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Cobalt Catalyzed *Z*-Selective Hydroboration of Terminal Alkynes and Elucidation of the Origin of Selectivity

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Supporting Information

ABSTRACT: A bis(imino)pyridine cobalt-catalyzed hydroboration of terminal alkynes with HBPin (Pin = pinacolate) with high yield and (*Z*)-selectivity for synthetically valuable vinylboronate esters is described. Deuterium labeling studies, stoichiometric experiments, and isolation of catalytically relevant intermediates support a mechanism involving selective insertion of an alkynylboronate ester into a Co−H bond, a pathway distinct from known precious metal catalysts where metal vinylidene intermediates have been proposed to account for the observed (*Z*) selectivity. The identity of the imine substituents dictates the relative rates of activation of the cobalt precatalyst with HBPin or the terminal alkyne and, as a consequence, is responsible for the stereochemical outcome of the catalytic reaction.

Vinylboronate esters are versatile reagents in organic synthesis owing to their use as nucleophilic partners in C−C bond forming reactions.[1,2] Hydroboration of terminal alkynes is a straightforward and atom economical method for the preparation of vinylboronate esters and commonly yields products with (*E*) stereochemistry resulting from anti-Markovnikov, *syn* addition of the B−H group to the C≡C bond.[3,4] Methods for the synthesis of the corresponding (*Z*) isomers are more challenging and typically require multistep routes that are potentially complicated by competing isomerization to the more thermodynamically favored (*E*) isomer.[5,6a]

Examples of precious metal-catalyzed alkyne hydroboration to yield (*Z*)-vinylboronate esters are rare.[6b,7−9] Miyaura and coworkers reported that rhodium and iridium precursors in combination with P^iPr_3 and PCy_3 are selective for (*Z*)-vinylboronate esters in the presence of NEt_3.[7] The use of HBCat (Cat = catecholate) was required to achieve optimal selectivities, as direct hydroboration with HBPin resulted in lower (*Z*):(*E*) ratios. Ruthenium pincer catalysts have recently been reported by Leitner et al. that promote the (*Z*)-selective hydroboration of terminal alkynes at −15 °C.[8] Fürstner et al. have also described a rare example of (*Z*)-selective hydroboration of internal alkynes using $[(\eta^5\text{-}C_5Me_5)Ru(CH_3CN)_3]\text{-}PF_6$.[9] In each of these examples, deuterium labeling experiments supported formation of intermediates with metal−carbon double bonds that are responsible for the observed selectivity.

There has recently been intense interest in developing base metal catalysts for alkene and diene hydroboration.[10] Cobalt catalysts bearing redox-active bis(imino)pyridine[11] and related chelates[12] have proven to be effective for alkene isomerization−hydroboration where functionalization occurs selectively at remote, terminal positions. Modification of the ligand architecture to 2,2′-6′,2′-terpyridine or aryl-substituted α-diimines produced catalysts with unprecedented activity and selectivity for hindered tri- and tetrasubstituted alkenes.[13] Application of C_1-symmetric tridentate nitrogen-based ligands, a strategy pioneered for asymmetric hydrogenation,[14] has been applied to the enantioselective hydroboration of 1,1-disubstituted alkenes.[15] By contrast, base metal catalyzed hydroboration of alkynes has been much less thoroughly explored and is limited to a select few iron examples.[10b,d] Here we describe high activity bis(imino)pyridine cobalt catalysts for the selective anti-Markovnikov hydroboration of terminal alkynes. Modification of the ligand substituents or the conditions of the catalytic reactions allow manipulation of the stereochemical outcome and a straightforward method for the preparation of (*Z*)-vinylboronate esters. Mechanistic studies are consistent with (*Z*)-stereoselectivity arising from *syn*-hydrometalation of alkynylboronates arising from cobalt acetylides, a pathway distinct from previous mechanistic proposals invoking vinylidene compounds.

Initial catalytic experiments were conducted with (^{iPr}PDI)-$CoCH_3$ (**1**) given the demonstrated utility of this compound in alkene hydrogenation,[16] hydroboration,[11] and dehydrogenative silylation.[17] Stirring a 0.5 M THF solution containing a 1.2:1 mixture of 1-octyne and HBPin in the presence of 3 mol % of (^{iPr}PDI)$CoCH_3$ at 23 °C for 6 h produced >98% conversion (GC-MS) to the (*E*)-vinylboronate ester product arising from anti-Markovnikov addition of the borane. Repeating the catalytic hydroboration reaction with **2**, the bis(imino)pyridine cobalt methyl complex where the 2,6-diisopropyl substituents have been replaced with cyclohexyl groups,[18] yielded the (*Z*)-vinylboronate ester in 76% isolated yield with 92:8 stereoselectivity (Scheme 1).

