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Diastereoselective Aziridination of 2-B(pin)-Substituted Allylic Alcohols: An Efficient Approach to Novel Organoboron Compounds

Jorge Hernández-Toribio, Mahmud M. Hussain, Kevin Cheng, Patrick J. Carroll, and Patrick J. Walsh*

P. Roy and Diana T. Vagelos Laboratories, University of Pennsylvania, Department of Chemistry, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

pwalsh@sas.upenn.edu

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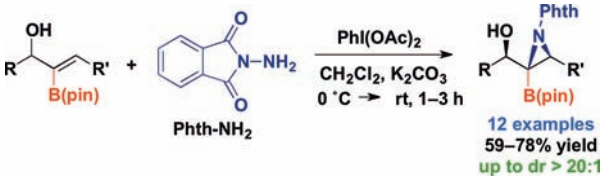
ABSTRACT



We report that 2-B(pin)-substituted allylic alcohols are good substrates for diastereoselective aziridinations in the presence of $PhI(OAc)_2$ and *N*-aminophthalimide. Under the aziridination conditions, the valuable B−C bond remains intact, affording a variety of novel boron-substituted aziridines in good yields and excellent diastereoselectivities. Oxidation of the aziridine B−C bond enables generation of *syn*-1,3-aminohydroxy-2-ketones with high diastereoselectivity.

The increasing utility of organoboron compounds as building blocks for the construction of complex molecules has attracted much attention.[1,2] Despite their utility, a serious limitation in the application of organoboron compounds is the high reactivity of B−C bonds. Thus, the vast majority of substrates containing B−C bonds undergo reaction at the boron center, as observed in catalytic cross-coupling processes[3] and oxidative transformations.[4] In this context, only a handful of efficient protocols involving epoxidation[5] or cyclopropanation[6a] of the double bond in vinylboronates have been reported. Even with impressive recent progress, the need to develop new transformations in which organoboron substrates retain their B−C bonds represents a considerable challenge.

We initially explored the oxidation of B(pin)-substituted allylic alcohols with TBHP and observed clean formation of the expected α-hydroxy ketones (Scheme 1, left).[4] To expand the range of transformations that can be performed on vinylboronate esters,[5,6] we diverted the reaction of TBHP with 2-B(pin)-substituted allylic alcohols from oxidation of the B−C bond to the epoxidation of the C=C bond (Scheme 1, right). This chemoselective epoxidation

(1) For recent general reviews, see: (a) *Contemporary Boron Chemistry*; Davidson, M., Hughes, A. K., Marder, T. B., Wade, K., Eds.; RSC: Cambridge, 2000. (b) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704.

(2) For biological and medicinal applications of boron-containing molecules, see: (a) Yang, W.; Gao, X.; Wang, B. *Med. Res. Rev.* **2003**, *23*, 346. (b) Petasis, N. A. *Aust. J. Chem.* **2007**, *60*, 795.

(3) For applications of vinylboronates in C−C bond formation, see: (a) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (b) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565 and references cited therein.

(4) For examples of oxidation of the B−C bond in vinylboronates, see: (a) Li, H.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 3521. (b) Waas, J. R.; Sidduri, A.; Knochel, P. *Tetrahedron Lett.* **1992**, *33*, 3717.

(5) (a) Brauer, D. J.; Pawelke, G. *J. Organomet. Chem.* **2000**, *604*, 43. (b) Molander, G. A.; Ribagorda, M. *J. Am. Chem. Soc.* **2003**, *125*, 11148. (c) Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130. (d) Fernandes, E.; Frey, W.; Pietruszka, J. *Synlett* **2010**, 1386. (e) Hussain, M. M.; Hernández-Toribio, J.; Carroll, P. J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 6337. (f) He, Z.; Yudin, A. K. *J. Am. Chem. Soc.* **2011**, *133*, 13770. (g) Li, J.; Burke, M. D. *J. Am. Chem. Soc.* **2011**, *133*, 13774.

(6) (a) Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516 and references therein. (b) Hussain, M. M.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1834.

