JOC The Journal of Organic Chemistry

Article

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00938 • Publication Date (Web): 01 May 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Quinine-Promoted, Enantioselective Boron-Tethered Diels–Alder Reaction by Anomeric Control of Transition State Conformation.

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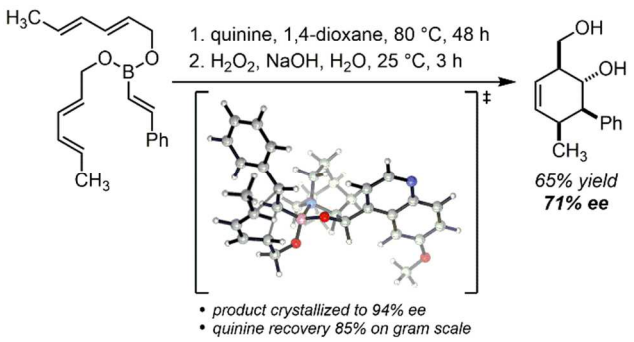
***KEYWORDS**: quinine, boron, Diels–Alder, enantioselective, cinchona alkaloids*

TOC:



Abstract

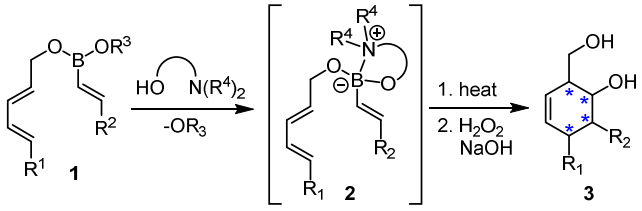
Diels–Alder reactions of tethered vinyl–metal species offer the opportunity to fashion highly functionalized diol intermediates for synthesis. We have developed the first enantioselective boron-tethered Diels–Alder reaction using quinine as a chiral promoter. Quinine recovery, enantioselectivity enhancement, and manipulation of the cyclohexene core are also investigated. DFT modeling calculations confirm the role of quinine as a bidentate ligand enhancing reaction rates. The enantioselectivity of the cycloaddition is proposed to originate from a boron-centered anomeric effect.

Introduction

We report a unique way to produce formal Diels–Alder (DA) adducts of substituted dienes and vinyl alcohols, versatile intermediates for synthesis.[1] The reaction is highly stereoselective where regioselectivity and diastereoselectivity are controlled utilizing a boronic acid tether. The absolute stereochemistry is imparted by use of naturally occurring chiral amino alcohol ligands. Theory shows that ligand chelation lowers the cycloaddition energy barrier, and anomeric effects at boron control enantioselectivity.

The tethering of a diene and vinyl boronate dienophile was initially reported by Batey and coworkers.[2,3] We envisioned that readily-available chiral amino alcohols could make this an enantioselective process. Boronate **1** contains two sites for ligand binding which would produce intermediate **2** after ligand exchange (Scheme 1). The chiral ligand modifies both electronic and steric properties of the dienophile and induces stereoselectivity. We discovered that the cyclic boronate complex **2** provides abundant control of stereoselectivity through the anomeric effect. Non-racemic diol **3**, containing four contiguous stereocenters, is produced upon work-up.

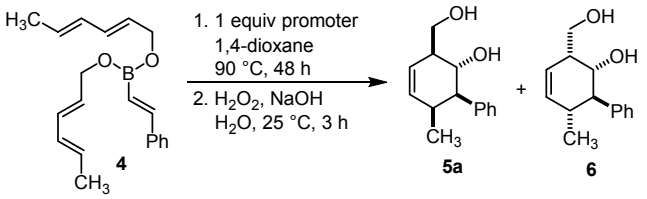
Scheme 1. Boron modification to control the tethered DA reaction.



Results and Discussion

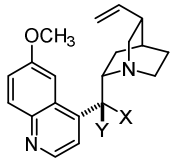
Boronate **4** was chosen for the initial investigation into a ligand-promoted DA reaction. Following cyclization, the carbon–boron bond was oxidized under basic peroxide conditions to produce diols **5a** and **6**. Original published conditions for cyclization of **4** required heating to 190 °C for 3 hours;[2a] however, at 90 °C only 10 % of the diol was isolated as a single diastereomer by ^{1}H NMR (entry 1, Table 1). An initial screen of common bidentate ligands pointed toward amine derivatives as reaction promoters. An amino acid (entry 2) and simple 1,2-amino alcohols (entries 2–6) produced promising levels of conversion and evidence of enantioselection. A significant increase in both values was observed with the cinchona alkaloids (entries 7–10). Efforts to increase the reaction enantioselectivity by structural modification were generally unproductive. Inversion of the C9 stereocenter[4] in quinine (Figure 1) was the most promising (entry 11), but quinine was chosen for investigation of the substrate scope due to its commercial availability. The lack of conversion and enantioselectivity for the 9-OTMS-quinine[5] (entry 12) suggests bidentate chelation of the promoter to boron is essential for the reaction.

Table 1. Survey of amine promoters for rate enhancement in the boron-tethered DA reaction.[a]



entry	promoter	yield (%)[b]	**5a**:**6**[b]	ee (%)[c]
1	none	10	>20:1	0
2	L-proline	57	>20:1	8
3	L-prolinol	14	>20:1	15
4	(+)-amino-2-indanol	28	>20:1	9
5	(+)-norephedrine	16	>20:1	12
6	(+)-pseudoephedrine	24	>20:1	17
7	quinine	74	>20:1	75
8	quinidine	66	15:1	-65
9	cinchonine	53	>20:1	-61
10	cinchonidine	56	>20:1	60
11	9-*epi*-quinine	37	>20:1	80
12	9-OTMS-quinine	8	>20:1	0

[a] Reactions were performed with 0.2 mmol of boronate tether **4** and 0.2 mmol of promoter in dioxane (0.2 M) at 90 °C for 48 h prior to oxidative work-up. [b]Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [c]Determined by HPLC.

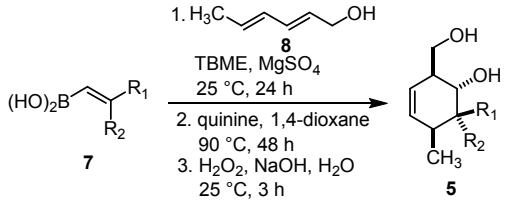


X = OH, Y = H: quinine
X = H, Y = OH: 9-*epi*-quinine
X = OTMS, Y = H: 9-OTMS-quinine

Figure 1. Structure of quinine and its derivatives.

Optimized conditions for the quinine-promoted boron-tethered DA reaction were applied to substrates containing structural variation on the dienophile portion. Tethered substrates were prepared by subjecting boronic acids (**7**) to anhydrous conditions in the presence of dienol **8**. The requisite tether was heated in the presence of quinine, followed by a basic peroxide workup. 1,3-Diols (**5**) were isolated in good yield for aryl substituted dienophiles (entries 1–7, Table 2). Pure *trans*-boronic acids (entries 1–7) led to the isolation of 1,3-diol **5** as a single diastereomer by ^{1}H NMR. The moderate levels of enantioselectivity remained unchanged as the electronic nature of the aromatic substituent was varied. Alkyl substituents were also investigated as the trans (entry 8) or cis (entry 9) boronate tether. These substrates required elevated reaction temperatures of 120 °C to achieve yields of 1,3-diol, which were much lower than aryl substrates. The moderate enantioselectivity for alkyl substituents (entries 8–9) was in line with vinyl aryl substituents.

