

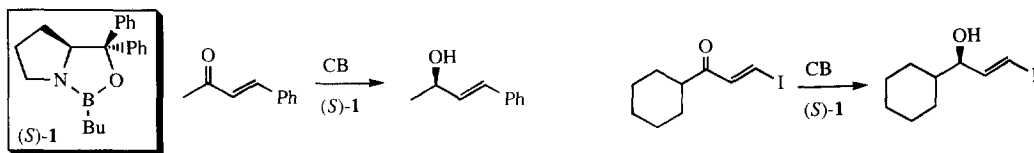
## Allylic Alcohols of Unexpected Configuration by Oxazaborolidine-Catalysed Reduction of $\alpha,\beta$ -Unsaturated Ketones. An Explanation Based on MO Calculations

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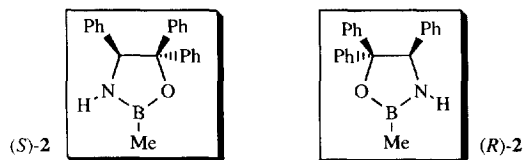
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**Abstract.** While the reduction of most  $\alpha,\beta$ -unsaturated ketones with  $\text{BH}_3\cdot\text{SMe}_2$  in the presence of (*R*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine [(*R*)-**2**] affords allylic alcohols of the *S* configuration, that of  $\alpha,\beta$ -unsaturated ketones branched at both the  $\alpha$  and  $\alpha'$  positions gives alcohols of the *R* configuration. Theoretical calculations on complexes of representative enones with  $\text{BH}_3$  (6-31G\*) or with  $\text{BH}_3$ :(*R*)-**2** (AM1) may account for the apparent changes in the steric requirements on either side of the CO group.

Enantiomerically pure allylic alcohols are valuable synthetic intermediates, as many useful stereoselective transformations<sup>1</sup> can be performed by taking advantage of the 1,3-allylic strain of such systems. Most syntheses of chiral allylic alcohols are based on the resolution of racemic alcohols by Sharpless' epoxidation<sup>2</sup> or enzyme-mediated processes;<sup>3</sup> examples of efficient enantioselective reductions of  $\alpha,\beta$ -unsaturated ketones are relatively scarce.<sup>4</sup> Since enantioselective oxazaborolidine-catalysed reduction of prochiral ketones with borane or catecholborane (CB) has emerged in recent years as an excellent route to alcohols of high enantiomeric purity,<sup>5</sup> it seemed logical to investigate whether the oxazaborolidine-catalysed reduction of  $\alpha,\beta$ -unsaturated ketones could afford allylic alcohols with high enantioselectivity. In this connection, among many oxazaborolidines described, only Corey's (*S*)-proline-derived, (*S*)-**1**, or stereochemically related oxazaborolidines, have been successfully applied to the reduction of a few enones to the expected *R* allylic alcohols,<sup>6</sup> e.g.:

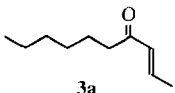
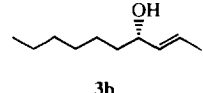
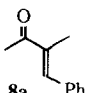
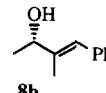
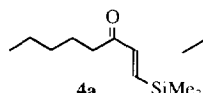
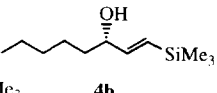
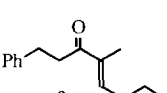
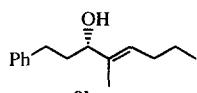
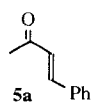
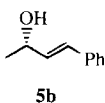
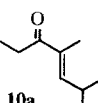
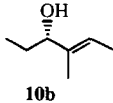
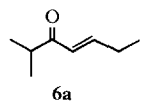
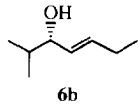
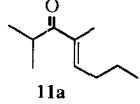
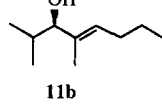
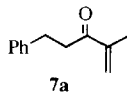
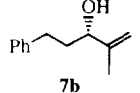
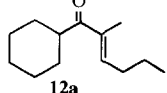
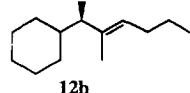