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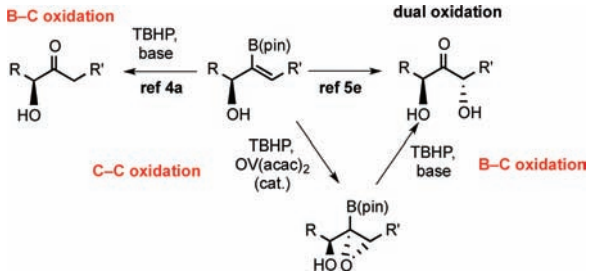
of 2-B(pin)-substituted allylic alcohols is catalyzed by $OV(acac)_2$[7] and generates the product with excellent diastereoselectivity (> 20:1). Subsequent oxidation of the B−C bond in the presence of NaOH and led to formation of the *anti*-2-keto-1,3-diols in good yields (55−96%).[5e] This method represents a new synthesis of synthetically important keto diols.[8]

Scheme 1. Control of Chemoselectivity in Oxidation of B(pin)-Substituted Allylic Alcohols

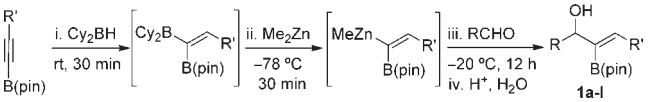


In considering other types of oxidations that could be performed in the presence of the vinyl boronate ester, we were attracted to aziridination. Aziridines are important structural components present in many biologically active natural products and are useful synthetic intermediates.[9] Herein we describe the highly diastereoselective aziridination of B(pin)-substituted allylic alcohols.

For any synthetic method to be useful, the substrates must be readily accessible. The B(pin)-substituted allylic alcohols were prepared as previously reported in one pot using our stereodefined 1-alkenyl-1,1-heterobimetallic reagents.[4b,5e,6] Thus, hydroboration of air-stable alkynyldioxaborolanes with dicyclohexylborane and selective B to Zn transmetalation of the vinyl-BCy_2 moiety generates the heterobimetallic intermediate. Addition of the Zn−C bond to aldehydes followed by quenching furnished (*E*)-2-B(pin)-substituted allylic alcohols **1a**−**1l** in 61−88% yield (Table 1). It is noteworthy that 2-B(pin)-substituted allylic alcohols can be prepared on gram scale.[5e]

Inspired by the seminal work of Che and Yudin describing a novel nitrene equivalent for aziridination of olefins,[10] we investigated the reaction of B(pin)-substituted allylic alcohol **1a** with *N*-aminophthalimide as the nitrogen source

Table 1. One-Pot Synthesis of 2-B(pin) Allylic Alcohols via 1-Alkenyl-1,1-heterobimetallic Intermediates



1a-l

entry	R	R′	allylic alcohol	yield (%)[a]
1	*n*-Bu	Ph	**1a**	70
2	*i*-Bu	Ph	**1b**	76
3	Bn	Ph	**1c**	68
4	Cy	Ph	**1d**	69
5	*i*-Pr	Ph	**1e**	81
6	$Ph(Me)CH_2$-	Ph	**1f**	62[a]
7	*i*-Pr	4-C_6H_4-OMe	**1g**	88
8	*i*-Pr	4-C_6H_4-Cl	**1h**	81
9	Cy	*n*-Bu	**1i**	85
10	*i*-Pr	*n*-Bu	**1j**	77
11	$PhCH_3(CH)$-	*n*-Bu	**1k**	61[b]
12	Bn	Cyclohexenyl	**1l**	79

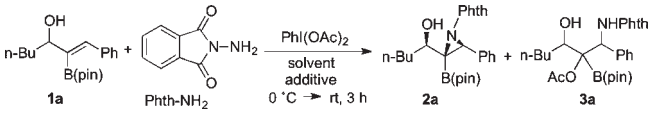
[a] Isolated yield. [b] dr = 7:1 (determined by ^1H NMR of crude reaction mixture); diastereomers separated by column chromatography and the major used in subsequent reactions.

mediated by the strong oxidant $PhI(OAc)_2$ (Table 2).[11] Aziridination product **2a** was not observed using $PhI(OAc)_2$ in CH_2Cl_2.[12] Instead a diastereomeric mixture of **3a** was formed, presumably via aziridine ring opening promoted by the AcOH generated during the nitrene formation (entry 1).[13] When excess K_2CO_3 was employed, however, aziridine **2a** was isolated in 46% yield with an encouraging diastereoselectivity (dr = 5:1, entry 2). Changing the solvent to toluene or CH_3CN led to complex mixtures (entries 3 and 4). Other additives or bases resulted in comparable diastereocontrol to K_2CO_3[14] and reduced yields (38−45%, entries 5−7) due to formation of byproduct **3a**. Surprisingly, by changing the addition order by adding $PhI(OAc)_2$ last, aziridine **2a** could be isolated in 62% yield with a good diastereomeric ratio (dr = 7:1) and only trace amounts of **3a** (**2a**/**3a** ≥ 95:5, entry 8).

