# Synthetic Applicability and In Situ Recycling of a *B*-Methoxy Oxazaborolidine Catalyst Derived from *cis*-1-Amino-Indan-2-ol

**Nathan J. Gilmore, Simon Jones* and Mark P. Muldowney**[†]

*Department of Chemistry, Dainton Building, University of Sheffield, Sheffield, Brook Hill, Sheffield, UK. S3 7HF.*

*Email Address simon.jones@sheffield.ac.uk*

[†]*Rhodia Pharma Solutions, Dudley, Northumberland, UK. NE23 7QG.*

## Supporting Information - Contents

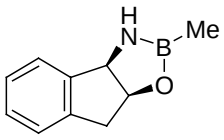
**Document A - Experimental**

**Document B - Copies of all $^{1}$H nmr spectra**

**General Experimental**

All solvents were 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 a nitrogen atompshere. 250 MHz $^{1}$H NMR and 63 MHz $^{13}$C NMR was carried out on a Bruker Avance 300 spectrometer. Residual proton signals from chloroform ($^{1}$H 7.25 ppm) were used as a reference. 500 MHz $^{11}$B NMR was conducted on JEOL (Japan Electron Optical Limited) λ 500 MHz spectrometer. Specific rotations were performed on a Polaar 2001 automatic polarimeter at 589 nm and measured at 20 $^{o}$C unless otherwise stated. $[\alpha]_D$ values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$. HPLC was carried out using a Spectra Physics Analytical system (consisting of a P4000 pump, an AS1000 auto sampler, a UV2000 detector and using PC 1000 version 2.0 software). A Chiralcel OD (4.8x250 mm) column and 10% IPA in heptane 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 Perkin Elmer Auto System instrument using flame ionisation detector. A fused silica capillary column was used with β-cyclodextrin as the stationary phase. Hydrogen was used as the carrier gas.

**Preparation of *B*-methyl-(1*R*, 2*S*)-1-amino-indan-2-ol**




Trimethylboroxine (0.19 cm$^3$, 1.34 mmol) was added to a solution of (l*R*,2*S*)-1-amino-indan-2-ol (2.01 mmol) in toluene (10 cm$^3$) under a nitrogen atmosphere 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 was stable for a limited period (48 h) at room temperature when stored under a nitrogen atmosphere.

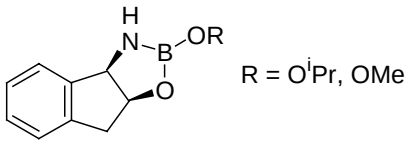
**Preparation of *B*-methyl-(1*R*,2*S*)-1-amino-indan-2-ol with methyl diisopropyl borate**

Methyl diisopropyl borate[1] (0.29 g, 2 mmol) was added to a solution of (l*R*,2*S*)-1-amino-indan-2-ol (2.01 mmol) in toluene (10 $cm^3$) under a nitrogen atmosphere 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 was stable for a limited period (48 h) at room temperature when stored under a nitrogen atmosphere.

**Preparation of *B*-methyl-(1*R*,2*S*)-1-amino-indan-2-ol with methyl boronic acid**

Methyl boronic acid[1] (0.12 g, 2mmol) was added to a solution of (l*R*,2*S*)-amino-1-indan-2-ol (2.01 mmol) in toluene (10 $cm^3$) under a nitrogen atmosphere 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 was stable for a limited period (48 h) at room temperature when stored under a nitrogen atmosphere.

**Preparation of the *B*-alkoxy-(1*R*,2*S*)-amino-1-indan-2-ol with trialkylborates**




Trialkylborate (1 mmol) was added to a solution of (l*R*,2*S*)-1-amino-indan-2-ol (2.01 mmol) in THF (2 $cm^3$) under a nitrogen atmosphere and stirred at room temperature for 30 min. The catalyst formed *in situ* is approximately 1.0 M concentration that was used in subsequent reactions without further isolation.

