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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b13876 • Publication Date (Web): 16 Feb 2020

Cobalt-Catalyzed Asymmetric Hydrogenation of *α*, *β*-Unsaturated Carboxylic Acids by Homolytic H_2 Cleavage

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ABSTRACT: The asymmetric hydrogenation of *α*, *β*-unsaturated carboxylic acids using readily prepared bis(phosphine) cobalt(0) 1,5-cyclooctadiene precatalysts is described. Di-, tri- and tetra-substituted acrylic acid derivatives with various substitution patterns as well as *dehydro-α*-amino acid derivatives were hydrogenated with high yields and enantioselectivities, affording chiral carboxylic acids including Naproxen, (*S*)-Flurbiprofen and a D-DOPA precursor. Turnover numbers of up to 200 were routinely observed. Compatibility with common organic functional groups was observed with the reduced cobalt(0) precatalysts, and protic solvents such as methanol and isopropanol were identified as optimal. A series of bis(phosphine) cobalt(II) bis(pivalate) complexes, which are structural analogs of the state-of-the-art ruthenium(II) catalysts, were synthesized, characterized and proved catalytically competent. X-band EPR experiments revealed bis(phosphine)cobalt(II) bis(carboxylate)s were generated in catalytic reactions and were identified as catalyst resting states. Isolation and characterization of a cobalt(II)-substrate complex from a stoichiometric reaction suggests that alkene insertion into the cobalt hydride occurred in the presence of free carboxylic acid, producing the same alkane enantiomer as from the catalytic reaction. Deuterium labeling studies established homolytic H_2 (or D_2) activation by Co(0) and *cis* addition of H_2 (or D_2) across alkene double bonds, reminiscent of rhodium(I) catalysts but distinct from ruthenium(II) and nickel(II) carboxylates that operate by heterolytic H_2 cleavage pathways.

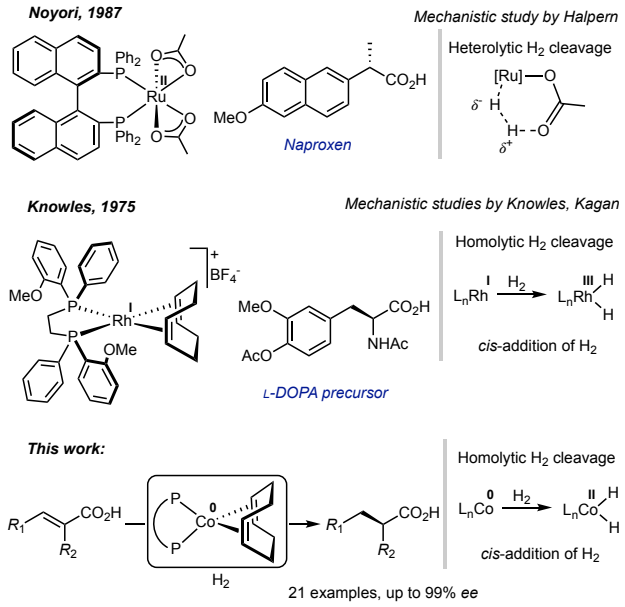
INTRODUCTION

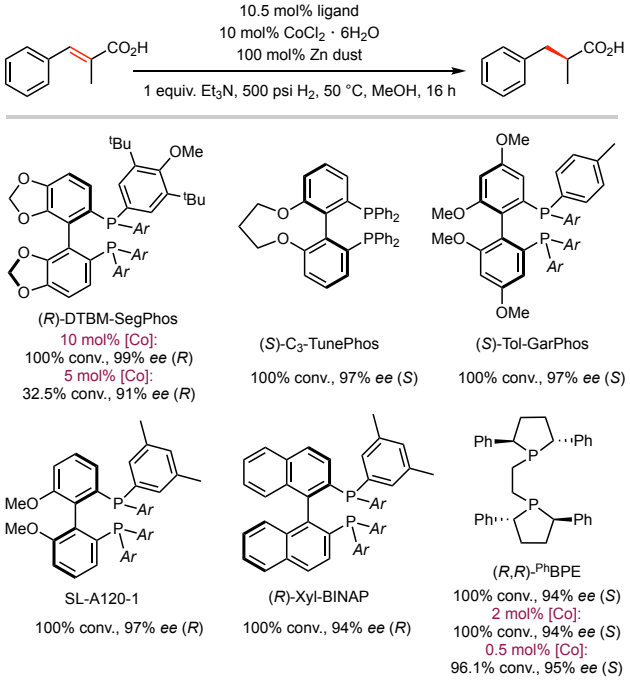
Transition metal-catalyzed asymmetric hydrogenation is one of the most efficient and powerful methods for the preparation of single enantiomer compounds.[1] Catalysis with second- and third-row transition metals such as Rh, Ru and Ir has witnessed widespread applications in the pharmaceutical, flavor and fragrance, agrochemical and fine chemical industries.[2] There has been a growing interest in the discovery of first-row transition metal catalysts and significant advances have been made in recent years.[3] In addition to benefits from high terrestrial abundance and cost, advantages of first-row metal catalysts include unique mechanisms of operation and in certain cases superior activity, stereoselectivity and solvent profile.[4] A salient example is the asymmetric synthesis of levetiracetam, a medication for epilepsy that was prepared by cobalt-catalyzed asymmetric hydrogenation on 200 gram scale with 0.08 mol% catalyst loading in methanol solvent.[5]

Asymmetric hydrogenation or transfer hydrogenation of prochiral alkenes with cobalt and nickel catalysts has recently been established with various classes of substrates, including minimally functionalized alkenes,[6] unsaturated esters,[7] enamides[5, 6b, 8] and related derivatives.[9] Unsaturated carboxylic acids are another common class of substrates[10] and rhodium-catalyzed asymmetric hydrogenation of *dehydro*-amino acids is among the earliest and most impactful examples of asymmetric catalysis with transition metals.[1b,11] Ruthenium[1c,12] and iridium catalysts[13] have also been extensively studied and have provided access to structurally diverse chiral carboxylic acids including pharmaceuticals such as L-DOPA,[11] Pregabalin[14] and numerous other examples.[15]

