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Brønsted Acid Catalyzed Benzylic C−H Bond Functionalization of Azaarenes: Nucleophilic Addition to Nitroso Compounds

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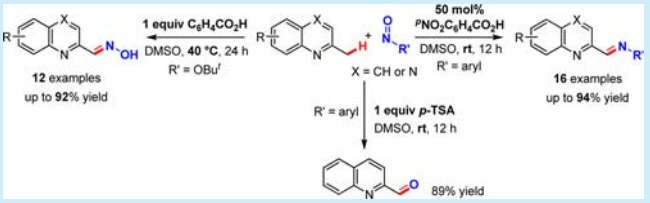
Supporting Information

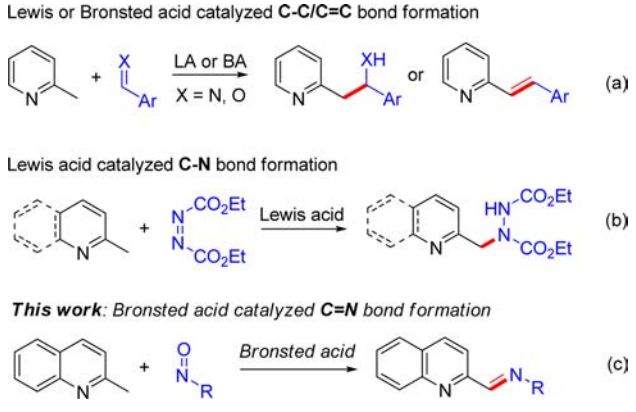
ABSTRACT: A practical Brønsted acid promoted benzylic C−H functionalization of 2-alkylazaarenes and nucleophilic addition to nitroso compounds was developed under mild conditions. Switched by Brønsted acids, this method can afford azaarene-2-aldimines, azaarene-2-carbaldehyde, or azaarene-2-oximes selectively. No metal, base, oxidant, or other additives were required.



Quinolines and their derivatives are important motifs in pharmaceutical and agricultural chemistry and are used as key building blocks in natural product synthesis.[1] Various preparative methods for the synthesis of quinolines, along with methods for the further transformation of these azaarenes, have therefore been developed.[2] Among them, the direct benzylic C−H bond functionalization of azaarenes has stimulated tremendous research interest.[3−8] While the traditional benzylic transformation via deprotonation−nucleophilic substitution/addition sequence requires a strong base such as ^{n}BuLi or LDA,[3] recent research revealed that this transformation can be accelerated by shifting the alkylazaarene to its enamine counterpart assisted by a suitable Lewis[4,7,8] or Brønsted acid[5] (Scheme 1, route a). This strategy has been successively applied to various nucleophilic additions of benzylic C−H bond of azaarenes for the C−C,[4−6] C═C[7] (Scheme 1, route a), and C−N[8] bond-forming reactions (Scheme 1, route b).

On the other hand, nitroso compounds have been widely used as attractive electrophiles in C−N and/or C−O bond-forming reactions such as aldol-type reactions,[9] ene reactions,[10] and Diels−Alder reactions[11] since the first preparation[12] of nitrosobenzene in 1874. In line with our interest in the C−H activation and nucleophilic additions,[5a,b,13] our previous studies[5a,b] have revealed that Brønsted acids turned out to be effective catalysts for converting 2-alkylazaarene to its more nucleophilic enamine counterpart, and thus promoted the benzylic C−H addition to carbonyl groups or iminium ion (generated in situ). To the best of our knowledge, the benzylic C−H addition of azaarenes to nitroso compounds in the absence of strong base has not been developed. Consequently, we envisioned a Brønsted acid catalyzed C═N bond-forming process for the functionalization of azaarenes by the nucleophilic addition to nitroso compounds (Scheme 1, route c).

Scheme 1. Benzylic C−H Functionalization of Azaarenes



Based on our previous work on Brønsted acid promoted nucleophilic addition of the benzylic C−H bond of azaarenes to aromatic aldehydes, where the Brønsted acid played a crucial role for the activation of alkylazaarenes and the aldehydes through a six-membered hydrogen-bonding transition state, we hypothesized that the nucleophilic addition of benzylic C−H bond should proceed similarly when the C═O bond was replaced by the reactive N═O bond of nitroso compounds.

