Doctoral Dissertation

Studies on Rhodium-Catalyzed Alkylation of C-H Bonds with Alkenes Utilizing an *N*,*N*-Bidentate Chelation System

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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 2011 and 2017. This thesis is concerned with the development of the Rh(I)-catalyzed direct functionalization of aromatic C-H bonds by using a *N*,*N*-bidentate-directing group.

I couldn't have done this thesis without advice, and support from many people and I feel truly grateful for their help over the past few years.

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Suita, Osaka
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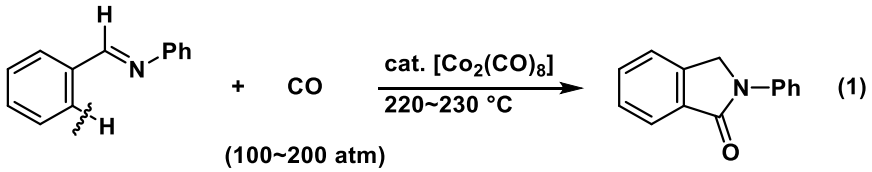
Contents

General Introduction

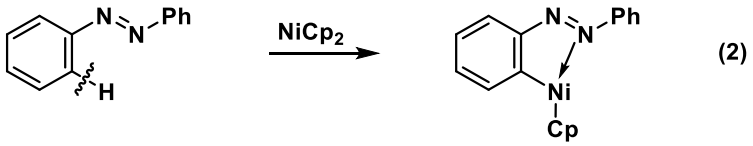
The direct functionalization of C-H bonds using transition metal catalysts can reduce the number of reaction steps needed to prepare pre-functionalized starting materials and suppress the formation of undesirable by-products. Using this approach, researchers have achieved remarkable progress in the field of C-H bond functionalization. C-H bond functionalization is now recognized to have significant potential as an alternative method to conventional cross coupling reactions.[1]

C-H bonds are truly ubiquitous in organic molecules. However, because they have similar characteristics, the regioselective functionalization of C-H bonds is an impediment. In order to obtain desired product, functionalization must occur with a high degree of regioselectivity at a specific position relative to the others in a complex molecule. The most common and reliable method for achieving the regioselective cleavage of desired C-H bonds is the utilization of chelation assistance by hetero atoms which can coordinate to a metal catalyst, thus allowing the catalyst to come into close proximity to the desired position. This method is generally referred to as chelation assisted direct C-H bond functionalization.[1]

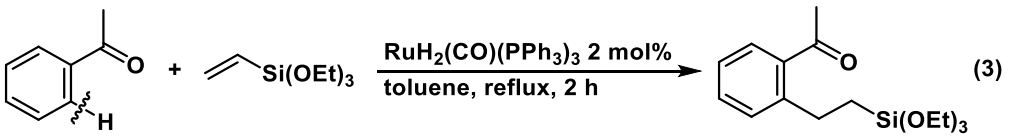
A pioneering example of the chelation-assisted direct C-H bond functionalization with a transition metal catalyst was reported by Murahashi in the 1950s. However, further applications did not progress for a long time because of the harsh reaction conditions needed, i.e., 220-230 °C and 100-200 atom of CO. (eq 1).[2]



Remarkably, this pioneering example was reported prior to the early example of the formation of a cyclometalated complex. In 1963, Kleiman and Dubeck reported on the cleavage of the *ortho* C-H bond of azobenzene with a stoiochiometric amount of a nickel complex (eq 2).[3] The driving force for this reaction is the formation of a stable 5-membered metallacycle. This finding suggests that heteroatoms could be utilized to assist the regioselective cleavage of C-H bond. However, it was rarely used in general organic synthesis reactions because the reaction requires a stoichiometric amount of metal complex. Practical systems for directed functionalization involving the cyclometalation process were subsequently developed in recent decades.



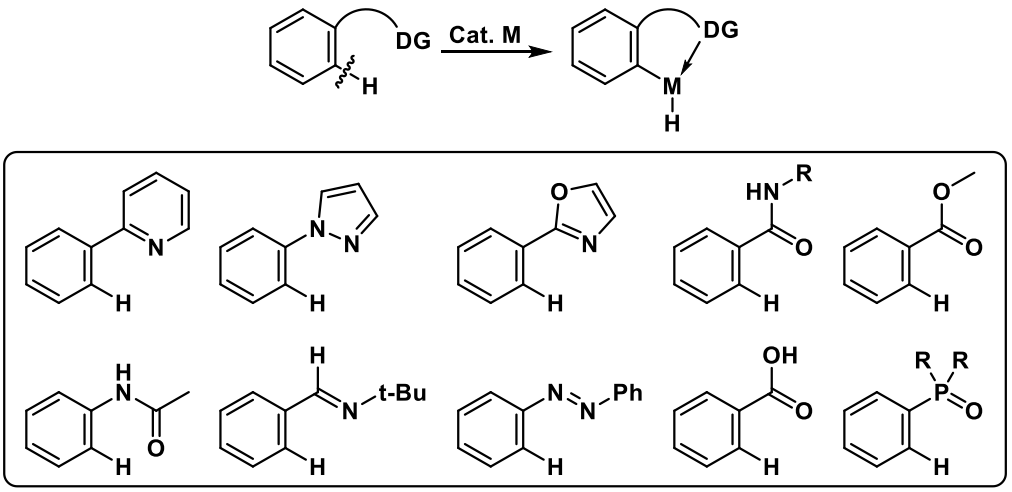
In 1993, Murai and co-workers reported on the alkylation of *ortho* C-H bonds of aromatic ketones with vinylsilane catalyzed by a ruthenium complex (eq 3).[4] This reaction was the first example of the transition metal-catalyzed-regioselective functionalization of C-H bond by utilizing a directing group. In this reaction, the coordination of the ketone is the key to a success of *ortho*-selective functionalization.



(3)

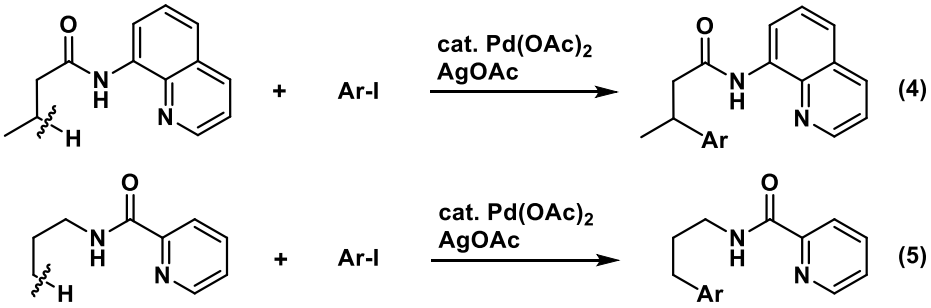
Following this pioneering work, a variety of regioselective C-H bond functionalization reactions were developed using various directing groups (Scheme 1).[5] In most cases, a carbonyl oxygen atom, as in ketone, ester, amide or N(sp^2) atoms, as in pyridine, pyrazole, oxazoline and imine moieties have been used in a wide variety of reactions (arylation, alkylation, oxidation, amination and so on). It is now possible to react C(sp^2)-H bonds of arenes, heteroarenes, alkenes, benzylic or even C(sp^3)-H bonds next to a heteroatom, and direct C-H bond functionalization is now considered to be one of the most reliable methods available for the construction of new C-X (X = C, N, O, F, Cl, Si, etc.) bonds. On the other hand, the direct functionalization of unactivated C(sp^3)-H bonds, a highly challenging reaction, has been much less studied. This is because the alkyl-metal species generated after the cleavage of the C-H bond is unstable compared to the arene-metal species and easily undergoes β-hydrogen elimination. In order to solve this problem and to extend the new field, developing a new type of directing group is strongly awaited.

Scheme 1. Representative monodentate directing groups

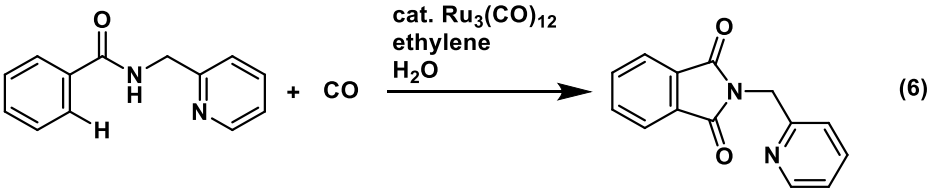


In 2005, Daugulis and co-workers overcame this drawback by utilizing a newly designed bidentate directing group which can coordinate to a metal at two nitrogen atoms (eq 4 and 5).[6] The

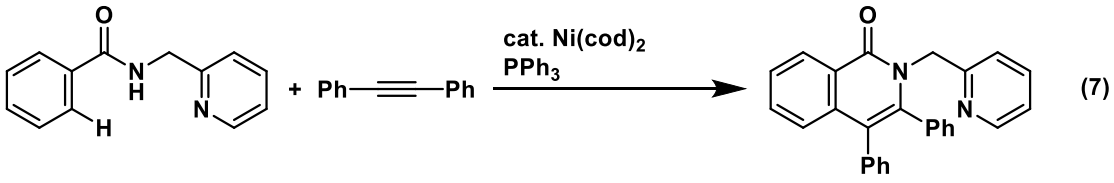
direct, $Pd(OAc)_2$ catalyzed C-H bond arylation of aromatic amides utilizing 8-aminoquinoline or picolinamide as a bidentate directing group was achieved. This reaction was applicable to both C(sp^2)-H and C(sp^3)-H bonds of aromatic or aliphatic amides. After their seminal work, the direct functionalization of C-H bonds utilizing bidentate directing groups has been studied by nmerous groups world-wide and various transition metal complexes have been shown to function as a catalyst.[7]



In 2009, Chatani and co-workers reported on the $Ru_3(CO)_{12}$ catalyzed carbonylation of aromatic amide C-H bond using 2-aminomethylpiridine as the bidentate directing group.[8] The bidentate system strongly coordinates to the ruthenium center, even under a high CO pressure, leading to the regioselective cleavage of the *ortho* C-H bond. This reaction is the first example of a ruthenium-catalyzed C-H functionalization involving the use of a bidentate directing group (eq 6). This reaction system was also successfully applied to the carbonylation of unactivated C(sp^3)-H bond of aliphatic amides.[9]

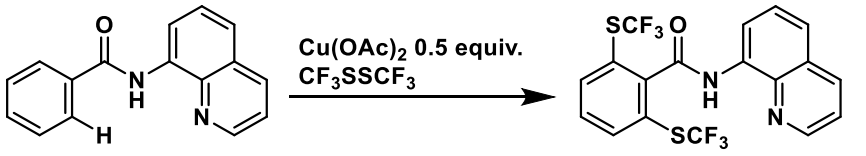


Although Kleimann and Dubeck reported the direct C-H bond activation by a nickel complex[3], a practical system for directed C-H bond functionalization with a nickel catalyst was developed much more recently. In 2011, Chatani and co-workers reported that Ni(0) showed the high catalytic activity for the functionalization of a C-H bonds with bidentate chelation systems. They developed the first Ni(0)-catalyzed oxidative cyclization of C-H bonds of aromatic amides with alkynes leading to the production of isoquinolinones (eq 7).[10]



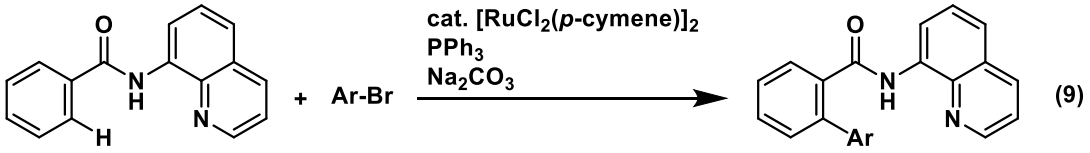
(7)

In 2012, Daugulis and co-workers reported on the first Cu-mediated sulfenylation of aromatic C-H bonds assisted by an 8-aminoquinoline moiety as a bidentate directing group (eq 8).[11] In the presence of a sub-catalytic amount (0.5 equivalent) of $Cu(OAc)_2$, a variety of aromatic amides derivatives were found to be sulfenylated.



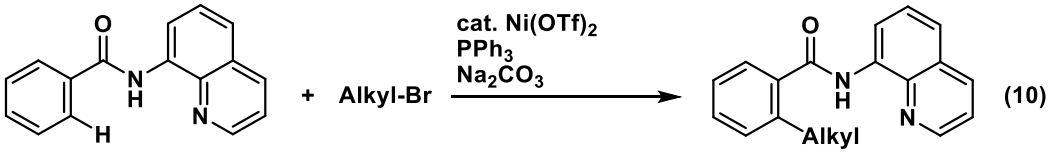
(8)

In 2013, the first Ru(II)-catalyzed arylation of aromatic amides with bidentate directing group was achieved by Chatani and co-workers (eq 9).[12] A variety aryl bromides, aryl iodides and aryl triflates were found to be applicable to this reaction.



(9)

In 2013, Chatani and co-workers repoted on the first example of a Ni(II)-catalyzed alkylation of aromatic amides assisted by an 8-aminoquinoline moiety as a bidentate directing group (eq 10).[13] This reaction was also applicable to vinyl C-H bonds of α,β-unsaturated amides. After this paper appeared in the literature, reactions with low-cost first-row transition metal catalysts such as Fe(III)(eq 11)[14], Co(II)(eq 12)[15], were widely developed. An Ir(III) catalyzed C-H amination reaction using picolinamids as the bidentate directing group was also reported in 2016 (eq 13).[16]



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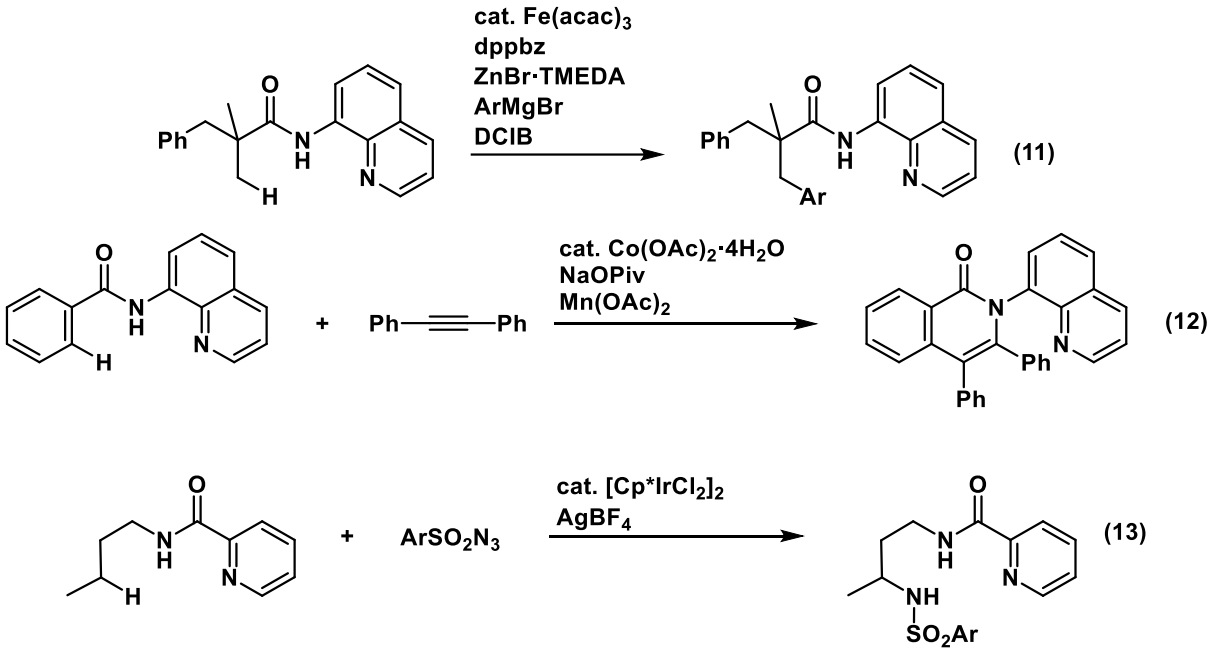
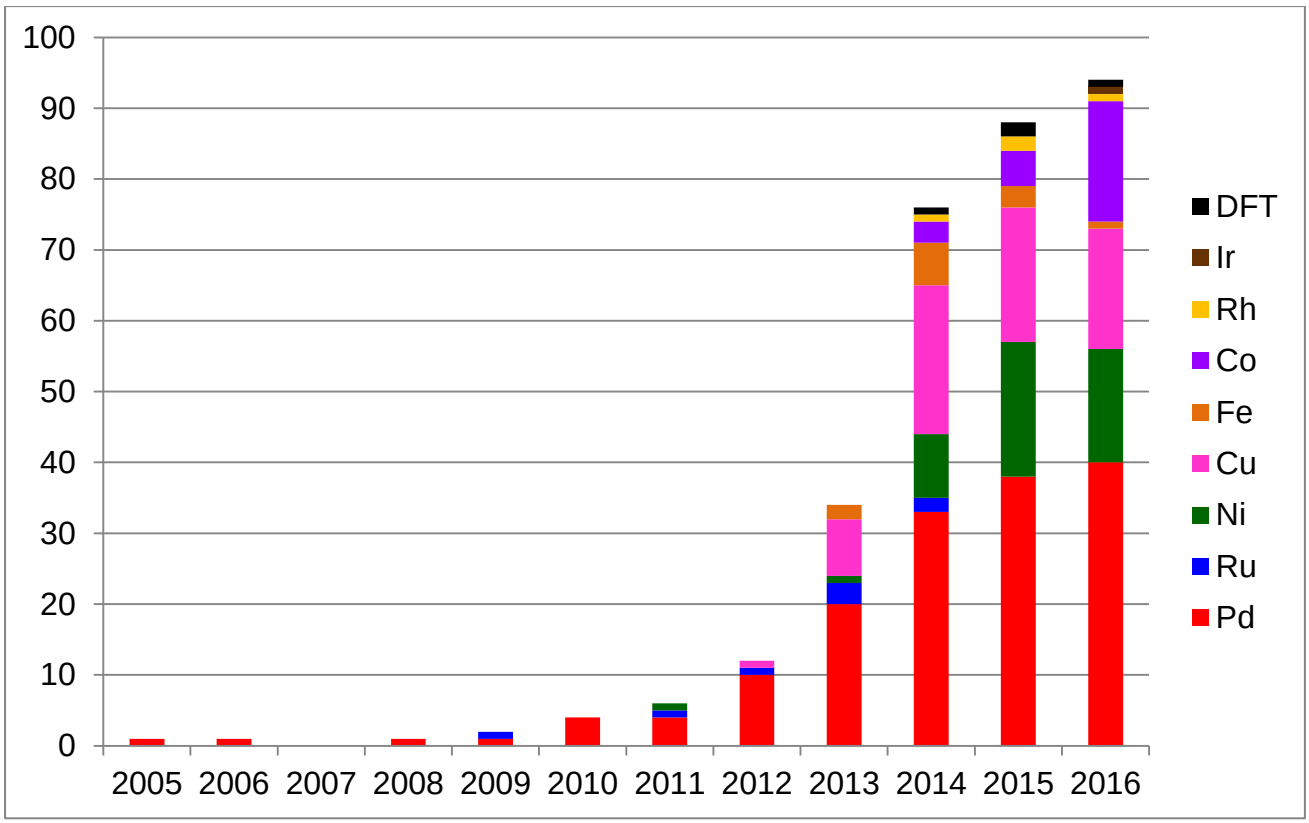


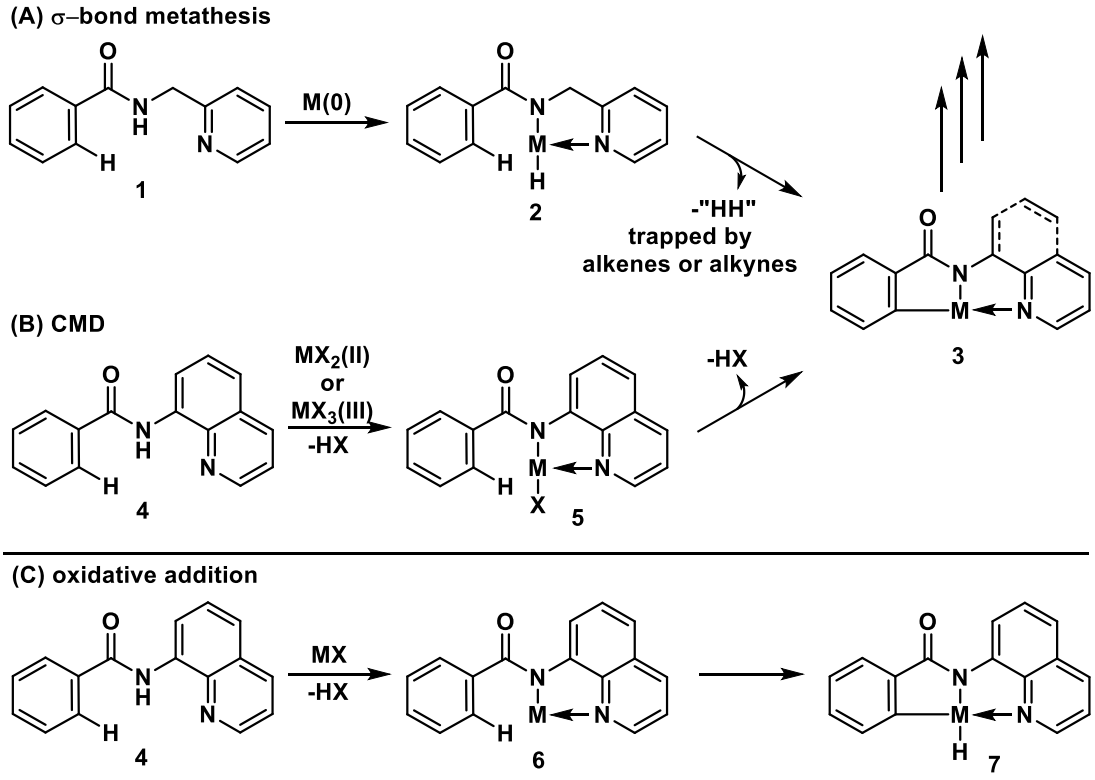
The number of C-H functionalizations utilizing bidentate chelation systems by transition metals is summarized in Fig. 1. Since Daugulis's promising work using $Pd(OAc)_2$ appeared[6], combinations of various transition metal catalysts and *N,N*-bidentate directing groups have emerged as a powerful method for the construction of carbon-carbon and carbon-heteroatom bonds through C-H bond cleavage. In recent years, not only second- and third-row transition metals such as ruthenium, rhodium, palladium and iridium but also first-row transition metals such as iron, cobalt, nickel and copper have been used as catalysts.

Although bidentate chelation systems have been shown to be effective for many catalytic reactions, focusing on the C-H bond cleavage step of these reactions, the mechanism for the cleavage of C-H bonds can be classified into two types, depending on the valence of the metal complex used (Scheme 2). First, when a low valent transition metal is used as a catalyst, the coordination of the pyridine N(sp^2) atom of **1** to the metal center followed by oxidative addition of N-H bond gives the metal hydride complex **2**. The *ortho* C-H bond of complex **2** is cleaved through σ-bond metathesis with the concomitant generation of the formal "H_2" (path A). However, this is not the actual mechanism. No direct cleavage of a C-H bond takes place in the absence of a hydrogen acceptor such as an alkene or an alkyne. The insertion of alkenes or alkynes into a M-H bond of complex **2** followed by σ-bond metathesis generates the cyclometalated complex **3**. On the other hand, when a high valent transition metal is used as a catalyst, the coordination of the quinoline N(sp^2) atom of **4** to the metal center followed by ligand exchange, an amide NH bond generates the metal amide complex **5**. The *ortho* C-H bond of **5** is cleaved via the concerted metalation deprotonation (CMD) with the generation of HX (path B). After forming the metallacycle **3**, the reaction proceeds with various reagents. The difference between two mechanisms involves how NH bonds are cleaved and how C-H bonds are cleaved.

Figure 1. Functionalization of C-H Bonds Using *N,N*-Bidentate Groups.



Scheme 2. Reaction Mechanism



The objective of this study was to develop new types of reactions, in which the C-H bonds are cleaved, not via σ bond metathesis (path A) or a CMD mechanism (path B), but via a new mechanism. For example, if the oxidative addition of the *ortho* C-H bond of **6** to the metal center would proceed after the ligand exchange, the metallacycle **7** with a hydride on the metal center would be formed (path C). In this case, reactions that take advantage of the M-H bond might proceed, such as the alkylation of C-H bonds with olefins which does not proceed via path A or B. These circumstances provided the motivation to study the transition metal catalyzed alkylation of C-H bonds by utilizing a bidentate chelation system. This thesis is composed of the following five chapters.

Chapter 1 discusses the rhodium catalyzed reaction of *ortho*-C-H bonds in aromatic amides with α,β-unsaturated esters using a bidentate directing group.

Chapter 2 discusses the rhodium catalyzed reaction of *ortho*-C-H bonds in aromatic amides with styrenes using a bidentate directing group.

Chapter 3 discusses the rhodium catalyzed reaction of *ortho*-C-H bonds in aromatic amides with α,β-unsaturated lactones and dihydrofurans using a bidentate directing group. In these reactions, the C-C bond is formed adjacent to the oxygen of the coupling partner.

Chapter 4 discusses the rhodium catalyzed reaction of *ortho*-C-H bonds in aromatic amides with norbornene using a bidentate directing group. In these reactions, an unusual *endo*-selective alkylated product was obtained.

Chapter 5 discusses the mechanisms responsible for these reactions.

Finally, the findings are summarized in the conclusion section.

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Chapter 1

Rhodium-Catalyzed Alkylation of C-H Bonds with α,ß-Unsaturated Esters

1.1 Introduction

The transition metal catalyzed direct arylation of C-H bonds is one of the most actively researched fields as an alternative method for conventional cross-coupling reactions such as the Suzuki-Miyaura or Negishi reactions. Prior to this, a variety electrophilic arylating reagents or nucleophilic arylating reagents have been developed. On the other hand, compared to the well developed arylation reaction, the alkylation of carbon-hydrogen bonds is limited because the alkyl metal complexes are susceptible to undergoing ß-hydride elimination.[1] C−H bond alkylation with olefins is one of the most efficient reactions because all of the atoms are involved in the alkylation products through this transformation, compared to the reaction with the corresponding alkyl halides or alkyl metal species. After Murai's pioneering work[2], regioselective alkylation reactions using olefins were developed by a number of groups.[3] However, in many cases, the range of applicable of olefins was limited to compounds such as vinylsilane and tert-butylethylene and olefins with no allyl hydrogen. Before starting this reaction, only a few examples of C-H bond alkylation with electron deficient olefins has been reported.[4] In addition, substrate scope is a problem in these reactions. Therefore, I initiated research directed at developing alkylation reactions using various electron deficient olefins. After our report, several examples of C-H bond alkylation reaction with electron deficient olefins appeared in the literature.[5]

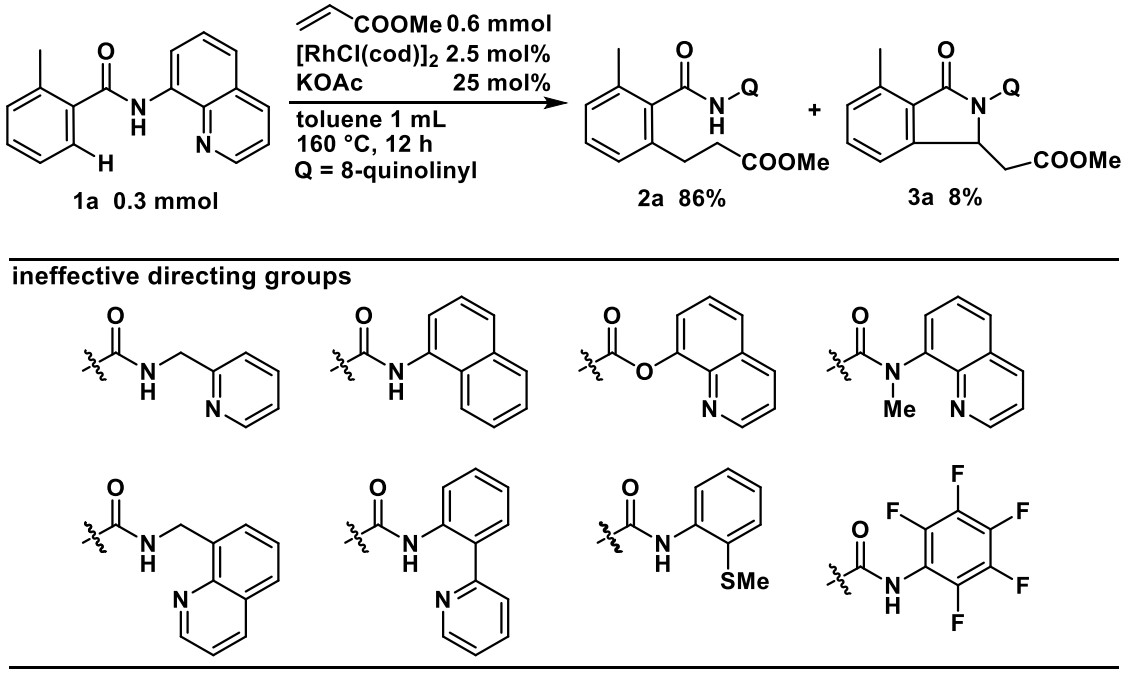
As discussed in Chapter 1, the direct, rhodium catalyzed alkylation of aromatic amides with α,ß-unsaturated esters takes advantage of a *N,N*-bidentate directing chelation system. This reaction is the first example of the use of rhodium as a catalyst for the functionalization of a C-H bond utilizing a bidentate directing group.

1.2 Results and Discussion

Motivated by working hypothesis described in general introduction, a variety types of transition metal catalysts and bidentate groups were examined to develop a new type of C-H bond alkylation reaction. The reaction of aromatic amide **1a** (0.3 mmol) with methyl acrylate (0.6 mmol) in the presence of $[RhCl(cod)]_2$ (0.0075 mmol) as the catalyst and KOAc (0.075 mmol) as the base in toluene (1 mL) at 160 °C for 12 h gave the alkylation product **2a** in 86% isolated yield along with the cyclized product **3a** in 8% yield (Scheme 1). The cyclized byproduct **3a** probably be generated by the oxidative alkenylation of C-H bonds followed by cyclization.[6] These produts **2a** and **3a** could be easily isolated by siica gel column chromatography. After the screening of rhodium catalysts, $[RhCl(cod)]_2$ and $[Rh(OAc)(cod)]_2$ were found to be the most active catalysts.[7] The effect of the directing group used in this reaction was examined. No reaction occurred when pyridinylmethylamine, naphthylamine or ester were used in place of 8-aminoquinoline. N-Me amide also failed to result in the formation of the

product, indicating that the presence of a proton on the amide nitrogen is required for the reaction to proceed, although NH is not included in the product formation at first sight. Furthermore, other directing groups were also ineffective. These results indicated that the presence of both a quinoline nitrogen and an amide NH group are essential for the success of the reaction.

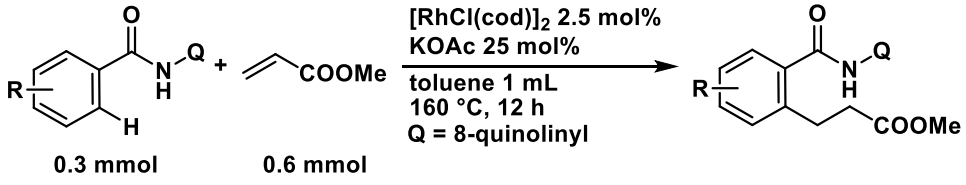
Scheme 1. The Rh-Catalyzed C-H Alkylatin with α,ß-Unsaturated Esters[a]

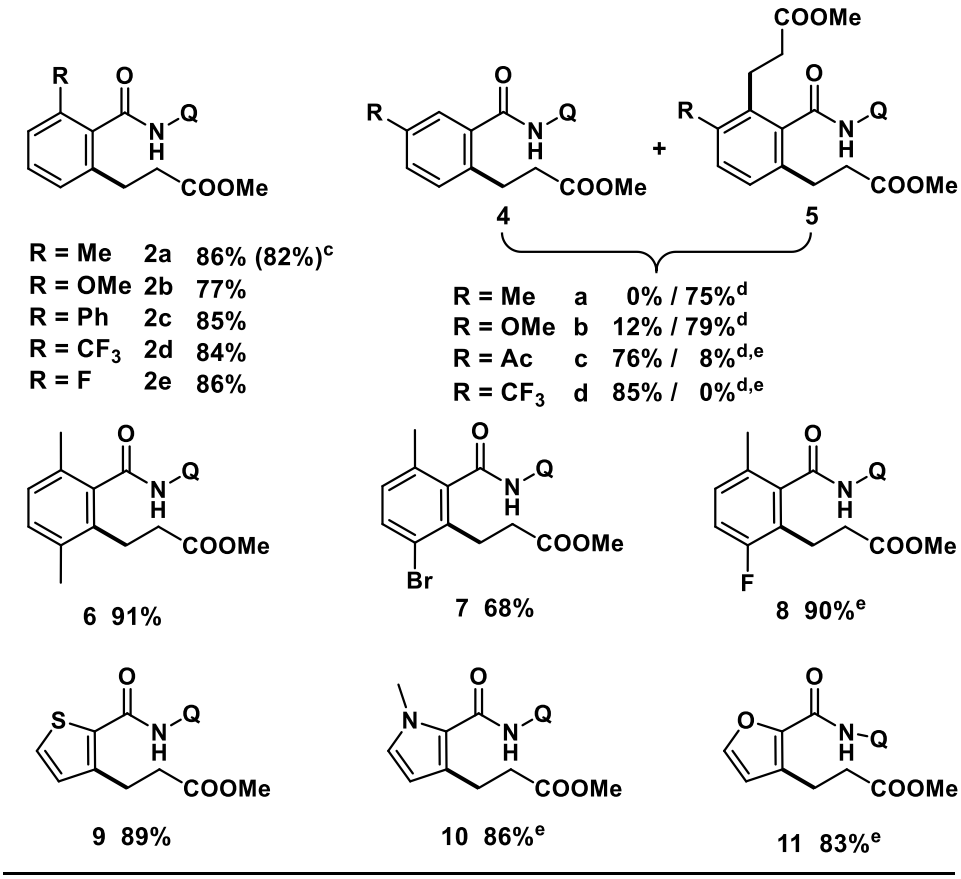


[a] Isolated yields.

Under the optimized reaction condition, we examined the scope of amides. Table 1 shows representative results for some reactions of aromatic amides with methyl acrylate under the standard reaction conditions. A variety of benzoic acid derivatives could be alkylated. The reactions were highly regioselective, exclusively producing alkylation products, in which C-C bond formation occurred between the *ortho* C-H bonds and the ß-position of the olefins. Both electron donating as well as electron withdrawing groups at the *ortho*-position of the amide gave the corresponding coupling products in high yield (**2a**-**2e**). In the case of *meta*-substituted aromatic amides, a mixture of mono-alkylation products **4** and di-alkylation products **5** were formed. When 4 equivalents of an ester was used, the di-alkylation products **5a** and **5b** were the major isomers in the case of an electron donating functional group, such as R = Me or OMe. In sharp contrast, mono-alkylation products **4c** and **4d** were obtained as the major isomer in the case of an electron withdrawing functional group, such as R = Ac or CF_3. Especially, in the case of CF_3 group, monoalkylation product **4d** was selectively obtained although an excess amount of acrylic ester was used. In this reaction, heteroaromatic systems were also applicable such as thiophene **9**, pyrrole **10** and furan **11**.

Table1. The Rh-Catalyzed C-H Alkylatin of C(sp^2)-H Bonds[a,b]



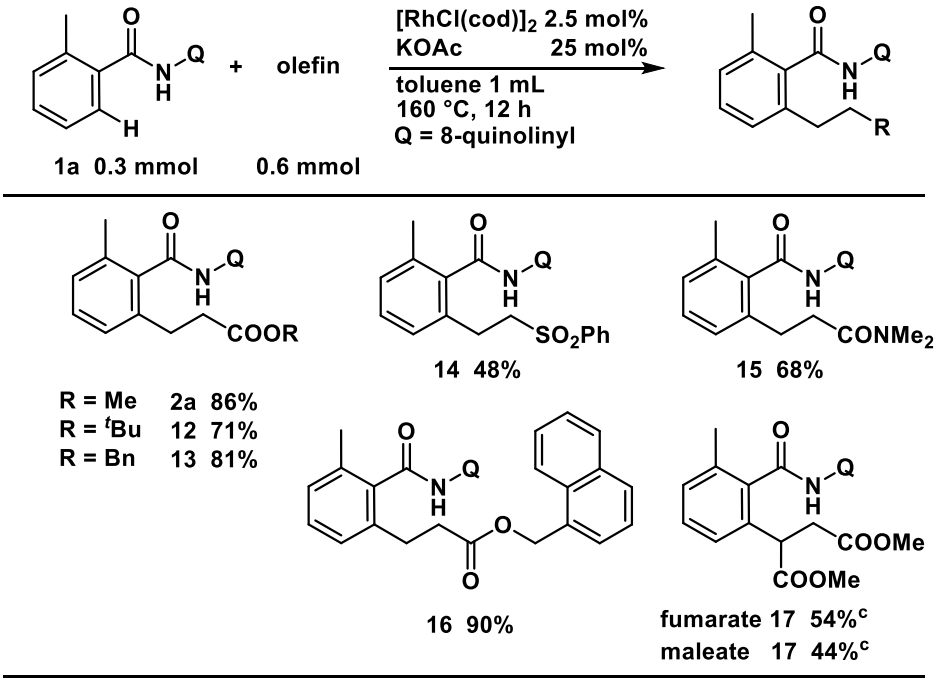


[a] Reaction conditions: amide (0.3 mmol), acrylic ester (0.6 mmol), $[RhCl(cod)]_2$ (0.0075 mmol), KOAc (0.075 mmol), toluene (1 mL), at 160 °C for 12 h. [b] Isolated yields. [c] The reaction was carried out using 1.31 g of **1a** (5 mmol) to give **2a** 1.43 g (82% yield). [d] Acrylic ester (1.2 mmol) was used. [e] K_2HPO_4 was used in place of KOAc.

Various acrylic esters, such as tert-butyl **12** and benzyl ester **13** were applicable to this reaction (Table 2). However, no reaction took place when substituted acrylic esters, such as methyl crotonate and methacrylate were used as coupling partners. Not only acrylic esters but also some other electron deficient olefins, such as phenyl vinyl sulphone **14** and *N,N*-dimethylacrylamide **15** gave the corresponding alkylation products. In addition, the reaction proceeded even with dimethyl fumarate or dimethyl maleate **17** which had not been reported so far.

The reaction mechanism is discussed in chapter 5.

Table 2. The Rh-Catalyzed Aromatic Amides with Activated Olefins[a,b]



[a] Reaction conditions: amide (0.3 mmol), acrylic ester (0.6 mmol), $[RhCl(cod)]_2$ (0.0075 mmol), KOAc (0.075 mmol), toluene (1 mL), at 160 °C for 12 h. [b] Isolated yields. [c] K_2HPO_4 was used in place of KOAc.

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. The rhodium catalyzed *ortho* alkylation of C(sp^2)-H bonds in aromatic amides with α,β-unsaturated carbonyl compounds by using a bidentate chelation system. This reaction is the first example using a rhodium as a catalyst for the functionalization of a C-H bond utilizing a bidentate directing group. Various functional groups are tolerated under this reaction conditions. The reaction is highly regioselective. The formation of C-C bonds occurs between the *ortho* C-H bonds in aromatic amides and the β–position of the acyclic α,β-unsaturated carbonyl compounds. The presence of an 8-aminoquinoline moiety as the directing group is essential for the reaction to proceed.

1.4 Experimental Section

General Information.

^1H 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 (δ), 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-4200 spectrometer; absorptions are reported in reciprocal centimeters with the following

relative intensities: s (strong), m (medium), or w (weak). Mass spectra and high resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Analytical gas chromatography (GC) was carried out on a Shimadzu GC-2014 gas chromatograph, equipped with a flame ionization detector. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

Materials.

Toluene (Kanto Chemical) was purified by passage through activated alumina using a GlassContour Solvent Dispensing System. $[RhCl(cod)]_2$ (CAS 12092-47-6) was purchased from Wako Pure Chemicals. KOAc (CAS 127-08-2), K_2HPO_4 (CAS 7758-11-4), Na_2CO_3 (CAS 497-19-8), were purchased from Nacalai Tesque. methyl acrylate (CAS 96-33-3) and 8-Aminoquinoline (CAS 578-66-5) were purchased from Tokyo Chemical Industry Co., Ltd.

Synthesis of $[Rh(OAc)(cod)]_2$.

To a solution of $[RhCl(cod)]_2$ (1.5 g, 3 mmol)in acetone (20 mL), KOAc (1 g, 15.3 mmol) was added. The mixture was stirred under reflux for 2 h. The solution was then filtered and the filtrate was dried in vacuo. The residu was recrystallized from ethyl acetate gave orange crystals of the pure product in 74% (1.2 g). HRMS Calcd for $C_{20}H_{30}O_4Rh_2$: 540.0254; Found: 540.0249.

Synthesis of Starting Amides.

All amides bearing an 8-aminoquinoline moiety were prepared by reacting the corresponding acid or the corresponding acid chlorides with 8-aminoquinoline. All starting amides were prepared following general procedure. All spectrum data of starting amides are cited in original paper.[8]

General Procedure for the Preparation of Stating Amides.

(1) Synthesis of amides from acid chlorides.

The acid chloride (15 mmol) was dissolved in CH_2Cl_2 (20 mL). After cooling the reaction mixture to 0 °C, a solution of 8-aminoquinoline (15 mmol) and triethylamine (36 mmol) in 10 mL of CH_2Cl_2 was added dropwise. The resulting mixture was allowed to warm to rt and was then stirred overnight. The crude mixture was then washed with saturated aqueous $NaHCO_3$ (20 mL), and CH_2Cl_2 (3x20 mL). The combined organic layers were washed with 1 M HCl aq. (20 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solution taken to dryness.The resulting crude amide was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 5/1).

(2) Synthesis of amides from carboxylic acid.

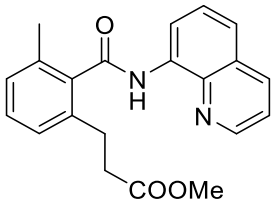
To a stirred solution of carboxylic acid (15 mmol) in CH_2Cl_2 (10 mL), $(COCl)_2$ (1.5 mL, 18 mmol) was added dropwise. The solution was magnetically stirred at room temperature for 2 h. The solvent was

then eliminated under reduced pressure, and the resulting residue was dissolved in CH_2Cl_2 (15 mL). After cooling the reaction mixture to 0 °C, a solution of 8-Aminoquinoline (15 mmol) and triethylamine (36 mmol) in 10 mL of the same solvent were added dropwise. The resulting mixture was allowed to warm to rt and stirred overnight. The crude product was washed with saturated aqueous $NaHCO_3$ (20 mL), and CH_2Cl_2 (3x20 mL). The organic phase was washed with 1 M HCl aq. (20 mL).The organic phase was dried over anhydrous Na_2SO_4 and the solvent removed by evaporation of the solvent. The resulting crude amide was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 5/1).

