Reaction Mechanisms

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Redefining the Mechanistic Scenario of Carbon–Sulfur Nucleophilic Coupling via High-Valent Cp*Co^{IV} Species

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Abstract: *The potential access to Co^{IV} species for promoting transformations that are particularly challenging at Co^{III} still remains underexploited in the context of Cp*Co-catalyzed C–H functionalization reactions. Herein, we disclose a combined experimental and computational strategy for uncovering the participation of Cp*Co^{IV} species in a Cp*Co-mediated C–S bond-reductive elimination. These studies support the intermediacy of high-valent Cp*Co species in C–H functionalization reactions, under oxidative conditions, when involving nucleophilic coupling partners.*

Over the past years, Cp*Co^{III} complexes have demonstrated their extraordinary capability for promoting C–H functionalization reactions using a wide range of electrophilic reagents.[1] This distinctive behavior is attributed to the low electronegativity of this first-row metal. The polarization of the Cp*Co^{III}–C bond after the C–H metalation tends to make the resulting cobaltacycle particularly reactive towards electrophilic moieties due to its nucleophilicity.[2] In sharp contrast, limited advances have been accomplished when using nucleophiles.[3] Among the scarce reported examples, sulfur-based coinage metal coupling partners have exhibited their capability for promoting C–S bond-forming reactions.[3a–b] Glorius pioneered these strategies with the in situ formation of an active thiolating agent, combining $Cu(OAc)_2$ and RSH (R = Ar, alkyl).[3a] In their work, the authors detected the presence of potential Cp*Co^{III} intermediates (type **III** in Figure 1) under catalytic conditions by ESI-MS. In 2017, Wang and co-workers employed a readily available silver reagent, $AgSCF_3$, for the C–H trifluoromethylthiolation of arenes.[3b] Although these methodologies provide exciting prospects in the field of Cp*Co^{III}-catalyzed C–H functionalization reactions, the mechanistic picture of the C–S bond formation still remains elusive. Putative cobalt(III) thiolate species (**III** in Figure 1), formed after a transmetalation step with the corresponding nucleophile, have been proposed as transient species in these transformations, yet none of them has been isolated or structurally characterized. Therefore, their participation in direct C–S reductive eliminations or the implication of more complex scenarios, via cobalt species with unusual high oxidation states, are fundamental questions that remain unsolved (Figure 1). Continuing our efforts on enhancing the fundamental knowledge of Cp*Co-based systems,[4] we herein disclose, for the first time, "hidden" mechanistic intricacies when involving nucleophiles as coupling partners. Our multidisciplinary approach, merging experimental and theoretical studies with a wide variety of analytical techniques, (i) provides an ideal platform for investigating C–SCF_3 coupling from putative Cp*Co^{III} intermediates in catalysis, (ii) reveals the multiple roles of silver species in these transformations, and (iii) exposes an unprecedented oxidatively induced reductive elimination (ORE) in Cp*Co systems[5] that can be triggered under chemical or electrochemical conditions.

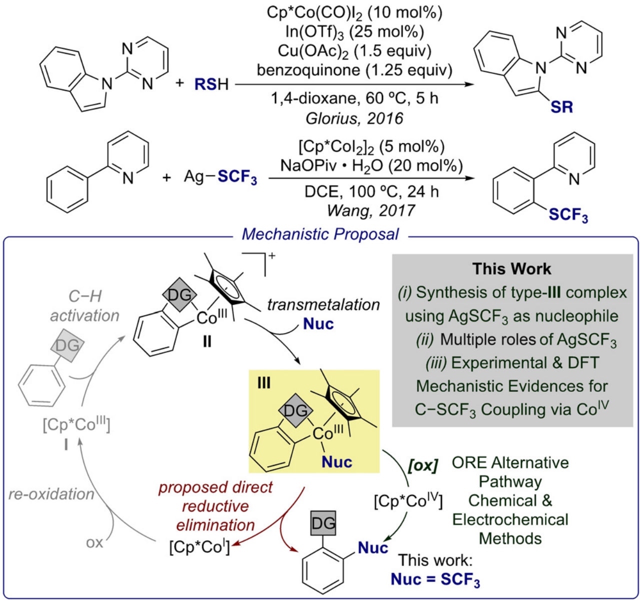

Figure 1. Literature precedents for Cp*Co-catalyzed C–S bond-forming reactions and proposed mechanistic picture.

