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Asymmetric reduction using *N*-methyl and *N*-benzyl oxazaborolidines based upon *cis*-1-amino-2-indanol: a preliminary mechanistic study

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Abstract

(1*R*)-Amino-(2*S*)-indanol and its *N*-methyl and *N*-benzyl derived oxazaborolidines were investigated in the asymmetric reduction of acetophenone in order to obtain insight into the reaction mechanism. Optimisation studies carried out with *B*-methyl (1*R*)-amino-(2*S*)-indanol resulted in enantioselectivities of 84% (by GC) and these applied to a series of aromatic ketones with differing degrees of enantioselectivity.

1. Introduction

Perhaps one of the most useful methods for preparing enantiomerically pure secondary alcohols has been the oxazaborolidine reduction originally described by Itsuno and Corey.[1] There has been huge interest in improving this reaction, especially in respect to finding a cheaper alternative to the prolinol derived precatalyst. *cis*-1-Amino-2-indanol has been employed in such a role in the asymmetric reductions of acetophenone derivatives,[2] and a number of *B*- and *N*-substituted derivatives have been prepared and tested as catalysts claiming quantitative yields and enantiomeric excess of greater than 80%.[3] Optimisation studies using the *B*-Me and *B*-H complexes employing an α-bromo acetophenone analogue as a substrate have also been carried out,[4] while independent studies have examined the reduction of a range of prochiral ketones with the parent *cis*-1-amino-2-indanol derived catalyst.[5] Somewhat surprisingly the catalyst that provided the best levels of reactivity and selectivity in these studies was the *N*-unsubstituted oxazaborolidine **1**. This is in direct contrast to the original catalyst devised by Itsuno and Corey that contains a secondary amine. Here complexation of the second equivalent of borane is thought to form an intermediate ylide that performs the reduction.[8]

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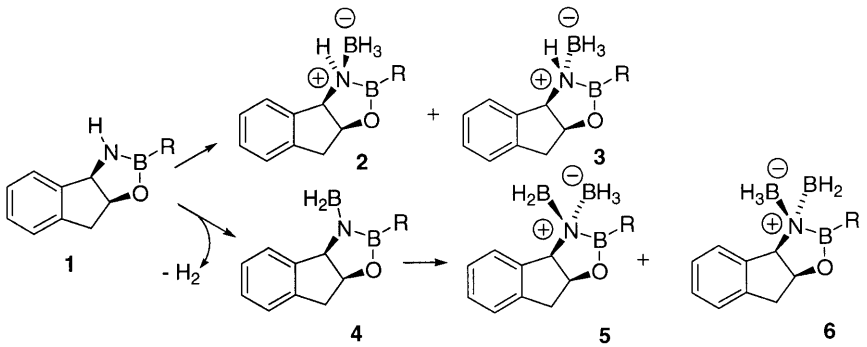
Our interest in the use of the *cis*-1-amino-2-indanol system led us to reconsider the catalytic process. In the *N*-unsubstituted catalysts, a more complex situation exists that cannot occur with the original prolinol compound. In the first instance, ylide formation can occur in an analogous fashion to the Corey catalyst and formation of diastereomeric complexes **2** and **3** can result (Scheme 1). A second possibility exists whereby elimination of hydrogen can occur to give the *N*-borane complex **4** which could act as an active catalyst or alternatively react with a second equivalent of borane to give diastereomeric ylide catalysts **5** and **6**.

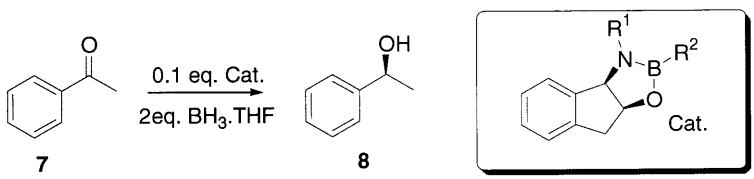


Scheme 1.

