

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

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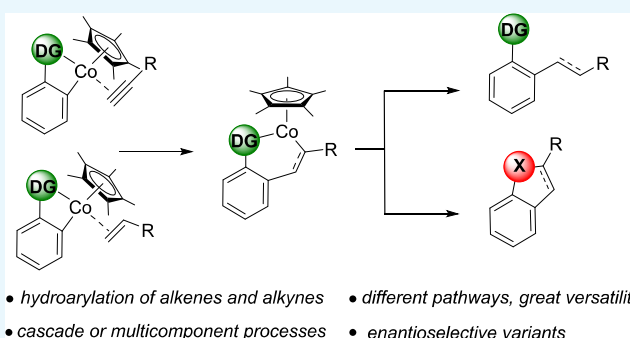
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**ABSTRACT:** The use of earth-abundant first-row transition metals, such as cobalt, in C–H activation reactions for the construction and functionalization of a wide variety of structures has become a central topic in synthetic chemistry over the last 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.

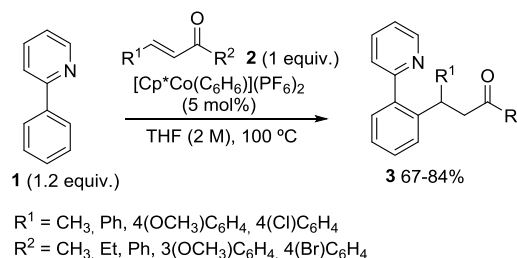


## 1. INTRODUCTION

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.<sup>1</sup> During the last two decades, palladium(II) has unarguably been in the limelight when accomplishing C–H bond-activation reactions,<sup>2</sup> although other transition metals, such as rhodium(III),<sup>3</sup> ruthenium(II),<sup>4</sup> and iridium(III),<sup>5</sup> 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.<sup>6</sup> Among them, cobalt catalysts bearing pentamethylcyclopentadienyl ligands (Cp\*) have recently started to gain center stage,<sup>7</sup> 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).<sup>8</sup> For this reaction, complex [Cp\*Co(C<sub>6</sub>H<sub>6</sub>)](PF<sub>6</sub>)<sub>2</sub> was utilized as a

### Scheme 1. Matsunaga and Kanai's Hydroarylation of Electron-Deficient Olefins **2**



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.<sup>9</sup> The complex [Cp\*CoCl<sub>2</sub>]<sub>2</sub> in

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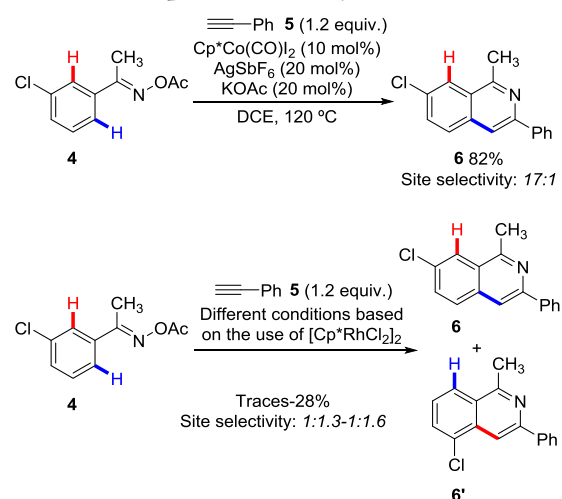


the presence of  $\text{AgPF}_6$  could also be used as a catalyst for this transformation.

Although that first  $\text{Cp}^*\text{Co(III)}$  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  $\text{Cp}^*\text{Co(CO)}_2$  complex<sup>10</sup> as a precursor for cationic (pentamethylcyclopentadienyl)cobalt(III) catalysis and its application to the C-2-selective C–H amidation of indoles<sup>11a</sup> and allylation of indoles, 6-arylpyridines, and aromatic amides.<sup>11b,c</sup> This  $\text{Cp}^*\text{Co(CO)}_2$  complex has become the most widely utilized catalyst to achieve  $\text{Cp}^*\text{Co(III)}$ -promoted C–H functionalization reactions. This same group also reported that complex  $[\text{Cp}^*\text{CoI}_2]_2$ ,<sup>11d</sup> which was obtained from the thermal decomposition of  $\text{Cp}^*\text{Co(CO)}_2$ , could also be an effective catalyst. However, it must be mentioned that, when using  $\text{Cp}^*\text{Co(CO)}_2$  or  $[\text{Cp}^*\text{CoI}_2]_2$ , the addition of cationic and Lewis-acidic silver salts is usually necessary, as they act as halide scavengers, activating the  $\text{Cp}^*\text{Co(III)}$  precatalysts. The counteranion of the cationic active  $\text{Cp}^*\text{Co(III)}$  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, acetonitrile complex  $[\text{Cp}^*\text{Co}(\text{CH}_3\text{CN})_3](\text{SbF}_6)_2$  was reported by Glorius to be able to catalyze these types of transformations.<sup>12</sup> 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:  $[\text{Cp}^*\text{Co}(\text{C}_6\text{H}_6)][\text{B}(\text{C}_6\text{F}_5)_4]_2$ ,<sup>13</sup> prepared from  $[\text{Cp}^*\text{Co}(\text{C}_6\text{H}_6)](\text{PF}_6)_2$ . In addition, they applied a variation of the method for the preparation of the precatalyst introduced by Matsunaga and Kanai in 2013, employing  $\text{Cp}^*\text{Co(CO)}_2$  as the starting material.

In  $\text{Cp}^*\text{Co(III)}$  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 metalation–deprotonation (CMD)<sup>14</sup> or a base-assisted intramolecular electrophilic substitution (BIES)<sup>15</sup> mechanism. The  $\text{Co(III)}$  complexes mentioned herein were initially designed to act as homologues of their  $\text{Cp}^*\text{Rh(III)}$  (and  $\text{Cp}^*\text{Ir}$ ) counterparts; however, cobalt has been proven to possess unique reactivity,<sup>16</sup> as will be shown in the following sections. For example, the ionic radius of  $\text{Co(III)}$  catalysts is much smaller than the radius of  $\text{Rh(III)}$  catalysts. This fact has a dramatic effect on reactivity and selectivity as under  $\text{Cp}^*\text{Co(III)}$  catalysis, the  $\text{Cp}^*$  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 **4** and alkynes (**Scheme 2**), demonstrated this in 2015. They observed that, due to the mentioned steric hindrance between the  $\text{Cp}^*$  “hat” and the substituents on the substrate, high regioselectivities were achieved toward functionalization

## Scheme 2. Difference in Positional Selectivity under $\text{Cp}^*\text{Co(III)}$ and $\text{Cp}^*\text{Rh(III)}$ Catalysis



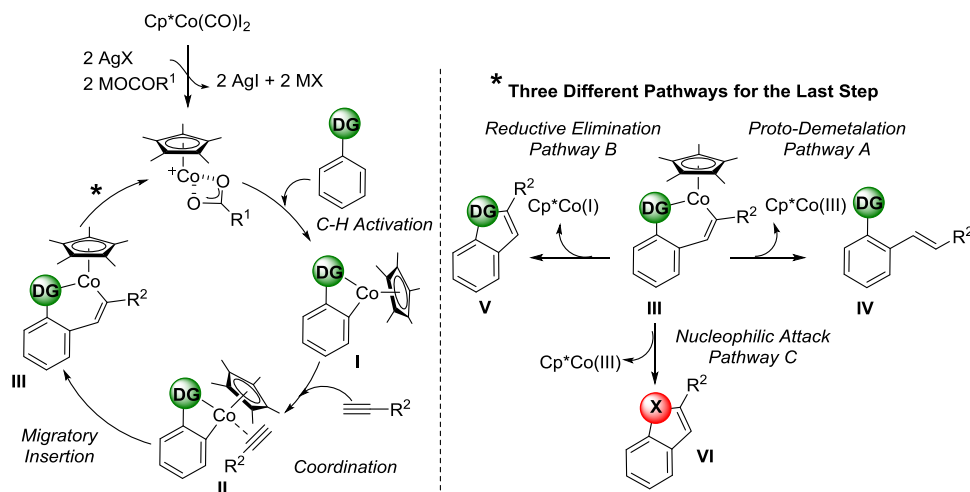
at the less sterically demanding position using  $[\text{Cp}^*\text{Co(CO)}_2]$  as a catalyst, whereas  $[\text{Cp}^*\text{RhCl}_2]_2$  led to no selectivity under various conditions.<sup>17</sup> **Scheme 2** shows the different selectivities obtained with each catalyst for the reaction of substrate **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,<sup>7</sup> herein, 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  $\text{Cp}^*\text{Co(III)}$ -catalyzed C–H hydroarylation of alkynes and alkenes.