Typical Procedures for the Rh-Catalyzed Reaction of Aromatic Amides with α,β-Unsaturated Esters.

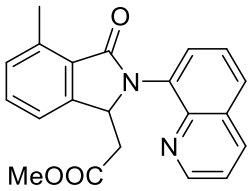
To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a** (79 mg, 0.3 mmol), methyl acrylate (52 mg, 0.6 mmol), $[RhCl(cod)]_2$ (3.7 mg, 0.0075 mmol), KOAc (7.4 mg, 0.075 mmol) and toluene (1.0 mL) were added. The mixture was stirred for 12 h at 160 °C followed by cooling. The mixture was filtered through a celite pad and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 10/1) to afford the desired alkylated product **2a** (90.0 mg, 86%) as a colorless oil.

Methyl 3-(3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (2a).



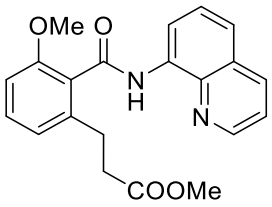
89.8 mg, 86% yield. colorless oil. R_f 0.23 (Hexane/EtOAc = 10/1). ^1H NMR ($CDCl_3$, 399.78 MHz) δ: 2.44 (s, 3H), 2.73 (t, J = 8.0 Hz, 2H), 3.06 (t, J = 8.0 Hz, 2H), 7.14-7.16 (m, 2H), 7.26-7.31 (m, 1H), 7.43-7.46 (m, 1H), 7.56-7.63 (m, 2H), 8.18 (dd, J = 8.4, 1.6 Hz, 1H), 8.74 (dd, J = 4.0, 1.6 Hz, 1H), 8.97 (dd, J = 7.6, 1.6 Hz, 1H), 9.94 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.5, 28.6, 35.7, 51.5, 116.9, 121.7, 122.1, 126.7, 127.4, 128.0, 128.5, 129.2, 134.3, 134.7, 136.3, 137.3, 137.9, 138.5, 148.3, 168.4, 173.2. IR (ATR): 3344 w, 2950 w, 1734 m, 1672 m, 1595 w, 1579 w, 1518 s, 1481 s, 1424 m, 1385 m, 1325 m, 1262 m, 1197 m, 1170 m, 1128 w, 1090 w, 1042 w, 985 w, 897 w, 827 m, 791 m, 760 m, 691 w. MS, *m/z* (relative intensity, %): 348 (M^+, 37), 317 (13), 299 (13), 205 (35), 204 (16), 177 (15), 176 (37), 173 (52), 163 (19), 146 (22), 145 (100), 144 (28), 133 (12), 130 (18), 117 (36), 116 (21), 115 (36), 105 (28), 91 (24). Exact Mass (EI): Calcd for $C_{21}H_{20}N_2O_3$ 348.1474, found 348.1472.

Methyl 2-(4-methyl-3-oxo-2-(quinolin-8-yl)isoindolin-1-yl)acetate (3a).



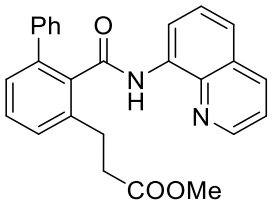
8.2 mg, 8% yield. pale yellow oil. R_f 0.29 (Hexane/EtOAc = 1/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.63 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.73 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.78 (s, 3H), 3.34 (s, 3H), 6.23 (t, *J* = 6.0 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.41 (dd, *J* = 8.0, 4.4 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 2H), 8.19 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.87 (dd, *J* = 4.0, 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 17.4, 38.2, 51.4, 58.7, 119.8, 121.4, 126.2, 128.0, 128.9, 129.3, 130.4, 130.5, 131.5, 133.6, 136.2, 138.4, 144.8, 146.0, 150.3, 169.0, 170.6. IR (ATR): 3006 w, 2952 w, 2362 w, 1735 m, 1688 s, 1599 w, 1574 w, 1500 w, 1474 w, 1436 w, 1395 m, 1370 m, 1335 w, 1309 w, 1269 w, 1201 m, 1151 m, 1062 w, 1027 w, 985 w, 903 w, 883 w, 830 w, 791 m, 747 s, 691 m, 664 m. MS, *m/z* (relative intensity, %): 346 (M^+, 20), 288 (19), 287 (100), 128 (10), 115 (11). Exact Mass (EI): Calcd for $C_{21}H_{18}N_2O_3$ 346.1317, found 346.1319.

Methyl 3-(3-methoxy-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (2b).



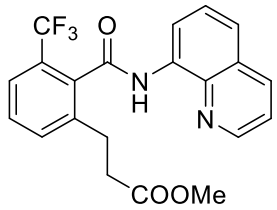
84.1 mg, 77% yield. colorless oil. R_f 0.10 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.74 (t, *J* = 8.0 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 3.59 (s, 3H), 3.82 (s, 3H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.51-7.60 (m, 2H), 8.15 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.73-8.75 (m, 1H), 8.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 10.15 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ:28.5, 35.5, 51.4, 55.7, 109.2, 116.7, 121.5, 121.7, 121.8, 126.7, 127.3, 127.9, 130.4, 134.6, 136.2, 138.4, 140.0, 148.1, 156.4, 165.9, 173.2 . IR (ATR): 3345 w, 3014 w, 2951 w, 2840 w, 2361 w, 2339 w, 1733 w, 1668 w, 1581 w, 1523 m, 1484 m, 1469 w, 1436 w, 1424 w, 1385 w, 1326 w, 1264 m, 1216 w, 1174 w, 1128 w, 1081 w, 1042 w, 987 w, 907 w, 826 w, 792 w, 749 s, 731 s, 666 m. MS, *m/z* (relative intensity, %): 364 (M^+, 72), 333 (20), 222 (13), 221 (100), 220 (40), 192 (12), 189 (39), 179 (13), 162 (12), 161 (78), 152 (12), 144 (12). Exact Mass (EI): Calcd for $C_{21}H_{20}N_2O_4$ 364.1423, found 364.1425.

Methyl 3-(2-(quinolin-8-ylcarbamoyl)-[1,1'-biphenyl]-3-yl)propanoate (2c).



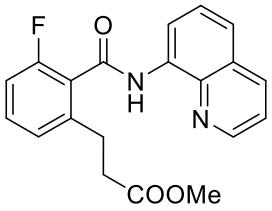
104.7 mg, 85% yield. colorless oil. R_f 0.23 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.81 (t, J = 8.0 Hz, 2H), 3.18 (t, J = 8.0 Hz, 2H), 3.59 (s, 3H), 7.0 (t, J = 7.2 Hz, 1H), 7.18 (t, J = 7.6 Hz, 2H), 7.28-7.35 (m, 3H), 7.40-7.52 (m, 5H), 8.01 (d, J = 8.4 Hz, 1H), 8.56 (dd, J = 4.0, 1.2 Hz, 1H), 8.73 (d, J = 7.6, Hz, 1H), 9.59 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 28.8, 35.7, 51.5, 116.4, 121.3, 121.7, 127.1, 127.2, 127.6, 128.1, 128.3, 128.6, 129.4, 134.2, 135.9, 136.6, 138.2, 138.5, 139.8, 140.1, 147.9, 167.8, 173.2. IR (ATR): 3340 w, 3018 w, 2952 w, 1732 w, 1668 m, 1593 w, 1521 m, 1483 m, 1453 w, 1424 w, 1386 w, 1326 w, 1263 m, 1216 m, 1173 w, 1131 w, 908 m, 826 w, 791 w, 750 s, 731 s, 699 m, 666 m. MS, *m/z* (relative intensity, %): 410 (M^+, 95), 379 (15), 268 (11), 267 (62), 266 (29), 238 (11), 235 (43), 225 (16), 208 (19), 207 (100), 179 (21), 178 (30), 175 (13), 165 (20), 152 (10), 144 (12). Exact Mass (EI): Calcd for $C_{26}H_{22}N_2O_3$ 410.1630, found 410.1626.

Methyl 3-(2-(quinolin-8-ylcarbamoyl)-3-(trifluoromethyl)phenyl)propanoate (2d).



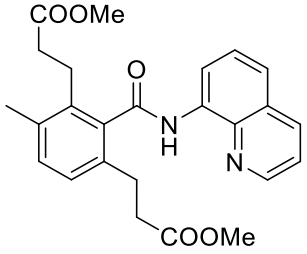
101.6 mg, 84% yield. colorless oil. R_f 0.11 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.76 (bs, 2H), 3.12 (t, J = 7.6 Hz, 2H), 3.59 (s, 3H), 7.41-7.44 (m, 1H), 7.49-7.64 (m, 5H), 8.16 (d, J = 8.4 Hz, 1H), 8.73 (dd, J = 4.4, 1.6 Hz, 1H), 8.94 (dd, J = 6.4, 2.0 Hz, 1H), 10.04 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 28.3, 35.3, 51.6, 117.0, 121.7, 122.4, 123.7 (q, J = 273 Hz), 124.4 (q, J = 4.8 Hz), 127.23 (q, J = 59.1 Hz), 127.5, 127.9, 129.5, 133.3, 134.0, 135.3, 136.3, 138.3, 139.3, 148.3, 165.3, 172.8. IR (ATR): 3335 w, 3019 w, 2953 w, 2362 w, 2339 w, 1734 m, 1677 m, 1523 m, 1485 m, 1425 w, 1387 w, 1320 m, 1264 w, 1215 w, 1170 m, 1129 m, 1108 w, 1085 w, 907 m, 826 w, 792 w, 751 s, 731 s, 667 m. MS, *m/z* (relative intensity, %): 402 (M^+, 100), 371 (25), 344 (12), 343 (55), 230 (19), 227 (56), 211 (13), 199 (73), 171 (26), 151 (15), 145 (14), 144 (67). Exact Mass (EI): Calcd for $C_{21}H_{17}F_3N_2O_3$ 402.1191, found 402.1187.

Methyl 3-(3-fluoro-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (2e).



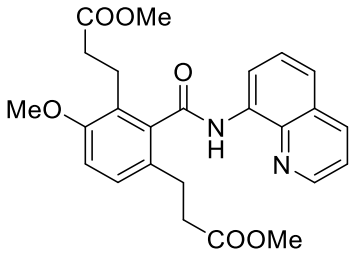
90.9 mg, 86% yield. colorless oil. R_f 0.14 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.76 (t, *J* = 8.0 Hz, 2H), 3.15 (t, *J* = 8.0 Hz, 2H), 3.61 (s, 3H), 7.04 (t, *J* = 8.8Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.34-7.39 (m, 1H), 7.42-7.45 (m, 1H), 7.54-7.61 (m, 1H), 8.16 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.76 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.95 (dd, *J* = 6.8, 1.6 Hz, 1H), 10.19 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ:28.4 (q, *J* = 1.9 Hz), 35.4, 51.5, 114.0 (d, *J* = 22.9 Hz), 116.8, 121.7, 122.2, 125.1 (d, *J* = 17.1 Hz), 125.5 (d, *J* = 2.9 Hz), 127.2, 127.9, 131.1 (d, *J* = 9.5 Hz), 134.2, 136.3, 138.3, 141.4 (d, *J* = 2.9 Hz), 148.3, 159.3 (d, *J* = 247.0 Hz), 163.1, 173.0. IR (ATR): 3341 w, 3017 w, 2952 w, 2361 w, 2339 w, 1734 m, 1673 m, 1613 w, 1597 w, 1577 w, 1523 s, 1485 m, 1459 w, 1424 w, 1387 w, 1327 m, 1249 w, 1200 w, 1173 w, 1127 w, 1080 w, 1041 w, 967 w, 907 m, 826 w, 792 m, 754 s, 729 s, 686 m, 667 m. MS, *m/z* (relative intensity, %): 352 (M^+, 100), 321 (24), 293 (46), 181 (12), 180 (36), 177 (38), 171 (11), 150 (14), 149 (78), 144 (35), 130 (11), 101 (11). Exact Mass (EI): Calcd for $C_{20}H_{17}FN_2O_3$ 352.1223, found 352.1220.

Dimethyl 3,3'-(4-methyl-2-(quinolin-8-ylcarbamoyl)-1,3-phenylene)dipropionate (5a).



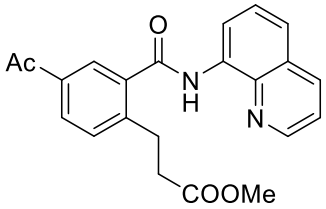
9.8 mg, 75% yield. colorless oil. R_f 0.07 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.36 (s, 3H), 2.70 (t, *J* = 7.6 Hz, 4H), 3.00-3.05 (m, 4H), 3.53 (s, 3H), 3.56 (s, 3H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.42-7.45 (m, 1H), 7.55-7.62 (m, 2H), 8.16 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.72 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.94 (d, *J* = 7.2, 2.4 Hz, 1H), 9.93 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.0, 26.1, 28.2, 34.4, 35.5, 51.4 (two overlapping peaks), 116.9, 121.6, 122.1, 127.2 (two overlapping peaks), 127.9, 131.4, 134.0, 134.8, 134.9, 135.3, 136.2, 138.2, 138.4, 148.2, 168.4, 173.0 (two overlapping peaks). IR (ATR): 3340 w, 3018 w, 2952 w, 2360 s, 2339 s, 1733 m, 1670 w, 1520 m, 1483 m, 1457 w, 1436 w, 1424 w, 1385 w, 1366 w, 1326 w, 1292 w, 1265 w, 1198 w, 1171 w, 1038 w, 984 w, 909 m, 826 w, 792 w, 753 m, 729 s, 698 m. MS, *m/z* (relative intensity, %): 434 (M^+, 100), 404 (11), 403 (43), 291 (44), 290 (50), 259 (14), 249 (20), 247 (26), 231 (21), 227 (51), 217 (13), 199 (28), 198 (13), 189 (14), 173 (31), 171 (41), 159 (25), 157 (15), 145 (15), 144 (41), 130 (10), 129 (13), 128 (12). Exact Mass (EI): Calcd for $C_{25}H_{26}N_2O_5$ 434.1842, found 434.1483.

Dimethyl 3,3'-(4-methoxy-2-(quinolin-8-ylcarbamoyl)-1,3-phenylene)dipropionate (5b).



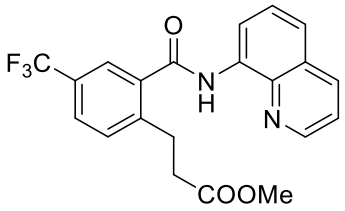
107.1 mg, 79% yield. colorless oil. R_f 0.07 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.70 (t, *J* = 7.6 Hz, 4H), 2.98-3.03 (m, 4H), 3.52 (s, 3H), 3.57 (s, 3H), 3.84 (s, 3H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.18 (d, 8.8 Hz, 1H), 7.41-7.45 (m, 1H), 7.55-7.61 (m, 2H), 8.17 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.72 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.93 (dd, *J* = 7.6, 2.0 Hz, 1H), 9.94 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 23.6, 279, 34.0, 35.8, 51.3, 51.4, 55.5, 111.1, 117.0, 121.6, 122.1, 125.6, 127.2, 127.9, 128.4, 128.8, 134.0, 136.2, 138.4, 138.8, 148.2, 156.1, 167.7, 173.2, 173.4. IR (ATR): 3341 w, 2950 w, 1733 s, 1672 m, 1581 w, 1519 s, 1480 s, 1455 m, 1435 m, 1384 m, 1366 m, 1325 m, 1271 s, 1196 s, 1170 s, 1090 m, 1070 w, 1042 m, 985 w, 914 w, 826 m, 792 m, 758 m, 732 m, 690 m. MS, *m/z* (relative intensity, %): 450 (M^+, 100), 420 (12), 419 (43), 307 (24), 306 (55), 279 (16), 278 (26), 275 (11), 266 (13), 265 (85), 263 (11), 247 (25), 243 (24), 233 (30), 215 (36), 214 (27), 205 (32), 189 (30), 188 (12), 187 (14), 175 (22), 173 (12), 172 (10), 171 (20), 159 (11), 158 (12), 145 (19), 144 (43). Exact Mass (EI): Calcd for $C_{25}H_{26}N_2O_6$ 450.1791, found 450.1790.

Methyl 3-(4-acetyl-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (4c).



85.4 mg, 76%yield. white solid. mp = 128 °C. R_f 0.06 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.64 (s, 3H), 2.81 (t, *J* = 7.6 Hz, 2H), 3.29 (t, *J* = 7.6 Hz, 2H), 3.62 (s, 3H), 7.45-7.49 (m, 2H), 7.57-7.63 (m, 2H), 8.00-8.03 (m, 1H), 8.17-8.21 (m, 1H), 8.27 (s, 1H), 8.78 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.90 (dd, *J* = 7.2, 2.0 Hz, 1H), 10.26 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 26.6, 28.7, 35.2, 116.7, 121.7, 122.2, 127.1, 127.2, 127.9, 130.1, 130.9, 134.3, 135.5, 136.3, 136.9, 138.4, 144.9, 148.4, 166.9, 172.9. IR (ATR): 3343 w, 2951 w, 1734 m, 1673 s, 1600 w, 1521 s, 1482 m, 1424 m, 1385 m, 1358 w, 1326 m, 1283 w, 1242 m, 1225 m, 1198 m, 1170 m, 1107 w, 914 w, 826 m, 791 m, 755 m, 690 w, 665 w. MS, *m/z* (relative intensity, %): 376 (M^+, 100), 345 (26), 317 (38), 205 (28), 204 (72), 201 (32), 191 (17), 189 (28), 174 (15), 173 (92), 171 (15), 151 (12), 145 (26), 144 (56), 130 (18), 116 (11). Exact Mass (EI): Calcd for $C_{22}H_{20}N_2O_4$ 376.1423, found 376.1421.

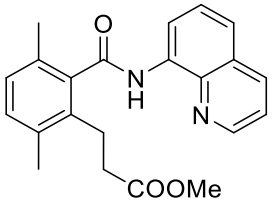
Methyl 3-(2-(quinolin-8-ylcarbamoyl)-4-(trifluoromethyl)phenyl)propanoate (4d).



102.5 mg, 85% yield. colorless oil. R_f 0.3 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.81 (t, *J* = 7.6 Hz, 2H), 3.128(t, *J* = 7.6 Hz, 2H), 3.63 (s, 3H), 7.46-7.52 (m, 2H), 7.58-7.63 (m, 2H), 7.69 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.91 (s, 1H), 8.20 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.80 (dd, *J* = 4.4, 2.0 Hz, 1H), 8.89 (dd, *J* = 6.4, 2.8 Hz, 1H), 10.23 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 28.6, 35.3, 51.6, 116.8, 121.8, 122.3, 123.7 (q, *J* = 270.8 Hz), 124.2 (d, *J* = 3.8 Hz), 127.1 (d, *J* = 3.8 Hz), 127.3, 128.0, 129.1 (q, *J* = 33.4 Hz), 131.2, 134.2, 136.4, 137.2, 138.5, 143.5, 148.5, 166.5, 172.9. IR (ATR): 3340 w, 2952 w, 1736 m, 1674 m, 1617 w, 1596 w, 1578 w, 1523 s, 1484 m, 1459 w, 1425 m, 1386 m, 1326 s, 1252 m, 1231 m, 1198 m, 1168 s, 1123 s, 1081 m, 1047 w, 986 w, 913 w, 827 m, 792 m, 760 w, 685 w. MS, *m/z* (relative intensity, %): 402 (M^+, 99), 371 (29), 344 (15), 343 (67), 325 (14), 279 (13), 231 (14), 230 (25), 227 (18), 200 (18), 199 (100), 171 (39), 167 (20), 151 (17), 149 (48), 145 (20), 144 (97), 130 (15), 129 (10), 116 (10).

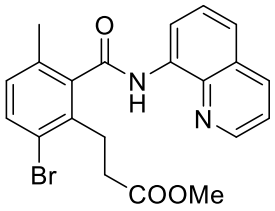
Exact Mass (EI): Calcd for $C_{21}H_{17}F_3N_2O_3$ 402.1191, found 402.1188.

Methyl 3-(3,6-dimethyl-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (6).



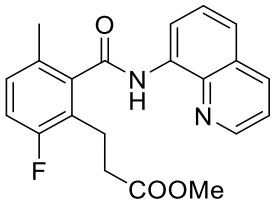
99.1 mg, 91% yield. colorless oil. R_f 0.19 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.35 (s, 3H), 2.39 (s, 3H), 2.68 (t, *J* = 8.4 Hz, 2H), 3.04 (t, *J* = 8.4 Hz, 2H), 3.55 (s, 3H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.40-7.43 (m, 1H), 7.54-7.61 (m, 2H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.71 (dd, *J* = 3.6, 1.2 Hz, 1H), 8.97 (dd, *J* = 7.6, 1.6 Hz, 1H), 9.91 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.0, 19.1, 26.2, 34.5, 51.4, 116.8, 121.6, 121.9, 127.2, 127.9, 128.3, 131.1, 132.0, 134.0, 134.2, 135.1, 136.2, 138.4, 148.2, 168.8, 173.1. IR (ATR): 3343 w, 3016 w, 2952 w, 2360 w, 2352 w, 1732 w, 1669 w, 1520 m, 1483 m, 1424 w, 1385 w, 1326 w, 1290 w, 1268 w, 1215 w, 1199 w, 1172 w, 1142 w, 1082 w, 1038 w, 983 w, 908 m, 825 w, 792 w, 753 s, 728 s, 666 m. MS, *m/z* (relative intensity, %): 362 (M^+, 79), 331 (19), 220 (14), 219 (100), 218 (28), 191 (13), 190 (21), 187 (36), 177 (48), 175 (20), 160 (11), 159 (47), 144 (23), 116 (10). Exact Mass (EI): Calcd for $C_{22}H_{22}N_2O_3$ 362.1630, found 362.1628.

Methyl 3-(6-bromo-3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (7).



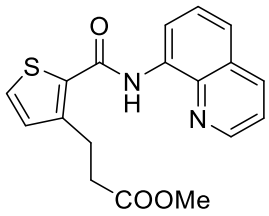
87.7 mg, 68% yield. white solid. mp = 123 °C. R_f 0.17 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.38 (s, 3H), 2.76 (t, *J* = 8.0 Hz, 2H), 3.16 (t, *J* = 8.4 Hz, 2H), 3.56 (s, 3H), 7.02 (d, *J* = 8.0Hz, 1H), 7.43-7.46 (m, 1H), 7.53 (d, *J* = 8.0Hz, 1H), 7.56-7.62 (m, 2H), 8.18 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.74 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.93 (dd, *J* = 6.8, 2.4 Hz, 1H), 9.92 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ:19.1, 29.3, 33.8, 51.5, 117.0, 121.7, 122.3(two overlapping peaks), 127.2, 127.9, 130.1, 133.5, 133.9, 134.1, 136.2, 136.3, 138.4, 140.0, 148.3, 167.2, 172.8. IR (ATR): 3337 w, 3018 w, 2952 w, 2361 w, 1733 w, 1671 w, 1521 m, 1483 w, 1452 w, 1424 w, 1385 w, 1326 w, 1291 w, 1263 w, 1214 w, 1176 w, 1144 w, 1112 w, 1074 w, 1045 w, 984 w, 908 w, 825 w, 792 w, 749 s, 666 w. MS, *m/z* (relative intensity, %): 429 (M^++3, 24), 428 (100), 427 (25), 426 (100), 397 (23), 395 (23), 348 (11), 347 (20), 285 (50), 284 (20), 283 (50), 282 (15), 257 (24), 256 (50), 255 (25), 254 (57), 253 (53), 251 (53), 243 (23), 241 (32), 239 (11), 226 (13), 225 (65), 224 (17), 223 (65), 203 (28), 197 (11), 183 (11), 171 (19), 145 (37), 144 (85), 143 (18), 130 (39), 129 (17), 117 (18), 116 (50), 115 (30). Exact Mass (EI): Calcd for $C_{21}H_{19}BrN_2O_3$ 426.0579, found 426.0577.

Methyl 3-(6-fluoro-3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (8).



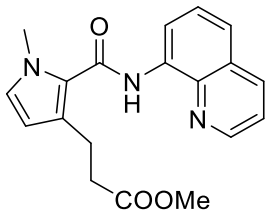
99.4 mg, 90% yield. colorless oil. R_f 0.16 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.40 (s, 3H), 2.73 (t, *J* = 8.0 Hz, 2H), 3.06 (t, *J* = 8.4 Hz, 2H), 3.57 (s, 3H), 7.03 (t, *J* = 8.4Hz, 1H), 7.11-7.14 (m, 1H), 7.44-7.47 (m, 1H), 7.58-7.63 (m, 1H), 8.19 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.75 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.94 (dd, *J* = 6.8, 2.4 Hz, 1H), 9.95 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ:19.0, 22.6, (d, *J* = 1.9 Hz), 34.4, 51.5, 115.9 (d, *J* = 21.9 Hz), 117.0, 121.7, 122.3, 124.5 (d, *J* = 17.1 Hz), 127.3, 127.9, 129.9 (d, *J* = 7.7 Hz), 130.2 (d, *J* = 2.8 Hz), 133.9, 136.3, 138.4, 139.3 (d, *J* = 2.8 Hz), 148.3, 159.5 (*J* = 243.1 Hz), 166.9 (d, *J* = 2.9 Hz), 172.9. IR (ATR): 3341 w, 2951 w, 1735 m, 1673 m, 1519 s, 1479 s, 1424 m, 1384 m, 1325 m, 1293 w, 1266 m, 1243 m, 1198 w, 1171 w, 1082 w, 1060 w, 1036 w, 984 w, 891 w, 825 m, 791 m, 756 m, 688 w. MS, *m/z* (relative intensity, %): 366 (M^+, 97), 335 (33), 317 (12), 307 (14), 223 (38), 222 (17), 195 (38), 194 (67), 191 (59), 181 (35), 171 (10), 164 (26), 163 (100), 145 (15), 144 (38), 135 (16), 130 (14), 123 (14), 116 (11), 115 (14). Exact Mass (EI): Calcd for $C_{21}H_{19}FN_2O_3$ 366.1380, found 366.1378.

Methyl 3-(2-(quinolin-8-ylcarbamoyl)thiophen-3-yl)propanoate (9).



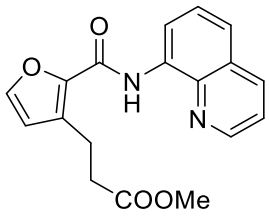
90.8 mg, 89% yield. colorless oil. R_f 0.20 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.82 (t, *J* = 8.0 Hz, 2H), 3.44 (t, *J* = 8.0 Hz, 2H), 3.66 (s, 3H), 7.04 (d, *J* = 5.2 Hz, 1H), 7.39 (d, *J* = 4.8 Hz, 1H), 7.41-7.45 (m, 1H), 7.49-7.56 (m, 2H), 8.13 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.79-8.82 (m, 2H), 10.42 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 24.9, 34.6, 51.5, 116.4, 121.6, 127.2, 127.4, 127.8, 131.2, 132.1, 134.4, 136.2, 138.4, 145.1, 148.2, 160.7, 173.1. IR (ATR): 3317 w, 3015 w, 2951 w, 2361 w, 2251 w, 1733 m, 1657 m, 1596 w, 1523 s, 1484 m, 1423 m, 1384 m, 1327 m, 1294 w, 1262 m, 1198 m, 1173 m, 1114 w, 1040 w, 984 w, 909 m, 881 w, 825 m, 790 m, 754 s, 72 s, 664 m. MS, *m/z* (relative intensity, %): 340 (M^+, 100), 309 (23), 281 (24), 197 (12), 171 (19), 169 (27), 168 (65), 155 (42), 144 (37), 137 (64), 125 (19). Exact Mass (EI): Calcd for $C_{18}H_{16}N_2O_3S$ 340.0882, found 340.0880.

Methyl 3-(1-methyl-2-(quinolin-8-ylcarbamoyl)-1H-pyrrol-3-yl)propanoate (10).



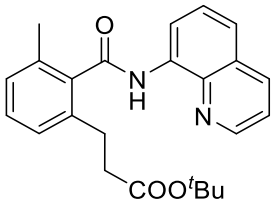
87.3 mg, 86% yield. pale yellow solid. mp = 100 °C. R_f 0.20 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.81 (t, *J* = 7.6 Hz, 2H), 3.32 (t, *J* = 7.6 Hz, 2H), 3.63 (s, 3H), 3.94 (s, 3H), 6.04 (d, *J* = 3.6 Hz, 1H), 6.69 (d, *J* = 3.6 Hz, 1H), 7.41-7.44 (m, 1H), 7.49 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 8.14 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.77 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 10.23 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 23.1, 35.2, 36.9, 51.4, 108.4, 116.1, 121.1, 121.5, 124.2, 126.4, 127.1, 127.3, 127.9, 134.9, 136.2, 138.6, 148.1, 160.4, 173.3. IR (ATR): 3363 w, 3014 w, 2952 w, 2360 w, 1733 w, 1652 w, 1523 s, 1483 m, 1424 m, 1384 w, 1327 w, 1265 w, 1215 w, 1172 w, 1120 w, 908 w, 825 w, 791 w, 749 s, 730 s, 665 m. MS, *m/z* (relative intensity, %): 373 (M^+, 40), 171 (65), 166 (13), 165 (29), 152 (100), 134 (18), 122 (11). Exact Mass (EI): Calcd for $C_{19}H_{19}N_3O_3$ 337.1426, found 337.1428.

Methyl 3-(2-(quinolin-8-ylcarbamoyl)furan-3-yl)propanoate (11).



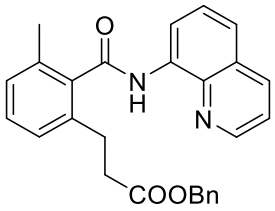
80.3 mg, 83% yield. white solid. mp = 107 °C. R_f 0.13 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.75 (t, *J* = 7.6 Hz, 2H), 3.28 (t, *J* = 7.6 Hz, 2H), 3.68 (s, 3H), 6.48 (d, *J* = 1.6 Hz, 1H), 7.42-7.46 (m, 1H), 7.48-7.56 (m, 3H), 8.14 (td, *J* = 8.0, 2.0 Hz, 1H), 8.85 (td, *J* = 5.6, 1.6 Hz, 2H), 10.72 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 21.0, 34.0, 51.5, 114.6, 116.3, 121.6, 127.2, 127.9, 131.6, 134.2, 136.2, 138.6, 142.5, 143.0, 148.3, 157.2, 173.3. IR (ATR): 3339 w, 3017 w, 2952 w, 2363 w, 2252 w, 1734 w, 1665 m, 1599 w, 1577 w, 1528 s, 1483 m, 1459 w, 1425 w, 1385 w, 1328 w, 1266 w, 1173 w, 1095 w, 1071 w, 1043 w, 984 w, 908 m, 875 m, 825 w, 790 w, 750 s, 728 s, 665 m. MS, *m/z* (relative intensity, %): 324 (M^+, 100), 293 (31), 279 (21), 265 (28), 263 (22), 247 (15), 237 (13), 222 (14), 221 (61), 171 (18), 144 (35), 139 (13), 121 (52), 109 (14). Exact Mass (EI): Calcd for $C_{18}H_{16}N_2O_4$ 324.1110, found 324.1111.

tert-Butyl 3-(3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (12).



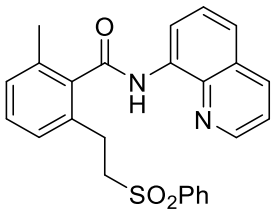
83.1 mg, 71% yield. colorless oil. Rf 0.14 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.32 (s, 9H), 2.44 (s, 3H), 2.63 (t, *J* = 8.0 Hz, 2H), 3.02 (t, *J* = 8.0 Hz, 2H), 7.13-7.17 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.42-7.45 (m, 1H), 7.55-7.62 (m, 2H), 8.17 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.73 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.98 (dd, *J* = 7.2, 1.6 Hz, 1H), 9.96 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.5, 27.9, 28.7, 37.0, 80.1, 116.8, 121.6, 122.0, 126.7, 127.3, 127.9, 128.3, 129.1, 134.3, 134.6, 136.3, 137.5, 137.8, 138.5, 148.2, 168.5, 172.1. IR (ATR): 3343 w, 3011 w, 2979 w, 2360 w, 2339 w, 1723 m, 1672 m, 1596 w, 1578 w, 1520 s, 1482 m, 1424 w, 1386 w, 1367 w, 1326 m, 1261 w, 1216 w, 1147 m, 1090 w, 1041 w, 957 w, 899 w, 846 w, 826 w, 791 w, 750 s, 695 w, 666 m. MS, *m/z* (relative intensity, %): 348 (M^+, 37), 390 (33), 334 (23), 317 (38), 192 (12), 191 (100), 190 (29), 163 (11), 162 (13), 149 (16), 145 (62), 144 (88), 117 (12), 57 (16). Exact Mass (EI): Calcd for $C_{24}H_{26}N_2O_3$ 390.1943, found 390.1947.

Benzyl 3-(3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (13).



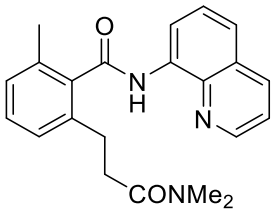
102.6 mg, 81% yield. colorless oil. R_f 0.21 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.43 (s, 3H), 2.79 (t, *J* = 7.6 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 5.03 (s, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.21-7.30 (m, 6H), 7.40-7.43 (m, 1H), 7.55-7.62 (m, 2H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.70 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.97 (dd, *J* = 7.2, 1.6 Hz, 1H), 9.95 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.5, 28.6, 35.9, 66.1, 116.9, 121.6, 122.0, 126.7, 127.3, 128.0 (two overlapping peaks), 128.36, 128.44, 129.2, 134.2, 134.7, 135.8, 136.3, 137.1, 137.8, 138.5, 148.3, 168.4, 172.5. IR (ATR): 3345 w, 3032 w, 2952 w, 1733 m, 1672 m, 1595 w, 1519 s, 1481 w, 1457 m, 1423 m, 1384 m, 1325 m, 1262 m, 1216 w, 1152 m, 899 w, 826 m, 791 m, 751 s, 734 s, 695 s. MS, *m/z* (relative intensity, %): 424 (M^+, 25), 91 (100). Exact Mass (EI): Calcd for $C_{27}H_{24}N_2O_3$ 424.1787, found 424.1789.

2-Methyl-6-(2-(phenylsulfonyl)ethyl)-N-(quinolin-8-yl)benzamide (14).



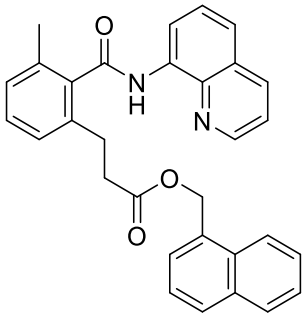
61.9 mg, 48% yield. white solid. mp = 135 °C. R_f 0.06 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 3.02-3.06 (m, 2H), 3.50-3.54 (m, 2H), 7.11-7.17 (m, 4H), 7.25-7.30 (m, 2H), 7.44-7.48 (m, 1H), 7.55-7.61 (m, 2H), 7.68 (d, *J* = 7.2 Hz, 2H), 8.20 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.68-8.71 (m, 2H), 9.75 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.3, 27.6, 57.4, 116.8, 121.7, 122.1, 127.0, 127.2, 127.7, 127.8, 128.7, 129.1, 129.5, 133.1, 133.6, 134.1, 134.9, 136.3, 137.7, 138.1, 138.2, 148.3, 167.6. IR (ATR): 3342 w, 2951 w, 2367 w, 2338 w, 1735 m, 1670 m, 1596 w, 1519 s, 1481 s, 1423 m, 1385 m, 1324 m, 1264 m, 1197 w, 1150 m, 1086 w, 899 w, 826 m, 791 m, 754 m, 688 m. MS, *m/z* (relative intensity, %): 430 (M^+, 1.9), 290 (16), 289 (79), 287 (28), 146 (12), 145 (100), 144 (11), 117 (13), 115 (12), 77 (15). Exact Mass (EI): Calcd for $C_{25}H_{22}N_2O_3S$ 430.1351, found 430.1350.

2-(3-(Dimethylamino)-3-oxopropyl)-6-methyl-N-(quinolin-8-yl)benzamide (15).



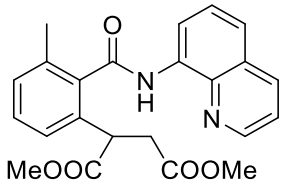
73.7 mg, 68% yield. white solid. mp = 147°C. R_f 0.03 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.44 (s, 3H), 2.71 (t, *J* = 8.0 Hz, 2H), 2.84 (s, 3H), 2.85 (s, 3H), 3.05 (t, *J* = 8.0 Hz, 2H), 7.14-7.21 (m, 2H), 7.27-7.31 (m, 1H), 7.41-7.45 (m, 1H), 7.55-7.61 (m, 2H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.72 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.96 (dd, *J* = 6.8, 2.0 Hz, 1H), 9.98 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.5, 29.5, 35.3, 35.9, 37.1, 116.8, 121.7, 122.1, 127.2, 127.3, 128.0, 128.3, 129.3, 134.3, 134.5, 136.4, 137.9, 138.2, 138.5, 148.3, 168.7, 172.1. IR (ATR): 3340 w, 3019 w, 2251 w, 1734 w, 1669 m, 1596 w, 1520 s, 1482 m, 1447 w, 1424 w, 1386 w, 1324 m, 1307 m, 1264 w, 1229 w, 1150 m, 1131 m, 1086 w, 901 w, 825 w, 748 s, 687 m, 666 m. MS, *m/z* (relative intensity, %): 361 (M^+, 33), 289 (10), 287 (10), 219 (15), 218 (100), 190 (10), 173 (19), 146 (11), 145 (52), 144 (17), 117 (11), 115 (10), 72 (30), 46 (14). Exact Mass (EI): Calcd for $C_{22}H_{23}N_3O_2$ 361.1790, found 361.1789.

Naphthalen-1-ylmethyl 3-(2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (16).



128.6 mg, 90% yield. colorless oil. R_f 0.21 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.41 (s, 3H), 2.79 (t, *J* = 8.0 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 5.49 (s, 2H), 7.08-7.11 (m, 2H), 7.02 (t, *J* = 8.0 Hz, 1H), 7.34-7.60 (m, 7H), 7.79-7.85 (m, 2H), 7.88-7.90 (m, 1H), 8.13 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.64 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.95 (d, *J* = 7.8 Hz, 1H), 9.93 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.4, 28.5, 35.8, 64.3, 116.8, 121.5, 122.0, 123.4, 125.1, 125.7, 126.3, 126.6, 127.1, 127.2, 127.8, 128.4, 128.5, 129.0, 129.1, 131.3, 131.4, 133.5, 134.1, 134.5, 136.2, 137.0, 137.7, 138.4, 148.2, 168.3, 172.5. IR (ATR): 3343 w, 3014 w, 1732 m, 1671 m, 1596 w, 1519 s, 1482 m, 1423 m, 1384 m, 1325 m, 1263 w, 1218 w, 1151 m, 960 w, 907 m, 826 w, 791 m, 774 m, 754 s, 729 s, 666 m. MS, m/z (relative intensity, %): 474 (M^+, 17), 144 (21), 142 (12), 141 (100). Exact Mass (EI): Calcd for $C_{31}H_{26}N_2O_3$ 474.1943, found 474.1940.

Dimethyl 2-(3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)succinate (17).



65.8 m, 54% yield(from fumarate). 54.8 mg, 44% yield(from maleate).colorless oil. R_f 0.10

(Hexane/EtOAc = 4/1).9 ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.46 (s, 3H), 2.82 (dd, J = 16.8, 4.4 Hz, 1H), 3.21 (dd, J = 16.8, 10.4 Hz, 1H), 3.59 (s, 1H), 3.62 (s, 1H), 4.35 (dd, J = 10.4, 4.4 Hz, 1H), 7.20-7.23 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.44-7.47 (m, 1H), 7.58-7.64 (m, 2H), 8.20 (dd, J = 8.0, 1.2 Hz, 1H), 8.75 (dd, J = 4.0, 1.6 Hz, 1H), 9.01 (dd, J = 6.8, 1.6 Hz, 1H), 10.1 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.7, 37.7, 43.8, 51.8, 52.4, 117.1, 121.6, 122.2, 124.5, 127.4, 128.0, 129.5, 129.7, 134.2, 134.4, 135.5, 136.4, 137.9, 138.6, 148.2, 167.7, 171.7, 173.3. IR (ATR): 3339 w, 3007 w, 2952 w, 1735 s, 1672 m, 1596 w, 1520 s, 1482 m, 1425 m, 1385 m, 1325 m, 1264 m, 1210 m, 1161 m, 1130 w, 1090 w, 1004 w, 899 w, 827 m, 792 m, 755 m, 731 m, 690 m. MS, *m/z* (relative intensity, %): 406 (M^+, 22), 375 (14), 263 (13), 262 (17), 235 (46), 234 (11), 203 (41), 193 (23), 175 (15), 159 (20), 145 (22), 144 (100), 143 (11), 115 (13). Exact Mass (EI): Calcd for $C_{23}H_{22}N_2O_5$ 406.1529, found 406.1531.

1.5 References and Notes

(1) For reviews on C−H bond alkylation with alkyl halidess: (a) Ackermann, L. *Chem. Commun*. **2010**, *46*, 4866. (b) Ackermann, L. *J. Org. Chem*. **2014**, *79*, 8948.

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(3) (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res*. **2002**, *35*, 826. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (c) Crisenza, G. E. M.; Bower, J. F. *Chem. Lett*. **2016**, *45*, 2.

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2011, *40*, 1165. (d) Zhu, C.; Falck, J. R. *Org. Lett*. **2011**, *13*, 1214. (e) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett*. **2011**, *13*, 5326. (f) Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett*. **2012**, *14*, 728. (g) Zhu, C.; Falck, J. R. *Tetrahedron* **2012**, *68*, 9192.

(7) It was also found that $[Rh(OAc)(cod)]_2$ showed the same catalytic reactivity as $[RhCl(cod)]_2$/CsOAc: see,5f

(8) Shibata, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5148.

