Remote, Diastereoselective Cobalt-Catalyzed Alkene Isomerization-Hydroboration: Access to Stereodefined 1,3-Difunctionalized Indanes

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ABSTRACT: The remote, diastereoselective hydroboration of 2- and 3-substituted indenes with a 2,2':6',2"-terpyridine cobalt alkyl precatalyst is described that maintains high regio- and stereoselectivity selectivity independent of the starting position of the alkene. Several 1,2- and 1,3-disubstituted indanyl boronate esters were obtained with exclusive (>20:1) selectivity for the *trans* diastereomer including synthetically versatile, stereodefined diboron derivatives. Alkene isomerization by a putative cobalt hydride intermediate precedes carbon–boron bond formation, leading to the observed regioselectivity for boron incorporation at the unsubstituted C(sp^3)-H benzylic site. The regio- and diastereoselectivity of the transformation was maintained independent of the starting position of the alkene, as demonstrated by hydroboration of three isomers of methyl-substituted indene. Deuterium labeling experiments support rapid and reversible insertion and β-hydride elimination to isomerize 3-methylindene and 1-*exo*-methylene-indane, accounting for the isotopic distribution observed in the products. Mechanistic studies, including stoichiometric experiments, DFT calculations, and kinetic analysis, support a mechanism in which 2,3-alkene insertion into a cobalt hydride intermediate determines both the regio- and diastereoselectivity of the catalytic reaction. Synthetic applications of the indanyl boronate esters were demonstrated through elaboration of the products to several examples of 1,3-disubstituted indanes, important carbocyclic structural motifs in both pharmacological and bioactive molecules.

KEYWORDS: Diasteroselective, hydroboration, cobalt catalysis, chain-walking, indanes

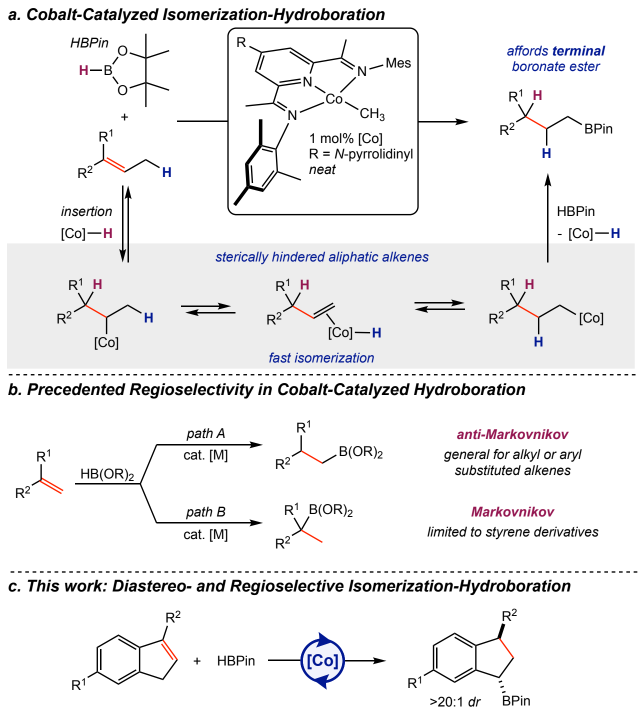
INTRODUCTION

The synthetic utility of organoboron compounds continues to motivate the development of methods for the selective incorporation of boron into unique molecular scaffolds.[1] Transition metal-catalyzed alkene hydroboration reactions that exhibit high chemo-, regio- and stereocontrol are particularly valuable for accessing synthetically valuable and modular targets.[2] In particular, catalysts that promote alkene isomerization coupled to a subsequent carbon-element bond-forming sequence are enabling tools in synthesis for the functionalization of remote C–H bonds that are distal to the reactive C=C double bond [3] This tandem reaction pathway is well established in important catalytic processes such as alkene hydroformylation[4] and polymerization.[5,6] Application of this strategy to the construction of bonds in fine chemicals and more complex molecules is an emerging frontier in catalysis directed toward synthesis.[7] Through insertion of an alkene into a transition-metal hydride bond followed by successive β-H elimination-reinsertion events, a remote carbon–element bond can be constructed site-selectively in the molecule without the need for a preinstalled directing group. Demonstration of stereo- and regioselective isomerization-hydroboration of alkenes is valuable for broadening the applicability of this method toward the synthesis of new organoboron compounds.

In 2013, our group reported pyridine(diimine) cobalt alkyl complexes that promote isomerization-hydroboration of tri- and tetrasubstituted alkenes with pinacolborane (HBPin) under neat conditions to generate terminal boronate esters (Scheme 1a).[8] Isotopic labeling experiments supported rapid migration of the cobalt center along the alkyl chain with C–B bond formation occurring exclusively at primary carbon positions. α-Diimine-ligated cobalt precatalysts were later developed and exhibited unprecedented activity for tetrasubstituted alkenes, however sluggish reactivity was observed with styrene likely due to the formation of inactive η^3-allyl complexes.[9]

While isomerization-hydroboration was initially observed in rhodium-catalyzed alkene hydroboration,[10,11] contemporary interest in the development of Earth-abundant metal catalysts[12] has demonstrated that this tandem process is frequently observed with first-row transition-metals to form terminal alkyl boronate esters from internal alkenes. Recently, Stradiotto, Turculet and coworkers reported a comprehensive experimental and computational study of (*N*-phosphinoamidinate) complexes based upon Mn, Fe, Co, and Ni for isomerization-hydroboration of octene isomers.[13] Facile isomerization as well as significantly lower barriers for boron transfer to the terminal metal alkyl complex versus isomeric secondary metal alkyl intermediates are the origin of the terminal selectivity observed in the final *n*-octylboronate ester. This conclusion is further supported by the several well-established examples of cobalt-catalyzed anti-Markovnikov selective hydroborations of acyclic alkenes (Scheme 1b, path A)[14] including the enantioselective hydroboration of 1,1-disubstituted aryl alkenes independently developed by Huang[15] and Lu.[16]

Scheme 1. Strategies for Selectivity Control in Alkene Hydroboration.