Our laboratory has recently reported well-defined four-coordinate bis(phosphine) cobalt(0) 1,5-cyclooctadiene(COD) complexes[5,16a] that exhibit high activity at 60 psi of H_2 for the directed hydrogenation of hydroxyl-alkenes[16] and the asymmetric hydrogenation of enamides.[5] Despite the typical sensitivity of many first-row transition metal alkene hydrogenation catalysts to air and water, protic solvents such as methanol, ethanol and trifluoroethanol were discovered as the optimal reaction medium for catalyst activity, an unusual feature considering the anticipated reducing nature of the cobalt(0) precatalysts and basicity of the related cobalt hydride and cobalt alkyl species.[5,8a,16] High-throughput experimentation (HTE) demonstrated the versatility of the *in situ* zinc reduction method in methanol as almost *all* 192 chiral bidentate ligands in the library in combinations with $CoCl_2{\cdot}6(H_2O)$ produced quantitative conversion for the hydrogenation of methyl 2-acetamidoacrylate.[5] Given this remarkable performance, extension of this method to other important classes of alkenes was pursued. Here we describe the discovery of a versatile class of enantiopure bis(phosphine) cobalt precatalysts that promote the asymmetric hydrogenation of a host of *α*, *β*-unsaturated carboxylic acids. Structurally diverse di-, tri- and tetra-substituted unsaturated acids and *dehydro-α*-amino acid derivatives were all well tolerated and underwent hydrogenation to afford chiral carboxylic acids in high yields and enantiomeric excesses (*ee*). Deuterium labeling studies support homolytic H_2 cleavage by cobalt(0), a mechanistic diversion from nickel and ruthenium carboxylates where heterolytic, solvent-assisted pathways are operative (**Scheme 1**).

Scheme 1. Ruthenium, Rhodium and Cobalt-Catalyzed Asymmetric Hydrogenation of *α*, *β*-Unsaturated Carboxylic Acids and H_2 Activation Pathways.





RESULTS AND DISCUSSION

Asymmetric hydrogenation of 1,1-disubstituted, trisubstituted and tetra-substituted *α, β*-unsaturated carboxylic acids. An initial HTE study was conducted using (*E*)-*α*-Me-cinnamic acid (**3a**) as a representative substrate for identification of optimal cobalt-ligand combinations. Because of the potentially higher metal coordination affinity of carboxylate anions than free carboxylic acids,[10] a stoichiometric amount of the weak base Et_3N was pre-mixed with **3a** in initial experiments. In a typical experiment, incubation of ligands and $CoCl_2 \cdot (H_2O)_6$ followed by zinc reduction and solvent removal generated active cobalt precatalysts across a 96 well plate. A methanol solution containing an equimolar of Et_3N and **3a** was then dispensed into the 96 well plate, and the reaction vessel was pressurized with 500 psi of H_2 and heated to 50 °C for 16 hours. Analysis of the corresponding saturated carboxylic acid products by supercritical fluid chromatography (SFC) identified that among a library of 192 chiral bidentate ligands, bidentate, axial chiral tris(aryl) phosphines generated particularly enantioselective cobalt catalysts using the zinc-methanol activation protocol (**Scheme 2**, see Supporting Information, Figures S20-S32 for HTE results). For example, air-stable (*R*)-DTBM-SegPhos ((*R*)-(-)-5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole) which produces a highly sterically encumbered environment around the metal center and has been applied extensively in asymmetric copper catalysis,[17] formed an active cobalt catalyst that hydrogenated **3a** in 99% *ee*. The bis(phospholane) (*R,R*)-^{Ph}BPE(1,2-bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane), which has established coordination chemistry with cobalt in promoting highly active and enantioselective asymmetric hydrogenation,[5] was among the most active for hydrogenation of **3a**. Subsequent catalyst loading studies identified (*R,R*)-^{Ph}BPE as the ligand responsible for generating the most active cobalt catalyst with loadings as low as 0.5 mol%. As such, this ligand was selected for additional studies using preformed catalysts, exploration of substrate scope and mechanistic studies.

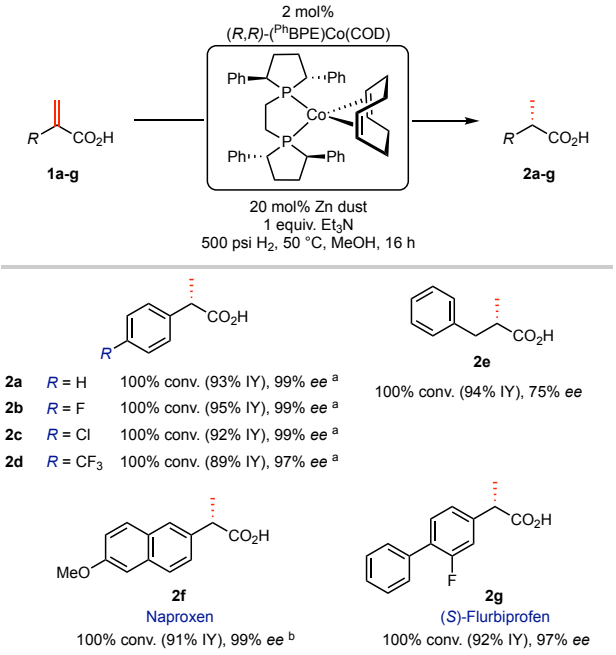
Scheme 2. Chiral Bidentate Ligands Identified by HTE that Produced the Highest Enantioselectivities for Hydrogenation of (*E*)-*α*-Me-Cinnamic Acid.

Our previous studies have established that bis(phosphine) cobalt(0) 1,5-cyclooctadiene (COD) compounds are straightforward to prepare from zinc reduction of the corresponding cobalt(II) dihalide precursors and are effective organometallic precatalysts for asymmetric alkene hydrogenation, even in methanol solvent.[5] In addition, the cobalt(0) precatalysts were highly active at lower pressure (60 psi) of H_2, unlike neutral cobalt(I) chloride-bridged precatalysts such as $[P_2Co(\mu\text{-}Cl)]_2$ (P_2 = (*R,R*)-^{Ph}BPE or (*R,R*)-^{iPr}DuPhos); (*R,R*)-^{iPr}DuPhos = 1,2-bis((2*R*,5*R*)-2,5-diisopropylphospholano)benzene), where unfavorable chloride coordination equilibria require higher pressure (500 psi) of H_2 to access the active catalyst.

Using 2 mol% of preformed (*R,R*)-(^{Ph}BPE)Co(COD), synthesized from zinc reduction of (*R,R*)-(^{Ph}BPE)$CoCl_2$ in the presence of excess COD,[5] 2-phenylacrylic acid (**1a**) was successfully hydrogenated with 500 psi of H_2 and the saturated carboxylic acid **2a** was obtained in >99% conversion and 99% *ee* favoring the (*S*) enantiomer (**Scheme 3**). Although (*R,R*)-(^{Ph}BPE)Co(COD) was a competent single-component precatalyst without additional reductant, excess Zn dust was used in substrate scope studies as improved performance was observed, similar to ruthenium catalysis.[12] Quantitative conversions and excellent (97-99%) enantiomeric excesses were also obtained upon introduction of fluoro-, chloro- and trifluoromethyl substituents (**1b-1d**) at the 4-position of phenyl ring. These high levels of activity and enantioinduction were maintained with **1a-1d** when the catalyst loading was dropped from 2 to 0.5 mol%. With the benzylated substrate **1e**, complete conversion and a slightly reduced *ee* of 75% was obtained. Catalytic activity was observed at 60 psi of H_2 although 500 psi was used to obtain optimal performance in scope studies.

