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Efficient desymmetrisation of a *meso*-imide using a chiral oxazaborolidine catalyst

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Abstract—Desymmetrisation of a *meso*-imide by enantioselective reduction using a chiral oxazaborolidine catalyst derived from (1*R*,2*S*)-*cis*-1-amino-2-indanol followed by reduction of the hydroxylactam product proceeded with good enantiomeric excess (80–91%) at significantly lower catalyst loadings compared to reactions using the prolinol-derived catalyst. Models for the selectivity observed are proposed based upon structural probes and experimental observations.

1. Introduction

Desymmetrisation of a *meso* starting material using a chiral reagent or catalyst provides a powerful and versatile strategy in asymmetric synthesis as the differentiation of two enantiotopic groups facilitates the formation of multiple stereocentres in a single transformation.[1] In recent years there have been several reports of the use of asymmetric reducing agents in the desymmetrisation of *meso*-imides including optically active BINAL-H[2] and thiazazincolidine[3] complexes. Of particular interest is the use of oxazaborolidines such as the α,α-diphenylprolinol complex **1** as catalysts in this reaction. Speckamp and co-workers reported the combination of this catalyst with borane for the enantioselective reduction of a variety of *meso*-imides,[4] giving good enantioselectivities (average e.e. 84%). However, significant quantities of the catalyst (ranging from 20 to 50 mol%) were required to affect the transformation (Fig. 1).

Previous reports from this laboratory have described the use of oxazaborolidines derived from (1*R*,2*S*)-*cis*-1-amino-2-indanol **2** in the asymmetric reduction of prochiral ketones.[5] During this work we became interested in comparing the mechanism of reduction of this catalyst in relation to the prolinol derived system **1**. To this end we have been exploring the scope of catalyst **2** in a number of different asymmetric reduction reactions and we describe herein its application in the desymmetrisation of a *meso*-imide.

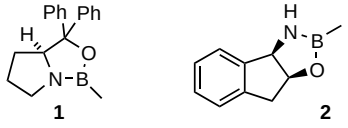

Figure 1.

2. Results and discussion

2.1. Optimisation of conditions

The test substrate used throughout these studies was the hexahydrophthalimide derivative **3**, which in the first instance was treated with 5 mol% of catalyst **2** and 1 equiv. of BH_3·THF at 0°C for 2 h to yield a mixture of the optically active *cis*- and *trans*-5-hydroxy-2-pyrrolidinones **4** (Scheme 1). In order to simplify analysis, the crude mixture was treated with TFA and Et_3SiH and the lactam **5**, isolated as the sole product in 57% overall yield after silica gel chromatography. The TFA/Et_3SiH reduction conditions did not affect imide **3** which would have otherwise eroded the observed enantiomeric excess of lactam **5** that was established to be 84% by HPLC.

The sense of enantioselectivity of the reduction was established by conversion of the hydroxy lactam **4** to the previously reported ethoxy lactam **6** in 77% yield. Comparison of the sign of the specific rotation of the ethoxy lactam **6** with that reported in the literature for

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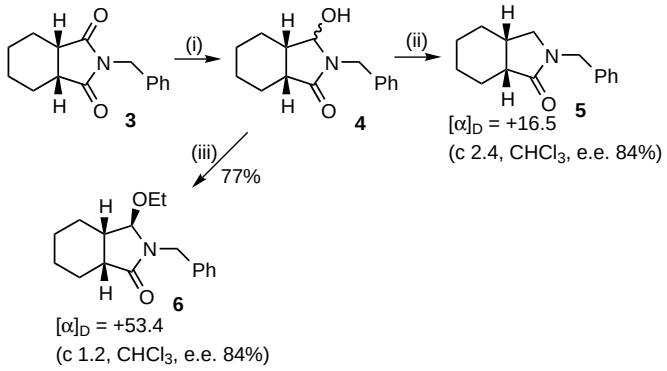


Scheme 1. *Reagents and conditions*: (i) catalyst **2** (see Table 1 for quantities), 1 equiv. BH_3·THF, THF; (ii) TFA, Et_3SiH, CH_2Cl_2; (iii) 2 M H_2SO_4, EtOH.

the enantiomeric compound gave the absolute configuration of the reduction product **6**, and by inference compounds **4** and **5**, to be as depicted (Scheme 1).

