C–H Activation by Isolable Cationic Bis(phosphine) Cobalt(III) Metallacycles

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ABSTRACT: Five- and six-coordinate cationic bis(phosphine) cobalt(III) metallacycle complexes were synthesized with the general structures, [(depe)Co(cycloneophyl)(L)(L')][BAr^F_4] (depe = 1,2-bis(diethylphosphino)ethane; cycloneophyl = [κ-*C*:*C*-($CH_2C(Me)_2$)C_6H_4]; L/L' = pyridine, pivalonitrile, or vacant site; BAr^F_4 = B[(3,5-(CF_3)$_2$)C_6H_3]$_4$). Each of these compounds promoted facile directed C(sp^2)–H activation with exclusive selectivity for *ortho*-alkylated products, consistent with the selectivity of reported cobalt-catalyzed arene-alkene-alkyne coupling reactions. The direct observation of C–H activation by cobalt(III) metallacycles provided experimental support for the intermediacy of these compounds in this class of catalytic C–H functionalization reaction. Deuterium labeling and kinetic studies provided insight into the nature of C–H bond cleavage and C–C bond reductive elimination from isolable cobalt(III) precursors.

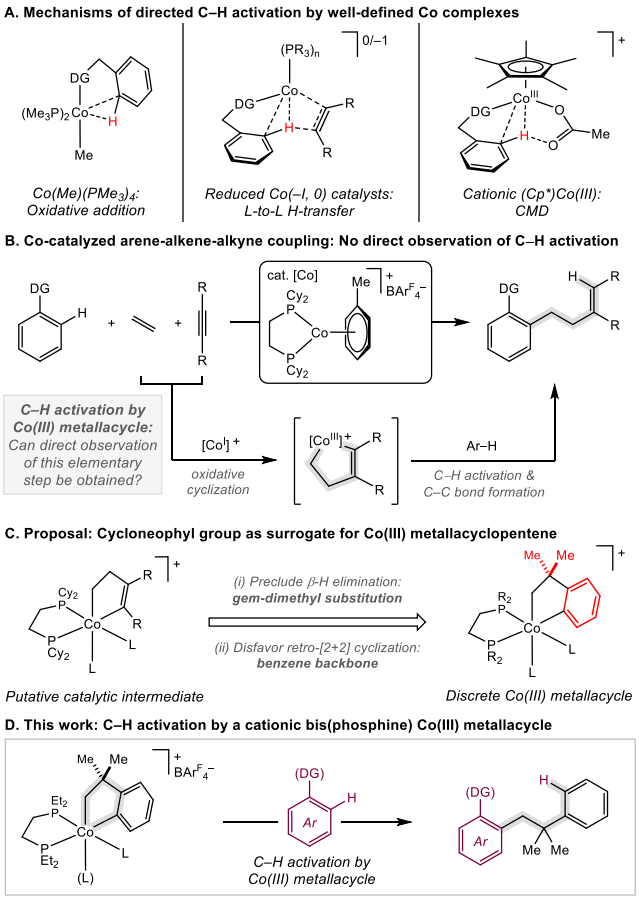
INTRODUCTION

Developments in transition metal-catalyzed C–H activation have led to important advances in synthetic disconnection strategy by enabling the direct transformation of ubiquitous C–H bonds into C–C or C–heteroatom bonds. Directed arene C(sp^2)–H activation has been widely exploited in catalytic reactions and a diverse array of mechanisms have been proposed.[1,2] Among earth-abundant metals that promote directed C(sp^2)–H functionalization, cobalt has proven to be particularly versatile due to its ability to promote C–H activation through a number of distinct pathways depending on the oxidation state, overall charge, and ligand environment of the cobalt center.[3]

Mechanisms for cobalt-mediated C–H activation have been elucidated as part of both stoichiometric and catalytic studies using well-defined cobalt precursors (Scheme 1A). Stoichiometric studies by Klein[4] using Co(Me)(PMe_3)$_4$ established that a neutral cobalt(I) complex mediates facile cyclometallation reactions likely proceeding by C–H oxidative addition followed by reductive elimination of methane (Scheme 1A). More recently, cobalt-catalyzed hydroarylation reactions using reduced Co(0) and Co(–I) precatalysts, Co(PMe_3)$_4$[5] and [Co(PPh_3)$_3$(N_2)][Li],[6] have been reported and concerted ligand-to-ligand hydrogen transfer[7] of the arene C–H bond to the unsaturated coupling partner with concomitant 2-electron oxidation of the cobalt center was proposed. Additionally, redox-neutral concerted metalation-deprotonation (CMD) by cobalt(III) complexes has been frequently invoked with [C_5Me_5]-ligated cobalt(III) precatalysts in the presence of carboxylate additives.[8] Notable experimental support for Co(III)-mediated CMD was obtained by Ribas[9] as part of stoichiometric studies using a tetradentate ligand to access isolable cationic Co(III)-aryl complexes.

