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# Co(III) Intermediates in Cobalt-Catalyzed, Bidentate Chelation Assisted C($sp^2$)-H Functionalizations

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**Abstract:** The C-H bond activation and functionalization is a powerful tool that provides efficient access to various organic molecules. The cobalt-catalyzed oxidative C-H bond activation and functionalization has earned enormous interest over the past two decades. Since then, a wide diversity of synthetic protocols have been published for C-C, C-Het, and C-Hal bond formation reactions. To gain some insights into the reaction mechanism, the authors performed a series of experiments and collected evidence. Several groups have successfully isolated reactive Co(III) intermediates to elucidate the reaction mechanism. In this review, we will summarize information concerning the isolated and synthesized Co(III) intermediates in cobalt-catalyzed, bidentate chelation assisted C-H bond functionalization and their reactivity based on the current knowledge about the general reaction mechanism.

**Keywords:** cobalt; C-H bond functionalization; Co(III) intermediate

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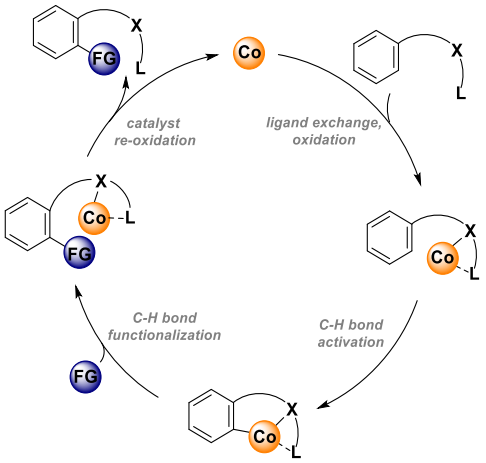
## 1. Introduction

The directed C-H bond functionalization methodology using transition metal catalysis has proven itself as a valuable organic synthesis tool [1–8]. Nowadays, using the directed C-H bond functionalization methodology, a diverse range of selective transformations can be achieved, including C-C, as well as C-O, C-N, C-Hal, C-S, etc. bond formation, allowing to obtain more complicated products from simple starting materials in step- and atom-economic fashion [1–8]. C-H bond functionalization using first-row transition metal catalysts recently has emerged not only as an attractive alternative to noble metals, but also as an opportunity to expand the scope of C-H bond functionalization methodology due to their unique reactivity [9]. Among other 3d elements, cobalt is considered to be a sustainable catalyst due to its price, biorelevance, earth abundance and lower toxicity. Since 2010, great progress in the development of novel methods using cobalt catalysis had been achieved [10–20]. In general, C-H bond functionalization using cobalt catalysis can be divided in two categories: low valent and high valent, depending on the catalyst used for cobaltation [21]. However, high valent cobalt catalysis can be divided in two main directions, reactions using Cp*Co(III) complexes as catalysts and reactions using simple Co(II) and Co(III) salts in combination with bidentate chelation assistance [18]. Herein, we will focus on last direction, which after pioneering work by Daugulis in 2014 [22] was proven to be efficient for wide range of C-H functionalizations [10–22].

## 2. General Mechanism for Cobalt-Catalyzed, Bidentate Chelation Assisted C-H Bond Functionalization

Over the last two decades, gathered mechanistic experiments and collected evidence provided a general idea of the operative mechanism in cobalt-catalyzed, bidentate chelation assisted C-H bond functionalization. According to the literature, it is believed that for the major part of the found transformations, the Co(II)-Co(III)-Co(I) catalytic cycle is operative [18,23]. The general mechanism is shown in Scheme 1, which consists of four elementary steps:

- ligand exchange (substrate coordination)/oxidation;
- C-H bond activation;
- C-H bond functionalization;
- catalyst re-oxidation to return active species in catalytic cycle [23].



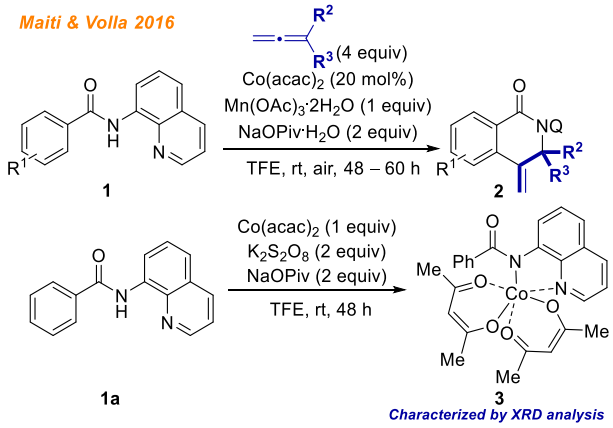

**Scheme 1.** General mechanism for the cobalt-catalyzed C($sp^2$)-H bond functionalization [23].

To the date, several intermediate Co(III) complexes have been isolated. In this review, these species will be discussed in such order as they participate in the catalytic cycle.

## 3. Ligand Exchange, Oxidation

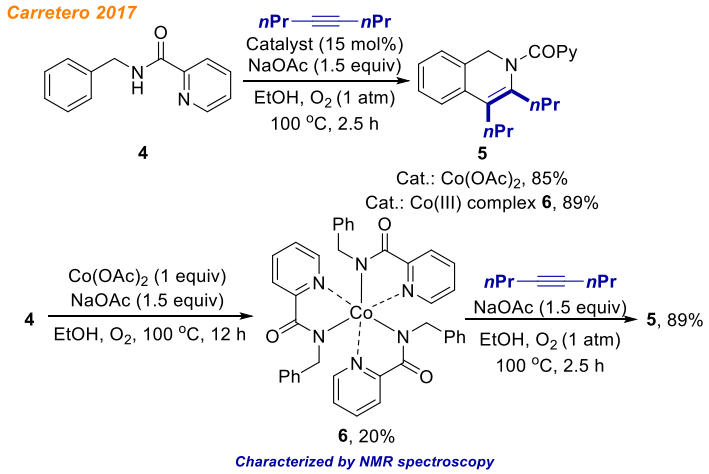
The first step of the catalytic cycle is ligand exchange/substrate coordination and oxidation of Co(II) species to Co(III) species. According to the literature data, two operative pathways are plausible for this step. First, the catalytic cycle could be initiated with substrate coordination to Co(II) salt to form a Co(II)-substrate complex, which is further oxidized to a Co(III) complex that undergoes the C-H activation step. In the second operative pathway, the Co(II) catalyst might be first oxidized to Co(III) salt. Next, substrate coordination takes place. In the literature, there is support for both of these pathways. Most likely, the operative pathway depends on the reaction conditions and/or substrate used for the transformation [23].

In 2016, Maiti and Volla reported a novel cobalt-catalyzed methodology for the intermolecular heterocyclization of benzamides **1** (Scheme 2) [24]. In their work, the following conditions were used: allene as the C-H bond functionalization reagent, $Co(acac)_2$ as the catalyst, $Mn(OAc)_3 \cdot 2H_2O$/air as reaction oxidant, and sodium pivalate in TFE. Using the developed methodology, authors were able to provide a broad substrate scope with respect to both allenes and benzamides, delivering 41 different products with yields up to 90%. The authors conducted series of mechanistic experiments to study the reaction mechanism in detail. The authors concluded that electrophilic cobaltation is unlikely based on competitive experiments between methoxy- and fluoro-substituted benzamides. Experiments with deuterium labeled substrates indicated that C-H bond activation might not be the rate-limiting step. Additionally, authors were able to isolate cobalt(III)-benzamide intermediate **3**, whose structure was confirmed with XRD analysis. Along with complex **3**, authors detected the formation of C-H activated Co(III)-intermediate by HRMS, although they were not able to isolate corresponding complex. Based on the mechanistic experiments as well as isolated complex **3**, the authors proposed the plausible reaction mechanism, which is consistent with the general Co(II)-Co(III)-Co(I) catalytic cycle.




**Scheme 2.** Cobalt-catalyzed benzamide **1** cyclization with allenes [24].

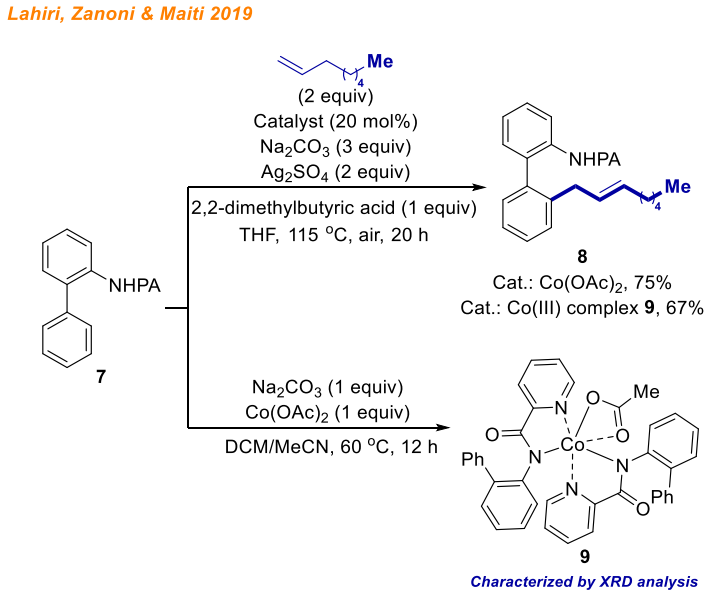
In 2017, the Carretero group reported an efficient protocol for the cobalt-catalyzed, picolinamide-directed C-H bond functionalization/annulation of benzylamine derivatives **4** with various alkynes (Scheme 3) [25]. The reaction proceeds in the presence of $Co(OAc)_2$ catalyst, $O_2$ oxidant, and NaOAc additive in EtOH at 100 °C temperature. The authors were able to ensure good functional group tolerance under the reaction conditions as well as a variety of terminal and internal alkynes delivered the desired products **5** predominantly with good and excellent yields. According to the mechanistic hypothesis, the authors propose that this reaction proceeds through the octahedral cobalt intermediate **6**, which was successfully isolated. The structure of Co(III) complex **6** was proven by ESI-HRMS and NMR analysis, although no crystals for X-ray diffraction analysis were obtained. In the stoichiometric experiment, Co(III)-species **6** reacted with 4-octyne to afford product **5** in 89% yield. Moreover, Co(III) complex **6** was found to be catalytically competent in the reaction of **4** with alkyne, delivering product **5** in 89% yield. In comparison, under the standard reaction conditions using $Co(OAc)_2$ salt, the same product **5** was obtained in 85% yield. These results indicated that complex **6** could be the active catalyst precursor for the transformation. Additionally, the authors performed ESI-HRMS experiments of the reaction mixture to shed some more light on the reaction mechanism, and deciphered different cobalt complexes being present in the reaction mixture, although none of them was isolated and characterized.




