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Catalytic Asymmetric Syntheses of Secondary Alcohols Using *cis*-1-Amino-2-indanols as Chiral Ligands

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Abstract: Both enantiomers of *cis*-1-amino-2-indanols (**1a,b**) have been used as chiral ligands in the catalytic asymmetric reduction of ketones with $BH_3 \cdot SMe_2$ affording secondary alcohols with enantiomeric excesses up to 95%. Furthermore, some N,N-diakyl derivatives of **1a,b** catalyzed the enantioselective addition of diethylzinc to aldehydes.

Asymmetric catalysis is a very rapidly growing field in stereocontrolled organic synthesis. Two main advantages have emerged for this strategy over more conventional approaches: a) small amounts of enantiomerically pure starting material are used; b) no chemical bond has to be broken for separating the reaction product from the chiral auxiliary. Asymmetric catalysis has been applied successfully to many organic transformations, but the degree of stereoselectivity is dependent on the particular substrate/chiral catalyst couple. Since the best "fit" is still unpredictable, the development and investigation of new chiral ligands will continue for the forseeable future.

The enantioselective reduction of prochiral ketones has been realised recently by a catalytic process based on borane-dimethysulfide as reductant and an 1,3,2-oxazaborolidine as chiral catalyst,[1] usually prepared *in situ* by the reaction of an enantiomerically pure 1,2-aminoalcohol with $BH_3 \cdot SMe_2$. We have applied the same protocol by exploiting the readily available enantiomers of *cis*-1-amino-2-indanols[2] **1a,b** (Scheme 1).
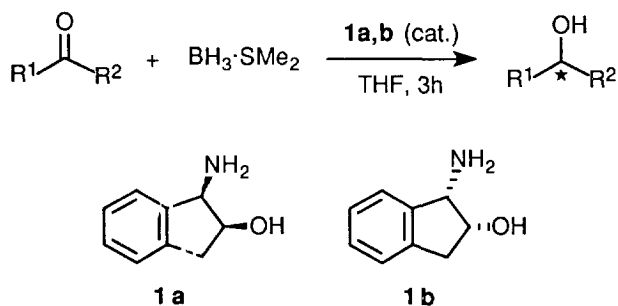
Scheme 1

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
Table 1. Catalytic Asymmetric Reduction of Ketones.

ketone	ligand. (mol%)	product [a]	yield (%) [b]	e.e. (%) [c]
	1a (5)		99	95
,,	1b (10)		99	96
	1a (10)		99	90
	1a (5)		90	88
	1a (5)		99	86 [d]
	1a (10)		90	84 [d]
	1b (10)		94	88 [d]
	1b (10)		89	85 [d]
	1a (10)		95	95
	1b (10)		92	79 [e]

(a) The absolute configuration was determined by comparison of the specific optical rotation with that of the commercially available compound or with the literature value: Brown, H. C.; Mandel, A. K. *J. Org. Chem.* **1984**, *49*, 2558. Gottarelli, G.; Samorì, B. *Tetrahedron Lett.* **1970**, 2055. Ploavarapu, P. L.; Fontana, L. P.; Smith, H. E. *J. Am. Chem. Soc.* **1986**, *108*, 94. Soai, K.; Yamanoi, T.; Hikima, H. *J. Organomet. Chem.* **1985**, *290*, C23. (b) Yield of the product purified by chromatography. (c) Determined by GC analysis on a chiral MEGADEX 5 column. (d) Determined by GC analysis of the corresponding TMS ethers on a chiral MEGADEX 5 column. (e) Determined by comparison of the specific optical rotation, as *(R)* and *(S)*-2-octanol were not separated on MEGADEX 5 column.

