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Asymmetric reduction of acetophenone using lithium aluminium hydride modified with some novel amino alcohol Schiff bases

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Abstract—Some new chiral Schiff bases have been prepared in good yields from various carbonyl groups and two 2-amino alcohols. $LiAlH_4$ was treated with different equivalents of the Schiff bases. Enantioselective reduction of acetophenone is achieved in high chemical yield (up to 93%) with moderate enantiomeric excess (up to 22%) by use of the new reducing agents.
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1. Introduction

The synthesis of new types of chiral ligands is widespread in asymmetric synthesis. Most of the common ligands are bidentate; DIOP and BINAP as neutral or TADDOL and BINNOL as dianionic structures. Among higher coordinating ligands are the tetradentate salen ligands, which are widely used in epoxidation, epoxide ring opening and aziridination reactions.[1,2]

Schiff bases can behave as multidentate ligands, depending on the number of donor atoms in their structure. If there is any –OH or –SH, groups *ortho* to the azomethine bond, then six membered rings can form with metals, giving unreactive complexes.[3]

In recent years, salen type chiral Schiff bases have been extensively described. Symmetric and asymmetric transition metal complexes of these bases have been developed and used as ligands/catalysts in many reactions such as epoxidation,[4] asymmetric synthesis,[5] asymmetric sulfoxidation,[6] asymmetric silylcyanation[7] and many other applications.[8–10]

The reported explanation for the reduction mechanism was based on formation of a six membered ring.[11,12] In this study we found that the enantioselectivity of reducing agents was dependent on the mole ratios of the modified hydride/acetophenone.

Chiral modifiers are often easily obtained in only one enantiomeric form, thus limiting control of the chiral sense of the hydride transfer to the ketone.[12]

2. Results and discussion

In order to reach the pre-designed structure, initially commercial and inexpensive L-amino acids were selected. Only L-phenylalanine and L-valine have been used. Firstly the amino acids were converted into the corresponding amino alcohols by reduction with $NaBH_4$ in THF under inert atmosphere. Generally, the reduction method gave a single enantiomer in high yield.[11]

Next in order to achieve suitable symmetry and to create a better steric barrier in general, different carbonyl compounds were selected. These were benzaldehyde, salicylaldehyde, benzil and 3-oxa-1,5-bis-(*o*-carboxaldehyde phenoxy)pentane. The carbonyl compounds were treated with the two amino alcohols to synthesize various Schiff bases.

The synthesis of chiral Schiff bases according to a general literature reaction[12] is shown in Scheme 1 to generate ligands **I**–**VI** (Fig. 1).

Asymmetric reduction experiments have been carried out with new Schiff bases **I**–**IV**, which have various donor atoms (Scheme 2).

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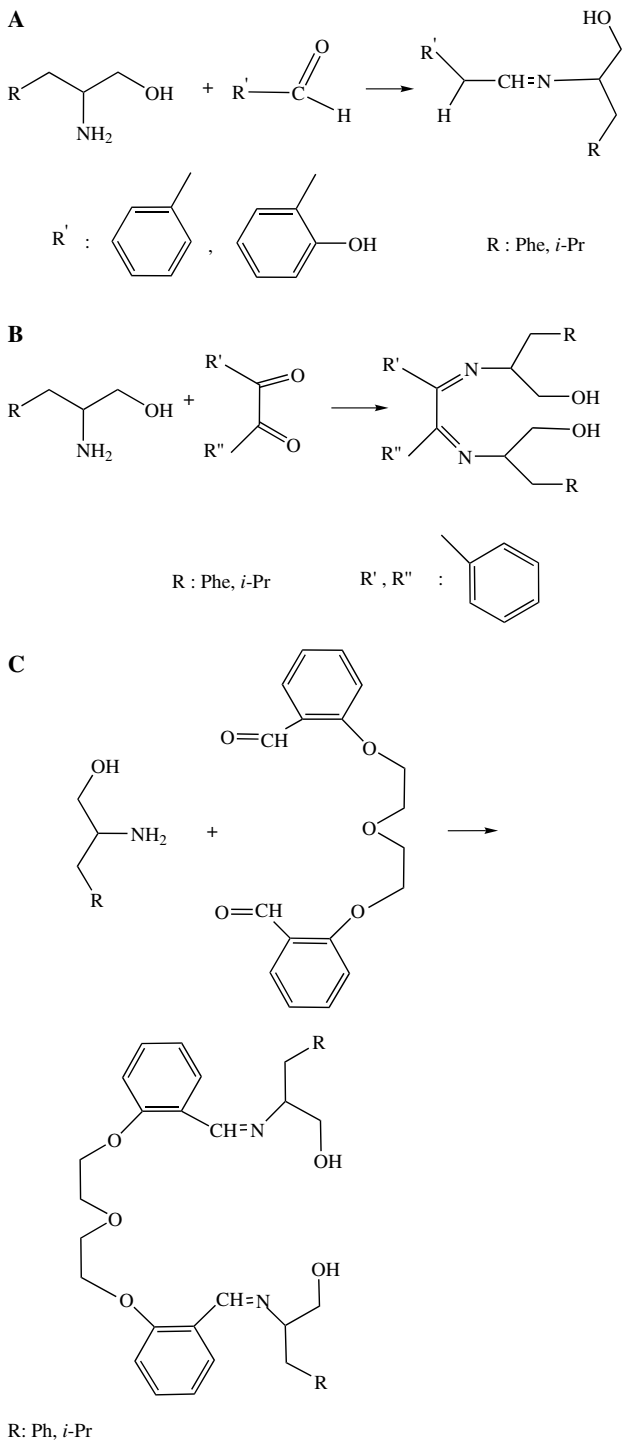


