The reductive amination of aldehydes and ketones by catalytic use of dibutylchlorotin hydride complex†

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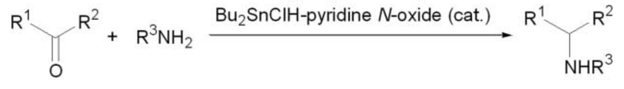
The reductive amination of aldehydes or ketones using Ph_2SiH_2 or $PhSiH_3$ has been effectively promoted by the direct use of Bu_2SnClH–pyridine *N*-oxide as a catalyst; this method has advantages in terms of its mild conditions and wide application to various carbonyls and amines, including aliphatic examples.

The reductive amination of aldehydes and ketones is one of the most useful routes to secondary amines, in which the three components of carbonyl, amine and reductant are easily combined in one pot.[1] The advantage of this reaction is that there is no need to isolate intermediate imines, in particular, in cases where combinations of aromatic amines and aliphatic carbonyls would give expectedly unstable imines. The choice of reductant is very critical because the undesirable reduction of starting carbonyls must be suppressed. A number of reducing agents have been developed, sodium cyanoborohydride ($NaBH_3CN$),[2] sodium triacetoxyborohydride ($NaBH(OAc)_3$)[3] and borane–pyridine (BH_3–Py)[4] being the most commonly used. However, these reagents have serious problems, requiring excess amounts of starting amines and acidic conditions. We have already overcome these problems by developing the Bu_2SnClH system, which effects the reductive amination with equimolar amounts of amines under mild and neutral conditions.[5,6] However, the use of aliphatic amines caused the decomposition of the tin hydride. In addition, an equimolar amount of environmentally hazardous tin reagent is necessary, and so a catalytic application is desirable. Apodaca and Xiao demonstrated reductive amination with phenylsilane ($PhSiH_3$) in the presence of a catalytic amount of Bu_2SnCl_2.[7] More recently, Kangasmetsa and Johnson have improved the same system by using microwave-assisted heating.[8] They suggest that Bu_2SnClH, generated *in situ*, is an active species. However, discussions on the effects of Bu_2SnCl_2 and by-product water are unclear. Since Bu_2SnClH has been already noted to be an elegant reagent for reductive amination and easily available by redistribution between Bu_2SnCl_2 and Bu_2SnH_2, without forming any acidic by-products,[5] we have re-investigated the reaction by the direct use of Bu_2SnClH as the catalyst. Consequently, we found that the addition of a small amount of pyridine *N*-oxide achieved a catalyst system that is applicable to a wide range of carbonyls and amines, including aliphatic examples, under mild conditions (Scheme 1).

Initially, we examined hydride sources and additives in reductive aminations using a catalytic amount of Bu_2SnClH, as shown in Table 1. Triethylsilane (Et_3SiH) did not give the desired amine **3a** in satisfactory yield (Table 1, entry 1). In contrast, diphenylsilane (Ph_2SiH_2) completed the reaction within 15 min to afford **3a** in 89% yield (Table 1, entry 2). The yields of **3a** and **3b** were increased to quantitative by the addition of only 2 mol% of HMPA (Table 1, entries 3 and 4). A similar effect to HMPA has been observed in the equimolar reaction.[5] However, because the use of hazardous HMPA should be avoided, we investigated the affect of other additives, such as DMPU, DMF and phosphine oxides. While these additives did not give satisfactory results, pyridine *N*-oxide worked well, giving amine **3b** in 94% yield when combined with $PhSiH_3$ instead of Ph_2SiH_2 (Table 1, entry 6). Moreover, an interesting effect was observed in the reaction with acetophenone (**1b**). Although the system of Bu_2SnClH–HMPA and $PhSiH_3$ only promoted the reaction of **1b** with 58% yield (Table 1, entry 8), the addition of pyridine *N*-oxide gave a higher yield of 89% (Table 1, entry 9).

Next, we applied the optimized system, using 2 mol% of Bu_2SnClH–pyridine *N*-oxide, to the reaction between aliphatic ketones or aldehydes with amines (Table 2). In all entries, sub-stoichiometric quantities of $PhSiH_3$ performed the reactions, in contrast to the microwave-assisted method that required two equivalents of the silane to consume all the imine formed.[8] This result may indicate a different mechanism to the reduction. The reductive amination of aliphatic ketones or aliphatic aldehydes with aromatic amines readily took place to give high yields (Table 2, entries 1–7). In particular, the reaction of the primary aliphatic aldehyde **1g** with **2a** (Table 2, entry 7) demonstrates the advantage of this catalyst system over the equimolar one because only 30% yield of **3j** was given, even with the stoichiometric use of Bu_2SnClH–HMPA. A stronger base, aliphatic amine **2c**, could be also applied without decomposition of the tin hydride and $PhSiH_3$ (Table 2, entry 8), while facile decomposition of tin hydrides by the amine has been reported.[5] Even combinations of aliphatic ketone and aliphatic amines were allowed, giving **3k** and **3l** (Table 2, entries 8 and 9).



