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ASYMMETRIC REDUCTION OF PROCHIRAL HYDROXY KETONES WITH A CHIRAL REDUCING AGENT PREPARED FROM TIN(II) CHLORIDE, A CHIRAL DIAMINE, AND DIISOBUTYLALUMINUM HYDRIDE

Teruaki MUKAIYAMA, Koji TOMIMORI, and Takeshi ORIYAMA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Asymmetric reduction of prochiral α- and β-hydroxy ketones with a reagent, generated from tin(II) chloride, a chiral diamine, and diisobutylaluminum hydride, afforded the corresponding dihydroxy compounds in good chemical and optical yields. Optical yields depended on the nature of the protective groups of hydroxyl function.

Stereoselective introduction of oxygen functionalities provides the most effective way to the synthesis of polyoxygenated natural products such as macrolides, carbohydrates and so on. Among many chiral transformations, asymmetric reduction of carbonyl compounds has been extensively studied and fairly high level of enantioselectivity has been achieved.[1)]

During our continuous study on the asymmetric reduction with the chiral reducing agent, generated from tin(II) chloride and diisobutylaluminum hydride (DIBAH) in the presence of chiral diamine derived from (S)-proline, it was demonstrated that prochiral ketones[2)] and various (α-, β-, and γ-) keto esters[3)] are readily reduced to the corresponding optically active secondary alcohols and hydroxy esters respectively. In connection with our efforts in exploring useful synthetic precursors possessing chiral centers, we investigated asymmetric reduction of hydroxy ketones which is considered to be one of the important subjects. Such reductions have never been reported in the literature.

Now, we wish to report an asymmetric reduction of α- and β-hydroxy ketones utilizing the non-covalent bonded interaction between the chiral diamine and tin(II) metal center of the reducing agent.

In the first place, we undertook to examine the reduction of 2-hydroxyacetophenone according to the procedure similar to that shown in the previous paper.[3)] Phenyl-1,2-ethanediol was obtained in 35% chemical yield and the optical purity of this product was shown to be 47% ee based on the highest reported value of rotation.[4)] Next, we examined the reduction of the O-silylated α-hydroxy ketone (Table 1, Entry 2) and it was observed that chemical yield increased from 35% to 78% and optical yield increased from 47% ee to 65% ee. Screening of the effect of the protective groups of hydroxyl function on both chemical and optical yields, taking 2-hydroxyacetophenone as a model, revealed that 2-methoxyethoxymethyl (MEM) ether was the most effective in controlling the asymmetric induction

(Entry 6). The affinity of oxygen atom of MEM moiety for tin(II) atom of the reducing agent rendered the transition state profitable to achieve higher enantioselection. Other examples are listed in Table 1. None of the protective groups were affected under the reaction conditions and optically active mono protected 1,2-diols were obtained in good yields. Higher enantioselectivities could be accomplished by the use of (S)-1-ethyl-2-(piperidinomethyl)pyrrolidine as a ligand instead of (S)-1-methyl-2-(piperidinomethyl)pyrrolidine (Entries 3, 7, and 10).

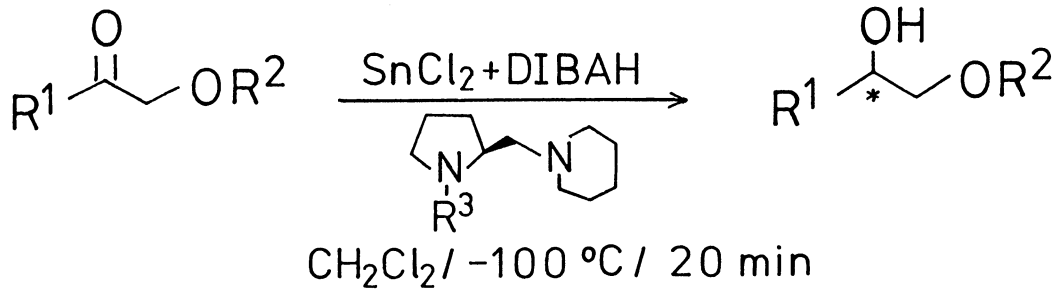

Table 1. Asymmetric Reduction of α-Hydroxy Ketones[a)]

