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Enantioselective Reduction of Acetophenone with 1,3,2-Oxazaborolidines Derived from Ephedrine, Pseudoephedrine, and Phenylglycine

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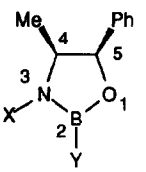
Abstract: The performance of several 1,3,2-oxazaborolidines as chiral catalysts in the reduction of acetophenone has been compared, to gain insight into the more relevant structural factors as far as yield and enantioselectivity are concerned. *B*-Alkyl-4,5,5-triphenyl-1,3,2-oxazaborolidines have emerged as effective catalysts for this reaction when nitrogen is not substituted. The origin of the enantioselectivity for this kind of catalysts is discussed.

Enantioselective methodology is an active field in Organic Chemistry and much effort has been devoted to the development of efficient catalytic versions of synthetically useful reactions. Regarding the enantioselective ketone reduction methods, one of the more successful has been based on the use of borane and a chiral 1,2-aminoalcohol as pioneered by Itsuno et al.[1] Corey et al.[2] soon afterwards isolated the oxazaborolidine derived from α,α-diphenyl-2-pyrrolidinemethanol and applied it in the reduction of ketones with borane (CBS method). Ever since, other chiral 1,3,2-oxazaborolidines have been reported by several groups.[3]

In connection with a research line aimed at obtaining chiral auxiliaries from non-expensive natural products, avoiding either tedious stepwise syntheses or racemic resolutions, we have prepared ephedrine-derived (**1a-g**) and pseudoephedrine-derived (**2**) 1,3,2-oxazaborolidines[4,5] and we have evaluated their performance as reagents in the reduction of acetophenone with BH_3:Me_2S (or BH_3:THF) as the source of borane.



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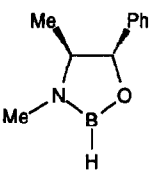
a	X = Me	Y = H
b	X = Me	Y = Me
c	X = Me	Y = Bu
d	X = CH_2Ph	Y = H
e	X = CH_2Bu^t	Y = H
f	X = SO_2Ph	Y = H
g	X = SO_2Me	Y = H



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In practice, to either 0.2 or 1.0 mmol of oxazaborolidines (**1a-g**, **2**) in 3 ml of anh. THF, maintained at 0°C under Ar, 1.2 mmol of BH_3:Me_2S (or, indistinctly, BH_3:THF) was added;[6] ten min later on, 1 mmol of acetophenone was introduced, and the reaction was monitored by TLC. The main results are summarised in Table 1. It is to be noted that:

(i) The reaction rate decreases with B-substitution (compare entries 3 and 4 with entry 1, corresponding to the BH derivative **1a**) but the e.e. does not practically change. This agrees with the results reported for oxazaborolidines arising from diphenylprolinol.[3d,7]

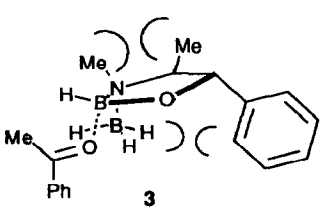
(ii) Although not pointed out in Table 1 for the sake of simplicity, **1e**, **1f**, and **1g** gave poor reduction yields (15-60%) and very low e.e. (10-22%) values. Thus, large substituents and/or electron-withdrawing groups on the nitrogen are not suitable, likely because the N-BH_3 interaction is disfavoured. This is in accordance with the mechanism proposed by Corey et al.[2,8] for analogous reactions, in which the borane (R_2BH) is activated by coordination to the nitrogen. In this connection, we have observed by ^{11}B NMR spectroscopy that, in mixing BH_3:THF with equimolar amounts of either **1d**, **1e**, **1f**, or **1g** in THF, the signals corresponding to BH_3:THF (ca. -1 ppm, external ref.= BF_3:Et_2O) and the oxazaborolidines (30-35 ppm) did not change; in fact, quartet signals at ca. -15 ppm, as expected for the complexes **1d**:BH_3 and so on, did not appear.

Table 1. Reduction of acetophenone with BH_3:Me_2S in the presence of **1-2**

Entry	Reagent (equiv.)	t (min)[a]	Yield (%)[b]	e.e. (%)[c]	Config.
1	**1a** (1)	<5	95	72	R
2	**1a** (0.2)	10	90	63	R
3	**1b** (1)	45	98	69	R
4[d]	**1c** (1)	60	78	68	R
5[d]	**1c** (0.2)	60	74	66	R
6	**1d** (1)	60	77	10	R
7	**2** (1)	<5	90	22	S

[a] First TLC control 5 min after the ketone addition. [b] Isolated yields. Crude yields were quantitative (TLC). [c] Determined from the ^1H-NMR spectrum of Mosher's ester. [d] Reaction was quenched after 60 min; 10-15% of ketone was recovered.

