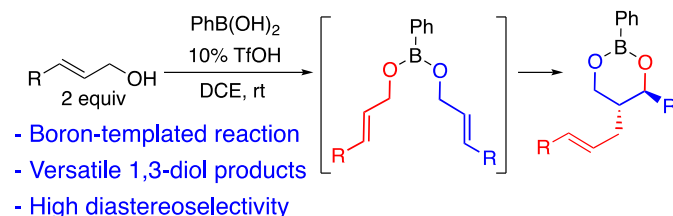


Boron-Templated Dimerization of Allylic Alcohols to Form Protected 1,3-Diols via Acid Catalysis.

S. Hadi Nazari, †,‡ Kelton G. Forson,‡ Erin E. Martinez, Nicholas J. Hansen,§ Kyle J. Gassaway, Nathan M. Lyons, Karissa C. Kenney, Gabriel A. Valdivia-Berroeta, Stacey J. Smith, David J. Michaelis*

Brigham Young University, Provo, UT 84602, USA

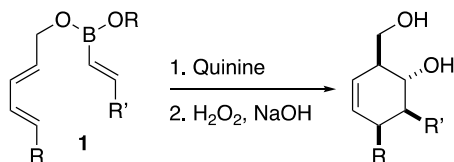
Supporting Information Placeholder



ABSTRACT: We report an unprecedented boron-templated dimerization of allylic alcohols that generates a 1,3-diol product with two stereogenic centers in high yield and diastereoselectivity. This acid-catalyzed reaction is achieved via in situ formation of a boronic ester intermediate that facilitates selective cyclization and formation of a cyclic boronic ester product. High yields are observed with a variety of allylic alcohols, and mechanistic studies confirm the role of boron as a template for the reaction.

Templated organic transformations are reminiscent of enzyme-mediated processes because, like enzymes, they rely on the preorganization of reacting substrates in close proximity to achieve high yield and high selectivity. Various innovative and efficient strategies that employ substrate preorganization for organic catalysis have recently been reported, and include the use of organic or metal ion templates,^{1–5} porous coordination frameworks (e.g. MOFs),^{6–10} removable covalent tethers such as silicon tethers,^{11–14} and work from our group in bifunctional peptide catalysis.¹⁵ These types of templated processes can enable selective intramolecular cyclizations such as macrocyclization,^{16–17} as well as achieve selective dimerization/trimerization with unique regio- or stereoselectivity.^{6,18–19} Boron-based tethers are particularly attractive because the dynamic nature of B–O bonds under acidic or basic conditions can enable boronic ester formation as a route to activate allylic and benzylic alcohols²⁰ and enable templated reactions.^{21–23} Indeed, Morgan and coworkers recently reported boron-tethered, enantioselective Diels-Alder reactions that rely on a boron-based tether between the diene and dienophile (**1**, Figure 1a).^{24–29} Boron-tethered rad-

a) Previous work.



b) This report.

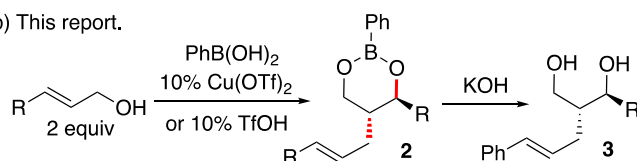


Figure 1. Boron-tethered transformations.

ical cyclizations,^{30–31} carboborations of alkenes and alkynes,^{32–34} and cyclotrimerizations^{18–19} have also been reported. Boronic ester tethers can also be easily removed under basic conditions and B–C bonds are readily transformed to new C–O bonds upon oxidation.

Our research group is interested in the use of simple allylic alcohol substrates as coupling partners for transition metal-catalyzed reactions.^{35–36} Recently, while investigating the use of nickel catalysts for Suzuki reactions with unprotected allylic alcohol electrophiles,³⁶ we discovered that copper(II) triflate catalyzed a unique dimerization of allylic alcohols to form new C–C and C–O bonds (red) across one of the alkenes (Figure 1b). In this unprecedented transformation, the boronic acid is incorporated into the structure of the product (**2**), but can be easily removed under basic conditions to reveal a new 1,3-diol structure (**3**). Herein we report the development of this new selective dimerization of allylic alcohols, demonstrate good substrate tolerance, and confirm the necessity and role of the boronic acid template in forming the dimerized product. We also demonstrate that the resulting boron-protected 1,3-diol product is a versatile intermediate for chemical synthesis through a series of derivatization studies.