Somewhat surprised by the excellent level of enantioselectivity obtained with such a low catalyst loading, further investigations were carried out. For comparison purposes, reduction of the imide **3** using the Corey catalyst **1** at the same 5 mol% catalyst loading gave product **5** in variable yield (44–74%) and significantly lower enantioselectivity (45% e.e.). The sense of stereoselectivity with the prolinol catalyst **1** was opposite to that observed with the indanol derived catalyst **2**, a result which is in accordance with our observations made for asymmetric reduction of prochiral ketones using this catalyst.[5]

Several experiments were conducted to explore the scope of the reaction (Table 1). Reduction in the amount of catalyst **2** to as low as 1 mol% showed no significant drop in enantioselectivity, the observed enantiomeric excess remaining constant at around 85%, although a slight drop in the overall yield was noted. This is probably a result of the standard reaction time used in these experiments (2 h) rather than the catalyst being less effective. Similar effects were observed when the loading was increased to 10% with a corresponding increase in yield. However, catalyst loadings of 0.1% or lower led to low yields (14%) and very low enantioselectivities (e.e. $\leq$10%). It was also observed that the temperature of the reaction could be varied by 30°C with only minor variations in the enantioselectivities being obtained.

Table 1. Optimisation of reduction conditions

Loading **2** (mol%)	Temperature (°C)	Yield **5** (%)[a]	E.e. **5** (%)
5	0	57[b]	84
1	0	57[b]	82
10	0	75[b]	86
0.1	0	14	10
5	−30	48	88
5	30	50	76

[a] Refers to isolated yield of **5** after a two-step procedure.
[b] Yields are averaged values from three separate reaction sequences.

Although the enantioselectivity remained approximately constant for all reactions performed, the overall yield of the reaction varied in some cases from 38 to 81% and some yields indicated are averaged from three separate reactions. The origins of this discrepancy have not yet been fully resolved but could result from the moisture content of the solvent or the quality of the commercial BH_3·THF solution, a well-documented problem in this reaction.[6] Attempts made to resolve these issues first involved addition of molecular sieves to the reaction to remove water, but this did not improve the yield nor the selectivity. Other borane sources or equivalents were also investigated, catecholborane giving no conversion to product. The application of BH_3·DMS gave a slightly reduced enantiomeric excess (e.e. 70%) and yield (45%) in THF that improved when toluene was used as a solvent (e.e. 80%, yield 54%). Minor changes in yield and selectivity have been previously reported for the oxazaborolidine-catalysed reduction of prochiral ketones with BH_3·DMS under these conditions[7] and further investigations of this effect with the amino indanol catalyst are currently underway. The order of addition of the reagents, catalyst and substrate did not appear to be important, however, slow addition of the imide **3** to the reaction mixture did improve the enantioselectivity (e.e. 91%) and yield (89%).

2.2. Mechanistic considerations

We have previously proposed hypothetical intermediates and reaction pathways for oxazaborolidines derived from amino indanol catalysts[5] and the large discrepancy between the yields and selectivities observed between the aminoindanol and prolinol catalysts in this study led us to consider the mechanism of this process more carefully. In the first instance, a linear dependence was observed with respect to the effect that the enantiomeric excess of the catalyst had on the enantioselectivity of the reaction (Fig. 2). This excludes a dimeric catalytic species enhancing the enantioselectivity observed with this catalyst.

