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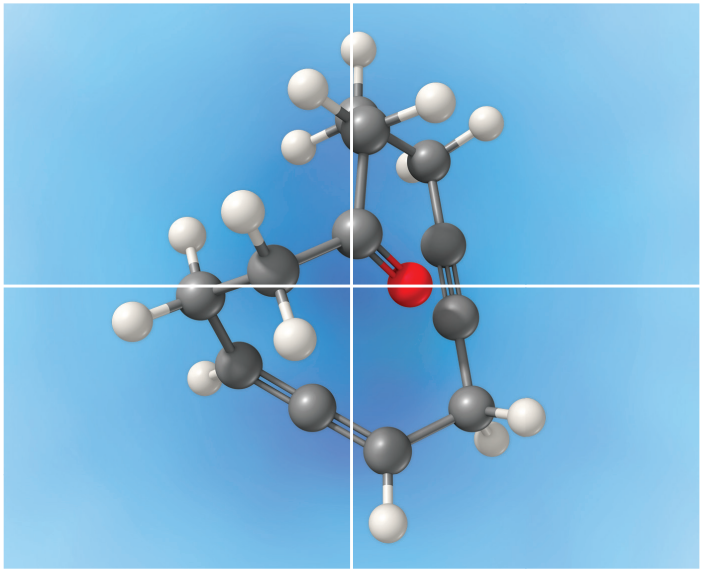

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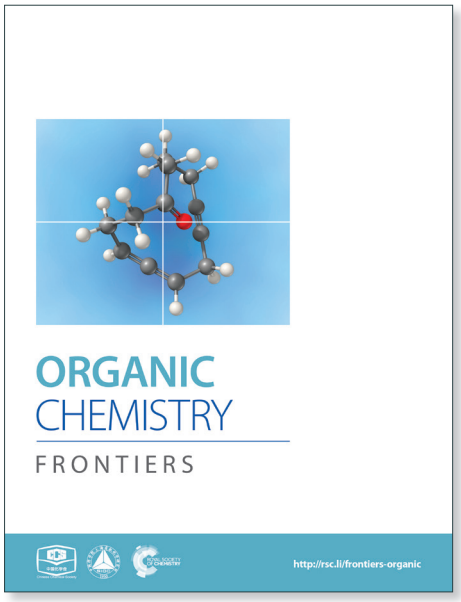

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ARTICLE TYPE

Generation of 1-amino-isoquinoline-*N*-oxides via a tandem reaction of 2-alkynylbenzaldoxime with secondary amines in the presence of silver(I) and copper(I)

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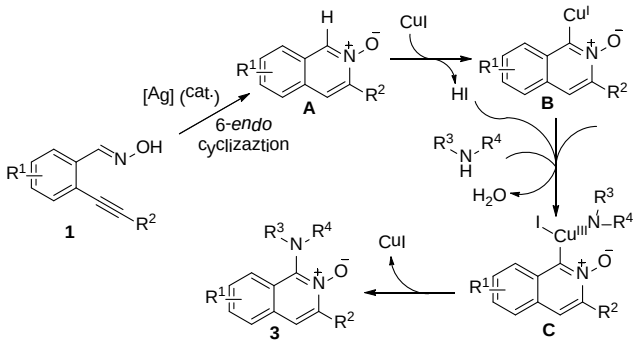
1-Amino-isoquinoline-*N*-oxides are generated under mild conditions through a tandem reaction of 2-alkynylbenzaldoxime with secondary amines in the prsence of a silver(I) and copper(I). The reaction proceeds smoothly at room temperature under air, leading to the corresponding products in good yields. During the reaction process, a silver-catalyzed 6-*endo* cyclization and a copper(I)-catalyzed C-H bond activation are involved.

