Doctoral Dissertation

Studies on Nickel-Catalyzed C-H Bond Functionalization Utilizing *N*,*N*-Bidentate Directing Assistance

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Preface and Acknowledgements

The findings presented in this thesis were carried out under the direction of Professor Naoto Chatani of the Department of Applied Chemistry, Faculty of Engineering, Osaka University between April 2010 and March 2016. The thesis is concerned with the development of the nickel(II)-catalyzed direct functionalization of aromatic and aliphatic C-H bonds utilizing an *N*,*N*-bidentate directing group.

This thesis would not be possible without help, advice, and support from many people and I would like to express my sincerest appreciation to all of them.

I would like to express my utmost gratitude to Professor Chatani for his guidance and suggestions throughout this work. His enthusiasm for chemistry has always motivated me. I also admire him for his wit and humor in daily life. He also arranged for me to be involved in research at The Scripps Research Institute in America for four months, and provided a financial support for this experience. I had one of the most exciting times in my life there.

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techniques about total synthesis. I also acknowledge Ms. Patrece, who provided me with lodging, and all member of Baran's Group, especially Dr. Yoshihiro Ishihara, Mr. Hai Dao, Dr. Quentin Michaudel, Dr. Chung-Mao Pan, Dr. Bart Roman, Dr. Yuki Yabe Mr. Daisuke Ogasawara and Dr. Syuhei Kawamura. They taught me many things about the culture, food, and life of Americans.

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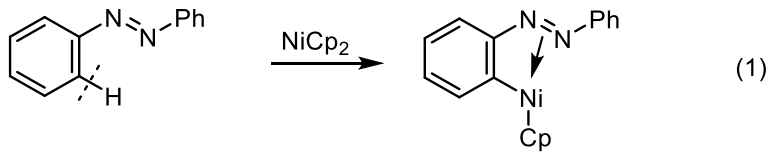
Contents

General Introduction

The transition metal-catalyzed functionalization of C-H bonds has emerged as a powerful tool for the synthesis organic molecule in recent years.[1] From the point of view of economy of steps and its environmentally friendly nature, the direct functionalization of C-H bonds has been developed as an alternative method for conventional cross coupling reactions. Palladium, rhodium and ruthenium are mainly used for functionalization of C-H bonds. On the other hand, there are only limited examples of the direct functionalization of C-H bonds using low-cost and more abundant metals, such as iron, copper and nickel, but this area of research has attracted recent attention.

Focusing on C-H bond activation using a nickel complex, a pioneering example of activation of benzene C-H bond by chelation-assistant was achieved by utilizing a stoichiometric amount of a nickel complex and azobenzene (eq 1).[3a] Remarkably, this cyclometalation was published earlier than cyclometalation with palladium complex (eq 2),[4] although cyclopalladation has been widely used method for C-H bonds actication.[5] Cyclometalation via the cleavage of C-H bonds using nickel has been undeveloped even when a stoichiometric amount of nickel is used. Zargarian and co-workers recently reported on cylcometalation via the cleavage of benzene C-H bonds using a stoichiometric amount of a nickel complex prepared from phenol (eq 3).[3b]



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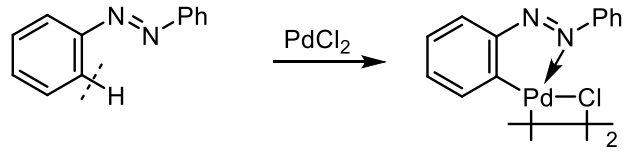

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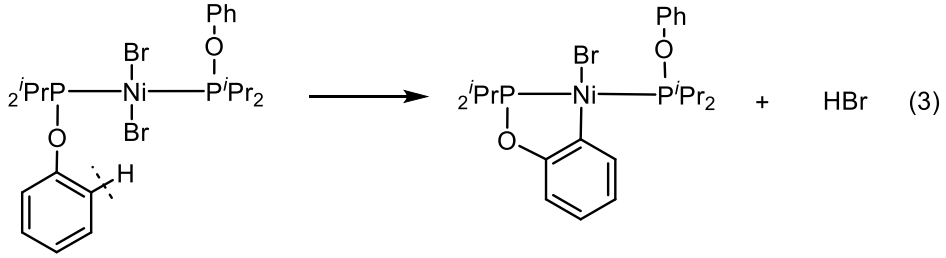
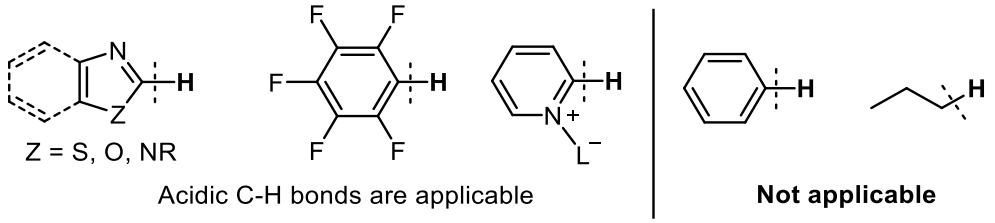


(3)

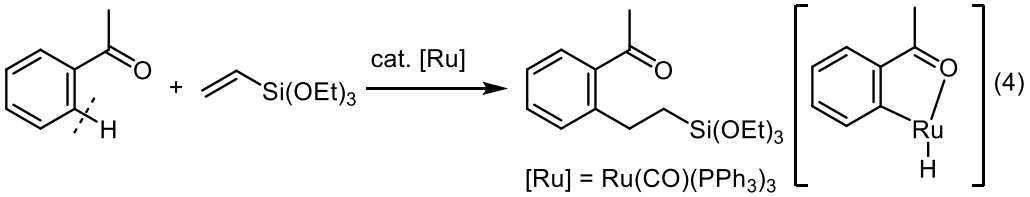
Most of the known nickel-catalyzed transformations of C-H bonds are limited to acidic C-H bonds, such as activated C(sp^2)-H bonds in azole, perfluorobenzene derivatives and

activated pyridine derivatives (Figure 1),[2] although the use of nickel in cyclometalation has been reported (eq 1 and 3). The transformation of non-activated benzene or aliphatic C-H bonds with a nickel-catalyst represent undeveloped and challenging topics, due to the low-reactivity of nickel complexes.

Figure1. Scope and Limitation of C-H bonds with Ni-catalyst

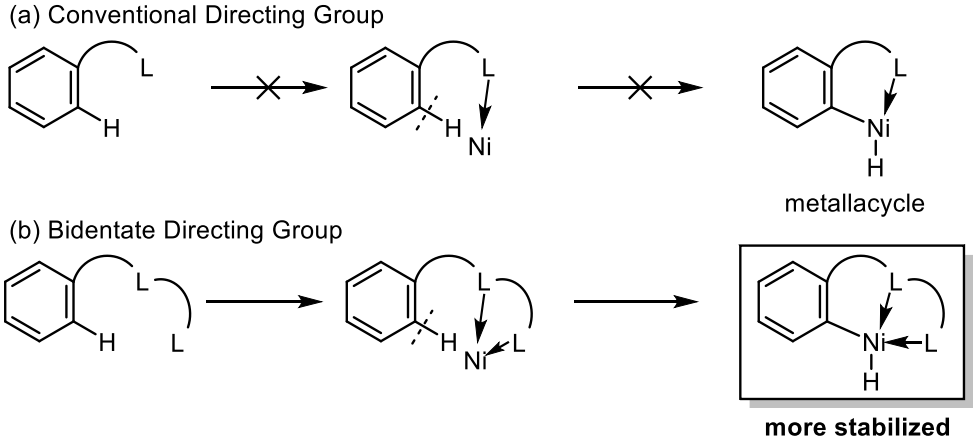


Incidentally, one of the methods for the regioselective functionalization of C-H bonds, which are ubiquitous in organic molecules, is the use of directing groups. Murai and co-workers reported on a pioneering concept of the use of a directing group for activating C-H bonds in 1993, the reaction of acetophenone and vinylsilane in the presence of a Ru-catalyst gave the ortho-alkylation product via the formation of a metallacycle intermediate generated by the activation of aromatic C-H bonds (eq 4).[6]

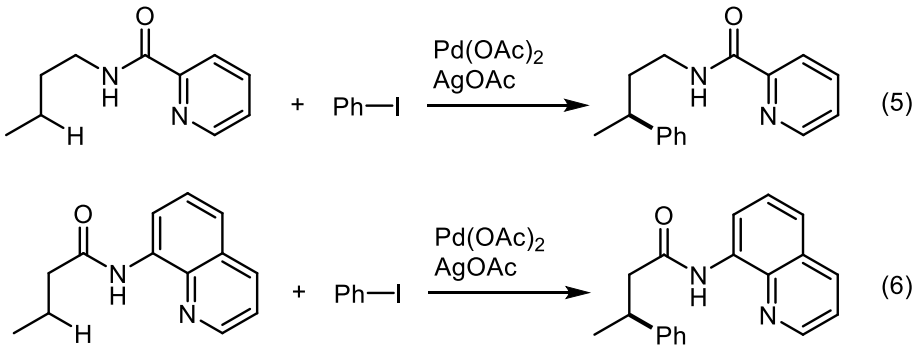


Directing groups, especially ketones or sp^2 nitrogen-containing compounds, such as pyridine coordinated to a metal, can be used to selectively activate C-H bonds, and, after activation, the reaction proceeds via a metallacycle intermediate (Figure 2a). The driving force for the activation of inert C-H bonds in a directing group system is the formation of a metallacycle intermediate. Various types of directing groups for C-H functionalizations have been developed, since the appearance of Murai's significant work.[7] The transformation of C-H bonds using nickel-catalyst has been limited, even if conventional directing groups are used. The low interaction between the nickel(II) complex and directing group and the low affinity between nickel(II) and C-H bonds make the activation of C-H bonds with a nickel-catalyst difficult (Figure 2a).

Figure 2. Working Hypothesis: Ni-Catalyzed Activation of C-H Bonds



In this study, I hypothesized that the use of a strong coordinating directing group and more stabilized metallacycle would provide sufficient driving force to permit inert C-H bonds to be activated when a low reactive nickel-catalyst was used. On the basis of this hypothesis, many experiments that were intended to increase the reactivity of nickel were carried out. The combination of a nickel(II) complex and a bidentate directing group which has two coordinating atoms within the directing group has the potential to activate inert C-H bonds because the bidentate directing group can strongly coordinate to nickel(II) complexes and stabilize the metallacycle by coordinating two atoms within the bidentate directing group (Fiugre 2b). The successful pioneering example of the bidentate directing group assisted functionalization of C−H bonds was reported by Daugulis, who discovered the Pd(II)-catalyzed arylation of C−H bonds in aliphatic amides that contain a picolinamide and 8-aminoquinoline moiety (eq 5 and 6).[8] The transformation of C−H bonds using bidentate directing groups and a palladium catalyst has grown in popularity since this seminal discovery by Daugulis.[9] The use of a bidentate directing group in conjunction with another transition metal catalyst in the transformation of C-H bonds had not still been developed before I started this study, except for our example of the direct Ru-catalyzed functionalization of C-H bonds utilizing a 2-aminopyridylmethylamine moiety as a bidentate directing group.[9]



Based on this working hypothesis, the activation of C-H bonds using a nickel(II)-catalyst and a bidentate directing group were examined. This thesis includes various types of transformations of C-H bonds utilizing a nickel(II)-catalyst and a bidentate directing group. This thesis is composed of the following three chapters.

Chapter 1 discusses the nickel(II)-catalyzed direct alkylation of C(sp^2)-H bonds containing an 8-aminoquinline moiety as a bidentate directing group with an alkyl halide.

Chapter 2 deals with the nickel(II)-catalyzed direct arylation of aliphatic amide possessing a bidentate directing group with an aryl halide via cleavage of a C(sp^3)-H bond.

Chapter 3 is concerned with the nickel(II)-catalyzed oxidative coupling of C(sp^2)-H bond in benzamides and benzylic C-H bond in toluene derivatives using hetafluoroisopropyl iodide as a mild oxidant. This reaction involves the catalytic cleavage of two different C-H bonds, C(sp^2)-H and benzylic C-H bonds.

Finally, the findings are summarized in the conclusion section of the thesis.

References

(1) Reviews on C-H bond transformation: (a) Kakiuchi, F.; Kochi, T. *Synthesis* **2008,** 3013. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010,** *110*, 1147. (c) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010,** *50*, 605. (d) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010,** *39*, 712. (e) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012,** *51*, 10236. (f) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012,** *51*, 8960. (g) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013,** *42*, 5744. (h) Gao,K.; Yoshikai, N. *Acc. Chem. Res.* **2014,** *47*, 1208. (i) Sarkar, S. D.; Liu, W.; Kozhushkov, S. I.; Ackerman, L. *Adv. Synth. Catal.* **2014**, *356*, 1461. (j) Hirano, K.; Miura, M. *Chem. Lett.* **2015**, *44*, 868.

(2) (a) Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544. (b) Vabre, B.; Deschamps, F.; Zargarian, D. *Organometallics* **2014**, *33*, 6623.

(3) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc*. **1965**, *87*, 3272.

(4) Aguilar, D.; Cuesta, L.; Nieto, S.; Serrano, E.; Urriolabeitia, E. P. *Current Organic Chemistry* **2011**, *15*, 3415.

(5) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19.

(6) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(7) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front*. **2015**, *2*, 1107.

(8) Zaitsev, V.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(9) Reviews on C-H bond transformation utilizing bidentate directing group: (a) Corbet, M.; De Campo, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9896. (b) Rouquet, G.; Chatani, N *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. (c) Misal Castro, L. C.; Chatani, N. *Chem. Lett.*

2015, *44*, 410. (d) Daugulis. O; Roane, J.; Tran, L. D. *Acc. Chem. Res*. **2015**, *48*, 1053. (e) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450.

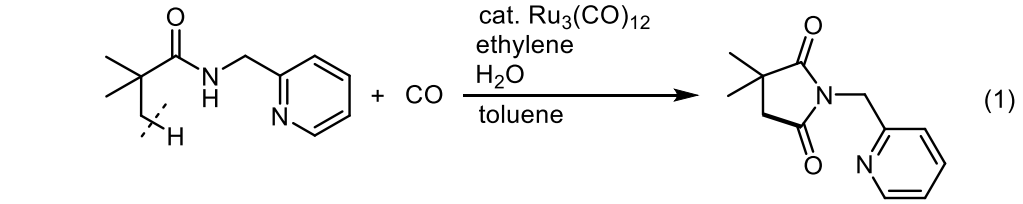
Chapter 1

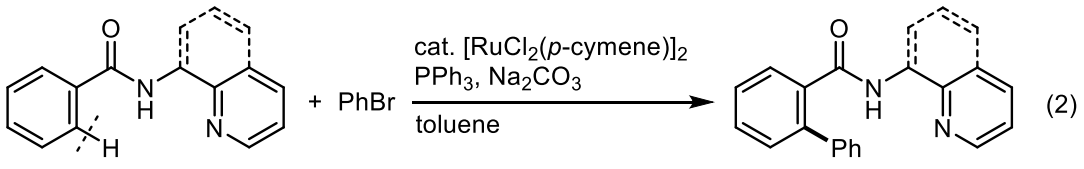
Nickel(II)-Catalyzed Direct Alkylation of C-H Bonds in Aromatic Amides Containing an 8-Aminoquinoline Moiety as the Directing Group

1.1 Introduction

Transition metal-catalyzed direct arylation of C-H bonds with aryl halides or aryl metal reagents has been developed and emerged as a powerful method for the construction of organic molecules. Compared to these arylation reactions, examples of the direct alkylation of C-H bonds with alkyl halide remain limited, because of the unfavorable of alkyl halides toward oxidative addition and the fact that the resulting alkyl metal complexes are susceptible to *β*–hydride elimination.[1] Conventional approaches to the synthesis of alkylated arenes rely on Friedel-Crafts type reactions or S_EAr type reactions, both of which have some limitations including i) only electron rich arenes were applicable ii) a low functional group tolerance, ii) low regioselectivities, and iii) a mixture of normal and branched products are often produced.[2] Numerous efforts have been made to address these limitations, and transition metal-catalyzed direct alkylation with alkyl halides has emerged as an alternative method for the synthesis alkylated arenes. Due to those efforts, direct alkylation using alkyl halides as the alkylating reagent with Pd,[3] Ru,[4] Fe,[5] and Co[6] catalysts have been developed over the past few years, while a direct alkylation with nickel-catalyst has been undeveloped.

Our group has focused on the use of 2-aminopyridylmethylamine as a bidentate directing groups in a catalytic functionalization of C-H bonds, such as the Ru-catalyzed carbonylation of aliphatic C-H bond utilizing 2-aminopyridylmethylamine (eq 1),[7a] and the Ru-catalyzed direct arylation of aromatic amides with aryl halides by talking advantage of 2-aminopyridylmethylamine and 8-aminoquinoline (eq 2). [7b]





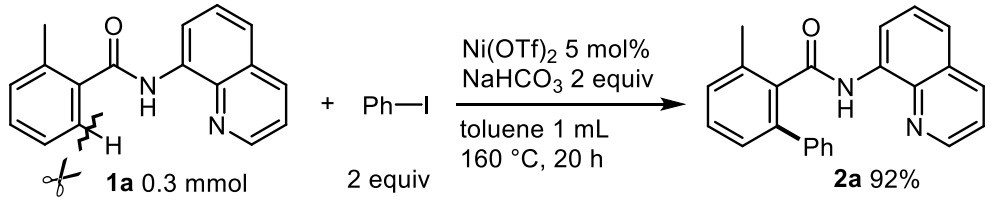
Chapter 1 describes the Ni(II)-catalyzed direct alkylation of aromatic amides with alkyl halides by talking advantage of *N*,*N*-bidentate directing chelation system. This reaction represents the first example of Ni-catalyzed direct alkylation of aromatic C-H bonds.

1.2. Results and Discussion

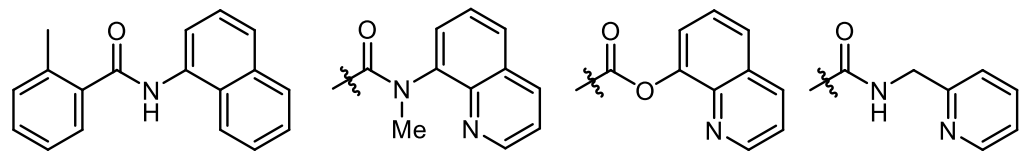
Motivated by previous our results and working hypothesis described in general introduction, various type of directing groups and additives were examined to find the new method for transformation of C-H bond with Ni(II)-catalyst. The arylation with aryl halide was examined as a preliminary experiment. The reaction of aromatic amide **1a** containing an 8-aminoqunoline moiety and iodobenzene in the presence of $Ni(OTf)_2$ and sodium bicarbonate furnished direct ortho-arlyation product **2a** in excellent yield (Scheme 1).[8] This result represented that the cleavage of non-activated aromatic C-H bonds with low reactive nickel-catalyst was achieved. Screening of directing groups were examined. The reaction with amide without qunoline nitrogen, *N*-methylated amide and corresponding ester were resulted in no reaction (Scheme 1). These results indicated that both of NH and quinolone nitrogen atoms are necessary for the transformation of C-H bond.

To expand the utility of the present chelation system, we examined the alkylation reaction using alkyl halides. When the amide **1a** was reacted with butyl bromide under the arylation condition,[8] the alkylation did not procced (entry 1 in Table 1). However, the addition of PPh_3 increased the alkylation product **3a** yield to 41% NMR yield, along with 54% of unreacted **1a** being recovered (entry 2). The yield was strongly depended on the choice of the base, and the sodium carbonate was chosen as a best base (entry 3). The use of PCy_3 decreased **3a** in 26% NMR yield (entry 6). The use of 2 equivalents of butyl bromide improved the yield of **3a** in 88% isolated yield (entry 7).

Scheme 1. The Ni-Catalyzed Direct Arylation with Iodide Benzene[a]

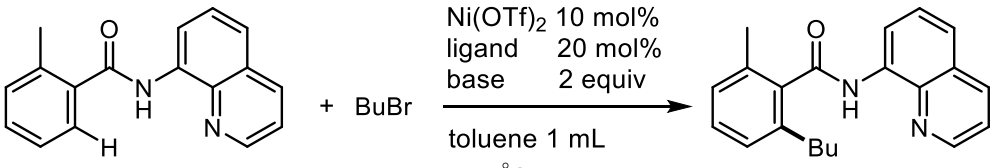


ineffective directing groups



[a] Isolated yields.

Table 1. The Nickel-Catalyzed Butylation of **1a** with Butyl Bromide



1a 0.3 mmol 0.45 mmol **3a**

entry	ligand	base	yields (**3a**/**1a**)[a]
1	none	$NaHCO_3$	0% / 101%
2	PPh_3	$NaHCO_3$	41% / 54%
3	PPh_3	Na_2CO_3	79% / 15%
4	PPh_3	Li_2CO_3	3% / 109%
5	PPh_3	K_2CO_3	0% / 90%
6	PCy_3	Na_2CO_3	26% / 63%
7[b]	**PPh_3**	**Na_2CO_3**	**91% (88%) / 0%**

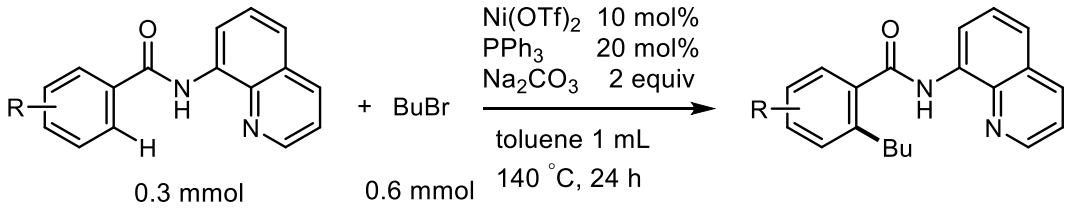
[a] NMR yields. The number in parenthesis is the isolated yield of **2a**. [b] BuBr (0.6 mmol) was used.

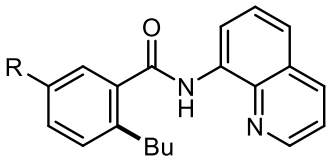
With the optimized reaction conditions in hand, we examined the scope of the substrate. Table 2 shows the results for reactions of various aromatic amides with butyl bromide under the standard reaction conditions. A variety of functional groups were found to be tolerated and, even the iodide was survived, as in **3h**. The reaction of meta-substituted substrates resulted in selective alkylation at the less hindered C-H bonds, irrespective of the electronic nature of the substituent. In general, electron-withdrawing groups tended to give butylation products in higher yields. The addition of NaI was found to improve the product yields in the reaction with electron donating substituents, as in **3b** and **3c**. The C-H bonds in heterocyclic compounds could be alkylated, as in **8**, **9** and **10**. This C-H bond alkylation reaction was applicable to α,β-unsaturated amides. The cyclic amides, **11**, **12**, and **13** gave the butylation products in good yields.

Various of alkyl halides, such as benzyl, allyl and methyl halide, were also applicable to this reaction (Table 3). Octyl iodide and octyl bromide gave the octylation product **24** in high yield. While no reaction took place in the case of octyl chloride, the addition of sodium iodide (2 equivalents) dramatically improved the product **24** yield to 88% isolated yield, generating the alkyl iodide in situ. This effect of sodium iodide was also observed in the reaction with sterically demanding alkyl bromides or some functionalized alkyl bromides. The use of 2-methylpropyl bromide and cyclopentylmethyl bromide without addition of sodium iodide resulted in almost no reaction, but the yields of **19** and **20** were dramatically improved to 44% and 45% yields when sodium iodide was added. While the reaction with methyl iodide gave the methylation product **29** and *N*-methylated product, the combination of methyl tosylate and sodium iodide gave the only methylation product **29** in excellent yields. The reaction of a cyclopentyl bromide under optimized reaction conditions gave only a trace amount of the

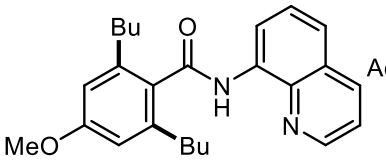
alkylation product **30**. After screening of the reaction conditions, using $IMes^{Me}$ and PPh_3 as the ligand improved the product **30** yield to 51%.[9]

Table 2. The Ni-Catalyzed Butylation of C(sp^2)-H Bonds[a]

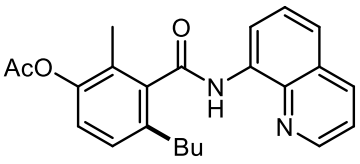




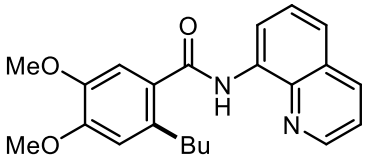
R = OMe **3b** 74% (89%)[b]
OCH$_2$Ph **3c** 72% (85%)[b]
OSiMe$_2$Bu^t **3d** 75%
Me **3e** 92%[c]
Ph **3f** 81%[c]
Cl **3g** 92%[d]
I **3h** 68%[d]
C(O)CH$_3$ **3i** 75%[c]
CF$_3$ **3j** 95%[c]



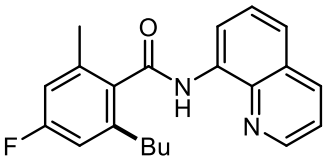
4 88%[c, e]



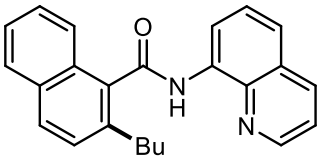
5 52%



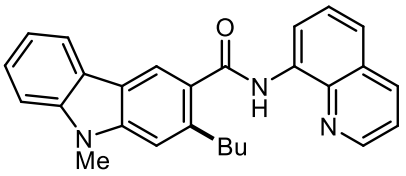
6 92%



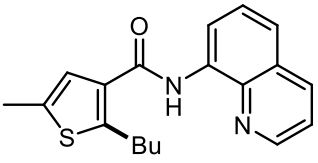
7 87%



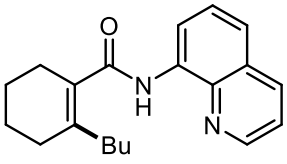
8 71%[c]



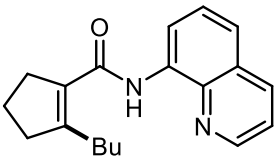
9 76%[c, e]



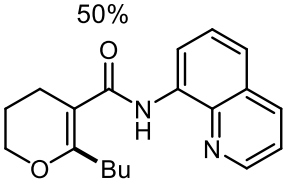
10 50%



11 81%



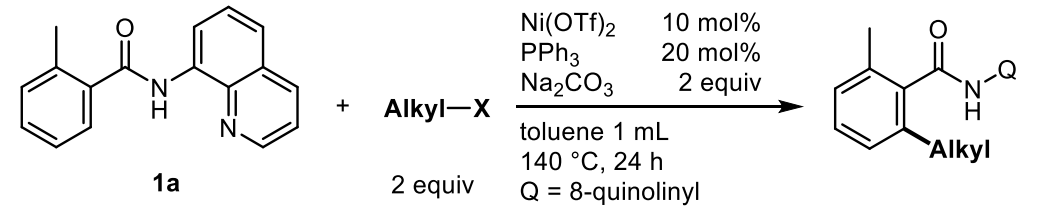
12 67%

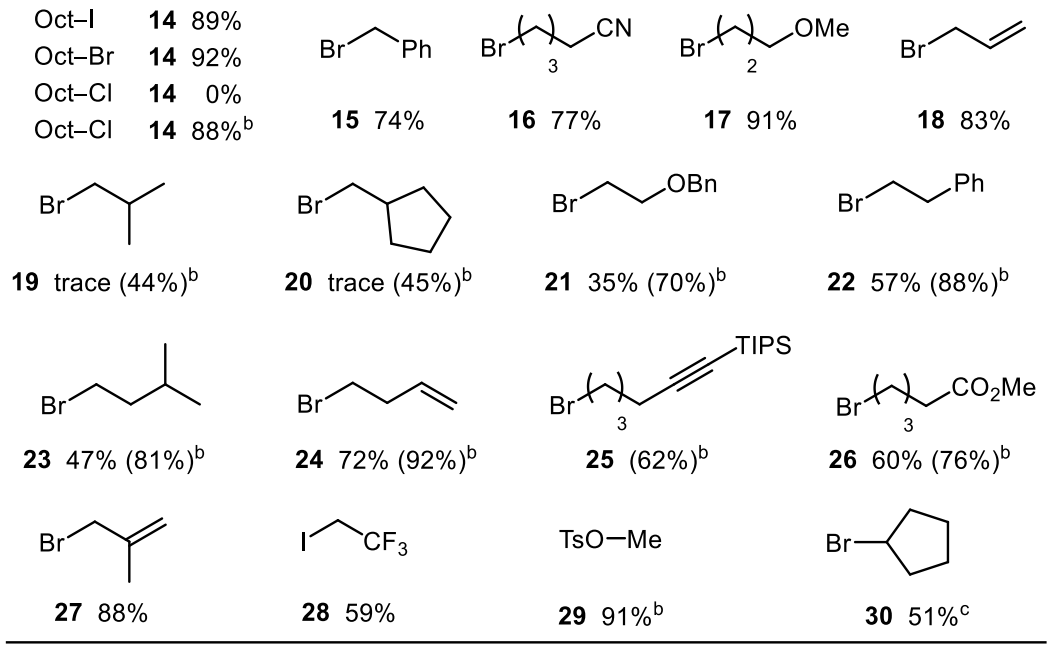


13 72%

[a] Reaction conditions: amide (0.3 mmol), BuBr (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. [b] NaI (0.6 mmol) was used as an additive. [c] Run at 160 °C. [d] BuI (0.6 mmol) was used instead of BuBr. [e] BuBr (1.2 mmol) was used.

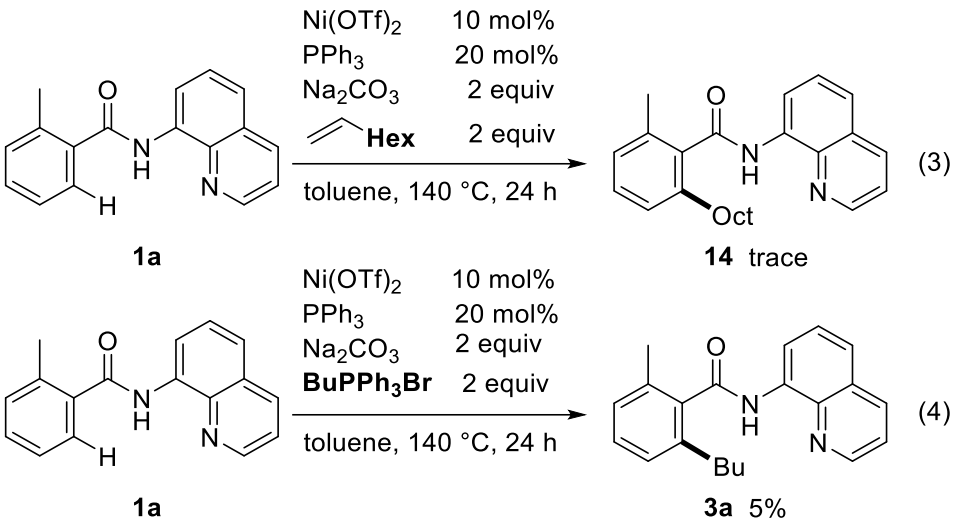
Table 3. The Ni-Catalyzed Alkylation of C-H Bonds in Aromatic Amides[a]





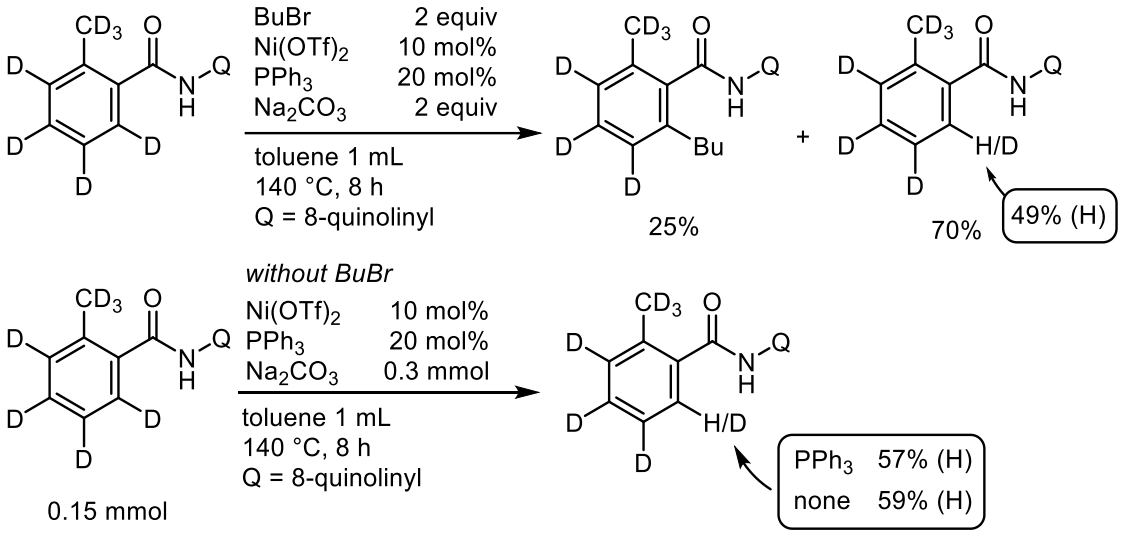
[a] Reaction conditions: amide (0.3 mmol), Aklyl halide (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. [b] NaI (0.6 mmol) was used as an additive. [c].$IMes^{Me}$ • HCl (0.06 mmol) and NaO^tBu (0.07 mmol) was added as a ligand.

Several mechanistic studies were carried out to gain mechanistic information. We anticipated that under the reaction conditions, the alkylation takes place via the addition of the C−H bond with the alkene, which may generate from an alkyl halide via dehydrobromination. However, when **1a** was reacted with octane resulted in no reaction (eq 3). A quaternary phosphonium bromide is also another candidate for alkylating reagent. However, the corresponding butylation product **3a** was obtained in only 5% yield (eq 4). These results indicate that the alkyl halide itself functions as a coupling partner.



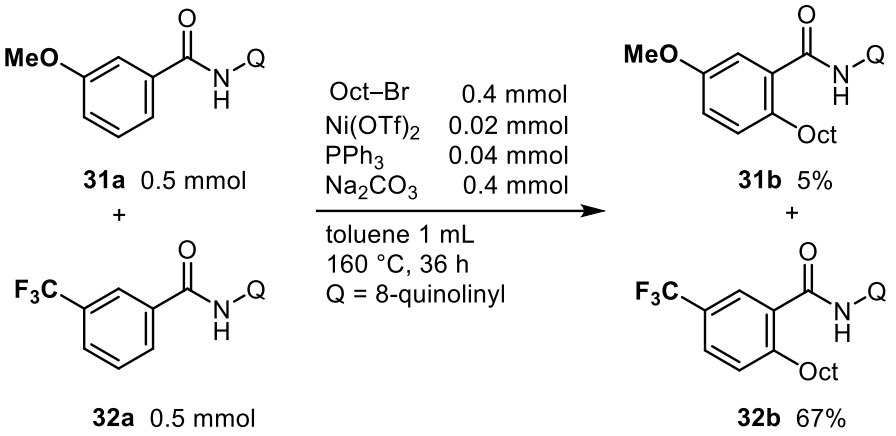
The deuterated amide **1a-d**$_7$ was reacted with BuBr for 8 h under the standard reaction condition (Scheme 2). A significant amount of H/D exchange at the ortho C-D bond (the d-content decreased from >98% to 51% (49%H)) and N-H on the amide nitrogen in the recovered amide was observed. A significant amount of H/D exchange occurred, even in the absence of BuBr, indicating that the cleavage of C-H bonds occurs before the reaction with an alkyl halide. It was also found that the presence of PPh_3 had no effect on the H/D exchange reaction. These results indicate that the cleavage of C-H bonds is reversible and rapid step and not likely the rate determining step in the reaction.

Scheme 2. Deuterium labeling experiments



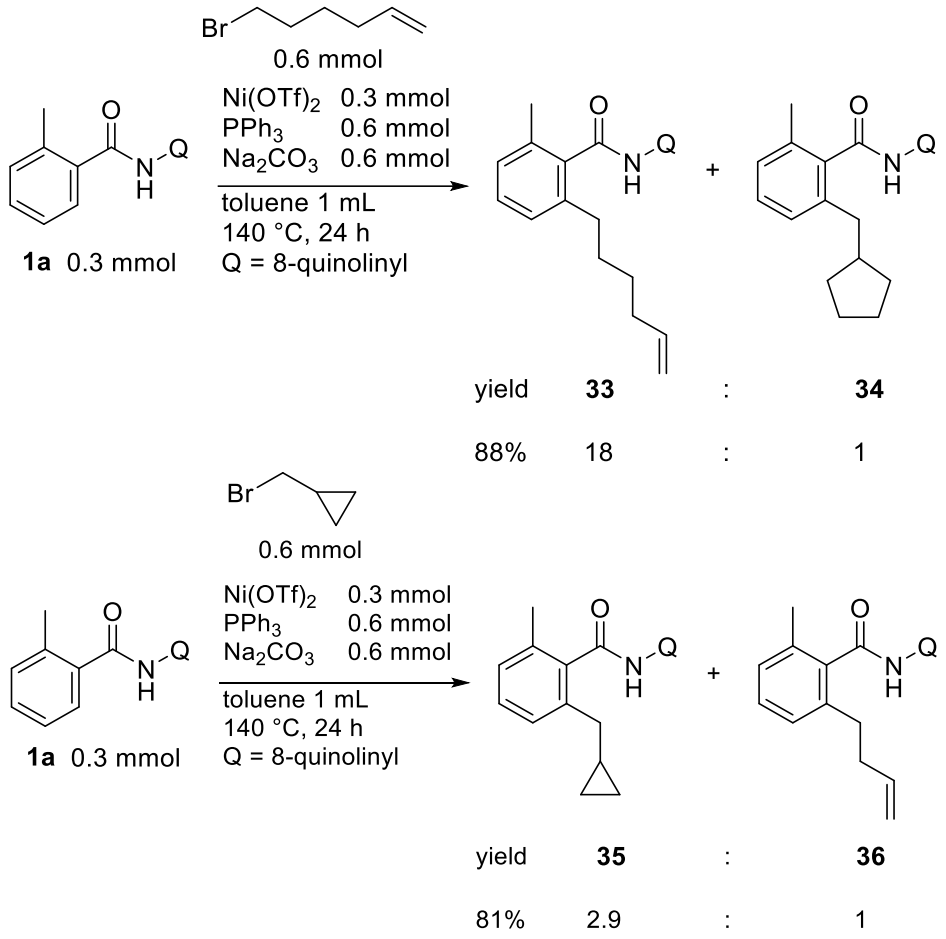
We next performed a competition experiment using a 1:1 mixture of **31a** and **32a** in a reaction with octyl bromide (Scheme 3). The findings indicate that **32a** reacted to give **32b** as the major product. This result indicates that the presence of an electronic withdrawing group on aromatic amides facilitates the reaction.

Scheme 3. Competition experiment



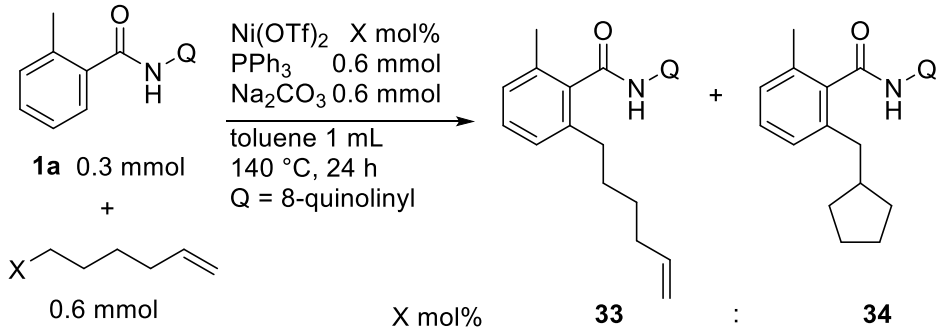
To confirm the alkyl radical species, which were generated single electron transfer from nickel complex to alkyl halides were involved this reaction. The addition of radical scavengers were examined. The reaction in the presence of radical scavengers, such as TEMPO (2 equivalents) and GALVINOXYL (2equivalents), resulted in no reaction. The radical clock experiments were carried out to gain more information. The use of 6-bromohex-1-ene gave the mixture of products, and the unrearranged alkylation product **33** was the major product (Scheme 4). We next used cyclopropylmethyl bromide, since the cyclopropylmethyl radical is known to undergo ring-opening faster than the cyclization of the 5-hexenyl radical.[10] The reaction with cyclopropylmethyl bromide gave a mixture of the unrearranged product **35** and the rearranged product **36** in a total isolated yield of 81% in favor of the unrearranged product (Scheme 4).

