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

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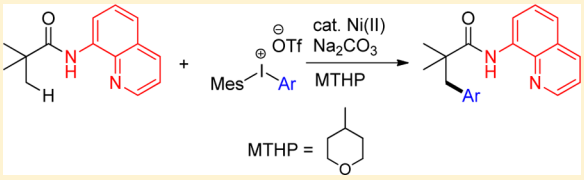
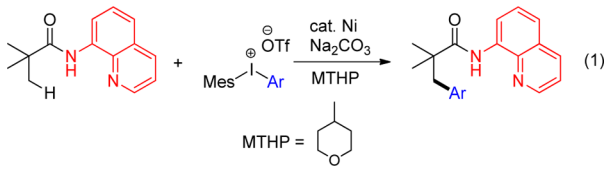
Supporting Information

ABSTRACT: The Ni(II)-catalyzed direct arylation of C(sp^3)−H (methyl and methylene) bonds in aliphatic amides containing an 8-aminoquinoline moiety as the directing group with diaryliodonium salts as coupling electrophiles is described. A wide variety of functional groups are tolerated in the reaction. The reaction represents the first example of the Ni-catalyzed direct arylation of C(sp^3)−H bonds with diaryliodonium salts.



INTRODUCTION

The transition metal catalyzed direct functionalization of C−H bonds has been extensively studied as an alternative method to traditional cross coupling reactions.[1] A wide variety of electrophiles, such as halides, and nucleophiles, including organo-boron, zinc, and Grignard reagents, have been utilized as coupling partners in the direct functionalization of C−H bonds. In 2005, Sanford and co-workers reported the first example of the Pd-catalyzed chelation-assisted arylation of C−H bonds with diaryliodonium salts as electrophilic coupling partners.[2] After this successful example appeared in the literature, the utilization of diaryliodonium salts in the functionalization of C−H bonds as coupling electrophiles has been of great interest, because the reactions proceeded under relatively milder reaction conditions than reactions with aryl halides. However, despite this progress, only palladium, platinum, and copper catalysts have been used in the arylation of C−H bonds with diaryliodonium salts, and the most of arylation reactions in which diaryliodonium salts are used involve the functionalization of C(sp^2)−H bonds.[3] We also recently reported on the Ru(II)-catalyzed direct arylation of C−H bonds in 2-arylpyridines with diaryliodonium salts.[4] However, the direct arylation of C(sp^3)−H bonds with diaryliodonium salts was limited to only two examples, and both involved the use of a palladium complex as the catalyst. Sanford and co-workers reported on the Pd-catalyzed arylation of benzyl C(sp^3)−H bonds in 8-methylquinoline,[2] and Shi and co-workers developed the Pd-catalyzed arylation of C(sp^3)−H bonds in aliphatic amides containing an 8-aminoquinoline moiety as the directing group.[5] Herein, we report on the Ni-catalyzed direct arylation of C(sp^3)−H bonds in aliphatic amides with diaryliodonium salts via the use of bidentate chelation assistance (eq 1). This reaction represents the first example of the Ni-catalyzed direct arylation of C(sp^3)−H bonds with diaryliodonium salts.



(1)

RESULTS AND DISCUSSION

The functionalization of C−H bonds by taking advantage of an 8-aminoquinoline directing group has been extensively studied in recent years,[6,7] and this chelation-system has been found to be applicable to the development of various functionalization of C(sp^3)−H bonds in the presence of transition metal complexes, such as palladium,[8] ruthenium,[9] copper,[10] nickel,[11] and iron.[12] We previously reported on the Ni-catalyzed arylation of C(sp^3)−H bonds in aliphatic amides containing an 8-aminoquinoline moiety with aryl iodides.[11a] Thus, in an initial attempt, we carried out the reaction under the same reaction conditions as were used in a previously reported reaction.[11a] The reaction of amide **1** (0.3 mmol) with the diaryliodonium salt **2b** (0.36 mmol) in the presence of Ni(OTf)$_2$ (0.03 mmol) as a catalyst, MesCOOH (0.06 mmol) as a ligand, and Na_2CO_3 (0.6 mmol) as a base in DMF (0.6 mL) at 140 °C for 24 h gave the β-arylation product **3a** in 23% NMR yield along with 74% of **1** being recovered (Table 1, entry 1). No evidence was found for the formation of the biarylated product or any other product resulting from a reaction at the benzyl and phenyl C−H bonds. Importantly, only a 4-methoxyphenyl group in **2b** was introduced into the arylated product due to the steric hindrance of the mesityl group. The use of 1,4-dioxane as the solvent instead of DMF resulted in a dramatically improved yield of **3a** to 81% (entry 2). The addition of a sterically bulky carboxylic acid was required for the reaction to proceed efficiently when

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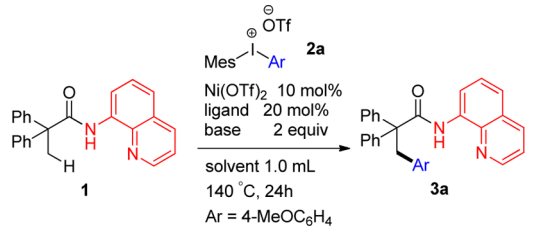
Table 1. Optimization of the Nickel-Catalyzed Direct Arylation of Aliphatic Amide 1 with Diaryliodonium Salt 2a[a]



entry	ligand	base	solvent	yields 3a/1[b] (%)
1	$MesCO_2H$	Na_2CO_3	DMF	23/74
2	$MesCO_2H$	Na_2CO_3	dioxane	81/17
3	*N*-Boc-L-Ala	Na_2CO_3	dioxane	trace/96
4	$AdCO_2H$	Na_2CO_3	dioxane	57/8
5	TfOH	Na_2CO_3	dioxane	44/13
6	none	Na_2CO_3	dioxane	74 (71)/25 (20)
7	none	NaOAc	dioxane	0/101
8	none	$NaHCO_3$	dioxane	trace/97
9	none	Li_2CO_3	dioxane	trace/96
10	none	K_2CO_3	dioxane	36/63
11	none	Cs_2CO_3	dioxane	trace/95
12	none	Na_2CO_3	MTHP	76 (72)/22 (19)

[a]Reaction conditions: amide **1** (0.3 mmol), diaryliodonium salt (0.36 mmol), $Ni(OTf)_2$ (0.03 mmol), ligand (0.06 mmol), and base (0.6 mmol) in solvent (1.0 mL) at 140 °C for 24 h. [b]NMR yields. Values in parentheses are the isolated yields.

aryl iodides were used as the coupling partner.[11a] In contrast to the previous reaction, the arylated product was obtained in good yield even in the absence of a carboxylic acid (entry 6). Product yield is dependent on the base used in the reaction. The use of Na_2CO_3 resulted in a high yield of product, but the use of other bases resulted in almost no reaction (entry 6–11). MTHP (4-methyltetrahydro-2*H*-pyran), which has a higher boiling point (105 °C) and is a better solvent to dissolve organic compounds than dioxane, was the solvent of choice (entry 12).

