A Boron Activating Effect Enables Cobalt-Catalyzed Asymmetric Hydrogenation of Sterically Hindered Alkenes

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ABSTRACT: Unsymmetric 1,1-diboryl alkenes bearing one –[BPin] (BPin = pinacolatoboryl) and one –[BDan] (BDan = 1,8-diaminonaphthalatoboryl) substituent each were hydrogenated in high yield and enantioselectivity using C_1-symmetric pyridine(diimine) (PDI) cobalt complexes. High activities and stereoselectivities were observed with an array of 2-alkyl, 2-aryl, and 2-boryl-substituted 1,1-diboryl alkenes, giving rise to enantioenriched diborylalkane building blocks. Systematic study of substrate substituent effects identified competing steric and electronic demands in the key activating role of the boron substituents, whereby sterically unencumbered boronates such as –[BDan], –[BCat] (BCat = catecholatoboryl), and –[Beg] (Beg = ethyleneglycolatoboryl) promote the hydrogenation of trisubstituted alkenes by enabling irreversible α-boron directed insertion pathways to achieve otherwise-challenging hydrogenations of trisubstituted alkenes. Deuterium labeling studies with 1,1-diboryl alkenes support an insertion pathway generating a chiral intermediate with two different boron substituents and cobalt bound to the same carbon.

INTRODUCTION

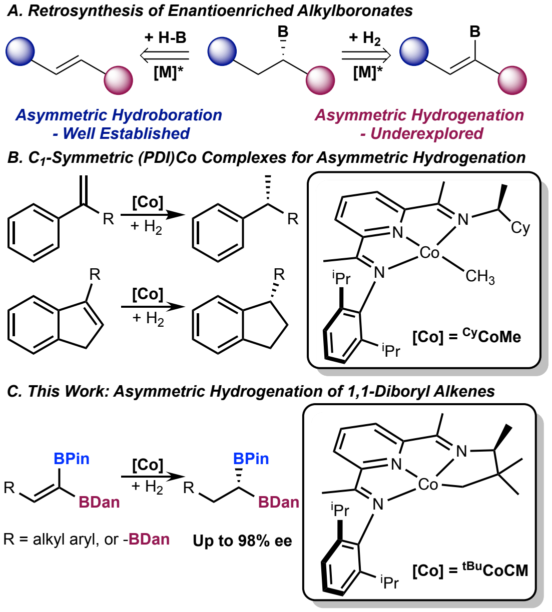
The asymmetric hydrogenation of alkenes is a well-established and powerful method for the preparation of enantioenriched compounds with widespread application in the synthesis of pharmaceuticals, fragrances, and fine chemicals.[1] With state-of-the-art rhodium and ruthenium catalysts, activated alkenes with coordinating functional groups proximal to the C=C bond are often required to obtain high enantioselectivities.[2] Unfunctionalized olefins, however, are a challenging class of substrate owing to a lack of directing assistance from coordinating functional groups.[3] Accordingly, the hydrogenation of unactivated alkenes lacking directing groups with synthetically useful enantioselectivities remains a frontier for catalyst development, although significant advances have been made with iridium,[4] titanium,[5] zirconium[6] and lanthanide[7] complexes (Scheme 1A). Nevertheless, opportunities remain to apply asymmetric hydrogenation to the synthesis of new enantioenriched building blocks for organic synthesis.

Catalysts comprised of Earth-abundant, 3*d* transition metals such as cobalt and nickel have exhibited outstanding performance in asymmetric alkene hydrogenation and in many instances offer distinct advantages over their precious metal counterparts.[8] For example, bis(phosphine) cobalt catalysts have been discovered that operate optimally in methanol at lower loadings and with higher enantioselectivities than reported rhodium catalysts for the asymmetric hydrogenation of functionalized alkenes and precursors to active pharmaceutical ingredients.[9] Catalysts supported by redox-active, C_1-symmetric pyridine(diimine) ligands have proven both active and in some cases highly enantioselective for the hydrogenation of pure hydrocarbon substrates such as styrenes and indenes.[10,11] Similarly, C_1-symmetric oxazoline iminopyridine (OIP) ligands have been subsequently applied to a host of cobalt-catalyzed enantioselective hydrofunctionalization reactions.[12,13]

