Weakly Coordinated Cobaltacycles: Trapping Catalytically Competent Intermediates in Cp*CoIII Catalysis

Sara Martínez de Salinas,[a] Jesús Sanjosé-Orduna,[a] Carlota Odena,[a] Sergio Barranco,[a] Jordi Benet-Buchholz,[a] Mónica H. Pérez-Temprano*[a]

Abstract: *Herein, we disclose the synthesis of metallacyclic Cp*CoIII complexes containing weakly-chelating functional groups. We have employed these compounds not only as an exceptional platform for accessing some of the most widely invoked transient intermediates in C–H functionalization processes but also as competent catalysts in different Cp*Co-catalyzed transformations, including a benchmark coupling reaction.*

Over the past several decades, C–H functionalization reactions directed by weakly-coordinated functional groups have emerged as powerful strategies for forming carbon–carbon and carbon–heteroatom bonds.[1] A key advantage of this approach is that the directing substrates contain common moieties found in synthetically relevant organic compounds (e.g., ketones, aldehydes, amides or esters). Therefore, extra synthetic steps for their installation/removal are often not necessary.[2] Usually, the weaker coordination of these directing groups to the metal center affords highly reactive metallacyclic intermediates towards subsequent functionalization. However, this entails a major obstacle, even when employing noble metals:[3] the low thermodynamic stability of the resulting transient species hinders their detection and/or isolation (Figure 1a). The inherent lack of stability has shown to be even more problematic with first-row metals systems, such as cobalt-based platforms.[4] While important synthetic advances have been made in the field of Cp*CoIII catalysis,[5] characterizing the putative cobalt intermediates in these transformations remains challenging.[5f] This profound lack of fundamental understanding at the molecular level precludes the rational design and development of novel and more efficient Cp*Co-catalyzed processes. As part of our ongoing interest in uncovering the mechanistic "black box" of Cp*CoIII-catalyzed C–H functionalization reactions,[6] we have recently reported the synthesis of well-defined cobaltacycles stabilized by strong σ-donor moieties such as pyridine or pyrimidine. In the present study (Figure 1b), we describe the synthesis of metallacyclic Cp*CoIII complexes (**A**) supported by weakly chelating ligands commonly used in Cp*Co-catalyzed C–H functionalizations, via an alternative oxidative addition route. We have leveraged these compounds to explore the access to direct analogues of long-sought-after cationic transient cobalt species (**A⁺**) that have been widely proposed as key reactive intermediates. Moreover, we demonstrate the intermediacy of the **A**-type compounds in selected Cp*CoIII-catalyzed C–H

functionalizations, as well as their potential participation in the functionalization of aryl halides, using a benchmark reaction.
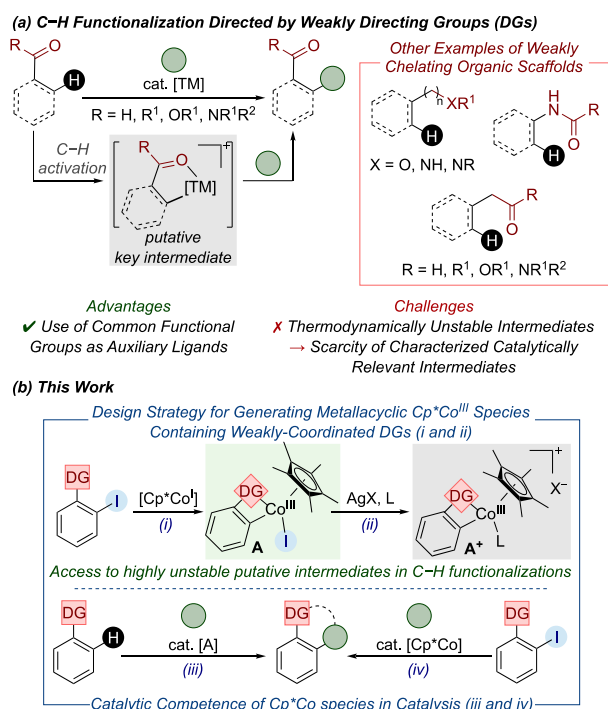

Figure 1. (a) State-of-the-art of C–H functionalization reactions assisted by weakly-coordinated directing groups; (b) the present work.

