学位論文　（要約）

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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Abstract

The present thesis describes the development of iron-catalyzed site-selective C–H bond functionalization of arene- and alkene substrates possessing a bidentate amide directing group. The author achieved to generate an organometallic species from an iron(III) salt and an amide substrate possessing an appropriate (quinolin-8-yl) directing group, which enables site-selective functionalizations of a C(sp^2)–H bond with electrophiles and multiple bonds as coupling partners.

Chapter 1 describes the importance of utilizing sp^2 carbon–hydrogen bonds as a reactive site for organic synthesis, using iron as a catalyst. Chelation-assisted regioselective activation of a C–H bond by taking advantage of a directing group is main focus of this thesis. Challenges in iron catalysis and the goal of this study are also described in this chapter.

Chapter 2 describes attempts to stabilize the organoiron species generated after the C–H activation event, through stoichiometric reactions. The directing group on the substrate and an external ligand were found to be a key to stabilize the organoiron species, and the design of an aromatic substrate possessing a bidentate amide directing group and of a diphosphine ligand enabled the creation of an efficient organoiron species. The newly formed organometallic species are stable under heated comditions and showed tolerance of organic oxidant.

In Chapter 3, development of C–H bond amination of aromatic amides using iron catalysis is described. The stoichiometric organoiron species that was designed in the previous chapter was found to react with electrophilic nitrogen to give a C–N bond. Catalytic amination of a C–H bond was also achieved by careful control of the addition

sequence of reagents and of the electronic property of the ligand, producing anthranilic acid derivatives in good yield with tolerance of various functionalities.

In Chapter 4, the author investigated the reaction of the organometallic intermediate with alkyl electrophiles, aimed for alkylation of a C–H bond. Delicate tuning of the base successfully enabled the control of the reactivity of iron for the desired pathway, with suppression of "low-valent" iron-catalyzed reactions such as cross- and homo-coupling, and β-hydride elimination. Mechanistic studies revealed that a stable "high-valent" organoiron(III) species may be involving in the reaction.

Chapter 5 depicts the development of the reaction of organoiron species with multiple bonds such as alkenes and alkynes. The reactions smoothly proceeded through a carbometalation pathway, producing a variety of products including potentially-bioactive heterocyclic compounds and precursors for π-extended molecules. These reaction modes are highly dependent on the base or additive, and the author succeeded tuning of the product-selectivity.

Finally, a conclusion and future perspectives are provided in Chapter 6.

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Chapter 1.

General Introduction

1-1. Functionalization of a C(sp^2)–H bond using transition-metal catalyst

Since the pioneering works by using iron,[1] copper,[2] nickel,[3] and and other metals, [4] transition-metal-catalyzed cross-coupling reactions between organic nucleophiles and electrophiles have been investigated so extensively that now provide one of the most common, easy and practical way to construct new chemical bonds from simple starting materials. These reactions enabled chemists to create a variety of chemical bonds such as C–C, C–N or C–O bonds, which was worth being awarded Nobel Prize Chemistry in 2010 (Figure 1).[5]

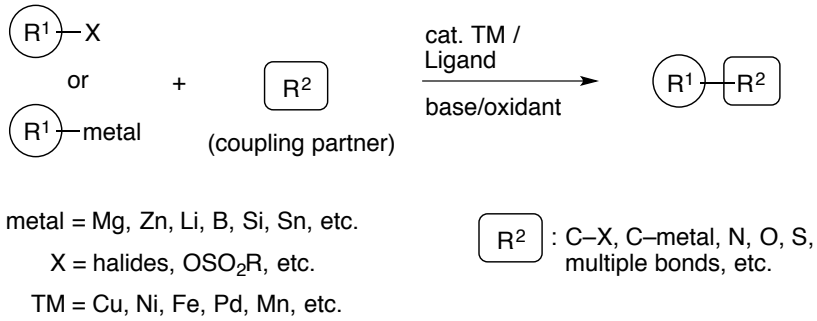


Figure 1. Transition-metal-catalyzed cross-coupling reactions

On the other hand, one of the drawbacks of the cross-coupling reaction is the utilization of functionalized compounds as a substrate (R^1–X or R^1–metal in Figure 1), which limits the substrate scope, because these starting materials are not easily available in most cases. Preparation of these compounds requires halogenation [6] and/or metalation[7,8] of a simpler substrate, which needs toxic reagents and harsh reaction conditions.

If the cross-coupling reactions could be performed from common and ubiquitous substrates, one could shortcut the troublesome pre-functionalization steps, and facile coupling reactions with atom-, waste-, and step-economy could be achieved. In this context, activation of a carbon-hydrogen bond (C–H bond) using a transition-metal catalyst, followed by cross-coupling with an appropriate reaction

partner has been regarded as an important concept for next generation of organic syntheses (Figure 2), and has been rapidly expanding during past several decades[9] enough to be applied for synthesis of bioactive compounds[10] or π-extended molecules for materials science.[11] C–H activation has numerous advantages: streamlines synthetic methodologies, provides alternative or even otherwise impossible strategies, and enables different reactivity from C–X or C–M bond, all of these being useful in reconsidering retrosynthetic strategies for complex molecules such as natural compounds.[10b] Thus, the C–H bond activation reaction has a multifaceted value, and is now regarded as a hot-topic in organic chemistry.[12]

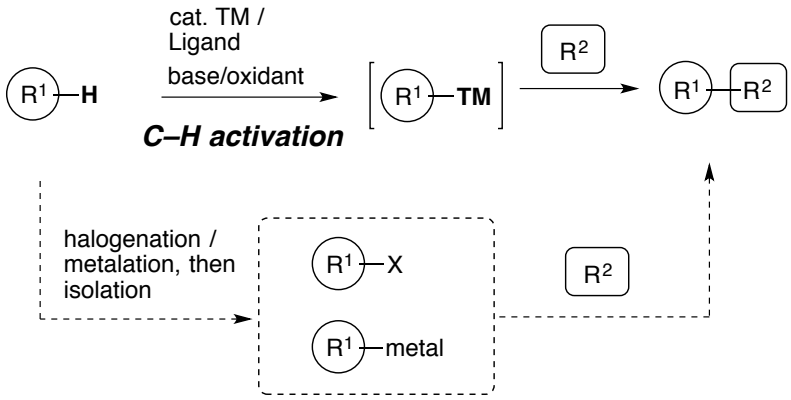


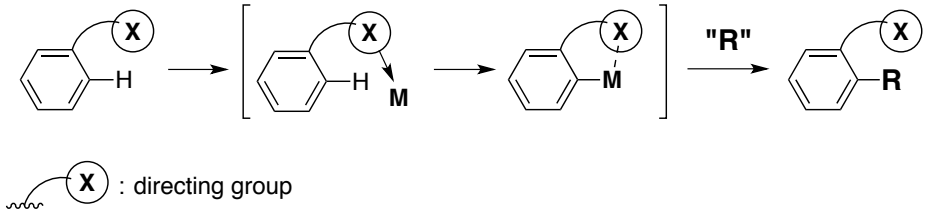
Figure 2. Schematic comparison of C–H bond functionalization reactions with traditional multi-step coupling reactions

1-2. Directed C(sp^2)–H bond activation

One of the biggest concerns in development of C–H bond functionalization reactions is how to activate a C–H bond regioselectively, which is the most difficult and important step in many cases. While a great number of methodologies for regioselective C–H activation has been developed,[13,14] chelation-assisted (directed) C–H bond activation, where substrate possessing internal ligand (directing group) that can chelate metals and make it closer to the adjacent C–H bond, is one of the most effective

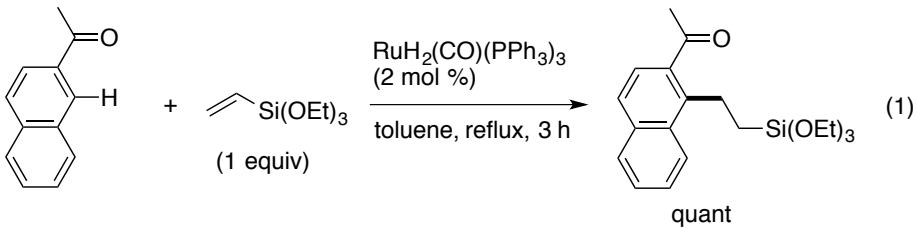
methodologies because of its perfect predictable regioselectivity at mostly the *ortho*-position,[15] and it typically enables reactions under mild reaction conditions (Scheme 1).

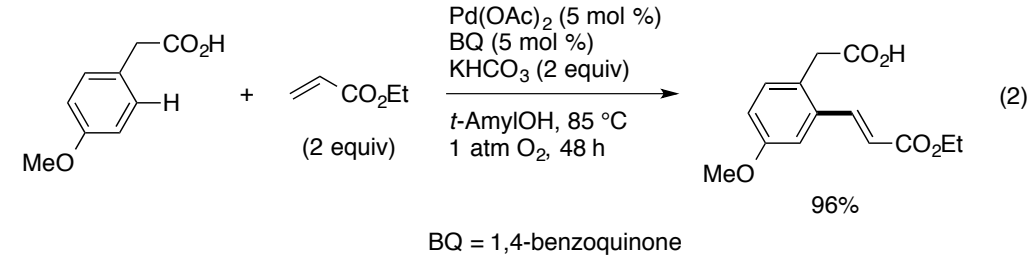
Scheme 2. Directed C–H bond activation



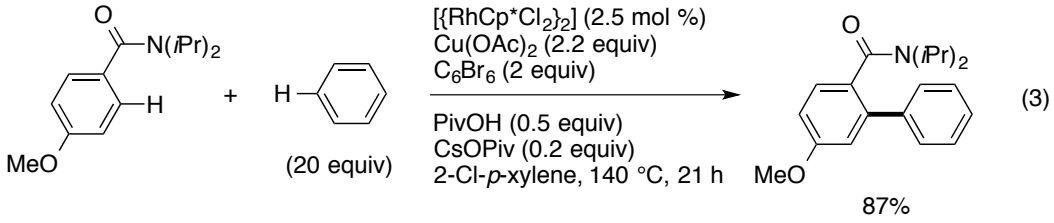
1-3. Recent examples and future directions of directed C–H bond activation

Since the initial discovery of transition-metal-mediated[16] or -catalyzed[17] reactions (eq. 1), directed C–H activations have been widely investigated and provide one of the common methodologies for *ortho*-functionalization.[18] Representative examples are shown below, where a C–H bond can be functionalized with common and simple functional group such as carboxylic acid (eq. 2),[19] and arene coupling partner such as benzene (eq. 3).[20] These examples highlight the great potential and synthetic utility of directed C–H bond activation reactions.

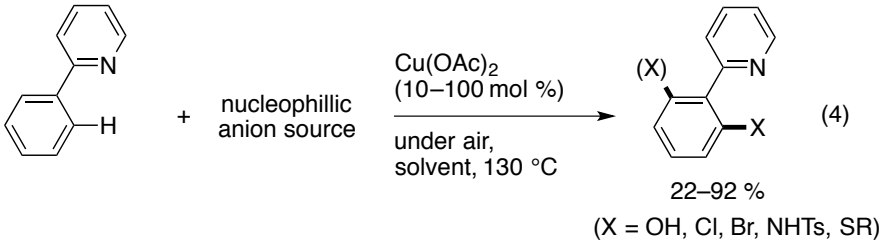




BQ = 1,4-benzoquinone



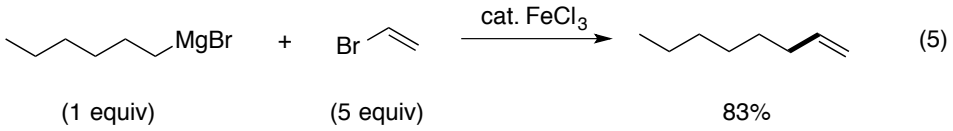
In spite of these progresses, most reports rely on using expensive reagents especially for the catalysts such as palladium and rhodium, metals that suffer from high cost and toxicity. Therefore, replacement of these metals with inexpensive and non-toxic metals should be the direction to go for the sustainable development of our society.[21] Thus, achieving such reactions uisng early transition-metals has been a longstanding goal. First-low transition-metal-catalyzed directed activation of a C(sp^2)–H bond was firstly achieved in 2006, when Yu[22] and Chatani[23] independently reported the first directed C–H functionalization using inexpensive copper as a catalyst or a stoichiometric additive (eq. 4). Later the modified reaction conditions with copper catalyst,[24] as well as reactions catalyzed by cobalt,[25] nickel,[26] and manganese[27] have been reported. However, these reactions still cannot compete with late-transition-metal catalysts from the viewpoint of reaction versatility, partially because of the scarce understanding of the active species.



(4)

1-4. Iron-catalyzed directed C(sp^2)–H bond activation reactions

Iron is the most abundant and inexpensive among all transition-metals with negligible toxicity, therefore development of organic reactions using iron catalyst should have great impact on the synthetic chemistry and even the whole human society.[28,29] While iron has been traditionally known as a Lewis acid or radical initiator,[30] its reactivity as an organometallic catalyst has been largely ignored, until the pionering reports by Kharasch,[31] Tamura and Kochi (eq. 5).[32] After these reports, a large number of reports on cross-coupling reaction had appeared.[1a]

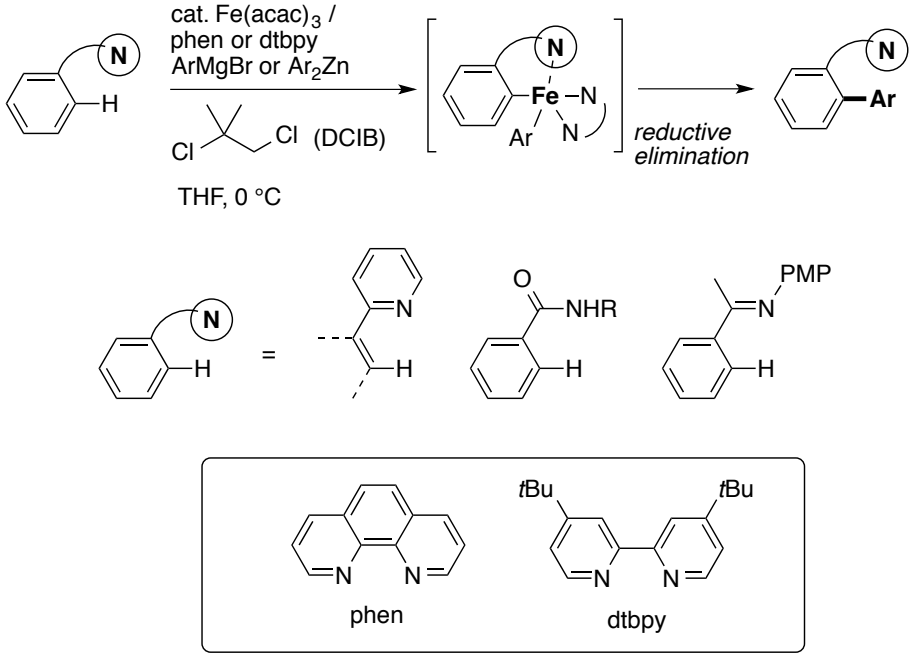


(5)

Importantly, iron as an organometallic catalyst exhibits unique and high reactivity that overwhelms that of late transition-metals,[33] which motivated chemists to further investigate its potential. In this context, in 2008 Nakamura and co-workers reported the first example of iron-catalyzed directed oxidative arylation of C(sp^2)–H bonds using diarylzinc reagent as a base and an aryl donor, with a dichloroalkane (DCIB) as a mild oxidant.[34] Later, the same group[35] and other groups[36] have contributed to expand this chemistry (Scheme 2). Taking its low-cost, high reactivity and mildness of the reaction condition into consideration, exploiting the iron-catalyzed reaction system would considered to have great potential for contributing to our

sustainable developments.

Scheme 3. Iron-catalyzed directed C(sp^2)–H arylations under oxidative conditions



1-5. Objective and survey for this thesis

Difficulty for expanding the scope of the iron-catalyzed directed C–H bond activation reaction associates with the unpredictability of "low-valent" iron species generated through homocoupling of organometallic reagents,[37,38] which can be ascribed to inadequate support of active iron species by directing group and ligand, and lack of mechanistic understanding.[35d] To overcome this problem, my Ph.D. studies focused on the development of directed functionalization of C(sp^2)–H bonds using iron as a catalyst through sufficient stabilization of the organoiron intermediate by appropriate directing group and ligand, aiming for establishment of coupling reactions using electrophiles including multiple bonds as coupling partners (Figure 3). To this end, I started an investigation to stabilize the organoiron species by examination of appropriate directing group and ligand for iron by stoichiometric reactions, and found that a bidentate amide

directing group and diphosphine ligands are effective for its stability (Chapter 2). Then, the reactivity of organoiron species toward an aminating reagent was investigated, and a rare example of intermolecular C(sp^2)–H amination reaction has achieved (Chapter 3). Reaction with alkyl electrophiles was also examined, and C(sp^2)–H alkylation reaction with primary and secondary alkanol derivatives such as alkyl tosylates was accomplished (Chapter 4). The organoiron intermediate found to be reactive towards multiple bonds such as alkenes and alkynes, to achieve coupling reactions producing a variety of molecules, including cyclic ones such as indenones and pyridones (Chapter 5). The reactions described herein highlight the unique reactivity of iron catalyst for C–H bond activations, which can compete or even overwhelm that of late transition-metals.

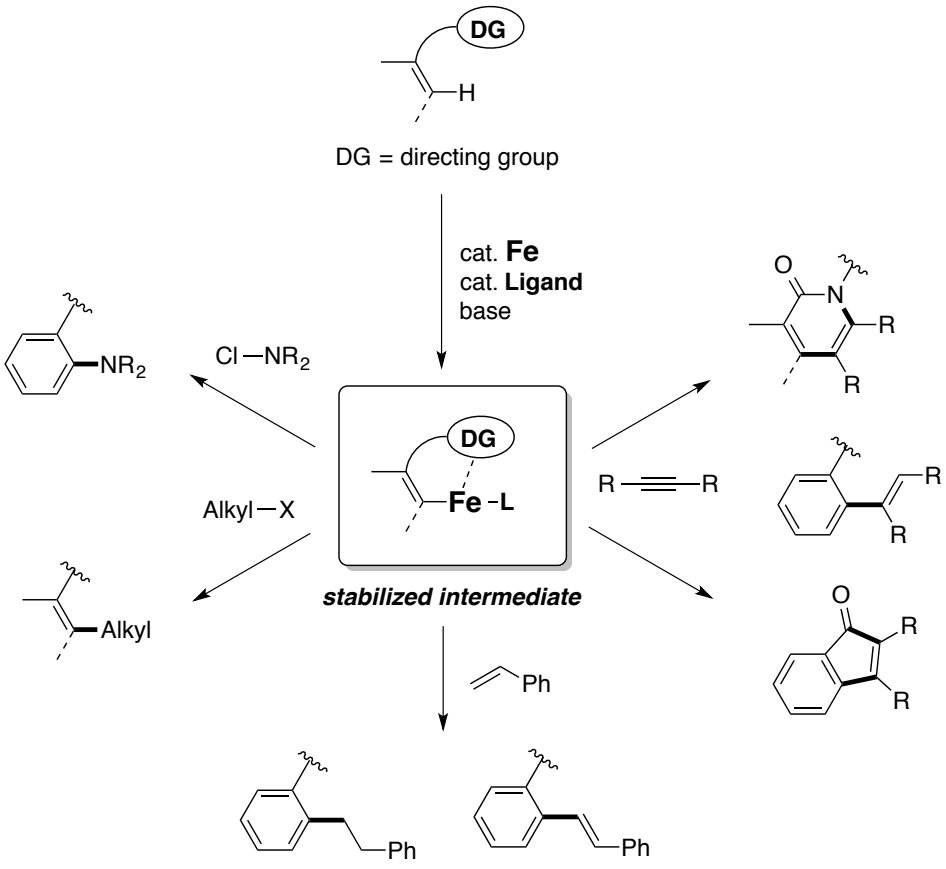


Figure 3. Overview of this thesis

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Chapter 2.

Generation of Organoiron using Aromatic Amides Possessing Bidentate Directing Group

2-1. Introduction

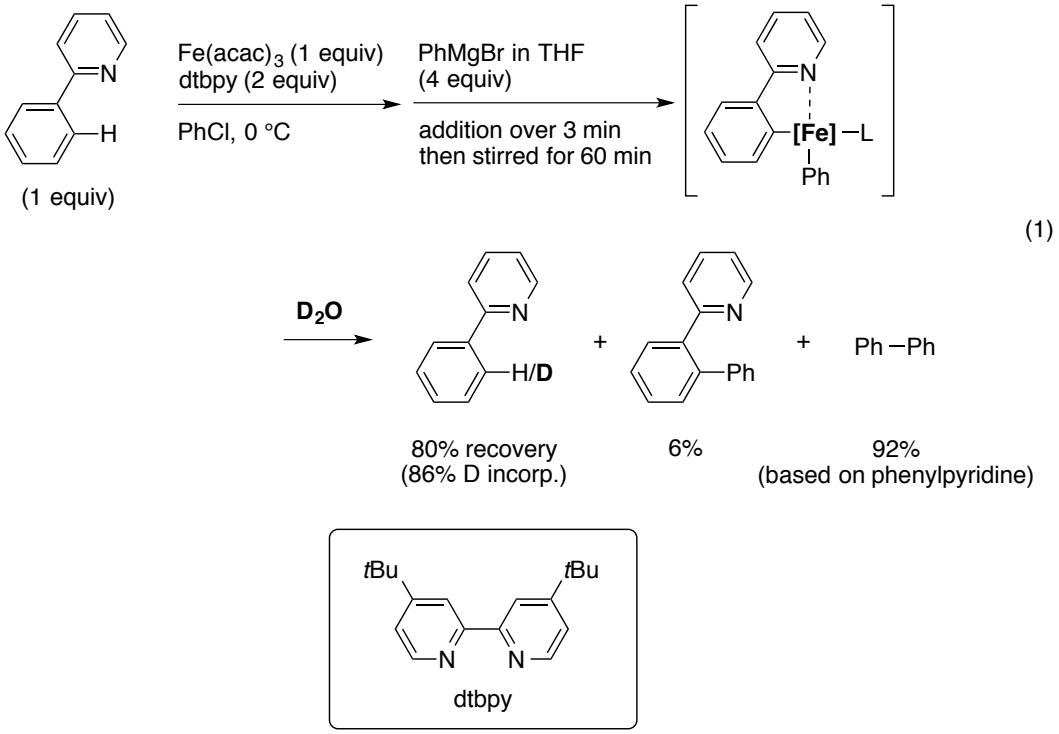
• Investigation of active species through stoichiometric experiments

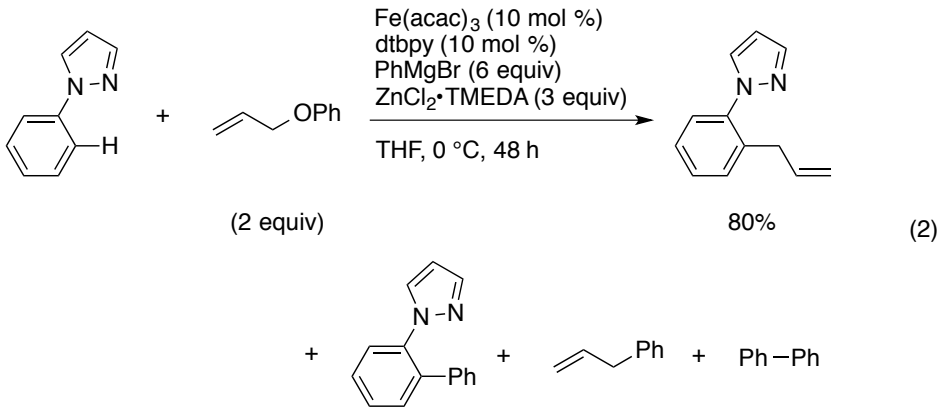
Experiments using a stoichiometric amount of transition-metal (stoichiometric reactions) are often employed in many organometallic reactions to investigate information on the reaction mechanism and determine the active organometallic species.[1] This is also the case for in C–H activation reactions: organometallic species generated from a C–H substrate and a catalyst have been isolated or prepared *in situ*, and then subjected to the reaction with coupling partners to determine the intermediate involved in a catalytic cycle.[2,3] Stoichiometric reactions are also effective when exploring new reactions, through discovery of coupling partners that would react with the organometallic species.

• Previous studies on stoichiometric reactions in C–H activation with iron

As discussed in the previous chapter, one of the most serious problems causing the limited scope of iron catalysis is the instability of the organoiron species. Previously, Nakamura and coworkers investigated the stability of organoiron through stoichiometric experiments using Grignard reagents.[4] When they performed a stoichiometric reaction in the absence of the oxidant, the organoiron species was generated in THF at 0 °C, as indirectly confirmed by *ortho*-deuterium incorporation after quenching by D_2O (eq. 1). The reaction also produced biphenyl (92%, based on phenylpyridine) along with an *ortho*-phenylated compound (6%), suggesting that the intermediate is not stabilized enough and is competing with these side-reactions. Attempts to develop coupling reactions between the organoiron intermediate and electrophiles mostly failed,[5] with one exception when using allyl phenyl ether as the electrophile and 1-phenylpyrazole as the substrate, which was later developed into a catalytic reaction (eq. 2).[6] In most cases, the organoiron species readily produces *ortho*-phenylation via reductive elimination, rather than couple with electrophiles,

which may also act as an oxidant to accelerate reductive elimination.





• Stabilization of the organoiron by bidentate directing group

To establish a robust catalytic system for iron-catalyzed C–H functionalization, the instability problem of the organoiron species should be overcome. One possible reason and a strategy are shown below. According to the putative coordination geometry shown in Figure 1, the instability of organoiron species can be

caused by fast reductive elimination from diaryliron ate species **int2**[7] after coordination of another aryl nucleophile to **int1**. To suppress this undesired pathway, it is necessary to occupy the vacant coordination site of **int1**,[8] and another coordinating heteroatom on the directing group (such as a bidentate directing group) can be considered to occupy the coordination site, through formation of **int3** (Figure 2).

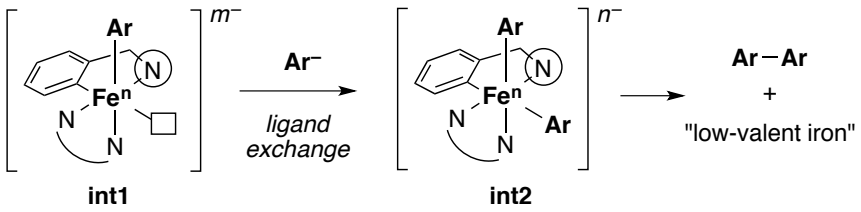


Figure 1. Possible coordination geometry of iron in directed C–H bond activation

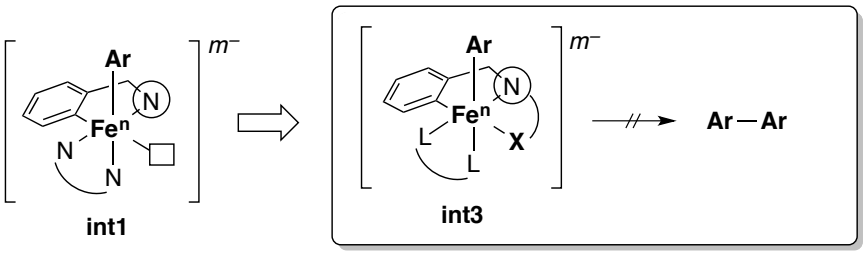
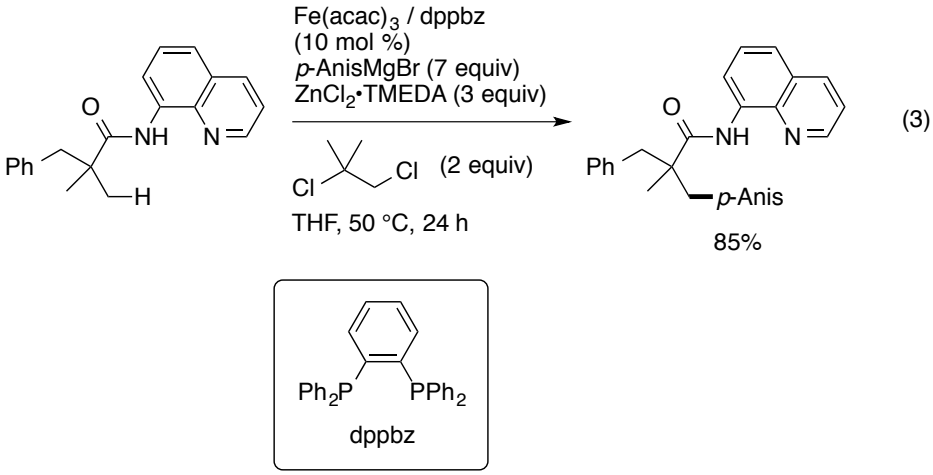


Figure 2. Working hypothesis using a bidentate directing group

The feasibility of using a bidentate directing group for the reaction is supported by successful literature reports using Pd,[9] Cu,[10] Ni[11] and other transition-metal catalysts,[12] including iron-catalyzed directed arylation of C(sp^3)–H bonds reported by Nakamura and coworkers (eq. 3).[13] Based on these backgrounds, I hypothesized that a bidentate directing group might be effective for C(sp^2)–H bond activation using iron catalysys, and enables coupling reactions with electrophiles through stabilization of the organoiron species.



• Investigations described in this chapter

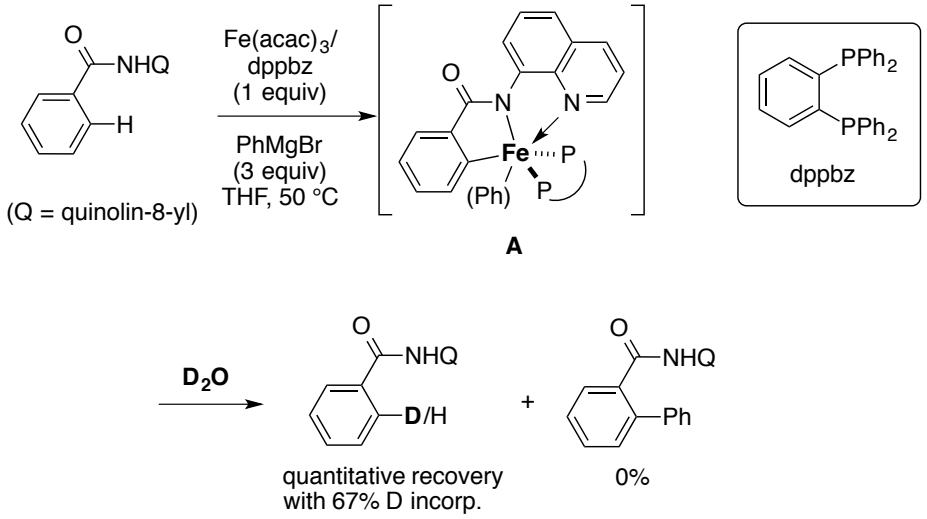
This chapter describes my investigation of a stoichiometric reaction of iron for directed C–H bond activation using a bidentate directing group, aimed to stabilize the organoiron intermediate. Through discovery of an appropriate base and ligand, organoiron species with coordinated by a bidentate directing group was generated, and it was found to be stable even upon heating. Reductive elimination induced by an oxidant was considerably slow, suggesting that the species possesses different reactivity from the species coordinated by a monodentate directing groups.[4]

2-2. Investigation of directing group/ligand in stoichiometric reactions

I performed stoichiometric reactions using aromatic substrates possessing a bidentate directing group according to the reaction sequence developed previously,[4] where an organometallic base (3–4 equiv) was added to the THF solution of substrate (1 equiv), $Fe(acac)_3$ (1 equiv) and ligand (1–2 equiv). After extensive investigations, I discovered that organoiron species (plausible structure is shown as **A** in Scheme 1) could be generated from *N*-(quinolin-8-yl)amide as a substrate, 1,2-bis(diphenylphosphino)benzene (dppbz) as a ligand, and phenylmagnesium bromide as an organometallic base, after mixing for 1 hour at 50 °C (Scheme 1). Following the

literature,[4] existence of **A** was indirectly confirmed by *ortho*-deuteration after quenching with D_2O, and 67% of deuterium incorporation was observed.[14] The intermediate **A** did not decompose at all, and the *ortho*-phenylated product was not observed under the reaction conditions. Homocoupling of the base was observed in ca. 50% yield, suggesting that iron(III) was reduced to generate iron(II)[15] that might be an active species.

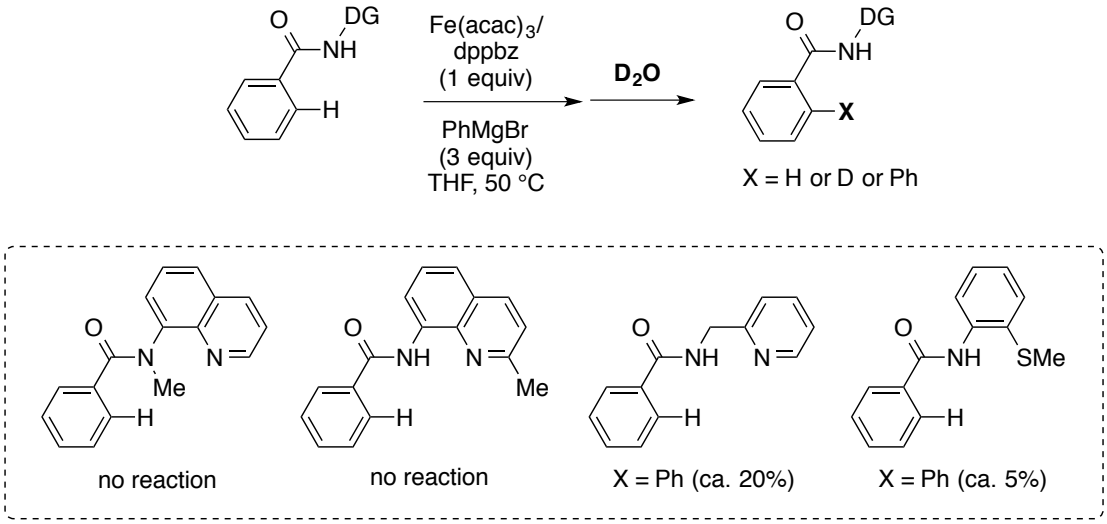
Scheme 1. Organoiron species **A** from *N*-(quinolin-8-yl)amide directing group and a diphosphine ligand



Other bidentate directing groups that worked poorly are shown in Scheme 2. Amide directing groups were chosen because they are easily removed by hydrolysis.[9] Reaction using *N*-(quinolyn-8-yl)benzamide with methyl substituent on amide nitrogen did not work, which means the amide nitrogen is covalently attached to the center iron atom. C2 position of the quinoline completely shut down the reaction, suggesting the sensitivity of the organoiron species to sterics. Reaction with *N*-picolinylbenzamide gave *ortho*-phenylated product in around 20% yield together with a mixture of unidentified compounds, which is possibly caused by the flexibility of the picolinyl group and the acidic proton at the benzyl position. *N*-(2-thioanysyl)benzamide as a N,S-type directing group was almost unreactive. Overall, quinolylamide was found to

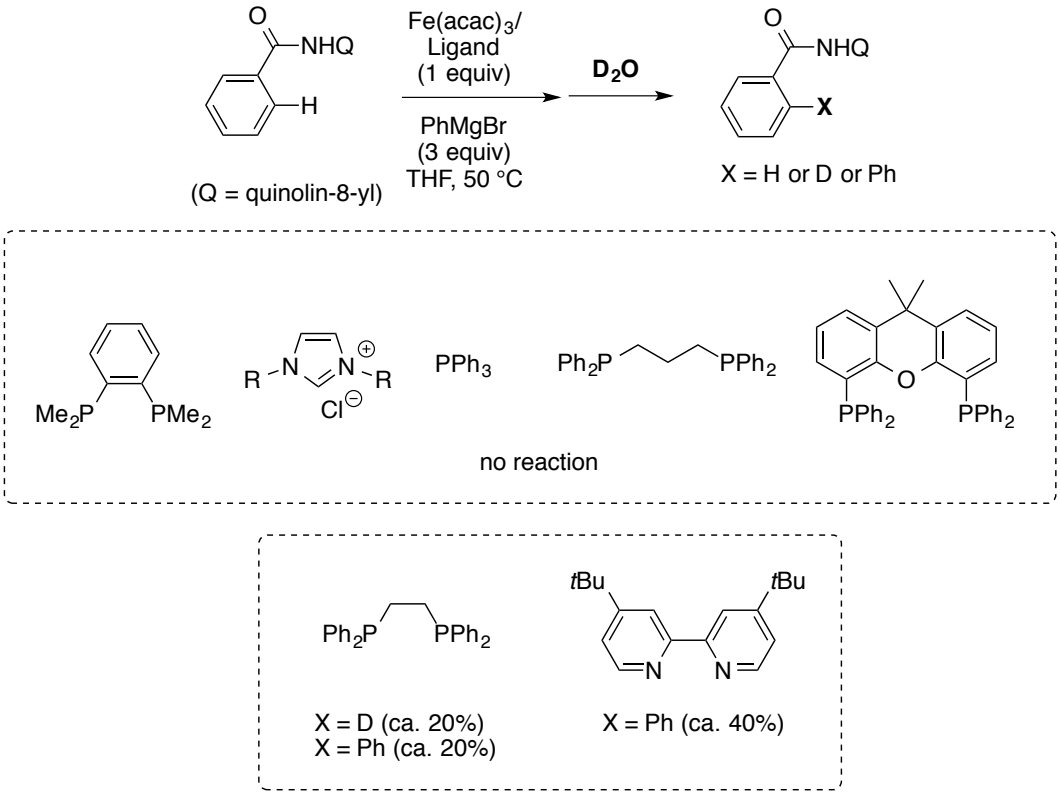
be uniquely effective, probably due to its rigidity and strong coordination ability of nitrogen to iron.

