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Research Article

Cationic Bis(η^6-arene) Cobalt(I) Complexes: Enabling Catalyst Discovery by High-Throughput Experimentation

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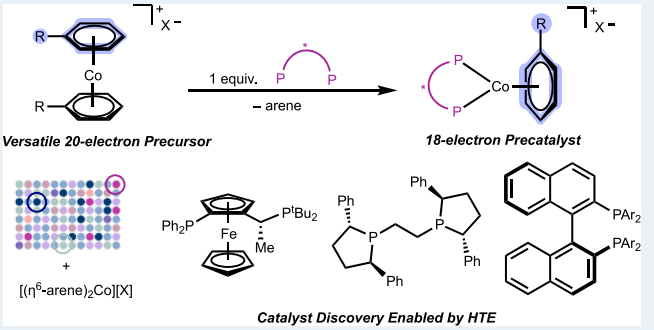
ABSTRACT: Cationic, 20-electron bis(η^6-arene)Co(I) complexes have been synthesized and evaluated as precursors for the generation of bis(phosphine) cobalt(I) η^6-arene precatalysts. The arenes and anions in the precursors were varied, with isolated examples, including $[Al(pftb)_4]^-$ ($pftb$ = $(CF_3)_3CO$), $[BAr^F{}_4]^-$ (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), and $[SbF_6]^-$. Treatment of the isolated precursors with a series bis(phosphines) resulted in arene displacement and isolation of well-defined [(bis(phosphine))Co(η^6-arene)][X] (X = $Al(pftb)_4^-$ and SbF_6^-; arene = C_6H_6, C_6H_5Me, and C_6H_5Et) complexes in 84−99% yield. This ligand substitution enabled unprecedented generation of catalyst libraries using high-throughput experimentation (HTE) for asymmetric alkene hydrogenation, as well as formal [2 + 2] cycloaddition, hydroboration, and C(sp^2)−H functionalization. These versatile precursors simplify increasingly complex chemical transformations by introducing single-component, well-defined precatalysts through general ligand substitution.



KEYWORDS: *asymmetric catalysis, cobalt sandwich complex, high-throughput experimentation, hydrogenation*

INTRODUCTION

Bis(phosphine) cobalt complexes have emerged as a privileged class of earth-abundant transition metal catalysts with applications in asymmetric alkene hydrogenation,[1] diene hydrovinylation,[2] cycloadditions,[3] and C−H functionalization.[4] Distinct reactivity differences have been observed between well-defined neutral and cationic bis(phosphine) cobalt compounds,[5−7] highlighting the importance of accessing precursors in discrete Co(0), Co(I), and Co(II) oxidation states. Effective in situ methods to access neutral Co(0)/Co(II) catalysts have been developed that rely on the addition of a bis(phosphine) ligand to a mixture of cobalt(II) dihalide and zinc, typically in methanol solvent.[5] By contrast, a robust cationic cobalt(I) precursor, analogous to that of $[Rh(NBD)_2][BF_4]$, is lacking (Scheme 1A).

Cationic 18-electron bis(phosphine) cobalt(I) arene complexes are air-stable[6] and earth abundant[8] precatalysts that serve as Schrock−Osborn type catalyst analogs. Routes to well-defined cationic cobalt(I) complexes are limited to a select few bis(phosphines), complicated by multistep activation, and use of expensive anions. The synthesis of these compounds dates back to Jolly et al.'s seminal report of [(bis(phosphine))Co(η^6-arene)][BF_4] through a multistep route involving strongly acidic HBF_4, a method incompatible with in situ activation.[9] Reports invoking cationic cobalt(I) intermediates from the reduction and subsequent halide abstraction of (bis(phosphine))$CoCl_2$ with Zn and $NaBAr^F{}_4$ in the presence of dienes or arenes[10] led to isolation of cobalt(I) precatalysts through halide abstraction from [(*R*,*R*)-(^{iPr}DuPhos)Co(μ-Cl)]$_2$ (Scheme 1B).[11] However, only bis(phosphines) capable of forming bridging cobalt(I) chloride dimers were effective for generating the precatalyst.[10−12]

In 2022, our laboratory described a more general method to access [(bis(phosphine))Co(η^6-C_6H_6)][$BAr^F{}_4$] complexes through oxidatively induced reductive elimination (OIRE) (Scheme 1B).[6] This route relied on the addition of a bis(phosphine) ligand to $(py)_2Co(CH_2SiMe_3)_2$ and oxidation with $Fc BAr^F{}_4$ (Fc = $(\eta^5$-$C_5H_5)_2Fe$)) in the presence of benzene. While effective with a broader range of bis(phosphines), the multistep synthesis, semisolid $(py)_2Co(CH_2SiMe_3)_2$, and incompatibility with wide-bite angle (P−Co−P > 90°) and chiral ferrocenyl-based bis(phosphine) ligands, limited the method's adoption. Most recently, Casitas and coworkers reported a two-step synthesis to well-defined bis(phosphine) cobalt(I) cations beginning from $(PPh_3)_3CoCl$ (Scheme 1B).[13]

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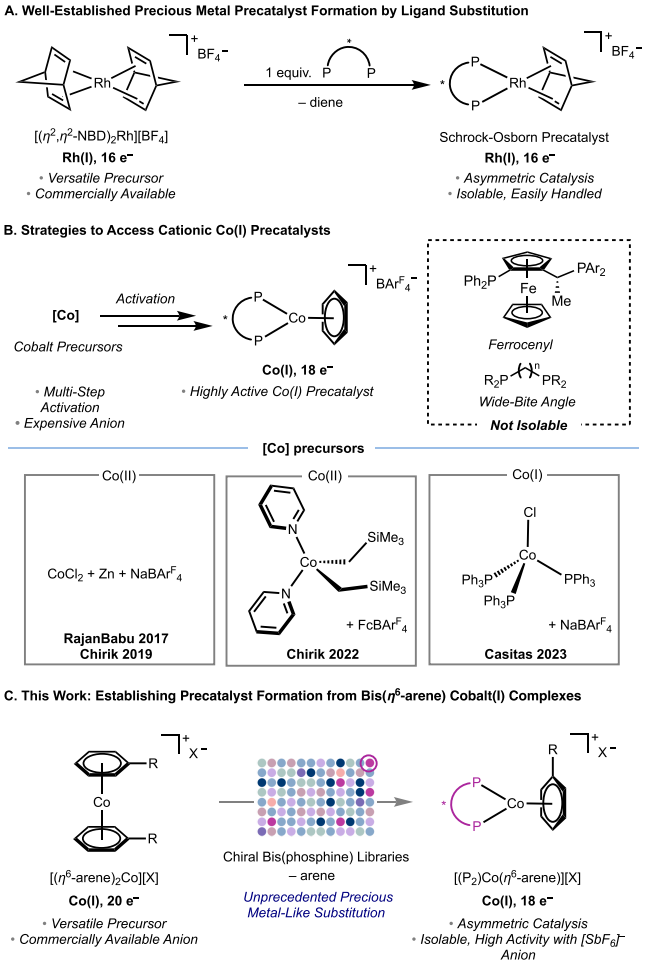
Scheme 1. (A) Well-Established Precious Metal Precatalyst Formation Through Ligand Substitution;(B) Strategies to Access Cationic Cobalt(I) Precatalysts; (C) This Work: Establishing Precatalyst Formation from Bis(η^6-arene) Cobalt(I) Complexes



However, minimal ligand compatibility motivated exploration of other cationic cobalt(I) precursors.

