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C–N Bond Formation

Dehydrogenative N-Incorporation: A Direct Approach to Quinoxaline *N*-Oxides under Mild Conditions**

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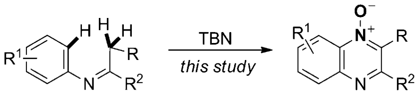
Abstract: *An efficient method for the synthesis of quinoxaline N-oxides proceeds by the dehydrogenative N-incorporation of simple imines by C(sp^2)–H and C(sp^3)–H bond functionalization. The overall transformation involves the cleavage of three C–H bonds. The reaction is easily handled and proceeds under mild conditions. Simple and readily available tert-butyl nitrite (TBN) was employed as the NO source.*

Nitrogen-containing molecules, especially nitrogen-containing heterocyclic compounds, are ubiquitous in natural and bioactive products,[1] drugs,[2] and materials.[3] Accordingly, the construction of C–N bonds is an essential issue in organic chemistry and has received much attention. Transition-metal-catalyzed C–N bond-forming reactions have been intensively investigated over the past decades; they have become an efficient synthetic strategy[4,5] and include the palladium- and copper-catalyzed formation of C–N bonds from aryl halides and amines.[6–8]

Recently, the transition-metal-catalyzed direct C–H bond activation for the construction of C–N bonds has been heavily investigated.[5] For example, intermolecular and intramolecular C(sp^3)–H and C(sp^2)–H aminations or C(sp)–H amidations for the formation of C–N bonds have been disclosed.[5,9] Despite the significance of these methods, there are still some challenging issues that remain to be addressed: 1) the control of the chemo- and regioselectivity in intermolecular amination reactions, 2) the development of new and versatile nitrogen sources to replace the traditionally required nitrogen sources with strongly electron-withdrawing groups, and 3) the implementation of one-pot methods for nitrogen atom incorporation by the functionalization of multiple C–H bonds in a substrate. Hence, the development of new methods for the incorporation of nitrogen atoms into simple substrates by concise and efficient routes is still attractive.

N-heterocyclic *N*-oxides are ubiquitous structural motifs in biologically active compounds[10] and chiral ligands.[11] Various organic oxidants have been explored to synthesize *N*-oxides from the corresponding nitrogen-containing heterocycles.[12] However, these N-heterocycles need to be prepared in advance, and other nitrogen atoms of the substrates would be unselectively over-oxidized. Some transition-metal-catalyzed reactions for the synthesis of *N*-oxides through C–H bond functionalization have been disclosed, but the parent *N*-oxide derivatives were employed as the substrates.[13] The direct synthesis of *N*-oxides from simple substrates through the cleavage of several C–H bonds has not been reported.

Herein, we reported a novel and efficient intermolecular dehydrogenative nitrogen atom incorporation through the functionalization of C(sp^2)–H and C(sp^3)–H bonds for the synthesis of quinoxaline *N*-oxides from imines, which are readily available through the condensation of anilines with ketones and commonly employed synthons for some useful organic compounds [Eq. (1)]. Notably, the cleavage of one C(sp^2)–H bond and two C(sp^3)–H bonds is achieved for multiple C–N bond formation with simple and readily available *tert*-butyl nitrite (TBN) as the nitrogen source under mild conditions.



(1)

triple dehydrogenative C–N bond-forming reactions

This nitrogen incorporation reaction was initially studied with (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline[14] (**1a**) and TBN[15] (**2**). The desired product **3a** was isolated in 64% yield after heating the starting materials in MeNO$_2$ at 60 °C for 60 minutes (entry 1, Table 1). The structure of **3a** was confirmed by X-ray single-crystal diffraction. When some other solvents, such as DMF, alcohols, or acetone, were tested, the desired product was not obtained (see the Supporting Information). Copper and palladium catalysts could not improve the efficiency of this transformation (Supporting Information, Table S1). When tetrabutylammonium bromide (TBAB, 10 mol%) was added to the reaction, the yield could be improved to 76% (entry 2, Table 1), whereas the addition of LiBr, NaBr, KBr, TBAI (tetrabutylammonium iodide), and TBAC (tetrabutylammonium chloride) resulted in lower

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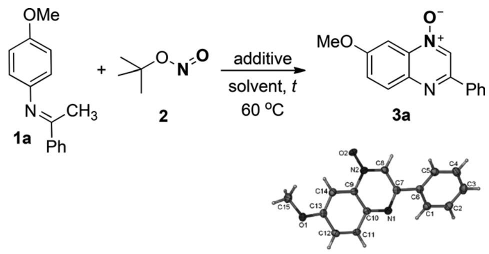
Table 1: Screening of the reaction conditions.[a]



