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A New Rhodium/Copper-Cocatalyzed C–H Oxidation for the Preparation of Isoquinolin-1-ones

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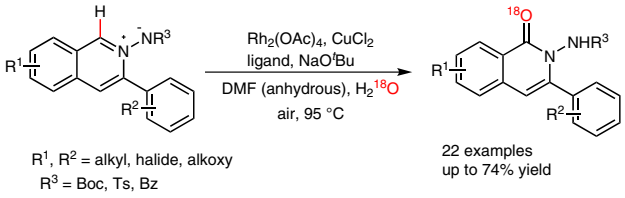

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Abstract A new and efficient rhodium/copper-cocatalyzed C–H oxidation reaction of isoquinolinium *N*-amides has been developed. In the presence of rhodium(II) acetate dimer, copper(II) chloride, a ligand and sodium *tert*-butoxide, a variety of isoquinolin-1-ones were prepared in moderate to good yields via *ortho* C–H oxidation.

Key words rhodium(II) acetate dimer, copper(II) chloride, isoquinolinium *N*-amides, C–H oxidation, isoquinolin-1-ones

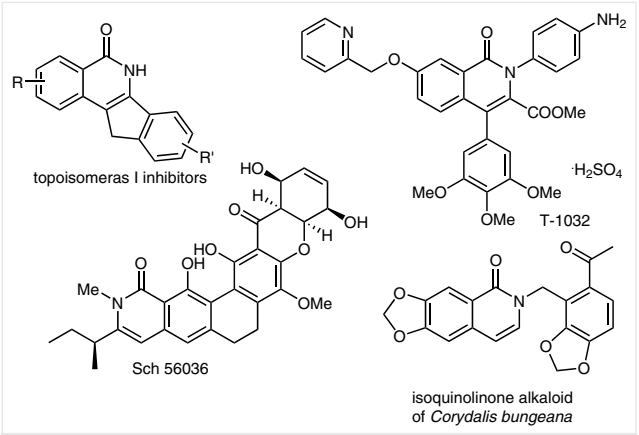
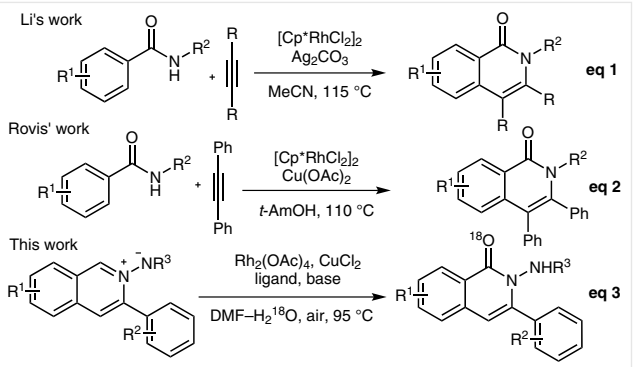


Figure 1 Compounds containing the isoquinolin-1-one motif

Nitrogen-containing heterocycles are the key components of many bioactive natural products and potent drugs.[1] The isoquinolin-1-ones, an important class of heterocyclic compounds, make up the core structures of several alkaloids and pharmacologically active compounds such as those shown in Figure 1.[2] Due to their chemical stability, isoquinolin-1-one units are regularly used as building blocks in organic synthesis, and have also received significant interest in medicinal chemistry.[3]

During the past decades, the transition-metal-catalyzed functionalization of C–H bonds in an atom-economic fashion has attracted much attention in organic synthesis.[4] Transition-metal-catalyzed *ortho* C–H oxidation represents a powerful tool for the formation of isoquinolin-1-ones,[5] and a variety of different directing groups and catalysts have been extensively explored in terms of their impact on this transformation.[6] Several recent studies have outlined the use of rhodium-catalyzed *ortho* C–H oxidation reactions for the construction of an isoquinolin-1-one skeleton. For example, Li and co-workers reported a method for the preparation of isoquinolones from benzamides and alkynes via a rhodium-catalyzed *ortho* C–H oxidation (Scheme 1, eq 1).[7] Hyster and Rovis utilized the rhodium-catalyzed oxidative cycloaddition of benzamides and alkynes for the construction of isoquinolones (Scheme 1, eq 2).[8] Although both of these reactions involve the use of an amide directing group with high activity, these methods generally suffer from some limitations, including harsh reaction conditions or a stoichiometric amount of oxidant. To address these drawbacks, the development of an efficient, milder, environmentally benign and highly regioselective C–H oxidation reaction[9] still remains an outstanding challenge. Herein, we report a new and efficient rhodium/copper-cocatalyzed *ortho* C–H oxidation reaction for the synthesis of isoquinolin-1-one derivatives (Scheme 1, eq 3). Interestingly, this reaction involves the use of an *N*-amide directing group.

