

Insights into a Chemoselective Cobalt Catalyst for the Hydroboration of Alkenes and Nitriles

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Supporting Information

ABSTRACT: A chemoselective hydroboration protocol with terminal alkene substrates is reported using an electron-rich, low-valent cobalt pincer compound. The process is catalytic and leads to exclusive formation of anti-Markovnikov products, tolerating amino groups, esters, epoxides, ketones, and other functionalities. The protocol was successfully extended toward the hydroboration of nitriles, generating the corresponding amines in moderate to good yields. Labeling studies with deuterated pinacolborane gave insights into the mechanism, establishing the intermediacy of a cobalt hydride, as well as an



insertion, β -hydride elimination, and alkene isomerization pathway. These insights provide a rationale for the observed regioselectivity and allow us to propose a catalytic mechanism.

KEYWORDS: hydroboration, alkene, nitrile, cobalt, chemoselective, catalysis

C atalytic hydroboration is a powerful synthetic tool for the reduction and functionalization of unsaturated bonds, providing products that can serve as valuable synthons in a variety of chemical transformations. The widely employed Suzuki–Miyaura coupling, for example, effectively uses organoboronates as nucleophiles for the construction of C–C bonds, cementing its status as one of the most versatile and employed reactions in the pharmaceutical industry.^{1,2} Accordingly, several catalysts have been reported for the preparation of organoboron reagents, traditionally via the hydroboration of alkenes or the borylation of olefinic or alkane substrates.^{3–5} Catalysts have typically featured noble-metal centers, primarily Rh and Ir.⁵ However, the high cost, low abundance, and environmental impacts associated with the use of such metals has motivated the development of first-row transition-metal congeners.^{6,7}

Recent reports from the laboratories of Ritter, Chirik, Huang, and others have provided new Fe, Co, and Cu catalysts for the hydroboration of alkynes and terminal alkenes.⁸⁻¹⁸ Such systems boast operational simplicity and provide powerful platforms for the reduction of unsaturated bonds. Huang and co-workers reported a potent Co(PNN) (PNN = 6-[(dialkylphosphino)methyl]-2,2'-bipyridine) hydroboration catalyst that tolerates a variety of functional groups, including ketones, allyl ethers, tertiary amines, and substituted amides. Similarly, Chirik reported a complement of simple cobalt catalyst precursors for the hydroboration of simple alkenes, including a $(PPh_3)_3CoH(N_2)$ system that is competent toward the catalytic isomerization-hydroboration of alkenes.²⁰ Recent reports from Thomas,²¹ Lu,²² and Huang¹⁷ have paralleled such developments with Fe-based hydroboration catalysts, conferring a notable degree of functional group tolerance or

enantioselectivity where applicable, as in the case of the chiral iminopyridine oxazoline iron complexes reported by Lu.²² Although there has been significant research in this area, we sought to remove the activators, such as Grignard reagents and NaBHEt₃, from the system and extend the functional group tolerance to ketone-bearing alkene substrates which has not been widely reported with earth-abundant metal catalysts.

Similar functional group constraints have also been noted in the copper-catalyzed systems, several of which feature the use of activated or simple alkene and alkyne substrates. Recent reports from the Ito group^{12,23} and Takaki group²⁴ have obviated some of these limitations, providing copper-based systems that can be modulated to provide interesting Markovnikov regioselectivity or that otherwise confer an improved functional group tolerance.

We recently reported the hydrosilylation of terminal alkene substrates with a Co^I catalyst bearing an electron-rich CCC pincer ligand.²⁵ Mechanistic studies suggested that the catalyst engages in oxidative addition of the Si–H bond to generate a catalytically active Co^{III} hydrido silyl complex and then proceeds along a Chalk–Harrod reaction profile reminiscent of noble-metal catalysts to afford the targeted alkylsilane product. This reactivity, as well as the impressive chemoselectivity of the (^{DIPP}CCC)CoN₂ (1; ^{DIPP}CCC = bis(2,6-diisopropylphenylbenzimidazol-2-ylidene)phenyl) catalyst, prompted us to explore the hydroboration of alkenes bearing ketones and other traditionally challenging oxygen-containing