1. Introduction

In the past decade, the achievement for the diversity-oriented synthesis of natural product-like compounds with privileged scaffolds has been witnessed.[1] A range of *N*-heterocycles has been applied broadly in the drug discovery process. We also involved in the libraries construction of small molecules with privileged scaffolds.[2] Some hits have been identified during the subsequent biological assays. For instance, 2-alkynylbenzaldoxime as a versatile building block has been applied widely for the construction of *N*-heterocycles.[3] Since it could be easily transferred to isoquinoline *N*-oxide via intramolecular 6-*endo* cyclization in the presence of metal catalysts or electrophiles,[4] the subsequent [3+2] cycloaddition/nucleophilic addition and rearrangement could be expected. On the other hand, a Beckmann rearrangement could be happened first since an oxime moiety is present in the molecule, which would then undergo an intramolecular cyclization to furnish nitrogen-containing heterocycles.[5] Therefore, 2-alkynylbenzaldoxime is recognized as a good candidate for the generation of small molecules' libraries. In most cases, the chemistry is related to isoquinoline *N*-oxide, which could be isolated and obtained from 2-alkynylbenzaldoxime via 6-*endo* cyclization. A large collection of small molecules would be produced if diverse isoquinoline *N*-oxides could be easily accessible.

Recently, transition metal catalyzed direct C-H oxidative amination of arenes has attracted much attention.[6] For instance, Wu and Cui reported a copper(I)-catalyzed reaction of quinoline-*N*-oxide with amines.[6a] During the process, the C-H bond at the *ortho*-position of *N*-oxide was activated, thus undergoing the subsequent amination. Encouraged by this result, we envisioned that the C-H bond at the *ortho*-position of isoquinoline *N*-oxide could be activated as well, which would react with amines to provide diverse 1-amino-isoquinoline-*N*-oxides. The proposed synthetic route is present in Scheme 1. We conceived that in the presence of silver(I) and copper(I) salts as co-catalysts, the reaction of 2-alkynylbenzaldoxime **1** with amines **2** would produce the corresponding 1-amino-isoquinoline-*N*-oxides. During the transformation, a silver(I)-catalyzed 6-*endo* cyclization would occur first to afford isoquinoline *N*-oxide **A**. Subsequently, a C-H bond activation would take place in the presence of copper(I) salt to form intermediate **B**. If the reaction was performed under air atmosphere, the oxygen would act as an oxidant to involve in the transformation with amines, leading to



Scheme 1 A proposed synthetic route to 1-amino-isoquinoline-*N*-oxides

intermediate **C** with the release of a molecular water. Following by reductive elimination would deliver 1-amino-isoquinoline-*N*-oxides **3**. With the consideration in mind, we thus initiated a program for the generation of 1-amino-isoquinoline-*N*-oxides.

2. Results and discussion

At the outset, the studies were initially performed for a model reaction of 2-alkynylbenzaldoxime **1a** with piperidine **2a** at 50 °C in toluene under air atmosphere (Table 1). A control experiment catalysed by 10 mol % of silver triflate without the addition of copper(I) salt indicated that no desired product **3a** was formed (Table 1, entry 1). Only isoquinoline-*N*-oxide **A1** was isolated. This result demonstrated the important role of copper(I) catalyst in the reaction process for the activation of C-H bond at the *ortho*-position of isoquinoline *N*-oxide. As expected, 1-amino-

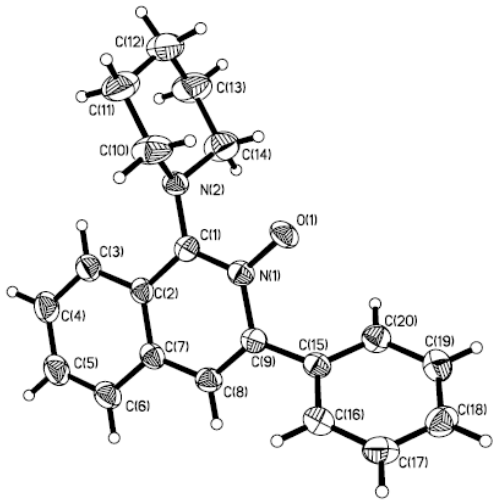
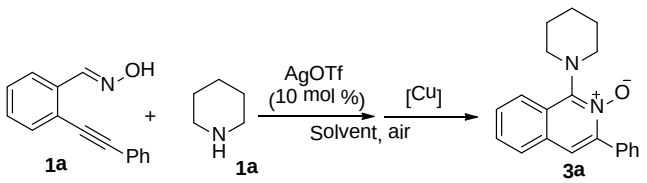


