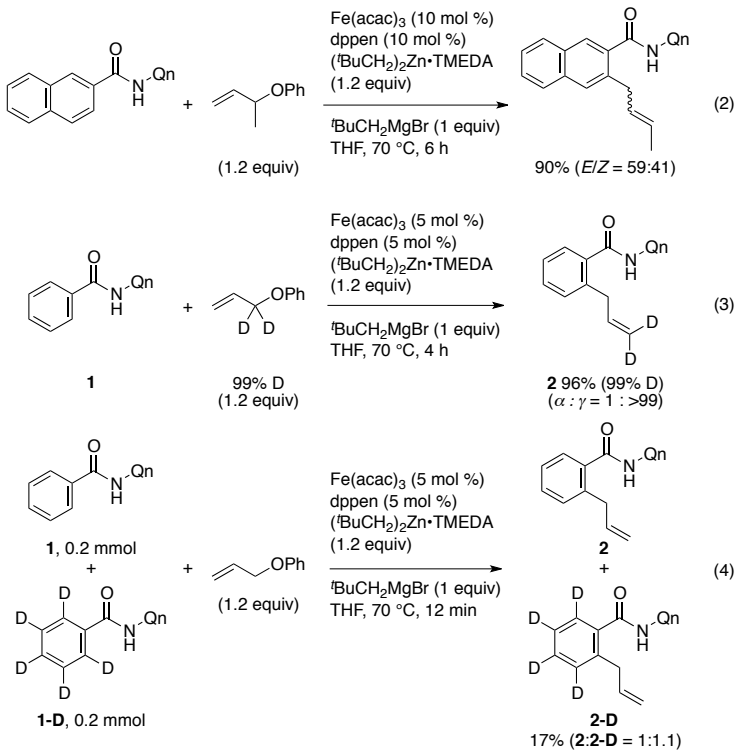
such as chloride, bromide, trifluoromethyl, and ester are tolerated. Meta-substituted carboxamides reacted smoothly at the less hindered ortho position. The allylation of ortho-substituted substrate on the opposite ortho position proceeded slowly but still in good yield when higher catalyst loading and longer reaction time were employed. The slow rate of this reaction accounts for the selective mono allylation under the standard conditions. The C–H bond of naphthalene, pyrene, and heteroarenes such as indole and thiophene could also be allylated in a regioselective manner. Isomeric styrene compounds were not observed, despite the known reports on double bond isomerization of terminal olefins in the presence of an iron catalyst and an organometallic reagent.

Table 1.



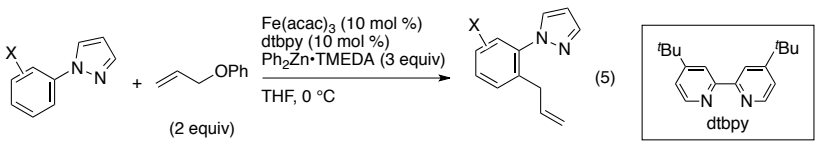
[a] The reaction was performed under the conditions in eq. 1 on 0.4 mmol scale. Qn = quinolin-8-yl [b] 50 °C. [c] 10 mol % catalyst. [d] 20 mol % catalyst. [e] 1.5 equiv of (^{t}BuCH$_2$)$_2$Zn. [f] 2 equiv of (^{t}BuCH$_2$)$_2$Zn. [g] 1.5 equiv of AllylOPh. [h] 2 equiv of AllylOPh.

The reaction with an allyl phenyl ether possessing a methyl group at the α position gave only the γ product in high yield as a mixture of stereoisomers (*E*/*Z* = 59:41) (eq 2). The *E*/*Z* ratio remained constant throughout the reaction, indicating that the stereo mixture is not due to product isomerization, but due to the allylation step itself. Attempts to control the *E*/*Z* ratio using ligands with different electronic and steric properties resulted in little change of the ratio. Allyl phenyl ethers possessing a substituent at β or γ position did not participate in the reaction. The reaction of ((1,1-dideuterioallyl)oxy)benzene selectively gave the γ product in 96% yield, which confirmed the preferred γ selective allylation (eq 3). An intermolecular competitive reaction using an equimolar amount of **1** and **1-D** was stopped at 17% conversion to give an intermolecular KIE value of 1.1 (eq 4). The observed small KIE value suggests that the C–H bond cleavage step is not involved in the turnover-limiting step unlike the iron-catalyzed oxidative C–H bond arylation reaction, which showed a large KIE.



