Chemoselective Reductions of Imino Groups by Dibutyltin Chloride Hydride Complex

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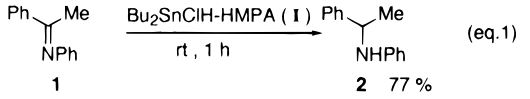
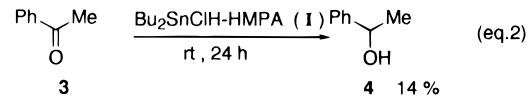
Chemoselective reductions of imino groups are very important for the synthesis of multifunctionalized amines. Nevertheless, little attention has been paid to imino-selective reductions by metal hydrides in the presence of carbonyl groups because of the lower electrophilicity of imino groups.[1] Organotin hydrides have been generally used for the selective removal of halide moieties *via* a radical process,[2] while ionic reactions with tin hydrides have been rarely reported.[3] Recently, we have developed a set of organotin hydrides that reduce polar multiple bonds such as C=O and C=N in an ionic manner,[4] and with which chemoselective reductions of bifunctional substrates could be achieved.[5] For example, in the reaction with 2,3-epoxy ketones, Bu_2SnFH−HMPA selectively reduced the carbonyl group to furnish predominantly the *anti*-2,3-epoxy alcohols,[5a] whereas Bu_2SnIH−HMPA preferentially reduced the epoxy group to provide 3-hydroxy ketones.[5c] Thus, the introduction of a halogen substituent or a ligand onto the tin atom can change the character of the original tin hydrides[5c] to provide different chemoselectivities in the reduction of multifunctional substrates. We now present use of Bu_2SnClH−HMPA (**I**) as a chemoselective reductant of imines in the presence of carbonyls.

The five-coordinate tin hydride, prepared from Bu_2SnClH[6] and a ligand, has been briefly reported to reduce imines effectively under mild conditions.[4e] For example, *N*-α-phenethylidene phenylamine (**1**) was reduced by Bu_2SnClH−HMPA (**I**) to the corresponding secondary amine **2** in 77% yield at room temperature for 1 h (eq 1). Among the ligands used, HMPA was best to give a high yield of **2**. The low reducing ability of **I** toward acetophenone **3** is noteworthy, as the corresponding alcohol **4** was formed in only 14% yield at room temperature after 24 h (eq 2). This fact indicates that the tin hydride system **I** would exhibit a high imino-selectivity even in the presence of carbonyl groups. As shown in Table 1, a mixture of



1 **2** 77 %



3 **4** 14 %

aromatic imine **1** (1 mmol) and acetophenone **3** (1 mmol) was treated with tin hydride **I** (1 mmol) at room temperature for 2 h.[7] After hydrolysis of the mixture, amine **2** was obtained in 85% yield (Table 1, entry 2), and unreacted ketone **3** was recovered quantitatively. In place of HMPA, other ligands such as Ph_3PO and DMI were not effective, although imino selectivities were observed (Table 1, entries 3 and 4). An iodo-substituted tin hydride, Bu_2SnIH−HMPA, also gave chemoselective reduction of imine **1**. The yield of **2**, however, was lower compared with the case of tin hydride **I** (Table 1, entry 5). Either reaction using Bu_2SnClH or Bu_2SnIH without HMPA was accompanied by the reduction of ketone **3** (Table 1, entries 1 and 6). Thus the complexation of tin hydrides with HMPA is important for the chemoselective reductions,[8] where the reducing ability for imino groups was also increased.[4e] In contrast, the introduction of a fluorine substituent into the tin hydride (Bu_2SnFH−HMPA) afforded the predominant reduction of the carbonyl group to give the corresponding alcohols **4** in 69% yield, where only 4% of imine **1** was reduced (Table 1, entry 7).

