ORGANOMETALLICS

Communication

pubs.acs.org/Organometallics

Thermodynamically Controlled, Dynamic Binding of Diols to a 1,2-BN Cyclohexane Derivative

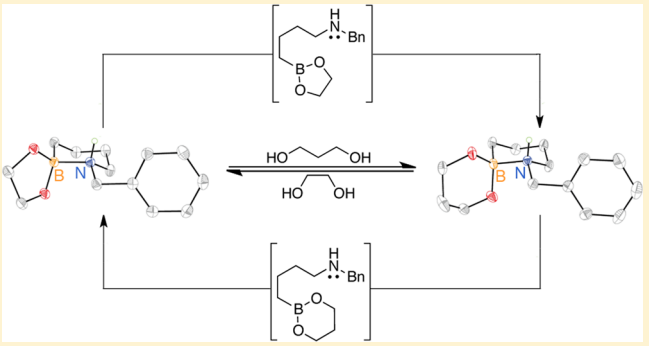
Gregory P. Harlow,[†] Lev N. Zakharov,[†,§] Gang Wu,[‡] and Shih-Yuan Liu*[,†]

[†]Department of Chemistry and Biochemistry, University of Oregon, Eugene, Oregon 97403-1253, United States

[‡]Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada

Supporting Information

ABSTRACT: The reversible covalent binding of diols to an *N*-Bn 1,2-BN cyclohexane has been studied by ^{11}B and ^{1}H NMR spectroscopy and single-crystal X-ray diffraction analysis. The activation barrier for the reversible B−N Lewis acid−base interaction has been measured by variable-temperature NMR with bound (2*R*,3*R*)-(−)-2,3-butanediol (T_c = −40 °C, $\Delta G^{\ddagger}$ = 11.2 ± 0.2 kcal mol^{-1}). Deuterium labeling experiments demonstrate that ligand exchange is reversible and rapid at room temperature, and competitive binding studies establish diol association as a thermodynamically controlled process.



Polyhydroxylated molecules play a pivotal role in biochemical processes as signaling compounds. Considerable effort has been devoted to mimic nature's receptors to bind important classes of biomolecules, such as saccharides,[1] nucleosides,[2] and catecholamines.[3] Boron-containing compounds have become attractive targets as small-molecule chemosensors, given their propensity to form reversible, high-affinity covalent interactions with *cis*-diols.[4] For example, the mechanism of action for a family of antibacterial diazaborine compounds relies on formation of a tetrahedral boronate ion by a covalent B−O linkage to the NAD^+ nicotinamide ribose 2′-hydroxyl group.[5a] The significance of this interaction to affect the drug's inhibitory properties was demonstrated by replacement of the diazaborine boron (B)−nitrogen (N) bond with an isoelectronic carbon−carbon unit. Despite similarities in both their chemical and physical properties, the carbonaceous analogue of the diazaborine ring is shown to be biologically inactive.[5b]

Our research group seeks to expand upon the structural diversity achieved in nature through the application-driven synthesis and characterization of BN-containing heterocycles (Figure 1).[6] The BN/CC isosterism strategy has led to the development of compounds possessing unique reactivity profiles[7] and photophysical[8] and biological[9] properties distinct from those of their all-carbon analogues. In this tradition, we were interested in exploring the potential of 1,2-BN heterocycles as a new class of boron-containing receptors for polyol sensing. Herein, we describe the synthesis and structural characterization of a 1,2-BN cyclohexane derivative chelated to 1,2-, 1,3-, and 1,4-diols. Furthermore, we establish that ligand exchange at boron is rapid and that diol binding is a thermodynamically controlled process.

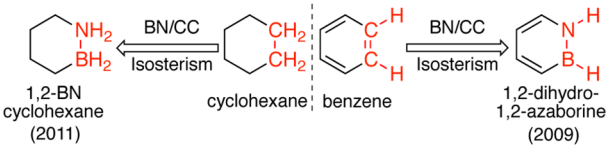


Figure 1. BN/CC isosterism.

