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Evaluating the role of solvent and borane on the enantioselectivity of the oxazaborolidine reduction of prochiral ketones using catalysts derived from *cis*-(1*R*,2*S*)-1-amino-indan-2-ol

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Abstract—The dependency of the enantioselectivity on the solvent and hydride source for the asymmetric reduction of acetophenone catalysed by the oxazaborolidine derived from *cis*-(1*R*,2*S*)-1-amino-indan-2-ol have been investigated. ^{11}B NMR studies have implied that monomer/dimer ratios are important for achieving high enantioselectivities.

Oxazaborolidine catalysed reductions of prochiral ketones,[1] imides[2] and lactones[3] have opened up new avenues in the armory of tools available to the synthetic chemist. Using these catalysts, asymmetric reduction using a borane source as the reductant now allows high and predictable selectivities to be obtained for substrates that are used in subsequent asymmetric syntheses.[4] It has been shown that the nature of the borane source employed as the hydride donor plays a crucial role in optimizing the catalytic cycle and maximizing enantioselectivity, while direct comparisons of different borane hydride sources have been reported for the Corey catalyst.[5,6] A key feature of this catalyst system is the equilibrium that exists between the monomeric **1** and postulated dimeric **2** form of the oxazaborolidine (Fig. 1), the latter of which breaks down to the active monomeric form **1** in the presence of a coordinating solvent such as THF.[1] Nevalainan has reported ab initio molecular calculations that suggest that solvent effects not only play an important role in the monomer/dimer equilibrium of the free oxazaborolidines but are also important in stabilizing the reactive intermediates involved in the transition state.[7,8]

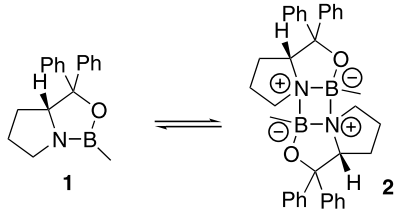

Figure 1.

We have recently focused effort on the use of oxazaborolidine catalysts **3** derived from *cis* 1-amino-indan-2-ol in the reduction of ketones[9] and imides[10] which have resulted in unusual selectivities and reactivities. These results have prompted us to investigate further mechanistic details of reactions of the catalyst **3** and herein we report the dependency of the enantioselectivity of the asymmetric reduction of acetophenone with solvent and borane source employed.

In each case, a standard set of reaction conditions was employed using 10% of pre-formed catalyst **3** and 1.1 equiv. of hydride source unless otherwise stated (Scheme 1).[11] The effect that the use of different solvents had on the enantioselectivity of the reduction of acetophenone was examined (Table 1) and ^{11}B NMR spectroscopy was used to calculate the monomer/dimer ratio **3**:**4** of the oxazaborolidine in solution (Table 1, Fig. 2).[12] The effect that the borane source **5a**–**f** had on the enantioselectivity was also evaluated (Table 2).

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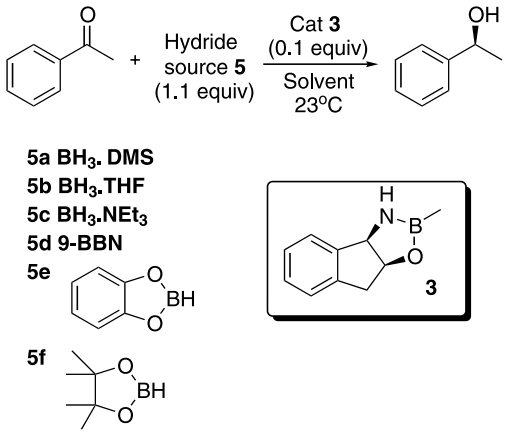

Scheme 1.

Table 1. Effect of solvent on the enantioselectivity of the reduction of acetophenone[a]

Solvent	Yield (%)	Ee[b] (%)	Monomer/dimer ratio[c]
THF	100	85	37:1
Et_2O	100	85	33:1
1,4-Dioxane	98	78	14:1
DME	66	73	35:1
Toluene	100	75	15:1
CH_2Cl_2	100	73	13:1
Dimethyl carbonate	15	59	20:1
DMPU/THF[d]	100	57	5:1
DMSO	9	45	7.6:1
Acetonitrile	60	0	12:1
DMF	0	NA	11:1

[a] All reductions were carried out with acetophenone:**3**:BH_3·DMS (1:0.1:1.1). BH_3·DMS and **3** were stirred for 30 min prior to addition of acetophenone. Reactions were left for 30 min before quench with methanol.

