Three-Component Coupling of Arenes, Ethylene, and Alkynes Catalyzed by a Cationic Bis(phosphine) Cobalt Complex: Intercepting Metallacyclopentenes for C–H Functionalization

William G. Whitehurst,[a] Junho Kim,[a] Stefan G. Koenig,[b,*] Paul J. Chirik[a,*]

[a]Department of Chemistry, Frick Laboratory, Princeton University, Princeton, New Jersey 08544, United States
[b]Small Molecule Process Chemistry, Genentech Inc., 1 DNA Way, South San Francisco, California 94080, United States

ABSTRACT: A cobalt-catalyzed intermolecular three-component coupling of arenes, ethylene and alkynes was developed using the well-defined air-stable cationic bis(phosphine) cobalt(I) complex, [(dcype)Co(η^6-C_7H_8)][BAr^F_4] (dcype = 1,2-bis(dicyclohexylphosphino)ethane; BAr^F_4 = B[(3,5-$(CF_3)_2$)C_6H_3]$_4$), as the precatalyst. All three components were required for turnover and formation of *ortho*-homoallylated arene products. A range of directing groups including amide, ketone and 2-pyridyl substituents on the arene promoted the reaction. The cobalt-catalyzed method exhibited broad functional group tolerance allowing for the late-stage functionalization of two drug molecules, fenofibrate and haloperidol. A series control reactions, deuterium labelling studies, resting state analysis, as well as synthesis of substrate- and product-bound η^6-arene complexes supported a pathway involving C(sp^2)–H activation from a cobalt(III) metallacycle.

INTRODUCTION

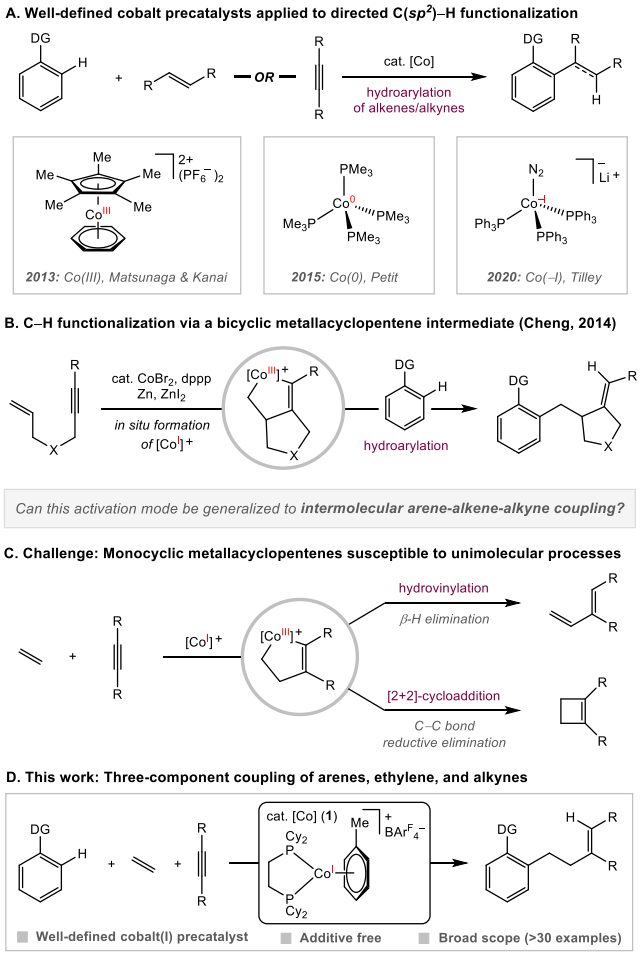
Transition metal-catalyzed C(sp^2)–H functionalization of arenes directed by commonly occurring functional groups such as amides and ketones has become established as a reliable approach to generate 1,2-substitution patterns in aromatic molecules.[1] In particular, hydroarylation, the addition of a C–H bond across an unsaturated alkene or alkyne coupling partner, has been extensively investigated as an atom-efficient method for forming C–C bonds.[1b-e] While early developments in transition metal-catalyzed hydroarylation relied on the use of precious metals, recent emphasis has shifted to the development of Earth-abundant first-row transition metal catalysts.[2] Cobalt-catalyzed directed C(sp^2)–H functionalization[3] has gained attention due to the tolerance of cobalt catalysts to a host of directing groups and coupling partners, often under mild conditions.[4]

Central to the advancement of cobalt-catalyzed directed C(sp^2)–H functionalization has been the development of well-defined precatalysts to ensure the efficient generation of the active catalyst species and gain mechanistic insight (Scheme 1A).[5] A pioneering example is the dicationic cobalt(III) complex reported by Matsunaga and Kanai in 2013, [(η^5-C_5Me_5)Co(η^6-C_6H_6)][$(PF_6)_2$], originally reported for catalytic hydroarylation and subsequently applied to a wide array of *ortho*-C–H functionalization reactions (Scheme 1A).[5a] Reduced cobalt(0) and cobalt(–I) precatalysts have also been applied to C–H functionalization: $Co(PMe_3)_4$[5b] by Petit in 2015,[5c] and [$Co(PPh_3)_3(N_2)$][$Li(THF)_3$][5d] by Tilley in 2020.[5e] Despite these advances, well-defined precatalysts for cobalt-catalyzed directed C–H functionalization remain few in number, and moreover, the aforementioned examples are not readily modified with different ligands, making the tuning of catalyst properties challenging. Consequently, the discovery of a modular cobalt precatalyst for directed C–H functionalization would facilitate the development and optimization of new catalytic transformations.

A bis(phosphine) cobalt-catalyzed C–H functionalization involving a tandem cyclization-hydroarylation process between a 1,6-enyne and an arene containing a coordinating group was reported by Cheng and coworkers (Scheme 1B).[6,7] In situ formation of a cationic bis(phosphine) cobalt(I) complex mediates the oxidative cyclization of the tethered alkene and alkyne components of the enyne to form a putative bicyclic metallacyclopentene intermediate. The metallacyclopentene was proposed to be functionalized by a directed C–H activation that results in 1,4-addition of the aryl C–H bond across the metallacycle, with the hydrogen atom being selectively transferred to the sp^2-carbon of the metallacycle, and the aryl group forming a C–C bond with the sp^3-carbon. While little is known about the nature of metallacycle-mediated C–H activation, this mechanistic proposal is supported by analogy with organometallic and theoretical investigations on [2+2+2] cycloadditions using isolated cyclopentadienyl-ligated cobalt(III) metallacyclopentadiene complexes.[8,9] Despite the versatility of the metallacycle-mediated C–H functionalization in being compatible with a range of directing groups,[10,11,12] this mode of C–H activation has only been demonstrated with 1,n-enyne substrates (n = 6, 7), limiting its application to selected classes of cyclized products.[13] To expand the scope and synthetic utility of this type of transformation, intermolecular coupling of alkene and alkyne

components is desirable, resulting in a three-component intermolecular arene-alkene-alkyne coupling reaction[14] to form *ortho*-homoallylated arene products.[15]

Scheme 1. Three-component coupling of arenes, ethylene, and alkynes with a cationic cobalt(I) catalyst.



