学位論文

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）

平成 27 年 12 月博士（理学）申請

東京大学大学院理学系研究科
化学専攻

松原立明

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.

Table of Contents

Chapter 4.

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]

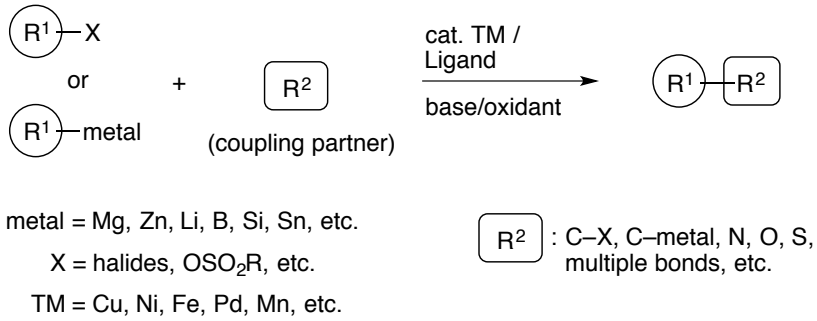


Figure 1. Transition-metal-catalyzed cross-coupling reactions

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]

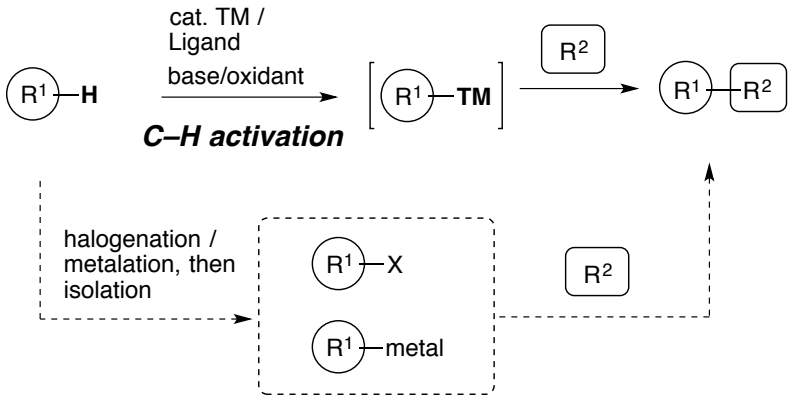


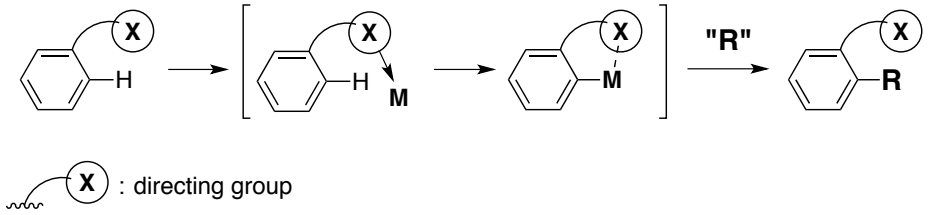
Figure 2. Schematic comparison of C–H bond functionalization reactions with traditional multi-step coupling reactions

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

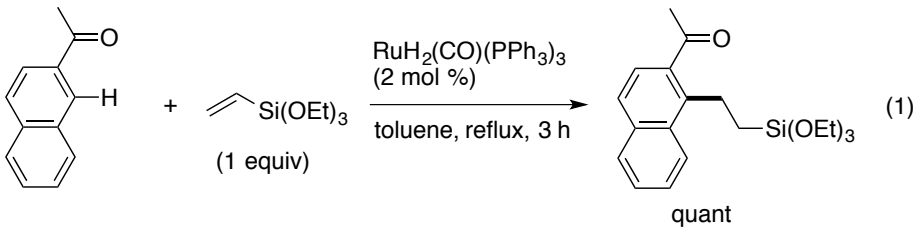
methodologies because of its perfect predictable regioselectivity at mostly the *ortho*-position,[15] and it typically enables reactions under mild reaction conditions (Scheme 1).

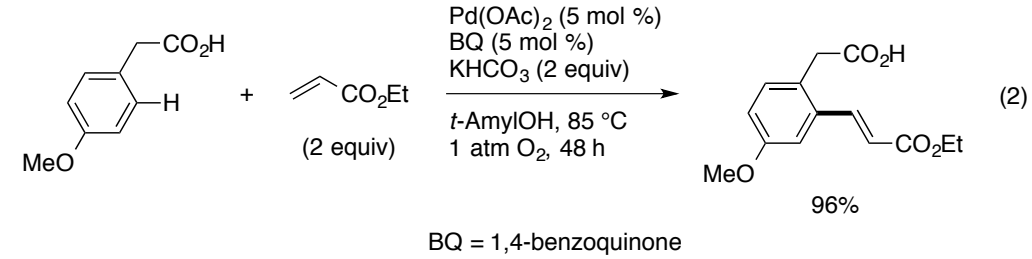
Scheme 2. Directed C–H bond activation



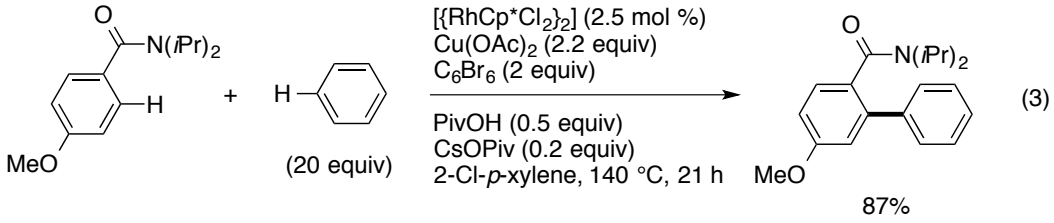
1-3. Recent examples and future directions of directed C–H bond activation

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.

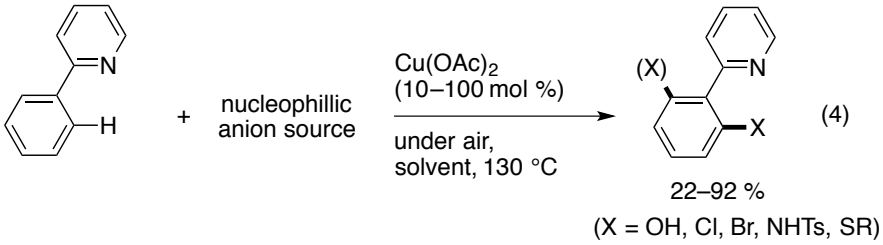




BQ = 1,4-benzoquinone



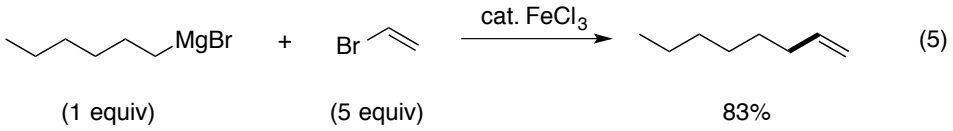
In spite of these progresses, most reports rely on using expensive reagents especially for the catalysts such as palladium and rhodium, metals that suffer from high cost and toxicity. Therefore, replacement of these metals with inexpensive and non-toxic metals should be the direction to go for the sustainable 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]

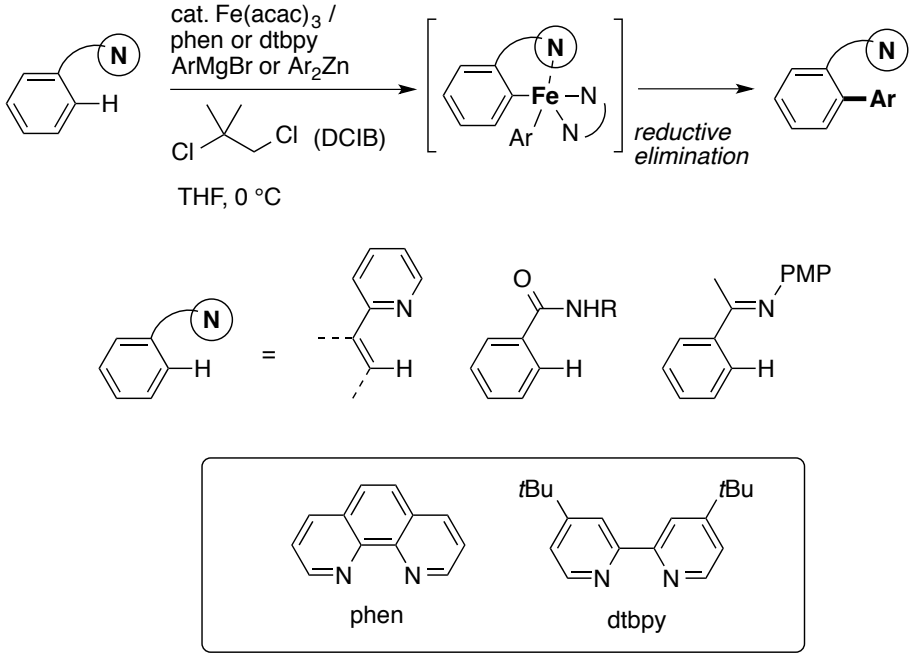


(5)

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.

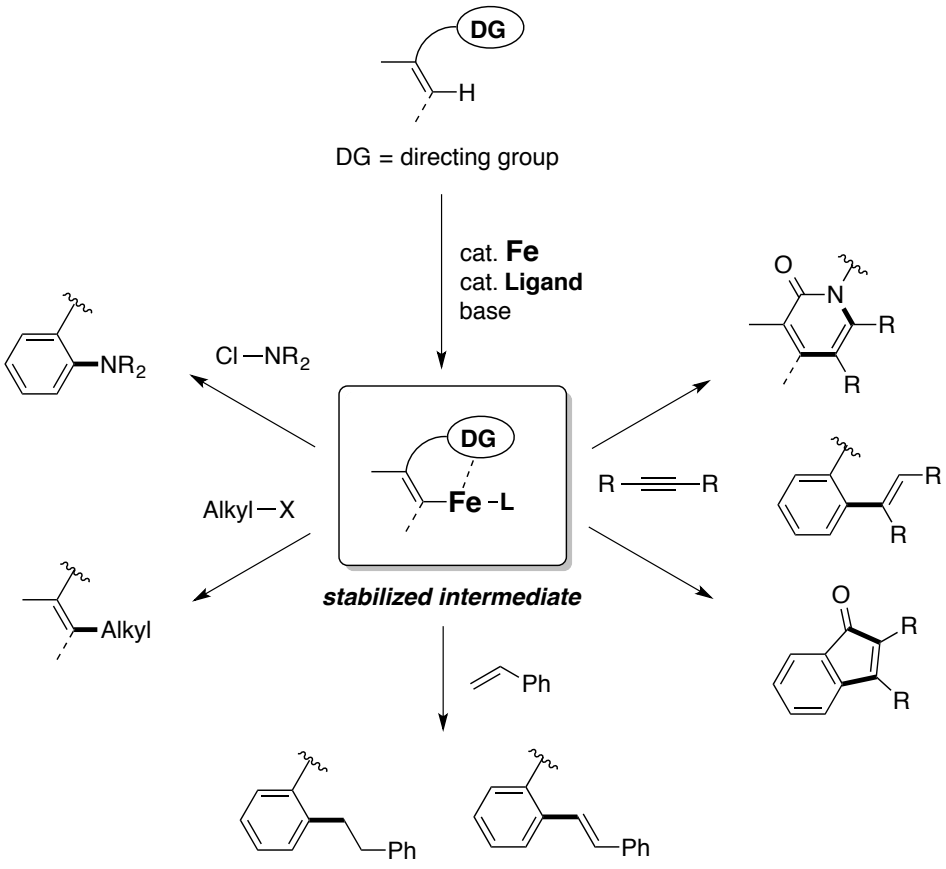


Figure 3. Overview of this thesis

1-6. References and Notes

[1] (a) Ilies, L.; Nakamura, E. In *The Chemistry of Organoiron Compounds*; Marek, I.; Rappoport, Z., Eds.; John Wiley & Sons, Ltd: Chichester, UK **2014** and references therein.

[2] (a) Hassan, J.; Sévingnon, M.; Gozzi, C.; Schltz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int, Ed.* **2003**, *42*, 5400–5449 and references therein.

[3] (a) Tamaru, Y., Ed.; *Modern Organonickel Chemistry*; Wiley-VCH, Weinheim, 2005. (b) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908. (c) Tasker, S.; Standley, E.; Jamison, T. F. *Nature* **2014**, *509*, 299–309.

[4] Palladium: (a) Seechrn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Sniekus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085 and references therein. Cobalt: (b) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435–1462. Manganese: (c) Rueping, M.; Ieawsuwan, W. *Synlett*, **2007**, 247–250.

[5] PALLADIUM–CATALYZED CROSS COUPLINGS IN ORGANIC SYNTHESIS; http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/advanced-chemistryprize2010.pdf.

[6] (a) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240–248. (b) Prakash, G. K.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770–15776.

[7] Selected examples of directed *ortho*-metalation: (a) Kauch, M, Hoppe, D. *Synthesis* **2006**, 1575–1577. (b) Nguyen, T.-H.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2006**, *8*, 765–768. (c) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *J. Org. Chem.* **2007**, *72*, 1271–1275.

[8] Metalation with $(TMP)_2Zn•2MgCl_2•2LiCl$: (a) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685–7688. (b) Wunderlich, S. H.; Knochel, P. *Chem. Commun.* **2008**, 6387–6389. (c) Kienle, M.; Dunst, C.; Knochel, P. *Org. Lett.* **2009**, *11*, 5158–5161.

[9] (a) *C–H Activation*; Yu, J.-Q.; Shi, Z., Eds.; Topics in Current Chemistry; Springer: Berlin, **2010**. For recent reviews, see: (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu,

J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (c) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109. (d) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236–10254. (e) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369–375.

[10] (a) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960–9009.

[11] Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem., Int. Ed.* **2014**, *54*, 66–81.

[12] C–H activation as one of the "Hot-Topics" in WILEY-VCH: http://www.wiley-vch.de/util/hottopics/c-h-activation/.

[13] Selected examples of steric-controlled C–H activation: (a) Saito, Y.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2015**, *137*, 5193–5198. (b) Obligacion, J. V.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 4133–4136.

[14] Selected examples of electronic-controlled C–H activation: (a) Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287–4299. (b) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748–11749. (c) Feve, G.; Mahe, A.; Berroir, J. M.; Kontos, T.; Placais, B.; Glatti, D. C.; Etienne, B.; Jin, Y. *Science*, **2007**, *316*, 1169–1172. For a review, see: (d) Seregin, I. V.; Gevorgyam, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193.

[15] Recently *meta*- or *para*-C–H activation to the directing group has been reported with special design of the directing group: (a) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2013**, *486*, 518–522. (b) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. *J. Am. Chem. Soc.* **2015**, *137*, 11888–11891.

[16] Nickel: (a) Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544–1545. Platinum and Palladium: (b) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272–3273. Cobalt: (c) Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403–6404.

[17] Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A. *Nature* **1993**, *366*, 529–531.

[18] Recent reviews on directed C–H bond activation: (a) Daugulis, O.; Do, H.-Q.;

Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (c) Engle, K. M.; Mei, T.-S.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655.

[19] Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315–319.

[20] Wencel-Delord, J.; Nimphius, C.; Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 13001–13005.

[21] (a) Clark, J. H. *Green Chem.* **1999**, *1*, 1–8. (b) Poliakoff, M.; Fitspartrick, J. M.; Farren, T. R.; Anastas, P. T. *Science* **2002**, *297*, 807–810.

[22] Chen, X.; Hao, X.-S. Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791.

[23] Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842–843.

[24] Selected examples: (a) Shang, M.; Sun, S.-Z.; Wang, H.-L.; Laforteza, B. N.; Dai, H.-X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 10439–10442. (b) Li, Q.; Zhang, S.-Y.; He, G.; Ai, Z.; Nack, W. A.; Chen. G. *Org. Lett.* **2014**, *16*, 1764–1767. (c) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842–5845.

[25] (a) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249. (b) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428–429. For reviews, see: (c) Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 843–857. (d) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948–8954.

[26] Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955.

[27] (a) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6518–6520. (b) Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 1264–1267.

[28] (a) Nakamura, E.; Sato, K. *Nat. Mater.* **2011**, *10*, 158–161. (b) Bolm, C. *Nat. Chem.* **2009**, *1*, 420.

[29] Selected reviews for iron catalysis: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217−6254. (b) Plietker, B., Ed.; *Iron Catalysis in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, **2008**. (c) En-thaler, S.; Junge, K.; Beller,

M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317−3321. (d) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500−1511. (e) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Jacobi von Wangelin, A. *ChemSusChem* **2009**, *2*, 396−417. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293−1314.

[30] Vrancken, E.; Campagne, J.-M. In *The Chemistry of Organoiron Compounds*; Marek, I.; Rappoport, Z., Eds.; John Wiley & Sons, Ltd: Chichester, UK **2014** and references therein.

[31] Kharasch, M. S.; Weiner, M.; Nudenberg, W.; Bhattacharya, A.; Wang, T.-I.; Yang, N. C. *J. Am. Chem. Soc.* **1961**, *83*, 3232–3234.

[32] Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489.

[33] (a) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061–6087.

[34] Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859.

[35] (a) Yoshikai, N. Matsumoto, A.; Norinder, J. Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925–2928. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J. Nakamura, E. *Synlett* **2010**, 313–316. (c) Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 7672–7675. (d) Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem. Asian. J.* **2011**, *6*, 3059–3065. (e) Ilies, L.; Kobayashi, M.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2012**, *354*, 593–596. (f) Ilies, L.; Konno, E.; Chen, Q.; Nakamura, E. *Asian J. Org. Chem.* **2012**, *1*, 142–145.

[36] (a) Sirois, J. J.; Davis, R.; DeBoef, B. *Org. Lett.* **2014**, *16*, 868–871. (b) Gu, Q.; Al Mamari, A, H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3868–3871.

[37] (a) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491–493. (b) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943–1946.

[38] Bedford, R. B. *Acc. Chem. Res.* **2015**, *48*, 1485–1493 and references therein.

Chapter 2.

Generation of Organoiron using Aromatic Amides Possessing Bidentate Directing Group

2-1. Introduction

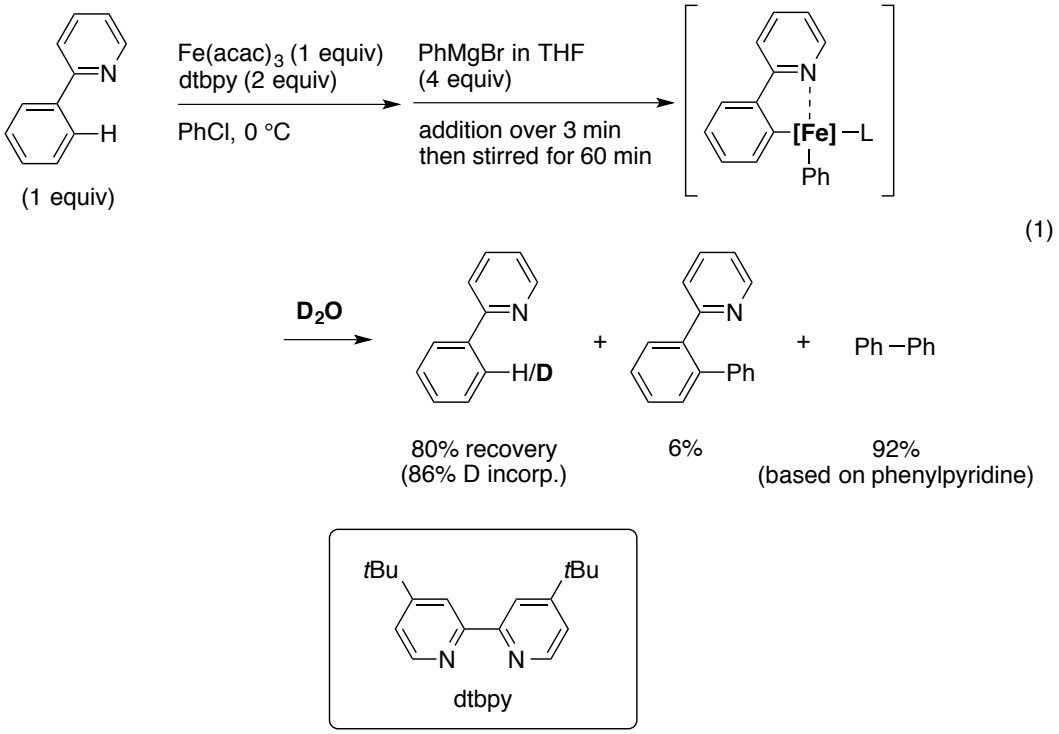
• Investigation of active species through stoichiometric experiments

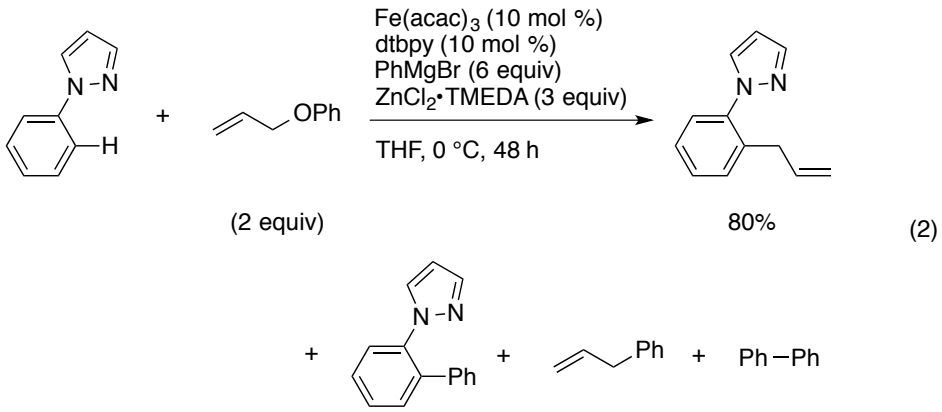
Experiments using a stoichiometric amount of transition-metal (stoichiometric reactions) are often employed in many organometallic reactions to investigate information on the reaction mechanism and determine the active organometallic species.[1] This is also the case for in C–H activation reactions: 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).

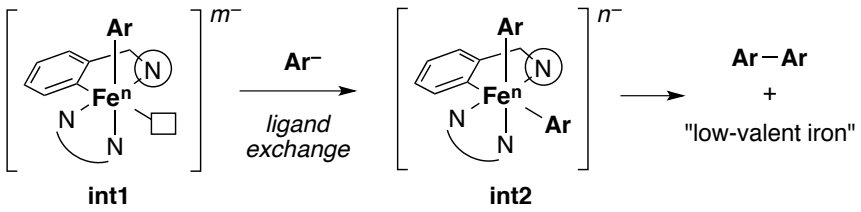


Figure 1. Possible coordination geometry of iron in directed C–H bond activation

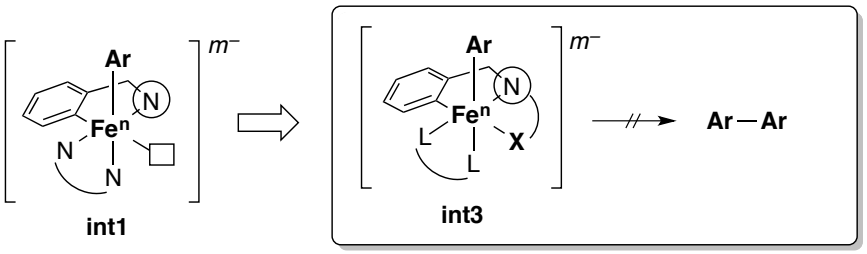
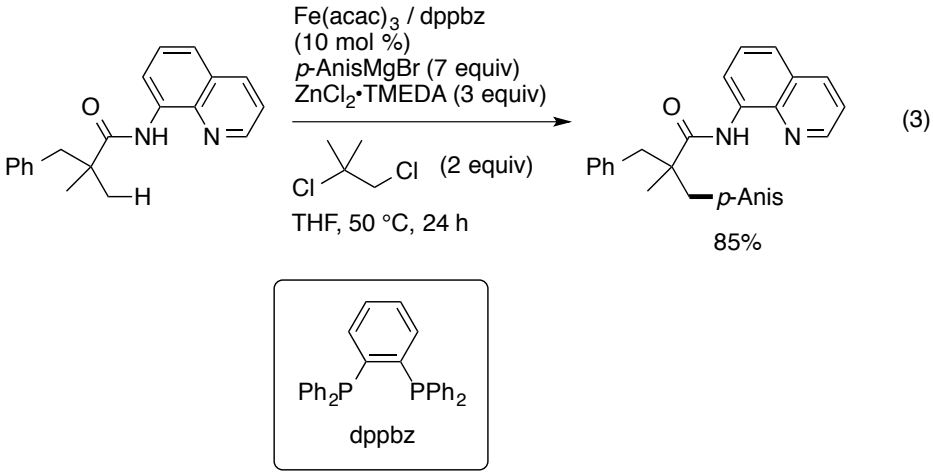


Figure 2. Working hypothesis using a bidentate directing group

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

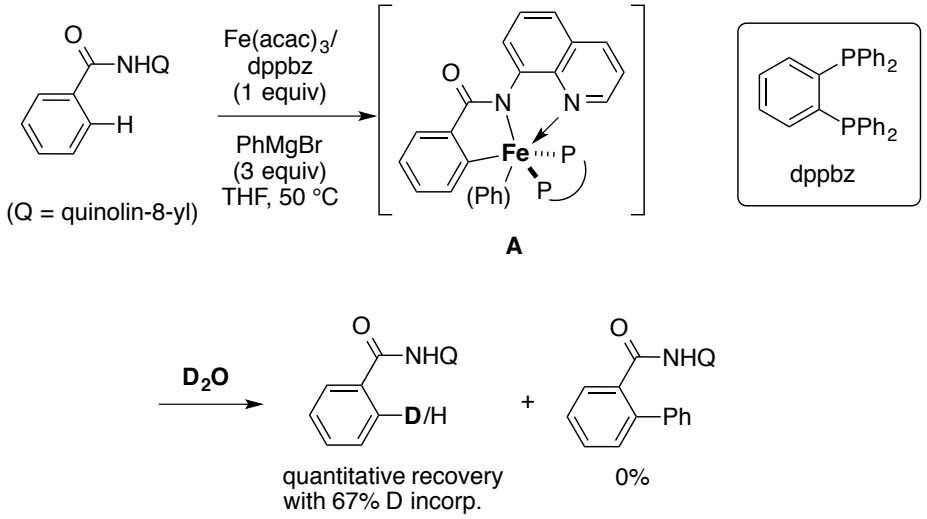
This chapter describes my investigation of a stoichiometric reaction of iron for directed C–H bond activation using a bidentate directing group, aimed to stabilize the organoiron intermediate. Through discovery of an appropriate base and ligand, organoiron species with coordinated by a bidentate directing 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.

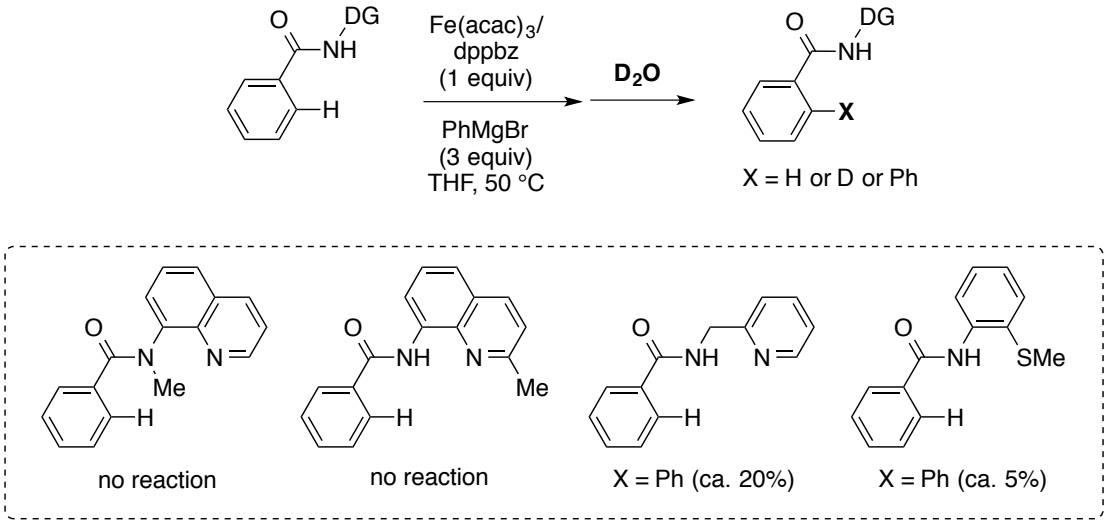
Scheme 1. Organoiron species **A** from *N*-(quinolin-8-yl)amide directing group and a diphosphine ligand



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

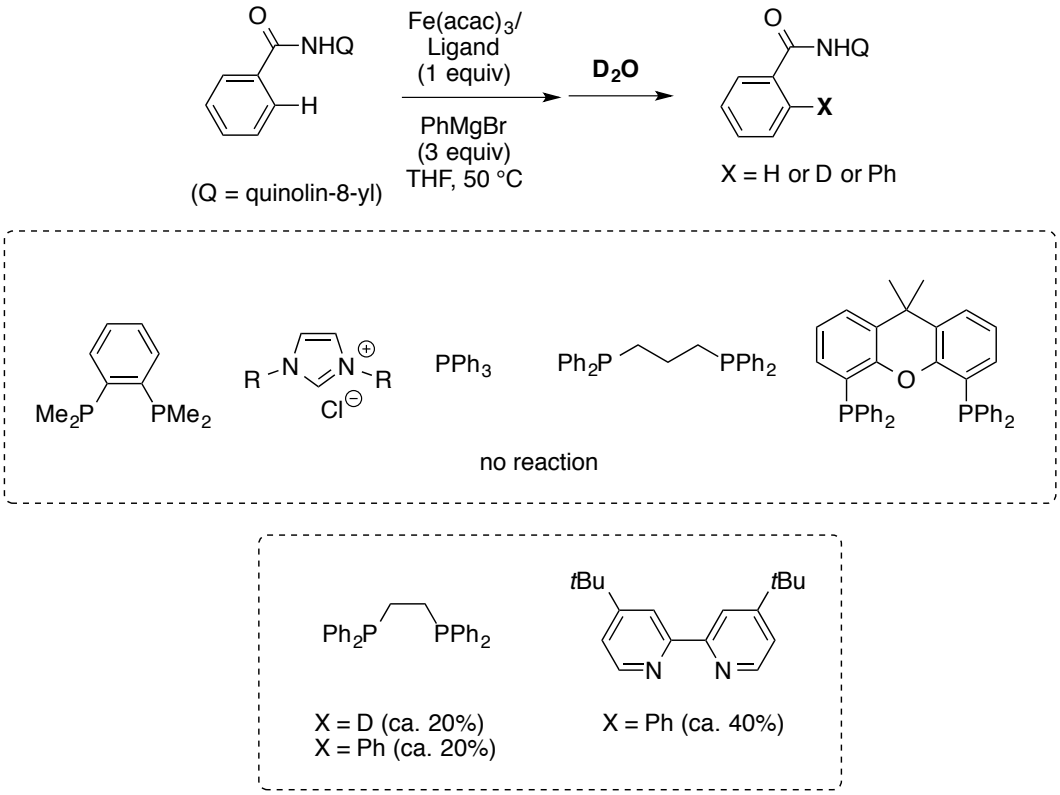
be uniquely effective, probably due to its rigidity and strong coordination ability of nitrogen to iron.

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.

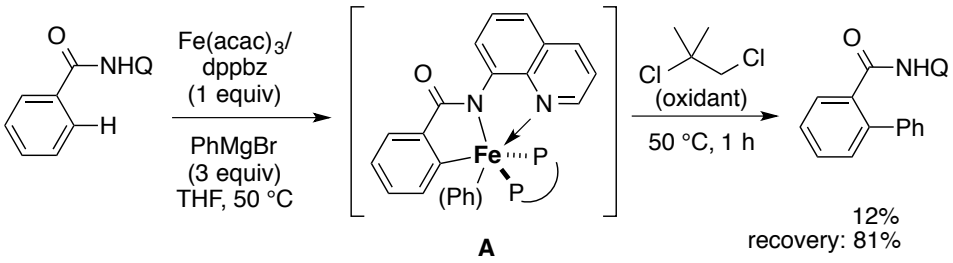
Scheme 3. Examples of ineffective ligands



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]

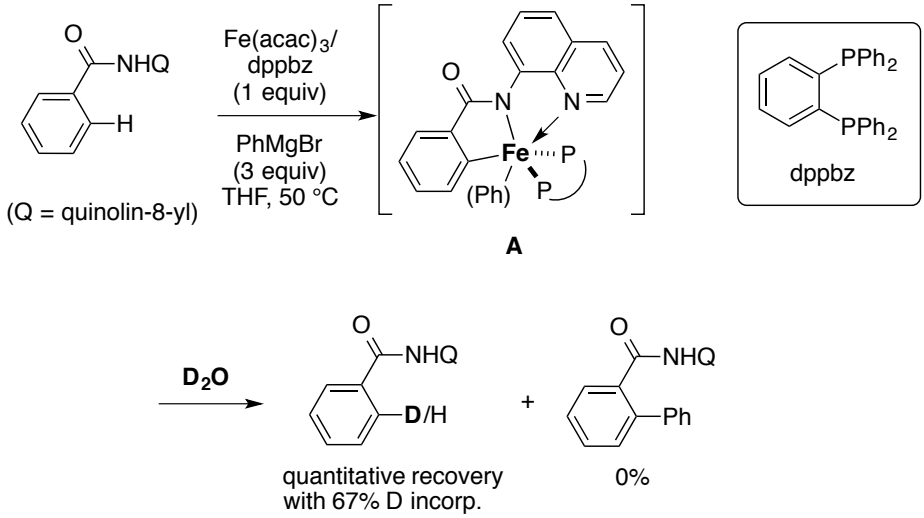
Preparation of the starting materials

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

Benzoyl chloride (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.

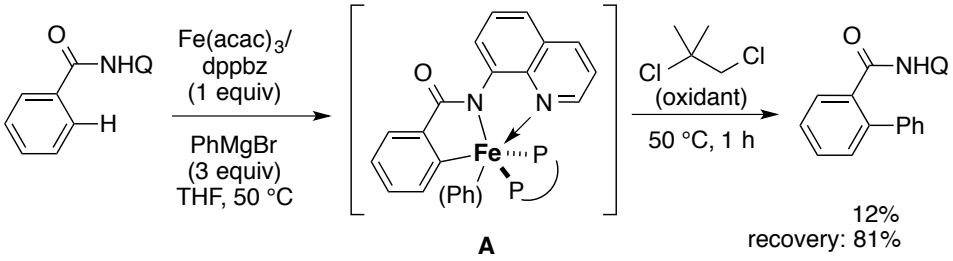
Compound data for amides described in this chapter were in good agreement in previous literatures.[21]

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.

2-6. References and Notes

[1] Selected examples for stoichiometric reactions with organoiron complexes: (a) Adams, C. J.; Bedford, R. B.; Carter, E.; Gower, N. J.; Haddow, M. F.; Harvey, J. N.; Huwe, M.; Carter, M, Á.; Mansell, S. M.; Mendoza, C. *J. Am. Chem. Soc.* **2012**, *134*, 10333–10336. (b) Fürstner, A.; Krause, H.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 440–444. (c) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787.

[2] Selected examples: Rhodium: (a) Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 1482–1485. (b) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492–2502. Ruthenium: (c) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884. Cobalt: (d) Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283–17295. Iridium: (e) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. *J. Am. Chem. Soc.* **2013**, *135*, 12861–12868. Manganese: (f) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950–4953.

[3] Ikemoto, K.; Inokuma, Y.; Rissanen, K.; Fujita, M. *J. Am. Chem. Soc.* **2014**, *136*, 6892–6895.

[4] Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem. Asian. J.* **2011**, *6*, 3059–3065.

[5] Asako, S. Ph.D. thesis.

[6] Asako, S.; Norinder, J.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2014**, *356*, 1481–1485.

[7] Bedford, R. B. *Acc. Chem. Res.* **2015**, *48*, 1485–1493 and references therein.

[8] Occupation of coordination site of iron by a fluorine anion is effective in cross coupling reaction: Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949–11963.

[9] Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.

[10] (a) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043–6046. (b) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*,

4457–4461. (c) Shang, M.; Sun, S.-H.; Dai, H.-D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354–3357.

[11] (a) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955. (b) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 2477–2480. (c) Aihara, Y.; Wuelbern, J.; Chatani, N. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 438–446.

[12] Selected examples: Cobalt: (a) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209–10212. (b) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4684–4687. (i) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4688–4690. (j) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2015**, *17*, 1204–1207. Ruthenium: (k) Shibata, K.; Hasegawa, N.; Fukumoto, Y. Chatani, N. *ChemCatChem* **2012**, *4*, 1733–1736. (l) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664–670. (c) Rouquet, G.; Chatani, N. *Chem. Sci.* **2013**, *4*, 2201–2208. Rhodium: (d) Shibata, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5148–5151. (e) Shibata, K.; Yamaguchi, T.; Chatani, N. *Org. Lett.* **2015**, *17*, 3584–3587.

[13] Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030–6032.

[14] Estimated by EI-MS analysis and determined by ^{1}H NMR spectrum.

[15] Adams, C. J.; Bedford, R. B.; Carter, E. C.; Gower, N. J.; Haddow, M. F.; Harvey, J. N.; Huwe, M.; Cartes, M. Á.; Mansell, S. M.; Mendoza, C.; Murphy, D. M.; Neeve, E. C.; Nunn, J. *J. Am. Chem. Soc.* **2012**, *134*, 10333–10336.

[16] DCIB as an effective oxidant for iron to induce reductive elimination: (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859. (b) Nakamura, Y.; Ilies, L.; Nakamura, E. *Org. Lett.* **2011**, *13*, 5998–6001.

[17] At the same time, our group discovered *ortho*-allylation of amides with allylic electrophile using a bidentate directing group: Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755–17757.

[18] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2924.

[19] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

[20] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.

[21] (a) Li, X.; Liu, Y.-H.; Gu, W.-J.; Li, B.; Chen, F.-L.; Shi, B.-F. *Org. lett.* **2014**, *16*, 3904–3907. (b) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797–9804. (c) Wang, K.; Shen, M.; Sun, W.-H. *Dalton Trans.* **2009**, 4085–4095.

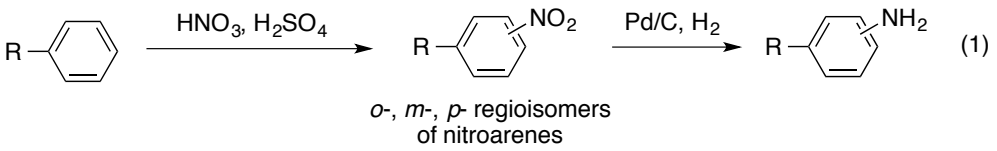
Chapter 3.

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

3-1. Introduction

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

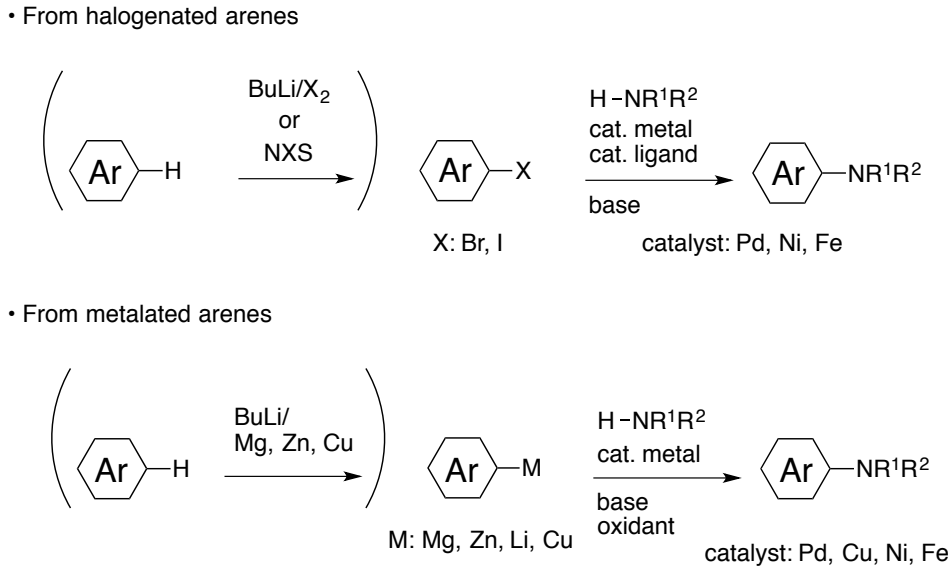
Formation of a C(sp^2)–N bond from an aromatic substrate and a nitrogen source provides rapid access to functionalized anilines, compounds widely utilized and have attracted much attention in medicinal chemistry and materials science.[1] Traditional approaches for anilines from arenes include the direct 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.