Recently, a series of bis(phosphine)Co-catalyzed arene and alkene C(sp^2)–H functionalizations have been reported that invoke a distinct mechanism involving a directed C–H activation by a putative Co(III) metallacyclopentene, formed by an alkene-alkyne oxidative [2+2] cyclization.[10,11] While this class of reaction was initially limited to 1,n-enyne coupling partners (n = 6, 7), we recently reported an intermolecular three-component arene-ethylene-alkyne variant using the well-defined cationic cobalt(I) precatalyst [(dcype)Co(η^6-C_7H_8)][BAr^F_4] (dcype = 1,2-bis(dicyclohexylphosphino)ethane; Scheme 1B).[12] Exclusive selectivity for *ortho*-alkylated products was observed, relating to a C–H activation step that transferred the hydrogen to the sp^2 carbon of the metallacycle, followed by C–C bond formation with the sp^3 carbon remaining coordinated to cobalt. The lack of reactivity in two-component control experiments provided circumstantial evidence for the formation of a cationic cobalt(III) metallacyclopentene intermediate prior to arene functionalization, yet direct observation of C–H activation by a well-characterized organometallic complex proved elusive. Computational studies by RajanBabu and co-workers[10d] on the reaction of a 1,6-enyne substrate with methyl acrylate supported the energetic feasibility of a cobalt(III) metallacyclopentene that promotes C–H activation by a σ-bond metathesis mechanism[13,14] directed by the acrylate carbonyl group. With the exception of a sole related example of C(sp^2)–H activation by a cyclopentadienyl cobalt(III) metallacyclopentadiene,[15] direct experimental support for C–H activation by an isolable cobalt(III) metallacycle has been lacking.

Scheme 1. Accepted mechanisms of cobalt-mediated C–H activation and investigation of C–H activation by a cationic bis(phosphine) Co(III) metallacycle.



A primary challenge preventing the study of C–H activation by a cobalt(III) metallacycle is the kinetic instability of the putative metallacyclopentene intermediate (Scheme 1C).[16] Although the general structure of cobalt(III) metallacyclopentene complexes is not well-established in examples without cyclopentadienyl ligands,[17,18] with bis(phosphines)[19] an octahedral low-spin d^6 cobalt center would be expected. However, such a complex would be unlikely to be isolable due to facile *β*-hydride elimination and retro-[2+2] cyclization processes. Consequently, cobalt(III) complexes containing a cycloneophyl group as a surrogate for a metallacyclopentene were targeted given the precedent for this carbocycle to stabilize high oxidation states of Group 10 metals.[20,21] Both *β-gem*-dimethyl substitution and benzene incorporation in the metallacycle backbone are expected to minimize undesired reactivity.

Here we describe the synthesis of a series of bis(phosphine) cobalt(III) cycloneophyl complexes supported by pyridine and nitrile ligands and demonstrate their ability to promote the C(sp^2)–H functionalizations of arenes and alkenes forming directed-*ortho* alkylated products (Scheme 1D). Isolation of discrete metallacycle complexes provided direct observation of C–H activation across the metallacycle and allowed for the mechanism of activation to be explored independently of other steps involved in catalytic functionalization reactions.