Chapter 2
Rhodium-Catalyzed Alkylation of C-H Bonds with Styrenes

2.1 Introduction

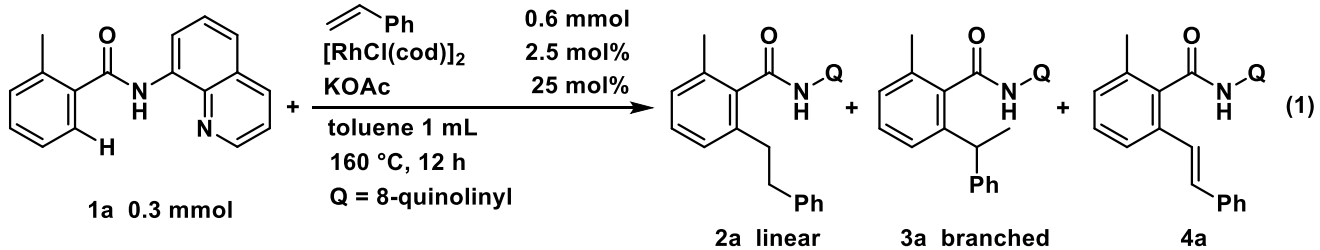
As mentioned in the general introduction and chapter 1, transition-metal-catalyzed regioselective alkylation reactions of C(sp^2)-H bonds with activated olefins have been actively researched and a represent a powerful method for the formation of C-C bonds.[1] Recently, in addition to active olefins such as α,ß-unsaturated carbonyl compounds or vinylsilane, C-H bond alkylation reactions with styrene derivatives have also been achieved by several groups.[2] However, to the best of our knowledge, arene C-H bond alkylation reactions with styrene derivatives utilizing an amide directing group are known only for Co or Ir catalyzed systems.[3]

Chapter 2 describes the direct, rhodium catalyzed alkylation of aromatic amides with styrene derivatives by taking advantage of an *N,N*-bidentate directing chelation system. The resulting 2-phenethylbenzoic acid moiety is a common structure in natural products and displays various bioactivities.[4] To the best of our knowledge, this reaction is the first synthetically useful application of the use of an amide directing group in rhodium catalyzed alkylation reactions with styrene derivatives.

2.2 Results and Discussion

The reaction of aromatic amide **1a** (0.3 mmol) with styrene (0.6 mmol) in the presence of $[RhCl(cod)]_2$ (0.0075 mmol) as the catalyst and KOAc (0.075 mmol) as the base in toluene (1 mL) at 160 °C for 12 h gave the alkylation product in 47% NMR yield (linear **2a**:branced **3a** = 96:4) along with the alkenylation product **4a** in 7% yield and recovery of 41% of the starting amide **1a** (Scheme 1). The product yield could be significantly improved to a satisfactory value by using $[Rh(OAc)(cod)]_2$ as a catalyst. Furthermore, the addition of 1 equivalent of pivalic acid suppressed the formation of the alkenylation product **4a.** The reaction is highly regioselective, namely the formation of C-C bonds

Scheme 1. The Rh-Catalyzed C-H Alkylatin with Styrene



		47% (NMR)	l:b = 96:4	7% (NMR)
$[Rh(OAc)(cod)]_2$	2.5 mol%	86% (NMR)	l:b = 96:4	5% (NMR)
$[Rh(OAc)(cod)]_2$	2.5 mol%	97% (NMR)	l:b = 96:4	2% (NMR)
PivOH	0.3 mmol	85% (isolated)	l:b = 96:4	

occurres at the terminal position of styrene and the *ortho* C-H bonds in aromatic amides to form the linear product **2a.**

The effect of directing groups was next examined (Figure 1.). When naphthylamine was introduced in the directing group, no reaction occurred. The other directing groups similar to 8-aminoquinoline showed no acitivity. These results indicated that the coordination in an *N,N*-fashion is a key step for this reaction.

Figure 1. Ineffective Directing Groups

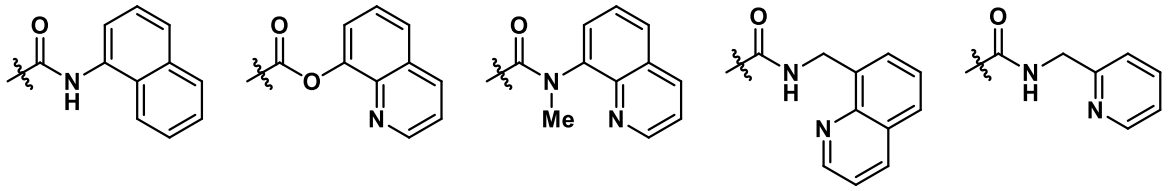
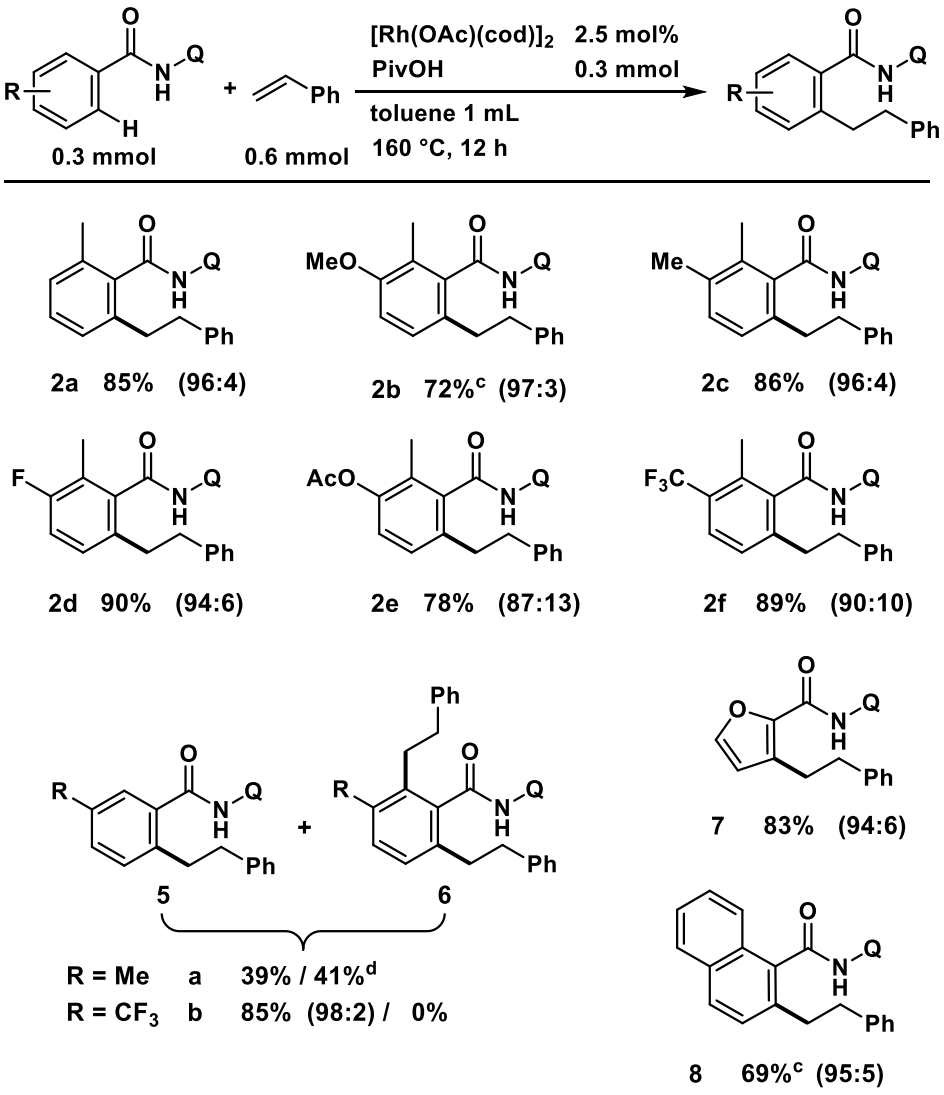


Table 1 showed the scope of amide bearing a variety of functional groups. Under the optimized reaction conditions, various functional groups, such as OMe, F, OAc, and CF_3 groups were tolerated and gave the corresponding alkylation products in good yields, as in **2b**, **2d**, **2e** and **2f**. The number in parenthesis is the ratio of linear **2** and branched **3** type product. In all cases, a tiny amount of alkenylation products **4** were formed. In the case of meta-methyl substituted aromatic amides, both mono-alkylated products **5a** and di-alkylated products **6a** were obtained. However, mono-alkylation was selectively observed in the case of meta-CF_3 sustituted aromatic amide. In this reaction system, gratifyingly furan ring and naphthalene ring system could be successfully applied, leading to the regioselective formation of alkylated products **7** and **8**.

Table1. The Rh-Catalyzed C-H Alkylatin of C(sp^2)-H Bonds[a,b]



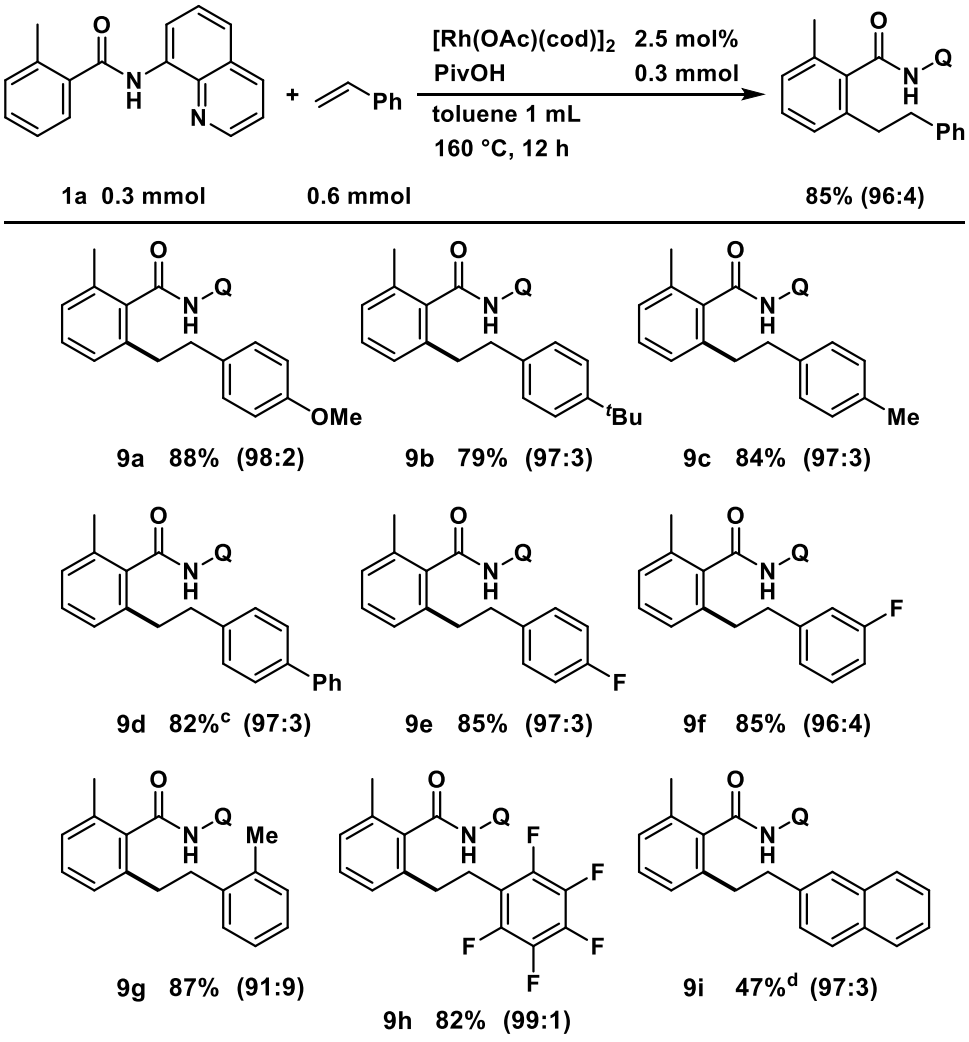
[a] Reaction conditions: amide (0.3 mmol), styrene (0.6 mmol), $[Rh(OAc)(cod)]_2$ (0.0075 mmol), PivOH (0.3 mmol), toluene (1 mL), at 160 °C for 12 h. [b] Isolated yields. Values in parenthesis are the ratio of linear and branched alkylation products. [c] $[Rh(OAc)(cod)]_2$ (0.015 mmol) was used for 24 h. [d] Styrene (1.2 mmol) was used.

Table 2 shows the results of the scope of styrene derivatives under the standard reaction conditions. In all cases, the desired linear alkylated products were obtained in good yields and selectivity. Various functional groups at 4-position of the styrene derivatives were survived and gave the corresponding desired products in excellent yields (**9a**-**9e**). A sterically hindered styrene derivative having a methyl group at the 2-position was also applied to this reaction without impairing the yield **9g**. We were pleased to find that a strong electron deficient pentafluorophenylethene did not hamper the reactivity **9h**. To our delight, a 2-vinylnaphthalene was also applicable in this reaction **9i**. However no reactions were observed when α-methyl styrene or

2-pyridyl styrene were used as the coupling partners.

The reaction mechanism is discussed in chapter 5.

Table 2. The Rh-Catalyzed Aromatic Amides with Styrene Derivatives[a,b]



[a] Reaction conditions: amide (0.3 mmol), styrene (0.6 mmol), $[Rh(OAc)(cod)]_2$ (0.0075 mmol), PivOH (0.3 mmol), toluene (1 mL), at 160 °C for 12 h. [b] Isolated yields. Values in parenthesis are the ratio of linear and branched alkylation products. [c] $[Rh(OAc)(cod)]_2$ (0.015 mmol) was used for 24 h. [d] $[Rh(OAc)(cod)]_2$ (0.0225 mmol) was used for 24 h.

2.3 Conclusion

In summary, we have reported the rhodium catalyzed *ortho* alkylation of $C(sp^2)$-H bonds in aromatic amides with styrene derivatives by using a bidentate chelation system. It is very important to use an 8-aminoquinoline moiety as a bidentate directing group. This reaction is the first example of applying a rhodium catalyst to alkylation of arene $C(sp^2)$-H bond with styrene derivatives using an amide directing group.

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. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra and high resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

Materials.

Toluene (Kanto Chemical) was purified by passage through activated alumina using a GlassContour Solvent Dispensing System. Styrene (CAS 100-42-5) and pivalic acid (CAS 75-98-9) were purchased from Nacalai Tesque. 8-Aminoquinoline (CAS 578-66-5) was purchased from Tokyo Chemical Industry Co., Ltd. $[Rh(OAc)(cod)]_2$ was prepared by chapter 1 procedure.

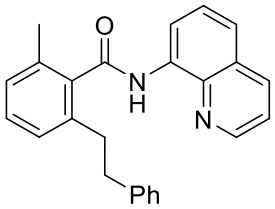
Synthesis of Starting Amides.

All amides bearing an 8-aminoquinoline moiety were prepared by reacting the corresponding acid or the corresponding acid chlorides with 8-aminoquinoline. All starting amides were prepared by chapter 1 procedure. All spectrum data of starting amides are cited in original paper.[5]

Typical Procedures for the Rh-Catalyzed Reaction of Aromatic Amides with styrenes.

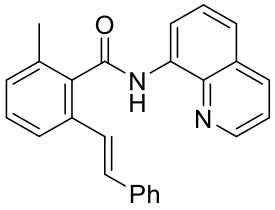
To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a** (79 mg, 0.3 mmol), styrene (63 mg, 0.6 mmol), $[Rh(OAc)(cod)]_2$ (4.1 mg, 0.0075 mmol), pivalic acid (31 mg, 0.3 mmol) and toluene (1 mL) were added. The mixture was stirred for 12 h at 160 °C followed by cooling. The mixture was filtered through a celite pad and the filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 10/1) to afford the alkylation product (92.9 mg, 85%, linear/branched = 96:4) as a colorless oil.

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



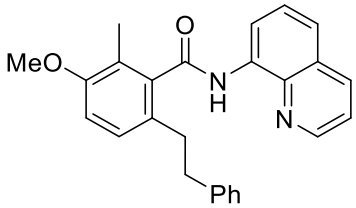
92.9 mg, 85% yield (linear/branched = 96:4). R_f 0.29 (hexane/EtOAc = 5/1). Colorless Oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 2.45 (s, 3H), 2.96-3.05 (m,4H), 7.05-7.09 (m,3H), 7.12-7.16 (m, 4H), 7.28 (t, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.0, 4.0 Hz, 1H), 7.56-7.65 (m, 2H), 8.18 (dd, J = 8.4, 1.6 Hz, 1H), 8.72 (dd, J = 4.0, 1.6 Hz, 1H), 9.01 (dd, J = 8.0, 1.6 Hz, 1H), 9.95 (brs, 1H). [branched] δ: 1.65 (d, *J* = 7.2 Hz, 3H), 4.45 (q, *J* = 7.2 Hz, 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.

(*E*)-2-methyl-*N*-(quinolin-8-yl)-6-styrylbenzamide (4a).



R_f 0.28 (Hexane/EtOAc = 5/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.47 (s, 3H), 7.12-7.25 (m, 5H), 7.30 (d, *J* = 16.4 Hz, 1H), 7.35-7.43 (m, 4H), 7.57-7.65 (m, 3H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.67 (dd, *J* = 4.8, 2.0 Hz, 1H), 9.03 (dd, *J* = 7.6, 1.2 Hz, 1H), 9.98 (brs, 1H). Exact Mass (EI): Calcd for $C_{25}H_{20}N_2O$ 364.1576, found 364.1574.

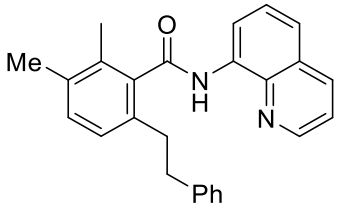
3-methoxy-2-methyl-6-phenethyl-*N*-(quinolin-8-yl)benzamide (2b).



86.1 mg, 72% yield (linear/branched = 97:3). colorless oil. R_f 0.29 (Hexane/EtOAc = 5/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.31 (s, 3H), 2.95-2.96 (m, 4H), 3.85 (s, 3H), 6.85 (d, *J* = 8.0 Hz, 1H), 7.04-7.16 (m, 6H), 7.41 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.55-7.63 (m, 2H), 8.16 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.70-8.71 (m, 1H), 9.00-9.02 (m, 1H), 9.94 (brs, 1H). [branched] δ: 4.37 (q, *J* = 6.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 13.18, 35.32, 38.44, 55.76, 110.90, 116.87, 121.79, 122.09, 123.37, 125.84, 127.53, 127.79, 128.11, 128.31, 128.54, 130.16, 134.46, 136.43, 138.58, 139.07, 141.96, 148.40, 156.15, 168.62. IR (ATR): 3348 w, 3025 w, 2933 w, 1677 m, 1582 w, 1520 s, 1481 m, 1385 w, 1325 w, 1269 m, 1096 w,

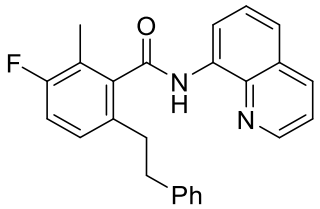
1044 w, 907 w, 825 w, 791 w, 755 w, 699 w. MS, *m/z* (relative intensity, %): 396 (M^+, 45), 305 (26), 254 (12), 253 (70), 252 (100), 175 (21), 147 (13), 145 (11), 144 (78), 135 (11), 91 (14). Exact Mass (EI): Calcd for $C_{26}H_{24}N_2O_2$ 396.1838, found 396.1837.

2,3-dimethyl-6-phenethyl-*N*-(quinolin-8-yl)benzamide (2c).



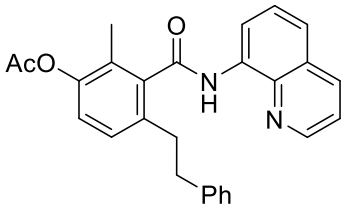
98.2 mg, 86% yield (linear/branched = 96:4). colorless oil. R_f 0.18 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.30 (s, 3H), 2.34 (s, 3H), 2.97 (brs, 4H), 7.03-7.08 (m, 4H), 7.12-7.18 (m, 3H), 7.42 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.55-7.64 (m, 2H), 8.17 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.71 (dd, *J* = 4.1, 1.8 Hz, 1H), 9.03 (d, *J* = 7.4 Hz, 1H), 9.95 (brs, 1H). [branched] δ: 4.39 (q, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 16.63, 19.91, 35.66, 38.19, 116.71, 121.61, 121.92, 125.69, 126.71, 127.36, 127.94, 128.15, 128.33, 130.41, 132.80, 134.32, 134.99, 135.77, 136.27, 138.01, 138.40, 141.75, 148.21, 169.27. IR (ATR): 3345 w, 3056 w, 3025 w, 2925 w, 2857 w, 1722 w, 1671 m, 1598 w, 1577 w, 1520 s, 1482 s, 1424 m, 1385 m, 1326 m, 1267 w, 1148 w, 908 w, 875 w, 824 m, 791 m, 751 m, 698 m. MS, *m/z* (relative intensity, %): 380 (M^+, 22), 238 (18), 237 (100), 236 (59), 179 (12), 159 (19), 145 (13), 144 (91), 131 (17), 91 (12). Exact Mass (EI): Calcd for $C_{26}H_{24}N_2O$ 380.1889, found 380.1891.

3-fluoro-2-methyl-6-phenethyl-*N*-(quinolin-8-yl)benzamide (2d).



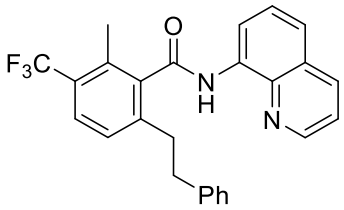
104.1 mg, 90% yield (linear/branched = 94:6). colorless oil. R_f 0.33 (Hexane/EtOAc = 5/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.35 (d, *J* = 1.8 Hz, 3H), 2.94-3.00 (m, 4H), 7.00-7.08 (m, 5H), 7.12-7.16 (m, 2H), 7.45 (dd, *J* = 8.2, 4.6 Hz, 1H), 7.58-7.65 (m, 2H), 8.19 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.74 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.99 (dd, *J* = 7.3, 1.8 Hz, 1H), 9.93 (brs, 1H). [branched] δ: 1.62 (d, *J* = 6.9 Hz, 3H), 4.40 (q, *J* = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 11.75 (d, *J* = 4.8 Hz), 35.22, 38.04, 115.66 (d, *J* = 22.9 Hz), 116.81, 121.71, 121.86, 122.20, 125.82, 127.30, 127.93, 128.20, 128.33, 128.38, 133.86 (d, *J* = 3.8 Hz), 134.01, 136.32, 138.36, 139.36 (d, *J* = 2.8 Hz), 141.32, 148.34, 159.54 (d, *J* = 243.2 Hz), 167.22 (d, *J* = 2.8 Hz). IR (ATR): 3342 w, 3059 w, 3025 w, 2927 w, 2860 w, 1722 w, 1674 m, 1597 w, 1521 s, 1482 s, 1424 m, 1385 m, 1326 m, 1265 w, 1161 w, 1085 w, 875 w, 825 m, 791 m, 751 m, 698 m. MS, *m/z* (relative intensity, %): 384 (M^+, 21), 241 (24), 240 (52), 163 (16), 145 (14), 144 (100), 135 (14), 91 (13). Exact Mass (EI): Calcd for $C_{25}H_{21}FN_2O$ 384.1638, found 384.1635.

2-methyl-4-phenethyl-3-(quinolin-8-ylcarbamoyl)phenyl acetate (2e).



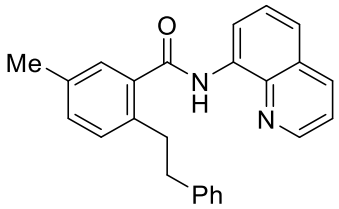
98.7 mg, 78% yield (linear/branched = 87:13). colorless oil. R_f 0.13 (Hexane/EtOAc = 5/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.26 (s, 3H), 2.35 (s, 3H), 2.99 (brs, 4H), 7.05-7.09 (m, 4H), 7.12-7.17 (m, 3H), 7.45 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.58-7.64 (m, 2H), 8.18 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.99 (dd, *J* = 7.3, 1.4 Hz, 1H), 9.98 (brs, 1H). [branched] δ: 1.63 (d, *J* = 7.3 Hz, 3H), 4.41 (q, *J* = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 13.30, 20.85, 35.55, 38.01, 116.86, 121.75, 122.18, 122.77, 125.84, 126.97, 127.34, 127.96, 128.03, 128.25, 128.35, 134.15, 136.27, 136.31, 138.41, 139.18, 141.49, 147.58, 148.39, 167.60, 169.44. IR (ATR): 3343 w, 3053 w, 3025 w, 2952 w, 2927 w, 2857 w, 1761 w, 1722 w, 1673 m, 1597 w, 1577 w, 1521 s, 1482 s, 1425 m, 1385 m, 1326 m, 1263 w, 1203 m, 1085 w, 1034 w, 1015 w, 899 w, 875 w, 826 m, 792 m, 751 m, 699 m. MS, *m/z* (relative intensity, %): 424 (M^+, 13), 281 (21), 239 (41), 238 (52), 161 (14), 145 (13), 144 (100), 91 (16). Exact Mass (EI): Calcd for $C_{27}H_{24}N_2O_3$ 424.1787, found 424.1786.

2-methyl-6-phenethyl-*N*-(quinolin-8-yl)-3-(trifluoromethyl)benzamide (2f).



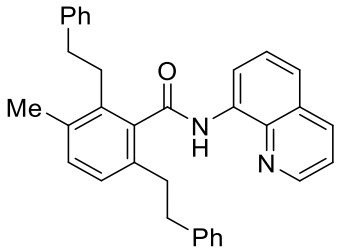
116.6 mg, 89% yield (linear/branched = 90:10). colorless oil. R_f 0.20 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.56 (s, 3H), 3.00-3.04 (m, 4H), 7.05-7.20 (m, 6H), 7.45 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.59-7.66 (m, 3H), 8.19 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.75 (d, *J* = 4.1 Hz, 1H), 8.99 (d, *J* = 6.9 Hz, 1H), 9.96 (brs, 1H). [branched] δ: 4.45 (q, *J* = 6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 16.15 (d, *J* = 1.9 Hz), 35.78, 37.60, 117.00, 121.80, 122.42, 124.35 (q, *J* = 272.7 Hz), 126.01, 126.48 (q, *J* = 5.7 Hz), 127.02, 127.35, 127.65, 127.95, 128.00, 128.33, 133.64, 133.92, 136.42, 138.37, 139.91, 141.00, 142.36, 148.44, 167.49. IR (ATR): 3341 w, 3059 w, 3021 w, 2954 m, 2926 m, 2872 w, 2854 w, 1678 m, 1593 w, 1523 s, 1484 m, 1457 m, 1424 m, 1387 m, 1320 s, 1250 w, 1211 w, 1176 m, 1121 s, 1075 w, 1033 w, 826 m, 792 m, 771 m, 735 m, 699 s. MS, *m/z* (relative intensity, %): 434 (M^+, 9), 291 (15), 290 (21), 213 (12), 185 (19), 145 (12), 144 (100), 91 (21). Exact Mass (EI): Calcd for $C_{26}H_{21}F_3N_2O$ 434.1606, found 434.1609.

5-methyl-2-phenethyl-*N*-(quinolin-8-yl)benzamide (5a)



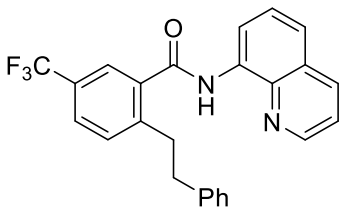
43.2 mg, 39% yield (linear/branched = 96:4). colorless solid. R_f 0.20 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.40 (s, 3H), 3.01–2.97 (m, 2H), 3.20–3.16 (m, 2H), 7.24–7.03 (m, 7H), 7.46–7.43 (m, 2H), 7.63–7.54 (m, 2H), 8.17 (d, J = 8.2 Hz, 1H), 8.76 (d, J = 4.1 Hz, 1H), 8.96 (d, J = 7.3 Hz, 1H), 10.12 (s, 1H).[branched] δ: 1.67 (d, *J* = 6.8 Hz, 3H), 4.79 (q, *J* = 6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 21.0, 35.2, 38.2, 116.5, 121.6, 121.7, 125.7, 127.4, 127.7, 127.9, 128.1, 128.5, 130.5, 131.0, 134.8, 135.9, 136.3, 136.6, 137.3, 138.5, 141.8, 148.2, 168.4.

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



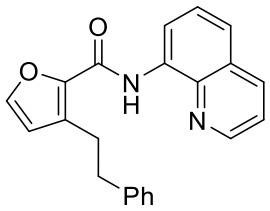
58.2 mg, 41% yield. colorless oil. R_f 0.20 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.41 (s, 3H), 2.99 (brs, 8H), 7.06-7.16 (m, 11H), 7.20-7.22 (m, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.65 (t, *J* = 8.2 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.68 (dd, *J* = 4.6, 1.8 Hz, 1H), 9.06 (dd, *J* = 7.3, 1.4 Hz, 1H), 10.00 (brs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.19, 33.86, 35.68, 36.97, 38.20, 116.78, 121.67, 121.994, 125.75, 125.80, 127.27, 127.45, 127.99, 128.20 (two overlapping peaks), 128.27, 128.35, 131.20, 134.30, 134.55, 136.02, 136.31, 136.53, 138.16, 138.38, 141.75, 142.04, 148.29, 169.03. IR (ATR): 3349 w, 3059 w, 3025 w, 2948 w, 2867 w, 1674 m, 1599 w, 1577 w, 1519 s, 1482 m, 1454 w, 1424 w, 1385 w, 1326 w, 1266 w, 1221 w, 1131 w, 1076 w, 1028 w, 913 w, 825 w, 771 m, 699 m. MS, *m/z* (relative intensity, %): 470 (M^+, 12), 328 (11), 327 (43), 326 (20), 235 (14), 145 (17), 144 (100), 105 (28), 91 (17). Exact Mass (EI): Calcd for $C_{33}H_{30}N_2O$ 470.2358, found 470.2357.

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



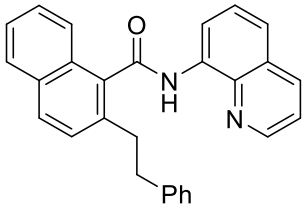
106.9 mg, 85% yield (linear/branched = 98:2). white solid. mp = 130 °C. R_f 0.23 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 3.00-3.04 (m, 2H), 3.25-3.29 (m, 2H), 7.04-7.08 (m, 1H), 7.12-7.19 (m, 4H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.58-7.67 (m, 3H), 7.89 (s, 1H), 8.21 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.79 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.93 (dd, J = 7.3, 1.8 Hz, 1H), 10.15 (brs, 1H). [branched] δ: 4.86 (q, *J* = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 35.44, 37.65, 116.74, 121.77, 122.23, 123.82 (q, *J* = 270.8 Hz), 124.09 (d, *J* = 3.8 Hz), 126.02, 126.80 (d, *J* = 2.8 Hz), 127.30, 127.93, 128.29, 128.46, 128.67 (q, *J* = 33.4 Hz), 131.19, 134.28, 136.38, 137.28, 138.40, 140.91, 144.38, 148.39, 166.71. IR (ATR): 3344 w, 3056 w, 3026 w, 2959 w, 2863 w, 1675 m, 1596 w, 1579 w, 1521 s, 1482 m, 1424 w, 1386 w, 1326 m, 1261 w, 1169 w, 1126 m, 1080 w, 899 w, 825 w, 791 w, 756 w, 699 w. MS, *m/z* (relative intensity, %): 420 (M^+, 12), 276 (13), 171 (12), 145 (13), 144 (100), 91 (13). Exact Mass (EI): Calcd for $C_{25}H_{19}F_3N_2O$ 420.1449, found 420.1451.

3-phenethyl-*N*-(quinolin-8-yl)furan-2-carboxamide (7).



85.0 mg, 83% yield (linear/branched = 94:6). white solid. mp = 133 °C. R_f 0.30 (Hexane/EtOAc = 5/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.98-3.02 (m, 2H), 3.29-3.33 (m, 2H), 6.33 (d, *J* = 1.8 Hz, 1H), 7.18-7.21 (m, 1H), 7.26-7.31 (m, 4H), 7.43-7.47 (m, 2H), 7.50-7.58 (m, 2H), 8.15 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.86 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.89 (dd, *J* = 7.3, 1.4 Hz, 1H), 10.74 (brs, 1H). [branched] δ: 1.65 (d, *J* = 7.4 Hz, 3H), 5.27 (q, *J* = 7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 27.27, 35.93, 114.50, 116.33, 121.49, 121.60, 125.89, 127.33, 127.99, 128.25, 128.56, 132.82, 134.41, 136.28, 138.64, 141.46, 142.32, 142.86, 148.29, 157.49. IR (ATR): 3341 w, 3026 w, 2925 w, 2858 w, 1666 m, 1598 w, 1577 w, 1524 s, 1482 m, 1454 m, 1424 m, 1405 w, 1384 m, 1327 m, 1266 w, 1181 w, 1148 w, 1129 w, 1094 w, 1068 w, 1031 w, 905 w, 874 m, 824 m, 747 s, 696 s. MS, *m/z* (relative intensity, %): 342 (M^+, 100), 313 (16), 297 (13), 251 (35), 223 (14), 197 (12), 171 (25), 144 (51), 141 (11), 91 (14). Exact Mass (EI): Calcd for $C_{22}H_{18}N_2O_2$ 342.1368, found 342.1366.

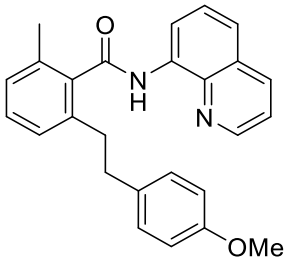
2-phenethyl-*N*-(quinolin-8-yl)-1-naphthamide (8).



83.1 mg, 69% yield (linear/branched = 95:5). Colorless oil. R_f 0.29 (Hexane/EtOAc = 5/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 3.06-3.10 (m, 2H), 3.18-3.22 (m, 2H), 7.04-7.16 (m, 5H), 7.39-7.42 (m, 2H),

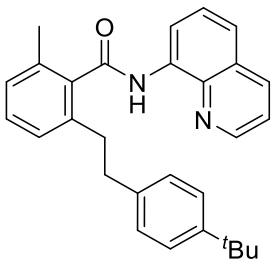
7.46-7.50 (m, 2H), 7.60 (dd, J = 8.2, 1.4 Hz, 1H), 7.67 (t, J = 8.2 Hz, 1H), 7.85-7.89 (m, 2H), 8.00-8.03 (m, 1H), 8.17 (dd, J = 8.2, 1.8 Hz, 1H), 8.64 (dd, J = 4.6, 1.8 Hz, 1H), 9.14 (d, J = 7.3 Hz, 1H), 10.13 (brs, 1H). [branched] δ: 4.66 (q, J = 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 36.20, 38.02, 116.86, 121.67, 122.12, 124.93, 125.74, 125.87, 127.03, 127.41, 127.59, 127.97 (two overlapping peaks), 128.25, 128.38, 129.31, 130.23, 131.95, 134.15, 134.40, 136.13, 136.29, 138.37, 141.44, 148.26, 168.20. IR (ATR): 3342 w, 3057 w, 3025 w, 2952 w, 2928 w, 2864 w, 1672 m, 1518 s, 1482 s, 1424 m, 1385 w, 1325 m, 1259 w, 1215 w, 1150 w, 893 w, 823 m, 791 m, 750 m, 699 m. MS, *m/z* (relative intensity, %): 402 (M^+, 32), 260 (19), 259 (100), 258 (92), 244 (10), 215 (19), 181 (24), 153 (20), 145 (10), 144 (83), 141 (11), 140 (16), 139 (11), 91 (27). Exact Mass (EI): Calcd for $C_{28}H_{22}N_2O$ 402.1732, found 402.1734.

2-(4-methoxyphenethyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (9a).



104.9 mg, 88% yield (linear/branched = 98:2). colorless oil. R_f 0.20 (Hexane/EtOAc = 7/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.44 (s, 3H), 2.90-3.02 (m, 4H), 3.66 (s, 3H), 6.65-6.68 (m, 2H), 6.96-7.00 (m, 2H), 7.13 (t, J = 7.4 Hz, 2H), 7..27 (t, J = 7.8 Hz, 1H), 7.42 (dd, J = 8.3, 4.1 Hz, 1H), 7.55-7.64 (m, 2H), 8.17 (dd, J = 8.3, 1.4 Hz, 1H), 8.72 (dd, J = 4.1, 1.4 Hz, 1H), 9.00 (dd, J = 7.3, 1.4 Hz, 1H), 9.91 (brs, 1H). [branched] δ: 1.61 (d, J = 6.9 Hz, 3H), 4.39 (q, J = 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.49, 35.99, 37.16, 55.00, 113.53, 116.69, 121.60, 121.93, 126.94, 127.31, 127.92, 127.99, 128.98, 129.22, 133.67, 134.27, 134.46, 136.25, 137.75, 138.37, 138.42, 148.24, 157.59, 168.66. IR (ATR): 3346 w, 2927 w, 2856 w 1675 m, 1514 s, 1481 s, 1424 m, 1385 m, 1325 m, 1246 m, 1176 w, 1126 w, 1038 w, 897 w, 824 s, 792 m, 755 m, 698 m. MS, *m/z* (relative intensity, %): 396 (M^+, 2.4), 252 (11), 145 (23), 144 (100), 121 (34). Exact Mass (EI): Calcd for $C_{26}H_{24}N_2O_2$ 396.1838, found 396.1839.

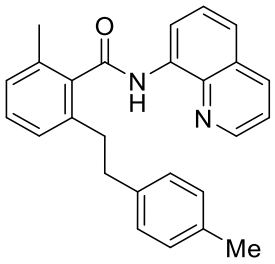
2-(4-(*tert*-butyl)phenethyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (9b).



100.5 mg, 79% yield (linear/branched = 97:3). colorless oil. R_f 0.23 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.23 (s, 9H), 2.46 (s, 3H), 2.96-3.02 (m, 4H), 7.03 (d, J = 8.4 Hz, 2H), 7.14-7.19 (m, 4H), 7.29 (t, J = 7.6 Hz, 1H), 7.43 (dd, J = 8.4, 4.0 Hz, 1H), 7.56-7.65 (m, 2H), 8.17 (dd, J = 8.4, 1.6

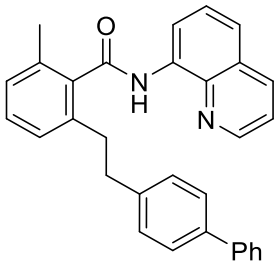
Hz, 1H), 8.72 (dd, *J* = 4.0, 1.2 Hz, 1H), 9.02 (d, *J* = 7.6 Hz, 1H), 9.98 (brs, 1H). [branched] δ: 4.44 (q, J = 6.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.51, 31.30, 34.24, 35.82, 37.69, 116.81, 121.65, 121.96, 125.11, 126.88, 127.41, 127.95 (two overlapping peaks), 128.04, 129.07, 134.32, 134.59, 136.33, 137.75, 138.44, 138.64, 138.68, 148.28, 148.56, 168.71. IR (ATR): 3346 w, 3059 w, 3014 w, 2959 w, 2867 w, 1675 m, 1595 w, 1519 s, 1481 s, 1423 m, 1385 m, 1325 m, 1264 w, 1126 w, 898 w, 823 m, 790 m, 754 s, 691 w. MS, *m/z* (relative intensity, %): 422 (M^+, 2.1), 263 (11), 223 (16), 145 (18), 144 (100), 57 (10). Exact Mass (EI): Calcd for $C_{29}H_{30}N_2O$ 422.2358, found 422.2360.

2-methyl-6-(4-methylphenethyl)-*N*-(quinolin-8-yl)benzamide (9c).



95.5 mg, 85% yield (linear/branched = 97:3). colorless oil. R_f 0.21 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.18 (s, 3H), 2.45 (s, 3H), 2.94-3.03 (m, 4H), 6.92-6.98 (m, 4H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.42 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.55-7.64 (m, 2H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.71 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.99-9.01 (m, 1H), 9.92 (brs, 1H). [branched] δ: 1.62 (d, *J* = 6.9 Hz, 3H), 4.40 (q, *J* = 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.49, 20.83, 35.89, 37.66, 116.72, 121.59, 121.92, 126.90, 127.32, 127.92, 128.00, 128.18, 128.85, 129.00, 134.27, 134.48, 135.14, 136.25, 137.75, 138.39, 138.49, 138.54, 148.22, 168.65. IR (ATR): 3347 w, 3043 w, 3016 w, 2925 w, 2861 w, 1675 m, 1595 w, 1518 s, 1481 s, 1424 m, 1385 m, 1325 m, 1261 w, 1126 w, 897 w, 825 m, 792 m, 757 m. MS, *m/z* (relative intensity, %): 380 (M^+, 3.0), 237 (18), 236 (18), 145 (32), 144 (100), 117 (12), 105 (15). Exact Mass (EI): Calcd for $C_{26}H_{24}N_2O$ 380.1889, found 380.1891.

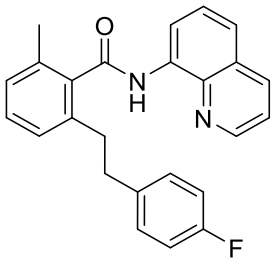
2-(2-([1,1'-biphenyl]-4-yl)ethyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (9d).



109.3 mg, 82% yield (linear/branched = 97:3). white solid. mp = 123 °C. R_f 0.23 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.46 (s, 3H), 3.05-3.07 (m, 4H), 7.13-7.17 (m, 4H), 7.25-7.39 (m, 7H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.55-7.64 (m, 2H), 8.14 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.68 (dd, *J* = 4.0, 1.6 Hz, 1H), 9.02 (dd, *J* = 7.2, 1.2 Hz, 1H), 9.94 (brs, 1H). [branched] δ: 1.67 (d, *J* = 6.8 Hz, 3H), 4.49 (q, *J* = 6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.53, 35.73, 37.73, 116.75, 121.62, 121.98, 126.80,

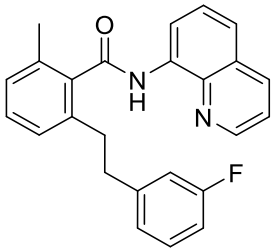
126.89, 126.94, 127.34, 127.94, 128.11, 128.56, 128.76, 129.07, 134.27, 134.56, 136.25, 137.78, 138.36, 138.39, 138.62, 140.75, 140.85, 148.25, 168.66. IR (ATR): 3346 w, 3056 w, 3026 w, 2925 w, 2860 w, 1674 m, 1520 s, 1482 s, 1424 m, 1386 w, 1326 m, 1263 w, 1127 w, 898 w, 826 m, 791 w, 759 m, 697 m. MS, *m/z* (relative intensity, %): 442 (M^+, 2.0), 167 (23), 145 (23), 144 (100). Exact Mass (EI): Calcd for $C_{31}H_{26}N_2O$ 442.2045, found 442.2046.

2-(4-fluorophenethyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (9e).