**General procedure for the racemic reduction of ketones**

Reduction of acetophenone with sodium borohydride is a representative. Sodium borohydride (1.66mmol) was added to ethanol (3 $cm^3$) and stirred at room temperature. Ketone (1.66 mmol) was added drop-wise with stirring and the reaction was left for 1 h at room temperature. Water (10 $cm^3$) was added, the mixture extracted with $CH_2Cl_2$ ($3 \times 10$ $cm^3$), the organic layer washed with water ($2 \times 10$ $cm^3$) and dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. NMR chemical shifts and other relevant characterisation is detailed in the asymmetric reduction section.

**General procedure for the two-step asymmetric reduction of ketones**

$BH_3$.DMS (1.83 mmol) was added to a solution of previously prepared *B*-methyl-(l*R,2S)*-1-amino-indan-2-ol (0.17 $cm^3$, 0.166 mmol) in THF (2 $cm^3$) and stirred at room temperature under a nitrogen atmosphere for 30 min. The resulting solution was cooled to 0 °C and the ketone (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 was added (5 $cm^3$) and the solvent removed under reduced pressure. The product was extracted into $CH_2Cl_2$ ($3 \times 10$ $cm^3$), the organic phase washed with 1M HC1 (30 $cm^3$), water (30 $cm^3$) and dried over $MgSO_4$. Filtration, and removal of the solvent under reduced pressure produced the crude product that could be purified if necessary by silica gel chromatography eluting with ethyl acetate / petroleum ether.

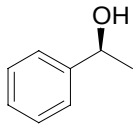
**General procedure for the one-pot *B*-OMe catalyst preparation and reduction of prochiral ketones**

Trimethyl borate (0.2 $cm^3$, 0.17 mmol) was added to a solution of the (l*R*,2*S*)-1-amino-indan-2-ol (25 mg, 0.17 mmol) in THF (1 $cm^3$) and stirred at room temperature under a nitrogen atmosphere for 30 min. $BH_3$.DMS complex (0.11 $cm^3$, 1.83 mmol) was added, the reaction stirred for 30 min, then acetophenone (0.2 $cm^3$, 1.67 mmol) in THF (2 $cm^3$) added via cannula. The reaction mixture was stirred for a further 30 min at room temperature then quenched with methanol (5 $cm^3$). Water (10 $cm^3$) was added and the solvent removed under reduced pressure. The mixture was extracted with $CH_2Cl_2$ ($3 \times 10$ $cm^3$), the organic phase washed with 1M HC1 (30 $cm^3$), water (30 $cm^3$) and dried over $MgSO_4$. Filtration, and removal of the solvent under reduced

pressure produced the crude product that could be purified if necessary by silica gel chromatography eluting with ethyl acetate / petroleum ether.

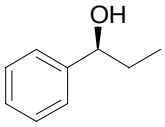
The following compounds were all reduced using the 'one-pot' reduction procedure detailed immediately above.

**(*S*)-1-Phenylethanol 1**[2]



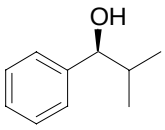

$\delta_H$ (250 MHz, $CDCl_3$) 7.31 – 7.08 (5H, m, ArH), 4.80 (1H, q, *J* 6.5, C*H*OH), 1.97 (1H, br, OH), 1.41 (3H, d, *J* 6.5, C$H_3$); $[\alpha]_D$ -47.3 (*c* 1, $CHCl_3$), ee 85% (5% *i*-PrOH in heptane, Chiralcel OD); lit.[2] -46.8 (*c* 1, $CHCl_3$); ee 82 %.