Metallacyclopentenes[16,17] most commonly react by unimolecular pathways, including β-hydride elimination followed by C–H reductive elimination to form hydrovinylation products,[3b,16a,18] or direct C–C bond reductive elimination to form cyclobutenes (Scheme 1C).[19] The selectivity of these product-forming processes is known to be highly dependent on the identity of the ligand bound to the cationic cobalt center.[10,19d] For example, cyclobutene formation is favored over β-hydride elimination when a wide bite angle bis(phosphine) such as dppf (1,1′-bis(diphenylphosphino)ferrocene) is used.[19f,19g,20] Conversely, hydrovinylation has been reported with dppp- and dppe-ligated cobalt catalysts (dppp = 1,3-bis(diphenylphosphino)propane; dppe = 1,2-bis(diphenylphosphino)ethane).[18b] Significantly, hydroarylation of the metallacyclopentene requires the intermediate to be sufficiently long-lived to promote a bimolecular C–H activation event. Compared with enyne substrates, which generate bicyclic metallacyclopentene intermediates by intramolecular oxidative cyclization, the intermolecular variant would form a potentially more reactive monocyclic metallacyclopentene. Unimolecular reactivity would be expected to be more facile from the monocyclic metallacycle, given that a bicyclic intermediate contains fewer accessible β-hydrogens, disfavoring hydrovinylation, and would form a highly strained 4,5-bicycle upon C–C reductive elimination.[19b] Given the pronounced ligand effect on the reactivity of metallacyclopentenes, we envisioned a cationic cobalt(I) catalyst supported by a more strongly donating alkyl bis(phosphine) ligand could be developed to promote intermolecular three-component couplings by slowing the rate of unimolecular processes from the metallacycle.

Our group has reported the synthesis of a series of well-defined cobalt(0) and cationic cobalt(I) complexes bearing chiral bis(phosphine) ligands and demonstrated that both oxidation states are active precatalysts for asymmetric alkene hydrogenation.[21] Similarly, (dppf)Co(COD) and [(dppf)Co(η^6-C_7H_8)][BAr^F_4] (COD = 1,5-cyclooctadiene) were prepared and the cationic cobalt(I) variant was shown to catalyze olefin-alkyne [2+2]-cycloaddition.[20] Here we describe the synthesis and evaluation of a series of well-defined cationic bis(phosphine) cobalt(I) complexes as precatalysts for intermolecular, three component arene-alkene-alkyne coupling (Scheme 1D). The variant with an electron-rich alkyl bis(phosphine), [(dcype)Co(η^6-C_7H_8)][BAr^F_4] (**1**), was most effective and exhibited broad functional group compatibility, enabling the functionalization of marketed pharmaceutical compounds fenofibrate and haloperidol. Importantly, elucidation of the side-product profile, control reactions, and deuterium labelling experiments provided evidence for the intermediacy of a metallacyclopentene prior to C–H bond activation.

RESULTS AND DISCUSSION

Precatalyst Synthesis, Reaction Optimization, and Two-Component Control Reactions. A series of cationic cobalt(I) complexes were synthesized bearing dppf, dppe, dppbz (1,2-bis(diphenylphosphino)benzene), and dcype as representative bis(phosphines) and a labile η^6-toluene ligand. Whereas the dppf-ligated complex [(dppf)Co(η^6-C_7H_8)][BAr^F_4] was previously reported,[20] the dppe, dppbz and dcype-ligated variants were synthesized by analogy with our recently reported protocol using oxidatively induced reductive elimination from the corresponding cobalt(II) dialkyl derivative.[21e]

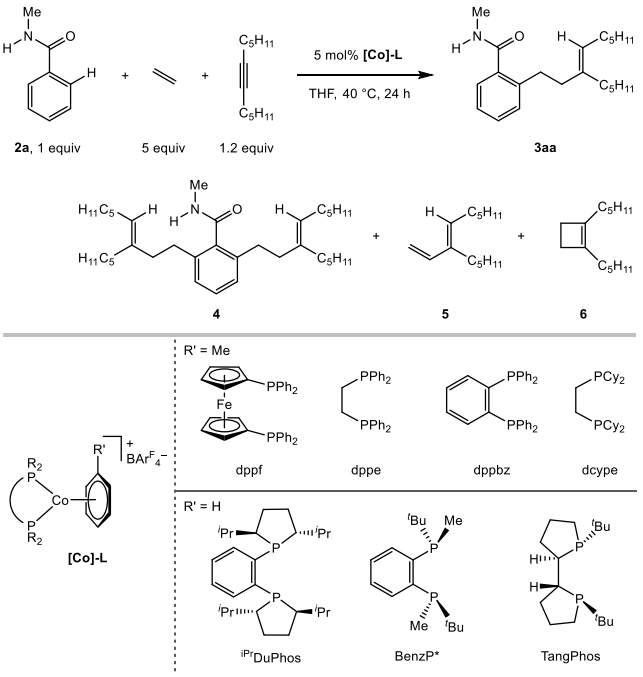
To investigate catalytic intermolecular arene-alkene-alkyne coupling, *N*-methylbenzamide (**2a**, 1 equivalent), ethylene (5 equivalents) and 6-dodecyne (1.2 equivalents) were used as representative coupling partners, with 5 mol% of the cobalt precatalyst in THF and stirring at 40 °C for 24 h. Note that, as the alkyne was used in slight excess, the maximum theoretical yield of alkyne-derived products was 120%, accounting for the >100% overall yields reported in Table 1. With [(dppf)Co(η^6-C_7H_8)][BAr^F_4] as the precatalyst, the desired three-component coupling product **3aa** was obtained in 30% yield (Table 1, entry 1). Notably, along with remaining starting material **2a**, **3aa** was the only other benzamide-containing component observed in the reaction mixture, indicating a selective *ortho*-C–H functionalization had occurred with incorporation of one unit of ethylene and one unit of alkyne in the product, and with no difunctionalized product **4** observed. The balance of the

alkyne had predominantly been converted to cyclobutene **6** (73%), with hydrovinylation also being observed as a minor side-product (**5**, 12%). While the observation of **6** as the major product is unsurprising, as cobalt complexes bearing dppf have previously been reported as efficient catalysts for [2+2]-cycloaddition,[19f,19g,20] the observation of *ortho*-functionalized product **3aa** motivated the exploration of other cationic bis(phosphine) cobalt(I) precatalysts.