Very recently, we have described the synthesis of (*S*)- and (*R*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine, (*S*)-**2** and (*R*)-**2**, two new catalysts arising from inexpensive (*S*)- and (*R*)-phenylglycine, respectively, which we have utilised in the reduction of prochiral ketones.<sup>7</sup> Owing to our interest in some chiral allylic alcohols as building blocks for total syntheses,<sup>8</sup> we have launched a previous systematic study of the behaviour of different types of  $\alpha,\beta$ -unsaturated ketones with borane in the presence of either (*S*)-**2** or (*R*)-**2**. We wish to report here the performance of (*R*)-**2** in this connection.



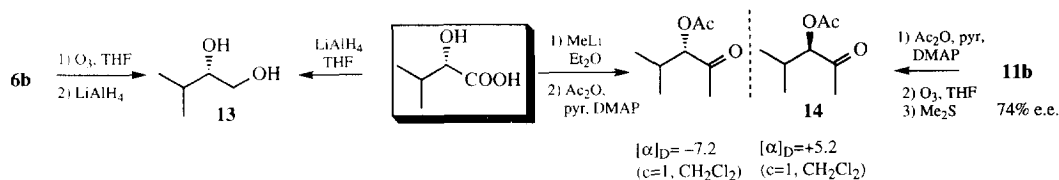
Typically, reductions were carried out by slow addition (~1 h) of a solution of the ketone (1 M in THF) over an ice-cooled 0.5-1 M THF solution of  $\text{BH}_3\cdot\text{SMe}_2$  and (*R*)-**2** (0.1-1.0 equiv.)<sup>9</sup> under Ar, to afford alcohols **3b-12b** in >90% yields.<sup>10</sup> As shown in Table 1, good selectivities are noted for the reactions involving linear enones (**3a-5a**);<sup>11</sup> also, allylic alcohols of the expected *S* configuration are obtained in 83-93% e.c. from *n*-alkyl  $\alpha$ -methyl-1-alkenyl ketones (**7a-10a**), even when only 0.1 equiv. of (*R*)-**2** are used.

**Table 1.** Reduction of Ketones **3a-12a** with  $\text{BH}_3\text{:SMe}_2$  and (*R*)-**2**

ketone	alcohol	e.e. <sup>a</sup>	ketone	alcohol	e.e. <sup>a</sup>
		85% (80%)			93% (87%)
		85% (70%)			88% (83%)
		88% (82%)			87% (83%)
		80% (75%)			74% (50%)
		91% (91%)			88% (63%)

<sup>a</sup>E.e. values are given for reactions performed with 1 equiv. of (*R*)-**2**. Within parentheses, e.e. values using 0.1 equiv. of (*R*)-**2**.

Unexpectedly, the reduction of  $\alpha,\alpha'$ -disubstituted ketones catalysed by (*R*)-**2** led to compounds with the *R* configuration (alcohols **11b** and **12b**), just the configuration opposite to that of the remaining examples (alcohols **3b-10b**). A chemical correlation was carried out in order to confirm the absolute configuration of alcohols **6b** and **11b**. Diol **13** and the acetoxy-ketone **14**, derived from **6b** and **11b** respectively, were compared with the corresponding compounds arising from commercially available (*S*)-2-hydroxy-3-methylbutyric acid, as shown in the next scheme:

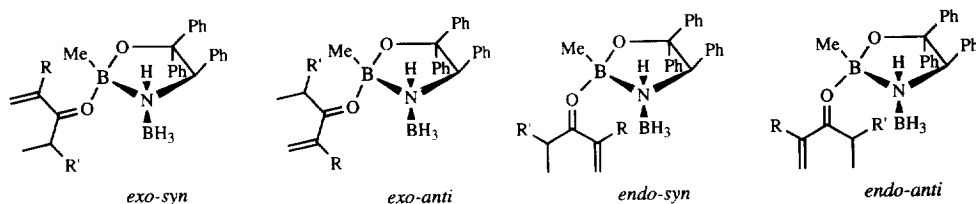


These intriguing results are difficult to explain in the light of the widely accepted mechanism<sup>5,6</sup> for oxazaborolidine-mediated reductions, which postulates as a key intermediate an *exo* complex between  $\text{BH}_3\text{:S-1}$  and  $\text{R}_1\text{COR}_2$ , in which the bulkier  $\text{R}_1$  group is *anti* to the B-Bu moiety and from which an intramolecular hydride transfer takes place (*si* face attack to give the *R* alcohol). In the **3-10** cases (Table 1), the stereochemical results can be similarly accounted for by assuming that the unsaturated chain behaves as a group larger than the saturated chain (even if branched!). However, if the established mechanistic model is still valid, when the branches are found at both the  $\alpha$  and  $\alpha'$  positions as in cases **11-12**, the unsaturated chain seems to behave as a group smaller than the saturated chain.

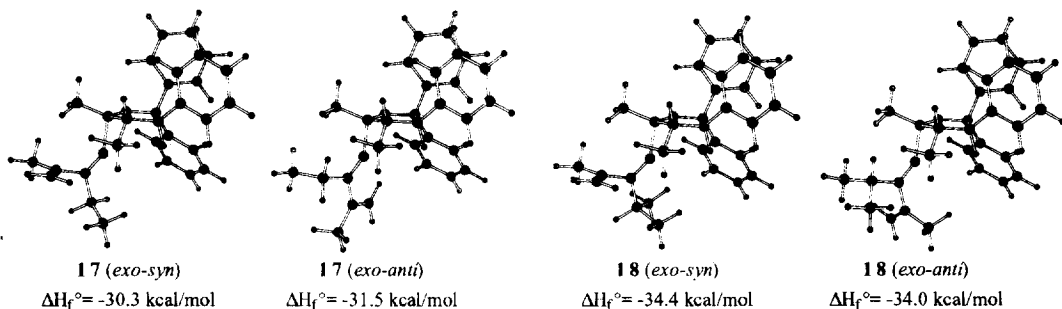
In an attempt to explain the enantioselectivity reversal shown in Table 1 we started a theoretical study on the subject.<sup>12</sup> First of all, we calculated the more relevant  $\text{BH}_3$  complexes of model enones **15-18** in order to establish their relative stabilities.



*Ab initio* 6-31G\* calculations<sup>13</sup> revealed a few *syn* and *anti* conformations of quite similar energy for most borane complexes. However, while the lower energy conformers of *syn* complexes of **15-16** were predicted to be almost co-planar (either *s-cis* or *s-trans*), there was two low-energy conformers (rel. energy 0.0 and 0.3 kcal/mol with regard to the lowest energy *anti* complex) of **18** showing C<sub>1</sub>C<sub>2</sub>C<sub>3</sub>O torsion angles of 54° and 64°, respectively. In the case of **17** co-planar and non-planar *syn* conformers of nearly identical energy were located but they lay ca. 3.5 kcal/mol above the lowest energy *anti* conformer. Thus, although some differences were noted, these BH<sub>3</sub> complexes appeared to be too simplified to justify all the experimental data, so that we decided to calculate the real oxazaborolidine-BH<sub>3</sub> complexes of enones **15-18**. In this case, AM1 calculations<sup>13</sup> showed that each enone gave complexes possessing several conformations close in energy for almost every approach shown below:



In general, the *endo* complexes have been found to be less stable than the corresponding *exo* ones by ca. 1.6-5.8 kcal/mol. Moreover, the more stable conformers of the *exo-anti* complexes of enones **15-17** are 0.7, 0.2, and 1.2 kcal/mol lower in energy than the corresponding *exo-syn* ones. Apparently (e.g., see **17** in the Figure below) steric interactions between the enone and the oxazaborolidine moiety do not 'permit' a co-planar C=C-O arrangement of the *exo-syn* complexes and, therefore, destabilise them in front of the 'co-planar' *exo-anti* adducts. Only in the case of the  $\alpha,\alpha'$ -disubstituted enone, **18**, both *exo-syn* and *exo-anti* complexes were found to be non-planar; in this case, **18** (*exo-syn*), which leads to the product with reverse enantioselectivity, was 0.4 kcal/mol lower in energy than **18** (*exo-anti*).



These results are in qualitative agreement with the experimental data despite the fact that the calculated differences in energy are probably too small to account for the high enantioselectivities. We believe that calculations of the complexation barriers would afford a more reliable picture of the differences among the alternative pathways (in fact, preliminary AM1 results point out that in our systems the carbonyl complexation step, rather than the intramolecular hydride transfer, is the rate-limiting step). Work is in progress in this connection.

### Acknowledgements

The Human Capital and Mobility Program (EU contract ERBCHRX-CT93-0141), the "Comisión Interministerial de Ciencia y Tecnología" (CICYT, Project SAF93-0201) and the CIRIT (Generalitat de Catalunya, fellowship to J.B.) are gratefully acknowledged.

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- Compound **2** also catalyses reductions with catecholborane but with much lower enantioselectivity. When 0.1 equiv. of **2** is used in the reduction of **7a**, hydroboration of the olefin is detected by TLC. In addition, for such  $\beta$ -unsubstituted ketones, the time of addition is also critical and the optimum is around 15-20 min. For instance, faster addition gives **7b** of lower optical purity (over 1-2 min, 87% e.e.) and slower addition rates do not improve the e.e. values but yields go down with concomitant olefine hydroboration (over 1 h, 91% e.e., 85% yield).
- Standard workup: Reaction is quenched by addition of methanol and the mixture is concentrated under vacuum. The crude is then separated by chromatography on silica gel to obtain the allylic alcohol. Further elution gives the chiral triphenylaminoethanol derived from **2**, which can be reutilised. Alternatively, the reaction mixture can be partitioned between 0.2 M HCl and CH<sub>2</sub>Cl<sub>2</sub>. The organic layer, free from the auxiliary aminoalcohol, is then washed with brine and dried to yield the allylic alcohol almost pure. Care must be taken during the workup as in some cases partial racemisation of allylic alcohols has been noted during treatment with acid. Enantioselectivities were determined by <sup>1</sup>H and <sup>19</sup>F NMR of Mosher's esters or, in the case of **3b**, by GLC. Absolute configuration was established by the method of Kakisawa *et al.* (Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092) and confirmed by comparison with allylic alcohols derived from the Sharpless resolution of the racemic mixtures.
- It is worth noting that ketone **4a** was readily reduced to alcohol **4b** (98% yield, 85% e.e.), a key intermediate in Knochel's synthesis of the antitumor antibiotic (-)-methylenolactocin (Vaupel, A.; Knochel P. *Tetrahedron Lett.* **1995**, *6*, 231).
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- All calculations have been performed on a SGI Power Indigo2 R8000 machine using the MSI Cerius2 modelling environment. All *ab initio* calculations were carried out using GAUSSIAN-94 (rev. B.3) series of programs while MOPAC6 package was used for the semiempirical AM1 calculations. GAUSSIAN-94: Gaussian, Inc., Pittsburg PA, 1995. MOPAC 6.0: Stewart, J.J.P. *QCPE* **1990**, 455. AM1: Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902; Dewar, M.J.S.; Jie, C.; Zoebisch, E.G. *Organometallics* **1988**, *7*, 513.