Our initial efforts to complex 1,2-azaborines with diols in a bidentate fashion proved unsuccessful, presumably due to the aromatic nature of these heterocycles.[10] We therefore shifted our attention toward the all-saturated analogue 1,2-BN cyclohexane.[11] The *N*-benzyl derivative **1**, previously reported by Rona et al.,[12] was envisioned to serve as a versatile precursor for the synthesis of the desired bidentate adduct upon diol addition (Scheme 1). Gratifyingly, addition of 1,3-propanediol proceeded cleanly to afford the air- and moisture-stable complex **2** in 96% isolated yield. Single crystals suitable for X-ray diffraction were grown from a saturated solution in chloroform-*d*, thereby unambiguously confirming bidentate boron coordination and nitrogen protonation. Structural parameters for **2** are consistent with simultaneous boron coordination by the chelating 1,3-diol, as both B−O bond distances are nearly identical in length (B−O(1) = 1.458(3) Å vs B−O(2) = 1.476(3) Å).

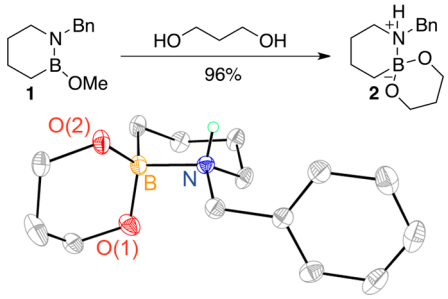
Synthesis and solid-state characterization have also been accomplished for the five- and seven-membered chelate ring

Special Issue: Applications of Electrophilic Main Group Organometallic Molecules

Received: July 16, 2013
Published: August 15, 2013

   dx.doi.org/10.1021/om400697r | *Organometallics* 2013, 32, 6650−6653

Scheme 1. Synthesis of the 1,3-Diol Complex 2[a]



[a]ORTEP illustration for **2** drawn with thermal ellipsoids at the 35% probability level (hydrogen atoms have been omitted for clarity). Bn = benzyl.

sizes by analogous protocols.[13] Distinct peak separation by ^{11}B NMR illustrates a convenient method to distinguish among 1,2-, 1,3-, and 1,4-adducts in solution (Table 1). Unexpectedly,

Table 1. Comparison of Solution (CH_2Cl_2) and Solid-State ^{11}B NMR Chemical Shifts (ppm) for 1,2-, 1,3-, and 1,4-Diol Complexes

ring size	solution	solid state
5	9.8	8.6
6	25.4	3.7
7	6.6	6.2

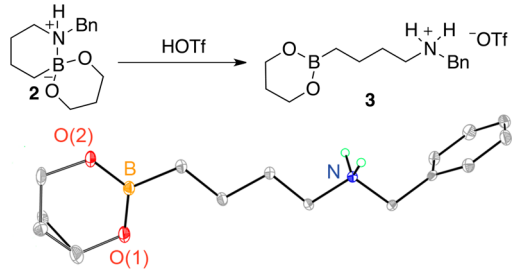
the six-membered complex is observed to possess a ^{11}B resonance at 25.4 ppm in solution, suggesting substantial trigonal-planar character at boron.[14] A comparison with solid-state ^{11}B NMR reveals a significant discrepancy between solution and solid-state chemical shifts. On the basis of prior investigations by Anslyn and co-workers with *o*-(aminomethyl)-arylboronates, we postulate that the 25.4 ppm ^{11}B resonance is a time-averaged signal between a tetracoordinate (3.7 ppm) and trigonal-planar (~30 ppm) boron atom.[15] This observation is consistent with the in situ dynamics reported previously for Wulff-type boronic acids, where a dative 1,5-N→B interaction participates in reversible association.[1a,b,16]

This foregoing observation motivated us to perform a series of mechanistic studies to elucidate the strength and nature of the N→B dative bond. Addition of 1 equiv of triflic acid to a −30 °C solution of **2** in methylene chloride afforded a single resonance by ^{11}B NMR at 31.3 ppm. Unambiguous structural assignment by single-crystal X-ray analysis confirmed the identity of **3** as the acyclic ammonium salt (Scheme 2). Significant contraction of both B−O bond distances is consistent with strengthening of the covalent B−O interaction due to increased electron donation of the oxygen lone pair into the p orbital of boron (B−O(1) = 1.353(2) Å and B−O(2) = 1.364(2) Å).