The effect of the directing group was examined. The formation of arylated products was not observed at all when other directing groups, such as **4** or **5**, or *N*-2-naphthylbenzamide **6** or the ester **7** were used (Figure 1). These results indicate the importance of a quinoline nitrogen and an NH bond.

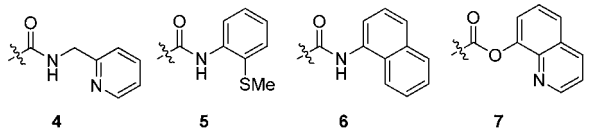
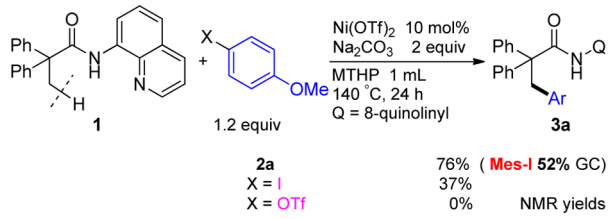


Figure 1. Ineffective directing groups.

It is known that diaryliodonium salts undergo decomposition to give aryl iodides and aryl triflates at high temperatures or under the basic conditions (eq 2).[13] In order to examine

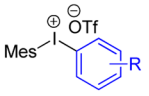
whether diaryliodonium salts themselves can function as a coupling partner, we carried out the reaction with an aryl iodide and an aryl triflate (Scheme 1). Mes-I (2-iodo-1,3,5-trimethylbenzene) was formed in 52% yield in the reaction with the diaryliodonium salt **2a**. This result suggests that an aryl triflate might be generated during the reaction, as shown in eq 2. While the reaction with an aryl iodide gave the arylated product **3a** in 37% yield under the standard reaction conditions, the reaction with aryl triflate resulted in no reaction. These results suggest that the main pathway to **3a** involves a reaction with the diaryliodonium salt **2a**, but the possibility that a small amount of **3a** is produced by a reaction with aryl iodide generated via the decomposition of the diaryliodonium salt cannot be completely excluded.

Scheme 1. Reaction with Various Electrophiles



With the optimized reaction conditions in hand, we examined the scope of the reaction (Table 2). We examined the effect of the counteranion of the diaryliodonium salt. The reaction with a triflate (OTf) or a chloride (Cl) salt gave the arylated product **3b**, but tetrafluoroborates (BF_4) and hexafluorophosphates (PF_6) as counterions resulted in no

Table 2. Arylation of Aliphatic Amide 1 with Various Diaryliodonium Salts[a]

diaryliodonium salt		yield
Ph_2IOTf (**8a**)	**3b**	68% (11%)[b]
Ph_2ICl (**8b**)	**3b**	30% (71%)[b]
Ph_2IBF_4 (**8c**)	**3b**	0% (94%)[b]
Ph_2IPF_6 (**8d**)	**3b**	0% (96%)[b]
		
R = *p*-CF_3 (**2b**)	**3c**	65% (19%)[c]
= *p*-CO_2Me (**2c**)	**3d**	62% (18%)
= *p*-Ac (**2d**)	**3e**	57% (28%)
= *p*-NO_2 (**2e**)	**3f**	43% (38%)[c]
= *p*-Cl (**2f**)	**3g**	57% (24%)[c]
= H (**2g**)	**3b**	61% (20%)
= *p*-OMe (**2a**)	**3a**	72% (19%)
= *p*-Me (**2h**)	**3h**	70% (15%)[c]
= *m*-Me (**2i**)	**3i**	50% (40%)
= *o*-Me (**2j**)	**3j**	0% (93%)[b]

[a]Reaction conditions: amide **1** (0.3 mmol), diaryliodonium salt (0.36 mmol), $Ni(OTf)_2$ (0.03 mmol), and Na_2CO_3 (0.6 mmol) in MTHP (1.0 mL) at 140 °C for 24 h. Values in parentheses are the yields of recovered starting amide. [b]NMR yields. [c]Purified by GPC.

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reaction. A variety of diaryliodonium triflates **2b**–**2i** were applicable to the arylation reaction. The reaction shows a high functional group compatibility, tolerating methoxy, ester, and chloride groups. A mesityl group was not introduced in all cases, due to steric hindrance. Electron donating aryl groups resulted in slightly higher yields than electron withdrawing aryl groups.

Table 3 shows the results for reactions of various aliphatic amides with the diaryliodonium salt **2a**. The reaction was sensitive to the structure of the amide used, and unreactive amides are listed at the bottom of Table 3. Aliphatic amides possessing no hydrogen at the α-position reacted exclusively at the methyl group, and methylene and benzene C–H bonds were not arylated. Although the reaction of 1-methylcyclohexanecarboxamide **13** resulted in selective monoarylation only at the methyl group, 1-methylcycloheptanecarboxamide **14** gave a mixture of monoarylated **14a** and diarylated products **14b**, the latter of which was produced by a reaction at the cyclic methylene C–H bonds. This difference in reactivity as a function of ring size probably stemmed from differences in the stability of the cyclometalated complexes between the cleavage of the methyl C–H bond and the methylene C–H bond, as evidenced by B3LYP/SDD (Ni)/6-31G* (C, H, O, N) calculations. The results show that the complex involving the activation of a methyl C–H bond is 4.6 kJ/mol more stable than a complex involving the activation of a methylene C–H bond in **13** and the complex activated methylene C–H bond is 13.9 kJ/mol more stable in **14** (Figure 2). When 1-phenylcyclobutanecarboxamide **15** and 1-phenylcyclopentanecarboxamide **16** were used, the cleavage of β-methylene C–H bonds was the predominant reaction, and β-benzene C(sp^2)–H bonds were completely unreactive.

