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On the use of boronates in the Petasis reaction

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Abstract—Alcohols are solvents of choice to react boronates, aldehydes and either primary or secondary amines. Thus, while the reaction proceeds sluggishly, or not at all, in aprotic solvents, the desired aminoacids are in most cases obtained in high yields when conducted in methanol or hexafluoro-*iso*-propanol. In the case of secondary amines, microwave activation is shown to strongly accelerate the process without altering the yields.

1. Introduction

One of the most efficient ways to rapidly increase the molecular complexity of products is represented by the multicomponent processes (MCP), in which at least three chemical entities are brought together to produce a multifunctional compound.[1] An additional feature of these reactions is the numerous possible reagent combinations, which usually result in a high exploratory power.[2] Among the various MCP at the disposal of the chemists, the borono-Mannich reaction, or Petasis reaction, has received much attention due to its power to produce variously substituted aminoacids and heterocyclic compounds.[3] In most of the reported cases, the Petasis reaction results from the interaction between a boronic acid **1**, an aldehyde **3** and an amine **4** to form product **5** and boric acid (**6**) (Scheme 1).

Two isolated examples of the use of boronic esters have also been described by Petasis and Hall, and, recently, Scobie has reported a more extensive study on the use of boronates.[3d,4] Primary amines were described as unreactive and only six of the 15 entries involving secondary amines resulted in isolated yields greater than 28%. The main reason behind Scobie's efforts was the possible development of a new diastereoselective variant of the reaction, involving the use of chiral boronic esters as auxiliaries.[5] This letter describes our own efforts to improve the use of boronates in the Petasis reaction. As detailed below, these efforts secured the efficient use of primary amines, and the original procedure was greatly improved in the case of secondary amines.

2. Results and discussion

The Petasis reaction has been reported as being strongly dependent on the solvent.[6] Screening aprotic solvents at room temperature or under reflux, when starting from pinacolyl 2-styrylboronate (**2a**), glyoxylic acid (**3a**) and benzylamine (**4a**) confirmed the observed lack of any reaction reported in the original letter (Table 1, entry 1). Alcohols, including electron-poor ones, have been increasingly used to accelerate reactions.[7] Indeed, carrying out the reaction in methanol (0.14 M) at room temperature resulted in a 65% conversion after 24 h, and in the isolation of the desired 4-phenyl-1-(*N*-benzylamino)but-3-enoic acid (**5a**) in 60% yield (entry 2). Reflux conditions, high pressures (12 kbar) or addition of water did not lead to any improvement. Carrying out the reaction in a more concentrated medium (1 M), however, resulted in a complete conversion after 72 h, and in a 67% isolated yield. Microwave activation proved to be deleterious, leading to tarry materials.

Alcohols with higher ionizing powers were then considered. Among these, hexafluoro-*iso*-propanol (HFIP) was

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Keywords: Boronates; Petasis reaction; Hexafluoropropanol.

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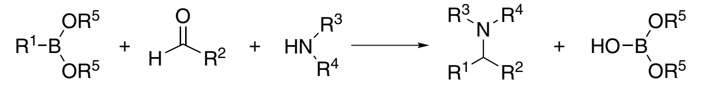
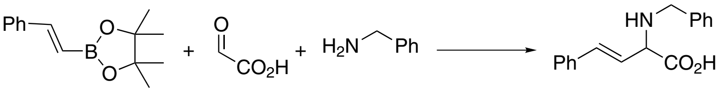


1: R^5 = H **3** **4** **5** **6**: R^5 = H

2: R^5, R^5= -C(CH$_3$)$_2$-(CH$_3$)$_2$C- **7**: R^5, R^5= -C(CH$_3$)$_2$-(CH$_3$)$_2$C-

Scheme 1.