98.1 mg, 85% yield (linear/branched = 97:3). colorless oil. R_f 0.19 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.45 (s, 3H), 2.94-3.01 (m, 4H), 6.79 (dd, J = 8.7, 8.7 Hz, 2H), 7.00 (dd, J = 8.2, 5.5 Hz, 2H), 7.09 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 7.27 (t, J = 7.3 Hz, 1H), 7.43 (dd, J = 8.2, 4.1 Hz, 1H), 7.56-7.64 (m, 2H), 8.17 (dd, J = 8.2, 1.4 Hz, 1H), 8.72 (dd, J = 4.1, 2.0 Hz, 1H), 9.00 (d, J = 7.8 Hz, 1H), 9.90 (brs, 1H). [branched] δ: 1.62 (d, J = 6.9 Hz, 3H), 4.42 (q, J = 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ:.19.49, 35.83, 37.13, 114.85 (d, J = 21.0 Hz), 116.65, 121.64, 121.99, 126.92, 127.30, 127.93, 128.12, 129.01, 129.68 (d, J = 7.7 Hz), 134.22, 134.51, 136.28, 137.14 (d, J = 3.8 Hz), 137.76, 138.06, 138.36, 148.27, 161.09 (d, J = 242.1 Hz), 168.60. IR (ATR): 3345 w, 3045 w, 2926 w, 2864 w, 1673 m, 1597 w, 1518 s, 1481 s, 1423 m, 1385 m, 1325 m, 1262 w, 1220 m, 1157 w, 1126 w, 897 w, 824 s, 791 m, 755 s, 695 m. MS, *m/z* (relative intensity, %): 384 (M^+, 15), 241 (41), 240 (42), 145 (34), 144 (100), 117 (17), 109 (16). Exact Mass (EI): Calcd for $C_{25}H_{21}FN_2O$ 384.1638, found 384.1636.

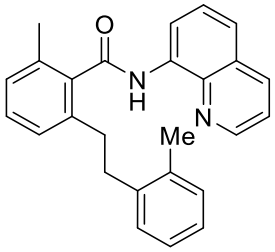
2-(3-fluorophenethyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (9f).



97.9 mg, 85% yield (linear/branched = 96:4). colorless oil. R_f 0.15 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.45 (s, 3H), 2.97-3.03 (m, 4H), 6.72-6.79 (m, 2H), 6.84 (d, J = 7.2 Hz, 1H), 7.05-7.16 (m, 3H), 7.27 (t, J = 7.6 Hz, 1H), 7.42 (dd, J = 8.4, 4.4 Hz, 1H), 7.56-7.64 (m, 2H), 8.17 (dd, J = 8.8, 2.0 Hz, 1H), 8.72 (dd, J = 4.0, 1.2 Hz, 1H), 9.01 (dd, J = 7.6, 1.2 Hz, 1H), 9.94 (brs, 1H). [branched] δ: 1.62 (d, J = 7.2 Hz, 3H). 4.43 (q, J = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.52, 35.50, 37.75, 112.64 (d, J = 20.1 Hz), 115.19 (d, J = 20.0 Hz), 116.75, 121.68, 122.04, 124.01 (d, J = 1.9

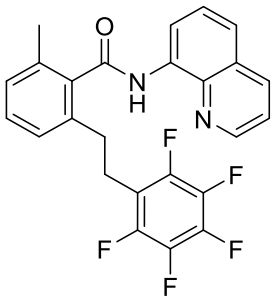
Hz), 126.91, 127.37, 127.97, 128.23, 129.08, 129.56 (d, J = 8.6 Hz), 134.21, 134.62, 136.33, 137.76, 137.96, 138.40, 144.13 (d, J = 7.6 Hz), 148.29, 162.67 (d, J = 244.1 Hz), 168.59. IR (ATR): 3346 w, 3061 w, 2928 w, 2867 w, 1674 m, 1589 w, 1520 s, 1482 s, 1424 m, 1386 w, 1326 m, 1261 w, 1128 w, 897 w, 826 w, 788 m, 690 w. MS, *m/z* (relative intensity, %): 384 (M^+, 40), 242 (16), 241 (99), 240 (86), 197 (11), 196 (13), 183 (14), 145 (31), 144 (100), 132 (11), 117 (21), 109 (11). Exact Mass (EI): Calcd for $C_{25}H_{21}FN_2O$ 384.1638, found 384.1637.

2-methyl-6-(2-methylphenethyl)-*N*-(quinolin-8-yl)benzamide (9g).



99.5 mg, 87% yield (linear/branched = 91:9). colorless oil. R_f 0.33 (Hexane/EtOAc = 5/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.15 (s, 3H), 2.46 (s, 3H), 2.95-2.98 (m, 4H), 6.98-7.06 (m, 4H), 7.16 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 7.6 Hz, 1H), 7.41 (dd, J = 8.0, 4.4 Hz, 1H), 7.55-7.63 (m, 2H), 8.16 (dd, J = 8.4, 1.6 Hz, 1H), 8.71 (dd, J = 4.4, 1.6 Hz, 1H), 9.01 (dd, J = 7.2, 1.2 Hz, 1H), 9.97 (brs, 1H). [branched] δ: 1.61 (d, J = 7.2 Hz, 3H), 2.08 (s, 3H), 2.42 (s, 3H), 4.59 (q, J = 7.2 Hz, 1H), 8.12 (dd, J = 8.4, 1.6 Hz, 1H), 8.97 (dd, J = 7.6, 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.03, 19.49, 34.62, 35.95, 116.74, 121.63, 121.96, 125.85, 125.97, 127.00, 127.35, 127.93, 128.07, 128.91, 129.10, 130.00, 134.30, 134.56, 135.93, 136.32, 137.78, 138.39, 138.60, 139.85, 148.23, 168.68. [branched] δ: 19.61, 22.22, 38.12, 116.35, 121.44, 124.71, 126.49, 127.23, 147.96. IR (ATR): 3345 w, 3061 w, 3015 w, 2952 w, 2869 w, 1674 m, 1595 w, 1519 s, 1481 s, 1423 m, 1385 m, 1325 m, 1263 w, 1127 w, 898 w, 826 m, 753 m, 691 w. MS, *m/z* (relative intensity, %): 380 (M^+, 12), 237 (31), 236 (34), 145 (36), 144 (100), 117 (14), 105 (19). Exact Mass (EI): Calcd for $C_{26}H_{24}N_2O$ 380.1889, found 380.1890.

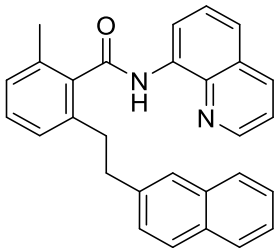
2-methyl-6-(2-(perfluorophenyl)ethyl)-*N*-(quinolin-8-yl)benzamide (9h).



111.7 mg, 82% yield (linear/branched = 99:1). white solid. mp = 159 °C. R_f 0.23 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.44 (s, 3H), 2.99-3.07 (m, 4H), 7.11 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.0, 4.0 Hz, 1H), 7.57-7.65 (m, 2H), 8.18 (dd, J =

8.0, 1.6 Hz, 1H), 8.72 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 9.87 (brs, 1H). [branched] δ: 4.86 (q, *J* = 6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz, ^{19}F-decoupled) δ: 19.53, 24.44, 32.86, 114.19, 116.78, 121.64, 122.08, 126.86, 127.40, 127.94, 128.73, 129.22, 134.08, 134.64, 136.34, 136.87, 137.20, 137.91, 138.38, 139.48, 144.95, 148.30, 168.20. IR (ATR): 3347 w, 2953 w, 1723 w, 1679 w, 1597 w, 1521 s, 1502 m, 1482 m, 1424 w, 1385 w, 1325 m, 1262 m, 1175 w, 1139 w, 1043 w, 965 w, 951 w, 840 s, 792 m, 761 m, 696 m. MS, *m/z* (relative intensity, %): 456 (M^+, 50), 314 (16), 313 (100), 312 (70), 144 (20), 132 (15). Exact Mass (EI): Calcd for $C_{25}H_{17}F_5N_2O$ 456.1261, found 456.1264.

2-methyl-6-(2-(naphthalen-2-yl)ethyl)-*N*-(quinolin-8-yl)benzamide (9i).



58.8 mg, 47% yield (linear/branched = 97:3). orange oil. R_f 0.17 (Hexane/EtOAc = 10/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.46 (s, 3H), 3.10-3.16 (m, 4H), 7.14-7.16 (m, 2H), 7.20-7.35 (m, 4H), 7.40 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.46 (s, 1H), 7.53-7.66 (m, 5H), 8.14-8.17 (m, 1H), 8.67 (dd, *J* = 4.1, 1.4 Hz, 1H), 9.02 (d, *J* = 7.3 Hz, 1H), 9.92 (brs, 1H). [branched] δ: 1.72 (d, *J* = 6.9 Hz, 3H), 4.59 (q, *J* = 6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.55, 35.72, 38.28, 116.78, 121.63, 121.98, 124.95, 125.63, 126.40, 127.00, 127.19, 127.28, 127.36, 127.39 (two overlapping peaks), 127.71, 127.95, 128.12, 129.07, 131.83, 133.39, 134.27, 134.59, 136.26, 137.80, 138.37, 139.11, 148.26, 168.69. IR (ATR): 3418 w, 3024 w, 2918 w, 1658 w, 1598 w, 1579 w, 1522 m, 1479 m, 1452 m, 1423 w, 1387 w, 1328 m, 1268 w, 1249 w, 1221 w, 1132 w, 1091 w, 1072 w, 1029 w, 952 w, 895 w, 855 w, 823 w, 789 m, 759 m, 726 s, 699 s. MS, *m/z* (relative intensity, %): 416 (6.8, M^+), 273 (14), 272 (23), 145 (29), 144 (100), 141 (27), 117 (10). Exact Mass (EI): Calcd for $C_{29}H_{24}N_2O$ 416.1889, found .416.1893.

2.5 References and Notes

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Chapter 3
Rhodium-Catalyzed Alkylation of C-H Bonds with α,β-Unsaturated Lactones and Dihydrofurans

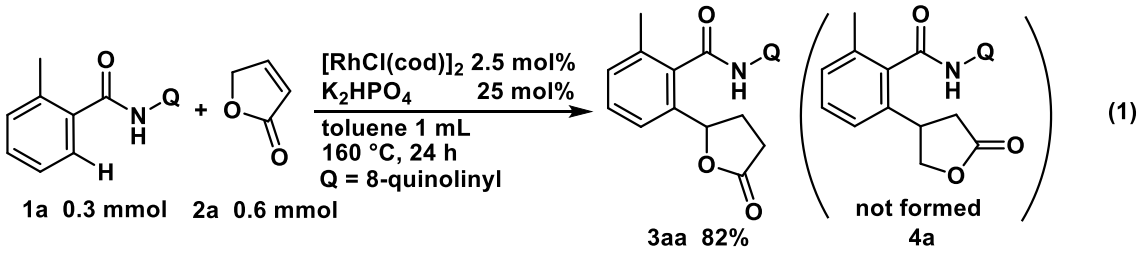
3.1 Introduction

As mentioned in the general introduction, Chapter 1 and Chapter 2, the regioselective alkylation reactions of C(sp^2)-H bonds with various olefins catalyzed by transition metal complex is one of the most reliable strategies for the construction of C-C bonds. Recently, unactivated olefins such as terminal olefins have also been used in regioselective alkylation reactions of C(sp^2)-H bonds.[1] As describe above, a wide variety of olefins have now been found to be applicable. However, only a few examples of the use of internal olefins as coupling partners are known.[2] Motivated by our previous results, we hypothesized that utilizing a bidentate chelation system would permit internal olefins to participate in direct C-H bond alkylation reactions.

Chapter 3 describes the rhodium catalyzed direct alkylation of aromatic amides with α,β-unsaturated lactones and dihydrofurans by taking advantage of *N,N*-bidentate directing chelation system. Unexpectedly, C-C bonds were formed between the *ortho*-position of aromatic amides and the carbon adjacent to the oxygen atom.

3.2 Results and Discussion

The reaction of aromatic amides **1a** (0.3 mmol) with γ-butyrolactone **2a** (0.6 mmol) in the presence of $[RhCl(cod)]_2$ (0.0075 mmol) as the catalyst and K_2HPO_4 (0.075 mmol) as the base in toluene (1 mL) at 160 °C for 24 h did not give the expected alkylation product **4a**, in which the reaction occurred at the β-position, instead **3aa** was obtained (eq 1).



(1)

First, we examined the effectiveness of the directing groups (Figure 1). As in chapter 1 and 2, no reaction was proceeded when the directing groups shown in Fig. 1 were used in place of 8-aminoquinoline. It is noteworthy that even the 2-pyridil group which has a great potential as a directing group in C-H bond functionalization was ineffective. This result indicates that utilizing a new type of directing group could lead to develop a new type of reaction.

Figure 1. Ineffective Directing Groups

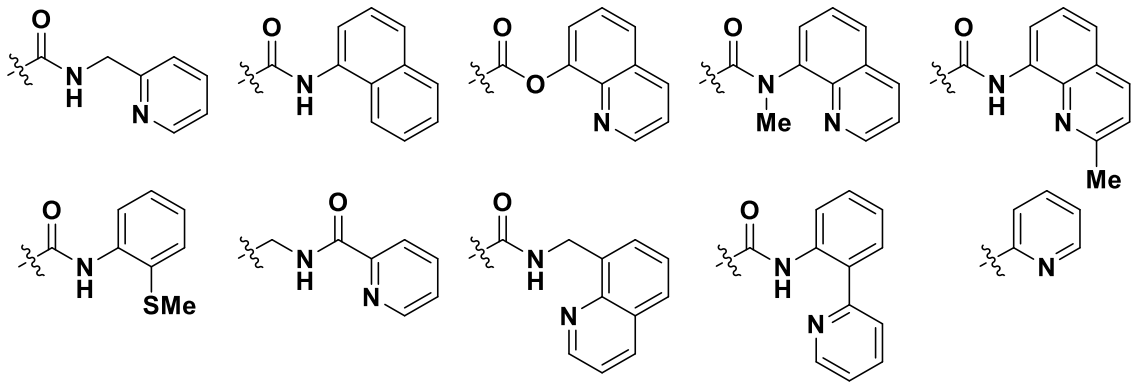
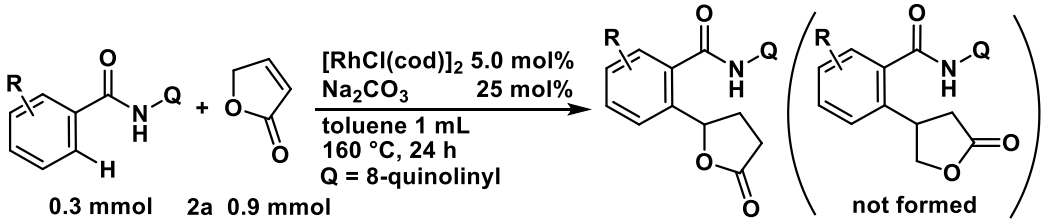
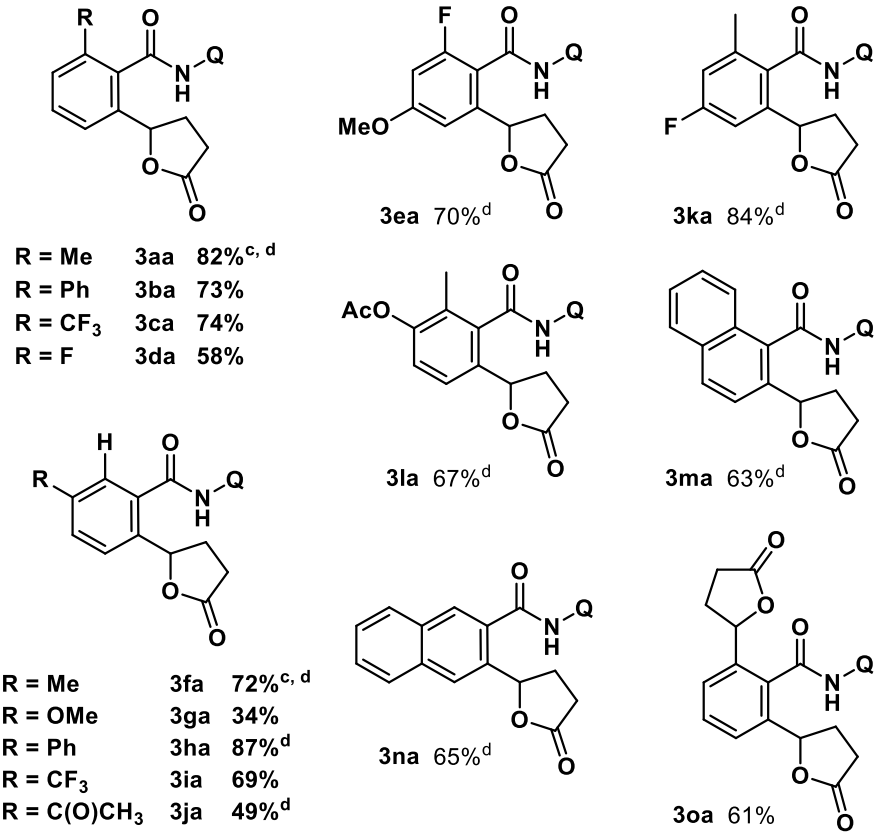


Table1. The Rh-Catalyzed C-H Alkylatin of C(sp^2)-H Bonds[a,b]

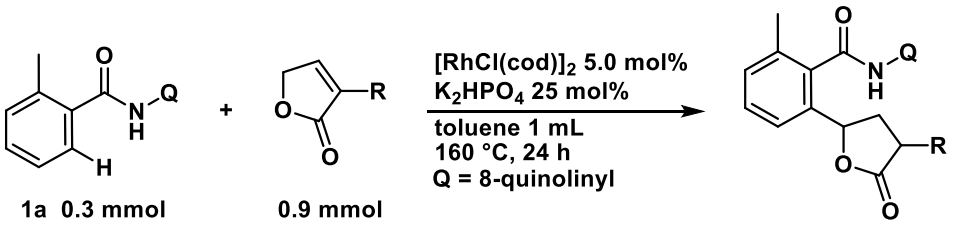


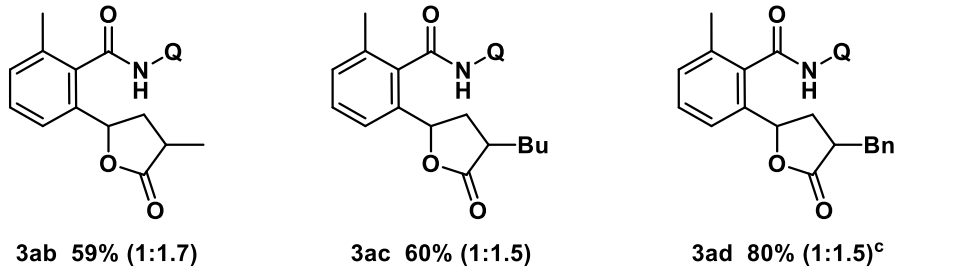


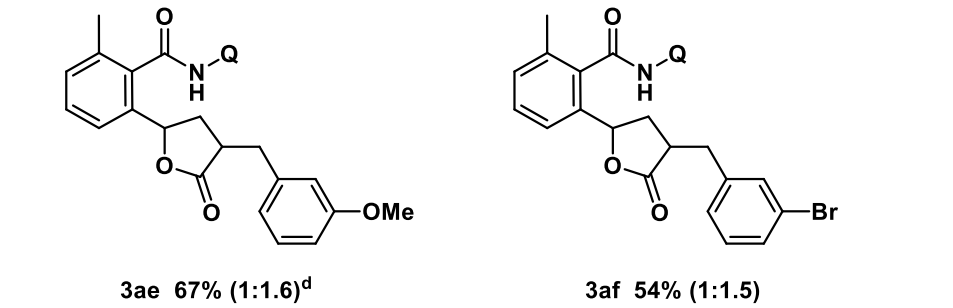
[a] Reaction conditions: amide **1** (0.3 mmol), lactone **2a** (0.9 mmol), $[RhCl(cod)]_2$ (0.015 mmol), Na_2CO_3 (0.075 mmol), toluene (1 mL), at 160 °C for 24 h. b Isolated yields. [c] Lactone (0.6 mmol), $[RhCl(cod)]_2$ (0.0075 mmol) were used. [d] K_2HPO_4 was used in place of Na_2CO_3.

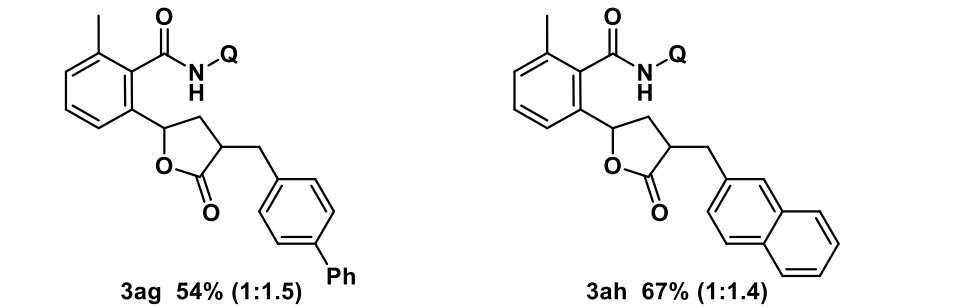
Table 1 shows representative results of aromatic amides. In these reactions, the choice of base is important. In general, K_2HPO_4 or Na_2CO_3 gave the satisfied results. A variety of benzoic acid derivatives could be alkylated. Both electron donating as well as electron withdrawing groups at the *ortho*-position of the amide gave the corresponding coupling products in high yield, as in **3aa**-**3da**. In the case of *meta*-substituted aromatic amides, alkylation proceeded selectively at the less hindered position, as in **3fa**-**3ja**. These results are different from the results of chapter 1 and 2. This is probably due to the steric hindrance of secondary alkyl group is much larger than primary alkyl group. This reaction was also applicable to di substituted amides **3ea**, **3ka**-**3ma** and naphthalene ring systems **3na**. When the amide derived from benzoic acid was used, only di alkylated product **3oa** was obtained.

Table 2. The Rh-Catalyzed Aromatic Amides with α,β-Unsaturated γ-Butyrolactones[a,b]







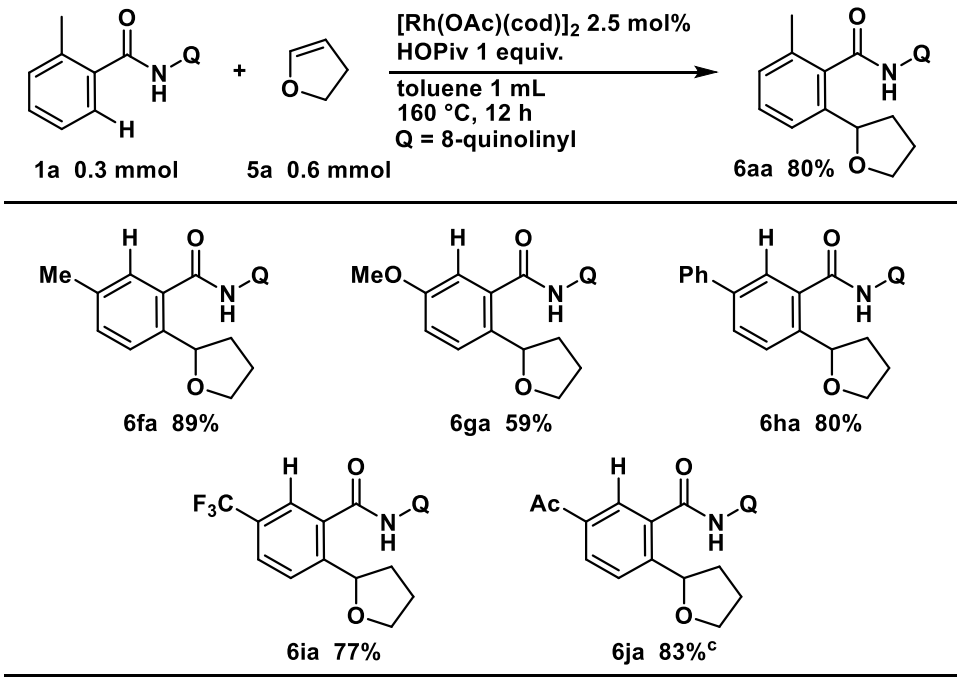


[a] Reaction conditions: amide **1a** (0.3 mmol), lactone **2** (0.9 mmol), $[RhCl(cod)]_2$ (0.015 mmol), K_2HPO_4

(0.075 mmol), toluene (1 mL), at 160 °C for 24 h. [b] Isolated yields. The number in parenthesis denotes the ratio of cis and trans isomers [c] The reaction was run for 12h. [d] KOAc was used in place of K_2HPO_4.

Several substituted lactons could also be used for this reaction (Table 2). Lactones bearing Me, Bu or Bn group at the α-position of the carbonyl group gave the corresponding alkylated product **3ab**, **3ac** and **3ad** in good yields. The product was obtained as a mixture of cis and trans isomers. In each case, selectivity was scarcely observed, and almost the same amount of isomer was produced. The selectivity was nearly constant, although various conditions were examined to improve. The ratio was constant even when the reaction was stopped after a short reaction time, suggesting that the ratio obtained is a thermodynamic ratio. Benzyl lactones bearing some functional groups on the phenyl ring, such as Br, MeO were tolerated under the reaction conditions **3ae**-**3ah**.

Table 3. The Rh-Catalyzed Aromatic Amides with 2,3-dihydrofuran[a,b]

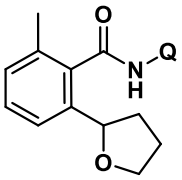
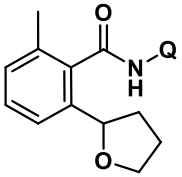
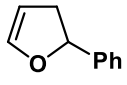
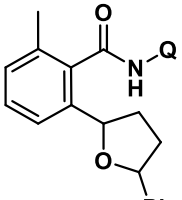
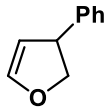
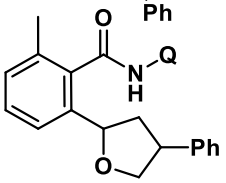


[a] Reaction conditions: amide **1a** (0.3 mmol), dihydrofuran **5a** (0.6 mmol), $[Rh(OAc)(cod)]_2$ (0.0075 mmol), PivOH (0.3 mmol), toluene (1 mL), at 160 °C for 12 h. [b] Isolated yields. [c] $[Rh(OAc)(cod)]_2$ (0.015 mmol) for 24 h.

To this reaction, 2,3-dihydrofuran **5a** was also applicable (Table 3). The C-C bond was formed selectively at the α-position of the oxygen atom **6aa**. Aromatic amides bearing various functional groups at the meta-position gave corresponding alkylated products in good yields **6fa**-**6ja**. In all cases, alkylation reaction took place only at the less hindered C-H bonds, leading to monoalkylation product.

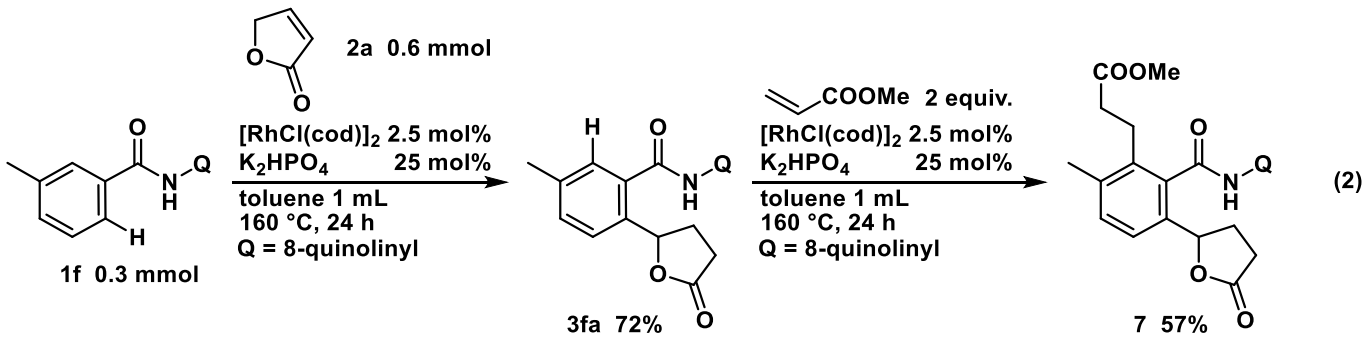
Table 4 showed the representative results of dihydrofurans. While the two different conditions were carried out, almost the same results were observed. When the 2,5-dihydrofuran **5b** was used in place of 2,3-dihydrofuran **5a**, the same product **6aa** was obtained. This means that, C-C bond was formed at the α-position, irrespective of the position of the C-C double bond. Phenyl substituted dihydrofurans **5c** and **5d** were also applicable to this reaction, although no selectivity was appeared.

Table 4. The Rh-Catalyzed Aromatic Amides with Ddihdrofurans[a,b,c]

alkene	product	
 **5a**		**6aa 69%[a]** **6aa 80%[b]**
 **5b**		**6aa 74%[a]** **6aa 68%[b]**
 **5c**		**6ac 76% (1:1.3)[a]** **6ac 70% (1:1.5)[b,d]**
 **5d**		**6ad 79% (1:1.1)[a]** **6ad 76% (1:1.3)[b]**

[a] Reaction conditions: **Method A:** amide **1a** (0.3 mmol), dihydrofuran (0.6 mmol), $[RhCl(cod)]_2$ (0.0075 mmol, KOAc (0.075 mmol), toluene (1 mL), at 160 °C for 12 h. [b] Reaction conditions: **Method B:** amide **1a** (0.3 mmol), dihydrofuran (0.6 mmol), $[Rh(OAc)(cod)]_2$ (0.0075 mmol), PivOH (0.3 mmol), toluene (1 mL), at 160 °C for 12 h. [c] Isolated yields. The number in parenthesis denotes the ratio of cis and trans isomers. [d] NMR yield.

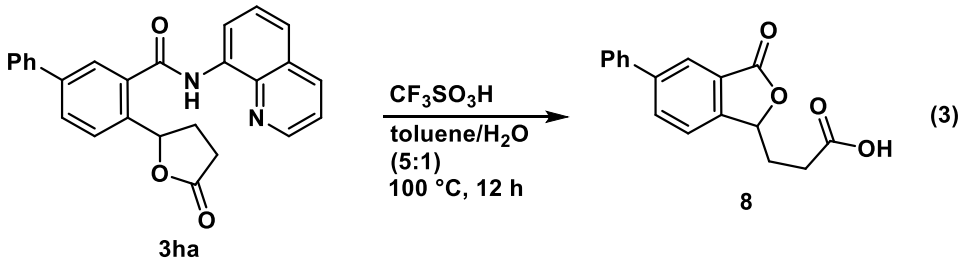
The synthetic application was shown in eq 2. By combining the reactions of Chapter 1 and Chapter 3, a highly substituted alkylated product could be synthesized. The rhodium catalyzed alkylation reaction of aromatic amides **1f** with lactone **2a** gave the only mono-alkylated product **3fa**. The remained less hindered *ortho* C-H bond could be reacted with methyl acrylate catalyzed by rhodium complex to give compound **7** which possesses three different type of carbonyl groups.



(2)

We could successfully remove the 8-aminoquinolin directing group under the acidic condition (eq 3), although the product is ring-opend isobenzofuran-1(3H)-one derivative **8.**

The reaction mechanism is discussed in chapter 5.



(3)

3.3 Conclusion

In summary, we have reported the rhodium catalyzed *ortho* alkylation of C(sp^2)-H bonds in aromatic amides with α,β-unsaturated lactones and dihydrofurans by using a bidentate chelation system. This reaction is the first example of C-H bond alkylation with α,β-unsaturated lactone. In this reaction, C-C bond was formed between the *ortho*-position in an aromatic amide and the α-position of a butenolide carbonyl oxygen atom. In addition, dihydrofurans were also applicable to this alkylation reaction. In this case, C-C bond formation occurs between the *ortho*-position in an aromatic amide and the α-position of a dihydrofuran, irrespective of the position of C-C double bond.

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 (δ), 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-4200 spectrometer; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra and high resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Analytical gas chromatography

(GC) was carried out on a Shimadzu GC-2014 gas chromatograph, equipped with a flame ionization detector. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

Materials.

Toluene (Kanto Chemical) was purified by passage through activated alumina using a GlassContour Solvent Dispensing System. $[RhCl(cod)]_2$ (CAS 12092-47-6) was purchased from Wako Pure Chemicals. KOAc (CAS 127-08-2), K_2HPO_4 (CAS 7758-11-4), Na_2CO_3 (CAS 497-19-8), were purchased from Nacalai Tesque. 2(5*H*)-Furanone (CAS 497-23-4), 3-methylfuran-2(5H)-one (CAS 22122-36-7), 2,3-dihydrofuran (CAS 1191-99-7), 2,5-dihydrofuran (CAS 1708-29-8), 8-Aminoquinoline (CAS 578-66-5) were purchased from Tokyo Chemical Industry Co., Ltd. $[Rh(OAc)(cod)]_2$ was prepared by chapter 1 procedure.

Synthesis of Starting Amides.

All amides bearing an 8-aminoquinoline moiety were prepared by reacting the corresponding acid or the corresponding acid chlorides with 8-aminoquinoline. All starting amides were prepared by chapter 1 procedure. All spectrum data of starting amides are cited in original paper.[3]

Synthesis of Starting Lactones.

To a stirred solution of 3-bromo-2-triisopropylsilyloxyfuran (10 mmol) in THF (20 mL) at -78 °C, *n*-BuLi (1.6 M in hexanes, 11 mmol) was added dropwise. After stirring for 2 h, the mixture was warmed to -25 °C and, a solution of benzylbromide (13 mmol) was added dropwise. The temperature was kept at -25 °C for 30 min, the mixture was then allowed to warm to room temperature and 1 M HCl aq. (25 mL) was added. The solution was magnetically stirred at room temperature for 1 h. After separating the organic phase, the aqueous phase was washed with Et_2O (3x20 mL). The organic phase was dried over $MgSO_4$ and the solvent removed by evaporation of the solvent. The resulting crude product was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 3/1).

Typical Procedures for the Rh-Catalyzed Reaction of Aromatic Amides with lactones.

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a** (79 mg, 0.3 mmol), furan-2(5H)-one (76 mg, 0.9 mmol), $[RhCl(cod)]_2$ (7.4 mg, 0.015 mmol), K_2HPO_4 (13 mg, 0.075 mmol) and toluene (1.0 mL) were added. The mixture was stirred for 24 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 alkylated product **3aa** (85 mg, 82%) as a colorless oil.

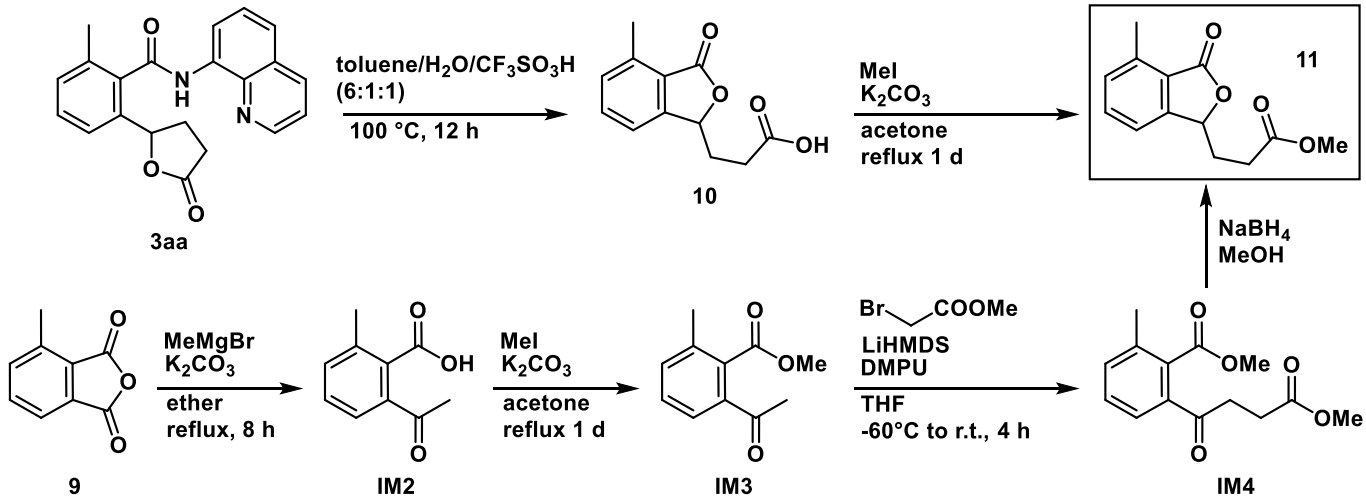
Typical Procedures for the Rh-Catalyzed Reaction of Aromatic Amides with lactones (Method A).
To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a** (79 mg, 0.3 mmol), 2,3-dihydrofuran (42 mg, 0.6 mmol), $[RhCl(cod)]_2$ (3.7 mg, 0.0075 mmol), KOAc (7.4 mg, 0.075 mmol) and toluene (1.0 mL) were added. The mixture was stirred for 12 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 alkylated product **6aa** (69 mg, 69%) as a colorless oil.

Typical Procedures for the Rh-Catalyzed Reaction of Aromatic Amides with lactones (Method B).
To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a** (79 mg, 0.3 mmol), 2,3-dihydrofuran (42 mg, 0.6 mmol), $[Rh(OAc)(cod)]_2$ (4.1 mg, 0.0075 mmol), HOPiv (30.6 mg, 0.3 mmol) and toluene (1.0 mL) were added. The mixture was stirred for 12 h at 160 °C followed by cooling. The crude product was washed with saturated aqueous Na_2CO_3 (2x3 mL), and EtOAc (2x3 mL). The organic phase was washed with Brine (5 mL).The organic phase was dried over anhydrous Na_2SO_4 and the solvent removed by evaporation of the solvent. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 10/1) to afford the desired alkylated product **6aa** (79 mg, 80%) as a colorless oil.

The Rh-Catalyzed alkylation of 3fa (eq 2).
To an oven-dried 5 mL screw-capped vial, **3fa** (0.15 mmol), methylacrylate (0.3 mmol), $[RhCl(cod)]_2$ (0.00375 mmol), K_2HPO_4 (0.00375 mmol) and toluene (1.0 mL) were added. The mixture was stirred for 24 h at 160 °C and then allowed to cool. The resulting mixture was filtered through a celite pad and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 3/1) to afford the desired alkylated product **7**.

Removal of directing group (eq 3).
Compound **3ha** (0.2 mmol) and CF_3SO_3H (0.5 mL) were dissolved in a mixture of toluene (2.5 mL) and water (0.5 mL) and the resulting solution was heated at 100 °C for 12 h. The reaction mixture was diluted with EtOAc, and extracted with a saturated aqueous Na_2CO_3 solution. The combined aqueous layers were then acidified to pH 2 with 1 N HCl. The aqueous layers were extracted with EtOAc, the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent removed by evaporation to give the carboxylic acid **8**.

The structure of **8** was confirmed by an alternative synthesis, as shown below.

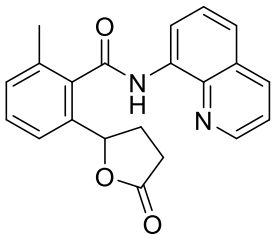


6-Methyl-2-acetylbenzoic acid(**IM2**) was prepared as a minor product accoding to literature procedure.[4]

IM2(1 equiv.), K_2CO_3(2.4 equiv.) and MeI(1.2 equiv.) were dissolved in acetone and the resulting solution was refluxed for 1 d. The reaction mixture was cooled to room temperature. The mixture was diluted with ether, and washed with 1M HCl aq, Na_2CO_3 aq and Brine. The organic phase was dried over Na_2SO_4 and the solvent was removed by evaporation. The resulting crude product was purified by flash chromatography on silica gel. (eluent: hexanes/EtOAc = 3/1, Rf=0.37 (**IM3** as a minor product), 0.29(major product))

IM4 was prepared accoding to a literature procedure[1].
11 was prepared accoding to a literature procedure[2].

2-methyl-6-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3aa).

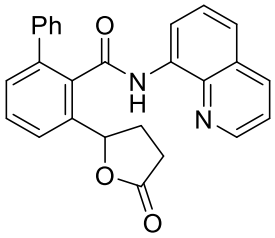


colorless oil. R_f 0.09 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.21-2.28 (m, 1H), 2.48 (s, 3H), 2.53- 2.68 (m, 2H), 2.71-2.79 (m, 1H), 5.73 (dd, *J*= 8.0, 6.4 Hz, 1H), 7.28 (dd, *J*= 7.2, 1.2 Hz, 1H), 7.38-7.47 (m, 3H), 7.58-7.63 (m, 2H), 8.19 (dd, *J*= 8.0, 1.6 Hz, 1H), 8.75 (dd, *J*= 4.0, 1.6 Hz, 1H), 8.93 (dd, *J*= 6.4, 2.8 Hz, 1H), 10.0 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.5, 29.0, 31.8, 79.3, 116.7, 121.8, 122.39, 122.43, 127.2, 127.9, 129.8, 130.4, 133.8, 134.7, 135.4, 136.3, 137.1, 138.3, 148.5, 167.3,

[1] Eur. *J. Org. Chem*. **2014**, *22*, 4714.
[2] K. Inoue, Y. Shiobara, H. Inouye *Chem. Pharm. Bull*. **1977**, *25*, 1462.

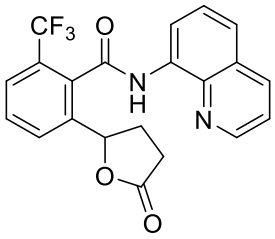
176.9. IR (ATR): 3339 w, 3013 w, 1777 m, 1737 w, 1669 m, 1596 w, 1578 w, 1519 s, 1482 s, 1423 m, 1385 m, 1325 m, 1265 m, 1216 w, 1178 m, 1138 m, 1033 m, 986 w, 901 m, 827 m, 791 m, 753 s, 732 m, 690 m. MS, m/z (relative intensity, %): 346 (M^+, 44), 203 (11), 202 (45), 186 (13), 185 (14), 174 (13), 171 (35), 160 (14), 157 (18), 145 (14), 144 (100), 91 (10). Exact Mass (EI): Calcd for $C_{21}H_{18}N_2O_3$ 346.1317, found 346.1319.

