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Aminolysis of Aryl Ester Using Tertiary Amine as Amino Donor via C−O and C−N Bond Activations

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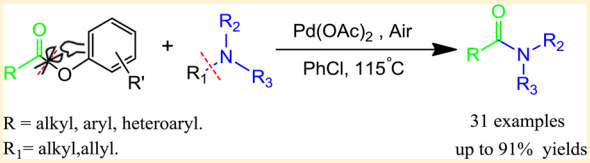
Supporting Information

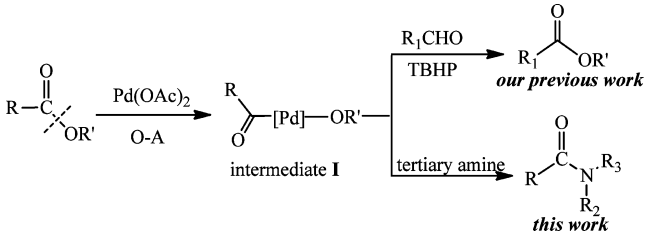
ABSTRACT: An aminolysis reaction between various aryl esters and inert tertiary amines by C−O and C−N bond activations has been developed for the selective synthesis of a broad scope of tertiary amides under neutral and mild conditions. The mechanism may undergo the two key steps of oxidative addition of acyl C−O bond in parent ester and C−N bond cleavage of tertiary amine via an iminium-type intermediate.



Many esters are produced on an industrial scale and are primarily used as solvents. The use of these fine chemicals as substrates of transition-metal catalytic reactions may offer more environmentally benign and atom-economical processes. When a transition metal undergoes oxidative addition into a ester, it can either insert into the acyl C−O bond or the alkyl C−O bond.[1,2] The alkyl C−O bond cleavage has been studied extensively in the field of cross-coupling reaction,[3] but there are challenges associated with acyl C−O bond cleavage because of decarbonylation phenomenon.[4] So far, in the rare cases when the acyl C−O bond is activated and decarbonylation is suppressed, the acyl metal alkoxide complexes can undergo additional transformations.[5]

Our previous work confirmed that *N*-heteroarene-2-carboxylate can oxidative add to palladium via acyl C−O bond activation, and its alkoxy part could combine with the acyl group of aldehyde to give a new ester.[6] The mechanism proposed herein indicates that the intermediate **I** is likely to be produced in this reaction (see Scheme 1). We consider that under the right circumstances its acyl part can be taken on to further chemical transformations. Catalyzed by palladium, tertiary amine could undergo C−N bond cleavage and generate a metal complex containing a M−N bond.[7] Because an amide is more stable than ester on the energetic level, we postulated that acyl part of intermediate **I** could combine via amino group bonding on the palladium to produce amide.

Scheme 1. Proposed New Strategy for Acyl C−O Bond Activation of Ester



Here, we report the first example of aminolysis of aryl ester using inert tertiary amine as amino donor via C−O and C−N bond activations. Initially, a set of experiments was carried out using perfluorophenyl quiline-2-carboxylate **1a** with a *N*-heteroarene moiety as a coordinating group and *N*,*N*-diethylaniline **2a** as model substrates. To our delight, in the presence of $Pd(OAc)_2$ (5 mol %), the desired product, *N*-ethyl-*N*-phenylquinoline-2-carboxamide **3aa**, was isolated after refluxing **1a** and **2a** in toluene (Table 1, entry 1). Various palladium sources and other transition-metal catalysts were also tested, and the results demonstrated that $Pd(OAc)_2$ was the best catalyst (entries 2−4). It was noteworthy that no desired amide **3aa** was obtained without any catalyst (entry 5). A series of ligands were screened in the reaction. The yields of **3aa** did not rise but rather reduced remarkably (entries 6−9). The same disappointing results were obtained by adding bases LiOAc and CsF to the reaction solution (entries 10 and 11). Switching to other solvents, PhCl showed good conversion to the best yield of 81% (entries 12 and 13). Increasing the temperature to 130 °C does not increase the yield (entry 14).

