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N–B dative bond-induced [3.3.0] bicyclic boronate-tethered *exo*-selective intramolecular Diels–Alder reaction†

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We report herein a highly *exo*-selective intramolecular Diels–Alder reaction of alkenyl boronates which employs an N–B dative bond-involved bicyclic rigid tether. Complex C(sp^3)-rich polycyclic molecules containing up to 8 stereocenters can be readily formed *via* an operationally simple two-step procedure.

The Diels–Alder reaction, constructing six-membered rings by stereospecific [4 + 2] cycloadditions, has shown unparalleled efficiency in the field of chemical synthesis, especially of natural products.[1,2] Still, however, many complex biologically important molecules, such as the ones shown in Fig. 1,[3] contain highly functionalized six-membered rings that may not be directly disconnected by the conventional [4 + 2] mode due to the presence of multiple oxygen and/or nitrogen substituents. One possible solution to this problem would be using a convenient precursor that can be readily transformed to the desired functional groups. Boron-substituted building blocks therefore provide an attractive strategy because C–B bonds may be reliably installed before and converted into C–O, C–N or C–C bonds after the Diels–Alder reaction. Alkenyl boronates were first used in [4 + 2] cycloadditions more than five decades ago by Matteson[4] and Woods.[5] Later on, various alkenylboron reagents including dialkyl boranes,[6] boron dihalides,[7] boronic acids and boronates[8] have been studied and a review has summarized the important progress.[9] Recently, this strategy has been successfully applied in the total synthesis of pancratistatin and lycorine.[10] Despite the mentioned significant advancement, in many cases, the reactions suffered from low reactivity, low *endo*/*exo* selectivity and/or low functional group tolerance. During our studies on new organoboron reagents,[11] we have been interested in the stereoselective cycloadditions of alkenyl boronic acids taking advantage of new masking structures on boron atoms. Herein, we wish to report a highly *exo*-selective intramolecular Diels–Alder reaction with a broad substrate scope.

N-methyliminodiacetic acid boronates (MIDA)[12] and diethanolamineboronates (DABO)[13] are relatively stable surrogates of boronic acids and the former, particularly, have shown great potential in chemoselective Suzuki–Miyaura coupling.[11a,12,14] Structurally, these compounds include a rigid [3.3.0] bicyclic moiety where the bridgehead nitrogen and boron atoms are connected by an N to B dative bond.[15] Thus the two substituents R and Y (Scheme 1a) are of *cis* configuration with little

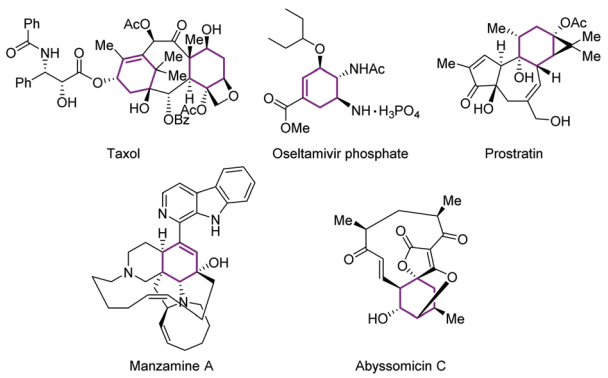
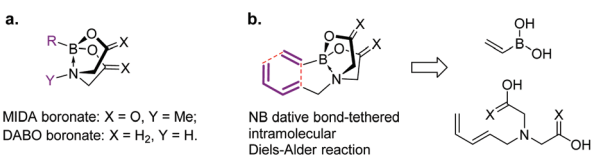


Fig. 1 Selected examples of six-membered carbon rings in natural products.



Scheme 1 N–B dative bond-tethered intramolecular Diels–Alder reaction.