To test the feasibility of the hypothesis above, we first examined the reaction of 2-methylquinoline (**1a**) and *p*-chloronitroso benzene (**2a**) catalyzed by acetic acid (Table 1, entry 1). Unexpectedly, when the reaction was performed in DMSO, most of the starting materials were consumed after stirring at room temperature overnight,[14] and the product was characterized as aldimine **3a**, which was obtained from the further dehydration of the anticipated nucleophilic addition product.

To examine the influence of acidity to the reaction, different Brønsted acids such as pivalic acid (PivOH), benzoic acid, *p*-

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Table 1. Optimization of the Brønsted Acid Promoted Benzylic Nucleophilic Addition of Azaarenes[a]

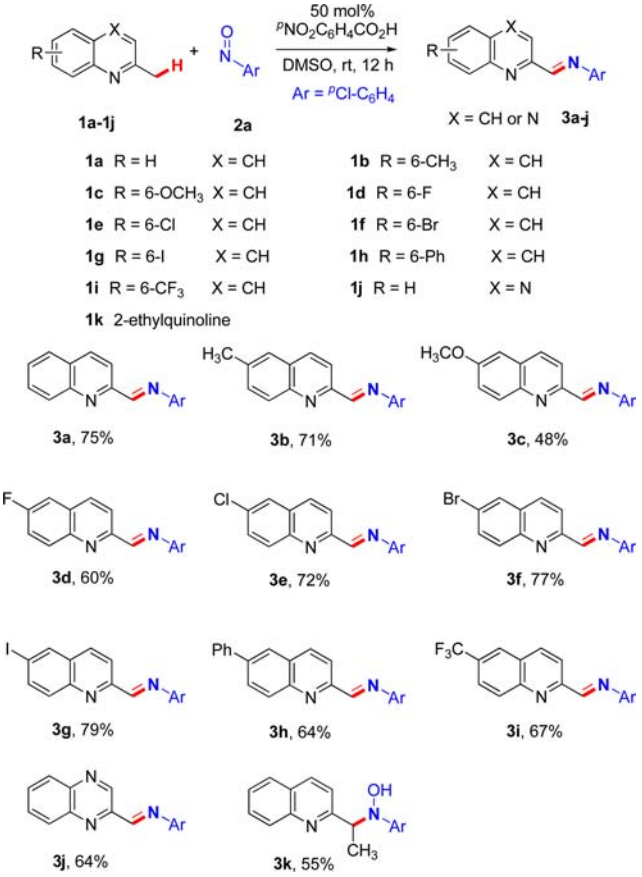
entry	BA (mol %)	solvent	3a yield[b] (%)
1	AcOH (100)	DMSO	41
2		DMSO	0
3	PivOH (100)	DMSO	55
4	$PhCO_2H$ (100)	DMSO	62
5	*p*-$NO_2C_6H_4CO_2H$ (100)	DMSO	67
6	2,4-$(NO_2)_2C_6H_3CO_2H$ (100)	DMSO	59
7[c]	*p*-TSA (100)	DMSO	<5 (89)
8	**$^pNO_2C_6H_4CO_2H$ (50)**	**DMSO**	**75**
9	*p*-$NO_2C_6H_4CO_2H$ (20)	DMSO	65
10[d]	*p*-$NO_2C_6H_4CO_2H$ (100)	DMSO	52
11[c]	*p*-$NO_2C_6H_4CO_2H$ (100)	DMSO	54
12	*p*-$NO_2C_6H_4CO_2H$ (100)	DMF	53
13	*p*-$NO_2C_6H_4CO_2H$ (100)	1,4-dioxane	39
14	*p*-$NO_2C_6H_4CO_2H$ (100)	DCE	<5
15	*p*-$NO_2C_6H_4CO_2H$ (100)	CH_3CN	trace
16	*p*-$NO_2C_6H_4CO_2H$ (100)	toluene	trace