Using the conditions from Table 1, entry 13, the scope of the aminolysis reaction was investigated with a variety of tertiary amines. As shown in Table 2, both trialkyl tertiary amines **2b**, **2c** and unsaturated triallyl amine **2d** were found to react smoothly with **1a** to give the aminolysis products **3ab**−**ad** in yields up to 91% (Table 2, entries 1−3). Surprisingly, no product formation was observed with triphenylamine **2e** as an amine source, in which the *N* atom conjugated with three benzene rings, thus suggesting that the sp^2 C−N bond does not cleave under these conditions. Because *N*,*N*-dimethylaniline can be oxidized by oxygen in the presence of palladium,[8] we used Michler's ketone **2f** as an aniline analogue and obtained

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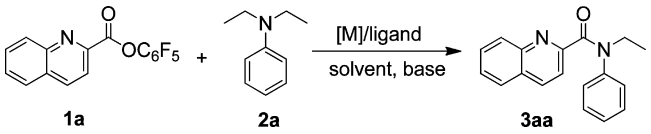
Table 1. Optimization of Aminolysis Reaction between Perfluorophenyl Quiline-2-carboxylate 1a and *N*,*N*-Diethylaniline 2a[a]



1a 2a 3aa

entry	catalyst	ligand	base	solvent	*T* (°C)	yield[b] (%)
1	$Pd(OAc)_2$			toluene	115	67
2	$PdCl_2$			toluene	115	16
3	$CuCl_2$			toluene	115	
4	$FeCl_3$			toluene	115	
5				toluene	115	
6	$Pd(OAc)_2$	PPh_3		toluene	115	27
7	$Pd(OAc)_2$	Pcy_3		toluene	115	26
8	$Pd(OAc)_2$	dppe		toluene	115	63
9	$Pd(OAc)_2$	dipyridyl		toluene	115	
10	$Pd(OAc)_2$		LiOAc	toluene	115	56
11	$Pd(OAc)_2$		CsF	toluene	115	45
12	$Pd(OAc)_2$			xylene	130	75
13	$Pd(OAc)_2$			PhCl	115	81
14	$Pd(OAc)_2$			PhCl	130	82

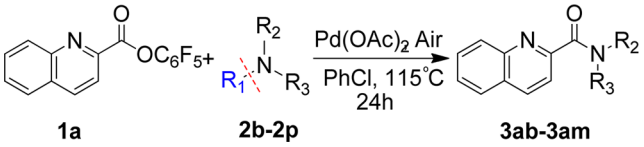
[a]General conditions: **1a** (0.20 mmol), **2a** (1.5 equiv), catalyst (5 mol %), ligand (10 mol %), 24 h. [b]Isolated yield.

the desired amide **3af** (Table 2, entry 5). Interestingly, 4-(diethylamino)benzaldehyde **2g** gave the same product **3aa** as **2a** by means of aminolysis and decarbonylation processes (Table 2, entry 6). The regioselectivity was observed in the reaction of **1a** with **2h** to exclusively cleave the C−N bond of the sterically less hindered methyl group giving a pair of stereoisomers **3ah** in high yield (Table 2, entry 7). Likewise, *N*-alkyl heterocyclic amines **2i−m** reacted exclusively at their exocyclic C−N bond to give cyclic amides **3ai**, **3ak**, and **3am** in 61−84% yield (Table 2, entries 8−12), but when *N*-methylpyrrole **2n** and *N*-methylpyrrolidone **2o** were used as substrates, no product formation was observed (Table 2, entries 13 and 14). This further confirmed the hypothesis that the lone-pair electrons of te *N* atom participating in the conjugating system are likely to hinder the C−N bond activation by palladium.

Next, the scope of this reaction was investigated with respect to multiple perfluorophenyl carboxylates under the optimized conditions. As shown in Table 3, every carboxylic ester **1b−l**, including indole-2-carboxylate, furan-2-carboxylate, benzoate, saturated fatty acid ester, and unsaturated fatty acid ester, reacts with **2a** to give the corresponding amide in 63−82% yield. This indicates that even without chelation of nitrogen, carboxylates could undergo acyl−oxygen cleavage as well using the reported conditions. However, it is clear that the yield of *N*-heteroarene-2-carboxylate is significantly higher than the others. In addition, the aminolysis reaction has good generality and tolerates various functional groups, such as nitro, cyano, bromo, and trifluoromethyl groups. Our experiments indicated these substituent groups on the benzene rings of perfluorophenyl benzoate showed less of an effect on the yields.