Table 2. Boronic acid substrate scope.[a]

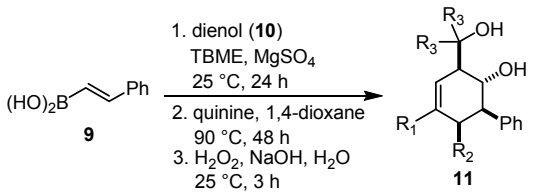


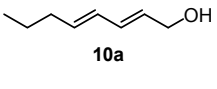
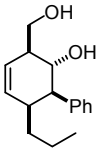
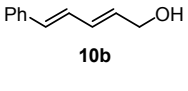
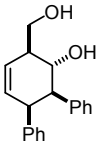
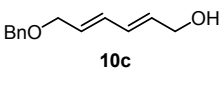
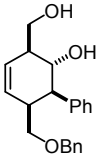
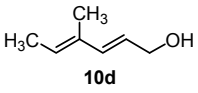
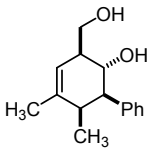
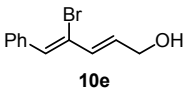
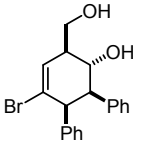
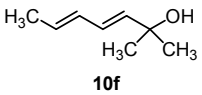
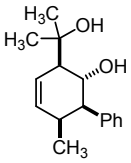
entry	R_1	R_2	yield (%)[b]	ee (%)[c]
1	Z = H	H	**5a**, 76	60
2	= CH_3	H	**5b**, 77	65
3	= Ph	H	**5c**, 50	64
4	= F	H	**5d**, 74	61
5	= Cl	H	**5e**, 71	69
6	= OCH_3	H	**5f**, 52	66
7	= CF_3	H	**5g**, 76	65
8[d]	CH_2Ph	H	**5h**, 13	50
9[d]	H	CH_3	**5i**, 27	64

[a]Reactions were performed by first generating a boronate tether with 1 equiv of **7**, 2 equiv of **8**, and 5 equiv $MgSO_4$ in TBME (0.5 M). A stock solution of boronate tether (0.3 mmol) in dioxane (0.2 M) was reacted with quinine (0.3 mmol) at 90 °C for 48 h prior to oxidative work-up. [b]Isolated yield for an average of 2 or more runs. [c]Determined by HPLC. [d]Reactions were performed at 120 °C in chlorobenzene.

The diene structure was varied to explore limitations in the enantioselective boron-tethered DA (Table 3). Dienols (**10**) were tethered to boronic acid **9**, and used without purification. 1,3-Diols (**11**) were again isolated as single diastereomers from geometrically pure dienols in similar yields and enantioselectivities as observed in Table 2. Manipulation of the dienol at C5 was well tolerated, where arenes and ethers could be employed in moderate yield (entries 1–3, Table 3). Addition of substituents at C4 was uneventful (entry 4), and the introduction of a vinyl bromide was possible (entry 5). A gem-dimethyl dienol participated with reduced yield (entry 6) even though no tether was observed by ^{1}H NMR prior to quinine-promoted cyclization. The reaction enantioselectivity was unchanged throughout the series of dienol substrates.

Table 3. Substrate scope with respect to dienols.[a]



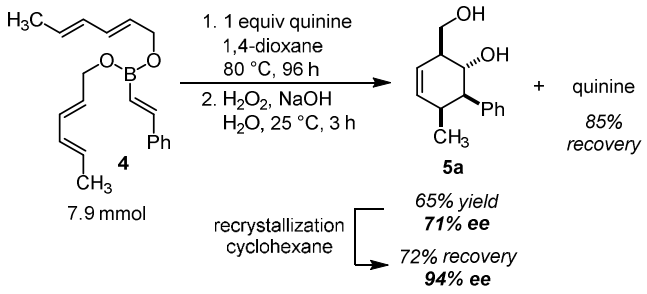
entry	dienol	product	yield (%)[b]	ee (%)[c]
1	 **10a**		**11a**, 59	58
2	 **10b**		**11b**, 61	53
3	 **10c**		**11c**, 60	59
4	 **10d**		**11d**, 72	59
5	 **10e**		**11e**, 54	56
6[d]	 **10f**		**11f**, 45	61

[a]Reactions were performed by first generating a boronate tether with 1 equiv of **9**, 2 equiv of **10**, and 5 equiv $MgSO_4$ in TBME (0.5 M). A stock solution of boronate tether (0.3 mmol) in dioxane (0.2 M) was reacted with quinine (0.3 mmol) at 90 °C for 48 h prior to oxidative work-up. [b]Isolated yield for an average of 2 or more runs. [c]Determined by HPLC. [d]Boronate tether was not preformed.

Moderate enantioselectivities and a requirement for stoichiometric amounts of quinine are two major aspects of the enantioselective boron-tether DA reaction that diminish its practical use in synthesis. A large-scale reaction was performed with boronate tether **4** to address these concerns (Scheme 2). Standard conditions were employed, but the reaction was heated to 80 °C for 96 hours in an effort to improve enantioselectivity. Diol **5a** was isolated in 65% yield with

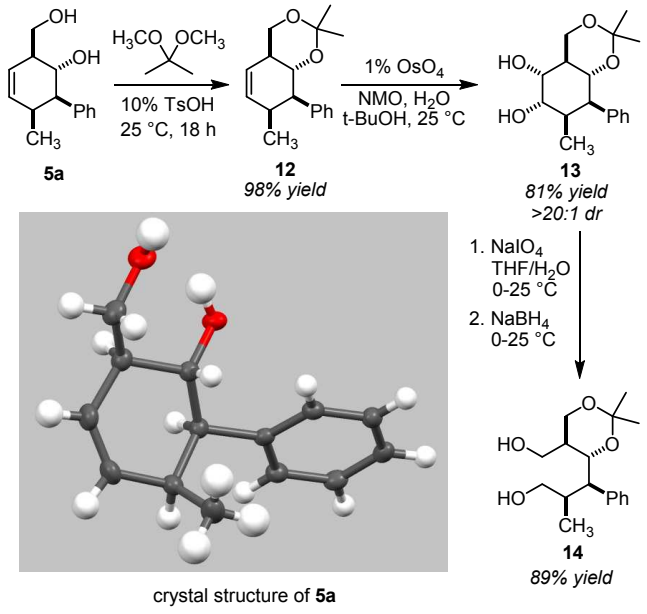
71% ee. A majority of the quinine promoter could be recovered unchanged from the organic extraction solution by an aqueous acid wash. Recrystallization of **5a** in cyclohexane provided an increase in enantiomeric excess with 72% recovery and 94% ee. The re-isolation of quinine and increased enantioselectivity greatly improve the method's synthetic potential.

Scheme 2. Reaction scale-up with quinine recovery and enantioenrichment of **5a**.



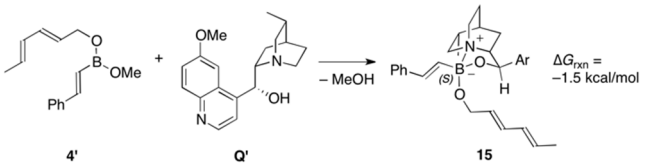
Highly enantioenriched diol **5a** contains four contiguous stereocenters and represents a molecule with significant synthetic utility. The absolute stereochemistry of **5a** was obtained from single crystal X-ray analysis following enantioenrichment (Scheme 3). Functionalization of **5a** began with protection of the 1,3-diol as the acetonide (**12**) in 98% yield. We anticipated that acetonide formation would lock the cyclohexene conformation where the allylic methyl group is in the axial position. Dihydroxylation occurred on the opposite face relative to the methyl group to produce diol **13** as a single diastereomer in 81% yield. Ring cleavage of **13** can be accomplished to generate the acyclic diol **14** in excellent yield after aldehyde reduction without epimerization. Diol **14** represents additional synthetic potential as an acyclic synthon containing four contiguous stereocenters.

Scheme 3. Crystal structure and functionalization of diol **5a**.



We explored the mechanism and origins of stereoselectivity by density functional theory (DFT) computations.[6] The geometry optimizations and frequency computations were performed at the B3LYP[7]/6-31G(d) level of theory, and single-point energies were obtained on the optimized geometries using the more accurate M06-2X functional[8] and the def2-TZVPP basis set.[9] The vinyl group of quinine was truncated to a methyl group (**Q'**) for simplicity. Molecule **4'**, in which a methyl group replaces one of the dienyl chains of **4**, was also used in the computations for simplicity. The ligand exchange between **4'** and **Q'**, leading to the bidentate complex **15** and methanol, is exergonic (ΔG_{rxn} = –1.5 kcal/mol; Scheme 4). The boron atom in complex **15** has an *S* configuration (Figure 1). The corresponding *R*-configured bidentate complex (**16**) is 4.8 kcal/mol less stable than **15** and thus its formation by the ligand exchange process is thermodynamically uphill.

Scheme 4. Ligand exchange between **4'** and **Q'** to form **15** and methanol.