As shown in Table 1, the reaction of 3-phenylisoquinolinium-2-yl amide **1a** was used as a model reaction to determine the optimal reaction conditions. When **1a** in toluene was heated at 95 °C for 24 hours under air in the pres-



Scheme 1 Selected strategies for the preparation of isoquinolin-1-ones

ence of $Rh_2(OAc)_4$ (3 mol%), IMes·HCl (**L1**, 6 mol%) and NaO*t*-Bu (2.5 equiv), the desired 3-phenylisoquinolin-1(2*H*)-one product **2a** was formed in 45% yield together with the reduced byproduct 3-phenylisoquinoline (**3a**) in 17% yield (Table 1, entry 1). The structure of product **2a** was confirmed by single-crystal X-ray diffraction analysis (Figure 2). When the reaction was conducted in the absence of rhodium or base, none of the target product **2a** was observed; only 11% or 15% yield of **3a** was obtained, demonstrating that the rhodium and base play a critical role in this oxidation (Table 1, entries 2 and 3). Encouraged by this result, we proceeded to evaluate several different bases, including KO*t*-Bu, LiO*t*-Bu and Cs_2CO_3 (Table 1, entries 4–6). The results revealed that the use of NaO*t*-Bu as base provided the highest yield of the desired product. Several other ligands (Figure 3), such as $Bu_3P{\cdot}HBF_4$ (**L2**) and 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (**L3**), were also investigated (Table 1, entries 7 and 8); they were less effective than IMes·HCl (**L1**). Screening also revealed that three other rhodium species, namely $RhCl_3$, $[Cp^*RhCl_2]_2$ and $(Ph_3P)_3RhCl$, have reactivity to catalyze the

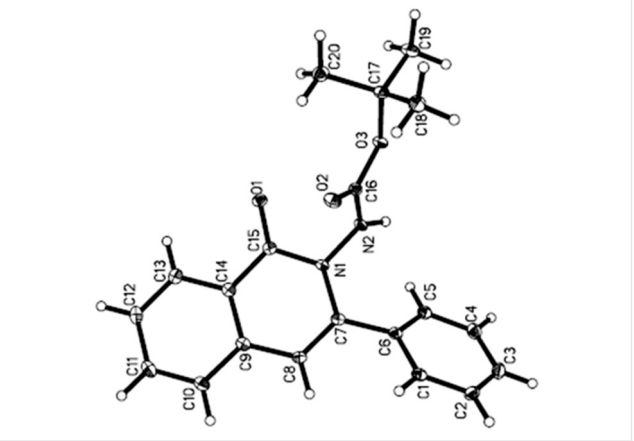
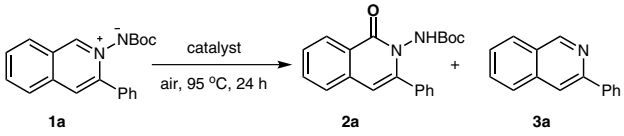


Figure 2 ORTEP diagram of the single-crystal X-ray structure of compound **2a**

Table 1 Screening for the Optimal Reaction Conditions[a]

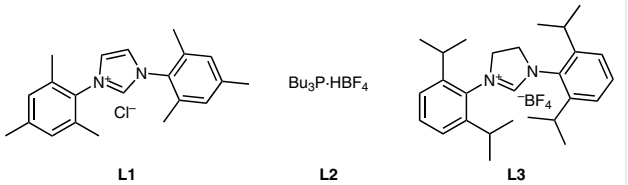


1a 2a 3a

Entry	Catalyst	Ligand	Base	Solvent	Yield[b] (%)	
					2a	3a
1	$Rh_2(OAc)_4$	L1	NaO*t*-Bu	toluene	45	17
2	–	L1	NaO*t*-Bu	toluene	0	11
3	$Rh_2(OAc)_4$	L1	–	toluene	0	15
4	$Rh_2(OAc)_4$	L1	KO*t*-Bu	toluene	34	17
5	$Rh_2(OAc)_4$	L1	LiO*t*-Bu	toluene	39	22
6	$Rh_2(OAc)_4$	L1	Cs_2CO_3	toluene	0	26
7	$Rh_2(OAc)_4$	L2	NaO*t*-Bu	toluene	22	29
8	$Rh_2(OAc)_4$	L3	NaO*t*-Bu	toluene	25	24
9	$RhCl_3$	L1	NaO*t*-Bu	toluene	21	15
10	$[Cp^*RhCl_2]_2$	L1	NaO*t*-Bu	toluene	38	23
11	$(Ph_3P)_3RhCl$	L1	NaO*t*-Bu	toluene	10	25
12	$Rh_2(OAc)_4$	L1	NaO*t*-Bu	xylene	36	27
13	$Rh_2(OAc)_4$	L1	NaO*t*-Bu	DMA	48	trace
14	$Rh_2(OAc)_4$	L1	NaO*t*-Bu	DMF	50	trace
15	$Rh_2(OAc)_4$ + CuCl	L1	NaO*t*-Bu	DMF	63	trace
16	$Rh_2(OAc)_4$ + $CuCl_2$	L1	NaO*t*-Bu	DMF	74	<5
17	$Rh_2(OAc)_4$ + $Cu(OAc)_2$	L1	NaO*t*-Bu	DMF	64	trace
18	$CuCl_2$	L1	NaO*t*-Bu	DMF	10	7
19[c]	$Rh_2(OAc)_4$ + $CuCl_2$	L1	NaO*t*-Bu	DMF	60	trace
20[d]	$Rh_2(OAc)_4$ + $CuCl_2$	L1	NaO*t*-Bu	DMF	52	<5

[a] Reaction conditions: **1a** (0.4 mmol), [Rh] (3 mol%), [Cu] (3 mol%), ligand (6 mol%), base (2.5 equiv), solvent (3 mL), 95 °C, under air, 24 h.
[b] Isolated yield.
[c] Conducted at 80 °C.
[d] Conducted at 120 °C.

