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Diastereoselective Reduction of Acyclic Hydroxyketones and Diketones with an Indium Hydride Reagent

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Abstract: Hydroxyketones and diketones have been reduced with lithium indium hydride to give *meso*-diols selectively. α-Hydroxyketones and α-diketones are reduced to *meso*-1,2-diols with high diastereoselectivities, whereas the selectivities of β-hydroxyketones and β-diketones are less satisfactory. © 1997 Elsevier Science Ltd.

INTRODUCTION

Selective reduction is a fundamental process in organic synthesis. A large number of studies on stereoselective reduction have been carried out.[1] In particular, stereoselectivities of the hydrometalation of unsaturated functional groups with various boron-, aluminium-, and gallium hydrides have been extensively examined and several useful results have been obtained.[2] We have recently reported the preparation and reaction behaviour of a new indium hydride reagent ($LiInH_4$), and demonstrated that this indium hydride has enough reduction ability for various organic functional groups.[3] In this paper are described highly diastereoselective reductions of acyclic hydroxyketones and diketones with lithium indium hydride.

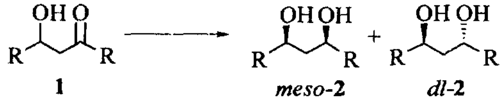
RESULTS AND DISCUSSION

1. Reduction of β-hydroxyketones.

Stereoselective reductions of acyclic β-hydroxyketones have hitherto been intensively studied, because *syn*- and *anti*-1,3-diols are recurring units in a variety of polyacetate- and polypropionate-derived natural products.[4] In order to elucidate the diastereoselectivity of $LiInH_4$, reductions of representative β-hydroxyketones **1** were undertaken. To a suspension of $LiInH_4$ was added **1** and the mixture was ultrasonicated at 10 °C for 2 h. Then the reaction mixture was stirred overnight at room temperature. After an aqueous workup, a mixture of the corresponding 1,3-diol **2** was obtained. Table 1 shows the results together with those of $NaBH_4$ and $LiAlH_4$ for comparison.

When two molar equivalents of $LiInH_4$ were used, **2** was obtained in only 70% yield (Run 1). However, with four molar equivalents of the reductant the reduction proceeded quantitatively and the *meso* : *dl* ratio of **2** increased (86 : 14). The reduction with $NaBH_4$ in ethanol went on quantitatively and the yields of **2** increased compared with that in ether (Run 1). $LiAlH_4$ reduced **1** smoothly, but the selectivity was lower than that of $LiInH_4$. Although the diastereoselectivities of the three reductants are not very high, $LiInH_4$ shows the highest selectivity. It is reported that in the reduction of β-hydroxyketones **1**, the reductant such as $LiAlH_4$ and $LiBH_4$ combines with a substrate to form a six-membered intermediate and the reduction

Table 1. Reduction of β-hydroxyketones[a)]



Run	R	$LiInH_4$ (%)	*meso* : *dl*	$NaBH_4$ (%)	*meso* : *dl*	$LiAlH_4$ (%)	*meso* : *dl*
1[b)]	Ph	**1**: 30		**1**: 67 (0)[c)]		**1**: 0	
		2: 70	74 : 26	**2**: 33 (100)[c)]	52 : 48 (68 : 32)[c)]	**2**: 100	60 : 40
2[d)]	Bu	**1**: 4		**1**: 32		**1**: 0	
		2: 90	78 : 22	**2**: 67	36 : 64	**2**: 100	56 : 44

a) All reactions were carried out with a substrate (1 mmol) and a reductant (2 mmol) in Et_2O (20 ml) overnight at room temperature. b) Yields and ratios were estimated by ^1H-NMR. c) Figures in parentheses refer to the reactions in EtOH. d) Isolated yields. Ratios were determined by ^1H-NMR, after the diastereomers were converted to the corresponding phenylboronic esters.[5]

proceeds via an intermolecular process.[2a,2b] Therefore, it is possible that $LiInH_4$ also forms a six-membered intermediate with a substrate (Fig. 1). As the atom radius of indium is larger than those of boron and aluminium, it can be presumed that *meso*-**2** was obtained more selectively owing to the higher steric interaction between $LiInH_4$ and the α-hydrogen.