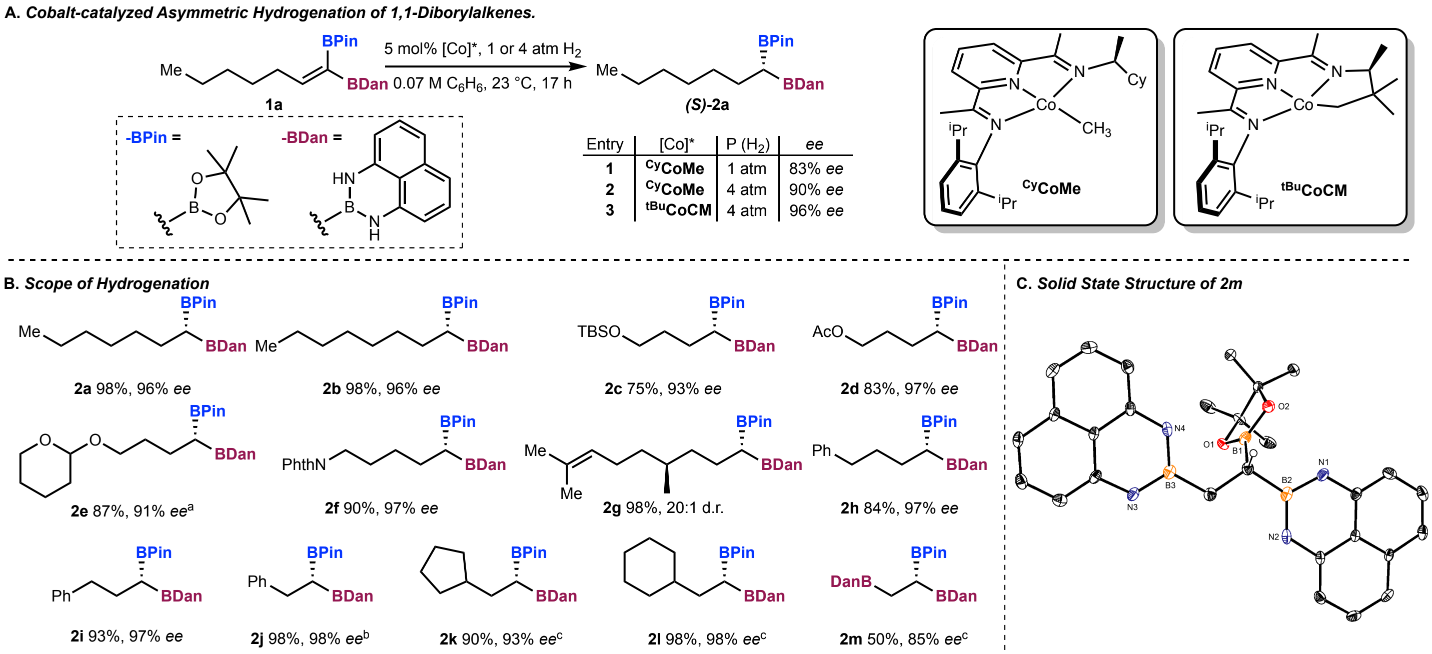
Of these hydrofunctionalization reactions, asymmetric alkene hydroboration to prepare enantioenriched alkylboronates has been explored extensively given the diverse array of transformations available from the carbon–boron bond.[14] Hence, the preparation of enantioenriched polyorganoboron compounds is arguably among the most powerful transformations in asymmetric synthesis – generating a single chiral building block that could be used to prepare a host of stereochemically defined products by known stereoretentive, stereoinvertive or iterative transformations.[15,16]

The asymmetric hydrogenation of prochiral vinyl boronates is an attractive alternative for the preparation of enantioenriched building blocks, and has been explored previously, principally with precious metal catalysts.[17,18] Such transformations can be powerful given the array of transformations for the preparation of vinyl boronates.[19] Most recently, Lu has described a class of sequential asymmetric hydrometalation-hydrogenation reactions utilizing C_1-symmetric, enantioenriched cobalt dihalide complexes activated in situ by borohydride reagents.[20] Despite these advances, the effect of boronate substitution on the rate and enantioselectivity of the hydrogenation has not been elucidated, although it has been proposed that the π-electron withdrawing nature of boron as well as its σ-donating properties promote the catalytic reaction.[18c]

Scheme 1. Transition-Metal Catalyzed Asymmetric Hydrofunctionalization.



