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A Rapid Assay for the Enantiomeric Purity of Secondary Alcohols using 4S,5R-4-methyl,5-phenyl-1,3,2-oxazaborolidine (Ephedrineborane).

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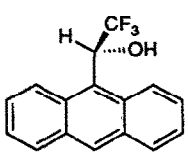
Abstract. Reaction of the title compound with a series of racemic and optically enriched secondary alcohols in C_7D_8 solution at 20°C leads to rapid formation of the corresponding borate. The N-CH_3 protons of the ephedrine moiety, and frequently other resonances, were generally resolved in the ^1H NMR spectrum, permitting an estimation of the enantiomeric purity of the alcohol.

With the rapid advance in effective methods for asymmetric synthesis, there is a concomitant need for analytical methods which permit the accurate determination of enantiomeric purity. The current emphasis is on capilliary GC[1], HPLC[2] and NMR methods[3]; the latter are attractive for several reasons provided that certain criteria can be met. Thus the method should be easy to operate, the enantiomers of the analyte should be distinguishable through baseline separation of an appropriate resonance in the spectrum, and the relevant signals should be sharp enough to permit quantitative estimation. Chiral lanthanide shift reagents[4], which in principle can fulfil these criteria, have fallen into relative recent disfavour because of frequent problems encountered through broadening of key signals at the LSR concentration required for their separation. H-Bonding complexation with the anthranol (1)[5] can produce sufficient signal separation for analysis but the method is not always successful and substantial quantities of the expensive reagent (up to 10:1 molar excess) are required. For alcohols, amines and related substrates, the most established method involves Mosher's reagent (2)[6], for which the derived ester or amide can be assayed by ^1H or ^{19}F NMR. Typically, the derivative is formed by protracted reflux of reagent and substrate, followed by a workup and transfer procedure. Recent work[7] has revealed however that commercially available carboxylic acid precursor of (2), which is an oil, is 97.9 -99.7% enantiomerically pure depending on the commercial source, making it unsuitable for determinations where the analyte is itself of this order of purity. Alternatives available for alcohols include the O-methyl and O-acetylmandelate esters (3)[8]. Whilst commercially available (R)-mandelic acid and its derivatives are enantiomerically pure, the derivatisation procedure involves reaction of the alcohol with DCC and 4-dimethylaminopyridine and can lead to the risk of a small degree of racemisaton in cases where the coupling is slow[9]. A simple method for determining the enantiomeric purity of alcohols by ^{31}P NMR involves reaction with PCl_3 in a 3:1 ratio in the presence of an excess of pyridine. This results in the formation of a mixture of secondary phosphonites (4) (four from a racemic alcohol with a single stereogenic centre) with distinct phosphorus chemical shifts; the third alkyl group

is converted into RCl by Arbuzov reaction[10]. Recently it has been suggested that conditions leading to the phosphite $P(OR)_3$ gave superior results in ^{31}P NMR analysis[11]. A related method involving reaction of the alcohol with Ph_2SiCl_2, giving *meso* and *dl*-diastereomers of silyl acetal, and analysing these by ^1H NMR, has as yet been applied only to 2-butanol, 2-octanol and menthol[12].



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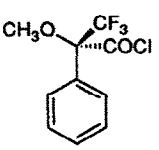

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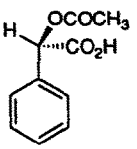

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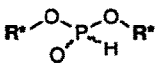

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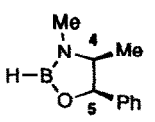
In the course of a project intended to develop new methods of asymmetric oxidation, it was expedient to be able to analyse the enantiomeric purity of secondary allylic alcohols routinely, rapidly and accurately, and existing methods fell short of this ideal. Recent work on enantioselective catalytic hydroboration in the laboratory involved the successful application of secondary boranes derived from ephedrine and φ-ephedrine (respectively 4S,5R-4-methyl,5-phenyl-1,3,2-oxazaborolidine [ex. ephedrine] and 4R,5R-4-methyl,5-phenyl-1,3,2-oxazaborolidine [ex. φ-ephedrine]) in Rh-complex catalysed addition to alkenes[13], and in the course of this we had observed rapid methanolysis of the B-H bond to form the corresponding O-methyl borate[14].

