CHEMISTRY LETTERS, pp. 813-816, 1985.

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

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Asymmetric reduction of prochiral keto esters with a reagent, generated by treatment of a mixture of tin(II) chloride and a chiral diamine derived from (S)-proline with diisobutylaluminum hydride, afforded the corresponding optically active hydroxy esters.

Optically active hydroxy esters are important and versatile synthetic intermediates for the construction of chiral organic frameworks.[1] Asymmetric reduction of keto esters to hydroxy esters by microbial transformation[2] or catalytic hydrogenation[3] has been widely studied, however, relatively little is known about the asymmetric reduction of keto esters by chiral reducing agents[4] in spite of dramatic progress in the area of asymmetric reduction of prochiral ketones.[5]

In the previous paper,[6] we reported that a chiral reducing agent, generated from tin(II) chloride and diisobutylaluminum hydride (DIBAH) in the presence of a chiral diamine derived from (S)-proline, reacts smoothly with prochiral ketones to yield optically active secondary alcohols in good enantioselectivity. In these reductions, efficient coordination of the bidentate chiral diamine to the divalent tin hydride plays an important role and a *cis*-fused five-membered ring chelate complex is found to be effective for optical induction. During our continuous study on the asymmetric reduction of a wide variety of prochiral carbonyl substrates, we discovered that various α-, β-, and γ-keto esters are readily reduced to the corresponding hydroxy esters by the chiral reducing agent.

In the first place, we undertook to examine the reduction of ethyl benzoylformate according to the procedure similar to that shown in the previous paper on simple ketones. Ethyl mandelate was obtained in 90% chemical yield and the optical purity of this product was shown to be 85% ee based on the reported optical rotation.[7]

Screening of the effect of the ester group on the optical yield, taking benzoylformic acid as a model, revealed that methoxymethyl (MOM) or 2-methoxyethoxymethyl (MEM) ester was effective in controlling the asymmetric induction. The affinity of oxygen atom of MOM (or MEM) moiety for tin(II) atom of the reducing agent rendered the transition state profitable to achieve higher enantioselection.

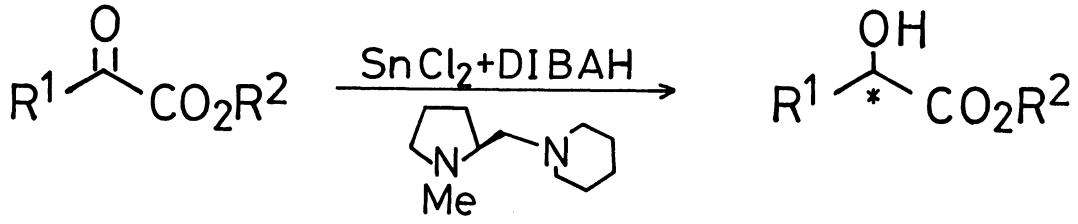


Table 1. Asymmetric Reduction of α-Keto Esters[a)]

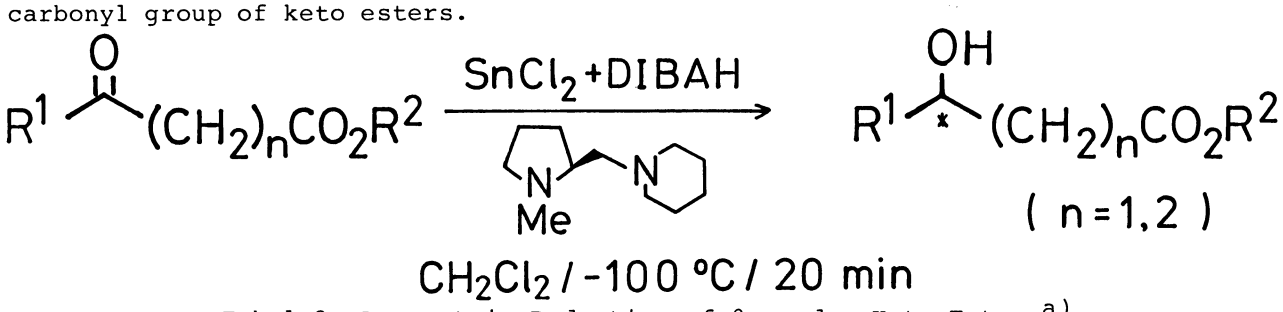
Entry	Keto ester R^1	R^2	Yield/%[b)]	$[\alpha]_D$	Optical yield/% ee	Abs. config.
1	Ph	Me	88	$[\alpha]_D^{25}$ +117.6°(c 0.72, $CHCl_3$)	68[c)]	S[c)]
2		Et	90	$[\alpha]_D^{20}$ +107.8°(c 4.38, $CHCl_3$)	85[d,e)]	S[d)]
3		MOM	69	$[\alpha]_D^{21}$ +94.4°(c 3.32, $CHCl_3$)	89[e)]	S[e)]
4		MEM	82	$[\alpha]_D^{27}$ +73.2°(c 2.66, $CHCl_3$)	89[e)]	S[e)]
5	Me	Et	60	$[\alpha]_D^{26}$ -3.8°(c 2.38, Me_2CO)	40[f)]	S[g)]
6		MOM	60	$[\alpha]_D^{20}$ -8.6°(c 1.20, Me_2CO)	48[f)]	S[h)]
7	Me_2CH	Me	50	$[\alpha]_D^{20}$ -8.7°(c 2.73, $CHCl_3$)	46[f)]	R[i)]
8	Me_2CHCH_2	Me	64	$[\alpha]_D^{24}$ +1.5°(c 3.55, $CHCl_3$)	40[f)]	S[j)]

