Article

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On the Carbohydrate/DBU Co-Catalyzed Alkene Diboration: Mechanistic Insight Provides Enhanced Catalytic Efficiency and Substrate Scope

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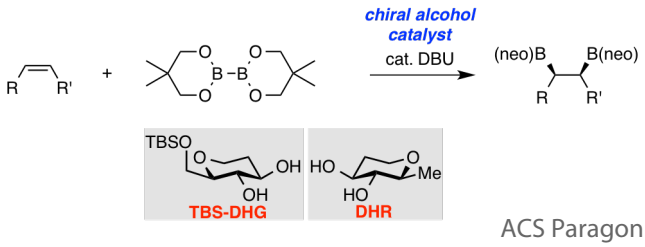
ABSTRACT: A mechanistic investigation of the carbohydrate/DBU co-catalyzed enantioselective diboration of alkenes is presented. These studies provide an understanding of the origin of stereoselectivity and also reveal a strategy for enhancing reactivity and broadening the substrate scope.

1. INTRODUCTION

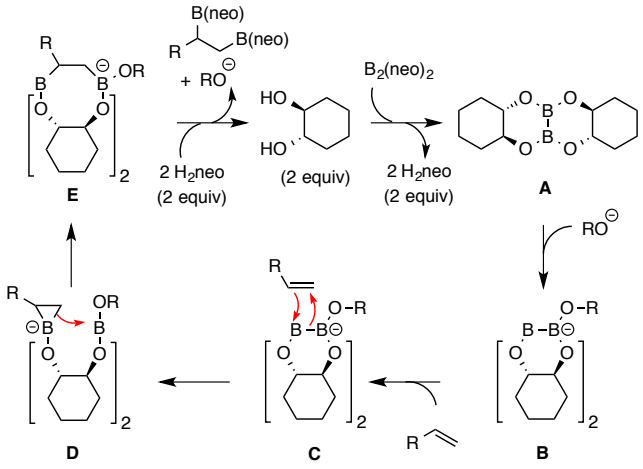
Catalytic enantioselective 1,2-diboration of alkenes[1,2] is a valuable strategy for transforming alkenes to a variety of functionalized products.[3] Most often, this process operates by transition-metal based activation of a diboron reagent, followed by reaction of a resulting metal-boryl complex with the unsaturated substrate.[4] Alternatively, and aligned with seminal studies by Hoveyda[5] on the Lewis-base catalyzed activation of diboron reagents for nucleophilic conjugate addition reactions, Fernandez made the remarkable discovery that 1,2-diboration of unactivated alkenes could be catalyzed by simple metal alkoxides.[6] In an effort to render the metal-free diboration enantioselective, Fernandez employed two equivalents of a chiral alkoxide activator, and achieved modest selectivity (up to 40% ee).[6c] To render the alkoxide-promoted 1,2-alkene diboration reactions *catalytic* and *highly enantioselective*, we studied this process in the presence of exogenous diol catalysts that were proposed to undergo reversible boronic ester exchange with the diboron reagent.[7] The expectation was that an appropriate alcohol might a) enhance reactivity of the diboron nucleus; b) control facial selectivity of the diboration reaction; c) undergo a second boronic ester exchange to release the product, thereby rendering the entire process catalytic and enantioselective. Preliminary studies revealed that cyclic *trans*-1,2-diols are ideally suited for this catalysis strategy with the carbohydrate derivatives **TBS-DHG** and **DHR** (Scheme 1) being readily available, inexpensive, and able to serve as competent catalysts.[8] While preliminary studies revealed an operative system, they also exposed limitations: long reaction times (24-48 h), high catalyst loading (10-20 mol %), elevated temperatures (60 °C), and a restricted substrate scope (inefficient reaction with other than 1-alkenes). In this Article, we present mechanistic studies on carbohydrate catalyzed diboration that allow for an understanding of stereoselectivity, and that has facilitated the development of a more efficient reaction system that has an expanded substrate scope.

Scheme 1. Glycol-Catalyzed Alkene Diboration



Preliminary mechanistic experiments on alkene diboration catalyzed by *trans*-1,2-cyclohexane diol and related compounds suggested that transesterification of the catalytic diol with the stoichiometric achiral diboron reagent furnishes 1,2-bonded diboron species **A** (Scheme 2).[9,10] Similar to the hypothesis put forward by Fernandez, we considered that the diboron may be activated by association of an alkoxide thereby furnishing **B**. Subsequent enantioselective diboration is accomplished by a singlet-carbenoid-like reaction[11] via ensemble **C,** followed by internal trap of the derived boracyclic ate complex **D**[12] to provide **E**. Ligand exchange then releases both the product and the catalyst. While computational experiments provided support for the general pathway from **A** to **E**, it was not clear why stereoselection should emerge from the addition of an alkene to **B**, nor was the slow step in the cycle identified such that attempts might be made to improve catalytic efficiency.

Scheme 2. Mechanism of Cyclic Diol-Catalyzed Alkene Diboration



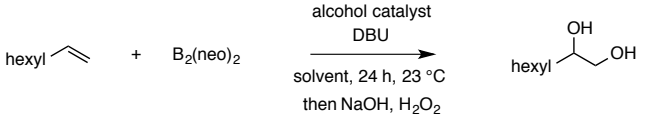
2. RESULTS AND DISCUSSION

Overview. Mechanistic studies were first directed to validate the structure of diboron species **A** as being a 1,2-bonded compound and to demonstrate that it can engage in enantioselective addition to alkenes. Subsequently, studies on transesterification of $B_2(neo)_2$ and *trans*-cyclic diols were examined to demonstrate that exchange occurs and that it operates under catalytic reaction conditions. Kinetic studies established the turnover-limiting step for catalytic reactions with $B_2(neo)_2$ and provided clues to developing faster processes. These im-

proved reactions were then subjected to a kinetic analysis and computational modeling to provide a more complete understanding of the process.

It was anticipated that some mechanistic experiments would benefit from the use of *trans*-cyclohexanediol (TCD) in place of TBS-DHG and DHR, and from the use of alternate solvents. To demonstrate the impact of these permutations on the reaction outcome, we examined the impact of catalyst and solvent selection on reaction conditions. As shown in Table 1, it was found that in comparison to TBS-DHG and DHR, the chiral diol TCD furnishes diminished yield and only slightly diminished selectivity suggesting that it can serve as a surrogate for the carbohydrate-derived catalysts in mechanistic experiments. It should also be noted that inclusion of diazabicycloundecane is required for all three catalysts to operate and that reactions can be conducted in CH_2Cl_2 and $CHCl_3$ solvents with similar selectivity suggesting that NMR studies conducted in $CDCl_3$ and CD_2Cl_2 would bear relevance to the catalytic reaction.