Encouraged by this observation, we examined the reaction of freshly distilled ephedrineborane[15] (**5**) with racemic alcohol (**6**), assaying by ^1H NMR in C_7D_8 at 500 MHz. It was observed that formation of the diastereomeric borate esters in equal amounts occurred over a few minutes, and that clear separation of several of the resonances corresponding to the diastereomers of (**7**) was apparent. This included all the methyl groups, and the methine protons, with baseline separation of many of the multiplets. When enantiomerically enriched alcohol (S)-(**6**), prepared by Sharpless kinetic resolution[16] of the racemic starting material[17] under previously described conditions, was analysed in this way, only one set of resonances was apparent. The enantiomeric purity of part-enriched alcohol (**6**) could be assayed by the N-Me peaks in (**7**) ; that from the S-alcohol is at 2.537 ppm and that from the R-alcohol at 2.526 ppm in C_7D_8, 4 Hz apart at 500 MHz. A rather larger separation was exhibited in the high-field 4-Me group protons centred at 0.50 ppm. This encouraged us to extend the method to a diverse range of secondary chiral alcohols, mostly as the racemate, and the results are recorded in Table 1 (aliphatic alcohols) and Table 2 (aromatic alcohols). In order to ensure that the borane reagent was pure it was freshly distilled before use, having been prepared according to the protocol described in the Experimental Section.



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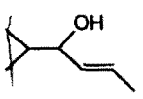

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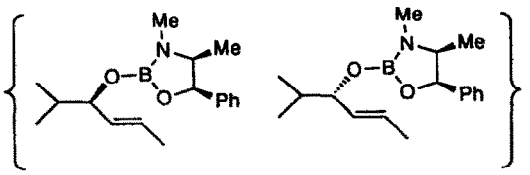

7 - diastereomers

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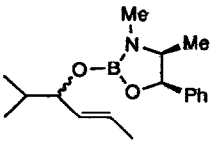
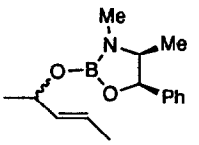
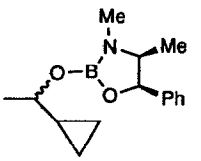
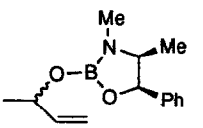
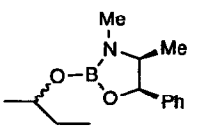
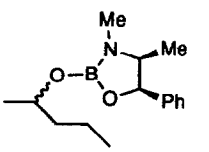
1		N-Me 8 MeCH= 14 4-Me 22 Me(i-Pr) 52, 52 CHOB 50	Solvent C_7D_8. Kinetic resolution shows (R) N-Me to lower frequency.
2		N-Me 8 MeCHOB 32 4-Me 14	Solvent C_7D_8. N-Me and MeCHOH both in clear windows.
3		MeCHOB 38 MeCHOB 80 4-Me 18	Solvent C_7D_8. All signals, except N-Me and Ar split. Cyclopropane region complex
4		MeCHOB 44 4-Me 12	Solvent C_7D_8. No N-Me splitting seen. Alkene region split, but complex.
5		MeCHOB 38 4-Me 12	Solvent C_7D_8. No N-Me splitting seen. CH_2CHO resolved.
6		MeCHOB 38 4-Me 14	Solvent C_7D_8. No N-Me splitting seen.

Table 1. Borates derived from (5) and aliphatic alcohols, as described. Splittings are quoted in ppb at 27 °C.

The method described herein has been found to be useful for determining the enantiomeric purity of a series of simple secondary alcohols. It has limitations where the desired resonances are obscured by others in the adduct, and when the reactant contains reducible groups (carbonyl, epoxide) or other proton donors (carboxylic acids). The advantage is that the borane derivative is simply prepared in situ using one equivalent of the reagent in a rapid reaction, and analysis is carried out by ^1H NMR, using the most accessible of all nuclei.

