HFIP-assisted C–H functionalization by Cp*CoIII: Promoted Access to Key Reactive Cobaltacycles and Implication in Catalysis

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Abstract: Described here is a synthetic approach to access two of the most widely invoked cationic cobaltacycles in Cp*CoIII-catalyzed C–H functionalization reactions by C–H activation. The unique stabilizing capability of MeCN was used to surmount the previously proposed reversible nature of the C–H metalation step. Moreover, it is revealed the boosting effect of 1,1,1,3,3,3-hexafluoroisopropanol in the metalation step and in the reaction between N-pyrimidinylindole and diphenylacetylene under catalytic conditions.

Over the past few years, Cp*CoIII complexes have emerged as a potential alternative to noble metals in one of the cornerstones of modern organic synthesis: ligand-directed C–H functionalization reactions. These cobalt catalysts can not only emulate the same reaction patterns of analogous Rh and Ir systems, but also exhibit a unique reactivity due to the inherent properties of this first-row metal such as its low electronegativity, hard nature or small radius. Despite the remarkable progress achieved in this field since the seminal work by Kanai and Matsunaga in 2013, there is still an important lack of fundamental understanding of these Cp*CoIII-catalyzed transformations. In sharp contrast to analogous rhodium systems, the investigation of the underlying reaction mechanisms of Cp*Co-catalyzed directed C–H functionalizations has been hampered by the difficulty of capturing transient key reaction intermediates, since, in most cases, the formation of C–H activated Cp*CoIII metallacycles is proposed to be reversible. To tackle this situation, our group has recently reported the employment of acetonitrile as stabilizing ligand to access a direct analogue of a long-sought cyclometalated cobalt(III) complex ([1ppy-MeCN in Figure 1), by a ligand-assisted oxidative addition, in order to bring light into the mechanistic insights of C–H oxidative alkyne annulations. Inspired by these results, we wondered whether it would be possible to overcome the reversibility of the C–H cobaltation by taking advantage of the unique ability of MeCN to stabilize otherwise highly reactive cobalt species. Herein, we provide a direct synthetic route to two of the most widely invoked cationic metalacyclic intermediates in Cp*CoIII-catalyzed C–H functionalization reactions by C–H bond cleavage. Our studies not only demonstrate the intermediacy of this type species in the oxidative alkyne annulation and alkyne insertion benchmark transformations, but also reveal the crucial role of fluorinated alcohols, such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), to improve the efficiency, not only of the C–H activation step, but also of catalytic transformations using diphenylacetylene as coupling partner.

Figure 1. Proposed synthetic approach for accessing long-sought key reactive Cp*CoIII intermediates via C–H activation.
We started our investigations by targeting the synthesis of 1ppy-MeCN through a C–H metalation step using [Cp*Co(III)(MeCN)3]X2 as the cobalt source. We selected this Cp*Co(III) complex to test our working hypothesis because: a) it is commonly used as catalyst in Cp*Co-catalyzed C–H functionalizations, b) the cationic nature of this Cp*Co(III) system simplifies the reaction conditions, avoiding the use of silver salts to generate the active species, and c) it already contains our desired stabilizing ligand.

Gratifyingly, the reaction of [Cp*Co(III)(MeCN)3](BF4)2 with 10 equiv of 2-ppyH, used not only as substrate but also as surrogate base, afforded the smooth formation of the targeted acetonitrile-stabilized cobaltacycle 1ppy-MeCN along with protonated substrate as determined by 1H NMR spectroscopic analysis (Figure 2).

