Cationic Bis(phosphine) Cobalt(I) Arene Complexes as Precatalysts for the Asymmetric Synthesis of Sitagliptin

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ABSTRACT: The cobalt-catalyzed asymmetric hydrogenation of dehydro-sitagliptin was studied and applied to the synthesis of sitagliptin (Januvia®). Catalyst discovery efforts were accelerated by the application of a general method for the synthesis of cationic bis(phosphine) cobalt η^6-arene complexes. One-electron oxidation of bis(phosphine) cobalt(II) dialkyl complexes in the presence of arenes furnished the corresponding, bench stable cobalt precatalysts, $[(P\text{-}P)Co(\eta^6\text{-}C_6H_6)][BAr^F{}_4]$. Asymmetric hydrogenation utilized 0.5 mol% of the optimal catalyst, $[(R,R)\text{-}(^{iPr}DuPhos)Co(\eta^6\text{-}C_6H_6)][BAr^F{}_4]$ in THF solution and produced sitagliptin in >99% yield with 97% *ee*. Cobalt catalysts were compatible with a range of solvents and maintained excellent activity and selectivity after standing in air in the solid state for two weeks. Deuterium labeling studies support an enamine-imine tautomerization process resulting in reduction of the metalated imine. Notably, state-of-the-art neutral bis(phosphine) cobalt precatalysts were ineffective, emphasizing the utility of a class of cationic cobalt precatalyst.

Keywords: asymmetric catalysis, cobalt, hydrogenation, pharmaceuticals, deuterium labeling

INTRODUCTION

Transition metal-catalyzed asymmetric hydrogenation is a transformative technology for the synthesis of single enantiomer compounds with widespread application in the pharmaceutical and agrochemical industries.[1] Knowles' pioneering application of cationic rhodium(I) complexes bearing enantiopure phosphine ligands for the asymmetric synthesis of L-DOPA demonstrated the utility of the transformation for the large scale synthesis of active pharmaceutical ingredients (APIs).[2] Subsequent work by Noyori[3b] and others established the utility of precious metal catalyzed asymmetric hydrogenation for the synthesis of single enantiomer drugs.[4] The development of well-defined and versatile metal precursors in combination with diverse ligand libraries enabled the acceleration of catalyst discovery and optimization.[5] In 2009, the Merck & Co., Inc., Kenilworth, NJ, USA catalysis group discovered that combinations of $[Rh(COD)Cl]_2$ (COD = 1,5-cyclooctadiene) and ferrocene-based enantiopure bis(phosphines) were effective for the asymmetric synthesis of sitagliptin (Januvia®), the dipeptidyl peptidase IV (DPP-4) inhibitor used in the treatment of type 2 diabetes mellitus (Figure 1A). The rhodium-catalyzed hydrogenation of an *N*-unfunctionalized enamine amide was performed in the enantiodetermining step of the industrial synthesis.[6a] A biocatalytic route relying on an evolved transaminase has since replaced the rhodium-catalyzed reaction in generating the chiral sitagliptin amine, principally due to higher enantioselectivity (>99%) and the generally high cost and price volatility of rhodium.[6b]

Increasing emphasis on sustainability in the pharmaceutical industry has inspired a renewed focus on finding alternatives to precious metal catalysis including the development of catalysts using first-row transition metals.[7] Earth-abundant, first-row transition metals are attractive both for their broad availability and comparatively low cost and toxicity.[8] In the context of asymmetric hydrogenation, cobalt catalysts offer distinct performance compared to more traditional catalysts that rely on second- and third-row transition metals have been an area of increased attention.[8b] The combination of the readily available cobalt salt, $CoCl_2{\cdot}6H_2O$ and enantiopure bidentate phosphines in the presence of zinc generated highly active and enantioselective hydrogenation catalysts that have been applied to the synthesis of levetiracetam (Keppra®), and more recently in the preparation of enantiopure carboxylic- and α-amino acid derivatives.[9] Notably, the catalyst loadings are low (<1 mol%), enantioselectivities are generally high, and optimal performance was observed in methanol solvent.

