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The first example of chiral induction using homochiral boronic esters in the Petasis reaction

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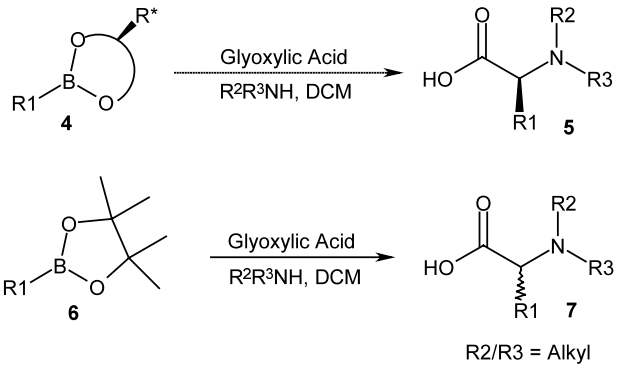
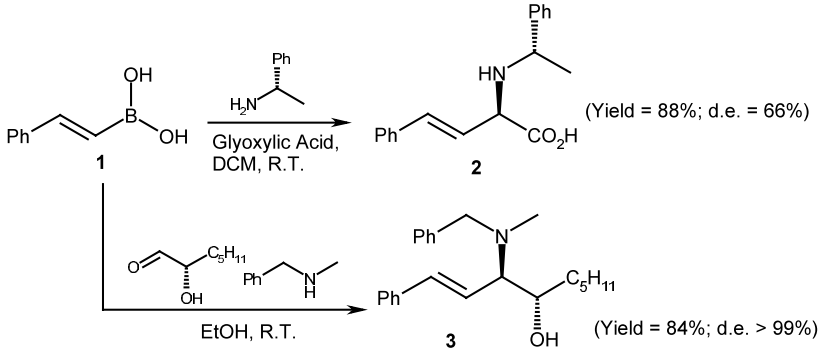
Abstract—The present study demonstrates the first enantioselective version of the Petasis reaction (boronic Mannich reaction), using glyoxylic acid, morpholine and a homochiral boronic ester as the chiral auxiliary. Chiral boronic esters are readily prepared by condensation of vinylboronic acids and chiral 1,2-diols. In the resulting Petasis reaction, 2-morpholin-1-yl-4-phenylbut-3-enoic acids are formed in high yields and moderate enantioselectivity.

Although adequate levels of diastereoselectivity have been reported for the Petasis reaction utilising chiral amines or aldehydes as substrates (Scheme 1),[1–3] an enantioselective version involving an achiral imine intermediate has not yet been described. A strategy (Scheme 2) based on homochiral boronic esters **4** is attractive and potentially more general since it would allow the use of achiral amines in combination with achiral aldehydes. Furthermore, the chiral auxiliary is not retained as a feature of the final product **5** and could in principle be recovered from the reaction mixture for recycling.

In the preceding communication, we demonstrated that pinacolylboronic esters **6** participate in the Petasis reaction of glyoxylic acid with secondary amines (Scheme 2).[4]



Scheme 2.



Scheme 1.

Keywords: chiral boronic ester; enantioselective reaction; Petasis reaction; chiral auxiliary.

