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Enhanced asymmetric induction in cycloadditions to bridgehead-chiral vinyl dioxazaborocines

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Abstract

Vinyl dioxazaborocines **5** with asymmetric centres on the nitrogen bridgehead substituent have been prepared and assayed in nitrile oxide and nitrone cycloadditions, giving asymmetric inductions of up to 70 and 74% *ee*, respectively.

Keywords: asymmetric synthesis; boron and compounds; cycloaddition; isoxazolines; nitrile oxides; nitrones.

The control of absolute stereochemistry in dipolar cycloadditions continues to occupy the attention of organic chemists. In contrast to the Diels–Alder reaction, progress towards catalytic asymmetric dipolar cycloadditions has been limited and is generally restrictive in terms of both substrate structure and the nature of the dipole.[1] In particular, there has been only one approach outlined towards catalytic asymmetric nitrile oxide cycloadditions,[2] and so the development of efficient and general chiral auxiliaries for these transformations remains an important goal.[3]

We have previously shown that chiral vinyl dioxazaborocines **1** can be prepared from vinyl boronic acids and readily available diethanolamine ligands, and that these compounds undergo diastereoselective nitrile oxide cycloadditions (with concomitant loss of the boronyl group) to yield 5-substituted Δ^2-isoxazolines **2** in up to 33% *ee*.[4] From the X-ray crystal structure of the β-boronyl acrylate derived dioxazaborocine, we were able to rationalise the observed sense of asymmetric induction in terms of attack upon the exposed face of the olefin in one of two extreme conformations derived from rotation about the B–C bond. The sole solid state conformer (and presumed major solution phase conformer) shown (Fig. 1) is favoured since the alternative conformation suffers eclipsing interactions between the α-vinyl proton and the pseudo-axial proton on the dioxazaborocine ring.

Given the close proximity of the nitrogen substituent at the bridgehead to the olefin, we were interested to investigate the effects of incorporating a further asymmetric centre at this position upon the levels of asymmetric induction observed. Herein we disclose the results of this investigation.

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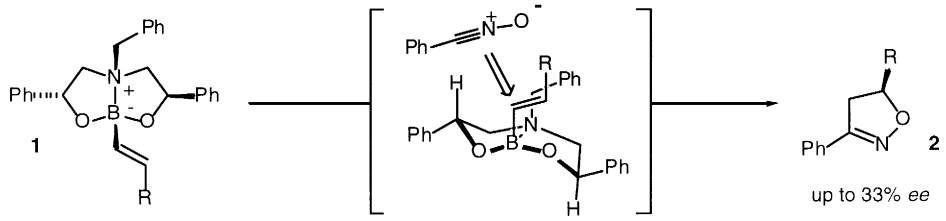
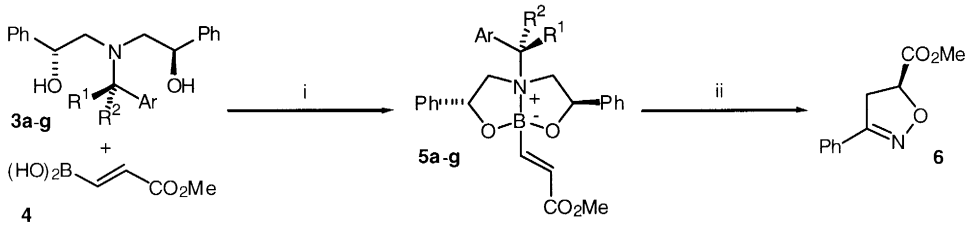


Fig. 1.

A range of diethanolamines **3a**–**g** were prepared from the appropriate α-chiral amines and (*R*)-styrene oxide[5] and condensed with the β-boronyl acrylate **4**[6] to yield the corresponding dioxazaborocines **5a**–**g**. As expected, ^{1}H NMR indicated that these compounds exist entirely in the closed form. These compounds were then subjected to 1,3-dipolar cycloaddition with in situ generated benzonitrile oxide under our optimised conditions[4] to yield isoxazoline **6** (Scheme 1). The optical purity of the isoxazolines was assayed by chiral shift ^{1}H NMR studies in the presence of (*R*)-binaphthol.[7] The results are shown in Table 1.