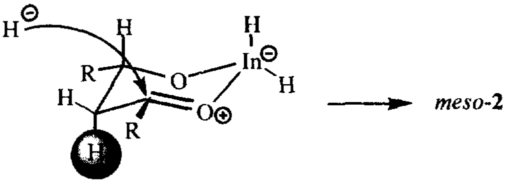


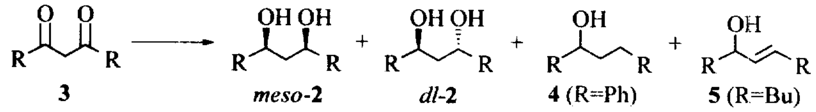
Figure 1

2. Reduction of β-diketones.

The diastereoselectivity toward β-diketones **3** was examined in a similar manner as above (Table 2). The reduction of **3** with $LiInH_4$ gave the corresponding diol **2** in low yields, whereas the selectivity was higher than those of $NaBH_4$ and $LiAlH_4$. When the reduction with $NaBH_4$ was carried out in ether, the yields and selectivity of **2** were also low even with a large excess of the reductant. In ethanol, however, the yield of **2** increased and the diastereoselectivity was reversed. $LiAlH_4$ reduced **3** quantitatively, but the diastereoselectivity was only modest. Furthermore, unexpected products such as 1,3-diphenylpropan-1-ol (**4**) and 6-undecen-5-ol (**5**) were formed. These compounds are considered to be produced via intermediate enolate and α,β-unsaturated ketone.[6] On the low reactivity of $NaBH_4$ toward β-diketones **3**, it is suggested that electrostatic repulsion between the enolate ion and the borohydride ion prevents the reduction of **3** with $NaBH_4$.[2c] Similarly, the low reactivity of $LiInH_4$ may be for the same reason.

In conclusion, $LiInH_4$ has been found to be useful for the stereoselective reduction of β-hydroxyketones to 1,3-diols. On the contrary, this reagent is not suitable for the reduction of β-diketones owing to its diminished reactivity.

Table 2. Reduction of β-diketones



3 *meso*-**2** *dl*-**2** **4** (R=Ph) **5** (R=Bu)

Run	R	$LiInH_4$ (%)$^{b)}$	*meso* : *dl*	$NaBH_4$ (%)$^{c)}$	*meso* : *dl*	$LiAlH_4$ (%)$^{b)}$	*meso* : *dl*
$1^{a)}$	Ph	**3**: 72		**3**: 55$^{d)}$ (35)		**3**: 0	
		2: 28	76 : 24	**2**: 44$^{d)}$ (65)	46 : 54 (55 : 45)	**2**: 66$^{d)}$	48 : 52
						4: 30$^{d)}$	
$2^{e)}$	Bu	**3**: 61		**3**: 35 (0)		**3**: 0	
		2: 38	80 : 20	**2**: 62 (100)	37 : 63 (68 : 32)	**2**: 15	46 : 54
						5: 85	

a) Yields and ratios were estimated by ^{1}H-NMR. b) All reactions were carried out with a substrate (1 mmol) and a reductant (2 mmol) in Et_2O (20 ml) overnight at room temperature. c) All reactions were carried out with a substrate (1 mmol) and $NaBH_4$ (5 mmol) in Et_2O (20 ml) overnight at room temperature. Figures in parentheses refer to the reactions with a substrate (1 mmol) and $NaBH_4$ (2 mmol) in EtOH. d) Isolated yields. e) Isolated yields. Ratios were determined by ^{1}H-NMR, after the diastereomers were converted to the corresponding phenylboronic esters.[5]

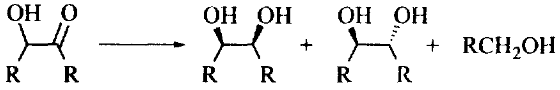
3. Reduction of α-hydroxyketones.

For the stereoselective synthesis of olefins, single diastereomers of 1,2-diol **7** are useful precursors.[7] Detailed studies on the reduction of α-hydroxyketones **6** using several reductants have been published.[1b,8] Table 3 summarizes the results on the reduction of **6** with $LiInH_4$, $NaBH_4$, and $LiAlH_4$. All the reductions of aromatic α-hydroxyketones with $LiInH_4$ gave *meso*-**7** quantitatively (Runs 1-4). On the contrary, the selectivity of the reduction of butyroin, an aliphatic α-hydroxyketone, was not very high (Run 5). Similar results were obtained with $NaBH_4$ and $LiAlH_4$. The diastereoselectivity of $NaBH_4$ was inferior to that of $LiInH_4$. For the complete reduction of anisoin, five molar equivalents of $NaBH_4$ were required; with two molar equivalents of $NaBH_4$, the yield of **7** was only 32% (Run 4). Similarly, 4,4'-dibromobenzoin was reduced in only 41% yield with two molar equivalents of $NaBH_4$ (Run 2). The reduction with $LiAlH_4$ proceeded quantitatively, whereas the diastereoselectivity was lower than that of $LiInH_4$. Furthermore, when the reduction of 4,4'-dibromobenzoin was carried out overnight, unidentified by-products were produced and the yield of **7** dropped to 60%. For the reduction of butyroin, the yield of **7** was lowest when $LiAlH_4$ was used (Run 5), probably owing to the formation of 1-butanol judging from the other cases (Runs 3 and 4). Thus, it has been found that $LiInH_4$ is an excellent reductant for obtaining high yields of *meso*-**7** from **6**.

