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Synthesis of enantioenriched 1,2-*trans*-diamines using the borono-Mannich reaction with *N*-protected α-amino aldehydes†

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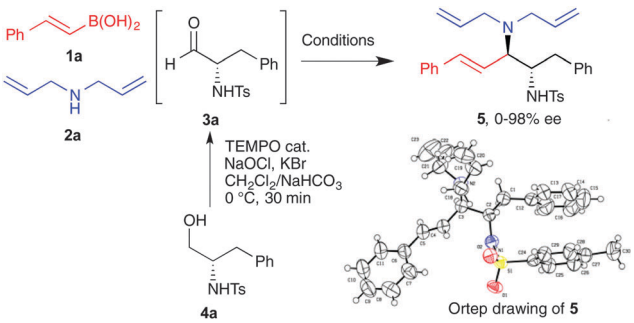
The three-component Petasis borono-Mannich reaction starting with easily accessible *N*-protected α-amino aldehydes produces efficiently and diastereoselectively 1,2-*trans*-diamines with an enantiomeric excess of up to 98%.

The Petasis borono-Mannich (PBM) process is a one-pot coupling of an aryl or a vinylic boronic acid with an amine and a carbonyl compound.[1] This powerful reaction constitutes one of the most direct and mild methods for preparing geometrically pure allylamines. Usually, the Petasis reaction relies on the presence of a hydroxyl or a carboxylic acid group proximate to the reacting carbonyl group. This allows the activation of the organoboronic acid as an "ate" complex followed by intramolecular organyl ligand transfer to a transient iminium species.[2] By taking advantage of the directing effect of the α-hydroxyl group of chiral aldehydes,[3] this reaction leads to the corresponding enantiopure β-amino alcohols with an exclusive *anti*-diastereoselectivity.[4,5] This approach has been beneficially applied to the synthesis of many bioactive molecules and complex natural products.[6,7] The possibility of using a nitrogen atom to activate the boronic acid was also investigated using 2-pyridinecarbaldehyde[8] and 2-sulfamidobenzaldehyde,[9] which successfully reacted in the PBM reaction. Very recently, aziridine-containing vicinal diamines were synthesized in a high *syn*-selective fashion using the PBM reaction employing amphoteric aziridine aldehyde dimers.[10] We report herein the direct use of *N*-protected α-amino aldehydes as substrates for the Petasis reaction to produce enantioenriched 1,2-diamines with pure *trans*-selectivity. The use of this class of aldehydes is particularly challenging since it is known to be unstable and prone to racemization.[11]



Scheme 1 Three-component coupling between boronic acid **1a**, *N*,*N*-diallylamine **2a** and *N*-tosyl amino aldehyde **3a**. X-ray structure of diamine **5**. For conditions see Table 1.

We initially focused on the three-component coupling between commercially available (*E*)-phenyl vinyl boronic acid **1a**, *N*,*N*-diallylamine **2a**, and *N*-tosylated amino aldehyde **3a** derived from L-phenylalanine (Scheme 1 and Table 1). The latter compound was obtained after oxidation[12] of the corresponding amino alcohol **4a** using NaOCl solution in the presence of KBr with a catalytic amount of TEMPO and buffering with $NaHCO_3$. It was used directly after the oxidation workup in the next Petasis condensation.[13]

According to our previous work with α-hydroxyaldehydes,[7,14] the reaction was first carried out with an excess of **3a** and **2a** (2 equiv. each) in CH_2Cl_2 at 120 °C for 30 min under microwave radiation (entry 1). The reaction proceeded with a high degree of diastereocontrol leading exclusively to *anti*-adduct **5**[15] in 85% yield, however, in low 30% ee.[16] Upon conventional heating, the reaction required 36 h at 50 °C to obtain the desired compound in 52% yield with a slight increase of the ee to 42% (entry 2). Using a mixture of CH_2Cl_2/HFIP (9/1) increased the reaction rates[17] but had a detrimental effect on the enantiomeric purity and when the reaction was carried out at 50 °C for 12 h, PBM adduct **5** was obtained in 70% yield and 8% ee (entry 3). Performing the reaction with this mixture of solvents was also possible at 0 °C but led, after 48 h, to racemic **5** in 76% yield (entry 5).[18] The use of

