Organic & Biomolecular Chemistry

RSC Publishing

COMMUNICATION

View Article Online
View Journal



Cite this: DOI: 10.1039/c3ob40782a

Received 18th April 2013,
Accepted 28th May 2013

DOI: 10.1039/c3ob40782a

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# Organocatalytic functionalization of heteroaromatic *N*-oxides with C-nucleophiles using *in situ* generated onium amide bases†

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**Organocatalytic functionalization of heteroaromatic *N*-oxides was investigated using *in situ* generated onium amide bases, and C-nucleophiles were efficiently introduced by the sequential addition–elimination reaction under metal-free conditions, affording 2-substituted nitrogen heteroaromatics generally in good to high yields.**

Heteroaromatic *N*-oxides have attracted wide attention as useful synthetic intermediates, catalysts and ligands, and some compounds are known to exhibit important biological activities.[1] One of the important methods for functionalization of heteroaromatic *N*-oxides is the process using organometallic C-nucleophiles.[2] Among them, aryl Grignard reagents (ArMgX) have been employed to efficiently introduce carbon functionalities at the α-position of *N*-oxides.[3] Addition of ArMgX to pyridine *N*-oxides followed by the treatment of the intermediary 2,4-dienal oximes with acetic anhydride provides a range of 2-substituted pyridines in good to high yields.[3a] A method involving the addition of ArMgX to pyridine *N*-oxides and the subsequent treatment with electrophiles has recently been reported for the synthesis of 2,3-dihydropyridine *N*-oxides, which can be further transformed into 2,3-disubstituted piperidines.[3b] A similar procedure can be utilized for the synthesis of substituted piperidines in an enantioselective manner with the aid of a chiral ligand.[3f] On the other hand, when pyridine *N*-oxides are treated with alkyl Grignard reagents (RMgX), proton abstraction at the α-position occurs. The *ortho*-magnesiated intermediates can successfully be trapped with electrophiles such as aldehydes, ketones and halogens.[4] Halogen–magnesium exchange reaction of 2-halopyridine *N*-oxides using RMgX also leads to the formation of magnesiated pyridine *N*-oxides.[5] As for deprotonation, regioselective α-zincation of *N*-oxides using TMPZnCl is also achieved.[6] Heteroaromatic *N*-oxides have also recently been regarded as an ideal choice of substrates for transition metal-catalyzed C–H functionalization processes.[7] Fagnou *et al.* extensively studied the Pd-catalyzed C–H arylation of azine and azole *N*-oxides.[7a,c] The Ni-catalyzed alkyne insertion into the C–H bonds α- to the *N*-oxide moiety has also been reported, providing 2-alkenylpyridine *N*-oxides under mild conditions.[8] Another important approach for functionalization of heteroaromatic *N*-oxides involves transition metal-free systems.[9] The oxidative cross-coupling reaction of heteroaromatic *N*-oxides and alkanes under the influence of peroxides has been developed.[9a] Effective utilization of a phosphonium salt as a means of pyridine *N*-oxide activation for introducing various nucleophiles at the 2-position has also been reported, which provides 2-substituted pyridine derivatives.[9b] In view of the current strict guidelines limiting the transition metal levels in pharmaceuticals, the development of C–C bond-forming reactions without using a transition metal is considered to be an important subject. During the course of our studies on organocatalytic transformation of aromatic and heteroaromatic compounds,[10] we recently reported a novel catalytic method for deprotonative functionalization of heteroaromatic compounds under metal-free, mild conditions in the presence of onium amide bases generated *in situ* from the combination of aminosilanes and onium fluorides (Fig. 1).[11] In connection with our method involving the organocatalytic functionalization of heteroaromatic *N*-oxides using a phosphazene superbase,[12] we investigated a metal-free, transformation process of heteroaromatic

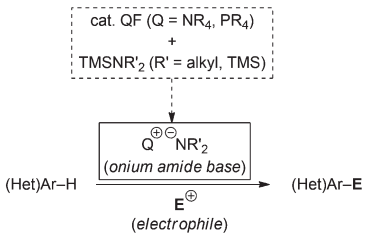


**Fig. 1** Deprotonative functionalization of heteroaromatics using onium amide bases.

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†Electronic supplementary information (ESI) available: Experimental procedures and spectral/analytical data. See DOI: 10.1039/c3ob40782a