**(*S*)-1-Phenylpropan-1-ol 2**[2]



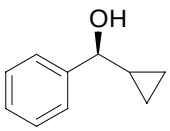

$\delta_H$ (250 MHz, $CDCl_3$) 7.33 – 7.26 ppm (5H, m, Ar*H*), 4.59 (1H, t, *J* 6.4, C*H*OH), 1.84 (1H, br O*H*), 1.90 – 1.65 (2H, m, C$H_2$$CH_3$), 0.95 – 0.88 (3H, t, *J* 7.3, C$H_3$$CH_2$); $[\alpha]_D$ -45.4 (*c* 1, $CHCl_3$), ee 65% (β-cyclodextrin, initial temp. 100 $^oC$, ramp at 1.0 $^oC$ / min to 150 $^oC$, hold for 10 min); lit.[2] -36.6 (*c* 1, $CHCl_3$); ee 69 %.

**(*S*)-1-Phenyl-2-methypropan-1-ol 3**[3]



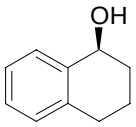

$\delta_H$ (250 MHz, $CDCl_3$) 7.35 – 7.25 (5H, m, Ar*H*), 4.35 (1H, br d, *J* 6.7 C*H*OH), 1.90 [1H, m, C*H*$(CH_3)_2$], 1.78 (1H, br s, O*H*), 1.05 (3H, d, *J* 6.4, C$H_3$), 0.88 (3H, d, *J* 6.4, C$H_3$); $[\alpha]_D$ -17.5 (*c* 1, $CHCl_3$); ee 22% (β-cyclodextrin, 130 $^oC$ for 30 min); lit.[3] +8 (*c* 5, $Et_2O$); ee 16.8 %.

**(*S*)-1-Cyclopropyl-phenylmethanol 4**[2]



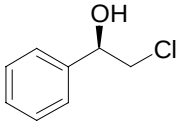
$\delta_H$ (250 MHz, $CDCl_3$) 7.50 – 7.25 (5H, m, Ar*H*), 4.07 (1H, d, *J* 6.7, C*H*OH), 1.91 (1H, br, O*H*), 1.25 – 1.19 [1H, m, CH(OH)C*H*], 0.69 – 0.33 (4H, m, C$H_2$); $[\alpha]_D$ -10.9 (*c* 1, $CHCl_3$), ee 30% (β-cyclodextrin, 140 °C for 20 min); lit.[2] -6.1 (*c* 1, $CHCl_3$); ee 25 %.

**(*S*)-1,2,3,4-Tetrahydronaphthalen-1-ol 5**[2]



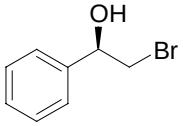

$\delta_H$ (250 MHz, $CDCl_3$) 7.44 (1H, m, Ar*H*), 7.28 – 7.08 (3H, m, Ar*H*), 4.80 (1H, br, C*H*OH), 2.75 (2H, m, C$H_2$), 2.10 – 1.60 (5H, m, O*H* & C$H_2$); $[\alpha]_D$ +30.4 (*c* 1, $CHCl_3$), ee 85% (2% *i*-PrOH in heptane, Chiralcel OD); lit.[2] +25.1 (*c* 1, $CHCl_3$); ee 78 %.

**(*R*)-2-Chloro-1-phenylethanol 6**[2]



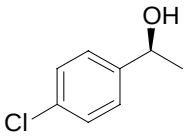

$\delta_H$ (250 MHz, $CDCl_3$) 7.50 – 7.30 (5H, m, Ar*H*), 4.90 (1H, dd, *J* 3.6 and 8.7, C*H*OH), 3.75 (1H, dd, *J* 11.2 and 3.6, C$H_2$Cl), 3.64 (1H, dd, *J* 11.2 and 8.7, C$H_2$Cl), 2.65 (1H, br, O*H*); $[\alpha]_D$ -50.5 (*c* 1, $CHCl_3$), ee 86% (5% *i*-PrOH in heptane, Chiralcel OD); lit.[2] -53.4 (*c* 1, $CHCl_3$); ee 87 %.