With [(dppe)Co(η^6-C_7H_8)][BAr^F_4] and [(dppbz)Co(η^6-C_7H_8)][BAr^F_4], the standard catalytic procedure produced trace **3aa** (entries 2 and 3). The major products obtained from both precatalysts were higher molecular weight hydrocarbons arising from hydrovinylation, and resulting from multiple additions of ethylene across 6-dodecyne.[22] Conversely, employing [(dcype)Co(η^6-C_7H_8)][BAr^F_4] (**1**), which bears a more electron-rich alkyl-substituted bis(phosphine), produced a near-quantitative yield of **3aa**, which was isolated in 96% yield after chromatographic separation (entry 4). Other products included a trace amount of difunctionalized product **4** and a small amount (15%) of hydrovinylation product **5**. Increasing the amount of alkyne to 2 equivalents, **4** was obtained in higher (42%) yield, indicating that [(dcype)Co(η^6-C_7H_8)][BAr^F_4] was a sufficiently active precatalyst to mediate the second *ortho*-C–H functionalization (entry 5). The improved catalytic performance of the dcype derivative compared to other cobalt complexes supported by arylated bis(phosphine) ligands is consistent with the hypothesis of greater persistence of the dcype-ligated metallacyclopentene intermediate, which promotes intermolecular C–H activation of the arene substrate over unimolecular decomposition pathways.

Given the significant improvement observed with an alkyl-substituted bis(phosphine) ligand, other cobalt precatalysts bearing alkylated phosphines were evaluated in the three-component coupling reaction. Bench-stable, cationic cobalt(I) arene complexes have been synthesized for applications in asymmetric alkene hydrogenation and examples with ^{iPr}DuPhos, BenzP* and TangPhos have been prepared.[21c,21e] One example, [(^{iPr}DuPhos)Co(η^6-C_6H_6) proved to be a highly efficient and selective precatalyst for the three-component coupleing to yield **3aa** and **4** in 90 and 10% yields, respectively (Table 1). Both [(BenzP*)Co(η^6-C_6H_6)][BAr^F_4] and [(TangPhos)Co(η^6-C_6H_6)][BAr^F_4] provided lower yields of **3aa** (39% and 18%, respectively), with the latter resulting in near exclusive hydrovinylation (98% **5**). The observation that all the alkyl bis(phosphine)-ligated precatalysts studied gave appreciable yields of functionalized arene products highlights the greater activity and selectivity afforded by more electron-donating bis(phosphine) ligands in the three-component coupling. Although [(^{iPr}DuPhos)Co(η^6-C_6H_6)][BAr^F_4] produced **3aa** in high yield and selectivity, **1** was the favored precatalyst due to the lower cost of the dcype ligand and the transformation does not set a stereocenter. Because [(^{iPr}DuPhos)Co(η^6-C_6H_6)][BAr^F_4] is a bench stable alkene hydrogenation precatalyst,[21e] the air stability of **1** was explored. A sample of **1** stored on the benchtop (in air, room temperature) for 7 days remained highly active, maintaining a near-quantitative yield of **3aa**.

Table 1. Reaction Optimization.[a]

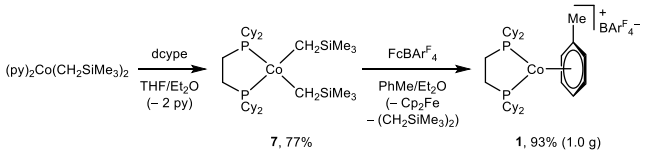


Entry	L	**3aa**, %	**4**, %	**5**, %	**6**, %
1	dppf	30	0	12	73
2	dppe	<5	0	0	0
3	dppbz	<5	0	0	0
4	dcype	98 (96)[b]	2	15	0
5[c]	dcype	55	42 (41)[b]	18	0
6	^{iPr}DuPhos	90	10	8	0
7	BenzP*	39	0	18	0
8	TangPhos	18	0	98	0
9[d]	dcype	99	1	16	0

[a]Yields determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures against an internal standard. Combined theoretical yield of alkyne-derived products is 120%. [b]Isolated yield. [c]2 equiv of 6-dodecyne. [d]Precatalyst **1** exposed to air for 7 days.

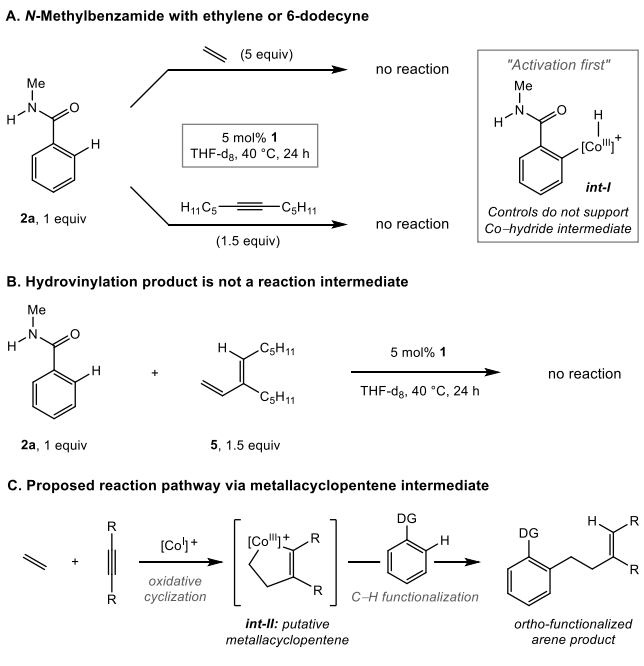
Having optimized the conditions and precatalyst for the three-component coupling, the synthetic procedure to access [(dcype)Co(η^6-C_7H_8)][BAr^F_4] (**1**) was scaled to produce larger quantities of the precatalyst (Scheme 2).[23] Beginning from cobalt(II) dialkyl precursor $(py)_2Co(CH_2SiMe_3)_2$,[24] coordination of the bis(phosphine) (**7**, 77%) followed by oxidation with $FcBAr^F_4$ provided **1** as a yellow solid in 93% isolated yield. The procedure was routinely conducted to obtain gram-scale quantities of precatalyst **1**. Both **7** and **1** were isolated by straightforward precipitation and filtration of the reaction mixtures.

Scheme 2. Gram-scale synthesis of [(dcype)Co(η^6-C_7H_8)][BAr^F_4], 1.



To assess the intermediacy of a metallacyclopentene, two-component control reactions were conducted. Using **1** as the precatalyst, benzamide **2a** was not functionalized in the presence of either ethylene or 6-dodecyne alone (Scheme 3A). The lack of functionalized products suggests that C–H oxidative addition is unlikely to be the first mechanistic step of three-component coupling, given that the putative Co–hydride (**int-I**) would be expected to mediate insertion of unsaturated coupling partners to form ethylated or alkenylated products. Furthermore, no reaction was observed when subjecting **2a** to hydrovinylation product **5**, indicating that **5** is not an intermediate in the formation of functionalized products **3aa** or **4** (Scheme 3B). While attempts to isolate or directly observe a bis(phosphine)-ligated metallacyclopentene have thus far been unsuccessful, the results from these two-component reactions, in addition to side-product distributions observed in the reaction optimization and additional insight gained during the investigation of reaction scope (*vide infra*), are most reasonably accounted for by a reaction pathway in which cobalt-mediated oxidative cyclization of the alkyne and ethylene, forming a monocyclic metallacyclopentene (**int-II**), occurs prior to *ortho*-C–H functionalization of the arene (Scheme 3C).