**Scheme 3.** Cobalt-catalyzed C-H bond functionalization/annulation of benzylamine derivatives **4** [25].

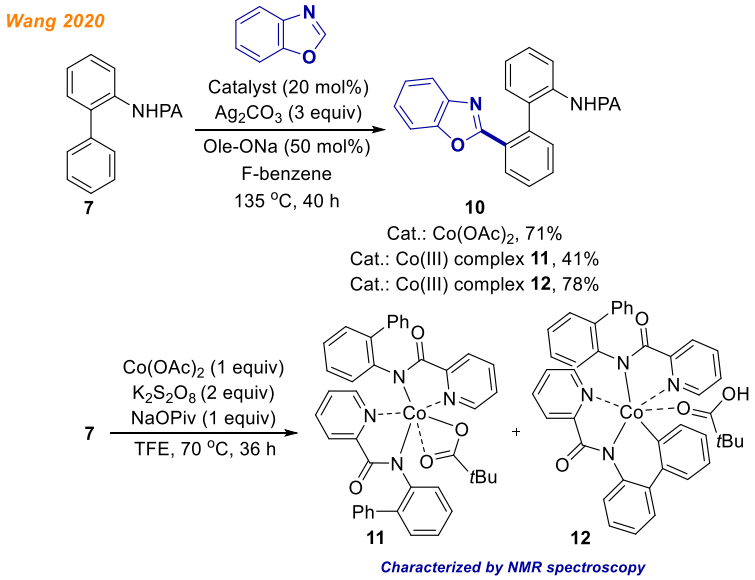
Two years later, in 2019, Lahiri, Zanoni and Maiti reported a cobalt-catalyzed C-H bond allylation reaction using arylanilines **7** as substrates and unbiased terminal olefins (Scheme 4) [26]. The most common problem in these reactions is products' styrenyl/allylic

regioselectivity of the double bond, which arises from the metal center's ability to unselectively perform β-hydride elimination. In this context, authors successfully overcame the challenge and were able to deliver 36 different aryl(allyl)anilines **8** with yields up to 96% in a highly selective fashion. In addition, the authors demonstrated that picolinamide directing group (PA) can be easily removed upon slight heating in basic conditions. To gain insight into the reaction mechanism, among kinetic and labeling studies, authors were able to isolate five-membered Co(III) intermediate **9**, whose structure was confirmed using XRD and ESI-MS analyses. The isolated Co(III) complex **9** was found to be catalytically competent, delivering product **8** in 67% yield, suggesting the involvement of a catalytically active high-valent Co(III) species.



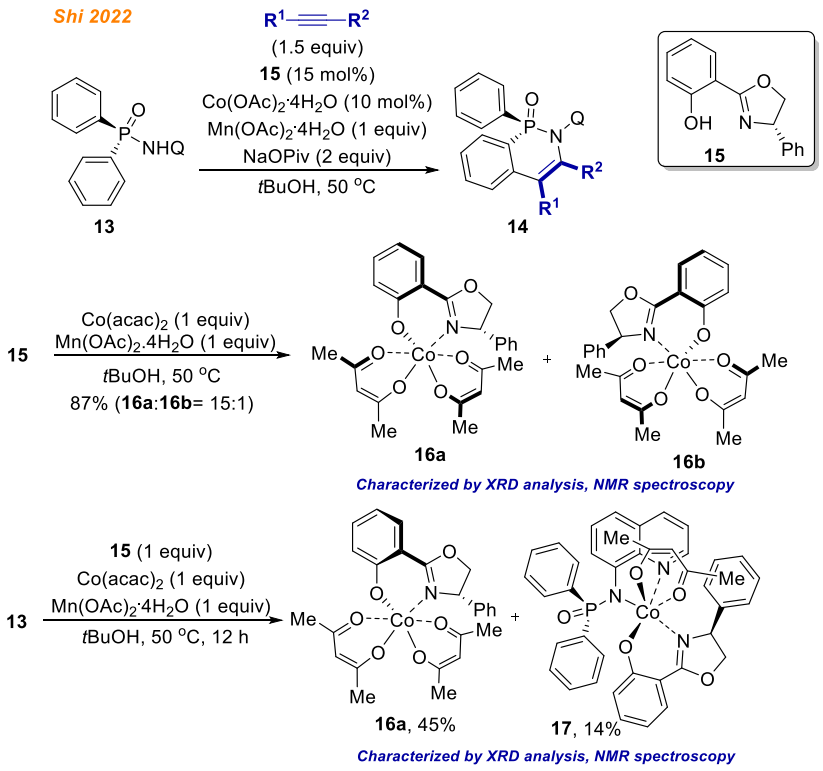

**Scheme 4.** Cobalt-catalyzed allylation of biphenyl amines **7** with terminal olefins [26].

In 2020, Wang and colleagues demonstrated a novel cobalt-catalyzed C-H/C-H bond cross-coupling reaction between benzoxazole and aryl aniline **7** (Scheme 5) [27]. The use of $Co(OAc)_2$ catalyst, $Ag_2CO_3$ oxidant, and Ole-ONa base in fluorobenzene was found to represent the optimal conditions for the successful reaction. The main advantage of the developed transformation was the straightforward access to biphenyls **10** in good yields (up to 73%), which possess antifungal activities and COX-2 inhibition potency. To investigate the reaction mechanism, the authors performed series of control experiments, including H/D exchange and KIE experiments, which led to conclusion that the C-H activation step is irreversible, but not the rate-determining step. Additionally, two Co(III) intermediates **11** and **12** were obtained by the reaction of aniline **7** with a stoichiometric amount of $Co(OAc)_2$, oxidant and base. Both Co(III) complexes **11** and **12** were characterized using NMR spectroscopy and high-resolution mass spectrometry. According to the suggested reaction mechanism, Co(III) complex **12** could be obtained from Co(III) complex **11** via a C-H activation step, which most likely occurs via a base-promoted concerted metalation-deprotonation mechanism. Notably, cobaltacycles **11** and **12** provided the desired product **8** in 41% and 78% yield, respectively, whereas using $Co(OAc)_2$ as the catalyst, the product yield was 71%, which confirmed the hypothesis that both isolated Co(III) complexes are most likely intermediates of the developed reaction.




**Scheme 5.** Cobalt-catalyzed synthesis of arylanilines **10** [27].

Recently, in 2022, the Shi group reported an elegant enantioselective C-H bond functionalization methodology exploiting diarylphosphinamides **13** (Scheme 6) [28]. In their study, employing $Co(OAc)_2 \cdot 4H_2O$ catalyst and Salox ligand **15**, azaphosphinines **14** were obtained with yields up to 99% with fascinating product enantioselectivities (up to >99% ee). The authors demonstrated great substrate/alkyne scope, delivering 45 different enantiopure products with excellent yields. Great emphasis was put on the understanding of the reaction mechanism and isolation of potential intermediates of the catalytic cycle.

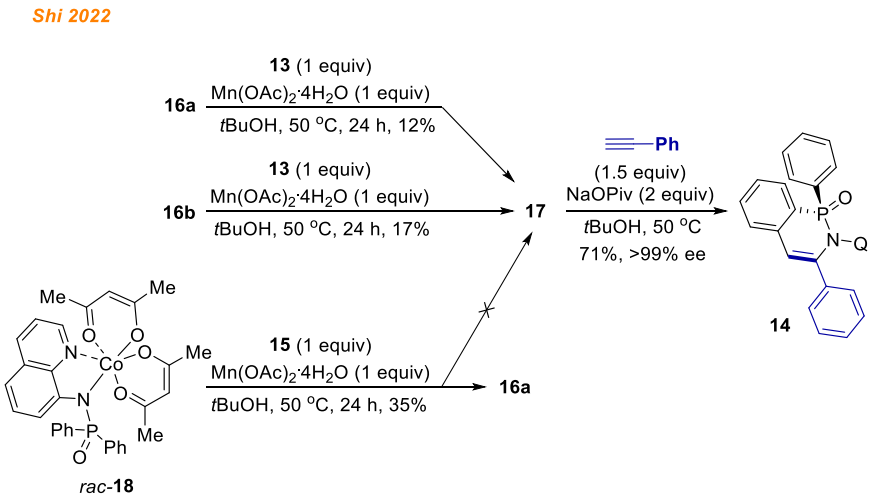



**Scheme 6.** Cobalt-catalyzed enantioselective C-H functionalization of arylphosphinamides **13** [28].

First, to test the proof of concept, authors synthesized chiral octahedral Co(III)-Salox complexes **16**, which were hypothesized to act as the reaction catalysts. Accordingly,

$Co(acac)_2$ in combination with $Mn(OAc)_2 \cdot 4\ H_2O$ in the presence of chiral ligand **15** gave Co(III)-Salox complex diastereomers **16a** and **16b** (**16a**:**16b** = 15:1) in high yield.

With both Co(III) complex isomers **16a** and **16b** in hand, the authors proved their hypothesis and demonstrated that both complexes **16** are suitable chiral catalysts for enantioselective desymmetrizing C-H annulation of diarylphosphinamides **13** with alkynes thereby demonstrating the structure of the active cobalt catalyst which participates in developed reaction. Next, the reaction of diarylphosphinamide **13** with ligand **15** and $Co(acac)_2$ under oxidative conditions resulted in the simultaneous formation of Co(III) complexes **16a** and **17** with 45% and 14% yield, respectively. Additionally, both **16a** and its diastereomer **16b** in the reaction with diarylphosphinamide **13** in the presence $Mn(OAc)_2 \cdot 4H_2O$ gave Co(III) complex **17** (Scheme 7) [28]. The authors speculated that $Mn(OAc)_2 \cdot 4H_2O$ likely promotes the formation of **17** by facilitating ligand exchange, as without $Mn(OAc)_2 \cdot 4H_2O$, complex **17** was not observed. In contrast, ligand exchange between the pre-formed *rac*-**18** and ligand **15** provided complex **16a**, not **17**. Finally, complex **17** in reaction with phenylacetylene gave product **14** in 71% yield, suggesting that all of the obtained cobalt complexes **16**–**18** might be the reaction intermediates.