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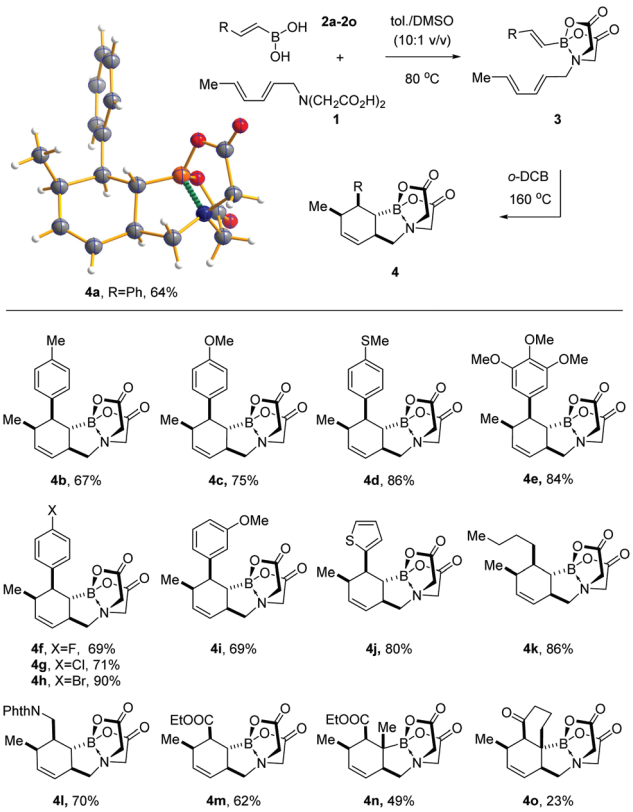
conformational flexibility. We therefore wondered if such a structural preorganization might be employed in intramolecular Diels–Alder reaction to promote the reaction of electronically unactivated substrates and to induce not only high regioselectivity but also high stereoselectivity. To forge this well-defined framework in a highly modular manner, we planned to condense an alkenyl boronic acid and an aminodiacetic acid or an aminodiethanol on which a diene is preinstalled (Scheme 1b).

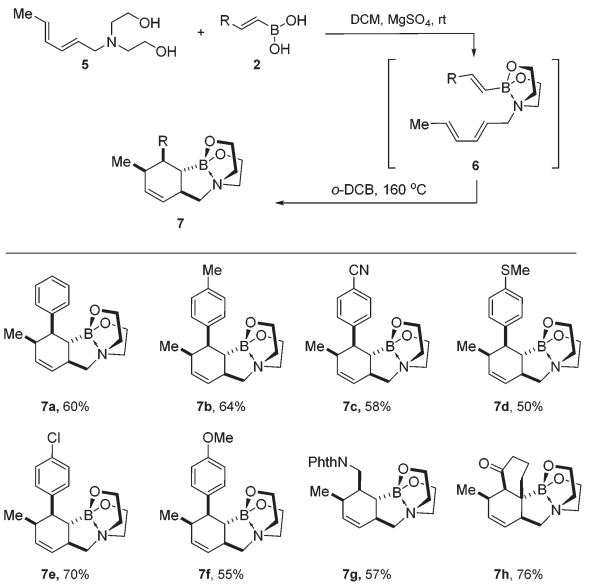
We firstly chose to use an iminodiacetic acid tether, *i.e.* where X is O in Scheme 1b. The diene-incorporated iminodiacetic acid **1** and the alkenyl boronic acids **2** were readily prepared by routine methods (for Experimental details, see the ESI†). We then tested the design by a two-step process involving intermolecular dehydrative condensation and intramolecular cycloaddition. Thus, heating a mixture of (*E*)-styryl boronic acid (**2a**, 1.0 equiv.) and *N*-dienyliminodiacetic acid (**1**, 1.1 equiv.) in toluene and DMSO (10 : 1, v/v) containing 4 Å molecular sieves at 80 °C cleanly gave the desired MIDA boronate-type compound **3a**, as evidenced by the characteristic AB-type $-CH_2-$ signals in ^{1}H NMR spectrum of the crude product (chemical shift 4.06, 4.16 ppm, coupling constant 16.8 Hz). This crude compound can be used without further purification for the key [4 + 2] cycloaddition reaction. Thus, simply heating a solution of **3a** in 1,2-dichlorobenzene at 160 °C for 8 hours led to full conversion, affording a single observable isomer according to ^{1}H NMR analysis of the crude product. After purification by flash chromatography on silica gel, extensive NMR experiments including ^{1}H–^{1}H COSY, HSQC and HMBC supported an *exo*-[4 + 2] cycloaddition product **4a** (64% yield over two steps based on (*E*)-styryl boronic acid). The structure was further confirmed by X-ray diffraction analysis of a single crystal of **4a**.[16] Notably, this compact cage-like heteropropellane structure contains five rings and four of them are annulated non-aromatic rings.