Table 1. Impact of Reaction Parameters on Diol-Catalyzed Diboration of 1-Octene



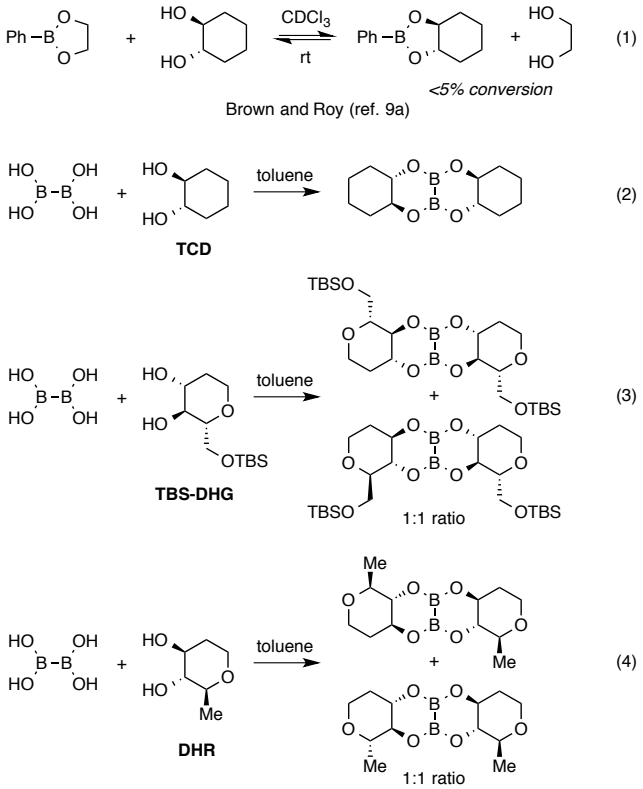
entry	alcohol	% DBU	solvent	yield (%)[a]	er[b]
1	10% TBS-DHG	10	THF	80	96:4
2	10% TBS-DHG	0	THF	<5	n.r.
3	none	10	THF	<5	n.r.
4	10% DHR	10	THF	50	5:95
5	10% TCD	10	THF	40	7:93
6	10% TBS-DHG	10	$CHCl_3$	43	93:7
7	10% TBS-DHG	10	CH_2Cl_2	49	93:7

(a) Yield determined after purification by silica gel chromatography. (b) Enantiomer ratio (er) determined by chiral GC analysis of the derived acetonide.

Preparation and characterization of B_2(trans-1,2-diol)$_2$ complexes. To learn more about structures involved in catalytic diboration, preliminary experiments examined the products of reaction between $B_2(neo)_2$ and TBS-DHG in the absence of alkene substrate.[7] HRMS analysis of this reaction mixture revealed the presence of B_2(TBS-DHG)$_2$ and $B_2(neo)_2$, but not the mixed diboron reagent B_2(neo)(TBS-DHG). This outcome is in contrast to the analogous reaction between $B_2(neo)_2$ and styrenediol which affords $B_2(neo)_2$, B_2(styrenediolato)$_2$ as well as the mixed diboronic ester B_2(neo)(styrenediolato) (data not shown). Minimally, this observation suggests that ligand exchange indeed occurs between $B_2(neo)_2$ and TBS-DHG, but the absence of the mixed diboron in the exchange reaction with TBS-DHG pointed to unique behavior of this diol ligand.

That transesterification can occur between *trans*-1,2-diols and diboron reagents is noteworthy in light of observations by Brown who found that, because of strain engendered in the *trans*-fused bicyclic ring framework, <5% transesterification occurred between *trans*-cyclohexanediol (TCD) and ethylene glycolato phenyl boronic ester (eq. 1).[9a] To learn more about the composition of diboronic esters derived from the exchange process with cyclic diols, the complexes were prepared independently by an alternate route. Thus, TBS-DHG, DHR, and TCD were treated with $B_2(OH)_4$ under dehydrating reaction conditions (refluxing toluene, Dean-Stark trap). As depicted in Scheme 3 (eq. 2-4), these reactions provide access to diboron compounds that, collectively, have spectral features consistent with 1,2-bonded diboron complexes. Due to the C_2 symmetry axis in *trans*-1,2-cyclohexanediol, the ^{13}C NMR spectrum of $B_2(TCD)_2$ ($[^1H]^{13}C$ δ: 81.8, 32.9, 24.3 ppm) is consistent with both 1,1-bonded and 1,2-bonded diboron species. However, lack of a symmetry element in TBS-DHG and DHR results in structural isomerism for 1,2-bonded diboron species, whereas 1,1-bonded complexes would bear a C_2-axis that would render associated carbohydrate ligands equivalent. Thus, the presence of two sets of ^{13}C resonances for both B_2(TBS-DHG)$_2$ and B_2(DHR)$_2$ is suggestive of 1,2-bonding mode for these compounds and, by analogy, is considered likely for TCD as well.

Scheme 3. Preparation of Carbohydrate-Derived Diboron Reagents



While 1,2-bonded diboron species are less common isomers of diboron species derived from diol ligands, they do have precedent. The crystal structure of $B_2(binol)_2$[13] and $B_2(cat)(NMe_2)_2$[14] show 1,2-bonding although for the latter compound this bonding mode may arise by kinetic control during the synthesis. Also of relevance, $B_2(cat)_2$ exhibits dynamic isomerism, exchanging between 1,1-bonded and 1,2-bonded upon addition of Lewis basic reagents (DBN, 4-picoline).[15]

While significant effort was invested in preparing x-ray quality crystals of 1,2-bonded diboron complexes derived from TBS-DHG, DHR, and non-racemic TCD, these efforts proved fruitless. In contrast, dehydration of $B_2(OH)_4$ and *rac*-TCD furnished a solid material whose ^{13}C NMR and HRMS spectra are consistent with a dimer. From this material, x-ray

quality crystals could be obtained (Figure 1). The crystal structure includes two enantiomeric molecules of $B_6(TCD)_5$(*ent*-TCD) per unit cell, with each molecule composed of three tethered diboron subunits. Each of the diboron subunits bears a 1,2-bonded TCD group and is tethered by an additional diol ligand to a neighboring subunit. Of the six diols ligands in the molecular structure, five are of the same configuration and the sixth is the opposite. While this species is clearly unavailable when using non-racemic ligand, the bonding present in the trimeric structure gives credence to the importance of 1,2-bonded TCD groups in diboron reagents. Of note, the B-B bond distances (1.706, 1.721, and 1.724 Å) are not substantially distorted relative to other diboron compounds (1.720Å for $B_2(OMe)_4$[16]; 1.711Å for $B_2(pin)_2$[17]).

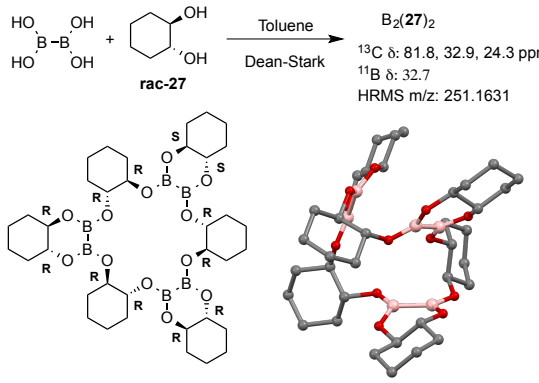


Figure 1. Preparation of [B_2(*rac-trans*-cyclohexanediol)$_2$] and crystal structure analysis of $B_6(TCD)_5$(*ent*-TCD) revealing the 1,2-bonding mode for the *trans*-cyclohexanediol ligand.

