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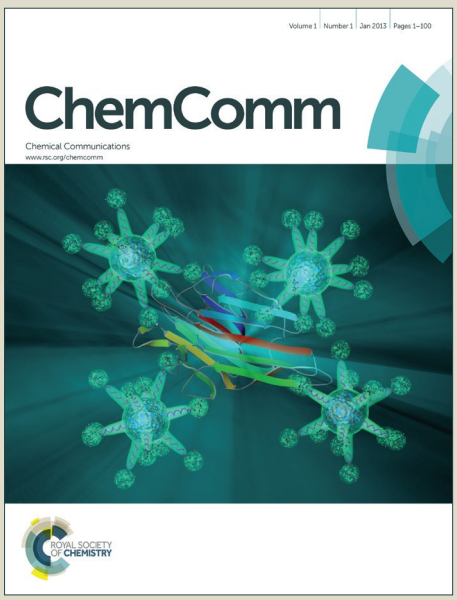

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Communication

Mechanistic Insights into the Potassium *tert*-Butoxide-Mediated Synthesis of *N*-Heterobiaryls

David E. Stephens,[a] Johant Lakey-Beitia,[a,b,c] Jessica E. Burch,[a] Hadi D. Arman,[a] and Oleg V. Larionov*[a]

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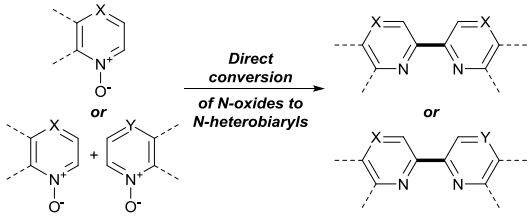
We report herein that symmetrical and non-symmetrical *N*-heterobiaryls are produced by a potassium *tert*-butoxide-mediated dimerization of heterocyclic *N*-oxides. The reaction is scalable and transition metal-free, and can be carried out under thermal and microwave conditions. Preliminary mechanistic studies point to the involvement of radical anionic intermediates arising from the *N*-oxide substrates and potassium *tert*-butoxide.

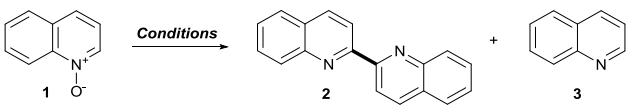
Homo- and heterodimeric *N*-heterocyclic motifs have increasingly important roles in catalysis,[1] materials science,[2] and drug discovery.[3] Most of the synthetic approaches to these compounds rely on the transition metal-catalyzed homocoupling of haloheteroarenes or their cross-coupling with prefunctionalized *N*-heterocyclic nucleophiles (e.g, organoboron, -zinc, and -tin derivatives). In particular, the Ullmann-type reactions of 2-haloazines require harsh conditions with stoichiometric quantities of transition metal catalysts and phosphine ligands at low concentrations.[4] Although improved methods for the synthesis of 2,2'-diazines have recently been developed,[5] a one-step, scalable, transition metal-free conversion to these structural motifs directly from heterocyclic *N*-oxides (Scheme 1) will greatly simplify access to these valuable *N*-heterocycles.



Scheme 1. C2-homocoupling and cross-coupling of heterocyclic *N*-oxides directly to *N*-heterobiaryls.

We have recently developed a regioselective Pd-catalyzed C8–H homocoupling of quinoline *N*-oxides that provides access to the structurally important 8,8'-biquinoline core.[6] In the course of the studies it was noticed that quinoline *N*-oxide (**1**) produces small quantities of 2,2'-biquinoline (**2**) and quinoline (**3**) in the presence of bases (Table 1). Although formation of 2,2'-diazine mono-*N*-oxides from azine *N*-oxides under basic conditions is known,[7] examples of direct conversion of heterocyclic *N*-oxides to *N*-heterobiaryls are rare and lack generality. Natsume and Itai reported that formation of **2** was observed from **1** in a low yield with potassium *tert*-butoxide under irradiation and in the presence of oxygen.[8] Under these conditions, the deoxygenative dimerization of quinoline proceeded in 34% yield, while the reactions of 4-, and 6-methylquinolines gave the respective products in 1 and 9% yields. More recently, Inamoto and Kondo described one example of conversion of *N*-oxide **1** to 2,2'-biquinoline (**2**) using $TMSNMe_2$ and tetramethylammonium fluoride.[9] We began our study by examining the influence of bases on the deoxygenative homocoupling of *N*-oxide **1**. While weaker bases did not promote formation of **3** (Table 1, entry 1, and Table S1, in the SI), the reaction with potassium *tert*-butoxide in toluene, DMF and 2-methyltetrahydrofuran produced 2,2'-biquinoline (**2**) in 27–54% yields (Table 1, entries 2–4). Concomitant formation of quinoline (**3**) was observed, along with evolution of small amounts of oxygen.[10] Addition of lithium fluoride or magnesium chloride that proved instrumental in the Cu-catalyzed deoxygenative reaction of *N*-oxides with Grignard reagents[11] had a detrimental effect on the C2-homocoupling (Table 1, entries 5 and 6). Similarly, addition of TMEDA and other amines led to much lower conversions to **2** and **3**. On the other hand, use of azoisobutyronitrile (AIBN) as a catalyst resulted in 87% conversion to **2** (Table 1, entry 8).