We next explored the scope of this tethered D–A reaction. The results are shown in Scheme 2. Remarkably, in all cases, only one stereoisomer was observed, in sharp contrast to previous DA reactions of alkenyl boronates where a mixture of *endo* and *exo* products were usually formed.[9,17] Various substituents on the phenyl ring (Me, OMe, SMe, F, Cl and Br) were well tolerated, affording the respective cycloaddition products (**4b–4i**) in two steps in good to excellent yields. 2-Thiophenyl was also compatible in this D–A approach (**4j**), giving the product in 80% yield. In addition, aliphatic alkenyl boronic acids could be successfully used in this process and the products were isolated in high yields and high *exo*-selectivity (**4k** and **4l**). These results suggest that the generally excellent stereocontrol is governed by the N–B dative bond-induced rigid [3.3.0] bicyclic moiety. Alkenyl boronic acids bearing electron-withdrawing groups are often prone to decomposition due to protodeboronation, thus posing challenges for further transformations. To our satisfaction, β-carbonyl alkenyl boronic acids were also viable in our system, although only moderate yields were obtained (**4m–4o**). Interestingly, in the case of **4m**, D–A reaction occurred during the dehydrative condensation process. Therefore, in a single step, the final product was readily prepared.

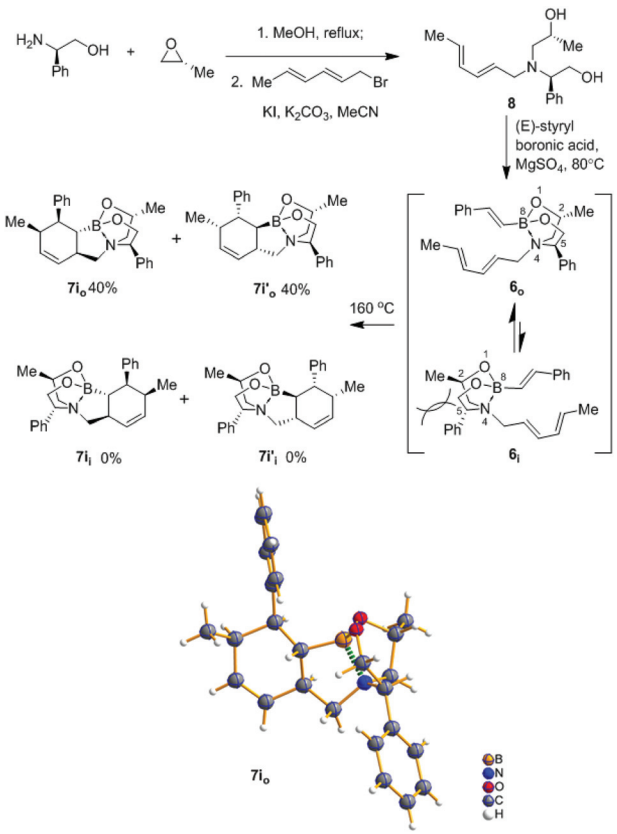


Scheme 2 Substrate scope of MIDA-type boronate tethered intramolecular Diels–Alder reactions.

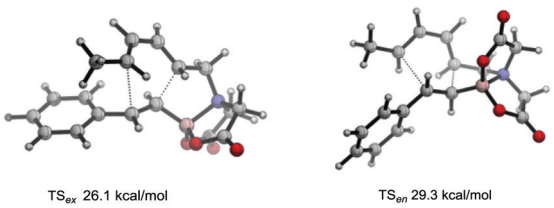
Encouraged by the above results, we extended the process to DABO boronate-like substrates. Literature studies have indicated that the DABO structures are less rigid than the MIDA counterparts.[12b] In this work, nevertheless, we were able to employ the DABO-type N–B coordination tether for successful intramolecular [4 + 2] reaction. The dehydration step could be smoothly done under mild conditions. Thus, the two components (**5** and **2**, Scheme 3) were stirred with anhydrous magnesium sulphate in dichloromethane at ambient temperature to complete the condensation step. After the removal of the solids by filtration, the crude product was immediately used in the intramolecular [4 + 2] reaction with conditions similar to the MIDA-like cases. Again, only the *exo*-stereoisomer was obtained. The substrate scope was briefly surveyed. In all cases, a very good *exo*-selectivity was achieved. Substituents such as methyl, methoxy, methylmercapto, nitro and chlorine groups on the phenyl rings (**7b–7f**), and a phthalimide group (**7g**) were all tolerated and the corresponding cycloaddition products were isolated in moderate to good yields. It is worth noting that cyclohexenone-3-boronic acid (**2o**), which had led to low yield of the product (**4o**) in the MIDA-type case, now served as an efficient dienophile, giving a D–A product **7h** in good yield. This outcome might be attributable to the mild condensation conditions that prevent the decomposition of **2o**.



Scheme 3 Substrate scope of DABO-type boronate tethered intramolecular Diels–Alder reactions.



Scheme 4 NB tether-induced stereoselective intramolecular [4 + 2] reaction.



