

Development of Transition Metal-Catalyzed Carbon–Carbon Bond  
Forming Reactions Based on Carbon–Hydrogen Bond Activation  
via Metalacycles

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# Chapter 1

## General Introduction

### 1-1. C–H Bond Activation

The activation of the carbon–hydrogen (C–H) bonds has been regarded as a challenging task. This is because of unique characteristics of them such as (i) the second highest bond dissociation energy among carbon-containing  $\sigma$  bonds, (ii) a short bond length, and (iii) difficulty in selective substitution (Table 1-1).<sup>[2]</sup>

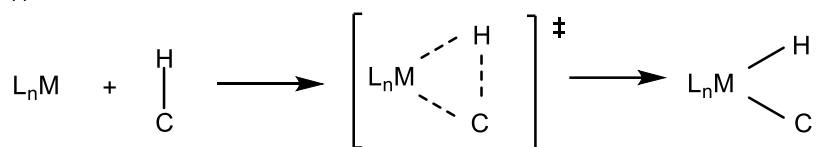
Table 1-1.

Atom (X)	Average C—X bond lengths / Å	Bond dissociation energy C—X / kcal mol <sup>-1</sup>
H	1.09	98.8
C	1.54	83.1
N	1.47	69.7
O	1.43	84.0
F	1.35	105.4
Cl	1.77	78.5
Br	1.93	65.9
I	2.13	57.4

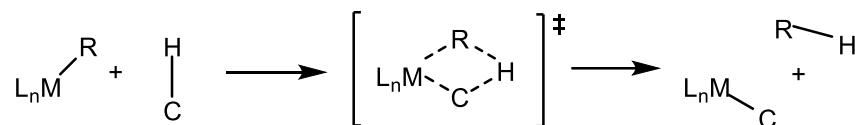
To solve the problem in synthetic organic chemistry, the methods for metal-mediated activation of unactivated C–H bonds have been increasingly developed in the past couple of decades. Conventional C–H bond cleavage mediated by metal complexes is generally divided into four types of processes according to how C–H bonds react with metal complexes (Scheme 1-1). For example, (i) oxidative addition, (ii)  $\sigma$ -bond metathesis, and (iii) concerted metallation–deprotonation (CMD) as illustrated in Scheme 1-1 are known as typical elementary steps for metal-mediated C–H bond cleavage. In these reactions, both cleavage of the C–H bond and formation of the C–M (Metal) bond proceed in one concerted step. In contrast, in (iv) electrophilic substitution, the formation of C–M bond proceeds prior to the cleavage of the C–H bond. In total, C–H bonds are thus transformed to C–M bonds in a stepwise manner.

Scheme 1-1.

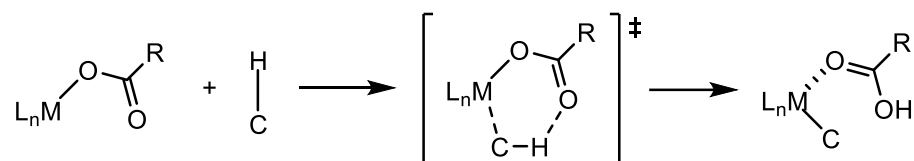
(i) oxidative addition



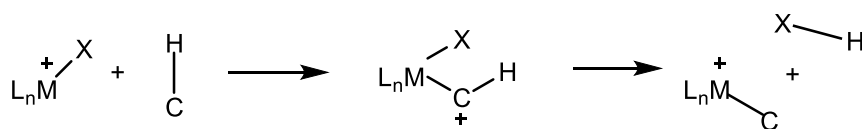
(ii)  $\sigma$ -bond metathesis



(iii) concerted metallation deprotonation



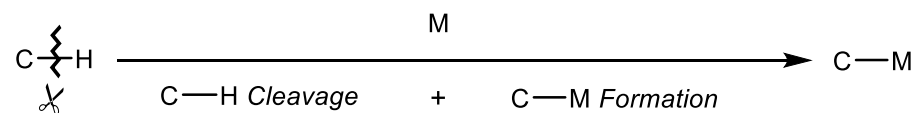
(iv) electrophilic substitution



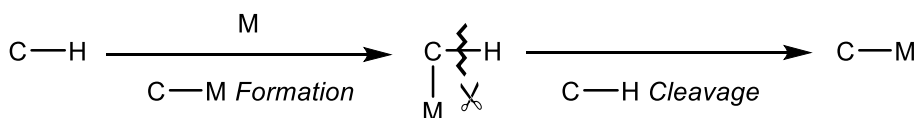
In this doctoral dissertation, C–H bond activation reactions involving simultaneous C–H cleavage and C–M formation, such as processes (i), (ii), and (iii), and stepwise C–H cleavage and C–M formation, such as process (iv), are defined as *direct* and *indirect* C–H bond activation, respectively (Scheme 2). Most of the C–H bond activation reactions reported to date are *direct* C–H bond activation.

Scheme 1-2.

## 1. *Direct* C–H Bond Activation



## 2. *Indirect* C–H Bond Activation

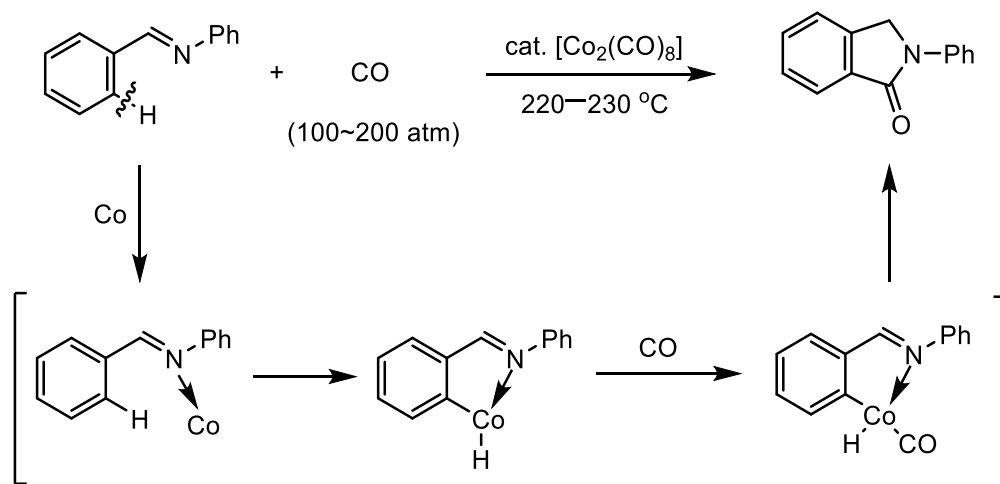


## 1-2. Transition Metal-Catalyzed C–H Bond Activation Using Chelation System

The transition metal-catalyzed functionalization via C–H bond activation is a powerful tool for synthetic organic chemistry in recent years. This method can reduce not only the number of reaction steps from starting materials but also harmful wastes compared to typical transition metal-catalyzed cross-coupling reactions of organometallic nucleophiles with halide electrophiles, which are used as conventional, general methods for forming carbon–carbon bonds. Precious transition metals such as palladium, rhodium, iridium, and ruthenium have been mainly used for functionalization via C–H bond activation. In contrast, there has been only a few examples of C–H bond activation using cheap and common metals such as nickel, copper, cobalt, and iron. Developing reactions using these ubiquitous metals remains a challenging task. The following paragraphs overview a historical background of transition metal-mediated and -catalyzed *direct* C–H bond activation, which promote chelation-assisted C–H bond cleavage.

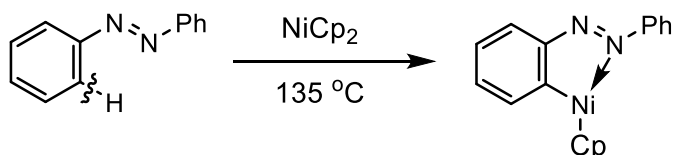
In 1955, Murahashi reported a cobalt-catalyzed chelation-assisted C–H bond functionalization of an aromatic imine (Scheme 1-3).<sup>[3]</sup> In this reaction, the nitrogen atom of the imine first coordinates to the cobalt, which helps the approach of cobalt to the *ortho* C–H bond on the benzene ring and thus cleave it through oxidative addition to form a chelation-stabilized cobaltacycle intermediate. Subsequent carbonylation with hydrogen transfer proceeds to afford *N*-phenylisoindolinone. This reaction is the first example of the chelation-assisted C–H bond functionalization with a transition metal catalyst. However, further application had not been developed for a long time because the harsh reaction conditions were needed.

Scheme 1-3.



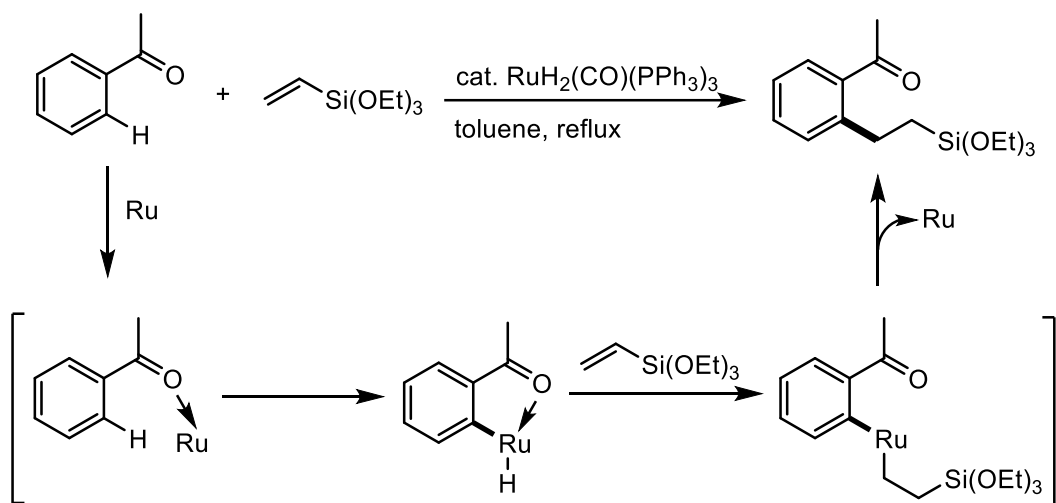
In 1963, Kleiman and Dubeck reported a similar method for activation of C(sp<sup>2</sup>)-H bond in azobenzene by using nickel-mediated chelation system (Scheme 4).<sup>[4]</sup> The key intermediate in this reaction is a chelation-stabilized five-membered nickelacycle. Although this reaction had not been studied further, the coordination ability of the heteroatoms was proved to be effective for regioselective C-H bond activation.

Scheme 1-4.



In 1993, Murai reported an epoch-making catalytic C-H bond activation reaction. In the presence of a ruthenium catalyst, treatment of acetophenone with a vinylsilane gave an *ortho*-alkylated product via aromatic C-H bond activation (Scheme 1-5).<sup>[5]</sup> In this reaction, oxidative addition of the *ortho* C-H bond to a Ru(0) species, generated *in situ* via H<sub>2</sub> elimination, is promoted by coordination of the acetyl group to Ru(0), which is followed by insertion of a vinylsilane into the Ru-H bond. Subsequent reductive elimination affords the product and regenerates the active Ru(0) species. This reaction proceeds catalytically under much milder conditions compared to those of Murahasi's reaction.

Scheme 1-5.

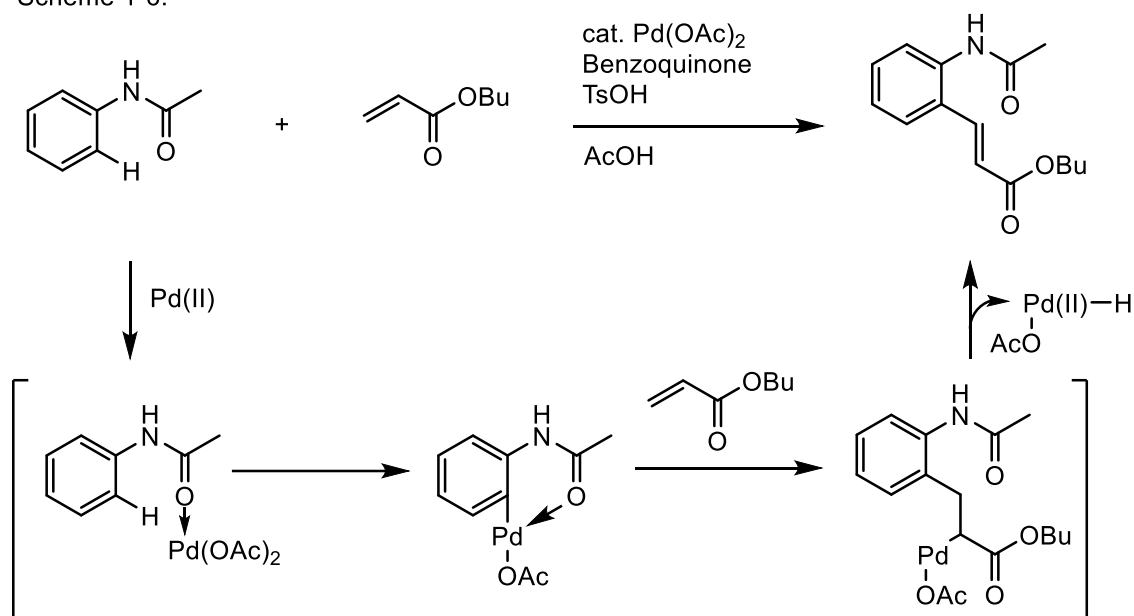


Since Murai's pioneering work appeared in the world, Not only acetyl group but also other coordinating functional groups have been utilized as directing groups for transition metal-catalyzed C-H bond activation. For example, in 2002, Leeuwen reported palladium-catalyzed oxidative coupling between acetanilides and

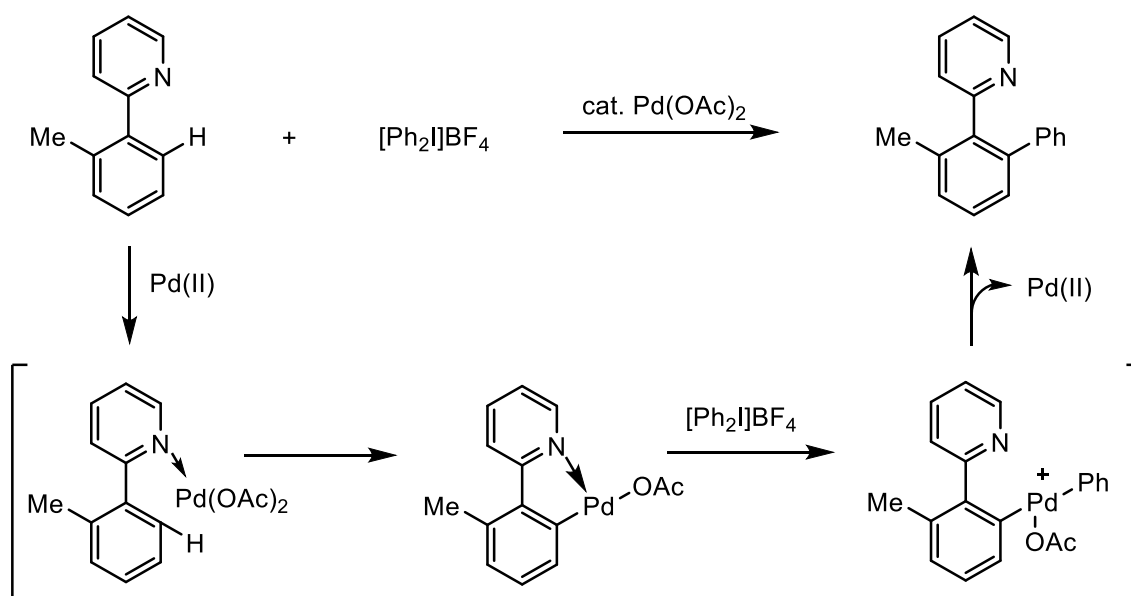


acrylates via aromatic *ortho* C–H bond activation (Scheme 1-6).<sup>[6]</sup> Here the amide group serves as a directing group to promote Pd-mediated C–H bond cleavage via the CMD mechanism. The coupling products are obtained via the following insertion of acrylate and  $\beta$ -hydrogen elimination. Moreover, in 2005, Sanford reported Pd-catalyzed phenylation of aromatic C–H bond using a pyridinyl group as a directing group (Scheme 1-7).<sup>[7]</sup> In this reaction, C–H bond cleavage via the CMD mechanism proceeds via coordination of nitrogen atom of the pyridine moiety to Pd in the same manner as oxygen directing groups. Subsequent oxidative phenylation of Pd by  $[\text{Ph}_2\text{I}]\text{BF}_4$  and reductive elimination afforded phenylated products.

Scheme 1-6.

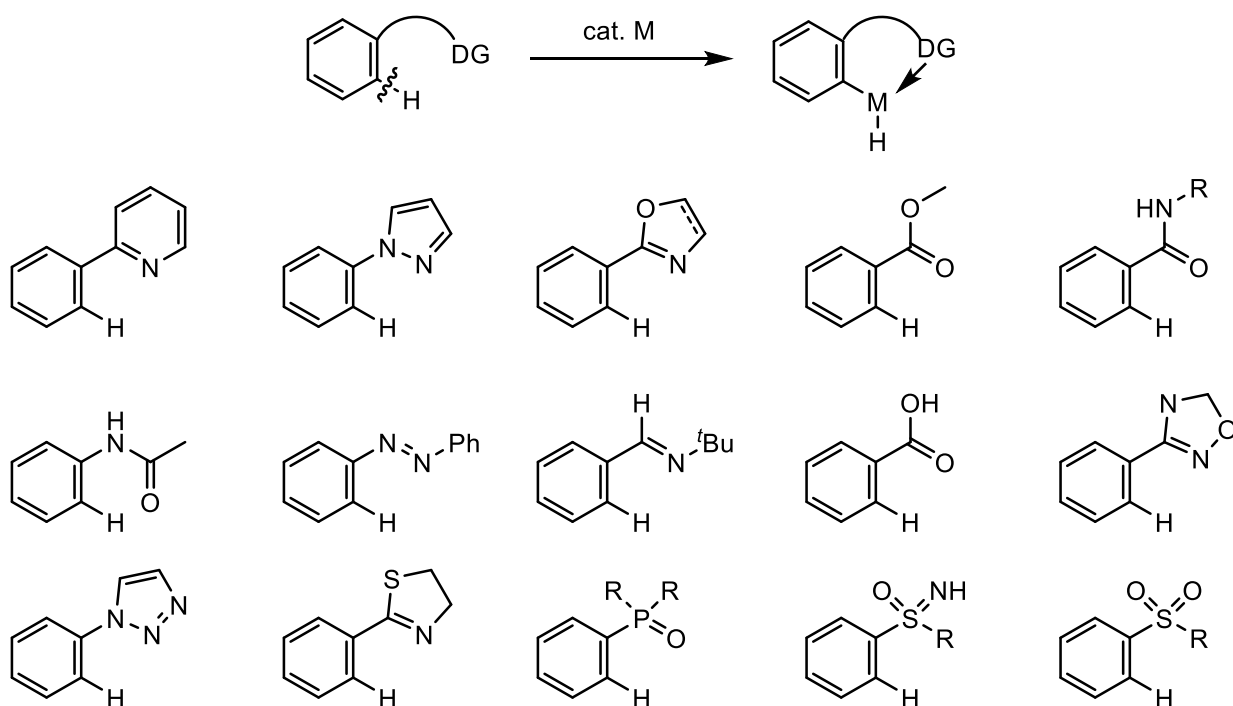


Scheme 1-7.

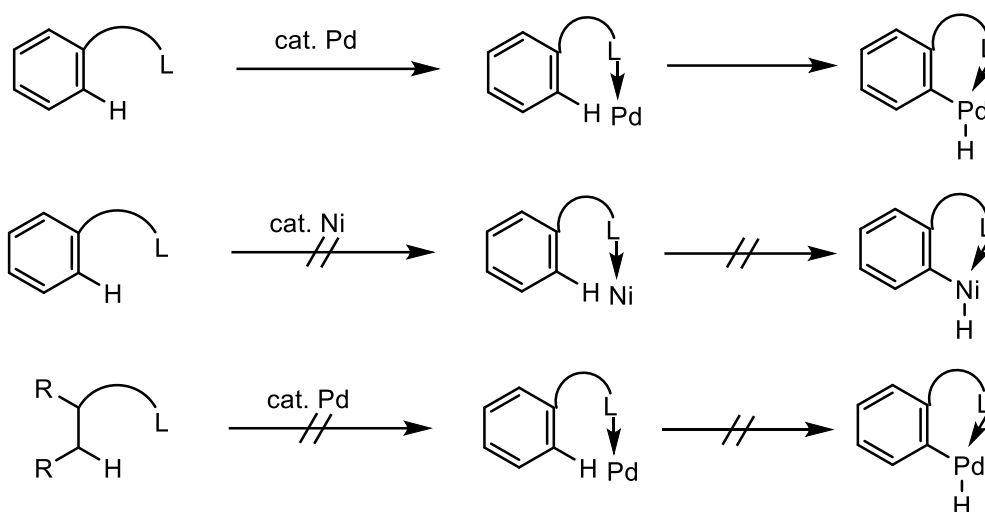


There have been many other directing groups used in metal-catalyzed C–H bond activation reactions. Oxygen atoms of carbonyl groups in esters, ketones, phosphine oxides, sulfonamides, and sulfoximines or nitrogen atoms in pyrazoles, oxazolines, triazoles, thiazoles, and imines have been typically used in a variety of reactions (Scheme 1-8).<sup>[1j]</sup> Although these directing groups had been used for selective activation of C(sp<sup>2</sup>)–H bonds, the metals used with them were mostly limited to specific precious metals such as palladium, rhodium, iridium, and ruthenium. At that time, C–H bond functionalization using common metals such as nickel, iron, and copper had been hardly achieved because of their low reactivity upon C–H bond cleavage. Functionalization of inert C(sp<sup>3</sup>)–H bonds using transition metal catalysts had also remained a major problem in synthetic organic chemistry (Scheme 1-9).

Scheme 1-8.

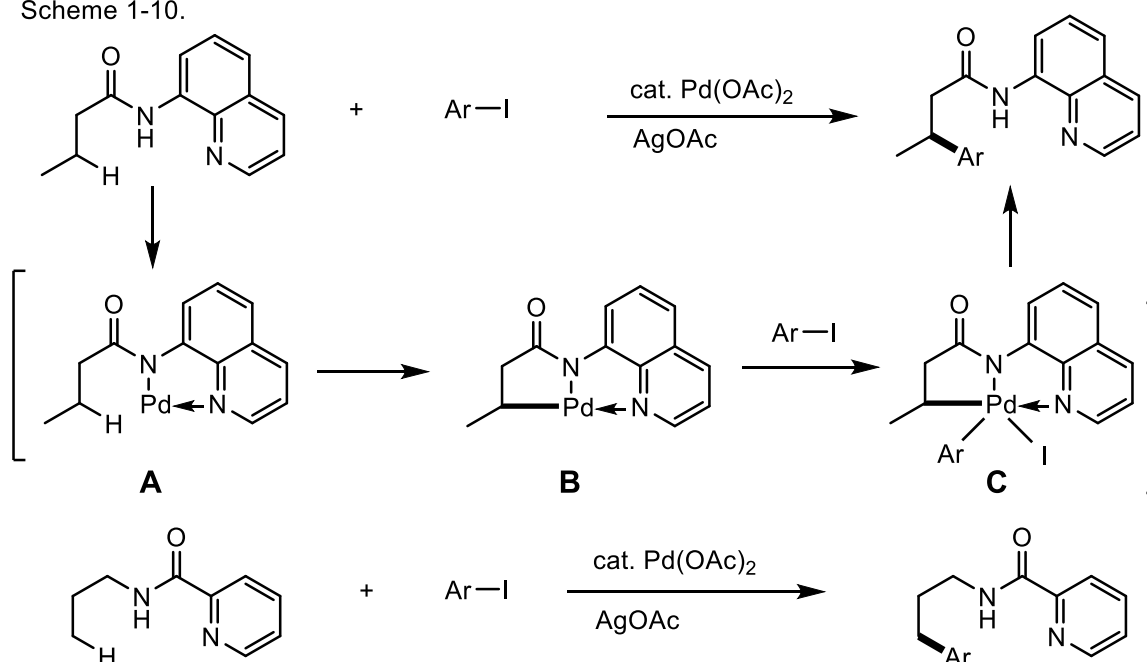


Scheme 1-9.



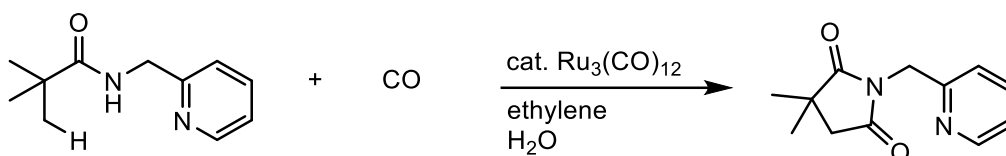
In 2005, Daugulis reached a solution to the former issue (Scheme 1-10).<sup>[8]</sup> They achieved Pd(II)-catalyzed arylation of C(sp<sup>3</sup>)-H bonds in aliphatic amides bearing a picolinamide or a 8-aminoquinoline moiety as a bidentate directing group. The chelate coordination of the amide moiety to a Pd(II) species followed by a ligand exchange process generates palladium complex **A**, which gave rise to the intermediate **B** via C-H bond cleavage through a CMD mechanism. The oxidative addition of aryl iodides to intermediate **B** followed by reductive elimination affords the product. The combination of a Pd(II) complex and a bidentate directing group activates inert C(sp<sup>3</sup>)-H bonds because the bidentate directing group strongly coordinate to Pd(II), stabilizing the formed metalacycles and thus Pd(II) readily approach the C(sp<sup>3</sup>)-H bonds.

Scheme 1-10.



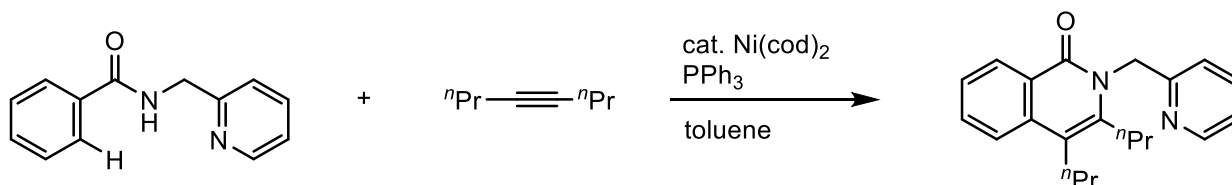
After the renaissance, the *direct* functionalization via C–H bond activation using various bidentate directing groups had been extensively studied for development of C–H bond activation, which was hardly achieved by conventional methods using monodentate directing groups. For example, Chatani demonstrated the Ru-catalyzed carbonylative cyclization via aliphatic C–H bond activation promoted by a 2-aminomethylpyridine moiety as the bidentate directing group (Scheme 1-11).<sup>[9]</sup>

Scheme 1-11.

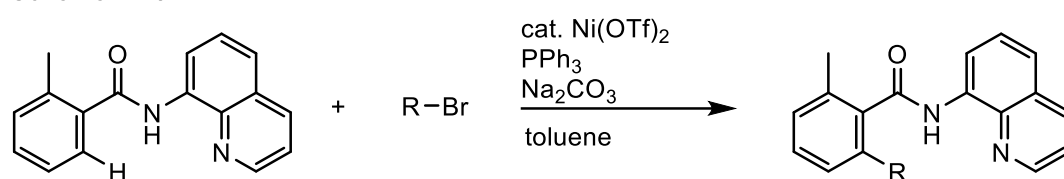


Use of bidentate directing groups enabled participation of ubiquitous metals (Ni, Cu and Fe) in catalytic C–H bond activation. In 2011, Chatani demonstrated the Ni-catalyzed oxidative annulation between aromatic amides and alkynes via aromatic C–H bond activation, which led to the synthesis of isoquinolines (Scheme 1-12).<sup>[10]</sup> This reaction represented the first example of Ni-catalyzed transformation via C–H bond activation assisted by a bidentate chelation. The combination of nickel catalysts with bidentate directing groups also allowed use of alkyl electrophiles as coupling counterparts in C–H bond activation reactions. First, nickel-catalyzed direct alkylation via aromatic C–H bond activation with primary alkyl halides was developed by Chatani (Scheme 1-13).<sup>[11]</sup> Compared with the primary alkyl halides, secondary alkyl halides are considered to be more difficult to use in C–H functionalization because of their reluctance to undergo oxidative additions to transition metals. However, in 2014, Ackermann developed nickel-catalyzed C–H bond alkylation with secondary alkyl bromides using a 8-aminoquinoline directing group (Scheme 1-14).<sup>[12]</sup>

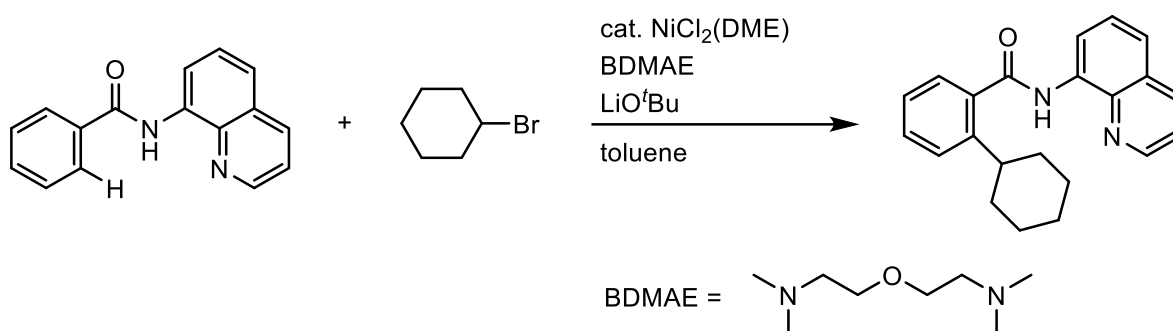
Scheme 1-12.



Scheme 1-13.

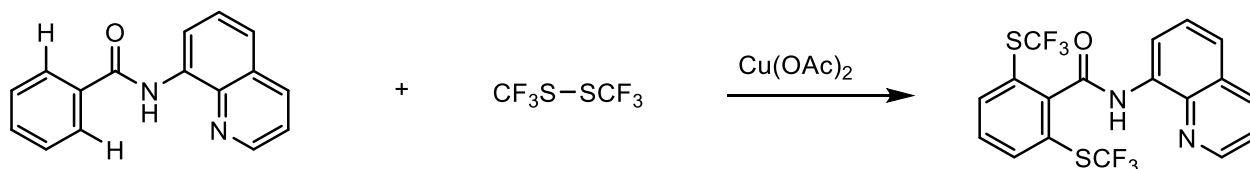


Scheme 1-14.

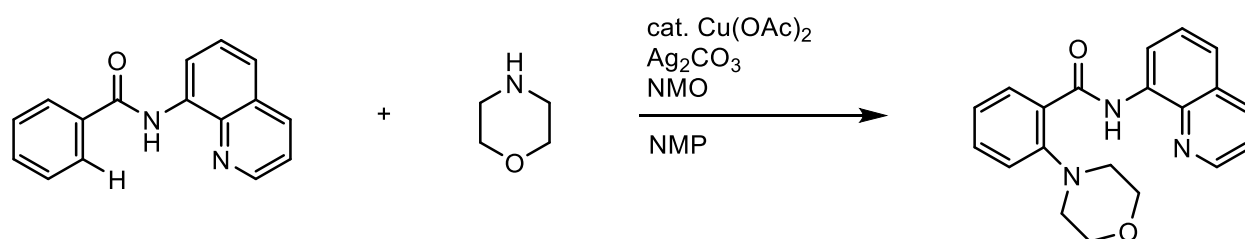


A cheap copper complex was also used for aromatic C–H bond activation. In 2012, Daugulis reported the copper-promoted C–H (trifluoromethyl)thiolation by treating aromatic amides bearing a 8-aminoquinoline moiety with bis(trifluoromethyl) disulfide (Scheme 1-15).<sup>[13]</sup> Moreover, the copper-catalyzed intermolecular C(sp<sup>3</sup>)–H bond amination was reported by Daugulis (Scheme 1-16).<sup>[14]</sup>

Scheme 1-15.

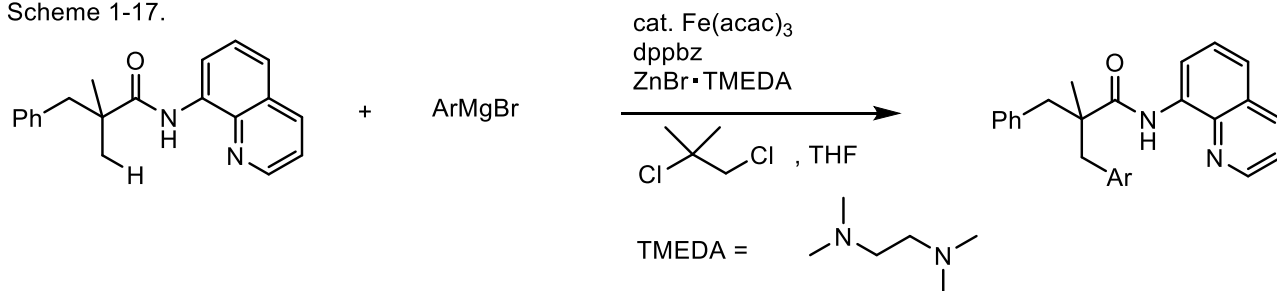


Scheme 1-16.



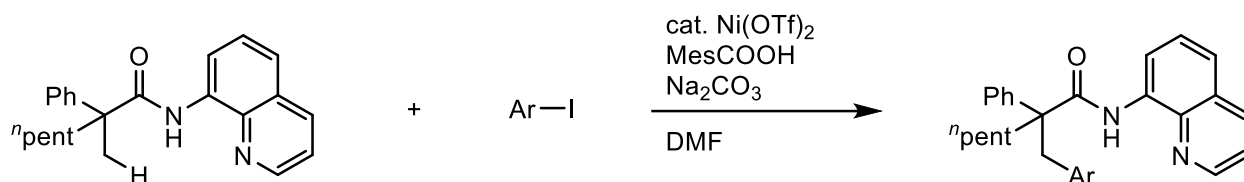
The iron-catalyzed  $\beta$ -arylation of 2,2-disubstituted propionamides with organozinc reagents in the presence of an organic oxidant and a bisphosphine ligand was disclosed by Nakamura (Scheme 1-17)<sup>[15]</sup>. The 8-aminoquinolinyl directing group and 1,2-bis(diphenylphosphino)benzene (dppbz) ligand were found to be essential for the transformation.

Scheme 1-17.

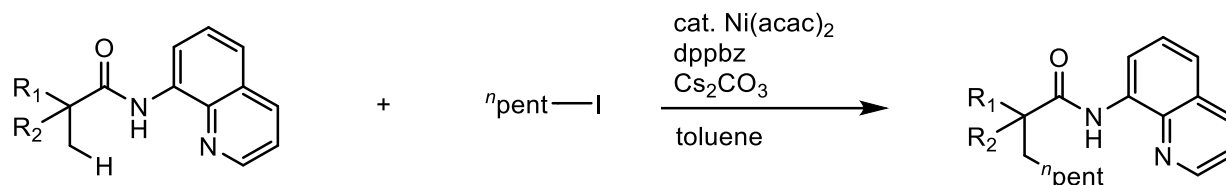


Eventually, aliphatic C–H bond activation was achieved by ubiquitous metals. Nickel-catalyzed direct arylation and alkylation via activation of inert C(sp<sup>3</sup>)–H bonds of 2,2-disubstituted propionamides bearing a 8-aminoquinolinyl group were developed by Chatani and Ge, respectively (Scheme 1-18, 1-19),<sup>[16,17]</sup>

Scheme 1-18.

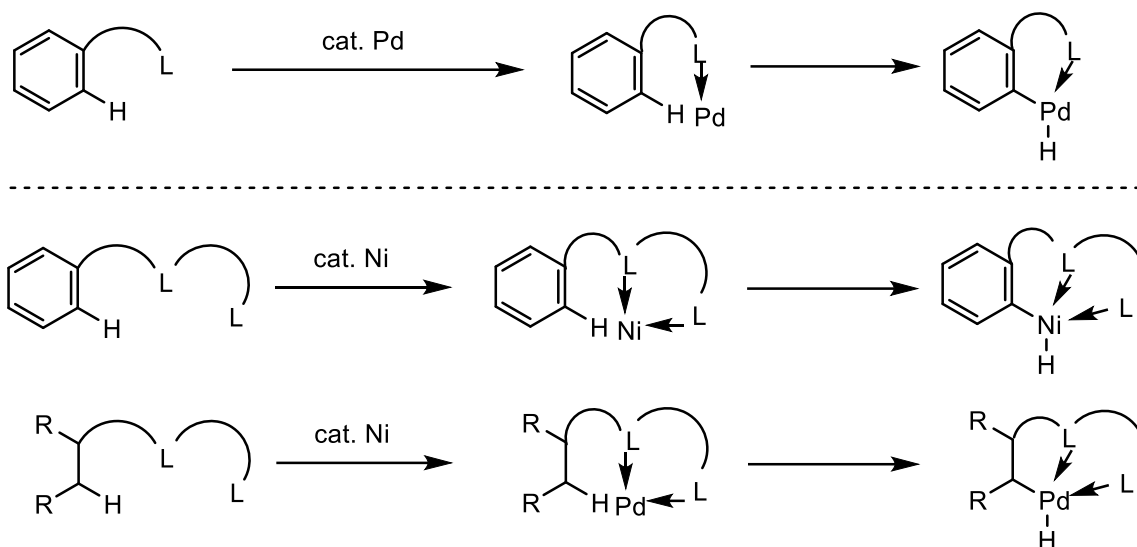


Scheme 1-19.



