$Yb(OTf)_3$-catalyzed One-Pot Three Component Synthesis for Tertiary Amines

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Tertiary amine functionality is found in many natural bioactive products such as alkaloids, amino acids, nucleic acids, pharmaceuticals, and agrochemicals.[1] Tertiary amines have also been used as building blocks for nitrogen-containing organic compounds and synthetic polymers.

N-Alkylation of amines with alkyl halides has been widely used.[2] However, such alkylation reactions lack chemoselectivity and result in over-alkylated products.

Transition metal complex-catalyzed alkylation of ammonia or amines with alcohols produces amines via alcohol oxidation, imine formation, and imine reduction.[3] Transition metal catalyzed reactions require high catalyst loadings and harsh reaction conditions.

The reductive amination of aldehydes and ketones with nitrogen sources such as ammonia, urea, ammonium salts, and amines in the presence of a reducing agent is a powerful tool for synthesizing structurally diverse amines.[4] Practically, direct amination of carbonyl compounds is attractive because there is no need to isolate unstable iminium intermediates. This one-pot procedure offers operational simplicity and avoids the preparation of unstable iminium intermediates. Catalytic hydrogenation and metal hydrides are the most commonly used reducing agents for iminium intermediates.[5] Catalytic hydrogenation is limited due to low tolerance of functional groups such as carbon–carbon multiple bonds, nitro, and cyanide. Borohydride derivatives such as $NaBH_4$,[6] $NaBH_3CN$,[7] $NaBH(OAc)_3$,[8] and borane[9] are also commonly used as reducing agents in the direct reductive amination of carbonyl compounds. Among these, $NaBH_3CN$ and $NaBH(OAc)_3$ show high chemoselectivity for iminium intermediates over the parent carbonyl compounds with high functional group tolerance. However, a large excess of amine is needed to prohibit the competitive reduction of parent carbonyl compounds.

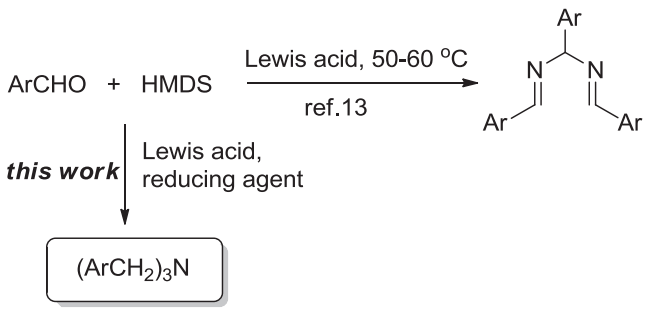
Hexamethyldisilazane (HMDS) is one of the most widely used reagents for silylation of hydroxyl groups.[10] It is cheap, stable, commercially available, and easy to handle. HMDS has also been employed in organic synthesis as a nitrogen source instead of harmful and odorous ammonia.[11]

We report a direct reductive amination protocol for the synthesis of tertiary amines employing HMDS as a nitrogen source in the presence of $Yb(OTf)_3$ at room temperature.

This one-pot reductive amination reaction offers mild, efficient reaction conditions to result in high yields of tertiary amines. Due to its high reactivity, easy handling, and inertness toward air and water, $Yb(OTf)_3$ is an efficient Lewis acid catalyst in organic transformations.[12]

Reactions of carbonyl compounds and HMDS without a reducing reagent at high temperature gave the condensation product *N*,*N*′-bis(phenylmethylidene)phenylmethanediamine (Scheme 1).[13] We hypothesized that iminium reaction intermediates might be reduced using a suitable reducing agent to produce amines.

Prevention of the competitive reduction of parent carbonyl compounds is of great importance for direct reductive amination of carbonyl compounds. The reducing agent should favor reaction with the iminium intermediate over parent carbonyl compounds. Several reducing reagents were screened to find a suitable reducing agent for the reaction (Table 1). Benzaldehyde was chosen as a model compound. The reaction of benzaldehyde (1 equiv) with HMDS (1.5 equiv) and $NaBH_3CN$ (1 equiv) in the presence of $Yb(OTf)_3$ (0.1 equiv) in CH_2Cl_2 was performed at room temperature (entry 1). This reaction afforded the expected tertiary amine **2a** in 68% yield without reduced product of the parent carbonyl compound, benzyl alcohol, **3a**. The same reaction using $NaBH(OAc)_3$ instead of $NaBH_3CN$ resulted in lower yield of **2a** (entry 2). These two borohydrides showed high chemoselectivity for the iminium intermediate over the carbonyl compound. Reactions with $NaBH_4$ or BH_3 produced the reduced product of aldehyde



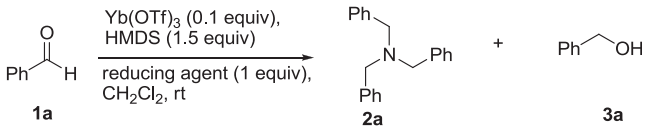
Scheme 1. Reaction of arylaldehyde with HMDS in the presence or absence of a reducing reagent.