**Scheme 7.** Mechanistic studies of the Cobalt/Salox-catalyzed synthesis of azaphosphinines **14** [28].

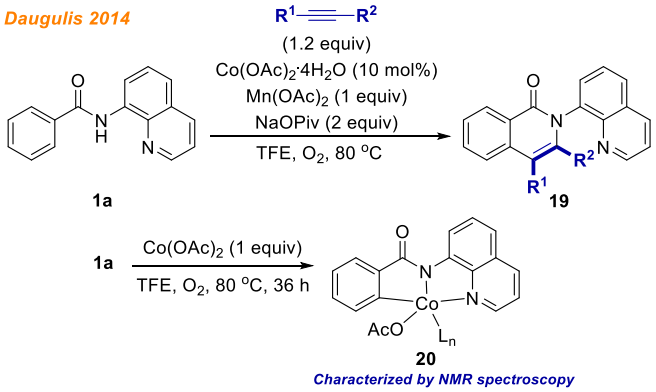
## 4. C-H Bond Activation

The key elementary step of C-H bond functionalization is the C-H bond activation. For high-valent cobalt catalysis, several C-H bond activation mechanisms leading to the formation of Co(III)-aryl complex are considered to be operative:

- electrophilic aromatic substitution;
- base-assisted intramolecular electrophilic substitution;
- concerted metalation–deprotonation;
- single-electron transfer [23,29].

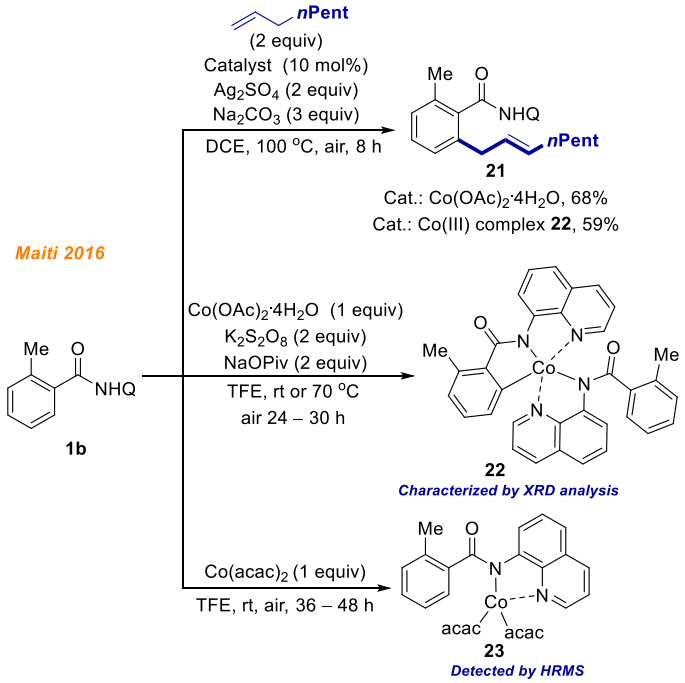
In the literature, there are several examples of isolated relatively stable Co(III)-aryl complexes obtained via direct C-H bond activation. Such complexes are proven to be invaluable assets for the mechanistic studies.

In early 2014, the Daugulis group developed benzamide **1a** $C(sp^2)$-H bond alkenylation with alkynes, using 8-aminoquinoline (Q) as a directing group (Scheme 8) [22]. The reaction conditions were mild and provided products **19** in good to excellent yields, tolerating a wide range of alkynes and substituents at benzene ring moiety. The authors hypothesized that due to the aminoquinoline stabilization of metals in high oxidation state, cobalt complex **20** could be the reaction intermediate. In addition, they successfully synthesized complex **20**, the structure of which was confirmed by NMR analysis, providing strong evidence for $C(sp^2)$-H bond activation of phenyl moiety and Co(III) species.




**Scheme 8.** Cobalt-catalyzed aminoquinoline-directed C($sp^2$)-H bond alkenylation by alkynes [22].

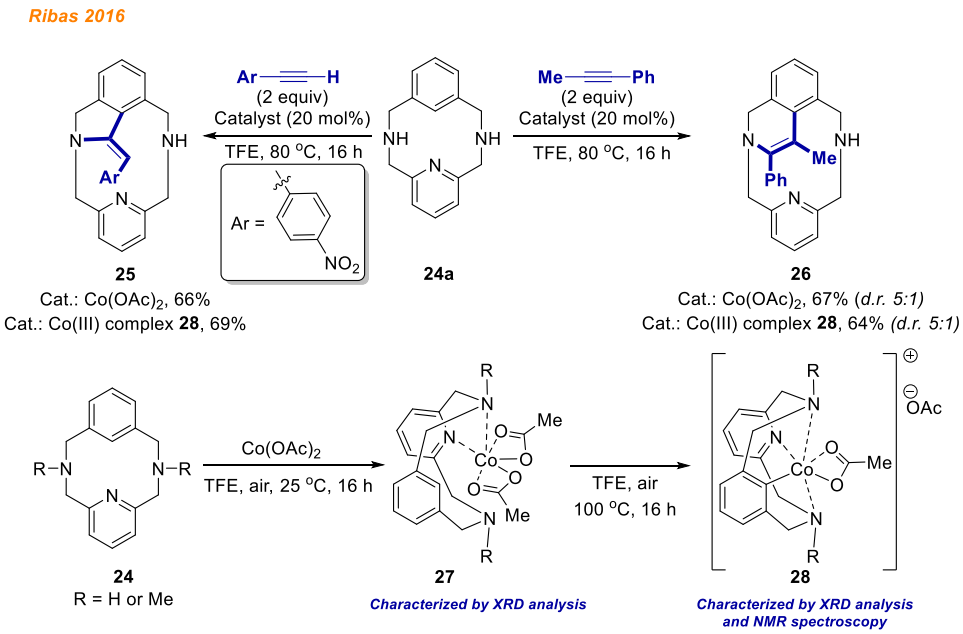
Maiti and co-workers in 2016 disclosed a novel methodology for benzamide **1b** C($sp^2$)-H bond allylation (Scheme 9) [30]. The optimization studies showed that the combination of $Co(OAc)_2 \cdot 4H_2O$ catalyst, $Ag_2SO_4$ oxidant, and 8-aminoquinoline directing group was the most suitable for the developed transformation. Both electron-donating and electron-withdrawing amides were successfully applied and yielded allylamides **21** with moderate to very good yields. In order to thoroughly outline all the aspects of this reaction, a series of control experiments were performed, including kinetic and labeling studies along with radical quenching experiments. Moreover, the authors succeeded in isolation of C-H activated Co(III)-aryl intermediate **22**, and proved its catalytic competency towards developed reaction. Employment of complex **22** as the catalyst yielded allylamide **21** in 59% yield. Additionally, they identified and characterized cobalt(III) complex **23** by HRMS, which underwent C-H bond activation/ligand exchange steps and formed Co(III)-aryl complex **22** after the addition of a stoichiometric amount of NaOPiv to the reaction mixture.




**Scheme 9.** Cobalt-catalyzed C-H bond allylation of benzamide derivatives **1b** [30].

In 2016, Ribas and co-workers described the synthesis and characterization of benchtop-stable organometallic aryl-Co(III) complexes obtained through C-H bond activation, using a 12-membered macrocyclic substrate **24a** (Scheme 10) [31]. Cobalt (II) coordination compounds **27** were prepared by the reaction of $Co(OAc)_2$ with macrocycles **24** (R = H or Me) at

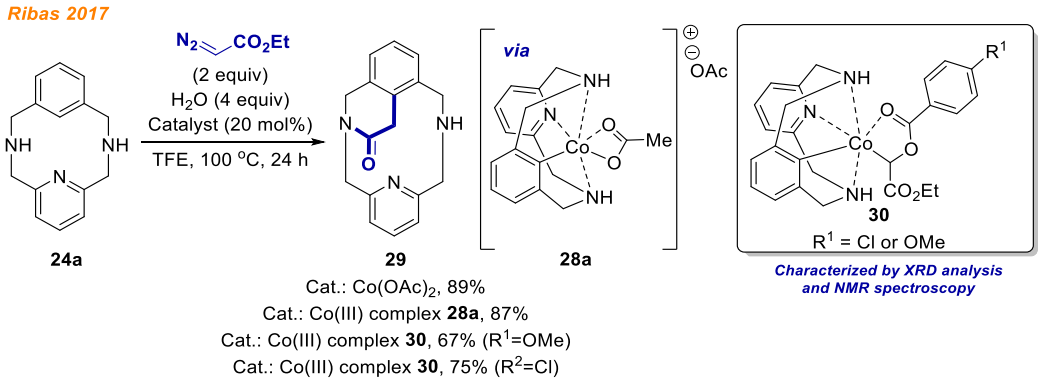
room temperature in TFE solution, and their structures were initially confirmed by HRMS and XRD analysis. Careful analysis of solid-state molecular structure indicated that Co(II) complexes **27** possess two acetates coordinated in a bidentate fashion. Notably, tridentate macrocycles **24** act as bidentate ligands, coordinated only through the pyridine and one amine. Upon increasing the temperature, the desired C-H activated cobalt(III) complexes **28** were obtained. Due to the stability of obtained Co(III)-aryl complexes **28**, they were successfully characterized by NMR and HRMS, providing spectra consistent with a Co(III) low spin diamagnetic metal center. Additionally, the authors explored the reactivity of isolated Co(III)-aryl compounds **28** in stoichiometric reactions with terminal and internal alkynes. Employing internal alkynes, the expected six-membered 1,2-dihydroisoquinolines **26** could be obtained in yields up to 72%, whereas terminal alkynes led to the formation of dihydroisoindoline **25** (5-membered ring) as a thermodynamically more stable product. It was observed that decreasing the reaction temperature or changing the electronic effects in alkynes, e.g., using phenylacetylene instead of 4-nitrophenylacetylene, led to the formation of a kinetic product (six-membered ring). In addition, using isolated Co(III) intermediates **28**, annulation reactions were also studied in a catalytic fashion. As a result, the desired products were obtained in very good yields, indicating that Co(III)-aryl complexes **28** are the reaction intermediates.