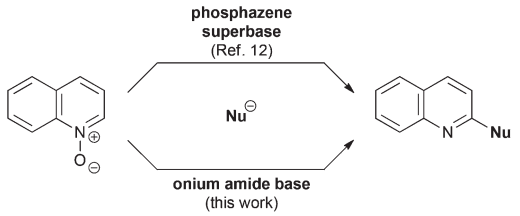



**Fig. 2** Functionalization of heteroaromatic *N*-oxides.

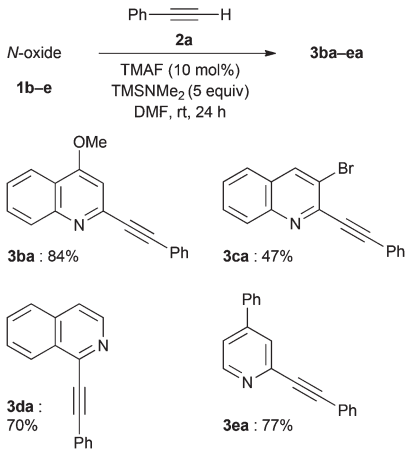
*N*-oxides making use of *in situ* generated onium amide bases, the results of which are detailed in this paper (Fig. 2).

We commenced our studies by exploring the addition–elimination reaction of quinoline *N*-oxide (**1a**) with phenylacetylene (**2a**) using *in situ* generated onium amide bases (Table 1). When 10 mol% of TBAF was used as an onium fluoride in the presence of dimethylaminotrimethylsilane in toluene, the reaction proceeded at room temperature to give 2-phenylethynylquinoline (**3aa**) in 27% yield (entry 1). The screening of solvents revealed that the use of THF and DMF improved the yields (entries 2 and 3). Increasing the amount of aminosilane resulted in the formation of **3aa** in high yield (entry 4). Moreover, the use of TMAF instead of TBAF gave an excellent result, affording **3aa** in 97% yield (entry 5). Using the optimized reaction conditions, the reaction of **1a** with 4-methoxyphenylacetylene (**2b**), 4-bromophenylacetylene (**2c**) and 3-thienylacetylene (**2d**) smoothly proceeded as well to provide the corresponding 2-substituted quinolines **3ab–3ad** in good to high yields (entries 6–8).[13]

Substituted quinoline *N*-oxides **1b** and **1c** were also found to be suitable for the process (Scheme 1). In addition, another class of substrates such as isoquinoline *N*-oxide (**1d**) and 4-phenylpyridine *N*-oxide (**1e**) successfully reacted with phenylacetylene (**2a**) to give the corresponding phenylethynylated compounds **3da** and **3ea** in high yields.

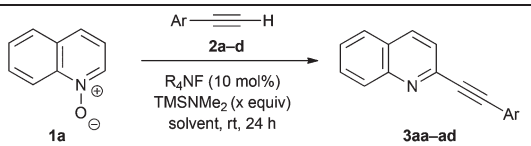
We next focused our attention on the reaction of quinoline *N*-oxide **1a** with benzothiazole **4a** (Table 2). The above obtained optimal reaction conditions, however, turned out to be ineffective for the process (entry 1). While the use of the elevated temperature such as 120 °C had little effect (entry 2), the reaction utilizing tristrimethylsilylamine instead of dimethylaminotrimethylsilane provided the improved yield (entry 3). Furthermore, an increased amount of TMAF led to better results: the reaction in the presence of 50 mol% of TMAF gave rise to **5aa** in high yield (entry 5). Similarly, benzoxazole (**4b**) and 1-phenylbenzimidazole (**4c**) also participated in the addition–elimination reaction of **1a**, and the corresponding coupling products **5ab** and **5ac** were obtained, albeit in relatively low yields (entries 6 and 7).

In the reaction of 1-phenylbenzimidazole (**4c**), 2,2′-biquinoline (**7**) was isolated as a side product. In order to examine the reaction pathway for the formation of **7**, **1a** was treated with TMAF and dimethylaminosilane at room temperature in the absence of a nucleophile, which provided 2,2′-biquinoline *N*-oxide (**6**) in 40% yield (Scheme 2).[14] On the other hand, the same reaction conducted at 120 °C delivered deoxygenated 2,2-biquinoline (**7**) in 70% yield. To clarify the difference of the products, independently prepared 2,2′-biquinoline




**Scheme 1** Reaction of various heteroaromatic *N*-oxides **1b–e** with **2a**.

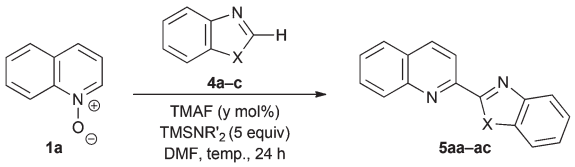
**Table 1** Reaction of quinoline *N*-oxide (**1a**) with acetylenes **2a–d**[a]




| Entry | Ar | 2 | $R_4NF$ | *x* | Solvent | 3 | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | Ph | **2a** | TBAF | 2.5 | Toluene | **3aa** | 27 |
| 2 | Ph | **2a** | TBAF | 2.5 | THF | **3aa** | 41 |
| 3 | Ph | **2a** | TBAF | 2.5 | DMF | **3aa** | 49 |
| 4 | Ph | **2a** | TBAF | 5 | DMF | **3aa** | 89 |
| 5 | Ph | **2a** | TMAF | 5 | DMF | **3aa** | 97 |
| 6 | $(4\text{-MeO})C_6H_4$ | **2b** | TMAF | 5 | DMF | **3ab** | 80 |
| 7 | $(4\text{-Br})C_6H_4$ | **2c** | TMAF | 5 | DMF | **3ac** | 50 |
| 8 | 3-Thienyl | **2d** | TMAF | 5 | DMF | **3ad** | 82 |