oxidation (Table 1, entries 9–11), although they were less efficient than $Rh_2(OAc)_4$. Subsequently, a series of solvents (xylene, DMA, DMF) were investigated, with DMF medium providing the best result (Table 1, entries 12–14). Interestingly, product **2a** was selectively furnished in moderate yield, together with only trace amounts of byproduct **3a**, when polar solvents were used (Table 1, entries 13 and 14). To our surprise, the addition of CuCl (3 mol%) to the reac-

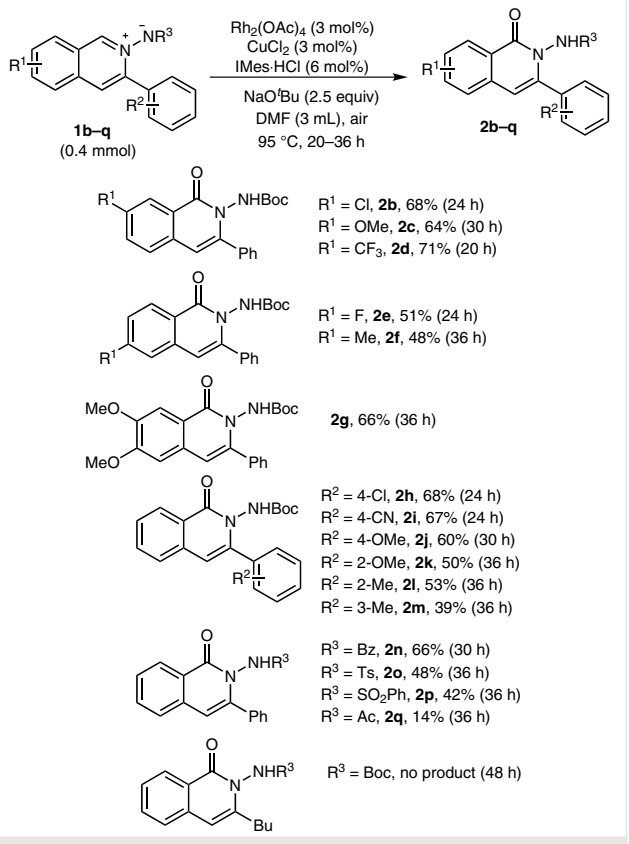


L1 L2 L3

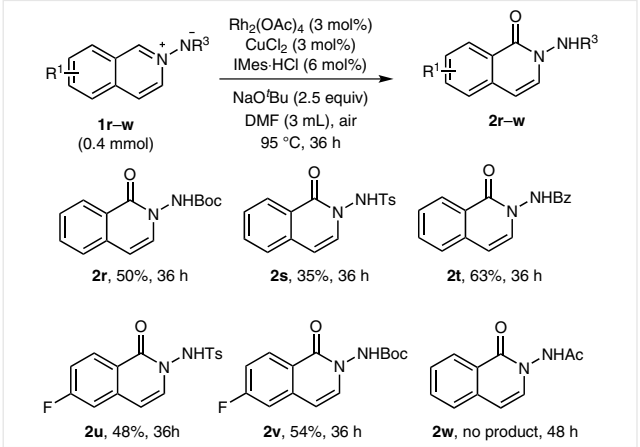
Figure 3

tion mixture led to a significant increase in the yield of desired product **2a** (Table 1, entry 15). Based on these results, we also investigated two other copper salts, namely $CuCl_2$ and $Cu(OAc)_2$. Both of these salts promoted the yield of **2a**, with $CuCl_2$ providing the highest yield of 74% (Table 1, entries 16 and 17). However, the yield of **2a** was dramatically decreased to 10% when $CuCl_2$ was used independently as the catalyst (Table 1, entry 18). Finally, the reaction temperature was also investigated. When the oxidation was performed at 80 °C or 120 °C, there was a significant decrease in the yield of **2a** (Table 1, entries 19 and 20).

With the optimal reaction conditions in hand, a variety of substrates **1** were examined, and the results are summarized in Scheme 2. Initially, the electronic effects of R^1 groups on the isoquinoline ring were examined. The results indicated that several functional groups, both electron donating and electron deficient, are well-tolerated. Compounds bearing an electron-deficient group, such as the chloro-, trifluoromethyl- and fluoro-substituted substrates, underwent the transformation in good yields, providing the target products **2b**, **2d** and **2e** in 68%, 71% and 51% yield, respectively. Electron-donating groups, such as in methoxy- or methyl-substituted substrates **1**, are also well-tolerated;



Scheme 2 Rhodium/copper-cocatalyzed reaction of 3-arylisoquinolinium-2-yl amides **1b–q**



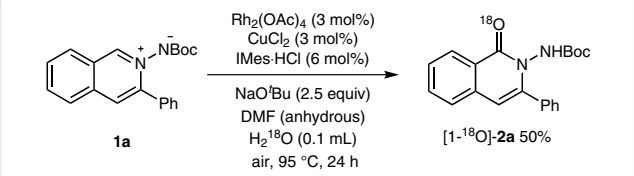
Scheme 3 Regioselective rhodium/copper-cocatalyzed reaction of isoquinolinium-2-yl amides **1r–v**

the corresponding products **2c**, **2f** and **2g** were provided in moderate yields. Subsequently, we proceeded to evaluate the impact of different R^2 groups on the aromatic ring (at the 3-position) of **1** and found that the reaction of substrates bearing electron-withdrawing groups at the *para* position proceeded quickly to give the target products **2h** and **2i** in 68% and 67% yield, respectively. However, an electron-donating group led to a slightly lowered 60% yield of **2j**. The impact of steric hindrance and electronic effects resulting from substituent R^2 was also evaluated with methoxy- and methyl-substituted substrates; the order of activity was determined to be *para* > *ortho* > *meta* in terms of yields (**2j–m**). Finally, a series of isoquinolines **1** bearing different R^3 groups (replacing Boc) on the nitrogen atom were examined under the optimized conditions. The results demonstrated that R^3 groups such as benzoyl, tosyl and phenylsulfonyl are also compatible, with the corresponding *N*-substituted isoquinolinone products being formed in moderate to good yields (**2n–p**). Unfortunately, only 14% yield of target product **2q** was obtained when R^3 was an acetyl group. The reaction did not work when 3-butylisoquinolinium-2-yl *tert*-butoxycarbonylamide was used as substrate in the transformation.