a) Molar ratio of keto ester : $SnCl_2$: DIBAH : diamine = 0.3-0.5 : 1 : 0.5-0.8 : 1
b) Isolated yields. All samples gave satisfactory ^{1}H-NMR and IR spectra.
c) Optically pure (R)-methyl mandelate gives $[\alpha]_D^{20}$ -174.2°(c 4.05, $CHCl_3$).[8)]
d) Optically pure (R)-ethyl mandelate gives $[\alpha]_D$ -126.4°(c 3.33, $CHCl_3$).[7)]
e) Determined by the optical rotation of corresponding styrene glycol[9)] obtained from lithium aluminum hydride reduction.
f) Determined by ^{1}H-NMR or ^{19}F-NMR measurement of its MTPA ester.[10)]
g) Optically active (R)-ethyl lactate gives $[\alpha]_D^{20}$ +9.6°(c 1.2, Me_2CO).[2b)]
h) Determined by the optical rotation of corresponding 1,1-diphenyl-1,2-propanediol obtained from Grignard reaction with phenyl magnesium bromide.[11)]
i) Determined by the optical rotation of corresponding 3-methyl-1,1-diphenyl-1,2-butanediol obtained from Grignard reaction with phenyl magnesium bromide.[11)]
j) Optically pure (S)-methyl 2-hydroxy-3-methylpentanoate gives $[\alpha]_D$ +2.7°(c 1.0, $CHCl_3$).[12)]

Other several examples of asymmetric reduction of α-keto esters are listed in Table 1. All of the α-keto esters are consistently reduced to the corresponding α-hydroxy esters in good yields. In general, hydride attacks preferentially from *si*-face of the carbonyl group, except for the keto ester having α-branched alkyl group (entry 7).

Next, we examined the asymmetric reduction of β- and γ-keto esters and the results are summarized in Table 2. The enantiomeric excesses which were observed by the reduction of γ-keto esters (entries 3 and 4) were similar to that of simple prochiral ketones[6)] such as propiophenone (74% ee) and 2-octanone (61% ee)

respectively. These results indicate that ester group at γ-position to the carbonyl group has no significant influence on the asymmetric reduction of carbonyl group of keto esters.



Tabel 2. Asymmetric Reduction of β- and γ-Keto Esters[a)]

Entry	Keto ester R^1	R^2	n	Yield/%[b)]	$[\alpha]_D$	Optical yield/% ee	Abs. config.
1	Ph	Et	1	59	$[\alpha]_D^{22}$ +23.6°(c 2.21, $CHCl_3$)	44[c,e)]	R[c)]
2	Me	Et	1	59	$[\alpha]_D^{20}$ -15.3°(c 0.97, $CHCl_3$)	35[d,e)]	R[d)]
3	Ph	Me	2	88	$[\alpha]_D^{25}$ +27.4°(c 3.56, $CHCl_3$)	72[e)]	
4	Me	Et	2	77	$[\alpha]_D^{20}$ -7.74°(c 1.87, $CHCl_3$)	60[e)]	R[f)]

a), b) See Table 1 footnotes a), b).

c) Optically pure (S)-ethyl 3-hydroxy-3-phenylpropionate gives $[\alpha]_D^{22}$ -54.9°(c 3.5, $CHCl_3$).[13)]

d) Optically pure (R)-ethyl 3-hydroxybutanoate gives $[\alpha]_D^{21}$ -43.4°(c 1.36, $CHCl_3$).[2c)]

e) Determined by ^{1}H-NMR or ^{19}F-NMR measurement of its MTPA ester.[10)]

f) Determined by the optical rotation of corresponding γ-butyrolactone.[14)]

A typical procedure is described for the reduction of ethyl benzoylformate; to a suspension of anhydrous tin(II) chloride (167 mg, 0.88 mol) and (S)-1-methyl-2-(piperidinomethyl)pyrrolidine (160 mg, 0.88 mol) in 4 ml of dichloromethane was added dropwise DIBAH (85.3 mg, 0.6 mol) in 0.60 ml of dichloromethane at -100 °C under argon atmosphere. Then ethyl benzoylformate (64.5 mg, 0.36 mol) in 2 ml of dichloromethane was added dropwise at -100 °C. The resulting mixture was stirred for 20 min at this temperature and was quenched with pH 7 phosphate buffer. After addition of 15 ml of ether, the precipitates were filtered off and washed with ether. Organic layer was washed with 10% $KHSO_4$ and brine, and dried over anhyd. Na_2SO_4. Filtration and concentration in vacuo gave an oily residue (66 mg) which was purified by thin layer chromatography (SiO_2, Et_2O-hexane 1:1) to afford (S)-(+)-ethyl mandelate (58.8 mg, 90%). $[\alpha]_D^{20}$ +107.8°(c 4.38, $CHCl_3$). Chiral diamine was recovered in over 80% yield without racemization by washing the precipitates with hydrochloric acid.

The present asymmetric reduction which is well controlled by the use of the bidentate chiral diamine as a ligand is found to be applicable to the asymmetric reduction of various keto esters by the operationally simple procedure within a short reaction time.

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(Received March 18, 1985)