Table 1. Base-mediated C2-homocoupling of quinoline *N*-oxide (**1**).[a]



Entry	Base (equiv.)	Additive (equiv.)	Solvent	Temperature (°C)	Yield (%)[b] 1	2	3
1	K_2CO_3 (3)	–	THF	100	100	0	0
2	KO*t*-Bu (3)	–	PhMe	100	38	27	35
3	KO*t*-Bu (3)	–	DMF	100	14	28	58
4	KO*t*-Bu (3)	–	MeTHF	100	17	54	29
5	KO*t*-Bu (3)	$MgCl_2$ (2)	DMF	65	89	1	10
6	KO*t*-Bu (3)	LiF (2)	DMF	65	91	3	6
7[c]	KO*t*-Bu (3)	TMEDA (2)	DMF	65	76	14	10
8	KO*t*-Bu (2)	AIBN (0.2)	DMF	65	7	87	6
9[d]	KO*t*-Bu (2)	AIBN (0.2)	MeTHF	65	18	81	1
10[d]	KO*t*-Bu (2)	AIBN (0.2)	DMF	65	9	90	1

[a] Reaction conditions: quinoline *N*-oxide (0.2mmol), base, additive, solvent (c = 2M), 2 h. [b] Yields were determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard. [c] c = 1M. [d] The reaction was carried out under microwave irradiation at c = 0.5M.

The AIBN-catalyzed reaction also performed well under microwave irradiation (Table 1, entries 9 and 10). The deoxygenative C2-homocoupling was successfully carried out on a 5 g scale and afforded product **2** in 78% yield (Table 2).

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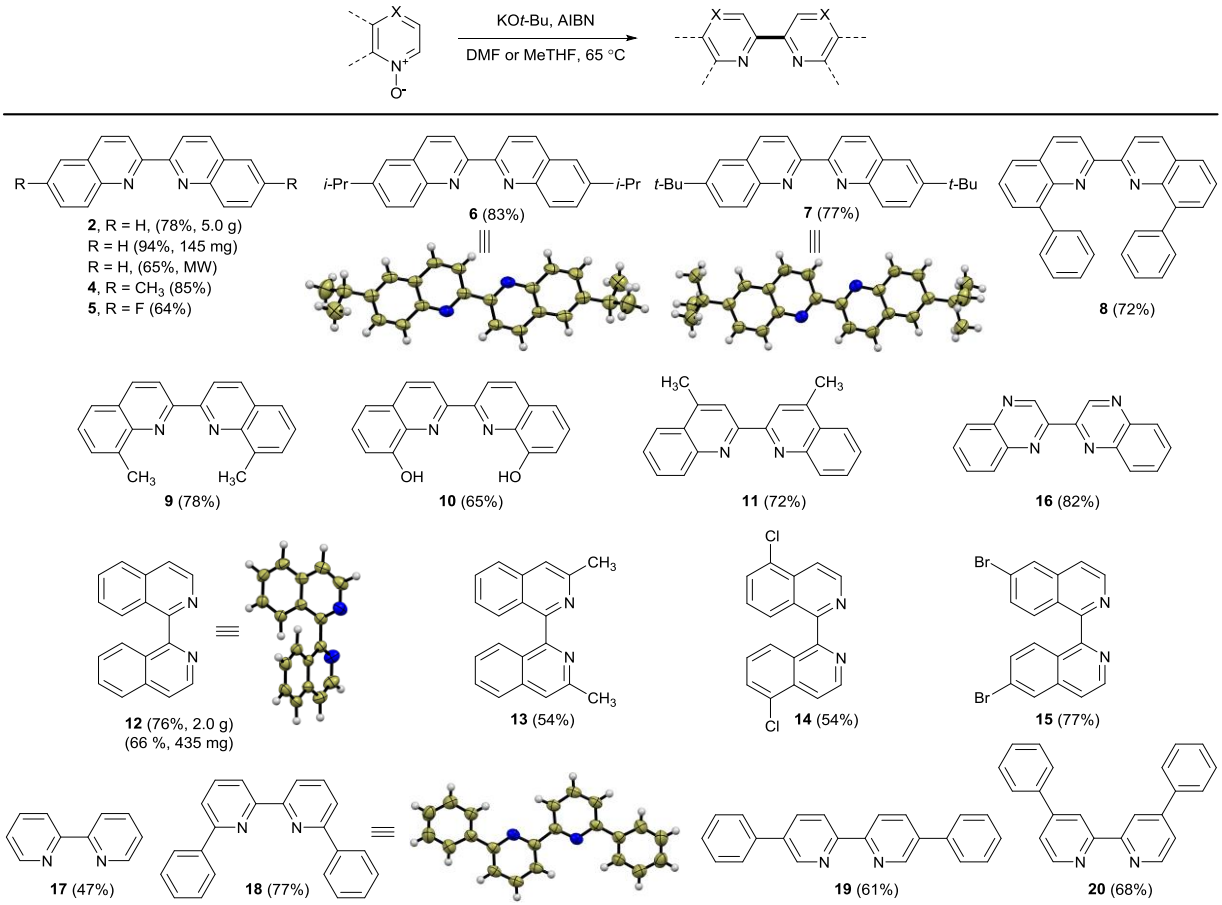
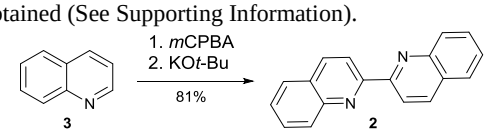
Table 2. Scope of the potassium *tert*-butoxide-mediated C2-homocoupling reaction.