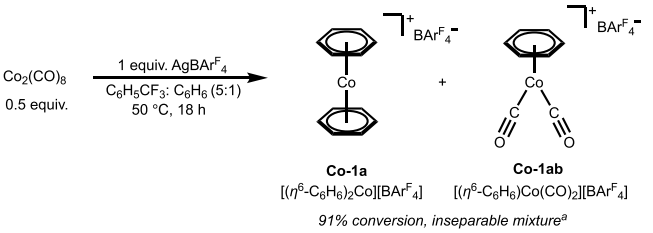
Development of well-defined precursors to broadly access cationic bis(phosphine) cobalt(I) precatalysts would be enabling for catalyst discovery and optimization (Scheme 1C). The formally 20-electron, cationic bis(η^6-arene) cobalt compounds, $[(\eta^6\text{-arene})_2Co][PF_6]$ with an $S = 1$ ground state, were first reported by Lindner and Fischer.[14] Examples were limited to arenes bearing sterically encumbering, electron-donating substituents, such as hexamethylbenzene and mesitylene (1,3,5-$(Me)_3$-C_6H_3). In 2018, Krossing and coworkers reported isolation of the first sterically attenuated cationic bis(η^6-benzene) cobalt(I) complex from one electron oxidation of $Co_2(CO)_8$ in a mixture of 1,2-difluorobenzene and benzene.[15]

Here, we describe the synthesis and characterization of cationic cobalt(I) bis(η^6-arene) sandwich complexes with sterically attenuated arenes—C_6H_6, C_6H_5Me, and C_6H_5Et—stabilized by $[SbF_6]^-$ and $[Al(pftb)_4]^-$ anions (Scheme 1C). The $[SbF_6]^-$ variants were preferred due to their anion availability, comparatively low cost, and lower molecular weight. The substitution of one arene by a host of bis(phosphine) ligands enabled the synthesis of often air-stable, 18-electron cobalt(I) precatalysts. Notably, wide bite-angle bis(phosphine) cobalt complexes of dppp, dppf, and SL-J002-1 that were not isolable using the previously reported methods[6,10−13] were isolated in high yields, demonstrating the ability of the sandwich complexes to expand well-defined cobalt precatalyst space. This method was applied to catalyst discovery and evaluation in asymmetric alkene hydrogenation using high throughput experimentation (HTE), previously incompatible with other cationic Co(I) precursors. Precatalyst reactivity was extended to formal [2 + 2] cycloaddition, hydroboration, and C(sp^2)−H functionalization. Examples with high activity and enantioselectivity were demonstrated with minimal influence of arene or anion, encouraging further development of precatalysts stabilized by a commercially available $[SbF_6]^-$ anion.

RESULTS AND DISCUSSION

Synthesis of Cationic Bis(η^6-arene) Cobalt Sandwich Complexes. Studies commenced with the exploration of cationic bis(η^6-arene) cobalt complexes where the identities of the arene and anion were varied to access stable yet substitutionally labile precursors. Using a modified procedure reported by Krossing and coworkers[15] the synthesis of $[(\eta^6\text{-}C_6H_6)_2Co][BAr^F{}_4]$ (**Co-1a**) was pursued. A solution of $Co_2(CO)_8$ in a mixture of C_6H_6 and $C_6H_5CF_3$ was treated with $AgBAr^F{}_4$ and heated to 50 °C for 18 h, followed by three freeze−pump−thaw cycles (Scheme 2). This procedure

Scheme 2. Synthesis of Co-1a[a]



[a]Ratio varied between syntheses.

furnished a mixture of the desired **Co-1a** sandwich complex along with $[(\eta^6\text{-}C_6H_6)Co(CO)_2][BAr^F{}_4]$(**Co-1ab**), an intermediate arising from incomplete substitution of the carbonyl ligands by a second equivalent of arene. Variations in temperature, equivalents of $AgBAr^F{}_4$, solvent ratios, time, and resubmission to the reaction conditions did not cleanly generate **Co-1a**. Single crystals of **Co-1a** suitable for X-ray diffraction were obtained from the crude mixture in a $C_6H_5CF_3$ solution layered with pentane at −35 °C (Figure 1). In the solid state, **Co-1a** had Co(1)−centroid distances of 1.758 Å (C(1)−C(6)) and 1.750 Å (C(7)−C(12)), in agreement with published values.[15]

Because of the challenges associated with separating **Co-1ab** and **Co-1a**, coupled with the expense and sourcing of the $[BAr^F{}_4]^-$ anion, the synthesis and isolation of cobalt sandwiches with other commercially available anions were explored. The oxidations of $Co_2(CO)_8$ with $AgPF_6$, AgOTf, $AgBF_4$, and $AgSbF_6$ were conducted in $C_6H_5CF_3$:C_6H_6 (5:1) mixtures and independent of solvent, reaction time, or temperature, none of the desired products were isolated. In many cases, the products were insoluble or reactive toward common organic solvents, such as diethyl ether, THF, dichloromethane, acetonitrile, nitroethane, or benzene. Anal-