## 2. ALKYNES AS COUPLING PARTNERS UNDER $\text{Cp}^*\text{Co(III)}$ CATALYSIS

Alkynes have been widely utilized as coupling partners in  $\text{Cp}^*\text{Co(III)}$  catalysis, since they usually allow the formation of alkenylated (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  $\text{Cp}^*\text{Co(III)}$ -based precatalyst with the additives added. Then, the  $\text{Cp}^*\text{Co(III)}$  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,  $\text{C}(\text{sp}^2)\text{--Co(III)--Cp}^*$  complex **III** is formed. Once this happens, **III** can undergo protodemetalation to form an acyclic alkenylated 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  $\text{Cp}^*\text{Co(I)}$  species formed to the catalytically active  $\text{Cp}^*\text{Co(III)}$  complex. Finally, advantage can be taken of the unique reactivity of  $\text{Cp}^*\text{Co(III)}$  catalysts: cobalt is less electronegative 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

## Scheme 3. General Catalytic Cycle for the Alkenylation of (Hetero)arenes Using Alkynes as Coupling Partners

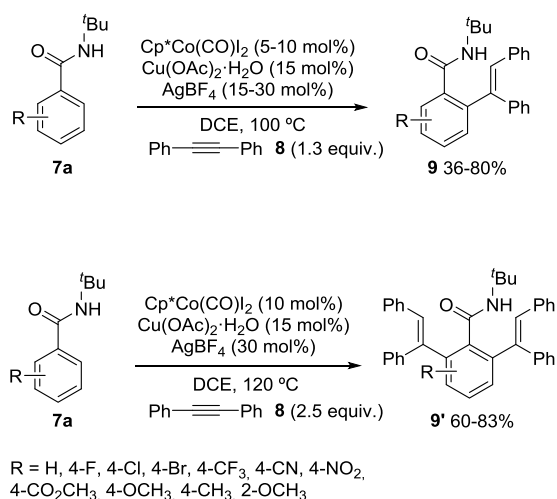


counterparts, making C–Co bonds more nucleophilic. This higher nucleophilicity facilitates the addition of the organocobalt species III to the directing group, releasing cyclized product VI (pathway C). It is worth mentioning that, although it is not very usual, when pathways B and/or C are operating, 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-Demetallation 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.<sup>18</sup> 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).<sup>19</sup> 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

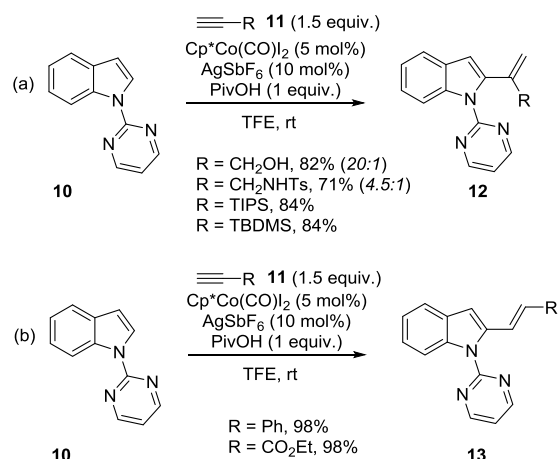
Scheme 4. Selective Mono- and Di-Alkenylation of *N-tert*-Butylbenzamides **7** with Internal Alkynes **8**



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,

Scheme 5. Selective Branched (a) and Linear (b) Alkenylation of Indoles **10** Using Terminal Alkynes **11**



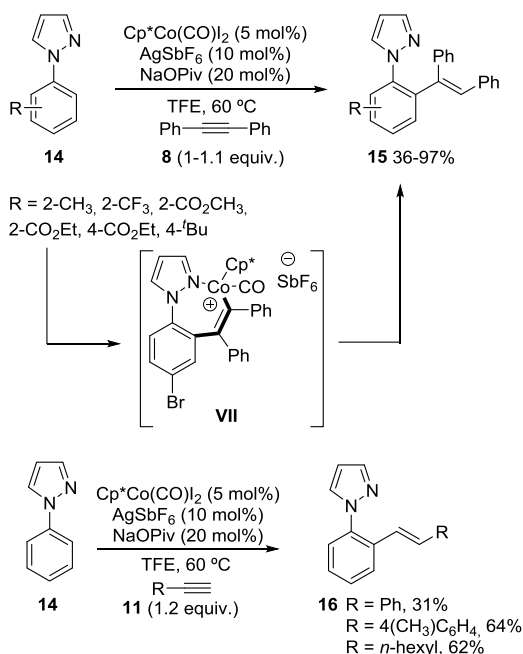
propargyl alcohols (**11**, R = CH<sub>2</sub>OH) and protected amines (**11**, R = CH<sub>2</sub>NHTs) were utilized as coupling partners, providing moderate to high positional selectivities due to the electronic factors. For those cases, the alkyne insertion process was the step in which the regioselectivity 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 = CO<sub>2</sub>Et) 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.<sup>20</sup>

The effect of different Cp<sup>\*</sup>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).<sup>21</sup> To prove that the reaction proceeds via

**Scheme 6. Coupling of *N*-Phenylpyrazoles **14** with Internal **8** and Terminal Alkynes **11****

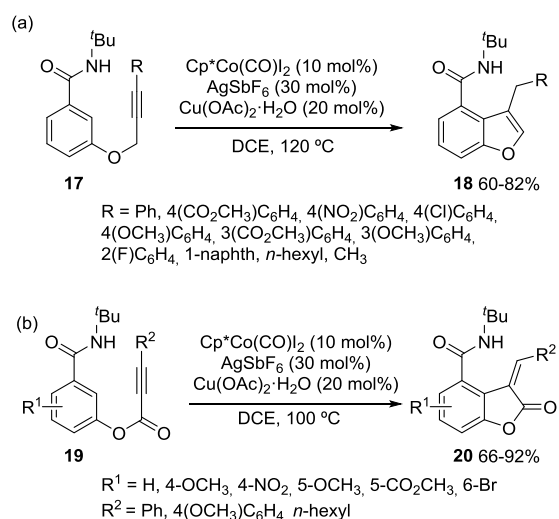


intermediate **VII**, this intermediate was independently synthesized and used as a catalyst for this transformation, obtaining the corresponding product in a high yield. Besides, different mechanistic studies (experimental and DFT studies) showed that the C–H activation event is reversible.

That same year, Maji and co-workers reported the intramolecular variant for the Cp<sup>\*</sup>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.<sup>22</sup> The mechanistic studies performed suggested that the C–H metalation is reversible.

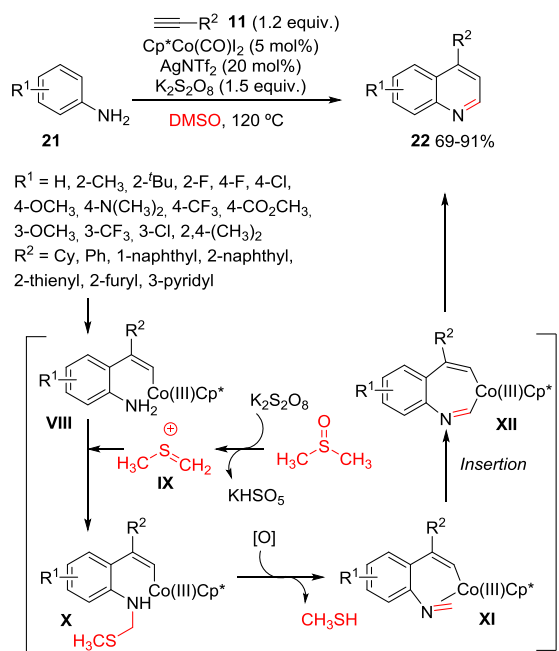
As has been demonstrated throughout this section, the proto-demetalation pathway has been proven to be an efficient tool for the alkenylation of several aromatic rings; however, some variations of this methodology have been equally effective for the functionalization of arenes. For example, in 2018, Zhang and Yi were able to synthesize 4-substituted

**Scheme 7. Intramolecular Hydroarylation of Alkynes Leading to Benzofurans **18** (a) and Benzofuranones **20** (b)**



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).<sup>23</sup>

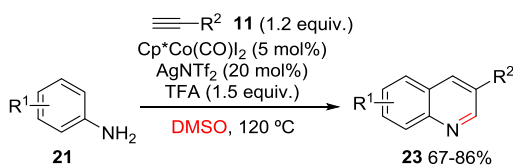
**Scheme 8. Synthesis of 4-Substituted Quinolines **22** Using DMSO as the C1 Building Block**



According to the mechanism proposed by the authors, the active catalytic species would coordinate to the aniline, allowing C–H activation ortho to the –NH<sub>2</sub> group, followed by insertion of the alkyne to form **VIII**. Afterward, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> 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(sp<sup>2</sup>)–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 of

$K_2S_2O_8$  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).<sup>24</sup> 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.

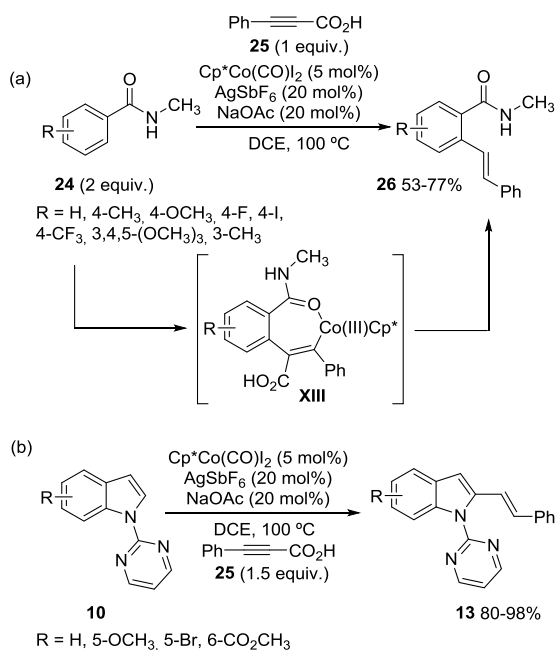
### Scheme 9. Synthesis of 3-Substituted Quinolines **23** Using DMSO as the C1 Building Block