Our study started by establishing a synthetic route to a benchmark [Cp*Co^{III}(C^N)(SCF_3)] complex.[3b] We envisioned to synthesize a well-defined compound by thiolation of

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a cobalt(III)-halide derivative with $AgSCF_3$.[6] The selection of this specific system was not arbitrary, and it was prompted by several considerations. First, the above-mentioned Cp*Co-catalyzed C–H thiolation methodologies suggest the formation of C–S bonds from this type of species.[3a–b] Second, we targeted [Cp^*Co^{III}(2-ppy)(I)] (**1**) as initial cobalt precursor since it is readily accessible via oxidative addition.[4a] Third, the multiple role of silver species in transition metal catalysis is well-established, including their exceptional capability as transmetalating agent.[7] Finally, the installation of the SCF_3 moiety, using the commercially available $AgSCF_3$ reagent, will provide a distinctive chemical shift by ^{19}F NMR spectroscopy, facilitating the identification of new cobalt thiolate species. When examining our hypothesis, we were pleased to observe that the treatment of **1** with 1 equiv of $AgSCF_3$ in DCM at room temperature for 15 minutes afforded [Cp^*Co^{III}(2-ppy)(SCF_3)] (**2**) in 90% isolated yield (Figure 2a).[8] Complex **2**, stable upon exposure to air, was unambiguously characterized by 1D (^1H, ^{13}C, and ^{19}F) and 2D NMR spectroscopy and single-crystal X-ray diffraction studies.[9] This compound, analogous to the type-**III** intermediate shown in Figure 1, represents the first example of an isolated Cp^*Co^{III} cyclometalated compound bearing a Nuc-type ligand after reaction with a nucleophilic coupling partner. Having a reliable synthetic procedure for the post-transmetalation complex in hand, we next sought to determine whether complex **2** could be catalytically competent in the C–SCF_3 bond-forming reaction. To our delight, the trifluoromethylthiolation of 2-phenylpyridine proved feasible and efficient using **2** as catalyst (Figure 2b).[10] This result, comparable to the one obtained by Wang and co-workers using $[Cp^*CoI_2]_2$ as catalyst (65% yield),[3b] strongly suggests that **2** is a key reactive intermediate during catalysis.

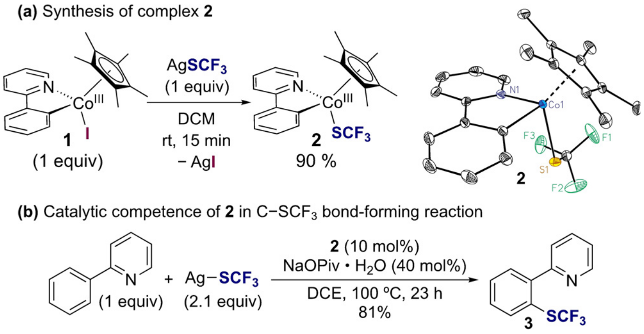
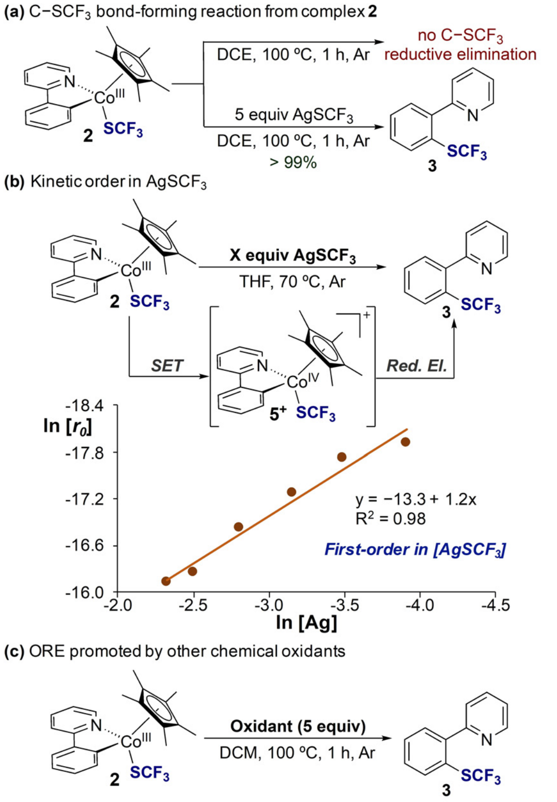


Figure 2. a) Synthesis and characterization of **2** through a transmetalation reaction with $AgSCF_3$. ORTEP diagram of **2** is shown at 50% of probability (H atoms have been omitted for clarity). b) Catalytic activity of **2** in the trifluoromethylthiolation of 2-phenylpyridine.