RESULTS AND DISCUSSION

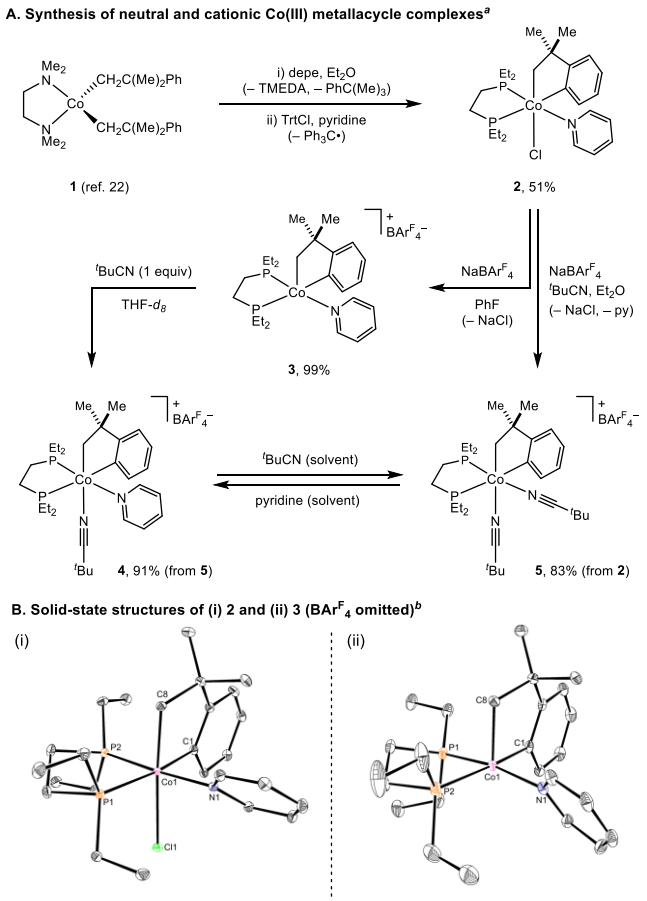
Synthesis of cobalt(III) metallacycle complexes. Bis(phosphine)cobalt(III) metallacycle complexes were synthesized from the cobalt(II) dialkyl precursor (TMEDA)Co($CH_2C(Me)_2Ph)_2$ (**1**) reported by Walter and co-workers.[22] The published procedure involves addition of depe to **1** resulting in displacement of the TMEDA ligand and spontaneous cyclometallation to form cobalt(II) complex (depe)Co(cycloneophyl). Inspired by this precedent, a modified procedure was developed whereby depe-promoted cyclometallation of **1** was followed by single-electron oxidation with trityl chloride and addition of pyridine to furnish the neutral six-coordinate (depe)cobalt(III) metallacycle complex, **2** (Scheme 2A).[23] Formation of a cobalt(III) complex was confirmed by the observation of a diagnostic pair of equal area singlets at 52.0 and 36.1 ppm in the $^{31}P\{^1H\}$ NMR spectrum recorded in benzene-d_6. Complex **2** was isolated in 51% yield as an orange crystalline solid and was characterized by single crystal X-ray diffraction (Scheme 2B, I). The solid-state structure of **2** established that the chloride ligand was *trans* to the sp^3 carbon of the metallacycle. Attempts to synthesize the dcype-ligated analogue of **2** were unsuccessful as the addition of dcype to **1** resulted in rapid consumption followed by decomposition to an unidentified mixture of products.

To access a cationic cobalt(III) metallacycle, **2** was treated with one equivalent of $NaBAr^F_4$ in fluorobenzene to abstract the chloride ligand. Fluorobenzene was chosen as a non-coordinating polar solvent. An immediate color change from orange to blue was observed upon addition of $NaBAr^F_4$, and after removal of NaCl by filtration and recrystallization in fluorobenzene/pentane at –35 °C, a blue crystalline solid was isolated in quantitative yield. The $^{31}P\{^1H\}$ NMR spectrum in THF-d_8 exhibited two singlets at 59.4 and 40.9 ppm that are shifted downfield compared to those of **2**. Single crystal X-ray diffraction confirmed the identity of the product as the five-coordinate cationic cobalt(III) metallacycle **3**, having an idealized square pyramidal geometry with a vacant site *trans* to the sp^3 carbon ligand. Minimal structural differences were apparent from the solid-state structures of **2** and **3** upon replacement of the chloride ligand for the outer-sphere $[BAr^F_4]^-$ anion. Notably, examples of five-coordinate organo cobalt(III) complexes are relatively rare in the absence of tetradentate porphyrin or salen ligands.[24]

To investigate the interaction of neutral ligands with coordinatively unsaturated complex **3**, stoichiometric or solvent quantities of pivalonitrile were added to **3** and produced the mixed pyridine/nitrile- and bis(nitrile)-ligated six-coordinate complexes **4** and **5**, respectively. Analysis of the reactions by $^{31}P\{^1H\}$ NMR spectroscopy in THF-d_8 established that **4** formed immediately and quantitatively in solution (singlets at 58.3 and 36.4 ppm), whereas conversion to **5** (singlets at 66.8 and 49.2 ppm) required multiple cycles of dissolution in pivalonitrile and evaporation *in vacuo* to fully displace the pyridine ligand. Complex **5** was synthesized on preparative scale directly from **2** and was isolated as a yellow solid in 83% yield. Adding excess pyridine to **5** displaced only the nitrile ligand *trans* to the phosphine and resulted in the isolation of **4** as a yellow solid in 91% yield, which was additionally characterized by X-ray diffraction after recrystallization.[25] Interestingly, adding excess pyridine to **3** led to formation of a putative six-coordinate bis(pyridine) complex in solution that was unstable to vacuum, reforming **3**, indicating that two ligat-

ed pyridines around the Co(III) center incur a significant steric penalty that in turn result in increased substitutional lability.

Scheme 2. Synthesis and structural elucidation of five- and six-coordinate cobalt(III) metallacycle complexes.