Scheme 4. Radical clock experiments



We next examined the effect of catalyst concentration on the ratio of products in the reaction of **1a** with 6-bromohex-1-ene. If a radical chain mechanism were operative, then the **33**/**34** ratio would increase at higher catalyst concentrations because the radical would have less time to rearrange before reacting with another nickel.[11] In contrast, if a radical chain were not involved, the **33**/**34** ratio would be expected to be unchanged as a function of catalyst concentration. The ratio was found to be constant, irrespective of the catalyst concentration used (Scheme 5), suggesting that the radical chain mechanism is not operative. These results shown in Scheme 4 and 5 suggest that free radical species are not involved in the reaction. The possibility that the key intermediate has a radical character, but that a radical species is not free, but instead remains in the coordination sphere in a nickel center and rearrangement from alkyl nickel complex cannot be excluded.

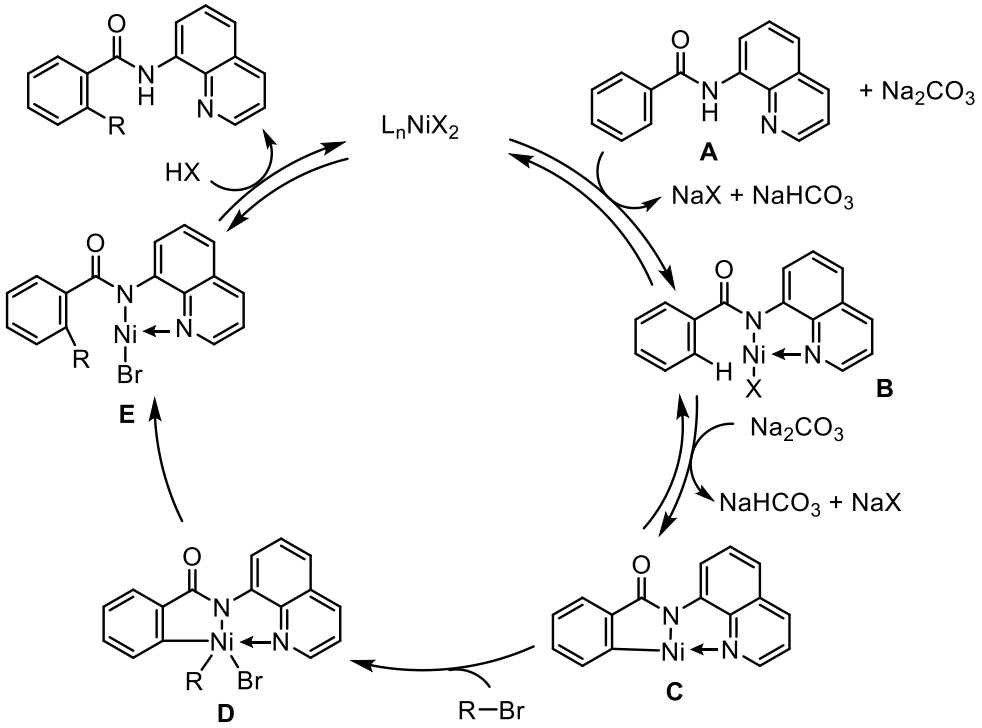
Scheme 5. Dependence of the ratio of **33** and **34** on the concentration of nickel



X mol%	**33**	:	**34**
5 mol%	20	:	1
10 mol%	18	:	1
15 mol%	19	:	1

The ratio of product was determined by ^{1}H-NMR.

Scheme 6. Proposed reaction mechanism



The alkylation of C-H bonds proceeds through a mechanism as shown in Scheme 6. Amide **A** coordinates to NiX_2 followed by a ligand exchange, which is accelerated by sodium carbonate, to give the nickel complex **B**. Complex **B** then undergoes a reversible cyclometalation to give complex **C** via a concerted metalation deprotonation (CMD) mechanism, which is also accelerated by sodium carbonate. The oxidative addition of an alkyl halide to the complex **C** gives the nickel(IV) species **D**.[12] Complex **D** undergoes a reductive

elimination to give **E**, which is then protonated to afford the alkylation product with the regeneration of the nickel(II) catalyst.

1.3 Conclusion

In summary, we have reported the development of a new catalytic system that takes advantage of chelation assistance by an 8-aminoquinoline moiety. This represents the first example of Ni(II)-catalyzed direct ortho-alkylation of benzamides and acrylamide derivatives with unactivated alkyl halides. Various groups, such as alkyl, allyl, benzyl, and methyl groups can be introduced at the ortho position. A variety of functional groups are tolerated in the reaction. The proposed mechanism involves a Ni(II)/Ni(IV) catalytic cycle, which is rare in nickel-catalyzed cross coupling reaction.[13] The key intermediate appears to have a radical character, but the reaction probably does not proceed via a radical chain mechanism.

After this paper appeared, another groups have reported the Ni(II)-catalyzed direct alkylation with alkyl halides, such as the direct alkylation of C(sp^3)-H bonds,[14a] alkylation with secondary alkyl halides,[9] allyl halides[14c] and phosphates[14b] as alkylating reagents by utilizing the nickel(II)-catalyst and 8-aminoquinoline system.

1.4 Experimental Section

General Information.

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. The data is reported as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad peak, and m = multiplet), coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a Horiba FT-700 spectrometer. Absorption is reported in reciprocal centimeters (cm-^{1}) with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained on a Shimadzu GCMS-QP 2010 instrument. High resolution mass spectra (HRMS) were obtained using a JEOL JMS-DX303 spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SilicaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

Materials.

Na_2CO_3 (CAS 497-19-8) was purchased from Nacalai Tesque, Inc. Iodobenzene (CAS 591-50-4), 1-bromobutane (CAS 109-65-9) and 8-Aminoquinoline (CAS 578-66-5), were purchased from Tokyo Kasei Kogyo Co., Ltd. PPh_3 (CAS 603-35-01) and toluene super dehydrated (CAS 68-12-2) was purchased from Wako Pure Chemicals.

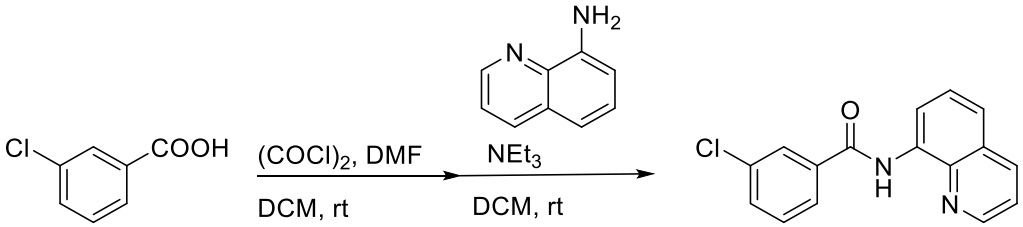
Synthesis of Nickel(II) Trifluoromethanesulfonate .

To a clear green solution of $Ni(OAc)_2$ (0.519 g, 2.95 mmol) in MeCN (40 mL) trifluoromethanesulfonic acid (1.33 g, 8.84 mmol) was added dropwise; the color changed the blue. The mixture was evaporated under reduced pressure until 10 mL, diethyl ether (80 mL) was added, this resulted in precipitation of blue powder. The suspension was decanted, and the residual powder washed diethyl ether and hexane, and dried in vacuum at 70 °C; the color changed light green powder. $Ni(OTf)_2$ was obtained in 72% (0.754 g). HRMS Calcd for $C_2F_6O_6S_2Ni$: 355.8394; Found: 355.8401.

Synthesis of the Starting Amides.

All amides containing an 8-aminoquinoline were prepared by the reaction of the corresponding acid chlorides and 8-aminoquinoline. All starting amides were synthesize following general procedure. All spectrum data of starting amides are cited in original paper.[15]

General Procedure for the Preparation of Starting Amide.



To an oven-dried 100 mL three-necked flask, 3-bromobenzoic acid (2.3 g, 15 mmol), DMF (5 drops) and DCM (30 mL) were added under a N_2 atmosphere. Oxalyl chloride (1.5 mL, 18 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 (2.9 g, 20 mmol, 1.3 equiv.), Et_3N (4.1 mL, 30 mmol, 2 equiv.) and DCM (30 mL) were added. A solution of the acid chloride in DCM (10 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. $NaHCO_3$ (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 $MgSO_4$, filtered and evaporated *in vacuo*. The resulting crude amide was purified by column chromatography on silica gel (eluant: hexane/EtOAc = 5/1) to afford the desired amide.

General Procedure for Direct Arylation: Ni-Catalyzed Reaction of Amide 1a with PhI.

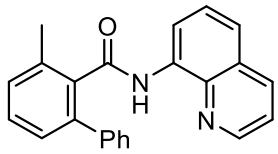
To an oven-dried 5 mL screw-capped vial, in a glove box 2-methyl-N-(8-quinolinyl)benzamide **1a** (79 mg, 0.3 mmol), iodobenzene (122 mg, 0.6 mmol), $Ni(OTf)_2$ (5 mg, 0.015 mmol), $NaHCO_3$ (50 mg, 0.6 mmol) and toluene (1 mL) were added. The mixture was stirred for 20 h at 160 °C followed by cooling. The 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 arylated product **2a** (97 mg, 94%) as a colorless oil.

General Procedure for Direct Alkylation: Ni-Catalyzed Alkylation of Amides 1a with BuBr

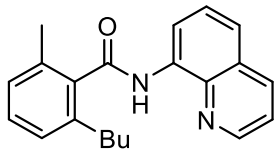
To an oven-dried 5 mL screw-capped vial, in a glove box 2-methyl-N-(8-quinolinyl)benzamide **1a** (79 mg, 0.3 mmol), 1-bromobutane (82 mg, 0.6 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (15.6 mg, 0.06 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and toluene (1 mL) were added. The mixture was stirred for 24 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= 20/1) to afford the desired alkylated product **3a** (84 mg, 88%) as a colorless oil.

3-Methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (2a) [CAS 1436849-34-1].



R_f 0.23 (hexane/EtOAc = 5/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) 2.53 (s, 3H), 7.08 (t, J = 8.0 Hz, 1H), 7.19-7.24 (m, 2H), 7.28-7.33 (m, 3H), 7.38-7.54 (m, 5H), 8.04 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 4.0 Hz, 1H), 8.77 (d, J = 7.6 Hz, 1H), 9.64 (brs, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) 19.94, 116.54, 121.57, 121.79, 127.34, 127.37, 127.74, 127.86, 128.29, 128.75, 129.32, 129.61, 134.48, 135.94, 136.18, 136.96, 138.45, 139.77, 140.48, 148.08, 168.41;

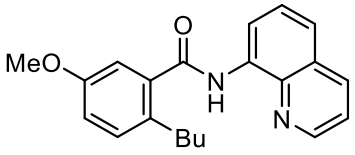
2-Butyl-6-methyl-*N*-(quinolin-8-yl)benzamide (3a).



Rf 0.43 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.80 (t, J = 7.6 Hz, 3H), 1.25-1.34 (m, 2H), 1.64-1.70 (m, 2H), 2.43 (s, 3H), 2.71 (t, J = 8.0 Hz, 2H), 7.13 (dd, J =12, 4.0 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.45 (dd, J = 8.0, 4.0 Hz, 1H), 7.56-7.64 (m, 2H), 8.19 (dd, J = 8.0, 1.6 Hz, 1H), 8.74 (dd, J = 4.0, 1.6 Hz, 1H), 8.99 (dd, J = 7.2, 1.6 Hz, 1H), 9.94 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.92, 20.94, 22.62, 32.66, 33.98, 116.65, 121.67, 121.69, 127.48, 128.00, 130.26, 134.78, 135.52, 136.42, 138.16, 138.51, 148.15, 168.69; IR (neat) 3347 w, 2954 w, 2864 w, 1675 m, 1518 s, 1481 s, 1423 m, 1384 m, 1325 m, 1262 m, 1126 w, 897 w, 826 m; MS *m/z* (relative intensity, %) 318 (M^+, 35), 176

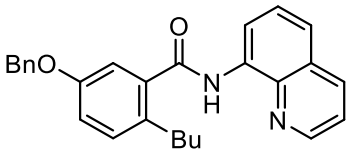
(12), 175 (100), 174 (32), 146 (11), 145 (38), 144 (12), 105 (26); HRMS Calcd for $C_{23}H_{18}N_2O$: 318.1732; Found: 318.1733.

2-Butyl-5-methoxy-*N*-(quinolin-8-yl)benzamide (3b).



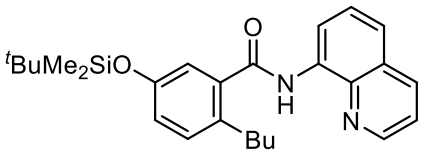
Rf 0.31 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.85 (t, J = 7.2 Hz, 3H), 1.28-1.38 (m, 2H), 1.61-1.69 (m, 2H), 2.84 (t, J = 8.0 Hz, 2H), 3.84 (s, 3H), 6.97 (dd, J = 8.0, 2.8 Hz, 1H), 7.17 (d, J = 2.8 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 8.0, 4.0 Hz, 1H), 7.54-7.62 (m, 2H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 8.77 (dd, J = 4.0, 1.2 Hz, 1H), 8.94 (d, J = 7.2 Hz, 1H), 10.15 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.90, 22.55, 32.24, 34.07, 55.45, 112.51, 115.98, 116.64, 121.64, 121.74, 127.40, 127.96, 131.41, 133.08, 134.67, 136.32, 137.45, 138.52, 148.20, 157.51, 168.21; IR (neat) 3349 w, 2954 w, 2858 w, 1675 m, 1607 w, 1575 w, 1520 s, 1481 s, 1423 m, 1384 m, 1325 m, 1285 m, 1107 m, 1040 m, 825 m; MS *m/z* (relative intensity, %) 335 (11), 334 (M^+, 45), 191 (25), 190 (37), 162 (17), 161 (100), 149 (22), 144 (19), 121 (27); HRMS Calcd for $C_{21}H_{22}N_2O_2$: 334.1681; Found: 334.1682.

5-(Benzyloxy)-2-butyl-*N*-(quinolin-8-yl)benzamide (3c).



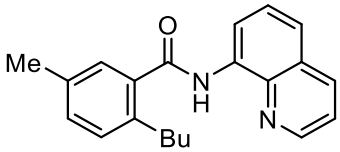
Rf 0.23 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.85 (t, J = 7.2 Hz, 3H), 1.28-1.38 (m, 2H), 1.61-1.69 (m, 2H), 2.84 (t, J = 7.6 Hz, 2H), 5.09 (s, 2H), 7.04 (dd, J = 8.8 , 2.8 Hz, 1H), 7.23-7.27 (m, 2H), 7.30-7.53 (m, 6H), 8.16 (dd, J = 8.0, 1.6 Hz, 8.76 (dd, J = 4.0, 1.6 Hz, 1H), 8.94 (d, J = 7.2 Hz, 1H), 10.15 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.91, 22.56, 32.25, 34.04, 70.20, 113.51, 116.53, 116.77, 121.63, 121.77, 127.37, 127.54, 127.93, 128.02, 128.59, 131.46, 133.47, 136.29, 136.70, 137.45, 138.52, 148.21, 156.72, 168.10; IR (neat) 3348 w, 2954 w, 2860w, 1674 m, 1604 w, 1574 w, 1520 s, 1481 s, 1423 m, 1383 m, 1352 m, 1325 m, 1285 m, 1024 w, 825 m; MS *m/z* (relative intensity, %) 410 (M^+, 20), 319 (17), 267 (10), 266 (14), 237 (19), 144 (10), 91 (100); HRMS Calcd for $C_{27}H_{26}N_2O_2$: 410.1994; Found: 410.1994.

2-Butyl-5-((tert-butyldimethylsilyl)oxy)-*N*-(quinolin-8-yl)benzamide (3d).



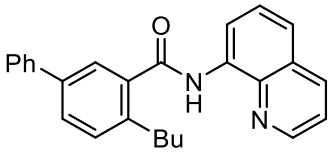
Rf 0.54 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.25 (s, 6H), 0.86 (t, J = 7.2 Hz, 3H), 1.01 (s, 9H), 1.29-1.38 (m, 2H), 1.61-1.69 (m, 2H), 2.84 (t, J = 8.0 Hz, 2H), 6.90 (dd, J = 8.0, 2.8 Hz, 1H), 7.13 (d, J = 2.8 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.0, 4.0 Hz, 1H), 7.53-7.61 (m, 2 H), 8.16 (dd, J = 8.0, 1.6 Hz, 1H), 8.77 (dd, J = 4.0, 1.6 Hz, 1H), 8.93 (d, J = 6.4 Hz, 1H), 10.17 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ -4.44, 13.93, 18.17, 22.59, 25.66, 32.28, 34.03, 116.44, 118.70, 121.63, 121.68, 121.95, 127.94, 131.44, 134.02, 134.72, 136.28, 137.32, 138.55, 148.18, 153.49, 168.06; IR (neat) 3350 w, 2954w, 2858 w, 1678 m, 1603 w, 1522 s, 1482 s, 1424 m, 1385 m, 1326 m, 1290 m, 1257 m, 973 m, 889 m, 837 s; MS *m/z* (relative intensity, %) 435 (21), 434 (M^+, 63), 292 (13), 291 (52), 262 (26), 261 (100), 249 (11), 234 (11), 233 (32), 215 (42), 205 (17), 174 (20), 171 (10), 165 (19), 163 (20), 144 (22), 73 (66); HRMS Calcd for $C_{23}H_{18}N_2O$: 434.2390; Found: 434.2388.

2-Butyl-5-methyl-*N*-(quinolin-8-yl)benzamide (3e).



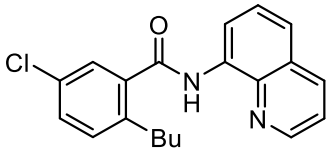
Rf 0.40 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.85 (t, J = 7.6 Hz, 3H), 1.29-1.38 (m, 2H), 1.62-1.70 (m, 2H), 2.39 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H), 7.20-7.25 (m, 2H), 7.44-7.47 (m, 2H), 7.54-7.62 (m, 2H), 8.18 (dd, J = 7.6, 1.6 Hz, 1H), 8.78 (dd, J = 4.0, 1.6 Hz, 1H), 8.95 (d, J = 7.6 Hz, 1H), 10.13 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.92, 20.94, 22.62, 32.67, 33.98, 116.65, 121.61, 121.69, 127.48, 127.83, 128.00, 130.26, 130.88, 134.78, 135.52, 136.42, 136.58, 138.16, 138.51, 148.15, 168.69; IR (neat) 3351 w, 2955 w, 2860 w, 1673 m, 1596 w, 1518 s, 1481 s, 1423 m, 1383 m, 1325 m, 1262 w, 824 m; MS *m/z* (relative intensity, %) 319 (13), 318 (M^+, 54), 175 (45), 174 (22), 146 (17), 145 (100), 144 (26), 133 (13), 105 (33); HRMS Calcd for $C_{21}H_{22}N_2O$: 318.1732; Found: 318.1734.

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



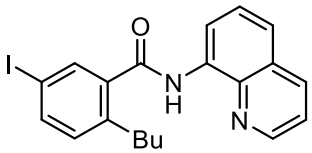
Rf 0.40 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.88 (t, J = 7.2 Hz, 3H), 1.34-1.43 (m, 2H), 1.69-1.76 (m, 2H), 2.94 (t, J = 7.6 Hz 2H), 7.34-7.47 (m, 4H), 7.55-7.68 (m, 5H), 7.85 (d, J = 2.0 Hz, 1H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 8.75 (dd, J = 4.0, 1.6 Hz, 1H), 8.98 (d, J = 7.2 Hz, 1H), 10.21 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.93, 22.66, 32.76, 33.87, 116.58, 121.17, 121.81, 125.86, 127.00, 127.40, 127.95, 128.70, 128.84, 130.08, 134.69, 136.31, 137.19, 138.53, 138.89, 140.21, 140.29, 148.25, 168.41; IR (neat) 3348 w, 2955 w, 2860 w, 1674 m, 1519 s, 1481 s, 1423 m, 1384 m, 1326 m, 1244 w, 825 m; MS *m/z* (relative intensity, %) 381 (16), 380 (M^+, 54), 237 (40), 236 (32), 208 (24), 207 (100), 165 (12), 178 (12), 167 (33), 166 (11), 165 (21), 152 (10), 144 (18); HRMS Calcd for $C_{26}H_{24}N_2O$: 380.1889; Found: 380.1890.

2-Butyl-5-chloro-*N*-(quinolin-8-yl)benzamide (3g).



Rf 0.37 (hexane/EtOAc = 5/1). White Solid. Mp = 79-80 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.86 (t, J = 7.6 Hz, 3H), 1.29-1.38 (m, 2H), 1.61-1.69 (m, 2H), 2.86 (t, J = 7.6 H, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.0, 2.4 Hz, 1H), 7.47 (dd, J = 8.0, 4.4 Hz, 1H), 7.56-7.63 (m, 2H), 8.19 (dd, J = 8.0, 1.6 Hz, 1H), 8.79 (dd, J = 4.4, 1.6 Hz, 1H),8.91 (dd, J = 7.6, 1.6 Hz, 1H), 10.13 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.87, 22.54, 32.51, 33.74, 116.72, 121.74, 122.07, 127.19, 127.37, 127.95, 130.14, 131.54, 131.75, 134.38, 136.42, 138.04, 138.43, 139.77, 148.31, 166.92; IR (neat) 3343 w, 2956 w, 2867 w, 1677 m, 1521 s, 1482 s, 1424 m, 1385 m, 1326 m, 1259 w, 1120 w, 824 m; MS *m/z* (relative intensity, %) 338 (17), 339 (12), 338 (M^+, 49), 311 (11), 309 (32), 195 (13), 167 (32), 166 (12), 165 (100), 153 (13), 144 (66), 142 (11), 130 (11), 125 (28), 116 (11), 89 (12); HRMS Calcd for $C_{20}H_{19}ClN_2O$: 338.1186; Found: 338.1186.

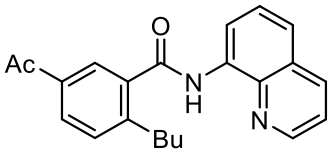
2-Butyl-5-iodo-*N*-(quinolin-8-yl)benzamide (3h).



Rf 0.37 (hexane/EtOAc = 5/1). White Solid. Mp = 101 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.85 (t, J = 7.6 Hz, 3H), 1.28-1.38 (m, 2H), 1.61-1.68 (m, 2H), 2.83 (t, J = 7.6 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 7.47 (dd, J = 8.0, 4.0 Hz, 1H), 7.56-7.62 (m, 2H), 7.72 (dd, J = 8.0, 1.6 Hz, 1H), 7.93 (d, J = 1.2 Hz, 1H), 8.19 (dd, J = 8.0, 1.6 Hz, 1H), 8.79 (dd, J = 4.0, 1.6 Hz, 1H), 8.90 (dd, J = 7.6, 1.6 Hz, 1H), 10.10 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.86, 22.53, 32.66, 33.62, 90.43, 116.71, 121.73, 122.06, 127.35, 127.93, 132.21, 134.35, 135.75,

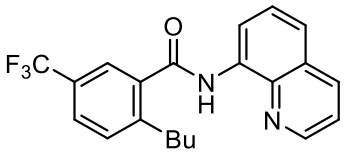
136.39, 138.40, 138.76, 138.99, 140.82, 148.30, 166.62; IR (neat) 3342 w, 2955 w, 2865 w, 1675 m, 1521 s, 1483 s, 1423 m, 1384 m, 1326 m, 1259 m, 905 w, 825 m; MS *m/z* (relative intensity, %) 431 (17), 430 (M^+, 78), 401 (29), 287 (17), 286 (13), 258 (12), 257 (100), 245 (10), 217 (13), 194 (11), 145 (11), 144 (63), 142 (15), 130 (15), 117 (14), 116 (22), 115 (10), 102 (10), 90 (18), 89 (14); HRMS Calcd for $C_{20}H_{19}IN_2O$: 430.0542; Found: 430.0539.

5-Acetyl-2-butyl-*N*-(quinolin-8-yl)benzamide (3i).



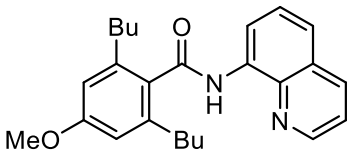
Rf 0.11 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 88-90 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.87 (t, J = 7.6 Hz, 3H), 1.32-1.41 (m, 2H), 1.66-1.74 (m, 2H), 2.64 (s, 3H), 2.96 (t, J = 7.6 Hz, 2H), 7.43-7.48 (m, 2H), 7.57-7.64 (m, 2H), 8.01 (dd, J = 8.0, 1.6 Hz, 1H), 8.19 (dd, J = 8.0, 1.6 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.78 (dd, J = 4.0, 1.6 Hz, 1H), 8.93 (dd, J = 7.6, 1.6 Hz, 1H), 10.19 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.83, 22.60, 26.60, 33.22, 33.52, 116.69, 121.73, 122.08, 127.33, 127.94, 129.76, 130.66, 134.39, 134.92, 136.37, 137.01, 138.44, 146.91, 148.31, 167.46, 197.10; IR (neat) 3346 w, 2956 w, 2867 w, 1677 s, 1600 w, 1521 s, 1482 m, 1424 m, 1385 w, 1326 m, 1226 m, 826 m; MS *m/z* (relative intensity, %) 347 (15), 346 (M^+, 62), 317 (23), 203 (21), 174 (15), 173 (100), 145 (10), 144 (42); HRMS Calcd for $C_{22}H_{22}N_2O_2$: 346.1681; Found: 346.1684.

2-Butyl-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (3j).



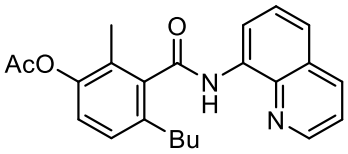
Rf 0.40 (hexane/EtOAc = 5/1). White Solid. Mp = 94-95 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.87 (t, J = 7.2 Hz, 3H), 1.29-1.40 (m, 2H), 1.68-1.74 (m, 2H), 2.95 (t, J = 7.6 Hz, 2H), 7.45-7.549 (m, 2H), 7.58-7.88 (m, 3H), 7.88 (s, 1H), 8.20 (dd, J = 8.0, 2.0 Hz, 1H), 8.79 (dd, J = 4.0, 1.6 Hz, 1H), 8.92 (dd, J = 7.2, 1.6 Hz, 1H), 10.17 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.82, 22.59, 29.69, 33.01, 33.59, 116.86, 121.77, 122.21, 124.7 (d, J = 3.9 Hz), 123.89 (q, J = 271 Hz), 126.74 (d, J = 2.8 Hz), 127.38, 127.99, 128.68 (q, 33.4 Hz), 130.83, 134.31, 145.35, 148.37, 166.98; IR (neat) 3343 w, 2958 w, 2870 w, 1678 m, 1523 s, 1484 m, 1424 w, 1386 w, 1327 s, 1215 w, 1169 m, 1123 s, 1079 m, 826 m; MS *m/z* (relative intensity, %) 373 (14), 372 (M^+, 64), 344 (11), 343 (54), 200 (16), 199 (94), 171 (12), 159 (22), 145 (14), 144 (100); HRMS Calcd for $C_{21}H_{19}F_3N_2O$: 372.1449; Found: 372.1452.

2,6-Dibutyl-4-methoxy-*N*-(quinolin-8-yl)benzamide (4).



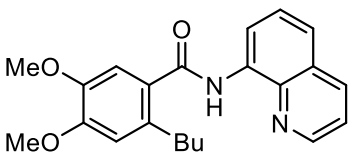
Rf 0.34 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.81 (t, J = 7.6 Hz, 6H), 1.24-1.33 (m, 4H), 1.62-1.70 (m, 4H), 2.69 (t, J = 8.0 Hz, 4H), 3.88 (s, 3H), 6.68 (s, 2H), 7.43 (dd, J = 8.0, 4.0 Hz, 1H), 7.54-7.62 (m, 2H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 8.72 (dd, J = 4.0, 1.6 Hz, 1H), 8.97 (dd, J = 8.0, 1.2 Hz, 1h), 9.90 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.82, 22.62, 33.39, 33.69, 55.17, 111.98, 116.57, 121.58, 121.70, 127.95, 130.59, 134.50, 136.24, 138.45, 141.37, 148.13, 159.73, 168.92; IR (neat) 3352 w, 2954 w, 1673 m, 1600 m, 1517 s, 1480 s, 1423 m, 1383 m, 1323 s, 1155 s, 826 m; MS *m/z* (relative intensity, %) 390 (M^+, 7), 249 (17), 248 (100); HRMS Calcd for $C_{25}H_{30}N_2O_2$: 390.2304; Found: 390.2307.

4-Butyl-2-methyl-3-(quinolin-8-ylcarbamoyl)phenyl acetate (5).



Rf 0.20 (hexane/EtOAc = 5/1). White Solid. Mp = 122-123 °C.. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.79 (t, J = 7.6 Hz, 3H), 1.24-1.33 (m, 2H), 1.61-1.69 (m, 2H), 2.24 (s, 3H), 2.34 (s, 3H), 2.69 (t, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.44 (dd, J = 8.0, 4.0 Hz, 1H), 7.56-7.63 (m, 2H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 8.75 (dd, J = 4.0, 1.6 Hz, 1H), 8.97 (dd, J = 8.0, 1.6 Hz, 1H), 9.96 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.22, 13.79, 20.82, 22.55, 32.83, 33.65, 116.77, 121.70122.06, 122.63, 126.75, 127.30, 127.93, 134.22, 136.24, 137.25, 138.45, 139.06, 147.27, 148.31, 167.76, 169.44; IR (neat) 3346 w, 2956 w, 2867 w, 1763 w, 1675 m, 1598 w, 1519 s, 1482 s, 1424 m, 1384 m, 1325 m, 1262 w, 1204 w, 1138 w, 826 w; MS *m/z* (relative intensity, %) 377 (15), 376 (M^+, 60), 235 (15), 233 (100), 232 (52), 203 (43), 191 (54), 190 (29), 162 (10), 161 (36), 149 (14), 145 (10), 144 (29), 121 (25), 91 (11);. HRMS Calcd for $C_{23}H_{24}N_2O_3$: 376.1787; Found: 376.1786.

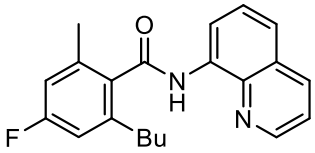
2-Butyl-4,5-dimethoxy-*N*-(quinolin-8-yl)benzamide (6).



Rf 0.11 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.88 (t, J = 7.6 Hz, 3H), 1.32-1.40 (m, 2H), 1.67-1.74 (m, 2H), 2.89 (t, J = 8.0 Hz, 2H), 3.92 (s, 3H), 3.95 (s, 3H), 6.800 (s, 1H), 7.19 (s, 1H), 7.45 (dd, J = 8.0, 4.0 Hz, 1H), 7.53-7.62 (m, 2H), 8.17 (dd,

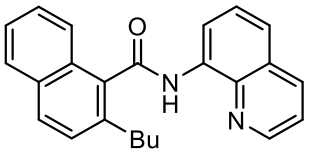
J = 8.0, 1.6 Hz, 1H), 8.78 (dd, J = 4.0, 1.6 Hz, 1H), 8.93 (dd, J = 7.6, 1.2 Hz, 1H), 10.16 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.26, 22.62, 32.95, 34.26, 55.90, 56.06, 110.85, 112.91, 116.37, 121.56, 121.57, 127.38, 127.92, 128.46, 134.60, 134.76, 136.38, 138.52, 146.77, 148.14, 150.29, 160.99; IR (neat) 3353 w, 2955 w, 1669 m, 1604 w, 1511 s, 1481 s, 1462 s, 1423 m, 1382 m, 1325 m, 1261 s, 1210 s, 1153 s, 824 m; MS *m/z* (relative intensity, %) 364 (M^+, 27), 222(14), 221 (100), 220 (25), 192 (12), 191 (65), 179 (15), 151 (13); HRMS Calcd for $C_{22}H_{24}N_2O_3$: 364.1787; Found: 364.1789.

2-Butyl-4-fluoro-6-methyl-*N*-(quinolin-8-yl)benzamide (7).



Rf 0.40 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.80 (t, J = 7.6 Hz, 3H), 1.24-1.33 (m, 2H), 1.61-1.69 (m, 2H), 2.42 (s, 3H), 2.71 (t, J = 7.6 Hz, 2H), 6.83 (t, J = 10.8 Hz, 2H), 7.45 (dd, J = 8.4, 4.0 Hz, 1H), 7.56-7.63 (m, 2H), 8.18 (dd, J = 8.4, 2.0 Hz, 1H), 8.74 (dd, J = 4.8, 2.0 Hz, 1H), 8.97 (dd, J = 8.0, 2.0 Hz, 1H), 9.91 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.78, 19.59, 22.46, 33.07, 33.39, 113.24 (d, J = 21 Hz), 114.44 (d, J = 21.0 Hz), 116.73 , 121.68, 122.02, 127.35, 127.96, 133.91 (d, J = 2.8 Hz), 134.23, 136.32, 13137.33 (d, J = 8.6 Hz), 138.42, 142.142.33 (d, J = 7.6 Hz), 148.28, 162.64 (d, J = 246 Hz), 168.11; IR (neat) 3343 w, 2955 w, 2866 w, 1761 m, 1676 m, 1519 s, 1481 s, 1424 m, 1384 m, 1325 m, 1200 s, 898 m, 827 m; MS *m/z* (relative intensity, %) 337 (10), 336 (M^+, 40), 194 (13), 193 (100), 192 (26), 164 (11), 163 (11), 144 (14), 137 (13), 123 (17); HRMS Calcd for $C_{21}H_{21}FN_2O$: 336.1638; Found: 336.1636.

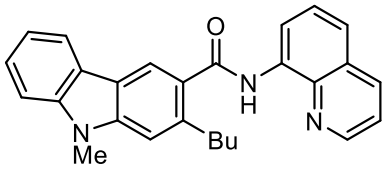
2-Butyl-*N*-(quinolin-8-yl)-1-naphthamide (8).



Rf 0.34 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.82 (t, J = 7.6 Hz, 3H), 1.31-1.37 (m, 2H), 1.74-1.78 (m, 2H), 2.89 (t, J = 8.0 Hz, 2H), 7.38-7.49 (m, 4H), 7.58 (dd, J = 8.0, 1.6 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.83-7.88 (m, 2H), 7.98-8.00 (m, 1H), 8.16 (dd, J = 8.0, 2.0 Hz, 1H), 8.65 (dd, J = 4.0, 2.0 Hz, 1H9, 9.13 (d, J = 7.6 Hz, 1H), 10.13 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.87, 22.68, 33.60, 33.81, 116.81, 121.65, 122.02, 124.90, 125.56, 126.93, 127.41, 127.51, 127.92, 127.98, 129.21, 130.27, 131.81, 133.91, 134.49, 136.26, 137.19, 138.44, 148.20, 168.41; IR (neat) 3343 w, 2954 m, 2862 m, 1672 s, 1596 w, 1517 s, 1481 s, 1423 m, 1383 m, 1325 m, 1257 w, 1212 w, 892 w, 823 m;

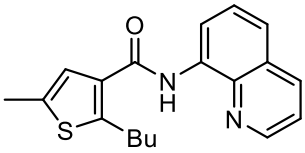
MS *m/z* (relative intensity, %) 354 (M^+, 34), 212 (17), 211 (100), 210 (35), 182 (13), 181 (42), 141 (42); HRMS Calcd for $C_{24}H_{22}N_2O$: 354.1732; Found: 354.1732.

2-butyl-9-methyl-*N*-(quinolin-8-yl)-9H-carbazole-3-carboxamide (9).



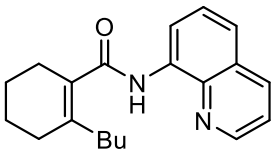
R_f 0.29 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 69 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.91 (t, J = 7.2 Hz, 3H), 1.38-1.47 (m, 2H), 1.75-1.83 (m, 2H), 3.16 (t, J = 8.0 Hz, 2H), 3.87 (s, 3H), 7.33-7.30 (m, 2H), 7.40-7.56 (m, 4H), 7.63 (t, J = 7.6 Hz, 1H), 8.19 (d, J = 7.6 Hz, 1H), 8.18 (dd, J = 8.0, 2.0 Hz, 1H), 8.42 (s, 1H), 8.78 (dd, J = 4.0, 2.0 Hz, 1H), 9.01 (d, J = 7.6 Hz, 1H), 10.33 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.03, 22.79, 29.17, 34.12, 34.48, 108.63, 109.69, 116.43, 119.33, 120.06, 120.23, 120.34, 121.42, 121.57, 122.71, 125.81, 127.51, 127.98 (two overlapping peaks), 135.12, 136.39, 138.54, 140.12, 141.48, 142.05, 148.11, 169.25.; IR (neat) 3356 w, 2954 w, 1667 m, 1600 m, 1517 s, 1478 s, 1382 m, 1324 s, 1252 s, 746 s; MS *m/z* (relative intensity, %) 407 (M^+, 15), 265 (20), 264 (100), 263 (24), 194 (17); HRMS Calcd for $C_{27}H_{25}N_2O$: 407.1998; Found: 407.1995.

2-Butyl-5-methyl-*N*-(quinolin-8-yl)thiophene-3-carboxamide (10).



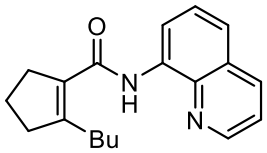
Rf 0.51 (hexane/EtOAc = 5/1). White Solid. Mp = 54-55 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.95(t, J = 7.2 Hz, 3H), 1.41-1.50 (m, 2H), 1.72-1.79 (m, 2H), 2.50 (s, 3H), 3.23 (t, J = 7.2 Hz, 2H), 7.12 (s, 1H), 7.46-7.60 (m, 3H), 8.19 (dd, J = 8.4, 2.0 Hz, 1H), 8.84 (dd, J = 4.0, 2.0 Hz, 1H), 8.88 (dd, J = 7.6, 1.6 Hz, 1H), 1.031 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 113.90, 15.17, 22.49, 28.97, 34.02, 116.29, 121.28, 121.57, 124.48, 127.44, 127.95, 131.75, 134.80, 136.16, 136.32, 138.57, 148.11, 149.84, 162.67; IR (neat) 3360 w, 2955 w, 2859 w, 1666 m, 1522 s, 1484 s, 1424 m, 1383 m, 1327 m, 1245 w, 1165 w, 824 m; MS *m/z* (relative intensity, %) 325 (21), 324 (M^+, 91), 182 (16), 181 (98), 180 (92), 152 (11), 151 (100), 144 (16), 141 (10), 139 (54), 111 (15), 110 (14); HRMS Calcd for $C_{19}H_{20}N_2OS$: 324.1296; Found: 324.1297.

2-Butyl-*N*-(quinolin-8-yl)cyclohex-1-enecarboxamide (11).



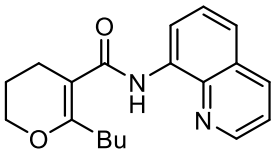
Rf 0.37 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.82 (t, J = 6.8 Hz, 3H), 1.21-1.30 (m, 2H), 1.50-1.58 (m,2H), 1.67-1.75 (m, 4 H), 2.13-2.14 (m, 2H), 2.26 (t, J = 8.0, 2H), 2.43 (m, 2H), 7..45 (dd, J = 8.4, 4.0 Hz, 1H), 7.49-7.57 (m, 2H), 8.16 (dd, J = 8.0, 2.0 Hz, 1H), 8.80 (dd, J = 4.0, 2.0, 1H), 8.87 (d, J = 7.6 Hz, 1H), 9.83 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 13.98, 22.41, 22.80, 27.13, 28.95, 30.72, 34.88, 116.42, 121.31, 121.52, 127.44, 127.94, 129.92, 134.70, 136.29, 138.49, 139.81, 148.02, 170.46; IR (neat) 3326 w, 2930 m, 2870 w, 1738 w, 1666 m, 1597 m, 1520 s, 1483 s, 1423 m, 1382 m, 1325 m, 1261 m, 1114 m, 1087 w, 825 w; MS *m/z* (relative intensity, %) 308 (M^+, 33), 165 (55), 164 (24), 145 (13), 144 (100), 135 (32), 95 (24), 81 (18); HRMS Calcd for $C_{20}H_{24}N_2O$: 308.1889; Found: 308.1887.

