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Copper-Mediated Formally Dehydrative Biaryl Coupling of Azine *N*-Oxides and Oxazoles

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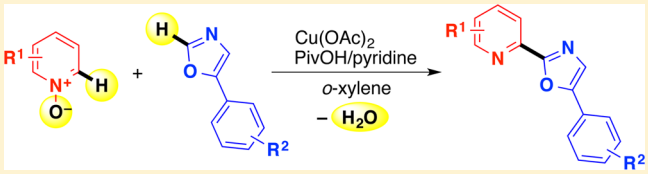
Supporting Information

ABSTRACT: A copper-mediated formally dehydrative biaryl coupling of azine *N*-oxides and oxazoles has been developed. The C−C bond-forming process proceeds, accompanied by the removal of the oxygen atom from the azine core, to directly afford the azine−oxazole biaryl linkage. Moreover, this system requires no noble transition metals such as palladium and rhodium, which are common promotors in the related dehydrogenative couplings with the azine *N*-oxide. Thus, the present protocol can provide a unique and less expensive approach to the azine-containing biheteroaryls of substantial interest in pharmaceutical and medicinal chemistry.



INTRODUCTION

Pyridines are representative six-membered *N*-heteroaromatics and constitute an important class of compounds in organic chemistry. Particularly, pyridine-containing heterobiaryls are prevalent structural motifs in biologically active compounds and natural products.[1] The most reliable approach to the above heteroaromatic cores is the transition-metal-catalyzed cross-coupling reaction with (hetero)aryl halides and (hetero)arylmetals.[2] However, recent advances in metal-promoted C−H activation[3] can obviate prefunctionalization steps, such as halogenation or stoichiometric metalation, of starting (hetero)arenes and provide a useful complement to the conventional cross-coupling technology. However, probably because of their electron deficiency, the direct C−H arylation of pyridine and related azine compounds still remains a challenge, except for several cases.[4] To overcome such a lower reactivity of the azines toward direct arylation, an appropriate activating substituent, namely, an oxygen atom[5] or an acylated imino group,[6] is introduced to the nitrogen atom on the azine ring. In particular, the oxygen-based activation strategy has made great progress and now allows the otherwise reluctant azine core to be adopted in the metal-catalyzed C−H arylation with aryl halides or organometallic reagents (Scheme 1a)[5c−g] and even more challenging C−H/C−H coupling with simple arenes or heteroarenes (Scheme 1b).[7] Although the latter process is especially appealing because both starting materials are nonhalogenated and nonmetalated and azine-heteroarene conjugations of biological importance are readily accessible,[7b−i] an additional deoxygenation step is inevitable for obtaining the desired azine-containing heterobiaryls.

Meanwhile, our group[8] and others[9] recently focused on the unique reactivity of less expensive and abundant copper salts in C−H functionalization and developed some noble-metal-free, copper-mediated C−H/C−H biaryl couplings. During our continuous interest in this research field, we next tested the azine *N*-oxide as a coupling partner[10] for oxazoles in copper-promoted dehydrogenative biaryl coupling. The C−C bond forming reaction proceeded, however, with concomitant unexpected removal of the oxygen from the azine aromatic core to directly furnish the azine−oxazole π-conjugation (Scheme 1c). Different from the above precedents, the copper-based system required no individual reduction step for the removal of the oxygen from the coupling products. Similar deoxygenative C2-arylations of azine *N*-oxides are reported, but they employ prefunctionalized, reactive aryl nucleophiles such as Grignard reagents[5f] or arylboronates[5g] (Scheme 1a). In this work, we report in detail the copper-mediated formally *dehydrative* biaryl coupling of azine *N*-oxides and oxazoles. The present dehydrative coupling[11] occurs even under noble-metal-free conditions and thus provides a unique and potentially effective access to pyridine- and relevant azine-containing biheteroaryls of substantial interest in pharmaceutical and medicinal chemistry (Scheme 2). A related dehydrative coupling of azine *N*-oxides with alkenes under Pd catalysis was already reported by Cui and Wu,[11a] but the dehydrative coupling with (hetero)arenes is not trivial, to the best of our knowledge.

RESULTS AND DISCUSSION

On the basis of our previous work on copper-mediated dehydrogenative biaryl coupling with 1,3-azoles,[8] we first tested the coupling reaction of quinoline *N*-oxide monohydrate (**1a**) with 5-phenyloxazole (**2a**) in heating *o*-xylene under representative $Cu(OAc)_2$/PivOH-promoted conditions (Table 1). To our delight, the C−C bond-forming reaction proceeded, but surprisingly, the observed product was not the originally expected **3aa-O** but the formally dehydrative coupling product **3aa** (entry 1). Careful monitoring by GC and GCMS also indicated no formation of **3aa-O** during the course of the

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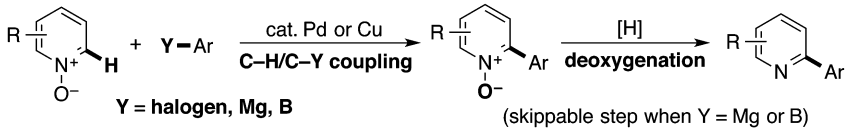
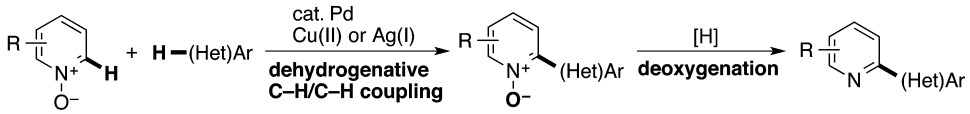
Scheme 1. Approaches to 2-Arylpyridines via C−H Arylation of Pyridine *N*-Oxides

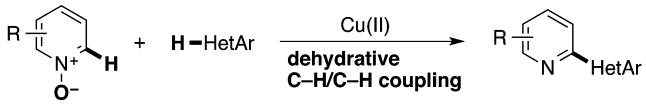
a) C–H Arylation with aryl halides or arylmetal reagents