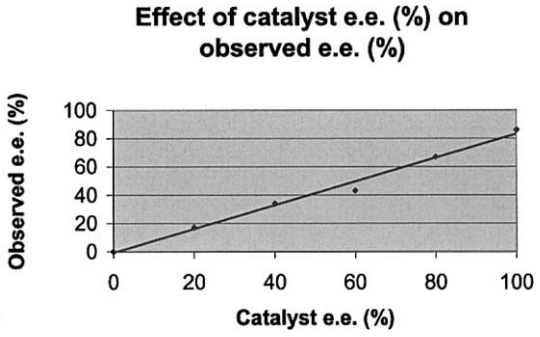


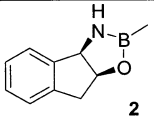
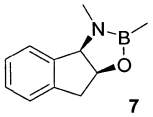
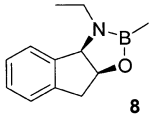
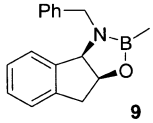
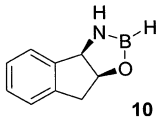
Figure 2. Effect of enantiomeric purity of catalyst on enantioselectivity.

Next, a number of simple structural analogues were prepared and tested as catalysts. The results are summarised in Table 2.

The *B*-methyl *N*-alkyl catalysts show a steady decrease in enantioselectivity and yield as the size of the alkyl group increases. High levels of enantioselectivity are observed with the *B*-H, *N*-H catalyst, which is in contrast to results obtained for the reduction of prochiral ketones.[5] This is due to the background reaction rate of the imide system with [BH_3·THF] being essentially zero, as is reduction using the *B*-H compound **10** as a stoichiometric reducing agent.

The requirement for a small substituent group located on the nitrogen atom for high levels of enantioselectivity can be rationalised by assuming a classical model for asymmetric reduction using oxazaborolidine catalysts.[8] A key feature of this model is a pre-equilibrium involving coordination of borane on the least hindered *exo*-face of the aminoindanol in readiness for delivery to the complexed carbonyl group. This equilibrium is a reversible process indicated by an equilibrium constant, $K=220$, for prolinol oxazaborolidines **1**.[6] As the size of the substitutent on the nitrogen atom is increased, steric interactions now result in the equilibrium favouring placement of the larger alkyl group on the least hindered *exo*-face, with the borane coordinating to the *endo*-face of the amino indanol (Scheme 2).

Table 2. Effect of *B*- and *N*-substituents on the yield and enantioselectivity

Catalyst	Yield (%)[a,b]	E.e. (%)
 **2**	75	86
 **7**	52	55
 **8**	28	2
 **9**	25	30
 **10**	50	80

[a]Reactions performed under standard conditions using 10 mol% catalyst at 0 °C

[b]Refers to isolated yield of **5** after a two step procedure.

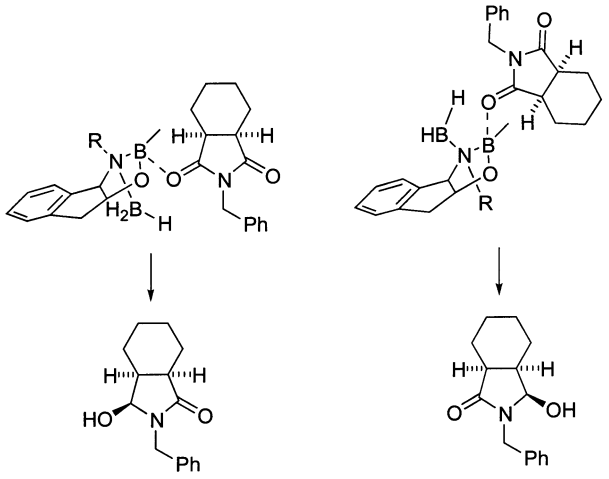
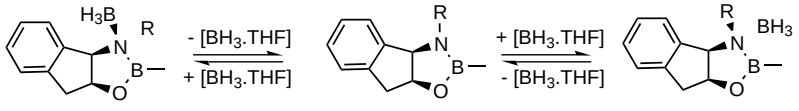


Figure 3. Proposed model for observed enantioselectivities.