4. Reduction of α-diketones.

Similarly, the diastereoselectivity toward α-diketone **9** was examined (Table 4). All the reductions of aromatic α-diketones with $LiInH_4$ gave the corresponding diols **7** quantitatively and the *meso*-isomer was obtained preferentially. Although the reduction of **9** with $NaBH_4$ in ether did not proceed at all, the reduction went on smoothly in ethanol, but the selectivity decreased. Such solvent effect was also observed in $NaBH_4$ reduction of α,β-epoxy ketones[9] and β-diketones.[2b] The reduction with $LiAlH_4$ went on quantitatively, but diastereoselectivity was lower than that of $LiInH_4$. Furthermore, small amounts of benzyl alcohols **8** were produced. For the reduction of 4,5-octanedione (Run 5), all the reductants showed lower selectivity compared with the aromatic α-diketones. Nevertheless, the selectivity of $LiInH_4$ was the highest of the three reductants.

Table 3. Reduction of α-hydroxyketones [a]

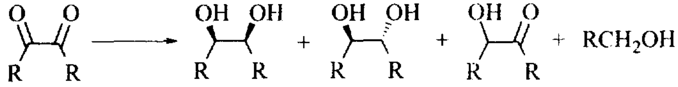


6 *meso*-7 *dl*-7 8

Run	R	$LiInH_4$ (%)	*meso* : *dl*	$NaBH_4$ (%)	*meso* : *dl*	$LiAlH_4$ (%)	*meso* : *dl*
1	Ph	6: 0 7: 100	100 : 0	6: 0 (0) 7: 95 (100)	98 : 2 (89 : 11)	6: 0 7: 94	97 : 3
2	*p*-BrC_6H_4	6: 0 7: 100	99 : 1	6: 52[b] 7: 41[b]	90 : 10	6: 0[c] 7: 100[c]	93 : 7
3	*p*-MeC_6H_4	6: 0 7: 99 8: 1	99 : 1	6: 0 7: 99 8: 1	98 : 2	6: 0 7: 92 8: 8	90 : 10
4	*p*-$MeOC_6H_4$	6: 0 7: 100	100 : 0	6: 3[d] 7: 97[d]	98 : 2	6: 0 7: 92 8: 8	93 : 7
5	Pr	6: 0 7: 94	88 : 12	6: 0 7: 96	83 : 17	6: 0 7: 85	73 : 27

a) Yields and ratios were estimated by ^1H-NMR. All reactions were carried out with a substrate (1 mmol) and a reductant (2 mmol) in Et_2O (20 ml) overnight at room temperature. Figures in parentheses refer to the reaction in EtOH. b) Isolated yield. c) Reaction time 5 h. d) This reaction was carried out with the substrate (1 mmol) and $NaBH_4$ (5 mmol) in Et_2O (20 ml).

Table 4. Reduction of α-diketone [a]



9 *meso*-7 *dl*-7 6 8

Run	R	$LiInH_4$ (%)[b]	*meso* : *dl*	$NaBH_4$ (%)[c]	*meso* : *dl*	$LiAlH_4$ (%)[b]	*meso* : *dl*
1	Ph	9: 0 7: 100	99 : 1	9: 80 (0) 7: 6 (100) 6: 14	93 : 7 (85 : 15)	9: 0 7: 99	91 : 9
2	*p*-BrC_6H_4	9: 0 7: 100	99 : 1	9: 100 (0) 7: 0 (100)	(79 : 21)	9: 0[d] 7: 100[d]	92 : 8
3	*p*-MeC_6H_4	9: 0 7: 100	98 : 2	9: 100 (0) 7: 0 (100)	(85 : 15)	9: 0 7: 93 8: 6	90 : 10
4	*p*-$MeOC_6H_4$	9: 0 7: 100	100 : 0	9: 100 (0) 7: 0 (100)	(86 : 14)	9: 0 7: 95 8: 5	91 : 9
5	Pr	9: 0 7: 96	72 : 28	9: 55 (0) 7: 8 (90) 6: 19	(50 : 50)	9: 0 7: 92	65 : 35

a) Yields and ratios were estimated by ^1H-NMR. b) All reactions were carried out with a substrate (1 mmol) and a reductant (2 mmol) in Et_2O (20 ml) overnight at room temperature. c) Runs 1 and 5 were carried out with a substrate (1 mmol) and $NaBH_4$ (2 mmol) in Et_2O (20 ml) and Runs 2-4 were carried out with a substrate (1 mmol) and $NaBH_4$ (5 mmol). Figures in parentheses refer to the reactions with a substrate (1 mmol) and $NaBH_4$ (2 mmol) in EtOH. d) Reaction time 7 h.