Further, Bu_2SnClH−HMPA (**I**) possessed higher imino-selectivity compared with other conventional reductants such as $LiAlH_4$, DIBAL, and $NaBH_4$ which reduced the carbonyl group predominantly (Table 1, entries 8−10). Another hydride, $NaBH_3CN$, which has been known as an effective reductant for imino groups,[9] exhibited no reducing ability under the neutral conditions employed here (Table 1, entry 11). $NaBH_3CN$ reduction under acidic conditions also resulted in the predominant reduction of carbonyl group (Table 1, entry 12).

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(7) We used *N*-aryl imines as substrates because the reduction of *N*-alkyl imines resulted in low yields. For example, when a mixture of *N*-benzylidene methylamine and benzaldehyde was reduced with tin hydride **I** at 0 °C for 1 h, the reaction barely proceeded. Benzyl alcohol was obtained in 6% yield and the imine was recovered quantitatively.

(8) When Bu_2SnClH was reacted with acetophenone **3** at room temperature for 24 h, 1-phenylethanol **4** was obtained in 20% yield. On the other hand, Bu_2SnClH−HMPA provided **4** in lower yield (14%) as shown in eq 2.

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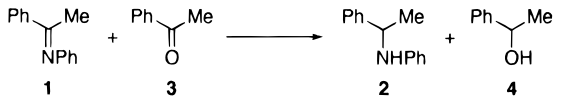
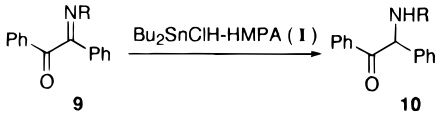
Table 1. Intermolecularly Competitive Reduction of Ketimine and Ketone[a]



entry	reducing system	conditions	yield (%) 2	4
1	Bu_2SnClH	rt, 2 h	60	9
2	Bu_2SnClH−HMPA (**I**)	rt, 2 h	85	0
3	Bu_2SnClH−Ph_3PO	rt, 2 h	27	5
4	Bu_2SnClH−DMI	rt, 2 h	42	3
5	Bu_2SnIH−HMPA	rt, 2 h	68	0
6	Bu_2SnIH	rt, 2 h	63	13
7	Bu_2SnFH−HMPA	rt, 2 h	4	69
8	$LiAlH_4$[b]	0 °C → rt, 2 h	43	49
9	DIBAL[c]	0 °C → rt, 2 h	0	42
10	$NaBH_4$[b]	0 °C → rt, 2 h	21	70
11	$NaBH_3CN$[b]	0 °C → rt, 2 h	0	0
12	$NaBH_3CN$[b,d]	0 °C → rt, 2 h	9	77

[a] Ketimine **1**/ketone **3**/reducing system = 1/1/2 mmol, THF 2 mL. [b] Reducing system 1 mmol. [c] DIBAL 5 mmol. [d] Reaction was performed in acidic media (HCl/MeOH pH ∼ 3).

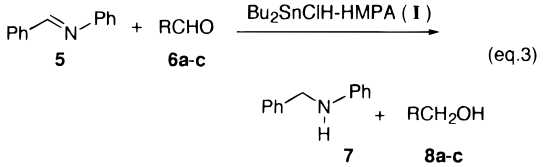
Table 2. Intramolecularly Chemoselective Reduction of Imino Ketones[a]



entry	R	conditions	product	yield (%)
1	Ph	rt, 20 h	**10a**	73
2	Ph	rt, 20 h	**10a**	8[b]
3	*p*-ClC_6H_4	rt, 20 h	**10b**	54
4	*p*-BrC_6H_4	rt, 20 h	**10c**	57
5	*p*-$MeOC_6H_4$	0 °C → rt, 20 h	**10d**	78

[a] Imino ketone **9**/Bu_2SnClH−HMPA (**I**) = 1/2 mmol, THF 1 mL. [b] Ph_3PO was used instead of HMPA.