3-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (3ba).



colorless oil. R_f 0.37 (Hexane/EtOAc = 1/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.23-2.33 (m, 1H), 2.63-2.68 (m, 2H), 2.85-2.93 (m, 1H), 5.90 (dd, J = 8.4, 6.8 Hz, 1H), 7.03-7.07 (m, 1H), 7.20 (t, J = 8.0 Hz, 2H), 7.32-7.35 (m, 1H), 7.44-7.52 (m, 5H), 7.56-7.61 (m, 2H), 8.05 (dd, J = 8.4, 1.6 Hz, 1H), 8.55 (dd, J = 4.0, 1.6 Hz, 1H), 8.69 (dd, J = 7.6, 1.6 Hz, 1H), 9.61 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 29.1, 31.9, 79.5, 116.2, 121.5, 122.1, 124.0, 127.0, 127.56, 127.61, 128.3, 128.5, 130.1, 130.1, 133.9, 134.2, 136.0, 138.1, 138.6, 139.5, 139.9, 148.0, 167.0, 177.1. IR (ATR): 3331 w, 3017 w, 1775 m, 1666 m, 1595 w, 1521 s, 1483 m, 1460 w, 1424 m, 1387 w, 1326 m, 1294 w, 1266 w, 1218 w, 1183 m, 1139 m, 1029 w, 985 w, 948 w, 905 w, 826 w, 792 w, 755 s, 733 m, 699 m. MS, *m/z* (relative intensity, %): 408 (M^+, 62), 265 (25), 264 (35), 247 (11), 237 (15), 236 (12), 222 (27), 221 (42), 219 (20), 203 (18), 191 (19), 186 (15), 181 (15), 178 (31), 171 (38), 165 (22), 153 (19), 152 (42), 151 (10), 145 (13), 144 (100), 116 (11). Exact Mass (EI): Calcd for $C_{26}H_{20}N_2O_3$ 408.1474, found 408.1472.

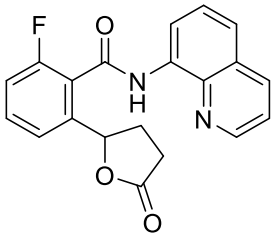
2-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)-6-(trifluoromethyl)benzamide (3ca).



colorless oil. R_f 0.06 (Hexane/EtOAc = 3/2). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.14-2.25 (m, 1H), 2.63 (bd, J = 8.4 Hz, 2H), 2.81 (bs, 1H), 5.74 (bs, 1H), 7.44-7.47 (m, 1H), 7.58-7.68 (m, 3H), 7.76-7.82 (m, 1H), 8.75 (dd, J = 4.0, 1.6 Hz, 1H), 8.87-8.2 (m, 1H), 10.2 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 29.0, 32.2, 78.4, 117.0, 121.9, 122.8, 123.8 (q, J = 272.7 Hz), 126.2 (d, J = 4.7 Hz), 127.2, 127.3 (q, J = 34.3 Hz), 127.9, 128.9, 130.3, 133.2, 133.6, 136.4, 138.2, 139.2, 148.5, 164.2, 176.4. IR (ATR): 3330 w, 3017 w, 1778 m, 1674 m, 1523 s, 1485 m, 1424 m, 1388 w, 1317 s, 1264 w, 1217 w, 1171 s, 1128 s, 1107 m, 1086 m, 1029 w, 901 m, 826 m, 792 m, 756 s, 733 m, 678 w, 665 m. MS, m/z (relative intensity, %): 400 (M^+, 43), 371 (22), 272 (18), 228 (12), 214 (12), 201 (13), 173 (13), 171 (60), 145 (23), 144 (100), 143

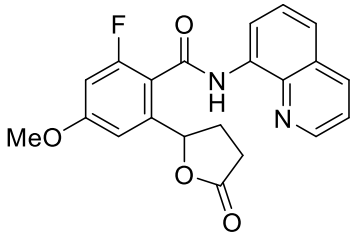
(10), 116 (15). Exact Mass (EI): Calcd for $C_{21}H_{15}F_3N_2O_3$ 400.1035, found 400.1037.

2-fluoro-6-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3da).



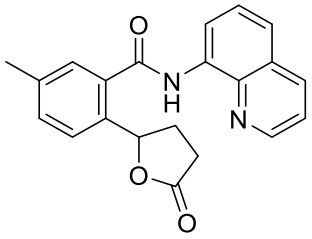
colorless oil. R_f 0.10 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.17-2.27 (m, 1H), 2.63-2.67(m, 2H), 2.88- 2.97 (m, 1H), 5.95 (t, J = 7.6 Hz, 1H), 7.20 (td, J = 8.8, 0.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.47-7.56 (m, 2H), 7.59-7.61 (m, 2H), 8.20 (dd, J = 8.0, 2.0 Hz, 1H), 8.81 (dd, J = 4.0, 1.6 Hz, 1H), 8.87-8.91 (m, 1H), 10.43 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 28.8, 31.7, 78.9 (d, J = 1.9 Hz), 115.9 (d, J = 22.9 Hz), 116.9, 121.2 (d, J = 2.9 Hz), 121.8, 122.55 (d, J = 17.1 Hz), 122.57, 127.2, 128.0, 132.1 (d, J = 8.5 Hz), 134.0, 136.4, 138.3, 141.8, 148.5, 159.3 (d, J = 246.9 Hz), 162.1, 177.0. IR (ATR): 3344 w, 2950 w, 1776 m, 1735 m, 1671 m, 1614 w, 1579 w, 1522 s, 1483 m, 1459 m, 1425 m, 1385 m, 1326 m, 1269 m, 1175 m, 1142 m, 1090 w, 1042 w, 979 w, 915 m, 826 m, 792 m, 756 m, 686 w. MS, m/z (relative intensity, %): 350 (M^+, 43), 321 (15), 222 (22), 206 (20), 178 (18), 171 (38), 164 (20), 151 (13), 145 (17), 144 (100), 133 (14), 123 (13), 116 (11), 115 (13), 95 (11). Exact Mass (EI): Calcd for $C_{20}H_{15}FN_2O_3$ 350.1067, found 350.1065.

2-fluoro-4-methoxy-6-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3ea).



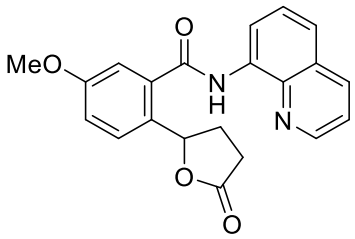
pale yellow oil. R_f 0.10 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.14-2.22 (m, 1H), 2.62- 2.66 (m, 2H), 2.94-3.02 (m, 1H), 3.87 (s, 3H), 6.06 (t, J = 7.2 Hz, 1H), 6.71 (dd, J = 12.0, 2.0 Hz, 1H), 6.95 (s, 1H), 7.47 (dd, J = 8.0, 4.0 Hz, 1H), 7.56-7.61 (m, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.81 (dd, J = 4.0, 1.6 Hz, 1H), 8.87 (dd, J = 6.0, 3.6 Hz, 1H), 10.47 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 28.7, 31.6, 55.9, 79.0 (d, J = 3.8 Hz), 101.3 (d, J = 27.7 Hz), 107.3 (d, J = 1.9 Hz), 114.4 (d, J = 16.2 Hz), 116.6, 121.8, 122.2, 127.2, 127.9, 134.2, 136.3, 138.4, 143.7 (d, J = 3.8 Hz), 148.4, 160.9 (d, J = 273.7 Hz), 162.0, 162.4, 177.0. IR (ATR): 3346 w, 3012 w, 1776 m, 1665 m, 1620 m, 1577 w, 1526 s, 1484 m, 1425 m, 1386 w, 1325 m, 1266 m, 1217 w, 1178 m, 1152 s, 1076 w, 1040 w, 982 w, 963 w, 914 w, 854 w, 827 m, 792 w, 756 m, 733 m, 699 w. MS, m/z (relative intensity, %): 380 (M^+, 70), 351 (10), 252 (13), 237 (23), 236 (67), 219 (12), 209 (15), 208 (39), 194 (23), 193 (18), 191 (20), 181 (23), 175 (11), 171 (44), 163 (18), 153 (22), 145 (33), 144 (100), 129 (11), 116 (14). Exact Mass (EI): Calcd for $C_{21}H_{17}FN_2O_4$ 380.1172, found 380.1170.

5-methyl-2-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3fa).



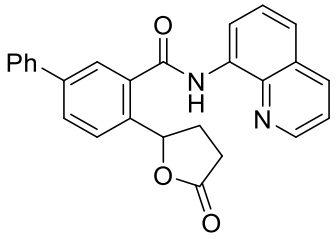
colorless oil. R_f 0.09 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.13-2.22 (m, 1H), 2.48 (s, 3H), 2.63- 2.67 (m, 2H), 2.93-3.01 (m, 1H), 6.09 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.45-7.53 (m, 2H), 7.57-7.62 (m, 3H), 8.20 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.82-8.86 (m, 2H), 10.37 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 21.1, 29.0, 31.9, 79.4, 116.5, 121.8, 122.2, 125.8, 127.3, 127.6, 128.0, 132.0, 134.0, 134.4, 136.4, 136.8, 138.3, 138.5, 148.4, 166.9, 177.5. IR (ATR): 3344 w, 2925 w, 1774 m, 1668 m, 1596 w, 1577 w, 1520 s, 1481 s, 1423 m, 1385 m, 1325 m, 1293 w, 1263 m, 1173 m, 1135 m, 1024 m, 988 w, 938 m, 910 w, 826 m, 791 m, 755 m, 731 m, 687 m. MS, m/z (relative intensity, %): 346 (M^+, 67), 317 (22), 287 (12), 218 (11), 203 (11), 202 (63), 185 (20), 175 (12), 174 (38), 171 (33), 160 (56), 157 (13), 147 (10), 145 (17), 144 (100), 129 (13), 119 (12), 116 (11), 91 (13). Exact Mass (EI): Calcd for $C_{21}H_{18}N_2O_3$ 346.1317, found 346.1316.

5-methoxy-2-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3ga).



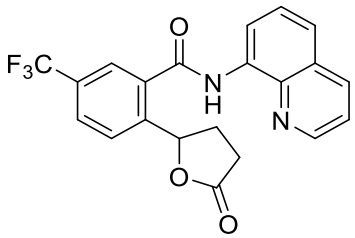
pale yellow oil. R_f 0.07 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.13-2.24 (m, 1H), 2.65 (dd, *J* = 9.6, 7.2 Hz, 2H), 2.90- 2.98 (m, 1H),3.90 (s, 3H), 6.04 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.10 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.49 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.58-7.62 (m, 2H), 8.20 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.81 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.84 (dd, *J* = 6.0, 3.2 Hz, 1H), 10.38 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 29.2, 32.0, 55.6, 79.3, 113.1, 116.1, 116.5, 121.8, 122.3, 127.2, 127.4, 128.0, 131.4, 134.2, 135.5, 136.4, 138.5, 148.4, 159.2, 166.5, 177.4. IR (ATR): 3343 w, 2934 w, 1773 m, 1671 m, 1607 w, 1579 w, 1522 s, 1482 s, 1424 m, 1385 m, 1326 m, 1293 w, 1266 m, 1210 w, 1173 m, 1135 w, 1099 w, 1039 w, 985 w, 940 w, 911 w, 892 w, 857 w, 825 m, 791 m, 753 m, 732 m, 684 w. MS, m/z (relative intensity, %): 362 (M^+, 56), 333 (25), 303 (16), 234 (11), 218 (40), 201 (13), 191 (13), 190 (39), 177 (11), 176 (100), 173 (10), 171 (30), 163 (11), 145 (20), 144 (100), 135 (20), 129 (11). Exact Mass (EI): Calcd for $C_{21}H_{18}N_2O_4$ 362.1267, found 362.1265.

4-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)-[1,1'-biphenyl]-3-carboxamide (3ha).



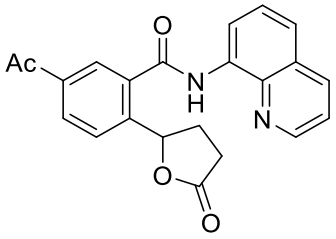
colorless oil. R_f 0.11 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.19-2.29 (m, 1H), 2.67 (dd, *J* = 9.6, 6.8 Hz, 2H), 2.97- 3.06 (m, 1H), 6.14 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 6.8 Hz, 1H), 7.45-7.50 (m, 3H), 7.57-7.66 (m, 4H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.79 (d, *J* = 4.0 Hz, 1H), 8.87 (dd, *J* = 6.8, 2.0 Hz, 1H), 10.46 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 29.0, 31.8, 79.2, 116.5, 121.8, 122.3, 125.6, 126.3, 127.1, 127.2, 127.9, 128.0, 129.0, 130.0, 134.2, 134.7, 136.4, 138.45, 138.55, 139.4, 141.3, 148.4, 166.7, 177.3. IR (ATR): 3340 w, 3030 w, 1774 m, 1668 m, 1597 w, 1522 s, 1482 w, 1424 m, 1386 w, 1326 m, 1262 w, 1213 w, 1174 m, 1137 m, 1105 w, 1019 w, 990 w, 938 w, 910 m, 826 m, 791 m, 757 s, 731 s, 697 m. MS, m/z (relative intensity, %): 408 (M^+, 46), 264 (34), 247 (15), 237 (11), 236 (33), 223 (16), 222 (100), 219 (12), 191 (12), 181 (12), 178 (17), 171 (26), 165 (10), 153 (10), 152 (22), 145 (13), 144 (85). Exact Mass (EI): Calcd for $C_{26}H_{20}N_2O_3$ 408.1474, found 408.1471.

2-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (3ia).



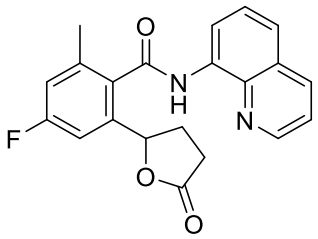
colorless oil. R_f 0.11 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.13-2.23 (m, 1H), 2.62-2.74 (m, 2H), 2.99-3.07 (m, 1H), 6.11 (t, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 7.6, 4.0 Hz, 1H), 7.59-7.62 (m, 2H), 7.79-7.86 (m, 2H), 8.03 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.82-8.83 (m, 2H), 10.43 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 28.8, 31.6, 78.7, 116.8, 121.9, 122.7, 123.4 (q, *J* = 271.1 Hz), 124.0 (d, *J* = 3.7 Hz), 126.5, 127.2, 127.9, 128.0 (d, *J* = 3.9 Hz), 130.6 (q, *J* = 33.1 Hz), 133.9, 134.7, 136.5, 138.4, 143.7, 148.6, 165.3, 176.8. IR (ATR): 3334 w, 3014 w, 1779 m, 1737 w, 1672 m, 1619 w, 1596 w, 1579 w, 1523 s, 1484 m, 1460 w, 1424 m, 1387 m, 1326 s, 1297 w, 1251 m, 1231 w, 1213 m, 1172 s, 1127 s, 1083 m, 1025 m, 994 w, 939 w, 912 m, 850 w, 827 m, 792 m, 759 m, 732 m, 691 w. MS, m/z (relative intensity, %): 400 (M^+, 40), 371 (22), 315 (13), 272 (25), 256 (11), 228 (22), 214 (26), 171 (35), 145 (26), 144 (100), 116 (14). Exact Mass (EI): Calcd for $C_{21}H_{15}F_3N_2O_3$ 400.1035, found 400.1037.

5-acetyl-2-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3ja).



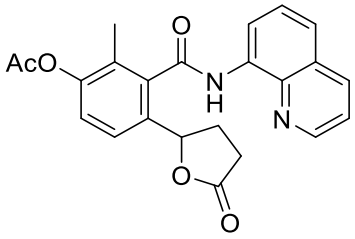
pale yellow oil. R_f 0.06 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.13-2.23 (m, 1H), 2.65-2.72 (m, 5H), 2.99-3.08 (m, 1H), 6.14 (t, J = 8.0 Hz, 1H), 7.50 (dd, J = 8.0, 4.4 Hz, 1H), 7.61 (d, J = 4.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.81-8.84 (m, 2H), 10.46 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 26.7, 28.8, 31.6, 78.9, 116.7, 121.9, 122.5, 126.1, 126.8, 127.2, 127.9, 131.1, 134.0, 134.4, 136.4, 136.7, 138.4, 144.7, 148.5, 165.9, 177.0, 196.6. IR (ATR): 3338 w, 3011 w, 1776 m, 1670 s, 1600 w, 1576 w, 1523 s, 1483 m, 1424 m, 1386 m, 1358 w, 1326 m, 1291 w, 1261 w, 1227 m, 1173 m, 1137 m, 1025 m, 984 w, 938 w, 914 w, 827 m, 792 m, 753 m, 732 m, 688 w, 667 w. MS, m/z (relative intensity, %): 374 (M^+, 49), 246 (14), 230 (27), 202 (26), 188 (32), 187 (11), 171 (43), 145 (24), 144 (100), 143 (10), 129 (11), 117 (12), 116 (11), 115 (12). Exact Mass (EI): Calcd for $C_{22}H_{18}N_2O_4$ 374.1267, found 374.1266.

4-fluoro-2-methyl-6-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3ka).



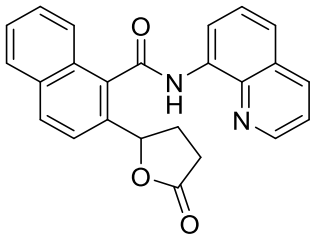
pale yellow oil. R_f 0.10 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.17-2.28 (m, 1H), 2.48 (s, 3H), 2.55- 2.68 (m, 2H), 2.73-2.81 (m, 1H), 5.72 (dd, J = 8.8, 6.8 Hz, 1H), 6.98 (dd, J = 8.8, 2.4 Hz, 1H), 7.11 (dd, J = 9.6, 2.4 Hz, 1H), 7.48 (dd, J = 8.0, 4.0 Hz, 1H), 7.59-7.64 (m, 2H), 8.21 (dd, J = 8.0, 1.6 Hz, 1H), 8.77 (dd, J = 4.0, 2.0 Hz, 1H), 8.88-8.92 (m, 1H), 10.04 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.7, 28.9, 31.7, 78.6, 109.7 (d, J = 22.9 Hz), 116.8, 117.1 (d, J = 21.0 Hz), 121.9, 122.6, 127.2, 128.0, 131.5 (d, J = 3.8 Hz), 133.7, 136.4, 138.0 (d, J = 8.6 Hz), 138.3, 140.2 (d, J = 7.6 Hz), 148.5, 163.0 (d, J = 247.9 Hz), 166.6, 176.5. IR (ATR): 3338 w, 2956 w, 1779 m, 1668 m, 1602 m, 1521 s, 1482 m, 1423 m, 1385 m, 1325 m, 1305 m, 1264 w, 1216 w, 1177 m, 1139 m, 1036 m, 977 w, 912 m, 892 w, 866 w, 827 w, 792 m, 756 m, 730 s, 699 m. MS, m/z (relative intensity, %): 364 (M^+, 32), 220 (37), 203 (10), 192 (13), 186 (10), 178 (14), 175 (21), 171 (35), 165 (12), 145 (15), 144 (100), 109 (12). Exact Mass (EI): Calcd for $C_{21}H_{17}FN_2O_3$ 364.1223, found 364.1222.

2-methyl-4-(5-oxotetrahydrofuran-2-yl)-3-(quinolin-8-ylcarbamoyl)phenyl acetate (3la).



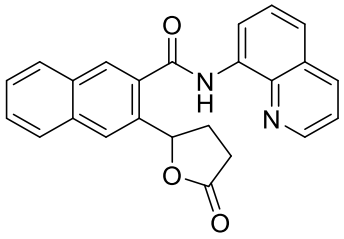
white solid. mp = 129 °C. R_f 0.06 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.18-2.26 (m, 1H), 2.29 (s, 3H), 2.37 (s, 3H), 2.52-2.76 (m, 3H), 5.70 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.48 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.61 (dd, *J* = 8.8, 4.0 Hz, 2H), 8.20 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.77 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.89-8.93 (m, 1H), 10.07 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 13.3, 20.8, 29.0, 31.7, 79.0, 116.9, 121.9, 122.6, 123.6, 123.8, 127.2, 127.4, 127.9, 133.7, 134.8, 136.4, 137.1, 138.3, 148.5, 149.2, 166.3, 169.1, 176.8. IR (ATR): 3336 w, 3015 w, 2360 w, 1767 m, 1671 m, 159 w, 1521 s, 1483 m, 1424 m, 1385 w, 1370 w, 1325 m, 1268 w, 1202 s, 1175 s, 1139 m, 1084 w, 1033 m, 979 w, 905 m, 867 w, 827 m, 792 m, 753 , 701 w. MS, m/z (relative intensity, %): 404 (M^+, 27), 260 (23), 219 (10), 218 (15), 201 (15), 190 (14), 186 (13), 176 (17), 173 (10), 171 (32), 145 (19), 144 (100). Exact Mass (EI): Calcd for $C_{23}H_{20}N_2O_5$ 404.1372, found 404.1375.

2-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)-1-naphthamide (3ma).



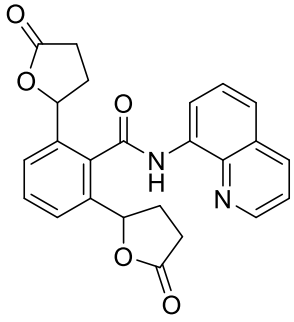
pale yellow oil. R_f 0.09 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.27-2.35 (m, 1H), 2.61- 2.74 (m, 2H) , 2.78-2.89 (m, 1H), 5.73 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.43 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.50-7.57 (m, 2H), 7.61-7.68 (m, 3H), 7.92 (dd, *J* = 6.8, 2.0 Hz, 1H), 8.01-8.07 (m, 2H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.66 (dd, *J* = 4.0, 1.6 Hz, 1H), 9.07 (dd, *J* = 6.8, 1.2 Hz, 1H), 10.26 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 29.3, 31.8, 79.5, 116.9, 121.8, 122.0, 122.6, 125.1, 126.9, 127.2, 127.6, 128.0, 128.2, 129.5,130.5, 132.9, 133.1, 134.0, 134.2, 136.3, 138.3,148.5, 166.8, 176.9. IR (ATR): 3331 w, 3014 w, 1777 m, 1668 m, 1597 w, 1576 w, 1520 s, 1482 m, 1460 w, 1424 m, 1388 w, 1324 m, 1258 w, 1216 w, 1177 m, 1135 m, 1028 w, 986 w, 910 m, 825 m, 792 m, 750 s, 731 s, 698 w. MS, m/z (relative intensity, %): 382 (M^+, 28), 239 (13), 238 (41), 221 (20), 196 (28), 195 (10), 193 (12), 186 (17), 183 (11), 177 (11), 171 (31), 167 (15), 165 (27), 155 (12), 15 (13), 145 (13), 144 (100), 127 (25). Exact Mass (EI): Calcd for $C_{24}H_{18}N_2O_3$ 382.1317, found 382.1316.

3-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)-2-naphthamide (3na).



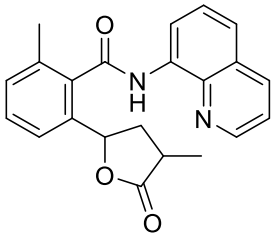
white solid. mp = 114 °C. R_f 0.13 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.21-2.30 (m, 1H), 2.64- 2.68 (m, 2H), 2.98-3.07 (m, 1H), 6.31 (t, *J* = 7.2 Hz, 1H), 7.47 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.56-7.63 (m, 4H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.07 (s, 1H), 8.19 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.31 (s, 1H), 8.81 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.89 (dd, *J* = 7.2, 1.6 Hz, 1H), 10.55 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 28.7, 31.6, 79.4, 116.5, 121.8, 122.2, 124.9, 127.16, 127.25, 127.8, 127.96, 128.02, 128.19, 128.24, 131.8, 131.9,134.0, 134.4, 136.3, 136.4, 138.5, 148.4, 166.9, 177.5. IR (ATR): 3342 w, 3014 w, 1774 m, 1668 m, 1596 w, 1577 w, 1522 s, 1483 m, 1458 w, 1423 m, 1385 m, 1325 m, 1267 w, 1217 w, 1179 m, 1136 m, 1025 w, 991 w, 941 w, 909 m, 826 m, 791 m, 750 s, 731 m, 666 w. MS, m/z (relative intensity, %): 382 (M^+, 74), 354 (15), 353 (37), 323 (12), 254 (10), 238 (23), 221 (16), 211 (17), 210 (51), 197 (13), 196 (85), 194 (10), 193 (32), 183 (13), 171 (27), 167 (16), 166 (11), 165 (32), 155 (23), 154 (10), 152 (13), 145 (14), 144 (100), 127 (25). Exact Mass (EI): Calcd for $C_{24}H_{18}N_2O_3$ 382.1317, found 382.1318.

2,6-bis(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3oa).



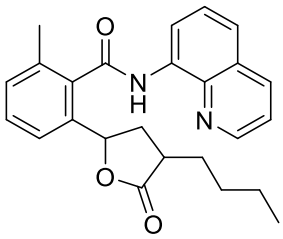
dr = 1:1.1. white solid. mp = 128 °C. R_f 0.17 (Hexane/EtOAc = 1/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.20-2.32 (m, 4.3H), 2.52- 2.78 (m, 12.9H), 5.71-5.75 (m, 4.3 H), 7.47-7.51 (m, 2.2H), 7.55-7.65 (m, 10.8H), 8.21 (dd, *J* = 8.0, 2.0 Hz, 2.2H), 8.76-8.78 (m, 2.2H), 8.86-8.91 (m, 2.2H), 10.09 (bs, 1.2H), 10.16 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 28.91, 28.97, 31.62(two overlaping peaks), 78.74, 78.75, 116.98, 117.08, 121.99, 122.02, 122.97(two overlaping peaks), 125.27, 125.40, 127.08, 127.18, 127.97, 127.99, 130.62, 130.68, 133.36, 133.42, 133.49(two overlaping peaks), 136.41, 136.51, 137.24, 137.30, 138.24, 138.29, 148.67, 148.74, 165.88, 166.02, 176.47(two overlaping peaks). IR (ATR):3329 w, 3017 w, 1771 s, 1668 m, 1597 w, 1520 m, 1483 m, 1423 w, 1387 w, 1325 m, 1299 w, 1267 w, 1217 w, 1181 m, 1137 m, 1028 m, 905 m, 827 w, 793 m, 747 s, 698 m, 665 m. MS, m/z (relative intensity, %): 417 (15), 416 (M^+, 52), 387 (25), 357 (18), 301 (13), 272 (18), 216 (24), 171 (52), 145 (17), 144 (100), 143 (12), 115 (12). Exact Mass (EI): Calcd for $C_{24}H_{20}N_2O_5$ 416.1372, found 416.1371.

2-methyl-6-(4-methyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3ab).



dr = 1:1.6. colorless oil. R_f 0.27 (Hexane/EtOAc = 4/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.25 (d, *J* = 7.6 Hz, 3H), 1.28 (d, *J* = 7.6 Hz, 4.8H), 1.88 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1.6H), 2.34-2.41 (m, 1H), 2.47-2.57 (m, 8.8H), 2.68 (m, 2.6H), 2.90-2.97 (m, 1.6H), 5.58 (dd, *J* = 10.4, 5.6 Hz, 1.6H), 5.84 (dd, *J* = 8.4, 5.6 Hz, 1H), 7.28-7.32 (m, 3.6H), 7.38 (d, *J* = 7.6 Hz, 1.0H), 7.42 (d, *J* = 5.6 Hz, 3.2H), 7.46 (dd, *J* = 8.0, 4.8 Hz, 2.6H), 7.59-7.64 (m, 5.2H), 8.19 (dd, *J* = 8.0, 1.6 Hz, 2.6H), 8.75 (dd, *J* = 4.0, 1.6 Hz, 2.6H), 8.93 (dd, *J* = 6.0, 2.4 Hz, 2.6H), 10.04 (bs, 2.6H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 14.82, 15.45, 19.48, 19.54, 33.48, 36.25, 38.70, 40.94, 76.56, 116.75, 121.80, 121.99, 122.39, 122.64, 127.18, 127.93, 129.61, 129.81, 130.29, 130.37, 133.83, 133.86, 134.58, 135.00, 135.18, 135.66, 136.33, 136.88, 137.53, 138.37, 148.45, 167.29, 167.42, 179.08, 180.09. IR (ATR): 3340 w, 2956 w, 2930 w, 2861 w, 1772 m, 1671 m, 1597 w, 1579 w, 1520 s, 1482 m, 1424 m, 1386 m, 1325 m, 1262 w, 1213 w, 1158 m, 1130 w, 1107 w, 1033 w, 956 w, 900 w, 849 w, 827 m, 791 m, 755 m, 731 s, 694 m. MS, m/z (relative intensity, %): 361 (11), 360 (M^+, 52), 217 (16), 216 (48), 200 (13), 189 (11), 188 (31), 172 (12), 171 (93), 147 (100), 145 (16), 144 (74), 91 (13). Exact Mass (EI): Calcd for $C_{22}H_{20}N_2O_3$ 360.1474, found 360.1475.

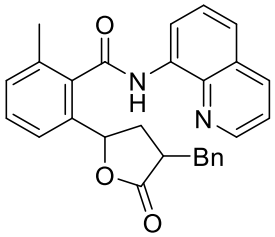
2-(4-butyl-5-oxotetrahydrofuran-2-yl)-6-methyl-N-(quinolin-8-yl)benzamide (3ac).



dr = 1:1.5. colorless oil. R_f 0.17 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 0.81 (t, *J* = 6.0 Hz, 3H), 0.87 (t, *J* = 6.4 Hz, 4.5H), 1.20-1.30 (m, 10H), 1.39-1.48 (m, 2.5H), 1.76-1.95 (m, 4.0H), 2.39-2.52 (m, 9.5H), 2.60-2.71 (m, 2.5H), 2.88-2.95 (m, 1.5H), 5.56 (dd, *J* = 10.4, 5.6 Hz, 1.5H), 5.80 (m, 1.0H), 7.27-7.31 (m, 3.5H), 7.38-7.42 (m, 4.0H), 7.45-7.48 (m, 2.5H), 7.59-7.64 (m, 5.0H), 8.19 (dd, *J* = 8.0, 1.2 Hz, 2.5H), 8.75 (dd, *J* = 4.0, 1.2 Hz, 2.5H), 8.93 (dd, *J* = 6.0, 2.0 Hz, 2.5H), 10.04 (bs, 2.5H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 13.72, 13.80, 19.47, 19.51, 22.25, 22.31, 29.24, 29.29, 29.79, 30.14, 36.91, 38.69, 39.11, 41.24, 76.91,121.79, 121.98, 122.39, 122.63, 127.18, 127.94, 129.63, 129.82, 130.26, 130.34, 133.83, 133.86, 134.57, 134.98, 135.18, 135.64, 136.33, 137.07, 137.69, 138.37, 148.43, 167.33, 167.44, 178.61, 179.55. IR (ATR): 3339 w, 2973 w, 1772 m, 1670 m, 1597 w, 1578 w, 1519 s, 1482 m, 1457 m, 1424 m, 1385 m, 1325 m, 1264 w, 1186 m, 1159 m, 1129 w, 1082 w, 1011 w, 900 w, 827 m, 791 m, 755 m, 731 m, 696 m. MS, m/z (relative intensity, %): 403 (16), 402 (M^+, 57), 259 (12), 258 (46), 230 (17), 213 (11), 199 (39), 172 (12), 171 (100), 161 (18), 160 (20), 147 (61), 145 (25), 144

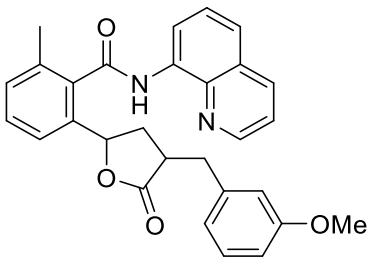
(97), 129 (10), 91 (14). Exact Mass (EI): Calcd for $C_{25}H_{26}N_2O_3$ 402.1943, found 382.1318.

2-(4-benzyl-5-oxotetrahydrofuran-2-yl)-6-methyl-N-(quinolin-8-yl)benzamide (3ad).



dr = 1:1.5. colorless oil. R_f 0.20 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.92-2.01 (m, 1.5H), 2.30- 2.37 (m, 1H), 2.88 (s, 3H), 2.45 (s, 3H), 2.48-2.53 (m, 1H), 2.75-2.84 (m, 4H), 2.91-3.09 (m, 3.5H), 3.28 (dd, J = 13.6, 4.0 Hz, 1.5H), 5.5 (dd, J = 6.8, 6.8 Hz, 1H), 5.51 (dd, J = 10.8, 6.0 Hz, 1.5H), 6.91-6.94 (m, 1H), 6.99-7.05 (m, 4H), 7.13 (d, J = 8.0 Hz, 3H), 7.17-7.29 (m, 9.5H), 7.35-7.40 (m, 2.5H), 7.42-7.48 (m, 2.5H), 7.57-7.67 (m, 5H), 8.17 (d, J = 8.0 Hz, 1.5H), 8.21 (d, J = 8.0 Hz, 1H), 8.66 (d, J = 4.0 Hz, 1.5H), 8.70 (d, J = 4.0 Hz, 1H), 8.85-8.89 (m, 1.5H), 8.93 (dd, J = 6.8, 2.0 Hz, 1H), 9.93 (bs, 1H), 9.99 (bs, 1.5H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.42, 19.46, 36.10, 36.17, 38.69, 41.01, 43.18, 77.51, 116.86, 121.77, 121.91, 122.38, 122.39, 122.77, 126.54, 127.18, 127.24, 127.92, 128.45, 128.54, 128.78, 129.62, 129.85, 130.23, 130.41, 133.76, 133.86, 134.59, 134.95, 135.16, 135.67, 136.35, 136.82, 137.28, 137.55, 138.30, 148.40, 167.19, 167.34, 177.70, 178.78. IR (ATR): 3338 w, 3026 w, 2925 w, 1771 m, 1670 m, 1597 w, 1520 s, 1483 m, 1455 w, 1424 w, 1386 w, 1325 m, 1266 w, 1205 w, 1162 m, 1129 w, 1087 w, 1037 w, 1007 w, 963 w, 907 m, 826 w, 791 m, 750 s, 729 s, 699 s. MS, m/z (relative intensity, %): 437 (19), 436(M^+, 60), 292 (22), 276 (13), 275 (33), 229 (17), 173 (40), 172 (10), 171 (84), 161 (15), 149 (10), 147 (64), 145 (21), 144 (100), 132 (24), 104 (10), 91 (59). Exact Mass (EI): Calcd for $C_{28}H_{24}N_2O_3$ 436.1787, found 436.1780.

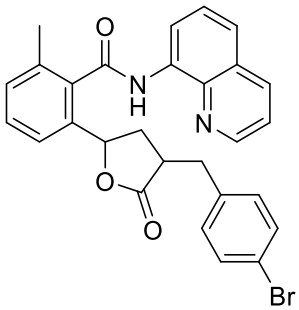
2-(4-(3-methoxybenzyl)-5-oxotetrahydrofuran-2-yl)-6-methyl-N-(quinolin-8-yl)benzamide (3ae).



dr = 1:1.6. colorless oil R_f 0.16 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.96 (ddd, J = 12.0, 12.0, 12.0 Hz, 1.6H), 2.32-2.39 (m, 1H), 2.44- 2.54 (m, 8.8H), 2.71-2.83 (m, 4.2H), 2.91-3.04 (m, 2.6H), 3.06-3.11 (m, 1H), 3.27 (dd, J = 13.6, 4.0 Hz, 1.6H), 3.68 (s, 3H), 3.75 (s, 4.8H), 5.49-5.55 (m, 2.6H), 6.54 (dd, J = 8.0, 2.4 Hz, 1H), 6.62-6.76 (m, 6.8H), 6.92 (t, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1.6H), 7.26-7.30 (m, 4.8H), 7.35-7.48 (m, 5.6H), 7.58-7.66 (m, 5.2H), 8.16-8.22 (m, 2.6H), 8.67 (d, J = 4.0 Hz, 1.6H), 8.70 (d, J = 4.0 Hz, 1.0H), 8.85-8.90 (m, 1.6H), 8.92 (dd, J = 7.2, 2.0 Hz, 1H), 9.94 (bs, 1H), 9.98 (bs, 1.6H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.49, 36.12, 36.20, 36.24, 38.82, 40.84, 43.19,

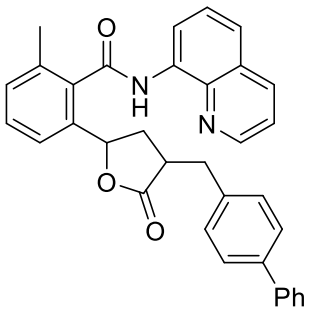
54.99, 55.07, 77.55, 111.99, 112.18, 114.22, 114.33, 116.82, 121.08, 121.12, 121.78, 121.94, 122.37, 122.40, 122.80, 127.18, 127.24, 127.92, 129.46, 129.56, 129.64, 129.87, 130.28, 130.44, 133.79, 133.86, 134.61, 134.98, 135.18, 135.69, 136.31, 136.81, 137.33, 138.35, 139.23, 139.91, 148.44, 159.57, 159.67, 167.20, 167.33, 177.74, 178.85. IR (ATR): 3339 w, 3011 w, 2938 w, 1769 m, 1670 m, 1597 w, 1520 s, 1483 s, 1424 m, 1386 w, 1325 m, 1263 m, 1205 w, 1156 m, 1129 w, 1091 w, 1039 m, 1008 w, 907 w, 827 m, 790 m, 754 s, 732 m, 697 m. MS, m/z (relative intensity, %): 467 (20), 466 (M^+, 63), 305 (23), 259 (21), 173 (12), 171 (54), 163 (11), 162 (100), 147 (36), 145 (17), 144 (83), 121 (22), 91 (14). Exact Mass (EI): Calcd for $C_{29}H_{26}N_2O_4$ 466.1893, found 466.1891.

2-(4-(4-bromobenzyl)-5-oxotetrahydrofuran-2-yl)-6-methyl-N-(quinolin-8-yl)benzamide (3af).



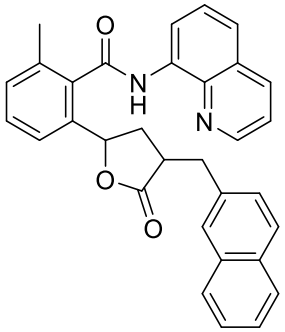
dr = 1:1.5. white solid. mp = 84 °C. R_f 0.20 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.92 (m, 1.5H), 2.30-2.37 (m, 1H), 2.45-2.53 (m, 8.5H), 2.71-2.80 (m, 4H), 2.88-3.05 (m, 3.5H), 3.21 (dd, J = 14.0, 4.0 Hz, 1.5H), 5.48-5.54 (m, 2.5H), 6.91 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.0 Hz, 3H), 7.12 (d, J = 8.8 Hz, 2H), 7.24-7.29 (m, 5H), 7.33-7.41 (m, 5.5H), 7.45-7.50 (m, 2.5H), 7.59 (d, J = 4.4 Hz, 3H), 7.63-7.68 (m, 2H), 8.19 (dd, J = 8.4, 1.6 Hz, 1.5H), 8.22 (dd, J = 8.4, 1.6 Hz, 1H), 8.65 (dd, J = 4.0, 1.6 Hz, 1.5H), 8.69 (dd, J = 4.0, 1.6 Hz, 1H), 8.85-8.89 (m, 1.5H), 8.94 (dd, J = 6.4, 2.8 Hz, 1H), 9.94 (bs, 1H), 9.97 (bs, 1.5H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.46, 19.49, 35.44, 35.49, 36.06, 38.54, 40.74, 42.95, 77.54, 116.77, 116.85, 120.50, 120.62, 121.80, 121.83, 121.88, 122.46, 122.49, 122.66, 127.21, 127.28, 127.96, 128.03, 129.68, 129.90, 130.31, 130.49, 130.55, 130.59, 131.59, 131.64, 133.77, 133.86, 134.69, 135.03, 135.11, 135.59, 136.38, 136.43, 16.55, 136.72, 137.18, 137.26, 138.32, 138.34, 148.45, 148.50, 167.21, 167.33, 177.35, 178.39. IR (ATR): 3339 w, 2930 w, 2361 w, 1773 m, 1671 m, 1596 w, 1521 s, 1483 m, 1424 w, 1386 w, 1325 m, 1264 w, 1216 w, 1162 w, 1072 w, 1011 w, 963 w, 898 w, 827 w, 792 m, 754 m, 697 w. MS, m/z (relative intensity, %): 517 (12), 516 (40), 515 (13), 514 (M^+, 39), 372 (22), 370 (22), 355 (13), 353 (13), 287 (11), 245 (10), 173 (61), 172 (10), 171 (80), 169 (28), 161 (25), 147 (67), 145 (21), 144 (100), 116 (11), 91 (14). Exact Mass (EI): Calcd for $C_{28}H_{23}BrN_2O_3$ 514.0892, found 514.0890.

2-(4-([1,1'-biphenyl]-4-ylmethyl)-5-oxotetrahydrofuran-2-yl)-6-methyl-N-(quinolin-8-yl)benzamide (3ag).



dr = 1:1.5. white solid. mp = 95 °C. R_f 0.07 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.00 (ddd, *J* = 12.4, 12.0, 10.8 Hz, 1.5H), 2.34-2.41 (m, 1H), 2.43 (s, 3.0H), 2.45 (s, 4.5H), 2.54-2.61 (m, 1H), 2.79-2.90 (m, 4H), 2.94-3.14 (m, 3.5H), 3.32 (dd, *J* = 13.6, 4.0 Hz, 1.5H), 5.45-5.55 (m, 2.5H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.19-7.24 (m, 6H), 7.26-7.39 (m, 15H), 7.42-7.60 (m, 6H), 7.54-7.62 (m, 8.5H), 8.13 (td, *J* = 8.0, 1.6 Hz,2.5H), 8.63 (td, *J* = 4.0, 1.6 Hz,2.5H), 8.87 (dd, *J* = 6.4, 2.4 Hz, 1.5H), 8.94 (dd, *J* = 6.4, 2.0 Hz, 1.0H), 9.93 (bs, 1H), 9.98 (bs, 1.5H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.46, 19.49, 35.77, 35.85, 36.31, 38.72, 41.09, 43.19,77.55, 116.74, 116.85, 121.77, 121.85, 122.40, 122.42, 122.76, 126.85, 126.93, 127.04, 127.19, 127.22, 127.27, 127.91, 127.93, 128.57, 128.74, 129.28, 128.69, 129.89, 130.24, 130.44, 133.79, 133.88, 134.64, 134.94, 135.13, 135.65, 136.29, 136.32, 136.6, 136.88, 137.38, 138.28, 138.37, 139.50, 139.56, 140.53, 140.71, 148.40, 148.44, 167.24, 167.37, 177.71, 178.76 IR (ATR): 3338 w, 3027 w, 2925 w, 2251 w, 1770 m, 1670 m, 1597 w, 1520 s, 1483 m, 1424 m, 1386 m, 1325 m, 1265 w, 1202 w, 1161 m, 1129 m, 1039 w, 1008 w, 963 w, 907 m, 858 w, 826 m, 791 m, 757 s, 729 s, 696 s. MS, m/z (relative intensity, %): 513 (28), 512 (M^+, 73), 351 (21), 305 (11), 287 (10), 209 (11), 208 (70), 207 (18), 171 (39), 168 (14), 167 (100), 165 (14), 147 (33), 145 (17), 144 (88). Exact Mass (EI): Calcd for $C_{34}H_{28}N_2O_3$ 512.2100, found 512.2101.

