AN ASYMMETRIC REDUCTION OF PROCHIRAL KETONES WITH A CHIRAL HYDRIDE REAGENT PREPARED FROM LITHIUM ALUMINIUM HYDRIDE AND (S)-2-(2,6-XYLIDINOMETHYL)PYRROLIDINE

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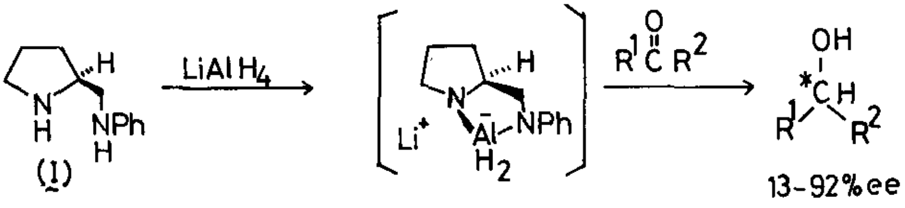
Abstract -- An asymmetric reduction of aromatic ketones with a chiral hydride reagent, prepared from lithium aluminium hydride and (S)-2-(2,6-xylidinomethyl)pyrrolidine, affords optically active secondary alcohols with excellent optical purities having S-configurations.

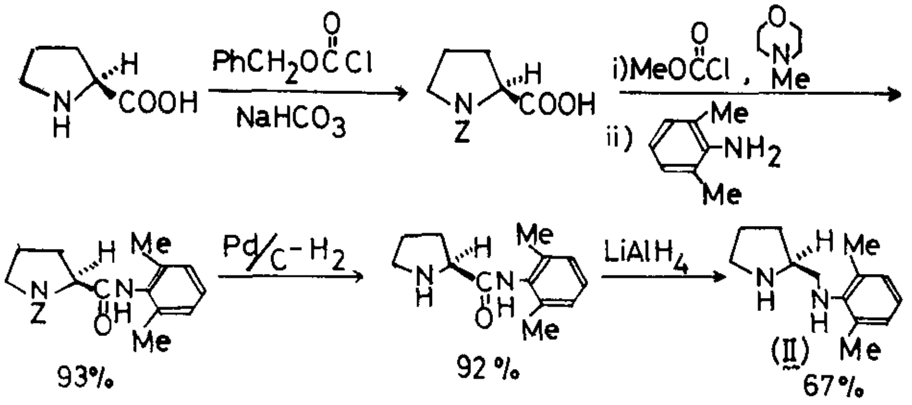
In this decade, an asymmetric reduction of prochiral ketones to optically active secondary alcohols with chiral hydride reagents have been studied extensively.[1] We recently reported[2] that chiral hydride reagents prepared from lithium aluminium hydride and chiral diamines, (S)-2-(N-substituted aminomethyl)-pyrrolidines, are the most superior chiral hydride reagents. In the paper it was shown that (N-aryl aminomethyl)pyrrolidines give good results among various (N-aryl, alkyl or alicyclic aminomethyl)pyrrolidines examined. The introduction of an electron-donating or an electron-withdrawing substituent to the aromatic ring of the diamine was not effective for an improvement of the optical yield of the asymmetric reduction of acetophenone. Thus, it was concluded that (S)-2-(anilinomethyl)pyrrolidine (I) is the best chiral ligand in this asymmetric reduction (equation).



(eq.)

In this communication, we wish to report an excellent diamine, (S)-2-(2,6-

xylidinomethyl)pyrrolidine (II)[3], for the asymmetric reduction of aromatic ketones. The optical yields were increased to excellent values in the case of aromatic ketones by an employment of the diamine II-$LiAlH_4$ complex. (S)-2-(2,6-xylidinomethyl)pyrrolidine was prepared easily from (S)-proline by a similar method previously reported in the case of (S)-2-(anilinomethyl)pyrrolidine, except the final reduction step carried out under refluxing THF (scheme).



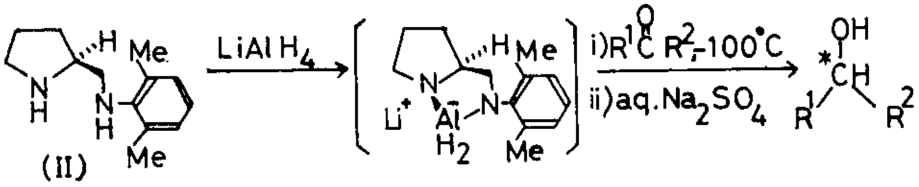
Scheme

The asymmetric reduction of prochiral ketones was carried out under a preferable condition ($LiAlH_4$:diamine II:ketone=2.5:3.0:1.0, -100°C) and the excellent optical yields were obtained for the aromatic ketones. In the case of phenylacetone the optical yield was 11% ee, therefore, the previously reported diamine I was reexamined under the condition above mentioned. Then the optical yield was increased to 42% ee. The results obtained by using the diamine II-$LiAlH_4$ complex were summarised in a Table.