**Scheme 10.** Cobalt-catalyzed alkyne annulation and synthesis of Co(III)-aryl complexes **28** [31].

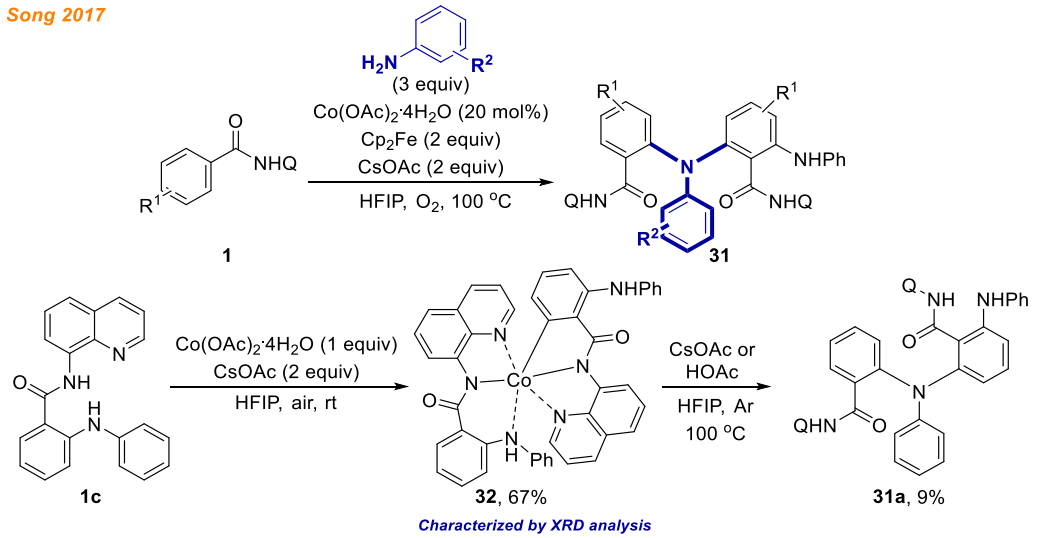
One year later, in 2017, Ribas group explored the formation of Aryl-Co(III) masked carbenes in cobalt-catalyzed C-H bond functionalization with diazo esters as a continuation of their previous work (Scheme 11) [32]. Optimization studies revealed that the developed protocol requires $Co(OAc)_2$ catalyst and $H_2O$ as an additive to afford the desired isoquinoline **29** via annulation reaction with ethyl diazoacetate (EDA). The authors utilized previously isolated cobalt complex **28a** as the substrate and performed detailed mechanistic investigation under anhydrous reaction conditions. When **28a** reacted with ethyl diazoacetate, a single peak was observed by HRMS analysis. Authors proposed the formation of a putative aryl-Co(III)-carbene intermediate. Although attempts to unravel its nature by crystallographic analysis were unsuccessful, suitable crystals for XRD analysis were obtained by replacement of acetate anion in **28a** with *p*-substituted benzoates. This anion exchange facilitated a rapid color switch from red to orange in the reaction with EDA, and recrystallization from $CHCl_3$/pentane afforded orange crystals of Co(III) complex **30**. Similar to a previous report [31], isolated cobalt intermediates **28a** and **30** were used as cat-

alysts, providing the desired product **29** with yields 67–87%, indicating that organometallic complexes **28a** and **30** are catalytically active species. Ribas and co-workers are continuing the investigation of Co(III)-aryl complex **28** reactivity towards other transformations [33].




**Scheme 11.** Cobalt-catalyzed C-H bond functionalization with ethyl diazoacetate [32].

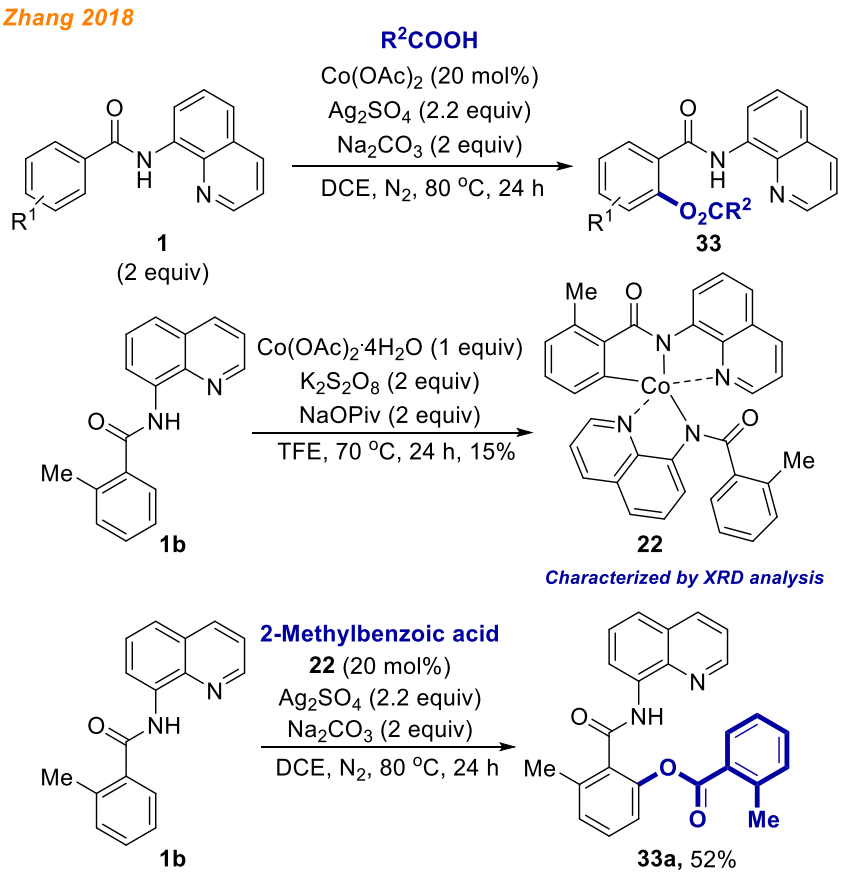
In the same year, Song and co-workers reported a selective and facile access to triarylamines **31** via cobalt-catalyzed oxidative C-H/N-H cross-coupling reaction (Scheme 12) [34]. During optimization of reaction conditions, authors were able to push the selectivity towards the desired product **31** over the dimerization side reaction of benzamides **1**. The best results were achieved, using optimized catalytic system, which consisted of $Co(OAc)_2 \cdot 4H_2O$ catalyst, ferrocene cooxidant and CsOAc in HFIP at 100 °C temperature under aerobic conditions. Furthermore, Co(III) complex **32** was obtained from the reaction of benzamide **1c** with stoichiometric amount of $Co(OAc)_2 \cdot 4H_2O$ at room temperature under air. Pleasingly, its structure was confirmed by XRD analysis. The authors demonstrated that cobaltacycle **32** under basic or acidic conditions delivered the triarylamine product **31a** only in 9% yield. Although other mechanistic experiments suggest a Co(II)-Co(III)-Co(I) catalytic cycle, based on the low yield of product **31a** formation from Co(III) complex **32**, the involvement of Co(IV) catalytic species cannot be excluded.




**Scheme 12.** Cobalt-catalyzed synthesis of triarylamines **31** [34].

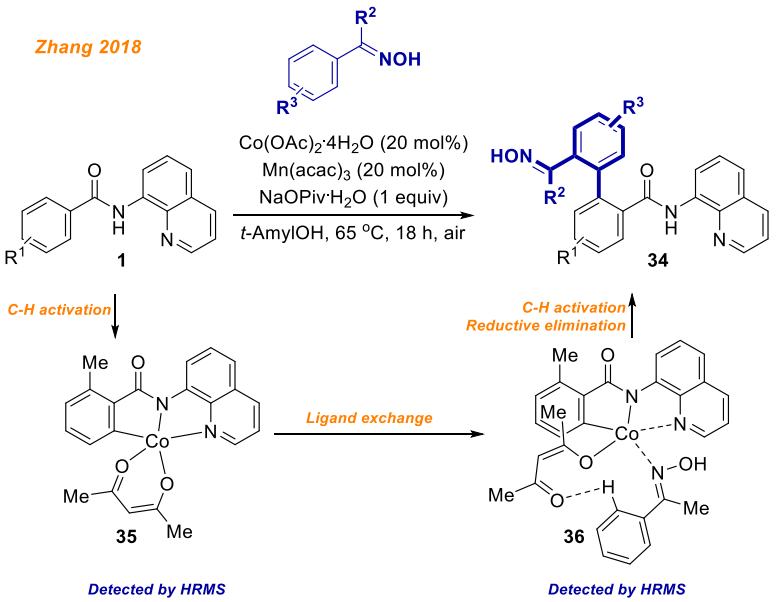
In 2018, Zhang and co-workers reported a facile and powerful protocol for the cobalt-catalyzed C-H bond acyloxylation of benzamides **1** (Scheme 13) [35]. In the developed methodology anhydrous $Co(OAc)_2$ in combination with $Ag_2SO_4$ and $Na_2CO_3$ in DCE was found to be the catalytic system of choice. The optimized reaction conditions were compatible with a diverse substrate scope, delivering a broad variety of *o*-substituted

benzamides **33** (44 products) with yields up to 99%. Additionally, radical-trapping and deuterium-labeling experiments were performed to understand the reaction mechanism in detail. Besides, authors synthesized Co(III)-aryl complex **22** based on a procedure previously described by Maiti and co-workers in 2016 [30], starting from methylbenzamide **1b**, and confirmed its structure by single-crystal X-ray diffraction analysis. Authors suggested that Co(III) complex **22** could be the key intermediate in this reaction as it catalyzed the model reaction, delivering product **33a** in 52% yield.



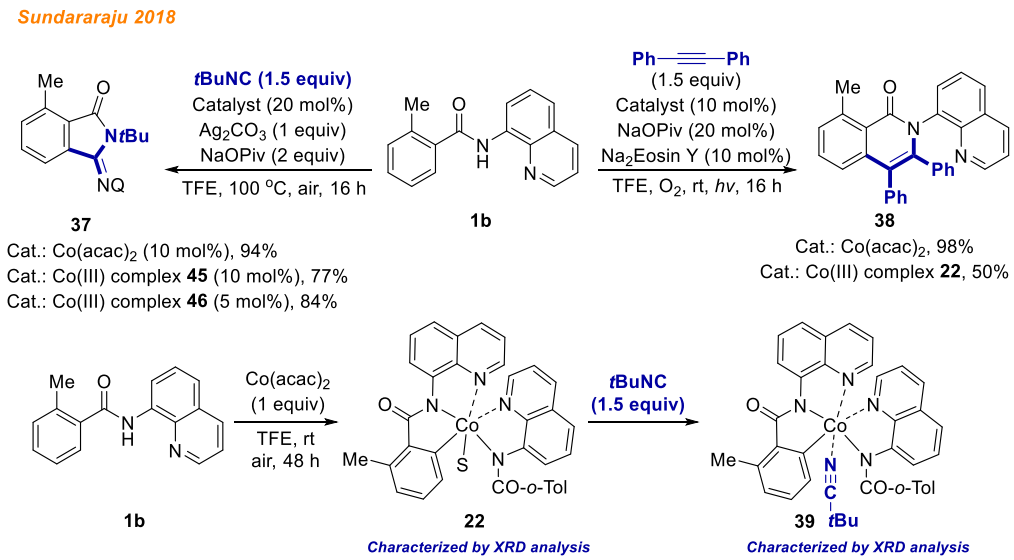

**Scheme 13.** Cobalt-catalyzed acyloxylation of benzamides **1** [35].

In the same year, the Zhang group reported a novel strategy for the synthesis of difunctional biaryls **34** from readily available benzamides **1** and oximes (Scheme 14) [36]. In contrast to the majority of cobalt-catalyzed benzamide **1** C-H bond functionalization reactions, the reported protocol is very mild as this transformation takes place at 65 °C temperature under air. The reported methodology demonstrates broad substrate scope as well as remarkable chemoselectivity towards cross-coupling. To gain insight into the reaction mechanism, the authors performed an intermolecular competition experiment of electronically differentiated benzamides as well as KIE experiments. In addition, both, C-H activated Co(III)-aryl complex **35** and oxime-coordinated Co(III)-aryl complex **36** were successfully detected by HRMS. Mechanistic studies along with detected Co(III) intermediates helped authors to propose the reaction mechanism, which is in accordance with the general Co(II)-Co(III)-Co(I) mechanism.