In our early optimization studies, we found that copper(II) triflate facilitated the formation of dimerization product **2** in moderate yield (Table 1, entry 1). Due to difficulty in isolating the boronic ester product early on, we subsequently cleaved the boronic ester under basic aqueous conditions and isolated the diol product **3**. We next screened various Cu(II) and Cu(I) salts and found that only copper(II) triflate enabled product formation (entries 2–4). These latter results made us question whether triflic acid (TfOH) was not in fact responsible for the catalysis we observed.³⁷ When TfOH was employed as the sole catalyst instead of copper triflate, the identical product was formed in improved yield (entry 5). Thus, our continuing optimization studies focused on the use of TfOH as catalysts.

We next screened temperature (entry 5, 6), solvents (entries 7–9), and acid catalyst loading (entry 9, 10) and found that high yield (>90%) could be obtained with just 10% TfOH in DCE or toluene as solvent at room temperature. In control studies, we found that no reaction occurs in the absence of triflic acid (entry 10) and that the boronic acid was necessary for formation of the 1,3-diol product (entry 11). Furthermore, the addition of molecular sieves to soak up the water formed in the reaction had no impact on the rate or yield of the reaction, suggesting that triflic acid is indeed acting as catalyst and that the reaction is not likely under boronic

Table 1. Optimization studies.

entry ^a	Catalyst	Solvent	Temp.	% Yield (3) ^b
1 ^c	Cu(OTf) ₂ + dppf	Toluene	60 °C	42%
2	CuCl ₂ + dppf	Toluene	60 °C	0
3	Cu(OAc) ₂ + dppf	Toluene	60 °C	0
4	CuI + dppf	Toluene	60 °C	0
5	TfOH	Toluene	60 °C	90
6	TfOH	Toluene	rt	96
7	TfOH	DCE	rt	90
8	TfOH	THF	rt	0
9	TfOH _d	DCE	rt	30
10	None	DCE	rt	0
11 ^e	TfOH	DCE	rt	0

^a Reactions run with 1 mmol cinnamyl alcohol, 0.5 mmol PhB(OH)₂ and 10 mol% catalyst in solvent (0.06 M) for 12 hr. ^b Isolated yields of **3** (~10:1 d.r) after hydrolysis of the boronic ester with aq. KOH. ^c After 16 hr. ^d Reaction run with 5 mol% TfOH. ^e No PhB(OH)₂ was added

acid promoted hydronium catalysis.^{20,39} In all of our optimization studies, the cyclization product was obtained with high diastereomeric ratio (~10:1 dr), favoring the anti isomer.

The high yield and selectivity observed in this new transformation, and the versatility of the 1,3-diol product as a synthetic intermediate, led us to explore the substrate scope of the transformation. For these studies, we found that purification of the boronic ester product directly on silica gel that was deactivated with Et₃N allowed us to isolate this intermediate (**2**) without the need to hydrolyze the boronic ester and reveal the diol product (**3**). When exploring variations of the allylic alcohol structure, we found that a variety of aryl substituents were tolerated in the reaction, including substituents at the para (**2a–2i**), meta (**2j**, **2k**), and ortho positions (**2l**, **2m**). Various electron donating (**2c–2g**, **2m**) and electron withdrawing (**2b**, **2h**) substituents could also be employed, as well as heterocyclic (**2r**) and polycyclic aromatic substrates (**2n**). We also found that trisubstituted non-aryl allylic alcohols worked well in the

reaction (**2s**), but disubstituted non-conjugated allylic alcohols did not (**2t**). Cinnamyl alcohols with strong electron-withdrawing groups (**2i**, **2q**) react slowly and provide low yield in the reaction, presumably due to the low nucleophilicity of the conjugated alkene. In all cases, the product was isolated in ~10:1 diastereoselectivity. The reaction is