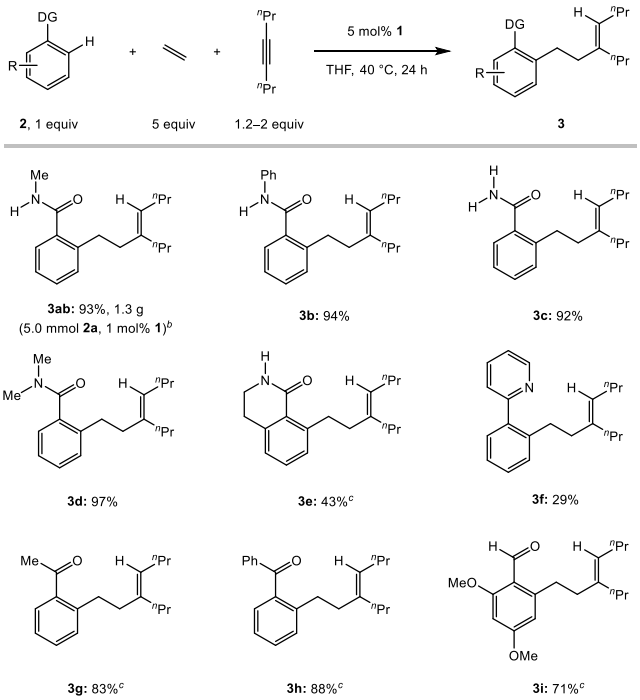
Scheme 3. Two-component control reactions and proposed reaction pathway.



Scope of Arenes and Alkynes. The scope of the three-component coupling was investigated with a range of arene and alkyne coupling partners. Using standard conditions, the reaction was generally effective with ethylene as the alkene component. Other alkenes such as propylene, styrene, and methyl acrylate were explored, but no reaction was observed in each case. Both cyclic and strained alkenes such as cyclopentene or norbornene were unsuccessful as coupling partners in the reaction.

The scope of directing groups on the arene was first examined (Scheme 4). Secondary amides with *N*-alkyl and *N*-phenyl substituents, as well as primary and tertiary amides, gave excellent yields of the three-component coupling products (**3ab**, **3b-d** 92–97%), while a bicyclic secondary amide substrate gave a moderate yield (**3e**, 43%). Notably, product **3ab** was synthesized on gram-scale with a lower precatalyst loading of 1 mol% (1.3 g **3ab**). Interestingly, the more strongly donating pyridine directing group was inferior and produced **3f** in 29% yield, whereas other carbonyl-containing directing groups such as ketones and aldehydes afforded high yields of functionalized products when using modified conditions with the arene being used in excess (**3g-i**, 71–88%). Ester and anilide directing groups were also evaluated but provided low yields,[25] presumably due to weak coordination of the carbonyl in the former case, and the carbonyl group being more distant relative to the *ortho*-C(*sp*^{2})–H bond in the latter.

Scheme 4. Scope of directing groups in cobalt-catalyzed three-component coupling.[a]

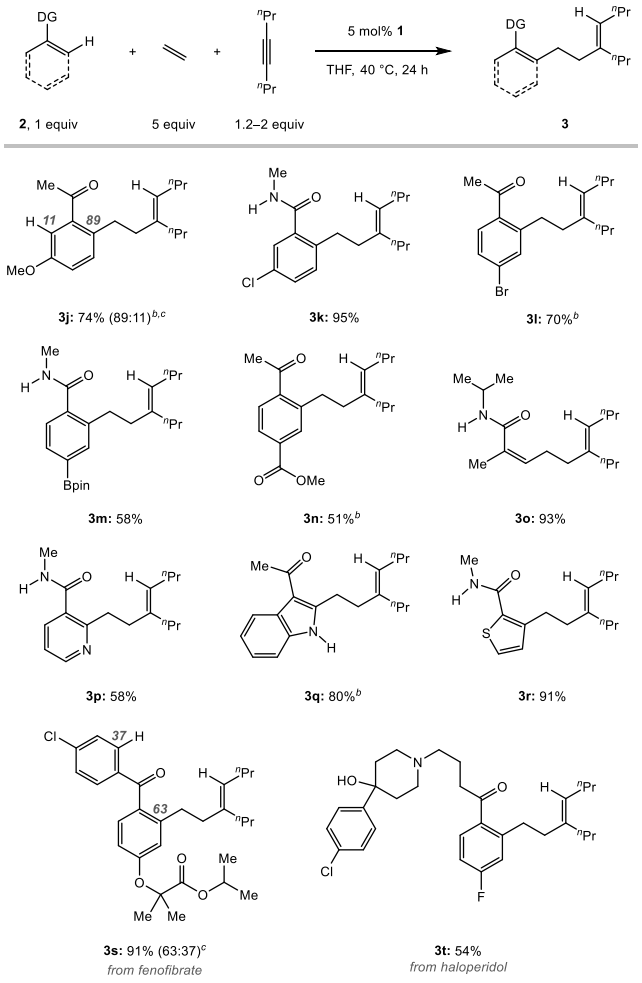


[a]Reactions carried out on 0.5 mmol scale (unless stated). [b]48 h reaction time. [c]2 equiv **2** and 1 equiv 4-octyne were used.

The functional group compatibility in the arene component was also explored (Scheme 5). Electron-donating and -withdrawing substituents were effectively tolerated in the reaction (**3j-n**, 51–95%), including functional handles such as halides and a boronate ester. For 3-substituted arenes, *ortho*-functionalization occurred at the least sterically hindered position, with 3-methoxy substitution giving a 89:11 mixture of 1,2,5- and 1,2,3-substituted products (**3j**). In the

case of a 3-chloro substituent, exclusive formation of 1,2,5-substituted product **3k** was observed. For substrate **2n**, which contains both ketone and ester functional groups, functionalization was only observed *ortho* to the ketone (**3n**). Significantly, the catalyst also efficiently mediated alkenyl C(sp^2)–H functionalization, with the isolated product having (*Z*)-alkene stereochemistry of the acrylamide, as expected from amide-directed C–H bond activation (**3o**, 93%). Various heterocycles were suitable substrates for the three-component coupling, including pyridine, indole and thiophene (**3p-r**, 58-91%). Furthermore, marketed pharmaceutical drugs, fenofibrate and haloperidol, provided good yields in the reaction (respectively, **3s**, 91%, and **3t**, 54%). For fenofibrate, the 4,4′-substitution of the benzophenone gives rise to an intramolecular competition of 4-chloro and 4-alkoxy-susbtituted ring systems, and the cobalt-catalyzed method provided a 63:37 ratio of isomers. The major isomer resulted from C–H functionalization of the more electron-rich alkoxy-substituted ring.