Figure 1 X-ray ORTEP illustration of compound **3a**

isoquinoline-*N*-oxide **3a** was obtained in 87% yield when Cu_2O (5 mol %) was added in the reaction system (Table 1, entry 2). The structure of **3a** was confirmed by the X-ray crystallographic analysis in the meantime (Figure 1). A similar result was observed when the copper salt was changed to CuCl or CuBr (Table 1, entries 3 and 4). The reaction co-catalyzed by silver triflate and palladium acetate gave rise to the expected product **3a** in 17% yield (data not shown in Table 1). Gratifyingly, the corresponding product **3a** was furnished in 95% yield when

Table 1 Initial studies for the reaction of 2-alkynylbenzaldoxime **1a** with piperidine **2a**



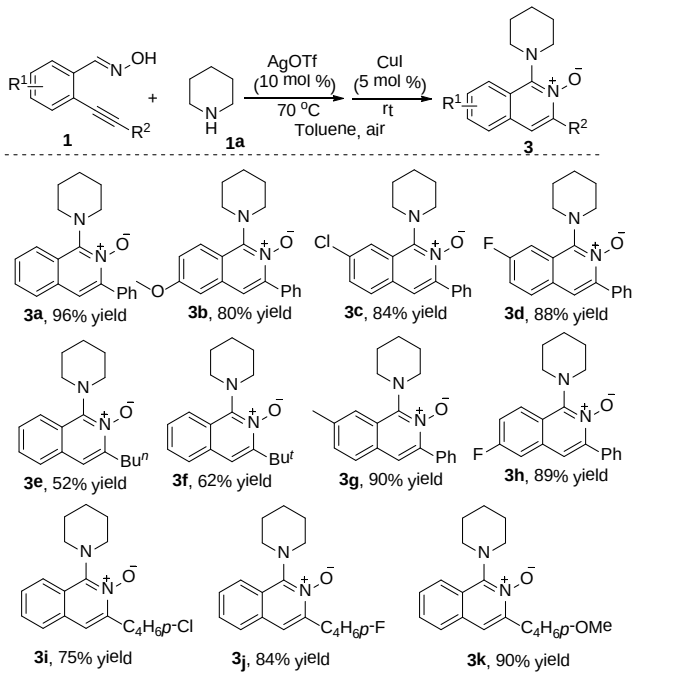
Entry	[Cu]	Temp (°C)	Solvent	Yield (%)[a]
1	-	50	toluene	nr
2	Cu_2O	50	toluene	87
3	CuCl	50	toluene	85
4	CuBr	50	toluene	88
5	CuI	50	toluene	95
6	CuI	50	DCE	82
7	CuI	50	MeCN	79
8	CuI	50	1,4-dioxane	83
9	CuI	50	THF	80
10	CuI	50	DMA	76
11	CuI	25	toluene	96
12	CuI	80	toluene	95
13[b]	CuI	25	toluene	21

[a] Isolated yield based on 2-alkynylbenzaldoxime **1a**;
[b] In the absence of AgOTf

copper(I) iodide was used as the catalyst (Table 1, entry 5). No better yields were isolated when other solvents were utilized (Table 1, entries 6-10). The efficiency was not affected when the reaction occurred at room temperature (Table 1, entry 11). The same result was observed when the reaction was performed at 80 °C (Table 1, entry 12).

The above mild optimized conditions prompted us to explore the scope of this silver(I) and copper(I) co-catalyzed reaction of 2-alkynylbenzaldoximes **1** with amines **2**. The results are summarized in Table 2 and Table 3. At the beginning, reactions of 2-alkynylbenzaldoximes **1** with piperidine **2a** were examined (Table 2). It was found that in most cases, the reactions worked well to afford the expected products **3** in good to excellent yields. 2-Alkynylbenzaldoximes **1** with different groups attached on the aromatic ring were all good reactants under the standard conditions. Reactions of 2-alkynylbenzaldoximes **1** with aryl groups attached on the triple bond (R^2) proceeded smoothly,

Table 2 Synthesis of 1-amino-isoquinoline-*N*-oxides **3** through a silver(I) and copper(I) co-catalyzed reaction of 2-alkynylbenzaldoxime **1** with piperidine **2a**[a]

