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ENANTIOFACE-DIFFERENTIATING (ASYMMETRIC) ADDITION OF ALKYLLITHIUM TO ALDEHYDES BY USING (2S, 2'S)-2-HYDROXYMETHYL-1-[(1-METHYLPYRROLIDIN-2-YL)METHYL]-PYRROLIDINE AS CHIRAL LIGAND

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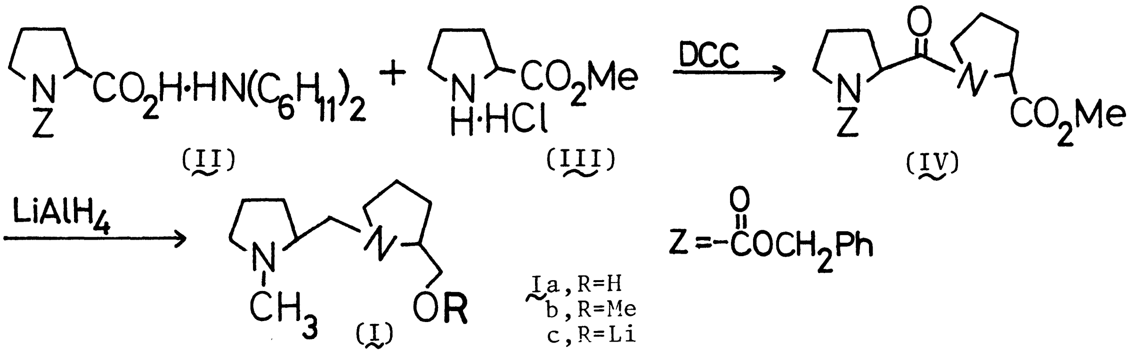
Optically active alcohols are produced in good optical yields by treating aromatic and aliphatic aldehydes with alkyllithium by using (2S, 2'S)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]-pyrrolidine as chiral ligand.

Many attempts have been reported to effect asymmetric synthesis of optically active alcohols by the enantioface-differentiating reaction of organometallic reagents with carbonyl compounds.1) For example, in the case of asymmetric reduction of unsymmetrical ketone with metal hydrides, relatively high optically pure alcohols have been obtained by several methods.2) On the other hand, optical yields in the asymmetric reactions of organometallic reagents, such as Grignard reagents,3a-3e) alkyllithium,3b),4) organocopper(II)5) or alkylcadmium,6) with carbonyl compounds by using chiral ligand or in chiral solvent are very low (0-25 %), except for the formation of 1-cyclohexyl-1-phenylethanol from cyclohexyl phenyl ketone and MeMgBr by using D-glucofuranose derivative (70% optical yield) as chiral ligand.3e)

Now we wish to report the enantioface-differentiating reaction of alkyllithium with various aldehydes by using a new and efficient ligand, (2S, 2'S)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (**Ia**).

The amino alcohol (**Ia**) was prepared according to the following scheme; to a stirred mixture of dicyclohexylamine salt of (S)-N-benzyloxycarbonylproline7) (**II**) (2.15g, 5 mmol) and (S)-proline methyl ester hydrochloride8) (**III**) (0.83g, 5 mmol) in chloroform (15 ml) was added a chloroform (5 ml) solution of dicyclohexylcarbodiimide (1.04g, 5 mmol) at 0°C under an argon atmosphere and stirred at 0°C for 3 hr, and then at room temperature over night. By the usual work-up (2S, 2'S)-N-(N-benzyloxycarbonylprolyl)proline methyl ester[9] (IV) (1.65g, m.p. 69-71°C, $[\alpha]_D^{28}$ -83.45° (c 2.10, CH_2Cl_2)) was obtained in 92% yield. Reduction of IV (1.65g, 4.6 mmol) with $LiAlH_4$ (0.607g, 16 mmol) in THF (25 ml) under refluxing for 14 hr gave Ia[10] (0.734g, b.p. 112°C/4.5 mmHg, $[\alpha]_D^{28}$ -130° (c 0.36, EtOH)) in 81% yield.

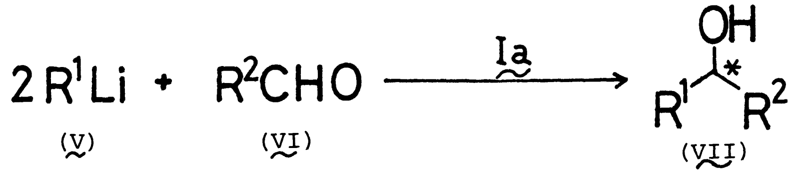
Scheme



The following experimental procedure is representative of the preparation of optically active alcohols. To an ether (17.7 ml) solution of Ia (0.803g, 4.05 mmol) was added a hexane (4.66 ml) solution of n-butyllithium (6.75 mmol) at 0°C under an argon atmosphere. The reaction mixture was stirred for 30 minutes and then was cooled to -123°C (liq N_2-ether bath). An ether (1.5 ml) solution of benzaldehyde (0.106g, 1 mmol) was added, and the stirring was continued for 2 hr. The reaction mixture was quenched with 6N hydrochloric acid, extracted with ether. The organic layer was washed successively with 6N hydrochloric acid and brine, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel TLC and the isolated product was further purified by short path vacuum distillation. 1-Phenyl-1-pentanol (0.098g, 60%S.Y, 72%O.P.) was obtained as a colorless oil, whose spectral data (IR and NMR) were identical with those of an authentic sample.