Reduction can now take place from either of these two complexes. In the case of the *exo*-borane species, delivery of hydride occurs to the coordinated carbonyl of the substrate that is orientated such that the benzylic imide is regarded as the large group occupying a position away from the *B*-methyl group (Fig. 3). The same model applies to the *endo*-borane complex except that the opposite enantiomer of product is now produced. The drop in yield for those catalysts favouring the *exo*-borane complex implies that the rate of reduction is significantly lower than that with the *endo*-complex. Thus, it appears that the equilibrium ratio of *exo*- and *endo*-borane complexes dominates in determining the enantioselectivity of these *N*-substituted catalysts, implying that higher levels of enantioselectivity could *theoretically* be obtained if an oxazaborolidine with a greater preference for binding borane on the *exo*-face could be prepared.

3. Conclusions

We have shown oxazaborolidine **2** to be an effective catalyst for the enantioselective reduction of a *meso*-imide that functions at only 1 mol% catalyst loading and provides similar selectivities to those reported using the oxazaborolidine **1**, where a 20–50 fold quantity of catalyst was required. We are currently investigating the scope of the reaction with respect to employing



Scheme 2.

substrates other than *meso*-imides and further examining the role that the binding equilibrium of BH_3·THF to the oxazaborolidine has upon the selectivity of the catalyst.

4. Experimental

4.1. General

All solvents used were freshly dried over sodium (except dichloromethane which was dried over lithium aluminium hydride). Glassware was flame dried and cooled under vacuum before use. All reactions were carried out under nitrogen. TLC was carried out using Merck aluminium TLC sheets (silica gel 60 F_{254}). Visualisation of the TLC plates was carried out using a UV lamp or by dipping in $KMnO_4$ then exposure by heating. Flash column chromatography was carried out with Fluorochem Limited Silica Gel 40–63u 60A. 200 MHz ^{1}H NMR were carried out on a Bruker AC200 spectrometer using the Bruker Aspect 3000 system. 300 MHz ^{1}H NMR were carried out on a Bruker Avance 300 spectrometer. 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR were carried out on a JEOL (Japan Electron Optical Limited) λ 500 MHz spectrometer. Residual proton signals from the deuteriated solvents were used as references [chloroform (^{1}H 7.25 ppm, ^{13}C 77 ppm) and DMSO [^{1}H 2.50 ppm, ^{13}C 39.7 ppm)]. Coupling constants were measured in Hz. Specific rotations were performed 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}. All infrared spectra were recorded on a Genesis series FT-IR spectrophotometer and mass spectra were recorded on a Micromass Autospec M spectrometer. HPLC was carried out using a Spectra Physics Analytical system (consisting of a P4000 pump, an AS1000 autosampler, a UV2000 detector and using PC 1000 version 2.0 software). A Chiralcel OD (4.8×250 mm) column was used with 10% IPA in heptane as the solvent (unless otherwise stated). The flow rate was 1.00 cm^3 per minute and the detector was set at 254 nm. BH_3·THF complex (Lancaster) and trimethylboroxine (Aldrich) were used as received. *N*-Alkyl catalysts **7** and **9** were prepared as noted previously.[5] 2-Benzylhexahydroisoindole-1,3-dione **3** was prepared according to literature procedure.[4]

