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ASYMMETRIC REDUCTION OF ACETOPHENONE WITH CHIRAL HYDRIDE REAGENT PREPARED FROM LITHIUM ALUMINIUM HYDRIDE AND (S)-2-(ANILINOMETHYL)PYRROLIDINE

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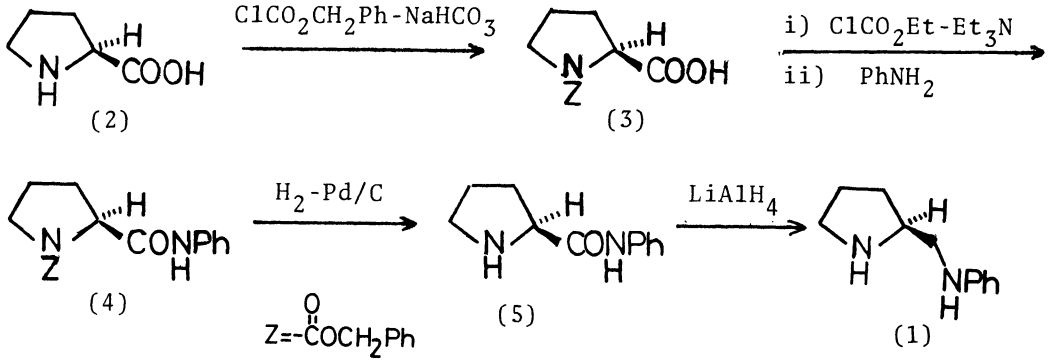
(S)-2-(Anilinomethyl)pyrrolidine (1), new chiral diamine, is easily prepared by four steps starting from (S)-proline. Asymmetric reduction of acetophenone with chiral hydride reagent, prepared from (1) and lithium aluminium hydride, gives (S)-1-phenylethanol in 92% optical yield (93% yield).

During the course of our synthetic investigation utilizing the onium salts of azaaromatics, we have recently reported the convenient and efficient methods for the optical interconversion of chiral secondary alcohols[1a], and transformation of the alcohols to chiral halides[1b], thiols[1c], and primary amines[1d]. Consequently, a wide variety of optically active substances become availabe when we could explore an efficient method for the preparation of chiral alcohols from carbonyl compounds. With such a concept in mind we have set up the asymmetric reduction of carbonyl compounds by utilizing a new chiral diamine.

As for the asymmetric reduction of a prochiral carbonyl compound by chiral hydride reagent, a number of methods have been reported[2]. In the case of the reduction of acetophenone, considerably high optical yield (60-83%) was achieved by using chiral hydride reagent prepared from lithium aluminium hydride and aminoalcohols[3], sugar derivatives[4] or chiral oxazolines[5].

Now we wish to report here the preparation of new chiral diamine, (S)-2-(anilinomethyl)pyrrolidine (1), and preliminary results demonstrating its usefulness as a ligand in the asymmetric reduction of acetophenone. The diamine (1) was easily prepared from readily available (S)-proline as shown in the following scheme: (S)-Proline (2) was converted to N-benzyloxycarbonyl-(S)-proline (3)[6] (97%, $[\alpha]_D^{22}$ -40.4° (c 1.027, EtOH)) by treatment with benzyloxycarbonyl chloride (30-35% toluene solution) and sodium hydrogencarbonate in water (r.t., 5hr). Then (3) was transformed into its anilide (4)[6] ($ClCO_2C_2H_5$,

Scheme



$(C_2H_5)_3N$ and aniline, THF, -15 - 0°C) in 79% yield (m.p. 141-141.5°C, $[\alpha]_D^{23}$ -63.2° (c 0.997, EtOH)). (S)-Prolinanilide (5)[6] (m.p. 74-76°C, $[\alpha]_D^{27}$ -69.3° (c 1.025, EtOH)), obtained by removing the benzyloxycarbonyl group by hydrogenolysis (Pd/charcoal) of (4) (94%), was reduced to the required chiral diamine (S)-2-(anilinomethyl)pyrrolidine (1)[7] (b.p. 111-112°C/0.55mmHg, $[\alpha]_D^{24}$+18.5° (c 1.087, EtOH)) with lithium aluminium hydride in 66% yield (THF, r.t., 24hr).

The asymmetric reduction of acetophenone using chiral hydride reagent, prepared from the diamine (1) and lithium aluminium hydride, was tried under various conditions as shown in Table.