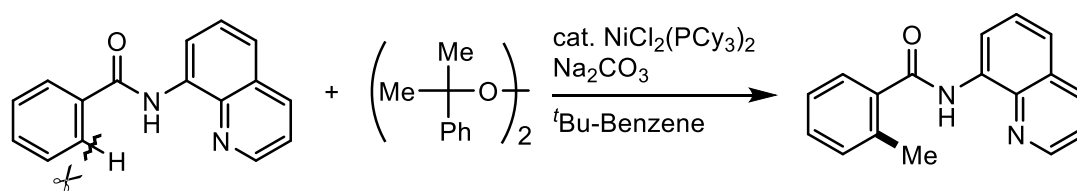
As described above, bidentate directing groups were found to serve as powerful tools for C–H bond activations involving (i) inexpensive and low active metal catalysts and/or (ii) cleavage of inert aliphatic C–H bonds (Scheme 1-20). In this doctoral dissertation, I challenged development of new types of *direct* C–H bond activation reactions by taking full advantage of bidentate directing groups (Chapters 2 and 3).

Scheme 1-20.



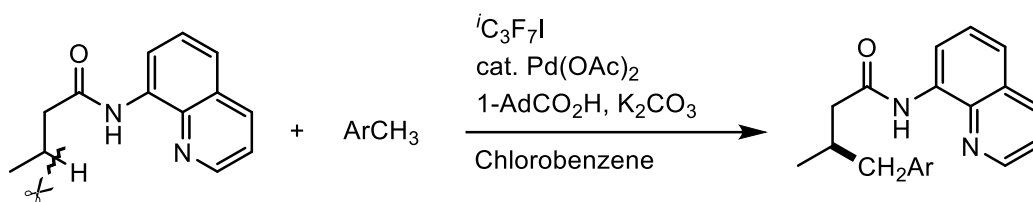
Chapter 2 describes the nickel-catalyzed methylation with dicumyl peroxide via *ortho* C–H bond activation in aromatic amides containing an 8-aminoquinoline moiety as a bidentate directing group (Scheme 1-21). In this chapter, I disclosed the first example of radical-driven C–H methylation via C–H bond activation, while conventional methods for metal-catalyzed C–H methylation were limited to electrophilic or nucleophilic methylation with methyl halides or methylmetal reagents, respectively.

Scheme 1-21.



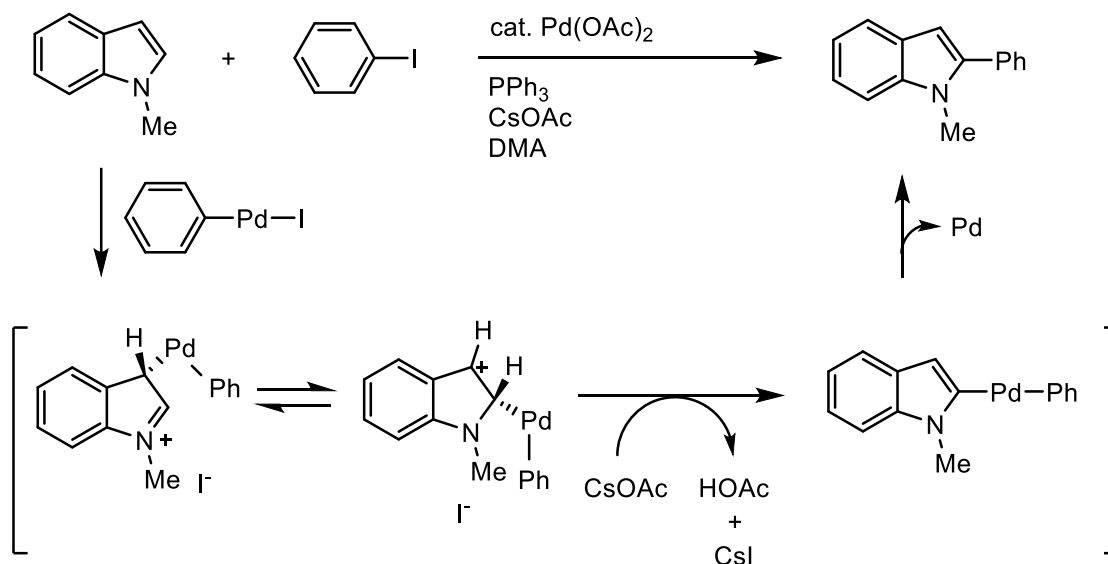
In Chapter 3, I achieved the palladium-catalyzed cross dehydrogenative coupling of aliphatic amides containing an 8-aminoquinoline moiety as a bidentate directing group with toluene derivatives (Scheme 1-22). This reaction involves chemoselective cross-coupling via C–H bond cleavage of both substrates via benzylic iodides as key intermediates.

Scheme 1-22.



Furthermore, I focus on metal-mediated *indirect* C–H bond activation as illustrated in Scheme 1-1 (iv). For example, Sames reported palladium-catalyzed C–H arylation of indoles. In this reaction, electrophilic addition of arylpalladium species to indoles proceeds to generate indolylpalladium intermediates via deprotonation. Subsequent reductive elimination affords 3-arylated indoles in a stepwise manner (Scheme 1-23).<sup>[18]</sup>

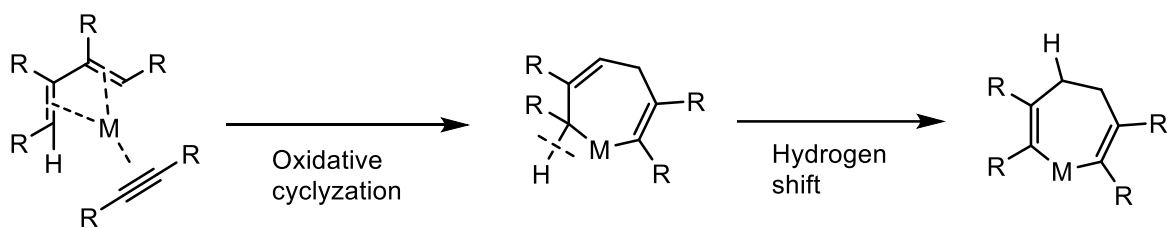
Scheme 1-23.



Apart from electrophilic substitution, I sought another method for *indirect* C–H bond activation facilitated by a transition metal-mediated elementary step. Oxidative cyclization is known as a typical elementary step mediated by transition metal species, and proceeds with multiple unsaturated substrates such as alkenes and alkynes. A hydrogen shift from the formed metalacycles induces C–H bond cleavage. Thus, *indirect* C–H bond activation can be achieved through a sequence of C–M bond formation and C–H bond cleavage via metalacycles as key intermediates (Scheme 1-24).

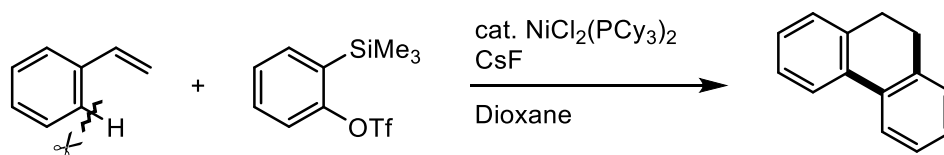


Scheme 1-24.



In Chapter 4, I succeeded in the nickel-catalyzed [4 + 2] cycloaddition of styrenes with arynes via 1:1 cross-coupling toward the synthesis of 9,10-dihydrophenanthrenes (Scheme 1-25). This type of *indirect* C–H bond activation has been unprecedented, in which the formation of C–M bond and the cleavage of the C–H bond proceed in a stepwise manner via oxidative cyclization.

Scheme 1-25.



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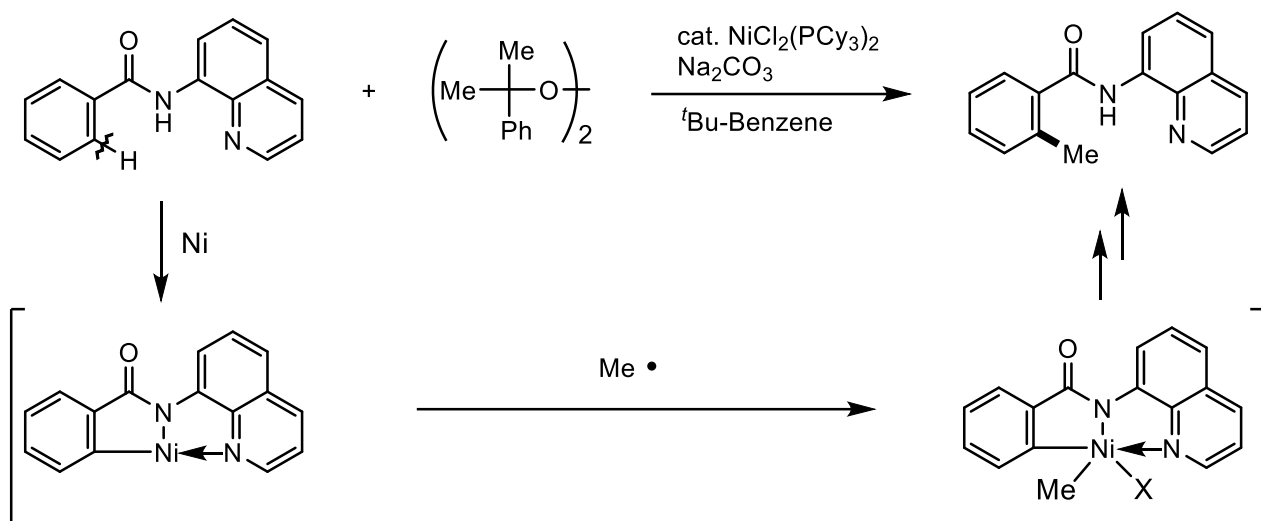
## Chapter 2

### Nickel-Catalyzed Methylation via *ortho* C–H Bond Activation in Aromatic Amides Using Dicumyl Peroxide

#### Abstract

The direct methylation of *ortho* C–H bonds in aromatic amides with dicumyl peroxide (DCP) using a nickel complex as the catalyst is accomplished. The reaction shows a high functional group tolerance and is inhibited by radical scavengers. In the cases of *meta*-substituted aromatic amides, the reaction proceeds in a highly selective manner at the less hindered C–H bonds.

Scheme 2-1.



#### 2-1. Introduction

The transition metal-catalyzed functionalization of C–H bonds is emerging as a powerful method for use in C–C bond formation and has received a great deal of attention in recent years. Various C–C bond formation reactions such as arylation, alkylation, benzylation, allylation, and carbonylation with the cleavage of C–H bonds have been reported to date. However, methylation of C–H bonds continues to remain an undeveloped area<sup>[1]</sup> compared with the other types of C–C bond formation reactions. Although the methyl group is one of the simplest functional groups, the introduction of a methyl group at the carbon bearing a C–H bond can have a significant effect on the biological and physical properties of a drug. The most

extensively studied direct methylation at the carbon bearing a C–H bond involves the use of electrophilic reagents, such as MeI and its equivalents<sup>[2]</sup> and PhMe<sub>3</sub>Ni.<sup>[3]</sup> Nucleophilic organometallic reagents, such as Me<sub>4</sub>Sn,<sup>[4]</sup> methylboron reagents,<sup>[5]</sup> MeMgCl,<sup>[6]</sup> Me<sub>3</sub>Al,<sup>[7]</sup> and Me<sub>2</sub>Zn<sup>[8]</sup> also can be used in the oxidative methylation of C–H bonds. In addition, peroxide,<sup>[9]</sup> DMSO,<sup>[10]</sup> and other reagents<sup>[11]</sup> have been found to function as methylating reagents.

Chatani previously reported a series of Ni-catalyzed chelation-assisted functionalizations of C–H bonds in which a combination of a Ni(II) catalyst and an 8-aminoquinoline directing group was found to be a superior system for Ni catalyzed chelation-assisted C–H bond activation.<sup>[12]</sup> This represents the first general system for Ni-catalyzed chelation-assisted functionalization of C–H bonds. Although the precise mechanism responsible for the functionalization remains unclear, a radical species is thought to be involved as a key intermediate on the basis of mechanistic experiments. Peroxides such as di-*tert*-butyl peroxide (TBP) and dicumyl peroxide (DCP) are known to undergo thermal decomposition to generate a methyl radical through  $\beta$ -scission of an alkoxy radical, which initiates the polymerization of alkenes<sup>[13]</sup> or functions as a methylating reagent.<sup>[14]</sup> In addition, the functionalization of C–H bonds with a radical species would demonstrate the potential for a new generation of C–H bond activation reactions.<sup>[15],[16]</sup> Our working hypothesis involves a reaction sequence in which an intermediate nickelacycle reacts directly with a methyl radical generated during the reaction. I herein describe the Ni-catalyzed methylation at the carbon bearing a C–H bond in aromatic amides with DCP.

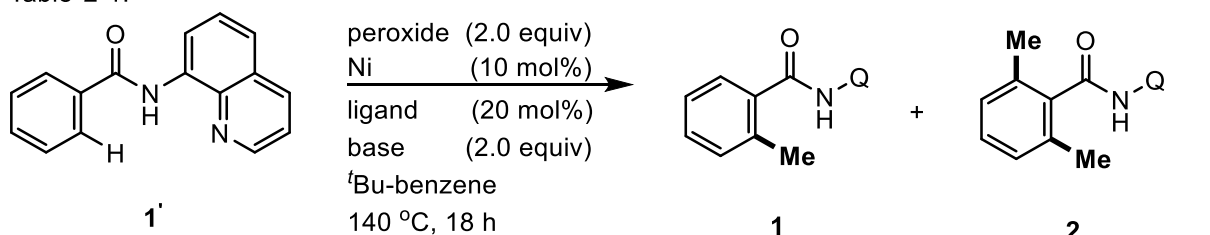
## 2-2. Nickel-Catalyzed Methylation via Aromatic C–H Bond Activation

### 2-2-1. Optimaization of Reaction Conditions for Ni-Catalyzed Methylation

First, the nickel-catalyzed methylation was examined by using amide **1'** as a model substrate (Table 2-1). When amide **1** (0.30 mmol) was reacted with TBP (0.60 mmol) in the presence of Ni(acac)<sub>2</sub> (0.03 mmol) as a catalyst, PPh<sub>3</sub> (0.06 mmol) as a ligand, and Na<sub>2</sub>CO<sub>3</sub> (0.60 mmol) as a base in *t*-Bu-benzene (0.7 mL) at 140 °C for 18 h, monomethylated product **1** and dimethylated product **2** were obtained in 19% and 6% yields, respectively (entry 1). Next, I examined Ni complexes (entries 1–3), bases (entries 3–5), and peroxides

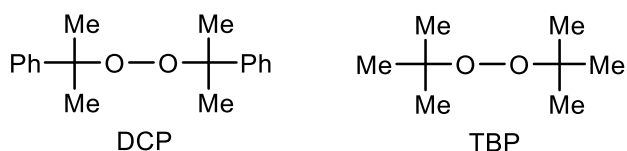
(entries 3, 6). Changing the peroxide from TBP to DCP and the Ni complexes improved the yield of methylated product **1** up to 34% (entry 6). The total yield of **1** and **2** was drastically improved upon use of NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> as a catalyst instead of the individual use of Ni complexes and ligands (entry 7). Increasing the amount of DCP lowers the material balance, while the dimethylated product **2** was selectively obtained (entry 8). Since controlling selective monomethylation or dimethylation of **1**' was found to be difficult, methylation of **1** was then examined.

Table 2-1.



entry	peroxide	Ni	ligand	base	<b>1</b> (%)	<b>2</b> (%)	<b>1</b> ' (%)
1	TBP	Ni(acac) <sub>2</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	19	6	47
2	TBP	Ni(OAc) <sub>2</sub> · 4H <sub>2</sub> O	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	11	1	31
3	TBP	NiI <sub>2</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	28	9	39
4	TBP	NiI <sub>2</sub>	PPh <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	15	6	32
5	TBP	NiI <sub>2</sub>	PPh <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	9	trace	35
6	DCP	NiI <sub>2</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	34	13	26
<b>7</b>	<b>DCP</b>	<b>NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub></b>	-	<b>Na<sub>2</sub>CO<sub>3</sub></b>	<b>36</b>	<b>45</b>	<b>12</b>
8 <sup>[a]</sup>	DCP	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	0	42	0

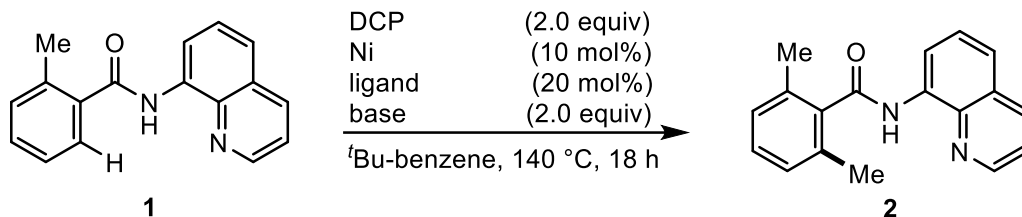
Yield was determined by <sup>1</sup>H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. Molar percentage of peroxide, Ni, PPh<sub>3</sub> and base are based on the amount of **1**'. Reaction conditions, unless otherwise stated: **1**' (0.30 mmol), Peroxide (0.60 mmol), Ni (0.03 mmol), PPh<sub>3</sub> (0.06 mmol), base (0.60 mmol) and <sup>t</sup>Bu-benzene (0.7 mL). [a] DCP (1.2 mmol) was used.



When amide **1** (0.3 mmol) was reacted with DCP (0.6 mmol) in the presence of a Ni(II) complex as a catalyst and Na<sub>2</sub>CO<sub>3</sub> as a base in *tert*-butylbenzene at 140 °C for 18 h, the expected methylation product **2** was not produced (Table 2-2, entries 1–3). However, the addition of PPh<sub>3</sub> gave **2**, albeit in low yields (entries 4–7). The yield was dramatically increased when PCy<sub>3</sub> was used as a ligand (entries 8 and 9). The efficiency

of the reaction was also significantly affected by the nature of the base used, and  $\text{Na}_2\text{CO}_3$  was found to be the base of choice (entries 9–11). The use of TBP decreased the yield of **2** (entry 12). Carrying out the reaction at 120 °C (entry 13), for a shorter reaction time (e.g., 12 h; entry 14), or with a decreased amount of DCP (entry 15) had no positive effect on the efficiency of the reaction. Increasing the amount of the base to three equivalents improved the yield, and product **2** was obtained in 78% yield, and substrate **1** was completely consumed (entry 16). Use of bidentate ligands or other Ni catalysts reduced the product yield (entries 17–20).  $\text{Pd}(\text{OAc})_2$ ,  $\text{CoBr}_2$ , and  $[\text{RuCl}_2(p\text{-cymene})]_2$  did not show any catalytic activity. Finally, the condition of entry 16 was determined to be the best reaction condition.

Table 2-2.

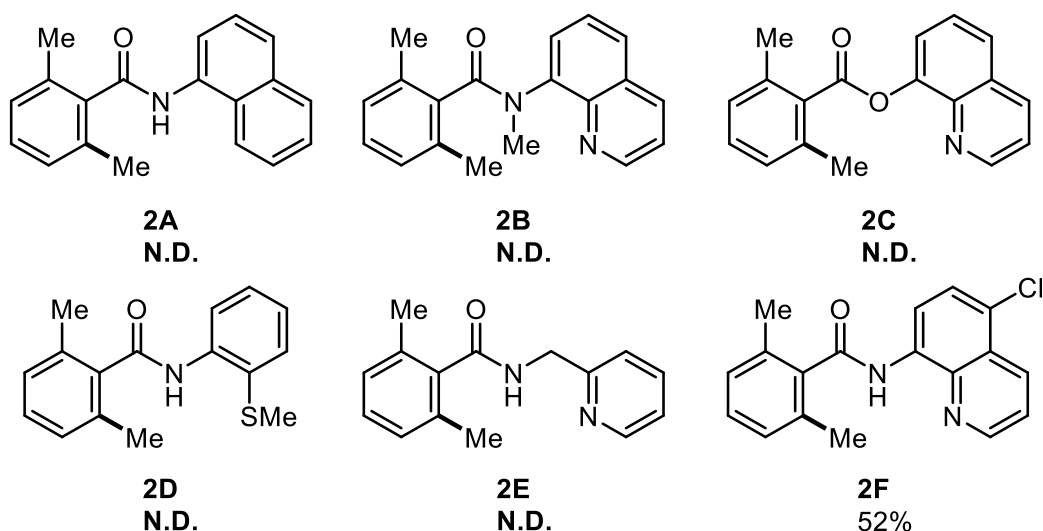


entry	Ni	ligand	base	2 (%)	1 (%)
1	NiI <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	3	49
2	NiCl <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	0	36
3	NiCl <sub>2</sub> (glyme)	-	Na <sub>2</sub> CO <sub>3</sub>	trace	46
4	NiI <sub>2</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	26	26
5	Ni(acac) <sub>2</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	18	46
6	Ni(OAc) <sub>2</sub> · 4H <sub>2</sub> O	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	13	47
7	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	11	49
8	NiCl <sub>2</sub>	PCy <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	71	12
9	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	75	2
10	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	K <sub>2</sub> CO <sub>3</sub>	53	11
11	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	K <sub>3</sub> PO <sub>4</sub>	54	0
12 <sup>[a]</sup>	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	28	30
13 <sup>[b]</sup>	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	71	6
14 <sup>[c]</sup>	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	74	3
15 <sup>[d]</sup>	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	72	15
<b>16<sup>[e]</sup></b>	<b>NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub></b>	-	<b>Na<sub>2</sub>CO<sub>3</sub></b>	<b>81 (78)</b>	<b>0</b>
17 <sup>[e]</sup>	NiCl <sub>2</sub> (dppe)	-	Na <sub>2</sub> CO <sub>3</sub>	49	13
18 <sup>[e]</sup>	NiCl <sub>2</sub> (dppp)	-	Na <sub>2</sub> CO <sub>3</sub>	58	4
19 <sup>[e]</sup>	NiBr <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	60	9
20 <sup>[e]</sup>	Ni(cod) <sub>2</sub>	PCy <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	36	23

Yield was determined by <sup>1</sup>H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. Yield of isolated product is given in parentheses. Molar percentage of DCP, Ni, ligand and base are based on the amount of **1**. Reaction conditions, unless otherwise stated: **1** (0.30 mmol), DCP (0.60 mmol), Ni (0.03 mmol), ligand (0.06 mmol), base (0.60 mmol) and <sup>t</sup>Bu-benzene (0.7 mL). [a] TBP was used. [b] Run at 120 °C. [c] Run for 12 h. [d] DCP (0.48 mmol) was used. [e] Na<sub>2</sub>CO<sub>3</sub> (0.9 mmol) was used.

### 2-2-2. Optimaization of Directing Groups

Scheme 2-2.



Subsequently, I examined directing groups used in the reaction (Scheme 2-2). The desired reaction did not proceed, when compounds **1A**, **1B** and **1C** were used instead of **1**. Thus, the reaction was found to require bidentate coordination and a N–H bond in amide moieties. Although compounds **1D** and **1E** had bidentate directing groups, they were unsuitable for this reaction. When aromatic amide **1F** bearing a quinoline skeleton was used, the desired reaction proceeded to give the target methylated product **2F** in 52% isolated yield. From the above results, 8-aminoquinoline was the most effective bidentate directing group.

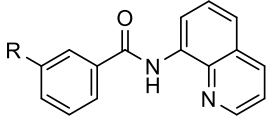
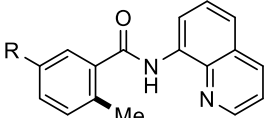
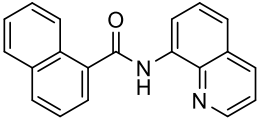
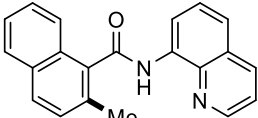
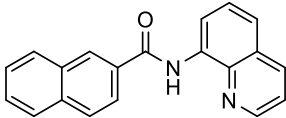
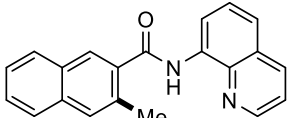
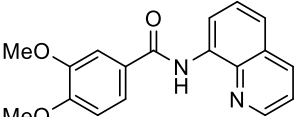
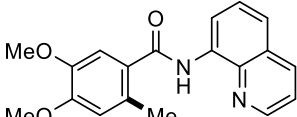
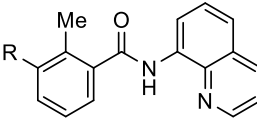
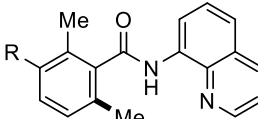
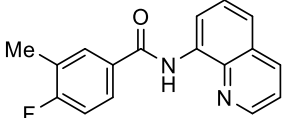
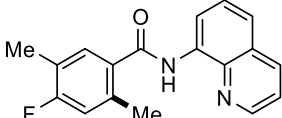
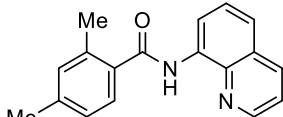
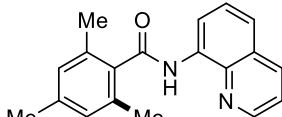
### 2-2-3. Scope of Substrates

With the optimal conditions in hand, the scope of the amides was investigated (Scheme 2-3). Aromatic amides **3a–3c** bearing electron-donating groups (*m*-OMe, *m*-OCH<sub>2</sub>Ph, and *m*-Me) underwent methylation effectively to afford the corresponding monomethylated products **4a–4c** in 72%, 53% and 71% yields, respectively. The reaction of aromatic amide **3d** bearing phenyl group proceeded to give **4d** in 81% yield. Aromatic amides **3e** and **3f** bearing halogen substituents such as chlorine and bromine substituents underwent catalytic methylation without loss of halogens (**4e** and **4f** in 79% and 61% yields, respectively). Aromatic Amides **3g–3i** bearing electron-withdrawing groups (*m*-Ac, *m*-CF<sub>3</sub> and *m*-CN) also underwent methylation effectively to afford the corresponding monomethylated products **4g–4i** in 75%, 82%, and 44%



yields, respectively. Thus, in case of *meta*-substituted aromatic amides, only the less hindered C–H bond was methylated. Naphthyl groups (**5**) and dimethoxyphenyl groups (**7**, **9**) were tolerated in this reaction, which effectively afforded the corresponding methylated products **6**, **8**, and **10**. *Ortho*-methyl aromatic amides **11a–11e** bearing electron-donating groups (*m*-OMe, *m*-OCH<sub>2</sub>Ph and *m*-Me) and electron-withdrawing groups (*m*-F and *m*-CF<sub>3</sub>) also underwent methylation to afford the corresponding methylated products **12a–12e** in 58%, 50%, 57%, 68%, and 59% yields, respectively. The reaction proceeded with disubstituted aromatic amides **13** and **15** to give the corresponding products **14** and **16**, respectively.

Scheme 2-3.

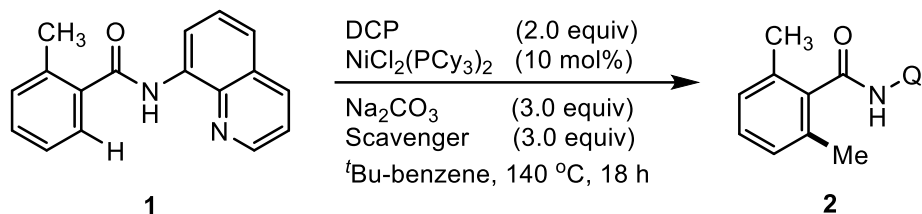
amide	product
 <p>R = OMe (<b>3a</b>)  OCH<sub>2</sub>Ph (<b>3b</b>)  Me (<b>3c</b>)  Ph (<b>3d</b>)  Cl (<b>3e</b>)  Br (<b>3f</b>)  C(O)Me (<b>3g</b>)  CF<sub>3</sub> (<b>3h</b>)  CN (<b>3i</b>)</p>	 <p><b>4a</b> 72%  <b>4b</b> 53%  <b>4c</b> 71%  <b>4d</b> 81%  <b>4e</b> 79%  <b>4f</b> 61%<sup>[a]</sup>  <b>4g</b> 75%  <b>4h</b> 82%  <b>4i</b> 44%<sup>[a], [b]</sup></p>
 <p><b>5</b></p>	 <p><b>6</b> 84%</p>
 <p><b>7</b></p>	 <p><b>8</b> 66%<sup>[b]</sup></p>
 <p><b>9</b></p>	 <p><b>10</b> 70%</p>
 <p>R = OMe (<b>11a</b>)  OC(O)Me (<b>11b</b>)  Me (<b>11c</b>)  F (<b>11d</b>)  CF<sub>3</sub> (<b>11e</b>)</p>	 <p><b>12a</b> 58%  <b>12b</b> 50%  <b>12c</b> 57%  <b>12d</b> 68%  <b>12e</b> 59%<sup>[a]</sup></p>
 <p><b>13</b></p>	 <p><b>14</b> 80%</p>
 <p><b>15</b></p>	 <p><b>16</b> 69%</p>

Isolated yield. Molar percentage of DCP, NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> and Na<sub>2</sub>CO<sub>3</sub> are based on the amount of amide. Reaction conditions, unless otherwise stated: amide (0.3 mmol), DCP (0.6 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (0.03 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.9 mmol) in <sup>t</sup>Bubenzene (0.7 mL) at 140 °C for 18 h. [a] NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (0.045 mmol) was used. [b] Isolated by GPC.

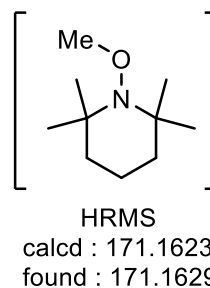
## 2-3. Mechanistic Studies

### 2-3-1. Radical Trap Experiments

Table 2-3.



entry	Scavenger	<b>2</b> (%)	<b>1</b> (%)
1		0	87
2		0	86
3		16	81
4		0	95



<sup>1</sup>H NMR yield.

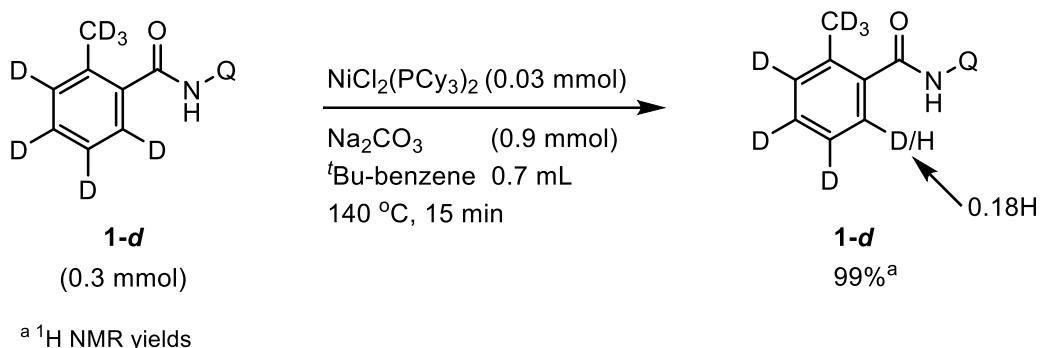
Next, I performed a series of experiments in order to gain insight into the mechanism. When the reactions were carried out in the presence of 3.0 equivalent of a typical radical scavenger such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), 1,4-cyclohexadiene, or  $\alpha$ -methylstyrene otherwise under standard reaction conditions, the reaction was completely inhibited (Table 2-3). TEMPO methyl ether was detected by high-resolution mass spectroscopy when TEMPO was added. These results clearly indicate that a free radical species is involved in the reaction.

### 2-3-2. Deuterium Labeling Experiments

To gain further insights into the reaction mechanism, a deuterium labeling experiment was also carried out with deuterium-labeled amide **1-d**. On treatment of **1-d** under the standard conditions without DCP, a

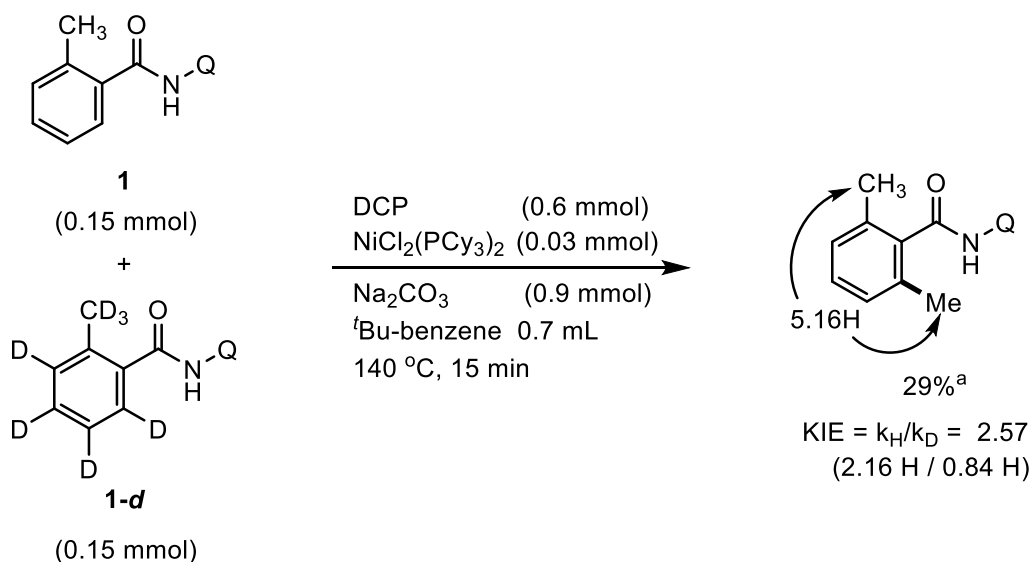
significant amount of H/D exchange was observed but only at the *ortho* C–H bond in the recovered amide **1-d**, indicating that C–H bond cleavage is reversible (Scheme 2-4).

Scheme 2-4.



Next, when equimolar **1** and **1-d** were put in the same reaction vessel and treated under the standard conditions, kinetic isotope effects (KIEs) of 2.57 (= 2.16 H / 0.84 H) was observed from the product whose number of protons of methyl group is 5.16 (Scheme 2-5). These results suggest that the C–H bond cleavage process is the rate-determining step. However, this result is not the critical evidence that determines the rate-limiting step.

Scheme 2-5.

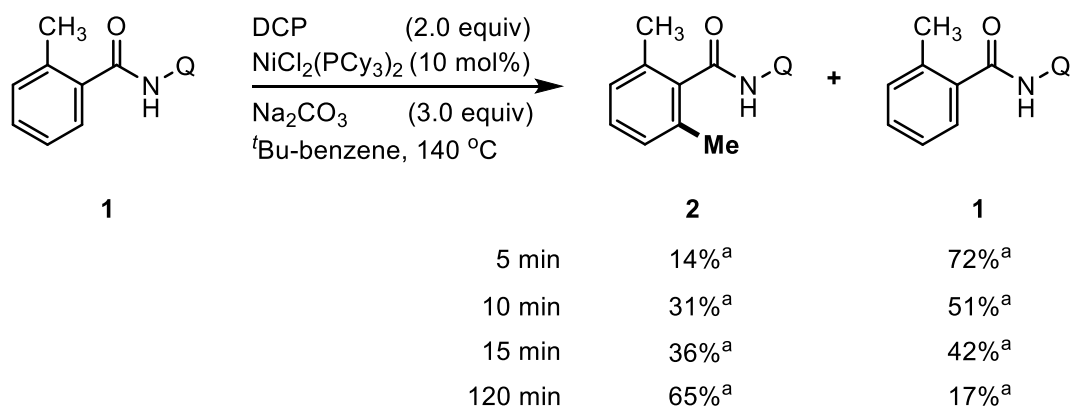
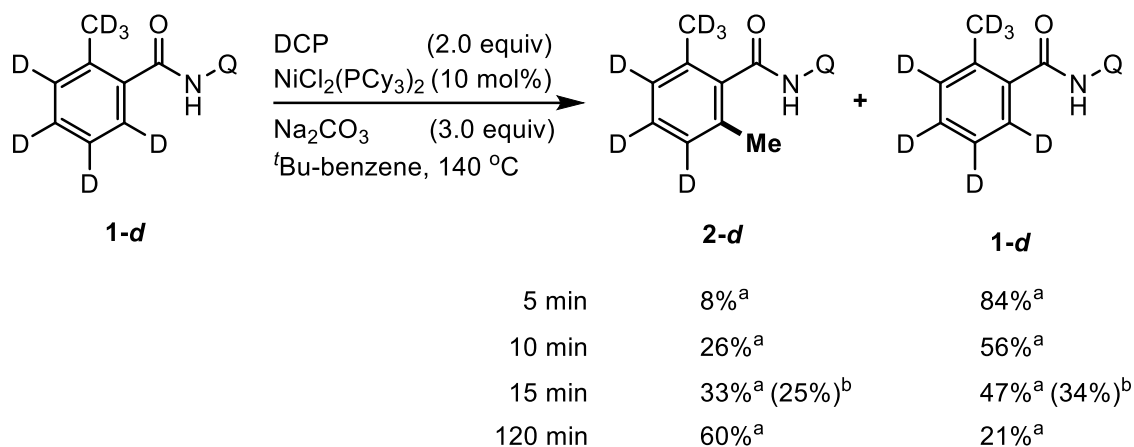


<sup>a</sup> Isolated by GPC.

In addition, **1** and **1-d** were put in separate reaction vessels respectively, and were subjected to the reaction for 5 min, 10 min, 15 min and 120 min under the standard conditions (Scheme 2-6). From the yield of

obtained methylated product **2** and **2-d** and the recovered substrate **1** and **1-d**, intermolecular KIE of 1.15 was observed (for parallel experiments). This result suggests that C–H bond cleavage is not involved in the rate-determining step.

Scheme 2-6.