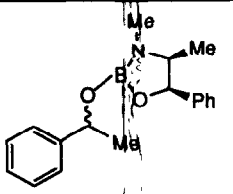
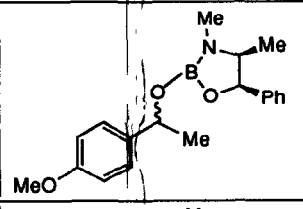
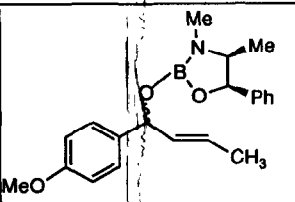
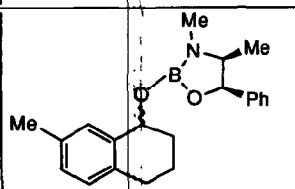
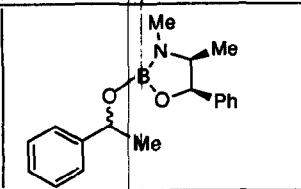
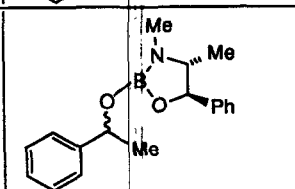
ENTRY	ADDUCT	SPLITTINGS	COMMENTS
1		N-Me 7 MeCHOB 30 MeCHOB 94 4-Me 70	Solvents C_7D_8 or C_6D_6 give similar results. See Figure 1 for part-resolved mixtures.
2		MeCHOB 30 PhCHOB 24 4-Me 72	Solvent C_7D_8. No N-Me splitting. (S)-enriched sample 74.6 e.e. by rotation, 74.1 e.e. by this method.
3		N-Me 5 MeCH= 58 MeO- 10 CHOB 62	Solvent C_7D_8. MeO peaks over residual borane signal.
4		N-Me 15 4-Me 12	Solvent C_7D_8. 4- Ãn clear window. N-Me coincident with ring CH_2.
5		N-Me 7 MeCHOB 30 MeCHOB 94 4-Me 70	Solvent C_6D_6 ; c.f. Entry 1.
6		N-Me 24 MeCHOB 18 MeCHOB 90	Solvent C_6D_6.c.f. Entry 1 but with φ-ephedrineborane (S)-enriched sample 88.3% by optical rotation, 87.5% by this method.

Table 2. Borates formed from (5) and aromatic alcohols. Splittings are quoted in ppb at 27 °C.

For a method of e.e. determination involving diastereomer formation to be useful, it is necessary to demonstrate that the reaction is kinetically unselective. Experiments were carried out with samples of 1-phenylethanol, enriched to different degrees in the S-enantiomer[18]. The plot of measured versus calculated e.e. shows good correlation with measurements of the specific rotation in $CHCl_3$ (Figure 1). Furthermore, the reaction of racemic

alcohol with reagent (5) was followed over 1h and the proportion of diastereomers did not change significantly as reaction proceeded to completion.

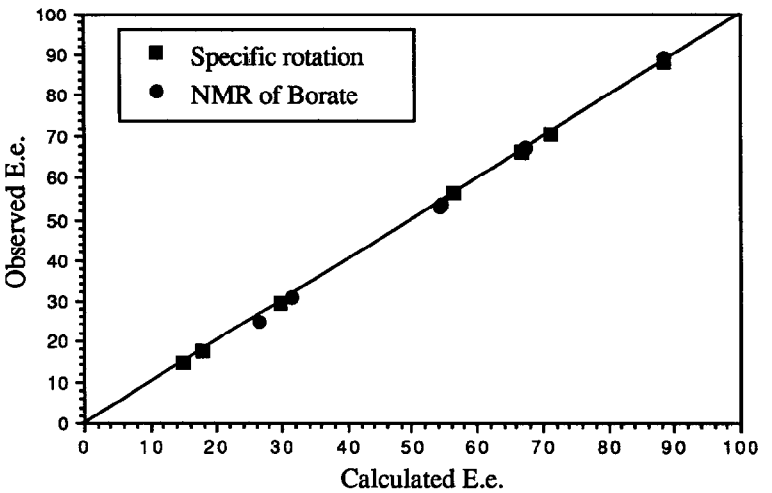


Figure 1. E.e. determination by specific rotation (squares) or the borane method (circles). A commercial sample (Sigma) of (S)-phenylethanol was employed which was 93.3% optically pure $[\alpha]_D^{25}$ *= -50.7 (c 1, $CHCl_3$) Lit[18]* $[\alpha]_D^{25}$ *= -54.0 (c 5.1, $CHCl_3$). The enantiomeric purity decreases very slowly with time on storage in glass.*