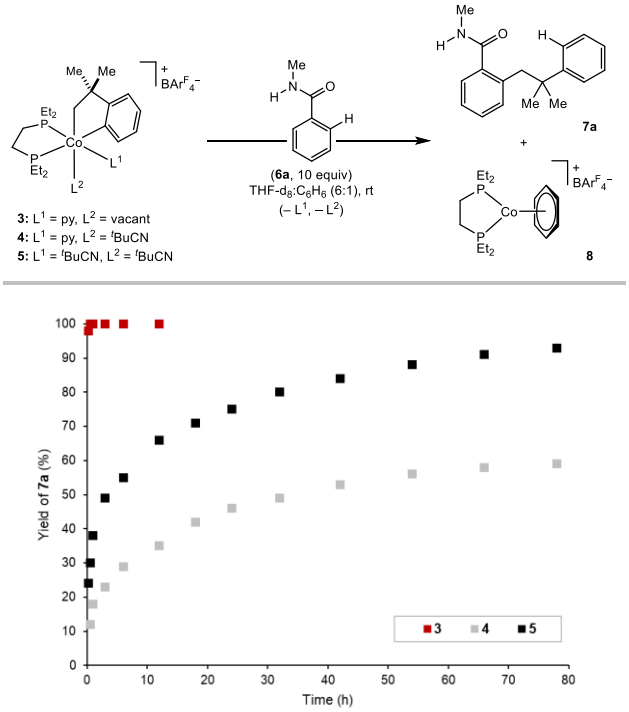


[a]Isolated yields. [b]Ellipsoids at 30% probability with hydrogen atoms omitted for clarity.

Directed C(*sp²*)–H activation and deuterium labeling studies. *N*-Methylbenzamide (**6a**) was selected as a representative substrate to investigate the C–H functionalization reactivity of **3**, **4**, and **5**, given its efficacy as substrate in cobalt-catalyzed arene-ethylene-alkyne coupling reactions.[12] Addition of ten equivalents of **6a** to a 6:1 THF-d_8:benzene solution of **3** (14 mM) resulted in quantitative conversion to *ortho*-alkylated product **7a** in less than 10 minutes at room temperature as determined by ^{1}H NMR spectroscopy (Scheme 3). The rapid reaction provided **7a** with complete selectivity, in which the Co–C(*sp²*) and Co–C(*sp³*) bonds of the metallacycle were converted to C(*sp²*)–H and C(*sp²*)–C(*sp³*) linkages in **7a**, analogous to the selectivity of C–H activation for reported catalytic arene-alkene-alkyne coupling reactions.[10,12] The *ortho*-functionalization was accompanied by simultaneous formation of the organometallic cobalt(I) product, [(depe)Co(η^6-C_6H_6)][BAr^F_4] (**8**). Complex **8** was independently synthesized by oxidatively-induced reductive elimination of (depe)Co(CH_2SiMe_3)$_2$ with FcBAr^F_4, in agreement with the previously reported method,[12,26] and shown to be catalytically competent for cobalt-catalyzed arene-alkene-alkyne coupling.[27]

Complexes **4** and **5** were also treated with **6a** and produced the same outcome, albeit with reduced rates of reaction in the order **3** >> **5** > **4**. Monitoring the reactions by ^{31}P NMR spectroscopy, no organometallic intermediates were observed during the conversion of starting material to complex **8**. The curvature of the time courses with **4** and **5** indicated that the nitrile and pyridine ligands released over the course of the reactions were likely inhibiting the subsequent functionalization. As expected, addition of ten equivalents of pivalonitrile to the reaction of **5** with **6a** led to a dramatically decreased rate (<10% yield, 24 h). By contrast, addition of ten equivalents of pyridine to the reaction of **3** with **6a** did not observably decrease the reaction rate (>95% **7a**, 10 min). Whereas pyridine coordination to the vacant site of **3** is out-competed by coordination of the carbonyl of the substrate, the diminished rates of **4** and **5** is primarily attributed to the dissociation of the nitrile ligand *trans* to the metallacycle alkyl group prior to substrate binding and subsequent *ortho*-C–H activation.