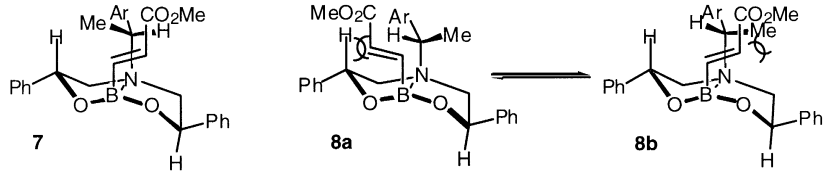


Scheme 1. Reagents and conditions: (i) **3**, **4**, Et_2O, rt; (ii) (Ph)ClC=N-OH, Et_3N, THF, rt

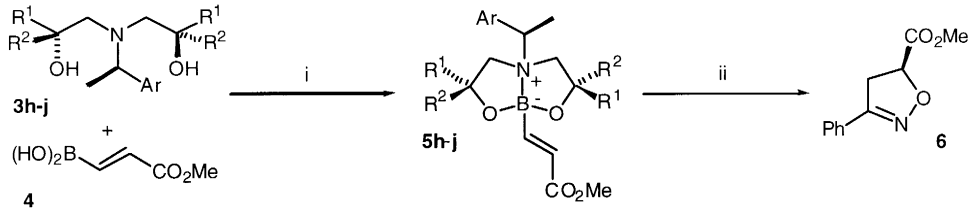
Table 1
Synthesis and dipolar cycloaddition reactions of vinyl dioxazaborocines **5a**–**g**

	Ar	R^1	R^2	Yield of **5**	Yield of **6**	*ee* of **6**
a	Ph	Me	H	94	55	70
b	Ph	H	Me	43	61	-18
c	2-naphthyl	Me	H	48	37	70
d	2-naphthyl	H	Me	23	41	0
e	Ph	CH_2OTBS	H	94	28	-10
f	$C_6H_4CH_2$-	CH_2-	H	43	53	25
g	$C_6H_4CH_2$-	H	CH_2-	71	27	-2

Several observations arise from these results. Firstly, it can be seen from entries a and c that the introduction of an extra asymmetric centre on the nitrogen bridgehead can lead to much improved levels of asymmetric induction compared to the simple *N*-benzyl substrates **1**. Secondly, these two entries also demonstrate that there is no advantage to be gained by increasing the bulk of the aryl group: this is to be expected since the X-ray structure of **1** clearly shows that the aryl substituent is oriented to the rear of the dioxazaborocine ring, well away from the site of reaction. Thirdly, as can be clearly seen from comparison of entries a and b, c and d, and f and g, a matched/mismatched situation exists between the ring and bridgehead substituents. Thus, in matched situations the bridgehead substituent is located in the same region as the pseudo-axial hydrogen, as in structure **7**, leading to an increased preference for the olefin to be oriented as shown. In the mismatched cases, the bridgehead substituent and the pseudo-axial hydrogen are in opposite regions, leading to competing conformers **8a** and **8b**, which expose diastereotopic faces of the olefin.



Given that the influence of the asymmetric centre on the nitrogen bridgehead appears to override that of the dioxazaborocine ring, we were interested to investigate the effect of changing the ring substituents in bridgehead-chiral systems. Thus, dioxazaborocines **5h–j** were prepared by the usual method from diethanolamines **3h–j**[8] and their behaviour in cycloaddition reactions examined (Scheme 2, Table 2).

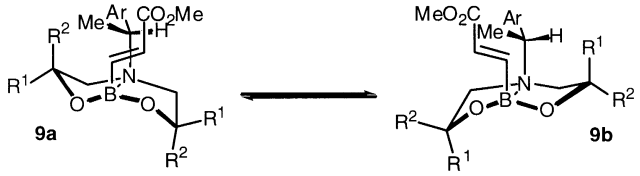


Scheme 2. (i) **1**, **2**, Et_2O, rt; (ii) (Ph)ClC=N-OH, Et_3N, THF, rt

Table 2
Synthesis and dipolar cycloaddition reactions of vinyl dioxazaborocines **5h–j**

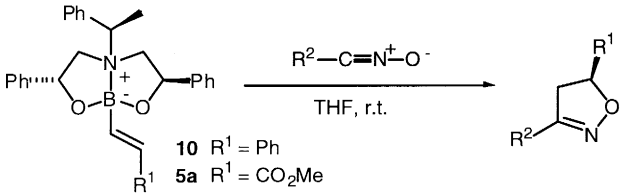
	R^1	R^2	Yield of **5**	Yield of **6**	*ee* of **6**
h	Me	H	59	56	56
i	H	H	41	53	50
j	Me	Me	16	37	- 22

From these results it can be seen that the presence of ring substituents is not crucial for asymmetric induction but does lead to enhanced selectivity. We believe that a large substituent is required to control the conformation of the dioxazaborocine rings. If R^1 is large and R^2 is hydrogen, conformer **9a** should dominate, with the olefin being oriented as shown. If R^1 is methyl or hydrogen, contributions from conformer **9b** in which the opposite diastereotopic face of the olefin is presented might become important, leading to a lower overall asymmetric induction. Supporting evidence for this theory is the broadened nature of the dioxazaborocine ring proton signals in the ^{1}H NMR spectrum of **5h** and **5i** compared to the sharp signals observed for **5a**, which could be indicative of conformational mobility. The tetramethyl substituted dioxazaborocine **5j** gives compound **6** of the opposite configuration to that from **5a**,**h**,**i**. This is presumed to arise because conformer **9a** is destabilised relative to **9b** when R^1=R^2=Me, and so predominant attack on **9b** as shown would lead to the observed enantiomer.



