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Copper-Catalyzed Base-Free N-Arylation of 8-Aminoquinoline Amides through Chelation Assistance

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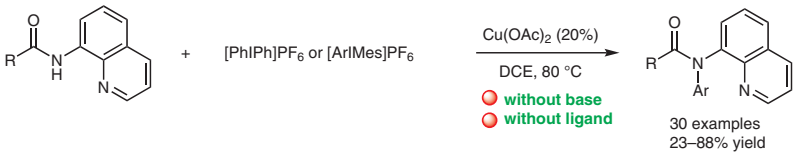

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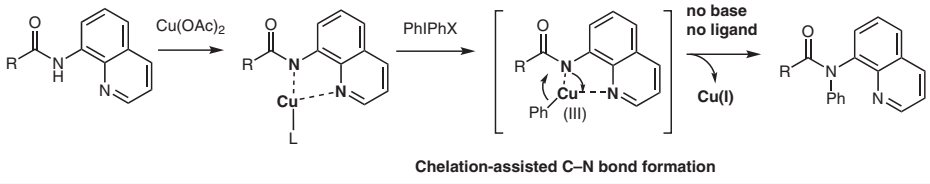
Abstract A new and efficient approach for the N-arylation of 8-aminoquinoline amides with diaryliodonium salts has been developed. This chelation-assisted selective C–N cross-coupling reaction gave the desired N-arylated 8-aminoquinoline in moderate to good yields. In contrast to previous reports, no additional ligands and bases are used in this transformation. In addition, the anion of the diaryliodonium salt plays an important role in the success of the process.

Key words copper catalysis, diaryliodonium salts, arylation, aminoquinolines, chelation assistance, quinolinylarylamides

8-Aminoquinolines, as important synthetic intermediates, are widely used in dye chemistry, medicinal chemistry, and materials chemistry.[1] Since the pioneering work of Daugulis and co-workers,[2] 8-aminoquinolines have been widely used as auxiliary chelating directing groups to assist C(sp^2 or sp^3)–H functionalization, thereby providing a powerful tool for the syntheses of diverse molecules.[2] Recently, the C2-H, C4-H, C5-H, and C7-H transformations of 8-aminoquinoline frameworks have also been studied for the construction of C–C, C–O, C–N, C–halogen, C–P, and C–S bonds.[3] However, due to difficulties in controlling its regioselectivity, direct C–H bond functionalization of 8-aminoquinolines has encountered some significant challenges.[4] In addition, although considerable progress has been made in transformations of 8-aminoquinolines skeletons, direct functionalization of the N–H bond of 8-aminoquinolines has rarely been reported. In 2015, the Nicholls group reported a copper-catalyzed amidation of aryl halides with 8-aminoquinoline through chelation assistance.[5] Li and co-workers recently realized a copper-promoted N-arylation of 8-acylaminoquinolines with triarylbismuth reagents.[6] During the preparation of our manuscript, the Yin group reported a copper(0)-induced arylation of phosphinamides with arylboronic acids.[7] Consequently, the development of an efficiently alternative synthetic route for the functionalization of the N–H bond of 8-aminoquinolines remains of utmost importance.

Diaryliodonium salts are important electrophilic arylating reagents in organic synthesis due to their low toxicity, ease of handling, and excellent selectivity, and they can be used for regiospecific arylation of a variety of nucleophiles.[8] Recently, metal-catalyzed arylations of lactams and of primary and secondary acyclic amides with diaryliodonium salts have also been realized.[9] However, most *N*-arylation reactions require several equivalents of base in the reaction, which limits their widespread application in large-scale synthesis. Therefore, development of base-free arylation using an diaryliodonium salt was highly desirable. As a continuation of our long-term interest in the functionalization of 8-aminoquinolines,[3d] we report a general protocol for the

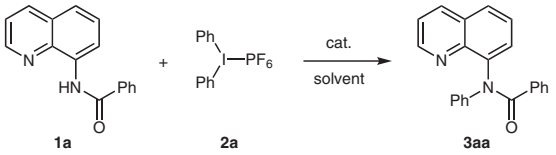


Scheme 1 Our reaction design

N-arylation of 8-aminoquinolines amides through 8-amide chelation assistance, which permits the introduction of sterically hindered aryl groups under copper-catalyzed base-free conditions (Scheme 1).