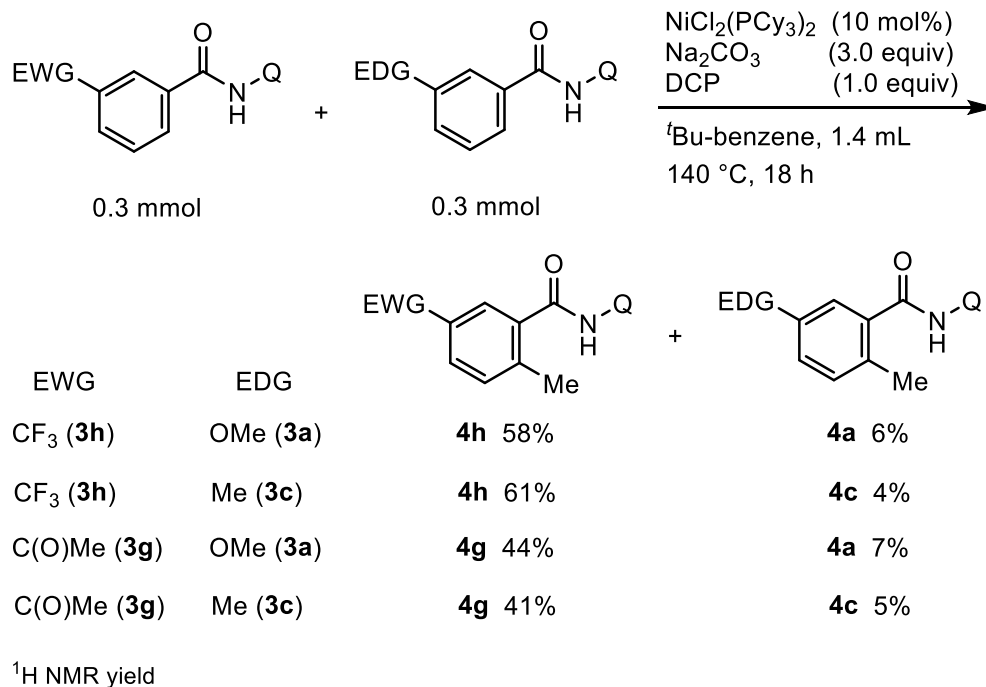


<sup>a</sup> <sup>1</sup>H NMR yields. <sup>b</sup> Isolated by GPC.

### 2-3-3. Competition Experiments

To collect additional information regarding the mechanism, I examined the effect of the electronic nature of the substituents (Scheme 2-7). Two equimolar *meta*-substituted aromatic amides were added to the same reaction vessel, where one amide bears an electron-withdrawing group (CF<sub>3</sub>, Ac) and another bears an electron-donating group (OMe, Me), and the reaction was carried out under reduced DCP (1.0 equiv) conditions. As a result of four combinations, the reaction was found to proceed preferentially with the aromatic amides bearing an electron-withdrawing group than those bearing an electron-donating group.

Scheme 2-7

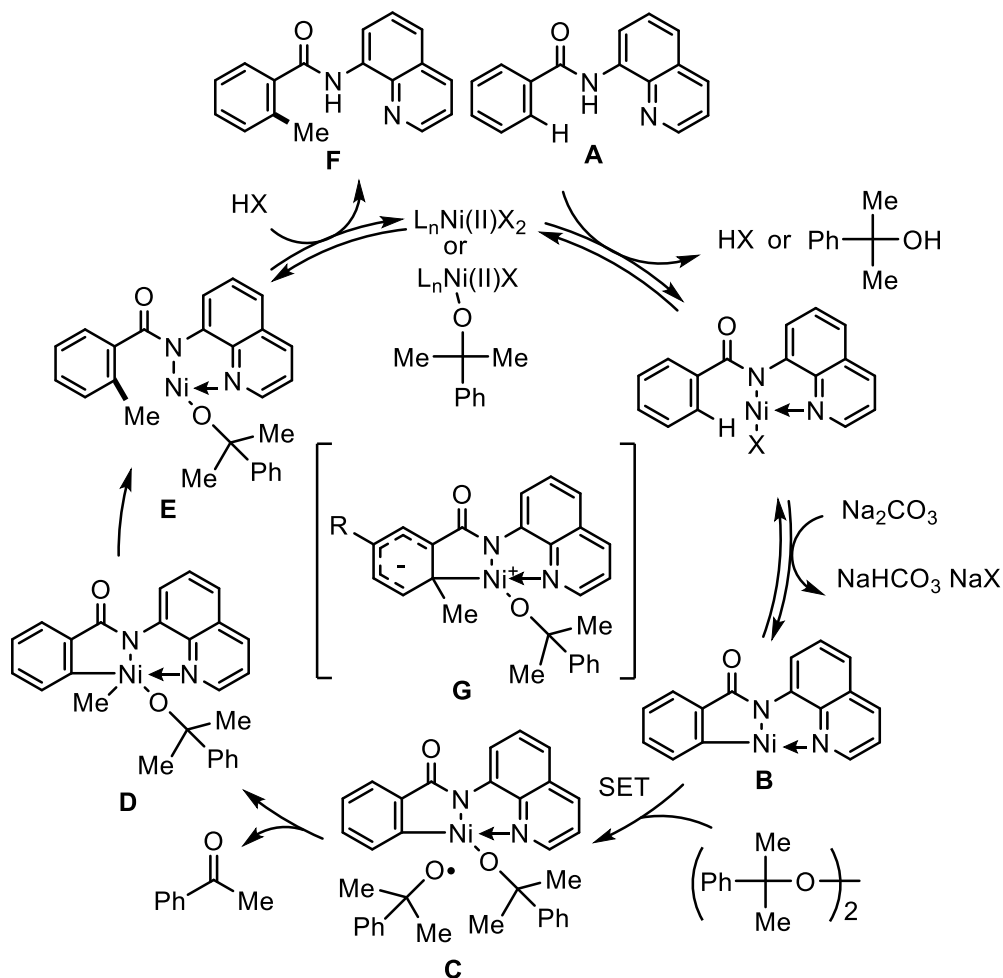


### 2-3-4. Proposed Mechanism

Taking these observations, I propose a mechanism for this reaction (Scheme 2-8). The reaction begins with coordination of amide **A** to a Ni(II) species, followed by ligand exchange and subsequent reversible cleavage of the ortho C–H bond to give nickelacycle **B**. A plausible mechanism involves a single electron transfer (SET) type process from **B** to DCP, which gives the Ni(III) species **C** and alkoxy radical, which are in close proximity to one another. The alkoxy radical undergoes decomposition with concomitant elimination of acetophenone to give a methyl radical, which immediately reacts with the unstable Ni(III) species **C** to give the Ni(IV) species **D**. Reductive elimination followed by protonation gives the expected product **F** with regeneration of Ni(II). The aforementioned competition experiments suggests that reductive elimination could be the rate-determining step, because the aromatic amide has an electron-withdrawing group on the *meta*-position, the reductive elimination process (from intermediate **D** to **E**) easily proceeds presumably due to stabilization of the Meisenheimer-type intermediate. High validity of the plausible mechanism was

theoretically confirmed later by Liu.<sup>[17]</sup>

Scheme 2-8.



### 2-3-5. Conclusion

In summary, I have demonstrated the successful development of a highly efficient process for Ni(II)-catalyzed methylation of C-H bonds. This is the first example of the use of DCP for Ni-catalyzed methylation at the carbon bearing a C-H bonds. The presence of the PCy<sub>3</sub> ligand is essential for the success of the reaction. The reaction displays a broad substrate scope and high functional group tolerance. The reaction is inhibited by radical scavengers, such as TEMPO, 1,4-cyclohexadiene, and  $\alpha$ -methylstyrene. The results of deuterium labeling experiments and KIE experiments suggest that the C-H bond cleavage is reversible. The results of competition experiments suggest that a reductive elimination is likely to be a rate-determining step.

## 2-4. Experimental Section

### 2-4-1. General Information.

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a JEOL ECS-400 spectrometer in  $\text{CDCl}_3$  with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4000; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained using Shimadzu GCMS-QP 2014 and Shimadzu GCMS-QP 5000 instruments instrument with ionization voltages of 70 eV. High resolution mass spectra (HRMS) were obtained on a JEOL JMS-700 instrument. Analytical gas chromatography (GC) was carried out on Shimadzu GC-14B, Shimadzu GC-2014 and Shimadzu GC-8A gas chromatographs, equipped with a flame ionization detector. Melting points were determined using a Stanford Research Systems apparatus. Column chromatography was performed with  $\text{SiO}_2$  (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

### 2-4-2. Materials.

$\text{Na}_2\text{CO}_3$  (CAS 497-19-8) was purchased from Nacalai Tesque, Inc.  $\text{NiCl}_2(\text{PCy}_3)_2$  (CAS 19999-87-2),  $t\text{-Bu}$ -benzene (CAS 98-06-6) and 8-aminoquinoline (CAS 578-66-5) were purchased from Tokyo Kasei Kogyo Co., Ltd. Dicumyl peroxide (CAS 80-43-3) was purchased from Sigma-Aldrich.

### 2-4-3. Synthesis of the Starting Amides.

All amides bearing an 8-aminoquinoline moiety were prepared by reacting the corresponding acid or the corresponding acid chlorides with 8-aminoquinoline.<sup>[18]</sup>

#### General Procedure for the Preparation of Starting Amide.

To an oven-dried 100 mL three-necked flask, 2-methylbenzoic acid (1.5 g, 10 mmol), DMF (5 drops) and

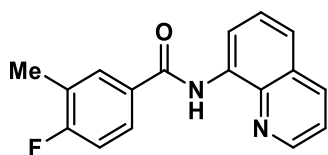


DCM (30 mL) were added under a N<sub>2</sub> atmosphere. Oxalyl chloride (1.0 mL, 12 mmol, 1.2 equiv.) was added dropwise at 0 °C resulting in vigorous bubbling. The mixture was stirred for 3 h at room temperature, and the solvent was then removed *in vacuo*. The resulting acid chloride was used immediately without further purification.

To another oven-dried 100 mL three-necked flask, 8-aminoquinoline (1.6 g, 11 mmol, 1.1 equiv.), Et<sub>3</sub>N (2.5 mL, 24 mmol, 2.4 equiv.) and DCM (15 mL) were added. A solution of the acid chloride in DCM (30 mL) was added dropwise to the solution at 0 °C, and the solution was then warmed to room temperature. After stirring overnight, the reaction system was quenched with sat. aq. NaHCO<sub>3</sub> (30 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic layers were washed with 1 M HCl aq. (30 mL) and brine (30 mL), dried over MgSO<sub>4</sub>, filtered and evaporated *in vacuo*. The obtained crude amide was purified by column chromatography on silica gel (hexane / EtOAc = 5 / 1) to afford the desired amide as a white solid (2.4 g, 93%).

### Spectroscopic Data for Starting Amides

#### 4-fluoro-3-methyl-*N*-(quinolin-8-yl)benzamide (13)



R<sub>f</sub> 0.41 (hexane/EtOAc = 2/1). White Solid. Mp = 104 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.40 (d, *J* = 1.8 Hz, 3H), 7.16 (t, *J* = 8.9 Hz, 1H), 7.49 (q, *J* = 4.1 Hz, 1 H), 7.52-7.64 (m, 2H), 7.85-7.92 (m, 1H), 7.94 (d, *J* = 7.3 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.86 (dd, *J* = 5.0, 1.8 Hz, 1H), 8.91 (dd, *J* = 7.8, 1.4 Hz, 1H), 10.66 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 14.62 (d, *J* = 2.8 Hz), 115.29 (d, *J* = 23.0 Hz), 116.45, 121.63, 125.52 (d, *J* = 17.2 Hz), 126.60 (d, *J* = 8.6 Hz), 127.38, 127.92, 130.92 (d, *J* = 2.8 Hz), 130.99, 131.06, 134.45, 136.34, 138.66, 148.23, 163.51 (d, *J* = 251.1 Hz), 164.54; IR (neat) ; 3355 w, 3050 w, 1674 m, 1528 s, 1502 m, 1483 s, 1425 m, 1385 m, 1328 m, 824 m, 791 w, 758 m; MS *m/z* (relative intensity, %) 281 (13), 280 (M<sup>+</sup>, 62), 137 (100), 109 (24); HRMS Calcd for C<sub>17</sub>H<sub>13</sub>FN<sub>2</sub>O: 280.1012; Found: 280.1013.

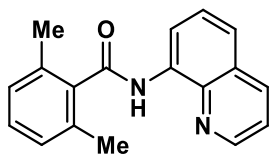
#### 2-4-4. General Procedure for Direct Methylation

##### General Procedure for Direct Methylation: Ni-Catalyzed Methylation of Amides **1** with Dicumyl peroxide.

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(quinolin-8-yl)benzamide (**1**) (79 mg, 0.3 mmol), Dicumyl peroxide (162 mg, 0.60 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (20.7 mg, 0.03 mmol), Na<sub>2</sub>CO<sub>3</sub> (95 mg, 0.9 mmol) and <sup>t</sup>Bu-benzene (0.7 mL) were added in Air. The mixture was stirred for 18 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 10/1) to afford the desired alkylated product **2** (65 mg, 78%) as a white solid.

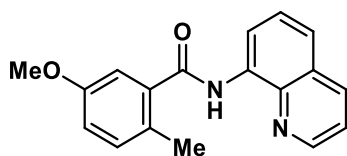
#### 2-4-5. Spectroscopic Data for Products

##### 2,6-dimethyl-*N*-(quinolin-8-yl)benzamide (**2**).



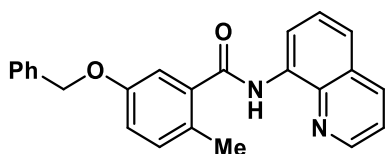
R<sub>f</sub> 0.31 (hexane/EtOAc = 10/1). White Solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.44 (s, 6H), 7.11 (d, *J* = 7.3 Hz, 2 H), 7.25 (t, *J* = 7.6 Hz, 3H), 7.45 (q, *J* = 4.1 Hz, 1H), 7.54-7.66 (m, 2H), 8.18 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.74 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.99 (dd, *J* = 7.3, 1.4 Hz, 1H), 9.93 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 19.43, 116.75, 121.64, 121.92, 127.39, 127.69, 127.99, 128.95, 134.38, 134.53, 136.32, 138.01, 138.50, 148.26, 168.87; MS *m/z* (relative intensity, %) 276 (M<sup>+</sup>, 37), 259 (13), 134 (10), 133 (100), 132 (22), 105 (29); HRMS Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O: 276.1263; Found: 276.1260.

##### methyl 4-benzyl-6-((5-chloroquinolin-8-yl)amino)-6-oxohexanoate (**4a**).



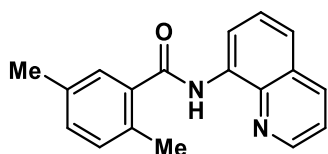
R<sub>f</sub> 0.09 (hexane/EtOAc = 10/1). White Solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.53 (s, 3 H), 3.84 (s, 3H), 6.95 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.16-7.28 (m, 2H), 7.45 (q, *J* = 4.1 Hz, 1H), 7.51-7.63 (m, 2H), 8.17 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.77 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.94 (d, *J* = 6.9 Hz, 1H), 10.20 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 19.21, 55.46, 112.71, 115.99, 116.49, 121.63, 121.77, 127.36, 127.94, 128.12, 132.31, 134.61, 136.31, 137.39, 138.57, 148.25, 157.63, 167.93; MS *m/z* (relative intensity, %) 293 (15), 292 (M<sup>+</sup>, 71), 275 (28), 248 (14), 150 (11), 149 (100), 148 (54), 121 (40), 120 (40), 91 (14), 77 (11); HRMS Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: 292.1212; Found: 292.1210.

**5-(benzyloxy)-2-methyl-N-(quinolin-8-yl)benzamide (4b).**



R<sub>f</sub> 0.27 (hexane/EtOAc = 5/1). White Solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.53 (s, 3H), 5.11 (s, 2H), 7.02 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.29-7.42 (m, 4H), 7.42-7.49 (m, 3H), 7.51-7.63 (m, 2H), 8.17 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.77 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.93 (d, *J* = 6.9 Hz, 1H), 10.19 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 19.27, 70.24, 113.74, 116.51, 116.87, 121.64, 121.77, 127.37, 127.52, 127.94, 128.01, 128.56, 128.59, 132.37, 134.61, 136.31, 136.70, 137.39, 138.56, 148.25, 156.81, 167.85; MS *m/z* (relative intensity, %) 369 (20), 368 (M<sup>+</sup>, 68), 278 (17), 277 (84), 226 (11), 225 (65), 224 (32), 133 (10), 91 (100); HRMS Calcd for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: 368.1525; Found: 368.1529.

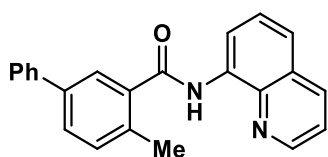
**2,5-dimethyl-N-(quinolin-8-yl)benzamide (4c).**



R<sub>f</sub> 0.21 (hexane/EtOAc = 10/1). White Solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.39 (s, 3 H), 2.55 (s, 3 H), 7.16-7.23 (m, 2H), 7.44 (q, *J* = 4.3 Hz, 1H), 7.48 (s, 1H), 7.51-7.62 (m, 2H), 8.17 (dd, *J* = 8.2, 1.4 Hz, 1H),

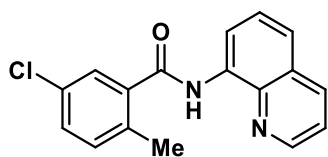
8.78 (dd,  $J = 4.0, 1.2$  Hz, 2H), 8.94 (d,  $J = 7.3$  Hz, 1H), 10.18 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.68, 20.91, 116.48, 121.60, 121.67, 127.39, 127.80, 127.96, 130.99, 131.21, 133.27, 134.72, 135.56, 136.32, 136.52, 138.58, 148.21, 168.39; MS  $m/z$  (relative intensity, %) 276 ( $\text{M}^+$ , 36), 259 (19), 134 (10), 133 (100), 132 (29), 105 (33), 77 (11); HRMS Calcd for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$ : 276.1263; Found: 276.1266.

**4-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-3-carboxamide (4d).**



$R_f$  0.19 (hexane/EtOAc = 10/1). White Solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.63 (s, 3H), 7.28-7.50 (m, 5H), 7.50-7.68 (m, 5H), 7.90 (d,  $J = 1.8$  Hz, 1H), 8.15 (dd,  $J = 8.2, 1.4$  Hz, 1H), 8.75 (dd,  $J = 4.4, 1.2$ , 1H), 8.97 (d,  $J = 7.3$  Hz, 1H), 10.26 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.80, 116.55, 121.65, 121.82, 125.85, 126.98, 127.38, 127.45, 127.95, 128.81, 128.85, 131.81, 134.66, 135.49, 136.32, 137.18, 138.57, 139.01, 140.17, 148.29, 168.15; MS  $m/z$  (relative intensity, %) 339 (15), 338 ( $\text{M}^+$ , 61), 320 (22), 196 (15), 195 (100), 194 (50), 167 (37), 166 (22), 165 (34), 152 (25); HRMS Calcd for  $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}$ : 338.1419; Found: 338.1418.

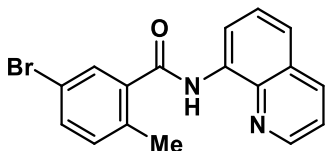
**5-chloro-2-methyl-*N*-(quinolin-8-yl)benzamide (4e).**



$R_f$  0.20 (hexane/EtOAc = 10/1). White Solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.55 (s, 3H), 7.23 (d,  $J = 8.4$  Hz, 1H), 7.35 (dd,  $J = 8.2, 2.3$  Hz, 1H), 7.46 (q,  $J = 4.1$  Hz, 1H), 7.53-7.63 (m, 2H), 7.65 (d,  $J = 1.8$  Hz, 1H), 8.17 (dd,  $J = 8.2, 1.4$  Hz, 1H), 8.79 (dd,  $J = 4.4, 1.6$  Hz, 1H), 8.90 (dd,  $J = 3.2, 1.2$  Hz, 1H), 10.17 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.59, 116.63, 121.73, 122.06, 127.18, 127.31, 127.93, 130.19, 131.63, 132.64, 134.34, 134.94, 136.36, 138.01, 138.49, 148.36, 166.64; MS  $m/z$  (relative intensity, %) 298 (27), 297

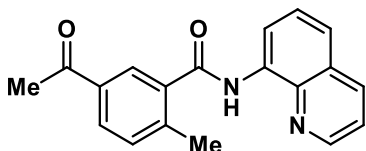
(16), 296 ( $M^+$ , 76), 281 (17), 280 (10), 279 (52), 252 (25), 171 (16), 155 (33), 153 (100), 152 (31), 144 (50), 127 (17), 125 (51), 116 (12), 89 (23); HRMS Calcd for  $C_{17}H_{13}ClN_2O$ : 296.0716; Found: 296.0714.

**5-bromo-2-methyl-N-(quinolin-8-yl)benzamide (4f).**



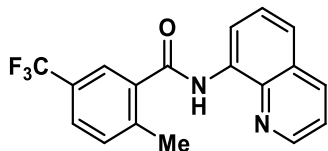
$R_f$  0.27 (hexane/EtOAc = 10/1). White Solid.  $^1H$  NMR ( $CDCl_3$ , 399.78 MHz)  $\delta$  2.53 (s, 3H), 7.18 (d,  $J$  = 8.2 Hz, 1H), 7.47 (q,  $J$  = 4.1 Hz, 1H), 7.51 (dd,  $J$  = 8.0, 2.1 Hz, 1H), 7.56-7.61 (m, 2H), 7.79 (d,  $J$  = 2.3 Hz, 1H), 8.18 (dd,  $J$  = 8.2, 1.8 Hz, 1H), 8.80 (d,  $J$  = 4.0, 1.4 Hz, 1H), 8.90 (dd,  $J$  = 3.6, 1.2 Hz, 1H), 10.16 (brs, 1H);  $^{13}C$  NMR ( $CDCl_3$ , 100.53 MHz)  $\delta$  19.65, 116.65, 119.42, 121.74, 122.08, 127.33, 127.94, 130.01, 132.93, 133.16, 133.34, 135.44, 136.37, 138.41, 138.51, 148.37, 166.53; MS  $m/z$  (relative intensity, %) 342 (78), 340 ( $M^+$ , 80), 325 (51), 323 (56), 298 (34), 296 (40), 279 (10), 211 (10), 199 (96), 197 (100); HRMS Calcd for  $C_{17}H_{13}BrN_2O$ : 340.0211; Found: 340.0208.

**5-acetyl-2-methyl-N-(quinolin-8-yl)benzamide (4g).**



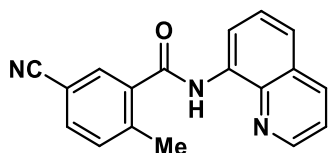
$R_f$  0.11 (hexane/EtOAc = 5/1). White Solid.  $^1H$  NMR ( $CDCl_3$ , 399.78 MHz)  $\delta$  2.64 (s, 3H), 2.65 (s, 3H), 7.41 (d,  $J$  = 7.8 Hz, 2H), 7.47 (q,  $J$  = 4.1 Hz, 1H), 7.54-7.66 (m, 2H), 7.98 (dd,  $J$  = 7.8, 1.8 Hz, 1H), 8.19 (dd,  $J$  = 8.2, 1.4 Hz, 1H), 8.26 (d,  $J$  = 1.8 Hz, 1H), 8.78 (dd,  $J$  = 4.0, 1.4 Hz), 8.92 (dd,  $J$  = 7.1, 1.1 Hz, 1H), 10.24 (brs, 1H);  $^{13}C$  NMR ( $CDCl_3$ , 100.53 MHz)  $\delta$  20.37, 26.57, 116.64, 121.72, 122.08, 127.21, 127.30, 127.93, 129.87, 131.64, 134.35, 135.05, 136.35, 136.99, 138.48, 142.19, 148.35, 167.20, 197.05; MS  $m/z$  (relative intensity, %) 305 (14), 304 ( $M^+$ , 66), 287 (26), 260 (13), 171 (11), 162 (11), 161 (100), 160 (27), 144 (28), 133 (14), 131 (12), 105 (13), 89 (10); HRMS Calcd for  $C_{19}H_{16}N_2O_2$ : 304.1212; Found: 304.1212.

**2-methyl-N-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (4h).**



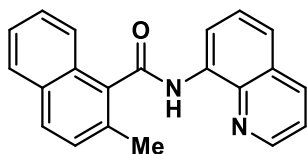
$R_f$  0.36 (hexane/EtOAc = 10/1). White Solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.65 (s, 3H), 7.44 (d,  $J = 7.8$  Hz 1H), 7.48 (q,  $J = 4.3$  Hz 1 H), 7.56-7.67 (m, 2H), 7.92 (s, 1H), 8.19 (dd,  $J = 8.5, 1.6$  Hz, 1H), 8.79 (dd,  $J = 4.0, 2.0$  Hz, 1H), 8.92 (dd,  $J = 7.1, 2.1$  Hz, 1H), 10.22 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  20.18, 116.72, 121.78, 122.22, 123.86 (q,  $J = 272.1$  Hz), 124.19 (q,  $J = 3.82$  Hz), 126.82 (q,  $J = 2.8$  Hz), 127.31, 127.94, 128.50 (q,  $J = 32.6$  Hz), 131.79, 134.23, 136.41, 137.21, 138.47, 140.61, 148.42, 166.71;; MS  $m/z$  (relative intensity, %) 331 (18), 330 ( $\text{M}^+$ , 84), 313 (53), 311 (10), 286 (21), 187 (100), 186 (10), 171 (21), 159 (54), 145 (10), 144 (90), 116 (11), 109 (22); HRMS Calcd for  $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2\text{O}$ : 330.0980; Found: 330.0982.

**5-cyano-2-methyl-N-(quinolin-8-yl)benzamide (4i).**



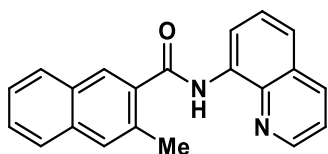
$R_f$  0.18 (hexane/EtOAc = 5/1). White Solid. Mp = 161 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.66 (s, 3H), 7.43 (d,  $J = 7.8$  Hz, 1H), 7.50 (q,  $J = 4.3$  Hz, 1H), 7.58-7.63 (m, 2H), 7.68 (dd,  $J = 8.0, 1.6$  Hz, 1H), 7.96 (d,  $J = 1.8$  Hz, 1H), 8.21 (dd,  $J = 8.2, 1.4$  Hz, 1H), 8.81 (dd,  $J = 4.0, 1.8$  Hz, 1H), 8.89 (q,  $J = 2.9$  Hz, 1H), 10.22 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  20.57, 110.14, 116.74, 118.28, 121.86, 122.39, 127.30, 127.95, 130.78, 132.25, 133.45, 134.06, 136.45, 137.70, 138.43, 142.46, 148.49, 165.70; IR (neat) 3341 w, 2924 w, 2852 w, 2229 w, 1678 m, 1523 s, 1483 m, 1424 m, 1384 m, 1326 m, 825 m, 792 m, 757 w; MS  $m/z$  (relative intensity, %) 288 (11), 287 ( $\text{M}^+$ , 52), 270 (29), 243 (11), 171 (13), 149 (12), 145 (11), 144 (100), 116 (31), 89 (15); HRMS Calcd for  $\text{C}_{18}\text{H}_{15}\text{FN}_2\text{O}$ : 287.1059; Found: 287.1056.

**2-methyl-N-(quinolin-8-yl)-1-naphthamide (6).**



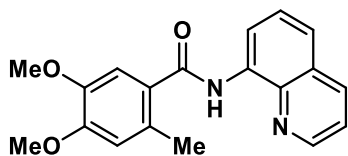
$R_f$  0.17 (hexane/EtOAc = 10/1). White Solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.62 (s, 3H), 7.35-7.43 (m, 2H), 7.44-7.52 (m, 2H), 7.58 (dd,  $J=8.2, 1.4$  Hz, 1H), 7.65 (t,  $J=7.8$  Hz, 1H), 7.82-7.88 (m, 2H), 7.96-8.04 (m, 1H), 8.16 (dd,  $J=8.5, 1.6$  Hz, 1H), 8.65 (dd,  $J=4.0, 1.4$  Hz, 1H), 9.14 (dd,  $J=7.6, 1.1$  Hz, 1H), 10.13 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.81, 116.83, 121.65, 122.06, 124.70, 125.49, 127.01, 127.40, 127.96, 127.99, 128.53, 129.16, 130.25, 131.77, 132.38, 134.20, 134.47, 136.28, 138.47, 148.26, 168.40; MS  $m/z$  (relative intensity, %) 312 ( $\text{M}^+$ , 32), 170 (13), 169 (100), 168 (19), 141 (40), 115 (17); HRMS Calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}$ : 312.1263; Found: 312.1264.

**3-methyl-N-(quinolin-8-yl)-2-naphthamide (8).**



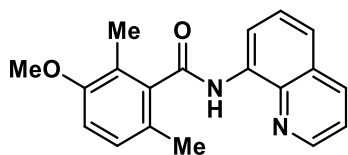
$R_f$  0.23 (hexane/EtOAc = 10/1). White Solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.74 (s, 3H), 7.42-7.59 (m, 4H), 7.62 (t,  $J=7.8$  Hz, 1H), 7.74 (s, 1H), 7.81 (d,  $J=8.2$  Hz, 1H), 7.91 (d,  $J=8.2$  Hz, 1H), 8.17 (d,  $J=1.2$  Hz, 1H), 8.19 (s, 1H), 8.77 (dd,  $J=4.0, 1.8$  Hz, 1H), 8.98 (d,  $J=7.3$  Hz, 1H), 10.34 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  20.46, 116.56, 121.67, 121.82, 125.88, 127.06, 127.12, 127.40, 127.42, 127.98, 128.20, 129.44, 131.22, 133.44, 134.22, 134.76, 135.45, 136.35, 138.59, 148.28, 168.13; MS  $m/z$  (relative intensity, %) 312 ( $\text{M}^+$ , 40), 295 (15), 268 (13), 170 (13), 169 (100), 168 (27), 142 (11), 141 (48), 115 (21); HRMS Calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}$ : 312.1263; Found: 312.1258.

**4,5-dimethoxy-2-methyl-N-(quinolin-8-yl)benzamide (10).**



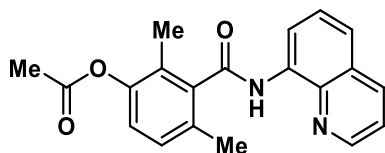
$R_f$  0.14 (hexane/EtOAc = 5/1). White Solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.60 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 6.78 (s, 1H), 7.26 (s, 1H), 7.45 (q,  $J = 4.1$  Hz, 1H), 7.50-7.64 (m, 2H), 8.17 (dd,  $J = 8.5, 1.1$  Hz, 1H), 8.78 (dd,  $J = 4.0, 1.4$  Hz, 1H), 8.92 (d,  $J = 7.3$  Hz, 1H), 10.22 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  20.12, 55.90, 56.12, 111.10, 113.99, 116.31, 121.54, 121.57, 127.38, 127.93, 128.37, 129.65, 134.71, 136.30, 138.57, 146.83, 148.20, 150.37, 167.67; MS  $m/z$  (relative intensity, %) 322 ( $\text{M}^+$ , 31), 180 (12), 179 (100), 151 (10); HRMS Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$ : 322.1317; Found: 322.1321.

### 3-methoxy-2,6-dimethyl-N-(quinolin-8-yl)benzamide (12a).



$R_f$  0.31 (hexane/EtOAc = 5/1). White Solid. Mp = 125 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.29 (s, 3H), 2.36 (s, 3H), 3.85 (s, 3H), 6.84 (d,  $J = 8.2$  Hz, 1H), 7.08 (d,  $J = 8.7$  Hz, 1H), 7.44 (q,  $J = 4.1$  Hz, 1H), 7.53-7.64 (m, 2H), 8.17 (dd,  $J = 8.5, 1.6$  Hz, 1H), 8.73 (dd,  $J = 4.0, 1.8$  Hz, 1H), 8.99 (dd,  $J = 7.3, 1.4$  Hz, 1H), 9.91 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  12.96, 18.70, 55.67, 110.78, 116.74, 121.64, 121.90, 123.32, 126.03, 127.39, 127.99, 128.20, 134.40, 136.31, 138.52, 139.11, 148.25, 155.86, 168.70 ; IR (neat) 3345 w, 2936 w, 2835 w, 1674 m, 1518 s, 1480 s, 1383 m, 1325 m, 1266 m, 1097 m, 1044 m, 907 m, 792 m, 731 m; MS  $m/z$  (relative intensity, %) 306 ( $\text{M}^+$ , 43), 164 (11), 163 (100), 162 (53), 105 (21), 91 (16); HRMS Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$ : 306.1368; Found: 306.1367.

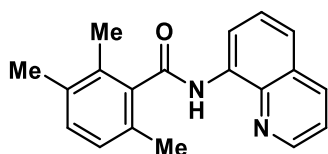
### 2,4-dimethyl-3-(quinolin-8-ylcarbamoyl)phenyl acetate (12b).





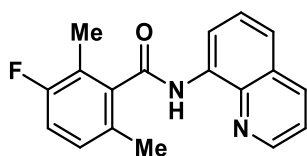
$R_f$  0.30 (hexane/EtOAc = 2/1). White Solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.25 (s, 3H), 2.34 (s, 3H), 2.41 (s, 3H), 7.02 (d,  $J = 8.2$  Hz, 1H), 7.14 (d,  $J = 8.2$  Hz, 1H), 7.44 (q,  $J = 4.1$  Hz, 1H), 7.53-7.68 (m, 2H), 8.16 (dd,  $J = 8.2, 1.8$  Hz, 1H), 8.74 (dd,  $J = 4.0, 1.6$  Hz, 1H), 8.97 (dd,  $J = 7.1, 1.6$  Hz, 1H), 9.97 (brs, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  13.19, 19.10, 20.76, 116.75, 121.68, 122.09, 122.59, 126.88, 127.25, 127.91, 128.69, 132.36, 134.17, 136.24, 138.43, 139.29, 147.35, 148.32, 167.71, 169.40; MS  $m/z$  (relative intensity, %) 335 (16), 334 ( $\text{M}^+$ , 73), 275 (26), 192 (12), 191 (96), 190 (30), 150 (10), 149 (100), 148 (38), 145 (14), 121 (21), 91 (17); HRMS Calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3$ : 334.1317; Found: 334.1313.

**2,3,6-trimethyl-N-(quinolin-8-yl)benzamide (12c).**



$R_f$  0.33 (hexane/EtOAc = 10/1). White Solid. Mp = 159 °C.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.30 (s, 3H), 2.32 (s, 3H), 2.39 (s, 3H), 7.03 (d,  $J = 7.8$  Hz, 1H), 7.14 (d,  $J = 7.8$  Hz, 1H), 7.45 (q,  $J = 4.1$  Hz, 1H), 7.54-7.65 (m, 2H), 8.18 (dd,  $J = 8.2, 1.4$  Hz, 1H), 8.73 (dd,  $J = 4.0, 1.4$  Hz, 1H), 9.00 (dd,  $J = 7.3, 1.4$  Hz, 1H), 9.91 (brs, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  16.56, 19.18, 19.82, 116.72, 121.61, 121.87, 127.38, 127.46, 127.98, 130.30, 131.81, 132.76, 134.44, 134.54, 136.29, 138.29, 138.51, 148.22, 169.50; IR (neat) 3350 w, 2950 w, 2874 w, 1678 m, 1520 s, 1483 m, 1423 m, 1384 m, 1326 m, 826 w, 792 w; MS  $m/z$  (relative intensity, %) 290 ( $\text{M}^+$ , 26), 148 (10), 147 (100), 146 (27), 119 (27), 91 (11); HRMS Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$ : 290.1419; Found: 290.1423.

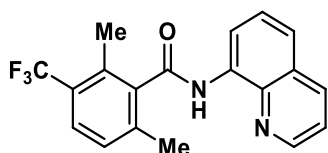
**3-fluoro-2,6-dimethyl-N-(quinolin-8-yl)benzamide (12d).**



$R_f$  0.43 (hexane/EtOAc = 5/1). White Solid. Mp = 166 °C.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.34 (d,  $J = 2.3$

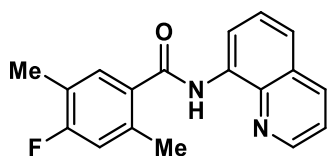
Hz, 3H), 2.39 (s, 3 H), 7.01 (t,  $J = 8.9$  Hz, 1H), 7.05-7.11 (m, 1H), 7.47 (q,  $J = 4.1$  Hz, 1H), 7.56-7.66 (m, 2H), 8.20 (dd,  $J = 8.2, 1.8$  Hz, 1H), 8.76 (dd,  $J = 4.0, 1.4$  Hz, 1H), 8.97 (dd,  $J = 7.1, 1.6$  Hz, 1H), 9.93 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  11.69 (d,  $J = 4.8$  Hz), 18.89, 115.55 (d,  $J = 23.0$  Hz), 116.83, 121.71, 121.90, 122.16, 127.33, 127.98, 128.88 (d,  $J = 8.5$  Hz), 129.93 (d,  $J = 3.9$  Hz), 134.11, 136.35, 138.45, 139.49 (d,  $J = 3.8$  Hz), 148.35, 159.46 (d,  $J = 243.4$  Hz), 167.44; IR (neat) 3343 w, 2953 w, 2874 w, 1677 m, 1520 s, 1481 s, 1424 m, 1384 m, 1325 m, 825 m, 791 m, 731 m; MS  $m/z$  (relative intensity, %) 294 ( $\text{M}^+$ , 57), 277 (23), 152 (10), 151 (100), 150 (40), 144 (11), 123 (32), 77 (12); HRMS Calcd for  $\text{C}_{18}\text{H}_{15}\text{FN}_2\text{O}$ : 294.1168; Found: 294.1172.