The reaction exhibits a broad scope and tolerates a number of *N*-heterocyclic systems and a variety of substituents. Halogen substituents (F, Cl, Br) were well tolerated, and no side reactions were observed at benzylic positions. In the quinoline series, substituents in 3, 4, 5, 6, and 8 were well tolerated, including 8-hydroxy group (**4**-**11**). Similarly, substituted 2,2'-bisisoquinolines **12**-**15** were prepared in good yields, and the scalability was confirmed for 2,2'-bisisoquinoline (**12**).

In addition, quinoxaline *N*-oxide produced the C2-homocoupling product **16** in high yields. Substituted pyridine *N*-oxides were also converted to the corresponding 2,2'-bipyridines **17**-**20** in good yields. The structures of products **6**, **7**, **12** and **18** were further confirmed by means of X-ray crystallographic analysis. In addition, X-ray structures for several *N*-oxide substrates were also obtained (See Supporting Information).

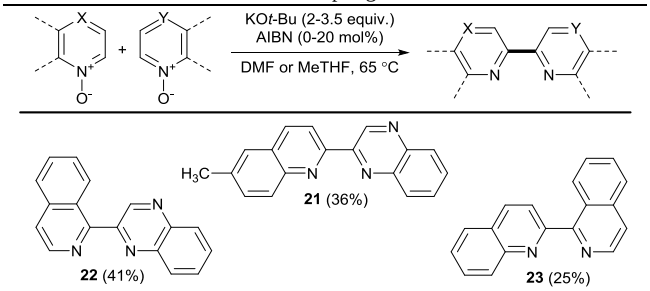


Scheme 2. Tandem N-oxidation/C2-homocoupling reaction.

A sequential N-oxidation of quinoline (**3**) followed by the base-mediated C2-homocoupling was also carried out in a one-flask fashion (Scheme 2). Since N-oxidation by aqueous hydrogen peroxide[12] was deemed incompatible with the C2-homocoupling, oxidation with *meta*-chloroperbenzoic acid was carried out, and the in situ formed *N*-oxide **1** was subjected to the KO*t*-Bu-mediated C2-homocoupling reaction. The single-flask procedure afforded 2,2'-biquinoline (**2**) in 81% yield. This method can provide a simple and straightforward shortcut from *N*-heterocycles to the corresponding *N*-heterobiaryls. We next studied the cross-coupling of two different heterocyclic *N*-oxides (Table 3). The reaction produced the desired unsymmetrical *N*-heterobiaryls, however, substantial amounts of homocoupling products were also formed, thus resulting in reduced yields of products **23**-**25**. Nevertheless, this reaction represents the first example of direct conversion of heterocyclic *N*-oxides to unsymmetrical *N*-heterobiaryls.

KO*t*-Bu-catalyzed C–C bond-forming reactions have recently attracted significant attention, due to the operational simplicity distinctive mechanistic profile,[13] and involvement of radical anionic species.[14] The mechanism of the homocoupling reaction

Table 3. Base-mediated C2-cross-coupling reaction of *N*-oxides.