Despite this promising result, we surmised that this synthetic strategy could not be effective when exploring substrates containing less basic directing groups. This assumption proved correct since the metalation of one of the most commonly used substrates in Cp*Co-catalyzed transformations, N-pyrimidinylindole (pmiH), was rather slow, under the conditions described above for accessing 1ppy-MeCN when monitored by 1H NMR spectroscopy (Figure 3a). After some experimentation, this limitation was addressed by the use of 2,6-Di-tert-butylpyridine (DTBP) as external base, which provided the quantitative formation of 1pmi-MeCN, in CH2Cl2 at 35 ºC after 20 h by 1H NMR spectroscopy (Figure 3b). The structure of 1pmi-MeCN was unequivocally confirmed by NMR spectroscopy and single-crystal X-ray diffraction. The use of HFIP as solvent caused a dramatic increase in the reaction efficiency, reducing the reaction time to less than 5 minutes (Figure 3c). Although the beneficial effect of this fluorinated solvent is commonly acknowledged in transition metal-catalyzed C–H functionalization processes, its real role still remains unclear. To gain insights into this unique capability, we performed 1H NMR spectroscopic titrations of [Cp*Co(III)(MeCN)3](BF4)2 with HFIP to test whether the accelerating effect during the metalation step is due to an initial ligand displacement. Importantly, in these experiments, we do not observe MeCN replacement by the perfluorinated alcohol. Furthermore, we conducted a series of preliminary experiments, monitoring the formation of 1pmi-MeCN by 1H NMR, using HFIP as additive. Addition of even just 1 equiv of HFIP accelerated the C–H metalation step, suggesting that the polarity of solvent alone is not responsible of the dramatic effect on the reaction rate. These results along with literature precedents may hint towards HFIP acting as proton-shuttle during the C–H activation step. Indeed, in the presence of 50 equiv of the fluorinated alcohol, we observed the quantitative formation of 1pmi-MeCN in less than 5 minutes (Figure 3). We were able to isolate 1pmi-MeCN in 91% yield in the presence of 50 equiv of HFIP at 35 ºC, after 1 hour using DCE as solvent (Figure 3d).
Encouraged by the dramatic effect of HFIP on the C–H activation step, we next sought to explore the influence of this fluorinated alcohol on subsequent elementary steps involved in a potential catalytic cycle. In particular, we targeted as benchmark the reactivity of 1\textsubscript{pmi}-MeCN with diphenylacetylene in the context of Cp*Co-catalyzed hydroarylation and oxidative annulation reactions. Based on the mechanistic proposals found in the literature, at the beginning both reactions share identical reactive intermediates, as is depicted in Scheme 3. However, the two pathways differ in the steps that follow the migratory insertion: protodemetalation in the presence of a protic source\textsuperscript{15} versus reductive elimination/re-oxidation sequence.\textsuperscript{15}\textsuperscript{15} Therefore, the comparison of the HFIP effect on these two reactivity patterns represents a particular interesting case, since a priori, the fluorinated alcohol could affect them differently.

![Diagram](https://static.chem.ox.ac.uk/fig.png)

**Scheme 1.** Mechanistic proposals for Cp*Co-catalyzed hydroarylation and oxidative annulation reactions. DG = directing group.

On this basis, our first objective was to confirm the formation of 2-type complexes. The treatment of 1\textsubscript{pmi}-MeCN with 2 equiv of diphenylacetylene in CD\textsubscript{2}Cl\textsubscript{2} at \textasciitilde20°C resulted in the quantitative formation of 2\textsubscript{pmi}-MeCN within 1 hour, as determined by \textsuperscript{1}H NMR spectroscopy. This compound, whose structure was also characterized by single crystal X-ray diffraction, is analogous to seven-membered catonic cobaltacycles reported by our group and that of Sundararaju (see Scheme 2).\textsuperscript{5,11,17c} We then carried out a series of stoichiometric studies, not only to provide consistent experimental evidences of the proposed divergent reactivities from 2\textsubscript{pmi} but also to unravel the potential impact of HFIP as additive on both reaction pathways.\textsuperscript{18} We first studied the hydroarylation process using PivOH as proton source (Scheme 2a). The reaction of 1\textsubscript{pmi}-MeCN with 3 equiv of diphenylacetylene in the presence of 10 equiv of PivOH at rt for 1 h in DCE resulted in the selective formation of 3\textsubscript{pmi} in 85% yield by \textsuperscript{1}H NMR. Gratifyingly, under these conditions, the presence of HFIP as additive led to higher yield of the desired product (97%). This increase in yield could be consistent with the potential role of the fluorinated alcohol as proton shuttle.\textsuperscript{15} Following a similar strategy, we next investigated the annulation reaction. No traces of 3\textsubscript{pmi} or 4\textsubscript{pmi} were detected by \textsuperscript{1}H NMR spectroscopy upon treatment of 1\textsubscript{pmi}-MeCN with 3 equiv of diphenylacetylene at rt for 1 h in DCE (Scheme 2b).\textsuperscript{19} At 60 °C (Scheme 2c), we observed the formation of 4\textsubscript{pmi} in 34% yield along with traces (<5%) of 3\textsubscript{pmi}, indicating that the reductive elimination is accelerated at higher temperature. In this system, the addition of HFIP resulted in competing hydroarylation and annulation processes, favoring the formation of the hydroarylated product (3\textsubscript{pmi}/4\textsubscript{pmi} = 46/29). This result strongly suggests HFIP can act as proton source.\textsuperscript{20}

