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COMMUNICATION

Copper-catalyzed reductive coupling of tosylhydrazones with amines: A convenient route to α-branched amines†

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A general procedure for the reductive coupling of *N*-tosylhydrazones with amines in the presence of $Cu(acac)_2$ and Cs_2CO_3 has been developed. The protocol is very effective and chemoselective with various primary and secondary aliphatic amines, aminoalcohols as well as azole derivatives to give α-branched amines in good yields.

α-Branched amines, including aryl- and diarylmethylamine derivatives represent an important class of organic compounds regarding their various biological and pharmacological activities (Fig. 1).[1] For instance, the diarylmethylamine moiety is a common pharmacophore for multiple drug classes such as histamine H_1 receptor antagonists (cetirizine),[2] calcium channel blockers (lomerizine),[3] and aromatase inhibitors (letrozole).[4] In addition, these structural motifs are highly valuable intermediates in organic synthesis.[5] Thus, efficient syntheses of α-branched amines are of interest in medicinal chemistry and for the synthesis of screening libraries. The most common route for their preparation is undoubtedly the reductive amination of carbonyl compounds with metal hydrides.[6] Alternative procedures consist of addition of carbon nucleophiles to imines[7] or related derivatives,[8] displacement of polymer-supported benzotriazole using Grignard reagents,[9] addition of organo-lithium and -magnesium reagents to selenoamides[10] and thioformamides,[11] or acid-catalyzed reaction of diarylmethanols with phenyl carbamate followed by an extra cleavage step under alkaline media.[12] Systems related to three-component coupling of aromatic zinc reagents, secondary amines and aromatic aldehydes has also been reported.[13] Although the aforementioned transformations are suitable procedures, however, most of them require the use of stoichiometric amounts of organometallic compounds or metal hydrides, thus generating waste from reagents. Therefore, the development of alternative and general protocols for the preparation of α-branched amines, which operate under environmentally friendly conditions, is still desirable.[14]

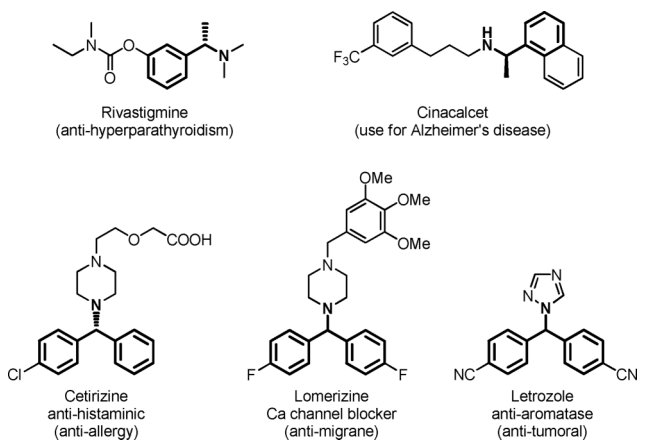

Fig. 1 α-Branched drugs with aryl- and diarylmethylamine moieties.

In recent years, *N*-tosylhydrazones have attracted extensive attention because of their various useful applications in organic synthesis.[15] In particular, they are valuable and readily available reagents in C–C,[16] C–O,[17] and C–S[18] bond-forming reactions through metal-catalyzed and metal-free processes. Although significant progress has been achieved on the aforementioned transformations, application in $C(sp^3)$–N bond-forming reactions is still a relatively unexplored process. To our knowledge, the formation of amines from tosylhydrazones had been previously reported by Cuevas-Yañez and co-workers[19] by employing $Cu(acac)_2$ as the catalyst and a large excess of tetra-*n*-butylammonium bromide. In their study, the $C(sp^3)$–N bond coupling reaction was only described with imidazole and benzimidazole derivatives, and therefore, its scope seems to be very limited. A supplementary drawback of this methodology was the need to pre-form a THF-solution of tosylhydrazone sodium salts with NaH, followed by a change of the reaction solvent to toluene, thus limited the practicality of the process.