The preference for the *S* configuration at the boron atom of the reactant can be explained by the structure of the five-membered ring formed upon chelation by the amino alcohol moiety of quinine (Figure 2). In **15**, the ring adopts an envelope conformation with boron at the flap position, while in **16** the ring is slightly more twisted. In both **15** and **16**, the chelating ring is rigidified by fusion with the quinuclidine cage along its N–C bond and by the presence of the quinoline ring, which occupies a pseudoequatorial position. The oxygen substituent is positioned axial on the flap in **15** and pseudoequatorial in **16**. This axial preference is as expected for an anomeric effect, minimizing O-O lone pair repulsions and maximizing $n_O \rightarrow \sigma_{BO}^*$ hyperconjugation.[10] To investigate the impact of the orientation of the oxygen substituent on energy, geometry optimizations of models **17-ax** and **17-eq**, with the ring dihedrals constrained at the values found in **15** and **16**, respectively, were performed (Figure 3). Both **17-ax** and **17-eq** display an envelope conformation. **17-ax** is more stable than **17-eq** by 2.4 kcal/mol. Thus, the oxygen substituent prefers an axial position, as in pyranoses, forming the favored conformation resulting from the exo-anomeric effect. In **15**, or the model **17-ax**, the COBOC unit is gauche+,gauche+, while in **16**, or the model **17-eq**, it is anti,anti, and the former is strongly preferred in dimethoxymethane or related anomeric systems due to hyperconjugative stabilization.

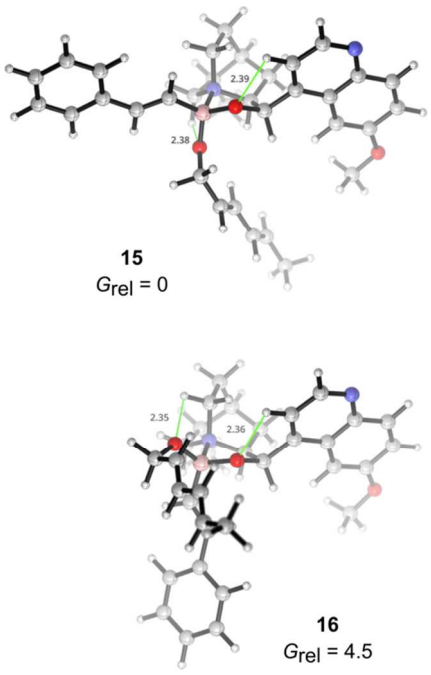


Figure 2. Computed structures and energies (in kcal/mol) of bidentate complexes **15** and **16**.

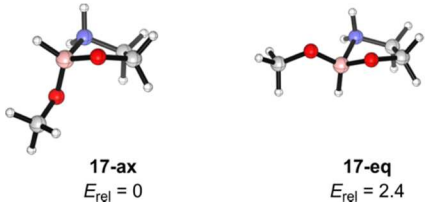


Figure 3. Structures and energies (in kcal/mol) of axial and equatorial conformers **17-ax** and **17-eq**.

The free energy of activation of the intramolecular DA reaction of **4'** was calculated as 30.5 kcal/mol. Reaction from the bidentate complexes was predicted to be more facile, ($\Delta G^{\ddagger}$ = 26.8 kcal/mol), while the monodentate pathway (not shown) has a higher activation free energy ($\Delta G^{\ddagger}$ = 34.1 kcal/mol) than the reaction of **4'**. Thus, only the bidentate transition structures are discussed in detail here. Figure 4 shows the lowest energy transition structures for the formation of the four possible DA stereoisomers. View (A) reveals the forming fused 6/5 rings and the conformation of the tether in detail, while view (B) emphasizes the quinine moiety and the chelated ring. The tether's B–O bond occupies a pseudoaxial position with respect to the chelated rings in all of the transition structures. The major stereoisomer arises from the $endo_1$ TS. This TS is lower in energy than the exo_1-TS by 2.2 kcal/mol, in good agreement with the exclusive endo diastereoselectivity observed experimentally. The $endo_1$-TS is also favored to the $endo_2$-TS by 0.6 kcal/mol. This is consistent with the sense of enantiocontrol experimentally observed, although the level of enantioselectivity was underestimated.

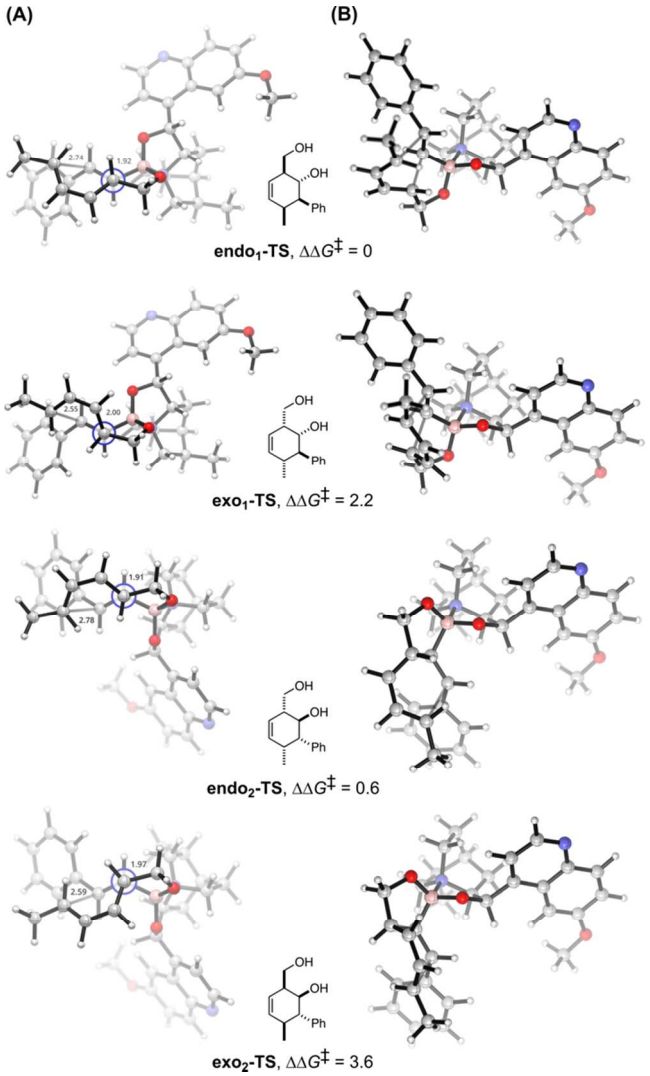


Figure 4. DA transition structure geometries and energies (in kcal/mol). (A) Newman projections along the shorter of the forming C–C bonds. (B) View emphasizing the quinine moieties and the chelated rings.

The $endo_1$ and exo_1 transition structures expose the same face of the dienophile for cycloaddition. The configuration of boron in both transition structures is *S*, as formed by the anomeric effect. As shown in the overlay in Figure 5, these two transition structures have practically the same geometries with respect to the dienophile, the chelated ring, and the quinine moieties. The $endo_1$-TS is less strained because of the trans 6/5 ring junction formed by the partial C–C bond. The intrinsic stereoselectivity in the intramolecular DA reaction of nona-1,3,8-triene is only slightly (69:31 at 250 °C) in favor of trans fusion (endo),[11] but here the exo_1-TS experiences significant 1,3-diaxial repulsion between the cyclic B–O bond and the diene C–H bond.

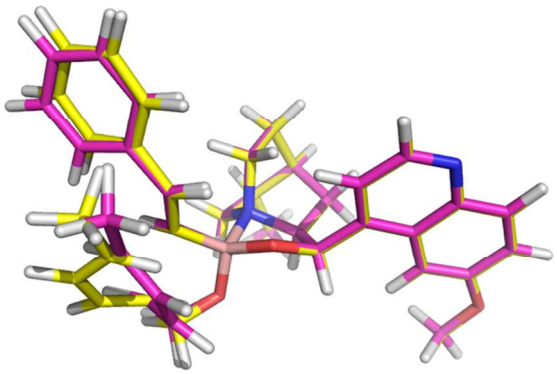


Figure 5. Overlay of endo$_1$ (yellow) and exo$_1$ (magenta) transition structures.

The endo$_1$ and endo$_2$ transition structures, which lead to opposite enantiomers, feature the boron atom in opposite absolute configurations. The boron atom in the endo$_1$-TS has the *S* configuration, while the higher energy endo$_2$-TS display the less favorable *R* configuration. Thus, the preference for a boron-*S* configuration observed in the reactant, due to the anomeric effect, is preserved at the transition state and critical for enantioinduction.

