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Base-Promoted Cross-Dehydrogenative Coupling of Quinoline *N*-Oxides with 1,3-Azoles

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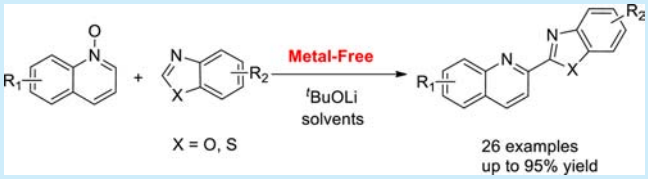
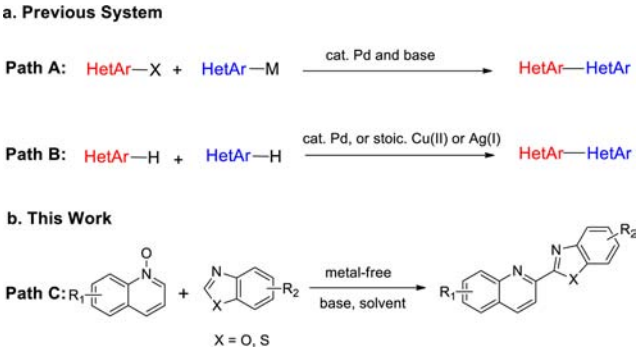
Supporting Information

ABSTRACT: An efficient cross-dehydrogenative coupling of quinoline *N*-oxides and 1,3-azoles has been developed under external oxidant and metal free conditions. The desired products were isolated in good to excellent yields for 26 examples. This methodology provides a practical pathway to biheteroaryls and features high practicality, high efficiency, and environmental friendliness.



Biheteroaryls have attracted considerable attention due to their wide application in organic synthesis, advanced functional materials, and pharmaceuticals.[1] Enormous efforts have been devoted to developing efficient methods for building such a structure. Transition-metal-catalyzed coupling reactions of heteroaryl halides with heteroaryl boronates or metal reagents, such as Kumada−Tamao−Corriu, Suzuki−Miyaura, Negishi, Migita−Kosugi−Stille, and Hiyama reactions, provided powerful protocols to construct biheteroaryls (Scheme 1, path A).[2] However, the instability of 2-heteroaryl boronates or metal reagents limited their application. Oxidative coupling, which is different from the traditional coupling, occurs between two nucleophiles.[3] Recent efforts have been made via metal-catalyzed direct oxidative cross-dehydrogenative coupling of two heteroarenes (Scheme 1, path B).[4−6] The representative example developed by You and co-workers involves the cross-coupling of xanthines with thiophenes or furans uses palladium salt as a catalyst and Cu salt as an oxidant.[7] Miura et al. also described a successful copper-mediated intermolecular direct cross-coupling of two aromatic heterocycles.[8] However, some problems still exist with these procedures, such as (1) the homocoupling reaction is difficult to avoid and (2) the requirement of transition metal may contaminate the products, thereby limiting their application, especially in the pharmaceutical industry and in advanced functional materials. Therefore, the development of simple, efficient, and environmentally benign methods for synthesizing various biheteroaryls is quite appealing.

Scheme 1. Synthesis of Biheteroaryls via Cross-Coupling Reaction



On the other hand, the electron-withdrawing effect of N−O group can activate the ortho C−H bond of heteroaryls, which results in its easier cleavage.[9] Our group succeeded in realizing the olefination, sulfonylation, alkylation, acetoxylation, phosphonation, and amination of quinoline *N*-oxides, which showed that *N*-oxides could serve as a directing group to allow the C−H functionalization at the 2-position.[10] In continuation of our effort on C2−H functionalization of quinoline, we embark on development of a simple and practical procedure to synthesize biheteroaryls via a cross-coupling of quinoline *N*-oxides and 1,3-azoles under metal-free[11] conditions (Scheme 1, path C).