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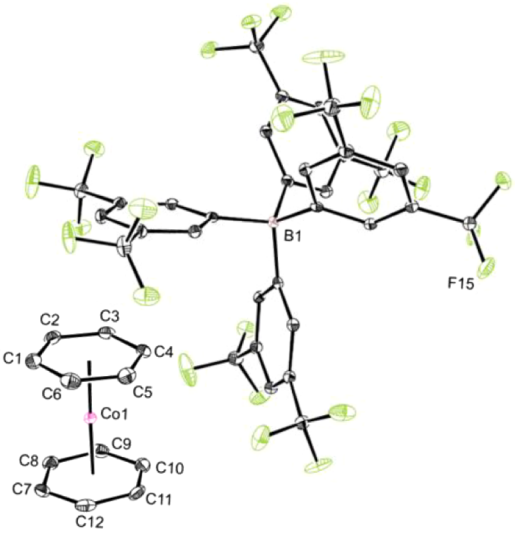
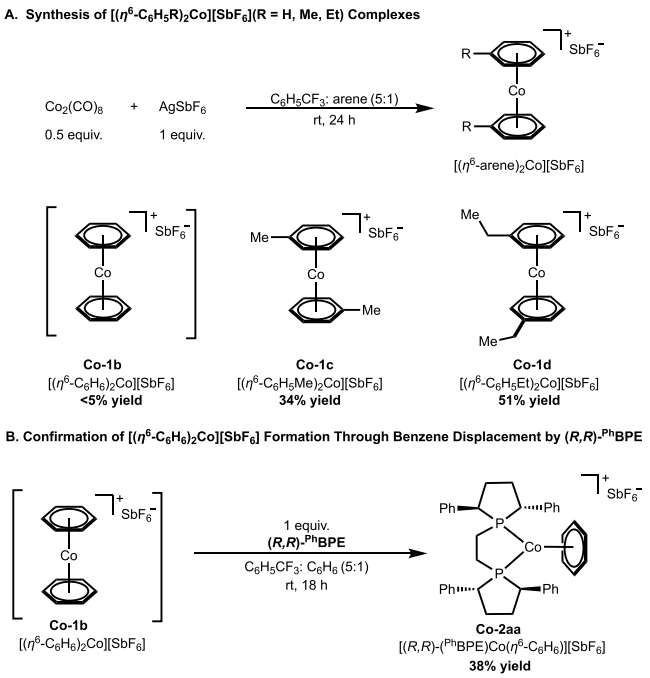


Figure 1. Solid-state structure of **Co-1a** at 30% probability; ellipsoids and hydrogen atoms are omitted for clarity. Co−centroid(C1,C6): 1.758 Å, Co−centroid(C7,C12): 1.750 Å.

ysis by either EPR or NMR spectroscopy provided little information. The characterization was therefore limited to infrared spectroscopy, X-ray diffraction, and derivatization by the addition of a bis(phosphine) ligand.

Introduction of alkyl substituents on the arene was explored with the goal of increasing the solubility and enabling the isolation of the resulting cobalt compound. The oxidation of $Co_2(CO)_8$ with $AgSbF_6$ in a $C_6H_5CF_3$:C_6H_5Me (5:1) mixture followed by recrystallization from the crude mixture furnished a yellow-brown solid identified as $[(\eta^6\text{-}C_6H_5Me)_2Co][SbF_6]$ (**Co-1c**) in 34% isolated yield (Scheme 3A). Isolation of the pure cobalt sandwich was enabled by the distinct solubility difference between **Co-1c** and $[(\eta^6\text{-}C_6H_5Me)Co(CO)_2][SbF_6]$ in the $C_6H_5CF_3$:C_6H_5Me (5:1) mixture. Repeating the procedure using a $C_6H_5CF_3$:C_6H_5Et (5:1) mixture resulted in a 51% isolated yield of $[(\eta^6\text{-}C_6H_5Et)_2Co][SbF_6]$ (**Co-1d**), consistent with a longer alkyl chain improving solubility (Scheme 3A). Solution effective magnetic moments of 2.7(4) and 2.5(2) μ_B respectively, were measured at 23 °C (Evans method),[16] consistent with S = 1 ground states.[15] The ^{1}H NMR spectra for **Co-1c** and **Co-1d** in $C_6H_5CF_3$ with a C_6D_6:TMS (1:1) capillary exhibited downfield signals at 37.4 and 47.3 ppm, respectively, corresponding to a single alkyl peak, which indicates both symmetry and rotation about the arene rings. Both **Co-1c** and **Co-1d** were stored for several months under an inert atmosphere at −35 °C without detectable degradation.

Scheme 3. (A) Synthesis of $[(\eta^6\text{-}C_6H_5R)_2Co][SbF_6]$ (R = H, Me, Et) Complexes; (B) Confirmation of $[(\eta^6\text{-}C_6H_6)_2Co][SbF_6]$ Formation Through Benzene Displacement by (R,R)-^{Ph}BPE



To determine whether the desired cobalt sandwich $[(\eta^6\text{-}C_6H_6)_2Co][SbF_6]$ (**Co-1b**) formed within the nearly insoluble crude mixture, one equivalent of bis(phosphine) ligand was added to intercept bis(η^6-arene) sandwich with the goal of isolating an 18-electron bis(phosphine) cobalt arene complex. Oxidation of $Co_2(CO)_8$ with $AgSbF_6$ in a $C_6H_5CF_3$:C_6H_6 (5:1) mixture followed by the addition of (R,R)-^{Ph}BPE resulted in isolation of $[(R,R)\text{-}(^{Ph}BPE)Co(\eta^6\text{-}C_6H_6)][SbF_6]$ (**Co-2aa**) in 38% yield (Scheme 3B). A diagnostic singlet was observed at 110.1 ppm in the ^{31}P NMR spectrum recorded in THF-d_8 at ambient temperature, as well as a resonance at 5.01 ppm in the ^{1}H NMR spectrum assigned to the coordinated benzene, identical to the reported spectra for the $[(R,R)\text{-}(^{Ph}BPE)Co(\eta^6\text{-}C_6H_6)][BAr^F{}_4]$.[6] The identity of the **Co-2aa** was confirmed by independent synthesis by OIRE whereby (R,R)-$(^{Ph}BPE)Co(CH_2SiMe_3)_2$ was treated with $AgSbF_6$, furnishing the desired product in 38% yield. The cobalt cation was recrystallized from a saturated solution of THF at −35 °C to unambiguously assign the solid-state structure by X-ray crystallography (Figure 2). **Co-2aa** Co−centroid (C1,C6) distances of 1.581 and 1.593 Å, respectively, and the Co1−P1 and Co1−P2 distances were consistent with the cationic cobalt(I) complexes were reported previously.[6]

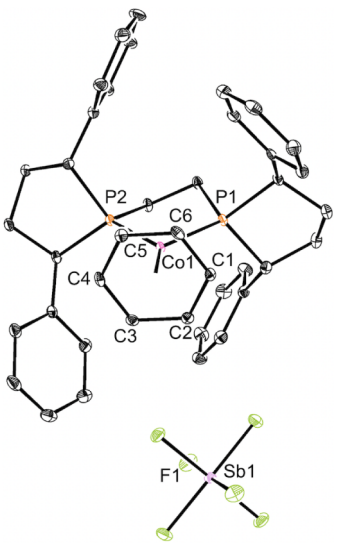


Figure 2. Solid-state structure of **Co-2aa** at 30% probability; ellipsoids and hydrogen atoms omitted for clarity. Co−centroid (C1,C6): 1.581 Å; Co−P1: 2.147(1) Å; Co−P2: 2.148(1) Å.