Scheme 1. Synthesis of Schiff bases.

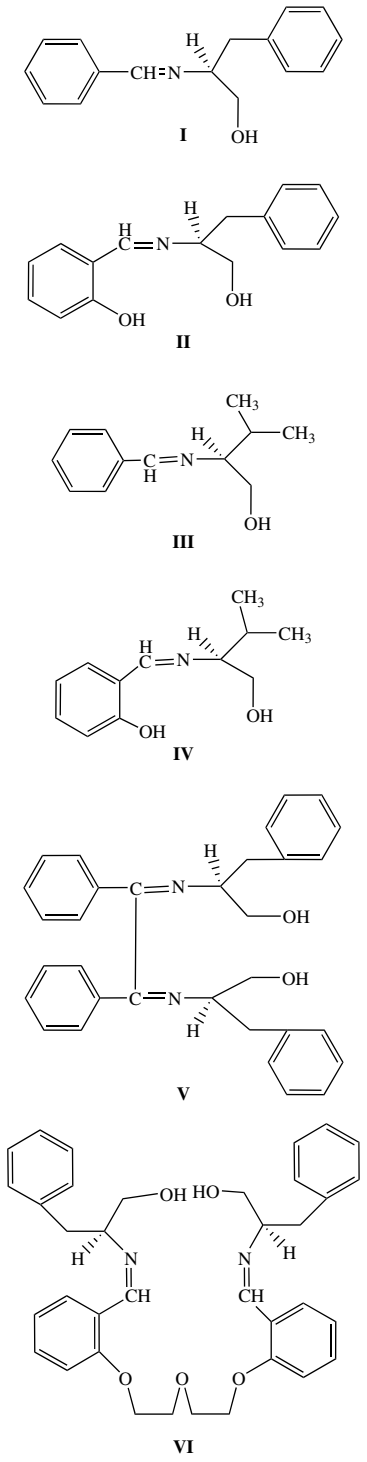


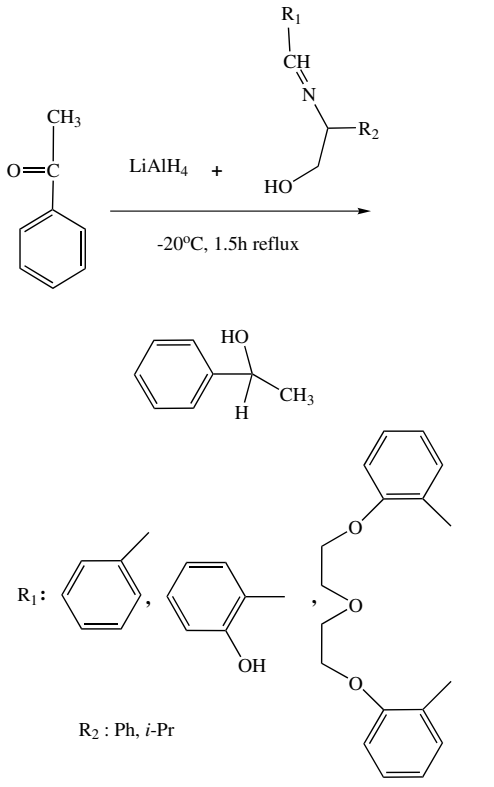
Figure 1.

