Cp*Co(III)-Catalyzed C−H Hydroarylation of Alkynes and Alkenes and Beyond: A Versatile Synthetic Tool

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Cite This: ACS Omega 2020, 5, 24974−24993

ABSTRACT: The use of earth-abundant first-row transition metals, such as cobalt, in C−H activation reactions for the construction and functionalization of a wide variety of structures has become a central topic in synthetic chemistry over the last few years. In this context, the emergence of cobalt catalysts bearing pentamethylcyclopentadienyl ligands (Cp*) has had a major impact on the development of synthetic methodologies. Cp*Co(III) complexes have been proven to possess unique reactivity compared, for example, to their Rh(III) counterparts, obtaining improved chemo- or regioselectivities, as well as yielding new reactivities. This perspective is focused on recent advances on the alkylation and alkenylation reactions of (hetero)arenes with alkenes and alkynes under Cp*Co(III) catalysis.

1. INTRODUCTION

The transition-metal-catalyzed formation of carbon−carbon (C−C) or carbon−heteroatom (C−X) bonds has been proven to be a powerful tool for the construction and functionalization of many useful molecules. Among all of the methods available for the achievement of this goal, activation of inert C−H bonds stands out as an attractive, atom-economical, and environmentally friendly approach, since the use of prefunctionalized substrates bearing active C-halide or C-triﬂate bonds is avoided, along with the complications and waste associated with their preparation. This approach has enabled the synthesis of many compounds of interest, such as natural products, materials, and pharmaceuticals. During the last two decades, palladium(II) has unarguably been in the limelight when accomplishing C−H bond-activation reactions, although other transition metals, such as rhodium(III), ruthenium(II), and iridium(III), have also been capable of efficiently carrying out these kinds of transformations. Nonetheless, the use of the aforementioned second- and third-row-transition metals comes with the disadvantage of toxicity and high cost. Therefore, with the aim of overcoming those issues, the use of more earth-abundant first-row transition metals (nickel, iron, manganese, copper, and cobalt, for instance) has started to gain importance. Among them, cobalt catalysts bearing pentamethylcyclopentadienyl ligands (Cp*) have recently started to gain center stage, after the publication of Matsunaga and Kanai’s pioneering work, reported in 2013, on the utilization of high-valent Cp*Co(III). They demonstrated that a nucleophilic Co(III) organometallic species was generated via C−H activation, exempliﬁed by the conjugate addition of 2-phenylpyridine 1 to unsaturated ketones 2 (Scheme 1). For this reaction, complex [Cp*Co(C6H6)](PF6)2 was utilized as a catalyst, which is proposed to work similarly to Cp*Rh(III) catalysts on the addition of phenylpyridine 1 to sulfonylimines: the benzene ligand is proposed to thermally dissociate, allowing the catalyst to undergo complexation with 2-phenylpyridine (1), followed by C−H activation/metalation ortho to the directing group. The complex [Cp*CoCl2]2 in

![Scheme 1. Matsunaga and Kanai’s Hydroarylation of Electron-Deﬁcient Oleﬁns 2](https://dx.doi.org/10.1021/acsomega.0c03639)

Received: July 29, 2020
Accepted: September 2, 2020
Published: September 15, 2020
the presence of AgPF₆ could also be used as a catalyst for this transformation.

Although that first Cp*Co(III) complex efficiently catalyzed the aforementioned C–H activation reaction, a glovebox was required for its synthesis. Consequently, responding to the need for more bench-stable catalysts that could be easily synthesized without the need for an extremely inert atmosphere, Matsunaga reported the use of the Cp*Co(CO)I₃ complex as a precursor for cationic (pentamethylcyclopentadienyl)cobalt(III) catalysis and its application to the C-2-selective C–H amidation of indoles and allylation of indoles, 6-arylpurines, and aromatic amides. This Cp*Co(III) complex has become the most widely utilized catalyst to achieve Cp*Co(III)-promoted C–H functionalization reactions. This same group also reported that complex [Cp*CoCl]₂, which was obtained from the thermal decomposition of Cp*Co(CO)I₃, could also be an effective catalyst. However, it must be mentioned that, when using Cp*Co(CO)I₃ or [Cp*CoCl]₂, the addition of cationic and Lewis-acidic silver salts is usually necessary, as they act as halide scavengers, activating the Cp*Co(III) precatalysts. The counteranion of the cationic active Cp*Co(III) species usually has a dramatic effect on both the reactivity and stability of a catalytic system. Due to this, the fact that the counteranion can be easily tuned just by changing the silver additive comes as a huge advantage. Nevertheless, to avoid the use of expensive silver salts, acetoniutile complex [Cp*Co(CH₃CN)₃]2(SbF₆)2 was reported by Glorius to be able to catalyze these types of transformations.

During the last few years, this compound has also become a very common catalyst, being, in many instances, the complex of choice to promote C–H bond activation reactions efficiently. As commented later, Ellman’s group reported several three-component reactions that required the utilization of a catalyst bearing an inert and noncoordinating counteranion, which they had previously synthesized: [Cp*Co(C₆H₆)][B(C₆F₅)₄]2, prepared from [Cp*Co(C₆H₆)][PF₆]₂. In addition, they applied a variation of the method for the preparation of the precatalyst introduced by Matsunaga and Kanai in 2013, employing Cp*Co(CO)I₃ as the starting material.

