ger, Jr., *Biochemistry* **1998**, *37*, 14659; d) J. A. Broadwater, J. Ai, T. M. Loehr, J. Sanders-Loehr, B. G. Fox, *Biochemistry* **1998**, *37*, 14664.

[23] a) K. Kim, S. J. Lippard, *J. Am. Chem. Soc.* **1996**, *118*, 4914; b) T. Ookubo, H. Sugimoto, T. Nagayama, H. Masuda, T. Sato, K. Tanaka, Y. Maeda, H. Okawa, Y. Hayashi, A. Uehara, M. Suzuki, *J. Am. Chem. Soc.* **1996**, *118*, 701; c) D. D. LeCloux, A. M. Barrios, T. J. Mizoguchi, S. J. Lippard, *J. Am. Chem. Soc.* **1998**, *120*, 9001.

[24] a) J. N. Burstyn, J. A. Roe, A. R. Miksztal, B. A. Shaevitz, G. Lang, J. S. Valentine, *J. Am. Chem. Soc.* **1988**, *110*, 1382; b) E. Münck, L. Que, Jr., unpublished results; c) A. J. Simaan, F. Banse, J.-J. Girer, K. Wieghardt, E. Bill, *Inorg. Chem.* **2001**, ASAP.

[25] a) N. Kitajima, N. Tamura, H. Amagai, H. Fukui, Y. Moro-oka, Y. Mizutani, T. Kitagawa, R. Mathur, K. Heerwegh, C. A. Reed, C. R. Randall, L. Que, Jr., K. Tatsumi, *J. Am. Chem. Soc.* **1994**, *116*, 9071; b) B. A. Brennan, Q. Chen, C. Juarez-Garcia, A. E. True, C. J. O'Connor, L. Que, Jr., *Inorg. Chem.* **1991**, *30*, 1937; c) A. L. Balch, Y.-W. Chan, R.-J. Cheng, G. N. La Mar, L. Latos-Grażyñski, M. W. Renner, *J. Am. Chem. Soc.* **1984**, *106*, 7779.

[26] a) A. L. Feig, S. J. Lippard, *Chem. Rev.* **1994**, *94*, 759; b) E. I. Solomon, T. C. Brunold, M. I. Davis, J. N. Kemsley, S.-K. Lee, N. Lehnert, F. Neese, A. J. Skulan, Y.-S. Yang, J. Zhou, *Chem. Rev.* **2000**, *100*, 235.

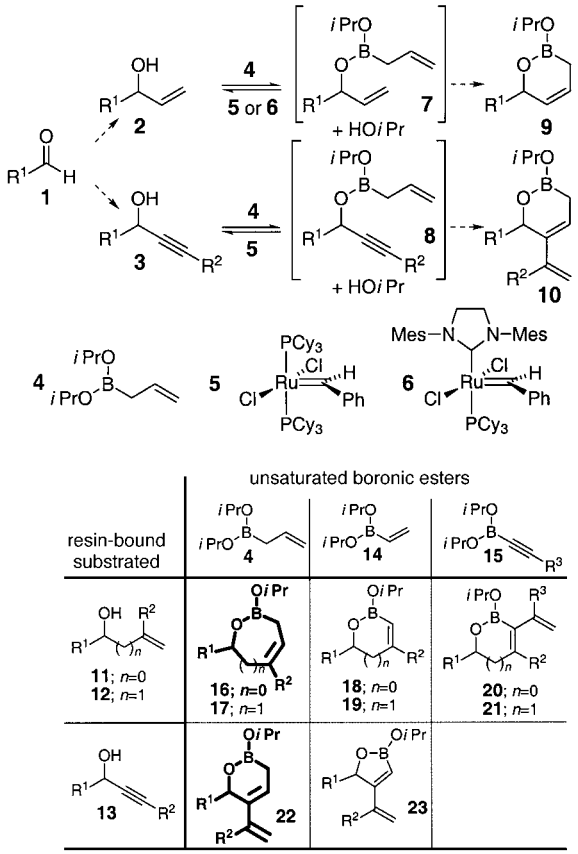
[27] R. L. Rardin, W. B. Tolman, S. J. Lippard, *New J. Chem.* **1991**, *15*, 417.