4.2. *N*-Ethyl amino indanol

Acetaldehyde (0.75 cm^3, 13.4 mmol) was added to (1*R*,2*S*)-*cis*-1-amino-2-indanol (2.00 g, 13.4 mmol) in methanol (20 cm^3) at 0°C and stirred at this temperature for 2 h. Sodium borohydride (0.509 g, 13.4 mmol) was added slowly (**CARE**! effervescence!) and the mixture was allowed to stir for 18 h. Water (20 cm^3) and EtOAc (20 cm^3) were added, the organic layer was separated and the aqueous layer was further extracted with EtOAc (2×10 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated to give a solid that was recrystallised from petroleum ether:ethyl acetate to give the title compound as white needles (1.63 g, 69%), mp 94°C; $[\alpha]_D$ −5.1 (*c* 1, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.23 (3H, t, *J* 7.0 CH_3), 2.78–3.12 (4H, m, CH_3CH_2, ArCH_2), 4.09 (1H, d, *J* 5.0, C*H*NH), 4.40–4.44 (1H, m, C*H*OH), 7.22–7.29 (4H, m, ArC*H*); δ_C (500 MHz; $CDCl_3$) 15.8 (CH_3), 39.8 (CH_3CH_2), 43.2 (ArCH_2), 65.9 (*C*HNH), 70.6 (*C*HOH), 123.7 (Ar*C*H), 125.8 (ArC*H*), 126.7 (ArC*H*), 128.1 (ArC*H*), 141.3 (Ar*C*H), 142.5 (Ar*C*H); υ_{max} (NaCl disc)/cm^{-1} 3200 brd, 2920, 1455; *m*/*z* (EI) 177.1154 (MH$^+$ $C_{11}H_{15}NO$ requires 177.1158) 177 (9%), 148 (100), 133 (26), 103 (29), 77 (14).

4.3. General procedure for the preparation of *N*-methyl catalysts

A *cis*-1-amino-2-indanol analogue (4.0 mmol) was suspended in dry toluene (10 cm^3) and treated with trimethylboroxine (2.7 mmol). After stirring at room temperature for 30 min, toluene (10 cm^3) was added and the reaction mixture was concentrated to 2 cm^3. A further quantity of toluene (10 cm^3) was added, the reaction was concentrated to 2 cm^3 and this process was repeated. The remaining 2 cm^3 were removed under vacuum to leave an off-white solid.

4.4. 2-Benzyl-octahydro-isoindol-1-one 5—optimised procedure

Imide **3** (0.200 g, 0.82 mmol) in THF (3 cm^3) was added via a syringe pump (0.0132 cm^3/min) to a pre-stirred solution (15 min) of catalyst **2** (10 mol%, from a 1.0 M solution in THF, 0.08 cm^3, 0.08 mmol) and BH_3·THF (1.0 M solution, 0.82 cm^3, 0.82 mmol) at 0°C and left to stir at this temperature for 1 h. The reaction was then quenched with 5% HCl and the aqueous layer was extracted into CH_2Cl_2 (2×25 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield the hydroxylactam as a clear oil. This was immediately dissolved in CH_2Cl_2 (2 cm^3) and treated with a solution of TFA (0.25 cm^3) and Et_3SiH (0.25 cm^3) in CH_2Cl_2 (1.0 cm^3). After stirring at room temperature for 3 h the reaction was poured into a mixture of ice-water. The organic layer was separated and washed with $NaHCO_3$ (2×20 cm^3), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to yield the lactam as a yellow oil. Purification by column chromatography (petrol:EtOAc, 1:1) gave the pure lactam **5** as a clear oil (0.169 mg, 91%). $[\alpha]_D$ +19.6 (*c* 0.5, $CHCl_3$, e.e. 91%); υ_{max} (NaCl disc)/cm^{-1} 2925, 2854, 1692; δ_H (200 MHz; $CDCl_3$) 1.12–1.30 (2H, m), 1.64–1.52 (5H, m), 2.07 (1H, m), 2.30 (1H, m, C*H*CH_2N), 2.52 (1H, m, C*H*CO), 2.77 (1H, dd, *J* 9.5, 2.5, CH*H*N), 3.25 (1H, dd, *J* 9.5 and 6.0, C*H*HN), 4.40 (1H, d, *J* 14.5, CH*H*Ph), 4.54 (1H, d, *J* 14.5, C*H*HPh), 7.24–7.38 (5H, m, Ph); δ_C (125 MHz; $CDCl_3$) 23.0, 23.5 (×2), 27.9, 32.2, 41.9 (*C*HC=O), 46.8 (CH*C*H_2N), 50.7 (N*C*H_2Ar), 127.4 (Ar*C*H), 128.2 (Ar*C*H), 128.6 (Ar*C*H), 136.8 (Ar*C*), 175.9 (*C*=O); *m*/*z* (EI) 229.14666 (M$^+$ $C_{15}H_{19}NO$ requires 229.1474) 229 (100%), 174 (11), 138 (19), 91 (94), 41 (13).