In Cp*Co(III) catalysis, noncoordinating or weakly coordinating solvents, such as 1,2-dichloroethane (DCE), hexafluoro-2-propanol (HFIP), and 2,2,2-trifluoroethanol (TFE), are usually employed. Besides, sometimes, the addition of carboxylates is beneficial or even crucial to promote those transformations, probably because they enable or facilitate C–H bond activation via a concerted metatalation–deprotonation (CMD) or a base-assisted intramolecular electrophilic substitution (BIES). The Co(III) complexes mentioned herein were initially designed to act as homologues of their Cp*Rh(III) (and Cp*Ir) counterparts; however, cobalt has been proven to possess unique reactivity, as will be shown in the following sections. For example, the ionic radius of Co(III) catalysts is much smaller than the radius of Rh(III) catalysts. This fact has a dramatic effect on reactivity and selectivity as under Cp*Co(III) catalysis, the Cp* ligand is closer to the substituents of the coupling partners due to the smaller size of cobalt. Matsunaga and Kanai, who performed the reaction between unsymmetrically substituted O-acyloximes and alkynes (Scheme 2), demonstrated this in 2015. They observed that, due to the mentioned steric hindrance between the Cp* “hat” and the substituents on the substrate, high regioselectivities were achieved toward functionalization at the less sterically demanding position using [Cp*Co(CO)I₃] as a catalyst, whereas [Cp*RhCl₂] led to no selectivity under various conditions. Scheme 2 shows the different selectivities obtained with each catalyst for the reaction of substrate 4 bearing a chlorine atom at the meta position and phenylacetylene 5. Thus, in most of the examples that will be described throughout this perspective article, when an unsymmetrically substituted substrate is used, functionalization takes place at the less hindered position.

Since some reviews on this field have recently been published, here, we will present our perspective on the state of the art of this emerging area of catalysis. In this perspective article, we will focus on the development and the latest advances of Cp*Co(III)-catalyzed C–H hydroarylation of alkynes and alkenes.

2. ALKYNES AS COUPLING PARTNERS UNDER Cp*CO(III) CATALYSIS

Alkynes have been widely utilized as coupling partners in Cp*Co(III) catalysis, since they usually allow the formation of alkylated (hetero)arenes, being three of the most common pathways to achieve that goal, each of which would provide different products. The general catalytic cycle for these types of couplings is depicted in Scheme 3. First, the active catalytic species is formed by the reaction of the Cp*Co(III)-based precatalyst with the additives added. Then, the Cp*Co(III) complex is coordinated to the directing group of the (hetero)arene substrate and C–H activation as well as metalation occur ortho to the auxiliary group, furnishing I. After coordination of the alkyne to the metal center and migratory insertion, C(sp)–Co(III)–Cp* complex III is formed. Once this happens, III can undergo protodemetalation to form an acyclic alkylated arene IV (pathway A) or reductive elimination to form the cyclic adduct V (pathway B). When this last mechanism is operating in the reaction, an external or internal oxidant must be used to reoxidize the Cp*Co(I) species formed to the catalytically active Cp*Co(III) complex. Finally, advantage can be taken of the unique reactivity of Cp*Co(III) catalysts: cobalt is less electron-negative than rhodium; thus, the Lewis acidity of cobalt catalysts is higher than that of rhodium complexes. In addition, carbon–cobalt bonds are more polarized than their rhodium
counterparts, making C−Co bonds more nucleophilic. This higher nucleophilicity facilitates the addition of the organo-cobalt species III to the directing group, releasing cyclized product VI (pathway C). It is worth mentioning that, although it is not very usual, when pathways B and/or C are operating, acyclic products can be obtained instead of annulated products, as will be reported later.

Selected examples organized according to these three distinct mechanistic pathways are presented in the following section.

2.1. Proto-Demetalation Pathway. This pathway is usually employed to synthesize nonannulated alkenylated arenes and allows us to obtain those products without the requirement of internal or external oxidants.18 In this context, in 2017, Maji reported a method for the mono- and di-alkenylation of a variety of N-tert-butylbenzamides 7 with internal alkynes, such as 8 (Scheme 4).19 However, in some cases, the reaction was not completely selective, affording small amounts of the corresponding di- and mono-alkenylated arenes, 9′ and 9, as byproducts, respectively. After some experiments to elucidate the mechanism of the reaction, it was seen that the C−H activation is irreversible and could be part of the rate-determining step.

That same year, Li et al. carried out the alkenylation of indole 10 with terminal alkynes 11, selectively achieving the branched product 12 (Scheme 5). For that purpose, initially, propargyl alcohols (11, R = CH₃OH) and protected amines (11, R = CH₂NHTs) were utilized as coupling partners, providing moderate to high positional selectivities due to the electronic factors. For those cases, the alkyne insertion process was the step in which the regioselectivity is determined, according to density functional theory (DFT) calculations (Scheme 5a). Besides, when silyl-substituted alkynes were employed (11, R = triisopropylsilyl (TIPS), tert-butyldimethylsilyl (TBDMS)), the selectivity is driven by the steric effects of the substituents during the protonolysis event (Scheme 5a). It was observed that bulkier silyl groups gave better site selectivities. On the other hand, when phenylacetylene (11, R = Ph) and ethyl propiolate (11, R = CO₂Et) were used as the alkyne coupling partners, the linear trans-olefins 13 were obtained exclusively (Scheme 5b). DFT and experimental studies also showed that PivOH played a crucial role in C−H activation and protonolysis. Furthermore, the C−
H activation step would probably be partially involved in the rate-limiting step.