The substrate scope of this method was next examined. As shown in Table 3, a wide range of B(pin)-substituted allylic alcohols were evaluated under the optimized conditions, providing the corresponding B(pin)-substituted aziridines **2b**−**l** in good yields (59−78%) with high levels of diastereoselectivity (typically ≥15:1). Because these products are prone to decompose in the presence of trace acid or Lewis acidic silica gel, their isolation was performed by passing a solution of the aziridine through a small pad of

(7) Sharpless, K.; Michaelson, R. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
(8) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1304.
(9) For reviews, see: (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006. (c) Hou, X. L.; Wu, J.; Fan, R.; Ding, C. H.; Luo, Z. B.; Dai, L. X. *Synlett* **2006**, 181. (d) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509.
(10) (a) Li, J.; Liang, J.-L.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 2685. (b) Krasnova, L. B.; Hili, R. M.; Chernoloz, O. V.; Yudin, A. K. *ARKIVOC* **2005**, *4*, 26. (c) Krasnova, L. B.; Yudin, A. K. *Org. Lett.* **2006**, *8*, 2011. (d) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194.
(11) For related examples on hypervalent iodine-mediated aziridination processes, see: (a) Richardson, R. D.; Desaize, M.; Wirth, T. *Chem.—Eur. J.* **2007**, *13*, 6745. (b) Fan, R.; Pu, D.; Gan, J.; Wang, B. *Tetrahedron Lett.* **2008**, *49*, 4925. (c) Moriarty, R. M.; Tyagi, S. *Org. Lett.* **2010**, *12*, 364.
(12) Other hypervalent iodine derivatives were also tested, but less satisfactory results were obtained. See SI for details.
(13) For the beneficial effect of the in situ generation of AcOH under these reaction conditions in a Pd-catalyzed aminoacetoxylation of alkenes, see: Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.
(14) See SI for a more detailed screening of additives.
(15) Unfortunately, aromatic groups at the carbinol position were not compatible with our reaction conditions, resulting in the oxidation of the B−C bond and leading to the corresponding α-hydroxy ketones as major byproducts.

Table 2. Optimization of the Reaction Conditions[a]



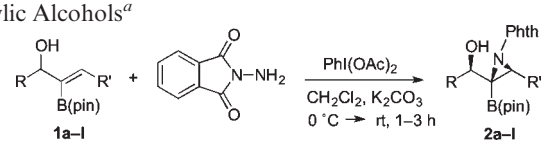
entry	solvent	additive	**2a**/**3a**[b]	dr (**2a**)[b]	yield (%)[c]
1	CH_2Cl_2	none	<5:95	--	--
2	CH_2Cl_2	K_2CO_3	83:17	5:1	46
3	Toluene[d]	K_2CO_3		*complex mixture*	
4	CH_3CN	K_2CO_3		*complex mixture*	
5	CH_2Cl_2	MS 4 Å	70:30	10:1	38
6	CH_2Cl_2	Cs_2CO_3	94:6	2:1	42
7	CH_2Cl_2	MgO	70:30	7:1	45
8[e]	CH_2Cl_2	K_2CO_3	>95:5	7:1	62

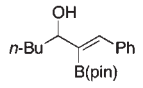
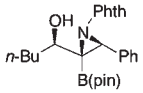
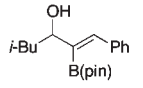
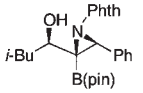
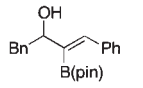
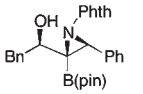
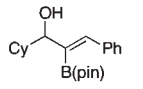
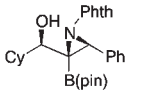
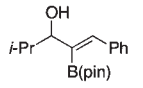
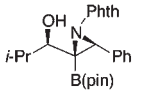
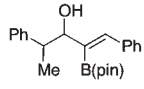
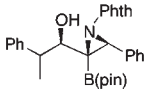
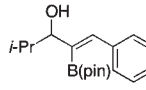
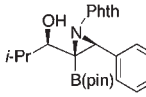
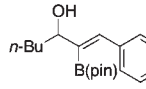
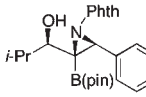
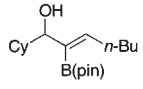
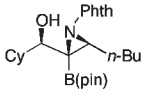
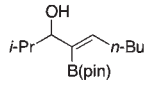
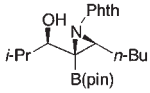
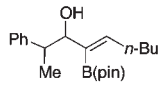
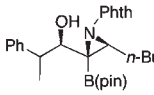
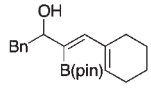
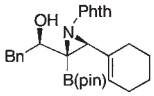
[a] Unless otherwise noted, all the reactions were performed by adding $PhI(OAc)_2$ to a suspension of **1a**, *N*-aminophthalimide, and the additive. [b] Determined by ^1H NMR of the crude reaction mixture. [c] Isolated yield. [d] 12 h. [e] Allylic alcohol **1a** was added the last.