To support our hypothesis that the 25.4 ppm ^{11}B resonance for **2** is averaged on the NMR time scale, low-temperature ^{11}B NMR was performed in 10 K increments to 234 K in CH_2Cl_2 (Scheme 3). Upon gradual temperature depression, an upfield shift toward the 3.7 ppm solid-state resonance is observed. This trend is consistent with increasing sp^3 character at boron, likely resulting from a stronger, more covalent N→B interaction.[14,16a]

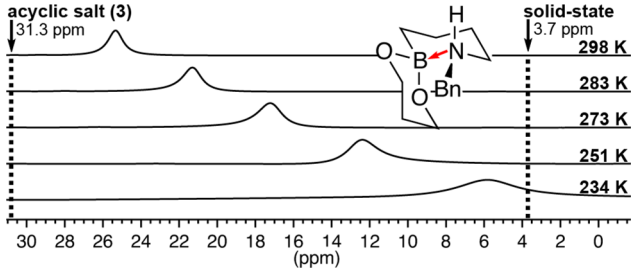
We anticipated that the synthesis of chiral complex **4** would allow for the proposed process of reversible N→B association to be observable by variable-temperature ^{1}H NMR (Scheme 4).

Scheme 2. Synthesis of Acyclic Ammonium Salt 3[a]

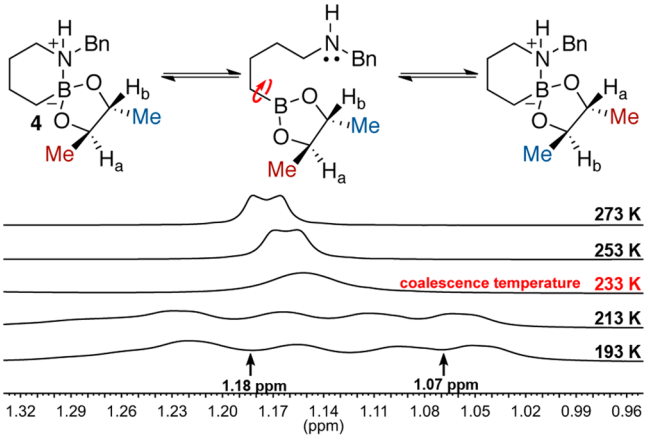


[a]ORTEP illustration for **3** drawn with thermal ellipsoids at the 35% probability level. One of the carbon atoms in the six-membered B−O cycle is disordered over two positions in the ratio 0.815/0.185 (hydrogen atoms and triflate counterion have been omitted for clarity). Bn = benzyl, Tf = trifluoromethanesulfonyl.

Scheme 3. Temperature Dependence of the ^{11}B Chemical Shift for Complex 2 in CH_2Cl_2



Scheme 4. Temperature Dependence of the ^{1}H Signals for the Diastereotopic Methyl Groups in 4 in CD_2Cl_2