The effect of different Cp*^M catalysts was also checked, and it was observed that when TIPS-substituted alkynes (11, R = TIPS) were employed as coupling partners, the yield of the branched product 12 considerably decreased under Rh(III) catalysis, although the site selectivity was still high. The Ir(III) catalyst exclusively provided the linear product in a moderate yield. When using propargyl alcohol, Rh(III) gave the branched product in a low yield, while Ir(III) was unable to catalyze the coupling.

In 2018, Sundararaju developed an efficient method for the alkenylation of N-phenylpyrazoles 14 using both internal and terminal alkynes 8 and 11, respectively, as coupling partners (Scheme 6). To prove that the reaction proceeds via intermediate VII, this intermediate was independently synthesized and used as a catalyst for this transformation, obtaining the corresponding product in a high yield. Besides, different mechanistic studies (experimental and DFT studies) showed that the C−H activation event is reversible.

That same year, Maji and co-workers reported the intramolecular variant for the Cp*Co(III)-catalyzed alkenylation of different phenyl propargyl ethers 17, as well as several phenyl propiolates 19, leading to the formation of the corresponding benzofurans 18 (Scheme 7a) and benzofuranones 20, respectively (Scheme 7b). This transformation proceeds through a 5-exo-dig cyclization process and N-tert-butylamide acts as the directing group. The mechanistic studies performed suggested that the C−H metalation is reversible.

As has been demonstrated throughout this section, the proto-demetalation pathway has been proven to be an efficient tool for the alkenylation of several aromatic rings; however, some variations of this methodology have been equally effective for the functionalization of arenes. For example, in 2018, Zhang and Yi were able to synthesize 4-substituted quinolines 22 starting from the corresponding anilines 21 and different terminal alkynes 11. This reaction was carried out in dimethyl sulfoxide (DMSO), which not only played the role of the solvent but also the role of the building block that provides the C1 carbon atom (Scheme 8). According to the mechanism proposed by the authors, the active catalytic species would coordinate to the aniline, allowing C−H activation ortho to the −NH2 group, followed by insertion of the alkyne to form VIII. Afterward, K2S2O8 is thought to activate DMSO, providing species IX, which reacts with the aniline to give X. This intermediate undergoes oxidation to imine XI. Insertion of the C(sp2)−Co species would release XII, forming the quinoline product 22. Later, they observed that when the reaction was accomplished under acidic conditions (using trifluoroacetic acid (TFA) instead
K₂S₂O₈ as an additive, which is also capable of generating species IX from DMSO, the coordination of the cobalt center was affected and the site selectivity of the migratory insertion step could be switched, furnishing the corresponding 3-substituted quinolines 23 (Scheme 9). In this case, contrary to their previous report, kinetic isotopic experiments showed that the C—H activation step could be involved in the rate-limiting event.

Scheme 9. Synthesis of 3-Substituted Quinolines 23 Using DMSO as the C1 Building Block

Also in 2018, Prabhu and co-workers could efficiently accomplish the alkenylation of N-methylbenzamides 24 using alkynyl carboxylic acids 25 as the reaction partners (Scheme 10a). This transformation is proposed to proceed through a decarboxylative coupling that would involve the intermediacy of XIII, which is thought to release the corresponding product after decarboxylation and proto-demetalation. This reaction could also be extended to the use of N-pyrimidyl indoles 10 as the substrates, affording 2-alkenylated products 13 (Scheme 10b).

2.2. Reductive Elimination Pathway. This pathway has been extensively applied to the annulative alkenylation of a variety of aromatic rings under Cp*Co(III) catalysis, using different alkyne derivatives. As an example, in 2017, Sun and Ding accomplished the efficient synthesis of isoquinolines 29 starting from benzimidates 27, whose imine group would act as the directing group (Scheme 11). In this case, the Co(I) species formed after reductive elimination could be reoxidized by running the reaction under air, the oxygen present there being able to recover the catalytically active Cp*Co(III) species.

In 2018, Dutta and Sen used benzoimidazoles as the directing groups to achieve the reaction between different aromatic rings 30 and alkynes such as 8, leading to the annulated products 31 via an oxidative cyclization. In this case, AgOAc is the oxidant of choice to recover the catalytically active Cp*Co(III) complex from the Cp*Co(I) species formed in the course of the reaction. This transformation could be further extended to the use of simple imidazoles as the directing groups (Scheme 12).

Later, Liu et al. carried out the annulation of several aromatic aldehydes 32 with internal alkynes 28 (Scheme 13a). The reaction proceeded with high regioselectivity when unsymmetrical alkynes 37 were used (Scheme 13b). In this work, an in situ oxidation of the aldehyde takes place to form carboxylic acid, which acts as the directing group. In this way, after alkyne insertion and reductive elimination, different isocoumarins 33 or 35 are released, along with Co(I), which is reoxidized by Cu(II). The proposed pathway was supported by the fact that benzoic acid could also undergo this transformation when subjected to the optimal reaction conditions, providing the corresponding isocoumarin. However, a pathway involving the intermediacy of the corresponding peroxides cannot be ruled out.

Also in 2019, Zhao and co-workers reported the hydroarylation of propiolates 37 with N-phenoxyamides 36, followed by migration of the directing group, leading to the corresponding carboamination products 38 (Scheme 14). Some experiments were conducted to understand the
mechanism and it was found that, although the C−H activation event was reversible, it could have an influence on the rate-determining step. According to their mechanistic proposal, after C−H activation and alkyne insertion, intermediate XIV would be formed, which would evolve to XV via reductive elimination. Then, the Cp*Co(I) complex released would perform oxidative addition to the N−O bond, which would act as an internal oxidant, providing XVI. After proto-demetalation of this last species, 38 would be obtained.