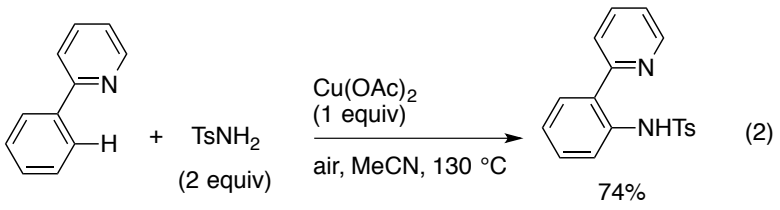
Scheme 1. Transition-metal-catalyzed cross-coupling for the synthesis of aniline derivatives

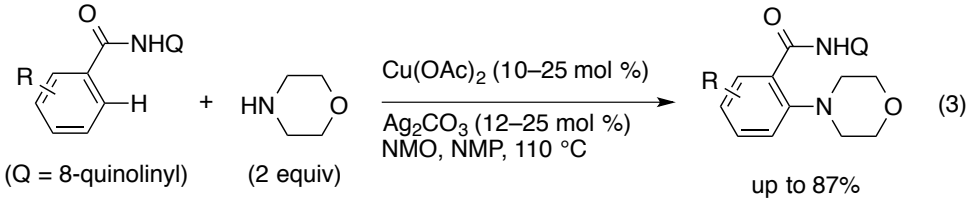


• Amination of a C(sp^2)–H bond with a nucleophilic amine under oxidative conditions

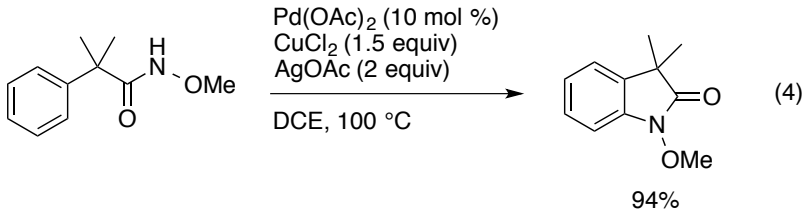
Because of the reasons mentioned above, regioselective activation of the C(sp^2)–H bond of an aromatic substrate, followed by reaction with a nucleophilic amine to form a C–N bond is considered to be an ideal synthesis of anilines, but such reactions have rarely been achieved because of the difficulty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

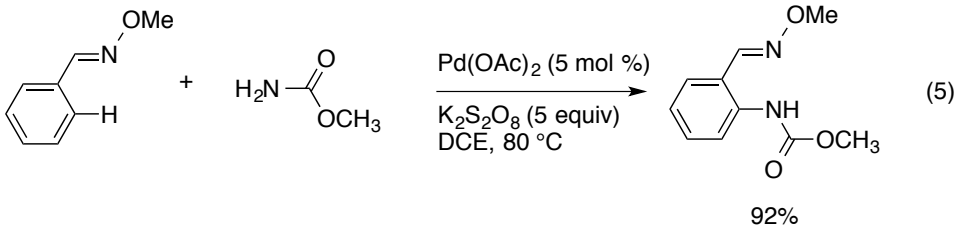
In 2006, Yu and coworkers reported the first example of the amination of C(sp^2)–H bonds of an aromatic substrate, where the *ortho* C–H bond of 2-phenylpyridine is activated through radical pathway using a stoichiometric amount of copper, followed by reaction with a tosylamine to produce an *ortho*-aminated 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.

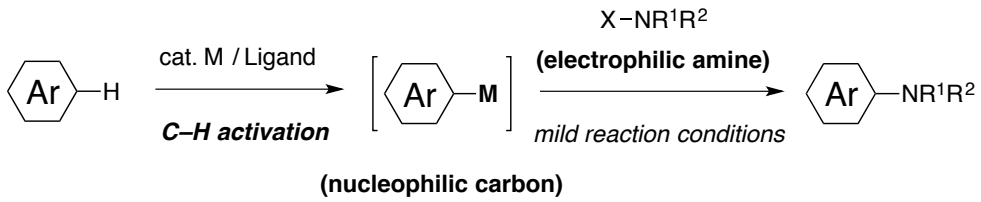




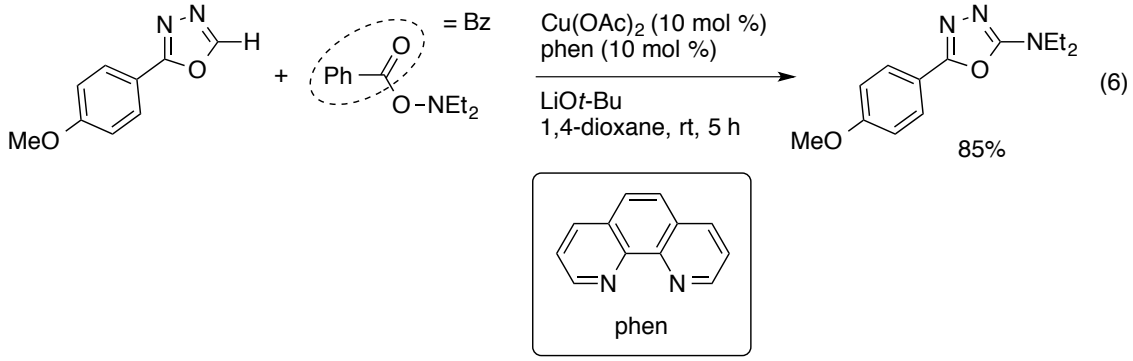
• Umpolung amination with electrophilic nitrogen source

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.

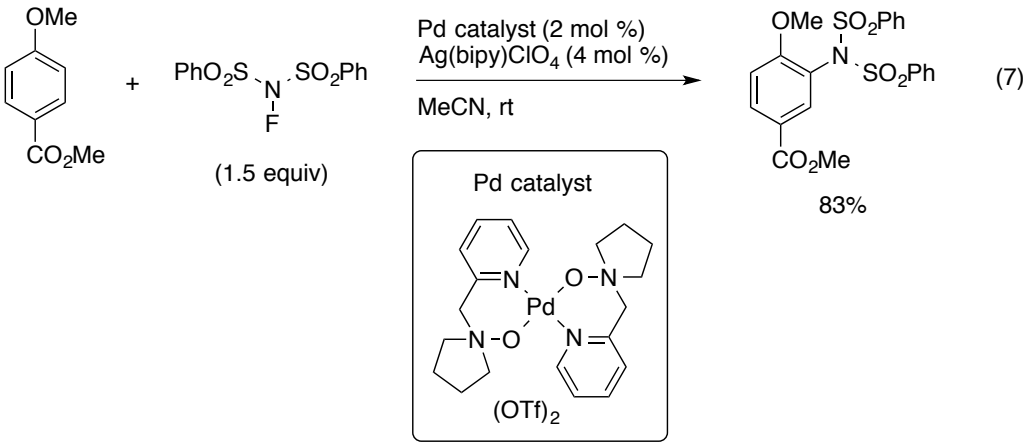
Scheme 2. Concept for "umpolung" C–H amination



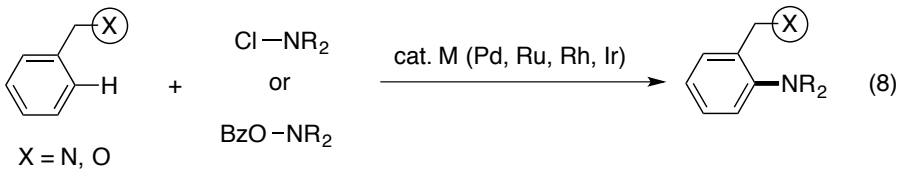
The umpolung amination strategy enabled synthetic chemists to achieve a variety of methodologies for C–H amination reactions using transition-metal catalysts. Hirano, Miura and coworkers achieved copper-catalyzed amination of electron-deficient heteroaromatic C–H bonds using *N*-oxyamines (eq. 6).[23]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

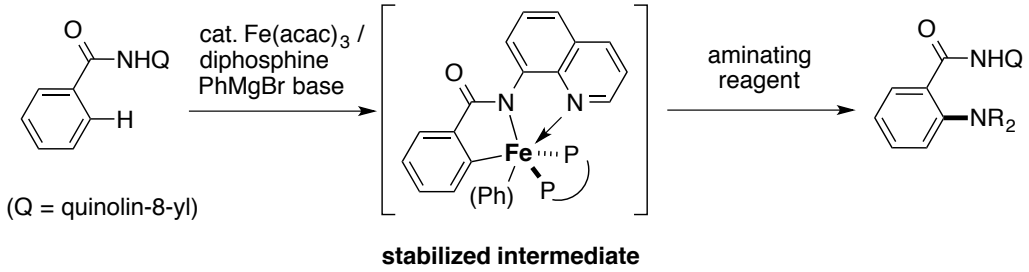


• Reactions described in this chapter

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]

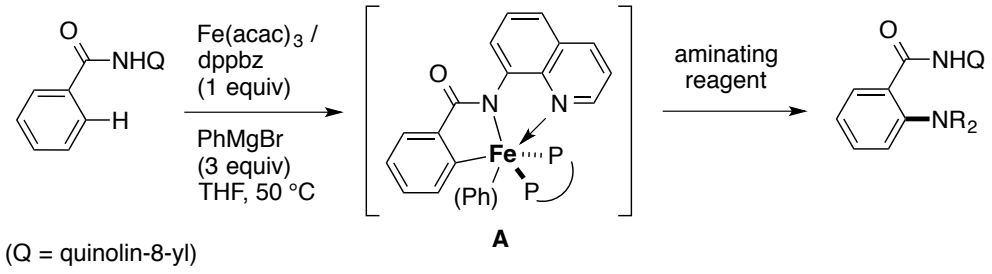
Scheme 3. Working hypothesis for *ortho*-amination of amide using iron catalysis, through reaction of organoiron with an amine



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.

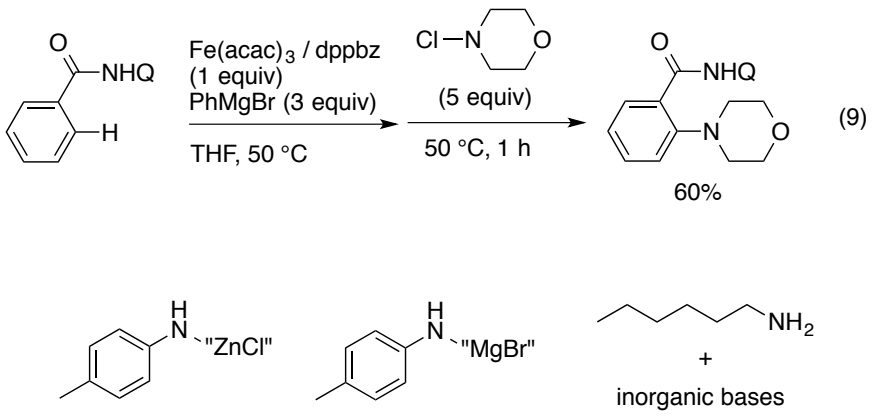
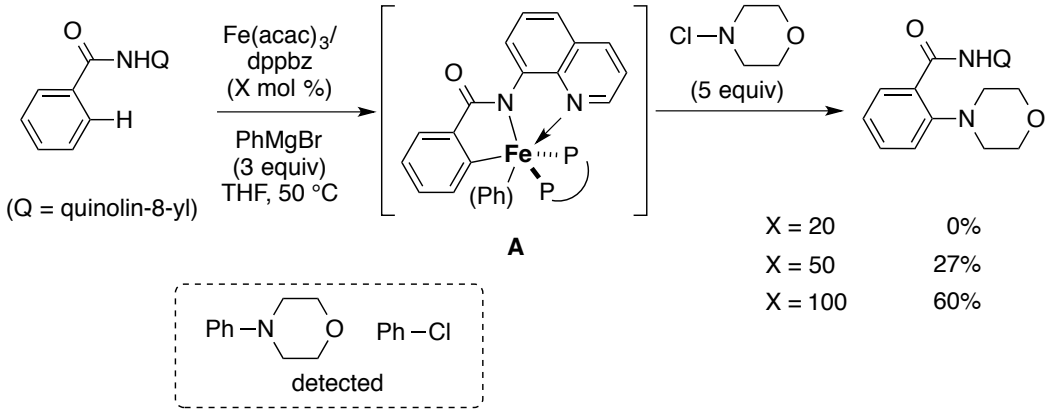


Figure 1. Examples of unreactive nucleophilic amines

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

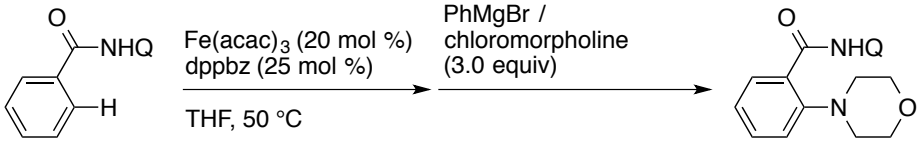
With the result of a stoichiometric reaction in hand, next I performed the reaction with a chloroamine using a catalytic amount of iron/diphosphine, to confirm the reaction would proceed with catalytically (Scheme 5). The reaction was largely suppressed when 50 mol % of $Fe(acac)_3$/dppbz was used, and 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



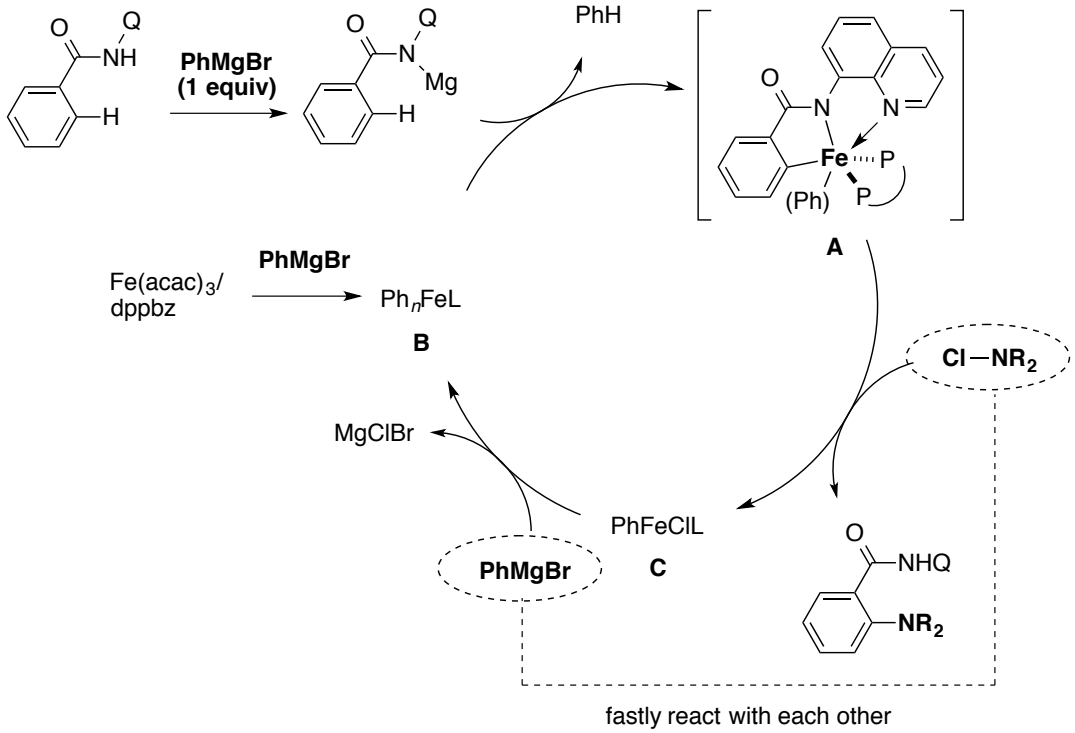
slow addition reagent	yield of the product (%)
PhMgBr	0
chloromorpholine	0

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).

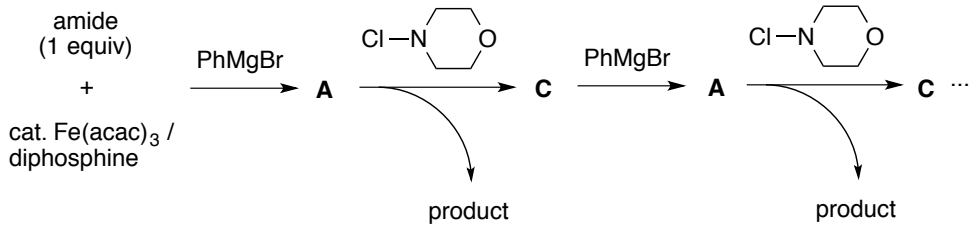
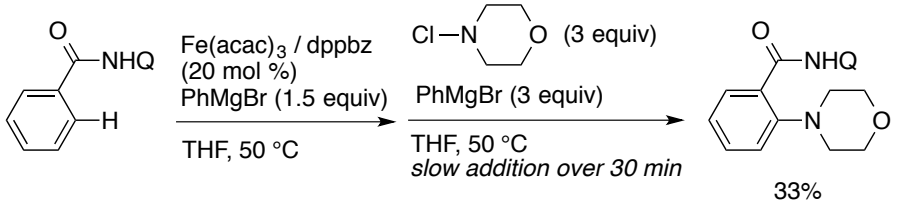


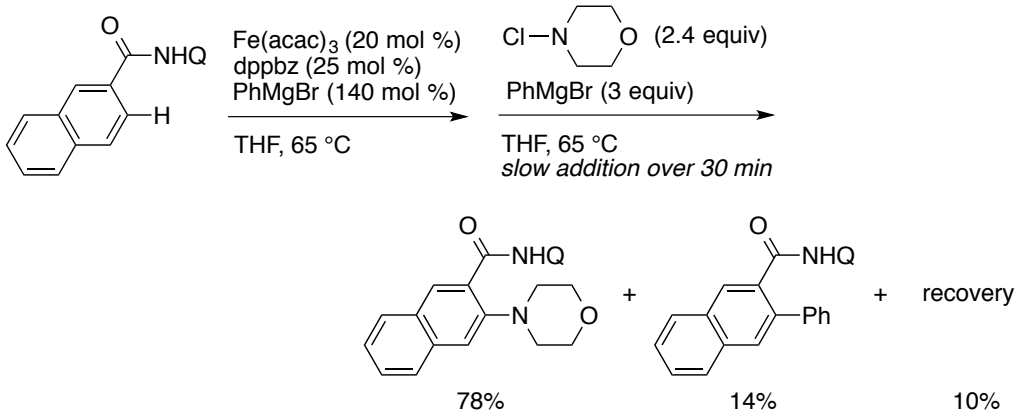
Figure 2. Strategy to obtain catalytic turnover:
mimicking the catalytic cycle by controlling the addition sequence

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



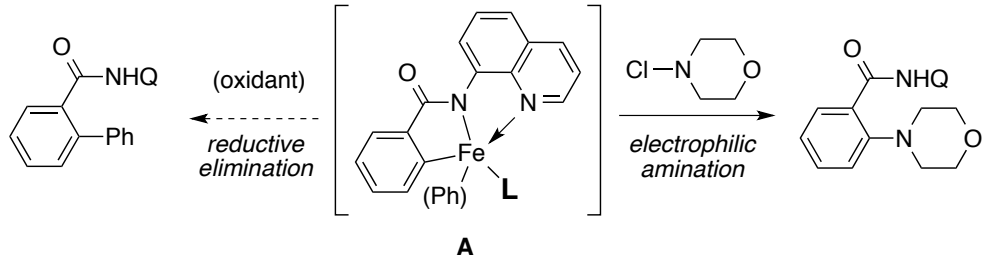
Scheme 9. Optimized result for catalytic amination of C–H bond with iron/dppbz



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

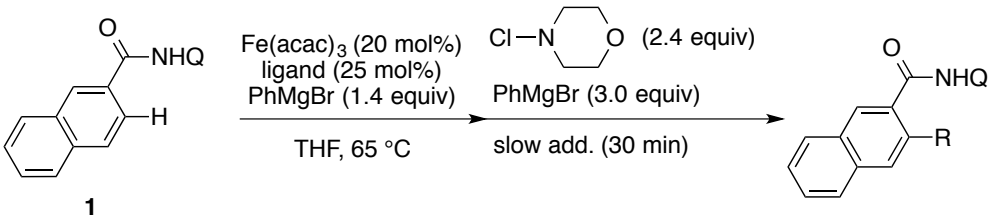


A

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

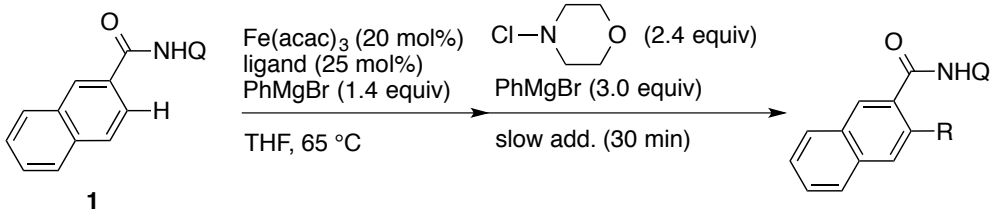
entry	Ligand	NMR yield (%)		
		2	**3**	**1**
1	none	0	4	59
2	TMEDA (1.5 eq)	0	0	98
3	dtbpy	0	41	51
4	dppe	27	30	1
5	dppen	81	12	10
6	dppbz	78	14	10

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).

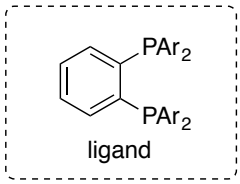
Table 2. Amination with electronically-biased dppbz derivatives



1

2: R = —N O

3: R = Ph



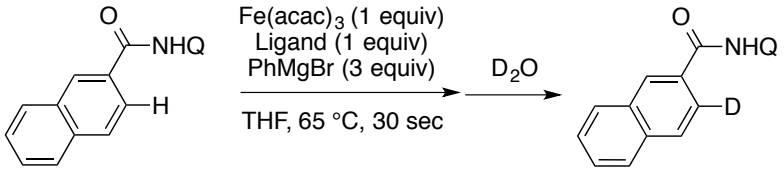
entry	ligand (Ar)	NMR yield (%)		
		2	**3**	**1**
1	**L1** (Ph)	78	14	10
2	**L2** (4-$MeOC_6H_4$)	44	34	31
3	**L3 (4-FC_6H_4)**	**87**	**1**	**17**
4	**L4** (3,4-$F_2C_6H_3$)	42	3	55
5	**L5** (3,4,5-$F_3C_6H_2$)	22	2	81

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



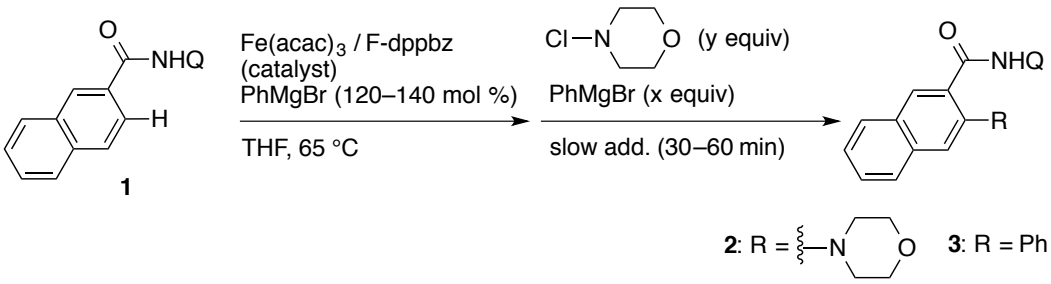
entry	ligand	**D incorp. (%)**
1	**L1** (dppbz)	**67**
2	**L2** (MeO-dppbz)	**52**
3	**L3** (F-dppbz)	**62**
4	**L4** (F_2-dppbz)	**25**
5	**L5** (F_3-dppbz)	**7**

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



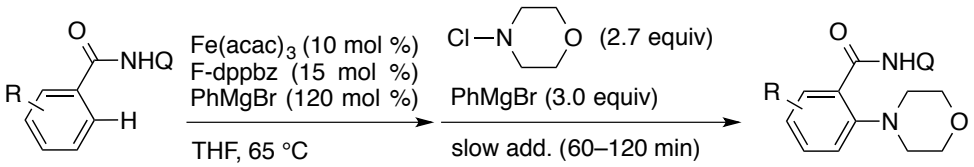
entry	$Fe(acac)_3$/F-dppbz (mol %)	PhMgBr : Cl–NR_2 (x : y)	NMR yield (%)		
			2 (R = NR_2)	**3** (R = Ph)	**1** (recov)
1	20/25	3.0 : 2.4	69	5	25
2	20/25	2.8 : 2.4	81	1	16
3	20/25	2.7 : 2.4	87	1	17
4	20/25	2.6 : 2.4	93	2	6
5	10/15	2.15 : 2.0	80	3	21
6	10/15	2.6 : 2.4	90	3	10
7	**10/15**	**3.0 : 2.7**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



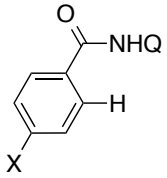
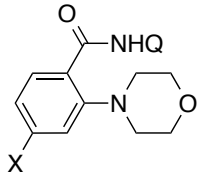
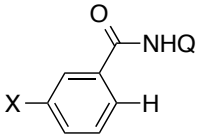
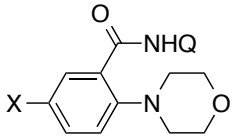
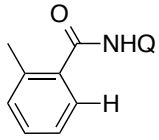
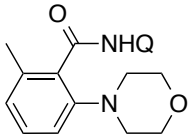
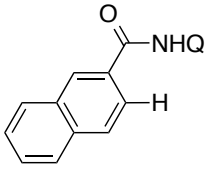
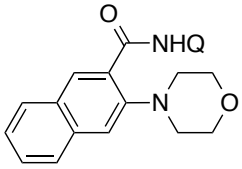
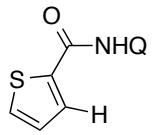
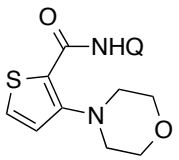
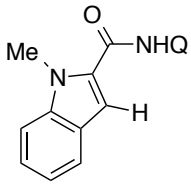
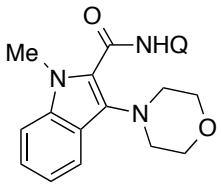
entry	substrate	product			yield (%)
1			X =	H	91
2				Me	96
3				OMe	92
4				CF_3	91
5				F	92
6				Cl	100
7				Br	54 [a]
8				Me	99
9				OMe	100
10 [b]				NMe_2	94
11 [b]				F	81
12				CF_3	40 [c]
13 [b]					0
14					99

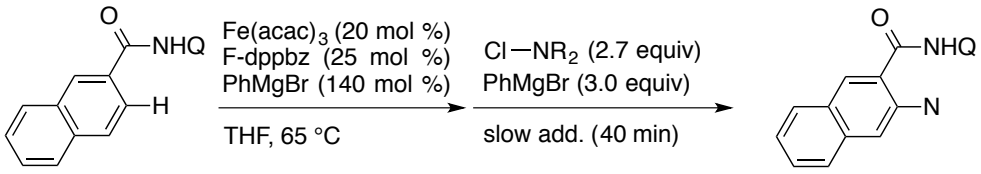
Table 5. (continued)

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



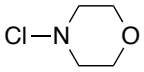
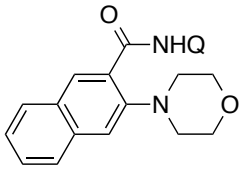
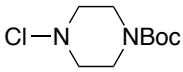
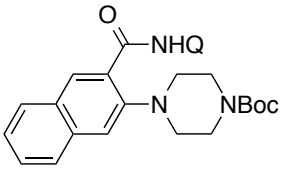
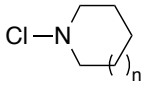
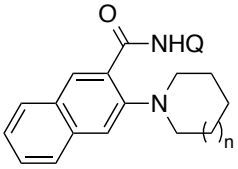
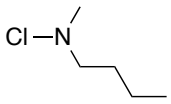
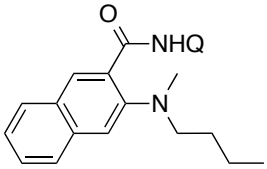
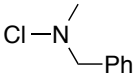
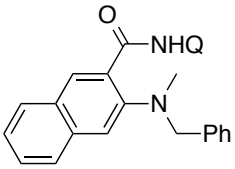
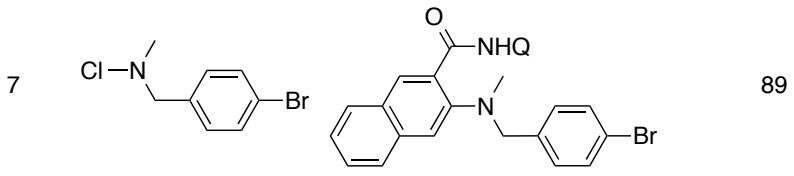
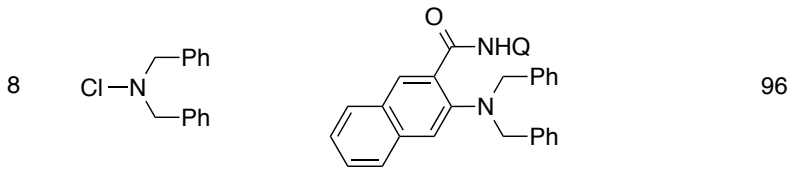
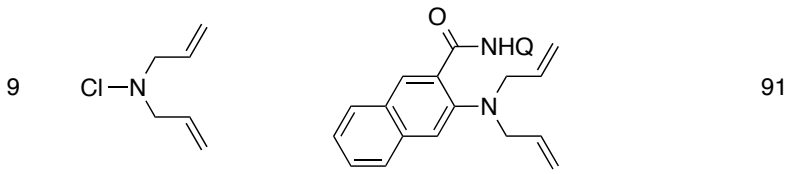
entry	chloroamine	product[b]		yield (%)
1				99
2				99
3			n = 1	98
4			2	93
5				94
6				96

Table 6. (continued)







See experimental section for detailed reaction conditions.

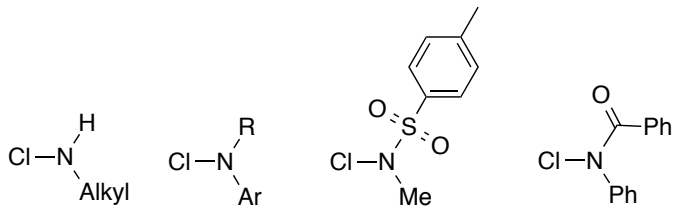
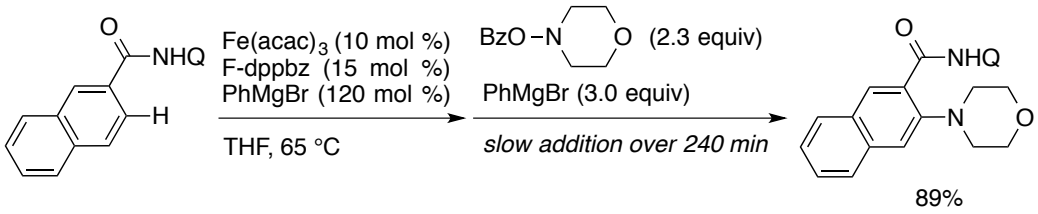


Figure 3. Examples of unreactive *N*-chloroamines and *N*-chloroamides

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



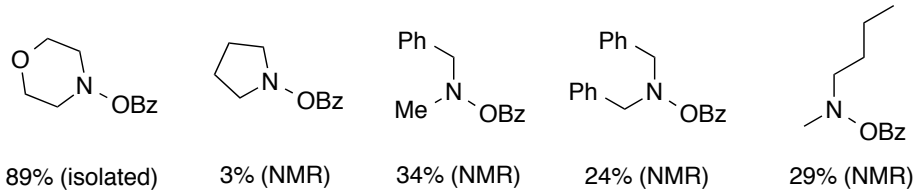
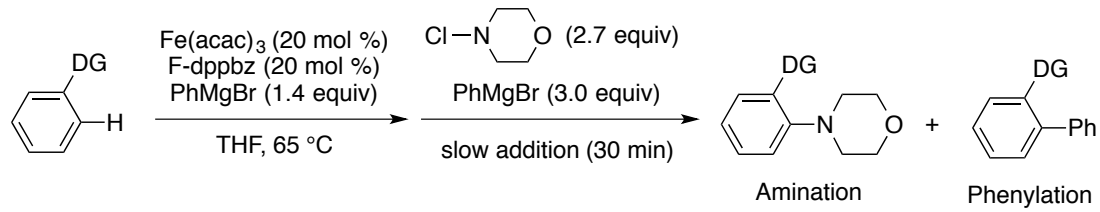
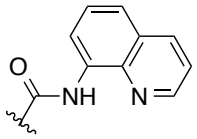


Figure 4. Scope for the amination with *N*-oxyamines

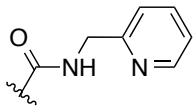
3-9. Effect of the directing group

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.

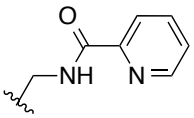




(**SM-1**)

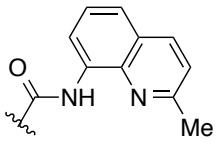


(**SM-2**)

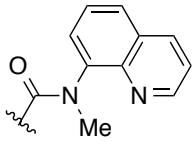


(**SM-3**)

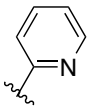
Amination:	95%	20%	0%
Phenylation:	2%	20%	0%
Recovery:	3%	2%	95%



(**SM-4**)

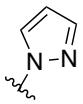


(**SM-5**)

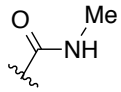


(**SM-6**)

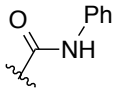
Amination:	0%	0%	3%
Phenylation:	0%	0%	2%
Recovery:	72%	91%	93%



(**SM-7**)



(**SM-8**)



(**SM-9**)

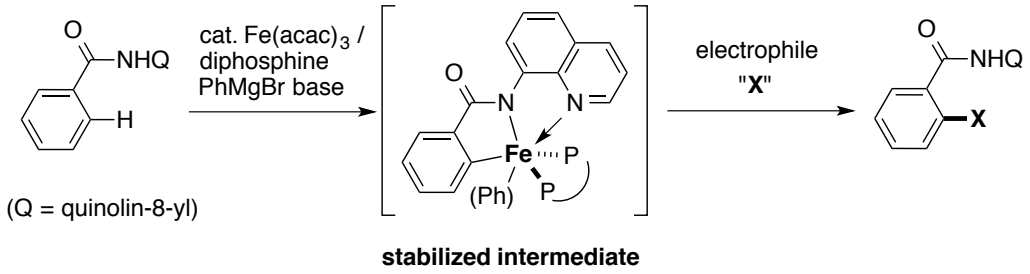
Amination:	0%	0%	0%
Phenylation:	22%	2%	0%
Recovery:	72%	97%	97%

Figure 5. Product distribution with different directing groups

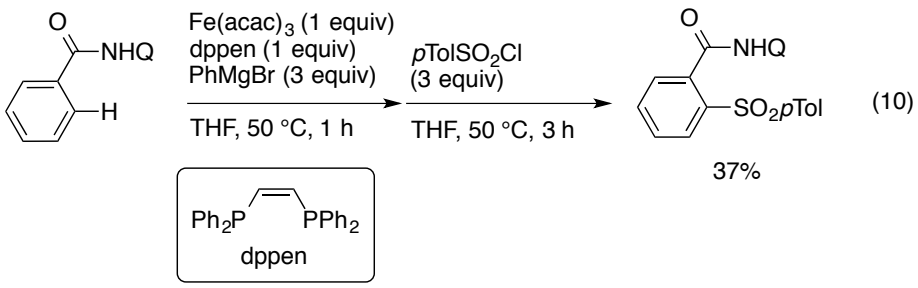
3-10. Reaction of the organoiron with sulfonyl chloride

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.

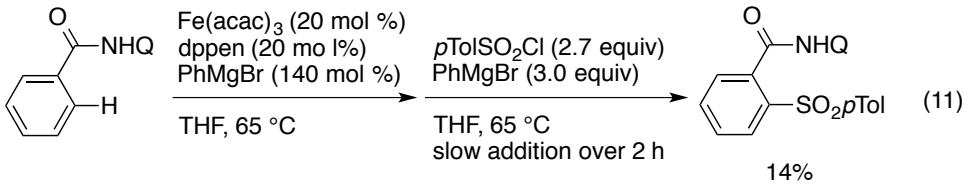
Scheme 12. Generalized scenario for coupling of the intermediate with electrophiles



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

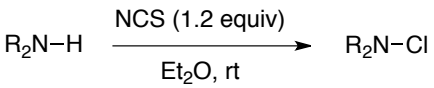
• *Preparation of amides*

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.

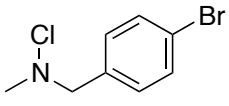
• *Preparation of N-chloroamines*



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.

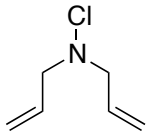


^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 3.98 (s, 2H), 2.95 (s, 3H).

^{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.

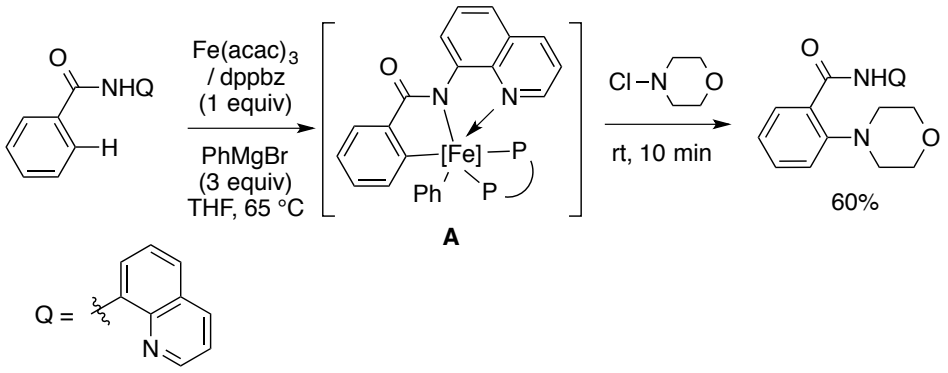


^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99–5.90 (m, 2H), 5.30–5.26 (m, 4H), 3.60–3.58 (m, 4H).

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

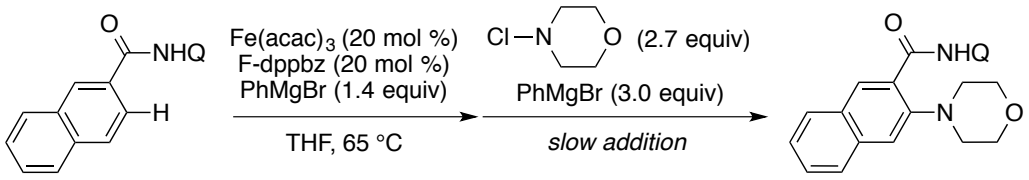
GC MS (EI) *m/z* (relative intensity): 133 (M^+, 21), 132 (10), 131 (M^+, 63), 130 (15), 106 (36), 104 (100), 102 (10), 98 (15), 96 (77), 94 (93), 90 (20), 80 (29).

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



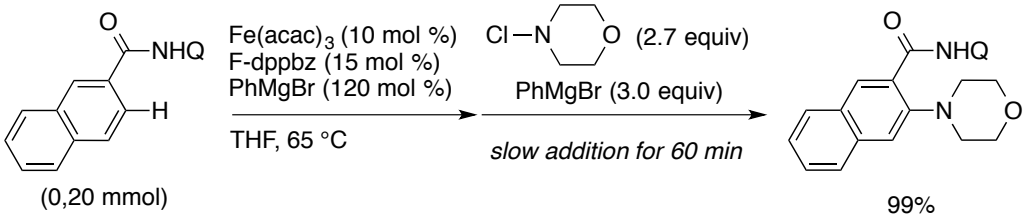
1.00 g (3.4 mmol) 1.05 g (82% yield)

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

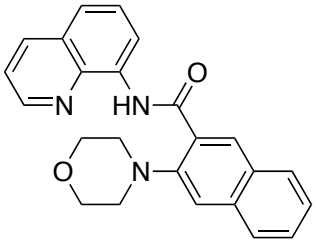
the same reaction was performed with 1 mmol (298 mg) of the starting amide, the aminated product was obtained in 89%.

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.

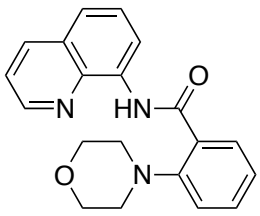
^{1}H NMR (500 MHz, $CDCl_3$): δ 12.67 (s, 1H), 9.18 (dd, J = 7.5, 1.2 Hz, 1H), 8.89 (dd, J = 3.9, 1.4 Hz, 1H), 8.71 (s, 1H), 8.21 (dd, J = 8.0, 1.4 Hz, 1H), 7.93 (d, J =8.0 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.64–7.44 (m, 6H), 4.00 (t, J = 4.3 Hz, 4H), 3.26 (t, J = 4.5 Hz, 4H).

^{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]



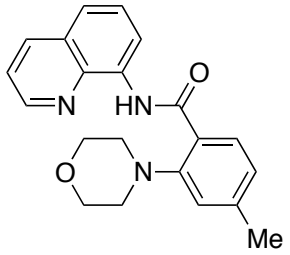
Melting point: 122–124 °C.

^{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]



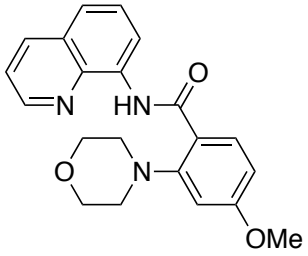
Melting point: 184–185 °C.

^{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.



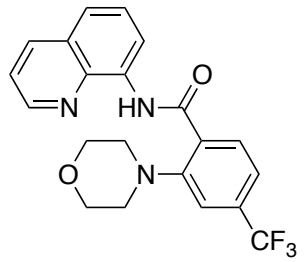
Melting point: 171–173 °C.

^{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]



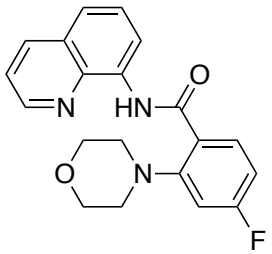
Melting point: 172–174 °C.

^{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.



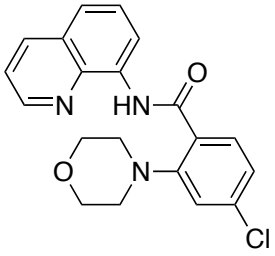
Melting point: 177–179 °C.

