Dibutyltin Chloride Hydride Complex as a Novel Reductant for Chemoselective Reductive Amination

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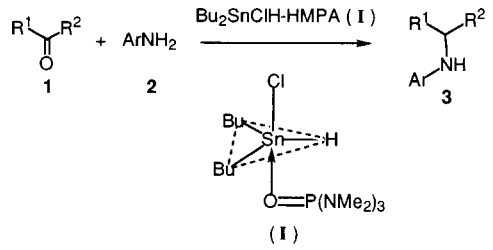
Abstract: Imine-selective reducing agent Bu_2SnClH-HMPA (**I**) performed effective reductive amination of carbonyl compounds. Various functionalized amines could be prepared in a one-pot procedure. Noteworthy is that highly chemoselective reactions were achieved with the co-existence of other functionalities such as halogen, carbon-carbon double bond and hydroxyl groups.

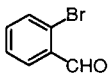
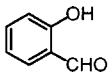
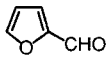
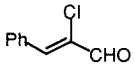
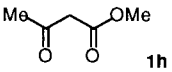
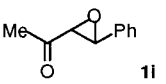
Reductive amination of aldehydes is one of the most convenient routes to various secondary amines, in which three components of carbonyls, amines and reductants are treated in one portion.[1] By this procedure, a wide range of functionalized amines can be prepared because intermediate imines, in particular unstable ones, do not have to be isolated. The choice of the reductant is very critical since the undesirable reduction of the carbonyls must be depressed to form intermediate imines. Sodium cyanoborohydride ($NaBH_3CN$) has been used because of its wide applicability.[2] However, there are some drawbacks because of the requirement of excess amounts of amines and inapplication to weak bases such as aromatic amines. To solve these problems, modified borohydrides have been developed.[3] However, alternative metal hydride reagents have scarcely been focused so far. We have provided a set of organotin hydrides by the introduction of a halogen substituent or a ligand on the tin atom to achieve highly chemoselective reductions of multifunctionalized substrates.[4] The five-coordinated tin hydride, Bu_2SnClH-HMPA (**I**),[5] easily formed *in situ* from Bu_2SnClH[6] and HMPA, has been revealed to reduce imines even in the presence of carbonyls.[7] This high imine-selectivity indicates that the reagent **I** would be a good candidate for the reductive amination. We present here the first use of tin hydrides for reductive amination of aldehydes and ketones under mild and neutral conditions (Scheme 1). The characteristic features are as follows. 1) Effective reactions proceeded in particular for the case using aromatic amines as starting substrates. 2) Stoichiometric amounts of substrates and tin reductant were adequate. 3) Co-existence of other functionalities was allowed in the starting carbonyls **1** and amines **2**.



Scheme 1

Table 1 summarizes the reductive aminations of various carbonyl compounds by using Bu_2SnClH-HMPA (**I**). The three reagents, the tin hydride **I**, carbonyl compound **1** and aniline **2a** were successively added to THF solvent. Initially, we examined the reductive aminations of benzaldehyde **1a**. The reaction with aniline **2a** proceeded smoothly to give the corresponding secondary amines, **3aa** in good yield (entry 1).[8] Benzyl alcohol derived from the reduction of starting material **1a** was not produced under these conditions. Instead of **2a**, the use of more weakly basic *p*-chloroaniline **2b** also gave the corresponding secondary amine **3ab** in good yield (entry 2). Next, other aromatic aldehydes were examined. In entry 3, the reducing system (**I**) did not affect the bromine functionality at all, which is generally reducible by trialkyltin hydrides.[9] In the reaction of **1c**, the hydroxy group on the aromatic ring did not affect the reaction at all (entry 4). The reaction using 2-furylaldehyde **1d** also afforded the amine **3d** (entry 5). In the case of aliphatic aldehyde **1e**, the reactions proceeded smoothly to give *N*-alkyl arylamines **3ea** and **3eb** (entries 6 and 7). Unsaturated aldehyde **1f** was converted to *N*-allyl phenylamines **3f** by the regioselective 1,2-addition to the intermediate unsaturated imine (entry 8). Ketones were also reactive to give branched amines. Cyclic ketone **1g** gave **3g** (entry 9). In the case of functionalized ketones such as **1h** and **1i**, effective amination of the carbonyl group took place to give **3h** and **3i**, where undesired side reaction such as ring cleavage of epoxide did not proceed at all (entries 10 and 11).

Table 1. Reductive Amination of Carbonyls **1** with Aniline **2a**[a]

entry	Carbonyls (1)		Conditions	Product (**3**)	Yield (%)
1	PhCHO	**1a**	0 °C, 1 h	**3aa**	81
2[b]		**1a**	0 °C, 1 h	**3ab**	99
3		**1b**	0 °C, 1 h	**3b**	87
4		**1c**	0 °C, 1 h	**3c**	99
5		**1d**	0 °C, 1 h	**3d**	78
6	BnCHO	**1e**	0 °C, 1 h	**3ea**	70
7[b]		**1e**	0 °C, 1 h	**3eb**	99
8		**1f**	0 °C, 1 h	**3f**	83
9		**1g**	0 °C, 1 h	**3g**	99
10		**1h**	0 °C-> rt, 22 h	**3h**	73
11		**1i**	0 °C, 4 h	**3i**	99[c]

[a]Bu_2SnClH 1 mmol, HMPA 1 mmol, Aldehyde **1** 1 mmol, Aniline **2a** 1 mmol, THF 1 mL. [b]Instead of aniline, *p*-chloroaniline **2b** was used.
[c]*Erythro*/*threo*=69/31

In this way, compared with $NaBH_3CN$, tin reagent **I** was especially useful in the reaction using weakly basic aromatic amines. For the formation of imine intermediates, promoters such as acids and dehydrating agents[10] were not necessary. Probably, tin reagent **I** not only acted as a reductant of imino groups but also accelerated the formation of imines.[11] In all cases, highly chemoselective reactions were achieved even with the co-existence of aryl halides, vinyl halides, hydroxyl group, double bonds and epoxide functionalities. Functionalized amines were prepared effectively in a one-pot procedure. We are now further investigating the development of the reductant to apply to a wide range of corbonyl compounds and amines.

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(8) Representative procedure is as follows. To the solution of Bu_2SnH_2 (0.5 mmol) and Bu_2SnCl_2 (0.5 mmol) in 1 mL of THF was added HMPA (1 mmol). The mixture was stirred at room temperature for 10 min. To the solution were added **1a** (1 mmol) and aniline **2a** (1 mmol), and the mixture was stirred at 0°C until the Sn-H absorption (1862 cm^{-1}) disappeared in the IR spectrum. After quenching with MeOH (5 mL), volatiles were removed under reduced pressure. The residue was subjected to column chromatography (Fuji-gel FL100DX) eluting with hexane-EtOAc (9:1) to give pure product **3aa**.

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