In 2020, Kumaran and Parthasarathy developed a protocol for the annulative coupling of 2-arylquinazolines 39 with symmetrical (a) and unsymmetrical (b) alkynes. The reaction proceeds efficiently with symmetrical alkynes 28 (Scheme 15a) and when unsymmetrical coupling partners 34 were employed, the insertion took place regioselectively (Scheme 15b). When a 3,4-dimethoxyphenyl ring was used as the substituent attached to the quinazoline scaffold (39b), the functionalization took place at the less hindered position, due to the steric hindrance between the substituent and the Cp* ligand of the cobalt (Scheme 15c). In this case, to recover the Co(III) catalyst from the Co(I) species released after reductive elimination, CuO/Cu(OAc)2 had to be added as external oxidants.

Interestingly, the reductive elimination methodology and the use of internal oxidants have also been applied to the intramolecular version of these Cp*Co(III)-catalyzed alkenylative couplings. In 2017, Pawar and co-workers were able to prepare indolizidines 43 diastereoselectively by reacting N-methoxybenzamides 41 with alkynedione 42 (Scheme 16). To achieve this transformation, the reaction is proposed to proceed through intermediate XVIII, which would be formed after reductive elimination of XVII. The Co(I) species released would be reoxidized to Co(III) with the aid of the N−OCH3 group that would act as an internal oxidant: Cp*Co(I) is oxidatively added to the N−O bond, forming a Cp*Co(III) species that undergoes proto-demetalation, releasing the active catalytic species alongside the product. Once the catalytically active Cp*Co(III) is recovered, it would coordinate to one of the carbonyl groups of the newly introduced alkynedione, activating it thanks to its Lewis acidity and allowing the nucleophilic attack of the nitrogen onto that group. Several substitution patterns are tolerated in the arene; however, when substituents are placed ortho to the directing group, the reaction does not proceed, definitely due to the steric hindrance caused by the Cp* ligand of the catalyst.

In this case, the regioselectivity of the insertion onto the alkyne is attributed to weak coordination between the Co(III) metal center and a carbonyl group from the alkynedione in an intermediate XIV. Besides, after running some experiments to
elucidate the mechanism, it was found that the C−H activation event is irreversible and may be part of the rate-limiting step. The same year, Glorius and co-workers developed an intramolecular alkenylation reaction to synthesize isoquinolines 45 starting from different N-alkoxybenzamides 44 bearing alkynes tethered to the N-alkoxy moiety (Scheme 17). This annulative coupling is proposed to proceed via cobaltacyle XIX, which would be furnished after migratory insertion of the aryl-Co(III) species into the alkyne (Scheme 3, III) are more nucleophilic than other organometallic species, such as their organorhodium counterparts. In this way, those alkynyl−cobalt(III) species can undergo nucleophilic addition onto the directing group. One of the seminal examples of this methodology was reported by Matsunaga and Kanai in 2014. They reported the reaction between N-carbamoyl-protected indoles 46 and 48 and a variety of alkynes 37 to selectively obtain 2-alkenyalted indoles and pyrroloindoles 47 and 49, respectively. When using dimethyl carbamoyl-protected indoles 46, the reaction proceeded selectively to furnish the corresponding 2-alkenyldiones 47 (Scheme 18a). On the other hand, lowering the concentration, thus decelerating the intermolecular proto-demetalation event, and changing the dimethylamine of the N-carbamoyl group to morpholine (48), the nucleophilic addition of species XXI to the directing group could be promoted, generating intermediate XXII, which evolves to 49 upon release of morpholine (Scheme 18b). To unarguably confirm that the reaction was not proceeding via protonolysis, a hydroarylation product 47 was subjected to the reaction conditions, and the formation of the annulated product could be observed.

2.3. Nucleophilic-Addition Pathway. As has been previously explained, it is possible to take advantage of the fact that organocobalt compounds formed after migratory insertion of the aryl-Co(III) species into the alkyne (Scheme 3, III) are more nucleophilic than other organometallic species, such as their organorhodium counterparts. In this way, those alkynyl−cobalt(III) species can undergo nucleophilic addition onto the directing group. One of the seminal examples of this methodology was reported by Matsunaga and Kanai in 2014. They reported the reaction between N-carbamoyl-protected indoles 46 and 48 and a variety of alkynes 37 to selectively obtain 2-alkenyalted indoles and pyrroloindoles 47 and 49, respectively. When using dimethyl carbamoyl-protected indoles 46, the reaction proceeded selectively to furnish the corresponding 2-alkenyldiones 47 (Scheme 18a). On the
compound 49 was not observed. It is worth mentioning that, under Cp*Rh(III) catalysis, due to its lower nucleophilicity, only the proto-demetalation product 47 was obtained, with trace amounts of the annulated product. Experimental and DFT studies were run, and it was observed that the C-2 C−H activation event was reversible. Those experiments also suggested that the acetate unit played a fundamental role in promoting this step.