[b] Determined by HPLC. The (*S*) enantiomer was formed as the major stereoisomer throughout.

[c] Calculated from the ^{11}B NMR spectrum from comparison of the signals at approximately +10 ppm (dimer) and +35 ppm (monomer).

[d] DMPU:THF (1:3).

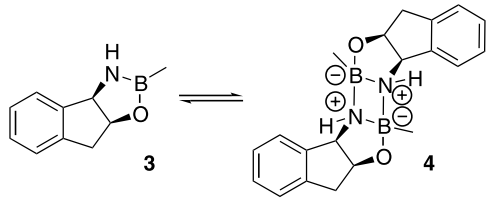

Figure 2.

The usual solvent employed for conducting oxazaborolidine reductions is THF and unsurprisingly, Lewis basic solvents such as THF and diethyl ether gave a somewhat better enantiomeric excess (both 85% ee) than solvents such as toluene and CH_2Cl_2 (75% ee and 73% ee, respectively). It is clear that those reactions that return an enantiomeric excess of 85% give a very high monomer/dimer ratio of the oxazaborolidine **3**:**4**. 1,4-Dioxane might have been expected to give similar results to those obtained with THF or diethyl ether and the reason for the apparent drop in monomer/dimer ratio and enantioselectivity is not clear. DME is intriguing since there is a very high monomer/dimer ratio, but low enantioselectivity. This is probably due to this solvent retarding the rate of reaction (reflected in the reduced yield), which will make the racemic background reaction of acetophenone more important, ultimately leading to a loss of selectivity. This balance between obtaining high monomer/dimer ratios and maximising the rate of the oxazaborolidine catalysed reaction appears essential for obtaining high selectivities and correlates well with ab initio work previously reported.[7] Interestingly, strongly co-ordinating solvents such as dimethyl carbonate, DMPU DMSO and acetonitrile generally gave poor conversion with disappointing enantioselectivities. The use of DMF as a solvent gave anomalous results since this was the only case that resulted in returned acetophenone, implying that this solvent either completely inhibited the catalyst or was used as a substrate itself.

Generally the results obtained are in line with those reported for other oxazaborolidines, although other groups have reported that the drop in enantioselectivity in reactions using CH_2Cl_2 as a solvent is larger than observed here.[5,6,13,14]

Reductions using the oxazaborolidine **3** were much more sensitive to changes in the borane source (Table 2). The low selectivities noted for boranes **5c** and **5d** have been noted for other oxazaborolidine catalysts,[5,6] and reductions in ee and yield have been noted when using BH_3·THF **5b** due to impurities in the commercial reagent.[15,16] The most surprising result in this study is that obtained with catachol borane **5e** which is reported to give excellent enantioselectivities with the Corey oxazaborolidine catalyst system. However, this gave no conversion with the indanol derived catalyst **3**, a feature that has been noted in attempted reductions of *meso*-imides.[10]

The nature of the catalyst **3** under optimum reaction conditions (BH_3·DMS in THF) was further explored using ^{11}B NMR spectroscopy. In its resting state catalyst **3** indicated signals for the monomer **3** at +36.21 ppm and the dimer **4** at +9.97 ppm. Addition of BH_3·DMS (1 equiv.) to catalyst **3** (0.1 equiv.) gave rise to a quartet at −18.2 ppm (BH_3·DMS), a quartet at 1.4 ppm (BH_3·THF formed in situ), signals for the borane complexed catalyst **6** at −16.1 ppm (BH_3-NH) and at +40.7 ppm (N–B–O) and free catalyst **3** (+36.3 ppm) (Fig. 3). Several other minor components were also observed in the region δ −20 to −10 region of the ^{11}B NMR spectrum.

These results indicate that the ylide **6** is probably in equilibrium with the catalyst **3** where the catalyst **3** is favored at this temperature. Thus only a small amount of active catalyst is present at any time. It has been postulated from previous work in this laboratory that alternative mechanistic pathways may be operating in this system involving other catalysts including ylide **6**

Table 2. Effect of borane source on the enantioselectivity of the reduction of acetophenone[a]

Hydride source	Equiv. of hydride source	Time (min)	Yield (%)	Ee (%)[b]
5a	1.1	30	100	85
5b	1.1	30	5	70
	1.1	120	91	78
5c	1.1	30	0	NA
5d	1.1	30	92	4
5e	1.1	30	0	NA
	1.1	120	0	NA
	2.0	120	0	NA
5f	1.1	30	0	NA
	1.1	120	0	NA
	2.0	120	10	25

[a] All reductions were carried out with acetophenone:**3**:hydride source (1:0.1:1.1). Hydride source and **3** were stirred for 30 min prior to addition of acetophenone. Reaction was left for 30 min before quench with methanol.
[b] Determined by HPLC. The (*S*)-enantiomer was formed as the major stereoisomer throughout.