The discovery of a cobalt-catalyzed method for the selective 1,1-diboration of terminal alkynes has provided a facile route for the preparation of 1,1-diborylalkenes.[21] Notably, use of the mixed diboron



Scheme 2. Method Development. A. Reactions conducted on 0.1 mmol scale in a thick walled glass vessel. B. Scope of the cobalt-catalyzed asymmetric hydrogenation. Standard conditions: 0.1 mmol alkene, 5 mol % ^{tBu}**CoCM**, 4 atm of H_2, 0.07 M benzene, 23 °C, 17 h. [a] Isolated as a 1:1 mixture of diastereomers. [b] 0.025 mmol alkene, 10 mol % ^{tBu}**CoCM**, 24 h. [c] 10 mol % ^{tBu}**CoCM**, 24 h. Isolated yields. Enantioselectivities determined by chiral SFC chromatography. Absolute stereochemistry of **2a-l** assigned based on the solid-state structure of **2k** (See SI). C. Solid-state structure of **2m**. Thermal ellipsoids at 30% probability. H-atoms at non-stereogenic sites omitted for clarity.

reagent, BPin–BDan (-BPin = pinacolatoboryl, -BDan = 1,8-diaminonaphthalatoboryl)[22] led to a stereoselective reaction resulting in the formation of isomerically pure 1,1-diborylalkenes. These compounds represent an unexplored yet promising class of prochiral alkenes as asymmetric hydrogenation would provide enantiomerically enriched 1,1-diborylalkanes containing two chemically inequivalent boronates on one carbon. These reagents have been shown to be versatile building blocks for the iterative preparation of enantioenriched compounds.[23]

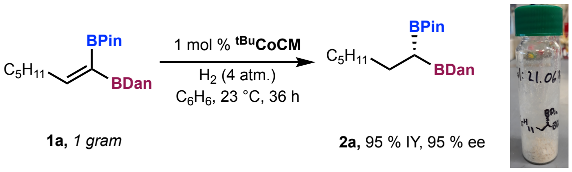
In addition to their synthetic utility, the hydrogenation of 1,1-diborylalkenes is of fundamental interest as electron-deficient alkenes are activated toward hydrogenation as compared to their more electron-rich counterparts[24] and α-boryl substituents appear to stabilize metal alkyls as evidenced by transition-metal-mediated alkene isomerizations that favor α-boryl metal intermediates.[25] These properties may be exploited to enhance both the activity and selectivity of asymmetric hydrogenation. Here we describe the cobalt-catalyzed asymmetric hydrogenation of 1,1-diborylalkenes as a route to enantioenriched diborylalkanes. Systematic variation of the boronate ester established the BDan substituent as activating for hydrogenation catalysis, as well as for supporting α-boryl metal intermediates. Mechanistic investigations revealed the insertion preferences for boron-substituted alkenes. The resulting enantioenriched 1,1-diboron species have been shown to be versatile synthons in enantioretentive Suzuki couplings as well as homologation-type reactions,[23] and our synthetic approach to these building blocks is complementary to existing methods for the enantioselective hydroboration of mono-boryl alkenes.

RESULTS AND DISCUSSION

Because previous studies from our group established that ^{Cy}**CoMe** (^{Cy}CoMe = 2-(2,6-iPr$_2$-C$_6$H$_3$N=CMe)-6-(C(Me)=N-((*S*)-(CH(CH$_3$)Cy)))-(C$_5$H$_3$N)CoCH$_3$) is an effective precatalyst for the enantioselective hydrogenation of minimally functionalized alkenes,[10a] this compound was explored for the hydrogenation of 1,1-diborylalkenes. With 1 atmosphere of H_2, the hydrogenation of **1a** in the presence of 5 mol% of ^{Cy}**CoMe** produced the corresponding 1,1-diborylalkane in 83% enantiomeric excess (*ee*), favoring the (*S*) enantiomer (Scheme 2A, entry 1). Increasing the H_2 pressure to 4 atm improved the *ee* to 90% (Scheme 2A, entry 2). Previous studies established that the *tert*-butyl variant ^{tBu}**CoCM** (^{tBu}CoCM = 2-(2,6-iPr$_2$-C$_6$H$_3$N=CMe)-6-(C(Me)=N-((*S*)-(CH(CH$_3$)C(CH$_3$)$_2$CH$_2$-))-(C$_5$H$_3$N)Co) produced little activity for the hydrogenation of *1,1-di*substituted styrene derivatives. However this precatalyst produced high activity for the asymmetric hydrogenation of **1a** with 4 atm of H_2, improving the enantioselectivity to 96% (Scheme 2A, entry 3).