#### 2,6-dimethyl-*N*-(quinolin-8-yl)-3-(trifluoromethyl)benzamide (12e).



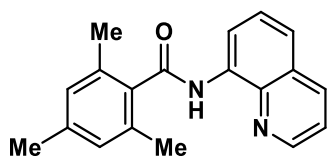
$R_f$  0.23 (hexane/EtOAc = 10/1). White Solid. Mp = 100 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.47 (s, 3H), 2.54 (s, 3H), 7.21 (d,  $J = 7.8$  Hz, 2H), 7.46 (q,  $J = 4.1$  Hz, 1H), 7.56-7.66 (m, 3H), 8.20 (dd,  $J = 8.5, 1.1$  Hz, 1H), 8.76 (dd,  $J = 4.0, 1.4$  Hz, 1H), 8.98 (dd,  $J = 6.9, 1.8$  Hz, 1H), 9.95 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  16.05 (d,  $J = 1.9$  Hz), 19.58, 116.97, 121.78, 122.37, 124.41 (q,  $J = 273.1$  Hz), 126.41 (q,  $J = 5.4$  Hz), 127.08, 127.33, 127.71, 128.01, 133.47, 134.00, 136.41, 138.45, 138.74, 140.12, 148.42, 167.68; IR (neat) 3340 w, 2971 w, 1739 m, 1675 m, 1521 s, 1483 m, 1316 s, 1213 m, 1109 s, 826 m, 792 m; MS  $m/z$  (relative intensity, %) 345 (13), 344 ( $\text{M}^+$ , 56), 327 (28), 202 (11), 201 (100), 200 (18), 173 (36), 144 (35); HRMS Calcd for  $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_2\text{O}$ : 344.1136; Found: 344.1136.

#### 4-fluoro-2,5-dimethyl-*N*-(quinolin-8-yl)benzamide (14).



R<sub>f</sub> 0.34 (hexane/EtOAc = 5/1). White Solid. Mp = 135 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.31 (s, 3H), 2.56 (s, 3H), 6.94 (d, *J* = 10.5 Hz, 1H), 7.46 (q, *J* = 4.3 Hz, 1H), 7.49-7.68 (m, 3H), 8.18 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.79 (dd, *J* = 4.0, 1.4 Hz, 1H), 8.91 (d, *J* = 7.3 Hz, 1H), 10.16 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 14.12 (d, *J* = 11.6 Hz), 19.91, 116.48, 117.69 (d, *J* = 22.0 Hz), 121.66, 121.77, 122.34 (d, *J* = 17.3 Hz), 127.40, 127.97, 130.72 (d, *J* = 6.7 Hz), 132.44 (d, *J* = 3.8 Hz), 134.62, 136.37, 136.75 (d, *J* = 7.6 Hz), 138.57, 148.27, 162.00 (d, *J* = 249.2 Hz), 167.40; IR (neat) 3352 w, 2926 w, 1674 m, 1522 s, 1482 s, 1424 m, 1383 m, 1326 m, 1141 m, 826 w, 791 m; MS *m/z* (relative intensity, %) 294 (M<sup>+</sup>, 39), 277 (19), 152 (10), 151 (100), 150 (20), 123 (20); HRMS Calcd for C<sub>18</sub>H<sub>15</sub>FN<sub>2</sub>O: 294.1166; Found: 294.1168.

#### 2,4,6-trimethyl-*N*-(quinolin-8-yl)benzamide (16).



R<sub>f</sub> 0.17 (hexane/EtOAc = 10/1). White Solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.33 (s, 3H), 2.40 (s, 6H), 6.93 (s, 2H), 7.44 (q, *J* = 4.1 Hz, 1H), 7.50-7.69 (m, 2H), 8.17 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.73 (dd, *J* = 4.0, 1.8 Hz, 1H), 8.99 (dd, *J* = 7.7, 1.4 Hz, 1H), 9.92 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 19.37, 21.11, 116.61, 121.58, 121.77, 127.36, 127.94, 128.37, 134.45, 134.47, 135.32, 136.26, 138.48, 138.70, 148.20, 169.07 ; MS *m/z* (relative intensity, %) 290 (M<sup>+</sup>, 26) 148 (11), 147 (100), 146 (14), 119 (17); HRMS Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O: 290.1419; Found: 290.1415.

#### 2-4-6. Radical Trap Experiments (Scheme 2-3)

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(quinolin-8-yl)benzamide (**1**) (79 mg, 0.3 mmol), Dicumyl peroxide (162 mg, 0.60 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (20.7 mg, 0.03 mmol), Na<sub>2</sub>CO<sub>3</sub> (95 mg, 0.9 mmol), Radical Scavengers such as TEMPO, 1,4-cyclohexadiene, and α-methylstyrene (0.9 mmol or 0.6 mmol) and <sup>t</sup>Bu-benzene (0.7 mL) were added in Air. The mixture was stirred for 18 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The yields of **2** and **1** were

determined by  $^1\text{H-NMR}$ .

#### 2-4-7. Deuterium Labeling Experiments (Scheme 2-6)

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(quinolin-8-yl)benzamide (**1**, **1-*d***) (79 mg, 0.3 mmol), Dicumyl peroxide (162 mg, 0.60 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (20.7 mg, 0.03 mmol),  $\text{Na}_2\text{CO}_3$  (95 mg, 0.9 mmol), and  $t\text{Bu}$ -benzene (0.7 mL) were added in Air. The mixture was stirred for 5 min, 10 min, 15 min and 120 min at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The yields of **2**, **2-*d*** and **1**, **1-*d*** were determined by  $^1\text{H-NMR}$ .

#### 2-4-8. Competition Experiments (Scheme 2-7)

To an oven-dried 5 mL screw-capped vial, *N*-(quinolin-8-yl)-3-(trifluoromethyl)benzamide (**3h**) (95 mg, 0.3 mmol), 3-methoxy-*N*-(quinolin-8-yl)benzamide (**3a**) (83 mg, 0.3 mmol), Dicumyl peroxide (81 mg, 0.30 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (20.7 mg, 0.03 mmol),  $\text{Na}_2\text{CO}_3$  (95 mg, 0.9 mmol) and  $t\text{Bu}$ -benzene (1.4 mL) were added in Air. The mixture was stirred for 18 h at 140 °C followed by cooling (Entry 1). The resulting mixture was filtered through a celite pad and concentrated in vacuo. The yields of **4h**, **4a** were determined by  $^1\text{H-NMR}$ .

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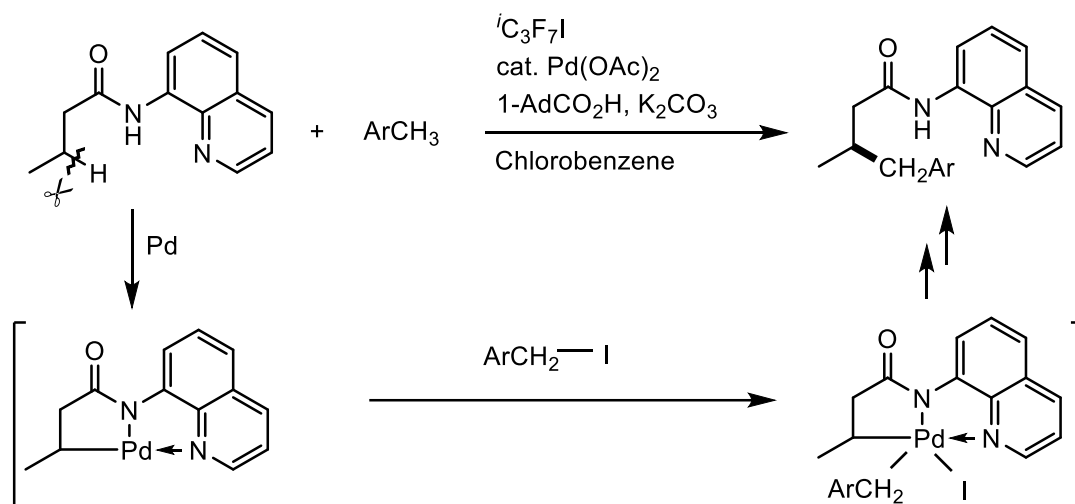
## Chapter 3

# Palladium-Catalyzed Cross Dehydrogenative Coupling between Unactivated C–H Bonds in Aliphatic Amides and Benzylic C–H Bonds in Toluene Derivatives

### Abstract

The chelation-assisted cross dehydrogenative coupling of C(sp<sup>3</sup>)–H bonds is achieved by the Pd(II)-catalyzed reaction of aliphatic amides that contain a 5-chloro-8-aminoquinoline moiety as the directing group with toluene derivatives in the presence of heptafluoroisopropyl iodide. A variety of functional groups are tolerated.

Scheme 3-1.

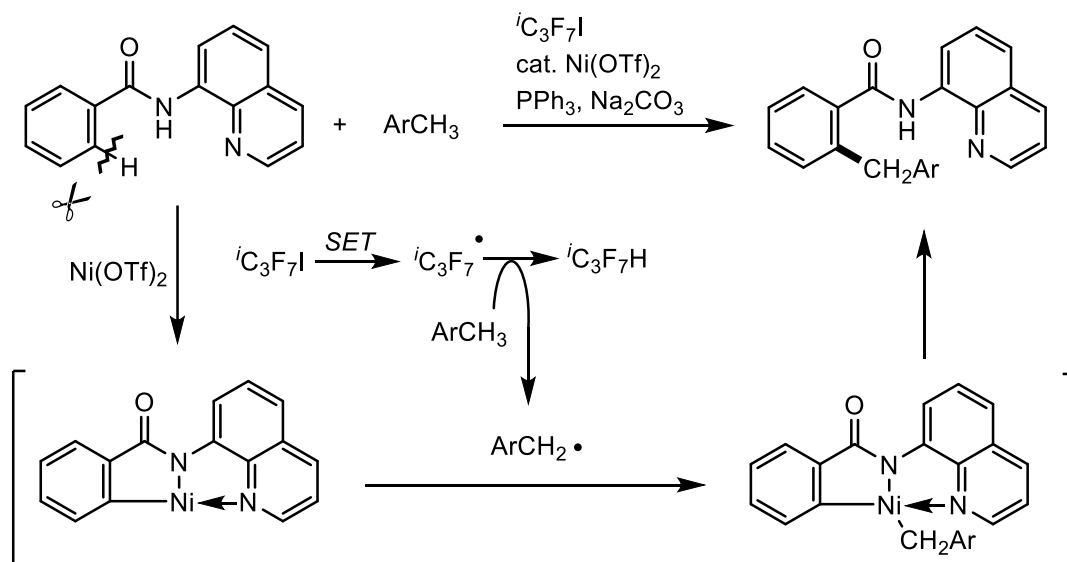


### 3-1. Introduction

Cross-coupling reactions, such as Suzuki–Miyaura coupling are one of the most powerful methods for the formation of C–C bonds.<sup>[1]</sup> In contrast, the cross dehydrogenative coupling (CDC) of C–H bonds represents an ideal transformation,<sup>[2]</sup> in that there is no need for the time-consuming pre-functionalization of the two substrates. Following the pioneering examples reported by Fagnou<sup>[3]</sup> and Sanford,<sup>[4]</sup> a number of CDC reactions of C–H bonds has been developed. However, the majority of examples reported thus far involves coupling between C(sp<sup>2</sup>)–H and C(sp<sup>2</sup>)–H bonds. CDC involving the activation of C(sp<sup>3</sup>)–H bonds has been a subject of extensive study. Li reported on the CDC between C(sp<sup>2</sup>)–H and C(sp<sup>3</sup>)–H bonds in the

Ru(II)-catalyzed reaction of 2-arylpyridines with cycloalkanes.<sup>[5]</sup> Some examples of intramolecular CDC involving C(sp<sup>3</sup>)-H bonds have also been reported.<sup>[6]</sup> Recently, various reactions which are demonstrated as CDC of C(sp<sup>3</sup>)-H bonds have been reported. However, most of these reactions involve aldol-type reactions in which one of two substrates is activated in the form of an enolate or the equivalent if they contain acidic C-H bonds and the other is activated as an oxonium or iminium intermediate if oxygen or nitrogen atoms are located adjacent to the C(sp<sup>3</sup>)-H bonds that react, indicating that the transition-metal catalyst is not involved in the key step, such as C-C bond formation.<sup>[2b], [7]</sup> To the best of my knowledge, no examples of the intermolecular CDC of unactivated C(sp<sup>3</sup>)-H bonds, have been reported. I wish to demonstrate the first example of such a CDC of C(sp<sup>3</sup>)-H bonds by taking advantage of *N,N*-bidentate chelation assistance.<sup>[8]</sup>

Scheme 3-2.



### 3-2. Palladium-Catalyzed Benzylation via Aliphatic C-H Bond Activation

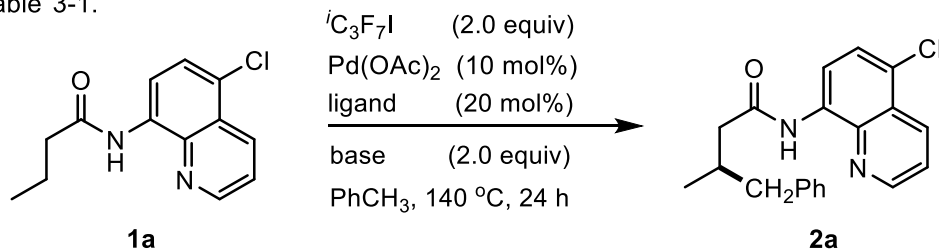
#### 3-2-1. Optimization of Reaction Conditions for Pd-Catalyzed Benzylation

Chatani recently reported the Ni(II)-catalyzed CDC between *ortho* C-H bonds in aromatic amides and benzylic C-H bonds in toluene derivatives.<sup>[9]</sup> Ni(II) was not effective in the CDC of C(sp<sup>3</sup>)-H bonds in the aliphatic amide **1a**. However, I found that the reaction of amide **1a** (0.3 mmol) with heptafluoroisopropyl iodide (0.6 mmol) in the presence of Pd(OAc)<sub>2</sub> (0.03 mmol) as the catalyst, K<sub>2</sub>CO<sub>3</sub> (0.6 mmol) as the base in toluene (1 mL) at 140 °C for 24 h gave the benzylation product **2a** in 38% NMR yield,



along with recovery of **1a** in 33% NMR yield (Table 3-1, entry 1). Addition of PPh<sub>3</sub> lowered the yield of **2a** (entry 2). Screening of phosphoric acids and carboxylic acids as ligands such as (BnO)<sub>2</sub>PO<sub>2</sub>H, MesCO<sub>2</sub>H, *N*-Boc-glycine, AcOH, PivOH and 1-AdCO<sub>2</sub>H revealed that 1-AdCO<sub>2</sub>H was the most effective for the reaction (entries 3–8). Subsequently, among K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, KOAc, Na<sub>2</sub>CO<sub>3</sub>, Li<sub>2</sub>CO<sub>3</sub>, Ag<sub>2</sub>CO<sub>3</sub> and AgOAc, K<sub>2</sub>CO<sub>3</sub> was found to be the base of choice in the reaction (entries 8–15).

Table 3-1.

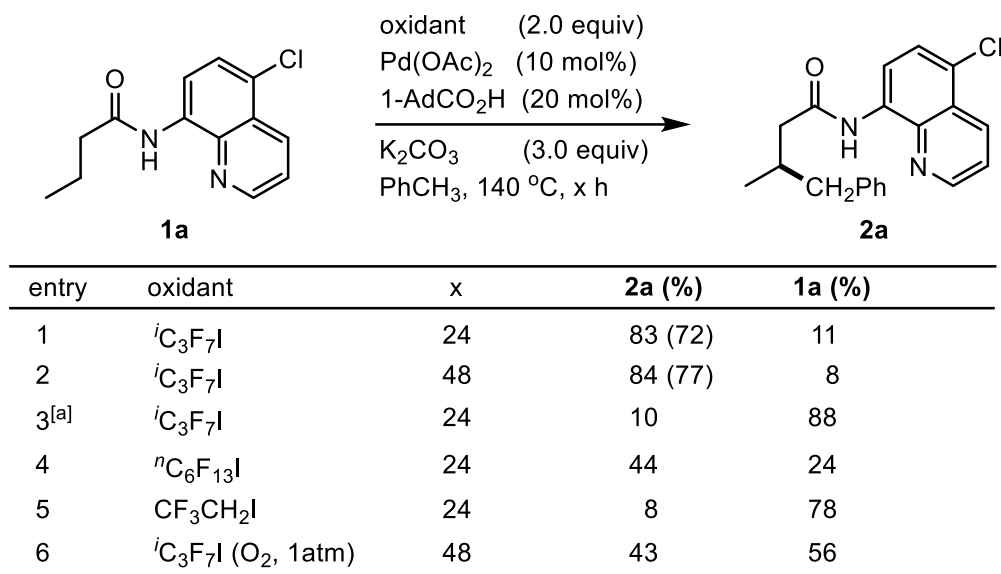


entry	ligand	base	<b>2a</b> (%)	<b>1a</b> (%)
1	none	K <sub>2</sub> CO <sub>3</sub>	38	33
2	PPh <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	10	78
3	(BnO) <sub>2</sub> POOH	K <sub>2</sub> CO <sub>3</sub>	56	14
4	MesCOOH	K <sub>2</sub> CO <sub>3</sub>	56	26
5	<i>N</i> -Boc-glycine	K <sub>2</sub> CO <sub>3</sub>	31	64
6	AcOH	K <sub>2</sub> CO <sub>3</sub>	54	36
7	PivOH	K <sub>2</sub> CO <sub>3</sub>	66	11
8	1-AdCOOH	K <sub>2</sub> CO <sub>3</sub>	75 (70)	20
9	1-AdCOOH	none	0	101
10	1-AdCOOH	K <sub>3</sub> PO <sub>4</sub>	56	34
11	1-AdCOOH	KOAc	13	83
12	1-AdCOOH	Na <sub>2</sub> CO <sub>3</sub>	0	98
13	1-AdCOOH	Li <sub>2</sub> CO <sub>3</sub>	0	87
14	1-AdCOOH	Ag <sub>2</sub> CO <sub>3</sub>	51	39
15	1-AdCOOH	AgOAc	39	41

Yield was determined by <sup>1</sup>H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. Yield of isolated product by column chromatography is given in parentheses. Molar percentage of <sup>i</sup>C<sub>3</sub>F<sub>7</sub>I, Pd(OAc)<sub>2</sub>, ligand and base are based on the amount of **1a**. Reaction conditions, unless otherwise stated: **1a** (0.30 mmol), <sup>i</sup>C<sub>3</sub>F<sub>7</sub>I (0.60 mmol), Pd(OAc)<sub>2</sub> (0.03 mmol), ligand (0.06 mmol), base (0.60 mmol) and toluene (1.0 mL).

In addition, I sought suitable oxidants (Table 3-2). When <sup>i</sup>C<sub>3</sub>F<sub>7</sub>I was used as an oxidant, the reaction of **1**

for 24 h gave product **2** in 83% yield (entry 1). Increasing the reaction time to 48 h improved the yield of **2a** in 84% (entry 2). Lowering the temperature to 80 °C (entry 3) decreased the yield of **2a**. Neither  ${}^n\text{C}_6\text{F}_{13}\text{I}$  (entry 4) nor  $\text{CF}_3\text{CH}_2\text{I}$  (entry 5) improved the yield of **2a**. Carrying out the reaction under  $\text{O}_2$  (entry 6) had no positive effect on the efficiency of the reaction. Finally, the standard reaction conditions were determined to the condition of entry 2.



Yield was determined by  ${}^1\text{H}$  NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. Yield of isolated product by column chromatography is given in parentheses.

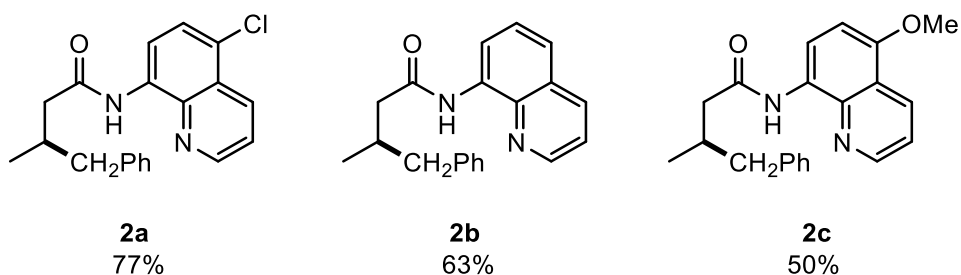
Molar percentage of oxidant,  $\text{Pd}(\text{OAc})_2$ ,  $1\text{-AdCO}_2\text{H}$  and  $\text{K}_2\text{CO}_3$  are based on the amount of **1a**. Reaction conditions: **1a** (0.30 mmol), oxidant (0.60 mmol),  $\text{Pd}(\text{OAc})_2$  (0.03 mmol),  $1\text{-AdCO}_2\text{H}$  (0.06 mmol),  $\text{K}_2\text{CO}_3$  (0.60 mmol) and toluene (1.0 mL).

[a] Run at 80 °C.

## 2-2-2. Optimization of Directing Groups

Subsequently, directing groups were examined. Although benzylation reactions using aliphatic amides **1b** and **1c** bearing 8-aminoquinoline and 5-methoxy-8-aminoquinoline moieties also proceeded, 5-chloro-8-aminoquinoline was proved to be the most effective as the bidentate directing group (Scheme 3-3).

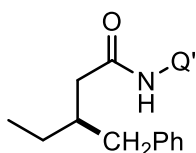
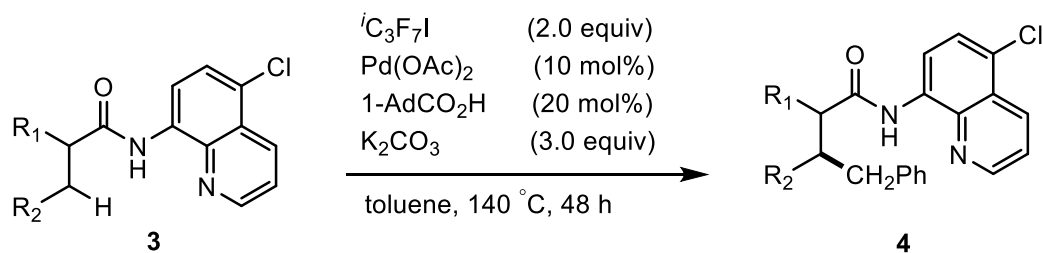
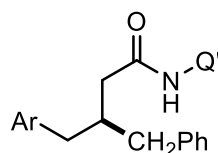
Scheme 3-3.



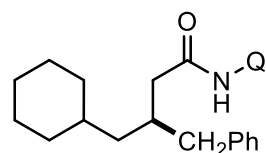
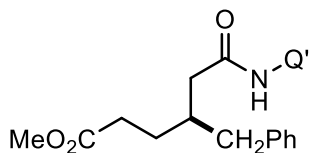
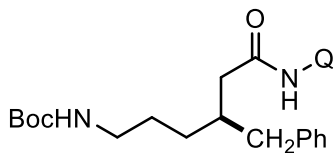
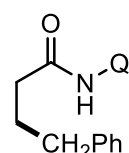
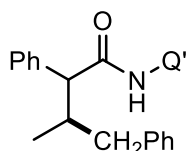
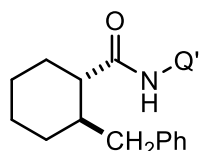
### 2-2-3. Scope of Substrates

Scheme 3-4 shows representative results of reactions with various aliphatic amides, where benzylation proceeded only at the  $\beta$ -position of amides. Various functional groups are tolerated under the reaction conditions. The benzylation effectively proceeded with pentanoic amide derivative **3a** to afford **4a**. The reactions proceeded even bearing an aryl group or cyclohexyl group on the edge of the propyl group to give **4b**, **4c**, **4d**, and **4e**. Substrates **3f** and **3g** with an ester group and a Boc-protected amide group underwent the reaction without loss of the substituents. In the reaction of the propanoic amide derivative **3h**, a mixture of the mono-benylation product **4h** and the dibenylation product was produced, in favor of **4h**. The reaction of **3i** gave the benzylation product **4i** as a single stereoisomer. The reaction of **3j** gave *trans*-**4j**.

Scheme 3-4.

**4a** 67% (26%)

**4b** Ar = Ph 53% (34%)<sup>[a]</sup>  
**4c** = 4-MeOC<sub>6</sub>H<sub>4</sub> 43% (48%)<sup>[a]</sup>  
**4d** = 4-FC<sub>6</sub>H<sub>4</sub> 40% (51%)<sup>[a]</sup>

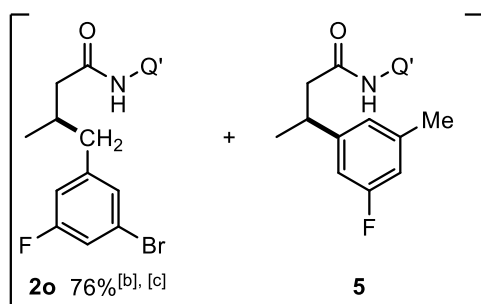
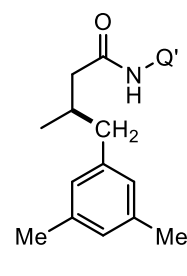
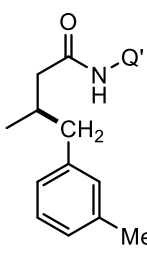
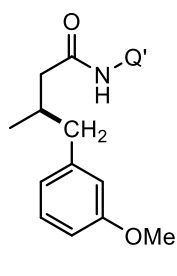
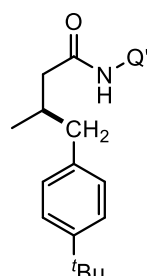
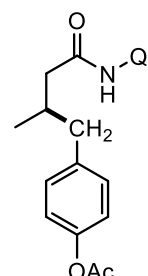
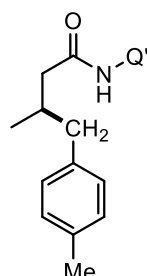
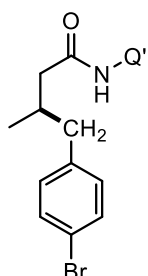
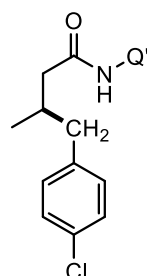
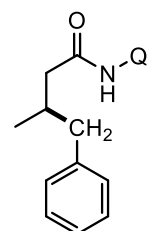
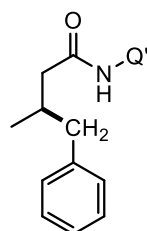
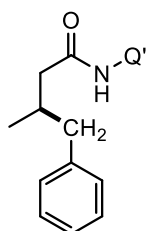
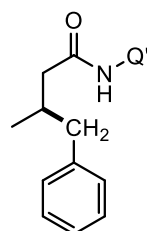
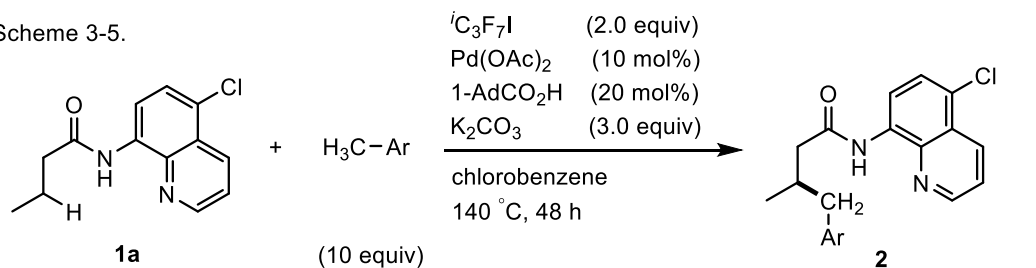
**4e** 55% (25%)**4f** 45% (42%)<sup>[a]</sup>**4g** 51% (46%)**4h** 66%<sup>[b]</sup> / 11%<sup>[a], [c]</sup> (8%)<sup>[a]</sup>**4i** 47%<sup>[d]</sup> (26%)<sup>[a]</sup>**4j** 35%<sup>[e]</sup> (51%)<sup>[a]</sup>

Q' = 5-chloro-8-aminoquinoliny group. Yield of isolated product by column chromatography. The numbers in parentheses show the amount of starting amide recovered.

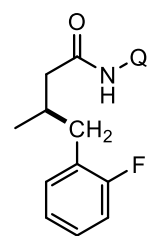
Molar percentage of  $i\text{C}_3\text{F}_7\text{I}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $1\text{-AdCO}_2\text{H}$  and  $\text{K}_2\text{CO}_3$  are based on the amount of **3**. Reaction conditions, unless otherwise stated: **3** (0.30 mmol),  $i\text{C}_3\text{F}_7\text{I}$  (0.60 mmol),  $\text{Pd}(\text{OAc})_2$  (0.03 mmol),  $1\text{-AdCO}_2\text{H}$  (0.06 mmol),  $\text{K}_2\text{CO}_3$  (0.60 mmol) and toluene (1.0 mL). [a] <sup>1</sup>H NMR yield with 1,1,2,2-tetrachloroethane as an internal standard. [b]  $\text{K}_3\text{PO}_4$  and  $(\text{BnO})_2\text{PO}_2\text{H}$  were used instead of a base and ligand. [c] The dibenylation product was formed in 11 <sup>1</sup>H NMR yield. [d] One isomer. [e]  $\text{Pd}(\text{OAc})_2$  (0.06 mmol) and  $\text{PivOH}$  (0.12 mmol) were used. .

I next examined the use of functionalized toluene derivatives as the reagent in an unreactive solvent. Finally, chlorobenzene was found to be the solvent of choice. Some representative results are shown in Scheme 3-5. The reaction again shows a high functional group compatibility. Toluene derivatives bearing electron-withdrawing groups (*p*-CF<sub>3</sub> and *p*-C(O)OMe), halogen group (*p*-F, *p*-Cl, and *p*-Br), and electron-donating groups (*p*-Me, *p*-OAc, and *p*-<sup>*i*</sup>Bu) participated in the reaction effectively to afford the corresponding benzylated products **2d–2k**. Toluenes bearing methoxy and methyl groups at the *meta*-position successfully underwent the coupling to afford benzylated products **2l–2n**. The reaction of **1a** with 3-bromo-5-fluorotoluene under the standard reaction conditions gave a 3:2 mixture of the benzylation product **2o** and the C–H arylation product **5**, the latter of which was produced by the arylation of C–H bonds (C–H/C–Br coupling). The ratio of the products is highly dependent on the amount of <sup>*i*</sup>C<sub>3</sub>F<sub>7</sub>I used in the reaction. When the reaction was carried out in the absence of <sup>*i*</sup>C<sub>3</sub>F<sub>7</sub>I, the arylation product **5** was obtained in 60% yield as the single product. The use of 6 equivalents of <sup>*i*</sup>C<sub>3</sub>F<sub>7</sub>I gave **2o** in 76% yield as the major isomer.

Scheme 3-5.



$i\text{C}_3\text{F}_7\text{I}$ equiv	ratio	
	<b>2o</b>	<b>5</b>
0	0	1
2	3	2
6	10	1

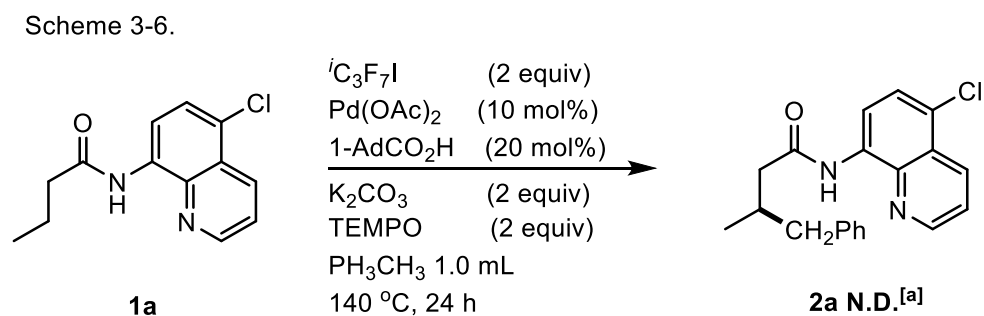


Q' = 5-chloro-8-aminoquinolinyl group. Yield of isolated product by column chromatography. Molar percentage of  $i\text{C}_3\text{F}_7\text{I}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $1\text{-AdCO}_2\text{H}$  and  $\text{K}_2\text{CO}_3$  are based on the amount of **1**. Reaction conditions, unless otherwise stated: **3** (0.30 mmol),  $i\text{C}_3\text{F}_7\text{I}$  (0.60 mmol),  $\text{Pd}(\text{OAc})_2$  (0.03 mmol),  $1\text{-AdCO}_2\text{H}$  (0.06 mmol),  $\text{K}_2\text{CO}_3$  (0.60 mmol), toluene derivatives (3.0 mmol) and chlorobenzene (0.7 mL). [a] Arene (1.0 mL) was used as a solvent. [b]  $^1\text{H}$  NMR yield with 1,1,2,2-tetrachloroethane as an internal standard. [c]  $i\text{C}_3\text{F}_7\text{I}$  (1.8 mmol) was used.

### 3-3. Mechanistic Studies

#### 3-3-1. Radical Trap Experiments

To probe the reaction mechanism, I first performed a radical trap experiment. When the reaction was carried out in the presence of 2.0 equiv of a typical radical scavenger, TEMPO otherwise under standard reaction conditions, the reaction was completely inhibited (Scheme 3-6). These results clearly indicate that a free radical species is involved in the reaction.

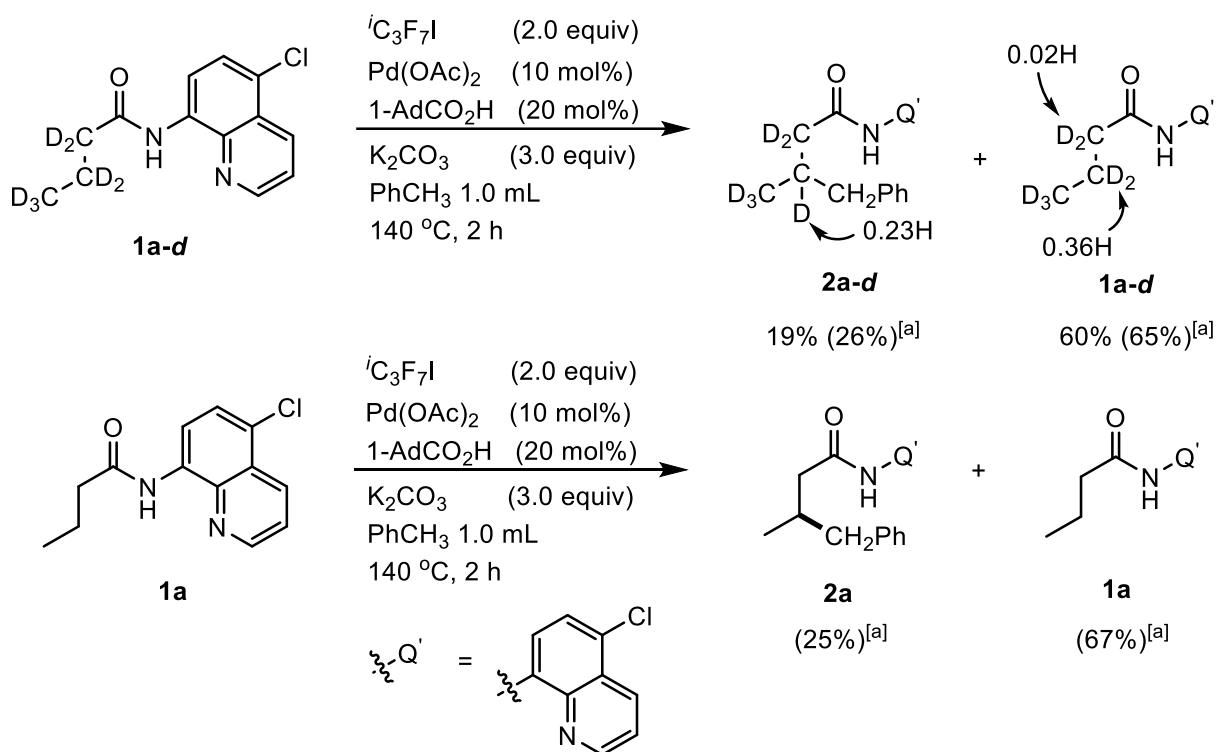


[a] <sup>1</sup>H NMR yield

#### 3-3-2. Deuterium Labeling Experiments

To probe the reaction mechanism, we carried out a series of experiments using the deuterium-labelled amide **1a-d** and toluene-*d*<sub>8</sub>. First, an equimolar amount of **1** and **1a-d** were put in separate reaction vessels, and were subjected to the reaction for 2 h under the standard conditions (Scheme 3-7). H/D exchange occurred only at the β-position in both benzylated product **2a-d** recovered from **1a-d**, indicating that the C–H bonds cleavage is reversible. From the yield of **2a-d** and **2a**, intermolecular KIE was not observed (for parallel experiments). This result suggests that C–H bond cleavage is not involved in the rate-determining step.

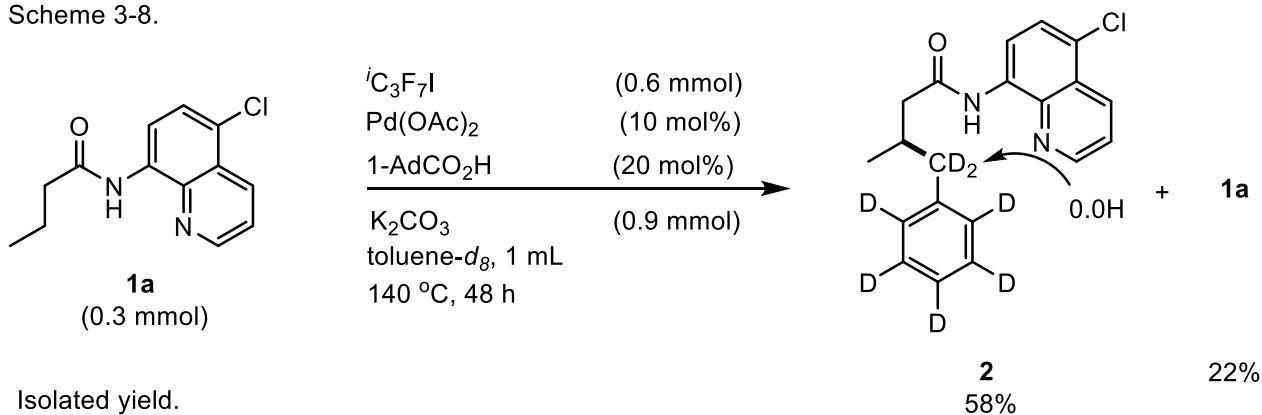
Scheme 3-7.