In the reductions of α-hydroxyketones **6** and α-diketones **9**, it was found that the substrates having aryl groups were reduced more selectively than the substrates having alkyl groups (Tables 3 and 4, Runs 1-4 vs. 5). On the other hand, β-hydroxyketones **1** and β-diketones **3** showed very little difference between aromatic and aliphatic compounds. This difference may be explained by comparison between their intermediates. In the reduction of **6** and **9**, reductants might be combined with a substrate to form a five-membered intermediate (Fig. 2). Since the R group in an axial position is an interfering factor in the reduction of **6** and **9**, the substituent significantly affects the stereoselectivities. On the contrary, since the hydrogen atom is an interfering factor in the cases of **1** and **3**, the R group contributes little to the selectivity (Fig. 1).

In summary, it has been found that $LiInH_4$ reduces hydroxyketones and diketones more stereoselectively than $NaBH_4$ and $LiAlH_4$. In particular, this reductant is useful for the stereoselective reduction of α-hydroxyketones and α-diketones to *meso*-1,2-diols.

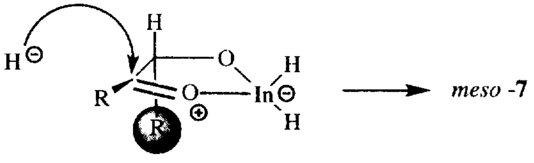


Figure 2

EXPERIMENTAL

General

All reactions were carried out under argon. Indium bromide was obtained from Kishida Reagents Chemicals. Lithium hydride was obtained from Nacalai Tesque Co., Ltd. Solvents were distilled before use. Following substrates were prepared according to the methods in literature: *3-hydroxy-1,3-diphenylpropan-1-one*,[5] *7-hydroxyundecan-5-one*,[5] *5,7-undecanedione*[10] (keto/enol = 20/80 by ^{1}H-NMR[11]), *4,4'-dibromobenzoin*,[12] *4,4'-dimethylbenzoin*,[12] *4,4'-dimethylbenzil*,[13] *4,4'-dimethoxybenzil*,[13] and *4,5-octanedione*.[14] Other substrates were commercially obtained.

Preparation of $LiInH_4$

As ether is the solvent of choice,[3b] all the reduction with $LiInH_4$ were carried out in ether. A mixture of $InBr_3$ (710 mg, 2 mmol) and LiH (64 mg, 8 mmol) in ether (20 ml) was stirred at -30 °C for 5 h to give a white suspension of $LiInH_4$. The suspension was directly used for the next reduction. Although the yield of $LiInH_4$ was not determined, it is regarded that the preparation went on quantitatively.

General reduction procedure

Reduction with $LiInH_4$: To a suspension of $LiInH_4$ prepared as described above, a substrate (1 mmol) was added in solid state or neat. The mixture was ultrasonicated at 10 °C for 2 h and then stirred overnight at room temperature. The reaction was quenched with 0.1N-HCl and the product was extracted with ether. The extracts were dried (Na_2SO_4) and then concentrated. The product was characterized by comparing the ^{1}H-NMR spectrum with that in literature: *1,3-diphenylpropane-1,3-diol*,[15] *5,7-undecanediol*,[5] *1,3-*

diphenylpropan-1-ol,[16] *6-undecen-5-ol*,[17] *hydrobenzoin*,[13] *4,4'-dibromohydrobenzoin*,[18] *4,4'-dimethylhydrobenzoin*,[13] *4,4'-dimethoxyhydrobenzoin*,[13] and *4,5-octanediol*.[19]

Reduction with $\boldsymbol{NaBH_4}$ ***or*** $\boldsymbol{LiAlH_4}$: To a suspension of $NaBH_4$ or $LiAlH_4$ (2 mmol) in ether (10 ml) was added a solution of a substrate (1 mmol) in ether (10 ml) at 0 °C. The mixture was stirred overnight at room temperature and worked up as above.

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