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Volume 52 | Number 1 | 4 January 2016 | Pages 1–216

ChemComm

Chemical Communications
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ISSN 1359-7345

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Copper-Catalyzed Mannich-Type Oxidative β-Functionalization of Tertiary Amines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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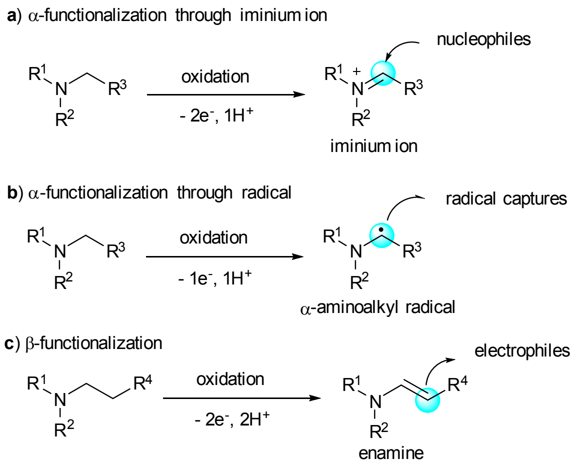
A copper-catalyzed Mannich-type oxidative β-functionalization reaction of amines has been developed. In the presence of oxidant and the copper catalyst the tertiary amines reacted with *N*-tosylimines, providing synthetically important 1,3-diamines and enamines, respectively. Preliminary mechanistic studies suggested that oxidation of the tertiary amine to enamine intermediate by copper(II) salts triggers subsequent Mannich-type reactions with *N*-tosylimines and thus enables direct β-functionalization of the tertiary amines.

Site-selective functionalization of C(sp^3)–H bonds of molecules bearing amino groups provides an efficient method for constructing complex *N*-containing moieties, which are ubiquitous in bioactive natural products, pharmaceuticals, and agrochemicals.[1] Oxidative α-functionalization of amines via capture of iminium ion intermediates generated in situ is a well-established method (Scheme 1a).[2] Recently, oxidative α-functionalization of amines via trapping of α-aminoalkyl radical intermediates has also been reported (Scheme 1b).[3] However, oxidative β-functionalization of amines via capture of enamine intermediates by electrophiles is challenging (Scheme 1c). Several early examples of oxidative β-functionalization of amines via substitution reactions with specific electrophilic reagents[4] such as *p*-quinones,[4a] trichloroacetyl chloride,[4b] trifluoroacetic anhydride,[4c] hexachloroacetone,[4d] and fluoroalkyl iodides[4e–g] have been reported. A few successful examples of the oxidative β-functionalization of amines via addition reactions with highly active conjugated olefins[5] or aldehydes[6] were documented. However, only limited number of electrophilic reagents have been utilized in the oxidative β-functionalization of amines, which hampered the development of the reaction and its application in the synthesis.[7] Herein, we report a copper-catalyzed oxidative Mannich-type β-functionalization of acyclic and cyclic aryl amines with *N*-tosylimines as electrophiles to produce 1,3-diamines and enamines, which are useful building blocks in organic synthesis.[8]



Scheme 1. Oxidative α- and β-functionalization of amines

We began by investigating the reactions of diethyl aniline (**1a**) and *N*-tosylimine **2a** in the presence of various transition-metal catalysts and oxidants (Table 1). Because acyclic enamine **3a**, which can be detected by ^{1}H NMR, is unstable, the coupling product was isolated after reduction to saturated 1,3-diamine **4a** with NaBH(OAc)$_3$. First, we evaluated various oxidants with CuCl$_2$ as the catalyst in DMSO (entries 1–4). *tert*-Butyl peroxyacetate (AcOO^{t}Bu) afforded the desired product in 68% yield, whereas *tert*-butyl hydroperoxide and benzoyl peroxide showed very low yields. Using AcOO^{t}Bu as the oxidant, we then examined other transition-metal catalysts (entries 5–9; see also Table S1). Among the catalysts tested, only CuCl gave a yield comparable to that of CuCl$_2$ (entry 8) and the use of Cu(OAc)$_2$, CuBr$_2$, CuBr and FeCl$_3$ resulted in low conversions of the *N*-tosylimine **2a** or even no reaction. The reaction was sensitive to temperature. Increasing the temperature decreased the yield or resulted in a messy reaction (entries 10 and 11). DMSO was the best solvent,the use of other solvents such as THF, dichloromethane (DCM), and *N*,*N*,-dimethylformamide (DMF) gave low yield or trace amount of product (entries 12–14; see also Table S2). When the loadings of amine **1a** and oxidant were increased to 8 and 4 equiv, respectively, the yield of **4a** improved to 85% (isolated yield 84%, entry 15). Notably, the yield remained good even when

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† Electronic Supplementary Information (ESI) available: For experimental procedures and characterization data. See DOI: 10.1039/x0xx00000x

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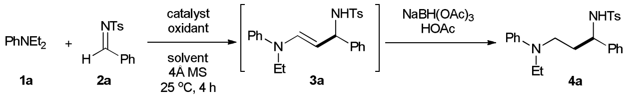
the catalyst loading was lowered to 5 or 2.5 mol% (entries 16 and 17). Control experiments clearly showed that both the copper catalyst and the oxidant were indispensable for this reaction (entries 18 and 19).