Scheme 2. Examples for ineffective directing groups



The reactions is also very sensitive to the nature of the external ligand (Scheme 3). 1,2-bis(dimethylphosphino)benzene, a dppbz analogue with methyl substituents on phosphine was not effective at all. Other ineffective ligands include monodentate ones such as *N*-heterocyclic carbenes and triphenylphosphine, and diphosphines with wider bite angle such as dppp (1,3-diphenylphosphinopropane) and Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene). A diphosphine possessing a saturated backbone and similar bite angle with dppbz, dppe (1,2-diphenylphosphinoethane) worked less efficiently, give the *ortho*-phenylated product. An organoiron in the presence of dtbpy as a ligand was mostly decomposed to give the phenylated product. From these results, it can be concluded that a diphosphine with aromatic substituent and rigid backbone is necessary for stabilization of the organoiron.

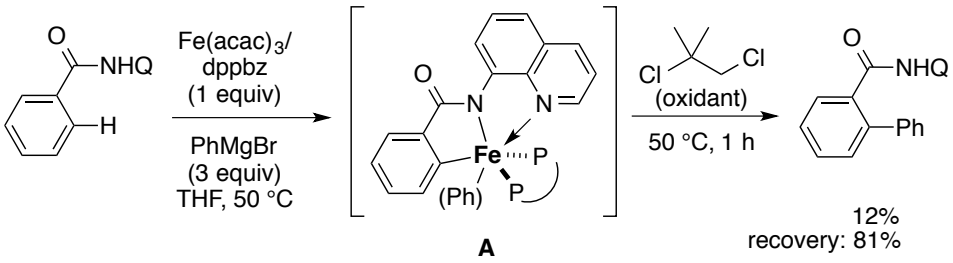
Scheme 3. Examples of ineffective ligands



2-3. Examination of stability of the intermediate against organic oxidant

The newly formed organoiron species was found to be stable at 50 °C, which is sharp contrast to the species coordinated by a monodentate directing group. To further assess the stability, next I examined the reactivity of **A** toward oxidant that might induce reductive elimination (Scheme 4). Into the solution of **A**, 1,2-dichloroisobutane (DCIB)[16] was added and stirred at 50 °C for 1 hour, to find that the *ortho*-phenylation product was formed in 12% yield, while 59% of phenylation product was obtained when the monodentate directing group was used.[4] Thus, I could confirm the improved stability of organoiron even in the presence of an oxidant accelerates reductive elimination, which is promising to develop novel reactions with coupling partners such as electrophiles.[17]

Scheme 4. Reaction of **A** with an organic oxidant DCIB



2-4. Conclusion

In conclusion, a stabilized ferracycle intermediate could be generated from an aromatic substrate possessing *N*-(quinolin-8-yl)amide as a bidentate directing group and dppbz as a ligand. The intermediate is stable and does not decompose below 50 °C, which is sharp contrast to the case of monodentate directing group. Reductive elimination affording *ortho*-arylation in the presence of DCIB was considerably slow, which means that the organoiron was also stable toward oxidant. Results obtained herein will be used to design a robust catalytic system using iron as a catalyst, as described in the next chapters.

2-5. Experimental

Materials and instruments

All reactions dealing with air- or moisture-sensitive compounds were performed by standard Schlenk techniques in oven-dried Schlenk tubes under an argon atmosphere. Flash chromatography was performed as described by Still *et al.*,[18] employing Kanto Silica gel 60 (spherical, neutral, 140-325 mesh). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECA-500 (500 and 125 MHz) and JEOL ECX-400 (400 and 100 MHz) NMR spectrometer. ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (7.26 and 77.0 ppm), respectively. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-14B instrument equipped with an FID detector and a capillary column, HR-1 (25 m x 0.25 mm i.d., 0.25 mm film).

Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used after appropriate purification before use. Anhydrous tetrahydrofuran was purchased from KANTO Chemical Co. and purified prior to use by a solvent purification system (GlassContour) equipped with columns of activated alumina and copper catalyst.[19] The water content was determined with a Karl-Fischer moisture titrator (MKC-210, Kyoto Electronics Company) to be less than 30 ppm. Phenylmagnesium bromide was prepared from bromobenzene and magnesium turnings in anhydrous tetrahydrofuran, and titrated prior to use using I_2 in THF saturated with LiCl (0.5 M).[20]

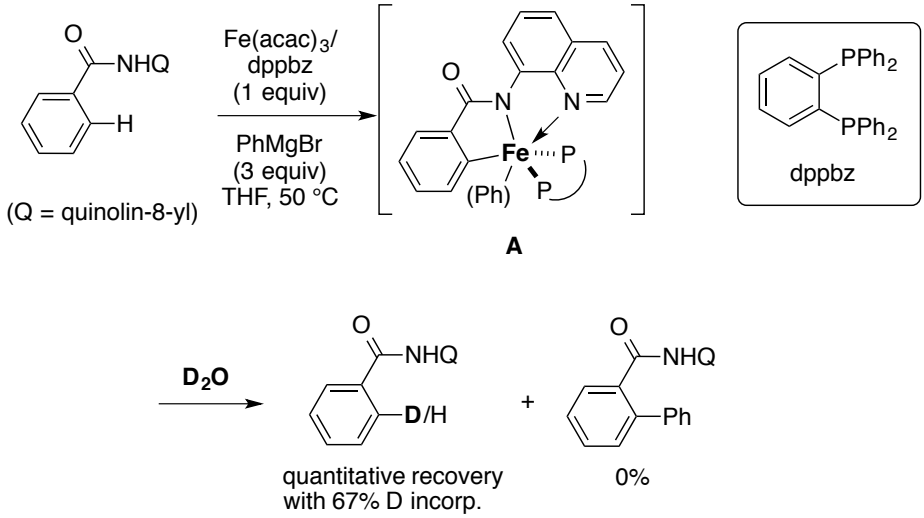
Preparation of the starting materials

General procedure for preparation of amides: synthesis of N-(quinolin-8-yl)benzamide

Benzoic acid (10 mmol) was placed in an oven-dried two-necked flask and thionyl chloride (10 mL) was added under a nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 60 min, and then the excess thionyl chloride was removed *in vacuo*. The flask was cooled to 0 °C, the reaction mixture was diluted with dichloromethane (100 mL), then triethylamine (5 mmol) and 8-aminoquinoline (11 mmol) were added and the reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution, and the organic layer was separated, and the aqueous layer was extracted with dichloromethane for 3 times. The organic layer was dried over magnesium sulfate, and then the solvent was evaporated. The residue was passed through a pad of silica gel to remove unreacted 8-aminoquinoline. The crude compound was recrystallized to afford the pure amide.

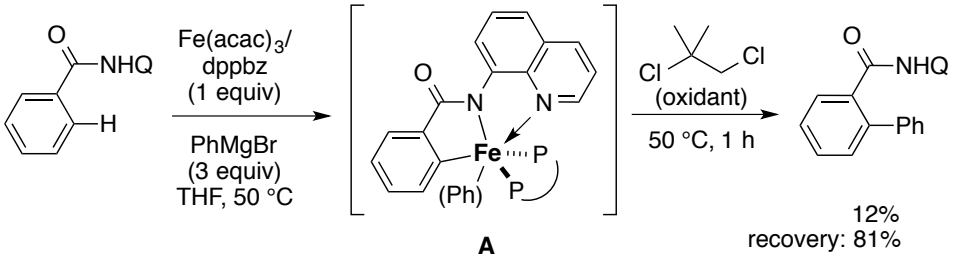
Compound data for amides described in this chapter were in good agreement in previous literatures.[21]

Procedure for stoichiometric reactions: reaction with D_2O (Scheme 1).



In a Schlenk tube *N*-(quinolin-8-yl)benzamide (25 mg, 0.10 mmol), $Fe(acac)_3$ (35 mg, 0.10 mmol), and 1,2-bis(diphenylphosphino)benzene (dppbz, 45 mg, 0.10 mmol) were dissolved in THF (1 mL). A solution of PhMgBr in THF (0.34 mL, 0.89 mol/L, 0.30 mmol) was added dropwise and the resulting mixture was stirred at 50 °C to generate the intermediate **A**. D_2O was added to this solution and the mixture was stirred at rt for 5 min. The reaction mixture was quenched by the addition of a saturated solution of potassium sodium tartrate (0.3 mL). After aqueous workup, the organic layer was extracted with EtOAc (2 mL × 3). The combined organic layers were passed through a pad of Florisil, and concentrated *in vacuo*. The amount of recovery and the degree of deuterium incorporation were determined by ^{1}H NMR. *Ortho*-phenylated product was not detected by ^{1}H NMR.

Procedure for stoichiometric reactions: reaction with DCIB (Scheme 4).



A solution of **A** was prepared according to the procedure described in the reaction with D_2O. 1,2-Dichloroisobutane (23 μL, 0.2 mmol) was added to this solution and the mixture was stirred at 50 °C for 30 min. After workup, the amount of phenylation product and the recovery were determined by ^1H NMR measurement of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard.

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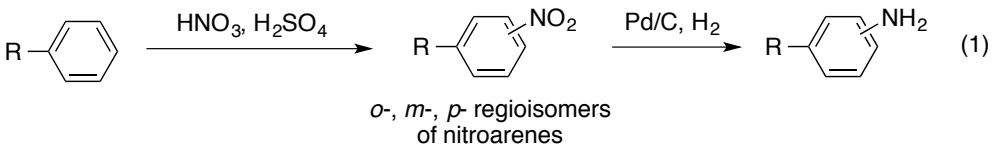
Chapter 3.

Ortho-Amination of Aromatic Carboxamides with *N*-Chloroamines

3-1. Introduction

• Synthesis of anilines through C(sp^2)–N bond forming reactions

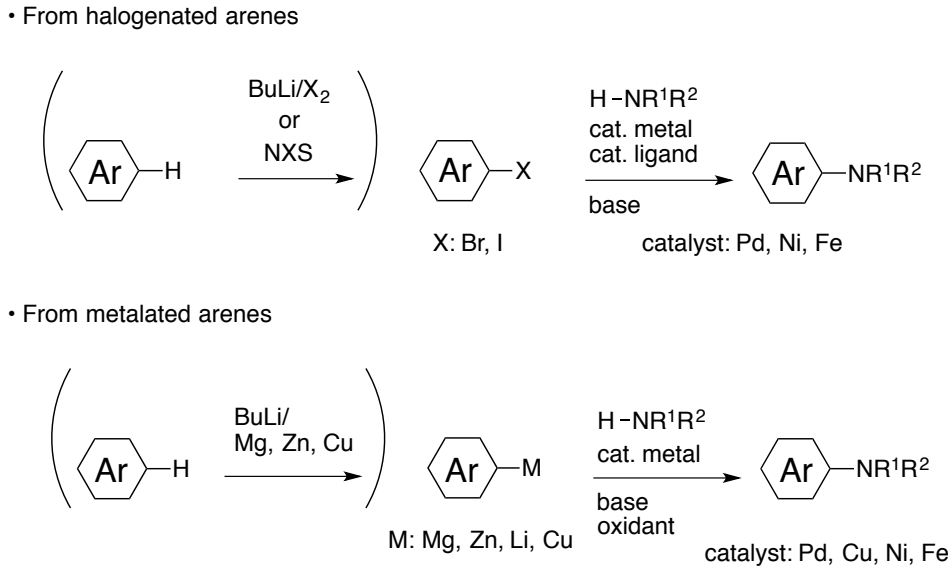
Formation of a C(sp^2)–N bond from an aromatic substrate and a nitrogen source provides rapid access to functionalized anilines, compounds widely utilized and have attracted much attention in medicinal chemistry and materials science.[1] Traditional approaches for anilines from arenes include the direct nitration of an arene with nitronium ion generated from nitric acid and sulfuric acid,[2] followed by reduction to afford the aniline product (eq. 1).[3] However, this approach suffers from poor regioselectivity when a substituted arene is used as the starting material, and the reaction efficiency is strongly affected by substituents. For example, electron-withdrawing substituents on the substrate shut down the reaction.



(1)

Transition-metal-catalyzed cross-coupling reactions between a (pseudo)halogenated[4,5,6] or metalated[7,8] aromatic substrate and an amine is an alternative approach, where the C–N bond is formed under much milder reaction conditions (Scheme 1).[9] However, as already discussed in chapter 1, cross coupling reactions require pre-halogenation/metalation of an aromatic substrate that also suffers from poor regioselectivity, additional synthetic steps and costs.

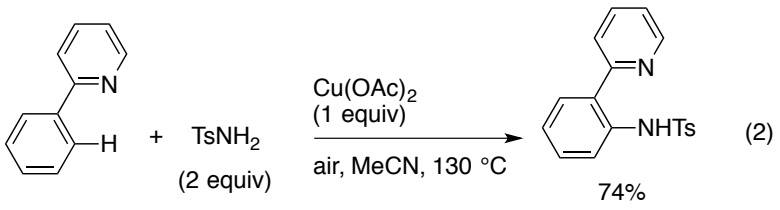
Scheme 1. Transition-metal-catalyzed cross-coupling for the synthesis of aniline derivatives

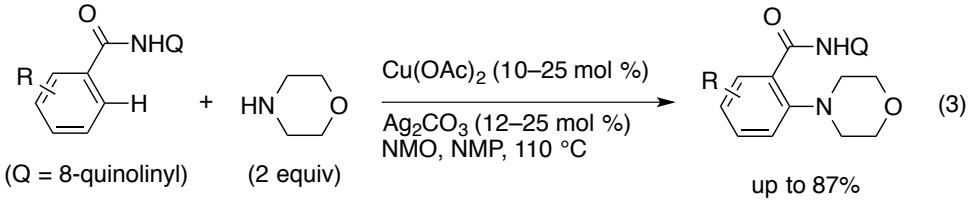


• Amination of a C(sp^2)–H bond with a nucleophilic amine under oxidative conditions

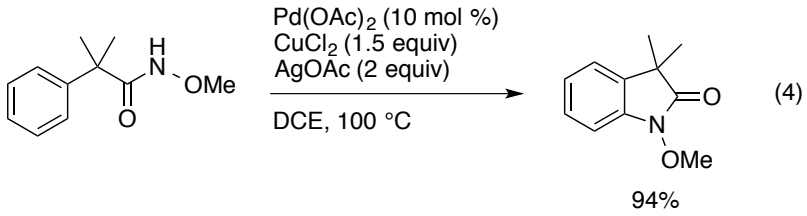
Because of the reasons mentioned above, regioselective activation of the C(sp^2)–H bond of an aromatic substrate, followed by reaction with a nucleophilic amine to form a C–N bond is considered to be an ideal synthesis of anilines, but such reactions have rarely been achieved because of the difficulty of either C–H bond activation or C–N bond forming steps.[10]

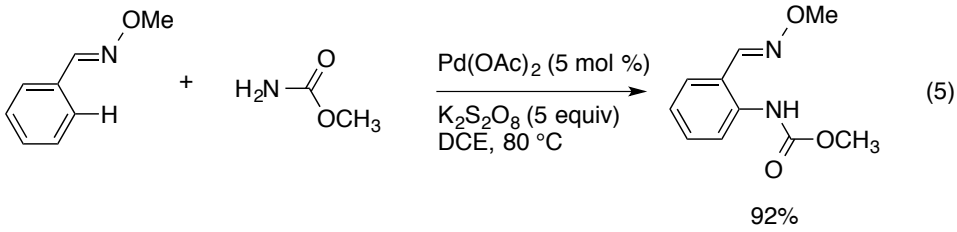
In 2006, Yu and coworkers reported the first example of the amination of C(sp^2)–H bonds of an aromatic substrate, where the *ortho* C–H bond of 2-phenylpyridine is activated through radical pathway using a stoichiometric amount of copper, followed by reaction with a tosylamine to produce an *ortho*-aminated product in good yield (eq. 2).[11] A similar reaction was reported by Chatani at almost the same time, using an aromatic amine as the aminating reagent with lower efficiency.[12] The reaction system was modified by Daugulis and coworkers recently, where a *N*-(quinolin-8-yl)benzamide was employed as a substrate (eq. 3).[13] However, the reaction still requires large amount of copper and toxic oxidants, and in most cases the reaction does not give the product in satisfactory yield.[14,15]





Other literature examples for C(sp^2)–H amination using nucleophilic amines include palladium-catalyzed intra-[16] and intermolecular[17] amidations (eqs. 4 and 5), which mostly suffer from limited scope.[18,19,20] Moreover, these reactions have to be operated under harsh reaction conditions with strong/toxic oxidants to accelerate C–N bond forming reductive elimination, which will decompose sensitive substituents and limits versatility of the reaction.

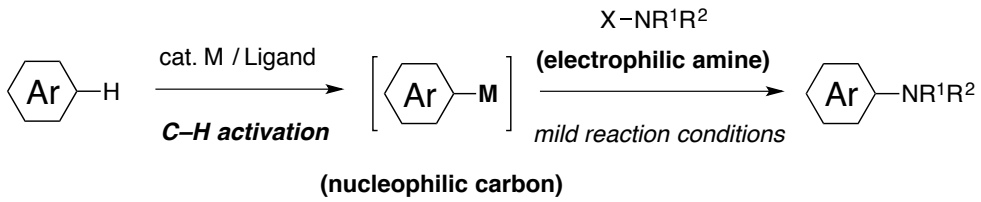




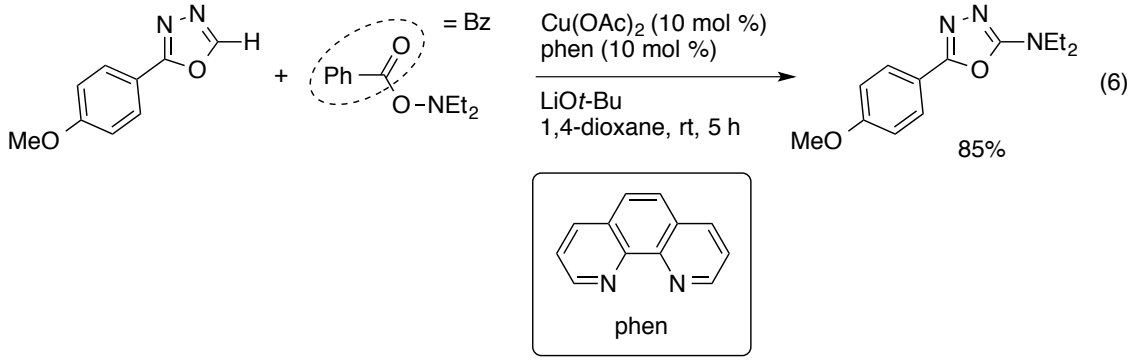
• Umpolung amination with electrophilic nitrogen source

Recently the repertoire of C(sp^2)–H bond amination reactions has been rapidly expanding, after the discovery of an "umpolung" amination strategy using an electrophilic nitrogen as the amine source (Scheme 2).[21] Because the electrophilic amine can react with a nucleophilic organometal intermediate through electrophilic amination,[22] the reaction can be operated under milder reaction conditions with broader scope.

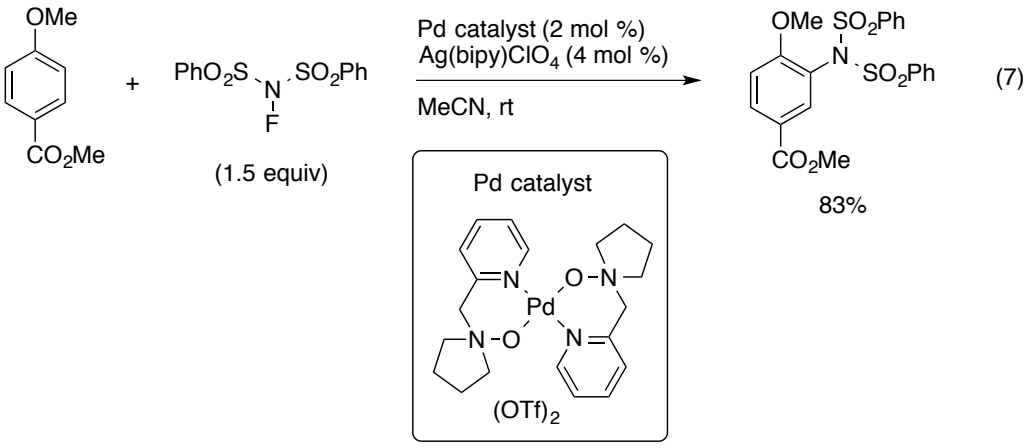
Scheme 2. Concept for "umpolung" C–H amination



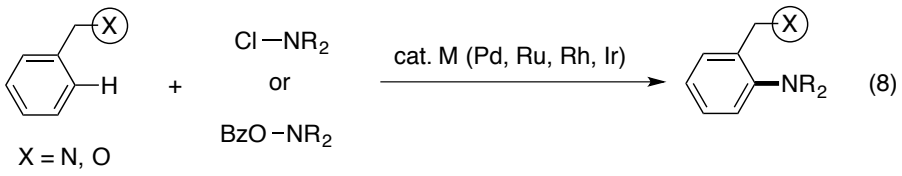
The umpolung amination strategy enabled synthetic chemists to achieve a variety of methodologies for C–H amination reactions using transition-metal catalysts. Hirano, Miura and coworkers achieved copper-catalyzed amination of electron-deficient heteroaromatic C–H bonds using *N*-oxyamines (eq. 6).[23] Similarly, Ritter and coworkers developed amination of electron-rich anisole derivatives using palladium catalysis (eq. 7).[24]



(6)



Importantly, the amination reaction of an aromatic substrate possessing a directing group has also been recently established, using late transition-metals (eq. 8).[25,26,27] Thus, amination of a C(sp^2)–H bond became much easier to proceed using electrophilic nitrogen. To further improve its utility, achievement of such a reaction using an inexpensive metal catalyst[23,28] is highly desired.[29]

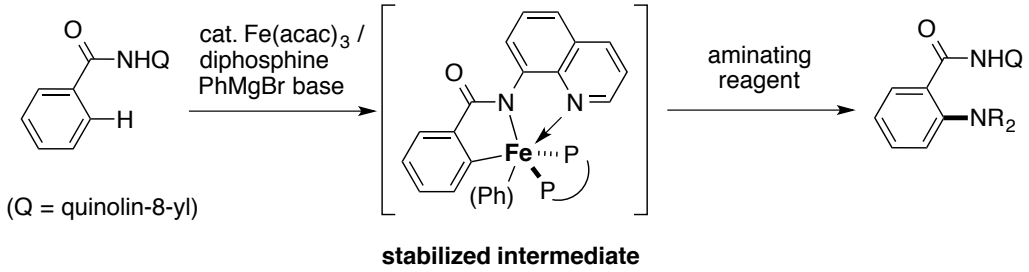


• Reactions described in this chapter

Taking into account this backgrounds, I focused on achieving directed C(sp^2)–H amination using iron as a catalyst, which is described in this chapter. In previous chapter, I achieved the generation of an organoiron species using a bidentate directing group that is stable upon heating and hardly decomposes in the presence of an oxidant. With this species in hand, I hypothesized that the organoiron intermediate would react with nucleophilic or electrophilic aminating reagents, to afford aniline derivatives through C–N bond formation (Scheme 3). To this end, I discovered that the reaction of organoiron with a *N*-chloroamine proceeded to give *ortho*-aminated product,

and finally achieved *ortho*-amination of aromatic amides using iron as a catalyst. Importantly, the reaction does not require any toxic oxidants, and can be performed under mild reaction conditions, to produce anthranilic acid derivatives that exhibit interesting biological and photochemical properties.[30]

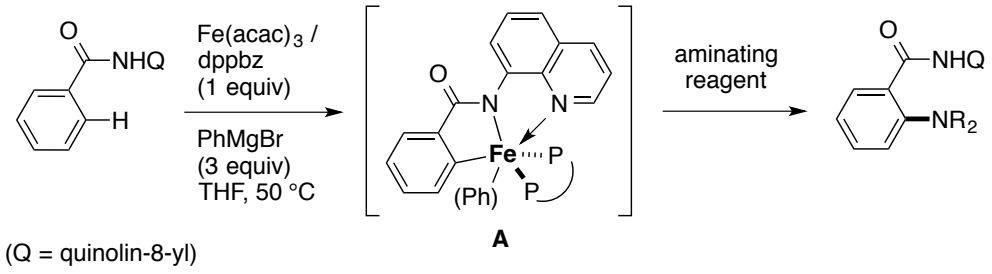
Scheme 3. Working hypothesis for *ortho*-amination of amide using iron catalysis, through reaction of organoiron with an amine



3-2. Reaction design for *ortho*-aminaton of aromatic amides through C–H activation with stoichiometric amount of iron

To achieve the *ortho*-amination reaction using iron, initially I designed conditions for a stoichiometric reaction according to the previous investigations described in chapter 2, where organoiron species **A** was generated from an aromatic amide possessing *N*-(quinolin-8-yl)amide as a bidentate directing group, 1,2-diphenylphosphinobenzene (dppbz) as a ligand and aryl Grignard reagent as a base. I explored an appropriate aminating reagent that would react with **A** to form a C–N bond at the *ortho*-position of the amide (Scheme 4).

Scheme 4. Design of a stoichiometric reaction for *ortho*-amination



(Q = quinolin-8-yl)

After investigations, I found that *N*-chloromorpholine reacts with **A** to give an *ortho*-aminated product in 60% yield (eq. 9). Other amine sources such as nucleophilic zinc- and magnesium amides[6,8a,c] and amines in the presence of inorganic bases were also investigated, but they were not reactive at all (Figure 1). Control experiments revealed that the bidentate directing group, the diphosphine ligand and the iron salt are necessary. Other ligands such as dinitrogen ligands or NHC (*N*-Heterocyclic Carbene) ligands were not effective: recovery of the starting material, or *ortho*-phenylated product was observed.[31] Other organometallic reagents such as alkyl Grignard reagents or organozinc reagents were not effective for the *ortho*-amination reaction.

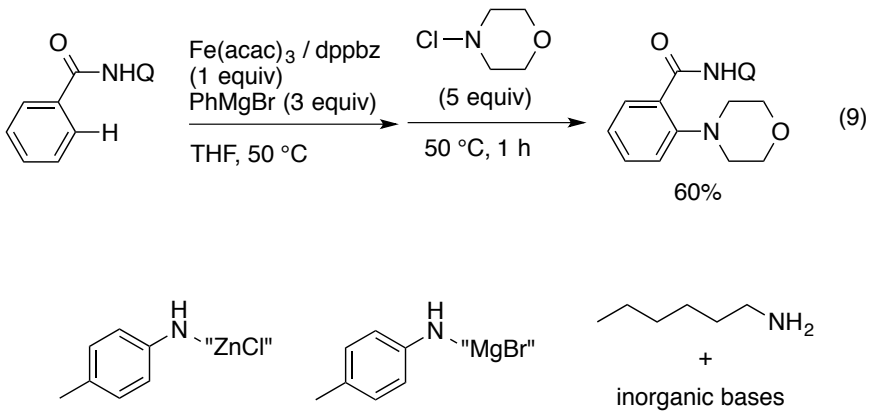
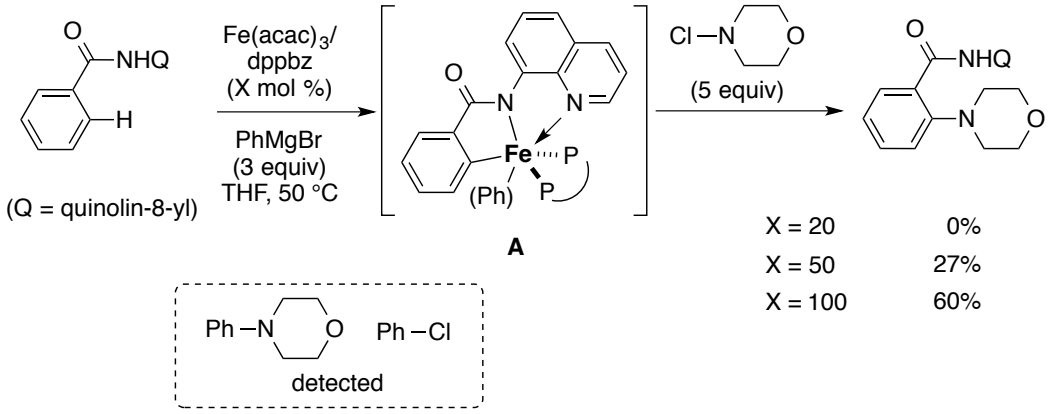


Figure 1. Examples of unreactive nucleophilic amines

3-3. *Ortho*-amination of amides using a catalytic amount of iron

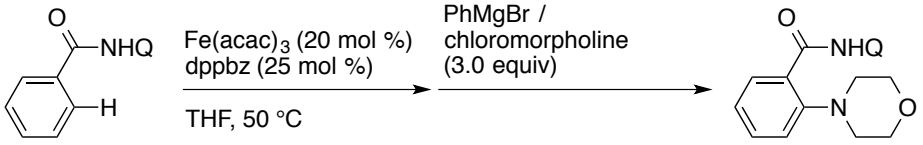
With the result of a stoichiometric reaction in hand, next I performed the reaction with a chloroamine using a catalytic amount of iron/diphosphine, to confirm the reaction would proceed with catalytically (Scheme 5). The reaction was largely suppressed when 50 mol % of $Fe(acac)_3$/dppbz was used, and did not take place with 20 mol % of the catalyst. In all entries, the yield of the aminated product did surpass the amount of catalyst loading, which means the reaction is not catalytic in iron. As a matter of fact, I observed *N*-phenylmorpholine and chlorobenzene by GC analysis, suggesting these reagents were decomposed through a side reaction between *N*-chloroamine and PhMgBr.[32]

Scheme 5. Amination reaction with a catalytic amount of iron/dppbz



Then I changed the reaction operation to suppress the side reaction, and I slowly added the reagents. Slow addition of a reagent is sometimes effective to obtain product selectivity, if the desired reaction is faster than the side reaction.[33,34] However, slow addition of PhMgBr or chloroamine was not effective to achieve catalytic turnover, and the desired product was not obtained at all (Scheme 6). This suggests that the side reaction[32] is much faster than the desired ferracycle formation / electrophilic amination pathway.

Scheme 6. Slow addition of PhMgBr or chloroamine



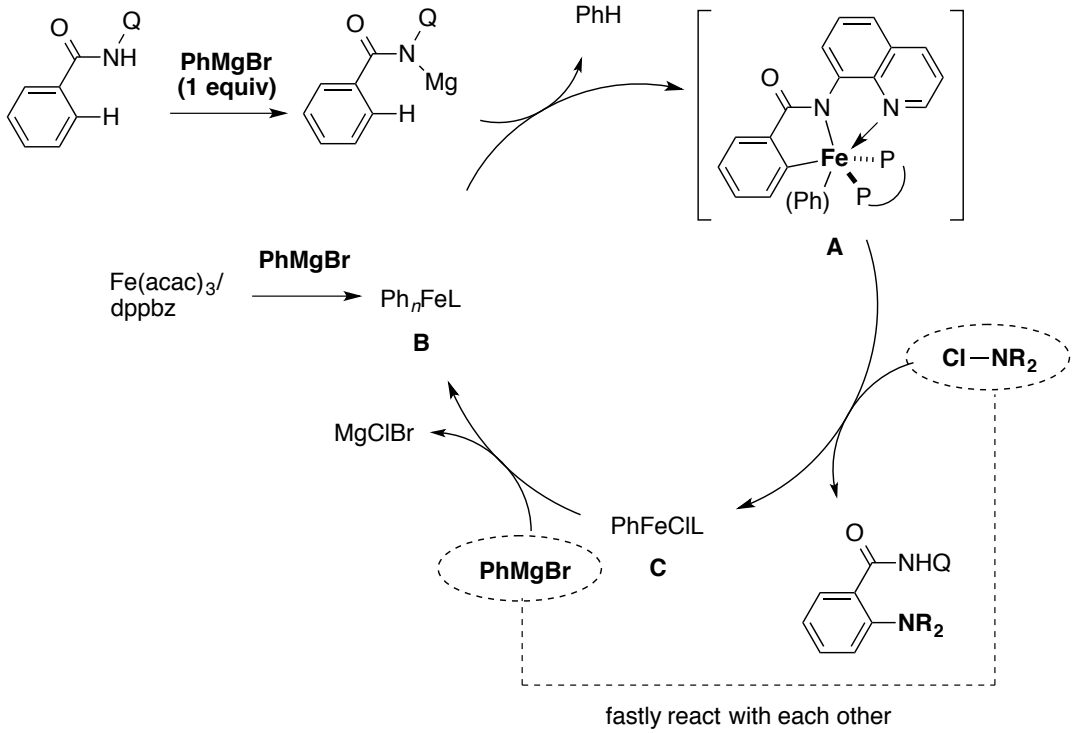
slow addition reagent	yield of the product (%)
PhMgBr	0
chloromorpholine	0

3-4. Strategy to obtain catalytic turnover

The problem and the strategy to achieve catalytic turnover can be explained

by considering the possible catalytic cycle (Scheme 7). According to the catalytic cycle, PhMgBr is consumed to generate an iron active species **B**, as well as deprotonating the starting amide substrate. The amide and **B** form ferracycle **A**, which then reacts with chloroamine to give the product and iron species **C**. If **C** reacts with PhMgBr to regenerate **B**, catalytic turnover should be achieved. However, as already discussed, PhMgBr and chloroamine will react with each other,[32] and this is the problem to overcome in order to obtain catalytic turnover.