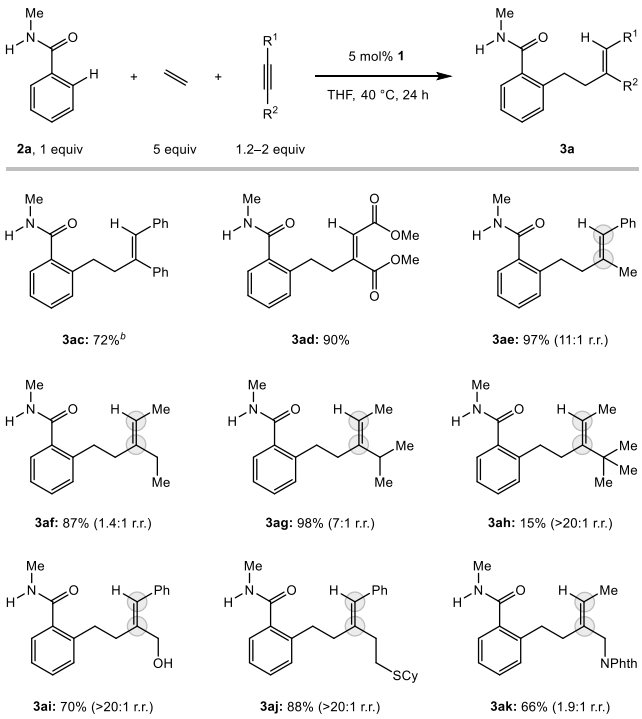
Scheme 5. Determination of arene scope in cobalt-catalyzed three-component coupling.[a]



[a]Reactions carried out on 0.5 mmol scale. [b]2 equiv **2** and 1 equiv 4-octyne were used. [c]Site selectivity determined after purification by ^{1}H NMR spectroscopy.

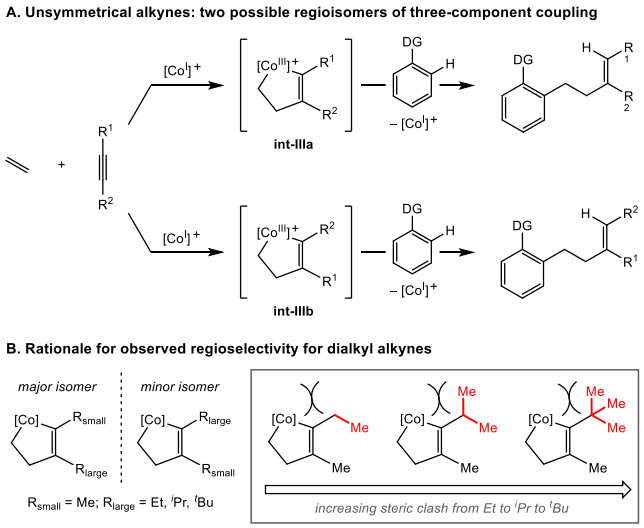
Finally, the scope of the alkyne coupling partners was explored (Scheme 6). Changing from a dialkyl alkyne coupling partner to diphenylacetylene, the three-component coupling product was obtained in good yield (**3ac**, 72%). The *ortho*-functionalized arene was unambiguously characterized by single-crystal X-ray diffraction,[26] confirming the trisubstituted alkene (*Z*)-stereochemistry. In all examples examined, only *syn*-addition across the alkyne component was observed in the isolated products, and thus positional or stereochemical isomerization of the product alkene did not occur under catalytic conditions. Dimethyl acetylenedicarboxylate also proved to be a competent symmetrical alkyne coupling partner, affording the desired product in high yield (**3ad**, 90%). Unsymmetrical alkynes were next explored in the reaction. It is important to note that two potential regioisomers of the product are possible depending on which carbon atom of the alkyne the C–C and C–H bonds form with en route to the product (Scheme 7A). Assuming the intermediacy of a metallacyclopentene, the two regioisomers relate to the two possible metallacyclopentenes that could be obtained from oxidative cyclization of the alkyne with ethylene (**int-IIIa** or **int-IIIb**). Employing 1-phenyl-1-propyne, the functionalized product was formed in high yield and regioisomeric purity (**3ae**, 97%, 11:1 r.r.). Analysis by NMR spectroscopy identified the major isomer as having the phenyl substituent at the terminal alkene position and the methyl group at the

Scheme 6. Alkyne scope in cobalt-catalyzed three-component coupling.[a]



[a]Reactions carried out on 0.5 mmol scale; r.r. determined after purification by ^{1}H NMR spectroscopy. [b]80 °C in 2-MeTHF solvent.

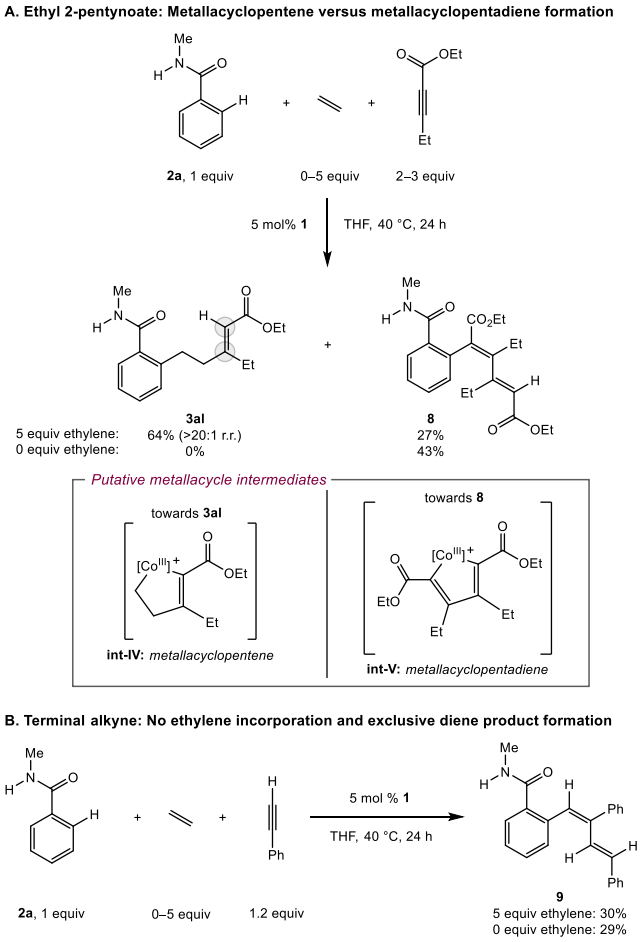
Scheme 7. Unsymmetrical alkynes: relating product r.r. to regioselectivity of metallacyclopentene formation.



internal position. To examine the effect of sterics on the regioselectivity of the reaction, a series of alkynes containing a methyl substituent and alkyl substituent of increasing size (ethyl, *iso*-propyl, *tert*-butyl) were used. Ethyl and *iso*-propyl substituted alkynes gave high yields of three-component coupling products (**3af-ag**, 87–98%), whereas the *tert*-butyl group resulted in noticeably decreased conversion (**3ah**, 15%). In each case the major regioisomer had the smaller methyl substituent at the terminal alkene position. Notably, this contrasts to the reaction using 1-phenyl-1-propyne which favored the larger phenyl group being placed at the terminus of the product. Increasing the size of the alkyl substituent from ethyl to *iso*-propyl to *tert*-butyl increased the regioselectivity from 1.4:1 to 7:1 to >20:1 r.r., likely reflecting the increasing steric clash between the catalyst and alkyne substituent upon metallacycle formation when the larger substituent is proximal to the metal center (Scheme 7B). Lastly, in terms of functional group tolerance in the alkyne component, alkynes containing pendant hydroxyl, thioether, and protected amine groups performed well in the reaction (**3ai-k**, 66-90%).