The presence of oligomeric species in rac-TCD-derived diboron structures, suggests higher-order species might be both accessible and relevant to processes involving non-racemic diols. To measure diffusion coefficients that may be correlated with molecular weight of complexes in solution, diffusion ordered spectroscopy (DOSY) NMR[18] analysis was performed on B_2(TBS-DHG)$_2$. As depicted in Figure 2, $CDCl_3$ was employed as the DOSY NMR solvent and naphthalene was used as the molecular weight reference for calibration. The 2D NMR spectrum of B_2(TBS-DHG)$_2$ shows that only one species exists in solution and it exhibits an average diffusion

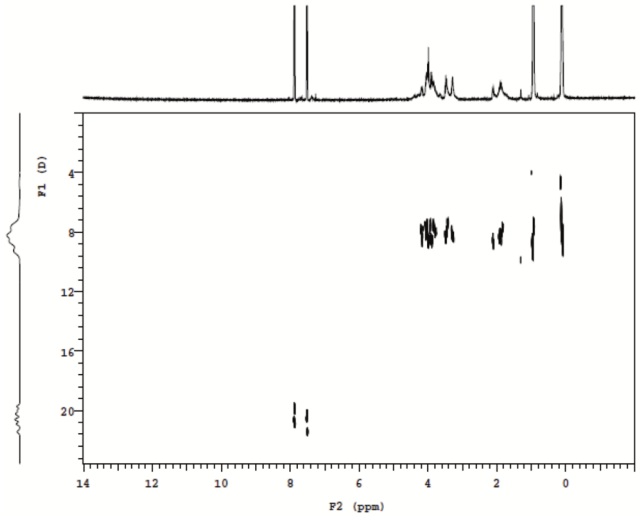
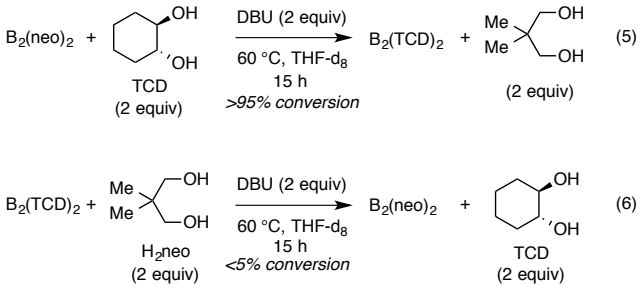


Figure 2. DOSY NMR analysis of B_2(TBS-DHG)$_2$in comparison to naphthalene as a molecular weight reference. Analysis was performed in $CDCl_3$ by 600 MHz ^{1}H NMR.

of 8.085. For the estimation of the molecular weight, an external calibration curve method developed by Stalke[19] was employed. Using this technique with naphthalene as a reference, the calculated solution molecular weight for the diboron complex B_2(TBS-DHG)$_2$ in $CDCl_3$ solvent is 536.4 g/mol. Considering that the molecular weight of B_2(TBS-DHG)$_2$ is 543.3 g/mol suggests that, for this diboron compound in chloroform solvent, the monomeric diboron species predominates over higher-order aggregates.

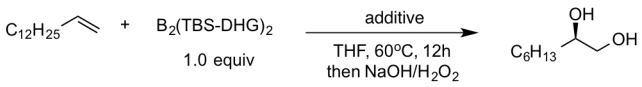
Equilibria between B_2(neo)$_2$ and *trans*-cyclohexanediol. The experiments described above establish the likely structure of $B_2(TCD)_2$ and related complexes; however, for effective catalysis to emanate from a cycle that involves the chiral diboron complex, boronic ester exchange between the stoichiometric achiral diboron reagent and the chiral cyclic diol is a necessary prerequisite. To establish the capacity for such a transesterification under catalytic reaction conditions, B_2(neo)$_2$ was treated with 2 equiv of TCD in THF at 60 °C (Scheme 4). When the reaction was examined by ^{1}H NMR, it was found that exchange indeed occurs and that it requires the presence of DBU. After 15 h, the reaction achieves >95% conversion, suggesting that K_{eq} for the exchange reaction is >20. Importantly, this exchange could also be conducted with 10 mol% DBU and it still proceeds to completion (data not shown). As a control experiment, the reverse reaction was conducted where $B_2(TCD)_2$ was treated with neopentyl glycol under identical conditions and <5 % conversion was observed.

Scheme 4. Equilibrium Between Neopentyl Glycol and *trans*-Cyclohexanediol Diboron Reagents



Stoichiometric reactions of chiral diboron complexes and alkenes. With available evidence suggesting that ligand exchange between B_2(neo)$_2$ and *trans*-cyclic diols provides 1,2-bonded diboron species, the reaction between

Table 2. Additive Effects in the Addition of B_2(TBS-DHG)$_2$ to 1-Octene



entry	additive	yield (%)[a]	er[b]
1	20% DBU	<5	n.d.
2	20% DBU; 20% 1,3-propanediol	43	92:8
3	20% DBU; 20% *n*-BuOH	40	90:10
4	20% DBU; 20% *i*-PrOH	25	86:14
5	20% DBU; 20% *t*-BuOH	30	80:20
6	20% KO*t*Bu	52	73:27
7	20% KOMe	46	81:19

(a) Yield determined after purification by silica gel chromatography. (b) Enantiomer ratio (er) determined by chiral GC analysis of the derived acetonide.

these chiral complexes and alkenes was examined. As depicted in Table 2, when 1-tetradecene was treated with B_2(TBS-DHG)$_2$ at 60 °C for 12 h in the presence of DBU, and the reaction mixture subjected to oxidative work-up, it was found that no reaction occurred (Table 2, entry 1). However, the addition of an achiral alcohol to this reaction did serve to promote the diboration of 1-octene in an enantioselective fashion (entry 2). Of note, the stereoselectivity is dependent upon the nature of the added alcohol, with *tert*-butanol and isopropanol giving the product in selectivity that is less than that observed in the catalytic reaction whereas unhindered alcohols, such as 1-butanol and 1,3-propanediol, affording product with selectivity that is comparable to that observed in the catalytic process. We considered that the function of the added alcohol in these experiments may be to react with DBU thereby providing an alkoxide activator for the diboration. Such alkoxide activation was proposed by Fernandez[6] for reactions of alkenes with achiral diboron reagents and DBU/CH_3OH-based alkoxide activation of B_2(pin)$_2$ had been documented by Hoveyda[5d]; consistent with these observations, the DBU-alcohol combination in the stoichiometric process can be replaced with a metal alkoxide and comparable selectivity is observed (Table 2, entry 6, 7).