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functional groups, particularly given the need for earthabundant complexes tolerant of such functionalities. Pursuant to this end, we investigated the hydroboration of 5-hexen-2-one as a model substrate. Gratifyingly, hydroboration with pinacolborane proceeded with anti-Markovnikov selectivity at the alkene at room temperature, with no evidence of ketone hydroboration. The use of an air-stable Co^{III} analogue, (^{DIPP}CCC)CoCl₂py,²⁶ was also successful with the addition of NaHBEt₃ or TMSCH₂Li activators, albeit in reduced yield. A recent report by Thomas and co-workers,²⁷ published during the preparation of this paper, led us to also investigate the use of sodium tert-butoxide as an activator. Although the target product was obtained, the presence of a significant impurity precluded the use of this method with our catalytic system. Finally, optimization of catalytic loading led us to select 2.5 mol % of Co¹ catalyst for catalytic reactivity (Table S1 in the Supporting Information).

Following the determination of catalytic conditions, we sought to investigate the substrate scope of the cobalt catalyst (Table 1). The hydroboration of 1-octene and styrene proceeded in excellent yield, furnishing the anti-Markovnikov product in both cases with no evidence of dehydrogenative borylation. The hydroboration of 4-vinylcylohexene, a substrate bearing both an internal alkene and a terminal alkene, proceeded selectively at the terminal alkene position, with complete retention of the internal olefin (2d). More sterically hindered substrates were not amenable to the hydroboration protocol. The hydroboration of limonene, a gem-disubstituted alkene, did not result in any detectable conversion, while the hydroboration of cyclohexene resulted in only trace product formation after 17 h, highlighting the steric influence on the selectivity observed. This sensitivity to steric effects was previously observed in the hydrosilylation protocol established with this Co^I system and has been observed with the PNN pincer Co system used by Huang.¹

Informed by the steric constraints of the catalytic system and given the difficulties associated with 1,2-selective additions to conjugated dienes,²⁸ we turned to the hydroboration of isoprene (**2e**), a conjugated diene bearing both a *gem*-disubstituted alkene and a monosubstituted alkene. Addition was 1,2-selective across the less-substituted olefinic bond, as previously observed in our hydrosilylation studies. Such examples of 1,2-hydroboration with cobalt or iron catalysts are uncommon.²⁹ Although Ritter reported the 1,4-hydroboration of conjugated dienes with an iron iminopyridine catalyst,⁸ the analogous 1,2-addition has rarely been realized with iron or cobalt catalysts, given the thermodynamic favorability of π -allyl intermediates.²⁸ Indeed, with few exceptions, general reports of 1,2-addition with conjugated dienes are infrequent.

Extension of the catalytic protocol to alkenes bearing oxygencontaining functional groups proved to be similarly successful. Allyl ethers, esters, and epoxides were found to be compatible with the catalyst, with no evidence of competing dehydrogenative borylation pathways. Addition across carbonyl moieties, with substrates such as 5-hexen-2-one (2a) and 2-allylcyclohexenone (2f), was not detected under these conditions.

Encouraged by the tolerance of oxygen-containing functional groups, we turned our attention to the hydroboration of amines. The hydroboration of 9-vinylcarbazole with pinacolborane proceeded in 80% yield, as assayed by ¹H NMR spectroscopy, after 1 h. Interestingly, *N*-allylaniline, a secondary amine, was also tolerated under the hydroboration protocol



 Table 1. Substrate Scope for the Hydroboration of Alkenes and Nitriles

with no concomitant formation of the N-borylated amine. To the best of our knowledge, the catalytic compatibility of unprotected amines has only been reported for a single iron hydroboration catalyst,²¹ while the use of such substrates has not been previously realized with a cobalt system. Interestingly, the corresponding reaction with 4-aminostyrene, a primary amine, did not result in the formation of the target organoboronate ester, suggesting that the observed chemoselectivity may be sterically modulated.