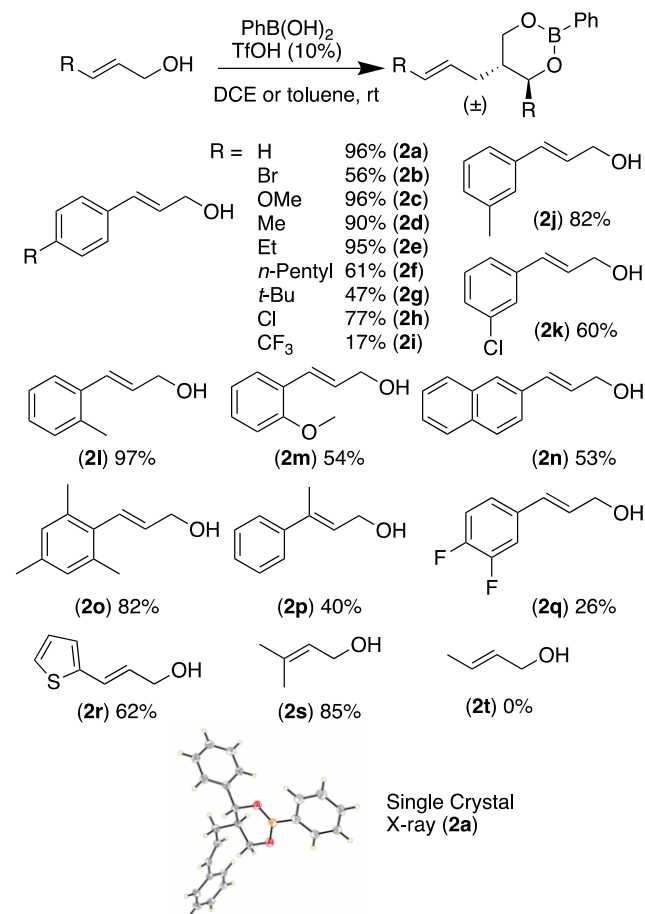


Figure 2. Substrate scope for acid-catalyzed dimerization.

also readily scalable and when performed on 11.2 mmol scale, product **2a** (3.65 g) was isolated in 96% yield. The structure of the boronic ester product and the trans diastereoselectivity of the reaction were confirmed by single crystal X-ray analysis of **2a** (Figure 2).

Having established the generality of this reaction for selective alcohol dimerization, we next investigated the mechanism of the transformation. We hypothesize that the phenylboronic acid used in the reaction condenses with two equivalents of the allylic alcohol. This boronic ester intermediate then facilitates selective cyclization and product formation. When the boronic ester of cinnamyl alcohol was formed stoichiometrically (**4**), then treated with TfOH, the desired dimerization product (**2a**) was isolated in 98% yield (Figure 3a). We also considered the possibility of boronic acid promoted hydronium catalysis, which is a possible mechanism in the presence of the water formed in the reaction.^{38,39} However, when molecular sieves were added to the reaction to sequester the water formed, no enhancement in rate or yield was observed, as previously noted. We next asked whether the boronic ester tether was a strict

requirement or if other tethers such as a silicon tether could be employed. However, when we employed silicon tether cinnamyl alcohol (**5**), no product was observed (Figure 3b). An additional mechanistic consideration is the fact that only styrenyl or trisubstituted allylic alcohols participate in the reaction, which suggests that stabilization of a cationic intermediate might be necessary for efficient reaction to occur.

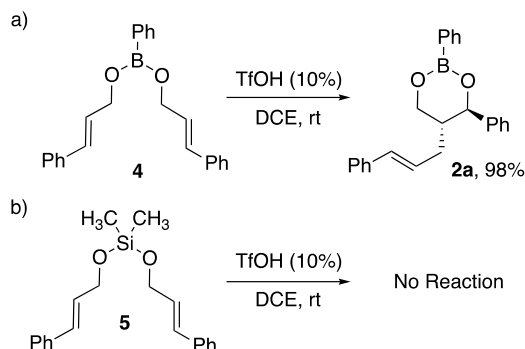


Figure 3. Tether studies.