Chain-walking enables access to trans-1,3-disubstitution

The preference of transition metal catalysts to favor terminally selective C–B bond formation at primary sites has presented a challenge for the development methods for branched (Markovnikov) selective hydroboration.[17] This particularly pronounced in cyclic alkenes where the absence of primary sites to drive C–B bond formation translate on to limitations with scope. In cobalt catalysis, achieving Markovnikov selectivity or more generally secondary C–B bonds is largely substrate dependent and typically limited to styrene derivatives (Scheme 1b, path B).[18,19] Our laboratory has reported the synthesis of a 2,2':6',2"-terpyridine cobalt alkyl complex that promotes the selective hydroboration of styrene with 25:1 regioselectivity for the Markovnikov product.[9] The regioselective hydroboration of 1,1-diborylalkenes was also effectively catalyzed, resulting in formation of the 1,1,1-triboronate ester, likely due to a stabilizing α-boryl effect on the cobalt alkyl intermediate.[20] Utilization of tandem isomerization-hydroboration to yield branched alkyl boronate esters is rarer, however and cyclic alkenes are an unexplored yet important class of substrates. Our group reported the isomerization-hydroboration of linear terminal alkenes to yield branched products with boron incorporation adjacent to π-systems.[21] Employing a pre-isomerization step prior to HBPin addition, high regioselecivities were achieved. Lu and coworkers later expanded this mode of reactivity and developed a general method for the enantioselective synthesis of benzyl boronate esters with excellent enantioselectivity.[22]

Extending catalytic alkene isomerization-hydroboration to the formation of secondary C–B bonds in cyclic alkenes is attractive for developing remote regio- and stereoselective reactions. Given the observed preference for 2,2':6',2"-terpyridine cobalt-derived catalysts to yield branched alkyl boronate esters, application of this catalyst to the isomerization-hydroboration of 3-substituted indenes was explored (Scheme 1c). In addition to presenting a sterically challenging and unexplored carbocyclic core for cobalt-catalyzed hydrofunctionalization reactions, the indanyl unit is an important, recurring substructure in a variety of pharmaceuticals, bioactive compounds and natural products (Figure 1).[23,24,25,26] Common methods to prepare indanes include Friedel-Crafts or Michael-type cyclizations, ring-expansion or contraction methods, and direct C-H activation.[27] However, competing side reactions can complicate these methods and prohibit modular incorporation of substituents around the indanyl ring.[28] Metal-catalyzed hydroboration of readily synthesized 3-substituted indenes is attractive as a complementary method owing to the versatility of boronate esters to be readily transformed to other groups with control of stereochemistry.[29]

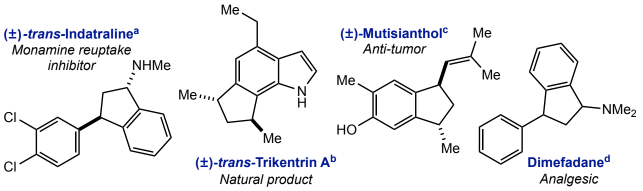


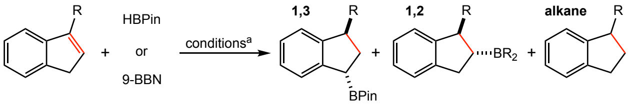
Figure 1. Examples of 1,3-disubstituted indanes in pharmaceuticals and bioactive molecules. [a]Ref. 23. [b]Ref. 24. [c]Ref. 25. [d]Ref. 26.

Here we describe the remote, diastereoselective cobalt-catalyzed hydroboration of 3-substituted indenes to selectively yield *trans*-1,3-disubstituted indanes. Comprehensive investigations into the mode of action for alkene isomerization and subsequent hydroboration are presented. Deuterium labeling studies provide insight into the regio- and facial preferences for alkene insertion with the cobalt catalyst. The synthetic utility of the *trans*-1,3-disubstituted indanyl boronate esters was demonstrated through a host of bond constructions from the boron group including vinylation and arylation.

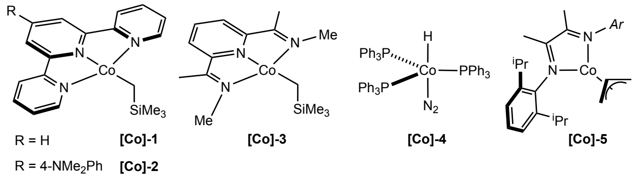
RESULTS AND DISCUSSION

Initial method development employed 0.10 mmol of the indene substrate, and 1.05 equivalents of HBPin in the presence of 5 mol% of cobalt precatalyst at 23 °C for 20 h in 0.10 M toluene. Several cobalt alkyl complexes were examined (Scheme 2, see Supplemental Information for full details) with 2,2':6',2"-terpyridine cobalt alkyl (**[Co]-1**) exhibiting the highest yield of boronate ester for both the methyl and phenyl substituted indenes (entries 1 and 2, respectively), as determined by gas chromatograpy. Analysis of the products by ^{1}H, ^{13}C and ^{1}H correlation NMR experiments established exclusive formation of 1,3-substituted products with an *anti* disposition of the boron substituent to the R group. Isolated yields of 96% and 90% were obtained for the phenyl and methyl substituted indanes, respectively. Complexes **[Co]-3** and **[Co]-4** exhibited similar regio- and diastereoselectivities (entries 7-10) however, a significant side reaction yielding alkane was observed with these precatalysts. The diimine cobalt η^3-allyl complex (**[Co]-5**) yielded no hydroborated product, likely due to formation of a stabilized π-indanyl complex.[9] By contrast, uncatalyzed hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) resulted in 1,2-substituted products (entries 3 and 4), further highlighting the unique regioselectivity enabled by the cobalt-catalyzed method.