To demonstrate the synthetic utility of the method, other aryl or alkyl picolinates were used instead of perfluorophenyl picolinate to react with Et_3N **2b**. As shown in Table 4, all six aryl picolinates performed this aminolysis reaction to give the same product **3bb** in satisfactory yields. The results show that

Table 2. Aminolysis of Perfluorophenyl Quiline-2-carboxylate 1a with Versatile Tertiary Amines 2[a]



1a 2b-2p 3ab-3am

entry	amine	product	yield (%)[b]
1	2b	3ab	89
2	2c	3ac	90
3	2d	3ad	91
4	2e	NP	
5	2f	3af	55
6	2g	3aa	51
7	2h	3ah	64
8	2i	3ai	62
9	2j	3ai	61
10	2k	3ak	65
11	2l	3ak	69
12	2m	3am	84
13	2n	NP	
14	2o	NP	

[a]General conditions: **1a** (0.20 mmol), **2** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), 24 h. [b]Isolated yield.

electron-withdrawing groups on the benzene rings of aryl picolinate $\mathbf{1b}_{a-d}$ are more beneficial to this reaction. Further experiments showed that naphthyl-2-yl picolinate $\mathbf{1b}_f$ as well as phenyl picolinate performed the aminolysis reaction expediently to give the same product in 64% yield. But when ethyl indole-2-carboxylate $\mathbf{1b}_g$ react with **2b**, no product was detected. The result indicated that benzene ring in carboxylates **1** is necessary in the aminolysis reaction and could control the acyl C−O bond cleavage with the aid of palladium.

We also examined the possibility of the aminolysis reaction of primary and secondary amines using the reported conditions (Scheme 2). The reaction of *n*-butylamine **2p** and *N*-ethylaniline **2q** with perfluorophenyl 4-cyanobenzoate **1j** resulted in higher yields of amides than tertiary amine **2a**, possibly because N−H bond activation is easier than C−N bond activation. Interestingly, when we surveyed the aminolysis reaction for the common organic base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), which contains two nitrogen

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Table 3. Screening Perfluorophenyl Carboxylates Scope

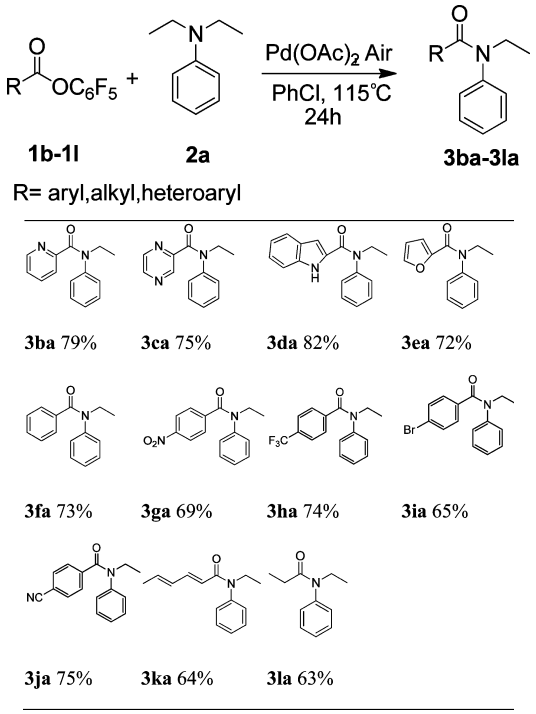
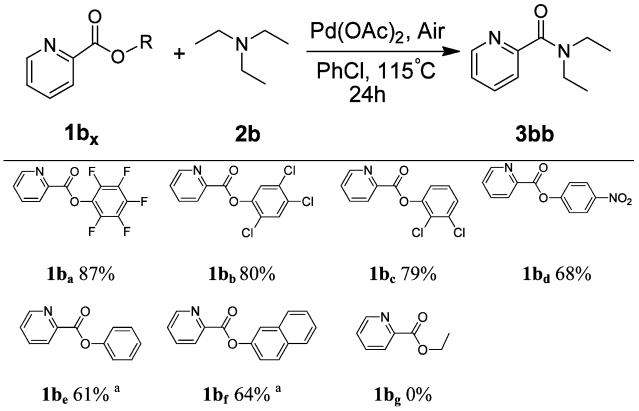
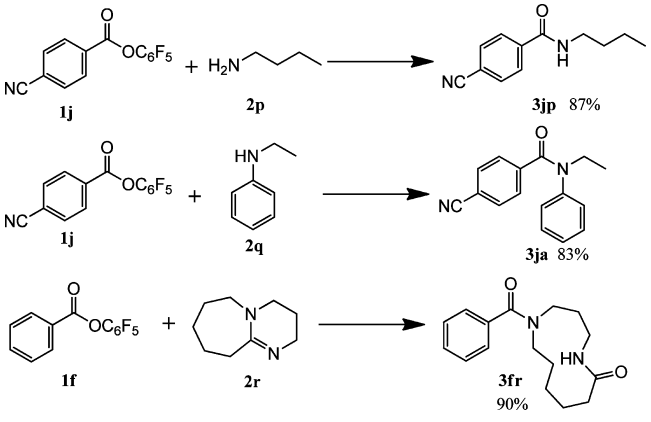