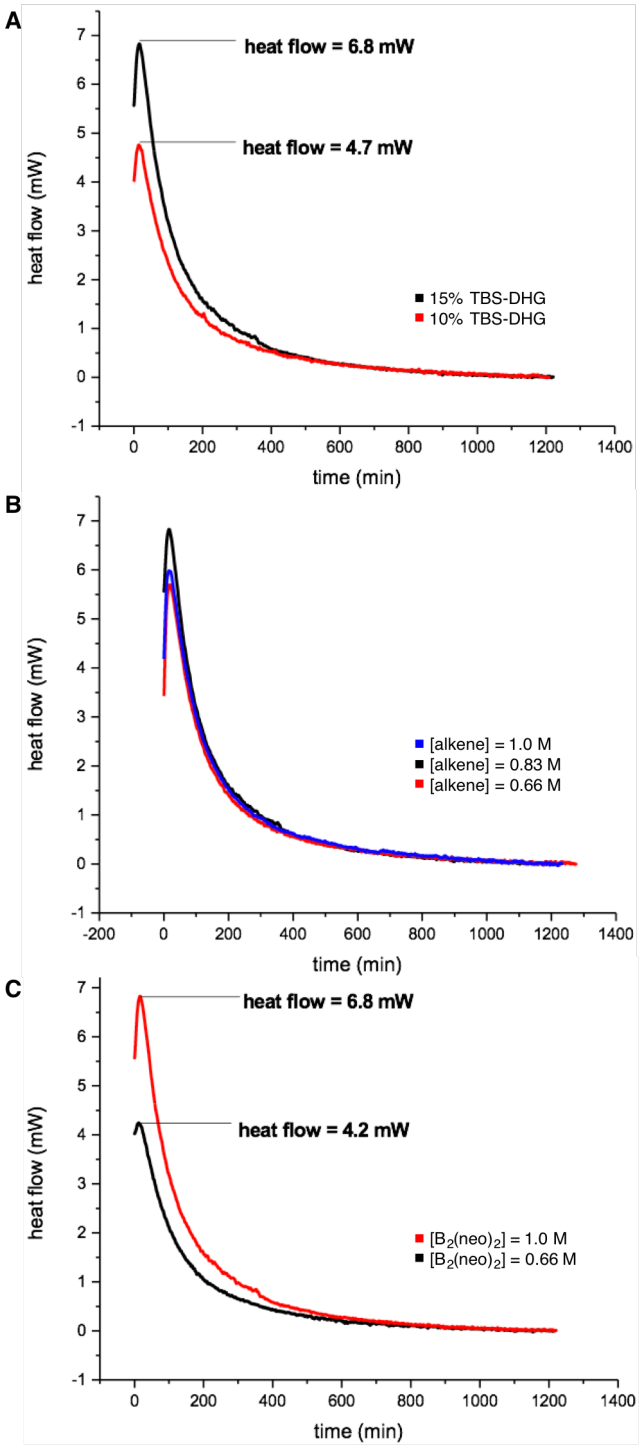
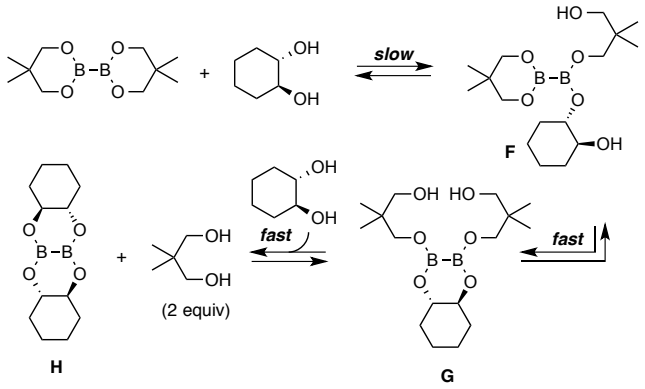


Figure 3. Kinetic analysis of TBS-DHG catalyzed diboration of 4-phenyl-1-butene with B_2(neo)$_2$ as stoichiometric diboron reagent. Effect of (a) catalyst concentration, (b) alkene concentration, and (c) diboron concentration.

Preliminary kinetic analysis of catalytic diboration with B_2(neo)$_2$. Further information about the diol-catalyzed diboration was obtained by studying the reaction kinetics. Because of its experimental convenience and because it can collect data continuously throughout the entire course of the reaction, calorimetry was chosen for these studies. As depicted in Figure 1a, the diboration of 4-phenyl-1-butene (0.83 M conc) with B_2(neo)$_2$ (1.0 M conc) was monitored by calorimetry in the presence of either 10 mol% or 15 mol% TBS-DHG catalyst. While neither process achieved complete conversion, analysis of the heat flow versus time profile (Figure 3A) indicates a 45% increase in the initial rate at the higher catalyst loading, suggestive of a first-order dependence of the reaction rate on catalyst concentration. As depicted in Figure 3b, the rate of catalytic diboration did not exhibit a significant dependence on initial concentration of alkene, but did appear to exhibit positive-order dependence on [B_2(neo)$_2$] (Figure 3c).

Impact of diboron reagents on catalytic efficiency and selectivity. The zero-order dependence of reaction rate on alkene concentration suggests that steps involving boronic ester exchange rather than the diboration reaction itself are turnover-limiting. With a first-order dependence upon catalyst concentration and also a positive-order dependence upon [B_2(neo)$_2$], it was suspected that formation of B_2(TCD)$_2$ from B_2(neo)$_2$ and *trans*-cyclohexanediol was likely the slow step with the initial association of TCD and B_2(neo)$_2$ likely turnover-limiting and association of a second TCD being fast (Scheme 5). This hypothesis was considered plausible since dislodging a primary alcohol from B_2(neo)$_2$ with a secondary alcohol from TCD (giving **F**) is likely to be slow relative to subsequent intramolecular transesterification giving **G** and displacement of monodentate ligands in **G** with TCD giving **H**.

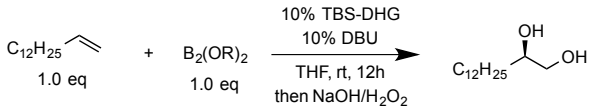
Scheme 5. Proposed Exchange Process for Reaction of Cyclic Diol Ligands and B_2(neo)$_2$

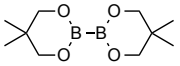
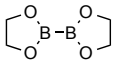
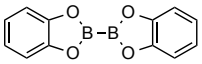
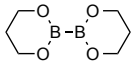
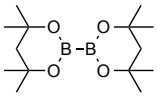
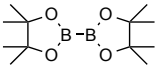


Effect of diboron reagent structure on reactivity and selectivity. With experiments suggesting that formation of the chiral 1,2-bonded diboron complex is the turno-

ver-limiting step of the catalytic cycle, we sought to develop a more efficient process by employing diboron reagents that would be prone to more rapid ligand exchange. As depicted in Table 3, catalytic diboration reactions with varied diboron reagents were carried out under conditions where conversion with $B_2(neo)_2$ is modest (rt, 12 h, 40% yield). When $B_2(neo)_2$ was replaced with $B_2(ethyleneglycol)_2$, a compound that should undergo faster transesterification because of decreased steric encumbrance and increased strain in the cyclic boronic ester motif, a significant improvement in the reaction efficiency was observed; however, the reaction suffers from a measureable decrease in enantioselectivity. Like $B_2(eg)_2$, the catechol group on $B_2(cat)_2$ is also readily displaced and this provides outstanding reactivity. However, presumably due to facile background reaction, $B_2(cat)_2$ furnished racemic product. The reagent $B_2(pro)_2$[8] (entry 4) provided the optimal combination of both enhanced efficiency while maintaining high enantioselectivity. It should be noted that, consistent with the mechanistic proposal described above, more hindered diboron reagents that likely suffer diminished rates of transesterification, react with severely diminished efficiency (entry 5, 6).

Table 3. Effect of Diboron Reagent Structure on the Efficiency and Selectivity of 1-Tetradecene Diboration[a]



entry	diboron	abbrev.	yield (%)[b]	er[c]
1		$B_2(neo)_2$	40	96:4
2		$B_2(eg)_2$	75	91:9
3		$B_2(cat)_2$	98	51:49
4		$B_2(pro)_2$	56	95:5
5		$B_2(tmpd)_2$	15	81:19
6		$B_2(pin)_2$	10	69:31

(a) Reactions were performed on 0.2 mmol scale of alkene and at [alkene] = 1.0 M. (b) Yield determined after purification by silica gel chromatography. (c) Enantiomer ratio (er) determined by chiral GC analysis of the derived acetonide.