A Boronic Ester Annulation Strategy for Diversity-Oriented Organic Synthesis**

Glenn C. Micalizio and Stuart L. Schreiber*

Diversity-oriented organic synthesis[1] can be used to prepare complex and diverse small molecules efficiently. By coupling this approach to phenotypic and proteomic screening, a systematic means to explore biology may be realized.[2, 3] Although efficient pathways leading to families of structurally complex small molecules are being reported with increasing frequency,[4] pathways leading to structurally diverse products, with many different skeletal arrays, are rare. The primary reason for this gap in our planning capabilities is that efficient and effective "branching" pathways remain elusive. Such pathways require the identification of a substrate or class of substrates that can be differentially manipulated, in single transformations, to afford products containing distinct skeletal arrays of connecting atoms. Here we report new annulation reactions of unsaturated boronic esters with allylic and propargylic alcohols, as well as oxidation and cycloaddition reactions of the resulting cyclic organoboronic esters, which are well-suited for diversity-generating, branching pathways.[5, 6]

We anticipated that the transesterification of unsaturated boronic esters (**4**) with allylic (**2**) or propargylic alcohols (**3**) would transiently provide mixed organoboronic esters (**7** or **8**) (Scheme 1),[7] which could be trapped using ring-closing metathesis[8] to afford cyclic boronic esters (**9** and **10**).[9] The pairing of unsaturated carbinols (**11**, **12**, or **13**) and unsaturated boronic esters (**4**, **14**, or **15**) was envisioned to provide a diverse family of boron-containing heterocycles (**16**–**23**) whose unsaturation would facilitate subsequent functionalization rections.



Scheme 1. Boronic ester annulation and conceptual matrix of resulting boron-containing heterocycles; bolded structures illustrate the skeletal types realized in this study. Mes = mesitoyl = 2,4,6-trimethylphenyl.

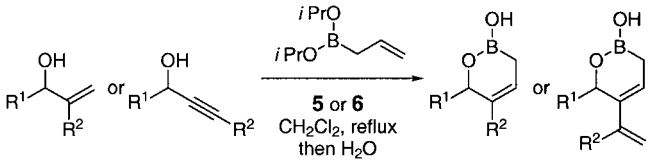
The annulation was tested with the triisopropylsilyl ether containing propargylic (**24**) and allylic alcohols (**25** and **26**) as a model for the alkylsilyl-tethered, high-capacity solid support[10] used in a one-bead, one-stock solution technology platform.[11] Treatment of propargylic alcohol **24** with allylboronic ester **4**[12] and Grubbs' catalyst (**5**) in CH_2Cl_2 at reflux afforded the cyclic dienylic boronic acid **31** in 91% yield (Table 1, entry 1). The allylic alcohol **25** was transformed under similar reaction conditions to the cyclic allylboronic acid **32** (84% yield), whereas the substituted allylic alcohol **26** afforded **33**, which, after oxidation, gave the stereodefined trisubstituted olefin **38** in 56% overall yield (Table 1, entries 2 and 3). The annulation-oxidation sequence was similarly