Table 4. Screening Aryl Groups of Ester



[a]Reaction time is 48 h; no reaction in toluene.

Scheme 2. Aminolysis of Primary, Secondary, And Cyclic Tertiary Amine



atoms in cyclic systems, DBU exclusively cleaved the C−N bond of bridge of the bicyclic moiety to give diamide **3fr**. Therefore, the aminolysis reaction could be used for the ring-opening reaction of cyclic tertiary amine and then manipulate the structure of natural products like as cinchona alkaloids.

To gain some insight into the mechanism of the present aminolysis process, radical scavenger TEMPO was employed in the standard reaction, and the desired product **3aa** was still obtained in 80% yield (see the Experimental Section). This result suggested that a free-radical process is not a requirement for the present reaction. One could imagine that the carboxylate is first decomposed to the corresponding carboxylic acid, which then reacts with the amine to form an amide. However, no sign of amide formation was observed when the reaction was carried out with quinoline-2-carboxylic acid under the same conditions. Therefore, we infer that the aminolysis does not proceed via an carboxylic acid but via intermediate **I**. To identify a byproduct, which is formed by the cleavage of the C−N bond, the reaction solution of **1d** with *N*-benzyl-*N*-ethylaniline **2s** (the higher molecular weight amine) was detected with GCMS after the end of the reaction (see the Supporting Information). Two kinds of aminated products *N*-benzyl-*N*-phenylindole-2-carboxamide **3ds** and **3ds′** (**3da**) were detected in an almost 35:1 ratio, which indicated that the sterically less hindered ethyl group is much more facile for cleavage. The GC area % data showed that along with with **3ds′** a similar amount of benzaldehyde was obtained. So this aminolysis reaction proceed via the formation of an iminium intermediate, which would cause formation of an aldehyde.[9] The GCMS analysis of reaction solution of 2,3-dichlorophenyl picolinate $\mathbf{1b_c}$ with **2m** indicated that alkoxyl group of ester eliminated to 2,3-dichlorophenol (see the Supporting Information).

On the basis of the experiments and previously reported literature, the possible mechanism and intermediates **I**−**V** in the aminolysis pathway are postulated as follows (Scheme 3). Initially, Pd^0, which is generated from $Pd(OAc)_2$, coordinated with aryl ester **1** to form intermediate **I**. Then palladium underwent an oxidative addition with the acyl C−O bond in aryl ester **1**, generating a Pd^{II} intermediate **II**. Compound **II** coordinated to the nitrogen of tertiary amine **2** to give intermediate **III**.[7] Subsequently, the alkoxide attack on the α position of the tertiary amine resulted in the phenol, generating iminium-type intermediate **IV** via the generally accepted mechanism.[7,10] Intermediate **IV** was then hydrolyzed to be converted into the intermediate **V** by elimination of aldehyde.[11] Reductive elimination of **V** results in the desired tertiary amide **3** and regenerate Pd^0 to complete the catalytic cycle.