In general, the three-component coupling selectively generated mono-*ortho*-functionalized products, with di-*ortho*-functionalization obtained as a minor product in some instances. During the exploration of alkyne scope, it was found that using ethyl 2-pentynoate resulted in a mixture of two mono-*ortho*-functionalized products (Scheme 8A). The major product was the expected three-component coupling product derived from the arene, ethylene, and alkyne, which was formed in high regioselectivity with the ester group at the terminal alkene position in the product (**3al**, 64%, >20:1 r.r.). The minor product was derived from the arene and two equivalents of the alkyne without incorporation of ethylene, resulting in an *ortho*-functionalized product containing a 1,3-diene moiety (**8**, 27%). Significantly, the two-component reaction in the absence of ethylene afforded **8** as the sole functionalized product in 43% yield. Given that the hydroarylation products resulting from insertion of only one equivalent of alkyne, or from insertion of more than two equivalents, were not observed corroborates with the intermediacy of a metallacyclopentadiene[7a,7b,9] formed from the oxidative cyclization of the cobalt catalyst with two equivalents of ethyl 2-pentynoate. In the presence of ethylene, the formation of both **3al** and **8** indicates that the formation of metallacyclopentene **int-IV** and metallacyclopentadiene **int-V** are competitive under the reaction conditions.

Scheme 8. Observation of competing metallacyclopentene and metallacyclopentadiene formation.[a]



[a]Reactions carried out on 0.5 mmol scale; r.r. determined after purification by ^{1}H NMR spectroscopy.

The formation of diene-containing arene products was not observed in other three-component coupling reactions conducted with internal alkynes. Conversely, the use of phenylacetylene, a terminal alkyne coupling partner, resulted in exclusive formation of the diene product derived from the arene and two equivalents of alkyne (**9**, Scheme 8B). In both the presence or absence of ethylene, diene **9** was formed as the sole product, albeit in moderate yields (30% and 29% yield, respectively), indicating that metallacyclopentadiene formation is facile compared with metallacyclopentene formation.

Deuterium Labeling Studies. To gain additional insight into the reaction mechanism, deuterium labeling studies were conducted. Using *N*-methylbenzamide-d_5 (**2a-*d*$_5$**, >99% D in ring positions), ethylene, and 6-dodecyne as coupling partners, the d_5-labeled three-component coupling product (**3aa-(*sp*^{2})*d*$_5$**) was obtained in >98% assay yield (Scheme 9A). While the *ortho*-deuterium atom in **2a-*d*$_5$** was predominantly transferred to the alkenyl position in product **3aa-(*sp*^{2})*d*$_5$**, a small but significant deviation from complete transfer was observed (88% D at the

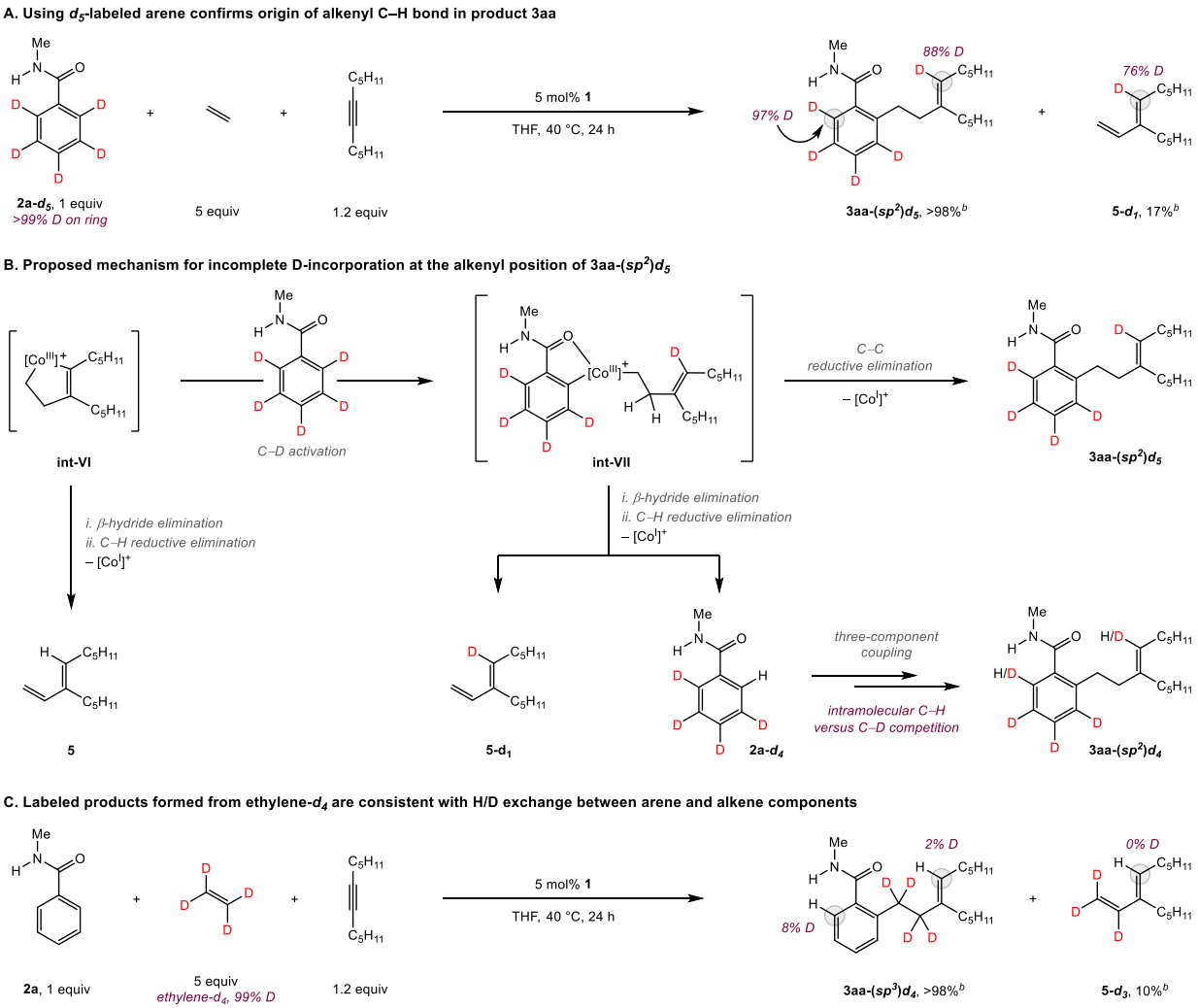
alkenyl position in **3aa-(sp^2)d_5**). In addition, H/D exchange occurred to a minor extent at the unfunctionalized *ortho* position in **3aa-(sp^2)d_5** (97% D), whereas the other remaining ring positions remained fully labeled (>99% D). Analysis of the unpurified reaction mixture from the three-component coupling by NMR spectroscopy revealed that loss of deuterium in **3aa-(sp^2)d_5** was traced to the hydrovinylation side-product, which was substantially deuterated at the alkenyl position of the trisubstituted alkene (**5-d_1**, 76% D). More specifically, the amount of deuterium incorporated in **5-d_1** (0.17 × 76% = 13% D) correlated with the amount of deuterium lost at the alkenyl and *ortho*-aryl positions in **3aa-(sp^2)d_5** (12% + 3% = 15% H), indicating that the extent of hydrovinylation was related to the observed H/D exchange.[27]

