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COMMUNICATION

Dimerization of heteroaromatic *N*-oxides under metal-free conditions

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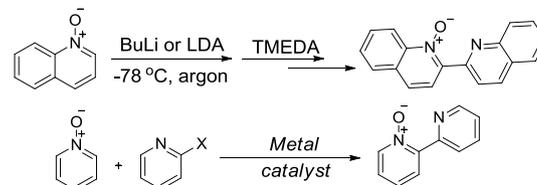
5 A novel procedure for the dimerization of heteroaromatic *N*-oxides under transition-metal-free conditions has been developed. The protocol features with being effective and convenient. The biheteroaromatic mono *N*-oxides products were obtained in up to 93% yield.

10 Biheteroaromatic *N*-oxides have been found wide application as structure motifs in pharmaceuticals, functional materials and organic synthesis as ligands¹. Conventional strategies to build such a structure typically involve multistep reaction sequences², or transition-metal-catalyzed coupling-reactions of a heteroaryl halide or pseudohalide with a heteroaryl organometallic reagent³ (Scheme 1, path a). These approaches always require harsh reaction conditions, or transition metals, most of which are expensive and nonenvironmentally benign. The removal of harmful transition-metal contamination is often costly and difficult in pharmaceuticals.⁴ Therefore an environmentally benign and practical access to construct biheteroaromatic *N*-oxide compounds is highly desired. Recently, the dimerization of quinoline *N*-oxide was achieved under organocatalytic reaction conditions by Kondo group.⁵ However, an organosilicon additive is required and the biquinoline *N*-oxide is obtained in lower yield. Then, they developed a similar procedure using onium amide bases in situ generated.⁶ To the best of our knowledge, one-pot protocol to synthesize biquinoline *N*-oxide under transition metals and catalysts free conditions has not been reported so far. Herein, we disclosed an efficient, simple method to construct the biheteroaromatic mono *N*-oxides under metal-free conditions (Scheme 1, path b).

At the outset of the study, we chose quinoline *N*-oxide (**1a**) as a model substrate to screen the reaction parameters (Table 1).

35 Firstly, the reaction was carried out in the presence of 10 mol% Pd(OAc)₂ and 2.0 equiv of ^tBuOLi in toluene at 120 °C for 20 h. The desired product **2a** was isolated in 56% yield (entry 1). Encouraged by this result, we further optimized the reaction conditions. Surprisingly, 87% yield could be obtained in the absence of Pd(OAc)₂ (entry 2). We found that reducing reaction

a) previous work



b) this work

50 **Scheme 1** Dimerization of heteroaromatic *N*-oxides through different methods

time was beneficial for the reaction, as the yield of **2a** was improved to 91% (entry 3). For this process, examination of the amount of ^tBuOLi indicated that 1.5 equiv of ^tBuOLi was optimal (entries 3-6). Base screening disclosed that ^tBuOLi was superior to others (entries 4, 7-11). Investigation of different solvents showed that toluene was the best suitable solvent (entries 4, 12-17). Furthermore, decreasing the temperature of the reaction brought a significant decrease in the yields (entries 18-20). Finally, the optimal conditions for the dimerization were identified to be ^tBuOLi (1.5 equiv) as the base and toluene as the solvent at 120 °C for 3 hours.

65 **Table 1** Optimization of reaction conditions^a

	1a		2a	
Entry	Catalyst	Bases (equiv)	Solvents	Yield(%) ^b
1 ^c	Pd(OAc) ₂ (10%)	^t BuOLi(2.0)	toluene	56
2 ^c	–	^t BuOLi(2.0)	toluene	87
3	–	^t BuOLi(2.0)	toluene	91
4	–	^tBuOLi(1.5)	toluene	93
5	–	^t BuOLi(2.5)	toluene	93
6	–	^t BuOLi(1.0)	toluene	81
7	–	^t BuONa(1.5)	toluene	58
8	–	K ₂ CO ₃ (1.5)	toluene	0
9	–	K ₃ PO ₄ (1.5)	toluene	0
10	–	Cs ₂ CO ₃ (1.5)	toluene	0
11	–	DBU(1.5)	toluene	0
12	–	^t BuOLi(1.5)	DMSO	nd ^d
13	–	^t BuOLi(1.5)	THF	0