Kinetic analysis of carbohydrate-catalyzed diboration with $B_2(pro)_2$. In addition to exhibiting enhanced reactivity and scope (*vide infra*), $B_2(pro)_2$ has the significant advantage that it is more soluble in THF solvent than $B_2(neo)_2$ and therefore is more amenable to kinetic analysis. Using a reference set of reaction conditions ([4-phenyl-1-butene] = 1.0 M, $[B_2(pro)_2]$ = 2.0 M, 10 mol% TBS-DHG, 10 mol% DBU), calorimetry showed the diboration of 4-phenyl-1-butene was complete within 4 h and the calorimetric reaction rate data was corroborated by NMR analysis versus an internal standard. When the heat flow versus time data was integrated (Figure 4), it becomes apparent that the reaction approximates first-order behavior over its entire course. The two plots in Figure 4a show the effect of diboron concentration on the reaction rate and are consistent with a first-order dependence (the 1.33-fold increase in diboron concentration between reaction run at 2.0 M vs. 1.5 M results in a 1.30-fold increase in rate); while the plots in Figure 4b and 4c reveal a zero-order dependence on alkene and DBU concentration.

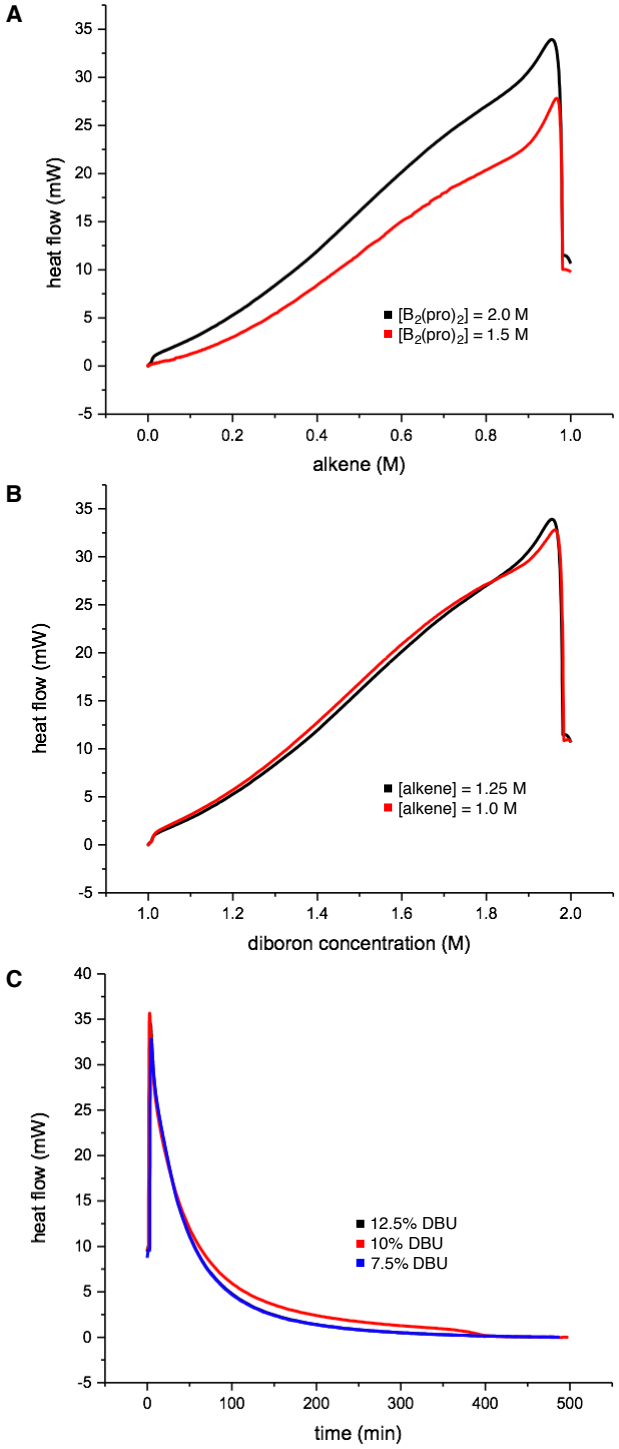


Figure 4. Kinetic analysis of TBS-DHG catalyzed diboration of 4-phenyl-1-butene with $B_2(pro)_2$. Effect of (a) diboron concentration, (b) alkene concentration, (c) DBU concentration.

The dependence of reaction rate upon catalyst concentration was also analyzed by reaction calorimetry (Figure 5) and clearly show that the reaction is first-order in TBS-DHG with a reduction in catalyst to 5 mol% loading giving a rate that is approximately half that of the standard reaction.

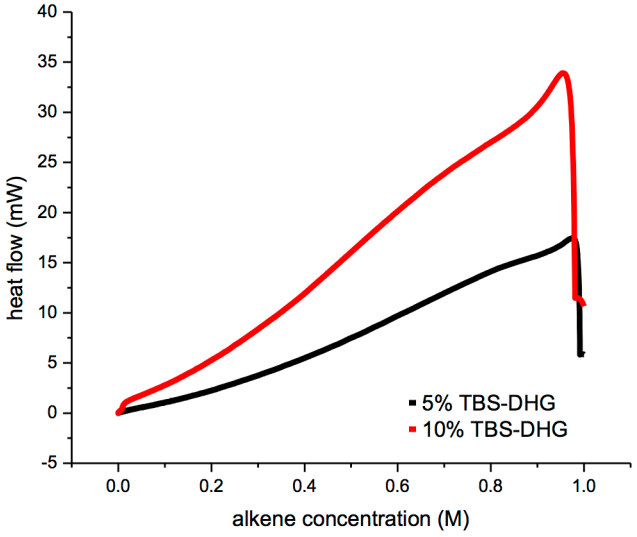


Figure 5. Kinetic analysis of diboration of 4-phenyl-1-butene with $B_2(pro)_2$ catalyzed by TBS-DHG.

Origin of rate acceleration and stereoinduction in *trans*-glycol catalyzed diboration. *A. Rate Acceleration.* Previous computational studies carried out by DFT methods provided support for a mechanism involving reaction of an alkene with 1,2-B_2(TCD)$_2$•OMe by a two-step mechanism involving initial rupture of the B-B bond (**TS-1**, Figure 6) and formation of an anionic boracycle[12] tethered to a trivalent borate ester (**INT**). Mechanistically, this first step appears to be isoelectronic with cyclopropanation involving singlet-carbenes.[11] Subsequent to cycloboration, intramolecular reaction between the trivalent borate and the anionic boracycle occurs (via **TS-2**) in a stereoretentive fashion and delivers a macrocyclic vicinal diboronate (**PDT**); ligand exchange between this species and propanediol would release the 1,2-glycol catalyst from the reaction product. Of note, the calculated barrier for **TS-1** is too high for a reaction that occurs at room temperature. Moreover, the energy of **TS-1** suggests it should be kinetically relevant, which is inconsistent with kinetic data. Part of this error arises because calculations overestimate the decrease in translational entropy for association of ethylene with the diboron precursor.[20] Thus, subsequent calculations have focused on relative comparisons of similar transition states where systematic errors are expected to cancel.