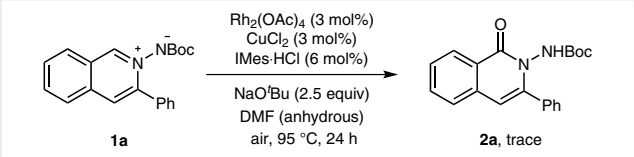
To our delight, during the workup process we discovered that the catalytic system is highly regioselective, as shown in Scheme 3. When isoquinolinium-2-yl amides **1r–v** were subjected to the reaction under the optimal conditions, they afforded the corresponding products **2r–v** in which selective oxidation took place at the 1-position, with none of the 3-position oxidation product being observed, demonstrating the high regioselectivity of this oxidation. For instance, treatment of substrates **1r–t** under the optimal conditions generated the desired products **2r–t** in 50%, 35% and 63% yield, respectively. Fluoro-containing substrates **1u** and **1v** were compatible with the optimal condi-

tions, providing **2u** and **2v** in moderate yields. However, when R^3 was an acetyl group, the reaction failed to provide the desired product **2w**.

To determine the source of the oxygen atom in the products, an ^{18}O-labeling experiment was carried out (Scheme 4). In the presence of $Rh_2(OAc)_4$, $CuCl_2$, IMes·HCl, NaO*t*-Bu, anhydrous DMF and $H_2{}^{18}O$ (0.1 mL), the reaction gave the ^{18}O-containing product [1-^{18}O]-**2a** in 50% yield. This control experiment confirmed that the oxygen atom of the product is derived from aqueous DMF. We also performed a control experiment under the standard conditions in anhydrous DMF, and only a trace amount of the corresponding product **2a** was obtained (Scheme 5). This implies that the appropriate amount of water is important in the reaction. Excess water probably lowers the concentration of base, and hydrolysis of the catalysts leads to a lower yield of target product.



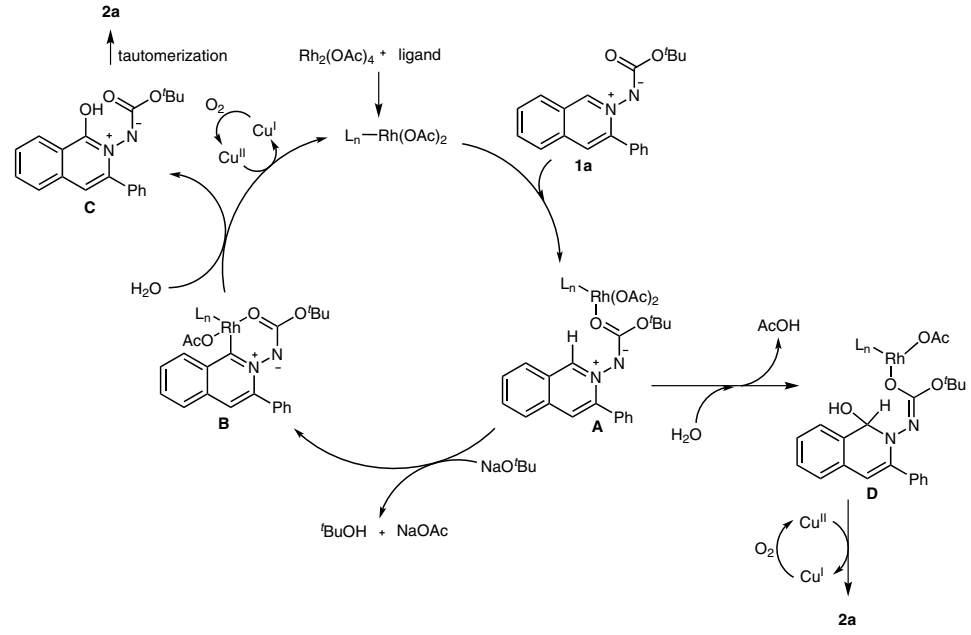
Scheme 4 ^{18}O-Labeling experiment



Scheme 5 Control experiment (anhydrous conditions)

Based on previous reports,[4d,7,10] as well as our results, a possible mechanism for the oxidation reaction of **1a** is proposed, as outlined in Scheme 6. The initial combination of $Rh_2(OAc)_4$ with the ligand would give a rhodium species, which on coordination to the substrate **1a** provides the intermediate **A**. With the assistance of NaO*t*-Bu, the intramolecular insertion of rhodium into the C–H bond at the 1-position of **A** would lead to the formation of intermediate **B** together with byproducts.[11] Subsequently, nucleophilic attack of intermediate **B** by H_2O as the nucleophilic reagent affords intermediate **C**; meanwhile, regeneration of the rhodium species with copper salt as oxidant would complete the catalytic cycle. Finally, the target product **2a** could be obtained from intermediate **C** via tautomerization. Another possible pathway is that H_2O as the nucleophilic reagent directly attacks the iminium intermediate **A**, resulting in formation of the water-addition product **D** which is further oxidized by copper/air to afford product **2a**.