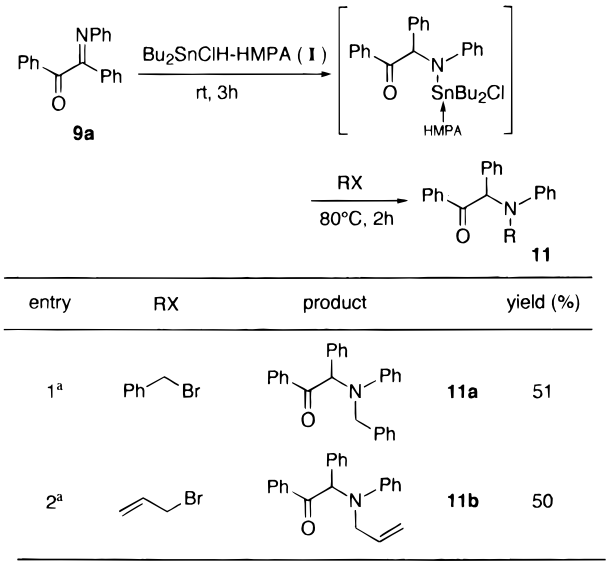
The tin hydride **I** also allows the coexistence of more reducible aldehydes during the reduction of the imino group. In a competitive reduction between aldimine **5** and aldehyde **6a** at room temperature, amine **7** was obtained in 89% yield, whereas aldehyde **6a** was reduced to alcohol **8a** in only 5% yield (eq 3). Moreover, aldehydes **6b** and **6c** were not affected by tin hydride **I**.



R = Ph (**6a**)	rt , 2h	89 %	5 %
$PhCH_2CH_2$ (**6b**)	-78 °C, 2h	74 %	trace
c-Hex (**6c**)	-78 °C, 2h	98 %	trace

Next, we performed the reduction of 1, 2-imino ketones **9** which bear both reducible imino and carbonyl groups (Table 2). In this case, imino-selective reduction is very difficult because the facile reduction of both functional groups provides 1,2-amino alcohols.[1,10] For example, the reduction of **9a** was performed with tin hydride **I** at room temperature for 20 h. After the reaction mixture was quenched with MeOH, 2-amino ketone **10a** was obtained selectively, where no formation of 1,2-amino alcohol was detected at all (Table 2, entry 1). Here HMPA was revealed as a suitable ligand to tin species because using Ph_3PO in place of HMPA gave **10a** in only 8% yield (entry 2). It is noteworthy that not only carbonyl but also halogen groups were tolerated in the reduction of **9b** and **9c** (Table 2, entries 3 and 4).

Table 3. Synthesis of Tertiary Amines[a]



entry	RX	product	yield (%)
1[a]		**11a**	51
2[a]		**11b**	50

[a] Imino ketone **9a** / Bu_2SnClH-HMPA (**I**) = 1 / 1.2 mmol, THF 1 mL. [b] 15 mmol. [c] 20 mmol.

The above reductions progress stoichiometrically, where the adducts bearing a nucleophilic Sn−N bond are generated *in situ* without protonation by tin hydride **I**. Multifunctionalized unsymmetric amines **11** could be prepared directly by the subsequent N-alkylation of the tin amide with benzyl bromide and allyl bromide to afford unsymmetric tertiary amines **11a** and **11b**, respectively (Table 3).

Although the mechanism of the activation of imines is not yet clear, we believe that the ability of Bu_2SnClH−HMPA (**I**) to act as hydride donor is low, hence iminium salts are formed from imines **1** before hydride attack. The electrophilicity of the imino group would be increased by the formation of the iminium salt. In the tin hydride complex **I**, we have shown that Cl and HMPA occupy apical positions on the trigonel bipyramidal geometry.[4e] Thus the Sn−Cl bond is effectively activated by the coordination of HMPA in tin hydride **I** and would play an important part for the formation of the iminium salts. In the case of Bu_2SnFH−HMPA, the iminium salt could not be formed because of the strong Sn−F bond.

In conclusion, a highly coordinated tin hydride, Bu_2-SnClH−HMPA, effectively reduces imines even in the presence of carbonyl groups to furnish secondary amines. Moreover, the resulting tin amides from hydrostannation of imines subsequently react with organic halides to furnish unsymmetrical tertiary amines in a one-pot procedure.