[a]Conditions: **1a** (0.4 mmol), **2a** (0.8 mmol), Brønsted acid (BA), solvent (0.6 mL), reacted for 12 h at rt under argon atmosphere unless otherwise noted. [b]Isolated yields for aldimine **3a**. Yield for **4a** was given in parentheses. [c]Reacted at 40 °C. [d]Reacted at 0 °C.

nitrobenzoic acid, and 2,4-dinitrobenzoic acid were tested (entries 1−7); among them, *p*-nitrobenzoic acid was found to be the best choice (entry 5). When the acidity was too weak, the reaction was sluggish, and when the acidity was too strong, part of the product (aldimine **3a**) would be further hydrolyzed to afford quinoline-2-carbaldehyde (**4a**).[15] The loading of *p*-nitrobenzoic acid was carefully evaluated next, and the best yield was obtained when 50 mol % of acid was used (entries 6, 8, and 9). It is worth noting that excess *p*-chloronitrosobenzene (**2a**, 2 equiv) was required for the complete conversion of 2-methylquinoline (**1a**) because part of the *p*-chloronitrosobenzene would undergo homocoupling to yield azodioxy dimmer in acidic condition. When much stronger *p*-TSA was used, the yield of aldimine product was very low (<5%) and the quinoline-2-carbaldehyde (**4a**) turned out to be the main product in 89% yield. We were pleased to find that this benzylic addition can also be realized at 0 °C with moderate yield (entry 10). Next, the effect of solvents on this reaction was also investigated. The reaction proceeded much faster in polar solvents such DMSO and DMF (entry 12) and much slower in 1,4-dioxane and DCE (entries 13 and 14). Acetonitrile was not a good choice either, which may be due to its ability to neutralize the Brønsted acid (entry 15).

Under the optimized conditions (Table 1, entry 8, with 50 mol % of *p*-nitrobenzoic acid as catalyst), the substrate scope and limitation of this benzylic C−H addition to form C═N bonds was explored. The effect of substituents on the alkylazaarene moiety is listed in Table 2. 2-Methylquinolines bearing electron-donating or -withdrawing substituents were successfully transformed into the desired aldimine products in moderate to high yields, such as methyl (**1b**), methoxy (**1c**), halo (**1d**−**1g**), phenyl (**1h**), and trifluoromethyl groups (**1i**). Besides 2-methylquinolines, the optimized reaction conditions can also be applied to the benzylic C−H functionalization of 2-methylquinoxaline (**1j**) with *p*-chloronitrosobenzene (**2a**), but for the 2-ethylquinoline (**1k**), the reaction afforded the nucleophilic addition product **3k**

Table 2. Effect of Substituents on the Azaarene Moiety[a]



[a]Conditions: **1a**−**k** (0.4 mmol), **2a** (0.8 mmol), *p*-nitrobenzoic acid (0.2 mmol), DMSO (0.6 mL), reacted for 12 h at rt under argon atmosphere unless otherwise noted. Isolated yields.

(which was not dehydrated) in 55% yield. However, the reaction of 2-methylpyridine (and also 2,6-lutidine) under the same conditions was failed even at elevated temperature for unknown reason.

On the other hand, for the different nitroso compound (Table 3), the reaction yields relied on the electronic effect of substituents; for example, the 4-(methoxycarbonyl)-nitrosobenzene (**2c**) afforded the aldimine **3o** in 94% yield, while the relatively electron-rich 4-methylnitrosobenzene (**2e**) led to a lower yield of 45%. The reasons for above results should be attributed to that the electron-withdrawing groups would increase the electroaffinity of nitroso compounds.