Based on our observations about the requirements for this new transformation, we proposed the mechanism shown in Figure 4. An acid-catalyzed boronic ester formation leads to the boronic ester intermediate (**A**), which we know converts to the desired product. We believe protonation of the boronic ester by triflic acid (**B**) is followed by attack of one of the olefins onto the activated C-O bond to generate intermediate **C**. The electron-withdrawing ability of boron could help explain why boron tethers facilitate the transformation but silicon tethers do not.³⁸ Formation of carbocation intermediate **C** could also help explain the substrate requirements of the reaction, where styryl alcohols and trisubstituted olefins perform efficiently in the reaction due to formation of stabilized benzylic or tertiary carbocations. Subsequent rotation of the C-C bond and addition of the boronic acid OH to the carbocation would then generate cyclized product **D**. The high preference for trans diastereoselectivity in the reaction is likely due to formation of a cyclic

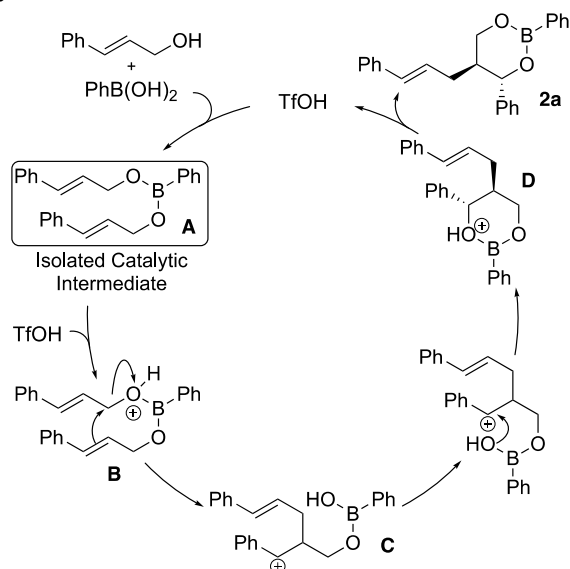


Figure 4. Proposed catalytic cycle.

6-membered transition state that places both the phenyl and cinnamyl substituents on **C** in the equatorial position (see supporting information for proposed structure). In addition, participation by the boronic acid OH as a nucleophile in this fashion is similar to the mechanism of the Nagata reaction, where a boronic acid adds to an ortho-quinone methide.^{20-21, 23} Regeneration of the acid catalyst and formation of **2a** terminates the cycle.

Next, we wondered whether we could generate enantioenriched 1,3-diol product via use of a chiral acid or incorporation of a chiral auxiliary. As such, (R)-camphorsulfonic acid ((R)-CSA) was employed in the reaction and the product was isolated in 33% yield after 12 h (Figure 5a). Unfortunately, no enantioselectivity we observed in the process and therefore the approach was not pursued further. We also synthesized enantiopure 1,1'-binaphthylboronic acid and subjected it to the reaction. The product was isolated in 70% yield, but as a 1:1 mixture of diastereomers, indicating that no diastereoselection was achieved in the process (Figure 5b).

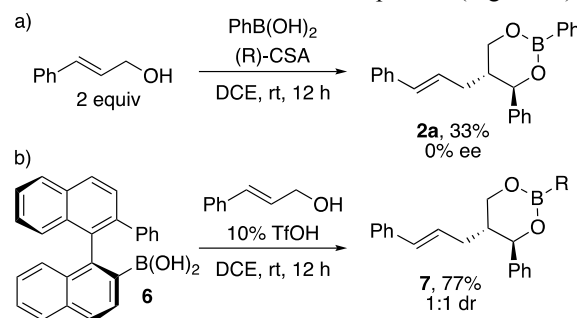


Figure 5. Attempts at stereoinduction.

Due to the potential synthetic value of our protected 1,3-diol product, we also desired to demonstrate that the product could be readily derivatized and that the boronic ester protecting group could survive various reaction conditions for functionalization of the olefin (Figure 5). Oxidative cleavage of the alkene with OsO_4 and sodium periodate (Lemieux-Johnson oxidation) provided the aldehyde product (**8**) in 98% yield. While the dimerization reaction necessitates that two equivalent phenyl groups be incorporated into the product, this transformation allows for removal of the second phenyl group for further