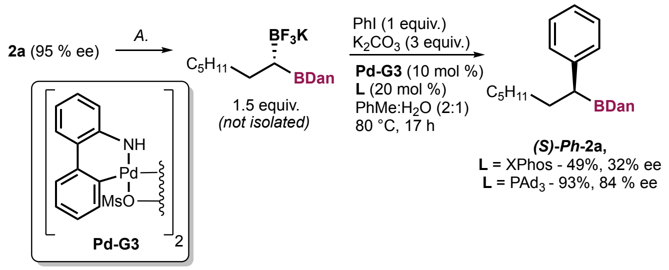
Having identified an active and enantioselective cobalt catalyst for the hydrogenation of **1a**, the scope of the transformation was evaluated. A range of linear, alkyl-substituted 1,1-diborylalkenes underwent hydrogenation using the standard, optimized reaction conditions (Scheme 2B). Common functional groups such as a silyl protected alcohol (**2c**), an ester (**2d**), an acetal (**2e**), and phthalimide (**2f**) were all tolerated. Notably, the citronellol-derived diene, **2g** was selectively hydrogenated at the diboryl alkene, leaving the all-aliphatic alkene untouched. This chemoselectivity demonstrates the activating effect of the 1,1-diboryl substituent as compared to 1,1-dimethyl substituent. More sterically hindered 1,1-diborylalkenes incorporating cyclopentyl (**2k**) and cyclohexyl (**2l**) substituents also underwent hydrogenation in high yield and enantioselectivity. A phenyl-substituted diboryl alkene was also hydrogenated with high enantioselectivity (**2j**), suggesting that an aryl group does not perturb the preferred insertion pathway. Additionally, unsymmetric, trisubstituted 1,1,2-triborylalkene (**1m**) was sucessfully hydrogenated with **^{tBu}CoCM** to the corresponding hindered alkane (**2m**) and was obtained in 85% *ee* favoring the (*S*) enantiomer. The absolute configuration of the triborylalkane product was established by X-ray crystallography (Scheme 2C).

For synthetic utility, the cobalt-catalyzed asymmetric hydrogenation should be scalable. With 1 mol % of **^{tBu}CoCM** and 4 atm of H_2 gas, 1.0 gram of **1a** was hydrogenated to the corresponding 1,1-diboryl alkane in 95 % isolated yield with 95 % enantiomeric excess without the need of further purification (Scheme 3). Efficient and rapid stirring was key to achieving high enantiomeric excess. The scalability of the hydrogenation highlights a potential advantage of this method compared to hydroboration for the preparation of enantioenriched alkyl boronates.



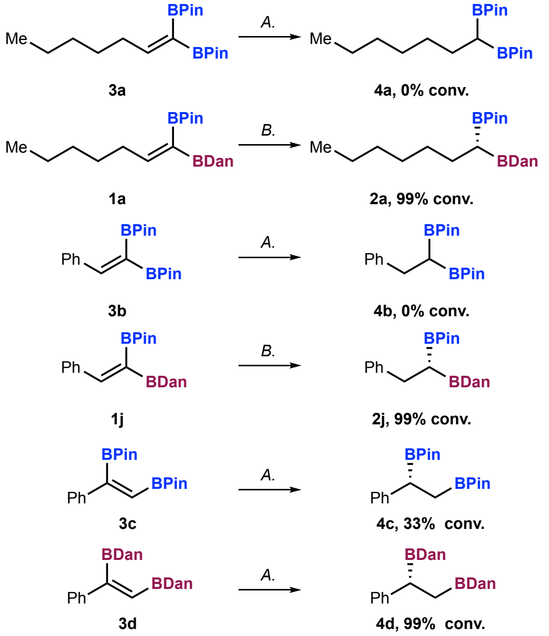
Scheme 3. Gram Scale Enantioselective Hydrogenation of the 1,1-Diboryl Alkene (1a).