Scheme 7. Possible catalytic cycle for the amination reaction



To overcome this dilemma, I considered mimicking the catalytic cycle by controlling the addition sequence of reagents. If the active ferracycle **A** could form from **C**, and if **A** would react with chloroamine to give the product again, then the amination reaction would proceed catalytically. To achieve this scenario, I considered adding alternative addition of PhMgBr and chloroamine in the presence of the amide substrate and catalyst (Figure 2).

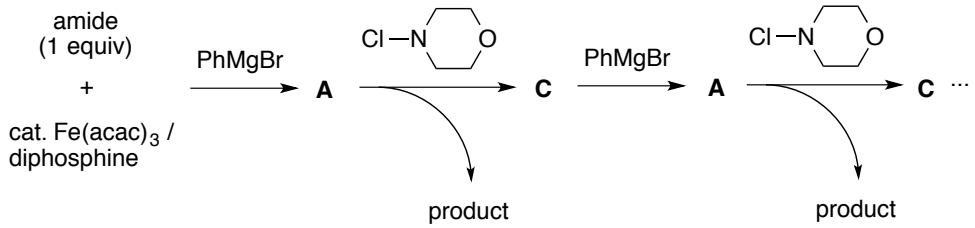
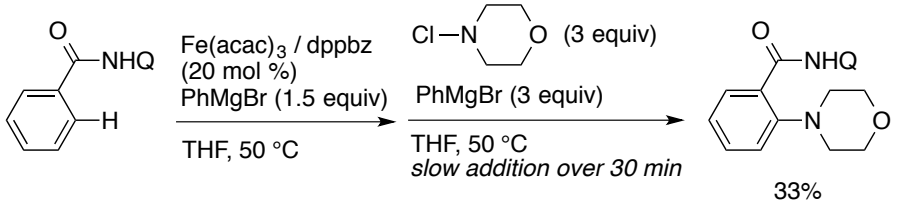


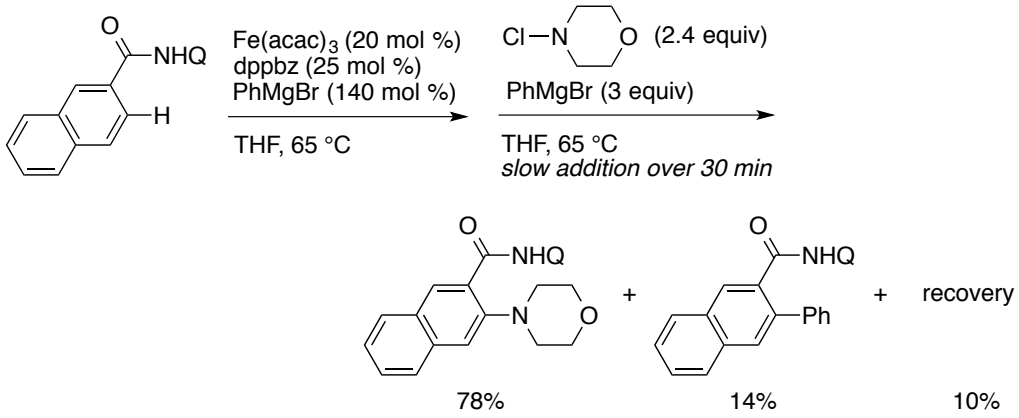
Figure 2. Strategy to obtain catalytic turnover:
mimicking the catalytic cycle by controlling the addition sequence

I designed the reaction conditions according to this hypothesis. Thus, after deprotonation of the amide and generation of organoiron **A** by adding PhMgBr (1.5 equiv), a THF solution of PhMgBr and a THF solution of chloroamine (3 equiv each) were added simultaneously to the mixture over 30 min, to find 33% of the *ortho*-aminated product was obtained with 20 mol % of iron catalyst (Scheme 8), which is a strong evidence for catalyst turnover by "double" slow addition. Further optimizations were performed motivated by this result, to find that careful tuning of the addition rate and ratio of the reagents dramatically affects the reaction outcome. Finally I obtained 78% of the aminated product along with the 14% of the phenylated product, with 20 mol % of iron catalyst. (Scheme 9). C–H activation and electrophilic amination steps are both fast enough to complete the reaction within 30 minutes.

Scheme 8. "Double" slow addition of PhMgBr and chloroamine



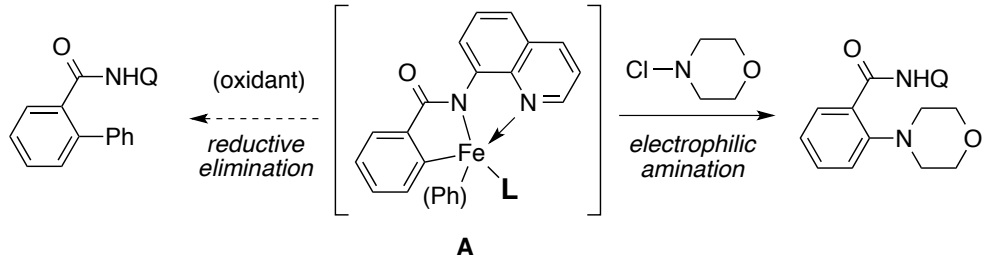
Scheme 9. Optimized result for catalytic amination of C–H bond with iron/dppbz



3-5. Effect of ligand on product selectivity

To improve the product selectivity, further optimization of the reaction conditions was performed. The formation of a phenylated product in 14% (Scheme 9) suggests that the iron intermediate partially decomposed through reductive elimination,[31] in the presence of oxidant (chloroamine). Therefore, further improvement of stability of **A** toward oxidant was considered to be effective for suppression of the phenylation pathway (Scheme 10).

Scheme 10. Possible pathways from **A**: phenylation and amination

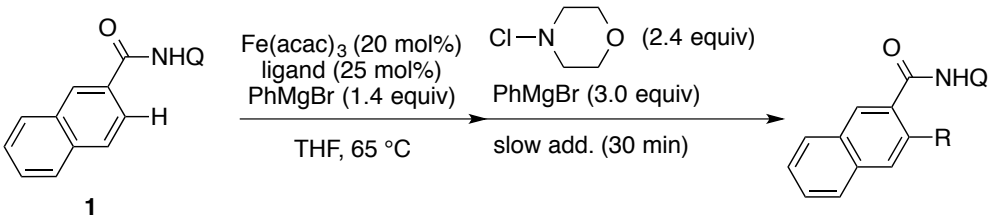


A

I investigated the ligand for the amination reaction, because the nature of ligand on **A** strongly affects its stability (Table 1).[31] Initially the reaction was performed without any ligand, to find that the starting amide was recovered together with a mixture of unidentified side products (entry 1). TMEDA as a ligand was also ineffective for the

desired amination (entry 2), suggesting that the active species is different from an organomagnesium species, as suggested in a previous study by other chemists.[32] A dinitrogen ligand such as dtbpy is not effective for amination, and the reaction mostly gave the phenylated product through reductive elimination (entry 3). Reactions using diphosphine ligands afforded the aminated product (entries 4–6), but a diphosphine bearing a saturated backbone produced a mixture of the aminated and phenylated product in almost 1:1 ratio, suggesting that **A** is not stablilized enough to produce the amination product selectively (entry 4). Diphosphines with a conjugated backbone such as dppbz (entry 5) and dppen (entry 6) gave products with higher selectivity.

Table 1. Effect of ligands on product selectivity



1

2: R = N O

3: R = Ph

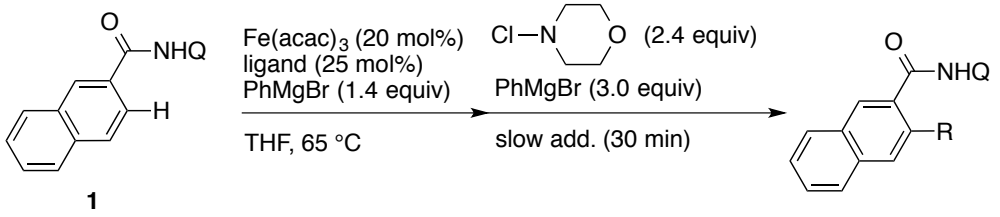
entry	Ligand	NMR yield (%)		
		2	**3**	**1**
1	none	0	4	59
2	TMEDA (1.5 eq)	0	0	98
3	dtbpy	0	41	51
4	dppe	27	30	1
5	dppen	81	12	10
6	dppbz	78	14	10

using 1,1,2,2-tetrachloroethane as an internal standard.

Next I examined the electronic effect of the dppbz ligand on the product selectivity,[35] because stability of organometallic complexes is typically highly affected by electronic bias of ligands.[36] I prepared a series of dppbz derivatives possessing methoxy or fluoro substituents, and used them for the amination reaction (Table 2). The ligand with electron-donating methoxy substituent (**L2**, MeO-dppbz) accelerated the

phenylation and the product selectivity became lower, suggesting that intermediate **A** became less stable toward oxidation (entry 1). On the other hand, a ligand with electron-withdrawing fluorine substituent (**L3**, F-dppbz) gave the desired product with improved selectivity, and I obtained the product in 87% yield with a trace amount of phenylated byproduct (entry 2). This indicates that decreasing the electron density on the iron center by introducing electron-withdrawing substituents on the ligand stabilized intermediate **A** toward oxidation. Further installation of fluorine on the ligand (**L4**, F_2-dppbz and **L5**, F_3-dppbz) slowed down the reaction (entries 4 and 5).

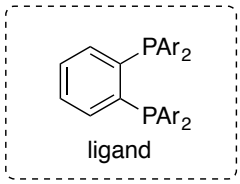
Table 2. Amination with electronically-biased dppbz derivatives



1

2: R = —N O

3: R = Ph



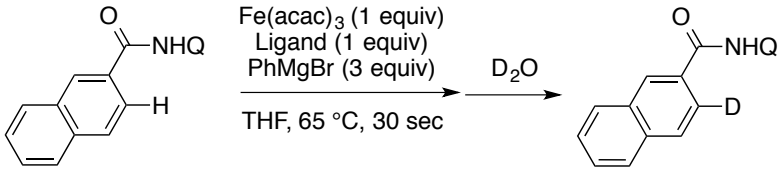
entry	ligand (Ar)	NMR yield (%)		
		2	**3**	**1**
1	**L1** (Ph)	78	14	10
2	**L2** (4-$MeOC_6H_4$)	44	34	31
3	**L3 (4-FC_6H_4)**	**87**	**1**	**17**
4	**L4** (3,4-$F_2C_6H_3$)	42	3	55
5	**L5** (3,4,5-$F_3C_6H_2$)	22	2	81

using 1,1,2,2-tetrachloroethane as an internal standard.

The results with ligand **L4** and **L5** in Table 2 suggest that the electronic property of a ligand can also affect the efficiency of C–H activation step. I performed stoichiometric reactions with ligands **L1**–**L5** and quenched the reaction after 30 seconds with D_2O to compare the initial rate of the C–H activation step (Table 3). Reaction with **L1**–**L3** smoothly proceeded to generate the intermediate **A** in 30 seconds, producing *ortho*-deuterated benzamide in similar yields (entries 1–3). On the other hand, when I used **L4** or **L5** as a ligand, the reaction was considerably slower and deuterium

incorporation was only 25% and 7%, respectively (entries 4–5). From these results, **L3** was determined to be the best ligand with respect to stabilization of organoiron **A** toward oxidation, while also maintaining the efficiency of the C–H activation step.

Table 3. Ligand effect on the rate of the C–H activation event



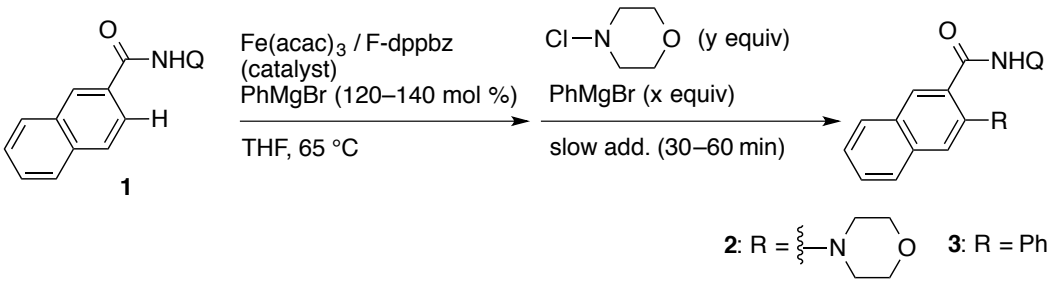
entry	ligand	**D incorp. (%)**
1	**L1** (dppbz)	**67**
2	**L2** (MeO-dppbz)	**52**
3	**L3** (F-dppbz)	**62**
4	**L4** (F_2-dppbz)	**25**
5	**L5** (F_3-dppbz)	**7**

Determined by EI-MS.

3-6. Optimization of the PhMgBr : chloroamine ratio

The reaction was further optimized using F-dppbz as a ligand (Table 4). Changing the ratio of PhMgBr : chloroamine improved both product selectivity and the yield of the aminated product, and I finally discovered that a slight excess amount of PhMgBr to chloroamine (ratio of 2.6:2.4) was the best ratio for the reaction (entries 1–4), probably due to undesired consumption of PhMgBr in homocoupling.[37] The catalyst loading could be decreased to 10 mol %, retaining the reaction efficiency (entry 6). Increasing the amount of the reagents while keeping their ratio (ratio of 3.0:2.7) furnished almost quantitative conversion of the amide into the aminated product (entry 7). In all entries, the phenylated product was suppressed by using F-dppbz as the ligand.

Table 4. Optimization of the PhMgBr : chloroamine ratio



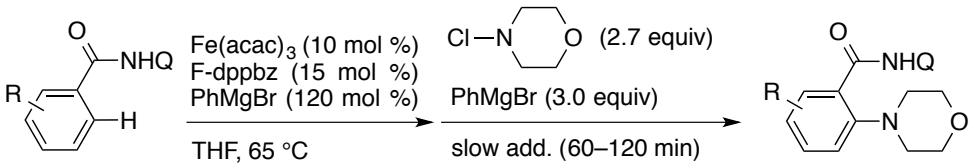
entry	$Fe(acac)_3$/F-dppbz (mol %)	PhMgBr : Cl–NR_2 (x : y)	NMR yield (%)		
			2 (R = NR_2)	**3** (R = Ph)	**1** (recov)
1	20/25	3.0 : 2.4	69	5	25
2	20/25	2.8 : 2.4	81	1	16
3	20/25	2.7 : 2.4	87	1	17
4	20/25	2.6 : 2.4	93	2	6
5	10/15	2.15 : 2.0	80	3	21
6	10/15	2.6 : 2.4	90	3	10
7	**10/15**	**3.0 : 2.7**	**99**	**3**	**6**

3-7. Substrate scope for *ortho*-amination

With the optimized reaction conditions in hand, I investigated the scope of aromatic amide substrates (Table 5). Most of the substrates that I examined gave the desired amination product in over 90% yield, which demonstrates the high reactivity of iron as a catalyst compared to other transition-metals.[21–28] Benzamides *para*-substituted by methyl (entry 2), methoxy (entry 3), trifluoromethyl (entry 4), and halide groups (entries 5–6) were successfully aminated in good yield with complete monoselectivity.[38] Amides bearing electron-withdrawing substituents (entry 4–6) required longer time for slow addition to complete the reaction, because the C–H activation step slower for electron-deficient substrates.[39,40] The reaction of 4-bromobenzamide also took place to give the product in 54% yield, with debrominated product in 9% yield (entry 7). The

reaction of amides *meta*-substituted by methyl (entry 8), methoxy (entry 9), dimethylamino (entry 10), and fluorine groups (entry 11) also took place smoothly, but strong electron-withdrawing substituents such as trifluoromethyl slowed down the reaction even with elongated reaction time (entry 12). *Ortho*-substitution on benzamide completely shut down the reaction, highlighting the high sensitivity of iron catalysis to sterics (entry 13).[38] Naphthaleneamide also participated into the reaction to give the aniline derivatives quantitatively (entry 14). Amination of thiophene (entry 15) and indole (entry 16) also proceeded, which is rare example of directed amination reaction of hetroaromatic substrate.

Table 5. Scope of aromatic amides for *ortho*-amination



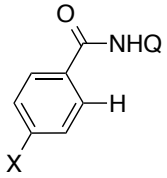
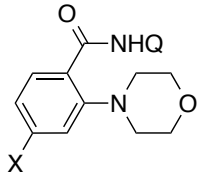
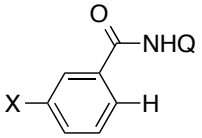
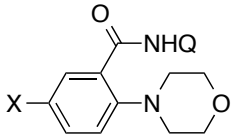
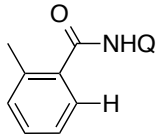
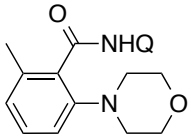
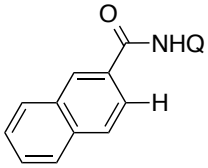
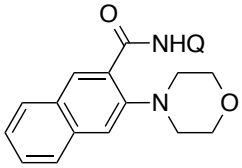
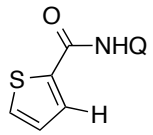
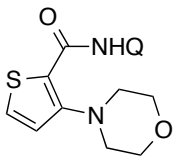
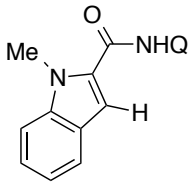
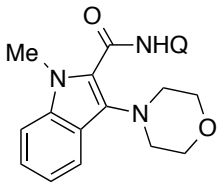
entry	substrate	product			yield (%)
1			X =	H	91
2				Me	96
3				OMe	92
4				CF_3	91
5				F	92
6				Cl	100
7				Br	54 [a]
8				Me	99
9				OMe	100
10 [b]				NMe_2	94
11 [b]				F	81
12				CF_3	40 [c]
13 [b]					0
14					99

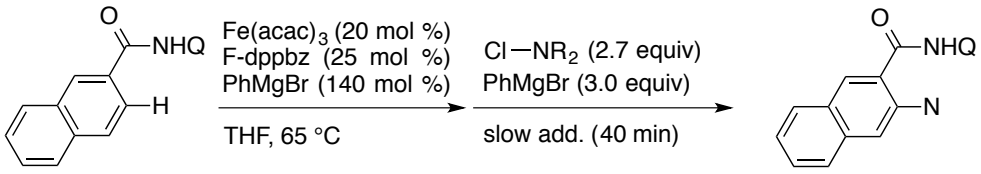
Table 5. (continued)

15			75
16[b]			60

See experimental section for detailed reaction conditions.
[a] Debrominated compound was obtained in 9%. [b] 20 mol % of catalyst was used.
[c] Yield was determined by ^{1}H NMR.

The scope of chloroamines was also examined (Table 6) and I also obtained the aminated products in over 90% yield in most cases. Dialkylamines such as morpholine (entry 1), *N*-protected piperazine (entry 2), cyclic amines (entries 3–4) and acyclic dialkylamines (entry 5) could participate in the reaction, producing the corresponding aminated products. Substituents such as benzyl (entries 6–8) and allyl (entry 9) groups are well tolerated. Arylbromide was also well tolerated (entry 7). On the other hand, primary amines, aromatic amines or amides could not be utilized for this reaction, probably due to their instability (Figure 3).[41] Overall, the reaction has a broad scope of *N*-chlorodialkylamines, and a variety of aniline derivatives can be prepared under these reaction conditions.

Table 6. Scope of *N*-chloroamines for *ortho*-amination



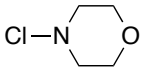
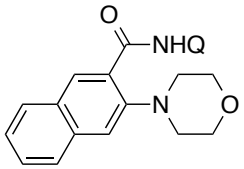
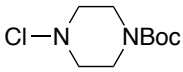
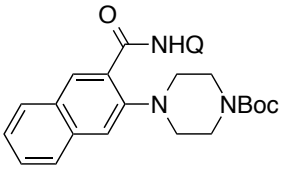
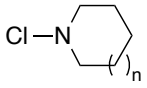
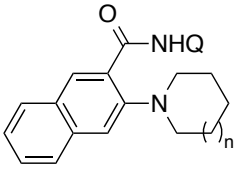
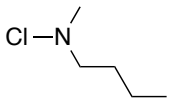
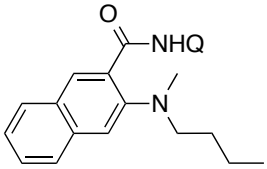
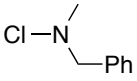
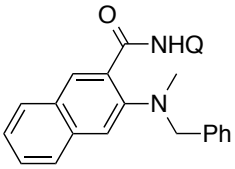
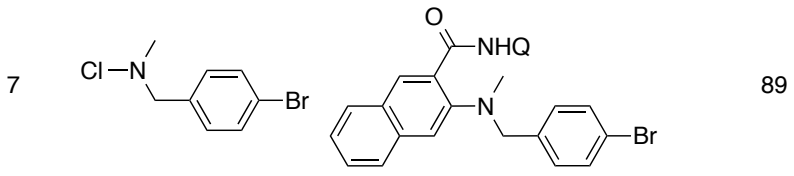
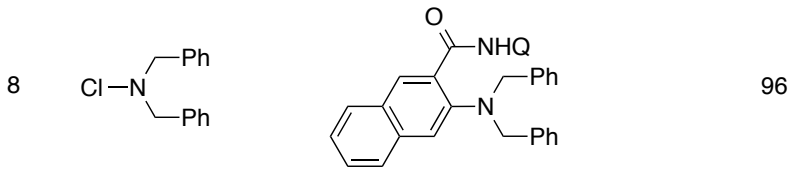
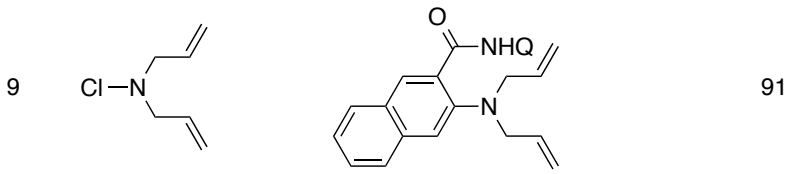
entry	chloroamine	product[b]		yield (%)
1				99
2				99
3			n = 1	98
4			2	93
5				94
6				96

Table 6. (continued)







See experimental section for detailed reaction conditions.

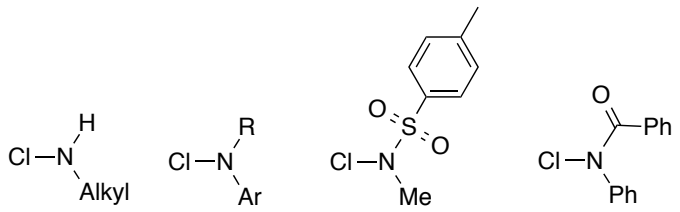
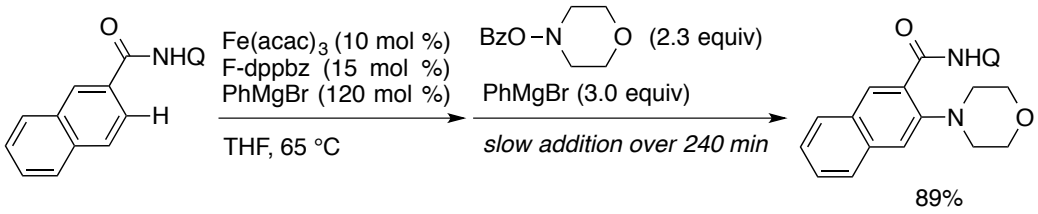


Figure 3. Examples of unreactive *N*-chloroamines and *N*-chloroamides

3-8. Reactions with *N*-oxyamines

I also found that another electrophilic amine, *N*-oxyamine can be utilized as an amine source for the reaction. The reaction was performed using *N*-benzoyloxymorpholine as an aminating reagent, to afford the *ortho*-aminated product in 89% isolated yield (Scheme 11). The use of benzoyloxyamines is synthetically useful because they are typically more stable than chloroamines. However, other benzoyloxyamines gave poor results, probably because of their high stability and poor reactivity toward the organoiron intermediate (Figure 4).

Scheme 11. *Ortho*-amination of amides with *N*-benzoyloxymorpholine



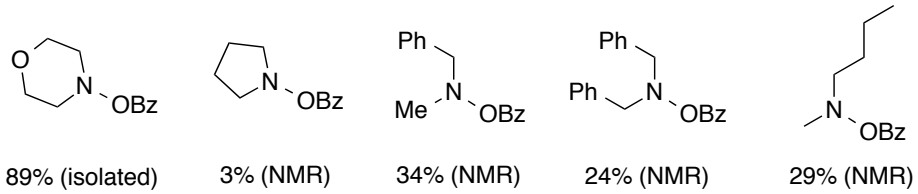
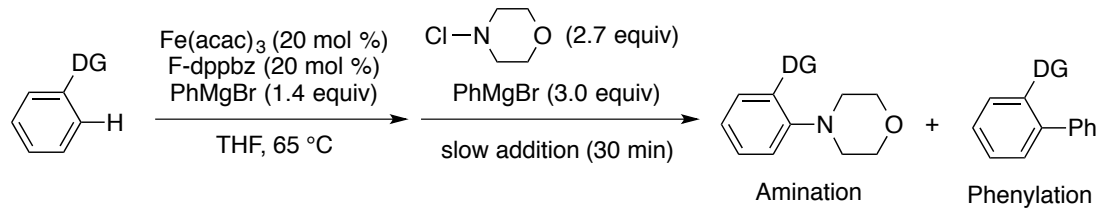
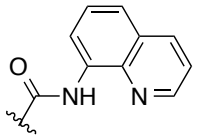


Figure 4. Scope for the amination with *N*-oxyamines

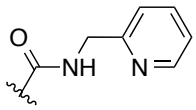
3-9. Effect of the directing group

Success of the double slow addition for amination can also be ascribed to the choice of quinolylamide directing group, which can be concluded from the result of control experiments using different kinds of directing groups (Figure 5). While *N*-(quinolyn-8-yl)benzamide (**SM-1**) gave the best result, similar bidentate directing group, *N*-picolinylbenzamide (**SM-2**) gave a mixture of an aminated product and a phenylated product with poor mass balance, probably because of the decomposition of the amide through abstraction of benzyl C–H bond. *N*-picolinoylbenzylamine (**SM-3**)[42] did not react at all, which reflects the unique effect of benzamide as a directing group. Reaction with *N*-methyl-*N*-(quinoln-8-yl)benzamide (**SM-4**) or *N*-(2-methylquinolin-8-yl)benzamide (**SM-5**) did not proceed at all. [31] Arenes with monodentate directing groups such as 2-phenylpyridine (**SM-6**), 1-phenylpyrazole (**SM-7**), *N*-methyl- (**SM-8**) or *N*-phenylbenzamide (**SM-9**) are not reactive at all, again demonstrating the importance of bidentate auxiliary for the reaction with chloroamines.

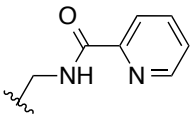




(**SM-1**)

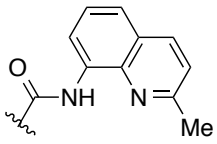


(**SM-2**)

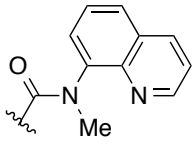


(**SM-3**)

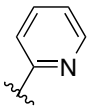
Amination:	95%	20%	0%
Phenylation:	2%	20%	0%
Recovery:	3%	2%	95%



(**SM-4**)

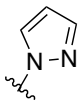


(**SM-5**)

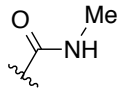


(**SM-6**)

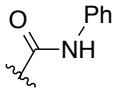
Amination:	0%	0%	3%
Phenylation:	0%	0%	2%
Recovery:	72%	91%	93%



(**SM-7**)



(**SM-8**)



(**SM-9**)

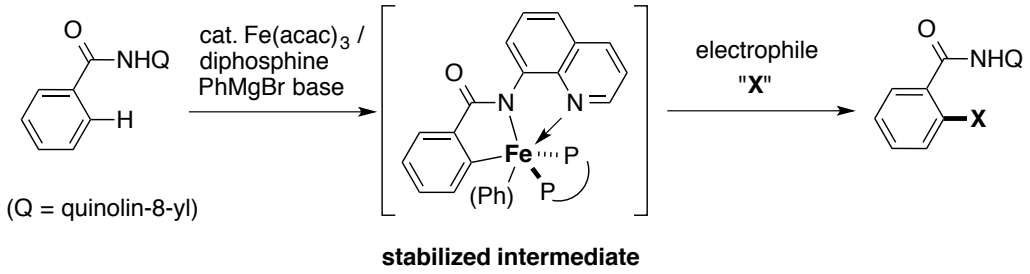
Amination:	0%	0%	0%
Phenylation:	22%	2%	0%
Recovery:	72%	97%	97%

Figure 5. Product distribution with different directing groups

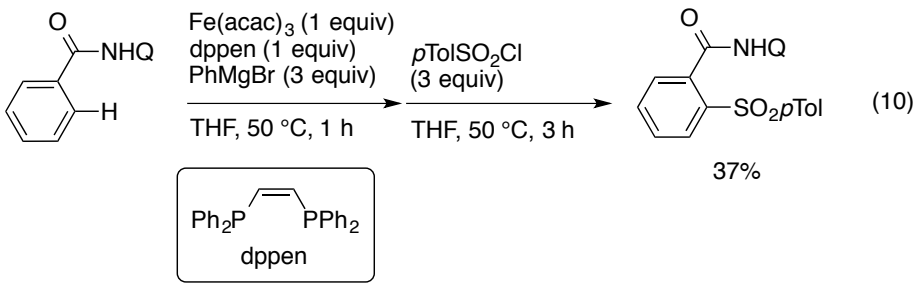
3-10. Reaction of the organoiron with sulfonyl chloride

To expand the scope for *ortho*-functionalization of amides with iron catalyst, I examined possibility of carbon-heteroatom (C–X) bond formation with other electrophiles, according to a generalized scenario shown in Scheme 12. Thus, I explored other electrophiles (**"X"**) that may react with organoiron **A**, producing *ortho*-functionalized product.

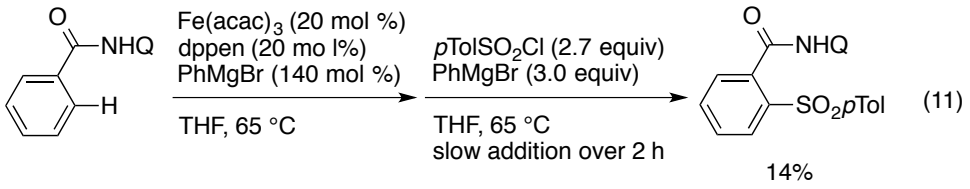
Scheme 12. Generalized scenario for coupling of the intermediate with electrophiles



I focused on sulfonylation reaction using sulfonyl chloride as an electrophile. Directed *ortho*-sulfonyltion is hardly known[43] despite of the potential bioactivity of the resulting sulfones.[44] After investigations, I discovered that *p*-toluenesulfonyl chloride reacted with **A**, producing *ortho*-sulfonylated amide in 37% yield (eq. 10). However, the yield did not improve using the double slow addition protocol (eq. 11). Rendering the reaction catalytic in iron will be subjected for future studies, along with further understanding of the property and reactivity of an organoiron **A**.



(10)



(11)

3-11. Conclusion

In conclusion, *ortho*-amination of aromatic substrates possessing a *N*-(quinolin-8-yl)amide bidentate directing group was achieved by using an aryl Grignard reagent as a base and *N*-chloroamine as an aminating reagent. Slow addition of these reagents effectively suppressed side-reactions, and gave an aminated product in >90% yield in most cases in 40–120 min reaction time, with complete monoselectivity. These features highlight the high reactivity and steric-sensitivity of organoiron as a catalyst. Bidentate directing group and conjugated diphosphine ligand are both essential for the success of this reaction, because they stabilize active organoiron species. The high and unique reactivity of organoiron species toward electrophilic species can be utilized for further development of iron catalysis.

3-12. Experimental

Materials and instruments

All reactions dealing with air- or moisture-sensitive compounds were performed by standard Schlenk techniques in oven-dried Schlenk tubes under an argon atmosphere. Flash chromatography was performed as described by Still *et al.*,[45] employing Kanto Silica gel 60 (spherical, neutral, 140-325 mesh). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECA-500 (500 and 125 MHz) and JEOL ECX-400 (400 and 100 MHz) NMR spectrometer. ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (7.26 and 77.0 ppm), respectively. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-14B instrument equipped with an FID detector and a capillary column, HR-1 (25 m x 0.25 mm i.d., 0.25 mm film).

Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used after appropriate purification before use. Anhydrous tetrahydrofuran was purchased from KANTO Chemical Co. and purified prior to use by a solvent purification system (GlassContour) equipped with columns of activated alumina and copper catalyst.[46] The water content was determined with a Karl-Fischer moisture titrator (MKC-210, Kyoto Electronics Company) to be less than 30 ppm. Phenylmagnesium bromide was prepared from bromobenzene and magnesium turnings in anhydrous tetrahydrofuran, and titrated prior to use using I_2 in THF saturated with LiCl (0.5 M).[47]

Preparation and compound data of amides, ligands, and *N*-chloroamines

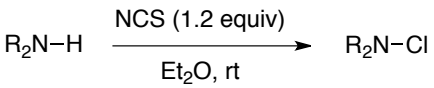
• *Preparation of amides*

The starting materials were prepared same method shown in Chapter 2. These compounds are all known and data was in good agreement with the literatures.[48]

• *Preparation of ligands*

The diphisphine ligands were prepared from bis(1,2-dichlorophosphino)benzene and aryl Grignard reagent according to the literature.[35] All compound data was in good agreement with the literature.

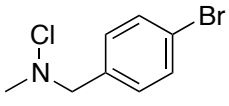
• *Preparation of N-chloroamines*



N-Chloroamines were prepared according to the literature.[25h] Compound data of known compounds were in good agreement with the literature. Because of its instability, we could not perform any analyses that require high temperature, such as APCI-MS analysis.

All the N-chloroamines can be stored at –30 °C for several weeks. Before the reaction, the purity of the chloroamine was confirmed by ^{1}H NMR. For best results, the use of freshly prepared/distilled N-chloroamines is recommended. We sometimes observed partial decomposition of the chloroamine when a steel needle was used, and therefore we used a Teflon cannula for transfer of these compounds.

***N*-Chloro-4-bromo-*N*-methylbenzylamine:** obtained as colorless oil.

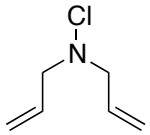


^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 3.98 (s, 2H), 2.95 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.8, 131.5, 130.8, 121.9, 69.2, 52.1.