In summary, based on our previous work, we found a special aminolysis reaction of aryl esters **1** with inert tertiary amine **2** by C−O and C−N bond activations for the synthesis of a broad scope of tertiary amides **3** under neutral and mild conditions. By using $Pd(OAc)_2$ as a catalyst, without base and ligand, various carboxylic esters, including *N*-heteroarene-2-carboxylate, indole-2-carboxylate, furan-2-carboxylate, benzoate, saturated fatty acid ester, and unsaturated fatty acid ester **1a**−**l**, could undergo aminolysis with trialkyl, triallyl, *N*,*N*-dialkylaniline, and *N*-alkyl heterocyclic amines **2a**−**d**,**f**−**m** and DBU **2r** to furnish versatile tertiary amides **3** in yields up to 91%. This study not only increased our understanding of the character of acyl C−O bond activation but also shed important light on how to further expand its scope and utility. The interesting selectivity between the Ar−OAc and ArO−Ac bond activations

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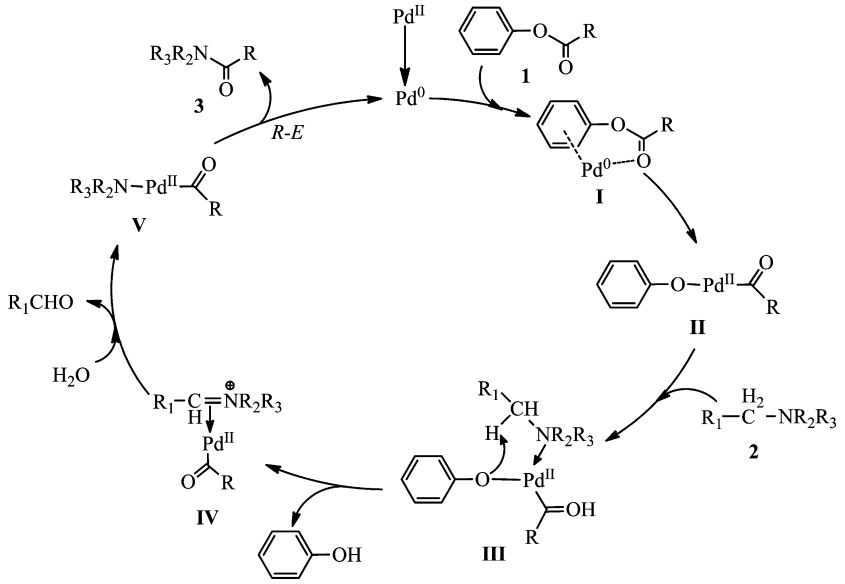
Scheme 3. Possible Mechanism of the Aminolysis Reaction



deserves further research into changes in traditional ester chemistry.

EXPERIMENTAL SECTION

1. Preparation of Aryl Esters (1a–l). A mixture of carboxylic acid (10 mmol), phenol (10 mmol), DMAP (4-(dimethylamino)pyridine, 1 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiamide hydrochloride (EDC·HCl, 10 mmol) in THF (50 mL) was stirred overnight at 25 °C. The resulting mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl ether/petroleum ether = 1:3 as eluent) to afford a corresponding aryl ester **1a–l**.

2. General Procedure for the Aminolysis Reaction. General procedure for the aminolysis reaction: A mixture of ester **1** (0.20 mmol), tertiary amine **2** (0.30 mmol), and $Pd(OAc)_2$ (2.25 mg, 0.01 mmol, 5 mol %) in PhCl (1 mL) was sealed in a 30 mL vial. The reaction mixture was refluxed at 115 °C for 24 h. After being cooled to room temperature, the mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1: 2–1: 5 as an eluent) to afford the desired amide **3**.

N-Ethyl-N-phenylquinoline-2-carboxamide ***3aa:*** yield 81% (44.2 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.79–7.57 (m, 2H), 7.55–7.35 (m, 2H), 7.25–6.97 (m, 5H), 4.06 (d, J = 6.6 Hz, 2H), 1.27 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 154.2, 146.7, 142.2, 136.3, 129.9, 129.7, 129.4, 129.0, 128.0, 127.5, 127.0, 120.4, 45.2, 12.8; MS (ESI) m/z 277.10 $[M + H]^+$. Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.17; H, 5.80; N, 10.31.

N,N-Diethylquinoline-2-carboxamide ***3ab:***[12] yield 89% (40.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.79–7.71 (m, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.63–7.56 (m, 1H), 3.63 (q, J = 7.1 Hz, 2H), 3.45 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 154.5, 146.6, 137.1, 130.0, 129.6, 128.0, 127.7, 127.4, 120.2, 43.5, 40.5, 14.4, 12.9; MS (ESI) m/z 229.05 $[M + H]^+$.