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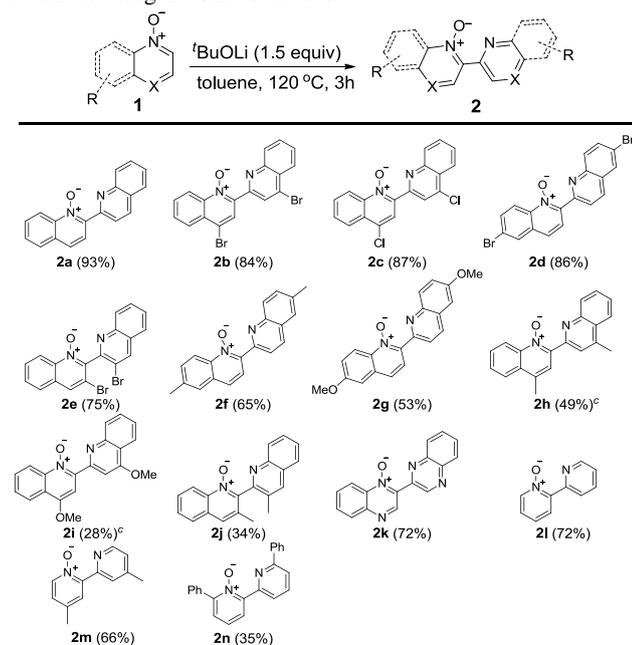
† Electronic Supplementary Information (ESI) available: experimental procedures and spectral data for all products. See DOI: 10.1039/b000000x/

14	–	^t BuOLi(1.5)	DMF	40
15	–	^t BuOLi(1.5)	CH ₃ CN	0
16	–	^t BuOLi(1.5)	dioxane	72
17	–	^t BuOLi(1.5)	DCE	trace
18 ^e	–	^t BuOLi(1.5)	toluene	81%
19 ^f	–	^t BuOLi(1.5)	toluene	75%
20 ^g	–	^t BuOLi(1.5)	toluene	72%

^a Reaction conditions: **1a** (0.5 mmol), solvent (2.5 mL), 3 h at 120 °C. ^b Isolated yields. ^c 20h. ^d nd is not detected. ^e 110 °C. ^f 100 °C. ^g 90 °C

Having established the optimal reaction conditions in hand, we investigated the generality and scope of substrates for this transition-metal-free transformation. The results in Table 2 demonstrated that this reaction had a good functional group tolerance. The reaction of quinoline *N*-oxide and its derivatives with moderate electron-withdrawing group, such as Br and Cl, readily proceeded smoothly and provided the desired products in 75–93% yields (**2a–2e**). When Br group at 3-position of quinoline *N*-oxide was also well tolerated and the product was obtained in 75% yield (**2e**), indicating that this reaction was not sensitive significantly to steric hindrance in the substrate. Electron-rich substrates, such as methyl, methoxyl groups substituted on the aromatic rings, provide the dimerization products in moderate yields (**2f, 2g**). However, when the pyridine rings were substituted by methyl or methoxyl groups, the dimerization products were obtained in 49%, 28% and 34% yields, 20 respectively (**2h–2j**). Good yield was afforded when the reaction system was applied to quinoxaline *N*-oxide (**2k**). In addition, pyridine *N*-oxide derivatives were also shown to be possible substrates and gave the desired products in moderate to good yields (**2l–2m**).

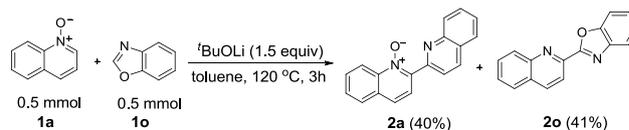
Table 2 Substrate scope for the dimerization of heteroaromatic *N*-oxides using ^tBuOLi as the base^{a,b}



^a Reaction conditions: **1** (0.5 mmol), solvent (2.5 mL), 3 h, 120 °C.

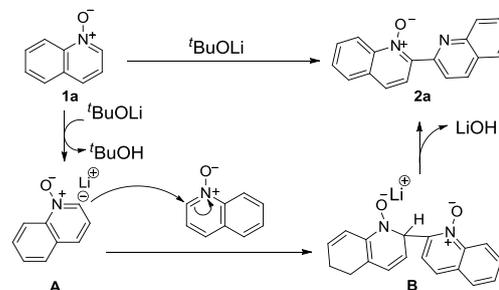
^b Isolated yields. ^c 130 °C

The controlled experiment was carried out to see if the dimerization was achieved *via* a nucleophilic addition-elimination process^{5–7} (**Scheme 2**). When benzoxazole was employed in the reaction, the corresponding products **2a** and **2o** could be given in 40% and 41% (based on **1a**) yields, respectively, which suggested that benzoxazole carbanion was generated by the aid of base and served as an external nucleophile.



Scheme 2 Controlled experiment

A possible mechanism for this dimerization of quinoline *N*-oxide was proposed and described as follows (**Scheme 3**): (i) Deprotonation of quinoline *N*-oxide in situ-generated carbanion **A** firstly by ^tBuOLi. (ii) Subsequently, the intermediate **B** was formed by attacking at the α -position of another quinoline *N*-oxide. (iii) The final product **2a** was generated with concomitant release of the LiOH.



Scheme 3 Proposed reaction mechanism

In conclusion, a mild and efficient method for the dimerization of heteroaromatic *N*-oxides under metal-free conditions has been developed. A broad range of 2,2'-biheteroaromatic mono *N*-oxides were obtained in up to 93% yield. Further efforts on the reaction mechanism will be studied in the future research.

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The authors declare no competing financial interest.

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