Conclusions

In summary, an enantioselective boronate-tethered intramolecular Diels–Alder reaction has been developed. The mechanism and origins of enantioselection by the quinine promoter were delineated by DFT calculations. The highly functionalized diol products are produced in good yield with moderate enantioselectivity that can be enhanced by crystallization. The endo/exo stereoselectivity is determined by the anomeric effect and the stereochemistry of the 6/5 ring junction formed upon cycloaddition. Quinine controls the sense of asymmetric induction through binding the boron atom in a five-membered ring, such that the quinoline ring is pseudoequatorial and the B–O bond in the tether occupies the anomerically favorable axial position (Figure 6). Future experiments will be directed toward improvement of enantioselectivities based on the proposed transition state model and development of a catalytic, enantioselective process.

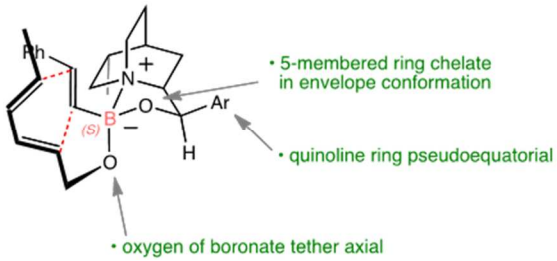


Figure 6. Origins of asymmetric induction by quinine in the endo boronate-tethered DA reaction.

Experimental Section

General: ^{1}H NMR spectra were recorded on a 300 MHz, 400 MHz, or 600 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on the same spectrometers (75, 100, or 151 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). High resolution mass spectrometry data was acquired with a MicrOTOF-Q instrument with electron spray ionization (ESI, positive mode). Infrared (IR) spectra were obtained using an FT-IR spectrometer.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 32 to 63μm). Thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60 plates with visualization by a UV lamp (254 nm) or basic potassium permanganate in water followed by heating. Analytical high performance liquid chromatography (HPLC) was performed on an instrument equipped with an autosampler and a UV detector. A Daicel CHIRALPAK column 0.46 cm x 25 cm) using a mixed solvent (hexane/isopropanol) at a flow rate of 1 mL/minute for data pertaining to enantiomeric excess calculations.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of argon. All solvents were purchased as anhydrous solvents and used under an inert atmosphere. Quinine and *trans, trans*-2,4-hexadien-1-ol was purchased from Alfa Aesar. (2E,4E)-octa-2,4-dien-1-ol was purchased from Ark Pharm. Boronic acids, boronic acid pinacol esters, and DL-proline were purchased from Sigma Aldrich and used as received.

Dienol Synthesis. (2E,4E)-5-phenylpenta-2,4-dien-1-ol (**10b**),[12] (2E,4E)-4-methylhexa-2,4-dien-1-ol (**10d**),[13] and (3E,5E)-2-methylhepta-3,5-dien-2-ol (**10f**)[14] were synthesized by known procedures.

(2E,4E)-6-(Benzyloxy)hexa-2,4-dien-1-ol (10c): *trans*-4-(Benzyloxy)but-2-enal[15] (0.969 g, 5.5 mmol, 1 eq) and dichloromethane (11 mL) were added to a flame-dried round bottom flask containing a magnetic stir bar. (Ethoxycarbonylmethylene)triphenylphosphorane (2.090 g, 6.0 mmol, 1.1 equiv) was added at room temperature and the reaction turned pale yellow. The reaction was stirred under argon at room temperature for 24 h. The crude mixture was concentrated to a brown oil, which was taken to the next step without further purification. Toluene (11 mL) and a magnetic stir bar were added to the crude diene ester. The flask was purged with argon and cooled to 0 °C. A 1.0 M solution in toluene of DIBAL-H (11 mL, 11 mmol, 2 equiv) was added dropwise fast, and the reaction was warmed to room temperature and stirred for 3 h. Saturated Rochelle's salt (9 mL) and ethyl acetate (10 mL) were added. The solution was stirred 30 min until two visible layers formed. The mixture was transferred to a separatory funnel and diluted with H_2O (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with saturated brine (35 mL) and dried with $MgSO_4$. All solids were filtered off through a vacuum fritted filter, and the solution was concentrated to a brown residue. Purification by flash chromatography afforded 488.0 mg (44%, 8:1 (2E,4E):(2E:4Z)) of the title compound as a viscous oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.38-7.32 (4H, m), 7.32-7.28 (1H, m), 6.33-6.24 (2H, m), 5.89-5.78 (2H, m), 4.53 (2H, s), 4.19 (2H, d, *J* = 5.2 Hz), 4.09 (2H, d, *J* = 5.6 Hz), 1.72 (1H, br s). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 137.7, 132.4, 129.8, 129.2, 128.0, 127.4,

127.3, 71.7, 69.9, 62.4. IR (KBr plate): 3381.1, 3029, 2854, 1453, 1361, 1085 cm^{-1}. HRMS: Calculated for $C_{13}H_{16}O_2Na^+$: 227.1048 ($M+Na^+$), found 227.1048 ($M+Na^+$).

(2*E*,4*Z*)-4-bromo-5-phenylpenta-2,4-dien-1-ol (10e): α-Bromocinnamaldehyde (2.110 g, 10 mmol, 1 equiv) and dichloromethane (20 mL) were added to a flame-dried round bottom flask containing a magnetic stir bar. (Ethoxycarbonylmethylene)triphenylphosphorane (3.83 g, 11 mmol, 1.1 equiv) was added to the solution in one portion. The reaction was stirred at room temperature for 24 h and concentrated to afford ethyl (2E,4Z)-4-bromo-5-phenylpenta-2,4-dienoate (2.6513 g, 94%) as a crude residue. NMR data collected matched previously reported spectra.[16] Crude (2E,4Z)-4-bromo-5-phenylpenta-2,4-dienoate (2.6513 g, 9.4 mmol, 1 equiv) was dissolved in toluene (12 mL) and a magnetic stir bar was added. A 1.0 M solution of DIBAL-H in toluene (18.8 mL, 18.8 mmol, 2 equiv) was added at 0 °C under argon. The reaction was warmed to room temperature and stirred for 4 hours. Saturated Rochelle's salt (18 mL) and ethyl acetate (20 mL) were added. The solution was stirred 30 min until two visible layers formed. The mixture was transferred to a separatory funnel and diluted with H_2O (20 mL) and ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with saturated brine (35 mL) and dried with $MgSO_4$. The mixture was filtered and concentrated by rotary evaporation. The crude residue was purified by flash chromatography to afford 1.8430 g (82%) of the title compound as a viscous oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71-7.67 (2H, m), 7.42-7.29 (3H, m), 6.99 (1H, br s), 6.52-6.47 (1H, m), 6.41-6.34 (1H, m), 4.39 (2H, br s), 1.50 (1H, br s). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 135.6, 134.1, 131.9, 131.1, 129.5, 128.3, 128.2, 122.6, 62.7. IR (KBr plate): 3328, 2919, 1445 cm^{-1}. HRMS: Calculated for $C_{11}H_{11}BrONa^+$: 260.9885 ($M+Na^+$), found 260.9884 ($M+Na^+$).

Procedure for Amine Promoter Screening: *trans, trans*-2,4-Hexadien-1-ol (785.1 mg, 8 mmol, 2 equiv), *trans*-2-phenylvinylboronic acid (591.9 mg, 4 mmol, 1 equiv), and $MgSO_4$ (20 mmol, 5 equiv) were suspended in methyl *tert*-butyl ether (8 mL) in an oven-dried 20 mL vial containing a Teflon-coated magnetic stir bar. The reaction was stirred under argon at room temperature for 24 h. The suspension was filtered over Celite and concentrated *in vacuo,* yielding the boronate tether (**4**) which was dissolved in dry 1,4-dioxane (0.2 M final concentration) and used without further purification.

An oven-dried 4 mL vial containing a Teflon-coated magnetic stir bar was charged with a 0.2 M stock solution of boronate tether **4** (0.5 mL, 0.1 mmol) in 1,4-dioxane. A promoter (0.1 mmol) was added, and the vial was sealed under argon with a screw cap containing a Teflon insert. The reaction was stirred at 90 °C for 48 h. The reaction was cooled to room temperature and diluted with THF (0.5 mL). 10% NaOH (0.5 mL) was added, followed by dropwise addition of 30% H_2O_2 (0.3 mL) (CAUTION: EXOTHERMIC). The mixture was stirred at room temperature for 2 h. After this time, the reaction was quenched with 1 mL of 10% sodium thiosulfate. The layers were separated, and the aqueous layer was extracted two times with 5 mL ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The ratio of **5a**:**6** was determined by ^1H-NMR. The yield of **5a** was determined after purification by silica gel chromatography (1:1 hexanes/ethyl acetate).

