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Diastereoselective Petasis Mannich reactions accelerated by hexafluoroisopropanol: a pyrrolidine-derived arylglycine synthesis

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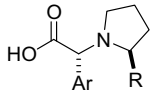
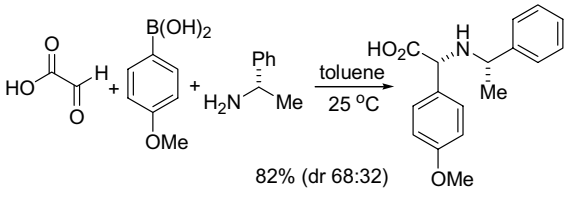
Abstract—A diastereoselective synthesis of pyrrolidine-derived arylglycines has been developed using the Petasis boronic acid Mannich reaction. High diastereoselectivities in the reactions of chiral amines, aryl boronic acids, and glyoxylic acid monohydrate have been demonstrated for the first time. Key to the implementation of this method is the discovery that hexafluoroisopropanol accelerates the Petasis process, reducing reaction times from multiple days to less than 24 h.

In the course of a recent drug discovery program, we required a diastereoselective synthesis of pyrrolidine-derived arylglycines of structure **I**.



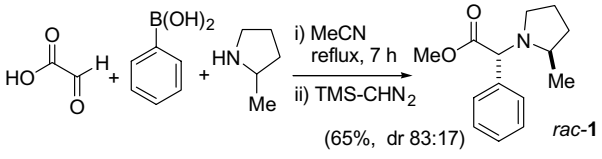
I

The Petasis boronic acid Mannich reaction[1] provides an operationally simple route to arylglycines ideally suited to variation of Ar and R. Diastereoselective Petasis reactions of alkenyl boronic acids and chiral amines have been reported[2] for the synthesis of α-amino acids. Petasis and co-workers have also reported[3] high diastereoselectivity in the analogous synthesis of β-amino alcohols from chiral α-hydroxy aldehydes and achiral amines. However, the only reported attempt at stereoselective arylglycine synthesis from chiral amines using these methods proceeds with poor diastereoselectivity (Eq. 1).[4] Petasis and co-workers speculated that facile epimerization of the α-stereocenter might be responsible for this result.[5,6] In this letter we report the diastereoselective synthesis of arylglycines **I** via a Petasis boronic acid Mannich reaction and document a significant acceleration of this reaction upon addition of hexafluoroisopropanol as a co-solvent.



(1)

Our initial investigations identified refluxing acetonitrile[7] as an optimal medium for reaction of cyclic secondary amines in the Petasis process. These conditions provided useful yields and reasonable reaction times. Further, we observed that the reaction of 2-methylpyrrolidine, phenyl boronic acid, and glyoxylic acid monohydrate under these conditions and subsequent esterification[8] provided methyl ester **1** in 65% yield with a diastereomeric ratio of 83:17 (Scheme 1) favoring the isomer shown (vide infra). Improved diastereoselectivity was realized by lowering the reaction temperature to 25 °C, resulting in a diastereomeric ratio of 94:6 (Table 1, entry 1). However, long reaction times (ca. 1 week)



Scheme 1.

Keywords: Petasis; Boronic acid Mannich; Arylglycine; Diastereoselective.
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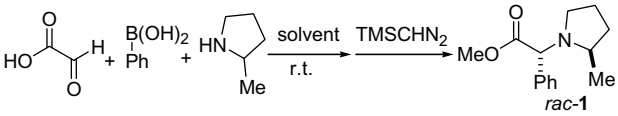
Table 1. Effect of solvent on the reaction rate and the diastereoselectivity



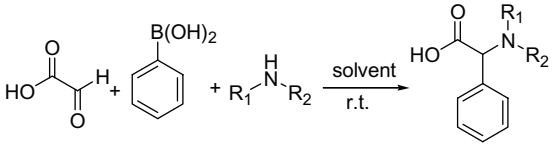
rac-**1**

Entry	Solvent	Time (days)	Diastereomeric ratio[a]	Isolated yield[b] (%)
1	CH_3CN	8	94:6	64
2	CH_2Cl_2	6	>95:5	80
3	Toluene	6	93:7	53
4	C_2H_5OH	6	93:7	53
5	CF_3CH_2OH	6	>95:5	78
6	$(CF_3)_2CHOH$	6	—	26% conv.[c]
7	CH_2Cl_2–HFIP 90:10	1	>95:5	80