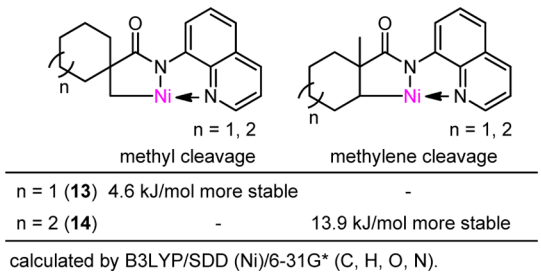
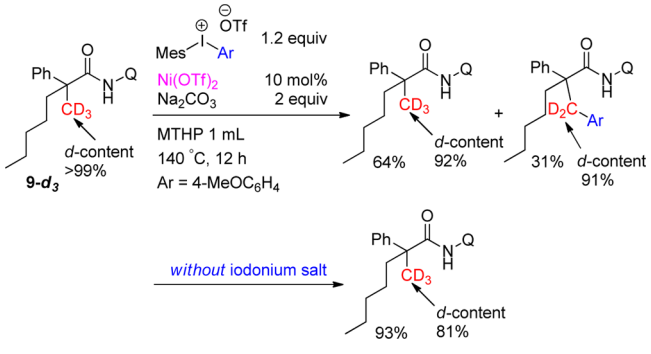


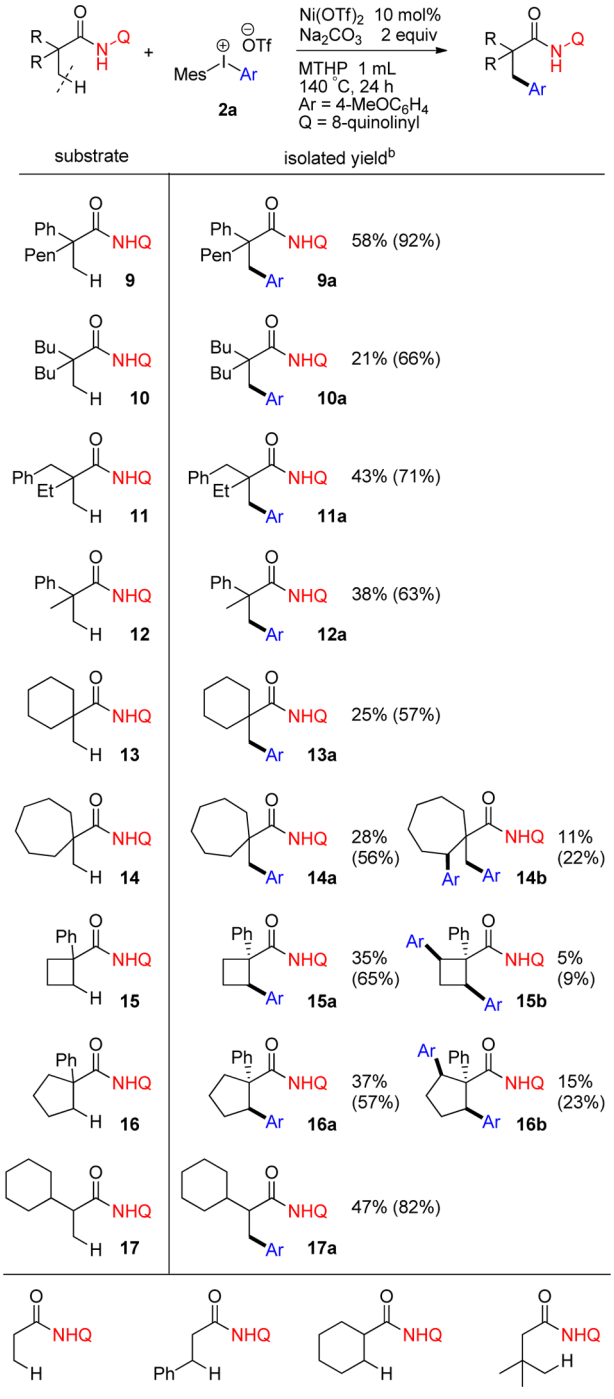
Figure 2. DFT calculation of the energy difference in a cyclometalated complex.

Scheme 2. Deuterium Labeling Experiments



To obtain mechanistic insights into the reaction, the deuterated amide **9**-d_3 was reacted with the diaryliodonium salt **2a** for 12 h (Scheme 2). H/D exchange between the methyl

Table 3. Nickel-Catalyzed Direct Arylation of Aliphatic Amides with Diaryliodonium Salt 2a[a]



[a]Reaction conditions: amide (0.3 mmol), diaryliodonium salt **2a** (0.36 mmol), $Ni(OTf)_2$ (0.03 mmol), and Na_2CO_3 (0.6 mmol) in MTHP (1.0 mL) at 140 °C for 24 h. [b]Values in parentheses are the isolated yields based on the reacted amide.

C–H bonds and the N–H bond occurred. The D content in the recovered amide decreased from >99% to 92%. But the extent of H/D exchange in the present reaction is smaller than a previously reported reaction with aryl iodides,[11a] because the efficiency of cleavage of C–H bonds depends on the nature of the additive and solvent used, and in addition, the oxidative addition of the diaryliodonium salt is irreversible and proceeds more smoothly than that of aryl iodides. H/D exchange was

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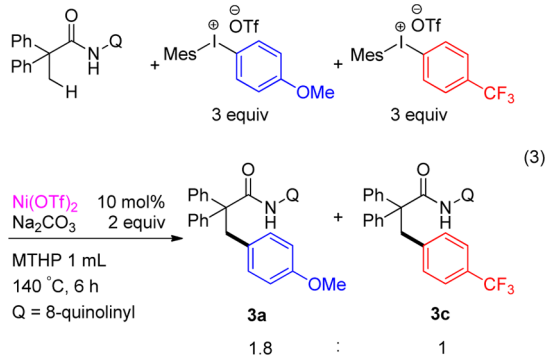
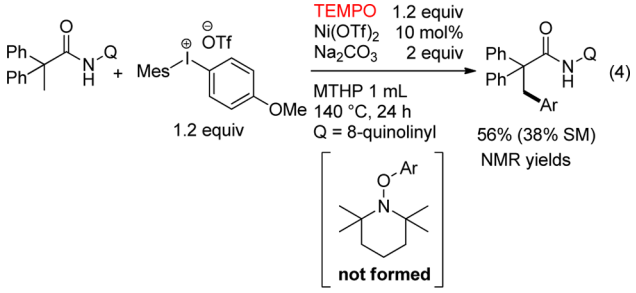
also observed in the absence of the diaryliodonium salt. These results indicate that the cleavage of the C−H bond is a reversible step and that it occurs before the oxidative addition of the diaryliodonium salt.