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Experimental Section

Analysis. ^1H and ^{13}C spectra were recorded at 400 and 100, MHz, respectively. Samples for ^1H and ^{13}C NMR spectra of produced amines were examined in deuteriochloroform ($CDCl_3$) containing 0.03% (w/v) of tetramethylsilane. GLC analyses were performed with a FFAP (2-m × 3-mm glass column). Column chromatography was performed by using Wakogel C-200 mesh silica gel. Preparative TLC was carried out on Wakogel B-5F silica gel. Yields were determined by ^1H NMR or GLC using internal standards.

Materials. Di-*n*-butyltin dihydride (Bu_2SnH_2) was prepared by the reduction of di-*n*-butyltin dichloride (Bu_2SnCl_2) with $LiAlH_4$.[11] Di-*n*-butyltin halide hydrides (Bu_2SnXH; X = Cl, I) were synthesized from Bu_2SnH_2 and Bu_2SnX_2.[12] Bu_2SnFH−HMPA was synthesized by the mixing of Bu_2SnH_2 and Bu_2SnF_2 in the presence of HMPA. Ketimine **1** and 1,2-imino ketones **9** were prepared by the azeotropic dehydration of a ketone or diketones and anilines in toluene at reflux temperature.[13] THF was freshly distilled over sodium benzophenone ketyl, and HMPA was distilled over finely powdered calcium hydride. All reactions were carried out under dry nitrogen.

Representative Procedure for the Competitive Reduction between Imines and Ketone or Aldehyde. To the solution of Bu_2SnH_2 (1 mmol) and Bu_2SnCl_2 (1 mmol) in 1 mL of THF was added HMPA (2 mmol). The mixture was stirred at room temperature for 10 min. To the solution of *N*-α-phenethylidenephenylamine **1** (1 mmol) and acetophenone **3** (1 mmol) in 1 mL of THF was added the mixture of tin hydride system at rt, and then the solution was stirred 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 eluting with hexanes−EtOAc (9:1) to give almost pure product **2**. Further purification of **2** was performed by TLC eluting with hexanes−EtOAc (9:1).

Amines **2** and **7** were identified in comparison with the authentic spectral data which we have previously reported.[4e] *sec*-Phenethyl alcohol (**4**) [98-85-1], benzyl alcohol (**8a**) [100-51-6], 2-phenyl-1-propanol (**8b**) [1123-85-9], and cyclohexymethanol (**8c**) [100-49-2] were identified in comparison with commercially available samples.

Representative Procedure for the Intramolecular Chemoselective Reduction of Imino Ketones. To the solution of Bu_2SnH_2 (1 mmol) and Bu_2SnCl_2 (1 mmol) in 1 mL of THF was added HMPA (2 mmol). The mixture was stirred at room temperature for 10 min. Imino ketone **9** (1 mmol) was added, and the solution was stirred until the Sn−H absorption (1862 cm^{-1}) disappeared in the IR spectrum. After quenching the reaction with MeOH (5 mL), volatiles were removed under reduced pressure. The residue was subjected to column chromatography eluting with hexanes−EtOAc (9:1) to give a crude product **10**. Further purification was performed by TLC eluting with hexanes−EtOAc (9:1).

***N*-Phenyl-2-aminodeoxybenzoin (10a):** pale yellow solid; IR (KBr) 3360, 1670, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.40 (d, 1H, J = 6.83 Hz), 6.02 (d, 1H, J = 6.83 Hz), 6.65-8.01 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 62.7, 113.5, 117.9, 128.1, 128.1, 128.7, 128.9, 129.1, 129.2, 133.5, 135.1, 137.7, 146.1, 197.1; HRMS calcd for $C_{20}H_{17}ON$, 287.1311, found 287.1306.

