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AgOTf catalyzed direct amination of benzyl alcohols with sulfonamides

B. Sreedhar,* P. Surendra Reddy, M. Amarnath Reddy, B. Neelima and R. Arundhathi

Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—AgOTf catalyzed direct amination of primary alcohols with sulfonamides is described. This effective catalyst requires no preactivation of the hydroxy group of alcohols and the reaction is environmentally benign with water as a by-product. Various primary alcohols on amination with sulfonamides gave the corresponding products in moderate to good yields.

Catalytic amination reactions have received significant interest. Substituted amines are of considerable importance in the pharmaceutical, agrochemical and fine chemical industries.[1,2] Numerous biologically active molecules such as alkaloids, amino acids and nucleotides contain the amine group.

Nucleophilic substitution of the hydroxy group in alcohols by amines generally requires preactivation of the alcohols by transformation into good leaving groups such as halides, carboxylates and carbonates. Palladium- and copper-catalyzed aminations of aryl halides, hydroamination and hydroaminomethylation of alkenes and alkynes are well-known methods.[3–5] However, these methods have drawbacks in terms of atom economy, since they generate large amounts of solid waste and also require a stoichiometric amount of base. Recently, ruthenium-catalyzed amination of alcohols has been reported.[6] This domino reaction sequence involves in situ dehydrogenation of the alcohol to give the corresponding carbonyl compound, which on subsequent imination followed by reduction with the initially produced hydrogen (Scheme 1) leads to the formation of the N-alkylated amine.

Direct amination of alcohols with amines would involve no stoichiometric hydroxy group activators and would be an environmentally benign method, with the formation of only water as the by-product.[7] Prim and coworkers have reported the Lewis acid catalyzed direct amination of benzhydryl alcohols.[8] Very recently, bismuth-catalyzed direct substitution of the hydroxy groups of allylic and propargylic alcohols with sulfonamides, carbamates and carboxamides was reported.[9] However, the development of more active catalysts and an environmentally attractive and simple procedure for direct amination of primary alcohols is highly desirable.

We report here an efficient method for the direct amination of benzyl alcohols with sulfonamides using silver triflate as catalyst, using no other additives (Scheme 2). The advantages of this type of amination are the ready availability of alcohols and high atom efficiency with the formation of water as the only by-product. Moreover, as opposed to typical reductive aminations, it is possible to run these reactions in the absence of additional hydrogen.

Initially, we examined the influence of different solvents using *p*-chlorobenzyl alcohol and *p*-toluenesulfonamide as model substrates in the presence of 5 mol % AgOTf as catalyst at 100 °C. The results are summarized in Table 1. It was observed that on using 1 equiv of alcohol and amine, mono- and disubstituted products (**3aa** and **4aa**) were obtained in a ratio of 3:1 using toluene as the solvent in 60% yield (Table 1, entry 1). Reaction in DMF, DMSO or 1,4-dioxane resulted in lower yields (Table 1, entries 2–4), and there was no reaction in acetonitrile (Table 1, entry 5). In nitromethane, the products were obtained in a ratio of 3:2 in 72% yield

Keywords: Direct amination; Benzyl alcohol; Sulfonamides; Silver triflate.
* Corresponding author. Tel.: +91 40 27193510; fax: +91 40 27160921; e-mail: sreedharb@iict.res.in

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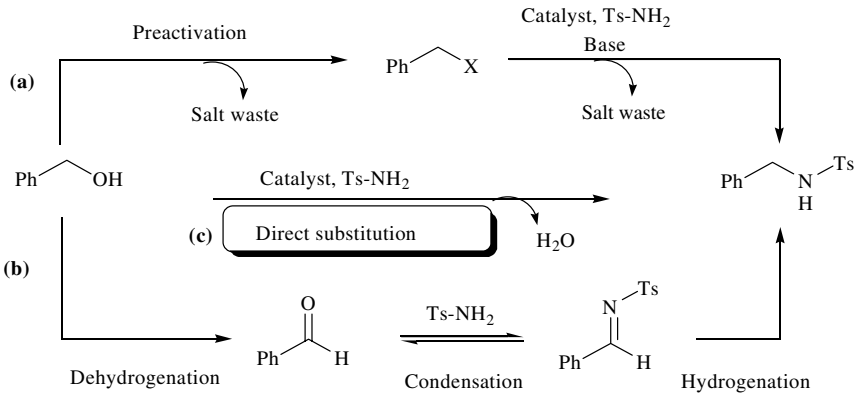
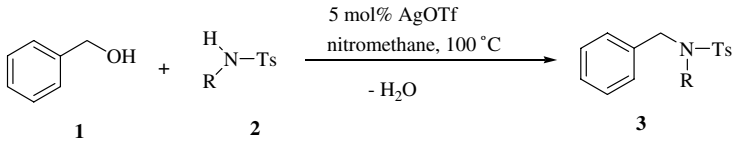