One distinguishing feature of catalysis with first row transition metals is the ability to prepare precatalysts in oxidation states that differ by one electron. This redox flexibility has the potential to be a powerful variable in catalyst design and optimization. For example, in the asymmetric hydrogenation applied to the synthesis of levetiracetam, highly enantioselective reactions were observed when initiating catalysis from both cobalt(0) and neutral cobalt(I) precatalysts along with widely-available Co(II) precursors (Figure 1B).[9a]

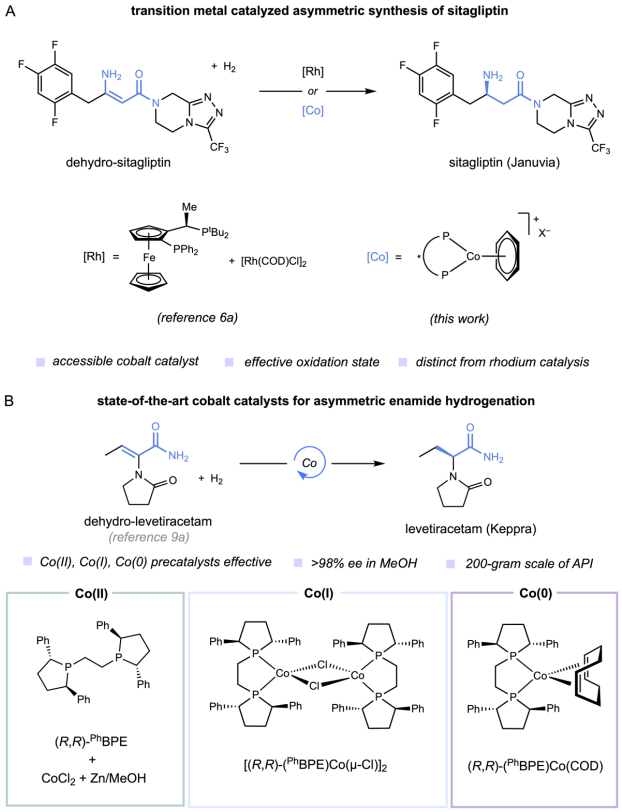


Figure 1. A. Rh-catalyzed asymmetric hydrogenation for the synthesis of sitagliptin. B. State-of-the-art Co(II), Co(I), and Co(0) precatalysts for the asymmetric hydrogenation of enamides. C. Cobalt-catalyzed synthesis of sitagliptin.

Despite these advances, the direct cobalt analogs of cationic bis(phosphine)rhodium(I) precatalysts used in the industrial syntheses of L-DOPA and sitagliptin remained synthetically elusive and hence their comparative catalytic performances unknown.[10] Recently, the synthesis of [(*R*,*R*)-(^{iPr}DuPhos)Co(COD)][BAr^F_4] was reported from chloride abstraction from [(*R*,*R*)-(^{iPr}DuPhos)CoCl]$_2$ with $NaBAr^F_4$ (Ar^F = 3,5-$(CF_3)_2$-C_6H_3) in the presence of 1,5-cyclooctadiene.[10a] This compound proved active for the hydrogenation of enamides with synthetically useful enantioselectivities. Since this report, Parsutkar and RajanBabu described the synthesis of [(*R*,*R*)-(^{Ph}BPE)Co(diene)][BAr^F_4] derivatives and their application as precatalysts for the hydroacylation of dienes.[11] Concurrently, our group has reported the synthesis of [(dppf)Co(η^6-arene)][BAr^F_4] (dppf = 1,1'- Bis(diphenylphosphino)ferrocene) and demonstrated its utility in the [2+2] cycloaddition of alkenes and alkynes to form cyclobutenes.[12]

State-of-the-art methods for the synthesis of cationic cobalt(I) complexes bearing enantiopure bis(phosphine) ligands rely on accessibility of the neutral cobalt(I) chloride dimers, [(*R*,*R*)-(^{iPr}DuPhos)Co(μ-Cl)]$_2$ and [(*R*,*R*)-(^{Ph}BPE)Co(μ-Cl)]$_2$ for subsequent treatment with $NaBAr^F_4$. For applications in asymmetric hydrogenation including the synthesis of sitagliptin, more versatile and robust routes are needed to prepare a larger array of cationic bis(phosphine)cobalt(I) precatalysts. Here we describe the preparation of cationic cobalt(I) complexes using an oxidatively-induced reductive elimination strategy that proved general across several commercially available chiral bidentate phosphine ligands. This class of isolable cationic cobalt(I) derivatives was evaluated in asymmetric hydrogenation for the synthesis of sitagliptin. High activity and enantioselectivities were achieved using air-stable precatalysts at room temperature and the method was compatible with a host of solvents. Isotopic labeling with D_2 gas supports enamine-imine tautomerization as the major pathway during catalytic hydrogenation. Notably, cationic bis(phosphine)cobalt(I) complexes were uniquely effective for this transformation as analogous neutral cobalt(0), (I) and (II) derivatives were inactive by comparison, highlighting the advantage of accessible one-electron redox state changes with first row transition metal catalysts.

