Highly Stereocontrolled One-Step Synthesis of *anti*-β-Amino Alcohols from Organoboronic Acids, Amines, and α-Hydroxy Aldehydes

Nicos A. Petasis* and Ilia A. Zavialov

Department of Chemistry
Loker Hydrocarbon Research Institute
University of Southern California
Los Angeles, California 90089-1661

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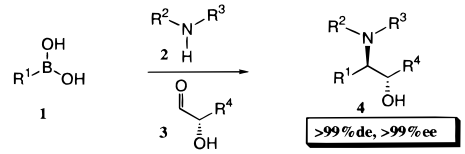
The stereocontrolled synthesis of β-amino alcohols continues to be the focus of numerous studies.[1] This highly versatile functionality can be easily converted to many other molecules, including amino acids[2] and amino sugars.[3] It is also a common subunit of a large variety of bioactive compounds, such as many protease inhibitors.[4] β-Amino alcohols are also useful as chiral auxiliaries[1,5] and as transition metal ligands[5,6] for asymmetric synthesis and catalysis. The most common synthetic routes to these molecules[1] involve functional group interconversions, including the reduction of amino acids[7] or amino ketones,[8] the hydroboration of enamines,[9] the aminohydroxylation of olefins,[10] and the nucleophilic substitution of epoxides,[11] diol derivatives,[12] or aziridines.[13] Many of these approaches, however, proceed with low or mixed stereoselectivity, involve multiple steps, or allow only limited types of substituents. Somewhat more versatile are methods involving the simultaneous construction of a C−C bond, such as the addition of various C-nucleophiles to carbonyl derivatives,[14] to N-protected α-amino aldehydes,[15] or to N-derivatives of α-alkoxy aldehydes.[16] Methods of this type, however, often require highly reactive organometallics that involve cumbersome experimental conditions and necessitate additional protection−deprotection steps. Moreover, the stereoselectivity in these cases is usually low or mixed, due to conflicting stereoelectronic effects and chelation effects.[16a]

Following our recently reported one-step α-amino acid synthesis from organoboronic acids,[17] we describe herein a new, practical, and highly diastereocontrolled approach to a variety of *anti*-β-amino alcohols. This method involves the one-step three-component reaction of an organoboronic acid (**1**), an amine (**2**),



and an α-hydroxy aldehyde (**3**) to give directly the corresponding β-amino alcohol (**4**). The reaction proceeds with a very high degree of diastereocontrol, forming exclusively the *anti* products in greater than 99% de. Moreover, when optically pure α-hydroxy aldehydes are used, no racemization occurs, and the products are obtained as single enantiomers, with greater than 99% ee.

Table 1 shows a number of examples of this chemistry. A variety of organoboronic acids, including alkenyl (**1b**, **f**, and **g**), 2-bromoalkenyl (**1a**), aryl (**1c** and **d**), and heteroaryl (**1e**, **h**, and **i**) participate readily in this process. The experimental procedure[18] is very simple and generally involves mixing and stirring the three components together at ambient temperature for 12−48 h. A typical solvent is ethanol although ethanol/dichloromethane or ethanol/water mixtures can also be used. It is noteworthy that the reaction does not require anhydrous or oxygen-free conditions and is readily adaptable to parallel synthesis for the construction of combinatorial libraries.[19]

The use of glycolaldehyde dimer (**3a**) in this process gives the primary amino alcohol products in good yields (entries 1−2). Chiral α-hydroxy aldehydes (**3b** and **c**), readily available by a variety of methods,[20] give the corresponding β-amino alcohols as single diastereomers (entries 3−5). The relative configuration of the products was established to be *anti* by ^{1}H NMR spectroscopy and other techniques.[21]