**Scheme 14.** Cobalt-catalyzed synthesis of biaryls **34** via C-H bond activation [36].

In 2018, the Sundararaju group developed a novel pathway for isonitrile insertion/acyl group migration between N-H and C-H bonds of benzamides **1b** through intramolecular *trans*-amidation catalyzed by $Co(acac)_2$ (Scheme 15) [37]. The authors demonstrated broad substrate scope yielding a wide variety of iminoisoindolinone derivatives **37** (42 products, yields up to 94%). Besides, significant mechanistic studies were performed, including KIE, H/D exchange, and radical trapping experiments. Moreover, the stoichiometric reaction of benzamide **1b** with $Co(acac)_2$ yielded C-H activated Co(III)-aryl complex **22**, which was previously described by Maiti [30], as well as later by the Zhang group [35]. The reaction of Co(III)-aryl complex **22** with *tert*-butyl isocyanide at room temperature in 10 min yielded Co(III) intermediate **39**, which was isolated and its structure was confirmed by HRMS and XRD analysis. Both intermediates **22** and **39** were used as catalysts for the transformation of benzamide **1b** to iminoisoindolinone derivative **37** under standard reaction conditions and were found to be active in catalysis.

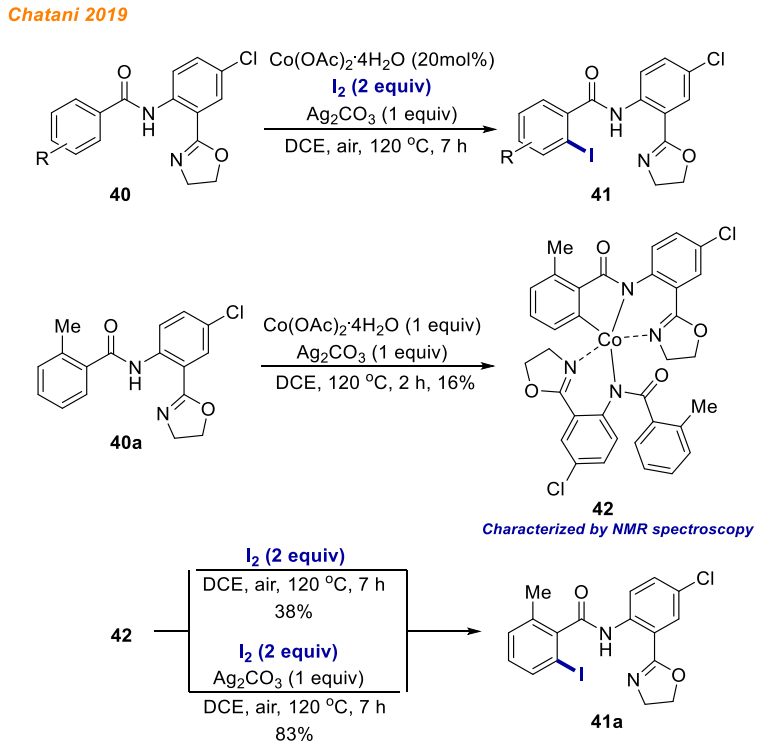



**Scheme 15.** Cobalt-catalyzed C-H bond functionalization of benzamide **1b** [37,38].

Later the same year, Sundararaju and colleagues reported a strategy for benzamide **1b** C-H and N-H bond annulation with alkynes by merging cobalt-mediated catalysis with

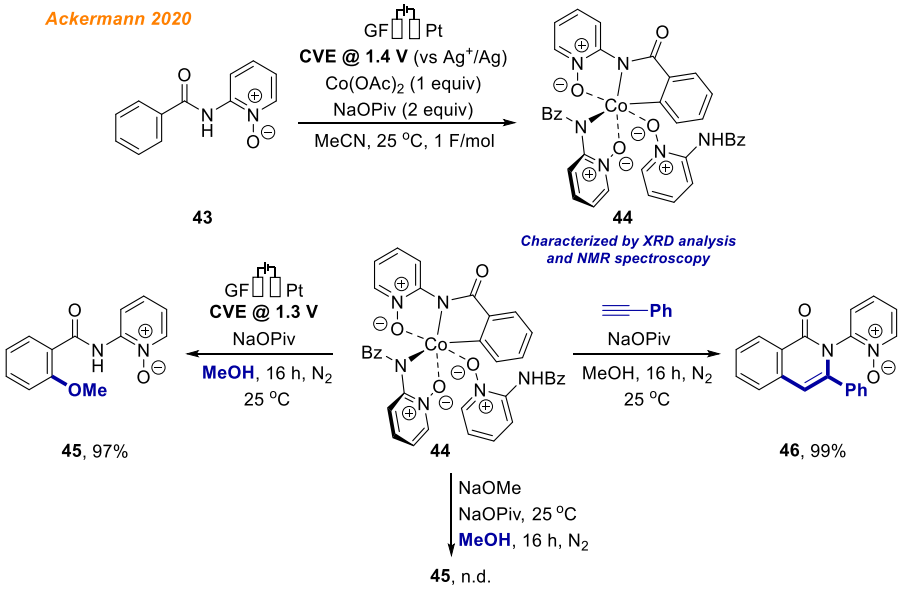
photocatalysis (Scheme 15) [38]. Employing relatively similar reaction conditions to the group's previous report [35] and $Na_2$Eosin Y as the photoredox catalyst, various electron-donating and electron-withdrawing benzamides delivered isoquinolones with yields up to 99%. In addition, Co(III) complex **22** was found to be catalytically active in reaction with benzamide **1b**, delivering isoquinolone **38** with 50% yield in contrast to $Co(acac)_2$, which furnished the desired product with 98% yield.

A year later, in 2019, Chatani reported an efficient protocol for cobalt-catalyzed C-H bond iodination of benzamides **40** with elemental iodine (Scheme 16) [39]. Thus, 2-Aminophenyloxazoline-based bidentate chelation as a directing group in combination with $Co(OAc)_2{\cdot}4H_2O$ catalyst and $Ag_2CO_3$ oxidant were found to represent the optimal catalytic system for the synthesis of 2-iodobenzamides **41** in moderate to great yields. When methylbenzamide **40a** was treated with equimolar amount of $Co(OAc)_2{\cdot}4H_2O$ and $Ag_2CO_3$ in DCE at 120 °C for 2 h, the Co(III) complex **42** was successfully isolated and characterized by HRMS and NMR spectroscopy. Interestingly, without the oxidant Co(III), complex **42** furnished the iodination product only in 38% yield along with a significant amount of unidentified byproducts, whereas in the presence of $Ag_2CO_3$ the yield increased to 83%, and no byproducts were detected. Based on these experiments, the authors concluded that despite the catalytic activity of Co(III) complex **42**, silver oxidant is an essential component of the reaction, promoting the iodination reaction and eliminating the formation of byproducts. The authors therefore speculated that Co(III) complex **42** is not the key intermediate of the reaction, but exists as a resting state.




**Scheme 16.** Cobalt-catalyzed iodination of benzamides **40** with molecular iodine [39].

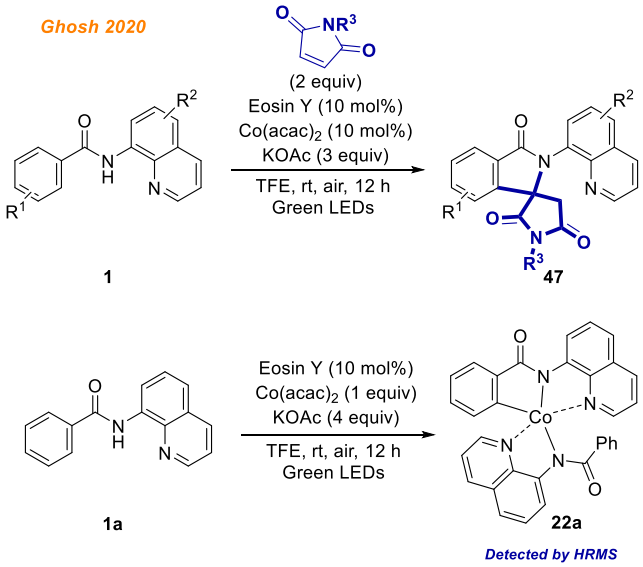
In 2020, the Ackermann group identified and characterized electrochemically generated high valent cobalt (III/IV) complexes as crucial intermediates in electrochemical cobalt-catalyzed C-H bond functionalization reactions (Scheme 17) [40].




**Scheme 17.** Electrochemical synthesis of Co(III)-aryl complex 44 and its reactivity studies [40].

The envisioned 18e$^-$ cobaltacycle **44** was electrochemically synthesized starting from benzamide **43** and an equimolar amount of $Co(OAc)_2$, and its structure was unambiguously confirmed by NMR spectroscopy, ESI-MS, and XRD analysis. Investigating the red-ox potential by means of voltammetry, the authors were able to affirm the anodic generation of Co(IV) complexes. Interestingly, the authors observed the formation of alkoxylated product **45** from Co(III)-aryl complex **44** only when voltage was applied. Such a result supports the oxidation-induced reductive elimination pathway involving Co(IV) species. At the same time, Co(III) complex **44** reaction with phenylacetylene proceeded smoothly, allowing to obtain product **46** in 99% yield. These findings are indicative of different mechanisms being operative for the C-O versus C-H formations.

A novel methodology merging visible-light photocatalysis and cobalt catalysis was reported by the Ghosh group in 2020 (Scheme 18) [41].