^{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]



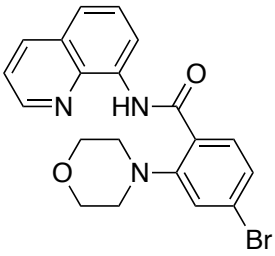
Melting point: 148–150 °C.

^{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]



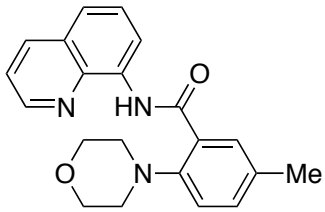
Melting point: 148 °C (decomp).

^{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]



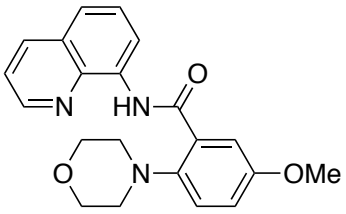
Melting point: 149–151 °C.

^{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.



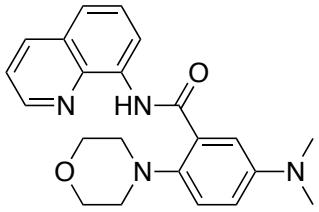
Melting point: 151–153 °C.

^{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]



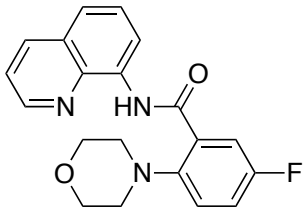
Melting point: 216–218 °C.

^{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]



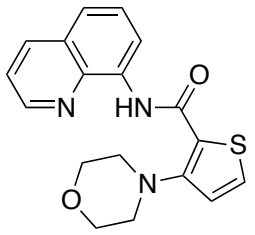
Melting point: 158–159 °C.

^{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]



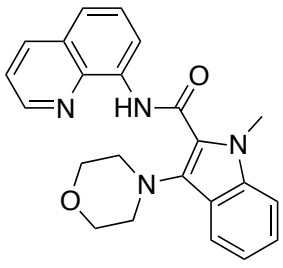
Melting point: 170–171 °C.

^{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.

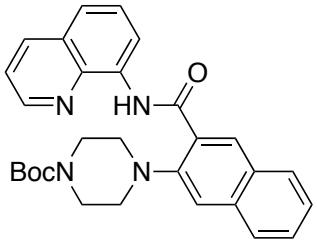
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.23 (s, 1H), 9.11 (d, J = 7.5 Hz, 1H), 8.98 (dd, J = 4.0, 1.3 Hz, 1H), 8.20 (dd, J = 8.2, 1.3 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.61–7.48 (m, 4H), 7.35 (dd, J = 7.7, 7.7 Hz, 1H), 7.16 (dd, J = 7.5, 7.3 Hz, 1H), 4.25–4.24 (m, 7H), 3.50 (br, 4H).

^{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).

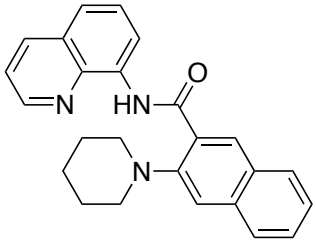
^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 154.8, 148.0, 147.9, 138.9, 136.5, 135.6, 135.2, 133.7, 130.0, 129.0, 128.5, 128.4, 128.2, 127.6, 126.8, 125.6, 121.9, 121.7, 117.9, 116.4, 79.9, 28.4. Piperazine's carbon signals are overlapping with those of the solvent ($CDCl_3$).

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.

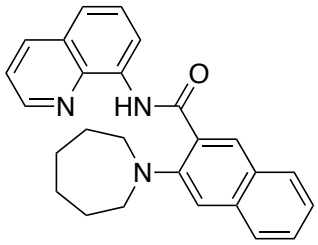
^{1}H NMR (500 MHz, $CDCl_3$): δ 12.8 (s, 1H), 9.20 (d, J = 7.5 Hz, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.70 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.64–7.40 (m, 6H), 3.17 (br, 4H), 1.86 (br, 4H), 1.52 (br, 2H).

^{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.

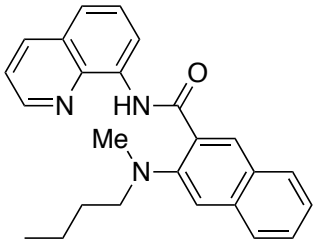
^{1}H NMR (500 MHz, $CDCl_3$): δ 12.72 (s, 1H), 9.14 (dd, J = 7.7, 1.2 Hz, 1H), 8.84 (dd, J = 4.2, 1.7 Hz, 1H), 8.67 (s, 1H), 8.17 (dd, J = 8.2, 1.7 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.63–7.58 (m, 2H), 7.55–7.38 (m, 4H), 3.48 (t, J = 5.3 Hz, 4H), 1.95(br, 4H), 1.65–1.63 (m,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

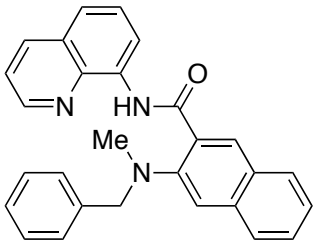
^{1}H NMR (500 MHz, $CDCl_3$): δ 14.15 (s, 1H), 9.13 (d, J = 6.7 Hz, 1H), 8.89 (s, 1H), 8.85 (dd, J = 4.1, 1.5 Hz, 1H), 8.16 (dd, J = 8.2, 1.6 Hz, 1H), 7.96 (d, J =8.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.64 (dd, J = 7.9, 7.9 Hz, 1H), 7.55–7.52 (m, 2H), 7.47–7.44 (m, 2H), 3.27–3.24 (m,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

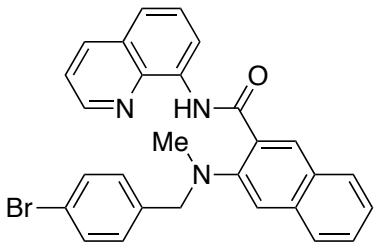
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.7 (s, 1H), 9.12 (d, J = 7.6 Hz, 1H), 8.81–8.78 (m, 2H), 8.17 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 7.9, 7.8 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.50–7.40 (m, 4H), 7.24 (d, J = 6.1 Hz, 2H), 7.10–7.05 (m, 3H), 4.41 (s,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



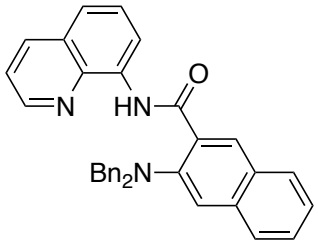
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.62 (s, 1H), 9.11 (dd, J = 7.8, 1.2 Hz, 1H), 8.81 (s, 1H), 8.76 (dd, J = 4.0, 1.6 Hz, 1H), 8.18 (dd, J = 8.3, 1.5 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 7.9, 7.9 Hz, 1H), 7.55–7.41 (m, 5H), 7.17 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.6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

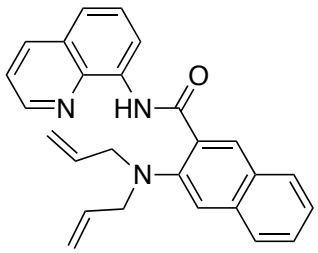
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.40 (s, 1H), 9.15 (d, J = 7.6 Hz, 1H), 8.86 (d, J = 4.0 Hz, 1H), 8.76 (s, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.66 (dd, J = 7.8, 7.7 Hz, 1H), 7.61–7.56 (m, 2H), 7.50 (dd, J = 8.2, 4.2 Hz, 1H), 7.46–7.38 (m, 2H), 7.29 (d, J = 7.3 Hz, 4H), 7.13–7.07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

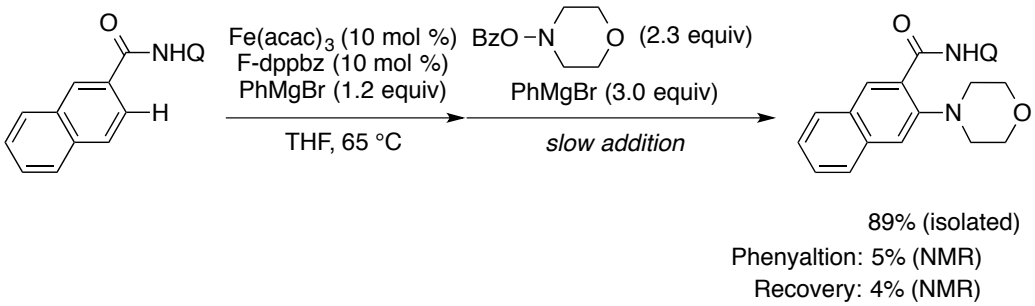
^{1}H NMR (500 MHz, $CDCl_3$): δ 13.8 (s, 1H), 9.14–9.13 (m, 1H), 8.87–8.85 (m, 2H), 8.16 (dd, J = 8.2, 1.4 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.63–7.43 (m, 6H), 6.10–6.02 (m, 2H), 5.18 (dd, J = 17.2, 1.0 Hz, 2H), 5.09 (d, J = 10.2 Hz, 2H), 3.92 (d, J = 6.7 Hz, 4H).

^{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).

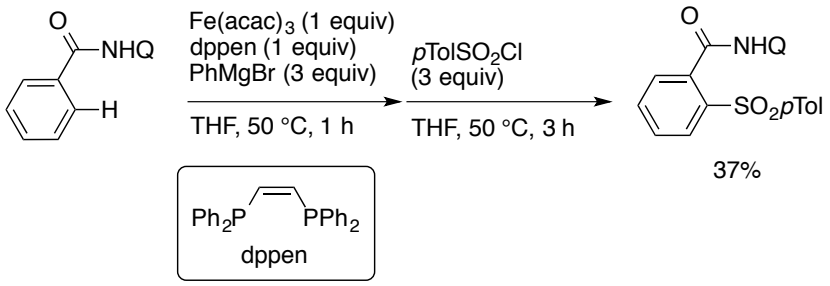
HRMS (APCI+): *m/z* calcd for $C_{26}H_{23}N_3O$ [M+H$^+$] 394.1914; found: 394.1901.

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]

3-13. References and Notes

[1] Lawrence, S. A. *Amines: Synthesis, Properties and Applications;* Cambridge University Press: Cambridge, U. K., **2004**.

[2] (a) Esteves, P. M.; de M. Carneiro, J. W.; Cardoso, S. P.; Barbosa, A.; G. H. Laali, K. K.; Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 4836–4849. (b) de Queiroz, J. F.; de M. Carneiro, J. W.; Sabino, A. A.; Sparrapan, R.; Eberlin, M. N.; Esteves, P. M.; *J. Org. Chem.* **2006**, *71*, 6192–6203.

[3] Booth, G. "Nitro Compounds Aromatic" In: *Ullman's Encyclopedia of Industrial Chemistry.*, John Wiley & Sons: New York., **2007**.

[4] (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473. (b) Surry, D. S.; Buchwald. S. L. *Chem. Sci.* **2011**, *2*, 27–50. (c) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544.

[5] (a) Wolfe, J. P.; Buchwald, S. L.; *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058. (b) Brenner, E.; Fort, Y.; *Tetrahedron Lett.* **1998**, *39*, 5359–5362. (c) Chen, C.; Yang, L.-M. *Org. Lett.* **2005**, *7*, 2209–2211. (d) Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429–1434. (e) Gao, C.-Y.; Yang, L.-M. *J. Org. Chem.* **2008**, *73*, 1624–1627.

[6] Iron-catalyzed aromatic amination using aryl halides and amines: Hatakeyama, T.; Imayoshi, R.; Yoshimoto, Y.; Ghorai, S. K.; Jin, M.; Takaya, H.; Norisue, K.; Sohrin, Y.; Nakamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 20262–20265.

[7] (a) Yamamoto, J.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739–2740. (b) Antilla, J. C.; Buchwald, S. L.; *Org. Lett.* **2001**, *3*, 2077–2079. (c) Kienle, A.; Dubbaka, S. R.; del Amo, V.; Knochel, P. *Synthesis* **2007**, 1272–1278.

[8] For other metal-catalyzed oxidative amination, See: (Fe) Nakamura, Y.; Ilies, L.; Nakamura, E. *Org. Lett.* **2011**, *13*, 5998–6001. (Ni) (b) Raghuvanshi, D. S.; Gupta, A. K.; Singh, K. N. *Org. Lett.* **2012**, *14*, 4326–4329. (c) Ilies, L.; Matsubara, T.; Nakamura, E. *Org. Lett.* **2012**, *14*, 5570–5573.

[9] Review: Bariwai, J.; Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 9283–9303.

[10] Reviews for amination of C–H bond: (a) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901–910. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.*

2011, *40*, 5068–5083.

[11] Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791.

[12] Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842–843.

[13] Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043–6046.

[14] Other catalytic systems using copper: (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607–1610. (b) Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Catal.* **2010**, *352*, 1301–1306. (c) Miyasaka, M.; Hirano, M.; T.; Kowalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359–361.

[15] Recently nickel-catalyzed directed amination under similar reaction conditions has reported: Yan, Q.; Chen, Z.; Yu, W.; Yin, H.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 2482–2485.

[16] Selected examples: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560–14561. (b) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934. (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058–14059. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184−16186. (e) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806−10807. (f) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676−3677. (g) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466−1474. (h) Nadres, E.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7−10.

[17] (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049. (b) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466.

[18] Ruthenium catalyst: (a) Louliat, M.-L.; Patureau, F. W. *Org. Lett.* **2013**, *15*, 164–167. Cobalt or Manganese catalyst: (b) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899–9903.

[19] Other examples also include iron-catalyzed homo-dimerization of anilines through C–H amination: Aoki, Y.; Imayoshi, R.; Hatakeyama, T.; Takaya, H.; Nakamura, M. *HETEROCYCLES* **2015**, *90*, 893–900.

[20] For transition-metal-free amination of aromatic substrates under oxidative

conditions: (a) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382−16385. (b) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960−19965.

[21] For a review, see: Barker, T.; Jarvo, E. *Synthesis* **2011**, 3954–3964.

[22] Selected examples of umpolung cross coupling for aromatic amines and amides: (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219–224. (c) Berman, A. M.; Johnson, J. S. *Org. Lett*, **2007**, *9*, 1521–1524. (d) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414–6417. (e) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799–1801. (f) Barker, T. J.; Jarvo, E. R.; *J. Am. Chem. Soc.* **2009**, *131*, 15598–15599.

[23] Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Synthesis* **2012**, 1792–1797 and references therein.

[24] Boursalian, G. B.; Ngai, M.-Y.; Hojczyk, K. N.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 13278–13281.

[25] Palladium catalyst: (a) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862–12864. (b) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan. K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652–7655. Ruthenium catalyst: (c) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L. *Org. Lett.* **2013**, *15*, 5106–5109. (d) Shang, M.; Zeng, S.-H.; Sun, S.-H.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 5286–5289. Iridium catalyst: (e) Kim, H.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 5904–5907. (f) Patel, P.; Chang, S. *Org. Lett.* **2014**, *16*, 3328–3331. Rhodium catalyst (g) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2012**, *14*, 272−275. (h) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656− 659. (i) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Chem. Commun.* **2013**, *49*, 7031−7033.

[26] With *N*-arenesulfonated imides: (a) Yu, S.; Wan, B.; Li, X. *Org. Lett.* **2013**, *15*, 3706−3709. With *N*-fluorosulfonimides: (b) Tang, R.-J.; Luo, C.-P.; Yang, L.; Li, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 869−873. With *in situ* generated nitrene species: (c) Zhao, H.; Shang, Y.; Su, W. *Org. Lett.* **2013**, *15*, 5106−5109.

[27] Azides as electrophilic aminating reagents for C–H amination: (a) Ryu, J.; Kwak, J.;

Shin, K.; Lee, D.; Chang, S. *J. Am. Chem. Soc.* **2013**, *135*, 12861−12868. (b) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040–1052 and references therein. (c) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang. S. *J. Am. Chem. Soc.* **2012**, *134*, 9110–9113. (d) Shin, K.; Baek, Y.; Chang, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8031–8036. (e) Park, S. H.; Park, Y.; Chang. S. *Org. Synth.* **2014**, *91*, 52–59. (f) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang. S. *J. Am. Chem. Soc.* **2014**, *136*, 2492–2502.

[28] Recently, cationic cobalt species has found to catalyze *ortho*-amnation using *N*-oxyamine as an aminating reagent: Patel, P.; Chang, S. *ACS Catal.* **2015**, *5*, 853–858.

[29] See Chapter 1 for details.

[30] (a) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067–2081. (b) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K.-I.; Nakajima, S.; *Chem. Pharm. Bull.* **1981**, *29*, 2689–2691. (c) Nitta, K.; Yamamoto, Y.; Inoue, T.; Hyodo, T. *Chem. Pharm. Bull.* **1966**, *14*, 363–369.

[31] See Chapter 2 for details.

[32] Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516–1519.

[33] Slow addition of the Grignard reagent was effective to suppress side reactions. (a) Nakamura, M.; Matsuo, K.; Ito, S. Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687. (b) Ghorai, S. K.; Jin, M.; Hatakeyama, T.; Nakamura, M. *Org. Lett.* **2012**, *14*, 1066–1069.

[34] Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem. Asian. J.* **2011**, *6*, 3059–3065.

[35] Ito, S.; Itoh, T.; Nakamura, M. *Angew. Chem., Int. Ed.* **2010**, *50*, 454–457.

[36] Hartwig, J. F. *Organotransition metal chemistry: from bonding to catalysis*; University Science Books: Sausalito, CA, **2010**.

[37] (a) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491–493. (b) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943–1946.

[38] Ilies, L.; Konno, E.; Chen, Q.; Nakamura, E. *Asian J. Org. Chem.* **2012**, *1*, 142–145.

[39] (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**,

130, 5858–5859. (b) Yoshikai, N. Matsumoto, A.; Norinder, J. Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925–2928. (c) Ilies, L.; Kobayashi, M.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2012**, *254*, 593–596.

[40] See experimental section for details.

[41] When *N*-chloroamides were used, bromination of quinoline on the amide was observed, probably through electrophilic aromatic substitution of the bromine cation.

[42] (a) Zhao, Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2948–2951. (b) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7–10. (c) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124–2127.

[43] Zhao, X.; Dimitrijevi´c, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466–3467.

[44] Selected examples: (a) Yoshiharam S.-i.; Tatsumi, K. *Drug Metab. Dispos.* **1990**, *18*, 876–881. (b) Dinsmore, C. J.; Williams, T. M.; O'Neil, T. J.; Liu, D.; Rands, E.; Culberson, J. C.; Lobell, R. B.; Koblan, K. S., Kohl, N. E.; Gibbs, J. B.; Oliff, A. J.; Graham, S. L.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3301–3306. (c) Sun, Z. Y.; Botros, E.; Su, A. D.; Kim, Y.; Wang, E.; Baturay, N. Z.; Kwon, C. H. *J. Med. Chem.* **2000**, *43*, 4160–4168.

[45] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2924.

[46] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

[47] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890–891.

[48] (a) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342–9345. (b) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043–6046. (c) Yang, Y.; Shi, L.; Zhou, Y.; Li, H.-Q.; Zhu, Z.-W.; Zhu, H.-L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6653–6656. (d) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237–18240. (e) Rouquet, G.; Chatani, N. *Chem. Sci*. **2013**, *4*, 2201–2208. (f) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797–9804.

[49] Yan, Q.; Chen, Z.; Yu, W.; Yin, H.; Lin, Z.; Zhang, Y.; *Org. Lett.* **2015**, *17*, 2482–2485.

[50] Liu, J.; Yu, L.; Zhuang, S.; Gui, Q.; Chen, X.; Wang, W.; Tan, Z. *Chem. Commun.*

2015, *51*, 6418–6421.

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.

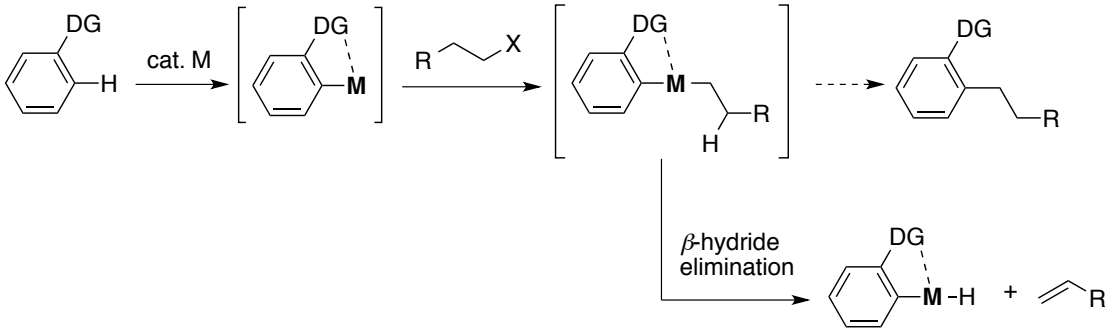
The substitution reaction of aromatic and olefinic nucleophiles using alkyl electrophiles,[6] and transition-metal-catalyzed cross coupling reactions[7,8] are alternative methods to synthesize alkylated compounds. However, these reactions have a strong limitation with respect to substrates and functionalities, 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

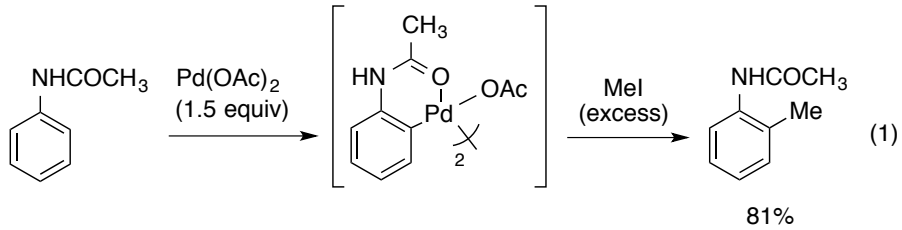
Transition-metal-catalyzed directed activation of a C(sp^2)–H bond of aromatic and olefinic substrates,[9] following the reaction with an alkyl electrophile[10] such as an alkyl halide would provide an efficient methodology, in that the reaction could be performed with high and predictable regioselectivity 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

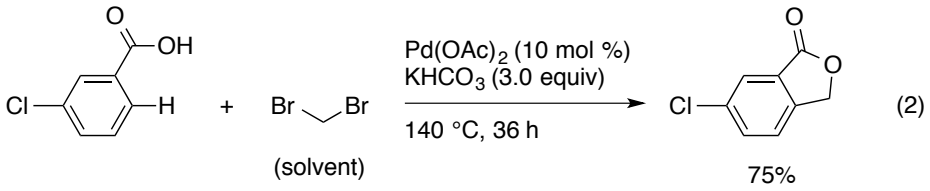
that induces side-reactions (Scheme 1).[11]

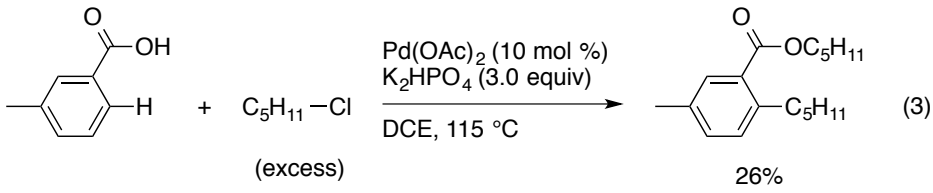
Scheme 1. Competing *β*-hydride elimination in transition-metal-catalyzed alkylation of a $C(sp^2)$–H bond



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).



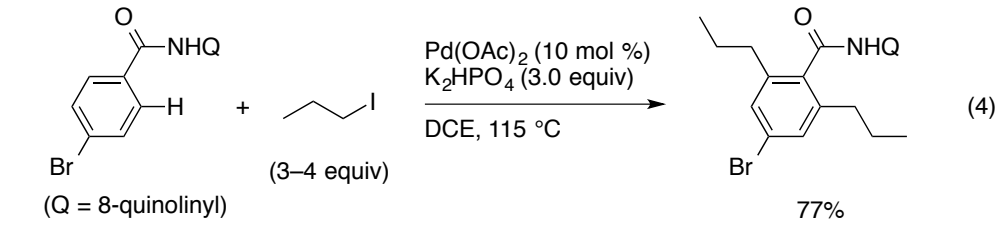


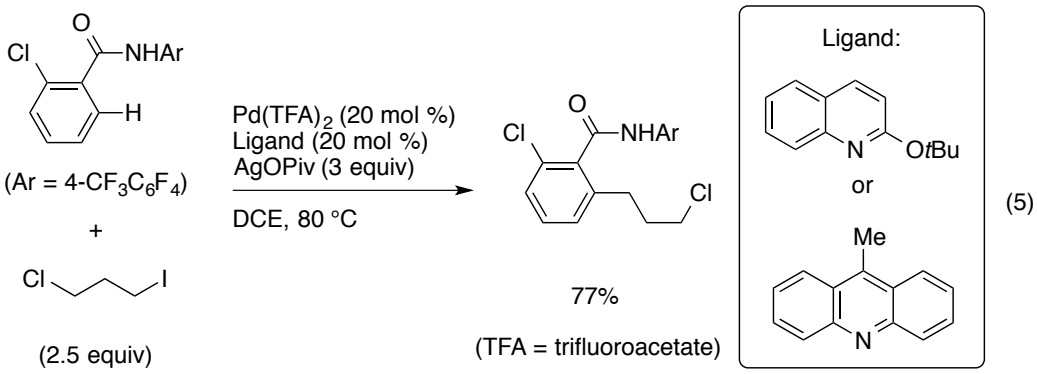


• Suppression of *β*-hydride elimination

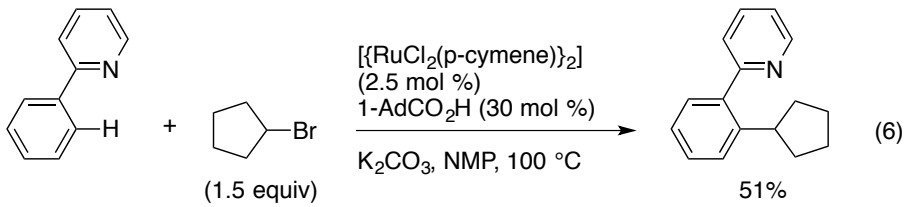
The difficulty associated with *β*-hydride elimination in palladium-catalyzed directed alkylations is so problematic that such reactions have mostly been limited to the methylation or benzylation.[10–15,16,17] However, recently chemists have discovered ways to suppress this side reaction, and achieved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

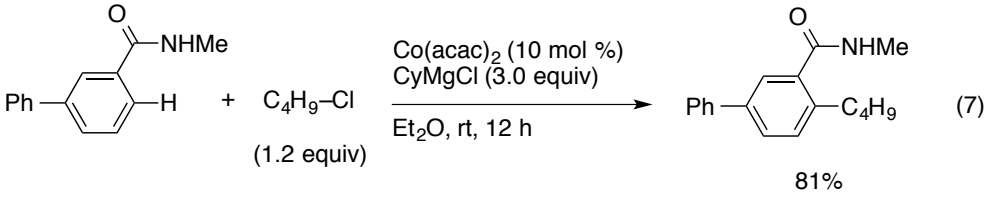
In 2010, Daugulis and a coworker succeeded to suppress the *β*-hydride elimination by using a bidentate directing group through occupation of the coordination site of palladium, and achieved the alkylation with primary alkyl iodides possessing *β*-hydrogen (eq. 4).[18] Later Chen and coworkers reported 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]

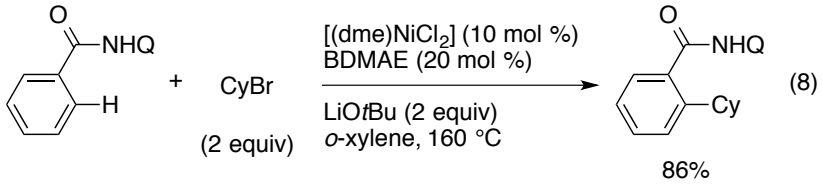




Employing a different transition-metal as the catalyst was also found to be effective, although the efficiency of these reactions are not high compared with palladium catalysis described above. Ackermann and coworkers reported a ruthenium-catalyzed directed alkylation using primary and secondary alkyl 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.







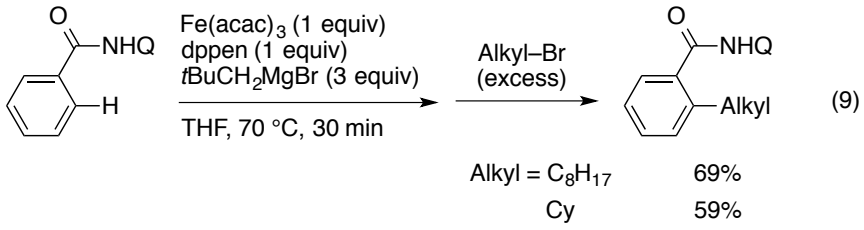
BDMAE = bis(2-dimethylaminoethyl)ether

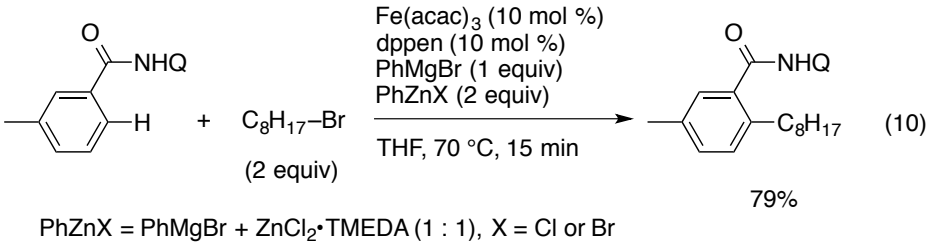
• The reaction described in this chapter

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.

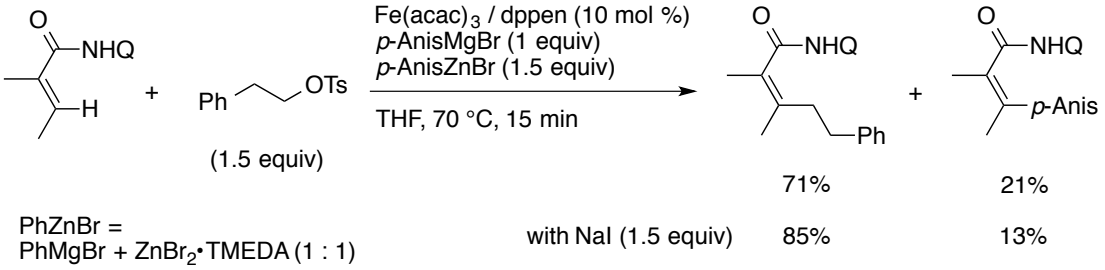




4-3. Discovery of *β*-alkylation of alkeneamides using alkyl sulfonates

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

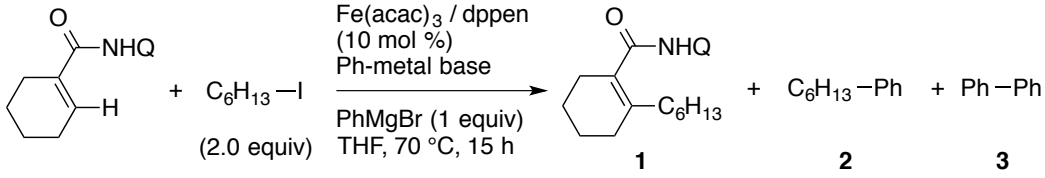


4-4. Effect of the organometallic base on *β*-alkylation of alkeneamide

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.

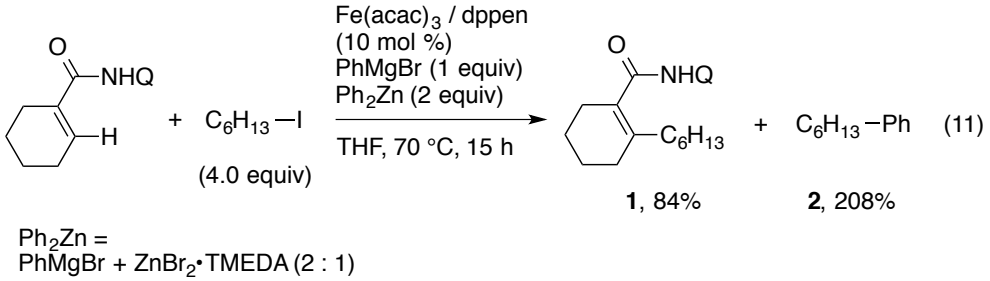
Table 1. Effect of base for *β*-alkylation of amides



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.

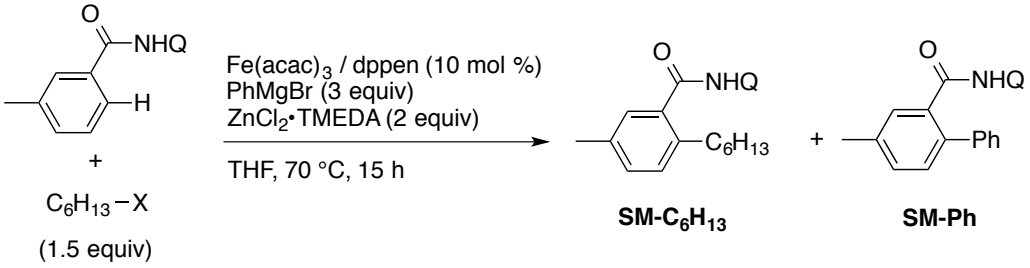
When the reaction was performed using diarylzinc as a base, cross coupling initially proceeded to afford **2**, as previously shown in entry 2 in Table 1. However, when excess electrophile was used for the reaction, desired alkylation also proceeded (eq. 11). The result indicates that monoarylzinc species 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.

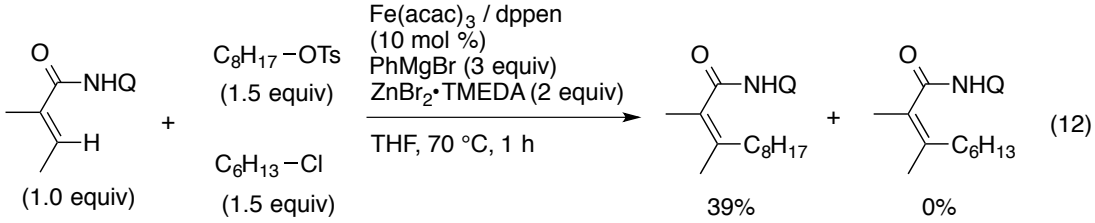
Table 2. Investigation of leaving group of the alkyl electrophile



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

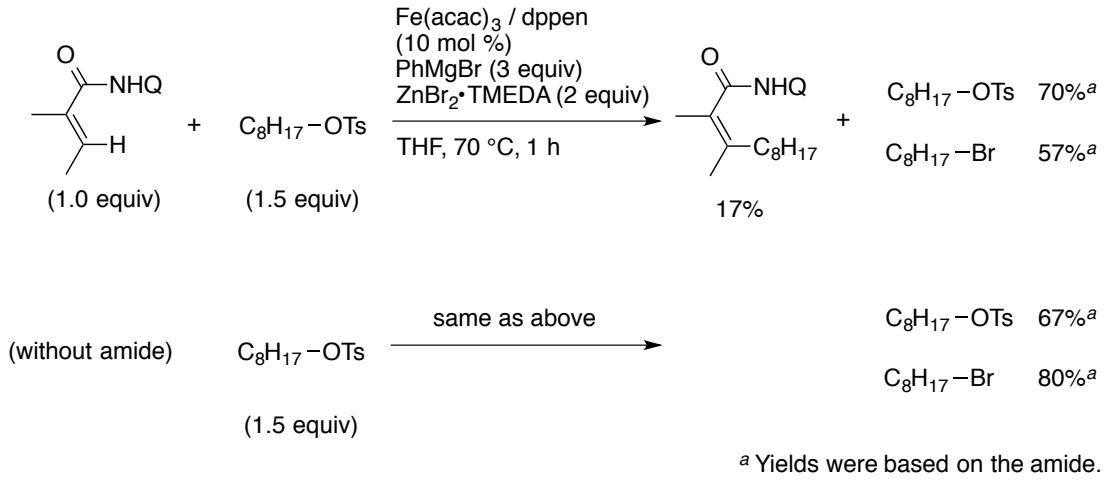
Then a competition experiment was performed to compare the reactivity of alkyl chloride and alkyl tosylate as the alkyl donor (eq. 12). The reaction was performed in the presence of octyl tosylate and hexyl chloride in the same reaction pot, and the product distribution was investigated after 1 hour 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.



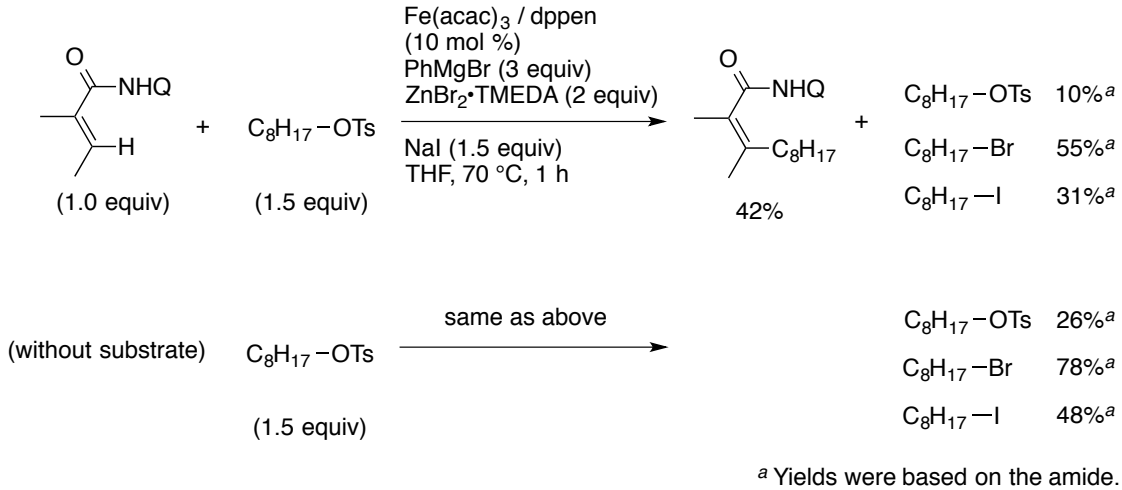
However, the experiments shown in Scheme 3 and 4 imply that alkyl tosylates may function as an alkyl donor after conversion to the corresponding alkyl bromide or

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).

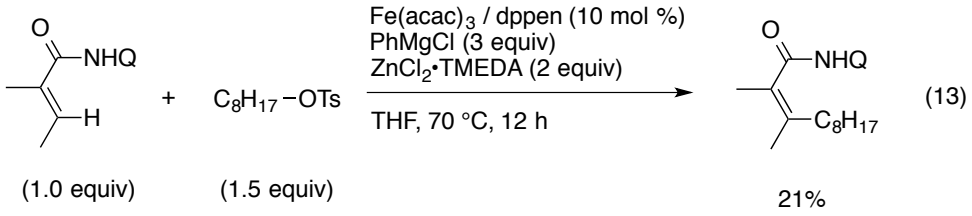
Scheme 3. *In situ* generation of alkyl bromide via tosylate/bromide exchange



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



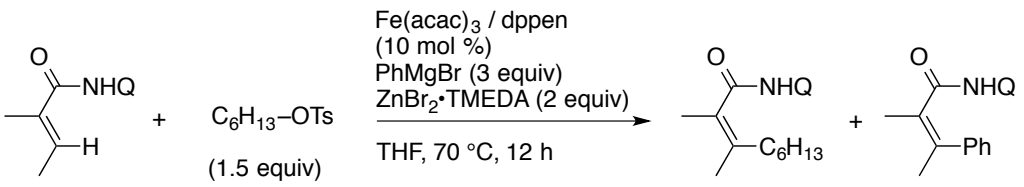
Then the innate reactivity of alkyl tosylate or alkyl chloride as the alkyl donor was investigated, by excluding the bromide/iodide anion from the reaction mixture. I performed the reaction using $ZnCl_2$•TMEDA and PhMgCl to exclude bromide and iodide anions, to find that the reaction was considerably 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.

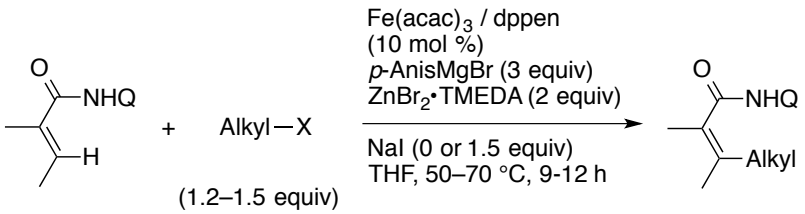
4-7. Scope of the reaction using olefinic amides

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



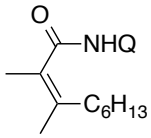
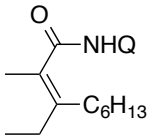
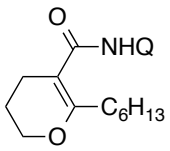
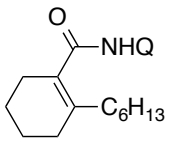
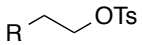
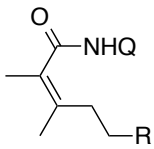
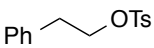
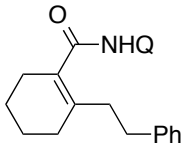
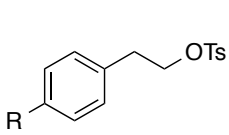
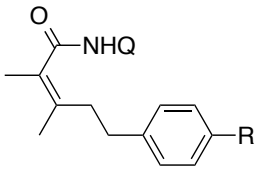
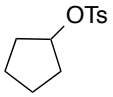
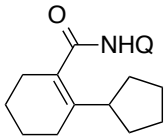
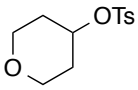
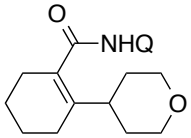
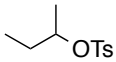
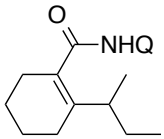
entry	alkyl–X	product	yield (%)
1	C_6H_{13}–OTs		85
2	C_6H_{13}–OTs		87
3	C_6H_{13}–OTs		61
4	C_6H_{13}–X		[89] (X = I)
5			[79] (X = Br)
6			[70] (X = Cl)
7			89 (R = $(CH_2)_2Cl$)
8			83 (R = $(CH_2)_3CO_2Et$)
9			93

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.