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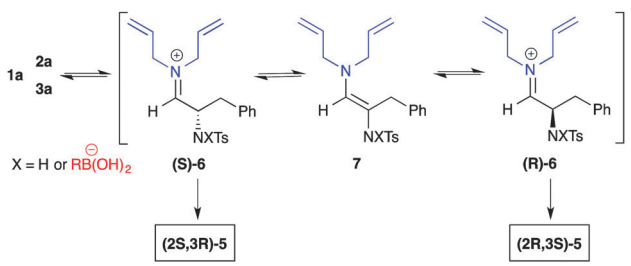
Table 1 Optimization of the Petasis borono-Mannich process with boronic acid **1a**, *N*,*N*-diallylamine **2a** and *N*-tosylated amino aldehyde **3a**

	Equiv. **3a**/**2a**/**1a**	Solvent	*T* (°C)	Time (h)	Additive	Yield[b] (%)	ee[c] (%)
1	2/2/1	CH_2Cl_2	120 (MW)	0.5	—	85	30
2	2/2/1	CH_2Cl_2	50	36	—	52	42
3	2/2/1	CH_2Cl_2–HFIP[a]	50	12	—	70	8
4	2/2/1	CH_2Cl_2–TFE[a]	50	12	—	42	29
5	2/2/1	CH_2Cl_2–HFIP	0	48	4 Å MS[d]	76	0
6	2/2/1	CH_2Cl_2	rt	36	—	19	50
7	2/2/1	CH_2Cl_2	rt	36	4 Å MS	46–85	37–84
8	2/2/1	$CHCl_3$	rt	36	4 Å MS	21	31
8	2/2/1	CH_3CN	rt	36	4 Å MS	18	54
9	2/2/1	MTBE	rt	36	4 Å MS	51	42
10	2/2/1	THF	rt	36	4 Å MS	4	65
11	2/2/1	$PhCH_3$	rt	36	4 Å MS	40	97
12	2/2/1	Mesitylene	rt	36	4 Å MS	14	86
13	2/2/1	$PhCF_3$	rt	36	4 Å MS	50–53	95–98
14	1.3/1.25/1	$PhCF_3$	rt	36	4 Å MS	54	93
15	1/1/1	$PhCF_3$	rt	36	4 Å MS	45	86
16	1/1/1.5	$PhCF_3$	rt	36	4 Å MS	57	74

[a] 9 : 1 CH_2Cl_2/HFIP or 9 : 1 CH_2Cl_2/TFE. [b] Isolated yield after chromatography, based on boronic acid. [c] Determined by chiral HPLC. [d] Commercial powdered 4 Å molecular sieves were activated at 150 °C under vacuum for 1 h. rt = room temperature.

HFIP[19] as an additive polar solvent of high ionizing power is well-known to accelerate the Petasis reaction probably by favoring the formation of the transient iminium species **6** (Scheme 2). However, it also apparently favored the formation of enamine **7** that would explain the erosion of the enantiomeric purity of **5** (Scheme 2). The same effect was also observed with the less acidic TFE (pK_a 12.4 *versus* 9.3 for HFIP) as an additive (entry 4) but to a lesser extent (29% *versus* 8% ee at 50 °C).

Since the reaction in CH_2Cl_2 was very slow at room temperature (19% yield after 36 h, entry 6), the three-component coupling was attempted in the presence of 4 Å molecular sieves (4 Å MS, entry 7). MS are also known to accelerate the PBM reactions[20] and proved to be effective also in our case for both the yield and the enantiomeric purity with ees increasing up to 84%. However, the results were non-reproducible and the search for other solvents was carried out. Among all the solvents tested (entries 8 to 13), aromatic solvents provided higher ee values. In particular with environmentally friendly trifluorotoluene,[4,21] **5** could be obtained in 50–53% yield and 95–98% ee (entry 13). Therefore, $PhCF_3$ was chosen as the standard solvent for further exploration of the reaction conditions.



Scheme 2 Possible pathway to explain the erosion of the enantiomeric purity of PBM adduct **5**.

The influence of the reactants' stoichiometry was then investigated (entries 14 to 16). Both the amount of aldehyde and amine could be reduced (1.3 equiv. of **3a** and 1.25 equiv. of **2a**), which provided **5** in a similar yield with a minimal decrease of the ee (93%, entry 14). Using stoichiometric amounts of all the reactants (entry 15) or an excess of the boronic acid (entry 16) had a negative effect on the enantiomeric purity and afforded **5** with ees between 74 and 86%.

