JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

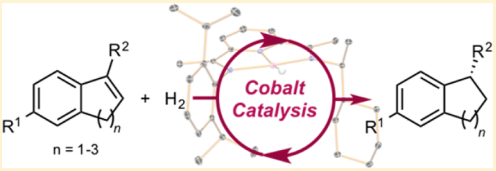
Cobalt-Catalyzed Enantioselective Hydrogenation of Minimally Functionalized Alkenes: Isotopic Labeling Provides Insight into the Origin of Stereoselectivity and Alkene Insertion Preferences

Max R. Friedfeld,[†] Michael Shevlin,[‡] Grant W. Margulieux,[†] Louis-Charles Campeau,[‡] and Paul J. Chirik*[,†]

[†]Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States
[‡]Department of Process & Analytical Chemistry, Merck Research Laboratories, Rahway, New Jersey 07065, United States

Supporting Information

ABSTRACT: The asymmetric hydrogenation of cyclic alkenes lacking coordinating functionality with a C_1-symmetric bis(imino)pyridine cobalt catalyst is described and has been applied to the synthesis of important substructures found in natural products and biologically active compounds. High activities and enantioselectivities were observed with substituted benzo-fused five-, six-, and seven-membered alkenes. The stereochemical outcome was dependent on both the ring size and exo/endo disposition. Deuterium labeling experiments support rapid and reversible 2,1-insertion that is unproductive for generating alkane product but accounts for the unusual isotopic distribution in deuterated alkanes. Analysis of the stereochemical outcome of the hydrogenated products coupled with isotopic labeling, stoichiometric, and kinetic studies established 1,2-alkene insertion as both turnover limiting and enantiodetermining with no evidence for erosion of cobalt alkyl stereochemistry by competing β-hydrogen elimination processes. A stereochemical model accounting for the preferred antipodes of the alkanes is proposed and relies on the subtle influence of the achiral aryl imine substituent on the cobalt catalyst.



INTRODUCTION

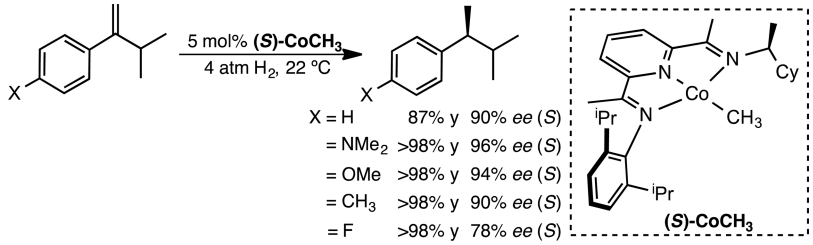
The enantioselective hydrogenation of minimally functionalized alkenes, those lacking coordinating functionality and hence stereodirecting elements, remains a largely unmet need in asymmetric catalysis.[1] Specifically, the asymmetric hydrogenation of dihydronaphthalenes (dialins)[2] and 1,1-diarylethenes[3] is of considerable interest due to the biological activity and therefore potential therapeutic value of the resulting enantiopure alkanes. Considerable effort has been devoted to the discovery of both precious metal catalysts[4] and more recently organocatalysts[5] for the hydrogenation of these substrates. However, in many cases, specific catalyst−substrate combinations are required or the substrate must contain coordinating directing groups to achieve synthetically useful enantioselectivities. Analogues of Crabtree's iridium catalyst bearing enantiopure phosphine oxazoline[6a] and related ligands[6] have emerged as the most effective systems for this type of alkene hydrogenation although in many cases the most active and selective catalysts are highly substrate dependent and can be tedious to prepare. Because the catalytic cycle is proposed to involve substitutionally inert iridium(III) intermediates,[7,8] noncoordinating solvents such as dichloromethane are required for optimal performance.

Base metal catalysts, those that rely on earth abundant elements such as iron and cobalt, are attractive due to their reduced environmental footprint and potential economic benefits.[9] More significantly, the distinct electronic structures and high density of states of first row transition metals[10] compared to heavier congeners offer new opportunities for catalyst design and approaches to transfer of chirality from the metal complex to challenging substrate classes. While highly active iron alkene hydrogenation catalysts have been discovered,[9b,11] enantioselectivity has remained elusive. By contrast, cobalt catalysts exhibit a rich catalytic asymmetric alkene hydrogenation chemistry, tracing their origins to seminal independent studies of Ohgo,[12] Pfaltz,[13] Corma,[14] and Shmidt.[15] In these examples, the number of alkene substrates that were reduced with high yields and enantioselectivities was limited and in many cases H_2 could not be used as the stoichiometric reductant. Limited experimental data are available regarding the nature of the catalytically active species, raising questions as to the preferred oxidation and spin states of cobalt best suited for asymmetric hydrogenation. Our laboratory, in collaboration with the Merck Catalysis Laboratory, has recently reported that Co(II) dialkyl complexes bearing widely used and commercially available C_2-symmetric, chiral bidentate phosphines produced highly active and enantioselective catalysts for the asymmetric hydrogenation of functionalized alkenes such as methyl acetamidoacrylate.[16] Isolation of catalytically relevant intermediates during hydroxyl-directed, diastereoselective hydrogenations using related achiral Co(II) complexes with bidentate phosphines supported a Co(0)−Co(II) redox cycle.[17] Enantioselective hydrogenation

Received: September 27, 2015
Published: February 8, 2016

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314−3324

Scheme 1. Enantiopure, C_1-Bis(imino)pyridine Cobalt Complexes for Asymmetric Hydrogenation of 4-Substituted α-Isopropylstyrenes (See Ref 26)



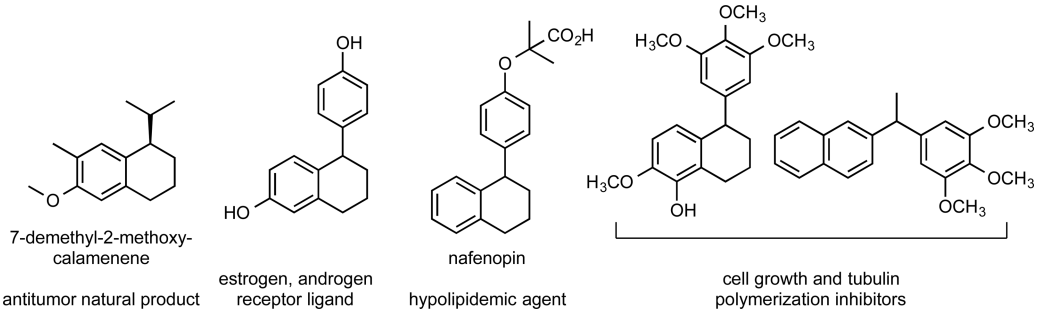


Figure 1. Potential targets for asymmetric hydrogenation of minimally functionalized cyclic alkenes.

of minimally functionalized alkenes with base metal catalysts have thus far been limited to the asymmetric reduction of *trans*-methylstilbene using a specific class of BiPhep ligands.[16]

Cobalt complexes bearing redox-active bis(imino)pyridines and related variants exhibit rich catalytic chemistry including ethylene polymerization,[18−20] alkene[21] and alkyne[22] hydroboration, cycloaddition,[23] and alkene dehydrogenative silylation.[24] Using an approach pioneered by Bianchini in polymerization catalysis,[25] C_1 symmetric bis(imino)pyridines bearing a 2,6-disubstituted aryl imine and an enantiopure alkyl imine were first demonstrated to be enantioselective catalysts for the asymmetric hydrogenation of a selected number of α-substituted styrene derivatives.[26] Balancing competing cyclometalation of the chiral imine substituent with productive hydrogenation activity resulted in identification of the bis(imino)pyridine cobalt methyl complex **(*S*)-CoCH$_3$** as one of the most active and enantioselective catalysts (Scheme 1).[27] This catalyst design concept has since been applied to asymmetric alkene hydroboration,[28] hydrosilylation,[29] and the hydrofunctionalization of ketones.[30] In both base- and precious metal-catalyzed enantioselective reductions of minimally functionalized alkenes, little is known experimentally about the mechanism of catalyst action, preferred oxidation states during turnover, or the mode of asymmetric induction from the catalyst to the alkene substrate. Computational studies have examined the preferred spin states of catalytic intermediates,[31] the regiochemical preferences for alkene insertion into the cobalt−hydride bond for selected substrates,[31,32] and in one case the full catalytic cycle for asymmetric alkene hydrogenation.[32] As amply demonstrated in rhodium-catalyzed asymmetric hydrogenation of amino acid precursors,[33] a detailed mechanistic understanding is critical for future catalyst design, expansion of substrate scope, and ultimately industrial implementation.[34] Here we describe more comprehensive investigations into the asymmetric hydrogenation performance of **(*S*)-CoCH$_3$** with challenging classes of minimally functionalized alkenes, including dialins and 1,1-diarylethenes. Deuterium labeling studies and an expanded substrate scope have provided insight into the mechanism of turnover including the regio- and enantiofacial preferences for alkene insertion.

