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ASYMMETRIC SYNTHESIS OF α-HYDROXY ALDEHYDES

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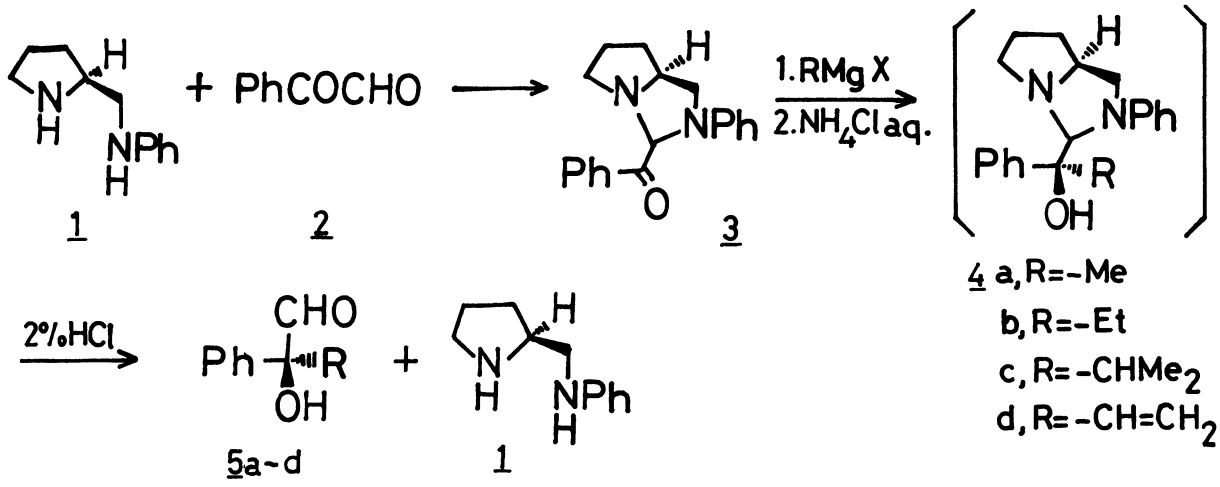
An asymmetric synthesis of α-hydroxy aldehydes was achieved in high optical yields starting from a keto aminal, prepared from phenylglyoxal and (S)-2-(anilinomethyl)pyrrolidine. By treating the keto aminal with the Grignard reagents and the hydrolysis of resulting hydroxy aminals, α-hydroxy aldehydes were obtained in 94-95% optical yields.

Recently we reported that new chiral hydride reagents, prepared from lithium aluminium hydride and chiral diamines, (S)-2-(substituted aminomethyl)pyrrolidines, are very effective in the asymmetric reduction of prochiral ketones and various chiral alcohols were obtained in high optical yields.[1] We assumed that the high asymmetric induction might be due to a formation of a cis-fused bicyclic ring from lithium aluminium hydride and the chiral diamine, and it afforded an efficient chiral environment in the reduction process.

This prompted us to study the asymmetric synthesis of α-hydroxy aldehyde by using the aminal 3, obtained easily from the chiral diamine 1 and phenylglyoxal 2, having a similar bicyclic ring with an efficient chiral moiety. Treatment of the aminal 3 with the Grignard reagent would afford the hydroxy aminal 4, which in turn was hydrolyzed to yield α-alkyl- -hydroxyphenylacetaldehyde 5.



The results obtained by using various Grignard reagents are summarized in Table. In every case, resulting chiral α-hydroxy aldehydes[2] have S configuration with 94-95% optical purity and most of the used diamine can be recovered unchanged from the reaction mixture.

Table Asymmetric synthesis of α-hydroxy aldehydes

Grignard reagent	Solv.	Yield (%)[a]	$[\alpha]_D$ (c, C_6H_6)	Optical purity (%)
a MeMgI	ether	67	+244°(1.138)	95[b]
b EtMgI	ether	76	+239°(1.048)	94[c]
c Me_2CHMgI	ether	82	+310°(1.031)	>95[d]
d CH_2=CHMgBr	THF	67	+179°(0.983)	96[e]

a) Yields are based on phenylglyoxal and the diamine.

b) The optical yield was determined by deriving the hydroxy aminal 4a to methyl atrolactate methyl ether. The hydroxy aminal 4a was converted to its methyl ether by NaH/MeI, and then subsequently it was hydrolyzed to α-methoxy-α-phenylpropionaldehyde with 2% HCl, ($[\alpha]_D^{27}$-139° (c 1.02, $CHCl_3$)). α-Methoxy-α-phenylpropionaldehyde was oxidized with Jones' reagent and then converted to methyl atrolactate methyl ether ($[\alpha]_D^{28}$+13.8° (c 0.94, MeOH)), whose enantiomer excess was 95%, based on $[\alpha]_D^{25}$+6.4° (MeOH) as 44% ee reported in reference 4).

c) The optical yield was determined by reducing α-hydroxy-α-phenylbutyraldehyde 5b to 2-phenyl-1,2-butanediol with $NaBH_4$, ($[\alpha]_D^{28}$-10.7° (c 3.7, EtOH)), whose enantiomer excess was 94%, based on $[\alpha]_D$-11.4° (EtOH), reported in reference 5).

