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Reduction of Aldehyde with Tributyltin Hydride-HMPA Combined System

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Bu_3SnH-HMPA combined system is an efficient reagent for the reduction of aldehydes. The reaction proceeds in good yields, and chemoselective carbonyl reduction is achieved for the substrate which includes another reducible group. Moreover, the intermediate, tin alkoxide, undergoes further reaction such as the preparation of ethers and heterocyclic compounds in the one pot procedure.

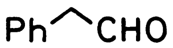
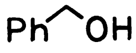
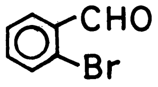
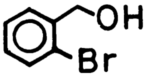
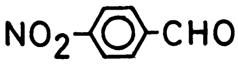
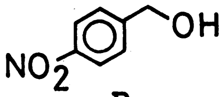
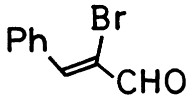
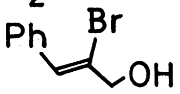
Trialkyltin hydrides are widely used in organic synthesis,¹⁾ and generally act as reducing agents of organic halides under radical conditions using radical initiator such as AIBN and U.V. irradiation.²⁾ Recently, we have demonstrated that the addition of phosphine oxide ligands such as hexamethylphosphoric triamide (HMPA) and tributylphosphine oxide (Bu_3PO) induced an unusual reactivity of Bu_3SnH in the reduction of α-chloroketones,³⁾ where the selective reduction of carbonyl group occurred without the chloro group reduction. This result indicates that the combination with HMPA increase the reducing ability of Bu_3SnH toward the carbonyl group.

Here we report the reduction of various aldehydes by Bu_3SnH-HMPA. This combined system appears to be an efficient reducing agent of aldehydes. The results are summarized in Table 1. In the reduction of phenylacetaldehyde, Bu_3SnH alone gave only 6% yield of phenethyl alcohol at room temperature for 2 hours (entry 1). On the other hand, the addition of HMPA caused the effective reduction to produce phenethyl alcohol in good yield (entry 2). The dramatic effect of HMPA was also observed in the reduction of benzaldehyde (entries 3 and 4). Moreover, the selective reduction of aldehyde was achived in good yield even in the presence of ketone, where acetophenone was recovered quantitatively (entry 5). In the case of cinnamaldehyde, 1,2-reduction occurred selectively to give cinnamyl alcohol (entry 6).

The following procedure is representative. Under nitrogen, to the mixture of Bu_3SnH (6 mmol) and HMPA (6 mmol) was added 3 mmol of benzaldehyde. The reaction mixture was stirred at 60 °C for 2 hours, when the IR band at 1800 cm^{-1} due to Sn-H disappeared. The reaction was quenched by MeOH and GLC analyses showed the formation of benzyl alcohol, which was purified by column chromatography (Silica gel, eluted by benzene).

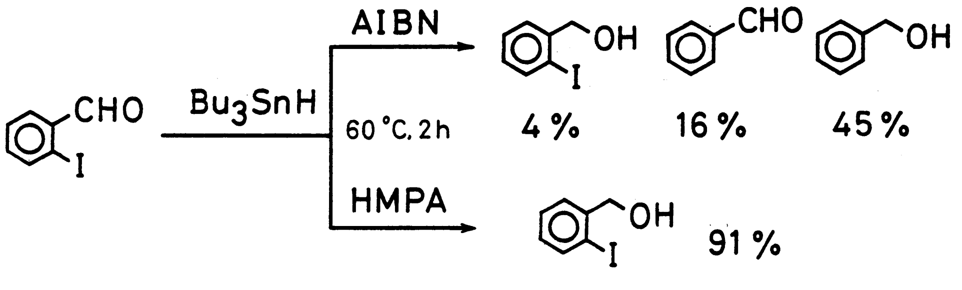
It is noteworthy that the reduction of aldehydes took place cleanly even in the case of the substrate bearing another reducible functional group such as

Table 1. Reduction of Aldehydes by Bu_3SnH-HMPA System[a)]

Entry	Substrate	Conditions	Product	Yield/%[b)]
1		r.t., 2 h		6[c)]
2	"	"	"	99
3	PhCHO	60 °C, 2 h		tr[c)]
4	"	"	"	88
5	PhCHO + PhCOMe[d)]	"	"	86
6		"		70
7		"		85
8		"		84
9		"		86

a) Bu_3SnH/HMPA/RCHO= 6/6/3 mmol. b) Based on RCHO. c) Without HMPA.
d) Bu_3SnH/HMPA/PhCHO/PhCOMe= 6/6/3/3 mmol.