The highest (*Z*) selectivity for 1-octyne was observed when a slight excess (1.2 equiv) of the alkyne relative to HBPin was used. In the absence of excess alkyne, postcatalytic isomerization of the (*Z*) product to the thermodynamically preferred (*E*) isomer becomes competitive, likely promoted by a residual cobalt hydride (see Figures S4−S5). Figure 1 reports the results of hydroboration of a family of terminal alkynes with HBPin at 23 °C using these optimized conditions. High yield and (*Z*) selectivity were observed for protected propargyl ethers, propargyl phthalamide, and aryl- and alkyl-substituted alkynes.

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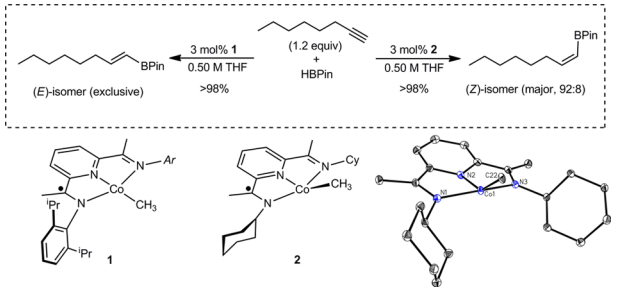
Scheme 1. Hydroboration of 1-Octyne with 1 and 2 along with Solid State Structure of 2 at 30% Probability Ellipsoids



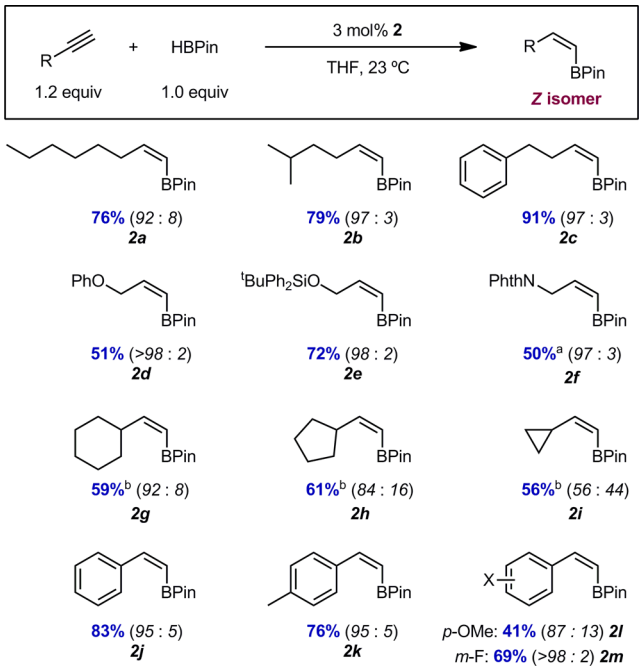
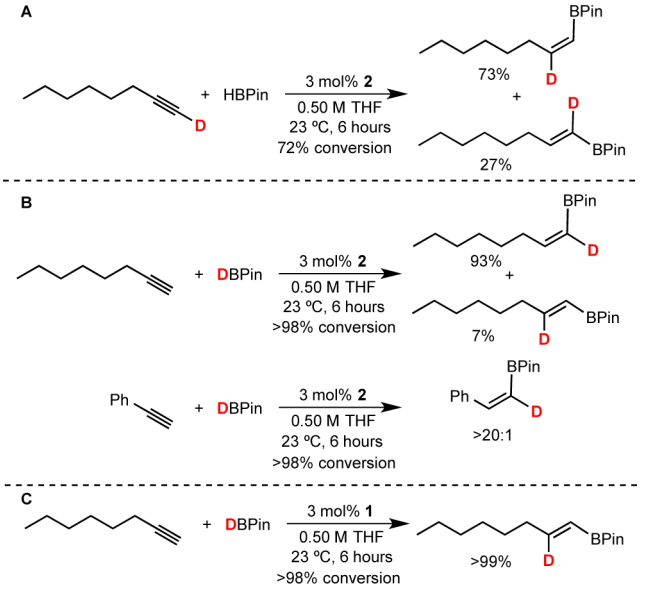


Figure 1. Hydroboration of terminal alkynes with (^{Cy}APDI)CoCH$_3$. Reaction conditions: 3 mol % (^{Cy}APDI)CoCH$_3$, 23 °C, 0.50 M in THF, 6 h. Reported numbers are isolated yields obtained after column chromatography. Numbers in parentheses are Z/E selectivities determined by NMR spectroscopy. [a] NMR yield. [b] Reaction run in neat substrate for 24 h.