Table 1 Copper-catalyzed Mannich-type oxidative β-functionalization of *N*,*N*-diethyl aniline **1a** with *N*-tosylimine **2a**: optimization of reaction conditions[a]

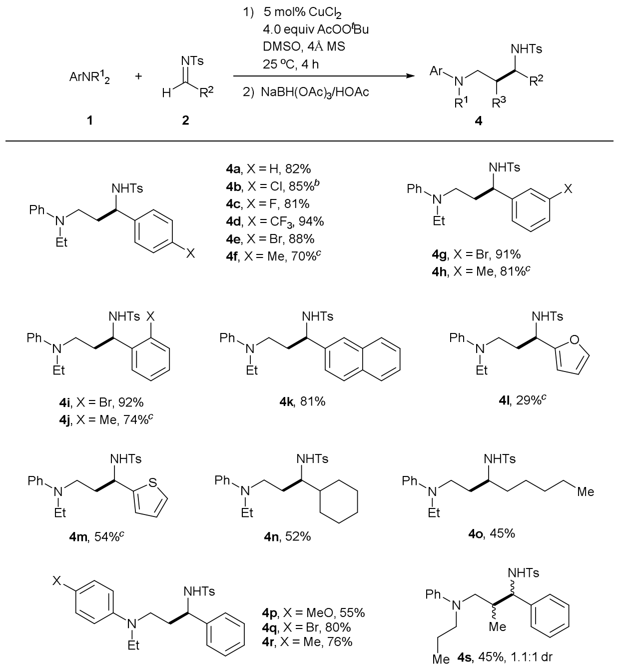


entry	catalyst (mol %)	oxidant (equiv)	solvent	yield (%)[b]
1	$CuCl_2$ (10)	TBP (2.5)	DMSO	ND
2	$CuCl_2$ (10)	TBHP (2.5)	DMSO	15
3	$CuCl_2$ (10)	$AcOO^tBu$ (2.5)	DMSO	68
4	$CuCl_2$ (10)	BPO (2.5)	DMSO	16
5	$Cu(OAc)_2$ (10)	$AcOO^tBu$ (2.5)	DMSO	ND
6	$CuBr_2$ (10)	$AcOO^tBu$ (2.5)	DMSO	25
7	CuBr (10)	$AcOO^tBu$ (2.5)	DMSO	24
8	CuCl (10)	$AcOO^tBu$ (2.5)	DMSO	67
9	$FeCl_3$ (10)	$AcOO^tBu$ (2.5)	DMSO	ND
10[c]	$CuCl_2$ (10)	$AcOO^tBu$ (2.5)	DMSO	42
11[d]	$CuCl_2$ (10)	$AcOO^tBu$ (2.5)	DMSO	Trace
12	$CuCl_2$ (10)	$AcOO^tBu$ (2.5)	THF	Trace
13	$CuCl_2$ (10)	$AcOO^tBu$ (2.5)	DCM	ND
14	$CuCl_2$ (10)	$AcOO^tBu$ (2.5)	DMF	18
15[e]	$CuCl_2$ (10)	$AcOO^tBu$ (4)	DMSO	85 (84)
16[e]	$CuCl_2$ (5)	$AcOO^tBu$ (4)	DMSO	83 (82)
17[e]	$CuCl_2$ (2.5)	$AcOO^tBu$ (4)	DMSO	79 (77)
18	none	$AcOO^tBu$ (4)	DMSO	ND
19	$CuCl_2$ (5)	none	DMSO	ND

[a] Reaction conditions: **1a** (1.0 mmol, 5.0 equiv), **2a** (0.2 mmol, 1.0 equiv), metal catalyst, oxidant, 4Å MS (50 mg) and solvent (2.0 mL) at 25 °C for 4 h; TBP = di-*tert*-butyl peroxide; TBHP = *tert*-butyl hydroperoxide; BPO = benzoyl peroxide; ND = not detected. [b] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. Number in parentheses is the isolated yield. [c] At 40 °C. [d] At 60 °C. [e] **1a** (1.6 mmol, 8.0 equiv).