N,N-dibutylquinoline-2-carboxamide ***3ac:***[13] yield 90% (51.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.78–7.70 (m, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.63–7.51 (m, 1H), 3.56 (t, J = 7.9 Hz, 2H), 3.43 (t, J = 7.6 Hz, 2H), 1.82–1.57 (m, 4H), 1.44 (td, J = 14.8, 7.3 Hz, 3H), 1.15 (td, J = 14.7, 7.3 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H), 0.78 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 154.8, 146.6, 136.8, 129.9, 129.7, 127.9, 127.6, 127.3, 120.6, 48.8, 45.9, 31.1, 29.8, 20.4, 19.9, 14.0, 13.7; MS (ESI) m/z 285.10 $[M + H]^+$.

N,N-Diallylquinoline-2-carboxamide ***3ad:*** yield 91% (45.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.79–7.68 (m, 2H), 7.65–7.54 (m, 1H), 6.04–5.86 (m, 2H), 5.37–5.21 (m, 2H), 5.21–5.03 (m, 2H), 4.22 (d, J = 6.0 Hz, 2H), 4.10 (d, J = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 153.9, 146.5, 137.0, 133.9, 132.7, 130.0, 129.8, 128.1, 127.6, 127.5, 120.7, 118.0, 117.9, 50.9, 47.7; MS (ESI) m/z 253.10 $[M + H]^+$. Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.98; H, 6.33; N, 11.29.

N-(4-(4-(Dimethylamino)benzoyl)phenyl)-N-methylquinoline-2-carboxamide ***3af:*** yield 55% (45.0 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 8.5 Hz, 1H), 7.89–7.73 (m, 2H), 7.73–7.59 (m, 4H), 7.59–7.45 (m, 3H), 7.21 (d, J = 7.6 Hz, 2H), 6.60 (d, J = 8.9 Hz, 2H), 3.64 (s, 3H), 3.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 168.6, 153.5, 153.3, 147.0, 146.7, 137.1, 136.7, 132.6(2C), 130.3(2C), 130.0, 129.7, 127.8, 127.6, 127.5, 126.0(2C), 124.5, 120.7, 110.5(2C), 40.02 (3C); MS (ESI) m/z 410.10 $[M + H]^+$. Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 76.40; H, 5.48; N, 10.29.

N-Cyclohexyl-N-methylquinoline-2-carboxamide ***3ah*** *(stereoisomers):* yield 64% (34.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 8.4, 3.3 Hz, 2H), 8.17–8.05 (m, 2H), 7.84 (t, J = 7.2 Hz, 2H), 7.80–7.70 (m, 2H), 7.64 (dd, J = 8.3, 7.3 Hz, 2H), 7.61–7.54 (m, 2H), 4.77–4.50 (m, 1H), 3.80–3.62 (m, 1H), 3.07 (s, 3H), 2.94 (s, 2H), 2.00–1.82 (m, 6H), 1.82–1.67 (m, 4H), 1.66–1.44 (m, 6H), 1.12–0.96 (m, 4H); MS (ESI) m/z 269.10 $[M + H]^+$.

Piperidin-1-yl(quinolin-2-yl)methanone ***3ai:***[13] yield 62% (29.7 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.8–7.71 (m, 1H), 7.71–7.54 (m, 2H), 3.80 (t, J = 5.0 Hz, 2H), 3.51 (t, J = 5.4 Hz, 2H), 1.85–1.66 (m, 4H), 1.65–1.55 (m, 2H); MS (ESI) m/z 241.10 $[M + H]^+$.

Morpholino(quinolin-2-yl)methanone ***3ak:***[12] yield 65% (31.4 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (dd, J = 8.2, 4.9 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.82–7.70 (m, 2H), 7.70–7.52 (m, 1H), 3.87 (t, J = 4.8 Hz, 4H), 3.75 (t, J = 4.3 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.71, 152.96, 146.44, 137.56, 130.36, 129.52, 128.17, 127.90, 127.72, 120.78, 67.02, 66.82, 47.89, 42.92; MS (ESI) m/z 243.05 $[M + H]^+$.