Encouraged by the exciting results obtained between the nucleophilic additions of alkylazaarenes to substituted nitrosobenzenes, the application of this reaction to *tert*-butyl nitrite (^{t}BuONO) was investigated next.[16] The nucleophilic addition product was found to be oxime, but not the anticipated dehydration product, maybe due to their different thermodynamics stabilities (Table 4).[17] Considering that both the starting material (the *tert*-butyl nitrite would not dimerize) and the products are more stable than substituted nitrosobenzenes and aldimines, the reaction conditions were finely adjusted. When the nucleophilic addition of alkylazaarenes to *tert*-butyl nitrite was promoted by 1 equiv of benzoic acid at slightly elevated temperature (40 °C vs rt), good to excellent yields were obtained for all of the alkylazaarenes tested.

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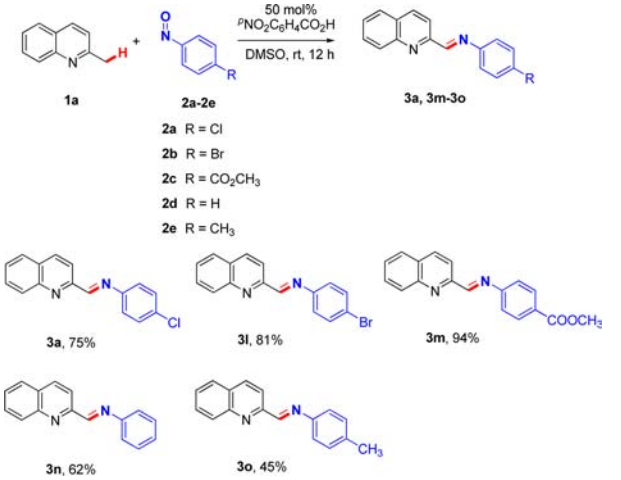
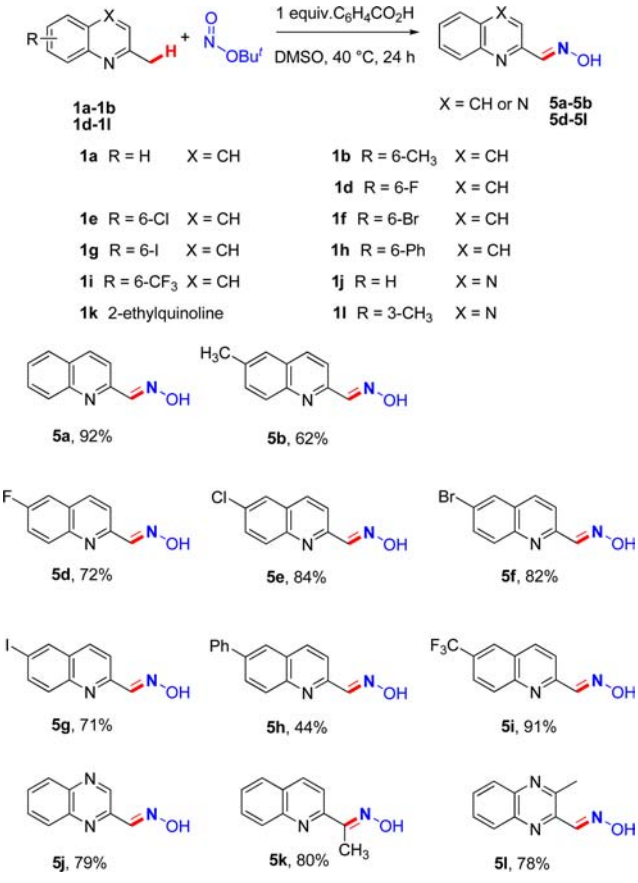
Table 3. Effect of Substituents on the Nitroso Moiety[a]



[a]Conditions: **1a** (0.4 mmol), **2** (0.8 mmol), *p*-nitrobenzoic acid (0.2 mmol), DMSO (0.6 mL), reacted for 12 h at rt under Argon atmosphere unless otherwise noted. Isolated yields.