1 **2** **3**

Scheme 1

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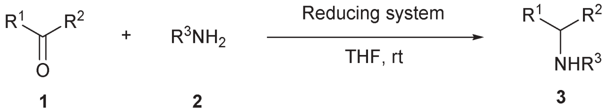
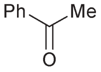
† Electronic supplementary information (ESI) available: Experimental details, characterisation data and NMR spectra. See DOI: 10.1039/b610614e

Table 1 Reductive amination of carbonyls **1** with amines **2** by various reducing systems[a]

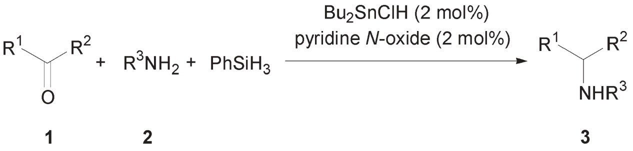


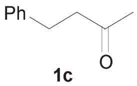
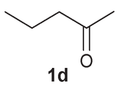
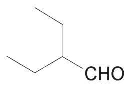
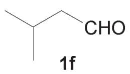
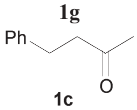
Entry	Carbonyl **1**	Amine **2**	Reducing system	Time/min	Product **3**	Yield (%)
1	PhCHO **1a**	$PhNH_2$ **2a**	Bu_2SnClH (10 mol%)[b]/Et_3SiH	120	**3a**	9
2			Bu_2SnClH (2 mol%)/Ph_2SiH_2	15		89
3			Bu_2SnClH–HMPA (2 mol%)/Ph_2SiH_2	15		98
4	PhCHO **1a**	*p*-$FC_6H_4NH_2$ **2b**	Bu_2SnClH–HMPA (2 mol%)/Ph_2SiH_2	15	**3b**	99
5			Bu_2SnClH–pyridine *N*-oxide (2 mol%)/Ph_2SiH_2	15		52
6			Bu_2SnClH–pyridine *N*-oxide (2 mol%)/$PhSiH_3$	15		94
7	 **1b**	$PhNH_2$ **2a**	Bu_2SnClH–HMPA (10 mol%)[b]/Ph_2SiH_2	1200	**3c**	24
8			Bu_2SnClH–HMPA (10 mol%)[b]/$PhSiH_3$	1200		58
9			Bu_2SnClH–pyridine *N*-oxide (10 mol%)[b]/$PhSiH_3$	1200		89
10			Bu_2SnClH–pyridine *N*-oxide (2 mol%)/$PhSiH_3$	1800		68

[a] Bu_2SnClH: 0.05 mmol, additive: 0.05 mmol, $PhSiH_3$: 2.7 mmol, **1**: 2.5 mmol, **2**: 2.5 mmol, THF: 2.5 mL. [b] Bu_2SnClH: 0.2 mmol, additive: 0.2 mmol, $PhSiH_3$: 2.2 mmol, **1**: 2 mmol, **2**: 2 mmol, THF: 2 mL.

Apodaca's system[7] was not applied to aliphatic aldehydes or aliphatic primary amines, perhaps because of the decomposition of $PhSiH_3$ by amine and water, and microwave-assisted method[8] is not applicable to ketones. In contrast, Table 2 shows that various substrates, including aliphatic ketones, aldehydes and amines, could be employed without decomposition of the tin hydride and $PhSiH_3$. Unfortunately, combinations of aliphatic aldehydes and aliphatic amines did not provide the desired amines. This is the limitation of our method at this stage.

Table 2 Reductive amination of various carbonyls **1** with amines **2**[a]