With the optimized conditions in hand, we evaluated reactions of amines **1** and *N*-tosylimines **2** (Table 2). Reactions between *N*,*N*-diethylaniline (**1a**) and aromatic *N*-tosylaldimines bearing *ortho*, *meta*, or *para* substituents with different electronic properties provided 1,3-diamine products **4a**–**4j** in good to excellent yields. In general, aromatic *N*-tosylaldimines containing an electron-withdrawing group showed higher yields than those containing an electron-donating group. When the reaction of **2b** was performed on a gram scale, the yield remained high (85%), even when the $CuCl_2$ catalyst loading was only 2 mol%. A naphthyl-substituted aldimine gave comparable results (**4k**, 81%), but heteroaryl aldimines afforded lower yields (**4l** and **4m**). Aliphatic aldimines also reacted with **1a** to generate the corresponding 1,3-diamines (**4n** and **4o**) in moderate yields. The tolerance of the reaction for various amines was then explored. *N*,*N*-Diethyl anilines with a methyl, methoxyl, or bromo group on the aryl ring were tolerated (**4p**–**4r**). The reaction of an aniline having longer alkyl chains (R = propyl) with **2a** ran smoothly to give desired product **4s** with modest yield (45%) and dr (1.1:1). In contrast, tertiary aliphatic amines were unsuitable substrates, giving complicated product mixtures (data not shown). When the protecting group on the aldimine was changed to *t*-butoxycarbonyl or *p*-methoxyphenyl, a complex mixture was obtained.

Table 2 Copper-catalyzed Mannich-type oxidative β-functionalization of *N*,*N*-diethyl anilines **1** with *N*-tosylimines **2**.[a]



[a] Reaction conditions: **1** (1.6 mmol), **2** (0.2 mmol), $CuCl_2$ (0.01 mmol, 5 mol%), $AcOO^tBu$ (0.8 mmol), 4Å MS (50 mg) and DMSO (2.0 mL) at 25 °C for 4 h, unless otherwise noted. Isolated yield was given. [b] The gram-scale reaction: **2b** (4.0 mmol, 1.2 g), $CuCl_2$ (0.08 mmol, 2 mol%). [c] The 6 equiv of $AcOO^tBu$ (1.2 mmol) was used.

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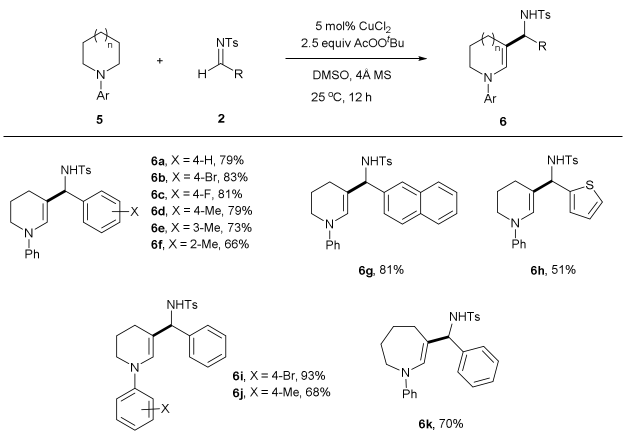
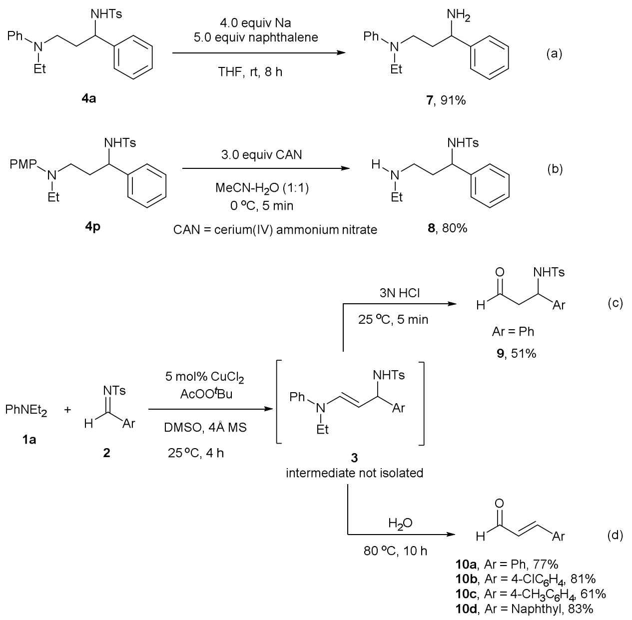
Table 3 Copper-catalyzed Mannich-type oxidative β-functionalization of cyclic amines **5** with *N*-tosylimines **2**.[a]