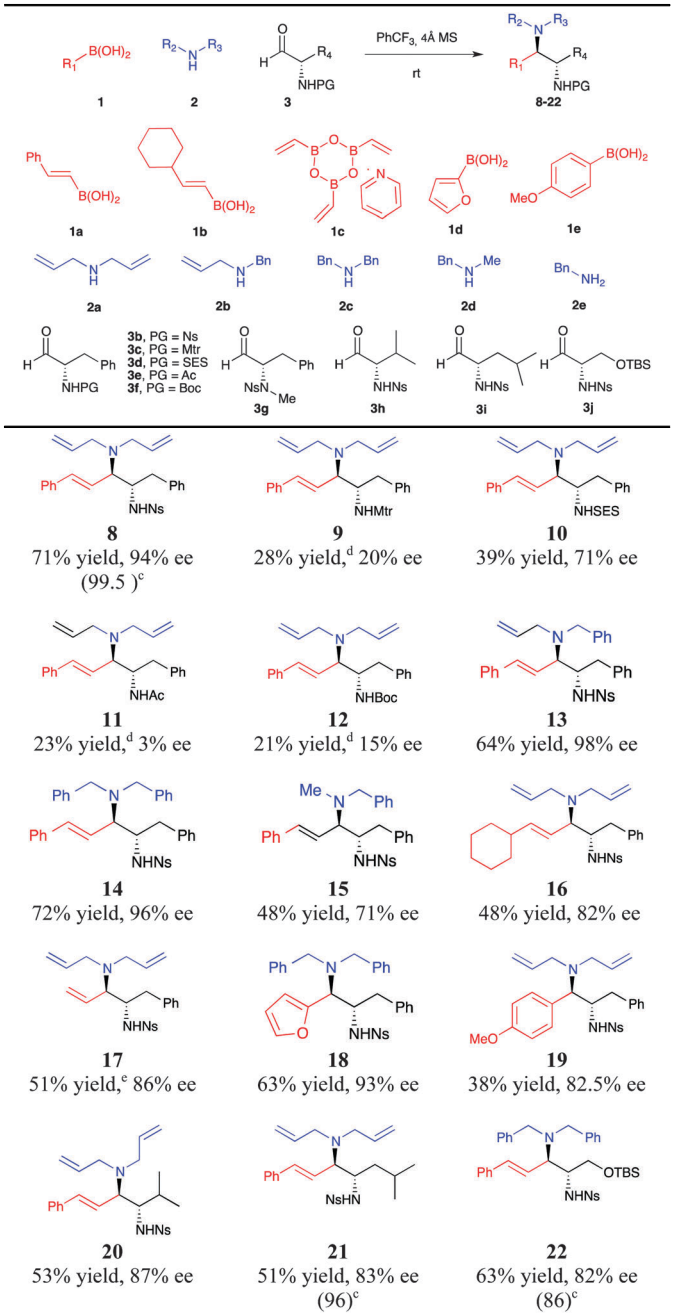
The protecting group of the amino aldehyde had a decisive influence on both the yield and the enantiomeric purity of the condensation products. Taking as a model study the reaction of vinyl boronic acid **1a** and *N*,*N*-diallylamine **2a** with *N*-protected aldehydes **3** derived from L-phenylalanine, we found that the lower the pK_a of the corresponding NH-groups, the higher the chemical yields and ees of the diamine products (Table 2 and Fig. 1). Thus, acetamide **3e** (pK_a 15)[22–24] and *tert*-butyl carbamate **3f** (pK_a 11.4) gave ineffective results (diamines **11**, 23% yield, 3% ee and **12**, 21% yield, 15% ee, respectively) while *N*-tosylated (pK_a 9.5) and *N*-nosylated (pK_a 8.2) substrates **3a** and **3b** provided good solutions (diamines **5**, 54% yield, 93% ee and **8**, 71% yield, 94% ee,[25] respectively), with the *N*-nosylated group being the best option.‡ The other sulfonamide derivatives (4-methoxy-2,3,6-trimethylphenylsulfonamide **3c** and 2-(trimethylsilyl)ethanesulfonamide **3d**, pK_a around 10) gave unsatisfactory results in terms of yields and ees. These trends are illustrated in Fig. 1. It is also worth noting that no reaction occurred with *N*-methyl *N*-tosyl amino aldehyde **3g**. These findings suggest that the protecting group on nitrogen is important for modulating the coordination to boron as well as the racemization of the asymmetric center.