Entry	TBAB [mol%]	Solvent	*t* [min]	Yield[b] [%]
1	–	$MeNO_2$	60	64
2	10	$MeNO_2$	60	76
3	10	$MeNO_2$	15	74
4	5	MeCN	15	77
5[c]	5	MeCN	15	75
6	–	MeCN	50	67

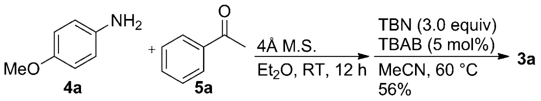
[a] Reaction conditions: **1a** (0.4 mmol), **2** (1.2 mmol), TBAB, and solvent (3 mL) with stirring under air at 60°C. [b] Yield of isolated product. [c] Conducted on a 5 mmol scale (1.13 g).

yields (Table S1). To our delight, the reaction finished within 15 minutes, producing the desired product in 74% yield (entry 3). The reaction temperature was also screened, and 60°C was found to be optimal (Table S1). A yield of 77% was obtained when MeCN was used as the solvent instead of $MeNO_2$ (entry 4). In contrast, the reaction in the absence of TBAB took longer and proceeded with low efficiency (67% yield, entry 6). A gram-scale experiment was also conducted under the standard conditions; the desired product **3a** was obtained in 75% yield (entry 5).

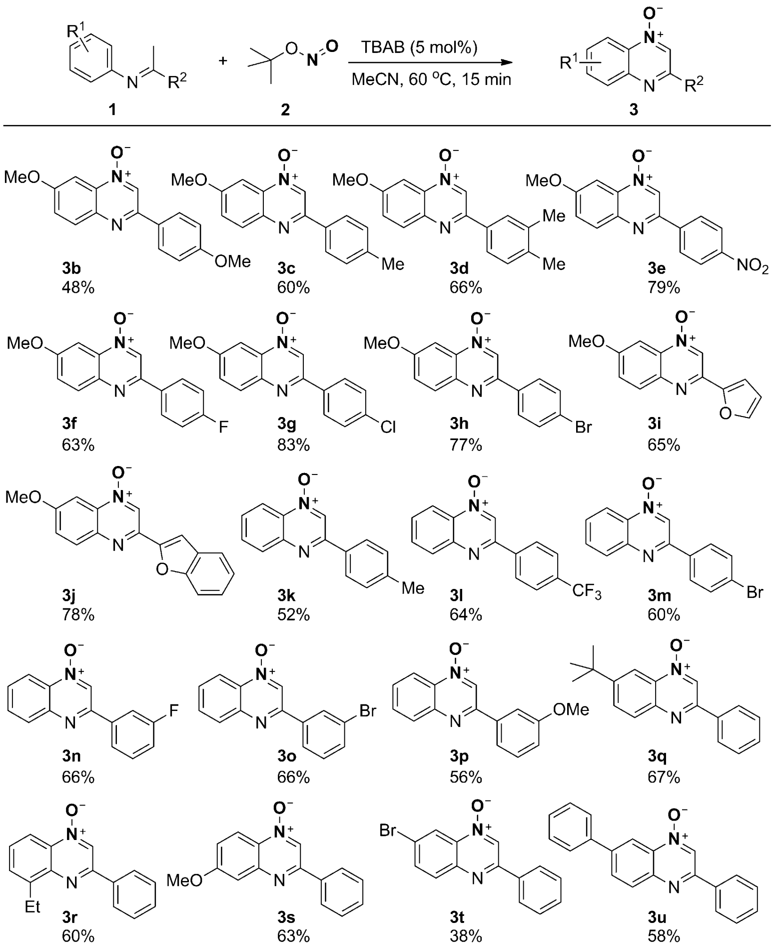
With the optimized reaction conditions in hand, the scope of this nitrogen incorporation reaction was investigated (Scheme 1). The functional-group compatibility of this transformation is wide. Several substituted methyl imines, which were easily prepared from 4-methoxyaniline and various acetophenone derivatives, reacted smoothly with TBN to generate the corresponding quinoxaline *N*-oxides in moderate to good yields under the standard conditions (**3b**–**3j**). Electron-donating and electron-withdrawing groups at the aryl ring of the acetophenone moiety were compatible with this transformation. Halide substituents, such as F, Cl, and Br, did not affect the reactivity of the substrates (**3f**–**3h**, **3m**–**3o**, and **3t**). Imines **1i** and **1j**, which were generated from heteroaryl methyl ketones with 4-methoxyaniline, could be converted into the desired products **3i** and **3j** in 65% and 78% yield, respectively. Some other substituted methyl imines, which were synthesized from aniline with different acetophenone derivatives, could also be converted into the corresponding quinoxaline *N*-oxides in moderate to good yields (**3k**–**3p**). Meanwhile, some substrates that were generated from various aromatic amines with substituents at the *para*, *meta*, or *ortho* position and acetophenone also performed well (**3q**–**3u**).