3a with low yields of tertiary amine **2a** (entries 3 and 4). Silanes were not active reducing agents for the reaction (entries 5 and 6).[4,14]

Next, solvent effects on the reaction were examined (Table 2). Reactions in acetonitrile proceeded with a high yield of tertiary amine **2a** without reduced product **3a** (entry 1). In tetrahydrofuran (THF), the reduced product was obtained with decreased yield of tertiary amine (entry 2). A reaction in EtOAc gave low yield of the tertiary amine along with the reduced product. Reactions in CH_3Cl and toluene were very sluggish. The reactions were incomplete even for prolonged reaction times, with poor yields of the desired product.

Further optimization was performed by varying the ratio of reagents (Table 3). A reaction with 0.2 equiv of HMDS produced a large amount of the reduced product **3a** (entry 1). Reactions with 0.3 equiv of HMDS produced tertiary amine **2a** without the formation of reduced product **3a** (entries 2–5). Yields were decreased with more than 0.3 equiv of HMDS, although the reaction took place faster (entries 3–5). The aldehyde to HMDS ratio that gave the best result was 1:0.3 (entry 2). The present reaction did not require a large amount of carbonyl compounds to prevent reduction of the parent carbonyl compounds.[14a]

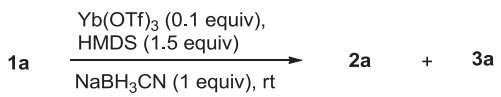
Table 1. Screening reducing agents for synthesis of tertiary amine **2a**.[a]



Entry	Reducing agent	Time (h)	**2a** (%)	**3a** (%)	**1a** (%)
1	$NaBH_3CN$	96	68	0	0
2	$NaBH(OAc)_3$	72	21	0	0
3	$NaBH_4$	24	10	51	0
4	BH_3·THF	96	0	33	30
5	$PhSiH_3$	96	0	0	100
6	Ph_2SiH_2	96	0	0	100

[a] Isolated yield.

Table 2. Solvent effects on reductive amination of **1a**.[a]

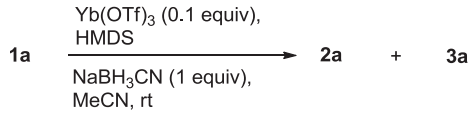


Entry	Solvent	Time (h)	**2a** (%)	**3a** (%)	**1a** (%)
1	MeCN	24	70	0	0
2	THF	72	65	10	0
3	EtOAc	96	45	14	0
4	$CHCl_3$	96	23	14	29
5	Toluene	129	22	11	36

[a] Isolated yield.

With optimal reaction conditions assessed, the scope and limitations of the present reaction were investigated. Results are summarized in Table 4. Aromatic aldehydes containing electron-withdrawing substituents efficiently proceeded to afford the corresponding tertiary amines in high yields (83–85%) regardless of the substituent position (entries 1–6). For *p*-methoxybenzaldehyde, the reaction was sluggish with a low yield of the corresponding tertiary amine (entry 7). This might be attributed to the strong electron-donating property of the methoxy group.[13b] The proposed mechanism in Scheme 2 implies that electron-rich aldehydes retard nucleophilic addition to the carbonyl group to give condensation products. With conversion of both cyclic and acyclic aliphatic aldehydes to tertiary amines, the corresponding tertiary amines were obtained in high yields (entries 8–11). 2-Methylbutanal (**1l**) gave a lower yield, which is attributed to

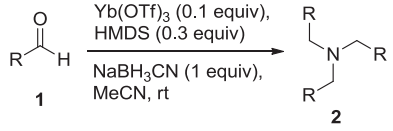
Table 3. Optimization of reaction conditions with varied ratios of reagents.[a]



Entry	HMDS (equiv)	Time (h)	**2a** (%)	**3a** (%)
1	0.2	72	64	21
2	0.3	72	83	0
3	0.5	24	73	0
4	1	24	72	0
5	2	24	69	0