Owing to the rigid, cyclic framework, **1a,b** appear suitable ligands for asymmetric synthesis. In fact, they have already found some applications in this context.[3] Notably the reduction of acetophenone by means of the oxazaborolidines prepared from stoichiometric amounts of **1a,b** and $BH_3 \cdot SMe_2$ has been reported;[3c] however, the catalytic version of this reaction has not been described. In our hands the catalytic reduction of ketones proceeded smoothly and a number of secondary alcohols could be prepared in good to excellent yields and stereoselectivities; the best enantiomeric excesses were obtained working on cyclic and hindered ketones (Table 1).

It is likely that the reaction follows the same pathway proposed by Corey for the analogous reaction catalyzed by proline derived aminols.[4] The oxazaborolidine **2** should be first formed by the reaction of **1a** and BH_3 with loss of hydrogen. Subsequent coordination of **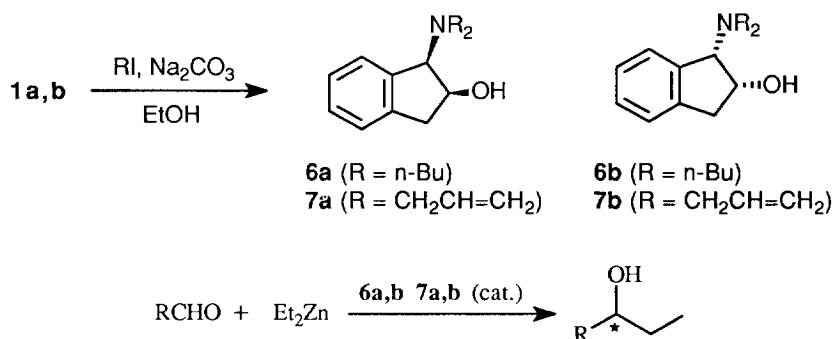2** with another BH_3 molecule and then with the ketone (to the amino and boron centres respectively) should take place preferentially with *anti* stereochemistry with respect to the indanyl substituent of **2**, so affording the complex **3** where the coordinated BH_3 and ketone groups have a *cis* relationship. Intramolecular hydride addition should eventually occur through a cyclic six-membered transition state (TS). Either the chair- and boat-like TS's[5] **4** and **5** can be envisaged to explain the observed sense of asymmetric induction, the *re* enantioface of the carbonyl being attacked when **1a** is involved. However, in our opinion, the boat-like TS **4** is more easily attained than **5**.

2

3

4

5
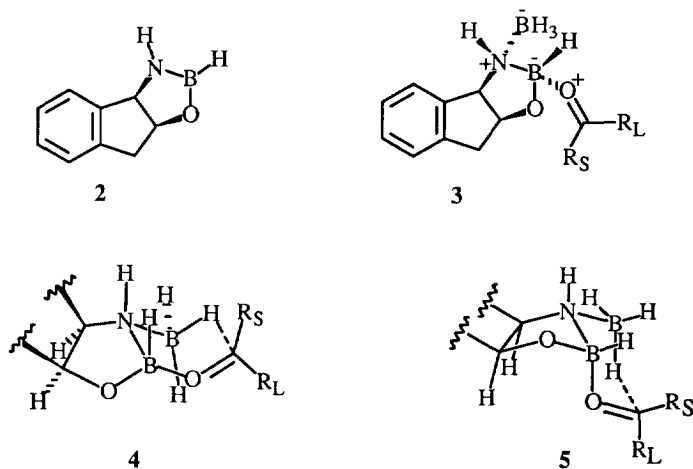
We also looked for a catalytic role of *cis*-1-amino-2-indanols in the addition of diethylzinc to aldehydes.[6] For this aim we synthesized the previously unknown derivatives of **1a,b**, N,N-diallyl- and N,N-dibutyl-1-amino-2-indanols **6a,b** and **7a,b**, respectively (Scheme 2). These compounds effectively catalyzed the addition of diethylzinc to aromatic aldehydes with good to excellent yields of secondary alcohols, but only fair stereoselectivity (Table 2). Some reactions were performed on benzaldehyde in hexane with the dibutyl derivatives **6a,b** as catalysts. This change for **7a,b** did not affect the e.e., but a significant decrease of the yield was observed. On the contrary, use of toluene as solvent and prior mixing of $ZnEt_2$ and catalyst lead to a slight improvement in stereoselectivity. Data obtained from 4-methoxybenzaldehyde confirmed the trend.