As part of our continuing studies on the Pd-catalyzed coupling of *N*-tosylhydrazones with aryl halides,[20] combined with our interest in C–N bond forming reactions,[21] we decided to explore the ability of *N*-tosylhydrazones to participate in metal-catalyzed C–N coupling reactions with various nitrogen nucleophiles. In this study, we report our success in achieving the reductive coupling of tosylhydrazones with amines in the presence of Cs_2CO_3 as the base and a catalytic amount of easily available $Cu(acac)_2$ in dioxane. Under these simple and general reaction conditions, various arylsulfonylhydrazones **1** derived from ketones and aldehydes reacted with primary and secondary aliphatic amines as well as

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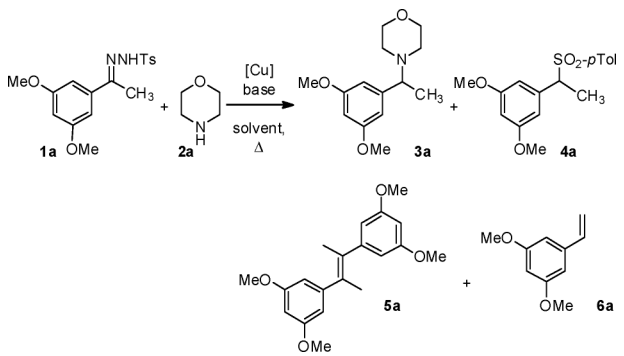
azole derivatives to give aryl- and diarylmethylamine derivatives **3** in reasonable to good yields.

In our initial study, tosylhydrazone **1a** and morpholine **2a** were chosen as model substrates for the C(sp^3)–N bond-forming process. The reaction was first investigated according to the conditions described by Cuevas-Yañez and co-workers[19] ($NaH/Cu(acac)_2/Bu_4NBr$/THF/Toluene, 85 °C for 36 h). However, this transformation was inefficient and resulted in concomitant formation of the expected amine **3a** and products derived from the evolution of the diazo compound generated from **1a**, sulfone **4a**,[18a,b] the homocoupling product **5a** and Bamford–Stevens alkene **6a**[22] (Scheme 1). After a tedious separation, **3a** was isolated in a low 17% yield. To promote the formation of **3a**, an extensive screening of various reaction parameters (base, copper source, solvent, temperature) was conducted (for more details, see ESI†). Optimal conditions for the reaction of **1a** with morpholine required the use of 10 mol% $Cu(acac)_2$ as the catalyst and Cs_2CO_3 as the base (2.2 equiv) in dioxane at 100 °C for 3 h. Under this protocol, the desired amine **3a** was isolated in a good yield (80%, Table 1, entry 1). A control experiment revealed that the copper catalyst plays an important role for this coupling reaction. Attempts to carry out the reaction in the absence of $Cu(acac)_2$ failed to provide any cross-coupled product **3a**, and by-product alkene **6a** was formed mainly. It should be noted that this reductive coupling of **1a** with morpholine is not limited to a small scale (0.25 mmol) as it could be conveniently performed on a 2 g scale (5.7 mmol; 20-fold scale up) in 72% yield.

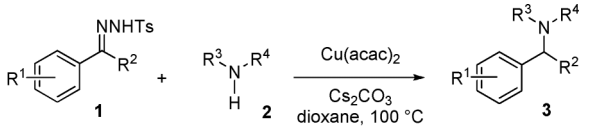


Scheme 1 Cu-catalyzed reductive coupling of **1a** with morpholine **2a**.

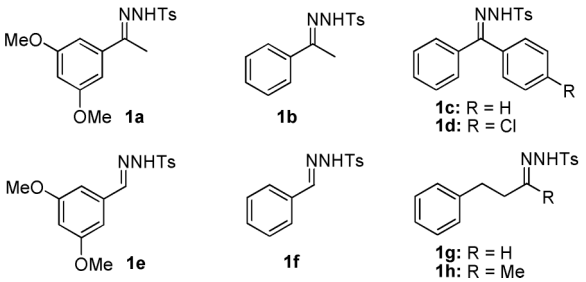
To establish the generality of this protocol, a series of hydrazones **1a–h** were coupled with various amines, including azole derivatives. As summarized in Table 1, the transformation seems to be general, as tosylhydrazones derived from ketones or aldehydes were converted into corresponding amines **3** by using the above-mentioned optimized conditions. Satisfactory to good yields were obtained with secondary aliphatic amines (entries 1–10) as well as with primary aliphatic amines (entries 11 and 12), including benzylic amines **2h** and **2i** (entries 13 and 14). Unfortunately, with aniline **2j**, none of the desired product **3o** was detected; instead alkene **6a** was formed (entry 15).