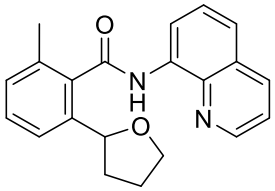
2-methyl-6-(4-(naphthalen-2-ylmethyl)-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (3ah).



dr = 1:1.5. white solid. mp = 108 °C. R_f 0.17 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.97-2.06 (m, 1.5H), 2.33- 2.40 (m, 1H), 2.42 (s, 3H), 2.43 (m, 4.5H), 2.51-2.58 (m, 1H), 2.79 (ddd, *J* = 13.6, 8.0, 5.2 Hz, 1.5H), 2.89-3.16 (m, 5H), 3.29 (dd, *J* = 13.6, 4.0 Hz, 1H), 3.46 (dd, *J* = 13.6, 4.0 Hz, 1.5H), 5.51 (dd, *J* = 10.4, 6.0 Hz, 1.5H), 5.58 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.19-7.39 (m, 14H), 7.42-7.47 (m,

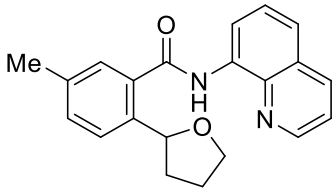
3H), 7.52-7.65 (m, 11H), 7.71 (d, J = 8.0 Hz, 3H), 7.77-7.81 (m, 1.5H), 8.12 (dd, J = 8.0, 1.6 Hz, 1.5H), 8.16 (dd, J = 8.0, 1.6 Hz, 1H), 8.45 (dd, J = 4.0, 1.2 Hz, 1.5H), 8.54 (dd, J = 4.0, 1.6 Hz, 1H), 8.84 (dd, J = 5.2, 4.0 Hz, 1.5H), 8.89 (dd, J = 6.4, 2.0 Hz, 1H), 9.89 (bs, 1H), 9.93 (bs, 1.5H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.46, 36.13, 36.31, 36.36, 38.88, 40.81, 43.22, 77.17, 77.59, 116.80, 116.85, 121.71, 121.75, 121.89, 122.37, 122.75, 125.46, 125.54, 125.98, 126.08, 126.98, 127.02, 127.16, 127.28, 127.41, 127.43, 127.50, 127.56, 127.89, 127.94, 128.24, 128.29, 129.63, 129.85, 130.28, 130.42, 132.14, 132.22, 133.30, 133.44, 133.76, 133.86, 134.66, 135.03, 135.13, 135.26, 135.62, 135.85, 136.25, 136.79, 137.36, 138.30, 148.35, 167.20, 167.29, 177.69, 178.76. IR (ATR): 3339 w, 3015 w, 2361 w, 1771 s, 1670 m, 1597 w, 1520 s, 1482 m, 1424 m, 1385 m, 1325 m, 1265 w, 1217 m, 1163 m, 1039 w, 964 w, 898 w, 859 w, 826 w, 791 m, 751 s, 696 w, 667 w. MS, m/z (relative intensity, %): 487 (30), 486 (M^+, 84), 325 (24), 287 (13), 279 (18), 183 (14), 182 (100), 181 (20), 173 (12), 171 (45), 167 (10), 147 (33), 145 (20), 144 (99), 142 (11), 141 (78), 115 (12). Exact Mass (EI): Calcd for $C_{32}H_{26}N_2O_3$ 486.1943, found 486.1946.

2-methyl-N-(quinolin-8-yl)-6-(tetrahydrofuran-2-yl)benzamide (6aa).



colorless oil. R_f 0.34 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.81-1.93 (m, 2H), 1.95-2.04 (m, 1H), 2.34-2.40 (m, 1H), 2.44 (s, 3H), 3.80-3.85 (m, 1H), 4.05 (dd, J = 14.8, 7.2 Hz, 1H), 5.08 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.41-7.44 (m, 2H), 7.54-7.62 (m, 2H), 8.16 (dd, J = 8.4, 2.0 Hz, 1H), 8.73 (dd, J = 4.4, 1.6 Hz, 1H), 8.97 (dd, J = 7.6, 1.6 Hz, 1H), 9.98 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.34, 26.27, 35.31, 68.82, 78.67, 116.58, 121.64, 121.90, 123.02, 127.30, 127.95, 129.12, 129.29, 134.28, 134.38, 135.87, 136.21, 138.44, 140.73, 148.30, 168.36. IR (ATR): 3343 w, 2976 w, 2871 w, 1672 m, 1596 w, 1578 w, 1519 s, 1481 s, 1424 m, 1385 m, 1325 m, 1263 m, 1127 w, 1063 m, 903 m, 826 m, 791 m, 754 s, 730 , 693 m, 667 m. MS, m/z (relative intensity, %): 332 (M^+, 7), 190 (13), 189 (100), 188 (45), 160 (14), 147 (66), 145 (13), 144 (17), 91 (12). Exact Mass (EI): Calcd for $C_{21}H_{20}N_2O_2$ 332.1525, found 332.1519.

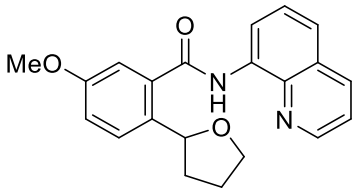
5-methyl-N-(quinolin-8-yl)-2-(tetrahydrofuran-2-yl)benzamide (6fa).



white solid. mp = 201 °C. R_f 0.40 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.79-1.88 (m, 1H), 1.91-2.01 (m, 2H), 2.41 (s, 3H), 2.48-2.56 (m, 1H), 3.87 (dd, J = 14.4, 7.6 Hz, 1H), 4.08 (dd, J

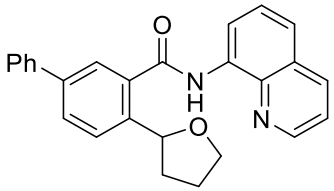
= 14.4, 7.6 Hz, 1H), 5.38 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.41-7.44 (m, 1H), 7.47 (s, 1H), 7.52-7.60 (m, 3H), 8.15 (d, *J* = 8.2 Hz, 1H), 8.77 (d, *J* = 4.0 Hz, 1H), 8.91 (d, *J* = 7.6 Hz, 1H), 10.26 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 20.97, 26.12, 34.96, 68.67, 78.13, 116.44, 121.58, 121.75, 126.27, 127.26, 127.43, 127.91, 131.26, 134.68, 134.99, 136.22, 136.87, 138.52, 139.46, 148.20, 167.99. IR (ATR): 3347 w, 2971 w, 2868 w, 2360 w, 1736 w, 1670 m, 1597 w, 1574 w, 1519 s, 1481 m, 1423 m, 1383 m, 1324 m, 1261 w, 1196 w, 1172 w, 1106 w, 1057 m, 940 w, 914 w, 825 m, 790 m, 754 m, 695 w. MS, m/z (relative intensity, %): 332 (M^+, 16), 190 (12), 189 (81), 188 (100), 171 (12), 161 (14), 160 (59), 159 (12), 147 (84), 145 (25), 144 (67), 143 (27), 130 (13), 129 (17), 128 (19), 119 (42), 117 (10), 116 (1), 115 (17), 105 (11), 91 (31), 89 (11), 71 (12), 65 (10). Exact Mass (EI): Calcd for $C_{21}H_{20}N_2O_2$ 332.1525, found 332.1522.

5-methoxy-N-(quinolin-8-yl)-2-(tetrahydrofuran-2-yl)benzamide (6ga).



white solid. mp = 101 °C. R_f 0.31 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.80-1.89 (m, 1H), 1.92-2.02 (m, 2H), 2.45-2.52 (m, 1H), 3.83-3.88 (m, 4H), 4.08 (dd, *J* = 14.4, 7.6 Hz, 1H), 5.28 (t, *J* = 7.2 Hz, 1H), 7.05 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.20 (d, *J* = 2.8 Hz, 1H), 7.44 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.53-7.61 (m, 3H), 8.16 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.77 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.91 (d, *J* = 6.8 Hz, 1H), 10.31 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 26.15, 34.83, 55.46, 68.59, 78.00, 112.46, 116.04, 116.55, 121.64, 121.89, 127.27, 127.84, 127.94, 134.04, 134.63, 136.25, 136.30, 138.55, 148.28, 158.47, 167.58. IR (ATR): 3344 w, 2946 w, 2868 w, 2361 w, 1671 m, 1606 w, 1574 w, 1520 s, 1481 m, 1423 m, 1383 m, 1324 m, 1285 m, 1262 m, 1239 w, 1220 w, 1173 w, 1133 w, 1100 w, 1055 m, 1042 m, 914 w, 825 m, 790 m, 755 m, 732 m, 695 w. MS, m/z (relative intensity, %): 348 (M^+, 30), 303 (12), 205 (70), 204 (100), 177 (17), 176 (85), 163 (53), 145 (13), 144 (88), 135 (35). Exact Mass (EI): Calcd for $C_{21}H_{20}N_2O_3$ 348.1474, found 348.1477.

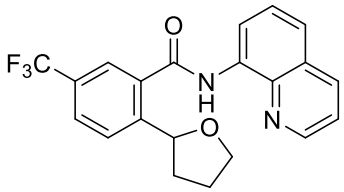
N-(quinolin-8-yl)-4-(tetrahydrofuran-2-yl)-[1,1'-biphenyl]-3-carboxamide (6ha).



white solid. mp = 73 °C. R_f 0.54 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.86-1.95 (m, 1H), 1.96- 2.04 (m, 2H), 2.54-2.60 (m, 1H), 3.91 (dd, *J* = 14.6, 7.2 Hz, 1H), 4.13 (dd, *J* = 14.6, 7.2 Hz, 1H), 5.39-5.43 (m, 1H), 7.34-7.38 (m, 1H), 7.40-7.47 (m, 3H), 7.53-7.65 (m, 4H), 7.75 (dd, *J* = 11.2, 8.0

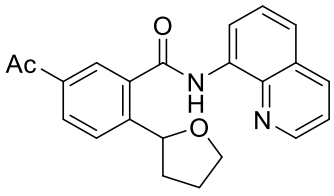
Hz, 2H), 7.89 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.75 (d, J = 4.0 Hz, 1H), 8.93-8.94 (m, 1H), 10.34 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 26.22, 35.06, 68.83, 78.13, 116.53, 121.64, 121.91, 125.52, 126.88, 127.05, 127.27, 127.57, 127.92, 128.84, 129.15, 134.63, 135.58, 136.25, 138.51, 140.02, 140.10, 141.56, 148.30, 167.8. IR (ATR): 3343 w, 2972 w, 2869 w, 1671 m, 1596 w, 1578 w, 1520 s, 1481 m, 1424 m, 1383 m, 1325 m, 1260 w, 1243 w, 1228 w, 1177 w, 1147 w, 1108 w, 1057 m, 1024 w, 912 w, 825 m, 790 m, 756 s, 697 m. MS, m/z (relative intensity, %): 394 (M^+, 16), 252 (11), 251 (67), 250 (100), 223 (16), 222 (70), 209 (49), 205 (14), 181 (24), 178 (14), 167 (13), 165 (13), 153 (14), 152 (29), 144 (49). Exact Mass (EI): Calcd for $C_{26}H_{22}N_2O_2$ 394.1681, found 394.1683.

N-(quinolin-8-yl)-2-(tetrahydrofuran-2-yl)-5-(trifluoromethyl)benzamide (6ia).



white solid. mp = 70 °C. R_f 0.40 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.80-1.89 (m, 1H), 1.96-2.03 (m, 2H), 2.54-2.62 (m, 1H), 3.92 (dd, J = 15.2, 8.4 Hz, 1H), 4.12 (dd, J = 15.2, 8.4 Hz, 1H), 5.40 (t, J = 7.6 Hz, 1H), 7.46 (dd, J = 8.0, 4.0 Hz, 1H), 7.58-7.63 (m, 2H), 7.76 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 8.19 (dd, J = 8.0, 1.6 Hz, 1H), 8.80 (dd, J = 4.0, 1.6 Hz, 1H), 8.88 (dd, J = 6.0, 2.4 Hz, 1H), 10.28 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 26.19, 35.10, 69.05, 77.95, 116.74, 121.81, 122.31, 123.77 (d, J = 3.9 Hz), 123.88 (q, J = 270.8 Hz), 127.00, 127.22, 127.26, 127.97, 129.48 (q, J = 32.4 Hz), 134.29, 135.47, 136.36, 138.51, 146.88, 148.48, 166.43. IR (ATR): 3340 w, 2973 w, 2872 w, 2361 w, 1734 w, 1674 m, 1617 w, 1596 w, 1578 w, 1522 s, 1482 m, 1424 m, 1385 m, 1324 s, 1248 m, 1231 w, 1167 m, 1123 s, 1077 m, 1059 s, 915 w, 826 m, 790 m, 756 m, 699 w. MS, m/z (relative intensity, %): 386 (M^+, 30), 341 (10), 330 (17), 243 (34), 342 (89), 215 (16), 214 (96), 202 (10), 201 (100), 197 (10), 173 (47), 172 (12), 171 (10), 145 (29), 144 (96), 130 (11), 129 (10), 116 (12), 115 (10). Exact Mass (EI): Calcd for $C_{21}H_{17}F_3N_2O_2$ 386.1242, found 386.1244.

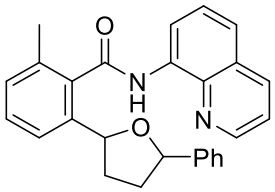
5-acetyl-N-(quinolin-8-yl)-2-(tetrahydrofuran-2-yl)benzamide (6ja).



white solid. mp = 125 °C. R_f 0.23 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.82-1.89 (m, 1H), 1.96-2.03 (m, 2H), 2.55- 2.63 (m, 1H), 2.66 (s, 3H), 3.93 (dd, J = 15.2, 6.8 Hz, 1H), 4.13 (dd, J = 15.2, 6.8 Hz, 1H), 5.41 (t, J = 7.2 Hz, 1H), 7.48 (dd, J = 8.0, 4.0 Hz, 1H), 7.58-7.63 (m, 2H), 7.81 (d, J = 8.4 Hz, 1H), 8.09 (dd, J = 8.0, 1.6 Hz, 1H), 8.20 (dd, J = 8.0, 1.6 Hz, 1H), 8.26 (d, J = 1.2 Hz, 1H),

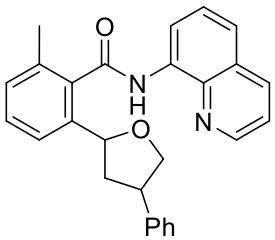
8.79 (dd, J = 4.0, 2.0 Hz, 1H), 8.89 (dd, J = 6.4, 2.0 Hz, 1H), 10.30 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 26.20, 26.65, 35.11, 69.04, 78.12, 116.65, 121.75, 122.18, 126.67, 126.84, 127.25, 127.96, 130.32, 134.37, 135.24, 135.89, 136.34, 138.48, 148.17, 148.40, 166.95, 197.03. IR (ATR): 3342 w, 2971 w, 2870 w, 2361 w, 1734 w, 1672 s, 1599 w, 1573 w, 1520 s, 1482 m, 1424 m, 1384 m, 1356 w, 1325 m, 1286 w, 1240 m, 1225 w, 1173 w, 1131 w, 1058 m, 972 w, 915 w, 826 m, 790 m, 756 m, 731 m, 690 w, 667 w. MS, m/z (relative intensity, %): 360 (M^+, 26), 217 (53), 216 (100), 189 (11), 188 (62), 175 (71), 173 (21), 171 (12), 147 (23), 145 (11), 144 (55), 129 (10), 115 (10). Exact Mass (EI): Calcd for $C_{22}H_{20}N_2O_3$ 360.1474, found 360.1477.

2-methyl-6-(5-phenyltetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (6ac).



dr = 1:1.3. white solid. mp = 54 °C. R_f 0.43 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 1.84-2.15 (m, 4.6H), 2.28- 2.36 (m, 1.3H), 2.40-2.56 (m, 10.2H), 4.88 (t, J = 7.6 Hz, 1.3H), 5.20-5.26 (m, 2.3H), 5.45 (dd, J = 8.8, 6.4 Hz, 1H), 7.12-7.42 (m, 16.1H), 7.51-7.64 (m, 6.9H), 8.14 (d, J = 8.4 Hz, 2.3H), 8.66-8.69 (m, 2.3H), 8.98 (dd, J = 7.2, 6.0 Hz, 2.3H), 10.04 (bs, 2.3H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.36, 19.41, 34.09, 34.88, 35.90, 36.17, 78.74, 79.51, 80.96, 81.66, 116.62, 121.62, 121.64, 121.95, 121.97, 123.17, 123.30, 125.38, 125.93, 126.90, 127.18, 127.26, 127.92, 128.03, 128.20,129.27, 129.31, 129.34, 129.42, 134.26, 134.31, 134.46, 135.92, 136.04, 136.17, 138.40, 139.92, 140.59, 142.45, 143.22, 148.29, 168.28, 168.41. IR (ATR): 3343 w, 2952 w, 2908 w,2874 w, 2361 w, 2340 w, 1675 m, 1587 w, 1519 s, 1482 s, 1423 m, 1385 m, 1325 m, 1263 w, 1127 w, 1057 m, 943 w, 899 w, 827 m, 788 m, 744 s, 699 s. MS, m/z (relative intensity, %): 408 (M^+, 7), 304 (10), 286 (14), 247 (15), 233 (41), 229 (18), 207 (18), 147 (34), 145 (14), 144 (100), 104 (14), 91 (17). Exact Mass (EI): Calcd for $C_{27}H_{24}N_2O_2$ 408.1838, found 408.1831.

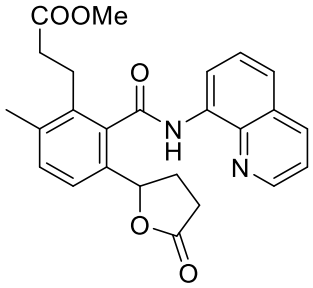
2-methyl-6-(4-phenyltetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (6ad).



dr = 1:1.1. white solid. mp = 68 °C. R_f 0.57 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.08-2.16 (m, 1.1H), 2.40-2.55 (m, 8.3H), 2.79-2.86 (m, 1.1H), 3.47-3.57 (m, 2.1H), 3.78 (t, J = 8.0 Hz, 1H), 3.97 (t, J = 8.4 Hz, 1.1H), 4.24 (t, J = 8.4 Hz, 1.1H), 4.42 (t, J = 8.0 Hz, 1H), 5.29 (dd, J = 10.8, 6.0

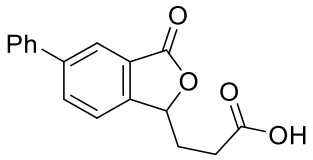
Hz, 1H), 5.46 (t, *J* = 6.0 Hz, 1H), 7.09-7.27 (m,10.5H), 7.36-7.41 (m, 4.2H), 7.47-7.60 (m, 6.3H), 8.12 (dd, *J* = 8.4, 1.6 Hz, 2.1H), 8.70 (m, 2.1H), 8.98 (ddd, *J* = 10.8, 7.6, 1.6 Hz, 2.1H), 10.01 (bs, 2.1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ:19.33, 19.35, 42.58, 44.20, 44.25, 46.00, 75.12, 75.26, 78.71, 80.02, 116.57, 116.61, 121.62, 121.94, 123.09, 123.14, 126.34, 126.47, 127.15, 127.19, 127.25, 127.91, 128.34, 128.42, 129.26, 129.34, 129.41,134.24, 134.29, 134.39, 134.52, 135.60, 135.89, 136.20, 138.36, 139.97, 140.71, 141.22, 141.49, 148.25, 148.27, 168.22, 168.32. IR (ATR): 3342 w, 3026 w, 2940 w, 2869 w, 1671 m, 1596 w, 1579 w, 1517 s, 1481 s, 1423 m, 1384 m, 1324 m, 1263 w, 1172 w, 1127 w, 1069 w, 1045 w, 990 w, 900 w, 826 m, 790 m, 754 s, 732 m, 698 s. MS, *m/z* (relative intensity, %): 408 (M^+, 7), 265 (33), 264 (43), 247 (16), 229 (15), 148 (10), 147 (100), 144 (17), 104 (15), 91 (21). Exact Mass (EI): Calcd for $C_{27}H_{24}N_2O_2$ 408.1838, found 408.1838.

methyl-3-(4-(5-oxotetrahydrofuran-2-yl)-3-(quinolin-8-ylcarbamoyl)-[1,1'-biphenyl]-2-yl)propanoate (7).



colorless oil. R_f 0.27 (Hexane/EtOAc = 1/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 2.17-2.27 (m, 1H), 2.41 (s, 3H), 2.50-2.72 (m, 5H), 3.06 (t, *J* = 8.4 Hz, 2H), 3.54 (s, 3H), 5.66 (dd, *J* = 8.8, 6.4 Hz, 1H), 7.34 (s, 3H), 7.47 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.60-7.64 (m, 2H), 8.20 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.75 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.89-8.93 (m, 1H), 10.01 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 19.34, 26.05, 29.16, 31.83, 34.33, 51.57, 79.19, 117.01, 121.84, 122.55, 123.26, 127.25, 127.97, 132.02, 133.78, 134.56, 135.51, 136.21, 136.40, 137.36, 138.36, 48.50, 167.47, 172.93, 176.87. IR (ATR): 3337 w, 2952 w, 1776 m, 1733 m, 1669 m, 1595 w, 1577 w, 1518 s, 1482 m, 1458 m, 1424 m, 1386 w, 1324 m, 1294 w, 1268 w, 1176 m, 1139 m, 1081 w, 1031 w, 985 w, 913 w, 866 w, 828 m, 809 w, 792 w, 755 m, 731 m. MS, m/z (relative intensity, %): 433 (15), 432 (M^+, 49), 401 (17), 373 (29), 289 (12), 288 (21), 257 (46), 246 (10), 186 (22), 173 (15), 171 (39), 145 (21), 144 (100), 143 (13). Exact Mass (EI): Calcd for $C_{25}H_{24}N_2O_5$ 432.1685, found 432.1688.

3-(3-oxo-5-phenyl-1,3-dihydroisobenzofuran-1-yl)propanoic acid (8).



pale yellow solid. mp = 175 °C. R_f 0.06 (Hexane/EtOAc = 3/1). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ:

1.99-2.08 (m, 1H), 2.47-2.59 (m, 2H), 2.63-2.72 (m, 1H), 5.62 (dd, J = 8.8, 4.8 Hz, 1H), 7.38-7.44 (m,1H), 7.47-7.51 (m, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.61-7.62 (m, 2H), 7.92 (dd, J = 8.0, 1.6 Hz, 1H), 8.11 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 29.03, 29.65, 79.78, 122.18, 124.1, 126.80, 127.24, 128.23, 129.10, 133.36, 139.28, 143.10, 147.75, 170.17, 177.15. IR (ATR): 3370 w, 2976 w, 1720 m, 1579 w, 1523 s, 1484 m, 1456 w, 1424 w, 1385 w, 1367 w, 1327 w, 1289 w, 1246 m, 1218 m, 1155 s, 1090 w, 1069 w, 1030 w, 1001 m, 913 w, 866 w, 850 w, 825 w, 789 w, 753 s, 699 w, 664 w. MS, m/z (relative intensity, %): 283 (14), 282 (M^+, 58), 236 (31), 223 (50), 222 (100), 210 (11), 209 (70), 182 (10), 181 (52), 153 (23), 152 (54), 151 (12). Exact Mass (EI): Calcd for $C_{17}H_{14}O_4$ 282.0892, found 282.0894.

3.5 References and Notes

(1) (a) Lim, Y.-G.; Kim, Y. H.; Kang, J.-B. *J. Chem. Soc. Chem. Commun*. **1994**, 2267. (b) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem. Int. Ed*. **2000**, *39*, 2267. (c) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc*. **2011**, *133*, 5221. (d) Kwakj, J.; Ohk, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc*. **2012**, *134*, 17778. (e) Schinkel, M.; Marek, I.; Ackermann, L. *Angew. Chem. Int. Ed*. **2013**, *52*, 3977. (f) Bair, J. S.; Schramm, Y.; Sergeev, A. G.; Clot, E.; Eisenstein, O.; Hatwig, J. F. *J. Am. Chem. Soc*. **2014**, *136*, 13098. (g) Xu, W.; Yoshikai, N. *Angew. Chem. Int. Ed*. **2016**, *55*, 12731. (h) Okumura, S.; Tnag, S.-W.; Saito, T.; Semba, K.; Saakki, S.; Nakao, Y. *J. Am. Chem. Soc*. **2016**, *138*, 14699.

(2) (a) Ebe, Y.; Nishimura, T. *J. Am. Chem. Soc*. **2015**, *137*, 5899. (b) Hatano, M.; Ebe, Y.; Nishimura, T.; Yorimitsu, H. *J. Am. Chem. Soc*. **2016**, *138*, 4010.

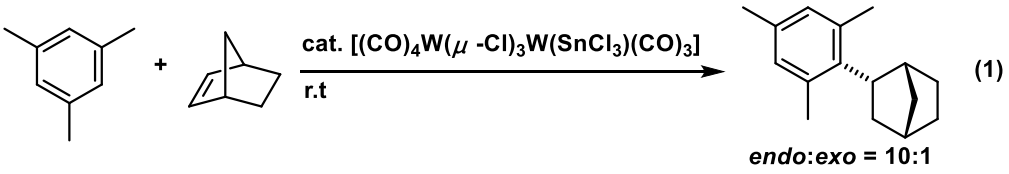
(3) Shibata, K.; Chatani, N. *Chem. Sci*. **2016**, *7*, 240.

(4) P. R. Jones, P. J. Desio. *J. Org. Chem.* **1965**, *30*, 4293.

Chapter 4
Rhodium-Catalyzed Alkylation of C-H Bonds with Norbornene

4.1 Introduction

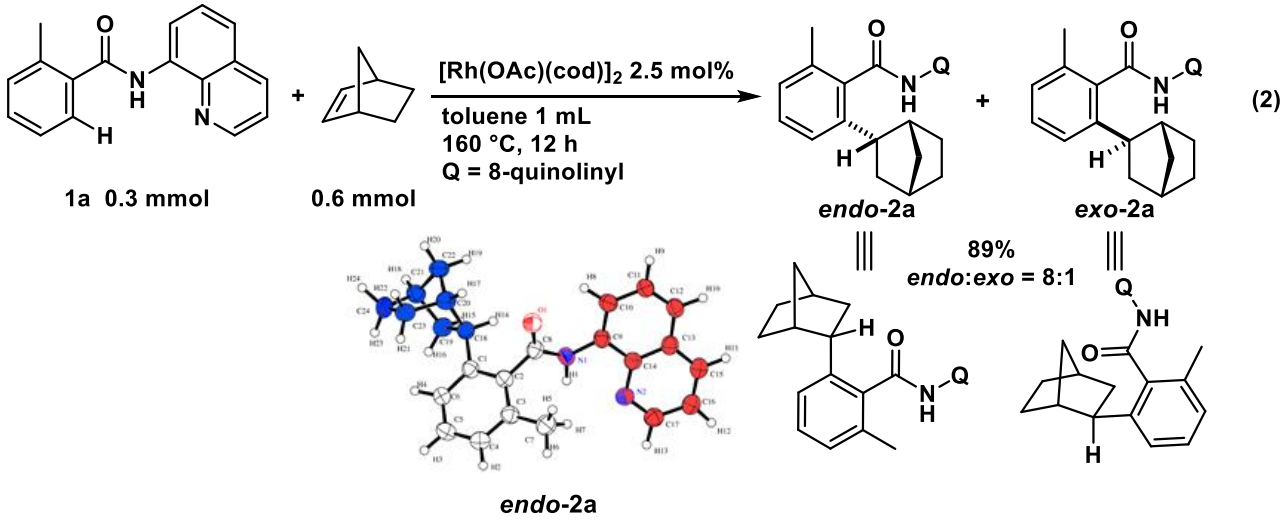
As mentioned in the general introduction, Chapter 1, Chapter 2, and Chapter 3, the chelation assisted regioselective alkylation of C(sp^2)-H bonds with various olefins has been accomplished. Focusing on bicycle[2.2.1]hept-2-ene (norbornene), which contains a highly reacttivity of C-C double bond derived from ring strain, a variety of alkylation reactions have been developed.[1] Except for one specific example, the alkylation of C-H bonds with norbornene proceeds in an *exo*-selective manner, irrespective of the reaction mechanism including hydrometalation, carbometalation or Friedel-Crafts type reactions.[2] Szymańska-Buzar and co-workers reported that the reaction of mesitylene with norbornene catalyzed by a tungsten(II) carbonyl complex gave the *endo* product as the major isomer (eq. 1).[3] In that report however, *exo* products were selectively produced when benzene, toluene, or *p*-xylene were used in place of mesitylene. Details of these reactions were not discussed.



Chapter 4 describes the unusual direct, rhodium catalyzed, *endo* selective alkylation of aromatic amides with norbornene by taking advantage of an *N,N*-bidentate directing chelation system. The addition of pivalic acid was found to be effective for improving *endo* selectivity.

4.2 Results and Discussion

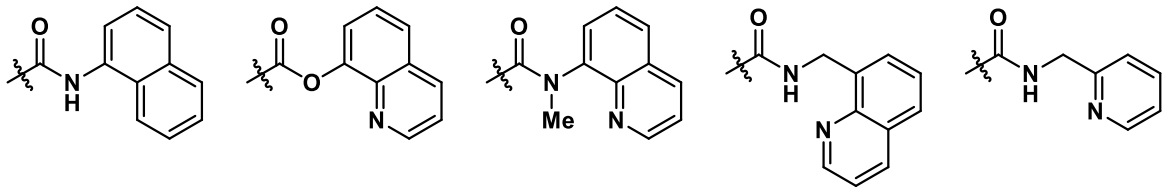
The reaction of aromatic amides **1a** (0.3 mmol) with nerbornene (0.6 mmol) in the presence of



$[Rh(OAc)(cod)]_2$ (0.0075 mmol) as the catalyst in toluene (1 mL) at 160 °C for 12 h gave alkylation product **2a** in 89% yield (eq. 2). Curiously, the major isomer was not the predicted *exo*-product ***exo*-2a**, but the *endo*-product ***endo*-2a** and the ratio was 1:8. Fortunately, the major product ***endo*-2a** was obtained in crystalline form and its structure was determined by X-ray crystallographic analysis.

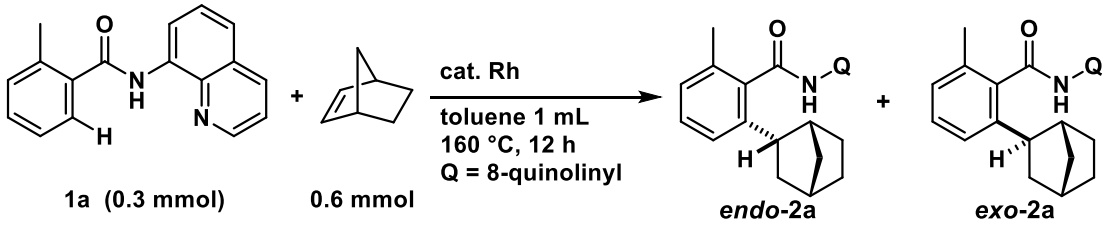
Motivated by an unexpected and unusual promising result, the effect of directing groups were examined (Figure 1). As is the case with chapter 1, 2 and 3, no reaction was occurred with the directing groups shown in Fig. 1. The presence of an 8-aminoquinoline directing group is crucial for the reaction to proceed.

Figure 1. Ineffective Directing Groups



First, we screened the rhodium catalysts (Table 1). When $[RhCl(cod)]_2$ was used as the catalyst in place of $[Rh(OAc)(cod)]_2$, only a trace amount of product **2a** was obtained (entry 2). However, addition of KOAc improved the reactivity (entry 3). This result implied that a acetate on the rhodium complex is important. After the several rhodium complexes examined, $[Rh(OAc)(cod)]_2$ showed the highest

Table 1. Screening of Reaction Conditions.

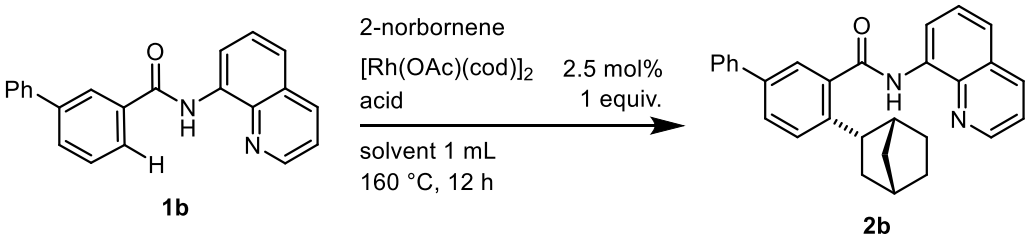


entry	catalyst (mol%)	T °C/ time	NMR yields 2a	NMR yields 1a	endo : exo
1	$[Rh(OAc)(cod)]_2$ (2.5)	160 °C/ 12 h	89%	3%	8 : 1
2	$[RhCl(cod)]_2$ (2.5)	160 °C/ 12 h	2%	93%	4.3 : 1
3	$[RhCl(cod)]_2$ (2.5) / KOAc 25 mol%	160 °C/ 12 h	49%	47%	7.2 : 1
4	$[RhCl(ethylene)]_2$ (2.5) / KOAc 25 mol%	160 °C/ 12 h	60%	48%	5.0 : 1
5	RhCl(IMes)(cod) (2.5) / KOAc 25 mol%	160 °C/ 12 h	63%	32%	6.1 : 1
6	RhCl(IPr)(cod) (2.5) / KOAc 25 mol%	160 °C/ 12 h	12%	77%	6.7 : 1
7	$[Rh(OAc)(cod)]_2$ (2.5)	160 °C/ 9 h	77%	10%	7.8 : 1
8	$[Rh(OAc)(cod)]_2$ (2.5)	140 °C/ 12 h	88%	10%	9.3 : 1
9	$[Rh(OAc)(cod)]_2$ (1.0)	160 °C/ 12 h	70%	35%	6.4 : 1

reactivity. A shorter reaction time or lower reaction temperature resulted in the reaction not being completed (entry 7 and 8). Although the product was obtained in moderate yield, a significant amount of starting amide was remained in the low catalyst loading condition (entry 9).

To improve the *endo* selectivity, the reaction conditions were examined in the reaction of m*eta*-phenyl-substituted benzamide **1b** (Table 2). When toluene was used as the solvent, the product **2b** was obtained in good yield (entry 1). The other solvent were also applicable to this reaction (entry 2-5). However, in the case of MTHP (4-methyltetrahydropyrane), almost no *endo*-*exo* selectivity was observed. The addition of sterically balky carboxylic acid improved the *endo* selectivity. When the pivalic acid was added, *endo*-selectivity was improved from 4.5:1 to 10.3:1 (entry 7). Other acids also showed a good effect. Finally, the addition of 3 equivalents of pivalic acid or 2,6-dimethylbenzoic acid gave the best results in terms of both yield and *endo*-selectivity. However, the more acid was added, the reaction mixture was become dirtier.

Table 2. Screening of Reaction Conditions to Improve *Endo*-Selectivitity.



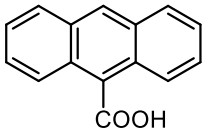
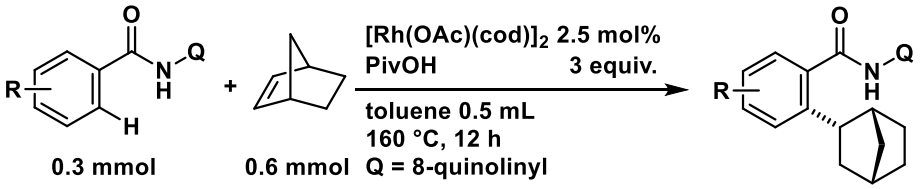
entry	solvent	acid	NMR yields 2b	NMR yields 1b	endo : exo
1	toluene	-	95%	0%	4.5 : 1
2	acetic acid	-	82%	14%	5.7 : 1
3	p-xylene	-	95%	2%	3.9 : 1
4	mesitylene	-	46%	43%	4.5 : 1
5	methylcyclohexane	-	87%	trace	4.9 : 1
6	4-methyltetrahydropyran	-	85%	1%	1.6 : 1
7	toluene	PivOH	87%	0%	10.3 : 1
8	toluene	C_6H_5COOH	81%	5%	11.0 : 1
9	toluene	2-MeC_6H_4COOH	89%	trace	10.7 : 1
10	toluene	2,6-$Me_2C_6H_3COOH$	98%	trace	13.4 : 1
11	toluene	2,4,6-$Me_3C_6H_2COOH$	87%	trace	8.3 : 1
12	toluene		84%	8%	13.1 : 1

Table 3 shows representative results of aromatic amides in the presence of 3 equivalents of pivalic acid or 2,6-dimethylbenzoic acid. Either the electron donating or the electron withdrawing group at

Table 3. The Rh-Catalyzed C-H Alkylatin of C(sp^2)-H Bonds



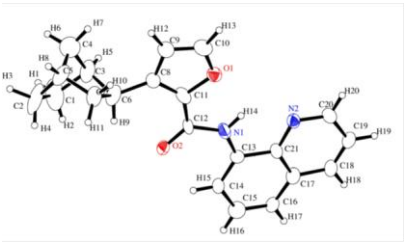
(*endo* : *exo*)

R = Me	1a	89% (8 : 1)[a]	R = NMe_2	1f	91% (7.5 : 1)[a,d]	R = OMe	1	96% (15 : 1)[a,c]
		59% (15.0 : 1)[h]			94% (9.8 : 1)[a]		i	80% (24.7 : 1)[f]
Ph	1c	61% (6.4 : 1)[a,b,d]	Ph	1b	93% (5 : 1)[a]	OAc	1	51% (10 : 1)[a,h]
		65% (6.7 : 1)[a,h]			79% (13.6 : 1)[e]		j	65% (16.3 : 1)[h]
F	1d	85% (6 : 1)[a,b]	Cl	1g	71% (3.3 : 1)[a,b,h]	Me	1	86% (10 : 1)[a]
		66% (19.0 : 1)[a,h]			65% (9.2 : 1)[a,h]		k	63% (14.3 : 1)
CF_3	1e	92% (7.2 : 1)[a,c]	CF_3	1h	95% (3 : 1)[a]	Br	1	84% (13.8 : 1)
		85% (8.2 : 1)[c]			88% (11.8 : 1)		l	
						Cl	1	77% (15.1 : 1)[h]
							m	
						F	1	95% (9 : 1)[a]
							n	93% (16.3 : 1)
						CF_3	1	85% (5 : 1)[a]
							o	87% (9.5 : 1)

1p 91% (6 : 1)[a]
67% (13.7 : 1)[a]

1q 61% (11.7 : 1)[a]

1r 56% (0 : 1)[a,g]
64% (0 : 1)[d,g,h]



1s 57% (1 : 1.1)[a,b,h]

1t 72% (1.2 : 1)[a,b]

[a]The reaction was carried out in the absence of pivalic acid. [b]The reaction was carried out for 24 h with catalyst (5.0 mol%). [c]The reaction was carried out for 24 h. [d]The reaction was carried out with catalyst (4.0 mol%). [e]2,6-dimethylbenzoic acid was used in place of pivalic acid. [f]The reaction was carried out with pivalic acid (1 equiv) in toluene (1 mL). [g]The reaction was carried out at 120 °C. [h]Isolated by GPC.

the *ortho* position of aromatic amides, the desired products were obtained in good yield (**1a**, **1c**-**1e**). In the case of meta-substituted aromatic amides, the less hindered C-H bonds were alkylated selectively, irrespective of the functional groups (**1b**, **1f**-**1h**). These results suggested that regioselectivity was mainly determined by steric hindrance. In this reaction, a variety of substituent groups such as OMe,

OAc, Br, Cl, F, and CF_3 groups were tolerated (**1i-1o**). In all cases, *endo*-selectivity could be increased by the addition of acid. In sharp contrast, when a furancarboxamide **1r** was used as the substrate, only the *exo*-product was generated regardless of the presence of acid. The structure of alkylated product was confirmed by X-ray crystallographic analysis. In the case of *N*-methyl pyrrolecarboxamide **1s** or thiophencarboxamide **1t**, both the *endo*-product and the *exo*-product were generated in the almost same ratio. The difference of *endo*-*exo*-selectivity between benamides derivatives and hetero aromatic amides derivatives is not clear.

The reaction mechanism is discussed in chapter 5.

4.3 Conclusion

In summary, we have reported the rhodium catalyzed an unusual *endo* selective *ortho* alkylation of C(sp^2)-H bonds in aromatic amides with norbornene by using a bidentate chelation system. The *endo* selectivity was improved by the addition of sterically bulky carboxylic acid. The success of this reaction relies on the use of an 8-aminoquinoline bidentate directing group.

4.4 Experimental Section

General Information.

^1H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer and Bruker AVANCE III spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. In some cases, some peaks in the ^{13}C NMR spectra cannot be analyzed because of overlapping peaks. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra and high resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

Materials.

Toluene (Kanto Chemical) was purified by passage through activated alumina using a GlassContour Solvent Dispensing System. Pivalic acid (CAS 75-98-9) was purchased from Nacalai Tesque. 8-Aminoquinoline (CAS 578-66-5), 2-norbornene (CAS 498-66-8), 2,6-dimethylbenzoic acid (CAS 632-46-2) were purchased from Tokyo Chemical Industry Co., Ltd. $[Rh(OAc)(cod)]_2$ was prepared prepared by chapter 1 procedure.

Synthesis of Starting Amides.

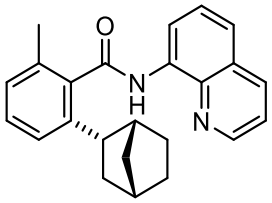
All amides bearing an 8-aminoquinoline moiety were prepared by reacting the corresponding acid or

the corresponding acid chlorides with 8-aminoquinoline. All starting amides were prepared by chapter 1 procedure. All spectrum data of starting amides are cited in original paper.[4]

Typical procedure for the Rh-catalyzed reaction of Aromatic Amides with norbornene.

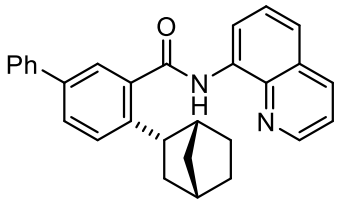
To an oven-dried 5 mL screw-capped vial, 3-fluoro-2-methyl-*N*-(quinolin-8-yl)benzamide (**1n**) (84 mg, 0.3 mmol), 2-norbornene (57 mg, 0.6 mmol), $[Rh(OAc)(cod)]_2$ (4.1 mg, 0.0075 mmol), pivalic acid (92 mg, 0.9 mmol) and toluene (0.5 mL) were added. The mixture was stirred for 12 h at 160 °C and then allowed to cool. The resulting mixture was filtered through a celite pad and the filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) and the organic phase concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 50/1) to afford the alkylation product **2n** (104.4 mg, 93%, *endo*:*exo*= 16.3:1) as a colorless oil.

2-(Bicyclo[2.2.1]heptan-2-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (2a).