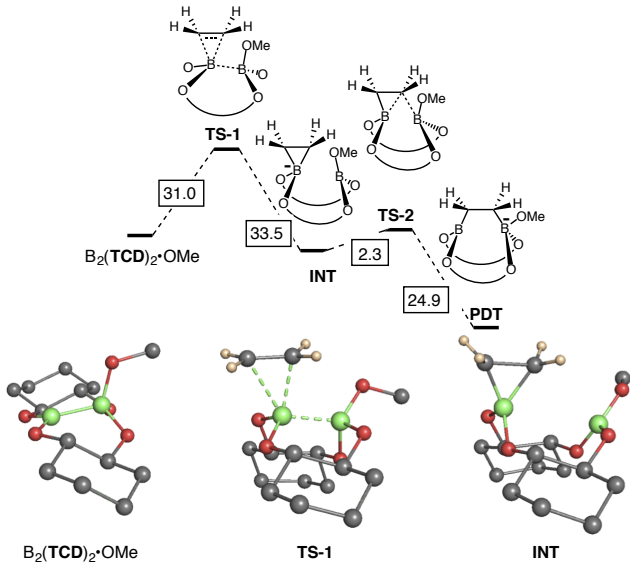


Figure 6. Calculated reaction mechanism for alkene diboration with B_2(**TCD**)$_2$.

For effective catalysis, reaction through **TS-1** must be favored over the analogous reaction between the alkene and stoichiometric achiral diboron compounds. Along these lines, calculations performed previously[7] suggested that **TS-1** is favored relative to the corresponding transition state originating from 1,1-bonded B_2(neo)$_2$. To learn more about background reaction rates for both 1,1- and 1,2-bonded B_2(pro)$_2$ and to better understand rate acceleration and stereoinduction with TCD, TBS-DHG, and DHR, additional computational investigations were undertaken. Calculations were performed with Gaussian 09 and optimized with M06-2X[21] density functional and 6-31+G* basis set using PCM solvation model (THF). Thus, the transition state energies were calculated 1,1-bonded and 1,2-bonded transition states derived from TCD, 1,3-propanediol, and ethylene glycol (Figure 7). As the results indicate, the relative TS energy for 1,2-bonded TCD (**TS-1A**) is far lower in energy than the TS for 1,1-bonded TCD (**TS-1B**) as well as both 1,1 and 1,2-bonded propanediol (**TS-1C** and **TS-1D**). **TS-1A** is also lower in energy than both transition states that would arise from B_2(eg)$_2$ as a stoichiometric reagent (**TS-1E**, **TS-1F**), although the difference in catalyzed (**TS-1A**) and background (**TS-1E**) energy is less in the latter case suggesting that competing background reaction would likely be more problematic when B_2(eg)$_2$ is employed as a reagent. Of note, observations in Table 3 (entry 2) indicate lower reaction enantioselectivity with B_2(eg)$_2$, in line with calculations.

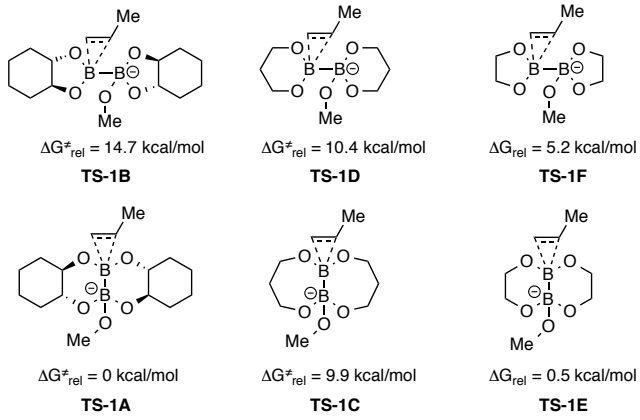


Figure 7. Comparison of relative transition state energies for cycloboration employing TCD, ethylene glycol and 1,3-propanediol ligands in both the 1,1 and 1,2 bonding modes. To make meaningful comparison of transition states, the total energy for each ensemble was compared relative to the ensemble for **TS-1A** (ensemble energy includes the calculated transition state energy and the ground state energy for non-participating diols; see Supporting Information for additional discussion). Calculations performed with M06-2x/6-31+G*.

Consistent with preferred 1,2-bonding mode for TCD in the ground state diboron structure, the six-membered ring in TCD imposes significant strain that penalizes the 1,1-bonding mode in transition state **TS-1B**, thereby favoring **TS-1A**. It is noteworthy that when this strain element is removed in the case of the B_2(eg)$_2$, the 1,2-bonded **TS-1E** is still favored over 1,1-bonded **TS-1F** suggesting a general preference for 1,2-bonded transition states in the alkoxide promoted diboration, even in the absence of strain. With 1,3-propane diol as ligand, the benefit of 1,2-bonding in transition state **TS-1C** appears to be offset by strain in the seven membered rings and thus neither the 1,1- or 1,2-bonding mode allows B_2(pro)$_2$-based background reaction to effectively compete with the catalyzed reaction through **TS-1A.**

The origin of transition state stabilization with 1,2-bonded versus 1,1-bonded diolato ligands merits comment. Analysis of ^{11}B NMR chemical shifts in non-coordinatign chloroform solvent for compounds that are 1,2-bonded (^{11}B δ $B_2(TCD)_2$ = 32.05 ppm; $B_2(TBS\text{-}DHG)_2$ = 32.7 ppm) are consistently downfield relative to 1,1-bonded compounds (^{11}B δ $B_2(neo)_2$ = 28.4 ppm; $B_2(pin)_2$ = 30.7 ppm, $B_2(pro)_2$ = 28.3 ppm), suggesting decreased O→B π bonding in the 1,2 bonding mode likely as a result of less effective orbital overlap.[22] Similarly, abbreviated transition state structures **I** and **J** shown in Figure 8 reveal a substantial difference in the orientation of the diolato oxygen atom lone pair electrons. For the 1,2-bonded transition state **J**, much of the lone pair electron density is directed away from the breaking B-B bond, whereas in the 1,1-bonded complex **I**, the breaking B-B bond bisects the oxygen lone pairs. It was considered that during the course of bond reorganization in the cycloboration, the B-B bond cleaves in a manner that that leads to increased electron density on boron atom B^A and, due to orbital orientation, the 1,1-bonding mode may suffer enhanced electron-electron repulsion relative to the 1,2-bonding mode. To gain an understanding of the magnitude of this effect, we computed the ground state energy of conformers of the boryl anion $(HO)_2B^{\ominus}$. As depicted in Figure 8, of the two conformers, structure **K** (reflective of the 1,1-bonding mode) is found to be 2.8 kcal/mol higher in energy than **L**, a feature consistent with destabilization of the 1,1-bonded transition state relative to the 1,2 mode.

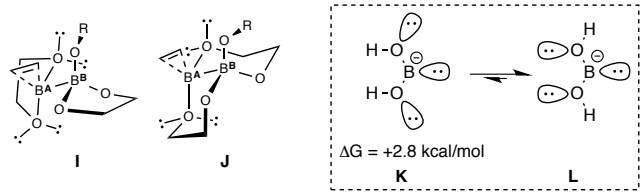


Figure 8. General comparison of 1,1- and 1,2-bonded transition states in metal-free diboration.

