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Asymmetric Epoxidation of Unfunctionalized Alkenes using Chiral Borates

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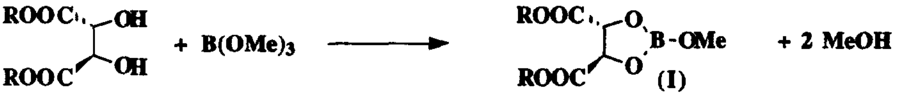
Abstract A new system for asymmetric epoxidation of various unfunctionalized alkenes using a chiral borate and an alkyl hydroperoxide is described. The highest enantioselectivity (51% ee) is obtained for trans-stilbene.

In 1980, K.B.Sharpless[2] introduced the titanium-tartrate asymmetric epoxidation of prochiral allylic alcohols by alkyl hydroperoxides. With this very efficient method a large range of 2,3-epoxyalcohols can be obtained in good yields and with very high enantioselectivities. However the development of a general method for asymmetric epoxidation of unfunctionalized olefins represents an extremely important synthetic problem but so far only partially resolved. Despite the reported asymmetric epoxidations with chiral reagents such as oxaziridines[3] or by means of enzymatic reactions[4], most of the efforts have focused on transition metal catalysed epoxidations. Some impressive achievements such as the use of chiral porphyrins[5] or chiral (salen)manganese complexes[6,7] have been reported.

The interest of a transition metal catalyst in such a reaction is based on the ability of the substrate to be complexed at the metal center through interactions with the chiral ligands for control of asymmetry. Here we describe a very simple system based on the same concept but using a boron atom instead of a transition metal center. Asymmetric boron-catalysed reactions including reduction, Diels Alder and aldol reactions have been recently reviewed[8]. On the other hand, orthoborates were known since the early sixties[9] to be efficient pro-reagents for the epoxidation of simple olefins in the presence of alkyl hydroperoxides. We assumed that borates of chiral alcohols could be used for asymmetric epoxidation of prochiral unfunctionalized alkenes. We here report our first results with the compounds (I).

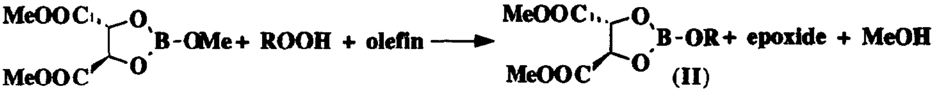
(I) were prepared from (+)-(R,R) tartrate esters and trimethylborate in a nearly quantitative yield[10,11]as a colourless viscous oil which can be used without further purification (reaction 1).



(1)

Ia : R = Me ; Ib : R = Et ; Ic : R = iPr

Epoxidations with Ia were carried out in dry cyclohexane under an argon atmosphere. Eliminating the methanol from the solution is an important factor determining the advancement and the yield of the transformation[12]. The overall reaction is :



(2)

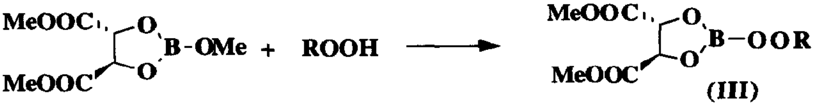
Asymmetric epoxidation of a variety of unfunctionalized alkenes with Ia and *tert*-butyl hydroperoxide (TBHP) was investigated and the results obtained are presented in Table I. Compound Ia displays a good enantioselectivity with *trans*-stilbene. Lower enantioselectivities were found for the epoxidation of other substrates especially non aromatic olefins. Use of compounds Ib or Ic instead of Ia does not affect within the experimental error the enantioselectivity or the yield of the reaction.

Table I[a] **Asymmetric Epoxidation of Unfunctionalized Alkenes Using (Ia)**

Entry	Alkene	time	consumed TBHP[d] %	yield / consumed TBHP[e] %	enantiomeric excess[f] %	major enantiomer
1	*trans*-stilbene[b]	30h	78	65	51	(-), 1S, 2S
2	*cis*-stilbene[b]	20h	90	62	--[h]	
3	1-phenyl-cyclohexene[b]	18h	99	35	22	(-), 1S, 2S
4	p-chloro-α-methylstyrene[c]	20h	70	60	19	(-)[g]
5	E-β-methylstyrene[c]	22h	90	75	18	(-), 1S, 2S
6	p-chlorostyrene[c]	16h30	60	45	13	(-), 2S
7	1-octene[b]	17h30	76	35	10	(-), 2S
8	4-octene[c]	20h	75	40	6	(-)[g]

[a] Reactions were run in 50 ml of refluxing dry cyclohexane (80°C) with 3 mmol of (Ia), 3 mmol of TBHP, 0.18 mmol of MeONa and 3 or 6 mmol of olefin; [b] 3 mmol of olefin; [c] 6mmol of olefin; [d] determined by iodometric titration; [e] determined by GC; [f] determined by analysis of the isolated epoxides by ^1H NMR using $Eu(hfc)_3$; [g] no data on the absolute configuration; [h] *cis*-stilbene oxide is the only product obtained.