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The solid-state structures of both **Co-1c** and **Co-1d** were determined by X-ray diffraction and exhibited distinct confirmations of the bound arene (Figure 3). For **Co-1c**, a

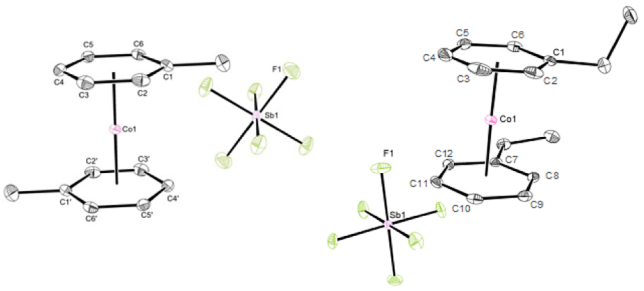

Figure 3. Solid-state structures of **Co-1c** (left) and **Co-1d** (right). Molecular structures at 30% probability; ellipsoids and hydrogen atoms omitted for clarity. **Co-1c**: Co−centroid (C1,C6): 1.745 Å, Co−centroid (C7,C12): 1.745 Å; **Co-1d**: Co−centroid (C1,C6): 1.743 Å, Co−centroid (C7,C12): 1.752 Å.

highly symmetric structure was observed with the toluene methyl groups oriented 180° from each other. A Co−centroid (C1,C6; C7,C12) distance of 1.745 Å was observed for both rings that are related by symmetry. The solid-state molecular geometry of **Co-1d** showed alkyl groups in an staggered conformation. Cobalt−centroid (C1,C6; C7,C12) distances of 1.743 and 1.752 Å were measured. Both **Co-1d** and **Co-1c** distances correspond to previously reported values.[15] The isolation of **Co-1c** and **Co-1d** accomplished with sterically attenuated arenes provides a unique platform for precatalyst generation given the use of an accessible, low molecular weight anion, paired with the relative ease of handling and reproducibility of the syntheses.

Synthesis of Cationic Bis(phosphine) Co(I) Precatalysts. The substitutional lability of **Co-1c** and **Co-1d** in the presence of bis(phosphines) was investigated and compared with previously reported $[(\eta^6\text{-}C_6H_6)_2Co][Al(pftb)_4]$ (**Co-1e**).[15] Bis(phosphine) cobalt(I) precatalysts are desirable due to their extended stability at room temperature[6,17] and versatility in numerous catalytic transformations.[6,7,11,13,17,21] A general ligand substitution procedure was developed for both wide and narrow bite-angle bis(phosphines). Precatalysts were initially synthesized by using a 5:1 mixture of $C_6H_5CF_3$ and C_6H_6. However, decomposition to bis(phosphine)$CoCl_2$ was observed, arising from adventitious $C_6H_5CCl_3$ in commercial sources of $C_6H_5CF_3$ that had an exaggerated effect on precatalyst formation using wide bite-angle ligands. The use of 1,2-difluorobenzene suppressed this deleterious reactivity. A solution of the desired cobalt(I) bis(η^6-arene) complex in a mixture of 1,2-difluorobenzene:arene (5:1) was added to the bis(phosphine) and stirred for 15 min. This procedure furnished the targeted bis(phosphine) cobalt(I) arene products in 84−99% yield (Scheme 4A). **Co-1c**, **Co-1d**, and **Co-1e** were compatible with substitution by rigid and flexible C_2-bridged bis(phosphines) including: (*R*,*R*)-^{Ph}BPE, (*R*,*R*)-^{iPr}DuPhos, (*R*,*R*)-BenzP*, (*R*,*R*',*S*,*S*')-DuanPhos, and dycpe (Scheme 4A). Confirmation of precatalyst formation was based on ^{1}H and ^{31}P NMR spectroscopy by comparison to literature values.[6,11,17] Wide-bite angle bis(phosphine) precatalysts dppp, dppf, and JosiPhos ligand, SL-J002-1, were also isolated in high yields.

These results demonstrate the generality and versatility of the cobalt sandwich complexes as a means to generate diverse precatalysts in a single step and are comparable with HTE. The redox neutral substitution enabled single-crystal isolation of compounds not-otherwise isolable with previously reported methods,[10−13] including [(dppf)Co(η^6-C_6H_6)][Al(*pftb*)$_4$] (**Co-2m**), [(dppf)Co(η^6-C_6D_6)][SbF_6] (**Co-2n**),[a] [(dppp)Co-(η^6-C_6H_5Me)][SbF_6] (**Co-2t**), and [(SL-J002-1)Co(η^6-C_6H_6)][Al(*pftb*)$_4$] (**Co-2v**) (Scheme 4B).

Applications in Cobalt-Catalyzed Reactions. The access to well-defined cationic cobalt(I) precatalysts from a single-component precursor is advantageous insofar as it eliminates the requirement for activators and other additives. With arene substitution for bis(phosphines) established, a selection of cationic cobalt(I)-mediated reactions was evaluated, including asymmetric hydrogenation, formal [2 + 2] cycloaddition, hydroboration, and C(sp^2)−H functionalization.

Bis(phosphine) cobalt complexes have emerged as highly effective precatalysts for asymmetric alkene hydrogenation and have been applied to the enantioselective synthesis of active pharmaceutical ingredients (API).[5−7] To date, cobalt catalyst discovery using HTE for these reactions has been limited to $CoCl_2$ activated with zinc.[5] These methods typically generate neutral, open shell bis(phosphine)cobalt(0) or (II) intermediates that operate by an unsaturated mechanism.[18] This approach has been applied to the asymmetric synthesis of a phenylalanine derivative (MAC)[18] and Levetiracetam,[5] the chiral product used in the treatment of epilepsy (Scheme 5). Recognizing the recent developments in cationic cobalt(I) catalyzed asymmetric alkene hydrogenations,[6,7,11] HTE precursors capable of accessing comparable ligand space to that of $CoCl_2$/Zn were sought.