2-Btyl-*N*-(quinolin-8-yl)cyclopent-1-enecarboxamide (12).



Rf 0.51 (hexane/EtOAc = 5/1). White Solid. Mp = 63-64 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.93 (t, J = 7.6 Hz, 3H), 1.36-1.45 (m, 2H), 1.51-1.59 (m, 2H), 1.96 (f, J = 7.6 Hz, 2H), 2.58 (t, J = 7.2 Hz, 2H), 2.72 (t, J = 8.0 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 7.44-7.57 (m, 3 H), 8.16 (dd, J = 8.0, 1.6 Hz, 1H), 8.80 (dd, J = 4.0, 1.6 Hz, 1H), 8.86 (dd, J = 18.0, 1.6 Hz, 1H), 10.02 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 14.07, 21.67, 22.95, 29.81, 30.41, 34.09, 37.99, 116.29, 121.09, 121.48, 127.46, 127.92, 129.98, 134.83, 136.28, 138.57, 148.03, 156.08, 165.28; IR (neat) 3357 w, 2954 w, 2858 w, 1739 w, 1665 m, 1520 s, 1483 s, 1423 m, 1382 m, 1325 m, 1259 w, 1202 w, 1123 w, 824 m; MS *m/z* (relative intensity, %) 294 (M^+, 29), 151 (48), 150 (13), 145 (12), 144 (100), 121 (14), 81 (12); HRMS Calcd for $C_{19}H_{22}N_2O$: 294.1732; Found: 294.1731.

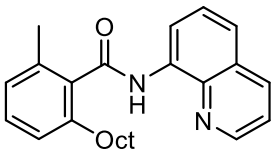
6-Butyl-*N*-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide (13).



Rf 0.49 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.90 (t, J = 7.6 Hz, 3H), 1.32-1.41 (m, 2H), 1.63-1.71 (m, 2H), 1.97 (f, J = 6.4 Hz, 2H), 2.56 (t, J = 6.4 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 4.08 (t, J = 5.2 Hz, 2H), 7.43-7.49 (m, 2H), 7.54 (t, J = 7.6 Hz,

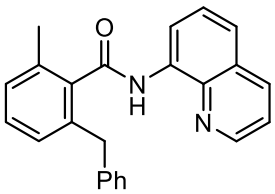
1H), 8.15 (dd, J = 7.6, 1.2 Hz, 1H), 8.79 (dd, J = 4.0, 1.6 Hz, 1H), 8.83 (dd, J = 7.6, 1.2 Hz, 1H), 9.99 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 14.01, 21.92, 22.30, 22.68, 30.03, 32.71, 66.05, 105.14, 116.12, 120.85, 121.46, 127.51, 127.95, 135.08, 136.31, 138.63, 147.93, 163.15, 168.03; IR (neat) 3359 w, 2927 m, 2858 w, 1669 m, 1517 s, 1481 s, 1422 m, 1383 m, 1324 m, 1244 m, 1107 w, 899 w, 825 m; MS *m/z* (relative intensity, %) 310 (M^+, 18), 168 (11), 167 (100), 166 (14), 85 (12); HRMS Calcd for $C_{19}H_{22}N_2O_2$: 310.1681; Found: 310.1680.

2-Methyl-6-octyl-*N*-(quinolin-8-yl)benzamide (14).



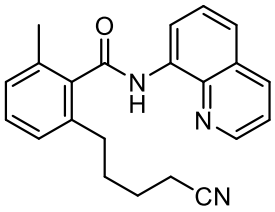
Rf 0.37 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.79 (t, J = 7.6 Hz, 3H), 1.09-1.18 (m, 8H), 1.22-1.29 (m, 2H), 1.63-1.71 (m, 2H), 2.43 (s, 3H), 2.71 (t, J = 7.6 Hz, 2H);7.10-7.15 (m, 2H), 7.27 (t, J = 7.6 Hz, 1H), 7.43 (dd, J = 7.6, 4.0 Hz, 1H), 7.55-7.63 (m,2H), 8.17 (dd, J = 7.6, 2.0 Hz, 1H), 8.72 (dd, J = 4.0, 2.0 Hz, 1H), 9.00 (dd, J = 7.6, 1.6 Hz, 1H), 9.93 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 14.04, 19.48, 22.52, 29.05, 29.26, 29.51, 31.67, 31.75, 33.42, 116.71, 121.61, 121.86, 126.74, 127.39, 127.66, 127.97, 128.93, 134.39, 134.47, 136.28, 137.72, 138.48, 139.51, 148.20, 168.89; IR (neat) 3348 w, 2924 w, 2854 w, 1677 m, 1518 s, 1481 s, 1423 m, 1384 m, 1325 m, 1262 w, 1126 w, 897 w, 825 m; MS *m/z* (relative intensity, %) 375 (12), 374 (M^+, 42), 232 (16), 231 (100), 230 (34), 146 (20), 145 (71), 144 (29), 143 (13), 131 (14), 29 (105); HRMS Calcd for $C_{25}H_{30}N_2O$: 374.2358; Found: 374.2361.

2-Benzyl-6-methyl-*N*-(quinolin-8-yl)benzamide (15).



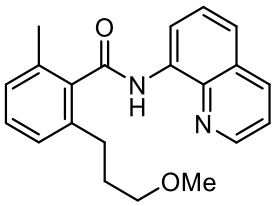
Rf 0.23 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 2.45 (s, 3H), 4.10 (s, 2H), 7.00 (t, J = 8.0 Hz, 1H), 7.05-7.11 (m, 3H), 7.13-7.17 (m, 3H), 7.26 (t, J = 7.6 Hz, 1H), 7.40 (dd, J = 8.0, 4.0 Hz, 1H), 7.53-7.61 (m, 2H), 8.14 (dd, J = 8.0, 1.6 Hz, 1H), 8.65 (dd, J = 4.0, 1.6 Hz, 1H), 8.96 (dd, J= 8.0, 1.6 Hz, 1H), 9.82 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 19.51, 39.10, 116.67, 121.55, 121.90, 125.88, 127.30, 127.56, 127.86, 128.25 (two overlapping peaks), 129.01, 129.09, 134.24, 134.66, 136.18, 137.83, 137.92, 138.39, 140.32, 148.10,168.60; IR (neat) 2924 w, 1674 s, 1518 s, 1481 s, 1423 m, 1384 m, 1325 m, 1262 w, 1125 w, 897 w, 825 m; MS *m/z* (relative intensity, %) 352 (M^+, 33), 209 (69), 208 (100), 194 (31), 166 (11), 165 (29); HRMS Calcd for $C_{24}H_{20}N_2O$: 352.1576; Found: 352.1574.

2-(4-Cyanobutyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (16).



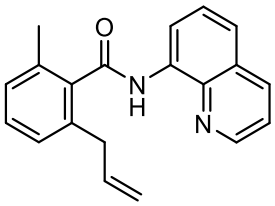
Rf 0.09 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 1.61-1.68 (m, 2H), 1.80-1.88 (m, 2H), 2.25 (t, J = 7.6 Hz, 2H), 2.44 (s, 3H), 2.76 (t, J = 7.6 Hz, 2H), 7.13-7.16 (m, 2H), 7.29 (t, J = 8.0 Hz, 1H), 7.46 (dd, J = 8.0, 4.0 Hz, 1H), 7.57-7.64 (m, 2H), 8.19 (dd, J = 8.0, 1.2 Hz, 1H), 8.75 (dd, J = 4.4, 1.6 Hz, 1H), 8.97 (dd, J = 7.6, 1.6 Hz, 1H), 9.93 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 16.88, 19.48, 24.93, 30.33, 32.36, 116.73, 119.60, 121.74, 122.10, 126.62, 127.35, 127.99, 128.19, 129.16, 134.16, 134.67, 136.37, 137.77, 137.86, 138.41, 148.37, 168.62; IR (neat) 3346 w, 2945 w, 2866 w, 1673 m, 1595 w, 1518 s, 1481 s, 1423 m, 1385 m, 1325 m, 1263 m, 1127 w, 897 w, 827 m; MS *m/z* (relative intensity, %) 343 (M^+, 35), 201 (13), 200 (100), 199 (16), 171 (48), 145 (17), 144 (16), 131 (19), 105 (11); HRMS Calcd for $C_{22}H_{21}N_3O$: 343.1685; Found: 343.1686.

2-(3-Methoxypropyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (17).



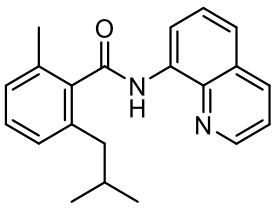
Rf 0.11 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 1.92-1.99 (m, 2H), 2.43 (s, 3H), 2.80 (t, J = 8.0 Hz, 2H), 3.23 (s, 3H), 3.34 (t, J = 6.4 Hz, 2H), 7.12-7.18 (m, 2H), 7.29 (t, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.4, 4.0 Hz, 1H), 7.56-7.63 (m, 2H), 8.18 (dd, J = 8.4, 1.6 Hz, 1H), 8.73 (dd, J = 4.0, 1.6 Hz, 1H), 8.99 (dd, J = 8.0, 1.6 Hz, 1H), 9.93 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 19.48, 29.83, 31.21, 58.29, 71.87 116.74, 121.64, 121.92, 126.87, 127.36, 127.91, 127.95, 129.02, 134.33, 134.54, 136.31, 137.82, 138.45, 138.60, 148.24, 168.73; IR (neat) 3347 w, 2923 w, 2869 w, 1675 m, 1595 w, 1518 s, 1480 s, 1423 m, 1385 m, 1325 m, 1263 w, 1117 m, 897 w, 826 m; MS *m/z* (relative intensity, %) 335, (10), 334 (M^+, 44), 190 (28), 145 (33), 144 (19), 132 (16), 131 (100), 117 (12), 105 (21), 61 (19); HRMS Calcd for $C_{21}H_{22}N_2O_2$: 334.1681; Found: 334.1684.

2-Allyl-6-methyl-*N*-(quinolin-8-yl)benzamide (18).



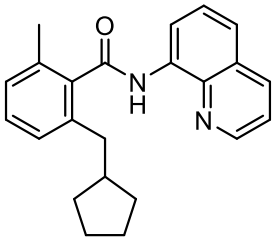
Rf 0.37 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 2.44(s, 3H), 3.51 (d, J = 6.8 Hz, 2H), 4.97-5.04 (m, 2H), 5.94-6.04 (m, 1H), 7.15 (d, J = 8.0, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.44 (dd, J = 8.4, 4.0 Hz, 1H), 7.56-7.63 (m, 2H), 8.17 (d, J = 8.4 Hz, 1H), 8.73 (d, J = 4.0 Hz, 1H), 8.99 (d, J = 7.2 Hz, 1H), 9.95 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 19.49, 37.71, 116.22, 116.74, 121.64, 121.95, 121.01, 127.35, 127.95, 128.23, 129.12, 134.27, 134.71, 136.29, 136.62, 136.86, 137.70, 138.41, 148.21, 168.53; IR (neat) 3345 w, 2921 w, 1675 m, 1595 w, 1519 s, 1482 s, 1424 m, 1385 m, 1326 m, 1264 w, 1127 w, 902 w, 826 w; MS *m/z* (relative intensity, %) 303 (13), 302 (M^+, 59), 301 (28), 160 (10), 159 (89), 158 (100), 157 (11), 144 (41), 131 (47), 130 (13), 129 (18), 128 (12), 116 (32), 115 (30), 91 (26); HRMS Calcd for $C_{20}H_{18}N_2O$: 302.1419; Found: 302.1420.

2-Isobutyl-6-methyl-*N*-(quinolin-8-yl)benzamide (19).



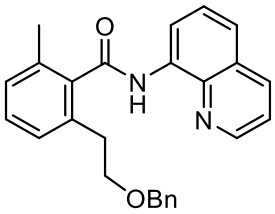
Rf 0.37 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.87 (d, J = 7.2 Hz, 6H), 1.97-2.04 (m, 1H), 2.43 (s, 3H), 2.61 (d, J = 7.2 Hz, 2H), 7.12 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 87.6 Hz, 1H), 7.45 (dd, J = 8.0, 4.0 , 1H), 7.56-7.64 (m, 2H), 8.18 (dd, J = 8.0, 1.6 Hz, 1H), 8.73 (dd, J = 4.0, 1.6 Hz, 1H), 8.99 (dd, J = 7.6, 1.6 Hz, 1H), 9.90 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 19.67, 22.68, 30.01, 31.07, 42.65, 116.82, 121.76, 121.98, 127.51, 127.54, 127.88, 128.11, 128.80, 134.52, 134.58, 136.41, 138.27, 138.43, 138.62, 148.37, 169.02; IR (neat) 3347 w, 2954 w, 2867 w, 1676 m, 1595 w, 1519 s, 1481 s, 1423m, 1384 m, 1325 m, 1263 w, 1126 w, 899 w, 826 w; MS *m/z* (relative intensity, %) 318 (M^+, 66), 176 (12), 175 (97), 174 (58), 159 (56), 158 (14), 157 (100), 145 (14), 144 (53), 132 (16), 131 (11), 129 (11), 116 (11), 105 (24), 104 (13), 103 (12), 91 (11); HRMS Calcd for $C_{21}H_{22}N_2O$: 318.1735; Found: 318.1732.

2-(cyclopentylmethyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (20 and 34).



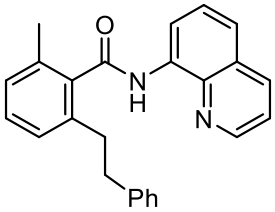
R_f 0.40 (hexane/EtOAc = 5/1). Colorless Oil, ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.11-1.20 (m, 2H), 1.41-1.58 (m, 4H), 1.64-1.69 (m, 2H), 2.21 (se, J = 3.6 Hz, 1H), 2.43 (s, 3H), 2.73 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.44 (dd, J = 4.0, 2.0 Hz, 1H), 7.56-7.64 (m, 2H), 8.18 (dd, J = 8.0, 2.0 Hz, 1H), 8.73 (dd, J = 4.0, 1.6 Hz, 1H), 8.99 (dd, J = 7.6, 1.6 Hz, 1H), 9.92 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.54, 24.72, 32.59, 39.07, 41.60, 116.71, 121.64, 121.86, 127.08, 127.40, 127.65, 127.95, 128.75, 134.37, 134.42, 136.29, 137.88, 138.47, 138.86, 148.20, 168.93; IR (neat) 3347 w, 2949 m, 1676 m, 1520 s, 1482 s, 1424 m, 1326 m, 1126 w; MS *m/z* (relative intensity, %) 345 (11), 344 (M^+, 46), 201 (36), 200 (49), 184 (15), 200 (49), 184 (15), 183 (100), 182 (16), 168 (10), 159 (10), 157 (15), 155 (25), 149 (13), 145 (15), 144 (70), 143 (10), 142 (10), 132 (14), 129 (14), 129 (14), 128 (10), 105 (31), 104 (11); 144 (42); HRMS Calcd for $C_{23}H_{24}N_2O_2$: 344.1889; Found: 344.1891.

2-(2-(Benzyloxy)ethyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (21).



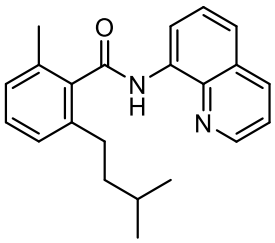
Rf 0.20 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 2.44, 3.05 (t, J = 7.2 Hz, 2H), 3.74 (t, J = 7.2 Hz, 2H), 4.45 (s, 2H), 7.15-7.20 (m, 7H), 7.29 (t, J = 7.6 Hz, 1H), 7.44 (dd, J = 8.0, 4.0 Hz, 1H), 7.57-7.65 (m, 2H), 8.20 (dd, J = 8.4, 1.6 Hz, 1H), 8.69 (dd, J = 4.4, 1.6 Hz, 1H), 9.00 (dd, J = 7.6, 1.6 Hz, 1H), 10.05 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 19.53, 33.79, 70.97, 72.70, 116.87, 121.60, 121.98, 127.29, 127.37, 127.39, 127.98, 128.12, 128.31, 128.98, 134.35, 134.58, 135.50, 136.28, 138.28 (two overlapping peaks), 138.49, 148.19, 168.66; IR (neat) 3344 w, 2925 w, 2858 w, 1673 m, 1595 w, 1519 s, 1481 s, 1424 m, 1385 m, 1325 m, 1264 m, 1095 m, 898 w, 826 m; MS *m/z* (relative intensity, %) 396 (M^+, 7), 289 (11), 288 (7), 287 (17), 234 (13), 233 (14), 145 (12), 144 (38), 129 (12), 91 (100); HRMS Calcd for $C_{26}H_{24}N_2O_2$: 396.1836; Found: 396.1838.

2-Methyl-6-phenethyl-*N*-(quinolin-8-yl)benzamide (22).



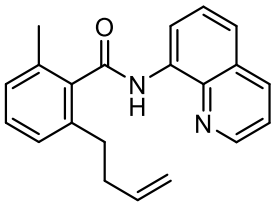
Rf 0.29 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 2.45 (s, 3H), 2.96-3.05 (m,4H), 7.05-7.09 (m,3H), 7.12-7.16 (m, 4H), 7.28 (t, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.0, 4.0 Hz, 1H), 7.56-7.65 (m, 2H), 8.18 (dd, J = 8.4, 1.6 Hz, 1H), 8.72 (dd, J = 4.0, 1.6 Hz, 1H), 9.01 (dd, J = 8.0, 1.6 Hz, 1H), 9.95 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 19.53, 35.83, 38.14, 116.82, 121.66, 121.98, 125.78, 126.95, 127.42, 127.99, 128.09, 128.21, 128.37, 129.05, 134.30, 134.59, 136.36, 137.79, 138.42, 141.66, 148.26, 168.70; IR (neat) 3345 w, 3025 w, 2927 w, 1738 w, 1674 m, 1595 w, 1518 s, 1481 s, 1423 m, 1384 m, 1325 m, 1262 w, 1126 w, 897 w, 826 m; MS *m/z* (relative intensity, %) 366 (M^+, 17), 224 (10), 223 (61), 222 (46), 179 (12), 178 (13), 165 (12), 145 (37), 144 (100), 132 z811), 117 (27), 103 (11), 91 (20); HRMS Calcd for $C_{25}H_{22}N_2O$:366.1732; Found: 366.1730.

2-Isopentyl-6-methyl-*N*-(quinolin-8-yl)benzamide (23).



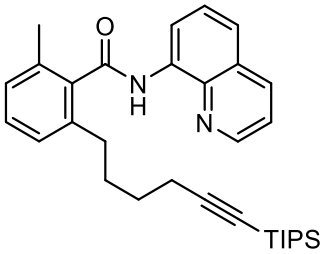
Rf 0.26 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.77 (d, J = 6.4 Hz, 6H), 1.47-1.60 (m, 3H), 2.43 (s, 3H), 2.70 (t, J = 8.0 Hz, 2H), 7.10-7.15 (m, 2H), 7.27 (t, J = 7.6 Hz, 1H), 7.45 (dd, J = 8.4, 4.0 Hz, 1H), 7.56-7.64 (m, 2H), 8.18 (dd, J = 8.4, 1.6 Hz, 1H), 8.74 (dd, J = 4.4, 1.6 Hz, 1H), 8.99 (dd, J = 8.4, 1.6 Hz, 1H), 9.93 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 19.49, 22.33, 27.95, 31.39, 41.17, 116.79, 121.63, 121.87, 126.77, 127.44, 127.65, 127.98, 128.98, 134.37, 134.55, 136.35, 137.69, 138.44, 139.73, 148.19, 168.87; IR (neat) 3348 w, 2953 w, 2868 w, 1677 m, 1595 w, 1519 s, 1481 s, 1424 m, 1385 m, 1325 m, 1263 w, 1126 w, 898 w, 826 w; MS *m/z* (relative intensity, %) 333 (13), 332 (M+, 52), 289 (14), 189 (55), 188 (31), 171 (13), 147 (12), 146 (13), 145 (100), 144 (25), 132 (11), 131 (42), 105 (32), 59 (32); HRMS Calcd for $C_{22}H_{24}N_2O$: 332.1889; Found: 332.1890.

2-(But-3-en-1-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (24).



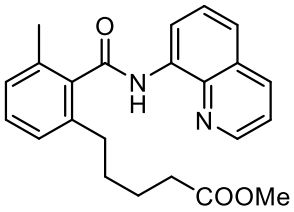
Rf 0.29 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 2.41-2.47 (m,5H), 2.2.80-2.84 (m, 2H), 4.86-4.95 (m, 2H), 5.75-5.82 (m, 1H), 7.14 (t, J = 8.0 Hz, 2H), 7.27 (t, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.0, 4.0 Hz, 1H), 7.56-7.63 (m, 2H), 8.17 (dd, J= 8.4, 16 Hz, 1H), 8.73 (dd, J = 4.0, 1.6 Hz, 1H), 8.99 (dd, J = 8.0, 1.6 Hz, 1H), 9.93 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 19.49, 32.87, 35.54, 115.05, 116.74, 121.65, 121.93, 126.80, 127.38, 127.93, 127.96, 128.96, 134.31, 134.50, 136.31, 137.82, 137.89, 138.38, 138.46, 148.24, 168.72; IR (neat) 3345 w, 2924 w, 1674 m, 1595 w, 1518 s, 1481 s, 1423 m, 1385 m, 1325 m, 1263 w, 1127 w, 899 w, 826 m; MS *m/z* (relative intensity, %) 316 (M^+, 32), 173 (67), 172 (58), 171 (17), 157 (18), 146 (10), 145 (82), 144 (100), 143 (10), 132 (11), 131 (14), 130 (21), 129 (19), 128 (15), 115 (1), 105 (18), 104 (11); HRMS Calcd for $C_{21}H_{20}N_2O$:316.1576; Found: 316.1576.

2-Methyl-*N*-(quinolin-8-yl)-6-(6-(triisopropylsilyl)hex-5-yn-1-yl)benzamide (25).



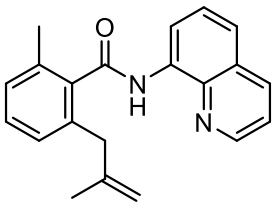
Rf 0.34 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.95-1.17 (m, 21H), 1.49-1.57 (m, 2H), 1.79-1.86 (m, 2H), 2.19 (t, J = 7.2 Hz, 2H), 2.43 (s, 3H), 2.74 (t, J = 7.6 Hz, 2H), 7.11-7.16 (m, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.45 (dd, J = 8.0,. 4.0 Hz, 1H), 7.56-7.64 (m, 2H), 8.19 (d, J = 7.6 Hz, 1H), 8.73 (d, J = 3.6 Hz, 1H), 8.98 (d, J = 7.6 Hz, 1H), 9.92 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 111.20, 18.59, 19.50, 19.63, 28.65, 30.50, 32.71, 80.04, 108.90, 116.81, 121.66, 121.94, 126.58, 127.41, 127.80, 127.99, 129.00, 134.31, 134.48, 136.35, 137.74, 138.43, 138.94, 148.21, 168.80; IR (neat) 3349 w, 2941 m, 2863 m, 2170 w, 1679 m, 1520 s, 1482 s, 1463 m, 1424 m, 1385 m, 1325 m, 1263 w, 1126 w, 883 m, 826 m; MS *m/z* (relative intensity, %) 498 (M^+, 2), 457 (10), 456 (37), 455 (100); HRMS Calcd for $C_{32}H_{42}N_2OSi$: 498.3066; Found: 498.3062.

Methyl 5-(3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)pentanoate (26).



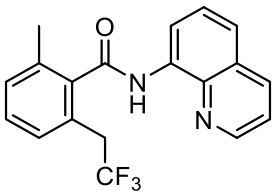
Rf 0.11 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 1.60-1.76 (m,4H), 2.24 (t, J = 7.6 Hz, 2H), 2.43 (s, 3H), 2.74 (t, J = 7.6 Hz, 2H), 3.56 (s, 3H), 7.13 (t, J = 7.2 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.45 (dd, J = 8.4, 4.0 Hz, 1H), 7.56-7.64 (m, 2H), 8.18 (dd, J = 8.4, 1.6 Hz, 1H), 8.73 (dd, J = 4.0, 1.6 Hz, 1H), 8.98 (dd, J = 8.0, 1.6 Hz, 1H), 9.92 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 19.47, 24.72, 31.00, 33.04, 33.78, 51.33, 116.75, 121.65, 121.95, 126.70, 127.37, 127.90, 127.97, 129.01, 134.28, 134.54, 136.31, 137.71, 138.45, 138.70, 148.26, 168.72, 173.95; IR (neat) 3347 w, 2948 w, 2864 w, 1734 m, 1675 m, 1595 w, 1518 s, 1481 s, 1424 m, 1384 m, 1325 m, 1262 m, 1127 m, 896 w, 827 m; MS *m/z* (relative intensity, %) 377 (19), 376 (M^+, 72), 245 (20), 234 (14), 233 (99), 232 (100), 201 (14), 200 (13), 173 (24), 163 (20), 159 (21), 158 (13), 157 (13), 155 (10), 146 (14), 145 (84), 144 (39), 143 (10), 119 (12), 117 (12), 116 (14), 115 (15), 105 (21), 91 (14); HRMS Calcd for $C_{23}H_{18}N_2O$: 376.1787; Found: 376.1789.

2-Methyl-6-(2-methylpropen-3-yl)-*N*-(quinolin-8-yl)benzamide (27).



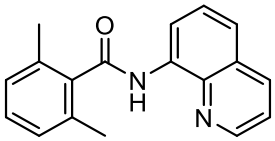
R_f: 0.31 (hexane/EtOAc = 5/1). Yellow oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.63 (s, 3H), 2.43 (s, 3H), 3.44 (s, 2H), 4.65 (s, 1H), 4.76 (s, 1H), 7.13-7.15 (m, 2H), 7.26-7.62 (m, 4H), 8.17 (dd, J = 2.0, 8.4 Hz, 1H), 8.71 (dd, J = 2.0, 4.4 Hz, 1H), 8.97 (dd, J = 1.2, 7.2 Hz, 1H), 9.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.66, 22.48, 41.67, 112.85, 116.83, 121.76, 122.01, 127.41, 127.51, 128.08, 128.38, 129.05, 134.49, 134.88, 136.32, 136.38, 138.24, 138.61, 144.62, 148.31, 168.72; IR (neat): 3345 w, 3066 w, 2969 w, 2916 w, 1737 w, 1674 s, 1595 w, 1578 w, 1517 s, 1481 s, 1423 m, 1384 m, 1325 s, 1263 m, 1170 w, 1126 m, 1088 w, 1071 w, 1042 w, 977 w, 894 m, 825 m, 790 m, 760 m, 685 m; MS *m/z* (relative intensity, %): 326 (M^+, 29), 315 (20), 173 (18), 172 (21), 157 (14), 145 (65), 144 (100), 130 (16), 129 (21), 128 (17), 115 (12), 105 (14); HRMS Calcd for $C_{18}H_{13}F_3N_2O$: 316.1576; Found: 316.1571.

2-methyl-*N*-(quinolin-8-yl)-6-(2,2,2-trifluoroethyl)benzamide (28).



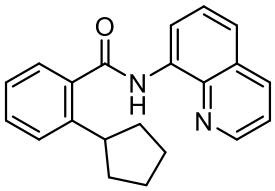
R_f 0.37 (hexane/EtOAc = 5/1). White Solid. Mp = 148 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.48 (s, 2H), 3.59 (q, J = 10.8 Hz, 2H), 7.30 (t, J = 8.0 Hz, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.45 (dd, J = 8.4, 4.4 Hz, 1H), 7.58-7.64 (m, 2H), 8.18 (dd, J = 8.0, 2.0 Hz, 1H), 8.74 (dd, J = 4.4, 1.6 Hz, 1H), 8.97 (dd, J = 7.6, 1.6 Hz, 1H), 10.05 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.78, 37.08 (q, J = 29.6 Hz), 116.82, 121.50, 121.73, 122.28, 125.64 (q, J = 275.5 Hz), 127.15 (d, J = 3 Hz), 127.27, 127.97, 128.25, 128.61, 129.01, 129.28, 130.37, 134.02, 135.15, 136.30, 138.45, 139.05, 148.38, 167.64; IR (neat) 3343 w, 1671 m, 1520 s, 1483 s, 1326 m, 1260 m, 1134 m, 792 m; MS *m/z* (relative intensity, %)344 (M^+, 41), 202 (24), 201 (100), 200 (19), 181 (16), 144 (21), 123 (25); HRMS Calcd for $C_{19}H_{15}F_3N_2O$: 344.1136; Found: 344.1134.

2,6-Dimethyl-*N*-(quinolin-8-yl)benzamide (29).



R_f: 0.37 (hexane/EtOAc = 5/1). White Solid. Mp = 125 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.44 (s, 6H), 7.12 (d, J = 7.2 Hz, 2H), 7.25 (t, J = 7.6 Hz, 1H), 7.45 (dd, J = 8.0, 4.4 Hz, 1H), 7.56-7.64 (m, 2H), 8.19 (d, J = 8.0 Hz, 1H), 8.74 (d, J = 4.0 Hz, 1H), 9.00 (d, J = 7.2 Hz, 1H), 9.95 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.45, 116.82, 121.65, 121.94, 127.43, 127.89, 127.99, 128.95, 134.34, 134.53, 136.42, 137.99, 138.42, 148.21, 168.89; IR (neat) 3345 w, 1673 m, 1518 s, 1481 s, 1424 m, 1385 m, 1325 m, 1127 w; MS *m/z* (relative intensity, %): 276 (M^+, 29), 259 (12), 133 (100), 132 (21), 105 (26); HRMS Calcd for $C_{18}H_{16}N_2O$: 276.1263; Found: 276.1261.

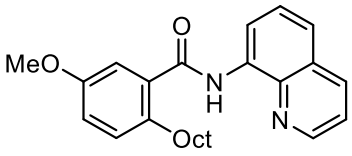
2-cyclopentyl-*N*-(quinolin-8-yl)benzamide (30).



R_f 0.49 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.62-1.82 (m, 6H), 2.14-2.22 (m, 2H), 3.48-3.54 (m, 1H), 7.27-7.31 (m, 1H), 7.43-7.47 (m, 3H), 7.54-7.63 (m, 3H), 8.18 (dd, J = 8.4, 1.2 Hz, 1H), 8.76 (dd, J = 4.0, 1.6 Hz, 1H), 8.97 (dd, J = 7.6, 1.6 Hz, 1H), 10.14 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 25.85, 35.44, 41.95, 116.60, 121.63, 121.79, 125. 71, 126.91, 126.93, 127.41, 127.96, 130.28, 134.68, 136.40, 137.17,

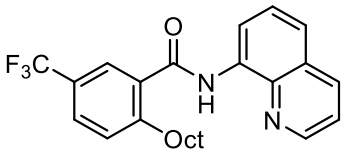
138.40, 144.83, 148.15, 168.91; IR (neat) 3347 w, 2952 w, 1672 m, 1519 s, 1482 s, 1424 m, 1385 m, 1326 m, 1260 w; MS *m/z* (relative intensity, %) 316 (M^+, 41), 173 (29), 172 (100), 171 (17), 155 (41), 154 (16), 153 (14), 145 (16), 144 (92), 131 (15), 130 (18), 129 (33), 128 (15), 117 (10), 116 (12), 115 (19), 91 (15); HRMS Calcd for $C21H_{20}N_2O$: 316.1576; Found: 316.1576.

5-Methoxy-2-octyl-*N*-(quinolin-8-yl)benzamide (31b).



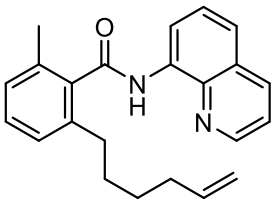
Rf 0.40 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.80 (t, J = 7.2 Hz, 3H), 1.11-1.29 (m, 10H), 1.66 (t, J = 7.6 Hz, 2H), 2.83 (t, J = 7.6 Hz, 2H), 3.84 (s, 3H), 6.97 (dd, J = 8.0, 1.6 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 8.4, 4.4 Hz, 1H), 7.54-7.62 (m, 2H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 8.76 (dd, J = 4.0, 1.6 Hz, 1H), 8.94 (dd, J = 7.6, 1.2 Hz, 1H), 10.15 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 14.04, 22.55, 39.16, 29.34, 29.45, 31.77, 31.89, 32.47, 55.42, 112.45, 115.93, 116.52, 121.63, 121.76, 127.37, 127.76, 131.40, 133.08, 134.64, 136.29, 137.46, 138.51, 148.20, 157.48, 168.22; IR (neat) 3349 w, 2924 w, 2853 w, 1676 m, 1607 w, 1520 s, 1481 s, 1423 m, 1384 m, 1325 m, 1285 m, 1109 w, 1040 m, 824 m; MS *m/z* (relative intensity, %) 391 (14), 390 (M^+, 50), 305 (10), 247 (15), 246 (35), 217 (15), 176 (11), 161 (100), 149 (23), 147 (13), 146 (12), 144 (34), 121 (30). HRMS Calcd for $C_{25}H_{30}N_2O_2$: 390.2307; Found: 390.2306.

2-Octyl-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (32b).



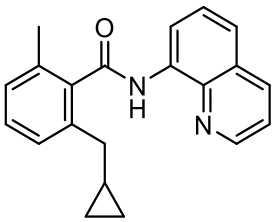
Rf 0.51 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 0.80 (t, J = 7.2 Hz, 3H), 1.11-1.35 (m, 10H), 1.67-1.74 (m, 2H), 2.94 (t, J = 8.0 Hz, 2H), 7.45-7.49 (m, 2H), 7.57-7.68 (m, 3H), 7.88 (s, 1H), 8.19 (dd, J = 8.0, 4.0, 1H), 8.78 (dd, J = 4.0, 1.6 Hz, 1H), 8.93 (dd, J = 7.6, 4.0 Hz, 1H), 10.17 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 14.02, 22.54, 29.09, 29.25, 29.44, 31.45, 31.74, 33.28, 116.76, 121.76, 122.19, 123.88 (q, J = 271 Hz), 124.21 (d, J = 2.9 Hz), 126.71 (d, J = 3.8 Hz), 127.73, 127.95, 128.35 (q, J = 33Hz), 130.82, 134.28, 136.38, 137.23, 138.44, 145.35, 148.37, 166.97; IR (neat) 3344 w, 2926 w, 2855 w, 1678 m, 1522 s, 1483 s, 1424 m, 1385 m, 1326 s, 1258 m, 1169 m, 1125 s, 1080 w, 910 w, 826 m; MS *m/z* (relative intensity, %) 429 (11), 428 (M^+, 41), 344 (11), 343 (52), 213 (11), 200 (12), 199 (59), 145 (13), 144 (100); HRMS Calcd for$C_{25}H_{27}F_3N_2O$: 428.2075; Found: 428.2073.

2-(hex-5-en-1-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (33).



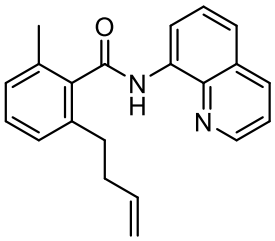
R_f 0.40 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.37 (f, J = 7.6 Hz, 2H), 1.66-1.73 (m, 2H), 1.96 (q, J = 7.6 Hz, 2H), 2.43 (s, 3H), 2.72 (t, J = 8.0 Hz, 2H), 4.78 (dd, J = 10.4, 1.6 Hz, 1H), 4.86 (dd, J = 17.2, 1.6 Hz, 1H), 5.62-5.72 (m, 1H), 7.13 (t, J = 8.0 Hz), 7.28 (t, J = 7.6 Hz, 1H), 7.45 (dd, J = 8.0, 4.0 Hz, 1H), 7.56-7.64 (m, 2H), 8.19 (dd, J = 8.0, 1.2 Hz, 1H), 8.74 (dd, J = 4.0, 1.2 Hz, 1H) 9.00 (dd, J = 7.2, 1.6 Hz, 1H), 9.93 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.50, 28.73, 31.09, 33.27, 33.48, 114.21, 116.80, 121.64, 121.92, 126.73, 127.44, 127.74, 127.99, 128.97, 134.34, 134.51, 136.39, 137.72, 138.41, 138.74, 139.24, 148.20, 168.87; IR (neat) 3347 w, 1676 m, 1519 s, 1481 s, 1423 m, 1385 m, 1325 m, 1126 w; MS *m/z* (relative intensity, %) 344 (M^+, 13), 201 (32), 200 (22), 159 (47), 145 (30), 144 (100), 131 (20), 130 (11), 116 (10), 105 (28); HRMS Calcd for $C_{22}H_{22}N_2O_2$: 344.1889; Found: 344.1890.

2-(cyclopropylmethyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (35).



R_f 0.41 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.18 (q, J = 5.2 Hz, 2H), 0.47 (q, J = 5.6 Hz, 2H), 1.03-1.09 (m, 1H), 2.44 (s, 3H), 2.67 (d, J = 6.8 Hz, 2H), 7.15 (d, J = 8.4 Hz, 1H), 7.29-7.34 (m, 2H), 7.44 (dd, J = 4.4, 2.4 Hz, 1H), 7.56-7.63 m, 2H), 8.17 (d, J = 8.0 Hz, 1H), 8.73 (dd, J = 4.0, 1.6 Hz, 1H), 9.00 (d, J = 6.8 Hz, 1H), 9.96 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 4.95, 11.72, 19.49, 37.59, 116.77, 121.64, 126.51, 127.39, 127.92, 127.97, 129.00, 134.31, 134.33, 136.34, 137.58, 138.39, 138.86, 148.20, 168.89; IR (neat) 3346 w, 1676 m, 1520 s, 1482 s, 1424 m, 1385 m, 1326 m, 1263 w; MS *m/z* (relative intensity, %)316 (M^+, 21), 315 (11), 173 (17), 172 (37), 171 (15), 157 (14), 146 (11), 145 (89), 144 (100), 130 (19), 129 (21), 128 (17), 115 (17), 105 (15); HRMS Calcd for $C_{21}H_{20}N_2O$: 316.1576; Found: 316.1573.

2-(but-3-en-1-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (36).



R_f 0.41 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.41-2.47 (m, 5H), 2.82 (t, J = 8.0 Hz, 2H), 4.86-4.95 (m, 2H), 5.74-5.84 (m, 1H), 7.14 (t, J = 8.4 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.45 (dd, J = 8.0, 4.0 Hz, 1H), 7.56-7.64 (m, 2H), 8.19 (dd, J = 8.4, 1.6 Hz, 1H), 8.74 (dd, J = 4.0, 2.0 Hz, 1H), 8.99 (dd, J = 7.2, 1.2 Hz, 1H), 9.94 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.52, 32.88, 35.56, 115.05, 116.90, 121.65, 121.97, 126.80, 127.46, 127.94, 128.01, 128.98, 134.27, 134.52, 136.48, 137.80, 137.92, 138.34, 138.39, 148.18, 168.77; IR (neat) 3346 w, 1675 m, 1519 s, 1481 s, 1424 m, 1385 m, 1325 m, 1263 w, 826 w; MS *m/z* (relative intensity, %) 316 (M^+, 32), 173 (64), 172 (56), 171 (18), 157 (19), 146 (11), 145 (86), 144 (100), 143 (11), 132 (12), 131 (14), 130 (22), 129 (22), 128 (18), 115 (14), 105 (21), 104 (11), 103 (11); HRMS Calcd for $C_{21}H_{20}N_2O$: 316.1576; Found: 316.1574.

Deuterium Labeling Experiments (Scheme 2).

To an oven-dried 5 mL screw-capped vial in a glove box, 2-methyl-*N*-(8-quinolinyl)benzamide **1a-*d*$_7$** (79 mg, 0.3 mmol), 1-bromobutane (82 mg, 0.6 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (15.6 mg, 0.06 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and toluene (1 mL) were added. The mixture was stirred for 8 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}H-NMR.

Competition Experiment (Scheme. 3).

To an oven-dried 5 mL screw-capped vial, *N*-(8-Quinolinyl)-3-(trifluoromethyl)benzamide **32a** (158 mg, 0.5 mmol), 3-Methoxy-*N*-(quinolin-8-yl)benzamide **31a** (139 mg, 0.5 mmol), 1-bromooctane (79 mg, 0.4 mmol), $Ni(OTf)_2$, (7.1 mg, 0.02 mmol), PPh_3 (10 mg, 0.04 mmol), Na_2CO_3 (42 mg, 0.4 mmol) and toluene (1 mL) were added in a glove box. The mixture was stirred for 36 h at 160 °C followed by cooling. The mixture was filtered through a celite pad and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluant: hexane/EtOAc= 20/1) to afford the desired alkylated product **32b** (115 mg, 67% based on Oct-Br) as a colorless oil and alkylated prduct **31b** (7 mg 5% based on Oct-Br) as a colorless oil. *N*-(8-Quinolinyl)-3-(trifluoromethyl)benzamide **32a** and 3-Methoxy-*N*-(quinolin-8-yl)benzamide **31a** was recovered 41% and 90%.

