

Lewis Acid-Catalyzed Reductive Amination of Carbonyl Compounds with Aminohydrosilanes¹

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Abstract: The TiCl₄-catalyzed reaction of aromatic carbonyl compounds with (dialkylamino)dimethylsilanes gave tertiary amines in moderate to high yields. The reductive amination of aliphatic aldehydes was effectively catalyzed by ZnI₂. Methyl *N*-(dimethylsilyl)carbamate as well could be used for reductive amination of carbonyl compounds in the presence of Ph₃CClO₄.

Key words: Lewis acids, reductive aminations, amines, aldehydes, bifunctional silicon reagents

Reductive amination of aldehydes and ketones, that is reduction of in situ generated imines and iminium salts of ammonia, primary and secondary amines, provides a most useful and important tool for the synthesis of amines.² Some reducing agents are known to be available for this tandem reaction.³ Particularly, the utility of sodium cyanoborohydride (NaBH₃CN) is well recognized.^{2,4} The reductive amination with NaBH₃CN is noted for its versatility and compatibility; however, the reducing agent is highly toxic and produces toxic by-products. In addition, the reaction requires up to a fivefold excess of the amine. Although sodium triacetoxyborohydride (NaBH(OAc)₃) has been developed as a non-toxic substitute for NaBH₃CN,^{3a} there is still a need for a new safe and efficient method for direct reductive amination with a wide range of applicability.

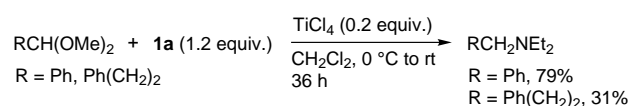
We have recently reported that the fluoride ion-catalyzed reaction of aldehydes with dimethylsilyl (SiHMe₂) enolates gives 1,3-diols with high diastereoselectivity.⁵ In this tandem process, the enolates function as carbon and hydride nucleophiles. This work induced us to develop a new tandem reaction using a bifunctional silicon reagent.^{6,7} Our interest was focused on the reactivity of aminohydrosilanes toward reductive amination because aminosilanes work as nucleophilic amination agents,⁸ and hydrosilanes can reduce imines or iminium salts to amines.⁹ We herein describe that, in the presence of a Lewis acid catalyst, certain aminodimethylsilanes (R¹R²NSiHMe₂) are valuable for direct reductive amination of aldehydes and ketones.^{10,11}

Initially, the reaction of benzaldehyde with (diethylamino)dimethylsilane (**1a**) was selected to find an effective catalyst for reductive amination.¹² The use of Bu₄NF, a

fluoride ion source, resulted in the exclusive formation of benzyl alcohol, while Lewis acids promoted the reductive amination to give benzyldiethylamine (**2aa**). In particular, TiCl₄ showed the highest catalytic activity among the Lewis acids examined.¹³ The TiCl₄ (0.20 equiv)-catalyzed reaction with a small excess of **1a** (1.2 equiv) in CH₂Cl₂ achieved 90% isolated yield of **2aa** (entry 1 in Table 1).^{14,15} This reductive amination was applicable to various aromatic aldehydes including furfural (entries 2–9). Introduction of an electron-donating group on the benzene ring did not affect the reaction efficiency. The present reaction was compatible with polar functional groups such as methoxy-carbonyl, nitro, and cyano groups. Aromatic ketones also underwent the TiCl₄-catalyzed reductive amination although the yields of amines were not so high (entries 10–12).

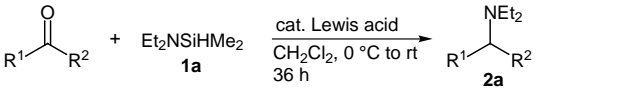
The TiCl₄-catalyzed reaction of 3-phenylpropanal with **1a** gave a complex mixture including the desired product (<27%). Screening of Lewis acid catalysts disclosed that ZnI₂ was an effective catalyst for the reductive amination of aliphatic aldehydes (entries 13–14 in Table 1). In the amination of 4-phenyl-2-butanone, however, TiCl₄ was slightly more effective than ZnI₂ (entry 15).

Unlike the conventional method using NaBH₃CN, the present method enabled the direct conversion of aldehyde dimethyl acetals into the corresponding tertiary amines (Scheme 1).



Scheme 1

As shown in Table 2, the reductive amination with other aminohydrosilanes was also examined. (Dimethylamino)-dimethylsilane (**1b**) showed slightly lower reactivity toward aromatic aldehydes than **1a**. An increased amount of TiCl₄ or prolonged reaction time improved the reaction efficiency (entries 1–3). Aminohydro-silanes **1c** and **1d**, derived from pyrrolidine and morpholine, were also available for the Lewis acid-catalyzed reductive amination (entries 7–10). The behavior of **1c** and **1d** toward aromatic and aliphatic aldehydes was similar to that of **1a**. In contrast, diisopropylamino- and dibenzylamino-dimethylsilane were quite insensitive to benzaldehyde.