Furthermore, quinoxaline *N*-oxides with a substituent in the 2-position could be obtained smoothly through the nitrogen incorporation process of the corresponding imines (**3v**–**3x**, Scheme 2). In particular, *N*-oxide **3x** with a fused heterocycle was directly afforded in 65% yield. Therefore, substituted imines, which were easily synthesized from various amines with different aromatic ketones, were suitable substrates for direct *N*-oxide synthesis.

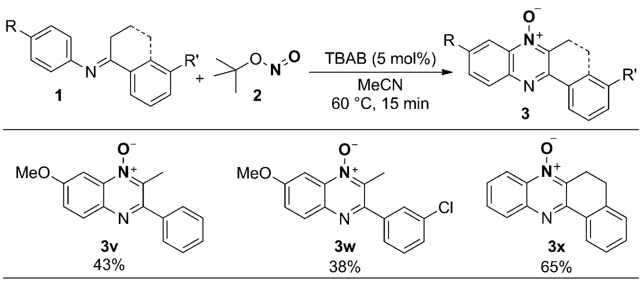
The practicability and applicability of this quinoxaline *N*-oxide synthesis are remarkable. With this concise method, an efficient one-pot synthesis of quinoxaline *N*-oxides from amines and ketones was developed [Eq. (2)]. Aniline (**4a**)

 (2)

and acetophenone (**5a**) underwent a condensation reaction in the presence of 4 Å molecular sieve (M.S.),[16] and the subsequent nitrogen-incorporation process gave the desired



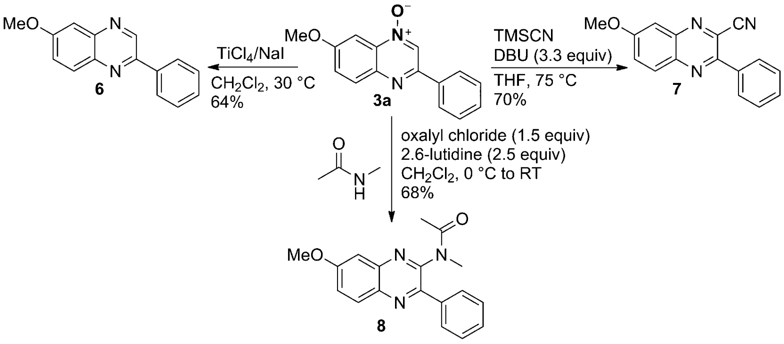
Scheme 1. Direct transformation of substituted imines into quinoxaline *N*-oxides. Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol), TBAB (0.02 mmol), and MeCN (3 mL) with stirring under air for 15 minutes.



Scheme 2. Synthesis of 2-substituted quinoxaline *N*-oxides.

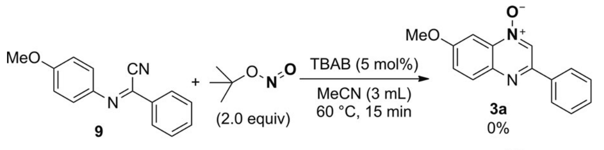
quinoxaline *N*-oxide **3a** in 56% yield [Eq. (2)]. However, the reaction of aniline with acetone did not yield the corresponding quinoxaline *N*-oxide.

Quinoxaline *N*-oxides are versatile intermediates in organic synthesis and generally undergo further transformations with high reactivity and regioselectivity. For instance, product **3a** could be deoxidized into quinoxaline derivative **6** in 64% yield using $TiCl_4$/NaI as the reducing agent (Scheme 3).[17] Furthermore, quinoxaline *N*-oxides are suitable precursors to various quinoxaline derivatives through C–C and C–N bond formation. Product **3a** could be converted into cyanoquinoxaline **7** in 70% yield in the presence of TMSCN and DBU (Scheme 3).[18] *N*-(7-Methoxy-3-phenylquinoxalin-2-yl)-*N*-methylacetamide (**8**) was also easily prepared from **3a** with *N*-methylacetamide through C–N bond formation (Scheme 3).[19]



Scheme 3. Synthetic transformations of quinoxaline *N*-oxides. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, TMS = trimethylsilyl.