59% yield. endo : exo = 15.0 : 1. R_f 0.11 (hexane/EtOAc = 10/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.19-1.70 (m, 7H), 1.93 (m,1H), 2.26 (brs, 1H), 2.42 (s, 3H), 2.45 (s, 1H), 3.46 (t, J= 5.5 Hz, 1 H), 7.22 (d, J= 4.1 Hz, 1H), 7.32 (m, 1H), 7.44 (dd, J= 4.1 Hz, 1H), 7.59 (m, 2H), 8.18 (dd, J= 8.2, 1.4 Hz, 1H), 8.73 (dd, J= 1.8 Hz, 1H), 8.99 (dd, J= 7.3, 1.4 Hz, 1H), 9.91 (brs, 1H), (exo) 2.22 (brs, 1H), 2.95 (t, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 19.67, 23.21, 29.95, 35.70, 37.80, 41.59, 43.54, 43.66, 116.98, 121.80, 122.04, 125.03, 127.59, 127.93, 128.18, 128.49, 134.59 (two overlapping peaks), 136.46, 138.70, 139.23, 140.15, 148.42 (exo) 28.56, 30.78, 36.71, 36.94, 40.29, 44.31, 116.87, 123.27, 125.54, 129.09; IR (neat) 3346 w, 2952 w, 2871 w, 1673 m, 1595 w, 1578 w, 1517 s, 1481 s, 1423 m, 1385 m, 1325 m, 1262 w, 1127 w, 898 w, 826 m, 790 m, 754 s, 689 w, 667 w; MS *m/z* (relative intensity, %) 213 (45), 212 (100), 183 (11), 171 (18), 147 (15), 146 (13), 145 (33), 144 (32), 143 (16), 129 (15), 128 (15), 117 (11), 116 (10), 115 (22), 105 (20), 91 (14), 67 (44); HRMS Calcd for $C_{24}H_{24}N_2O$: 356.1189; Found: 356.1889.

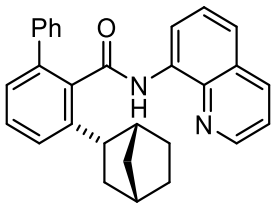
2-(Bicyclo[2.2.1]heptan-2-yl)-5-phenyl-*N*-(quinolin-8-yl)benzamide (2b).



79% yield. endo : exo = 13.6 : 1. R_f 0.11 (hexane/EtOAc = 10/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78

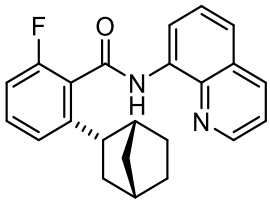
MHz) (endo) δ: 1.20-1.69 (m, 7H), 2.02 (tt, *J* = 11.9, 3.7 Hz, 1H), 2.30 (brs, 1H), 2.60 (s, 1H), 3.76 (dt, *J* = 11.4, 5.1 Hz, 1 H), 7.33-7.36 (m, 1H), 7.42-7.51 (m, 4H), 7.53-7.70 (m, 5H), 7.81 (d, *J* = 1.8 Hz, 1H), 8.17 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.74 (dd, *J* = 2.0 Hz, 1H), 8.97 (dd, *J* = 7.6, 1.1 Hz, 1H), 10.15 (brs, 1H), (exo) 1.87 (m, 1H), 2.56 (s, 1H), 3.30 (dd, *J* = 9.2, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz)(endo) δ: 23.30, 30.12, 35.58, 37.75, 41.33, 42.95, 43.16, 116.83, 121.81, 122.02, 125.90, 127.15, 127.57, 128.06, 128.14, 128.76, 129.00, 134.88, 136.47, 138.70, 138.84, 139.09, 140.32, 140.62, 148.44, 169.25 (exo) 28.74, 30.67, 36.88, 37.13, 40.35, 43.62, 126.86, 128.46, 128.64, 137.88; IR (neat) 3347 w, 2952 w, 2871 w, 1671 m, 1519 s, 1481 m, 1423 w, 1385 w, 1326 m, 1245 w, 1216 m, 906 w, 825 w, 752 s, 697 m, 668 w; MS *m/z* (relative intensity, %) 418 (9), 275 (26), 274 (100), 247 (10), 246 (49), 245 (28), 233 (17), 218 (32), 217 (10), 207 (17), 205 (11), 203 (11), 202 (13), 195 (11), 191 (12), 179 (18), 178 (37), 167 (28), 166 (12), 165 (26), 152 (21), 144 (58), 129 (13), 115 (10), 91 (19), 77 (12), 67 (48); HRMS Calcd for $C_{29}H_{26}N_2O$: 418.1606; Found: 418.2048.

2-(Bicyclo[2.2.1]heptan-2-yl)-6-phenyl-*N*-(quinolin-8-yl)benzamide (2c).



67% yield. endo : exo = 5.6 : 1. R_f 0.11 (hexane/EtOAc = 10/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 0.83-1.81 (m, 7H), 1.99 (t, *J* =12.1 Hz, 1H), 2.30 (brs, 1H), 2.52 (brs, 1H), 3.63 (s, 1H), 7.07 (dd, *J* = 6.7 Hz, 1 H), 7.19 (dd, *J* = 6.7 Hz, 2H), 7.25 (d, *J* =1.4 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.35 (dd, *J* = 4.1 Hz, 1H), 7.46 (m, 6H), 8.07 (d, *J* = 8.2 Hz, 1H), 8.61 (d, *J* = 4.1 Hz, 1H), 8.72 (d, *J* = 7.3 Hz, 1H), 9.60 (brs, 1H), (exo) 3.16 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 23.34, 30.02, 35.73, 37.85, 41.64, 43.47, 116.64, 121.57, 121.72, 126.69, 127.25, 127.41, 127.84, 127.91, 128.64, 128.87, 134.55, 136.20, 138.14, 138.53, 139.90, 140.74, 141.11, 148.10, 168.69; IR (neat) 3345 w, 2952 w, 2871 w, 2363 w, 1673 m, 1578 w, 1520 s, 1482 m, 1424 w, 1386 w, 1326 m, 1265 w, 1174 w, 1130 w, 896 w, 826 w, 791 w, 759 w, 700 w; MS *m/z* (relative intensity, %) 418 (17), 276 (11), 275 (62), 274 (100), 207 (12), 179 (10), 178 (15), 165 (11), 144 (13); HRMS Calcd for $C_{29}H_{26}N_2O$: 418.1606; Found: 418.2045.

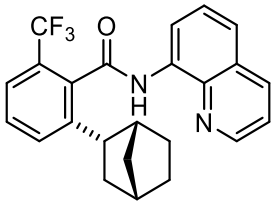
2-(Bicyclo[2.2.1]heptan-2-yl)-6-fluoro-*N*-(quinolin-8-yl)benzamide (2d).



66% yield. endo : exo = 19.0 : 1. R_f 0.17 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78

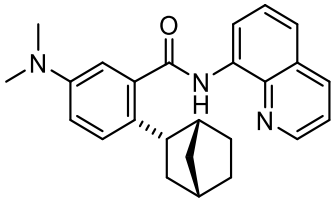
MHz) (endo) δ: 1.22-1.69 (m, 7H), 1.97 (tt, *J* = 12.0, 3.6 Hz, 1H), 2.29 (brs, 1H), 2.51 (brs, 1H), 3.56 (dt, *J* = 11.6, 5.0 Hz, 1 H), 7.01 (t, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.40 (dd, *J* = 14.2, 7.8 Hz, 1H), 7.46 (dd, *J* = 4.1 Hz, 1H), 7.60 (m, 2H), 8.19 (dd, *J* = 8.2 Hz, 1H), 8.77 (dd, *J* = 4.1 Hz, 1H), 8.97 (d, *J* = 7.3 Hz, 1H), 10.06 (brs, 1H), (exo) 3.08 (dd, *J* = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 21.21, 29.96, 35.46, 37.04, 37.69, 41.36, 42.98, 43.24, 43.44, 113.33 (d, *J* = 22 Hz), 117.07, 121.18, 122.27, 123.45 (d, *J* = 2 Hz), 126.78 (d, *J* = 17 Hz), 127.56, 128.15, 130.13 (d, *J* = 9 Hz), 134.51, 136.48, 138.60, 144.00, 148.48, 159.51 (d, *J* = 245 Hz); IR (neat) 3345 w, 2954 w, 2872 w, 1722 m, 1680 m, 1611 w, 1573 w, 1523 s, 1483 w, 1523 s, 1483 m, 1425 m, 1384 m, 1327 m, 1303 m, 1258 m, 1207 m, 1126 m, 1062 w, 1016 w, 900 w, 855 w, 826 w, 793 w, 768 m, 683 w; MS *m/z* (relative intensity, %) 361 (15), 360 (59), 217 (18), 216 (100), 188 (49), 187 (17), 175 (25), 149 (16), 144 (37); HRMS Calcd for $C_{23}H_{21}FN_2O$: 360.1638; Found: 360.1636.

2-(Bicyclo[2.2.1]heptan-2-yl)-6-trifluoromethyl-*N*-(quinolin-8-yl)benzamide (2e).



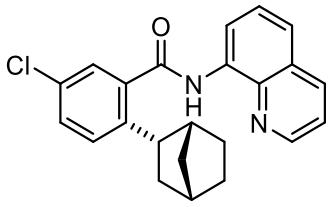
85% yield. endo : exo = 8.2 :1. R_f 0.11 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 0.92- 1.80 (m, 7H), 1.97 (m,1H), 2.29 (brs, 1H), 2.48 (m, 1H), [3.45, 3.61 (two triplet peaks, *J* = 5.5 Hz, 1 H)], 7.44 (dd, *J* = 4.1 Hz, 1H), 7.56 (m, 5H), 8.17 (dd, *J* = 8.2 Hz, 1H), 8.73 (dd, *J* = 3.7 Hz, 1H), 8.95 (dd, *J* = 6.9 Hz, 1H), 9.98 (brs, 1H), (exo) [3.00, 3.06 (two broad singlet, 1H)]; ^{13}C NMR ($CDCl_3$, 150.90 MHz) δ: 23.15, 23.25, 28.42, 29.84, 29.88, 35.87, 36.18, 36.88, 37.72, 37.91, 41.68, 41.80, 42.93, 43.41, 43.87, 44.23, 117.04, 117.12, 117.19, 121.35, 121.83, 122.31, 122.43, 123.17, 123.86, 124.99, 126.80, 127.39, 127.57, 127.67, 127.78, 128.00, 128.16, 128.58, 128.74, 128.80, 128.90, 128.43, 131.36, 131.66, 134.19, 134.35, 134.53, 136.44, 136.55, 137.68, 138.63, 142.22, 142.56, 148.45, 148.51, 165.96, 166.27; IR (neat) 3341 w, 2954 w, 2873 w, 1678 m, 1597 w, 1578 w, 1521 s, 1483 m, 1424 m, 1386 m, 1319 w, 1260 w, 1211 w, 1169 m, 1127 s, 1088 w, 899 w, 825 m, 791 m, 755 s, 668 w; MS *m/z* (relative intensity, %) 410 (10), 267 (10), 266 (45), 238 (14), 237 (10), 225 (28), 205 (13), 199 (23), 197 (11), 171 (13), 151 (20), 145 (19), 144 (100), 130 (11), 129 (12), 116 (11), 67 (46); HRMS Calcd for $C_{24}H_{21}F_3N_2O$:410.1606; Found: 410.1602.

2-(Bicyclo[2.2.1]heptan-2-yl)-5-dimethylamino -*N*-(quinolin-8-yl)benzamide (2f).



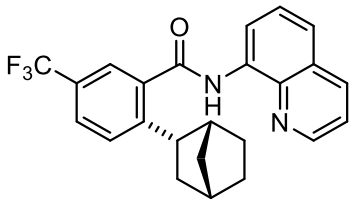
94% yield. endo : exo = 9.8 : 1. R_f 0.16 (hexane/EtOAc = 5/1). Yellow oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.15-1.69 (m, 7H), 1.95 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.25 (brs, 1H), 2.50 (brs, 1H), 2.96 (s, 6H), 3.61 (dt, *J* = 11.9, 5.0 Hz, 1 H), 6.84 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.95 (d, *J* = 2.8 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.43 (dd, *J* = 4.3 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.75 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.96 (dd, *J* = 7.6, 1.1 Hz, 1H), 10.10 (brs, 1H), (exo) 2.29 (brs, 1H), 2.47 (brs, 1H), 3.14 (dd, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 23.23, 30.16, 35.60, 37.70, 40.80, 41.16, 42.17, 43.11, 111.57, 113.71, 116.71, 121.73, 121.76, 127.56, 128.11, 128.66, 128.94, 135.03, 136.39, 138.73, 139.15, 148.32, 148.66, 169.98 (exo) 28.77, 30.66, 36.69, 37.03, 40.29, 42.97, 111.69, 114.23, 127.06; IR (neat) 3349 w, 2950 w, 2871 w, 2804 w, 1719 w, 1674 m, 1607 w, 1519 s, 1481 s, 1423 w, 1384 m, 1356 w, 1325 m, 1257 w, 1229 w, 1211 m, 1158 w, 1130 w, 1096 w, 1063 w, 973 w, 907 w, 824 m, 790 m, 753 s, 695 w; MS *m/z* (relative intensity, %) 386 (15), 385 (53), 242 (25), 241 (100), 214 (33), 213 (94), 212 (28), 186 (12), 185 (58), 174 (21), 172 (10), 169 (13), 162 (22), 153 (12), 146 (12), 134 (15); HRMS Calcd for $C_{29}H_{26}N_2O$: 385.2154; Found: 385.2149.

2-(Bicyclo[2.2.1]heptan-2-yl)-5-chloro -*N*-(quinolin-8-yl)benzamide (2g).



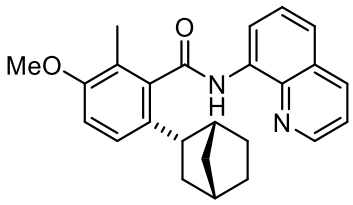
65% yield. endo : exo = 9.2 : 1. R_f 0.14 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.14-1.38 (m, 5H), 1.49-1.63 (m, 2H), 1.98 (tt, *J* = 12.2, 3.6 Hz, 1H), 2.28 (brs, 1H), 2.53 (brs, 1H), 3.68 (dt, *J* = 11.5, 5.3 Hz, 1 H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.40 (td, *J* = 9.0, 2.4 Hz, 1H), 7.47 (dd, *J* = 4.0 Hz, 1H), 7.57 (m, 1H), 8.18 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.78 (dd, *J* = 2.0 Hz, 1H), 8.91 (dd, *J* = 6.9, 1.8 Hz, 1H), 10.06 (brs, 1H), (exo) 1.82 (tt, *J* = 9.8, 2.6 Hz, 1H), 2.30 (brs, 1H), 2.48 (brs, 1H), 3.21 (dd, *J* = 9.2, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 23.16, 30.02, 35.56, 37.66, 41.24, 42.72, 43.00, 116.92, 121.90, 122.26, 127.26, 127.51, 128.13, 129.50, 129.72, 131.60, 134.58, 136.51, 138.64, 139.91, 140.15, 148.51, 167.69 (exo) 28.63, 30.58, 36.78, 37.10, 40.36, 42.82, 43.43, 127.86, 130.05; IR (neat) 3341 w, 2953 w, 2872 w, 1721 w, 1675 m, 1521 s, 1481 m, 1424 m, 1385 m, 1326 w, 1304 w, 1257 w, 1209 w, 1128 w, 1060 w, 908 w, 824 w, 790 m, 754 s, 687 w, 668 w; MS *m/z* (relative intensity, %) 376 (14), 234 (31), 233 (17), 232 (93), 206 (20), 205 (15), 204 (61), 203 (23), 193 (11), 191 (33), 179 (12), 176 (21), 169 (13), 167 (11), 165 (27), 163 (10), 149 (11), 145 (19), 144 (100), 141 (13), 137 (10), 130 (22), 129 (19), 128 (21), 127 (13), 125 (18), 117 (12), 116 (16), 115 (22), 102 (24), 101 (20), 89 (11), 67 (42); HRMS Calcd for $C_{23}H_{21}ClN_2O$: 376.1342; Found: 376.1345.

2-(Bicyclo[2.2.1]heptan-2-yl)-5-trifluoromethyl-*N*-(quinolin-8-yl)benzamide (2h).



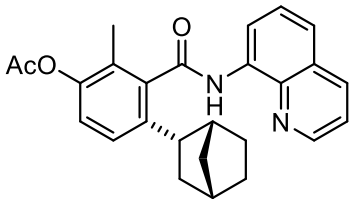
88% yield. endo : exo = 11.8 : 1. R_f 0.14 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.16-1.69 (m, 7H), 2.02 (tt, *J* = 12.1, 3.6 Hz, 1H), 2.30 (brs, 1H), 2.59 (brs, 1H), 3.76 (dt, *J* = 11.4, 4.9 Hz, 1 H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.46 (dd, *J* = 4.1 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.59 (m, 2H), 7.70 (d, *J* = 9.6 Hz, 1H), 7.81 (d, *J* = 14.2 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.77 (dd, *J* = 1.8 Hz, 1H), 8.93 (dd, *J* = 6.9, 1.8 Hz, 1H), 10.11 (brs, 1H), (exo) 1.86 (tt, *J* = 10.8, 2.6 Hz, 1H), 2.53 (brs, 1H), 3.29 (dd, *J* = 8.7, 6.4 Hz); ^{13}C NMR ($CDCl_3$, 150.90 MHz) (endo) δ: 23.22, 29.93, 35.58, 37.68, 41.32, 43.09, 43.35, 117.02, 121.93, 122.39, 124.23 (d, *J* = 3.5 Hz), 124.08 (q, *J* = 270.3 Hz), 126.18 (d, *J* = 3.5 Hz), 126.89, 127.51, 128.15, 128.33 (q, *J* = 32.7 Hz), 128.80, 134.51, 136.54, 138.65, 139.06, 145.94, 148.56, 167.87 (exo) 28.60, 29.84, 30.61, 35.47, 36.88, 37.14, 40.35, 42.78, 43.98, 116.95, 137.87; IR (neat) 3345 w, 2953 w, 2873 w, 2360 w, 1722 w, 1677 m, 1522 s, 1483 m, 1386 w, 1328 s, 1256 m, 1207 w, 1169 m, 1209 w, 1125 s, 1081 w, 907 w, 850 w, 825 m, 791 w, 755 m, 683 w; MS *m/z* (relative intensity, %) 410 (16), 266 (49), 238 (62), 237 (20), 225 (26), 210 (13), 199 (15), 171 (13), 151 (15), 145 (20), 144 (100), 130 (20), 129 (14), 128 (10), 116 (10), 67 (27); HRMS Calcd for $C_{24}H_{21}F_3N_2O$: 410.1606; Found: 410.1605.

2-(Bicyclo[2.2.1]heptan-2-yl)-5-methoxy-6-methyl-*N*-(quinolin-8-yl)benzamide (2i).



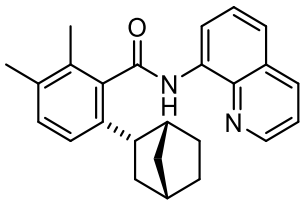
80% yield. endo : exo = 24.7 : 1. R_f 0.26 (hexane/EtOAc = 5/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.30-1.65 (m, 7H), 1.92 (brs, 1H), 2.35 (m, 5H), 3.39 (s, 1 H), 3.85 (s, 3H), 6.91 (d, *J* = 8.7 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.43 (dd, *J* = 4.1 Hz, 1H), 7.59 (m, 2H), 8.17 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.72 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.99 (dd, *J* = 7.3, 1.4 Hz, 1H), 9.90 (brs, 1H), (exo) 2.89 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 13.12, 23.14, 30.01, 35.85, 37.74, 41.48, 43.35, 55.77, 110.26, 166.92, 121.78, 122.01, 123.31, 125.88, 127.55, 128.15, 131.55, 134.55, 136.42, 138.66, 140.29, 148.39, 155.93, 169.18; IR (neat) 3345 w, 2952 w, 2871 w, 1722 w, 1676 m, 1580 w, 1520 s, 1481 s, 1425 m, 1385 m, 1325 m, 1304 m, 1267 m, 1209 m, 1156 w, 1129 m, 1096 m, 1044 w, 911 w, 853 w, 826 m, 791 m, 756 s, 687 w; MS *m/z* (relative intensity, %) 386 (17), 243 (35), 242 (100), 214 (12), 175 (9), 144 (9); HRMS Calcd for $C_{25}H_{26}N_2O_2$:386.1994; Found: 389.1992.

2-(Bicyclo[2.2.1]heptan-2-yl)-5-acetoxy-6-methyl-*N*-(quinolin-8-yl)benzamide(2j).



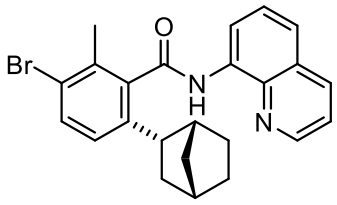
65% yield. endo : exo = 16.3 : 1. R_f 0.11 (hexane/EtOAc = 10/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.26-1.67 (m, 7H), 1.93 (s, 1H), 2.23 (brs, 3H), 2.25 (t, *J* = 4.1 Hz, 1H), 2.34 (s, 3H), 2.43 (m, 1H), 3.41 (brs, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.44 (dd, *J* = 4.1 Hz, 1H), 7.59 (m, 2H), 8.17 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.75 (dd, *J* = 2.0 Hz, 1H), 8.97 (dd, *J* = 7.3, 1.8 Hz, 1H), 9.94 (brs, 1H), (exo) 1.82 (tt, *J* = 9.8, 2.6 Hz, 1H), 2.30 (brs, 1H), 2.48 (brs, 1H), 3.21 (dd, *J* = 9.2, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 13.40, 20.99, 23.18, 29.94, 35.82, 37.74, 41.54, 43.52, 117.00, 121.86, 122.13, 122.21, 126.18, 126.87, 127.47, 128.13, 134.42, 136.39, 137.97, 138.64, 140.53, 147.48, 148.51, 168.30, 169.52; IR (neat) 3342 w, 2953 w, 2872 w, 1762 m, 1722 w, 1676 m, 1520 s, 1481 m, 1425 m, 1383 m, 1371 m, 1325 m, 1304 m, 1261 w, 1203 s, 1167 m, 1145 m, 1132 m, 1084 w, 1063 w, 1015 w, 899 w, 854 w, 827 m, 792 m, 754 s, 668 w; MS *m/z* (relative intensity, %) 414 (20), 271 (34), 270 (100), 229 (28), 228 (33), 161 (10), 144 (17); HRMS Calcd for $C_{26}H_{26}N_2O_2$: 414.1943; Found: 414.1943.

2-(Bicyclo[2.2.1]heptan-2-yl)-5,6-dimethyl-*N*-(quinolin-8-yl)benzamide (2k).



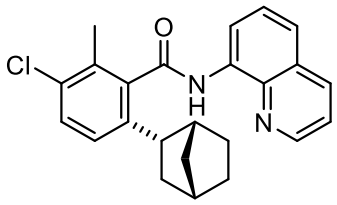
63% yield. endo : exo = 14.3 : 1. R_f 0.14 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.26-1.64 (m, 7H), 1.91 (s, 1H), 2.25-2.26 (m, 1H), 2.30 (s, 6H), 2.34-2.49 (m, 1H), [3.36, 3.44 (two broad singlet, 1 H)], 7.13 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 4.1 Hz, 1H), 7.60 (m, 2H), 8.17 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.72 (dd, *J* = 2.0 Hz, 1H), 9.01 (dd, *J* = 7.3, 1.4 Hz, 1H), [9.89, 9.91 (two broad singlet, 1H)], (exo) 2.90 (t, *J* = 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 16.79, 20.01, 23.23, 29.99, [35.43, 35.97 (two broad peaks)], 37.76, 41.60, [43.60, 43.80 (two broad peaks)], 116.94, 121.78, 121.96, [124.66, 125.14 (two broad peaks)], 127.60, 128.18, 129.92, 132.88, 134.53, 134.83, 136.44, 137.39, 138.69, 139.47, 148.38, 169.96; IR (neat) 3349 w, 2979 w, 2952 w, 2872 w, 1738 s, 1677 m, 1519 m, 1481 m, 1424 w, 1374 m, 1323 m, 1238 w, 1125 w, 1045 w, 938 w, 912 w, 826 w, 791 w, 759 w, 684 w; MS *m/z* (relative intensity, %) 227 (63), 226 (100), 185 (12), 161 (16), 160 (11), 159 (25), 145 (11), 144 (29), 129 (13), 128 (14), 119 (26), 116 (14), 115 (14), 91 (16), 67 (39); HRMS Calcd for $C_{25}H_{26}N_2O$: 370.2045; Found:370.2048.

2-(Bicyclo[2.2.1]heptan-2-yl)-5-bromo-6-methyl-*N*-(quinolin-8-yl)benzamide (2l).



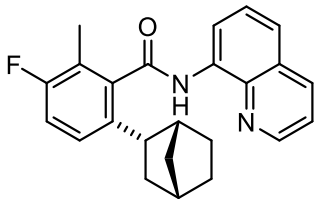
84% yield. endo : exo = 13.8 : 1. R_f 0.26 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.25-1.60 (m, 7H), 1.93 (t, *J* = 11.2 Hz, 1H), 2.26 (brs, 1H), 2.34-2.48 (m, 4H), [3.33, 3.41 (two broad singlet, 1H)], 7.16 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.45 (dd, *J* = 4.1 Hz, 1H), 7.59 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.62 (t, *J* =7.8 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.74 (dd, *J* = 1.8 Hz, 1H), 8.97 (dd, *J* = 6.9, 1.8 Hz, 1H), [9.87, 9.91 (two broad singlet, 1H)], (exo) 2.89 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 20.28, 23.01, 29.73, [35.33, 35.88 (two broad peaks)], 37.53, 37.66, 41.43, [43.07, 43.59 (two broad peaks)], 116.91, 121.76, 122.17, 123.03, [126.37, 126.80 (two broad peaks)], 127.38, 128.02, 132.39, 134.01, 136.36, 138.46, [139.36, 139.54 (two broad peaks)], 140.49, 148.39, 168.11; IR (neat) 3341 w, 2953 m, 2872 w, 1675 m, 1521 s, 1483 m, 1424 m, 1385 m, 1325 m, 1262 w, 1176 w, 1115 w, 903 w, 844 m, 827 m, 791 m, 757 m, 698 w; MS *m/z* (relative intensity, %) 436 (21), 434 (22), 293 (28), 292 (100), 291 (29), 290 (100), 249 (12), 225 (15), 223 (13), 194 (13), 144 (31), 116 (13), 115 (11); HRMS Calcd for $C_{24}H_{23}BrN_2O$: 434.0994; Found: 434.0995.

2-(Bicyclo[2.2.1]heptan-2-yl)-5-chloro-6-methyl-*N*-(quinolin-8-yl)benzamide (2m).



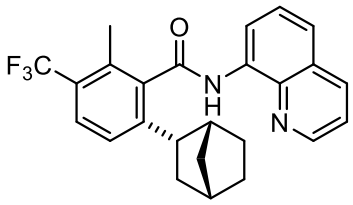
77% yield. endo : exo = 15.1 : 1. R_f 0.23 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.26-1.61 (m, 7H), 1.93 (brs, 1H), 2.26 (brs, 1H), 2.36-2.49 (m, 4H), [3.35,3.44 (two broad singlet, 1H)], 7.07 (d, *J* = 8.7 Hz, 1H), 7.45 (dd, *J* = 4.3 Hz, 1H), 7.59 (m, 3H), 8.18 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.74 (dd, *J* = 2.0 Hz, 1H), 8.96 (dd, *J* = 7.3, 1.8 Hz, 1H), [9.88, 9.91 (two broad singlet, 1H)], (exo) 2.87 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 17.39, 23.10, 29.84, [35.41, 35.50 (two broad peaks)], 37.72, 41.54, [43.21, 43.73 (two broad peaks)], 117.01, 121.85, 122.26, [126.13, 126.56 (two broad peaks)], 127.50, 128.14, 129.71, 132.57, [134.13, 134.25 (two broad peaks)], 136.46, 138.58, 138.73, 140.62, 148.48, 168.24; IR (neat) 3341 w, 2953 m, 2872 w, 2363 w, 1676 m, 1522 s, 1424 w, 1386 w, 1325 m, 1263 w, 1117 w, 904 w, 826 m, 792 w, 758 m, 688 w; MS *m/z* (relative intensity, %) 390 (22), 248 (34), 247 (28), 246 (100), 218 (10), 205 (13), 179 (15), 144 (21), 67 (11); HRMS Calcd for $C_{24}H_{23}ClN_2O$: 390.1499; Found: 390.1501.

2-(Bicyclo[2.2.1]heptan-2-yl)-5-fluoro-6-methyl-*N*-(quinolin-8-yl)benzamide (2n).



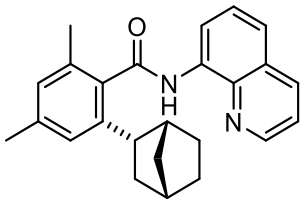
93% yield. endo : exo = 15.6 : 1. R_f 0.14 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.19-1.61 (m, 7H), 1.93 (t, *J* = 12.1 Hz, 1H), 2.26 (brs, 1H), 2.31-2.35 (m, 3H), 2.42 (brs, 1H), 3.41 (brs, 1H), 7.08 (t, *J* = 8.9 Hz, 1H), 7.17 (dd, *J* = 8.5, 5.3 Hz, 1H), 7.45 (dd, *J* = 4.1 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.75 (dd, *J* = 1.8 Hz, 1H), 8.97 (dd, *J* = 7.3, 1.8 Hz, 1H), 9.90 (brs, 1H), (exo) 2.90 (dd, *J* = 8.0, 6.6, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 11.77 (d, *J* = 4 Hz), 23.12, 29.94, 35.83, 37.74, 41.51, [43.19, 43.46 (two broad peaks)], 115.08 (d, *J* = 22 Hz), 117.06, 121.86 (d, *J* = 18 Hz), 121.89, 122.30, 126.41, 127.55, 128.19, 134.33, 135.58, 136.51, 138.65, 140.76, 159.56 (d, *J* = 243 Hz), 167.99 (exo) 28.51, 30.73, 36.61, 36.93, 40.37, 116.79; IR (neat) 3343 w, 2952 w, 2872 w, 2361 w, 1675 m, 1520 s, 1481 s, 1424 m, 1385 m, 1325 m, 1268 m, 1250 w, 1085 w, 915 w, 824 m, 753 s, 693 m, 667 w; MS *m/z* (relative intensity, %) 418 (19), 276 (11), 275 (62), 274 (100), 207 (12), 179 (10), 178 (15), 165 (11), 144 (13); HRMS Calcd for $C_{24}H_{23}FN_2O$: 374.1794; Found: 374.1790.

2-(Bicyclo[2.2.1]heptan-2-yl)-5-trifluoromethyl-6-methyl-*N*-(quinolin-8-yl)benzamide (2o).



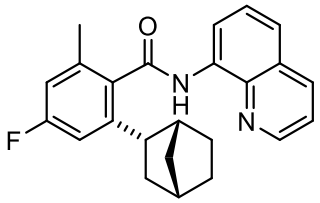
87% yield. endo : exo = 9.5 : 1. R_f 0.21 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.03-1.61 (m, 7H), 1.95 (m, 1H), 2.29 (brs, 1H), 2.36-2.52 (m, 4H), 3.46 (two triplet peaks, *J* = 5.4 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.46 (dd, *J* = 4.3 Hz, 1H), 7.64 (m, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.75 (dd, *J* = 1.8 Hz, 1H), 8.98 (dd, *J* = 6.9, 1.8 Hz, 1H), 8.98 (dd, *J* = 1.8 Hz, 1H), 9.92 (two singlet peaks, 1H), (exo) 2.95 (brs, 1H); ^{13}C NMR ($CDCl_3$, 150.90 MHz) δ: 16.24, 23.25, 23.23, 28.45, 28.85, 35.39, 36.02, 37.70, 37.86, 41.64, 41.74, 43.33, 43.54, 43.85, 44.22, 117.06, 117.17, 121.91, 122.40, 122.51, 123.71, 124.94, 125.39, 125.53, 126.00, 127.24, 127.34, 127.44, 127.52, 127.67, 127.83, 127.99, 128.21, 128.57, 128.72, 133.47, 133.64, 134.10, 134.22, 134.37, 136.53, 137.68, 138.64, 141.28, 144.38, 144.56, 148.55, 168.11, 168.29; IR (neat) 3341 w, 2954 w, 2873 w, 1676 m, 1597 w, 1521 s, 1483 m, 1424 m, 1386 m, 1320 s, 1261 w, 1212 m, 1173 m, 1121 s, 1009 w, 907 w, 825 m, 791 m, 754 s, 667 w; MS *m/z* (relative intensity, %) 425 (10), 424 (35), 281 (29), 280 (100), 252 (13), 239 (14), 213 (18), 144 (22), 67 (10); HRMS Calcd for $C_{25}H_{23}F_3N_2O$: 424.1762; Found: 424.1761.

2-(Bicyclo[2.2.1]heptan-2-yl)-4,6-dimethyl-*N*-(quinolin-8-yl)benzamide (2p).



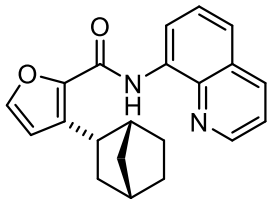
67% yield. endo : exo = 13.7 : 1. R_f 0.19 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.24-1.63 (m, 7H), 1.91 (tt, *J* = 12.1, 3.7 Hz, 1H), 2.25 (brs, 1H), 2.36-2.45 (m, 7H), 3.44 (t, *J* = 5.7 Hz, 1H), 6.93 (d, *J* = 11.9 Hz, 1H), 7.02 (d, *J* = 10.1 Hz, 1H), 7.43 (dd, *J* = 4.1 Hz, 1H), 7.55 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.61 (t, *J* = 7.8 HZ, 1H), 8.17 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.72 (dd, *J* = 2.0 Hz, 1H), 8.98 (dd, *J* = 7.3, 1.4 Hz, 1H), 9.89 (brs, 1H), (exo) 2.94 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 19.60, 21.76, 23.21, 30.03, 35.56, 37.77, 41.55, 43.42, 43.58, 116.88, 121.77, 121.93, 125.64, 127.59, 128.17, 128.65, 134.51, 134.70, 136.42, 136.65, 138.09, 138.70, 140.09, 148.38, 169.75; IR (neat) 3345 w, 2953 m, 2871 w, 1674 m, 1521 s, 1482 m, 1424 m, 1384 m, 1325 m, 1252 w, 1177 w, 1110 w, 1076 w, 916 w, 890 w, 844 m, 828 m, 791 m, 758 m, 699 w; MS *m/z* (relative intensity, %) 370 (24), 227 (86), 226 (100), 159 (13), 144 (14); HRMS Calcd for $C_{25}H_{26}N_2O$: 370.2045; Found:370.2049.

2-(Bicyclo[2.2.1]heptan-2-yl)-6-dimethyl-4-fluoro-*N*-(quinolin-8-yl)benzamide (2q).



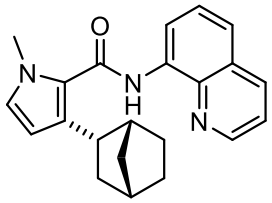
61% yield. endo : exo = 11.7 : 1. R_f 0.17 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.01-1.55 (m, 5H), 1.49-1.55 (m, 1H), 1.86 (t, *J* = 11.9 Hz, 1H), 2.19 (brs, 1H), 2.34-2.39 (m, 4H), 3.38 (d, *J* = 10.5 Hz, 1H), 6.76 (d, *J* = 9.2 Hz, 1H), 6.83 (d, *J* = 10.5 Hz, 1H), 7.38 (dd, *J* = 4.1 Hz, 1H), 7.53 (m, 1H), 8.11 (d, *J* = 8.2 HZ, 1H), 8.67 (t, *J* = 2.1 Hz, 1H), 8.89 (d, *J* = 7.3 Hz, 1H), 9.81 (brs, 1H), (exo) 2.88 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (endo) δ: 19.78, 23.17, 29.88, 35.79, 37.69, 41.5, [43.50, 43.69 (two broad peaks)], 112.02 (d, *J* = 22 Hz), 144.59 (d, *J* = 21 Hz), 117.00, 121.87, 122.21, 127.57, 128.18, 134.43, 135.31 (d, *J* = 3 Hz), 136.51, 137.32 (d, *J* = 9 Hz), 138.64, 143.49 (d, *J* = 8 Hz), 148.51, 162.65 (d, *J* =245 Hz), 168.73 (exo) 25.65, 26.12, 28.43, 30.69, 36.71, 36.89, 40.36, 44.27; IR (neat) 3347 w, 2953 w, 2872 w, 1598 m, 1521 s, 1483 m, 1424 w, 1385 w, 1325 m, 1301 w, 1261 w, 1141 w, 983 w, 849 w, 826 w, 792 w, 759 w, 668 m; MS *m/z* (relative intensity, %) 374 (21), 231 (53), 230 (100), 189 (10), 163 (17), 146 (10), 144 (14), 67 (10); HRMS Calcd for $C_{24}H_{23}FN_2O$: 374.1794; Found:374.1792.

3-(Bicyclo[2.2.1]heptan-2-yl)-*N*-(quinolin-8-yl)furan-2-carboxamide (2r).



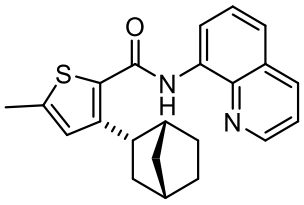
64% yield. endo : exo = 0 : 1. R_f 0.11 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (exo) δ: 1.26-1.39 (m, 2H), 1.49-1.66 (m, 5H), 1.97 (m, 1H), 2.33 (brs, 1H), 2.36 (brs, 1H), 3.59 (dd, *J* = 8.7, 5.5 Hz, 1H), 6.53 (s, 1H), 7.51 (m, 4H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.88 (m, 2H), 10.72 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) (exo) δ: 28.79, 30.42, 36.83, 36.99, 37.74, 39.58, 43.40, 112.30, 116.54, 121.54, 121.73, 127.52, 128.19, 134.70, 136.44, 138.89, 139.53, 141.63, 143.05, 148.42, 157.82; IR (neat) 3341 w, 2952 w, 2872 w, 1668 m, 1591 w, 1576 w, 1525 s, 1483 m, 1456 w, 1425 w, 1384 w, 1328 m, 1261 w, 1252 w, 1175 w, 1071 w, 873 m, 844 m, 826 w, 750 m, 697 w; MS *m/z* (relative intensity, %) 333 (11), 332 (43), 287 (14), 265 (13), 209 (41), 188 (14), 172 (13), 171 (100), 160 (45), 159 (23), 145 (16), 144 (75), 130 (11), 129 (12), 128 (11), 121 (34), 117 (13), 116 (16), 109 (12), 95 (11), 91 (23), 81 (12), 79 (18), 77 (19), 67 (20), 65 (19); HRMS Calcd for $C_{21}H_{20}N_2O_2$: 332.1525; Found:332.1527.

3-(Bicyclo[2.2.1]heptan-2-yl)-1-methyl-*N*-(quinolin-8-yl)-1*H*-pyrrole-2-carboxamide (2s).



57% yield. endo : exo = 1 : 1.1. R_f 0.26 (hexane/EtOAc = 5/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.17-1.71 (m, 7H), 2.02 (m, 1H), 2.30 (d, *J* = 14.2 Hz, 1H), 2.79 (brs, 1H), 3.75 (m, 1H), 3.93 (d, *J* = 10.1 Hz, 1H), 6.11 (dd, *J* = 11.2, 2.5 Hz, 1H), 6.70 (dd, *J* = 17.2, 2.5 Hz, 1H), 7.43 (dd, *J* = 4.1 Hz, 1H), 7.49 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.79 (td, *J* = 3.0, 1.2 Hz, 1H), 8.88 (m, 1H), 10.25 (brs, 1H), (exo) 2.53 (d, *J* =3.2 Hz, 1H), 3.26 (dd, *J* = 8.7, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 23.40, 28.94, 30.40, 36.89, 37.13, 37.30, 37.56, 38.86, 40.11, 40.84, 40.90, 43.13, 43.89, 106.26, 108.01, 116.30, 116.39, 121.18, 121.68, 121.70, 123.73, 125.07, 126.78, 126.93, 127.60, 127.62, 128.15, 130.77, 135.24, 135.45, 136.33, 138.87, 148.02, 148.06, 161.08, 161.14.; IR (neat) 3359 w, 2951 w, 2871 w, 2361 w, 1722 w, 1652 m, 1521 s, 1482 m, 1423 m, 1382 m, 1326 m, 1303 m, 1259 m, 1207 m, 1123 m, 1062 w, 1016 w, 884 w, 855 w, 824 w, 790 w, 753 m, 665 w; MS *m/z* (relative intensity, %) 354 (21), 202 (13), 201 (10), 174 (100), 171 (12), 122 (18), 94 (14); HRMS Calcd for $C_{22}H_{23}N_3O$: 345.1845; Found:345.1843.

3-(Bicyclo[2.2.1]heptan-2-yl)-5-methyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide (2t).



72% yield. endo : exo = 1.2 : 1. R_f 0.19 (hexane/EtOAc = 20/1). Colorless oil. ^{1}H NMR ($CDCl_3$, 399.78 MHz) (endo) δ: 1.20-1.72 (m, 7H), 2.04 (tt, *J* = 12.1, 3.9 Hz, 1H), 2.35 (brs, 1H), 2.47 (brs, 1H), 2.53 (s, 3H), 3.53 (dd, *J* = 9.2, 5.5 Hz, 1H), 6.81 (d, *J* = 11.9 Hz, 1H), 7.45 (dd, *J* = 4.3 Hz, 1H), 7,50 (d, *J* = 8.2 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.82 (d, *J* = 4.1 Hz, 1H), 8.84 (d, *J* =7.3 Hz, 1H), 10.37 (brs, 1H), (exo) 2.17 (m, 1H), 2.51 (s, 3H), 2.77 (brs, 1H), 3.53 (dd, *J* = 9.2, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 15.88, 23.82, 28.85, 30.24, 30.68, 36.77, 36.93, 37.39, 37.81, 40.52, 40.86, 41.00, 42.12, 43.24, 43.29, 116.57, 116.65, 121.46, 121.73, 127.20, 127.62, 128.11, 128.51, 129.53, 131.05, 135.08, 135.14, 136.45, 138.77, 142.01, 142.90, 148.19, 148.26, 149.09, 152.40, 161.47; IR (neat) 3356 w, 2952 w, 2871 w, 1643 w, 1521 s, 1483 m, 1445 w, 1424 m, 1383 m, 1327 m, 1259 w, 1221 w, 1176 w, 1107 w, 876 w, 825 m, 790 m, 756 m, 698 w, 664 w; MS *m/z* (relative intensity, %) 362 (22), 219 (32), 218 (100), 190 (22), 177 (12), 171 (30), 151 (10), 144 (10), 111 (14); HRMS Calcd for $C_{22}H_{22}N_2OS$: 362.1453; Found:362.1454.