That same group published in 2017 a work developing the above-mentioned chemistry. They were able to carry out the C-2 alkenylation of indoles 48 with alkynes 37, followed by migration of the directing group, leading to the formation of tetrasubstituted alkenes 50 (Scheme 19).37

Scheme 19. Alkenylative Coupling between Indoles 48 and Alkynes 37, Followed by Migration of the Directing Group

8, the organocobalt species formed after metalation and migratory insertion undergoes annulation through nucleophilic attack onto the protecting group, followed by dehydration. In 2016, Glorius reported the synthesis of a variety of quinolines 54 following this methodology, using Lewis acids to achieve the transformation (Scheme 21a). Interestingly, on adding an oxidant instead of a Lewis acid, intermediate XXV underwent isomerization and reductive elimination to provide the corresponding indoles 55 (Scheme 21b).41 The migratory insertion into alkyne 8 was computationally studied and, in accordance with the experimental results, it was concluded that reductive elimination was preferred for the more electron-rich aryliurea substrates 53c and 53d, whereas nucleophilic attack was slightly favored for acetanilides 53a and 53b, leading to the formation of quinolones 54 (this preference could also be experimentally confirmed). With these results in hand, they proposed that the Lewis acid promoted nucleophilic attack onto the directing group, by lowering the activation energy for that process. In both cases, the C−H activation event could be involved in the rate-determining step.

Recently, the nucleophilic-addition pathway was employed by Ackermann’s group for the synthesis of a variety of indolizinones 58 from N-pyridyl-protected 2-pyridones 56 and bulky propargyl carbonates 57 (Scheme 22).42 After carrying out DFT and experimental studies to elucidate the reaction mechanism, it was found that intermediate XXVI would be formed after a reversible (and not rate determining) metalation of the aromatic ring, followed by migratory insertion into the triple bond of the corresponding propargyl carbonate 57. Then, nucleophilic addition of that species to the directing
groups would lead to its migration, forming XXVII. Finally, intramolecular nucleophilic attack would occur, causing annihilation upon the extrusion of the carbonate-leaving group. In this way, indolizinone 58 would be released (Scheme 22). This case again highlights the unique reactivity of Cp*Co(III) catalysts, as this reaction cannot be promoted under rhodium(III) or ruthenium(II) catalysis.

3. ALKENES AS COUPLING PARTNERS UNDER CP*Co(III) CATALYSIS

Although not so widely used as alkynes, olefins are also popular coupling partners under Cp*Co(III) catalysis, mainly to accomplish the alkylation of a variety of (hetero)arenes. The general catalytic cycle for this kind of reactions is very similar to the one depicted in Scheme 3: first, the active Cp*Co(III) species would undergo C−H activation of the aromatic ring, providing I, which is proposed to coordinate to the olefin and evolve through migratory insertion, forming XXIX. This species can now follow three different pathways, two of which would provide alkylated products, while the last one releases alkenylated arenes (Scheme 23). On the one hand, (pathway A) proto-demetalation can happen, furnishing the product and recovering the catalytically active species. On the other hand (pathway B), taking advantage of the coordination of the Co(III) to the directing group, reductive elimination can occur, giving an annulated product and a Co(I) species. Due to the formation of that cobalt species, an oxidant (external or internal) is required to recover the catalyst. Last but not least, alkenylation can also take place instead of the alkylation event. To achieve the alkenylation, the proto-demetalation and reductive elimination pathways should be precluded, allowing the β-hydride elimination to occur (pathway C), releasing the alkenylated product and a Cp*Co(I) species, after reductive elimination. Therefore, to recover the catalytically active Cp*Co(III) catalyst, this methodology also requires an oxidant.

3.1. Proto-Demetalation Pathway. Since Matsunaga and Kanai’s seminal work (Scheme 1),8 several reports have been published regarding the hydroarylation of activated electron-deficient olefins.43 For example, Ackermann and Li reported a protocol to carry out the alkylation of different indole derivatives 10 and either maleimides 59 or maleate esters 61 as coupling partners (Scheme 24).44 Additionally, deuterium-labeling experiments indicated that the C−H metalation step was not rate determining. Matsunaga showed that this transformation can also be carried out in an enantioselective manner using a chiral carboxylic acid derived from 1,1′-bi-2-naphthol (BINOL) (CCA I), obtaining, in general, modest to good enantiomeric ratios for 60 (Scheme 25).45 The enantioinduction would occur via selective proto-demetalation: after the C−H activation event, the reversible insertion of the alkene occurs, leading to the formation of two different enantiotopic intermediates, one of which would be selectively protonated by the chiral carboxylic acid, thus enantioselectively furnishing the alkylation product. Surprisingly, in this work, a dramatic increase of the yield was observed when changing the catalytic system from the more commonly used Cp*Co(CO)I2/AgSbF6 to [Cp*Co(CH2CN)4]2(SbF6)2/MS13X. In this case, the molecular sieves used as additives would remove the acetonitrile molecules bound to the cobalt, generating the cationic active catalytic species.

Using maleimides 59 as coupling partners for the alkylation of heterocycles, Ravikumar has recently been able to promote the C-7 selective alkylation of indolines 63 using a pivalate group tethered to the nitrogen atom as the directing group. In this way, the 1,4-addition of this heterocyclic scaffold over different maleimides 59 was efficiently accomplished (Scheme
26a) and the reaction could be successfully extended to the use of acrylates such as \( \text{65a} \) as the Michael acceptors (Scheme 26b). Mechanistic experiments suggested that the C–H activation step might be reversible.

Although several studies have been published regarding the hydroarylation of activated olefins with heterocycles, these reactions are not only limited to those scaffolds. As an example, in 2018, Wu et al. developed a methodology for the alkylation of differently substituted benzene derivatives \( \text{67} \) using oximes as directing groups and maleimides \( \text{59} \) as coupling partners (Scheme 27). Deuterium-labeling experiments gave some interesting insights about the reaction: the C–H activation step was reversible and not rate determining. Besides, TFE was responsible for the proto-demetalation step.