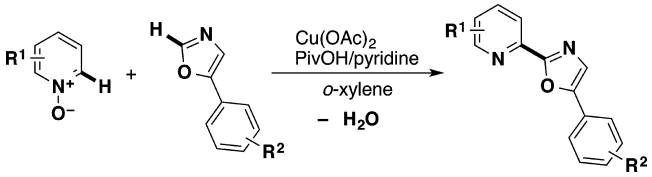
b) Dehydrogenative C–H Arylation with simple arenes or heteroarenes



c) Dehydrative C–H arylation with heteroarenes (**This work**)

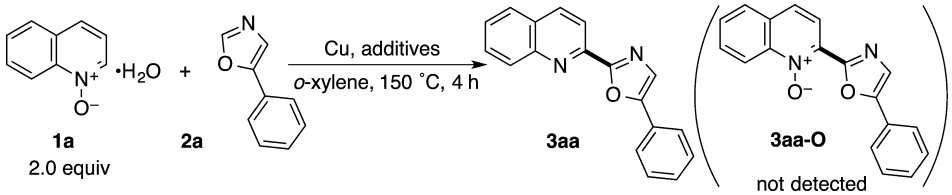


Scheme 2. Copper-Mediated Formally Dehydrative Biaryl Coupling of Azine *N*-Oxides and Oxazoles



reaction. The preliminary but intriguing result prompted us to optimize conditions for unique dehydrative coupling. The brief screening of carboxylic acids proved PivOH to be the optimal (entries 2 and 3). Subsequent investigations of bases showed positive effects of pyridine (entry 4), while other organic and inorganic bases decreased the reaction efficiency (entries 5–10). Even with basic pyridine, the addition of PivOH was still necessary (entry 11). With **1a** as the limiting reagent, the yield significantly decreased (entry 12). Although we subjected other Cu(I) and Cu(II) salts instead of $Cu(OAc)_2$, **3aa** was formed in

Table 1. Optimization Studies for Copper-Mediated Formally Dehydrative Coupling of Quinoline *N*-Oxide monohydrate (1a) with 5-Phenyloxazole (2a)[a]



entry	Cu (0.50 mmol)	additives (0.25 mmol)	yield of **3aa** (%)[b]
1	$Cu(OAc)_2$	PivOH	52 (48)
2	$Cu(OAc)_2$	none	41
3	$Cu(OAc)_2$	AcOH	36
4	$Cu(OAc)_2$	PivOH, pyridine	59 (54)
5	$Cu(OAc)_2$	PivOH, 2,6-lutidine	27
6	$Cu(OAc)_2$	PivOH, acridine	50
7	$Cu(OAc)_2$	PivOH, *i*-Pr_2NEt	8
8	$Cu(OAc)_2$	PivOH, DBU	13
9	$Cu(OAc)_2$	PivOH, K_2CO_3	20
10	$Cu(OAc)_2$	PivOH, K_3PO_4	3
11	$Cu(OAc)_2$	pyridine	48 (41)
12[c]	$Cu(OAc)_2$	PivOH, pyridine	34
13	CuOAc	PivOH, pyridine	1
14	CuO	PivOH, pyridine	0
15	Cu_2O	PivOH, pyridine	0
16	CuI	PivOH, pyridine	0
17	CuBr	PivOH, pyridine	0
18[d]	$Cu(OAc)_2$	PivOH, pyridine	0

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (0.25 mmol), Cu (0.50 mmol), additives (0.25 mmol), solvent (1.5 mL), and N_2. [b]GC yield. The yield is given in parentheses. [c]With **1a** (0.25 mmol) and **2a** (0.50 mmol). [d]With quinoline instead of quinoline *N*-oxide (**1a**).

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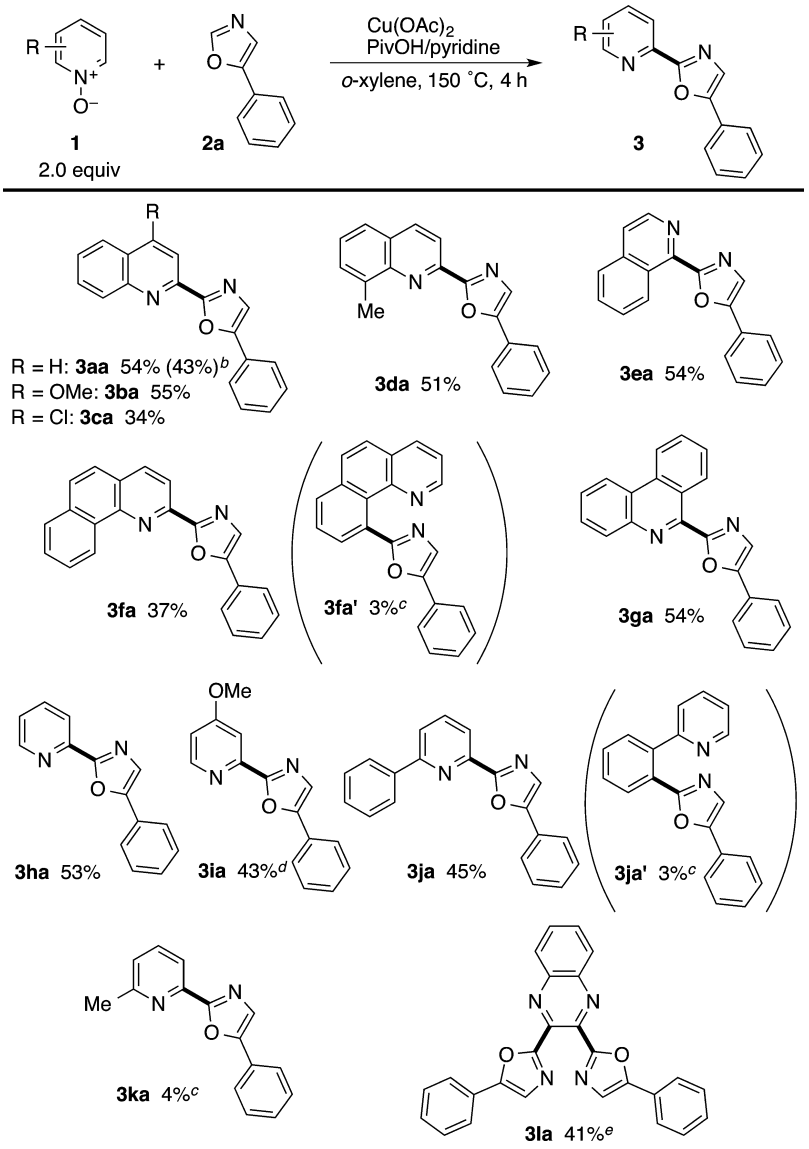
Scheme 3. Copper-Mediated Formally Dehydrative Biaryl Coupling of Various Azine *N*-Oxides 1 with 5-Phenyloxazole (2a)[a]