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(2) (a) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon Press: Oxford, 1989. (b) Yokomatsu, T.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1992**, *33*, 1051. (c) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. (d) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
(3) (a) Golebiowski, A.; Jurczak, J. *Synlett* **1992**, 241. (b) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677.
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(8) (a) Paleo, M. R.; Sardina, F. J. *Tetrahedron Lett.* **1996**, *37*, 3403. (b) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (c) Shimizu, M.; Tsukamoto, K.; Fujisawa, T. *Tetrahedron Lett.* **1997**, *38*, 5193. (e) Chung, S.-K.; Kang, D.-H. *Tetrahedron: Asymmetry* **1997**, *8*, 3027.
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(10) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483, and references therein.
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(13) (a) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999. (b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449.
(14) (a) Murakami, M.; Ito, H.; Ito, Y. *J. Org. Chem.* **1993**, *58*, 6766. (b) Shono, T.; Kise, N.; Fujimoto, T.; Yamanami, A.; Nomura, R. *J. Org. Chem.* **1994**, *56*, 1730. (c) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677.
(15) (a) Jurczack, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Reetz, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (c) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469. (d) Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org. Chem.* **1994**, *59*, 5139. (e) Ciapetti, P.; Taddei, M.; Ulivi, P. *Tetrahedron Lett.* **1994**, *35*, 3183. (f) Andres, J. M.; Barrio, R.; Martinez, M. A.; Pedrosa, R.; Perez-Encabo, A. *J. Org. Chem.* **1996**, *61*, 4210. (g) Dondoni, A.; Perrone, D. *Aldrichimica Acta* **1997**, *30*, 35. (h) Hanessian, S.; Park, H.; Yang, R.-Y. *Synlett*, **1997**, 353. (i) Panek, J. S.; Liu, P. *Tetrahedron Lett.* **1997**, *38*, 5127.
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(17) (a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (b) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463.
(18) For a typical experimental procedure see the Supporting Information.
(19) For other approaches to 1,2-amino alcohol libraries see refs 11b,c.
(20) (a) Corey, E. J.; Jones, G. B. *Tetrahedron Lett.* **1991**, *32*, 5713. (b) Hayashi, M.; Yoshiga, T.; Nakatani, K.; Ono, K.; Oguni, N. *Tetrahedron* **1994**, *50*, 2821. (c) Alexakis, A.; Tranchier, J.-P.; Lensen, N.; Mangeney, P. *J. Am. Chem. Soc.* **1995**, *117*, 10767. (d) Enders, D.; Reinhold: U. *Liebigs Ann. Chem.* **1996**, 11. (f) Vettel, S.; Lutz, C.; Diefenbach, A.; Haderlein, G.; Hammerschmidt, S.; Kuehling, K.; Mofid, M. R.; Zimmermann, T.; Knochel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 779.

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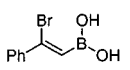
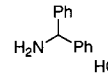
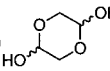
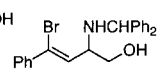
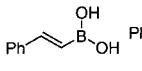
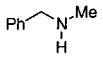
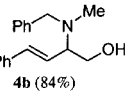
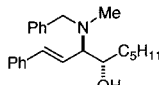
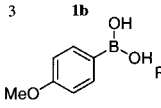
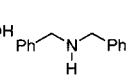
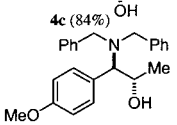
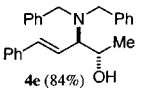
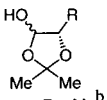
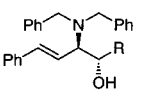
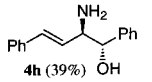
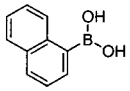
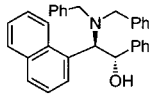
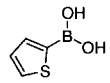
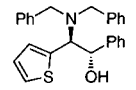
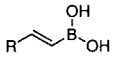
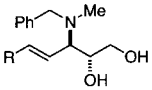
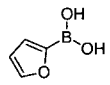
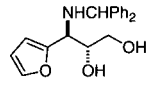
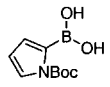
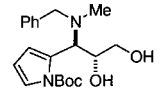
Table 1. Synthesis of *anti*-β-Amino Alcohols (**4**) by the Reaction of Organoboronic Acids (**1**) with Amines (**2**) and α-Hydroxy Aldehydes (**3**)[a]