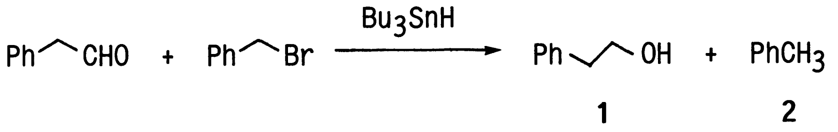
halogen and nitro group (entries 7-9). It is considered that the reduction of these substrates gives complex mixtures, because organotin hydrides can also act as dehalogenating agents.[2)] In fact, as shown in Eq. 1, under radical conditions using AIBN (10 mol%), the reduction of o-iodobenzaldehyde with Bu_3SnH induced the competitive reaction to give complex mixtures, 4% of o-iodobenzyl alcohol, 16% of benzaldehyde, and 45% of benzyl alcohol. In contrast, the reduction with Bu_3SnH-HMPA resulted in the clean reaction. The carbonyl group was reduced selectively, giving o-iodobenzyl alcohol in good yield, and the reducible iodo group was tolerated.[4)]



(1)

When equimolar mixtures of phenylacetaldehyde and benzyl bromide were treated with 1 equiv. of Bu_3SnH, the reaction course depended upon the conditions (Table 2). Under radical conditions, the dehalogenation predominantly took place to afford toluene (70%), and phenethyl alcohol, derived from the carbonyl reduction,

Table 2. Chemoselective Reduction by $Bu_3SnH^{a)}$



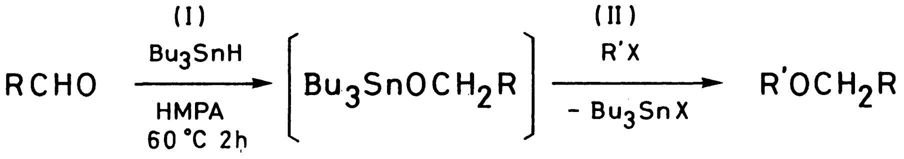
Entry	Reducing system	Conditions	Yield/% 1	Yield/% 2
1	Bu_3SnH-AIBN	60 °C, 1 h	26	70
2	Bu_3SnH-HMPA	r.t., 1 h	43	50
3	Bu_3SnH-HMPA-$DNB^{b)}$	r.t., 1 h	94	6

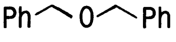
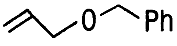
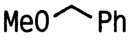
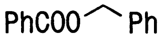
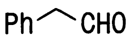
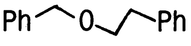
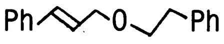
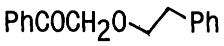
a) $Bu_3SnH/PhCH_2CHO/PhCH_2Br$=5/5/5 mmol, HMPA 5 mmol, AIBN, 0.5 mmol. b) p-Dinitrobenzene 0.5 mmol.

was formed in only 26% yield (entry 1). While, in the presence of HMPA, the yield of phenethyl alcohol was increased to 43%, although toluene was also obtained in 50% yield (entry 2). Moreover, noteworthy is that the addition of a radical inhibitor, p-dinitrobenzene (DNB),[5)] to Bu_3SnH-HMPA system caused the selective reduction of the aldehyde in 94% yield (entry 3). Toluene was formed in only 6% yield, where almost unreacted benzyl bromide was recovered. From these facts, it appears that the reduction by Bu_3SnH-HMPA proceeds via an ionic pathway.[6)]

The intermediate tin alkoxide could be utilized for further reaction. As an application of the presented reduction, we attempted the reductive O-alkylation of