To establish the utility of cationic bis(η^6-arene) cobalt(I) complexes as HTE compatible precursors, eight representative chiral bis(phosphine) ligands were selected for the asymmetric hydrogenations of dehydro-MAC and dehydro-Levetiracetam. The three precursors were first plated with ligands to form the precatalyst in C_6H_5Me or $C_6H_5CF_3$, similar to the approach used in precious metal catalyst discovery.[19] The hydrogenations were conducted in MeOH or THF with 500 psi of H_2 at 50 °C (Scheme 5). With 10 mol % catalyst loading, minimal deviation in the yield and selectivity between **Co-1e**, **Co-1c**, and **Co-1d** was observed (Scheme 5). Gratifyingly, SL-J002-1 and SL-J004-1 were both active and selective (>65% ee) in the hydrogenation of dehydro-Levetiracetam. At 1 mol % catalyst loading, **Co-1e**, **Co-1c**, and **Co-1d** maintained high activity as well as enantioselectivity with narrow bite-angle bis(phosphines), including (*R*,*R*)-^{iPr}DuPhos and (*S*,*S*)-^{Ph}BPE. Yields for both MAC and Levetiracetam were comparable to literature values (Scheme 5).[5,12] The evaluation of **Co-1e**, **Co-1c**, and **Co-1d** as precursors in catalyst discovery by HTE has demonstrated consistent reactivity regardless of the arene or anion. From these findings, additional studies were pursued with **Co-1d** given the commercial availability of the anion, the relative ease of handling, and the low molecular weight. Having identified **Co-1d** as the preferred precursor, 192 chiral bis(phosphines) were evaluated in the asymmetric hydrogenation of dehydro-Levetiracetam to compare cationic cobalt(I) catalysts with state-of-the-art cobalt(0) analogs.[5] To the best of our knowledge, this represents the first comparative evaluation of single-electron-differentiated cobalt catalysts by HTE.[7] **Co-1d** was first added to chiral ligands in C_6H_5Me to form the precatalyst followed by removal of excess solvent. Substrate was then added in MeOH followed by the

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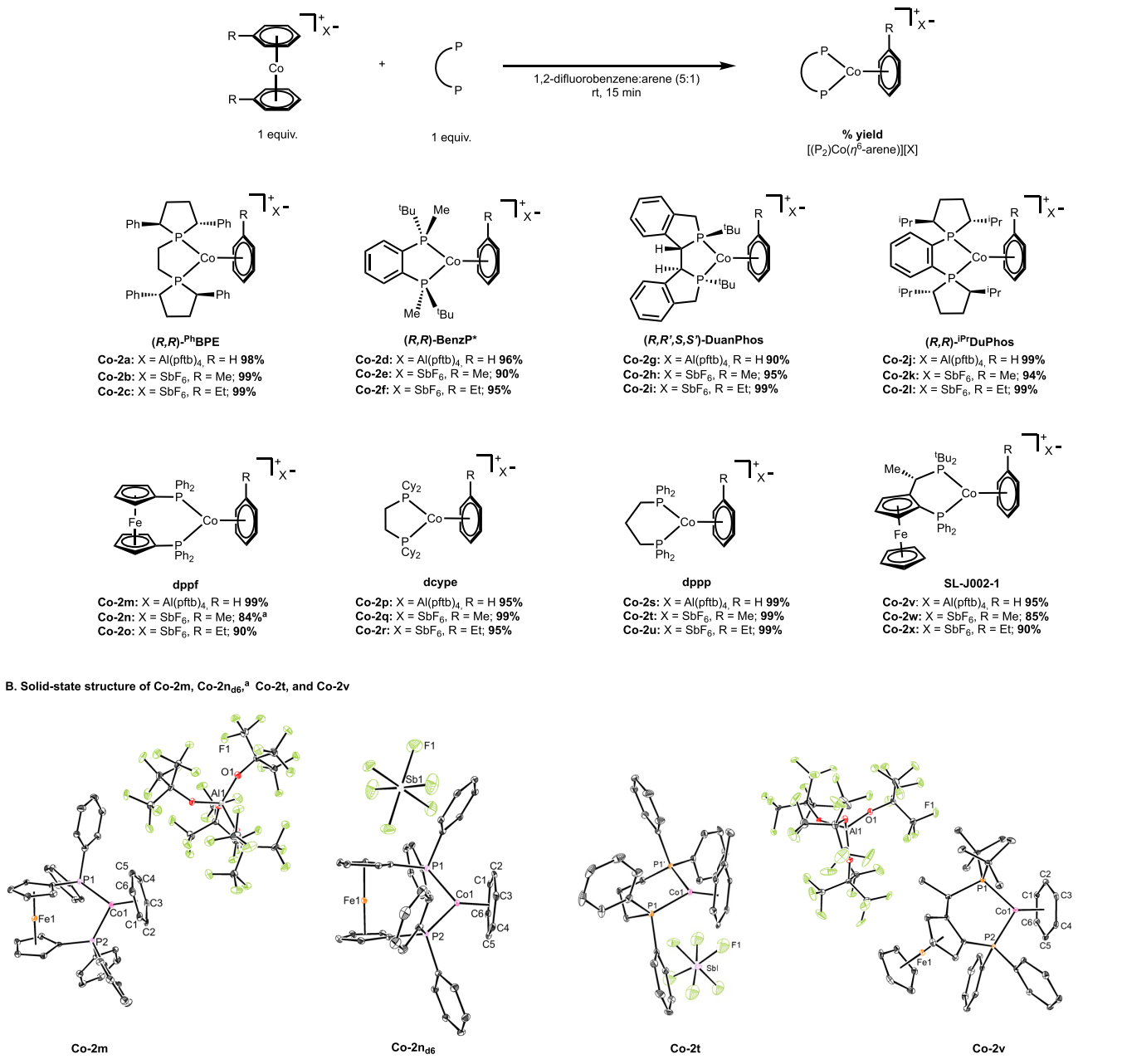
Scheme 4. (A) Synthesis of [(Bis(phosphine))Co(η^6-arene)][X]; (B) Solid-State Structures of Co-2m, Co-2n$_{d6}$, Co-2t, and Co-2v at 30% Probability; Ellipsoids and Hydrogen Atoms are Omitted for Clarity[a]



[a]Co-2n$_{d6}$ was isolated from the solution of $C_6H_5CF_3$:C_6D_6 (1:1)

addition of 500 psi H_2 (Scheme 6). The optimal ligands were (*R*,*R*)-^{Ph}BPE, (*R*,*R*)-^{R}DuPhos (*R* = Me, Et, ^{i}Pr), (*R*,*R*′,*S*,*S*′)-DuanPhos, (*S*,*S*)-ChiraPhos, and (*S*,*S*,*S*,*S*)-Me-KetalPhos, all producing synthetically useful enantiomeric excesses above 88% (Scheme 6). These results represent a new method for single component cobalt(I) precursors to comprehensively evaluate the chiral ligands in the asymmetric hydrogenation of pharmaceutically relevant intermediates. The phosphines for cationic cobalt(I) catalysis were consistent with the collection of ligands best suited for cobalt(0).[5] However, cobalt(0) and cationic cobalt(I) catalysts should both be evaluated in parallel as distinct reactivity differences have been observed.[6,7]