The anti-inflammatory drug, Naproxen, **2f** was also obtained in quantitative conversion and 99% *ee* ((*S*) enantiomer) from hydrogenation of **1f**. Enantioenriched Flurbiprofen (**2g**) was obtained in a similar manner with >99% conversion and 97% *ee*. While the synthesis of Naproxen and (*S*)-Flurbiprofen by asymmetric hydrogenation of **1f** and **1g** is well established with Ru, Rh and Ir catalysts,[12a,18] the current examples using (*R,R*)-(^{Ph}BPE)Co(COD) represents the first highly enantioselective synthesis with a first-row transition metal catalyst.

Scheme 3. Asymmetric Hydrogenation of 1,1-Disubstituted *α, β*-Unsaturated Carboxylic Acids.

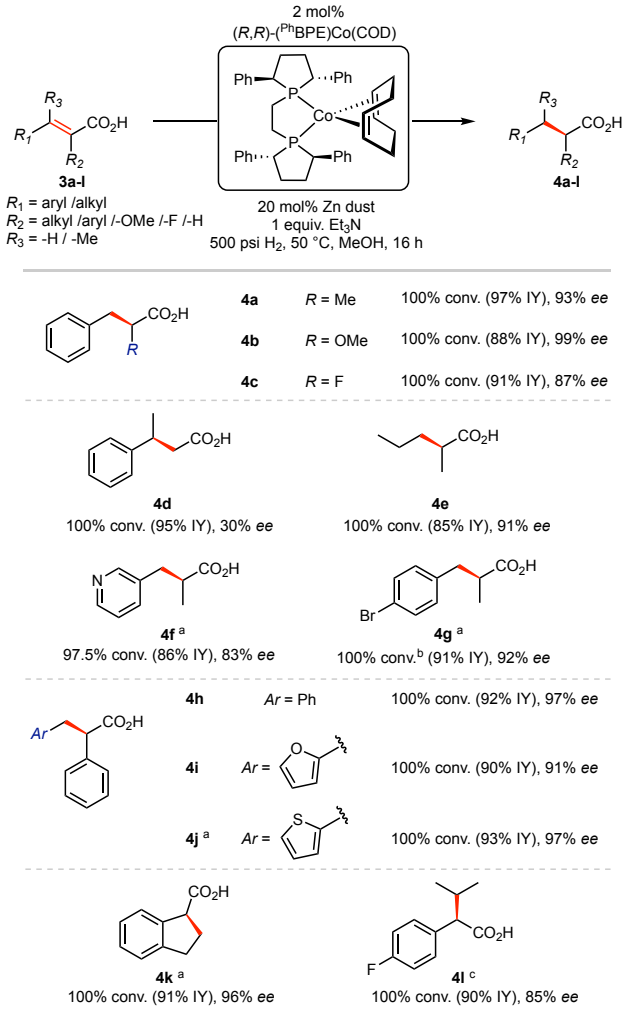


2 mol% catalyst loading, 0.5 mmol substrates were used unless otherwise noted. % conv. and %*ee* were determined by chiral SFC analysis. IY = isolated yield. Bonds highlighted in red are the C=C bonds that were reduced. a. 0.5 mol% catalyst loading, 1.0 mmol substrates were used. b. The absolute (*S*) configuration was assigned with an authentic sample.

The hydrogenation of more hindered, tri-substituted *α, β*-unsaturated carboxylic acids was also studied using 2-5 mol% (*R,R*)-(^{Ph}BPE)Co(COD) as the precatalyst (**Scheme 4**). When the *α*-substituent of substrate **3a** used in initial HTE studies was changed from methyl to a more electron donating methoxy group, full conversion to the enantioenriched acid **4b** was obtained with an increase in *ee* from 93 to 99%. Substrate **3c** with an electron-withdrawing *α*-fluoro substituent was also successfully hydrogenated to afford the chiral *α*-fluoro acid **4c** product in quantitative conversion and 87% *ee* with no evidence for formation of the defluorination product. The transition metal-catalyzed asymmetric hydrogenation of alkenyl fluorides is a potentially powerful method to access otherwise challenging-to-prepare enantioenriched organofluorine compounds.[19] However, intermediate metal alkyl compounds with *α* or *β*-fluorine substituents generated from insertion of an alkenyl fluoride into metal hydrides are prone to fluoride elimination, formation of metal-fluorides and ultimately catalyst deactivation.[19a,b,e, 20] The clean preparation of **4c** with the cobalt(0) precatalyst demonstrates the faster rate of C=C reduction as compared to competing defluorination.

The *β*-Me substituted cinnamic acid (**3d**) was hydrogenated to complete conversion to **4d** with only 30% *ee*, likely originating from different alkene insertion preferences for *α*- versus *β*-Me-substituted substrates. Likewise, attempts to hydrogenate the ethyl ester of **3a** under optimized conditions furnished only 28% conversion in toluene; lower conversions were observed in alcohol solvents. The cobalt-catalyzed method was not limited to aryl-substituted alkenes as the aliphatic acid, **3e** underwent hydrogenation with 2 mol% of (*R,R*)-(^{Ph}BPE)Co(COD) as the precatalyst to >99% conversion and 91% *ee*. Traditionally, this has been a challenging class of substrate to hydrogenate with high enantioselectivity, owing to the relative similarity of the alkene substituents rendering facial selectivity difficult.[10] Functional groups such as a pyridine and an aryl bromide that are typically poisons for reducing first-row metal catalysts were well-tolerated, affording the corresponding enantioenriched carboxylic acids in 83% (**4f**) and 92% *ee* (**4g**), respectively. The 1,2-diaryl substituted substrates, **3h**, **3i** and **3j**, with extended π-conjugation of the alkene, were also hydrogenated with excellent enantioselectivities. Thiophene substitution (**3j**) was well tolerated and the chiral acid (**4j**) was obtained in 97% *ee*. The indene-derived acid (**3k**) was hydrogenated with complete conversion and 96% *ee*. Tetra-substituted unsaturated acid **3l**, a sterically-hindered and challenging class of substrate for transition metal-catalyzed hydrogenation,[21] was previously hydrogenated with Ru, Rh and Ir catalysts to afford the key chiral building block for Mibefradil, a calcium antagonist.[22] With a higher loading(10 mol%) and elevated pressure (750 psi), the enantioenriched carboxylic acid (**4l**) was obtained with complete conversion and 85% *ee*.