Scheme 2. Precatalyst Evaluation Studies.[a]



entry	catalyst	borane	R	1,3 (%)[d]	1,2 (%)	alkane (%)[d]
1	**[Co]-1**	HBPin	Me	>98 (>20:1 *dr*)	<5	<5
2	**[Co]-1**	HBPin	Ph	>98 (>20:1 *dr*)	<5	<5
3[b]	**none**	9-BBN	Me	—	52 (>20:1 *dr*)	—
4[b]	**none**	9-BBN	Ph	—	69 (>20:1 *dr*)	—
5	**[Co]-2**	HBPin	Me	88 (>20:1 *dr*)	<5	12
6	**[Co]-2**	HBPin	Ph	61 (>20:1 *dr*)	<5	<5
7	**[Co]-3**	HBPin	Me	65 (>20:1 *dr*)	<5	35
8	**[Co]-3**	HBPin	Ph	63 (>20:1 *dr*)	<5	20
9	**[Co]-4**	HBPIn	Me	35 (>20:1 *dr*)	<5	54
10[c]	**[Co]-4**	HBPin	Ph	40 (>20:1 *dr*)	<5	56
11[c]	**[Co]-5**	HBPin	Me	<5	<5	<5
12[c]	**[Co]-5**	HBPin	Ph	<5	<5	33

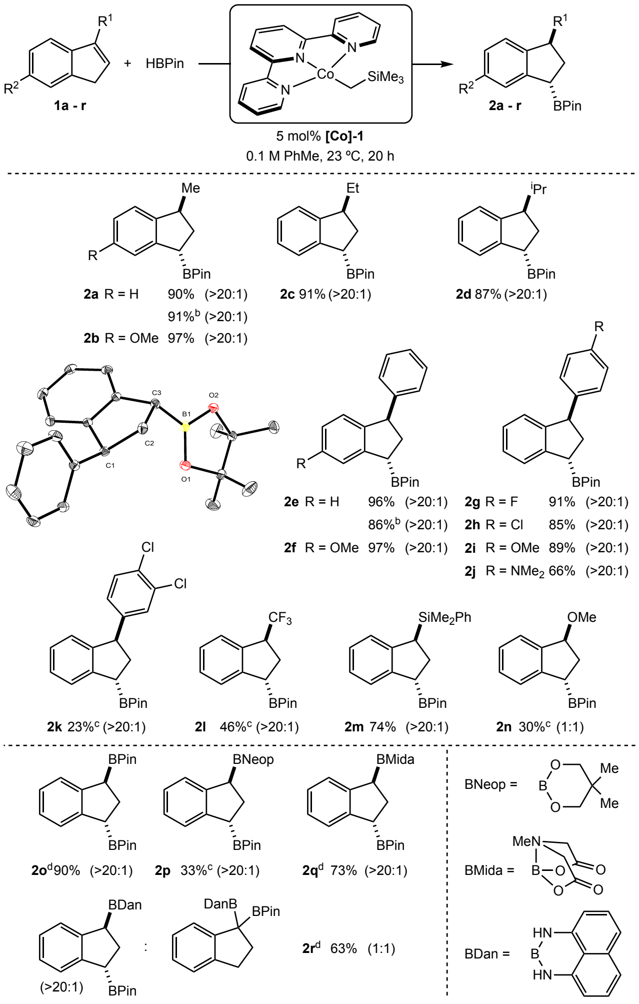


[a] Unless otherwise noted, reactions conducted with 0.10 mmol of indene, 0.105 mmol HBPin, 0.005 mmol precatalyst, in 1.0 mL toluene at 23 °C for 20 h. [b] Reactions conducted with 0.10 mmol of indene, 0.50 mmol 9-BBN at 75 °C for 48 h. Reported NMR yield of alcohol resulting from oxidation of trialkyl borane. See SI for full details. [c] Reactions conducted for 48 h. [d] Yield and *dr* was determined from the calibrated relative integrals of product and cyclooctane signals measured by gas chromatographic analysis of the unpurified reaction mixture.

The scope of the isomerization-hydroboration reaction was investigated and the results of these experiments are reported in Scheme 3. Standard conditions employed a 0.1 M solution of indene in toluene with 5 mol% of [**Co**]-**1** and 1.05 equiv of HBPin. The cobalt-catalyzed isomerization-hydroboration of alkyl-substituted indenes (**1a**-**1d**) proceeded with high yields and diastereoselectivities, even for bulky isopropyl substituted **1d**, to the desired indanyl boronate esters with complete selectivity for the *trans* isomer in all cases. X-ray crystallography of the phenyl-substituted product **2e** provided further structural confirmation for the selective *anti* arrangement of the boron. Aryl substituents containing electron-withdrawing (**1g**-**1h**) or electron-donating (**1i** and **1j**) groups at the 4-position were also compatible with the catalytic protocol. For the 3,4-dichloroaryl substituted **1k**, hydroboration proceeded accompanied by significant competing protodeborylation, resulting in the desired indanyl boronate ester being isolated as a mixture. Trifluoromethyl substituted indene (**1l**) was tolerated, yielding 46% of the desired hydroborated product. Additionally, substrates containing methoxy-group substitution at the 6-position of the indene (**1b** and **1f**) underwent hydroboration with no loss in isolated yield of the desired indanes. Heteroatom-substituted indenes (**1m**-**1o**) were also tolerated, however in the latter case a 1:1 mixture of diastereomers was obtained, possibly due to a directing effect of the methoxy group overcoming the inherent selectivity of the reaction.

Boron-substituted indenes (**1p**-**1s**) were also explored. Given the synthetic versatility of the boron substituent, 1,3-disubstituted indanyl diboron compounds are interesting building blocks for the rapid construction of complex molecular structures. Examples with two different organoboron groups are particularly attractive for selective, sequential functionalization reactions made possible by the chemically differentiated boron groups.[30] Boron substituted indenes **1o** and **1p** underwent hydroboration to yield the corresponding 1,3-diboronate esters. However, for the neopentyl glycol boronate ester (BNeop, **1p**), significant exchange of the pinacolato and glycolato groups was observed, resulting in a 1:1 mixture of **2o** and **2p**. To suppress this process, the *N*-methyliminodiacetic acid (BMida, **1q**) and 1,8-diaminonaphthalene (BDan, **1r**) derivatives were hydroborated. Interestingly, hydroboration of **1r** resulted in a 1:1 mixture of regioisomers identified as the desired *trans*-1,3-diboron product and the 1,1-diboron indane. It is possible that the geminal regioisomer results from a combined electronic and steric effect of the BDan group in which the naphthyl ring can stabilize cobalt at the substituted position.[31] To highlight the practicality of the method, products **2a** and **2e** were prepared on gram scale in 91% and 86% isolated yields, respectively (see SI for details).