In summary, we have developed a new and efficient method for the rhodium/copper-cocatalyzed C–H oxidation of isoquinolinium *N*-amides. This new method involves the use of the *N*-amide group as a directing moiety. Importantly, this protocol could be applied to the synthesis of isoquinolin-1-ones, making it particularly attractive for use in studies involving organic synthesis and medicinal chemistry. Work to extend the scope and application of this reaction is currently underway.



Scheme 6 Proposed mechanism for the oxidation

Chemicals were either used as purchased or purified by standard techniques. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance III 500-MHz spectrometer (^{1}H: 500 MHz, ^{13}C: 125 MHz), using $CDCl_3$ as the solvent with TMS as internal standard at r.t. Chemical shifts are given in δ relative to TMS and the coupling constants *J* are given in Hz. High-resolution mass spectra were recorded on a Bruker micro TOF QII ESI-Q-TOF mass spectrometer. IR spectra were recorded on a Nicolet iS10 spectrophotometer (Thermo Scientific). Melting points were measured using a Colid X-4 apparatus (Beijin TECH). All reactions were conducted under air atmosphere using standard Schlenk techniques. Column chromatography was performed using EM silica gel 60 (300–400 mesh).

Isoquinolin-1-ones 2a–v; General Procedure

To a Schlenk tube were added an isoquinolinium-2-yl amide **1** (0.4 mmol), $Rh_2(OAc)_4$ (5.3 mg, 3 mol%), $CuCl_2$ (1.6 mg, 3 mol%), IMes·HCl (8.2 mg, 6 mol%) and NaO*t*-Bu (96.1 mg, 2.5 equiv) in DMF (3 mL). Then, the tube was stirred at 95 °C (oil bath temperature) under air atmosphere for the indicated time (see Schemes 2 and 3) until complete consumption of starting material, as monitored by TLC and GC-MS analysis. After the reaction was finished, the reaction mixture was cooled to r.t., diluted with EtOAc and washed with brine. The aqueous phase was re-extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified via silica gel chromatography (hexane–EtOAc) to afford the corresponding isoquinolin-1-one product **2**.

tert-Butyl (1-Oxo-3-phenylisoquinolin-2(1*H*)-yl)carbamate (2a)

White solid; yield: 99.5 mg (74%); mp 174.6–176.0 °C.

IR (KBr): 2974, 1749, 1646, 1617, 1524, 1368, 1245, 1149, 1053 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.0 Hz, 1 H), 7.61 (t, *J* = 7.5 Hz, 1 H), 7.55 (s, 1 H), 7.52–7.51 (m, 2 H), 7.46–7.38 (m, 5 H), 6.46 (s, 1 H), 1.35 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0, 155.1, 144.8, 136.5, 134.4, 132.8, 129.0, 128.6, 128.1, 127.8, 126.5, 126.0, 124.8, 107.1, 81.9, 27.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_2O_3$: 337.1547; found: 337.1541.

tert-Butyl (7-Chloro-1-oxo-3-phenylisoquinolin-2(1*H*)-yl)carbamate (2b)

White solid; yield: 100.7 mg (68%); mp 186.7–188.4 °C.

IR (KBr): 2960, 1743, 1646, 1613, 1587, 1477, 1365, 1245, 1152, 1066 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 2.5 Hz, 1 H), 7.57 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.50 (dd, *J* = 7.0, 2.0 Hz, 2 H), 7.43–7.41 (m, 4 H), 7.32 (br s, 1 H), 6.45 (s, 1 H), 1.38 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.0, 155.0, 145.3, 134.9, 134.2, 133.4, 132.6, 129.0 (2 C), 128.0, 127.7, 127.5, 125.9, 106.5, 82.4, 27.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}N_2O_3Cl$: 371.1157; found: 371.1155.

tert-Butyl (7-Methoxy-1-oxo-3-phenylisoquinolin-2(1*H*)-yl)carbamate (2c)

White solid; yield: 93.7 mg (64%); mp 197.0–198.8 °C.

IR (KBr): 2976, 1739, 1606, 1497, 1358, 1242, 1156, 1027 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 2.5 Hz, 1 H), 7.51–7.49 (m, 2 H), 7.45 (d, *J* = 8.5 Hz, 1 H), 7.41–7.39 (m, 3 H), 7.28 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.04 (br s, 1 H), 6.47 (s, 1 H), 3.92 (s, 3 H), 1.41 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6, 158.6, 155.2, 142.5, 134.6, 130.7, 129.1, 129.0, 128.6, 127.9, 126.0, 123.6, 108.0, 107.0, 82.3, 55.7, 27.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_2O_4$: 367.1652; found: 367.1651.

tert-Butyl (1-Oxo-3-phenyl-7-(trifluoromethyl)isoquinolin-2(1*H*)-yl)carbamate (2d)

White solid; yield: 114.7 mg (71%); mp 186.6–188.4 °C.