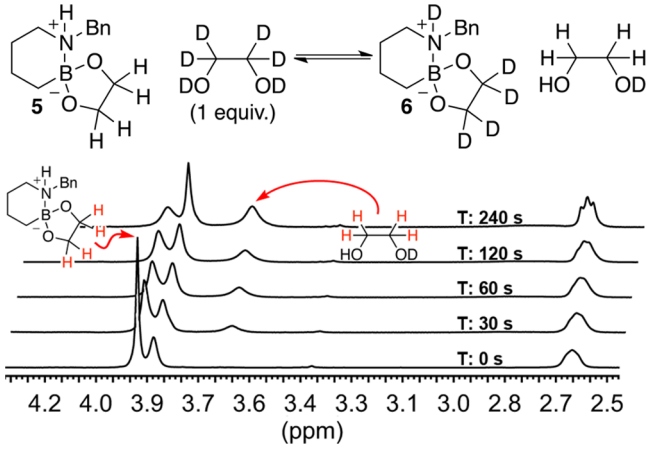


A J. Young tube containing **4** in CD_2Cl_2 was cooled to 273 K, and its ^{1}H NMR spectrum was recorded in 20 K increments. At 298 K, the diastereotopic methyl groups resonate together as a single, sharp doublet integrating to six protons. When the temperature was lowered to 233 K, the reversible Lewis acid−base interaction became sufficiently slow on the NMR time scale that broadening and distinct signal separation into two sets of doublets was observed. By a modified Arrhenius equation, the activation energy for the proposed dynamic process in Scheme 4 is estimated to be 11.2 ± 0.2 kcal mol^{-1} (T_c = −40 °C, $\Delta\nu$ = 33 Hz).[17,18]

We examined the viability of ligand exchange from complex **5** using deuterium labeling (Scheme 5). When 1 equiv of ethylene glycol-d_6 was added to a CD_2Cl_2 solution containing **5**, a decrease in the relative intensity of the 3.93 ppm signal

dx.doi.org/10.1021/om400697r | *Organometallics* 2013, 32, 6650−6653

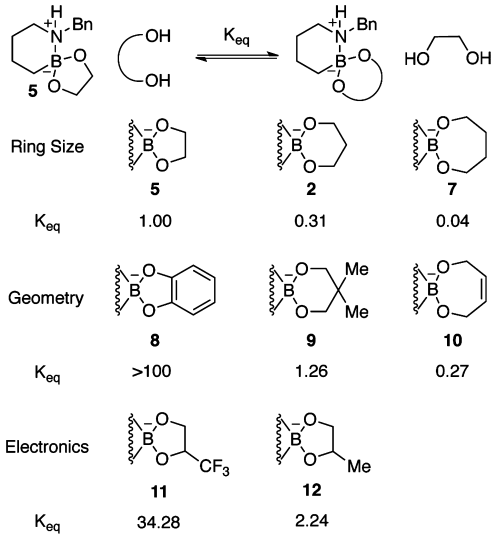
Scheme 5. ^{1}H NMR Analysis of Ligand Exchange for Complex 5 in CD_2Cl_2



corresponding to the four glycol protons was observed. In tandem, a new resonance emerged at 3.66 ppm, confirmed by spiking experiments to be consistent with ejected ethylene glycol.[13] Within 4 min, the integrated areas of free and bound ethylene glycol were approximately equal, and no further change in the NMR spectrum was observed ($K_{eq} \approx 1$). The reverse process, beginning with a solution containing deuterated complex **6**, was shown to be consistent with these results.[13]

We used ^{11}B and ^{1}H NMR spectroscopy to determine trends in preferential polyol complexation by quantifying the equilibrium constant for the exchange reaction illustrated in Table 2. The observed K_{eq} values demonstrate that binding of

Table 2. Equilibrium Constants Calculated by Competitive Exchange Starting with 5[a]



[a]Experimental procedure adapted from ref 20. Equilibrium constants measured in CD_2Cl_2.