Radical Trapping Experiment.

To an oven-dried 5 mL screw-capped vial in a glove box, 2-methyl-*N*-(8-quinolinyl)benzamide **1a-*d*$_7$** (79 mg, 0.3 mmol), 1-bromobutane (82 mg, 0.6 mmol), TEMPO or GALVINOXYL (0.6 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (15.6 mg, 0.06 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and toluene (1 mL) were added. The mixture was stirred for 24 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The yield of product was determined by ^{1}H-NMR.

Radical Clock Experiments (Scheme. 4 and 5).

To an oven-dried 5 mL screw-capped vial in a glove box, 2-methyl-N-(8-quinolinyl)benzamide **1a** (79 mg, 0.3 mmol), 6-bromohex-1-ene (97 mg, 0.6 mmol) or (bromomethyl)cyclopropane (80 mg, 0.6 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (15.6 mg, 0.06 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and toluene (1 mL) were added. The mixture was stirred for 24 h at 140 °C followed by cooling. The resulting mixture was filtered through a celite pad and concentrated in vacuo. The ratio of products was determined by ^{1}H-NMR.

1.5 References and Notes

(1) Reviews on direct alkylation of C-H bond with alkyl halides: (a) Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495. b) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (c) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948.

(2) Smith, M. B. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*. John Wiley & Sons: 2013.

(3) (a) Tremont, S. J.; Hayat Ur, R. *J. Am. Chem. Soc.* **1984,** *106*, 5759. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009,** *48*, 6097. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010,** *132*, 3965. (d) Jang, M. J.; Youn, S. W. *Bull. Korean Chem. Soc.* **2011,** *32*, 2865. (e) Zhao, Y.; Chen, G *Org. Lett.* **2011,** *13*, 4850. (f) Tran, L. D.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012,** *51*, 5188. (g) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013,** *4*, 3906. (h) Zhang, S. Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013,** *135*, 2124. (i) Zhang, S. Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013,** *135*, 12135. (j) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013,** *135*, 616. (k) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014,** *136*, 13194. (l) Chen, K.; Shi, B.-F. *Angew. Chem. Int. Ed*. **2014**, *53*, 11950. (m) Zhang, S.-Y.; Li, Q.; He, G.; Nack, A.; Chen, G. *J. Am. Chem. Soc.* **2014**, *137*, 531. (n) Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu, R.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *138*, 11574.

(4) (a) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009,** *48*, 6045. (b) Hoffmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877. (c) Li,

J.; Warratz, S.; Zell, D.; De Saralar, S.; Ishikawa, E. E.; Akermann, L. *J. Am. Chem. Soc.* **2015**, *138*, 13894.

(5) (a) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010,** *133*, 428. (b) Gao, K.; Yoshikai. N. *J. Am. Chem. Soc.* **2013,** *135*, 9279. (c) Punji, B.; Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem. Eur. J.* **2013**, *19*, 10605. (d) Gao, K.; Yamakawa, T.; Yoshikai, N. *Synthesis* **2014**, *46*, 2024.

(6) (a) Fruchey, E. R.; Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014,** *136*, 13130. (b) Ilies, L.; Matsubara, T.; Ichikawa, S.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014,** *136*, 13126. (c) Monks, B. M.; Fruchey, E. R.; Cook, S. P. *Angew. Chem. Int. Ed.* **2014,** *53*, 11065.

(7) (a) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011,** *133*, 8070. (b) Aihara, Y.; Chatani, N. *Chem. Sci*. **2013**, *4*, 664.

(8) Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922.

(9) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014,** *53*, 2477.

(10) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

(11) (a) Kinney, R. J.; Jones, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 7902. (b) Ash, C. E.; Hurd, P. W.; Darensbourg, M. Y.; Newcomb, M. *J. Am. Chem. Soc*. **1987**, *109*, 3313. (c) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc*. **2013**, *135*, 16192. (d) Breitenfeld,J.; Ruiz, J.; Wodrich, M. D.; Hu, X. *J. Am. Chem. Soc.* **2013**, *135*, 12004. (e) Choi, J.; Martín-Gago, P.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 12161. (f) Zhao, C.; Jia, X.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2014**, *136*, 17645.

(12) (a) Camasso, N. M.; Sanford, M. S. *Science* **2015**, *347*, 1218. (b) Bour, J. R.; Camasso, N. M.; Sanford. M. S. *J. Am. Chem. Soc.* **2015,** *137*, 8034.

(13) Terao, J.; Kambe, N. *Acc. Chem. Res*. **2008**, *41*, 1545.

(14) (a) Wu, X.; Zhao, Y; Ge, H. *J. Am. Chem. Soc.* **2014,** *136*, 1789. (b) X. Cong, Y. Li, Y. Wei, X. Zeng. *Org. Lett.* **2014,** *16*, 3926. (c) Barsu, N.; Kalsi, D.; Sundararaju, B. *Chem. Eur. J.* **2015**, *21*, 9364.

(15) (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013,** *135*, 5308. (b) Aihara, Y.; Wuelbern, J.; Chatani, N. *Bull. Chem. Soc. Jpn*. **2015**, *88*, 438.

Chapter 2

Nickel(II)-Catalyzed Direct Arylation of C(sp^3)-H Bonds in Aliphatic Amides via Bidentate-Chelation Assistance

2.1 Introduction

As described in general introduction and chapter 1, the transition metal-catalyzed functionalization of C(sp^2)-H bonds has emerged as a powerful tool for the formation of C-C and C-heteroatom bonds in recent years.[1] Compare to those functionalization of C(sp^2)-H bonds, the functionalization of C(sp^3)-H bonds has been limited and continues to be a challenging issue.[2] However, most of the functionalization reactions of C(sp^3)-H bonds reported so thus have involved the use of palladium complexes as catalysts. One of the method for the functionalization of C(sp^3)-H bonds is the utilization of a bidentate directing group discovery by Daugulis,[3] and various types of functionalization of C(sp^3)-H bonds have been achieved using the bidentate-chelation system in conjunction with Pd(II) catalysts.[4] Another method for functionalization of C(sp^3)-H bond with Pd-catalyst is the use of electron deficient directing groups, which is reported by Yu.[5] The Functionalization of C-H bonds using transition metal complexes other than palladium complexes have been limited.[6] To the best of our knowledge, Ni-catalyzed transformation of C(sp^3)-H bonds have been restricted to only one example, i.e., the Ni(0)-catalyzed cycloaddition of formamide with alkynes.[7]

Chapter 2 deals the Ni(II)-catalyzed direct arylation of aliphatic amide containing an 8-aminoquinoline moiety with aryl iodides via a cleavage of C(sp^3)-H bond. This reaction represents the first general method for functionalization of C(sp^3)-H bond with nickel-catalyst.

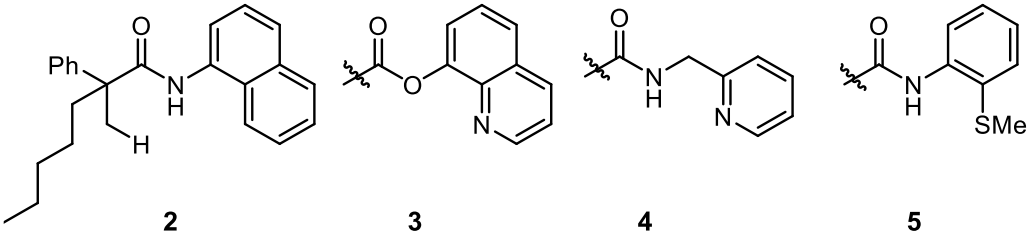
2.2 Result and Discussion

The reaction of amide **1a** (0.3 mmol) with 4-iodoanisole (0.6 mmol) in the presence of $Ni(OTf)_2$ (0.03 mmol) as a catalyst and Na_2CO_3 (0.6 mmol) as a base in DMA (0.6 mL) at 140 °C for 24 h gave the β-arylation product **1b** in 40% NMR yield along with the recovery of 44% of the unreacted **1a**, and no evidence of any biarylated product or any other products produced by reaction at the methylene or γ-benzene C-H bonds was found (entry 1 in Table 1). The addition of benzoic acid as a ligand improved the yield of **1a** to 70% (entry 2). Further investigation revealed that the addition of a sterically bulky carboxylic acid, such as 2,4,6-trimethylbenzoic acid (MesCOOH) or [1,1':3',1''-terphenyl]-2'-carboxylic acid (2,6-$Ph_2C_6H_3COOH$), also improved the product yield (entries 3-7). The efficiency of the reaction was also significantly affected by the choice of the base used. Na_2CO_3 was determined to be the best base for this reaction (entries 8-11). Among the solvents examined,

DMF was the solvent of choice. Curiously, not only a Ni(II) complex but also a Ni(0) complex showed a high catalytic activity, resulting in high yields of the *β*-arylation product (entries 15-17).

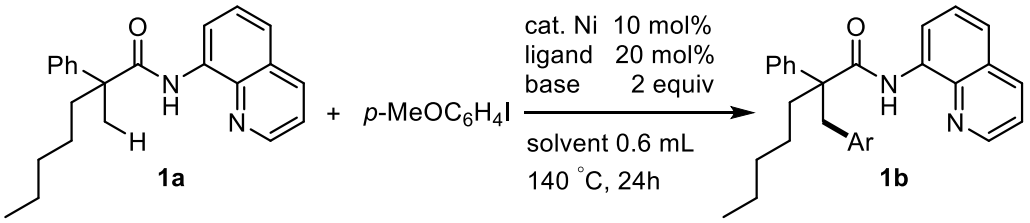
We next examined the effect of directing groups (Figure 1). The reaction did not proceed at all when the corresponding *N*-2-naphthylbenzamaide **2** or the ester **3** was used. The use of other bidentate directing groups, such as 2-pyridinylmethylamine **4** or 2-(methylthio)aniline **5**, also resulted in no reaction.

Figure 1. Ineffective Directing Groups



2 **3** **4** **5**

Table 1. Optimaization of the Nickel-Catalyzed Direct Arylation of Aliphatic Amide **1a** with 4-Iodoanisole[a]



entry	catalyst	ligand	base	solvent	yield (**1b**/**1a**)[b]
1	$Ni(OTf)_2$	none	Na_2CO_3	DMA	40% / 44%
2	$Ni(OTf)_2$	PhCOOH	Na_2CO_3	DMA	70% / 22%
3	$Ni(OTf)_2$	2-PhC_6H_4COOH	Na_2CO_3	DMA	72% / 24%
4	**$Ni(OTf)_2$**	**MesCOOH**	**Na_2CO_3**	**DMA**	**82% (78%) /17%**
5	$Ni(OTf)_2$	2,6-$^{i}Pr_2C_6H_3COOH$	Na_2CO_3	DMA	74% / 23%
6	$Ni(OTf)_2$	2,6-$Ph_2C_6H_3COOH$	Na_2CO_3	DMA	81% / 21%
7	$Ni(OTf)_2$	1-AdCOOH	Na_2CO_3	DMA	72% / 27%
8	$Ni(OTf)_2$	MesCOOH	Li_2CO_3	DMA	49% / 35%
9	$Ni(OTf)_2$	MesCOOH	$NaHCO_3$	DMA	14% / 72%
10	$Ni(OTf)_2$	MesCOOH	K_2CO_3	DMA	0% / 103%
11	$Ni(OTf)_2$	MesCOOH	NaOAc	DMA	0% / 105%
12	**$Ni(OTf)_2$**	**MesCOOH**	**Na_2CO_3**	**DMF**	**88% (83%) / 12%**
13	$Ni(OTf)_2$	MesCOOH	Na_2CO_3	toluene	59% / 38%
14	$Ni(OTf)_2$	MesCOOH	Na_2CO_3	AcOH	0% / 99%
15	$NiCl_2$	MesCOOH	Na_2CO_3	DMF	81% / 10%
16	$Ni(OAc)_2$	MesCOOH	Na_2CO_3	DMF	81% / 10%
17	$Ni(cod)_2$	MesCOOH	Na_2CO_3	DMF	79% / 10%

[a] Reaction conditions: amide **1a** (0.3 mmol), 4-iodoanisole (0.6 mmol), catalyst (0.03 mmol), ligand (0.06 mmol), base (0.6 mmol) in solvent (0.6 mL) at 140 °C for 24 h. [b] NMR yields. The number in parenthesis is the isolated yield.

Table 2 shows the scope of the substrates under the standard reaction conditions. Aliphatic amides possessing three substituents at the α-position reacted efficiently. The reactions proceeded exclusively at the methyl group in a highly regioselective manner, as in the cases of **6**, **7**, **8**, and **9**, and methylene and benzene C-H bonds were not arylated. Although the reaction of 1-methylcyclohexanecarboxamide **10a** resulted in selective mono arylation only at the methyl group, 1-methylcycloheptanecarboxamide **11a** gave a mixture of monoarylated

11b and biarylated products **11c**, the latter involving the arylation at the cyclic methylene C-H bonds.[8] When 1-phenylcyclobutanecarboxamide **12a** and 1-phenylcyclopentanecarboxamide **13a** were used, the cleavage of β-methlyene C-H bonds was the predominant reaction and γ-benzenes C(sp^2)-H bonds reacted to a lesser extent. The structure of **12c** was confirmed from X-ray crystallography, which show that the introduced aryl groups are located *syn* to the directing group. This also indicates the importance of the directing group. The presence of two substituents on the α-carbon, as in **14a** resulted in a low conversion and the arylation product **14b** was obtained in 30% yield.

Phenyl bromides and triflates did not give arylation products (Table 3). The scope of aryl iodides with various substituents at the para position was examined using **1a** as the substrate (Table 3). The results showed that common functional groups, including esters, iodide, bromides, chlorides and amines, were compatible in the present reaction. Electron rich aryl iodides tended to give the products in slightly higher yields than electron poor aryl iodides. Ortho-substituted aryl iodides resulted in no reaction. The heterocyclic aryl iodide, such as thiophene and indole gave the arylated product.

A gram scale reaction of **6a** was successfully performed in a 30-mL two-necked flask under the 5 mol% of nickel catalyst (eq 1).

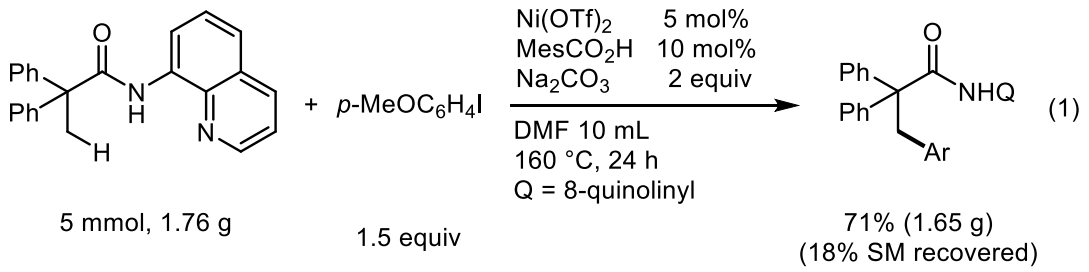
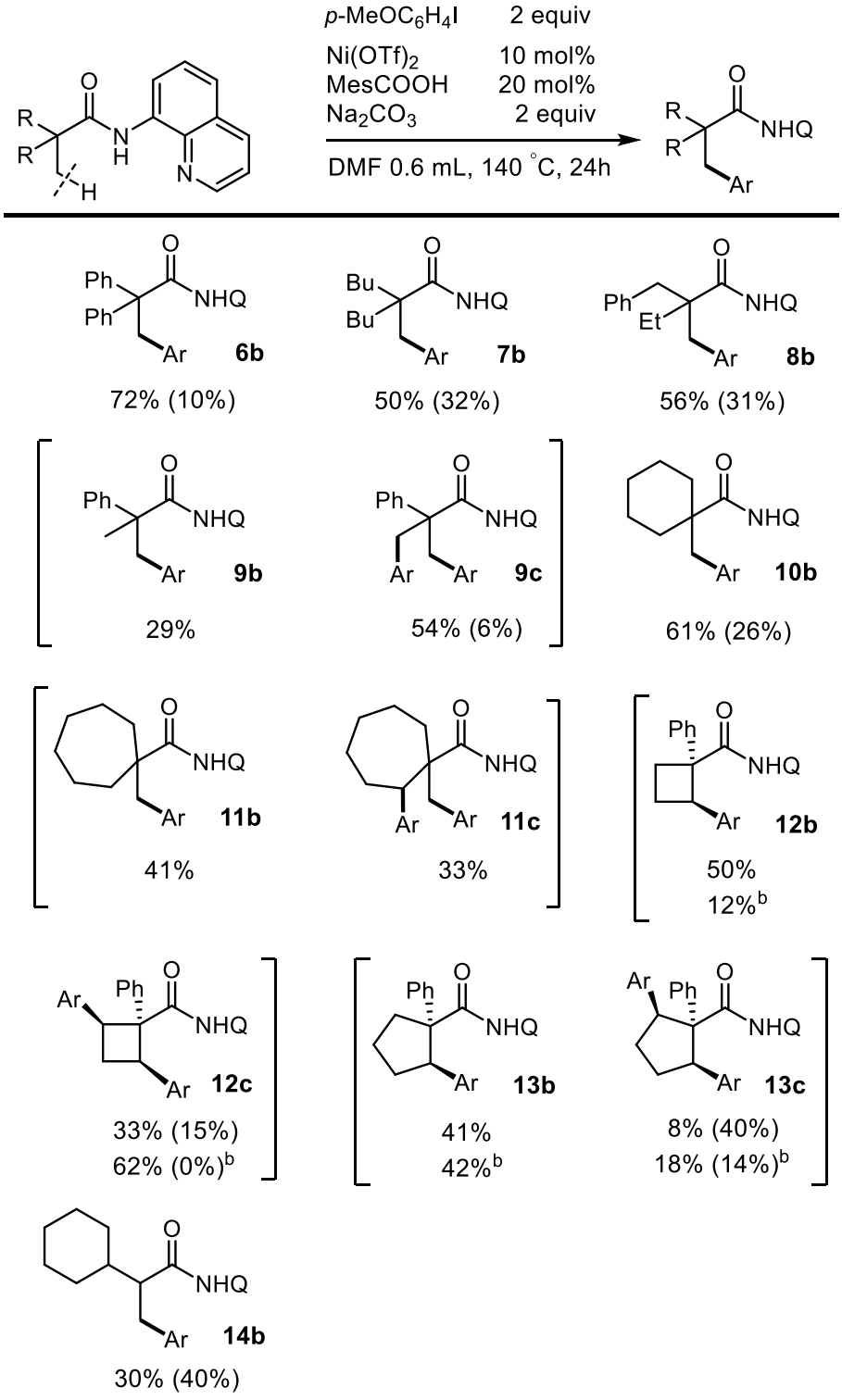
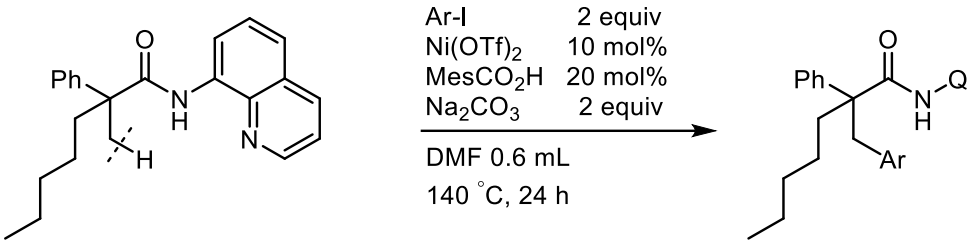


Table 2. The Nickel-Catalyzed Direct Arylation of Aliphatic Amides with 4-Iodoanisole[a]

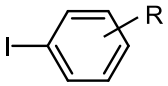


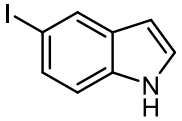
[a] Reaction conditions: amide (0.3 mmol), aryl iodides (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), MesCOOH (0.06 mmol), Na_2CO_3 (0.6 mmol) in DMF (0.6 mL) at 140 °C for 24 h. Isolated yields by column chromatogrphy. The number in parenthesis is the yield of the recovered starting amide. [b] [1,1':3',1''-terphenyl]-2'-carboxylic acid (2,6-$Ph_2C_6H_3COOH$) was used instead of MesCOOH and 4-iodoanisole (0.9 mol) was used.

Table 3. Scope of Aryl Halides in Ni-Catalyzed Direct Arylation of C(sp^3)-H Bonds[a]

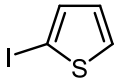


Ph-I **1c**	83%[b]	R = *p*-CF_3 **1d**	49% (22%)[c]
Ph-Br	9%[b]	= *p*-CO_2Me **1e**	44% (19%)
Ph-OTf	0%[b]	= *p*-I **1f**	61% (trace)[c]
		= *p*-Cl **1g**	60% (12%)[c]
		= *p*-Me **1h**	76% (13%)[c]
		= *p*-OMe **1i**	83% (12%)
		= *p*-NH_2 **1j**	68% (10%)
		= *p*-NMe_2 **1k**	75% (12%)
		= *o*-Me **1l**	0%





1 m75% (11%)

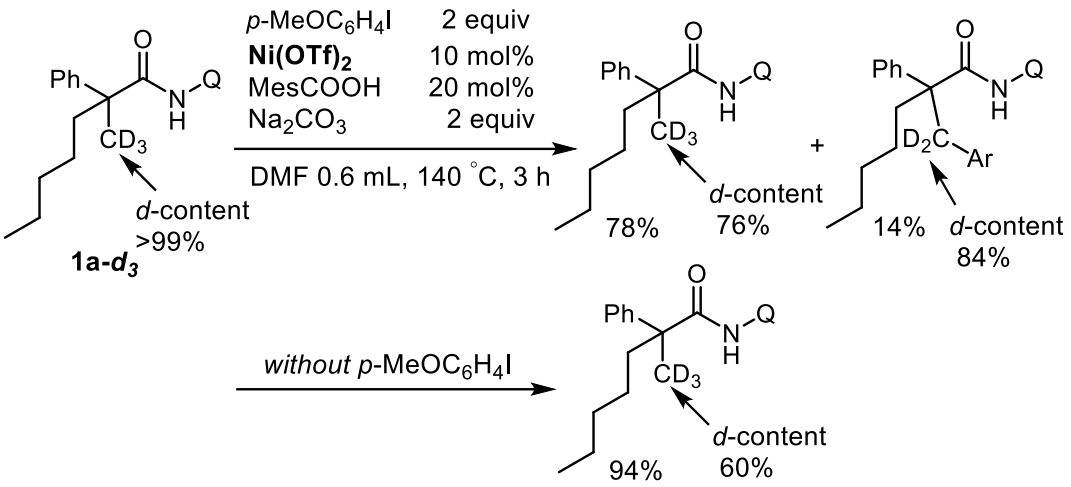


1n 60% (trace)

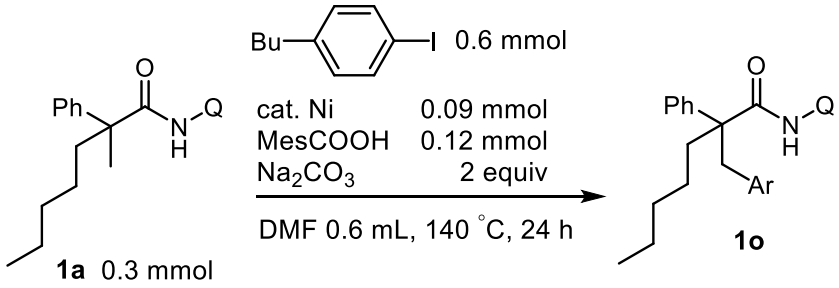
[a] Reaction conditions: amide (0.3 mmol), aryl iodides (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), MesCOOH (0.06 mmol), Na_2CO_3 (0.6 mmol) in DMF (0.6 mL) at 140 °C for 24 h. The number in parentheses is the yield of recovered starting amides. [b] NMR yields. [c] Purified by GPC.

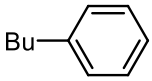
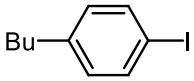
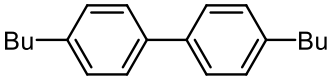
To gain additional insights into the mechanism for the reaction, deuterium labeling experiments were carried out (Scheme 1). The deuterated amides **1a-*d*$_3$** were reacted with 4-iodoanisole for 3h under standard conditions (Scheme 1). A significant amount of H/D exchange between the methyl C-D bond and N-H bond was detected. Thus, the D content in the recovered amide decreased from >99% to 76%, and the D content of the amide nitrogen increased from 0% to 23%. A significant amount of H/D exchange was observed, even in the absence of 4-iodoanisole. These results suggest that the cleavage of C-H bonds is rapid and reversible, and the cleavage of C-H bonds occurs before the reaction with the aryl iodide.

Scheme 1. Deuterium Labeling Experiments



Scheme 2. Product Distribution[a]



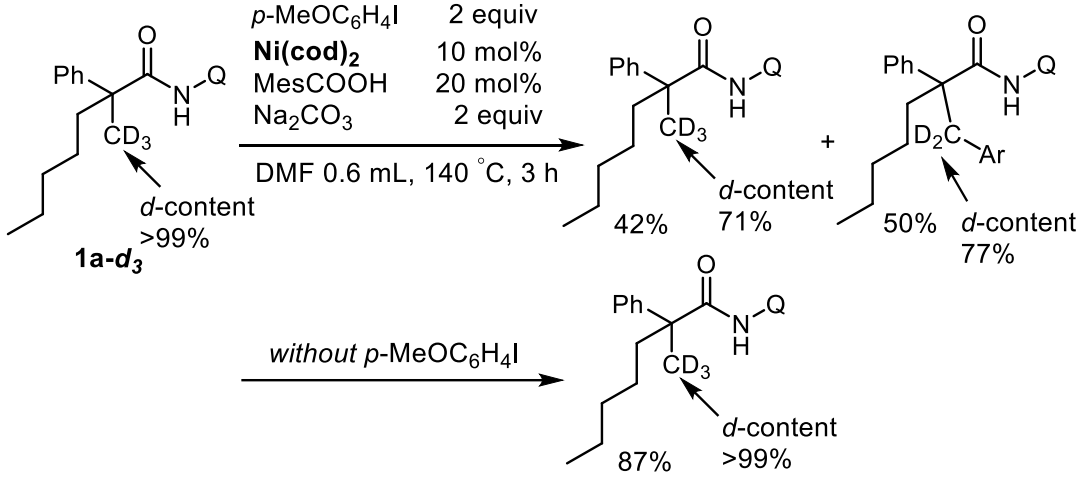
cat. Ni	**1o**			
Ni(cod)$_2$	67% (32%)	0.077 mmol 86%/Ni(0)	0.20 mmol	not observed
Ni(OTf)$_2$	65% (36%)	trace	0.37 mmol	not observed

[a] The yields were determined by GC and ^{1}H-NNMR.

Product distribution was examined in detail, in order to develop a better understanding of the difference between Ni(0) and Ni(II)-catalyzed reactions (Scheme 2). In the reaction of **1a** with 1-butyl-4-iodobenzene in the presence of 30 mol% Ni(cod)$_2$, the arylation product **1o** was obtained in 67% NMR yield with 32% of the starting amide **1a** being recovered. When Ni(0) was used, butylbenzene was produced in 86% yield/Ni(0) and no biaryl derivative was formed. In sharp contrast, when Ni(OTf)$_2$ was used as the catalyst, neither butylbenzene nor biaryl were detected. The arylation product **1o** was obtained in 65% NMR yield with 36% of the starting amide being recovered, along with the corresponding amount of 4-iodo-biphenyl. It is known that Ni(0) complexes react with Ar-X to give homocoupling products Ar-Ar with

the generation of a Ni(II) complex,[9] however the results in Scheme 2 indicate that such a reaction did not take place. Instead, the results suggest that the Ni(0) complex was oxidized by 1-butyl-4-iodobenzene with the generation of butylbenzene.[10] The source of hydrogen is probably the N-H bonds of the amide. The results of the above analyses indicate that the catalytic active species in this reaction is not Ni(0)-complex but rather, the Ni(II) complex.

Scheme 3. Deuterium Labeling Experiments with Ni(0)-Catalyst

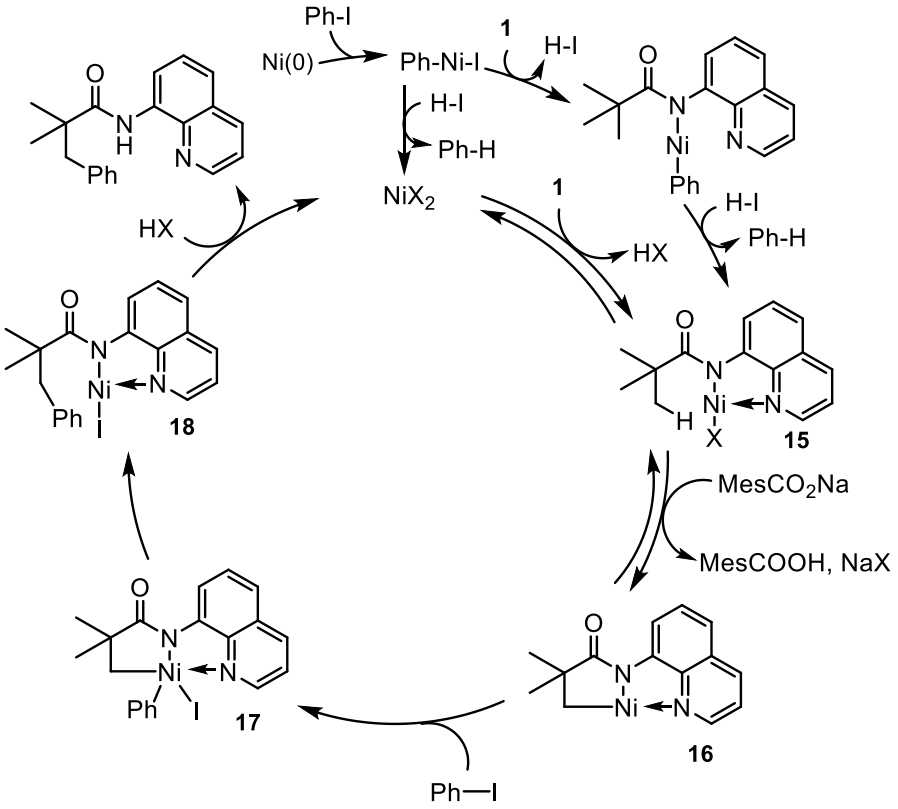


To gain more information, deuterium labeling experiment using nickel(0)-catalyst was examined. The deuterated amides **1a-*d*$_3$** were reacted with Ni(0)-catalyst for 3h under standard conditions (Scheme 3). As the result with Ni(II)-catalyst, the H/D exchange at methyl group was observed (Scheme 1). Contrast to the Ni(II)-catalyst, the H/D exchange did not take place in the case of the absence of 4-iodoanisole, suggesting that the presence of an aryl iodide is required for the cleavage of C-H bonds with Ni(0)-catalyst to take place. These results also indicate that Ni(0)-complex was not catalytic active species and Ni(0)-complex was oxidized by the aryl iodide to generate Ni(II)-complex.

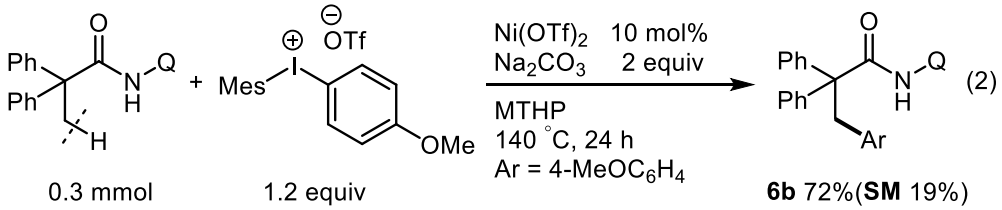
A proposed mechanism for the reaction is shown in Scheme 4. Coordination of the amide to the Ni center followed by ligand exchange with the concomitant generation of HX gives the Ni complex **15**, which undergoes reversible cyclometalation to give **16** probably via a concerted-metalation−deprotonation mechanism. The oxidative addition of iodobenzene gives the high-valent Ni(IV) complex **17** which is stabilized by the *N*,*N*-bidentate directing group. The Ni(IV) complex **17** underwent reductive elimination to give **18**, which, on protonation, affords the desired arylation product with the regeneration of Ni(II). In the case of the Ni(0)-catalyst, the reaction of the Ni(0) complex and iodobenzene gives the aryl-nickel species, following protonation or ligand exchange with amide N-H and protonation to give the Ni(II) complex **15** with the generation of benzene.[10] In order to gain additional insight into the mechanism, we performed some radical trapping experiments. The addition of

2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) did not inhibit the reaction and the arylation product was obtained in moderate yield (53%). This suggests that a single electron transfer (SET) was not involved in this reaction.

Scheme 4. Proposed Mechanism



Not only aryl iodide but also diaryliodonium salt is applicable as an arylated reagent (eq 2).[11] Although the addition of a sterically bulky carboxylic acid was required for the reaction with aryl iodides, the arylated product was obtained in the absence of a carboxylic acid. A Ni(II)/Ni(IV) cycle is also operative in this reaction.



2.3 Conclusion

In summary, we report on the first example of the nickel-catalyzed direct arylation of unactivated C(sp^3)-H bonds in aliphatic amides having 8-aminoquinoline moiety as a bidentate directing group with aryl halides and diaryliodonium salts. Some mechanistic experiments revealed that the reaction proceeded via not Ni(0)/Ni(II) or Ni(I)/Ni(III) cycle but Ni(Ii)/Ni(IV) cycle, which is not common for nickel-catalyzed cross coupling reaction. After

published this paper, about 10 reports about the Ni(II)-catalyzed functionalization of C(sp^3)-H bonds using a combination of nickel(II)-catalyst and bidentate directing group were reported by another researchers.[12]

2.4 Experimental Section

General Information.

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. The data is reported as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad peak, and m = multiplet), coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a Horiba FT-700 spectrometer. Absorption is reported in reciprocal centimeters (cm-^{1}) with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained on a Shimadzu GCMS-QP 2010 instrument. High resolution mass spectra (HRMS) were obtained using a JEOL JMS-DX303 spectrometer. Melting points were determined using a SRS MPA 100 instrument. Column chromatography was performed with SiO_2 (Silicycle SilicaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC). X-Ray crystallographic structure analysis performed on Rigaku R-AXIS RAPID imaging plate diffract meter with graphite monochromated Cu Kα radiation (λ= 1.54187 Å).

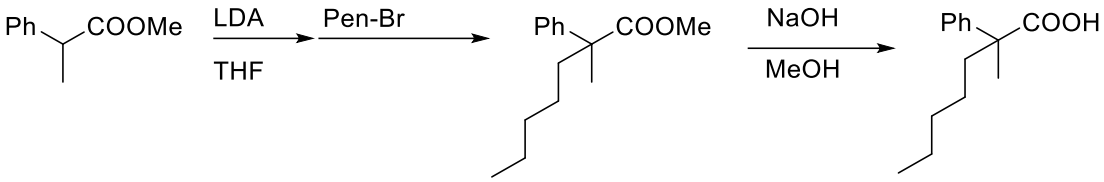
Materials.

Na_2CO_3 (CAS 497-19-8) was purchased from Nacalai Tesque, Inc. 4-Iodoanisole (CAS 696-62-8) and 8-Aminoquinoline (CAS 578-66-5), 2,4,6-Trimethylbenzoic Acid (CAS 480-63-7) and methyl 2-methylbenzoate (CAS 89-71-4) were purchased from Tokyo Kasei Kogyo Co., Ltd. *N*,*N*-dimethylformamide, super dehydrated (CAS 68-12-2) was purchased from Wako Pure Chemicals. $Ni(OTf)_2$ (CAS 60871-84-3) was prepared by chapter 1 procedure.

Synthesis of the Starting Amides.

All amides bearing an 8-aminoquinoline moiety were prepared by the reaction of the corresponding acid chlorides with 8-aminoquinoline. 1-Phenylcyclobutanecarboxylic acid (SM for **12a**) was synthesized by a literature procedure.[13] 2-Phenylheptanoic acid (SM for **1a-*d*$_3$**) was synthesized by a literature procedure.[14] 1-Methyl-*N*-(quinolin-8-yl)cyclohexanecarboxamide **10a** (CAS 1429896-59-2) and 2-methyl-2-phenyl-*N*-(quinolin-8-yl)propanamide **9a** (CAS 1327475-16-0) were prepared by a literature procedure.[15] All spectrum data of starting amides are cited in original paper.[16]

General Procedure for the Preparation of the Starting Carboxylic Acid.

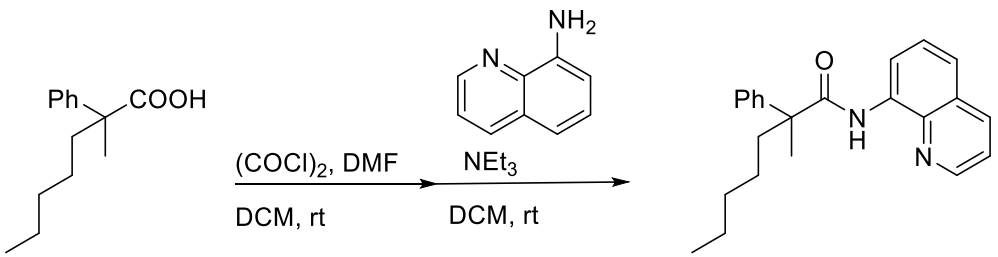


A solution of *n*-buthyllithium in hexane (1.6M, 15 mL, 24 mmol) was added dropwise to a solution of diisopropylamine (2.4 g, 24 mmol) in 30 mL of THF at -78 °C. The solution was stirred for 1h and a solution of methyl 2-phenylpropanoate (3.3 g, 20 mmol) in 10 ml of THF was added dropwise to the LDA solution. The solution was stirred for 1h at -78 °C and 1-bromopentane (6.0 g, 40 mmol) was added dropwise to the solution. The solution was stirred for 1 h at -78 °C and then 4h at r.t. The reaction mixture was quenched with water and the organic layer was separated. The aqueous layer was extracted with ether (2 x 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the desired methyl 2-methyl-2-phenylheptanoate (4.5 g, 96%).

The ester was hydrolyzed in 30 mL of 4N NaOH aq. and MeOH at 100 °C for 1day. After cooling the solution, the aqueous layer was extracted with DCM (2 x 15 mL). The aqueous layer was acidified with aqueous HCl and the aqueous layer was extracted with DCM (2 x 15 mL) and brine (30 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the desired carboxylic acid (2.9 g, 70%).

2-Butyl-2-methylhexanoic acid (SM for **7a**) was synthesized by the reaction of methyl 2-butylhexanoate with methyl iodide. 2-Benzyl-2-methylbutanoic acid (SM for **8a**) was synthesized by the reaction of methyl 2-methyl-3-phenylpropanoate with ethyl iodide. 1-Methylcycloheptanecarboxylic acid (SM for **11a**) was synthesized by the reaction of methyl cycloheptanecarboxylate with methyl iodide. 2-Cyclohexylpropanoic acid (SM for **14a**) was synthesized by the reaction of methyl 2-cyclohexylacetate with methyl iodide. 2-methyl-***d*$_3$-2-phenylheptanoic acid (SM for **1a**-***d*$_3$) was synthesized by the reaction of methyl 2-phenylheptanoate with metyl iodide-d_3.

General Procedure for the Preparation of Starting Amide.



To an oven-dried 100 mL three-necked flask, 2-methyl-2-phenylheptanoic acid (3.3 g, 15 mmol), DMF (5 drops) and DCM (30 mL) were added under a N_2 atmosphere. Oxalyl chloride (1.5 mL, 18 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

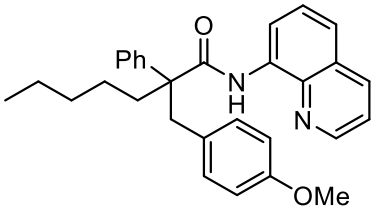
removed *in vacuo*. The resulting acid chloride was used immediately without further purification.

To another oven-dried 100 mL three-necked flask, 8-aminoquinoline (2.9 g, 20 mmol, 1.3 equiv.), Et_3N (4.1 mL, 30 mmol, 2 equiv.) and DCM (30 mL) were added. A solution of the acid chloride in DCM (10 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. $NaHCO_3$ (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 $MgSO_4$, filtered and evaporated *in vacuo*. The resulting crude amide was purified by column chromatography on silica gel (eluant: hexane/EtOAc = 5/1) to afford the desired amide as a white solid (4.6 g, 90%).