Table 3. Reductive Alkylation of $Aldehydes^{a)}$

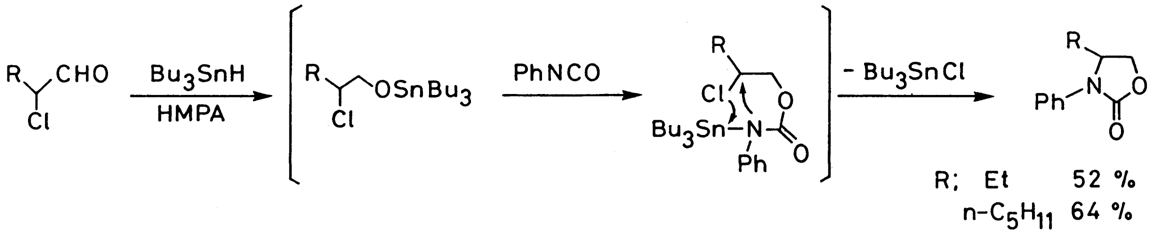


Entry	Aldehyde	R'X	Conditions (II)	Product	$Yield/\%^{b)}$
1	PhCHO		60 °C, 48 h		68
2	"		"		64
3	"	MeI	40 °C, 48 h		75
4	"	PhCOCl	r.t., 10 min		86
5			60 °C, 48 h		99
6	"		"		98
7	"	$PhCOCH_2Br$	"		50

a) Bu_3SnH 5 mmol, HMPA 5 mmol, PhCHO 10 mmol, $PhCH_2CHO$ 5 mmol, R'X 5 mmol. b) Based on R'X.

aldehydes in the one pot procedure (Table 3). After the reduction of the aldehyde, the electrophile was added to the reaction mixture, and heating induced the O-alkylation. These reactions proceeded under neutral conditions in good yields. For example, with benzyl bromide, benzyl ether was obtained (entries 1 and 5). Allyl, alkyl, acyl and phenacyl halides are used as electrophiles.

We have also demonstrated the preparation of heterocyclic compounds. Tributyltin β-chloroalkoxide[7] was formed selectively from the chemoselective reduction of α-chloroaldehyde at 60 °C for 2 hours. Next, PhNCO inserted to the Sn-O bond easily at room temperature and subsequent cyclization at 60 °C for 2 hours afforded 2-oxazolidones (Eq. 2).



(2)

Thus the Bu_3SnH-HMPA combined system is a versatile reagent for the chemoselective reduction of aldehydes, and the intermediate tin alkoxide could be utilized for further reaction in the one pot procedure.

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References

1) See for example, W. P. Neumann, Synthesis, 1987, 665; M. Pereyre, J. P. Quintard, and A. Rahm, "Tin in Organic Synthesis," Butterworth, 1987, p. 33.

2) H. G. Kuivila, L. W. Menapace, and C. R. Warner, J. Am. Chem. Soc., 84, 3584 (1962).

3) I. Shibata, T. Suzuki, A. Baba and H. Matsuda, J. Chem. Soc., Chem. Commun., 1988, 882.

4) In the reduction of α-haloketones by Bu_3SnH-HMPA, the selective C=O group reduction was achieved for only α-chloroketones,[2] and α-bromo analogue gave complex mixtures.

5) D. D. Tanner, and H. K. Singh, J. Org. Chem., 51, 5182 (1986).

6) As to the reduction of carbonyl group, Bu_3SnH, being a typical free radical agent, exhibits a hydride donor ability in several cases. M. Pereyre, and J. Y. Godet, Tetrahedron Lett., 1970, 3653; W. P. Neumann, and E. Heymann, Liebigs Ann. Chem., 683, 11 (1965); N. Y. M. Fung, P. de Mayo, J. H. Schauble and A. C. Weedon, J. Org. Chem., 43, 3977 (1978).

7) We have already reported the preparation of heterocycles using organotin-β-haloalkoxides and heterocumulenes. A. Baba, H. Kishiki, I. Shibata, and H. Matsuda, Organometallics, 4, 1329 (1985).

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