CHEMISTRY LETTERS, pp. 307-310, 1991.

Characteristic Reduction of Ketones by Bu_3SnH-Bu_4NX System

Ikuya SHIBATA,* Tomoyuki YOSHIDA, Akio BABA, and Haruo MATSUDA
Department of Applied Chemistry, Faculty of Engineering,
Osaka University, 2-1 Yamadaoka, Suita, Osaka 565

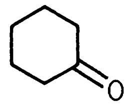
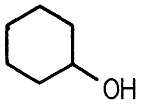
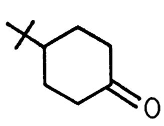
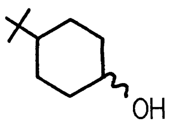
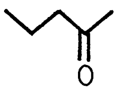
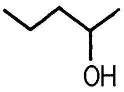
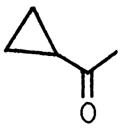
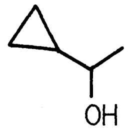
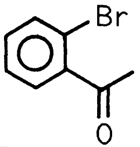
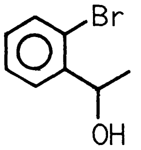
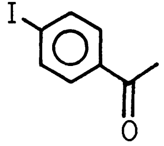
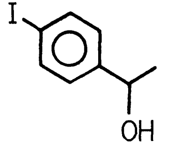
Various ketones were reduced cleanly by Bu_3SnH-Bu_4NX (X=halogen) combined systems. The reaction proceeds effectively under mild conditions. Chemoselective reduction was performed in bifunctional compounds, and marked diastereoselective reduction was noted for α-methoxy propiophenone.

Trialkyltin hydrides are widely used in organic synthesis.$^{1)}$ Because the reducing ability of most commonly used tri-n-butyltin hydride (Bu_3SnH) is low, the reaction is usually performed by using radical initiators such as AIBN and UV irradiation. Recently, we demonstrated that the activation by HMPA increased the reducing ability of Bu_3SnH,$^{2)}$ where the reaction proceeded in a polar process. Aldehydes and activated ketones such as α-chloro ketones are reduced chemoselectively with Bu_3SnH-HMPA. However, the Bu_3SnH-HMPA system does not reduce inactivated ketones at all. Here we have found that Bu_3SnH-tatrabutylammonium halide (Bu_4NX) combined system exhibits higher reducing ability than Bu_3SnH-HMPA. This combined system appears to be an efficient reducing agent of ketones, and several characteristic features are noted in chemoselectivity and diastereoselectivity.

As shown in Table 1, Bu_3SnH alone exhibits no reducing ability. For example, cyclohexanone was not reduced at all at 60 °C for 2 hours (entry 1). Whereas, the addition of an equimolar amount of tetra-n-butylammonium chloride (Bu_4NCl) or tetra-n-butylammonium fluoride (Bu_4NF) dramatically increased the reactivity to afford **1** in good yields (entries 2 and 3). tert-Butylcyclohexanone was reduced to give thermodynamically stable trans-alcohol **2** as a major product (entries 5 and 6). The effect of the additive was also noted in the formation of acyclic alcohol **3** (entries 7-9).

In the reduction of cyclopropyl methyl ketone, cyclopropyl methyl carbinol **4** was obtained chemoselectively (entries 10 and 11). This fact indicates

Table 1. Reduction of Ketones by Bu_3SnH-Bu_4NX System [a)]

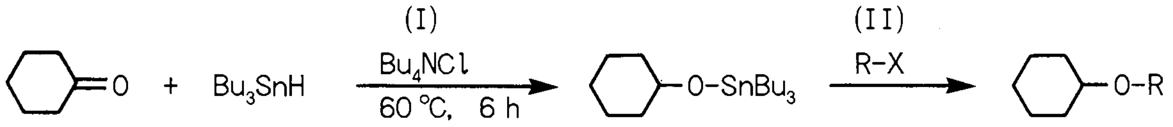
Entry	Substrate	Reducing system	Conditions	Product	Yield/%
1		Bu_3SnH	60 °C, 24 h	 **1**	tr
2		Bu_3SnH-Bu_4NCl	60 °C, 6 h		85
3		Bu_3SnH-Bu_4NF[b)]	rt, 5 h		99
4		Bu_3SnH	60 °C, 24 h	 **2**	tr[c)]
5		Bu_3SnH-Bu_4NCl	60 °C, 6 h		90[d)]
6		Bu_3SnH-Bu_4NF[b)]	rt, 5 h		82
7		Bu_3SnH	60 °C, 24 h	 **3**	tr
8		Bu_3SnH-Bu_4NCl	60 °C, 5 h		74
9		Bu_3SnH-Bu_4NF[b)]	rt, 4 h		78
10		Bu_3SnH-Bu_4NCl	60 °C, 5 h	 **4**	24
11		Bu_3SnH-Bu_4NF[b)]	rt, 4 h		44
12		Bu_3SnH-Bu_4NCl	60 °C, 4 h	 **5**	61
13		Bu_3SnH-Bu_4NCl	60 °C, 5 h	 **6**	74

a) Bu_3SnH 4 mmol, Bu_4NX 4 mmol, ketone 2 mmol, THF 4 ml. b) THF solution was used. c) cis:trans= 27:73. d) cis:trans= 21:79.

that the reaction proceeds in a polar process. Previous reports show that the products depend upon the reaction conditions, that is, **4** is obtained under polar conditions whereas ring opening of the cyclopropane function to give n-propyl methyl ketone takes place under radical conditions using AIBN and UV irradiation.[3)] The chemoselective carbonyl reduction to provide **5** and **6** was also performed with halo ketones (entries 12 and 13). This chemoselectivity is notable because, in general, organotin hydrides are used as efficient dehaloganating agents.[1)] In fact, the reduction of p-iodoacetophenone with Bu_3SnH gave acetophenone exclusively.