Having settled on the amine **3a** as the optimal ligand for dioxazaborocine formation, we investigated its application in two further nitrile oxide cycloadditions (Scheme 3). We examined the effect of making changes in both the olefin and nitrile oxide substituents. Thus, styryl dioxazaborocine **10** reacted with benzonitrile oxide to yield isoxazoline **11** of 61% *ee*, while carboethoxycarbonylnitrile oxide reacted

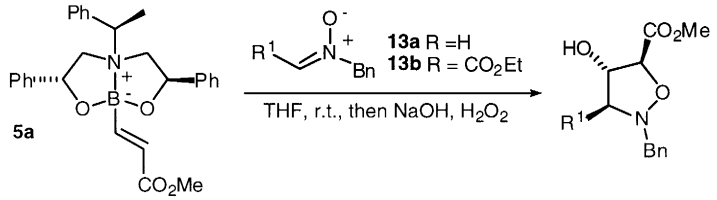
with acryloyl dioxazaborocine **5a** to give isoxazoline **12** of 59% *ee*. Thus, it appears that the auxiliary will prove applicable to the asymmetric synthesis of a range of isoxazolines.



	R^1	R^2	Yield	*ee*
11	Ph	Ph	31	61
12	CO_2Me	CO_2Et	65	59

Scheme 3.

We also investigated the use of dioxazaborocine **5a** in nitrone-olefin cycloadditions (Scheme 4). Cycloaddition with formaldehyde or glyoxalate derived benzyl nitrones **13a**,**b** gave isoxazolidines with the boron still appended; this could be oxidatively cleaved using basic peroxide to generate hydroxylated heterocycles **14a** and **14b**. The enantiomeric purities of the heterocycles were determined by Mosher' ester derivitisation, and found to be 65 and 74%,respectively. The sense of asymmetric induction has not been rigorously proven but is indicated as shown by analogy with the facial selectivity demonstrated in the nitrile oxide cycloadditions. Compound **14b** was isolated as a single diastereoisomer which is tentatively assigned as shown, although the low yield means that claims regarding the influence of the auxiliary upon *endo*/*exo* selectivity in the cycloaddition are premature.



	R^1	Yield	*ee*
14a	H	42	65
14b	CO_2Et	20	74

Scheme 4.

In summary, we have developed much improved dioxazaborocine auxiliaries for asymmetric dipolar cycloadditions to acrylates by the incorporation of bridgehead chirality. Nitrile oxide cycloadditions yield isoxazolines from which the auxiliary has been cleaved in up to 70% *ee*. Nitrones also undergo cycloaddition, and the extra degree of saturation allows for the retention of the boronyl function. Oxidative removal of the boron yields hydroxylated isoxazolidines in up to 74% *ee*. Further applications of chiral vinyl dioxazaborocines in synthesis will be reported in due course.[9]

Acknowledgements

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References

1. For example, chiral Lewis acids have been used to promote nitrone cycloadditions to oxazolidinone-substituted olefins (Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem*. **1997**, *62*, 2471–2477 and references cited therein) or enol ethers (Simonsen, K. B.; Bayón, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc*. **1999**, *121*, 3845–3853 and references cited therein), while chiral rhodium catalysts have been used to promote asymmetric

cycloadditions of oxonium ylides. (Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun*. **1999**, 2185–2186 and references cited therein).
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4. Davies, C. D.; Marsden, S. P.; Stokes, E. S. E. *Tetrahedron Lett*. **1998**, *39*, 8513–8516.
5. Owing to the availability to us of only a single enantiomer of 2-aminoindan, amine **3g** was in fact prepared from (*R*)-aminoindan and (*S*)-styrene oxide-the enantiomeric structure is shown in the paper for ease of comparison of data.
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7. Addition of (*R*)-binaphthol (0.044 g) to a sample of racemic isoxazoline (**6**) (0.005 g) in $CDCl_3$ resolved the signals for H_{4a}/H_{4b} from an overlapping multiplet at 3.65 ppm such that the outer doublets could be distinguished for each enantiomer in the ^1H NMR spectrum recorded at 400 MHz. We thank Mr. Dick Sheppard and Mr. Paul Hammerton of this department and Mr. Rob Horton of AstraZeneca for running these experiments.
8. Compound **3h** was prepared from (*S*)-α-methylbenzylamine and (*S*)-propylene oxide; the enantiomeric structure is shown here for clarity. Compound **3i** was prepared from (*R*)-α-methylbenzylamine and ethylene oxide. Compound **3j** was prepared by condensation of (*R*)-α-methylbenzylamine with two equivalents of ethyl bromoacetate followed by exposure to excess methylmagnesium bromide.
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