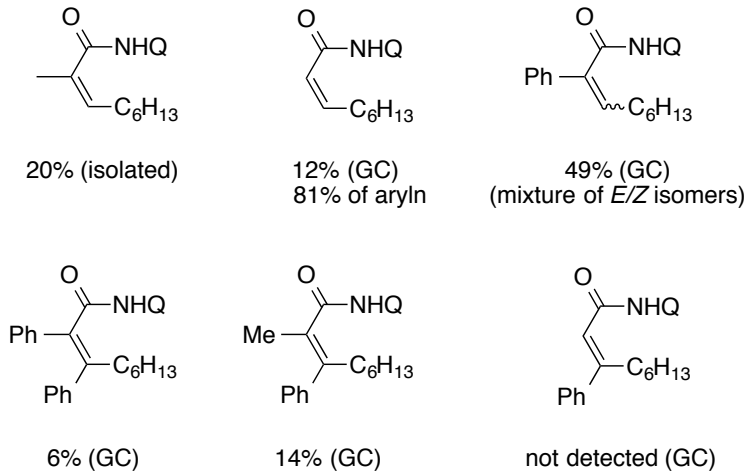


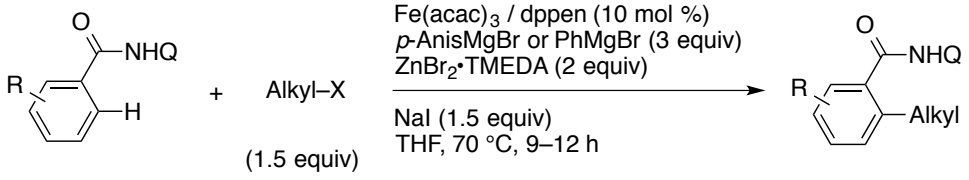
Figure 1. Examples of unreactive substrates: reaction using hexyl iodide as an alkyl electrophile

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



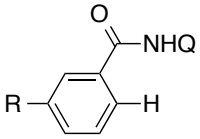
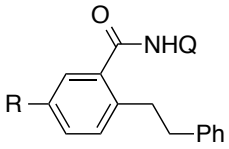
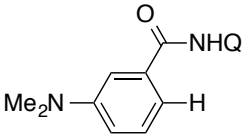
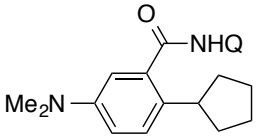
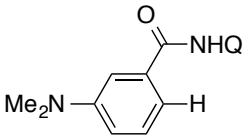
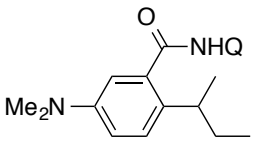
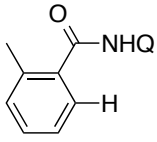
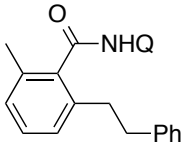
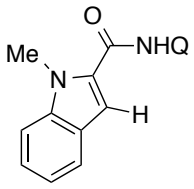
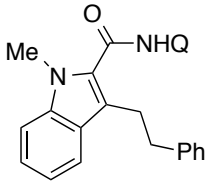
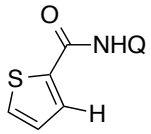
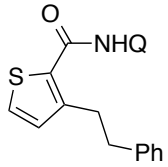
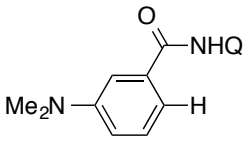
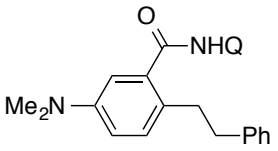
entry	substrate	product			yield (%)
1			R =	Me	82
2				OMe	87
3				NMe_2	93
4				F	75
5				Cl	60
6				Br	53
7					89
8					83[a]
9					70[b]

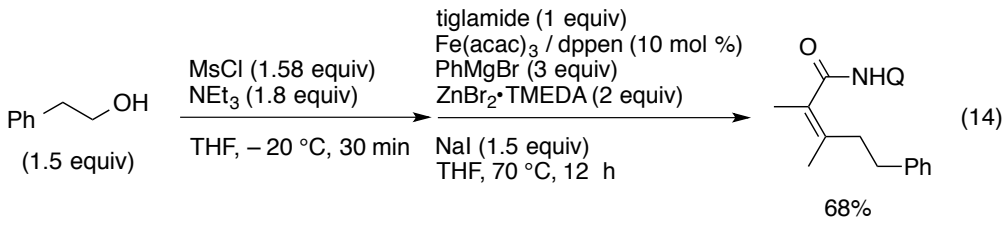
Table 5. (continued)

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

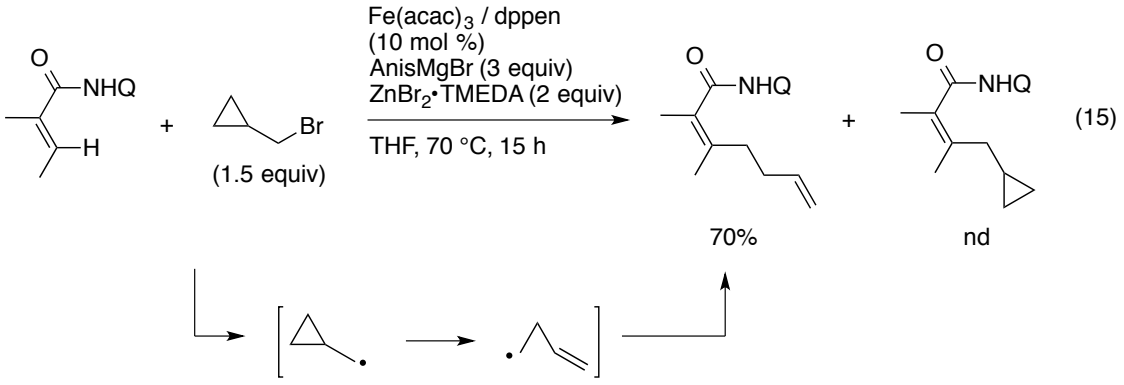
An alcohol could also be used as the alkyl donor for the reaction, through *in situ* mesylation. Thus, phenetyl alcohol was mesylated by treating with methanesulfonyl chloride and a triethylamine base to give phenetyl mesylate *in situ*, which was then utilized for the alkylation reaction without isolation, 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.

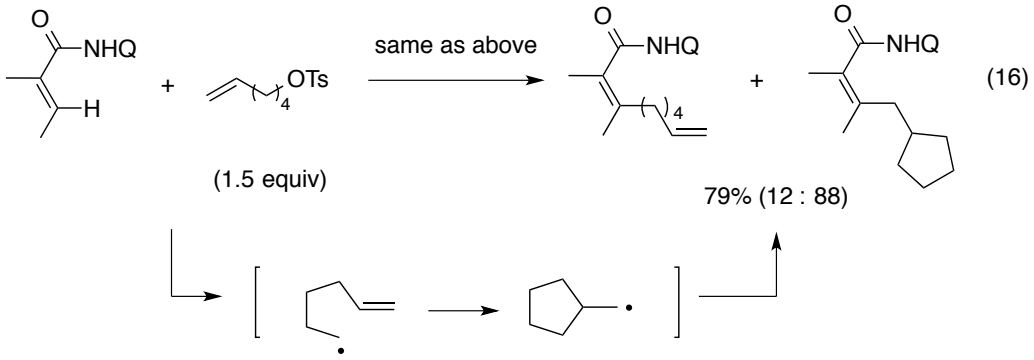


4-10. Proof of alkyl radical intermediate

• Radical clock experiments

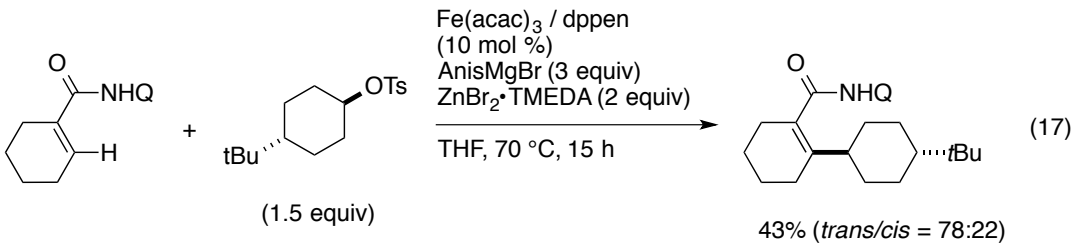
To proof the existence of the radical species that was implied in the previous study (Table 3, entry 7), I performed radical clock experiments [46] using bromomethylcyclopropane and 5-hexenyl tosylate as electrophiles. The reaction with bromomethylcyclopropane gave *cis*-3-butenylated amide as the sole 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.

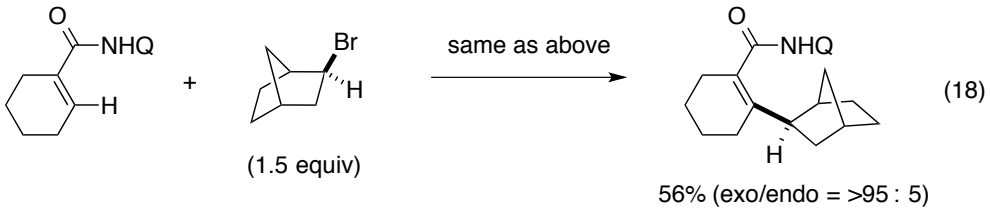




• Loss of stereoselectivities

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.

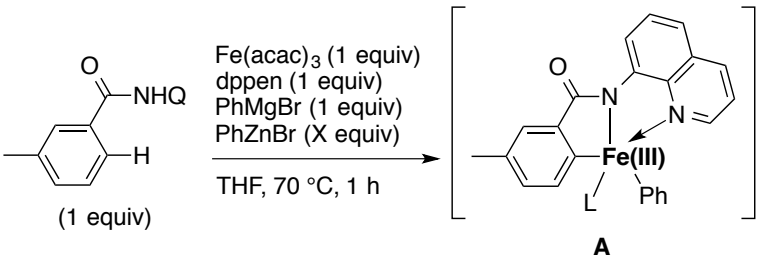




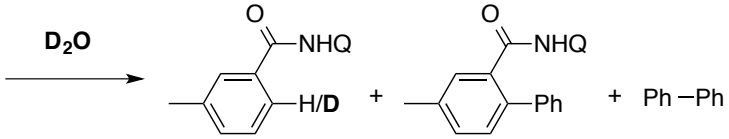
4-11. Stoichiometric reactions

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).

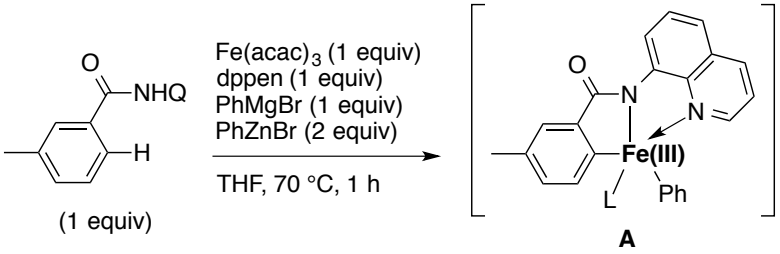
Scheme 5. Stoichiometric reactions using arylzinc halide as a base

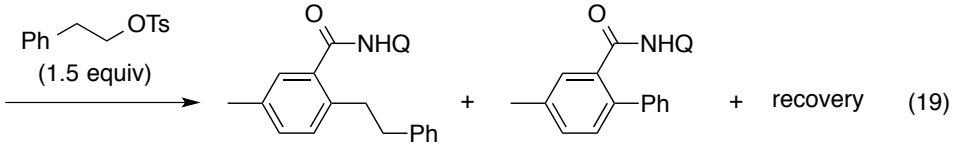


$PhZnBr = PhMgBr + ZnBr_2 \cdot TMEDA$



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

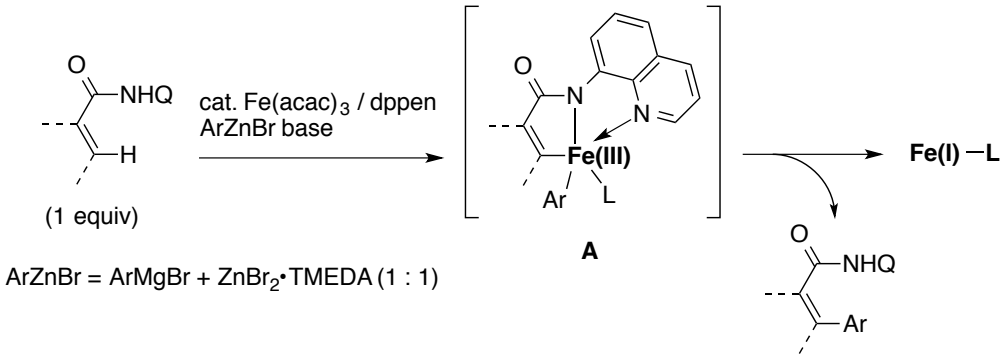




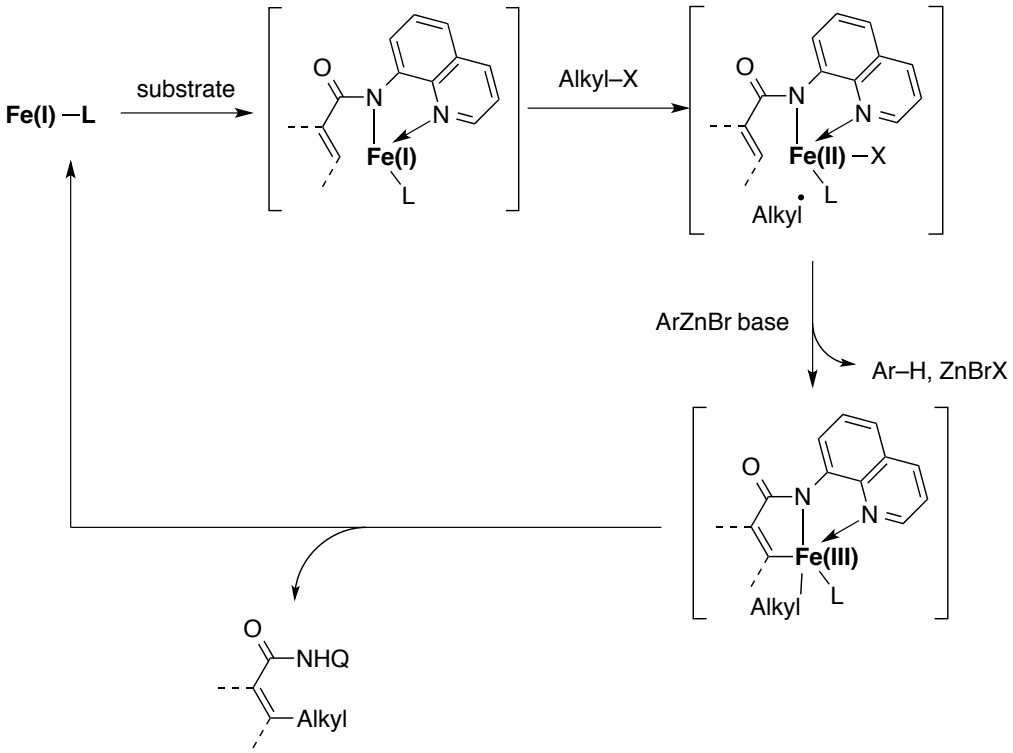
4-12. Possible catalytic cycle

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.

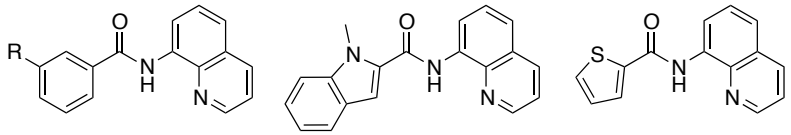
Materials. Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used after appropriate purification before use. Anhydrous tetrahydrofuran was purchased from KANTO Chemical Co. and purified prior to use by a solvent purification system (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.



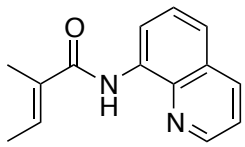
R = Me, OMe, NMe_2, F, Cl, Br

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.

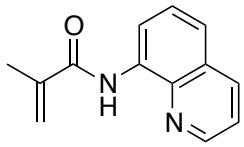
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (s, 1H), 8.84–8.80 (m, 2H), 8.15 (dd, J = 8.4, 1.6 Hz, 1H), 7.56–7.43 (m, 3H), 6.76 (d, J = 6.9 Hz, 1H), 2.07 (s, 3H), 1.88 (d, J = 6.9 Hz, 3H).

^{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.

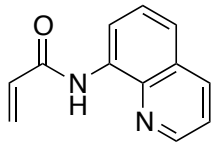
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.37 (s, 1H), 8.84–8.80 (m, 2H), 8.15 (d, J = 8.5 Hz, 1H), 7.56–7.50 (m, 2H), 7.46–7.43 (m, 1 H), 6.05 (s, 1H), 5.56 (m, 1H), 2.19 (s, 3H).

^{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.

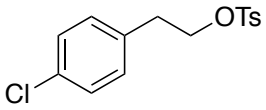
GC MS (EI) *m/z* (relative intensity): 198 (M^+, 51), 171 (28), 169 (13), 155 (19), 144 (100), 129 (22), 117 (25), 116 (28), 89 (24).

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]

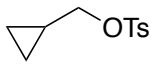
Melting point: 76–78 °C.

^{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]

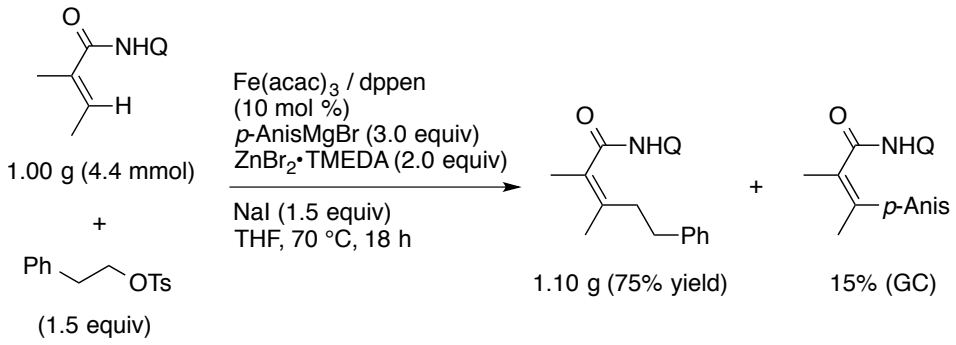
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 4.78–4.75 (m, 1H), 2.44 (s, 3H), 2.20–2.13 (m, 4H), 1.75–1.73 (m, 1H), 1.62–1.48 (m, 1H).

^{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

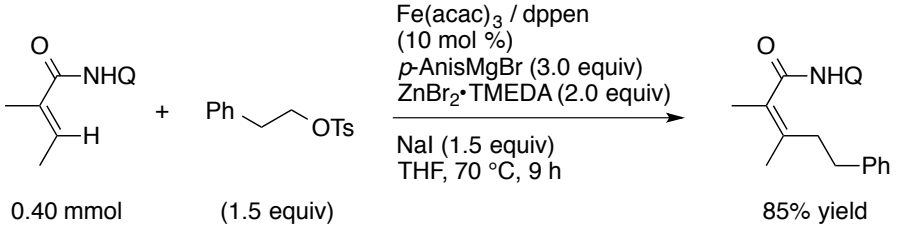
Alkylation of N-(quinolin-8-yl)-(E)-2-methylbut-2-enoic amide on 1 g scale



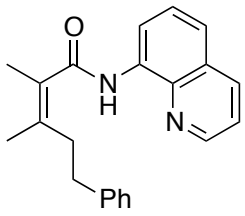
Sodium iodide (994 mg, 6.6 mmol) was placed in an oven-dried two-necked flask and it was carefully dried by heating with a heat gun *under vacuo*. *N*-(quinolin-8-yl)-(*E*)-2-methylbut-2-enoic amide (1.00 g, 4.4 mmol), and $ZnBr_2$•TMEDA (3.02 g, 8.8 mmol) were added, and the mixture was dissolved in 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.



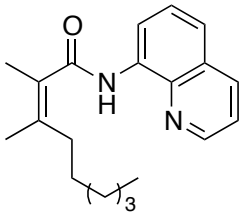
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.85 (d, J = 7.5 Hz, 1H), 8.78 (dd, J = 4.0, 2.0 Hz, 1H), 8.17 (dd, J = 8.5, 1.5 Hz, 1H), 7.58–7.51 (m, 2H), 7.45 (dd, J = 8.5, 4.0 Hz, 1H), 7.12–7.02 (m, 5H), 2.90–2.87 (m, 2H), 2.59–2.55 (m, 2H), 2.04 (s, 3H), 1.86 (s, 3H).

^{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.



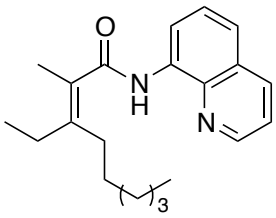
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.86 (d, J = 7.5 Hz, 1H), 8.79 (d, J = 4.0 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.57–7.23 (m, 3H), 2.25 (t, J = 8.0 Hz, 2H), 2.01 (s, 3H), 1.79 (s, 3H), 1.57–1.52 (m, 2H), 1.22–1.17 (m, 6H), 0.74 (t, J = 6.5 Hz, 3H).

^{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.



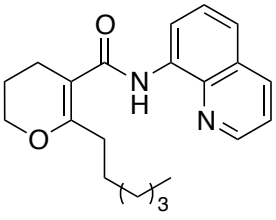
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.87 (dd, J = 7.6, 1.1 Hz, 1H), 8.79 (dd, J = 4.1, 1.6 Hz, 1H), 8.15 (dd, J = 8.2, 1.4 Hz, 1H), 7.57–7.42 (m, 3H), 2.26–2.15 (m, 4H), 2.02 (s, 3H), 1.57–1.53 (m, 2H), 1.21–1.15 (m, 6H), 1.08 (t, J = 7.6 Hz, 3H), 0.73–0.70 (m, 3H).

^{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

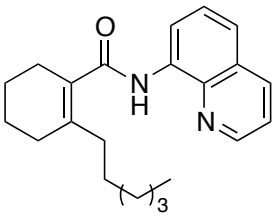
= 5.0 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.55 (t, *J* = 6.5 Hz, 2H), 1.99–1.94 (m, 2H), 1.71–1.64 (m, 2H), 1.35–1.26 (m, 6H), 0.84 (t, *J* = 6.6 Hz, 3H).

^{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.



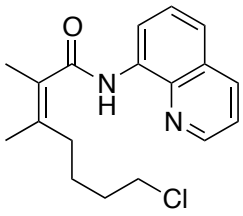
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.79 (d, *J* = 7.5 Hz, 1H), 8.71 (d, *J* = 4.0 Hz, 1H), 7.48–7.18 (m, 3H), 2.35 (s, br, 2H), 2.16 (t, *J* = 8.0 Hz, 3H), 2.04 (s, br, 2H), 1.62–1.11 (m, 12H), 0.66 (t, *J* = 6.5 Hz, 3H).

^{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.



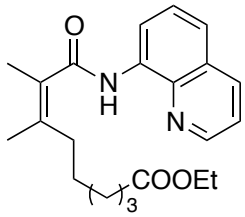
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.82 (d, J = 7.5 Hz, 1H), 8.76 (dd, J = 4.0, 1.5 Hz, 1H), 8.12 (dd, J = 8.5, 1.5 Hz, 1H), 7.53–7.40 (m, 3H), 3.44 (t, J = 6.0 Hz, 3H), 2.26 (t, J = 6.8 Hz, 3H), 1.99 (s, 3H), 1.76 (s, 3H), 1.70–1.66 (m, 4H).

^{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.



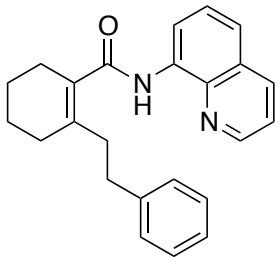
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.79 (s, 1H), 8.85 (d, J = 3.5 Hz, 1H), 8.80 (dd, J = 4.3, 1.5 Hz, 1H), 8.17 (dd, J = 8.3, 1.5 Hz, 1H), 7.57–7.27 (m, 3H), 4.05 (q, J = 7.0 Hz, 2H), 2.26 (t, J = 7.5 Hz, 2H), 2.19 (t, J = 7.5 Hz, 2H), 2.01 (s, 3H), 1.79 (s, 3H), 1.61–1.18 (m, 9H).

^{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.



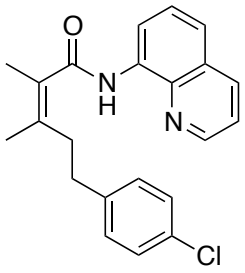
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 8.87 (d, J = 7.5 Hz, 1H), 8.79 (dd, J = 4.0, 1.5 Hz, 1H), 8.16 (dd, J = 8.0, 1.5 Hz, 1H), 7.58–7.43 (m, 3H), 7.12–7.02 (m, 5H), 2.88 (t, J = 8.3 Hz, 2H), 2.57 (t, J = 8.3 Hz, 2H), 2.46 (br, 2H), 2.18 (br, 2H), 1.73 (br, 4H).

^{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.

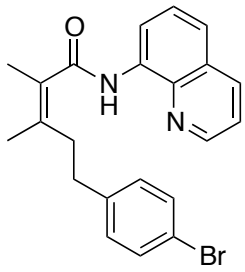
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.83 (d, J = 7.5 Hz, 1H), 8.78 (d, J = 4.0 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.58–7.52 (m, 2H), 7.45 (dd, J = 7.8, 4.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 2.84 (t, J = 8.0 Hz, 3H), 2.56 (t, J = 8.0 Hz, 3H), 2.03 (s, 3H), 1.84 (s,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

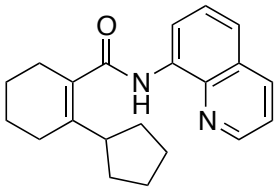
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.84–8.78 (m, 2H), 8.17 (d, J = 8.2 Hz, 1H), 7.56–7.44 (m, 3H), 7.20 (d, J = 7.9 Hz, 2H), 6.92 (d, J =8.2 Hz, 2H), 2.83 (t, J = 8.1 Hz, 2H), 2.55 (t, J = 7.9 Hz, 2H), 2.03 (s, 3H), 1.84 (s, 3H).

^{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).

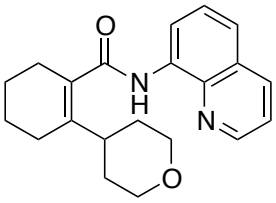
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 148.0, 140.6, 138.4, 136.2, 134.7, 130.2, 127.9, 127.4, 121.5, 121.3, 116.4, 43.7, 30.8, 27.3, 25.9, 23.5, 22.5, 22.4.

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.



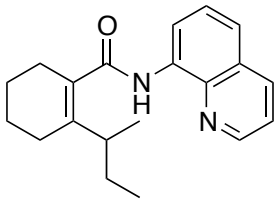
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.85 (d, J = 7.5 Hz, 1H), 8.77 (dd, J = 4.3, 1.5 Hz, 1H), 8.17 (dd, J = 8.5, 2.0 Hz, 1H), 7.59–7.28 (m, 3H), 3.94–3.91 (m, 2H), 3.28 (t, J = 11.8 Hz, 2H), 2.93–2.88 (m, 1H), 2.45 (br, 2H), 2.11 (br, 2H), 1.85–1.60 (m, 8H).

^{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.



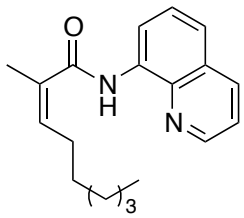
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.86 (d, J = 7.6 Hz, 1H), 8.79 (dd, J = 4.6, 1.6 Hz, 1H), 7.57–7.43 (m, 3H), 2.72–2.66 (m, 1H), 2.50–2.37 (m, 2H), 2.11–1.95 (m, 2H), 1.73–1.64 (m, 4H), 1.49–1.26 (m, 2H), 1.07 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 7.4 Hz, 3H).

^{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.



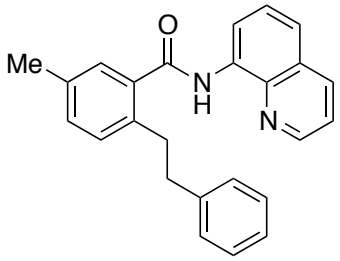
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.86 (dd, J = 7.3, 1.5 Hz, 1H), 8.79 (dd, J = 4.3, 2.0 Hz, 1H), 8.16 (dd, J = 8.5, 1.5 Hz, 1H), 7.57–7.26 (m, 3H), 5.76–5.74 (m, 1H), 2.43–2.38 (m, 2H), 2.11 (s, 3H), 1.69 (br, 1H), 1.51–1.46 (m, 2H), 1.35–1.24 (m, 5H), 0.83 (t, J = 7.0 Hz, 3H).

^{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.

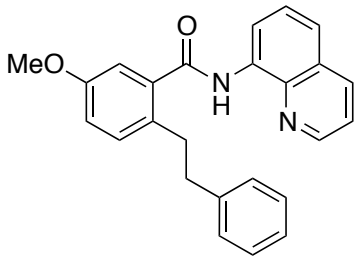
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 8.96 (d, J = 7.3 Hz, 1H), 8.76 (d, J = 4.1 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.63–7.54 (m, 2H), 7.46–7.43 (m, 2H), 7.24–7.03 (m, 7H), 3.20–3.16 (m, 2H), 3.01–2.97 (m, 2H), 2.40 (s, 3H).

^{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.

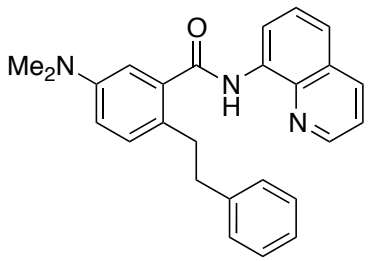
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.95 (d, J = 7.0 Hz, 1H), 8.77 (dd, J = 4.0, 2.0 Hz, 1H), 8.18 (dd, J = 8.0, 1.5 Hz, 1H), 7.63–7.55 (m, 2H), 7.45 (dd, J = 8.3, 4.5 Hz, 1H), 7.20–6.94 (m, 8H), 3.85 (s, 3H), 3.17–3.14 (m, 3H), 2.99–2.96 (m, 3H).

^{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.

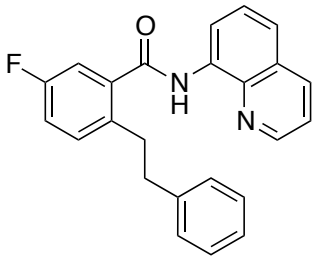
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.96 (d, J = 7.3 Hz, 1H), 8.75 (dd, J = 4.1, 1.4 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.63–7.54 (m, 2H), 7.44 (dd, J = 8.2, 4.1 Hz, 1H), 7.16–6.99 (m, 7H), 6.80 (dd, J = 8.6, 2.7 Hz, 1H), 3.12–3.09 (m, 2H), 2.98–2.95 (m, 8H).

^{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.

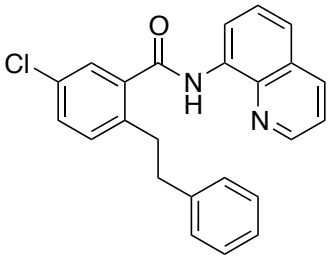
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.11 (s, 1H), 8.92 (d, J = 7.0 Hz, 1H), 8.78 (dd, J = 4.3, 1.5 Hz, 1H), 8.19 (dd, J = 8.0, 1.5 Hz, 1H), 7.63–7.57 (m, 2H), 7.47 (dd, J = 8.3, 4.0 Hz, 1H), 7.36 (dd, J = 8.5, 2.5 Hz, 1H), 7.25–7.02 (m, 7H), 3.21–3.18 (m, 2H), 3.00–2.96 (m, 2H).

^{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.

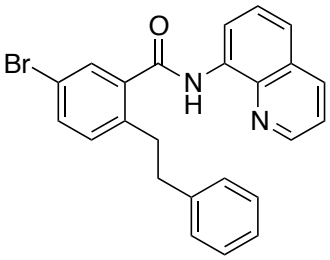
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.91 (d, J = 6.4 Hz, 1H), 8.79 (d, J = 3.2 Hz, 1H), 8.20 (d, J = 7.3 Hz, 1H), 7.63–7.57 (m, 3H), 7.47 (dd, J = 8.2, 4.1 Hz, 1H), 7.37 (dd, J = 8.2, 2.1 Hz, 1H), 7.21–7.01 (m, 6H), 3.19 (t, J = 7.9 Hz, 2H), 2.98 (t, J = 8.0 Hz, 2H).

^{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.

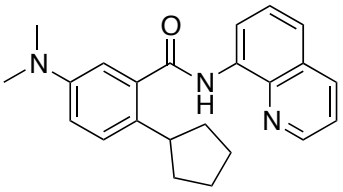
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.91 (d, J = 7.1 Hz, 1H), 8.78 (d, J = 4.1 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.76 (s, 1H), 7.62–7.44 (m, 4H), 7.30–7.01 (m, 6H), 3.17 (t, J = 7.9 Hz, 2H), 2.97 (t, J = 7.9 Hz, 2H).

^{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.

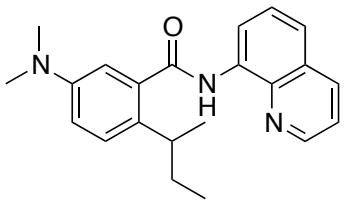
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.97 (d, J = 7.5 Hz, 1H), 8.75 (d, J = 4.5 Hz, 1H), 8.17 (dd, J = 8.3, 0.5 Hz, 1H), 7.60 (dd, J = 8.0, 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.5, 4.5 Hz, 1H), 7.32 (J = 9.0 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.86 (dd, J = 8.8, 2.5 Hz, 1H), 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.

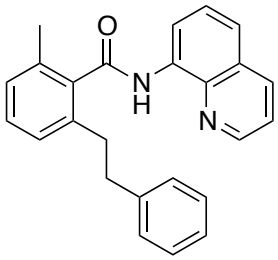
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.12 (s, 1H), 8.96 (dd, J = 7.3, 1.5 Hz, 1H), 8.74 (dd, J = 4.3, 1.5 Hz, 1H), 8.16 (dd, J = 8.3, 1.5 Hz, 1H), 7.60 (dd, J = 8.0, 8.0 Hz, 1H), 7.54 (dd, J = 8.3, 1.5 Hz, 1H), 7.43 (dd, J = 8.3, 4.0 Hz, 1H), 7.25 (dd, J = 4.5, 4.0 Hz, 1H), 6.91 (d, J = 3.0 Hz, 1H), 6.87 (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]

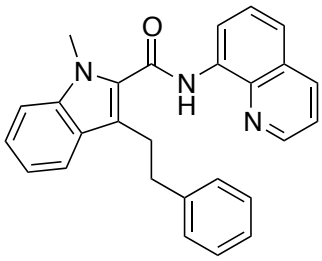


^{1}H NMR (500 MHz, $CDCl_3$): δ 9.95 (s, 1H), 9.01 (d, J = 7.5 Hz, 1H), 8.72 (dd, J = 4.0, 1.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 8.0 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.42 (dd, J = 8.3, 4.0 Hz, 1H), 7.27 (dd, J = 7.5, 2.5 Hz, 1H), 7.24–7.05 (m, 7H), 3.04–2.98 (m, 4H), 2.45 (s, 3H).

^{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.



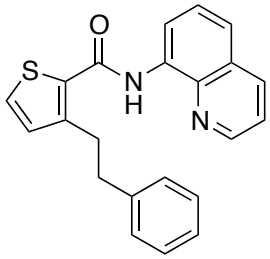
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.40 (s, 1H), 8.84 (dd, J = 7.5, 1.5 Hz, 1H), 8.54 (dd, J = 4.3, 2.0 Hz, 1H), 8.06 (dd, J = 8.3, 2.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.52–7.45 (m, 2H), 7.33–7.25 (m, 3H), 7.15–7.02 (m, 6H), 3.91 (s, 3H), 3.40–3.36 (m, 2H), 3.12–3.09 (m, 2H).

^{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.

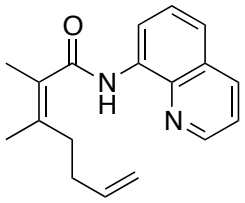
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.46 (s, 1H), 8.86 (d, J = 7.5 Hz, 1H), 8.72 (d, J = 4.0 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.60–7.53 (m, 2H), 7.45 (dd, J = 8.5, 4.0 Hz, 1H), 7.38 (d, J = 5.0 Hz, 1H), 7.27–7.16 (m, 5H), 6.94 (d, J = 4.5 Hz, 1H), 3.46 (t, J = 8.3 Hz, 3H), 3.09 (t, J = 8.0 Hz, 3H).

^{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.



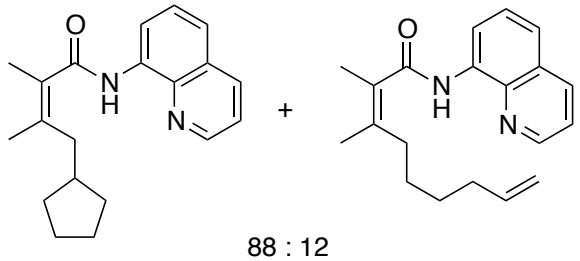
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.86–8.80 (m, 2H), 8.16 (dd, J = 8.3, 2.0 Hz, 1H), 7.57–7.50 (m, 2H), 7.45 (dd, J = 8.3, 4.5 Hz, 1H), 5.80–5.74 (m, 1H), 4.96–4.88 (m, 2H), 2.37–2.31 (m, 4H), 2.02 (s, 3H), 1.80 (s, 3H).

^{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

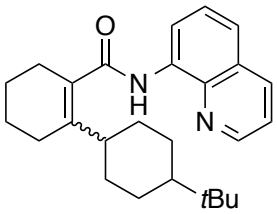
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.85 (d, J = 7.5 Hz, 1H), 8.79 (dd, J = 4.0, 1.5 Hz, 1H), 8.16 (dd, J = 8.0, 1.0 Hz, 1H), 7.57–7.27 (m, 2H), 2.32 (d, J = 7.5 Hz, 2H), 2.28–2.01 (m, 1H), 2.01 (s, 3H), 1.79 (s, 3H), 1.72–1.66 (m, 2H), 1.59–1.31 (m, 4H), 1.15–1.09 (m, 2H).

^{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).

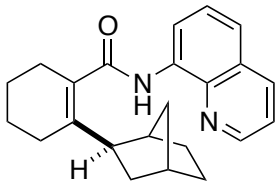
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 148.1, 142.9, 138.5, 136.3, 134.8, 129.5, 128.0, 127.4, 121.5, 116.5, 47.7, 42.9, 42.8, 37.1, 32.3, 31.4, 27.9, 27.7, 27.6, 27.6, 27.5, 27.5, 27.4, 27.0, 25.4, 24.1, 23.7, 22.6, 22.5, 22.4, 22.3.

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)

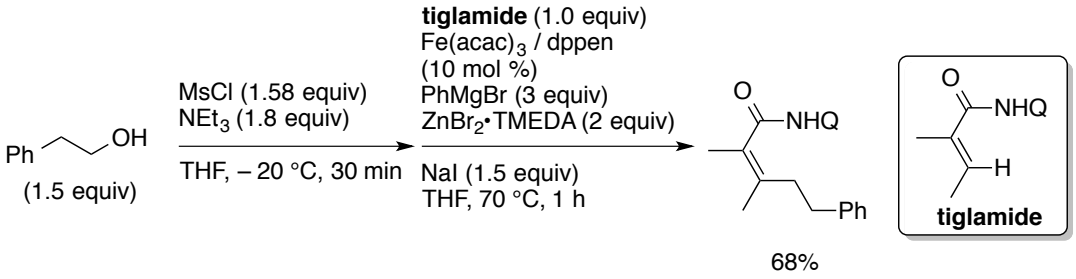
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.80–8.73 (m, 2H), 8.09 (dd, J = 8.5, 1.5 Hz, 1H), 7.57–7.37 (m, 3H), 2.58 (dd, J = 8.0, 7.8 Hz, 1H), 2.38–2.28 (m, 2H), 2.14–2.00 (m, 4H), 1.71–0.79 (m, 12H).

^{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.