Furthermore, that same year, Whiteoak’s group could accomplish the hydroarylation of methyl vinyl ketone \( \text{69a} \) with benzamides 7 (Scheme 28a). Besides, they found that when acrolein \( \text{71} \) was utilized instead of \( \text{69a} \), the directing group underwent nucleophilic attack on the aldehyde after the hydroarylation event, leading to a Lewis-acid-catalyzed
Dehydrative cyclization that gave access to a variety of azepinones \(72\) (Scheme 28b). DFT-based methods were also used to explain why \(\alpha,\beta\)-unsaturated ketones provide alkylation products \(70\) through proto-demetalation, instead of alkenylated products through a \(\beta\)-elimination pathway. These DFT studies suggest metallo-keto/enol isomerization as being a key step in the mechanism. Interestingly, this isomerization is significantly destabilized when employing an \(\alpha,\beta\)-unsaturated ester, driving the reaction toward olefinic products.

The 1,4-addition reactions using \(\alpha,\beta\)-unsaturated carbonyl compounds that have been described in this section are proposed to take place via an oxa-\(\pi\)-allyl cobalt species, which would be in equilibrium with the corresponding cobalt enolate. Taking advantage of the formation of this species, Ellman and co-workers developed an efficient and highly stereoselective three-component C−H addition cascade of N-phenylpyrazoles \(14\) with \(\alpha,\beta\)-unsaturated ketones \(69\) and aldehydes \(73\). To achieve this transformation, they used a high-valent-cobalt complex \([\text{Cp}^*\text{Co(C_6H_6)}][\text{B(C_6F_5)}_2]\), bearing a noncoordinating counteranion, as a catalyst. After performing some mechanistic experiments and DFT studies, they proposed that this transformation starts with the 1,4-addition of the N-phenylpyrazole \(14\) to the enone \(69\) to give the racemic cobalt enolate XXXIII, whose nucleophilic addition to the aldehyde \(73\) via the corresponding chair transition state XXXIV would afford the target alcohols \(74\) diastereoselectively after protonolysis (Scheme 29a).49 However, a mechanism that would involve reaction of the Z-enolate with the aldehyde \(73\) via boat transition state, with coordination of the directing-group nitrogen could not be discarded. The use of enantiomerically pure \(\text{N-tert-butanesulfinylimines} \ 75\), instead of aldehydes \(73\) in this cascade reaction, led to the asymmetric synthesis of different \(\text{N-protected amines} \ 76\) (Scheme 29b).

Moving to the use of unactivated alkenes as coupling partners, in 2017, Ackermann’s group reported an interesting method for the C-2 alkylation of different indoles \(77\) using unactivated monosubstituted olefins \(78\). The reaction could be switched from the branched \(79\) to the linear regioisomers \(80\) just by using the bulky 1-AdCO2H as an additive (Scheme 30a).50 After carrying out several experiments and DFT studies, they rationalized the change of the positional selectivity focusing on the C−H activation step. When no additive was added, it was proposed to proceed via a ligand-to-ligand hydrogen transfer (LLPT), affording the linear product \(80\) upon proto-demetalation. On the other hand, in the presence of AdCO2H, the mechanism of the C−H activation event would proceed through base-assisted intramolecular electrophilic substitution (BIES) to provide the branched scaffold \(79\) after a proto-demetalation step facilitated by the carboxylic acid. A year later, in 2018, that same group reported the enantioselective variant of the branched-selective alkylation, employing for that purpose a specially designed chiral carboxylic acid (Scheme 30b).51 In this work, the enantioinduction is proposed to take place via insertion/selective proto-demetalation, since according to DFT studies, this event would afford enantiomer \(R\) preferentially. H/D scrambling experiments showed that the C−H activation was reversible.

As has been observed throughout this review, Cp*Co(III)-catalyzed intramolecular reactions for the formation of C−C bonds are not very usual. To the best of our knowledge, only two examples have been reported involving the use of alkynes (Scheme 27a and 1733), while no examples regarding the use of...
olefins as coupling partners had been reported until recently. In fact, our group has reported the first Cp*Co(III)-catalyzed intramolecular hydroarylation reaction of a variety of allyl phenyl ethers for the efficient synthesis of benzofurans, using an amide-directing group (Scheme 31a). This reaction could also be extended to homoallyl phenyl ethers to access different chromanes (Scheme 31b). The use of the indole scaffold as the arene coupling partner was also tolerated, obtaining dihydropyrrolo[1,2-a]indoles (Scheme 31c). The presence of a substituent in the internal position of the olefin proved to be crucial for the reaction to proceed, while the use of internal alkenes hampered the transformation. The active catalytic species is proposed to bind directly to the nitrogen atom of the directing group since when an N,N-dimethylamide was used as the director instead of N-methylamide, the reaction did not proceed.

3.2. Reductive Elimination Pathway. As has been previously stated, the final step of the catalytic cycle for the coupling between an aryl ring and an olefin may consist of a reductive elimination between the newly introduced moiety and the directing group. For example, in 2018, Volla and co-workers reported the redox-neutral [4 + 2] alkylative annulation reaction of N-methoxybenzamides with 7-oxa benzonorbornadienes to form diastereoselective epoxybenzophenanthridinones. In this case, the Co(I) species formed after reductive elimination is reoxidized to the catalytically active Cp*Co(III) species by the methoxyl group attached to the nitrogen, which acts as an internal oxidant (Scheme 32). After some kinetic isotope effect (KIE) and deuterium exchange experiments, the authors concluded that the C–H activation step was irreversible and not rate determining.