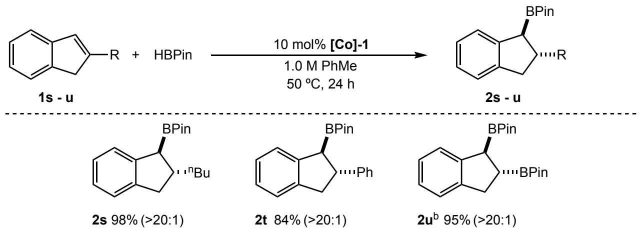
Scheme 3. Diastereoselective Hydroboration of Substituted Indenes.[a]



[a]Unless indicated otherwise, reactions were run on 0.1 mmol scale with 5 mol% [Co] precatalyst. Percentages are isolated yields unless otherwise noted. Diastereomeric ratio as determined by GC and quantitative $^{13}C\{^1H\}$ NMR analysis reported in parentheses. See SI for full experimental details. [b]Yield for gram scale reaction. See SI for details. [c]Yield determined by quantitative $^{13}C\{^1H\}$ NMR spectroscopy due to overlapping signals in the ^1H NMR. [d]Reaction conducted at 50 °C for 20 h in THF.

Regioisomeric 1,2-disubstituted boronate esters were prepared by hydroboration of symmetrical 2-substituted indenes (Scheme 4). *n*-Butyl (**1s**), phenyl (**1t**), and BPin (**1u**) variants proceeded with high yields and diastereoselectivities to yield the *trans*-1,2-disubstituted indane regioisomers, as confirmed by analysis of the products by ^1H, ^{13}C and ^1H correlation NMR experiments.

Scheme 4. Access to *trans*-1,2-Disubstituted Indanes through Hydroboration.[a]

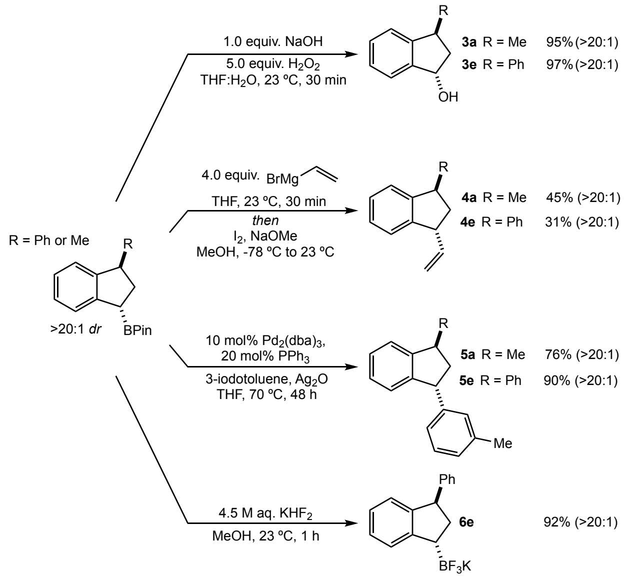


[a]Unless indicated otherwise, reactions were run on 0.1 mmol scale with 10 mol% [Co] precatalyst. Percentages are isolated yields. Diastereomeric ratio as determined by GC and quantitative $^{13}C\{^1H\}$ NMR analysis reported in parentheses. See SI for full experimental details. [b]Reaction conducted in THF.

Synthetic Applications of Indanyl Boronate Esters

The synthetic utility of selected examples of indanyl boronate esters prepared in this study was investigated and the results of these studies are presented in Scheme 5. A host of stereospecific transformations are available to convert secondary boronate esters to other functional groups.[32] The sterodefined indanyl boron compounds prepared by the cobalt-catalyzed method are attractive and versatile synthons for additional elaboration. Oxidation[33] of **2a** and **2e** was achieved using a NaOH/H_2O_2 solution to yield the *trans* alcohols, **3a** and **3e**, in 95% and 97% yield, respectively. Vinylation of **2a** and **2e**, using Zweifel olefination conditions,[34] afforded **4a** and **4e** in 45% and 31% yield, respectively. Using conditions for the palladium-catalyzed cross coupling of secondary organoboronate esters developed by Crudden and coworkers,[35] cross-coupled products **5a** and **5e** were isolated in 76% and 90% yields with retention of configuration. The trifluoroborate salt[36] **6e** was also isolated in 92% yield. These derivatization reactions demonstrate the high synthetic utility of the indanyl boronate esters formed from cobalt-catalyzed isomerization-hydroboration. Importantly, compounds **3a**-**6e** are not accessible directly via existing cyclization methods selectively,[28] further highlighting the utility of the products formed to yield disubstituted indanes with a high degree of stereocontrol.

Scheme 5. Representative Synthetic Applications of Indanyl Boronate Esters. [a]



[a]Percentages are isolated yields unless otherwise noted. Diastereomeric ratio as determined by quantitative $^{13}C\{^1H\}$ NMR analysis reported in parentheses. See SI for full experimental details. dba = dibenzylideneacetone.