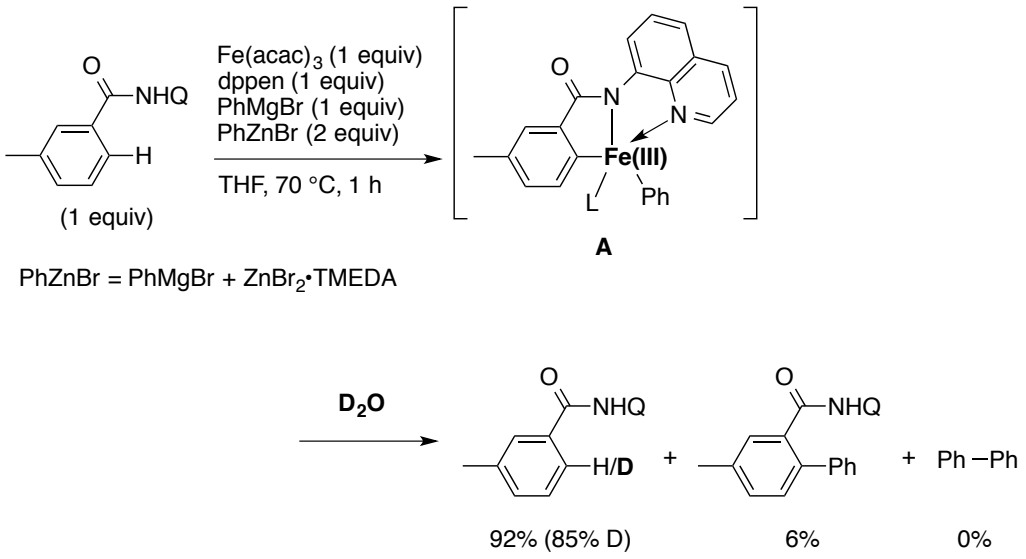
Procedure of the reaction using *in situ* generated alkyl mesylate (eq. 14)



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

[1] (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Shultz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470. (b) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245–2267. (c) Wang, J.-R.; Manabe, K. *Synthesis* **2009**, 1405–1427.

[2] Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry. A Century of Discovery.* Marcel Dekker, New York, **1984**.

[3] (a) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501–1507. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556.

[4] Selected examples: (a) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 238–242. (b) Prades, A.; Corberán, R.; Poyatos, M.; Peris, E. *Chem. Eur. J.* **2009**, *15*, 4610–4613. (c) Wang, B.-Q.; Xiang, S.-K.; Guan, B.-T.; Hu, P.; Zhao, K.-Q.; Shi, Z.-J. *Tetrahedron Lett.* **2008**, *49*, 4310–4312. (d) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033–1037. (e) Liu, J.; Muth, E.; Flörke, U.; Henkel, G.; Merz, K.; Sauvageau, J.; Schwake, E.; Dyker, G. *Adv. Synth. Catal.* **2006**, *348*, 456–462. (f) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691–695. (g) Mühlthau, F.; Stadler, D.; Goeppert, A.; Olah, G. A.; Prakash, K. S.; Bach, T. *J. Am. Chem. Soc.* **2006**, *128*, 9668–9675. (h) Choudhury, J.; Podder, S.; Roy, S. *J. Am. Chem. Soc.* **2005**, *127*, 6162–6163. (i) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913–3917.

[5] Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

[6] Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667–2722 and references therein.

[7] *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F. Eds; Wiley-VCH, Weinheim, **2004**.

[8] Selected Reviews: (a) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670. (b) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545–1554. (c) Fisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (d) Netherton, M. R.; Fu,

G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532.

[9] See Chapter 1.

[10] Alkylation of C(sp^2)–H bond with alkenes: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826−834. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624−655. (c) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400−402. (d) Ilies, L.; Chen, Q.; Zeng, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221−5223. Reactions with alkyl nucleophiles: (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677− 685. (f) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588−5598. (g) Giri, R.; Thapa, S.; Kafle, A. *Adv. Synth. Catal.* **2014**, *356*, 1395−1411. (h) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232−3234.

[11] Hartwig, J. F. *Organotransition metal chemistry: from bonding to catalysis*; University Science Books: Sausalito, CA, **2010**.

[12] (a) Tremont, S. J.; Rahmen, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759–5760. (b) McCallum, S. S.; Gasdaska, J. R.; Liebeskind, L. S.; Tremont, S. J. *Tetrahedron Lett.* **1989**, *30*, 4085–4088.

[13] They also reported that usage of silver acetate as an oxidant enabled catalytic turnover for palladium.

[14] Intramolecular alkylations of C(sp^2)–H bond have reported: (a) Hennessy, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084–12085. (b) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158–16159.

[15] Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097–6100.

[16] Selected examples for palladium-catalyzed direct alkylation of heteroarenes: (a) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647–650. (b) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160–4163. (c) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360–1363. (d) Ackermann, L.; Barfüßer, S.; Pospech, *Org. Lett.* **2010**, *12*, 724–726.

[17] Nichel-catalyzed alkylation of heteroarenes using alkyl-electrophiles with β-hydrogen: Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061–3064.

[18] Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972.

[19] Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850–4853.

[20] Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531–539.

[21] Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194–13197.

[22] Reactions with primary alkyl halides are shown: Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu, R.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 11574–11577.

[23] Pd-cat. alkylation of pyridine *N*-oxides using secondary alkyl halides: Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616–619.

[24] Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048.

[25] Ruthenium-catalyzed *meta*-alkylation using secondary alkyl halides is also reported: Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884.

[26] (a) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428–429. (b) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251–8254. (c) Punji, B.; Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem. Eur. J.* **2013**, *19*, 10605–10610. (d) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279–9282.

[27] (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308–5311. (b) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 2477–2480.

[28] See Chapter 2 and Chapter 3.

[29] Selected examples: (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687. (b) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett*, **2005**, 1794–1798. (c) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297–1299. (d) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955–3957. (e) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822–2823. (f) Bica, K.; Garetner, P. *Org. Lett.* **2006**, *8*, 733–735. (g) Rao Volla, C. M.; Vogel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1305–1307. (h) Ito, S.; Fujiwara, Y.-i.; Nakamura, E.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4306–4309.

[30] (a) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491–493. (b) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943–1946.

[31] (a) Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755–17757. (b) Asako, S. Ph.D. thesis.

[32] Ichikawa, S. Graduation thesis.

[33] Do, H.-Q.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288–16291.

[34] There has been only one example, where alkyl tosylate was used as an alkyl donor in C–H alkylation. See ref. 26d.

[35] (a) Ilies, L.; Okabe, J.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2010**, *12*, 2838–2840. (b) Ilies, L.; Yoshida, T.; Nakamura, E. *J. Am. Chem. Soc.* **2012**, *134*, 16951–16954.

[36] Investigation in Chapter 2 revealed that the C–H activation becomes slow at lower temperature.

[37] *Handbook of Grignard Reagents*; Silverman, G. S.; Rakita, P. E., Eds.; Marcel Decker: New York, **1996**.

[38] Impurity of the ethereal solvent sometimes kill the reactivity of iron: Ilies, L.; Kobayashi, M.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2012**, *354*, 593–596.

[39] See eq. 11.

[40] C–H methylation with high turnover of iron catalyst: Shang, R.; Ilies, L. Nakamura, E. *J. Am. Chem. Soc.* **2015**, *137*, 7660–7663.

[41] Ilies, L.; Konno, E.; Chen, Q.; Nakamura, E. *Asian J. Org. Chem.* **2012**, *1*, 142–145.

[42] See section 4-5.

[43] Phenetylmetal intermediate is amenable to give styrene and metal hydride species.

[44] For an althernative reaction of Fe-cat. *ortho*-allylation using allyl phenyl ether: See ref. 31a.

[45] See the experimental section for details.

[46] (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024. (b) Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 6078–6079.

[47] Ratio of the product was determined by ^{1}H NMR.

[48] Estimated rates of the ring opening of cyclopropylmethyl radical and radical

cyclization of 5-hexenyl radical are 1.3×10^8 and 1.0×10^5 respectively, at 25 °C see ref. 46a.

[49] Adams, C. J.; Bedford, R. B.; Carter, E. C.; Gower, N. J.; Haddow, M. F.; Harvey, J. N.; Huwe, M.; Cartes, M. Á.; Mansell, S. M.; Mendoza, C.; Murphy, D. M.; Neeve, E. C.; Nunn, J. *J. Am. Chem. Soc.* **2012**, *134*, 10333–10336.

[50] Bedford, R. B. *Acc. Chem. Res.* **2015**, *48*, 1485–1493.

[51] Asako, S.; Shang, R. Ilies, L.; Nakamura, E. unpublished data.

[52] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2924.

[53] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics,* **1996**, *15*, 1518–1520.

[54] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890–891.

[55] (a) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342–9345. (b) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043–6046. (c) Yang, Y.; Shi, L.; Zhou, Y.; Li, H.-Q.; Zhu, Z.-W.; Zhu, H.-L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6653–6656. (d) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237–18240. (e) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797–9804. (f) Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755–17757. (g) Rouquet, G.; Chatani, N. *Chem. Sci*. **2013**, *4*, 2201–2208.

[56] (a) Suri, S.; Marcischak, J. C. *Org. Prep. Proc. Int*. **2013**, *45*, 154–161. (b) Burns, D. H.; Miller, J. D.; Chan, H.-K.; Delaney, M. O. *J. Am. Chem. Soc.* **1997**, *119*, 2125–2133. (c) Ankner, T.; Hilmersson, G. *Org. Lett*. **2009**, *11*, 503–506. (d) Barnett, C. J.; Wilson, T. M.; Wendel, S. R.; Winningham, M. J.; Deeter, J. B. *J. Org. Chem.* **1994**, *59*, 7038–7045. (e) Poth, D.; Wollenberg, K. C.; Vences, M.; Schults, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2187–2190. (f) Roberts, D. D. *J. Org. Chem.* **1997**, *62*, 1857–1859. (g) Patent: WO2007/87488 A2, **2007**. (h) Galynker, I.; Still, W. C. *Tetrahedron Lett.* **1982**, *23*, 4461–4464. (i) Spiniello, M.; White, J. M. *Org. Biomol. Chem.* **2003**, *1*, 3094–3101. (j) Blasco, I.; Prez, H.; Guijarro, A. *J. Phys. Org. Chem.* **2015**, *28*, 388–395.

Chapter 5.

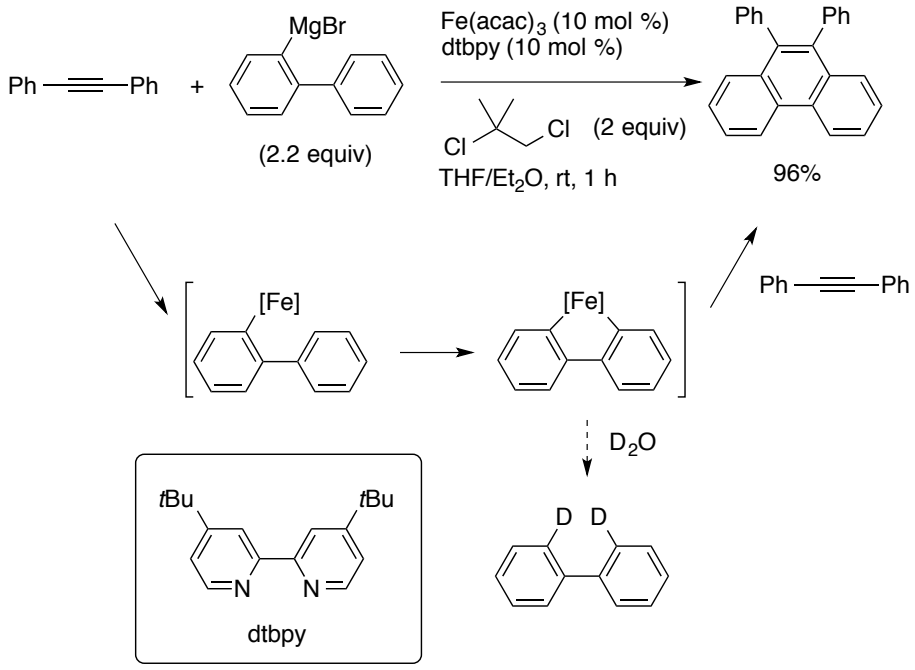
Iron-Catalyzed Coupling Reactions of Amides with Multiple Bonds through C–H Bond Activation

5-1. Introduction

• Iron-catalyzed reaction of aromatic and olefinic substrates with multiple bonds through C(sp^2)–H bond activation

Directed functionalization of C(sp^2)–H bond using alkenes and alkynes provides a facile construction of complex molecules such as fused aromatics and heterocyclic molecules, which can be utilized for tremendous applications.[1] While iron-catalyzed reaction of alkenes[2] and alkynes[3] with organometallic reagents has been widely investigated,[4] reactions through C(sp^2)–H bond activation are very rare. There have been several reports including one by Nakamura and coworkers, which describe the syntheses of fused aromatics such as phenanthrene and naphthalene by reaction of an aromatic Grignard reagent through intramolecular C(sp^2)–H bond activation generating to generate a biaryl ferracycle, followed by reaction with an internal alkyne (Scheme 1).[5,6] However, the reactivity of the ferracycle is difficult to control due to its insufficient stability, which results in poor substrate scope and chemoselectivity. Therefore increasing the stability of the organoiron intermediate is considered to be the key to improve the reaction efficiency.

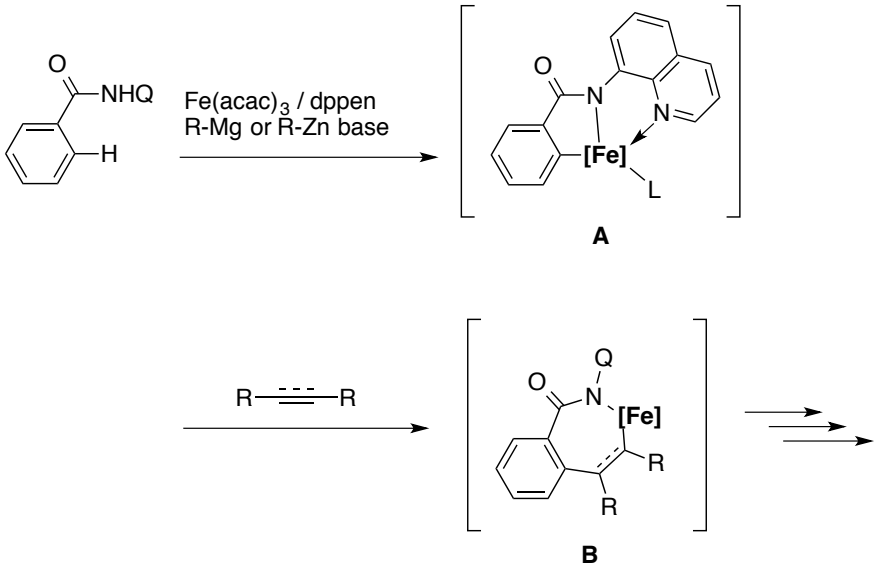
Scheme 1. An example of iron-catalyzed activation of a C(sp^2)–H bond, followed by reaction with alkyne



• Possibility for the development of directed functionalization of a C(sp^2)–H bond with multiple bonds

In the previous chapters, I described the high stability and reactivity of an organoiron species generated through C(sp^2)–H bond activation of an amide possessing a bidentate directing group with assistance of a diphosphine ligand, and the reaction of this species with electrophiles with suppression of undesired side reactions. I hypothesized that the bidentate amide/diphosphine ligand system for organoiron would also enable coupling with multiple bonds such as alkenes and alkynes, which would provide various reaction modes. Thus, as shown in Scheme 2, the organoiron **A** was hypothesized to react with multiple bonds to generate **B** through a carbometalation pathway, and **B** could be used as a key intermediate for further transformations.

Scheme 2. Working hypothesis for iron-catalyzed coupling of amides with alkynes



• Reactions described in this chapter

In this chapter, I describe investigations of the reaction of amides with multiple bonds through directed C(sp^2)–H bond activation (Figure 1). I developed the *ortho*-alkylation and alkenylation of aromatic amides using terminal olefins such as styrene with complete linear selectivity, reacton that proceeds through a carbometalation pathway producing an alkylmetal intermediate. Reactions with internal alkynes enabled several reaction pathways producing indenones, alkenylated amides and isoquinolones, through an alkenylmetal intermediate with switchable reactivity. A reaction using olefinic amides and unsymmetrical alkynes under oxidative conditions produced 2-pyridones with high regioselectivity, which illustrates the sensitivity of organoiron to sterics.

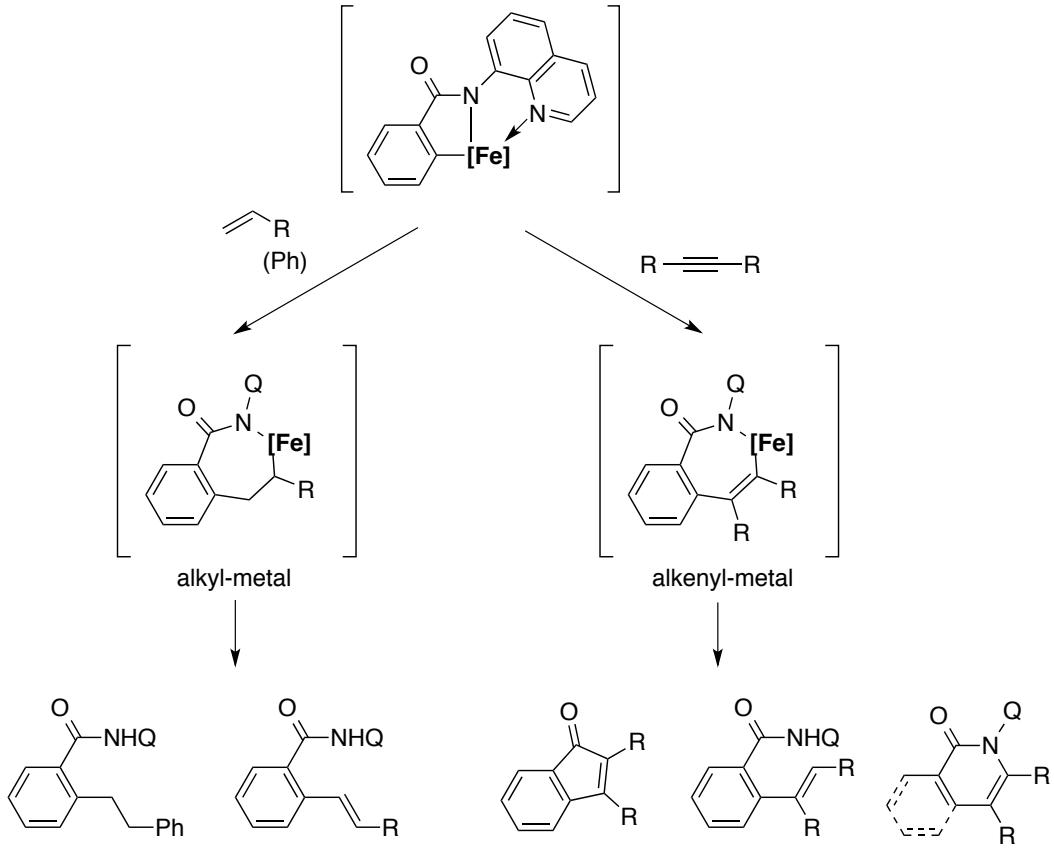
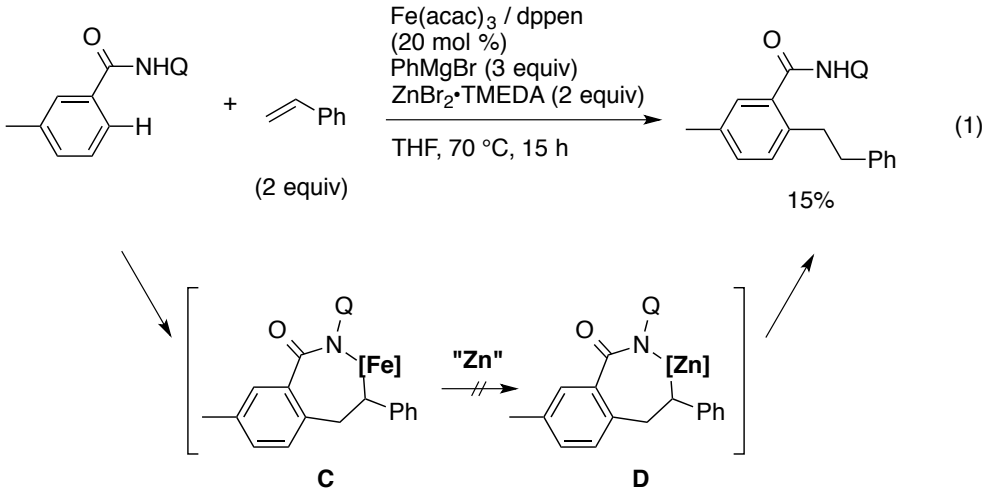


Figure 1. Overview of this chapter: reaction using multiple bonds as coupling partners

5-2. Reaction of amides with styrene for alkylation and alkenylation

• Initial discovery of directed alkylation of a C(sp^2)–H bond using styrene

Since the pioneering work by Murai and coworkers,[7] the *ortho*-alkylation of C–H bond using olefins[8] is a valuable method for alkylation, with respect to its high atom-economy as well as low price and wide availability of olefins. To achieve such an alkylation using iron catalysis, a reaction was performed using styrene as the coupling partner and a monoorganozinc as the base, to produce the desired product in 15% yield, which means the reaction stops without turnover of the catalyst (eq. 1). It can be considered that acceleration of transmetalation step from organoiron **C** to organozinc **D** might be a key to improve the reaction efficiency.



It is necessary for TMEDA to dissociate from zinc in order to accelerate the transmetalation forming **D**, because two coordination sites of zinc will be occupied by a quinolylamide (Figure 2). According to this hypothesis, a reaction using $ZnBr_2$ instead of $ZnBr_2$•TMEDA was performed, and the reaction successfully proceeded with catalyst turnover to produce the desired product in 65% yield (eq. 2). The existence of the intermediate **D** was supported by deuterium incorporation into the product after quenching with D_2O. The reaction provided an *ortho*-alkylated amide with complete linear selectivity.[8]

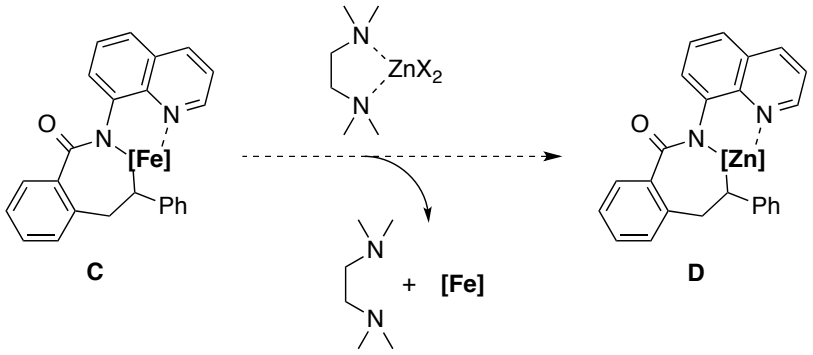
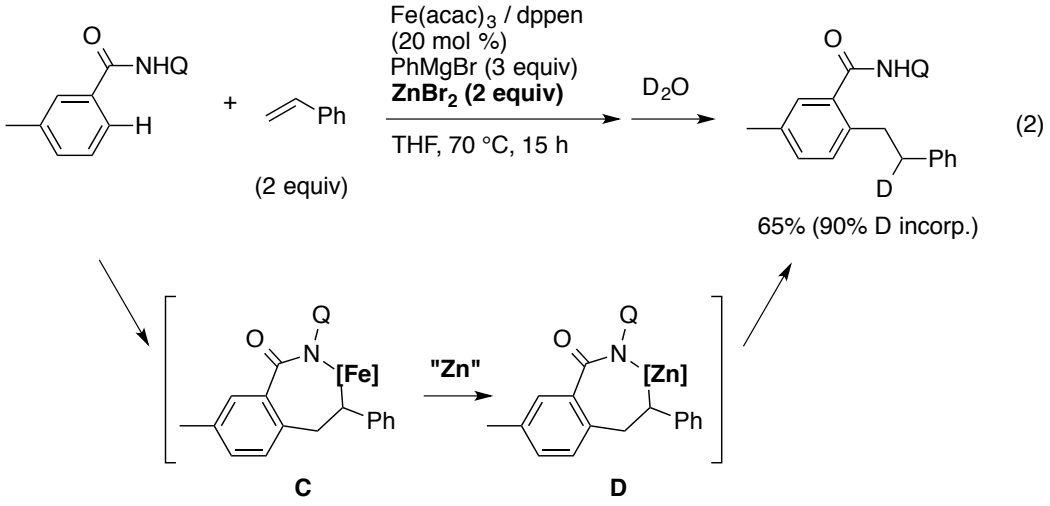
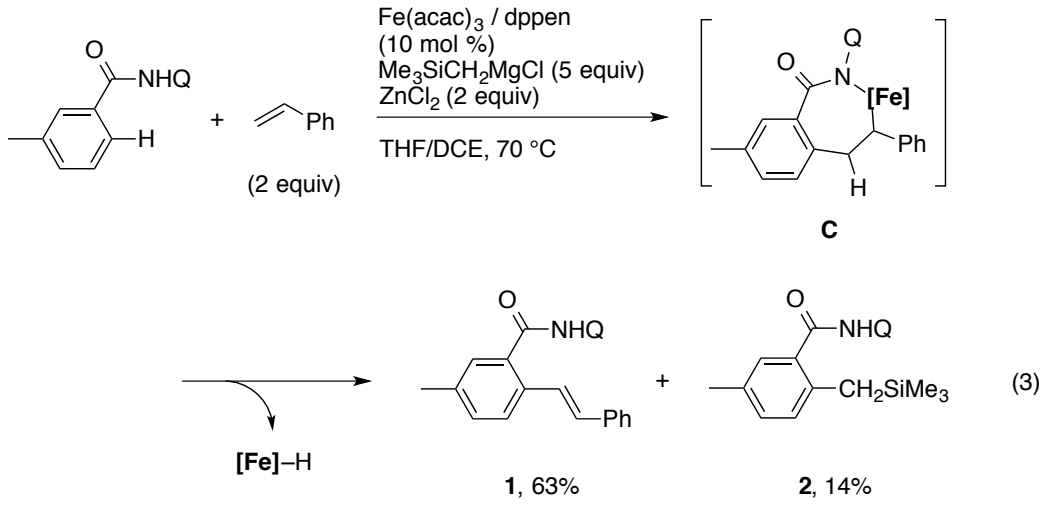


Figure 2. Possible effect of TMEDA for transmetalation



• *Ortho*-alkenylation of C–H bond with styrene under oxidative conditions

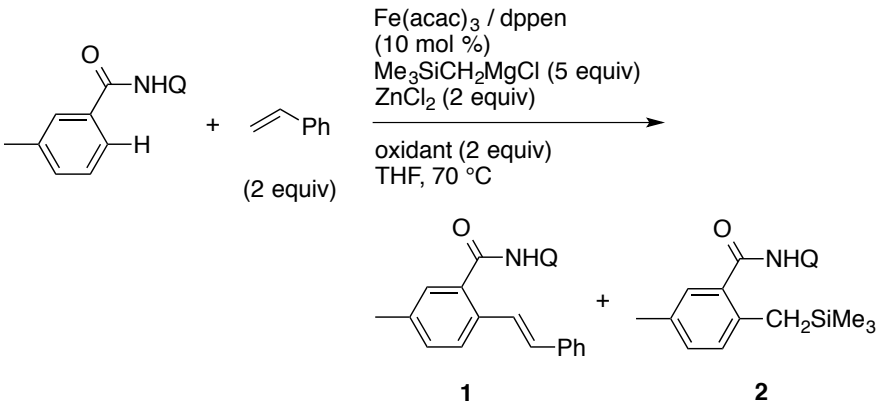
The reactivity of the alkyliron **C** was further explored, and I discovered that acceleration of *β*-hydride elimination from **C** under oxidative conditions affords an *ortho*-alkenylated product.[9] Thus, the reaction using $(Me_3SiCH_2)_2Zn$, prepared *in situ* from Me_3SiCH_2MgBr and $ZnCl_2$, with excess 1,2-dichloroethane as an oxidant enabled olefination of amide (product **1**) possibly through *β*-hydride elimination from **C**, which is a rare case of Heck-type reaction under iron catalysis (eq. 3).[2,4,10]

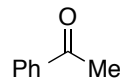
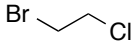
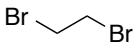
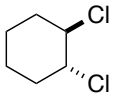
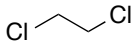
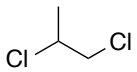
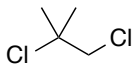
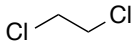


The reaction conditions were further investigated, and I found that the nature of the oxidant was crucial for product selectivity (Table 1). When using 1,2-dichloroethane as a solvent amount, side poduct **2**[11] was generated, possibly through oxidative coupling of the amide with the Griganrd reagent (entry 1). An oxidant is necessary for the reaction to regenerate active iron species from an iron-hydride species generated through *β*-hydride elimination (entry 2).[2] Acetophenone might be an effective hydride acceptor according to the literature,[2] but it was ineffective for current reaction conditions (entry 3). While bromoalkanes such as 1-bromo-2-chloroehtane and 1,2-dibromoethane were ineffective as oxidants (entries 4–5), dichloroalkanes were effective (entry 6–9). 1,2-Dichloroethane (entry 7) and 1,2-dichloropropane (entry 8) showed similar efficiency to turnover the catalyst, although using them in a solvent

amount induced side reaction (entry 1). DCIB (1,2-dichloroisobutane) promoted the reaction with poor product selectivity (entry 9).[12] TMEDA as an additive accelerated oxidative alkylation to afford **2** and retarded the desired pathway (entry 10). Thus I concluded that 1,2-dichloroethane and 1,2-dichloropropane are the most effective oxidants for the directed alkenylation of amides using styrene as a coupling partner.

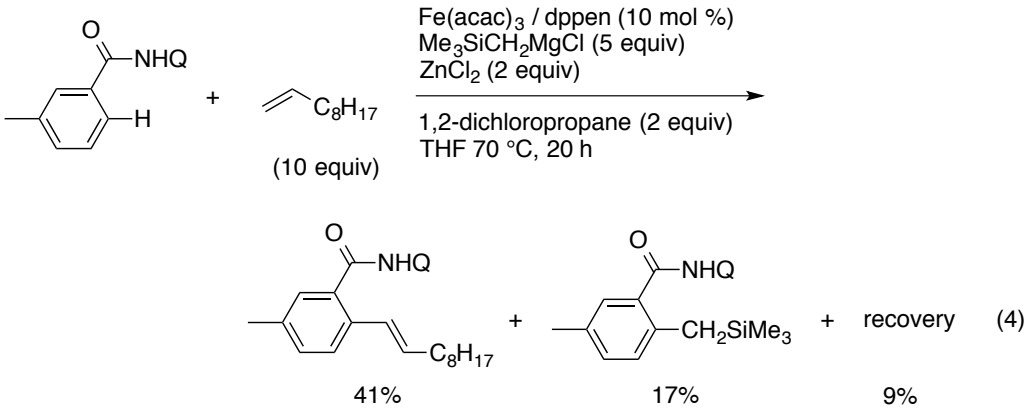
Table 1. Effect of oxidant for oxidative alkenylation with styrene



entry	oxidant	**1** (%)	**2** (%)	recov (%)
1	DCE (solvent)	63	14	0
2	without oxidant	18	trace	82
3		0	0	quant
4		19	8	trace
5		trace	26	20
6		68	8	20
7		88	trace	11
8		80	2	21
9		42	9	13
10	 (with TMEDA)	15	36	5

Encouraged by the result, I attempted to achieve a more challenging reaction: *ortho*-olefination of amides using unactivated alkenes such as 1-decene (eq. 4). Although the reaction was slow, I obtained the corresponding product in 41% yield with linear selectivity, along with an alkylated side product in 17% yield.[13] Improving the

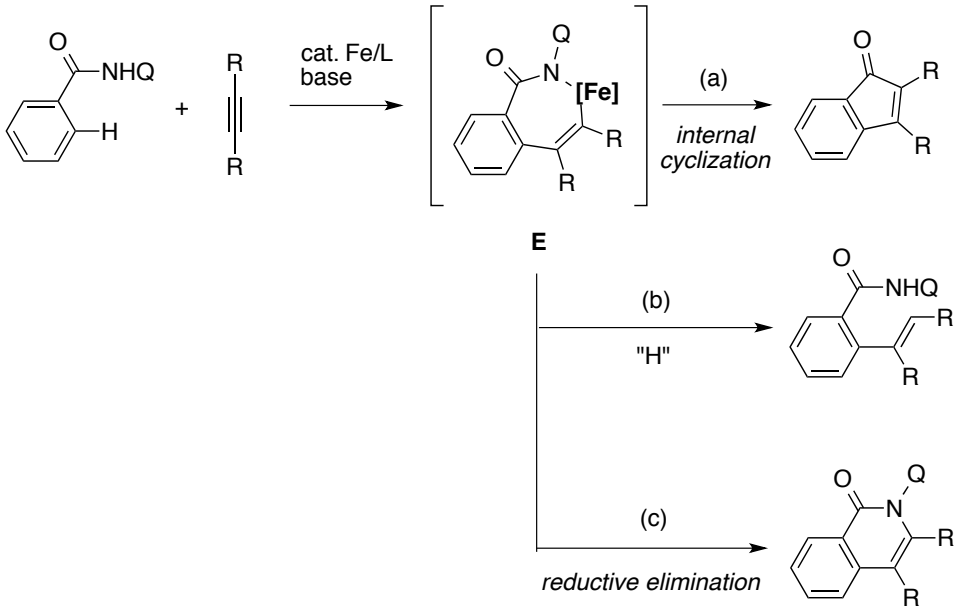
yield and product selectivity will be the subject of further studies.



5-3. Overview of reaction with internal alkynes: reactivity switch of alkenylmetal intermediate

Considering the reaction mechanism of alkylation/alkenylation through alkyliron **C** described above, a similar reaction using an alkyne instead of alkene would be feasible, through generation of an alkenylmetal intermediate **E** (Scheme 3). The intermediate **E** may produce several different products by switching the reactivity: (a) internal nucleophilic addition to the carbonyl group, followed by hydrolysis will produce indenone derivatives; (b) reaction with a hydrogen source will afford alkenylated amides; (c) reductive elimination to form C–N bond will produce isoquinolone derivatives.[14] According to this strategy, I initiated an investigation on the reaction of amides using alkynes by controlling reactivity of the intermediate **E**, as described in the next sections.

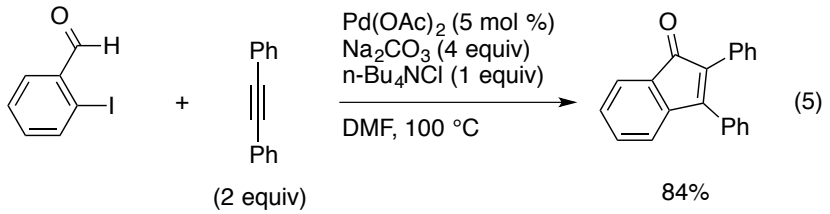
Scheme 3. Possible reaction pathways of alkenylmetal intermediate

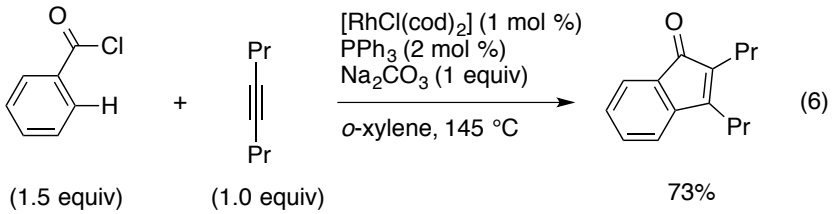


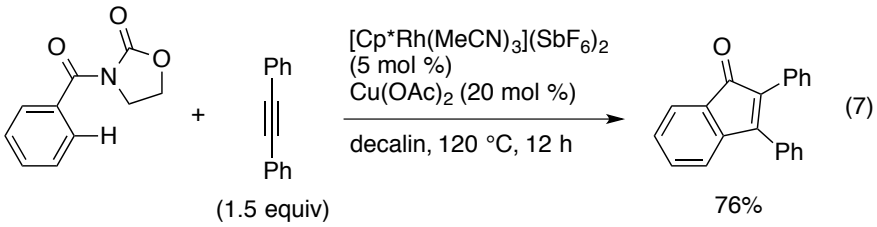
5-4. Internal cyclization producing indenones

• Indenone as a useful precursor of π-extended molecules

Indenone is a conjugated aromatic compound possessing an internal ketone, and it is a useful precursor for a variety of complex molecules such as steroids,[15] hormones,[16] and π-extended molecules.[17] Traditionally it can be prepared through intramolecular Friedel-Crafts acylation or coupling between α-halo-benzoyl chloride and alkynes (eq. 5).[18] However, these starting materials are typically difficult to prepare. There is an alternative synthetic methodology through rhodium-catalyzed *ortho* C–H bond activation of an aromatic substate directed by aldehyde[19] or acidhalide[20] to form a rhodacycle intermediate, followed by alkyne insertion to generate an indenone with poor substrate scope (eq. 6). A similar reaction starting from a more accessible amide substrate is desirable, but such reactions have been scarcely investigated: only one example is known using a specially designed amide as a substrate (eq. 7).[21,22]

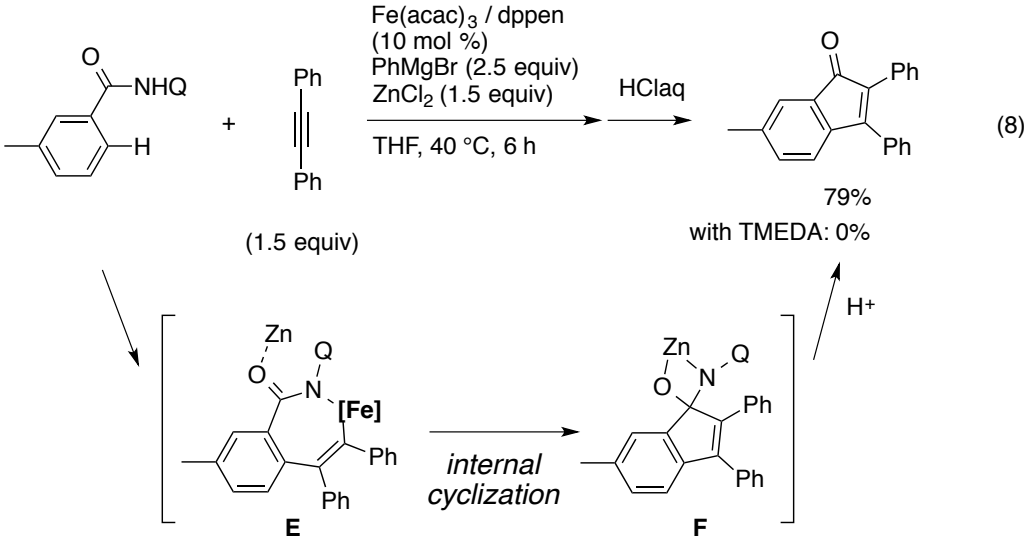






• Initial discovery for indenone synthesis using amides and alkynes

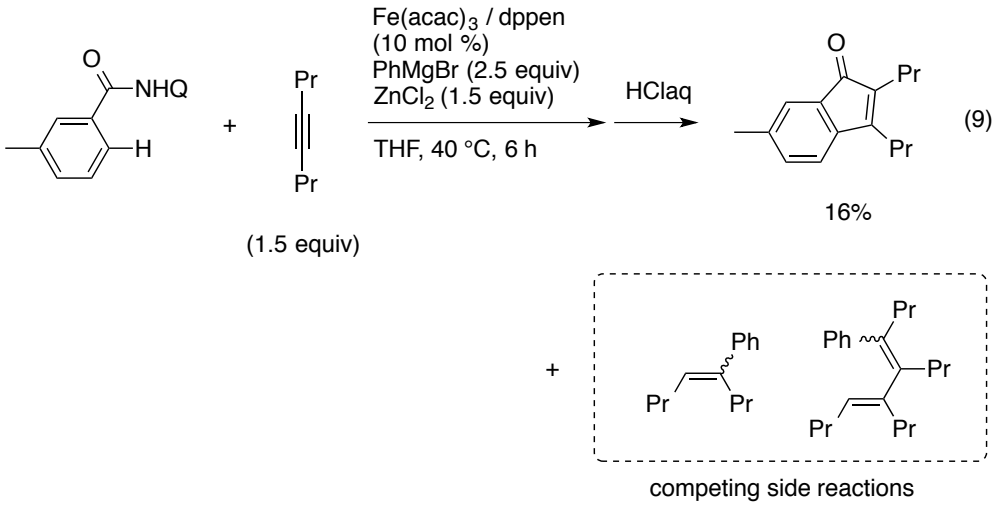
A reaction between an amide and an internal alkyne was performed using monoarylzinc halide as a base, conditions similar to those used for alkylation with styrene. Fortunately the reaction afforded the desired indenone product in 79% yield after quenching the reaction with aqueous HCl (eq. 8).[23] The reaction might proceed through formation of alkenylmetal intermediate **E**, followed by zinc-mediated internal cyclization to afford the hemiaminal intermediate **F**,[24] which is then hydrolyzed to produce the final product. TMEDA as an additive completely shut down the reaction (a possible reason is shown in the next section).

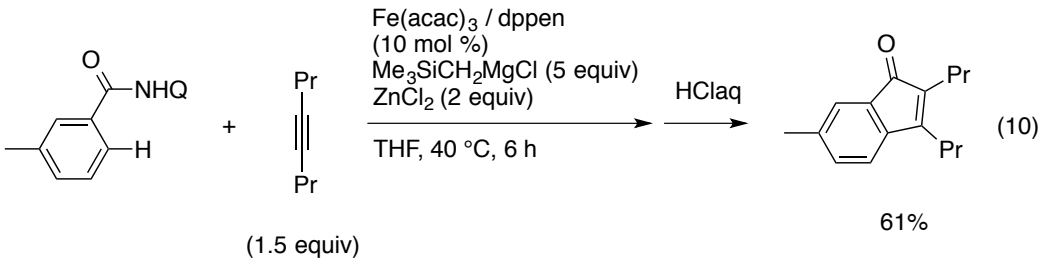


• Usage of dialkylzinc base for the reaction using dialkylalkynes

Encouraged by the initial result with arylalkyne, alkylalkyne was used as a

coupling partner. However, the reaction using dialkylalkyne was sluggish, due to competing carbometalation reaction with the arylzinc reagent (eq. 9).[25] To suppress this reaction, I explored an alternative base to promote the formation of 1,2-dialkylindenone while suppressing carbometalation, and finally discovered that $(Me_3SiCH_2)_2Zn$ is an effective base: the desired 2,3-dipropylindenone was obtained in 61% yield using 4-octyne as the coupling partner (eq. 10). Thus, monoarylzinc base and dialkylzinc base were determined to promote desired indenone synthesis through coupling of amides with alkynes.