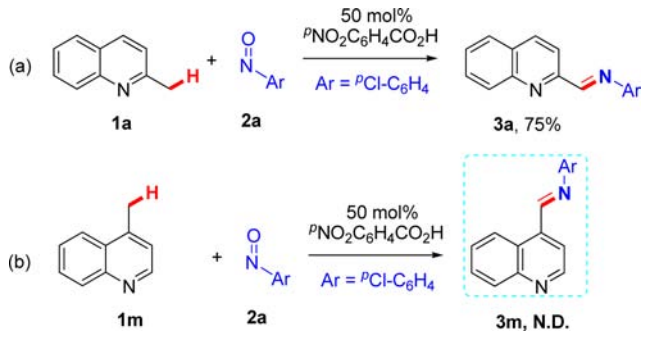
Table 4. Nucleophilc Addition of Alkylazaarenes to *tert*-Butyl Nitrite[a]



[a]Conditions: **1a**−**1k** (0.4 mmol), **2a** (0.8 mmol), benzoic acid (0.4 mmol), DMSO (0.6 mL), reacted for 24 h 40 °C under argon atmosphere unless otherwise noted. Isolated yields.

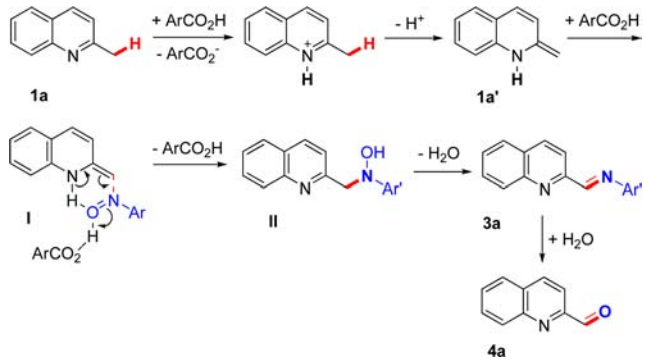
To shed some light on the mechanism of this benzylic C−H functionalization, the reaction of 4-methylquinoline (**1m**) with *p*-chloronitrosobenzene (**2a**) was carried out under the same reaction conditions (Scheme 2b). However, the corresponding nucleophilic addition product of the C4 methyl C−H to N═O

Scheme 2. Control Experiments between 2- and 4-Methylquinolines



was not detected by GC−MS, which was similar to our previous results obtained from the benzylic C−H addition to carbonyl groups. These results seem to suggest a six-membered hydrogen-bonding transition state (Scheme 3, I), in which the Brønsted acid not only accelerates the imine−enamine transformation but also activates the nitrosobenzene through the hydrogen bond.

Scheme 3. Proposed Mechanism for the Benzylic C−H Functionalization



We proposed a plausible mechanism to rationalize this Brønsted acid catalyzed benzylic C−H nucleophilic addition to N═O (Scheme 3). First, 2-methylquinoline (**1a**) is converted to its more nucleophilic enamine counterpart catalyzed the by the aromatic acid, which can also activate the polarized N═O bond through hydrogen bond to make it more electrophilic. Then, the subsequent nucleophilic addition of the enamine to activated N═O takes place spontaneously to generate the hydroxyamination intermediate **II**, which can undergo dehydration to produce aldimine **3a** assisted by Brønsted acid. The hydroxyamination intermediate **II** is supported by the isolation and characterization of product **3k** (Table 2). When the Brønsted acidity is strong enough (for example, *p*-TSA, Table 1, entry 7), the aldimine **3a** was further hydrolyzed to afford quinoline-2-carbaldehyde (**4a**).

In conclusion, we have developed an efficient benzylic C−H functionalization of azaarenes by its nucleophilic addition to nitroso compounds under mild conditions. Switched by Brønsted acids, the nucleophilic addition to nitrosoarenes can afford azaarene-2-aldimines or azaarene-2-carbaldehyde selectively, and the nucleophilic addition to *tert*-butylnitrite yields azaarene-2-oximes in high yields. This reaction has provided an efficient method for the benzylic C−H transformation of 2-alkylazaarenes to C═N and C═O bonds. The cheapness and abundance of the two starting materials, the usage of benzoic acid

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as the catalyst, and the mild reaction conditions should make this method attractive for the synthesis of bioactive quinoline and quinoxaline derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compounds characterization data, and copies of NMR spectra. 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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