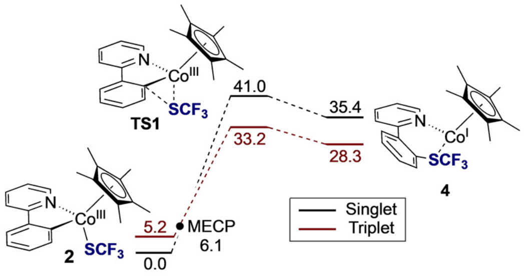


Oxidant	AgF	AgF_2	AgOAc	$Cu(OAc)_2$	$Mn(OAc)_3$ $2H_2O$
NMR Yield (%)	37	30	traces	12	quantitative

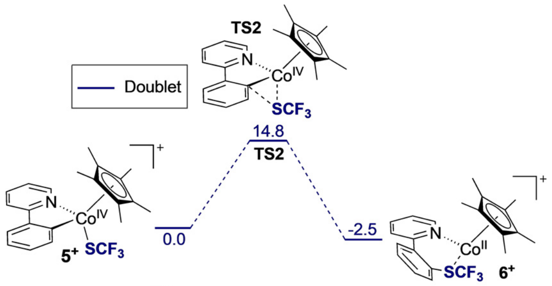
Figure 3. a) Reductive elimination from **2** in the absence or presence of $AgSCF_3$. b) Kinetic order in $AgSCF_3$. c) Reductive elimination in the presence of other 1-electron chemical oxidants. The reported yields were determined by ^{19}F NMR spectroscopy of the crude reaction mixture using 4,4′-difluorobiphenyl as internal standard.

Next, we interrogated the mechanism of the C–S bond-forming reaction (Figure 3). Since complex **2** is stable in solution at rt, we evaluated whether it directly undergoes C–S reductive elimination upon thermolysis. Contrary to previous proposals, we did not observe the formation of the desired trifluoromethylthiolated product (**3**) by ^{19}F NMR spectroscopy after heating a DCE solution of complex **2** at 100 °C for 1 h.[11] Prompted by this outcome and aiming to mimic the reported catalytic conditions, we next explored whether the presence of excess of $AgSCF_3$ triggered the C–SCF_3 reductive elimination. Gratifyingly, **3** was obtained in almost quantitative yield by reaction of **2** with 5 equivalents of $AgSCF_3$ in DCE after 1 h at 100 °C.[12] This result suggests the participation of an oxidatively induced reductive elimination (ORE) step via high-valent cobalt(IV) or cobalt(V) species (Figure 3a).[13] In order to determine if the ORE process involves the transfer of one or two electrons, we conducted kinetic studies to ascertain the order in $AgSCF_3$ (Figure 3b). The initial rates (r_0) of the stoichiometric formation of **3** in the presence of different amounts of $AgSCF_3$ (from 0.02 to 0.1 M) were determined at 70 °C in THF.[14] Under these conditions, the reaction is approximately first-order in $AgSCF_3$ (1.2). This implies the formation of Co^{IV} species via a single-electron transfer (SET) oxidation pathway prior to the C–SCF_3 coupling.[15] Encouraged by the these results, we examined whether other typical 1-electron oxidants could also promote the C–SCF_3 reductive elimination event (Figure 3c).[16,17] Silver salts, such as AgF or AgF_2, afford **3** in yet lower yields. AgOAc and $Cu(OAc)_2$, commonly used additives in homogeneous catalysis, were inefficient in this transformation. However, quantitative yield for **3** was observed when using $Mn(OAc)_3{\cdot}2H_2O$ as external oxidant.