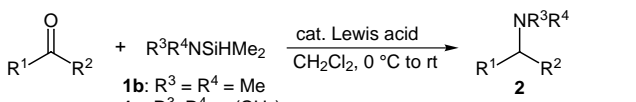
Table 1 Reductive Amination with Aminohydrosilane **1a**^a


Entry	Substrate		Cat. (equiv)	Yield/%
	R ¹	R ²		
1	Ph	H	TiCl ₄ (0.2)	90
2	4-MeC ₆ H ₄	H	TiCl ₄ (0.2)	91
3	4-MeOC ₆ H ₄	H	TiCl ₄ (0.2)	92
4	4-PhC ₆ H ₄	H	TiCl ₄ (0.2)	86
5	4-ClC ₆ H ₄	H	TiCl ₄ (0.2)	78
6	4-MeO ₂ CC ₆ H ₄	H	TiCl ₄ (0.2)	84
7	4-O ₂ NC ₆ H ₄	H	TiCl ₄ (0.2)	85
8	4-NCC ₆ H ₄	H	TiCl ₄ (0.2)	84
9	2-Furyl	H	TiCl ₄ (0.2)	65
10	Ph	Me	TiCl ₄ (0.2)	65
11	Ph	Et	TiCl ₄ (0.2, 0.4)	39, 76
12	Ph	Ph	TiCl ₄ (0.2)	46
13	Ph(CH ₂) ₂	H	ZnI ₂ (0.1)	72
14	<i>c</i> -C ₆ H ₁₁	H	ZnI ₂ (0.1)	81
15	Ph(CH ₂) ₂	Me	TiCl ₄ (0.2)	56, 46 ^b

^a For general procedure, see ref 14.^b With 0.1 equiv of ZnI₂.

We further attempted the reductive amination using methyl *N*-(dimethylsilyl)carbamate (**1e**). The TiCl₄- and ZnI₂-catalyzed reactions of benzaldehyde with **1e** resulted in no desired product; however, Ph₃CClO₄ was found to be an effective catalyst for this reductive amination. The Ph₃CClO₄ (0.05 equiv)-catalyzed reaction was completed in 1 h to give methyl *N*-benzylcarbamate in 94% yield (entry 11). Under the same conditions, the reductive amination of acetophenone was not efficient due to unidentified side reactions (entry 12). In the case with 3-phenylpropanal, its cyclotrimerization forming a trioxane caused a low yield of the amination product. This side reaction could be retarded by slow addition of the aldehyde, which brought about high reaction efficiency (entry 13). 4-Phenyl-2-butanone as well as benzaldehyde showed high reactivity toward the reductive amination with **1e** (entry 14).

Judging from the nucleophilic property of amines, a plausible mechanism of the present reaction includes nucleophilic attack of the amino group of an aminohydrosilane to a carbonyl compound activated by a Lewis acid (path a in Scheme 2).¹⁶ The subsequent hydride reduction of the *O,N*-acetal intermediate **3** gives the corresponding amine **2**. Another possible mechanism is that the substrate under-

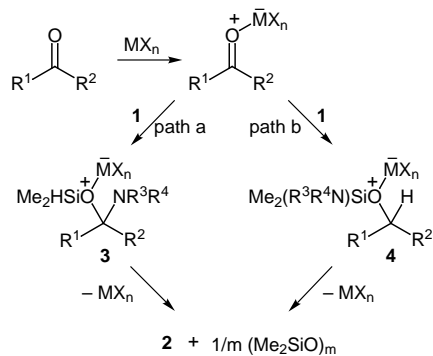
Table 2 Reductive Amination with Aminohydrosilanes **1b–e**^a