**(*R*)-2-Bromo-1-phenylethanol 7**[4]



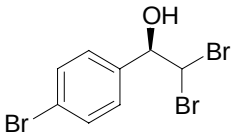

$\delta_H$ (250 MHz, $CDCl_3$) 7.42 – 7.30 (5H, m, Ar*H*), 4.93 (1H, dd, *J* 3.4 and 8.8, C*H*OH), 3.65 (1H, dd, *J* 10.4 and 3.4, C$H_2$Br), 3.53 (1H, dd, *J* 10.4 and 8.8, C$H_2$Br), 2.62 (1H, br, O*H*); $[\alpha]_D$ -30.9 (*c* 1, $CHCl_3$), ee 79% (β-cyclodextrin, 120 °C for 15 min); lit.[4] -39.7 (*c* 8.4, $CHCl_3$); ee 97 %.

**(*S*)-1-(4-Chlorophenyl)-ethanol 8**[5]



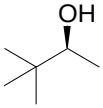
$\delta_H$ (250 MHz, $CDCl_3$) 7.35 (4H, m, Ar*H*), 4.88 (1H, q, *J* 6.4, C*H*OH), 1.83 (1H, brd, O*H*), 1.48 (3H, d, *J* 6.4, C$H_3$); $[\alpha]_D$ +25.9 (*c* 1, $CHCl_3$), ee 84% (β-cyclodextrin, 160 $^oC$ for 15 min); lit.[5] -48.5 (*c* 2.11, $Et_2O$); ee -98 %.

**(*R*)-2,2-Dibromo-1-(4-bromophenyl)-ethanol 9**



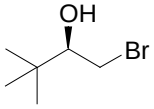

$\nu_{max}$ ($cm^{-1}$) 3396, 1591, 1485; $\delta_H$ (200 MHz, $CDCl_3$) 7.52 (2H, d, *J* 7.1, Ar*H*), 7.29 (2H, d, *J* 7.1, Ar*H*), 5.74 (1H, d, *J* 5.2, C*H*$Br_2$), 5.01 (1H, t, *J* 4.1, C*H*OH), 2.95 (1H, d, *J* 4.0, O*H*); $\delta_C$ (63 MHz, $CDCl_3$) 136.9, 131.6, 128.7, 123.1, 78.3, 51.5; Found C, 26.92; H, 1.96; Br, 66.79. $C_8H_7Br_3O$ requires C, 26.78; H, 1.97; Br, 66.80%; $[\alpha]_D$ -13.0 (*c* 2, $CHCl_3$); ee 57% (β-cyclodextrin, 220 $^oC$ for 15 min); *m/z* 362 (4%), 360 (10), 358 (12), 355.8057 (4, $M^+$, $C_8H_7{}^{79}Br_3O$ requires 355.8047), 187 (90), 185 (100), 157 (16), 77 (54).

**(*S*)-3,3-Dimethyl-butan-2-ol 10**[6]



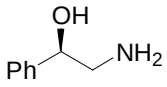

$\delta_H$ (250 MHz, $CDCl_3$) 3.40 (2H, q, *J* 6.4, C*H*OH), 1.75 (1H, br O*H*), 1.04 (2H, d, *J* 6.4, C$H_3$), 0.81 (9H, s, C$H_3$); $[\alpha]_D$ +31.0 (*c* 1, $CHCl_3$), ee 60% (β-cyclodextrin 70 $^oC$ for 15 min); lit.[6] -39.4 (*c* 2.2, EtOH); ee -98.4%.

**(*S*)-1-Bromo-3,3-dimethyl-butan-2-ol 11**[7]




$\delta_H$ (250 MHz, $CDCl_3$) 3.64 (1H, dd, *J* 10.0 and 1.0, C*H*OH), 3.45 (1H, brd d, *J* 10.0, C$H_2$Br), 3.30 (1H, t, *J* 10.0, C$H_2$Br), 2.23 (1H, d, *J* 3.1, O*H*), 0.90 (9H, s, C$H_3$); $\delta_C$ (63 MHz, $CDCl_3$) 79.2, 38.5, 26.7, 25.9; $[\alpha]_D$ –11.3 (*c* 1, $CHCl_3$), ee 28% (5% *i*-PrOH in heptane, Chiralcel OD); Lit. +1.42 (no other data given), ee 4%.