With these mechanistic insights in hand, we explored the global effect of HFIP under catalytic conditions. In alignment with our stoichiometric experiments, when we used HFIP as additive in the hydroarylation of diphenylacetylene with pmiH in DCE at room temperature using [Cp*Co(MeCN)\textsubscript{2}](BF\textsubscript{4})\textsubscript{2} (5 mol%) as catalyst and 0.5 equiv of PivOH as proton source, we observed a significant increase in yield (Table 1, entries 1–2).\textsuperscript{21} The efficiency of the reaction was improved in the presence of higher amounts of PivOH (1.5 equiv), obtaining the desired product in 86% yield (entry 3). Interestingly, the use of 1\textsubscript{pmi}-MeCN as catalyst provided 3\textsubscript{pmi} in 98% isolated yield (entry 4).\textsuperscript{22} This result confirms not only the catalytically competence of this type of cobaltacyle species, formed via C–H metatation from [Cp*Co(MeCN)\textsubscript{2}](BF\textsubscript{4})\textsubscript{2}, but also their excellent efficiency.
In summary, we have designed a new strategy for circumventing the reversible nature of the C–H metatalation step when using Cp*Co complexes to access two of the most widely invoked cationic cobaltacyclic intermediates. Our work reveals the boosting effect of HFIP as additive, not only in the C–H activation step, but also on benchmark catalytic processes involving alkynes as coupling partners, presumably due its capability as proton-shuttle and polar nature. Further investigations into the role of fluorinated alcohol in catalysis are currently underway.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H activation • cobalt catalysis • reaction mechanisms • reactive intermediates • synthetic methods

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Table 2. Hydroarylation of diphenylacetylene.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>PivOH (equiv)</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Cp*Co(MeCN)][BF_4]</td>
<td>0.5</td>
<td>12 [b]</td>
</tr>
<tr>
<td>2</td>
<td>[Cp*Co(MeCN)][BF_4]</td>
<td>0.5</td>
<td>50 [d]</td>
</tr>
<tr>
<td>3</td>
<td>[Cp*Co(MeCN)][BF_4]</td>
<td>1.5</td>
<td>98 [d]</td>
</tr>
<tr>
<td>4</td>
<td>1:3 MeCN</td>
<td>No HFIP</td>
<td>1.5</td>
</tr>
</tbody>
</table>

[b] Reactions run at 0.20 mmol scale and 0.1 M concentration. [d] Isolated yield. [d] Stoichiometric NMR experiment.

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Table 2. Oxidative annulation of diphenylacetylene.  

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>HFIP/DCE (1/10)</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Cp*Co(MeCN)][BF_4]</td>
<td>No HFIP</td>
<td>4</td>
</tr>
</tbody>
</table>

[a] NMR-scale reactions: 0.025 mmol scale, see SI for details.


Unlike the analog Rh-based systems, the formation of a cationic cobaltacycle stabilized by a second molecule of 2-ppyH is not observed. This is presumably due to the smaller atomic radius of cobalt which prevents its coordination. See ref 3a, 3d-e.

We also tested the use of carboxylic bases, such as NaOAc, to promote the base-assisted cyclometalation of 2-ppyH by [Cp*Co(CO)2(MeCN)]X. Under these reaction conditions, we observed a complex mixture of products, including 1pmi-MeCN and an inactive dimeric cobalt species (S1) containing bridging acetate groups. See SI p S2-4 for further details.

We discarded the use of carboxylic bases based on the preliminary results described in reference 8 and in the SI.

This result along with the use of 2-ppyH as external base support a base-assisted intermolecular C–H metation step.

CCDC 1846807 (S1), CCDC 1846808 (1pmi-MeCN) and CCDC 1846809 (2pmi-MeCN) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.


During the titration and metation experiments, we do not observe, by 1H NMR spectroscopy, the formation of additional monomeric or dimeric Cp*CoII species. See SI for further details.

Apart of increasing the solubility of ionic additives, the polar nature of HFIP could potentially contribute to facilitate MeCN dissociation to access reactive unsaturated species involved in the catalytic cycle.