(iii) The scarce enantioselectivity induced by **2**, as well as the fact that enantiomer *S* slightly predominates for the first time, must be attributed to the phenyl group (now *trans* to CH_3). Whereas in compound **1** the approach of both borane and acetophenone is towards the α face, in **2** the complexes arising from approaches to α and β faces (see **3** and **4**, respectively) may have similar energies. Apparently, the transition state related to complex **4**, of a bit lower energy, is responsible for the slight e.e. in favour of (*S*)-1-phenylethanol.



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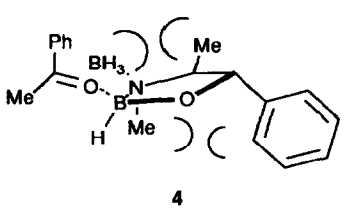

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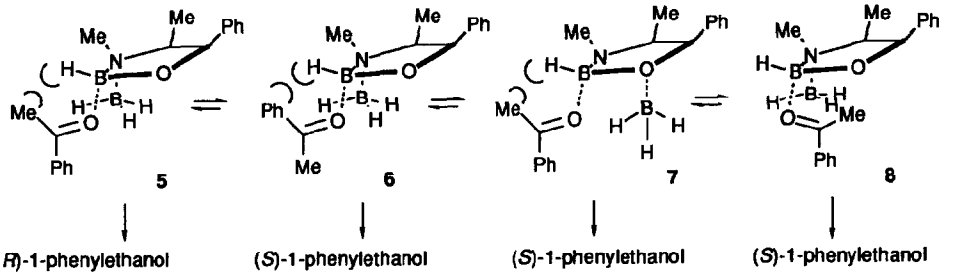
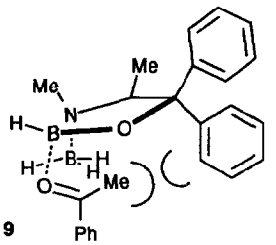
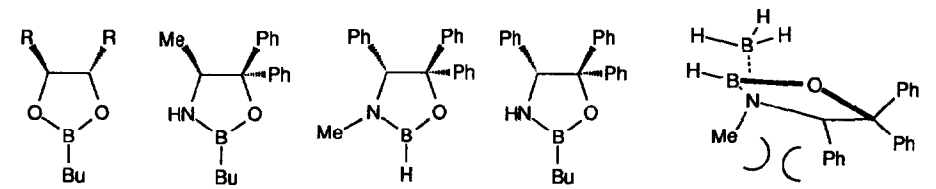
For future work, it was also interesting to elucidate the causes of the observed enantioselectivity in **1a** and related cases. A complex like **5**, in agreement with literature precedents,[2,8] explains the origin of the major enantiomer via hydride transfer from N-BH_3 to carbonyl groups. However, in our opinion, the main question is which complex (**6**, **7**, or **8**) gives rise to the minor enantiomer.



Really, (*S*)-1-phenylethanol could come from **6**, but this may be ruled out by the fact that different substituents on the boron do not change significantly the enantioselectivity (see entries 1-5 of Table 1). Previous work[3] has demonstrated that, even though complexation through the α face is desired, it is necessary a large substituent on the α face of position 5 to enhance the enantioselectivity. This requirement may be related with the convenience of either blocking the oxygen atom (to destabilize intermediate **7**) or disfavouring an arrangement like **8** in which the methyl group is located inside the oxazaborolidine ring, due to the steric repulsion between that methyl group and the α-substituent at C-5, as shown in **9**.



To discard one or another of these two possibilities, i.e. whether enantiomer *S* arises from **7** or **8**, as well as to look for a better catalyst, we have synthesised oxazaborolidines **10-13**.[10]



Compounds **10a** and **10b** did not show any catalytic activity; this fact suggests that the minor stereoisomer did not come from the O-BH_3 complex **7**, but from the complex with an "endo" conformation (**8**).[11] On the other hand, oxazaborolidine **11** afforded (*R*)-1-phenylethanol in 91% yield and with 88% e.e. The comparison of **11** and **1c** confirms that the presence of an α-phenyl group improves the enantioselectivity. By contrast, **12** showed a poor catalytic activity, a fact that may be due to the steric interaction between the methyl and phenyl groups in the assumed complex with BH_3 (see **12:BH_3**). *B*-Butyl-4,5,5-triphenyl-1,3,2-oxazaborolidine **13** gave the best result in the acetophenone reduction: 90% yield and 96% e.e.

In summary, the experimental results suggest that, in the oxazaborolidine-catalysed reduction of acetophenone with borane, the minor stereoisomer arises from an "endo" conformation such as **8/9**. Thus, to improve the stereoselectivity, this arrangement should be hindered. From many points of view (availability of chiral precursors, easy preparation of catalysts, efficiency, and selectivity) *B*-alkyl-4,5,5-triphenyl-1,3,2-oxazaborolidines (e.g. **13**) seem to be reagents of choice for this kind of reactions. Synthetic aplications of these catalysts are in course.