4.5. Reduction with *B*-H catalyst 10

BH_3·THF (1.0 M solution, 0.08 cm^3, 0.08 mmol) was added to a solution of (1*R*,2*S*)-*cis*-1-amino-2-indanol (0.012 g, 0.08 mmol) in THF (1 cm^3) and left to stir at room temperature under nitrogen for 15 min. The reaction was cooled to 0°C, and a further portion of BH_3·THF (1.0 M solution, 0.82 cm^3, 0.82 mmol) was added, followed by a solution of the imide **3** (0.200 g, 0.82 mmol) in THF (2 cm^3). After stirring the mixture for 2 h at 0°C, the reaction was quenched with 5% HCl and the aqueous layer was extracted into CH_2Cl_2 (2×25 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to yield the hydroxylactam as a clear oil. This was immediately dissolved in CH_2Cl_2 (2 cm^3) and treated with a solution of TFA (0.25 cm^3) and Et_3SiH (0.25 cm^3) in CH_2Cl_2 (1.0 cm^3). After stirring at room temperature for 1.5 h, the reaction was poured into a mixture of ice-water. The organic layer was separated and washed with $NaHCO_3$ (2×20 cm^3), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure to yield the lactam **5** as a yellow oil. Purification by column chromatography (petrol:EtOAc, 1:1) gave the pure lactam **5** as a clear oil (0.094 g, 50%, e.e. 80%).

4.6. (3*R*,3a*S*,7a*R*)-2-Benzyl-3-ethoxy-octahydro-inden-1-one 6

Acidified ethanol (2 M H_2SO_4 in ethanol) was added to a solution of the hydroxylactam **4** (0.055 g, 0.22 mmol, e.e. 75% by derivatisation) in ethanol (10 cm^3) until the solution was approximately pH 2. The reaction was stirred at room temperature for 3 h, quenched with saturated $NaHCO_3$ (10 cm^3) and the aqueous phase was extracted with CH_2Cl_2 (3×20 cm^3). The organic extracts were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to yield the ethoxylactam **6** as a clear oil (47 mg, 77%) $[\alpha]_D$ +53.4 (*c* 1.2, $CHCl_3$, e.e. 75%), (ent-6, lit.[3] $[\alpha]_D$ −53.7, *c* 1.2, $CHCl_3$, e.e. 80%); δ_H (300 MHz; $CDCl_3$) 1.10 (3H, t, *J* 7, OCH_2CH_3), 1.04–1.15 (3H, m), 1.19–1.56 (4H, m), 2.12–2.20 (2H, m), 2.74 (1H, m, C*H*CO), 3.37 (2H, m, $CHOCH_2CH_3$), 3.93 (1H, d, *J* 14.7, PhCH*H*N), 4.03 (1H, s, C*H*OEt), 4.92 (1H, d, *J* 14.7, PhC*H*HN), 7.18–7.29 (5H, m, Ph); δ_C (125 MHz; $CDCl_3$) 15.8, 23.3 (×2), 23.9, 27.2, 37.0, 38.1 (*C*HC=O), 44.8 (NCH_2Ar), 63.7 (OCH_2CH_3), 92.6 (N*C*H), 127.9 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (Ar*C*H), 137.3 (Ar*C*), 176.7 (*C*=O).

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