RESULTS AND DISCUSSION

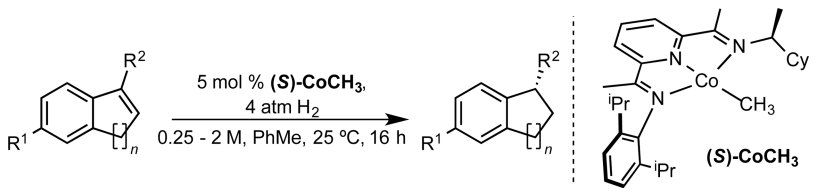
Asymmetric Hydrogenation of Minimally Functionalized Cyclic and 1,1-Disubstituted Alkenes. The representative molecules shown in Figure 1 highlight the types of structures available from the asymmetric hydrogenation of minimally functionalized cyclic alkenes. Examples include 7-demethyl-2-methoxycalamenene, a natural product first isolated from *Heterotheca grandiflora* with established antitumor activity,[35] an estrogen receptor ligand,[36] the hypolipidemic agent nafenopin,[37] and two potent cell growth and tubulin polymerization inhibitors.[2b,3a]

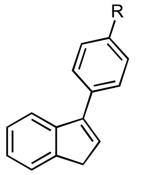
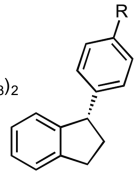
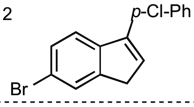
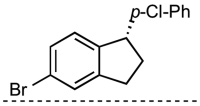
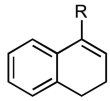
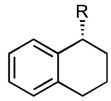
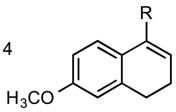
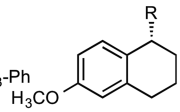
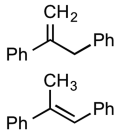
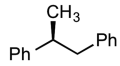
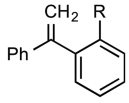
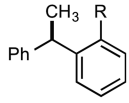
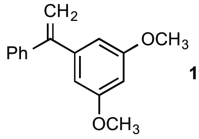
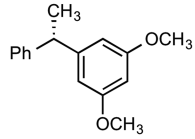
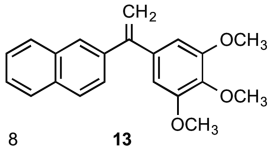
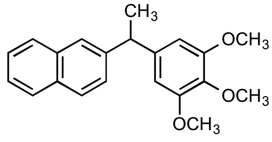
The success of **(*S*)-CoCH$_3$** in the enantioselective hydrogenation of α-isopropylstyrenes (Scheme 1) prompted exploration of the application of the base metal-catalyzed method to the synthesis of enantiopure 1,1-diaryl alkanes. Using a 0.25 M solution of 3-phenyl-1*H*-indene (**1a**) in toluene with 5 mol % of **(*S*)-CoCH$_3$** and 4 atm of H_2, the phenyl-substituted indane **2a** was isolated in 98% yield and 94% *ee*. Similarly high yields and enantioselectivities were maintained upon introduction of methoxy, dimethylamino, or chlorine substitution into the *para*-position of the phenyl substituent (Table 1, entry 1). A slight erosion in enantioselectivity (85% *ee*) was observed with *p*-fluorine substitution on the phenyl ring (**1e**) although the isolated yield remained near quantitative. Repeating the hydrogenation of **1e** at reduced hydrogen pressure (1 atm) however yielded **2e** in 97% *ee*. Bromine-atom substitution in the 6-position of the indene (**1f**) resulted in lower conversion, but the enantioselectivity remained high (93% *ee*). X-ray diffraction was used to establish the absolute configurations of **2b**, **2c**, **2d**, and **4b** (Figure 2), and the absolute configurations of the other alkane products were assigned based on analogy and comparison of optical rotations to known compounds.

Cobalt precatalyst **(*S*)-CoCH$_3$** also proved effective for the hydrogenation of substituted dialins (Table 1, entries 3 and 4), core structures of the molecules shown in Figure 1. Hydro-

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314−3324

Table 1. Enantioselective Hydrogenation of Minimally Functionalized Cyclic and 1,1-Disubstituted Alkenes with 5 mol % (*S*)-$CoCH_3$ and 4 atm of H_2 at 25 °C[a]



Entry	Substrate		Product	Isolated yield, % *ee*
1		**1a** R = H **1b** R = OCH_3 **1c** R = $N(CH_3)_2$ **1d** R = Cl **1e** R = F		**2a** 98%, 94% (*S*)-(–) **2b** 94%, 95% (*S*)-(–) **2c** 97%, 99% (*S*)-(–) **2d** 89%, 96% (*S*)-(–) **2e** 96%, 97% (*S*)-(–)[b]
2		**1f**		**2f** 41%, 91% (*S*)-(–)[c,d,e]
3		**3a** R = Ph **3b** R = *p*-OCH_3-Ph		**4a** 94%, 98% (*S*)-(+)[e,f] **4b** 96%, 98% (*S*)-(+)[e,f]
4		**5a** R = iPr **5b** R = *p*-OCH_3-Ph		**6a** 96%, 94% (*S*)-(–)[e,f] **6b** 73%, 92% (*S*)-(+)[d,f]
5		**7a** **7b**		**(*S*)-8** 92%, 66% (*S*)-(+)[b,f] **(*S*)-8** 93%, 56% (*S*)-(+)[b,f]
6		**9a** R = CH_3 **9b** R = Cl **9c** R = Et **9d** R = OCH_3		**10a** 95%, 76% (–)[b,f] **10b** 90%, 67% (+)[b,c,e,f] **10c** 91%, 77% (+)[b,f] **10d** 94%, 36% (+)[b,f]
7		**11**		**(*S*)-12** 94%, 27% (*S*)-(+)[b,f]
8		**13**		**14** >95%, <5%[b,c,f]

[a]Reactions run at 0.25 M, 4 mL of PhMe, 1 mmol of alkene substrate, 4 atm of H_2, 5% (*S*)-$CoCH_3$ at 25 °C for 16 h. [b]1 atm of H_2. [c]Yield determined by NMR; remainder of material was alkene. [d]1 M reaction. [e]48 h reaction time. [f]2 M reaction.

genation of the phenyl-substituted substrate **3a** yielded (*S*)-1-phenyltetralin (**4a**) in 94% isolated yield and 98% *ee* (Table 1). A more concentrated, 2 M solution of the alkene in toluene was required for full conversion. Under more dilute conditions, the enantioselectivity was maintained but conversion was lower. High yield and selectivity (98% *ee*) were maintained with the introduction of a 4-methoxy substituent in **3b** using the 2 M conditions, constituting a formal, enantioselective synthesis of nafenopin.[37] In a previous study, **4b** was synthesized using an iridium catalyst in 96% *ee*.[4g] The isopropyl-substituted dialin **5a** was also hydrogenated with 5 mol % (*S*)-$CoCH_3$ to the (*S*)-enantiomer of the alkane **6a** in 96% isolated yield and 94% *ee*. The iridium-catalyzed hydrogenation of **5a**[38] has been previously applied in a concise, enantioselective total synthesis[38a] of (*R*)-7-demethyl-6-methoxycalamenene. Extending the cobalt-catalyzed method to **5b** resulted in isolation of (*S*)-**6b** in 85% *ee*, demonstrating a formal enantioselective synthesis of 1-(*p*-hydroxyphenyl)-6-hydroxytetralin, which has been reported to have strong affinity as a ligand for estrogen and androgen receptors.[36]

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314–3324

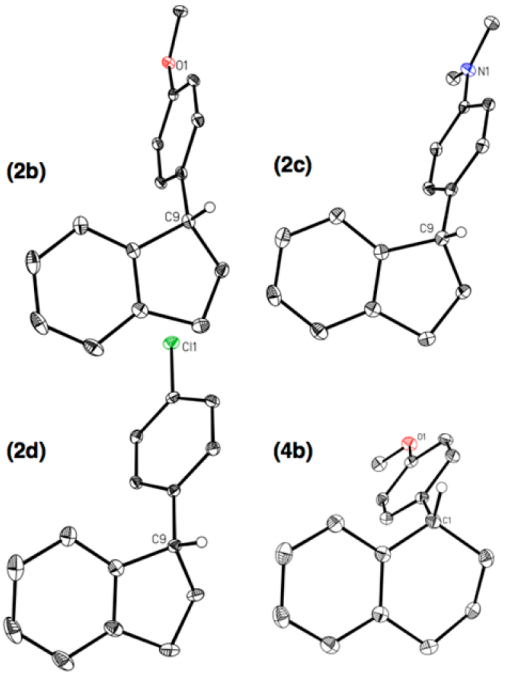


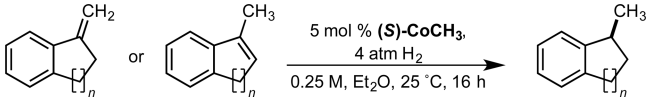
Figure 2. Solid-state structures of enantiopure alkanes **2b**, **2c**, **2d**, and **4b** synthesized by cobalt-catalyzed asymmetric hydrogenation.