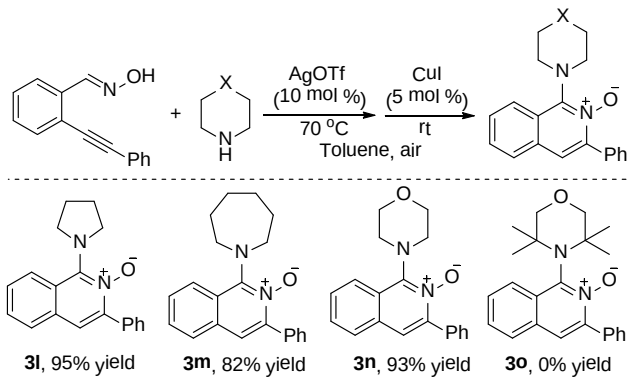


[a] Isolated yield based on 2-alkynylbenzaldoxime **1**.

leading to the corresponding products in good yields. Inferior results were obtained for the reaction of 2-alkynylbenzaldoximes **1** with alkyl groups attached on the triple bond (compounds **3e** and **3f**).

We next investigated the silver(I) and copper(I) co-catalyzed reaction of 2-alkynylbenzaldoxime **1a** with various amines (Table 3). Not only pyrrolidine but also azepane was a good partner in this transformation. Reaction of 2-alkynylbenzaldoxime **1a** with morpholine gave rise to the expected product **3n** in 93% yield. Howover, reaction of 2-alkynylbenzaldoxime **1a** with 2,2,6,6-tetramethylpiperidine did not afford the desired product **3o**. From these results, it showed that the outcome was affected by the steric hinderance of substrates. Other acyclic amines such as diethyl amine and dihexyl amine were employed in the reaction, which afforded a trace amount of the desired products. Morever, primary amines are also not effective under the conditions (data not shown in Table 3), and no expected products **3** were detected

Table 3 Synthesis of 1-amino-isoquinoline-*N*-oxides **3** through a silver(I) and copper(I) co-catalyzed reaction of 2-alkynylbenzaldoxime **1a** with secondary amines **2**[a]



[a] Isolated yield based on 2-alkynylbenzaldoxime **1a**

when primary amines were used as reaction partners under the conditions.

3. Conclusion

In conclusion, we have reported the synthesis of 1-amino-isoquinoline-*N*-oxides through a silver(I) and copper(I) co-catalyzed reaction of 2-alkynylbenzaldoxime with secondary amines under mild conditions. The transformation proceeds smoothly at room temperature under air, leading to the corresponding products in good yields. During the reaction process, a silver-catalyzed 6-*endo* cyclization and a copper(I)-catalyzed C-H bond activation are involved. The reaction scope has been demonstrated and a range of 1-amino-isoquinoline-*N*-oxides is produced efficiently. Currently, application of the 1-amino-isoquinoline-*N*-oxides for the construction of diverse *N*-heterocycles is ongoing in our laboratory.

4. Experimental Section

General experimental procedure for the synthesis of 1-amino-isoquinoline-*N*-oxides **3** through a silver(I) and copper(I) co-catalyzed reaction of 2-alkynylbenzaldoximes **1** with amines **2**: A mixture of silver triflate (0.02 mmol, 5.1 mg) and 2-alkynylbenzaldoxime **1** (0.2 mmol) in toluene (1.0 mL) was stirred at 70 °C for 1 hour. Then secondary amine **2** (1.6 mmol), CuI (0.01mmol, 1.9 mg), and toluene (1.0 mL) were added subsequently. The reaction was stirred at 25 °C until completion of the reaction as indicated by TLC. The solvent was evaporated and the residue was purified by column chromatography on silica gel to provide the product **3**.

3-Phenyl-1-(trifluoromethyl)isoquinoline **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.75 - 7.70 (m, 3H), 7.61 - 7.49 (m, 3H), 7.49 - 7.38 (m, 3H), 3.79 (s, 2H), 3.17 (s, 2H), 1.83 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 147.5, 133.8, 130.2, 129.9, 128.9, 128.2, 128.0, 127.5, 127.3, 126.9, 124.2, 120.8, 49.7, 26.6, 24.4; HRMS (ESI) calcd for $C_{20}H_{20}N_2O$: 305.1648 (M + H^+), found: 305.166.

