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Asymmetric Synthesis of the Both Enantiomers of α-Hydroxy Acids by the Diastereoselective Reduction of Chiral α-Keto Amides with (Complex) Metal Hydrides in the Presence of Metallic Salt

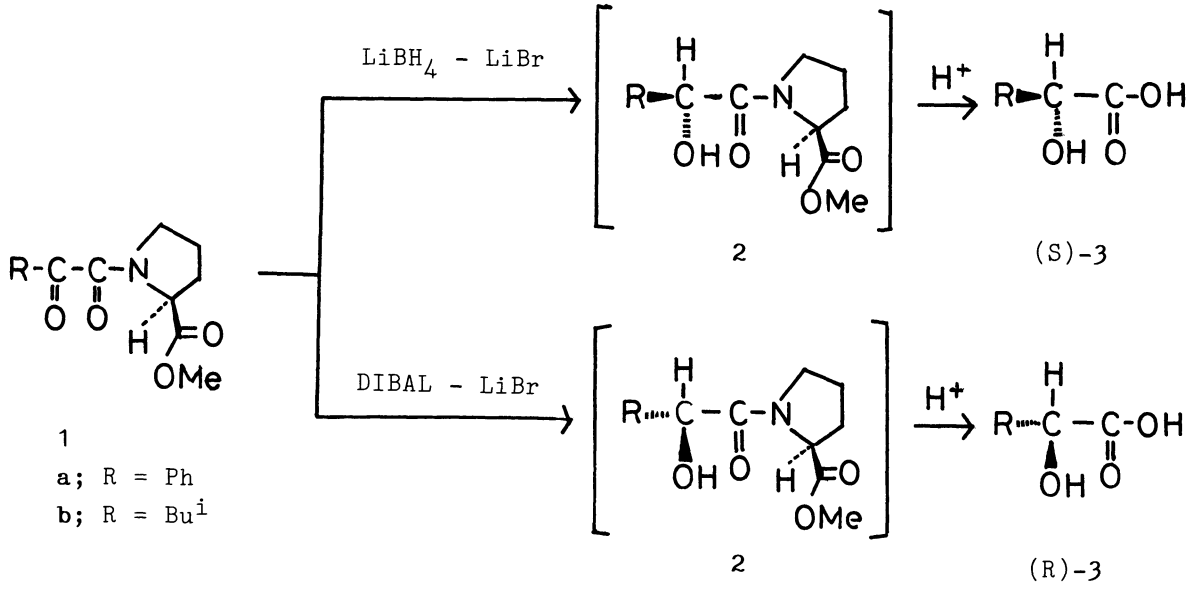
Kenso SOAI,* Takeshi ISODA, Hitoshi HASEGAWA, and Miyuki ISHIZAKI
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Shinjuku, Tokyo 162

Effects of the metallic salts and the reducing reagents in the diastereoselective reduction of chiral α-keto amides derived from (S)-proline methyl ester were examined. Lithium borohydride afforded (S)-α-hydroxy acids, whereas diisobutylaluminum hydride afforded (R)-isomers. In the presence of lithium bromide, reduction with $LiBH_4$ afforded (S)-mandelic acid in over 80% e.e.

Although the diastereoselective reduction of chiral α-keto esters has been well documented, only little study has been reported on the diastereoselective reduction of chiral α-keto amides with (complex) metal hydride.[1,2] Diastereoselective reduction of chiral α-keto amides with sodium borohydride ($NaBH_4$) shows only low to moderate asymmetric induction {44% diastereomeric excess(d.e.)}.[2c] During our continuing study on asymmetric reductions,[3] we recently reported the effect of mixed solvent on the diastereoselective reduction of α-keto amides with $NaBH_4$ (up to 69% d.e.).[4]

We wish to report the effects of (complex) metal hydride and metallic salts in the diastereoselective reduction of chiral α-keto amides (**1**) derived from (S)-proline methyl ester. Reduction of **1a** with various (complex) metal hydrides, and the subsequent hydrolysis of the resulting compound (**2a**) afforded mandelic acid (**3a**). Enantiomeric excesses(e.e.'s) of **3a** were determined by the optical rotation (and GLC analyses of the corresponding MTPA esters).[5] The results are summarized in Table 1.