4.5 References and Notes

(1) Tanaka, K., Tanaka, M. & Suemune, H. *Tetrahedron Lett.* **2005**, *46*, 6053. and references cited therein.

(2) Representative examples. (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpm.* **1995**, *68*, 62. (b) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*. 6616. (c) Aufdenblatten, R.; Diezi, S.; Togni, A. *Monatsh. Chem.* **2000**, *131*, 1345. (d) Jun, C-H.; Moon, C. W.; Hong, J-B.; Lim, S-G.; Chung, K-Y.; Kim, Y-H. *Chem. Eur. J.* **2002**, *8*, 485. (e) Dorta, R.; Togni, A. *Chem. Commun.* **2003**, 760. (f) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*. 14542. (g) Tsuchikama, K.; Kasagawa, M.; Hashimoto, Y.; Endo, K.; Shibata, T. *J. Org. Chem.* **2008**, *693*, 3939. (h) Yamamoto, Y.; Itonaga, K. *Chem. Eur. J.* **2008**, *14*, 10705. (i) Wentzel, M. T.; Reddy, V. J.; Hyster, T. K.; Douglas, C. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6121. (j) Watson, A. J. A.; Maxwell, A. C.; Williams, M. J. *Org. Lett.* **2010**, *12*, 3856. (k) Bowring, M. A.; Bergman, R. G.; Tilley, T. D. *Organometallics* **2011**, *30*, 1295. (l) Oyamada, J.; Hou, Zhaomin. *Angew. Chem. Int. Ed.* **2012**, *51*, 12828. (m) Hartwig, J. F.; Sevov, C. S. *J. Am. Chem. Soc.* **2013**, *135*. 2116. (n) Motti, E.; Ca, N. D.; Xu, D.; Armani, S.; Aresta, B. M.; Catellani, M. *Tetrahedron* **2013**, *69*. 4421. (o) Liu, S.; Zhou, J. S. *Chem. Commun* **2013**, *49*, 11758. (p) Tan, B-H.; Yoshikai, N. *Org. Lett.* **2014**, *16*, 3392. (q) Sunada, Y.; Soejima, H.; Nagashima, H. *Organometallics*, **2014**, *33*, 5936. Bair, J. S.; Schramm, Y.; Sergeev, A. G.; Clot, E.; Eisenstein, O.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 13098. (r) Hu, X.; Martin, D.; Melaimi, M.; Bertrand, G. *J. Am. Chem. Soc.* **2014**, *136*, 13594. (s) Shirai, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 9894. (t) Hu, F.; Patel, M.; Luo, F.; Flach, C.; Mendelsohn, R.; Garfunkel, E.; He, H.; Szostak, M. *J. Am. Chem. Soc.* **2015**, *137*, 14473.

(3) Malinowska, A., Czeluśniak, I., Górski, M. & Szymańska-Buzar, T. *Tetrahedron Lett.* **2005**, *46*, 1427.
(4) Shibata, K.; Natsui, S.; Tobisu, M.; Fukumoto, Y.; Chatani, N. submitted for publication.

Chapter 5
The Reaction Mechanism of Rhodium-Catalyzed Alkylation of C-H Bonds

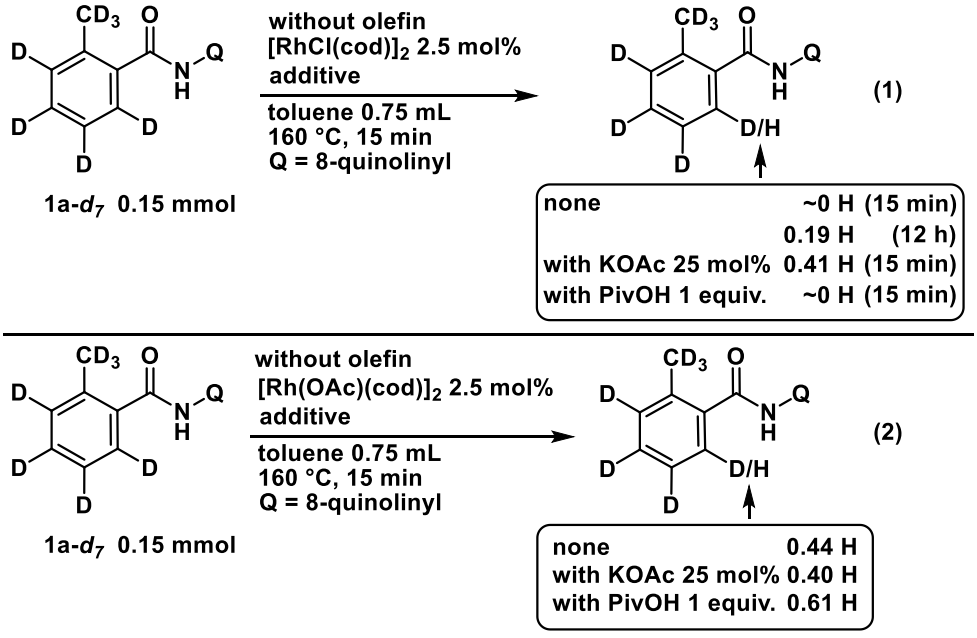
5.1 Introduction

We developed a series of alkylation reactions as described in chapters 1, 2, 3 and 4. In this chapter, the reaction mechanism of these reactions is discussed. In these reactions, the commonly-accepted hydrometalation or carbometalation in catalytic hydroarylation reactions were not involved as the key step. Rather, we propose a carbene mechanism.

5.2 Results and Discussion

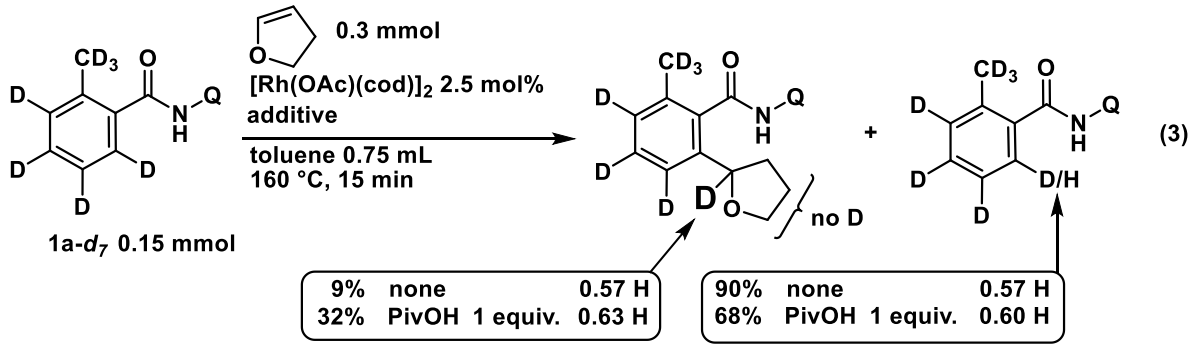
In order to collect information regarding the reaction mechanism, deuterium labeling experiments using **1-*d*$_7$** were carried out in the absence of a coupling partner (Scheme 1). When $[RhCl(cod)]_2$ was used as the catalyst, no H/D exchange at the *ortho*-position of aromatic amide was detected after 15 min (eq 1 in Scheme 1). Even after 12 hours, H/D exchange was very slow (only 0.19H). In contrast, in the presence of 25 mol% of KOAc, a significant amount of H/D exchange had occurred even after 15 min (0.41H). Next, the base was replaced with 1 equivalent of pivalic acid. In this case, no H/D exchange was observed after 15 min. In sharp contrast, the presence of an additive had no effect on H/D exchange when $[Rh(OAc)(cod)]_2$ was used as the catalyst (eq 2 in Scheme 1). When pivalic acid was used as the additive, H/D exchange occurred and was slightly higher than the previous other case due to the fact that pivalic acid itself functions as a proton source. These results indicate that the C-H bond cleavage step is reversible and tha the role of additive is to generate

Scheme 1. Deuterium Labeling Experiments without the olefin.

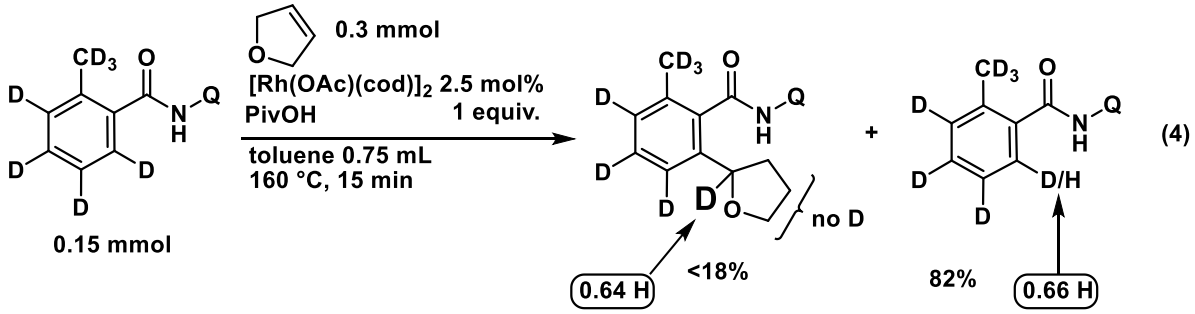


$[Rh(OAc)(cod)]_2$. The proton source is assumed to be the NH group of the amide or trace amounts of water contained in the reaction system.

Next, deuterium labeling experiments were took place with 2,3-dihydrofuran (eq 3.). After 15 min, the alkylated product was obtained in 9% yield. Surprisingly, deuterium was incorporated into only at the α-position of the THF ring oxygen atom of the product (0.57H). In other words, both carbon and deuterium at the *ortho*-position of the starting amide were bound to the same position on the THF ring of the product. No deuterium was observed at other positions. This result indicated that hydrometalation or carbometalation, which are common mechanism in catalytic hydroarylation reactions reported thus far are not involved in this reaction, instead, the generation of a carbene is probably involved. The H/D exchange at the *ortho*-position of recovered amide was also detected (0.57H or 0.57H). Almost same result was obtained when 1 equivalent of pivalic acid was added to this reaction.

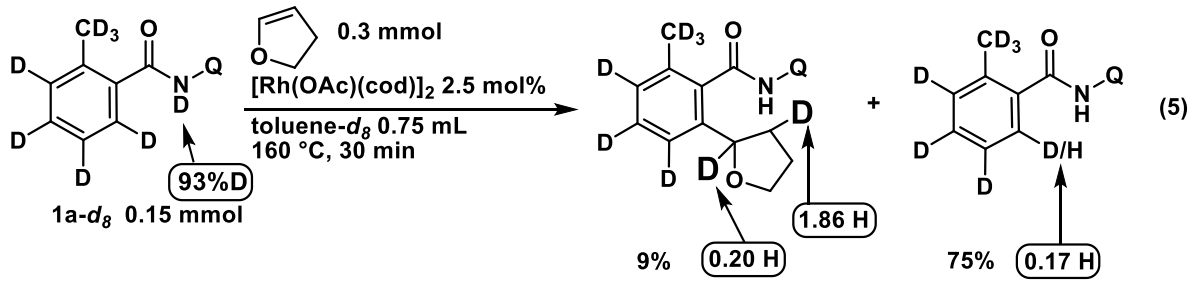


A similar result was also observed even when 2,5-dihydrofuran was used instead of 2,3-dihydrofuran (eq 4). Deuterium was incorporated only at the α-position of oxygen atom of the product (0.64H). To exclude the possibility that H/D exchange at the α-position of the THF ring after the formation of product, the reaction of product with CD_3COOD was conducted at 160 °C in the presence of a rhodium complex. But, no H/D exchange was detected (Scheme being not shown). This means that the deuterium was incorporated to the alkylated product only through the catalytic reaction condition.



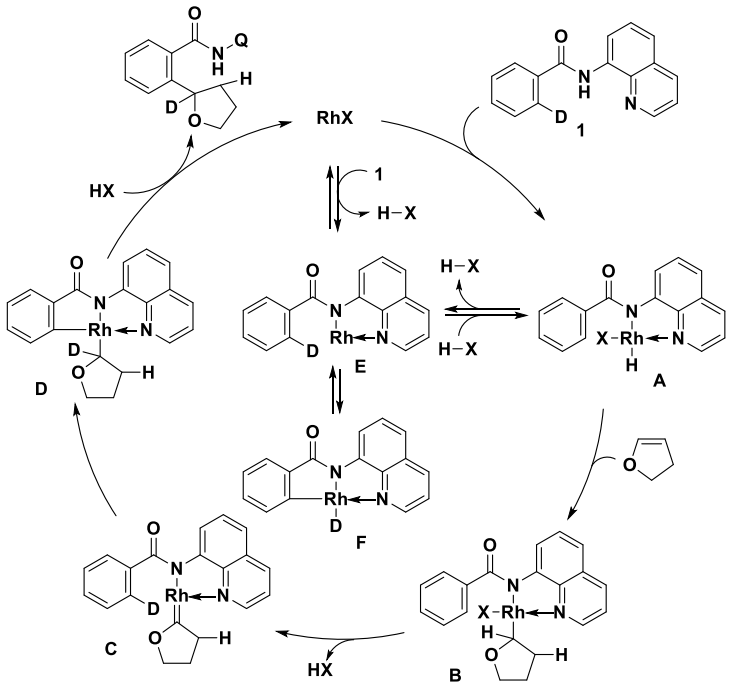
In these reactions (eq 3 and 4), the rate of deuterium incorporation at the α-position of the product THF ring decreased due to rapid H/D exchange between the deuterium at the *ortho*-position of amide and amide NH. Therefore, in order to prevent the deuteration ratio from decreasing, the

reaction was carried out in toluene-d_8 using the **1-d_8** amide with a deuterium atom also on the amide nitrogen in place of **1-d_7** amide (eq 5). As a result, as expected, more deuterium (80 %, 0.20H) was incorporated into the same position. Furthermore, unlike the result of eq 3, a small amount of deuterium was also incorporated into the β-position of the THF ring. Taken together with the results for eq 3, the deuterium at the β-position is derived from the amide N-D and the deuterium at the α-position is from the *ortho*-position of the starting amide **1a-d_8**. H/D exchange at the *ortho*-position of the recovered starting amide was also detected, but the ratio was smaller than that in the previous experiment (0.17H).



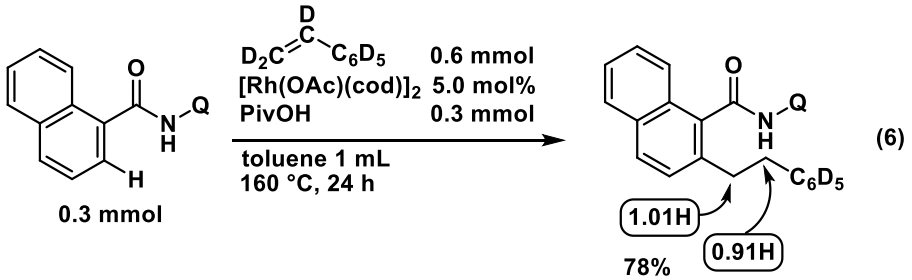
Based on these results, a proposed mechanism is shown in Scheme 2. The coordination of the quinoline nitrogen to the rhodium center followed by the oxidative addition of an amide N-H bond[1] gives rhodium hydride complex **A**. The insertion of dihydrofuran into Rh-H bond generates rhodium alkyl complex **B**. The HX elimination from this complex **B** generates Rh carbene complex **C**.[2] The reaction of the *ortho* C-H bond eith a carbene moiety gives complex **D**.[3,4] Reductive elimination

Scheme 2. Proposed mechanism with dihydrofuran



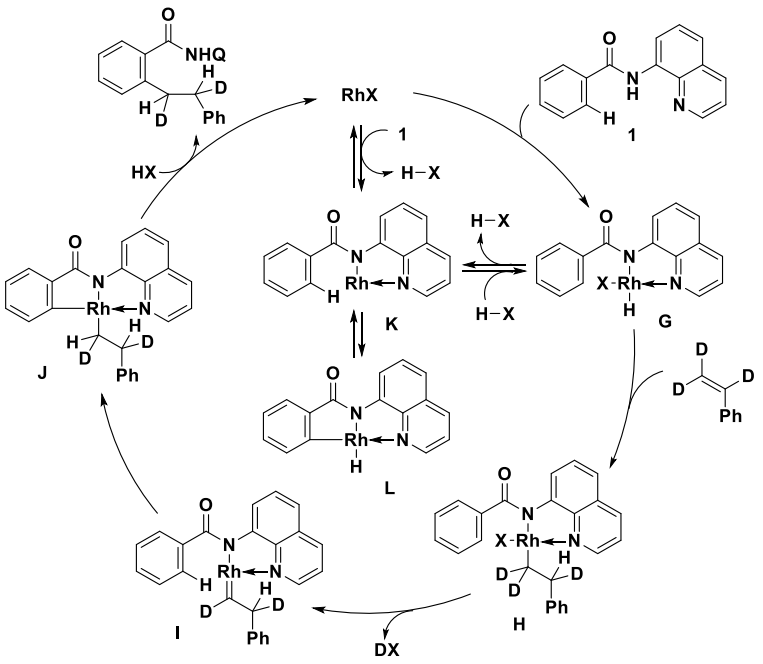
followed by protonation gives the alkylation product with the regeneration of rhodium catalyst. In this mechanism, the hydrogen on the amide nitrogen is incorporated into the ß-position of the product THF ring through the dihydrofuran insertion step (**A** to **B**). The deuterium at the *ortho*-position is incorporated into the α-position of the product THF ring through the reaction with carbene (**C** to **D**). Another mechanism is also considered for the formation of rhodium hydride complex **A**. The coordination of a quinolone nitrogen to the Rh(I) center, a ligand exchange to generate the Rh(I) complex **E** with the concomitant generation of HX, followed by the reaction of the complex **E** with HX. The reversible oxidative addition of *ortho* C-H bond to the rhodium center generates the cyclometalated Rh-H complex **F**.[5] The formation of this complex **F** accounts for the reversible C-H bonds cleavage at the *ortho*-position of benzamides without olefins (eq 1 in Scheme 1).[6]

The deuterium experiment was also conducted in the reaction of naphthalenecarboxamide with styrene-d_8 (eq 6). After 24 h, the starting amide was completely consumed and the alkylated product was obtained in 78%. In this case, nearly one proton each was incorporated into both of the alkyl chain of the product (1.01H + 0.91H = 1.92H). Namely, one deuterium atom at the terminal position of styrene-d_8 was lost after the reaction.

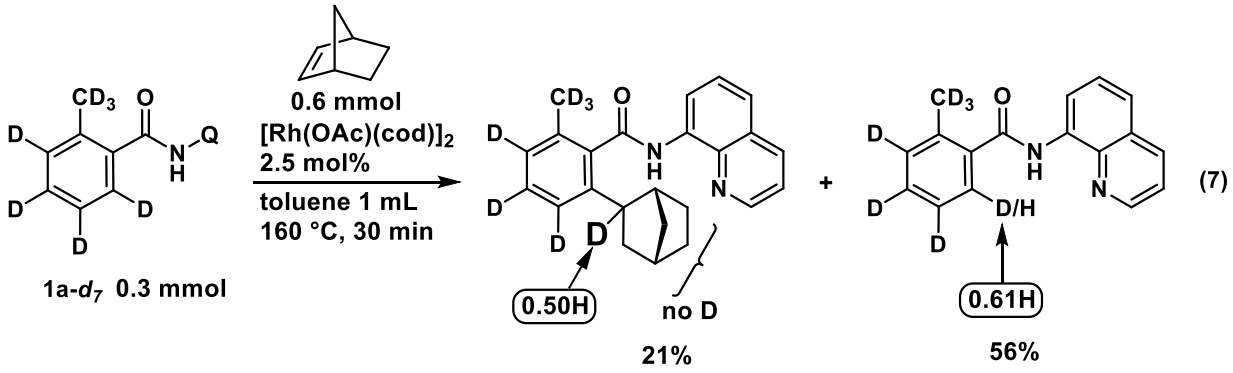


This result also indicates that conventional hydrometalation or carbometalation are not involved. The same reaction mechanism as in Scheme 2 is proposed for this reaction (Scheme 3). After the formation of the Rh-H complex **G** by the oxidative addition of the amide N-H bond to the Rh center, styrene is inserted into Rh-H bond to generate the Rh-alkyl complex **H**. Following the elimination of DX, a rhodium carbene complex **I** is obtained, and the migratory insertion of the *ortho* C-H bond to a carbene moiety gives a rhodium alkyl complex **J**. Subsequent reductive elimination, protonation gives the desired product with the regeneration of the catalyst. This mechanism provides an explanation for the fact that 1H is incorporated into each of the alkyl chains of the product. One H is incorporated into the product via the styrene insertion step (**G** to **H**) and the other is incorporated into the product during the carbene migration step (**I** to **J**).

Scheme 3. Proposed mechanism with styrene

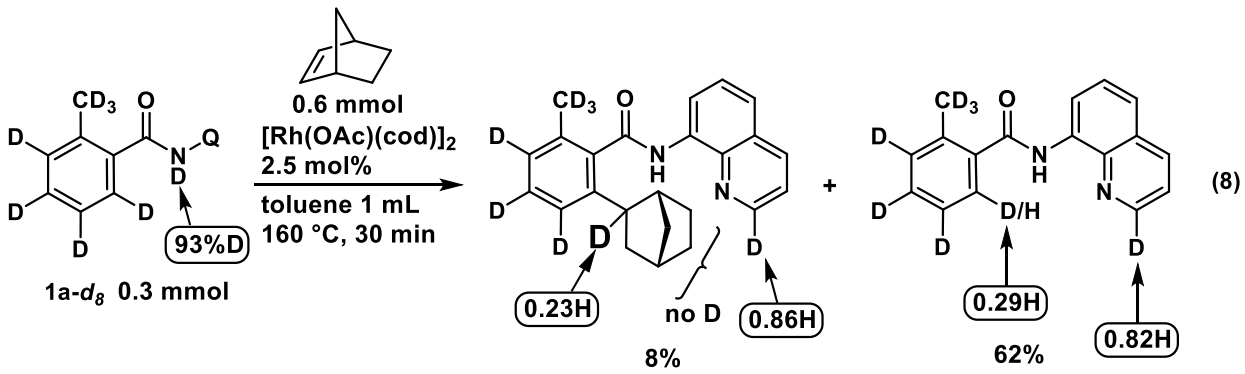


The deuterium experiment was performed with norbornene (eq 7). As is the same with eq 3, deuterium was detected only at the 2-position of the norbornane ring of the product. No deuterium incorporation was detected at the other positions. H/D exchange at the *ortho*-position was observed in the recoverd starting amide.



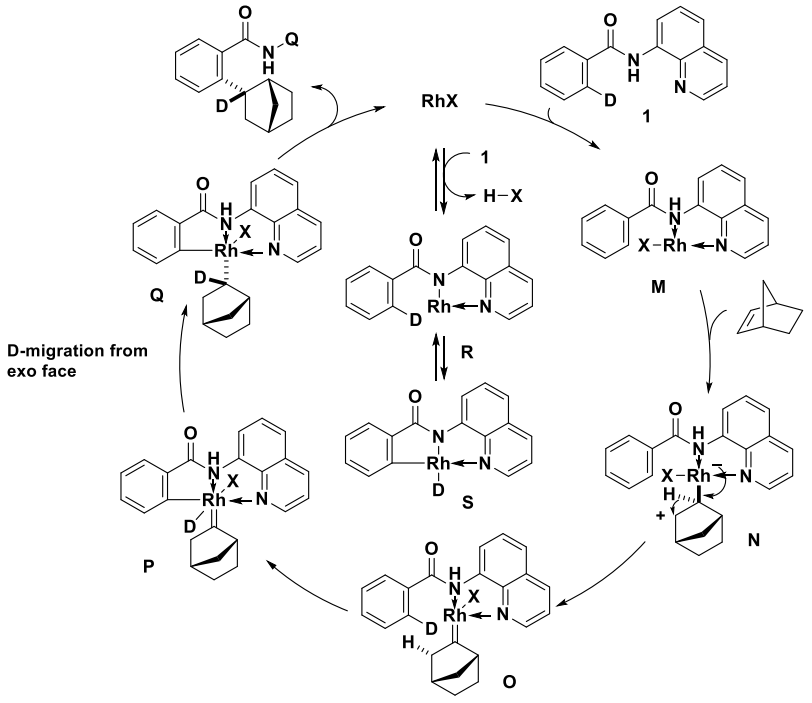
Next, in order to prevent degradation of the deuteration rate by rapid H/D exchange with amide NH, the reaction was carried out using ND amide as in the case of dihydrofuran (eq 8). As expected, the deuterium incorporation at the 2-position of the norbornane ring was increased to 77% (0.23H) and proton incorporation at the *ortho*-position of recorverd amide was decreased to 29% (0.29H).In addition, H/D exchange was also occurred at the adjacent to the N(sp^2) atom of the quinoline ring, indicating that this proton has a potential to behave as a proton source for these deuterium labeling experiments. It should be noted that no deuterium incorporation was detected at the other norbornan skelton in the alkylated product in contrast to the case of dihydrofuran (eq 5). This result means that amide NH is not included in the reaction sequence. Based on these results, the proposed

mechanism is shown in Scheme 4.



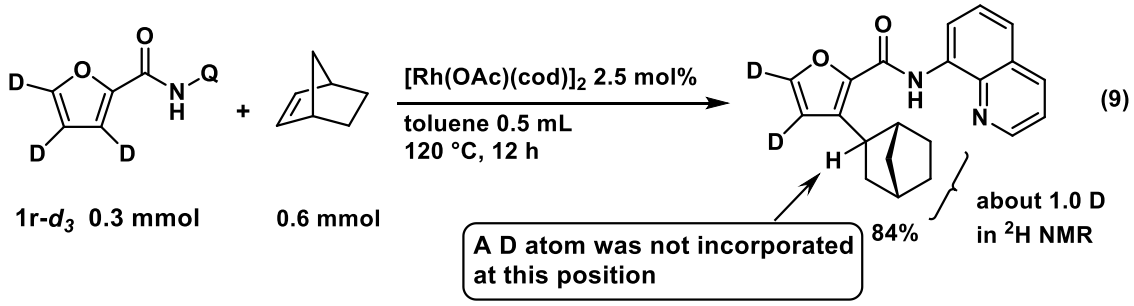
The coordination of the quinoline nitrogen and amide nitrogen to the rhodium center gives Rh complex **M**. The electrophilic addition of norbornene to the rhodium center generates an anionic rhodium complex **N**.[7] The 1,2-hydride migration gives rhodium carbene complex **O**. The oxidative addition of *ortho* C-H bond of amide to rhodium center and hydride migration from the *exo* face to the carbene carbon generates rhodium alkyl complex **Q** in which the C-Rh bond is *endo*-position. Reductive elimination gives the *endo* product with the regeneration of rhodiun catalyst. The stereo-determining step is the hydride migration step from the rhodium to carbene carbon (**P** to **Q**). But, the concerted oxidative addition of C-H bonds directly from **O** to **Q** can't be excluded. The difference between the reaction with norbornene and the previous reactions with dihydrofurans or styrene is the process before the carbene complex formation. In this reaction, we are considering a

Scheme 4. Proposed mechanism with norbornene



mechanism for activating olefin electrophilically (**M** to **N**). After the formation of the carbene complex, we proposed that the reaction would proceed in the same way as before.

Eq 9 shows the result of reaction of furan amide **1r-*d*$_3$** with norbornene. In sharp contrast, completely different result was obtained in this reaction. Only the *exo*-product was produced and deuterium was not detected at the 2-position of the norbornane skelton of the product. This result indicated that carbene mechanism is not performed but, different mechanism such as hydrometalation or carbometalation are probably involved.



(9)

5.3 Conclusion

When the reaction is carried out with the deuterated substrate **1a-*d*$_7$**, a deuterium atom is incorporated exclusively at the α-position of the THF ring of the product or at the 2-position of the norbornane ring of the product. Furthermore, no deuterium atoms were detected at any other positions (eq 3 and 7). These results are consistent with reaction proceeding via a carbene mechanism. However, there are minor differences, depending on the reactants used. In addition, we currently have no evidence regarding the formation of a carbene species. To better understand the reaction mechanism, more experiments such as DFT calculations will be needed. In eq 9, the reaction could proceed through a conventional hydrometalation or carbometalation mechanism, although we are not able to explain the difference in the mechanism at the present stage.

5.4 Experimental Section

Representative Procedure of Deuterium Labeling Experiments without Olefin (Scheme 1,eq 1).

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a-*d*$_7$** (40 mg, 0.15 mmol), [Rh(Cl)(cod)]$_2$ (1.8 mg, 0.00375 mmol), PivOH (15.3 mg, 0.15 mmol) and toluene (0.75 mL) were added. The mixture was stirred for 15 min at 160 °C followed by cooling. The mixture was filtered through a celite pad and concentrated *in vacuo*. The ratio of deuterium was determined by ^{1}H NMR.

Representative Procedure of Deuterium Labeling Experiments without Olefin (Scheme 1,eq 2).

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a-*d*$_7$** (40 mg, 0.15 mmol), [Rh(OAc)(cod)]$_2$ (2.0 mg, 0.00375 mmol), PivOH (15.3 mg, 0.15 mmol) and toluene (0.75 mL)

were added. The mixture was stirred for 15 min at 160 °C followed by cooling. The mixture was filtered through a celite pad and concentrated *in vacuo*. The ratio of deuterium was determined by ^{1}H NMR.

Representative Procedure of Deuterium Labeling Experiments with 2,3-Dihydrofuran (eq 3).

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a-*d*$_7$** (40 mg, 0.15 mmol), 2,3-dihydrofuran (21 mg, 0.3 mmol), [Rh(OAc)(cod)]$_2$ (2.0 mg, 0.00375 mmol), PivOH (15.3 mg, 0.15 mmol) and toluene (0.75 mL) were added. The mixture was stirred for 15 min 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= 20/1) to afford the desired alkylated product and starting amide. The ratio of deuterium was determined by ^{1}H NMR.

Deuterium Labeling Experiment with 2,5-Dihydrofuran (eq 4).

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a-*d*$_7$** (40 mg, 0.15 mmol), 2,5-dihydrofuran (21 mg, 0.3 mmol), [Rh(OAc)(cod)]$_2$ (2.0 mg, 0.00375 mmol), PivOH (15.3 mg, 0.15 mmol) and toluene (0.75 mL) were added. The mixture was stirred for 15 min 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= 20/1) to afford the desired alkylated product and starting amide. The ratio of deuterium was determined by ^{1}H NMR.

Deuterium Labeling Experiment of Amide (1a-*d*$_8$) with 2,3-Dihydrofuran (eq 5).

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a-*d*$_8$** (40 mg, 0.15 mmol), 2,3-dihydrofuran (21 mg, 0.3 mmol), [Rh(OAc)(cod)]$_2$ (2.0 mg, 0.00375 mmol), and toluene-*d*$_8$ (0.75 mL) were added. The mixture was stirred for 15 min 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= 20/1) to afford the desired alkylated product and starting amide. The ratio of deuterium was determined by ^{1}H NMR and ^{2}H NMR.

Deuterium Labeling Experiment with Styrene-*d*$_8$ (eq 6).

To an oven-dried 5 mL screw-capped vial, N-(quinolin-8-yl)-1-naphthamide (90 mg, 0.3 mmol), styrene-*d*$_8$ (67 mg, 0.6 mmol), [Rh(OAc)(cod)]$_2$ (8.1 mg, 0.015 mmol), PivOH (31 mg, 0.3 mmol) and toluene (1 mL) were added. The mixture was stirred for 24 h at 160 °C followed by cooling. The mixture was filtered through a celite pad and the filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 10/1) to afford the desired alkylated product. The ratio of deuterium was determined by ^{1}H NMR.

Deuterium Labeling Experiment with Norbornene (eq 7).

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a-*d*$_7$** (80 mg, 0.3 mmol), norbornene (57 mg, 0.6 mmol), $[Rh(OAc)(cod)]_2$ (4.1 mg, 0.0075 mmol) and toluene (1 mL) were added. The mixture was stirred for 30 min 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= 50/1) and GPC to afford the desired alkylated product and starting amide. The ratio of deuterium was determined by ^{1}H NMR and ^{2}H NMR.

Deuterium Labeling Experiment of Amide (1a-*d*$_8$) with Norbornene (eq 8).

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1a-*d*$_8$** (80 mg, 0.3 mmol), norbornene (57 mg, 0.6 mmol), $[Rh(OAc)(cod)]_2$ (4.1 mg, 0.0075 mmol) and toluene (1 mL) were added. The mixture was stirred for 30 min 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= 50/1) and GPC to afford the desired alkylated product and starting amide. The ratio of deuterium was determined by ^{1}H NMR and ^{2}H NMR.

Deuterium Labeling Experiment of Amide (1r-*d*$_3$) with Norbornene (eq 9).

To an oven-dried 5 mL screw-capped vial, N-(quinolin-8-yl)furan-2-carboxamide **1r-*d*$_3$** (72 mg, 0.3 mmol), norbornene (57 mg, 0.6 mmol), $[Rh(OAc)(cod)]_2$ (4.1 mg, 0.0075 mmol) and toluene (0.5 mL) were added. The mixture was stirred for 12 min at 120 °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= 50/1) to afford the desired alkylated product. The ratio of deuterium was determined by ^{1}H NMR. The ratio of deuterium was determined by ^{1}H NMR and ^{2}H NMR.

5.5 References and Notes

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Conclusion

Although the transition metal catalyzed alkylation of C-H bonds with olefins has been well developed, these reactions proceed via the hydrometallation or carbometallation which are the generally accepted mechanisms. In sharp contrast, the findings reported herein clearly show that the alkylation of C-H bonds with olefins proceeds via an unprecedented carbene mechanism, when the combination of a rhodium catalyst and an *N,N*-bidentate directing group are involved in the reaction.

Chapter 1 discusses bidentate directing group directed, rhodium catalyzed alkylation of *ortho*-C-H bonds in aromatic amides with α,β-unsaturated esters. Aromatic amides bearing various functional groups and a variety of activated olefins are tolerated under these reaction conditions. Selective C-C bond formation occurred between the *ortho* C-H bonds in aromatic amides and the ß position of the α,β-unsaturated carbonyl compounds.

Chapter 2 discusses the use of a bidentate directing group in the rhodium catalyzed alkylation of *ortho*-C-H bonds in aromatic amides with styrenes. The reaction is highly regioselective. The formation of C-C bonds occurs between the *ortho* C-H bonds in aromatic amides and the terminal position of the styrene derivative.

Chapter 3 discusses the use of a bidentate directing group in the rhodium catalyzed alkylation of *ortho*-C-H bonds in aromatic amides with α,β-unsaturated lactones and dihydrofurans. In these reactions, the C-C bond is formed between the *ortho* C-H bonds in aromatic amides and the bond adjacent to the oxygen atom of the lactone or dihydrofuran.

Chapter 4 discusses the use of a bdentate directing group in the rhodium catalyzed alkylation of *ortho*-C-H bonds in aromatic amides with norbornen. In these reactions, an unusual *endo*-selective alkylated product was produced. The *endo* selectivity was improved by the addition of a sterically bulky carboxylic acid.

Chapter 5 discusses mechanisms responsible for these reactions. The results of deuterium-labeling experiments clearly suggest that hydrometallation or carbometallation, which are commonly accepted mechanisms for the catalytic hydroarylation of C-H bonds, are not involved as the key step in these reactions, and strongly suggest that the reaction involves a rhodium carbene complex intermediate generated from the olefin as the key intermediate.

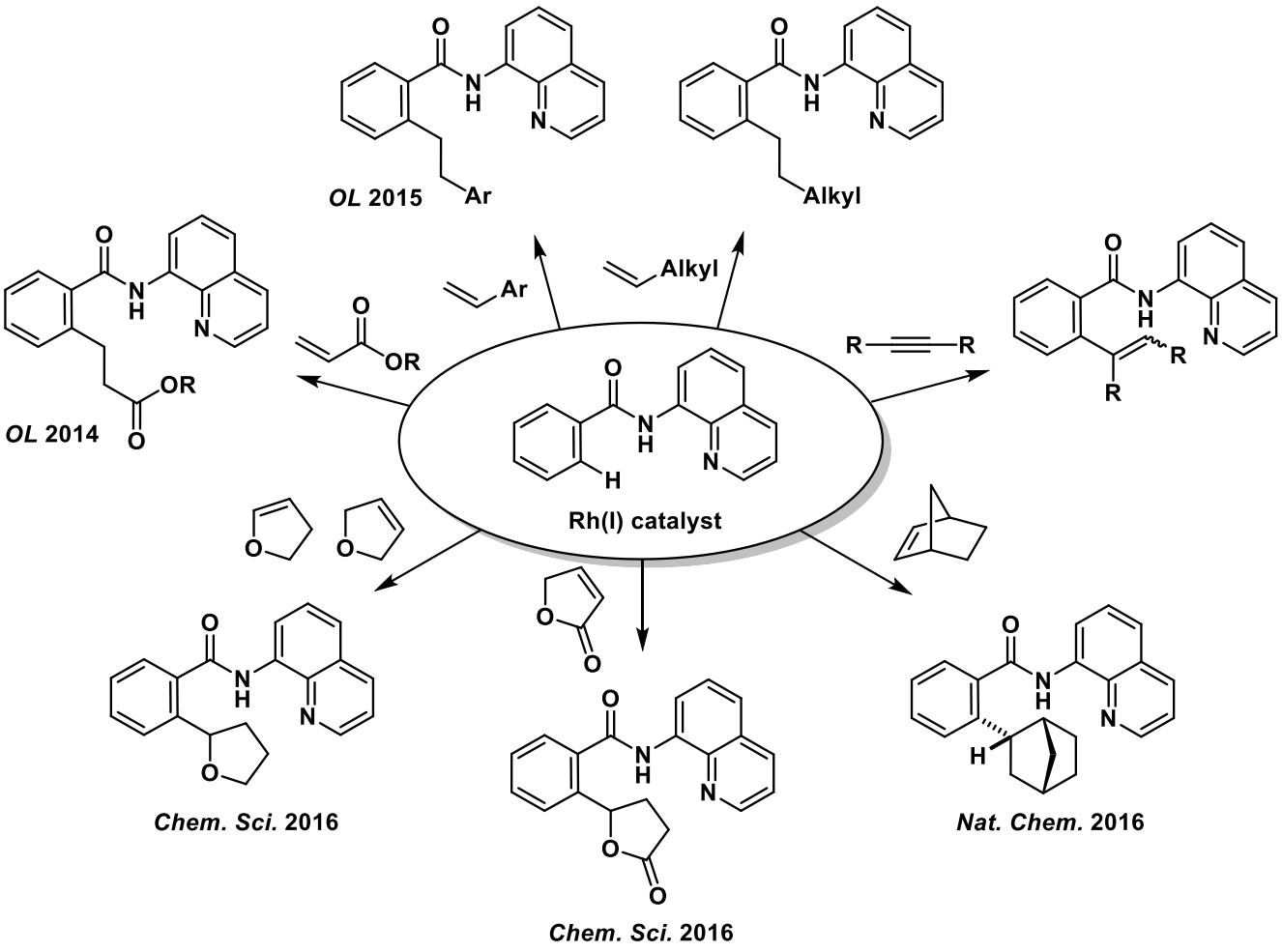
In all cases, the presence of an 8-aminoquinoline moiety as the bidentate directing group is essential for the reaction to proceed.

In these reactions, carbene species could be generated from simple olefins. Many synthetic methods for the preparation of carbene species have been reported to date, however, to the best of our knowledge, no example of the use of a simple olefin as a precursor of a carbene are known. Reactions in which olefins are used as carbene precursors by utilizing a bidentate directing group and a rhodium catalyst would be developed in the near future.

It should also be noted that the alkylation reactions with various olefins does not appear to proceed via the generally accepted mechanism (hydrometalation / carbometalation) but in an

unprecedented mechanism. These results imply that utilizing a combination of various transition metal complexes and new directing groups has the potential to alter the reaction mechanism. Continuing to develop new directing groups promises to be effective for developing new types of C-H functionalizations that cannot be currently achieved.

Scheme 1. Summary of this thesis



List of Publication

(1) Rhodium-Catalyzed Alkylation of C-H Bonds in Aromatic Amides with α,β-Unsaturated Esters

Kaname Shibata and Naoto Chatani

Org. Lett. **16**, 5148-5151 (2014).

(2) Rhodium-Catalyzed Alkylation of C-H Bonds in Aromatic Amides with Styrenes via Bidentate-Chelation Assistance

Kaname Shibata, Takuma Yamaguchi, and Naoto Chatani

Org. Lett. **17**, 3584-3587 (2015).

(3) Rhodium-Catalyzed Regioselective Addition of the *ortho* C-H Bond in Aromatic Amides to the C-C Double Bond in α,β-Unsaturated γ-Lactones and Dihydrofurans

Kaname Shibata and Naoto Chatani

Chem. Sci. **7**, 240-245 (2016).

(4) An Unusual *Endo*-Selective C-H Hydroarylation of Norbornene by the Rh(I)-Catalyzed Reaction of Aromatic Amides: A Carbene Intermediate

Kaname Shibata, Satoko Natsui, Mamoru Tobisu, Yoshiya Fukumoto, and Naoto Chatani

submitted for publication.

Supplementary List of Publications

(1) Ruthenium-Catalyzed Carbonylation of *ortho* C-H Bnods in Arylacetamides: C-H Bond Activation Utilizing a Bidentate-Chelation System

Kaname Shibata, Nao Hasegawa, Yoshiya Fukumoto, and Naoto Chatani

ChemCatChem **4**, 1733-1736 (2012).

(2) Ruthenium-Catalyzed Cyclocarbonylation of Aliphatic Amides through the Regioselective Activation of Unactivated C(sp^3)-H Bonds

Nao Hasegawa, Kaname Shibata, Valentine Charra, Satoshi Inoue, Yoshiya Fukumoto and Naoto Chatani

Tetrahedron **69**, 4466-4472 (2013).

(3) The $Pd(OAc)_2$-Catalyzed Lactonization of Aromatic Acetoamides Involving Oxidation of C-H Bonds

Takeshi Uemura, Takuya Igarashi, Moe Noguchi, Kaname Shibata, and Naoto Chatani

Chem. Lett. **44**, 621-623 (2015).

(4) Rhodium-Catalyzed Alkylation of C-H Bonds in Aromatic Amides with Unactivated Alkenes and Styrenes: A Newly Proposed Mechanism Involving the Generation of Carbene Intermediate from 1-Alkenes

Takuma Yamaguchi, Kaname Shibata, and Naoto Chatani

in preparation.

(5) Rhodium-Catalyzed Alkenylation of C-H Bonds in Aromatic Amides with Alkynes

Kaname Shibata, Satoko Natsui, and Naoto Chatani

in preparation.