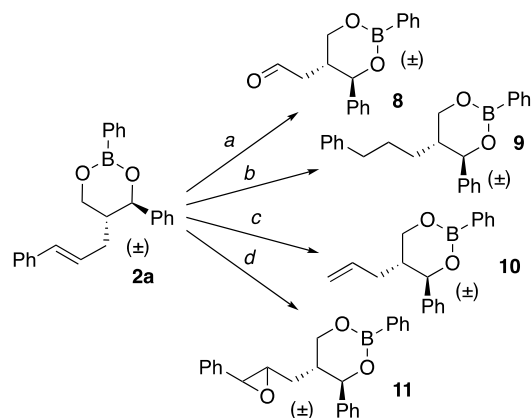


Figure 6. Derivatization studies. a) OsO_4 , NaIO_4 , 98% yield; b) H_2 , 10% Pd/C, 91% yield; c) Hoveyda-Grubbs 2nd Gen (5 mol%), C_2H_4 (balloon), 72% yield; d) DMDO, acetone, 71% yield, 1:1 dr.

derivatization studies. Hydrogenation of **2a** with palladium on carbon also went smoothly to provide to saturated product (**9**) without loss of the boronic ester protecting group (91% yield). Olefin cross metathesis with Hoveyda-Grubbs 2nd generation catalyst and ethylene afforded the corresponding terminal alkene (**10**) in good yield (72%). Finally, epoxidation of the alkene with dimethyldioxirane (DMDO) afforded the corresponding epoxide (**11**) as a 1:1 mixture of diastereomers (71% yield).

In conclusion, we have developed an expeditious route to 1,3-diol products via a boron-templated dimerization of allylic alcohols. This transformation provides access to highly versatile protected 1,3-diol building blocks for organic synthesis, which contain a dense arrangement of alcohol and alkene functional groups and two stereogenic centers. The reaction also proceeds with high diastereoselectivity, and we confirmed the necessity of both the boron tether and the acid catalyst in the reaction. Future work on this transformation is focused on achieving high enantioselectivity in the formation of the two stereogenic centers.

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge.

Experimental procedures and compound characterizations (PDF) X-ray crystallography data (CIF)

AUTHOR INFORMATION

Present Addresses

†Current location: Acme Bioscience Inc., 3941 E. Bayshore Rd, Palo Alto, CA 94303, USA.

§Home institution: Department of Chemistry, Marquette University, Milwaukee, WI 53233

Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Acknowledgment is made to the donors of the American Chemical Society Petroleum Research Fund for support of this research (PRF No. 56371-DNI1). Financial support was also provided by the National Science Foundation (CHE-1665015). Funding for Nicholas Hansen was provided by the National Science Foundation Chemistry and Biochemistry REU Site to Prepare Students for Graduate School and an Industrial Career under award CHE-1757627.