1,3-propanediol (**2**) and 1,4-butanediol (**7**) is energetically unfavorable relative to formation of the 1,2-glycol complex **5**. The K_{eq} data for systems **8**–**10** show that preorganization of the ligand into a *cis* geometry can improve the binding strength. Complex **9**, in which a 1,3-diol is geminally disubstituted at the C(2) position, exhibits a nearly 4-fold increase in K_{eq} relative to **2**. We attribute this result to a Thorpe–Ingold effect, where a dimethyl repulsion contracts the inner ∠C–C–C of the 2,2-dimethyl-1,3-propanediol ligand to promote *cis* chelation.[19] Notably, the conformational rigidity imparted by a *cis*-olefin relays a significant increase in the association constants for **8** and **10** relative to **5** and **7**, respectively. Finally, the substantial difference in the binding constants between **11** and **12** illustrates that an increase in the acidity of the chelating ligand has a marked impact on the strength of diol association. This observation is consistent with the conclusions reported by Pizer and co-workers for related binding studies on boronic acids.[4c] The data for **8** and **11** reveal that, among the parameters studied, the most significant consideration for high-affinity binding is the diminished pK_a value of the complexing diol ligand.

To conclude, we have synthesized a new class of polyol complexes derived from the 1,2-BN cyclohexane framework. Diol binding is shown to be a high-affinity process that affords air- and moisture-stable bidentate complexes in near-quantitative yield. ^{11}B NMR is used as a technique to conveniently distinguish among five-, six-, and seven-membered diol complexes in solution. Molecular dynamics analysis by VT NMR reveals an activation barrier of approximately 11.2 ± 0.2 kcal mol^{-1} for the reversible Lewis acid–base N→B interaction. Deuterium labeling experiments established that ligand exchange is reversible and rapid at room temperature. We have also shown through competitive binding experiments that the 1,2-BN cyclohexane framework possesses an inherent thermodynamic preference for a five-membered chelate ring size, *cis*-binding geometry, and acidic diol ligands.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and CIF files giving experimental procedures, spectroscopic data, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for S.-Y.L.: lsy@uoregon.edu.

Author Contributions

§Correspondence regarding crystal structures should be directed to Dr. Lev Zakharov: lev@uoregon.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for G.P.H. has been provided by the Arnold and Mabel Beckman Foundation and the Camille & Henry Dreyfus Foundation. Funding for the University of Oregon Chemistry Research and Instrumentation Services has been furnished in part by the NSF (CHE-0923589). We thank Andrew Baggett for fruitful intellectual discussions and for serving as a graduate student mentor to G.P.H.

■ REFERENCES

(1) (a) James, T. D.; Sandanayake, K. R. A. S.; Iguchi, R.; Shinkai, S. *J. Am. Chem. Soc.* **1995**, *117*, 8982–8987. (b) Wulff, G. *Pure Appl. Chem.* **1982**, *54*, 2093–2102. (c) Badugu, R.; Lakowicz, J. R.; Geddes, C. D. *Curr. Opin. Biotechnol.* **2005**, *16*, 100–107. (d) Suri, J. T.; Cordes, D. B.; Cappuccio, F. E.; Wessling, R. A.; Singaram, B. *Angew.*