[a]The formed C−C bonds are illustrated with a bold line. Reaction conditions: **1** (0.50 mmol), **2a** (0.25 mmol), $Cu(OAc)_2$ (0.50 mmol), PivOH (0.25 mmol), pyridine (0.25 mmol), *o*-xylene (1.5 mL), N_2. Except for quinoline *N*-oxide monohydrate (**1a**), azine *N*-oxides were used as the nonhydrate. [b]On a 1.0 mmol scale for 24 h. [c]GC yield. [d]Without pyridine. [e]Quinoxaline 1,4-dioxide (0.25 mmol), 5-phenyloxazole (**2a**, 0.50 mmol), $Cu(OAc)_2$ (1.0 mmol), PivOH (0.50 mmol), pyridine (0.50 mmol), and *o*-xylene (2.0 mL).

less than 2% yield (entries 13−17). The control experiment with the parent quinoline under otherwise identical conditions resulted in no formation of **3aa** (entry 18). In all entries of Table 1, the major byproducts was the homocoupling product, bisoxazole, derived from **2a**,[12] but the oxygen-retaining product **3aa-O** was not detected at all.[13]

The yield of **3aa** is relatively moderate, but if the C−C formation and deoxygenation were performed separately as in Scheme 1a and b, the average yield of each step would be ca. 75%, which can be a useful level from the synthetic point of view. Thus, while still preliminary, under conditions of entry 4 in Table 1 we implemented the dehydrative coupling of various azine *N*-oxides **1** with 5-aryloxazole (**2a**). Representative products are shown in Scheme 3. The quinoline *N*-oxides bearing an electron-donating methoxy and an electron-withdrawing chloro group at the C4 position underwent the reaction, while the former showed better reactivity (**3ba** and **3ca**). The conceivable C8-heteroarylation of quinoline *N*-oxides was not observed at all.[14] The methyl substituent at the C8 position did not interfere with the coupling (**3da**), despite its conceivable steric hindrance. The isoquinoline system could also be employed, and C−C bond formation occurred exclusively at the C2 position (**3ea**). Moreover, higher fused azines *N*-oxides were also accommodated. Tricyclic benzo[*h*]-quinoline and phenanthridine *N*-oxides coupled with **2a** under the standard conditions to furnish **3fa** and **3ga** in 37% and 54%, respectively. In the case of **3fa**, the C10-arylated product **3fa′** was also detected by GC and GCMS analyses, which could be formed via Cu(II)-mediated dehydrogenative coupling of **2a** with the deoxygenated benzo[*h*]quinoline generated in situ.[8a] However, an amount of **3fa′** was small (3% by GC), thus indicating that the dehydrative coupling proceeded more smoothly. Additionally, **3fa** and **3fa′** could be separated from each other readily by column chromatography. Simpler

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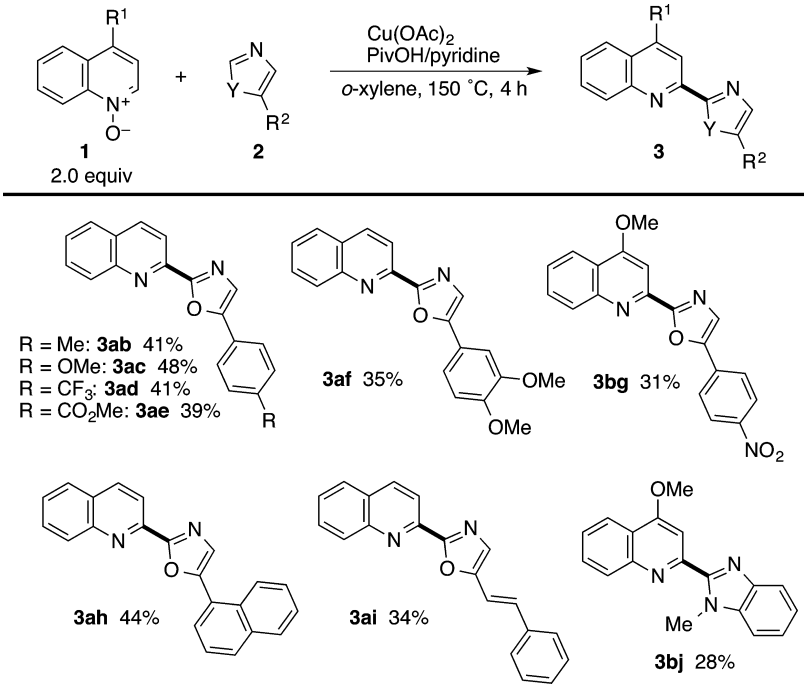
Scheme 4. Copper-Mediated Formally Dehydrative Biaryl Coupling of Azine *N*-Oxides 1 with Various 5-Aryloxazoles 2[a]