It was found that the presence of metallic salt increased



diastereoselectivities considerably in the reduction of **1a** with lithium borohydride ($LiBH_4$) and diisobutylaluminum hydride (DIBAL). Among various lithium salts examined, the highest asymmetric induction was observed in the case of lithium bromide (LiBr). Thus, the presence of LiBr afforded (S)-**3a** in over 80% e.e.'s, whereas without LiBr e.e. of (S)-**3a** dropped to 63% e.e. When the molar ratio of LiBr to **1a** was 3, e.e. of (S)-**3a** was better than when the ratio was 1. Surprisingly, opposite diastereoselectivity was observed in the case of DIBAL. Thus, (R)-**3a** of 66% e.e. was obtained in the presence of LiBr. Homogeneous reaction system was essential for the high diastereoselectivity. Thus, the reaction at -78 ℃ (entry 2, homogeneous) was more stereoselective than that at -100 ℃ (heterogeneous mixture). Efficiency of LiBr was consistent in both nucleophilic and electrophilic reducing reagents and in both aromatic **1a** and aliphatic **1b**.

One of the explanations of the high diastereoselectivity may be the coordination of metallic salt with oxygen atom(s) of α-keto amides (**1**) which may reduce the number of possible conformations of α-keto amide.

In a typical experiment (Table 1, entry 2), to a solution of LiBr (1.0 mmol) and **1a** (0.5 mmol) in THF (2 ml), 0.5 ml of $LiBH_4$ (0.5 mmol, 1.0 M THF solution) was added at -78 ℃ during 10 min under an argon atmosphere. The mixture was stirred for 1 h, and was quenched with 1 M HCl (5 ml). After the aqueous layer was extracted with CH_2Cl_2, the extract was dried over anhydrous Na_2SO_4 and was

Table 1. Diastereoselective reduction of 1 in the presence of metallic salt[a)]

Entry	Compound (1)	Reducing reagent	Metallic salt	Temp/ ℃	Time/h	Product (3)		
						Yield/%	E.e./%e.e.[b)]	Config.
1	**a**	$LiBH_4$	---	-78	3	89	63	S
2	**a**	$LiBH_4$	LiBr[c)]	-78	1	85	87 (81)[d)]	S
3	**a**	$LiBH_4$	LiCl	-78	1	68	66	S
4	**a**	$LiBH_4$	LiI	-78 → -40	8	80	72	S
5	**a**	$LiBH_4$	$LiClO_4$	-78 → -40	8	75	72 (71)[d)]	S
6	**a**	$LiBH_4$	ZnI_2	-78 → 0	16	77	54	S
7	**a**	$NaBH_4$	LiBr	-78	2	47	65 (36)[e)]	S
8	**a**	Bu^i_2AlH	LiBr	-78	3	59	66 (54)[e)]	R
9	**b**	$LiBH_4$	LiBr	-78	5	85	58 (52)[e)]	S
10	**b**	Bu^i_2AlH	LiBr	-78	3	81	10	R

a) Unless otherwise noted, molar ratio was as follows. **1** : reducing reagent : metallic salt = 1 : 1 : 1. Tetrahydrofuran (THF) was used.
b) Enantiomeric excess. Based on the reported values of the specific rotation. (S)-(+)-**3a** $[\alpha]_D$ +158 (H_2O). See Ref. 6. (S)-(-)-**3b** $[\alpha]_D$ -27.2° (c 1.5, 1 M NaOH). M. Winitz, L. B. Frakenthal, N. Izumiya, S. M. Birnbaum, C. G. Balcer, and J. P. Greenstein, J. Am. Chem. Soc., 78, 2423 (1956).
c) Molar ratio, **1a** : $LiBH_4$: LiBr = 1 : 1 : 2.
d) Determined by GLC analysis of the corresponding (-)-α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) ester,[5)] after **3a** was converted to methyl ester with trimethylsilyldiazomethane.[7)]
e) Results without LiBr.

evaporated under reduced pressure. Then 5 ml of 4 M H_2SO_4 was added to the residue and the mixture was refluxed for 2 h. The mixture was extracted with ether. The solvent was dried over anhydrous Na_2SO_4 and was evaporated in vacuo. Purification of the crude product by bulb-to-bulb distillation afforded (S)-**3a** {$[\alpha]_D$ +137.5°(c 1, H_2O)} in 85% yield and in 87% e.e. by optical rotation.[6)] The compound was determined to be 85% e.e. as (S)-methyl mandelate[7,8)] and 81% e.e. as MTPA ester.[5)]

As described, in the presence of metallic salts, chiral α-keto amides were reduced diastereoselectively. By choosing the appropriate reagent ($LiBH_4$ or DIBAL), the both enantiomers of α-hydroxy acids were obtained in good to high e.e.'s.[9]

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