Scheme 2

6a (R = n-Bu)   **6b** (R = n-Bu)
7a (R = CH₂CH=CH₂)   **7b** (R = CH₂CH=CH₂)

$$\text{RCHO} + \text{Et}_2\text{Zn} \xrightarrow{\text{6a,b 7a,b (cat.)}}$$

Table 2. Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by 6, 7. [a]

R	cat.	solvent	t (h)	yield (%) [b]	e.e. (%) [c]	config.[d]
C_6H_5	6a	n-Hexane	5	84	40	S
C_6H_5	6b	n-Hexane	5	97	40	R
C_6H_5 [e]	6a	Toluene	5	98	50	S
C_6H_5	7b	n-Hexane	5	78	40	R
4-MeOC$_6$H$_4$	6a	Toluene	5	98	40	S
4-MeOC$_6$H$_4$	7a	Toluene	5	95	43	S

(a) All the reactions were carried out at 0 °C by adding diethylzinc (2 mol equiv.) to a solution of the aldehyde and the catalyst (0.06 mol equiv.). (b) Yield of product purified by chromatography. (c) Determined by GC analysis on chiral MEGADEX 5 column. (d) Determined by comparison of the sign of specific rotation with literature data: Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264. (e) The aldehyde was added to the mixture of diethylzinc and catalyst.

The results decribed show that readily available *cis*-1-amino-2-indanols and their derivatives can be profitably employed as an alternative to more complex or less easily available aminols in asymmetric synthesis. Expecially, the excellent enantioselectivities obtained in the reduction of prochiral ketones prompt us to explore deeply this and other possible applications.

Experimental Section

General: ^{1}H-NMR spectra have been recorded in CDCl$_3$ solutions at 300 MHz by means of a Varian Gemini 300 instrument. Chemical shifts are given in δ units with respect to TMS and coupling constants (J) are in Hz. IR spectra have been obtained with a Nicolet 205 FT spectrometer and are given in cm^{-1}. MS spectra have been taken by EI ionization at 70 eV on a Hewlett-Pakard 5971 spectrometer with GC injection. They are reported as follows: m/z (rel. intens.). Enantiomeric excesses were determined by gas chromatography with a Fisons GC 8000 instrument equipped with a MEGADEX 5 (pentyldimethyl-β-cyclodextrin) column (25 m length, 0.25 mm i.d., 0.15 μm film thickness, H$_2$ carrier gas 0.7 Kpa). Column chromatographies were run over 270-400 mesh silica gel under medium pressure. All the reactions were carried out under oven dried glassware under nitrogen atmosphere. Hexane and THF were distilled from LiAlH$_4$, and toluene was distilled from sodium-benzophenone ketyl; they were stored under nitrogen and handled with syringe techniques. All other chemicals were commercially pure compounds and were used as received. All the produts obtained showed satisfactory elemental analysis (C ± 0.1%, H ± 0.1%, N ± 0.1%).

Enantioselective Reduction of Prochiral Ketones Catalyzed by 1a,b. General Procedure. To a solution of 1-amino-2-indanol (1a or 1b, 0.044g, 0.3 mmol) in THF (10 mL) was added BH$_3$·SMe$_2$ (2M in THF, 1 mL) and the mixture was stirred for 16 h, then the ketone (3 mmol) dissolved in THF (20 mL) was added over 2h. After one additional hour the mixture was cooled at 0 °C and quenched with MeOH (5 mL) and water (10 mL). Extraction with CH$_2$Cl$_2$ (3 x 20 mL), drying (Na$_2$SO$_4$), and concentration afforded the crude alcohol, which was purified by flash chromatography (cyclohexane:Et$_2$O 90/10) and identified by comparison of the spectroscopic properties with those reported in the literature.