$\text{R}^1 = \text{H}, 2\text{-CH}_3, 2\text{-Et}, 2\text{-F}, 4\text{-F}, 4\text{-Cl}, 4\text{-OCH}_3, 4\text{-N}(\text{CH}_3)_2, 4\text{-CF}_3, 4\text{-CH}_3, 3\text{-OCH}_3, 3\text{-CH}_3, 3\text{-Cl}, 2,4\text{-(CH}_3)_2$   
 $\text{R}^2 = \text{Ph}, 2\text{-naphthyl}, 2\text{-thienyl}, 2\text{-pyridyl}, \text{CO}_2\text{CH}_3$

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).<sup>25</sup> This transformation is proposed to proceed through a

### Scheme 10. Decarboxylative Alkenylation of *N*-Methylbenzamides **24** (a) and *N*-Pyrimidyl Indoles **10** (b)

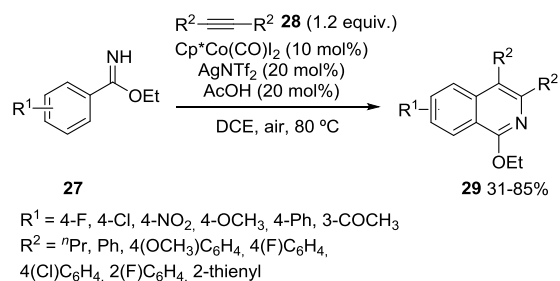


decarboxylative coupling that would involve the intermediacy of **XIII**, which is thought to release the corresponding product after decarboxylation and proto-demetalation. This reaction could also be extended to the use of *N*-pyrimidyl indoles **10** as the substrates, affording 2-alkenylated products **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  $\text{Cp}^*\text{Co}(\text{III})$  catalysis, using different alkyne derivatives.<sup>26</sup> 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).<sup>27</sup> In this case, the Co(I)

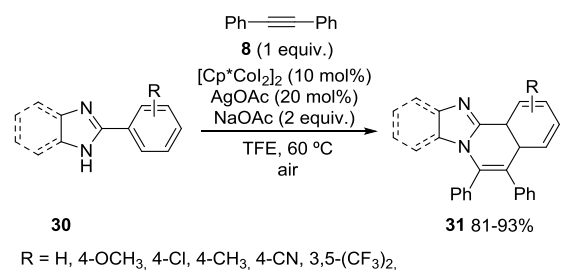
### Scheme 11. Synthesis of Isoquinolines **29** from Benzimidates **27**



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  $\text{Cp}^*\text{Co}(\text{III})$  species.

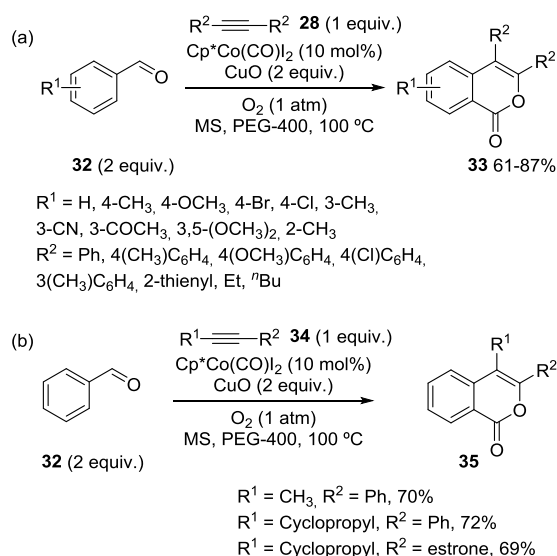
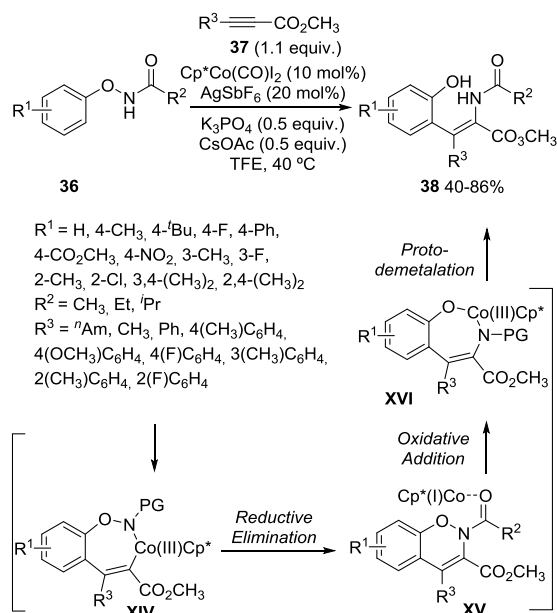
In 2018, Dutta and Sen used benzoimidazoles as the directing groups to achieve the reaction between different aromatic rings **30** and alkynes such as **8**, leading to the annulated products **31** via an oxidative cyclization. In this case, AgOAc is the oxidant of choice to recover the catalytically active  $\text{Cp}^*\text{Co}(\text{III})$  complex from the  $\text{Cp}^*\text{Co}(\text{I})$  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).<sup>28</sup>

### Scheme 12. Oxidative Annulations Using (Benzo)imidazole as the Directing Group



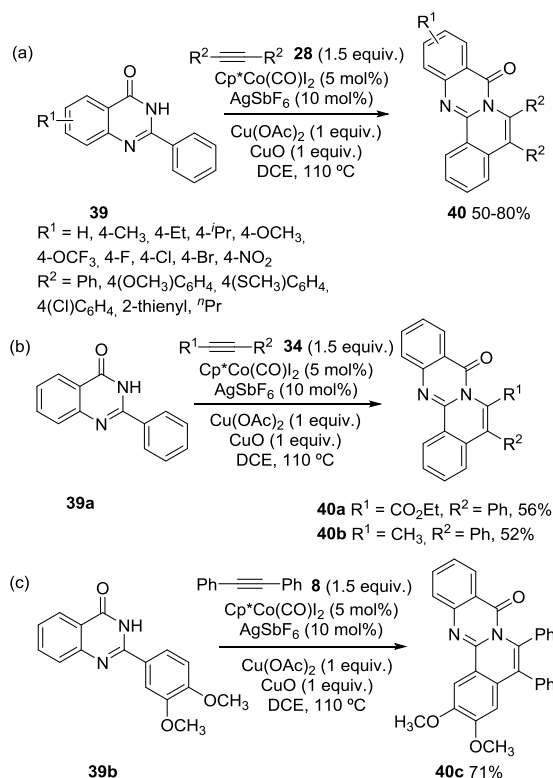
Later, Liu et al. carried out the annulation of several aromatic aldehydes **32** with internal alkynes **28** (Scheme 13a). The reaction proceeded with high regioselectivity when unsymmetrical alkynes **37** were used (Scheme 13b). In this work, an in situ oxidation of the aldehyde takes place to form 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).<sup>29</sup> 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).<sup>30</sup> Some experiments were conducted to understand the

**Scheme 13. Synthesis of Isocoumarins 33 (a) and 35 (b) from Benzaldehydes 32**

**Scheme 14. Carboaminative Coupling Between *N*-Phenoxyamides 36 and Propiolates 37**


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  $\text{Cp}^*\text{Co(I)}$  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 different 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

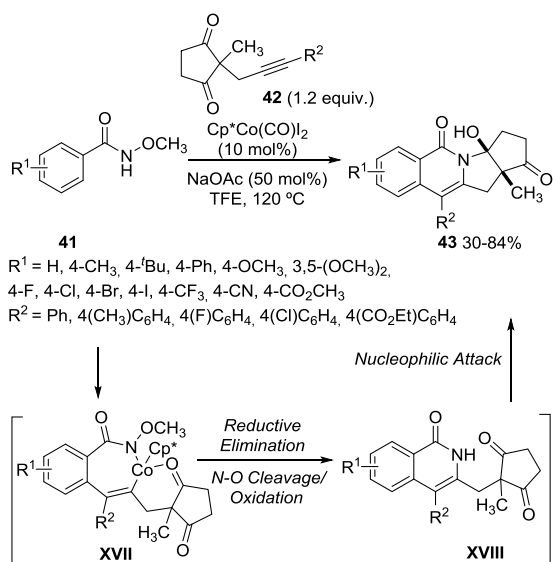
**Scheme 15. Annulative Coupling of 2-Arylquinazolines 39 with Symmetrical (a) and Unsymmetrical (b) Alkynes; Functionalization at the Less Hindered Position (c)**


to the quinazolinone scaffold (**39b**), the functionalization took place at the less hindered position, due to the steric hindrance between the substituent and the  $\text{Cp}^*$  ligand of the cobalt (Scheme 15c).<sup>31</sup> In this case, to recover the  $\text{Co(III)}$  catalyst from the  $\text{Co(I)}$  species released after reductive elimination,  $\text{CuO/Cu(OAc)}_2$  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  $\text{Cp}^*\text{Co(III)}$ -catalyzed alkenylative couplings. In 2017, Pawar and co-workers were able to prepare indolizidines **43** diastereoselectively by reacting *N*-methoxybenzamides **41** with alkyneone **42** (Scheme 16).<sup>32</sup> To achieve this transformation, the reaction is proposed to proceed through intermediate **XVIII**, which would be formed after reductive elimination of **XVII**. The  $\text{Co(I)}$  species released would be reoxidized to  $\text{Co(III)}$  with the aid of the N– $\text{OCH}_3$  group that would act as an internal oxidant:  $\text{Cp}^*\text{Co(I)}$  is oxidatively added to the N–O bond, forming a  $\text{Cp}^*\text{Co(III)}$  species that undergoes proto-demetalation, releasing the active catalytic species alongside the product. Once the catalytically active  $\text{Cp}^*\text{Co(III)}$  is recovered, it would coordinate to one of the carbonyl groups of the newly introduced alkyneone, 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  $\text{Cp}^*$  ligand of the catalyst.