Initial studies were focused on designing a suitable platform for interrogating the accessibility to isolable Cp*CoIII complexes containing weakly-coordinated scaffolds. We explored an oxidative addition route to access complex **A**, which would circumvent the proposed reversibility of the Cp*CoIII-mediated C–H metalation.[4,5,6] We selected 2-iodobenzaldehyde (**1ald-I**) as the ideal substrate for this oxidative addition given its synthetic relevance, widespread availability, and the opportunity to utilize the aldehydic proton as a spectroscopic handle in 1H NMR analyses. Moreover, reported examples of Cp*CoI aldehyde complexes support the feasible coordination of this carbonyl group to a cobalt metal center.[7]

The treatment of **1ald-I** with [Cp*CoI(VTMS)₂] (**2-VTMS**) in THF at room temperature for 15 minutes afforded the oxidative addition product **3ald-I** as a greenish-black solid in 91% isolated yield (Figure 2).[8] The metallacyclic compound was fully characterized by 1D (1H, 13C) and 2D NMR spectroscopy, MS-ESI and single-crystal X-ray diffraction, showing the coordination of the aldehyde group in a σ-fashion.[9] 1H NMR spectroscopy revealed an upfield shift of the aldehydic proton in **3ald-I** (δ = 9.04 ppm) compared to **1ald-I** (δ = 10.03 ppm) due to its interaction with the cobalt center.

[a]   Sara Martínez de Salinas,[a] Jesús Sanjosé-Orduna,[a] Carlota Odena,[a] Sergio Barranco,[a] Jordi Benet-Buchholz,[a] Mónica H. Pérez-Temprano*[a]
        Institute of Chemical Research of Catalonia (ICIQ)
        Avgda. Països Catalans 16, 43007 Tarragona (Spain)
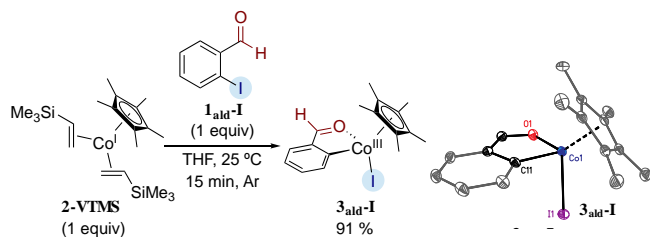   E-mail: mperez@iciq.es

Figure 2. Synthesis and Characterization of **3_ald-I** via Oxidative Addition. ORTEP Diagram of **3_ald-I** is shown at 50% of probability (H atoms have been omitted for clarity).

We next explored the influence of the (pseudo)halide in the formation of **3_ald-X** (X = I, Br, Cl, OMe) (Figure 3). As expected, the nature of X affects the oxidative addition event,[10] as **1_ald-Br** reacted more slowly than the iodide derivative (Figure 3).[11] **3_ald-Br** was fully characterized by NMR spectroscopy and X-ray diffraction. Under the same reaction conditions, **1_ald-Cl** and **1_ald-OMe** did not oxidatively add to the metal center, leading to decomposition of **2-VTMS** over time.
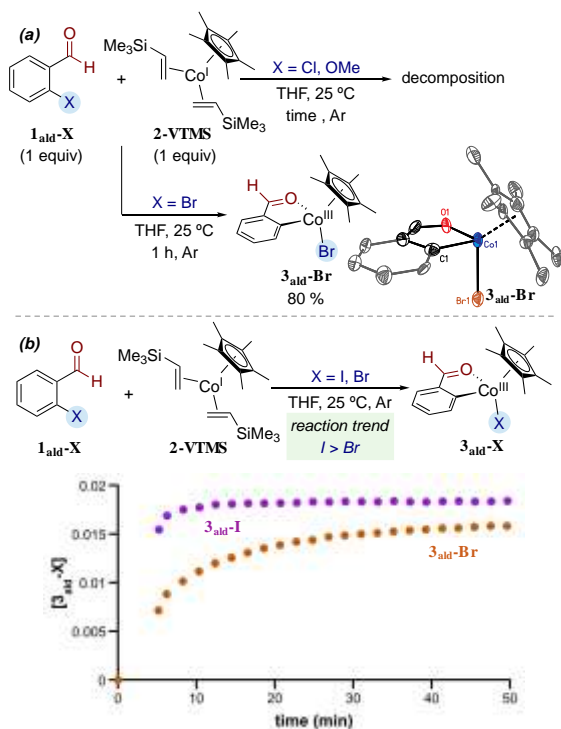