***N*-(*p*-Chlorophenyl)-2-aminodeoxybenzoin (10b):** pale yellow solid, purified by recrystallization from hexanes−EtOAc (4:1); IR (KBr) 3400, 1670, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.44 (d, 1H, J = 6.35 Hz), 5.88 (d, 1H, J = 6.35 Hz), 6.56−8.00 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 62.7, 114.6, 122.4, 128.1, 128.2, 128.7, 128.8, 129.1, 129.1, 133.6, 134.9, 137.2, 144.6, 196.6; HRMS calcd for $C_{20}H_{16}ONCl$ 321.0922, found 321.0918.

***N*-(*p*-Bromophenyl)-2-aminodeoxybenzoin (10c):** pale yellow solid, purified by recrystallization from hexanes−EtOAc (4:1); IR (KBr) 3390, 1665, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.47 (d, 1H, J = 6.83 Hz), 5.97 (d, 1H, J = 6.83 Hz), 6.52−8.00 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 62.6, 109.5, 115.1, 128.1, 128.3, 128.7, 128.8, 129.1, 131.9, 133.6, 134.8, 137.2, 145.0, 196.5; HRMS calcd for $C_{20}H_{16}ON^{79}Br$, 365.0416, found 365.0421.

***N*-(*p*-Methoxyphenyl)-2-aminodeoxybenzoin (10d):** pale yellow solid, purified by flash chromatography (eluted by hexanes−EtOAc, 5:1); IR (KBr) 3400, 1675, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H), 5.11 (br, 1H), 5.96 (s, 1H), 6.61−8.00 (m, 14H); HRMS calcd for $C_{21}H_{19}O_2N$, 317.1417, found 317.1435.

N-(*p*-Methoxyphenyl)-2-aminodeoxybenzoin (**10d**) [RN 19339-72-1] was identified in comparison with the authentic data.[14]

Representative Preparation of Unsymmetric Tertiary Amines. To the solution of Bu_2SnH_2 (0.6 mmol) and Bu_2SnCl_2 (0.6 mmol) in 1 mL of THF was added HMPA (1.2 mmol). The mixture was stirred at room temperature for 10 min. Imino ketone **9** (1 mmol) was added, and the solution was stirred for 3 h. Benzyl bromide (15 mmol) was added to the mixture and stirred at 80 °C for 2 h. After quenching with MeOH (5 mL), volatiles were removed under reduced pressure. The residue was subjected to column chromatography eluting with hexanes−EtOAc (9:1) to give the product **11a**. Further purification of **11a** was achieved by recrystallization from hexane.

***N*-Benzyl-*N*-phenyl-2-aminodeoxybenzoin (11a):** pale yellow solid; IR (KBr) 1680, 1260, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.62 (d, 1H, J = 17.81 Hz), 4.72 (d, 1H, J = 17.81 Hz), 6.67 (s, 1H), 6.71−7.93 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 52.6, 67.7, 114.2, 118.2, 126.1, 126.4, 127.9, 128.1, 128.3, 128.5, 128.7, 129.2, 130.0, 133.3, 135.5, 135.9, 139.9, 149.3, 199.0; HRMS calcd for $C_{27}H_{23}ON$, 377.1781, found 377.1786. Anal. Calcd for $C_{27}H_{23}ON$, C, 85.91: H, 6.14; N, 3.71. Found: C, 85.04; H, 6.15; N, 3.70.

***N*-Allyl-*N*-phenyl-2-aminodeoxybenzoin (11b):** pale yellow liquid, purified by Kugelrohr distillation at 120 °C (0.09 mmHg); IR (neat) 1670, 1320, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97 (dd, 1H, J = 6.84 and 13.67 Hz), 3.14 (dd, 1H, J = 7.33 and 13.67 Hz), 4.18 (s, 1H), 5.07 (m, 2H), 5.73 (m, 1H), 6.86−8.00 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 43.9, 81.4, 120.4, 125.6, 128.1, 128.1, 128.8, 128.9, 129.0, 129.1, 129.3, 129.9, 130.1, 132.3, 132.7, 134.9, 200.8; HRMS calcd for $C_{23}H_{21}ON$, 327.1624, found 327.1628.

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Supporting Information Available: Copies of NMR spectra (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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