IR (KBr): 2974, 1746, 1656, 1627, 1514, 1371, 1322, 1242, 1126 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.53 (s, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.49 (d, *J* = 8.5 Hz, 1 H), 7.42 (d, *J* = 7.5 Hz, 2 H), 7.36–7.32 (m, 3 H), 7.26 (br s, 1 H), 6.42 (s, 1 H), 1.29 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6, 154.8, 147.4, 139.2, 134.1, 129.2, 129.0 (q, J_{C-F} = 3.5 Hz), 128.9, 128.5 (q, J_{C-F} = 32.5 Hz), 128.0, 127.0, 125.8 (q, J_{C-F} = 7.5 Hz), 124.4, 123.8 (q, J_{C-F} = 270.0 Hz), 106.4, 82.6, 27.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}N_2O_3F_3$: 405.1421; found: 405.1415.

tert-Butyl (6-Fluoro-1-oxo-3-phenylisoquinolin-2(1*H*)-yl)carbamate (2e)

White solid; yield: 72.2 mg (51%); mp 198.7–200.7 °C.

IR (KBr): 2959, 1746, 1656, 1607, 1484, 1245, 1149 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.38 (dd, *J* = 8.5, 5.5 Hz, 1 H), 7.51–7.49 (m, 2 H), 7.43–7.39 (m, 4 H), 7.16–7.10 (m, 2 H), 6.41 (s, 1 H), 1.36 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6 (d, J_{C-F} = 251.2 Hz), 161.3, 155.1, 146.3, 138.9 (d, J_{C-F} = 10.0 Hz), 136.3, 134.2, 131.5 (d, J_{C-F} = 10.1 Hz), 129.0, 127.9, 121.5, 115.3 (d, J_{C-F} = 23.7 Hz), 111.0 (d, J_{C-F} = 21.2 Hz), 106.4, 82.3, 27.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}N_2O_3F$: 355.1452; found: 355.1444.

tert-Butyl (6-Methyl-1-oxo-3-phenylisoquinolin-2(1*H*)-yl)carbamate (2f)

White solid; yield: 67.3 mg (48%); mp 148.5–149.9 °C.

IR (KBr): 2972, 1749, 1650, 1626, 1491, 1245, 1156 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.5 Hz, 1 H), 7.44–7.42 (m, 2 H), 7.33–7.29 (m, 4 H), 7.19 (d, *J* = 6.5 Hz, 2 H), 6.33 (s, 1 H), 2.38 (s, 3 H), 1.30 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9, 155.2, 144.8, 143.6, 136.7, 134.6, 129.0, 128.6, 128.2, 128.1, 127.8, 125.9, 122.6, 107.0, 82.0, 27.9, 21.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_2O_3$: 351.1703; found: 351.1697.

tert-Butyl (6,7-Dimethoxy-1-oxo-3-phenylisoquinolin-2(1*H*)-yl)carbamate (2g)

White solid; yield: 104.5 mg (66%); mp 188.5–190.3 °C.

IR (KBr): 2968, 1736, 1646, 1593, 1507, 1404, 1242, 1152, 1040 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (s, 1 H), 7.50 (dd, *J* = 7.0, 2.5 Hz, 2 H), 7.40 (dd, *J* = 5.0, 2.0 Hz, 3 H), 7.23 (br s, 1 H), 6.84 (s, 1 H), 6.40 (s, 1 H), 3.97 (s, 6 H), 1.40 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.2, 155.5, 153.9, 149.0, 143.4, 134.6, 132.2, 129.1, 128.6, 127.8, 118.6, 108.0, 106.7, 106.2, 82.0, 56.1, 56.0, 27.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{25}N_2O_5$: 397.1757; found: 397.1765.

***tert*-Butyl (3-(4-Chlorophenyl)-1-oxoisoquinolin-2(1*H*)-yl)carbamate (2h)**

White solid; yield: 100.8 mg (68%); mp 210.4–211.9 °C.

IR (KBr): 2970, 1752, 1643, 1617, 1491, 1368, 1245, 1149, 1090 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.0 Hz, 1 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 7.39 (dd, *J* = 18.5, 8.5 Hz, 4 H), 7.32 (dd, *J* = 18.0, 5.5 Hz, 3 H), 6.38 (s, 1 H), 1.30 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9, 143.6, 136.4, 134.9, 133.1, 133.0, 130.4, 129.0, 128.1, 126.9, 126.2, 124.9, 112.2, 107.3, 82.4, 27.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}N_2O_3Cl$: 371.1157; found: 371.1156.

***tert*-Butyl (3-(4-Cyanophenyl)-1-oxoisoquinolin-2(1*H*)-yl)carbamate (2i)**

White solid; yield: 96.7 mg (67%); mp 186.7–188.4 °C.

IR (KBr): 2968, 1732, 1656, 1630, 1590, 1484, 1391, 1278, 1159, 1046 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.0 Hz, 1 H), 7.62 (t, *J* = 7.5 Hz, 3 H), 7.58 (dd, *J* = 11.5, 4.5 Hz, 2 H), 7.45–7.41 (m, 2 H), 7.34 (br s, 1 H), 6.42 (s, 1 H), 1.30 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7, 155.4, 142.8, 138.9, 136.1, 133.3, 131.7, 129.8, 128.2, 127.3, 126.4, 125.1, 118.4, 112.6, 107.8, 82.7, 27.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}N_3O_3$: 362.1499; found: 362.1501.

***tert*-Butyl (3-(4-Methoxyphenyl)-1-oxoisoquinolin-2(1*H*)-yl)carbamate (2j)**

White solid; yield: 87.8 mg (60%); mp 225.9–227.2 °C.

