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Chiral Vinyl Dioxazaborocines in Synthesis: Asymmetric Synthesis of 5-Substituted Δ^2-Isoxazolines *via* Nitrile Oxide Cycloaddition

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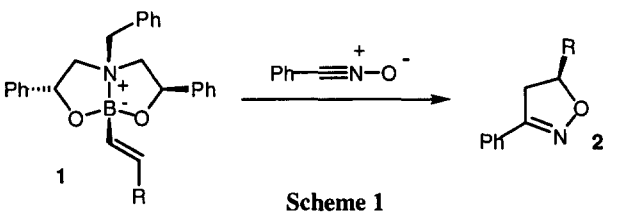
Abstract: Vinyl dioxazaborocines **1a-c** have been subjected to 1,3-dipolar cycloadditions with benzonitrile oxide. The products are enantiomerically enriched 5-substituted Δ^2-isoxazolines **2a-c**.

Keywords: Asymmetric Synthesis; Boron and compounds; Cycloaddition; Isoxazolines; Nitrile Oxides

Vinyl boronic acids and esters are widely used in synthesis, as precursors to stereochemically defined olefins (through Suzuki couplings), halo-olefins, and allyl amines (through the boron Mannich reaction).[1] Addition reactions to vinyl boronates, whereby the unsaturation is lost and up to two new stereocentres are generated, are much less common: there have been reports of 1,3-dipolar cycloadditions,[2] [4+2] cycloadditions,[3] cyclopropanations[4] and radical additions.[5] Progress in the control of the absolute stereochemistry in these processes through the attachment of chiral auxiliaries to the boron group has been limited. Imai[4d] and Pietruszka[4a] have reported the directed cyclopropanation of tartrate substituted vinyl boronates using Simmons-Smith reagents and $PdCl_2$/diazomethane respectively. Examples of asymmetric additions not directed by a metal have been limited to the reactions of diethyl tartrate substituted ethenyl boronate. Avery has examined its participation in Diels-Alder reactions with a range of dienes, with enantiomeric excesses in the range 0 to 33% following oxidative removal of the auxiliary.[3a] Carboni has reported an isolated example of the asymmetric trapping of a chiral α-boronyl radical generated by radical addition to the ethenyl boronate (20% *de*).[5]

We have been interested in the design and synthesis of alternative chiral ligands to control the absolute stereochemistry in additions to vinyl boronates. Chiral vinyl boronates are attractive intermediates for asymmetric synthesis, since (a) vinyl boronic acids of varying substitution patterns are readily available in geometrically pure form; (b) attachment and removal of the chiral auxiliary are efficient and take place under essentially neutral conditions; and (c) after acting as a point of attachment for the auxiliary, the boron group can be used as a handle to introduce further functionality. One potential problem is that the planar geometry of vinyl boronates inevitably means that any chiral centres on the ligand are relatively remote from the prochiral olefin. We reasoned that ligands bearing an additional Lewis basic function would quaternise the boron leading to improved stereochemical induction. We report herein our preliminary results in the synthesis of chiral dioxazaborocines **1a-c** and their application in asymmetric 1,3-dipolar cycloadditions.



Scheme 1

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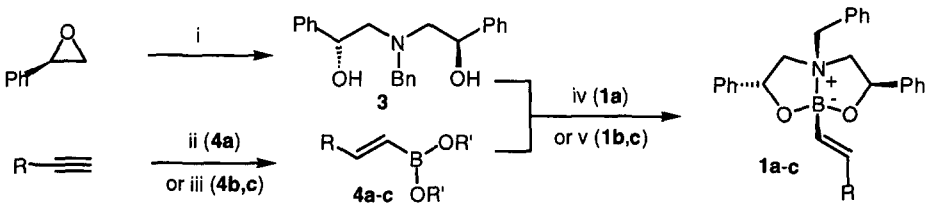
Tertiary amino diols were chosen as the ligands since it is well known that they form stable, tetrahedral complexes with boronic acids[6] and they are readily available in enantiomerically pure form. Our initial studies focused on the known C_2 symmetric ligand **3**,[7] available in either antipodal form by the nucleophilic ring opening of commercially available (*R*) or (*S*)-phenyloxirane with benzylamine (Scheme 2). Three (*E*)-monosubstituted vinyl boronic acid derivatives with differing electronic properties were prepared by hydroboration of the corresponding alkyne. Methyl propiolate was converted to the 1,3-propanediolate ester **4a**,[8] which furnished the crystalline dioxazaborocine **1a** when mixed with ligand **3** in ether. Phenylacetylene and 1-octyne were converted to boronic acids **4b/c**,[9] which underwent condensation with **3** in refluxing ether under a Soxhlet thimble containing 3Å molecular sieves to give dioxazaborocines **1b/c** in excellent yields.