Entry	R^1	R^2	R^3	Yield/%[b)]	$[\alpha]_D$	Optical yield/% ee	Abs. config.
1	Ph	H	Me	35	$[\alpha]_D^{17}$ +21.4°(c 1.32, Me_2CO)	47[c)]	S[c)]
2		t-$BuMe_2Si$	Me	78	$[\alpha]_D^{27}$ +17.8°(c 3.81, CH_2Cl_2)	65[d,e)]	S[e)]
3		t-$BuMe_2Si$	Et	67	$[\alpha]_D^{22}$ +24.8°(c 2.57, CH_2Cl_2)	76[d,e)]	S[e)]
4		CPh_3	Me	85	$[\alpha]_D^{16}$ +2.4°(c 1.96, $CHCl_3$)	32[f)]	S[f)]
5		MOM	Me	83	$[\alpha]_D^{22}$ +24.9°(c 4.25, c-C_6H_{12})	70[d,e)]	S[e)]
6		MEM	Me	81	$[\alpha]_D^{20}$ +37.7°(c 3.64, $CHCl_3$)	91[e)]	S[e)]
7		MEM	Et	74	$[\alpha]_D^{18}$ +37.6°(c 2.99, $CHCl_3$)	93[e)]	S[e)]
8		MeCO	Me	68	$[\alpha]_D^{18}$ +39.4°(c 2.83, $CHCl_3$)	78[d)]	S[e)]
9		PhCO	Me	63	$[\alpha]_D^{20}$ +20.7°(c 3.28, CH_2Cl_2)	65[d)]	S[e)]
10	Me	MEM	Et	42	$[\alpha]_D^{23}$ -6.8°(c 1.35, $CHCl_3$)	71[d)]	
11		THP	Me	86	$[\alpha]_D^{19}$ -4.0°(c 2.28, $CHCl_3$)	60[d)]	
12		PhCO	Me	88	$[\alpha]_D^{25}$ -11.5°(c 4.07, $CHCl_3$)	53[g)]	R[g)]

a) Molar ratio of hydroxy ketone : $SnCl_2$: DIBAH : diamine = 0.35-0.5 : 1 : 0.5-0.8 : 1.

b) Isolated yields. All samples gave satisfactory ^{1}H-NMR and IR spectra.

c) Optically active (R)-phenyl-1,2-ethanediol gives $[\alpha]_D^{25}$ -45.8°(c 2, Me_2CO).[4)]

d) Determined by ^{1}H-NMR or ^{19}F-NMR measurement of its MTPA ester.[5)]

e) Determined by the optical rotation of corresponding phenyl-1,2-ethanediol[6)] obtained from the removal of the protective group.

f) Optically pure (S)-1-phenyl-2-trityloxyethanol gives $[\alpha]_D$ +7.5°(c 1.94, $CHCl_3$).[7)]

g) Optically pure (S)-1-benzoyloxy-2-propanol gives $[\alpha]_D^{24}$ +21.8°($CHCl_3$).[8)]

Also in the case of the asymmetric reduction of β-hydroxy ketones, the MEM ethers gave the best results as shown in Table 2 (Entries 3 and 5).