The scope and limitations of the three-component Petasis reaction were further surveyed using a variety of reaction partners, and the results are shown in Table 2. The data were obtained using the best reaction conditions for the preparation of **5** from boronic acid **1a** (1.3 equiv. of aldehyde, 1.25 equiv. of amine at rt in $PhCF_3$ with 4 Å MS) and the yields were not optimized. With *N*-nosylated amino aldehyde **3b** and boronic acid **1a**, the reaction can be performed with other secondary amines such as *N*-allyl-*N*-benzyl amine **2b** or *N*,*N*-dibenzyl amine **2c** and led to **13** and **14** in 64 and 72% yield, respectively, and good enantiomeric purity (98% and 96% ee). The reaction carried out using *N*-methyl-*N*-benzyl amine **2c** was less efficient affording **15** in 48% yield and a lower 71% ee. Using primary *N*-benzylamine **2e**, however, did not provide the desired product.

For the boronic acid component, (*E*)-(2-cyclohexylvinyl)boronic acid **1b**, 2,4,6-trivinylcyclotriboroxane pyridine complex **1c** and 4-anisylboronic acid **1e** were used in combination with *N*,*N*-diallylamine **2a** and *N*-nosylated amino aldehyde **3b**. The reaction provided the expected products **16**, **17** and **19** in 48, 51 and 38% yield, respectively, with some erosion of the enantiomeric purity (82, 86% and 82.5% ee). 2-Furanboronic acid **1d** was a good reaction partner with *N*,*N*-dibenzyl amine **2c** and aldehyde **3b**, providing the corresponding PBM adduct **18** in 63% yield and 93% ee.

A short survey of the aldehyde component was performed with *N*-nosylated amino aldehydes **3h**, **3i** and **3j** derived from L-valine, L-leucine and protected L-serine. Their combination with **1a** and **2a** or **2c** gave the corresponding desired products

Table 2 Substrate scope for the Petasis borono-Mannich process with *N*-protected α-amino aldehydes[a,b]



[a] Reaction conditions: boronic acid (1 equiv.), *N*-protected α-amino-aldehyde (1.3 equiv.), amine (1.25 equiv.), $PhCF_3$, 4 Å MS, 48 h at rt, unless otherwise stated. [b] Isolated yield after chromatography, based on boronic acid, ee determined by chiral HPLC. [c] ee after recrystallization. [d] *N*-Protected α-amino aldehyde (2 equiv.) and amine (2 equiv.) were used. [e] Boronic acid (1 equiv.), α-hydroxyaldehyde (1.3 equiv.) and amine (1 equiv.) were used, yield based on amine.

20, **21** and **22** in moderate to good yield (51 to 63%) with ees from 82 to 87%.

As a preliminary evaluation for synthetic purposes, orthogonal removal of the *N*-protecting groups was also carried out (Scheme 3). Selective deprotection of the nosyl group was easily achieved by treatment of **8** with thiophenol in the presence of

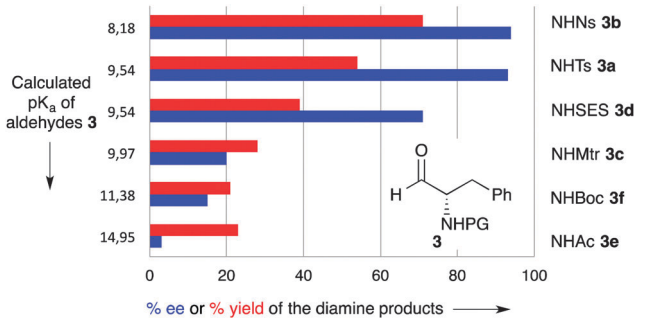
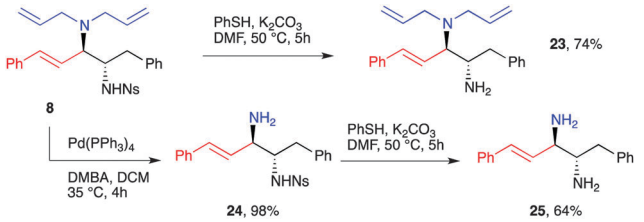


Fig. 1 Enantiomeric purity (blue bar) and chemical yield (red bar) of the diamine products as a function of the calculated pK_a (aqueous medium) of *N*-protected aldehydes **3** derived from L-phenylalanine and condensed with (*E*)-phenyl vinyl boronic acid **1a** and *N*,*N*-diallylamine **2a**.



Scheme 3 Orthogonal deprotection of **8**. DMBA = *N*,*N*′-dimethylbarbituric acid.