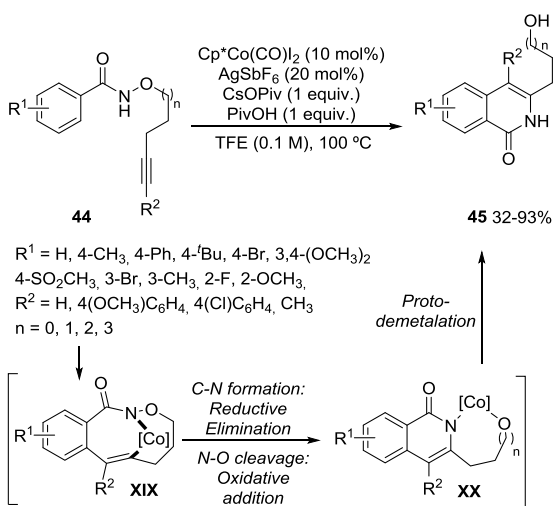
In this case, the regioselectivity of the insertion onto the alkyne is attributed to weak coordination between the  $\text{Co(III)}$  metal center and a carbonyl group from the alkyneone in an intermediate **XIV**. Besides, after running some experiments to

### Scheme 16. Synthesis of Indolizidines 43 from *N*-Methoxybenzamides 41



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 isoquinolones 45 starting from different *N*-alkoxybenzamides 44 bearing alkynes tethered to the *N*-alkoxy moiety (Scheme 17).<sup>33</sup> This annulative coupling is proposed to proceed via

### Scheme 17. Intramolecular Alkenylation Coupling for the Formation of the Isoquinolone Core 45



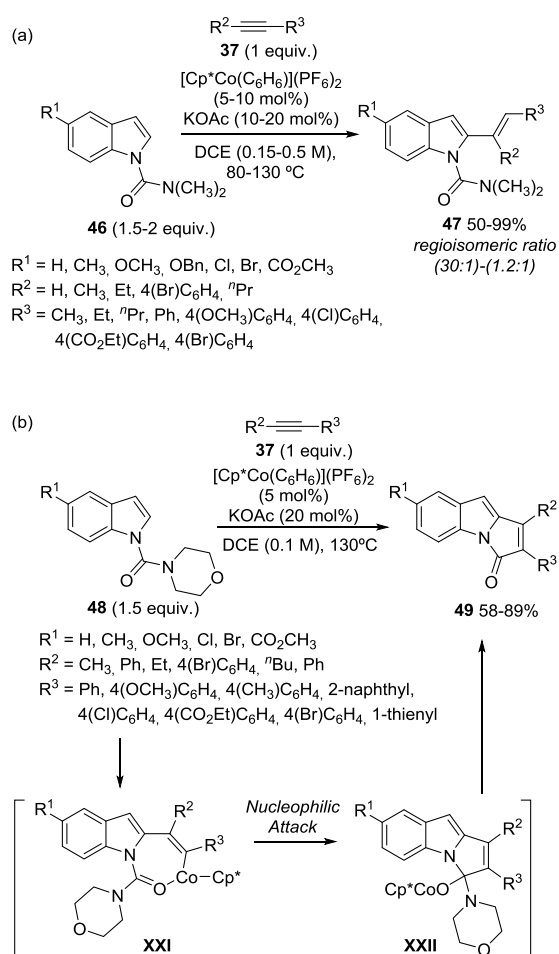
cobaltacycle XIX, which would be furnished after migratory insertion of the aryl-Co(III) species formed after metalation of the aromatic ring to the alkyne. This species XIX is proposed to undergo reductive elimination, followed by oxidative addition of the Co(I) species to the N–O bond (intermediate XX), releasing the product after protonolysis.

This transformation could be employed to perform the synthesis of aromathecin, protoberberine, and tylophora alkaloids. Interestingly, when this reaction was accomplished under Cp\*Rh(III) catalysis, only internal alkynes could be

used;<sup>34</sup> however, Cp\*Co(III) catalysis allowed the reaction to take place even with terminal alkynes.

**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 alkenyl–cobalt(III) species can undergo nucleophilic addition onto the directing group.<sup>35</sup> One of the seminal examples of this methodology was reported by Matsunaga and Kanai in 2014.<sup>36</sup> They reported the reaction between *N*-carbamoyl-protected indoles 46 and 48 and a variety of alkynes 37 to selectively obtain 2-alkenylated indoles and pyrroloindoles 47 and 49, respectively. When using dimethyl carbamoyl-protected indoles 46, the reaction proceeded selectively to furnish the corresponding 2-alkenylindoles 47 (Scheme 18a). On the

### Scheme 18. Alkenylative (a) and Annulative (b) Couplings between Indoles 46 and 48 and Alkynes 37

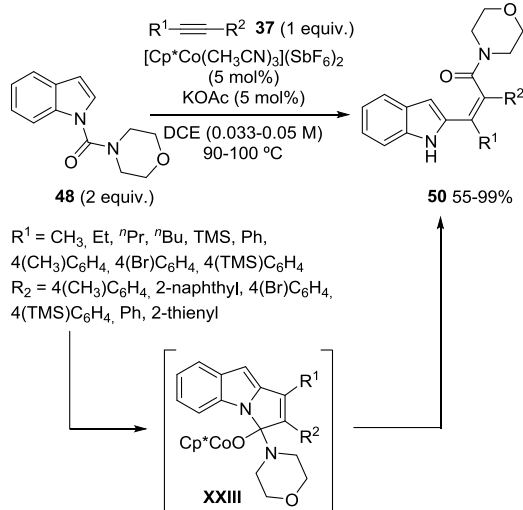


other hand, lowering the concentration, thus decelerating the intermolecular proto-demetalation event, and changing the dimethylamine of the *N*-carbamoyl group to morpholine (48), the nucleophilic addition of species XXI to the directing group could be promoted, generating intermediate XXII, which evolves 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

compound **49** was not observed. It is worth mentioning that, under Cp<sup>\*</sup>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).<sup>37</sup>

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

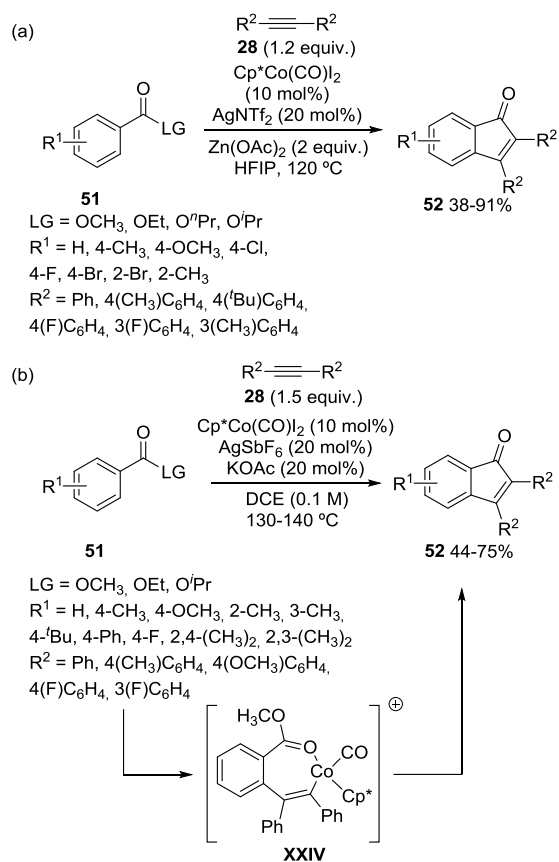


This last step was possible thanks to the higher nucleophilicity of Co(III), as the same reaction with rhodium just provided small amounts of the protonolysis product. Thus, the transformation is proposed to proceed through intermediate **XXIII**, which furnishes the product after the extrusion of the indole moiety. When they subjected the formed migration products **50** to [Cp<sup>\*</sup>Co(C<sub>6</sub>H<sub>6</sub>)](PF<sub>6</sub>)<sub>2</sub> and KOAc or just KOAc, the compound underwent cyclization, forming the corresponding pyrroloindoles **49**. This fact suggests that the tetrasubstituted alkenes **50** obtained upon migration of the directing group are kinetically favored, while the cyclization products **49** are thermodynamically preferred.

This pathway can also be applied when ester groups are used as directors. In 2016, the groups of Li<sup>38</sup> (Scheme 20a) and Zhang<sup>39</sup> (Scheme 20b) independently reported the annulative coupling between different benzoates **51** with alkynes **28**, leading to the formation of indenones **52**. Both groups concluded that the C–H activation step was part of the rate-limiting step. Besides, Zhang's group could detect species **XXIV** via mass spectrometry matrix-assisted laser desorption/ionization time-of-flight (MS-MALDI-TOF). They also demonstrated that the reaction proceeded directly from **XXIV**, without the intermediacy of the hydroarylation product.