RESULTS AND DISCUSSION

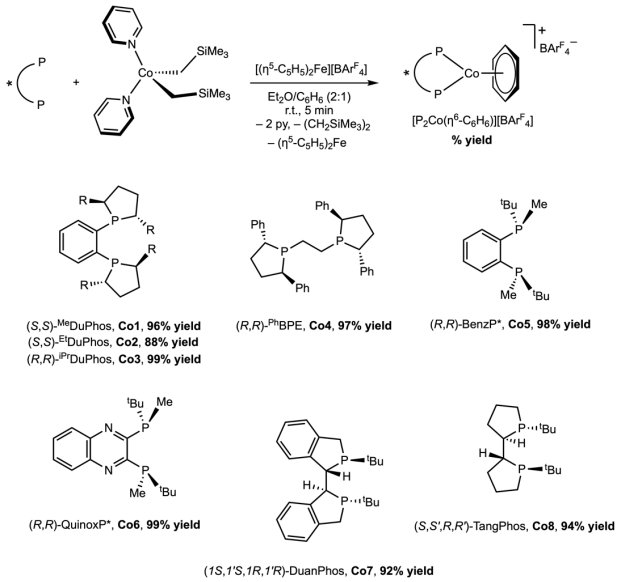
Evaluation of Neutral Cobalt(0), (I) and (II) Complexes for the Asymmetric Synthesis of Sitagliptin. Progress in asymmetric hydrogenation of *N*-unfunctionalized (unprotected) enamines has been challenged by the incompatibility of transition metals with nucleophilic amino groups in the resulting products that inhibit the reaction by poisoning the active catalyst.[1c] Using procedures previously reported for the generation of highly active and enantioselective cobalt hydrogenation catalysts,[9] combinations of enantiopure bis(phosphines) with cobalt(II) halides in the presence of zinc reductant were evaluated with dehydrositagliptin. Under 500 psi of H_2 at 50 °C, no conversion was observed after 18 h. Well-defined organometallic precatalysts, (*R*,*R*)-(^{iPr}DuPhos)Co(CH_2SiMe_3)$_2$ and (*R*,*R*)-(^{Ph}BPE)Co(COD) were also evaluated at 500 psi and 50 °C for 18 h. Despite high precatalyst loadings (>10 mol%), no catalytic hydrogenation activity was observed. Use of the neutral cobalt(I) dimer, [(*R*,*R*)-(^{iPr}DuPhos)CoCl]$_2$ provided sitagliptin in 39% yield with high enantioselectivity (92%). Other cobalt(I) sources such as $(Ph_3P)_3CoCl$ were combined with enantiopure bis(phosphines) but did not provide any activity in the desired hydrogenation of **1**. From these studies, it was apparent that neutral cobalt(0) and (II) precatalysts were ineffective for the asymmetric synthesis of sitagliptin.

Synthesis of Cationic Bis(phosphine) Cobalt(I) Arene Complexes. The poor catalytic performance of state-of-the-art bis(phosphine) cobalt complexes prompted exploration of cationic variants, closer analogs of the industrially relevant rhodium catalyst.[2,6a] Routes to 18-electron, cationic bis(phosphine) cobalt(I) arene cations were explored to rapidly generate precatalysts for the asymmetric synthesis of sitagliptin. One-pot methods were initially sought to minimize synthetic manipulations with the goal of developing procedures that are compatible with high throughput experimentation. Seminal examples of cationic cobalt(I) arene complexes bearing achiral bidentate phosphines have been reported by Jolly and were synthesized by hydride abstraction from the corresponding neutral cobalt hexadienyl derivative or protonation of η^3-cyclooctenyl compounds in the presence of arenes.[13]

A more straightforward procedure would rely on direct complexation of some well-defined cobalt precursor by a chiral bidentate phosphine.[14] Seeing as the cobalt analogs of versatile precious metal precursors such as [Rh(COD)Cl]$_2$ and [Rh(nbd)$_2$][BF_4] are unknown, neutral bis(phosphine) cobalt(II) dialkyl complexes were explored as possible synthons, given that libraries of these compounds have been prepared by pyridine displacement from (py)$_2$Co(CH_2SiMe_3)$_2$.[15,16] Oxidatively-induced reductive elimina-

tion in the presence of a suitable neutral ligand was envisioned as route to a host of the corresponding cationic bis(phosphine) cobalt(I) precatalysts (Scheme 1).

Scheme 1. Oxidatively-induced reductive elimination from cobalt dialkyls as a route to cationic cobalt(I) arene complexes.