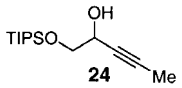
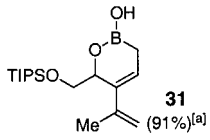
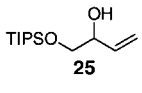
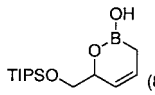
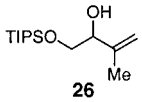
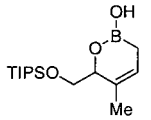
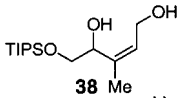
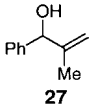
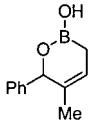
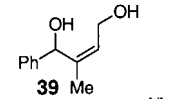
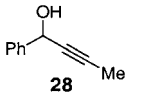
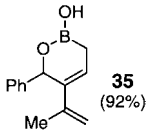
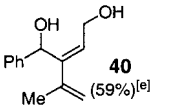
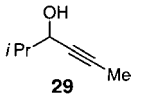
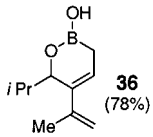
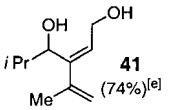
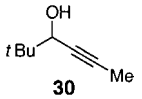
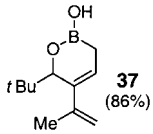
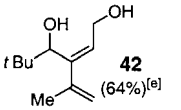
[*] Prof. S. L. Schreiber, Dr. G. C. Micalizio
Howard Hughes Medical Institute
Department of Chemistry and Chemical Biology, and
Harvard Institute of Chemistry and Cell Biology (ICCB)
Harvard University, 12 Oxford St.
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-0751
E-mail: sls@slsiris.harvard.edu

[**] We thank the National Institute of General Medical Sciences (GM-52067) for support of this work. The Harvard ICCB is supported by Merck & Co., Merck KGaA, the Keck Foundation, and the National Cancer Institute. G.C.M. is a Merck Postdoctoral Fellow of the Helen Hay Whitney Foundation. S.L.S. is an Investigator with the Howard Hughes Medical Institute at the Department of Chemistry and Chemical Biology, Harvard University.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

Table 1. Allylboronic ester annulation.

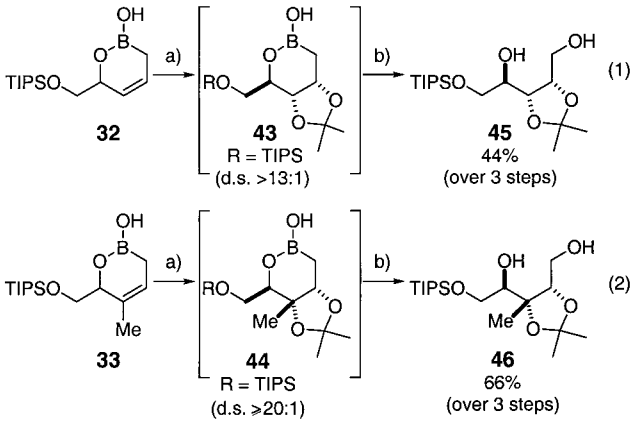


Entry	Substrate	Annulation product (yield)	Oxidation product
1	 **24**	 **31** (91%)[a]	
2	 **25**	 **32** (84%)[b]	
3	 **26**	 **33**	 **38** (56% over 2 steps)[c]
4	 **27**	 **34**	 **39** (60% over 2 steps)[d]
5	 **28**	 **35** (92%)	 **40** (59%)[e]
6	 **29**	 **36** (78%)	 **41** (74%)[e]
7	 **30**	 **37** (86%)	 **42** (64%)[e]

Annulation conditions: [a] **4** (3 equiv), **5** (20 mol%), CH_2Cl_2, reflux; [b] **4** (3 equiv), **5** (10 mol%), CH_2Cl_2, reflux; [c] **4** (2 equiv), **6** (12 mol%), CH_2Cl_2, reflux; [d] **4** (2 equiv), **6** (7 mol%), CH_2Cl_2, reflux; [e] **4** (2 equiv), **5** (8–9 mol%), CH_2Cl_2, reflux. Oxidation conditions: H_2O_2, NaOH (1N), THF, RT.

effective with the doubly activated allylic alcohol **27** to afford the trisubstituted *Z* olefin **39** in 60% yield (Table 1, entry 4). Aromatic- as well as alkyl-substituted propargylic alcohols (**28**–**30**) were excellent substrates for the annulation and provided the cyclic dienylic boronic acids **35**–**37** in 78–92% yield (Table 1, entries 5–7). Oxidation of **35**–**37** then gave the stereodefined trisubstituted dienylic carbinols **40**–**42** (59–74% yield).