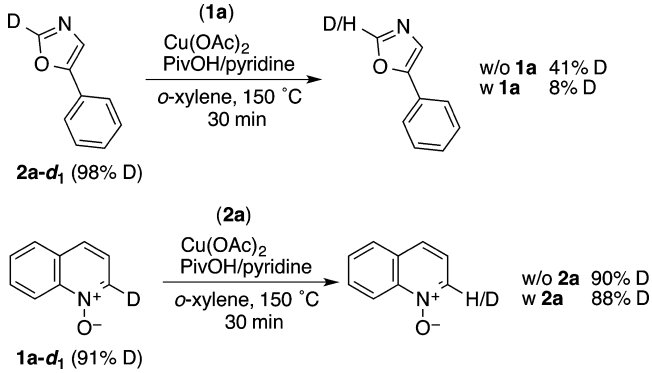
[a]The formed C−C bonds are illustrated with a bold line. Reaction conditions: **1** (0.50 mmol), **2** (0.25 mmol), $Cu(OAc)_2$ (0.50 mmol), PivOH (0.25 mmol), pyridine (0.25 mmol), *o*-xylene (1.5 mL), N_2. Except for quinoline *N*-oxide monohydrate (**1a**), azine *N*-oxides were used as the nonhydrate.

monocyclic pyridine *N*-oxides were also promising substrates: pyridyl, 4-methoxypyridyl, and 2-phenylpyridyl aromatic rings were introduced to the oxazole core directly (**3ha**, **3ia**, and **3ja**). Similar to the case of **3fa**, **3ja** was obtained, contaminated with 3% of *ortho*-arylated **3ja′**. Just one exception is 2-methylpyridine *N*-oxide, and the corresponding product **3ka** was detected in only 4% yield. This is probably because the substrate might poison the Cu salt probably through the formation of tightly chelated metalacycles.[7a,f] Particularly notable is the doubly dehydrative coupling of quinoxaline 1,4-dioxide: two C−C bonds were formed simultaneously to afford the 2,3-bisarylated quinoxaline **3la** in one attempt. Moreover, the reaction of **1a** with **2a** could be successfully performed on a 1.0 mmol scale, and **3aa** was obtained in 43% yield.

We next investigated the scope of 1,3-azoles (Scheme 4). The copper-based conditions were compatible with electronically diverse substituents on the oxazole, including methyl, methoxy, trifluoromethyl, methoxycarbonyl, and nitro functions (**3ab**, **3ac**, **3ad**, **3ae**, **3af**, and **3bg**). The naphthalene and styryl moieties were also tolerated under reaction conditions (**3ah** and **3ai**). Among other 1,3-azoles, only *N*-methylbenzimidazole gave the corresponding biaryl **3bj**, albeit with 28% yield. As far as we tested, thiazole, benzothiazole, and oxadiazoles produced the desired products in less than 5% yields (data not shown). This is the current limitation, but the observed unique reactivity of oxazoles is complementary to the precedented Pd-catalyzed dehydrogenative coupling of azine *N*-oxides and azoles.[7f] In most cases, we found the competitive homocoupling of azoles (ca. 20%), which was the major reason for the relatively low reaction efficiency. The starting oxazoles were also recovered intact in ca. 10%. The fates of others could not be identified, but the ring opening decomposition may competitively occur.[15]

To obtain mechanistic insight, we prepared deuterated starting materials **1a**-d_1 and **2a**-d_1 and performed the following experiments (Scheme 5). At an early stage (30 min), the 2-deuterio-5-phenyloxazole (**2a**-d_1) underwent the rapid H/D

Scheme 5. H/D Scrambling Experiments with 1a-d_1 and 2a-d_1



exchange even in the presence or absence of the coupling partner quinoline *N*-oxide (**1a**), which was common in our previous Cu(II)-mediated dehydrogenative couplings.[8] In sharp contrast, we observed negligible H/D scrambling of 2-deuterioquinoline *N*-oxide (**1a**-d_1) regardless of the addition of 5-phenyloxazole (**2a**). These phenomena suggest that the C−H cupration of the oxazole occurs rapidly and reversibly, while the azine *N*-oxide C−H cannot be metalated under the present conditions.

Given the above considerations and literature information, we propose the reaction course of **1a** and **2a** as shown in Scheme 6. An initial acetate-ligand-assisted[16] C−H cupration of **2a** generates the key oxazolylcopper intermediate **4**. Subsequent nucleophilic addition is followed by deoxygenative elimination with concomitant rearomatization of the quinoline

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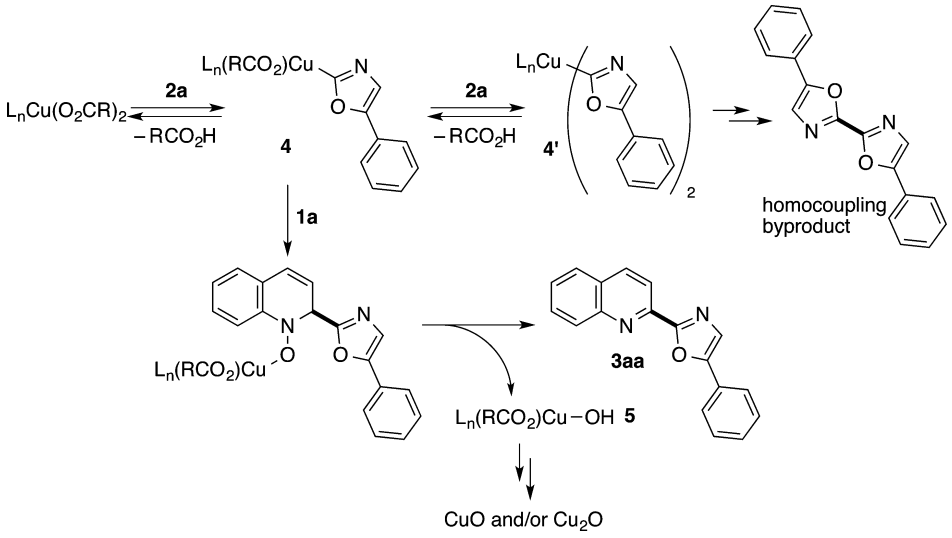
Scheme 6. Plausible Mechanism[a]