We initiated our investigation on the model reaction of quinoline *N*-oxide (**1a**) with benzoxazole (**2a**) to optimize various reaction parameters (Table 1). First, the reaction was carried out in the presence of CuI. The desired product was not detected (entry 1), and $Pd(OAc)_2$ gave a trace amount of the desired product (entry 2). To our delight, the product **3a** was isolated in 40% yield in the absence of any metal catalyst. The molecular structure of the 2-(2-benzoxazolyl)quinoline (**3a**) was confirmed by NMR spectra and single-crystal X-ray

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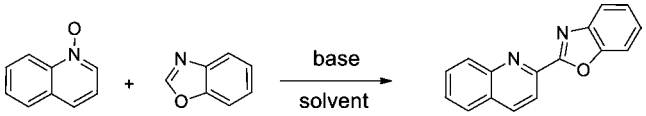
Table 1. Screening the Various Reaction Parameters for the Cross-Coupling Reaction of Quinoline *N*-Oxide 1a with Benzoxazole 2a[a]



1a 2a 3a

entry	catalyst	base	solvent	yield[b] (%)
1	CuI	^{t}BuOLi	toluene	NR[f]
2	$Pd(OAc)_2$	^{t}BuOLi	toluene	trace
3		^{t}BuOLi	toluene	40
4		^{t}BuOLi	CH_3CN	40
5		^{t}BuOLi	DMF	20
6		^{t}BuOLi	dioxane	15
7		^{t}BuOLi	DCE	trace
8		^{t}BuOLi	xylene	75
9		KCO_3	xylene	NR
10		DBU	xylene	NR
11		^{t}BuOK	xylene	30
12		^{t}BuONa	xylene	NR
13[c]		^{t}BuOLi	xylene	30
14[d]		^{t}BuOLi	xylene	21
15[e]		^{t}BuOLi	xylene	70

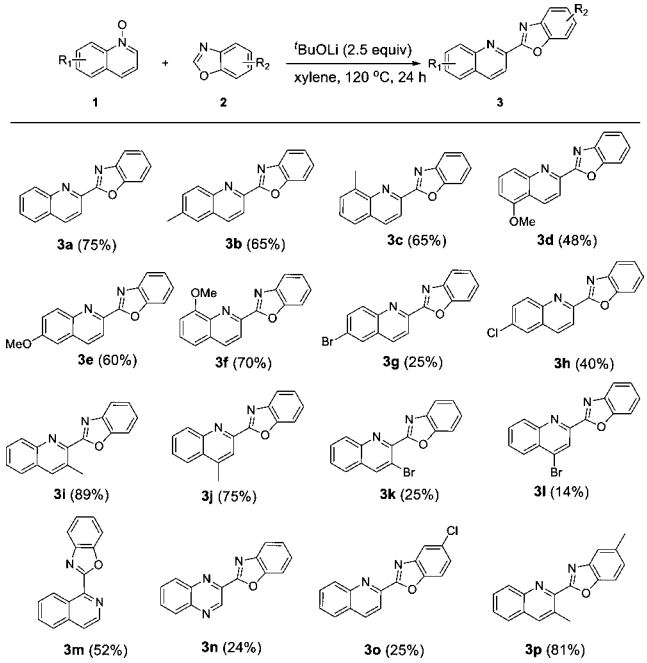
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), catalyst (10 mol %), base (0.75 mmol), solvent (2.0 mL), under air, 120 °C, 24 h. [b]Isolated yields. [c]80 °C. [d]Room temperature. [e]Under N_2. [f]NR = not detected.

diffraction analysis shown in Figure 1 in the Supporting Information.

Encouraged by this result, we further optimized other reaction parameters. The solvent was crucial for this reaction. Moderate or low yields were obtained when this reaction was carried out in acetonitrile, DMF, dioxane, and DCE (entries 4−7). A 75% yield was achieved when xylene was used as the solvent. Among the bases examined (^{t}BuOLi, K_2CO_3, DBU, ^{t}BuOK, ^{t}BuONa), ^{t}BuOLi was the best (entry 8 vs entries 9−12). Decreasing the temperature resulted in a significant decrease in the yield (entries 13 and 14). A 21% yield of product was afforded at room temperature. When the reaction was carried out under nitrogen atmosphere, the desired product **3a** was obtained in 70% yield (entry 15), which indicated that the oxygen in air did not effect this transformation. After surveying a variety of catalysts, bases, solvents, and temperatures, the optimal reaction conditions were assigned as follows: 2.5 equiv of ^{t}BuOLi in xylene at 120 °C for 24 h under air.