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References and notes

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2. E.J. Corey, R.K. Bakshi, S. Shibata, *J.Am.Chem.Soc.*, 1987, **109**, 5551.
3. (a) I.K. Youn, S.W. Lee, C.S. Pak, *Tetrahedron Lett.*, 1988, **29**, 4453; (b) E.J. Corey, S. Shibata, R.K. Bakshi, *J.Org.Chem.*, 1988, **53**, 2861; (c) E.J. Corey, C.P. Chen, G.A. Reichard, *Tetrahedron Lett.*, 1989, **30**, 5547; (d) E.J. Corey, J.O. Link, *Tetrahedron Lett.*, 1989, **30**, 6275; (e) A.V. Rama Rao, M.K. Gurjar, P.A. Sharma, V. Kaiwar, *Tetrahedron Lett.*, 1990, **31**, 2341; (f) S. Wallbaum, J. Martens, *Tetrahedron:Asymmetry*, 1991, **2**, 1093; (g) E. Didier, B. Loubinoux, G.M. Ramos Tombo, G. Rihs, *Tetrahedron*, 1991, **47**, 4941; (h) K. Tanaka, J. Matsui, H. Suzuki, *J.Chem.Soc.Chem.Commun.*, 1311 (1991); (i) K. Stingl, J. Martens, S. Wallbaum, *Tetrahedron:Asymmetry*, 1992, **3**, 223; (j) J. Martens, Ch. Dauelsberg, W. Behnen, S. Wallbaum, *Tetrahedron:Asymmetry*, 1992, **3**, 347; (k) W. Behnen, Ch. Dauelsberg, S. Wallbaum, J. Martens, *Synthetic Commun.*, 1992, **22**, 2143
4. Compounds **1a**, **1b** and **2** have been used previously as catalysts in Et_2Zn additions to aldehydes (N.N. Joshi, M. Srebnik, H.C. Brown, *Tetrahedron Lett.*, 1989, **30**, 5551). Didier et al. used a reducing mixture of ephedrine and borane, but **1a** was not isolated (ref 3g). When most of the present work had been accomplished, **1d** and **1e** have also been isolated but no synthetic application has been reported (H. Tlahuext, R. Contreras, *Tetrahedron:Asymmetry*, 1992, **3**, 727). All the new oxazaborolidines have been characterized by ^1H, ^{13}C, and ^{11}B NMR.
5. Oxazaborolidines **1a**, **1d**, **1e**, **1g** and **2** were obtained by reaction of the corresponding aminoalcohol with 1.25 equiv. of borane-dimethyl sulphide (BMS) for 2 h at r.t. in anh. THF. The solution was then refluxed for 1 h, the solvent was removed, and the remaining liquid was distilled under vacuum. For **1f** heating was not necessary. Compounds **1b** and **1c** were obtained from the aminoalcohol and the corresponding boronic acid in refluxing toluene, followed by azeotropic removal of water in a Dean-Stark apparatus.
6. Other conditions attempted, changing temperature (-20 °C, rt or boiling THF), solvent (methylene chloride, pentane, benzene), and reducing agent (cathecolborane, chloroborane and dichloroborane) gave worse results.
7. D.J. Mathre, T.K. Jones, L.C. Xavier, T.J. Blacklock, R.A. Reamer, J.J. Mohan, E.T.T. Jones, K. Hoogsteen, M.W. Baum, E.J.J. Grabowski, *J.Org.Chem.*, 1991, **56**, 751. See also reference 3d.
8. A X-ray crystal structure of the complex BH_3-Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole has been just reported (E.J. Corey, M. Azimioara, S. Sarshar, *Tetrahedron Lett.*, 1992, **33**, 3429).
9. For an *ab initio* theoretical study of this reaction, see V. Nevalainen, *Tetrahedron:Asymmetry*, 1992, **3**, 921.
10. Oxazaborolidines **11**, **12**, and **13** were synthesised from the appropiate aminoalcohol and butylboronic acid in refluxing toluene for 10 h. After removing the solvent, the liquid was distilled under vacuum to yield pure compounds. The aminoalcohols were obtained by addition of methyl (*S*)-alaninate hydrochloride or methyl (*R*)-phenylglycinate hydrochloride to an excess of phenylmagnesium bromide in THF. Boronates **10a** and **10b** were obtained by mixing the diol and 1.05 equiv. of butylboronic acid in pentane at rt for a few minutes. The organic layer was dried with anh. sodium sulfate, filtered and the solvent distilled to afford the boronates almost pure which were used without further purification.
11. Itsuno et al. reported in the reduction of PhCOR by borane and (*S*)-2-amino-3-methyl-1,1-diphenyl-1-butanol an increasing enantioselectivity along the series R= Me, Et, Pr, Bu (S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, S. Nakahama, *J.Chem.Soc.Perkin Trans. I*, 1985, 2039). This result, which is difficult to explain by a different steric hindrance on both sides of the carbonyl group, can be related with a more crowded "endo" arrangement along that series. The possibility that a substantial amount of the minor enantiomer arises from external borane can be ruled out since we have noted no significant yield and e.e. variations when the addition order is changed (for instance, slow addition of borane-dimethylsulfur to an equimolar mixture of ketone and **13** at 0 °C).