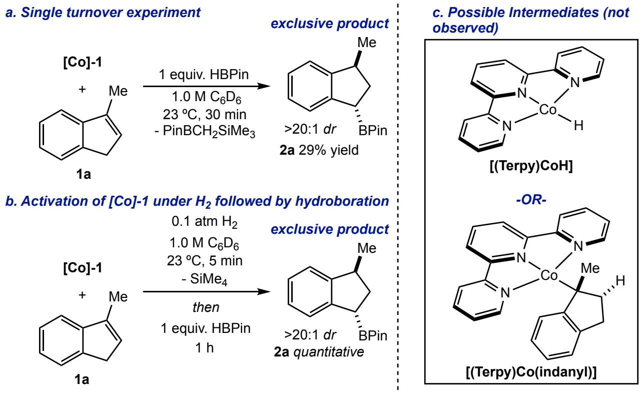
Mechanistic Studies

To gain insight into the mechanism of the catalytic hydroboration reaction and importantly, the origins of the regio- and diastereoselectivity, a series of additional studies were conducted. The hydroboration of 3-methyl-1*H*-indene (**1a**) was selected as a representative reaction and monitored by ^1H NMR spectroscopy in benzene-d_6. Immediately upon addition of HBPin to a 1.0 M solution of **1a** in benzene-d_6 with 5 mol% [**Co**]-**1**, complete consumption of [**Co**]-**1** was observed. Additional monitoring over the course of the reaction by ^1H NMR spectroscopy demonstrated clean conversion of **1a** to product **2a**. No peaks corresponding to a new cobalt species were observed over the course of the transformation. An additional set of stoichiometric experiments was conducted in an attempt to determine the identity of the catalytically active cobalt intermediate or catalyst resting state (Scheme 6). First, addition of one equiv. HBPin to a 1:1 mixture of [**Co**]-**1** and **1a** in benzene-d_6 resulted in the immediate formation of a dark solution (Scheme 6a). The ^1H NMR spectrum exhibited broad peaks corresponding to **1a** with no observable signals corresponding to [**Co**]-**1**. Vacuum transfer of the volatiles from this reaction and analysis by ^1H NMR spectroscopy established the generation of (trimethylsilyl)methylpinacolborane. Continued monitoring of the non-volatile components of the reaction revealed formation of small amounts of **2a**, implicating formation of a cobalt–hydride following activation of the corresponding alkyl with HBPin. In related cobalt-catalyzed asymmetric hydrogenation reactions of substituted indenes,[37] alkene insertion is slow and the resting state of the catalyst is the cobalt-hydride rather than a cobalt alkyl. In the present case, attempts to observe the cobalt–hydride by NMR spectroscopy have been unsuccessful. DFT calculations[38] (B3LYP) on the putative [(Terpy)CoH] (Terpy = 2,2':6',2"-terpyridine) were conducted for both the spin restricted (RKS, Co(I), S = 0) and spin unrestricted (UKS, Co(II), S = 0 or S = 1) electronic structures.[39] The UKS solution for the S = 1 case was the lowest in energy and is best described as a low spin Co(II) with a ferromagnetically coupled ligand centered radical. Attempts to calculate a high-spin solution converged to the low-spin description. Nearly isoenergetic is the broken symmetry (1,1) electronic structure, which is 1 kcal/mol higher in energy. The small relative difference between the energies of the singlet and triplet states may contribute to the difficulty in spectroscopic observation of [(Terpy)CoH]. However, additional experimental studies are required to distinguish these possibilities. The RKS solution was significantly higher in energy (+10 kcal/mol) than the spin unrestricted solutions consistent with ligand-centered radicals as important in potential catalytic intermediates.

The computational results support a similar electronic structure to that assigned to the cobalt alkyl derivatives, which are best described as a cobalt(II) center engaged in antiferromagnetic coupling with a terpyridine radical anion.[9] This electronic structure parallels that of bis(imino)pyridine cobalt alkyl complexes.[37] Detailed computational studies by Hopmann on the mechanism of bis(imino)pyridine cobalt-catalyzed hydrogenation support broken symmetry electronic configurations throughout the catalytic cycle[40] and it is likely that a similar feature is conserved here.

To further support the intermediacy of a cobalt-hydride, 0.1 atm of H_2 was added to a J-Young NMR tube containing a benzene-d_6 solution of an equimolar mixture of [**Co**]-**1** and **1a** (Scheme 6b). Again, a dark solution immediately formed and broad ^{1}H NMR signals were observed. Subsequent addition of HBPin by vacuum transfer resulted in formation of the boronate ester product **2a** after 1 hour as judged by ^{1}H NMR spectroscopy, providing addition evidence for a catalytically competent cobalt hydride that likely forms but is unobservable by ^{1}H NMR spectroscopy.

Scheme 6. Stoichiometric Studies Probing the Catalyst Resting State.



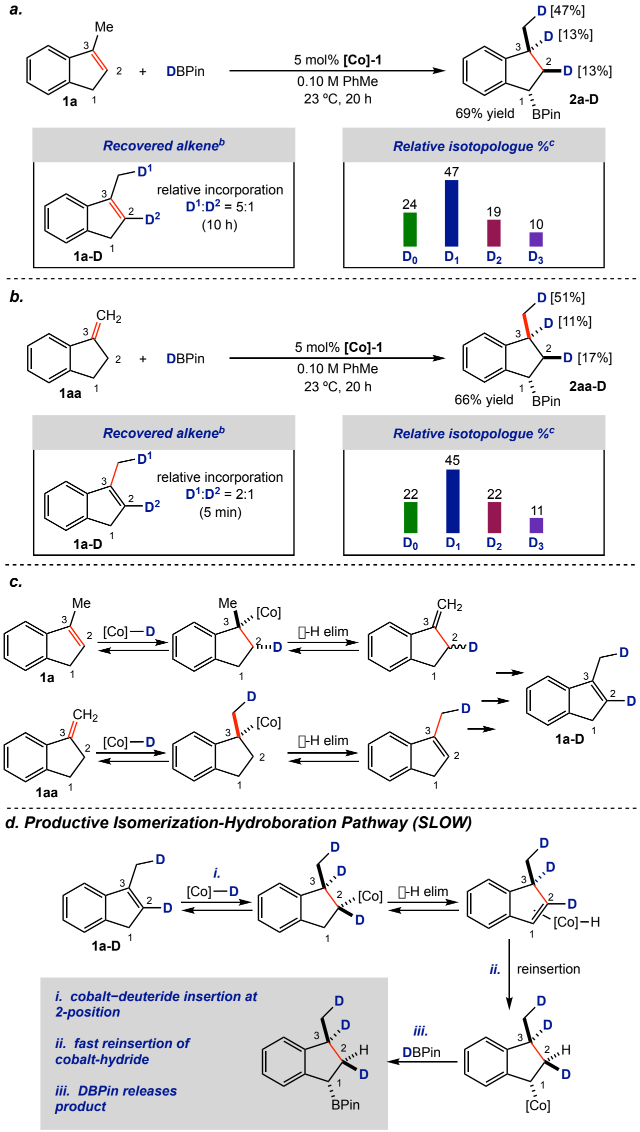
a. Single turnover experiment with [**Co**]-**1**, HBPin, and **1a**. b. Activation of precatalyst [**Co**]-**1** under H_2 (0.1 atm) followed by hydroboration of **1a**. c. Possible catalytic intermediates.