A competition experiment with electronically different diaryliodonium salts was carried out to obtain additional mechanistic information (eq 3). Electron donating aryl groups facilitate the reaction, and this tendency conforms to our previously reported reaction with aryl iodides.[11a,14]



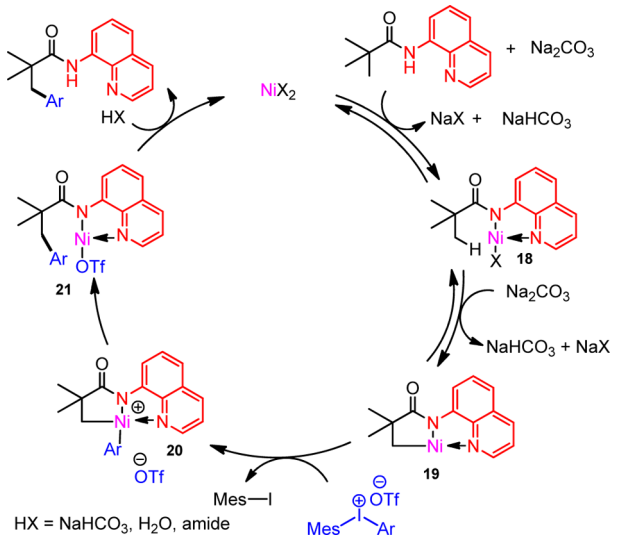
Diaryliodonium salts are also known to function as aryl radical precursors.[15] To investigate the possibility that an aryl radical is involved in the present reaction, a radical trapping experiment was carried out (eq 4). The addition of TEMPO



had no effect on the reaction, the arylated product was obtained in a moderate yield of 56%, and the byproduct of the reaction resulting from the reaction of TEMPO with an aryl radical was not formed.

A proposed mechanism for the reaction is shown in Scheme 3. Coordination of the amide to the Ni center followed by ligand exchange gives the Ni complex **18**, which undergoes reversible cyclometalation to give **19**, probably via a CMD mechanism. The oxidative addition of the diaryliodonium salt with the concomitant generation of a Mes-I gives the high valent Ni(IV) complex **20** stabilized by an 8-aminoquinoline moiety. The complex **20** undergoes reductive elimination and protonation to afford the desired arylation product with the regeneration of Ni(II). The competition experiment clearly shows that the electron donating aryl group facilitates the reaction, and the data from the deuterium experiments suggests that the cleavage of C−H bonds proceeds in the absence of diaryliodonium salts. Based on these results, the rate determined step is not likely to be the cleavage of the C−H bond or the oxidative addition of the diaryliodonium salt and is likely to be the reductive elimination step. The advantage of this reaction is that the reaction proceeds in the absence of a carboxylic acid in contrast to the reaction with aryl iodides.[11a] In the reaction with aryl iodides, one of the roles of the

Scheme 3. Proposed Mechanism



carboxylic acid is to accelerate the reductive elimination to generate a cationic Ni(IV) intermediate, thus replacing the iodide with a carboxylate from the Aryl−Ni(IV)−I complex. However, the reaction with diaryliodonium salts directly forms the cationic Ni(IV) intermediate **20** because the counteranion of diaryliodonium salt is a triflate.

CONCLUSIONS

We report herein on the development of the Ni(II)-catalyzed direct arylation of C(sp^3)−H bonds (methyl and methylene) in aliphatic amides with diaryliodonium salts, taking advantage of a bidentate chelation assistance. The reaction represents the first example of the Ni-catalyzed functionalization of C−H bonds with diaryliodonium salts. The reaction is sensitive to the nature of bases used in the reaction. The reaction shows high functional group compatibility. The cleavage of C−H bonds is reversible. The 8-aminoquinoline directing group is easily removed and converted to more useful functional groups.[16]

EXPERIMENTAL SECTION

General Comments. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz in $CDCl_3$ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. For infrared spectra (IR), absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained with ionization voltages of 70 eV. High resolution mass spectra (HRMS) were obtained by EI using a double focusing mass spectrometer. Analytical gas chromatography (GC) was carried out with a flame ionization detector. Column chromatography was performed with SiO_2 (Silicycle SiliaFlash F60 (230−400 mesh)). Some compounds were purified by gel permeation chromatography (GPC).

Synthesis of the Starting Amides. All amides containing an 8-aminoquinoline moiety were prepared by the reaction of the corresponding acid chlorides with 8-aminoquinoline.[11a,17]

Synthesis of the Diaryliodonium Salts. 4-Methoxyphenyl(mesityl)iodonium trifluoromethanesulfonate, **2a**, was prepared by Gaunt's method.[18] 4-Methylphenyl(mesityl)iodonium trifluoromethanesulfonate (**2h**) and 3-methylphenyl(mesityl)iodonium trifluoromethanesulfonate (**2i**) were prepared by Olofsson's method.[19] The other diaryliodonium triflate salts (Ar^1Ar^2IOTf) were prepared by

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MacMillan's method.[20] Diphenyliodonium tetrafluoroborate (**8c**) was prepared by Ochiai's method.[21]

General Procedure for the Arylation of Aliphatic Amide with Diaryliodonium Salts. To an oven-dried 5 mL screw-capped vial in a glovebox, 2,2-diphenyl-*N*-(quinolin-8-yl)propanamide (**1**, 106 mg, 0.3 mmol), 4-methoxyphenyl(mesityl)iodonium trifluoromethanesulfonate (**2a**, 181 mg, 0.36 mmol), $Ni(OTf)_2$ (10.6 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol), and 4-methyltetrahydropyrane (1 mL) were added. The mixture was stirred for 24 h at 140 °C. The resulting mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent, hexane/EtOAc = 10/1) to afford the desired arylated product **3a** (99 mg, 72%) as a white solid.

