Asymmetry in the boronic acid Mannich reaction: diastereocontrolled addition to chiral iminium species derived from aldehydes and (*S*)-5-phenylmorpholin-2-one

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(*S*)-5-Phenylmorpholin-2-one† and a range of aliphatic aldehydes form chiral iminium intermediates which undergo diastereoselective Mannich reactions with 2-furylboronic acid. Single crystal X-ray analysis of methylated derivative 4 derived from major adduct 2g confirms the stereochemical course of the reaction.

Our previous results using (*S*)-5-phenylmorpholin-2-one **1** as a chiral template for azomethine ylide cycloadditions may be rationalised by assuming that reaction proceeds *via* initial formation of an iminium species possessing *E*-geometry.[1] In an attempt to extend the application of this methodology, we reasoned that, in the presence of suitable nucleophiles, **1** could be a candidate for a diastereocontrolled Mannich reaction leading to optically active amine derivatives from aldehydes. However, initial attempts using electron rich alkenes such as enol ethers, vinyl thioethers, pyrroles and furan proved limited in application, with low yields of adducts being observed solely with paraformaldehyde.[2]

A report by Petasis and Akritopoulou,[3] that geometrically pure tertiary allylamines may be constructed from paraformaldehyde, vinylboronic acids and secondary amines in refluxing dioxane by a boronic acid Mannich reaction (Scheme 1) prompted us to investigate the application of this system to iminium species derived from morpholinone **1**.

An initial survey using paraformaldehyde indicated that reaction proceeded particularly efficiently with 2-furylboronic acid in refluxing THF (Scheme 2 and Table 1, entry 1). Introduction of the furan moiety has significance as a synthetic equivalent of the carboxylic acid functionality and 2-furylamine derivatives have been converted into α-amino acids[4] and Δ^4-3-piperidones[5] by oxidative modification. Applying our optimised conditions to aldehydes lacking α-substitution resulted in formation of mixtures of adducts in high material yield and with diastereoisomeric excesses in the range 86–93% (Table 1, entries 2–7).‡ In each case chromatography on silica permitted ready isolation of both isomers as colourless oils in the yields shown. α-Branched aldehydes underwent sluggish reaction to furnish a single diastereoisomer in low yield (Table 1, entries 8 and 9), possibly reflecting a more sterically congested situation.

By analogy with earlier studies, our model to rationalise the diastereocontrol invokes nucleophilic attack of the 2-furylboronic acid on the more accessible face of a conformationally locked *E*-iminium ion and predicts the structures of the major diastereoisomers to be **2b–i** (Fig. 1).

Analysis of NOE difference spectra obtained on the major adducts, although supportive of this prediction, did not permit unambiguous structural assignment. The diastereocontrol was eventually proven by X-ray crystallographic analysis of crystalline derivative **4** (Fig. 2),¶ obtained in 71% isolated yield (84% based upon recovered starting material) by alkylation of the sodium enolate of **2g** with iodomethane (Scheme 3).[6]

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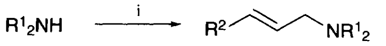
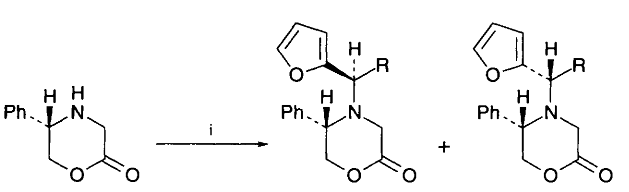
Table 1 Synthesis of **2a–i** and **3a–i** from **1** and RCHO

Entry	R	Product	Isolated yield (%) 2	Isolated yield (%) 3	de (%)[a]
1	H	**a**	69	—	—
2	Pr	**b**	59	2	93
3	Bu	**c**	69	5	90
4	$Ph(CH_2)_2$	**d**	66	4	89
5	$BnOCH_2$	**e**	64	3	86
6	Bu^i	**f**	71	3	92
7	Bu^tCH_2	**g**	75	3	92
8	$c\text{-}C_6H_{11}$	**h**	6	—	>95
9	Pr^i	**i**	7	—	>95

[a] See footnote §.



Scheme 1 *Reagents and conditions*: i, $[HCHO]_n$, $R^2CH{=}CHB(OH)_2$, dioxane, reflux



1 **2a–i** **3a–i**

Scheme 2 *Reagents and conditions:* i, RCHO, 2-furylboronic acid, THF, reflux

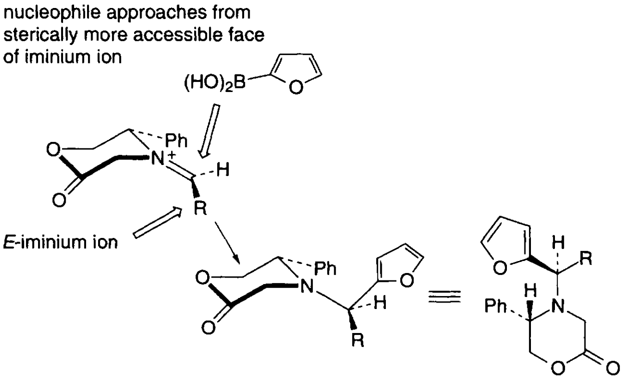
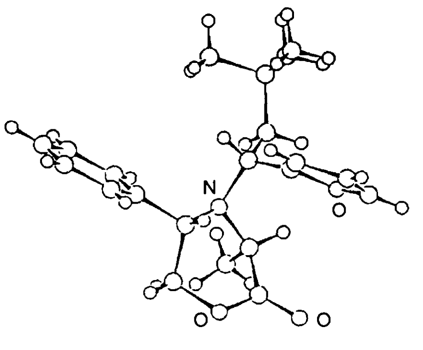