GC MS (EI) *m/z* (relative intensity): 235 (M^+, 10), 233 (M^+, 8), 172 (8), 171 (94), 170 (8), 169 (100), 157 (4), 155 (5), 118 (13), 90 (66), 75 (19).

***N*-Chlorodiallylamine:** obtained as colorless oil.

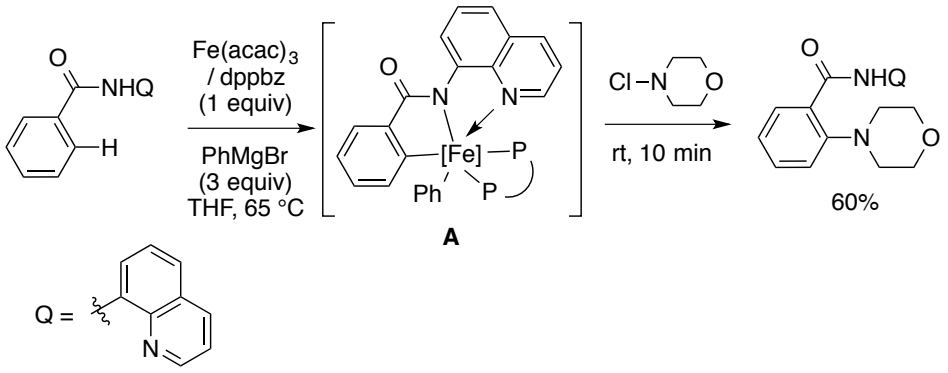


^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99–5.90 (m, 2H), 5.30–5.26 (m, 4H), 3.60–3.58 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 133.4, 119.4, 65.5.

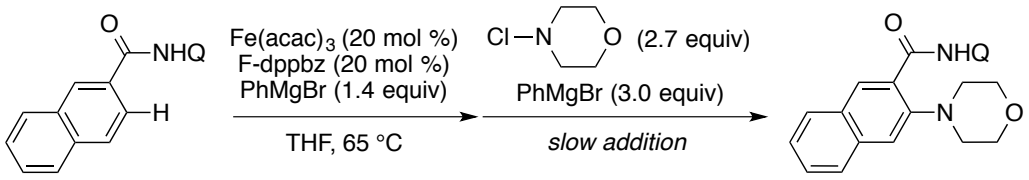
GC MS (EI) *m/z* (relative intensity): 133 (M^+, 21), 132 (10), 131 (M^+, 63), 130 (15), 106 (36), 104 (100), 102 (10), 98 (15), 96 (77), 94 (93), 90 (20), 80 (29).

Procedure for stoichiometric reactions (eq. 9)



In a Schlenk tube *N*-(quinolin-8-yl)benzamide (25 mg, 0.10 mmol), $Fe(acac)_3$ (35 mg, 0.10 mmol), and 1,2-bis(diphenylphosphino)benzene (dppbz, 45 mg, 0.10 mmol) were dissolved in THF (1 mL). A solution of PhMgBr in THF (0.34 mL, 0.89 mol/L, 0.30 mmol) was added dropwise and the resulting mixture was stirred at 65 °C to generate the intermediate **A**. After 1 hour the mixture was cooled to room temperature, and *N*-chloromorpholine (73 mg, 0.3 mmol) was added by syringe and stirred for 10 min. The reaction mixture was quenched by the addition of a saturated solution of potassium sodium tartrate (0.3 mL). After aqueous workup, the organic layer was extracted with EtOAc (2 mL × 3). The combined organic layers were passed through a pad of Florisil, and concentrated *in vacuo*. The yield of the product and recovery was estimated by ^{1}H NMR measurement of the crude mixture, using 1,1,2,2-tetrachloroethane as an internal standard. *Ortho*-phenylated product was not be detected by ^{1}H NMR.

Procedure for the reaction on 1 g scale



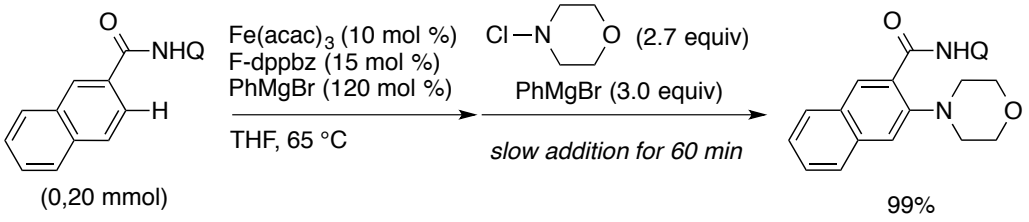
1.00 g (3.4 mmol) 1.05 g (82% yield)

In an oven-dried 200 mL strage flask *N*-(quinolin-8-yl)-2-naphthalenecarboxamide (1.00 g, 3.35 mmol), $Fe(acac)_3$ (237 mg, 0.67 mmol), and 1,2-bis[di-(4-fluorophenyl)phosphino]benzene (F-dppbz, 348 mg, 0.67 mmol) were dissolved in THF (15 mL). A solution of PhMgBr in THF (4.2 mL, 1.11 mol/L, 4.69 mmol) was added dropwise and the resulting mixture was stirred 1 min at room temperature, and then heated to 65 °C. In another flask, freshly-prepared *N*-chloromorpholine (91 mg, 0.75 mmol) was dissolved in THF (15 mL) at room temperature. A part of the resulting solution of chloromorpholine (10 mL, 9.05 mmol) and a solution of PhMgBr in THF (9.05 mL, 1.11 mol/L, 10.1 mmol) were added simultaneously to the reaction mixture at 65 °C over 60 min, using a dual syringe pump under vigorous stirring. *Caution*: *we recommend that a Teflon cannula to be used instead of a steel needle for the addition of the chloroamine. The chloroamine solution should be clear; when white precipitate was observed, the yield was significantly lower. This precipitate can be easily removed by passing over a cotton plug.* After the slow addition finished, the reaction mixture was quenched by the addition of a saturated solution of potassium sodium tartarate (10 mL). After aqueous workup, the organic layer was extracted with EtOAc (2 mL × 3). The combined organic layer was washed with $NaHCO_3$ (2 times) and brine, dried with magnesium sulfate, concentrated *in vacuo*, and purified by silica gel chromatography (ethyl acetate/hexane/0.5% triethylamine) to afford *N*-(quinolin-8-yl)-2-(*N*-morpholino)-3-naphthalenecarboxamide as a white solid (1.05 g, 82% yield). The compound data were in accordance with the literature.[48b] When

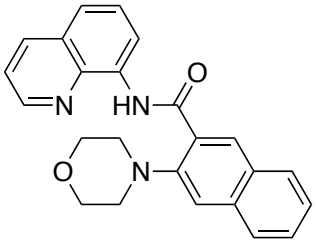
the same reaction was performed with 1 mmol (298 mg) of the starting amide, the aminated product was obtained in 89%.

General Procedure and compound data

Directed C–H amination of N-(quinolin-8-yl)-2-naphthalenecarboxamide (Table 4, entry 7; Table 5, entry 14; Table 6, entry 1)



In a Schlenk tube *N*-(quinolin-8-yl)-2-naphthalenecarboxamide (60 mg, 0.20 mmol), $Fe(acac)_3$ (7.1 mg, 0.02 mmol), and 1,2-bis[di-(4-fluorophenyl)-phosphino]benzene (F-dppbz, 15 mg, 0.03 mmol) were dissolved in THF (1 mL). A solution of PhMgBr in THF (0.27 mL, 0.89 mol/L, 0.24 mmol) was added dropwise and the resulting mixture was stirred 1 min at room temperature, and then heated to 65 °C. In another flask, freshly-prepared *N*-chloromorpholine (91 mg, 0.75 mmol) was dissolved in THF (1.0 mL) and stirred at room temperature. A part of the resulting solution of chloromorpholine (0.72 mL, 0.54 mmol) and a solution of PhMgBr in THF (0.67 mL, 0.89 mol/L, 0.60 mmol) were added simultaneously to the reaction mixture at 65 °C over 60 min, using a dual syringe pump. *Caution: we recommend that a Teflon cannula to be used instead of a steel needle for the addition of the chloroamine.* After the slow addition finished, the reaction mixture was quenched by the addition of a saturated solution of potassium sodium tartarate (0.3 mL). After aqueous workup, the organic layer was extracted with EtOAc (2 mL × 3). The combined organic layers were passed through a pad of Florisil, concentrated *in vacuo*, and purified by silica gel chromatography (ethyl acetate/hexane/0.5% triethylamine) to afford *N*-(quinolin-8-yl)-2-(*N*-morpholino)-3-naphthalenecarboxamide as a white solid (76 mg, 99% yield). The compound data were in accordance with the literature.[48b]



Melting point: 209–211 °C.

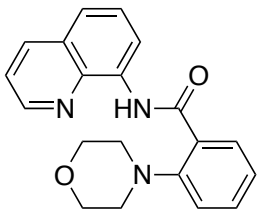
^{1}H NMR (500 MHz, $CDCl_3$): δ 12.67 (s, 1H), 9.18 (dd, J = 7.5, 1.2 Hz, 1H), 8.89 (dd, J = 3.9, 1.4 Hz, 1H), 8.71 (s, 1H), 8.21 (dd, J = 8.0, 1.4 Hz, 1H), 7.93 (d, J =8.0 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.64–7.44 (m, 6H), 4.00 (t, J = 4.3 Hz, 4H), 3.26 (t, J = 4.5 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 148.2, 147.8, 138.8, 136.4, 135.6, 135.2, 133.6, 129.9, 129.0, 128.5, 128.3, 128.1, 127.6, 126.8, 125.5, 121.9, 121.7, 117.8, 116.0, 66.1, 54.1.

GC MS (EI) *m/z* (relative intensity): 365 (11), 239 (–NHQ, 79), 196 (14), 182 (37), 167 (15), 155 (21), 144 (NHQ, 100), 127 (73).

Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 74.87; H, 5.61; N; 10.75.

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)benzamide (Table 5, entry 1):** obtained as a white solid (61 mg, 91% yield). Slow addition time: 60 min. Compound data were in good agreement in the literature.[49]



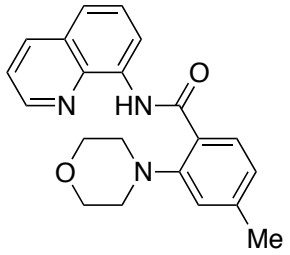
Melting point: 122–124 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.67 (s, 1H), 9.13 (d, J = 7.5 Hz, 1H), 8.87 (d, J = 2.7 Hz, 1H), 8.20–8.18 (m, 2H), 7.83 (dd, J = 7.9, 7.8 Hz, 1H), 7.55–7.46 (m, 3H), 7.27–7.24 (m, 2H), 3.97 (t, J = 4.4 Hz, 4H), 3.16 (t, J = 4.6 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 151.1, 148.1, 138.8, 136.4, 135.6, 132.3, 132.1, 128.9, 128.3, 127.6, 124.2, 121.7, 121.6, 119.2, 117.7, 66.1, 53.9.

GC MS (EI) *m/z* (relative intensity): 288 (1), 281 (2), 207 (7), 204 (2), 189 (–NHQ, 6), 172 (4), 160 (4), 144 (NHQ, 100), 132 (20), 117 (10), 105 (11), 91 (9), 77 (31).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-4-methylbenzamide (Table 5, entry 2):** obtained as a white solid (67 mg, 96% yield). Slow addition time: 120 min. Compound data were in good agreement in the literature.[49]



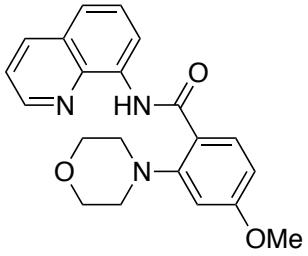
Melting point: 184–185 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.68 (s, 1H), 9.13 (d, J = 7.1 Hz, 1H), 8.87 (d, J = 2.7 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 7.7 Hz, 1H), 7.59 (dd, J = 8.0, 7.9 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.47 (dd, J = 8.2, 4.2 Hz, 1H), 7.07–7.05 (m, 2H), 3.98 (t, J = 4.3 Hz, 4H), 3.14 (t, J = 4.4 Hz, 4H), 2.42 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 151.1, 148.0, 142.9, 138.8, 136.3, 135.7, 132.2, 128.3, 127.6, 126.0, 125.0, 121.5, 119.9, 117.7, 66.1, 53.9, 21.6.

GC MS (EI) *m/z* (relative intensity): 302 (1), 203 (16), 186 (4), 174 (5), 160 (8), 158 (8), 144 (NHQ, 100), 130 (7), 119 (15), 105 (5), 91 (26).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-4-methoxybenzamide (Table 5, entry 3):** obtained as a white solid (67 mg, 92% yield). The compound data were in accordance with the literature.[48b] Slow addition time: 60 min.



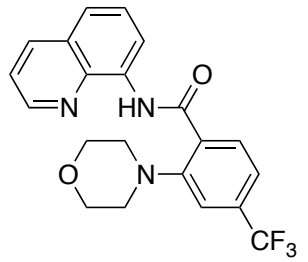
Melting point: 171–173 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.61 (s, 1H), 9.12 (d, J = 7.6 Hz, 1H), 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.19–8.17 (m, 2H), 7.59 (dd, J = 7.8, 7.7 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.47 (dd, J = 8.4, 4.2 Hz, 1H), 6.78–6.76 (m, 2H), 3.98 (t, J = 4.2 Hz, 4H), 3.88 (s, 3H), 3.14 (t, J = 4.6 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 162.8, 153.0, 148.0, 138.8, 136.4, 135.8, 134.0, 128.3, 127.6, 121.5, 121.5, 121.5, 117.6, 108.3, 106.1, 66.1, 55.4, 53.9.

GC MS (EI) *m/z* (relative intensity): 340 (2), 219 (–NHQ, 21), 193 (13), 170 (17), 162 (23), 144 (NHQ, 100), 135 (52).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-4-trifluoromethylbenzamide (Table 5, entry 4):** obtained as a white solid (78 mg, 97% yield). Slow addition time: 120 min. Compound data were in good agreement in the literature.[49]



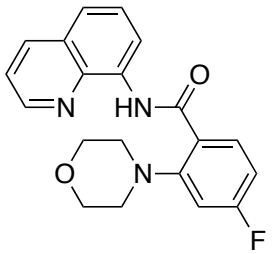
Melting point: 172–174 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.45 (s, 1H), 9.09 (dd, J = 7.4, 1.0 Hz, 1H), 8.87 (dd, J = 4.1, 1.4 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H), 8.21 (dd, J = 8.2, 1.4 Hz, 1H), 7.63–7.57 (m, 2H), 7.51–7.49 (m, 2H), 7.45 (s, 1H), 3.95 (t, J = 4.5 Hz, 4H), 3.19 (t, J = 4.5 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 151.3, 148.3, 138.7, 136.5, 135.0, 133.8 (q, J_{C-F} = 32.5 Hz), 132.8, 132.0, 128.3, 127.5, 123.6 (q, J_{C-F} = 271.2 Hz), 122.2, 121.8, 120.6, 117.8, 116.0, 66.0, 53.6.

GC MS (EI) *m/z* (relative intensity): 240 (1), 228 (2), 214 (2), 200 (7), 186 (1), 172 (4), 157 (3), 144 (NHQ, 100), 129 (9), 116 (7), 101 (3), 95 (5), 89 (5).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-4-fluorobenzamide (Table 5, entry 5):** obtained as a white solid (65 mg, 92% yield). The compound data were in accordance with the literature.[48b] Slow addition time: 120 min.



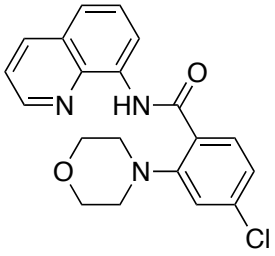
Melting point: 177–179 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.46 (s, 1H), 9.11–9.09 (m, 1H), 8.87 (dd, J = 4.2, 1.6 Hz, 1H), 8.20–8.16 (m, 2H), 7.61–7.48 (m, 3H), 6.95–6.91 (m, 2H), 3.96 (t, J = 4.5 Hz, 4H), 3.14 (t, J = 4.5 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1 (d, J_{C-F} = 251.6 Hz), 164.8, 153.2 (d, J_{C-F} = 8.4 Hz), 148.1, 138.7, 136.4, 135.4, 134.3 (d, J_{C-F} = 10.1 Hz), 128.3, 127.6, 125.0 (d, J_{C-F} = 3.0 Hz), 121.8, 121.7, 117.7, 110.9 (d, J_{C-F} = 20.9 Hz), 106.6 (d, J_{C-F} = 23.3 Hz), 65.9, 53.8.

GC MS (EI) *m/z* (relative intensity): 332 (2), 222 (2), 208 (–NHQ, 2), 190 (3), 178 (4), 162 (7), 150 (17), 144 (NHQ, 100), 122 (9), 95 (16).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-4-chlorobenzamide (Table 5, entry 6):** obtained as a white solid (74 mg, 100% yield). Slow addition time: 60 min. Compound data were in good agreement in the literature.[49]



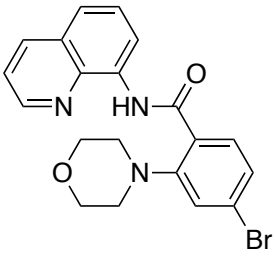
Melting point: 148–150 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.48 (s, 1H), 9.09 (dd, J = 7.7, 1.6 Hz, 1H), 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.20 (dd, J = 8.4, 1.6 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.62–7.56 (m, 2H), 7.50 (dd, J = 8.1, 4.2 Hz, 1H), 7.24–7.22 (m, 2H), 3.96 (t, J = 4.6 Hz, 4H), 3.14 (t, J = 4.6 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 152.1, 148.2, 138.8, 138.1, 136.5, 135.3, 133.5, 128.3, 127.6, 127.3, 124.3, 122.0, 121.7, 119.7, 117.8, 66.0, 53.8.

GC MS (EI) *m/z* (relative intensity): 224 (–NHQ, 2), 205 (2), 194 (2), 166 (8), 144 (NHQ, 100), 131 (4), 116 (6), 111 (9).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-4-bromobenzamide (Table 5, entry 7):** obtained as a white solid (44 mg, 54% yield). ^{1}H NMR analysis of the crude reaction mixture indicated the presence of the debrominated product in 9%. Slow addition time: 60 min. Compound data were in good agreement in the literature.[49]



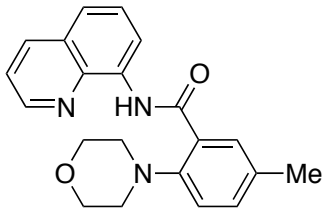
Melting point: 148 °C (decomp).

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.47 (s, 1H), 9.09 (d, J = 9.2 Hz, 1H), 8.87 (dd, J = 5.1, 1.7 Hz, 1H), 8.20 (dd, J = 10.3, 1.7 Hz, 1H), 8.03 (d, J = 10.4 Hz, 1H), 7.62–7.55 (m, 2H), 7.50 (dd, J = 10.3, 5.3 Hz, 1H), 7.40–7.26 (m, 2H), 3.95 (t, J = 5.2 Hz, 4H), 3.15 (t, J = 5.6 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 152.1, 148.2, 138.7, 136.5, 135.3, 133.6, 128.3, 127.8, 127.6, 127.3, 126.6, 122.7, 122.0, 121.7, 117.7, 66.0, 53.8.

GC MS (EI) *m/z* (relative intensity): 267 (–NHQ, 1), 265 (–NHQ, 1), 252 (1), 250 (1), 226 (1), 224 (1), 212 (3), 210 (3), 157 (5), 155 (5), 144 (NHQ, 100), 130 (7), 116 (4), 103 (5), 89 (5).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-5-methylbenzamide (Table 5, entry 8):** obtained as a white solid (69 mg, 99% yield). Slow addition time: 60 min. Compound data were in good agreement in the literature.[49]



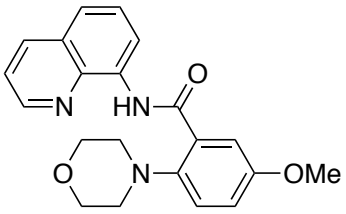
Melting point: 149–151 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.8 (s, 1H), 9.13 (d, J = 7.8 Hz, 1H), 8.88 (dd, J = 6.5, 1.5 Hz, 1H), 8.18 (dd, J = 8.2, 1.4 Hz, 1H), 8.03 (s, 1H), 7.60 (dd, J = 7.9, 7.9 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.47 (dd, J = 8.2, 4.2 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 3.98 (t, J = 4.3 Hz, 4H), 3.12 (t, J = 4.5 Hz, 4H), 2.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 148.7, 148.0, 138.8, 136.3, 135.7, 134.0, 132.9, 132.5, 128.5, 128.3, 127.6, 121.7, 121.5, 119.3, 117.8, 66.2, 54.0, 20.7.

GC MS (EI) *m/z* (relative intensity): 329 (3), 218 (2), 203 (–NHQ, 34), 174 (7), 160 (12), 144 (NHQ, 100), 130 (11), 119 (20), 91 (45).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-5-methoxybenzamide (Table 5, entry 9):** obtained as a white solid (69 mg, 95% yield). The compound data were in accordance with the literature. [48b] Slow addition time: 60 min.



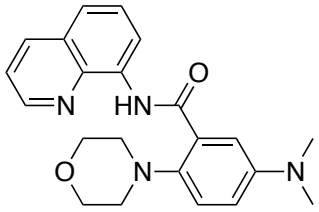
Melting point: 151–153 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 13.10 (s, 1H), 9.14 (dd, J = 7.7, 1.2 Hz, 1H), 8.90 (dd, J = 4.1, 1.5 Hz, 1H), 8.20 (dd, J = 8.2, 1.6 Hz, 1H), 7.83 (d, J = 3.3 Hz, 1H), 7.61 (dd, J = 7.8, 7.6 Hz, 1H), 7.56 (dd, J = 8.1, 1.4 Hz, 1H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 7.28–7.27 (d, J = 7.3 Hz, 1H), 7.07 (dd, J = 8.8, 3.1 Hz, 1H), 4.03 (t, J = 4.4 Hz, 4H), 3.88 (s, 1H), 3.11 (t, J = 4.5 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 156.6, 148.1, 144.6, 139.0, 136.4, 135.8, 129.9, 128.4, 127.5, 121.9, 121.6, 121.3, 119.0, 118.2, 115.6, 66.2, 55.7, 54.3.

GC MS (EI) *m/z* (relative intensity): 363 (M^+, 2), 345 (6), 234 (3), 218 (–NHQ, 100), 207 (52), 191 (10), 176 (14), 162 (38), 144 (NHQ, 84), 135 (15).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-5-dimethylaminobenzamide (Table 5, entry 10):** obtained as a yellow solid (71 mg, 94% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 20 min. Compound data were in good agreement in the literature.[49]



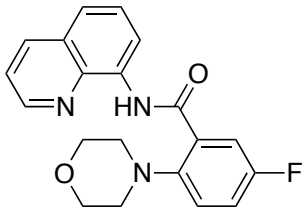
Melting point: 216–218 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 13.2 (s, 1H), 9.16 (d, J = 7.7 Hz, 1H), 8.89 (d, J = 3.9 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 2.9 Hz, 1H), 7.59 (dd, J = 7.8, 7.8 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.47 (dd, J = 8.1, 4.0 Hz, 1H), 7.24 (dd, J = 8.8, 7.6 Hz, 1H), 6.88 (dd, J = 8.7, 3.1 Hz, 1H), 4.03 (br, 4H), 3.09 (t, J = 4.3 Hz, 4H), 3.00 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 148.0, 147.9, 141.1, 139.1, 136.3, 136.0, 129.1, 128.3, 127.5, 121.7, 121.5, 121.1, 118.1, 116.3, 115.6, 66.3, 54.3, 40.8.

GC MS (EI) *m/z* (relative intensity): 376 (M^+, 14), 343 (2), 281 (3), 232 (–NHQ, 100), 218 (4), 207 (7), 188 (14), 175 (14), 160 (9), 144 (NHQ, 43), 134 (10), 104 (9), 91 (9).

***N*-(Quinolin-8-yl)-2-(*N*-morpholino)-5-fluorobenzamide (Table 5, entry 11):** obtained as a white solid (57 mg, 81% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 40 min. Compound data were in good agreement in the literature.[49]



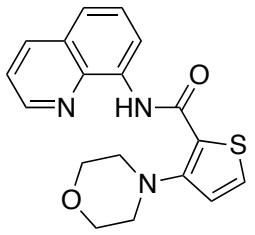
Melting point: 158–159 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.91 (s, 1H), 9.11 (dd, J = 7.5, 1.6 Hz, 1H), 8.89 (dd, J = 4.1, 1.7 Hz, 1H), 8.20 (dd, J = 8.2, 1.5 Hz, 1H), 7.95 (dd, J = 10.0, 3.1 Hz, 1H), 7.62–7.47 (m, 3H), 7.29–7.18 (m, 2H), 4.01 (t, J = 4.3 Hz, 4H), 3.12 (t, J = 4.5 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 159.6 (d, J_{C-F} = 242.6 Hz), 148.2, 147.3 (d, J_{C-F} = 3.0 Hz), 138.9, 136.5, 135.4, 130.9 (d, J_{C-F} = 7.2 Hz), 128.3, 127.5, 122.1, 121.7, 121.4 (d, J_{C-F} = 7.8 Hz), 118.9 (d, J_{C-F} = 22.1 Hz), 118.7 (d, J_{C-F} = 23.9 Hz), 118.1, 66.1, 54.2.

GC MS (EI) *m/z* (relative intensity): 333 (4), 306 (2), 222 (2), 208 (–NHQ, 2), 205 (2), 190 (3), 178 (4), 169 (2), 164 (6), 150 (15), 144 (NHQ, 100), 135 (5), 122 (11), 116 (6), 109 (6), 95 (20).

***N*-(Quinolin-8-yl)-3-(*N*-morpholino)-2-thiophenecarboxamide (Table 5, entry 15):** obtained as a white solid (51 mg, 75% yield). Slow addition time: 60 min. Compound data were in good agreement in the literature.[49]



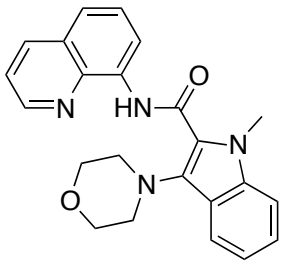
Melting point: 170–171 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.59 (s, 1H), 9.04 (d, J = 7.0 Hz, 1H), 8.93 (dd, J = 4.0, 1.6 Hz, 1H), 8.19 (dd, J = 8.2, 1.4 Hz, 1H), 7.60–7.49 (m, 4H), 7.20 (d, J = 5.4 Hz, 1H), 4.16 (br, 4H), 3.11 (t, J = 4.5 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 152.2, 148.0, 138.9, 136.4, 135.6, 130.2, 130.1, 128.2, 127.5, 122.1, 121.7, 121.6, 118.0, 66.4, 54.3.

GC MS (EI) *m/z* (relative intensity): 339 (M^+, 2), 321 (4), 309 (1), 294 (2), 253 (1), 210 (3), 196 (–NHQ, 5), 193 (5), 181 (4), 170 (62), 154 (8), 150 (10), 144 (NHQ, 41), 138 (19), 115 (27), 111 (100), 97 (10), 83 (14).

***N*-(Quinolin-8-yl)-3-(*N*-morpholino)-2-*N*-methylindolecarboxamide (Table 5, entry 16):** obtained as a white solid (46 mg, 60% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 60 min.



Melting point: 194–196 °C.

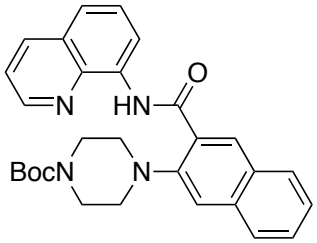
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.23 (s, 1H), 9.11 (d, J = 7.5 Hz, 1H), 8.98 (dd, J = 4.0, 1.3 Hz, 1H), 8.20 (dd, J = 8.2, 1.3 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.61–7.48 (m, 4H), 7.35 (dd, J = 7.7, 7.7 Hz, 1H), 7.16 (dd, J = 7.5, 7.3 Hz, 1H), 4.25–4.24 (m, 7H), 3.50 (br, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 147.9, 139.3, 137.8, 136.4, 136.2, 131.3, 128.4, 127.4, 124.8, 124.3, 122.2, 121.7, 121.7, 121.5, 119.7, 118.4, 110.8, 66.7, 53.4, 32.7.

GC MS (EI) *m/z* (relative intensity): 386 (M^+, 33), 371 (4), 341 (7), 327 (2), 258 (3), 242 (–NHQ, 28), 216 (50), 199 (17), 185 (18), 158 (100), 144 (NHQ, 57), 142 (74), 130 (29), 102 (28), 89 (34), 77 (32).

HRMS (APCI+): *m/z* calcd for $C_{23}H_{22}N_4O_2$ [$M+H^+$] 387.1816; found: 387.1786.

***N*-(Quinolin-8-yl)-2-(4-butoxycarbonyl-*N*-piperazino)-methylbutylamino-3-naphthalenecarboxamide (Table 6, entry 2):** obtained as a white solid (99 mg, 99% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 40 min.



Melting point: 92–94 °C (decomp).

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.71 (s, 1H), 9.18 (d, J = 7.7 Hz, 1H), 8.83 (dd, J = 4.2, 1.6 Hz, 1H), 8.73 (s, 1H), 8.20 (dd, J = 8.0, 1.2 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.64–7.45 (m, 6H), 3.76 (br, 4H), 3.20 (br, 4H), 1.46 (s, 9H).

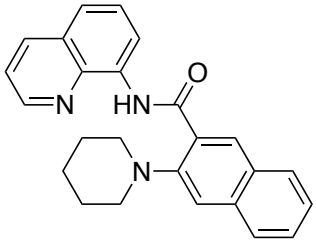
^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 154.8, 148.0, 147.9, 138.9, 136.5, 135.6, 135.2, 133.7, 130.0, 129.0, 128.5, 128.4, 128.2, 127.6, 126.8, 125.6, 121.9, 121.7, 117.9, 116.4, 79.9, 28.4. Piperazine's carbon signals are overlapping with those of the solvent ($CDCl_3$).

GC MS (EI) *m/z* (relative intensity): 365 (10), 354 (4), 340 (–NHQ, 16), 326 (6), 322 (7), 295 (2), 281 (19), 265 (4), 238 (31), 221 (12), 207 (80), 196 (71), 191 (15), 184 (23), 182 (37), 170 (19), 167 (13), 157 (34), 155 (23), 144 (NHQ, 68), 127 (80), 117 (20), 115 (21), 101 (14), 96 (21).

HRMS (APCI+): *m/z* calcd for $C_{29}H_{30}N_4O_3$ [$M+H^+$] 483.2391; found: 483.2385.

***N*-(Quinolin-8-yl)-2-(*N*-piperidino)-3-naphthalenecarboxamide (Table 6, entry 3):** obtained as a white solid (75 mg, 98% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were

used. Slow addition time: 40 min.



Melting point: 220–222 °C.

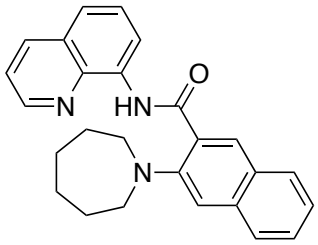
^{1}H NMR (500 MHz, $CDCl_3$): δ 12.8 (s, 1H), 9.20 (d, J = 7.5 Hz, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.70 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.64–7.40 (m, 6H), 3.17 (br, 4H), 1.86 (br, 4H), 1.52 (br, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 149.5, 147.8, 139.0, 136.2, 135.9, 135.3, 133.2, 129.7, 128.9, 128.7, 128.3, 127.8, 127.6, 126.6, 125.1, 121.6, 121.5, 117.9, 116.0, 55.4, 25.3, 24.1.

GC MS (EI) *m/z* (relative intensity): 363 (12), 236 (–NHQ, 100), 209 (7), 180 (15), 167 (13), 154 (12), 144 (NHQ, 57), 127 (45), 116 (10), 101 (6), 89 (5).

HRMS (APCI+): *m/z* calcd for $C_{25}H_{23}N_3O$ [M+H$^+$] 382.1914; found: 382.1914.

***N*-(Quinolin-8-yl)-2-(*N*-hexamethyleneimino)-3-naphthalenecarboxamide (Table 6, entry 4):** obtained as a white solid (74 mg, 93% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 40 min.



Melting point: 142–144 °C.

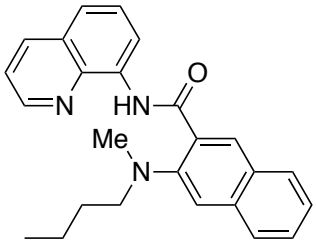
^{1}H NMR (500 MHz, $CDCl_3$): δ 12.72 (s, 1H), 9.14 (dd, J = 7.7, 1.2 Hz, 1H), 8.84 (dd, J = 4.2, 1.7 Hz, 1H), 8.67 (s, 1H), 8.17 (dd, J = 8.2, 1.7 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.63–7.58 (m, 2H), 7.55–7.38 (m, 4H), 3.48 (t, J = 5.3 Hz, 4H), 1.95(br, 4H), 1.65–1.63 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 150.1, 147.9, 139.3, 136.2, 135.8, 135.3, 132.9, 129.3, 128.9, 128.8, 128.2, 127.8, 127.5, 126.5, 124.8, 121.5, 121.4, 117.8, 117.2, 56.9, 27.9, 26.8.

GC MS (EI) *m/z* (relative intensity): 374 (17), 231 (100), 202 (59), 187 (5), 176 (2), 171 (4), 144 (NHQ, 10), 116 (11), 101 (5), 89 (7).

HRMS (APCI+): *m/z* calcd for $C_{26}H_{25}N_3O$ [M+H$^+$] 396.2070; found: 396.2072.

***N*-(Quinolin-8-yl)-2-*N*-(*N*-methylbutylamino)-3-naphthalenecarboxamide (Table 6, entry 5):** obtained as a white solid (72 mg, 94% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 40 min.



Melting point: 120–122 °C.

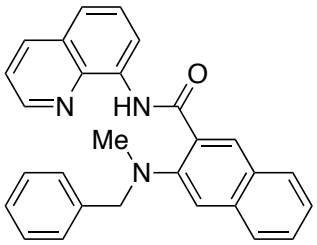
^{1}H NMR (500 MHz, $CDCl_3$): δ 14.15 (s, 1H), 9.13 (d, J = 6.7 Hz, 1H), 8.89 (s, 1H), 8.85 (dd, J = 4.1, 1.5 Hz, 1H), 8.16 (dd, J = 8.2, 1.6 Hz, 1H), 7.96 (d, J =8.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.64 (dd, J = 7.9, 7.9 Hz, 1H), 7.55–7.52 (m, 2H), 7.47–7.44 (m, 2H), 3.27–3.24 (m, 2H), 2.97 (s, 3H), 1.67–1.61 (m, 2H), 1.30–1.25 (m, 2H), 0.80 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 148.3, 148.0, 139.7, 136.3, 136.1, 135.2, 133.2, 130.2, 129.1, 128.6, 128.2, 127.9, 127.6, 126.6, 125.4, 121.4, 121.4, 119.1, 117.8, 57.0, 44.4, 28.7, 20.7, 14.0.

GC MS (EI) *m/z* (relative intensity): 365 (13), 340 (3), 309 (4), 239 (–NHQ, 100), 222 (5), 210 (7), 196 (54), 184 (38), 182 (14), 170 (4), 157 (35), 144 (NHQ, 56), 127 (30), 155 (9).