*3-(4-Methoxyphenyl)-2,2-diphenyl-N-(quinolin-8-yl)propanamide (**3a**).* R_f 0.18 (hexane/EtOAc = 10/1). White solid. Yield: 99 mg, 72%. Mp = 164 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.68 (s, 3H), 3.85 (s, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 7.54−7.32 (m, 7H), 7.36−7.38 (m, 4H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.52 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 10.22 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 43.6, 55.0, 64.5, 112.8, 116.0, 121.3, 121.4, 127.0, 127.3, 127.8, 128.0, 129.7, 129.8, 132.2, 134.7, 136.0, 138.7, 142.4, 148.1, 157.9, 172.2. HRMS Calcd for $C_{31}H_{26}N_2O_2$: 458.1994. Found: 458.1995.

*2,2,3-Triphenyl-N-(quinolin-8-yl)propanamide (**3b**).* R_f 0.31 (hexane/EtOAc = 10/1). Off white solid. Yield: 87 mg, 68%. Mp = 135−136 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.92 (s, 2H), 6.83 (d, *J* = 6.8 Hz, 2H), 6.99−7.08 (m, 3H), 7.25−7.31 (m, 7H), 7.36−7.39 (m, 4H), 7.42 (d, *J* = 8.0 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.52 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.79 (d, *J* = 8.0 Hz, 1H), 10.24 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 44.4, 64.4, 116.0, 121.3, 121.4, 126.0, 127.0, 127.0, 127.4, 127.7, 128.0, 129.7, 131.2, 134.6, 135.9, 137.9, 138.6, 142.2, 148.1, 172.1; IR (neat) 3330 w, 3027 w, 1678 m, 1522 s, 1483 m; MS *m*/*z* (relative intensity, %) 428 (M^+, 5), 220 (20), 172 (11), 171 (100), 144 (7). HRMS Calcd for $C_{30}H_{24}N_2O$: 428.1889. Found: 428.1891.

*2,2-Diphenyl-N-(quinolin-8-yl)-3-(4-(trifluoromethyl)phenyl)propanamide (**3c**).* R_f 0.25 (hexane/EtOAc = 10/1). Yield: 97 mg, 65%. White solid. Mp = 165 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.95 (s, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.27−7.32 (m, 9H), 7.33−7.39 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 1H) 7.51 (t, *J* = 8.0 Hz, 1H), 8.06 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.53 (dd, *J* = 4.0, 1.4 Hz, 1H), 8.76 (dd, *J* = 7.8, 1.4 Hz, 1H), 10.24 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 44.3, 64.4, 116.0, 121.5 (d, 2.81 Hz), 124.1 (d, 3.82 Hz), 124.3 (q, 271 Hz), 127.2, 127.3, 127.7, 127.8, 128.0, 128.2, 128.32, 128.7, 129.5, 131.5, 134.5, 136.0, 138.6, 141.6, 141.9, 142.3, 148.1, 171.7; IR (neat) 3329 w, 3058 w, 1680 m, 1522 s, 1484 m; MS *m*/*z* (relative intensity, %) 496 (M^+, 5), 220 (22), 172 (11), 171 (100), 144 (4). HRMS Calcd for $C_{31}H_{23}F_3N_2O$: 496.1762. Found: 496.1765.

*Methyl 4-(3-oxo-2,2-diphenyl-3-(quinolin-8-ylamino)propyl)benzoate (**3d**).* R_f 0.09 (hexane/EtOAc = 10/1). White solid. Yield: 90 mg, 62%. Mp = 169−170 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.83 (s, 3H), 3.95 (s, 2H), 6.91 (d, *J* = 7.6 Hz, 2H), 7.24−7.32 (m, 7H), 7.37−7.39 (m, 4H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.52 (d, *J* = 4.4 Hz, 1H), 8.76 (d, *J* = 7.6 Hz, 1H), 10.24 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 44.5, 51.9, 64.4, 116.0, 121.4, 127.2, 127.2, 127.8, 128.2, 128.6, 128.7, 129.5, 131.2, 134.5, 136.0, 138.6, 141.9, 143.7, 148.1, 167.2, 171.7; IR (neat) 3330 w, 2950 w, 1717 m, 1679 m, 1522 s, 1484 m; MS *m*/*z* (relative intensity, %) 487 (M^+, 2), 220 (23), 172 (11), 171 (100), 144 (6). HRMS Calcd for $C_{32}H_{26}N_2O_3$: 486.1943. Found: 486.1940.

*3-(4-Acetylphenyl)-2,2-diphenyl-N-(quinolin-8-yl)propanamide (**3e**).* R_f 0.11 (hexane/EtOAc = 10/1). Pale yellow solid. Yield: 80 mg, 57%. Mp = 179−180 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.50 (s, 3H), 3.96 (s, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 7.26−7.34 (m, 7H), 7.36−7.41 (m, 4H), 7.45 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2 H), 8.06 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.53 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.76 (dd, *J* = 7.6, 1.0 Hz, 1H), 10.23 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 26.5, 44.5, 64.4, 116.0, 121.5, 127.2, 127.2, 127.4, 127.8, 128.2, 128.5, 129.5, 131.4, 134.5, 134.9, 136.0, 138.6, 142.0, 144.0, 148.1, 171.7, 198.2; IR (neat) 3330 w, 3019 w, 1679 s, 1604 w, 1523 s, 1423 m; MS *m*/*z* (relative intensity, %) 471 (M^+, 2), 220 (23), 172 (12), 171 (100), 144 (5). HRMS Calcd for $C_{32}H_{26}N_2O_2$: 470.1994. Found: 470.1996.