Kinetic analysis using the method of variable time normalization developed by Burés[41] was also conducted. Given the limited spectroscopic evidence for the cobalt intermediates formed under catalytic conditions, these experiments were used to provide information on the turnover-limiting step for the cobalt-catalyzed hydroboration-isomerization. Kinetic trials were conducted in a J-Young NMR tube and the reaction of **1b** with HBPin was monitored by ^{1}H NMR spectroscopy at 23 °C with [**Co**]-**1** as the precatalyst. Full experimental details are presented in the Supporting Information. These experiments established an overall second order rate law that is first order with respect to both alkene and [**Co**]-**1** but zero order with respect to HBPin. These findings are consistent with alkene insertion into a cobalt-hydride as turnover limiting step followed by fast C–B bond formation.[42] This is distinct from turnover-limiting C–B bond formation commonly observed for *terminal-selective* hydroboration with acyclic alkenes[8,12] and as calculated by Stradiotto, Turculet and Sydora.[13a] Instead, the kinetic analysis supports a regime that is similar to that proposed for cobalt-catalyzed hydrogenation.[37,40]

Deuterium Labeling Experiments

The regio- and diastereoselectivity of the cobalt-catalyzed hydroboration was investigated through a series of deuterium labeling experiments. Pinacolborane-d_1 (DBPin) was prepared by cobalt-mediated isotopic exchange of HBPin with D_2 gas (see SI for full details) and generated DBPin in 85% isotopic purity. Deuteroboration of **1a** was achieved under standard catalytic conditions and produced the deuterated boronate ester in 69% isolated yield (Scheme 7a). For clarity, the numbering convention of the indenyl ring systems presented below and used throughout is based on placement of the substituents in the final product, regardless of the position of the starting alkene. Analysis of **2a-D** by ^{1}H, ^{2}H, and ^{13}C NMR spectroscopies established incorporation of deuterium at the 2-, 3-, and methyl positions. The total deuterium incorporation in the product is consistent with the isotopic purity of DBPin. Importantly, selective deuterium incorporation *syn* to the methyl group at the diastereotopic 2-position was observed. No deuterium was detected at the 1-position. Analysis of the boronate ester product by GC-MS revealed the formation of multiple deuterated isotopologues, with the d_1 derivative identified as the major product. Analysis of recovered alkene after 10 h of reaction time was consistent with preferential deuterium incorporation at the methyl position, with a 5:1 relative deuterium labeling observed for the methyl and 2-position, respectively. Spectroscopic data and complete assignments are reported in the Supporting Information.

Scheme 7. Deuterioboration of 1a and Isotopic Incorporation.[a]

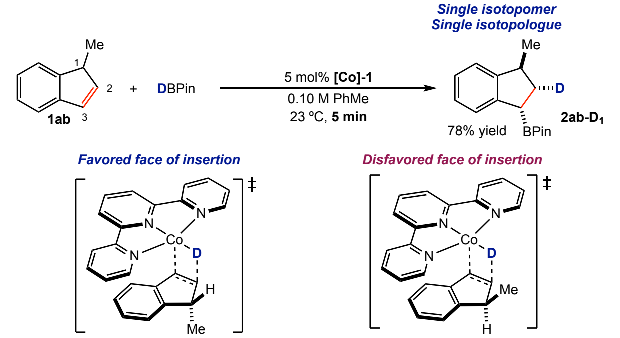


[a] Reactions conducted with 0.10 mmol of substrate in 1.0 mL toluene at 23 ºC for 20 h. Percentage yield of products are isolated yields. Percentage isotopic incorporation at the carbon positions determined by ^{2}H and quantitative ^{13}C{^{1}H} NMR spectroscopy included in brackets. [b] Recovered alkene from aliquot taken at partial conversion. Relative deuterium incorporation at methyl and 2-position determined by ^{2}H and quantitative ^{13}C{^{1}H} NMR spectroscopy. [c] Relative percentages of isotopologues determined by GC-MS. See SI for full details.

To rationalize the observation of the majority of the deuterium at the methyl position and to gain insight into the role of isomerization during catalysis, the deuteroboration procedure was conducted with 1-*exo*-methylene-indane, **1aa**. The boronate ester was obtained in 66% isolated yield with similar isotopic incorporation to that observed with **1a** (Scheme 7b). Analysis of an aliquot of the reaction mixture after 5 min revealed full conversion of **1aa** to **1a-D** with a 2:1 relative deuterium incorporation at the methyl position versus the 2-position of the alkene. These experiments support fast and reversible isomerization between **1a** and **1aa**, likely proceeding by preferential formation of a tertiary cobalt alkyl intermediate (Scheme 7c). Subsequent *β*-H elimination followed by alkene dissociation and reinsertion into a cobalt deuteride results in the observed deuterated alkene, **1a-D**. This isomerization pathway is ultimately unproductive for hydroboration and instead, insertion at the 2-position followed by *β*-hydride elimination from the 1-position is necessary before hydroboration to the final observed product (Scheme 7d).

To test this hypothesis and probe the pathway depicted in Scheme 7d, **1ab** was independently evaluated for hydroboration (Scheme 8). Full conversion of indene to the labeled boronate ester **2ab-D** (78% isolated yield) was observed after 5 min as a single isotopomer and isotopologue, as determined by ^{1}H, ^{2}H, quantitative ^{13}C{^{1}H} NMR spectroscopy and GC-MS analysis. This labeling study supports the straightforward *syn* 1,2-addition of the cobalt-deuteride to **1ab** with no evidence for isomerization prior to carbon-boron bond formation. Further, observed boron incorporation on the face *anti* to the methyl substituent is consistent with alkene coordination and subsequent insertion being selective for a single face of the alkene, accounting for the diastereotopically pure deuterium incorporation and *trans* selective arrangement of the final boronate ester product.

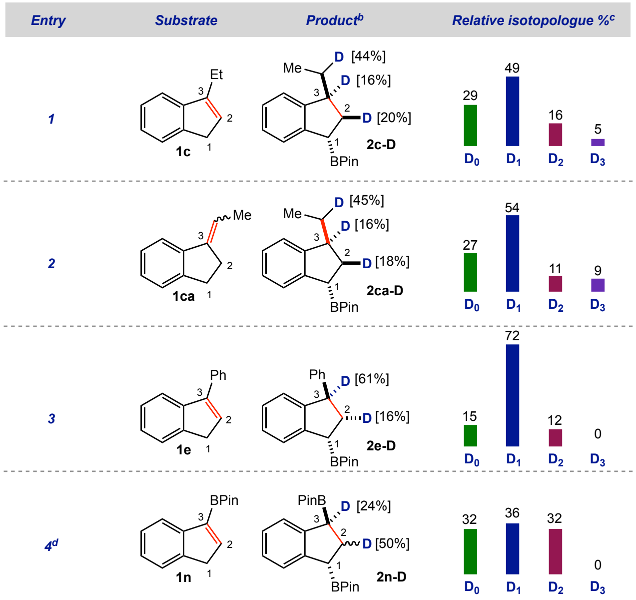
Scheme 8. Deuterioboration of 1ab.[a]



[a] Reactions conducted with 0.10 mmol of **1ab** in 1.0 mL toluene at 23 ºC. Percentage yield of product is isolated yield. Determination of isotopomer and isotopologue determined by ^{2}H and quantitative ^{13}C{^{1}H} NMR spectroscopy included in brackets. See Supporting Information for full spectroscopic data and complete assignments.