The synthesis of quinolines **54** has been efficiently achieved under Cp<sup>\*</sup>Co(III) catalysis using anilines **53** bearing a carbonyl-based *N*-protecting group.<sup>40</sup> In this context, after the reaction of the protected anilines **53** with different alkynes

### Scheme 20. Synthesis of Indenones **52** from Benzoates **51** and Internal Alkynes **28** Reported by Li (a) and Zhang (b)

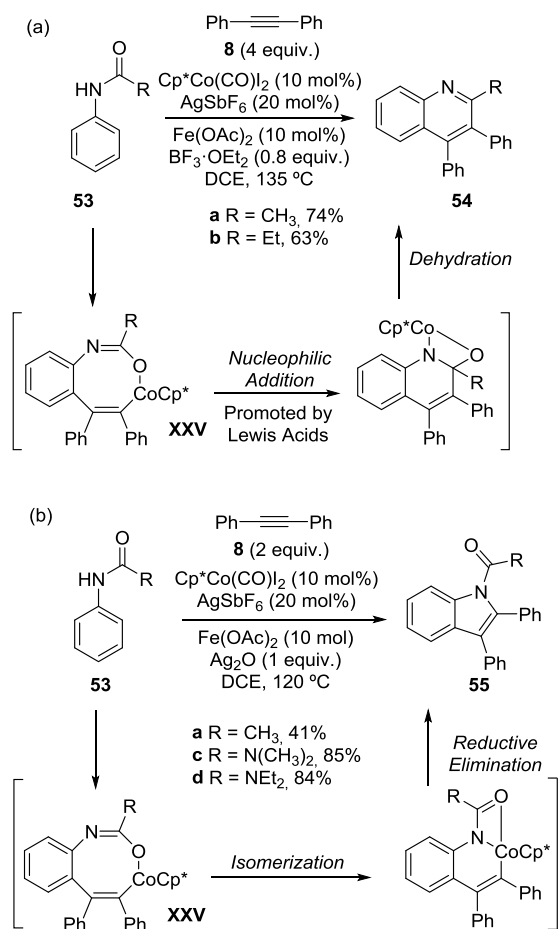


**8**, the organocobalt species formed after metalation and migratory insertion undergoes annulation through nucleophilic attack onto the protecting group, followed by dehydration. In 2016, Glorius reported the synthesis of a variety of quinolines **54** following this methodology, using Lewis acids 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).<sup>41</sup> The migratory insertion into alkyne **8** was computationally studied and, in accordance to the experimental results, it was concluded that reductive elimination was preferred for the more electron-rich arylurea 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.

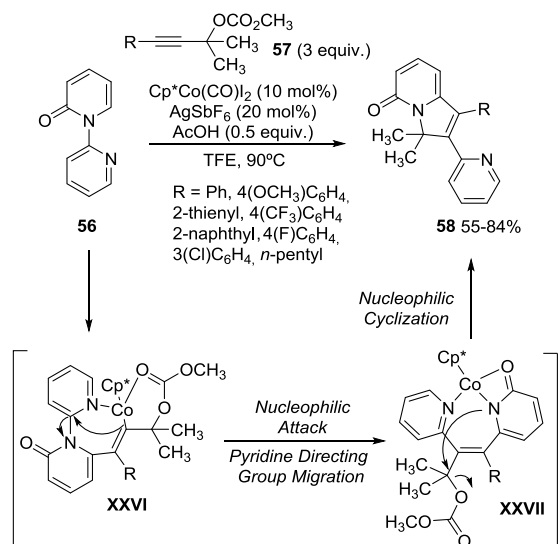
Recently, the nucleophilic-addition pathway was employed by Ackermann's group for the synthesis of a variety of indolizinones **58** from *N*-pyridyl-protected 2-pyridones **56** and bulky propargyl carbonates **57** (Scheme 22).<sup>42</sup> After carrying out DFT and experimental studies to elucidate 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



**Scheme 21. Selective Synthesis of Quinolines 54 (a) and Indoles 55 (b) from *N*-Protected Anilines 53**



**Scheme 22. Synthesis of the Indolizinone Core 58 Starting from Pyridones 56 and Propargyl Carbonates 57**



groups would lead to its migration, forming **XXVII**. Finally, intramolecular nucleophilic attack would occur, causing annulation 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

$\text{Cp}^*\text{Co(III)}$  catalysts, as this reaction cannot be promoted under rhodium(III) or ruthenium(II) catalysis.

### 3. ALKENES AS COUPLING PARTNERS UNDER $\text{Cp}^*\text{Co(III)}$ CATALYSIS

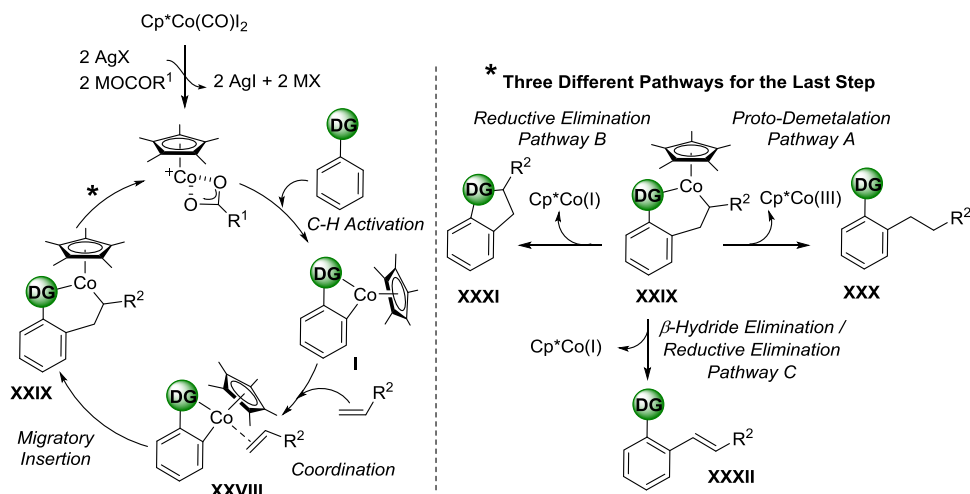
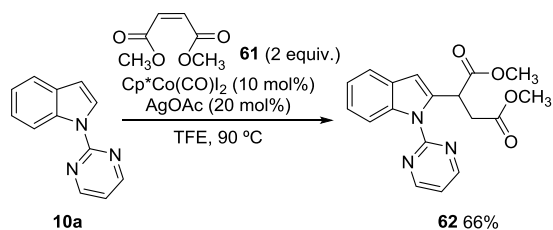
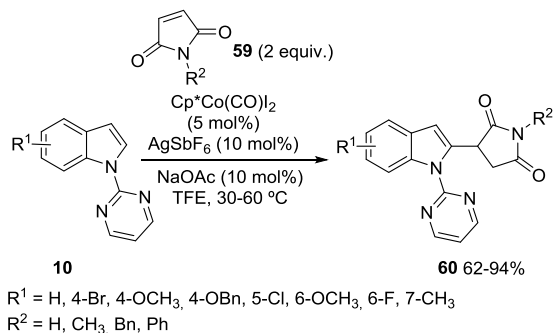
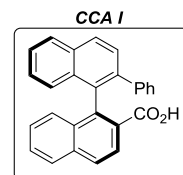
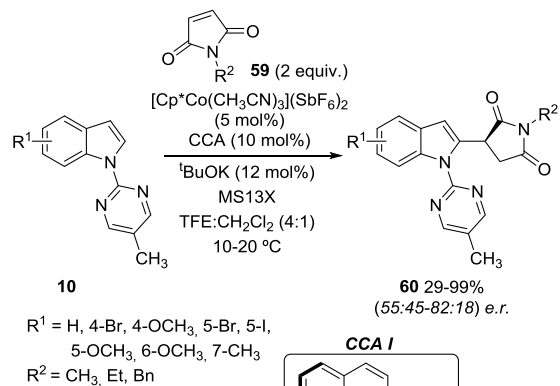
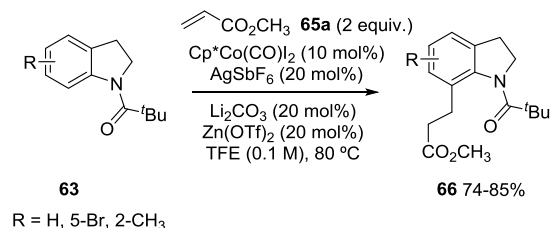
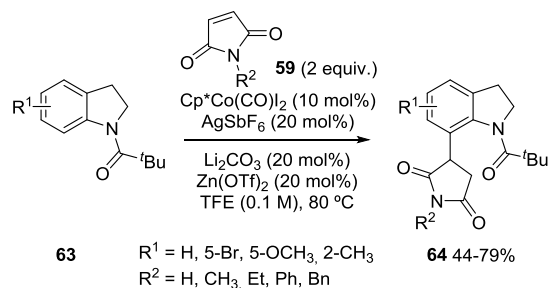
Although not so widely used as alkynes, olefins are also popular coupling partners under  $\text{Cp}^*\text{Co(III)}$  catalysis, mainly to accomplish the alkylation of a variety of (hetero)arenes. The general catalytic cycle for this kind of reactions is very similar to the one depicted in Scheme 3: first, the active  $\text{Cp}^*\text{Co(III)}$  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  $\beta$ -hydride elimination to occur (pathway C), releasing the alkenylated product and a  $\text{Cp}^*\text{Co(I)}$  species, after reductive elimination. Therefore, to recover the catalytically active  $\text{Cp}^*\text{Co(III)}$  catalyst, this methodology also requires an oxidant.