Our investigations began with the reaction of *N*-quinolin-8-ylbenzamide (**1a**) with diphenylodionium hexafluorophosphate (**2a**) with $Cu(OAc)_2{\cdot}H_2O$ as a catalyst (Table 1). To our delight, the N-arylation product **3aa** was obtained in 66% yield after 48 hours (Table 1, entry 1). In an attempt to improve the transformation, Ag_2O and Ag_2CO_3 were used as additives, but poor results were obtained (entries 2 and 3). When 10% $FeCl_3$ was used as a co-catalyst, a lower yield was obtained (entry 4). In addition, the ligands 1,10-phenanthroline (Phen) and PPh_3 were detrimental to the reaction (entries 5 and 6). Interestingly, when 4 Å MS was added as an additive, the yield increased to 73% (entry 7). When anhydrous $Cu(OAc)_2$ was used without 4 Å MS, a lower yield (46%) was obtained (entry 8). Interestingly, when 4 Å MS was added to the system with anhydrous $Cu(OAc)_2$, a higher yield was obtained (entries 9 and 8), demonstrating that 4 Å MS was essential for this transformation. In addition, the addition of two equivalents of water completely shut down the reaction (entry 10). No improved results were observed on decreasing or increasing the loading of the catalyst (entries 11 and 12). Several other copper catalysts [$Cu(OTf)_2$, CuCl, and CuI] were tried, but did not give better results (entries 13–15). Other solvents were also tested; CH_2Cl_2 gave only a 17% yield (entry 16), and no product was obtained when DMF or 1,4-dioxane was used as the solvent (entries 17 and 18). The copper catalyst was crucial for the transformation, and no target product was detected when it was omitted (entry 19). Finally, the influence of the iodonium counterion was investigated, and the triflate and tetrafluoroborate both failed to cause reaction under the standard conditions (entries 20 and 21). When mesityl(phenyl)iodonium hexafluorophosphate was used instead of its diphenyl analogue, a lower yield (63%) was obtained (entry 22), showing that $[PhI^+Ph]PF_6^-$ is more active than $[PhI^+Mes]PF_6^-$ in this transformation.

Table 1 Optimization of the Reaction[a]



1a **2a** **3aa**

Entry	Catalyst	Additive	Solvent	Yield[b] (%)
1	$Cu(OAc)_2{\cdot}H_2O$ (20%)	–	DCE	66
2	$Cu(OAc)_2{\cdot}H_2O$ (20%)	Ag_2O (1.2 equiv)	DCE	11
3	$Cu(OAc)_2{\cdot}H_2O$ (20%)	Ag_2CO_3 (1.2 equiv)	DCE	33
4	$Cu(OAc)_2{\cdot}H_2O$ (20%)	$FeCl_3$ (10%)	DCE	39
5	$Cu(OAc)_2{\cdot}H_2O$ (20%)	Phen (20%)	DCE	20
6	$Cu(OAc)_2{\cdot}H_2O$ (20%)	PPh_3 (20%)	DCE	14
7	**$Cu(OAc)_2{\cdot}H_2O$ (20%)**	**4 Å MS**	**DCE**	**73**
8	$Cu(OAc)_2$ (20%)	–	DCE	46
9	$Cu(OAc)_2$ (20%)	4 Å MS	DCE	57
10	$Cu(OAc)_2$ (20%)	H_2O (2.0 equiv)	DCE	<5
11	$Cu(OAc)_2{\cdot}H_2O$ (10%)	4 Å MS	DCE	49
12	$Cu(OAc)_2{\cdot}H_2O$ (30%)	4 Å MS	DCE	58
13	$Cu(OTf)_2$ (20%)	4 Å MS	DCE	49
14	CuCl (20%)	4 Å MS	DCE	37
15	CuI (20%)	4 Å MS	DCE	41
16	$Cu(OAc)_2{\cdot}H_2O$ (20%)	4 Å MS	CH_2Cl_2	17
17	$Cu(OAc)_2{\cdot}H_2O$ (20%)	4 Å MS	DMF	0
18	$Cu(OAc)_2{\cdot}H_2O$ (20%)	4 Å MS	1,4-dioxane	0
19	–	4 Å MS	DCE	0
20[c]	$Cu(OAc)_2{\cdot}H_2O$ (20%)	4 Å MS	DCE	0
21[d]	$Cu(OAc)_2{\cdot}H_2O$ (20%)	4 Å MS	DCE	0
22[e]	$Cu(OAc)_2{\cdot}H_2O$ (20%)	4 Å MS	DCE	63

[a] Reaction conditions: **1a** (0.2 mmol), salt **2a** (2.0 equiv), catalyst, additive, solvent (3.0 mL), in air, 80 °C, 48 h.
[b] Isolated yield.
[c] $[PhI^+Ph]BF_4^-$ (2 equiv) was used.
[d] $[PhI^+Ph]OTf^-$ (2 equiv) was used.
[e] $[PhI^+Mes]PF_6^-$ (2 equiv) was used.