Sigman, Biscoe and co-workers recently reported conditions for ligand-controlled, palladium-catalyzed stereoretentive and invertive cross couplings of enantioenriched alkyl trifluoroborates.[26] To determine whether such enantiodiversity can be applied to enantioenriched 1,1-diboryl alkanes, **1a** was converted to its respective trifluoroborate analogue, and directly subjected to Suzuki-Miyaura cross coupling conditions using **Pd-G3**[27a] as a precatalyst (Scheme 4). Interestingly, both XPhos[27b] and PAd$_3$[27c] produced the arylated product with stereoinversion, in 32% ee (49% yield), and 84% ee (93% yield) respectively. This demonstrates the unique reactivitiy in enantioenriched 1,1-diboryl alkanes from their purely alkyl substituted counterparts.



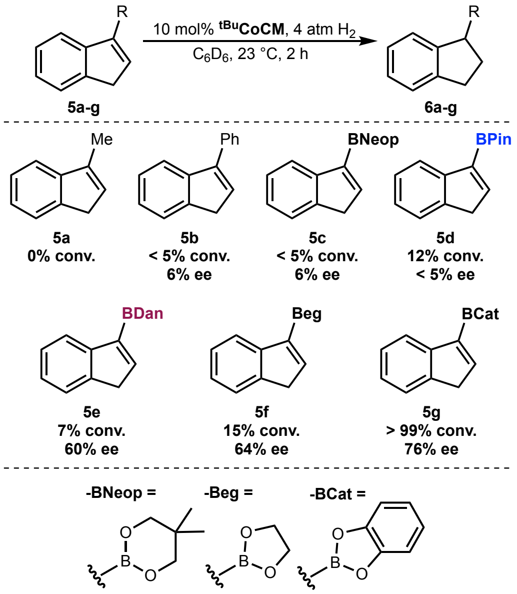
Scheme 4. Suzuki-Miyaura Cross-Coupling of an enantioenriched 1,1-diboryl alkane. Isolated yields. Enantioselectivities determined by chiral SFC chromatography. A. Sat. aq. KHF_2 (10 equiv.), MeCN (0.125 M), rt, 2 h. Absolute configuration of **(S)-Ph-2a** determined by deprotection and oxidation of boronate ester.

The discovery of a highly enantioselective route for the synthesis of polyboryl alkanes prompted studies to uncover the source of the high activity. Recall that **^{tBu}CoCM** was inactive for the hydrogenation of 1,1-disubstituted styrenes and only the boron-substituted alkene was hydrogenated en route to **2g.**[10a] This supports an activating effect of the boron groups – and despite its steric encumbrance in comparison to the alkyl substituted alkene – is hydrogenated in good yield. To elucidate the origins of this phenomenon, a systematic study of the hydrogenation of a selected group of boryl alkenes, styrenes and indenes was conducted (Scheme 5 & 6). Notably, the attempted hydrogenation of the 2,2-diborylheptene (**3a**), or 2,2-diborylstyrene (**3b**) with 5 mol % of **^{tBu}CoCM** under standard conditions produced no detectable amounts of alkane after 24 hours (Scheme 5, entry 1 & 3). Replacement of the *(E)*–[BPin] substituent with a –[BDan] group resulted in complete conversion to the alkane **1a** or **1j** under identical conditions. A similar effect was observed with 1,2-diborylstyrenes. The [BPin]-substituted variant (**3c**) was hydrogenated to 33% conversion after 24 hours under standard conditions while the [BDan] variant (**3d**) reached complete conversion to the desired alkane as observed by ^{1}H NMR spectroscopy.



Scheme 5. Hydrogenation of Alkenyl Boronates. A. Hydrogenation reaction was conducted in a J-Young NMR tube with 0.025 mmol alkene, in benzene-d_6 with 10 mol % **^{tBu}CoCM**, 4 atm H_2, 23 °C and the conversions determined by ^{1}H NMR spectroscopy after 24 h. See SI for experimental details. B. From scheme 2B.