Scheme 5 Computational study of the *endo*/*exo* selectivity of **3a**.

An enantiopure aminodiol (**8**, Scheme 4) was prepared from D-phenylglycinol and (*S*)-(−)-propylene oxide by epoxide opening and alkylation. When **8** was heated with (*E*)-styryl boronic acid at 80 °C, the condensation proceeded smoothly and was accompanied by concomitant partial intramolecular [4 + 2] reaction. Without separation, the crude product was subjected to the next reaction at 160 °C. Theoretically, dehydrative condensation of **8** with (*E*)-styryl boronic acid may form two *cis* diastereomers, (2*R*,4S_N,5*R*,8S_B)-**6$_o$** and (2*R*,4R_N,5*R*,8R_B)-**6$_i$** that are thermodynamically interconvertible *via* N–B bond cleavage, ring flipping and N–B bond reformation.[15a] Isomer **6$_i$** should be disfavoured because the steric collapsing between 2-methyl and 5-phenyl groups would lead to significant structural distortion. Further [4 + 2] cycloaddition of **6$_o$** and **6$_i$** therefore might form four stereoisomers (**7i$_o$**, **7i′$_o$**, **7i$_i$** and **7i′$_i$**). In practice, two isomers of the final product were observed in a 1 : 1 NMR ratio and isolated in high overall yield (80%). A single crystal of one isomer was obtained and its relative and absolute configuration was thus identified as **7i$_o$** (shown in Scheme 4) by X-ray diffraction analysis.[18] The other isomer was therefore deduced to be **7i′$_o$**. Remarkably, in this operationally simple two-step procedure, complex sp^3-rich polycyclic molecules containing up to 8 stereocenters were readily formed.

In order to understand the origin of the exceptionally high *exo*/*endo* selectivity in this tethered intramolecular [4 + 2] reaction, density functional theory (DFT) calculations were performed at the M06/6-31G* level of theory (Scheme 5). The intramolecular [4 + 2] reaction of **3a** was selected as the model reaction. TS_{en} and TS_{ex} represent the transition states of *endo*-selective and *exo*-selective reaction channel respectively. Compared with the lowest-lying conformation of **3a**, the gas phase activation free energy barrier for TS_{ex} is 26.1 kcal mol^{-1}, and TS_{en} is located 3.2 kcal mol^{-1} higher than TS_{ex}. This energy difference indicates the intramolecular [4 + 2] reaction to be highly *exo*-selective, in consistence with the experimental results.

Conclusions

In summary, a highly *exo*-selective intramolecular Diels–Alder reaction has been developed which utilizes an N–B dative bond-induced [3.3.0] bicyclic boronate unit as the structurally well-defined tether. In an operationally simple two-step process, various readily available alkenyl boronic acids were

successfully used as the dienophile, affording the [4 + 2] cycloaddition products in high yields and stereoselectivity. We are currently studying to extend this reaction for asymmetric synthesis of complex biologically important molecules.

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References

1 (*a*) K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2002, **41**, 1668; (*b*) K.-i. Takao, R. Munakata and K.-i. Tadano, *Chem. Rev.*, 2005, **105**, 4779; (*c*) M. Juhl and D. Tanner, *Chem. Soc. Rev.*, 2009, **38**, 2983.1; (*d*) P. Li and D. Menche, *Angew. Chem., Int. Ed.*, 2009, **48**, 5078.

2 For selected recent examples, see: (*a*) A. Mendoza, Y. Ishihara and P. S. Baran, *Nat. Chem.*, 2012, **4**, 21; (*b*) J. Deng, S. Zhou, W. Zhang, J. Li, R. Li and A. Li, *J. Am. Chem. Soc.*, 2014, **136**, 8185; (*c*) Y.-M. Zhao and T. J. Maimone, *Angew. Chem., Int. Ed.*, 2015, **54**, 1223; (*d*) C. Yuan, B. Du, L. Yang and B. Liu, *J. Am. Chem. Soc.*, 2013, **135**, 9291; (*e*) C. G. Newton, S. L. Drew, A. L. Lawrence, A. C. Willis, M. N. Paddon-Row and M. S. Sherburn, *Nat. Chem.*, 2015, **7**, 82; (*f*) J. Han, X. Li, Y. Guan, W. Zhao, W. D. Wulff and X. Lei, *Angew. Chem., Int. Ed.*, 2014, **53**, 9257.