**3.1. Proto-Demetalation Pathway.** Since Matsunaga and Kanai's seminal work (Scheme 1),<sup>8</sup> several reports have been published regarding the hydroarylation of activated electron-deficient olefins.<sup>43</sup> 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).<sup>44</sup> 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).<sup>45</sup> 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  $\text{Cp}^*\text{Co(CO)}_2/\text{AgSbF}_6$  to  $[\text{Cp}^*\text{Co}(\text{CH}_3\text{CN})_3](\text{SbF}_6)_2/\text{MS13X}$ . 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

Scheme 23. General Catalytic Cycle for the Alkylation of (Hetero)arenes Using Olefin Coupling Partners

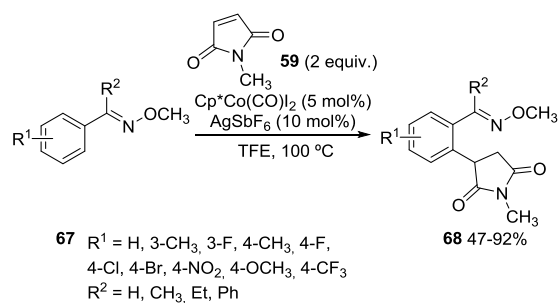
Scheme 24. Hydroarylation of Maleimides **59** and Maleate Esters **61** with Indoles **10**Scheme 25. Matsunaga's Enantioselective Alkylation of Indoles **10** Using a Chiral Carboxylic AcidScheme 26. Alkylation Reaction of Indolines **63** with Maleimides **59** and Acrylates **15**

26a) and the reaction could be successfully extended to the use of acrylates such as **65a** as the Michael acceptors (Scheme 26b).<sup>46</sup> Mechanistic experiments suggested that the C–H activation step might be reversible.

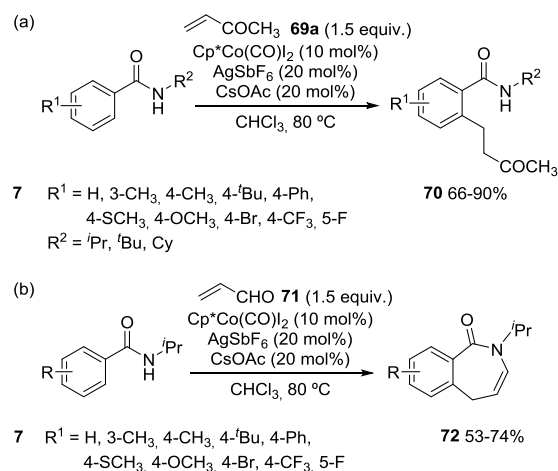
Although several studies have been published regarding the hydroarylation of activated olefins with heterocycles, these reactions are not only limited to those scaffolds. As an example, in 2018, Wu et al. developed a methodology for the alkylation of differently substituted benzene derivatives **67** using oximes as directing groups and maleimides **59** as coupling partners (Scheme 27).<sup>47</sup> 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 **69a** with benzamides **7** (Scheme 28a).<sup>48</sup> Besides, they found that when acrolein **71** was utilized instead of **69a**, the directing group underwent nucleophilic attack on the aldehyde after the hydroarylation event, leading to a Lewis-acid-catalyzed

### Scheme 27. Alkylation of Aromatic Oximes 65 with Maleimides 59



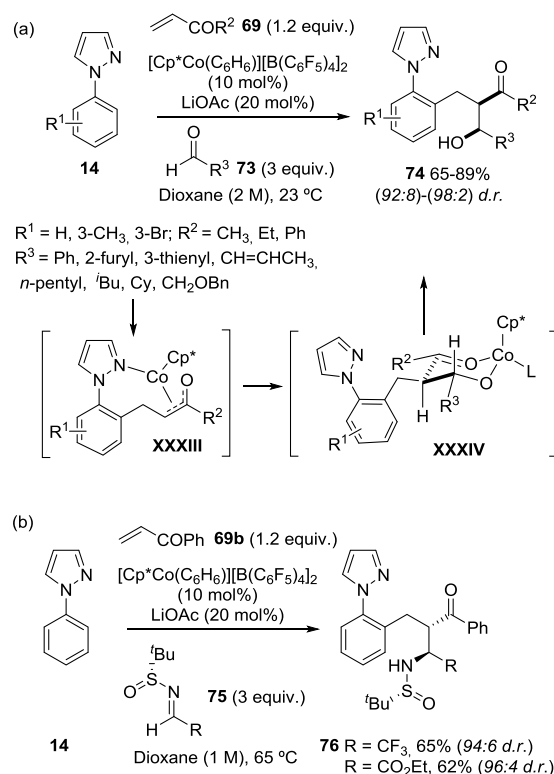
### Scheme 28. Alkylation of Benzamides 67 with Unsaturated Ketones (a) and Aldehydes (b)



dehydrative cyclization that gave access to a variety of azeponones **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  $[\text{Cp}^*\text{Co}(\text{C}_6\text{H}_6)][\text{B}(\text{C}_6\text{F}_5)_4]_2$ , bearing a noncoordinating counteranion, as a catalyst. After performing some mechanistic experiments, 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).<sup>49</sup> 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

### Scheme 29. Three-Component Cascade Reaction with Aldehydes 73 (a) and Sulfinylimines 75 (b)

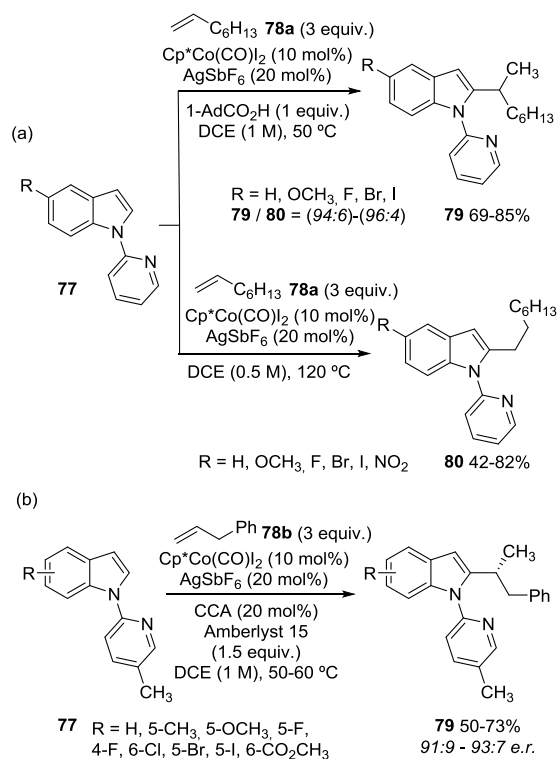


pure *N*-*tert*-butanesulfinylimines **75**, instead of aldehydes **73** in this cascade reaction, led to the asymmetric synthesis of different *N*-protected amines **76** (Scheme 29b).

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-AdCO<sub>2</sub>H as an additive (Scheme 30a).<sup>50</sup> 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 AdCO<sub>2</sub>H, 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 (CCA II) (Scheme 30b).<sup>51</sup> 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 7<sup>22</sup> and 17<sup>33</sup>), while no examples regarding the use of

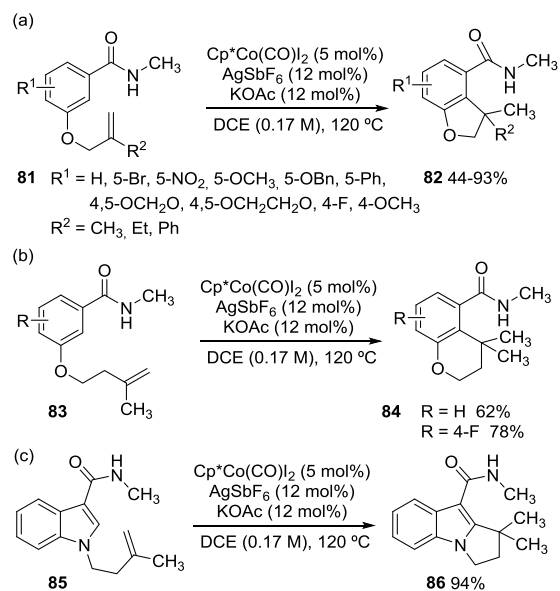
**Scheme 30. Linear and Branched Alkylation of Indoles 77 (a) and Their Enantioselective Version (b)**



olefins as coupling partners had been reported until recently. In fact, our group has reported the first  $\text{Cp}^*\text{Co(III)}$ -catalyzed intramolecular hydroarylation reaction of a variety of allyl phenyl ethers **81** for the efficient synthesis of benzofurans **82**, using an amide-directing group (Scheme 31a).<sup>52</sup> This reaction could also be extended to homoallyl phenyl ethers **83** to access different chromanes **84** (Scheme 31b). The use of the indole scaffold **85** as the arene coupling partner was also tolerated, obtaining dihydropyrrolo[1,2-*a*]indoles **86** (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.

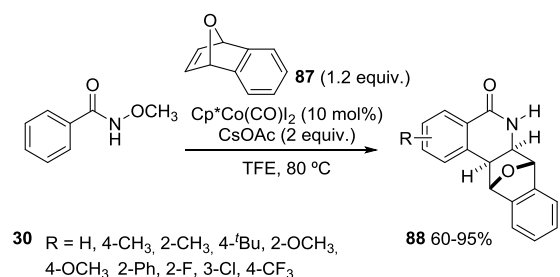
**3.2. Reductive Elimination Pathway.** As has been previously stated, the final step of the catalytic cycle for the coupling between an aryl ring and an olefin may consist of a reductive elimination between the newly introduced moiety and the directing group. For example, in 2018, Volla and co-workers reported the redox-neutral [4 + 2] alkylative annulation reaction of *N*-methoxybenzamides **30** with 7-oxa benzonorbornadienes **87** to form diastereoselective epoxybenzophenanthridinones **88**. In this case, the  $\text{Co(I)}$  species formed after reductive elimination is reoxidized to the catalytically active  $\text{Cp}^*\text{Co(III)}$  species by the methoxyl group attached to

**Scheme 31. Intramolecular Hydroarylation Involving Terminal Disubstituted Olefins for the Synthesis of Benzofurans 82 (a), Chromanes 84 (b), and Pyrroloindoles 86 (c)**



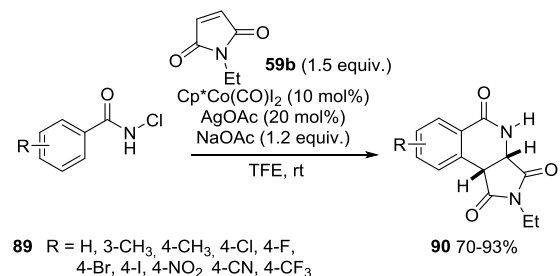
the nitrogen, which acts as an internal oxidant (Scheme 32).<sup>53</sup> After some kinetic isotope effect (KIE) and deuterium exchange experiments, the authors concluded that the C–H activation step was irreversible and not rate determining.