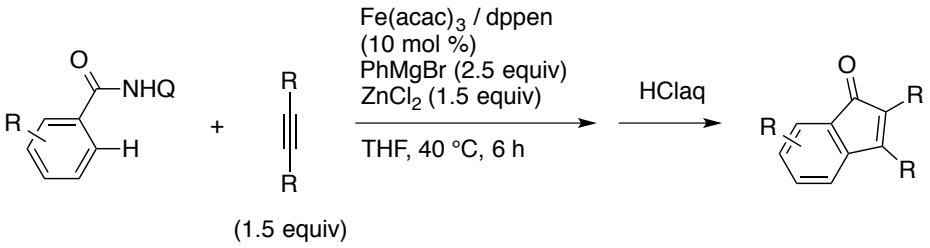


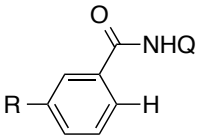
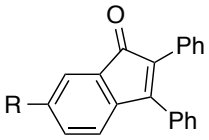
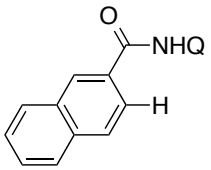
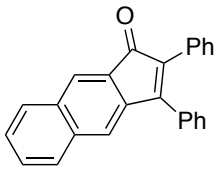
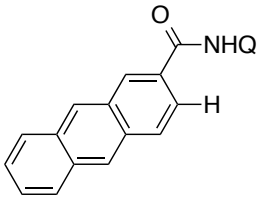
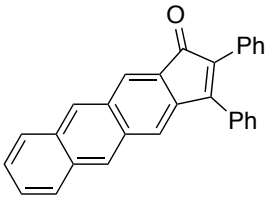
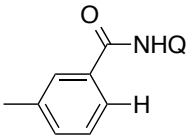
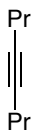
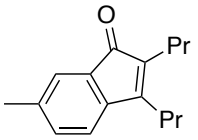


• Substrate scope for indenones

With these optimized reaction conditions in hand, the scope of amides and alkynes for the synthesis of indenone derivatives was then investigated, as summarized in Table 2. 2,3-Diarylindenones could be synthesized in good yield, using either PhZnBr or $(Me_3SiCH_2)_2Zn$ as the base (entries 1 and 2). The reactions of benzamides with electron-donating substituents such as methoxy (entry 3) and dimethylamino group (entry 4) proceeded well, whereas those with electron-withdrawing substituents such as ester became sluggish (data not shown). The reaction with biphenylamide (entry 5), naphthaleneamide (entry 6) and anthraceneamide (entry 7) also proceed well, producing the corresponding indenones that can be precursors for π-extended molecules. 2,3-Dialkylindenones could also be prepared in good yield by using $(Me_3SiCH_2)_2Zn$ base (entry 8), which cannot be achieved by the previous reaction system.[21] Reactions with unsymmetrical alkynes are not successful: producing indenones with poor regioselectivity.

Table 2. Substrate scope for indenone synthesis from the reaction of amides with alkynes



entry	amide	alkyne	product	yield (%)[a]
1				79 (R = Me)
2				73 (R = Me)[b,c]
3				72 (R = OMe)
4				73 (R = NMe_2)
5				69 (R = Ph)
6				70
7				80
8				61[b,c]

See experimental section for detailed reaction conditions.

[a] Yields were determined by isolation.

[b] The reaction was performed using Me_3SiCH_2MgCl (5 equiv) and $ZnCl_2$ (2 equiv) as a base.

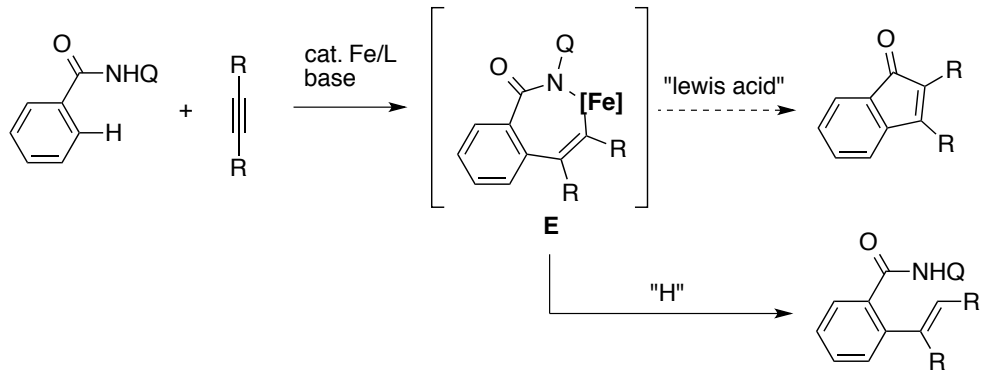
[c] Yield was determined by GC analysis using hexadecane as an internal standard.

5-5. Synthesis of *ortho*-alkenylated amides and isoquinolones

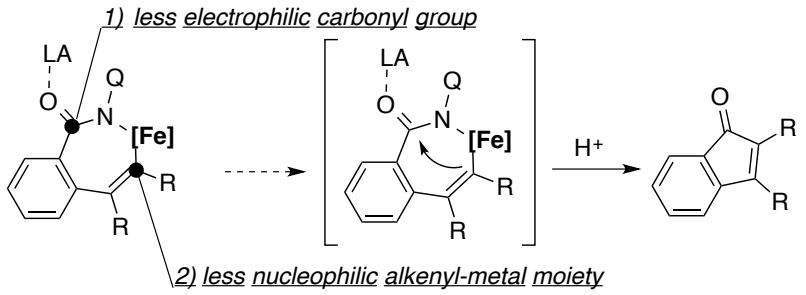
• Strategies to controlling the reactivity of alkenylmetal intermediate for *ortho*-alkenylation

Possible reaction pathways from alkenylmetal intermediate **E** also include the alkenylation of an amide, through reaction of **E** with a hydrogen source ("H") while suppressing the internal cyclization (Scheme 4).[26,27] To achieve this scenario, I considered that two strategies are necessary: (1) decreasing the nucleophilicity of the alkenylmetal species, and (2) decreasing the electrophilicity of the carbonyl group (Scheme 5).

Scheme 4. Strategy for *ortho*-alkenylation of amides



Scheme 5. Two strategies to suppress the internal cyclization leading indenone

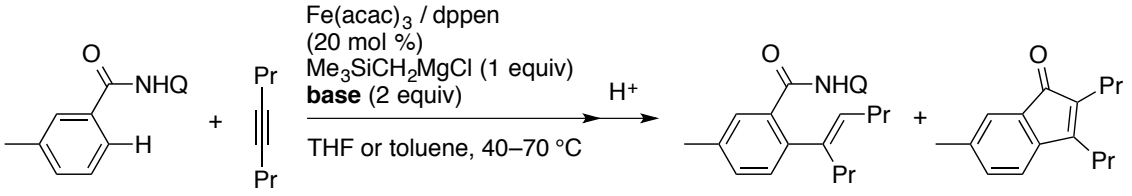


(LA = lewis acid)

• Effect of organometallic bases and additives on product selectivity

According to these strategies, effect of the base was investigated to control the product selectivity (Scheme 6). A reaction using less nucleophilic monoorganozinc base afforded the desired alkenylated amide in 39% yield along with indenone in 27%, which suggests that controlling the selectivity by a base is feasible (entry 2). To further suppress the undesired pathway, $ZnBr_2$•TMEDA complex was used instead of $ZnBr_2$, expecting that the TMEDA would act as a Lewis base to lower the Lewis acidity of zinc (entry 3). The additive effectively suppressed the cyclization, and desired alkenylation reaction proceeded to give the product in 63% yield without any production of the indenone.[28]

Scheme 6. Optimization of the base for *ortho*-alkenylation

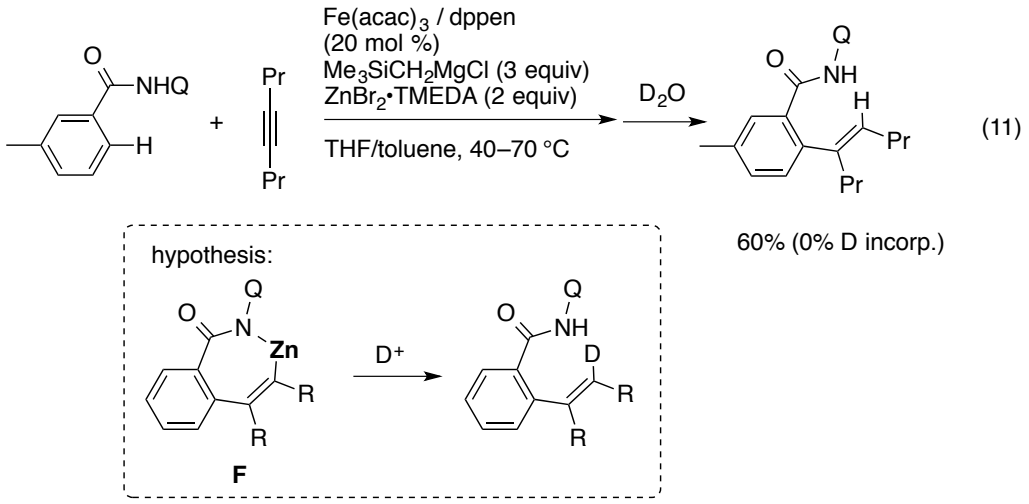


entry				
	1	2 Me_3SiCH_2MgCl / $ZnCl_2$	nd	60%
	2	Me_3SiCH_2MgCl / $ZnCl_2$	39%	27%
	3	Me_3SiCH_2MgCl / $ZnBr_2$•TMEDA	63%	nd

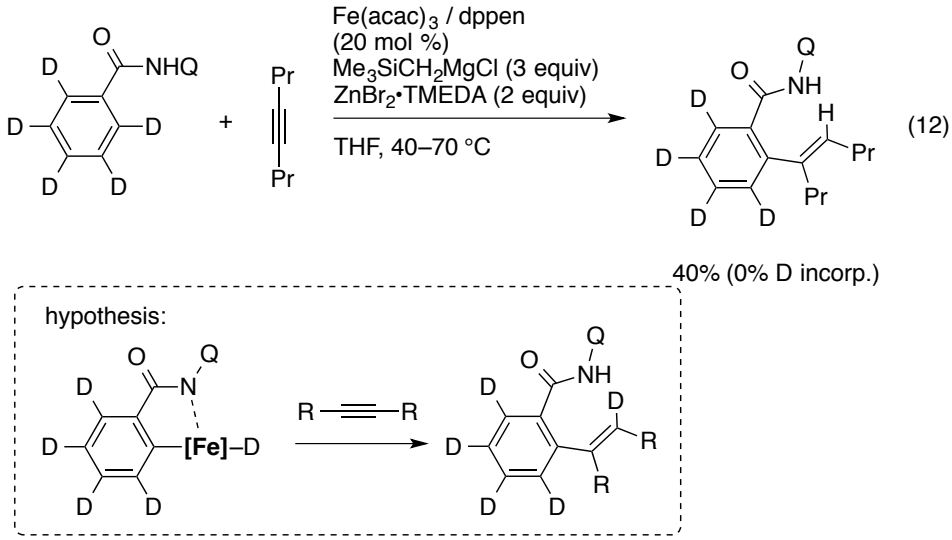
• Origin of hydrogen atom

Next origin of the hydrogen atom was investigated. I quenched the reaction with D_2O, expecting that an alkenylzinc intermediate such as **F** exists, similar with alkyliron **C** in the case of reactions using styrene as coupling partner. However, the product was not deuterated, suggesting that the alkenyliron intermediate **E** might react with a hydrogen source in the reaction mixture, instead of forming **F** (eq. 11). A possibility of hydroarylation pathway through oxidative addition was also denied, because deuterium on the alkenyl position was not observed when pentadeuterated

amide was used as the starting material (eq. 12).[26,27,28] Finally I could not clarify the origin of the hydrogen atom, although abstraction of hydrogen from THF through radical cleavage is one possibility.[29]



(11)



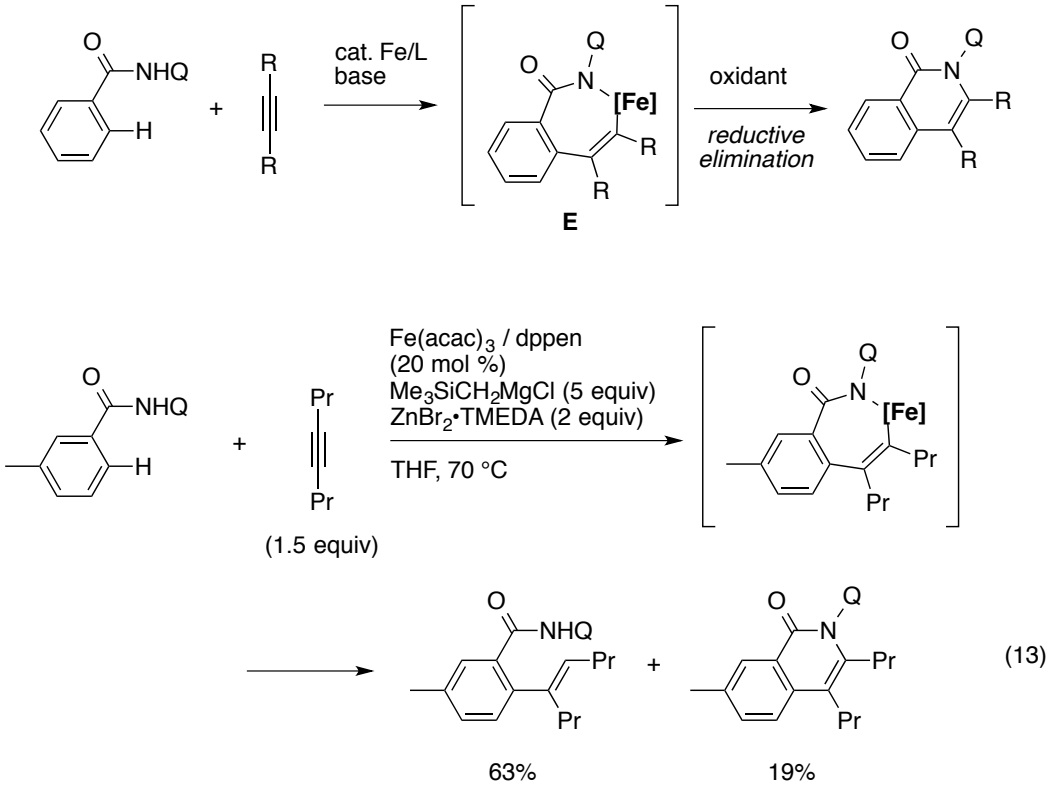
(12)

5-6. Oxidative approach to isoquinolones

• Synthesis of isoquinolones through reductive elimination of the alkenylmetal to form a C–N bond

Another possible reaction pathway of the alkenyliron intermediate **E** is C–N bond forming reductive elimination to afford isoquinolones,[30,31] compounds that exhibit unique bioactivities and are a part structure of in many natural compounds (Scheme 7).[32] A preliminary result of the isoquinolone synthesis was discovered when investigating the alkenylation reaction, where the isoquinolone was generated in a stoichiometric amount to the catalyst (19% yield with 20 mol % of the catalyst) (eq. 13). This result indicates that the iron catalyst is deactivated after reductive elimination.

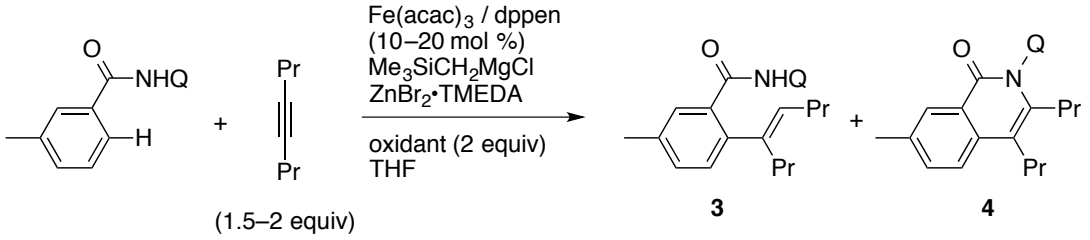
Scheme 7. Strategy to achieve isoquinolone synthesis



• Effect of base and oxidant for the product selectivity

Investigation of the reaction conditions in Table 3 indicates that the choice of base and oxidant highly affects the product selectivity, similar to the previous investigations. 1,2-Dichloroethane was added as an oxidant to accelerate reductive elimination: however, the product selectivity was not improved even at elevated temperature, and **4** was still obtained in a stoichiometric amount (entry 2). Then a diorganozinc base was employed instead of the monoorganozinc base, because previous reports by Nakamura and coworkers suggest that the use of such nucleophilic base under oxidative conditions accelerates reductive elimination through generation of iron ate species.[33] The use of $(Me_3SiCH_2)_2Zn$ as a base dramatically improved the reaction, and afforded the desired isoquinolone in 81% yield without any formation of alkenylated product **3**. Oxidant is crucial for the catalytic turnover, because in the absence of the oxidant, the product **4** was obtained in a stoichiometric amount with respect to the catalyst (entry 4). Decreased temperature (40 °C) improved the mass balance, affording stoichiometric conversion to the isoquinolone product **4** (entry 5).

Table 3. Optimization of reaction conditions for isoquinolone synthesis

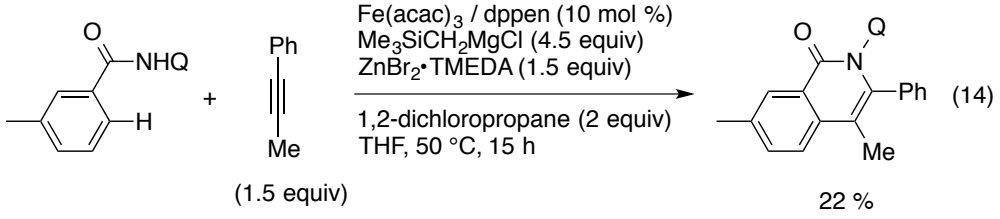


entry	Me_3SiCH_2MgCl (equiv)	$ZnBr_2$•TMEDA (equiv)	oxidant	temp	**3** (%)[a]	**4** (%)[a]
1	3.0	2.0	--	70 °C	63	19
2	3.0	2.0	DCE	100 °C	51	16
3	5.0	1.5	DCE	50 °C	nd	81
4	5.0	1.5	--	50 °C	nd	19
5	4.5	1.5	DCP	40 °C	nd	98[b]

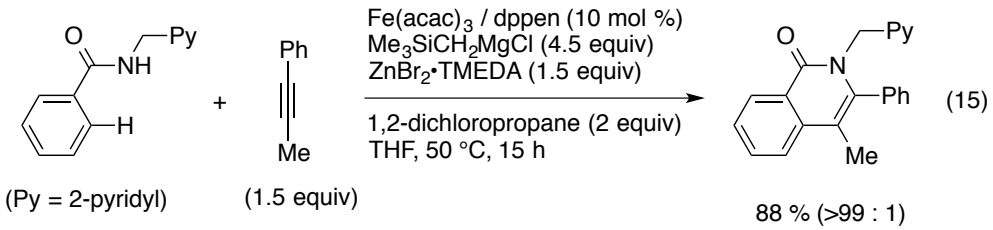
[a] Yields were determined by GC using hexadecane as an internal standard.
[b] isolated yield.

• Reaction with unsymmetrical alkynes

With the optimized reaction conditions in hand, next the reaction using 1-phenyl-1-propyne as an unsymmetrical alkyne was examined. While the reaction became sluggish when using a quinolylamide directing group (eq. 14), a similar reaction using a more flexible picolinylamide directing group afforded the desired isoquinoline in 88% yield with perfect regioselectivity (eq. 15). The 2-pycolinyl directing group can be removed using the methodology reported by Chatani and coworkers.[31e]



regioselectivity was not determined.



(15)

(Py = 2-pyridyl) (1.5 equiv) 88 % (>99 : 1)

5-7. Synthesis of 2-pyridones using olefinic amides

• 2-Pyridone syntheses through coupling of olefinic amides with alkynes

The oxidative cyclization using an olefinic amide as a starting material would produce a 2-pyridone, a molecule that is an ubiquitous structural motif often seen in biologically active compounds and commercially available drugs (Figure 3).[34,35] Among a variety of synthetic approach to these compounds,[36,37] the reaction from amides and alkynes proposed in Fig. 3 would provide a more useful methodology, with respect to the availability of the starting materials and predictable regioselectivity.

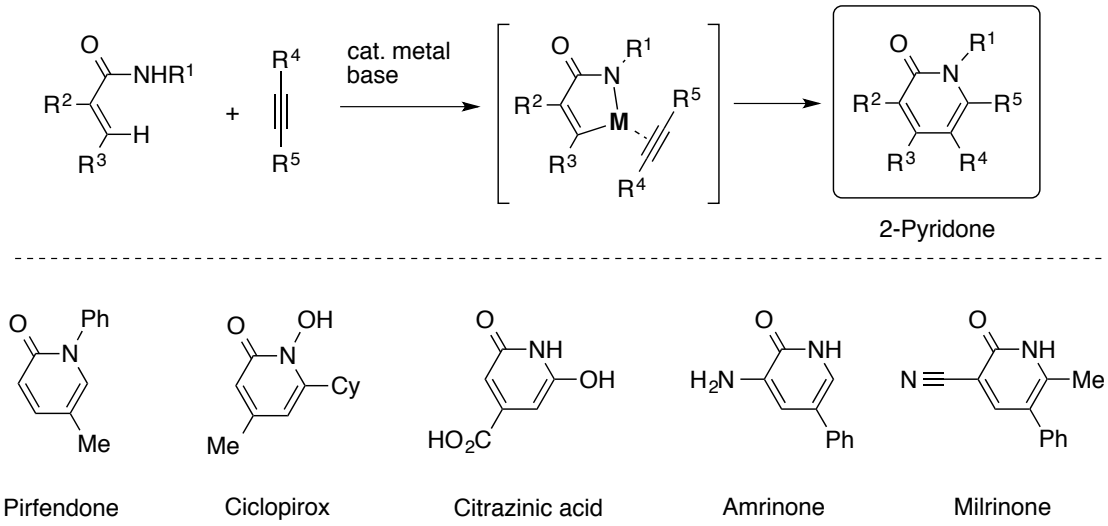
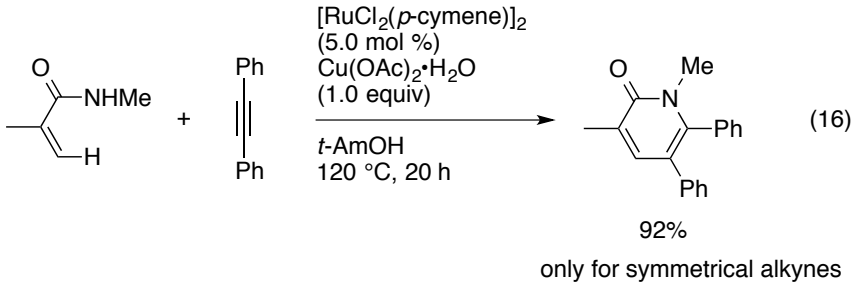
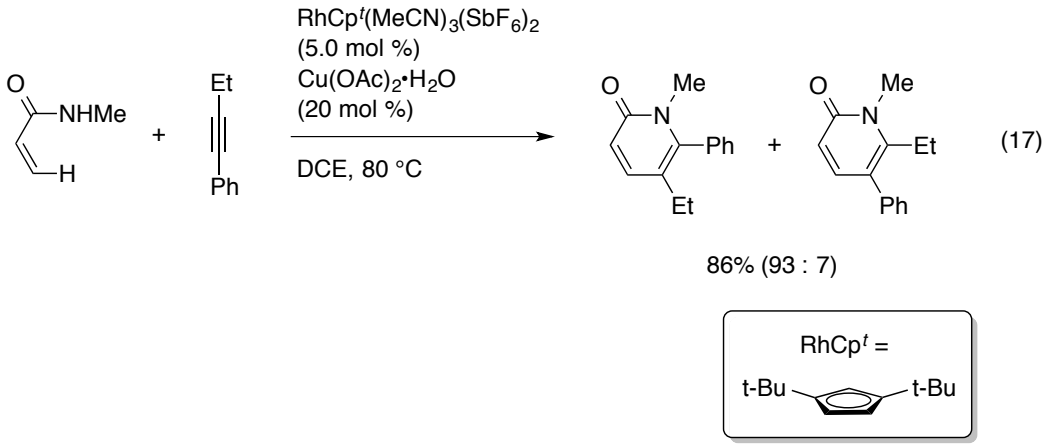


Figure 3. Approach to 2-pyridone and its derivatives as potentially bioactive molecules

While a number of coupling reactions of aromatic amides with alkynes producing isoquinolones have been developed,[31] the similar reaction using olefinic amides has suffered from limited success, because of the difficulty in either activating the C–H bond of olefinic amides, or achieving regioselectivity when unsymmetrical alkynes are used as coupling partners. Reported examples using rhodium or ruthenium catalyst[38] are limited to the use symmetrical alkynes (eq. 16)[38b] anda mixture of regioisomers is produced with unsymmetrical alkynes (eq. 17).[38d] Thus regioselective synthesis of pyridone through the reaction of an olefinic amide and an unsymmetrical

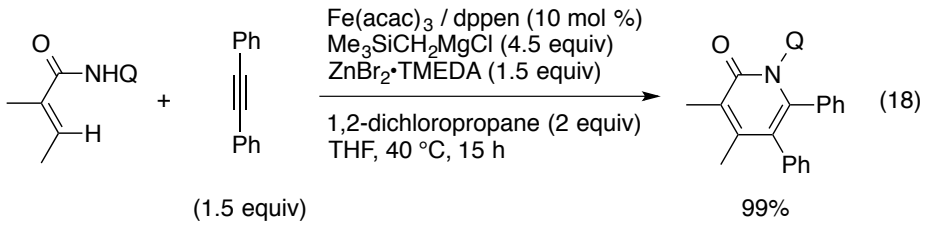
alkyne has remained an unsolved task.





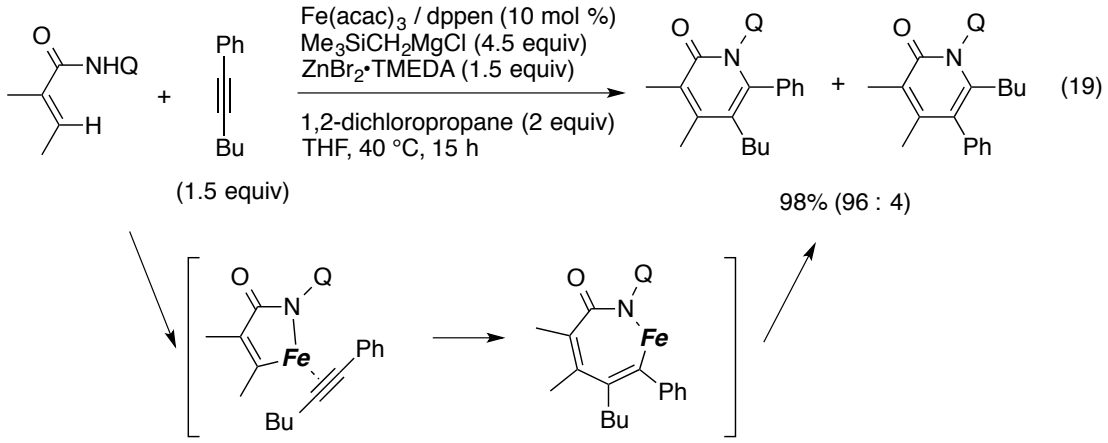
• Discovery of the pyridone synthesis using symmetrical alkynes with iron catalyst

In the previous sections, regioselective synthesis of isoquinolones through coupling of aromatic amides and alkynes under mild reaction conditions was developed (eq. 15), which demonstrates feasibility of the pyridone synthesis using an olefnic amide as a substrate. To this end, initially a reaction was performed using *N*-(quinolin-8-yl)tiglamide as the olefinic amide substrate and diphenylacetylene as a symmetrical coupling partner, to find that pyridone was obtained quantitatively under similar reaction condition to previous one (eq. 18).



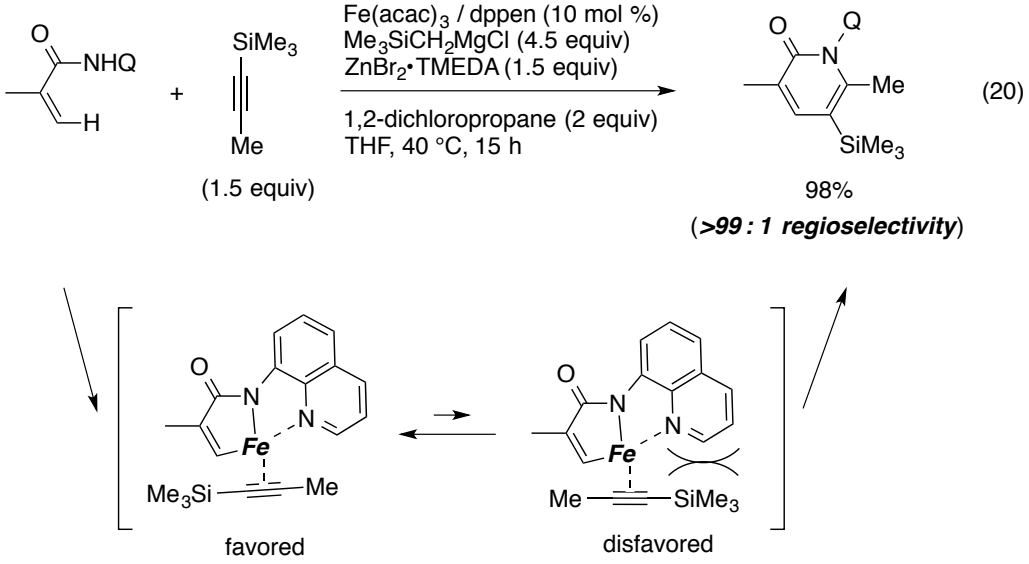
• Reactions with unsymmetrical alkynes

Under these reaction conditions, 1-phenyl-1-propyne was used as an unsymmetrical coupling partner to examine the possibility of regioselective pyridone synthesis, to afford the product with high selectivity (96:4), as determined by ^{1}H NMR spectra and single X-ray crystal diffraction analysis (eq. 19). The regioselectivity seems to be similar to that of iron-catalyzed carbomagnesiation of alkynes reported by Shirakawa, Hayashi and coworkers,[3a,b] where iron is typically placed at the same side with the aryl substituents on the alkyne.



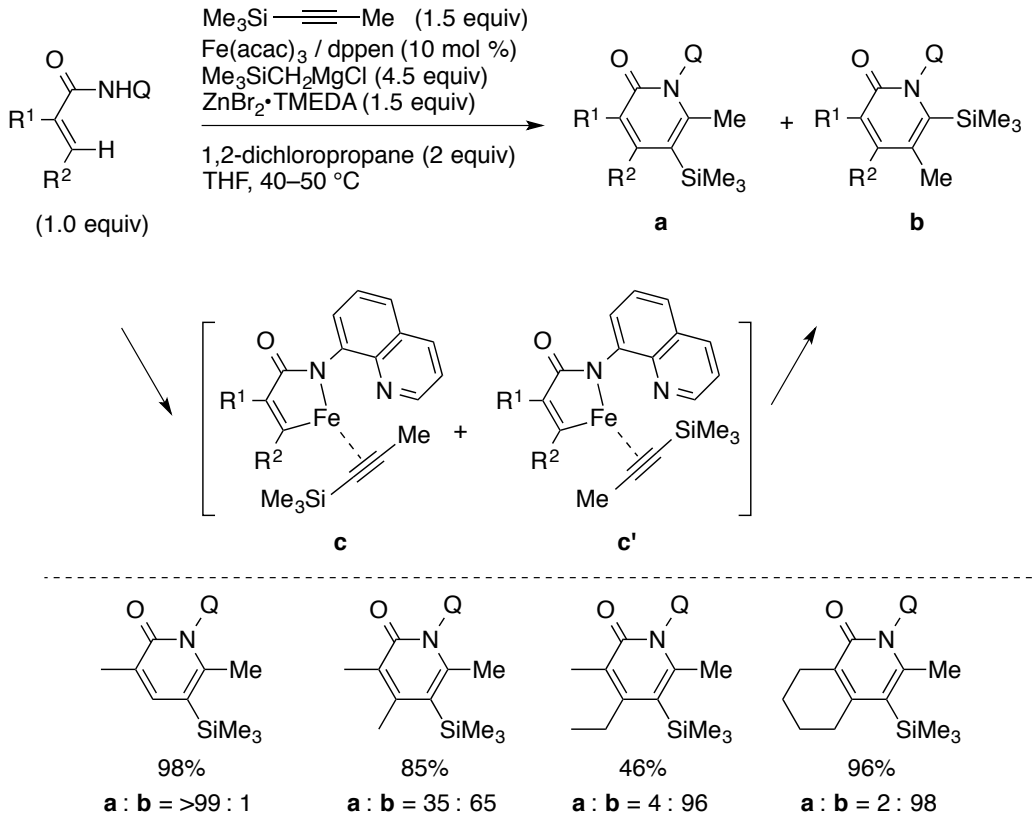
Motivated by this result, I investigated various amides and unsymmetrical alkynes for this reaction with the aim to improve selectivity, and finally I discovered that the steric effect of the substituents on amides and alkynes is crucial for the selectivity. Thus, the reaction using a β-unsubstituted amide with 1-trimethyl-1-propyne as an unsymmetrical coupling partner gave the corresponding product quantitatively

with perfect selectivity (eq. 20). The selectivity is possibly caused by a steric repulsion between the quinoline group on the amide and the trimethylsilyl group on the alkyne, which directs the alkyne to a less congested position.



Amides with different β-substituents were employed for this reaction, to find that the regioselectivity is considerably sensitive to the bulkiness of this substituent (Scheme 8). As discussed previously, the reaction with a β-unsubstitued alkeneamide gave the product with perfect regioselectivity (**a**:**b** = >99:1). A β-methyl substituent caused loss of selectivity and a mixture of regioisomers were obtained (**a**:**b** = 35:65), and a slightly larger ethyl substituent favored **b** over **a** in the ratio of 4:96 (**a**:**b**). Similarly, cyclohexenecarboxamide gave the product with good regioselectivity (2:98). These result can be explained by the sensitivity of the intermediate toward sterics during the alkyne insertion step, distinguishing **c** and **c'**. This might be ascribed to the small radius of the iron atom, which makes the intermediate more compact. Thus, regioselective synthesis of pyridones through coupling of amides with alkynes could be achieved.

Scheme 8. Effect of β-substituents for the selectivity

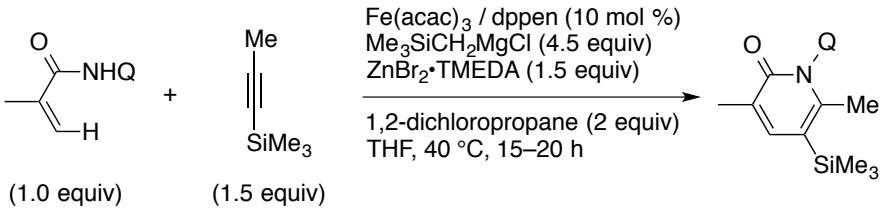


• Investigation of the reaction parameters

The key reaction parameters were investigated based on this reaction conditions (Table 4). In all entries, the pyridone product was obtained with perfect regioselectivity. The choice of the organometallic base largely affected to the efficiency of the reaction. The reaction stopped before completion when a Grignard reagent without zinc additive was used (entry 2), or when monoalkylzinc (Me_3SiCH_2MgCl:$ZnBr_2$•TMEDA = 1:1) was used as a base (entry 3). Dialkylzinc (Me_3SiCH_2MgCl:$ZnBr_2$•TMEDA = 2:1) base worked efficiently to give the product in 91% yield (entry 4), but slight excess of Grignard reagent gave full conversion to the pyridone product (entry 1). This is probably because of generation of iron ate species that accelerates C–N bond forming reductive elimination, as discussed before.[33] The nature of ligands also highly affected to the reaction outcome (entries 5–7). A

dinitrogen ligand (entry 5), and a diphosphine ligand with a saturated backbone (entry 6) were ineffective, which is consistent with previous discoveries.[39] Without the chloroalkane additive, the reaction proceeded in stoichiometric amount to the catalyst, which indicates that the additive is necessary for regenerating the iron active species through oxidation (entry 7). Dichloroethane as an oxidant was slightly ineffective, due to the instability of primary radical species compared with secondary or tertiary ones (entry 8). A bromoalkane oxidant was not effective, possibly because of side reaction with the diorganozinc base (entry 9).[40]

Table 4. Investigation on key parameters



(1.0 equiv) (1.5 equiv)

entry	conditions	yield (%)	recovery (%)
1	standard	98	nd
2	no $ZnBr_2$•TMEDA	33	33
3	Me_3SiCH_2MgCl (2.5 equiv)	40	60
4	Me_3SiCH_2MgCl (4.0 equiv)	91	10
5	bpy ligand	nd	61
6	dppe ligand	43	36
7	no oxidant	13	66
8	DCE oxidant	47	36
9	1,2-dibromopropane oxidant	48	7

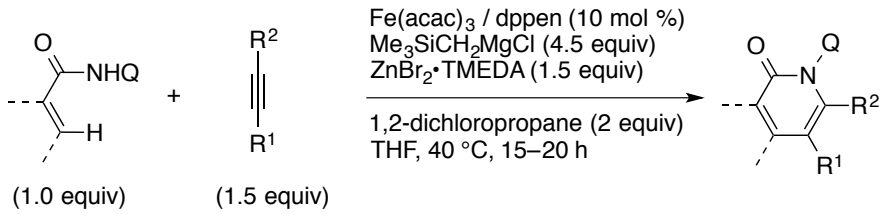
Yields were estimated by GC analysis using hexadecane as an internal standard.

• Scope of 2-pyridones

The scope of the reaction was investigated under optimized reaction

conditions, as summarized in Table 5. Oxygen at the *β*-position of the amide did not interfere with the reaction, and 87% of the desired pyridone was obtained (entry 1). As for the scope of alkynes, symmetrical alkylalkyne (entries 1–2) and aryalkyne (entry 3) both reacted to give the corresponding pyridones quantitatively. The reaction using an unsymmetrical alkyl-aryl alkyne gave the product in 98% yield with good selectivity, as described previously (entry 4). The reaction of *β*-unsubstituted methacrylamide with several 1-trimethylsilylalkynes was also investigated, and the product was obtained with perfect regioselectivity in all cases (entries 5–13). The reaction with an alkyne bearing methyl (entry 5) and phenyl (entry 6) substituents proceeded well. Chloro (entry 7), trifluoromethyl (entry 8), and bromo (entry 9) substituents were well tolerated, although small amount of debrominated product was obtained (entry 9). A conjugated enyne also reacted to give the product in good yield with the alkene part untouched (entry 10). Heteroaryl-substituted alkyne was also reactive, although the yield of the product was moderate (entry 11). Allyl-substituted alkyne could also be used for the reaction, producing a 6-allylated product in moderated yield, which is rare example of the synthesis of allylpyridones (entry 12). Reaction with 1,3-diyne also proceeded to afford a 6-alkynylated pyridone in good yield (entry 13).[41] Remote position of the alkyne from a reactive triple bond in diyne substrate was also unreacted, to produce an alkenylpyridone product in good yield (entry 14).

Table 5. Scope for iron-catalyzed pyridone synthesis from alkeneamides and alkynes



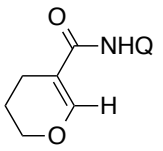
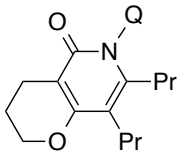
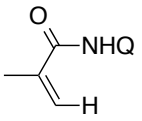
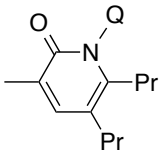
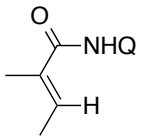
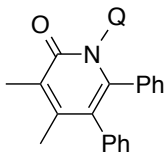
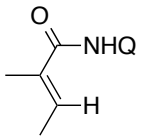
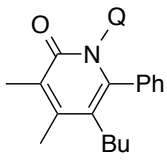
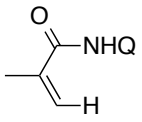
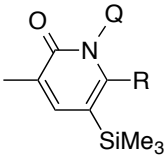
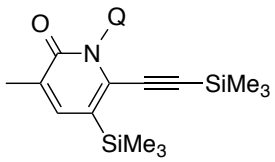
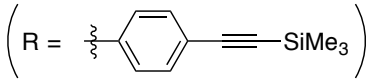
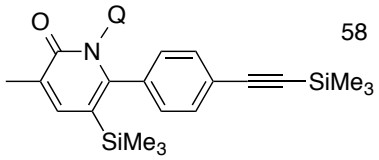
entry	amide	alkyne	product	yield (%)
1				98
2				99
3				99
4				98 (96:4)

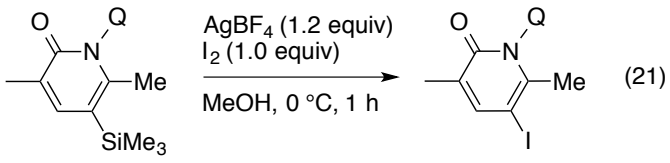
Table 5. (Continued)

5				98 (R = Me)
6				77 (R = Ph)
7				90 (R = 4-ClC_6H_4)
8				93 (R = 4-$CF_3C_6H_4$)
9				68[a] (R = 4-BrC_6H_4)
10				97 (R = 4-E-styryl)[b]
11				49 (R = 2-thenyl)
12				40 (R = allyl)
13				98
14				58

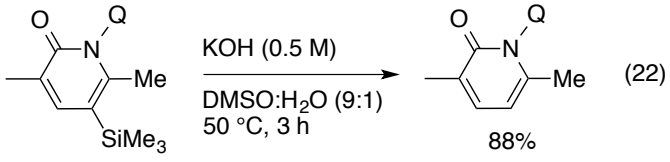
[a] Debrominated product was observed in 9% yield.
[b] *E/Z* = 92:8 of enyne was used as a coupling partner.