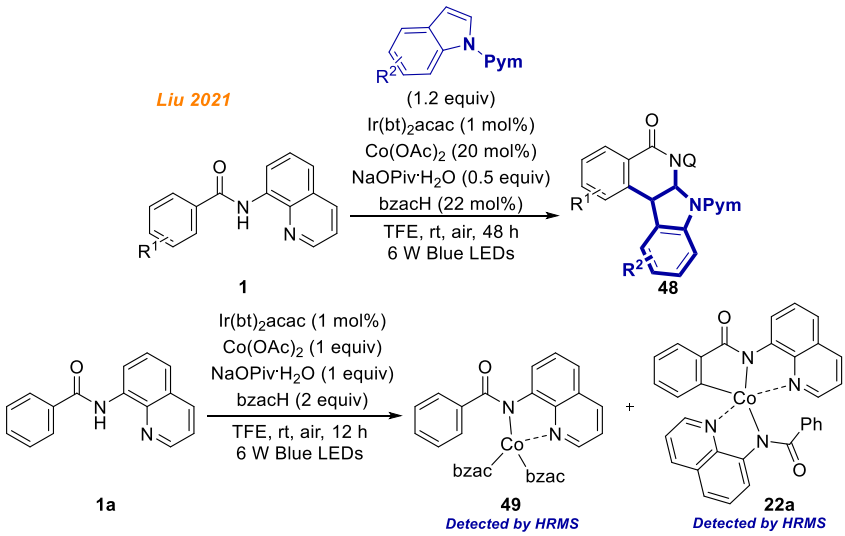



**Scheme 18.** Synthesis of isoindolone spirosuccinimides **47** by merging photocatalysis and cobalt-catalyzed C-H bond activation [41].

The developed protocol gives an efficient access to isoindolone spirosuccinimides **47** by the oxidative cyclization of benzamides **1** with maleimides. The main advantage of

the developed transformation was the use of photocatalyst Eosin Y, a commonly available organic dye, instead of sacrificial metal oxidant to reoxidize the in-situ formed low-valent Co(I) to active high valent Co(II)/Co(III) species to continue the catalytic cycle. Mild reaction conditions tolerated well a broad variety of benzamides **1** containing substituents both in phenyl moiety and in the aminoquinoline directing group moiety, delivering isoindolones **47** with yields up to 92%. It should be noted that authors were able to identify a five-membered Co(III)intermediate **22a** by HRMS, which validated the involvement of Co(III) complex **22a** in the reaction mechanism, although no further identification of reaction intermediates was performed.

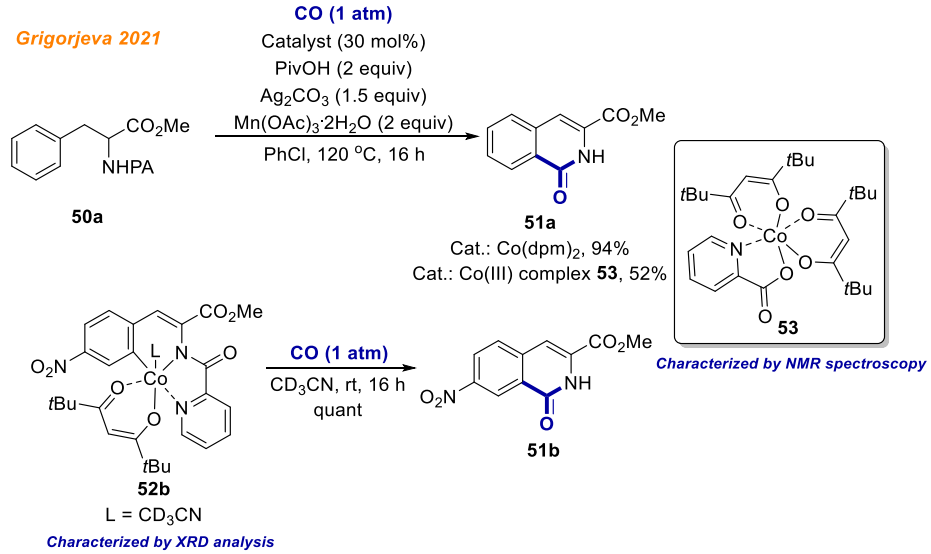
One year later, in 2021, Liu and co-workers depicted metallaphotoredox dearomatization of indoles for the facile generation of indoloisoquinolinones **48** via [4 + 2] annulation reaction with benzamides **1** (Scheme 19) [42]. The developed catalytic system employed $Co(OAc)_2$ catalyst and $Ir(bt)_2acac$ photocatalyst, sodium pivalate additive, and benzoylacetone ligand in TFE at room temperature. Similar to Ghosh's report [41], no external oxidant was required due to photocatalytic reoxidation of the catalyst. The substrate scope studies showed that both electron-rich and electron-poor substrates displayed similar reactivity and gave the products mostly in good to excellent yield (up to 92%). Control experiments revealed the involvement of single electron transfer processes, as with the addition of radical scavengers, the generation of product was entirely suppressed. To gain insight into the mechanism, the authors performed deuterium-labeling experiments, as well as studied KIE of the reaction. In addition, the authors synthesized $Co(bzac)_3$, which was found to be catalytically competent. Moreover, two Co(III) complexes **49** and **22a** were detected by ESI-HRMS, establishing the intermediacy of the related Co(III) system in the present reaction.




**Scheme 19.** Synthesis of indoloisoquinolinones **48** via metallaphotoredox catalysis [42].

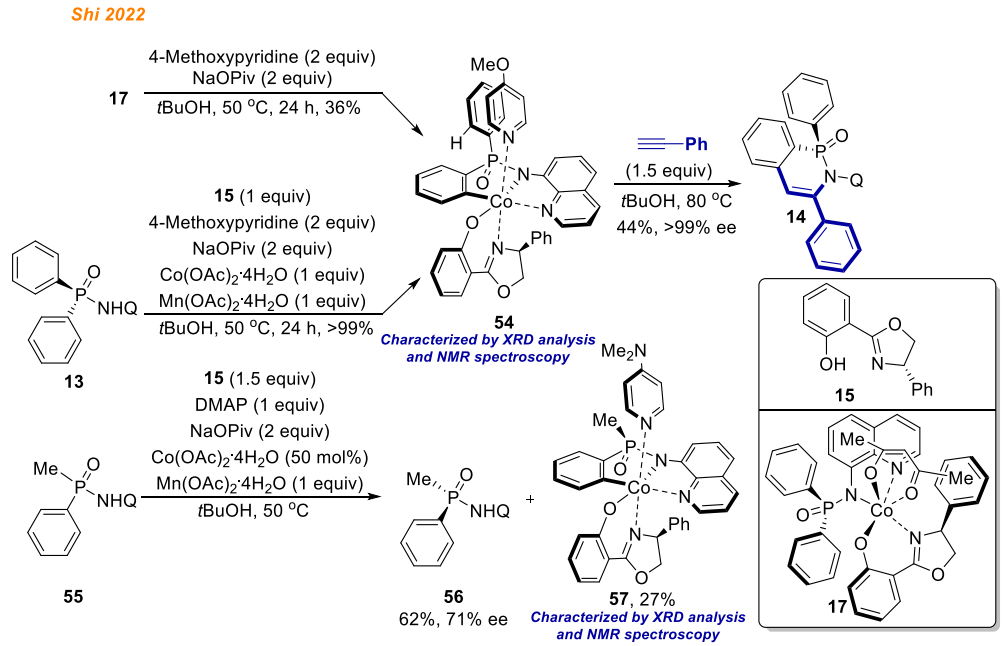
In the same year, Grigorjeva and co-workers reported an efficient methodology for the synthesis of dihydroisoquinolinolones **51** via cobalt catalyzed C-H bond carbonylation of phenylalanine derivatives **50** (Scheme 20) [43]. Interestingly, in this transformation, the picolinamide directing group revealed its traceless nature as it was cleaved in situ under the reaction conditions. The authors were able to demonstrate a diverse substrate scope, delivering the desired *N*-unsubstituted cyclization products **51** with moderate to excellent yields (up to 95%). Furthermore, it was shown that the developed methodology may be applicable to a late-stage functionalization of short peptides, although partial racemization of some products was observed. Besides, under the standard reaction conditions, authors were able to isolate the key intermediates, including Co(III) complex **53**. The employment of Co(III) intermediate **53** as the reaction catalyst gave product **51a** in 52% yield. In addition, C-H activated Co(III)-aryl intermediate **52b** was successfully isolated, and its structure

was unambiguously confirmed by XRD analysis. Pleasingly, under CO (1 atm) at room temperature, cobaltacycle **52b** quantitatively formed C-H carbonylation product **51b**, which supported the author's conclusion this complex most likely was the key intermediate of the reaction.




**Scheme 20.** Cobalt-catalyzed carbonylation of phenylalanine derivatives **50** [43].

In 2022, along with cobalt complexes formed in ligand exchange/oxidation step, the Shi group were able to synthesize and isolate C-H activated Co(III)-aryl intermediates (Scheme 21) [28]. For example, the reaction of previously isolated Co(III) complex **17** was conducted in the presence of NaOPiv and 4-methoxypyridine as a neutral ligand to stabilize the resulting cobalt complex. As a result, Co(III)-aryl complex **54** was obtained in 36% yield as a single octahedral diastereomer via asymmetric C-H activation step.

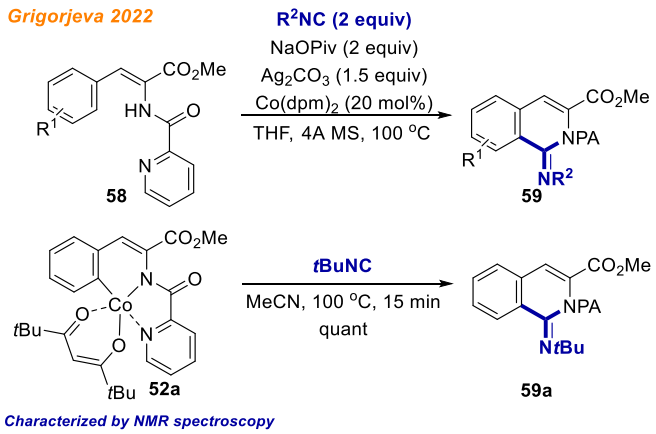



**Scheme 21.** Synthesis of Co(III)-aryl intermediate **54** [28].

Alternatively, cobalt(III) intermediate **54** was also obtained in quantitative yield directly from phosphinic amide **13** by the reaction with equimolar amount of ligand **15**, Co(II) acetate, oxidant, NaOPiv, and 4-methoxypyridine as a stabilizing ligand. Notably, the con-

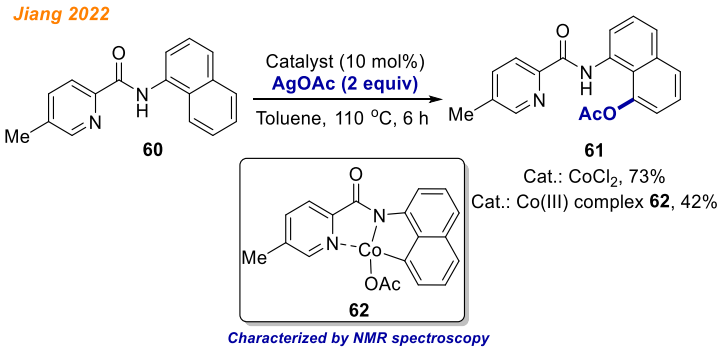
figuration of azaphosphinine oxide **14** matches the stereochemistry of phosphorus center in **17**, which led authors to consider enantio-determining C-H bond cleavage. Regarding this, authors performed stoichiometric kinetic resolution of racemic **55**. It was revealed that only one enantiomer gave corresponding Co(III) intermediate **57**, which further suggested that the chirality of the phosphorus center was established through enantio-determining C-H bond cleavage.