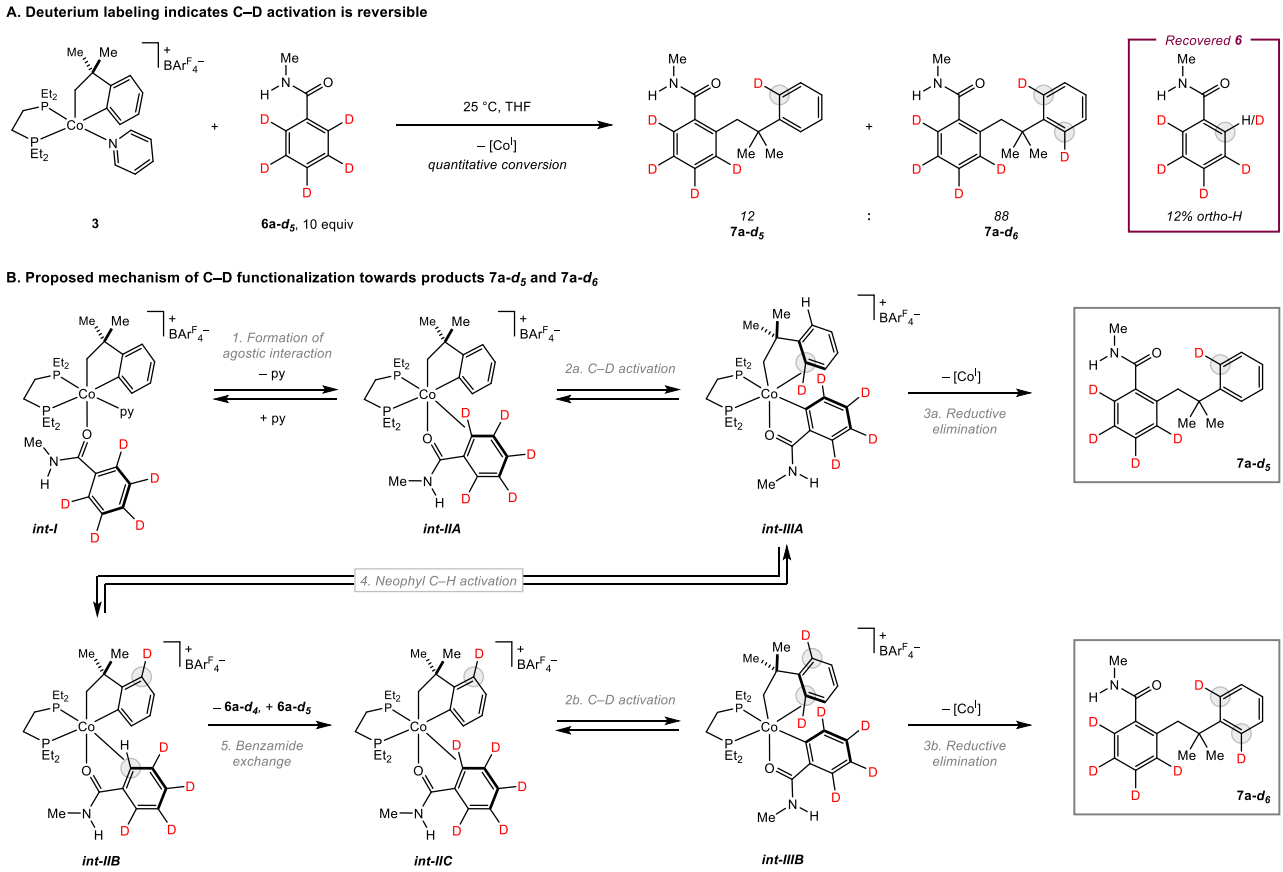
Scheme 3. Direct observation of metallacycle-mediated C–H activation and comparison of rates for 3, 4 and 5.[a]



[a]Yield determined by ^{1}H NMR spectroscopy against an internal standard.

Deuterium labeling studies were conducted with d_5-labeled **6a** (**6a-*d*$_5$**, >99% D at ring positions). Addition of ten equivalents of **6a-*d*$_5$** to a THF solution of **3** resulted in quantitative conversion to two predominant isotopologues of the functionalized product,[28] the minor (**7a-*d*$_5$**) containing one labeled *ortho*-position within the neophyl phenyl group, and the major (**7a-*d*$_6$**) with both phenyl *ortho*-positions labeled (12:88 **7a-*d*$_5$**:**7a-*d*$_6$**, Scheme 4A).

Scheme 4. Deuterium labeling and proposed mechanism of C–D activation.[a]

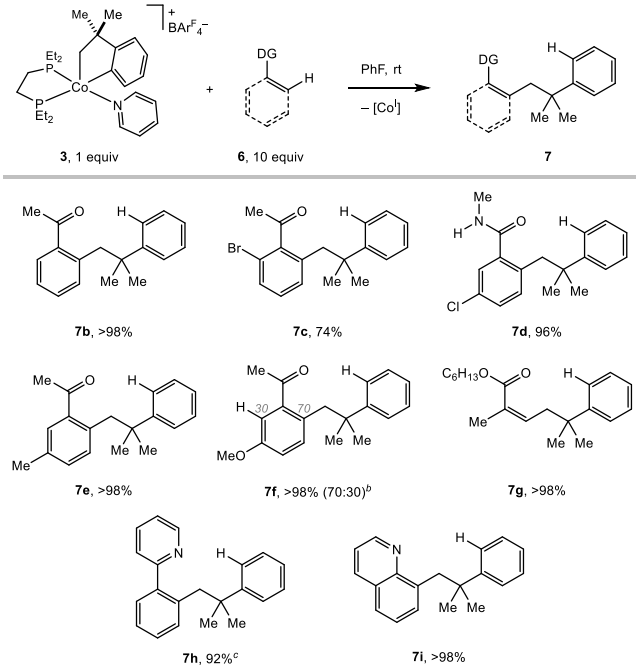


[a]Reaction carried out on 0.03 mmol scale. Ratio of isotopologues determined by ^{1}H, ^{2}H, and ^{13}C NMR spectroscopy.