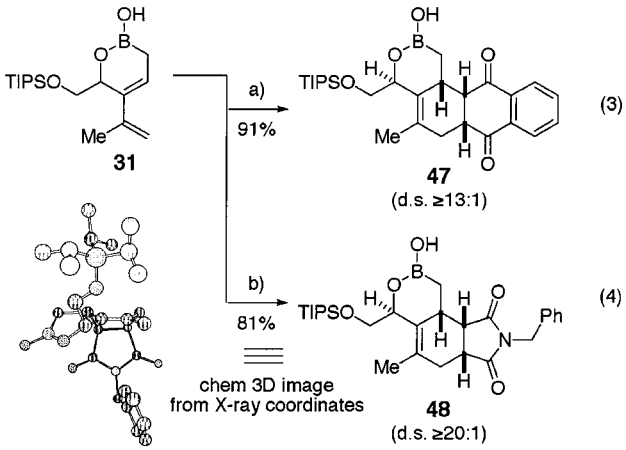
The cyclic allylboronic acids (**32** and **33**) are excellent substrates for diastereoselective dihydroxylation.[13] A three-step reaction sequence[14] converted the cyclic boronic acid **32** into the differentially functionalized xylitol derivative **45** with >13:1 diastereoselectivity [Scheme 2, Eq. (1)]. Similarly, the trisubstituted allylboronic acid **33** was converted into the



Scheme 2. Chemoselective and diastereoselective oxidation reactions of cyclic allylboronic acids. a) OsO_4, NMO, acetone, pH 7 buffer; then 2,2-dimethoxypropane, CH_2Cl_2, PPTS; b) H_2O_2, NaOH, THF. NMO = 4-methylmorpholine *N*-oxide, PPTS = pyridinium *p*-toluene sulfonate, TIPS = triisopropylsilyl.

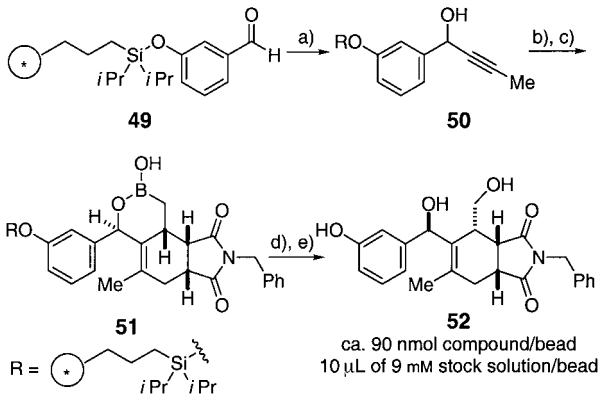
xylitol derivative **46** containing a tertiary ether with >20:1 diastereoselectivity [Scheme 2, Eq. (2)].[15]

The boracycles can be converted efficiently into small molecules having completely different skeletons. For example, Diels–Alder cycloadditions of the dienylic boronic acid **31** provided stereoselective access to the tetracyclic and tricyclic heterocycles **47** (d.s. ≥ 13:1) and **48** (d.s. ≥ 20:1; Scheme 3). Importantly, the entire reaction sequence leading to **52** was performed efficiently on the high-capacity bead-linker reagent used in a one-bead, one-stock solution platform[10] for chemical genetics (Scheme 4).[16]



Scheme 3. Diastereoselective Diels–Alder cycloaddition reactions of cyclic dienylic boronic acids. a) 1,4-Naphthoquinone, PhMe, 70°C; b) *N*-benzylmaleimide, PhMe, 70°C.

This boronic ester based approach to diversity-oriented synthesis yields complex structures (namely, **35**, **40**, **46**, **47**, and **48**) containing multiple rings, stereocenters, and unsaturated units in only one to four steps. The products of this approach are strikingly dissimilar—the result of "branching" as described in the introduction. Therefore, we believe that the chemistry reported herein is promising in terms of its



Scheme 4. Boronic ester annulation/Diels–Alder cycloaddition sequence performed on the high capacity bead-linker reagent used in a one-bead, one-stock solution platform for chemical genetics. a) 1-propynylmagnesium bromide, THF, 0 °C → RT; b) **4** (10 equiv), **5** (15 mol %), CH_2Cl_2, 40 °C; c) *N*-benzylmeleimide (8 equiv), PhMe, 80 °C; d) H_2O_2, NaOH, THF; e) HF · pyr/pyr, THF. pyr = pyridine.

potential to provide access to complex and diverse small molecules efficiently.