Some control experiments were conducted to gain insight into the mechanism of this transformation. Considering that α-iminonitrile **9** and quinoxaline **6** could be possible intermediates, they were prepared and subjected to the optimized reaction conditions [Eq. (3) and (4)]. However, the desired product **3a** was not obtained. The results exclude the possibility that α-iminonitriles and quinoxalines are involved as intermediates in this transformation. Hence, it is not possible that amination and oxidation occur by a relay mechanism. The NO moiety must therefore be introduced into the molecule as one unit.



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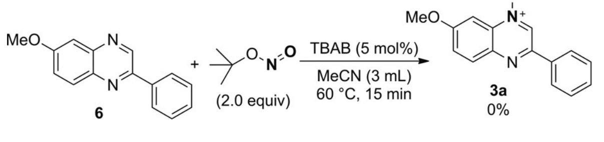


(4)

Moreover, the kinetic profile of the reaction was monitored by in situ Fourier transform infrared (FT-IR) spectroscopy in the presence or absence of TBAB. The results in Figure S5 clearly suggest that TBAB accelerates the reaction. Furthermore, the amount of the side products **6** and **9** could be reduced by the addition of TBAB (see the Supporting Information). Because of the results shown in Table 1 (entries 4 and 6), TBAB is not a catalyst of the reaction, but functions as an additive. However, the mechanism by which TBAB influences the outcome of this reaction is still not completely clear.

When the reaction of **1a** was monitored by EPR spectroscopy under the standard conditions in the presence of the free radical spin-trapping agent 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), a signal with six peaks, which corresponds to the adduct of DMPO and the carbon-centered radical,[20] was observed ($g = 2.011$, $\alpha_N = 15.3$ G, $\alpha_H^{\beta} = 22.4$ G; Figure S1 a). The EPR results indicate that the carbon-centered radical might be a key intermediate in the present reaction. Furthermore, no EPR signals could be recorded in the absence of TBN or **1a** (Figure S1 b and S1 c, respectively). These results demonstrate that the carbon-centered radical is formed by the reaction of **1a** with TBN.

To better understand the mechanism of this transformation, the nitrogen incorporation reaction of imine **1** and TBN, as a model reaction, was studied by density functional theory (DFT) calculations (Figure 1).[21] Initially, TBN decomposes into a NO radical and a *tert*-butoxy radical,[15] which is an endergonic process by 22.4 kcal mol^{-1}. The first step of the cascade reaction corresponds to the abstraction of a hydrogen atom of imine **1** by the *tert*-butoxy radical via transition state **TS1** with an activation free energy of 20.1 kcal mol^{-1} to afford methyl imine radical intermediate **INT1**. The NO radical is a poor hydrogen-atom abstractor ($\Delta G^{\ddagger} = 48.2$ kcal mol^{-1}). Then, **INT1** reacts with the NO radical to form **INT2**, which is an exergonic process by 21.6 kcal mol^{-1}. Further abstraction of a hydrogen atom in **INT2** by a *tert*-butoxy radical is facile, only requiring 15.5 kcal mol^{-1} in activation free energy. This process is significantly exergonic by 61.7 kcal mol^{-1}. The subsequent electrocyclic reaction of **INT3** readily proceeds through **TS3** with an activation free energy of only 14.7 kcal mol^{-1} to furnish cyclic intermediate **INT4**. Finally, the aromatization process that involves the abstraction of a hydrogen atom in **INT4** by a *tert*-butoxy radical is once again significantly exergonic by 137.1 kcal mol^{-1} and gives rise to the final quinoxaline *N*-oxide **3**. Reviewing the overall energy profile, we found that the *tert*-butoxy and NO radicals are the active species. Increasing the stability and concentration of these