Typical experimental procedure is described for the preparation of 1-phenyl-1-propanol; the diamine II (613.5 mg, 3.0 mmol) in 3 ml of ether was added to a standardised ethereal solution of $LiAlH_4$ (5.38 ml, 2.5 mmol) over ten minutes at room temperature, under an argon atmosphere. On addition of the diamine II, hydrogen gas evolved and white precipitates appeared. After stirring for 1 h at room temperature, propiophenone (134 mg, 1.0 mmol) in 3 ml of ether was added at -100°C, and the reaction mixture was stirred for 3 h. The mixture was hydrolized with saturated aqueous sodium sulfate sulution. The ethereal layer was washed successively with 15 ml of 2% aqueous HCl and saturated sodium chloride solution. The ethereal layer was dried over sodium sulfate and the solvent was removed. The crude product was purified by preparative TLC to give 1-phenyl-1-propanol (123 mg, 90%). Further it was purified for the measurement of specific rotation by bulb to bulb distillation and 117 mg of the alcohol was obtained, $[\alpha]_D^{28}$ -43.65° (c 5.20, $CHCl_3$). Most of the diamine was recovered from the aqueous layer by usual work up.

Table

Asymmetric Reduction of Various Ketones with $LiAlH_4$-diamine II



Ketone	Alcohol[b)]			
	Yield(%)	$[\alpha]_D$	(c,solv.)	ee(%)
PhCOMe	87(84)[a)]	$[\alpha]_D^{28}$ -41.1°	(7.23, C_5H_{10})	95[d)] (84)[a)]
PhCOEt	90(90)	$[\alpha]_D^{28}$ -43.7°	(5.20, $CHCl_3$)	96[e)] (85)
$PhCOCHMe_2$	97(80)	$[\alpha]_D^{28}$ -42.7°	(7.15, ether)	89[f)] (57)
α-Tetralone	85(94)	$[\alpha]_D^{28}$ +28.3°	(4.07, $CHCl_3$)	86[g)] (50)
$PhCH_2COMe$	82(85)	$[\alpha]_D^{20}$ +4.56°	(5.26, C_6H_6)	11[h)] (31)
$PhCH_2COMe$[c)]	78	$[\alpha]_D^{28}$ +17.8°	(4.00, C_6H_6)	42[h)]
$n\text{-}C_6H_{13}COMe$	83(77)	$[\alpha]_D^{30}$ +3.10°	(9.68, ether)	26[i)] (13)

a) The data obtained by using (S)-2-(anilinomethyl)pyrrolidine under the different condition ($LiAlH_4$:diamine:ketone=2.0:1.75:1.0, -78°C) are designated in parentheses.

b) All alcohols have S-configuration.

c) In this case (S)-2-(anilinomethyl)pyrrolidine was used under the preferable condition ($LiAlH_4$:diamine:ketone=3.0:2.5:1.0, -100°C).

d) Based on $[\alpha]_D^{21}$ -43.1° (c, 7.19, C_5H_{10}) reported in reference 4.

e) Based on $[\alpha]_D$ 45.45° (c 5.15, $CHCl_3$) reported in reference 5.

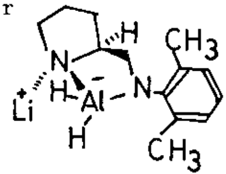
f) Based on $[\alpha]_D^{20}$ 47.7° (c 7, ether) reported in reference 6.

g) Based on $[\alpha]_D^{17}$ 32.7° (c 4.1, $CHCl_3$) reported in reference 7.

h) Based on $[\alpha]_D^{20}$ 41.8° (c 5.26, C_6H_6) reported in reference 5.

i) Based on $[\alpha]_D^{24}$ +12.3° (c 8.8, ether) reported in reference 8.

It is noted that the optical yields of the aromatic ketones such as acetophenone, propiophenone, phenyl isopropyl ketone and α-tetralone increased to excellent values (86-96% ee) by the introduction of two methyl groups into *o*-position of the phenyl ring. It might be due to the formation of the similar sterically restricted *cis*-fused bicyclic chiral hydride reagent from the diamine **II** and lithium aluminium hydride (figure) as previously proposed in the case of the diamine **I**. And two methyl groups in the vicinity of the reaction site may be more effective for the limitation of the direction of the approach of ketones.



figure

References and Note

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3. bp 116-123°C/0.7 mmHg; $[\alpha]_D^{26}$+19.1° (c 1.045, EtOH); IR(neat) ν=3325 cm^{-1} (N-H); NMR($CDCl_3$) δ=1.20-1.98 (m, 4H), 2.25 (s, 6H), 2.44-3.60 (m, 7H), 6.50-6.96 (m, 3H); MS (70eV), m/e, 204 (M^+), 135, 120, 105, 70, and 43.
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