deactivated silica gel. The reaction proceeded smoothly with styryl substrates bearing different alkyl substituents on the carbinol[15] to afford products **2a**–**f** (entries 1–6). Although the presence of an *i*-Bu group resulted in the formation of **2b** with moderate stereoselectivity (dr = 4:1, entry 2), excellent levels of diastereocontrol (dr ≥15:1) and yield (63–78%) were attained for other aliphatic substrates with either linear or branched chains (entries 3–6). Moreover, the method was successful with B(pin)-substituted allylic alcohols bearing 4-methoxy or 4-chloro substituents on the styryl moiety (**1g**–**h**). These substrates provided the desired products in 69–75% yield with excellent diastereoselectivity (dr > 20:1, entries 7–8). Likewise, substrates bearing alkyl groups on the vinyl moiety (**1i**–**k**) participated in the aziridination reaction to yield the corresponding adducts as single diastereomers (entries 9–11). Reaction with the challenging dienyl substrate **1l** occurred in good yield and diastereoselectivity (68%, dr = 15:1) with complete chemoselectivity in favor of aziridination at the allylic position (entry 12). This result suggests that these reactions are both accelerated and directed by the adjacent hydroxyl group.[16]

To confirm the stereochemistry of the aziridination and subsequent oxidation, X-ray diffraction analysis of product **2g** was carried out. The structure (Figure 1) clearly shows the relative *syn* stereochemistry between the aziridine ring and the hydroxy group.[17] The diastereoselection observed herein is consistent with other aziridinations of allylic alcohols that give rise to $A^{1,2}$ strain in one of the diastereomeric transition states.[18]

Table 3. Diastereoselective Aziridination of B(pin)-Substituted Allylic Alcohols[a]



entry	substrate		product		dr[b]	yield (%)[c]
1		**1a**		**2a**	7:1	62
2		**1b**		**2b**	4:1[d]	59
3		**1c**		**2c**	15:1	63
4		**1d**		**2d**	>20:1	76
5		**1e**		**2e**	>20:1	78
6		**1f**		**2f**	>20:1	71
7		**1g**		**2g**	>20:1	69
8		**1h**		**2h**	>20:1	75
9		**1i**		**2i**	>20:1	65
10		**1j**		**2j**	>20:1	72
11		**1k**		**2k**	>20:1	70
12		**1l**		**2l**	15:1	68

[a] All the reactions were carried out by adding $PhI(OAc)_2$ to a suspension of **1**, *N*-aminophthalimide, and K_2CO_3. [b] Determined by ^1H NMR from the crude reaction mixture. [c] Isolated yield. [d] Changing the addition order led to similar results

The B(pin)-substituted hydroxyaziridines were next evaluated as synthetic intermediates. We envisioned that further oxidation of the boronate ester would enable generation of valuable 1,3-aminohydroxy-2-ketones.[19] Preliminary studies on the oxidation of the B–C bond

(16) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(17) For related work on *syn*-diastereoselective aziridinations of allylic alcohols, see: (a) Atkinson, R. S.; Fawcett, J.; Russell, D. R.; Williams, P. J. *Tetrahedron Lett.* **1995**, *36*, 3241. (b) Atkinson, R. S.; Ulukanli, S.; Williams, P. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2121. (c) Coote, S. C.; O'Brien, P.; Whitwood, A. C. *Org. Biomol. Chem.* **2008**, *6*, 4299. (d) Cakici, M.; Karabuga, S.; Kilic, H.; Ulukanli, S.; Sahin, E.; Sevin, F. *J. Org. Chem.* **2009**, *74*, 9452.

(18) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.