$LiAlH_4$ complexes of the Schiff bases were prepared in situ. Then acetophenone was added dropwise. The reduction was complete in a short time at approximately 20 °C under inert atmosphere. As described in the literature, the structure of the complex formed is shown in Figure 2.

In complexes prepared according to this in situ reaction, the highest literature ee's were achieved when only one hydride remained on the Al.[13]

The optimum ratio of $LiAlH_4$/Schiff base was determined using ligands **I**–**IV** and acetophenone (Table 1). The best results were obtained with a molar ratio of **I**/$LiAlH_4$ of 1:2 for the reduction of acetophenone. Presumably with molar ratios of 2:1 or 3:2, all the reducing power of the aluminium hydride has been consumed by the reaction with the excess ligand.

After chromatography, the enantiomeric excess values were determined by optical rotation.



Scheme 2.

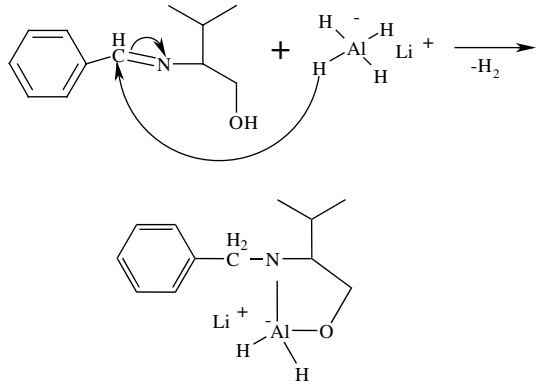


Figure 2. Stable five membered ring.

Table 1. Asymmetric reduction of acetophenone with Schiff base and $LiAlH_4$ complexes

Entry	Schiff base	Mole rate (Schiff/$LiAlH_4$)	% Yield	% Ee
1	**I**	1/1	66	9
2	**I**	1/2	93	22
3	**I**	2/1	0	0
4	**I**	3/2	0	0
5	**II**	1/3	0	0
6	**III**	1/3	35	4
7	**IV**	1/2	97	8

3. Experimental

Optical rotations were determined in a solution CH_3OH at 20 °C by using a Perkin–Elmer-341 digital polarimeter. IR spectra were determined by a Mattson 1000 spectrometer. ^1H NMR and ^{13}C NMR spectra were determined for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard on a Bruker Avence dpx-400 spectrometer. CH analysis with an Carlo–Erba 1800 analyzer.

3.1. Synthesis of amino alcohols

L-Phenylalaninol and L-valinol were prepared according to the literature.[11]

3.2. Synthesis of Schiff bases (general reaction)

Schiff base reactions were performed in ethanol at 65 °C. Amino alcohols and aldehydes in appropriate mole ratios, were put into a flask with 20 mL ethanol. This mixture was stirred for 24 h at 60 °C. Then the alcohol was evaporated. Schiff bases were recrystallized from appropriate solvents.

3.2.1. Benzaldehydene-(*S*)-2-amino-3-phenylpropanol I. White solid, yield 78%, mp: 84–86 °C, $[\alpha]_D^{20} = -246$ (*c* 5, MeOH); IR (KBr) 3236, 3070, 3030, 2921, 2858, 1645, 1580, 1495, 1452, 1413, 1150, 1053, 746, 613 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.67–2.95 (m, 2H), 3.48–3.66 (m, 1H), 3.67–3.95 (m, 2H), 7.22–7.67 (m, 10H), 7.90–7.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ ppm 39.42, 66.29, 74.75, 126.60, 128.69, 130.12, 131.18, 136.09, 138.97, 162.99; Anal. Calcd for $C_{16}H_{17}NO$: C, 80.33; H, 7.11. Found: C, 80.26; H, 6.95.

3.2.2. *o*-Hydroxy benzaldehydene-(*S*)-2-amino-3-phenylpropanol II. Yellow solid, yield 73%, mp: 62–64 °C, $[\alpha]_D^{20} = -265$ (*c* 5, MeOH); IR (KBr) 3394, 3066, 3032, 2924, 2875, 1642, 1581, 1497, 1465, 1430, 1155, 1045, 840, 750, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.83–2.88 and 2.97–3.01 (2H), 3.49–3.55 (m, 1H), 3.71–3.82 (2H), 6.82–7.32 (m, 10H), 8.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ ppm 39.43, 66.06, 73.44, 117.49, 119.05, 126.91, 128.91, 129.95, 132.04, 132.92, 138.34, 161.77, 166.32; Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67. Found: C, 74.97; H, 6.50.