Pyrrolidin-1-yl(quinolin-2-yl)methanone ***3am:***[12] yield 84% (37.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.78–7.72 (m, 1H), 7.63–7.56 (m, 1H), 3.88 (t, J = 6.4 Hz, 2H), 3.75 (t, J = 6.6 Hz, 2H), 2.04–1.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$)

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δ 166.7, 154.1, 146.5, 136.9, 129.9, 129.7, 128.2, 127.7, 127.6, 120.7, 49.3, 47.0, 26.6, 24.1; MS (ESI) *m/z* 227.05 [M + H]$^+$.

N-Ethyl-N-phenylpicolinamide **3ba:** yield 79% (35.7 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.69−7.53 (m, 1H), 7.37 (d, *J* = 5.7 Hz, 1H), 7.23−6.92 (m, 6H), 4.01 (q, *J* = 6.5 Hz, 2H), 1.25 (t, *J* = 8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 154.4, 148.4, 142.5, 136.3, 129.0 (2C), 127.9 (2C), 126.8, 123.8, 123.5, 45.1, 12.8; MS (ESI) *m/z* 227.05 [M + H]$^+$. Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.10; H, 6.33; N, 12.29.

N-Ethyl-N-phenylpyrazine-2-carboxamide **3ca:** yield 75% (34.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.34 (d, *J* = 26.4 Hz, 2H), 7.25−7.12 (m, 3H), 7.06 (d, *J* = 6.7 Hz, 2H), 4.03 (q, *J* = 6.8 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 150.2, 144.6, 144.3, 143.2, 129.3(2C), 128.0(2C), 127.4, 124.2, 45.22, 12.72; MS (ESI) *m/z* 228.10 [M + H]$^+$. Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.56; H, 5.90; N, 18.28.

N-Ethyl-N-phenylindole-2-carboxamide **3da:** yield 82% (43.3 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.55−7.46 (m, 3H), 7.40−7.28 (m, 4H), 7.25−7.16 (m, 1H), 7.05−6.94 (m, 1H), 5.18 (d, *J* = 1.1 Hz, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 142.4, 135.2, 130.3, 129.8 (2C), 129.1 (2C), 128.6, 127.7, 124.4, 122.2, 120.2, 111.5, 107.0, 45.8, 12.9; MS (ESI) *m/z* 265.05 [M + H]$^+$. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.14; H, 6.31; N, 10.56.

N-Ethyl-N-phenylfuran-2-carboxamide **3ea:**[14] yield 72% (30.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.35 (m, 3H), 7.30 (d, *J* = 1.0 Hz, 1H), 7.21−7.19 (m, *J* = 1.9 Hz, 1H), 7.19−7.17 (m, 1H), 6.18 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.74 (d, *J* = 3.1 Hz, 1H), 3.91 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 147.1, 144.3, 142.3, 129.6 (2C), 128.5 (2C), 128.1, 116.3, 110.9, 45.5, 12.8; MS (ESI) *m/z* 216.05 [M + H]$^+$.

N-Ethyl-N-phenylbenzamide **3fa:**[15] yield 73% (32.8 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.11 (m, 8H), 7.07−6.98 (m, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 142.9, 136.0, 129.6, 129.2 (2C), 128.6(2C), 127.9(2C), 127.7(2C), 126.9, 45.6, 12.9; MS (ESI) *m/z* 226.05 [M + H]$^+$.

N-Ethyl-4-nitro-N-phenylbenzamide **3ga:**[16] yield 69% (37.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.29−7.22 (m, 2H), 7.22−7.17 (m, 1H), 7.02 (d, *J* = 7.4 Hz, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* 271.05 [M + H]$^+$.

N-Ethyl-N-phenyl-4-(trifluoromethyl)benzamide **3ha:** yield 74% (43.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.35 (m, 4H), 7.27−7.21 (m, 2H), 7.21−7.15 (m, 1H), 7.02 (d, *J* = 7.5 Hz, 2H), 4.00 (q, *J* = 6.8 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 142.6, 139.9, 131.2 (q, J_{C-F} = 32.4 Hz), 129.4(2C), 128.9(2C), 128.0(2C), 127.2, 124.8, 124.7, 122.6, 45.4, 12.8; MS (ESI) *m/z* 294.33 [M + H]$^+$. Anal. Calcd for $C_{16}H_{14}F_3NO$: C, 65.52; H, 4.81; N, 4.78. Found: C, 65.58; H, 4.71; N, 4.85.