[a] Determined by ^1H NMR of the unpurified reaction mixture.
[b] Isolated yield of the major diastereomer unless otherwise noted.
[c] Conversion estimated by LC/MS of the reaction mixture.

proved to be a major limitation of room temperature processes. Examination of several solvents indicated that CH_2Cl_2 provided slightly shorter reaction times and higher conversion than other aprotic solvents. Among the protic solvents examined, the more acidic CF_3CH_2OH provided better conversion than C_2H_5OH; however, use of the even more acidic $(CF_3)_2CHOH$ (HFIP) resulted in a much slower reaction (entry 6). We speculated that the fluorinated alcohols might indeed be promoting the desired reaction but exhibiting undesirable solvent effects. We were thus gratified to find that use of HFIP as an additive in CH_2Cl_2 solution dramatically accelerated the reaction[9,10] while preserving yield and stereoselectivity.[11] This phenomenon appears to be general for a variety of cyclic and acyclic amines (Table 2).

Table 2. Effect of HFIP on reaction rate



Entry	HNR_1R_2	Time (h)	% Conversion[a]	
			CH_2Cl_2–HFIP[b]	CH_2Cl_2
1		20	86	25
2		20	68	15
3		20	59	42
4		92	26	0
5		20	7	0

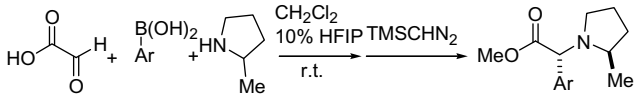
[a] Determined by LC/MS of the reaction mixture.
[b] CH_2Cl_2–HFIP (90:10, v/v).

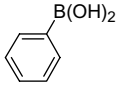
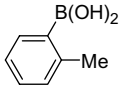
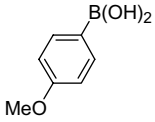
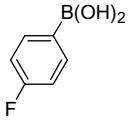
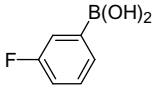
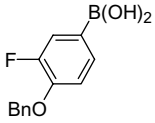
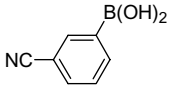
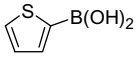
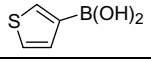
The scope of this diastereoselective process with regard to aryl boronic acids was examined using the improved reaction conditions (Table 3). In general, both electron-rich and sterically hindered aryl boronic acids provided good yields and diastereoselectivities (Table 3, products **1**, **2**, **3**, and **6**), whereas electron-deficient aryl boronic acids such as 3-cyanophenyl boronic acid did not react under the same conditions. 3-Fluorophenyl and 4-fluorophenyl boronic acids provided good yields and good diastereoselectivities. A difference in both reactivity and diastereoselectivity was observed for 2- and 3-thiophene boronic acids (Table 3, products **8** and **9**).

The scope of the reaction with regard to the amine component was also explored. Table 4 summarizes the results from reactions of different amines with phenyl boronic acid and glyoxylic acid monohydrate. 2-Substituted pyrrolidines underwent reaction with excellent diastereoselectivities and good yields (Table 4, products **1**, **10**, **11**, **12**). When 2,6-dimethylpyrrolidine was used as the amine component, it failed to react (Table 4, **13**). Similar behavior was also observed in the case of 2-methylpiperidine. The lower basicity[12] of piperidine in comparison to pyrrolidine along with greater steric congestion may render it inert under these conditions. No diastereoselectivity was observed in reactions of 3-substituted pyrrolidines (Table 4, **15**). It should be noted that the reaction in Eq. 1 was also accelerated under these conditions but did not show any improvement in diastereoselectivity.[13,14]

To establish the relative stereochemistry between the two chiral centers in these arylglycines, a single crystal X-ray structure of **11a**·HCl was obtained.[15] The crystal structure[16] (Fig. 1) shows the relative stereochemistry between the two chiral centers as *R* and *S*. The observed diastereoselectivity is consistent with addition of the aryl group to an intermediate iminium ion, where approach of the aryl group occurs from the face opposite the