**Scheme 32. [4 + 2] Annulation of *N*-Methoxybenzamides 30 with 7-Oxa Benzonorbornadienes 87 Using an Internal Oxidant**



With the use of internal oxidants, very recently, Prabhu and co-workers described an efficient protocol for the [4 + 2] annulation of *N*-chlorobenzamides **89** and maleimides **59** to give pyrroloisoquinolones **90** (Scheme 33). This is interesting

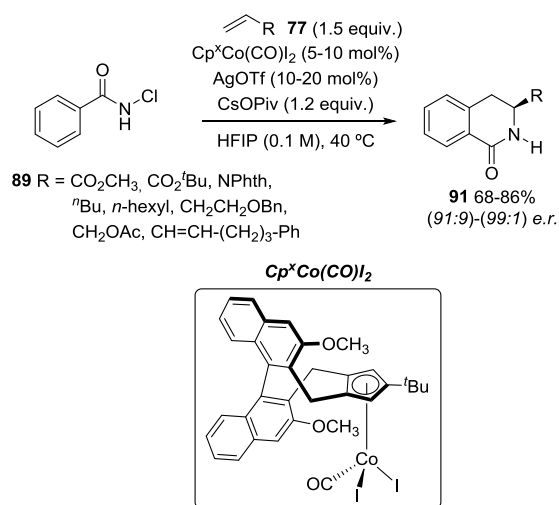
**Scheme 33. [4 + 2] Annulation of *N*-Chlorobenzamides 89 with Maleimides 59 Using an Internal Oxidant**



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.<sup>54</sup> 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).<sup>55</sup> In this case, the enantioinduction would occur

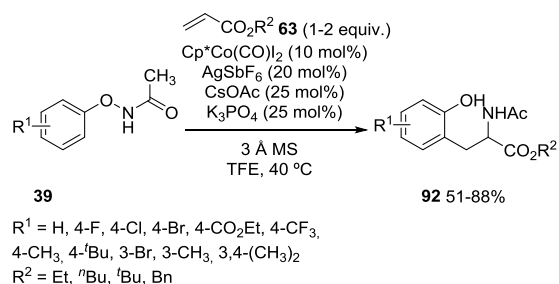
### Scheme 34. Enantioselective [4 + 2] Annulation of *N*-Chlorobenzamides **89** with Olefins **77** Using an Internal Oxidant and a Chiral Cp\*Co(III) Precatalyst



in the C–H activation/migratory insertion step. The optimal catalyst used in this work showed better enantio-<sup>56</sup> and regioselectivities<sup>57</sup> 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.

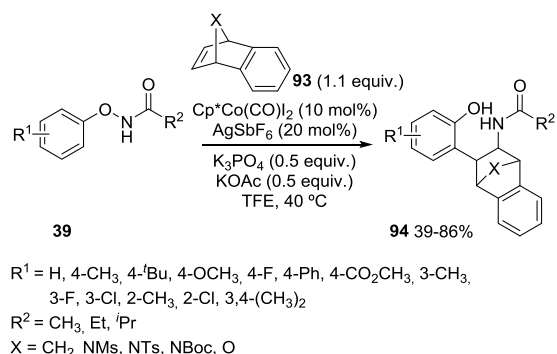
In 2016, Glorius' group developed a regioselective intermolecular carboamination of acrylates **63** with *N*-phenoxyacetamides **39a** for the synthesis of unnatural amino acid derivatives **92** (Scheme 35).<sup>58</sup> In this case, the reaction would proceed through a mechanism similar to the one

### Scheme 35. Alkylation of Phenols **39** Using Acrylates **63**, Followed by Migration of the Directing Group



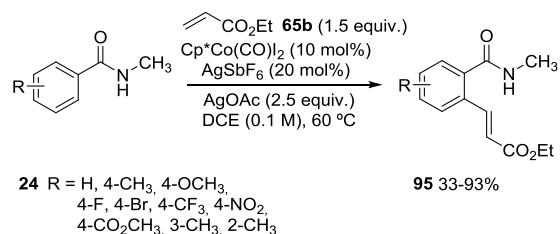
proposed for the reaction of between propiolates **37** and *N*-phenoxyamides **36**, discussed in previous sections (Scheme 14). It is worth mentioning the difference of reactivity between Cp\*Co(III) and Cp\*Rh(III). In fact, Rovis<sup>59</sup> has previously shown that these types of substrates prefer to undergo β-hydride elimination, forming the corresponding alkenylated phenols under Cp\*Rh(III) catalysis. However, in the case of Cp\*Co(III), a saturated metal center is not required and the carboamination process is favored over β-hydride elimination. This happens because, according to the hard and soft acids and bases (HSAB) concept, Cp\*Co(III) is harder than Cp\*Rh(III); therefore, the softer Rh(III) catalyst prefers to bind to the soft hydride, undergoing β-hydride elimination. Similarly, and inspired by this work, in 2019, Zhao and co-workers carried out the coupling between bicyclic alkenes **93** with *N*-phenoxyamides **39**, followed by the migration of the directing group, furnishing the corresponding carboamination products **94** (Scheme 36).<sup>30</sup>

### Scheme 36. Carboaminative Coupling between Bicyclic Alkenes **93** and *N*-Phenoxyamides **39**



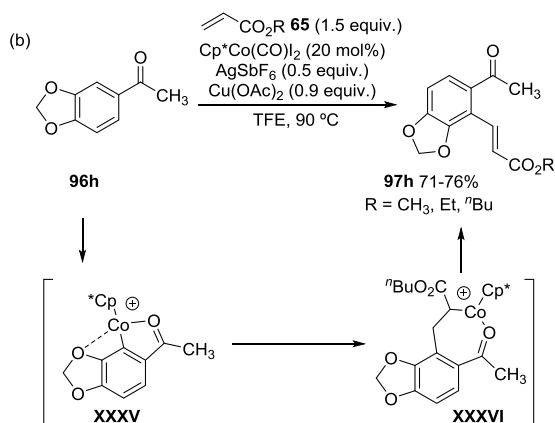
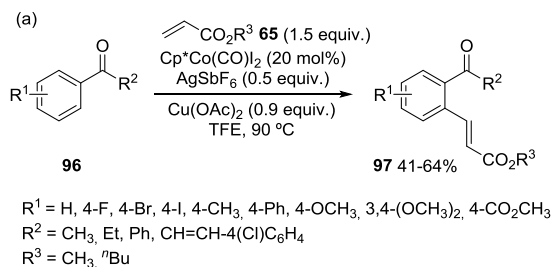
**3.3. β-Hydride Elimination Pathway.** Some oxidative Heck couplings have been efficiently achieved under Cp\*Co(III) catalysis via a β-hydride elimination pathway. In 2015, Matsunaga and co-workers described a procedure for the alkenylation of *N*-methylbenzamides **24** with ethyl acrylate **65b**, using Cp\*Co(CO)<sub>2</sub> as the catalyst, AgSbF<sub>6</sub> as the Lewis-acidic silver salt, and AgOAc as the external oxidant to obtain acrylates **95** (Scheme 37).<sup>60</sup> In 2019, Maji expanded the scope

### Scheme 37. Alkenylation of Benzamides **24** with Ethyl Acrylate **65b**



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).<sup>61</sup> 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

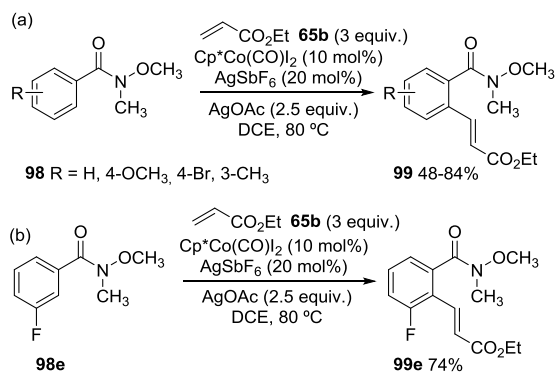
**Scheme 38. Alkenylation of Aromatic Ketones **96** with Acrylates **65** (a); Alkenylation at the Most Hindered Position (b)**



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.<sup>62</sup> 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 functionaliza-