Scheme 4. Asymmetric Hydrogenation of Tri- and Tetra-Substituted *α, β*-Unsaturated Carboxylic Acids.



2 mol% catalyst loading, 0.5 mmol substrates were used unless otherwise noted. % conv. and %*ee* were determined by SFC. Bonds highlighted in red are the C=C bonds that were reduced. a. 5 mol% catalyst

loading was used. b. 96.5% conv. to desired product, 3.5% conv. to debromination product. c. 10 mol% catalyst loading, 750 psi H_2.

With the cobalt(0) precatalyst, (*R,R*)-(^{Ph}BPE)Co(COD), hydrogenation of an array of tri- and tetra-substituted unsaturated acids(**3a-l**) with distinct structural features was achieved with good to excellent enantioselectivities. One class of alkenes of particular interest is *dehydro-a*-amino acids as these substrates were Knowles' pioneering examples in the development of rhodium-catalyzed asymmetric hydrogenation leading to a commercial route to L-DOPA.[11] Motivated by this historical precedent, the hydrogenation of (*Z*)-*dehydro-N*-acetyl-(4-acetoxy-3-methoxy)phenylalanine (**5b**) was explored with well-defined organometallic cobalt precatalysts. With 10 mol% of (*R,R*)-(^{Ph}BPE)Co(COD) and 500 psi of H_2, complete conversion was observed but the *ee* was only 9%. With another readily prepared cobalt(0) precatalyst, (*R,R*)-(^{iPr}DuPhos)Co(COD)[5] under the same catalytic conditions, the *ee* improved to 65%. To accelerate discovery of more optimal ligands, HTE was conducted with the 192 chiral ligand library. From this evaluation, the P-stereogenic ligand, (*R,R*)-1,2-Bis(t-butylmethylphosphino)benzene ((*R,R*)-BenzP*) emerged as optimal for promoting the enantioselective hydrogenation with >99% conversion and 97% *ee* (*R*) for formation of **6b**.

The success of the BenzP* ligand in cobalt-catalyzed asymmetric hydrogenation prompted synthesis of a well-defined cobalt(0) organometallic precursor. Reduction of (*R,R*)-(BenzP*)$CoCl_2$ with zinc in the presence of 1,5-cyclooctadiene followed by extraction with n-pentane resulted in isolation of (*R,R*)-(BenzP*)Co(COD) as a brown solid in 62% yield. The solid-state structure was determined by X-ray diffraction (**Figure 1**) and best described as an idealized tetrahedral geometry at cobalt. The X-band EPR spectrum of the compound in toluene glass (**Figure 2**) exhibits diagnostic hyperfine coupling of g_x tensor to the ^{59}Co nucleus (I = 7/2, 100% natural abundance) similar to other reported P_2Co(COD) complexes.[5, 16a]

Because transesterification of the acetoxy group of **5b** and **6b** with MeOH was observed in the presence of stoichiometric Et_3N used in the HTE study, the hydrogenation reactions were repeated in isopropanol to avoid modification of the substrate and product during the course of the reaction and **6b** was generated in >99% conversion and 99% *ee* (**Scheme 5**). Likewise, hydrogenation of the parent phenyl substrate, **5a** also proceeded with complete conversion and 99% *ee*.

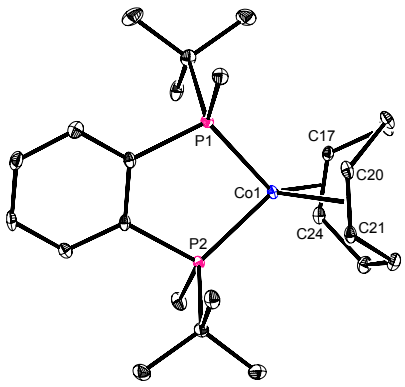


Figure 1. Solid-state structure of (*R,R*)-(BenzP*)Co(COD) at 30% probability ellipsoids with hydrogen atoms omitted for clarity. Selected bond distances(angstrom): Co1–C17, 2.062(5), Co1–C20, 2.114(5), Co1–C21, 2.141(5), Co1–C24, 2.048(4), C20–C21, 1.386(6), C17–C24, 1.409(7).

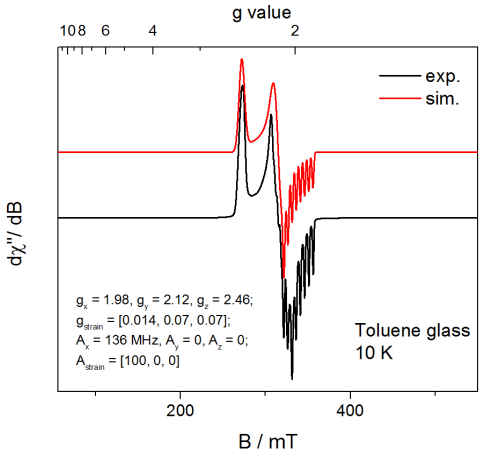
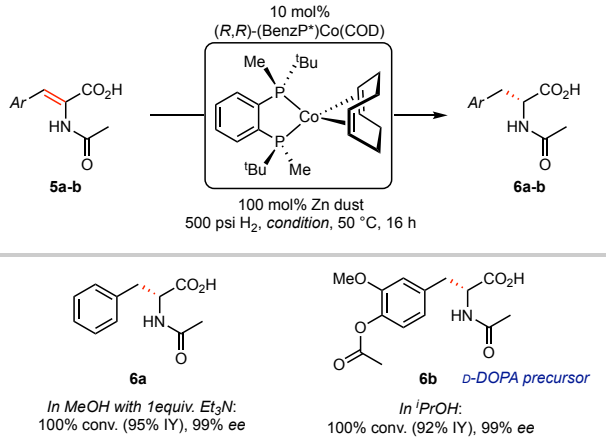


Figure 2. X-band EPR Spectrum of (*R,R*)-(BenzP*)Co(COD) Recorded in Toluene Glass at 10 K. Microwave frequency = 9.38 GHz, power = 0.02 mW and modulation amplitude = 0.4 mT/100 kHz. Simulation of EPR signal supports an $S = ½$ ground state. Simulation parameters: $g_x = 1.98$, $g_y = 2.12$, $g_z = 2.46$, $g_{strain} = [0.014, 0.07, 0.07]$, $A_x = 136$ MHz, $A_y = 0$, $A_z = 0$, $A_{strain} = [100, 0, 0]$.