*3-(4-Nitrophenyl)-2,2-diphenyl-N-(quinolin-8-yl)propanamide (**3f**).* R_f 0.2 (hexane/EtOAc = 10/1). Pale yellow solid. Yield: 61 mg, 43%. Mp = 210 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.99 (s, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.27−7.33 (m, 7H), 7.36−7.40 (m, 4H), 7.45 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 8.07 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.54 (dd, *J* = 4.2, 1.2 Hz, 1H) 8.74 (dd, *J* = 8.0, 1.2 Hz, 1H), 10.23 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 44.4, 64.4, 116.0, 121.5, 121.6, 122.4, 127.2, 127.5, 128.4, 129.4, 132.0, 134.4, 136.0, 138.6, 141.7, 146.3, 146.3, 148.2, 171.4; IR(neat) 3328 w, 3059 w, 1680 m, 1520 s, 1485 m; MS *m*/*z* (relative intensity, %) 473 (M^+, 5), 220 (23), 172 (12), 171 (100). HRMS Calcd for $C_{30}H_{23}N_3O_3$:473.1739. Found: 473.1737.

*3-(4-Chlorophenyl)-2,2-diphenyl-N-(quinolin-8-yl)propanamide (**3g**).* R_f 0.26 (hexane/EtOAc = 10/1). Pale yellow solid. Yield: 79 mg, 57%. Mp = 178−179 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 3.86 (s, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.28−7.32 (m, 7H), 7.33−7.38 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.53 (dd, *J* = 4.0, 1.4 Hz, 1H), 8.75 (dd, *J* = 7.6, 1.4 Hz, 1H), 10.23 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 43.8, 64.4, 116.0, 121.4, 121.4, 127.2, 127.2, 127.4, 127.8, 128.2, 129.6, 131.9, 132.5, 134.5, 136.0, 136.4, 138.6, 142.0, 148.1, 171.8; IR (neat) 3330 w, 3020 w, 1679 m, 1522 s, 1485 s; MS *m*/*z* (relative intensity, %) 462 (M^+, 5), 220 (24), 172 (11), 171 (100), 144 (9). HRMS Calcd for $C_{30}H_{23}ClN_2O$: 462.1499. Found: 462.1501.

*2,2-Diphenyl-N-(quinolin-8-yl)-3-(p-tolyl)propanamide (**3h**).* R_f 0.26 (hexane/EtOAc = 10/1). Off white solid. Yield: 93 mg, 70%. Mp = 150−151 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.20 (s, 3H), 3.87 (s, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 7.28−7.31 (m, 7H), 7.36−7.42 (m, 5H), 7.49 (t, *J* = 8.0 Hz, 1H), 8.03 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.51 (dd, *J* = 2.4, 1.2 Hz, 1H), 8.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 10.23 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 21.0, 44.0, 64.3, 116.0, 121.3, 121.4, 127.0, 127.2, 127.7, 128.0, 128.1, 129.7, 131.1, 134.6, 134.6, 135.5, 135.9, 138.6, 142.3, 148.0, 172.2; IR (neat) 3331 w, 3020 w, 1679 m, 1521 s, 1483 m; MS *m*/*z* (relative intensity, %) 442 (M^+, 16), 220 (21), 172 (12), 171 (100), 144 (21). HRMS Calcd for $C_{31}H_{26}N_2O$: 442.2045. Found: 442.2044.

*2,2-Diphenyl-N-(quinolin-8-yl)-3-(m-tolyl)propanamide (**3i**).* R_f 0.26 (hexane/EtOAc = 10/1). Off white solid. Yield: 66 mg, 50%. Mp = 164 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.08 (s, 3H), 3.87 (s, 2H), 6.50 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.85−6.93 (m, 2H), 7.28−7.31 (m, 7H), 7.36−7.39 (m, 4H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.52 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.78 (dd, *J* = 8.0, 1.6 Hz, 1H), 10.24 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 21.2, 44.3, 64.4, 116.0, 121.3, 121.4, 126.7, 127.0, 127.2, 127.2, 127.4, 127.8, 128.0, 128.0, 129.7, 132.2, 134.7, 136.0, 136.7, 137.6, 138.7, 142.3, 148.1, 172.1; IR (neat) 3331 w, 3056 w, 1681 m, 1523 s, 1485 m; MS *m*/*z* (relative intensity, %) 442 (M^+, 6), 220 (20), 172 (11), 171 (100), 144 (11). HRMS Calcd for $C_{31}H_{26}N_2O$: 442.2045. Found: 442.2048.

*2-(4-Methoxybenzyl)-2-phenyl-N-(quinolin-8-yl)heptanamide (**9a**).* R_f 0.26 (hexane/EtOAc = 10/1). White solid. Yield: 79 mg, 58%. Mp = 144 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.83 (t, *J* = 6.4 Hz, 3H), 1.26−1.55 (m, 6H), 2.01 (t, *J* = 8.0, 2H), 3.35 (d, *J* = 14.0 Hz, 1H), 3.51 (d, *J* = 13.6 Hz, 1H), 3.72 (s, 3H), 6.63 (s, 4H), 7.25−7.36 (m, 6H), 7.46 (d, *J* = 8.0, 1H), 7.54 (t, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.58 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 9.81 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.0, 22.4, 24.1, 32.3, 34.0, 40.8, 55.1, 56.6, 113.0, 116.0, 21.01, 121.4, 127.0, 127.3, 127.7, 127.8, 128.4, 129.3, 131.2, 134.7, 138.6, 143.0, 148.1, 158.0, 174.7. HRMS Calcd for $C_{30}H_{32}N_2O_2$: 452.2464. Found: 452.2469.

*2-Butyl-2-(4-methoxybenzyl)-N-(quinolin-8-yl)hexanamide (**10a**).* R_f 0.28 (hexane/EtOAc = 10/1). Pale brown solid. Yield: 26 mg, 21%. Mp = 97−98 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 0.92 (t, *J* = 6.8 Hz, 6H), 1.32−1.38 (m, 8H), 1.59−1.80 (m, 4H), 3.01 (s, 2H), 3.68 (s, 3H), 6.70 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.42 (dd, *J* =

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8.4, 4.0, 1H), 7.48−7.57 (m, 2H), 8.14 (dd, J = 8.4, 1.6 Hz, 1H), 8.74 (dd, J = 4.4, 1.6 Hz, 1H), 8.82 (dd, J = 8.0, 1.6 Hz, 1H), 10.15 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 14.0, 23.2, 26.2, 34.3, 40.2, 51.6, 55.0, 113.3, 116.2, 121.1, 121.4, 127.4, 127.9, 129.8, 130.9, 134.4, 136.2, 138.7, 148.1, 158.0, 175.4. HRMS Calcd for $C_{27}H_{34}N_2O_2$: 418.2620. Found: 418.2617.