The origin of erosion of selectivity observed with cyclopropylacetylene is not currently understood. More electron-rich alkynes with secondary alkyl substitution underwent slower hydroboration, requiring neat conditions and 24 h of reaction time. Aryl substituted alkynes with electron-donating (*p*-OMe) and electron-withdrawing (*m*-F) groups maintained high (Z) selectivity. The use of deactivated silica was required for product isolation and to prevent isomerization.

Deuterium labeling experiments were conducted to gain insight into the origin of (Z)-selectivity (Scheme 2). Hydroboration of 1-d_1-1-octyne with HBPin under standard conditions furnished a 73:27 mixture of (Z)- and (E)-vinylboronate esters. The (Z) product contained deuterium exclusively at the 2-position (^{2}H, ^{13}C NMR) while the (E) isomer had the isotopic label exclusively at the terminal position geminal to the boron substituent (Scheme 2A). Introduction of the isotopic label decreased the (Z):(E) ratio, as well as the rate of the reaction (~72% vs >98% conversion with the natural abundance alkyne).[19] The converse labeling experiments for

Scheme 2. Deuterium Labeling Experiments with 2 and 1

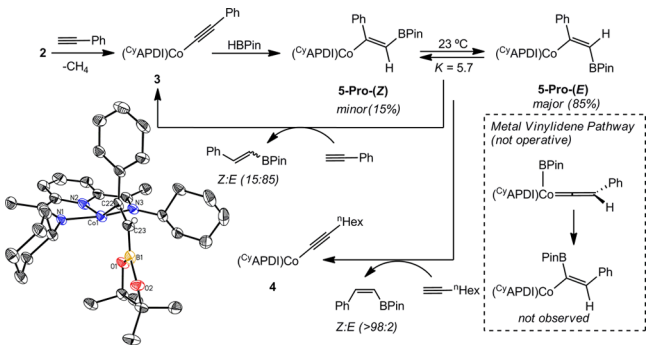


the catalytic deuterioboration of 1-octyne and phenylacetylene produced the opposite result; using DBPin placed the deuterium geminal to the [BPin] group in the (Z)-vinylboronate esters while the (E) isomer (for 1-octyne) contained the isotopic label exclusively at the 2-position (Scheme 2B).

Isotopic purity >98% was observed in all cases in the position of deuteration. With **1**, the same deuterium labeling experiment exclusively furnished the (E) isomer where the deuterium is at the 2-position (Scheme 2C). The combination of deuterium labeling experiments coupled with the observation of a rapid cobalt hydride formation upon treatment of (^{iPr}PDI)CoCH$_3$ with HBPin[11] supports a conventional mechanism for (E) selectivity involving terminal alkyne insertion to a metal hydride and product release from interaction of an intermediate cobalt-vinyl compound with HBPin (see Figure S14).[4f] Importantly, reaction of **1** with terminal alkynes was sluggish and produced intractable mixtures of products over the course of hours at 23 °C.

For precious metal catalysts, the generally accepted mechanism for (Z)-selective alkyne hydroboration invokes vinylidene intermediates and metal-boron bond formation (Scheme 3). Stoichiometric experiments with **2** eliminate this possibility. Addition of 1 equiv of either 1-octyne or

Scheme 3. Stoichiometric Experiments Exploring the Activation Modes of 2 in Catalytic (Z)-Selective Alkyne Hydroboration and Solid State Structure of 5-Pro-(E)