2.2. Iron-Catalyzed Directed Allylation of Arylpyrazoles

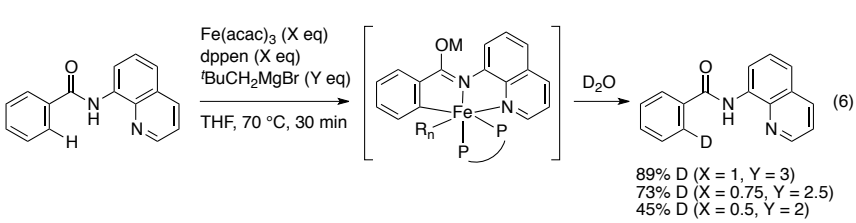
I then focused on expanding the scope of the substrate to arene possessing other directing groups, and found that 1-arylpyrazoles, compounds of interest for



medicinal chemistry, also underwent the allylation reaction when the reaction was performed with Ph_2Zn•TMEDA as a base and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) as a ligand at 0 °C (eq 5). Ortho-phenylated product and diallylated product were observed in a small amount under these conditions. Other substrates bearing a directing group such as pyridine, imine, and amide preferentially gave the phenylated products (path c) over the allylated products (path a). Besides the pyrazolyl directing group, the choice of allylic electrophile is important. Thus, allylic substrates possessing a better leaving group such as allyl chloride, acetate, and carbonate were much less effective due to the fast cross-coupling between Ph_2Zn and these electrophiles (path b).

2.3. Iron Intermediate

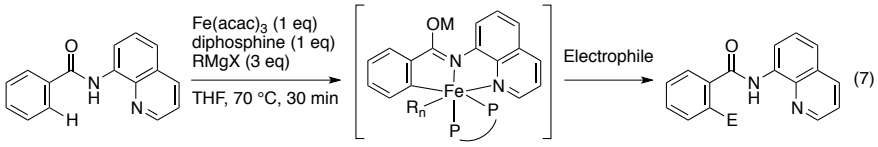
In order to obtain the information on the putative metallacyclic iron intermediate, the stoichiometric reaction was performed using 1 equiv of $Fe(acac)_3$, 1 equiv of dppen, and 3 equiv of *t*-$BuCH_2MgBr$ (eq 6). The addition of D_2O after stirring at 70 °C for 30 min afforded the recovered starting material with 89% D incorporation, suggesting the existence of a stable metallacyclic intermediate. No D incorporation was observed with (*t*-$BuCH_2)_2Zn$ or *t*-$BuCH_2MgBr$ in the absence of $Fe(acac)_3$, excluding the possibility of simple zincation or magnesiation for the C–H bond cleavage. The D incorporation was found to be nearly proportional to the amount of $Fe(acac)_3$ used, i.e., 73% D and 45% D for 0.75 equiv and 0.5 equiv of $Fe(acac)_3$, respectively. Therefore, it seems that the chelated metal is not zinc or magnesium but the chelated iron intermediate is formed after the C–H bond activation by an active iron species. The addition of allyl phenyl ether to the in-situ generated iron intermediate afforded the allylated product **2**.



(6)

3. Iron-Mediated C–H Bond Functionalization with Electrophiles

The reactivity of the stable iron intermediate derived from *N*-(quinolin-8-yl)benzamide towards electrophiles were found to be more general. Thus, the stoichiometrically prepared iron intermediate reacted with various carbon- and nitrogen-electrophiles such as primary and secondary alkyl halide, and *N*-chloroamine (eq 7).



(7)

4. Conclusion

In conclusion, a new concept of iron-based directed aromatic C–H bond activation followed by reaction with an electrophile was demonstrated for the first time. Iron-catalyzed ortho allylation of arenes via directed C–H bond activation was developed, which proceeds smoothly under mild conditions to give allylbenzene derivatives with high γ selectivity and without isomerization of the double bond to styrene derivatives. Iron-mediated C–H bond functionalization with electrophiles was further demonstrated using the stoichiometrically generated iron intermediate derived from *N*-(quinolin-8-yl)benzamide.