HRMS (APCI+): *m/z* calcd for $C_{25}H_{25}N_3O$ [M+H$^+$] 384.2070; found: 384.2071.

***N*-(Quinolin-8-yl)-2-*N*-(*N*-methylbenzylamino)-3-naphthalenecarboxamide (Table 6, entry 6):** obtained as a white solid (80 mg, 96% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 40 min.



Melting point: 112–114 °C.

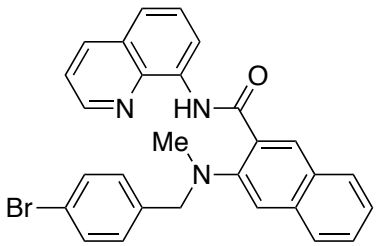
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.7 (s, 1H), 9.12 (d, J = 7.6 Hz, 1H), 8.81–8.78 (m, 2H), 8.17 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 7.9, 7.8 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.50–7.40 (m, 4H), 7.24 (d, J = 6.1 Hz, 2H), 7.10–7.05 (m, 3H), 4.41 (s, 2H), 2.99 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2, 148.2, 147.1, 139.6, 136.1, 136.1, 136.0, 135.0, 133.3, 130.0, 129.5, 129.0, 128.5, 128.2, 128.0, 127.8, 127.6, 127.2, 126.6, 125.3, 121.5, 121.4, 119.2, 117.7, 61.2, 43.1.

GC MS (EI) *m/z* (relative intensity): 399 (11), 323 (9), 294 (5), 273 (–NHQ, 40), 244 (16), 230 (4), 207 (4), 182 (18), 155 (10), 144 (NHQ, 34), 127 (31), 114 (8), 101 (8), 91 (100).

HRMS (APCI+): *m/z* calcd for $C_{28}H_{23}N_3O$ [M+H$^+$] 418.1914; found: 418.1906.

***N*-(Quinolin-8-yl)-2-*N*-(*N*-methyl-*p*-bromobenzylamino)-3-naphthalenecarboxamide (Table 6, entry 7):** obtained as yellow solid (89 mg, 89% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 40 min.



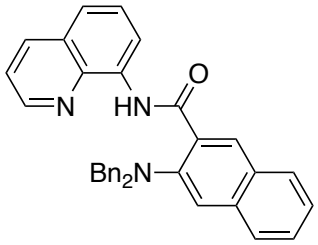
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.62 (s, 1H), 9.11 (dd, J = 7.8, 1.2 Hz, 1H), 8.81 (s, 1H), 8.76 (dd, J = 4.0, 1.6 Hz, 1H), 8.18 (dd, J = 8.3, 1.5 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 7.9, 7.9 Hz, 1H), 7.55–7.41 (m, 5H), 7.17 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 4.35 (s, 2H), 2.97 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): d 165.0, 148.1, 146.7, 139.5, 136.2, 135.8, 135.2, 134.9, 133.4, 131.1, 131.1, 130.0, 129.0, 128.4, 128.2, 128.0, 127.6, 126.6, 125.5, 121.6, 121.4, 121.2, 119.1, 117.7, 60.5, 43.2.

GC MS (EI) *m/z* (relative intensity): 479 (14), 477 (14), 353 (–NHQ, 34), 351 (–NHQ, 34), 338 (6), 336 (6), 322 (25), 293 (2), 273 (3), 244 (9), 229 (5), 196 (9), 182 (48), 171 (40), 169 (40), 155 (25), 144 (NHQ, 100), 127 (66), 114 (14), 101 (14), 90 (41), 77 (17).

HRMS (APCI+): *m/z* calcd for $C_{28}H_{22}BrN_3O$ [M+H$^+$] 496.0979 and 498.0997; found: 496.1019 and 498.1003.

***N*-(Quinolin-8-yl)-2-*N*-(*N*-dibenzylamino)-3-naphthalenecarboxamide (Table 6, entry 8):** obtained as a yellow solid (95 mg, 96% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 40 min.



Melting point: 144–146 °C.

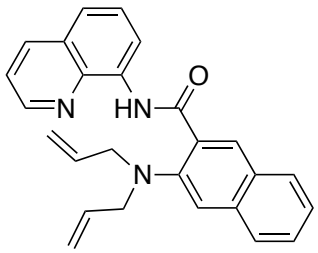
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.40 (s, 1H), 9.15 (d, J = 7.6 Hz, 1H), 8.86 (d, J = 4.0 Hz, 1H), 8.76 (s, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.66 (dd, J = 7.8, 7.7 Hz, 1H), 7.61–7.56 (m, 2H), 7.50 (dd, J = 8.2, 4.2 Hz, 1H), 7.46–7.38 (m, 2H), 7.29 (d, J = 7.3 Hz, 4H), 7.13–7.07 (m, 7H), 4.47 (s, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): d 165.6, 148.2, 143.9, 139.5, 136.4, 136.1, 135.9, 134.5, 133.4, 129.7, 129.6, 129.2, 128.9, 128.3, 128.1, 127.7, 127.7, 127.2, 126.7, 125.3, 121.7, 121.6, 121.1, 117.9, 58.9.

GC MS (EI) *m/z* (relative intensity): 402 (–Bn, 28), 280 (12), 258 (–NHQ, –Bn, 68), 229 (12), 207 (16), 144 (NHQ, 9), 127 (24), 91 (Bn, 100).

HRMS (APCI+): *m/z* calcd for $C_{34}H_{27}N_3O$ [M+H$^+$] 494.2227; found: 494.2217.

***N*-(Quinolin-8-yl)-2-(*N*-diallylamino)-3-naphthalenecarboxamide (Table 6, entry 9):** obtained as a white solid (72 mg, 91% yield). 20 mol % of $Fe(acac)_3$ and F-dppbz were used. Slow addition time: 40 min.



Melting point: 120–121 °C.

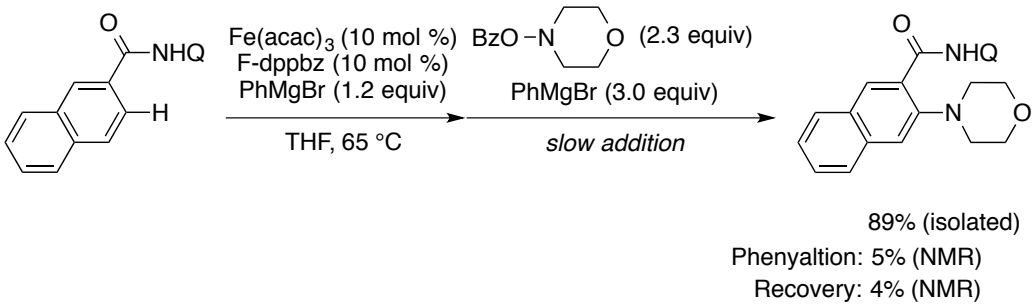
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.8 (s, 1H), 9.14–9.13 (m, 1H), 8.87–8.85 (m, 2H), 8.16 (dd, J = 8.2, 1.4 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.63–7.43 (m, 6H), 6.10–6.02 (m, 2H), 5.18 (dd, J = 17.2, 1.0 Hz, 2H), 5.09 (d, J = 10.2 Hz, 2H), 3.92 (d, J = 6.7 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 147.9, 145.6, 139.6, 136.1, 136.1, 134.8, 133.7, 133.3, 130.2, 129.1, 129.0, 128.2, 127.9, 127.6, 126.7, 125.6, 121.5, 121.4, 120.8, 118.8, 117.9, 57.5.

GC MS (EI) *m/z* (relative intensity): 393 (M$^+$, 11), 350 (30), 249 (–NHQ, 20), 234 (36), 220 (51), 208 (36), 194 (25), 180 (53), 165 (30), 152 (32), 144 (NHQ, 30), 127 (21), 115 (17), 101 (10), 89 (11).

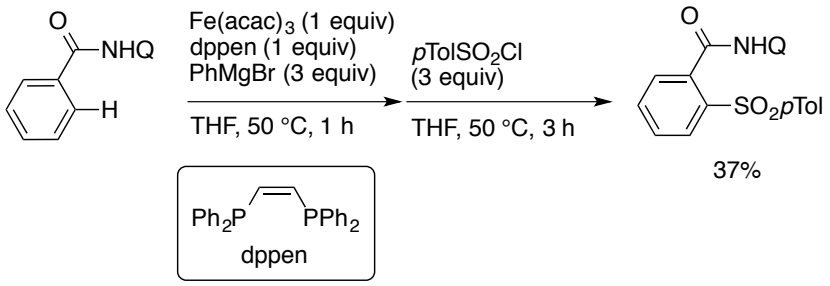
HRMS (APCI+): *m/z* calcd for $C_{26}H_{23}N_3O$ [M+H$^+$] 394.1914; found: 394.1901.

Procedure for the iron-catalyzed directed amination of carboxamides using *N*-benzoyloxymorpholine (Scheme 11)



In a Schlenk tube *N*-(quinolin-8-yl)-2-naphthalenecarboxamide (60 mg, 0.20 mmol), $Fe(acac)_3$ (7.0 mg, 0.020 mmol), and 1,2-bis[di-(4-fluorophenyl)phosphino]benzene (10 mg, 0.020 mmol) were dissolved in THF (1 mL). A solution of PhMgBr in THF (0.27 mL, 0.89 mol/L, 0.24 mmol) was added dropwise and the resulting mixture was stirred 1 min at room temperature, and then heated to 65 °C. In another flask, *N*-benzoyloxymorpholine (138 mg, 0.67 mmol) was dissolved in THF (1.0 mL) at room temperature. A part of this solution (0.72 mL) and a solution of PhMgBr in THF (0.67 mL, 0.89 mol/L, 0.60 mmol) were added simultaneously to the reaction mixture at 65 °C over 240 min, using a dual syringe pump. After the slow addition finished, the reaction mixture was quenched by the addition of a saturated solution of potassium sodium tartrate (0.3 mL). After aqueous workup, the organic layer was extracted with EtOAc (2 mL × 3). The combined organic layers were passed through a pad of Florisil, concentrated *in vacuo*, and purified by silica gel chromatography (10% ethyl acetate/hexane/0.5% triethylamine) to afford the corresponding aminated compound as a white solid (69 mg, 89% yield). The starting material was recovered in 4%, and the *ortho*-phenylated product was produced in 5%, as estimated by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

Procedure for iron-mediated *ortho*-sulfonylation reaction (eq. 10)



In a Schlenk tube *N*-(quinolin-8-yl)benzamide (25 mg, 0.10 mmol), $Fe(acac)_3$ (35 mg, 0.10 mmol), and *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 39 mg, 0.10 mmol) were dissolved in THF (1 mL). A solution of PhMgBr in THF (0.34 mL, 0.89 mol/L, 0.30 mmol) was added dropwise and the resulting mixture was stirred at 50 °C to generate the intermediate **A**. After 1 hour the mixture was cooled to room temperature, and THF solution of *p*-toluenesulfonyl chloride (57 mg, 3 equiv) was added by syringe and stirred for 3 hours under 50 °C. The reaction mixture was quenched by the addition of a saturated solution of potassium sodium tartrate (0.3 mL). After aqueous workup, the organic layer was extracted with EtOAc (2 mL × 3). The combined organic layers were passed through a pad of Florisil, and concentrated *in vacuo*, and purified by silica gel chromatography (10% ethyl acetate/hexane/0.5% triethylamine) to afford the product as a white solid (15 mg, 37% yield). Compound data were in good accordance with the literature.[50]

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Chapter 4.

Directed Alkylation of Aromatic and Olefinic Amides with Alkyl Tosylates, Mesylates, and Halides

4-1. Introduction

• Alkylation of aromatic and olefinic substrates

Alkylation of aromatic and olefinic substrates is an indispensable strategy to tune the properties of molecules, such as increasing the solubility and controlling morphology, which are typically employed for preparation of pharmaceutical and agrochemical ingredients, and molecules for materials science.[1] The Friedel-Crafts alkylation[2,3] or other electrophilic aromatic substitutions[4] using alkyl electrophiles are valuable reactions, but both of them are typically highly affected by the electronic properties of the substrate (i.e. only electron-rich substrates react well), and suffer from poor regioselectivity.[5] Moreover, the cationic alkyl intermediates are prone to undergo rearrangements, which results in formation of byproducts that are difficult to isolate from a desired product.

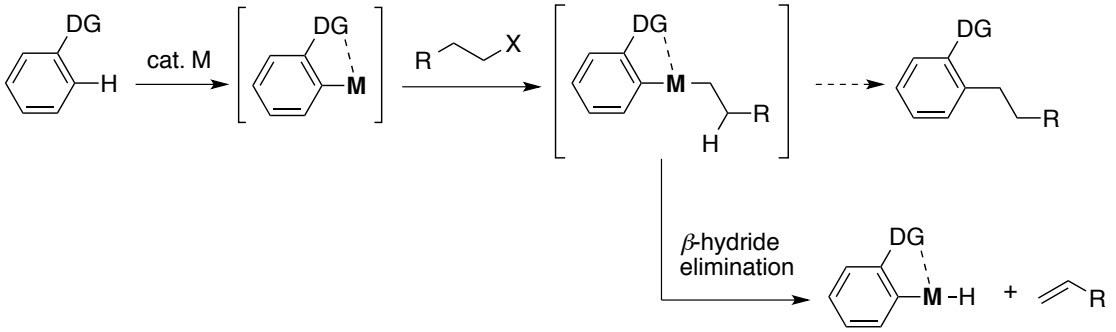
The substitution reaction of aromatic and olefinic nucleophiles using alkyl electrophiles,[6] and transition-metal-catalyzed cross coupling reactions[7,8] are alternative methods to synthesize alkylated compounds. However, these reactions have a strong limitation with respect to substrates and functionalities, because they require highly reactive and unstable reagents as starting materials. Therefore achievement of such an alkylation reaction using stable and substrates has been desired.

• Transition-metal-catalyzed directed C(sp^2)–H bond activation, followed by reaction with alkyl electrophiles

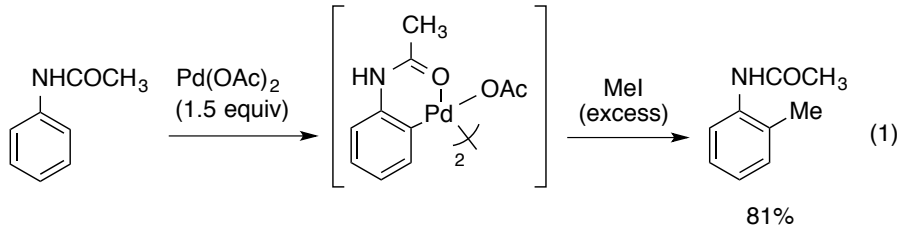
Transition-metal-catalyzed directed activation of a C(sp^2)–H bond of aromatic and olefinic substrates,[9] following the reaction with an alkyl electrophile[10] such as an alkyl halide would provide an efficient methodology, in that the reaction could be performed with high and predictable regioselectivity without the use of unstable starting materials. However, such a reaction had been difficult to achieve, because of competing β-hydride elimination of the alkylmetal intermediate, producing metal hydride species

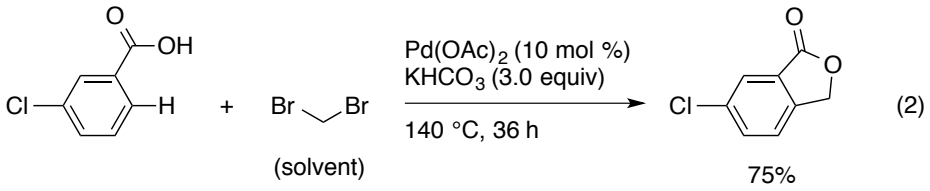
that induces side-reactions (Scheme 1).[11]

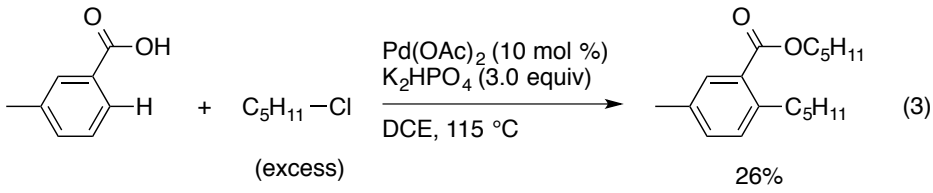
Scheme 1. Competing *β*-hydride elimination in transition-metal-catalyzed alkylation of a $C(sp^2)$–H bond



Because of this limitation, alkyl donors employed in these reactions had been limited to those without *β*-hydrogens. Tremont and coworkers developed the first example of an alkylation of a $C(sp^2)$–H bond using methyl iodide, mediated by palladium acetate (eq. 1). [12,13] It took 25 more years[14] until Yu and coworkers reported an improved reaction system using a benzoic acid and dibromomethane as an alkyl donor to produce a cyclized product (eq. 2).[15] They also investigated the alkylation using pentyl chloride in this report, but the yield was not satisfactory because of competing S_N2 reaction (eq. 3).



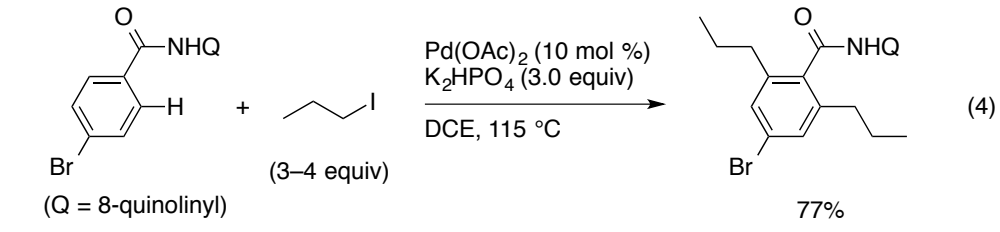


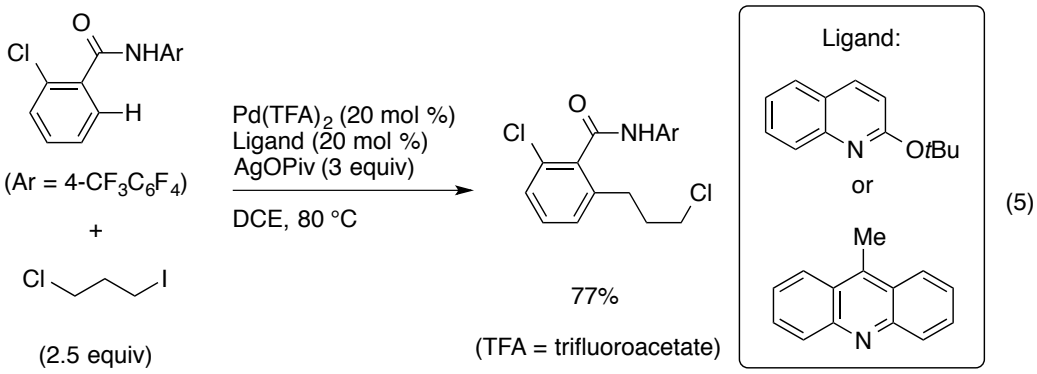


• Suppression of *β*-hydride elimination

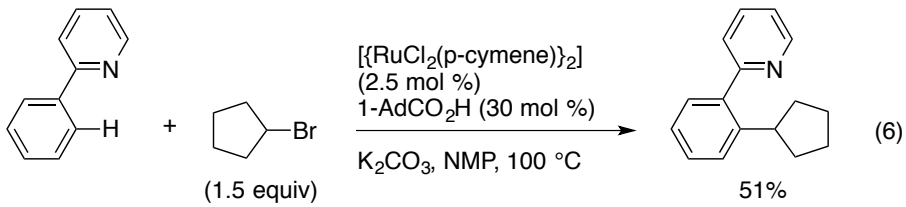
The difficulty associated with *β*-hydride elimination in palladium-catalyzed directed alkylations is so problematic that such reactions have mostly been limited to the methylation or benzylation.[10–15,16,17] However, recently chemists have discovered ways to suppress this side reaction, and achieved the directed alkylation using alkyl electrophiles possessing *β*-hydrogens.

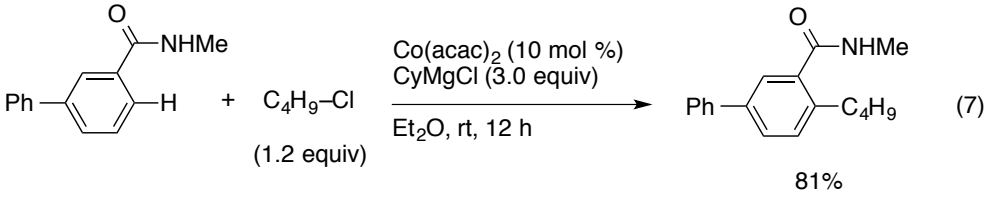
In 2010, Daugulis and a coworker succeeded to suppress the *β*-hydride elimination by using a bidentate directing group through occupation of the coordination site of palladium, and achieved the alkylation with primary alkyl iodides possessing *β*-hydrogen (eq. 4).[18] Later Chen and coworkers reported a modified reaction system using alkyl bromides and chlorides,[19] as well as challenging secondary alkyl halides as coupling partners.[20] Yu and coworkers discovered ligands that promote the desired alkylation while suppressing *β*-hydride elimination, and achieved directed *ortho*-[21] or *meta*-alkylation[22] of amides with primary alkyl iodides using palladium catalysis (eq. 5).[23]

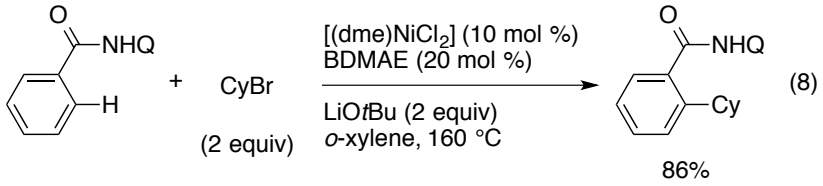




Employing a different transition-metal as the catalyst was also found to be effective, although the efficiency of these reactions are not high compared with palladium catalysis described above. Ackermann and coworkers reported a ruthenium-catalyzed directed alkylation using primary and secondary alkyl electrophiles, affording an *ortho*-alkylated product in moderate yield (eq. 6).[24,25] More recently, inexpensive cobalt- (eq. 7)[26] or nickel- (eq. 8) [27] catalyzed reactions have also been developed. However, these reactions suffer from chain-walking and/or isomerization of alkyl halides, which results in low efficiency of the reactions. Moreover, reactions using olefinic substrates,[27a] and more inexpensive and accessible alkanol derivatives[26d] have been scarcely investigated despite of their merits.







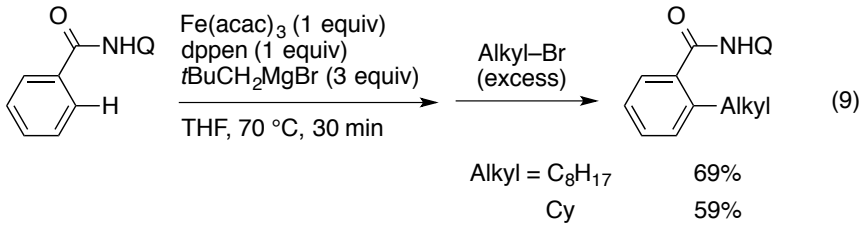
BDMAE = bis(2-dimethylaminoethyl)ether

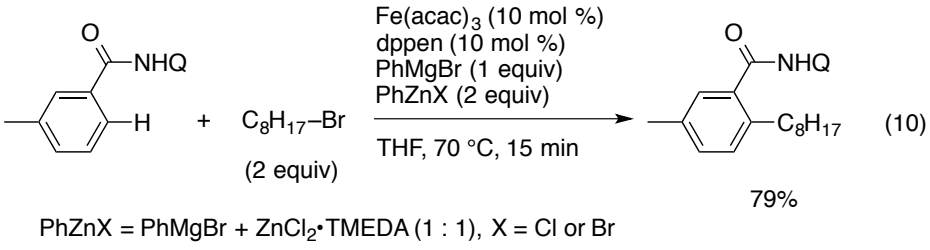
• The reaction described in this chapter

In this chapter, I describe the development of an iron-catalyzed directed alkylation of aromatic and olefinic amides using primary and secondary alkyl sulfonates and halides as electrophiles. An organoiron species prepared from *N*-(quinolin-8-yl)benzamide and iron/diphosphine ligand[28] was reacted with primary and secondary alkyl electrophiles, to give an alkylated amide in good yield. The organozinc halide base promotes the reaction while suppressing possible side-reactions such as cross coupling between the organometallic base and the alkyl electrophile,[29] and homocoupling of the organometallic base.[30] The alkylation proceeded with tolerance of a variety of functional groups such as ester and halogens, without any rearrangement or isomerization of alkenes on substrates.

4-2. Initial discovery of *ortho*-alkylation using iron catalysis

The preliminary result for a directed C(sp^2)–H alkylation with iron catalyst was discovered by other members in our laboratory, when they investigated the reaction of the organoiron[28] with electrophiles. Thus, an organoiron species generated by treating *N*-(quinolin-8-yl)amide with a stoichiometric amount of $Fe(acac)_3$/dppen ((*Z*)-1,2-bis(diphenylphopshino)ethylene) and 3 equiv of neopentylmagnesium bromide, was added to an *n*-octyl bromide and cyclohexyl bromide as electrophiles, to give the corresponding *ortho*-alkylated products in 69% and 59% yield, respectively (eq. 9).[31] The alkylation with a catalytic amount of iron/diphosphine ligand was also achieved using arylzinc halide as a base (eq. 10).[32] Based on these results, I started investigation on the reaction to enhance the value, and explore the unique reactivity peculiar to iron catalysis. Considered from backgrounds discussed in the previous section, I aimed to achieve a reaction that has remained as a challenging task: alkylation of olefinic C(sp^2)–H bond using alkanol derivatives as an alkyl donor.

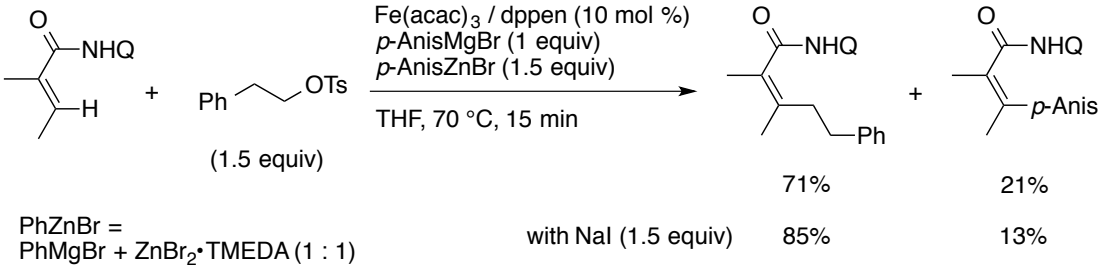




4-3. Discovery of *β*-alkylation of alkeneamides using alkyl sulfonates

I examined the possibility of the alkylation using olefinic amide as a substrate, which has been hardly achieved because of isomerization and/or reduction of the double bond.[27a] I used *N*-(quinolyn-8-yl)-(*Z*)-tiglamide as a substrate, 2-phenetyl tosylate as an alkyl donor and *p*-anisylzinc halide as a base in the presence of $Fe(acac)_3$/dppen catalyst, to afford a *β*-phenetylated amide in 71% yield with complete *cis* configuration, along with a *β*-anisylated product in 21% yield (Scheme 2). Sodium iodide was found to improve the yield by ca. 10%.[27,33] As discussed, usage of alkyl sulfonate as an alkyl donor is rare,[34] despite of its wide availability as an alkyl donor compared with that of alkyl iodide or bromide.

Scheme 2. Iron-catalyzed *β*-alkylation of alkeneamides with alkyl tosylates

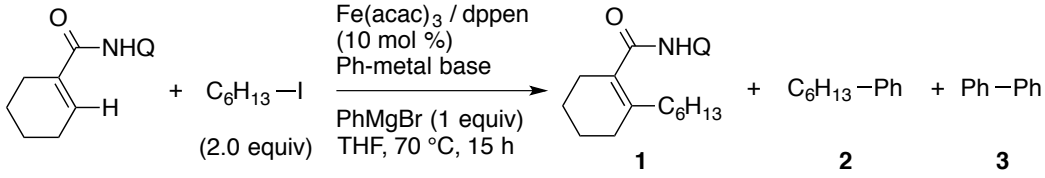


4-4. Effect of the organometallic base on *β*-alkylation of alkeneamide

Encouraged by this result, I continued investigation on the *β*-alkylation of olefinic amides (Table 1), inspired by the effect the organometallic bases previously discovered by other members in our laboratory.[32] When a phenyl Grignard reagent was used as a base without zinc additive, cross coupling between the alkyl halide and the Grignard reagent to give **2**[29] and homocoupling to give **3**[30] proceeded predominantly, and the desired reaction affording **1** hardly occurred (entry 1). Diarylzinc, a base that was prepared *in situ* from an aryl Grignard reagent and a zinc additive in 2:1 ratio, was

also ineffective for the desired reaction (entry 2). These results are consistent with previous investigations by Nakamura and others, where these organometallic reagents are effective for cross coupling with alkyl electrophiles using iron catalyst,[29] and it suggests that suppression of these reactions is difficult using a Grignard reagent or a diarylzinc as base. On the other hand, a monoarylzinc halide, prepared *in situ* from an aryl Grignard reagent and a zinc additive in 1:1 ratio, was uniquely effective for the desired alkylation to give a desired product **1** (entry 3). In this reaction, homocoupling of the arylzinc halide and cross coupling with the alkyl electrophile could be suppressed. Styrene, which is generated through *β*-hydride elimination of the alkyliron intermediate[35] was not detected by GC, suggesting that *β*-hydride elimination was also suppressed under the current reaction conditions. Thus, the monoarylzinc halide base was determined as a unique base for the alkylation of C(sp^2)–H bond using iron catalysis.

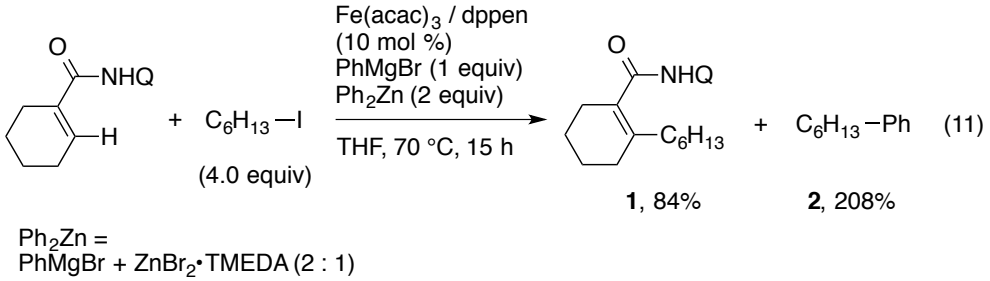
Table 1. Effect of base for *β*-alkylation of amides



entry	Ph-metal base (equiv)	GC yield (%)			
		1	**2**	**3**	recovery
1	PhMgBr (2 equiv)	2	97	18	90
2	[2 PhMgBr + $ZnBr_2$•TMEDA] (2 equiv)	5	168	6	88
3	[PhMgBr + $ZnBr_2$•TMEDA] (1.5 equiv)	91	3	0	0

Yields are based on starting amide used.

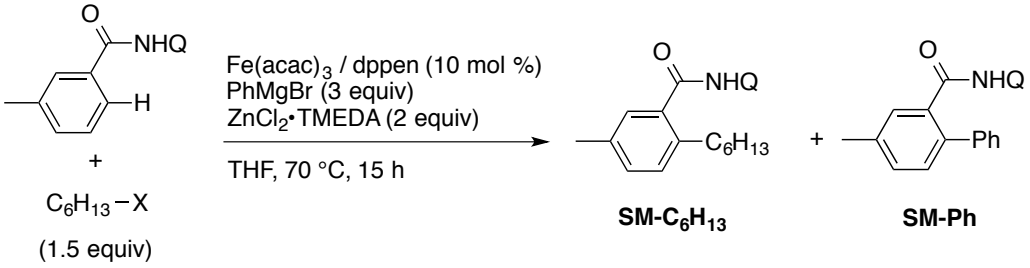
When the reaction was performed using diarylzinc as a base, cross coupling initially proceeded to afford **2**, as previously shown in entry 2 in Table 1. However, when excess electrophile was used for the reaction, desired alkylation also proceeded (eq. 11). The result indicates that monoarylzinc species was generated *in situ* from a diarylzinc base, after donating an aryl group for cross coupling. Then the monoarylzinc worked as a base for desired alkylation, affording the product **1**.



4-5. Effect of the leaving group of the alkyl electrophile

After finding the arylzinc halide as an optimal base, the effect of leaving groups of the alkyl electrophile was investigated (Table 2).[32] Alkyl iodide was an efficient alkyl donor to give the product in 89% yield (entry 1). Alkyl bromide and chloride were less efficient (79% and 70% respectively), and the yield of the *β*-arylated product increased (entries 2–3). An alkyl tosylate worked similarly with an alkyl chloride (entry 4), and the yield was improved when sodium iodide was used as an additive (entry 5), as already shown in Scheme 2.

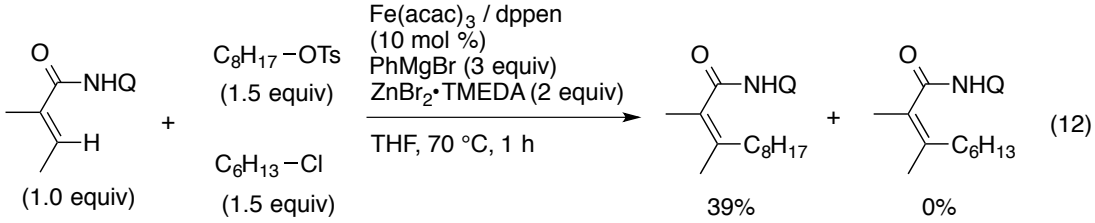
Table 2. Investigation of leaving group of the alkyl electrophile



entry	C_6H_{13}–X	GC yield (%)		
		SM-C_6H_{13}	SM-Ph	recovery
1	C_6H_{13}–**I**	89	9	0
2	C_6H_{13}–**Br**	79	15	8
3	C_6H_{13}–**Cl**	70	19	0
4	C_6H_{13}–**OTs**	70	12	0
5	C_6H_{13}–**OTs** + NaI (1.5 equiv)	83[a]	10	0

[a] Yield was determined by isolation of the product

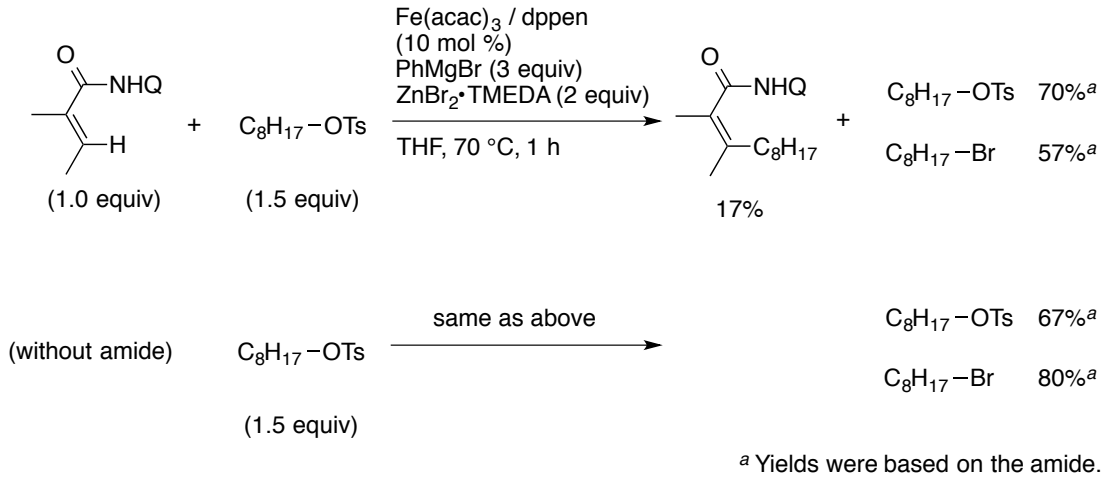
Then a competition experiment was performed to compare the reactivity of alkyl chloride and alkyl tosylate as the alkyl donor (eq. 12). The reaction was performed in the presence of octyl tosylate and hexyl chloride in the same reaction pot, and the product distribution was investigated after 1 hour of reaction time. As a result, the *β*-octylated amide was obtained as a sole product, which means the alkyl tosylate is much more reactive than the alkyl chloride.