Figure 3. (a) Addition of **1_ald-X** to [Cp*Co^I(VTMS)_2]. ORTEP Diagram of **3_ald-Br** is shown at 50% of probability (H atoms have been omitted for clarity). (b) Reaction Profile for the formation of **3_ald-X** (X = I, Br) at 25 °C in THF-d_8.

Having confirmed the accessibility and stability of **3_ald-I/Br**, we next aimed to expand the scope of chelating groups involved in the formation of these Co^III compounds. The oxidative addition approach used to access **3_ald-I** proved to be general for a range of substrates, such as ketones, esters and amides, enabling the synthesis of various **3_DG-I**-type complexes shown in Table 1.[12] **3_DG-I** (DG = ketone, ester, acetanilide) were fully characterized

by NMR spectroscopy at 25 °C, whereas **3_CONH2-I** and **3_CONHtBu-I** were characterized at −35 °C due to their comparatively lower stability. The nature of the synthesized compounds was confirmed by X-ray diffraction (Figure 4). The solid-state structures of **3_DG-I** containing amide groups show its coordination to the cobalt metal center by the oxygen atom, which is the most basic site for neutral amides. The isolation and characterization of **3_acetanilide-I** is particularly interesting since access to a six-membered Cp*Co^III cobaltacycle had not previously been reported in the literature.

Table 1. Scope of **3_DG-I** Containing Different Weakly Chelating Functional Groups[a]
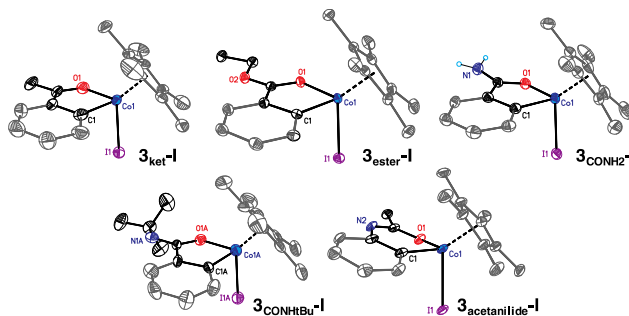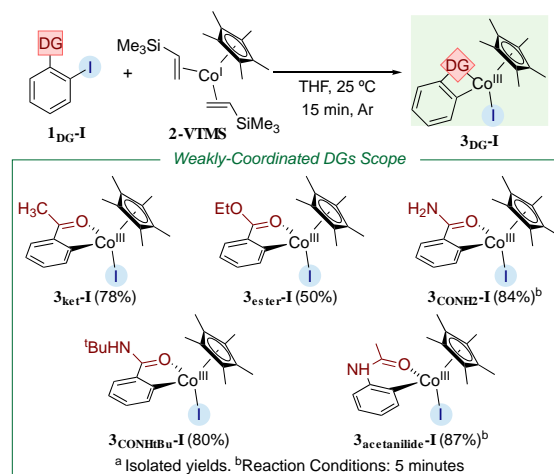

Figure 4. ORTEP Diagrams of **3_DG-I**. Thermal ellipsoids drawn at 50% of probability (H atoms have been omitted for clarity).