Seeking to further probe the chemoselectivity of the $(^{\text{DIPP}}\text{CCC})\text{CoN}_2$ system, the hydroboration of 4-pentenenitrile was attempted. In contrast to the exclusive alkene selectivity observed in the hydrosilylation protocol for this catalyst,²⁵ two organoboronate products corresponding to single and double additions of borane to the substrate, respectively, were detected by GC-MS. Intrigued by this reactivity, we sought to investigate the viability of nitrile reduction. Although such reductions can be accomplished stoichiometrically, established protocols typically require the use of LiAlH₄ and NaBH₄ reagents, which generate large quantities of inorganic side products.^{30,31}

The development of catalytic reduction strategies with hydrogen is also restricted, often requiring the use of poorly selective heterogeneous catalysts or the use of highly energetic conditions.³² Current strategies, developed by Beller,^{33,34} Milstein,^{35,36} Sabo-Etienne,³⁷ and others promise to mitigate some of these challenges but reports are otherwise limited.³² Alternate strategies featuring the use of silanes or boranes for the reduction of nitriles have gained traction, however. Recent reports by Szymcak³⁸ and Hill³⁹ have demonstrated homogeneous reductions of nitriles using boranes. However, such hydroborations with first-row transition metals remain rare. As such, a cobalt catalyst is an attractive option for the reduction of nitriles, particularly since current strategies are mostly limited to the use of noble-metal catalysts.³²

Initial investigations into the reduction of nitriles (Table 1) made use of simple aliphatic nitriles (3a,b). Heating a mixture of 1, pinacolborane, and butyronitrile at 70 °C in benzene afforded the desired bis(borylated) amine, as detected by GC-MS. Subsequent workup of the reaction mixture led to the isolation of the corresponding ammonium salt in good yields (3a). The reduction of acetonitrile was similarly successful, furnishing ethylammonium chloride in excellent yield following workup. To our delight, extension of the protocol to aromatic nitriles (3c-e) also furnished the corresponding ammonium salts upon isolation, demonstrating a tolerance for thiophene moieties (3d), as well as a fluorinated arene (3e).

Interested in obtaining further insights into hydroboration with the $(^{DIPP}CCC)Co^{I}$ platform, we turned to labeling experiments with deuterated pinacolborane. Upon reacting styrene with 1 equiv of deuterated pinacolborane, we observed deuterium incorporation into the targeted linear alkylboronate ester product at both the terminal and benzylic positions in approximately equal proportion (Figure 1). Moreover,



Figure 1. ²H NMR spectrum of the hydroboration of styrene.

deuterium resonances corresponding to incorporation at vinylic positions of the styrene starting material were also detected. These observations are consistent with the intermediacy of a cobalt hydride over the course of catalysis, as well as β -hydride elimination processes to regenerate alkene substrate. The absence of a deuterium resonance at 6.57 ppm, corresponding to the vinylic proton at the benzylic position of the styrene substrate, suggests that 1,2-insertion is immediately followed by liberation of the targeted boronate ester while 2,1-insertion is reversible and not productive toward the formation of product, as only the linear alkylboronate ester is formed. This process is generalizable to non-vinylarene substrates. Upon reaction of 1-octene with deuterated pinacolborane in the presence of the cobalt catalyst, evidence of both 2,1- and 1,2-insertions is

observed; deuterium is incorporated at both the α and β carbons of the alkylboronate ester product. Additionally, the exclusive generation of the linear alkylboronate ester product, rather than a combination of the branched and linear products, suggests liberation of product immediately follows 1,2-insertion: i.e., β -hydride elimination from this insertion mode is not competitive with elimination of the target organoboronate ester while 2,1-insertion is not a productive pathway to the formation of alkylboronate ester product.