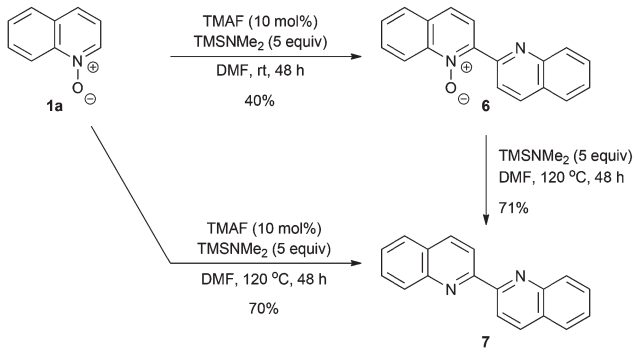
[a] Performed on a 0.30 mmol scale.

**Table 2** Reaction of quinoline *N*-oxide (**1a**) with azoles **4a–c**[a]




| Entry | X | 4 | *x* | R′ | Temp. | 5 | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | S | **4a** | 10 | Me | rt | **5aa** | 4 |
| 2 | S | **4a** | 10 | Me | 120 °C | **5aa** | 18 |
| 3 | S | **4a** | 10 | TMS | 120 °C | **5aa** | 39 |
| 4 | S | **4a** | 30 | TMS | 120 °C | **5aa** | 65 |
| 5 | S | **4a** | 50 | TMS | 120 °C | **5aa** | 92 |
| 6 | O | **4b** | 50 | TMS | 120 °C | **5ab** | 45 |
| 7 | NPh | **4c** | 50 | TMS | 120 °C | **5ac** | 20 |

[a] Performed on a 0.30 mmol scale.




**Scheme 2** Formation of 2,2-biquinoline **7**.

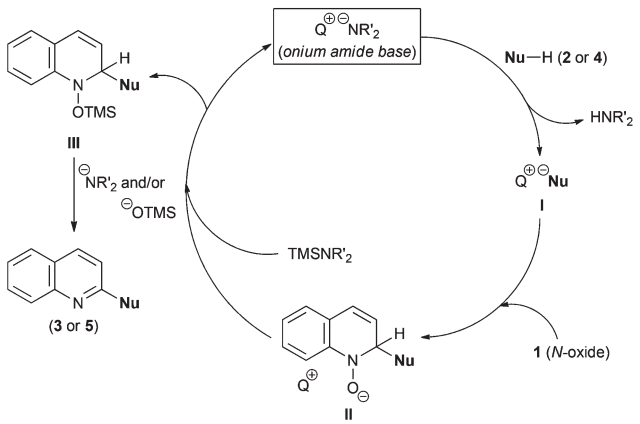



**Fig. 3** Plausible reaction pathway.

*N*-oxide (**6**) was treated with dimethylaminosilane at 120 °C, which resulted in the formation of **7** in 71% yield, suggesting that dimethylaminosilane works as a deoxygenating agent of biquinoline *N*-oxide (**6**).

Although the precise reaction mechanism remains to be elucidated, the functionalization of *N*-oxide **1** may be proceeding *via* a pathway as depicted in Fig. 3. Deprotonation of a nucleophile (**2** or **4**) by *in situ*-generated onium amide bases first occurs and the resultant anion **I** attacks the α-position of *N*-oxide **1**, forming the adduct **II**. The reaction of **II** with aminosilane provides the silylated compound **III** along with onium amide bases. Deprotonation of **III** results in the formation of the desired product (**3** or **5**), in which onium amide bases and/or other anionic species (*e.g.* OTMS anion) might involve. Further systematic studies are necessary to clarify the mechanism.

In summary, *in situ* generated onium amide base-catalyzed reactions are found to be effective for selective functionalization of heteroaromatic *N*-oxides. Using the method, both alkynylation and heteroarylation can be successfully performed, affording the coupling products generally in good to high yields. Further optimization of reaction conditions as well as expansion of the scope of the organocatalytic process using onium amide bases is under investigation.

This work was partly supported by a Grant-in-Aid for Scientific Research (B) (No. 23390002), a Grant-in-Aid for Challenging Exploratory Research (No. 23659001) and a Grant-in-Aid for Young Scientists (B) (No. 23790002) from Japan Society for the Promotion of Science, and a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysis" (No. 23390002) from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

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