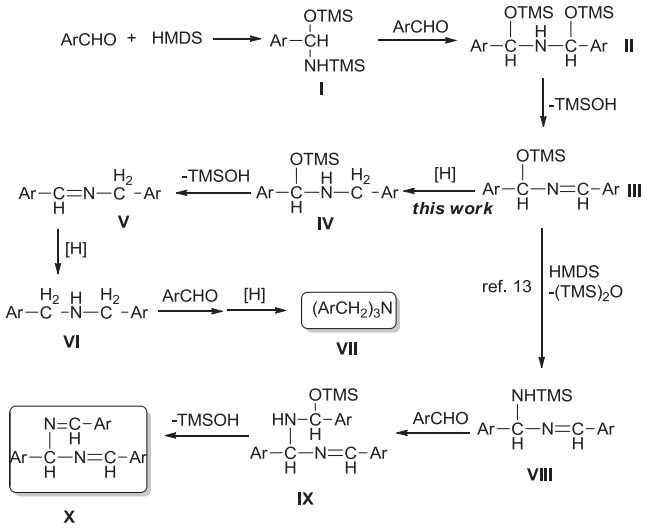
[a] Isolated yield.

Table 4. Synthesis of various tertiary amines.[a]



Entry	R	Time (h)	Product	Yield (%)
1	*p*-F-C_6H_4-, **1b**	24	**2b**	85
2	*m*-F-C_6H_4-, **1c**	24	**2c**	85
3	*o*-F-C_6H_4-, **1d**	24	**2d**	82
4	*p*-Cl-C_6H_4-, **1e**	24	**2e**	83
5	*o*-Cl-C_6H_4-, **1f**	48	**2f**	82
6	*o*-Br-C_6H_4-, **1g**	48	**2g**	83
7	*p*-MeO-C_6H_4-, **1h**	120	**2h**	32
8	$PhCH_2CH_2$-, **1i**	48	**2i**	72
9	*n*-Heptyl-, **1j**	48	**2j**	73
10	Cyclohexyl-, **1k**	48	**3b**[b]	86
11	$CH_3CH_2(CH_3)CH$-, **1l**	72	**3c**[b]	32

[a] Isolated yield.
[b] The corresponding alcohol.



Scheme 2. Plausible mechanism.

steric hindrance of the substrate (entry 11).[13a] These results imply that the reaction is very sensitive to the electronic and steric effects of the substituent. The reaction did not proceed at all with acetophenone.

By reviewing the intermediates and previous reports,[13] a plausible mechanism was proposed, as shown in Scheme 2. The $Yb(OTf)_3$-catalyzed nucleophilic addition of Si–N bonds to the carbonyl group of the aldehyde occurs twice to give the 1:1-adduct **I** and the 1:2-adduct **II**. This was followed by elimination of timetylosilanol (TMSOH) to give *N*-benzylidenephenylmethane derivative **III**. Intermediate **III** was detected in a small amount and confirmed by ^{1}H NMR when R was a *p*-fluorophenyl group. Intermediate **III** was reduced to **IV** following elimination of TMSOH to give intermediate **V**, which was detected when R was an *o*-chlorophenyl group. Reduction of intermediate **V** leads to secondary amine **VI**. Condensation of **VI** with an aldehyde and reduction of the resulting product affords the final product, tertiary amine **VII**. Without reducing agents, condensation of intermediate **III** with HMDS occurs to give intermediate **VIII**, which is condensed further with another aldehyde.[13] Elimination of TMSOH from intermediate **IX** affords the final product *N*,*N*′-bis(arylmethylidene)arylmethanediamine **X**. $Yb(OTf)_3$ promotes each addition reaction of a Si–N bond to the carbonyl group.

In summary, a one-pot method for direct reductive amination of aldehydes has been developed to synthesize tertiary amines using HMDS as a nitrogen source in the presence of $Yb(OTf)_3$. With a stoichiometric amount of HMDS, the reaction afforded the desired tertiary amines without competitive reduction of the parent carbonyl compounds. This reaction offers a convenient and efficient protocol for synthesizing aromatic and aliphatic tertiary amines under mild reaction conditions.

Experimental

Typical Procedure for One-Pot Reductive Amination. To a solution of aldehyde (0.81 mmol) and $Yb(OTf)_3$ (50 mg, 0.08 mmol) in acetonitrile (2 mL), HMDS (44 mg, 0.27 mmol) and $NaBH_3CN$ (0.8 mL, 1 M solution in THF) were added under argon. The reaction was stirred at room temperature until completion (monitored with thin-layer chromatography). After reaction completion, the volatile materials were removed in vacuum. The residue was dissolved in CH_2Cl_2, washed with water, and dried with anhydrous $MgSO_4$. After filtration and concentration, the residue was purified with silica gel column chromatography to give tertiary amines. For **2a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 6H, —CH_2—), 7.14–7.20 (m, 3H, Ar), 7.26 (t, 6H, Ar, J = 7.5 Hz), 7.38 (d, 6H, Ar, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.1, 127.0, 128.4, 128.9, 139.8; MS *m/z* (relative intensity) 287 (M^+, 9), 210 (13), 196 (10), 91 (100).

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