Possible pathways to account for the outcome of the cobalt-catalyzed three-component coupling using deuterated arene are presented in Scheme 9B. Firstly, *β*-hydride elimination directly from the metallacyclopentene (**int-VI**) and C–H reductive elimination liberates the natural abundance hydrovinylation product **5**. Alternatively, the metallacyclopentene **int-VI** may promote C–D bond activation, where the *ortho*-deuterium atom is transferred to the sp^2-carbon of the metallacycle. The resulting cobalt(III) intermediate (**int-VII**) may undergo either product-forming C–C bond reductive elimination, forming **3aa-(sp^2)d_5**, or alternatively, the Co-alkyl could undergo β-hydride elimination and C–H bond reductive elimination to yield d_1-labeled hydrovinylation product **5-d_1**, along with **2a-d_4** in which *ortho*-D-for-H exchange has taken place. If **2a-d_4** re-engages the metallacyclopentene to promote *ortho*-functionalization, an intermolecular competition between C–H and C–D activation would then occur. The preference for *ortho*-C–H over C–D activation within **2a-d_4** accounts for the greater loss of deuterium at the alkenyl position relative to the unfunctionalized *ortho*-position observed in the isolated three-component coupling product (89% D compared to 97% D). Based on this proposal, the relative amount of **5-d_1** compared to three-component coupling product formed in the reaction reflects the efficiency of the catalyst to promote product-forming reductive elimination over β-hydride elimination from the putative cobalt(III) intermediate **int-VII**.

In the context of the proposed mechanism, the three-component coupling using ethylene-d_4 with natural abundance **2a** and 6-dodecyne was conducted (Scheme 9C). As expected, functionalized product **3aa-(sp^3)d_4** was formed in high yield with fully deuterated carbon atoms within the linking ethylene unit (>99% D). Small but detectable amounts of deuterium were also incorporated at the *ortho*-to-amide and alkenyl positions in **3aa-(sp^3)d_4** (8 and 2% D, respectively), which correlated with the yield of d_3-labeled hydrovinylation product, **5-d_3** (10%). The observation of **5-d_3** is consistent with H/D-exchange between ethylene and arene during the three-component coupling. Interestingly, d_4-labeled **5** was not detected, indicating that **5** was no longer formed directly from the metallocyclopentane and is attributed to slower β-D elimination from this metallocyclic intermediate.

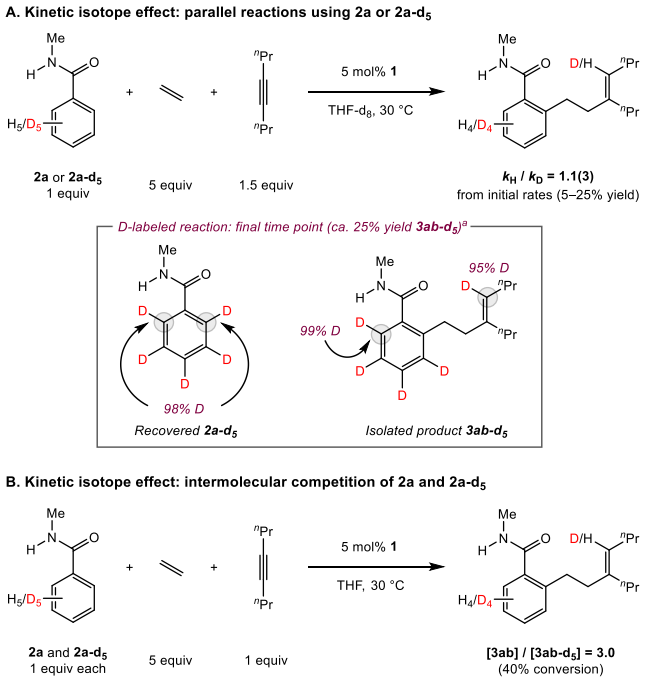
Parallel reactions using **2a** or **2a-d_5** with ethylene and 4-octyne were conducted to measure the deuterium kinetic isotope effect for the catalytic reaction by measuring the initial rate of formation of the three-component coupling product (5–25 % yield). A k_H/k_D value of 1.1(3) was obtained at 30 ºC, suggesting that C–H activation does not occur during the turnover-limiting step (Scheme 10A). Recognizing that *ortho*-D-for-H exchange within the substrate likely occurs over the course of the reaction with the deuterated substrate, chromatographic separation of the remaining starting material **2a-d_5** and product **3ab-d_5** at the final time point from the initial rate experiments was carried out. Compared with the isolated material of **3aa-(sp^2)d_5** from the reaction that was run to completion (Scheme 9A), minimal loss of deuterium was observed for both recovered **2a-d_5** (98% D across two *ortho* carbons) as well as the isolated product **3ab-d_5** (95% D at alkenyl position and 99% D at *ortho*-position). The greater deuterium incorporation observed at partial conversion not only validates the measured KIE from the parallel experiments, but also provides additional support for the proposed mechanism which suggests that *ortho*-D-for-H exchange would be more substantial at later time points of the reaction. Finally, an intermolecular competition KIE for **2a** and **2a-d_5** was also measured (Scheme 10B). A KIE of 3.0 was obtained at 30 °C, consistent with irreversible C–H activation that occurs following the rate-limiting step.

Scheme 9. Deuterium labeling study to assay reductive elimination.[a]



[a]Reaction carried out on 0.5 mmol scale; deuterated positions >99% D unless otherwise stated. [b]Yield determined by ^{1}H NMR spectroscopy against an internal standard. Percentage deuteration determined by ^{1}H, ^{2}H or quantitative ^{13}C NMR spectroscopy, and H/D-isotopologues detected by HRMS.

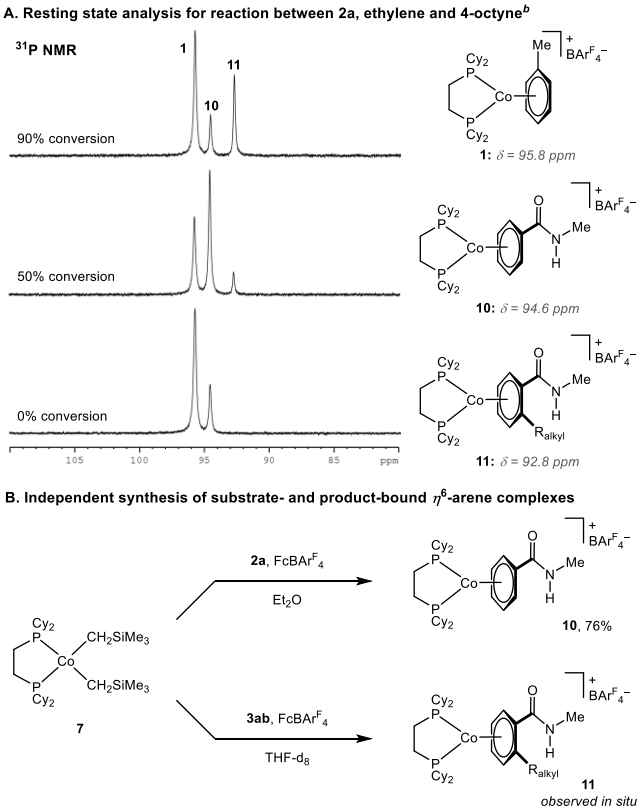
Scheme 10. Determination of a deuterium kinetic isotope effect at 30 °C to examine the nature of C–H bond cleavage in cobalt-catalyzed three-component C(sp²)–H functionalization.