With the optimized reaction conditions in hand, the scope of substrates was examined. The results are summarized in Scheme 2. The reaction could proceed well with a series of substituted heteroaryl *N*-oxides and oxazoles, affording the corresponding products **3a−s** in moderate to good yields. Quinoline *N*-oxide with electron-donating groups, such as methyl or MeO groups substituted in the aromatic rings, readily proceeded smoothly and provided the desired products in 48−75% yields (**3a−f**). Moderate electron-withdrawing groups, such as Br and Cl, afforded the desired products in 25% and 40% yields, respectively (**3g**,**h**). When the pyridine ring was substituted by methyl, the products were isolated in 89% and 75% yields (**3i** and **3j**). In addition, Br and Cl were tolerated

Scheme 2. Substrate Scope for the Cross-Coupling of Heteroaromatic *N*-Oxides with Oxazoles[a,b]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), xylene (2.0 mL), 24 h at 120 °C under air. [b]Isolated yields.

albeit in low yields (**3k**,**l**). This reaction system was also applied to isoquinoline *N*-oxide and quinoxaline *N*-oxide and gave the products **3m** and **3n** in 52% and 24% yields. This reaction proceeded smoothly with substituted benzo[*d*]oxazole derivatives (**3o** and **3p**). Similarly, the electron-donating group was beneficial for the reaction.

Encouraged by the results obtained with oxazoles, we applied this catalytic system to benzothiazole. It was found that benzothiazoles could be employed as suitable substrates in DMF, giving the corresponding products **4a−j** in good to excellent yields for most cases. The results are summarized in Scheme 3. When either group substituted in the aromatic ring or pyridine ring the ideal results could be obtained. The Cl group substituted on the aromatic ring also provided the products in 75% yield (**4g**), which made this reaction particularly attractive for increasing the molecular complexity through cross-dehydrogenation coupling reactions. Finally, we were delighted to find that isoquinoline *N*-oxide also worked well and provided the product in 95% yield (**4i**). Quinoxaline *N*-oxide showed low efficiency as a substrate (**4j**). Other thiazoles, for example, 4,5-dimethylthiazole, were not beneficial for this transformation, and no desired product was isolated.

According to the previous reports,[12] the cross-dehydrogenative coupling might be achieved via a nucleophilic addition−elimination process, and then the controlled experiments were carried out (Scheme 4). When the reaction of quinoline with **2a** was carried out, the desired product **3a** was not detected (eq 1). The mixture of 1:1 3-methylquinoline *N*-oxide **1i** and quinoline was added to the reaction system consisting 2.0 equiv of **2a** under the optimized reaction conditions. Compound **3i** was obtained in 80% yield. However, **3a** was not observed (eq 2), suggesting *N*-oxide might play a crucial role in this transformation. In order to examine the reaction pathway, two parallel reactions were conducted under the standard reaction