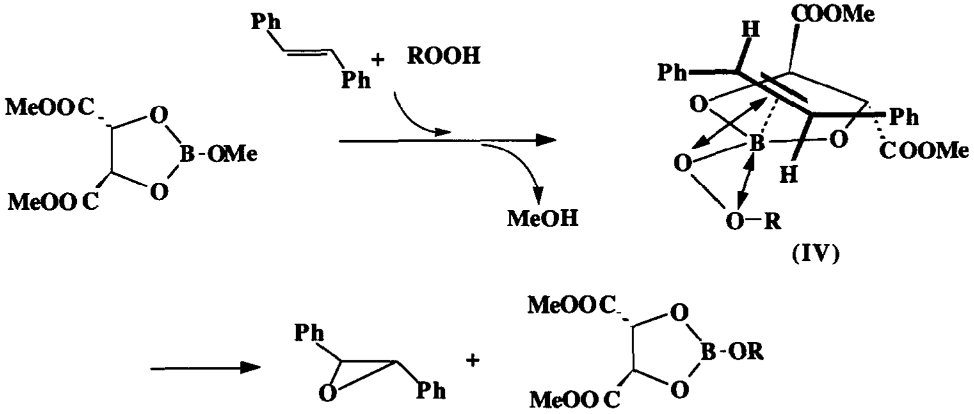
According to the well documented nature of this oxidation system[13,14] the epoxidation proceeds presumably through a perborate III :



(III)

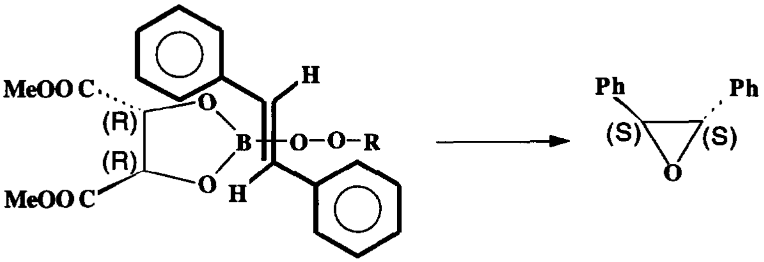
+ MeOH (3)

The methoxy group bonded to the boron atom in I can be readily displaced by the ROO moiety of the alkyl hydroperoxide. Nevertheless all our attempts to prepare the perborates III failed althought $B(OOtBu)_3$ and $B(OO\text{-cyclohexyl})_3$ have previously been isolated and described as stable enough to be kept at room temperature during several weeks[13]. However, the formation and stabilization of perborates III could occur through a complexation with the olefin as shown in scheme 1 for the *trans*-stilbene. Indeed, when the reaction components Ia, *trans*-stilbene and TBHP are mixed in 1/1/1 ratio in C_6D_{12}, after a reaction period of 1h and elimination of methanol off the solution, the ^1H NMR spectrum shows the desappearance of Ia while the epoxide is not yet produced and the iodometric titration indicates that it remains 96% of the initial amount of the peroxidic oxygen. Furthermore the shift of the ^1H NMR signals of *trans*-stilbene in this reaction mixture (δ_{ppm} = 7.48 (4H, d); 7.30(6H, m); 7.07 (2H, s); 4.78 (2H, d); 3.76 (6H, s); 1.24 (9H, s)) in comparison with the spectrum of pure *trans*-stilbene in C_6D_{12} (δ_{ppm}= 7.38(4H, d); 7.20(6H, m), 7.0(2H, s)) is also consistent with the formation of a complex IV between III and *trans*-stilbene. The reaction corresponds to the transfer of the peroxidic oxygen atom to the coordinated alkene ligand. A catalytic process could be envisaged if the borate II liberated at the end of the reaction is able to undergo like I reaction with the alkyl hydroperoxide to produce the perborate. For a reactive alkene like *trans*-stilbene the reaction was run under catalytic conditions but with a low turn over (5mmol of (Ia), 25 mmol of *trans*-stilbene, 0.18 mmol of MeONa, 30 mmol of cyclohexyl hydroperoxide in 200 ml of refluxing dry cyclohexane ; yield 50% ; ee: 49%).



Scheme 1

The sense and extent of enantioselectivity in asymmetric epoxidations reported in Table I are well explained by the initial enantiofacial selectivity occuring in the alkene complexation resulting from a perpendicular approach of the double bond to the boron peroxydic oxygen bond of the C_2 symmetrical putative perborate intermediate as illustrated in scheme 2 for the epoxidation of *trans*-stilbene.



Scheme 2

A new method for the asymmetric epoxidation of unfunctionalized alkenes, very simple from a practical viewpoint and using inexpensive commercially available reagents is outlined in this paper and our results could open a new direction of research in this field. In order to offer an alternative way useful in synthesis and to obtain chiral epoxide with higher enantiomeric excess, we are currently investigating the optimisation of the conditions and the use of other chiral borates.

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11 The physical data are consistant with the monomeric formula written above
^{1}H NMR (250 MHz, $CDCl_3$) δ : 4.86 ppm (s, large, 2) , 3.85 ppm (s, 6) , 3.73 ppm (s, 3)
^{13}C NMR (62.9 MHz, $CDCl_3$) δ : 52.7 ppm , 53.1 ppm , 76.0 ppm , 169.7 ppm
^{11}B NMR (80.2 MHz, $CDCl_3$, reference $BF_3.Et_2O$) δ : 22.87 ppm (s, large)
Elemental analysis : Found : C,38.2 , H, 5.1, B, 4.7 ; Calculated : C,38.57 , H, 5.09, B, 4.96 .
$[\alpha]_{23}^{D} = -34$ (c=3.7, CH_2Cl_2)

12 A typical epoxidation procedure is as follows : Into a 100-ml round bottomed flask equipped with a distillation apparatus and flushed with argon are placed 3 (or 6) mmol of olefin, 0.65g of (I) (3 mmol), 10 mg of MeONa (0.18 mmol) and 50 ml of dry cyclohexane. The mixture is warmed up to reflux and methanol is distilled off during about 3 h (azeotrope methanol/cyclohexane: bp = 54°C) The reaction is continued under reflux (80°C) for 7-19h. After cooling, the mixture is hydrolyzed at room temperature. with 80-ml of an aqueous solution containing 30g of NaOH and 10g of NaCl and stirred for 3h. The organic phase is washed with saturated NaCl solution (2x10ml), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography column (pentane-dichloromethane).

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