Table 1. Conversion of **2a**, **3a** and **4a** into **5a** in various solvents after 4 h at room temperature



2a **3a** **4a** **5a**

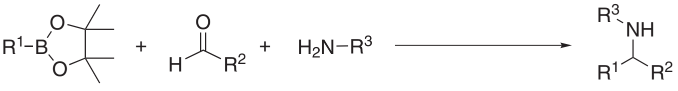
Entry	Solvent	% Conversion
1	Toluene, THF, CH_2Cl_2 or dioxane	0
2	CH_3OH	52 (65)[a]
3	CF_3CH_2OH	74
4	$(CF_3)_2CHOH$	88
5	CH_2Cl_2/CH_3OH (9:1)	24
6	CH_2Cl_2/CF_3CH_2OH (9:1)	34
7	$CH_2Cl_2/(CF_3)_2CHOH$ (9:1)	42
8	$CH_3OH/(CF_3)_2CHOH$ (9:1)	53

[a] Conversion after 24 h, see text.

introduced by Schleyer more than 30 years ago, and has received increasing attention during the last decade.[8] Substituting methanol with HFIP at room temperature allowed reaction times to be shortened to 4 h, and an 85% isolated yield in **5a** was obtained (entry 4). Expectedly, trifluoroethanol (TFE) led to intermediate results (entry 3). Attempts to use these alcohols as additives afforded less effective results than TFE and HFIP (entries 5–8).[9]

The conditions above were next used to generate a small library on a semi-automated synthesizer, using either methanol or HFIP (Table 2).[10] In most of the cases, the reaction proceeded smoothly and allowed the isolation of the desired product in fair to good yields (entries 1–6 and 9–12). The results indicated that HFIP generates a more appropriate medium than methanol for the transformation. Of particular note is the observed, improved diastereoselectivity in the case of (*R*)-(α-methyl)benzyl-

Table 2. Products **5** and yields of the reaction between boronates **2**, aldehydes **3** and primary amines **4** in MeOH, and in HFIP[11]



2 **3** **4** **5**

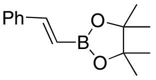
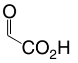
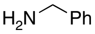
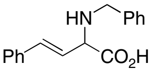
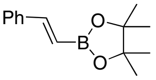
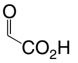
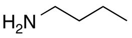
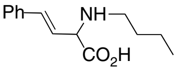
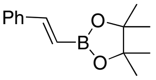
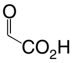
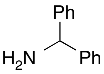
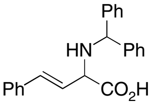
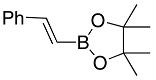
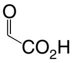
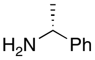
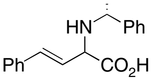
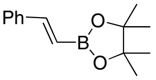
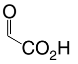
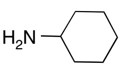
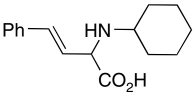
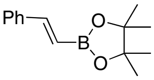
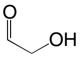
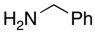
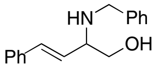
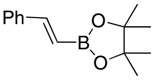
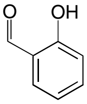
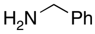
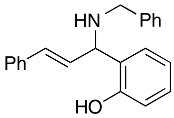
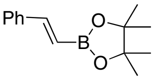
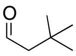
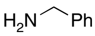
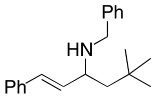
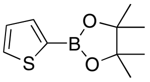
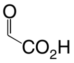
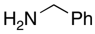
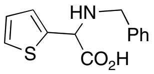
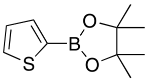
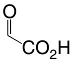
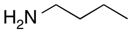
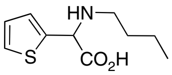
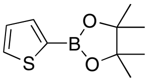
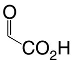
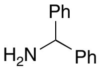
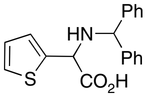
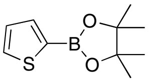
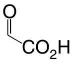
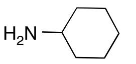
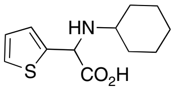
Entry	Boronate		Aldehyde		Amine		Product		Yield[a] (%)	Yield[b] (%)
1		**2a**		**3a**		**4a**		**5a**	67	85
2		**2a**		**3a**		**4b**		**5b**	66	77
3		**2a**		**3a**		**4c**		**5c**	64	92
4		**2a**		**3a**		**4d**		**5d**	70 (ed = 33%)	77 (ed = 81%)
5		**2a**		**3a**		**4e**		**5e**	60	78