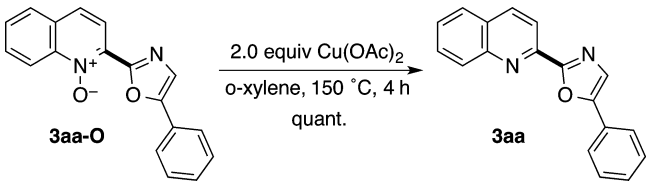


[a]L = pyridine or solvent. R = Ac or Piv.

ring to furnish the formally dehydrative coupling product **3aa** and a hydroxylcopper species **5**. The latter can be finally converted to inactive and insoluble copper oxides. Thus, a stoichiometric amount of $Cu(OAc)_2$ is essential, despite the fact that this process is overall redox-neutral.[17] A similar addition/elimination-type mechanism is proposed in the Cu(I)-catalyzed dehydrative coupling of nitrones with terminal alkynes.[18] However, if the second **2a** reacted with **4**, the homocoupling byproduct would be formed via a bis(oxazolyl) copper **4′**. Although the origin of the unique reactivity of $Cu(OAc)_2$ observed in Table 1 is still unclear, its inherent acetate ligand and relatively high Lewis acidic nature might play important roles in the C−H cleavage of **2a** and addition step of **4** to **1a**, respectively.

Nevertheless, we cannot completely exclude the possibility of the stepwise dehydrogenative C-H/C-H coupling/deoxygenation mechanism[19] such as the on in Scheme 1b: the dehydrogenative coupling product **3aa-O**, which was independently prepared from **3aa** and mCPBA,[20] readily underwent deoxygenation in the presence of 2.0 equiv $Cu(OAc)_2$ to furnish **3aa** in quantitative yield (Scheme 7).[21] The detailed mechanism remains to be elucidated and is currently under investigation in our laboratory.

Scheme 7. Deoxygenation of Independently Prepared 3aa-O



CONCLUSIONS

We have developed a copper-mediated formally dehydrative coupling of azine *N*-oxides and oxazoles. The Cu(II)-based system directly provides, without an additional reduction step, azine-containing biheteroaryls of prevalent aromatic cores in pharmaceutical targets and biologically active compounds. Thus, the current work can complement the known C−H arylation protocols of azine *N*-oxides,[5,7] while the substrate scope is still relatively limited. Consequently, further studies on the detailed mechanism and development of related copper-promoted dehydrative and dehydrogenative C−C forming reactions are ongoing.

EXPERIMENTAL SECTION

Instrumentation and Chemicals. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 400, 100, and 376 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by EI or APCI using a double-focusing mass spectrometer or TOF, respectively. GC analysis was carried out using a silicon OV-17 column (i.d. 2.6 mm × 1.5 m) or a CBP-1 capillary column (i.d. 0.5 mm × 25 m). Silica gel was used for column chromatography. Gel permeation chromatography (GPC) was performed with a $CHCl_3$ eluent (3.5 mL/min, UV detector). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. *o*-Xylene was freshly distillated from CaH_2. Azine *N*-oxides **1a**, **1d**, **1e**, **1h**, **1i**, and **1k** are commercially available, and other **1b**,[22a] **1c**,[22a] **1f**,[22a] **1g**,[10d] **1j**,[22b] **1l**,[10d] and **1a-d_1**[10c] compounds were prepared according to the literature. 5-Substituted oxazoles **2** were synthesized by the van Leusen reaction with TosMIC and the corresponding aldehydes.[23] Unless otherwise noted, all reactions were carried out under N_2 conditions.

Procedure for the Preparation of 2-Deuterio-5-phenyloxazole (2a-d_1). 5-Phenyloxazole (**2a**, 1.5 g, 10 mmol) was placed in a 100 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. The flask was cooled to −78 °C with a dry ice-acetone bath, and THF (15 mL) and butyllithium (1.64 M hexane solution, 6.7 mL, 11 mmol) were then added to the flask. After the mixture was stirred for 1 h at the same temperature, deuterium oxide (1.8 mL, 100 mmol) was added dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for an additional 20 h. The mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. After concentration in vacuo, silica gel column purification with hexane/ethyl acetate (3/1, v/v) afforded 2-deuterio-5-phenyloxazole (**2a-d_1**, 876 mg, 6.0 mmol, 98% D) in 60% yield.

2-Deuterio-5-phenyloxazole (2a-d_1). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent; 876 mg (98%D, 60%), mp 35−37 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.37 (m, 2H), 7.41−7.46 (m, 2H), 7.65−7.68 (m, 2H), 7.92 (s, 0.02H); $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$) δ 121.4, 124.4, 127.7, 128.6, 128.9, 150.2 (t, J = 35 Hz), 151.5; HRMS (APCI) m/z ($[M + H]^+$) calcd for C_9H_7DNO 147.0665, found 147.0684.

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Typical Procedure for Cu-Mediated Formally Dehydrative Coupling of Azine *N*-Oxides and Oxazoles. The synthesis of **3aa** is representative (Table 1, entry 4). $Cu(OAc)_2$ (91 mg, 0.50 mmol), quinoline *N*-oxide monohydrate (**1a**, 82 mg, 0.50 mmol), and 5-phenyloxazole (**2a**, 36 mg, 0.25 mmol) were placed in a 20 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. A solution of PivOH (26 mg, 0.25 mmol) in *o*-xylene (1.5 mL) and pyridine (20 μL, 0.25 mmol) were sequentially injected via a syringe. The suspension was stirred for 4 h at 150 °C. The resulting mixture was allowed to cool to room temperature and then quenched with water. A small amount of ethylenediamine was then added to dissolve the residual copper salts into the aqueous phase. Extraction with ethyl acetate, concentration under reduced pressure, and silica gel column purification with hexane/ethyl acetate (3/1, v/v) followed by GPC afforded 5-phenyl-2-(quinolin-2-yl)oxazole (**3aa**, 37 mg, 0.14 mmol) in 54% yield.