(a) DFT profile for direct C–SCF$_3$ coupling from a Cp*Co^{III} species



(b) DFT profile for C–SCF$_3$ coupling from a Cp*Co^{IV} species



(c) Computed Co$^{III/IV}$ redox potential

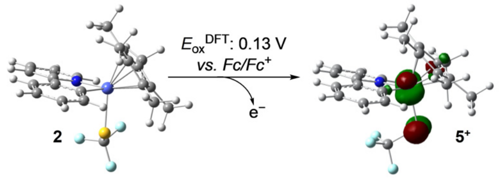
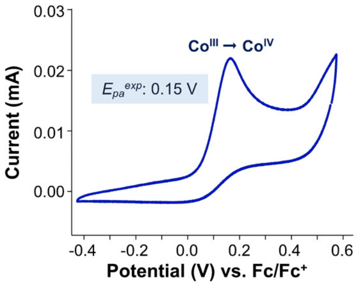


Figure 4. a) Computed free energy profile (kcal mol^{-1}) of the direct C–SCF$_3$ coupling from complex **2**. b) Computed free energy profile (kcal mol^{-1}) of the reductive elimination step from complex **5**$^+$ at 100 °C. c) Computed 1-electron oxidation of **2**. The figure shows the semioccupied orbital (isovalue = 0.06) in the Co^{IV} complex (**5**$^+$) resulting from the oxidation of **2.**

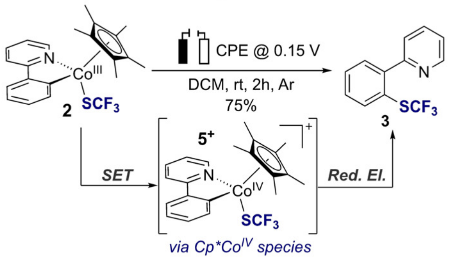
In line with the experimental results, DFT calculations at the M06-D3 level in DCM solvent (Figure 4 a)[18] revealed a high energy barrier for the concerted C–S bond-forming reaction from a structure in the triplet spin state (33.2 kcal mol^{-1}). Indeed, the viability of the ORE C–S coupling mechanism from **5**$^+$ was further confirmed computationally (Figure 4 b). The reductive elimination from Co^{IV} is thermodynamically favored (−2.5 kcal mol^{-1}) and presents an accessible energy barrier of 14.8 kcal mol^{-1} (Figure 4 b). As observed for related transition-metal systems,[11,19] the oxidation state of the metal center is key for enabling the coupling of nucleophilic partners, providing a lower energy barrier and more downhill routes when oxidizing the metal. The analysis of the natural orbitals shows an orbital centered between the Co and S atoms (Figure 4 c). Moreover, the spin analysis of the doublet **5**$^+$ shows spin density of 0.908 centered at Co, which corresponds to the unpaired electron of Co^{IV}. These results corroborate the propensity of Co to undergo one-electron oxidation events and the charge mismatch in the coupling of Cp*Co^{III}–C with the nucleophilic SCF$_3$ moiety.

Cognizant of the involvement of an oxidative coupling mechanism and the increasing interest in electrocatalysis within first-row metal-catalyzed C–H functionalization reactions,[20] we explored whether we could drive the reaction electrochemically, without the addition of any external oxidant. The cyclic voltammetry of **2** (Figure 5 a) shows an irreversible redox event at a low oxidation potential (0.15 V vs. Fc/Fc$^+$) that is consistent with the computed Co$^{III/IV}$ redox couple (0.13 V), since the calculated oxidation potential for Co^{IV}/V^{1} is significantly higher (1.86 V). The irreversibility of the redox wave also indicates that **2** is transformed into another product upon oxidation, suggesting an electrosynthetic process. In order to uncover the identity of the resulting product, we carried out, in a divided cell, the bulk electrosynthesis in a stirred solution of the post-transmetalated compound (**2**) in DCM at rt and at a constant potential of 0.15 V vs. Fc/Fc$^+$ (Figure 5 b). The chronoamperometry (CA) was performed for the time required to transfer a stoichiometric total charge equivalent to one electron per complex (Figure 5 c). Satisfyingly, this resulted in the formation of the desired organic product (**3**) in 75 % yield, as determined by ^{19}F NMR spectroscopy.[21] This experimental outcome supports the oxidatively induced C–SCF$_3$ reductive elimination event and rules out the participation of Co^{V} intermediates,[22] or additional redox reactions that may involve the coordination sphere.[23] Magnetic measurements of the cobalt complex