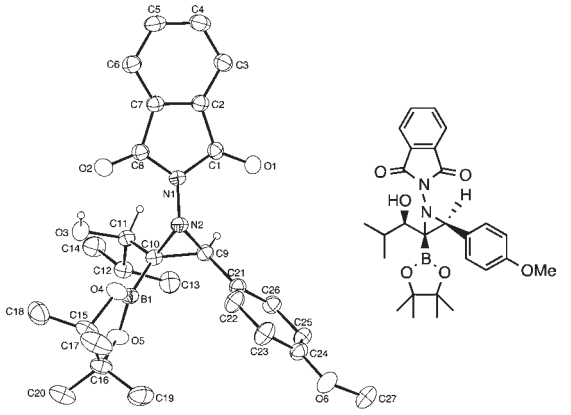


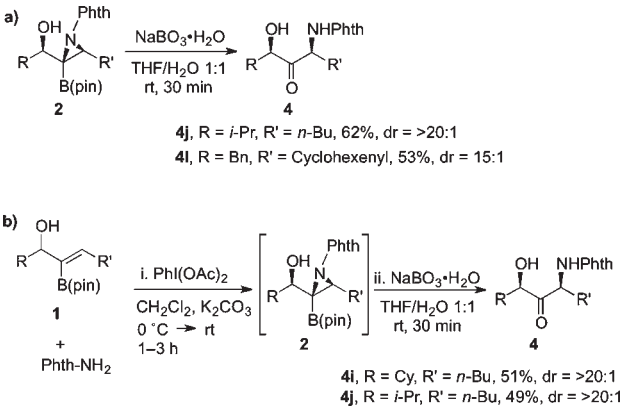
Figure 1. Crystal X-ray structure of aziridine **2g**.

under mild conditions ($NaBO_3 \bullet H_2O$ in THF/water at rt for 30 min) afforded the corresponding products **4j** and **4l** in moderate yields (53−62%, Scheme 2a). In addition, the tandem aziridination/B−C bond oxidation was studied to circumvent isolation of the B(pin)-substituted aziridine. Thus, after the completion of the aziridination, removal of the solvent and subsequent addition of $NaBO_3 \bullet H_2O$ in THF/water led to products **4i** and **4j** in 49−51% over two steps (Scheme 2b). Interestingly, the desired *syn*-aminohydroxyketones were formed as single diastereomers in both cases, suggesting that epimerization of the α-C−H's did not occur under the basic reaction conditions. The *syn* relative stereochemistry of the amino and hydroxy groups was established by single X-ray diffraction analysis of **4i** (Figure 2).

In summary, we have demonstrated that B(pin)-substituted allylic alcohols are very good substrates for aziridination reaction in the presence of hypervalent iodine $PhI(OAc)_2$ and *N*-aminophthalimide. This reaction gives rise to novel *syn*-B(pin)-substituted hydroxyaziridines in good yields (59−78%) and with high levels of diastereocontrol (typically ≥15:1). In addition, preliminary results demonstrate that the aziridination can be followed by oxidation of the B−C bond, delivering *syn*-1,3-aminohydroxy-2-ketones with excellent diastereoselectivity (dr > 20:1). Significantly, these studies indicate that the oxidation-sensitive three-coordinate B(pin) group is sufficiently

(19) For applications of 1,3-aminoalcohol derivatives in medicinal and synthetic chemistry, see for example: (a) Haight, A. R.; Stuk, T. L.; Allen, M. S.; Bhagavatula, L.; Fitzgerald, M.; Hannick, S. M.; Kerdesky, F. A. J.; Menzia, J. A.; Parekh, S. I.; Robbins, T. A.; Scarpetti, D.; Tien, J.-H. J. *Org. Process Res. Dev.* **1999**, *3*, 94. (b) Sham, H. L.; Zhao, C.; Li, L.; Betebenner, D. A.; Saldivar, A.; Vasavanonda, S.; Kempf, D. J.; Plattner, J. J.; Norbeck, D. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3101. (c) Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2007**, *48*, 3793. (d) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.

Scheme 2. Synthesis of 1,3-Aminohydroxy-2-ketones



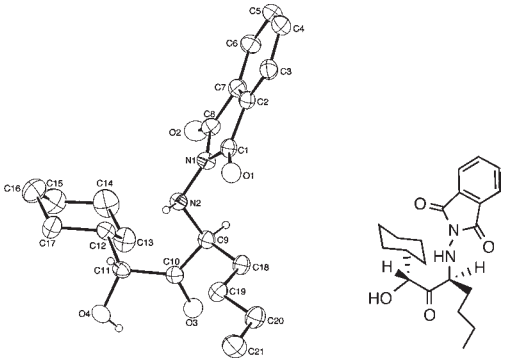


Figure 2. Crystal X-ray structure of 1,3-aminohydroxy-2-ketone **4i**.

stable to withstand the oxidant $PhI(OAc)_2$ and the aziridination agent. Thus, this study illustrates a surprising change in chemoselectivity.

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Supporting Information Available. Experimental and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.