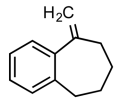
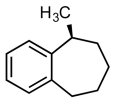
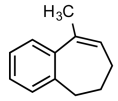
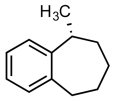
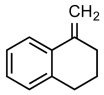
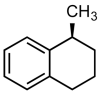
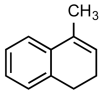
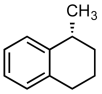
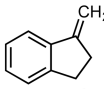
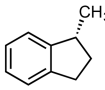
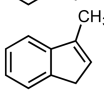
Comparing the performance of **(*S*)-CoCH$_3$** with precious metal catalysts, high throughput experimentation was used to evaluate ruthenium, rhodium, and iridium precursors in combination with libraries of 204 chiral, bidentate phosphines and 12 phosphine oxazoline ligands for the hydrogenation of 3-phenyl-1*H*-indene (**1a**). Each hydrogenation was conducted at 34 atm of H_2 with three precious metal precursors: (methylallyl)$_2$Ru(COD), [(NBD)$_2$Rh]BF$_4$, and [(COD)$_2$Ir]-BArF$_{24}$ (COD = 1,5-cyclooctadiene, NBD = norbornadiene; BArF$_{24}$ = B(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_4$). With the Ru and Rh precursors (see Supporting Information,SI, for details), no metal−ligand combinations were identified that produced alkane in >50% *ee*. The iridium precursor, in combination with two ferrocenyl-based P,N ligands in dichloromethane solution and one axially chiral phosphine ligand in methanol, gave full conversion to product in greater than 90% *ee*, with one combination generating the alkane in 98% *ee*. These results demonstrate that the C_1-bis(imino)pyridine cobalt complex is relatively unique among homogeneous catalysts for the asymmetric hydrogenation of minimally functionalized alkenes and offers a base metal alternative to more specialty iridium catalysts.

The performance of **(*S*)-CoCH$_3$** was also evaluated for the asymmetric hydrogenation of minimally functionalized 1,1-diaryl ethenes and related alkenes (Table 1, entries 5−8). Hydrogenation of α-benzylstyrene (**7a**) proceeded in high yield (92%) with modest enantioselectivity (66% *ee*). A similar outcome was observed with *trans*-methylstilbene (**7b**). In this case, enantioselectivity was found to be essentially invariant at hydrogen pressures between 1 and 68 atm (see SI for details). Each of the diaryl ethenes examined (**9a−d**, **11**, **13**) underwent cobalt-catalyzed hydrogenation with high isolated yields (>90%). *o*-Alkyl- and -chloro-substituted products **10a−c** were synthesized with the highest enantioselectivity of 67−77% *ee* at 1 atm of H_2. Hydrogenation of **12** and **14**, substrates lacking *ortho* substitution, resulted in lower enantioselectivity, producing essentially racemic product in the case of 14 (entry 8). The reduced enantioselectivity observed with **12** and **14** highlight the stereochemical influence of *ortho* substitution, contrary to *meta*-substituent effects reported in iridium catalysis.[4f]

To gain additional insight into the origin of stereocontrol in bis(imino)pyridine cobalt-catalyzed asymmetric hydrogenation, a series of isomeric exo- and endocyclic alkenes was studied (Table 2). Hydrogenation of seven-membered cyclic alkenes

Table 2. Enantioselective Hydrogenation of Isomeric Exo- and Endocyclic Alkenes[a]



Entry	Substrate		Product		Isolated yield, % *ee*[a]
1		**15a**		**(*S*)-16**	97%, 85% (S)-(−)
2		**15b**		**(*R*)-16**	95%, 89% (*R*)-(+)
3		**17a**		**(*S*)-18**	87%, 53% (*S*)-(+)
4		**17b**		**(*R*)-18**	88%, 95% (*R*)-(−) 96%, 93% (*R*)-(−)[b]
5		**19a**		**(*R*)-20**	84%, 74% (*R*)-(+)
6		**19b**		**(*R*)-20**	88%, 89% (*R*)-(+)[c]

[a]Reactions run at 0.25 M, 4 mL of Et$_2$O, 1 mmol of alkene substrate, 5% **(*S*)-CoCH$_3$** at 25 °C for 16 h. [b]Neat, 70 mmol of alkene, 0.1% [Co], 34 atm. [c]Reaction run at 2 M, 1 atm of H_2.

(**15a** and **15b**) with **(*S*)-CoCH$_3$** proceeded with high yields and good enantioselectivities (entries 1 and 2). Notably, hydrogenation of exocyclic alkene **15a** yielded the (*S*)-enantiomer of the alkane while analogous hydrogenation of the isomeric, endocyclic alkene **15b** furnished the (*R*)-antipode, establishing different stereochemical outcomes for the geminal, exocyclic alkene compared to the endocyclic alkene with this ring size. Contraction to a six-membered ring system (entries 3 and 4) significantly reduced enantioselectivity (53% *ee*) with the exocyclic-methylene substrate **18a** favoring the (*S*)-antipode of the alkane. By contrast, the cobalt-catalyzed hydrogenation of the isomeric endocyclic alkene **17b** proceeded to the opposite (*R*)-antipode with 95% *ee*. High enantioselectivity was maintained when the hydrogenation was carried out on multigram scale (70 mmol) in neat alkene using 0.1 mol % of **(*S*)-CoCH$_3$**.

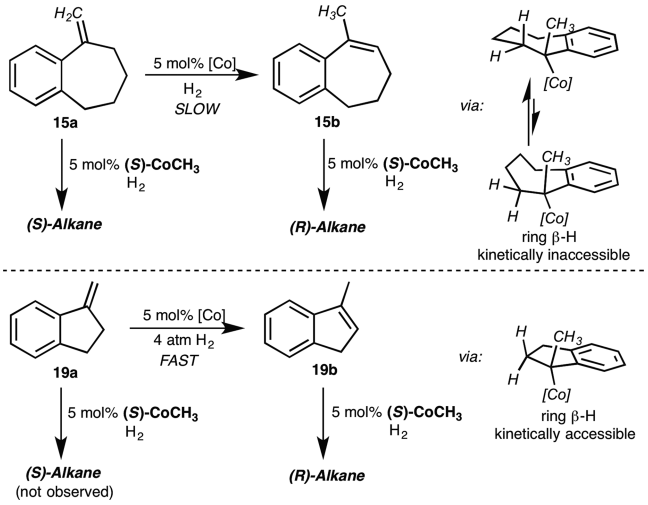
The hydrogenation of the analogous indene derivatives was also examined to explore additional substrate scope and to provide insight into the low enantioselectivity observed with **17a**. Cobalt-catalyzed hydrogenation of the exocyclic-methylene substrate (**19a**) and the isomeric endocyclic alkene (**19b**) both yielded the (*R*)-enantiomer of the corresponding alkane in 74

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314−3324

and 89% *ee*, respectively, in stark contrast to the seven-membered ring substrates **15a** and **15b**. The observation of variable enantioselectivity as a function of alkene position and ring size suggests that with certain substrates alkene isomerization is competitive with or faster than alkene hydrogenation. In support of this hypothesis, monitoring the hydrogenation of **19a** by ^{1}H NMR spectroscopy established rapid formation of **19b** during the course of the reaction. We also note that in our initial communication the hydrogenation of **19a** was reported to yield 39% *ee* (*R*).[27] The discrepancy in the values is a result of the pressure and concentration dependence of the reaction resulting from competing alkene isomerization processes.

Scheme 2 summarizes the relative rates of hydrogenation and isomerization between the seven- and five-membered ring substrates. Under standard conditions with 4 atm of H_2, isomerization of the alkene from the exo- to endocyclic position with the seven-membered ring was not detected whereas the corresponding five-membered ring substrate underwent rapid isomerization. As will be presented in a later section, deuterium labeling studies also established that with the seven-membered ring, the tertiary alkyl cobalt intermediate is formed but undergoes β-hydrogen elimination preferentially from the methyl positions over the ring methylene position. With five- and six-membered rings, the β-hydrogens on the methylene ring positions become accessible and rapid isomerization is observed. Because ring strain is approximately equal in the five- and seven-membered rings,[39] conformational preferences are likely the origin of the rate differences. The indenyl substrates are the most planar within the series and place the ring β-hydrogen in the necessary *syn*-periplanar arrangement required for transfer to the metal.[40] The increased conformational flexibility of the seven-membered ring disfavors this process and reduces the propensity for alkene isomerization. The six-membered exocyclic substrate **17a** is between these extremes, and because isomerization is competitive with productive hydrogenation, the enantioselectivity of the overall reaction is consequently eroded because the alkene isomer is reduced with the opposite stereochemical preference.