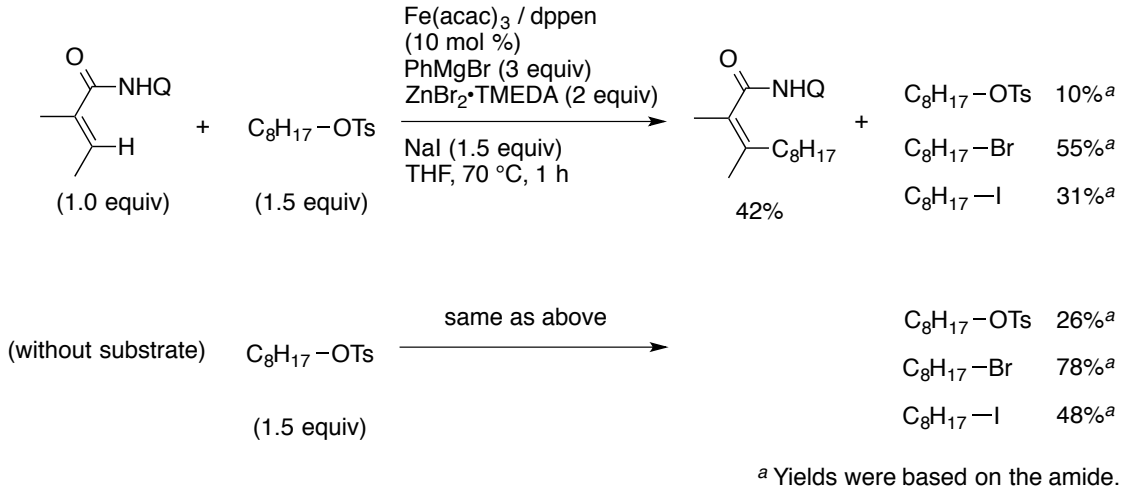
However, the experiments shown in Scheme 3 and 4 imply that alkyl tosylates may function as an alkyl donor after conversion to the corresponding alkyl bromide or

iodide via tosylate/halide exchange. Thus, I observed the presence of octyl bromide in 57% (based on the amide) at the end of the reaction using octyl tosylate as the alkyl donor, possibly through tosylate/bromide exchange with zinc bromide as the bromide source (Scheme 3). The exchange occurred regardless of the presence or absence of the amide substrate. Similarly, octyl iodide was observed in 31% yield when sodium iodide was used as an additive, after 1 hour reaction time (Scheme 4).

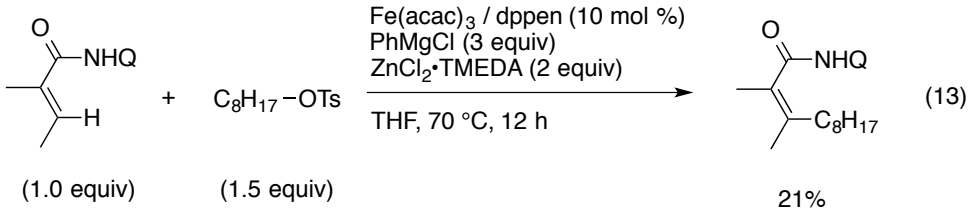
Scheme 3. *In situ* generation of alkyl bromide via tosylate/bromide exchange



Scheme 4. Reaction with sodium iodide and distribution of unreacted alkyl electrophiles



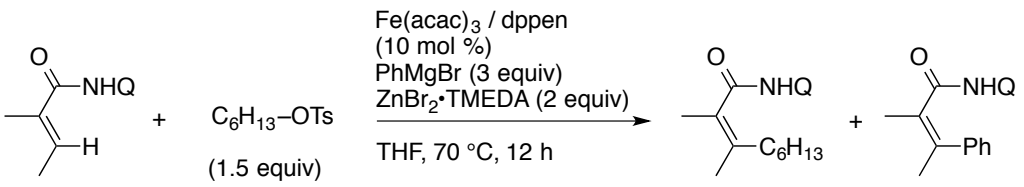
Then the innate reactivity of alkyl tosylate or alkyl chloride as the alkyl donor was investigated, by excluding the bromide/iodide anion from the reaction mixture. I performed the reaction using $ZnCl_2$•TMEDA and PhMgCl to exclude bromide and iodide anions, to find that the reaction was considerably slower, and I obtained the product in 21% yield after 12 hours reaction time (eq. 13). From these investigations regarding alkyl electrophiles, it can be concluded that the trend of the reactivity is: I > Br >> Cl, and alkyl tosylate has similar reactivity to alkyl bromide or iodide, through *in situ* tosylate/halide exchanges.



4-6. Investigation of the reaction parameters

Next I investigated the effect of key reaction parameters on the alkylation reaction (Table 3). The reaction performed at room temperature was slower, probably because of slow C–H bond activation at lower temperature, as suggested from stoichiometric reactions (entry 2). [36] Other ether solvents such as cyclopentylmethylether (CPME), functioned less efficiently probably due to different constant of the Schlenk equilibrium of the Griganrd reagent, generating less active $R_2Mg•MgBr_2$ (entry 3).[37,38] Decreasing the amount of the zinc additive (1 equiv) for producing the diarylzinc base still promotes the reaction to afford the product, through generation of monoarylzinc base *in situ* (entry 4).[39] 1 equiv of alkyl tosylate produced the product with slightly lower efficiency (entry 5), and low concentration of the reaction also slowed down the reaction (entry 6). These results suggest that concentration of the alkyl electrophile might be an important factor for catalyst turnover. A radical scavenger such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) shut down the reaction, which implies involvement of a radical intermediate, although possible intermediates were not trapped by TEMPO (entry 7). A lower amount of catalyst (5 mol %) slowed down the reaction, implying that the catalyst is deactivated with moderate turnover (entry 8).[40] The use of commercially available phenylzinc bromide instead of pre-mixed $PhMgBr/ZnBr_2•TMEDA$ completely shut down the reaction (entry 9), suggesting that a magnesium salt is necessary for the C–H bond activation event.[41]

Table 3. Investigation of the key reaction parameters



1
0.40 mmol
0.4 M

alkyln

aryln

Entry	Variation from the "standard" reaction conditions	GC yield (%)[a]		
		alkyln	aryln	recov. of **1**
1	none	72	13	0
2	room temp	34	4	67
3	CPME/THF (1:1) as a solvent	57	8	30
4	$ZnBr_2$•TMEDA (1 equiv)	60	7	22
5	C_6H_{13}–OTs (1.0 equiv)	73	13	2
6	0.1M instead of 0.4 M	63	12	3
7	TEMPO (2 equiv) as an additive	0	0	53
8	$Fe(acac)_3$ / dppen (5 mol %)	55	13	3
9	PhZnBr (3 equiv) instead of PhMgBr/$ZnBr_2$•TMEDA	0	0	86

[a] GC yields were determined using hexadecane as an internal standard.

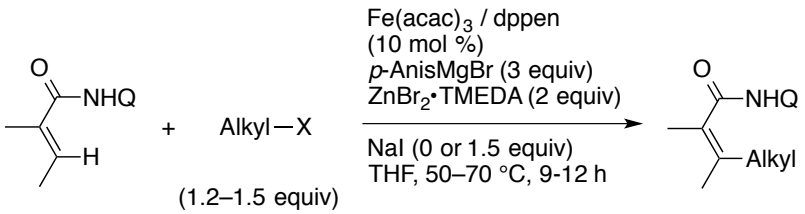
4-7. Scope of the reaction using olefinic amides

With the optimized reaction conditions in hand, scope of the alkyl electrophiles was examined using olefinic amides as the substrate (Table 4). The hexyl group was successfully incorporated using hexyl tosylate as an electrophile, to the *cis* *β*-position of the alkene substrate (entries 1–2). A dehydropyraneamide substrate was slightly less effective, probably due to the coordination of *β*-oxygen to the iron catalyst leading to deactivation (entry 3). Alkyl iodide, bromide and chloride could be used as

alkyl donors with the reactivity trend of I > Br > Cl, as observed previously (entries 4–6).[42] 4-Chlorobutyl tosylate was used as an alkylating reagent to give 4-chlorobutylated amide as a sole product, which means the reaction took place much faster at tosylate position than at chloride (entry 7). Ester group was also tolerated, highlighting the broad substrate scope using monoarylzinc as a milder base (entry 8). A phenetyl tosylate was also successfully reacted without any β-hydride elimination producing a styrene (entries 9–10).[43] Aryl chloride and bromide on the electrophiles were completely tolerated (entries 11–12).

Scope of the reaction also includes secondary alkyl electrophiles, which are challenging substrates due to fast β-hydride elimination in many cases (entries 13–15). Cyclopentyl group was a good alkyl donor (entry 13), and the reaction using a 4-pyranyl group proceeded selectively without the formation of any isomers, which indicates that there is no chain-walking as it was observed in cobalt catalysis (entry 14).[26] Isobutyl group was also introduced without any isomerization to linear butyl group (entry 15). Tertiary alkyl, and allyl electrophiles were not compatible with these reaction conditions. [44]

Table 4. Substrate scope for iron-catalyzed *β*-alkylation of alkeneamides using alkyl electrophiles



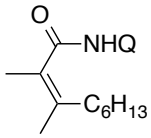
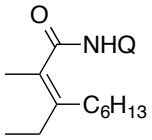
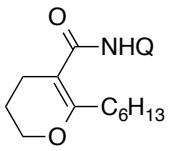
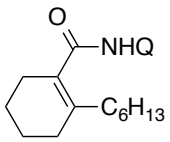
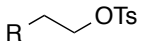
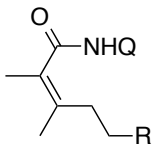
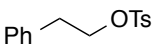
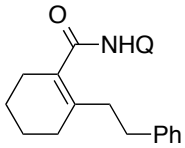
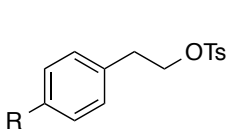
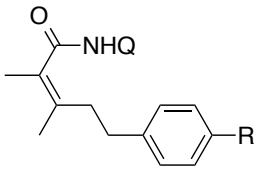
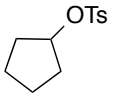
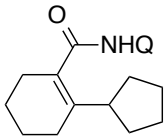
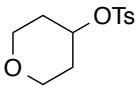
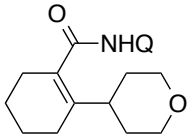
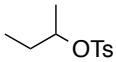
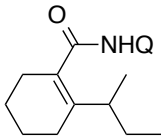
entry	alkyl–X	product	yield (%)
1	C_6H_{13}–OTs		85
2	C_6H_{13}–OTs		87
3	C_6H_{13}–OTs		61
4	C_6H_{13}–X		[89] (X = I)
5			[79] (X = Br)
6			[70] (X = Cl)
7			89 (R = $(CH_2)_2Cl$)
8			83 (R = $(CH_2)_3CO_2Et$)
9			93

Table 4. (continued)

10 11 12			85 [71] (R = H) 84 (R = Cl) 85 (R = Br)
13			77
14			49
15			63[a]

See experimental section for detailed reaction conditions.
For the entries 4–6, the yields were determined by GC analysis.
The yields in brackets are for the reaction performed in the absence of NaI.
All reactions formed an arylation side product in 10–20% yield.
[a] The reaction produced 100% 2-butylated product and none of the 1-butylated product.

Figure 1 summarizes unreactive alkeneamide substrates. Substitution at α- and β-position of the amide are necessary probably due to stability of the organoiron intermediates, but aryl substituents on α-position of the amide leads to isomerization due to extended π-conjugation. The reaction using α- or β-unsubstituted acrylamide resulted in low conversion, or large amount of β-arylated product.

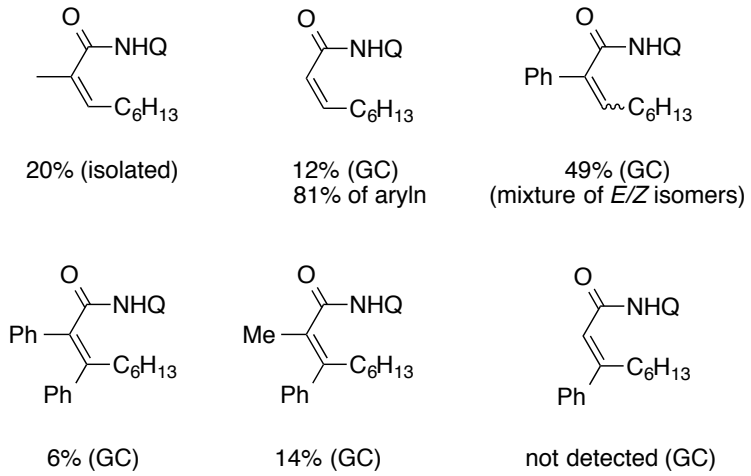


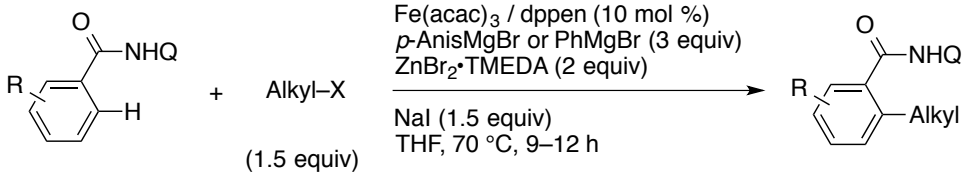
Figure 1. Examples of unreactive substrates: reaction using hexyl iodide as an alkyl electrophile

4-8. Scope of the reaction using aromatic carboxamides

Scope of aromatic carboxamides for the alkylation reaction was also examined (Table 5). At entries 1–6, I examined aromatic substrates with different substituents on the *meta*-position, using phenetyl tosylate as an alkyl electrophile. Arenes with electron-donating substituents such as methyl (entry 1), methoxy (entry 2) and dimethylamino (entry 3) gave the product in over 80% yield, with arylated side-product in less than 10%. On the other hand, the reaction of amides possessing electron-withdrawing halide groups (entries 4–6) proceeded less efficiently, and the yield of the arylated product increased.[45] The results suggest that the arylation of the amide is an alternative pathway from the same organoiron intermediate, if the desired alkylation reaction is slow. Debromination of the amide was not observed at all, which demonstrates improved chemoselectivity as compared with the previous reactions that used a Griganrd reagent as the base (entry 6).[28] Secondary alkyl groups such as a cyclopentyl (entry 7) and isobutyl (entry 8) groups were successfully incorporated into the amide without any isomerization, as also observed in the case using olefinic amides. The reaction using an *ortho*-substituted benzamide was slow, but the product was

obtained in satisfactory yield when the reaction time was elongated (entry 9). Heteroaryl amides such as indoleamide (entry 10) and thienylamide (entry 11) were also *ortho*-alkylated successfully. Alkyl bromides and chlorides could be also used as alkyl donors, affording the products in good yields (entries 12–13).

Table 5. Scope for *ortho*-alkylation of aromatic amides



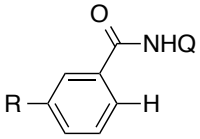
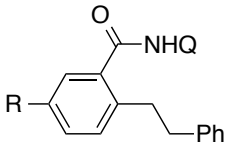
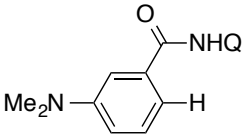
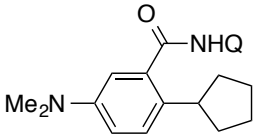
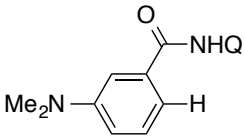
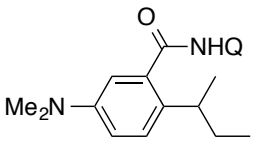
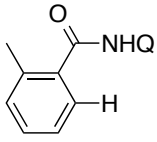
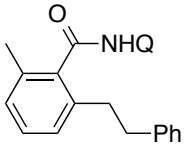
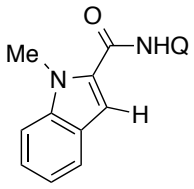
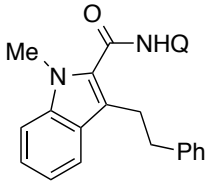
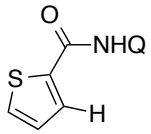
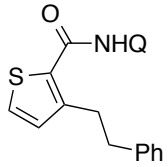
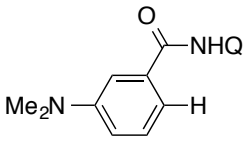
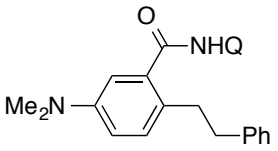
entry	substrate	product			yield (%)
1			R =	Me	82
2				OMe	87
3				NMe_2	93
4				F	75
5				Cl	60
6				Br	53
7					89
8					83[a]
9					70[b]

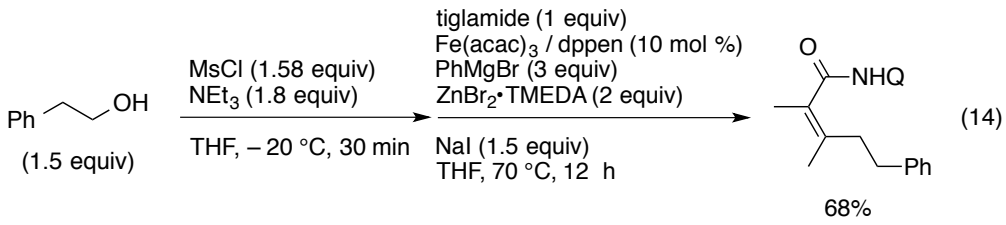
Table 5. (continued)

10			81
11			41
12[c]			84
13[d]			72

See experimental section for detailed reaction conditions.
All reactions formed an arylation side product as a side product.
[a] The reaction produced 100% 2-butylated product and none of the 1-butylated product.
[b] 30 hours of reaction time.
[c] 2-Phenetyl bromide was used as a starting material.
[d] 2-Phenetyl chloride was used as a starting material.

4-9. One-pot mesylation / *β*-alkylation using alcohol as an alkyl donor

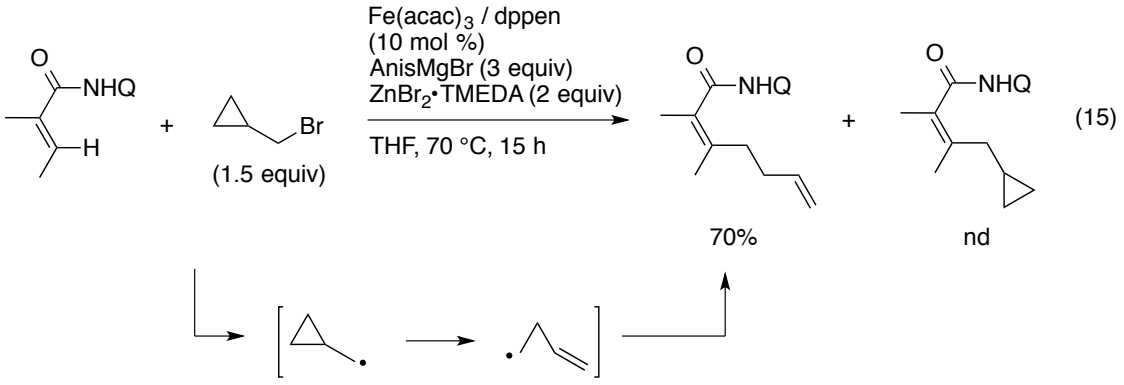
An alcohol could also be used as the alkyl donor for the reaction, through *in situ* mesylation. Thus, phenetyl alcohol was mesylated by treating with methanesulfonyl chloride and a triethylamine base to give phenetyl mesylate *in situ*, which was then utilized for the alkylation reaction without isolation, to give the product in 68% yield (eq. 14). This result highlights the synthetic utility of the reaction, starting from inexpensive and widely available alcohol as an alkyl donor.

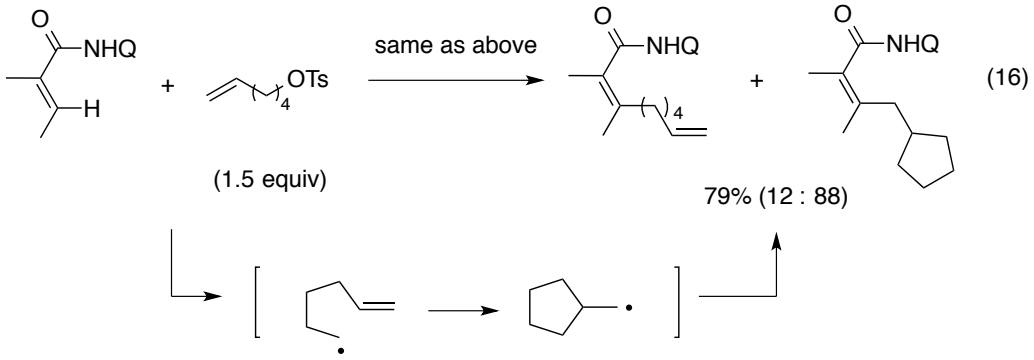


4-10. Proof of alkyl radical intermediate

• Radical clock experiments

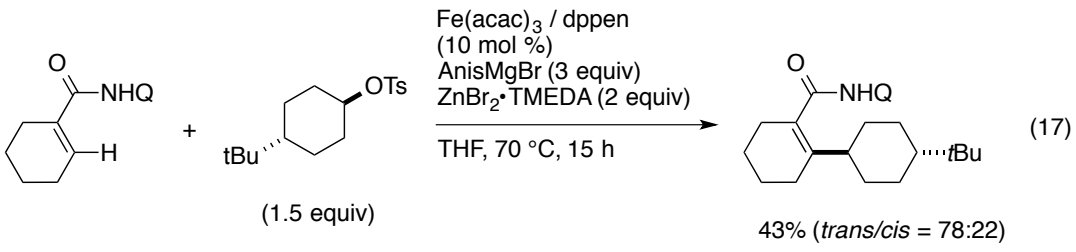
To proof the existence of the radical species that was implied in the previous study (Table 3, entry 7), I performed radical clock experiments [46] using bromomethylcyclopropane and 5-hexenyl tosylate as electrophiles. The reaction with bromomethylcyclopropane gave *cis*-3-butenylated amide as the sole product through radical rearrangement, which is a clear evidence for involvement of a radical-like intermediate (eq. 15). Similarly, reaction with 5-hexenyl tosylate afforded a mixture of a 5-hexenylated amide and a cyclized product in the ratio of 12:88 (eq. 16).[47] Because of the lifetime of the 5-hexenyl radical is relatively long,[48] it can be said that a radical-like intermediate with long lifetime is involved in this reaction.

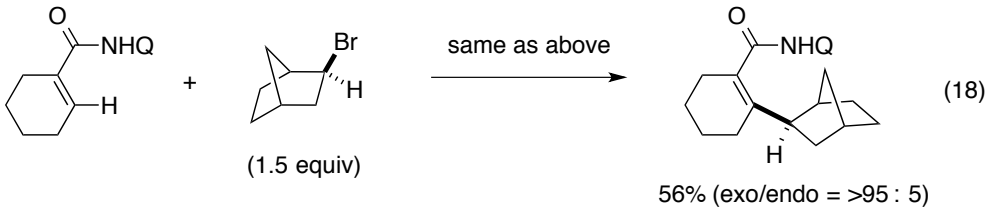




• Loss of stereoselectivities

Further investigations were performed using other alkyl electrophiles, which also supports the radical character of the reaction. When the reaction was performed using *trans*-4-*tert*-butylcyclohexyl tosylate, the stereochemistry decreased to 78:22 (*trans/cis*) (eq. 17). The loss of stereochemistry on the sp^3 carbon center connected to the tosyloxy group indicates radical character of intermediate.[29h] On the other hand, the reaction with *cis*-4-*tert*-butylcyclohexyl tosylate did not proceed at all, possibly due to competitive *β*-eliminative loss of tosyloxy group. Similarly, coupling with 2-bromonorbornane mostly proceed at less-hindered *exo*-position of norbornene (eq. 18), which also indicates the existence of an intermediate having radical character.

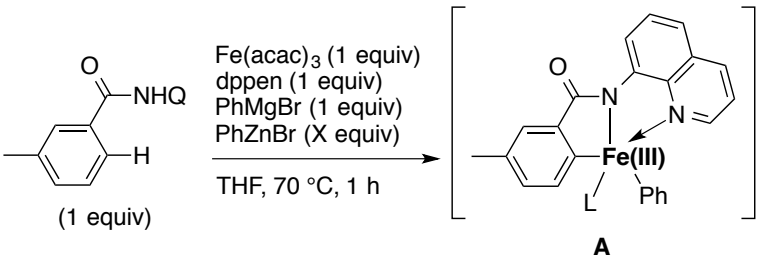




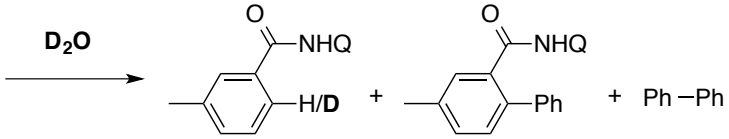
4-11. Stoichiometric reactions

Stoichiometric reactions were performed to gain information into the nature of the organoiron intermediate, prepared with monoarylzinc base (Scheme 5). I added different amounts (1–3 equiv) of phenylzinc bromide to a solution of deprotonated amide (1 equiv) and a stoichiometric amount of $Fe(acac)_3$/dppen (1 equiv), and generation of the intermediate was confirmed by deuterium incorporation after D_2O quench, similar with previous investigations.[28] While 1 equiv of base was not enough to form the organoiron intermediate (23% D incorporation for 92% recovery), the amount of deuterium incorporation improved with 2 equiv of the base (85% D incorporation for 92% recovery). Given that 1 equiv of the base would be used as a base to accept the hydrogen of the C–H bond, another 1 equiv of aryl group might be on the iron atom in **A**, which might be the active species for the reaction. Excess amount of the base (3 equiv) induced reductive elimination to give *ortho*-phenylation, probably through the formation of an iron ate species. Notably, homocoupling of the base to yield biphenyl was not observed in all entries, which indicates that iron is not reduced by the base. Taking also into consideration that homocoupling of the organometallic base through reductive elimination is the only the way for iron to be reduced,[49] it can be said that organoiron(III) species is the active species for this reaction, which is very rare example of catalysis with organoiron species reported so far.[50] The involvement of organoiron(III) species might be a reason for the unique reactivity of this reaction, such as suppression of cross coupling and homocoupling. Addition of alkyl electrophile into the solution of organoiron **A** gave mixture of alkylation and arylation, which means the oxidative addition of the alkyl electrophile to the organoiron(III) is difficult (eq. 19).

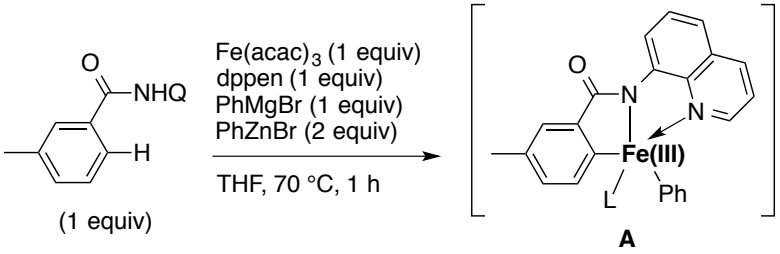
Scheme 5. Stoichiometric reactions using arylzinc halide as a base

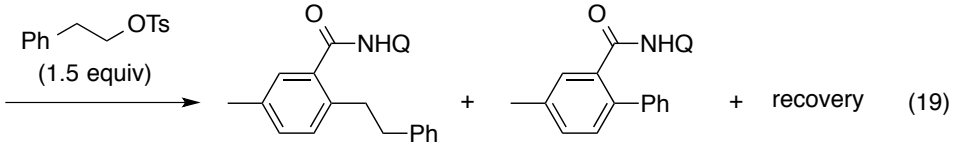


$PhZnBr = PhMgBr + ZnBr_2 \cdot TMEDA$



X = 1	92% (23% D)	5%	0%
X = 2	92% (85% D)	6%	0%
X = 3	39% (45% D)	51%	0%

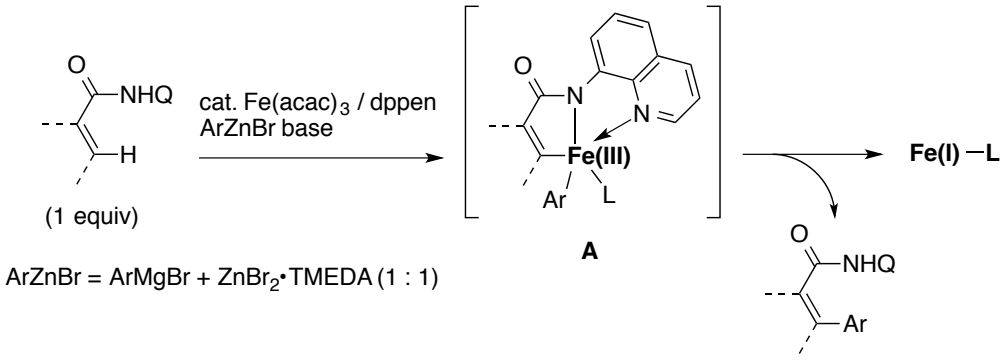




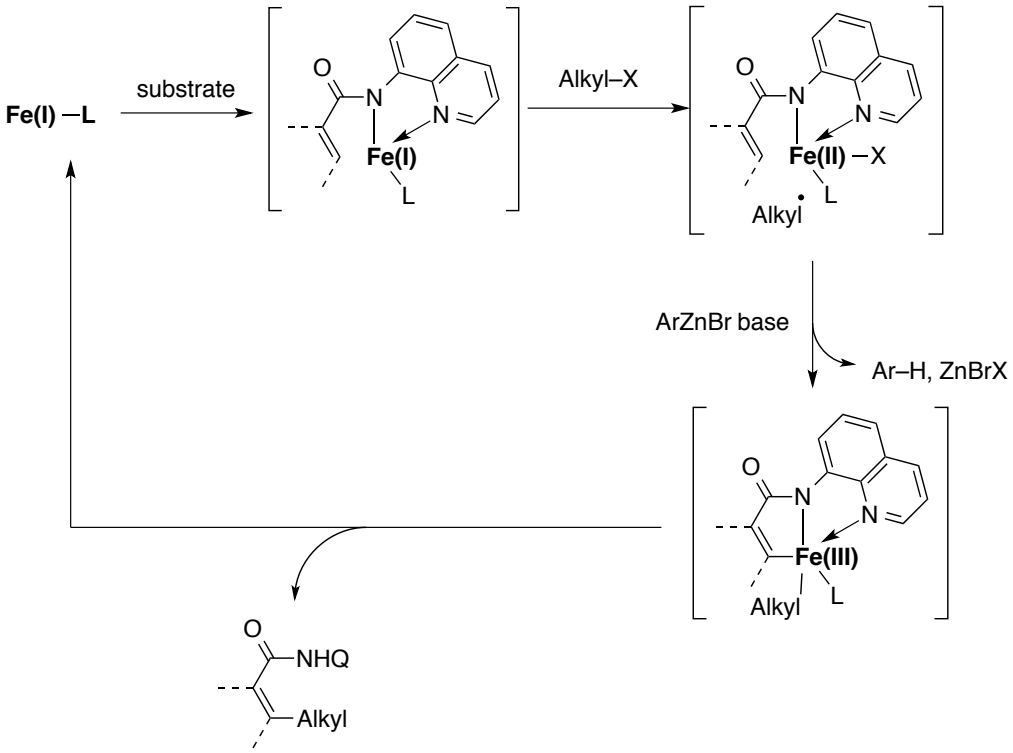
4-12. Possible catalytic cycle

Based on the information obtained from the mechanistic studies, I suggest one of the possible catalytic cycles (Schemes 6 and 7). In the first cycle (Scheme 6), organoiron(III) species **A** generates as suggested in the stoichiometric reactions. Then the arylated product is produced from the species **A** through reductive elimination in stoichiometric amount to the catalyst, together with unstable iron(I) species. In the beginning of the second cycle (Scheme 7), the iron(I) would be immediately captured and stabilized by quinolylamide and diphosphine,[51] and then it will be oxidized through oxidative addition of an alkyl electrophile through radical pathway to give radical-like iron(II) species. Recombination of the radical species will give alkyliron(III), and following reductive elimination produce the product, regenerating iron(I).

Scheme 6. Possible catalytic cycle: first cycle



Scheme 7. Possible catalytic cycle: from second cycles



4-13. Conclusion

In conclusion, iron-catalyzed directed alkylation of aromatic and olefinic amides using alkyl electrophiles was developed. Monoarylzinc halide is an uniquely effective base to promote the reaction while suppressing competing reactions such as cross coupling, homocoupling and *β*-hydride elimination. Primary and secondary alkyl tosylate can be used as an alkyl donor without any isomerization, which is synthetically useful as well as mechanistically intriguing. Sodium iodide as an additive improves the yield through *in situ* iodide/tosylate exchange, but the reaction also proceeded in its absence. Through mechanistic studies, the radical-like nature of alkylmetal intermediate and an unusual organoiron(III) species are suggested, as a possible reason for the high and unique reactivity observed. Thus, the present study has revealed robust and high reactivity of iron catalysis, which would be great motivation to pursue further unique

reactions.

4-14. Experimental

Materials and Instruments

General. All reactions dealing with air- or moisture-sensitive compounds were performed by standard Schlenk techniques in oven-dried Schlenk tubes under an argon atmosphere. Flash chromatography was performed as described by Still *et al.*,[52] employing Kanto Silica gel 60 (spherical, neutral, 140-325 mesh). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECA-500 (500 MHz) and JEOL ECX-400 (400 MHz) NMR spectrometer. ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (7.26 and 77.0 ppm), respectively. Gel permeation column chromatography was performed on a Japan Analytical Industry LC-908 (eluent: toluene) with JAIGEL 1H and 2H polystyrene columns.

Gas chromatographic (GC) analysis was performed on a Shimadzu GC-14B instrument equipped with an FID detector and a capillary column, HR-1 (25 m x 0.25 mm i.d., 0.25 mm film). Mass spectra (GS MS) were taken at SHIMADZU Parvum 2 gas chromatograph mass spectrometer.