To further elucidate the effect of each boronate substituent, a series of substituted indenes was prepared from 1*H*-inden-3-yl boronic acid and subjected to standard hydrogenation conditions with **^{tBu}CoCM** as the precatalyst. Each conversion was determined by ^{1}H NMR spectroscopy after 2 hours (Scheme 6). Consistent with our previous study, both 1-methyl (**5a**) and 1-phenyl (**5b**) indenes were poor substrates for hydrogenation and only trace quantities of the corresponding alkane were detected. Introduction of common boronate esters such as [BNeop] (**5c**) (BNeop = neopentanolatoboryl), [BPin] (**5d**), [BDan] (**5e**), and [Beg] (**5f**) (Beg = ethyleneglycolatoboryl) all likewise produced low conversions during the two-hour reaction time frame. Notably, the hydrogenation of [BCat] (BCat = catecholatoboryl) (**5g**) reached full conversion over this time period, demonstrating a remarkable activating effect. Even when the conversions were low, the observed enantioselectivities also offered insight. Alkenes bearing a phenyl substituent (**5b**) as well as [BNeop] (**5c**) and [BPin] (**5d**) produced low selectivities (6, 8 and 0% *ee*, respectively) while [BDan] (**5e**) and [Beg] (**5f**) groups furnished the corresponding alkane in 60 and 64% *ee*, respectively. The most activated substrate in the series, **5g** ([BCat]) also gave the highest *ee* at 76% (Scheme 6). The higher enantioselectivities observed with the [BDan], [Beg] and [BCat] substituents suggest that sterically unencumbered boronates may be required for high enantioselectivity.



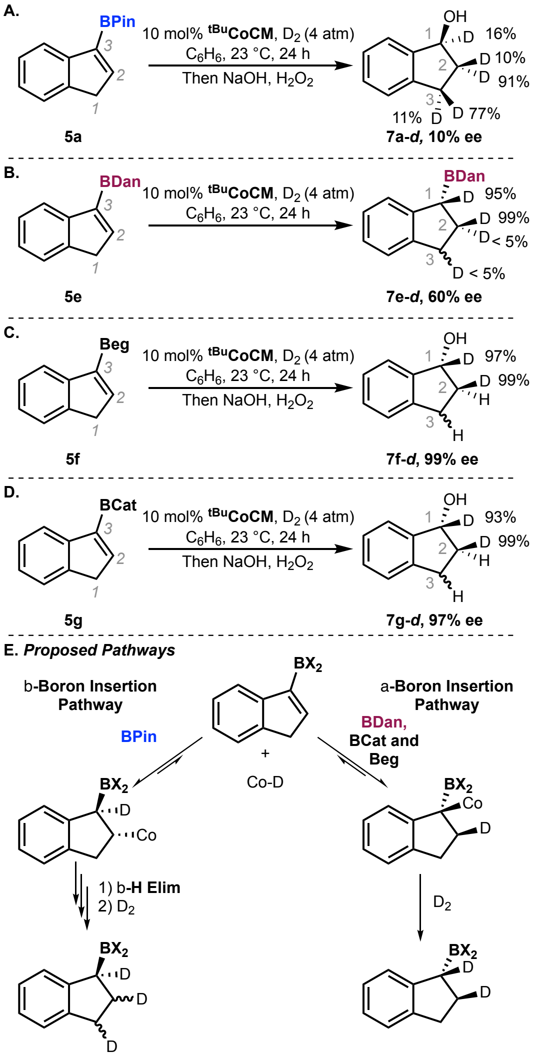
Scheme 6. **Hydrogenation of Indenyl Boronates.** Reactions were conducted on 0.025 mmol scale in a J-Young NMR tube and the conversions determined by ^{1}H NMR spectroscopy. Enantioselectivies of all boronates were determined by chiral SFC chromatography on the corresponding alcohols following oxidation with a THF:H_2O 10:1 solution of H_2O_2 and NaOH, with the exception of **6e,** which was determined directly. See SI for complete experimental details.

Previously reported isotopic labeling studies on the asymmetric hydrogenation of aryl-substituted indenes promoted by ^{Cy}**CoMe** with D_2 gas established deuterium incorporation occurred at every site of the indanyl core.[10b] These observations are consistent with a slow 2,3-insertion (for definition of the labeling scheme see Scheme 7), resulting in the cobalt bound to the less-substituted carbon as the most catalytically relevant insertion event. This step is followed by fast isomerization to the benzylic position along the π-face of the indene before release of alkane either by cyclometallation of a ligand substituent or reaction with dihydrogen. Because the enantioselectivity of the hydrogenation of indenyl boronates was strongly influenced by the substituent on the boronate, the identity of this substituent may also be influencing the preferred alkene insertion and ultimately turnover pathway.