Diol Esterification for HPLC Analysis: The cyclized diol (0.03 mmol), *p*-nitrobenzoyl chloride (0.075 mmol), triethylamine (0.09 mmol) and dichloromethane (0.3 mL) were added to an oven-dried 4 mL vial containing a Teflon-coated magnetic stir bar. The solution was stirred under argon at room temperature for 12 h, concentrated to a crude residue, and purified by flash chromatography. ^1H-NMR confirmed the sole formation of the least hindered, mono-ester product. Addition of 10 mol % of *N*,*N*-dimethylaminopyridine (DMAP) will facilitate the benzoylation of both alcohols to generate the di-ether product. The pure isolate was then redissolved and analyzed by chiral HPLC for determination of enantiomeric excess.

General Procedure for the Diels–Alder Cyclization Sequence: Boronate tethers were generated as 0.2 M solutions based on the boronic acid as described in Procedure A. All

tethers were checked for formation by ^{1}H-NMR in $CDCl_3$ and used without further purification. A 0.2 M solution of the crude boronate diene tether in dry 1,4-dioxane or chlorobenzene (1.5 mL, 0.3 mmol) and quinine (93.7 mg, 0.3 mmol) were added to an oven-dried 4 mL vial containing a Teflon-coated magnetic stir bar. The vial was sealed under argon with a screw cap containing a Teflon insert. The reaction was stirred under argon at 90 °C for 48-72 h before cooling to room temperature. The mixture was diluted with THF (1.5 mL) and 10% NaOH (1.5 mL) was added. 30% H_2O_2 (0.9 mL) was added dropwise (CAUTION: EXOTHERMIC), and the mixture was stirred under open air at room temperature for 2 h. After this time, the reaction was quenched by addition of 10% sodium thiosulfate (3 mL). The organic layer was separated, and the aqueous layer was extracted two times with 10 mL of ethyl acetate. The organic layers were combined and dried with anhydrous $MgSO_4$ and concentrated to a crude residue. Purification by flash chromatography afforded the cyclized diol where yield was based on the amount of boronic acid initially added. Racemic product for enantiomer separation was produced by the same general method with DL-Proline (34.5 mg, 0.3 mmol) as promoter.

(1R,2R,3S,6S)-3-(Hydroxymethyl)-6-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (5a):[2a] A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 58.9 mg (0.6 mmol) of *trans, trans*-2,4-hexadien-1-ol and 44.4 mg (0.3 mmol) of *trans*-2-phenylvinylboronic acid (44.3 mg, 0.3 mmol), was reacted via the general procedure. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded a white solid (39.0 mg, 60% yield, 60% ee). ^{1}H NMR (400Hz, $CDCl_3$) δ 7.39-7.35 (2H, m), 7.29-7.23 (3H, m), 5.85 (1H, ddd, *J* = 9.9, 4.9, 2.7 Hz), 5.38-5.35 (1H, m), 4.29 (1H, dd, *J* = 11.5, 8.3 Hz), 3.87 (1H, dd, *J* = 10.5, 4.1 Hz), 3.75 (1H, dd, *J* = 10.5, 8.2 Hz), 3.17 (1H, dd, *J* = 11.5, 5.7 Hz), 2.76 (1H, br s), 2.57-2.51 (1H, m), 2.50-2.45 (1H, m), 2.36 (1H, br s), 0.74 (3H, d, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 135.1, 129.0, 128.7, 126.7, 123.5, 69.2, 67.0, 51.3, 47.0, 37.0, 16.9. IR (KBr plate): 3371, 1663, 1448, 1035 cm^{-1}. HRMS: Calculated for $C_{14}H_{18}NaO_2^+$: 241.1199 (M+Na$^+$), found 241.1199 (M+Na$^+$).

(1R,2R,3S,6S)-3-(Hydroxymethyl)-4',6-dimethyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (5b): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 58.9 mg (0.3 mmol) of *trans, trans*-2,4-hexadien-1-ol and 48.6 mg (0.6 mmol) of *trans*-2-(4-methylphenyl)vinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded a white solid (52.4 mg, 75% yield, 65% ee). ^{1}H NMR ($CDCl_3$, 400Hz) δ 7.19-7.12 (4H, m), 7.13 (2H, d, *J* = 8.1 Hz), 5.84 (1H, ddd, *J* = 9.9, 5.0, 2.7 Hz), 5.35 (1H, ddd, *J*= 9.9, 2.2, 1.3 Hz), 4.27-4.22 (1H, m), 3.86-3.82 (1H, m), 3.73 (1H, dd, *J* = 10.5, 8.1 Hz), 3.13 (1H, dd, *J* = 11.5, 5.6 Hz), 2.92 (1H, br s), 2.55-2.49 (1H, m), 2.47-2.40 (2H, m), 2.35 (3H, s), 0.74 (3H, d, *J* = 7.3 Hz). Spectral data matched that previously published.[2a]

(1R,2R,3S,6S)-3-(Hydroxymethyl)-6-methyl-1,2,3,6-tetrahydro-[1,1':4',1''-terphenyl]-2-ol (5c): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 58.9 mg (0.6 mmol) of *trans, trans*-2,4-hexadien-1-ol and 67.2 mg (0.3 mmol) of *trans*-2-(4-biphenyl)vinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded a white solid (43.6 mg, 49% yield, 64% ee). ^{1}H NMR ($CDCl_3$, 400Hz) δ 7.63-7.60 (4H, m), 7.47-7.43 (2H, m), 7.38-7.35 (1H, m), 7.34-7.31 (2H, m), 5.87 (1H, ddd, *J* = 9.9, 4.9, 2.7 Hz), 5.39-5.36 (1H, m), 4.33 (1H, dd, *J* = 11.5, 8.2 Hz), 3.90 (1H, dd, *J* = 10.5, 4.1 Hz), 3.77 (1H, dd, *J* = 10.5, 8.2 Hz), 3.22 (1H, dd, J= 11.5, 5.6 Hz), 2.60-2.47 (3H, m), 1.28 (1H, br s), 0.79 (3H, d, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.8, 139.6, 138.8, 135.1, 129.5, 128.8, 127.3, 127.2, 127.0, 123.5, 69.2, 67.0, 51.0, 47.1, 37.0, 17.0. IR (KBr Plate): 3381, 2958, 1486, 1075 cm^{-1}. HRMS: Calculated for $C_{20}H_{22}NaO_2^+$: 317.1509 (M+Na$^+$), found 317.1512 (M+Na$^+$).

(1R,2R,3S,6S)-4'-Fluoro-3-(hydroxymethyl)-6-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (5d): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 58.9 mg (0.6 mmol) of *trans, trans*-2,4-hexadien-1-ol and 49.8 mg (0.3 mmol) of *trans*-2-(4-fluorophenyl)vinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (2:1 hexanes/ethyl acetate) afforded a white solid (53.2 mg, 75% yield, 61% ee). ^{1}H NMR ($CDCl_3$, 400Hz) δ 7.22-7.17 (2H, m), 7.08-7.02 (2H, m), 5.83 (1H, ddd, *J* = 9.9, 4.9, 2.7 Hz), 5.33 (1H, dt, *J* = 9.9, 1.5 Hz), 4.21 (1H, dd, *J* = 11.5, 8.2 Hz), 3.85 (1H, dd, *J* = 10.5, 4.1 Hz), 3.70 (1H, dd, *J* = 10.5, 8.4 Hz), 3.15 (1H, dd, *J* = 11.5, 5.6 Hz), 2.86 (1H, br s), 2.66 (1H, br s), 2.54-2.39 (2H, m), 0.71 (3H, d, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6 (d, *J*= 243.1 Hz), 135.5 (d, *J*= 3.3 Hz), 134.9, 130.4 (d, *J*= 7.7 Hz), 123.4, 115.3 (d, *J*= 21.1 Hz), 69.2, 66.9, 50.3, 47.1, 37.0, 16.7. IR (KBr Plate): 3257, 2877, 1886, 1267 cm^{-1}. HRMS: Calculated for $C_{14}H_{17}NaFO_2^+$: 259.1107 (M+Na$^+$), found 259.1105 (M+Na$^+$).