General Procedure for Direct Arylation: Ni-Catalyzed Arylation of Amides 1a with 4-iodoanisole.

To an oven-dried 5 mL screw-capped vial, in a glove box 2-methyl-2-phenyl-*N*-(quinolin-8-yl)heptanamide **1a** (104 mg, 0.3 mmol), 4-iodoanisole (140 mg, 0.6 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), MesCOOH (9.8 mg, 0.06 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and DMF (0.6 mL) were added. The mixture was stirred for 24 h at 140 °C followed by cooling. 30 mL of water was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with and brine (20 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 20/1) to afford the desired arylated product **1b** (112 mg, 83%) as a white solid.

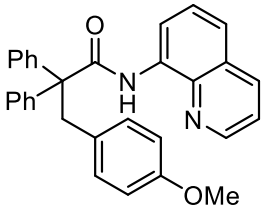
2-(4-methoxybenzyl)-2-phenyl-*N*-(quinolin-8-yl)heptanamide (1b).



R_f 0.34 (hexane/EtOAc = 5/1). White Solid. Mp = 144 °C. ^1H NMR ($CDCl_3$, 399.78 MHz) 0.83 (t, J = 6.4 Hz, 3H), 1.26-1.55 (m, 6H), 2.01 (t, J = 8.0, 2H), 3.35 (d, J = 14.0 Hz, 1H), 3.51 (d, J = 13.6 Hz, 1H), 3.72 (s, 3H), 6.64 (s, 4H), 7.25-7.36 (m, 6H), 7.46 (d, J = 8.0, 1H), 7.54 (t, J = 8.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.58 (dd, J = 4.0, 1.2 Hz, 1H), 8.78 (d, J = 7.6 Hz, 1H), 9.80 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.03, 22.42, 24.06, 32.31, 33.99, 40.79, 55.05, 56.60, 113.00, 116.02, 21.012, 121.40, 126.96, 127.32, 127.66, 127.84, 128.39, 129.30, 131.24, 134.65, 138.62, 142.99, 148.11, 158.01, 174.67; IR (neat) 3343 w, 2934 w, 1712 m, 1683 m, 1522 s, 1424 m, 1325 m, 1247 m, 1036 w, 825 m, 754 m; MS *m/z*

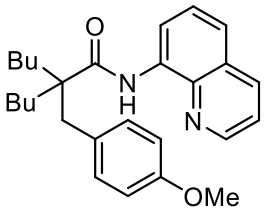
(relative intensity, %) 452 (M^+, 23), 264 (26), 167 (67), 144 (34), 119 (100), 13 (13); HRMS Calcd for $C_{30}H_{32}N_2O_2$: 452.2464; Found: 452.2469.

3-(4-methoxyphenyl)-2,2-diphenyl-*N*-(quinolin-8-yl)propanamide (6b).



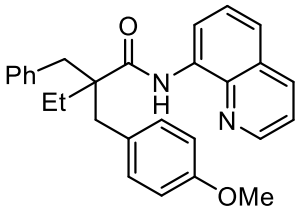
R_f 0.20 (hexane/EtOAc = 5/1). White Solid. Mp =164 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.68 (s, 3H), 3.85 (s, 2H), 6.56 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 7.54-7.32 (m, 7H), 7.36-7.38 (m, 4H), 7.42 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.52 (dd, J = 4.0, 1.2 Hz, 1H), 8.78 (dd, J = 8.0, 1.2 Hz, 1H), 10.23 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 43.59, 55.02, 64.45, 112.75, 115.98, 121.29, 121.40, 126.97, 127.24, 127.78, 128.02, 129.70, 129.79, 132.15, 134.65, 135.96, 138.66, 142.35, 148.07, 157.88, 172.18; IR (neat) 3330 w, 1679 m, 1512 s, 1484 m, 1384 m, 1326 m, 1250 m, 1178 w, 1036 w, 825 m, 753 s, 700 m; MS *m/z* (relative intensity, %) 458 (M^+, 12), 337 (29), 265 (10), 264 (51), 171 (40), 165 (13), 144 (17), 121 (100); HRMS Calcd for $C_{31}H_{26}N_2O_2$: 458.1994; Found: 458.1995.

2-butyl-2-(4-methoxybenzyl)-*N*-(quinolin-8-yl)hexanamide (7b).



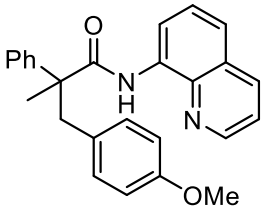
R_f 0.31 (hexane/EtOAc = 5/1). Pale Brown Solid. Mp =97-98 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.92 (t, J = 6.8 Hz, 6H), 1.32-1.38 (m, 8H), 1.59-1.80 (m, 4H), 3.01 (s, 2H), 3.69 (s, 3H), 6.70 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 7.42 (dd, J = 8.4, 4.0, 1H), 7.48-7.57 (m, 2H), 8.14 (dd, J = 8.4, 1.6 Hz, 1H), 8.74 (dd, J = 4.4, 1.6 Hz, 1H), 8.82 (dd, J = 8.0, 1.6 Hz, 1H), 10.15 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.05, 23.24, 26.25, 34.27, 40.18, 51.64, 55.04, 113.35, 116.23, 11.12, 121.45, 127.44, 127.87, 129.80, 130.92, 134.45, 136.16, 138.75, 148.11, 157.98, 175.39; IR (neat) 3361 w, 2931 w, 1672 m, 1524 s, 1466 m, 1423 m, 1384 m, 1325 m, 1249 m, 1178 w, 1038 w, 825 m, 792 m; MS *m/z* (relative intensity, %) 418 (M^+, 23), 361 (10), 297 (10), 246 (14), 217 (31), 171 (47), 145 (10), 144 (67), 121 (100); HRMS Calcd for $C_{27}H_{34}N_2O_2$: 418.2620; Found: 418.2617.

2-benzyl-2-(4-methoxybenzyl)-*N*-(quinolin-8-yl)butanamide (8b).



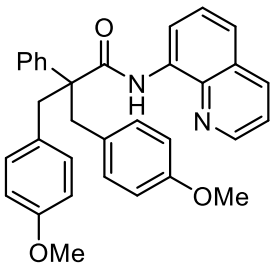
R_f 0.29 (hexane/EtOAc = 5/1). Pale Brown Solid. Mp =97-98 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.18 (t, J = 7.2 Hz, 3H), 1.75 (q, J = 7.2 Hz, 2H), 2.95 (dd, J = 20.8, 13.6 Hz, 2H), 3.29 (dd, J = 25.6, 14.0 Hz, 2H), 3.64 (s, 3H), 6.66 (d, J = 8.0 Hz, 2H), 7.07-7.21 (m, 7H), 7.36 (dd, J = 8.4, 4.0 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.60 (dd, J = 4.0, 1.2 Hz, 1H), 8.86 (dd, J = 8.0, 1.2 Hz, 1H), 9.95 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 8.68, 23.84, 40.93, 41.54, 53.25, 55.00, 113.37, 116.25, 121.26, 121.36, 126.24, 127.34, 127.75, 128.00, 129.50, 130.11, 131.03, 134.21, 136.02, 137.69, 138.62, 147.96, 158.00, 174.57; IR (neat) 3359 w, 2931 w, 1671 m, 1526 s, 1325 w, 1248 m, 1179 w, 1036 w, 826 w; MS *m/z* (relative intensity, %) 424 (M^+, 8), 334 (14), 333 (60), 190 (12), 189 (100), 171 (31), 144 (25), 121 (73) 91 (26); HRMS Calcd for $C_{28}H_{28}N_2O_2$: 424.2151; Found: 424.2145

3-(4-methoxyphenyl)-2-methyl-2-phenyl-*N*-(quinolin-8-yl)propanamide (9b).



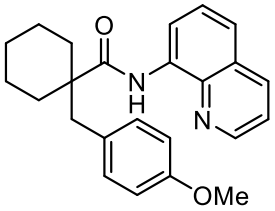
R_f 0.23 (hexane/EtOAc = 5/1). White Solid. Mp =136 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.68 (s, 3H), 3.34 (d, J = 13.6 Hz, 1H), 3.56 (d, J = 13.6 Hz, 1H), 3.71 (s, 3H), 6.66 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 7.27-7.38 (m, 4H), 7.43-7.45 (m, 3H), 7.52 (t, J = 8.4 Hz, 1H), 8.06 (dd, J = 8.4, 1.6 Hz, 1H), 8.57 (dd, J = 4.0, 1.6 Hz, 1H), 8.80 (d, J = 8.0 Hz, 1H), 9.89 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 22.80, 44.34, 52.89, 55.05, 113.06, 116.00, 121.24, 121.40, 127.08, 127.22, 127.29, 127.79, 128.53, 129.47, 131.53, 134.60, 136.04, 138.58, 143.16, 148.09, 158.05, 175.12; IR (neat) 3351 w, 1679 m, 1523 s, 1484 m, 1384 m, 1326 m, 1245 m, 1034 w, 824 m, 755 m; MS *m/z* (relative intensity, %) 396 (M^+, 9), 171 (40), 144 (23), 121 (100), 103 (16); HRMS Calcd for $C_{26}H_{24}N_2O_2$: 396.1838; Found: 396.1838.

2-(4-methoxybenzyl)-3-(4-methoxyphenyl)-2-phenyl-*N*-(quinolin-8-yl)propanamide (9c).



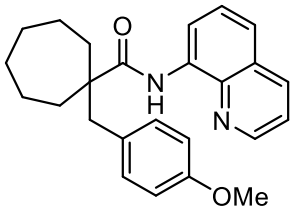
R_f 0.11 (hexane/EtOAc = 5/1). White Solid. Mp =157 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.43 (q, J = 10.8 Hz, 4H), 3.69 (s, 6H), 6.64 (d, J = 8.8 Hz, 4H), 6.87 (d, J = 8.8 Hz, 4H), 7.27-7.37 (m, 6H), 7.44 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 8.4 Hz, 1H), 8.06 (dd, J = 8.0, 1.2 Hz, 1H), 8.52 (dd, J = 4.0, 1.2 Hz, 1H), 8.73 (d, J = 7.2 Hz, 1H), 9.87 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 40.93, 55.01, 58.20, 113.12, 116.04, 121.15, 121.36, 127.16, 127.30, 127.78, 128.15, 128.38, 129.11, 131.55, 134.44, 135.94, 138.53, 142.40, 148.06, 158.03, 173.84; IR (neat) 3338 w, 1685 m, 1610 w, 1512 s, 1484 m, 1325 w, 1248 m, 1179 m, 1035 m, 824 m, 754 m; MS *m/z* (relative intensity, %) 502 (M^+, 2), 382 (19), 381 (69), 264 (13), 237 (50), 209 (17), 171 (46), 144 (10), 121 (100); HRMS Calcd for $C_{33}H_{30}N_2O_3$: 502.2249; Found: 502.2256.

1-(4-methoxybenzyl)-*N*-(quinolin-8-yl)cyclohexanecarboxamide (10b).



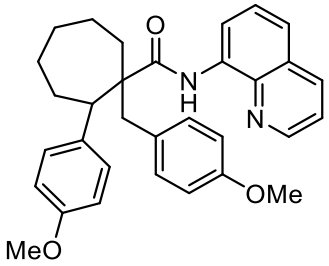
R_f 0.31 (hexane/EtOAc = 5/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.32-1.75 (m, 8H), 2.22-2.25 (m, 2H), 2.90 (s, 2H), 3.61 (s, 3H), 6.61 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 7.40 (dd, J = 8.4, 4.0 Hz, 1H), 7.47 (dd, J = 8.0, 4.0, 1H), 7.54 (t, J = 8.4 Hz, 1H), 8.12 (dd, J = 8.4, 2.0 Hz, 1H), 8.69 (dd, J = 4.0, 2.0 Hz, 1H), 8.80 (dd, J = 8.0, 1.6 Hz, 1H), 10.01 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 23.11, 25.92, 34.12, 46.40, 49.61, 54.99, 113.20, 116.22, 121.09, 121.36, 127.39, 127.81, 129.13, 130.99, 134.47, 136.09, 138.70, 148.02, 158.08, 174.69; IR (neat) 3359 w, 2928 w, 1672 m, 1512 s, 1468 m, 1324 m, 1245 s, 1178 m, 1035 m, 792 m, 753 s; MS *m/z* (relative intensity, %) 374 (M^+, 17), 253 (14), 202 (13), 171 (44), 145 (10), 144 (68), 121 (100), 109 (10); HRMS Calcd for $C_{24}H_{26}N_2O_2$: 374.1990; Found: 374.1994.

1-(4-methoxybenzyl)-*N*-(quinolin-8-yl)cycloheptanecarboxamide (11b).



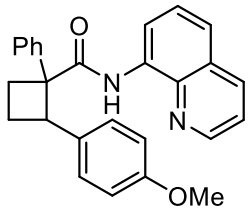
R_f 0.34 (hexane/EtOAc = 5/1). Pale yellow oil ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.58-1.78 (m, 10 H), 2.22-2.28 (m, 2H), 2.93 (s, 2H), 3.63 (s, 3H), 6.63 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.41 (dd, J = 8.4, 4.0 Hz, 1H), 7.48 (dd, J = 8.4, 1.6 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 8.13 (dd, J = 8.0, 1.6 Hz, 1H), 8.71 (dd, J = 4.0, 1.6 Hz, 1H), 8.82 (dd, J = 8.0, 1.2 Hz, 1H), 10.02 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 23.46, 30.02, 36.10, 46.90, 52.45, 55.00, 113.23, 116.18, 121.08, 121.39, 127.43, 127.83, 129.71, 131.01, 134.59, 136.13, 138.69, 148.03, 158.05, 175.87; IR (neat) 3359 w, 2924 w, 1672 m, 1523 s, 1465 m, 1324 m, 1246 s, 1178 m, 1036 m, 825 m, 753 s; MS *m/z* (relative intensity, %) 388 (M^+, 26), 267 (20), 216 (14), 171 (56), 145 (13), 144 (93), 121 (100); HRMS Calcd for $C_{25}H_{28}N_2O_2$: 388.2152; Found: 388.2152.

1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-*N*-(quinolin-8-yl)cycloheptanecarboxamide (11c).



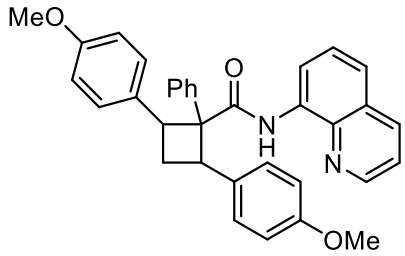
R_f 0.23 (hexane/EtOAc = 5/1). White Solid. Mp =79-80 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.44-1.68 (m, 5H), 1.92-1.95 (m, 3H), 2.31-2.49 (m, 3H), 2.79 (t, J = 10.0 Hz, 1H), 2.98 (d, J = 13.6 Hz, 1H), 3.11 (d, J = 14.0 Hz, 1H), 3.64 (s, 3H), 3.82 (s, 3H), 6.60 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.41 (dd, J = 8.0, 4.0 Hz, 1H), 7.48-7.56 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.72 (d, J = 4.4 Hz, 1H), 8.80 (d, J = 7.2 Hz, 1H), 10.12 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 23.76, 31.07, 35.74, 40.07, 40.74, 43.83, 45.85, 51.88, 55.02, 55.25, 113.37, 113.80, 116.26, 121.19, 121.45, 127.42 (two overlapping peaks), 127.85, 129.50, 131.01, 134.56, 136.18, 142.01, 148.14, 157.58, 158.07, 175.92; .18, IR (neat) 3358 w, 2924 w, 1670 m, 1611 m, 1511 s, 1484 m, 1325 m, 1245 s, 1178 m, 1035 m, 824 m, 752 s; MS *m/z* (relative intensity, %) 495 (18), 494 (M^+, 43), 373 (18), 172 (10), 171 (68), 145 (11), 144 (63), 122 (10), 121 (100); HRMS Calcd for $C_{32}H_{34}N_2O_3$: 494.2569; Found: 494.2568.

2-(4-methoxyphenyl)-1-phenyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide (12b).



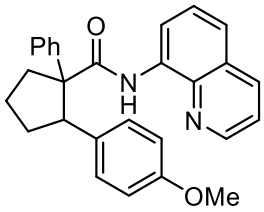
R_f 0.31 (hexane/EtOAc = 5/1). White Solid. Mp =128 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.26-2.37 (m, 2H), 2.70-2.78 (m, 1H), 3.27 (t, J = 7.6 Hz, 1H), 3.47 (s, 3H), 4.28 (t, J = 7.6 Hz, 1H), 6.57 (d, J = 2H), 7.23 (dd, J = 8.4, 4.0 Hz, 1H), 7.29-7.46 (m, 7H), 7.53 (d, J = 8.0 Hz, 2H), 7.96 (dd, J = 8.4, 1.6 Hz, 1H), 8.37 (dd, J = 4.0, 1.6 Hz, 1H), 8.57 (dd, J = 8.0, 1.6 Hz, 1H), 9.27 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 24.57, 29.03, 49.81, 54.94, 61.41, 113.50, 115.60, 120.88, 121.02, 126.33, 126.87, 127.03, 128.94, 129.20, 132.58, 134.51, 135.55, 138.45, 145.98, 147.57, 158.36, 171.53; IR (neat) 3324 w, 2944 w, 1674 m, 1524 s, 1485 m, 1327 w, 1251 m, 1178 w, 1035 w, 756 m; MS *m/z* (relative intensity, %) 409 (11), 408 (M^+, 36), 275 (20), 274 (95), 273 (12), 246 (11), 231 (12), 172 (12), 171 (100), 145 (10), 144 (69), 134 (69), 130 (17), 119 (17), 103 (42), 91 (10), 77 (10); HRMS Calcd for $C_{27}H_{24}N_2O_2$: 408.1838; Found: 408.1835.

2,4-bis(4-methoxyphenyl)-1-phenyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide (12c).



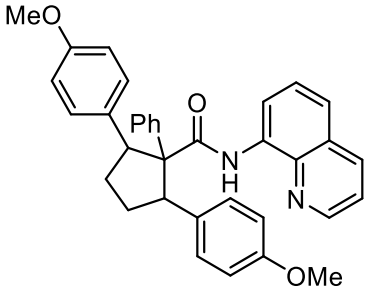
R_f 0.20 (hexane/EtOAc = 5/1). White Solid. Mp =87 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.72 (q, 8.0 Hz, 1H), 3.49 (q, J = 10.4 Hz, 1H), 3.69 (s, 6H), 4.09 (dd, J = 10.8, 8.0 Hz, 1H), 6.78 (d, J = 8.8 Hz, 4H), 7.20 (dd, J = 8.0, 4.0 Hz, 1H), 7.27-7.34 (m, 2H), 7.43-7.48 (m, 5H), 7.34 (t, J = 7.6 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.92 (dd, J = 8.0, 1.6 Hz, 1H), 8.31 (dd, J = 4.4, 1.6 Hz, 1H), 8.44 (dd, J = 7.6, 1.6 Hz, 1H), 9.38 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 30.83, 47.16, 55.11, 67.56, 113.38, 115.90, 120.87, 121.01, 127.06, 127.33, 127.45, 129.08, 129.57, 132.57, 134.32, 135.64, 138.51, 145.12, 147.58, 158.14, 169.56; IR (neat) 3318 w, 1674 m, 1610 w, 1512 s, 1483 m, 1326 w, 1248 s, 1178 m, 1035 m, 825 m, 755 m; MS *m/z* (relative intensity, %) 514 (M^+, 9), 381 (12), 380 (41), 525 (12), 251 (67), 238 (17), 237 (100), 210 (14), 209 (80), 171 (13), 165 (14), 144 (21); HRMS Calcd for $C_{34}H_{30}N_2O_3$: 514.2256; Found: 514.2253.

2-(4-methoxyphenyl)-1-phenyl-*N*-(quinolin-8-yl)cyclopentanecarboxamide (13b).



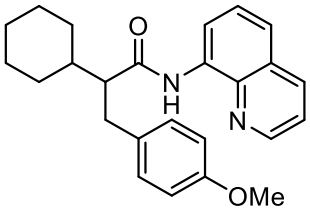
R_f 0.23 (hexane/EtOAc = 5/1). White Solid. Mp =130 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.74-1.81 (m, 1H), 2.14-2.33 (m, 4H), 3.40-3.11 (m, 1H), 3.53 (s, 3H), 3.92 (t, J = 8.0 Hz, 1H), 6.54 (d, J = 8.8 Hz, 2H), 7.23-7.31 (m, 4H), 7.33-7.44 (m, 4H), 7.62 (d, J = 8.8 Hz, 2H), 7.97 (dd, J = 8.0, 1.6 Hz, 1H), 8.39 (dd, J = 4.4, 1.6 Hz, 1H), 8.56 (dd, J = 8.0, 1.6 Hz, 1H), 9.35 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 22.42, 33.28, 38.24, 52.76, 54.90, 64.91, 113.25, 115.63, 120.87, 121.10, 126.89, 127.10, 127.51, 128.63, 129.92, 134.07, 134.49, 138.40, 144.08, 147.65, 157.92, 173.31; IR (neat) 3326 w, 2952 w, 1672 m, 1520 s, 1484 s, 1384 m, 1247 s, 1180 m, 1035 m, 826 m, 755 m; MS *m/z* (relative intensity, %) 423 (13), 422 (M^+, 40), 276 (20), 275 (100), 257 (16), 250 (26), 172 (10), 171 (70), 147 (12), 145 (10), 144 (76), 117 (18), 103 (30), 91 (10); HRMS Calcd for $C_{28}H_{26}N_2O_2$: 422.1994; Found: 422.1992.

2,5-bis(4-methoxyphenyl)-1-phenyl-*N*-(quinolin-8-yl)cyclopentanecarboxamide (13c).



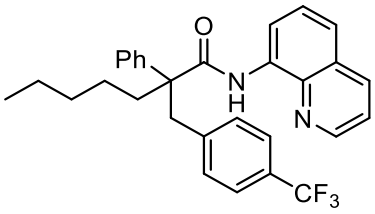
R_f 0.23 (hexane/EtOAc = 5/1). White Solid. Mp =130 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.31-2.38 (m, 2H), 2.81-2.86 (m, 2H), 3.57 (s, 6H), 3.74-3.78 (m, 2H), 6.57 (d, J = 8.8 Hz, 4H), 7.16 (dd, J = 8.4, 4.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 4H), 7.26-7.33 (m, 5H), 7.37 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (dd, J = 8.0, 1.6 Hz, 1H), 8.16 (dd, J = 4.0, 1.6 Hz, 1H), 8.76 (dd, J = 7.2, 1.6 Hz, 1H), 9.15 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 30.71, 54.94, 56.84, 69.23, 113.02, 115.78, 120.93, 120.98, 127.03, 127.11, 127.50, 127.96, 129.26, 130.79, 132.30, 134.53, 135.44, 138.46, 140.53, 147.51, 158.08, 171.52; IR (neat) 3325 w, 2933 w, 1672 m, 1513 s, 1483 m, 1246 s, 1179 m, 1036 m, 826 m; MS *m/z* (relative intensity, %) 529 (12), 528 (M^+, 28), 395 (10), 394 (34), 381 (29), 356 (12), 250 (16), 238 (17), 237 (94), 223 (14), 210 (12), 209 (58), 171 (33), 145 (14), 144 (100), 121 (15), 115 (10) 91 (10); HRMS Calcd for $C_{35}H_{32}N_2O_3$: 528.2413; Found: 528.2414.

2-cyclohexyl-3-(4-methoxyphenyl)-*N*-(quinolin-8-yl)propanamide (14b).



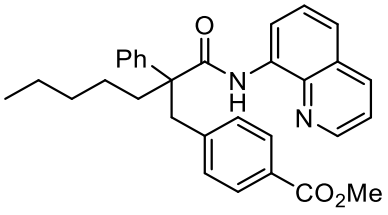
R_f 0.23 (hexane/EtOAc = 5/1). Pale wellow oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.34-1.31 (m, 5H), 1.64-1.87 (m, 5H), 2.04 (d, J = 8.4 Hz, 1H), 2.46-2.52 (m, 1H), 2.92-3.04 m, 2H), 3.62 (s, 3H), 6.69 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.36 (dd, J = 8.4, 4.0 Hz, 1H), 7.41-7.50 (m, 2H), 8.07 (dd, J = 8.4, 1.2 Hz, 1H), 8.70 (dd, J = 4.0, 2.0 Hz, 1H), 8.76 (d, J = 8.0 Hz, 1H), 9.53 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 26.33 (t, J = 5.7 Hz), 30.89, 31.05, 35.09, 40.63, 54.99, 58.02, 113.67, 116.28, 121.18, 121.36, 127.25, 127.74, 129.73, 132.26, 134.19, 136.11, 138.19, 147.90, 157.73, 173.34; IR (neat) 2925 w, 1683 m, 1523 s, 1484 m, 1324 m, 1246 m, 1037 w, 825 w; MS *m/z* (relative intensity, %) 388 (M^+, 29), 306 (15), 305 (49), 171 (30), 161 (56), 145 (16), 144 (100), 121 (54); HRMS Calcd for $C_{25}H_{28}N_2O_2$: 388.2151; Found: 388.2153.

2-phenyl-*N*-(quinolin-8-yl)-2-(4-(trifluoromethyl)benzyl)heptanamide (1d).



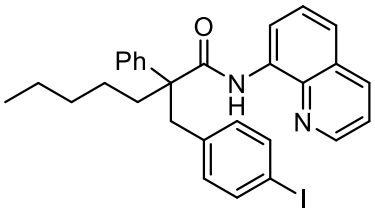
R_f 0.51 (hexane/EtOAc = 5/1). Pale Brown Solid. Mp =136 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.83 (t, J = 6.8 Hz, 3H), 1.27-1.57 (m, 6H), 1.94-2.07 (m, 2H), 3.45 (d, J = 13.6 Hz, 1H), 3.59 (d, J = 14.0 Hz, 1H), 6.79 (d, J = 7.6 Hz, 2H), 7.27-7.36 (m, 8H), 7.46 (d, J = 8.4 Hz, 1H), 7.54 (t, J = 8.4 Hz, 1H), 8.08 (dd, J = 8.0, 1.6 Hz, 1H), 8.56 (dd, J = 4.0, 1.6 Hz, 1H), 8.77 (d, J = 7.6 Hz, 1H), 9.79 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.11, 22.50, 24.23, 32.35, 34.27, 41.83, 56.63, 116.16, 120.33, 121.43, 121.58, 124.40 (q, J = 270 Hz), 124.52 (d, J = 3.8 Hz), 127.41 (d, J = 3.8 Hz), 127.72, 127.96, 128.69, 130.73, 134.59, 136.16, 138.69, 141.89, 142.37, 148.27, 147.23; IR (neat) 3340 w, 2934 w, 1682 m, 1523 s, 1485 m, 1323 s, 1163 m, 1119 s, 1067 m, 825 m, 700 m; MS *m/z* (relative intensity, %) 490 (M^+, 6), 172 (12), 171 (100), 144 (16); HRMS Calcd for $C_{30}H_{29}N_2O$: 490.2232; Found: 490.2228.

Methyl 4-(2-phenyl-2-(quinolin-8-ylcarbamoyl)heptyl)benzoate (1e).



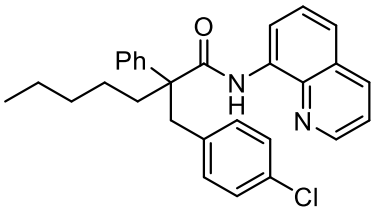
R_f 0.26 (hexane/EtOAc = 5/1). Off white solid. Mp =122 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.83 (t, J = 7.6 Hz, 3H), 1.26-1.60 (m, 6H), 1.93-2.03 (m, 2H), 3.43 (d, J = 14.0 Hz, 1H), 3.60 (d, J = 13.2 Hz, 1H), 3.86 (s, 3H), 6.76 (d, J = 8.4 Hz, 2H), 7.28-7.36 (m, 6H), 7.47 (d, J = 8.4 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.4 Hz, 1H), 8.56 (dd, J = 4.4, 1.2 Hz, 1H), 8.78 (d, J = 8.0 Hz, 1H), 9.79 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.02, 22.39, 24.09, 32.24, 34.08, 41.84, 51.94, 56.54, 116.05, 121.28, 121.44, 127.26, 127.30, 127.57, 127.84, 128.10, 128.53, 130.39, 134.49, 136.06, 138.56, 142.37, 143.20, 148.14, 167.14, 174.20; IR (neat) 3341 w, 2951 w, 1719 s, 1682 m, 1522 s, 1484 m, 1325 m, 1278 s, 1183 w, 1108 m, 754 m; MS *m/z* (relative intensity, %) 480 (M^+, 5), 172 (11), 171 (100), 144 (16); HRMS Calcd for $C_{31}H_{32}N_2O_3$: 480.2413; Found: 480.2414.

2-(4-Iodobenzyl)-2-phenyl-*N*-(quinolin-8-yl)heptanamide(1f).



R_f 0.51 (hexane/EtOAc = 5/1). Off white Solid. Mp =121 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.82 (t, J = 6.8 Hz, 3H), 1.25-1.54 (m, 6H), 1.93-2.05 (m, 2H), 3.33 (d, J = 13.6 Hz, 1H), 3.48 (d, J = 13.6 Hz, 1H), 6.43 (d, J = 8.4 Hz, 2H), 7.26-7.35 (m, 6H), 7.39 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 8.4 Hz, 1H), 8.06 (dd, J = 8.4, 1.6 Hz, 1H), 8.56 (dd, J = 4.0, 1.6 Hz, 1H), 8.77 (d, J = 8.0 Hz, 1H), 9.78 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.01, 22.38, 24.07, 32.24, 34.03, 41.33, 56.40, 91.84, 116.01, 121.24, 121.42, 127.19, 127.26, 127.60, 127.81, 128.51, 132.36, 134.48, 136.01, 136.60, 137.11, 138.55, 142.42, 148.13, 174.23; IR (neat) 3334 w, 2933 w, 1739 s, 1673 s, 1524 s, 1485 s, 1378 m, 1326 m, 1216 m, 822 m, 792 m; MS *m/z* (relative intensity, %) 548 (M^+, 15), 172 (12), 171 (100), 144 (24); HRMS Calcd for $C_{29}H_{29}N_2OI$: 548.1325; Found: 548.1323.

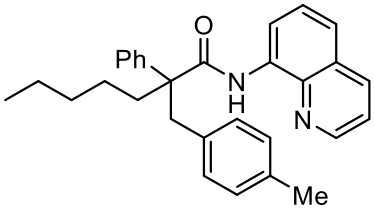
2-(4-chlorobenzyl)-2-phenyl-*N*-(quinolin-8-yl)heptanamide (1g).



R_f 0.51 (hexane/EtOAc = 5/1). White Solid. Mp =109 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.82 (t, J = 6.8 z, 3H), 1.26-1.55 (m, 6H), 1.94-2.07 (m, 2H), 3.36 (d, J = 13.6 Hz, 1H), 3.52 (d, J = 13.6 Hz, 1H), 6.62 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 7.25-7.35 (m, 6H), 7.45 (dd, J = 8.4, 1.2 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 8.07 (dd, J = 8.4, 1.2 Hz, 1H), 8.56 (dd, J = 4.4, 1.2 Hz, 1H), 8.77 (d, J = 8.0 Hz, 1H), 9.79 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz)

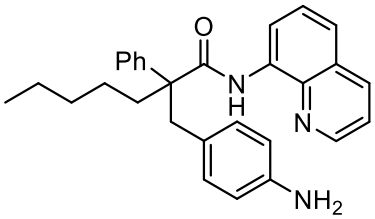
14.01, 22.38, 24.06, 32.24, 34.03, 41.15, 56.45, 116.02, 121.24, 121.42, 127.18, 127.27, 127.60, 127.68, 127.81, 131.61, 132.07, 134.49, 135.91, 136.01, 138.55, 142.46, 148.12, 174.26; IR (neat) 3342 w, 2932 w, 1683 m, 1522 s, 1485 m, 1326 m, 824 m, 754 m; MS *m/z* (relative intensity, %) 456 (M^+,7),172 (12), 171 (100), 144 (20); HRMS Calcd for $C_{29}H_{29}ClN_2O$: 456.1968; Found: 456.1970.

2-(4-methylbenzyl)-2-phenyl-*N*-(quinolin-8-yl)heptanamide (1h).



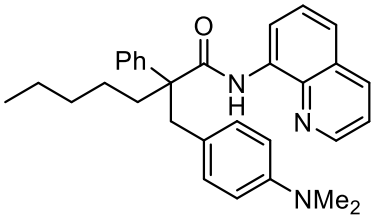
R_f 0.51 (hexane/EtOAc = 5/1). White Solid. Mp =101 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.82 (t, J = 7.2 Hz, 3H), 1.26-1.55 (m, 6H), 2.302 (t, J = 8.4 Hz, 2H), 2.23 (s, 3H), 3.36 (d, J = 13.2 Hz, 1H), 3.54 (d, J = 13.6 Hz, 1H), 6.61 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 7.26-7.33 (m, 6H), 7.43 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 8.04 (dd, J = 8.0, 1.2 Hz, 1H), 8.55 (dd, J = 4.0, 1.2 Hz, 1H), 8.79 (dd, J = 8.0, 1.2 Hz, 1H), 9.81 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.02, 20.98, 22.41, 24.05, 32.27, 33.92, 41.14, 56.49, 115.97, 121.09, 121.36, 126.94, 127.29, 127.60, 127.80, 128.31, 128.37, 130.17, 134.13, 134.63, 135.62, 135.97, 138.57, 143.01, 148.06, 174.63; IR (neat) 3342 w, 2931 w, 1638 m, 1521 s, 1484 m, 1383 m, 1325 m, 791 m, 753 m; MS *m/z* (relative intensity, %) 436 (M^+, 17), 172 (12), 171 (100), 144 (34), 105 (24), 91 (11); HRMS Calcd for $C_{30}H_{32}N_2O$: 436.2513; Found: 436.2515.

2-(4-aminobenzyl)-2-phenyl-*N*-(quinolin-8-yl)heptanamide (1j).



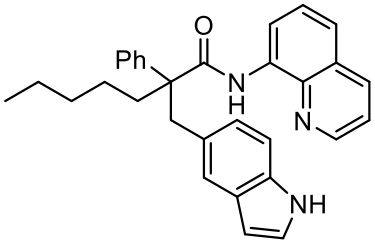
R_f 0.22 (hexane/EtOAc = 5/1). Pale yellow Solid. Mp =121 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.82 (t, J = 7.2 Hz, 3H), 1.25-1.45 (m, 6H), 1.99-2.04 (m, 2H), 3.29 (d, J = 13.6 Hz, 1H), 3.45-3.49 (m, 3H), 6.42 (d, J = 7.6 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 7.23-7.34 (m, 6H), 7.44 (dd, J = 8.4, 1.6 Hz, 1H), 7.52 (t, J = 8.4 Hz, 1H), 8.07 (dd, J = 8.0, 1.6 Hz, 1H), 8.57 (dd, J = 4.0, 1.6 Hz, 1H), 8.78 (dd, J = 8.0, 1.6 Hz, 1H), 9.80 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.04, 22.41, 24.03, 32.30, 33.89, 40.77, 56.59, 114.56, 115.96, 121.05, 121.37, 126.85, 127.15, 127.30, 127.65, 127.81, 128.32, 131.07, 134.66, 135.98, 138.58, 143.15, 144.49, 148.08, 174.80; IR (neat) 3352 w, 2931 w, 1680 m, 1622 w, 1521 s, 1484 m, 1326 m, 826 w, 755 m; MS *m/z* (relative intensity, %) 437 (M^+, 6), 332 (18), 171 (11), 144 (28), 106 (100); HRMS Calcd for $C_{29}H_{31}N_3O$: 437.2467; Found: 437.2465.

2-(4-(dimethylamino)benzyl)-2-phenyl-*N*-(quinolin-8-yl)heptanamide (1k).



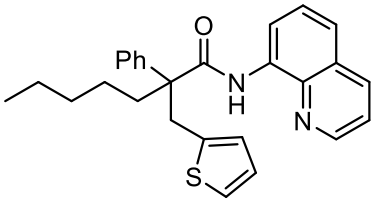
R_f 0.29 (hexane/EtOAc = 5/1). Pale yellow Solid. Mp =125 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.82 (t, J = 6.8 Hz, 3H), 1.26-1.51 (m, 6H), 2.02 (t, J = 8.4 Hz, 1H), 2.84 (s, 6H), 3.32 (d, J = 13.6 Hz, 1H), 3.50 (d, J =14.0 Hz, 1H), 6.49 (d, J = 8.4 Hz, 2H), 6.60 (d, J = 8.4 Hz, 2H), 7.24-7.36 (m, 6H), 7.43 (dd, J = 8.0, 1.2 Hz, 1H), 7.52 (t, J = 8.4 Hz, 1H), 8.06 (dd, J = 8.0, 1.2 Hz, 1H), 8.56 (dd, J = 4.4, 1.2 Hz, 1H), 8.79 (dd, J = 7.6, 1.2 Hz, 1H), 9.81 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.20, 22.58, 24.20, 32.47, 34.07, 40.78, 56.79, 112.23, 116.09, 121.16, 121.50, 125.26, 126.95, 127.45, 127.80, 127.96, 128.46, 131.11, 134.85, 136.11, 138.74, 143.44, 148.21, 149.13, 175.01; IR (neat) 3343 w, 2931 w, 1682 m, 1614 w, 1520 s, 1483 m, 1326 m, 791 m, 751 s, 699 m; MS *m/z* (relative intensity, %) 465 (M^+, 4), 135 (10), 134 (100); HRMS Calcd for $C_{31}H_{35}N_3O$: 465.2780; Found: 465.2778.

2-((1H-indol-5-yl)methyl)-2-phenyl-*N*-(quinolin-8-yl)heptanamide (1m).



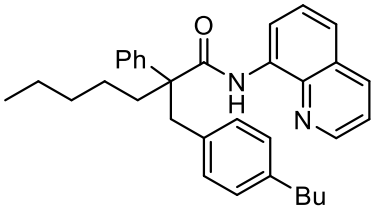
R_f 0.11 (hexane/EtOAc = 5/1). Off white Solid. Mp =90 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.82(t, = 7.2 Hz, 3H), 1.26-1.61 (m, 6H), 1.99-2.11 (m, 2H), 3.50 (d, J = 14.0 Hz, 1H), 3.69 (d, J = 14.0 Hz, 1H), 6.34 (t, J = 2.0 Hz, 1H), 6.49 (dd, J = 4.4, 1.2 Hz, 1H), 7.05 (t, J = 4.4 Hz, 3H), 7.23-7.33 (m, 6H), 7.43 (dd, J = 8.8, 1.2 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 8.05 (dd, J = 8.0, 1.6 Hz, 1H), 8.11 (brs, 1H), 8.55 (dd, J = 4.0, 1.6 Hz, 1H), 8.81 (dd, J = 7.6, 1.2 Hz, 1H), 9.85 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.21, 22.55, 24.23, 32.45, 34.78, 41.78, 56.99, 102.33, 110.16, 116.15, 121.53, 122.32, 124.15, 124.82, 126.99, 127.46, 127.66, 127.88, 127.97, 128.38, 128.47, 134.72, 134.85, 136.13, 138.77, 143.51, 148.24, 175.23; IR (neat) 3335 w, 2952 w, 1671 m, 1522 s, 1484 m, 1423 m, 1326 m, 825 w, 753 s; MS *m/z* (relative intensity, %) 461 (M^+, 13), 273 (18), 171)20), 144 (18), 131 (11), 130 (100); HRMS Calcd for $C_{31}H_{31}N_3O$: 461.2471; Found: 461.2471.

2-Phenyl-*N*-(quinolin-8-yl)-2-(thiophen-2-ylmethyl)heptanamide (1n).



R_f 0.51 (hexane/EtOAc = 5/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.82 (t, J = 6.8 Hz, 3H), 1.27-1.59 (m, 6H), 2.06-2.18 (m, 2H), 3.64 (d, J = 14.8 Hz, 1H), 3.83 (d, J = 15.2 Hz, 1H), 6.45 (d, 3.2 Hz, 1H), 6.79 (t, J = 4.0 Hz, 1H), 7.01 (d, J = 5.2 Hz, 1H), 7.25-7.54 (m, 8H), 8.07 (d, J = 7.2 Hz, 1H), 8.58 (d, J = 4.0 Hz, 1H), 8.77 (d, J = 7.6 Hz, 1H), 9.82 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.05, 22.39, 23.99, 32.25, 34.12, 36.00, 56.13, 116.03, 121.21, 121.41, 123.93, 126.12, 127.00, 127.28, 127.51, 127.80, 128.60, 134.53, 136.03, 138.55, 139.07, 142.43, 148.11, 174.10; IR (neat) 3342 w, 2931 w, 1681 m, 1523 s, 1484 s, 1384 m, 1326 m, 791 m; MS *m/z* (relative intensity, %) 429 (12), 428 (M^+, 38), 357 (14), 331 (20), 172 (13), 171 (100), 145 (11), 144 (59), 117 (13), 97 (19), 91 (11); HRMS Calcd for $C_{27}H_{28}N_2OS$: 428.1922; Found: 428.1924.