Scheme 5. Asymmetric Hydrogenation of *Dehydro-a*-Amino Acid Derivatives.



% conv. and %*ee* were determined by SFC. Bonds highlighted in red are the C=C bonds that were reduced. Absolute configuration(*R*) of **6a** was established with authentic sample.

Synthesis, characterization and hydrogenation activity of bis(phosphine)cobalt(II) bis(carboxylate) complexes. Ruthenium(II) carboxylate catalysts, exemplified by those pioneered by Noyori such as (BINAP)$Ru(O_2CR)_2$, are state-of-the-art for the asymmetric hydrogenation of *a, β*-unsaturated acids.[12a, 23] Isotopic labeling studies with H_2 gas and deuterated alcohol solvents support a heterolytic cleavage pathway for the activation of H_2.[24] The ruthenium carboxylate is capable of splitting dihydrogen into a proton and a ruthenium hydride. Hydride insertion and protonolysis with alcohol solvent result in formation of the corresponding alkane.[24]

Because interaction of reduced bis(phosphine) cobalt complexes and cobalt hydride species with carboxylic acids were postulated to form cobalt carboxylates driven by formation of strong cobalt-oxygen bonds, independent syntheses of bis(phosphine)Co(II) bis(carboxylate) compounds was pursued. Motivation for these studies included identification of spectroscopic handles for translation onto potential catalytically relevant intermediates and to de-

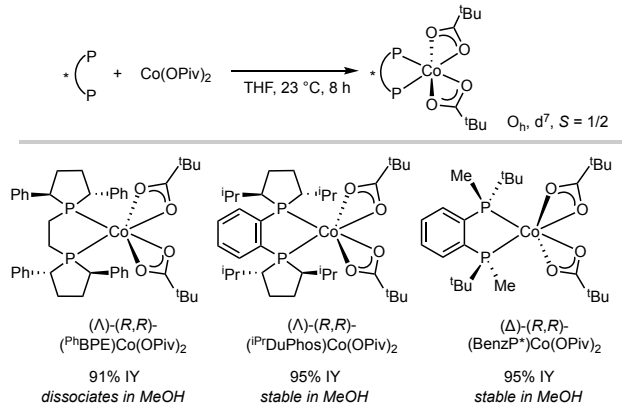
termine their catalytic competency. Cobalt(II) bis(pivalate) was used as the metal source given that it is readily prepared and has proven successful as a precursor for molecular catalysts in alkene hydrosilylation, hydroboration and C(sp^2)–H borylation.[25]

Three cobalt(II) pivalate complexes, (*R,R*)-(^{Ph}BPE) Co(OPiv)$_2$, (*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$ and (*R,R*)-(BenzP*)Co(OPiv)$_2$ were targeted due to the established roles of the bis(phosphines) in promoting enantioselective hydrogenation of the *α, β*-unsaturated acids. Each complex was prepared and isolated as a red crystalline solid in high yield following addition of the free phosphine to a THF slurry of Co(OPiv)$_2$ (**Scheme 6A**). The solid-state structure of each compound was determined by X-ray diffraction and the geometry about cobalt in each case is best described as idealized octahedral (**Figure 3**). Helical chirality resulting from the two κ^2-pivalate was identified to be (Λ)-configuration for (*R,R*)-^{Ph}BPE and (*R,R*)-^{iPr}DuPhos complexes, while (*R,R*)-(BenzP*)Co(OPiv)$_2$ adopts the (Δ)-configuration, likely results from minimizing steric interactions with the chiral ligand backbone.

For (*R,R*)-(^{Ph}BPE)Co(OPiv)$_2$, a benzene-d_6 solution magnetic moment of 1.7(1) μB was measured at 298 K, consistent with one unpaired electron. Accordingly, the X-band EPR spectrum of the compound recorded in THF glass at 10 K exhibits a rhombic signal that upon simulation has parameters consistent with a low-spin, S = 1/2 cobalt(II) compound (Figure S13). Similar magnetic and EPR spectroscopic data was obtained for both (*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$ and (*R,R*)-(BenzP*)Co(OPiv)$_2$, establishing that the bis(phosphine)s impart a sufficiently strong ligand field to enable low-spin cobalt(II). The EPR spectra of P$_2$Co(OPiv)$_2$ complexes exhibit hyperfine coupling to ^{59}Co (I=7/2, 100% natural abundance) and both ^{31}P (I=1/2, 100% natural abundance) nuclei (**Figures 4**, S11-S14).

Because previous studies from our laboratory have demonstrated the substitutional lability of bis(phosphines) such as (*R,R*)-^{Ph}BPE and (*R,R*)-^{iPr}DuPhos in cobalt(II) dihalide complexes in methanol solution,[5,8a] each of the corresponding bis(pivalate) derivatives were dissolved in a 1:1 THF:CH$_3$OH mixture and analyzed by EPR spectroscopy to probe for the formation of high-spin (S = 3/2) cobalt(II) solvento complexes. The EPR spectra of (*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$ and (*R,R*)-(BenzP*)Co(OPiv)$_2$ remained nearly unchanged in 1:1 THF:MeOH as compared to neat THF with no evidence for formation of high-spin complexes (**Figures 4** and S12). For (*R,R*)-(^{Ph}BPE)Co(OPiv)$_2$, however, disappearance of the starting S=1/2 complex and complete conversion to the S = 3/2 [Co(MeOH)$_6$]$^{2+}$ 2[OPiv]$^-$ solvento complex was observed (Figure S14). These observations demonstrate strong ligand dependency on substitutional lability of the Co(II) complexes in MeOH solution.

Scheme 6. Co(OPiv)$_2$ as a General Precursor for Synthesizing P$_2$Co(OPiv)$_2$ Complexes; Ligand-Dependent Substitutional Lability of P$_2$Co(OPiv)$_2$ in MeOH.



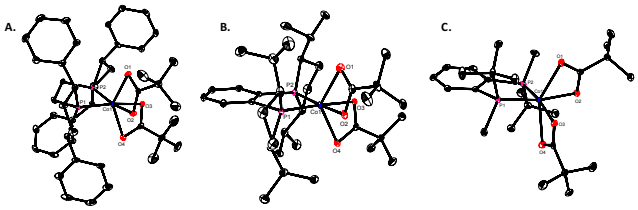


Figure 3. Solid State Structure of A. (Λ)-(*R,R*)-^{Ph}BPE)Co(OPiv)$_2$ B. (Λ)-(*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$ C. (Δ)-(*R,R*)-(BenzP*)Co(OPiv)$_2$ at 30% Probability Ellipsoids with H Atoms Omitted for Clarity.