Attempts to induce reductive elimination from cobalt(II) dialkyls in the absence of oxidant were unsuccessful as heating a benzene-d_6 solution of (*R*,*R*)-(^{iPr}DuPhos)Co(CH_2SiMe_3)$_2$ at 80 °C over several days produced no reaction as determined by NMR spectroscopy.[17–19] In the presence of oxidant, formation of the Co(I) arene cations occurs within seconds. Whereas a variety of arenes including toluene, anisole (Figure 2), and fluorobenzene were effective in stabilizing the cobalt(I) products, benzene was used for initial precatalyst isolation. This method proved general among a host of enantiopure bis(phosphines) and the desired cationic cobalt(I) derivatives were synthesized in one pot from (py)$_2$Co(CH_2SiMe_3)$_2$ without removal of pyridine. A limitation of this approach was revealed in the attempted preparation cationic cobalt(I) complexes bearing enantiopure ferrocenyl ligands such as Josiphos. Instead of the desired cationic cobalt(I) derivative, the ferrocenium salt [tBu-Josiphos][BAr^F_4] was isolated and characterized by X-ray diffraction (Figure S87).[20]

The oxidatively-induced reductive elimination protocol was used to prepare eight well-defined cationic cobalt arene compounds **Co1**–**Co8** containing an η^6-C_6H_6 ligand (Scheme 1). In each case, the cobalt complexes were isolated as diamagnetic crystalline solids in excellent yield and four examples were characterized by X-ray crystallography (Figure 2). The synthetic protocol was also compatible with ferrocenium salts containing BF_4^-, PF_6^-, and BPh_4^- anions and yielded well-defined complexes with the formula [(P$_2$)Co(η^6–C_6H_6)][X]. The crystallinity and prolonged stability of complexes **Co1**–**Co8** containing the $BAr^F_4^-$ anion prompted additional study of their reactivity. The solid-state structure of [(*R*,*R*)-(^{Ph}BPE)Co(η^6-C_6H_6)][BAr^F_4] (**Co4**) was compared to the previously reported 19-electron cobalt(0) complex, (*R*,*R*)-(^{Ph}BPE)Co(η^6-C_6H_6).[9a] Subtle elongation of the cobalt-phosphine bonds was observed in the cationic complex but the η^6-arene ligand (Co–centroid) does not differ significantly between Co(0) and Co(I) oxidation states. Notably, reductive elimination from putative bis(phosphine) cobalt(III) complexes proceeds in the absence of arene co-solvent. When the high-spin, neutral cobalt(II) dialkyl complex (*R*,*R*)-(^{iPr}DuPhos)Co(CH_2SiMe_3)$_2$ was formed *in situ* from (py)$_2$Co(CH_2SiMe_3)$_2$ (py = C_6H_5N) and (*R*,*R*)-^{iPr}DuPhos in diethyl ether, oxidatively-induced reductive elimination furnished the 16-electron product, [(*R*,*R*)-(^{iPr}DuPhos)Co(py)$_2$][BAr^F_4], with the exogenous pyridine ligands originating from the complexation of bis(phosphine) to (py)$_2$Co(CH_2SiMe_3)$_2$. X-ray crystallography confirmed a distorted square-planar geometry at the cobalt (Figure 3) with no significant difference in Co–P bonding compared to [(*R*,*R*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][BAr^F_4] (Figure 2). When benzene was added to a diethyl ether solution of [(*R*,*R*)-(^{iPr}DuPhos)Co(py)$_2$][BAr^F_4], a rapid color change from dark red to bright yellow took place, signifying the substitution of both pyridine ligands by benzene to form **Co3**. Attempts to characterize the former complex in pyridine-d_5 produced featureless NMR spectra likely resulting from the exchange of pyridine ligands on the timescale of the NMR experiment. The catalytic competency of [(*R*,*R*)-(^{iPr}DuPhos)Co(py)$_2$][BAr^F_4] was evaluated in the asymmetric hydrogenation of dehydro-sitagliptin. Relatively high catalyst loadings (10 mol%) were required to produce sitagliptin in quantitative yield with 93% *ee*. Reactions carried out using 1 mol% of [(*R*,*R*)-(^{iPr}DuPhos)Co(py)$_2$][BAr^F_4] suffered from lower yields (<70%) but maintained high enantioselectivity (90 % *ee*).