5-Phenyl-2-(quinolin-2-yl)oxazole (3aa). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent, followed by GPC; 37 mg (54%), mp 139−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.40 (m, 1H), 7.45−7.50 (m, 2H), 7.59 (s, 1H), 7.60 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 7.78 (ddd, J = 2.0, 6.8, 8.4 Hz, 1H), 7.84−7.87 (m, 3H), 8.26−8.30 (m, 3H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 119.3, 124.1, 124.8, 127.5, 127.6, 128.2, 128.9 (two signals were overlapped), 130.1, 130.2, 137.1, 145.8, 148.0, 153.0, 160.2 (one signal was overlapped by others); HRMS (EI) m/z (M^+) calcd for $C_{18}H_{12}N_2O$ 272.0950, found 272.0949.

2-(4-Methoxyquinolin-2-yl)-5-phenyloxazole (3ba). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent; 41 mg (55%), mp 171−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (s, 3H), 7.36−7.40 (m, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.53−7.57 (m, 2H), 7.65 (s, 1H), 7.73−7.77 (m, 1H), 7.87 (d, J = 7.6 Hz, 2H), 8.22 (dd, J = 3.6, 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 56.1, 98.2, 121.5, 121.8, 123.8, 124.9, 126.6, 127.6, 128.90, 128.92, 129.6, 130.4, 146.9, 149.0, 153.1, 160.4, 162.9; HRMS (EI) m/z (M^+) calcd for $C_{19}H_{14}N_2O_2$ 302.1055, found 302.1056.

2-(4-Chloroquinolin-2-yl)-5-phenyloxazole (3ca). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent; 26 mg (34%), mp 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.41 (m, 1H), 7.46−7.50 (m, 2H), 7.59 (s, 1H), 7.68 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 7.80−7.85 (m, 3H), 8.24 (dd, J = 1.2, 8.4 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.37 (s, 1H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 119.4, 124.1, 124.2, 124.8, 126.4, 127.4, 128.5, 128.9, 129.1, 130.5, 131.0, 143.4, 145.5, 148.8, 153.3, 159.2; HRMS (EI) m/z (M^+) calcd for $C_{18}H_{11}ClN_2O$ 306.0560, found 306.0561.

2-(8-Methylquinolin-2-yl)-5-phenyloxazole (3da). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent; 37 mg (51%), mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96 (s, 3H), 7.36−7.40 (m, 1H), 7.46−7.50 (m, 3H), 7.58 (s, 1H), 7.62 (dt, J = 1.2, 6.8 Hz, 1H), 7.68 (dd, J = 0.4, 8.0 Hz, 1H), 7.82−7.85 (m, 2H), 8.22−8.27 (m, 2H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 17.8, 119.0, 124.0, 124.6, 125.5, 127.3, 127.8, 128.2, 128.8, 128.9, 130.2, 137.1, 138.2, 144.6, 147.1, 152.6, 160.6; HRMS (EI) m/z (M^+) calcd for $C_{19}H_{14}N_2O$ 286.1106, found 286.1104.

2-(Isoquinolin-1-yl)-5-phenyloxazole (3ea). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 37 mg (54%), mp 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.40 (m, 1H), 7.45−7.49 (m, 2H), 7.65 (s, 1H), 7.73−7.78 (m, 3H), 7.85−7.91 (m, 3H), 8.72 (d, J = 5.6 Hz, 1H), 9.50−9.52 (m, 1H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 122.5, 123.7, 124.9, 126.5, 127.1, 127.3, 127.6, 128.7, 128.90, 128.94, 130.4, 137.0, 142.2, 145.0, 152.4, 159.6; HRMS (EI) m/z (M^+) calcd for $C_{18}H_{12}N_2O$ 272.0950, found 272.0948.

2-(Benzo[*h*]quinolin-2-yl)-5-phenyloxazole (3fa). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 29 mg (37%), mp 153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.60 (s, 1H), 7.67−7.75 (m, 2H), 7.78−7.92 (m, 5H), 8.24−8.26 (m, 1H), 8.35−8.37 (m, 1H), 9.51 (d, J = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 120.0, 124.0, 124.6, 124.9, 125.0, 126.6, 127.3, 127.80, 127.83, 128.6, 128.81, 128.84, 129.0, 131.4, 133.8, 136.5, 144.3, 146.4, 152.6, 160.6; HRMS (EI) m/z (M^+) calcd for $C_{22}H_{14}N_2O$ 322.1106, found 322.1108.

2-(Phenanthridin-6-yl)-5-phenyloxazole (3ga). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 44 mg (54%), mp 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.41 (m, 1H), 7.47−7.50 (m, 2H), 7.68 (s, 1H), 7.71−7.75 (m, 1H), 7.78−7.82 (m, 2H), 7.88−7.92 (m, 3H), 8.36 (dd, J = 1.2, 8.0 Hz, 1H), 8.61 (dd, J = 1.2, 8.0 Hz, 1H), 8.70 (d, J = 8.4 Hz, 1H), 9.53 (dd, J = 0.8, 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 122.0, 122.1, 123.6, 124.2, 124.5, 125.0, 127.7, 128.0, 128.2, 128.5, 128.9, 129.0 (two signals were overlapped), 130.87, 130.90, 133.5, 143.4, 145.6, 152.6, 159.4; HRMS (APCI) m/z ([M + H]$^+$) calcd for $C_{22}H_{15}N_2O$ 323.1179, found 323.1185.

5-Phenyl-2-(pyridin-2-yl)oxazole (3ha). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 30 mg (53%), mp 100−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.38 (m, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.52 (s, 1H), 7.78−7.85 (m, 3H), 8.17 (d, J = 8.0 Hz, 1H), 8.77 (dt, J = 0.8, 4.0 Hz, 1H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 122.0, 123.7, 124.4, 124.6, 127.6, 128.7, 128.8, 136.8, 146.1, 150.0, 152.5, 159.9; HRMS (EI) m/z (M^+) calcd for $C_{14}H_{10}N_2O$ 222.0793, found 222.0792.