The cobalt-catalyzed deuteroboration-isomerization of additional alkenes was also investigated, the results of which are summarized in Scheme 9. Under standard catalytic conditions, reaction of **1c** or its *exo*-methylene isomer, **1ca**, with DBPin resulted in 78% and 92% isolated yield of the deuterated product, respectively. Analogous to the labeling observed with the methyl substituted indenes, deuterium was incorporated at the 2-, 3-, and methylene position of the ethyl group in the indane products **2c-D** and **2ca-D**. Again, selective deuterium incorporation at the 2-position *syn* to the ethyl substituent was observed, indicating a similar insertion pathway as depicted in Scheme 7c and d. Substrates **1e** and **1n**, selected specifically to confine chain-walking during catalysis to the indenyl ring, were also investigated through labeling experiments. In contrast to the alkyl substituted examples explored, analysis of the labeled boronate ester products **2e-D** by ^{1}H, ^{2}H, and ^{13}C NMR spectroscopies established incorporation of deuterium at the 3- and 2-positions in a *syn* relationship. This is consistent with the pathways outlined in Scheme 7. The cobalt-deuteride can insert into the 3- or 2-position. However, in the absence of an alkyl substituent, alkene isomerization and subsequent hydroboration can only occur in the latter case.

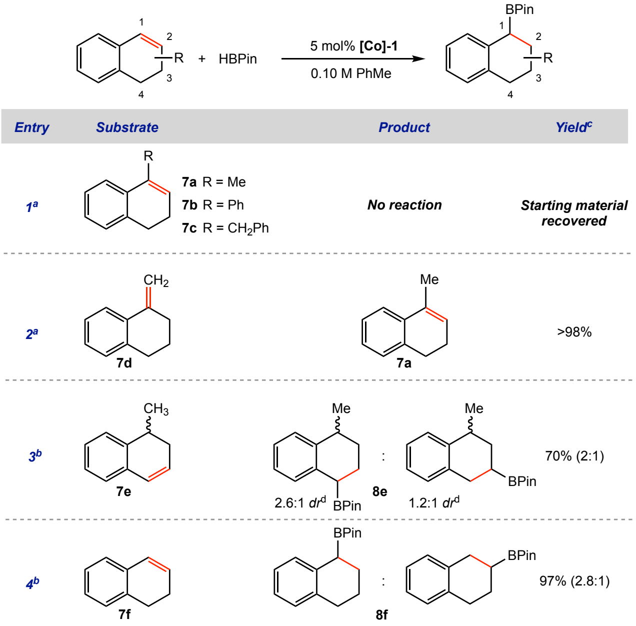
Scheme 9. Deuterium Labeling of a Selection of Substituted Indenes.[a]



[a] Reactions conducted with 0.10 mmol of indene, 0.105 mmol DBPin, and 5 mol% [Co] in 1.0 mL toluene at 23 °C for 20 h. [b] Percentage isotopic incorporation at the carbon position determined by ^{2}H and quantitative ^{13}C{^{1}H} NMR spectroscopies. [c] Relative percentages of isotopologues determined by GC-MS. [d] Reaction conducted with 0.10 mmol of indene, 0.105 mmol DBPin, and 5 mol% [Co] in 2.0 mL THF at 50 °C for 20 h.

Having established a model for isomerization of the 5-membered ring system, the cobalt-catalyzed hydroboration analogous 6-membered ring substrates (dialins) were explored (Scheme 10). A 0.10 M solution of 1-methyl-3,4-dihydronaphthalene (**7a**) in toluene was subjected to the standard catalytic conditions. The reaction was stirred at 23 °C and monitoring the reaction by ^{1}H NMR spectroscopy over 24 h showed no evidence for the hydroborated product. Other 1-substituted dialins explored, phenyl (**7b**) and benzyl (**7c**) substituted substrates, were similarly unreactive (entry 1). Increasing the temperature and reaction time to 80 °C and 72 h, respectively, produced no change in reactivity in all cases. The exocyclic-methylene substrate (**7d**) under standard catalytic conditions at 23 °C converted quantitatively to the endocyclic alkene (**7a**) in <5 min, as observed by ^{1}H NMR (entry 2). This is consistent with fast isomerization between exo- and endocyclic alkene isomers as observed with the 5-membered ring substrates. However, no evidence for further isomerization into the ring was observed for the 6-membered substrates. To rule out the possibility that 6-membered ring alkenes are inactive for the hydroboration catalyzed by [**Co**]-**1**, the hydroboration of isomer **7e** was carried out and proceeded to full conversion of the starting alkene in <5 min at 23 °C to furnish a 2:1 mixture of regio- and diastereoisomers (entry 3). Cooling the reaction to 0 °C did not change the regioselectivity, and the reaction still reached completion in <5 min. In contrast to the 5-membered ring analog, the methyl substituent for the 6-membered ring alkene had little to no influence on the diastereoselectivity of the reaction possibly due to smaller energy differences between different facially bound cobalt hydride(alkene) intermediates. In the absence of the methyl group, hydroboration of **7f** resulted in a slight increase in regioselectivity (2.8:1, entry 4). The marked difference in reactivity between the 5- and 6-membered ring substrates may be a consequence of the lower degree of ring strain in the 6-membered ring systems.[43] Ring strain release may drive alkene insertion for trisubstituted indenes, whereas for the dialins, insertion is not as favorable. This may explain why reactivity is only observed for the disubstituted dialins **7e** and **7f**.