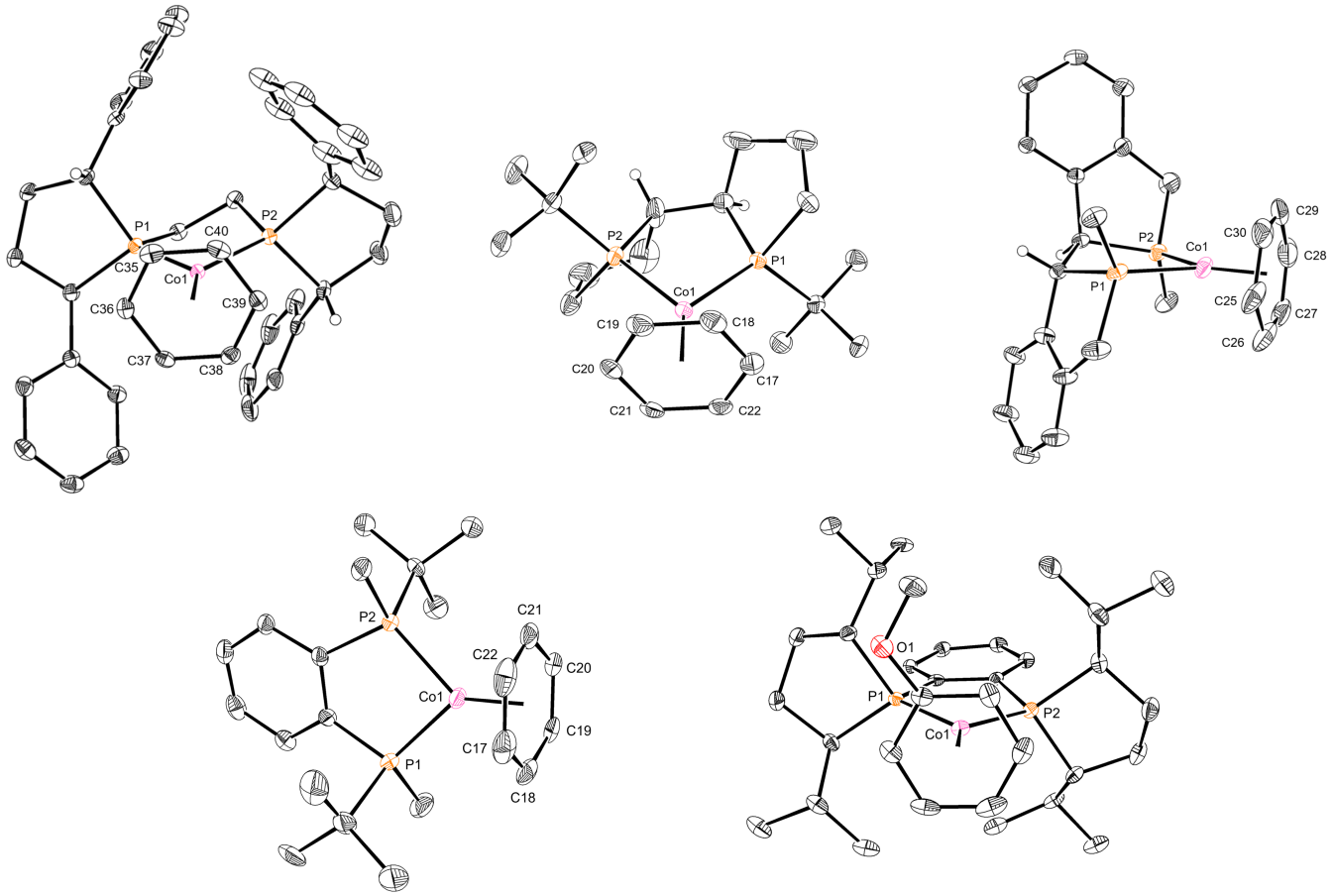


Figure 2. Solid-state structures of selected cationic bis(phosphine) cobalt(I) arene complexes reported in this work, shown at 30% probability ellipsoids with $BAr^F_4^-$ anions and hydrogen atoms at non-stereogenic centers omitted for clarity. Top row: (left to right) [(*R*,*R*)-(^{Ph}BPE)Co(η^6-C_6H_6)][BAr^F_4] (**Co4**); [(*S*,*S'*,*R*,*R'*)-(Tangphos)Co(η^6-C_6H_6)][BAr^F_4] (**Co8**); [(*1S*,*1S'*,*1R*,*1R'*)-(Duanphos)Co(η^6-C_6H_6)][BAr^F_4] (**Co7**); tBu groups are omitted for clarity; Second row: [(*R*,*R*)-(BenzP*)Co(η^6-C_6H_6)][BAr^F_4] (**Co5**); [(*R*,*R*)-(^{iPr}DuPhos)Co(η^6-C_6H_5OMe)][BAr^F_4].