Received: October 11, 2001 [Z18047]

[1] S. L. Schreiber, *Science* **2000**, *287*, 1964 – 1969.

[2] a) S. L. Schreiber, *Bioorg. Med. Chem.* **1998**, *6*, 1127 – 1152; b) T. J. Mitchison, *Chem. Biol.* **1994**, *1*, 3 – 6.

[3] For a recent example, see T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber, T. J. Mitchison, *Science* **1999**, *286*, 971 – 974.

[4] For recent examples, see a) R. Xu, G. Greiveldinger, L. E. Marenus, A. Cooper, J. A. Ellman, *J. Am. Chem. Soc.* **1999**, *121*, 4898 – 4899; b) D. Lee, J. K. Sello, S. L. Schreiber, *J. Am. Chem. Soc.* **1999**, *121*, 10648 – 10649; c) D. R. Spring, S. Krishnan, S. L. Schreiber, *J. Am. Chem. Soc.* **2000**, *122*, 5656 – 5657; d) D. Lee, J. K. Sello, S. L. Schreiber, *Org. Lett.* **2000**, *2*, 709 – 712; e) H. E. Pelish, N. J. Westwood, Y. Feng, T. Kirchhausen, M. D. Shair, *J. Am. Chem. Soc.* **2001**, *123*, 6740 – 6741.

[5] For a review of allylboration chemistry, see a) W. R. Roush, *Methods Org. Chem. (Houben-Weyl) 4th ed. 1952 –*, *Vol. E21b*, **1995**, pp. 1410 – 1486. For a review of Suzuki chemistry, see b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457 – 2483. For an example of vinyl addition to an imine, see c) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445 – 446. For examples of Diels – Alder cycloadditions, see d) D. S. Matteson, J. O. Waldbillig, *J. Org. Chem.* **1963**, *28*, 366 – 369; e) M. Vaultier, F. Truchet, B. Carboni, R. W. Hoffmann, I. Denne, *Tetrahedron Lett.* **1987**, *28*, 4169 – 4172. For examples of [3+2] cycloadditions, see f) D. S. Matteson, *J. Org. Chem.* **1962**, *27*, 4293 – 4300; g) R. H. Wallace, J. Liu, *Tetrahedron Lett.* **1994**, *35*, 7493 – 7496. For a general review of organoboronic ester chemistry in organic synthesis, see h) D. S. Matteson, *Stereodirected Synthesis with Organoboranes*, Springer, Berlin, **1995**, p. 405.

[6] T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2000**, *611*, 392 – 402.

[7] For examples of intramolecular allylation through temporary tethering through a B–O linkage, see a) Z. Wang, X.-J. Meng, G. W. Kabalka, *Tetrahedron Lett.* **1991**, *32*, 1945 – 1948; b) Z. Wang, X.-J. Meng, G. W. Kabalka, *Tetrahedron Lett.* **1991**, *32*, 4619 – 4622; c) Z. Wang, X.-J. Meng, G. W. Kabalka, *Tetrahedron Lett.* **1991**, *32*, 5677 – 5680; d) G. W. Kabalka, C. Narayana, N. K. Reddy, *Tetrahedron Lett.* **1996**, *37*, 2181 – 2184; e) L. J. Brzezinski, J. W. Leahy, *Tetrahedron Lett.* **1998**, *39*, 2039 – 2042. For examples of intramolecular Diels – Alder cycloaddition by temporary tethering through a B–O linkage, see f) R. A. Batey, A. N. Thadani, A. J. Lough, *J. Am. Chem. Soc.* **1999**, *121*, 450 – 451.

[8] For recent reviews of olefin metathesis, see a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413 – 4450; b) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140 – 3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012 – 3043.