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Experimental Section

4S,5R-4-Methyl,5-Phenyl-1,3,2-oxazaborolidine

1R,2S ephedrine (Aldrich), (16.00 g , 97 mmol) as a partial solution in tetrahydrofuran, (16 cm^3) under argon was treated dropwise at 0^0C with borane methylsulphide complex (Aldrich, as a 2.0 M solution in tetrahydrofuran) , (48.5 cm^3, 97 mmol) over a period of 1 h. The reaction was stirred to room temperature over a period of 12 h after which time hydrogen evolution ceased. The volatiles were removed *in vacuo* to afford a white foam and the reaction vessel purged with argon. On heating to 120^0C under argon for 3 h a further equivalent of hydrogen was evolved, affording a clear pale yellow oil. The oil was transferred *via* cannula to a distillation apparatus (Vigreux column) and the product collected at 40^0C, 0.12 mmHg to afford 4S,5R-4-methyl,5-phenyl-1,3,2-oxazaborolidine as a clear water white liquid (12.7 g, 75%); $[\alpha]^{20}_D$ -108.1 (c = 1.0, $CHCl_3$) , υ B-H (thin film on NaCl) 2562 cm^{-1}, δ_H ($CDCl_3$, 500 MHz), 7.31 (m, C_6H_5, 5H) , 5.58 (d, J 8.52, PhC*H*, 1H) , appx 3.8 (q, J 156, B*H*, 1H) , 3.68 (dq, J 8.52 and 6.57, CH_3CH ,1H) , 2.75 (s, CH_3N , 3H), and 0.632 (d, J 6.57, CH_3CH , 3H) , δ_C ($CDCl_3$, 125.8 MHz), 139.24 (C *ipso*) , 127.74, 127.00, 126.16 (*C*Ar) , 83.34 (Ph*C*H) , 59.27 (Me*C*H) , 30 .07 (CH_3N), and 15.15 (CH_3CH) , δ_B (C_6D_6, 80.12 MHz), 24.28 (d, J 156), m/z (GCMS, EI^+) 175.

Coupling of ephedrine-borane to a secondary alcohol

A solution of the purified alcohol (0.02 - 0.1 mmol) in thoroughly degassed C_7D_8 (0.5cm^3) was prepared in an nmr tube under an inert atmosphere. Ephedrine-borane (1.1 equivs), freshly distilled *in vacuo* (40^oC, 0.1mm Hg), was added under inert atmosphere to the alcohol solution. On gentle agitation evolution of gas occurred indicating that the reaction was proceeding. After 20 min the alcohol had completely reacted in

most cases, but an optimum reaction time of 1 h ensured full reaction. The ^1H 500 MHz NMR spectrum was then acquired immediately.

Kinetic Resolution of E-2-Methyl-4-Hexen-3-ol

The allylic alcohol[17] (b.p. 50°C, 0.1mmHg) was prepared by the reaction of i-PrMgBr with crotonaldehyde (activated Mg turnings[19], Et_2O, -5°C, 30 min, 93%). Into a jacketed Schlenk tube cooled to -5°C the following were introduced : freshly distilled CH_2Cl_2 (30 cm^3), activated powdered 4A sieves (0.5g), L-diethyl tartrate (10.8 cm^3, 0.053mol) and $Ti(OiPr)_4$ (12.49 cm^3, 0.44mol). After stirring for 30 min Bu^tOOH (8.6 cm^3, 3M in isooctane, 0.026mol) was added and after a further 10 min 2-methyl-4-hexen-3-ol (5g, 0.044mol) was added. The resulting mixture was stirred at -5°C for 3h. The reaction mixture was poured into a stirred solution of iron(II)sulphate (33g) and tartaric acid (11g) in H_2O (100 cm^3). The aqueous layer was extracted with ether (3x30 cm^3) and then the combined ether layers were stirred with 30% sodium hydroxide in satd. brine (5 cm^3) at 0°C for 1h. The ether layer was removed, the aqueous layer extracted with ether (3x30 cm^3), the ether layers combined, dried and the solvent removed *in vacuo*. Chromatography (flash silica, CH_2Cl_2) afforded (R)-2-methyl-4-hexen-3-ol $[\alpha]_D^{20}$ -8.39° (c = 0.41, $CHCl_3$), (Lit[17] $[\alpha]_D^{23}$ -24.11° (neat)). The ephedrineborane derivative (C_7D_8) shows a single peak in ^1H NMR at 2.52 ppm (N-Me).