The asymmetric hydrogenation of dehydro-Sitagliptin with cobalt is unique to bis(phosphine)Co(I) cations, where both bis(phosphine)$CoCl_2$/Zn and bis(phosphine)Co(COD) showed no reactivity.[6] However, the minimal ligand compatibility of $(py)_2Co(CH_2SiMe_3)_2$ (**Co-3**) in combination with FcBAr$^{F}_4$ remains a challenge with HTE adoption.[6] Using HTE, **Co-1d** was plated alongside **Co-1e** for comparison of anion performance in parallel to **Co-3** to benchmark catalyst formation using the OIRE. Eight representative chiral ligands were first complexed to Co(I) precursors (Scheme 7). A solution of dehydro-Sitagliptin in THF was added to the plates containing 10 mol % [Co] followed by addition of 500 psi H_2 and heating to 50 °C over 18 h. Precatalysts generated by

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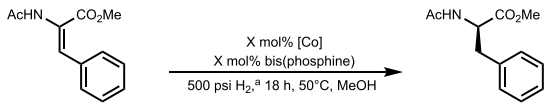
Scheme 5. HTE Evaluation of (A) Asymmetric Hydrogenation of Methyl (*E*)-2-acetamido-3-phenylacrylate (MAC); (B) Dehydro-Levetiracetam Using Co-1e, Co-1c, and Co-1d as Precursors[a]

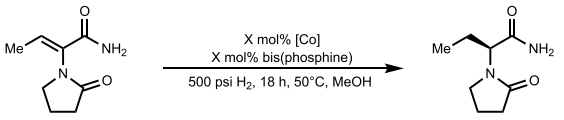
A. Asymmetric Hydrogenation of Dehydro-MAC



Literature Precursor: [(*R,R*)-(^iPrDuPhos)Co(η^6-arene)][BAr$^F_4$]$^{b,ref\ 11}$ > 99% yield, > 99% ee

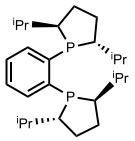
		Co-1c		Co-1d		Co-1e	
mol %	L	% yield	% ee	% yield	% ee	% yield	% ee
10	(*R,R*)-^{iPr}DuPhos	99.9	– 91.0	99.9	– 90.2	99.9	– 89
1	(*R,R*)-^{iPr}DuPhos	99.9	–88.4	95.2	–88.9	99.9	–86.5

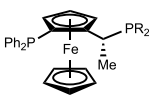
B. Asymmetric Hydrogenation of Dehydro-Levetiracetam



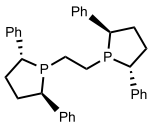
Literature Precursor: (*R,R*)-(^{Ph}BPE)CoCl$_2$$^{c,ref\ 5}$ 99.8% yield, –98.3% ee

		Co-1c		Co-1d		Co-1e	
mol %	L	% yield	% ee	% yield	% ee	% yield	% ee
10	SL-J002-1	37.1	–89.9	36.4	–90.7	45.6	–81.5
10	SL-J004-1	82.9	68.4	88.5	67.3	76.1	65.9
1	(*R,R*)-^{Ph}BPE	99.9	–97.7	99.9	–98.7	99.9	–97.7
1	(*R,R*)-^{iPr}DuPhos	99.9	87.9	99.8	85.3	99.9	85.7


(*R,R*)-^{iPr}DuPhos



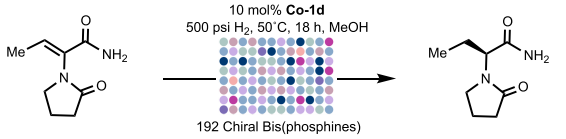
SL-J002-1; R = ^{t}Bu
SL-J004-1; R = Cy


(*R,R*)-^{Ph}BPE

[a]500 psi = 34 atm. [b]1 mol% [(*R,R*)-(^{iPr}DuPhos)Co(η^6-C$_6$H$_6$)][BAr$^F_4$] at 60 psi H$_2$ in THF. [c]0.2 mol% (*R,R*)-(^{Ph}BPE)CoCl$_2$ with 100 mol% Zn dust.

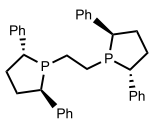
ligation of (*R,R*)-^{iPr}DuPhos to **Co-1d** furnished the product in only 16% yield, while both (*R,R*)-^{iPr}DuPhos and (*S,S*)-Binapine precatalysts derived from **Co-1e** and **Co-3** precursors provided the chiral product in >99% yield (Scheme 7). (*R,R*)-^{iPr}DuPhos precatalysts from **Co-1d** and **Co-1e** were independently synthesized in identical yields (Scheme 4), suggesting anion dependent reactivity for the asymmetric hydrogenation of dehydro-Sitagliptin. Enantiomeric excess >85% were obtained regardless of catalyst precursor. **Co-1e** was then further evaluated using the 192 bis(phosphine) ligand library, but no further reactivity with other bis(phosphines) was observed (Scheme 7). Additional catalyst formation studies with **Co-1d** were conducted to probe precatalyst formation and potential substrate-mediated deactivation. **Co-1d** was stirred with (*R,R*)-^{iPr}DuPhos, (*R,R*)-BenzP*, and (*S,S*)-^{Ph}BPE for 5 or 60 min in different solvents, followed by incubation with dehydro-Sitagliptin for an additional 5 or 60 min. Low activity and high enantioselectivity was observed for all conditions evaluated (Tables S13,S14). These results support anion effects likely due to the increased degree of coordination associated with [SbF$_6$]$^-$.[20]

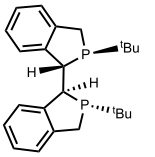
Scheme 6. HTE Evaluation of Chiral Ligand Libraries for the Asymmetric Hydrogenation of Dehydro-Levetiracetam Using Co-1d

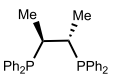


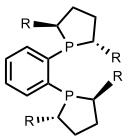
CoCl$_2$·6H$_2$O$^{ref\ 5}$ 15 ligands ee > 80%
Co-1d 9 ligands ee > 80%