5-Methoxy-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.77 - 7.74 (m, 3H), 7.48 - 7.38 (m, 4H), 6.86 (d, *J* = 7.7 Hz, 1H), 3.97 (s, 3H), 3.72 (s, 2H), 3.16 (s, 2H), 1.79 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 150.9, 146.6, 134.2, 130.9, 129.9, 128.7, 128.6, 127.9, 122.3, 116.2, 115.6, 106.4, 55.7, 49.6, 26.5, 24.4; HRMS (ESI) calcd for $C_{21}H_{22}N_2O_2$: 335.1754 (M + H^+), found: 335.1758.

7-Chloro-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 7.48 - 7.40 (m, 4H), 3.80 (s, 2H), 3.09 (s, 2H), 1.85 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.9, 134.3, 133.4, 130.9, 129.7, 129.1, 128.9, 128.5, 128.2, 128.1, 123.0, 120.6, 49.3, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}ClN_2O$: 339.1259 (M + H^+), found: 339.1256.

7-Fluoro-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 10.3, 2.0 Hz, 1H), 7.73 - 7.70 (m, 3H), 7.54 (s, 1H), 7.48 - 7.40 (m, 3H), 7.31 - 7.26 (m, 1H), 3.78 (s, 2H), 3.08 (s, 2H), 1.84 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, $^1J_{CF}$ = 247.4 Hz), 150.7, 147.1, 133.5, 130.9, 129.8, 129.0, 128.8, 128.1, 127.0, 120.7, 118.2 (d, $^2J_{CF}$ = 25.4 Hz), 108.1 (d, $^2J_{CF}$ = 24.0 Hz), 49.2, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}FN_2O$: 323.1554 (M + H^+), found: 323.1561.

3-Butyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 - 8.12 (m, 1H), 7.66 - 7.64 (m, 1H), 7.50 - 7.48 (m, 2H), 7.33 (s, 1H), 3.75 (s, 2H), 3.10 (s, 1H), 3.03 - 2.95 (m, 2H), 2.17 (s, 1H), 1.78 - 1.72 (m, 8H), 1.54 - 1.45 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 149.8, 130.2, 128.0, 127.3, 126.2, 124.1, 117.9, 49.6, 30.4, 29.2, 26.6, 24.3, 22.7, 13.9; HRMS (ESI) calcd for $C_{18}H_{24}N_2O$: 285.1961 (M + H^+), found: 285.1952.

3-(*tert*-Butyl)-1-(piperidin-1-yl)isoquinoline 2-oxide **3f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.51 - 7.43 (m, 3H), 3.63 (s, 2H), 3.11 (s, 2H), 1.84 - 1.75 (m, 6H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 151.9, 129.6, 127.5, 126.7, 123.5, 117.2, 49.1, 36.6, 28.3, 26.5, 24.3; HRMS (ESI) calcd for $C_{18}H_{24}N_2O$: 285.1961 (M + H^+), found: 285.1941.

7-Methyl-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.74 (d, *J* = 6.7 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.48 - 7.40 (m, 4H), 7.36 (d, *J* = 8.1 Hz, 1H), 3.74 (s, 2H), 3.14 (s, 2H), 2.56 (s, 3H), 1.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 146.6, 138.3, 133.9, 130.9, 130.4, 129.8, 128.7, 127.9, 127.4, 126.8, 123.1, 120.7, 49.4, 26.5, 24.3, 22.2; HRMS (ESI) calcd for $C_{21}H_{22}N_2O$: 319.1805 (M + H^+), found: 319.1802.

6-Fluoro-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (m, 1H), 7.73 (d, *J* = 6.6 Hz, 2H), 7.48 - 7.41 (m, 4H), 7.33 - 7.29 (m, 2H), 3.72 (s, 2H), 3.13 (s, 2H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (d, $^1J_{CF}$ = 249.6 Hz), 151.2, 148.6, 133.5, 131.3, 129.7, 129.1, 128.0, 127.3 (d, $^3J_{CF}$ = 8.9 Hz), 124.4, 120.1 (d, $^4J_{CF}$ = 5.0 Hz), 118.3 (d, $^2J_{CF}$ = 24.9 Hz), 110.9 (d, $^2J_{CF}$ = 21.7 Hz), 49.5, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}FN_2O$: 323.1554 (M + H^+), found: 323.1557.