Clearly the latter route would not be possible in *N*-substituted indanol derivatives whereby elimination of H_2 is impossible. In the case of these derivatives, selective formation of one of the diastereomeric complexes **2** or **3** would be required for high levels of selectivity in the subsequent reduction reaction. Intrigued by these possibilities, we have conducted some studies aimed at elucidating the reaction mechanism. We now report some preliminary investigations of the effect of catalyst structure and subsequent initial optimisation studies of a general set of reaction conditions for this process.

2. Results

We first attempted to find an optimum catalyst by screening the reduction of acetophenone **7** using (1*R*)-amino-(2*S*)-indanol **1** and the corresponding *N*-methyl ($R^1 = Me$)[6] and *N*-benzyl ($R^1 = Bn$)[7] compounds as their *B*-Me and *B*-H complexes (Scheme 2). A standard set of reaction conditions was initially used and background reactions performed for each of the *B*-H catalysts. Thus, BH_3·THF was added to 0.1 equiv. of catalyst at room temperature in THF under N_2 and aged for a period of time, then cooled to 0°C. Ketone was then added in THF and stirred at 0°C for 2 hours, before quenching with MeOH followed by standard workup. The results are summarised in Table 1.



Scheme 2.

Table 1

Catalyst (0.1 equiv.)	Equiv. BH_3	Ageing time (h)[a]	Conversion	E.e.[b]
$R^1=H$, $R^2=H$	2	1	>95%	30% (*S*)
	0.1	1	18%	7% (*S*)
$R^1=H$, $R^2=Me$	2	0.5	>95%	84% (*S*)
$R^1=Me$, $R^2=H$	2	1	>95%	32% (*S*)
	0.1	1	16%	6% (*R*)
$R^1=Me$, $R^2=Me$	2	0.5	>95%	28% (*S*)
$R^1=Bn$, $R^2=H$	2	1	>95%	6% (*S*)
	0.1	1	14%	3% (*S*)
$R^1=Bn$, $R^2=Me$	2	0.5	>95%	10% (*S*)

[a] Time from addition of BH_3·THF to addition of ketone.
[b] Major isomer detected by GC (see Section 4).

Noticeably it was observed that the *B*-H pre-catalysts themselves could promote efficient catalysis, although the observed enantioselectivities were essentially zero. Competitive reduction by these pre-catalysts could potentially result in a decreased enantiomeric excess of alcohol. Somewhat surprisingly it was found that the parent (1*R*)-amino-(2*S*)-indanol consistently gave poor enantioselectivities. More noticeably, a decrease in enantioselectivity was observed as the size of the *N*-alkyl group was increased. This is very surprising, as *N*-cyclohexylmethyl-*cis*-1-amino-2-indanol has been reported to give an enantiomeric excess of 90% with α-chloro-acetophenone.[3] Work is currently in progress preparing a series of other *N*-alkyl analogues with an aim of clarifying the role of this substituent in this reaction.

The reaction conditions were next optimised with the best catalyst (*B*-methyl-(1*R*)-amino-(2*S*)-indanol) in preparation for collecting further mechanistic data. It was found that reduction of acetophenone by BH_3·THF was essentially complete *during the reaction period in the absence of catalyst*. Further investigations indicated that the enantioselectivity was found to decrease from 86 to 78% when 3.0 equiv. BH_3·THF were used instead of 1.1 equiv. More interestingly the conversion and enantioselectivity of the product alcohol varied significantly with reaction temperature, the optimum being at 0°C (>95% conversion, 84% e.e.), dropping in selectivity at higher temperatures (25°C, e.e. 77%) and in conversion and selectivity at low temperatures (−78°C 12% conversion, 39% e.e.) (Table 2). Previous observations have noted a trade-off between the temperature required to allow efficient catalyst turnover and the selectivity observed.[8]

Table 2

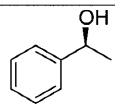
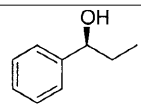
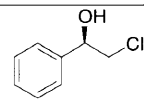
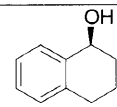
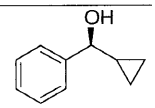
Temperature	Conversion (E.e.[a])
25°C	>95% (77%)
0°C	>95% (84%)
−20°C	>95% (50%)
−78°C	12% (39%)

[a] Major isomer detected by GC (see Section 4).