Entry	Substrate		Silane	Cat. (equiv)	Time /h	Yield/%
	R ¹	R ²				
1	Ph	H	1b	TiCl ₄ (0.2, 0.4)	36	64, 73
2	4-MeC ₆ H ₄	H	1b	TiCl ₄ (0.2, 0.4)	36	67, 85
3	4-O ₂ NC ₆ H ₄	H	1b	TiCl ₄ (0.2)	48	94
4	Ph	Me	1b	TiCl ₄ (0.4)	36	87
5	Ph(CH ₂) ₂	H	1b	ZnI ₂ (0.1)	36	72
6	Ph(CH ₂) ₂	Me	1b	TiCl ₄ (0.2)	48	67
7	Ph	H	1c	TiCl ₄ (0.3)	36	77
8	Ph(CH ₂) ₂	H	1c	ZnI ₂ (0.1)	36	71
9	Ph	H	1d	TiCl ₄ (0.2)	36	83
10	Ph(CH ₂) ₂	H	1d	ZnI ₂ (0.1)	36	66
11	Ph	H	1e	Ph ₃ CClO ₄ (0.05)	1	94
12	Ph	Me	1e	Ph ₃ CClO ₄ (0.05)	1	53
13	Ph(CH ₂) ₂	H	1e	Ph ₃ CClO ₄ (0.05)	3, 1 ^b	40, 88 ^b
14	Ph(CH ₂) ₂	Me	1e	Ph ₃ CClO ₄ (0.05)	1	86

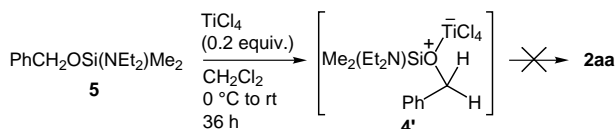
^a For the reaction conditions, see ref 14.^b 3-Phenylpropanal was added over 30 min at 0 °C. The resultant mixture was stirred for 10 min at 0 °C and for 20 min at room temperature.

goes hydride reduction in the initial step, then the resultant silyl ether **4** is converted into **2** by nucleophilic substitution of the amino group (path b in Scheme 2). To examine this possibility, alkoxyaminosilane **5** was prepared from dimethyldichlorosilane and subjected to a catalytic amount of TiCl₄ (Scheme 3). As a result, the expected amine **2aa** was not obtained. Accordingly, path b is unlikely in the present reductive amination.

In summary, we have demonstrated that aminohydrosilanes **1** work as bifunctional silicon reagents to enable the Lewis acid-catalyzed reductive amination of carbonyl compounds. The present method is superior to the conventional method using NaBH₃CN in terms of less toxicity and the amount of the reagents used, applicability to acetals, and introduction of a less nucleophilic *N*-protected amino group. We are now studying Lewis acid-catalyzed reductive etheration with alkoxyhydrosilanes. The results will be published in due course.



Scheme 2



Scheme 3

Acknowledgement

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- (10) Recently, a few research groups have developed the direct reductive amination with hydrosilanes: (a) Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745. (b) Chen, B.-C.; Sundeen, J. E.; Guo, P.; Bednarz, M. S.; Zhao, R. *Tetrahedron Lett.* **2001**, *42*, 1245. (c) Dubé, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295; in the latter two works, a stoichiometric amount of a promoter was used unlike the present method.
- (11) Stepwise (indirect) reductive amination with hydrosilanes including the preformation of the imine intermediates has been also reported, see ref 9c and: Chandrasekhar, S.; Reddy, C. R.; Ahmed, M. *Synlett.* **2000**, 1655.
- (12) (Diethylamino)dimethylsilane (**1a**) can be prepared from chlorodimethylsilane and 2 equiv of diethylamine in 81% yield.
- (13) The reactions using several Lewis acids (CH_2Cl_2 , r.t., 36 h) gave the following results. Lewis acid (equiv), yield of **2aa**: TiCl_4 (0.1), 75%; TiCl_4 (0.2), 84%; SnCl_4 (0.2), 53%; TMSOTf (0.2), 40%; InCl_3 (0.1), 70%; BiCl_3 (0.1), 20%; $\text{Yb}(\text{OTf})_3$ (0.1), 26%.
- (14) General procedure for the TiCl_4 -catalyzed reductive amination: To a solution of **1** (1.20 mmol) and a carbonyl compound (1.00 mmol) in CH_2Cl_2 (1.0 mL) at 0°C was added TiCl_4 (1.0 M in CH_2Cl_2 , 0.20 mL, 0.20 mmol). The mixture was stirred for 10 min and warmed to r.t. After 36 h, the reaction mixture was treated with 0.1 M HCl (20 mL) for 10 min and washed with *t*-BuOMe (3×10 mL). The aqueous layer obtained was alkalinized with 1.0 M aqueous NaOH (ca 5 mL) and extracted with *t*-BuOMe (3×10 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The product obtained was proved to be almost pure by ^1H NMR analysis. When ZnI_2 or Ph_3CClO_4 was used as a catalyst, **1** and a carbonyl compound were added to a suspension of ZnI_2 or Ph_3CClO_4 in CH_2Cl_2 .
- (15) We also found that the TiCl_4 (0.2 equiv)-catalyzed reaction among $\text{Et}_2\text{NSiMe}_3$, PhMe_2SiH , and benzaldehyde (1.2:1.2:1) gave **2aa** in 66% yield.
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