With the best reaction conditions in hand (Table 1, entry 7), we examined the scope of the reaction for the phenylation of 8-aminoquinoline amides **1** with the iodonium salt **2a** (Figure 1). First, the effects of various functional groups, including fluoro, chloro, bromo, trifluoromethyl, *tert*-butyl, and ether groups, in various positions of the benzoyl group of **1** were examined, and moderate to good yields were obtained. Electron-withdrawing substituents favored product formation (**3ae**, **3af**, **3ag**, and **3ai**), whereas electron-donating groups slightly hindered the reaction (**3ab**, **3ac**, **3ad**, and **3ah**). A sterically demanding *ortho*-methyl group did not hamper the transformation, and a high yield of **3ak** was obtained. Then, amides with butyl or cyclohexyl substituents on the acyl group were tried under the standard conditions, and moderate yields of the corresponding products **3al** and **3am** were obtained. A thienyl substituent was also tolerated, giving a 76% yield of product **3an**. A tosyl-protected 8-aminoquinoline was also suitable for this reaction, giving a 77% yield of product **3ao**. *N*-(6-Methoxyquinolin-8-yl)benzamide delivered the corresponding product **3ap** in moderate yield, whereas, due to steric hindrance, *N*-(2-methylquinolin-8-yl)benzamide gave only a low yield of **3aq**.

To confirm the structural assignment of the products from the present N-arylation, the structure of product **3ag** was unambiguously assigned by means of X-ray crystallography (Figure 2).[10]