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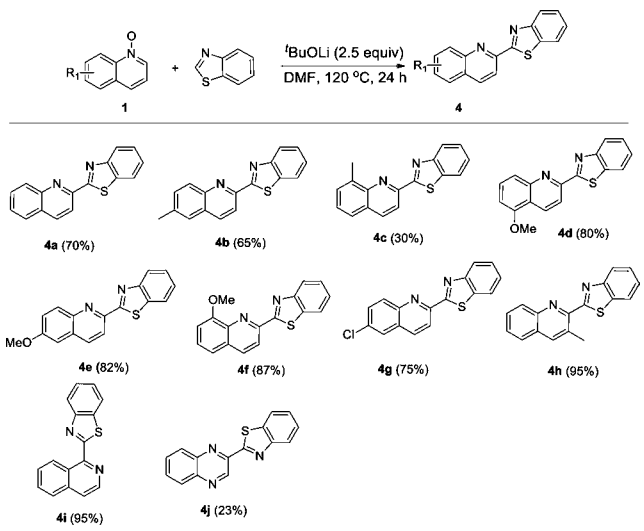
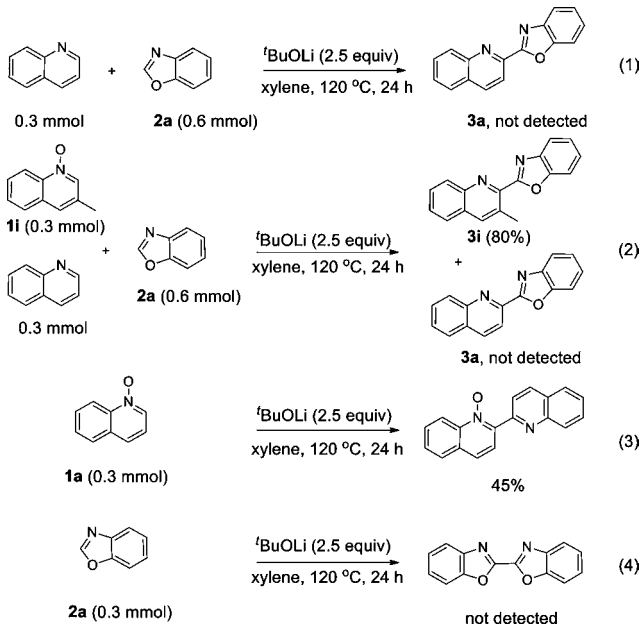
Scheme 3. Substrate Scope for the Cross-Coupling of Heteroaromatic *N*-Oxides and Benzothiazole[a,b]



[a]Reaction conditions: **1** (0.3 mmol), benzothiazole (0.6 mmol), DMF (2.0 mL), reacted for 24 h at 120 °C under air. [b]Isolated yields.

Scheme 4. Controlled Experiments

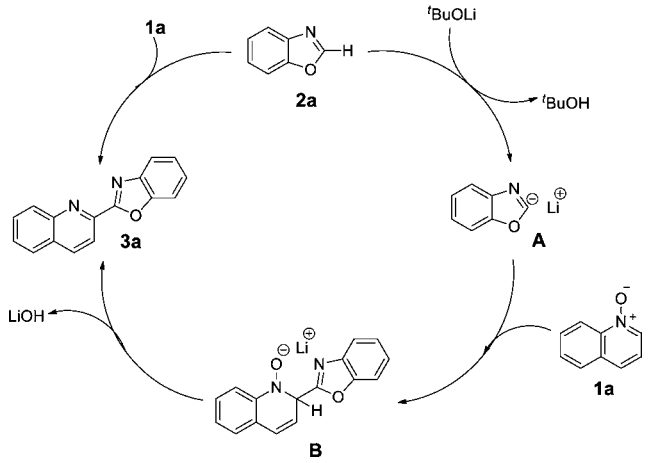


conditions. Dimerization of *N*-oxide (**1a**) was formed in the absence of **2a** (eq 3), while no homocoupling product was generated in the absence of **1a** (eq 4). Therefore, it indicated that quinoline *N*-oxide could be attacked as an electrophilic reagent in this reaction.

A reaction mechanism was proposed and outlined in Scheme 5 based on the results obtained and literature.[12] First, a benzoxazole carbanion **A** was generated from benzoxazole (**2a**) by deprotonation in the presence of ^{t}BuOLi. Subsequently, the intermediate **B** was formed by attack of carbanion **A** at the ortho-position of quinoline *N*-oxide (**1a**). Finally, the final product **3a** was produced with concomitant release of the LiOH.

In conclusion, a novel, simple, and efficient protocol for the synthesis of biheteroaryls via a cross-dehydrogenative coupling

Scheme 5. Proposed Reaction Mechanism



of heteroaryl *N*-oxides and 1,3-azoles under air atmosphere and metal-free conditions has been developed. A broad range of biheteroaryl products were obtained in up to 95% yield. Moreover, this metal-free approach was economically beneficial. The process provides concise access to biheteroaryls, is highly practical, efficient, atomic economic, and environmentally friendly, and features a transition-metal catalyst, ligand, additives, and finally, external oxidant-free conditions.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure, characterization data of the products, and CIF data of **3a**. 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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