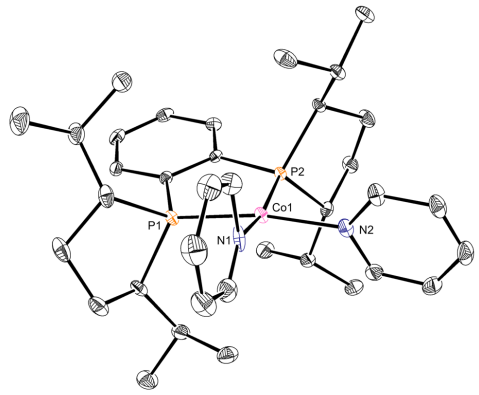


Figure 3. Solid-state structure of [(*R*,*R*)-(^{iPr}DuPhos)Co(py)$_2$][BAr^F_4] shown at 30% probability ellipsoids with the $BAr^F_4^-$ anion and hydrogen atoms omitted for clarity.

Application of Cationic Bis(phosphine) Cobalt(I) Complexes to the Asymmetric Synthesis of Sitagliptin. Having developed reliable synthetic routes to cationic bis(phosphine) cobalt(I) arene complexes, the performance of these precatalysts in the asymmetric synthesis of sitagliptin was evaluated. Each of the arene compounds studied proved to be air- and moisture-stable as dissolution in acetone-d_6 under an ambient atmosphere produced no changes in the NMR spectra for several hours. Initial screening results for the asymmetric hydrogenation of dehydro-sitagliptin **1** relied on 10 mol% of the isolated organometallic cobalt complexes in THF solution with 500 psi of H_2 at 50 °C (Figure 4). Efficient hydrogenation reactivity was observed across the series of isolated compounds **Co1**–**Co8**. Within the series of DuPhos complexes (Figure 4, entries 1–3), increasing the size of the phospholane substituent from Me to Et to ^{i}Pr increased the enantioselectivity of the reaction with [(*R*,*R*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][BAr^F_4] yielding 89% *ee* of the (*R*) enantiomer of chiral sitagliptin amine. A similar trend was observed in previous work describing the asymmetric hydrogenation of methyl-2-acetamidoacrylate (MAC) where $CoCl_2$ and $LiCH_2SiMe_3$ were combined with the same series of DuPhos ligands.[16a]

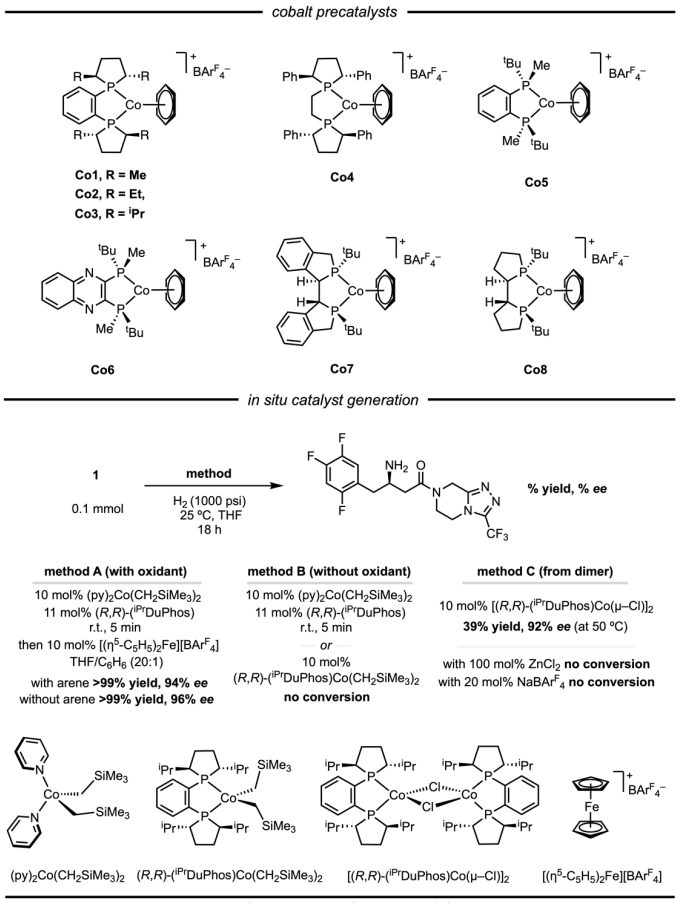
Because of the high conversion and enantiomeric excesses observed with [(*R*,*R*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][BAr^F_4], this precatalyst was selected for additional optimization studies. The catalytic reaction was effective in alcohol (MeOH and ^{i}PrOH) and ethereal (THF, 2-MeTHF, and CPME (cyclopentyl methyl ether)) solvents, as well as acetonitrile and ethyl acetate (entries 9–15, Figure 4). Notably, methanol was optimal for the rhodium-