K_2CO_3 in DMF at 50 °C for 5 h, leading to monoprotected diamine **23** in 74% yield. The other monoprotected diamine, **24**, was provided by the removal of allyl protecting groups using *N*,*N*-dimethylbarbituric acid, and a catalytic amount of Pd(0).[26] Finally, access to fully deprotected diamine **25** was carried out from **24** after treatment with PhSH.

In summary, we have shown that *N*-tosylated or *N*-nosylated α-amino aldehydes can be used successfully as substrates for the Petasis borono-Mannich reaction. This establishes a new way of producing enantioenriched 1,2-*trans*-diamines that may be useful as ligands for transition metals[27] or as motifs in biologically active molecules.[28] The preparation of such compounds as well as mechanistic investigations are currently underway in our laboratory.

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Notes and references

‡ Representative procedure (synthesis of compound **9**): **3b** (59 mg, 0.176 mmol), diallylamine **2a** (21 μL, 0.169 mmol), boronic acid **1a** (20 mg, 0.135 mmol) and activated 4 Å MS (100 mg) in $PhCF_3$ (0.85 mL) were stirred for 48 h at room temperature. After solvent evaporation, the mixture was purified by preparative TLC on silica gel (AcOEt/heptane 2 : 8) to yield **8** (51 mg, 0.098 mmol, 71%, 94% ee).

1 (*a*) N. A. Petasis and I. Akritopoulou, *Tetrahedron Lett.*, 1993, **34**, 583; (*b*) Review: N. R. Candeias, F. Montalbano, P. M. S. D. Cal and P. M. P. Gois, *Chem. Rev.*, 2010, **110**, 6169.
2 (*a*) N. Schlienger, M. R. Bryce and T. K. Hansen, *Tetrahedron Lett.*, 2000, **41**, 1303; (*b*) N. A. Petasis and S. Boral, *Tetrahedron Lett.*, 2001, **42**, 539; (*c*) A. S. Voisin, A. Bouillon, J. C. Lancelot, A. Lesnard,