With the use of internal oxidants, very recently, Prabhu and co-workers described an efficient protocol for the [4 + 2] annulation of N-chlorobenzamides and maleimides to give pyrroloisoquinolones (Scheme 33). This is interesting.

Scheme 30. Linear and Branched Alkylation of Indoles (a) and Their Enantioselective Version (b)

Scheme 31. Intramolecular Hydroarylation Involving Terminal Disubstituted Olefins for the Synthesis of Benzofurans (a), Chromanes (b), and Pyrroloindoles (c)

Scheme 32. [4 + 2] Annulation of N-Methoxybenzamides with 7-Oxa Benzonorbornadienes Using an Internal Oxidant

Scheme 33. [4 + 2] Annulation of N-Chlorobenzamides with Maleimides Using an Internal Oxidant
since as has been previously shown in this section when maleimides 59 are utilized as coupling partners under Cp*Co(III) catalysis, the 1,4-addition products are usually obtained.54 In this case, the N−Cl group acts as an internal oxidant. N-Methoxy or N-hydroxybenzamides were not able to promote the mentioned transformation, which shows the higher oxidative activity of N−Cl bonds to promote this coupling. Besides, the C−H activation event was reversible and rate determining.

This annulative strategy has also been applied to the enantioselective synthesis of isoquinolones 91 by reacting N-chlorobenzamide 89a with different olefins 77 using a Cp*Co(III) catalyst bearing a chiral cyclopentadienyl ligand (Scheme 34).55 In this case, the enantioinduction would occur in the C−H activation/migratory insertion step. The optimal catalyst used in this work showed better enantio- and regioselectivities than its rhodium counterparts, being able to promote efficiently the reaction with troublesome olefins. For example, 1-hexene and 1-octene performed well under Cp*Co(III), while these olefins usually give low positional selectivity and enantioinduction with chiral Rh(III) catalysts.

### Scheme 34. Enantioselective [4 + 2] Annulation of N-Chlorobenzamides 89 with Olefins 77 Using an Internal Oxidant and a Chiral CpxCo(III) Precatalyst

![Scheme 34](image)

3.3. β-Hydride Elimination Pathway. Some oxidative Heck couplings have been efficiently achieved under Cp*Co(III) catalysis via a β-hydride elimination pathway. In 2015, Matsunaga and co-workers described a procedure for the alkenylation of N-methylbenzamides 24 with ethyl acrylate 65b, using Cp*Co(CO)I2 as the catalyst, AgSbF6 as the Lewis-acidic silver salt, and AgOAc as the external oxidant to obtain acrylates 95 (Scheme 37).60 In 2019, Maji expanded the scope of the Cp*Co-catalyzed alkenylation reaction to the use of aromatic ketones 96 as directing groups in the reaction of arenes with a variety of acrylates 65 (Scheme 38a).61 After demonstrating that the C−H activation is reversible and not rate determining, the authors were able to detect species XXXV and XXXVI by LC-MS, unraveling the key factor of the mechanism. Besides, it must be mentioned that when the
aromatic ketone bearing a 3,4-methylenedioxy group 96h was subjected to the reaction conditions, the alkenylation took place at the most sterically hindered position, leading to the formation of 2-alkenylarenes 97h (Scheme 38b).

In 2018, Matsunaga proved that it was possible to carry out several types of C−H functionalization reactions over Weinreb amides 98: allylation using allyl carbonates, amidation with dioxazolones, iodination utilizing N-iodosuccinimide, and oxidative alkenylation employing ethyl acrylate 65b: This last transformation is depicted in Scheme 39a.62 This oxidative coupling could take place under the reaction conditions developed for the alkenylation of N-methylbenzamides 24 with ethyl acrylate 65b (Scheme 37); however, the temperature had to be increased. Interestingly, in contrast with the usual results under Cp*Co(III)-catalysis, when 3-fluoro-N-methoxybenzamide 98e was utilized as the substrate, the C−H functionalization occurred at the most sterically hindered position C-2 (Scheme 39b). Nevertheless, a more sterically demanding methyl group led to the alkenylation at the usual C-6 position. Kinetic isotopic experiments showed that the C−H activation step is rate determining for this coupling.

In 2019, Ravikumar et al. carried out the selective C-4 alkenylation of indoles 100 with different acrylates 65 using an acetyl group attached to the C-3 position as a directing group. To achieve this transformation, apart from the usual catalytic system [Cp*Co(CO)]2 and AgSbF6, Cu(OAc)2·H2O had to be used as the external oxidant (Scheme 40a).63 They confirmed that the reaction proceeds through species XXXVII (which is proposed to be formed after a reversible C−H activation event), as they were able to detect it by high-resolution mass spectrometry (HRMS) when carrying out an experiment with stoichiometric amounts of the catalyst. Besides, the scope of the reaction could be extended to the use of maleimides 59 as the electron-deficient olefins; however, in this case, Ag2CO3 was used as the oxidant (Scheme 40b).