B. Stereoinduction. According to the energy profile depicted in Figure 6, the stereochemical outcome of the carbohydrate-catalyzed diboration would appear to arise from the facial selectivity with which a prochiral alkene engages in **TS-1.** As depicted in Figure 9, four different reaction pathways were calculated for the addition of propene to 1,2-$B_2(TCD)_2$•OMe. Perhaps unsurprisingly in light of anticipated steric effects, the two transition states in which the alkene substituent is directed towards the activating alkoxy group (transition structures **TS-M** and **TS-N**) are highest in energy. The two lower energy structures are distinguished from each other by a $\Delta\Delta G^{\neq}$ of 0.27 kcal/mol, a number which appears reasonable given the lower selectivity observed in reactions promoted with potassium methoxide as activator (Table 2) instead of 1,3-propanediol/DBU. Examination of the **TS-major** and **TS-minor** does not reveal a clear difference in steric effects between the two structures; however, a key distinguishing feature is that the O2 oxygen atom in the higher energy structure (**TS-minor**) is positioned in such a way that its non-bonding electrons are directed towards the alkene substituent, whereas the alkene substituent in the lower energy structure is situated over an oxygen (O1) whose lone pairs are directed away from the olefin substituent. This difference in lone pair orientation can be discerned from the electrostatic potential surface calculated for the most favored transition structure (**TS-major**); from perspective B (inset Figure 9), the electron density associated with the O(2) oxygen encroaches on the substrate more than the electron density associated with O(1) simply as a result of orientation, and this is expected to provide an energetic preference for locating the small vinylic H over O(2) and the larger alkyl group over O(1).

G. Scope of diboration: *Terminal Alkenes.* With an appreciation of reaction mechanism and noting enhanced rates with $B_2(pro)_2$, we explored the scope of glycol catalyzed enantioselective diborations with both TBS-DHG and DHR catalysts. For consistently high reaction efficiency, we employed two equiv of $B_2(pro)_2$ and allowed reactions to proceed for 12 h (Table 4). Generally, high enantioselectivities and high yields were observed regardless of the nature of the olefin substituent: 1-octene, 1-tetradecene, and vinylcyclohexene furnished the corresponding diols in approximately 95:5 enantiomer ratios and 97%, 95%, 84% yield respectively (products **1, 2,** and **3**). Allyl- and homoallyl benzene derivatives also undergo the diboration reaction smoothly resulting in formation of the diol products in good yield and good enantioselectivity (products **4**-**7**). Heterocycle-containing alkenes such as furan, Boc-protected indole, thiophene and pyridine-containing substrates, afforded diol products in similarly good yield and enantioselectivity (**8**-**11**). Similarly, TBDPS protected allylic alcohol and homoallylic alcohols, survive the diboration/oxidation (**12, 13**) as to carbonyl-based functional groups such as ketone and ester derivatives (**14, 15**). Alkyl bromides also appear to be non-problematic (**16**) as are compounds containing pre-existing stereocenters (products **18**, **19**). Aromatic alkenes appear to be one type of substrates that did not react with high selectivity (**19**). Of note, the diboron intermediate in the synthesis of **13** could be isolated in 79%

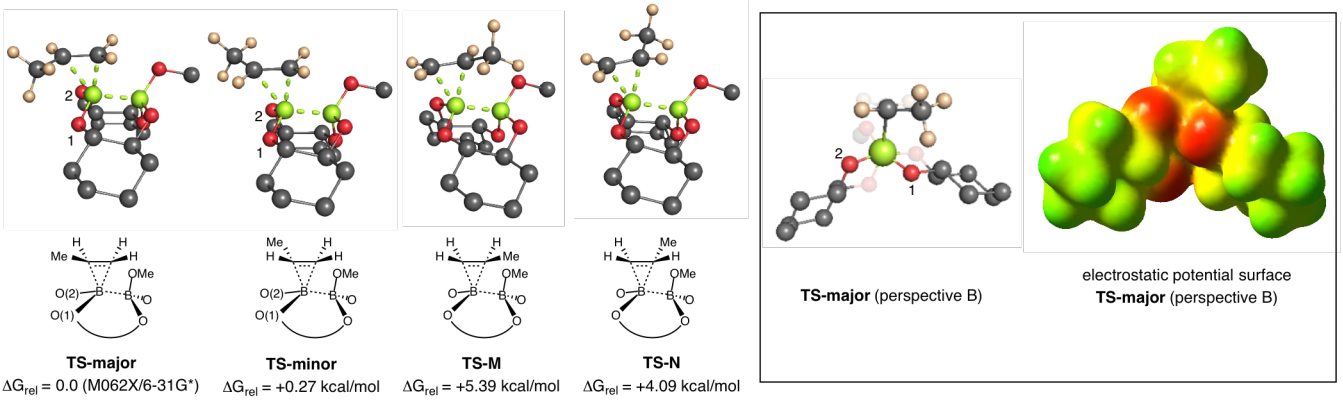
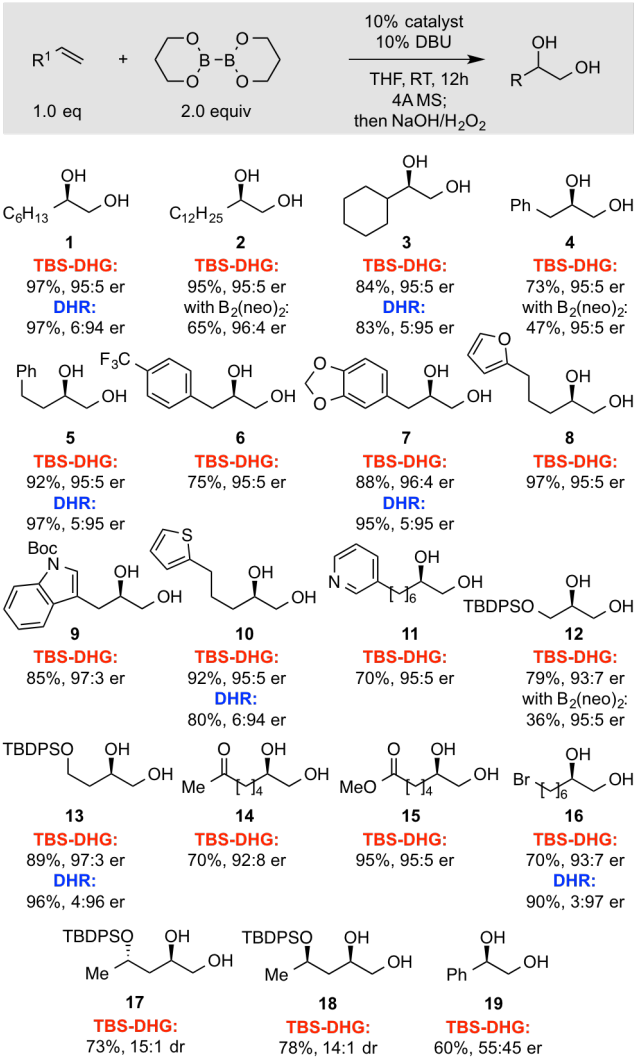


Figure 9. Calculated transition states for reaction of 1,2-B_2(**TCD**)$_2$•OMe with propene leading to enantiomeric reaction products. The inset structures depict and alternate perspective of the lowest energy transition state along with an electrostatic potential surface that suggests a possible origin of stereocontrol in diboration reactions.

yield and separated from the catalyst, which could be recovered in 96% yield (see Supporting Information for details). Lastly, it should be noted that DHR catalyzed reactions is generally just as efficient as TBS-DHG catalyzed process, furnishing diol **1**, **3**, **5**, **7**, **10**, **13**, **16** in similarly good yield and good enantioselectivity. corresponding