3 (*a*) Taxol: M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325; (*b*) Oseltamivir phosphate: V. Farina and J. D. Brown, *Angew. Chem., Int. Ed.*, 2006, **45**, 7330; (*c*) Prostratin: A. Cashmore, R. Seelye, B. Cain, H. Mack, R. Schmidt and E. Hecker, *Tetrahedron Lett.*, 1976, **17**, 1737; (*d*) Manzamine A: R. Sakai, T. Higa, C. W. Jefford and G. Bernardinelli, *J. Am. Chem. Soc.*, 1986, **108**, 6404; (*e*) Abyssomicin C: B. Bister, D. Bischoff, M. Stroebele, J. Riedlinger, A. Reicke, F. Wolter, A. T. Bull, H. Zaehner, H. P. Fiedler and R. D. Suessmuth, *Angew. Chem., Int. Ed.*, 2004, **43**, 2574.

4 D. S. Matteson and M. L. Talbot, *J. Am. Chem. Soc.*, 1967, **89**, 1123.

5 W. G. Woods and I. S. Bengelsdorf, *J. Org. Chem.*, 1966, **31**, 2769.

6 (*a*) D. A. Singleton, J. P. Martinez and G. M. Ndip, *J. Org. Chem.*, 1992, **57**, 5768; (*b*) D. A. Singleton and J. P. Martinez, *J. Am. Chem. Soc.*, 1990, **112**, 7423.

7 (*a*) Y.-K. Lee and D. A. Singleton, *J. Org. Chem.*, 1997, **62**, 2255; (*b*) N. Noiret, A. Youssofi, B. Carboni and M. Vaultier, *J. Chem. Soc., Chem. Commun.*, 1992, 1105.

8 (*a*) C. Rasset and M. Vaultier, *Tetrahedron*, 1994, **50**, 3397; (*b*) J. D. Bonk and M. A. Avery, *Tetrahedron: Asymmetry*, 1997, **8**, 1149; (*c*) G. Lorvelec and M. Vaultier, *Tetrahedron Lett.*, 1998, **39**, 5185; (*d*) A. M. Sarotti, P. L. Pisano and S. C. Pellegrinet, *Org. Biomol. Chem.*, 2010, **8**, 5069; (*e*) H. Yoshida, M. Mukae and J. Ohshita, *Chem. Commun.*, 2010, **46**, 5253; (*f*) R. A. Batey, A. N. Thadani and A. J. Lough, *J. Am. Chem. Soc.*, 1999, **121**, 450.

9 G. Hilt and P. Bolze, *Synthesis*, 2005, 2091.

10 (*a*) H.-K. Cho, H.-Y. Lim and C.-G. Cho, *Org. Lett.*, 2013, **15**, 5806; (*b*) H. S. Shin, Y. G. Jung, H. K. Cho, Y. G. Park and C. G. Cho, *Org. Lett.*, 2014, **16**, 5718.

11 (*a*) L. Xu, S. Ding and P. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 1822; (*b*) L. Xu and P. Li, *Synlett*, 2014, 1799; (*c*) L. Xu and P. Li, *Chem. Commun.*, 2015, **51**, 5656.

12 (*a*) E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2007, **129**, 6716; (*b*) E. P. Gillis and M. D. Burke, *Aldrichimica Acta*, 2009, **42**, 17.

13 (*a*) Y. Yamamoto, T. Seko and H. Nemoto, *J. Org. Chem.*, 1989, **54**, 4734; (*b*) M. K. Reilly and S. D. Rychnovsky, *Synlett*, 2011, 2392.

14 (*a*) Z. He and A. K. Yudin, *J. Am. Chem. Soc.*, 2011, **133**, 13770; (*b*) E. M. Woerly, J. Roy and M. D. Burke, *Nat. Chem.*, 2014, **6**, 484; (*c*) J. Li, S. G. Ballmer, E. P. Gillis, S. Fujii, M. J. Schmidt, A. M. Palazzolo, J. W. Lehmann, G. F. Morehouse and M. D. Burke, *Science*, 2015, **347**, 1221.

15 (*a*) R. Contreras, C. García, T. Mancilla and B. Wrackmeyer, *J. Organomet. Chem.*, 1983, **246**, 213; (*b*) T. Mancilla, R. Contreras and B. Wrackmeyer, *J. Organomet. Chem.*, 1986, **307**, 1; (*c*) T. Mancilla, L. S. Zamudio-Rivera, I. B. Hiram, R. Santillan and N. Farfán, *ARKIVOC*, 2005, **6**, 366.

16 CCDC 1058696.

17 M. M. Vallejos, N. Grimblat and S. C. Pellegrinet, *RSC Adv.*, 2014, **4**, 36385.

18 CCDC 1058694.