2-(4-Butylbenzyl)-2-phenyl-*N*-(quinolin-8-yl)heptanamide (1o).



R_f 0.50 (hexane/EtOAc = 5/1). White Solid. Mp =125 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.82 (t, J = 6.8 Hz, 3H), 0.88 (t, J = 7.6 Hz, 3H), 1.24-1.55 (m, 10H), 2.03 (t, J = 8.0 Hz, 2H), 2.49 (t, J = 7.2 Hz, 2H), 3.8 (d, J = 14.0 Hz, 1H), 3.55 (d, J = 13.6 Hz, 1H), 6.65 (d, J = 7.6 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 7.22-7.34 (m, 6H), 7.42 (dd, J = 8.0, 1.2 Hz, 1H), 7.51 (t, J = 8.4 Hz, 1H), 8.03 (dd, J = 8.0, 2.0 Hz, 1H), 8.54 (dd, J = 4.4, 1.6 Hz, 1H), 8.79 (dd, J = 7.6, 1.2 Hz, 1H), 9.82 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 13.90, 14.00, 22.29, 22.38, 24.03, 32.25, 33.44, 34.01, 35.12, 41.20, 56.53, 115.96, 121.06, 121.33, 126.90, 127.26, 127.59 (two overlapping peaks), 127.77, 128.33, 130.13, 134.34, 134.61, 135.93, 138.56, 140.63, 143.02, 148.03, 174.62; IR (neat) 3337 w, 2932 w, 1683 s, 1522 s, 1484 m, 1385 m, 1326 m, 1145 w, 822 m, 753 s, 703 m; MS *m/z* (relative intensity, %) 478 (M^+, 20), 331 (12), 172 (12), 171 (100), 144 (40), 14 (91); HRMS Calcd for $C_{33}H_{38}N_2O$: 478.2984; Found: 478.2989.

Deuterium Labeling Experiment (Scheme. 1 and 3).

To an oven-dried 5 mL screw-capped vial, in a glove box 2-methyl-2-phenyl-*N*-(quinolin-8-yl)heptanamide **1a-*d*$_3$** (104 mg, 0.3 mmol), 4-iodoanisole (140 mg, 0.6 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol) or $Ni(cod)_2$ (6.5 mg, 0.03 mmol),

MesCOOH (9.8 mg, 0.06 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and DMF (0.6 mL) were added. The mixture was stirred for 3 h at 140 °C followed by cooling. 30 mL of water was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with and brine (20 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 20/1) to afford the desired arylated product. The ratio of deuterium was determined by ^{1}H-NMR.

Product Distribution (Scheme. 2).

To an oven-dried 5 mL screw-capped vial, in a glove box 2-methyl-2-phenyl-*N*-(quinolin-8-yl)heptanamide **1a** (104 mg, 0.3 mmol), 1-butyl-4-iodobenzene (156 mg, 0.6 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol) or $Ni(cod)_2$ (6.5 mg, 0.03 mmol), MesCOOH (29 mg, 0.18 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and DMF (0.6 mL) were added. The mixture was stirred for 24 h at 140 °C followed by cooling. The yields of buthylbenzene, 1-butyl-4-iodobenzene, and 4,4'-dibutyl-1,1'-biphenyl were determined by GC. After determined GC yields, 30 mL of water was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with and brine (20 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The yield of product **1o** was determined by ^{1}H-NMR.

Radical Trapping Experiment.

To an oven-dried 5 mL screw-capped vial, in a glove box 2-methyl-2-phenyl-*N*-(quinolin-8-yl)heptanamide **1a** (52 mg, 0.15 mmol), 4-iodoanisole (70 mg, 0.3 mmol), TEMPO (47 mg, 0.3 mmol), $Ni(OTf)_2$ (5.3 mg, 0.015 mmol), MesCOOH (4.8 mg, 0.03 mmol), Na_2CO_3 (32 mg, 0.3 mmol) and DMF (0.6 mL) were added. The mixture was stirred for 24 h at 140 °C followed by cooling. 30 mL of water was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with and brine (20 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The yield of product **1b** was determined by ^{1}H-NMR.

General Procesure for Direct Arylation: Ni-Catalyzed Arylation of Amides with Diaryliodonium salt (eq 1).

To an oven-dried 5 mL screw-capped vial, in a glove box 2,2-diphenyl-*N*-(quinolin-8-yl)propanamide **6a** (106 mg, 0.3 mmol), 4-methoxyphenyl(mesityl)iodonium trifluoromethanesulfonate (181 mg, 0.36 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and 4-methyltetrahydropyrane (1 mL) were added. The mixture was stirred for 24 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 arylated product **6b** (99 mg, 72%) as a white solid.

2.5 References and Notes

(1) For recent reviews on functionalization of C(sp^2)-H bonds, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (b) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev*. **2010**, *110*, 824. (c) Xu, L.-M.; Li, B.-J., Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev*. **2010**, *39*, 712. (d) Ackermann, L. *Chem. Rev*. **2011**, *111*, 1315. (e) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 8960. (f) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev*. **2013**, 42, 5744. (g) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369.

(2) For recent reviews on functionalization of C(sp^3)-H bonds, see: (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.-Eur. J.* **2010**, *16*, 2654. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605. (e) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev*. **2011**, *40*, 1885. (f) Baudoin, O. *Chem. Soc. Rev*. **2011**, *40*, 4902.

(3) Zaitsev, V.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(4) Reviews on C-H bond transformation utilizing bidentate directing groups: (a) Corbet, M.; De Campo, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9896. (b) Rouquet, G.; Chatani, N *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. (c) Misal Castro, L. C.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410. (d) Daugulis. O; Roane, J.; Tran, L. D. *Acc. Chem. Res*. **2015**, *48*, 1053. (e) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450.

(5) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886.

(6) For a recent review on borylation of C(sp^3)-H bonds, see: Hartwig, J. F. *Chem. Soc. Rev*. **2011**, *40*, 1992. For a recent review on dehydrogenation of C(sp^3)-H bonds, see: (a) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (b) Haibach, M. C.; Kundu, S.; Brookhart, M.; Goldman, A. S. *Acc. Chem. Res.* **2012**, *45*, 947. (c) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 249.

(7) Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264.

(8) The energy difference of cyclometalated complexes between the cleavage of methyl C-H bond and of methylene C-H bond are calculated by B3LYP/SDD (Ni)/6-31G* (C, H, O, N). Although the complex of activated methyl C-H bond is 4.6 kJ/mol more stable in six-menbered ring, the complex of activated methlene C-H bond is 13.9 kJ/mol more stable in seven-menbered ring.

(9) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.***1971**, *93*, 5908.

(10) See Supporting Information of the paper by Weix et al. Shrestha, R.; Dorn, S. C. M.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 751.

(11) Iyanaga, M.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922.

(12) (a) Wu, X.; Zhao, Y; Ge, H. *J. Am. Chem. Soc.* **2014,** *136*, 1789. (b) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun*. **2014**, *50*, 3944. (c) Lin, C.; Yu, W.; Yao, J.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett*. **2015**, *17*, 1340. (d) Wang, X.; Yan, C.; Reddy, V. P.; Zhu, L.; Xu, X.; Yin, S.-F. *Org. Lett.* **2015**, *17*, 1970. (e) Li, M.; Yang, Y.; Zhou, D.; Wan, D.; You, J. *Org. Lett.* **2015**, *17*, 2546. (f) Wang, X.; Zhe, L.; Chen, S.; Xu, X.; Au, C.-T.; Qiu, R. *Org. Lett.* **2015**, *17*, 5228. (g) Maity, S.; Agasti, S.; Earasd, A. M.; Hazra, A.; Maiti, D. *Chem. Eur. J.* **2015**, *21*, 11320. (h) Yan, S.-Y.; Liu, Y.-J.; Liu, B.; Liu, Y.-H.; Zhang, Z.-Z.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 7341. (i) Liu, Y.-J.; Zhang, Z.-Z.; Yan, S.-Y.; Liu, Y.-H.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 7899.

(13) Francesco, S.; Jeffrey, S.; Shunqi, Y. *PCT Int. Appl.*, 2012092442, 05 Jul 2012.

(14) Wei, X.; Johnson, P.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1109.

(15) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030.

(16) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014,** *136*, 898.

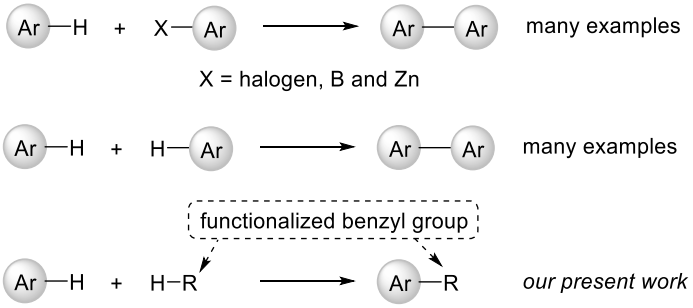
Chapter 3

Ni(II)-Catalyzed Oxidative Coupling between C(sp^2)−H in Benzamides and C(sp^3)−H in Toluene Derivatives

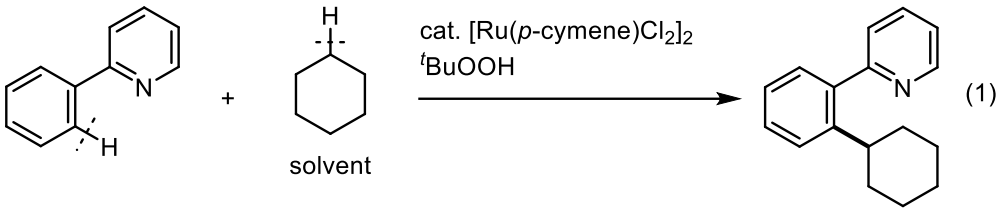
3.1 Introduction

The direct functionalization of C-H bonds has been developed, and most of them were divided into the reaction of C-H bonds and C-X bonds, such as halogen and organometallic reagents, as dealt in Chapter 1 and 2 (Figure 1). In contrast, oxidative coupling between C-H bonds and C-H bonds is an ideal and environmentally attractive strategy because the reaction does not require functionalized compounds for coupling and stoichiometric amounts of halogenated and organometallic byproducts are not generated (Figure 1). In a pioneering study, Fagnou reported on such a reaction: the Pd-catalyzed reaction of indole derivatives with benzene derivatives gave the arylation products.[1] Following this pioneering example, a number of reactions involving oxidative C-H/C-H coupling have been reported.[2] However, most of these examples involve the coupling of C(sp^2)-H/C(sp^2)-H bonds. The oxidative coupling of C(sp^2)-H/C(sp^3)-H bonds represent the next targeted reaction (Figure 1). To the best of our knowledge, only one example of the oxidative coupling between C(sp^2)-H bonds and C(sp^3)-H bonds is available.

Figure 1. Oxidative Cross Coupling of C-H/C-H bond**.**



In fact, Li reported on the Ru(II)-catalyzed oxidative coupling between C(sp^2)-H bonds in 2-arylpyridines and with C(sp^3)-H bonds in cycloalkanes, as the solvent, in the presence of a strong oxidant, such as di-tert-butyl peroxide(eq 1).[3] The role of di-tert-butyl peroxide is used to generate radical species from the cycloalkanes. The scope of cycloalkane is quite narrow, only cyclohexane, cycloheptane and cyclooctane were applicable, and functional group compatibility is low, due to the use a strong oxidant. The oxidative coupling of C(sp^2)-H/C(sp^3)-H bonds without the use of such strong oxidants and the high functional groups compatibility continues to be a challenging issue in the field of organic synthesis.

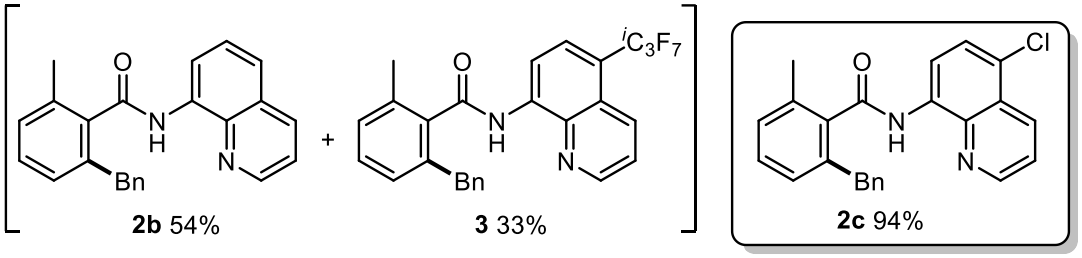


In this chapter, we report here on the Ni(II)-catalyzed oxidative coupling between *ortho* C-H bonds in aromatic amides and benzylic C-H bonds in toluene derivatives. Various functionalized benzyl groups can be introduced by using mild oxidant.

3.2 Results and discussion

Based on the result from chapter 1, we hypothesize that use of alkyl radical which is generated from alkane by hydrogen atom transfer instead of alkyl halide achieves oxidative coupling. Inspired by Fu work: tert-alkyl radical act as a hydrogen atom abstraction reagent in Ni-catalyzed cross coupling reaction.[4] Various alkyl halides were examined as alky radical sources, but all efforts were in vain. However, the benzylation of ortho C-H bonds proceeded, when $^{i}C_3F_7I$ was used as an alkyl halide. The reaction of amide **1a** (0.3 mmol) with $^{i}C_3F_7I$ (0.6 mmol) in the presence of $Ni(OTf)_2$ (0.03 mmol) as the catalyst, Na_2CO_3 (0.6 mmol) as the base and PPh_3 (0.03 mmol) as the ligand in toluene (1 mL) at 140 °C for 24 h gave the benzylation product **2a** in 91% isolated yield (Table 1, entry 1). The reaction also produced **2a** in 75% NMR yield in the absence of PPh_3 (entry 2). While the presence of PPh_3 as a ligand was not crucial for the reaction to proceed, PPh_3 was added because the product yields were consistently higher than the yields in the absence of PPh_3. Other perfluoroalkyl or aryl iodides, such as n-$C_6F_{13}I$, C_6F_5I, and CF_3CH_2I, or C_6Br_6 were not effective (entries 3-6). The reaction was also dependent on the base used in the reaction. Among the bases screened, carbonates were found to be effective. The nature of the cation portion is also important (entries 7-11). A 1.2 equivalent of $^{i}C_3F_7I$ (0.36 mmol, 1.2 equivalents to the amide **1a**) did not affect the product yield (entries 1 vs 12).

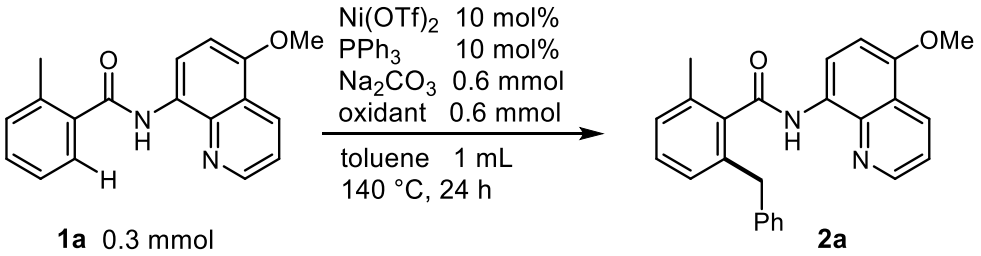
Figure 2. The effect of directing groups



Raction conditions: amide (0.3 mmol), $Ni(OTf)_2$ (10 mol%), PPh_3 (10mol%), Na_2CO_3 (0.6 mmol), $^{i}C_3F_7I$ (0.36 mmol) in toluene (1 mL) at 140 °C for 24 h. Isolated yield.

To examine the effect of 5-substitutent at a quinolone moiety, the screening of directing groups were conducted (Figure 2). The reaction of non-substituent at 5-position gave the mixture of benzylation product **2b** in 54% yield and heptafluoroisopropylation at 5-position **3** in 33% yield. The use of chlorine group instead of methoxy group increase the benzylation product **2c** in 94% yield. We choose an 8-amino-5-chloro-quinoline moiety as a suitable directing group.

Table 1. Optimization of reaction conditions[a]



1a 0.3 mmol **2a**

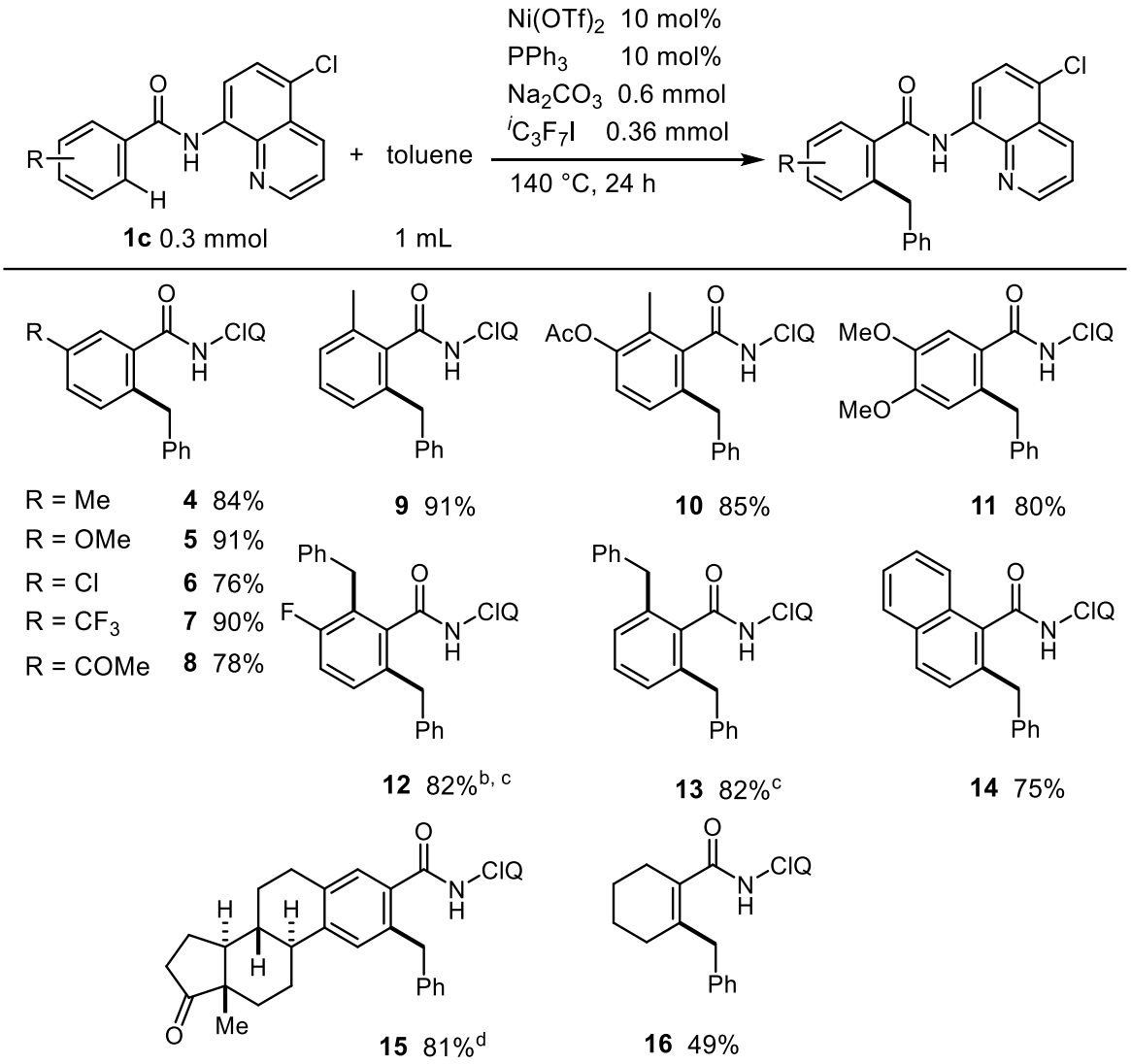
entry	oxidant	ligand	base	yields[b] **(2a / 1a)**
1	$^{i}C_3F_7I$	PPh_3	Na_2CO_3	94% (91%) / trace
2	$^{i}C_3F_7I$	–	Na_2CO_3	75% / 13%
3	$C_6F_{13}I$	PPh_3	Na_2CO_3	30% / 40%
4	C_6F_5I	PPh_3	Na_2CO_3	0% / 60%
5	CF_3CH_2I	PPh_3	Na_2CO_3	39% / 0%
6	C_6Br_6	PPh_3	Na_2CO_3	0% / 90%
7	$^{i}C_3F_7I$	PPh_3	Cs_2CO_3	73% / 13%
8	$^{i}C_3F_7I$	PPh_3	K_2CO_3	10% / 73%
9	$^{i}C_3F_7I$	PPh_3	$NaHCO_3$	59% / 37%
10	$^{i}C_3F_7I$	PPh_3	Li_2CO_3	0% / 63%
11	$^{i}C_3F_7I$	PPh_3	NaOAc	21% /63%
12[c]	$^{i}C_3F_7I$	PPh_3	Na_2CO_3	94% (91%) / trace

[a] Raction conditions: **1a** (0.3 mmol), $Ni(OTf)_2$ (10 mol%), PPh_3 (10mol%), Na_2CO_3 (0.6 mmol), oxidant (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. [b] NMR yields. The Number in parentheses is the isolated yield. [c] $^{i}C_3F_7I$ (0.36 mmol) was used.

With the optimized reaction conditions in hand, the reaction of various benzamides in toluene as the solvent was examined (Table 2). A wide variety of functional groups on benzamides are tolerated in the reaction. The less hindered C-H bonds were exclusively activated to give benzylation products, **4**-**8**, **11**, and **15** in the reaction of meta-substituted aromatic amides. In the case of a meta-fluoro substrate and a benzamide, di-benzylation

products **12** and **13** were obtained in high yields by using 3 equivalents of $^{i}C_3F_7I$. In all cases, no coupling between the *ortho* C-H bonds in benzamides and C(sp^2)-H bonds in toluene was observed.

Table 2. The Ni(II)-catalyzed ortho-benzylation of benzamides in toluene[a]

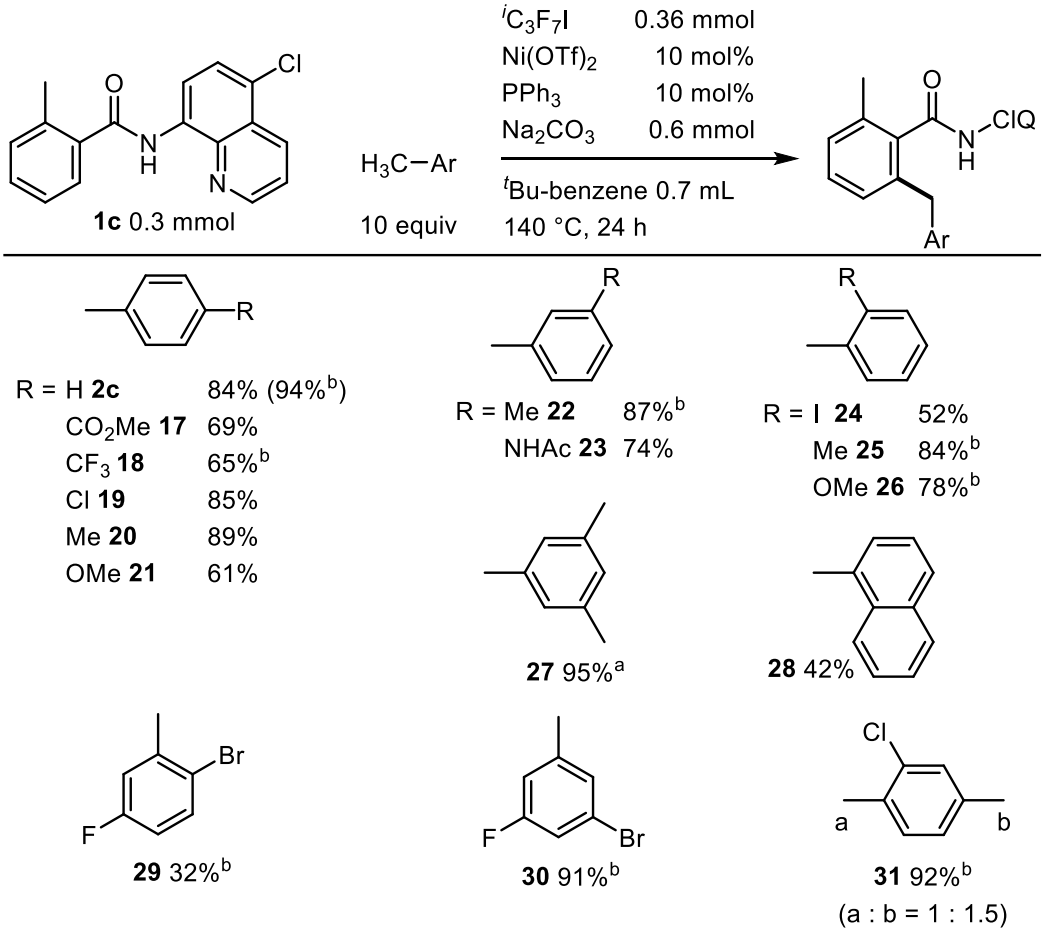


[a] Reactions were conducted on a 0.3 mmol scale. Reported yields are isolated yields. [b] Run at 160 °C. [c] $^{i}C_3F_7I$ (0.9 mmol) was used. [d] Reaction was conducted on a 0.15 mmol scale and 15 mol% catalyst was used.

In order to develop a more useful reaction in organic synthesis, we examined the reaction with functionalized toluene derivatives in unreactive solvent. When 5 equivalents of toluene in 0.7 mL of tert-buthylbenzene as the solvent were used under standard reaction condition, **2c** was obtained in 62% yield. The yield increased to 84% isolated yield when 10 equivalents of toluene were used. The results for the reaction of **1c** with various toluene derivatives in tert-buthylbenzene as a solvent were shown in Table 3. Various functional groups, even

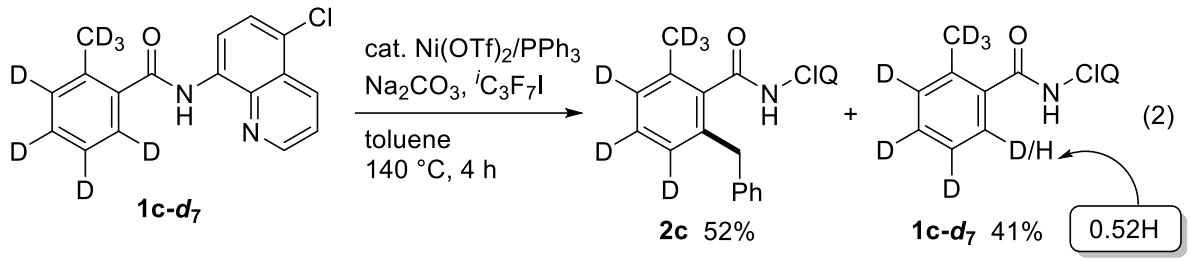
bromides, iodides and protected amine are tolerated under the current catalytic system. The presence of substituents at the ortho position had no effect on the efficiency of the reaction, as in **24**, **25**, **26**, **29** and **31**.

Table 3. The scope of toluene derivatives in oxidative coupling with benzamides[a]

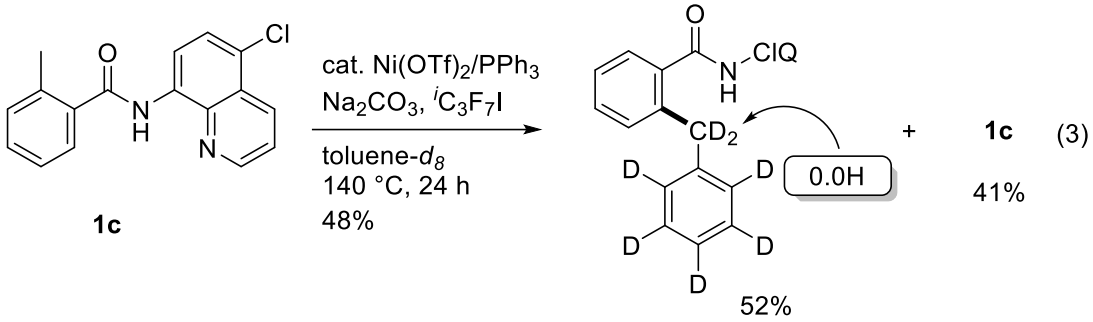


[a] Reactions were conducted on a 0.3 mmol scale. Reported yields are isolated yields. [b] Toluene derivatives (1.0 mL) were used as the solvent.

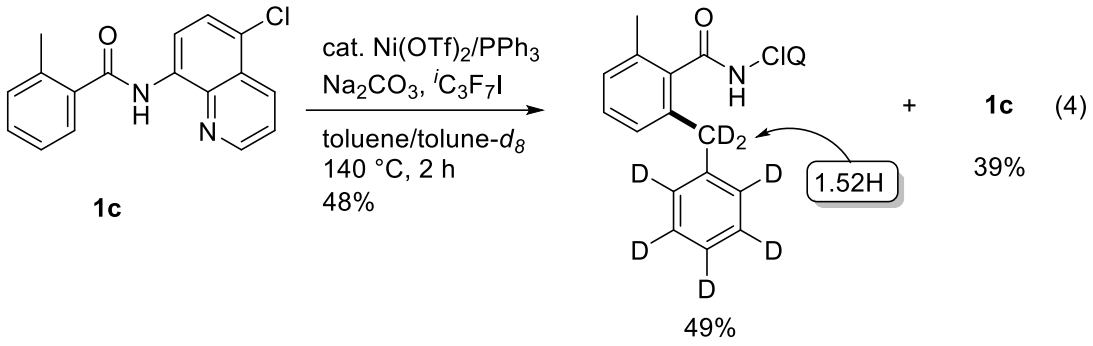
To gain insights into the reaction mechanism, deuterium-labeling experiments were performed. When the deuterated benzamide **1c-*d*$_7$** was reacted under standard reaction conditions for 4 h to recover the **1c-*d*$_7$**, **2c** was obtained in 52% isolated yield, along with 41% of **1c-*d*$_7$** being recovered, in which H/D exchange was observed between only at the ortho C-H bond and the NH bond. The D-content at the ortho C-H bond was decreased to 0.48D (eq 2). Even without a $^{i}C_3F_7I$, the H/D exchange was also observed in recovered stirting amide. These results clearly indicate that activation of aromatic C-H bond in benzamides is reversible under the reaction conditions, and $^{i}C_3F_7I$ is not involved in activation of aromatic C-H bond step.



When toluene-d_8 was used instead of toluene, the reaction was slower than the reaction in toluene. Furthermore, no H atom was detected in the benzyl moiety in the product and no deuterium atom was incorporated into the recovered **1c**, indicating the cleavage of benzylic C-H bond is irreversible step (eq 3).

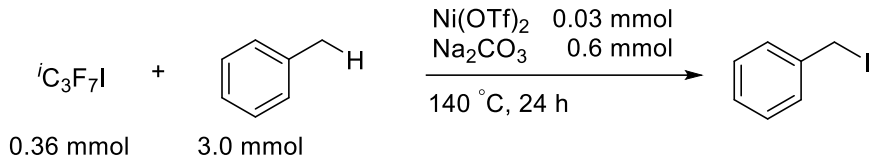


To collect additional information regarding the reaction mechanism, the reaction of **1c** in a 1:1 mixture of toluene and toluene-d_8 was carried out (eq 4). In the ^{1}H-NMR spectrum of the product, 1.52H was observed in the benzylic position, indicating that the reaction in toluene is 3.2 times faster when toluene-d_8 is used (1.52/0.48).



The most important issue to be addressed is what the real benzylation reagent is and how it is generated. A reaction of $^iC_3F_7I$ and toluene at 140 °C for 24 h resulted in no reaction (Scheme 1). But the in the presence of Na_2CO_3 gave the benzyl iodide in 21% NMR yield. The addition of $Ni(OTf)_2$ and Na_2CO_3 furnished benzyl iodide in 39% NMR yield. Although benzyl iodide was formed only in 39% yield, catalytic C-H benzylation proceeded smoothly as shown in Table 2. These results suggest that benzyl iodide is formed to some extent under the reaction conditions, but that it does not contribute to the benzylation as the major path. To gain the more information about formation of benzyl iodide, the addition of TEMPO as a radical scavenger was examined. The inhibition effect of TEMPO indicated the benzyl radical or perfluoroalkyl radical were intermediate for this reaction.

Scheme 1. Generation of Benzyl Iodide



additives	NMR yield
none	0%
Na_2CO_3	21%
$Ni(OTf)_2$, Na_2CO_3	39%
$Ni(OTf)_2$, Na_2CO_3, **TEMPO** (0.6 mmol)	0%

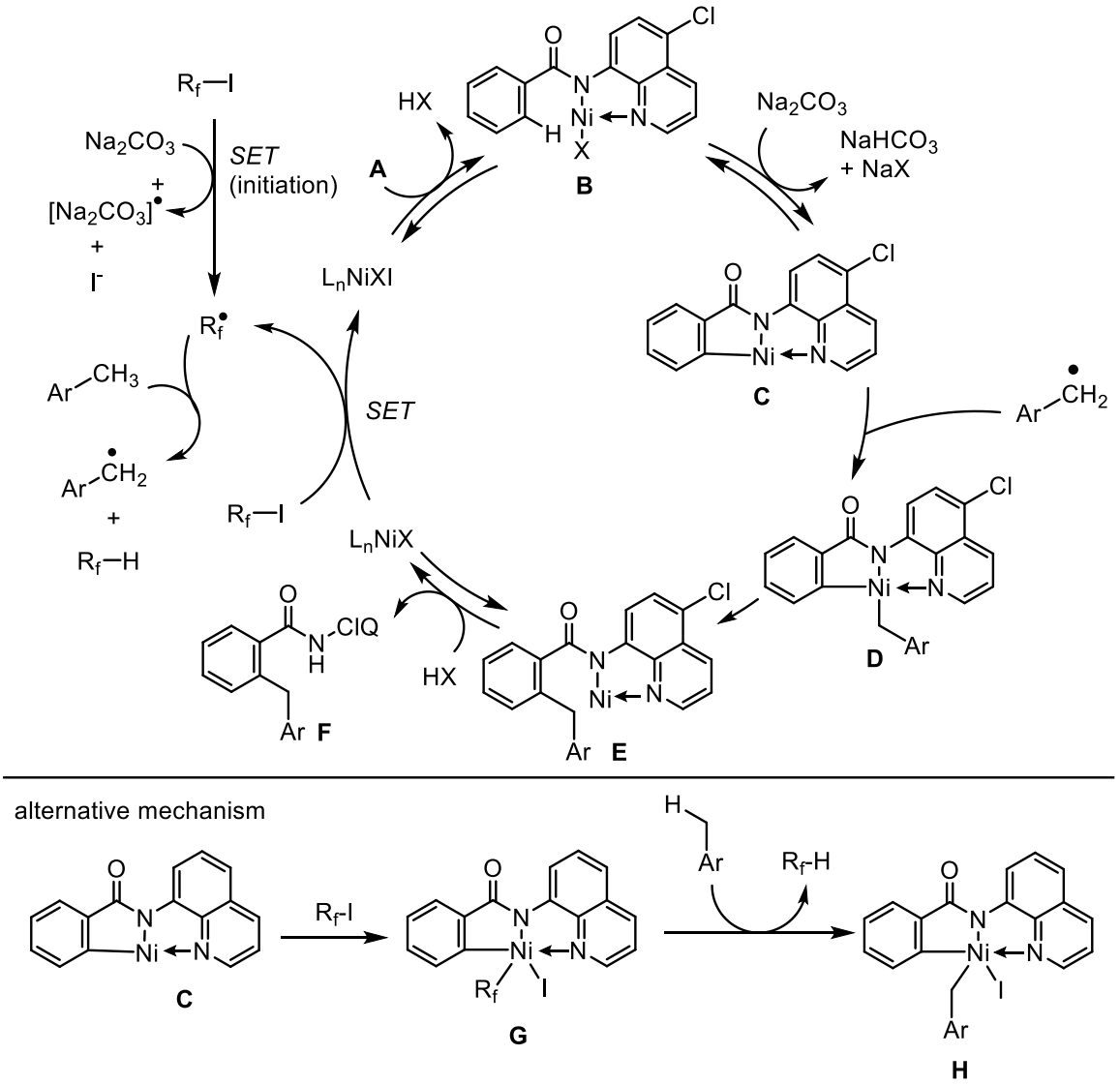
On the basis of these results and previous reports,[5] a plausible reaction mechanism is proposed in Scheme 2. The coordination of amide **A** to the nickel(II) center gives the nickel(II) complex **B** with the generation of HX, which is trapped by Na_2CO_3. The C-H bonds in complex **B** then undergo reversible cleavage via a concerted metalation deprotonation (CMD) mechanism to give nickelacycle **C**. The reaction of the complex **C** with a benzyl radical, which is generated by the base-promoted SET of R_f-I [6] followed by the abstraction of a hydrogen from toluene, generates a benzyl radical and R_f-H.[7] The reaction of the complex **C** with the benzyl radical affords the Ni(III) species **D**, from which the reductive elimination and protonation occurs to give the final product with the generation of Ni(I) complex. The reaction of Ni(I) with R_f-I regenerates the Ni(II) complex with the generation of an R_f radical,[8] which undergoes H-atom abstraction from toluene gives the benzyl radical and R_f-H. In fact, the formation of R_f-H was confirmed by ^{19}F NMR spectra of the reaction mixtures. A mechanism involving the oxidative addition of benzyl iodide to complex **C** cannot be excluded as the alternative mechanism, since we also observed the formation of benzyl iodide. However, this mechanism is not the major route for the present benzylation because the benzylation of C-H bonds proceeded smoothly even when the generation of benzyl iodides was not efficient.

Another alternative mechanism involves the oxidative addition of Rf-I to complex **C** to give complex **G**, which reacts with toluene to afford the complex **H**. The step from the complex **G** to **H** would be expected to proceed via a radical mechanism because the oxidative addition of $^{i}C_3F_7I$ to transition metal complexes[9] and the abstraction of a H-atom radical by a $^{i}C_3F_7$ radical are known.[10]

As shown in Table 1, $^{n}C_6F_{13}I$ was less reactive, although $^{i}C_3H_7I$ showed a high activity. It is known that secondary perfluoroalkyl radical undergoes the abstraction of H-atom faster than a primary perfluoroalkyl radical.[10] If perfluoroalkyl anion is involved in the reaction, perfluoroalkene would be generated by β-fluoro elimination.[11] However, no perfluoroalkene

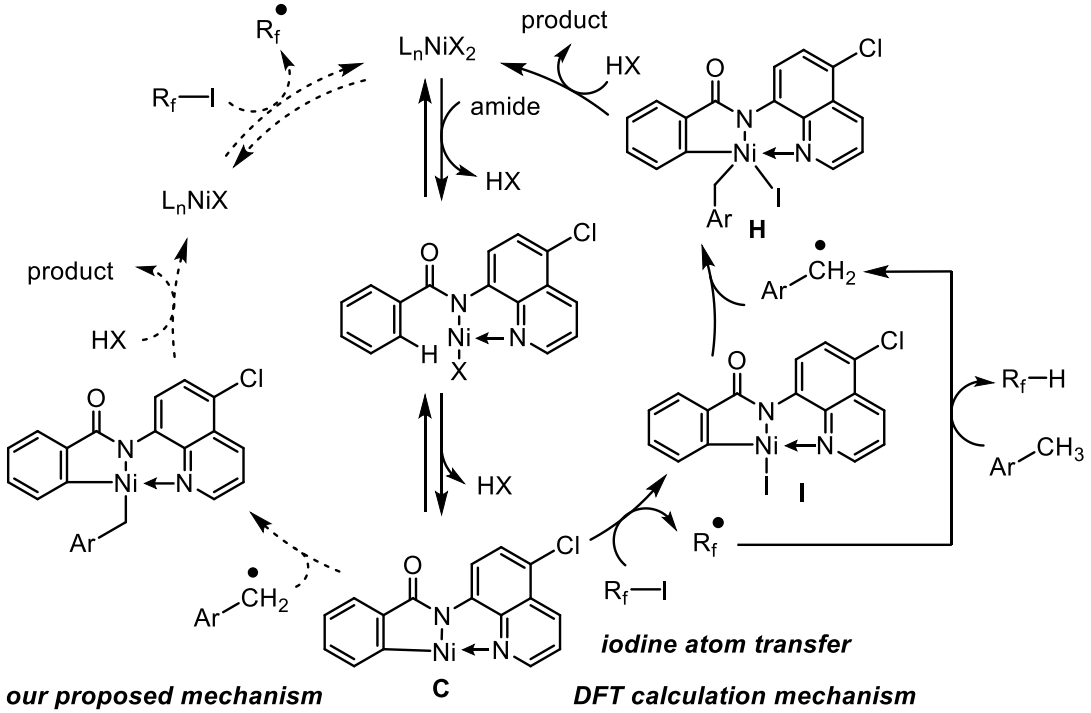
was detected. Furthermore, the addition of TEMPO completely quenched the reaction. These results suggest that the reaction involves the formation of a $^{i}C_3F_7$ radical and benzyl radical.

