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Oxazaborolidine-mediated reduction of prochiral 2-alkylidene cycloalkanones

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Abstract: Asymmetric reduction of enones 1a-g using either a stoichiometric or catalytic amount of oxazaborolidine 3 proceeds to give the synthetically useful allylic cycloalkanols 2a-g in 83-96% e.e. © 1997 Elsevier Science Ltd. All rights reserved.

The asymmetric reduction of ketones represents an important method for the synthesis of enantiomerically pure alcohols.¹ While the versatility of this process has been enhanced by new additions to the battery of reagents currently available, it is important that the demands and constraints associated with different carbonyl components are also properly defined.² Enones 1, based on cycloalkanones, represent a class of prochiral ketones that have not been widely studied³ as substrates for asymmetric reduction. This is in spite of the ready availability of the requisite enones and the obvious potential offered by the product allylic alcohols 2. In this paper we describe the asymmetric reduction of a structurally diverse series of enones based on general structure 1 with the Corey oxazaborolidine 3^{4-6} as the choice of asymmetric reductant. The reactivity of enones 1 towards 3 has been assessed and optimised (Scheme 1), and the use of 3 under catalytic conditions is also reported.





The synthesis of enones **1a**-e was carried out as described previously⁷ and the aza variants **1f** and **1g** were prepared *via* an intramolecular aldol condensation.⁸ Initial efforts focused on identifying optimal conditions for ketone reduction in terms of temperature $(-20^{\circ}\text{C } vs. +20^{\circ}\text{C } vs. +40^{\circ}\text{C})$ and the rate of addition of the enone substrate to the reaction mixture containing **3** (over 5 min *vs.* 35 min *vs.* 60 min). Using enones **1a** and **1b**, reactions were carried out on a small scale (0.2 mmol of enone) with a stoichiometric amount of oxazaborolidine **3**, and the resulting allylic alcohols, **2a** and **2b** respectively, were analysed to determine % enantiometric excess.⁹ Highest selectivities were observed when reduction was conducted *via* a slow (35 min) addition of enone to the reductant **3** at -20°C in CH₂Cl₂.¹⁰ These optimised conditions were then applied the full range of enones available and the results obtained (using a stoichiometric amount of **3**) are summarised in Table 1.¹¹

In general terms, good levels of asymmetric induction were observed and, in the case of allylic alcohol **2b**, the absolute stereochemical course of the reaction has been established. The enantiomer of alcohol **2b** has been described in the literature and our assignment is based on correlation with the available data: **2b** $[\alpha]_D^{22}$ +35.8 (c 1.2, CHCl₃); *ent*-**2b** lit.^{3b} $[\alpha]_D^{20}$ -35.2 (c 1.2, CHCl₃). It should

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also be noted that formation of (R)-2b from 1b is also consistent with sense of asymmetric induction predicted by the Corey mechanistic model.¹² It should, however, be made clear that stereochemical assignments (R vs. S) for the other allylic alcohols produced in this current study (as shown in Table 1) have not yet been made.¹³

The efficiency associated with reduction of this class of prochiral enones using a catalytic amount of oxazaborolidine **3** has been evaluated. Addition of the cyclopentyl-based enone **1a** (300 mg, 1.75 mmol) in CH₂Cl₂ (6 mL) over 5 h to oxazaborolidine **3** (0.34 mmol, 20 mol%) in CH₂Cl₂ (0.6 mL) containing Me₂S.BH₃ (1.75 mmol) at -20° C gave, after workup, allylic alcohol **2a** in 81% yield and 96% e.e. (as judged by HPLC).¹¹ Under the same conditions the sterically more demanding enone **1c** gave alcohol **2c** in 90% yield but in a slightly reduced 83% e.e.¹¹

In summary, exocyclic enones 1 are reduced efficiently using the Corey oxazaborolidine 3 to give the corresponding allylic alcohols 2. There are, in particular, a number of stereochemical issues still outstanding in this area which will be addressed. However, the value of allylic alcohols 2 should be appreciated given that a variety of useful transformations involving, for example, addition or rearrangement reactions associated with the alkenyl moiety, should be achievable with a high degree of stereochemical control.

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- 13. With the exception of alcohols 2a^{3b} and 2b^{3b}, the other allylic alcohols described in this paper have not previously been described in enantiomerically enriched form. All new compounds have been fully characterised.

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