Scheme 2. Hydrogenation versus Isomerization of Seven- versus Five-Membered Rings and Their Influences on the Stereochemical Outcome of the Reaction



Identification and Crystallographic Characterization of the Catalytic Resting State. Establishing the identity of the catalyst resting state is important not only to gain understanding of the mechanism of hydrogenation but also to determine the origin of stereoselectivity and ultimately improve catalyst performance and expand the substrate scope. To this end, the hydrogenations of both α-isopropylstyrene (**21**) and 3-phenyl-1*H*-indene (**1a**) were monitored by ^{1}H NMR spectroscopy in benzene-d_6. Immediately upon addition of 4 atm of H_2 to a 5 mol % solution of (*S*)-**CoCH$_3$** and **1a** at 23 °C, methane was generated and a new C_1-symmetric cobalt compound identified as the cobalt−hydride (*S*)-**CoH** was observed. The cobalt hydride, (*S*)-**CoH**, was also generated immediately following addition of H_2 to the previously reported cyclometalated compound, (*S*)-**CoCM**.[26] During the course of the hydrogenation of **1a** or **21**, only resonances for this new species was observed by ^{1}H NMR spectroscopy, indicating that (*S*)-**CoH** is the catalyst resting state. (*S*)-**CoH** exhibits a diagnostic upfield broad singlet located at −32.8 ppm ($\nu_{1/2}$ = 918 Hz) and identified as the Co−H resonance, which was further supported by deuteration. The solid-state structure of (*S*)-**CoH** was determined by X-ray diffraction (Figure 3), confirming the identity of the product and providing important structural information about the chiral environment around the cobalt. As is typical with bis(imino)pyridine metal complexes, the 2,6-disubstituted aryl ring is oriented orthogonal to the metal−ligand plane and the chiral imine adopts a similar conformation. The larger cyclohexyl group effectively shields one face of the square plane, placing the methyl substituent in the opposite quadrant.

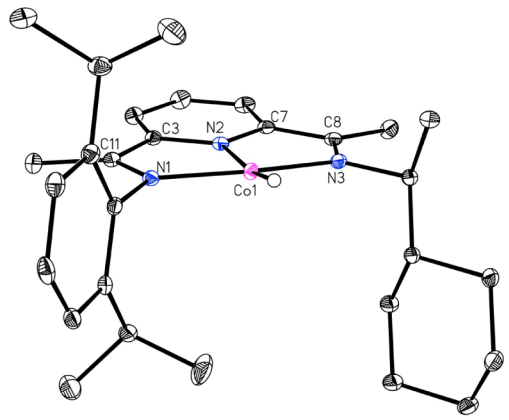


Figure 3. Solid-state structure of (*S*)-**CoH** at 30% probability ellipsoids. Hydrogen atoms, except for the cobalt hydride, omitted for clarity.

The N1−C2 and N3−C8 bond lengths in (*S*)-**CoH** are elongated (1.3349(18) and 1.3233(19) Å, respectively) while the C2−C3 and C7−C8 bond lengths are contracted (1.440(2) and 1.451(2) Å, respectively) consistent with one-electron reduction of the ligand, establishing a low-spin Co(II) center antiferromagnetically coupled to a radical anion.[41] This electronic configuration is well-established with planar bis(imino)pyridine cobalt alkyl complexes.[41a,42] The hydride ligand, which was located from the Fourier difference map, is lifted from the [N,N,N] ligand plane by 9.0° such that it is aligned away from the large cyclohexyl substituent. This lift value is somewhat smaller than the methyl ligand in the solid-state structure of (*S*)-**CoCH$_3$**.[26] Unlike the structure of (*S*)-**CoCH$_3$**, only one orientation of (*S*)-**CoH** exists in the unit cell, with the hydrogen atom of the chiral carbon orientated away

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314−3324

from the cobalt ion, minimizing $A^{1,3}$-type strain with the backbone methyl group.

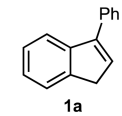
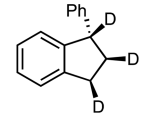
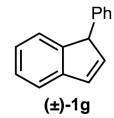
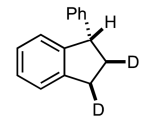
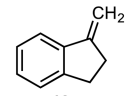
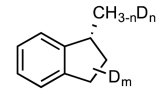
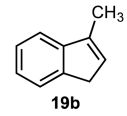
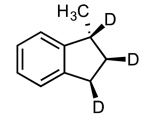
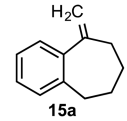
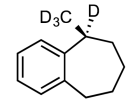
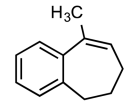
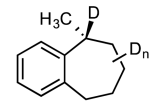
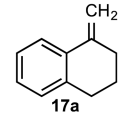
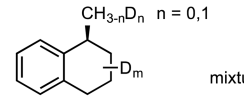
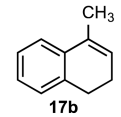
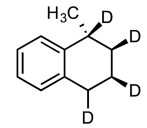
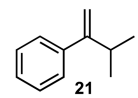
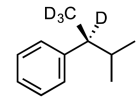
The observation of **(*S*)-CoH** during the hydrogenation of relatively hindered 1,1-disubstituted alkenes is consistent with alkene insertion as the turnover-limiting step. This observation contrasts those reported by Budzelaar[31] and Gibson[43] where ethylene and α-olefins, that is, smaller and more reactive alkenes, undergo rapid insertion into C_{2v} symmetric aryl-substituted bis(imino)pyridine cobalt hydrides to yield the corresponding alkyl complexes.

To further demonstrate the competency of **(*S*)-CoH** as a catalytic intermediate, a single-turnover experiment was performed. Addition of 1 equiv of α-iPr-styrene (**21**) to a benzene-d_6 solution of **(*S*)-CoH** at ambient temperature over the course of hours generated **(*S*)-CoCM** and alkane **22**.[26] The putative cobalt alkyl intermediate was not observed, indicating that alkene insertion is slow in the absence of H_2 and is followed by rapid cyclometalation. Importantly, the alkane obtained from this reaction was of similar enantiopurity (87% *ee*) to that formed from the catalytic reactions. Addition of H_2 to this mixture rapidly regenerated **(*S*)-CoH** as judged by ^{1}H NMR spectroscopy.

Deuterium Labeling Studies. A series of deuterium labeling experiments were conducted to determine the mode of stereocontrol by **(*S*)-CoCH$_3$** in the hydrogenation of minimally functionalized cyclic alkenes (Table 3). To achieve the highest levels of isotopic enrichment in the alkane products, the cobalt complex was pretreated with D_2 gas to avoid contamination from cyclometalation of bis(imino)pyridine substituents.[44] Exposure of **1a** to 4 atm of D_2 under standard catalytic conditions provided the deuterated alkane in 92% yield and 94% *ee*. Analysis by ^{1}H, ^{2}H, and ^{13}C NMR spectroscopies established exclusive formation of the d_3-isotopologue with all deuterium atoms in a *syn* relationship and on the opposite face from the phenyl substituent. Spectroscopic data and complete assignments are reported in the SI. Performing a similar experiment with (±)-**1g** (entry 2) yielded **2a**-d_2 also as a single isotopologue and isotopomer where the deuterium atoms are *syn* to each other and *anti* to the phenyl ring, highlighting the significant stereochemical influence of the phenyl substituent. Scheme 3 presents proposed pathways for olefin insertion and β-hydrogen elimination to account for the observed *syn* deuteration. With **1a**, stereoselective insertion into the 2-position followed by β-H elimination from the 1-position with dissociation of the alkene yields (*S*)-1-phenyl-1*H*-indene-d_1. The deuteration of **1g**-d_1 is rapid and occurs by either insertion into the 2- or 3-position of the resulting indene to generate the d_2 cobalt–alkyl isotopologue. While exclusive insertion into the 2-position seems plausible, insertion at the 1-position cannot be ruled out based on the available experimental data. Alkane formation by reaction with D_2 gas generates the *syn*-d_3-alkane, (*S*)-**2a**-d_3. Initial insertion at the 3-position of **1a** is also plausible but is unproductive toward net deuteration of the alkene. Formation of (*S*)-**2a**-d_3 in high enantioselectivity from **1a** and the observation of (±)-**2a**-d_2 with the phenyl substituent *anti* to the deuteria demonstrates the stereochemical influence of the phenyl substituent in determining the facial selectivity of the alkene insertion into the cobalt–hydride bond.