The susceptibility of 2,1-insertion products to β -hydride elimination and the general lack of turnover observed for this insertion mode may be a result of the substantial steric shielding of the generated secondary alkyl cobalt intermediates, which may preclude elimination with a boryl ligand to give the target compound. The inactivity of this cobalt system toward more substituted terminal alkenes is also consistent with this possibility, as greater substitution at the substrate would provide significant steric limitations even in the event of a 1,2insertion. To test this hypothesis, the addition of deuterated pinacolborane to cyclohexene, a substrate that generates only trace amounts of product after 24 h of stirring, was investigated. Although incorporation into the olefinic bond was not observed after 6.5 h of stirring, minor deuterium incorporation at the adjacent aliphatic carbons suggests an alkene-isomerizationtype event, where insertion into the olefin is followed by β hydride elimination from a proximal carbon to generate a deuterium-enriched cyclohexene. Importantly, the absence of the observed organoboronate product suggests that the generated secondary alkyl intermediate is unreactive toward turnover, in stark contrast to primary alkyl cobalt intermediates which can proceed along the reaction sequence. Interestingly, stirring the reaction mixture over a longer period (7 days) does eventually result in deuterium incorporation at all sites of the cyclohexene substrate, including the olefinic carbons.

Intrigued by this result, we sought to study these putative alkene isomerization events in greater detail. Accordingly, the hydroboration of the internal alkene trans-4-octene, a substrate with sterically differentiable primary and secondary alkyl sites, with deuterated pinacolborane was investigated. Deuterium incorporation was observed along the length of the substrate, consistent with alkene isomerization. In contrast to cyclohexene, however, minor resonances corresponding to the linear alkylboronate ester product were also observed in the ²H NMR spectrum, indicating that, upon isomerization to the more sterically accessible termini of the octyl chain, i.e. upon formation of a primary alkyl cobalt intermediate, liberation of the alkylboronate ester is viable. Given the profile of the cyclohexene substrate, i.e. any insertion or hydrocobaltation step necessarily generates a sterically hindered cobalt-secondary alkyl intermediate, the opportunity to generate the analogous alkylboronate is rendered far less likely and the catalysis is effectively arrested at the insertion step.

In addition to providing a rationale for the observed regioselectivity, these data may also explain some of the chemoselectivity observed for this catalyst platform. The reduction of a ketone functionality, for example, may be disfavored given the steric profile of the insertion product. By extension, reducible functionalities such as esters and substituted amines should also be, and are, tolerated, particularly in the presence of a more sterically accessible terminal alkene that is amenable to reduction with borane. The competing reductions of the formyl group in 2,2-dimethyl-4-pentenal (2n) and the nitrile moiety in 4-pentenenitrile (2m)

are also expected, as these reducible functionalities are sterically accessible and would generate insertion products with a steric profile comparable to that of monosubstituted terminal alkenes.

Informed by these insights and given the similarities to a hydrosilylation protocol previously reported for this system,²⁵ a mechanism was proposed for the observed reactivity (Figure 2).



Figure 2. Proposed catalytic cycle.

Oxidative addition of borane is proposed to commence the catalytic cycle and generate a Co^{III} hydrido boryl species (*I-1*) which is poised to coordinate alkene or nitrile substrates(*I-2*, nitrile coordination not shown). Unproductive migratory insertion of the hydride into the alkene in a 2,1-fashion affords a secondary alkyl Co^{III} intermediate (*I-3*) which can reversibly undergo β -hydride elimination, as established by deuterium labelling experiments, to reform *I-2*. A 1,2-insertion leads to the formation of a Co^{III} -alkyl (*I-4*), which upon reductive elimination furnishes the organoboronate ester product and regenerates the Co^{I} catalyst (1). In the event of an internal alkene, alkene isomerization to the terminal position may also generate product.

In conclusion, we have developed a highly selective Co^I system for the hydroboration of alkenes. This reaction sequence is selective for alkenes in the presence of several functional groups, furnishing the anti-Markovnikov product exclusively in all observed cases. Additionally, the protocol is amenable to the reduction of nitriles to their corresponding amines, a valuable chemical reaction that is relatively underdeveloped with earth-abundant first-row transition-metal systems. Deuterium labeling studies have provided important insights into the observed reactivity, demonstrating that the cobalt catalyst can negotiate insertion processes, β -hydride elimination pathways, and alkene isomerization events. These processes underpin the regioselectivity, and perhaps the chemoselectivity, of the system, as the generation of primary alkyl intermediates over the course of catalysis is required to liberate the alkylboronate esters.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b00362.

Spectral data and synthesis details for complexes 2a-k and 3a-e (PDF)

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Notes

The authors declare no competing financial interest.

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