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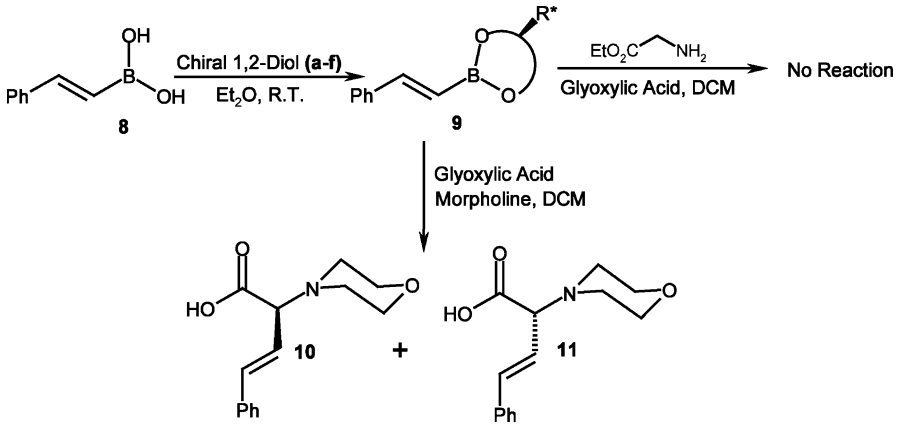
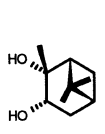
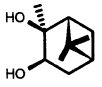
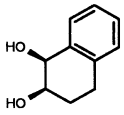
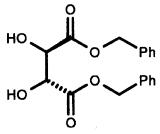
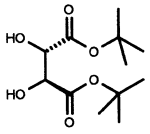
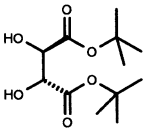


Scheme 3.

Table 1. Chiral 1,2-diols **a**–**f** as chiral auxiliaries in the Petasis reaction of **8** with morpholine and glyoxylic acid

	 **a**	 **b**	 **c**	 **d**	 **e**	 **f**
Boronic Ester **9** (Yield)	**9a** (83%)	**9b** (83%)	**9c** (70%)	**9d** (92%)	**9e** (91%)	**9f** (90%)
Product **10,11** (Combined Yield)	(78%)	(81%)	(78%)	(59%)	(71%)	(80%)
$[\alpha]_D$[a]	-14.9	+14.8	-10.7	+10.1	-6.6	+6.3
e.e.[b]	15.3%[b]	15.2%[b]	11.0%[c]	10.4%[c]	6.8%[c]	6.5%[c]

[a] The $[\alpha]_D$-values were measured on solutions of 10 mg/ml samples in 2 M NaOH.[6]
[b] Enantiomeric excesses determined by chiral HPLC.
[c] The enantiomeric excess was determined based on optical rotations with respect to entries **a** and **b**.

A logical extension to that work was investigation of related homochiral boronic esters of generic structure **4** as chiral auxiliaries in the Petasis reaction. The results of these studies are now presented below.

The preparation of the enantiomerically pure boronic esters was straightforward (Scheme 3); condensation of the vinylboronic acid **8** with a set of commercially available chiral 1,2-diols **a**–**f** gave the expected homochiral boronates **9a**–**f** in high yields and purity (Table 1). The resulting boronic esters **9a**–**f** were then used in the Petasis reaction with glyoxylic acid and morpholine in dichloromethane, to give the expected products **10** and **11** in high yields and with up to 15% e.e. (as determined by chiral HPLC[5]) for the pinane-derived boronates **10a** and **b**. The results are summarised below in Table 1. As expected, based on our earlier observations,[4] the chiral boronic ester **9a** failed to react with ethyl glycinate (Scheme 3). It is therefore likely that this methodology cannot be readily extended to involve primary amines.

In summary, the present studies demonstrate that modest enantioselectivity can be achieved in the Petasis reaction by using chiral boronic esters. We are currently continuing these studies to establish whether the asymmetric induction can be significantly improved on by judicious choice of boronic ester. Future work will also be concerned with extending these reactions to include primary amines.

References

1. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446.
2. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799.
3. Harwood, L. M.; Currie, G. S.; Drew, M. G. B.; Luke, R. W. A. *Chem. Commun.* **1996**, 1953–1954.
4. Koolmeister, T.; Södergren, M.; Scobie, M. *Tetrahedron Lett.* **2002**, *43*, 5965–5968.
5. Chiral HPLC analyses were performed using a Chirobiotec T reverse-phase column (50×4.6 mm).
6. $[\alpha]_D$ Values were recorded on a Perkin–Elmer 241 MC polarimeter using a sodium lamp at 589 nm.