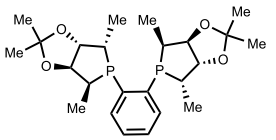
Select Chiral Ligands


(*R,R*)-^{Ph}BPE
99.6% yield, 97.4% ee

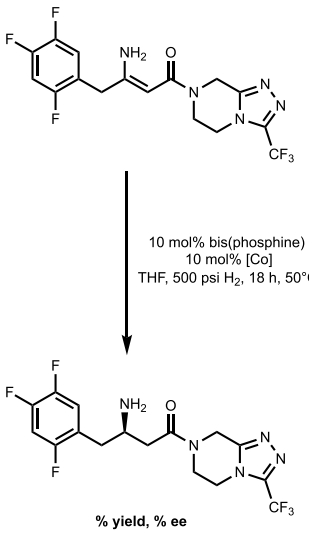

(*R,R′,S,S′*)-DuanPhos
94.0% yield, 95.7% ee

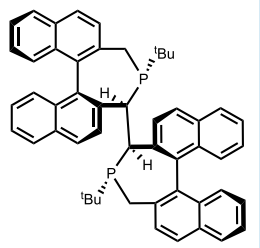

(*S,S*)-Chiraphos
99.6% yield, –88.1% ee

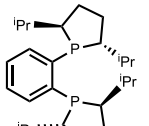

(*R,R*)-^{Me}DuPhos 99.7% yield, 98.2% ee
(*R,R*)-^{Et}DuPhos 99.9% yield, 98.0% ee
(*R,R*)-^{iPr}DuPhos 99.8% yield, –91.3% ee


(*S,S,S,S*)-Me-KetalPhos
99.7% yield, –96.7% ee

Scheme 7. HTE Evaluation of Asymmetric Hydrogenation of Dehydro-Sitagliptin[a]




(*S,S*)-Binapine


(*R,R*)-^{iPr}DuPhos

Only ligands with > 80% ee from 192 bis(phosphines) screened using ***Co-1e***

[(*R,R*)-(^{iPr}DuPhos)Co(η^6-C$_6$H$_6$)][BAr$^F_4$]$^{ref\ 6,a}$ >99% yield, 92% ee

	Co-1d		Co-1e		Co-3	
L	% yield	% ee	% yield	% ee	% yield	% ee
(*S,S*)-Binapine	16.0	–86.9	99.7	–89.0	99.7	–88.5
(*R,R*)-^{iPr}DuPhos	16.4	86.7	99.8	89.2	99.3	85.1

[a]1000 psi H$_2$ = 68 atm H$_2$.

Beyond asymmetric hydrogenation, a number of C−C and C−B bond-forming reactions have been reported using cationic cobalt(I) complexes as catalysts. Rajanbabu and coworkers have described the synthesis of chiral cyclobutanes and cyclobutenes through the formal [2 + 2] cycloaddition of commodity olefins and alkynes from in situ generated dppf cobalt(I) cations stabilized by the [BAr$^F_4$]$^-$ anion.[21] Our

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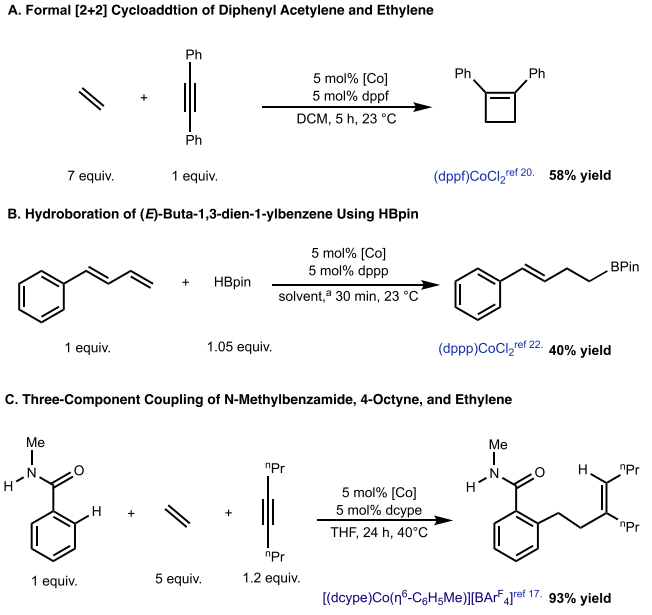
laboratory subsequently reported the synthesis of well-defined [(dppf)Co(η^6-arene)][$BAr^F{}_4$] complexes that are effective for the formal [2 + 2] cycloaddition of minimally functionalized alkynes with ethylene.[22] Of particular interest is whether the reactivity of this type can be promoted by cationic cobalt(I) catalysts bearing more cost effective, low molecular weight anions, such as $[SbF_6]^-$.

To evaluate the role of cobalt sandwich complexes as catalytic precursors for C−C bond formation, the formal [2 + 2] cycloaddition between diphenylacetylene and ethylene was probed using cobalt precursors stabilized by both $[SbF_6]^-$ and $[Al(pftb)_4]^-$ anions. [(dppf)Co(η^6-C_6H_6)][$Al(pftb)_4$] (**Co-2m**), [(dppf)Co(η^6-C_6H_5Me)][SbF_6] (**Co-2n**), and [(dppf)-Co(η^6-C_6H_5Et)][SbF_6] (**Co-2o**) were generated through the treatment of **Co-1e**, **Co-1c**, and **Co-1d** with phosphine prior to addition to the reaction mixture (Scheme 8A). Seven

Scheme 8. C−C and C−B Bond-Forming Reactions Promoted by Co-1e, Co-1c, and Co-1d Precursors for In Situ Catalyst Generation[a]



Entry	**Co-1c** (% yield)	**Co-1d** (% yield)	**Co-1e** (% yield)
[2+2] Cycloaddition	42	57	65
Hydroboration	41	60	48
Three-Component Coupling	17(73)[b]	29	56

[a]Solvent = THF except Et_2O for **Co-1e**. [b]Reaction time = 48 h.

equivalents of ethylene were added to a CH_2Cl_2 solution containing diphenyl acetylene and 5 mol % of [Co]. After stirring the reaction mixture for 5 h, cyclized products from **Co-2m**, **Co-2n**, and **Co-2o** precatalysts were obtained in 65%, 42%, and 57% yield, respectively. Consistent reactivity was observed regardless of anion or arene, similar to observations made in asymmetric hydrogenation, highlighting generality across two distinct catalytic transformations.