Isolated yields. [a]  $^1\text{H}$  NMR yields.

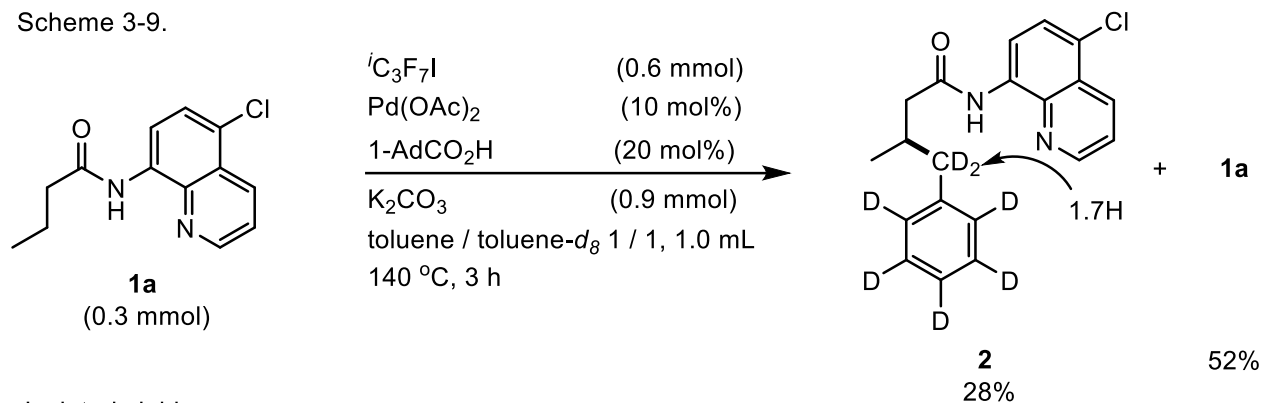
Subsequently, a deuterium-labeling experiment was performed using toluene- $d_8$ . The result of Scheme 3-8 indicates that no H/D exchange occurred at the benzylic position even when the reaction was extended to 48 h. When equimolar toluene and toluene- $d_8$  were put in the same reaction vessel and reacted under the standard conditions (3 h), a KIE of 5.7 was obtained by integration of the signal of the benzylic proton ( $1.7/0.3 = 5.7$ , Scheme 3-9).<sup>[10]</sup>

Scheme 3-8.





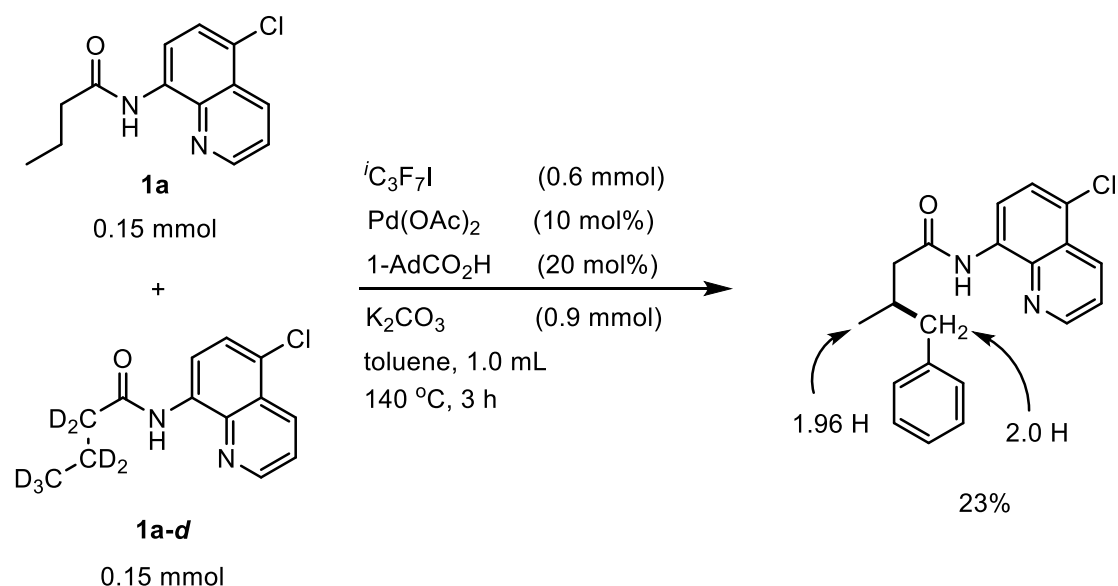
Scheme 3-9.



Isolated yield.

The result of a competition experiment between **1a** and **1a-d** indicated a KIE of 1.9 ( $1.96/1.04 = 1.88$ ) (Scheme 3-10). Although it is difficult to draw a final conclusion, it appeared that the cleavage of C–H bonds is probably not the rate-determining step.

Scheme 3-10.

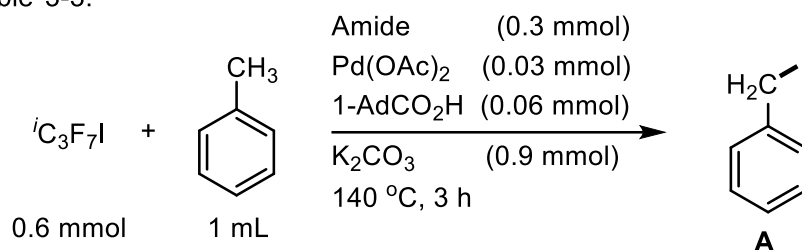


### 3-3-3. Confirmation of Intermediate

I conducted the following experiments to determine the active species as the benzylating agent, which could be generated as an intermediate. In the presence of  $i\text{C}_3\text{F}_7\text{I}$  and toluene, the reaction was carried out with or without adding each reagent (Table 3-3). When amide **1a**,  $\text{Pd}(\text{OAc})_2$  or  $\text{K}_2\text{CO}_3$  was added alone, benzyl iodide (**A**) was generated, albeit in low yield (entries 2–5). When  $\text{Pd}(\text{OAc})_2$ ,  $1\text{-AdCO}_2\text{H}$ , and  $\text{K}_2\text{CO}_3$  were used without amide **1a**, **A** was not formed (entries 6, 7). The coexistence of amide **1a** and  $\text{K}_2\text{CO}_3$  increased

the yield of **A** (entry 8). Addition of Pd(OAc)<sub>2</sub> further increased the yield of **A** (entry 9), and addition of all the reagents gave **A** in 49% yield, despite the 33% generation of benzylated products (entry 10). The result of Table 3-3 suggested that active species could be benzyl iodide.

Table 3-3.



entry	Amide	Pd(OAc) <sub>2</sub>	1-AdCOOH	K <sub>2</sub> CO <sub>3</sub>	<b>A</b> (%)
1	-	-	-	-	-
2	○	-	-	-	4
3	-	○	-	-	2
4	-	-	-	○	2
5 <sup>[a]</sup>	-	-	-	○	11
6	-	○	○	○	0
7 <sup>[a]</sup>	-	○	○	○	0
8	○	-	-	○	33
9	○	○	-	○	43
10	○	○	○	○	49
11 <sup>[a]</sup>	○	○	○	○	3

<sup>1</sup>H NMR yield with 1,1,2,2-tetrachloroethane as an internal standard.

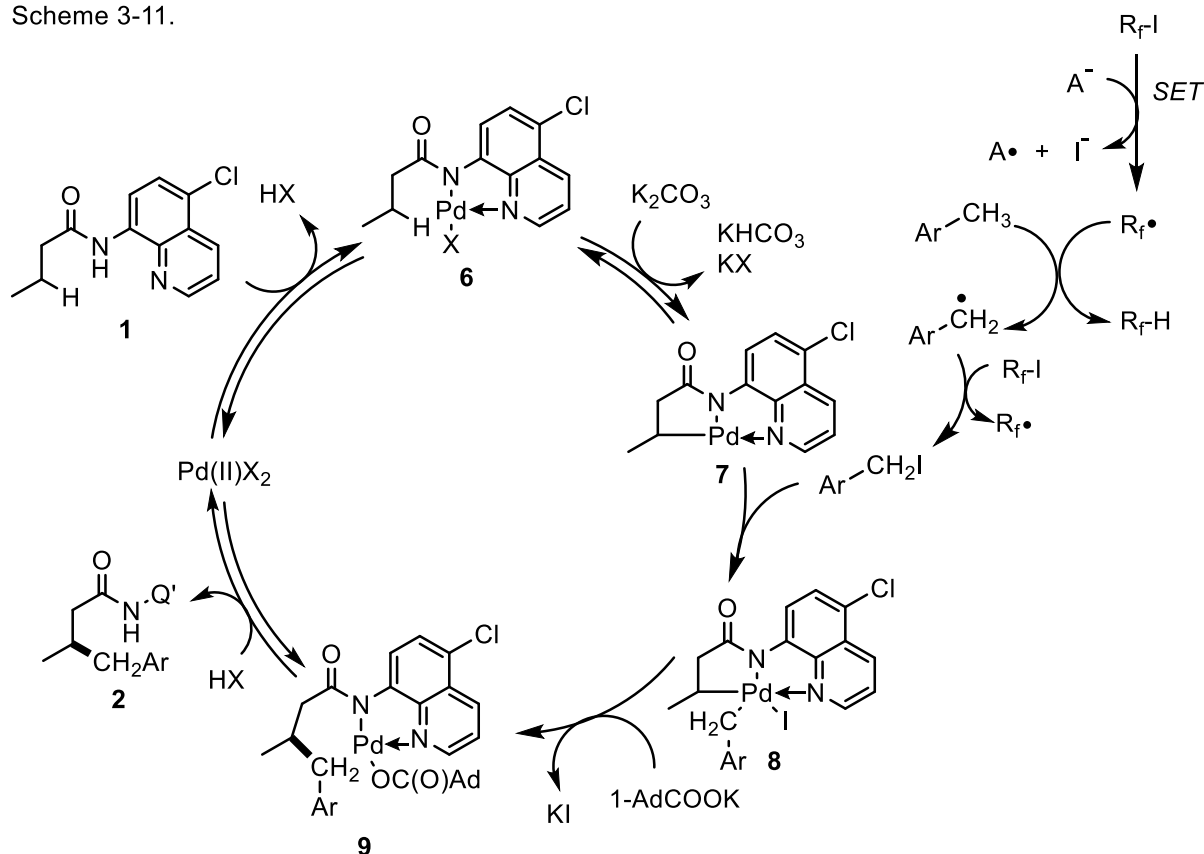
[a] Run for 24 h. Yield of benzylated amide: 33%

### 3-3-4. Proposed Mechanism

On the basis of the above experimental results and data obtained from previous reports, a plausible reaction mechanism for the present reaction is proposed in Scheme 3-11. The coordination of amide **1** to the Pd(II) center gives the Pd(II) complex **6** with the generation of HX, which is trapped by K<sub>2</sub>CO<sub>3</sub>. The C–H bonds in the complex **6** then undergo reversible cleavage to give the palladacycle **7**. A base-promoted single electron transfer to R<sub>f</sub>-I<sup>[11]</sup> from the anion of **1**, which is generated by **1** and K<sub>2</sub>CO<sub>3</sub>, gives a R<sub>f</sub> radical which

abstracts a hydrogen from toluene to generate a benzyl radical and  $R_f-H$ . The benzyl radical abstracts the iodide from  $R_f-I$  to give benzyl iodide and the  $R_f$  radical. The reaction of complex **7** with the benzyl iodide affords the Pd(II) species **8**, from which the reductive elimination and protonation occurs to give the final product **2** with the generation of a Pd(II) complex. In fact, the reaction of **1a** with benzyl iodide in the absence of  $^iC_3F_7I$  under otherwise standard reaction conditions afforded **2a** in 74% NMR yield. However, a mechanism in which **7** reacts with a benzyl radical cannot be excluded. The addition of TEMPO completely quenched the reaction. The finding reported herein indicates that the reaction involves the formation of a free radical.

Scheme 3-11.



### 3-3-5. Conclusion

I demonstrate the first example of the chelation-assisted CDC of unactivated  $C(sp^3)-H$  bonds with toluene  $C-H$  bonds. The reaction does not require the use of a toluene derivative as the solvent. Rather, toluene derivatives can be used as the coupling reagent in chlorobenzene. The scope of the reaction is broad with regard to both aliphatic amides and toluene derivatives.

## 3-4. Experimental Section

### 3-4-1. General Information.

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a JEOL ECS-400 spectrometer in  $\text{CDCl}_3$  with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4000; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained using Shimadzu GCMS-QP 2014 and Shimadzu GCMS-QP 5000 instruments instrument with ionization voltages of 70 eV. High resolution mass spectra (HRMS) were obtained on a JEOL JMS-700 instrument. Analytical gas chromatography (GC) was carried out on Shimadzu GC-14B, Shimadzu GC-2014 and Shimadzu GC-8A gas chromatographs, equipped with a flame ionization detector. Melting points were determined using a Stanford Research Systems apparatus. Column chromatography was performed with  $\text{SiO}_2$  (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

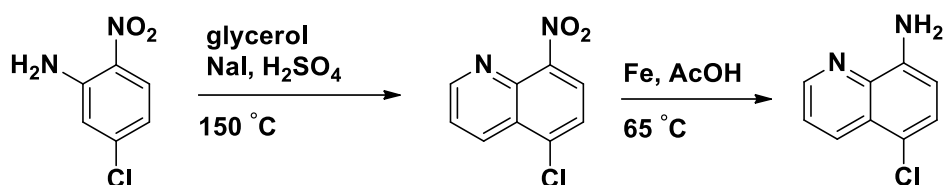
### 3-4-2. Materials.

$\text{K}_2\text{CO}_3$  (CAS 584-08-7) was purchased from Nacalai Tesque, Inc. Heptafluoroisopropyl iodide (CAS 677-69-0) and 8-aminoquinoline (CAS 578-66-5) were purchased from Tokyo Kasei Kogyo Co., Ltd.  $\text{Pd}(\text{OAc})_2$  (CAS 3375-31-3) and toluene, super dehydrated (CAS 68-12-2) were purchased from Wako Pure Chemicals.

5-Methoxyquinolin-8-amine (CAS 30465-68-0) was prepared by following procedure.

### 3-4-3. Synthesis of the Starting Amides.

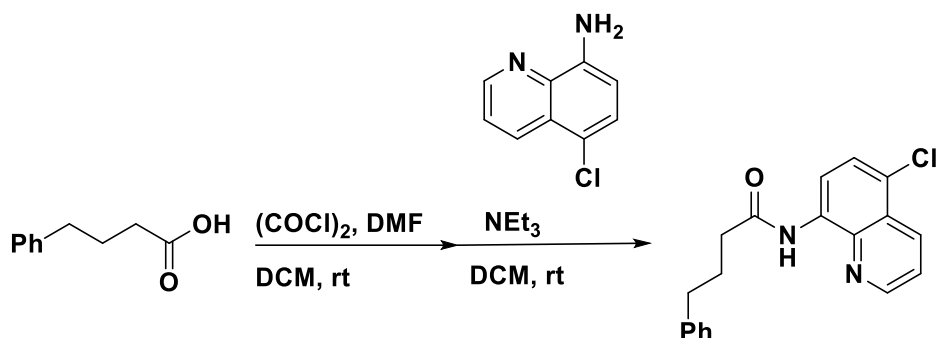
#### General Procedure for the Preparation of 8-amino-5-chloroquinoline.



Glycerol (57 mL, 782.5 mmol, 2.7 equiv) was added to an oven-dried 300 mL of three-necked flask and heated at 160 °C for 1 h, then cooled to 110 °C. 5-Chloro-2-nitroaniline (50 g, 290 mmol, 1 equiv) and NaI (850 mg, 6 mmol, 0.02 equiv) were added, and the mixture was heated to 150 °C with vigorous stirring. Conc. H<sub>2</sub>SO<sub>4</sub> (35.5 mL, 666.5 mmol, 2.3 equiv) was added dropwise, and the reaction was heated at 150 °C for 1 h, and then the reaction was cooled to rt. The reaction was diluted with 200 mL of water and 200 mL of DCM, and filtered through a celite pad. The filtrate was extracted with DCM(3x). The combined organic layer was washed with brine and dried by anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give 5-chloro-8-nitroquinoline (36.4 g, 175 mmol, 60%) which was used for next step without purification.

5-chloro-8-nitroquinoline (13.8 g, 66 mmol) was dissolved in 180 mL of acetic acid, and the iron powder (25 g, 455 mmol) was added to the solution. The mixture was heated to 65 °C for 2 h under nitrogen. The reaction was filtered through a celite pad, and washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The resulting brown gum was dissolved in 200 mL of DCM, and basified by 4N NaOH aq. until pH. 10, and the solution was filtered through a celite pad, and filtrate was extracted with DCM (3x). The combined organic layer was washed with brine and dried by anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give 5-chloroquinolin-8-amine (10.2 g, 57 mmol, 87%).

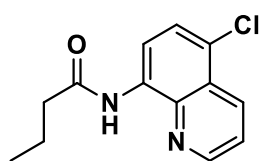
## General Procedure for the Preparation of Starting Amide.



To an oven-dried 100 mL three-necked flask, 4-phenylbutyric acid (1.6 g, 10 mmol), DMF (5 drops) and DCM (20 mL) were added under a N<sub>2</sub> atmosphere. Oxalyl chloride (1.0 mL, 12 mmol, 1.2 equiv.) was added dropwise at 0 °C resulting in vigorous bubbling. The mixture was stirred for 3 h at room temperature, and the solvent was then removed *in vacuo*. The resulting acid chloride was used immediately without further purification. To a solution of acid chloride in DCM (30 mL), the solution of 8-amino-5-chloroquinoline (2.1 g, 12 mmol, 1.2 equiv.), Et<sub>3</sub>N (2.5 mL, 24 mmol, 2 equiv.) in DCM (15 mL) were added dropwise to the solution at 0 °C, and the solution was then warmed to room temperature. After stirring overnight, the reaction system was quenched with sat. aq. NaHCO<sub>3</sub> (30 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic layers were washed with 1 M HCl aq. (30 mL) and brine (30 mL), dried over MgSO<sub>4</sub>, filtered and evaporated *in vacuo*. The resulting crude amide was purified by column chromatography on silica gel (hexane / EtOAc = 4 / 1) to afford the desired amide as a white solid (2.5 g, 77%).

## Spectroscopic Data for Starting Amides

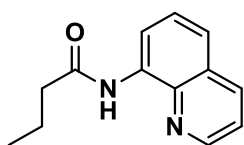
### *N*-(5-chloroquinolin-8-yl)butyramide (1a).



R<sub>f</sub> 0.29 (hexane/EtOAc = 5/1). White Solid. Mp = 62 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 1.06 (t, *J* = 7.3 Hz, 3H), 1.86 (sext, *J* = 8.0 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 7.53-7.63 (m, 2H), 8.57 (dd, *J* = 8.7, 1.4 Hz,

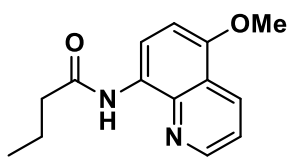
1H), 8.74 (d,  $J = 8.2$  Hz, 1H), 8.85 (dd,  $J = 4.0, 1.2$  Hz, 1H), 9.77 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  13.79, 19.05, 40.09, 116.43, 122.25, 124.06, 125.90, 127.30, 133.53, 133.75, 138.74, 148.45, 171.76; IR (neat) 3338 w, 2966 w, 2871 w, 1739 s, 1680 s, 1591 w, 1519 s, 1475 s, 1369 s, 1217 m, 961 m, 780 m, 688 m; MS  $m/z$  (relative intensity, %) 248 ( $\text{M}^+$ , 14), 205 (13), 180 (32), 179 (11), 178 (100); HRMS Calcd for  $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}$ : 248.0716; Found: 248.0717.

***N*-(quinolin-8-yl)butyramide (1b).**



$R_f$  0.37 (hexane/EtOAc = 3/1). White Solid. Mp = 53 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.06 (t,  $J = 7.6$  Hz, 3H), 1.86 (sext,  $J = 7.5$  Hz, 2H), 2.55 (t,  $J = 7.6$  Hz, 2H), 7.39-7.58 (m, 3H), 8.15 (dd,  $J = 8.2, 1.8$  Hz, 1H), 8.73-8.87 (m, 2H), 9.82 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  13.80, 19.11, 40.11, 116.38, 121.29, 121.52, 127.41, 127.88, 134.47, 136.33, 138.21, 148.02, 171.75; IR (neat) 3357 w, 2959 w, 2871 w, 1685 s, 1595 w, 1521 s, 1479 s, 1325 m, 913 w, 829 s, 796 s, 767 s, 670 m; MS  $m/z$  (relative intensity, %) 214 ( $\text{M}^+$ , 21), 171 (36), 145 (11), 144 (100); HRMS Calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$ : 214.1106; Found: 214.1105.

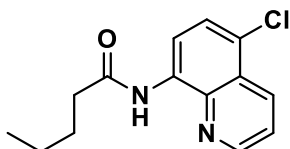
***N*-(5-methoxyquinolin-8-yl)butyramide (1c).**



$R_f$  0.29 (hexane/EtOAc = 3/1). White Solid. Mp = 61 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.06 (t,  $J = 7.3$  Hz, 3H), 1.85 (sext,  $J = 7.5$  Hz, 2H), 2.52 (t,  $J = 7.6$  Hz, 2H), 3.99 (s, 3H), 6.84 (d,  $J = 8.7$  Hz, 1H), 7.44 (q,  $J = 4.3$  Hz, 1H), 8.58 (dd,  $J = 8.2, 1.8$  Hz, 1H), 8.71 (d,  $J = 8.7$  Hz, 1H), 8.81 (dd,  $J = 4.4, 1.6$  Hz, 1H), 9.56 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  13.84, 19.20, 40.08, 55.73, 104.32, 116.48, 120.37, 120.65, 127.97, 131.23, 139.00, 148.54, 150.06, 171.35; IR (neat) 3351 w, 2961 w, 1666 m, 1593 w, 1528 s, 1495 m,

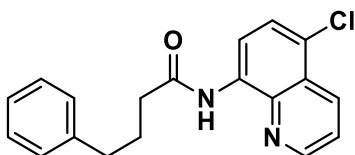
1397 m, 1268 s, 810 s, 793 s, 674 m; MS  $m/z$  (relative intensity, %) 244 ( $M^+$ , 54), 201 (23), 174 (79), 160 (11), 159 (100); HRMS Calcd for  $C_{14}H_{16}N_2O_2$ : 244.1212; Found: 244.1212.

***N*-(5-chloroquinolin-8-yl)pentanamide (3a).**



$R_f$  0.40 (hexane/EtOAc = 5/1). White Solid.  $Mp = 57\text{ }^\circ\text{C}$ .  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  0.99 (t,  $J = 7.3$  Hz, 3H), 1.40-1.54 (m, 2H), 1.75-1.86 (m, 2H), 2.57 (t,  $J = 7.8$ , 2H), 7.55-7.64 (m, 2H), 8.58 (dd,  $J = 8.7$ , 1.4 Hz, 1H), 8.74 (d,  $J = 8.7$ , 1H), 8.85 (dd,  $J = 4.4$ , 1.6 Hz, 1H), 9.77 (brs, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  13.83, 22.40, 27.65, 37.95, 116.26, 122.26, 124.02, 125.87, 127.25, 133.38, 133.80, 138.84, 148.54, 171.90; IR (neat) 3357 w, 3014 w, 2969 w, 2871 w, 1739 s, 1520 m, 1478 m, 1367 m, 1228 m, 837 m, 787 m; MS  $m/z$  (relative intensity, %) 262 ( $M^+$ , 10), 205 (12), 180 (32), 179 (12), 178 (100); HRMS Calcd for  $C_{14}H_{15}ClN_2O$ : 262.0873; Found: 262.0872.

***N*-(5-chloroquinolin-8-yl)-4-phenylbutanamide (3b).**

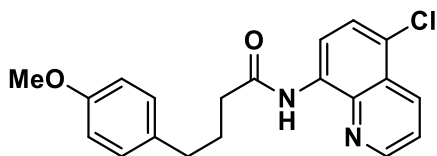


$R_f$  0.31 (hexane/EtOAc = 4/1). White Solid.  $Mp = 76\text{ }^\circ\text{C}$ .  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.15 (quin,  $J = 7.2$  Hz, 2H), 2.55 (t,  $J = 7.3$  Hz, 2H), 2.76 (t,  $J = 7.6$  Hz, 2H), 7.15-7.34 (m, 2H), 7.51 (q,  $J = 4.3$  Hz, 1H), 7.55 (d,  $J = 8.2$  Hz, 1H), 8.50 (dd,  $J = 8.8$ , 2.0 Hz, 1H), 8.70 (d,  $J = 8.2$  Hz, 1H), 8.79 (dd,  $J = 4.0$ , 1.6 Hz, 1H), 9.71 (brs, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  26.80, 35.02, 37.08, 116.13, 122.13, 123.92, 125.65, 125.88, 127.05, 128.31, 128.43, 133.16, 133.54, 138.55, 141.27, 148.36, 171.25; IR (neat) 3354 w, 3026 w, 2931 w, 2859 w, 1686 m, 1590 w, 1517 s, 1478 s, 1367 m, 1317 m, 947 w, 837 m, 787 m, 698 m; MS  $m/z$  (relative intensity, %) 324 ( $M^+$ , 10), 222 (14), 220 (43), 205 (10), 180 (32), 179 (12), 178 (100), 91 (16);



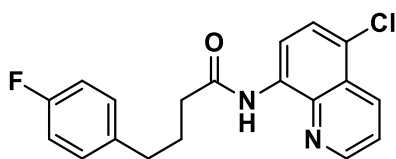
HRMS Calcd for C<sub>19</sub>H<sub>17</sub>ClN<sub>2</sub>O: 324.1029; Found: 324.1032.

***N*-(5-chloroquinolin-8-yl)-4-(4-methoxyphenyl)butanamide (3c).**



R<sub>f</sub> 0.34 (hexane/EtOAc = 3/1). White Solid. Mp = 90 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.11(quin, *J* = 7.6 Hz, 2H), 2.54 (t, *J* = 7.3 Hz, 2H), 2.70 (t, *J* = 7.3, 2H), 3.77 (s, 3H), 6.82 (dd, *J* = 9.2, 2.3 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.51 (q, *J* = 4.3 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 8.49 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.7 (d, *J* = 8.2 Hz, 1H), 8.79 (dd, *J* = 4.0, 0.8 Hz, 1H), 9.70 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 27.07, 34.13, 37.10, 55.11, 113.67, 116.17, 122.18, 123.94, 125.69, 127.09, 129.35, 133.22, 133.31, 133.59, 138.60, 148.40, 157.76, 171.38; IR (neat) 3343 w, 2937 w, 1667 s, 1585 w, 1529 s, 1483 m, 1385 m, 1314 m, 1240 m, 961 m, 779 m, 691 w; MS *m/z* (relative intensity, %) 354 (M<sup>+</sup>, 13), 222 (19), 220 (60), 180 (33), 179 (13), 178 (100), 121 (14); HRMS Calcd for C<sub>20</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>2</sub>: 354.1135; Found: 354.1134.

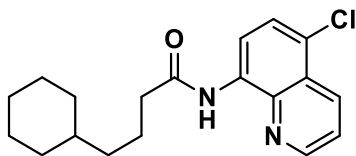
***N*-(5-chloroquinolin-8-yl)-4-(4-fluorophenyl)butanamide (3d).**



R<sub>f</sub> 0.37 (hexane/EtOAc = 3/1). Light Yellow Solid. Mp = 121 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.13 (quin, *J* = 7.6 Hz, 2H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 6.92-7.03 (m, 2H), 7.19 (td, *J* = 6.0 Hz, 2.1 Hz, 2H), 7.53-7.65 (m, 2H), 8.58 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.73 (d, *J* = 8.2, Hz, 1H), 8.84 (dd, *J* = 4.0, 2.0 Hz, 1H), 9.75 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 27.02, 34.28, 37.06, 115.13 (d, *J* = 21.1 Hz), 116.39, 122.31, 124.19, 125.89, 127.25, 129.84 (d, *J* = 7.6 Hz), 133.49, 133.63, 136.97 (d, *J* = 2.9 Hz), 138.73, 148.51, 161.31 (d, *J* = 243.5 Hz), 171.28; IR (neat) 3354 w, 1739 w, 1687 m, 1522 s, 1480 m, 1368 m, 1319 w, 1220 m, 836 w, 789 w; MS *m/z* (relative intensity, %) 342 (M<sup>+</sup>, 10), 222 (15), 220 (47), 205 (10),

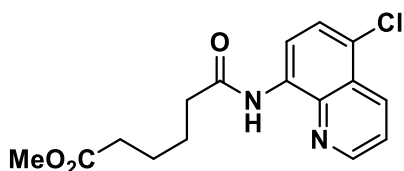
180 (32), 179 (13), 178 (100), 109 (15); HRMS Calcd for C<sub>19</sub>H<sub>16</sub>ClFN<sub>2</sub>O: 342.0935; Found: 342.0935.

***N*-(5-chloroquinolin-8-yl)-4-cyclohexylbutanamide (3e).**



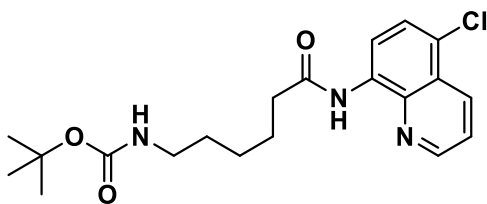
R<sub>f</sub> 0.57 (hexane/EtOAc = 3/1). Yellow Solid. Mp = 74 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 0.82-0.98 m, 2H), 1.08-1.37 (m, 6H), 1.53-1.92 (m, 9H), 2.54 (t, *J* = 7.8 Hz, 2H), 7.54-7.64 (m, 2H), 8.57 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.74 (d, *J* = 8.2 Hz, 1H), 8.85 (dd, *J* = 4.0, 1.6 Hz, 1H), 9.76 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 22.97, 26.35, 26.65, 33.27, 37.00, 37.48, 38.49, 116.34, 122.28, 124.04, 125.91, 127.29, 133.45, 133.81, 138.85, 148.54, 171.97; IR (neat) 3366 w, 2920 m, 2847 w, 1739 s, 1679 s, 1589 w, 1524 s, 1479 s, 1416 m, 1362 s, 1315 m, 1216 m, 927 m, 777 m, 698 w; MS *m/z* (relative intensity, %) 330 (M<sup>+</sup>, 5), 220 (15), 180 (32), 179 (14), 178 (100); HRMS Calcd for C<sub>19</sub>H<sub>23</sub>ClN<sub>2</sub>O: 330.1499; Found: 330.1495.

**methyl 6-((5-chloroquinolin-8-yl)amino)-6-oxohexanoate (3f).**



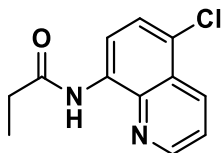
R<sub>f</sub> 0.17 (hexane/EtOAc = 3/1). White Solid. Mp = 95 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 1.69-1.94 (m, 4H), 2.41 (t, *J* = 7.1 Hz, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 3.68 (s, 3H), 7.50-7.67 (m, 2H), 8.58 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.72 (d, *J* = 8.2 Hz, 1H), 8.85 (dd, *J* = 4.0, 2.0 Hz, 1H), 9.76 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 24.48, 24.94, 33.77, 37.68, 51.58, 116.33, 122.33, 124.17, 125.89, 127.24, 133.43, 133.69, 138.83, 148.60, 171.23, 173.83; IR (neat) 3356 w, 2970 w, 2952 w, 1735 s, 1698 m, 1574 w, 1525 s, 1477 m, 1369 m, 1193 m, 984 m, 958 w, 832 m, 786 m, 672 m; MS *m/z* (relative intensity, %) 320 (M<sup>+</sup>, 10), 220 (15), 205 (17), 180 (32), 179 (16), 178 (100); HRMS Calcd for C<sub>16</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>3</sub>: 320.0928; Found: 320.0930.

**tert-butyl (6-((5-chloroquinolin-8-yl)amino)-6-oxohexyl)carbamate (3g).**



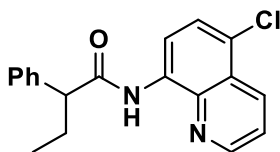
$R_f$  0.44 (hexane/EtOAc = 1/1). Light Yellow. Mp = 120 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.36-1.51 (m, 11H), 1.52-1.61 (m, 2H), 1.75-1.92 (m, 2H), 2.57 (t,  $J=7.3$  Hz, 2H), 3.15 (m, 2H), 4.60 (brs, 1H), 7.52-7.63 (m, 2H), 8.57 (d,  $J = 8.7$  Hz, 1H), 8.72 (d,  $J = 8.7$  Hz, 1H), 8.85 (d,  $J = 3.7$  Hz, 1H), 9.77 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  25.11, 26.38, 28.36, 29.82, 37.93, 40.34, 79.02, 116.36, 122.28, 124.11, 125.87, 127.23, 133.46, 133.65, 138.72, 148.53, 155.92, 171.57; IR (neat) 3353 w, 2931 w, 2863 w, 1686 m, 1590 w, 1519 s, 1479 m, 1365 m, 1168 m, 960 w, 838 w, 787 w; MS  $m/z$  (relative intensity, %) 391 ( $\text{M}^+$ , 3), 220 (17), 205 (14), 180 (32), 179 (17), 178 (100); HRMS Calcd for  $\text{C}_{20}\text{H}_{26}\text{ClN}_3\text{O}_3$ : 391.1663; Found: 391.1666.

***N*-(5-chloroquinolin-8-yl)propionamide (3h).**



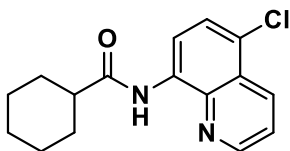
$R_f$  0.26 (hexane/EtOAc = 5/1). White Solid. Mp = 82 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.34 (t,  $J = 7.6$  Hz, 3H), 2.61 (q,  $J = 7.6$  Hz, 2H), 7.53-7.64 (m, 2H), 8.59 (dd,  $J = 8.5, 1.6$  Hz, 1H), 8.75 (d,  $J = 8.2$  Hz, 1H), 8.86 (dd,  $J = 4.4, 1.6$  Hz, 1H), 9.80 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  9.66, 31.21, 116.26, 122.28, 124.03, 125.88, 127.27, 133.40, 133.81, 138.86, 148.55, 172.47; IR (neat) 3340 w, 2965 w, 1685 m, 1589 w, 1529 s, 1480 s, 1369 m, 1259 m, 1191 m, 939 s, 797 s, 697 s; MS  $m/z$  (relative intensity, %) 296 ( $\text{M}^+$ , 20), 205 (20), 180 (32), 179 (12), 178 (100); HRMS Calcd for  $\text{C}_{12}\text{H}_{11}\text{ClN}_2\text{O}$ : 234.0560; Found: 234.0561.

***N*-(5-chloroquinolin-8-yl)-2-phenylbutanamide (3i).**



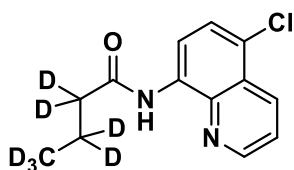
$R_f$  0.57 (hexane/EtOAc = 3/1). White Solid. Mp = 96 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  0.99 (t,  $J$  = 7.3 Hz, 3H), 1.87-2.07 (m, 1H), 2.23-2.43 (m, 1H), 3.61 (t,  $J$  = 7.6 Hz, 1H), 7.28 (t,  $J$  = 7.2, 1H), 7.37 (t,  $J$  = 7.6 Hz, 2H), 7.47 (d,  $J$  = 7.8 Hz, 2H), 7.53 (q,  $J$  = 4.1 Hz, 1H), 7.56 (d,  $J$  = 8.7 Hz, 1H), 8.52 (dd,  $J$  = 8.8, 1.2 Hz, 1H), 8.72 (d,  $J$  = 8.2 Hz, 1H), 8.78 (dd,  $J$  = 4.0, 1.4 Hz, 1H), 9.85 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  12.38, 26.50, 56.69, 116.22, 122.22, 124.15, 125.82, 127.14, 127.33, 128.02, 128.85, 133.29, 133.76, 138.95, 139.55, 148.57, 172.17; IR (neat) 3354 w, 2967 w, 2920 w, 1739 w, 1689 m, 1589 w, 1518 s, 1477 s, 1382 m, 1316 m, 1201 w, 959 w, 930 w, 834 m, 698 m; MS  $m/z$  (relative intensity, %) 324 ( $\text{M}^+$ , 9), 207 (32), 206 (12), 205 (100), 178 (21), 92 (15); HRMS Calcd for  $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}$ : 324.1029; Found: 324.1032.