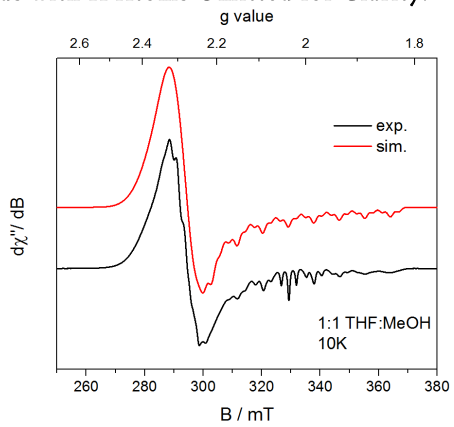
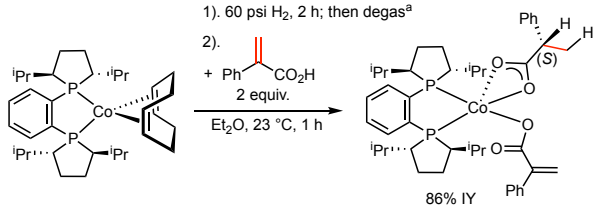


Figure 4. X-band EPR Spectrum of (*R,R*)-(BenzP*)Co(OPiv)$_2$ Recorded in 1:1 THF:MeOH Glass at 10 K. Microwave frequency = 9.38 GHz, power = 0.02 mW and modulation amplitude = 0.4 mT/100 kHz. Simulation of EPR signal supports an S = ½ ground state. Simulation parameters: g_x = 2.01, g_y = 2.27, g_z = 2.32, g_{strain} = [0.0126, 0.0510, 0.120]. $A^{Co}{}_x$ = 246 MHz, $A^{Co}{}_y$ = 0, $A^{Co}{}_z$ = 0, $A^{P1}{}_x$ = $A^{P2}{}_x$ = 80 MHz, $A^{P}{}_y$ = 0, $A^{P}{}_z$ = 0.

Having obtained the spectroscopic signatures for P$_2$Co(II)(O$_2$CR)$_2$ complexes, the generality of their formation under catalytically-relevant conditions and catalyst-substrate interactions were further explored. Exposure of ((*R,R*)-(^{iPr}DuPhos)Co(COD) in pentane solution to 60 psi H$_2$ was carried out to generate the putative cobalt(II) dihydride. Complete removal of excess H$_2$ followed by addition of two equivalents of 2-phenyl-acrylic acid (**1a**) resulted in an immediate color change from purple to red and isolation of a paramagnetic solid in 86% yield (**Scheme 7**). EPR analysis of the product exhibited a largely similar spectrum to (*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$, signaling formation of a cobalt bis(carboxylate) species (Figure S16). The solid-state structure was confirmed by X-ray crystallography as (Λ)-

(*R,R*)-(^{iPr}DuPhos)Co(κ^1-O_2C-C_8H_7)(κ^2-O_2C-C_8H_9) (**Figure 5**). Analysis of the bond distances and angles established that one of the two benzylic carbons in the cobalt-bound substrates adopts an sp^3 chiral (*S*)-configuration, arising from enantioselective hydrogenation of an alkene in **1a** and likely generated from an alkene insertion and C–H reductive elimination sequence. This result indicates insertion of alkene of the acid substrate into the cobalt–hydride was unaffected by the presence of free carboxylic acid protons.

Scheme 7. Independent Synthesis of a Catalyst-Substrate Complex, (Λ)-(*R,R*)-(^{iPr}DuPhos)Co(κ^1-O_2C-C_8H_7)(κ^2-O_2C-C_8H_9).



a. Degassed with three freeze-pump-thaw cycles.

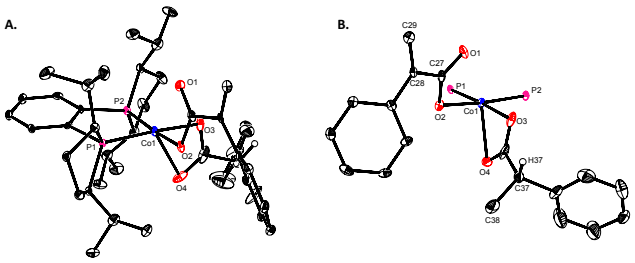
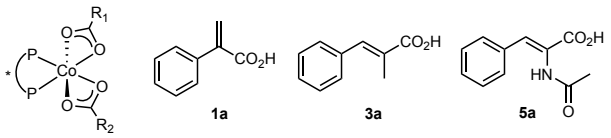


Figure 5. A. Solid State Structure of (Λ)-(*R,R*)-(^{iPr}DuPhos)Co(κ^1-O_2C-C_8H_7)(κ^2-O_2C-C_8H_9) at 30% Probability Ellipsoids with H atoms Omitted for Clarity. B. Truncated View at 30% Probability Ellipsoids with H atoms (except H37) Omitted for Clarity. Bond lengths: C28–C29 = 1.336(9) Å, C37–C38 = 1.47(2) Å, Bond angles (avg.): center at C28, 120.0(1)°, center at C37, 111.5(1)°.

To gain insight into catalyst speciation under catalytic conditions, the hydrogenation of **1a** with 10 mol% (*R,R*)-(^{iPr}DuPhos)Co(COD) or (*R,R*)-(^{Ph}BPE)Co(COD) and **5a** with 10 mol% (*R,R*)-(BenzP*)Co(COD) under 60 psi H_2 in MeOD-d_4 at 50 °C was first monitored by ^{1}H NMR spectroscopy. Because of the paramagnetism and the lack of diagnostic signals, these experiments proved largely uninformative. Because both $P_2Co(COD)$ and $P_2Co(O_2CR)_2$ compounds have distinct and diagnostic EPR signals, recording low-temperature in operando-type spectra would be useful for determining the presence or absence of these compounds. Repeating the same hydrogenations of **1a** and **5a** in MeOH under 60 psi H_2 and freezing the solution in liquid nitrogen (See Supporting Information for details) after 20 minutes reaction time revealed exclusively $P_2Co(O_2CR)_2$ signals in all three reactions with no evidence for remaining $P_2Co(COD)$ compounds (Figures S17-S19). EPR spectra of reaction aliquots after 16 hours showed no changes in the $P_2Co(O_2CR)_2$ signal. Notably, no $[Co(MeOH)_6]^{2+}$ solvento complex was observed in the (*R,R*)-(^{Ph}BPE)Co(II)$(O_2CR)_2$ spectrum, suggesting suppression of (*R,R*)-^{Ph}BPE ligand dissociation under catalytic conditions. These results indicate fast conversion of $P_2Co(COD)$ precatalysts under catalytic condition and $P_2Co(O_2CR)_2$ as an observable catalyst resting state.