*2-Benzyl-2-(4-methoxybenzyl)-N-(quinolin-8-yl)butanamide (**11a**).* R_f 0.23 (hexane/EtOAc = 10/1). Pale brown solid. Yield: 55 mg, 43%. Mp = 97−98 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.18 (t, J = 7.2 Hz, 3H), 1.75 (q, J = 7.2 Hz, 2H), 2.95 (dd, J = 20.8, 13.6 Hz, 2H), 3.29 (dd, J = 25.6,14.0 Hz, 2H), 3.64 (s, 3H), 6.66 (d, J = 8.0 Hz, 2H), 7.07−7.21 (m, 7H), 7.36 (dd, J = 8.4, 4.0 Hz,1H), 7.47 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.60 (dd, J = 4.0, 1.2 Hz, 1H), 8.86 (dd, J = 8.0, 1.2 Hz, 1H), 9.95 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 8.7, 23.8, 40.9, 41.5, 53.3, 55.0, 113.4, 116.2, 121.3, 121.4, 126.2, 127.3, 127.8, 128.0, 129.5, 130.1, 131.0, 134.2, 136.0, 137.7, 138.6, 148.0, 158.0, 174.6. HRMS Calcd for $C_{28}H_{28}N_2O_2$: 424.2151. Found: 424.2145.

*3-(4-Methoxyphenyl)-2-methyl-2-phenyl-N-(quinolin-8-yl)propanamide (**12a**).* R_f 0.11 (hexane/EtOAc = 10/1). White solid. Yield: 45 mg, 38%. Mp = 136 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.68 (s, 3H), 3.34 (d, J = 13.6 Hz, 1H), 3.56 (d, J = 13.6 Hz, 1H), 3.71 (s, 3H), 6.66 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 7.27−7.38 (m, 4H), 7.43−7.45 (m, 3H), 7.52 (t, J = 8.4 Hz, 1H), 8.06 (dd, J = 8.4, 1.6 Hz, 1H), 8.57 (dd, J = 4.0, 1.6 Hz, 1H), 8.80 (d, J = 8.0 Hz, 1H), 9.89 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 22.8, 44.3, 52.9, 55.0, 113.0, 116.0, 121.2, 121.4, 127.1, 127.2, 127.3, 127.8, 128.5, 129.5, 131.5, 134.6, 136.0, 138.6, 143.1, 148.1, 158.0, 175.1. HRMS Calcd for $C_{26}H_{24}N_2O_2$: 396.1838. Found: 396.1838.

*1-(4-Methoxybenzyl)-N-(quinolin-8-yl)cyclohexanecarboxamide (**13a**).* R_f 0.23 (hexane/EtOAc = 10/1). Colorless oil. Yield: 29 mg, 25%. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.32−1.75 (m, 8H), 2.22−2.25 (m, 2H), 2.90 (s, 2H), 3.61 (s, 3H), 6.61 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 7.40 (dd, J = 8.4, 4.0 Hz, 1H), 7.47 (dd, J = 8.0, 4.0, 1H), 7.54 (t, J = 8.4 Hz, 1H), 8.12 (dd, J = 8.4, 2.0 Hz, 1H), 8.69 (dd, J = 4.0, 2.0 Hz, 1H), 8.80 (dd, J = 8.0, 1.6 Hz, 1H), 10.00 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 23.1, 25.9, 34.1, 46.4, 49.6, 55.0, 113.2, 116.3, 121.1, 121.4, 127.4, 127.8, 129.1, 131.0, 134.5, 136.1, 138.7, 148.0, 158.1, 174.7. HRMS Calcd for $C_{24}H_{26}N_2O_2$: 374.1990. Found: 374.1994.

*1-(4-Methoxybenzyl)-N-(quinolin-8-yl)cycloheptanecarboxamide (**14a**).* R_f 0.34 (hexane/EtOAc = 5/1). Pale yellow oil. Yield: 33 mg, 28%. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.58−1.78 (m, 10 H), 2.22−2.28 (m, 2H), 2.93 (s, 2H), 3.63 (s, 3H), 6.63 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.41 (dd, J = 8.4, 4.0 Hz, 1H), 7.48 (dd, J = 8.4, 1.6 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 8.13 (dd, J = 8.0, 1.6 Hz, 1H), 8.71 (dd, J = 4.0, 1.6 Hz, 1H), 8.82 (dd, J = 8.0, 1.2 Hz, 1H), 10.02 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 23.5, 30.0, 36.1, 46.9, 52.5, 55.0, 113.2, 116.2, 121.1, 121.4, 127.4, 127.8, 129.7, 131.0, 134.6, 136.1, 138.7, 148.0, 158.1, 175.9. HRMS Calcd for $C_{25}H_{28}N_2O_2$: 388.2152. Found: 388.2152.

*1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-N-(quinolin-8-yl)cycloheptanecarboxamide (**14b**).* R_f 0.23 (hexane/EtOAc = 5/1). White solid. Yield: 16 mg, 11%. Mp = 79−80 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.44−1.68 (m, 5H), 1.92−1.95 (m, 3H), 2.31−2.49 (m, 3H), 2.79 (t, J = 10.0 Hz, 1H), 2.98 (d, J = 13.6 Hz, 1H), 3.11 (d, J = 14.0 Hz, 1H), 3.64 (s, 3H), 3.82 (s, 3H), 6.60 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.41 (dd, J = 8.0, 4.0 Hz, 1H), 7.48−7.56 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.72 (d, J = 4.4 Hz, 1H), 8.80 (d, J = 7.2 Hz, 1H), 10.12 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 23.8, 31.1, 35.7, 40.1, 40.7, 43.8, 45.8, 51.9, 55.0, 55.2, 113.4, 113.8, 116.3, 121.2, 121.4, 127.4 (two overlapping peaks), 127.8, 129.5, 131.0, 134.5, 136.2, 142.0, 148.1, 157.6, 158.1, 175.9. HRMS Calcd for $C_{32}H_{34}N_2O_3$: 494.2569. Found: 494.2568.