3.2.3. Benzaldehydene-(*S*)-2-amino-3-methylbutanol III. White solid, yield 64%, mp: 71–72 °C, $[\alpha]_D^{20} = -56.7$ (*c* 5, MeOH); IR (KBr) 3249, 3063, 2973, 2935, 1645, 1573, 1503, 1471, 1452, 1053, 1022, 836, 758, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 0.77–0.96 (d, 6H), 1.80–2.08 (m, 1H), 2.87–3.02 (s, 1H), 3.17–3.65 (m, 1H), 3.68–3.80 (m, 2H), 7.24–7.67 (m, 5H), 8.07–8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ ppm 19.78, 20.16, 30.38, 64.72, 79.74, 126.51, 128.82, 128.86, 130.98, 136.18, 162.44; Anal. Calcd for $C_{12}H_{17}NO$: C, 75.39; H, 8.91. Found: C, 75.29; H, 8.81.

3.2.4. *o*-Hydroxy benzaldehydene-(*S*)-2-amino-3-methylbutanol IV. Yellow solid, yield 55%, mp: 92–94 °C, $[\alpha]_D^{20} = -19.1$ (*c* 5, MeOH); IR (KBr) 3256, 2966, 2958,

2884, 1631, 1581, 1503, 1464, 1420, 1085, 1041, 836, 752, 655 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 0.83–1.05 (d, 6H), 1.80–2.03 (m, 1H), 2.93–3.13 (m, 1H), 3.62–3.89 (m, 2H), 6.76–7.38 (m, 4H), 8.33–8.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ ppm 18.87, 20.22, 30.37, 64.77, 117.52, 118.94, 131.93, 132.86, 162.00, 166.17; Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.56; H, 8.21. Found: C, 68.88; H, 8.30.

3.2.5. *N,N′*-Bis-(1,2-ethanedioniden)-(*S*)-2-amino-3-phenylpropanol V. Brown solid, yield 40%, mp: 138–141 °C, $[\alpha]_D^{20} = +4$ (*c* 5, MeOH); IR (KBr) 3351, 3176, 3033, 2909, 1676, 1621, 1578, 1493, 1454, 1433, 1079, 1025, 821, 738, 643 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.75–2.89 and 2.95–3.07 (m, 4H), 3.18–3.34 (m, 2H), 3.37–3.51 and 3.52–3.65 (m, 4H), 4.01–4.8 (s, 2H), 7.11–8.41 (m, 20H); ^{13}C NMR ($CDCl_3$) δ ppm 40.43, 60.10, 65.33, 132.10, 133.86, 134.41, 134.58, 137.89, 141.70, 199,87; Anal. Calcd for $C_{32}H_{32}N_2O_2$: C, 80.67; H, 6.72. Found: C, 79.81; H, 7.17.

3.2.6. *N,N′*-Bis-[3-oxa-1,5-bis-(*o*-carboxyaldehydenephenoxy)pentan]-(*S*)-2-amino-3-phenylpropanol VI. Brown, viscose, yield 50%, $[\alpha]_D^{20} = -103.7$ (*c* 5, MeOH); IR (KBr) 3460, 3063, 3031, 2979, 2928, 2870, 1638, 1490, 1452, 1053, 760, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.25–2.93 (m, 4H), 3.20–3.62 (m, 2H), 3.62–4.35 (m, 12H), 6.62–7.96 (m, 18H), 8.3–8.6 (s, 2H); ^{13}C NMR ($CDCl_3$) δ ppm 39.44, 66.18, 68.63, 70.06, 74.86, 112.90, 121.64, 126.43, 128.04, 128.58, 130.10, 132,40, 139.17, 158.36, 158.86; Anal. Calcd for $C_{36}H_{40}N_2O_5$: C, 74.48; H, 6.89. Found: C, 74.12; H, 6.15.

3.3. General reactions of asymmetric reduction

Under a nitrogen atmosphere, a molar solution of $LiAlH_4$ in dry ether was prepared. The Schiff base in dry ether (with different mole ratios) was added in one portion. After mixing at room temperature for 30 min, the mixture was cooled to −20 °C. Acetophenone–dry ether mixture in dropping funnel was transferred dropwise over 30 min. The mixture was stirred at −20 °C for 1.5 h and then 0.5 M NH_4Cl was added. Water and ether phases were separated. The ether phase was dried with Na_2SO_4 and evaporated. The product was purified in column (silica gel-60) (1:3 *n*-hexane–ethylacetate).

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