Table 2 (*continued*)

Entry	Boronate		Aldehyde		Amine		Product		Yield[a] (%)	Yield[b] (%)
6		**2a**		**3b**		**4a**		**5f**	78	46
7		**2a**		**3c**		**4a**		**5g**	0	0
8		**2a**		**3d**		**4a**		**5h**	0	0
9		**2b**		**3a**		**4a**		**5i**	40	90
10		**2b**		**3a**		**4b**		**5j**	68	83
11		**2b**		**3a**		**4c**		**5k**	78	79
12		**2b**		**3a**		**4e**		**5l**	35	75

[a] Isolated yields; experiments conducted in methanol (1 M).

[b] Isolated yields; experiments conducted in HFIP; see Ref. 12.

amine **4d** (entry 4). Both *o*-hydroxybenzaldehyde and 3,3-dimethylbutyraldehyde, however, were found to be inert under these conditions (entries 7 and 8).

Secondary amines were next considered. The use of Scobie's optimized conditions (methylene chloride, room temperature) to react with pinacol boronate **2a**, glyoxylic acid **3a** and piperidine **4f** allowed us to isolate the desired product **5m** in 62% yield. Conducting the above reaction in methanol led to a complete conversion in 72 h, which translated into a substantial increase in yield (92% isolated), while HFIP at room temperature yielded a 94% conversion after only 4 h, which led to a 90% isolated yield. The higher cost of HFIP, when compared to methanol, led us to subject the reaction in the latter to microwave activation (120 °C, 300 W).[13] Under these conditions, the transformation reached completion in only 10 min and resulted in an essentially identical result (89% isolated yield). Expectedly, a reduced, 62% isolated yield was obtained when activation by microwaves was carried out in dichloromethane. The versatility of the reaction was then further illustrated with other boronates, aldehydes and secondary amines (Table 3).

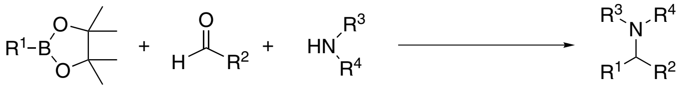
In most cases, the desired products were obtained in very good to excellent yields and the process was usually cleaner and more efficient when conducted in HFIP instead of methanol, even when microwave activation was used with the latter. The improvement is best illustrated by the case of components **2c**, **3a** and **4g** (entry 11). Thus, the yield obtained in methanol under microwave activation doubles than that reported by Scobie for the same substrates, and becomes nearly quantitative in HFIP. Here again, microwave activation shortened the reaction time from 4 h to 10 min without altering the isolated yield (94%). An identical analysis can be made on entry 12.

The superiority of HFIP over methanol as the solvent appears quite clearly from Tables 2 and 3. It is probably due to the effect of its ionizing power on both the formation of ionic intermediates and the stabilization of polarized or ionic transition states.[8a,15] In the case of primary amines, the increased acidity may also play a role in the efficacy of the process, although the results cannot be clearly explained on the basis of this sole parameter: the use of acidified methylene chloride led to a much lower conversion.[16]