***N*-(5-chloroquinolin-8-yl)cyclohexanecarboxamide (3j).**



$R_f$  0.60 (hexane/EtOAc = 3/1). White Solid. Mp = 95 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.24-1.48 (m, 3H), 1.56-1.69 (m, 2H), 1.74 (dd,  $J$  = 11.2, 3.0 Hz, 1H), 1.83-1.93 (m, 2H), 2.08 (dd,  $J$  = 11.8, 3.5 Hz, 2H), 2.47 (tt,  $J$  = 11.8, 3.5 Hz, 1H), 7.54-7.64 (m, 2H), 8.57 (dd,  $J$  = 8.5, 1.6 Hz, 1H), 8.75 (d,  $J$  = 8.2, 1H), 8.86 (dd,  $J$  = 4.0, 1.6 Hz, 1H), 9.85 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  25.71, 25.73, 29.69, 46.85, 116.36, 122.26, 123.98, 125.91, 127.29, 133.45, 133.89, 139.00, 148.54, 174.90; IR (neat) 3353 w, 3327 w, 2927 m, 2853 w, 1739 s, 1684 m, 1589 w, 1517 s, 1477 s, 1368 s, 1216 m, 953 m, 839 m, 786 m, 682 m; MS  $m/z$  (relative intensity, %) 355 ( $\text{M}^+$ , 22), 207 (12), 205 (36), 180 (32), 179 (12), 178 (100); HRMS Calcd for  $\text{C}_{16}\text{H}_{17}\text{ClN}_2\text{O}_3$ : 288.1029; Found: 288.1028.

### *N*-(5-chloroquinolin-8-yl)butanamide (**1a-d**).



$R_f$  0.29 (hexane/EtOAc = 5/1). Light Yellow Solid. Mp = 57 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  7.51-7.65 (m, 2H), 8.54-8.60 (m, 1H), 8.74 (d,  $J$  = 8.5 Hz, 1H), 8.79-8.89 (m, 1H), 9.77 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  ,116.39, 122.24, 124.03, 125.87, 127.28, 133.50, 133.70, 138.68, 148.43, 171.87; IR (neat) 3356 w, 2981 w, 1737 w, 1686 m, 1589 w, 1517 s, 1478 s, 1378 m, 1319 m, 942 m, 837 w, 787 m, 668 w; MS  $m/z$  (relative intensity, %) 255 ( $\text{M}^+$ , 18), 205 (16), 181 (31), 180 (11), 179 (100); HRMS Calcd for  $\text{C}_{13}\text{H}_6\text{D}_7\text{ClN}_2\text{O}$ : 255.1156; Found: 255.1157.

### 3-4-4. General Procedure for Direct Benzylation

#### General Procedure for Direct Benzylation: Pd-Catalyzed Dehydrogenative Cross Coupling of Amides **1a** with Toluene

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)butyramide (**1a**) (75 mg, 0.3 mmol), heptafluoroisopropyl iodide (178 mg, 0.60 mmol),  $\text{Pd}(\text{OAc})_2$  (6.7 mg, 0.03 mmol), 1-AdCOOH (10.8 mg, 0.06 mmol),  $\text{K}_2\text{CO}_3$  (124 mg, 0.9 mmol) and toluene (1 mL) were added in a glove box. The mixture was stirred for 48 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 2/1) to afford the desired alkylated product **2a** (78 mg, 77%) as a white solid.

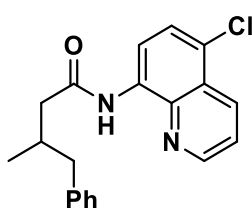
#### General Procedure for Direct Benzylation: Pd-Catalyzed Dehydrogenative Cross Coupling of Amides **1a** with Arenes

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)butyramide (**1a**) (75 mg, 0.3 mmol), heptafluoroisopropyl iodide (178 mg, 0.60 mmol),  $\text{Pd}(\text{OAc})_2$  (6.7 mg, 0.03 mmol), 1-AdCOOH (10.8 mg, 0.06 mmol),  $\text{K}_2\text{CO}_3$  (124 mg, 0.9 mmol), toluene (276 mg, 3.0 mmol) and chlorobenzene (0.7 mL) were

added in a glove box. The mixture was stirred for 48 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 2/1) to afford the desired alkylated product **2a** (61 mg, 60%) as a white solid.

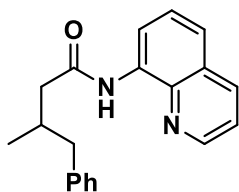
## V. Spectroscopic Data for Products

### *N*-(5-chloroquinolin-8-yl)-3-methyl-4-phenylbutanamide (**2a**).



$R_f$  0.53 (hexane/EtOAc = 2/1). White Solid. Mp = 77 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.05 (d,  $J$  = 6.4 Hz, 3H), 2.36 (q,  $J$  = 7.3 Hz, 1H), 2.42-2.69 (m, 3H), 2.77 (q,  $J$  = 6.4 Hz, 1H), 7.11-7.37 (m, 5H), 7.48-7.67 (m, 2H), 8.56 (dd,  $J$  = 8.4, 1.2 Hz, 1H), 8.73 (d,  $J$  = 8.2 Hz, 1H), 8.84 (dd,  $J$  = 4.4, 1.6 Hz, 1H), 9.73 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.63, 32.64, 43.04, 44.93, 116.29, 122.29, 124.10, 125.87, 126.02, 127.22, 128.26, 129.27, 133.39, 133.68, 138.81, 140.20, 148.55, 171.05; IR (neat) ; 3355 w, 2963 w, 2873 w, 1687 m, 1590 w, 1516 s, 1478 s, 1368 m, 1318 w, 836 w, 786 m, 673 w; MS  $m/z$  (relative intensity, %) 338 ( $\text{M}^+$ , 9), 269 (12), 222 (17), 220 (51), 180 (32), 179 (13), 178 (100), 91 (50); HRMS Calcd for  $\text{C}_{20}\text{H}_{19}\text{ClN}_2\text{O}$ : 338.1186; Found: 338.1184.

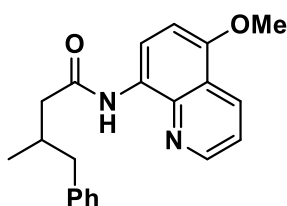
### 3-methyl-4-phenyl-*N*-(quinolin-8-yl)butanamide (**2b**).



$R_f$  0.43 (hexane/EtOAc = 3/1). Yellow Oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.05 (d,  $J$  = 6.4 Hz, 3 H), 2.38 (dd,  $J$  = 13.7, 7.8 Hz, 1H), 2.43-2.69 (m, 3H), 2.78 (dd,  $J$  = 12.8, 6.3 Hz, 1H), 7.11-7.38 (m, 5H), 7.40-7.62

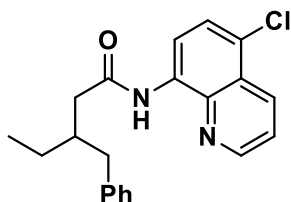
(m, 3H), 8.16 (dd,  $J = 8.2, 1.4$  Hz, 1H), 8.71-8.88 (m, 2H), 9.80 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.58, 32.66, 43.04, 44.98, 116.45, 121.37, 121.55, 125.96, 127.43, 127.90, 128.23, 129.28, 134.40, 136.42, 138.19, 140.28, 148.03, 171.06; IR (neat) 3355 w, 2956 w, 2925 w, 1684 m, 1596 w, 1522 s, 1484 m, 1384 w, 1325 m, 826 w, 792 m, 747 w, 700 m; MS  $m/z$  (relative intensity, %) 304 ( $\text{M}^+$ , 9), 186 (68), 171 (16), 145 (13), 144 (100), 91 (15); HRMS Calcd for  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}$ : 304.1576; Found: 304.1574.

***N*-(5-methoxyquinolin-8-yl)-3-methyl-4-phenylbutanamide (2c).**



$R_f$  0.31 (hexane/EtOAc = 3/1). White Solid. Mp = 66 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.04 (d,  $J = 6.0$  Hz, 3H), 2.34 (dd,  $J = 14.0, 7.2$  Hz, 1H), 2.43-2.66 (m, 3H), 2.78 (dd,  $J = 13.6, 6.0$  Hz, 1H), 3.98 (s, 3H), 6.83 (d,  $J = 8.8$  Hz, 1H), 7.11-7.35 (m, 5H), 7.44 (q,  $J = 4.3$  Hz, 1H), 8.57 (dd,  $J = 8.5, 1.6$  Hz, 1H), 8.71 (d,  $J = 8.7$  Hz, 1H), 8.81 (dd,  $J = 4.0, 1.2$  Hz, 1H), 9.54 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.56, 32.68, 43.05, 44.95, 55.72, 104.28, 116.50, 120.36, 120.66, 125.92, 127.89, 128.21, 129.29, 131.22, 138.98, 140.35, 148.54, 150.11, 170.60; IR (neat) 3362 w, 3011 w, 2958 w, 1734 w, 1672 w, 1596 w, 1525 m, 1493 m; MS  $m/z$  (relative intensity, %) 334 ( $\text{M}^+$ , 30), 216 (70), 201 (12), 175 (14), 174 (100), 159 (77), 91 (16); HRMS Calcd for  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$ : 334.1681; Found: 334.1684.

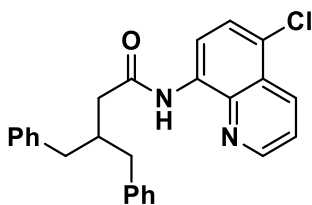
**3-benzyl-*N*-(5-chloroquinolin-8-yl)pentanamide (4a).**



$R_f$  0.46 (hexane/EtOAc = 3/1). Yellow Oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.00 (t,  $J = 7.6$  Hz, 3H), 1.40-1.55 (m, 2H), 2.27-2.42 (m, 1H), 2.48 (d,  $J = 6.9$  Hz, 2H), 2.68 (dd,  $J = 13.6, 7.2$  Hz, 1H), 2.76 (dd,  $J =$

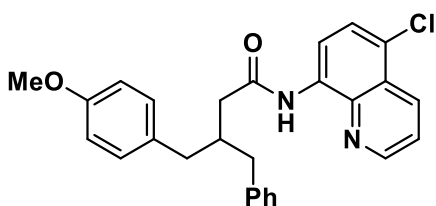
14.0, 6.8 Hz, 1H), 7.10-7.35 (m, 5H), 7.52-7.64 (m, 2H), 8.57 (dd,  $J = 8.7, 1.2$  Hz, 1H), 8.72 (d,  $J = 8.2$  Hz, 1H), 8.85 (dd,  $J = 4.1, 1.2$  Hz, 1H), 9.73 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  11.12, 26.13, 38.77, 39.82, 41.90, 116.29, 122.27, 124.06, 125.87, 125.93, 127.23, 128.25, 129.32, 133.39, 133.70, 138.79, 140.31, 148.52, 171.31; IR (neat) 3356 w, 3026 w, 2960 w, 2926 w, 1686 m, 1590 w, 1517 s, 1478 m, 1318 m, 1144 w, 959 w, 787 m, 742 w, 699 m; MS  $m/z$  (relative intensity, %) 352 ( $\text{M}^+$ , 8), 222 (18), 220 (57), 180 (32), 179 (15), 178 (100), 91 (28); HRMS Calcd for  $\text{C}_{21}\text{H}_{21}\text{ClN}_2\text{O}$ : 352.1342; Found: 352.1345.

**3-benzyl-*N*-(5-chloroquinolin-8-yl)-4-phenylbutanamide (4b).**



$R_f$  0.34 (hexane/EtOAc = 5/1). Yellow Oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.41-2.51 (m, 2H), 2.69-2.81 (m, 5H), 7.09-7.36 (m, 10H), 7.53-7.62 (m, 2H), 8.57 (dd,  $J = 8.8, 1.2$  Hz, 1H), 8.69 (d,  $J = 8.2$  Hz, 1H), 8.84 (dd,  $J = 4.4, 1.2$  Hz, 1H), 9.66 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  39.11, 40.00, 41.18, 116.27, 122.26, 124.06, 125.83, 126.05, 127.19, 128.32, 129.30, 133.37, 133.62, 138.72, 140.03, 148.46, 170.87; IR (neat) 3354 w, 3026 w, 2925 w, 2854 w, 1686 m, 1590 w, 1518 s, 1478 s, 1385 m, 1318 m, 838 w, 788 m, 743 m, 698 s; MS  $m/z$  (relative intensity, %) 414 ( $\text{M}^+$ , 11), 325 (10), 323 (30), 222 (20), 220 (64), 205 (10), 180 (32), 179 (23), 178 (100), 117 (12), 91 (44); HRMS Calcd for  $\text{C}_{26}\text{H}_{23}\text{ClN}_2\text{O}$ : 414.1499; Found: 414.1501.

**3-benzyl-*N*-(5-chloroquinolin-8-yl)-4-(4-methoxyphenyl)butanamide (4c).**

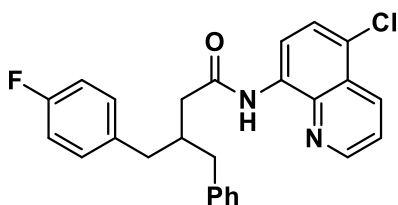


$R_f$  0.40 (hexane/EtOAc = 3/1). Yellow Oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.39-2.51 (m, 2h), 2.61-2.82 (m,



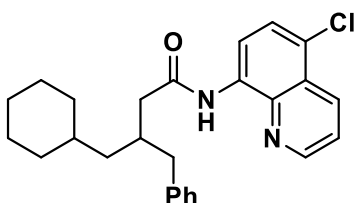
5H), 3.74 (s, 3H), 6.79 (d,  $J = 8.7$  Hz, 2H), 7.14 (d,  $J = 8.7$  Hz, 2H), 7.16-7.35 (m, 5H), 7.51-7.64 (m, 2H), 8.56 (dd,  $J = 8.2, 1.2$  Hz, 1H), 8.68 (d,  $J = 8.7$ , 1H), 8.83 (dd,  $J = 4.0, 1.2$  Hz, 1H), 9.65 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  39.14, 39.29, 40.04, 41.22, 55.13, 113.67, 116.34, 122.25, 124.04, 125.85, 126.02, 127.22, 128.31, 129.30, 130.21, 131.98, 133.45, 133.61, 138.65, 140.10, 148.40, 157.86, 170.99; IR (neat) 3355 w, 2929 w, 2835 w, 1686 m, 1587 w, 1515 s, 1479 m, 1387 w, 1247 m, 1036 w, 965 w, 746 w, 701 w; MS  $m/z$  (relative intensity, %) 444 ( $\text{M}^+$ , 14), 353 (18), 222 (29), 221 (12), 220 (91), 180 (32), 179 (23), 178 (10), 147 (11), 121 (25), 91 (19); HRMS Calcd for  $\text{C}_{27}\text{H}_{25}\text{ClN}_2\text{O}_2$ : 444.1605; Found: 444.1603.

**3-benzyl-N-(5-chloroquinolin-8-yl)-4-(4-fluorophenyl)butanamide (4d).**



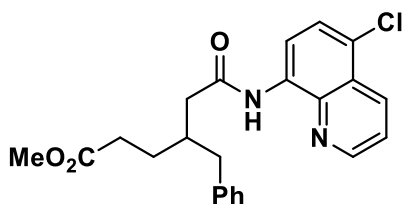
$R_f$  0.51 (hexane/EtOAc = 3/1). Yellow Oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  2.34-2.55 (m, 2H), 2.62-2.79 (m, 5H), 6.89-7.00 (m, 2H), 7.11-7.33 (m, 7H), 7.51-7.61 (m, 2H), 8.55 (dd,  $J = 8.5, 1.6$  Hz, 1H), 8.68 (d,  $J = 8.2$  Hz, 1H), 8.82 (dd,  $J = 4.0, 2.0$  Hz, 1H), 9.64 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  39.18, 39.25, 39.97, 41.06, 115.07 (d,  $J = 21.0$  Hz), 116.26, 122.29, 124.14, 125.85, 126.12, 127.18, 128.36, 129.26, 130.61 (d,  $J = 7.6$  Hz), 133.39, 133.56, 135.66 (d,  $J = 2.9$  Hz), 138.71, 139.88, 148.49, 161.37 (d,  $J = 244.4$  Hz), 170.73; IR (neat) 3353 w, 3027 w, 2925 w, 1739 w, 1685 m, 1600 w, 1518 s, 1478 s, 1368 m, 1219 m, 788 m, 747 m, 700 m; MS  $m/z$  (relative intensity, %) 432 ( $\text{M}^+$ , 4), 222 (17), 220 (51), 180 (33), 179 (19), 178 (100), 109 (20), 91 (20); HRMS Calcd for  $\text{C}_{26}\text{H}_{22}\text{ClFN}_2\text{O}$ : 432.1405; Found: 432.1403.

**3-benzyl-N-(5-chloroquinolin-8-yl)-4-cyclohexylbutanamide (4e).**



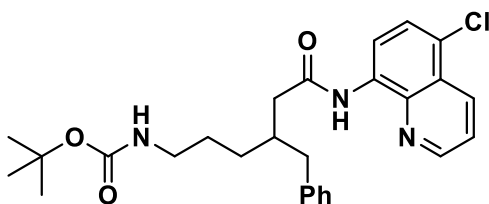
R<sub>f</sub> 0.60 (hexane/EtOAc = 2/1). Yellow Oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 0.70-1.00 (m, 2H), 1.01-1.36 (m, 5H), 1.36-1.52 (m, 1H), 1.52-1.87 (m, 5H), 2.34-2.59 (m, 3H), 2.65 (q, *J* = 6.9 Hz, 1H), 2.76 (dd, *J* = 13.7, 6.0 Hz, 1H), 7.11-7.30 (m, 5H), 7.52-7.63 (m, 2H), 8.49-8.63 (m, 1H), 8.71 (d, *J* = 8.5 Hz, 1H), 8.78-8.92 (m, 1H), 9.69 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 26.34, 26.59, 33.44, 34.14, 34.88, 40.57, 41.82, 42.55, 116.30, 122.27, 124.03, 125.88, 125.91, 127.26, 128.24, 129.37, 133.40, 133.74, 138.822, 140.28, 148.51, 171.26; IR (neat) 3355 w, 3026 w, 2921 w, 2848 w, 1685 m, 1590 w, 1518 s, 1478 m, 1318 m, 965 w, 838 w, 733 m, 699 m; MS *m/z* (relative intensity, %) 420 (M<sup>+</sup>, 7), 222 (7), 221 (26), 220 (80), 180 (32), 179 (18), 178 (100), 91 (21); HRMS Calcd for C<sub>26</sub>H<sub>29</sub>ClN<sub>2</sub>O: 420.1968; Found: 420.1965.

**methyl 4-benzyl-6-((5-chloroquinolin-8-yl)amino)-6-oxohexanoate (4f).**



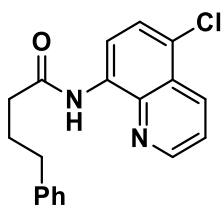
R<sub>f</sub> 0.57 (hexane/EtOAc = 1/1). Yellow Oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 1.80 (dd, *J* = 14.4, 8.0 Hz, 2H), 2.38-2.55 (m, 5H), 2.70 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.76 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.63 (s, 3H), 7.10-7.36 (m, 5H), 7.54-7.62 (m, 2H), 8.56 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.70 (d, *J* = 8.2 Hz, 1H), 8.84 (dd, *J* = 4.4, 1.6 Hz, 1H), 9.70 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 28.86, 31.56, 36.75, 40.11, 41.76, 51.60, 116.34, 122.32, 124.21, 125.87, 126.18, 127.20, 128.40, 129.28, 133.40, 133.60, 138.78, 139.62, 148.57, 170.59, 173.89; IR (neat) 3352 w, 3024 w, 2925 w, 2852 w, 1734 m, 1685 m, 1590 w, 1519 s, 1478 m, 1317 m, 838 w, 749 s, 700 m; MS *m/z* (relative intensity, %) 410 (M<sup>+</sup>, 7), 222 (21), 220 (64), 205 (12), 180 (33), 179 (17), 178 (100), 91 (15); HRMS Calcd for C<sub>23</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub>: 410.1397; Found: 410.1401.

**tert-butyl (4-benzyl-6-((5-chloroquinolin-8-yl)amino)-6-oxohexyl)carbamate (4g).**



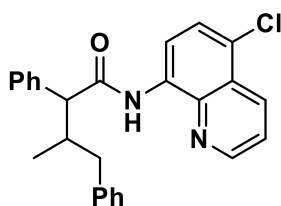
R<sub>f</sub> 0.23 (hexane/EtOAc = 3/1). Yellow Oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 1.37-1.49 (m, 11H), 1.54-1.68 (m, 2H), 2.33-2.59 (m, 3H), 2.67 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.76 (dd, *J* = 13.4, 6.7 Hz, 1H), 3.00-3.18 (m, 2H), 4.65 (brs, 1H), 7.09-7.43 (m, 5H), 7.51-7.63 (m, 2H), 8.57 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.70 (d, *J* = 8.2 Hz, 1H), 8.84 (dd, *J* = 4.0, 2.0 Hz, 1H), 9.71 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 27.13, 28.34, 30.61, 36.76, 40.17, 40.45, 41.98, 78.91, 116.38, 122.28, 124.15, 125.84, 126.06, 127.18, 128.33, 129.24, 133.45, 133.53, 138.66, 139.95, 148.50, 155.91, 170.99; IR (neat) 3353 w, 2974 w, 2930 w, 1689 m, 1590 w, 1520 s, 1479 m, 1388 m, 1169 m, 700 w; MS *m/z* (relative intensity, %) 481 (M<sup>+</sup>, 3), 222 (23), 221 (10), 220 (69), 180 (33), 179 (19), 178 (100), 91 (15); HRMS Calcd for C<sub>27</sub>H<sub>32</sub>ClN<sub>3</sub>O<sub>3</sub>: 481.2132; Found: 481.2136.

***N*-(5-chloroquinolin-8-yl)-4-phenylbutanamide (4h).**



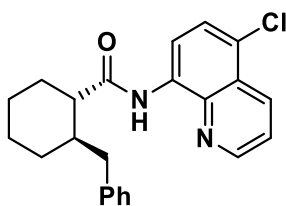
R<sub>f</sub> 0.31 (hexane/EtOAc = 4/1). White Solid. Mp = 76 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 2.15 (quin, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 7.15-7.34 (m, 2H), 7.51 (q, *J* = 4.3 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 8.50 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.70 (d, *J* = 8.2 Hz, 1H), 8.79 (dd, *J* = 4.4, 1.2 Hz, 1H), 9.71 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 26.80, 35.02, 37.08, 116.13, 122.13, 123.92, 125.65, 125.88, 127.05, 128.31, 128.43, 133.16, 133.54, 138.55, 141.27, 148.36, 171.25; IR (neat) 3354 w, 3026 w, 2931 w, 2859 w, 1686 m, 1590 w, 1517 s, 1478 s, 1367 m, 1317 m, 947 w, 837 m, 787 m, 698 m; MS *m/z* (relative intensity, %) 324 (M<sup>+</sup>, 10), 222 (14), 220 (43), 205 (10), 180 (32), 179 (12), 178 (100), 91 (16); HRMS Calcd for C<sub>19</sub>H<sub>17</sub>ClN<sub>2</sub>O: 324.1029; Found: 324.1032.

***N*-(5-chloroquinolin-8-yl)-3-methyl-2,4-diphenylbutanamide (4i).**



$R_f$  0.40 (hexane/EtOAc = 5/1). White Solid. Mp = 117 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  0.69 (d,  $J$  = 6.9 Hz, 3H), 2.42 (dd,  $J$  = 13.1, 9.8 Hz, 1H), 2.69-2.89 (m, 1H), 3.09 (dd,  $J$  = 13.1, 3.4 Hz, 1H), 3.44 (d,  $J$  = 10.1 Hz, 1H), 7.14-7.30 (m, 4H), 7.33 (dd,  $J$  = 14.1, 6.6 Hz, 1H), 7.47-7.60 (m, 4H), 8.54 (dd,  $J$  = 8.5, 1.1 Hz, 1H), 8.75 (d,  $J$  = 8.2 Hz, 1H), 8.84 (dd,  $J$  = 4.4, 1.1 Hz, 1H), 9.93 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  16.68, 38.19, 41.78, 61.57, 116.40, 122.27, 124.24, 125.85, 125.92, 127.13, 127.35, 128.16, 128.46, 128.70, 129.40, 133.35, 133.68, 138.56, 138.91, 140.39, 148.60, 171.83; IR (neat) 3350 w, 3027 w, 2969 w, 2927 w, 1685 m, 1591 w, 1518 s, 1478 s, 1319 w, 940 w, 838 w, 787 w, 699 m; MS  $m/z$  (relative intensity, %) 414 ( $\text{M}^+$ , 4), 298 (16), 296 (47), 207 (19), 205 (60), 180 (31), 179 (12), 178 (100), 91 (40); HRMS Calcd for  $\text{C}_{26}\text{H}_{23}\text{ClN}_2\text{O}$ : 414.1499; Found: 414.1497.

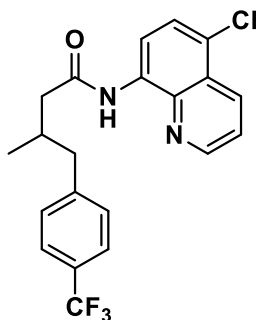
**2-benzyl-*N*-(5-chloroquinolin-8-yl)cyclohexane-1-carboxamide (4j).**



$R_f$  0.40 (hexane/EtOAc = 5/1). Colorless Oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  0.93-1.10 (m, 1H), 1.19-1.39 (m, 3H), 1.63-1.78 (m, 2H), 1.7-1.89 (m, 1H), 1.99-2.15 (m, 2H), 2.26 (td,  $J$  = 12.0, 3.2 Hz, 1H), 2.32 (dd,  $J$  = 13.3, 9.6 Hz, 1H), 2.93 (dd,  $J$  = 13.3, 3.2 Hz, 1H), 7.10-7.30 (m, 5H), 7.55-7.65 (m, 2H), 8.59 (dd,  $J$  = 8.7, 1.4 Hz, 1H), 8.79 (d,  $J$  = 8.8 Hz, 1H), 8.89 (dd,  $J$  = 4.4, 1.6 Hz, 1H), 9.86 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  25.61, 25.73, 30.64, 31.06, 41.12, 41.27, 53.61, 116.51, 122.32, 124.16, 125.76, 125.93, 127.27, 128.02, 129.38, 133.45, 133.75, 138.99, 140.13, 148.60, 174.63; IR (neat) 3357 w, 2925 m, 2854 w, 1734 w, 1686 m, 1590 w, 1519 s, 1479 m, 1318 w, 940 w, 839 w, 699 m; MS  $m/z$  (relative intensity, %) 378

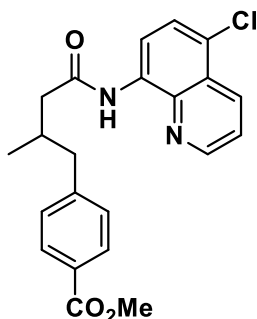
(M<sup>+</sup>, 9), 244 (20), 243 (100), 178 (20), 165 (23), 91 (16); HRMS Calcd for C<sub>23</sub>H<sub>23</sub>ClN<sub>2</sub>O: 378.1499; Found: 378.1495.

***N*-(5-chloroquinolin-8-yl)-3-methyl-4-(4-(trifluoromethyl)phenyl)butanamide (2d).**



R<sub>f</sub> 0.43 (hexane/EtOAc = 5/1). White Solid. Mp = 55 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 1.05 (d, *J* = 6.4 Hz, 3H), 2.35-2.72 (m, 4H), 2.85 (dd, *J* = 13.6, 6.0 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.55-7.64 (m, 2H), 8.58 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.71 (d, *J* = 8.2 Hz, 1H), 8.85 (dd, *J* = 4.1, 1.6 Hz, 1H), 9.73 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 19.63, 32.45, 42.71, 44.79, 116.35, 122.33, 124.28, 124.29 (q, *J* = 271.2 Hz), 125.19 (d, *J* = 3.8 Hz), 125.91, 127.22, 128.41 (q, *J* = 31.7 Hz), 129.54, 133.45, 133.58, 138.81, 144.40, 148.60, 170.63; IR (neat) 3355 w, 2960 m, 1687 m, 1590 w, 1521 s, 1479 m, 1387 w, 1324 s, 1067 m, 839 w, 789 w; MS *m/z* (relative intensity, %) 406 (M<sup>+</sup>, 9), 222 (12), 220 (38), 205 (12), 180 (32), 179 (13), 178 (100), 159 (19); HRMS Calcd for C<sub>21</sub>H<sub>18</sub>ClF<sub>3</sub>N<sub>2</sub>O: 406.1060; Found: 406.1061.

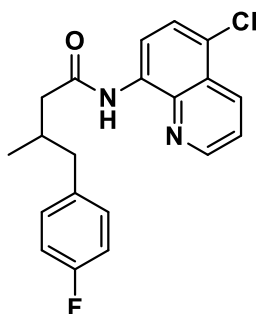
**methyl 4-(4-((5-chloroquinolin-8-yl)amino)-2-methyl-4-oxobutyl)benzoate (2e).**



R<sub>f</sub> 0.14 (hexane/EtOAc = 5/1). Colorless Oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 1.04 (d, *J* = 6.4 Hz, 3H), 2.44 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.49-2.73 (m, 3H), 2.85 (dd, *J* = 13.2, 6.0 Hz, 1H), 3.90 (s, 3H), 7.30 (d, *J* =

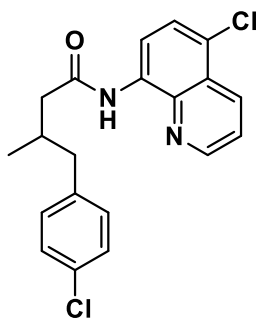
8.2, 2H), 7.57-7.66 (m, 2H), 7.94 (d,  $J = 8.2$  Hz, 1H), 8.63 (dd,  $J = 8.8, 1.2$  Hz, 1H), 8.74 (d,  $J = 8.7$  Hz, 1H), 8.87 (dd,  $J = 4.0, 1.2$  Hz, 1H), 9.81 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.68, 32.48, 42.95, 44.89, 52.00, 116.31, 122.34, 124.23, 125.88, 127.21, 128.01, 129.29, 129.61, 133.43, 133.59, 138.78, 145.80, 148.60, 167.06, 170.73; IR (neat) 3353 w, 3014 w, 2953 w, 1716 m, 1685 m, 1590 w, 1519 s, 1278 s, 1108 m, 838 w, 788 w, 751 s; MS  $m/z$  (relative intensity, %) 396 ( $\text{M}^+$ , 10) 222 (17), 220 (54), 205 (13), 180 (32), 179 (14), 178 (100); HRMS Calcd for  $\text{C}_{22}\text{H}_{21}\text{ClN}_2\text{O}_3$ : 396.1241; Found: 396.1242.

***N*-(5-chloroquinolin-8-yl)-4-(4-fluorophenyl)-3-methylbutanamide (2f).**



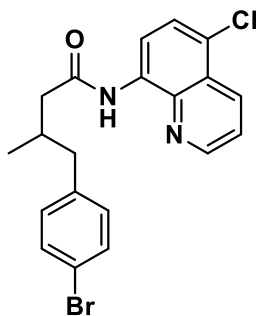
$R_f$  0.34 (hexane/EtOAc = 3/1). White Solid.  $\text{Mp} = 89$  °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.03 (d,  $J = 6.4$  Hz, 3H), 2.37 (dd,  $J = 13.6, 7.2$  Hz, 1H), 2.41-2.61 (m, 3H), 2.75 (dd,  $J = 13.2, 6.0$  Hz, 2H), 6.86-7.06 (m, 2H), 7.08-7.24 (m, 2H), 8.56 (dd,  $J = 8.5, 1.6$  Hz, 1H), 8.72 (d,  $J = 8.8$  Hz, 1H), 8.84 (dd,  $J = 4.0, 1.6$  Hz, 1H), 9.72 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.55, 32.70, 42.12, 44.80, 115.00 (d,  $J = 21.1$  Hz), 116.31, 122.30, 124.18, 125.88, 127.21, 130.56 (d,  $J = 7.6$  Hz), 133.40, 133.65, 135.82 (d,  $J = 2.9$  Hz), 138.81, 148.56, 161.39 (d,  $J = 243.4$  Hz), 170.89; IR (neat) 3355 w, 2958 w, 1685 m, 1518 s, 1478 s, 1385 m, 1318 m, 838 m, 815 m, 788 m; MS  $m/z$  (relative intensity, %) 356 ( $\text{M}^+$ , 7), 222 (17), 220 (50), 180 (32), 179 (14), 178 (100), 109 (22); HRMS Calcd for  $\text{C}_{20}\text{H}_{18}\text{ClFN}_2\text{O}$ : 356.1092; Found: 356.1094.

**4-(4-chlorophenyl)-N-(5-chloroquinolin-8-yl)-3-methylbutanamide (2g).**



$R_f$  0.47 (hexane/EtOAc = 2/1). Colorless Oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.03 (d,  $J$  = 6.4 Hz, 3H), 2.38 (dd,  $J$  = 14.0, 6.8 Hz, 1H), 2.42-2.60 (m, 3H), 2.75 (dd,  $J$  = 13.6, 6.0 Hz, 1H), 7.15 (d,  $J$  = 8.2 Hz, 2H), 7.24 (d,  $J$  = 8.2 Hz, 2H), 7.53-7.65 (m, 2H), 8.58 (d,  $J$  = 8.2 Hz, 1H), 8.72 (d,  $J$  = 8.2 Hz, 1H), 8.85 (d,  $J$  = 4.1 Hz, 1H), 9.72 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.59, 32.58, 42.28, 44.80, 116.33, 122.33, 124.23, 125.91, 127.24, 128.37, 130.58, 131.79, 133.45, 133.63, 138.67, 138.82, 148.59, 170.81; IR (neat) 3352 w, 2958 w, 2926 w, 1685 m, 1591 w, 1517 s, 1478 s, 1318 m, 836 m, 787 m; 736 m; MS  $m/z$  (relative intensity, %) 372 (8), 222 (21), 220 (66), 180 (36), 179 (15), 178 (100), 125 (19); HRMS Calcd for  $\text{C}_{20}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}$ : 372.0796; Found: 372.0795.

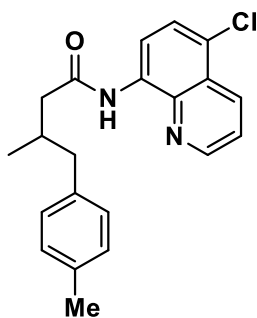
**4-(4-bromophenyl)-N-(5-chloroquinolin-8-yl)-3-methylbutanamide (2h).**



$R_f$  0.30 (hexane/EtOAc = 5/1). Colorless Oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.03 (d,  $J$  = 6.4 Hz, 3H), 2.38 (dd,  $J$  = 13.6, 7.2 Hz, 1H), 2.42-2.60 (m, 3H), 2.73 (dd,  $J$  = 13.3, 5.5 Hz, 1H), 7.10 (d,  $J$  = 8.2 Hz, 2H), 7.39 (d,  $J$  = 8.2 Hz, 2H), 7.50-7.68 (m, 2H), 8.58 (d,  $J$  = 8.7 Hz, 1H), 8.71 (d,  $J$  = 8.2 Hz, 1H), 8.85 (d,  $J$  = 4.1 Hz, 1H), 9.72 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.61, 32.52, 42.33, 44.80, 116.34, 119.84, 122.33, 124.23, 125.91, 127.24, 131.00, 131.32, 133.45, 133.61, 138.81, 139.19, 148.60, 170.81; IR (neat)

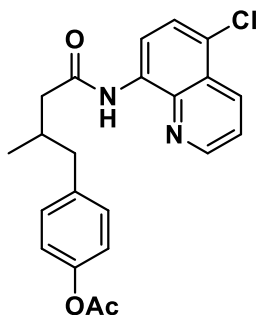
3353 w, 2958 w, 2926 w, 1684 m, 1590 w, 1518 s, 1478 s, 1319 m, 836 m, 787 m, 735 s, 701 m; MS  $m/z$  (relative intensity, %) 416 ( $M^+$ , 4), 222 (21), 220 (65), 180 (32), 179 (13), 178 (100); HRMS Calcd for  $C_{20}H_{18}BrClN_2O$ : 416.0291; Found: 416.0286.

***N*-(5-chloroquinolin-8-yl)-3-methyl-4-(*p*-tolyl)butanamide (2i).**



$R_f$  0.22 (hexane/EtOAc = 5/1). Colorless Oil.  $^1H$  NMR ( $CDCl_3$ , 399.78 MHz)  $\delta$  1.04 (d,  $J$  = 6.4 Hz, 2H), 2.30 (s, 3H), 2.40-2.65 (m, 3H), 2.72 (dd,  $J$  = 13.2, 6.4 Hz, 1H), 7.05-7.15 (m, 4H), 7.49-7.67 (m, 2H), 8.56 (dd,  $J$  = 8.7, 1.4 Hz, 1H), 8.73 (d,  $J$  = 8.7 Hz, 1H), 8.84 (dd,  $J$  = 4.4, 1.6 Hz, 1H), 9.72 (brs, 1H);  $^{13}C$  NMR ( $CDCl_3$ , 100.53 MHz)  $\delta$  19.67, 20.98, 32.67, 42.63, 44.95, 116.29, 122.28, 124.08, 125.87, 127.23, 128.94, 129.15, 133.39, 133.72, 135.47, 137.06, 138.82, 148.54, 171.14; IR (neat) 3356 w, 2956 w, 2923 w, 1685 m, 1590 w, 1516 s, 1478 m, 1318 m, 969 w, 837 w, 788 m, 736 w; MS  $m/z$  (relative intensity, %) 352 ( $M^+$ , 10), 222 (21), 220 (64), 180 (31), 179 (13), 178 (100), 105 (20); HRMS Calcd for  $C_{21}H_{21}ClN_2O$ : 352.1342; Found: 352.1340.