Analysis of the recovered *N*-methylbenzamide revealed incorporation of natural abundance hydrogen at the *ortho*-position (12% *ortho*-H), indicating transfer of more than one deuterium atom to the functionalized product originated from the presence of excess substrate. Significantly, the formation of **7a-*d*$_6$** demonstrated that C–H activation was reversible.

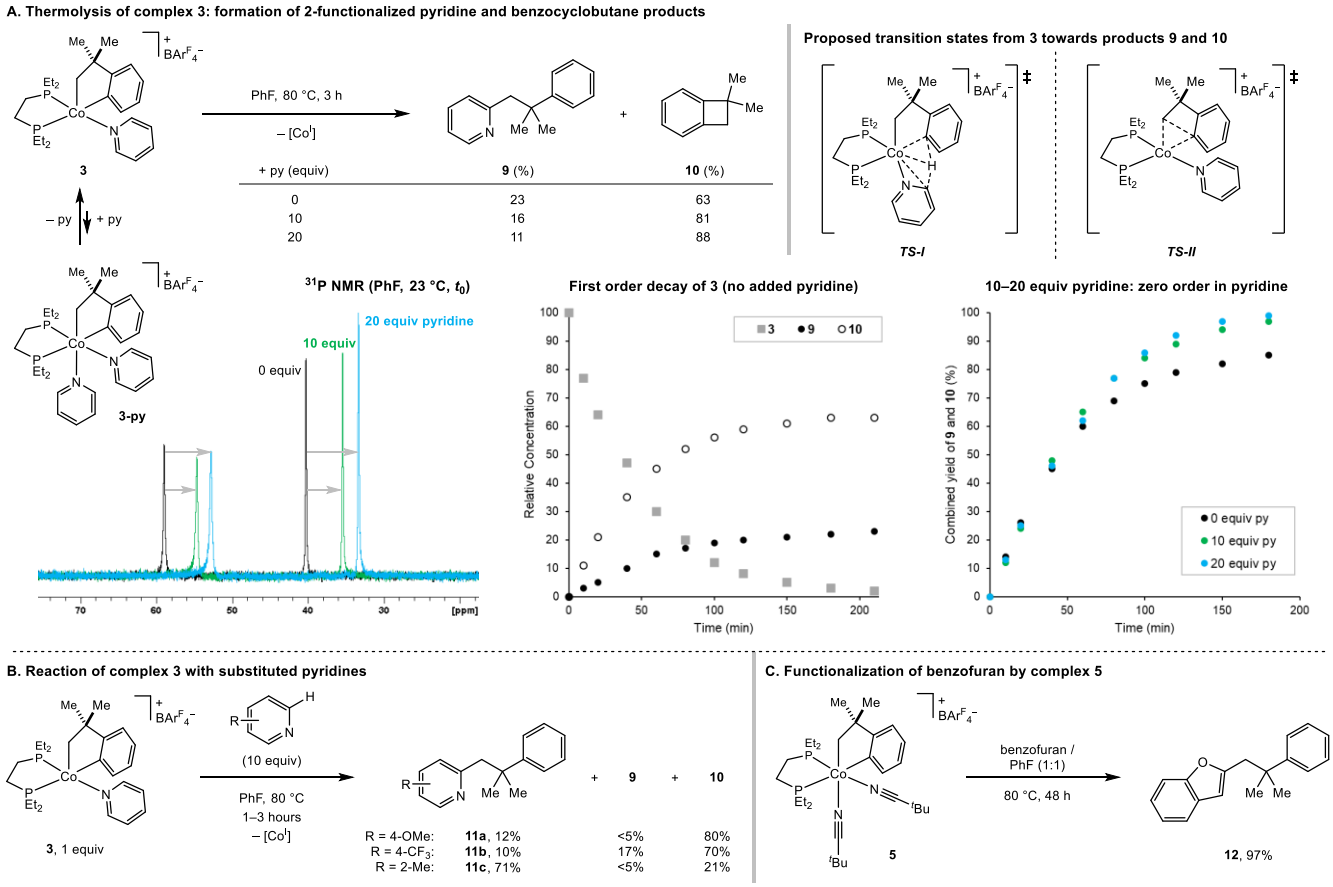
A proposed mechanism for the formation of isotopologues **7a-*d*$_5$** and **7a-*d*$_6$** is shown in Scheme 4B. Following coordination of the substrate carbonyl group to the cobalt (***int-I***), dissociation of the pyridine ligand opens a site for the formation of an agostic interaction of the *ortho*-C–D bond of the benzamide (***int-IIA***). Subsequent C–D activation by a proposed σ-complex assisted metathesis (σ-CAM)[13f,h] results in transfer of the *ortho*-D to the sp^2 carbon of the metallacycle with concomitant cyclometalation of the coordinated benzamide (***int-IIIA***). At this point, C(sp^2)–C(sp^3) bond reductive elimination from ***int-IIIA*** generates isotopologue **7a-*d*$_5$**. Alternatively, rotation of the phenyl in the pendant neophyl group of ***int-IIIA*** and *ortho*-C–H activation transfers a hydrogen to the *ortho*-position of the benzamide and forms a d_1-labeled cycloneophyl group (***int-IIB***). In the presence of excess substrate, exchange of the bound d_4-labeled benzamide (**6a-*d*$_4$**) for **6a-*d*$_5$** (***int-IIC***) followed by *ortho*-C–D activation (***int-IIIB***) and reductive elimination yields **7a-*d*$_6$**. The observation of **7a-*d*$_6$** as the major product indicates that benzamide exchange and benzamide/neophyl C–D/C–H activation are occurring rapidly under the reaction conditions.