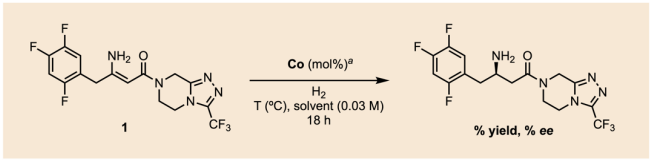
catalyzed method used industrially.[6a] Of the solvents evaluated, **1** was most soluble in THF (entry 13) under the conditions used for optimization even at 25 °C (Figure 4). Product yields (86–99%) and enantioselectivities (87–94%) were consistently high among the solvents used, highlighting the robustness of cationic cobalt precatalysts. The hydrogenation of **1** in MeOH is noteworthy and allows for a comparative study of cobalt(I) cations with state-of-the-art neutral cobalt catalysts in different oxidation states.[9a] Moreover, broad solvent compatibility exhibited by cationic cobalt arene precatalysts lowers the barrier to widespread adoption in the late-stage synthesis of pharmaceuticals.

The effect of H_2 pressure and precatalyst loading were evaluated with minor improvements to the enantioselectivity observed with 1000 psi of dihydrogen. When the catalyst loading was decreased to 0.5 mol% (entry 17), the reaction reliably afforded quantitative yields (>99%). Lowering the temperature of the reaction in THF from 50 to 25 °C produced sitagliptin in >99% yield with 97% ee (entry 20, Figure S16). Having determined the optimized conditions for the asymmetric hydrogenation of **1** using [(*R,R*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][$BAr^F{}_4$], a gram-scale synthesis was undertaken. With 0.5 mol% of the cobalt precatalyst in THF at 50 °C, sitagliptin was obtained in >99% yield with high enantioselectivity (92%). To highlight the versatility of this catalytic hydrogenation in targeting variable structures, the opposite enantiomer of the catalyst, [(*S,S*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][$BAr^F{}_4$] was prepared and favored the (*S*)-enantiomer of sitagliptin with 91% ee.

Samples of crystalline [(*R,R*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][$BAr^F{}_4$] stored on the benchtop in open air for 2 weeks (Figure S22) gave reproducibly high yields (>90%) of product with no erosion of enantioselectivity. The operational ease of handling well-defined, 18-electron cobalt cations is noteworthy, in analogy to the rhodium-catalyzed method that employs [Rh(COD)Cl]$_2$ and chiral ferrocenyl bis(phosphines) (Figure 1A), both of which are air-stable solids.[6a]

To gain insight into the mechanism of hydrogenation, high-pressure deuteration experiments were carried out using 5 mol% of [(*R,R*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][$BAr^F{}_4$] as the precatalyst. Full conversion of **1** was achieved in 18 hours with 450 psi D_2 in THF at 25 °C and the product was isolated with 89% *ee*. Analysis of the crude product mixture by LC/MS (ES-API) established formation of two parent ion peaks at m/z = 409.2 and 410.2, corresponding to d_1 and d_2 isotopologues of sitagliptin, respectively. Analysis of the product by ^{2}H NMR spectroscopy established incorporation of the deuterium label at both the α (d_1) and β (d_2) positions in an approximately 1:0.5 ratio. Repeating the deuteration at 60 psi of D_2 gas increased the ratio to favor the d_1 product to between 1:0.3 and 1:0.15 (Scheme 2A). Notably, when lower pressures of gas were used, enantioselectivity was higher. To further explore the origin of the observed isotopic distribution, an enantioenriched sample of sitagliptin (97% ee)





entry	precatalyst (mol%)	solvent	H_2 (psi)	T (°C)	yield (%)[b]	*ee* (%)[c]
	precatalyst screen					
1	**Co1** (10 mol%)	THF	500	50	68	64
2	**Co2** (10 mol%)	THF	500	50	88	70
3	**Co3** (10 mol%)	THF	500	50	73	89
4	**Co4** (10 mol%)	THF	500	50	96	77
5	**Co5** (10 mol%)	THF	500	50	74	–70
6	**Co6** (10 mol%)	THF	500	50	97	–67
7	**Co7** (10 mol%)	THF	500	50	42	–66
8	**Co8** (10 mol%)	THF	500	50	54	–68
	solvent compatibility					
9	**Co3** (10 mol%)	2-MeTHF	1000	50	98	89
10	**Co3** (10 mol%)	CPME	1000	50	96	90
11	**Co3** (10 mol%)	MeOH	1000	50	98	89
12	**Co3** (10 mol%)	iPrOH	1000	50	>99	87
13	**Co3** (10 mol%)	THF	1000	50	>99	92
14	**Co3** (10 mol%)	MeCN	1000	50	86	92
15	**Co3** (10 mol%)	EtOAc	1000	50	91	94
16	**Co3** (1 mol%)	THF	1000	50	>99	89
17	**Co3** (0.5 mol%)	THF	1000	50	>99	89
18	**Co3** (10 mol%)	THF	1000	25	>99	94
19	**Co3** (1 mol%)	THF	1000	25	>99	95
20	**Co3** (0.5 mol%)	THF	1000	25	>99	97