Other reducing agents were also tested, catechol borane giving poor conversion (18%) and low enantiomeric excess (8%) while BH_3·DMS gave quantitative conversion and an improved enantiomeric excess (92%). While this is currently being investigated further, a possible explanation is that BH_3·DMS retards the rate of the competing background reaction.

The optimised reaction conditions (1.1 equiv. BH_3·DMS, 0°C, 10% catalyst) were applied to a series of aromatic ketones and the results shown in Table 3. In these cases, HPLC was used to provide a more accurate analysis of enantiomeric excess and it was noted that there were significant differences between the results obtained by HPLC and GC. Comparative analysis with a sample of 1-phenylethanol prepared previously (84% e.e. by GC) gave an enantiomeric excess of 80% using HPLC. This confirmed that the enantiomeric excess obtained with the optimised reaction conditions (82% by HPLC) was indeed improved, although to a small extent.

Table 3[a]

Product Alcohol	 **1**	 **9**	 **10**	 **11**	 **12**
Conversion / e.e. (%)	>95 / 82	>95 / 69	>95 / 87	>95 / 78	>95 / 25
$[\alpha]_D$ (c 1, $CHCl_3$)	-46.8	-36.6	-53.4	+25.1	-6.1

[a] Major isomer assigned by comparison of literature specific rotation values. E.e. determined by HPLC (see Section 4).

The results obtained are somewhat surprising compared to those in the literature.[5] Whereas alcohols **1** and **10** are of comparable enantiomeric excess, **9** and **11** are significantly lower than those reported. More interestingly, the cyclopropyl alcohol was obtained in an enantiomeric excess of only 25%. As yet we do not have a clear explanation for the drop in selectivity observed.

3. Conclusion

The use of *N*-alkyl derivatives of *cis*-1-amino-2-indanol as catalysts in the reduction of acetophenone significantly effects the observed enantioselectivity of the product alcohol. The relative reaction rates of the individual components in the reaction mixture can drastically effect the conversion and hence the enantioselectivity observed. We are currently preparing other *N*-substituted derivatives and further investigating the reaction kinetics with an aim to elucidating the mechanism of this process.

4. Experimental

All solvents used were freshly dried over sodium. Glassware was flame dried before use and all reactions were conducted under a nitrogen atmosphere. Reaction conversions were determined by the ratio of starting material and product by ^{1}H NMR at 200 MHz. ^{1}H NMR spectra

were recorded on a Bruker AC200 spectrometer using the Bruker Aspect 3000 system. Residual proton signals from chloroform (^{1}H 7.25 ppm) was used as a reference. Coupling constants were measured in Hz. Specific rotations were determined on a Polaar 2001 automatic polarimeter at 589 nm and measured at 20°C unless otherwise stated. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. HPLC was carried out using a Beckman System Gold instrument with a Chiralcel OD (4.8×250 mm) column and IPA in heptane as the solvent system. The flow rate was 1.00 cm^3 per minute and the detector was set at 254 nm. Gas chromatography was carried out on a Packard Model 427 instrument using a flame ionisation detector. A fused silica capillary column was used with β-cyclodextrin as the stationary phase. Hydrogen was used as the carrier gas. *N*-Benzyl and *N*-methyl-(1*R*)-amino-(2*S*)-indanol were prepared by literature methods.[6,7]