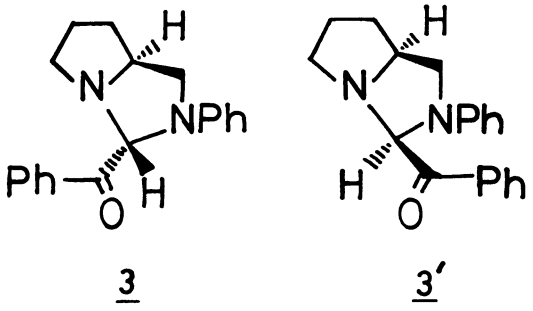
d) The optical yield was determined as follows. The hydroxy aldehyde 5c was reduced to 2-phenyl-3-methyl-1,2-butanediol ($[\alpha]_D^{27}$-17.1° (c 2.2, 90% EtOH)). The alcohol was converted to 2-hydroxy-2-phenyl-3-methylbutyl (R)-1-methoxy-1-trifluoromethylphenylacetate ((R)-MTPA ester), NMR spectrum of which showed only one diastereomer. The configuration of the alcohol was S as reported in reference 6).

e) The optical yield was determined by deriving the hydroxy aldehyde 5d to 2-phenyl-1,2-butanediol. The hydroxy aldehyde 5d was reduced with $NaBH_4$ to 2-phenyl-3-butene-1,2-diol ($[\alpha]_D^{29}$-39.9°(c 1.05, EtOH)). Then it was hydrogenated with $Rh(PPh_3)_3Cl$ to 2-phenyl-1,2-butanediol ($[\alpha]_D^{26}$-10.7° (c 0.99, EtOH)), whose enantiomer excess was 94%, based on $[\alpha]_D$-11.4° (EtOH), reported in reference 5).

Typical experimental procedure is described for the preparation of α-hydroxy α-phenylpropionaldehyde; phenylglyoxal monohydrate (4.7 mmol) was treated with an equimolar amount of 1 (4.7 mmol) with continuous removal of water in refluxing benzene for one hour. The solvent was evaporated under reduced pressure and the resulting aminal 3[3] was used without further purification. To a solution of 3 in ether was added dropwise methyl magnesium iodide (7.1 mmol) in ether at -70°C. After one hour, saturated ammonium chloride solution was added to the reaction mixture and allowed to warm up to room temperature. The ethereal layer was separated and the aqueous layer was neutralized with saturated sodium hydrogen carbonate solution, followed by extraction with ether. The ether extract was

combined and directly hydrolyzed with 2% hydrochloric acid at 0°C for 12 hours to yield oily substance (641 mg). The crude product was purified by silica gel column chromatography and α-hydroxy-α-phenylpropionaldehyde (471 mg) was isolated in 67% yield, which was thoroughly purified by short path distillation ($[\alpha]_D^{29}$+244° (c 1.14, benzene)).

Although an actual stereochemical course is not yet ascertained, the present asymmetric reaction consists of two stereoselective steps, namely, i) a selective formation of diastereomeric aminal 3 or 3' (figure 1), ii) an attack of Grignard reagents onto the aminal (figure 2). As for two possible diastereomers of the aminal only 3 would be formed as suggested by the fact that NMR spectrum of 3 shows only one peak at δ=5.4 ppm assigned to the methine proton. Consideration from CPK model also suggests that 3' would be more unstable because of its very crowded structure. In the second step, the selective formation of (S)-hydroxy aldehydes as shown in the Table, is interpreted by Cram's rule where the "cyclic model", in which hydroxyl group or amino group is adjacent to the chiral center, applies. The magnesium of the Grignard reagent complexes with the carbonyl oxygen of the aminal 3 and the nitrogen (N^1) on the pyrrolidine ring of the aminal 3, which presumably can more strongly complex with the magnesium than the more electron defficient nitrogen (N^2) substituted by phenyl group. This leads to a rigid structure, then the alkyl group originated from the Grignard reagent migrates to the carbonyl carbon from the less hindered side, the side of hydrogen, to yield (S)-hydroxy aminal 4 as sketched in figure 2.



3 3'

figure 1

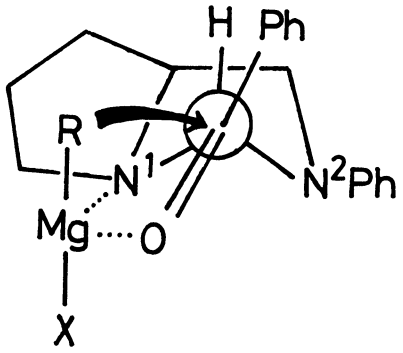


figure 2

Highly stereoselective Grignard reactions of chiral carbonyl compounds have been shown previously, however, in most cases, the chiral auxiliary could not be recovered. Recently Eliel resolved this problem to form α-hydroxy aldehyde in high optical yield by treating the chiral benzoyloxathiane with Grignard reagent.[4] But, in the above reaction, the preparation of the chiral auxiliary in high optical purity was not so easy, thus the resulted chiral hydroxy aldehyde was not so highly optically pure. In the present asymmetric synthesis there are many advantages, that is,the chiral auxiliary is very easily prepared from commercially available (S)-proline in almost pure form, and highly optically pure α-hydroxy aldehydes are obtained by a simple reaction procedure. Moreover, the chiral auxiliary is recovered unchanged.

Since it became apparent that the aminal possessing bicyclic ring affords an effective chiral environment, further experiment based on the chiral aminal is now under investigation.

References and notes

1) T. Mukaiyama, M. Asami, J. Hanna, and S. Kobayashi, Chem. Lett., 1977, 783. M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 51, 1869 (1978).
2) All α-hydroxy aldehydes showed correct IR and NMR spectra.
3) The aminal 3 could be recrystallized from MeOH; mp 101-102°C. IR ν=1698 cm^{-1}; NMR (CCl_4) δ=1.6-2.2 (4H, m), 2.4-3.9 (5H, m), 5.4 (1H, s), 6.1-7.9 (10H, m). Found: C, 78.26; H, 6.94; N, 9.36%. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58%.
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