[9] For examples of ring-closing metathesis of vinylboronic esters, see a) J. Renaud, S. G. Ouellet, *J. Am. Chem. Soc.* **1998**, *120*, 7995 – 7996; b) J. Renaud, C.-D. Graf, L. Oberer, *Angew. Chem.* **2000**, *112*, 3231 – 3234; *Angew. Chem. Int. Ed.* **2000**, *39*, 3101 – 3104. For an example of crossed metathesis of a vinylboronic ester, see c) H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A. Washenfelder, D. A. Bussmann, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 58 – 71. For ring-closing metathesis of aminoboranes, see d) A. J. Ashe III, X. Fang, *Org. Lett.* **2000**, *2*, 2089 – 2091. For ring-closing metathesis tethered through a silyl ether, see e) S. Chang, R. H. Grubbs, *Tetrahedron Lett.* **1997**, *38*, 4757 – 4760; f) R. E. Taylor, F. C. Engelhardt, M. J. Schmitt, H. Yuan, *J. Am. Chem. Soc.* **2001**, *123*, 2964 – 2969; g) Q. Yao, *Org. Lett.* **2001**, *3*, 2069 – 2072; h) S. E. Denmark, S.-M. Yang, *Org. Lett.* **2001**, *3*, 1749 – 1752.

[10] J. A. Tallarico, K. D. Depew, H. E. Pelish, N. J. Westwood, C. W. Lindsley, M. D. Shair, S. L. Schreiber, M. A. Foley, *J. Comb. Chem.* **2001**, *3*, 312 – 318.

[11] a) H. E. Blackwell, L. Perez, R. A. Stavenger, J. A. Tallarico, E. Cope Etough, M. A. Foley, S. L. Schreiber, *Chem. Bio.* **2001**, in press; b) P. A. Clemons, A. N. Koehler, B. K. Wagner, T. O. Sprigings, D. R. Spring, R. W. King, S. L. Schreiber, M. A. Foley, *Chem. Biol.* **2001**, in press.

[12] H. C. Brown, U. S. Racherla, P. J. Pellechia, *J. Org. Chem.* **1990**, *55*, 1868 – 1874.

[13] For an example of olefin dihydroxylation in the presence of phenylboronic acid, see N. Iwasawa, T. Kato, K. Narasaka, *Chem. Lett.* **1988**, 1721 – 1724.

[14] V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, 1973 – 1976.

[15] The stereochemistry of the acetonides (**43** and **44**) was established by analysis of NOE data (see Supporting Information).

[16] Cleavage of 100 beads containing the diol derived from oxidation of **51** provided 5.5 mg of crude **52** which was estimated to be > 70 % pure on inspection of the ^{1}H NMR data (see Supporting Information).

Microporous Supramolecular Coordination Compounds as Chemosensory Photonic Lattices**

Gary A. Mines, Biing-Chiau Tzeng, Keith J. Stevenson, Jialiang Li, and Joseph T. Hupp*

Chemical sensing—whether for human health assessment, environmental quality monitoring, or myriad other purposes—generally entails: a) recognition and binding, adsorption, or other interaction with the molecule or ion to be sensed, and b) transduction of the recognition/binding event into an externally observable signal.[1] Coordination-based supramolecular chemistry, with its ability to generate an enormous

[*] Prof. Dr. J. T. Hupp, Dr. G. A. Mines, Dr. B.-C. Tzeng, Dr. K. J. Stevenson, J. Li
Dept. of Chemistry and Center for Nanofabrication and Molecular Self-Assembly
Northwestern University
2145 Sheridan Road, Evanston, IL 60208 (USA)
Fax: (+1) 847-491-7713
E-mail: jthupp@chem.nwu.edu

[**] Support from the U.S. National Science Foundation and the Water Environment Research Foundation is gratefully acknowledged. We thank Ryan C. Bailey for performing AFM measurements and Melissa Merlau for donating samples of compound **1**.

  0044-8249/02/11401-0162 $ 17.50+.50/0