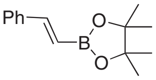
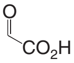
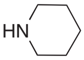
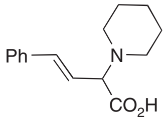
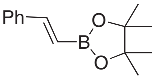
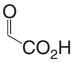
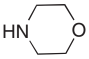
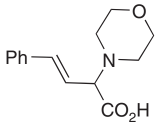
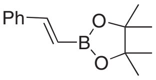
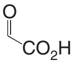
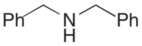
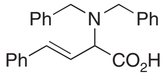
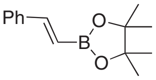
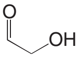
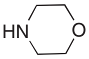
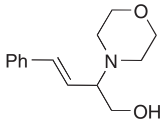
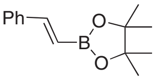
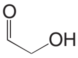
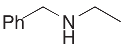
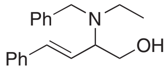
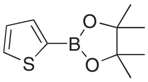
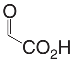
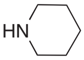
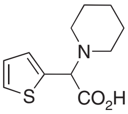
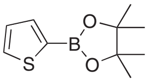
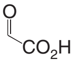
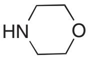
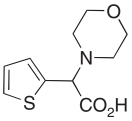
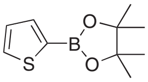
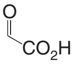
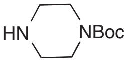
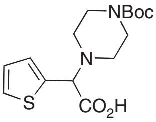
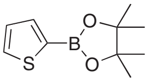
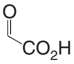
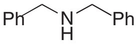
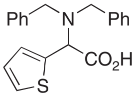
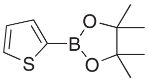
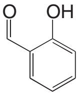
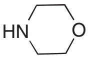
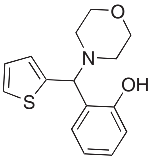
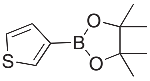
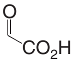
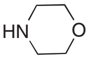
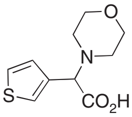
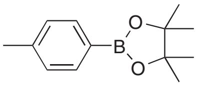
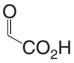
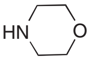
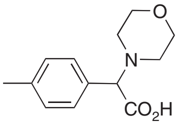
3. Conclusion

HFIP constitutes a very effective solvent to react aldehydes and amines with boronates. The ground is now firmly established to study the diastereoselection

Table 3. Products and yields of the reaction between boronates and secondary amines in MeOH under microwave activation and in HFIP[11]



2 **3** **4** **5**

Entry	Boronate	Aldehyde	Amine	Product	Yield[a] (%)	Yield[b] (%)
1	 **2a**	 **3a**	 **4f**	 **5m**	89	90
2	 **2a**	 **3a**	 **4g**	 **5n**	85	97
3	 **2a**	 **3a**	 **4h**	 **5o**	67	97
4	 **2a**	 **3b**	 **4g**	 **5p**	81	96
5	 **2a**	 **3b**	 **4i**	 **5q**	75	99
6	 **2b**	 **3a**	 **4f**	 **5r**	88	85
7	 **2b**	 **3a**	 **4g**	 **5s**	92	89
8	 **2b**	 **3a**	 **4j**	 **5t**	89	86
9	 **2b**	 **3a**	 **4h**	 **5u**	78	85
10	 **2b**	 **3c**	 **4g**	 **5v**	28	65
11	 **2c**	 **3a**	 **4g**	 **5w**	53 (25)[c]	97 (94)[d]
12	 **2d**	 **3a**	 **4g**	 **5x**	21 (12)[c]	81

[a] Isolated yields; experiments conducted in methanol under microwave activation; see Ref. 14.

[b] Isolated yields; experiments conducted in HFIP at room temperature for 4 h.

[c] See Ref. 4c.

[d] Experiment conducted in HFIP under microwave activation.

resulting from the use of chiral boronates. Work in that direction is actively pursued.