After demonstrating the accessibility and stability of various Co^III complexes supported by catalytically relevant scaffolds, we next pursued detecting the direct analogues of the reactive species formed after the C–H metalation step (Figure 5).[5b, 5d, 5g-h, 13] In this context, we have previously described the employment of coordinating ligands to access otherwise highly reactive cationic metallacyclic Cp*Co^III species. Following the same approach[14] and using **3_ald-I** as our initial platform, we were able to provide the first experimental evidence of a five-membered cationic cyclometalated Cp*Co^III complex bearing weakly coordinated functional groups. The reaction of **3_ald-I** with AgBF_4 in THF-d_8 afforded the *in situ* formation of **3_ald-THF** in full conversion by ^{1}H NMR spectroscopy. Although this complex was

too unstable for isolation,[15] its structure could be characterized by multinuclear NMR spectroscopy and X-ray diffraction. After some optimization, the remaining **3_DG-THF** analogues could be detected in the crude ^{1}H NMR spectra by treatment with AgNTf_2. **3_keto-THF** and **3_acetanilide-THF** were fully characterized by 1D and 2D NMR spectroscopy, whereas **3_CONH2-THF** and **3_CONHtBu-THF** were only characterized by ^{1}H NMR spectroscopic analyses due to their greater instabilities.
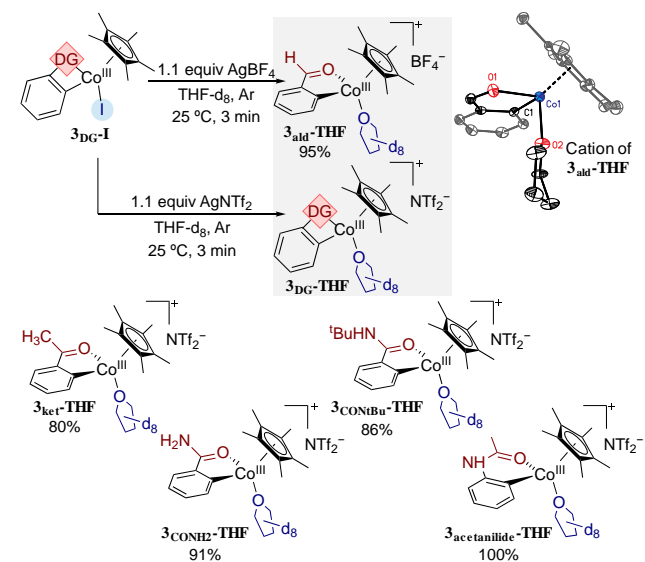

Figure 5. Conversion of **3_DG-I** to **3_DG-THF**. Reported yields were determined by the ^{1}H NMR spectroscopic analysis of the crude reaction mixture. ORTEP plot of **3_ald-THF**. Thermal ellipsoids drawn at 50% of probability, and the hydrogen/deuterium atoms and BF_4 anion are omitted for clarity.

Having established the synthesis, isolation and characterization of different **3_DG-I** complexes and the accessibility of their cationic analogues, we next sought to explore the reactivity of **3_DG-I** in Cp*Co^{III}-catalyzed C–H functionalization reactions (Figure 6). As mentioned above, these complexes are precursors of the putative intermediates involved in these transformations. However, their inaccessibility had previously hampered investigations of their catalytic competence. We therefore sought to utilize **3_ket-I**, **3_CONHtBu-I** and **3_acetanilide-I** as a platform for determining the intermediacy of these species in representative catalytic reactions. Importantly, these directing groups have been utilized in Cp*Co-catalyzed C–H functionalizations.[5h,13a-b] As shown in Figure 6, these cyclometalated complexes proved to be suitable catalysts for representative C–C coupling reactions, supporting the feasibility of the corresponding cationic intermediates in these transformations.[16]
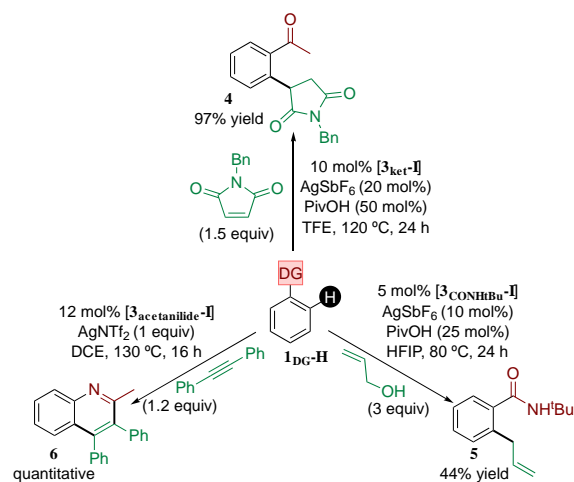

Figure 6. Catalytic competence of **3_DG-I**. Reported yields were determined via ^{1}H NMR spectroscopic analysis of the crude reaction mixture *versus* an internal standard using the substrate as the limiting reagent.