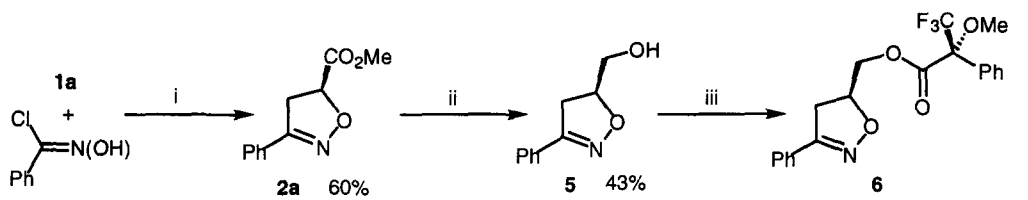


	R	R'	4 (Yield)	1 (Yield)
a	CO_2Me	$-(CH_2)_3-$	42%	79%
b	Ph	H	77%	95%
c	C_6H_{13}	H	70%	100%

Reagents and conditions: (i) 0.5 eq. $BnNH_2$, neat, 120°C; (ii) $BH_3{\cdot}Me_2S$, α-pinene, THF, followed by acetaldehyde, 1,3-propanediol; (iii) catecholborane, 0.05 eq. 9-BBN, THF, then water; (iv) **3**, Et_2O, r.t.; (v) Et_2O, reflux, 3Å sieves

Scheme 2

For our initial studies into the asymmetric reactions of **1a-c** we chose to study their 1,3-dipolar cycloadditions with benzonitrile oxide, since the analysis of the stereochemical outcome of these reactions would not be complicated by the creation of *endo*- and *exo*-isomers. Thus, **1a** was reacted with benzaldehyde chlorooxime and triethylamine in THF at room temperature, yielding the deboronated Δ^2-isoxazoline **2a** (60%, Scheme 3). The deboronation presumably occurs *via* a 1,3-boratropic shift in the intermediate isoxazoline, followed by protonolysis and tautomerisation. Such a process has been observed previously in nitrile oxide cycloadditions with vinyl boronates.[2f] The enantiomeric excess of **2a** was determined to be 33% by reduction of the carboxyl side chain to give alcohol **5**,[10] which was converted to a Mosher's ester derivative **6** (Scheme 4).[11] This was supported by chiral nmr analysis of **2a** in the presence of (*R*)-binaphthol, which indicated an *ee* of 34%. The absolute stereochemistry is assigned as shown by comparison of the sign of optical rotation for **5** with literature values.[10]



Reagents and conditions: (i) 1.2 eq. Ph(Cl)C=NOH, Et_3N, THF, r.t.; (ii) $NaBH_4$, MeOH, r.t. (iii) (*S*)-MTPA-Cl, DMAP, toluene

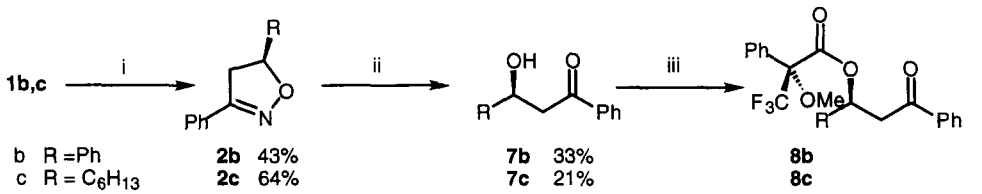
Scheme 3

Following this encouraging preliminary result, we surveyed the effects of solvent and temperature upon the yield and stereoselectivity of this reaction (Table 1).