Scheme 2. Reaction mechanism



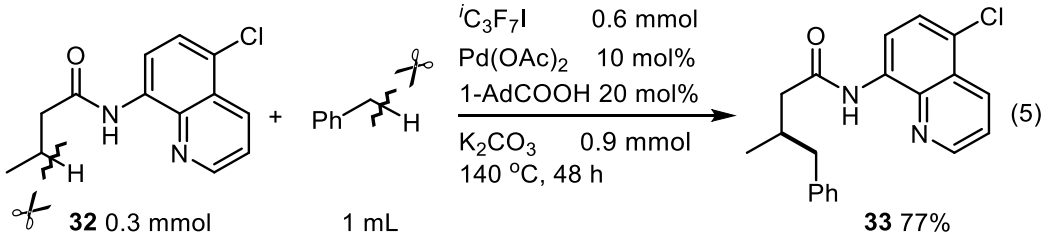
After published this reaction, Fu and co-workers performed computational studies of this reaction mechanism (Scheme 3).[12] The left catalytic cycle is our proposed mechanism. The reaction of nickel(II) and an amide gives a metallacycle **C**. A metallacycle **C** reacts with a benzyl radical to give the product. In contrast to our mechanism, DFT calculations indicate that an iodine atom transfer between alkyl iodide and complex **C** occurs, to give alkyl radical and Ni(III) intermediate **I**. The reaction of complex **I** and a benzyl radical gives the Ni(IV) complex **H**, which undergoes reductive elimination and protonation to give the final product. This catalytic cycle, including the iodine atom transfer and the formation of a Ni(IV) intermediate **H**, is more feasible based on DFT calculations.

Scheme 3. Reaction mechanism supported by computational studies



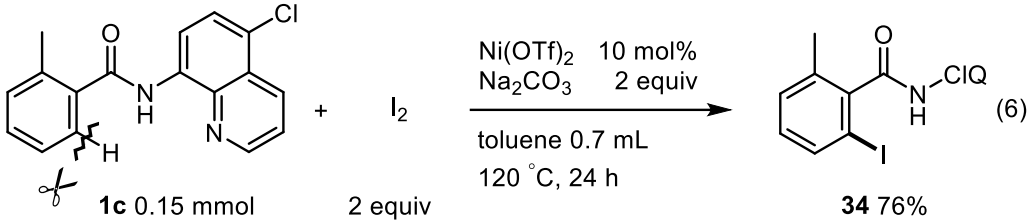
3.3 Conclusions

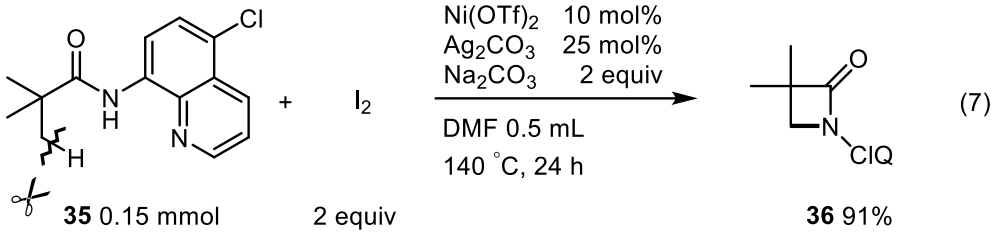
In summary, we report on a unique strategy that enables oxidative coupling between C(sp^2)-H and C(sp^3)-H bonds via a Ni(II)-catalyzed reaction of benzamides with toluene derivatives. The presence of $^{i}C_3H_7I$ is essential for the reaction to proceed. The role of $^{i}C_3H_7$ radical is to generate a benzyl radical via the abstraction of a H-atom from toluene derivatives, and high functional group compatibility was achieved by using a $^{i}C_3H_7I$ as a mild oxidant. This reaction system is applicable to oxidative coupling of two C(sp^3)-H bonds. The reaction of aliphatic amide and toluene in the presence of $^{i}C_3H_7I$, 1-AdCOOH as a ligand and $Pd(OAc)_2$ gave the β-benzylation product in good yield (eq 5).[13] The addition of caroboxylic acid is necessary to increase the product yields. The reaction in the presence of nickel-catalyst resulted in no reaction.



The reaction of aromatic amide containing an 8-amino-5-Chloroquinoline and iodine in the presence of nickel(II)-catalyst gave the ortho-iodination product (eq 6).[14] This reaction represents the first example of direct iodination of C-H bonds with nickel-catalyst. In contrast, the reaction of aliphatic amide and iodine didn't furnish the corresponding iodination products but the β-lactams (eq 7).[14] The synthesis of β-lactams via cleavage of C(sp^3)-H bonds with

nickel-catalyst was reported by using TEMPO as a oxidant.[15] The reaction with 5-methoxy directing group were ineffective, indicating that the role of chloro group at 5 position is not only to prevent the substitution reaction at 5-position but also to facilitate the reaction.





3.4 Experimental Section

General Information.

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = 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 SiO_2 (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

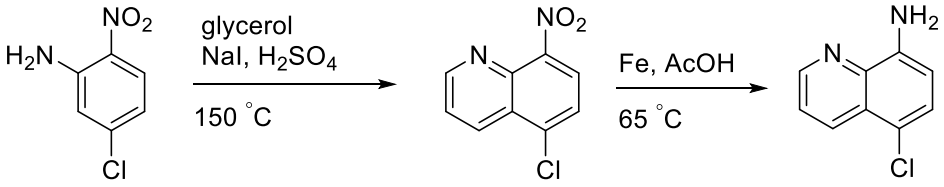
Materials.

Na_2CO_3 (CAS 497-19-8) 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. $Ni(OTf)_2$ (CAS 60871-84-3) was prepared by chapter 1 procedure. Toluene, super dehydrated (CAS 68-12-2) and PPh_3 (CAS 603-35-0) was purchased from Wako Pure Chemicals. 5-methoxyquinolin-8-amine (CAS 30465-68-0) was prepared by following procedure.[16]

Synthesis of the Starting Amides.

All amides containing an 8-aminoquinoline were prepared by the reaction of the corresponding acid chlorides and 8-aminoquinoline. All starting amides were synthesize following general procedure. All spectrum data of starting amides are cited in original paper.[17]

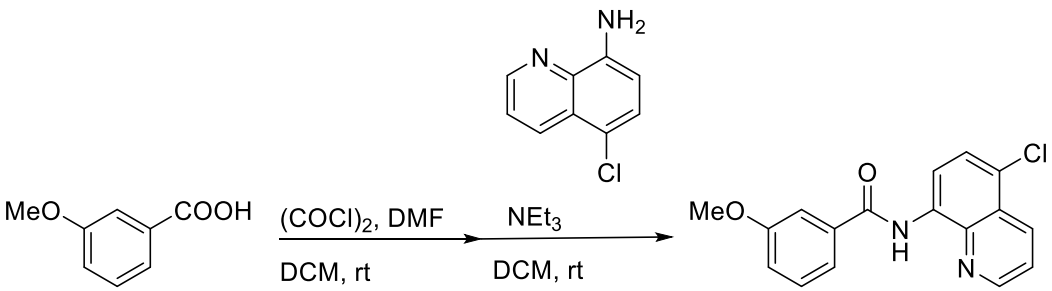
General Procedure for the Preparation of 8-amino-5-chroloquinoline.



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_2SO_4 (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_2SO_4, 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_2SO_4, 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, 3-methoxybenzoic acid (1.5 g, 10 mmol), DMF (5 drops) and DCM (20 mL) were added under a N_2 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-chroloquinoline (2.1 g, 12 mmol, 1.2 equiv.), Et_3N (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. $NaHCO_3$ (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 $MgSO_4$, filtered and evaporated *in vacuo*. The resulting crude amide was purified by column chromatography on silica gel (eluant: hexane/DCM = 3/1) to afford the desired amide as a white solid (2.3 g, 74%).

General Procedure for Direct Benzylation: Ni-Catalyzed Dehydrogenative Cross Coupling of Amides 1c with Toluene

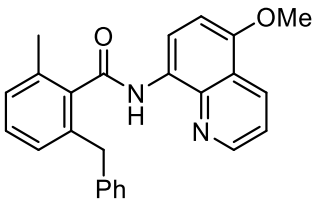
To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)-2-methylbenzamide **1c** (89 mg, 0.3 mmol), heptafluoroisopropyl iodide (107 mg, 0.36 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (7.8 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and toluene (1 mL) were added in a glove box. The mixture was stirred for 24 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= 20/1) to afford the desired alkylated product **2c** (108 mg, 94%) as a light yellow solid.

General Procedure for Direct Benzylation: Ni-Catalyzed Dehydrogenative Cross Coupling of Amides 1c with arene

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)-2-methylbenzamide **1c** (89 mg, 0.3 mmol), heptafluoroisopropyl iodide (107 mg, 0.36 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (7.8 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol), toluene (276 mg, 3.0 mmol) and tert-buthylbenzene (0.7 mL) were added in a glove box. The mixture was stirred for 24 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= 20/1) to afford the desired alkylated product **2c** (97 mg, 84%) as a light yellow solid.

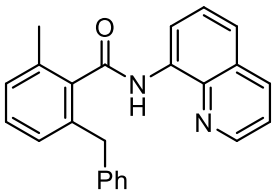
Spectroscopic Data for Products

2-benzyl-*N*-(5-methoxyquinolin-8-yl)-6-methylbenzamide (2a).



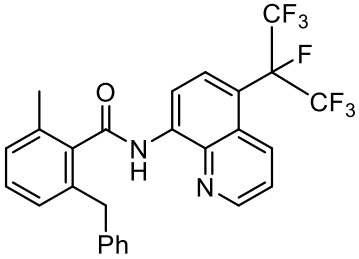
R_f 0.17 (hexane/EtOAc = 5/1). Light Yellow Solid. Mp = 149 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.45 (s, 3H), 4.02 (s, 3H), 4.10 (s, 2H), 6.89 (d, J = 8.4 Hz, 1H), 7.00-7.18 (m, 7H), 7.25 (t, J = 8.0 Hz, 1H), 7.41 (dd, J = 8.0, 4.0 Hz, 1H), 8.58 (dd, J = 8.4, 1.6 Hz, 1H), 8.67 (dd, J = 4.0, 1.6 Hz, 1H), 8.88 (d, J = 8.4 Hz, 1H), 9.59 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.53, 39.08, 55.81, 104.20, 116.96, 120.37, 120.66, 125.87, 127.49, 127.67, 128.18, 128.25, 128.97, 129.04, 131.19, 134.71, 137.85, 138.08, 139.08, 140.43, 148.52, 150.56, 168.16; IR (neat) 3351 w, 1664 m, 1594 w, 1521 s, 1490 s, 1396 m, 1325 w, 1260 m, 1148 m, 1090 m, 903 m; MS *m/z* (relative intensity, %) 383 (13), 382 (M^+, 45), 292 (11), 210 (11), 209 (77), 208 (100), 194 (37), 174 (35), 166 (13), 165 (31), 159 (18), 119 (22), 91 (12); HRMS Calcd for $C_{25}H_{22}N_2O_2$: 382.1681; Found: 382.1684.

2-Benzyl-6-methyl-*N*-(quinolin-8-yl)benzamide (2b).



R_f 0.23 (hexane/EtOAc = 5/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.45 (s, 3H), 4.10 (s, 2H), 7.00 (t, J = 8.0 Hz, 1H), 7.05-7.11 (m, 3H), 7.13-7.17 (m, 3H), 7.26 (t, J = 7.6 Hz, 1H), 7.40 (dd, J = 8.0, 4.0 Hz, 1H), 7.53-7.61 (m, 2H), 8.14 (dd, J = 8.0, 1.6 Hz, 1H), 8.65 (dd, J = 4.0, 1.6 Hz, 1H), 8.96 (dd, J= 8.0, 1.6 Hz, 1H), 9.82 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.51, 39.10, 116.67, 121.55, 121.90, 125.88, 127.30, 127.56, 127.86, 128.25 (overlapping peaks), 129.01, 129.09, 134.24, 134.66, 136.18, 137.83, 137.92, 138.39, 140.32, 148.10,168.60; HRMS Calcd for $C_{24}H_{20}N_2O$: 352.1576; Found: 352.1574.

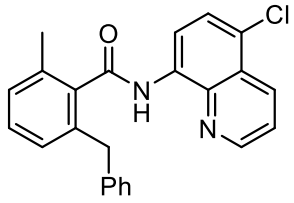
2-benzyl-6-methyl-*N*-(5-(perfluoropropan-2-yl)quinolin-8-yl)benzamide (3).



R_f 0.46 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 88 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.44(s, 3H), 4.09 (s, 2H), 6.95 (t, J = 7.2 Hz, 1H), 7.04-7.18 (m, 6H), 7.29 (t, J = 7.6 Hz, 1H),

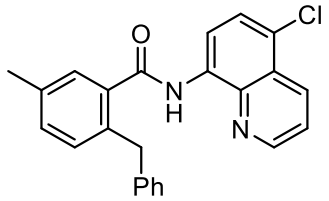
7.51 (dd, J = 7.6, 4.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 8.68 (dd, J = 4.0, 1.2 Hz, 1H), 8.77 (d, J = 8.4 Hz, 1H), 9.00 (dd, J = 7.6 Hz, 1H), 10.04 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.48, 39.18, 114.54, 115.44 (d, J = 19.1 Hz), 119.55 (d, J = 27.8 Hz), 122.32 (d, J = 27.6 Hz), 122.46, 125.90, 126.66, 127.79, 128.24, 128.38, 128.92, 129.35, 1134.19 (d, J = 21.0 Hz); 134.64, 137.49, 137.53, 137.79, 138.40, 140.15, 148.11, 169.02; IR (neat) 3336 w, 1712 s, 1517 m, 1359 m, 1266 m, 1220 s, 1096 m, 975 m, 888 m; MS *m/z* (relative intensity, %) 520 (M^+, 11), 210 (13), 209 (85), 208 (100), 194 (29), 166 (11), 165 (28), 119 (19), 91 (10); HRMS Calcd for $C_{27}H_{19}F_7N_2O$: 520.1386; Found: 520.1390.

2-benzyl-*N*-(5-chloroquinolin-8-yl)-6-methylbenzamide (2c and 9).



R_f 0.43 (hexane/EtOAc = 5/1). Light Yellow Solid. Mp = 122 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.43 (s, 3H), 4.09 (s, 2H), 6.98 (t, J = 7.2 Hz, 1H), 7.05-7.17 (m, 6H), 7.28 (t, J = 7.6 Hz, 1H), 7.54 (dd, J = 8.4, 4.0 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 8.56 (dd, J = 8.0, 1.6 Hz, 1H), 8.68 (dd, J = 4.0, 1.6 Hz, 1H), 8.90 (d, J = 8.4 Hz, 1H), 9.73 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.51, 39.17, 116.64, 122.27, 124.70, 125.87, 125.90, 127.71, 127.26, 128.26, 128.33, 128.93, 129.23, 1331.32, 133.45, 134.69, 137.71, 137.79, 138.88, 140.26, 148.53, 168.62; IR (neat) 3342 w, 1673 m, 1626 w, 1595 w, 1518 s, 1425 s, 1422 s, 1264 m, 1158 m; MS *m/z* (relative intensity, %) 386 (M^+, 17), 210 (15), 209 (100), 208 (93), 194 (35), 166 (13), 165 (32); HRMS Calcd for $C_{24}H_{19}ClN_2O$: 386.1186; Found: 386.1189.

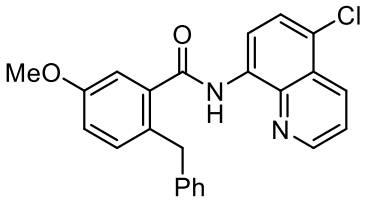
2-benzyl-*N*-(5-chloroquinolin-8-yl)-5-methylbenzamide (4).



R_f 0.40 (hexane/EtOAc = 5/1). White Solid. Mp = 112 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.40 (s, 3H), 4.25 (s, 2H), 7.04-7.08 (m, 1H), 7.13-7.24 (m, 6H), 7.46 (s, 1H), 7.55 (dd, J = 8.4, 4.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 8.57 (dd, J = 8.0, 1.6 Hz, 1H), 8.55 (dd, J = 4.0, 1.6 Hz, 1H), 8.85 (d, J = 8.8 Hz, 1H), 10.02 (brs); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 20.98, 38.44, 116.60, 122.28, 124.52, 125.87, 127.23, 127.77, 128.30, 129.01, 131.02, 131.21, 133.44, 133.85, 136.23, 136.52, 138.96, 140.84, 1487.56, 168.36; IR (neat) 3349 w, 1675 m, 1515 s, 1475 s, 1383 m, 1319 m, 1207 w, 950 m; MS *m/z* (relative intensity, %) 386 (M^+, 17), 209

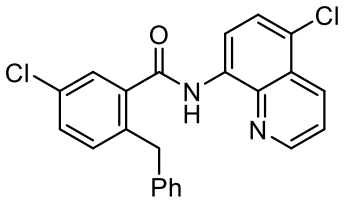
(49), 208 (100), 194 (28), 178 (10), 165 (29); HRMS Calcd for $C_{24}H_{19}ClN_2O$: 386.1186; Found: 386.1187

2-benzyl-*N*-(5-chloroquinolin-8-yl)-5-methoxybenzamide (5).



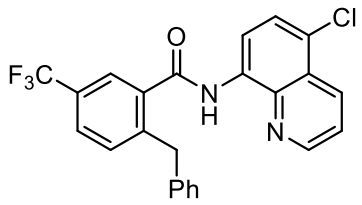
R_f 0.26 (hexane/EtOAc = 5/1). White Solid. Mp = 102 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.85(s、3H), 4.23 (s, 2H), 6.96 (dd, J = 8.0, 2.8 Hz, 1H), 7.04-7.08 (m, 1H), 7.13-7.20 (m, 6H), 7.54 (dd, J =8.8, 4.8 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 8.56 (dd, J = 8.4, 1.6 Hz, 1H), 8.73 (dd, J = 4.0, 1.6 Hz, 1H), 8.83 (d, J = 8.4 Hz, 1H), 10.03 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 38.03, 55.47, 112.66, 116.02, 116.53, 122.30, 124.61, 125.86, 127.15, 128.29, 128.93, 131.37, 132.26, 133.34, 133.73, 137.46, 138.96, 140.96, 148.61, 157.89, 167.87; IR (neat) 3347 w, 1675 m, 1605 w, 1516 s, 1475 s, 1319 m, 1219 m, 1038 m, 948 m; MS *m/z* (relative intensity, %) 402 (M^+, 18), 225 (36), 224 (100), 194 (10), 181 (12), 165 (12); HRMS Calcd for $C_{24}H_{19}ClN_2O_2$: 402.1135; Found: 402.1133.

2-benzyl-5-chloro-*N*-(5-chloroquinolin-8-yl)benzamide (6).



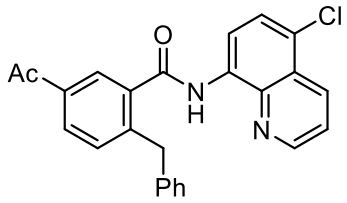
R_f 0.40 (hexane/EtOAc = 5/1). White Solid. Mp = 162 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 4.25 (s, 2H), 7.05 (q, J = 4.0 Hz, 1H), 7.16-7.21 (m, 5H), 7.38 (dd, J = 8.4, 2.4 Hz, 1H), 7.56 (dd, J = 8.4, 4.4 Hz, 1H), 7.62-7.64 (m, 2H), 8.57 (dd, J = 8.8, 1.2 Hz, 1H), 8.75 (4.4, 1.2 Hz, 1H), 8.81 (d, J = 7.6 Hz, 1H), 10.00 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 38.26, 116.63, 122.39, 124.93, 125.87, 126.17, 127.10, 127.14, 128.43, 129.01, 130.45, 132.23, 132.46, 133.38, 133.47, 137.96, 138.17, 138.92, 139.97, 148.74, 166.60; IR (neat) 3340 w, 1676 m, 1516 s, 1475 s, 1384 m, 13119 m, 1254 w, 941 m, 837 m; MS *m/z* (relative intensity, %) 408 (27), 407 (10), 406 (M^+, 33), 230 (34), 229 (22), 228 (100), 195 (10), 194 (69), 193 (83), 180 (20), 179 (24), 178 (60), 166 (19), 165 (90), 164 (20), 163 (20); HRMS Calcd for $C_{23}H_{16}Cl_2N_2O$: 406.0640; Found: 406.0642.

2-benzyl-*N*-(5-chloroquinolin-8-yl)-5-(trifluoromethyl)benzamide (7).



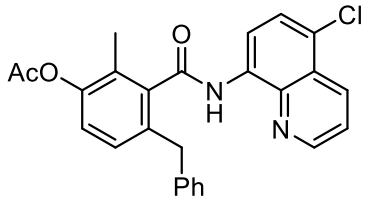
R_f 0.37 (hexane/EtOAc = 5/1). White Solid. Mp = 176 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 4.33(s, 2H),7.06-7.12 (m, 1H), 7.17-7.12 (m, 4H), 7.39 (d, J = 8.4, 1H), 7.57 (dd, J = 8.8, 4.0 Hz, 1H), 7.64-7.67 (m, 2H), 7.90 (s, 1H), 8.58 (d, J = 8.8 Hz, 1H), 8.76 (d, J = 4.0 Hz, 1H), 8.82 (d, J = 8.8 Hz, 1H), 10.04 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 38.78, 116.70, 122.37 (q, J = 270 Hz), 122.42, 124.14 (d, J = 3.8 Hz), 125.08, 125.87, 126.36, 127.03, 127.08, 128.53,129.05 (q, J = 65.8 Hz), 129.08, 131.55, 133.38, 137.17, 138.89, 139.39, 143.70, 148.78, 166.64; IR (neat) 3341 w, 1678 m, 1518 s, 1477 s, 1385 m, 133 s, 1253 m, 1171 m, 1123 s, 944 m; MS *m/z* (relative intensity, %) 442 (10), 440 (M^+, 31), 379 (12), 263 (30), 262 (100), 194 (32), 180 (16), 179 (10), 178 (51), 166 (11), 165 (47), 164 (11), 163 (11); HRMS Calcd for $C_{24}H_{16}ClF_3N_2O$: 440.0903; Found: 440.0901.

5-acetyl-2-benzyl-*N*-(5-chloroquinolin-8-yl)benzamide (8).



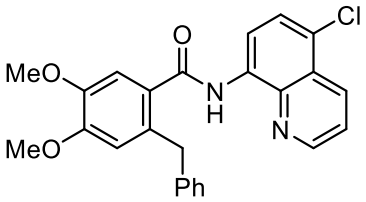
R_f 0.31 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 155 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.63 (s, 3H), 4.34 (s, 2H), 7.07-7.10 (m, 2H), 7.15-7.18 (m, 4H), 7.37 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 8.0, 4.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.98 (dd, J = 8.0, 2.0 Hz, 1H), 8.24 (d, J = 1.6 Hz, 1H), 8.57 (dd, J = 8.4, 1.6 Hz, 1H), 8.75 (d, J = 4.4, 1.6 Hz, 1H), 8.83 (d, J = 8.4 Hz, 1H), 10.07 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 26.62, 38.93, 116.64, 122.39, 124.94, 125.87, 126.28, 127.09, 128.48, 129.09, 130.36, 131.36, 133.37, 133.50, 135.30, 136.98, 138.91, 139.53, 145.10, 148.73, 167.20, 196.95; IR (neat) 3342 w, 1677 s, 1598 w, 1517 s, 1476 s, 1385 m, 1319 m, 1255 m, 942 m; MS *m/z* (relative intensity, %) 416 (17), 415 (14), 414 (M^+, 47), 237 (29), 236 (100), 221 (40), 195 (24), 194 (35), 193 (11), 180 (16), 179 (17), 178 (48), 165 (37); HRMS Calcd for $C_{25}H_{19}ClN_2O$: 414.1135; Found: 414.1138.

4-benzyl-3-((5-chloroquinolin-8-yl)carbamoyl)-2-methylphenyl acetate (10).



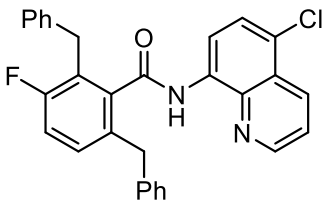
R_f 0.11 (hexane/EtOAc = 5/1). White Solid. Mp = 169 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 12.25 (s, 3H), 2.34 (s, 3H), 4.06 (s, 2H), 6.68-7.14 (m, 7H), 7.54 (dd, J = 8.0, 4.0 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 8.56 (d, J = 8.0 Hz, 1H), 8.71 (dd, J = 4.0, 1.2 Hz, 1H), 8.89 (d, J = 8.0 Hz, 1H), 9.78 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 13.31, 20.83, 38.82, 116.65, 122.34, 122.92, 124.91, 125.83, 126.03, 127.05 (overlapping peaks), 128.31, 128.70, 128.99, 133.24, 133.30, 135.60, 138.88, 139.04, 139.77, 147.73, 148.66, 167.49, 169.35; IR (neat) 3340 w, 1675 m, 1590 w, 1514 s, 1476 s, 1384 m, 1319 m, 1218 w, 939 m; MS *m/z* (relative intensity, %) 444 (M^+, 16), 267 (26), 266 (17), 226 (11), 225 (71), 224 (100), 223 (10), 210 (24), 181 (19), 179 (10), 178 (12), 165 (11), 152 (10); HRMS Calcd for $C_{26}H_{21}ClN_2O_3$: 444.1241; Found: 444.1245.

2-benzyl-*N*-(5-chloroquinolin-8-yl)-4,5-dimethoxybenzamide (11).



R_f 0.60 (hexane/EtOAc = 1/1). Yellow Solid. Mp = 60 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.85 (s, 3h), 3.94 (s, 3H), 4.29 (s, 2H), 6.73 (s, 1H), 7.11-7.23 (m, 6H), 7.54 (dd, J = 8.0, 4.0 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 8.56 (d, J = 8.8 Hz, 1H), 8.71 (d, J = 4.0, 1H), 8.82 (d, J = 8.4 Hz, 1H), 10.07 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 38.48, 55.88, 56.09, 110.65, 113.69, 116.40, 122.22, 124.36, 125.82, 125.94, 127.14, 128.33, 128.60, 128.77, 132.54, 133.29, 133.83, 138.74, 140.82, 147.19, 148.54, 150.53, 167.66; IR (neat) 3348 w, 1671 m, 1604 w, 1511 s, 1476 s, 1382 m, 1318 m, 1262 s, 1210 s, 1034 m, 397 m; MS *m/z* (relative intensity, %) 432 (M^+, 12), 256 (11), 255 (70), 254 (100), 224 (20), 165 (10); HRMS Calcd for $C_{25}H_{21}ClN_2O_3$: 432.1241; Found: 432.1239.

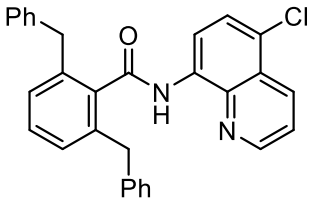
2,6-dibenzyl-*N*-(5-chloroquinolin-8-yl)-3-fluorobenzamide (12).



R_f 0.37 (hexane/EtOAc = 5/1). White Solid. Mp = 102 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 4.05 (s, 2H), 4.11 (s, 2H), 6.92-6.95 (m, 1H), 6.98-7.03 (m, 3H), 7.08-7.16 (m, 8H), 7.49 (dd, J = 8.8, 4.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 8.52-8.55 (m, 2H), 8.84 (dd, J = 8.0, 2.4 Hz, 1H), 9.56 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 32.53, 38.60, 116.28, 116.51, 122.18, 124.88, 125.05, 125.22, 125.68, 125.91, 126.07, 127.01, 128.18, 128.35, 128.43, 128.91, 129.97 (d, J = 8.6 Hz), 133.06 (d, J = 3.8 Hz), 133.76 (d, J = 3.8 Hz), 138.69, 139.21, 139.26,

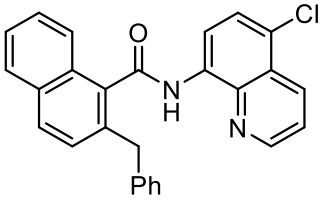
139.85, 148.41, 159.69 (d, J = 245 Hz), 166.79 (d, J = 2.8 Hz); IR (neat) 3333 w, 1676 m, 1515 s, 1475 s, 1384 m, 1319 m, 1265 m, 935 m, 724 s; MS *m/z* (relative intensity, %) 482 (13), 481 (12), 480 (M^+, 36), 317 (16), 303 (19), 302 (68), 301 (13), 226 (17), 225 (100), 224 (57), 212 (20), 197 (10), 196 (23), 183 (18), 179 (10), 178 (16), 91 (22); HRMS Calcd for $C_{30}H_{22}ClFN_2O$: 480.1405; Found: 480.1407.

2,6-dibenzyl-*N*-(5-chloroquinolin-8-yl)benzamide (13).



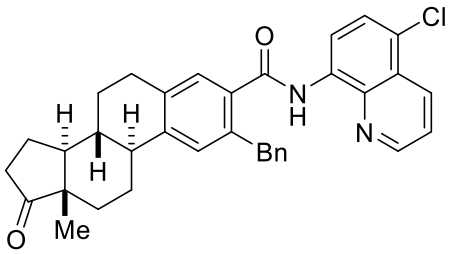
R_f 0.43 (hexane/EtOAc = 5/1).White Solid. Mp = 171 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 4.09 (s, 4H), 6.98 (t, J = 7.6 Hz, 1H), 7.06-7.15 (m, 10H), 7.27 (t, J = 7.6 Hz, 1H), 7.45 (dd, J = 8.0, 4.0 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 8.49 (dd, J = 8.4, 1.6 Hz, 1H), 8.57 (dd, J = 4.0, 1.2 Hz, 1H), 8.86 (d, J = 8.0 Hz, 1H), 9.63 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 39.13, 116.44, 122.14, 124.62, 125.67, 125.92, 127.02, 128.13, 128.25, 128.94, 129.31, 133.04, 133.30, 137.55, 137.90, 138.75, 140.06, 148.37, 168.27; IR (neat) 3339 w, 1674 m, 1514 s, 1384 m, 1319 m, 1260 w, 939 m; MS *m/z* (relative intensity, %) 462 (M^+, 18), 285 (29), 284 (74), 283 (11), 208 (17), 207 (100), 206 (30), 179 (18), 178 (31), 165 (15), 91 (28); HRMS Calcd for $C_{30}H_{23}ClN_2O$: 462.1499; Found: 462.1504.

2-benzyl-*N*-(5-chloroquinolin-8-yl)-1-naphthamide (14).



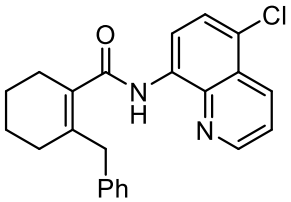
R_f 0.34 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 192 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 4.26 (s, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.2 Hz, 2H), 7.37 (d, J = 7.8 Hz, 1H), 7.47-7.51 (m, 3H), 7.69 (d, J = 8.4 Hz, 1H), 7.83-7.87 (m, 2H), 8.00 (dd, J = 8.4, 4.0 Hz, 1H), 8.55 (dd, J = 8.8, 4.4 Hz, 1H), 8.61 (dd, J = 4.4, 1.6 Hz, 1H), 9.05 (d, J = 8.0 Hz, 1H), 10.05 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 39.42, 116.76, 122.31, 124.91, 125.90, 125.98, 126.10, 127.17, 127.20, 1127.96, 128.04, 128.39, 129.00, 129.58, 130.15, 131.99, 133.28, 133.54, 134.18, 135.36, 138.87, 140.14, 148.57, 168.21; IR (neat) 3339 w, 1674 m, 1515 s, 1476 s, 1386 w, 1318 m, 1215 w, 937 w; MS *m/z* (relative intensity, %) 422 (M^+, 10), 246 (18), 245 (100), 244 (93), 227 (17), 226 (10), 216 (11), 215 (34), 202 (14); HRMS Calcd for $C_{27}H_{19}ClN_2O$: 422.1186; Found: 422.1185.

(8R,9S,13S,14S)-2-benzyl-*N*-(5-chloroquinolin-8-yl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3-carboxamide (15).



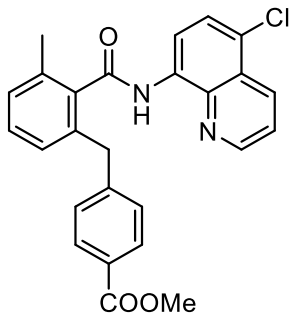
R_f 0.31 (hexane/EtOAc = 2/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.92 (s, 3H), 1.44-1.68 (m, 6H), 1.95-2.55 (m, 7H), 2.97 (dd, J = 9.6, 3.6 Hz, 2H), 4.26 (q, J = 15.6 Hz, 2H), 7.06 (t, J = 6.8 Hz, 1H), 7.13-7.22 (m, 5H), 7.40 (s, 1H), 7.54 (dd, J = 8.8, 4.0, 1H), 7.63 (dd,J = 8.8 Hz, 1H), 8.56 (dd, J = 8.4, 1.6 Hz, 1H), 8.73 (dd, J = 4.4, 1.6 Hz, 1H), 8.83 (d, J = 8.0 Hz, 1H), 10.01 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 13.81, 21.55, 25.57, 26.32, 28.95, 31.46, 35.80, 37.95, 38.74, 44.44, 47.89, 50.41, 116.43, 122.26, 124.41, 125.85, 127.19, 127.86, 128.26, 128.30, 128.90, 133.31, 133.92, 134.25, 134.79, 136.78, 139.01, 140.92, 142.26, 148.55, 168.19, 220.73; IR (neat) 3351 w, 2930 w, 1737 m, 1674 m, 1517 s, 1476 m, 1383 m, 1319 m, 938 w; MS *m/z* (relative intensity, %) 548 (M^+, 14), 372 (12), 371 (53), 370 (100), 368 (14), 207 (26); HRMS Calcd for $C_{35}H_{33}ClN_2O_2$: 548.2231; Found: 548.2228.

2-benzyl-*N*-(5-chloroquinolin-8-yl)cyclohex-1-enecarboxamide (16).



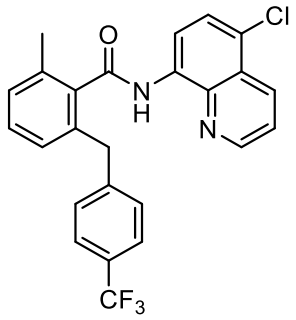
R_f 0.09 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.63-1.76 (m, 4H), 2.01-2.04 (m, 2H), 2.51-2.52 (m, 2H), 3.64 (s, 2H), 7.16-7.21 (m, 1H), 7.24-7.31 (m, 4H), 7.54 (dd, J = 8.0, 4.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 8.54 (dd, J = 8.0, 1.6 Hz, 1H), 8.76 dd, J = 4.4, 1.6 Hz, 1H), 8.81 (d, J = 8.4 Hz, 1H), 9.93 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 22.21, 22.23, 27.33, 28.77, 40.69, 116.52, 122.24, 124.23, 125.87, 126.01, 127.21, 128.33, 128.85, 131.26, 133.36, 133.76, 138.51, 138.93, 139.38, 148.47, 170.00; IR (neat) 3356 w, 2931 w, 1672 m, 1516 s, 1477 s, 1384 m, 1319 m, 939 w; MS *m/z* (relative intensity, %) 376 (M^+, 12), 199 (55), 198 (100), 178 (30), 157 (25), 129 (10), 91 (17); HRMS Calcd for $C_{23}H_{21}ClN_2O$: 376.1342; Found: 376.1341.

methyl 4-(2-((5-chloroquinolin-8-yl)carbamoyl)-3-methylbenzyl)benzoate (17).



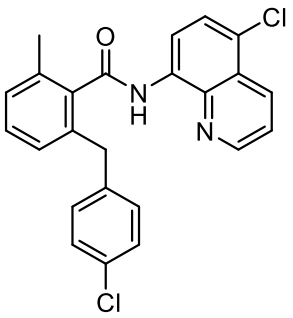
R_f 0.14 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 173 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.43 (s, 3H), 3.79 (s, 3H), 4.12 (s, 2H), 7.10-7.20 (m, 4H), 7.31 (t, J = 8.0 Hz, 1H), 7.50 (dd, J =8.8, 4.4 Hz, 1H), 7.63-7.66 (m, 3H), 8.54 (dd, J = 8.4, 1.6 Hz, 1H), 8.62 (dd, J = 4.0, 1.6 Hz, 1H), 8.85 (d, J = 8.8 Hz, 1H), 9.58 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.44, 39.38, 51.81, 116.53, 122.19, 124.78, 125.79, 127.08, 127.69, 127.88, 128.70, 128.84, 129.32, 129.54, 133.23, 133.28, 134.86, 136.86, 137.81, 138.66, 145.73, 148.50, 166.66, 168.38; IR (neat) 3341 w, 1718 m, 1676 m, 1514 s, 1476 s, 1319 m, 1278 m, 1108 m, 938 m, 753 m; MS *m/z* (relative intensity, %) 446 (14), 445 (12), 444 (37), 268 (16), 267 (88), 266 (100), 235 (13), 223 (14), 208 (57), 207 (67), 193 (13), 192 (19), 179 (27), 178 (30), 165 (30); HRMS Calcd for $C_{26}H_{21}ClN_2O_3$: 444.1241; Found: 444.1240.

***N*-(5-chloroquinolin-8-yl)-2-methyl-6-(4-(trifluoromethyl)benzyl)benzamide (18).**



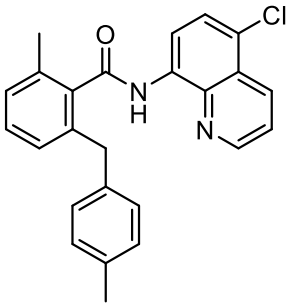
R_f 0.26 (hexane/EtOAc = 5/1). White Solid. Mp = 119 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.43 (s, 3H), 4.13 (s, 2H), 7.13 (d, J = 7.6 Hz, 1H), 7.19-7.26 (m, 5H), 7.33 (d, J = 8.0 Hz, 1H), 7.53 (dd, J = 8.4, 4.0 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 8.56 (dd, J = 8.8, 2.0 Hz, 1H), 8.62 (dd, J = 4.0, 1.6 Hz, 1H), 8.87 (d, J = 8.8 Hz, 1H), 9.59 (bes, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.47, 39.18, 116.55, 122.37, 124.03 (q, J = 271 Hz), 124.91, 125.12 (d, J = 3.8 Hz), 125.87, 127.10, 127.89, 128.15 (q, J = 32.4 Hz), 128.82, 129.06, 129.40, 133.18, 133.40, 135.02, 136.65, 137.82, 138.61, 144.44, 148.57, 168.37; IR (neat) 3342 w, 1678 m, 1516 s, 1477 s, 1385 m, 1323 s, 1162 m, 1121 m, 1066 m; MS *m/z* (relative intensity, %) 454 (M^+, 21), 278 (16), 277 (100), 276 (86), 262 (18), 208 (11), 165 (20); HRMS Calcd for $C_{25}H_{18}ClF_3N_2O$: 454.1060; Found: 454.1057.

2-(4-chlorobenzyl)-*N*-(5-chloroquinolin-8-yl)-6-methylbenzamide (19).