Chem., Int. Ed. **2003**, *42*, 5857−5859. (e) Dowlut, M.; Hall, D. G. *J. Am. Chem. Soc.* **2006**, *128*, 4226−4227.
(2) (a) Ojida, A.; Takashima, I.; Kohira, T.; Nonaka, H.; Hamachi, I. *J. Am. Chem. Soc.* **2008**, *130*, 12095−12101. (b) Li, H.; Wang, H.; Liu, Y.; Liu, Z. *Chem. Commun.* **2012**, *48*, 4115−4117.
(3) (a) Paugam, M.-F.; Valencia, L. S.; Boggess, B.; Smith, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 11203−11204. (b) Paugam, M.-F.; Bien, J. T.; Smith, B. D.; Chrisstoffels, L. A. J.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1996**, *118*, 9820−9825. (c) Secor, K. E.; Glass, T. E. *Org. Lett.* **2004**, *6*, 3727−3730.
(4) For leading references on the chemistry and reactivity of boron-based polyol complexes, see: (a) Kuivila, H. G.; Keough, A. H.; Soboczenski, E. J. *J. Org. Chem.* **1954**, *19*, 780−783. (b) Lorand, J. P.; Edwards, J. O. *J. Org. Chem.* **1959**, *24*, 769−774. (c) Babcock, L.; Pizer, R. *Inorg. Chem.* **1980**, *19*, 56−61. (d) Springsteen, G.; Wang, B. *Tetrahedron* **2002**, *58*, 5291−5300. (e) Tomsho, J. W.; Benkovic, S. J. *J. Org. Chem.* **2012**, *77*, 2098−2106. (f) Pizer, R.; Babcock, L. *Inorg. Chem.* **1977**, *16*, 1677−1681. (g) Schiller, A.; Wessling, R. A.; Singaram, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 6457−6459. (h) Gamsey, S.; Miller, A.; Olmstead, M. M.; Beavers, C. M.; Hirayama, L. C.; Pradhan, S.; Wessling, R. A.; Singaram, B. *J. Am. Chem. Soc.* **2007**, *129*, 1278−1286. (i) Breslau, R.; Rivera, F.; Lilie, E.; Cottman, M. *J. Org. Chem.* **2013**, *78*, 238−245. (j) Lee, D.; Williamson, C. L.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 8260−8267. (k) Beale, T. M.; Taylor, M. S. *Org. Lett.* **2013**, *15*, 1358−1361. (l) Dimitrijevic, E.; Taylor, M. S. *Chem. Sci.* **2013**, *4*, 3298−3033. (m) Edwards, N. Y.; Sager, T. W.; McDevitt, J. T.; Anslyn, E. V. *J. Am. Chem. Soc.* **2007**, *129*, 13575−13583. (n) Bérubé, M.; Dowlut, M.; Hall, D. G. *J. Org. Chem.* **2008**, *73*, 6471−6479.
(5) (a) Baldock, C.; Rafferty, J. B.; Sedelnikova, S. E.; Baker, P. J.; Stuitje, A. R.; Slabas, A. R.; Hawkes, T. R.; Rice, D. W. *Science* **1996**, *274*, 2107−2110. (b) Grassberger, M. A.; Turnowsky, F.; Hildebrandt, J. *J. Med. Chem.* **1984**, *27*, 947−953.
(6) For an overview, see: (a) Liu, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 242−244. (b) Campbell, P. G.; Marwitz, A. J. V.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 6074−6092. (c) Bosdet, M. J. D.; Piers, W. E. *Can. J. Chem.* **2009**, *87*, 8−29.
(7) (a) Marwitz, A. J. V.; Abbey, E. R.; Jenkins, J. T.; Zakharov, L. N.; Liu, S.-Y. *Org. Lett.* **2007**, *9*, 4905−4908. (b) Lamm, A. N.; Garner, E. B., III; Dixon, D. A.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 8157−8160. (c) Marwitz, A. J. V.; McClintock, S. P.; Zakharov, L. N.; Liu, S.-Y. *Chem. Commun.* **2010**, *46*, 779−781. (d) Rudebusch, G. E.; Zakharov, L. N.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2013**, *52*, DOI: 10.1002/anie.201304443.