[a]Deuterated positions >99% D unless otherwise stated.

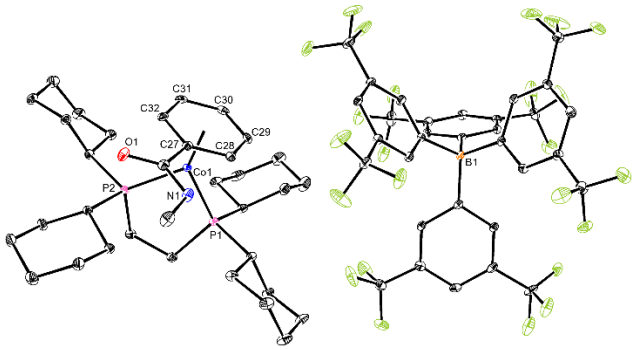
Resting State Analysis. The resting state of the catalytic three-component coupling reaction employing *N*-methylbenzamide, ethylene and 4-octyne, with [(dcype)Co(η^6-C_7H_8)][BAr^F_4] as the precatalyst, was monitored by ^{31}P NMR spectroscopy in THF-d_8 (Scheme 11A). Three phosphorus signals were observed during the reaction, one of which was identified as the precatalyst, [(dcype)Co(η^6-C_7H_8)][BAr^F_4] (δ = 95.8 ppm). Independent synthesis of the substrate- and product-bound η^6-arene complexes (**10** and **11**) confirmed the identity of the two other signals (δ = 94.6 and 92.8 ppm, respectively; Scheme 11B) and the solid-state structure of **10** was determined by X-ray diffraction (Figure 1). The toluene-bound complex **1** was observed throughout the reaction indicating that toluene binds more strongly to the cobalt center compared to the substrate or product benzamides. No other cobalt complexes other than η^6-arene complexes were detected by ^{31}P NMR spectroscopy. Having identified the catalyst resting states, coupled with the observation that C–H activation is not part of the turnover limiting step of the catalytic cycle, either displacement of the η^6-ligated arene by alkyne and ethylene, or the subsequent [2+2]-oxidative cyclization to form the metallacyclopentene, is likely the slow step in the reaction.

Scheme 11. Resting state analysis by ^{31}P NMR spectroscopy.[a]



[a]R_{alkyl} = $CH_2CH_2C(^nPr)CH(^nPr)$. [b]Reaction conditions: **2a** (1 equiv), ethylene (5 equiv), 4-octyne (1.2 equiv), **1** (10 mol%), THF-d_8, 40 °C.

Figure 1. Solid-state structure of 10 at 30% probability ellipsoids. Hydrogen atoms omitted for clarity.



CONCLUSIONS

A three-component arene-ethylene-alkyne coupling reaction has been developed using a cationic dcype-ligated cobalt(I) arene precatalyst. The reaction was effective with a range of arene and alkyne coupling partners, producing a broad array of functionally diverse *ortho*-homoallylated arene products. Deuterium labeling studies and KIE determination for the three-component coupling reaction found that C–H activation occurs irreversibly but is not part of the turnover-limiting step of the catalytic cycle. Resting state analysis identified that the catalytic resting state is distributed amongst a series of η^6-arene cobalt(I) complexes, including the toluene-bound precatalyst, and

substrate- and product-bound η^6-arene complexes. Two-component control reactions using an arene partner with a dialkyl alkyne or ethylene did not result in the generation of *ortho*-functionalized products. Conversely, two-component reactions employing an alkyne with an ester and an alkyl substituent, or use of a terminal alkyne, led to the selective formation of *ortho*-functionalized 1,3-diene-containing products derived from the arene and two equivalents of the alkyne. Taken together, the results of the two-component reactions suggest that cationic bis(phosphine) cobalt complexes promote C–H functionalization through a pathway involving oxidative [2+2]-cyclization followed by C–H activation en route to the *ortho*-functionalized products. In the case of the three-component coupling, a metallacyclopentene intermediate is formed by oxidative [2+2]-cyclization of an alkyne and ethylene, whereas formation of a functionalized product incorporating two units of the alkyne may occur via a metallacyclopentadiene generated by [2+2]-cyclization of two equivalents of alkyne. Overall, the discovery of a readily prepared bis(phosphine)-ligated cobalt precatalyst capable of promoting metallacycle-mediated C–H activation by intermolecular alkene-alkyne oxidative cyclization opens new opportunities in metal-catalyzed C(sp^2)–H functionalization and such applications are currently under investigation.

ASSOCIATED CONTENT

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

Accession Codes. CCDC 2122988, 2122990–2122992 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.

AUTHOR INFORMATION

Corresponding Authors

*Paul J. Chirik – *Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States;* orcid.org/0000-0001-8473-2898; Email: pchirik@princeton.edu

*Stefan G. Koenig – *Small Molecule Process Chemistry, Genentech Inc., 1 DNA Way, South San Francisco, California 94080, United States;* orcid.org/0000-0002-1878-614X; Email: koenig.stefan@gene.com

Authors

William G. Whitehurst – *Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States;* orcid.org/0000-0001-9789-1265

Junho Kim – *Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States;* orcid.org/0000-0002-8977-2925

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22. For a comparison of the ^{1}H NMR spectra of the crude reaction mixtures for entries 1–4 from Table 1, see the Supporting Information.

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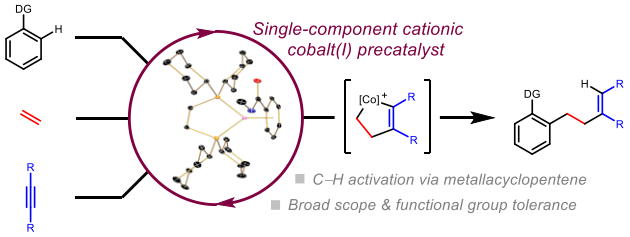
25. For a summary of low-yielding or unsuccessful substrates, see the Supporting Information.

26. The X-ray crystal structure of **3ac** can be found in the Supporting Information.

27. H/D exchange between ethylene and **2a-*d*$_5$** was not mediated by **1** in the absence of alkyne.


DG
H
R
R
Single-component cationic
cobalt(I) precatalyst
[Co]+
R
R
DG
H
R
R
C–H activation via metallacyclopentene
Broad scope & functional group tolerance