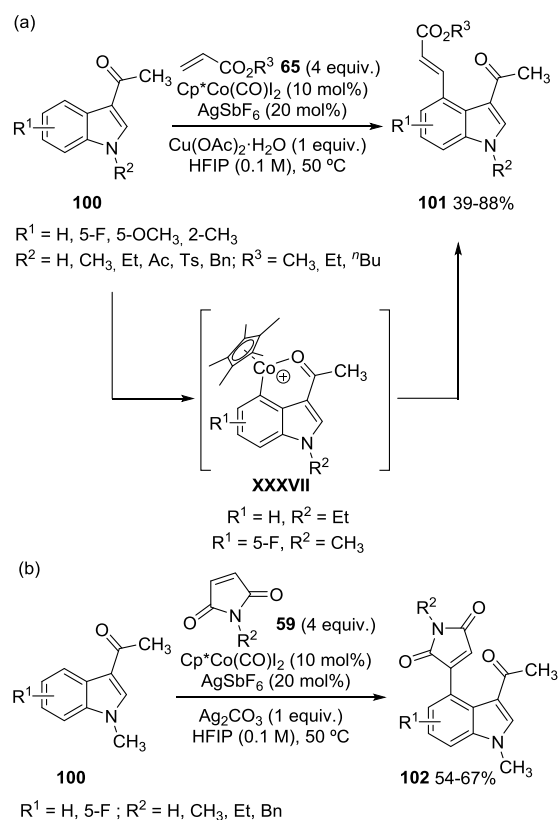
**Scheme 39. Alkenylation of Weinreb Amides **98** with Ethyl Acrylate **65b** (a); Alkenylation at the Most Hindered Position (b)**



tion 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)<sub>2</sub> and AgSbF<sub>6</sub>], Cu(OAc)·H<sub>2</sub>O had to be used as the external oxidant (Scheme 40a).<sup>63</sup> They

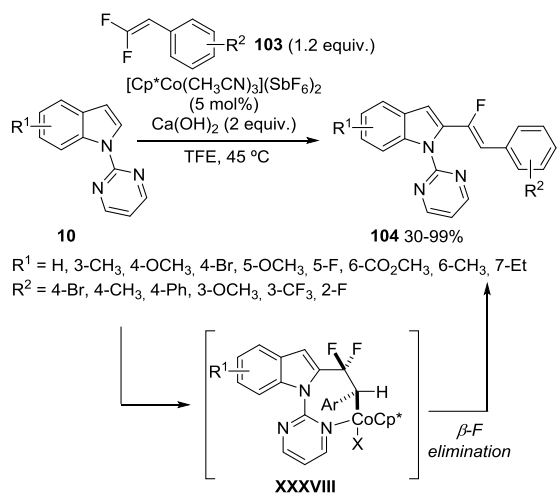
**Scheme 40. Ketone-Directed Alkenylation of Indoles **100** Using Acrylates **65** (a) and Maleimides **59** (b)**



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, Ag<sub>2</sub>CO<sub>3</sub> was used as the oxidant (Scheme 40b).

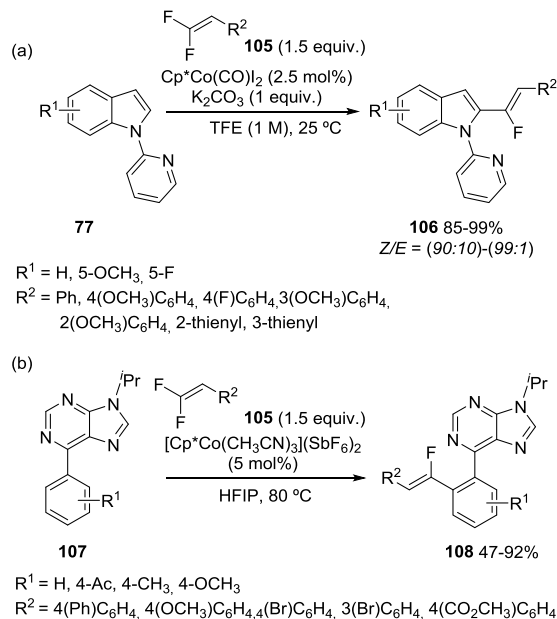
The alkenylation of arenes has also been successfully accomplished using *gem*-difluoroalkenes **103**, as demonstrated by Li et al. in the reaction of *N*-pyrimidyl-protected indoles **10** (Scheme 41).<sup>64</sup> In this case, after a non-rate-determining C–H activation step, followed by olefin insertion, 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 HSbF<sub>6</sub> (released in the C–H activation step) to the catalytically active Co(III) species. Therefore, the reaction proceeds in a redox-neutral manner,

### Scheme 41. Alkenylation of Indoles 10 Using *gem*-Difluoroalkenes 103 as Coupling Partners



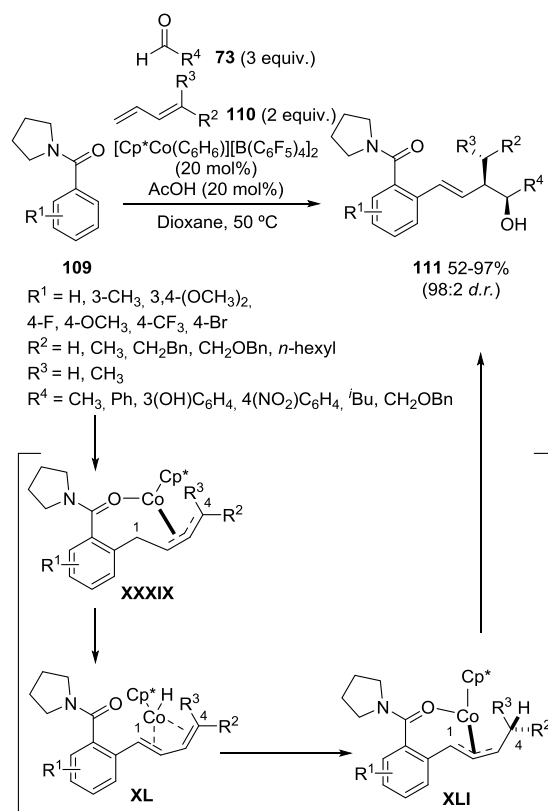
without the requirement of the addition of external oxidants. One year later, in 2017, Ackermann improved this methodology for the C-2 alkenylation of indoles 77 with *gem*-difluoroalkenes 105, reducing the catalyst loading to 2.5 mol% and using  $\text{K}_2\text{CO}_3$  instead of  $\text{Ca}(\text{OH})_2$  at room temperature (Scheme 42a).<sup>65</sup> Interestingly, in 2018, Matsunaga extended this procedure to the use of 6-arylpurines 107 as substrates (Scheme 42b).<sup>66</sup>

### Scheme 42. Alkenylation of Heteroarenes 77 (a) and 107 (b) Using *gem*-Difluoroalkenes 105 as Coupling Partners



In 2018, Ellman's group was able to expand the scope of their three-component  $\text{Cp}^*\text{Co}(\text{III})$ -catalyzed reaction (see Scheme 29)<sup>49</sup> to the use of dienes 110 instead of  $\alpha,\beta$ -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).<sup>67</sup> According to some experiments conducted to elucidate the mechanism operating

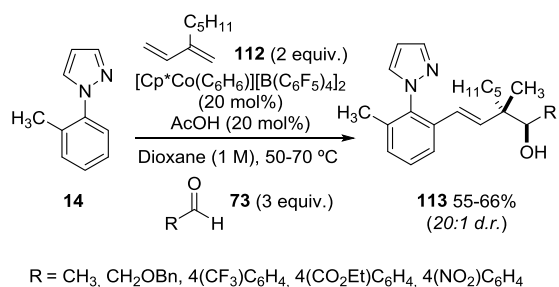
### Scheme 43. Three-Component Reaction Using Dienes 110 and Aldehydes 73



in the transformation, it is proposed to proceed through intermediate XXXIX that could be isolated, which would evolve to XLI 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.

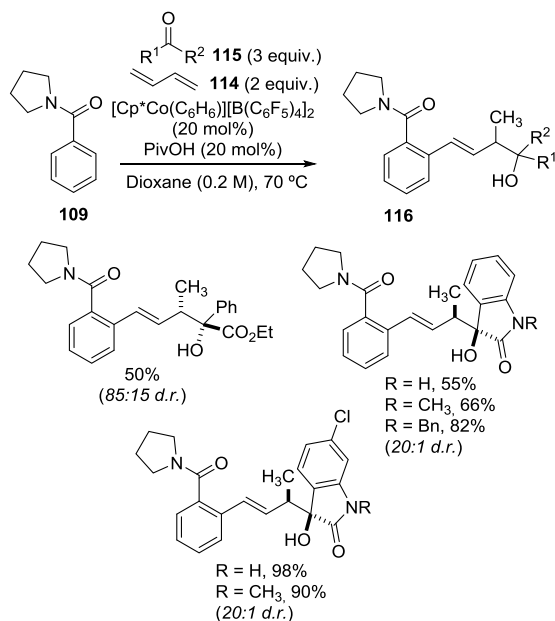
In 2019, this group extended the scope of their three-component reaction. This time, they managed to use internally substituted dienes 112, allowing the synthesis of a variety of homoallylic alcohols 113 possessing acyclic quaternary centers (Scheme 44).<sup>68</sup> Furthermore, regarding the carbonyl 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  $\text{Cp}^*\text{Rh}(\text{III})$  catalysis. In this article, two examples were given using

### Scheme 44. Three-Component Reaction Using Dienes 112 and Aldehydes 73



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.<sup>69</sup> 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).<sup>70</sup>

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



#### 4. CONCLUSIONS AND OUTLOOK

The development of  $\text{Cp}^*\text{Co}(\text{III})$  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  $\text{Cp}^*\text{Co}(\text{CO})_2$ , which is benchtop stable and can be easily stored and used, facilitates the application of these methodologies. The arene C–H activation event with the  $\text{Cp}^*\text{Co}(\text{III})$  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 alkenylated 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,  $\beta$ -elimination), a  $\text{Cp}^*\text{Co}(\text{I})$  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.<sup>71</sup> 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.

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