To broaden the scope of substrates, we further investigated the reaction selectivity with respect to functionalized amines. We found that primary and secondary aliphatic amino alcohols **2k–m** proved to be suitable substrates in this transformation leading exclusively to C–N bond-forming products **3p–r** in satisfactory to good yields (entries 16–18). Under our selective protocol, no

Table 1 Cu-catalyzed synthesis of α-branched amines **3** from tosylhydrazones **1**[a]



Tosylhydrazones used in this study



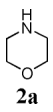
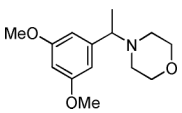
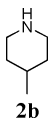
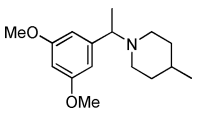
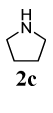
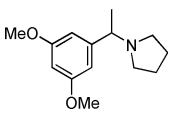
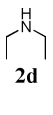
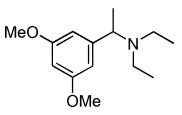
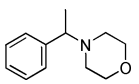
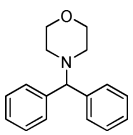
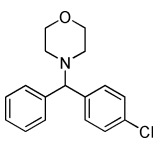
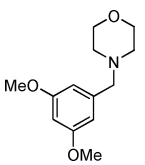
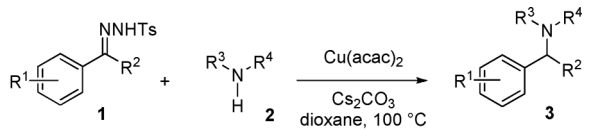
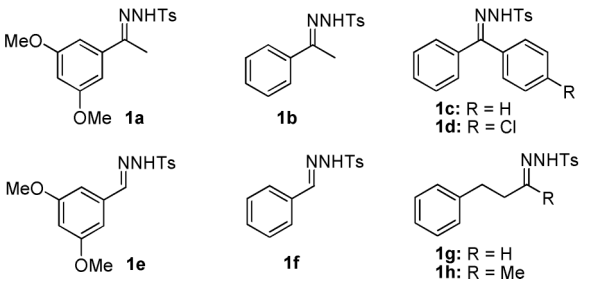
Entry	1	Amine **2**	Compound **3**		Yield (%)[b]
1	**1a**	 **2a**		**3a**	80[c,d]
2	**1a**	 **2b**		**3b**	75
3	**1a**	 **2c**		**3c**	82
4	**1a**	 **2d**		**3d**	55
5	**1b**	**2a**		**3e**	67
6	**1c**	**2a**		**3f**	84
7	**1d**	**2a**		**3g**	40[e]
8	**1e**	**2a**		**3h**	61

Table 1 *(Contd.)*



Tosylhydrazones used in this study



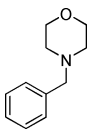
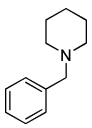
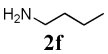
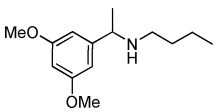
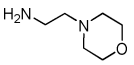
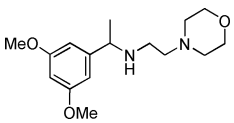
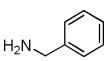
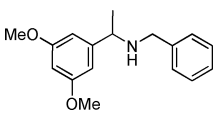
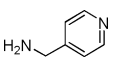
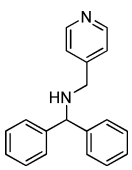
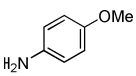
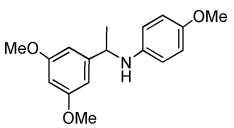
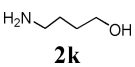
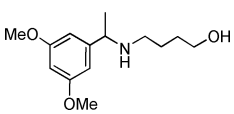
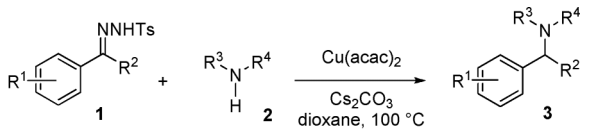
Entry	1	Amine 2	Compound 3		Yield (%)[b]
9	**1f**	**2a**		**3i**	71
10	**1f**	 **2e**		**3j**	60
11	**1a**	 **2f**		**3k**	50
12	**1a**	 **2g**		**3l**	62
13	**1a**	 **2h**		**3m**	53
14	**1c**	 **2i**		**3n**	42
15	**1a**	 **2j**		**3o**	0
16	**1a**	 **2k**		**3p**	60