The following procedure is representative (entry 2). Under nitrogen, to the mixture of Bu_3SnH (4 mmol) and Bu_4NCl (4 mmol) in 5 ml of THF was added 2 mmol of cyclohexanone. The mixture was stirred at 60 °C for 2 h. The IR band at 1800 cm^{-1} due to Sn-H disappeared. After quenching by MeOH, the mixture was chromatographed (Silica gel, eluted by Hexane-EtOAc).

The intermediate tin alkoxide could be utilized for further reactions. We next attempted the reductive O-alkylation (Eq. 1). After the reduction of cyclohexanone, an electrophile was added without isolation of the intermediate, and heating induced the O-alkylation. For example, from the reaction with benzyl bromide and cinnamyl bromide, the corresponding ethers, **7** and **8**, were obtained, and the reaction with benzoyl chloride afforded the ester **9** in the one-pot procedure.



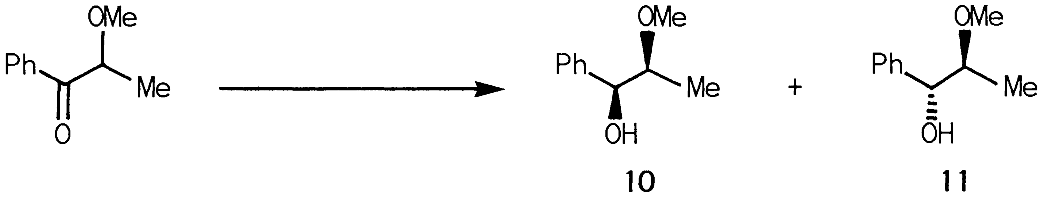
7-9 (1)

RX	Conditions (II)	Product	Yield/%
$PhCH_2Br$	80 °C, 64 h	**7**	70
$PhCH=CHCH_2Br$	80 °C, 64 h	**8**	48
PhCOCl	rt, 15 h	**9**	93

Finally, we found interesting diastereoselectivity in the reduction of α-methoxy propiophenone (Table 2). By using Bu_3SnH, the yield and the diastereoselectivity of the α-methoxy alcohols, **10** and **11**, were not so good (entry 1). In contrast, the addition of Bu_4NX enhanced the formation of threo-alcohol **10** (entries 2, 3).4) In particular, only **10** was obtained by Bu_3SnH-Bu_4NF system (entry 3). This threo-selective reaction is explained in term of Felkin-Ahn model in the transition state.5) This fact may indicate that halide ions of ammonium salts interact with Bu_3SnH to decrease the Lewis acidity of the tin atom,6) which prevents a chelation of Sn atom and methoxy oxygen.

In summary, Bu_3SnH-Bu_4NX systems exhibit mild and characteristic reducing ability of ketones. An attempt to control the diastereoselectivity for various α-alkoxy ketones by using tin hydride system is now under investigation.

Table 2. Diastereoselective Reduction of α-Methoxypropiophenone [a)]



Entry	Reducing system	Conditions	Yield / %	Selectivity[b)] 10 : 11
1	Bu_3SnH	60 °C, 24 h	16	43 : 57
2	Bu_3SnH-Bu_4NCl	rt, 2 h	92	69 : 31
3	Bu_3SnH-Bu_4NF	0 °C, 5 h	81	100 : 0

a) Bu_3SnH 4 mmol, Bu_4NX 4 mmol, ketone 2 mmol, THF 4 ml.
b) Determined by ^{1}H-NMR.

Thanks are due to Mrs. Y. Miyaji and Mr. H. Moriguchi, Faculty of Engineering, Osaka University for assistance in obtaining NMR (JEOL JNM-GSX-400) and MS (JEOL, JMS-DX-303) spectra.

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) I. Shibata, T. Suzuki, A. Baba, and H. Matsuda, J. Chem. Soc. Chem. Commun., 1989, 893; I. Shibata, T. Yoshida, A. Baba, and H. Matsuda, Chem. Lett., 1989, 619.
3) M. Pereyre and J. Y. Godet, Tetrahedron Lett., 1970, 3653.
4) The spectral data of ^{1}H-NMR ($CDCl_3$, 400 MHz) was as follows;
10: δ0.98 (d, 3H, *J*=6.35 Hz, CH_3), 2.54 (br, 1H, OH), 3.38 (dq, 1H, *J*=6.35 and 7.81 Hz, CHOMe), 3.43 (s, 3H, OCH_3), 4.40 (d, 1H, *J*=7.81 Hz, CHOH), 7.25-7.36 (m, 5H, Ar). **11**: δ0.98 (d, 3H, *J*=6.35 Hz, CH_3), 2.54 (br, 1H, OH), 3.42 (s, 3H, OCH_3), 3.54 (dq, 1H, *J*=3.42 and 6.35 Hz, CHOMe), 4.91 (d, 1H, *J*=3.42 Hz, CHOH), 7.25-7.36 (m, 5H, Ar).
5) M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., 18, 2199 (1968).
6) Similar postulation was noted in the reaction of allyltin derivatives. Y. Yamamoto, S. Hatsuya, and J. Yamada, J. Org. Chem., 55, 3118 (1990).

(Received November 21, 1990)