H. Oulyadi and S. Rault, *Tetrahedron Lett.*, 2006, **47**, 2165; (*d*) T. Jingcong and L. Shuhua, *Chin. J. Chem.*, 2010, **28**, 41.
3 N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1998, **120**, 11798.
4 A catalytic diastereoselective Petasis reaction was described for the formation of *syn*-β-amino alcohols, see G. Muncipinto, P. N. Moquist, S. L. Schreiber and S. E. Schaus, *Angew. Chem., Int. Ed.*, 2011, **50**, 8172.
5 For an intramolecular version of this reaction see: S. Norsikian, J.-F. Soulé, A. Cannillo, R. Guillot, M.-E. Tran Huu Dau and J.-M. Beau, *Org. Lett.*, 2012, **14**, 544.
6 (*a*) A. S. Davis, S. G. Pyne, B. W. Skelton and A. H. White, *J. Org. Chem.*, 2004, **69**, 3139; (*b*) S. G. Pyne, A. S. Davis, N. J. Gates, J. P. Hartley, K. B. Lindsay, T. Machan and M. Y. Tang, *Synlett*, 2004, 2670; (*c*) C. W. G. Au and S. G. Pyne, *J. Org. Chem.*, 2006, **71**, 7097; (*d*) Z. Hong, L. Liu, C. C. Hsu and C. H. Wong, *Angew. Chem., Int. Ed.*, 2006, **45**, 7417; (*e*) T. Machan, A. S. Davis, B. Liawruangrath and S. G. Pyne, *Tetrahedron*, 2008, **64**, 2725; (*f*) T. Ritthiwigrom and S. G. Pyne, *Org. Lett.*, 2008, **10**, 2769; (*g*) Z. Hong, L. Liu, M. Sugiyama, Y. Fu and C.-H. Wong, *J. Am. Chem. Soc.*, 2009, **131**, 8352; (*h*) P. Moosophon, M. C. Baird, S. Kanokmedhakul and S. G. Pyne, *Eur. J. Org. Chem.*, 2010, 3337; (*i*) P. Ghosal and A. K. Shaw, *J. Org. Chem.*, 2012, **77**, 7627; (*j*) M. E. Bouillon and S. G. Pyne, *Tetrahedron Lett.*, 2014, **55**, 475.
7 J.-F. Soulé, A. Mathieu, S. Norsikian and J.-M. Beau, *Org. Lett.*, 2010, **12**, 5322.
8 H. Mandai, K. Murota and T. Sakai, *Tetrahedron Lett.*, 2010, **51**, 4779.
9 N. A. Petasis and A. N. Butkevich, *J. Organomet. Chem.*, 2009, **694**, 1747.
10 S. K. Liew, Z. He, J. D. St. Denis and A. K. Yudin, *J. Org. Chem.*, 2013, **78**, 11637.
11 R. Hili, S. Baktharaman and A. K. Yudin, *Eur. J. Org. Chem.*, 2008, 5201.
12 (*a*) P. L. Anelli, C. Biffi, F. Montanari and S. Quici, *J. Org. Chem.*, 1987, **52**, 2559; (*b*) R. Siedlecka, J. Skarzewski and J. Mlochowski, *Tetrahedron Lett.*, 1990, **31**, 2177; J. Jurczak, D. Gryko, E. b. Kobrzycka, H. Gruza and P. Prokopowicz, *Tetrahedron*, 1998, **54**, 6051.
13 The configurational stability of amino aldehyde **3a** was confirmed after reduction with sodium borohydride, which led to the corresponding amino alcohol in 98% ee. Compound **3a** can be stored at −18 °C for one month with minimal racemization (97% ee).
14 (*a*) A. Cannillo, S. Norsikian, M. E. Tran Huu Dau, P. Retailleau, B. I. Iorga and J. M. Beau, *Chem. – Eur. J.*, 2014, **20**, 12133; (*b*) A. Cannillo, S. Norsikian, P. Retailleau, M. E. Dau, B. I. Iorga and J. M. Beau, *Chem. – Eur. J.*, 2013, **19**, 9127.
15 Determined by X-ray diffraction. See the ESI.† CCDC 1044004.
16 Enantiomeric purity of the product was confirmed by chiral HPLC analysis. See the ESI†.
17 K. K. Nanda and B. W. Trotter, *Tetrahedron Lett.*, 2005, **46**, 2025.
18 In this case, 4 Å MS were added to accelerate the reaction.
19 (*a*) J.-P. Bégué, D. Bonnet-Delpon and B. Crousse, *Synlett*, 2004, 18; (*b*) I. A. Shuklov, N. V. Dubrovina and A. Börner, *Synthesis*, 2007, 2925; (*c*) D. Vuluga, J. Legros, B. Crousse, A. M. Slawin, C. Laurence, P. Nicolet and D. Bonnet-Delpon, *J. Org. Chem.*, 2011, **76**, 1126.
20 X. Shi, D. Hebrault, M. Humora, W. F. Kiesman, H. Peng, T. Talreja, Z. Wang and Z. Xin, *J. Org. Chem.*, 2011, **77**, 1154.
21 (*a*) A. Ogawa and D. P. Curran, *J. Org. Chem.*, 1997, **62**, 450; (*b*) J. Maul, P. Ostrowski, G. Ublacker, B. Linclau and D. Curran, in *Modern Solvents in Organic Synthesis*, ed. P. Knochel, Springer, Berlin Heidelberg, 1999, vol. 206, p. 79; H. Matsubara and I. Ryu, *Top. Curr. Chem.*, 2012, **308**, 135.
22 These are calculated ionization constants in an aqueous medium using the ACD/pK_a DB program,[23,24] an empirical method based on linear free-energy relationships, for predicting the pK_a values of aldehydes **3** and their corresponding esters. (See ESI† for further details).
23 Advanced Chemistry Development, Inc., https://ilab.acdlabs.com/ilab2/.
24 C. Liao and M. C. Nicklaus, *J. Chem. Inf. Model.*, 2009, **49**, 2801.
25 The reaction on a higher scale, from 0.25 g of boronic acid **1a**, provided 0.63 g of diamine **8** in 72% yield and 91% ee that could be increased to 99.5% after recrystallization.
26 F. Garro-Helion, A. Merzouk and F. Guibé, *J. Org. Chem.*, 1993, **58**, 6109.
27 T. P. Yoon and E. N. Jacobsen, *Science*, 2003, **299**, 1691.
28 For reviews, see: (*a*) D. Lucet, T. Le Gall and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2580; (*b*) S. R. S. Saibabu Kotti, C. Timmons and G. Li, *Chem. Biol. Drug Des.*, 2006, **67**, 101; (*c*) S. De Jong, D. G. Nosal and D. J. Wardrop, *Tetrahedron*, 2012, **68**, 4067.