**4-(4-((5-chloroquinolin-8-yl)amino)-2-methyl-4-oxobutyl)phenyl acetate (2j).**

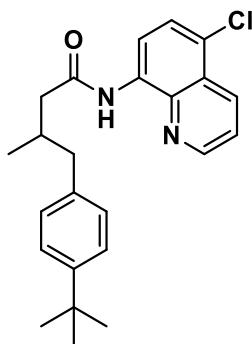


$R_f$  0.31 (hexane/EtOAc = 2/1). Yellow Oil.  $^1H$  NMR ( $CDCl_3$ , 399.78 MHz)  $\delta$  1.05 (d,  $J$  = 6.4 Hz, 3H), 2.29



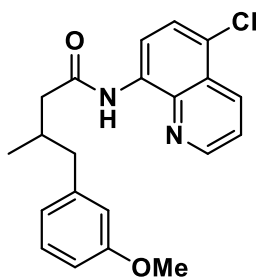
(s, 3H), 2.38 (dd,  $J = 14.4, 8.0$  Hz, 1H), 2.42-2.64 (m, 3H), 2.77 (dd,  $J = 13.2, 6.0$  Hz, 1H), 7.00 (d,  $J = 8.2$  Hz, 2H), 7.23 (d,  $J = 8.2$  Hz, 2H), 7.52-7.64 (m, 2H), 8.58 (dd,  $J = 8.2, 1.6$  Hz, 1H), 8.73 (d,  $J = 8.2$  Hz, 1H), 8.86 (dd,  $J = 4.1, 1.6$  Hz, 1H), 9.74 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.58, 21.15, 32.59, 42.32, 44.83, 116.32, 121.27, 122.31, 124.16, 125.88, 127.22, 130.16, 133.40, 133.66, 137.77, 138.82, 148.59, 148.92, 169.61, 170.94; IR (neat) 3355 w, 2958 w, 2925 w, 1756 m, 1685 m, 1590 w, 1518 s, 1478 s, 1367 m, 1192 s, 912 m, 838 w, 789 m; MS  $m/z$  (relative intensity, %) 396 ( $\text{M}^+$ , 7), 222 (21), 220 (66), 205 (10), 180 (32), 179 (16), 178 (100), 107 (12); HRMS Calcd for  $\text{C}_{22}\text{H}_{21}\text{ClN}_2\text{O}_3$ : 396.1241; Found: 396.1243.

**4-(4-(tert-butyl)phenyl)-N-(5-chloroquinolin-8-yl)-3-methylbutanamide (2k).**



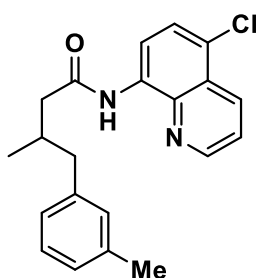
$R_f$  0.39 (hexane/EtOAc = 5/1). Colorless Oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.06 (d,  $J = 6.9$  Hz, 3H), 1.29 (s, 9H), 2.35 (dd,  $J = 14.2, 8.2$  Hz, 1H), 2.43-2.65 (m, 3H), 2.70 (dd,  $J = 13.2, 6.8$  Hz, 1H), 7.15 (d,  $J = 8.2$  Hz, 2H), 7.29 (d,  $J = 8.2$  Hz, 2H), 7.55-7.61 (m, 2H), 8.57 (dd,  $J = 8.5, 1.6$  Hz, 1H), 8.72 (d,  $J = 8.2$  Hz, 1H), 8.85 (dd,  $J = 4.0, 1.6$  Hz, 1H), 9.72 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.84, 31.36, 32.62, 34.32, 42.61, 44.98, 116.28, 122.29, 124.07, 125.13, 125.88, 127.25, 128.91, 133.40, 133.72, 137.06, 138.82, 148.55, 148.77, 171.19; IR (neat) 3357 w, 2960 w, 2869 w, 1686 m, 1590 w, 1518 s, 1478 m, 1385 m, 1319 w, 837 w, 787 m, 753 s, 667 w; MS  $m/z$  (relative intensity, %) 394 ( $\text{M}^+$ , 11), 222 (28), 221 (11), 220 (88), 180 (32), 179 (14), 178 (100); HRMS Calcd for  $\text{C}_{24}\text{H}_{27}\text{ClN}_2\text{O}$ : 394.1812; Found: 394.1815.

***N*-(5-chloroquinolin-8-yl)-4-(3-methoxyphenyl)-3-methylbutanamide (2l).**



$R_f$  0.26 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 72 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.05 (d,  $J$  = 6.4 Hz, 3H), 2.36 (dd,  $J$  = 14.4, 8.0 Hz, 1H), 2.43-2.66 (m, 3H), 2.74 (dd,  $J$  = 13.6, 6.0 Hz, 1H), 3.78, (s, 3H), 6.66-6.90 (m, 3H), 7.20 (t,  $J$  = 7.8 Hz, 1H), 7.49-7.67 (m, 2H), 8.56 (dd,  $J$  = 8.2, 1.4 Hz, 1H), 8.73 (d,  $J$  = 8.2 Hz, 1H), 8.85 (dd,  $J$  = 4.0, 1.2 Hz, 1H), 9.73 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.70, 32.56, 43.10, 44.94, 55.09, 111.30, 114.91, 116.28, 121.69, 122.28, 124.10, 125.87, 127.21, 129.19, 133.38, 133.68, 138.80, 141.83, 148.56, 159.51, 171.05; IR (neat) 3356 w, 2956 w, 1812 w, 1686 m, 1587 w, 1520 s, 1479 m, 838 w, 787 w, 696 w; MS  $m/z$  (relative intensity, %) 368 ( $\text{M}^+$ , 11), 222 (21), 220 (66), 180 (33), 179 (13), 178 (100), 121 (14); HRMS Calcd for  $\text{C}_{21}\text{H}_{21}\text{ClN}_2\text{O}_2$ : 368.1292; Found: 368.1294.

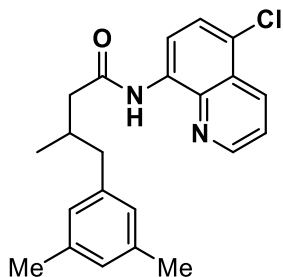
***N*-(5-chloroquinolin-8-yl)-3-methyl-4-(*m*-tolyl)butanamide (2m).**



$R_f$  0.37 (hexane/EtOAc = 5/1). White Solid. Mp = 110 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 399.78 MHz)  $\delta$  1.05 (d,  $J$  = 6.4 Hz, 3H), 2.32 (s, 3H), 2.36 (dd,  $J$  = 14.0, 7.6 Hz, 1H), 2.41-2.64 (m, 3H), 2.72 (dd,  $J$  = 13.2, 6.4 Hz, 1H), 6.97-7.07 (m, 3H), 7.17 (t,  $J$  = 7.3 Hz, 1H), 7.49-7.67 (m, 2H), 8.56 (dd,  $J$  = 8.5, 1.6 Hz, 1H), 8.73 (d,  $J$  = 8.2 Hz, 1H), 8.84 (dd,  $J$  = 4.0, 1.8 Hz, 1H), 9.73 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  19.71, 21.40, 32.64, 42.99, 44.97, 116.30, 122.29, 124.10, 125.88, 126.31, 126.75, 127.24, 128.12, 130.03, 133.41, 133.71, 137.80, 138.83, 140.13, 148.56, 171.14; IR (neat) 3356w, 2956 w, 2923 w, 1687 m, 1590 w, 1519 s, 1478 m, 1456 w, 1319 w, 838 w, 786 w, 697 w; MS  $m/z$  (relative intensity, %) 352 ( $\text{M}^+$ , 9), 222 (19), 220 (59), 180

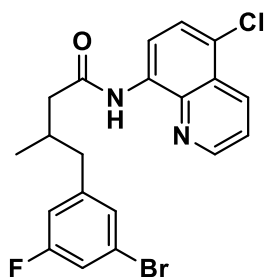
(32), 179 (13), 178 (100), 105 (16); HRMS Calcd for C<sub>21</sub>H<sub>21</sub>ClN<sub>2</sub>O: 352.1342; Found: 352.1345.

***N*-(5-chloroquinolin-8-yl)-4-(3,5-dimethylphenyl)-3-methylbutanamide (2n).**



R<sub>f</sub> 0.43 (hexane/EtOAc = 5/1). White Solid. Mp = 91 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 1.05 (d, *J* = 6.4 Hz, 3H), 2.27 (s, 2H), 2.35 (dd, *J* = 14.4, 8.0 Hz, 1H), 2.42-2.62 (m, 2H), 2.67 (dd, *J* = 12.4, 6.0 Hz, 1H), 6.80-6.86 (m, 3H), 7.51-7.63 (m, 2H), 8.57 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.74 (d, *J* = 8.2 Hz, 1H), 8.85 (dd, *J* = 4.1, 1.6 Hz, 1H), 9.72 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 19.79, 21.26, 32.62, 42.94, 45.02, 116.31, 122.28, 124.08, 125.89, 127.10, 127.25, 127.63, 133.41, 133.75, 137.67, 138.85, 140.10, 148.55, 171.21; IR (neat) 3356 w, 2955 w, 2918 w, 1686 m, 1517 s, 1478 s, 1385 m, 1318 m, 969 w, 836 m, 787 m, 736 w, 700 w; MS *m/z* (relative intensity, %) 366 (M<sup>+</sup>, 11), 220 (67), 180 (32), 179 (13), 178 (100), 119 (16); HRMS Calcd for C<sub>22</sub>H<sub>23</sub>ClN<sub>2</sub>O: 366.1499; Found: 366.1497.

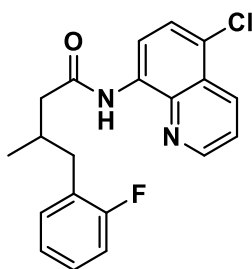
**4-(3-bromo-5-fluorophenyl)-*N*-(5-chloroquinolin-8-yl)-3-methylbutanamide (2o).**



R<sub>f</sub> 0.33 (hexane/EtOAc = 3/1). Yellow Oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 399.78 MHz) δ 1.05 (d, *J* = 5.5 Hz, 3H), 2.35-2.64 (m, 4H), 2.78 (dd, *J* = 12.4, 4.8 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 7.18 (s, 1H), 7.49-7.69 (m, 2H), 8.59 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.73 (d, *J* = 8.8 Hz, 1H), 8.88 (dd, *J* = 4.4, 1.6 Hz, 1H), 9.77 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.53 MHz) δ 19.58, 32.43, 42.38, 44.70, 115.11 (d, *J* = 20.2 Hz), 116.38, 116.83 (d, *J* = 24.9 Hz), 122.27 (d, *J* = 6.7 Hz), 122.36, 124.31, 125.91, 127.23, 128.11 (d, *J* = 2.8

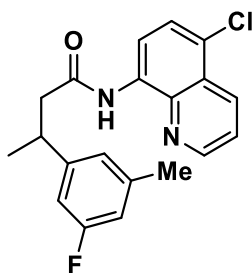
Hz), 133.47, 133.54, 138.80, 144.44 (d,  $J = 7.6$  Hz), 148.65, 162.55 (d,  $J = 250.1$  Hz), 170.47; IR (neat) 3353 w, 2925 w, 1686 m, 1580 s, 1522 s, 1480 m, 789 w, 669w; MS  $m/z$  (relative intensity, %) 434 ( $M^+$ , 4), 222 (13), 220 (39), 205 (11), 180 (32), 179 (13), 178 (100); HRMS Calcd for  $C_{20}H_{17}BrClFN_2O$ : 434.0197; Found: 434.0199.

***N*-(5-chloroquinolin-8-yl)-4-(2-fluorophenyl)-3-methylbutanamide (2p).**



$R_f$  0.43 (hexane/EtOAc = 3/1). Yellow Oil.  $^1H$  NMR ( $CDCl_3$ , 399.78 MHz)  $\delta$  1.06 (d,  $J = 6.4$  Hz, 3H), 2.41 (dd,  $J = 14.0, 8.0$  Hz, 1H), 2.46-2.73 (m, 3H), 2.78 (dd,  $J = 13.2, 6.4$  Hz, 1H), 6.95-7.29 (m, 4H), 8.60 (dd,  $J = 8.0, 1.6$  Hz, 1H), 8.73 (d,  $J = 8.2$  Hz, 1H), 8.86 (dd,  $J = 4.0, 1.2$  Hz, 1H), 9.79 (brs, 1H);  $^{13}C$  NMR ( $CDCl_3$ , 100.53 MHz)  $\delta$  19.61, 31.86, 35.74, 44.88, 115.22 (d,  $J = 23.0$  Hz), 116.71, 122.27, 123.88 (d,  $J = 3.9$  Hz), 124.21, 125.95, 127.07 (d,  $J = 16.3$  Hz), 127.38, 127.81 (d,  $J = 8.6$  Hz), 131.57 (d,  $J = 5.7$  Hz), 133.56, 133.82, 138.51, 148.36, 161.29 (d,  $J = 244.4$  Hz), 171.00; IR (neat) 3355 w, 2927 w, 1686 m, 1521 s, 1480 m, 1319 w, 788 w, 757 w; MS  $m/z$  (relative intensity, %) 356 ( $M^+$ , 10), 222 (13), 222 (37), 180 (31), 179 (13), 178 (100), 109 (22); HRMS Calcd for  $C_{20}H_{18}ClFN_2O$ : 356.1092; Found: 356.1090.

***N*-(5-chloroquinolin-8-yl)-3-(3-fluoro-5-methylphenyl)butanamide (5).**



$R_f$  0.43 (hexane/EtOAc = 3/1). Colorless Oil.  $^1H$  NMR ( $CDCl_3$ , 399.78 MHz)  $\delta$  1.38 (d,  $J = 7.3$  Hz, 3H), 2.29 (s, 3H), 2.74 (dd,  $J = 14.4, 8.0$  Hz, 1H), 2.85 (dd,  $J = 14.4, 7.2$  Hz, 1H), 3.43 (tq,  $J = 14.0, 7.0$  Hz, 1H),

6.69 (d,  $J = 9.6$  Hz, 1H), 6.83 (d,  $J = 10.1$  Hz, 1H), 6.9 (s, 1H), 7.47-7.65 (m, 2H), 8.55 (dd,  $J = 8.4, 1.6$  Hz, 1H), 8.69 (d,  $J = 8.2$  Hz, 1H), 8.80 (dd,  $J = 4.4, 1.6$  Hz, 1H), 9.65 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.53 MHz)  $\delta$  21.32, 21.76, 36.58, 46.52, 110.54 (d,  $J = 21.1$  Hz), 113.88 (d,  $J = 20.2$  Hz), 116.28, 122.23, 123.38 (d,  $J = 1.5$  Hz), 124.15, 125.74, 127.10, 133.28, 133.47, 138.65, 140.38 (d,  $J = 8.6$  Hz), 147.96 (d,  $J = 7.6$  Hz), 148.43, 162.95 (d,  $J = 244.4$  Hz), 169.99; IR (neat) 3354 w, 2925 w, 1688 m, 1591 w, 1522 s, 1480 m, 1387 w, 841 w, 789 w; MS  $m/z$  (relative intensity, %) 356 ( $\text{M}^+$ , 2), 222 (13), 220 (39), 205 (11), 180 (32), 179 (13), 178 (100); HRMS Calcd for  $\text{C}_{20}\text{H}_{18}\text{ClFN}_2\text{O}$ : 356.1092; Found: 356.1094.

### 3-4-5. Deuterium Labeling Experiments (Scheme 3-7, 8, 9, 10)

**Scheme 3-7;** To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)butyramide (**1a**) (75 mg, 0.3 mmol) / *N*-(5-chloroquinolin-8-yl)butyramide (**1a-d**) (77 mg, 0.3 mmol), heptafluoroisopropyl iodide (178 mg, 0.60 mmol),  $\text{Pd}(\text{OAc})_2$  (6.7 mg, 0.03 mmol), 1-AdCOOH (10.8 mg, 0.06 mmol),  $\text{K}_2\text{CO}_3$  (124 mg, 0.9 mmol) and toluene (1.0 mL) were added in a glove box. The mixture was stirred for 3 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The ratio of deuterium was determined by  $^1\text{H}$ -NMR.

**Scheme 3-8;** To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)butyramide (**1a-d**) (77 mg, 0.3 mmol), heptafluoroisopropyl iodide (178 mg, 0.60 mmol),  $\text{Pd}(\text{OAc})_2$  (6.7 mg, 0.03 mmol), 1-AdCOOH (10.8 mg, 0.06 mmol),  $\text{K}_2\text{CO}_3$  (124 mg, 0.9 mmol) and toluene (1 mL) were added in a glove box. The mixture was stirred for 2 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The ratio of deuterium was determined by  $^1\text{H}$ -NMR.

**Scheme 3-9;** To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)butyramide (**1a**) (75 mg, 0.3 mmol), heptafluoroisopropyl iodide (178 mg, 0.60 mmol),  $\text{Pd}(\text{OAc})_2$  (6.7 mg, 0.03 mmol), 1-AdCOOH (10.8 mg, 0.06 mmol),  $\text{K}_2\text{CO}_3$  (124 mg, 0.9 mmol) and toluene (0.5 mL) / toluene- $d_8$  (0.5 mL) were added

in a glove box. The mixture was stirred for 3 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The ratio of deuterium was determined by <sup>1</sup>H-NMR.

**Scheme 3-10;** To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)butyramide (**1a**) (75 mg, 0.3 mmol), heptafluoroisopropyl iodide (178 mg, 0.60 mmol), Pd(OAc)<sub>2</sub> (6.7 mg, 0.03 mmol), 1-AdCOOH (10.8 mg, 0.06 mmol), K<sub>2</sub>CO<sub>3</sub> (124 mg, 0.9 mmol) and toluene-*d*<sub>8</sub> (1 mL) were added in a glove box. The mixture was stirred for 48 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The ratio of deuterium was determined by <sup>1</sup>H-NMR.

#### **3-4-6. Observation of <sup>i</sup>C<sub>3</sub>F<sub>7</sub>H**

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)butyramide (**1a**) (75 mg, 0.3 mmol), heptafluoroisopropyl iodide (178 mg, 0.60 mmol), Pd(OAc)<sub>2</sub> (6.7 mg, 0.03 mmol), 1-AdCOOH (10.8 mg, 0.06 mmol), K<sub>2</sub>CO<sub>3</sub> (124 mg, 0.9 mmol) and toluene (1 mL) were added in a glove box. The mixture was stirred for 3 h at 140 °C. The resulting mixture was cooled at -78 °C, and transferred to sealed NMR tube. The formation of C<sub>3</sub>F<sub>7</sub>H was determined by <sup>19</sup>F-NMR.

### 3-5. References

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## Chapter 4

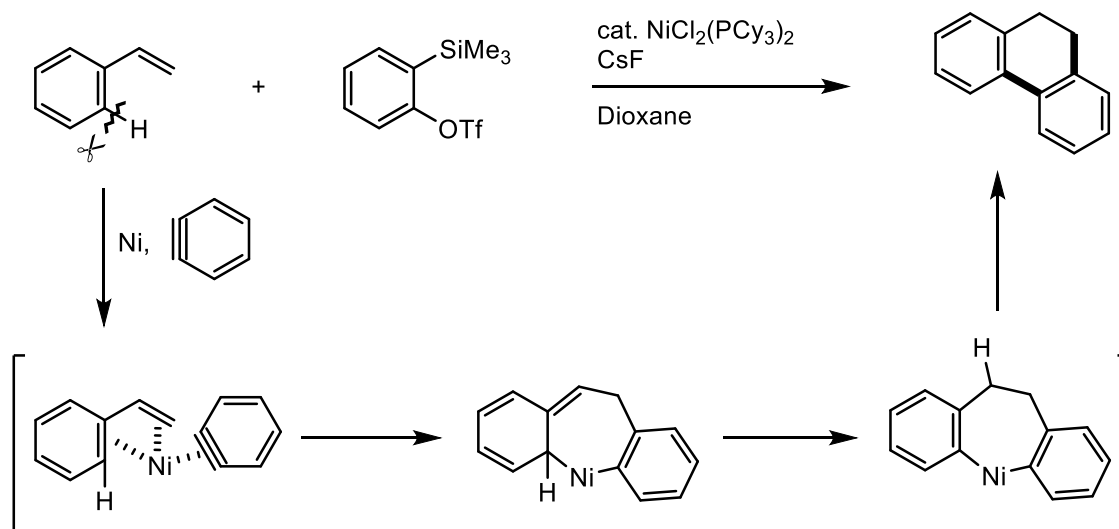
### Nickel-Catalyzed [4 + 2] Cycloaddition of Styrenes with Arynes via 1:1

### Cross-Coupling: Synthesis of 9,10-Dihydrophenanthrenes

#### Abstract

The [4 + 2] cycloaddition of styrenes with aryne was achieved via 1:1 cross-coupling by a nickel catalyst. This protocol applies to a variety of styrenes and aryne generated in situ from *o*-(trimethylsilyl)aryl triflates to afford 9,10-dihydrophenanthrenes involving substituted aromatic rings. By using this method, a naturally occurring stilbenoid is easily synthesized.

Scheme 4-1.



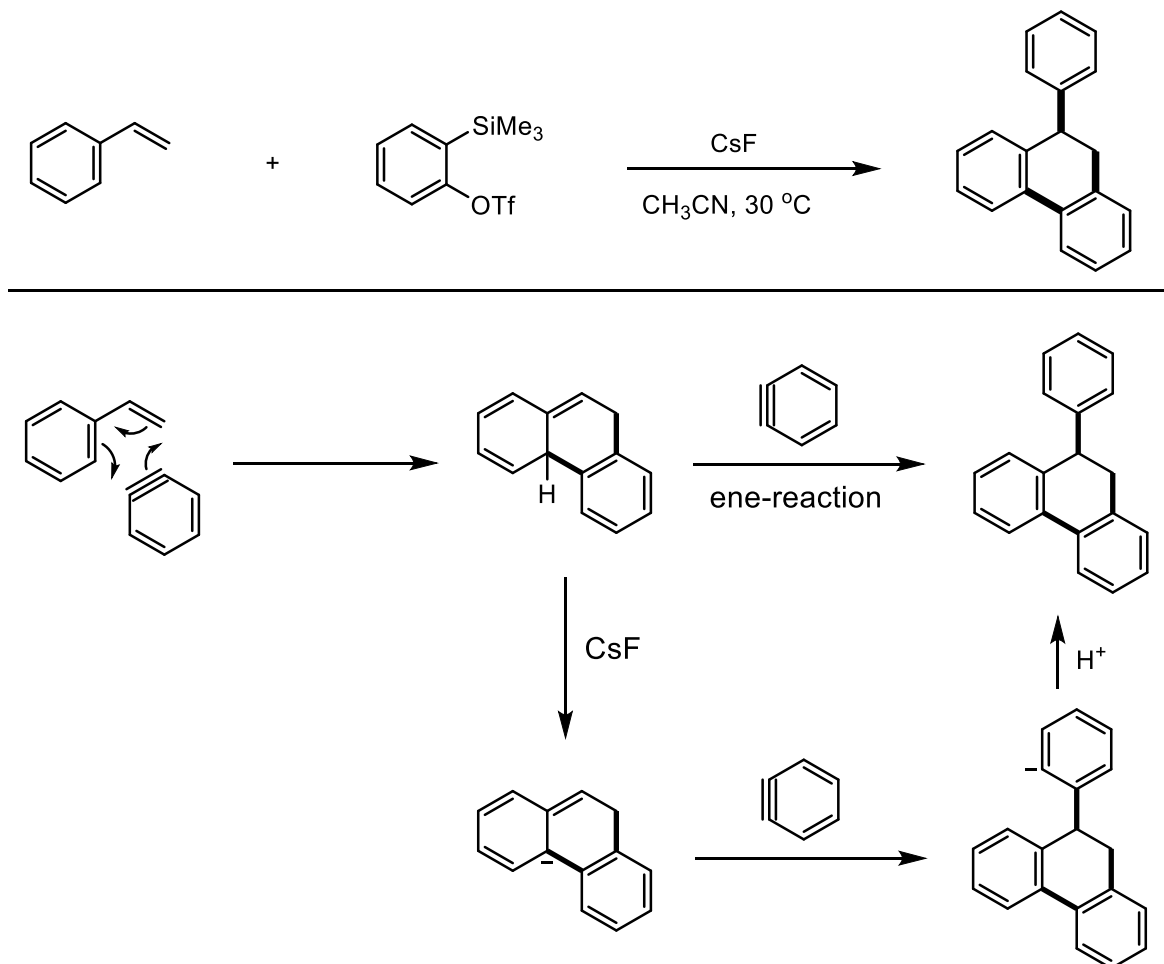
#### 4-1. Introduction

Arynes are attractive intermediates in synthetic organic chemistry.<sup>[1]</sup> The strength of their application to organic synthesis is providing efficient routes for diverse and complex molecules, because their reactions enable forming two adjacent bonds in a one-pot operation, creating benzene-fused structures. Since Kobayashi and Sonoda developed a mild and convenient method for aryne generation using fluoride-induced 1,2-elimination of 2(trimethylsilyl)aryl triflates,<sup>[2]</sup> aryne chemistry has drastically evolved. However, the high reactivities of aryne often cause introduction of multiple aryne.<sup>[3]-[4]</sup> Recently, Biju and co-workers reported synthesis of 9-aryl-9,10-dihydrophenanthrenes via Diels–Alder [4 + 2] cycloaddition of styrenes



with arynes, inevitably accompanied by a concerted ene reaction with a second molecule of aryne or a stepwise nucleophilic addition–protonation sequence (Scheme 4-2).<sup>[4b]</sup> In this reaction, only styrenes bearing an electron-withdrawing group (e.g., cyano, trifluoromethyl, and ester) at the 4-position provide the 1:1 cycloadducts, 9,10-dihydrophenanthrenes bearing no substituent at the 9 and 10-positions.<sup>[5], [6]</sup>

Scheme 4-2.



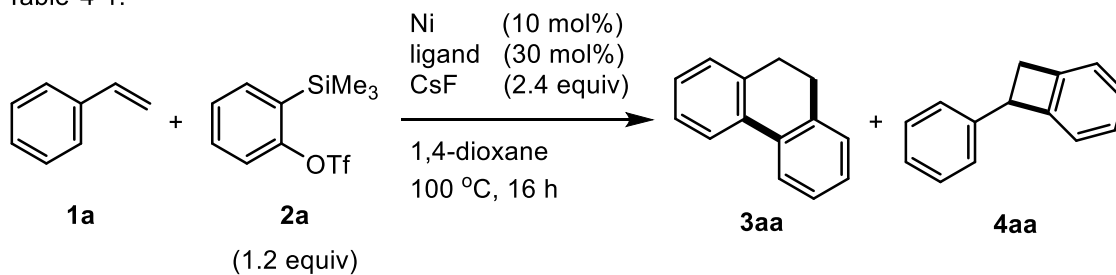
To suppress multiple reactions, I assumed that transition metal catalysts can control the reactivity of arynes. When transition metal complexes are present, metal-mediated oxidative cyclization of styrenes with arynes proceeds as the initial step (Scheme 4-1) instead of the Diels–Alder [4 + 2] cycloaddition.<sup>[4], [5], [6]</sup> Subsequent 1,3-hydrogen shift followed by reductive elimination may afford 1:1 cycloadducts selectively. Based on this working hypothesis, we achieved an efficient nickel-catalyzed formal [4 + 2] cycloaddition of styrenes with arynes,<sup>[7]</sup> enabling the synthesis of 9,10-dihydrophenanthrenes involving unsubstituted 9- and 10-positions. The reactivity of arynes was adequately controlled using nickel, facilitating the one-to-one coupling of styrenes with arynes.

## 4-2. Nickel-Catalyzed [4 + 2] Cycloaddition of Styrenes with Arynes

### 4-2-1. Optimization of Reaction Conditions for Ni-Catalyzed [4 + 2] Cycloaddition

First, I investigated suitable conditions for nickelcatalyzed [4 + 2] cycloaddition using styrene (**1a**) and benzyne precursor **2a** as model compounds in 1,4-dioxane (Table 4-1). When **1a** was treated with **2a** and CsF as a fluoride source for generating benzyne without any metal catalysts, the [4 + 2] cycloadduct, 9,10-dihydrophenanthrene **3aa** was obtained in only 3% yield (Entry 1). Under these conditions, the addition of a catalytic amount of NiCl<sub>2</sub> afforded **3aa** in 34% yield along with the [2 + 2] cycloadduct **4aa**, whereas the 1:2 adduct, 9-phenyl-9,10-dihydrophenanthrene was completely absent (Entry 2). To improve the yield of **3aa**, ligands used for NiCl<sub>2</sub> were screened (Entries 3–7). Among the ligands examined, PCy<sub>3</sub> dramatically increased the yield of **3aa** (Entry 6). Due to screening of Ni sources, NiCl<sub>2</sub> was revealed as most efficient and selective (Entries 6, 8–12). Employing NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>, instead of NiCl<sub>2</sub> and PCy<sub>3</sub> separately, improved the yield of **3aa** up to 65% (Entry 13). Finally, increasing the amount of **2a** (1.5 equiv) afforded **3aa** in 76% yield (Entry 14).

Table 4-1.



entry	Ni	ligand	<b>3aa</b> (%)	<b>4aa</b> (%)
1	-	-	3	N.D. <sup>[a]</sup>
2	NiCl <sub>2</sub>	-	34	3
3	NiCl <sub>2</sub>	PPh <sub>3</sub>	N.D. <sup>[a]</sup>	N.D. <sup>[a]</sup>
4	NiCl <sub>2</sub>	PMe <sub>3</sub>	46	7
5	NiCl <sub>2</sub>	P( <sup>t</sup> Bu) <sub>3</sub>	47	7
6	NiCl <sub>2</sub>	PCy <sub>3</sub>	59	10
7 <sup>[b]</sup>	NiCl <sub>2</sub>	IPr·HCl	52	9
8	NiF <sub>2</sub>	PCy <sub>3</sub>	47	8
9	NiBr <sub>2</sub>	PCy <sub>3</sub>	55	9
10	NiCl <sub>2</sub>	PCy <sub>3</sub>	47	7
11	Ni(OAc) <sub>2</sub>	PCy <sub>3</sub>	17	3
12	Ni(cod) <sub>2</sub>	PCy <sub>3</sub>	56	15
13	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	65	5
14 <sup>[c]</sup>	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	-	76 (67)	10

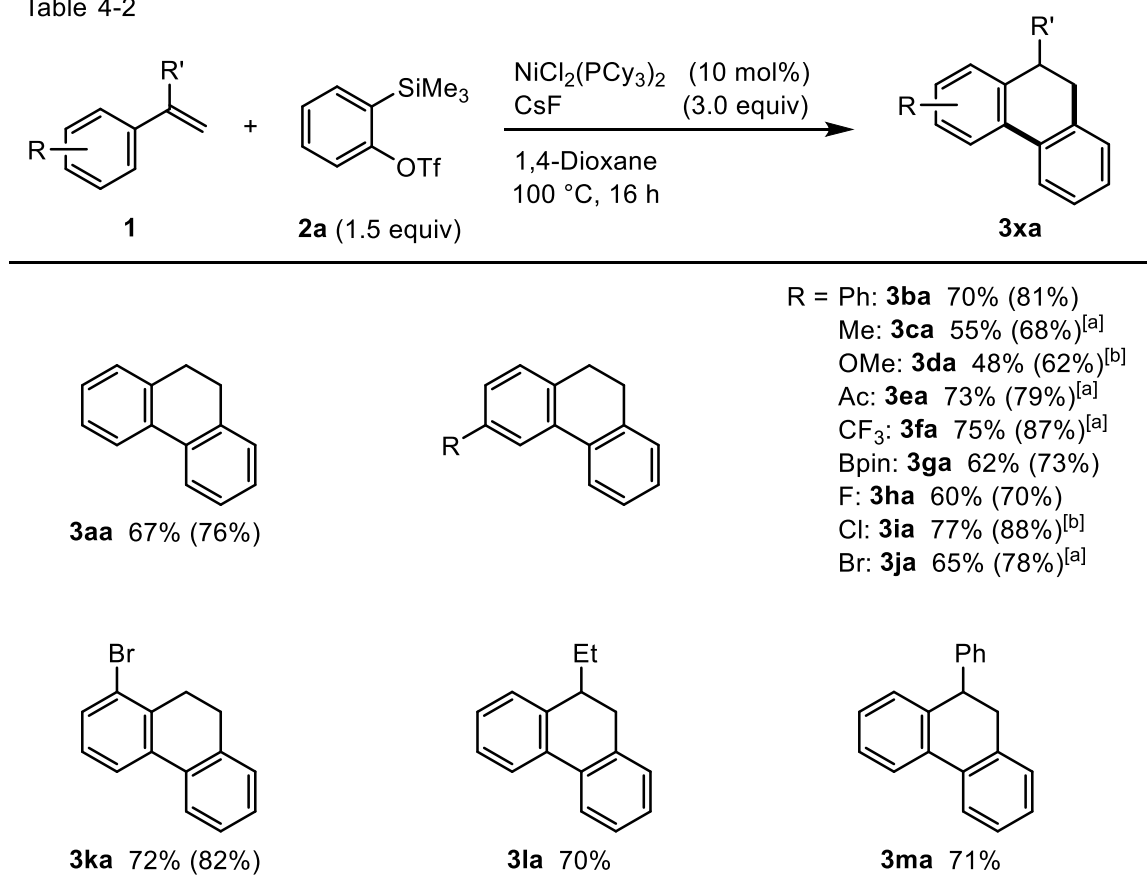
Yield was determined by <sup>1</sup>H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. Yield of isolated product is given in parentheses. Molar percentages of **2a**, Ni, ligand and CsF are based on the amount of **1a**. Reaction conditions, unless otherwise stated: **1a** (0.25 mmol), **2a** (0.30 mmol), Ni (0.025 mmol), ligand (0.075 mmol), CsF (0.60 mmol) and 1,4-dioxane (1.0 mL). [a] N.D. = Not detected. [b] IPr·HCl (20 mol%) and K<sub>2</sub>CO<sub>3</sub> (20 mol%) were used. [c] **2a** (1.5 equiv) and CsF (3.0 equiv) were used.

#### 4-2-2. Scope of Substrates

The scope of the reaction related to substituted styrenes **1** was explored under optimal conditions using **2a** (Table 4-2). Nonsubstituted and 4'-phenylated styrenes **1a** and **1b** underwent nickel-catalyzed [4 + 2] cycloaddition with **2a** to afford the corresponding 9,10-dihydrophenanthrenes **3aa** and **3ba** in isolated 67% and 70% yields, respectively, after purification by gel permeation chromatography (GPC). Reactions of styrenes **1c** and **1d** bearing electron-donating methyl and methoxy groups at the para positions proceeded

fairly, whereas utilizing electronwithdrawing acetyl- and trifluoromethyl-bearing styrenes **1e** and **1f** produced rather high yields. Since boryl and halogen substituents like pinacolboryl, fluorine, chlorine, and bromine were tolerated under the reaction conditions, dihydrophenanthrenes **3ga–3ka** bearing boryl and halogen substituents on the benzene rings were synthesized in high yields. A sterically demanding bromine substituent at the ortho position caused no negative effect on the reaction. Cycloaddition of  $\alpha$ -substituted styrenes were also investigated under the same conditions. The  $\alpha$ -alkylated and  $\alpha$ -arylated styrenes **1l** and **1m** were applicable to the reaction to afford dihydrophenanthrenes **3la** and **3ma**, respectively.

Table 4-2

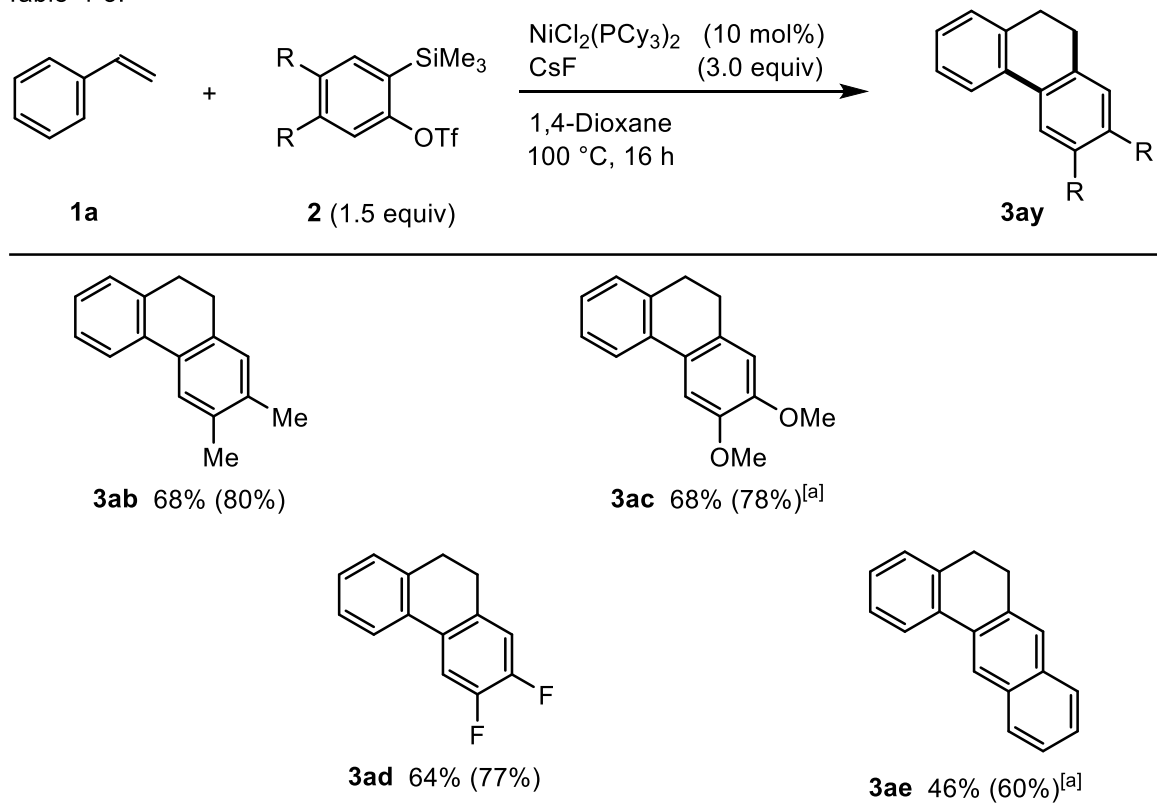


Isolated yield after purification by preparative GPC. Yield determined by <sup>1</sup>H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard is given in parentheses. Molar percentages of **2a**, NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> and CsF are based on the amount of **1**. Reaction conditions, unless otherwise stated: **1** (0.25 mmol), **2a** (0.375 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (0.025 mmol), CsF (0.75 mmol) and 1, 4-dioxane (1.0 mL). [a] **2a** (2.0 equiv) and CsF (4.0 equiv) were used. [b] NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (15 mol%) was used.