Table 1 Effect of temperature and solvent upon the cycloaddition reaction

Entry	Solvent	Temp.	Yield of **2a**/%	*de* of **6**
1	THF	reflux	19	36
2	THF	r.t.	60	33
3	THF	0°C	65	26
4	THF	-20°C	48	28
5	DCM	r.t.	47	23
6	Et_2O	r.t.	18	11
7	MeCN	r.t.	17	23
8	toluene	r.t.	63	28

As can be seen from the Table, changing the temperature had little effect upon the stereoselectivity of the reaction, while the yields dropped off at lower temperatures. Changing the solvent had only a deleterious effect upon the stereoselectivity, and thus our optimum conditions which we applied to the cycloadditions of **1b,c** were also our initial ones (THF at room temperature, Scheme 4).



Reagents and conditions: (i) 1.2 eq. Ph(Cl)C=NOH, Et_3N, THF, r.t.; (ii) H_2, Ra(Ni), $AlCl_3$, $MeOH/H_2O$, r.t.; (iii) (*S*)-MTPA-Cl, DMAP, toluene

Scheme 4

Both **1b** and **1c** gave good yields of the deboronated Δ^2-isoxazolines **2b** and **2c** (43% and 64% respectively). The enantiomeric excess of both compounds was deduced following reductive cleavage of the isoxazolines to the β-hydroxyketones **7b** and **7c**,[12] followed by conversion to their Mosher's ester derivatives. The enantiomeric excess was determined to be 18% in both cases by this method, and chiral nmr analysis of **2b** in the presence of (*R*)-binaphthol indicated an *ee* of 20%. The absolute stereochemistry of **2b** was determined by comparison of the sign of optical rotation of **7b** with literature values,[13] and we assign the absolute stereochemistry of **2c** by analogy to **2a** and **2b**.

X-ray crystallographic analysis[14] of compound **1a** shows that, in the crystalline state at least, the oxazaborolidine rings are oriented with the phenyl substituents in a pseudo-equatorial arrangement, as shown in Figure 1. In the crystal structure, the vinyl boronate is oriented as in structure **9**, with its most accessible face (*ie* that face which involves cycloaddition occurring *exo*- to the dioxazaborocine ring system) being the *si* -face (for substrate **1a**, with respect to the stereocentre retained in the isoxazoline). This matches the observed sense of asymmetric induction.

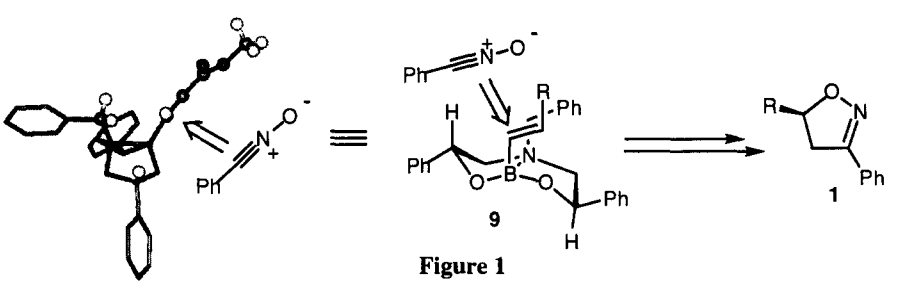
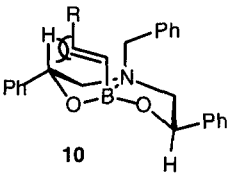


Figure 1

The preferential adoption of this geometry by the olefinic substituent is suggested to arise from a desire to minimise interactions of the olefin with the pseudo-axial hydrogen of the oxazaborolidine ring (*cf.* structure **10**), while the benzyl substituent ensures that the incoming dipole attacks from the *exo*-face of the olefin.



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In conclusion, we have demonstrated the first applications of chiral dioxazaborocines in asymmetric synthesis. Further refinements of the ligand system to improve the level of asymmetric induction, as well as the examination of other addition reactions to the olefins, are in progress and results will be reported in due course.

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