2-(4-Methoxypyridin-2-yl)-5-phenyloxazole (3ia). Purified by column chromatography on silica gel with hexane/ethyl acetate (2:1, v/v) as an eluent followed by GPC; 26 mg (41%), mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 6.90 (dd, J = 2.4, 6.4 Hz, 1H), 7.36−7.38 (m, 1H), 7.43−7.47 (m, 2H), 7.51 (s, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.79−7.81 (m, 2H), 8.57 (d, J = 6.4 Hz, 1H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 55.5, 107.5, 111.4, 123.6, 124.7, 127.6, 128.80, 128.84, 147.7, 151.2, 152.6, 160.0, 166.3; HRMS (EI) m/z (M^+) calcd for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0901.

5-Phenyl-2-(6-phenylpyridin-2-yl)oxazole (3ja). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 34 mg (45%), mp 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.39 (m, 1H), 7.44−7.54 (m, 5H), 7.55 (s, 1H), 7.80−7.83 (m, 3H), 7.89 (t, J = 7.6 Hz, 1H), 8.10 (dd, J = 1.2, 7.6 Hz, 1H), 8.15−8.18 (m, 2H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 120.4, 121.1, 123.8, 124.6, 127.1, 127.8, 128.7, 128.8, 128.9, 129.4, 137.6, 138.6, 146.0, 152.4, 157.6, 160.2; HRMS (EI) m/z (M^+) calcd for $C_{20}H_{14}N_2O$ 298.1106, found 298.1108.

2,3-Bis(5-phenyloxazol-2-yl)quinoxaline (3la). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 42 mg (41%), mp 173−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.39 (m, 6H), 7.59 (s, 2H), 7.62−7.65 (m, 4H), 7.93 (dd, J = 3.6, 6.4 Hz, 2H), 8.33 (dd, J = 3.6, 6.4 Hz, 2H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 124.0, 124.7, 127.3, 128.9, 129.0, 129.8, 132.1, 140.4, 141.5, 153.0, 157.7; HRMS (EI) m/z (M^+) calcd for $C_{26}H_{16}N_4O_2$ 416.1273, found 416.1277.

5-(4-Methylphenyl)-2-(quinolin-2-yl)oxazole (3ab). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 28 mg (41%), mp 133−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.27−7.29 (m, 2H), 7.54 (s, 1H), 7.59 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 7.73−7.79 (m, 3H), 7.85 (ddd, J = 0.4, 1.2, 8.0 Hz, 1H), 8.27−8.30 (m, 3H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 21.4, 119.3, 123.5, 124.7, 124.9, 127.4, 127.6, 128.2, 129.6, 130.11, 130.13, 137.0, 139.0, 145.9, 148.1, 153.2, 159.9; HRMS (EI) m/z (M^+) calcd for $C_{19}H_{14}N_2O$ 286.1106, found 286.1104.

5-(4-Methoxyphenyl)-2-(quinolin-2-yl)oxazole (3ac). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent; 37 mg (48%), mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.99 (d, J = 8.8 Hz, 2H), 7.46 (s, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.75−7.79 (m, 3H), 7.84 (d, J = 8.0 Hz, 1H), 8.26−8.29 (m, 3H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 55.3, 114.4, 119.3, 120.4, 122.7, 126.4, 127.4, 127.6, 128.1, 130.0, 130.1, 137.0, 145.9, 148.0, 153.1, 159.6, 160.2; HRMS (EI) m/z (M^+) calcd for $C_{19}H_{14}N_2O_2$ 302.1055, found 302.1056.

2-(Quinolin-2-yl)-5-{4-(trifluoromethyl)phenyl}oxazole (3ad). Purified by column chromatography on silica gel with hexane/

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ethyl acetate (3:1, v/v) as an eluent followed by GPC; 35 mg (41%), mp 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (ddd, J = 1.2, 2.8, 8.0 Hz, 1H), 7.68 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.79 (ddd, J = 1.6, 6.8, 8.4 Hz, 1H), 7.87 (dd, J = 0.8, 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 8.26−8.31 (m, 3H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ119.4, 123.9 (q, J = 271 Hz), 124.8, 125.7, 125.9 (q, J = 4 Hz), 127.7, 127.8, 128.3, 130.1, 130.3, 130.5 (q, J = 33 Hz), 130.8, 137.2, 145.5, 148.0, 151.4, 161.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ-62.69 (s); HRMS (EI) m/z (M^+) calcd for $C_{19}H_{11}F_3N_2O$ 340.0823, found 340.0825.

Methyl 4-{2-(quinolin-2-yl)oxazol-5-yl}benzoate (3ae). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 32 mg (39%), mp 169−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.61 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 7.70 (s, 1H), 7.79 (ddd, J = 1.6, 6.8, 8.4 Hz, 1H), 7.87 (dd, J = 0.8, 8.0 Hz, 1H), 7.92 (dt, J = 1.6, 8.4 Hz, 2H), 8.14 (dt, J = 1.6, 8.4 Hz, 2H), 8.27−8.31 (m, 3H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 52.3, 119.4, 124.5, 125.9, 127.6, 127.7, 128.3, 130.10, 130.14, 130.2, 130.3, 131.5, 137.1, 145.5, 148.2, 151.9, 160.9, 166.5; HRMS (EI) m/z (M^+) calcd for $C_{20}H_{14}N_2O_3$ 330.1004, found 330.1005.