*2-(4-Methoxyphenyl)-1-phenyl-N-(quinolin-8-yl)cyclobutanecarboxamide (**15a**).* R_f 0.31 (hexane/EtOAc = 5/1). White solid. Yield: 43 mg, 35%. Mp = 128 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.26−2.37 (m, 2H), 2.70−2.78 (m, 1H), 3.27 (t, J = 7.6 Hz, 1H), 3.48 (s, 3H), 4.28 (t, J = 7.6 Hz, 1H), 6.57 (d, J = 2H), 7.23 (dd, J = 8.4, 4.0 Hz, 1H), 7.29−7.46 (m, 7H), 7.53 (d, J = 8.0 Hz, 2H), 7.96 (dd, J = 8.4, 1.6 Hz, 1H), 8.37 (dd, J = 4.0, 1.6 Hz, 1H), 8.57 (dd, J = 8.0, 1.6 Hz, 1H), 9.27 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 24.6, 29.0, 49.8, 55.0, 61.4, 113.5, 115.6, 120.9, 121.0, 126.3, 126.9, 127.0, 129.0, 129.2, 132.6, 134.5, 135.6, 138.4, 146.0, 147.6, 158.4, 171.5. HRMS Calcd for $C_{27}H_{24}N_2O_2$: 408.1838. Found: 408.1835.

*2,4-Bis(4-methoxyphenyl)-1-phenyl-N-(quinolin-8-yl)cyclobutanecarboxamide (**15b**).* R_f 0.20 (hexane/EtOAc = 5/1). White solid. Yield: 8 mg, 5%. Mp = 87 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.72 (q, 8.0 Hz, 1H), 3.49 (q, J = 10.4 Hz, 1H), 3.69 (s, 6H), 4.09 (dd, J = 10.8, 8.0 Hz, 1H), 6.78 (d, J = 8.8 Hz, 4H), 7.20 (dd, J = 8.0, 4.0 Hz, 1H), 7.27−7.34 (m, 2H), 7.43−7.48 (m, 5H), 7.34 (t, J = 7.6 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.92 (dd, J = 8.0, 1.6 Hz, 1H), 8.31 (dd, J = 4.4, 1.6 Hz, 1H), 8.44 (dd, J = 7.6, 1.6 Hz, 1H), 9.38 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 30.8, 47.2, 55.1, 67.6, 113.4, 115.9, 120.9, 121.0, 127.1, 127.3, 127.5, 129.1, 129.6, 132.6, 134.3, 135.7, 138.5, 145.1, 147.6, 158.1, 169.6. HRMS Calcd for $C_{34}H_{30}N_2O_3$: 514.2256. Found: 514.2253.

*2-(4-Methoxyphenyl)-1-phenyl-N-(quinolin-8-yl)cyclopentanecarboxamide (**16a**).* R_f 0.23 (hexane/EtOAc = 5/1). White solid. Yield: 47 mg, 37%. Mp = 130 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.74−1.81 (m, 1H), 2.14−2.33 (m, 4H), 3.40−3.11 (m, 1H), 3.54 (s, 3H), 3.92 (t, J = 8.0 Hz, 1H), 6.54 (d, J = 8.8 Hz, 2H), 7.23−7.31 (m, 4H), 7.33−7.44 (m, 4H), 7.62 (d, J = 8.8 Hz, 2H), 7.97 (dd, J = 8.0, 1.6 Hz, 1H), 8.39 (dd, J = 4.4, 1.6 Hz, 1H), 8.56 (dd, J = 8.0, 1.6 Hz, 1H), 9.35 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 22.5, 33.3, 38.3, 52.8, 54.9, 65.0, 113.3, 115.7, 120.9, 121.1, 126.9, 127.2, 127.5, 128.7, 130.0, 134.1, 134.5, 138.4, 144.1, 147.7, 158.0, 173.4. HRMS Calcd for $C_{28}H_{26}N_2O_2$: 422.1994. Found: 422.1992.

*2,5-Bis(4-methoxyphenyl)-1-phenyl-N-(quinolin-8-yl)cyclopentanecarboxamide (**16b**).* R_f 0.23 (hexane/EtOAc = 5/1). White solid. Yield: 24 mg, 15%. Mp = 130 °C. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 2.31−2.38 (m, 2H), 2.81−2.86 (m, 2H), 3.57 (s, 6H), 3.74−3.78 (m, 2H), 6.57 (d, J = 8.8 Hz, 4H), 7.16 (dd, J = 8.4, 4.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 4H), 7.26−7.33 (m, 5H), 7.37 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (dd, J = 8.0, 1.6 Hz, 1H), 8.16 (dd, J = 4.0, 1.6 Hz, 1H), 8.76 (dd, J = 7.2, 1.6 Hz, 1H), 9.14 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 30.7, 54.9, 56.8, 69.2, 113.0, 115.8, 120.9, 121.0, 127.0, 127.1, 127.5, 128.0, 129.3, 130.8, 132.3, 134.5, 135.4, 138.5, 140.5, 147.5, 158.1, 171.5. HRMS Calcd for $C_{35}H_{32}N_2O_3$: 528.2413. Found: 528.2414.

*2-Cyclohexyl-3-(4-methoxyphenyl)-N-(quinolin-8-yl)propanamide (**17a**).* R_f 0.23 (hexane/EtOAc = 5/1). Pale yellow oil. Yield: 55 mg, 47%. ^{1}H NMR ($CDCl_3$, 399.78 MHz) 1.34−1.31 (m, 5H), 1.64−1.87 (m, 5H), 2.04 (d, J = 8.4 Hz, 1H), 2.46−2.52 (m, 1H), 2.92−3.04 m, 2H), 3.64 (s, 3H), 6.69 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.36 (dd, J = 8.4, 4.0 Hz, 1H), 7.41−7.50 (m, 2H), 8.07 (dd, J = 8.4, 1.2 Hz, 1H), 8.70 (dd, J = 4.0, 2.0 Hz, 1H), 8.76 (d, J = 8.0 Hz, 1H), 9.52 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz) 26.39 (t, J = 5.7 Hz), 30.9, 31.1, 35.1, 40.7, 55.1, 58.1, 113.7, 116.3, 121.2, 121.4, 127.3, 127.8, 129.8, 132.3, 134.3, 136.2, 138.3, 148.0, 157.8, 173.4. HRMS Calcd for $C_{25}H_{28}N_2O_2$: 388.2151. Found: 388.2153.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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