Similar pathways are likely operative during the deuteration of **19a** and **19b** (entries 3 and 4, Table 3). With the endocyclic alkene **19b**, D_2 addition furnished (*R*)-**20** in 89% yield and 96% *ee* as the d_3-*syn*-isotopologue and isotopomer. Importantly, no deuterium was observed in the methyl group of the alkane following deuteration. Unlike with **1a**, insertion at the 3-position of 3-methyl-1*H*-indene (**19b**) generates a cobalt tertiary alkyl intermediate that could, in principle, undergo β-H elimination to form **19a**, a reaction sequence that is endergonic. However, the absence of deuterium in the methyl group of the product excludes this possibility. The opposite is true for the hydrogenation and deuteration of **19a**, as isotopic label was observed both in the methyl group and in the methylene positions of the indane product. Because isomerization of **19a** to **19b** is competitive with hydrogenation to alkane, formation of the cobalt tertiary alkyl from the exomethylene alkene must be faster than productive hydrogenation under these conditions as

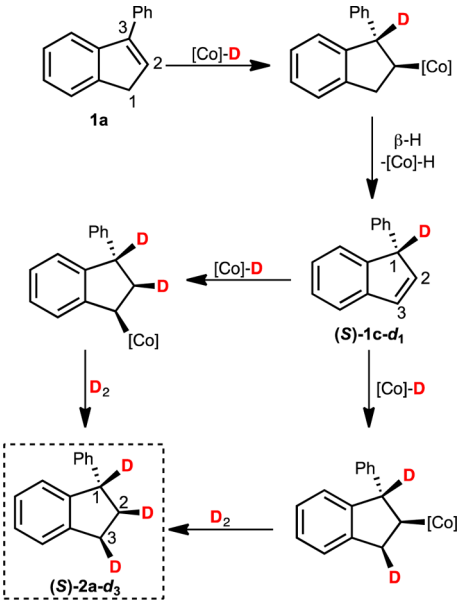
Table 3. Deuteration of Cyclic Alkenes with (*S*)-CoCH$_3$[a]

Entry	Substrate	Product	isolated yield, % ee, and isotopic composition
1[b]	 **1a**		**(*S*)-2a-d$_3$** 92% yield 94% ee (*S*)-(–) >90% single isotopologue
2[b]	 **(±)-1g**		**(±)-2a-d$_2$** 97% yield <2% ee (±) >72% single isotopologue
3	 **19a**		**(*R*)-20-d$_{n+m}$** 92% yield 85% ee (*R*)-(+) mixture of isotopologues
4	 **19b**		**(*R*)-20-d$_3$** 89% yield 96% ee (*R*)-(+) >70% single isotopologue
5	 **15a**		**(*S*)-16-*d*$_4$** 93% yield 91% ee (*S*)-(–) >70% single isotopologue
6	 **15b**		**(*R*)-16-*d*$_{n+1}$** 97% yield 91% ee (*R*)-(+) mixture of isotopologues
7	 **17a**		**(*S*)-18-*d*$_{n+m}$** 81%, 54% *ee* mixture of isotopologues
8	 **17b**		**(*R*)-18-*d*$_4$** 82% yield 98% ee (*R*)-(–) >85% single isotopologue
9[c]	 **21**		**(*S*)-22-*d*$_4$** 76% yield 90% ee (*S*)-(+) >90% single isotopologue

[a]Reactions run at 0.25 M in Et_2O, 1 mmol of alkene substrate, 5% (*S*)-**CoCH$_3$** at 25 °C for 16 h, 4 atm of D_2. [b]PhMe solvent. [c]2 M reaction with 1 atm of D_2.

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314–3324

Scheme 3. Proposed Alkene Insertion and β-Hydrogen Elimination Processes Operative during the Deuteration of 1a with (*S*)-CoH Accounting for the Exclusive Formation of the *Syn*-d_3 Isotopologue of 2a[a]



[a]Labeled carbon positions indene and indane molecules are numbered according to convention.

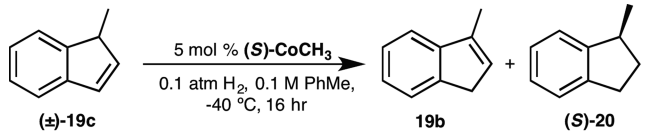
evidenced by the observed enantioselectivity and the isotopic labeling pattern in the resulting alkane.

The deuteration studies also provided additional insight into the role of alkene isomerization as a function of ring size of the cyclic alkene. Exposure of the seven-membered ring substrate **15a** to 4 atm of D_2 gas under standard catalytic conditions resulted in exclusive formation of the d_4-alkane in 85% *ee* (Table 3, entry 5), suggesting that 2,1-insertion is fast and reversible compared to productive turnover to alkane. Conformational flexibility in the larger ring of the tertiary cobalt alkyl intermediate formed from **15a** likely disfavors the geometry necessary for β-hydrogen elimination from the ring methylene position. (see Scheme 2). Because none of the isotopic label was detected in the methylene positions, this experiment established that, unlike with **19a**, the cobalt catalyst does not access the ring positions under the conditions of the deuteration. With the complementary endocyclic alkene **15b**, the enantioselectivity of the reaction remained high (91% *ee*) and a mixture of isotopologues was formed. Notably, no incorporation of the isotopic label into the methyl position was detected, demonstrating that once the catalyst accesses the seven-membered ring, migration to the methyl position does not occur. Definitive assignment of the position and stereochemistry of the deuterium in the ring positions was complicated by the complexity of the NMR spectra.

Deuteration of the six-membered ring substrates, **17a** and **17b**, proceeded analogously to the indene examples. With the exocyclic isomer **17a**, deuterium was detected both in the methyl and ring methylene positions, demonstrating that isomerization of the alkene into the ring is competitive with hydrogenation. Likewise, deuteration of the endocyclic alkene **17b** led to no isotopic label in the methyl group, demonstrating that the isomerization of the internal alkene to exocyclic position does not occur. Because the hydrogenation of **17a** and **17b** yields opposite enantiomers and isomerization of the former to the latter is competitive with alkane formation, the enantioselectivities obtained from the hydrogenation of **17a** are low. It is important to note that the deuteration and isomerization studies demonstrate that it is not the enantioinduction from the catalyst to the substrate that is poor but rather two selective hydrogenations that occur with opposite facial preferences acting against each other. The deuteration of α-isopropylstyrene (**21**), yielded **22**-d_4, a d_4-product analogous to (*S*)-**16**-d_4, establishing that isomerization of **21** does not occur and that 2,1-alkene insertion is also fast and reversible in acyclic alkenes.

Exploration of Enantioconvergent Hydrogenation. The observation that cobalt-catalyzed asymmetric hydrogenation accesses both alkene isomerization and productive alkane formation pathways suggested that enantioconvergent hydrogenation may be possible. In such a process, an alkene bearing a racemic allylic substituent is converted to the corresponding enantioenriched alkane. To experimentally evaluate this possibility, the hydrogenation of racemic 1-methyl-1*H*-indene (**19c**) was conducted with 5 mol % of (*S*)-**CoCH$_3$** and 0.1 atm of H_2 (Scheme 4). Low pressures of hydrogen were examined to avoid direct hydrogenation of the C=C bond and formation of pure racemic product, which is formed under the standard conditions in Tables 1 and 2. Under these conditions, (*S*)-**20** was obtained in 76% *ee*, albeit in partial (55%) conversion. The remainder of the material was identified as **19b**, an isomer of the starting alkene.