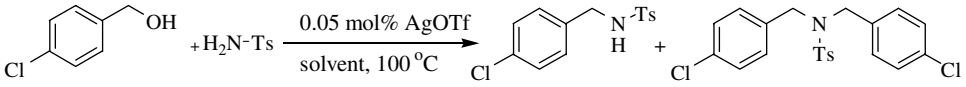
Scheme 1. Substitution of benzyl alcohol by (a) preactivation, (b) catalytic hydrogen transfer and (c) direct catalytic substitution.



1 2 3

Scheme 2.

Table 1. Optimization of the conditions for the reaction of **1a** with **2a**[a]



1a **2a** **3aa** **4aa**

Entry	**1b** (equiv)	**2a** (equiv)	Solvent	Product **3/4** ratio	Yield[b,c]
1	1	1	Toluene	3/1	60
2	1	1	DMF	1/1	15
3	1	1	DMSO	3/1	30
4	1	1	1,4-Dioxane	3/1	45
5	1	1	Acetonitrile	No reaction	
6	1	1	Nitromethane	3/2	72
7	1	1.5	Nitromethane	6/1	81
8	1	2	Nitromethane	19/1	90
9	2	1	Nitromethane	1/9	95

[a] Reaction conditions as exemplified in the typical experimental procedure.[10]
[b] Isolated yield.
[c] Products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.[11]

(Table 1, entry 6). Variation of the alcohol and amine ratio changed the yields as well as selectivities of the products formed. The reaction with 1.5 or 2 equiv of amine resulted in monosubstituted product in high yields, whereas the presence of 2 equiv of alcohol afforded the disubstituted product in good yield. Various other Lewis acids were screened for the reaction under the optimized conditions. As can be seen from Table 2, $Cu(OTf)_2$, $Sc(OTf)_3$ and $Bi(OTf)_3$ gave the corresponding products in 92, 90 and 90% yields, whereas $La(OTf)_3$ and $Ce(OTf)_4$ gave the products in only moderate yields (entries 4 and 5). $Zn(OTf)_2$ and Ag(0) afforded the desired products in poor yields (entries 6 and 7) and there was no reaction with $CuCl_2$ and $Ag(NO)_3$ (entries 8 and 9). Among the several catalysts screened, AgOTf was the catalyst of choice and, as can be seen, the nature of the counterion also plays a significant role in the amination reaction.

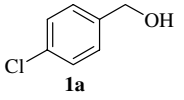
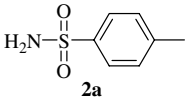
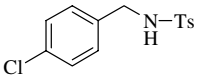
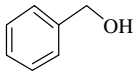
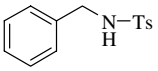
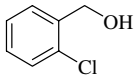
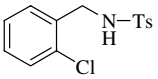
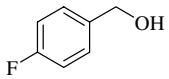
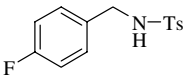
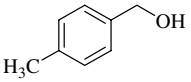
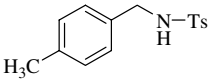
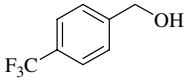
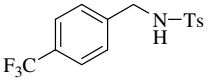
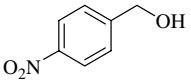
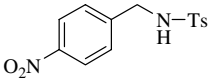
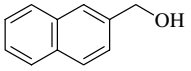
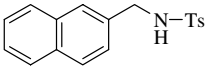
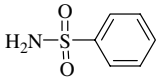
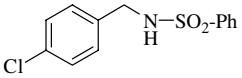
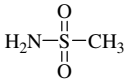
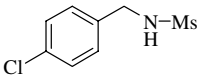
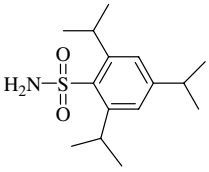
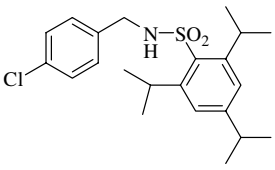
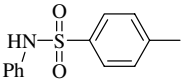
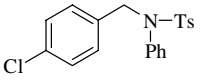
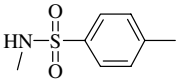
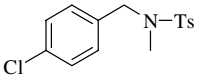
Under the optimized reaction conditions (2 equiv of amine and nitromethane as solvent), various primary