3-(4-Chlorophenyl)-1-(piperidin-1-yl)isoquinoline 2-oxide **3i**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.72 - 7.69 (m, 3H), 7.60 - 7.50 (m, 3H), 7.42 (d, *J* = 8.5 Hz, 2H), 3.73 (s, 2H), 3.19 (s, 2H), 1.85 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 146.2, 134.9, 132.2, 131.2, 130.2, 128.4, 128.3, 127.3, 126.9, 124.2, 120.7, 49.6, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}ClN_2O$: 339.1259 (M + H^+), found: 339.1258.

3-(4-Fluorophenyl)-1-(piperidin-1-yl)isoquinoline 2-oxide **3j**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.1 Hz, 1H), 7.76 -7.70 (m, 3H), 7.59 - 7.50 (m, 3H), 7.13 (t, *J* = 8.4 Hz, 2H), 3.73 (s, 2H), 3.19 (s, 2H), 1.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{CF}$ = 247.3 Hz), 151.2, 146.4, 131.9 (d, $^3J_{CF}$ = 8.2 Hz), 130.2, 129.8, 128.3 (d, $^3J_{CF}$ = 7.7 Hz), 127.2, 126.9, 124.2, 120.7, 115.0 (d, $^2J_{CF}$ = 21.6 Hz), 49.6, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}FN_2O$: 323.1554 (M + H^+), found: 323.1543.

3-(4-Methoxyphenyl)-1-(piperidin-1-yl)isoquinoline 2-oxide **3k** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.1 Hz, 1H), 7.73 - 7.68 (m, 3H), 7.59 - 7.48 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 3.73 (s, 2H), 3.17 (s, 2H), 1.84 -1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 151.1, 147.2, 131.3, 130.3, 128.1, 127.9, 127.0, 126.7, 126.1, 124.1, 120.4, 113.4, 55.4, 49.5, 26.6, 24.3; HRMS (ESI) calcd for $C_{21}H_{22}N_2O_2$: 335.1754 (M + H^+), found: 335.1753.

3-Phenyl-1-(pyrrolidin-1-yl)isoquinoline 2-oxide **3l**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.75 - 7.71 (m, 3H), 7.57 -7.52 (m, 3H), 7.50 - 7.41 (m, 3H), 3.64 -3.52 (m, 4H), 2.15 - 2.05 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 147.6, 133.9, 130.9, 129.9, 129.8, 128.9, 128.6, 128.2, 128.1, 126.7, 124.7, 120.9, 48.8, 26.5; HRMS (ESI) calcd for $C_{19}H_{18}N_2O$: 291.1492 (M + H^+), found: 291.1492.

1-(Azepan-1-yl)-3-phenylisoquinoline 2-oxide **3m**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.3 Hz, 1H), 7.76 -7.72 (m, 3H), 7.60 - 7.57 (m, 2H), 7.54 -7.50 (m, 1H), 7.48 - 7.40 (m, 3H), 3.43 (s, 4H), 1.83 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 147.6, 133.7, 130.9, 130.1, 129.8, 128.9, 128.4, 128.2, 128.0, 126.8, 124.4, 121.4, 51.1, 30.5, 28.2; HRMS (ESI) calcd for $C_{21}H_{22}N_2O$: 319.1805 (M + H^+), found: 319.1803.

1-Morpholino-3-phenylisoquinoline 2-oxide **3n**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.3 Hz, 1H), 7.75 -7.72 (m, 3H), 7.61 - 7.54 (m, 3H), 7.50 - 7.43 (m, 3H), 3.96 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 147.5, 133.5, 130.9, 130.2, 129.7, 129.0, 128.5, 128.4, 128.1, 127.1, 123.8, 121.3, 67.9, 48.5; HRMS (ESI) calcd for $C_{19}H_{18}N_2O_2$: 307.1441 (M + H^+), found: 307.1447.

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Notes and references

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† Author Contributions: J. Song and C. Fan contributed equally.

Electronic Supplementary Information (ESI) available: [Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3**, the CIF file of compound **3a**.]. See DOI: 10.1039/b000000x/

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