IR (KBr): 2961, 1742, 1643, 1603, 1511, 1361, 1252, 1146, 1033 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.0 Hz, 1 H), 7.58 (t, *J* = 7.0 Hz, 1 H), 7.44–7.36 (m, 4 H), 7.01 (br s, 1 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 6.40 (s, 1 H), 3.78 (s, 3 H), 1.35 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1, 160.0, 155.4, 144.6, 136.7, 133.0, 130.4, 128.2, 127.0, 126.5, 126.1, 124.7, 113.4, 107.0, 82.3, 55.3, 28.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_2O_4$: 367.1652; found: 367.1643.

***tert*-Butyl (3-(2-Methoxyphenyl)-1-oxoisoquinolin-2(1*H*)-yl)carbamate (2k)**

White solid; yield: 73.2 mg (50%); mp 197.1–199.0 °C.

IR (KBr): 2980, 1746, 1650, 1627, 1507, 1384, 1252, 1159, 1046 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.0 Hz, 1 H), 7.54 (t, *J* = 7.5 Hz, 1 H), 7.41–7.30 (m, 5 H), 6.91 (t, *J* = 7.5 Hz, 1 H), 6.86 (d, *J* = 8.5 Hz, 1 H), 6.36 (s, 1 H), 3.72 (s, 3 H), 1.17 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9, 156.9, 154.4, 142.9, 136.8, 132.7, 131.1, 130.6, 128.2, 126.4, 126.1, 125.3, 123.7, 120.5, 110.3, 107.2, 81.6, 55.6, 27.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_2O_4$: 367.1652; found: 367.1649.

***tert*-Butyl (1-Oxo-3-(*o*-tolyl)isoquinolin-2(1*H*)-yl)carbamate (2l)**

White solid; yield: 74.2 mg (53%); mp 197.3–199.0 °C.

IR (KBr): 2921, 1746, 1656, 1623, 1484, 1358, 1249, 1162 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 6.0 Hz, 1 H), 7.50–7.46 (m, 3 H), 7.34–7.20 (m, 4 H), 6.42 (s, 1 H), 2.21 (s, 3 H), 1.29 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0, 155.0, 144.7, 136.7, 134.1, 132.9, 130.3, 129.9, 129.3, 128.9, 128.2, 126.5, 126.1, 125.9, 125.1, 106.7, 82.1, 27.8, 19.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_2O_3$: 351.1703; found: 351.1709.

***tert*-Butyl (1-Oxo-3-(*m*-tolyl)isoquinolin-2(1*H*)-yl)carbamate (2m)**

White solid; yield: 54.6 mg (39%); mp 170.8–172.6 °C.

IR (KBr): 2981, 1749, 1653, 1617, 1477, 1368, 1249, 1152 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 7.5 Hz, 1 H), 7.50–7.45 (m, 2 H), 7.34–7.30 (m, 3 H), 7.24 (dd, *J* = 9.0, 5.5 Hz, 1 H), 7.11 (br s, 1 H), 6.48 (s, 1 H), 2.39 (s, 3 H), 1.42 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0, 155.4, 145.0, 137.6, 136.6, 134.5, 132.9, 129.7, 129.5, 129.0, 128.2, 127.8, 126.6, 126.1, 124.9, 107.1, 82.2, 27.9, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_2O_3$: 351.1703; found: 351.1701.

***N*-(1-Oxo-3-phenylisoquinolin-2(1*H*)-yl)benzamide (2n)**

White solid; yield: 89.7 mg (66%); mp 232.2–234.2 °C.

IR (KBr): 2914, 1676, 1643, 1613, 1504, 1467, 1272, 1156, 1020 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.67 (s, 1 H), 8.41 (d, *J* = 8.0 Hz, 1 H), 7.68 (t, *J* = 8.0 Hz, 1 H), 7.61–7.57 (m, 4 H), 7.54–7.48 (m, 2 H), 7.41–7.35 (m, 4 H), 7.22 (t, *J* = 8.0 Hz, 2 H), 6.57 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 162.4, 144.8, 136.8, 134.1, 133.1, 131.9, 131.2, 129.0, 128.9, 128.2, 128.1, 128.0, 127.4, 126.7, 126.3, 124.8, 107.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2O_2$: 341.1285; found: 341.1296.

4-Methyl-*N*-(1-oxo-3-phenylisoquinolin-2(1*H*)-yl)benzenesulfonamide (2o)

Yellow solid; yield: 74.9 mg (48%); mp 189.1–191.0 °C.

IR (KBr): 2934, 1670, 1593, 1431, 1156, 1090 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (s, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 7.68 (t, *J* = 7.5 Hz, 1 H), 7.53 (d, *J* = 7.5 Hz, 1 H), 7.46 (d, *J* = 7.5 Hz, 1 H), 7.47–7.41 (m, 2 H), 7.37–7.31 (m, 5 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 6.49 (s, 1 H), 2.34 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9, 144.4, 143.3, 136.3, 134.3, 134.1, 133.3, 129.3 (2 C), 128.5, 128.1, 128.0, 127.8, 126.9, 126.4, 124.2, 108.4, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2O_3S$: 391.1111; found: 391.1121.

***N*-(1-Oxo-3-phenylisoquinolin-2(1*H*)-yl)benzenesulfonamide (2p)**

White solid; yield: 63.1 mg (42%); mp 194.5–195.9 °C.