References and notes

1. Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005.
2. Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329.
3. (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583–586; (b) Harwood, L. M.; Currie, G. S.; Drew, M. G. B.; Luke, R. W. A. *Chem. Commun.* **1996**, 1953–1954; (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446; (d) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463–16470; (e) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799; (f) 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**, 2982–2990; (g) Jiang, B.; Yang, C.-G.; Gu, X.-H. *Tetrahedron Lett.* **2001**, *42*, 2545–2547; (h) Naskar, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 5819–5821; (i) Naskar, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 8865–8868; (j) Chang, Y. M.; Lee, S. H.; Nam, M. H.; Cho, M. Y.; Park, Y. S.; Yoon, C. M. *Tetrahedron Lett.* **2005**, *46*, 3053–3056.
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5. Koolmeister, T.; Södergren, M.; Scobie, M. *Tetrahedron Lett.* **2002**, *43*, 5969–5970.
6. The Petasis reaction proceeds efficiently in a variety of different solvents. However, cases have been reported in which a given solvent provides a particularly efficient medium. See, for instance, Ref. 3h.
7. See for instance: (a) Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381–3384; (b) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662–9663; (c) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336–1337.
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9. The accelerating effect of HFIP as additive on the Petasis reaction has been recently reported in the case of boronic acid. See: Nanda, K. K.; Trotter, B. W. *Tetrahedron Lett.* **2005**, *46*, 2025–2028.
10. A Quest™ synthesizer was used. Details can be obtained from Argonaut Technologies at the following web address: http://www.argotech.com. This synthesizer features vertical magnetic stirring.
11. All new compounds had analytical data in accordance with the depicted structures.
12. General procedure for products **5a**–**l**. The requisite boronic ester (0.5 mmol, 1 equiv) and aldehyde (0.5 mmol, 1 equiv) were dissolved in 1,1,1,3,3,3-hexafluropropan-2-ol (0.5 mL), and the primary amine (0.5 mmol, 1 equiv) was then added at room temperature to the resultant solution. The mixture was stirred for 4 h at room temperature after which period of time the solvent was evaporated. The crude residue was purified either by flash chromatography on silica and eluted with the appropriate eluant (**5f**: DCM/MeOH (97:3)), or by crystallization from diethyl ether (**5a**–**e** and **5i**–**l**).
13. For the use of microwave activation of the Petasis reaction conducted with boronic acids, see: (a) McLean, N. J.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 993–995; (b) Follmann, M.; Graul, F.; Schäfer, T.; Kopec, S.; Hamley, P. *Synlett* **2005**, 1009–1011.
14. General, microwave-activated procedure for products **5m**–**x**. The starting boronic ester (0.5 mmol, 1 equiv) and aldehyde (0.5 mmol, 1 equiv) were dissolved in methanol (0.5 mL) in a 10 mL microwave vessel. The requisite amine (0.5 mmol, 1 equiv) was then introduced to the resultant stirring solution at room temperature. The tube was sealed with a pressure cap and irradiated for 10 min at 120 °C (300 W). After cooling to room temperature, the solvent was evaporated. The crude residue was either purified by flash chromatography on silica and eluted with the appropriate eluant (**5o**–**q** and **5u**: DCM/MeOH (98:2); **5v**: cyclohexane/AcOEt (85:15)), or crystallized from diethyl ether (**5m**,**n**,**r**–**t**,**w** and **5x**).
15. (a) Bentley, T. W.; Schadt, F. L.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1972**, *94*, 992–994; (b) Bordwell, F. G. *Acc. Chem. Res.* **1998**, *21*, 456–463; (c) Habusha, U.; Rozental, E.; Shmaryahu, H. *J. Am. Chem. Soc.* **2002**, *124*, 15006–15011.
16. The use of HCl (1% mol^{-1}) in CH_2Cl_2 led to a 30% conversion of **2a**, **3a** and **4a** after 72 h. This acid presumably reacts with the amine to generate an ammonium salt, with a pK_a value lower than that of HFIP.