Table 3. Reactions of 2-methylpyrrolidine and glyoxylic acid monohydrate with different aryl boronic acids



Ester product	Ar–$B(OH)_2$	Time (h)	Diastereomeric ratio[a]	Isolated yield[b] (%)
rac-**1**		22	>95:5	80
rac-**2**		24	>95:5	91[c]
rac-**3**		20	94:6	93
rac-**4**		24	95:5	83
rac-**5**		22	95:5	71
rac-**6**		17	87:13	88[d]
rac-**7**		22	—	No reaction
rac-**8**		7	57:43	59[e]
rac-**9**		7	91:9	70[d]

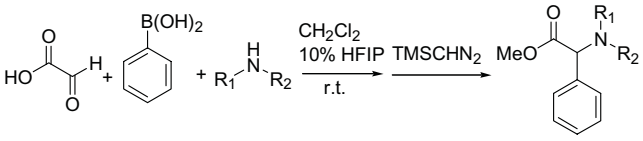
[a] Determined by 1H NMR of the unpurified reaction mixture.
[b] Isolated yield of the major diastereomer unless otherwise noted.
[c] dr > 95:5 in the isolated material.
[d] dr = 86:14 in the isolated material.
[e] dr = 56:44 in the isolated material.

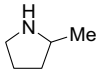
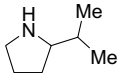
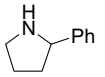
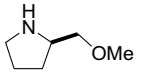
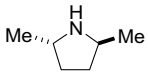
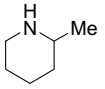
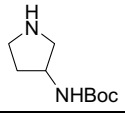
pyrrolidine 2-substituent. A graphical representation invoking the mechanism proposed by Hansen and co-workers is shown in Figure 2.[17]

In summary, a diastereoselective synthesis of pyrrolidine-derived arylglycines has been achieved via an accelerated Petasis boronic acid Mannich reaction. The use of HFIP as a co-solvent dramatically reduces reaction times, and this protocol may find application in other instances of the widely used Petasis synthesis.

Typical reaction procedure: To a suspension of glyoxylic acid monohydrate (89 mg, 0.968 mmol) in 4.5 mL of CH_2Cl_2 and 0.5 mL of hexafluoroisopropanol (HFIP) was added 2-methylpyrrolidine (82 mg, 0.968 mmol)

Table 4. Reactions of phenyl boronic acid and glyoxylic acid monohydrate with different amines



Ester product	HNR_1R_2	Time (h)	Diastereomeric ratio[a]	Isolated yield[b] (%)
rac-**1**		22	>95:5	80
rac-**10**		19	>95:5	90
rac-**11**		7	>95:5	96
(*S*)-**12**		24	>95:5	85
13		24	—	No reaction
14		24	—	No reaction
rac-**15**		24	50:50	80[c]

[a] Determined by ^1H NMR of the unpurified reaction mixture.
[b] Isolated yield of the major diastereomer unless otherwise noted.
[c] dr = 57:43 in the isolated material.

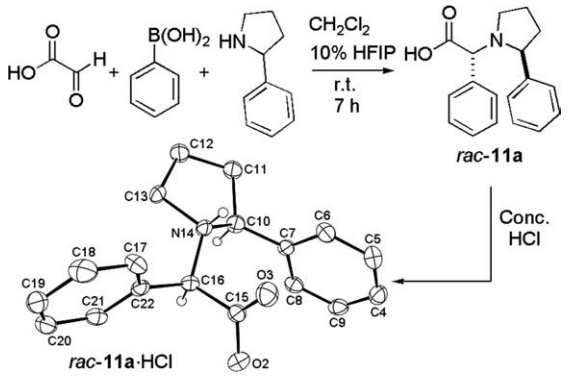


Figure 1. ORTEP representation of *rac*-**11a**·HCl. Non-hydrogen atoms are represented by ellipsoids corresponding to 50% probability.