(a) Electrochemical analysis of complex **2**



(b) Stoichiometric electrochemical synthesis of **3**



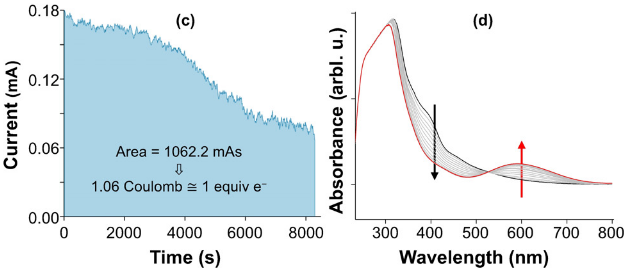


Figure 5. a) Cyclic voltammogram of complex **2** in DCM/nBu$_4$NPF$_6$ at a scan rate of 100 mV s^{-1}. To isolate the first oxidation peak, the cyclovoltammogram was recorded from −0.42 to 0.57 V vs. Fc/Fc$^+$. b) Electrochemical formation of **3** from [Cp*Co^{III}(2-ppy)(SCF$_3$)] (**2**; CPE = constant potential electrolysis). c) Calculated transferred charge during the experiment shown in (b). d) UV/Vis analysis of the electrochemical generation of **3** (red line) using **2** (black line) as starting material.

collected from the electrolyte solution after the electrosynthesis of **3** revealed the presence of a paramagnetic species distinct from the diamagnetic response of complex **2**.[24] This suggests the presence of a Co^{II} complex after the reductive elimination event.[25] We also followed the spectral changes associated to the electrochemical oxidatively induced elimination by UV/Vis spectroscopy (Figure 5 d). In these experiments we found the disappearance of the absorption peak of **2** at 400 nm concurrently with an increase at 600 nm. The occurrence of an isosbestic point at 525 nm indicates the interconversion of complex **2** to another short-lived cobalt species, presumably the highly oxidized Co^{IV}.

In summary, we have designed and synthesized a well-defined $Cp^{*}Co^{III}$ system to interrogate the mechanism of C–S coupling. Our study provides, for the first time, experimental and computational evidence for the involvement of high-valent Co^{IV} species during a reductive elimination event of C–H functionalization reactions. Moreover, we have demonstrated the competence of chemical and electrochemical approaches for facilitating this type of transformations. This study opens new avenues for exploring and designing alternative high-valent cobalt catalytic cycles when using nucleophiles as coupling partners. Ongoing studies along these lines are currently underway in our laboratories.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H functionalization · cobalt · homogeneous catalysis · reaction mechanisms · reductive elimination

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[9] Deposition Number 2021663 (for **2**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

[10] The catalytic experiments were carried out by duplicate. The reported yield was determined by ^{19}F NMR spectroscopy of the crude reaction mixture using 4,4′-difluorobiphenyl as internal standard. See SI for further details.

[11] Similar yield was obtained when the reaction was carried out in DCM.

[12] We have ruled out an alternative pathway that involves the nucleophilic attack of an external SCF_3 anion onto the Co–C bond of complex **2**. When we carried out the thermolysis of complex **2** in the presence of NMe_4SCF_3, we did not observe the formation of product **3**. See SI for further details.

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presence of a radical species with strong organic-centered character upon oxidation of complex **2**. See SI for further details.

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[21] When we investigated the generation of **3** under electrolytic conditions by EPR spectroscopy we did not observe any paramagnetic species. We hypothesize that, since the oxidation takes place exclusively inside the electric double layer at the electrode surface, the lifetime of the paramagnetic species is not long enough to survive during the diffusion process into the reaction mixture. See SI for further details.

[22] We have computationally investigated the C−S coupling from a cobalt(V) intermediate. Although the activation energy of this highly oxidized species is 10.9 $kcal\,mol^{-1}$, the reaction does not proceed through this pathway due to the prohibitive high redox potential for Co^{IV}/V. See SI for further details.

[23] We have ruled out the participation of free SCF_3 radicals during the formation of **3** when using chemical oxidants such as $AgSCF_3$ or $Mn(OAc)_3{\cdot}2\,H_2O$ since the addition of radical scavengers does not affect the reaction outcome. See SI for further details.

[24] See Figures S126, S127 of the Supporting Information.

[25] In addition, we have indirect experimental evidence that discards the presence of Co^{I} species after the reductive elimination event when using $AgSCF_3$ as terminal oxidant. See SI for further details.

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