References

1) V. Schurig, *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 747; V. Schurig and H. P. Novotny, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 939.
2) W. H. Pirkle and T. C. Pochapsky, *Chem. Rev.* **1989**, *89*, 347; W. H. Pirkle and T. C. Pochapsky, *Chromatographic Science*, **1990**, *47*, 783.
3) D. Parker, *Chem. Rev.*, **1991**, *91*, 1441.
4) H. L. Goering, J. N. Eikenberry and G. S. Koermer, *J. Am. Chem. Soc.*, **1971**, *93*, 5913; G. M. Whitesides and D. W. Lewis, *J. Am. Chem. Soc.*, **1971**, *93*, 5914; M. D. McCreary, D. W. Lewis, D. L. Wernick and G. M. Whitesides, *J. Am. Chem. Soc.*, **1974**, *96*, 1038; G. R. Sullivan, *Topics in Stereochem.*, **1978**, *10*, 287.
5) W. H. Pirkle and M. S. Hoekstra, *J. Org. Chem.*, **1976**, *98*, 1832; W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, **1980**, *45*, 4117, and intervening papers; S. G. Davies, J. Dupont and R. J. C. Easton, *Tetrahedron Asymmetry*, **1990**, *1*, 279.
6) J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, **1969**, *34*, 2543; J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **1973**, *95*, 512; G.R. Sullivan, J. A. Dale and H.S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143.
7) W. A. Konig, K. S. Nippe and P. Mischnik, *Tetrahedron Lett.*, **1990**, *31*, 6867.
8) J. M. Brown and D. Parker, *Tetrahedron Lett.*, **1981**, *22*, 2815; D. Parker, *J. Chem. Soc., Perkin 2*, **1983**, 83.
9) B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. G. Christy, G. S. Panticello, S. V. Varga and J. D. Springer, *J. Org. Chem.*, **1986**, *51*, 2370.
10) B. L. Feringa, A. Smaardijk and H. Wynberg, *J. Am. Chem. Soc.*, **1985**, *107*, 4798.
11) C. L. Welch, *Tetrahedron Asymmetry*, **1991**, *2*, 1127.
12) K. Wang, *Tetrahedron Lett.*, **1991**, *32*, 3651.
13) J. M. Brown and G.C. Lloyd-Jones, *Tetrahedron Asymmetry*, **1990**, *1*, 869.
14) G. C. Lloyd-Jones, unpublished work.
15) N. N. Joshi, M. Srebnik and H. C. Brown, *Tetrahedron Lett.*, **1989**, *30*, 5551.
16) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, **1987**, *109*, 5765.
17) M. M. Midland, A. Tromantano, A. Kazubski, R. S. Graham, D. J. S. Tsai and D. B. Cardin, *Tetrahedron*, **1984**, *40*, 1371.
18) Various specific rotations are quoted for this widely used chiral compound, the following are reliable for the S-enantiomer : U. Nagai, T. Shishido, R. Chiba and H. Mitsuhashi, *Tetrahedron*, **1965**, *21*, 1701 - $[\alpha]_D^{23}$ -52.5 (c = 2.27, CH_2Cl_2); *Beilstein*, IV Teil, *Band 6*, 3029 - $[\alpha]_D^{20}$ -54 (c = 5.11, $CHCl_3$); E. Brown, A. Penfornis, J. Bayma and J. Touet, *Tetrahedron Asymmetry*, **1991**, *2*, 339 - $[\alpha]_D^{20}$ -45.5 (c = 5, MeOH)
19) K. V. Baker, J. M. Brown, N. Hughes, A. J. Skarnulis and A. Sexton, *J. Org. Chem.*, **1991**, *56*, 698.