(1R,2R,3S,6S)-4'-Chloro-3-(hydroxymethyl)-6-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (5e): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 58.9 mg (0.6 mmol) of *trans, trans*-2,4-hexadien-1-ol and 54.7 mg (0.3 mmol) of *trans*-2-(4-chlorophenyl)vinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded a white solid (54.6 mg, 72% yield, 69% ee). ^{1}H NMR ($CDCl_3$, 400Hz) δ 7.36-7.32 (2H, m), 7.20.7.17 (2H, m), 5.84 (1H, ddd, *J* = 9.9, 4.9, 2.7 Hz), 5.34 (1H, dt, *J* = 9.9, 1.5 Hz), 4.24 (1H, dd, *J* = 11.5, 8.2 Hz), 3.89 (1H, m), 3.73 (1H, dd, *J* = 10.4, 8.4 Hz), 3.15 (1H, dd, *J* = 11.5, 5.7 Hz), 2.65-2.39 (4H, m), 0.72 (3H, d, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 134.9, 132.4, 130.3, 128.7, 123.4, 69.1, 67.0, 50.6, 47.1, 36.9, 16.8. IR (KBr Plate): 3365, 2875, 1492, 1089 cm^{-1}. HRMS: Calculated for $C_{14}H_{17}NaClO_2^+$: 275.0811 (M+Na$^+$), found 275.0809 (M+Na$^+$).

(1R,2R,3S,6S)-3-(Hydroxymethyl)-4'-methoxy-6-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (5f): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 58.9 mg (0.6 mmol) of *trans, trans*-2,4-hexadien-1-ol and 53.4 mg (0.3 mmol) of *trans*-2-(4-Methoxyphenyl)vinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded a white solid (40.8 mg, 55% yield, 66% ee). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.20-7.14 (2H, m), 6.95-6.89 (2H, m), 5.85 (1H, ddd, *J* = 9.9, 4.9, 2.7 Hz), 5.36 (1H, d, *J* = 10.0 Hz), 4.23 (1H, dd, *J* = 11.5, 8.3 Hz), 3.91-3.84 (1H, m), 3.82 (3H, s), 3.80-3.71 (1H, m), 3.12 (1H, dd, *J* = 11.5, 5.6 Hz), 2.65 (1H, br s), 2.58-2.50 (1H, m), 2.49-2.38 (1H, m), 2.20 (1H, br s), 0.75 (3H, d, *J* = 7.2 Hz). Spectral data matched that previously published.[2a]

(1R,2R,3S,6S)-3-(Hydroxymethyl)-6-methyl-4'-(trifluoromethyl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (5g): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 58.9 mg (0.6 mmol) of *trans, trans*-2,4-hexadien-1-ol and 64.8 mg (0.3 mmol) of *trans*-2-[4-(Trifluoromethyl)phenyl]vinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (3:1 hexanes/ethyl acetate) afforded the title compound (57.8 mg, 67% yield, 58% ee). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.60 (2H, d, *J* = 8.0 Hz), 7.35 (2H, d, *J* = 8.0 Hz), 5.93-5.78 (1H, m), 5.30 (1H, d, *J* = 9.9 Hz), 4.28 (1H, dd, *J* = 11.5, 8.1 Hz), 3.85 (1H, dd, *J* = 10.4, 4.1 Hz), 3.70-3.63 (1H, m), 3.21 (1H, dd, *J* = 11.5, 5.6 Hz), 2.94 (2H, br s), 2.54-2.40 (2H, m), 0.69 (3H, d, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.5, 134.8, 129.3, 128.8 (q, *J* = 32.4 Hz), 125.3 (q, *J* = 3.7 Hz), 124.23 (q, *J* = 271.9 Hz), 123.3, 69.0, 67.0, 50.8, 47.1, 36.9, 16.7. IR (KBr plate): 3272, 2922, 1327, 1158 cm^{-1}. HRMS: Calculated for $C_{15}H_{17}F_3O_2Na^+$: 309.1073 (M+Na$^+$), found 309.1078 (M+Na$^+$).

(1R,2S,5S,6S)-6-benzyl-2-(hydroxymethyl)-5-methylcyclohex-3-en-1-ol (5h): A 0.2 M chlorobenzene solution of the crude boronate diene tether, which corresponds to 58.9 mg

(0.6 mmol) of *trans, trans*-2,4-hexadien-1-ol and 48.6 mg (0.3 mmol) of *trans*-3-phenyl-1-propen-1-ylboronic acid, was reacted via the general procedure, except heating to 120 °C. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded a white solid (9.2 mg, 13% yield, 50% ee). ^{1}H NMR ($CDCl_3$, 400Hz) δ 7.33-7.24 (4H, m), 7.23-7.17 (1H, m), 5.72 (1H, ddd, *J* = 9.9, 5.3, 2.7 Hz), 5.22 (1H, ddd, *J* = 9.8, 2.3, 1.1 Hz), 3.90 (1H, dd, *J* = 10.3, 4.0 Hz), 3.80 (1H, dd, *J* = 11.0, 8.2 Hz), 3.67 (1H, dd, *J* = 10.3, 8.9 Hz), 3.33 (1H, dd, *J* = 14.1, 4.5 Hz), 2.80 (1H, br s), 2.49-2.40 (2H, m), 2.30 (1H, br s), 2.27-2.18 (1H, m), 2.18-2.08 (1H, m), 1.62 (1H, br s), 0.91 (3H, d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.7, 135.7, 128.9, 128.4, 125.8, 122.9, 72.4, 67.5, 47.8, 44.7, 33.5, 31.8, 15.4. IR (KBr Plate): 3348, 2875, 1495, 1092 cm^{-1}. HRMS: Calculated for $C_{15}H_{20}NaO_2^+$: 255.1359 (M+Na$^+$), found 255.1356 (M+Na$^+$).

(1R,2S,5S,6R)-2-(hydroxymethyl)-5,6-dimethylcyclohex-3-en-1-ol (5i): A 0.2 M chlorobenzene solution of the crude boronate diene tether, which corresponds to 58.9 mg (0.6 mmol) of *trans, trans*-2,4-hexadien-1-ol and 25.8 mg (0.6 mmol) of *cis*-1-propen-1-ylboronic acid, was reacted via the general procedure, except heating to 120 °C. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded a white solid (12.6 mg, 27% yield, 64% ee). ^{1}H NMR ($CDCl_3$, 400Hz) δ 5.65 (1H, ddd, *J* = 10.0, 4.0, 2.4 Hz), 5.30 (1H, ddd, *J* = 10.0, 2.9, 1.7 Hz), 3.89 (1H, dd, *J* = 6.7, 3.3 Hz), 3.81 (1H, dd, *J* = 10.5, 4.3 Hz), 3.60 (1H, dd, *J* = 10.5, 8.7 Hz), 2.42-2.20 (3H, m), 2.14-2.03 (1H, m), 1.72-1.62 (1H, m), 1.06 (3H, d, *J* = 7.2 Hz), 1.01 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 134.2, 122.6, 71.9, 66.6, 43.0, 38.4, 36.2, 20.6, 14.1. IR (KBr Plate): 3352, 2875, 1455, 1124 cm^{-1}. HRMS: Calculated for $C_9H_{16}NaO_2^+$: 179.1048 (M+Na$^+$), found 179.1043 (M+Na$^+$).

(1R,2R,3S,6S)-3-(hydroxymethyl)-6-propyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (11a): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 75.7 mg (0.6 mmol) of (2E,4E)-octa-2,4-dien-1-ol (**10a**) and 44.4 mg (0.3 mmol) of *trans*-2-phenylvinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (2:1 hexanes/ethyl acetate) afforded a white solid (44.9 mg, 61% yield, 58% ee). ^{1}H NMR ($CDCl_3$, 400Hz) δ 7.40-7.34 (2H, m), 7.30-7.20 (3H, m), 5.97 (1H, ddd, *J* = 10.0, 5.9, 2.7 Hz), 5.42 (1H, ddd, *J* = 10.0, 2.3, 1.2 Hz), 4.30 (1H, dd, *J* = 11.6, 8.1 Hz), 3.87 (1H, dd, *J* = 10.5, 4.2 Hz), 3.74 (1H, dd, *J* = 10.5, 8.1 Hz), 3.18 (1H, dd, *J* = 11.5, 5.6 Hz), 2.75 (1H, br s), 2.57-2.49 (1H, m), 2.37-2.29 (1H, m), 1.39-1.21 (1H, m), 1.17-0.91 (3H, m), 0.74 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.5, 133.3, 129.2, 128.6, 126.6, 124.2, 69.5, 66.9, 51.6, 47.2, 41.6, 33.8, 20.6, 14.1. IR (KBr Plate): 3445, 2957, 1602, 1496 cm^{-1}. HRMS: Calculated for $C_{16}H_{22}NaO_2^+$: 269.1516 (M+Na$^+$), found 269.1512 (M+Na$^+$).