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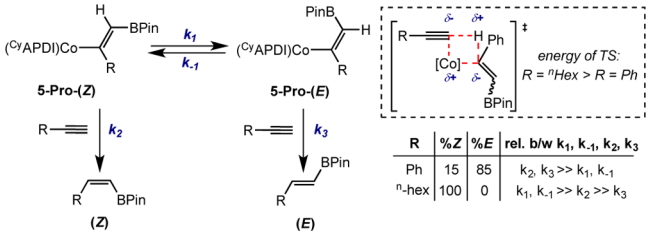
phenylacetylene to **2** resulted in immediate liberation of 1 equiv of methane along with the diamagnetic C_{2v} symmetric bis(imino)pyridine cobalt acetylide complexes, (^{Cy}APDI)-CoC≡CR (R = Ph, **3**; ^{n}Hex, **4**). Conducting the analogous experiment whereby HBPin was added to a benzene-d_6 solution of **2** resulted in generation of CH_3BPin and an unidentified paramagnetic cobalt compound. Importantly, the observation of CH_3BPin establishes that **2**, in analogy to **1**, forms a cobalt hydride upon treatment with HBPin and it is this compound that converts to an unidentified product. We note that hydrogenation of **2** in the absence of boron also yielded the same low symmetry cobalt compound, definitively eliminating a boron-containing product.

To assess the catalytic competency of the bis(imino)pyridine cobalt acetylides, a benzene-d_6 solution of **3** was treated with 1 equiv of HBPin. An 85:15 mixture of two isomeric cobalt vinyl complexes (**5**) was observed immediately upon addition of HBPin. A combination of ^{1}H and ^{13}C NMR spectroscopies and reactivity studies established the same regiochemistry in the isomers of **5**; the carbon bound to the cobalt is phenyl-substituted while the distal carbon is bound to the [BPin] group. For example, treatment of the isomers of **5** with excess DCl (1.0 M in Et_2O) yielded a 75:25 mixture of (*E*)- and (*Z*)-vinylboronate esters where deuterium was located exclusively in the position geminal to the phenyl group establishing only this carbon was bound to cobalt.[20] The difference in isomers of **5** arises from the stereochemistry about the C=C bond where the major isomer is designated **5-Pro-(*E*)** while the minor is **5-Pro-(*Z*)**. Definitive assignment of the stereochemistry was accomplished by measuring coupling constants from an HMBC NMR experiment (Figure S8). The nomenclature refers to the stereochemistry of the cobalt vinyl complex that would give rise to the corresponding stereochemistry of the vinylboronate ester product upon protonation. Formation of bis(imino)pyridine cobalt vinyl compounds with the [BPin] group located exclusively in the *β*-position definitively eliminates the traditionally proposed vinylidene pathway as responsible for formation of the (*Z*)-vinylboronate ester. Formation of **5** upon addition of a mixture of phenylacetylene and HBPin to **2** demonstrates that reactions of **2** with terminal alkynes are more facile than with HBPin (Scheme 3).

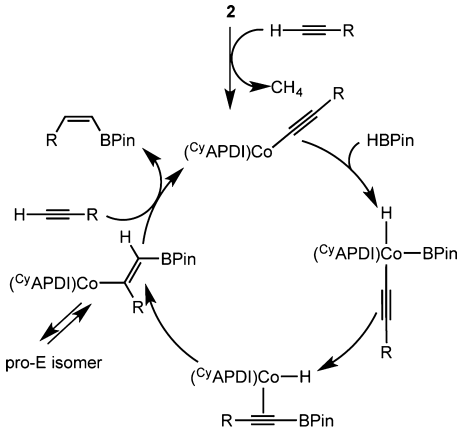
Recrystallization of the mixture of **5-Pro-(*E*)**- and **5-Pro-(*Z*)** from pentane at −35 °C produced crystals suitable for X-ray diffraction identified as **5-Pro-(*E*)** (Scheme 3). The cobalt−carbon bond is lifted out of the idealized metal-chelate plane with the phenyl substituent directed away from the cyclohexyl imine substituents. Short Co−O contacts of 2.430(9), 2.478(6), and 2.928(9) Å were observed between the metal and the BPin ligand in the three independent molecules in the asymmetric unit and, along with the *trans*-disposition of the large alkene substituents, are likely responsible for the thermodynamic preference for this isomer. Redissolving the crystals in benzene-d_6 and analysis by NMR spectroscopy revealed an 85:15 mixture of isomers, suggesting either fortuitous crystal selection or rapid equilibrium of the isomers at 23 °C.