In a similar manner, various optically active alcohols were obtained by the enantioface-differentiating reaction of alkyllithium with carbonyl compounds using Ia as the chiral ligand. The results are summarized in the table. As shown in the table, the chiral ligand Ia is very effective and the higher optical yields were realized compared with the previous methods. It is noteworthy that, even in the case of the reaction of aliphatic aldehyde, the corresponding alcohol was obtained in good optical yield (56%), and that the size of alkyllithium affected the configuration of the alcohols obtained.

Table Enantioface-differentiating Addition of Alkyllithium to Aldehydes Using Ia



	V	VI		Alcohol (VII)			
Exp	R^1	R^2	Temp (°C)	Yield (%)	$[\alpha]_D$ (c, solvent)	Optical purity(%)	Config.
1	Me	Rh	-78	82	$[\alpha]_D^{26}$+9.16° (6, cyclopentane)[11]	21	R
2	Et	Ph	-123	32	$[\alpha]_D^{27}$+17.5° (0.857, chloroform)[12]	39	R
3	n-Pr	Ph	-123	55	$[\alpha]_D^{27}$-17.7° (6.3, benzene)[13]	39	S
4	n-Bu	Ph	-123	60	$[\alpha]_D^{25}$-22.7° (3, benzene)[4]	72	S
5	i-Bu	Ph	-123	59	$[\alpha]_D^{28}$-5.2° (11.2, heptane)[14]	16	S
6	n-Bu	i-Pr	-123	47	$[\alpha]_D^{28}$-15.5° (10, ethanol)[15]	56	S
7	Ph	n-Bu	-123	46	$[\alpha]_D^{25}$+3.3° (2.4, benzene)	11	R

Further, it was found that both 2-hydroxymethyl-1-methylpyrrolidine and (2S, 2'S)-2-methoxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (Ib) had no efficacy as chiral ligands for asymmetric induction in the reaction of n-butyllithium with benzaldehyde. This result indicates that two pyrrolidine moieties and lithiated hydroxymethyl group are essential for the asymmetric

Figure 1

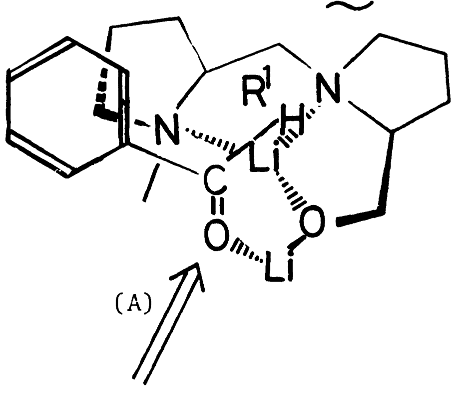
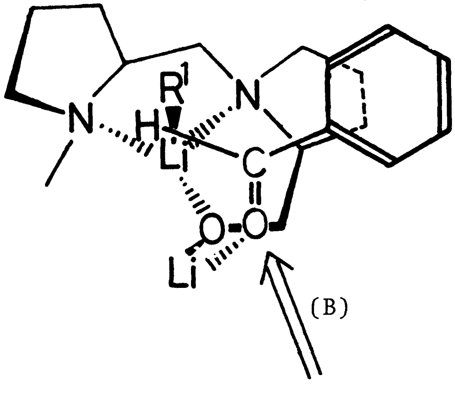


Figure 2



induction, and we tentatively present a possible model for the complex (VIII) of Ic and alkyllithium. The rigid structure, VIII, with four fused five-membered rings may be formed by the coordination of two nitrogen[16] and oxygen atoms to lithium metal of alkyllithium. Coordination of the oxygen atom of aldehyde to the lithium of the lithiated hydroxymethyl group may also limit the course (either A or B) of the approach of aldehydes to the rigid complex VIII. Although the detailed mechanism is not yet clear, it may be assumed that the size of alkyllithium would determine the course A or B. The approach of aldehydes through the course A may result in the formation of alcohols possessing the S-configuration (Exp. 3-5) as shown in figure 1, and the reverse configuration (Exp. 1 and 2) may be attained through the course B as shown in figure 2, as supported by CPK model.

Further study on the detailed mechanism is now in progress.

ACKNOWLEDGEMENT

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