Scheme 4. Enantioconvergent Hydrogenation of 1-Methyl-1*H*-indene (19c) with (*S*)-CoCH$_3$

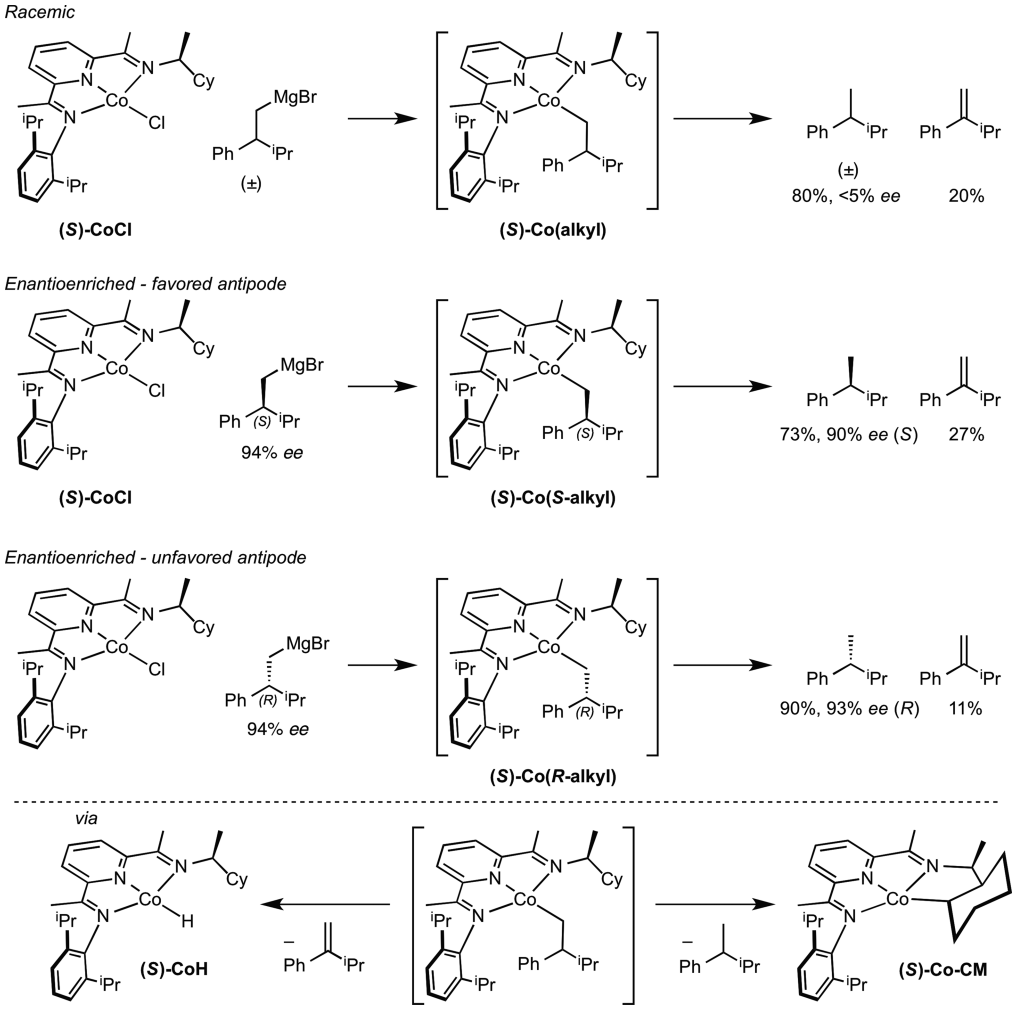


Preparation of Cobalt Alkyl Intermediates for Evaluation of 1,2- versus 2,1-Insertion. The deuterium labeling studies establish that 2,1-insertion and subsequent β-hydrogen elimination is competitive during turnover but its relevance to alkane formation has not been established. It is plausible that 2,1-insertion is a fast and reversible off-cycle pathway while 1,2-insertion leads to product. Establishing the regiochemical preferences for alkene insertion is essential for understanding the origin of stereocontrol imparted by (*S*)-**CoCH$_3$**. To address these possibilities, a series of alkylation experiments were conducted to determine the relative accessibility and stability of primary cobalt alkyl intermediates (Scheme 5).

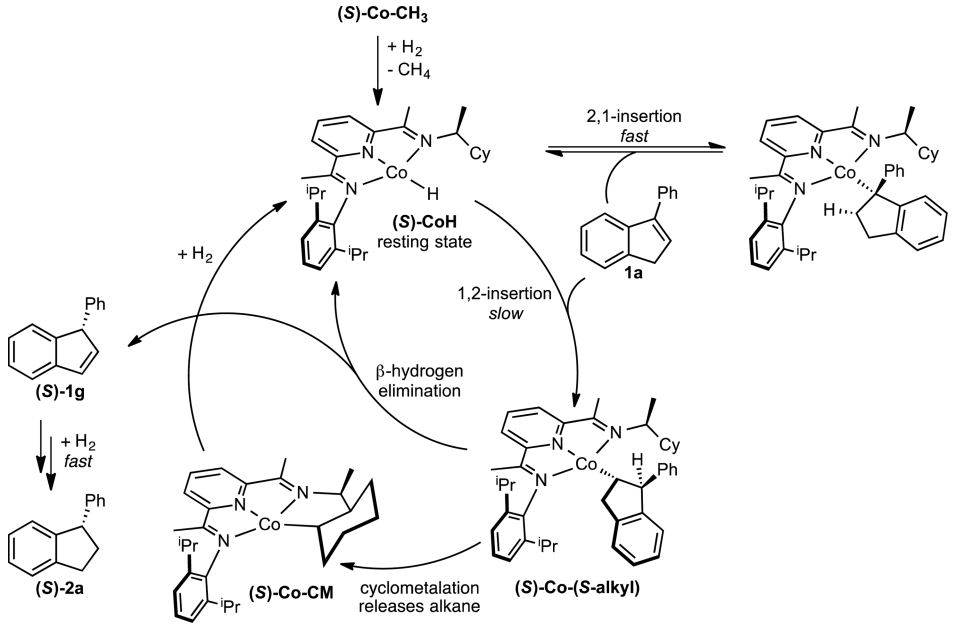
In an attempt to independently synthesize the product of 1,2-insertion, (*S*)-**CoCl** was treated with *rac*-(3-methyl-2-phenylbutyl)magnesium bromide. Immediately upon mixing, the anticipated cobalt alkyl complex (*S*)-**Co(alkyl)** (shown in brackets in Scheme 5) was not observed. Instead, an 80:20 mixture of alkane and alkene products were formed in addition to (*S*)-**CoH** and the previously characterized[26] cyclometalated complex (*S*)-**CoCM** where the cyclohexyl group on the chiral imine substitutent serves as the source of hydrogen to generate the alkane. Repeating the experiment with the (*S*)-enantiomer (94% *ee*) of the Grignard reagent, corresponding to the antipode of the alkane observed from alkene hydrogenation, produced a similar 73:27 mixture of alkane to alkene along with (*S*)-**CoH**

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314−3324

Scheme 5. Alkylation Studies To Determine the Kinetic Feasibility of 1,2-Insertion during Bis(imino)pyridine Cobalt-Catalyzed Enantioselective Hydrogenation

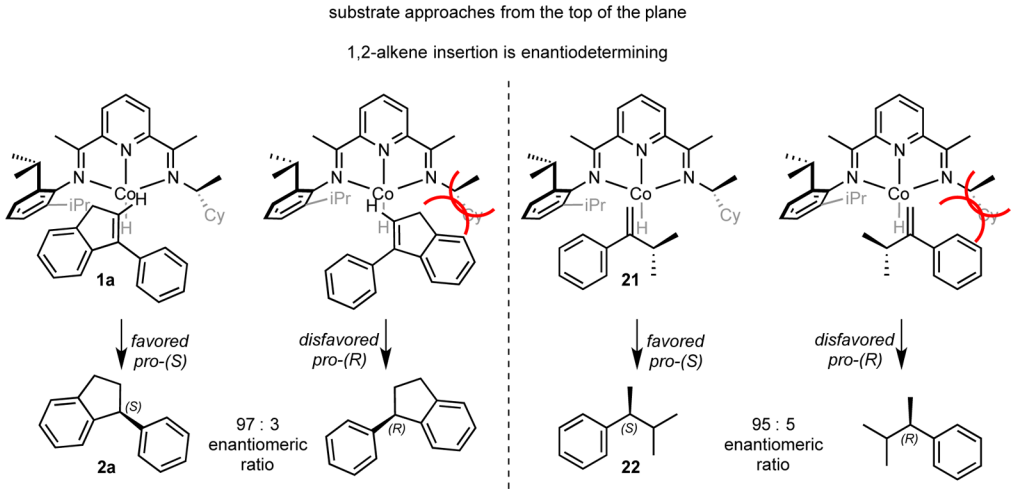


Scheme 6. Proposed Catalytic Cycle for the Enantioselective Hydrogenation of 1a with (*S*)-CoCH$_3$



DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314−3324

Scheme 7. Stereochemical Model Accounting for the Observed Hydrogenation Selectivity with (*S*)-CoCH$_3$ and Substrates 1a and 21



and (*S*)-**CoCM**. The enantiopurity of the liberated alkane was only slightly eroded to 90% *ee*. Addition of the opposite antipode of the Grignard reagent, (*R*)-(3-methyl-2-phenylbutyl) magnesium bromide (94% *ee*), to (*S*)-**CoCl** generated (*R*)-alkane with little erosion (93% *ee*) in the enantiopurity. These results establish that once the cobalt alkyl intermediate is formed, the stereochemistry of the alkyl ligand is fixed. That is, formation of alkane from the sterically congested cobalt ion does not affect the β-stereocenter. During catalysis, the enantiodetermining step is therefore 1,2-alkene insertion and that once on the metal, epimerization of the alkyl through reversible β-hydrogenation elimination and insertion events is not operative. In all of the stoichiometric experiments, the cobalt alkyl complex was not directly observed and demonstrates fast release of alkane by cyclometalation of the ligand in the absence of hydrogen gas. Thus, cyclometalation pathways and direct hydrogenolysis of the cobalt alkyl should both be considered as plausible pathways for the product release step. Computational studies by Hopmann have demonstrated that kinetic feasibility of imine substituent cyclometalation with (*S*)-**CoCH$_3$** in the absence of substrate.[32]

Rate Law. Experiments were also conducted to establish the rate law for cobalt-catalyzed enantioselective hydrogenation. Hydrogen uptake measurements were conducted during the hydrogenation of **17b** to determine the order in H_2. Reactions were run in a high-pressure autoclave equipped with a calibrated gas buret to measure gas uptake. Using 1 mol % (*S*)-**CoCH$_3$** and 10 mmol of alkene at 0.67 M in toluene, reactions were conducted at an internal temperature of 25 °C and 4 atm of H_2. The rate of the reaction was found to be independent of hydrogen concentration as a function of time, consistent with a process that is zero order in H_2. A separate series of experiments established first-order behavior in both the alkene and the cobalt precursor, (*S*)-**CoCH$_3$**, consistent with alkene insertion as turnover limiting.