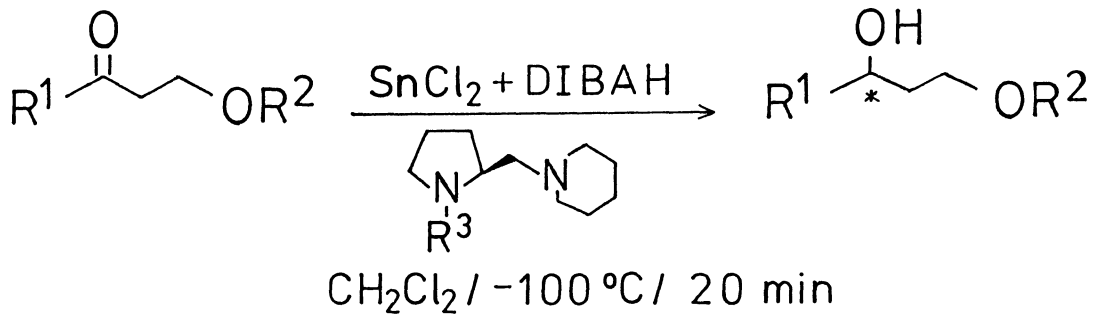

Table 2. Asymmetric Reduction of β-Hydroxy Ketones[a)]

Entry	R^1	R^2	R^3	Yield/%[b)]	$[\alpha]_D$	Optical yield/% ee	Abs. config.
1	Ph	*t*-$BuMe_2Si$	Me	92	$[\alpha]_D^{20}$ +24.7°(c 0.76, $CHCl_3$)	65[c)]	R[d)]
2		MEM	Me	65	$[\alpha]_D^{23}$ +21.3°(c 2.98, $CHCl_3$)	63[c)]	R[d)]
3		MEM	Et	75	$[\alpha]_D^{19}$ +32.2°(c 2.60, $CHCl_3$)	81[c)]	R[d)]
4		Ts	Me	92	$[\alpha]_D^{24}$ +12.0°(c 5.53, $CHCl_3$)	50[c)]	R[d)]
5	Me	MEM	Et	73	$[\alpha]_D^{18}$ -20.6°(c 2.47, $CHCl_3$)	87[c)]	

a) Molar ratio of hydroxy ketone : $SnCl_2$: DIBAH : diamine = 0.35-0.5 : 1 : 0.5-0.8 : 1.

b) Isolated yields. All samples gave satisfactory ^{1}H-NMR and IR spectra.

c) Determined by ^{1}H-NMR or ^{19}F-NMR measurement of its MTPA ester.[5)]

d) Determined by the optical rotation of corresponding 1-phenyl-1,3-propanediol[9)] obtained from the removal of the protective group.

A typical procedure is described for the reduction of 2-(2-methoxyethoxymethoxy)acetophenone; to a suspension of anhydrous tin(II) chloride (144 mg, 0.76 mmol) and (S)-1-ethyl-2-(piperidinomethyl)pyrrolidine (148 mg, 0.76 mmol) in 4 ml of dichloromethane was added dropwise DIBAH (54 mg, 0.38 mmol) in 0.38 ml of toluene at -100 °C under argon atmosphere. Then, 2-(2-methoxyethoxymethoxy)-acetophenone (60.0 mg, 0.27 mmol) in 2 ml of dichloromethane was added dropwise at -100 °C and the resulting mixture was stirred for 20 min at this temperature. The reaction was quenched with pH 7 phosphate buffer, and the precipitates were removed by filtration. The organic materials were extracted with dichloromethane and dried over anhydrous Na_2SO_4. 2-(2-Methoxyethoxymethoxy)-1-phenylethanol (44.9 mg, 74%) was isolated by thin layer chromatography on silica gel. $[\alpha]_D^{18}$ +37.6°(c 2.99, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 3.1-3.7 (m, 7H), 3.18 (s, 3H), 4.5-4.8 (m, 1H), 4.53 (s, 2H), 7.13 (s, 5H); IR (neat) 3450, 2900, 1460, 1120, 1100, 1040 cm^{-1}.

It is noted that the present asymmetric reduction procedure has considerable synthetic value, since higher enantioselectivity could be achieved by the choice of suitable protective group of hydroxyl function of hydroxy ketones. Application of this asymmetric reduction to the synthesis of chiral polyoxygenated compounds such as glycerol derivatives will be reported in due course.

References

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