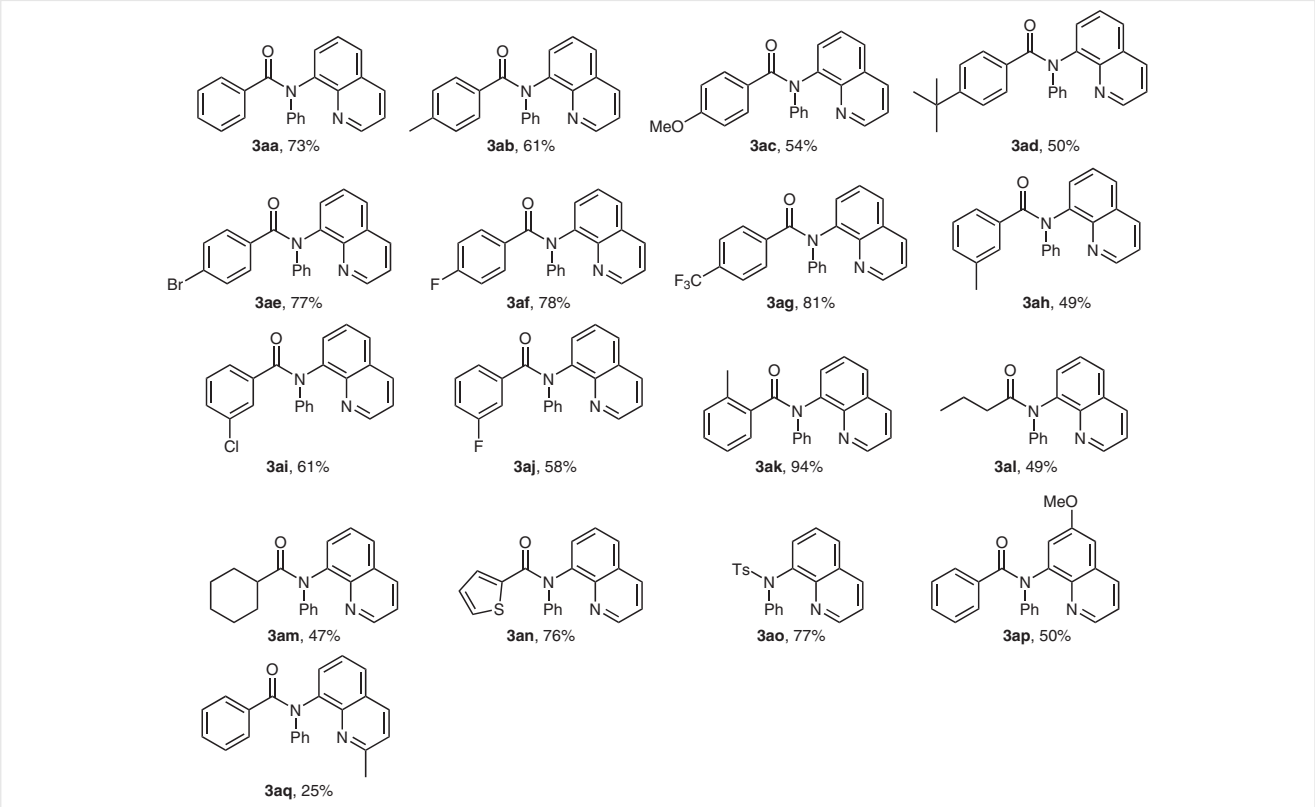


Figure 1 The scope of the 8-aminoquinoline amides

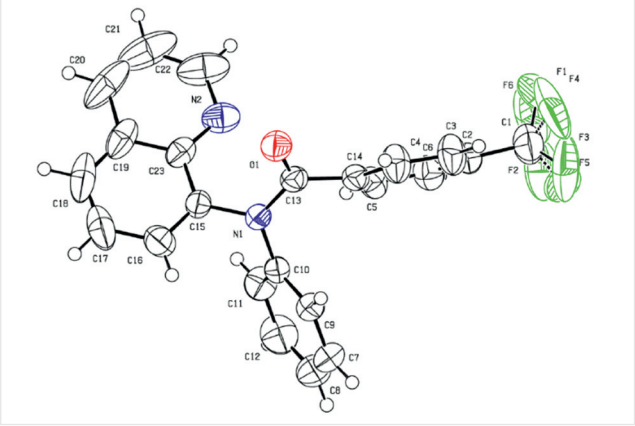
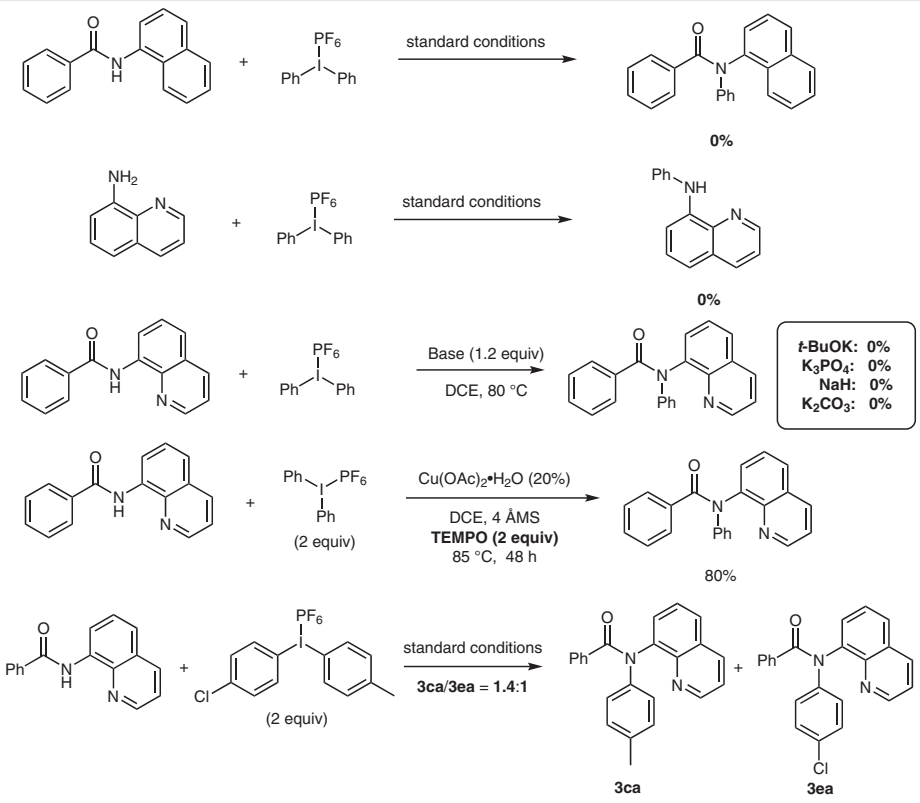