Mechanistic Summary and Origins of Stereocontrol. The isotopic labeling studies, stoichiometric experiments, and stereochemical outcome of the reaction provide a comprehensive picture of the preferred pathway for enantioselective cobalt-catalyzed alkene hydrogenation for endocyclic substrates (Scheme 6). With hindered alkenes, the catalyst resting state is the bis(imino)pyridine cobalt hydride, (*S*)-**CoH**, a low spin cobalt(II) complex. Alkene 1,2-insertion is the turnover-limiting and enantiodetermining step. While the 2,1-insertion pathway to form a tertiary alkyl intermediate is fast and reversible, 1,2-insertion is productive for alkane formation due to the lower barrier for product release, either by cyclohexyl group cyclometalation or by interaction with hydrogen gas. While the structures presented in Scheme 6 are depicted in their redox-neutral form, extensive studies into the electronic structure of bis(imino)pyridine cobalt hydride and alkyl complexes support low-spin Co(II), d^7 compounds engaged in antiferromagnetic coupling with bis(imino)pyridine radical anions.[31,42] Indeed, computational studied by Hopmann[32] on the mechanism of hydrogenation with (*S*)-**CoCH$_3$** also support principally broken symmetry electronic states throughout the catalytic cycle.[32]

Based on this understanding of the enantioselectivity-determining step and the absolute configurations established for a host of minimally functionalized alkenes, a model for enantioinduction from the catalyst to the substrate is proposed (Scheme 7). To achieve productive 1,2-insertion, the alkene must approach the metal−ligand plane from either the methyl- or cyclohexyl-substituted face—the planes defined by the C_1-symmetric chiral imine substituent. The structural data suggest that the cyclohexyl side of the molecule is more sterically hindered and blocks the approach of substrate, and the lifting of the Co−X (X = Cl, CH_3, H) bond vector in the solid-state structures of (*S*)-CoX derivatives also reflects the steric influence of the cyclohexyl group. To generate (*S*)-**2a**, the pro-(*S*) face of alkene **1a** must approach the Co−H axis oriented with the smaller phenyl substituent toward the chiral imine to avoid steric interactions (Scheme 7). With **21**, the smaller isopropyl will be oriented toward the chiral alkyl imine to obtain the observed enantiomer of product. In both models, the achiral 2,6-diisopropyl aryl substituent has an essential directing effect on the enantioselectivity of alkene insertion and is an important design feature in the synthesis of future generations of cobalt catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10148.

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314−3324

Crystallographic data for (*S*)-**CoH**, **2b**, **2c**, **2d**, and **4b** (CIF)

Additional experimental procedures, including general considerations and characterization data, for (*S*)-**CoH**, **2b**, **2c**, **2d**, and **4b** (PDF)

AUTHOR INFORMATION

Corresponding Author

*pchirik@princeton.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the U.S. National Science Foundation (NSF) for a Grant Opportunities for Academic Liaison with Industry (GOALI) grant (CHE-1265988) between Princeton and Merck. M.R.F. thanks the NSF for a Graduate Research Fellowship (DGE-1148900). We thank Iraklis Pappas (Princeton) for additional assistance with X-ray crystallography, Dr. Istvan Pelczer (Princeton) for interpretation of NMR spectra, Lotus Separations for preparative chiral separation, and Dr. Matthew Tudge (Merck) for helpful discussions.

REFERENCES

(1) (a) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. *Chem. Rev.* **2014**, *114*, 2130. (b) Zhu, Y.; Burgess, K. *Acc. Chem. Res.* **2012**, *45*, 1623. (c) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513. (d) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402. (e) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.

(2) (a) Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8851. (b) Rasolofonjatovo, E.; Provot, O.; Hamze, A.; Rodrigo, J.; Bignon, J.; Wdzieczak-Bakala, J.; Desravines, D.; Dubois, J.; Brion, J.-D.; Alami, M. *Eur. J. Med. Chem.* **2012**, *52*, 22. (c) Volonterio, A.; Zanda, M. *Tetrahedron Lett.* **2005**, *46*, 8723. (d) Xiao, Z.; Bastow, K. F.; Vance, J. R.; Sidwell, R. S.; Wang, H.-K.; Chen, M. S.; Shi, Q.; Lee, K.-H. *J. Med. Chem.* **2004**, *47*, 5140.

(3) (a) Cheltsov, A. V.; Aoyagi, M.; Aleshin, A.; Yu, E. C.-W.; Gilliland, T.; Zhai, D.; Bobkov, A. A.; Reed, J. C.; Liddington, R. C.; Abagyan, R. *J. Med. Chem.* **2010**, *53*, 3899. (b) Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; Rodrigo De Losada, J.; Bignon, J.; Liu, J.−M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.−D.; Alami, M. *ChemMedChem* **2011**, *6*, 488. (c) Gross, T.; Chou, S.; Dyke, A.; Dominguez, B.; Groarke, M.; Medlock, J.; Ouellette, M.; Reddy, J. P.; Seger, A.; Zook, S.; Zanotti-Gerosa, A. *Tetrahedron Lett.* **2012**, *53*, 1025. (d) Alami, M.; Messaoudi, S.; Hamze, A.; Provot, O.; Brion, J.-D.; Liu, J.- M.; Bignon, J.; Bakala, J. Patent WO/2009/147217 A1, Dec 10, 2009.

(4) (a) Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569. (b) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344. (c) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. - Eur. J.* **2010**, *16*, 14232. (d) Song, S.; Zhu, S.−F.; Yu, Y.−B.; Zhou, Q.−L. *Angew. Chem., Int. Ed.* **2013**, *52*, 1556. (e) Besset, T.; Gramage-Doria, R.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 8795. (f) Bess, E. N.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 646. (g) Qu, B.; Samankumara, L. P.; Ma, S.; Fandrick, K. R.; Desrosiers, J.-N.; Rodriguez, S.; Li, Z.; Haddad, N.; Han, Z. S.; McKellop, K.; Pennino, S.; Grinberg, N.; Gonnella, N. C.; Song, J. J.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 14428.

(5) Wang, Z.; Ai, F.; Wang, Z.; Zhao, W.; Zhu, G.; Lin, Z.; Sun, J. *J. Am. Chem. Soc.* **2015**, *137*, 383.

(6) (a) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897. (b) Bell, S.; Wüstenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, *311*, 642. (c) Perry, M. C.; Cui, X. H.; Powell, M. T.; Hou, D. R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113. (d) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995. (e) Coll, M.; Pàmies, O.; Diéguez, M. *Chem. Commun.* **2011**, *47*, 9215. (f) Rageot, D.; Woodmansee, D. H.; Pugin, B.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 9598. (g) Qu, B.; Samankumara, L. P.; Savoie, J.; Fandrick, D. R.; Haddad, N.; Wei, X.; Ma, S.; Lee, H.; Rodriguez, S.; Busacca, C. A.; Yee, N. K.; Song, J. J.; Senanayake, C. H. *J. Org. Chem.* **2014**, *79*, 993. (h) Busacca, C. A.; Qu, B.; Grět, N.; Fandrick, K. R.; Saha, A. K.; Marsini, M.; Reeves, D.; Haddad, N.; Eriksson, M.; Wu, J.-P.; Grinberg, N.; Lee, H.; Li, Z.; Lu, B.; Chen, D.; Hong, Y.; Ma, S.; Senanayake, C. H. *Adv. Synth. Catal.* **2013**, *355*, 1455.

(7) Shapley, J. R.; Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 2816.

(8) (a) Gruber, S.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 1896. (b) Brandt, P.; Hedberg, C.; Andersson, P. G. *Chem. - Eur. J.* **2003**, *9*, 339.