IR (KBr): 2940, 1673, 1557, 1442, 1341, 1152, 1090 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.49 (br s, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.46–7.42 (m, 6 H), 7.32–7.29 (m, 3 H), 7.23–7.20 (m, 2 H), 6.52 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8, 143.2, 137.2, 136.2, 134.0, 133.4, 129.3 (2 C), 128.7, 128.6, 128.1, 128.0, 127.9, 127.0, 126.4, 124.1, 108.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2O_3S$: 377.0955; found: 377.0973.

N-(1-Oxo-3-phenylisoquinolin-2(1*H*)-yl)acetamide (2q)

White solid; yield: 15.6 mg (14%); mp 157.0–159.0 °C.

IR (KBr): 2930, 1696, 1610, 1487, 1411, 1375, 1265, 1116 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.0 Hz, 1 H), 7.62–7.60 (m, 1 H), 7.47 (d, *J* = 7.5 Hz, 1 H), 7.37–7.36 (m, 2 H), 7.30–7.25 (m, 5 H), 6.45 (s, 1 H), 2.28 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8, 144.5, 136.3, 134.1, 133.3, 129.3, 128.5, 128.2, 128.0, 127.8, 126.9, 126.4, 124.2, 108.4, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}N_2O_2$: 279.1128; found: 279.1137.

tert-Butyl (1-Oxoisoquinolin-2(1*H*)-yl)carbamate (2r)

White solid; yield: 52 mg (50%); mp 196.6–197.5 °C.

IR (KBr): 2974, 1733, 1656, 1620, 1511, 1365, 1271, 1159, 1060 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.0 Hz, 1 H), 7.78 (br s, 1 H), 7.67–7.64 (m, 1 H), 7.53–7.46 (m, 2 H), 7.21 (d, *J* = 7.5 Hz, 1 H), 6.49 (d, *J* = 7.5 Hz, 1 H), 1.48 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1, 155.7, 137.0, 133.4, 132.7, 128.0, 126.8, 126.1, 125.9, 105.7, 82.7, 28.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}N_2O_3$: 261.1234; found: 261.1230.

4-Methyl-*N*-(1-oxoisoquinolin-2(1*H*)-yl)benzenesulfonamide (2s)

White solid; yield: 43.9 mg (35%); mp 239.4–241.4 °C.

IR (KBr): 2928, 1656, 1464, 1348, 1272, 1166, 1090 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (s, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 7.58 (t, *J* = 8.0 Hz, 1 H), 7.50–7.46 (m, 4 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 6.49 (d, *J* = 7.5 Hz, 1 H), 2.26 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 145.3, 136.4, 133.0, 132.6, 131.2, 129.6, 128.4, 127.6, 127.1, 126.4, 124.6, 106.3, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_3S$: 315.0798; found: 315.0796.

N-(1-Oxoisoquinolin-2(1*H*)-yl)benzamide (2t)

White solid; yield: 66.5 mg (63%); mp 216.1–218.0 °C.

IR (KBr): 2987, 1676, 1646, 1627, 1514, 1477, 1275 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.47 (s, 1 H), 8.38 (d, *J* = 8.0 Hz, 1 H), 7.91 (d, *J* = 7.5 Hz, 2 H), 7.66 (t, *J* = 7.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.47 (t, *J* = 7.0 Hz, 2 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.24 (d, *J* = 7.5 Hz, 1 H), 6.55 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6, 160.8, 137.0, 132.9 (2 C), 132.7, 131.2, 128.7, 128.0, 127.7, 127.0, 126.3, 125.9, 106.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_2O_2$: 265.0972; found: 265.0973.

N-(6-Fluoro-1-oxoisoquinolin-2(1*H*)-yl)-4-methylbenzenesulfonamide (2u)

White solid; yield: 63.7 mg (48%); mp 244.5–245.5 °C.

IR (KBr): 2981, 1650, 1610, 1560, 1461, 1272, 1166, 1093 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60 (s, 1 H), 8.05 (dd, *J* = 9.0, 5.5 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 3 H), 7.19–7.10 (m, 4 H), 6.52 (d, *J* = 7.5 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7 (d, J_{C-F} = 251.2 Hz), 158.4, 153.1, 145.5, 138.8 (d, J_{C-F} = 8.7 Hz), 132.5, 130.9 (d, J_{C-F} = 10.0 Hz), 129.7, 128.5, 121.2, 115.95 (d, J_{C-F} = 23.5 Hz), 111.5 (d, J_{C-F} = 22.2 Hz), 105.6, 21.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}N_2O_3SF$: 333.0704; found: 333.0705.

tert-Butyl (6-Fluoro-1-oxoisoquinolin-2(1*H*)-yl)carbamate (2v)

White solid; yield: 60 mg (54%); mp 195.1–196.9 °C.

IR (KBr): 2936, 1739, 1650, 1613, 1481, 1278, 1149 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (dd, *J* = 9.0, 5.5 Hz, 1 H), 7.57 (br s, 1 H), 7.24 (d, *J* = 7.5 Hz, 1 H), 7.18–7.15 (m, 2 H), 6.43 (d, *J* = 7.5 Hz, 1 H), 1.50 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.5 (d, J_{C-F} = 250.0 Hz), 160.4, 155.6, 134.7, 131.3 (d, J_{C-F} = 10.0 Hz), 129.0, 122.5, 115.6 (d, J_{C-F} = 23.7 Hz), 111.2 (d, J_{C-F} = 21.7 Hz), 105.0, 83.1, 28.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}N_2O_3F$: 279.1140; found: 279.1150.

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Supporting Information

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