Figure 2 The structure of **3ag**

Unsymmetrical phenyl(mesityl)iodonium salts with various substituents on the phenyl group proved successful under the optimized reaction conditions, giving the corresponding products **3ba–1a** (Figure 3). The iodonium salts with electron-donating substituents such as methyl or *tert*-butyl delivered better results than those with electron-withdrawing substituents such as F, Cl, Br, CF_3, Ac, or CO_2Me. When substrates containing *meta*-methyl or *meta*-fluoro substituents were tested in this transformation, moderate yields of the corresponding products **3ja** and **3ka** were obtained. A substrate containing an *ortho*-methyl was also tolerated, but gave a lower yield of product **3la** due to the steric hindrance. Unfortunately, the substrate containing a 2-pyridyl heteroaromatic group was not suitable for this transformation, and the starting material **3a** was recovered.

To gain insight into the mechanism, we performed several control experiments and mechanistic studies (Scheme 2). First, when *N*-(1-naphthyl)benzamide was subject to the standard conditions, none of the target product was obtained. This showed that internal chelation assistance is crucial for the success of the transformation. Unprotected quinoline-8-amine also failed to react under the standard conditions, highlighting the importance of the acyl group. In addition, a series of bases were tested instead of the copper catalyst, but no product was obtained. This confirmed the importance of the copper catalyst. When 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) was added to the reaction system as a radical quencher, a higher yield of the product was obtained, suggesting that the reaction does not involve a radical pathway. Finally, when an unsymmetrical diaryliodonium salt containing methyl and chloro groups was used in the reaction under standard conditions, a mix-



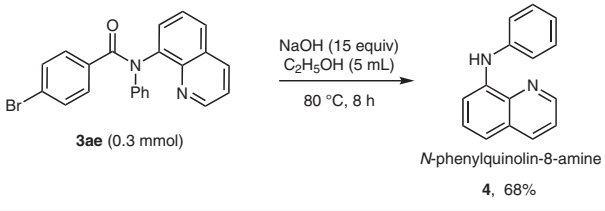
Scheme 2 Control experiments

ture of **3ca** and **3ea** in a ratio of 1.4:1 was obtained, implying that an electrophilic addition pathway might be involved in this transformation.

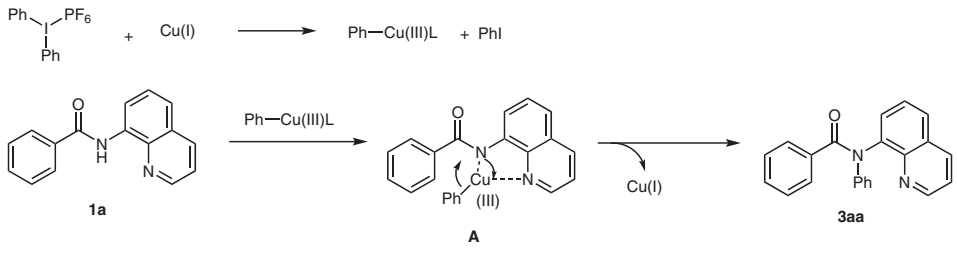
On the basis of the control experiments, mechanistic studies, and previous reports,[5,11] we propose the plausible reaction mechanism shown in Scheme 3. First, the copper catalyst reacts with the diaryliodonium salt to give an activated aromatic electrophile. Then the proposed Cu(III) aromatic electrophile undergoes ligand exchange with substrate **1a** to give intermediate **A**, which undergoes smooth reductive elimination to deliver product **3aa** with concurrent formation of low-valent Cu(I) species.

Importantly, the benzoyl protecting group on the products **3** can be easily removed by base hydrolysis (Scheme 4). For example, treatment of amide **3ae** with 15 equivalents of NaOH in ethanol at 80 °C for eight hours gave *N*-phenylquinolin-8-amine (**4**) in moderate yield (68%), thereby demonstrating the usefulness of the synthetic method.