(8) (a) Emslie, D. J.; Piers, W. E.; Parvez, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1252−1255. (b) Bosdet, M. J.; Piers, W. E.; Sorensen, T. S.; Parvez, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4940−4943. (c) Jaska, C. A.; Emslie, D. J.; Bosdet, M. J.; Piers, W. E.; Sorensen, T. S.; Parvez, M. *J. Am. Chem. Soc.* **2006**, *128*, 10885−10896. (d) Bosdet, M. J.; Jaska, C. A.; Piers, W. E.; Sorensen, T. S.; Parvez, M. *Org. Lett.* **2007**, *9*, 1395−1398. (e) Lepeltier, M.; Lukoyanova, O.; Jacobson, A.; Jeeva, S.; Perepichka, D. F. *Chem. Commun.* **2010**, *46*, 7007−7009. (f) Taniguchi, T.; Yamaguchi, S. *Organometallics* **2010**, *29*, 5732−5735. (g) Hatakeyama, T.; Hashimoto, S.; Seki, S.; Nakamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 18614−18617. (h) Hatakeyama, T.; Hashimoto, S.; Oba, T.; Nakamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 19600−19603. (i) Wang, X. Y.; Lin, H. R.; Lei, T.; Yang, D. C.; Zhuang, F. D.; Wang, J. Y.; Yuan, S. C.; Pei, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3117−3120. (j) Lu, J. S.; Ko, S. B.; Walters, N. R.; Kang, Y.; Sauriol, F.; Wang, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 4544−4548. (k) Marwitz, A. J. V; Jenkins, J. T.; Zakharov, L. N.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 7444−7447. (l) Marwitz, A. J. V.; Lamm, A. N.; Zakharov, L. N.; Vasiliu, M.; Dixon, D. A.; Liu, S.-Y. *Chem. Sci.* **2012**, *3*, 825−829.
(9) (a) Zhou, H.-B.; Nettles, K. W.; Bruning, J. B.; Kim, Y.; Joachimiak, A.; Sharma, S.; Carlson, K. E.; Stossi, F.; Katzenellenbogen, B. S.; Greene, G. L.; Katzenellenbogen, J. A. *Chem. Biol.* **2007**, *14*, 659−669. (b) Ito, H.; Yumura, K.; Saigo, K. *Org. Lett.* **2010**, *12*, 3386−3389. (c) Liu, L.; Marwitz, A. J. V.; Matthews, B. W.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 6817−6819. (d) Knack, D. H.; Marshall, J. L.; Harlow, G. P.; Dudzik, A.; Szaleniec, M.; Liu, S.-Y.; Heider, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2599−2601.
(10) (a) Marwitz, A. J. V.; Matus, M. H.; Zakharov, L. N.; Dixon, D. A.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 973−977. (b) Campbell, P. G.; Abbey, E. R.; Neiner, D.; Grant, D. J.; Dixon, D. A.; Liu, S.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 18048−18050. (c) Xu, S.; Mikulas, T. C.; Zakharov, L. N.; Dixon, D. A.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 7527−7531.
(11) Luo, W.; Zakharov, L. N.; Liu, S.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 13006−13009.
(12) Davies, K. M.; Dewar, M. J. S.; Rona, P. *J. Am. Chem. Soc.* **1967**, *89*, 6294−6297.
(13) See the Supporting Information for experimental details and characterization.
(14) Wrackmeyer, B. In *Annual Reports on NMR Spectroscopy*; Webb, G. A., Ed.; Academic Press: London, 1988; Vol. *20*, pp 61−203.
(15) Zhu, L.; Shabbir, S. H.; Gray, M.; Lynch, V. M.; Sorey, S.; Anslyn, E. V. *J. Am. Chem. Soc.* **2006**, *128*, 1222−1232.
(16) Hoang, C. T.; Prokes, I.; Clarkson, G. J.; Rowland, M. J.; Tucker, J. H. R.; Shipman, M.; Walsh, T. R. *Chem. Commun.* **2013**, *49*, 2509−2511.
(17) (a) The limit of error of this treatment for the free energy of activation has been estimated to be ±0.2 kcal mol^{-1}; see: Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*, 2nd ed.; Wiley-VCH: New York, 1993; Chapter 11. (b) For a related study with *o*-(aminomethyl)arylboronates, see: Toyota, S.; Ōhki, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1168−1173.
(18) Note: although the trapping experiments are consistent with a ligand exchange mechanism involving an initial B−N bond breakage, a mechanism involving an initial B−O bond dissociation cannot be disproven from our experiments.
(19) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735−1766.
(20) Henderson, W. G.; How, M. J.; Kennedy, G. R.; Mooney, E. F. *Carbohydr. Res.* **1973**, *28*, 1−12.