(1'S,2'R,3'R,4'S)-4'-(hydroxymethyl)-1',2',3',4'-tetrahydro-[1,1':2',1''-terphenyl]-3'-ol (11b): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 96.1 mg (0.6 mmol) of (2E,4E)-5-phenylpenta-2,4-dien-1-ol (**10b**) and 44.4 mg (0.3 mmol) of *trans*-2-phenylvinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (2:1 hexanes/ethyl acetate) afforded a white solid (55.2 mg, 66% yield, 56% ee). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.18-7.07 (6H, m), 6.73-6.66 (4H, m), 5.92 (1H, ddd, *J* = 9.9, 4.9, 2.8 Hz), 5.77-5.73 (1H, m), 4.31 (1H, ddd, *J* = 10.9, 8.3, 1.9 Hz), 4.06-3.99 (1H, m), 3.97-3.89 (1H, m), 3.73-3.68 (1H, m), 3.40 (1H, dd, *J* = 11.6, 6.0 Hz), 2.71-2.64 (1H, m), 2.66 (1H, m), 2.03 (1H, d, *J* = 2.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.9, 138.6, 130.6, 130.2, 129.1, 128.1, 127.4, 126.7, 126.6, 69.2, 66.8, 52.6, 49.3, 46.8. IR (KBr plate): 3418, 2923, 1652, 1453 cm^{-1}. HRMS: Calculated for $C_{19}H_{20}O_2Na^+$: 303.1361 (M+Na$^+$), found 303.1376 (M+Na$^+$).

(1R,2R,3S,6S)-6-((benzyloxy)methyl)-3-(hydroxymethyl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (11c): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which

corresponds to 58.9 mg (0.6 mmol) of **10c** and 44.4 mg (0.3 mmol) of *trans*-2-phenylvinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded the title compound as a white solid (59.2 mg, 61% yield, 59% ee). ^{1}H NMR ($CDCl_3$, 400 Hz) δ 7.38-7.26 (10H, m), 5.92 (1H, ddd, *J* = 10.0, 4.8, 2.7 Hz), 5.59 (1H, dt, *J* = 10.0, 1.9, 1.9 Hz), 4.58 (1H, dd, *J* = 11.5, 8.1 Hz), 4.37 (1H, s), 3.88 (1H, dd, *J* = 11.6, 4.0 Hz), 3.75 (1H, dd, *J* = 10.4, 7.7 Hz), 3.25-3.16 (3H, m), 2.86 (1H, br s), 2.61-2.57 (1H, m), 2.55-2.50 (1H, m), 2.38 (1H, br s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.2, 138.1, 130.6, 128.8, 128.7, 128.2, 127.5, 127.4, 126.8, 126.5, 73.0, 70.2, 69.8, 66.5, 50.7, 46.5, 42.8. IR (KBr plate): 3386, 3027, 2871, 1495, 1361 cm^{-1}. HRMS: Calculated for $C_{21}H_{24}O_3Na^+$: 347.1618 (M+Na$^+$), found 347.1612 (M+Na$^+$).

(1R,2R,3S,6R)-3-(hydroxymethyl)-5,6-dimethyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (11d): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 67.3 mg (0.6 mmol) of (2E,4E)-4-methylhexa-2,4-dien-1-ol (**10d**) and 44.4 mg (0.3 mmol) of *trans*-2-phenylvinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded a white solid (50.6 mg, 73% yield, 59% ee). ^{1}H NMR ($CDCl_3$, 400Hz) δ 7.40-7.33 (2H, m), 7.29-7.23 (3H, m), 5.09 (1H, br s), 4.30 (1H, dd, *J* = 10.4, 8.4 Hz), 3.87-3.79 (1H, m), 3.69 (1H, dd, *J* = 10.4, 8.1 Hz), 3.16 (1H, dd, *J*= 11.6, 5.3 Hz), 2.75 (1H, br s), 2.53-2.44 (1H, m), 2.40 (1H, br s), 2.22 (1H, p, *J* = 7.7, 7.3 Hz), 1.76-1.73 (3H, m), 0.79 (3H, d, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.5, 139.9, 129.1, 128.6, 126.6, 119.1, 68.8, 67.1, 51.9, 47.1, 41.3, 22.0, 15.0. IR (KBr Plate): 3254, 2882, 1602, 1251 cm^{-1}. HRMS: Calculated for $C_{15}H_{20}NaO_2^+$: 255.1358 (M+Na$^+$), found 255.1356 (M+Na$^+$).

(1'S,2'R,3'R,4'S)-6'-bromo-4'-(hydroxymethyl)-1',2',3',4'-tetrahydro-[1,1':2',1''-terphenyl]-3'-ol (11e): A 0.2 M 1,4-dioxane solution of the crude boronate diene tether, which corresponds to 143.5 mg (0.6 mmol) of **10e** and 44.4 mg (0.3 mmol) of *trans*-2-phenylvinylboronic acid, was reacted via the general procedure. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) afforded a yellow solid (56.4 mg, 52% yield, 58% ee). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.08 (6H, m), 6.84-6.54 (4H, m), 6.19 (1H, d, *J* = 2.5 Hz), 4.40-4.28 (1H, m), 4.08-3.92 (2H, m), 3.88 (1H, d, *J* = 6.0 Hz), 3.56 (1H, dd, *J* = 11.6, 5.8 Hz), 2.76-2.65 (1H, m), 2.46-2.33 (1H, m) 1.92 (1H, br s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.4, 136.6, 129.8, 129.10, 128.4, 127.8, 127.3, 124.6, 67.3, 65.7, 57.7, 53.9, 48.7; IR (KBr plate): 3348, 3027, 1452, 1048.2 cm^{-1}. HRMS: Calculated for $C_{19}H_{19}BrO_2Na^+$: 381.0160 (M+Na$^+$), found 381.0153 (M+Na$^+$).

(1R,2R,3R,6S)-3-(2-hydroxypropan-2-yl)-6-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-ol (11f): A 0.2 M 1,4-dioxane solution of 75.7 mg (0.6 mmol) of (3E,5E)-2-methylhepta-3,5-dien-2-ol (**10f**) and 44.4 mg (0.3 mmol) of *trans*-2-phenylvinylboronic acid was reacted via the general procedure. Purification by silica gel chromatography (3:1 hexanes/ethyl acetate) afforded a white solid (32.2 mg, 43% yield, 60% ee). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.30 (2H, m), 7.31-22 (3H, m), 5.84 (1H, ddd, *J* = 10.1, 5.2, 2.7 Hz), 5.42 (1H, d, *J* = 10.1 Hz), 4.52 (1H, dd, *J* = 11.4, 8.3 Hz), 3.50 (1H, br s), 3.17 (1H, dd, *J* = 11.4, 5.5 Hz), 3.0 (1H, br s), 2.54-2.47 (1H, m), 2.46-2.36 (1H, m), 1.39 (3H, s), 1.25 (3H, s), 0.75 (3H, d, *J* = 7.2 Hz). Spectral data matched that previously published.[2a]

Large Scale Diels–Alder and Product Recrystallization: *trans, trans*-2,4-Hexadien-1-ol (2.44 g, 15.8 mmol, 2 equiv), *trans*-2-phenylvinylboronic acid (1.17 g, 7.9 mmol, 1 equiv), and $MgSO_4$ (19 g, 158 mmol, 5 equiv) were suspended in methyl *tert*-butyl ether (8 mL) in an oven-dried round bottom flask containing a Teflon-coated magnetic stir bar. The reaction was stirred under argon at 50 °C for 24 h. The suspension was filtered over Celite and concentrated *in vacuo,* yielding the boronate tether which was dissolved in 40 mL of dry 1,4-dioxane (0.2 M

final concentration). Quinine (2.56 g, 7.9 mmol, 1 equiv) was added and the reaction was stirred under argon at 90 °C for 48 h, then cooled to room temperature. The mixture was diluted with THF (40 mL) and 10% NaOH (40 mL) was added. Aqueous 30% H_2O_2 (13.2 mL) was added dropwise, and the reaction was stirred under open air for 1 hour. The reaction was quenched with 25 mL of 10% sodium thiosulfate and extracted with 3 x 50 mL of ethyl acetate. To recover quinine, the combined organic layer was washed with 1 M HCl (40 mL). The combined organic layers were then washed with water (3 x 15 mL) and brine (1 x 30 mL). The solution was dried over anhydrous $MgSO_4$, and concentrated. The crude residue was purified by flash chromatography to afford 1.125 g (65%, 72% ee) of cyclized diol **5a**. Quinine was recovered by neutralizing the acidic wash with 3 M NaOH (40 mL) and extracting with methyl *tert*-butyl ether to provide 2.17 g (85% recovery) of pure quinine.