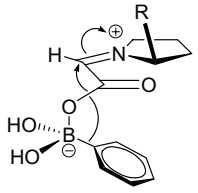


Figure 2. Aryl group approach from the face opposite the pyrrolidine 2-substituent.

followed by phenyl boronic acid (118 mg, 0.968 mmol). The reaction mixture was stirred for 22 h at room temperature and then concentrated. To a solution of this crude amino acid in a mixture of MeOH (2 mL) and CH_2Cl_2 (4 mL) was added TMS–diazomethane (2 mmol, 2 M in hexane) solution dropwise. The reaction mixture was stirred at room temperature for 2 h and concentrated, then purified by flash chromatography using a linear gradient of 3–30% EtOAc in hexanes. Product **1** was obtained as a colorless, viscous oil (181 mg, 80%).

Acknowledgements

We thank Nancy N. Tsou for obtaining the single crystal X-ray structure, Joan Murphy for mass spectral data and Christopher Dinsmore for helpful discussions.

Supplementary data

^{1}H NMR spectral data and high resolution mass spectral data for all compounds and Table S1 summarizing results from the reactions of different amines with phenyl boronic acid. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.151.

References and notes

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2. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.
3. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
4. Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463.
5. Arylglycine epimerization is well documented in the literature: (a) Mellin-Morliere, C.; Aitken, D. J.; Bull, S. D.; Davies, S. G.; Husson, H. H. *Tetrahedron: Asymmetry* **2001**, *12*, 149; (b) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.
6. Harwood and co-workers have reported a related diastereoselective reaction of 2-furyl boronic acid and formaldehyde in a non-epimerizable system: Currie, G. S.; Drew, M. G. B.; Harwood, L. M.; Hughes, D. J.; Luke, R. W. A.; Vickers, R. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2982.
7. Petasis, N. A.; Patel, Z. D. *Tetrahedron Lett.* **2000**, *41*, 9607.
8. Amino acids obtained from the boronic acid Mannich reactions were converted into the corresponding methyl esters (TMSCHN2) for ease of purification and characterization.
9. HFIP has been found to accelerate substitution reactions of dihydroartemisinin derivatives. Bonnet-Delpon and co-workers speculated that this is due to the strong hydrogen bond donor ability of HFIP: Magueur, G.; Crousse, B.; Ourevitch, M.; Begue, J. P.; Bonnet-Delpon, D. *J. Org. Chem.* **2003**, *68*, 9763.
10. For other HFIP-accelerated reactions see: (a) Iskra, J.; Bonnet-Delpon, D.; Begue, J. P. *Eur. J. Org. Chem.* **2002**, 3402; (b) Ichikawa, J.; Miyazaki, S.; Fujiwara, M.; Minami, T. *J. Org. Chem.* **1995**, *60*, 2320; (c) Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 4661.
11. Use of 10% CF_3CH_2OH in CH_2Cl_2 at room temperature provided 61% conversion by LC/MS after 26 h.
12. (a) Frenna, V.; Vivona, N. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1865; (b) Searles, S.; Tamres, M.; Block, F.; Quarterman, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 4917.
13. Interestingly, the reaction of α-methylbenzylamine with phenyl boronic acid did not proceed under our conditions (see Ref. 14) or under the conditions in Eq. 1. The relative rates of reactions of the more nucleophilic 4-methoxy phenyl boronic acid, α-methylbenzylamine and glyoxylic acid monohydrate in toluene and CH_2Cl_2–HFIP were estimated by LC/MS as follows: toluene, rt, 1 h, 46% conversion; CH_2Cl_2–HFIP, rt, 1 h, 96% conversion; toluene, 0 °C, 5.5 h, 36% conversion; CH_2Cl_2–HFIP, 0 °C, 5.5 h, 94% conversion, 92% yield, diastereomeric ratio 69:31.
14. Reactivities of several other acyclic and cyclic amines were examined. In general, acyclic amines showed no reaction or very little conversion to the desired arylglycines. See Table S1 in the supporting information.
15. The relative stereochemistry of all compounds was assigned by analogy to **11** and supported by similar chemical shift patterns in the ^{1}H NMR spectra of the isolated methyl esters.
16. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 254668. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
17. Although no detailed mechanism for the Petasis reaction has been elucidated, Hansen and co-workers have put forward a speculative proposal supported by ^{11}B NMR data: Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron* **2000**, *56*, 10023.