The catalytic hydrogenation activity of the isolated bis(phosphine) cobalt(II) bis(carboxylate) complexes was also explored. Using 10 mol% (*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$ as a single-component catalyst under standard catalytic conditions, 2-Ph acrylic acid (**1a**) and *α*-Me cinnamic acid (**3a**) were hydrogenated in quantitative conversions in MeOH, albeit with lower *ee*s of 21 and 19% (**Scheme 8**, entries 1,2). The catalyst-substrate complex, (*R,R*)-(^{iPr}DuPhos)Co(κ^1-O_2C-C_8H_7)(κ^2-O_2C-C_8H_9), also promoted the hydrogenation of **1a** in quantitative conversion and 23% *ee* (**Scheme 8**, entry 3). With 10 mol% (*R,R*)-(BenzP*)Co(OPiv)$_2$ in CH_3OH, (*Z*)-*dehydro*-*N*-acetyl-phenylalanine (**5a**) was hydrogenated in 50% conv. and 85% *ee* (**Scheme 8**, entry 4). Using 10 mol% (*R,R*)-(^{Ph}BPE)Co(OPiv)$_2$, **1a** and **3a** were hydrogenated in 100% and 80% conv. respectively, but <5% *ee* was observed in both cases (**Scheme 8**, entry 5,6). The diminished enantioselectivity suggests that a different mechanism for enantio-induction compared to cobalt(0) precatalysts under standard catalytic conditions. Nevertheless, these results demonstrate the catalytic activity of single-component bis(phosphine)Co(II) bis(carboxylate) complexes.

Scheme 8. Evaluation of Catalytic Activities of Bis(phosphine)Cobalt Bis(carboxylate) Complexes.



Entry	Cobalt precatalyst	Substrate	Hydrogenation result
1	(*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$	**1a**	100% conv. 21% *ee*
2		**3a**	100% conv. 19% *ee*
3	P_2 = (*R,R*)-^{iPr}DuPhos $R_1 = C_8H_7$, $R_2 = C_8H_9$	**1a**	100% conv. 23% *ee*
4	(*R,R*)-(BenzP*)Co(OPiv)$_2$	**5a**	50% conv. 85% *ee*
5	(*R,R*)-(^{Ph}BPE)Co(OPiv)$_2$	**1a**	100% conv. <5% *ee*
6		**3a**	80% conv. <5% *ee*

Hydrogenation using single-component precatalysts conducted under standard catalytic conditions (50 °C, 500 psi H_2, 16 h in MeOH) with 10 mol% catalyst loading. % conv. were determined by ^{1}H NMR spectroscopy. % *ee* were determined by SFC.

Deuterium labeling studies. Mechanistic investigations of the rhodium-catalyzed asymmetric hydrogenation of *dehydro*-*α*-amino acids by Kagan[26a] and Knowles[26b] established homolytic H_2 activation by oxidative addition to cationic rhodium(I) and exclusive 1:1 deuterium incorporation into resulting alkane when D_2 gas and natural abundance CH_3OH were used. The mechanism of *cis*-$H_2(D_2)$ addition by [P_2Rh(I)] complexes to olefins also resulted in diastereospecific deuterium incorporation at the *β* position of trisubstituted acids. Recently, Zhou and coworkers reported a mechanistic study on the iridium-catalyzed asymmetric hydrogenation of unsaturated acids.[27] Interception and characterization of iridium intermediates and computational studies support a mechanism of homolytic H_2 activation by oxidative addition.

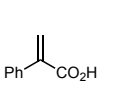
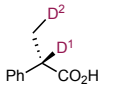
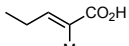
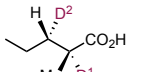
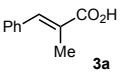
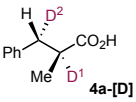
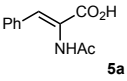
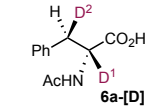
Heterolytic H_2 cleavage by metal carboxylate species is also well established for ruthenium and nickel-catalyzed asymmetric hydrogenation. Diagnostic 1:1 H:D incorporation into the resulting alkane was observed when H_2/MeOD or D_2/MeOH combinations were used, resulting from alkene insertion into metal hydride followed by metal-carbon bond protonolysis. Halpern and coworkers reported a comprehensive mechanistic study on Noyori's (BIN-

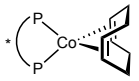
AP)Ru(O_2CR)$_2$-catalyzed asymmetric hydrogenation of tiglic acid.[24] Kinetic and deuterium labeling studies supported a pathway whereby heterolytic H_2 activation by a (BINAP)Ru(II) bis(carboxylate) generates a Ru(II) monohydride. Enantiodetermining alkene insertion forms a Ru(II) metallalactone intermediate and protonolysis of the Ru–C bond incorporates H^+/D^+ at the *β*-position of the alkene C=C bond with high diastereoselectivity. In our recent report on nickel-catalyzed asymmetric hydrogenation of *α, β*-unsaturated esters,[7a] deuterium-labeling studies also support heterolytic H_2/D_2 cleavage by a nickel acetate species. Stereoselective conjugate addition of nickel hydride and non-stereoselective protonation explain for the observed 1:1 H:D incorporation. In another study of cobalt-catalyzed hydrogenation of C=O bonds of esters/acids reported by de Bruin and coworkers, heterolytic H_2 cleavage mechanism by hydrogenolysis of "Co–O" bonds was computationally investigated.[28]

