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ASYMMETRIC REDUCTION OF PROCHIRAL KETONES WITH A CHIRAL REDUCING AGENT PREPARED FROM STANNOUS CHLORIDE, CHIRAL DIAMINE AS A LIGAND, AND DIISOBUTYLALUMINUM HYDRIDE

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A new chiral reducing agent, prepared by treatment of a mixture of stannous chloride and a chiral diamine derived from (S)-proline with diisobutylaluminum hydride, is effective for asymmetric reduction of prochiral ketones.

Asymmetric reduction of prochiral ketones to optically active secondary alcohols is one of the most important reactions in organic synthesis and has been extensively studied in recent years.1) High enantioselectivities in the asymmetric reductions of aryl alkyl ketones2) and α,β-unsaturated ketones3) have been achieved by the use of various chiral hydride reagents such as lithium aluminum hydride partially decomposed by optically active alcohols and amines. However, these hydride reagents yield fairly low optical induction in the case of aliphatic ketones. In the last couple of years, Alpine-Borane4) and NB-Enantride5) have emerged to be available for the asymmetric reduction of aliphatic ketones. In almost all of the asymmetric reduction mentioned above, chirality has been induced by chiral auxiliaries that are covalently bonded to the reducing agents.

Now, we wish to report an asymmetric reduction of prochiral ketones with a chelate complex formed from divalent tin hydride and a chiral diamine derived from (S)-proline.

In the previous paper,6) we described that the reducing agent prepared by treatment of stannous chloride with diisobutylaluminum hydride (DIBAH) was effective for debromination of α-bromo ketones and of *vic*-dibromoalkanes. On the other hand, in our laboratory, highly enantioselective cross-aldol reaction is achieved via divalent tin enolates employing chiral diamines derived from (S)-proline as ligands.7)

Based on these facts, asymmetric reduction was examined according to the following procedure. A mixture of stannous chloride and (S)-1-methyl-2-(piperidinomethyl)pyrrolidine as a chiral diamine was treated with DIBAH in dichloromethane,8) and then 1-phenyl-2-propanone was added. Usual work-up of this reaction mixture afforded the reduction product, 1-phenyl-2-propanol, in 77% yield and the optical purity of this product was shown to be 59% e.e. based on the optical rotation.9) A screening of the reaction conditions using 1-phenyl-2-

propanone as a prochiral ketone revealed that the molar ratio of DIBAH per $SnCl_2$ played an important role in the enantioselectivity of the present reaction as shown in Table 1.

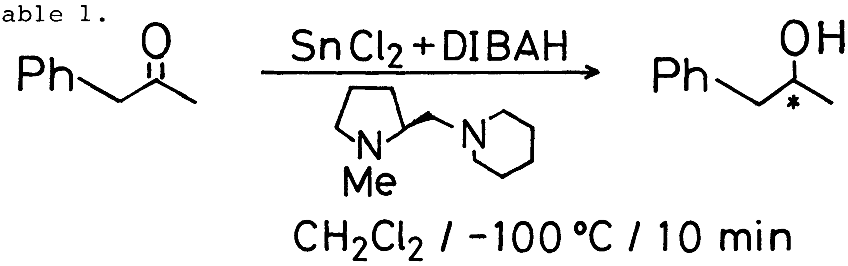


Table 1. The Effect of Molar Ratio of DIBAH per $SnCl_2$

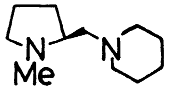
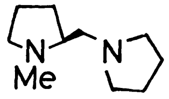
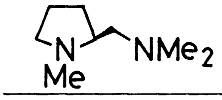
DIBAH/$SnCl_2$[a)]	Yield/%[b)]	$[\alpha]_D$ (C_6H_6)	Optical yield/% e.e.[c)]
2	79	-16.9° (c 3.06)	40
1.2	81	-24.5° (c 3.21)	59
1.0	77	-24.6° (c 3.23)	59
0.8	81	-27.2° (c 3.69)	65
0.6	81	-30.1° (c 3.71)	72
0.5	71	-32.5° (c 2.95)	78

a) Molar ratio of $SnCl_2$: diamine = 1 : 1.
b) Isolated yield. All these alcohols have (R)-configuration.
c) Based on $[\alpha]_D^{20}$ +41.8° (c 5.26, C_6H_6), see Ref. 8.

It is noted that efficient coordination of bidentate chiral auxiliary (diamine) to the tin(II) metal center (possessing vacant d orbitals) is thought to be crucial for enantioselection in this reduction.

In order to attain the best reaction conditions, we next examined various chiral diamines, and it was found that use of (S)-1-methyl-2-(piperidinomethyl)-pyrrolidine as a ligand gave the best result as shown in Table 2.