The regio- and enantioselective hydroboration of minimally functionalized alkenes has also been reported in high yields using cationic cobalt(I) catalysis.[23] The regioselectivity of the transformation was tuned based on the bis(phosphine)[10] or the phosphino oxazoline[24] ligand used. However, it is unclear from the in situ catalyst generation procedure how additives such as Zn and $NaBAr^F{}_4$,[10,23,24] influence catalyst performance. **Co-1e**, **Co-1c**, and **Co-1d** were used to generate single component cobalt precatalysts. The anti-Markovnikov hydroboration of (*E*)-buta-1,3-dien-1-ylbenzene using HBPin was selected as a representative reaction using dppp (Scheme 8B). A solution of (*E*)-buta-1,3-dien-1-ylbenzene in either THF or Et_2O was added to 5 mol % of [(dppp)Co(η^6-C_6H_6)][Al-($pftb)_4$] (**Co-2s**), [(dppp)Co(η^6-C_6H_5Me)][SbF_6] (**Co-2t**), and [(dppp)Co(η^6-C_6H_5Et)][SbF_6] (**Co-2u**) following ligation of dppp to **Co-1e**, **Co-1c**, and **Co-1d** in 1,2-difluorobenzene. 1.05 equiv of HBPin were added and the reaction stirred for 30 min. The functionalized product was obtained from **Co-2s**, **Co-2t**, and **Co-2u** precatalysts in 48%, 41%, and 60% yields, respectively (Scheme 8B). In the absence of Zn, single component dppp precatalysts achieved greater yields than previously reported methods.[23] Again, comparable performance was consistently observed independent of the anion or arene used in the cobalt precatalyst.

Cobalt(III) metallacycles accessed from cationic bis-(phosphine) cobalt(I) complexes have been shown to promote directed C(sp^2)−H functionalization.[25] Our group has generated the well-defined cobalt(I) precatalyst, [(dcype)Co-(η^6-C_6H_5Me)][$BAr^F{}_4$] and demonstrated its role in the three-component coupling of arenes, alkynes, and ethylene that proceeds through the same metallacycle intermediate.[17] Similar to the other transformations described, developing a more accessible, low molecular weight, single component precatalyst is desirable. Precatalyst evaluation was conducted in a representative three-component coupling of *N*-methyl benzamide, 4-octyne, and ethylene (Scheme 8C). The cobalt(I) sandwich precursors, [(dcype)Co(η^6-C_6H_6)][$Al(pftb)_4$] (**Co-2p**), [(dcype)Co(η^6-C_6H_5Me)][SbF_6] (**Co-2q**), and [(dcype)-Co(η^6-C_6H_5Et)][SbF_6] (**Co-2r**), were treated with dcype in 1,2-difluorobenzene prior to the addition of 1 equiv *N*-methyl benzamide and 1.2 equiv of 4-octyne in THF, followed by addition of 5 equiv of ethylene. After 24 h at 40 °C, the **Co-2q** and **Co-2r** precatalysts furnished the C−H functionalization product in 17% and 29% yield, respectively (Scheme 8C). The use of **Co-2p** as the cobalt precursor furnished the product in 56% yield after 24 h. While the $[SbF_6]^-$ containing cobalt catalysts reacted more slowly than their $[Al(pftb)_4]^-$ counterparts, their yield could be improved to 73% by stirring the reaction in a sealed vessel for 48 h.

CONCLUSION

Cationic bis(η^6-arene) cobalt sandwich complexes, **Co-1c** and **Co-1d** stabilized by the commercially available anion $[SbF_6]^-$, have been synthesized and characterized by multinuclear NMR spectroscopy and X-ray diffraction. Their resulting substitution chemistry with bis(phosphine) ligands was applied to the synthesis of a host of cationic cobalt(I) precatalysts. Three examples, **Co-1c**, **Co-1d**, **and Co-1e** were compatible with both narrow- and wide-bite angle bis(phosphines), an advance over existing methods of precatalyst generation. This method was applied in asymmetric hydrogenation, C−C, C−B bond-formation, and C−H functionalization chemistry, highlighting the extent of catalyst discovery enabled by well-defined organometallic precursors coupled with HTE.

METHODS

General Procedures for In Situ Precatalyst Formation. A 3.85 mL scintillation vial was charged with an *o*-$C_6H_4F_2$ solution of bis(phosphine) (1 equiv). In a separate 20 mL

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scintillation vial, a solution of crystalline yellow-brown bis(η^6-arene) Co(I) cation (1 equiv) in *o*-$C_6H_4F_2$ was prepared and added dropwise to the vial containing the bis(phosphine). The solution was stirred for 15 min at ambient temperature, followed by concentration under reduced pressure.

General Microscale High-Throughput Experimentation Procedure. Microscale reactions were carried out in 8 × 30 mm glass vial inserts in aluminum 96-well microliter plates. Solutions of the ligand (0.1 M THF) were added and concentrated on the plate. Metal precursor solutions were then added, and the mixture was stirred at room temperature for 10 min. Volatiles were removed by a vacuum centrifuge, with subsequent addition of substrate solutions. The plates were sealed in pressure vessels, removed from the glovebox, and connected to a gas manifold. The supply line and vessel headspace were purged ten times with N_2, followed by three purges with H_2. The desired hydrogen pressure and temperature were added to the vessel with 500 rpm shaking. After the desired reaction time, the vessel was vented, and the reactions were sampled for analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c03843.

Preparation of cobalt complexes; spectroscopic data; general procedure for catalytic transformations; references (PDF)

Solid-state structure of [(SL-J002-1)Co(η^6-C_6H_6)][Al(*pftb*)$_4$] (CIF)

Solid-state structure of [(dppf)Co(η^6-C_6H_6)][SbF_6] (CIF)

Solid-state structure of [(dppf)Co(η^6-C_6H_6)][Al(*pftb*)$_4$] (CIF)

Solid-state structure of [(dppp)Co(η^6-C_6H_5Me)][SbF_6] (CIF)

Solid-state structure of [dppf][Al(*pftb*)$_4$] (CIF)

Solid-state structure of [((*R*,*R*)−DuanPhos)Co(η^6-C_6H_5Et)][SbF_6] (CIF)

Solid-state structure of [((*R*,*R*)−BenzP*)$Co(CO)_3$][SbF_6] (CIF)

Solid-state structure of [(η^6-C_6H_5Et)$_2$Co][SbF_6] (CIF)

Solid-state structure of [((*R*,*R*)−PhBPE)Co(η^6-C_6H_6)][SbF_6] (CIF)

Solid-state structure of [(η^6-C_6H_5Me)$_2$Co][SbF_6] (CIF)

Solid-state structure of [((*R*,*R*)−BenzP*)Co(η^6-C_6H_5Me)][SbF_6] (CIF)

Solid-state structure of [(η^6-C_6H_6)$_2$Co][$BAr^F{}_4$] (CIF)

Accession Codes

CCDC deposition numbers 2348017−2348028 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.ca-m.ac.uk, or by contacting The Cambridge Crystallographic Data Centre,12 Union Road, Cambridge CB21EZ, UK; fax:+441223336033.

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Notes

The authors declare no competing financial interest.

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