A portion of the diol **5a** (990.5 mg) was dissolved in 30 mL cyclohexane and heated in an Erlenmeyer flask. Once dissolved completely, the solution was allowed to cool to room temperature. The product was filtered using a Buchner funnel yielding enantioenriched crystals of diol **5a** (716.2 mg, 72% recovery, 94% ee).

(4aR,7R,8S,8aS)-2,2,7-trimethyl-8-phenyl-4a,7,8,8a-tetrahydro-4H-benzo[d][1,3]dioxine (12): Diol **5a** (133 mg, 0.61 mmol, 1 equiv) was dissolved in 2,2-dimethoxypropane (3 mL) in a round bottom flask containing a Teflon-coated magnetic stir bar, and and *p*-toluenesulfonic acid monohydrate (11.4 mg, 0.06 mmol, 0.10 equiv) was added. The reaction was stirred at room temperature for 4 h, at which point it was transferred to a separatory funnel, diluted in dichloromethane (20 mL), and washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL), and the combined organic layers were washed with brine (20 mL). The reaction mixture was concentrated, and the crude residue was passed through a short silica column (6:1 hexanes/ethyl acetate) to afford 155 mg (98%) of acetonide **12** as a clear oil. ^{1}H NMR ($CDCl_3$, 400 Hz) δ 7.18-7.07 (6H, m), 6.73-6.66 (4H, m), 5.92 (1H, ddd, *J* = 10.0, 2.4 Hz), 5.75 (1H, dt, *J* = 10.0, 1.6 Hz), 4.30 (1H, q, *J* = 11.2, 3.2 Hz), 4.02 (1H, dd, *J* = 10.4, 6.4 Hz), 3.92 (1H, dd, *J* = 10.6, 2.4 Hz), 3.70 (1H, t, *J* = 5.2 Hz), 3.40 (1H, q, *J* = 11.6, 5.6 Hz), 2.75 (1H, bs), 2.66 (1H, m), 2.03 (1H, s), 1.65 (1H, bs). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.9, 138.5, 130.6, 130.2, 129.1, 128.1, 127.4, 126.7, 126.5, 69.2, 66.7, 52.5, 49.3, 46.8. IR (KBr plate): 2990, 1455, 1379, 1194 cm^{-1}. HRMS: Calculated for $C_{17}H_{22}O_2Na^+$: 281.1517 ($M+Na^+$), found 281.1515 ($M+Na^+$).

(4aS,5S,6R,7S,8S,8aS)-2,2,7-trimethyl-8-phenylhexahydro-4H-benzo[d][1,3]dioxine-5,6-diol (13): Alkene **12** (155 mg, 0.6 mmol, 1 equiv) and osmium tetraoxide (1% aqueous solution, 38 µL, 0.006 mmol, 0.01 equiv), 4-Methylmorpholine *N*-oxide (NMO solution) (50 wt. % in H_2O, 211 µL, 0.9 mmol, 1.5 equiv) were added to *tert*-butanol (2.5 mL) and H_2O (2.5 mL) in an oven-dried 20 mL vial containing a Teflon-coated magnetic stir bar. The reaction was stirred at room temperature for 6 h. The reaction mixture was diluted with 10 mL of H_2O and 10 mL of ethyl acetate. Organics were taken and the aqueous layer was extracted 2 x 20 mL of ethyl acetate. The combined organic layers were washed with 10 mL of brine and dried over $MgSO_4$. The mixture was filtered and concentrated via rotary evaporation. The crude residue was purified by silica gel chromatography (3:1 ethyl acetate/hexanes) to afford 142 mg (81%) of diol **13** as a white solid. ^{1}H NMR ($CDCl_3$, 300 Hz) δ 7.35-7.25 (2H, m), 7.23-7.09 (3H, m), 4.23 (1H, t, *J* = 10.7 Hz), 4.14 (1H, dd, *J* = 11.4, 4.5 Hz), 2.69 (1H, br s), 2.43-2.17 (3H, m), 1.71 (2H, br s), 1.57 (3H, s), 1.31 (3H, s), 0.68 (3H, d, *J* = 7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.0, 128.4, 127.9, 125.9, 98.8, 74.7, 67.9, 67.2, 63.3, 43.8, 41.5, 29.9, 19.0, 12.4. IR (KBr plate): 3436, 2908, 2880, 1383 cm^{-1}. HRMS: Calculated for $C_{17}H_{24}NaO_4^+$: 315.1572 ($M+Na^+$), found 315.1569 ($M+Na^+$).

(2S,3S)-3-((4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methyl-3-phenylpropan-1-ol (14): An oven-dried 4 mL vial containing a Teflon-coated magnetic stir bar was charged with diol **13** (58.5 mg, 0.20 mmol, 1 equiv) in a solution of THF (1.6 mL) and H_2O (0.4 mL). The solution was cooled to 0 °C, and $NaIO_4$ (55.6 mg, 0.26 mmol, 1.3 equiv) was added. The reaction was warmed to room temperature and stirred for 20 h, until consumption of starting material and formation of a dialdehyde intermediate was observed by TLC. The reaction was cooled to 0 °C, and $NaBH_4$ (30.3 mg, 0.80 mmol, 4 equiv) was added. The reaction was warmed to room temperature and stirred for 30 min. After disappearance of the dialdehyde, the reaction was cooled to 0 °C, and saturated NH_4Cl (3 mL) was added. The mixture was warmed to room temperature, transferred to a separatory funnel and diluted with H_2O (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash chromatography (1:1 hexanes/acetone) to afford 52.3 mg (89%) of diol **14** as a white solid. ^1H NMR ($CDCl_3$, 400 Hz) δ 7.37 (2H, d, *J* = 7.5 Hz), 7.30-7.20 (3H, m), 4.20 (1H, dd, *J* = 10.2, 3.1 Hz), 3.80 (1H, t, *J* = 10.9 Hz), 3.71 (1H, dd, *J* = 11.6, 5.2 Hz), 3.58-3.50 (2H, m), 3.33 (1H, dd, *J* = 10.8, 4.2 Hz), 3.15 (1H, dd, *J* = 10.8, 5.0 Hz), 2.66 (1H, dd, *J* = 9.6, 3.1 Hz), 2.23-2.16 (1H, m), 1.50 (4H, s), 1.45 (3H, s), 1.10 (3H, d, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 140.2, 130.2, 128.2, 126.7, 98.4, 70.3, 66.5, 62.2, 61.0, 49.9. 38.5, 37.7. 29.2, 19.2, 15.8. δ IR (KBr plate): 3386, 2989, 2935, 2878, 1453, 1380 cm^{-1}. HRMS: Calculated for $C_{17}H_{26}NaO_4^+$: 317.1729 ($M+Na^+$), found 317.1737 ($M+Na^+$).

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org."

- Experimental data, including HPLC traces and X-ray crystallography data
- Copies of NMR spectra
- Computational details
- Cartesian coordinates and thermodynamic parameters (in hartrees) of all stationary points

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All authors have given approval to the final version of the manuscript.

Acknowledgements
The authors thank Dr. John Bacsa and the Emory X-Ray Crystallography Facility for the X-ray structural analysis. We also acknowledge the use of the Rigaku SYNERGY diffractometer, supported by the National Science Foundation under grant CHE-1626172. JBM is grateful to the University of North Carolina Wilmington for financial support. HRMS data was collected from a Bruker MicrOTOF-Q II instrument purchased with funds from the National Science Foundation

(CHE-1039784) and University of North Carolina Wilmington. The 600 MHz NMR data was obtained using a Bruker instrument purchased with funds from the National Science Foundation (CHE-0821552). This work used computational and storage services associated with the Hoffman2 Shared Cluster provided by UCLA Institute for Digital Research and Education's Research Technology Group, and the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number ACI-1053575.

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