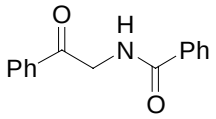
**(*R*)-2-Amino-1-phenyl-ethanol 13**[8]




$NaHCO_3$ (425 mg, 5.01 mmol) dissolved in ethanol (10 $cm^3$) was added to amino-acetophenone hydrochloride (286 mg, 1.67 mmol) under anhydrous conditions with

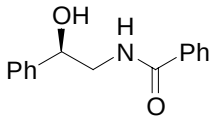
stirring. After 2 h the ethanol was removed under vacuum and the orange solid re-dissolved in THF (3 $cm^3$) to give an orange solution with a white precipitate. The solution was transported via for the 'one-pot' asymmetric reduction procedure highlighted above. $\delta_H$ (200 MHz, $CDCl_3$) 7.40 – 7.22 (9H, m, Ar*H*), 4.62 (1H, dd,, *J* 7.7 and 3.9, C*H*OH), 2.97 (1H, dd, *J* 12.7 and 3.9, C$H_2NH_2$), 2.80 (1H, dd, *J* 12.7 and 7.7, C$H_2NH_2$), 2.17 (3H, brs, O*H*, N$H_2$); $[\alpha]_D$ -31.3 (*c* 1, EtOH), ee 45% (β-cyclodextrin 220 °C for 20 min); lit.[8] -39.1 (*c* 1.3, EtOH); ee 98 – 99 %.

***N*-(2-Oxo-2-phenyl-ethyl)-benzamide 14**[9]



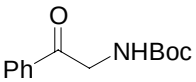

$NaHCO_3$ (0.198 mg, 2.36 mmol) was added to a solution of amino-acetophenone hydrochloride (0.135 mg, 0.79 mmol) in THF (20 $cm^3$) with stirring. Pyridine (0.21 $cm^3$, 1.58 mmol) and benzoylchloride (0.098 mg, 0.1 $cm^3$, 0.79 mmol) were added to the solution and stirred overnight. Water (30 $cm^3$) was added and the solvent removed under reduced pressure to leave a suspension of the product in aqueous phase. The product was extracted into dichloromethane (3 × 10 $cm^3$), the organic phase washed with water (30 $cm^3$) and dried over $MgSO_4$. Removal of the solvent produced the product as a white solid of sufficient purity to be used in the next step; mp 123 °C (lit.[10] 123 – 125 °C); $\delta_H$ (250 MHz, $CDCl_3$) 8.00 (2H, d, *J* 7.3, Ar*H*), 7.81 (2H, d, *J* 7.3, Ar*H*), 7.60 – 7.33 (6H, m, Ar*H*), 7.28 (1H, br, s, N*H*), 4.88 (2H, d, *J* 4.3, C$H_2$).

**(*R*)-*N*-(2-Hydroxy-2-phenyl-ethyl)-benzamide 15**[11]



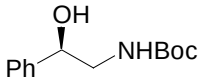

Prepared using the 'one-pot' reduction procedure detailed above. mp 151-152 °C (lit.[11] 143 – 145 °C); $\delta_H$ (250 MHz, $CDCl_3$) 7.69 (2H, d, *J* 6.7, ArC*H*), 7.49 – 7.21 (8H, m, ArC*H*), 6.52 (1H, brd, N*H*), 4.92 (1H, dd, *J* 7.5 and 3.4, C*H*OH), 3.87 (1H, ddd, *J* 14.0, 7.5 and 3.4, C$H_2$NH), 3.48 (ddd, *J* 14.0, 7.5 and 5.0, C$H_2$NH), 3.27 (1H, brd, O*H*); $[\alpha]_D$ -2.91 (*c* 1, MeOH), ee 42% by HPLC (5% IPA in heptane); (Despite full charcterisation, no specific rotation is included in the literature).