As a continuation of their previous work on amino acid C-H functionalization, in 2022, Grigorjeva and co-workers reported novel protocol for the cobalt-catalyzed C-H bond imination of α,β-unsaturated phenylalanine derivatives **58** using isocyanides (Scheme 22) [44]. The substrate scope was explored using several α,β-unsaturated phenylalanines **58** and different isocyanides, delivering 26 different iminoisoquinolines **59** in good to excellent yields (up to 96%). Although picolinamide did not act as a traceless directing group, as shown in their previous report [43], it can be easily cleaved under the reductive conditions using $LiAlH_4$ or Zn/AcOH. In addition, the developed methodology was applied for the synthesis of PDE5 inhibitor. In order to gain insight into the reaction mechanism, the authors performed series of control experiments, including ligand exchange and competition experiments, H/D scrambling and KIE studies. Besides, a stoichiometric experiment with Co(III)-aryl complex **52a** was performed. Interestingly, **52a** in the reaction with *tert*-butyl isocyanide gave product **59a** in quantitative NMR yield in the absence of external oxidant, indicating that **59a** is very likely the intermediate of proposed catalytic cycle.



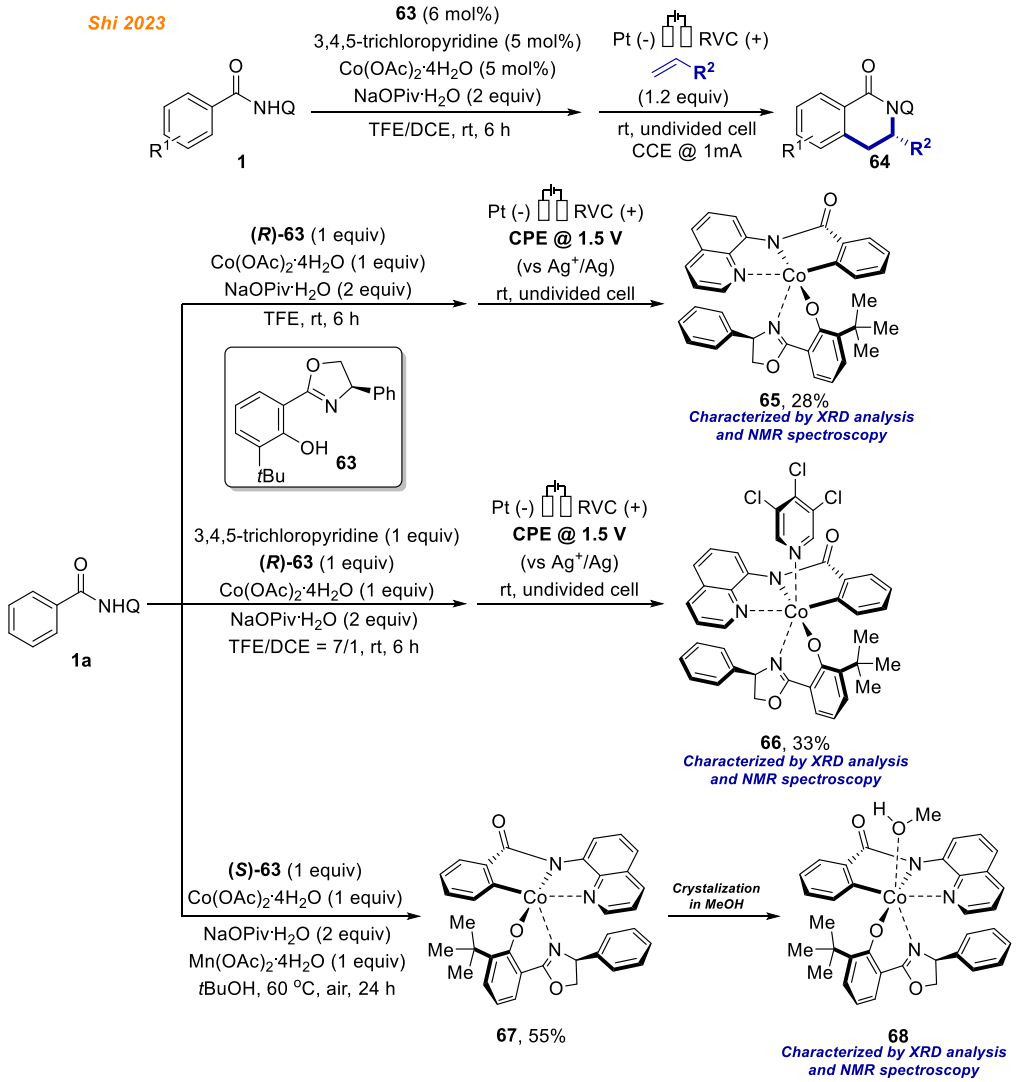

**Scheme 22.** Cobalt-catalyzed imination of phenylalanine derivatives **58** [44].

In the same year, Jiang and colleagues demonstrated an interesting approach towards C-H bond acyloxylation of picolinamides **60** with silver carboxylates under cobalt catalysis (Scheme 23) [45]. Generally, substituted silver carboxylates and substituted picolinamides **60** were reactive, delivering a very wide and diverse product scope consisting of 73 different products with good to excellent yields (up to 94%). Investigation of the reaction mechanism by means of KIE studies led to the conclusion that C-H bond activation may not be the turnover-limiting step. Furthermore, authors were able to obtain chelated Co(III)-aryl complex **62**, which was accurately characterized by NMR and HRMS analyses. The employment of Co(III) intermediate **62** as the reaction catalyst gave the desired product **61** in 42% yield, whereas under standard reaction conditions using $CoCl_2$ catalyst, it was obtained in 73% yield. From these results, the authors concluded that complex **62** was the key intermediate in the developed C-H bond acyloxylation reaction.




**Scheme 23.** Cobalt-catalyzed acetoxylation of picolinamide **60** [45].

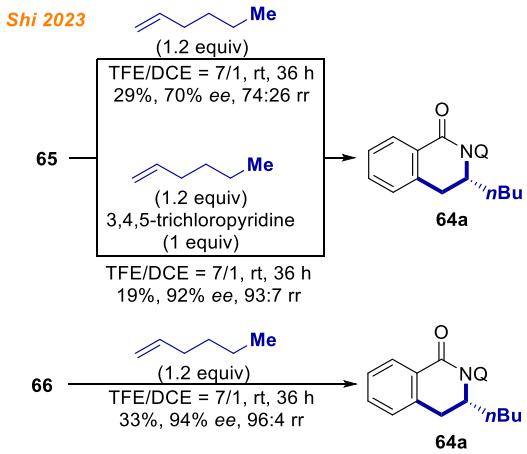
Very recently, an enantio- and regioselective electrooxidative cobalt-catalyzed C-H/N-H annulation reaction with alkenes was developed by Shi and co-workers (Scheme 24) [46]. In their report, π–π interactions between the phenyl ring in the oxazoline ligand **63** and the quinoline moiety of the benzamides **1** secured the chirality at cobalt, leaving chiral cave in one direction open for alkene coordination, facilitating the formation of annulation products **64** in high enantio- and regioselectivities (up to 99% *ee*).




**Scheme 24.** Synthesis of Co(III)-aryl complexes **65**–**68** [46].

Additionally, octahedral Co(III) complexes were synthesized and characterized to understand the coordination fashion of cobalt catalyst and the mode of stereoinduction. Benzamide **1a** in the reaction with an equimolar amount of $Co(OAc)_2 \cdot 4H_2O$ and oxazoline ligand (*R*)-**63** under electrolysis conditions provided *penta*-coordinated Co(III)-aryl complex **65** in 28% yield. The addition of 3,4,5-trichloropyridine as a coordinative ligand under similar reaction conditions provided *hexa*-coordinated Co(III)-aryl complex **66** in 33% yield. The authors note that both **65** and **66** were stable at ambient temperature and were fully characterized by NMR and ESI-MS analyses. However, attempts to obtain single-crystals for X-ray diffraction analysis were unsuccessful. On the other hand, under thermal conditions, using oxazoline ligand (*S*)-**63** analogous *penta*-coordinated Co(III)-aryl, complex **67** was obtained in 55% yield. Complex **67** crystallization from MeOH gave Co(III) complex **68**, whose structure was unambiguously confirmed by XRD analysis.

Interestingly, the stoichiometric reaction of Co(III)-aryl complex **65** with hex-1-ene yielded product **64a** with moderate enantioselectivity and poor regioselectivity, which was attributed to the lack of secondary bond interaction (Scheme 25) [46]. The authors found, that enantio- and regioselectivities reappeared with the addition of 1 equivalent of 3,4,5-trichloropyridine, which acted as a coordinative ligand. Moreover, *hexa*-coordinated Co(III)-aryl complex **66** gave product **64a** with excellent enantioselectivity and regioselectivity. These results led authors to conclusion that the combination of oxazoline and pyridine ligands is essential to ensure high enantio- and regio- selectivity for the developed methodology.