4.1. General procedure for the preparation of the B-*methyl catalysts*

Trimethylboroxine (0.19 cm^3, 1.34 mmol) was added to a solution of the (1*R*)-amino-(2*S*)-indanol (2.01 mmol) in toluene (10 cm^3) and stirred at room temperature for 30 minutes. Toluene (10 cm^3) was added and the resulting solution was concentrated to approximately 2 cm^3 by distillation. This process was repeated twice after which the toluene was removed under reduced pressure to give the catalyst as a white solid. THF (2 cm^3) was added to produce an approximately 1.0 M solution of catalyst in THF that was used in subsequent reactions. This solution was found to be stable for a limited period (48 hours) at room temperature when stored under a nitrogen atmosphere.

4.2. Optimised procedure for the reduction of aryl ketones

BH_3·DMS (0.45 cm^3, 4.71 mmol) was added to a solution of *B*-methyl-(1*R*)-amino-(2*S*)-indanol (0.42 cm^3, 0.43 mmol) in THF (4 cm^3) and stirred at room temperature under N_2 for 30 minutes. The resulting solution was cooled to 0°C and the ketone (4.29 mmol) in THF (3 cm^3) added via cannula. The reaction mixture was stirred for a further 2 hours at 0°C then quenched with methanol and allowed to warm to room temperature for 10 minutes. Water was added and the solvent removed under reduced pressure to leave the product in aqueous phase. The product was extracted into dichloromethane (3×10 cm^3), the organic phase washed with 1 M HCl, water and dried over $MgSO_4$. Removal of the solvent produced the product as a slightly cloudy colourless oil in most cases.

4.2.1. 1-Phenylethanol ***1***

δ_H 7.31–7.08 (5H, m, ArH), 4.80 (1H, q, *J* 6.5, C*H*OH), 1.97 (1H, br, OH), 1.41 (3H, d, *J* 6.5, C*H*$_3$CH); $[\alpha]_D$ −46.8 (*c* 1, $CHCl_3$); e.e. 82% (5% IPA in heptane).

4.2.2. 1-Phenylpropan-1-ol ***9***

δ_H 7.31–7.14 (5H, m, ArH), 4.50 (1H, t, *J* 6.6, C*H*OH), 1.96 (1H, br, OH), 1.70 (2H, m, C*H*$_2$CH$_3$), 0.83 (3H, d, *J* 6.6, C*H*$_3$CH); $[\alpha]_D$ −36.6 (*c* 1, $CHCl_3$); e.e. 69% (5% IPA in heptane).

4.2.3. 2-Chloro-1-phenylethanol ***10***

δ_H 7.39–7.25 (5H, m, ArH), 4.88 (1H, dd, *J* 3.7 and 8.6, C*H*OH), 3.69 (2H, m, C*H*$_2$Cl), 2.74 (1H, br, OH); $[\alpha]_D$ −53.4 (*c* 1, $CHCl_3$); e.e. 87% (5% IPA in heptane).

4.2.4. 1,2,3,4-Tetrahydronaphthalen-1-ol ***11***

δ_H 7.34 (1H, m, ArCH), 7.21–7.00 (3H, m, ArH), 4.69 (1H, m, C*H*OH), 2.80–2.55 (2H, m, CH_2Ar), 1.98–1.65 (4H, m, $2\times CH_2$); $[\alpha]_D$+25.1 (*c* 1, $CHCl_3$); e.e. 78% (2% IPA in heptane).

4.2.5. Cyclopropyl-phenylmethanol ***12***

δ_H 7.19–6.98 (5H, m, ArH), 3.73 (1H, d, *J* 8.3, C*H*OH), 1.91 (1H, br, OH), 0.96 [1H, CH(OH)C*H*], 0.48–0.07 (4H, m, cyclopropyl); $[\alpha]_D$ −6.1 (*c* 1, $CHCl_3$); e.e. 25% (2% IPA in heptane).

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