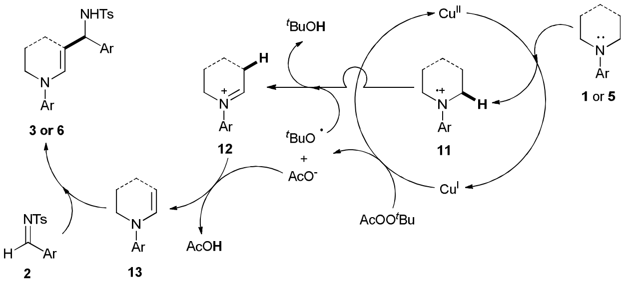
[a] Reaction conditions: **1** (1.0 mmol), **2** (0.2 mmol), $CuCl_2$ (0.01 mmol, 5 mol%), $AcOO^tBu$ (0.5 mmol), 4Å MS (50 mg) and DMSO (2.0 mL) at 25 °C for 12 h. Isolated yields were given.

We next investigated the reactions of cyclic amines **5** with imines **2** (Table 3). Unlike the acyclic amines, the cyclic amines produced enamines **6**, which were stable enough to be isolated. For example, *N*-phenyl piperidine **5a** reacted with various imines to afford the corresponding products (**6a**–**6h**) in moderate to good yields (51–83%). The substituent on the phenyl ring of various *N*-aryl piperidines markedly affected the reaction outcome. An electron-withdrawing Br atom (**6i**) increased the yield to 93%, whereas an electron-donating Me group (**6j**) lowered the yield to 68%. A seven-membered-ring amine also underwent the reaction to produce **6k** in good yield (70%).

The *N*-tosyl and *N*-*p*-methoxyphenyl groups in products **4** could be easily removed to afford the corresponding deprotected amines in high to excellent yields (Scheme 2a and 2b), which demonstrates the potential utility of this oxidative β-functionalization reaction in organic synthesis. In addition, the reaction could be used for the preparation of synthetically important β-amino aldehyde **9**[9] by hydrolysis of enamine intermediate **3** at room temperature for 5 min (Scheme 2c). Alternatively, when intermediates **3** were hydrolyzed at high temperature for 10 h, α,β-unsaturated aldehydes (**10a**–**10d**) could be obtained in good to high yields (Scheme 2d).



Scheme 2 Transformations of the products



Scheme 3 Proposed mechanism

A plausible mechanism for the reaction is outlined in Scheme 3 on the basis of the aforementioned experiments and previous reports.[10] Initially, amines **1** or **5** are oxidized by Cu(II) to generate aminiumyl radical **11** via single-electron transfer with simultaneous reduction of Cu(II) to Cu(I). A subsequent Fenton-type reaction[11] between Cu(I) and $AcOO^tBu$ forms Cu(II) and *tert*-butoxy radical ($^tBuO^·$), which captures the hydrogen atom adjacent to the nitrogen of **11**, affording iminium ion intermediate **12**.[12] Deprotonarion of **12** provides enamine intermediate **13**, which undergoes a nucleophilic addition reaction with *N*-tosylaldimine **2** to afford 1,3-diamine **3** or **6**.[13] There are at least two factors that facilitate the β-functionalization of amines. First, the excess amount of amine helps the transformation of iminium ion intermediate **12** to enamine intermediate **13**. Second, the appropriate oxidants can generate the iminium ion intermediate **12** but prevent the over oxidation of the enamine intermediate **13**.

In conclusion, we have developed a copper-catalyzed oxidative Mannich-type β-functionalization reaction of tertiary amines with *N*-tosylimines as electrophiles under mild reaction conditions. This reaction provides a new approach to 1,3-diamines and enamines from readily available acyclic and cyclic amines. This transformation converts the inert β-position of saturated amines to an active

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nucleophilic position via in situ oxidative dehydrogenation to form enamine intermediates, which are trapped by the *N*-tosylimines. Further studies focusing on expanding the reaction scope and elucidating the details of the reaction mechanism are underway in our laboratory.

We thank the National Natural Science Foundation of China (21532003, 21421062, 21625204), the National Basic Research Program of China (2012CB821600), the “111” project (B06005) of the Ministry of Education of China, and the National Program for Support of Top-notch Young Professionals for financial support.

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12 Another pathway cannot be excluded is that aminiumyl radical **11** is first deprotonated to give α-aminoalkyl radical intermediate, which then undergoes an electron transfer to give iminium ion intermediate **12**.
13 Enamine intermediate **3k** can be clearly detected by ^{1}H NMR. For experiment details, see the Supplementary Information.