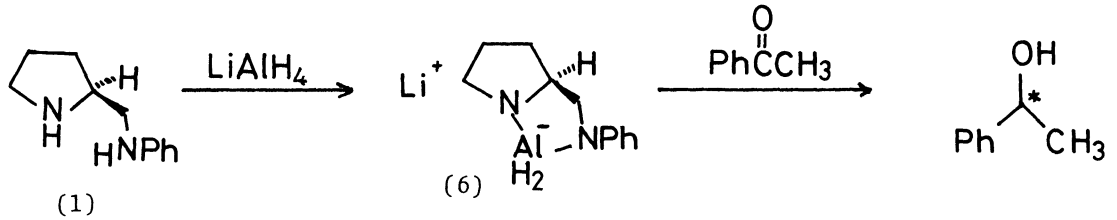


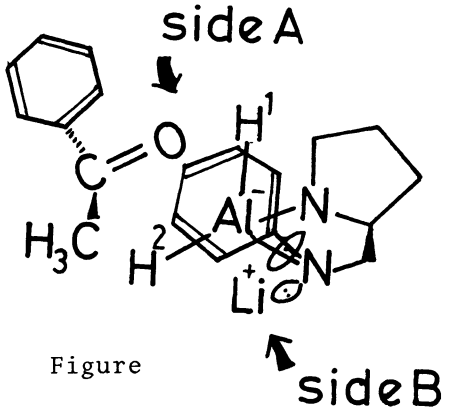
Table Reduction of Acetophenone by Chiral Hydride Reagent (6)

Exp.	Reduction temp. (°C)	(6)[a]/Acetophenone	Alcohol Yield (%)	$[\alpha]_D$ (Cyclopentane)[b]	c	Optical purity(%)
1	-78	1.1	68	$[\alpha]_D^{22}$-33.8°	7.27	78
2	-78	1.5	84	$[\alpha]_D^{22}$-36.1°	7.39	84
3	-78	2.0	88	$[\alpha]_D^{22}$-38.2°	7.17	89
4	-100	1.5	81	$[\alpha]_D^{25}$-37.5°	7.25	87
5	-100	2.0	93	$[\alpha]_D^{26}$-39.8°	7.28	92

a. $LiALH_4$: (1)=1.3:1.5 b. $[\alpha]_D^{20}$-43.1° (c 7.19, cyclopentane)[3a)]

It became clear that the optical yield increased by lowering the reaction temperature (Exp. 2 and 4, Exp. 3 and 5). Further the molar ratio of the chiral hydride reagent to acetophenone also affected both optical yield and synthetic yield, and treatment with 2 molar amounts of (6) at -100°C gave (S)-1-phenylethanol in 92% optical yield (93% yield). The typical experimental procedure is described for experiment 2; the diamine (1) (540.3 mg, 3.07 mmol) in ether (6 ml) was added to the ethereal solution (6.9 ml) of lithium aluminium hydride (101.0 mg, 2.66 mmol) over ten minutes at room temperature under an argon atmosphere. On addition of (1), hydrogen gas evolved and white preciptates appeared. After stirring for 1hr at room temperature, acetophenone (180.2 mg, 1.5 mmol) in ether (4 ml) was added at -78°C and stirred for 3hr. The mixture was hydrolyzed with 0.4 ml of water and washed successively with 0.5N hydrochloric acid (12 ml) and saturated sodium chloride solution. The ether layer was dried (Na_2SO_4) and concentrated to give a slightly yellow oil. The oily substance was purified by thin layer chromatography (developed with dichloromethane) to yield 153.4 mg (84%) of (S)-1-phenylethanol. Further it was purified for the measurement of specific rotation by bulb to bulb distillation (160°C (bath temperature)/17mmHg), and 145.7 mg of the alcohol was obtained, $[\alpha]_D^{22}$ -36.13° (c 7.39, cyclopentane). Most of the chiral diamine was recovered from the aqueous layer by usual work-up.

High optical yield in the present asymmetric reduction of acetophenone can be explained by assuming a formation of chiral hydride reagent (6) which posseses a rigid structure owing to the cis-fused five-membered rings. There is a clear-cut difference between the two hydrogen atoms (H^1 and H^2) in the reagent (6) based on the CPK model. The hydrogen atom H^1 is shielded by both pyrrolidine ring and phenyl ring, therefore, the only one hydrogen atom (H^2) may be responsible for reduction under a restricted manner as depicted in Figure. The precise mechanism of this asymmetric reduction is not clear at present, but we tentatively assume that acetophenone approaches from the less hindered side (side A) orientating the carbonyl oxygen to aluminium



Figure

atom and carbonyl carbon to the hydrogen atom H^2. The side B may be blocked by lithium cation leading to the predominant formation of (S)-1-phenylethanol.

It is noted that the simple diamine (1) produces an effective chiral hydride reagent (6) on treatment with lithium aluminium hydride, and the chiral space caused by (6) requires rigid orientation of acetophenone during the reduction leading to the formation of (S)-1-phenylethanol in high optical yield.

The asymmetric reduction of a wide variety of carbonyl compounds using (6) and its derivatives are now in progress.

References and Notes

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6) Satisfactory spectral and analytical data were obtained for all these compounds.

7) IR(neat) 3280, 3030, 1600, 1500, 755, and 697 cm^{-1}.
NMR($CDCl_3$) =0.9 2.1(m, 5H), 2.3 3.5(m, 5H), 4.1(br, 1H), 6.3 6.9(m, 3H), and 6.9 7.3(m, 2H).
MS(70eV), m/e, 176(M^+), 107, 77, 70, and 43.

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