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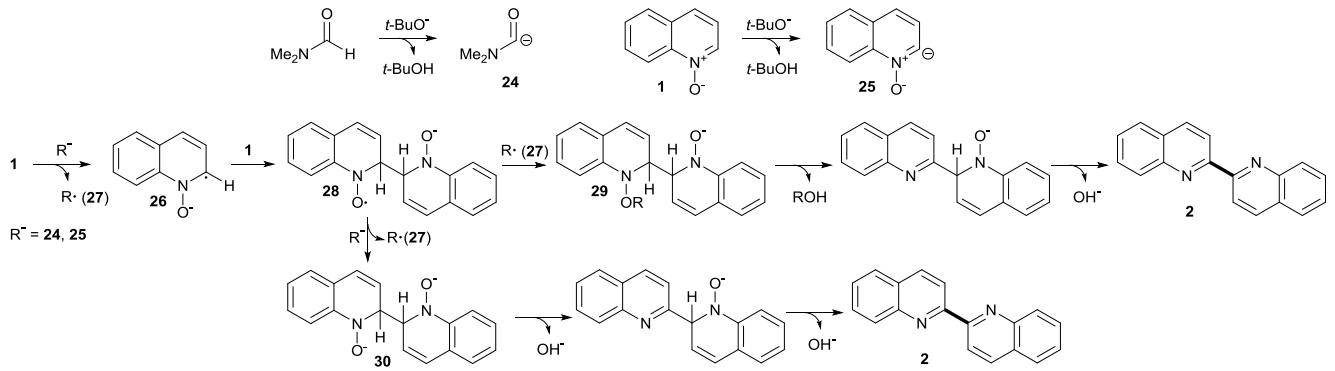

Scheme 3. Plausible mechanism of the base-mediated C2-homocoupling.

was briefly examined by means of electron paramagnetic resonance. While no signal was observed for KO*t*-Bu in MeTHF, addition of heterocyclic *N*-oxides resulted in formation of paramagnetic species that were detected by EPR (Figure S1 in the Supporting Information). The shape of the signal indicated that several paramagnetic species may be present in the solution. The signal for the mixture of quinoline *N*-oxide and KO*t*-Bu persisted for several weeks, pointing to significant stability of the radical species. An EPR signal was also detected for 2,2'-biquinoline/KO*t*-Bu system, indicating that a radical anionic species similar to that observed by Jutand and Li for the 1,10-phenanthroline/KO*t*-Bu system[14] can also be formed in this case. Further investigation by Tuttle and Murphy showed that deprotonation of DMF, azines, and other C–H acidic compounds by KO*t*-Bu generates carbanions that can serve as electron donors in the KO*t*-Bu-mediated processes.[15] It is possible that deprotonation of DMF or the C2–H of *N*-oxide **1** leads to the generation of carbanions **24**[16] and **25** that, upon an SET reduction of *N*-oxide **1**,[15] will produce radical anion **26** and radical **27**. An addition of radical anion **26** to *N*-oxide **1** can produce distonic radical anion **28** that, after the recombination with radical **27** gives rise to intermediate **29**. Base-mediated elimination[17] of ROH and hydroxide can then produce 2,2'-biquinoline (**2**). Production of intermediate **29** can be further assisted by the radicals generated from AIBN. In addition, an SET reduction of anion radical **28** can produce dianion **30** that is converted to 2,2'-biquinoline (**2**) via a stepwise base-mediated elimination of hydroxide anion. In MeTHF, hydrogen abstraction from the solvent by radical **27** produced from anion **25** can contribute to the regeneration of *N*-oxide **1**. Small amounts of oxygen can arise from decomposition of *tert*-butyl peroxide formed in a reaction of KO*t*-Bu with *N*-oxide **1** that also produces quinoline (**3**). Formation of oxygen was previously observed in a reaction of DMDO with *N*-oxides.[18] Quinoline (**3**) may also arise from reduction of *N*-oxide **1** with anions **24** and **25**.

In conclusion, we have developed an efficient base-mediated C2-homocoupling of heterocyclic *N*-oxides. The reaction proceeds directly to *N*-heterobiaryls that are isolated in good to excellent yields. Preliminary mechanistic studies point to involvement of radical anionic intermediates that are formed from the *N*-oxides and potassium *tert*-butoxide.

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Notes and references

[a] *Department of Chemistry, The University of Texas at San Antonio, San Antonio, TX 78249, United States. E-mail: oleg.larionov@utsa.edu*
[b] *Centre for Biodiversity and Drug Discovery, Institute for Scientific Research and High Technology Services (INDICASAT-AIP), City of Knowledge, Panama City, Republic of Panama.*
[c] *Department of Biotechnology, Acharya Nagarjuna University, Nagarjuna Nagar, India.*

† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/b000000x/

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