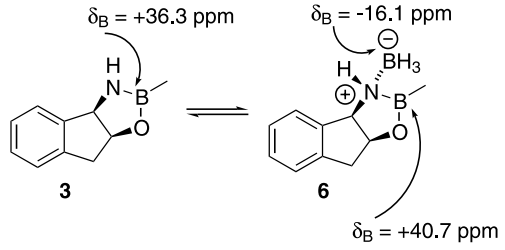

Figure 3. ^{11}B NMR shifts.

and its diastereoisomer.[9] Although not conclusive, this ^{11}B NMR data strongly suggests the existence of only one major isomeric ylide, which will probably be of configuration depicted placing the smaller H substitutent on the *endo* face of the molecule.

In summary we have demonstrated that BH_3·DMS in either THF or diethyl ether is the optimal hydride source and solvent for ketone reduction using catalyst **3**. The strong correlation of the monomer/dimer ratio and the high selectivities observed in THF and diethyl ether lends further support to the hypothesis that the predominance of the monomeric form of the catalyst **3** is essential for achieving high enantioselectivities. However, this cannot be at the expense of decreasing the reaction rate. The ^{11}B NMR data obtained will be of use to help further elucidate mechanistic pathways and in any catalyst optimisation.

Acknowledgements

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References

1. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
2. Romagnoli, R.; Roos, E. C.; Hiemstra, H.; Moolenaar, M. J.; Speckamp, W. N.; Kaptein, B.; Schoemaker, H. E. *Tetrahedron Lett.* **1994**, *35*, 1087–1090.
3. Bringmann, G.; Hartung, T. *Angew. Chem., Int. Ed.* **1992**, *31*, 761–762.
4. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
5. Cho, B. T.; Ryu, M. H. *Bull. Korean Chem. Soc.* **1994**, *15*, 1027–1029.
6. Cho, B. T.; Chun, Y. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2095–2100.
7. Nevalainen, V. *Tetrahedron: Asymmetry* **1991**, *2*, 827–842.
8. Nevalainen, V. *Tetrahedron: Asymmetry* **1992**, *3*, 933–945.
9. Jones, S.; Atherton, J. C. C. *Tetrahedron: Asymmetry* **2000**, *11*, 4543–4548.
10. Dixon, R. A.; Jones, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1115–1119.
11. *General procedure for the preparation of the B-methyl catalysts and reduction of acetophenone*: 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 min. 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 is stable for a limited period (48 h) at room temperature when stored under a nitrogen atmosphere. Borane hydride source (1.83 mmol) was added to a solution of *B*-methyl-(1*R*)-amino-(2*S*)-indanol (0.17 cm^3, 0.166 mmol) in solvent (2 cm^3) and stirred at room temperature under N_2 for 30 min. The resulting solution was cooled to 0°C and the acetophenone (1.67 mmol) in solvent (1 cm^3) added via cannula. The reaction mixture was stirred for a further 30 min at room temperature then quenched with methanol (5 cm^3). Water (20 cm^3) 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 HC1 (30 cm^3), water (30 cm^3) and dried over $MgSO_4$. Removal of the solvent produced the product as a slightly cloudy colourless in most cases.

12. The dimer **4** has been depicted as an *B–N*, *B–N* bridged species of stereochemistry shown based on work of Nevalainen [Ref. 8]. There are several other isomeric possibilities including stereoisomers, *B–O*, *B–O* bridged species and combinations thereof.
13. Zhou, H.-B.; Zhang, J.; Lü, S.-M.; Xie, R.-G.; Zhou, Z.-Y.; Choi, M. C. K.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron* **2001**, *57*, 9325–9333.
14. Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, J. J. *J. Org. Chem.* **1993**, *58*, 2880–2888.
15. Eckhardt, C.; Jockel, H.; Schimdt, R. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2155–2162.
16. Nettles, S. M.; Matos, K.; Burkhardt, E. R.; Rouda, D. R.; Corella, J. A. *J. Org. Chem.* **2002**, *67*, 2970–2976.