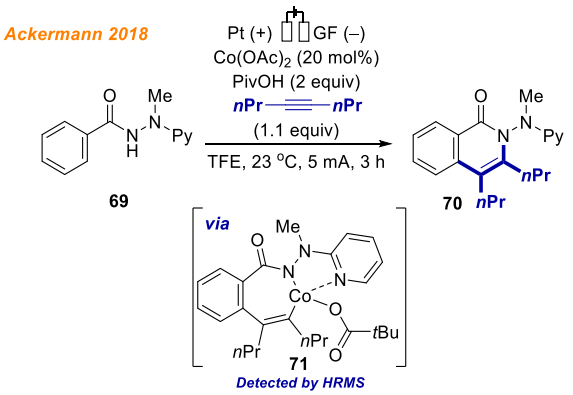



**Scheme 25.** Stoichiometric reactions of Co(III)-aryl complexes **65** and **66** with hex-1-ene [46].

## 5. C-H Bond Functionalization

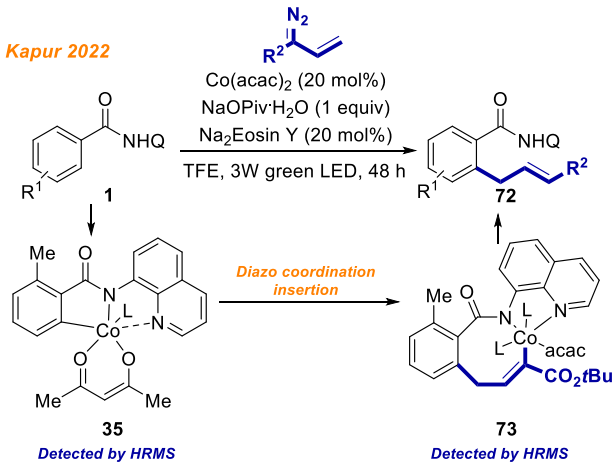
The C-H bond functionalization is the third elementary step in the generally accepted high-valent cobalt catalysis mechanism occurring after C-H bond cobaltation. As we described above, the plausible intermediacy of C-H activated Co(III)-aryl complexes has been evidenced by numerous groups by successfully exploiting such isolated or synthesized complexes as catalysts or substrates in stoichiometric amounts to obtain C-H bond functionalization products. However, the detection and/or isolation of potential cobalt intermediates, which are operative after the C-H bond metalation step, is a challenging task due to the reactivity of such cobalt complexes. As we described before, in 2018, Sundararaju and co-workers reported *tert*-butyl isocyanide coordinated cobalt complex **39**, which formed after Co(III)-aryl complex **22** reaction with *tert*-butyl isocyanide at room temperature (Please see Scheme 15). Although the complex was isolated and its structure was confirmed by HRMS and XRD analyses, the authors was not able to detect further reaction intermediates [38]. As far as we know, only two examples can be found in the literature describing Co(III) complexes formed after migratory insertion process.

In 2018, Ackermann's group reported the cobalt-catalyzed electro-oxidative C-H/N-H activation of benzamides **69** with internal alkynes (Scheme 26) [47]. In their study, the catalytic system employed a $Co(OAc)_2$ catalyst, PivOH additive, and electricity as the sole oxidant in TFE at room temperature to deliver isoquinolinones **70** in moderate to great yields (up to 96%). Additionally, the authors were able to detect by ESI-HRMS Co(III) intermediate **71**, which formed after the migratory insertion of alkyne into the Co-Ar bond. Moreover, computational mechanistic studies provided further support for the formation of the observed seven-membered Co(III) species **71**, which after reductive elimination delivered the desired product **70** and Co(I).




**Scheme 26.** Cobalt-catalyzed electrooxidative benzamide **69** reaction with alkyne [47].

Kapur and co-workers, in late 2022, reported an interesting approach towards benzamide **1** C-H bond allylation using merged cobalt and photoredox catalysis (Scheme 27) [48]. In contrast to Maiti's allylation with terminal alkenes [26,30], authors used vinyldiazo esters as allylating reagents. As a result, allylbenzamides **72** were obtained in moderate yield, although the developed methodology proved to be effective for the late-stage diversification of biologically active molecules, including cholesterol, nerol, and others. In the proposed reaction mechanism, after ligand exchange and C-H activation, cobalt intermediate **35** could form. The authors propose, that Co(III)-aryl complex **35** undergoes a diazo coordination and insertion, which leads to the formation of the Co(III) intermediate **73**. Both cobaltacycles **35** and **73** were observed by HRMS, although none of them was isolated from the reaction.

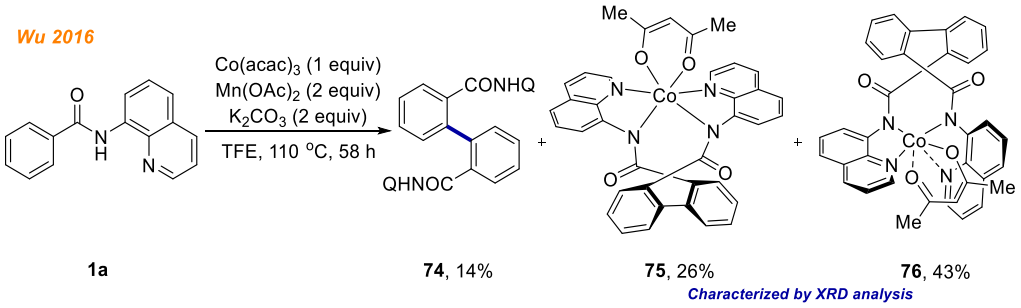



**Scheme 27.** Benzamide **1** C-H bond allylation using merged cobalt and photoredox catalysis [48].

## 6. Oxidation

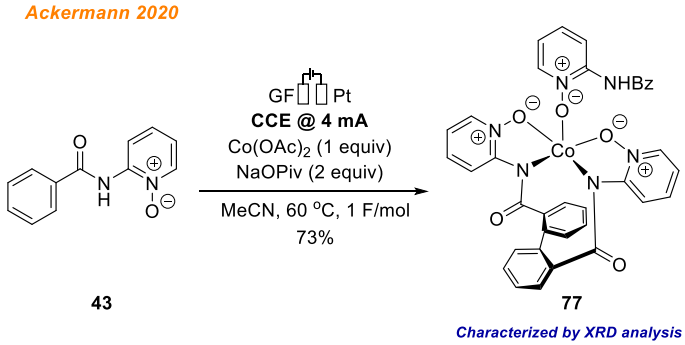
The last elementary step of C-H bond functionalization reactions is re-oxidation of the cobalt catalyst after reductive elimination to return the active Co(III) species to the catalytic cycle. Although no Co(I) species are isolated, there have been few reports on plausible reaction intermediates arising after oxidation of Co(I) species. For example, Grigorjeva and colleagues were able to isolate Co(III) catalyst coordinated to picolinamide, which formed after the hydrolysis of the directing group (please see Scheme 20) [43].

In 2016, Wu and colleagues studied the cobalt-catalyzed homo-coupling of benzamide **1** derivatives (Scheme 28) [49]. Prior to optimization of the reaction conditions, Daugulis and co-worker reported their results on the same transformation, focusing their attention on different substrates for the dimerization reaction. Nevertheless, during initial studies, authors were able to isolate Co(III) complexes **75** and **76** in 26% and 43% yields, respectively. The difference between **75** and **76** is the orientation of the acetylacetone group attached to the cobalt center. In addition, XRD analysis was performed, unambiguously confirming structures to be biaryl-linked Co(III) complexes, which would lead to the desired product **74** after demetallation.




**Scheme 28.** Cobalt-catalyzed benzamide **1a** dimerization [49].

In 2020, along with Co(III) complexes which were formed in the C-H bond activation step, Ackermann and colleagues noticed the formation of a significant amount of byproducts, especially with the electron rich substrates **43** [40]. Based on their mechanistic studies, authors hypothesized a possible oxidation of Co(III)-aryl species to Co(IV) complexes, which would undergo oxidation-induced reductive elimination for homo-coupling of the coordinated substrates **43**, leading to paramagnetic Co(II) complexes. Further, various solvents were probed, and the reaction temperature was adjusted. As a result, benzamide **43** delivered the desired Co(II) complex **77**, using MeCN at 60 °C (Scheme 29). Moreover, the structure **77** was completely verified by XRD characterization, providing strong support for an oxidation-induced reductive elimination from a high-valent Co(IV) intermediate.




**Scheme 29.** Synthesis of paramagnetic Co(II) complex **77** from benzamide **43** [40].

## 7. Conclusions and Outlook

In this review, we have summarized the overall current progress on the isolation and identification of key cobalt intermediates in cobalt-catalyzed, bidentate-chelation assisted

C-H bond functionalization reactions. The general Co(II)-Co(III)-Co(I) mechanism, which is based on literature reports, is overviewed in detail according to the elementary steps.

The identification and characterization of reaction intermediates over the years has become an essential approach for understanding the reaction mechanism, which along with additional mechanistic experiments, including kinetic isotope effects, labeling studies, competitive experiments, and others, can serve as direct and indirect evidence to decipher the full picture of the catalytic cycle. The first two elementary steps of the C-H functionalization reaction, i.e., substrate coordination/oxidation and C-H bond activation, are relatively well-studied and supported by a diverse scope of isolated key Co(III) intermediates. Most of the isolated key intermediates are Co(III) 18 e- complexes. Typically, octahedral Co(III) 18 e- complexes are considered as stable and relatively inert species, which tend to vacate at least one coordination site to participate in the reaction. Based on this fact, the most likely key reaction intermediates are coordinatively unsaturated 16 e- or 14 e-complexes, which react with solvent or other ligand upon isolation and/or crystallization to form stable species.

However, the next elementary steps of the reaction mechanism (C-H bond functionalization and catalyst re-oxidation) are studied much less and are supported by only a few examples of isolated or detected cobalt species. Difficulties in isolating potential key intermediates after the C-H bond activation step may be attributed to the high reactivity of such cobalt species, which makes it challenging even to detect by HRMS analysis. First reports appeared only five years ago and currently only two examples of Co(III) species after the migratory insertion step are known. Therefore, this part of general catalytic cycle remains underdeveloped. The creation of novel methods for the isolation and/or characterization of such intermediates will very likely be an enormous breakthrough for the understanding of the mechanism of cobalt-catalyzed C-H functionalization reactions and represent a valuable direction for future research.

Although many research groups have succeeded in the isolation of Co(III) key reaction intermediates, and the general Co(II)-Co(III)-Co(I) mechanism is studied in detail, currently, there is indisputable evidence for the Co(II)-Co(III)/Co(IV)-Co(II) catalytic cycle which could be operative depending on the used reaction component. Numerous examples of the cobalt-catalyzed C-H bond functionalization methodology that are not consistent with the Co(II)-Co(III)-Co(I) mechanism continue to be discovered. However, the Co(II)-Co(III)/Co(IV)-Co(II) pathway is not completely confirmed due to the lack of evidence and difficulties in obtaining it. From our perspective, this is another highly important future direction and a challenging task for researchers.

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**Data Availability Statement:** Additional data to those shown in this review can be obtained from the articles cited in our bibliography.

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**Conflicts of Interest:** The authors declare no conflict of interest.

## Abbreviations

acac = acetylacetone, bzac = benzoylacetone, CCE = constant current electrolysis, CPE = constant phase element, CVE = constant voltage electrolysis, Cp* = pentamethylcyclopentadienyl-, dpm = dipivaloylmethane, EDA = ethyl diazoacetate, $Ir(bt)_2acac$ = Bis(2-benzo[*b*]thiophen-2-ylpyridine)(acetylacetonate) iridium(III), PA = picolinamide, Q = 8-aminoquinoline.

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