The alkenylation of arenes has also been successfully accomplished using gem-difluoroalkenes 103, as demonstrated by Li et al. in the reaction of N-pyrimidyl-protected indoles 10 (Scheme 41).64 In this case, after a non-rate-determining C−H activation step, followed by olefin insertion, intermediate XXXVIII would be formed, which is proposed to undergo β-fluoride elimination, furnishing the corresponding product 104 along with a Cp*Co(III)−F species. This is thought to undergo an evolution mediated by HSBF6 (released in the C−H activation step) to the catalytically active Co(III) species. Therefore, the reaction proceeds in a redox-neutral manner.
without the requirement of the addition of external oxidants. One year later, in 2017, Ackermann improved this methodology for the C-2 alkenylation of indoles 77 with gem-difluoroalkenes 105, reducing the catalyst loading to 2.5 mol% and using K₂CO₃ instead of Ca(OH)₂ at room temperature (Scheme 42a).⁶⁵ Interestingly, in 2018, Matsunaga extended this procedure to the use of 6-arylpurines 107 as substrates (Scheme 42b).⁶⁶

In 2018, Ellman’s group was able to expand the scope of their three-component Cp*Co(III)-catalyzed reaction (see Scheme 29)⁴⁹ to the use of dienes 110 instead of α,β-unsaturated carbonyl compounds, allowing the alkenylation of arenes 109 with olefins in a redox-neutral manner. The reaction proceeded in high yields and diastereoselectivities, using amide-directing groups, to provide the corresponding homoallylic alcohols 111 (Scheme 43).⁶⁷ According to some experiments conducted to elucidate the mechanism operating in the transformation, it is proposed to proceed through intermediate XXXIX that could be isolated, which would evolve to XI after formal hydrogen transfer from C-1 to C-4 through XL. Reaction with the aldehyde 79 would release 111 after protonolysis. Besides, kinetic isotopic experiments showed that the C−H metalation event is the rate-limiting step.

In 2019, this group extended the scope of their three-component reaction. This time, they managed to use internally substituted dienes 112, allowing the synthesis of a variety of homoallylic alcohols 113 possessing acyclic quaternary centers (Scheme 44).⁶⁸ Furthermore, regarding the carbonyl coupling partners, in some cases, activated ketones could be used instead of aldehydes 73. It was proven that, in this case, the C−H cobaltation step is not the rate-limiting one. Before this work came to light, Zhao and co-workers had reported a three-component coupling using unsubstituted dienes under Cp⁹Rh(III) catalysis. In this article, two examples were given using...
internally substituted dienes; however, they were limited to the use of highly activated carbonyl coupling partners, such as ethyl glyoxylate, and the yields were modest. Finally, Ellman’s group recently reported a highly diastereoselective three-component reaction between benzamides 109, 1,3-butadiene 114, and activated ketones 115 (Scheme 45).  

**Scheme 45. Three-Component Reaction Using 1,3-Butadiene 114 and Activated Ketones 115**

![Scheme 45](https://pubs.acs.org/10.1021/acsomega.0c03639)

4. CONCLUSIONS AND OUTLOOK

The development of Cp*Co(III) complexes has had a major impact on the development of synthetic methodologies. The reduced electronegativity or the smaller ionic radius of cobalt compared to rhodium has led to more nucleophilic organometallic complexes that have been proven to possess unique reactivity, obtaining improved chemo- or regioselectivities, as has been shown throughout the examples discussed herein. The development of precatalysts such as Cp*Co(CO)I₂, which is benchtop stable and can be easily stored and used, facilitates the application of these methodologies. The arenne C–H activation event with the Cp*Co(III) active species usually takes place through CMD- or BIES-type mechanisms with the assistance of a directing group, which also controls the regioselectivity. When alkenes and alkynes are used as coupling partners, the possibility of three distinct termination pathways after the migratory insertion expands the synthetic versatility of these reactions. As has been shown, acyclic or cyclic alkylated or alkylated compounds can be obtained by the adequate selection of the substrate, directing group, and reaction conditions. As discussed, some of these pathways (e.g., proto-demetalation, nucleophilic addition) are redox neutral, and no external oxidant is required. In others (e.g., reductive elimination, β-elimination), a Cp*Co(I) intermediate is formed that requires the use of an external oxidant to close the catalytic cycle. In this context, the use of the directing group as an internal oxidant is a very attractive approach. This reactivity can also be applied for cascade processes or three-component reactions, strategies that have allowed the synthesis of more complex scaffolds very efficiently. On the other hand, although many mechanistic studies based on DFT calculations and experimental data (KIE) have been carried out, a deeper mechanistic understanding of each step of those complex catalytic cycles would allow further development, increasing the application scope. The enantioselective variants of those transformations are still underdeveloped. Although very important progress has been made in the development of chiral cyclopentadienyl ligands, their synthesis is not trivial. Besides, it has recently been demonstrated that chiral carboxylic acids combined with achiral Cp-type ligands allow highly enantioselective C–H functionalization reactions, although the structural diversity of the acids is still limited.  

The use of chiral carboxylic acids for the proto-demetalation step in these types of reactions also needs to be further studied to expand their applicability.

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**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

Ministerio de Ciencia e Innovación (PID2019-104148GB-I00) and Gobierno Vasco (IT1045-16) are gratefully acknowledged for their financial support. A.C.-M. wishes to thank Gobierno Vasco for a grant. Technical support provided by Servicios Generales de Investigación SGiker (UPV/EHU, MINECO, GV/EJ, ERDF, and ESF) is also acknowledged.

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Omega Conjugate Addition of Maleimide to Indole at the C-2 Position.

S.; Chen, K.; Zhu, J. Cp

Arylquinazolinones with Alkynes.

Migration Sequence.

Benzosultam.

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