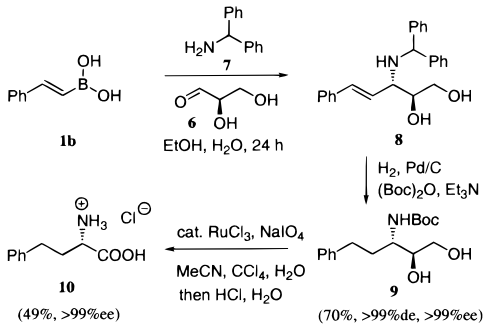
	Boronic acid	Amine	Aldehyde	Product (Yield)[a]
1	 **1a**	 **2a**	 **3a**	 **4a** (87%)
2	 **1b**	 **2b**	**3a**	 **4b** (84%)
3	**1b**	**2b**	 **3b**	 **4c** (84%)
4	 **1c**	 **2c**	 **3c**	 **4d** (63%)
5	**1b**	**2c**	**3c**	 **4e** (84%)
6	**1b**	**2c**	 **5a**, R = Me[b]	 **4f** (85%)
7	**1b**	**2c**	**5b**, R = Ph[b]	**4g** (88%)
8	**1b**	NH_3	**5b**[b]	 **4h** (39%)
9	 **1d**	**2c**	**5b**[b]	 **4i** (84%)
10	 **1e**	**2c**	**5b**[b]	 **4j** (86%)
11	 **1b**, R = Ph	**2b**	 **3d**	 **4k** (87%)
12	**1f**, R = $^nC_4H_7$	**2b**	**3d**	**4l** (73%)
13	**1g**, R = CH_2OMe	**2b**	**3d**	**4m** (67%)
14	 **1h**	**2a**	**3d**	 **4n** (86%)
15	 **1i**	**2b**	**3d**	 **4o** (73%)

[a] Unless otherwise indicated, reactions were performed with racemic aldehyde in EtOH at 25 °C. All products were obtained with >99% de and gave satisfactory spectroscopic and analytical data. [b] In this case, optically pure substrate was used and the corresponding products were obtained with >99% ee.

Since aldehyde racemization does not occur under the reaction conditions, enantiomerically pure (>99% ee)[22] amino alcohols can be obtained by using enantiomerically pure α-hydroxy aldehydes.[20] We have also found (entries 6−10) that this process works very well with 4-hydroxy-1,3-dioxolanes (**5**),[23] which can be easily obtained[24] from the corresponding α-hydroxy carboxylic acids via initial ketalization followed by DIBALH reduction.

The tolerance of hydroxy groups and aqueous media in this reaction prompted us to examine the use of glyceraldehyde (**3d**). Although the addition of organometallics to protected glyceraldehyde and its imine derivatives is a well-known process,[16e,g,25] these reactions generally require anhydrous conditions and proceed with variable stereocontrol. In contrast, the direct reaction of organoboronic acids and amines with the unprotected aldehyde, including its aqueous solutions, gave cleanly the corresponding *anti*-3-amino 1,2-diol products (entries 11−16), as single diastereomers (>99% de). Compounds of this type can be easily transformed to numerous other functionalized amines,[26] amino acids,[12b,16e,g,25d,27] amino epoxides,[27b] and peptidomimetics.[4,11b]

The use of enantiomerically pure glyceraldehyde (**6**) leads to enantiomerically pure 3-amino 1,2-diols (e.g., **8**). By using aminodiphenylmethane (**7**) as the amine component, followed by hydrogenolysis, conversion to the *N*-Boc derivative (**9**), and



oxidation,[16g,27a] we obtained (*S*)-homophenylalanine (**10**)[17a] in enantiomerically pure form (>99% ee). Comparison of **10** with authentic material confirmed the very high degree of diastereocontrol and the anti selectivity of this process.

Overall, this new synthesis of amino alcohols is practical, experimentally convenient, and highly versatile, and it proceeds with very high diastereoselectivity. Further studies on mechanistic and synthetic aspects as well as combinatorial applications of this chemistry are currently underway.

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Supporting Information Available: Typical experimental procedure and spectroscopic and analytical data of compounds (17 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(21) For example, catalytic hydrogenation of **4e** followed by treatment of the resulting free amino alcohol with triphosgene and Hunig's base, gave an oxazolidinone with a coupling constant of 8.0 Hz, corresponding to the expected *cis*-isomer.[14c,15f,i,16f]

(22) The % ee was established by HPLC and NMR. For example, catalytic hydrogenation of **4f** followed by formation of the Mosher amide and comparison with the amide derived from the racemic compound **4e** using ^{19}F NMR, indicated a single enantiomer.

(23) While these compounds are stable and can be isolated, under the reaction conditions they presumably undergo facile fragmentation to the free α-hydroxy aldehydes or their adducts.

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