To probe this hypothesis, a series of indenyl boronates were deuterated with D_2 gas in the presence of 5 mol % of ^{tBu}**CoCM** for 24 hours to maximize conversion of the alkene. The resulting boronates were subsequently oxidized to the corresponding alcohol for ease of analysis by ^{2}H and ^{13}C NMR spectroscopies (Scheme 7). The indanol obtained from deuteration of **5a** (BPin) (Scheme 7A) exhibited isotopic incorporation at all of the saturated positions and overall poor enantioselectivity (10% *ee*, *S*). By contrast, with the –[BDan]-substituted indene (**5e**), deuterium incorporation was observed predominantly at the 1- and 2-positions, although a small amount (<5%) of deuterium was observed in the 3-position. In addition, deuterium was incorporated at both positions at the 2 carbon. The enantioselectivity of this hydrogenation was modest (60% *ee*, *R*, Scheme 7B), and favored the opposite enantiomer. However hydrogenation of the –[Beg] (**5f**) and –[BCat] (**5g**) substituted indenes under deuterium atmosphere generated only one detectable isotopomer, where deuterium was exclusively incorporated at the 1- and 2-position with remarkably high enantioselectivities (97% *ee*, *R*, Scheme 7C; 99%, *R*, Scheme 7D respectively) to the opposite enantiomer than that derived from indenyl-BPin.

As the most hydrolytically sensitive alkenyl boronates (e.g. –[BCat] **6f, and** –[Beg] **6g**) are hydrogenated to the greatest enantioselectivity, the effect of free boronic acid was tested in this hydrogenation reaction. Upon H_2 gas addition (4 atm) to a C_6D_6 solution of 0.025 mmol **5g,** 10 mol % ^{tBu}**CoCM,** and 10 mol % of (1*H*-inden-3-yl)boronic acid resulted in a color change from dark purple to a light red, and showed no conversion of **5g.** It is concluded that the presence of free boronic acid is not involved in the hydrogenation of indenyl boronates.

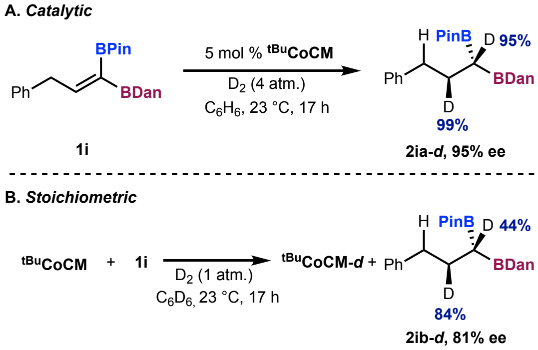
Selective deuterium incorporation at the 1- and 2-position of the indanol product is consistent with an α-boron-directed insertion pathway, where turnover proceeds through an α-boron alkyl cobalt intermediate (Scheme 7E). This pathway is favored with sterically unencumbered boronates such as –[Beg] and –[BCat]. Although –[BDan] is sterically unencumbered, the boron *p*-orbital is partially occupied as evidenced by its resistance to oxidation,[22] and the hyperconjugative stabilization from the boron to the cobalt-carbon bond may be less pronounced. Thus, a small amount of isomerization is observed. Sterically encumbered boronates such as –[BPin] prevent the bulky cobalt complex from inserting α to boron, and thus a large amount of isomerization originating from a β-boron-directed insertion pathway is observed (Scheme 7E, left). A similar effect has been observed by Yun, where a vinyl –[BDan] substrate shows greater α-boron selectivity in hydroboration than a vinyl –[BPin].[23b] This α-boron-directed insertion pathway enables high levels of enantioselectivity by outcompeting isomerization pathways (Scheme 7E, right).



Scheme 7. Deuteration of Indenyl Boronates. Reactions conducted on a 0.1 mmol scale in a thick-walled glass vessel. Enantioselectivities determined by chiral SFC. Relative configuration of (b) determined by conversion of BDan to BPin and oxidation with NaOH, H_2O_2.

The discovery that different boronates promote distinct insertion pathways prompted similar studies with 1,1-diboryl alkenes. Deuteration of **1i** in the presence of **^{tBu}CoCM** under 4 atmospheres of D_2 gas at room temperature for 17 hours generated a single isotopomer in high enantioselectivity (95% *ee*; Scheme 8A), implying that no isomerization events are competitive with catalytic turnover.