Scheme 5. Scope of directed C–H functionalization.[a]



[a]Reactions carried out on 0.02 mmol scale. Yields determined by ^{1}H NMR spectroscopy against an internal standard. [b]Site selectivity determined by ^{1}H NMR spectroscopy. [c]2 equivalents of 2-phenylpyridine used.

Scheme 6. Thermolysis of complex 3 and heteroarene functionalization.[a]



[a]Reactions carried out on 0.01–0.02 mmol scale. Yields determined by ^{1}H NMR spectroscopy using an internal standard.

To investigate the scope of metallacycle-mediated C–H activation, a series of substrates containing different coordinating groups and substitution patterns was added to **3** (Scheme 5). Reactions were conducted in fluorobenzene at ambient temperature[29] with a tenfold excess of substrate and in all cases a major functionalized product was observed arising from directed C(sp^2)–H alkylation. A ketone directing group promoted a facile reaction with **3** to provide the *ortho*-alkylated product in quantitative yield (**7b**, >98%). 2'-Bromoacetophenone generated the functionalized product **7c** in 74% yield, demonstrating the chemoselectivity of the cobalt(III) metallacycle for reaction with the *ortho*-C–H bond over the *ortho*-bromide substituent. Addition of 3-chloro-*N*-methylbenzamide led to complete site-selectivity of activation for the less hindered 6-position (**7d**, 96%), as did 3'-methylacetophenone (**7e**, >98%), suggesting that site-selectivity is largely under steric control. 3'-Methoxyacetophenone was predominantly functionalized at its 6-position, though with minor activation of the 2-position also observed (**7f**, >98%, 70:30 C(6)–H:C(2)–H functionalization). Hexyl methacrylate furnished product in quantitative yield with complete *Z*-selectivity (**7g**, >98%), consistent with the catalytic reactivity reported by RajanBabu.[10d] Finally, *N*-heterocycle-directed activation was demonstrated with 2-phenylpyridine (**7h**, 92%) and quinoline (**7i**, >98%). Functionalization of quinoline at the 8-position, demonstrated that a smaller chelate ring size between the directing group and metal is also compatible for C–H functionalization.

Thermolysis of cobalt(III) metallacycle complexes. Heating a solution of five-coordinate **3** in fluorobenzene at 80 °C resulted in full conversion after 3 hours (Scheme 6A).[30] A mixture of two organic products were identified along with formation of [(depe)Co(η^6-C_6H_5F)][BAr^F_4]. The minor product was the alkylated pyridine (**9**, 23%) arising from C–H activation of the 2-position followed by product-forming reductive elimination, while the major product was the benzocyclobutane (**10**, 63%) resulting from direct C(sp^2)–C(sp^3) bond reductive elimination of the metallacycle.[31,32] Authentic samples of **9** and **10** were synthesized by Ni-catalyzed Kumada cross-coupling[33] and Pd-catalyzed intramolecular C(sp^2)–H functionalization of 2-*tert*-butylbromobenzene.[34]

Monitoring the progress of the reaction by ^{1}H NMR spectroscopy established that **3** underwent first-order decay, demonstrating that the rate of conversion was not inhibited by the pyridine liberated during the course of the reaction. This was supported by the overlap of the plots for product yield versus time upon addition of 10 or 20 equivalents of free pyridine, although slightly higher yields of the organic products were obtained due to suppression of deleterious decomposition of **3**. The combined yields of **9** and **10** were 86%, 97%, and 99% with 0, 10, and 20 equivalents of added pyridine, respectively. At time-zero, the