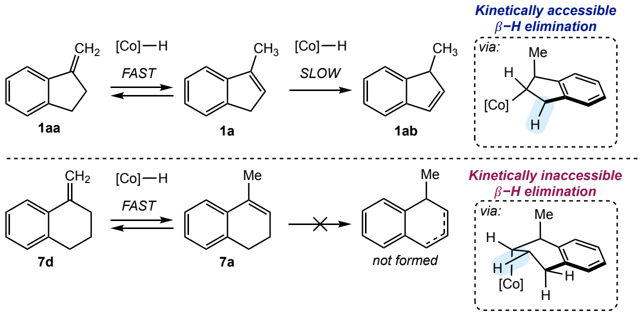
Scheme 10. Effect of Ring Substitution on the Cobalt-Catalyzed Hydroboration of Dialins.



[a] Reaction conducted with 0.10 mmol of dialin, 0.105 mmol HBPin, and 5 mol% [Co] in 1.0 mL toluene at 23 °C for 24 h. Heating at 80 °C for an additional 48 h produced no observable hydroborated product. [b] Reaction conducted with 0.50 mmol of dialin, 0.505 mmol HBPin, and 1 mol% [Co] in 1.0 mL toluene at 0 °C for 5 min. [c] Percentage yield are isolated yields. [d] Diastereomeric ratio as determined by GC and quantitative ^{13}C{^{1}H} NMR analysis. See SI for details.

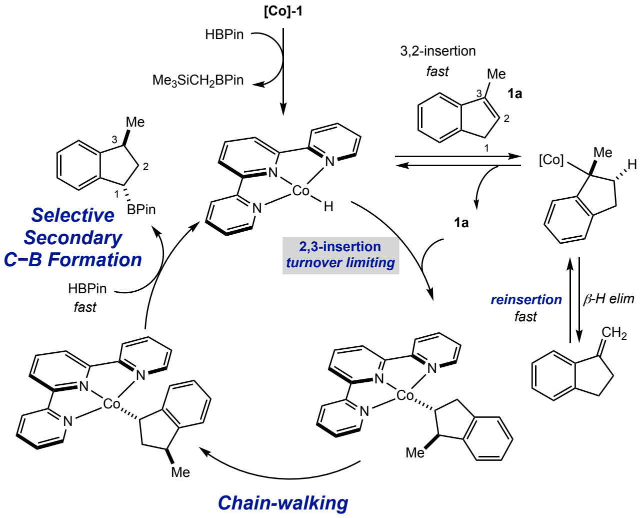
Scheme 11 presents further insights for the differing reactivity between the 5- and 6-membered ring substrates. In both cases, isomerization from the exo- to the endocyclic isomers is facile under standard conditions. With the indene, an additional isomerization event is accessible, albeit slow, to furnish **1ab** (Scheme 11, top). The accessibility of this pathway can be explained by the relative planarity of the indenyl substrate, placing the ring *β*-hydrogens in the necessary *syn*-periplanar arrangement required for transfer to the cobalt center. In contrast, the 6-membered substrate only has one kinetically accessible site for *β*-hydrogen elimination from the methyl group. The necessary conformational inversion required to access the ring methylene hydrogens may be kinetically disfavored. Additionally, performing a mixing experiment in which a 1:1 mixture of **1a** and **7a** were subjected to the standard hydroboration conditions in the presence of 5 mol% of [**Co**]-**1** showed full conversion of **1a** to **2a** in 20 h and no conversion of **7a**, indicating that while the 6-membered ring is not suitable for isomerization-hydroboration, it does not inhibit the reaction overall.

Scheme 11. Isomerization of 5- versus 6-Membered Rings.



The stoichiometric experiments, kinetic analysis, and isotopic labeling studies support the mechanistic picture for the cobalt-catalyzed diastereoselective hydroboration of substituted indenes presented in Scheme 12. Although the reactivity of the proposed cobalt intermediates has hindered their spectroscopic observation, insights have been gained on alkene insertion preferences and competitive isomerization pathways that are key to rationalizing the unique regioselectivity of this transformation. Alkene 2,3-insertion is the turnover-limiting step. For alkyl-substituted indenes, competitive 3,2-insertion is fast and reversible and ultimately unproductive for C–B bond formation. This presents a distinct mechanistic picture to that proposed for anti-Markovnikov selective hydroboration catalysts in which selectivity is controlled by favorable boron transfer to a terminal metal alkyl intermediate. The relatively open coordination environment imparted to the cobalt center by the terpyridine ligand may lower the barrier for secondary C–B bond formation, resulting in the observed regioselectivity.

Scheme 12. Proposed catalytic cycle for the diastereoselective isomerization-hydroboration of 1a with [Co]-1.



CONCLUDING REMARKS

The regio- and diastereoselective remote hydroboration of sterically hindered 2- and 3-substittued indenes by a terpyridine cobalt complex has been developed. This method provides remarkably selective access to *trans*-1,2- and 1,3-disubstituted indanyl boronate esters, the utility of which was demonstrated through a host of representative C-C, and C-O bond-forming reactions. Deuterium labeling studies allowed for rationalization of the observed regioselectivity of the isomerization-hydroboration and provide insight on how alkene insertion preferences dictate chain walking for remote functionalization in ring systems and extend the synthetic utility of the transformation.

ASSOCIATED CONTENT

Supporting Information

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

Crystallographic data for **2e** (CIF).
Additional experimental procedures, including general considerations, additional experimental details, full characterization data and complete NMR spectroscopic data (PDF).

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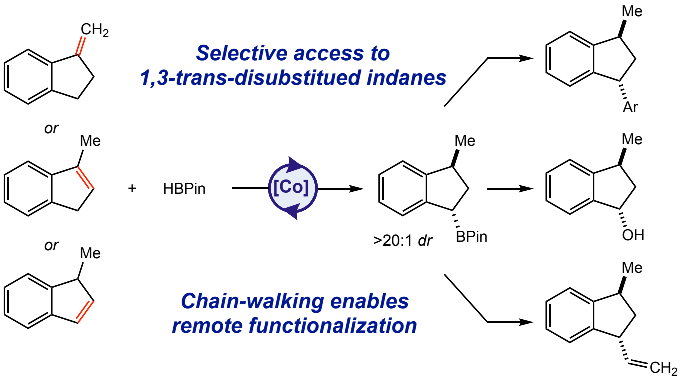
TOC Graphic


CH2
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