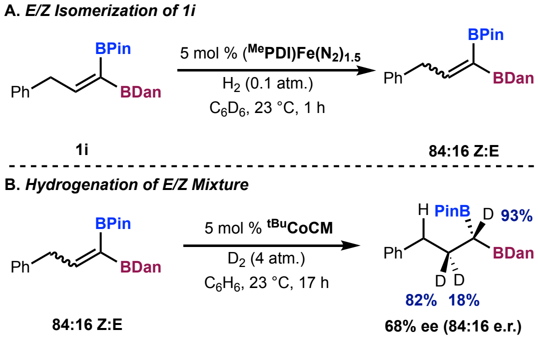
The insertion preferences of the diboryl alkene into the cobalt–hydride bond were also investigated. Ideally, the alkene could be added to an isolated cobalt deuteride, and the resulting intermediate of insertion could be quenched with a proton source. Because the cobalt–deuteride derived from **^{tBu}CoCM** has eluded isolation,[10a] a single turnover experiment with **1i** was conducted under a D_2 atmosphere to promote selective labeling of the product alkane that would in turn inform on the site of attachment of the putative cobalt–alkyl. Low (1 atm) pressures of deuterium were used to maximize turnover from a cyclometallation pathway, thus lowering deuterium incorperation at the position the cobalt inserted. Deuterium was predominantly and stereoselectively incorporated in a *syn* disposition at the β position (84%), and to a lesser extent α to boron (44%) (Scheme 8B). This result is consistent with a dominant α-boron directed insertion pathway, generating an intermediate where the metal center shares a carbon with two chemically inequivalent boronates. Similar behavior has been observed previously in the cobalt-catalyzed hydroboration of 1,1-diboryl alkenes used to selectively generated 1,1,1-triboryl alkanes.[21] Under stoichiometric conditions, the β-boron-directed insertion pathway was also competitive and is likely the origin of the diminished enantioselectivity (81% *ee*), however the lower pressure of D_2 (1 atm) is another possible source of the lower selectivity.



Scheme 8. Catalytic (A) and stoichiometric (B) deuteration studies of 1i.

An α-boron directed insertion pathway would place the metal center on the prochiral carbon of the alkane. This in turn may allow for the enantioselective hydrogenation of *E/Z* mixtures to the same enantiomer of the diboryl alkane.[3] The pyridine(diimine) iron dinitrogen complex, $(^{Me}PDI)Fe(N_2)_{1.5}$ (^{Me}PDI = 2,6-(2,6-Me_2-C_6H_3N=CMe)$_2C_5H_3N$)[28] was competent for the isomerization of **1i** under low H_2 pressure (0.1 atm), resulting in an 84:16 *Z*:*E* mixture (Scheme 9A).

After subjecting the *E/Z* mixture to the standard reaction conditions under an atmosphere of D_2 gas (4 atm D_2), deuterium incorporation was observed at both positions at the homobenzylic position (82% *syn*, 18% *anti*) and the alkane observed in 68% *ee* (84:16 e.r., Scheme 9B). This is consistent with each isomer of the alkene being hydrogenated to a different major enantiomer. Though it may suggest a β–boron-directed insertion pathway, the results of the stoichiometric deuterium labeling study (Scheme 8) supports an α-boron directed insertion pathway, thus a model where each isomer of the alkene is hydrogenated to a different enantiomer, while still proceeding through an α-boron-directed insertion pathway cannot be excluded.



Scheme 9. Preparation and hydrogenation of an *E/Z* mixture.

CONCLUDING REMARKS

A cobalt-catalyzed method for the asymmetric hydrogenation of 1,1-diboryl alkenes was discovered as a route to versatile, enantiopure polyboryl alkanes. Both the steric and electronic properties of the boronate substituents influence the yield and enantioselectivity of the hydrogenation reaction and in some cases activate the alkene for hydrogenation. Deuterium labeling experiments support an insertion pathway where the metal center is selectively bound to the sterically congested carbon of the substrate and demonstrate the powerful effects of alkenyl boronates to overcome otherwise repulsive steric effects. The results of the indene deuteration studies are in agreement with the deuteration studies with the 1,1-diboryl alkenes – where sterically unencumbered boronates containing available p-orbitals enabled high conversion and enantioselectivity. Leveraging this boron activating effect may be broadly applicable in asymmetric catalysis involving boron-containing substrates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Crystallographic information for **2k** and **2m** (CIF)

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Notes

The authors declare no competing financial interest.

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