REFERENCES

- Laughrey, Z. R.; Gibb, B. C. Macrocyclic synthesis through templation. *Top. Curr. Chem.* **2005**, *249*, 67–125.
- Evans, N. H.; Beer, P. D. Advances in Anion supramolecular chemistry: from recognition to chemical applications. *Angew. Chemie Int. Ed.* **2014**, *53*, 11716–11754.
- Rezaeivala, M.; Keypour, H. Schiff base and non-schiff base macrocyclic ligands and complexes incorporating the pyridine moiety – The first 50 years. *Coord. Chem. Rev.* **2014**, *280*, 203–253.
- Inthasot, A.; Tung, S.-T.; Chiu, S.-H. Using alkali metal ions to template the synthesis of interlocked molecules. *Acc. Chem. Res.* **2018**, *51*, 1324–1337.
- Tan, K. L. Induced Intramolecularity: An Effective Strategy in Catalysis. *ACS Catal.* **2011**, *1*, 877–886.
- Wei, Y.-S.; Zhang, M.; Liao, P.-Q.; Lin, R.-B.; Li, T.-Y.; Shao, G.; Zhang, J.-P.; Chen, X.-M. Coordination templated [2+2+2] cyclotrimerization in a porous coordination framework. *Nature Commun.* **2015**, *6*, 8348.
- Chen, Y.-Z.; Zhang, R.; Jiao, L.; Jiang, H.-L. Metal-organic framework-derived porous materials for catalysis. *Coord. Chem. Rev.* **2018**, *362*, 1–23.
- Hong, C. M.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. Self-Assembled Tetrahedral Hosts as Supramolecular Catalysts. *Acc. Chem. Res.* **2018**, *51*, 2447–2455.
- Bender, T. A.; Morimoto, M.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. Supramolecular Host-Selective Activation of Iodoarenes by Encapsulated Organometallics. *J. Am. Chem. Soc.* **2019**, *141*, 1701–1706.
- Xu, C.; Fang, R.; Luque, R.; Chen, L.; Lib, Y. Functional metal-organic frameworks for catalytic applications. *Coord. Chem. Rev.* **2019**, *388*, 268–292.
- Fensterbank, L.; Malacria, M.; McN Sieburth, S. Intramolecular reactions of temporarily silicon-tethered molecules. *Synthesis*, **1997**, *8*, 813–854.
- Bracegirdle, S.; Anderson, E. A. Recent advances in the use of temporary silicon tethers in metal-mediated reactions. *Chem. Soc. Rev.* **2010**, *39*, 4114–4129.
- Cusak, A. Temporary silicon-tethered ring-closing metathesis: Recent advances in Methodology development and natural product synthesis. *Chem. Eur. J.* **2012**, *18*, 5800–5824.
- Zhang, W.-X.; Zhang, S.; Xi, Z. Zirconocene and Si-tethered diynes: A happy match directed toward organometallic chemistry and organic synthesis. *Acc. Chem. Res.* **2011**, *44*, 541–551.
- Kinghorn, M. J.; Valdivia-Berroeta, G. A.; Chantry, D. R.; Smith, M. S.; Ence, C. C.; Draper, S. R. E.; Duval, J. S.; Masino, B. M.; Cahoon, S. B.; Flansburg, R. R.; Conder, C. J.; Price, J. L.; Michaelis, D. J. Proximity-Induced Reactivity and Selectivity with a Rationally Designed Bifunctional Helical Peptide Catalyst. *ACS Catal.* **2017**, *7*, 7704–7708.
- Marti-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V. Macrocyclization Reactions: The Importance of Conformational, Configurational, and Template-Induced Preorganization. *Chemical Reviews* **2015**, *115*, 8736–8834.
- Batiste, S. M.; Johnston, J. N. Evidence for ion-templation during macrocyclooligomerization of desipeptides. *J. Am. Chem. Soc.* **2018**, *140*, 4560–4568.