In conclusion, we have developed a copper-catalyzed 8-amide chelation-assisted N-arylation of 8-aminoquinoline



Scheme 4 Removal of a benzoyl group



Scheme 3 Proposed mechanism

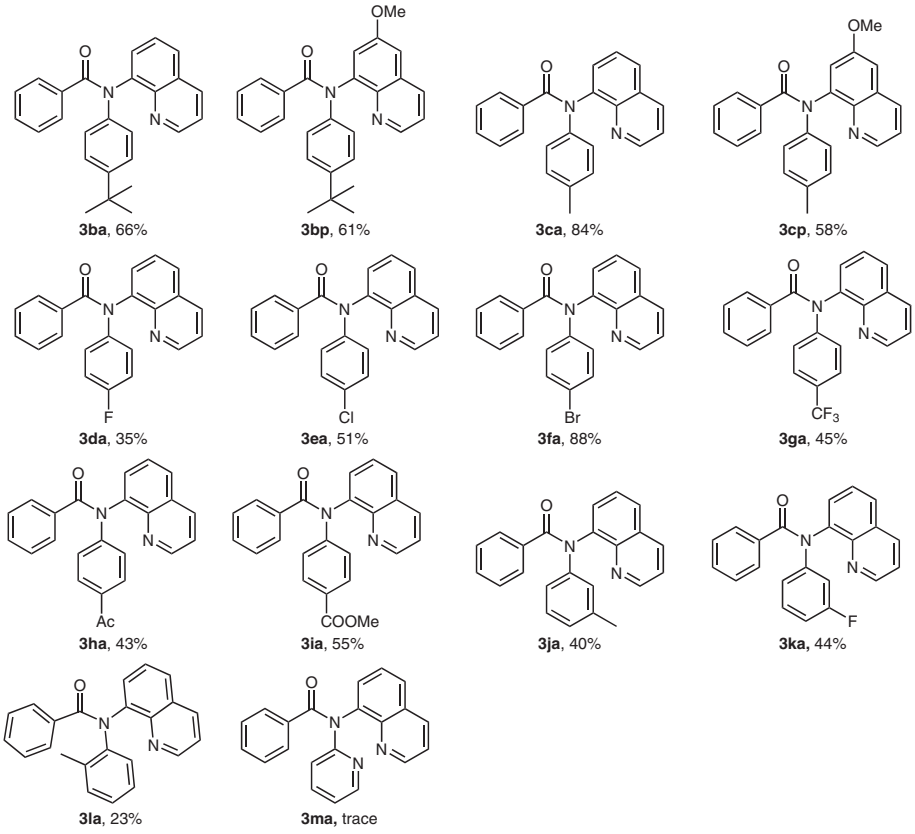


Figure 3 The scope of aryl(mesityl)iodonium hexafluorophosphates

amides with diaryliodonium salts.[12] This new strategy is operationally simple and provides a convenient synthetic route to N-arylated 8-aminoquinolines in moderate to good yields. No additional ligands or bases are used in the reaction, making this transformation sustainable and practical.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610906.

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(12) ***N*-Aryl-*N*-quinolin-8-ylaroylamides 3aa–3ma; General Procedure**

An oven-dried Schlenk tube (10 mL) equipped with a magnetic stirrer bar was charged with the appropriate *N*-quinolin-8-ylaroylamide **1** (0.3 mmol), diaryliodonium hexafluorophosphate **2** (0.6 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%, 0.06 mmol), and 4 Å MS (40 mg). DCE (3.0 mL) was then added from a syringe, and the mixture was stirred for 48 h at 80 °C in air. H_2O (6 mL) was added to quench the reaction, and the resulting mixture was extracted with EtOAc (×2). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash column chromatography [silica gel, PE–EtOAc (3:1)].

***N*-Phenyl-*N*-quinolin-8-ylbenzamide (3aa)**

Colorless solid; yield: 71 mg (73%); mp 125–128 °C. IR (KBr): 3054, 1660, 1594, 1493, 1463, 1343, 1310, 1269, 1177, 1132, 1075, 1028, 825, 789, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.89–8.91 (m, 1 H), 8.07–8.09 (m, 1 H), 7.70–7.72 (m, 1 H), 7.57–7.62 (m, 3 H), 7.45–7.49 (m, 1 H), 7.32–7.35 (m, 1 H), 7.22–7.24 (m, 4 H), 7.09–7.16 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 150.7, 144.7, 144.4, 141.8, 136.8, 135.8, 129.7, 129.3, 129.2, 128.9, 128.7, 127.6, 127.4, 126.9, 126.3, 125.8, 121.6. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O$: 325.13354; found: 325.13327.