Fig. 1 Model of nucleophile approach to *E*-iminium ion



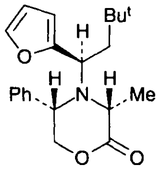


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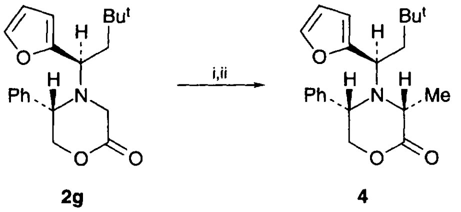
Fig. 2 X-Ray crystal structure of 4



Scheme 3 *Reagents and conditions*: i, NaHMDS, DME, THF, −78 °C; ii, MeI, 71% (84% based upon recovered starting material)

LINK scheme (to G. S. C.) and Reading University and the EPSRC for funding of the Marresearch Image Plate.

Footnotes

† In this communication we use the trivial morpholin-2-one nomenclature to describe the 3,4,5,6-tetrahydro-1*H*-1,4-oxazin-2-one ring system.

‡ *General procedure*: (*S*)-5-Phenylmorpholin-2-one **1** (100 mg, 0.56 mmol) and 2-furylboronic acid (251 mg, 2.24 mmol, 4.0 equiv.) were dissolved in THF (10 ml). To this stirred solution was added the aldehyde (0.62 mmol, 1.1 equiv.) in THF (2 ml). The reaction mixture was heated to reflux until TLC analysis indicated the complete consumption of starting material (*ca.* 1–2 h). The mixture was concentrated *in vacuo* and dichloromethane (1 ml) was added. The resulting suspension was filtered through Celite to remove excess 2-furylboronic acid and the solvent was removed under reduced pressure. Purification by chromatography on silica afforded both isomers as colourless oils.

§ The diastereoisomeric excesses quoted are based on isolated yields. The complexity of some of the crude NMR spectra did not always permit accurate integration of minor isomer signals. Where possible, analysis of spectra gave diastereoisomeric excesses in close agreement with those calculated from isolated yields. All novel compounds isolated gave spectroscopic data in accordance with their assigned structures. Adducts **2a–i** gave satisfactory combustion analyses.

¶ *Crystal data* for **4**: $C_{21}H_{27}NO_3$, $M = 341.44$, monoclinic, space group *C*2, $a = 16.120(9)$, $b = 11.511(9)$, $c = 11.189(8)$ Å, $\beta = 96.33(1)°$, $U = 2064$ Å^3, $Z = 4$, $D_c = 1.099$ g cm^{-3}, $F(000) = 736$, 3218 independent reflections were obtained from 95 × 2° frames, each collected for 2 min on the Marresearch Image Plate system. Data analysis was carried out with the XDS program.[7] The structure was determined by direct methods using SHELX86[8] and refined (non-heavy atoms anisotropic, hydrogen atoms in calculated positions, isotropic) by full-matrix least-squares[9] on F^2 using SHELXL to *R* 0.0617. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/150.

References

1 A. S. Anslow, L. M. Harwood, H. Phillips, D. J. Watkin and L. F. Wong, *Tetrahedron: Asymmetry*, 1991, **2**, 1343; L. M. Harwood, J. Macro, D. J. Watkin, C. E. Williams and L. F. Wong, *Tetrahedron: Asymmetry*, 1992, **3**, 1127; L. M. Harwood and I. A. Lilley, *Tetrahedron Lett.*, 1993, **34**, 537; L. M. Harwood and L. C. Kitchen, *Tetrahedron Lett.*, 1993, **34**, 6603; L. M. Harwood and I. A. Lilley, *Tetrahedron: Asymmetry*, 1995, **6**, 1557.

2 A. Manage, S. Robin and G. S. Currie, unpublished results.

3 N. A. Petasis and I. Akritopoulou, *Tetrahedron Lett.*, 1993, **34**, 583.

4 For instance see: K. Ramalingam, P. Nanjappan, D. M. Kalvin and R. W. Woodward, *Tetrahedron*, 1988, **44**, 5597; W. S. Zhou, Z. H. Lu and X. Y. Zhu, *Chin. J. Chem.*, 1994, **12**, 378; A. Dondoni, F. Junquera, F. L. Merchan, P. Merino and T. Tejero, *Synthesis*, 1994, 1450.

5 For examples see: W. S. Zhou, Z. H. Lu and Z. M. Wang, *Tetrahedron Lett.*, 1991, **32**, 1467; W. S. Zhou, Z. H. Lu and Z. M. Wang, *Tetrahedron*, 1993, **49**, 2641. See also T. Tejero, S. Franco, F. Junquera, A. Lanaspa, F. L. Merchán, P. Merino and I. Rojo, *Tetrahedron: Asymmetry.*, 1996, **7**, 1529 and references cited therein.

6 J. F. Dellaria and B. D. Santarsiero, *J. Org. Chem.*, 1989, **54**, 3916.

7 W. Kabsch, *J. Appl. Crystallogr.*, 1988, **21**, 916.

8 G. M. Sheldrick, SHELX86, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.

9 G. M. Sheldrick, SHELXL, a program for crystal structure refinement, University of Göttingen, 1993.

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