18. Yamamoto, Y.; Ishii, J.-I.; Nishiyama, H.; Itoh, K. Cp*-RuCl₂-catalyzed Formal Intermolecular cyclotrimerization of three unsymmetrical alkynes through a boron temporary tether: regioselective four-component coupling synthesis of phthalides. *J. Am. Chem. Soc.* **2005**, *127*, 9625–9631.
19. Yamamoto, Y.; Ishii, J.-I.; Nishiyama, H.; Itoh, K. Ru(II)-catalyzed Chemo- and Regioselective Cyclotrimerization of three unsymmetrical alkynes through boron temporary tether. One-pot four-component coupling via cyclotrimerization/Suzuki–Miyaura coupling. *J. Am. Chem. Soc.* **2004**, *126*, 3712–3713.
20. For a leading reference, see: Estopiñá-Durán, S.; Donnelly, L. J.; Mclean, E. B.; Hockin, B. M.; Slawin, A. M. Z.; Taylor, J. E. Aryl Boronic Acid Catalysed Dehydrative Substitution of Benzylic Alcohols for C–O Bond Formation. *Chem. Eur. J.* **2019**, *25*, 3950–3956.
21. Hall, D. G. Boronic acid catalysis. *Chem. Soc. Rev.* **2019**, *48*, 3475–3496.
22. Peer, H. G.; The reaction of phenol with formaldehyde. III. selective hydroxymethylation of phenols at the ortho-position. *Recl. Trav. Chim. Pays-Bas.* 1960, *79*, 825–835.
23. Nagata, W.; Okada, K.; Aoki, T. ortho-Specific α -Hydroxyalkylation of Phenols with Aldehydes. *Synthesis* **1979**, 365–368.
24. Scholl, K.; Dillshaw, J.; Timpy, E.; Lam, Y.-H.; De Ratt, L.; Benton, T. R.; Powell, J. P.; Houk, K. N.; Morgan, J. B. Quinine-promoted, enantioselective boron-templated Diels–Alder reaction by anomeric control of transition-state conformation. *J. Org. Chem.* **2018**, *83*, 5756–5765.
25. Batey, R. A.; Thadani, A. N.; Lough, A. J. Alkenylboronate tethered intramolecular Diels–Alder Reactions. *J. Am. Chem. Soc.* **1999**, *121*, 450–451.
26. Batey, R. A.; Thadani, A. N.; Lough, A. J. Diels–Alder reactions of dienylboron compounds with unactivated dienophiles: an application of boron tethering for substituted cyclohexanol synthesis. *Chem. Commun.* **1999**, 475–476.
27. Batey, R. A.; Lin, D.; Wong, A.; Hayhoe, C. L. S. Intramolecular Diels–Alder reactions of alkenylboranes – A stereoselective route to functionalized bicyclo[4.3.0]nonenes. *Tetrahedron Lett.* **1997**, *38*, 3699–3702.
28. Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. Phenylboronic Acid as a Template in the Diels–Alder Reaction. *Synthesis* **1991**, 1171–1172.
29. Nicolaou, K. C.; Liu, J. J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. Synthesis of a fully functionalized CD ring system of taxol. *J. Chem. Soc., Chem. Commun.* **1992**, 1118–1120.
30. Batey, R. A.; Smil, D. V. The first boron-tethered radical cyclizations and intramolecular homolytic substitutions at boron. *Angew. Chem. Int. Ed.* **1999**, *38*, 1798–1800.
31. Batey, R. A.; Smil, D. V. Tethered α -boryl radical cyclizations of haloalkyl boronates. *Tetrahedron Lett.* **1999**, *40*, 9183–9187.
32. Daini, M.; Yamamoto, A.; Sugimoto, M. Palladium-catalyzed *trans*- and *cis*-carboboration of alkynes tethered to chloroborane with organozirconium reagents: ligand-dependent complementary stereoselectivity. *J. Am. Chem. Soc.* **2008**, *130*, 2918–2919.
33. Daini, M.; Sugimoto, M. Palladium-catalyzed, stereoselective, cyclizative alkenylboration of carbon–carbon double bonds through activation of a boron–chlorine bond. *J. Am. Chem. Soc.* **2011**, *133*, 4758–4761.
34. Nogami, M.; Hirano, K.; Kanai, M.; Wang, C.; Saito, T.; Miyamoto, K.; Muranaka, A.; Uchiyama, M. Transition metal-free *trans*-selective alkynylboration of alkynes. *J. Am. Chem. Soc.* **2017**, *139*, 12358–12361.
35. Nazari, S. H.; Tiempos-Flores, N.; Forson, K. G.; Bourdeau, J. E.; Michaelis, D. J. “C–N Bond Formation from Allylic Alcohols Via Cooperative Nickel and Titanium Catalysis.” *J. Org. Chem.* **2018**, *83*, 10646–10654.
36. Nazari, S. H.; Bourdeau, J. E.; Talley, M. R.; Valdivia-Berroeta, G. A.; Smith, S. J.; Michaelis, D. J. “Nickel-Catalyzed Suzuki Cross Couplings with Unprotected Allylic Alcohols Enabled by Bidentate NHC/Phosphine Ligands.” *ACS Catal.* **2018**, *8*, 86–89.
37. Taylor, J. G.; Whittall, N.; Hii, K. K. “Copper-Catalyzed Intermolecular Hydroamination of Alkenes.” *Org. Lett.* **2006**, *8*, 3561–3564.
38. Zheng, H.; Hall, D. G. Zirconium-catalyzed Nagata reaction for the synthesis of 2-aryl-1,3,2-aryldioxaborins via a mild three-component condensation of phenols, aldehydes, and boronic acid. *Tetrahedron Lett.* **2010**, *51*, 4256–4259.
39. Ang, H. T.; Rygus, J. P. G.; Hall, D. G. Two-component boronic acid catalysis for increased reactivity in challenging Friedel–Crafts alkylations with deactivated benzylic alcohols. *Org. Biomol. Chem.* **2019**, *17*, 6007–6014.