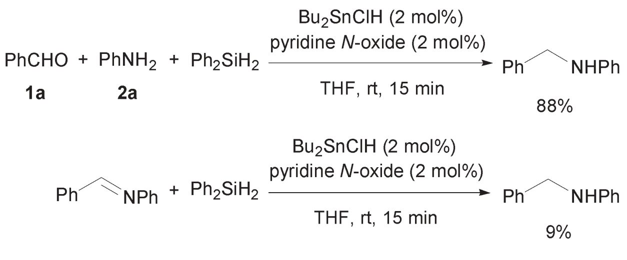


Entry	Carbonyl **1**	Amine	Time/h	Product **3**	Yield (%)
1	 **1c**	$PhNH_2$ **2a**	15	**3d**	89
2	 **1d**	$PhNH_2$ **2a**	20	**3e**	94
3	 **1e**	$PhNH_2$ **2a**	20	**3f**	99
4		*p*-$FC_6H_4NH_2$ **2b**	25	**3g**	94
5	 **1f**	$PhNH_2$ **2a**	25	**3h**	93
6		*p*-$FC_6H_4NH_2$ **2b**	25	**3i**	98
7	^{n}BuCHO **1g**	$PhNH_2$ **2a**	20	**3j**	48 (70)[b,c]
8[d]	 **1c**	$^nPrNH_2$ **2c**	4	**3k**	89
9		$PhCH_2NH_2$ **2d**	10	**3l**	81

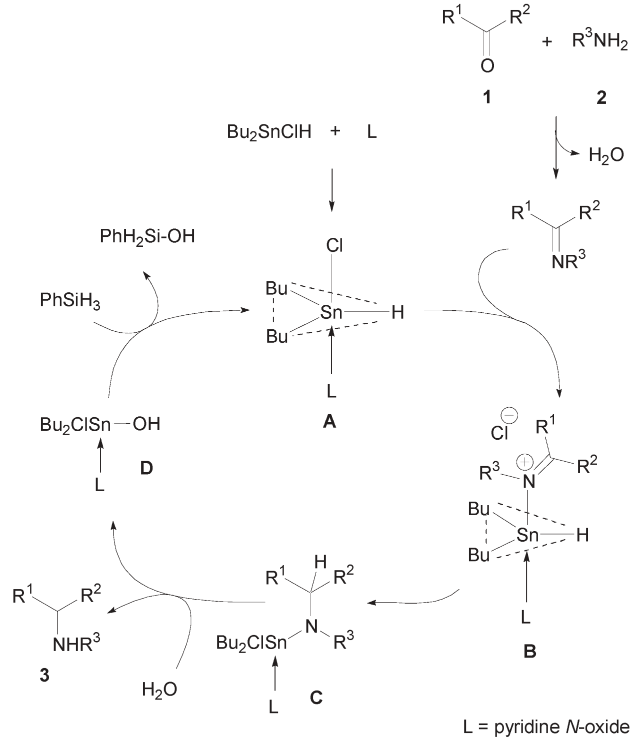
[a] Bu_2SnClH–pyridine *N*-oxide: 0.05 mmol, $PhSiH_3$: 2.7 mmol, **1**: 2.5 mmol, **2**: 2.5 mmol, THF: 2.5 mL. [b] HMPA was used instead of pyridine *N*-oxide. [c] Bu_2SnClH: 0.2 mmol, HMPA: 0.2 mmol, $PhSiH_3$: 2.2 mmol, **1**: 2 mmol, **2**: 2 mmol, THF: 2 mL. [d] The reaction was performed at 60 °C.

As shown in Scheme 2, it is noteworthy that the reduction of an isolated imine hardly took place, while the direct reductive amination of the **1a** with **2a** was smoothly promoted. The presence of water, generated by the formation of the imine, is likely to be crucial in this regard.[9]

A plausible catalytic cycle is shown in Scheme 3. Initially, a pentacoordinated tin hydride, Bu_2SnClH–L (**A**), is generated by simple mixing of Bu_2SnClH and L (L = pyridine *N*-oxide), which has a reactive Sn–Cl bond in an apical position of the trigonal bipyramidal structure.[5] Next, the formation of iminium salt **B** allows successive intramolecular hydride attack to furnish the tin amide **C**. The fact that no reduction of the isolated imine to amine **3** takes place under anhydrous conditions strongly suggests that the silyl hydride hardly reacts with the Sn–N bond of **C**.[10] Hence, the tin amide **C** is protonated by H_2O, generated during the imine formation step, furnishing the desired amine **3** and generating tin hydroxide **D**. In the final step, **D** reacts with $PhSiH_3$ to regenerate the tin catalyst **A**. Rapid completion of the catalytic cycle would suppress decomposition of the tin hydride, even in the presence of basic aliphatic amines. Thus, the catalyst tin hydride immediately reacts with imine prior to interaction with the starting amine. In addition, the low concentration of hydride **A** seems to disturb the interaction.



Scheme 2



Scheme 3 A plausible catalytic cycle.

In summary, silyl hydrides such as Ph_2SiH_2 and $PhSiH_3$ promoted reductive amination under very mild conditions in the presence of a catalytic amount of Bu_2SnClH complex. These reducing systems were superior to conventional reducing agents in terms of their wide applicability to substrates.

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