• Derivatization of the trimethylsilyl group

The silylpyridone product can be converted to iodopyridone by treating it with silver tetrafluoroborate and iodine in methanol solution (eq. 21). Also, the silylated pyridone can be desilylprotonated by heating a DMSO/H_2O solution of pyridone under basic conditions (eq. 22). These products can be subjected to further functionalization for the synthesis of multisubstituted pyridones.[42]



(21)



(22)

5-8. Conclusion

In conclusion, I developed a series of reaction modes for iron-catalyzed coupling of amides with multiple bonds such as alkenes and alkynes through directed C(sp^2)–H bond activation and subsequent carbometalation. The reaction using olefins enabled *ortho*-alkylation and alkenylation of amides, and reactions using alkynes enabled synthesis of indenones, alkenylated amides, and isoquinolones, where the product selectivity could be controlled by the nature of additive and base. A similar reaction of alkeneamides with unsymmetrical alkynes under oxidative conditions afforded pyridones with perfect regioselectively. The selectivity can be ascribed to the compactness of the iron atom, which making the organoiron active species sensitive to sterics during the alkyne insertion step. Thus, the study described in this chapter

demonstrates the versatility of reaction modes in the reaction of a C–H bond with multiple bonds under iron catalysis, and the tuning of these modes by additives, as well as the sensitivity of the organoiron species to sterics, which is useful for designing regioselective synthesis using iron catalysis.

5-9. Experimental section

Materials and methods

General. All reactions dealing with air- or moisture-sensitive compounds were performed by standard Schlenk techniques in oven-dried Schlenk tubes under a nitrogen atmosphere. Flash chromatography was performed as described by Still *et al.*,[43] 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-92XX II (eluent: chloroform) with JAIGEL 1H and 2H polystyrene columns.
Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2025 and GC-2014 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. Mass spectra were acquired by Bruker microTOF II (APCI) Spectrometer. High-resolution mass spectra were obtained with a calibration standard of polyethylene glycol (MW 600). Melting points of solid materials were measured on a Mel-Temp capillary melting-point apparatus and were uncorrected.

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.[44] 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).[45]

Preparation of starting materials

• *Synthesis of amide substrates:* **procedure A**

Carboxylic 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.

• *Synthesis of amide substrates:* **procedure B**

In a oven-dried two-necked flask, 8-aminoquinoline (11 mmol) was added to a dichloromethane solution of carboxylic acid (10 mmol), 1-hydroxybenzotriazole (12 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (15 mmol), and the mixture was pre-stirred at room temperature for 5 min. Then, triethylamine (12 mmol) was added dropwise, and the mixture was stirred at room temperature. The reaction was monitored by TLC, and additional 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was added until the reaction completed. After 18 hours, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ solution. 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. The crude compound was washed or recrystallized with appropriate solvent to afford the pure amide.

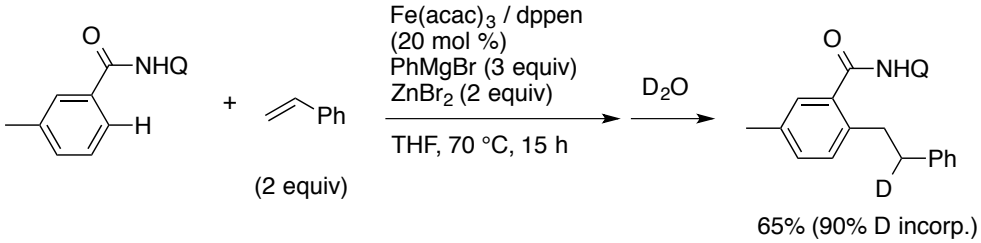
• *Synthesis of alkynes*

1-(Trimethylsilyl)-4-phenylbut-3-en-1-yne was prepared according to the literature procedure,[46] and then purified by column chromatography on silica gel (hexane eluent) and distilled to obtain the compound as orange oil. Compound data was in good agreement with the literature. ^{1}H NMR spectra indicated that the ratio of stereoisomers of this compound was *E/Z* = 92:8.

5-(Trimethylsilyl)-1-penten-4-yne was prepared according to the literature procedure,[47] and then purified by column chromatography on silica gel (hexane eluent) and distilled to obtain the compound as a colorless oil. Compound data was in good agreement with the literature.

Procedure for the directed alkylation reaction with styrene

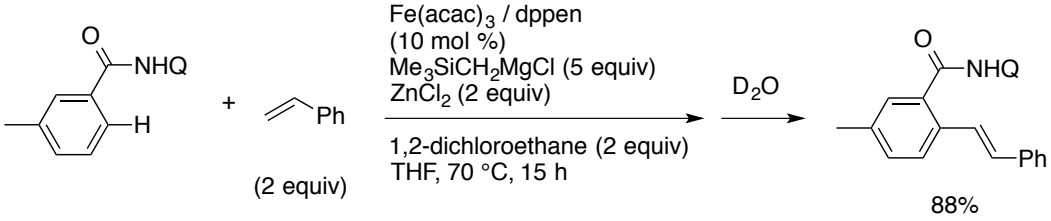
Synthesis of 5-methyl-2-phenethyl-N-(quinolin-8-yl)benzamide (eq. 2)



To an oven-dried Schlenk tube was added *N*-(quinolin-8-yl)-3-tolylamide (52.5 mg, 0.20 mmol), *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 15.9 mg, 0.040 mmol), and styrene (38 μL, 0.40 mmol, 2.0 equiv), and the mixture was dissolved in THF (0.5 mL). A solution of zinc bromide in THF (0.40 mL, 1.0 mol/L, 0.40 mmol) and solution of phenylmagnesium bromide chloride in THF (0.67 mL, 0.90 mol/L, 0.60 mmol, 3.0 equiv) was added dropwise. After stirring the solution at room temperature for several minutes, $Fe(acac)_3$ (14.1 mg, 0.040 mmol) was added, and the reaction mixture was heated to 70 °C. After stirring for 15 h, the reaction mixture was quenched by the addition of D_2O and mixed for 10 minutes. Then a saturated aqueous solution of potassium sodium tartrate and saturated aqueous solution of ammonium chloride were added. 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 column chromatography on silica gel (gradient hexane/EtOAc from 4:1 to 1:1, then EtOAc) to afford the title compound as a pale yellow solid (48 mg, 65% yield). Ratio of deuteration was determined by spectra of ^1H NMR and EI-MS. Compound data was in good agreement with the authentic sample obtained in Chapter 4.

Procedure for the directed alkenylation reaction with styrene

Synthesis of 5-methyl-2-(E)-styryl-N-(quinolin-8-yl)benzamide (Table 1, entry 7)



To an oven-dried Schlenk tube was added *N*-(quinolin-8-yl)-3-tolylamide (52.5 mg, 0.20 mmol), *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 7.9 mg, 0.020 mmol) and styrene (38 μL, 0.40 mmol, 2.0 equiv), and the mixture was dissolved in THF (0.5 mL). A solution of zinc chloride in THF (0.40 mL, 1.0 mol/L, 0.40 mmol) and solution of trimethylsilylmethylmagnesium chloride in THF (1.0 mL, 1.0 mol/L, 1.0 mmol, 5.0 equiv) was added dropwise, and then 1,2-dichloroethane (32 μL, 0.40 mmol, 2.0 equiv) was added. After stirring the solution at room temperature for several minutes, $Fe(acac)_3$ (7.1 mg, 0.020 mmol) was added, and the reaction mixture was heated to 70 °C. After stirring for 15 h, the reaction mixture was quenched by the addition of D_2O and mixed for 10 minutes. Then a saturated aqueous solution of potassium sodium tartrate and saturated aqueous solution of ammonium chloride were added. 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 column chromatography on silica gel (gradient hexane/EtOAc from 4:1 to 1:1, then EtOAc) to afford the title compound as a pale yellow solid (64 mg, 88% yield). Compound data was in good agreement with the literature.[48]

Compound data:

Mp 168–170 °C.

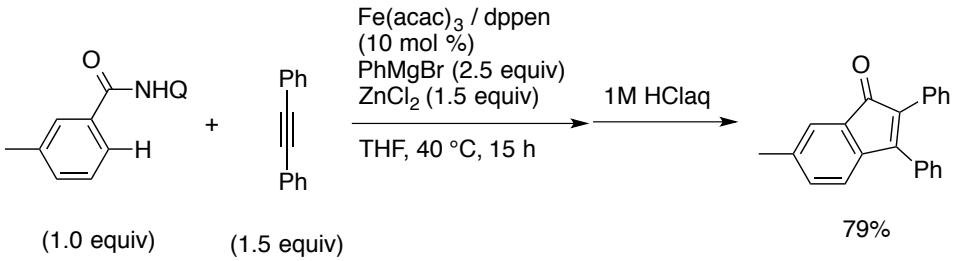
^{1}H NMR (500MHz, $CDCl_3$): δ 10.27 (s, 1H), 8.95 (d, J = 7.6 Hz, 1H), 8.45 (dd, J = 4.2, 1.6 Hz, 1H), 8.10 (d, J = 8.3, 1.7 Hz, 1H), 7.74–7.60 (m, 4H), 7.52 (dd, J = 8.3, 1.3 Hz, 1H), 7.23 (dd, J = 8.2, 6.5 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 16.2 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 167.7, 148.3, 138.7, 137.7, 137.3, 136.1, 135.5, 134.7, 133.4, 131.5, 131.3, 128.7, 128.6, 128.0, 127.6, 127.4, 126.8, 126.6, 126.0, 121.8, 116.7, 21.1.

GC-MS (EI) *m/z* (relative intensity): 364 (M^+, 32), 287 (21), 273 (82), 235 (27), 221 (40), 178 (100), 144 (30), 116 (20), 115 (34).

General procedure and compound data for indenones

Synthesis of 6-methyl-2,3-diphenyl-1H-inden-1-one (eq. 8; Table 2, entry 1)



In an oven-dried Schlenk tube was added 3-methyl-*N*-(quinolin-8-yl)benzamide (105 mg, 0.40 mmol), a THF solution of $ZnCl_2$ (0.60 mL, 1.0 mol/L, 1.5 equiv), and diphenylacetyrene (107 mg, 0.60 mmol, 1.5 equiv). Then, a solution of phenylmagnesium bromide in THF (1.4 mL, 0.72 mol/L, 1.0 mmol, 2.5 equiv) was added dropwise, and then 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. The reaction mixture was heated to 40 °C for 15 h. After that, 1M HCl aqueous solution (2 mL) was added and stirred additional 30 min at room temperature. 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 column chlomatography on silica gel (hexane, then hexane/EtOAc 20:1) to afford the title compound as a white solid (94 mg, 79% yield). Compound data was in good agreement in the literature.[21]

Compound data:

R_f = 0.50 (EtOAc/hexane = 1:10)

Mp 174–176 °C.

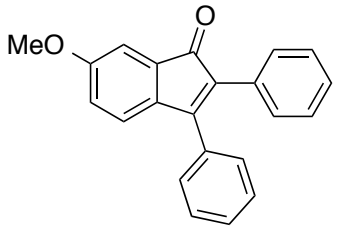
^{1}H NMR (500MHz, $CDCl_3$): δ 7.41–7.36 (m, 5H), 7.26–7.24 (m, 5H), 7.15 (d, J = 7.0 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 196.8, 155.6, 142.3, 139.3, 132.8, 131.8, 131.1, 130.9, 129.9, 129.2, 128.7, 128.5, 128.0, 127.6, 124.1, 121.1, 21.4.

GC-MS (EI) *m/z* (relative intensity): 296 (M^+, 100), 295 (43), 281 (45), 279 (13), 265 (13), 263 (10), 253 (22), 252 (46), 239 (7), 189 (10), 141 (14), 132 (15), 126 (32), 120 (10), 113 (14), 77 (7).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{16}O$ [$M+H^+$] 297.1274; found: 297.1248.

6-Methoxy-2,3-diphenyl-*1H*-inden-1-one (Table 2, entry 3)



The general procedure was applied to 3-methoxy-*N*-(quinolin-8-yl)benzamide (111 mg, 0.40 mmol) and diphenylacetylene (107 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chlomatography on silica gel (hexane then hexane/EtOAc 20:1) to afford the title compound as a dark red solid (90 mg, 72% yield). Compound data was in good agreement in the literature.[21]

Compound data:

R_f = 0.25 (hexane/EtOAc 10:1)

Mp 163–165 °C.

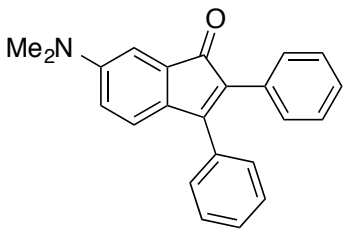
^{1}H NMR (500MHz, $CDCl_3$): δ 7.40–7.38 (m, 5H), 7.24–7.18 (m, 5H), 7.04 (d, J = 8.0 Hz, 1H), 6.79 (dd, J = 8.0, 2.0 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 196.2, 161.0, 156.3, 136.9, 132.9, 131.3, 130.9, 129.8, 129.3, 128.7, 128.4, 128.0, 127.4, 122.2, 116.2, 110.6, 55.8.

GC-MS (EI) *m/z* (relative intensity): 312 (M^+, 100), 297 (14), 269 (11), 241 (11), 239 (22), 120 (9).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{16}O_2$ [M+H$^+$] 313.1223; found: 313.1205.

6-Dimethylamino-2,3-diphenyl-*1H*-inden-1-one (Table 2, entry 4)



The general procedure was applied to 3-dimethylamino-*N*-(quinolin-8-yl)benzamide (111 mg, 0.40 mmol) and diphenylacetylene (117 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chlomatography on silica gel (hexane then hexane/EtOAc 10:1) to afford the title compound as a dark blue solid (96 mg, 73% yield).

Compound data:

R_f = 0.15 (hexane/EtOAc 10:1)

Mp 154–156 °C.

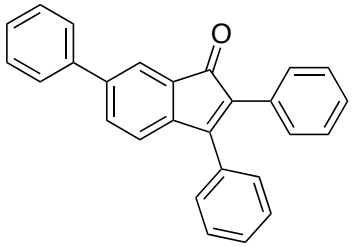
^{1}H NMR (500MHz, $CDCl_3$): δ 7.38 (br, 5H), 7.24–7.19 (m, 5H), 7.08 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 3.02 (s, 6H).

^{13}C NMR (125MHz, $CDCl_3$): δ 197.2, 157.8, 151.4, 133.4, 133.1, 131.5, 131.3, 129.7, 129.4, 129.1, 128.6, 128.4, 127.9, 127.0, 122.4, 112.8, 109.1, 40.6.

GC-MS (EI) *m/z* (relative intensity): 326 (M^{+1}, 26), 325 (M$^+$, 100), 324 (19), 252 (10).

HRMS (APCI+): *m/z* calcd for $C_{23}H_{19}NO$ [M+H$^+$] 326.1539; found: 326.1537.

6-Phenyl-2,3-diphenyl-*1H*-inden-1-one (Table 2, entry 5)



The general procedure was applied to 3-phenyl-*N*-(quinolin-8-yl)benzamide (111 mg, 0.40 mmol) and diphenylacetylene (117 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chlomatography on silica gel (hexane then hexane/EtOAc 10:1) to afford the title compound as a dark blue solid (99 mg, 69% yield).

Compound data:

R_f = 0.44 (hexane/EtOAc 10:1)

Mp 189–191 °C.

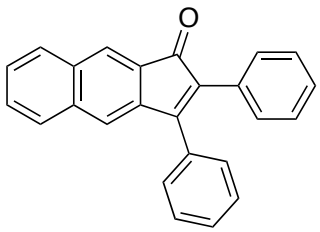
^{1}H NMR (500MHz, $CDCl_3$): δ 7.77 (d, J = 1.5 Hz, 1H), 7.55–7.51 (m, 3H), 7.39–7.28 (m, 8H), 7.20–7.17 (m, 5H), 7.13 (d, J = 8.0 Hz, 1H).

^{13}C NMR (125MHz, $CDCl_3$): δ 196.3, 155.4, 143.9, 142.2, 139.8, 132.7, 132.6, 131.6, 131.5, 130.7, 129.9, 129.3, 128.9, 128.8, 128.5, 128.1, 127.9, 127.7, 126.7, 121.9, 121.6.

GC-MS (EI) *m/z* (relative intensity): 359 (M^{+1}, 31), 358 (M^+, 100), 357 (34), 341 (12), 326 (11).

HRMS (APCI+): *m/z* calcd for $C_{27}H_{18}O$ [$M+H^+$] 359.1430; found: 359.1416.

2,3-Diphenylcyclopenta[b]naphthalene-1-one (Table 2, entry 6)



The general procedure was applied to 2-[*N*-(quinolin-8-yl)]naphthaleneamide (119 mg, 0.40 mmol) and diphenylacetylene (117 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chlomatography on silica gel (toluene eluent) to afford the title compound as an orange solid (93 mg, 70% yield). Compound data was in good agreement in the literature.[49]

Compound data:

R_f = 0.33 (hexane/EtOAc 10:1)

Mp 182–184 °C.

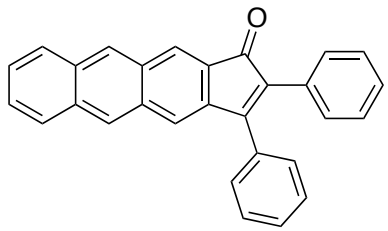
^{1}H NMR (500MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.43–7.34 (m, 8H), 7.25–7.18 (m, 5H).

^{13}C NMR (125MHz, $CDCl_3$): δ 194.7, 156.4, 139.9, 136.6, 136.1, 133.6, 132.8, 130.8, 130.6, 130.2, 130.0, 129.3, 129.1, 128.8, 128.8, 128.8, 128.6, 128.1, 127.9, 127.2, 124.4, 120.9.

GC-MS (EI) *m/z* (relative intensity): 332 (M^+, 100), 331 (78), 314 (26), 303 (17), 302 (39), 300 (16), 155 (5), 151 (12).

HRMS (APCI+): *m/z* calcd for $C_{25}H_{16}O$ [$M+H^+$] 333.1274; found: 333.1258.

2,3-Diphenylcyclopenta[b]anthracene-1-one (Table 2, entry 7)



The general procedure was applied to 2-[*N*-(quinolin-8-yl)]anthraceneamide (119 mg, 0.40 mmol) and diphenylacetylene (117 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by

column chlomatography on silica gel (toluene eluent) to afford the title compound as an orange solid (123 mg, 80% yield).

Compound data:

R_f = 0.29 (hexane/EtOAc 10:1)

Mp 220–223 °C.

^{1}H NMR (500MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.23 (s, 1H), 8.22 (s, 1H), 7.98 (t, J = 4.8 Hz, 1H), 7.92 (t, J = 5.0 Hz, 1H), 7.54–7.47 (m, 8H), 7.36–7.34 (m, 2H), 7.31–7.26 (m, 3H).

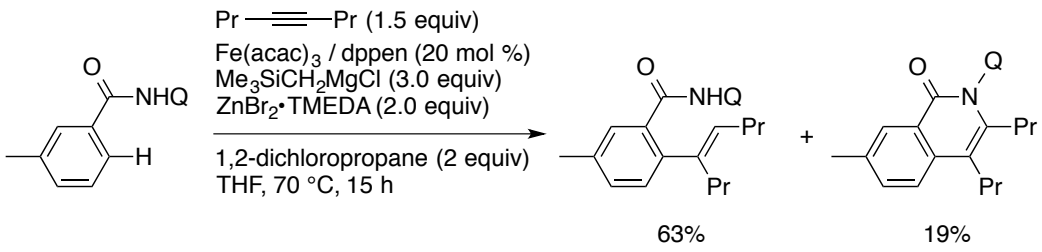
^{13}C NMR (125MHz, $CDCl_3$): δ 193.7, 156.6, 138.4, 138.4, 133.4, 133.0, 132.9, 132.3, 131.1, 130.9, 130.7, 130.5, 130.0, 129.3, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.1, 126.5, 125.4, 121.2.

GC-MS (EI) *m/z* (relative intensity): 332 (M^+, 100), 331 (78), 314 (26), 303 (17), 302 (39), 300 (16), 155 (5), 151 (12).

HRMS (APCI+): *m/z* calcd for $C_{29}H_{18}O$ [$M+H^+$] 383.1430; found: 383.1408.

Procedure for *ortho*-alkenylation of areneamide

Synthesis of (Z)-2-(oct-4-en-4-yl)-N-(8-quinolyl)-5-tolylamide via iron-catalyzed C–H bond alkenylation with an alkyne (Scheme 7, entry 3; Table 3, entry 1)



To an oven-dried Schlenk tube was added *N*-(quinolin-8-yl)-3-tolylamide (105 mg, 0.40 mmol), $ZnBr_2$•TMEDA (273 mg, 0.80 mmol), *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 32 mg, 0.080 mmol), and 4-octyne (66 mg, 0.60 mmol, 1.5 equiv), and the mixture was dissolved in THF (0.3 mL). A solution of trimethylsilylmethylmagnesium chloride in THF (1.2 mL, 1.0 mol/L, 1.2 mmol, 3.0 equiv) was added dropwise, and then 1,2-dichloropropane (78 μL, 0.80 mmol, 2.0 equiv) was added. After stiring the solution at room temperature for several minutes, $Fe(acac)_3$ (28 mg, 0.080 mmol) was added, and the reaction mixture was heated to 70 °C. After stirring for 15 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate and saturated aqueous solution of ammonium chloride. 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 column chromatography on silica gel (gradient hexane/EtOAc from 4:1 to 1:1, then EtOAc) and gel permeation column chromatography (chloroform eluent) to afford the title compound as a colorless oil (99 mg, 63% yield), along with 3,4-dipropyl-1-(quinolin-8-yl)isoquinolin-1(*2H*)-one in 19% yield.

Compound data:

^{1}H NMR (500MHz, $CDCl_3$): δ 10.39 (s, 1H), 8.98 (d, J = 6.9 Hz, 1H), 8.71 (dd, J = 4.3, 1.7 Hz, 1H), 8.13 (dd, J = 8.3, 1.4 Hz, 1H), 7.66 (s, 1H), 7.57 (dd, J = 7.9, 7.7 Hz, 1H), 7.50 (dd, J = 8.2, 1.5 Hz, 1H), 7.41 (dd, J = 8.3, 4.0 Hz, 1H), 7.25–7.23 (m, 1H), 7.15 (d, J = 7.7 Hz, 1H), 5.73 (t, J = 7.0 Hz, 1H), 2.39 (s, 3H), 2.31 (t, J = 7.9 Hz, 1H), 2.14–2.09 (m, 2H), 1.43–1.26 (m, 4H), 0.88 (t, J = 7.5 Hz, 3H), 0.79 (t, J = 7.3 Hz, 3H).

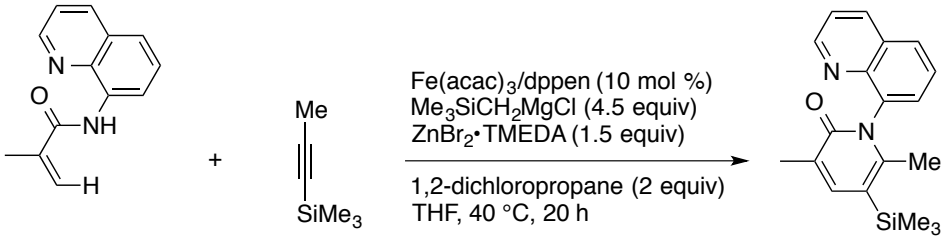
^{13}C NMR (125MHz, $CDCl_3$): δ 168.2, 148.0, 140.2, 140.0, 138.8, 136.7, 136.1, 135.1, 134.7, 132.2, 131.0, 130.3, 129.6, 128.0, 127.4, 121.5, 121.4, 116.6, 34.1, 30.5, 22.7, 21.7, 20.9, 14.0, 14.0.

GC-MS (EI) *m/z* (relative intensity): 372 (M^+, 3), 329 (71), 144 (100), 128 (26), 115 (18), 105 (11), 91 (11), 77 (5).

HRMS (APCI+): *m/z* calcd for $C_{25}H_{28}N_2O$ [$M+H^+$] 373.2274; found: 373.2263

Procedure for 1g scale reaction for pyridone synthesis

Synthesis of 3,6-Dimethyl-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(1H)-one on 1 g scale

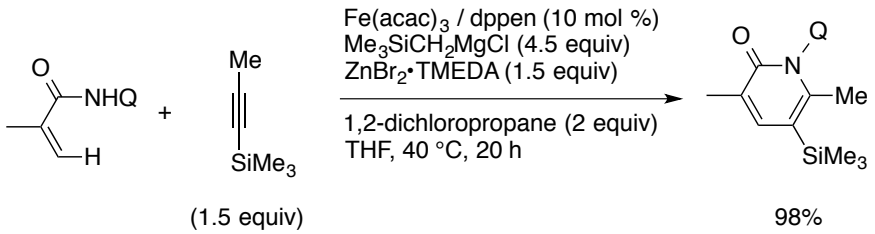


1.00 g (1.5 equiv) 1.27 g, 93%

To an oven-dried Schlenk tube was added *N*-(quinolin-8-yl)methacrylamide (1.00 g, 4.71 mmol), $ZnBr_2$•TMEDA (2.42 g, 7.1 mmol), *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 186 mg, 0.47 mmol), and 1-trimethylsilyl-1-propyne (797 mg, 7.1 mmol, 1.5 equiv), and the mixture was dissolved in THF (5 mL). A solution of trimethylsilylmethylmagnesium chloride in THF (21.2 mL, 1.0 mol/L, 21.2 mmol, 4.5 equiv) was added dropwise, and then 1,2-dichloropropane (917 μL, 9.4 mmol, 2.0 equiv) was added. After stiring the solution at room temperature for several minutes, $Fe(acac)_3$ (166 mg, 0.47 mmol) was added, and the reaction mixture was heated to 40 °C. After stirring for 20 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate and saturated aqueous solution of ammonium chloride. After aqueous workup, the organic layer was extracted with EtOAc (20 mL × 3). The combined organic layer was passed through a pad of Florisil, concentrated *in vacuo*, and purified by column chromatography on silica gel (gradient hexane/EtOAc from 4:1 to 1:1, then EtOAc) to afford the title compound as a pale yellow solid (1.27 g, 93% yield).

General Procedure and compound data for pyridone and isoquinolone

3,6-Dimethyl-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(1H)-one (eq. 20; Scheme 8; Table 4, entry 1; Table 5, entry 5)



(1.5 equiv) 98%

To an oven-dried Schlenk tube was added *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol), $ZnBr_2$•TMEDA (205 mg, 0.60 mmol), *cis*-1,2-bis(diphenylphosphino)ethylene (dppen, 15.9 mg, 0.040 mmol), and 1-trimethylsilyl-1-propyne (107 mg, 0.60 mmol, 1.5 equiv), and the mixture was dissolved in THF (0.5 mL). A solution of trimethylsilylmethylmagnesium chloride in THF (1.80 mL, 1.0 mol/L, 1.80 mmol, 4.5 equiv) was added dropwise, and then 1,2-dichloropropane (78 μL, 0.80 mmol, 2.0 equiv) was added. After stiring the solution at room temperature for several minutes, $Fe(acac)_3$ (14.1 mg, 0.040 mmol) was added, and the reaction mixture was heated to 40 °C. After stirring for 20 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate and saturated aqueous solution of ammonium chloride. 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 column chromatography on silica gel (gradient hexane/EtOAc from 4:1 to 1:1, then EtOAc) to afford the title compound as a pale yellow solid (126 mg, 98% yield). Single-crystal X-ray crystallographic analysis shows that the product is 5-trimethylsilyl-6-methyl.

Compound data:

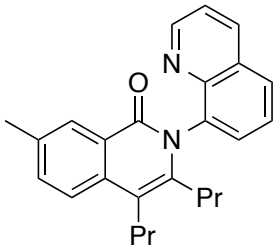
Mp 143–145 °C.

^{1}H NMR (500MHz, $CDCl_3$): δ 8.89 (d, J = 3.7 Hz, 1H), 8.21 (d, J = 9.7 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 7.67–7.61 (m, 2H), 7.42 (dd, J = 10.3, 5.2 Hz, 1H), 7.38 (s, 1H), 2.16 (s, 3H), 1.93 (s, 3H), 0.31 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 164.0, 151.3, 149.1, 143.8, 142.1, 137.4, 136.0, 129.2, 129.1, 128.8, 126.2, 125.5, 121.6, 110.9, 21.2, 16.8, 0.0.

GC-MS (EI) *m/z* (relative intensity): 322 (M+, 60), 321 (100), 307 (37), 305 (14), 249 (55), 170 (6), 128 (5), 101 (4), 73 (15).

3,4-Dipropyl-1-(quinolin-8-yl)isoquinolin-1(*2H*)-one (Table 3, entry 5)



The general procedure was applied to *N*-(quinolin-8-yl)-3-tolylamide (105 mg, 0.40 mmol) and 4-octyne (66 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chromatography on silica gel (gradient hexane/EtOAc from 4:1 to 1:1, then EtOAc) to afford the title compound as a white solid (145 mg, 98% yield). Compound data was in good agreement with the literature.[31e]

Compound data:

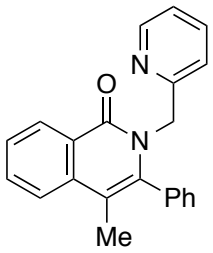
Mp 138–140 °C.

^{1}H NMR (500MHz, $CDCl_3$): δ 8.84 (dd, J = 4.3, 2.0 Hz, 1H), 8.25 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.95 (dd, J = 8.0, 1.0 Hz, 1H), 7.71–7.63 (m, 3H), 7.51 (dd, J = 8.3, 2.0 Hz, 1H), 7.41 (dd, J = 8.3, 4.0 Hz, 1H), 2.77–2.73 (m, 2H), 2.49–2.43 (m, 4H), 1.94–1.88 (m, 1H), 1.74–1.67 (m, 2H), 1.37–1.25 (m, 2H), 1.10 (t, J = 7.5 Hz, 3H), 0.52 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.1, 151.2, 144.8, 139.8, 137.6, 136.1, 135.4, 135.2, 133.7, 130.2, 129.2, 128.9, 128.2, 126.1, 125.4, 122.9, 121.6, 113.4, 32.6, 29.9, 23.7, 23.0, 21.2, 21.2, 14.5, 14.2.

GC-MS (EI) *m/z* (relative intensity): 370 (M^+, 80), 369 (100), 341 (45), 328 (15), 327 (52), 311 (40), 298 (23), 269 (11), 170 (10), 156 (27), 149 (5), 129 (17), 115 (11).

4-Phenyl-3-methyl-1-(2-picolinyl)isoquinolin-1(*2H*)-one (eq. 15)



The general procedure was applied to *N*-picolinylbenzamide (85 mg, 0.40 mmol) and 1-phenyl-1-propyne (70 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 50 °C for 15 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 4:1, EtOAc, then 1:1) to afford the title compound as a white solid (119 mg, 91% yield) as a single regioisomer. GC and GCMS analysis of the crude reaction mixture indicated that *N*-deprotected isoquinolone was obtained in 9% yield. Compound data was in good agreement with the literature.[31e]

Compound data:

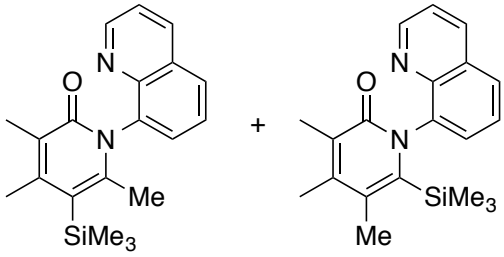
Mp 165–167 °C.

^{1}H NMR (500MHz, $CDCl_3$): δ 8.57 (d, J = 7.8 Hz, 1H), 8.39 (d, J = 4.3 Hz, 1H), 7.75–7.74 (m, 2H), 7.56–7.51 (m, 2H), 7.38–7.26 (m, 2H), 7.09–7.06 (m, 2H), 6.92 (d, J = 7.8 Hz, 1H), 5.20 (s, 2H), 2.02 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 162.4, 157.2, 149.0, 140.2, 137.4, 136.3, 135.1, 132.5, 129.5, 128.7, 128.5, 128.5, 126.6, 125.3, 123.3, 121.6, 120.6, 111.0, 51.0, 14.9.

GC-MS (EI) *m/z* (relative intensity): 325 (M^+, 100), 309 (16), 246 (13), 103 (16), 92 (27), 79 (25), 77 (31).

3,4,6-Trimethyl-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one and 3,4,5-Trimethyl-6-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Scheme 8)



The general procedure was applied to *N*-(quinolin-8-yl)-tiglamide (91 mg, 0.40 mmol) and 1-trimethylsilyl-1-propyne (107 mg, 0.60 mmol, 1.5 equiv), and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 1:1, then EtOAc) to afford the 3,4,6-Trimethyl-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one as a white solid (41 mg, 30% yield), and 3,4,5-Trimethyl-6-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one as a white solid (74 mg, 55% yield). The structure of the regioisomers was determined by NOE experiments.

Compound data for

3,4,5-Trimethyl-6-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(1H)-one:

Mp 198–200 °C.

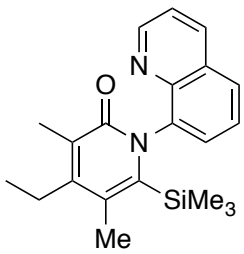
^{1}H NMR (400MHz, $CDCl_3$): δ 8.93 (dd, J = 4.2, 1.6 Hz, 1H), 8.20 (dd, J = 8.2, 1.6 Hz, 1H), 7.90 (dd, J = 8.2, 1.4 Hz, 1H), 7.61 (dd, J = 8.2, 7.8 Hz, 1H), 7.52 (dd, J = 7.2, 1.4 Hz, 1H), 7.42 (dd, J = 8.2, 4.1 Hz, 1H), 2.26 (s, 3H), 2.20 (s, 3H), 2.18 (s, 3H), –0.32 (s, 9H).

^{13}C NMR (100MHz, $CDCl_3$): δ 163.2, 151.2, 147.0, 145.6, 144.5, 140.9, 136.1, 129.5, 129.1, 128.9, 127.2, 126.2, 123.9, 121.6, 19.1, 17.0, 13.2, 1.7.

GC-MS (EI) *m/z* (relative intensity): 336 (M^+, 88), 321 (66), 263 (100), 235 (14), 233 (12), 220 (13), 155 (17), 81 (20), 73 (40).

HRMS (APCI+): *m/z* calcd for $C_{20}H_{24}N_2OSi$ [M+H$^+$] 337.1731; found: 337.1738.

3,5-Dimethyl-4-ethyl-6-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Scheme 8)



The general procedure was applied to (*Z*)-*N*-(quinolin-8-yl)-2-methyl-pent-2-enamide (96 mg, 0.40 mmol) and 1-trimethylsilyl-1-propyne (107 mg, 0.60 mmol, 1.5 equiv), and the reaction mixture was stirred at 50 °C for 15 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 4:1, then 1:1) to afford the title compound as a pale yellow oil (64 mg, 46% yield), along with the regioisomer, with the ratio of 96:4, which was determined by ^{1}H NMR analysis of the crude mixture. The minor isomer could be removed by column chromatography.

Compound data:

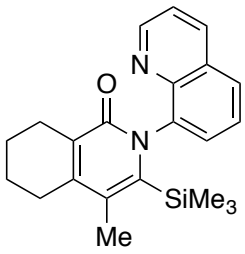
^{1}H NMR (500MHz, $CDCl_3$): δ 8.93 (d, J = 4.0 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 3.0 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.41 (dd, J = 8.2, 4.0 Hz, 1H), 2.66–2.59 (m, 2H), 2.30 (s, 3H), 2.19 (s, 3H), 1.21–1.15 (m, 3H), –0.32 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.5, 152.0, 151.1, 145.6, 145.2, 141.0, 136.1, 129.4, 129.0, 128.9, 126.8, 126.2, 123.2, 121.6, 23.5, 18.2, 12.6, 1.8.

GC-MS (EI) *m/z* (relative intensity): 350 (M$^+$, 90), 335 (26), 277 (46), 95 (8), 73 (100).

HRMS (APCI+): *m/z* calcd for $C_{21}H_{26}N_2OSi$ [M+H$^+$] 351.1887; found: 351.1882.

3-Methyl-4-trimethylsilyl-5,6,7,8-tetrahydro-1-(quinolyn-8-yl)-1(2*H*)-isoquinolone (Scheme 8)



The general procedure was applied to *N*-(quinolin-8-yl)-cyclohexenyl-1-carboxamide (50 mg, 0.20 mmol) and 1-trimethylsilyl-1-propyne (54 mg, 0.30 mmol, 1.5 equiv), and the reaction mixture was stirred at 50 °C for 15 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 4:1, then 1:1) to afford the title compound as a white solid (69 mg, 96% yield), along with the regioisomer, with the ratio of 98:2, which was determined by ^{1}H NMR analysis of the crude mixture. The minor isomer could be removed by column chromatography.

Compound data:

Mp 228–230 °C.

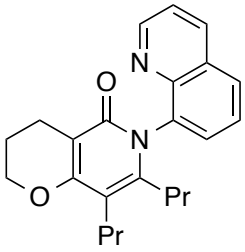
^{1}H NMR (500MHz, $CDCl_3$): δ 8.94 (br, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.60 (dd, J = 7.6, 7.5 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.41 (dd, J = 8.2, 4.3 Hz, 1H), 2.60–2.54 (m, 4H), 2.21 (s, 3H), 1.81–1.70 (m, 4H), –0.31 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 162.9, 151.3, 147.6, 145.7, 144.1, 140.8, 136.1, 129.6, 129.1, 128.9, 128.6, 126.2, 123.6, 121.6, 27.4, 24.0, 22.3, 21.6, 17.7, 1.7.

GC-MS (EI) *m/z* (relative intensity): 362 (M^+, 62), 347 (23), 289 (60), 73 (100).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{26}N_2OSi$ [$M+H^+$] 363.1887; found: 363.1892.

7,8-Dipropyl-1-(quinolin-8-yl)-4,5-dihydro-*2H*-pyrano[3,2-*c*]pyridin-2(*1H*)-one (Table 5, entry 1)



The general procedure was applied to 3,4-dihydro-*N*-(quinolin-8-yl)-*2H*-pyran-5-carboxamide (102 mg, 0.40 mmol) and 4-octyne (66 mL, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 1:1, then EtOAc/MeOH = 8:1) to afford the title compound as a white solid (126 mg, 87% yield).

Compound data:

Mp 74–76 °C.

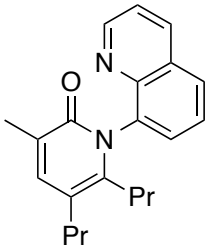
^{1}H NMR (500MHz, $CDCl_3$): δ 8.91 (d, J = 2.5 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.91 (dd, J = 4.5, 4.5 Hz, 1H), 7.63–7.61 (m, 2H), 7.43–7.40 (m, 1H), 4.23 (t, J = 4.8 Hz, 1H), 2.73–2.31 (m, 5H), 2.01–1.94 (m, 2H), 1.89–1.83 (m, 1H), 1.60–1.52 (m, 3H), 1.30–1.19 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H), 0.51 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.6, 162.0, 151.2, 144.6, 144.3, 137.1, 136.1, 130.2, 129.1, 128.8, 126.0, 121.5, 111.3, 105.3, 66.8, 66.7, 56.7, 32.2, 27.7, 23.5, 22.7, 21.3, 19.3, 14.4, 14.1.

GC-MS (EI) *m/z* (relative intensity): 362 (M^+, 90), 361 (100), 348 (21), 347 (80), 334 (18), 333 (46), 319 (69), 302 (36), 290 (16), 220 (15), 206 (14), 156 (21), 129 (15), 77 (8).

HRMS (APCI+): *m/z* calcd for $C_{23}H_{26}N_2O_2$ [$M+H^+$] 363.2067; found: 363.2065.

3-Methyl-5,6-dipropyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 2)



The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and 4-octyne (66 mL, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chromatography on silica gel (gradient hexane/EtOAc from 4:1 to 1:1, then EtOAc) to afford the title compound as a pale yellow oil (127 mg, 99% yield).

Compound data:

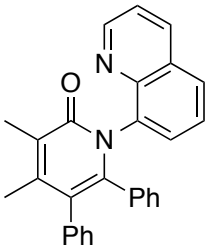
^{1}H NMR (500MHz, $CDCl_3$): δ 8.88 (d, J = 3.0, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.92 (dd, J = 6.3, 2.5 Hz, 1H), 7.64–7.63 (m, 2H), 7.40 (dd, J = 8.0, 4.0 Hz, 1H), 7.26 (d, J =7.5 Hz, 1H), 2.40 (t, J = 7.5 Hz, 2H), 2.35–2.29 (m, 1H), 2.15 (s, 3H), 1.87–1.81 (m, 1H), 1.64–1.61 (m, 2H), 1.29–1.19 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H), 0.52 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.5, 151.2, 144.3, 144.1, 140.4, 137.3, 136.1, 129.7, 129.1, 128.8, 126.5, 125.9, 121.6, 116.4, 33.0, 32.2, 24.1, 22.7, 16.9, 14.0, 14.0.