Preparation of N,N-dialkyl-1-amino-2-indanols.

(1R,2S)-**1-Dibutylamino-2-indanol (6a):** 1-Iodobutane (2.5 ml, 20 mmol) was added to a suspension of **1a** (1.5 g, 10 mmol) and Na$_2$CO$_3$ (2.3 g, 20 mmol) in EtOH (10 mL). The reaction mixture was heated at reflux for 12 h, then cooled to room temperature and concentrated *in vacuo*. Column chromatography of the residue afforded **6a** as an oil (1.09 g, 42%): [α]$_D$^{25} +52 (c 1.06, CHCl$_3$); IR 3300, 2950; MS 261(4), 232 (3), 218 (65), 204 (14), 134 (10), 133 (100), 103 (15), 86 (65), 77 (7); ^{1}H-NMR 0.9 (t, 6 H, J 7.3), 1.3 (m, 4 H), 1.5 (m, 4 H), 2.3 (dt, 2 H, J 13.7, 8.2), 2.5 (dt, 2 H, J 13.7, 8.0), 2.74 (dd, 1 H, J 16.5, 7.1), 3.27 (dd, 1 H, J 16.5, 7.8), 4.28 (d, 1 H, J 8.0), 4.4-4.35 (m, 1 H), 4.8 (br s, 1 H, OH), 7.2-7.3 (m, 4 H); found C,78.20; H, 10.20; N, 5.25. C$_{17}$H$_{27}$NO requires C, 78.16; H,10.34; N, 5.36.

(1S,2R)-**1-Dibutylamino-2-indanol (6b):** [α]$_D$^{25} -52 (c 1.06, CHCl$_3$).

According to the same procedure by using allyliodide we obtained:

(1R,2S)-**1-[Di-(2-propen-1-yl)amino]-2-indanol (7a):** 1.67 g, 73%; [α]$_D$^{25} +92.7 (c 1.87, CHCl$_3$); IR 3400, 1650; MS 229 (M^{+}, 10), 108 (100), 170 (14), 133 (53), 105 (28), 96 (24), 77 (25), 70 (21); ^{1}H-NMR 3.4-2.7 (m, 7 H) 4.45 (m, 2 H), 5.2 (m, 1 H), 6.0-5.8 (m, 1 H), 7.1-7.4 (m, 4 H); found C, 78.45; H, 8.4; N, 6.2. C$_{15}$H$_{19}$NO requires C, 78.60; H, 8.30; N, 6.13.

(1S,2R)-**1-[Di-(2-propen-1-yl)amino]-2-indanol (7b):** [α]$_D$^{25} -92.7 (c 1.87, CHCl$_3$).

Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by 6, 7. General Procedure: A solution of the aldehyde (10 mmol) and the catalyst (**6a, 6b, 7a** or **7b**) (0.6 mmol) in hexane (5 mL) or toluene (5 mL), according to Table 2, was stirred at room temperature for 20 min, then cooled to 0 °C. Diethylzinc (22 mL of 1 M solution in hexane, or 20 mL of 1.1 M solution in toluene) was then added over 20 min and the reaction mixture was kept at 0 °C for 5 h. After quenching with 1M HCl (5 mL), the organic layer was

separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). Drying (Na_2SO_4) and concentration of the combined organic phases afforded a residue that was chromatographed over silica gel (cyclohexane/Et_2O 80/20) to afford the secondary alcohol which was identified by comparison of the spectroscopic properties with those reported in the literature.

References and Notes

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2.   Racemic *cis*-1-amino-2-indanol was prepared from commercial *trans*-2-bromo-1-indanol. Enantiomerically pure **1a** and **1b** were then obtained by resolution of the racemic mixture *via* chromatographic separation of the diastereoisomeric amides formed with N-Boc phenylalanine and final deprotection with trifluoroacetic acid. : Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Shleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Numberg, J.; Springer, J. P.; Huff, J. R. *J. Med. Chem.* **1992**, *35*, 1685.

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