Substituted aryne precursors **2** were also examined in reactions using styrene (**1a**) under the optimal conditions (Table 4-3). Reactions of **1a** with aryne precursors **2b–2d** bearing two methyl, methoxy, and

fluorine substituents proceeded to afford corresponding 2,3-disubstituted 9,10-dihydrophenanthrenes **3ab**–**3ad** in high yields. Aryne precursor **2e** with a naphthalene ring formed tetracyclic dihydrotetraphene **3ae** in 46% isolated yield.

Table 4-3.

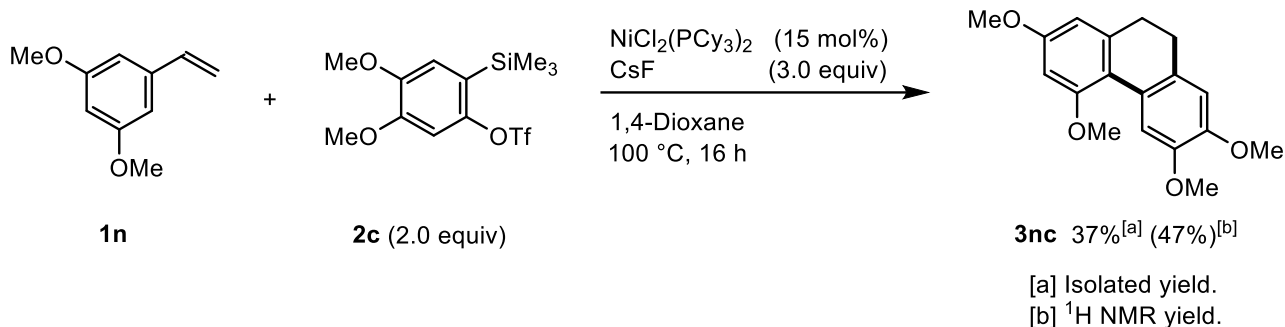


Isolated yield after purification by preparative GPC. Yield determined by  $^1\text{H}$  NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard is given in parentheses. Molar percentages of **2**,  $\text{NiCl}_2(\text{PCy}_3)_2$  and  $\text{CsF}$  are based on the amount of **1a**. Reaction conditions, unless otherwise stated: **1a** (0.25 mmol), **2** (0.375 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (0.025 mmol),  $\text{CsF}$  (0.75 mmol) and 1, 4-dioxane (1.0 mL). [a] **2a** (2.0 equiv) and  $\text{CsF}$  (4.0 equiv) were used.

#### 4-2-3. Application to Natural Product Synthesis

This protocol was applied for the synthesis of a natural product. Callosumin (**3nc**)<sup>[8], [9]</sup> a naturally occurring stilbenoid<sup>[10]</sup> was synthesized in 37% isolated yield via the nickel-catalyzed [4 + 2] cycloaddition using 3,5-dimethoxystyrene (**1n**) and aryne precursor **2c** (Scheme 4-4).

Scheme 4-4.

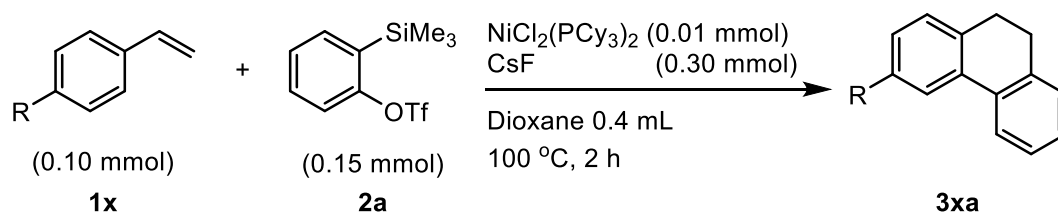


## 4-3. Mechanistic Studies

### 4-3-1. Competition Experiments

To collect additional information regarding the mechanism, I examined the effect of the electronic nature of the substituents (Scheme 4-5). Reactions were performed for 2 h under the standard conditions using styrenes bearing a substituent at the *para*-position. As a result, electron-withdrawing groups did not retard the reaction. This trend is in contrast with Biju's metal-free case, where reactions with electron-deficient styrenes are sluggish. The difference in reactivity of electron-deficient styrenes suggests that the current reaction proceeded not via the Diels–Alder-type [4 + 2] cycloaddition but via another mechanism.

Scheme 4-5.



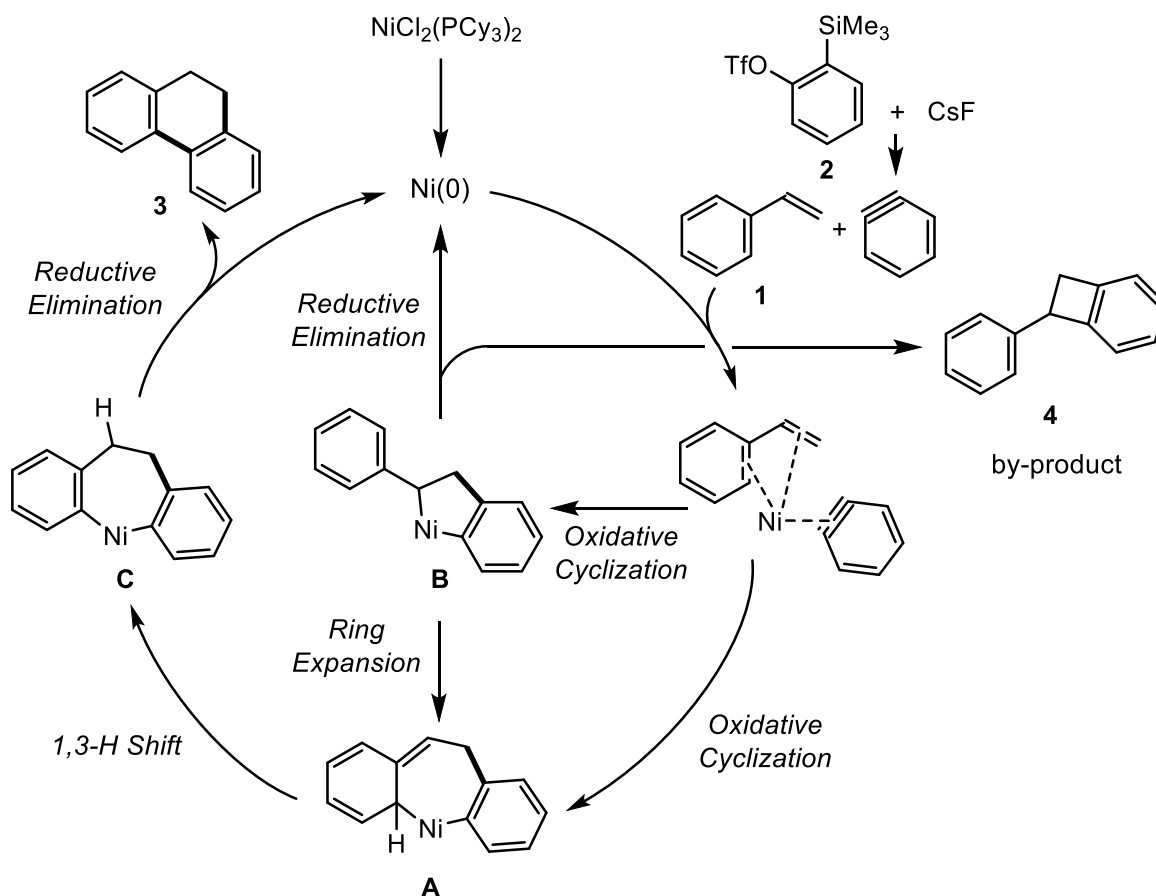
Entry	R	<b>3xa</b> (%)	Recovery of <b>1x</b> (%)
1	H	24	64
2	Me	2	96
3	OMe	0	96
4	F	12	24
5	Cl	14	78

<sup>1</sup>H NMR yield.

### 4-3-2. Proposed Mechanism

Due to the results of competition reactions and the formation of the [2 + 2] cycloadducts **4** along with 9,10-dihydrophenanthrenes **3**, I propose the reaction mechanism in Scheme 4-6. The reaction begins with coordination of styrenes **1** and arynes generated from **2** to *in-situ* generated Ni(0) species.<sup>[11]</sup> Two ways exist for subsequent nickel-mediated oxidative cyclization between **1** and arynes to produce: (i) seven-membered nickelacycles **A** and (ii) five-membered nickelacycles **B**. Styrenes **1** react as 1,3-dienes via dearomatization to form **A**, whereas the vinylic moieties of **1** only are involved in the formation of **B**. I speculate that by-products **4** are formed via reductive elimination from **B**. In addition, nickelacycles **A** are formed even from **B** via ring expansion. Rearomatizing 1,3-hydrogen shift in **A** followed by reductive elimination affords 9,10-dihydrophenanthrenes **3** along with catalytically active Ni(0) species. The addition of TEMPO, a radical scavenger, did not inhibit the reaction, indicating that no radical mechanism is involved.

Scheme 4-6.



### 4-3-3. Conclusion

In summary, nickel-catalyzed [4 + 2] cycloaddition of styrenes with arynes in a 1:1 ratio was accomplished. Consequently, I controlled the reactivity of arynes using a nickel catalyst. Although 9,10-dihydrophenanthrenes with no substituent at the 9- or 10-positions are vital as naturally occurring stilbenoids in pharmaceutical and agrochemical sciences, conventional approaches for their production often exhibit poor efficiency/selectivity<sup>[12]</sup> or narrow substrate scope.<sup>[13]</sup> These limitations were eliminated in this study by introducing an efficient method for the synthesis of 9,10-dihydrophenanthrenes.

## 4-4. Experimental Section

### 4-4-1. General Information.

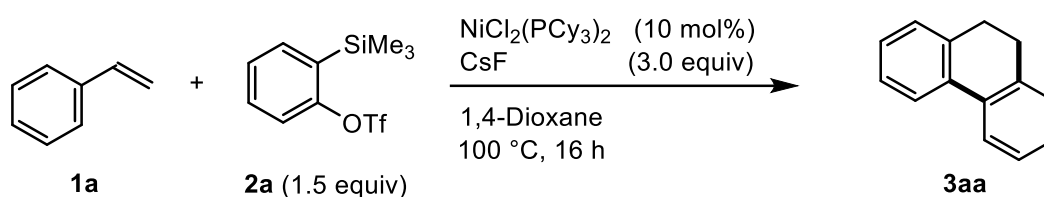
<sup>1</sup>H NMR and <sup>13</sup>C NMR <sup>19</sup>F NMR spectra were recorded on a JEOL ECS-400 spectrometer. Chemical shift values are given in ppm relative to internal Me<sub>4</sub>Si (for <sup>1</sup>H NMR: δ = 0.00 ppm) and CDCl<sub>3</sub> (for <sup>13</sup>C NMR: δ = 77.0 ppm). IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV spectrometer. Gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-908 apparatus equipped with a JAIGEL-1H and -2H assembly.

Column chromatography was performed on silica gel (Silica Gel 60, Kanto Chemical Co. Inc.). All the reactions were conducted under argon or nitrogen. 1,4-Dioxane was distilled from sodium, and stored over activated molecular sieves 4A. Styrenes **1d**,<sup>[14]</sup> **1e**,<sup>[15]</sup> **1g**,<sup>[14]</sup> **1k**,<sup>[14]</sup> **1l**<sup>[14]</sup> and 2-(trimethylsilyl)aryl triflates **2b–2d**<sup>[16]</sup> were prepared according to the literature procedures. Unless otherwise noted, materials were obtained from commercial sources and used directly without further purifications.



## 4-4-2. Synthesis of 9,10-Dihydrophenanthrenes 3

### 9,10-Dihydrophenanthrene (3aa)

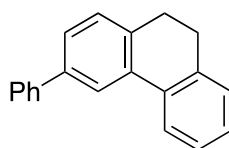


To a 30-mL Schlenk tube were added styrene (**1a**, 26 mg, 0.25 mmol), aryl precursor **2a** (112 mg, 0.38 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (17 mg, 0.025 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). After stirring at 100 °C for 16 h, the reaction mixture was filtered through a pad of silica gel (ethyl acetate). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give a mixture of dihydrophenanthrene **3aa** and benzocyclobutene **4aa** (37 mg). Further purification by GPC (chloroform) gave **3aa** (30 mg, 67%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.84 (s, 4H), 7.18–7.32 (m, 6H), 7.73 (d,  $J = 7.7$  Hz, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.0, 123.6, 126.9, 127.3, 128.1, 134.4, 137.3.

Spectral data for this compound showed good agreement with the literature data.<sup>[17]</sup>

### 3-Phenyl-9,10-dihydrophenanthrene (3ba)

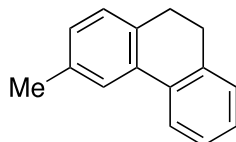


Compound **3ba** was synthesized by the method described for **3aa** using **1b** (45 mg, 0.25 mmol), **2a** (112 mg, 0.38 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (17 mg, 0.025 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ba** (45 mg, 70%) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.88 (s, 4H), 7.20–7.24 (m, 2H), 7.25–7.36 (m, 3H), 7.40–7.46 (m, 3H), 7.60–7.65 (m, 2H), 7.81 (d,  $J = 7.8$  Hz, 1H), 7.96 (d,  $J = 1.8$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.7, 29.1, 122.5, 123.7, 126.2, 127.0, 127.07, 127.10, 127.5, 128.2, 128.5, 128.7, 134.4, 134.8, 136.5, 137.4,

140.0, 141.4. IR (neat):  $\nu$  3028, 2933, 2835, 1600, 1483, 827, 758, 698, 636  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{20}\text{H}_{16}$   $[\text{M}]^+$ : 256.1252; Found: 256.1256.

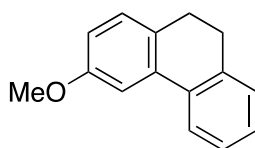
### 3-Methyl-9,10-dihydrophenanthrene (3ca)



Compound **3ca** was synthesized by the method described for **3aa** using **1c** (30 mg, 0.25 mmol), **2a** (149 mg, 0.50 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (17 mg, 0.025 mmol), CsF (152 mg, 1.0 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ca** (27 mg, 55%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.40 (s, 3H), 2.80–2.90 (m, 4H), 7.04 (dd,  $J = 7.3, 1.0$  Hz, 1H), 7.13 (d,  $J = 7.8$  Hz, 1H), 7.20–7.25 (m, 2H), 7.26–7.32 (m, 1H), 7.57 (s, 1H), 7.74 (d,  $J = 7.8$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.4, 28.6, 29.3, 123.6, 124.4, 126.8, 127.2, 128.0, 128.08, 128.08, 134.3, 134.4, 134.6, 136.3, 137.5. IR (neat):  $\nu$  2966, 2925, 1705, 1684, 1508, 1456, 1338, 1219, 771  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{15}\text{H}_{14}$   $[\text{M}]^+$ : 194.1096; Found: 194.1091.

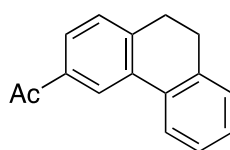
### 3-Methoxy-9,10-dihydrophenanthrene (3da)



Compound **3da** was synthesized by the method described for **3aa** using **1d** (34 mg, 0.25 mmol), **2a** (112 mg, 0.38 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (26 mg, 0.038 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3da** (25 mg, 48%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.78–2.90 (m, 4H), 3.86 (s, 3H), 6.79 (dd,  $J = 8.2, 2.5$  Hz, 1H), 7.15 (d,  $J = 8.2$  Hz, 2H), 7.20–7.25 (m, 2H), 7.25–7.32 (m, 1H) 7.72 (d,  $J = 7.7$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.1, 29.4, 55.4, 109.5, 112.7, 123.7, 126.9, 127.5, 128.1, 128.9, 129.7, 134.4, 135.5, 137.6, 158.7. IR (neat):  $\nu$  2931, 2834, 1684, 1600, 1508, 1456, 1300, 1219, 1037, 768  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{15}\text{H}_{14}\text{O}$   $[\text{M}]^+$ : 210.1045; Found: 210.1045.

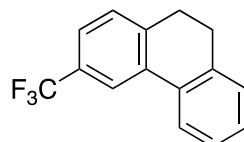
### 1-(9,10-Dihydrophenanthren-3-yl)ethan-1-one (3ea)



Compound **3ea** was synthesized by the method described for **3aa** using **1e** (37 mg, 0.25 mmol), **2a** (149 mg, 0.50 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (17 mg, 0.025 mmol), CsF (152 mg, 1.0 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane/ethyl acetate = 10:1) and GPC gave **3ea** (40 mg, 73%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.64 (s, 3H), 2.85–2.95 (m, 4H), 7.22–7.36 (m, 4H), 7.80 (dd,  $J = 7.8, 1.8$  Hz, 1H), 7.84 (d,  $J = 7.8$  Hz, 1H), 8.35 (d,  $J = 1.8$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  26.6, 28.5, 29.2, 123.5, 123.9, 127.2, 127.4, 128.0, 128.2, 128.3, 133.6, 134.9, 136.2, 137.1, 142.9, 197.9. IR (neat):  $\nu$  3032, 2931, 1682, 1608, 1410, 1358, 1240, 833, 766, 638  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{16}\text{H}_{14}\text{O}$   $[\text{M}]^+$ : 222.1045; Found: 222.1049.

### 3-(Trifluoromethyl)-9,10-dihydrophenanthrene (3fa)

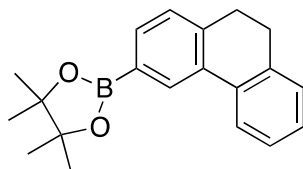


Compound **3fa** was synthesized by the method described for **3aa** using **1f** (43 mg, 0.25 mmol), **2a** (149 mg, 0.50 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (17 mg, 0.025 mmol), CsF (152 mg, 1.0 mmol), and 1,4-dioxane (1.0 mL).

Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3fa** (46 mg, 75%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.82–2.98 (m, 4H), 7.20–7.38 (m, 4H), 7.45 (d,  $J = 7.3$  Hz, 1H), 7.75 (d,  $J = 7.8$  Hz, 1H), 7.96 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.5, 28.9, 120.4 (q,  $J_{\text{CF}} = 4$  Hz), 123.8, 123.9, 124.4 (q,  $J_{\text{CF}} = 274$  Hz), 127.2, 128.25, 128.25, 128.5, 129.4 (q,  $J_{\text{CF}} = 33$  Hz), 133.2, 135.2, 137.3, 141.1.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  99.4 (s). IR (neat):  $\nu$  2925, 2854, 1684, 1558, 1508, 1458, 1338, 1132, 771  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{15}\text{H}_{11}\text{F}_3$   $[\text{M}]^+$ : 248.0813; Found: 248.0814

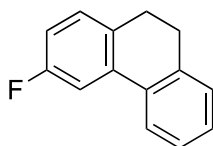
### 2-(9,10-Dihydrophenanthren-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3ga**)



Compound **3ga** was synthesized by the method described for **3aa** using **1g** (58 mg, 0.25 mmol), **2a** (112 mg, 0.38 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (17 mg, 0.025 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane/ethyl acetate = 3/1) and GPC (chloroform) gave **3ga** (47 mg, 62%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.33 (s, 12H), 2.82–2.92 (m, 4H), 7.20–7.32 (m, 4H), 7.68 (dd,  $J = 8.1, 1.0$  Hz, 1H), 7.88 (d,  $J = 7.8$  Hz, 1H), 8.21 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.9, 28.9, 29.3, 83.7, 124.1, 126.9, 127.3, 127.6, 128.0, 130.1, 133.89, 133.89, 134.4, 137.2, 140.8. IR (neat):  $\nu$  2978, 2931, 1610, 1402, 1362, 1146, 1099, 773, 683  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{20}\text{H}_{23}\text{BO}_2$   $[\text{M}]^+$ : 306.1791; Found: 306.1799.

### 3-Fluoro-9,10-dihydrophenanthrene (**3ha**)

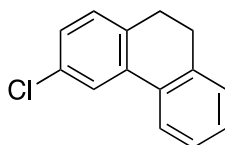


Compound **3ha** was synthesized by the method described for **3aa** using **1h** (31 mg, 0.25 mmol), **2a** (112

mg, 0.38 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (17 mg, 0.025 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ha** (30 mg, 60%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.78–2.92 (m, 4H), 6.91 (ddd, *J*<sub>HF</sub> = 8.4 Hz, *J* = 8.4, 2.4 Hz, 1H), 7.18 (dd, *J* = 8.4 Hz, *J*<sub>HF</sub> = 6.0 Hz, 1H), 7.22–7.26 (m, 2H), 7.26–7.34 (m, 1H), 7.43 (dd, *J*<sub>HF</sub> = 10.3 Hz, *J* = 2.4 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 28.2, 29.1, 110.4 (d, *J*<sub>CF</sub> = 22 Hz), 113.8 (d, *J*<sub>CF</sub> = 21 Hz), 123.8, 127.0, 128.0, 128.2, 129.3 (d, *J*<sub>CF</sub> = 77 Hz), 132.8 (d, *J*<sub>CF</sub> = 2 Hz), 133.6 (d, *J*<sub>CF</sub> = 2 Hz), 136.3 (d, *J*<sub>CF</sub> = 77 Hz), 137.3, 162.2 (d, *J*<sub>CF</sub> = 244 Hz). <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ 45.3–45.5 (m). IR (neat): ν 3070, 2931, 2850, 1682, 1603, 1496, 1448, 1280, 1196, 769 cm<sup>-1</sup>. HRMS (EI): *m/z* Calcd. for C<sub>14</sub>H<sub>11</sub>F [M]<sup>+</sup>: 198.0845; Found: 198.0846.

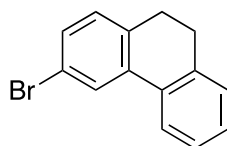
### 3-Chloro-9,10-dihydrophenanthrene (**3ia**)



Compound **3ia** was synthesized by the method described for **3aa** using **1i** (35 mg, 0.25 mmol), **2a** (112 mg, 0.38 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (26 mg, 0.038 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ia** (41 mg, 77%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.78–2.92 (m, 4H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.19–7.25 (m, 2H), 7.25–7.32 (m, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 28.4, 28.8, 123.76, 123.76, 127.08, 127.08, 128.0, 128.2, 129.3, 132.6, 133.3, 135.6, 136.2, 137.3. IR (neat): ν 3062, 2937, 2837, 1699, 1595, 1446, 1288, 1097, 837, 766 cm<sup>-1</sup>. HRMS (EI): *m/z* Calcd. for C<sub>14</sub>H<sub>11</sub>Cl [M]<sup>+</sup>: 214.0549; Found: 214.0549..

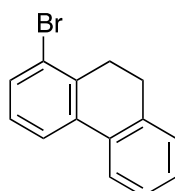
### 3-Bromo-9,10-dihydrophenanthrene (3ja)



Compound **3ja** was synthesized by the method described for **3aa** using **1j** (46 mg, 0.25 mmol), **2a** (149 mg, 0.50 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (17 mg, 0.025 mmol), CsF (152 mg, 1.0 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ja** (42 mg, 65%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.75–2.91 (m, 4H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.20–7.35 (m, 4H), 7.68 (d, *J* = 7.3 Hz, 1H), 7.85 (d, *J* = 1.4 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 28.4, 28.8, 120.6, 123.8, 126.7, 127.1, 128.0, 128.2, 129.7, 130.0, 133.2, 136.1, 136.6, 137.3. IR (neat): ν 3028, 2933, 1653, 1558, 1508, 1483, 1446, 1396, 811, 764 cm<sup>-1</sup>. HRMS (EI): *m/z* Calcd. for C<sub>14</sub>H<sub>11</sub><sup>79</sup>Br [M]<sup>+</sup>: 258.0044; Found: 258.0040.

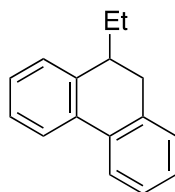
### 1-Bromo-9,10-dihydrophenanthrene (3ka)



Compound **3ka** was synthesized by the method described for **3aa** using **1k** (46 mg, 0.25 mmol), **2a** (112 mg, 0.38 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (17 mg, 0.025 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ka** (47 mg, 72%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.81–2.86 (m, 2H), 2.96–3.02 (m, 2H), 7.12 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.17–7.32 (m, 3H), 7.46 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.60–7.72 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 28.3, 28.4, 122.9, 124.0, 124.4, 127.0, 127.9, 127.95, 127.99, 131.4, 133.8, 136.79, 136.79, 137.1. IR (neat): ν 2927, 2834, 1684, 1558, 1508, 1446, 1047, 752, 638 cm<sup>-1</sup>. HRMS (EI): *m/z* Calcd. for C<sub>14</sub>H<sub>11</sub><sup>79</sup>Br [M]<sup>+</sup>: 258.0044; Found: 258.0044.

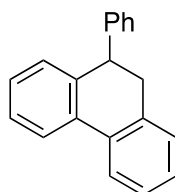
### 9-Ethyl-9,10-dihydrophenanthrene (**3la**)



Compound **3la** was synthesized by the method described for **3aa** using **1l** (33 mg, 0.25 mmol), **2a** (112 mg, 0.38 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (17 mg, 0.025 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3la** (36 mg, 70%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.30–1.50 (m, 2H), 2.66–2.76 (m, 1H), 2.80 (dd, *J* = 15.1, 3.4 Hz, 1H), 3.09 (dd, *J* = 15.1, 5.3 Hz, 1H), 7.15–7.33 (m, 6H), 7.70–7.77 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 12.1, 26.2, 33.6, 40.2, 123.4, 124.0, 126.8, 126.9, 127.2, 127.4, 128.3, 128.9, 133.5, 134.1, 135.6, 141.1. IR (neat): ν 3064, 2960, 2925, 1684, 1483, 1454, 750, 739, 669 cm<sup>-1</sup>. HRMS (EI): *m/z* Calcd. for C<sub>16</sub>H<sub>16</sub> [M]<sup>+</sup>: 208.1252; Found: 208.1248.

### 9-Phenyl-9,10-dihydrophenanthrene (**3ma**)

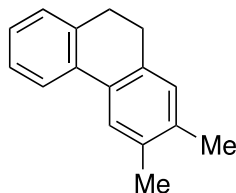


Compound **3ma** was synthesized by the method described for **3aa** using **1m** (90 mg, 0.50 mmol), **2a** (224 mg, 0.751 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (35 mg, 0.050 mmol), CsF (228 mg, 1.50 mmol), and 1,4-dioxane (2.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ma** (91 mg, 71%) as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.10–3.25 (m, 2H), 4.19 (dd, *J* = 8.4, 6.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 7.10–7.40 (m, 10H), 7.76–7.87 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 37.0, 44.8, 123.6, 123.8, 126.5, 127.1, 127.2, 127.60, 127.60, 128.3, 128.40, 128.40, 128.45, 134.3, 134.5, 135.8, 139.8, 143.4. IR (neat): ν

3062, 3026, 2931, 2889, 1601, 1485, 1452, 748, 700  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{20}\text{H}_{16}$   $[\text{M}]^+$ : 256.1252; Found: 256.1248.

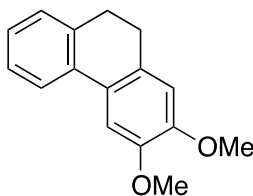
### 2,3-Dimethyl-9,10-dihydrophenanthrene (**3ab**)



Compound **3ab** was synthesized by the method described for **3aa** using **1a** (26 mg, 0.25 mmol), **2b** (122 mg, 0.37 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (17 mg, 0.025 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ab** (35 mg, 68%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.26 (s, 3H), 2.30 (s, 3H), 2.74–2.90 (m, 4H), 7.00 (s, 1H), 7.14–7.22 (m, 2H), 7.27 (ddd,  $J = 7.7, 7.7, 2.3$  Hz, 1H), 7.52 (s, 1H), 7.72 (d,  $J = 7.7$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.4, 19.7, 28.5, 29.3, 123.3, 124.9, 126.79, 126.81, 128.0, 129.4, 132.0, 134.6, 134.8, 134.9, 135.8, 137.1. IR (neat):  $\nu$  3010, 2931, 2835, 1689, 1489, 1448, 1020, 879, 768, 729, 673  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{16}\text{H}_{16}$   $[\text{M}]^+$ : 208.1252; Found: 208.1252.

### 2,3-Dimethoxy-9,10-dihydrophenanthrene (**3ac**)

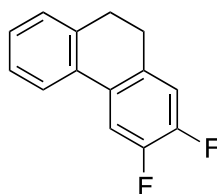


Compound **3ac** was synthesized by the method described for **3aa** using **1a** (26 mg, 0.25 mmol), **2c** (179 mg, 0.50 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (17 mg, 0.025 mmol), CsF (152 mg, 1.0 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane/ethyl acetate = 3/1) and GPC (chloroform) gave **3ac** (41 mg, 68%) as a white solid.



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.74–2.90 (m, 4H), 3.91 (s, 3H), 3.95 (s, 3H), 6.75 (s, 1H), 7.14–7.32 (m, 4H), 7.64 (d,  $J = 7.8$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.6, 29.2, 55.9, 56.1, 107.2, 111.3, 122.8, 126.5, 126.8, 126.9, 128.1, 130.1, 134.4, 136.5, 147.9, 148.4. IR (neat):  $\nu$  2933, 2833, 1608, 1516, 1452, 1279, 1238, 1144, 1045,  $769\text{ cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{16}\text{H}_{16}\text{O}_2$   $[\text{M}]^+$ : 240.1150; Found: 240.1147.

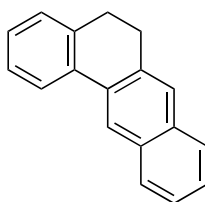
### 2,3-Difluoro-9,10-dihydrophenanthrene (3ad)



Compound **3ad** was synthesized by the method described for **3aa** using **1a** (26 mg, 0.25 mmol), **2d** (125 mg, 0.37 mmol),  $\text{NiCl}_2(\text{PCy}_3)_2$  (17 mg, 0.025 mmol), CsF (114 mg, 0.75 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ad** (34 mg, 64%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.74–2.92 (m, 4H), 7.02 (dd,  $J_{\text{HF}} = 10.6, 8.0$  Hz, 1H), 7.20–7.32 (m, 3H), 7.51 (dd,  $J_{\text{HF}} = 11.8, 7.7$  Hz, 1H), 7.60 (d,  $J = 7.6$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.3, 28.8, 112.6 (d,  $J_{\text{CF}} = 18$  Hz), 116.7 (d,  $J_{\text{CF}} = 17$  Hz), 123.6, 127.2, 127.8, 128.3, 131.2, 132.9, 133.9, 136.7, 149.3 (dd,  $J_{\text{CF}} = 249, 13$  Hz), 149.5 (dd,  $J_{\text{CF}} = 246, 13$  Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.5–20.7 (m, 1F), 21.4–21.6 (m, 1F). IR (neat):  $\nu$  3064, 2935, 2843, 1608, 1506, 1452, 1331, 1240, 879, 814,  $764\text{ cm}^{-1}$ . HRMS (EI):  $m/z$  Calcd. for  $\text{C}_{14}\text{H}_{10}\text{F}_2$   $[\text{M}]^+$ : 216.0751; Found: 216.0749.

### 5,6-Dihydrotetraphene (3ae)

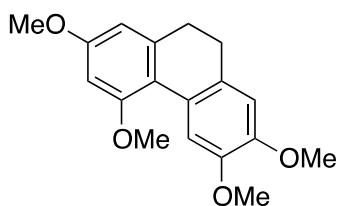


Compound **3ae** was synthesized by the method described for **3aa** using **1a** (52 mg, 0.50 mmol), **2e** (348

mg, 1.00 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (35 mg, 0.050 mmol), CsF (304 mg, 2.00 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3ae** (54 mg, 46%) as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.88–2.95 (m, 2H), 3.00–3.07 (m, 2H), 7.23–7.27 (m, 2H), 7.31–7.37 (m, 1H), 7.38–7.46 (m, 2H), 7.65 (s, 1H), 7.72–7.78 (m, 1H), 7.82–7.88 (m, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 8.17 (s, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 29.4, 29.7, 122.5, 124.3, 125.4, 125.8, 125.9, 127.0, 127.1, 127.6, 128.0, 128.3, 132.95, 132.97, 133.1, 134.5, 136.0, 138.0. IR (neat): ν 3055, 2922, 2837, 1496, 1437, 887, 775, 733 cm<sup>-1</sup>. HRMS (EI): *m/z* Calcd. for C<sub>18</sub>H<sub>14</sub> [M]<sup>+</sup>: 230.1096; Found: 230.1094.

### 2,3,5,7-Tetramethoxy-9,10-dihydrophenanthrene (Callosumin, 3nc)



Compound **3nc** was synthesized by the method described for **3aa** using **1n** (41 mg, 0.25 mmol), **2c** (179 mg, 0.50 mmol), NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (26 mg, 0.038 mmol), CsF (152 mg, 1.0 mmol), and 1,4-dioxane (1.0 mL). Purification by silica gel column chromatography (hexane) and GPC (chloroform) gave **3nc** (28 mg, 37%) as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.67–2.80 (m, 4H), 3.83 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.74 (s, 1H), 7.91 (s, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 29.2, 31.1, 55.3, 55.7, 55.8, 56.0, 97.7, 105.1, 110.7, 112.0, 116.6, 125.2, 130.5, 140.8, 146.6, 146.9, 157.5, 158.7. IR (neat): ν 2935, 2835, 1604, 1512, 1464, 1275, 1226, 1136, 1090, 1026, 870, 798 cm<sup>-1</sup>. HRMS (EI): *m/z* Calcd. for C<sub>18</sub>H<sub>20</sub>O<sub>4</sub> [M]<sup>+</sup>: 300.1362; Found: 300.1363.

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## Chapter 5

### Conclusions

I developed new and facile methodologies for C–C bond formation via C–H bond activation using Ni and Pd catalysts. These studies proved that metalacycle generation significantly contributes to functionalization of inert C–H bonds.

Chapter 2 discusses the nickel(II)-catalyzed direct methylation of aromatic amides containing an 8-aminoquinoline moiety as a bidentate directing group with dicumyl peroxide via C(sp<sup>2</sup>)–H bond activation. The driving force for C–H bond cleavage with a less active nickel catalyst would be the formation of metalacycle intermediates stabilized by an *N,N*-bidentate directing group. The reaction displayed a broad substrate scope and a high functional group tolerance. The reaction was inhibited by radical scavengers, such as TEMPO, 1,4-cyclohexadiene, and  $\alpha$ -methylstyrene. Thus, this reaction involves radical generation. Deuterium-labeling experiments indicated that the C–H bond cleavage is reversible and a reductive elimination is likely to be a rate-determining step. This reaction proceeded via a Ni(II)/Ni(III)/Ni(IV) cycle, which is unusual in Ni-catalyzed cross-coupling reactions.

Chapter 3 is concerned with the palladium(II)-catalyzed oxidative coupling via double activation of C(sp<sup>3</sup>)–H bonds in aliphatic amides and benzylic C(sp<sup>3</sup>)–H bonds in toluene derivatives using the hexafluoroisopropyl iodide as a mild oxidant. Mechanistic studies revealed that this reaction contains radical pathways and the active benzylation agents are benzylic iodides. Generation of benzylic iodides would be the key to success in unprecedented chemoselective C(sp<sup>3</sup>)–H/ C(sp<sup>3</sup>)–H cross-coupling.

Chapter 4, nickel-catalyzed [4 + 2] cycloaddition of styrenes with arynes in a 1:1 ratio was accomplished. I controlled the reactivity of arynes, which has been difficult to use in selective reactions, by using nickel catalyst. The key intermediates in the reaction were metalacycles generated by Ni-mediated oxidative cyclization of styrenes with arynes. Although 9,10-dihydrophenanthrenes with no substituent at the 9- or 10-positions are vital as naturally occurring stilbenoids in pharmaceutical and agrochemical sciences, conventional approaches for their production often exhibit poor efficiency/selectivity or narrow substrate scope. These limitations were eliminated in this study by introducing an efficient method for the synthesis of

9,10-dihydrophenanthrenes.

In this doctoral dissertation, I established new methods for C–H bond activation reactions involving simultaneous C–H cleavage and C–M formation (Chapter 2,3) and stepwise C–M formation and C–H cleavage (Chapter 4) which are defined as *direct* and *indirect* C–H bond activation, respectively. I hope that these method will be widely used in the future.

## LIST OF PUBLICATIONS

(1) Kubo, T.; Chatani, N

Dicumyl Peroxide as a Methylating Reagent in the Ni-Catalyzed Methylation of Ortho C–H Bonds in Aromatic Amides

*Org. Lett.* **2016**, *18*, 1698.

(2) Kubo, T.; Aihara, Y.; Chatani, N.

Pd(II)-catalyzed Chelation-assisted Cross Dehydrogenative Coupling between Unactivated C(sp<sup>3</sup>)–H Bonds in Aliphatic Amides and Benzylic C–H Bonds in Toluene Derivatives

*Chem. Lett.* **2015**, *44*, 1365.

(3) Kubo, T.; Fujita, T.; Ichikawa, J.

Nickel-Catalyzed [4 + 2] Cycloaddition of Styrenes with Arynes via 1:1 Cross-Coupling: Synthesis of 9,10-Dihydrophenanthrenes

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The thesis is concerned with the development of the nickel(II)-catalyzed [4 + 2] Cycloaddition of Styrenes with Arynes via 1:1 Cross-Coupling: Synthesis of 9,10-Dihydrophenanthrenes.

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