4-Bromo-N-ethyl-N-phenylbenzamide **3ia:**[17] yield 65% (39.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.20−7.13 (m, 3H), 7.01 (d, *J* = 7.6 Hz, 2H), 3.97 (q, *J* = 7.1 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 142.9, 135.2, 130.9(2C), 130.4(2C), 129.3(2C), 127.9(2C), 126.9, 123.9, 45.5, 12.8; MS (ESI) *m/z* 304.33 [M + H]$^+$.

4-Cyano-N-ethyl-N-phenylbenzamide **3ja:** yield 75% (37.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 2H), 3.99 (q, *J* = 6.9 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 142.2, 140.7, 131.6(2C), 129.5(2C), 129.1(2C), 128.0(2C), 127.4, 118.2, 113.0, 45.5, 12.8; MS (ESI) *m/z* 251.24 [M + H]$^+$. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.96; H, 5.61; N, 11.28.

(2E,4E)-N-Ethyl-N-phenylhexa-2,4-dienamide **3ka:** yield 64% (27.5 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.34 (m, 3H), 7.29−7.21 (m, 1H), 7.21−7.10 (m, 2H), 6.12−5.90 (m, 2H), 5.59 (d, *J* = 14.9 Hz, 1H), 3.84 (q, *J* = 7.1 Hz, 2H), 1.76 (d, *J* = 5.8 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 142.7, 141.8, 138.1, 130.1, 129.6(2C), 128.4(2C), 127.9, 119.6, 44.6, 18.5, 13.0; MS (ESI) *m/z* 216.10 [M + H]$^+$. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.15; H, 8.11; N, 6.37.

N-Ethyl-N-phenylpropionamide **3la:**[18] yield 63% (22.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.40 (m, 2H), 7.39−7.33 (m, 1H), 7.21−7.08 (m, 2H), 3.75 (q, *J* = 7.2 Hz, 2H), 2.04 (q, *J* = 7.4 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 142.3, 129.7(2C), 128.3(2C), 128.0, 44.2, 27.9, 13.0, 9.7; MS (ESI) *m/z* 178.10 [M + H]$^+$.

N,N-Diethylpicolinamide **3bb:**[19] yield 87% (30.9 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.7 Hz, 1H), 7.89−7.68 (m, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.40−7.30 (m, 1H), 3.57 (q, *J* = 7.1 Hz, 2H), 3.36 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). MS (ESI) *m/z* 379.15 [2 M + Na]$^+$.

N-Butyl-4-cyanobenzamide **3jp:**[20] yield 87% (35.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 6.40 (s, 1H), 3.45 (dd, *J* = 13.1, 7.1 Hz, 2H), 1.64−1.51 (m, 2H), 1.49−1.33 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 138.8, 132.4, 127.7, 118.1, 114.9, 40.1, 31.6, 20.1, 13.8.

1-Benzoyl-1,5-diazacycloundecan-6-one **3fr:**[21] yield 90% (49.3 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.97−7.86 (m, 2H), 7.54−7.35 (m, 3H), 3.59−3.48 (m, 2H), 3.48−3.31 (m, 4H), 2.66−2.52 (m, 2H), 1.80−1.68 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 167.1, 134.5, 131.2, 128.5, 127.1, 49.6, 45.0, 37.1, 35.4, 29.9, 28.4, 27.1, 23.4; MS (ESI) *m/z* 275.10 [M + H]$^+$.

3. Mechanism Studies. *3.1. Radical-Inhibiting Experiment.* A mixture of perfluorophenyl quiline-2-carboxylate **1a** (0.25 mmol), tertiary amine **2a** (0.375 mmol), TEMPO (58.9 mg, 0.375 mmol), and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol %) in PhCl (1 mL) was sealed in a 30 mL vial. The reaction mixture was refluxed at 115 °C for 24 h. After being cooled to room temperature, the mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl ether/petroleum ether = 1:5) to afford **3aa** in 80% yield.

3.2. Aminolysis Reaction of Carboxylic Acid. A mixture of quinoline-2- carboxylic acid (0.25 mmol), tertiary amine **2a** (0.375 mmol), and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol %) in PhCl (1 mL) was sealed in a 30 mL vial. The reaction mixture was refluxed at 115 °C for 24 h. After being cooled to room temperature, the mixture was detected by TLC, and no amide was detected.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR, ^{13}C NMR, and MS spectra and analysis of GCMS. 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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