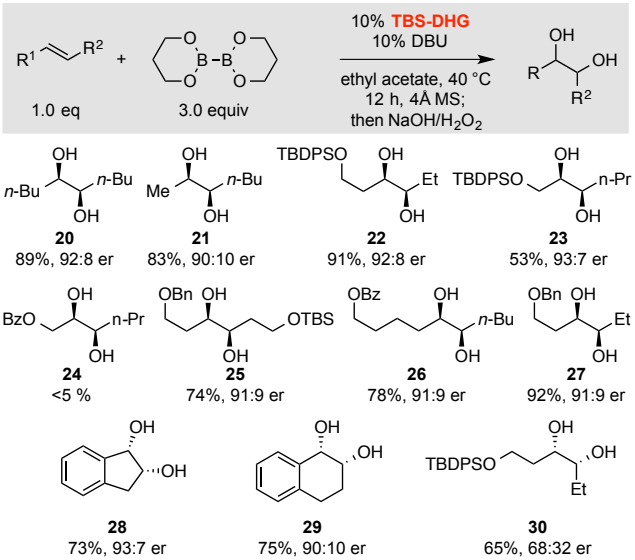
Internal Alkenes. Internal alkenes are less reactive than mono-substituted olefins under carbohydrate-catalyzed reaction conditions. Indeed, with more hindered substrates, diboration with $B_2(neo)_2$ required heating to 60 °C and use of the Cs_2CO_3 as the base. When the more reactive reagent $B_2(pro)_2$ is used, however, the reaction may be conducted at lower temperatures and with DBU as the base, and under these milder conditions appears to suffer from less background non-selective reaction. As depicted in Table 5, useful yields and selectivity could be obtained from carbohydrate catalyzed diboration of internal alkenes if 10% catalyst was employed with 3 equivalents of diboron reagent at 40 °C. A modest improvement in yield was also noted when the reaction was conducted in ethyl acetate solvent versus THF solvent. Under these reaction conditions a collection of functionalized disubstituted alkenes were examined. As noted in Table 2, the reaction operates on non-functionalized hydrocarbons (**20**, **21**) as well as those bearing adjacent oxygenated functional groups (**22, 23, 25-27**). From the data, it appears that electron-withdrawing allylic substituents decrease alkene reactivity (cf. **20**, **23**, **24**) such that with an allylic benzoate, no detectable diboration was observed. The reactivity enhancement observed with $B_2(pro)_2$ also extends to indene and dihydronaphthalene, substrates that exhibit low reactivity with $B_2(neo)_2$ as reagent. Importantly, these cyclic Z-alkenes, as well as product 30 from an acyclic Z-alkene precursor, provide additional support for the stereospecific cycloboration mechanism proposed for this reaction.

Table 4. Enantioselective Diboration of 1-Alkenes with $B_2(pro)_2$ and Carbohydrate-Derived Catalysts



(a) Conditions: [alkene]=1.0 M, 0.2 mmol scale. Yield refers to the isolated yield of the purified reaction product. Enantiomer ratio determined by chromatography with a chiral stationary phase (see Supplementary Material for details).

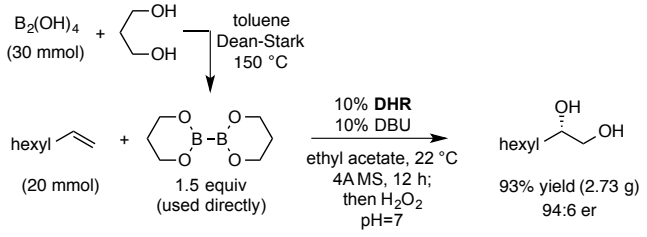
Table 5. Enantioselective Diboration of Internal Alkenes with $B_2(pro)_2$ and Carbohydrate-Derived Catalysts



(a) Conditions: [alkene]=1.0 M, 0.2 mmol scale. Yield refers to the isolated yield of the purified reaction product. Enantiomer ratio determined by chromatography with a chiral stationary phase (see Supplementary Material for details).

G. Practical features of carbohydrate-catalyzed diboration. As the examples above suggest, carbohydrate-catalyzed diboration reactions are markedly accelerated by the use of $B_2(pro)_2$ in place of $B_2(neo)_2$ and $B_2(pin)_2$. Moreover, due to its high solubility in water, removal of 1,3-propanediol from reaction products is easily accomplished by an aqueous wash and this makes product purification far easier than when neopentyl glycol or pinacol-derived boron reagents are employed. In spite of these attractive features, a use of $B_2(pro)_2$ is limited by the fact that it is less commonly available than other diboron reagents.[8] To address this, we have examined the direct preparation of $B_2(pro)_2$ from $B_2(OH)_4$ and 1,3-propane diol. As depicted in Scheme 6, it was found that heating a mixture of $B_2(OH)_4$ and 1,3-propanediol for 6 h in toluene with a Dean-Stark trap to remove water, followed by evaporation of the solvent provided $B_2(pro)_2$ of sufficient purity to be used directly in diboration. Moreover, it was determined that the reaction in the presence of the DHR catalyst was sufficiently rapid that it could proceed to completion within 12 h at room temperature and with only 1.5 equivalents of diboron reagent. Subsequent to buffered (pH=7) oxidation with H_2O_2, aqueous wash to remove 1,3-propanediol, and purification provided the product 1,2-diol in 93% yield on 20 mmol scale reaction.

Scheme 6. Single Vessel Catalytic Enantioselective Diboration with $B_2(OH)_4$ as Reagent



3. CONCLUSION

The glycol/DBU co-catalyzed diboration of alkenes is an efficient, enantioselective reaction that employs simple catalysts and reagents to convert unsaturated hydrocarbons into useful chiral building blocks. Importantly, with $B_2(pro)_2$ as a reagent, the reaction occurs in a reasonable time course and applies to both terminal and internal alkenes. Of note, the waste streams arising from the diboration/oxidation process employing $B_2(pro)_2$ as the reagent are 1,3-propanediol and boric acid, both of which are relatively innocuous. Thus, the catalytic diboration process described herein would appear to be an appealing method for the enantioselective transformation of olefins.

ASSOCIATED CONTENT

Supporting Information

Procedures, characterization and spectral data. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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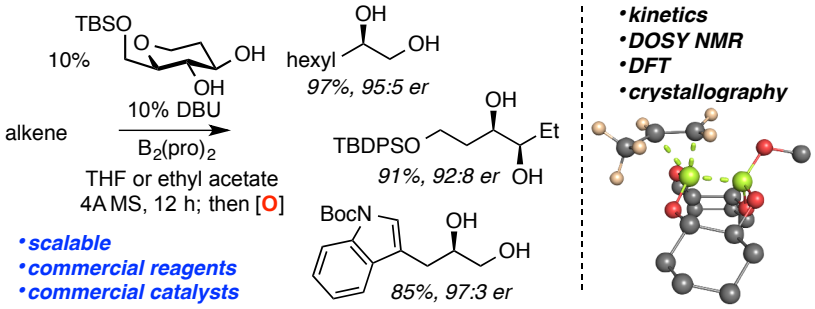
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10% DBU
$B_2(pro)_2$
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OH
hexyl
OH
97%, 95:5 er
OH
TBDPSO
Et
91%, 92:8 er
OH
BocN
OH
OH
85%, 97:3 er
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•DFT
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