Experimental support for isomer interconversion was obtained by treatment of the 85:15 mixture of the isomers of **5** with 1 equiv of 1-octyne (Scheme 3). Only (*Z*)-vinylboronate ester was observed with the cobalt quantitatively converted to **4**. Repeating the experiment with 0.5 equiv of PhC≡CH, the isomers of **5** yielded an 85:15 mixture of (*E*)- and (*Z*)-vinylboronate esters while the remaining vinyl compound

Scheme 4. Interconversion of 5-Pro-(*Z*) and 5-Pro-(*E*) and Product Distribution upon Treatment with Terminal of Alkynes



Scheme 5. Proposed Mechanism for the Formation of (*Z*)-Vinylboronate Esters with 2



maintained the 85:15 isomeric composition. The more acidic PhC≡CH, like DCl, promotes fast protonation on the vinyl ligand relative to isomerization (Scheme 4). With ^{n}HexC≡CH, protonolysis is slower allowing equilibration of the pro-(*E*) and pro-(*Z*) vinyl compounds likely due to a higher energy transition state. Under catalytic conditions, the large excess of alkyne likely facilitates rapid product release such that formation of **5-Pro-(*E*)** does not occur during turnover. It is likely that isomerization of **5** occurs through rotation of the single bond in the zwitterionic carbene intermediate, although additional support is required to verify this assertion.[21] Crossover experiments with **5** and free *p*-TolylC≡CBPin establish no exchange.

A mechanism for the cobalt catalyzed (*Z*)-selective hydroboration of terminal alkynes is presented in Scheme 5. Following formation of the cobalt acetylide, oxidative addition of HBPin followed by reductive elimination of the alkynylboronate and *syn*-hydrometalation generates the pro-(*Z*) cobalt vinyl intermediate. Reaction with the terminal alkyne, likely the turnover-limiting step, liberates the observed (*Z*)-vinylboronate ester. In the absence of the alkyne, isomerization of the pro-(*Z*) cobalt vinyl complex to the thermodynamically preferred pro-(*E*) isomer occurs. The mechanism in Scheme 5 accounts for the optimized catalytic conditions and observed ligand effects. With **2**, reaction with alkyne to form the metal acetylide is faster than hydride formation upon addition of HBPin. With **1**, the opposite trend is observed where HBPin is more reactive, the cobalt hydride is kinetically preferred, and (*E*)-selective catalysis results. The slight excess of alkyne (1.2:1) used for optimal (*Z*) selectivity suppresses Co−H formation at the end of the catalytic reaction, avoiding postcatalytic product isomerization. Allowing the

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reaction of phenylacetylene and 1.2 equiv DBPin to stand for 30 min after completion of the reaction yielded the (*E*) isomer with deuterium in the position geminal to the [BPin] substituent.

An additional stoichiometric experiment was performed to support the mechanism in Scheme 5. Addition of PhC≡CBPin to **2** in the presence of HBPin at 23 °C furnished CH_3BPin and an 85:15 mixture of **5-Pro-(*E*)** and **5-Pro-(*Z*)**, clearly supporting the competency of alkynylboronates for regioselective insertion into Co−H bonds as well as rapid isomerization between cobalt vinyl compounds in the absence of excess alkyne.

In summary, a cobalt catalyzed method for the synthesis of (*Z*)-vinylboronate esters by regio- and strereoselective hydroboration of terminal alkynes has been developed. Isotopic labeling and stoichiometric studies eliminate the possibility of metal vinylidene intermediates and support a previously unconsidered pathway for (*Z*)-selective hydrometalation reactions.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental details, representative NMR spectra and crystallographic data for **2** and **5-(Pro)-E** in cif format. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b00936.

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Notes

The authors declare no competing financial interest.

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(19) The lower *Z*/*E* selectivity results from slow catalyst initiation to form compound **3** and generates a small amount of a Co−H leading to the (*E*) isomer. The position of the deuterium in the (*E*)-vinylboronate ester product implies that the (*E*) isomer resulted from a Co−H rather than the isomerization of **5-Pro-(Z)** to **5-Pro-(E)**.

(20) The 85:15 ratio was determined from the ^{1}H NMR spectrum of the benzene-d_6 solution of the isomers of **5**. Upon quenching with DCl, the (*Z*):(*E*) ratio of the resulting organic product was measured by GC (the small GC response factor variations in the (*Z*) and (*E*) vinylboronate esters were not corrected) to be 80:20. Analyzing the organic product by quantitative ^{13}C NMR spectroscopy revealed a 75:25 ratio. We believe that this slight discrepancy in the isomeric ratio is not due to isomerization but rather due to the use of different analytical methods to determine the ratio.

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