Finally, inspired by the facile formation of **3_DG-I** complexes through oxidative addition, we wondered whether these Cp*Co species could promote cross-coupling reactions of aryl halides containing this type of auxiliary ligands. Different types of cobalt species, normally generated by the combination of cobalt salts and Grignard reagents, have shown to be effective catalysts in aryl halide cross coupling reactions. However, the involvement of Cp*Co intermediates in these types of transformations remains practically unexplored.[17,18] Guided by our previous studies on Cp*Co^{III}-catalyzed C–H functionalizations,[6] we selected alkyne annulations as a benchmark reaction. In the context of C–H functionalization reactions, these transformations proceed via Co$^{I/III}$ catalytic cycles and involve a re-oxidation step after product formation to regenerate the active Cp*Co^{III} species that subsequently participates in C–H bond cleavage. When using aryl halides as starting materials, we envisioned a similar catalytic cycle to the one proposed for the C–H activation but with an oxidative addition/halide abstraction sequence (Figure 7).
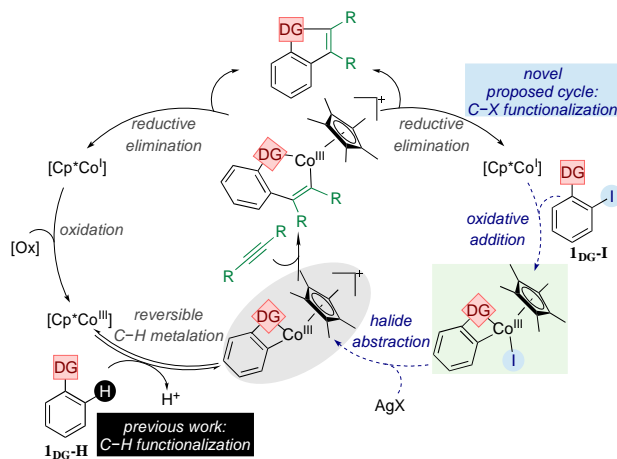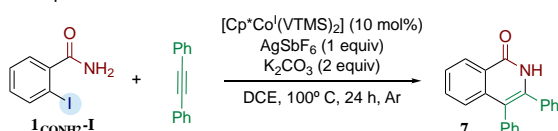

Figure 7. Proposed mechanism for known C–H oxidative alkyne annulation *vs* new pathway involving the activation of aryl halides.

In summary, we have developed a promising strategy that enables entry to catalytically relevant metallacyclic Cp*Co^{III} complexes supported by synthetically relevant scaffolds. We have demonstrated the competence of these 3_{DG}-I-type complexes, not only in select C–H functionalization reactions but also in a benchmark coupling reaction with aryl halides. This fundamental work is expected to open new avenues for accessing previously elusive reactive intermediates in Cp*Co catalysis and designing novel catalytic systems.

To test our working hypothesis, we chose the reaction between 2-iodobenzamide and diphenylacetylene as the representative system (Table 2). It should be noted that the formation of the desired product by Cp*Co-catalyzed C–H functionalization using benzamide as a coupling partner is currently unprecedented in the literature.[19] To our delight, after some experimentation, we found that the desired annulated product (7) was obtained in 75% yield in the presence of catalytic quantities of 2-VTMS in DCE at 100 ºC for 24 hours, using AgSbF$_6$ and K$_2$CO$_3$ as additives. While not anticipated, the choice of silver salt and base had an important effect on the reactivity (entries 4 and 7). 3_{CONH2}-I is a competent catalyst in the annulation reaction, although we observed the desired product in a slightly lower yield (66%) than with 2-VTMS. These preliminary results provide experimental evidence for the functionalization of 1_{DG}-type substrates by Cp*Co systems. We anticipate this type of cross-coupling reactions can be potentially applied to other Cp*Co-catalyzed transformations involving oxidative addition and reductive elimination steps.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