Table 1 *(Contd.)*



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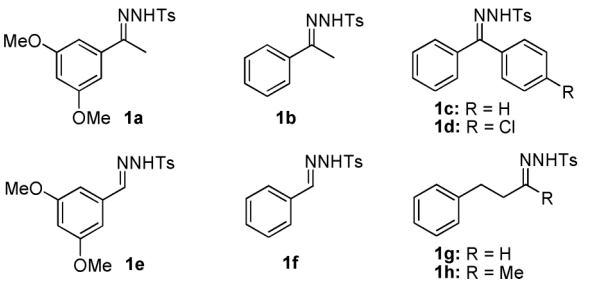
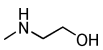
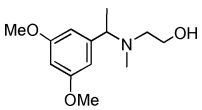
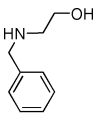
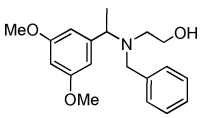
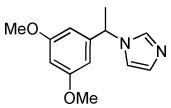
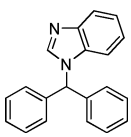
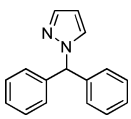
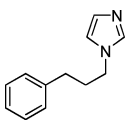
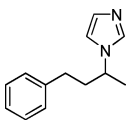


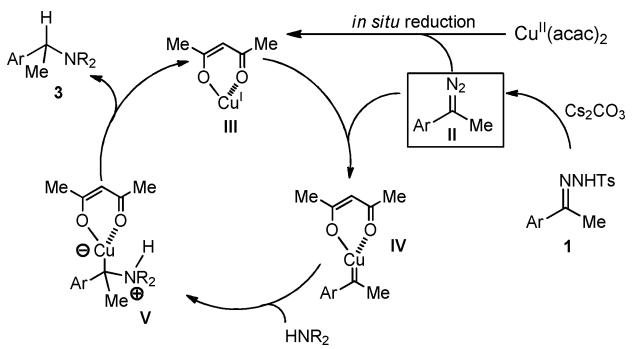
Entry	1	Amine 2	Compound 3		Yield (%)[b]
17	**1a**	 **2l**		**3q**	84
18	**1a**	 **2m**		**3r**	61
19	**1a**	 **2n**		**3s**	65
20	**1c**	 **2o**		**3t**	64
21	**1c**	 **2p**		**3u**	70
22	**1g**	**2n**		**3v**	63
23	**1h**	**2n**		**3w**	40

[a] Reactions conditions: tosylhydrazone **1** (0.25 mmol), amine **2** (2 equiv), $Cu(acac)_2$ (10 mol%), Cs_2CO_3 (2.2 equiv), dioxane (2.5 mL) in a sealed tube at 100 °C. [b] Isolated yield of **3**. [c] A 72% yield was obtained when the reaction was carried out on a 2 gram scale of tosylhydrazone **1a**. [d] Using open-vessel reaction conditions, a 71% yield was obtained within 3 h heating at 100 °C. [e] Reaction conducted in the presence of 20 mol% *N*,*N*′-dimethylethylenediamine (DMEDA); less than 10% of **3g** was obtained in the absence of DMEDA.

ether products resulting from C–O bond-forming reaction was observed, although tosylhydrazones have been recently reported to provide reductive etherification with alcohols.[17]

Finally, extending this chemistry to include azoles **2n–p** as substrates proved to be quite successful, with tosylhydrazones derived from aromatic ketones (entries 19–21) as well as aliphatic aldehydes (entry 22) and ketones (entry 23). Thus, imidazole, benzimidazole and pyrazole also underwent a C–N bond forming reaction providing coupling products **3s–w** in satisfactory to good yields.

Although there is no clear experimental evidence, we suppose that the reaction proceeds as shown in Scheme 2. Initially, *N*-tosylhydrazone **1** in basic media undergoes thermal decomposition through the Bamford–Stevens reaction to generate diazo compound **II** followed by *in situ* reduction of Cu(II) by **II** into the active catalytic Cu(I) species **III**.[23] This latter would react with **II** to give the copper(I) carbene complex[24] **IV**. Further copper carbene N–H insertion might proceed with attack of the nitrogen atom on the electrophilic carbene to generate copper species **V**, followed by hydrogen transfer[25] to produce amine **3**.



Scheme 2 Proposed mechanism for the Cu-catalyzed reductive coupling of *N*-tosylhydrazones **1** with amines.

In summary, we have demonstrated that the reductive coupling of tosylhydrazones with amines in presence of Cs_2CO_3 and a catalytic amount of $Cu(acac)_2$ represents a general, operationally simple, inexpensive and efficient approach for the synthesis of aryl- and diarylmethylamine derivatives. A variety of amines, including primary and secondary aliphatic amines as well as azole derivatives were used successfully. It is particularly noteworthy that this protocol is chemoselective allowing amino alcohols to react with hydrazones to give exclusively C–N bond forming products. Further development of this coupling methodology is under way.

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