GC-MS (EI) *m/z* (relative intensity): 321 (M+, 320), 320 (95), 319 (93), 306 (23), 305 (100), 292 (18), 291 (46), 290 (24), 278 (17), 277 (79), 263 (15), 262 (35), 261 (38), 249 (11), 248 (34), 233 (12), 218 (14), 178 (11), 170 (11), 157 (20), 156 (43), 155 (17), 154 (16), 143 (16), 130 (14), 129 (24), 128 (16), 101 (12), 77 (14).

HRMS (APCI+): *m/z* calcd for $C_{21}H_{24}N_2O$ [M+H$^+$] 321.1961; found: 321.1954.

3,4-Dimethyl-5,6-diphenyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 3)



The general procedure was applied to *N*-(quinolin-8-yl)tiglamide (91 mg, 0.40 mmol) and diphenylacetyrene (107 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chromatography on silica gel (gradient hexane/EtOAc from 4:1 to 1:1, then EtOAc) to afford the title compound as a white solid (160 mg, 99% yield).

Compound data:

Mp 230–232 °C.

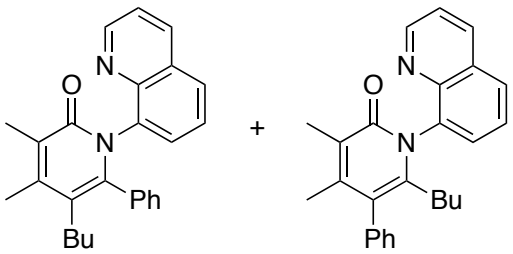
^{1}H NMR (500MHz, $CDCl_3$): δ 8.96 (d, J = 3.4 Hz, 1H), 8.02 (d, J = 9.7 Hz, 1H), 7.61 (d, J = 9.7 Hz, 1H), 7.42 (d, J = 9.2 Hz, 1H), 7.36–7.31 (m, 2H), 7.16–7.05 (m, 5H), 6.87 (d, J = 8.9 Hz, 1H), 6.78 (d, J = 9.4 Hz, 1H), 6.70–6.66 (m, 2H), 6.46 (t, J = 9.5 Hz, 1H), 2.30 (s, 3H), 2.04 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 162.5, 150.7, 146.5, 144.4, 143.7, 137.9, 137.8, 135.9, 134.7, 131.1, 131.1, 130.3, 130.3, 129.3, 128.6, 128.3, 127.7, 127.5, 127.0, 126.5, 126.3, 126.3, 125.6, 125.5, 121.7, 121.3, 18.7, 13.4.

GC-MS (EI) *m/z* (relative intensity): 402 (M^+, 100), 401 (92), 387 (21), 374 (11), 359 (12), 325 (13), 231 (9), 128 (15), 101 (9), 77 (9).

HRMS (APCI+): *m/z* calcd for $C_{28}H_{22}N_2O$ [$M+H^+$] 403.1805; found: 403.1804.

5-Butyl-3,4-dimethyl-6-phenyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one and 6-Butyl-3,4-dimethyl-5-phenyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (eq. 19; Table 5, entry 4)



The general procedure was applied to *N*-(quinolin-8-yl)tiglamide (91 mg, 0.40 mmol) and 1-phenyl-1-hexyne (105 mL, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 15 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 1:1, then EtOAc/MeOH = 10:1) to afford a mixture of the title compounds as a white solid (150 mg, 98% yield). ^{1}H NMR spectra indicated that the ratio of these compounds is 96:4. Single-crystal X-ray crystallographic analysis shows that the major isomer is 5-butyl-6-phenyl.

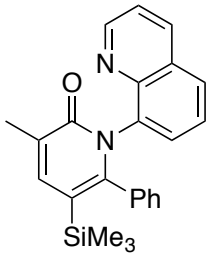
Compound data for the major isomer:

^{1}H NMR (500MHz, $CDCl_3$): δ 8.92 (dd, J = 5.0, 2.0 Hz, 1H), 7.99 (dd, J = 10.3, 1.4 Hz, 1H), 7.58 (d, J = 10.0 Hz, 1H), 7.39–7.30 (m, 3H), 7.12–7.05 (m, 2H), 6.92 (t, J = 9.0 Hz, 1H), 6.74 (d, J = 6.8 Hz, 1H), 6.69 (t, J = 9.5 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.20–2.13 (m, 2H), 1.38–1.34 (m, 2H), 1.16–1.10 (m, 2H), 0.71 (t, J = 0.92 Hz, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 162.2, 150.7, 147.0, 144.2, 142.9, 138.0, 135.8, 134.9, 130.3, 129.9, 128.7, 128.5, 128.2, 127.6, 127.0, 126.8, 126.0, 125.5, 121.2, 118.5, 32.7, 29.2, 22.7, 16.7, 13.5, 13.3.

GC-MS (EI) *m/z* (relative intensity): 383 (M^+, 12), 382 (42), 340 (27), 339 (100).

3-Methyl-6-phenyl-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 6)



The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and 1-phenyl-2-trimethylsilylacetylene (117 mL, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 20 hours. The crude product was

purified by column chromatography on silica gel (hexane/EtOAc 1:1, then EtOAc) to afford the title compound as a white solid (119 mg, 77% yield).

Compound data:

Mp 200–202 °C.

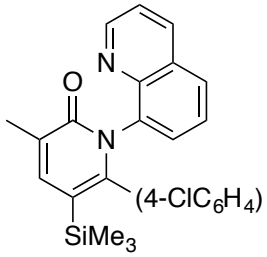
^{1}H NMR (500MHz, $CDCl_3$): δ 8.90 (d, J = 5.2 Hz, 1H), 7.98 (d, J = 10.3, 1H), 7.58 (d, J = 10.0 Hz, 1H), 7.50 (s, 1H), 7.35–7.28 (m, 3H), 7.09 (d, J = 9.5 Hz, 1H), 7.04 (t, J = 9.5 Hz, 1H), 6.92 (t, J = 9.3 Hz, 1H), 6.79 (d, J = 9.7 Hz, 1H), 6.64 (t, J = 9.5 Hz, 1H), 2.23 (s, 3H), –0.13 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.3, 152.5, 150.7, 144.2, 142.1, 137.5, 136.1, 135.8, 130.3, 130.2, 129.2, 128.5, 128.3, 128.1, 127.5, 126.7, 126.5, 125.5, 121.3, 112.7, 17.1, 0.0.

GC-MS (EI) *m/z* (relative intensity): 384 (M^+, 100), 368 (80), 341 (12), 325 (10), 311 (10), 294 (5), 283 (11), 200 (4), 73 (9).

HRMS (APCI+): *m/z* calcd for $C_{24}H_{24}N_2OSi$ [M+H^+] 385.1731; found: 385.1741.

6-(4-Chlorophenyl)-3-methyl-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 7)



The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and (4-chlorophenylethynyl)trimethylsilane (125 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 20 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 1:1, then EtOAc/MeOH 20:1) to afford the title compound as a white solid (150 mg, 90% yield).

Compound data:

Mp 224–226 °C.

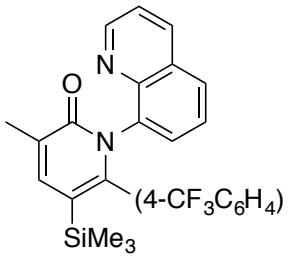
^{1}H NMR (500MHz, $CDCl_3$): δ 8.91 (d, J = 2.5 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.66 (dd, J = 5.0, 4.8 Hz, 1H), 7.51 (s, 1H), 7.37–7.26 (m, 3H), 7.05 (s, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 9.0 Hz, 1H), 2.25 (s, 3H), –0.09 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.1, 151.0, 150.7, 144.0, 141.8, 137.1, 135.9, 134.5, 134.0, 131.5, 130.5, 130.1, 128.6, 128.5, 127.9, 126.9, 126.7, 125.5, 121.4, 112.9, 17.0, 0.0.

GC-MS (EI) *m/z* (relative intensity): 421 (M^+, 12), 420 (41), 419 (M^+, 37), 418 (100), 417 (16), 405 (29), 404 (25), 403 (75), 401 (11), 375 (12), 317 (11), 73 (13).

HRMS (APCI+): *m/z* calcd for $C_{24}H_{23}N_2OSiCl$ [M+H^+] 419.1341; found: 419.1340.

3-Methyl-6-(4-trifluoromethylphenyl)-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 8)



The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and 1-[(trimethylsilyl)ethynyl]-4-(trifluoromethyl)benzene (145 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 20 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 1:1, then EtOAc) to afford the title compound as a white solid (168 mg, 93% yield).

Compound data:

Mp 210–212 °C.

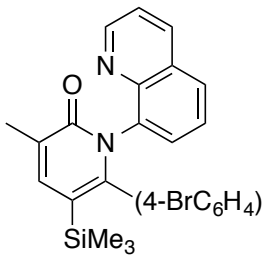
^{1}H NMR (500MHz, $CDCl_3$): δ 9.24 (d, J = 4.0 Hz, 1H), 8.36 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.84 (s, 1H), 7.70–7.66 (m, 4H), 7.58 (d, J = 5.5 Hz, 1H), 7.33–7.28 (m, 2H), 2.57 (s, 3H), 0.20 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.1, 150.8, 150.6, 144.0, 141.9, 139.6, 139.6, 137.0, 136.0, 130.7, 130.3, 130.2, 129.7, 128.8, 128.6, 128.4, 125.6, 123.7, 123.5, 123.5, 121.5, 112.9, 17.1, 0.0.

GC-MS (EI) *m/z* (relative intensity): 453 (M^+, 36), 452 (100), 438 (27), 437 (83), 436 (11), 435 (16), 409 (14), 350 (10).

HRMS (APCI+): *m/z* calcd for $C_{25}H_{23}F_3N_2OSi$ [M+H^+] 453.1605; found: 453.1602.

3-Methyl-6-(4-bromophenyl)-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 9)



The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and (4-bromophenylethynyl)trimethylsilane (152 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 20 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 1:1, then EtOAc), and gel permeation column chromatography ($CHCl_3$) to afford the mixture of the title compound and de-brominated product as a white solid (139 mg). From ^{1}H NMR spectra, the ratio of these compounds is found to be 78:22. This means the yield of the title compound is 68%, and that of de-brominated product is 9%.

Compound data (the NMR peaks of de-brominated product was omitted):

^{1}H NMR (500MHz, $CDCl_3$): δ 8.91 (dd, J = 4.3, 1.5 Hz, 1H), 8.05 (dd, J = 8.0, 1.5 Hz, 1H), 7.67 (t, J = 4.8 Hz, 1H), 7.51 (d, J = 1.0 Hz, 1H), 7.37–7.33 (m, 3H), 7.21 (dd, J =

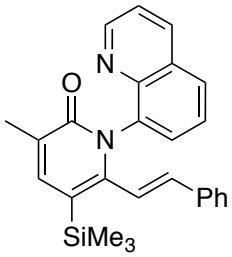
8.0, 2.0 Hz, 1H), 7.00 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.83 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.74 (dd, *J* = 8.3, 2.5 Hz, 1H), 2.25 (s, 3H), –0.09 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.1, 150.9, 150.7, 144.0, 141.8, 137.1, 135.9, 134.9, 131.8, 130.8, 130.1, 129.9, 129.7, 128.6, 128.5, 127.9, 125.5, 122.3, 121.4, 112.8, 17.0, 0.0.

GC-MS (EI) *m/z* (relative intensity): 465 (M^+, 31), 464 (100), 463 (M^+, 44), 462 (94), 461 (14), 449 (20), 449 (68), 448 (28), 447 (75), 420 (10), 418 (12), 362 (10), 360 (11), 73 (19).

HRMS (APCI+): *m/z* calcd for $C_{24}H_{23}BrN_2OSi$ [M+H$^+$] 465.0818; found: 465.0827.

(*E*)-3-Methyl-5-trimethylsilyl-6-styryl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 10)



E/Z = >99:1

The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and 1-styryl-2-(trimethylsilyl)acetylene (*E/Z* = 92:8, 120 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 20 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 4:1 then EtOAc) to afford the title compound as a white solid (160 mg, 97% yield). Stereoselectivity of the title compound was found to be *E/Z* = >99:1, determined by ^{1}H NMR spectroscopy.

Compound data:

Mp 165–167 °C.

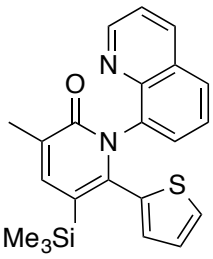
^{1}H NMR (500MHz, $CDCl_3$): δ 8.93 (dd, J = 4.0, 1.5 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.62–7.57 (m, 2H), 7.50 (s, 1H), 7.39 (dd, J = 8.0, 4.0 Hz, 1H), 7.15–7.14 (m, 3H), 6.89–6.88 (m, 2H), 6.46 (d, J = 16.0 Hz, 1H), 6.23 (d, J = 16 Hz, 1H), 2.23 (s, 3H), 0.25 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.5, 151.2, 150.6, 144.0, 142.6, 137.4, 136.2, 136.1, 135.5, 129.8, 129.1, 129.0, 128.5, 128.5, 128.3, 127.4, 126.4, 126.1, 123.7, 121.6, 112.5, 17.1, 1.0.

GC-MS (EI) *m/z* (relative intensity): 411 (M^+, 32), 410 (100), 409 (86), 395 (22), 338 (19), 337 (69), 230 (18), 73 (19).

HRMS (APCI+): *m/z* calcd for $C_{26}H_{26}N_2OSi$ [M+H^+] 411.1887; found: 411.1891.

3-Methyl-6-(2-thienyl)-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 11)



The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and 2-[(trimethylsilyl)ethynyl]thiophene (108 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 50 °C for 15 hours. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 4:1, EtOAc, then EtOAc/MeOH = 20:1) to afford the title compound as a pale yellow solid (77 mg, 49% yield).

Compound data:

Mp 174–176 °C.

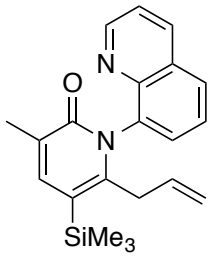
^{1}H NMR (500MHz, $CDCl_3$): δ 8.94 (d, J = 2.5 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.51 (s, 1H), 7.43–7.37 (m, 3H), 6.59 (s, 1H), 6.53 (br, 2H), 2.26 (s, 3H), 0.00 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.6, 151.0, 145.0, 144.7, 141.7, 137.5, 136.1, 130.2, 129.3, 128.8, 128.7, 127.0, 125.8, 125.4, 121.6, 116.5, 17.4, 0.0.

GC-MS (EI) *m/z* (relative intensity): 391 (M^+, 34), 390 (100), 376 (26), 375 (85), 347 (10), 317 (12), 289 (12), 73 (13).

HRMS (APCI+): *m/z* calcd for $C_{22}H_{22}N_2OSSi$ [M+H^+] 391.1295; found: 391.1291.

3-Methyl-5-trimethylsilyl-6-allyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 12)



The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and 1-trimethylsilyl-pent-1-yl-4-ene (83 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 20 hours. The crude product was purified by column chromatography on silica gel (gradient hexane/EtOAc 1:1 to 2:3) to afford the title compound as a white solid (56 mg, 40% yield).

Compound data:

Mp 146–148 °C.

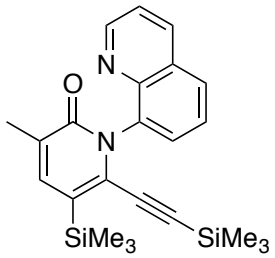
^{1}H NMR (500MHz, $CDCl_3$): δ 8.87 (d, J = 2.9 Hz, 1H), 8.19 (d, J = 7.7 Hz, 1H), 7.90 (dd, J = 6.0, 3.7 Hz, 1H), 7.59–7.58 (m, 2H), 7.43–7.39 (m, 2H), 5.44–5.39 (m, 1H), 4.67 (d, J = 10.0 Hz, 1H), 4.34 (d, J = 17.2 Hz, 1H), 3.26 (dd, J = 16.6, 4.9 Hz, 1H), 2.83 (dd, J = 16.6, 5.8 Hz, 1H), 2.17 (s, 3H), 0.31 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 164.3, 151.2, 150.2, 144.3, 142.4, 136.5, 136.1, 134.8, 130.6, 129.1, 126.6, 125.8, 121.6, 116.6, 112.4, 38.0, 17.1, 0.7.

GC-MS (EI) *m/z* (relative intensity): 348 (M^+, 39), 333 (19), 307 (36), 275 (85), 154 (21), 130 (21), 102 (14), 73 (100).

HRMS (APCI+): *m/z* calcd for $C_{21}H_{24}N_2OSi$ [M+H^+] 349.1731; found: 349.1750.

3-Methyl-5-trimethylsilyl-6-[(2-trimethylsilyl)ethynyl]-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 13)



The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and 1,4-bis(trimethylsilyl)-1,3-butadiyne (117 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 20 hours. The crude product was purified by column chromatography on silica gel (gradient hexane/EtOAc 1:1 to 2:3) to afford the title compound as a white solid (158 mg, 98% yield).

Compound data:

Mp 195–197 °C.

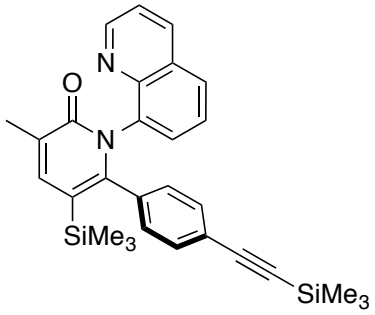
^{1}H NMR (500MHz, $CDCl_3$): δ 8.89 (br, 1H), 8.18 (d, J = 7.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.0 Hz, 1H), 7.41–7.36 (m, 2H), 2.23 (s, 3H), 0.29 (s. 9H), –0.34 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$): δ 163.0, 150.9, 144.4, 141.2, 137.8, 135.7, 134.3, 130.8, 129.5, 129.0, 128.7, 125.8, 121.4, 118.6, 105.2, 99.2, 17.4, –1.2, –1.3.

GC-MS (EI) *m/z* (relative intensity): 404 (M^+, 23), 403 (13), 389 (34), 332 (36), 331 (100), 303 (6), 73 (8).

HRMS (APCI+): *m/z* calcd for $C_{23}H_{28}N_2OSi_2$ [M+H^+] 405.1813; found: 405.1819.

3-Methyl-6-[4-(2-trimethylsilylethynyl)phenyl]-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (Table 5, entry 14)



The general procedure was applied to *N*-(quinolin-8-yl)methacrylamide (85 mg, 0.40 mmol) and 1,4-bis[(trimethylsilyl)ethynyl]benzene (162 mg, 0.60 mmol, 1.5 equiv) and the reaction mixture was stirred at 40 °C for 20 hours. The crude product was purified by column chromatography on silica gel (gradient hexane/EtOAc 1:1 to 1:4) to afford the title compound as a white solid (111 mg, 58% yield).

Compound data:

Mp 220–224 °C.

^{1}H NMR (500MHz, $CDCl_3$): δ 8.91 (d, J = 3.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.65 (dd, J = 7.3, 1.0 Hz, 1H), 7.51 (s, 1H), 7.37–7.34 (m, 3H), 7.18 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.81 (br, 2H), 2.25 (s, 3H), 0.17 (s, 9H), –0.13 (s, 9H).

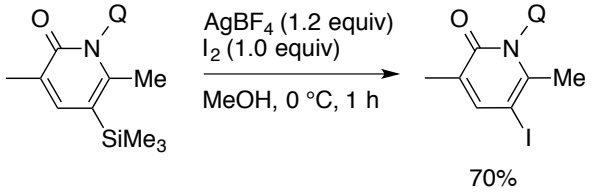
^{13}C NMR (125MHz, $CDCl_3$): δ 163.5, 151.9, 151.0, 144.4, 142.3, 142.3, 137.5, 136.5, 136.2, 130.7, 130.6, 130.5, 130.5, 129.4, 128.9, 128.9, 128.1, 125.9, 125.9, 123.0, 121.7, 113.1, 104.5, 95.3, 17.4, 0.4, 0.0.

GC-MS (EI) *m/z* (relative intensity): 481 (M^+, 42), 480 (100), 467 (65), 437 (8), 421 (6), 407 (8), 391 (5), 379 (10), 225 (7), 224 (5), 73 (13).

HRMS (APCI+): *m/z* calcd for $C_{29}H_{32}N_2OSi_2$ [$M+H^+$] 481.2126; found: 481.2110.

Iodination reaction

Synthesis of 3,6-dimethyl-5-iodo-1-(quinolin-8-yl)pyridin-2(1H)-one (eq. 21)



The synthetic procedure reported in the literature [50] was followed. 3,6-Dimethyl-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (32 mg, 0.1 mmol) was dissolved in dry methanol (3 mL, water content: 18.9 ppm) under a nitrogen atmosphere. Silver tetrafluoroborate (23.3 mg, 1.2 equiv) was added and allowed to dissolve. The solution was cooled to 0 °C. Then, iodine (127 mg, 1.0 equiv) in dry methanol (1 mL) was added dropwise and the mixture was stirred for 1 h. The reaction mixture was quenched by aqueous sodium sulfite and ammonium chloride. The organic compounds were extracted by ethyl acetate (3 mL × 3). The combined organic layer was passed through a pad of Florisil, concentrated *in vacuo*, and purified by column chromatography on silica gel (hexane/ethyl acetate from 4:1 to 1:1), to afford the title compound as a white solid (26.4 mg, 70% yield).

Compound data:

Mp 207–209 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.90 (d, J = 3.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.69–7.65 (m, 2H), 7.58 (d, J = 7.1 Hz, 1H), 7.45 (dd, J = 8.2, 4.1 Hz, 1H), 2.14 (s, 3H), 2.08 (s, 3H).

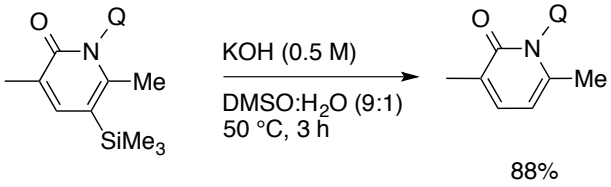
^{13}C NMR (100MHz, $CDCl_3$): δ 163.6, 151.6, 146.0, 144.8, 143.7, 137.8, 136.3, 129.4, 129.4, 129.1, 128.9, 126.4, 122.0, 70.1, 25.6, 16.6.

GC-MS (EI) *m/z* (relative intensity): 375 (M^+, 100), 249 (14), 206 (6), 128 (9), 77 (16).

HRMS (APCI+): *m/z* calcd for $C_{16}H_{13}IN_2O$ [$M+H^+$] 377.0145; found: 377.0157.

Protodesilylation reaction

Synthesis of 3,6-dimethyl-1-(quinolin-8-yl)pyridin-2(1H)-one (eq. 22)



3,6-Dimethyl-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one (32 mg, 0.1 mmol) and potassium hydroxide (28 mg, 0.5 mmol) were dissolved in DMSO (0.9 mL) and deionized water (0.1 mL). The mixture was stirred at 50 °C for 3 h. The organic compounds were extracted by ethyl acetate (3 mL × 3). The combined organic layer was passed through a pad of Florisil, concentrated *in vacuo*, and purified by column chromatography on silica gel (hexane/ethyl acetate from 4:1 to 1:1), to afford the title compound as a white solid (44 mg, 88% yield).

Compound data:

Mp 183–184 °C.

^{1}H NMR (500MHz, $CDCl_3$): δ 8.90 (d, J = 2.6 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.93 (dd, J = 7.6, 2.0 Hz, 1H), 7.67–7.63 (m, 2H), 7.42 (dd, J = 8.3, 4.3 Hz, 1H), 7.28 (d, J = 6.9 Hz, 1H), 6.13 (d, J = 6.9 Hz, 1H), 2.17 (s, 3H), 1.84 (s, 3H).

^{13}C NMR (125MHz, $CDCl_3$): δ 164.3, 151.4, 143.9 (2 Carbons), 137.3, 136.9, 136.2, 129.3, 129.3, 129.1, 126.7, 126.3, 121.8, 105.4, 20.7, 17.0.

GC-MS (EI) *m/z* (relative intensity): 249 (M^+, 100), 234 (14), 129 (14), 101 (14), 77 (28).

HRMS (APCI+): *m/z* calcd for $C_{16}H_{14}N_2O$ [M+H^+] 251.1179; found: 251.1189.

Single crystal X-ray diffraction analysis

Single crystals of the compounds were obtained by recrystallization over chloroform and ethanol. All measurements were performed on a RIGAKU R-AXIS RAPID II (imaging plate detector) diffractometer, using CuKα (graphite monochromated) radiation.

3,6-Dimethyl-5-trimethylsilyl-1-(quinolin-8-yl)pyridin-2(1*H*)-one

Empirical formula	$C_{19}H_{22}N_2OSi$	
Formula weight	322.15	
Crystal system	triclinic	
Unit cell dimensions	a = 11.3218(6) Å	α = 82.162(6) °
	b = 13.7043(7) Å	β = 76.405(5) °
	c = 14.1697(7) Å	γ = 79.506(6) °
Volume	2091.1(2) $Å^3$	
Space Group	P^{-1}	
Z	2	
D_{calc}	1.171 g/cm^3	
F_{000}	788.0	
R index ($I > 2\sigma(I)$)	R1 = 0.1251	
	wR2 = 0.3744	

5-Butyl-3,4-dimethyl-6-phenyl-1-(quinolin-8-yl)pyridin-2(*1H*)-one

Empirical formula	$C_{26}H_{26}N_2O$	
Formula weight	382.20	
Crystal system	triclinic	
Unit cell dimensions	a = 9.5344(7) Å	α = 99.625(7) °
	b = 10.5637(8) Å	β = 108.353(8) °
	c = 11.6075(8) Å	γ = 106.680(7) °
Volume	1019.39(14) Å^3	
Space Group	*P*-1	
Z	2	
D_{calc}	1.246 g/cm^3	
F_{000}	408.0	
R index ($I > 2\sigma(I)$)	R1 = 0.0889	
	wR2 = 0.2977	

5-10. References and Notes

[1] (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (b) Negishi, E. *Bull. Chem. Soc. Jpn,* **2007**, *80*, 233–257. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964.

[2] Ilies, L.; Okabe, J.; Yoshikai, N. Nakamura, E. *Org. Lett.* **2010**, *12*, 2838–2840.

[3] (a) Shirakawa, E.; Masui, S.; Narui, R.; Watabe, R.; Ikeda, D.; Hayashi, T. *Chem. Commun.* **2011**, *47*, 9714–9716. (b) Shirakawa, E.; Ikeda, D.; Masui, S.; Yoshida, M.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 272–279. (c) Ilies, L.; Yoshida, T.; Nakamura, E. *J. Am. Chem. Soc.* **2012**, *134*, 16951–16954. (d) Ilies, L.; Yoshida, T.; Nakamura, E. *Synlett* **2014**, 527–530.

[4] Iron-catalyzed Heck-type reaction using an aryl iodide: Loska, R.; Volla, C. M. R.; Vogel, P. *Adv. Synth. Catal.* **2008**, *350*, 2859–2864.

[5] (a) Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 6557–6559. (b) Ilies, L.; Matsumoto, A.; Kobayashi, M.; Yoshikai, N.; Nakamura, E. *Synlett* **2012**, 2381–2384. (c) Kischel, J.; Jovel, I.; Mertins, K.; Zapf, A.; Beller, M. *Org. Lett.* **2006**, *8*, 19–22.

[6] Matsumoto, A. Ph.D. thesis.

[7] Murai, S.; Kakiuchi, F.; Skine, S.; Tanaka, Y.; Kamatani, A. *Nature* **1993**, *366*, 529–531.

[8] Selected examples of *ortho*-alkylation using olefins: Cobalt catalyst: (a) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400–402. (b) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221–5223. Ruthenium catalyst: (c) Uchimaru, Y. *Chem. Commun.* **1999**, 1133–1134. Iridium catalyst: (d) Pan, S.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474–17477. (e) Crisenza, G. E. M.; McCreanor, N. G.; Bower, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 10258–10261. Rhodium catalyst: (f) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440–3442. (g) Lim, Y.-G.; Koo, B. K. *Tetrahedron Lett.* **2005**, *46*, 7997–8001.

[9] Selected examples for directed *ortho*-alkenyaltion using terminal olefins: Rhodium

catalyst: (a) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982–9983. (b) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094–7099. Palladium catalyst: (c) Nishikata, T.; Lipshuts, B. H. *Org. Lett.* **2010**, *12*, 1972–1975. (d) Rauf, W. R.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009**, 3874–3876. (e) Amatore, C.; Cammoun, C.; Jutand, A. *Adv. Synth. Catal.* **2007**, *349*, 292–296. (f) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587. (g) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666–7673. (h) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137–14151.

[10] Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320–2322.

[11] Ilies, L.; Ichilawa, S.; Asako, S.; Matsubara, T.; Nakamura, E. *Adv. Synth. Catal.* DOI: 10.1002/asia.201501095.

[12] Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859.

[13] Only two examples on directed alkenyaltion using unactivated terminal olefins are known: (a) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540–542. (b) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. *J. Am. Chem. Soc.* **2014**, *136*, 13602–13605.

[14] See reviews for C–H bond cleavage / alkyne insertion: (a) Vasil'ev, A. V. *Russ. J. Org. Chem.* **2009**, *45*, 1–17. (b) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111–1125. (c) Nakao, Y. *Chem. Rec.* **2010**, *11*, 242–251. (d) de Mendoza, P.; Echavarren, A. M. *Pure Appl. Chem.* **2010**, *82*, 801–820.

[15] (a) Chattejee, A.; Banerjee, S. *Tetrahedron* **1970**, *26*, 2599–2608. (b) Martens, H.; Hoornaert, G. *Synth. Commun.* **1972**, *2*, 147–156.

[16] House, H. O.; Larson, J. K. *J. Org. Chem.* **1968**, *33*, 448–451.

[17] Selected examples: (a) Delaunay, J.; Simonet, J. *Tetrahedron Lett.* **1988**, *29*, 543–544. (b) Xi, Q.; Zhang, W.; Zhang, X. *Synlett* **2006**, 945–947. (c) Finke, A. D.; Haberland, S.; Schweizer, W. B.; Chen, P.; Diederich, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9827–9830. (d) Buggle, K.; Ghógáin, Ú, N.; O'Sullivan, D. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 2075–2076. (e) Horspool, W. M. *J. Chem. Soc. C.* **1971**, 400–404.

[18] Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579–4583.

[19] (a) Kuninobu, Y.; Matsuki, T.; Takai, K. *Org. Lett.* **2010**, *12*, 2948–2950. (b) Chen, S.; Yu, J.; Jiang, Y.; Chen, F.; Cheng, J. *Org. Lett.* **2013**, *15*, 4754–4757.

[20] (a) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1996**, *61*, 6941–6946. (b) Kokubo, K.; Matsumasa, M.; Miura, M.; Nomura, M. *J. Organomet. Chem.* **1998**, *560*, 217–222.

[21] (a) Li, B.-L.; Wang, H-Y.; Zhu, Q.-L.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3948–3952. A similar reaction using thioamides: (b) Yokoyama, Y.; Unoh, Y.; Bohmann, R. A.; Satoh, T.; Hirano, K.; Bolm, C.; Miura, M. *Chem. Lett.* **2015**, *44*, 1104–1106.

[22] Similar reaction pathway using indole amide substrate give pyrroloindole derivatives: Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424–5431.

[23] Trace amount of tetraphenylnaphthalene that was formed through [2+2+2] cycloaddition was observed: See ref. 5b.

[24] When the mixture was quenched with neutral water, imine was observed, which also supports the mechanism.

[25] Similar reaction using strained olefins: Ito, S.; Itoh, T.; Nakamura, M. *Angew. Chem., Int. Ed.* **2010**, *50*, 454–457.

[26] Selected examples using rhodium or ruthenium catalyst through hydroarylation pathway: (a) Kakiuchi, F.; Sato, T.; Tsujimoto, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem, Lett.* **1998**, 1053–1054. (b) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759–2761. (c) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910–6911. (d) Zhao, P.; Niu, R.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 4166–4169. (e) Li, B.; Ma, J.; Liang, Y.; Wang, N.; Xu, S.; Song, H.; Wang, B. *Eur. J. Org. Chem.* **2013**, 1950–1962. (f) Wang, F.; Qi, Z.; Sun, J.; Zhang, X.; Li, X. *Org. Lett.* **2013**, *15*, 6290–6293. (g) Qian, Z.-C.; Zhou, J.; Li, B.; Hu, F.; Shi, B.-F. *Org. Biomol. Chem.* **2014**, *12*, 3594–3597. (h) Zhao, D.; Nimphius, C.; Lindale, M.; Glorius, F. *Org. Lett.* **2013**, *15*, 4504–4507. (i) Hashimoto, Y.; Hirano, K.; Satoh, K.; Kakiuchi, F.; Miura, M. *J. Org. Chem.* **2013**, *78*, 638–646.

[27] A cobalt-catalyzed reaction: Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283–17295.

[28] Very recently, aromatic alkenyaltion of C–H bond under similar reaction conditions has reported: Wong, M. Y.; Yamakawa, T.; Yoshikai, N. *Org. Lett.* **2015**, *17*, 442–445.

[29] Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568–5569.

[30] For a review on isoquinolone synthesis, see: Glushkov, V. A.; Shklyaev, Y. V. *Chem. Heterocycl. Compd.* **2001**, *37*, 663–687.

[31] Selected examples for isoquinolone synthesis from amides and alkynes through C–H bond activation: Rhodium catalyst: Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908–6909. (b) Hyster, T. Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569. (c) Wang, H.; Grohmann, C.; Nimphius, C. Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592–19595. Ruthenium catalyst: (d) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379–6382.; Nickel catalyst: (e) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955.

[32] Shamma, M. *The isoquinolone Alkaloids, Chemistry and Pharmacology*; Blomquist, A. T.; Wasserman, H. Eds; Academic Press New York and London, **1972**.

[33] Nakamura, Y.; Ilies, L.; Nakamura, E. *Org. Lett.* **2011**, *13*, 5998–6001.

[34] (a) Kozikowski, A. P.; Tückmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641–650. (b) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. I.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888–3890.

[35] (a) Mitscher, L. A.; *Chem. Rev.* **2005**, *105*, 559–592. (b) Lagoja, I. M.; *Chem. Biodiversity* **2005**, *2*, 1–50. (c) Hibi, S.; Ueno, K.; Nagato, S.; Kawano, K.; Ito, K.; Norimine, Y.; Takenaka, O.; Hanada, T.; Yonaga, M. *J. Med. Chem.* **2012**, *55*, 10584–10600.

[36] For a review of the 2-pyridone synthesis: Keller, P. A.; In *Science of Synthesis*; Black, D. StC., Ed.; Georg Thieme Verlag: Stuttgart • New York, **2005**, *15*, 285–387.

[37] Selected examples for 2-pyridone synthesis: (a) Fujii, M.; Nishimura, T.; Koshida, T.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2013**, *15*, 232–234. (b) Boisse, T.; Rigo,

B.; Millet, R.; Hénichart, J. P. *Tetrahedron* **2007**, *63*, 10511–10520. (c) Chen, L.; Zhao, Y.-L.; Liu, Q.; Cheng, C.; Piao, C.-R. *J. Org. Chem.* **2007**, *72*, 9259–9263. (d) Tsai, T.-H.; Chung, W.-H.; Chang, J.-K.; Hsu, R.-T.; Chang, N.-C. *Tetrahedron* **2007**, *63*, 9825–9835. (e) Imase, H.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 3563–3566. (f) Liu, J.; Liang, D.; Wang, M.; Liu, Q. *Synthesis* **2008**, 3633–3638. (g) Zhang, R.; Zhang, D.; Guo, Y.; Zhou, G.; Jiang, Z.; Dong, D. *J. Org. Chem.* **2008**, *73*, 9504–9507. (h) Smith, A. B., III.; Atasoylu, O.; Beshore, D. C. *Synlett* **2009**, 2643–2646.

[38] (a) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209–10212. (b) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278–3281. (c) Su, Y.; Han, K.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5462–5465. (d) Hyster, T. K.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1606–1610.

[39] See the previous chapters for details.

[40] Bromoalkane could be an alkyl donor for C–H activation, or cross-coupling reactions. See Chapter 4 for details.

[41] Yu, D.-G.; de Azanbuja, F.; Gensch, T.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 9650–9654.

[42] Selected examples for functionalization of pyridone core: (a) Itahara, T.; Ouseto, F. *Synthesis* **1984**, 488–489. (b) Cheng, D.; Gallagher, T. *Org. Lett.* **2009**, *11*, 2639–2641. (c) Chen, Y.; Wang, F.; Jia, A.; Li, X. *Chem. Sci.* **2012**, *3*, 3231–3236. (d) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Eur. J.* **2013**, *19*, 7691–7695. (e) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2014**, *79*, 1377–1385. (f) Modak, A.; Rana, S.; Maiti, D. *J. Org. Chem.* **2015**, *80*, 296–303. (g) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996–15997. (h) Tamura, R.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5679–5682. (i) Tsai, C.-C.; Shin, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887–11889.

[43] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2924.

[44] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics,* **1996**, *15*, 1518–1520.

[45] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890–891.

[46] Isogai, Y.; Menggenbateer; Khan, F. N.; Asao, N. *Tetrahedron* **2009**, *65*, 9575–9582.

[47] Zhu, G.; Negishi, E.-i. *Chem. Eur. J.* **2007**, *14*, 311–318.

[48] Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 14349–14352.

[49] Katsumoto, K.; Kitamura, C.; Kawase, T. *Eur. J. Org. Chem.* **2011**, 25, 4885–4891.

[50] Wilson, S. R.; Jacob, L. A. *J. Org. Chem.* **1986**, *51*, 4833–4836.

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)

Acknowledgements

All the research presented in this thesis was carried out under the supervision of Professor, Dr. Eiichi Nakamura at the Department of Chemistry, School of Science of The Univesity of Tokyo during April 2011 to December 2015.

First and foremost, I wish to express my deepest gratitude to Professor, Dr. Eiichi Nakamura for his kind direction, constructive discussion and advice, and considerable encouragement throughout this work. I would like to express my deep appreciation to Associate Professor, Dr. Laurean Ilies for his valuable advice, discussions and constant encouragement.

I am particularly grateful for insightful comments and suggestions about this thesis given by Professor, Dr. Makoto Onaka, Professor, Dr. Shū Kobayashi, Associate Professor, Dr. Masayuki Satake, and Associate Professor, Dr. Yoshinori Yamanoi.

I am also grateful to Associate Professor, Dr. Hayato Tsuji, Project Associate Professor, Dr. Koji Harano, Assistant Professor, Dr. Shunsuke Furukawa (Saitama University), Project Lecturer, Dr. Hideyuki Tanaka (The Univesity of Tokyo) for their support, helpful advice, and encouragement through this work.

I would like to be grateful for Professor, Dr. Kazunari Domen at the department of Applied Chemistry, School of Engineering of The Univesity of Tokyo, for insightful comments and suggestions though MERIT course curriculums.

Also I would like to be grateful for Professor, Dr. Jun Okuda (RWTH Aachen University) for his kind direction, constructive discussion and continuous support of my research in Germany, during December 2013 to March 2014. I am also grateful to Mr. Valeri Leich for his continuous support and helpful advice during that time.

I would like to show my appreciation to Assistant Professor, Dr. Arimasa Matsumoto (Tokyo University of Science), Assistant Professor, Dr. Yuki Nakamura (The Univesity of Tokyo), Dr. Masaki Sekine, Mr. Motoaki Kobayashi, Mr. Eita Konno,

Mr. Takumi Yoshida, Mr. Hiroki Sato, Ms. Mayuko Isomura and Mr. Takenari Sato for their helpful discussion and continuous encouragement for research and daily life. My appreciation also goes Assistant Professor, Dr. Sobi Asako (Okayama University), Dr. Rui Shang, Dr. Bingwei Zhou, Mr. Yuki Itabashi, Ms. Saki Ichikawa, Ms. Yi Zhou and Mr. Toki Go for valuable discussion and constructive advice for iron-catalyzed C–H bond activation chemistry, especially the work described in Chapter 4.

My delightful and exciting life during Ph.D. research is owed to wonderful members in Nakamura Laboratory, especially those who work in the same floor: Dr. Qifan Yan, Dr. Nai-Ti Lin, Mr. Hiroki Nishioka, Mr. Mizuki Kudo, Mr. Tomoya Nakamura, Mr. Kohei Hashimoto, Mr. Yuzuru Kanda, Ms. Anna Ichimura, Mr. Yuki Tachibana and Mr. Hiroyoshi Hamada. Daily life in Nakamura Laboratory was really full of fun.

I am very happy to work with excellent colleagues, Mr. Satoshi Okada, Mr. Kazutaka Shoyama and Mr. Junya Yamada. They always motivate me and give me enjoyable daily life in the Nakamura Lab.

I thank the Program for Leading Graduate Schools (MERIT) for financial support and giving me various opportunities for learning from both academia and industry. All of my MERIT colleagues are appreciated, who are always inspiring me. I also thank the Japan Society for Promotion of Science (JSPS) Research Fellowship for Young Scientists for financial support.

Finally, I express my deep appreciation to my family, Mr. Hiroshi Matsubara, Mrs. Naomi Matsubara and Mr. Keisuke Matsubara for their constant assistant and affectionate encouragement.

Tatsuaki Matsubara

February 2016