Deuterium labeling studies using 60 psi D_2 gas in natural abundance methanol were performed with 5 mol% (*R,R*)-(^{Ph}BPE)Co(COD). Using 2-Ph-acrylic acid (**1a**) as the substrate, exclusively 1,2-*d*$_2$-incorporation was observed and the deuterated product was obtained in quantitative conversion and 99% *ee* (**Scheme 9**, entry 1). Identical results were obtained when Zn or both Zn and Et_3N were excluded, suggesting the exclusive role of (*R,R*)-(^{Ph}BPE)Co(COD) in promoting homolytic D_2 cleavage (**Scheme 9**, entry 2 and 3). However, when zinc and Et_3N are present, we are unable to distinguish whether zinc carboxylates, the the ammonium carboxylate or low concentrations of the free acid are the species undergoing hydrogenation. For tri-substituted acids **3a** and **3e**, exclusively 1,2-*d*$_2$-incorporation was again observed and the products were obtained in >99% conv., 91% *ee* and 93% *ee* respectively (**Scheme 9**, entry 4 and 5). With (*R,R*)-(BenzP*)Co(COD), (*Z*)-*dehydro-N*-acetyl-phenylalanine (**5a**) was also deuterated under 60 psi D_2 with >99% conv., affording **6a** with exclusively 1,2-*d*$_2$-incorporation (**Scheme 9**, entry 6). Of the two diastereotopic *β*-positions, deuterium incorporation was confined to the position resulting from *cis*-D_2 addition, furnishing a single isotopomer similar to the deuterium labeling results with Rh.[25a] Using (*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$ and (*R,R*)-(BenzP*)Co(OPiv)$_2$ as single component catalysts, deuteration of **1a** and **5a** under 60 psi D_2 again afforded 1,2-*d*$_2$ products with 1:0.82 and 0.84:1 deuterium incorporation respectively (**Scheme 9**, entry 7 and 8).

These results support a dihydride mechanism whereby H_2 oxidative addition to Co(0) generates a transient Co(II) dihydride species.[29] Alkene insertion into Co–H bond followed by C–H reductive elimination affords 1,2-*d*$_2$ labeled alkanes. An additional D_2-labeling experiment suggests that a heterolytic H_2 cleavage pathway with P_2Co(II)(O_2CR)$_2$, where deuterium from D_2 was incorporated into solvent after prolonged heating (See *Supporting Information*, Figures S48-S50) is also operative. Nevertheless, the predominantly 1,1-*d*$_2$ labeling results using P_2Co(II)(O_2CR)$_2$ precatalysts supports a dihydride mechanism as the principal product-forming pathway, likely arising from the same active cobalt(II) dihydride generated by two H_2 heterolysis events. Attempts to detect the cobalt dihydride for the latter by *in situ* EPR experiments under 60 psi H_2 were unsuccessful owing to strong interference of the starting Co(II) bis(carboxylate) signal and likely an inadequate pressure of H_2.

Scheme 9. Deuterium Labeling Results with Cobalt Catalysts.

Substrate	Labeled product	Substrate	Labeled product
 **1a**	 **2a-[D]**	 **3e**	 **4e-[D]**
 **3a**	 **4a-[D]**	 **5a**	 **6a-[D]**

Entry	Cobalt precatalyst	Substrate	Condition	Labeling result [a]
1		**1a**	4 atm D_2, MeOH	D^1: >98%; D^2: >98%
2		**1a**	4 atm D_2, MeOH No Zn	D^1: >98%; D^2: >98%
3	 P_2 = (*R,R*)-^{Ph}BPE	**1a**	4 atm D_2, MeOH No Zn or Et_3N	D^1: >98%; D^2: >98%
4		**3a**	4 atm D_2, MeOH	D^1: >98%; D^2: >98%
5		**3e**	4 atm D_2, MeOH	D^1: >98%; D^2: >98%
6	(*R,R*)-(BenzP*)Co(COD)	**5a**	4 atm D_2, MeOH No Et_3N	D^1: >98%; D^2: >98%[b]
7	(*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$	**1a**	4 atm D_2, MeOH No Zn or Et_3N	D^1: >98%; D^2: 82%[c]
8	(*R,R*)-(BenzP*)Co(OPiv)$_2$	**5a**	4 atm D_2, MeOH No Zn or Et_3N	D^1: 84%; D^2: >98%[d]

Deuterium labeling studies were carried out under 60 psi D_2 in natural abundance MeOH. % deuteration were determined by ^{1}H NMR and ^{2}H NMR integration. a. 5 mol% catalyst loading, 50 mol% Zn, 1equiv. Et_3N, 50 °C, 16 h unless otherwise noted. % conv. were determined by ^{1}H NMR. % *ee* were determined by SFC. % conv. and % *ee* were identical to standard catalytic condition unless otherwise noted. b. 100% conv. 95% *ee*. c. 32% conv. 19% *ee*. d. 21% conv. 85% *ee*.

CONCLUDING REMARKS

A method for the asymmetric hydrogenation of *α, β*-unsaturated carboxylic acids with readily generated and handled bis(phosphine) cobalt(0) 1,5-cyclooctadiene precatalysts has been developed. Structurally diverse *α, β*-unsaturated acids were efficiently hydrogenated with tolerance to most common organic functional groups, affording chiral carboxylic acids in high yields and enantioselectivities. The active Co(0) precatalyst for hydrogenation of a D-DOPA precursor, (*R,R*)-(BenzP*)Co(COD), has been synthesized and characterized. A series of bis(phosphine)Co(II) bis(pivalate) complexes were prepared and also proven catalytically competent. A stoichiometric reaction between a cobalt hydride and 2-phenyl acrylic acid established alkene insertion in the presence of free carboxylic acid, generating a Co(II) bis(carboxylate) as a catalyst-substrate adduct. X-band EPR analysis revealed bis(phosphine)Co(II) bis(carboxylate) were generated in catalytic reactions and were identified as the catalyst resting state. Deuterium labeling experiments established homolytic H_2 cleavage by cobalt(0), distinct from ruthenium and nickel carboxylate catalysts whereby H_2 is cleaved heterolytically.

ASSOCIATED CONTENT

Supporting Information

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

Crystallographic information for (Λ)-(*R,R*)-(^{Ph}BPE)Co(OPiv)$_2$, (Λ)-(*R,R*)-(^{iPr}DuPhos)Co(OPiv)$_2$,

(Δ)-(*R*,*R*)-(BenzP*)Co(OPiv)$_2$ and **(Λ)-(*R*,*R*)-(^{iPr}DuPhos)Co(κ^1-O$_2$C-C$_8$H$_7$)(κ^2-O$_2$C-C$_8$H$_9$)** (CIF). Additional experimental details; characterization data including NMR and EPR spectra of new compounds; (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

H.Z. and P.J.C. acknowledge financial support from a National Science Foundation (NSF) Grant Opportunities for Academic Liaison with Industry (GOALI) grant (CHE-1855719).

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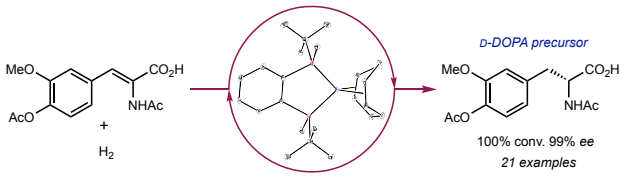
Cobalt-Catalyzed Asymmetric Hydrogenation of α, β-Unsaturated Carboxylic Acids:



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