5-(3,4-Dimethoxyphenyl)-2-(quinolin-2-yl)oxazole (3af). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent; 29 mg (35%), mp 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 4.01 (s, 3H), 6.95 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.43 (dd, J = 2.0, 8.0 Hz, 1H), 7.49 (s, 1H), 7.59 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 7.76 (ddd, J = 1.2, 6.8, 8.4 Hz, 1H), 7.85 (dd, J = 0.8, 8.0 Hz, 1H), 8.27−8.30 (m, 3H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 56.0, 56.1, 107.9, 111.3, 118.0, 119.3, 120.6, 123.0, 127.4, 127.6, 128.1, 130.0, 130.2, 137.0, 145.8, 148.0, 149.3, 149.8, 153.1, 159.7; HRMS (EI) m/z (M^+) calcd for $C_{20}H_{16}N_2O_3$ 332.1161, found 332.1160.

5-(Naphthalen-1-yl)-2-(quinolin-2-yl)oxazole (3ah). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 33 mg (44%), mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.64 (m, 4H), 7.69 (s, 1H), 7.78 (ddd, J = 1.2, 6.8, 8.4 Hz, 1H), 7.87 (dd, J = 1.2, 8.0 Hz, 1H), 7.93−7.97 (m, 3H), 8.29−8.34 (m, 3H), 8.40 (d, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 119.3, 124.9, 125.0, 125.3, 126.3, 127.1, 127.2, 127.5, 127.60, 127.61, 128.3, 128.8, 129.9, 130.20, 130.21, 130.24, 133.8, 137.1, 145.8, 148.1, 152.1, 160.6; HRMS (EI) m/z (M^+) calcd for $C_{22}H_{14}N_2O$ 322.1106, found 322.1108.

(*E*)-2-(Quinolin-2-yl)-5-styryloxazole (3ai). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent followed by GPC; 25 mg (34%), mp 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 16.4 Hz, 1H), 7.31−7.34 (m, 2H), 7.37−7.41 (m, 3H), 7.54−7.56 (m, 2H), 7.60 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 7.79 (ddd, J = 1.6, 6.8, 8.4 Hz, 1H), 7.86 (dt, J = 0.8, 8.0 Hz, 1H), 8.29−8.31 (m, 3H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 112.7, 119.5, 126.70, 126.74, 127.60, 127.64, 128.3, 128.5, 128.8, 130.1, 130.2, 131.4, 136.2, 137.1, 145.7, 148.0, 152.2, 160.0; HRMS (EI) m/z (M^+) calcd for $C_{20}H_{14}N_2O$ 298.1106, found 298.1105.

2-(4-Methoxyquinolin-2-yl)-5-(4-nitrophenyl)oxazole (3bg). Purified by column chromatography on silica gel with hexane/ethyl acetate (2:1, v/v) as an eluent followed by GPC; 27 mg (31%), mp 225−227 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 3H), 7.59 (td, J = 0.8, 7.2 Hz, 1H), 7.67 (s, 1H), 7.75 (s, 1H), 7.78 (td, J = 1.2, 6.8 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 8.8 Hz, 2H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 56.2, 98.5, 121.6, 121.9, 124.4, 125.2, 126.9, 127.0, 129.6, 130.6, 133.3, 146.4, 147.5, 149.0, 150.7, 161.9, 163.1; HRMS (APCI) m/z ([M + H]$^+$) calcd for $C_{19}H_{14}N_3O_4$ 348.0979, found 348.0983.

4-Methoxy-2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)quinoline (3bj). Purified by column chromatography on silica gel with hexane/ethyl acetate (3:1, v/v) as an eluent; 20 mg (28%), mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 3H), 4.46 (s, 3H), 7.34 (td, J = 1.2, 7.2 Hz, 1H), 7.38 (td, J = 1.2, 7.2 Hz, 1H), 7.48 (dd, J = 1.6, 7.2 Hz, 1H), 7.55 (ddd, J = 1.2, 6.4, 8.4 Hz, 1H), 7.74 (ddd, J = 1.2, 6.4, 8.4 Hz, 1H), 7.87−7.90 (m, 1H), 7.92 (s, 1H), 8.09 (dd, J = 0.4, 8.4 Hz, 1H), 8.24 (dd, J = 0.8, 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 33.2, 56.2, 100.5, 110.0, 120.1, 121.1, 121.9, 122.6, 123.5, 126.3, 129.1, 130.0, 137.6, 142.5, 148.3, 150.5, 151.7, 162.6; HRMS (APCI) m/z ([M + H]$^+$) calcd for $C_{18}H_{16}N_3O$ 290.1288, found 290.1290.

Procedure for the Preparation of 3aa-O. *m*-Chloroperoxybenzoic acid (mCPBA, 400 mg, 1.8 mmol) was added to a solution of 5-phenyl-2-(quinolin-2-yl)oxazole (**3aa**, 405 mg, 1.48 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 20 h. The resulting mixture was quenched with aq. $NaHCO_3$. Extraction with chloroform, concentration under reduced pressure, and silica gel column purification with dichloromethane/methanol (20/1, v/v) afforded 2-(5-phenyloxazol-2-yl)quinoline 1-oxide (**3aa-O**, 340 mg, 1.2 mmol) in 79% yield. X-ray quality crystals were grown from dichloromethane.

2-(5-Phenyloxazol-2-yl)quinoline 1-Oxide (3aa-O). Purified by column chromatography on silica gel with dichloromethane/methanol (20:1, v/v) as an eluent; 340 mg (79%), mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.41 (m, 1H), 7.46−7.50 (m, 2H), 7.67 (s, 1H), 7.67−7.71 (m, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.79−7.83 (m, 1H), 7.85−7.90 (m, 3H), 8.20 (d, J = 8.8 Hz, 1H), 8.90 (d, J = 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 120.2, 121.8, 124.0, 124.3, 124.7, 127.2, 128.0, 128.9, 129.1, 129.3, 129.9, 130.6, 133.4, 142.9, 152.3, 155.1; HRMS (APCI) m/z ([M + H]$^+$) calcd for $C_{18}H_{13}N_2O_2$ 289.0972, found 289.0970.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C{^{1}H} NMR spectra for products and an ORTEP drawing of **3aa-O**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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