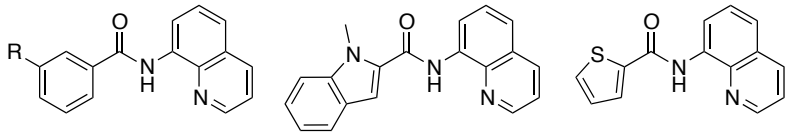
Materials. Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used after appropriate purification before use. Anhydrous tetrahydrofuran was purchased from KANTO Chemical Co. and purified prior to use by a solvent purification system (GlassContour) equipped with columns of activated alumina and copper catalyst.[53] The water content was determined with a Karl-Fischer moisture titrator (MKC-210, Kyoto Electronics Company) to be less than 30 ppm. Phenylmagnesium bromide and *p*-anisylmagnesium bromide were prepared from the corresponding bromoarene and magnesium turnings in

anhydrous tetrahydrofuran, and titrated prior to use using I_2 in THF saturated with LiCl (0.5 M).[54]

Preparation methods and compound data for the starting materials

Synthesis of the carboxamides

The following carboxamide substrates were prepared according to the literature.[55] The compound data was in good agreement with the literature.



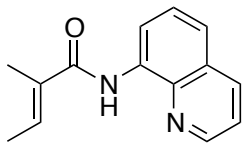
R = Me, OMe, NMe_2, F, Cl, Br

Alkenecarboxamides were synthesized according to the general procedure described below. *N*-(Quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide was prepared from *in situ* generated acid chloride[55] and 8-aminoquinoline. Compound data of *N*-(quinolin-8-yl)cyclohex-1-enecarboxamide, (*E*)-2-methyl-*N*-(quinolin-8-yl)pent-2-enamide, and *N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide were in good accordance with the literature.[55]

General procedure for the synthesis of amide substrates:
(E)-2-Methyl-N-(quinolin-8-yl)but-2-enamide

Tiglic acid (50 mmol, 5.01 g) was placed in an oven-dried two-necked flask and thionyl chloride (30 mL) was added under an argon atmosphere. The reaction mixture was stirred at 80 °C for 90 min, and then the excess thionyl chloride was removed *in vacuo*. The flask was cooled to 0 °C, the reaction mixture was diluted with dichloromethane (100 mL), then triethylamine (5 equiv) and 8-quinolylamine (1.5 equiv) were added and the reaction mixture was stirred for 10 h at room temperature. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution, and the organic layer was separated, and the aqueous layer was extracted with

dichloromethane for 3 times. The obtained crude amide was purified by silica gel column chromatography (10% ethyl acetate/hexane/0.5% triethylamine) to afford the title compound as yellow oil. The crude oil was carefully recrystalized from cooled hexane to afford the pure compound as a colorless solid.



Melting point: 42–44 °C.

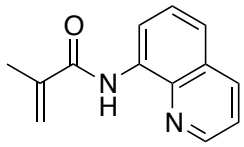
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (s, 1H), 8.84–8.80 (m, 2H), 8.15 (dd, J = 8.4, 1.6 Hz, 1H), 7.56–7.43 (m, 3H), 6.76 (d, J = 6.9 Hz, 1H), 2.07 (s, 3H), 1.88 (d, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 148.1, 138.7, 136.3, 134.7, 132.8, 131.9, 127.9, 127.4, 121.5, 121.2, 116.3, 14.2, 12.4.

GC MS (EI) *m/z* (relative intensity): 226 (M^+, 25), 211 (4), 183 (23), 182 (25), 171 (26), 145 (11), 144 (100), 128 (44), 117 (15), 116 (20), 89 (16), 83 (91).

HRMS (APCI+): *m/z* calcd for $C_{14}H_{14}N_2O$ [M+H^+] 227.1179; found: 227.1181.

_N_-(quinolin-8-yl)-2-methylacrylamide



The title compound was prepared from metacryloyl chloride and 8-aminoquinoline. The compound was obtained as a colorless solid.

Melting point: 62–66 °C.

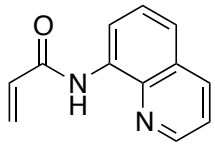
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.37 (s, 1H), 8.84–8.80 (m, 2H), 8.15 (d, J = 8.5 Hz, 1H), 7.56–7.50 (m, 2H), 7.46–7.43 (m, 1 H), 6.05 (s, 1H), 5.56 (m, 1H), 2.19 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 148.2, 140.7, 138.6, 136.3, 134.4, 127.9, 127.4, 121.6, 121.5, 120.6, 116.4, 18.7.

GC MS (EI) *m/z* (relative intensity): 212 (M^+, 32), 211 (8), 197 (11), 183 (17), 171 (100), 169 (56), 168 (32), 144 (20), 143 (18), 117 (14) 116 (31), 90 (11), 89 (24).

HRMS (APCI+): *m/z* calcd for $C_{13}H_{12}N_2O$ [M+H^+] 213.1022; found: 213.1028.

_N_-(quinolin-8-yl)acrylamide



The title compound was prepared from acryloyl chloride and 8-aminoquinoline. The compound was obtained as a light brown solid.

Melting point: 76–78 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.96 (s, 1H), 8.86 (d, J = 7.5 Hz, 1H), 8.80–8.79 (m, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.56–7.43 (m, 3H), 6.54–6.46 (m, 2H), 5.84–5.81 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 148.1, 138.4, 136.3, 134.3, 131.7, 127.9, 127.4, 127.3, 121.7, 121.6, 116.8.

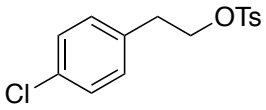
GC MS (EI) *m/z* (relative intensity): 198 (M^+, 51), 171 (28), 169 (13), 155 (19), 144 (100), 129 (22), 117 (25), 116 (28), 89 (24).

HRMS (APCI+): *m/z* calcd for $C_{12}H_{10}N_2O$ [M+H^+] 199.0866; found: 199.0868.

Synthesis of alkyl tosylates

The alkyl tosylate substrates were prepared according to the literature.[56] Compound data was in good agreement with the literature.[56]

2-(4-Chlorophenyl)-1-ethyltosylate



Obtained as a colorless solid. The compound data were in good accordance with the literature.[56]

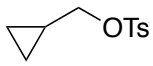
Melting point: 76–78 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 4.19 (t, J = 6.8 Hz, 2H), 2.91 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 134.8, 132.7, 132.7, 130.2, 129.7, 128.6, 127.7, 70.3, 34.6, 21.6.

GC MS (EI) *m/z* (relative intensity): 140 (34), 139 (11), 138 (100), 127 (9), 125 (30), 103 (16), 91 (35), 89 (12), 77 (12).

Cyclopropylmethyltosylate



Obtained as a colorless liquid. It contains small amount of impurity that may be the ring-opened product. The compound data were in good accordance with the literature.[56]

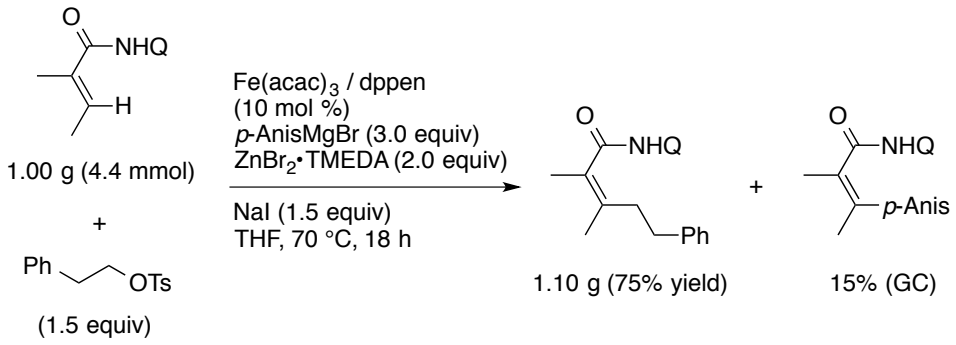
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 4.78–4.75 (m, 1H), 2.44 (s, 3H), 2.20–2.13 (m, 4H), 1.75–1.73 (m, 1H), 1.62–1.48 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 134.1, 129.7, 127.8, 74.1, 30.8, 21.6, 12.9.

GC MS (EI) *m/z* (relative intensity): 198 (12), 155 (64), 121 (9), 107 (3), 92 (17), 91 (100), 77 (4), 71 (5).

Procedure for 1g scale reaction

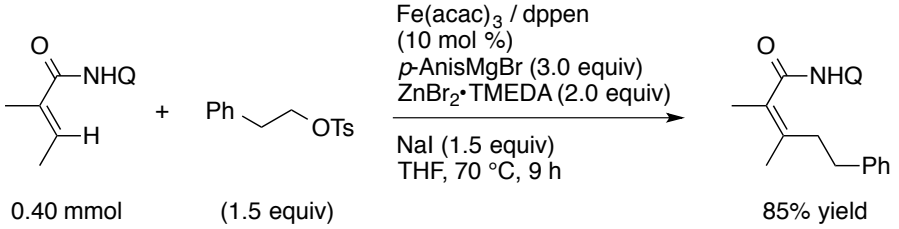
Alkylation of N-(quinolin-8-yl)-(E)-2-methylbut-2-enoic amide on 1 g scale



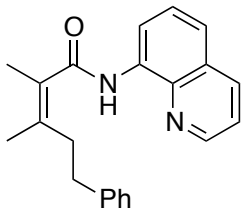
Sodium iodide (994 mg, 6.6 mmol) was placed in an oven-dried two-necked flask and it was carefully dried by heating with a heat gun *under vacuo*. *N*-(quinolin-8-yl)-(*E*)-2-methylbut-2-enoic amide (1.00 g, 4.4 mmol), and $ZnBr_2$•TMEDA (3.02 g, 8.8 mmol) were added, and the mixture was dissolved in THF (30 mL). A solution of *p*-anisylmagnesium bromide in THF (15.1 mL, 0.88 mol/L, 13.3 mmol) was added dropwise, and then phenethyl tosylate (1.83 g, 6.6 mmol) was added. Next, a solution of $Fe(acac)_3$ (156 mg, 0.44 mmol) and *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 175 mg, 0.44 mmol) in THF (3 mL) was added, and the reaction mixture was heated to 70 °C. After stirring for 18 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (10 mL). After aqueous workup, the organic layer was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with $NaHCO_3$ (2 times) and brine, dried over magnesium sulfate, concentrated *in vacuo*, and purified by silica gel chromatography (10% ethyl acetate/hexane/0.5% triethylamine) to afford *N*-(quinolin-8-yl)-(*Z*)-2,3-dimethyl-5-phenylpent-2-enoic amide as a colorless oil (1.10 g, 75% yield).

General Procedure and compound data

Directed C–H alkylation of N-(quinolin-8-yl)-(E)-2-methylbut-2-enoic amide (Table 4, entry 10)



Sodium iodide (90 mg, 0.60 mmol) was placed in an oven-dried Schlenk tube and and it was carefully dried by heating with a heat gun *under vacuo*. *N*-(quinolin-8-yl)-(*E*)-2-methylbut-2-enoic amide (90.5 mg, 0.40 mmol), and $ZnBr_2$•TMEDA (273 mg, 0.80 mmol) were added, and the mixture was dissolved in THF (0.5 mL). A solution of *p*-anisylmagnesium bromide in THF (1.36 mL, 0.88 mol/L, 1.20 mmol) was added dropwise, and then phenetyl tosylate (166 mg, 0.60 mmol) was added. Next, a solution of $Fe(acac)_3$ (14.1 mg, 0.040 mmol) and *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 15.9 mg, 0.040 mmol) in THF (0.3 mL), was added, and the reaction mixture was heated to 70 °C. After stirring for 9 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (2 mL). After aqueous workup, the organic layer was extracted with EtOAc (2 mL × 3). The combined organic layer was passed through a pad of Florisil, concentrated *in vacuo*, and purified by silica gel chromatography (10% ethyl acetate/hexane/0.5% triethylamine) to afford *N*-(quinolin-8-yl)-(*Z*)-2,3-dimethyl-5-phenylpent-2-enoic amide as a colorless oil in 85% yield.



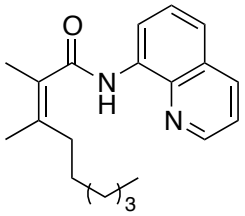
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.85 (d, J = 7.5 Hz, 1H), 8.78 (dd, J = 4.0, 2.0 Hz, 1H), 8.17 (dd, J = 8.5, 1.5 Hz, 1H), 7.58–7.51 (m, 2H), 7.45 (dd, J = 8.5, 4.0 Hz, 1H), 7.12–7.02 (m, 5H), 2.90–2.87 (m, 2H), 2.59–2.55 (m, 2H), 2.04 (s, 3H), 1.86 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 148.2, 141.9, 138.4, 137.0, 136.3, 134.6, 128.6, 128.2, 128.2, 128.0, 127.4, 125.7, 121.6, 121.5, 116.5, 38.4, 35.0, 18.3, 16.5.

GC MS (EI) *m/z* (relative intensity): 330 (M^+, 9), 239 (10), 187 (14), 171 (4), 159 (2), 145 (13), 144 (100), 129 (5), 117 (18), 109 (10), 105 (4), 91 (56).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{22}N_2O$ [M+H^+] 331.1805; found: 331.1789.

(*Z*)-*N*-(quinolin-8-yl)-2,3-dimethylnon-2-enamide (Table 4, entry 1): The reaction was performed at 70 °C for 12 h. The title compound was obtained as a colorless oil in 85% yield.



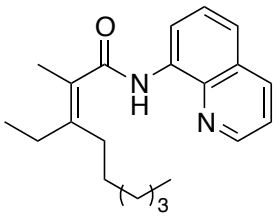
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.86 (d, J = 7.5 Hz, 1H), 8.79 (d, J = 4.0 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.57–7.23 (m, 3H), 2.25 (t, J = 8.0 Hz, 2H), 2.01 (s, 3H), 1.79 (s, 3H), 1.57–1.52 (m, 2H), 1.22–1.17 (m, 6H), 0.74 (t, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 148.0, 138.5, 137.7, 136.3, 134.7, 127.9, 127.8, 127.4, 121.5, 121.3, 116.4, 36.1, 31.7, 29.3, 28.5, 22.5, 17.9, 16.4, 14.0.

GC MS (EI) *m/z* (relative intensity): 310 (M^+, 7), 171 (7), 167 (23), 144 (100), 117 (6), 116 (6), 109 (19), 101 (2), 97 (5), 95 (4), 89 (3), 83 (16), 81 (5).

HRMS (APCI+): *m/z* calcd for $C_{20}H_{26}N_2O$ [M+H$^+$] 311.2118; found: 311.2097.

(*Z*)-*N*-(quinolin-8-yl)-2-methyl-3-ethylnon-2-enamide (Table 4, entry 2): The reaction was performed at 70 °C for 18 h. The title compound was obtained as a colorless oil in 87% yield.



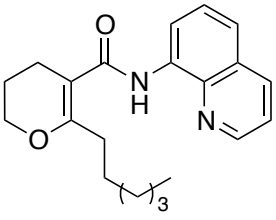
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.87 (dd, J = 7.6, 1.1 Hz, 1H), 8.79 (dd, J = 4.1, 1.6 Hz, 1H), 8.15 (dd, J = 8.2, 1.4 Hz, 1H), 7.57–7.42 (m, 3H), 2.26–2.15 (m, 4H), 2.02 (s, 3H), 1.57–1.53 (m, 2H), 1.21–1.15 (m, 6H), 1.08 (t, J = 7.6 Hz, 3H), 0.73–0.70 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 148.0, 143.1, 138.5, 136.3, 134.7, 127.9, 127.6, 127.4, 121.5, 121.3, 116.4, 33.6, 31.6, 29.5, 28.8, 24.4, 22.4, 15.8, 13.9, 12.4.

GC MS (EI) *m/z* (relative intensity): 324 (M$^+$, 5), 181 (16), 171 (3), 144 (100), 129 (2), 123 (17), 117 (5), 116 (5), 110 (4), 97 (11), 95 (5), 83 (21).

HRMS (APCI+): *m/z* calcd for $C_{21}H_{28}N_2O$ [M+H$^+$] 325.2274; found: 325.2260.

6-Hexyl-*N*-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide (Table 4, entry 3): The reaction was performed at 70 °C for 6 h. The title compound was obtained as a colorless oil in 61% yield.



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.84 (dd, J = 7.6, 1,2 Hz, 1H), 8.79–8.78 (m, 1H), 8.16–8.13 (m, 1H), 7.54 (dd, J = 8.0, 7.9 Hz, 1H), 7.46–7.42 (m, 2H), 4.07 (t, J

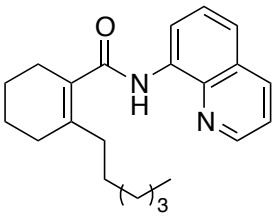
= 5.0 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.55 (t, *J* = 6.5 Hz, 2H), 1.99–1.94 (m, 2H), 1.71–1.64 (m, 2H), 1.35–1.26 (m, 6H), 0.84 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 163.1, 147.9, 138.6, 136.3, 135.1, 127.9, 127.5, 121.4, 120.8, 116.1, 105.1, 66.0, 32.9, 31.7, 29.2, 27.8, 22.5, 22.3, 21.9, 14.0.

GC MS (EI) *m/z* (relative intensity): 338 (M^+, 5), 195 (100), 171 (5), 152 (4), 144 (14), 137 (10), 126 (2), 117 (3), 116 (4), 113 (13), 111 (11), 109 (8), 98 (27), 83 (11).

HRMS (APCI+): *m/z* calcd for $C_{21}H_{26}N_2O_2$ [M+H$^+$] 339.2067; found: 339.2064.

2-Hexyl-*N*-(quinolin-8-yl)-cyclohex-1-enamide (Table 4, entries 4–6): The reaction was performed at 70 °C for 9 h. The title compound was obtained as a colorless oil.



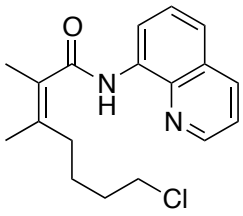
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.79 (d, *J* = 7.5 Hz, 1H), 8.71 (d, *J* = 4.0 Hz, 1H), 7.48–7.18 (m, 3H), 2.35 (s, br, 2H), 2.16 (t, *J* = 8.0 Hz, 3H), 2.04 (s, br, 2H), 1.62–1.11 (m, 12H), 0.66 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 148.0, 139.7, 138.4, 136.3, 134.7, 129.9, 127.9, 127.4, 121.5, 121.3, 116.4, 35.1, 31.7, 29.3, 28.9, 28.4, 27.1, 22.5, 22.4, 22.3, 14.0.

GC MS (EI) *m/z* (relative intensity): 336 (M^+, 14), 193 (33), 192 (14), 171 (5), 150 (11), 145 (14), 144 (100), 136 (8), 135 (55), 122 (5), 117 (7), 116 (7), 109 (11), 107 (10), 95 (39), 91 (11), 83 (10), 81 (23), 79 (28), 77 (14).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{28}N_2O$ [M+H$^+$] 337.2274; found: 337.2271.

(*Z*)-*N*-(quinolin-8-yl)-2,3-dimethyl-7-chlorohept-2-enamide (Table 4, entry 7): The reaction was performed at 50 °C for 12 h. The title compound was obtained as a colorless oil in 89% yield.



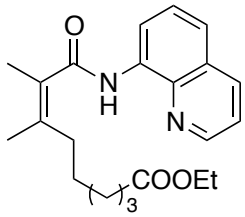
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.82 (d, J = 7.5 Hz, 1H), 8.76 (dd, J = 4.0, 1.5 Hz, 1H), 8.12 (dd, J = 8.5, 1.5 Hz, 1H), 7.53–7.40 (m, 3H), 3.44 (t, J = 6.0 Hz, 3H), 2.26 (t, J = 6.8 Hz, 3H), 1.99 (s, 3H), 1.76 (s, 3H), 1.70–1.66 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 148.1, 138.3, 136.8, 136.2, 134.4, 128.4, 127.8, 127.3, 121.5, 121.4, 116.2, 44.9, 35.0, 32.1, 25.4, 17.7, 16.4.

GC MS (EI) *m/z* (relative intensity): 318 (M^+, 1), 316 (4), 175 (4), 173 (12), 171 (3), 145 (12), 144 (100), 116 (6), 109 (14), 103 (4), 101 (1), 89 (4), 81 (4).

HRMS (APCI+): *m/z* calcd for $C_{18}H_{21}N_2O$ [M+H^+] 317.1415; found: 317.1416.

(*Z*)-Ethyl-7,8-dimethyl-9-oxo-9-(quinolin-8-ylamino)non-7-enoate (Table 4, entry 8): The reaction was performed at 50 °C for 12 h. The title compound was obtained as a colorless oil in 83% yield.



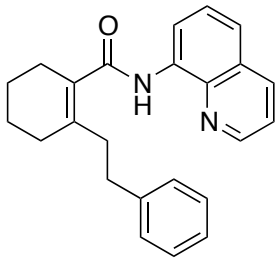
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.79 (s, 1H), 8.85 (d, J = 3.5 Hz, 1H), 8.80 (dd, J = 4.3, 1.5 Hz, 1H), 8.17 (dd, J = 8.3, 1.5 Hz, 1H), 7.57–7.27 (m, 3H), 4.05 (q, J = 7.0 Hz, 2H), 2.26 (t, J = 7.5 Hz, 2H), 2.19 (t, J = 7.5 Hz, 2H), 2.01 (s, 3H), 1.79 (s, 3H), 1.61–1.18 (m, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 170.8, 148.1, 138.4, 137.4, 136.3, 134.6, 128.0, 127.9, 127.4, 121.6, 121.4, 116.4, 60.1, 35.9, 34.1, 29.1, 28.1, 24.8, 17.9, 16.4, 14.2.

GC MS (EI) *m/z* (relative intensity): 368 (M^+, 6), 323 (7), 281 (3), 171 (5), 151 (12), 145 (12), 144 (100), 133 (5), 129 (3), 123 (8), 117 (4), 116 (5), 109 (26), 107 (6), 83 (6), 81 (13), 79 (6).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{28}N_2O_3$ [$M+H^+$] 369.2173; found: 369.2161.

2-Phenethyl-*N*-(quinolin-8-yl)-cyclohex-1-enamide (Table 4, entry 9): The reaction was performed at 70 °C for 12 h. The title compound was obtained as a colorless oil in 93% yield.



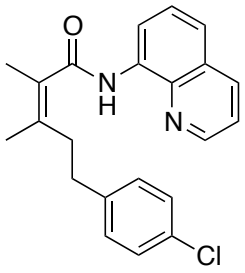
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 8.87 (d, J = 7.5 Hz, 1H), 8.79 (dd, J = 4.0, 1.5 Hz, 1H), 8.16 (dd, J = 8.0, 1.5 Hz, 1H), 7.58–7.43 (m, 3H), 7.12–7.02 (m, 5H), 2.88 (t, J = 8.3 Hz, 2H), 2.57 (t, J = 8.3 Hz, 2H), 2.46 (br, 2H), 2.18 (br, 2H), 1.73 (br, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 148.1, 142.0, 139.4, 138.4, 136.3, 134.6, 130.6, 128.3, 128.1, 127.9, 127.4, 125.7, 121.5, 121.4, 116.5, 37.3, 35.0, 29.4, 27.2, 22.4, 22.3.

GC MS (EI) *m/z* (relative intensity): 357 (M^+, 4), 356 (13), 265 (5), 237 (1), 213 (31), 212 (22), 197 (2), 184 (6), 169 (4), 155 (3), 145 (8), 144 (100), 129 (7), 117 (24), 92 (7), 91 (92), 77 (12).

HRMS (APCI+): *m/z* calcd for $C_{24}H_{24}N_2O$ [$M+H^+$] 357.1961; found: 357.1962.

(*Z*)-*N*-(quinolin-8-yl)-2,3-dimethyl-5-(4-chlorophenyl)pent-2-enamide (Table 4, entry 11): The reaction was performed at 50 °C for 15 h. The title compound was obtained as a light brown solid in 84% yield.



Melting point: 66–68 °C.

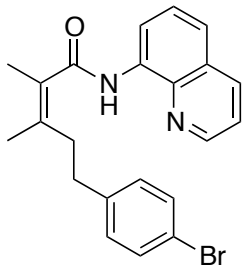
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.83 (d, J = 7.5 Hz, 1H), 8.78 (d, J = 4.0 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.58–7.52 (m, 2H), 7.45 (dd, J = 7.8, 4.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 2.84 (t, J = 8.0 Hz, 3H), 2.56 (t, J = 8.0 Hz, 3H), 2.03 (s, 3H), 1.84 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 148.2, 140.2, 138.3, 136.7, 136.4, 134.5, 131.4, 129.6, 128.8, 128.2, 128.0, 127.4, 121.6, 121.5, 116.4, 38.1, 34.2, 18.3, 16.5,

GC MS (EI) *m/z* (relative intensity): 366 (M^+, 27), 364 (M^+, 77), 239 (70), 223 (20), 221 (76), 211 (8), 205 (11), 195 (10), 186 (6), 181 (4), 171 (22), 168 (5), 165 (4), 157 (14), 151 (21), 145 (100), 144 (97), 127 (71), 125 (100), 116 (44), 109 (58), 101 (18), 99 (11), 96 (11), 89 (55).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{21}ClN_2O$ [M+H^+] 365.1404; found: 365.1415.

(*Z*)-*N*-(quinolin-8-yl)-2,3-dimethyl-5-(4-bromophenyl)pent-2-enamide (Table 4, entry 12): The reaction was performed at 50 °C for 15 h. The title compound was obtained as a colorless solid in 85% yield.



Melting point: 73–75 °C.

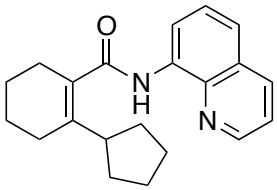
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.84–8.78 (m, 2H), 8.17 (d, J = 8.2 Hz, 1H), 7.56–7.44 (m, 3H), 7.20 (d, J = 7.9 Hz, 2H), 6.92 (d, J =8.2 Hz, 2H), 2.83 (t, J = 8.1 Hz, 2H), 2.55 (t, J = 7.9 Hz, 2H), 2.03 (s, 3H), 1.84 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 148.2, 140.7, 138.3, 136.7, 136.4, 134.5, 131.2, 130.0, 128.8, 128.0, 127.4, 121.6, 121.5, 119.4, 116.4, 38.0, 34.2, 18.3, 16.5.

GC MS (EI) *m/z* (relative intensity): 410 (M^+, 4), 412 (M^+, 4), 267 (3), 265 (3), 239 (9), 186 (2), 171 (15), 169 (12), 158 (3), 144 (100), 128 (4), 116 (6), 109 (6), 90 (10).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{21}BrN_2O$ [M+H^+] 409.0910 and 411.0892; found: 409.0903 and 411.0894.

2-Cyclopropyl-*N*-(quinolin-8-yl)cyclohex-1-enamide (Table 4, entry 13): The reaction was performed at 70 °C for 16 h. The title compound was obtained as a colorless oil in 77% yield.



^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.88 (d, J = 7.5 Hz, 1H), 8.81 (dd, J = 4.5, 1.5 Hz, 1H), 8.15 (dd, J = 8.5, 1.5 Hz, 1H), 7.57–7.27 (m, 3H), 3.04 (t, J = 8.5 Hz, 1H), 2.43 (br, 2H), 2.09 (br, 2H), 1.81–1.45 (m, 12H).

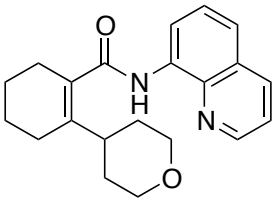
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 148.0, 140.6, 138.4, 136.2, 134.7, 130.2, 127.9, 127.4, 121.5, 121.3, 116.4, 43.7, 30.8, 27.3, 25.9, 23.5, 22.5, 22.4.

GC MS (EI) *m/z* (relative intensity): 320 (M^+, 9), 177 (48), 176 (100), 159 (14), 148 (58), 144 (43), 133 (6), 131 (8), 117 (17), 116 (10), 107 (11), 105 (9), 95 (13), 93 (13), 91 (25), 81 (43), 79 (40).

HRMS (APCI+): *m/z* calcd for $C_{21}H_{24}N_2O$ [M+H^+] 321.1961; found: 321.1949.

2-(4-Tetrahydropyran)-*N*-(quinolin-8-yl)cyclohex-1-enamide (Table 4, entry 14): The reaction was performed at 70 °C for 16 h. The title compound was obtained as a

colorless oil in 49% yield.



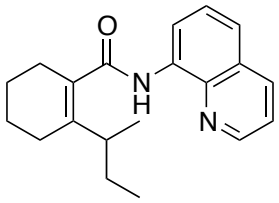
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.85 (d, J = 7.5 Hz, 1H), 8.77 (dd, J = 4.3, 1.5 Hz, 1H), 8.17 (dd, J = 8.5, 2.0 Hz, 1H), 7.59–7.28 (m, 3H), 3.94–3.91 (m, 2H), 3.28 (t, J = 11.8 Hz, 2H), 2.93–2.88 (m, 1H), 2.45 (br, 2H), 2.11 (br, 2H), 1.85–1.60 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 148.0, 141.2, 138.4, 136.4, 134.4, 130.4, 127.9, 127.4, 121.6, 121.6, 116.5, 67.9, 67.8, 40.1, 30.6, 27.4, 24.1, 22.3.

GC MS (EI) *m/z* (relative intensity): 337 (M^+, 6), 336 (24), 193 (12), 192 (100), 177 (23), 162 (9), 147(16), 144 (41), 119 (12), 105 (52), 91 (9).

HRMS (APCI+): *m/z* calcd for $C_{21}H_{24}N_2O_2$ [$M+H^+$] 337.1911; found: 337.1903.

2-(*sec*-Butyl)-*N*-(quinolin-8-yl)cyclohex-1-enamide (Table 4, entry 15): The reaction was performed at 70 °C for 16 h. The title compound was obtained as a yellow oil in 63% yield.



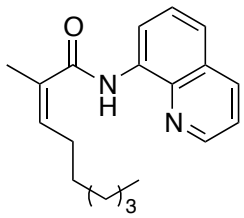
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.86 (d, J = 7.6 Hz, 1H), 8.79 (dd, J = 4.6, 1.6 Hz, 1H), 7.57–7.43 (m, 3H), 2.72–2.66 (m, 1H), 2.50–2.37 (m, 2H), 2.11–1.95 (m, 2H), 1.73–1.64 (m, 4H), 1.49–1.26 (m, 2H), 1.07 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 148.7, 141.5, 138.4, 136.2, 134.7, 130.5, 127.9, 127.4, 121.5, 121.3, 116.4, 39.0, 27.5, 27.4, 22.5, 22.3, 22.3, 19.3, 12.3.

GC MS (EI) *m/z* (relative intensity): 308 (M^+, 11), 165 (47), 164 (35), 150 (15), 149 (100), 145 (11), 144 (67), 135 (6), 130 (11), 119 (7), 117 (8), 116 (9), 95 (17), 93 (12), 91 (15), 81 (24), 79 (23).

HRMS (APCI+): *m/z* calcd for $C_{20}H_{24}N_2O$ [$M+H^+$] 309.1961; found: 309.1946.

***N*-(quinolin-8-yl)-2-methyl-non-2-enamide (Figure 1):** The reaction was performed at 50 °C for 12 h. The title compound was obtained as a colorless oil in 20% yield.



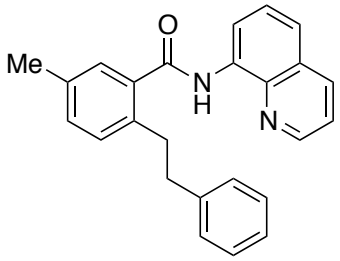
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.86 (dd, J = 7.3, 1.5 Hz, 1H), 8.79 (dd, J = 4.3, 2.0 Hz, 1H), 8.16 (dd, J = 8.5, 1.5 Hz, 1H), 7.57–7.26 (m, 3H), 5.76–5.74 (m, 1H), 2.43–2.38 (m, 2H), 2.11 (s, 3H), 1.69 (br, 1H), 1.51–1.46 (m, 2H), 1.35–1.24 (m, 5H), 0.83 (t, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 148.2, 138.6, 136.3, 135.6, 134.5, 132.1, 127.9, 127.4, 121.6, 121.5, 116.4, 31.7, 29.8, 29.6, 29.0, 22.6, 21.0, 14.0.

GC MS (EI) *m/z* (relative intensity): 296 (6), 225 (1), 153 (2), 145 (12), 144 (100), 117 (3), 116 (3), 95 (6).

HRMS (APCI+): *m/z* calcd for $C_{19}H_{24}N_2O$ [$M+H^+$] 297.1961; found: 297.1944.

5-Methyl-2-phenethyl-*N*-(quinolin-8-yl)benzamide (Table 5, entry 1): The reaction was performed at 70 °C for 12 h. The title compound was obtained as a colorless solid in 82% yield. Arylation side product was obtained in 2% yield (GC).



Melting point: 124–126 °C.

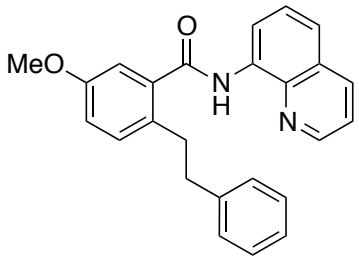
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 8.96 (d, J = 7.3 Hz, 1H), 8.76 (d, J = 4.1 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.63–7.54 (m, 2H), 7.46–7.43 (m, 2H), 7.24–7.03 (m, 7H), 3.20–3.16 (m, 2H), 3.01–2.97 (m, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 148.2, 141.8, 138.5, 137.3, 136.6, 136.3, 135.9, 134.8, 131.0, 130.5, 128.5, 128.1, 127.9, 127.7, 127.4, 125.7, 121.7, 121.6, 116.5, 38.2, 35.2, 21.0.

GC MS (EI) *m/z* (relative intensity): 366 (4), 275 (3), 223 (11), 222 (28), 194 (6), 179 (11), 178 (12), 165 (8), 145 (32), 144 (100), 131 (5), 117 (24), 104 (14), 103 (16), 91 (24).

HRMS (APCI+): *m/z* calcd for $C_{25}H_{22}N_2O$ [M+H$^+$] 367.1805; found: 367.1811.

5-Methoxy-2-phenethyl-*N*-(quinolin-8-yl)benzamide (Table 5, entry 2): The reaction was performed at 70 °C for 9 h. The title compound was obtained as a colorless solid in 87% yield. Arylation side product was obtained in 2% yield (GC).



Melting point: 96–98 °C.

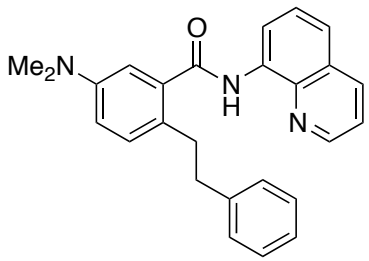
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.95 (d, J = 7.0 Hz, 1H), 8.77 (dd, J = 4.0, 2.0 Hz, 1H), 8.18 (dd, J = 8.0, 1.5 Hz, 1H), 7.63–7.55 (m, 2H), 7.45 (dd, J = 8.3, 4.5 Hz, 1H), 7.20–6.94 (m, 8H), 3.85 (s, 3H), 3.17–3.14 (m, 3H), 2.99–2.96 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 157.7, 148.2, 141.7, 138.5, 137.5, 136.3, 134.7, 132.2, 131.8, 128.5, 128.2, 128.0, 127.4, 125.7, 121.8, 121.7, 116.5, 115.8, 112.6, 55.5, 38.3, 34.7.