Table 2. Screening of catalysts for the reaction of **1a** with **2a**[a]

Entry	Catalyst	Product **3aa/4aa**	Yield (%)[b]
1	$Cu(OTf)_2$	9/1	92
2	$Sc(OTf)_3$	6/1	90
3	$Bi(OTf)_3$	19/1	90
4	$Ce(OTf)_4$	9/1	65
5	$La(OTf)_3$	9/1	75
6	$Zn(OTf)_2$	3/2	45
7	Ag(0) powder	3/2	30
8	$CuCl_2$	—	0
9	$AgNO_3$	—	0

[a] Reaction conditions as exemplified in the typical experimental procedure.[10]
[b] Isolated yield.

Table 3. Amination of benzyl alcohols with various sulfonamides[a]

Entry	Benzyl alcohol (**1**)	Sulfonamide (**2**)	Product[b] (**3**)	Yield[c] (%)
1	 **1a**	 **2a**		90
2		**2a**		74
3		**2a**		80
4		**2a**		85
5		**2a**		64
6		**2a**		72
7		**2a**		0
8		**2a**		45
9	**1a**			85
10	**1a**			90
11	**1a**			82
12	**1a**			64
13	**1a**			52

[a] Reaction conditions as exemplified in the typical experimental procedure.[10]
[b] Isolated yield.
[c] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.[11]

alcohols were subjected to amination with different sulfonamides and the results are given in Table 3. The reaction of electronically and structurally diverse benzyl alcohols such as *o*-chloro, *p*-fluoro, *p*-methyl and *p*-trifluoromethyl benzyl alcohols with **2a** gave the desired products in good yields (entries 1–6), whereas the presence of a strong electron-withdrawing substituent (*p*-nitrobenzyl) gave no product (entry 7). 2-Naphthyl methanol on reaction with **2a** gave the product in low yield (entry 8). Reaction of **1a** with benzenesulfonamide, methanesulfonamide and triisopropylbenzenesulfonamide gave the corresponding products in high yields

(entries 9–11) and the reaction of **1a** with N-substituted *p*-toluenesulfonamides gave the desired products in moderate yields (entries 12 and 13).

In conclusion, we have developed an efficient procedure to obtain benzylic amines from the corresponding primary alcohols and sulfonamides in the presence of silver triflate as catalyst. The methodology is straightforward and environmentally benign with the formation of water as the only by-product.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.087.

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10. *Typical experimental procedure:* A mixture of benzyl alcohol (1 mmol), sulfonamide (2.0 mmol) and silver triflate (5 mol %) in nitromethane (5 mL) was stirred at 100 °C for 8 h (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel to afford the pure product.
11. *Spectroscopic data for representative examples: N*-(4-chlorobenzyl)-4-methylbenzenesulfonamide (**3aa**): IR (KBr): ν 3053, 2924, 1596, 1344, 1185, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 4.07 (d, 2H, $J = 6.8$ Hz), 4.81 (t, 1H, $J = 6.8$ Hz), 7.11 (d, 2H, $J = 8.3$ Hz), 7.20–7.28 (m, 4H), 7.70 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.49, 46.43, 127.08, 128.66, 129.16, 129.67, 133.56, 134.85, 136.64, 143.67. LC MS (*m*/*z*): 295.9 $(M)^+$, 318.0 $(M+Na)^+$. *N*,*N*-Bis-(4-chlorobenzyl)-4-methylbenzenesulfonamide (**4aa**): IR (KBr): ν 3246, 2921, 1600, 1460, 1293, 1167, 812 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H), 4.23 (s, 4H), 6.842–7.07 (m, 8H), 7.31 (d, 2H $J = 8.0$ Hz), 7.72 (d, 2H, $J = 8.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.54, 47.26, 127.18, 127.91, 128.64, 129.70, 132.19, 133.4, 136.29, 143.54. LC MS (*m*/*z*): 420.1 $(M)^+$, 443.0 $(M+Na)^+$. Please see Supplementary data for spectral data of all other compounds.