(9) (a) Morris, R. H. *Acc. Chem. Res.* **2015**, *48*, 1494−1502. (b) Chirik, P. J. *Acc. Chem. Res.* **2015**, *48*, 1687.

(10) Hirsekorn, K. F.; Hulley, E. B.; Wolczanski, P. T.; Cundari, T. R. *J. Am. Chem. Soc.* **2008**, *130*, 1183.

(11) (a) Yu, R. P.; Darmon, J. M.; Hoyt, J. M.; Margulieux, G. W.; Turner, Z. R.; Chirik, P. J. *ACS Catal.* **2012**, *2*, 1760. (b) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13794. (c) Bart, S. C.; Hawrelak, E. J.; Lobkovsky, E.; Chirik, P. J. *Organometallics* **2005**, *24*, 5518.

(12) Ohgo, Y.; Takeuchi, S.; Natori, Y.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2124.

(13) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 60.

(14) Corma, A.; Iglesias, M.; del Pino, C.; Sánchez, F. *J. Organomet. Chem.* **1992**, *431*, 233.

(15) Nindakova, L. O.; Shainyan, B. A.; Shmidt, F. K. *Russ. J. Org. Chem.* **2004**, *40*, 973.

(16) Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, M. T.; Chirik, P. J. *Science* **2013**, *342*, 1076.

(17) Friedfeld, M. R.; Margulieux, G. W.; Schaefer, B. A.; Chirik, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 13178.

(18) (a) Small, B. L.; Brookhart, M.; Bennett, A. M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4049. (b) Britovsek, G. J. P.; Bruce, M.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; Mastroianni, S.; McTavish, S. J.; Redshaw, C.; Solan, G. A.; Strömberg, S.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 8728.

(19) Small, B. L. *Acc. Chem. Res.* **2015**, *48*, 2599.

(20) Flisak, Z.; Sun, W.-H. *ACS Catal.* **2015**, *5*, 4713.

(21) (a) Obligacion, J. V.; Chirik, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 19107−19110. (b) Zhang, L.; Zuo, Z.; Leng, X.; Huang, Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 2696.

(22) Obligacion, J. V.; Neely, J. M.; Yazdani, A. N.; Pappas, I.; Chirik, P. J. *J. Am. Chem. Soc.* **2015**, *137*, 5855.

(23) Schmidt, V. A.; Hoyt, J. M.; Margulieux, G. W.; Chirik, P. J. *J. Am. Chem. Soc.* **2015**, *137*, 7903.

(24) Atienza, C. C. H.; Diao, T.; Weller, K. J.; Nye, S. A.; Lewis, K. M.; Delis, J. G. P.; Boyer, J. L.; Roy, A. K.; Chirik, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 12108.

(25) Bianchini, C.; Mantovani, G.; Meli, A.; Migliacci, F.; Zanobini, F.; Laschi, F.; Sommazzi, A. *Eur. J. Inorg. Chem.* **2003**, *2003*, 1620.

(26) Monfette, S.; Turner, Z. R.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 4561.

(27) The absolute configurations of the products were incorrectly assigned in the initial communication. The correct enantiomers are shown here and in ref 32.

(28) (a) Zhang, L.; Zuo, Z. Q.; Wan, X. L.; Huang, Z. *J. Am. Chem. Soc.* **2014**, *136*, 15501. (b) Chen, J.; Xi, T.; Ren, X.; Cheng, B.; Guo, J.; Lu, Z. *Org. Chem. Front.* **2014**, *1*, 1306. (c) Chen, J.; Xi, T.; Lu, Z. *Org. Lett.* **2014**, *16*, 6452.

(29) Chen, J. H.; Cheng, B.; Cao, M. Y.; Lu, Z. *Angew. Chem., Int. Ed.* **2015**, *54*, 4661.

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314−3324

(30) (a) Guo, J.; Chen, J.; Lu, Z. *Chem. Commun.* **2015**, *51*, 5725. (b) Zuo, Z.; Zhang, L.; Leng, X.; Huang, Z. *Chem. Commun.* **2015**, *51*, 5073.
(31) Knijnenburg, Q.; Horton, A. D.; van der Heijden, H.; Kooistra, T. M.; Hetterscheid, D. G.H.; Smits, J. M.M.; de Bruin, B.; Budzelaar, P. H.M.; Gal, A. W. *J. Mol. Catal. A: Chem.* **2005**, *232*, 151.
(32) Hopmann, K. H. *Organometallics* **2013**, *32*, 6388.
(33) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746.
(34) (a) Gridnev, I. D.; Imamoto, T. *ACS Catal.* **2015**, *5*, 2911. (b) Etayo, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, *42*, 728. (c) Ager, D. J.; de Vries, A. H. M.; de Vries, J. G. *Chem. Soc. Rev.* **2012**, *41*, 3340. (d) Fabrello, A.; Bachelier, A.; Urrutigoity, M.; Kalck, P. *Coord. Chem. Rev.* **2010**, *254*, 273. (e) Johnson, N. B.; Lennon, I. C.; Moran, P. H.; Ramsden, J. A. *Acc. Chem. Res.* **2007**, *40*, 1291. (f) Rubin, A. E.; Tummala, S.; Both, D. A.; Wang, C. C.; Delaney, E. J. *Chem. Rev.* **2006**, *106*, 2794. (g) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37*, 633.
(35) (a) Bohlmann, F.; Zdero, C.; Robinson, H.; King, R. M. *Phytochemistry* **1979**, *18*, 1675. (b) Tietze, L. F.; Raschke, T. *Liebigs Ann.* **1996**, *1996*, 1981.
(36) Schneider, M. R.; Schiller, C. D. *Arch. Pharm.* **1990**, *323*, 17.
(37) (a) Elcock, F. J.; Deag, E.; Roberts, R. A.; Chipman, J. K. *Toxicol. Sci.* **2000**, *56*, 86. (b) Sallustio, B. C.; Nunthasomboon, S.; Drogemuller, C. J.; Knights, K. M. *Toxicol. Appl. Pharmacol.* **2000**, *163*, 176. (c) Chevalier, S.; Roberts, R. A. *Carcinogenesis* **1999**, *20*, 1209. (d) Furukawa, K.; Numoto, S.; Furuya, K.; Furukawa, N. T.; Williams, G. W. *Cancer Res.* **1985**, *45*, 5011. (e) Mogilenko, D. A.; Dizhe, E. B.; Shavva, V. S.; Lapikov, I. A.; Orlov, S. V.; Perevozchikov, A. P. *Biochemistry* **2009**, *48*, 11950.
(38) (a) Schrems, M. G.; Pfaltz, A. *Chem. Commun.* **2009**, 6210. (b) Woodmansee, D. H.; Müller, M.-A.; Neuburger, M.; Pfaltz, A. *Chem. Sci.* **2010**, *1*, 72. (c) Mazuela, J.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2013**, *355*, 2569. (d) Margalef, J.; Caldentey, X.; Karlsson, E. A.; Coll, M.; Mazuela, J.; Pàmies, O.; Diéguez, M.; Pericàs, M. A. *Chem. - Eur. J.* **2014**, *20*, 12201.
(39) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.
(40) Whitesides, G. M.; Gaasch, J. F.; Stedronsky, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 5258.
(41) (a) Knijnenburg, Q.; Hetterscheid, D.; Kooistra, T. M.; Budzelaar, P. H. M. *Eur. J. Inorg. Chem.* **2004**, *2004*, 1204. (b) Humphries, M. J.; Tellmann, K. P.; Gibson, V. C.; White, A. J. P.; Williams, D. J. *Organometallics* **2005**, *24*, 2039. (c) Bowman, A. C.; Milsmann, C.; Bill, E.; Lobkovsky, E.; Weyhermüller, T.; Wieghardt, K.; Chirik, P. J. *Inorg. Chem.* **2010**, *49*, 6110. (d) Bart, S. C.; Chlopek, K.; Bill, E.; Bouwkamp, M. W.; Lobkovsky, E.; Neese, F.; Wieghardt, K.; Chirik, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 13901. (e) Knijnenburg, Q.; Gambarotta, S.; Budzelaar, P. H. M. *Dalton Trans.* **2006**, 5442.
(42) Bowman, A. C.; Milsmann, C.; Atienza, C. C. H.; Lobkovsky, E.; Wieghardt, K.; Chirik, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 1676.
(43) Gibson, V. C.; Tellmann, K. P.; Humphries, M. J.; Wass, D. F. *Chem. Commun.* **2002**, 2316.
(44) In the recovered ligand, deuterium is observed in the isopropyl methyl groups of the aryl imine (see SI).

DOI: 10.1021/jacs.5b10148
J. Am. Chem. Soc. 2016, 138, 3314−3324