GC MS (EI) *m/z* (relative intensity): 382 (M^+, 5), 291 (10), 276 (1), 238 (29), 223 (5), 210 (6), 209 (6), 195 (4), 179 (6), 178 (7), 171 (3), 165 (7), 161 (14), 152 (3), 145 (12), 144 (100), 135 (4), 133 (11), 121 (12), 120 (13), 105 (5), 103 (6), 91 (24).

HRMS (APCI+): *m/z* calcd for $C_{25}H_{22}N_2O_2$ [M+H^+] 383.1754; found: 383.1749.

5-Dimethylamino-2-phenethyl-*N*-(quinolin-8-yl)benzamide (Table 5, entry 3, 12, and 13): The reaction was performed at 70 °C for 9 h. The title compound was obtained as a colorless solid in 93% yield. Arylation side product was obtained in 5% yield (GC, for entry 3).



Melting point: 102–104 °C.

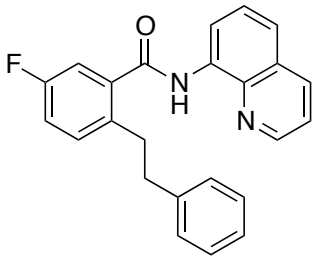
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.96 (d, J = 7.3 Hz, 1H), 8.75 (dd, J = 4.1, 1.4 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.63–7.54 (m, 2H), 7.44 (dd, J = 8.2, 4.1 Hz, 1H), 7.16–6.99 (m, 7H), 6.80 (dd, J = 8.6, 2.7 Hz, 1H), 3.12–3.09 (m, 2H), 2.98–2.95 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 148.9, 148.2, 142.1, 138.5, 137.3, 136.2, 134.8, 131.3, 128.5, 128.1, 127.9, 127.6, 127.4, 125.6, 121.6, 121.6, 116.5, 114.5, 111.3, 40.7, 38.4, 34.6.

GC MS (EI) *m/z* (relative intensity): 395 (M^+, 15), 305 (22), 304 (100), 288 (4), 281 (3), 251 (23), 222 (16), 207 (13), 155 (11), 148 (33), 134 (21), 120 (16), 91 (14).

HRMS (APCI+): *m/z* calcd for $C_{26}H_{25}N_3O$ [M+H^+] 396.2070; found: 396.2067.

5-Fluoro-2-phenethyl-*N*-(quinolin-8-yl)benzamide (Table 5, entry 4): The reaction was performed at 70 °C for 12 h. The title compound was obtained as a colorless solid in 75% yield. Arylation side-product was obtained in 13% yield (GC).



Melting point: 146–148 °C.

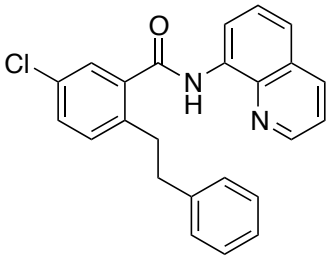
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.11 (s, 1H), 8.92 (d, J = 7.0 Hz, 1H), 8.78 (dd, J = 4.3, 1.5 Hz, 1H), 8.19 (dd, J = 8.0, 1.5 Hz, 1H), 7.63–7.57 (m, 2H), 7.47 (dd, J = 8.3, 4.0 Hz, 1H), 7.36 (dd, J = 8.5, 2.5 Hz, 1H), 7.25–7.02 (m, 7H), 3.21–3.18 (m, 2H), 3.00–2.96 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 161.8, 159.9, 148.3, 141.3, 138.5, 138.0, 137.9, 136.4, 136.1, 136.1, 134.4, 132.4, 132.3, 128.5, 128.5, 128.5, 128.2, 127.9, 127.4, 125.9, 122.1, 121.7, 117.2, 117.0, 116.6, 114.3, 114.1, 38.1, 34.8.

GC MS (EI) *m/z* (relative intensity): 370 (M^+, 2), 279 (2), 261 (1), 249 (2), 226 (10), 211 (3), 209 (2), 197 (5), 183 (6), 171 (2), 145 (12), 144 (100), 130 (4), 121 (13), 116 (4), 108 (11), 101 (5), 91 (22).

HRMS (APCI+): *m/z* calcd for $C_{24}H_{19}FN_2O$ [M+H^+] 371.1554; found: 371.1557.

5-Chloro-2-phenethyl-*N*-(quinolin-8-yl)benzamide (Table 5, entry 5): The reaction was performed at 70 °C for 24 h. The title compound was obtained as a colorless solid in 60% yield. Yield of the arylation product did not determined due to overlap of GC spectrum.



Melting point: 149–151 °C.

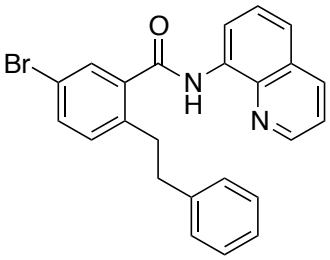
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.91 (d, J = 6.4 Hz, 1H), 8.79 (d, J = 3.2 Hz, 1H), 8.20 (d, J = 7.3 Hz, 1H), 7.63–7.57 (m, 3H), 7.47 (dd, J = 8.2, 4.1 Hz, 1H), 7.37 (dd, J = 8.2, 2.1 Hz, 1H), 7.21–7.01 (m, 6H), 3.19 (t, J = 7.9 Hz, 2H), 2.98 (t, J = 8.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 148.3, 141.2, 138.8, 138.4, 138.1, 136.4, 134.4, 132.1, 131.9, 130.2, 128.5, 128.2, 127.9, 127.3, 127.1, 125.9, 122.1, 121.8, 116.6, 37.9, 34.9.

GC MS (EI) *m/z* (relative intensity): 386 (M^+, 2), 295 (2), 242 (7), 207 (12), 178 (9), 167 (2), 165 (9), 145 (10), 144 (100), 124 (7), 91 (24), 89 (12).

HRMS (APCI+): *m/z* calcd for $C_{26}H_{25}N_3O$ [M+H^+] 387.1259; found: 387.1246.

5-Bromo-2-phenethyl-*N*-(quinolin-8-yl)benzamide (Table 5, entry 6): The reaction was performed at 70 °C for 24 h. The title compound was obtained as a colorless solid in 53% yield. Arylation side-product was obtained in 25% yield.



Melting point: 140–142 °C.

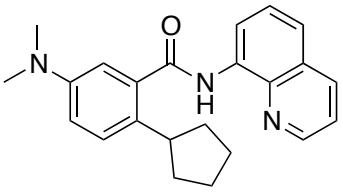
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.91 (d, J = 7.1 Hz, 1H), 8.78 (d, J = 4.1 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.76 (s, 1H), 7.62–7.44 (m, 4H), 7.30–7.01 (m, 6H), 3.17 (t, J = 7.9 Hz, 2H), 2.97 (t, J = 7.9 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 148.3, 141.1, 139.3, 138.5, 138.4, 136.4, 134.4, 133.1, 132.4, 129.9, 128.5, 128.3, 128.2, 127.9, 127.3, 125.9, 122.1, 121.7, 119.8, 116.6, 37.8, 35.0.

GC MS (EI) *m/z* (relative intensity): 432 (M^+, 1), 430 (M^+, 2), 401 (2), 342 (2), 341 (2), 328 (2), 327 (1), 311 (1), 309 (1), 287 (3), 281 (3), 207 (20), 191 (3), 183 (3), 179 (8), 178 (11), 171 (4), 165 (4), 145 (12), 144 (100), 130 (4), 116 (5), 102 (3), 91 (18), 89 (13).

HRMS (APCI+): *m/z* calcd for $C_{24}H_{19}N_2O$ [M+H^+] 431.0754 and 433.0736; found: 431.0737 and 433.0726.

5-Dimethylamino-2-cyclopropyl-*N*-(quinolin-8-yl)benzamide (Table 5, entry 7): The reaction was performed at 70 °C for 12 h. The title compound was obtained as a colorless solid in 89% yield.



Melting point: 129–132 °C.

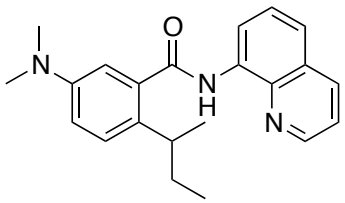
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.97 (d, J = 7.5 Hz, 1H), 8.75 (d, J = 4.5 Hz, 1H), 8.17 (dd, J = 8.3, 0.5 Hz, 1H), 7.60 (dd, J = 8.0, 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.5, 4.5 Hz, 1H), 7.32 (J = 9.0 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.86 (dd, J = 8.8, 2.5 Hz, 1H), 3.39–3.36 (m, 1H), 2.96 (s, 6H), 2.17–2.12 (m, 2H), 1.77 (br, 2H), 1.65–1.58 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 148.6, 148.1, 138.6, 137.8, 136.2, 134.9, 131.8, 128.0, 127.6, 127.4, 121.6, 121.6, 116.5, 114.9, 110.9, 41.3, 40.7, 35.4, 25.7.

GC MS (EI) *m/z* (relative intensity): 360 (5), 359 (M^+, 19), 281 (3), 230 (3), 216 (22), 215 (74), 207 (11), 188 (29), 187 (100), 186 (31), 172 (12), 158 (9), 147 (19), 146 (12), 143 (11), 134 (6), 129 (6), 116 (8), 115 (9).

HRMS (APCI+): *m/z* calcd for $C_{23}H_{25}N_3O$ [M+H^+] 360.2070; found: 360.2067.

5-Dimethylamino-2-(*sec*-butyl)-*N*-(quinolin-8-yl)benzamide (Table 5, entry 8): The reaction was performed at 70 °C for 12 h. The title compound was obtained as a colorless solid in 83% yield.



Melting point: 104–106 °C.

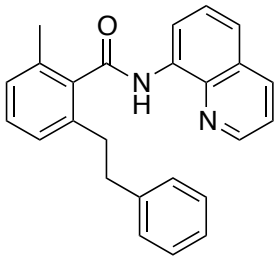
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.12 (s, 1H), 8.96 (dd, J = 7.3, 1.5 Hz, 1H), 8.74 (dd, J = 4.3, 1.5 Hz, 1H), 8.16 (dd, J = 8.3, 1.5 Hz, 1H), 7.60 (dd, J = 8.0, 8.0 Hz, 1H), 7.54 (dd, J = 8.3, 1.5 Hz, 1H), 7.43 (dd, J = 8.3, 4.0 Hz, 1H), 7.25 (dd, J = 4.5, 4.0 Hz, 1H), 6.91 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 8.8, 2.5 Hz, 1H), 3.09–3.05 (m, 1H), 2.97 (s, 6H), 1.71–1.55 (m, 2H), 1.27 (d, J = 7.0 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 148.5, 148.1, 138.5, 137.8, 136.2, 134.8, 133.0, 127.9, 127.4, 127.2, 121.6, 121.6, 116.4, 114.8, 110.7, 40.7, 31.2, 22.6, 12.3.

GC MS (EI) *m/z* (relative intensity): 348 (11), 347 (M^+, 36), 318 (9), 300 (27), 218 (4), 209 (3), 205 (5), 204 (38), 203 (94), 189 (17), 188 (30), 176 (19), 175 (71), 174 (100), 171 (18), 164 (7), 161 (11), 160 (34), 148 (35), 147 (13), 146 (39), 145 (14), 144 (22), 134 (14), 131 (30), 130 (14), 118 (8), 117 (15), 116 (16), 115 (13), 103 (10), 91 (17), 89 (10).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{25}N_3O$ [$M+H^+$] 348.2070; found: 348.2071.

6-Methyl-2-phenethyl-*N*-(quinolin-8-yl)benzamide (Table 5, entry 9): The reaction was performed at 70 °C for 30 h. The title compound was obtained as a colorless oil in 70% yield. Compound data was in good agreement with the literature.[27a]

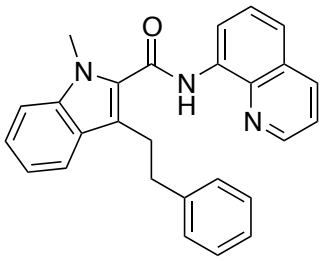


^{1}H NMR (500 MHz, $CDCl_3$): δ 9.95 (s, 1H), 9.01 (d, J = 7.5 Hz, 1H), 8.72 (dd, J = 4.0, 1.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 8.0 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.42 (dd, J = 8.3, 4.0 Hz, 1H), 7.27 (dd, J = 7.5, 2.5 Hz, 1H), 7.24–7.05 (m, 7H), 3.04–2.98 (m, 4H), 2.45 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 148.3, 141.6, 138.4, 137.8, 136.3, 134.6, 134.3, 129.0, 128.4, 128.3. 128.2, 128.1, 128.0, 127.4, 126.9, 125.8, 122.0, 121.7, 116.8, 38.1, 35.8, 19.5.

GC MS (EI) *m/z* (relative intensity): 366 (M^+, 3), 275 (2), 223 (26), 222 (26), 194 (3), 179 (8), 178 (9), 165 (9), 145 (46), 144 (100), 132 (7), 117 (38), 104 (12), 103 (16), 91 (30).

***N*-(quinolin-8-yl)-1-methyl-3-phenetylindoleamide (Table 5, entry 10):** The reaction was performed at 70 °C for 12 h. The title compound was obtained as a colorless oil in 81% yield.



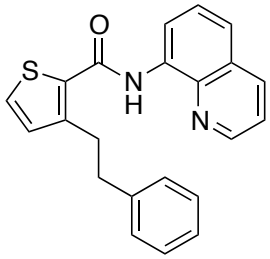
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.40 (s, 1H), 8.84 (dd, J = 7.5, 1.5 Hz, 1H), 8.54 (dd, J = 4.3, 2.0 Hz, 1H), 8.06 (dd, J = 8.3, 2.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.52–7.45 (m, 2H), 7.33–7.25 (m, 3H), 7.15–7.02 (m, 6H), 3.91 (s, 3H), 3.40–3.36 (m, 2H), 3.12–3.09 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 148.4, 141.8, 138.5, 138.3, 136.3, 134.5, 130.6, 128.3, 128.2, 128.0, 127.4, 126.6, 125.8, 124.3, 121.8, 121.7, 120.2, 119.8, 117.7, 116.6, 110.0, 37.7, 31.6, 27.3.

GC MS (EI) *m/z* (relative intensity): 405 (M^+, 12), 350 (2), 341 (2), 315 (18), 314 (74), 281 (4), 261 (5), 246 (3), 235 (8), 134 (16), 232 (8), 217 (7), 207 (9), 189 (4), 172 (5), 171 (37), 158 (30), 155 (12), 145 (13), 144 (100), 143 (23), 129 (6), 128 (14), 116 (11), 115 (13), 102 (7), 101 (7), 91 (12).

HRMS (APCI+): *m/z* calcd for $C_{27}H_{23}N_3O$ [M+H^+] 406.1914; found: 406.1907.

3-Phenethyl-2-*N*-(quinolin-8-yl)thienylamide (Table 5, entry 11): The reaction was performed at 70 °C for 24 h. The title compound was obtained as a colorless solid in 41% yield.



Melting point: 104–108 °C.

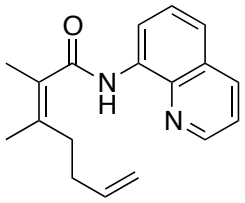
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.46 (s, 1H), 8.86 (d, J = 7.5 Hz, 1H), 8.72 (d, J = 4.0 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.60–7.53 (m, 2H), 7.45 (dd, J = 8.5, 4.0 Hz, 1H), 7.38 (d, J = 5.0 Hz, 1H), 7.27–7.16 (m, 5H), 6.94 (d, J = 4.5 Hz, 1H), 3.46 (t, J = 8.3 Hz, 3H), 3.09 (t, J = 8.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 61.1, 48.3, 45.8, 41.4, 38.6, 36.3, 34.7, 32.3, 31.2, 28.5, 28.5, 28.3, 28.3, 27.9, 27.5, 27.4, 26.0, 21.7, 21.6, 16.5.

GC MS (EI) *m/z* (relative intensity): 358 (M^+, 15), 341 (1), 267 (1), 249 (2), 237 (1), 214 (26), 207 (9), 197 (6), 185 (22), 171 (13), 153 (7), 145 (12), 144 (100), 137 (9), 130 (8), 124 (7), 116 (7), 109 (3), 103 (10), 97 (15), 96 (20), 91 (46), 89 (7).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{18}N_2OS$ [M+H^+] 359.1213; found: 359.1213.

(*Z*)-*N*-(quinolin-8-yl)-2,3-dimethylhepta-2,8-dienamide (eq. 15): The reaction was performed at 50 °C for 12 h. The title compound was obtained as a yellow oil in 70% yield.



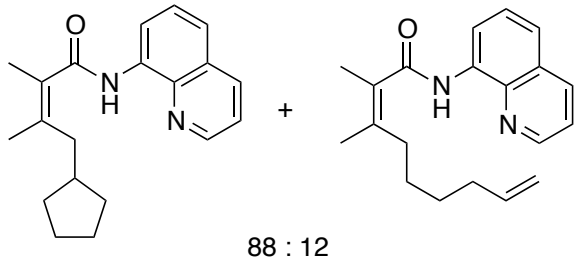
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.86–8.80 (m, 2H), 8.16 (dd, J = 8.3, 2.0 Hz, 1H), 7.57–7.50 (m, 2H), 7.45 (dd, J = 8.3, 4.5 Hz, 1H), 5.80–5.74 (m, 1H), 4.96–4.88 (m, 2H), 2.37–2.31 (m, 4H), 2.02 (s, 3H), 1.80 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 148.1, 138.4, 138.1, 136.6, 136.3, 134.6, 128.6, 127.9, 127.4, 121.6, 121.4, 116.4, 114.8, 35.5, 32.5, 17.9, 16.4.

GC MS (EI) *m/z* (relative intensity): 280 (M^+, 6), 239 (16), 171 (42), 144 (100), 137 (8), 128 (4), 116 (11), 109 (35), 95 (18), 89 (7), 81 (16).

HRMS (APCI+): *m/z* calcd for $C_{18}H_{20}N_2O$ [M+H$^+$] 281.1648; found: 281.1652.

(*Z*)-*N*-(quinolin-8-yl)-2,3-dimethylpent-(5-cyclopentyl)-enamide and (*Z*)-*N*-(quinolin-8-yl)-2,3-dimethylnona-2,8-dienamide (eq. 16): The reaction was performed at 50 °C for 9 h. The title compound was obtained as a colorless oil in 79% yield. ^{1}H NMR indicated that the ratio of the two compounds was 88:12.



88 : 12

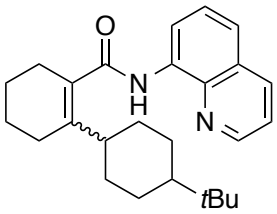
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.85 (d, J = 7.5 Hz, 1H), 8.79 (dd, J = 4.0, 1.5 Hz, 1H), 8.16 (dd, J = 8.0, 1.0 Hz, 1H), 7.57–7.27 (m, 2H), 2.32 (d, J = 7.5 Hz, 2H), 2.28–2.01 (m, 1H), 2.01 (s, 3H), 1.79 (s, 3H), 1.72–1.66 (m, 2H), 1.59–1.31 (m, 4H), 1.15–1.09 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 148.1, 138.5, 137.1, 136.3, 134.7, 128.2, 128.0, 127.4, 121.5, 121.4, 116.4, 41.4, 38.8, 32.5, 24.9, 18.0, 16.6.

GC MS (EI) *m/z* (relative intensity): 308 (M^+, 6), 239 (2), 171 (4), 165 (7), 166 (4), 155 (1), 145 (11), 144 (100), 123 (4), 116 (4), 111 (2), 109 (3), 107 (3), 95 (5), 91 (6), 81 (7).

HRMS (APCI+): *m/z* calcd for $C_{20}H_{24}N_3O$ [M+H^+] 309.1961; found: 309.1939.

***Trans*-2-(4-*tert*-Butyl))-cyclohexyl-*N*-(quinolin-8-yl)cyclohex-1-enamide and *cis*-2-(4-*tert*-Butyl))-cyclohexyl-*N*-(quinolin-8-yl)cyclohex-1-enamide (eq. 17):** The reaction was performed at 70 °C for 16 h. The title compound was obtained as a colorless oil in 43% yield as a mixture of *trans* and *cis* isomers, containing a trace amount of impurities that could not be separated by column chromatography or GPC. The *trans/cis* ratio was determined to be 78:22 by ^{1}H NMR (ratio of the of axial and equatorial H signal).



trans/cis = 78:22

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.86 (d, J = 7.5 Hz, 1H), 8.82–8.79 (m, 1H), 8.16 (d, J = 8.5, 1H), 7.58–7.44 (m, 3H), 2.87–2.81 (m, 1H), 2.57–2.29 (m, 3H), 2.15–0.89 (m, 14H), 0.74 (s, 9H).

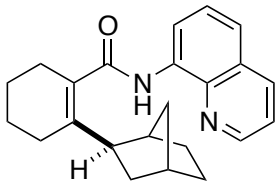
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 148.1, 142.9, 138.5, 136.3, 134.8, 129.5, 128.0, 127.4, 121.5, 116.5, 47.7, 42.9, 42.8, 37.1, 32.3, 31.4, 27.9, 27.7, 27.6, 27.6, 27.5, 27.5, 27.4, 27.0, 25.4, 24.1, 23.7, 22.6, 22.5, 22.4, 22.3.

GC MS (EI) *m/z* (relative intensity): 391 (M^+, 16), 341 (5), 326 (4), 218 (9), 247 (41), 246 (81), 247 (41), 246 (81), 217 (12), 207 (28), 189 (100), 173 (13), 171 (23), 161 (60), 149 (24), 145 (34), 144 (88), 133 (16), 131 (13), 130 (19), 119 (13), 117 (23), 116 (12),

109 (13), 107 (19), 105 (21), 95 (18), 93 (20), 91 (46), 83 (13), 81 (38), 79 (48), 77 (25).

HRMS (APCI+): *m/z* calcd for $C_{26}H_{34}N_2O$ [M+H$^+$] 391.2744; found: 391.2758.

2-(2-*exo*-Norbornyl)-*N*-(quinolin-8-yl)cyclohex-1-enamide (eq. 18): The reaction was performed at 70 °C for 12 h. The title compound was obtained as a colorless oil in 56% yield, containing a trace amount (< 5%) of unidentified compound that may be the *endo* isomer.



(exo/endo > 95:5)

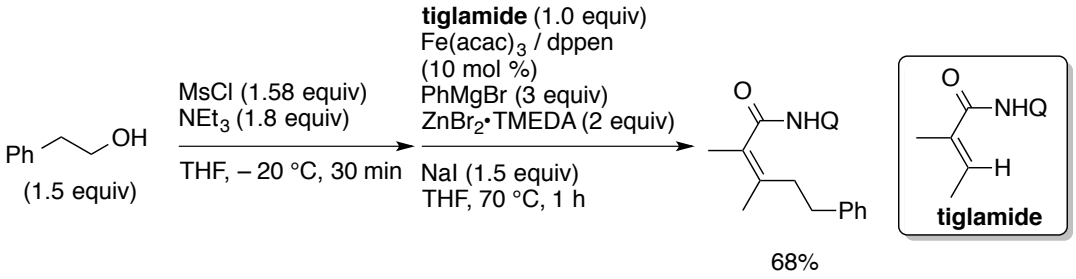
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.80–8.73 (m, 2H), 8.09 (dd, J = 8.5, 1.5 Hz, 1H), 7.57–7.37 (m, 3H), 2.58 (dd, J = 8.0, 7.8 Hz, 1H), 2.38–2.28 (m, 2H), 2.14–2.00 (m, 4H), 1.71–0.79 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 148.1, 141.6, 138.4, 136.3, 134.8, 131.7, 131.4, 130.1, 128.0, 127.4, 121.5, 121.4, 116.5, 45.5, 41.6, 38.2, 37.8, 36.3, 31.5, 27.7, 27.6, 24.5, 22.5, 22.2.

GC MS (EI) *m/z* (relative intensity): 347 (4), 346 (10), 309 (4), 283 (3), 203 (24), 202 (100), 174 (5), 171 (8), 161 (12), 148 (7), 144 (12), 135 (31), 129 (4), 117 (7), 107 (10), 103 (8), 91 (24), 81 (11), 77 (14).

HRMS (APCI+): *m/z* calcd for $C_{23}H_{26}N_2O$ [M+H$^+$] 347.2118; found: 347.2115.

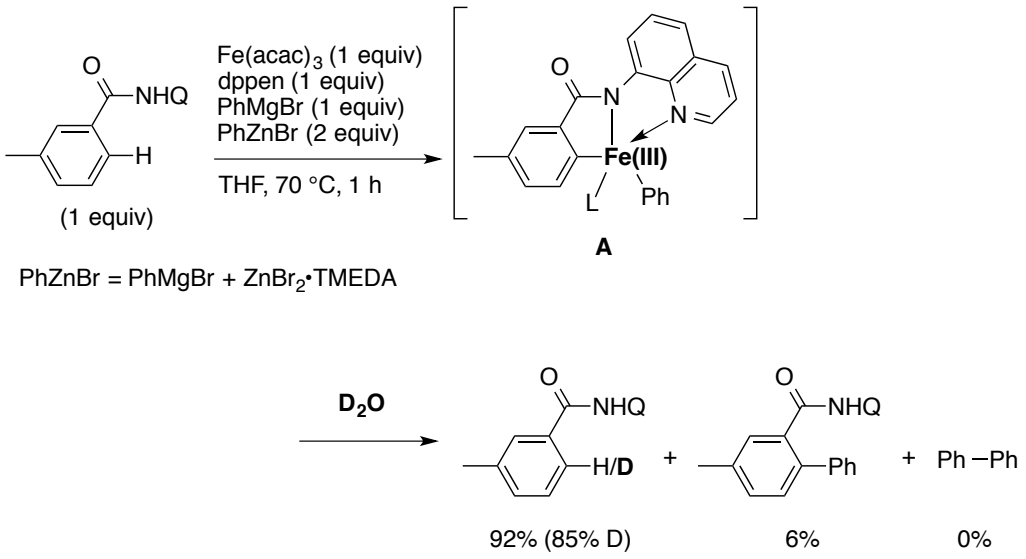
Procedure of the reaction using *in situ* generated alkyl mesylate (eq. 14)



Phenetyl alcohol (73 mg, 0.60 mmol) and triethylamine (72.9 mg, 0.72 mmol) was placed into an oven-dried schlenk tube, and then cooled to –20 °C. Mesyl chloride (72.2 mg, 0.63 mmol) was added and stirred for 30 min to generate phenetyl mesylate. Resulting white precipitation was filtered, and the filtrate was kept at –20 °C.

In another schlenk tube, sodium iodide (90 mg, 0.60 mmol) was placed and carefully dried by heating with a heat gun *under vacuo*. *N*-(quinolin-8-yl)-(*E*)-2-methylbut-2-enoic amide (tiglamide, 90.5 mg, 0.40 mmol), and $ZnBr_2$•TMEDA (273 mg, 0.80 mmol) were added, and the mixture was dissolved in THF (0.5 mL). A solution of *p*-anisylmagnesium bromide in THF (1.36 mL, 0.88 mol/L, 1.20 mmol) was added dropwise, and then the *in situ* generated phenetyl mesylate was added by syringe. Next, a solution of $Fe(acac)_3$ (14.1 mg, 0.040 mmol) and *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 15.9 mg, 0.040 mmol) in THF (0.3 mL), was added, and the reaction mixture was heated to 70 °C. After stirring for 9 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (2 mL). After aqueous workup, the organic layer was extracted with EtOAc (2 mL × 3). The combined organic layer was washed with $NaHCO_3$ (2 times) and brine, dried over magnesium sulfate, concentrated *in vacuo*, and purified by silica gel chromatography (10% ethyl acetate/hexane/0.5% triethylamine) to afford *N*-(quinolin-8-yl)-(*Z*)-2,3-dimethyl-5-phenylpent-2-enoic amide as a colorless oil (90.4 mg, 68% yield).

Procedure for stoichiometric reactions (Scheme 5)



In a Schlenk tube *N*-(quinolin-8-yl)-3-tolylamide (26 mg, 0.10 mmol), $Fe(acac)_3$ (35 mg, 0.10 mmol), *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 40 mg, 0.10 mmol) and $ZnBr_2$•TMEDA (68 mg, 0.20 mmol) were dissolved in THF (1 mL). A solution of PhMgBr in THF (0.34 mL, 0.89 mol/L, 0.30 mmol) was added dropwise and the resulting mixture was stirred at 70 °C for 1 h to generate the intermediate **A**. D_2O was added to this solution and the mixture was stirred at rt for 5 min. The reaction mixture was quenched by the addition of a saturated solution of potassium sodium tartrate (0.3 mL). After aqueous workup, the organic layer was extracted with EtOAc (2 mL × 3). The combined organic layers were passed through a pad of Florisil, and concentrated *in vacuo*. The amount of recovery and the degree of deuterium incorporation were determined by ^{1}H NMR. *Ortho*-phenylated product was observed in 6% yield, determined by ^{1}H NMR. Homocoupling of the base did not observed by GC.

4-15. References and Notes

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第５章

本章については，５年以内に雑誌等で刊行予定のため，非公開.

Chapter 6.

Conclusions and Perspectives

While development of reactions using iron as a catalyst is of much interest because of its low toxicity and high availability, the reactivity of an organoiron species is mostly unpredictable and difficult to control, which has limited reaction modes and scope of the substrates. In order to overcome these problems, during my Ph.D. work I focused on stabilizing an organoiron species with a directing group and an external ligand and utilizing the stabilized species for the activation of aromatic and olefinic C–H bonds. I have developed directed functionalization of amides through C(sp^2)–H bond activation using amino and alkyl electrophiles and multiple bonds, through the intermediacy of stabilized organoiron species.

In Chapter 2, the discovery of a directing group and a ligand that can stabilize organoiron species and effect stoichiometric reactions is described. An organoiron species generated from treating an iron salt with an organometallic base was efficiently stabilized by a *N*-(quinolyn-8-yl)amide directing group and a diphosphine ligand, and did not decompose upon heating. Typical organometallic species decomposes in the presence of oxidant through reductive elimination: however, such a reaction was considerably slow in this case, which means that the organoiron is stable toward decomposition in the presence of an oxidant. These features are promising for the development of a robust catalytic system while suppressing side reactions.

Chapter 3 describes the development of *ortho*-amination of amides using electrophilic nitrogen sources such as *N*-chloroamines. For stoichiometric reactions, an organoiron species is found to react with *N*-chloroamines selectively, to afford an *ortho*-aminated product. The amination using a catalytic amount of iron was also achieved by tuning the addition sequence of the reagents and the electronic properties of the ligand. The reaction typically finishes within 1 hour to produce anthranilic acid derivatives in >90% yield with complete monoselectivity, which illustrates the high efficiency of iron catalysis, enabled by control of reactivity through the design of the directing group and ligand.

In Chapter 4, development of iron-catalyzed directed alkylation of aromatic and olefinic amides using alkyl electrophiles is described. Monoarylzinc halide was found to be a uniquely effective base to promote the desired reaction while suppressing undesired cross coupling and homocoupling. *β*-Hydride elimination from alkyliron species was also completely suppressed, possibly due to involvement of a radical-like species, as indicated by radical clock experiments. The substrate scope includes primary and secondary alkyl tosylates and halides, without any isomerization or chain-walking. Through a mechanistic study, an unique organoiron(III) species was suggested as the active species, because reduction of iron through homocoupling of the organometallic species did not occur at all.

Chapter 5 describes the development of a series of reactions using alkenes and alkynes as coupling partners. The multiple bonds are incorporated into the ferracycle through a carbometalation pathway to generate alkyliron or alkenyliron species, which can be transformed into a variety of molecules depending on the reaction conditions. The reaction with olefins such as styrene enabled *ortho*-alkylation and olefination of carboxamides, and the reaction with alkynes allowed the synthesis of indenones, alkenylated amides, and isoquinolones. Additives and bases dramatically affected the nature of the organoiron species, and changed the product selectivity. The oxidative reaction of alkeneamides with unsymmetrical alkynes produced 2-pyridones with high regioselectivity, which can be ascribed to the small radius of the iron atom, making the intermediate sensitive to sterics.

In conclusion, the present study describes the unique stabilization effect of the quinolylamide/diphosphine ligand system for iron catalysis, which can effectively suppress previously problematic side reactions. Taking advantage of these discoveries, future objectives should be directed toward the development of more general and practical reaction system that would surpass the reactivity of late transition-metals.

Although iron as a catalyst has intrigued organic and organometallic chemists

due to its high and unpredictable reactivity, the results disclosed herein clearly demonstrate that control of the reactivity of organoiron is possible, with the design of ligands, reactants, and mechanistic understanding. Overall, the reactions and features described herein will be important and useful guidelines for the future design of iron catalysis, which will enable the sustainable development of our society.

List of Publications

Chapter 2 and Chapter 3.

1. “Synthesis of Anthranilic Acid Derivatives through Iron-Catalyzed Ortho Amination of Aromatic Carboxamides with *N*-Chloroamines”
   Tatsuaki Matsubara, Sobi Asako, Laurean Ilies, Eiichi Nakamura
   J. Am. Chem. Soc. **2014**, *136*, 646–649. (highlighted: *Synfacts* **2014**, *10*, 408.)

Chapter 4.

2. “Iron-Catalyzed Directed Alkylation of Aromatic and Olefinic Carboxamides with Primary and Secondary Alkyl Tosylates, Mesylates, and Halides”
   Laurean Ilies, Tatsuaki Matsubara, Saki Ichikawa, Sobi Asako, Eiichi Nakamura
   J. Am. Chem. Soc. **2014**, *136,* 13126–13129.

Chapter 5.

3. ”Oxidative C–H Activation Approach to Pyridone and Isoquinolone via Iron-Catalyzed Coupling of Amide with Alkyne”
   Tatsuaki Matsubara, Laurean Ilies, Eiichi Nakamura
   Chem. Asian J. **2016**, *11*, 380–384. (invited contribution to “Catalysis and Transformation of Complex Molecules” special issue)

Other Publications not included in this thesis.

4. "Nickel-Catalyzed Synthesis of Diarylamines via Oxidatively Induced C–N Bond Formation at Room Temperature"
   Laurean Ilies, Tatsuaki Matsubara, Eiichi Nakamura
   Org. Lett. **2012**, *14*, 5570–5573.

5. "Iron-Catalyzed Directed Alkylation of Alkenes and Arenes with Alkylzinc Halides"
   Laurean Ilies, Saki Ichikawa, Sobi Asako, Tatsuaki Matsubara, Eiichi Nakamura
   Adv. Synth. Catal. **2015**, 357, 2175–2179. (Very Important Publication, invited contribution to the special issue dedicated to Stephen L. Buchwald)

Review

6. "Regioselective Functionalization of 2-Pyridones through C–H Bond Activation"
   Tatsuaki Matsubara
   Synth. Org. Chem. Jpn., **2015**, *73*, 753–754. (Japanese)

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