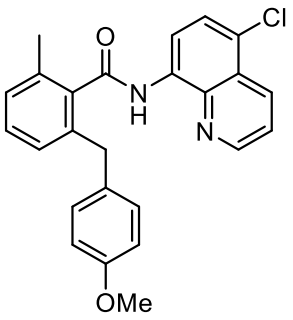
R_f 0.31 (hexane/EtOAc = 5/1). White Solid. Mp = 136 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.43 (s, 3H), 4.03 (s, 2H), 6.96 (dt, J = 8.4, 2.0 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.54 (dd, J = 8.0, 4.0 Hz, 1H), 7.65 (d, J = 8..8 Hz, 1H), 8.56 (dd, J = 8.4, 2.0 Hz, 1H), 8.66 (dd, J = 4.0, 1.6 Hz, 1H), 8.86 (d, J = 8.8 Hz, 1H), 9.60 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.45, 38.66, 116.49, 122.37, 124.81, 125.84, 127.07, 127.77, 128.31, 128.61, 129.30, 130.11, 131.70, 133.25, 133.32, 134.91, 137.15, 137.75, 138.73, 138.83, 148.65, 168.43; IR (neat) 3341 w, 1676 m, 1514 s, 1476 s, 1384 m, 1319 m, 938 m, 786 m; MS *m/z* (relative intensity, %) 422 (16), 420 (M^+, 22), 245 (24), 244 (41), 243 (71), 242 (100), 209 (10), 208 (59), 207 (86), 179 (20), 178 (25), 165 (41); HRMS Calcd for $C_{24}H_{18}Cl_2N_2O$: 420.0796; Found: 420.0793.

***N*-(5-chloroquinolin-8-yl)-2-methyl-6-(4-methylbenzyl)benzamide (20).**



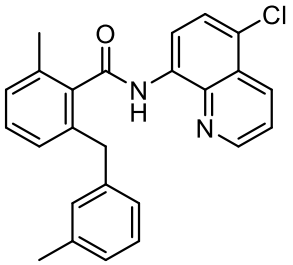
R_f 0.34 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 139 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.08 (s, 3H), 2.43 (s, 3H), 4.04 (s, 2H), 6.84 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.52 (dd, J = 8.0, 4.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 8.55 (dd, J = 8.8, 1.2 Hz, 1H), 8.67 (dd, J = 4.0, 1.2 Hz, 1H), 8.90 (d, J = 8.0 Hz, 1H), 9.68 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.45, 20.79, 38.79, 116.57, 122.18, 124.60, 125.82, 127.15, 127.66, 128.21, 128.76, 128.92, 129.16, 133.25, 133.51, 134.61, 135.30, 137.21, 137.68, 138.07, 138.82, 148.43, 168.64; IR (neat) 3343 w, 1677 m, 1513 s, 1476 s, 1383 m, 1319 m, 938 m, 786 m; MS *m/z* (relative intensity, %) 400 (M^+, 12), 224 (11), 223 (76), 222 (100), 208 (32), 179 (12), 178 (11), 165 (14); HRMS Calcd for $C_{25}H_{21}ClN_2O$: 400.1342; Found: 400.1341.

***N*-(5-chloroquinolin-8-yl)-2-(4-methoxybenzyl)-6-methylbenzamide (21).**



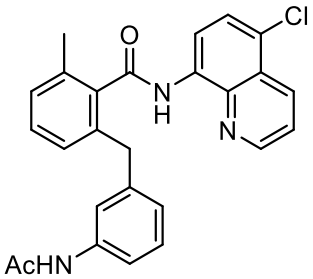
R_f 0.20 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.42 (s, 3H), 3.56 (s, 3H), 4.02 (s, 2H), 6.56 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.53 (dd, J = 8.4, 4.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H); 8.56 (dd, J = 8.8, 1.2 Hz, 1H), 8.67 (dd, J = 4.0, 1.2 Hz, 1H), 8.90 (d, J = 8.4 Hz, 1H), 9065 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.44, 38.39, 54.91, 113.56, 116.53, 122.23, 124.60, 125.81, 127.13, 127.64, 128.25, 129.17, 129.78, 132.39, 133.20, 133.51, 134.67, 137.65, 138.21, 138.83, 148.49, 157.68, 168.66; IR (neat) 3343 w, 1677 m, 1512 s, 1477 s, 1384 m, 1319 m, 1247 m, 1037 w, 939 m; MS *m/z* (relative intensity, %) 416 (M^+, 9), 239 (47), 238 (100), 224 (14); HRMS Calcd for $C_{25}H_{21}ClN_2O_2$: 416.1292; Found: 416.1293.

***N* -(5-chloroquinolin-8-yl)-2-methyl-6-(3-methylbenzyl)benzamide (22).**



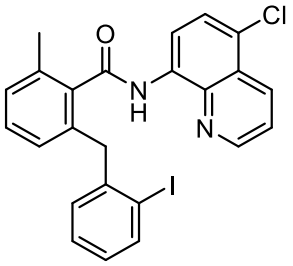
R_f 0.40 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.01 (s, 3H), 2.43 (s, 3H), 4.04 (s, 2H), 6.73 (d, J = 6.8 Hz, 1H), 6.91-6.97 (m, 3H), 7.10 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.51 (dd, J = 8.0, 4.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 8.54 (dd, J = 8.4, 1.6 Hz, 1H), 8.65 (dd, J = 4.4, 1.6 Hz, 1H), 8.91 (d, J = 8.4 Hz, 1H), 9.67 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.44, 21.05, 39.17, 116.49, 122.22, 124.60, 125.81, 125.90, 126.59, 127.10, 127.73, 128.12, 128.25, 129.66, 133.16, 133.51, 134.61, 137.73, 137.93, 138.90, 140.15, 148.46, 168.61; IR (neat) 3343 w, 1677 m, 1513 s, 1476 s, 1383 m, 1319 m, 938 m; MS *m/z* (relative intensity, %) 400 (M^+, 17), 224 (15), 223 (95), 222 (100), 208 (37), 179 (16), 178 (13), 165 (18); HRMS Calcd for $C_{25}H_{21}ClN_2O$: 400.1342; Found: 400.1341.

2-(3-acetamidobenzyl)-*N*-(5-chloroquinolin-8-yl)-6-methylbenzamide (23).



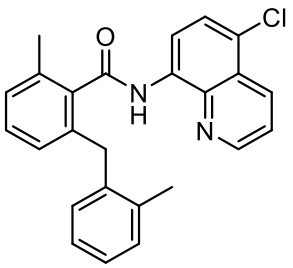
R_f 0.23 (hexane/EtOAc = 1/1). White Solid. Mp = 212 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.97 (s, 3H), 2.41 (s, 3H), 4.00 (s, 2H), 6.82 (d, J = 8.0, 1H), 6.95-6.99 (m, 2H), 7.08 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 6.8 Hz, 1H), 7.24-7.33 (m, 2H), 7.51 (dd, J = 8.0, 4.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 8.53 (dd, J = 8.4, 1.6 Hz, 1H), 8.65 (dd, J = 4.0, 1.6 Hz, 1H), 8.87 (d, J = 8.0 Hz, 1H), 9.651 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.40, 24.30, 39.16, 116.45, 117.45, 119.83, 122.39, 124.48, 124.75, 125.80, 126.99, 127.80, 128.42, 128.89, 129.28, 133.11, 133.38, 134.65, 137.41, 137.59, 137.96, 138.81, 140.94, 148.66, 168.11, 168.66; IR (neat) 3361w, 3291w, 1676m, 1657m, 1517 s, 1478 s, 1369 m, 1306 m, 1263 m, 941 m; MS *m/z* (relative intensity, %) 443 (M^+, 16), 225 (16), 224 (100), 223 (84), 180 (11), 178 (13); HRMS Calcd for $C_{26}H_{22}ClN_3O$: 443.1401; Found: 443.1404.

***N* -(5-chloroquinolin-8-yl)-2-(2-iodobenzyl)-6-methylbenzamide (24).**



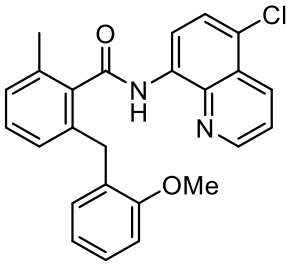
R_f 0.34 (hexane/EtOAc = 5/1). Light Yellow Solid. Mp = 148 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.46 (s, 3H), 4.21 (s, 2H), 6.79-6.87 (m, 2H), 7.15-7.27 (m, 4H), 7.54 (dd, J = 8.0, 4.0 Hz, 1H), 7.65 (d, J = 8.0, 1H), 7.69 (d, J = 8.0 Hz, 1H), 8.56 (dd, J = 8.0, 1.6 Hz, 1H), 8.71 (dd, J = 4.0, 1.6 Hz, 1H), 8.91 (d, J = 8.4 Hz, 1H); 9.91 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.55, 43.94, 101.36, 116.79, 122.30, 124.78, 125.92, 127.04, 127.19, 128.00, 128.36, 128.52, 129.27, 130.70, 133.39, 133.46, 134.73, 136.39, 137.80, 138.93, 139.38, 142.80, 148.58, 168.46; IR (neat) 3340 w, 1676 m, 1514 s, 1476 s, 1384 m, 1319 m, 939 m, 750 m; MS *m/z* (relative intensity, %) 514 (10), 512 (28), 335 (36), 209 (18), 208 (100), 207 (96), 193 (10), 179 (14), 178 (25), 165 (26); HRMS Calcd for $C_{24}H_{18}ClN_2OI$: 512.0152; Found: 512.0149.

***N* -(5-chloroquinolin-8-yl)-2-methyl-6-(2-methylbenzyl)benzamide (25).**



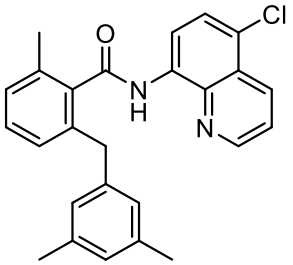
R_f 0.40 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.36 (s, 3H), 2.60 (s, 3H), 4.09 (s, 2H), 6.85 (d, J = 7.6 Hz, 1H), 6.97-7.02 (m, 2H), 7.06-7.07 (m, 2H), 7.15 (d, J = 7.2 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.52 (dd, J = 8.4, 4.0 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 8.54 (dd, J = 8.4, 1.6 Hz, 1H), 8.71 (dd, J = 4.4, 1.6 Hz, 1H), 8.90 (d, J = 8.4 Hz, 1H), 9.81 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.47, 19.64, 36.39, 116.57, 122.27, 124.70, 125.86, 125.94, 126.30, 126.87, 127.10, 128.12, 129.18, 129.94, 130.06, 133.24, 133.49, 134.60, 136.57, 137.16, 137.74, 138.02, 148.60, 168.63; IR (neat) 3345w, 1678 m, 1515 s, 1476 s, 1384 m, 1319 m, 939 m; MS *m/z* (relative intensity, %) 400 (M^+, 17), 224 (15), 223 (98), 222 (100), 208 (37), 179 (13), 178 (14), 165 (16); HRMS Calcd for $C_{25}H_{21}ClN_2O$: 400.1342; Found: 400.1340.

***N*-(5-chloroquinolin-8-yl)-2-(2-methoxybenzyl)-6-methylbenzamide (26).**



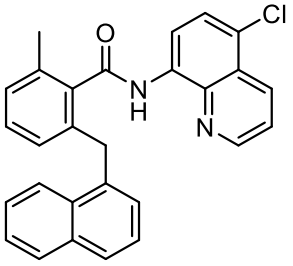
R_f 0.23 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 138 °C. Yellow Solid. Mp = 138 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.43 (s, 3H), 3.57, (s, 3H), 4.09 (s, 2H), 6.63 (d, J = 7.6 Hz, 1H), 6.77 (td, J = 7.2, 0.8 Hz, 1H), 7.02-7.12 (m, 4H), 7.23 (t, J = 7.6 Hz, 1H), 7.49 (dd, J = 8.4, 4.4 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 8.52 (dd, J = 8.4, 1.6 Hz, 1H), 8.67 (dd, J = 4.0, 2.0 Hz, 1H), 8.93 (d, J = 8.8 Hz, 1H), 9.82 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.47, 32.88, 55.03, 110.03, 116.51, 120.30, 122.20, 124.47, 125.78, 127.09, 127.32, 127.94, 128.58, 128.98, 130.52, 133.14, 133.66, 134.44, 137.65, 137.68, 138.92, 148.48, 157.04, 168.75; IR (neat) 3344 w, 1677 m, 1590 w, 1514 s, 1476 s, 1383 m, 1319 m, 1245 m, 939 m, 753 m; MS *m/z* (relative intensity, %) 416 (M^+, 15), 240 (15), 239 (88), 238 (100), 224 (21), 223 (1), 208 (10), 195 (11); HRMS Calcd for $C_{25}H_{21}ClN_2O_2$: 416.1292; Found: 416.1288.

***N*-(5-chloroquinolin-8-yl)-2-(3,5-dimethylbenzyl)-6-methylbenzamide (27).**



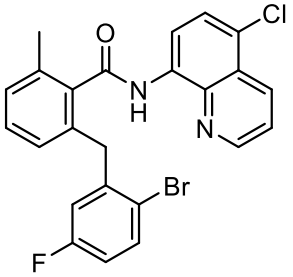
R_f 0.43 (hexane/EtOAc = 5/1). White Solid. Mp = 143 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.97 (s, 6H), 2.42 (s, 3H), 3.99 (s, 2H), 6.47 (s, 1H), 6.70 (s, 2H), 7.14 (t, J = 9.2 Hz, 2H), 7.28 (t, J = 8.0 Hz, 1H), 7.52 (dd, J = 8.0, 4.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 8.55 (dd, J = 8.4, 1.6 Hz, 1H), 8.65 (dd, J = 4.4, 1.6 Hz, 1H), 8.91 (d, J = 8.4 Hz, 1H), 9.61 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.42, 20.94, 39.18, 116.45, 122.20, 124.53, 125.79, 126.69, 127.11, 127.42, 127.78, 128.20, 129.13, 133.18, 133.53, 134.56, 137.60, 137.75, 138.07, 138.84, 141.08, 148.31, 168.67; IR (neat) 3343 w, 2+77 m, 1513 s, 1476 s, 1382 m, 1319 m, 938 m, 754 m; MS *m/z* (relative intensity, %) 414 (M^+, 16), 238 (14), 237 (82), 222 (34), 221 (11), 179 (20), 178 (12); HRMS Calcd for $C_{26}H_{23}ClN_2O$: 414.1499; Found: 414.1498.

***N* -(5-chloroquinolin-8-yl)-2-methyl-6-(naphthalen-1-ylmethyl)benzamide (28).**



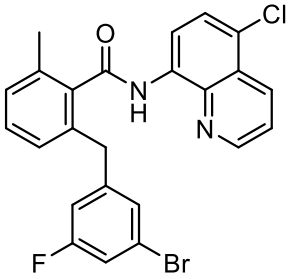
R_f 0.26 (hexane/EtOAc = 5/1). White Solid. Mp = 79 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.47 (s, 3H), 4.55 (s, 2H), 6.88 (d, J = 6.8 Hz, 1H), 7.14-7.21 (m, 2H), 7.28-7.36 (m, 4H), 7.52 (dd, J = 8.8, 4.0 Hz, 1H), 7.59-7.62 (m, 2H), 7.67-7.69 (m, 1H), 7.94-7.67 (m, 1H), 8.53 (dd, J = 8.4, 1.6 Hz, 1H), 8.69 (dd, J = 4.0, 1.6 Hz, 1H), 8.88 (d, J = 8.4 Hz, 1H), 9.85 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.52, 35.99, 116.69, 122.25, 124.16, 124.74, 125.39 (overlapping peaks), 125.85, 125.92, 127.06, 127.10, 127.16, 127.64, 128.33 (overlapping peaks), 129.23, 131.94, 133.31, 133.40, 133.74, 134.65, 135.77, 137.38, 137.59, 138.86, 148.56, 168.72; IR (neat) 3342 w, 1676 m, 1514 s, 1476 s, 1384 m, 1319 m, 939 w, 786 m; MS *m/z* (relative intensity, %) 436 (16), 259 (54), 258 (100), 244 (17), 215 (30), 178 (15); HRMS Calcd for $C_{28}H_{21}ClN_2O$: 436.1342; Found: 436.1340

2-(2-bromo-5-fluorobenzyl)-N-(5-chloroquinolin-8-yl)-6-methylbenzamide (29).



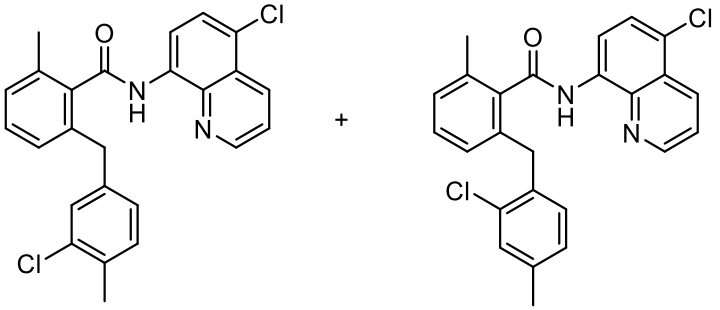
R_f 0.40 (hexane/EtOAc = 5/1). White Solid. Mp = 125 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.46 (s, 3H), 4.18 (s, 2H), 6.66 (td, J = 8.0, 2.8 Hz, 1H), 6.89 (dd, J = 9.6, 2.8 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.28-7.32 (m, 2H), 7.53 (dd, J = 8.4, 4.4 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 8.56 (dd, J = 8.4, 1.6 Hz, 1H), 8.71 (dd, J = 4.0, 1.6 Hz, 1H), 8.88 (d, J = 8.4 Hz, 1H), 9.81 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.54, 39.21, 115.95 (d, J = 21.9 Hz), 116.67, 118.11 (d, J = 22.9 Hz), 118.78 (d, J = 0.29 Hz), 122.34, 124.85, 125.87, 127.15, 127.33, 128.89, 129.42, 133.32, 133.61 (d, J = 0.85 Hz), 134.98, 134.46, 137.91, 138.96, 148.61, 161.99 (d, J = 245.1 Hz), 168.24; IR (neat) 3339 w, 1674 m, 1514 s, 1475 s, 1384 m, 1319 m, 1218 m, 1029 w, 938 m, 751 s; MS *m/z* (relative intensity, %) 484 (20), 482 (M^+, 15), 307 (40), 305 (41), 305 (41), 226 (44), 225 (100), 197 (10), 196 (11), 183 (41), 178 (11); HRMS Calcd for $C_{24}H_{17}BrClFN_2O$: 482.0197; Found: 482.0193.

2-(3-bromo-5-fluorobenzyl)-*N*-(5-chloroquinolin-8-yl)-6-methylbenzamide (30).



R_f 0.40 (hexane/EtOAc = 5/1). Yellow Solid. Mp = 160 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.44 (s, 3H), 4.01 (s, 2H), 6.71 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 9.6 Hz, 1H), 7.02 (s, 1H), 7.11 (d, J = 7.2 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.53 (dd, J = 8.0, 4.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.68 (d, J = 4.0 Hz, 1H), 8.86 (d, J = 8.4 Hz, 1H), 9.60 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.45, 38.84, 114.74 (d, J = 21.0 Hz,), 116.56, 116.57 (d, J = 23.8 Hz), 122.23 (d, J = 10.5 Hz), 122.34, 124.95, 125.90, 127.11, 127.67 (d, J = 2.9 Hz), 127.83, 129.00, 129.44, 133.15, 133.28, 135.03, 136.11, 137.82, 138.82, 144.43 (d, J = 7.7 Hz), 148.59, 162.41 (d, J = 248.8 Hz), 168.18; IR (neat) 3338 w, 1674 m, 1578 m, 1514 s, 1476 s, 1439 m, 1384 m, 1319 m, 1259 w, 938 w, 729 s; MS *m/z* (relative intensity, %) 486 (12), 485 (12), 484 (45), 483 (10), 482 (M^+, 33), 308 (15), 307 (97), 306 (89), 305 (99), 304 (77), 227 (33), 226 (58), 225 (41), 199 (19), 197 (29), 196 (26), 184 (18), 183 (100), 181 (11), 180 (14), 179 (25), 178 (39), 164 (15), 163 (14); HRMS Calcd for $C_{24}H_{17}BrClFN_2O$: 482.0197; Found: 482.0199.

2-(3-chloro-4-methylbenzyl)-*N*-(5-chloroquinolin-8-yl)-6-methylbenzamide (31a) and 2-(2-chloro-4-methylbenzyl)-*N*-(5-chloroquinolin-8-yl)-6-methylbenzamide (31b).

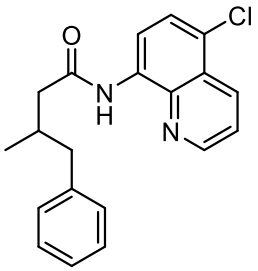


o > Δ

1.5 : 1

R_f 0.40 (hexane/EtOAc = 5/1). White Solid. Mp = 179 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.99 (○s, 3H), 2.15 (△s, 3H), 2.42 (○s, 3H), 2.44 (△s, 3H), 4.00 (○s, 2H), 4.17 (△s, 2H), 6.79 (○d, J = 7.6 Hz, 1H), 6.87-6.89 (○+△ m), 6.94 (△d, J = 7.6 Hz, 1H), 7.00-7.06 (○+△ m), 7.10-7.18 (○+△ m), 7.27-7.31 (○+△ m), 7.50-7.54 (○+△ m), 7.64 (○+△ d, J = 8.8 Hz, 1H), 8.53-8.56 (○+△ m), 8.66 (○dd, J = 4.4, 1.6 Hz, 1H), 8.71 (△dd, J = 4.0, 1.6 Hz, 1H), 8.87 (○d, J = 8.4 Hz, 1H), 8.91 (△d, J = 8.4 Hz, 1H), 9.59 (○brs, 1H), 9.84 (△brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 19.27, 19.41, 19.48, 20.57, 36.09, 38.63, 116.49, 116.65, 122.18, 122.24, 124.67, 125.80, 125.85, 127.13, 127.56, 127.78, 128.36, 128.57, 129.17, 129.26, 130.27, 131.11, 133.21, 133.29, 133.30, 133.50, 133.80, 134.06, 134.56, 134.61, 134.79, 136.56, 137.19, 137.59, 137.71, 137.76, 138.74, 138.90, 139.58, 148.43, 148.52; IR (neat) 3341 w, 1676 m, 1514 s, 1476 s, 1383 m, 1319 m, 1049 w, 938 m; MS *m/z* (relative intensity, %) 436 (16), 434 (M^+, 24), 259 (27), 258 (82), 256 (100), 242 (12), 222 (58), 221 (58), 179 (37), 178 (26); HRMS Calcd for $C_{25}H_{20}Cl_2N_2O$: 434.0953; Found: 434.0954.

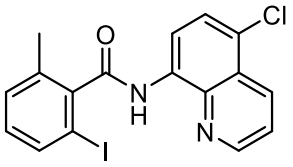
***N*-(5-methoxyquinolin-8-yl)-3-methyl-4-phenylbutanamide (33).**



Rf 0.31 (hexane/EtOAc = 3/1). White Solid. Mp = 66 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 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}C NMR ($CDCl_3$, 100.53 MHz) δ 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,

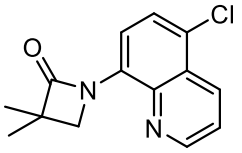
150.11, 170.60; IR (neat) 3362 w, 3011 w, 2958 w, 1734 w, 1672 w, 1596 w, 1525 m, 1493 m; MS *m/z* (relative intensity, %) 334 (M^+, 30), 216 (70), 201 (12), 175 (14), 174 (100), 159 (77), 91 (16); HRMS Calcd for $C_{21}H_{22}N_2O_2$: 334.1681; Found: 334.1684.

***N*-(5-chloroquinolin-8-yl)-2-iodo-6-methylbenzamide (34).**



R_f 0.43 (hexane/EtOAc = 5/1). White Solid. Mp = 210 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 2.46 (s, 3H), 7.05 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.57 (dd, J = 8.4, 4.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 8.59 (dd, J = 8.4, 1.6 Hz, 1H), 8.81 (dd, J = 4.0, 1.6 Hz, 1H), 8.91 (d, J = 8.4 Hz, 1H), 9.88 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 20.13, 92.85, 116.94, 122.43, 125.08, 126.02, 127.19, 130.08, 130.67, 133.37, 133.41, 136.61, 136.79, 139.07, 142.92, 148.83, 168.13; IR (neat) 3330 w, 1725 w, 1672 m, 1581 m, 1517 s, 1476 s, 1381 m, 1266 m; MS *m/z* (relative intensity, %) 424 (10), 422 (M^+, 30), 245 (100), 90 (18); HRMS Calcd for $C_{17}H_{12}ClIN_2O$: 421.9683; Found: 421.9687.

1-(5-chloroquinolin-8-yl)-3,3-dimethylazetidin-2-one (36).



R_f 0.26 (hexane/EtOAc = 5/1). White Solid. Mp = 155 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 1.45 (s, 6H), 4.33 (s, 2H), 7.49 (dd, J = 8.4, 4.0 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.53 (dd, J = 8.8, 6.0 Hz, 1H), 8.84 (dd, J = 4.0, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 21.44, 51.62, 60.79, 119.08, 121.89, 124.99, 126.58, 126.75, 132.75, 134.48, 140.82, 148.80, 173.71; IR (neat) 2966 w, 1739 s, 1502 m, 1466 m, 1399 m, 1350 m, 1140 m; MS *m/z* (relative intensity, %) 260 (M^+, 21), 232 (18), 217 (12), 206 (32), 205 (13), 204 (100), 189 (17), 165 (11), 163 (33); HRMS Calcd for $C_{14}H_{13}ClN_2O$: 260.0716; Found: 260.0716.

Deuterium Labeling Experiments (eq 2).

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)-2-methylbenzamide **1c-*d*$_7$** (90 mg, 0.3 mmol), heptafluoroisopropyl iodide (107 mg, 0.36 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (7.8 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and toluene (1 mL) were added in a glove box. The mixture was stirred for 4 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}H-NMR.

Deuterium Labeling Experiments (eq 3).

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)-2-methylbenzamide **1c** (89 mg, 0.3 mmol), heptafluoroisopropyl iodide (107 mg, 0.36 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (7.8 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and toluene-d_8 (1 mL) were added in a glove box. The mixture was stirred for 24 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}H-NMR.

Deuterium Labeling Experiments (eq 4).

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)-2-methylbenzamide **1c** (89 mg, 0.3 mmol), heptafluoroisopropyl iodide (107 mg, 0.36 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (7.8 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and toluene (0.5 mL) / toluene-d_8 (0.5 mL) were added in a glove box. The mixture was stirred for 4 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}H-NMR.

Observation of C_3F_7H.

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)-2-methylbenzamide **1c** (89 mg, 0.3 mmol), heptafluoroisopropyl iodide (177 mg, 0.60 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), PPh_3 (7.8 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol) and toluene (1 mL) were added in a glove box. The mixture was stirred for 4 h at 140 °C. The resulting mixture was cooled at -78 °C, and transferred to sealed NMR tube. The formation of C_3F_7H was determined by ^{19}F-NMR.

General Procedure for Direct Benzylation: Pd-Catalyzed Dehydrogenative Cross Coupling of Amides 32 with Toluene (eq 5).

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)butyramide **32** (75 mg, 0.3 mmol), heptafluoroisopropyl iodide (178 mg, 0.60 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 1-AdCOOH (10.8 mg, 0.06 mmol), K_2CO_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 **33** (78 mg, 77%) as a white solid.

General Procedure for Direct Iodination of Aromatic C-H Bonds (eq 6).

To an oven-dried 5 mL screw-capped vial, *N*-(5-chloroquinolin-8-yl)-2-methylbenzamide (45 mg, 0.15 mmol), iodine (76 mg, 0.3 mmol), $Ni(OTf)_2$ (5.3 mg, 0.015 mmol), Na_2CO_3 (32 mg, 0.3 mmol) and toluene (0.7 mL) were added in a glove box. The mixture was stirred for

24 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= 20/1) to afford the desired alkylated product **2c** (48 mg, 76%) as a white solid.

General Procedure for the formation of *β*-Lactams (eq 7).

To a 5 mL two necked flask equipped with condenser, *N*-(5-chloroquinolin-8-yl)pivalamide (39 mg, 0.15 mmol), iodine (76 mg, 0.3 mmol), $Ni(OTf)_2$ (5.3 mg, 0.015 mmol), Ag_2CO_3 (10 mg, 0.0375 mmol), Na_2CO_3 (32 mg, 0.3 mmol) and DMF (0.5 mL) were added in a glove box. The mixture was stirred for 24 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= 20/1) to afford the desired *β*-lactam (35 mg, 91%) as a white solid.

3.5 References and Notes

(1) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.

(2) For recent reviews of cross-dehydrogenative coupling, see: (a) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (b) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. (c) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74.

(3) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278.

(4) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624.

(5) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (b) Aihara, Y.; Wuelbern, J.; Chatani, N. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 438.

(6) Xu, T.; Cheung, C. W.; Hu, X. *Angew. Chem. Int. Ed.* **2014**, *53*, 4910. (b) Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 3990.

(7) The formation of R_f–H was confirmed by ^{19}F NMR spectra of the reaction mixtures.

(8) Mikhaylov, D.; Gryaznova, T.; Dudkina, Y.; Khrizanphorov, M.; Latypov, S.; Kataeva, O.; Vicic, D. A.; Sinyashin, O. G.; Budnikova, Y. *Dalton Trans.* **2012**, *41*, 165.

(9) Bourgeois, C. J.; Hughes, R. P.; Husebo, T. L.; Smith, J. M.; Guzei, I. M.; Liable-Sands, L. M.; Zakharov, L. N.; Rheingold, A. L. *Organometallics* **2005**, *24*, 6431.

(10) Brace, N. O. *J. Org. Chem.* **1963**, *28*, 3093.

(11) Hughes, R. P.; Maddock, S. M.; Guzei, I. A.; Liable-Sands, L. M.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 3279.

(12) Xu, Z.-Y.; Jiang, Y.-Y.; Yu, H.-Z.; Fu, Y. *Chem. Asian J.* **2015**, *10*, 2479.

(13) Kubo, T.; Aihara, Y.; Chatani, N. *Chem. Lett.* **2015**, *44*, 1365.

(14) Aihara, Y.; Chatani, N. in preparation.

(15) Wu, X.; Zhao, Y.; Ge, H. *Chem. Eur. J.* **2014**, *20*, 9530.

(16) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 11124.

(17) Aihara, Y.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 15509.

Conclusion

Although the Ni-catalyzed functionalization of C-H bonds has been limited to acidic C-H bonds, such as azole derivatives, perfluorobenzene and activated pyridine derivatives, these studies revealed that a combination of a nickel(II)-catalyst and an *N*,*N*-bidentate directing group permit inert C-H bonds to be functionalized.

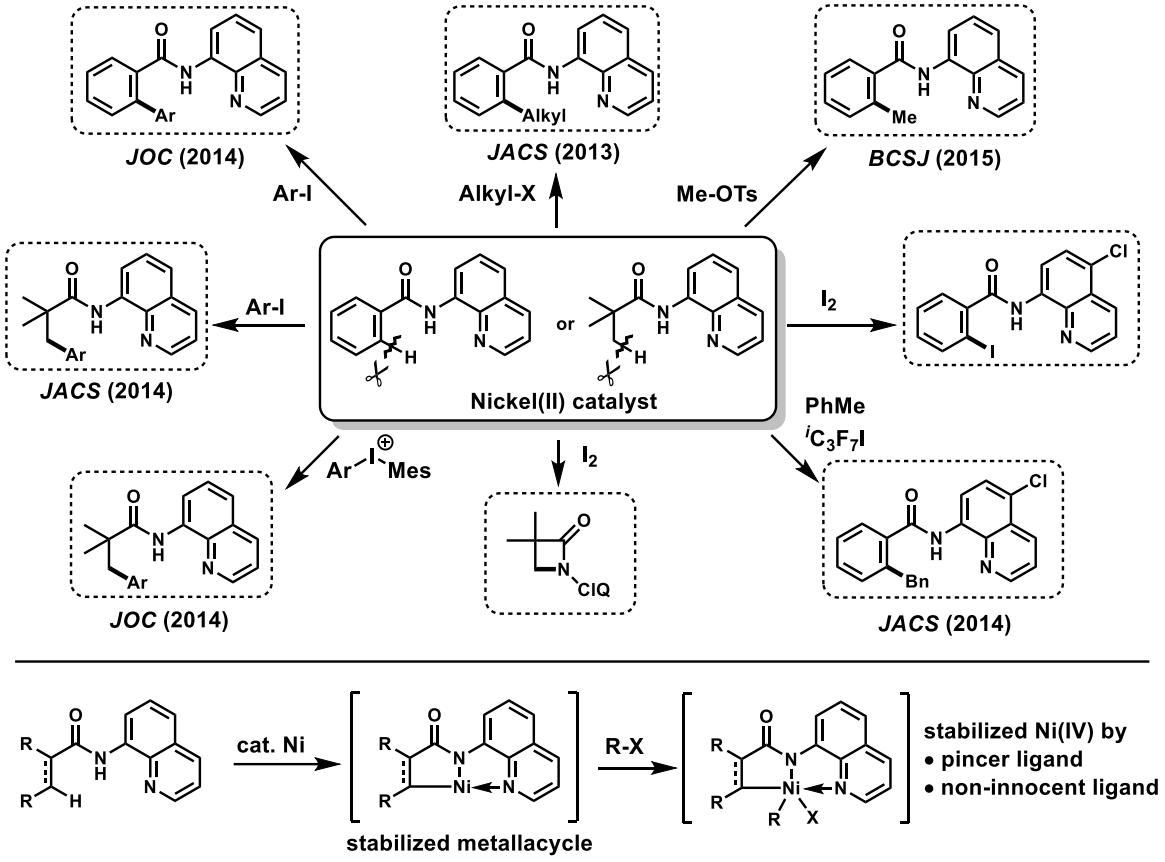
Chapter 1 discusses the nickel(II)-catalyzed direct alkylation of C(sp^2)-H bonds containing an 8-aminoquinline moiety as a bidentate directing group with an alkyl halide. The driving force for C-H bond cleavage with a low active nickel-catalyst is the formation of metallacycle intermediate stabilized by an *N*,*N*-bidentate directing group. Deuterium labeling experiments indicated that the cleavage of the C-H bond is not likely the rate determining step. This reaction proceeded via a Ni(II)/Ni(IV) cycle, which is unusual in Ni-catalyzed cross coupling reactions.

Chapter 2 deals with the direct arylation of aliphatic amides with aryl halides via the cleavage of C(sp^3)-H bonds by utilizing a combination of a nickel(II)-catalyst and an *N*,*N*-bidentate directing group. The C-H bond cleavage step proceeded rapidly and reversibly, even when a more inert C(sp^3)-H bond was used. Diaryliodonium salts instead of aryl halides could be used for arylation reagents.

Chapter 3 is concerned with the nickel(II)-catalyzed oxidative coupling of C(sp^2)-H bonds benzamides and benzylic C-H bonds in toluene derivatives using the hetafluoroisopropyl iodide as a mild oxidant. This reaction involves the catalytic cleavage of two different C-H bonds, C(sp^2)-H and benzylic C-H bonds. A high functional group compatibility was achieved when $^{i}C_3H_7I$ was used as a mild oxidant.

In this study, a combination of a nickel(II)-catalyst and an *N*,*N*-bidentate directing group has the potential to allow various functional groups to be introduced in benzene ring, such as aryl, alkyl, methyl and iodo groups, and benzyl moieties via oxidative coupling. Not only C(sp^2)-H bonds but also more inert C(sp^3)-H bonds could be functionalized by using this chelation system. Aryl groups were introduced by using aryl halides and diaryiodonium salts as arylation reagents, and β-lactams were prepared via the cleavage of C(sp^3)-H bonds.

Scheme 1. Summary of this thesis



Key to these successes derives from the nature of the *N*,*N*-bidentate directing group. The *N*,*N*-bidentate directing group efficiently and strongly coordinates to the nickel(II) complex by the formation of a N-Ni covalent bond with the amide N-H, and the subsequent C-H bond activation step was facilitated by the formation of a stabilized metallacycle. In chapter 1 and 2, a mechanism is proposed for the Ni(II)/Ni(IV) cycle. A high valent Ni(IV) intermediate generated after the reaction with the aryl or alkyl halide was probably stabilized by the *C, N, N* pincer type ligand or a non-innocent ligand which is derived from the 8-amonoquinoline moiety.

These studies can be expected to provide new methodology for use in the functionalization of C-H bonds and to the development of a new field of high valent Ni(IV) chemistry. In fact, more than 30 papers concerning C-H bond functionalization reactions utilizing a nickel(II)-catalyst and an *N*,*N*-bidentate directing group have been reported since we published the first report of the Ni(II)-catalyzed direct alkylation of aromatic C-H bonds containing a *N*,*N*-bidentate directing group in 2013.

List of Publications

(1) Nickel-Catalyzed Direct Alkylation of C-H Bonds in Benzamides and Acrylamides with Functionalized Alkyl Halides via Bidentate-Chelation Assistance

Yoshinori Aihara, and Naoto Chatani

J. Am. Chem. Soc. **2013**, *135*, 5308.

(2) Nickel-Catalyzed Direct Arylation of C(sp^3)-H Bonds in Aliphatic Amides via Bidentate-Chelation Assistance

Yoshinori Aihara, and Naoto Chatani

J. Am. Chem. Soc. **2014**, *136*, 898.

(3) Ni(II)-Catalyzed Oxidative Coupling between C(sp^2)-H in Benzamides and C(sp^3)-H in Toluene Derivatives

Yoshinori Aihara, Mamoru Tobisu, Yoshiya Fukumoto, and Naoto Chatani

J. Am. Chem. Soc. **2014**, *136*, 15509.

(4) The Nickel(II)-Catalyzed Direct Benzylation, Allylation, Alkylation, and Methylation of C-H Bonds in Aromatic Amides Containing an 8-Aminoquinoline Moiety as the Directing Group

Yoshinori Aihara, Jendrik Wuelbern, and Naoto Chatani

Bull. Chem. Soc. Jpn. **2015**, *88*, 438.

Supplementary List of Publications

(1) Nickel-Catalyzed Chelation-Assisted Transformations Involving the ortho C-H Bond Activation: The Regioselective Oxidative Cycloaddition of Aromatic Amides to Alkynes

Hirotaka Shiota, Yusuke Ano, Yoshinori Aihara, Yoshiya Fukumoto, and Naoto Chatani

J. Am. Chem. Soc. **2011**, *133*, 14952.

(2) Ruthenium-Catalyzed Direct Arylation of C-H Bonds in Aromatic Amides containing a Bidentate Directing Group: Significant Electronic Effects on Arylation

Yoshinori Aihara, and Naoto Chatani

Chem. Sci. **2013**, *4*, 664.

(3) The Ru(II)-Catalyzed Chelation-Assisted Arylation of C-H Bonds with Diaryliodonium Salts

Jordan Sun Ho, Luis C. Misal Castro, Yoshinori Aihara, Mamoru Tobisu, and Naoto Chatani

Asian J. Org. Chem. **2014**, 3, 48.

(4) Direct Arylation of C(sp^3)-H Bonds in Aliphatic Amides with Diaryliodonium Salts in the presence of a Nickel Catalyst

Miki Iyanaga, Yoshinori Aihara,and Naoto Chatani

J. Org. Chem. **2014**, *79*, 11933.

(5) Nickel(II)-Catalyzed Direct Arylation of C-H Bonds in Aromatic Amides Containing an 8-Aminoquinoline Moiety as a Directing Group

Ayana Yokota, Yoshinori Aihara, and Naoto Chatani

J. Org. Chem. **2014**, *79*, 11922.

(6) Pd(II)-Catalyzed Chelation-Assisted Cross Dehydrogenative Coupling between Unactivated C(sp^3)-H Bonds in Aliphatic Amides and Benzylic C-H Bonds in Toluene Derivatives

Teruhiko Kubo, Yoshinori Aihara, and Naoto Chatani

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

(7) Scalable C-H Oxidation with Copper: Synthesis of Polyoxypregnanes

Yi Yang See, Aaron T. Herrmann, Yoshinori Aihara, and Phil S. Baran

J. Am. Chem. Soc. **2015**, *137*, 13776.

(8) Chelation-Assisted Nickel-Catalyzed Oxidative Annulation via Double C-H Activation/Alkyne Insertion Reaction

Luis C. Misal Castro, Atsushi Obata, Yoshinori Aihara, and Naoto Chatani

Chem. Eur. J. **2016**, *22*, 1362.

(9) Nickel-Catalyzed Iodination of Aromatic Amide and Formation of β-Lactam via Cleavage of C(sp^3)-H Bond

Yoshinori Aihara, and Naoto Chatani

in preparation.