gram-scale synthesis of sitagliptin

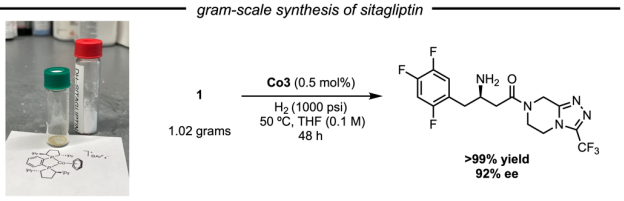
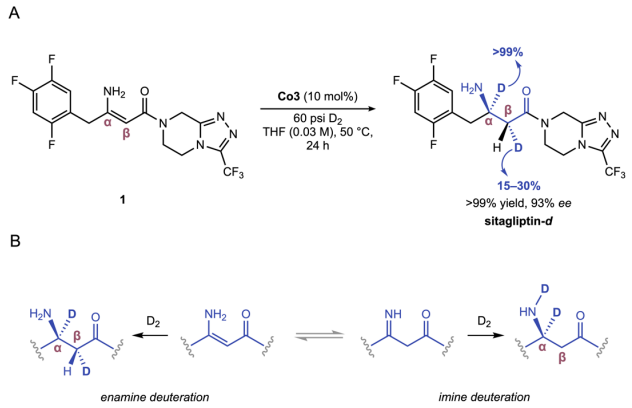


Figure 4. Evaluation of bis(phosphine) cobalt(I) cations in the asymmetric hydrogenation of the dehydro-sitagliptin. [a]Optimization reactions were carried out on 0.1 mmol scale. [b]Reported yields are of isolated material. [c]Reported %*ee* determined by supercritical fluid (CO_2) chromatography (SFC) analysis (see SI for details).

was exposed to catalytic conditions with 10 mol% of either [(*R*,*R*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][BAr^F_4] or [(*S*,*S*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][BAr^F_4]. Under 60 psi of D_2 at 25 °C over the course of 24 hours, no incorporation of deuteria into sitagliptin was observed. Analysis of this product by SFC showed no significant change in the enantiomeric excess. The observation of excess deuteria in the α position from the deuteration of **1** with [(*R*,*R*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][BAr^F_4] suggests that tautomerization of the enamide, and subsequent reduction of the metalated imine is operative during productive asymmetric hydrogenation (Scheme 2B). An imine pathway was first invoked in the rhodium-catalyzed hydrogenation of **1** with [Rh(COD)Cl]$_2$ and ^{tBu}JosiPhos,[6a] the key distinction being that incorporation of deuteria at the β position (Scheme 2B) was not observed.

Scheme 2. A. Cobalt-catalyzed asymmetric deuteration of 1. B. Enamine–imine tautomerization.



CONCLUDING REMARKS

In summary, application of air-stable organometallic precursors revealed high activity and synthetically useful enantioselectivities across a series of enantiopure bis(phosphine) ligands. Among these, [(*R*,*R*)-(^{iPr}DuPhos)Co(η^6-C_6H_6)][BAr^F_4] proved optimal and resulted in an asymmetric hydrogenation reaction that produced sitagliptin in quantitative yields with excellent enantioselectivities (>95%). The well-defined precatalyst maintained activity and enantioselectivity in a variety of solvents including EtOAc and was effective at loadings as low as 0.5 mol% at room temperature. Deuterium-labelling studies support a pathway involving substrate tautomerization and imine reduction promoted by cationic cobalt(I). These studies highlight the transformative impact that Earth abundant metal catalysis can have on the synthesis of pharmaceuticals by virtue of the breadth of available catalysts structures. Looking forward, access to catalyst platforms that are single-electron differentiated may serve as a powerful variable in reaction optimization whenever disparities in activity, enantioselectivity, or functional group tolerance exist between Co(0), Co(I), and Co(II) precatalysts. The application of these cationic precatalysts to other APIs and transformations beyond asymmetric alkene hydrogenation are currently under investigation.

ASSOCIATED CONTENT

Accession Codes

CCDC **2120428**–**2120435** and **2123880** contain the supplementary crystallographic data for this paper (CIF). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data–request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental data, including synthesis and characterization of precatalysts, catalytic data, labeling experiments, as well as SFC traces and NMR spectra (PDF).

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