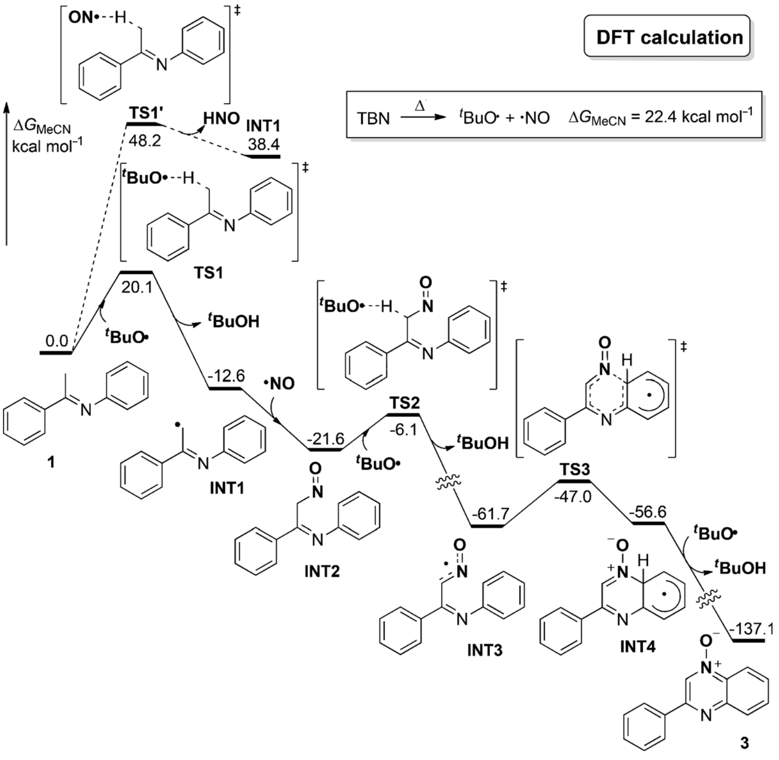
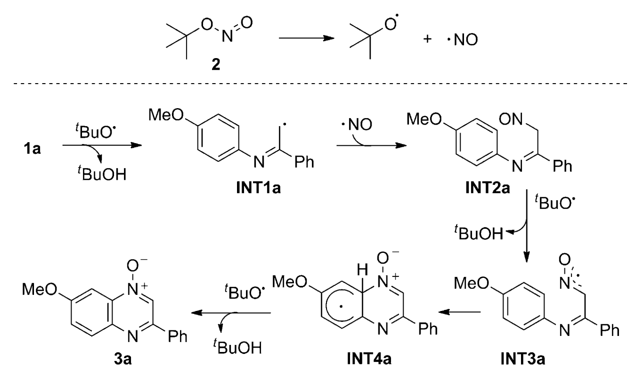


Figure 1. DFT energy profiles for the nitrogen incorporation reaction of imine **1** with TBN.

radicals would enhance the rate of reaction. The first abstraction of a hydrogen atom from imine **1** by a *tert*-butoxy radical is the rate-determining step, and the subsequent electrocyclic reaction of the radical intermediate serves as the key step, which is in good agreement with the experimental observations. TBAB is likely to stabilize the *tert*-butoxy and NO radicals and increase their concentrations in the reaction mixture.

Although it is known that the nitrosyl exchange reaction between *tert*-butyl nitrite and alcohols works well,[22] a nucleophilic substitution reaction on *tert*-butyl nitrite with an enamine nucleophile has not been reported. Furthermore, through DFT calculations, the ionic pathway, which involves nucleophilic attack of an enamine to TBN and tautomerization to an oxime intermediate followed by an electrocyclic reaction, could be ruled out because of much higher energy barriers (Figure S6). Furthermore, the fast reaction (less than 15 min) and the low efficiency in the presence of TEMPO [see Eq. (S1)] also support the hypothesis that the transformation proceeds through a single electron transfer (SET) process.



Scheme 4. Proposed pathway for the formation of quinoxaline *N*-oxides.

On the basis of the above preliminary results, a plausible mechanism for this synthesis of quinoxaline *N*-oxides under transition-metal-free conditions involves nitrogen atom incorporation through $C(sp^2)$–H and $C(sp^3)$–H bond functionalization (Scheme 4). Initially, *tert*-butyl nitrite could decompose into an NO radical and a *tert*-butoxy radical.[15] Methyl imine radical **INT1a** could be generated by the abstraction of a hydrogen atom with the *tert*-butoxy radical.[15c] Then, **INT1a** reacts with the NO radical to form **INT2a**, which is further attacked by a *tert*-butoxy radical to produce **INT3a**. The cyclic intermediate **INT4a** is then generated by the subsequent electrocyclic reaction of **INT3a**. Finally, aromatization of **INT4a** through the abstraction of a hydrogen atom by a *tert*-butoxy radical leads to the final product **3a** (Scheme 4).

In conclusion, we have developed a novel transition-metal-free approach to quinoxaline *N*-oxides that involves the functionalization of $C(sp^2)$–H and $C(sp^3)$–H bonds for nitrogen atom incorporation. One $C(sp^2)$–H bond and two $C(sp^3)$–H bonds are cleaved to achieve multiple C–N bond formation. The method employs simple and readily available methyl imines or even the corresponding parent aniline and acetophenone derivatives in a one-pot reaction. Simple and commercially available *tert*-butyl nitrite is employed as the NO source. All of these features as well as its transition-metal-free conditions make this method highly efficient and practical. EPR measurements and DFT calculations suggest that the nitrogen-incorporation reaction involves multiple SET processes.

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