**(2-Oxo-2-phenyl-ethyl)-carbamic acid tert-butyl ester 16**[12]



$NaHCO_3$ (1.47 g, 17.5 mmol) was added to a solution of amino-acetophenone hydrochloride (1.0 g, 5.8 mmol) in EtOH (50 $cm^3$). Di-*t*-butyl dicarbonate (1.33 g, 6.1 mmol) was added to this solution at 0˚C and the solution allowed to warm to room temperature and stir for 48 h. The mixture was filtered through Celite and the ethanol removed under reduced pressure. The resulting solid was re-dissolved in $Et_2O$ (30 $cm^3$), filtered again through Celite and the solvent removed under reduced pressure to leave a white solid which was pure enough to be used in the next step as obtained; mp 56˚C (lit.[12] 55-58 ˚C); $\delta_H$ (250 MHz, $CDCl_3$) 7.97 (2H, m, Ar*H*), 7.70 (1H, m, Ar*H*), 7.47 (2H, m, Ar*H*), 5.56 (1H, br, N*H*), 4.66 (2H, br d, *J* 4.5, C$H_2$), 1.48 (9H, s, C$H_3$).

**(*R*)-(2-Hydroxy-2-phenyl-ethyl)-carbamic acid tert-butyl ester 17**[13]




Asymmetric reduction was carried out by the previously described one-pot general procedure giving the desired product in 99%; $\delta_H$ (250 MHz, $CDCl_3$) 7.38 - 7.22 (5H, m, Ar*H*), 5.00 (1H, br, N*H*), 4.81 (1H, br, C*H*OH), 3.45 (1H, br, C$H_2$), 3.30 – 3.25 (2H, m, O*H* & C$H_2$), 1.43 (9H, s, C$H_3$); $[\alpha]_D$ -2.05 (*c* 1, EtOH), ee 90% by HPLC (5% *i*-PrOH in heptane); lit.[13] -2.62 (*c* 4, EtOH), ee 97%.

**References**


1 Brown, H. C.; Cole, T. E. *Organometallics* **1985**, *4*, 816-821.

2 Jones, S; Atherton, J. C. C. *Tetrahedron: Asymmetry* **2000**, *11*, 4543-4548.

3 Vigueron, J. P.; Jacquet, I. *Tetrahedron* **1976**, *32*, 939-944.

4 de Carvalho, M.; Okamoto, M. T.; Moran, P. J. S.; Rodrigues, J. A. R. *Tetrahedron* **1991**, *47*, 2073-2080.

5 Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. *J. Org. Chem.* **2001**, *66*, 1441-1449.

6 Imai, T.; Tamura, T.; Yamamuro, A. *J. Am. Chem. Soc.* **1986**, *108*, 7402-7404.

7 Takeichi, T.; Takakura, T.; Ishimori, M.; Tsuruta, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 603-605.

8 Watanabe, M.; Murata, K.; Ikariya, T. *J. Org. Chem.* **2002**, *67*, 1712-1715.

9 Yoon, U. C.; Cho, S. J. *J. Org. Chem.* **1995**, *60*, 2353-2360.

10 Mandel, S. M.; Krause Bauer, J. A.; Gudmundsdottir, A. D. *Org. Lett.* **2001**, *3*, 523-526.

[11] Cardus, G. J.; Carnell, A. J.; Trauthwein, H.; Riermeir, T. *Tetrahedron: Asymm.* **2004**, *15*, 239-243.

[12] Kawamoto, A. M.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1916-1928.

[13] Benedetti, F.; Norbedo, S. *Tetrahedron Lett.* **2000**, *41*, 10071-10074.