Table 2. The Effect of Employed Chiral Diamine on Optical Yield[a)]

Chiral diamine	Yield/%	Optical yield/% e.e.
	71	78
	59	64
	47	46

a) Reaction was carried out at -100 °C for 10 min. Molar ratio of 1-phenyl-2-propanone : $SnCl_2$: DIBAH : diamine = 0.45 : 1 : 0.5 : 1.

The reaction was conducted with representative ketones under the optimum conditions. These results are summarized in Table 3.

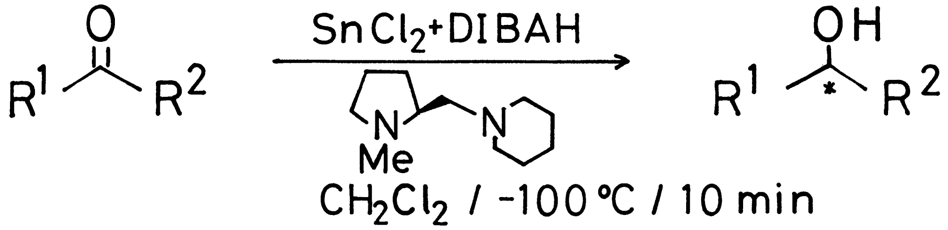


Table 3. Asymmetric Reduction of Prochiral Ketones[a)]

Ketone	Yield/%[b)]	$[\alpha]_D$	Optical yield/% e.e.	Configuration
$PhCH_2COCH_3$	71	$[\alpha]_D^{23}$ -32.5°(c 2.95, C_6H_6)	78[c)], 77[d)]	R
$Ph(CH_2)_2COCH_3$	91	$[\alpha]_D^{21}$ -11.1°(c 3.95, C_6H_6)	60[d)]	R
n-$C_6H_{13}COCH_3$	67	$[\alpha]_D^{27}$ -5.60°(c 2.43, EtOH)	56[e)], 61[h)]	R
$PhCOCH_3$	80	$[\alpha]_D^{28}$ +39.9°(c 2.74, CH_2Cl_2)	76[f)], 78[d)]	R
$PhCOCH_2CH_3$	74	$[\alpha]_D^{27}$ +33.6°(c 2.51, $CHCl_3$)	74[g)], 73[d)]	R

a) Molar ratio of ketone : $SnCl_2$: DIBAH : diamine = 0.35-0.45 : 1 : 0.5 : 1.
b) Isolated yield. All samples gave satisfactory ^1H NMR and IR spectra.
c) Based on $[\alpha]_D^{20}$ +41.8° (c 5.26, C_6H_6), see Ref. 8.
d) Determined by ^1H NMR or ^{19}F NMR measurement of its MTPA ester.[10)]
e) Based on $[\alpha]_D^{21}$ +10.1° (c 5.58, EtOH) reported by R. K. Hill, J. Am. Chem. Soc., 80, 1611 (1958).
f) Based on $[\alpha]_D^{22}$ -52.5° (c 2.27, CH_2Cl_2) reported by U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, Tetrahedron, 21, 1701 (1965).
g) Based on $[\alpha]_D$ -45.45° (c 5.15, $CHCl_3$), see Ref. 8.
h) Determined by ^{19}F NMR measurement of its MTPA ester in the presence of Eu(fod)$_3$.

A typical procedure is described for the reduction of 1-phenyl-2-propanone using (S)-1-methyl-2-(piperidinomethyl)pyrrolidine as a chiral ligand; to a suspension of anhydrous stannous chloride (192 mg, 1.01 mmol) and (S)-1-methyl-2-(piperidinomethyl)pyrrolidine (184 mg, 1.01 mmol) in 3 ml of dichloromethane was added dropwise DIBAH (72.5 mg, 0.51 mmol) in 0.51 ml of toluene at -100 °C under argon atmosphere. Then 1-phenyl-2-propanone (61.1 mg, 0.455 mmol) in 2 ml of dichloromethane was added dropwise at -100 °C. The resulting mixture was stirred for 10 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. 1-Phenyl-2-propanol (44.2 mg, 71%) was isolated by thin layer chromatography on silica gel.

It should be noted that the present asymmetric reduction by the use of chiral chelate complex prepared by treatment of divalent tin hydride with chiral diamine has the characteristics of experimental convenience and of higher enantioselectivity also in the case of aliphatic ketones. The asymmetric reductions of a wide variety of carbonyl compounds are now in progress.

References

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8) The debromination of α-bromo ketones to ketones proceeded selectively in THF,$^{6)}$ because the reducing agent prepared by treatment of stannous chloride with DIBAH did not react with ketones in THF. On the other hand, it was made clear that ketones were immediately reduced to alcohols with this reducing agent in dichloromethane even at -100 °C.

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