Table 2. Optimization of the Reaction Conditions[a]

Entry	Deviation from standard conditions	7 [%][b]
1	none	75 (66)[c]
2	DCE (0.1 M), AgBF$_4$, 40 ºC	0
3	DCE (0.1 M), AgBF$_4$	53
4	DCE (0.1 M), AgBF$_4$, KOAc	0
5	Dioxane (0.1 M), AgBF$_4$	38
6	DCE (0.1 M)	70
7	AgBF$_4$	67

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[8] Brookhart and co-workers have proposed the generation of Cp*Co^{III} acyl hydride complexes via the oxidative addition of an aldehydic C–H bond
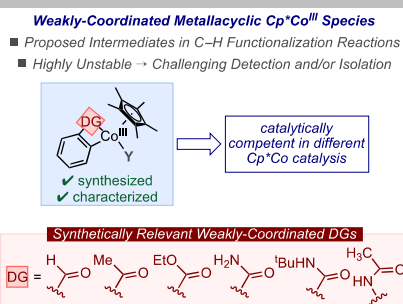
to [C$_5$Me$_5$Co(L)] during the hydroacylation of olefins with aromatic aldehydes (ref. 7a). Under our reaction conditions, we only observed the oxidative addition of the Csp^2–I bond.

[9] CCDC 1971411 (**3$_{ald}$-I**), CCDC 1971412 (**3$_{ald}$-Br**), CCDC 1971413 (**3$_{ket}$-I**), CCDC 1971414 (**3$_{ester}$-I**), CCDC 1971415 (**3$_{CONH2}$-I**), CCDC 1971416 (**3$_{CONHtBu}$-I**), CCDC 1971417 (**3$_{acetanilide}$-I**), CCDC 1971418 (**3$_{ald}$-THF**), CCDC 1971419 (**7**) contain the supplementary crystallographic data for these structures. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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[11] The participation of radical species in the oxidative addition reaction could not be confirmed or excluded, since the reaction of **2-VTMS** with **1$_{ald}$-I**, in the presence of TEMPO, afforded the formation of other unknown species. See SI for further details.

[12] Our attempts for synthesizing the corresponding **3$_{DG}$-I** complexes when using as starting material 2-iodobenzoic acid, 2-iodobenzyl alcohol, 2-iodonitrobenzene 2-iodophenol, 2-iodoaniline and 2-iodomethoxybenzoate led to the decomposition of **2-VTMS**.

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[14] Inspired by our previous works, initial trials targeting **3$_{ald}$-MeCN** afforded a mixture of the desired cobaltacycle and [Cp*Co(MeCN)$_3$][BF$_4$]$_2$, in 89:11 ratio, respectively. The amount of [Cp*Co(MeCN)$_3$][BF$_4$]$_2$ increases along time in solution. See SI for further details.

[15] When the solvent was removed on a rotary evaporator and the resulting precipitate was re-dissolved in CD$_2$Cl$_2$ we observed decomposition.

[16] Although the employment of **3$_{CONHtBu}$-I** resulted in moderate yields of **5**, this experimental result is comparable to the one described by Matsunaga and coworkers in the reference 13a when using [Cp*Co(CO)I$_2$] as pre-catalyst.

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Layout 1:

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Reported here is a versatile platform for capturing thermodynamically unfavoured cobaltacyclic species which contain weakly-chelating moieties. This strategy offers the opportunity to not only fully characterize direct analogues of key transient reactive species but also interrogate their efficient reactivity and intermediacy in different Cp*Co-catalyzed processes.

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Weakly-Coordinated Metallacyclic Cp*Co^{III} Species
- Proposed Intermediates in C–H Functionalization Reactions
- Highly Unstable → Challenging Detection and/or Isolation

catalytically competent in different Cp*Co catalysis

✔ synthesized
✔ characterized

Synthetically Relevant Weakly-Coordinated DGs

Sara Martínez de Salinas,[a] Jesús Sanjosé-Orduna,[a] Carlota Odena,[a] Sergio Barranco,[a] Jordi Benet-Buchholz,[a] Mónica H. Pérez-Temprano*[a]

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