addition of 10–20 equivalents of pyridine to complex **3** resulted in progressively upfield shifts in the signals of the $^{31}P\{^{1}H\}$ NMR spectra, providing evidence for fast and reversible coordination and dissociation of pyridine to the five-coordinate complex (**3-py**). Nevertheless, the observed reaction orders of 1 and 0 for the cobalt complex and pyridine, respectively, demonstrated that at 80 °C dissociation to the five-coordinate complex was facile.[35] Analysis of the ratio of **9**:**10** with 0–20 equivalents of added pyridine, a change in favor of benzocyclobutane formation was observed with increasing pyridine concentration, showing that large excesses of pyridine had a minor inhibitory effect on the formation of **9**.[36] Two competing transition states – pyridine C–H activation (***TS-I***) and benzocyclobutane formation (***TS-II***) – are proposed to occur from five-coordinate **3**. By analogy with carbonyl-directed C–H activation, the pyridine nitrogen likely assists in the C–H activation, explaining the exclusive selectivity for functionalization of the 2-position. The diminished yield of pyridine functionalization in the presence of excess pyridine is proposed to be the result of slower 2-pyridyl–neophyl C–C reductive elimination (c.f. ***int*-IIIA/B**), allowing for the C–H activation to be more readily reversed by neophyl group activation. Thermolysis of **3** in the presence of 10 equivalents of pyridine-d_5 resulted in <5% and 92% respective yields of *d*-labeled **9** and **10**, indicating that the transition state barriers for 2-pyridyl C–H activation and reductive elimination steps are comparable under these conditions.

To gain further insight into the pyridine functionalization, **3** was treated with a series of substituted pyridines (4-OMe, 4-CF_3, and 2-Me; 10 equivalents, Scheme 6B). Using 4-methoxypyridine or 4-(trifluoromethyl)pyridine, benzocyclobutane **10** remained as the major product of the reactions (80% and 70% **10**, respectively). However, while 4-methoxypyridine outcompeted pyridine in the functionalization of its 2-position (12% **11a** versus <5% **9**), pyridine was more readily activated than 4-(trifluoromethyl)pyridine (10% **11b** versus 17% **9**). The observed product distributions are consistent with a more facile C–H activation for electron-rich pyridines but with increasing inhibition of 2-pyridyl reductive elimination with pyridine Lewis basicity. Notably, 2-picoline switched the selectivity of the reaction in favor of pyridine functionalization (71% **11c**, <5% **9**, 21% **10**), indicating that the steric impact of 2-substitution has a more dramatic effect on product selectivity than the electronic properties of the heteroaromatic ring.

Heating a solution of six-coordinate cobalt(III) metallacycle complex **5** in fluorobenzene at 80 °C resulted in minimal conversion to benzocyclobutane **10** (<5%) after 16 h, demonstrating greater thermal stability of **5** compared to **3**. Given the absence of coordinated pyridine in **5**, addition of a different heteroarene was attempted with benzofuran being alkylated in 97% yield (**12**, Scheme 6C). Although a large excess of substrate and prolonged reaction time were required for high conversion (1:1 ArH:PhF, 80 °C, 48 h), the selective functionalization demonstrated that a strongly Lewis basic heteroaromatic nitrogen was not a requirement for C–H activation by a cobalt(III) metallacycle.

CONCLUSIONS

Five- and six-coordinate (depe)Co(III) metallacycle complexes bearing the cycloneophyl group were synthesized and promoted facile C(sp^2)–H functionalization with arene and alkene coupling partners. The selective formation of directed-*ortho* alkylated products reflected the selectivity reported in related cobalt-catalyzed reactions and provided direct experimental support for mechanistic proposals invoking a cobalt(III) metallacyclopentene intermediate prior to the C–H activation step. Deuterium labeling with a benzamide substrate established that C–H activation was fast and reversible compared to irreversible, product-forming reductive elimination. Thermolysis of the five-coordinate cationic cobalt(III) metallacycle **3** led to competing formation of 2-alkylated pyridine and benzocyclobutane products with kinetic studies indicating that pathways to either product require coordinative unsaturation at the cobalt(III) center. Overall, the experimental insights into the reactivity of cobalt(III) metallacycle complexes will guide future catalyst design in the development of more efficient C–H functionalization reactions proceeding through metallacyclic intermediates.

ASSOCIATED CONTENT

Supporting Information. General considerations and experimental procedures; preparation of transition metal complexes; spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes. CCDC 2193852–2193854 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.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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29. The reaction outcome between complex **3** and *N*-methylbenzamide was the same in THF and fluorobenzene solvent. Fluorobenzene was used for the reaction scope to facilitate *in situ* analysis by ^1H NMR spectroscopy.
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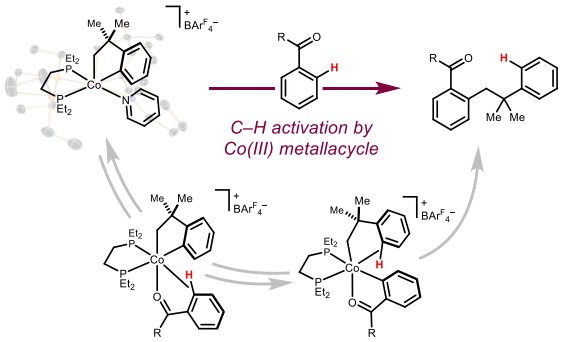
C–H activation by
Co(III) metallacycle