Exploration of Organometallic Cobalt Intermediates in an Aminoquinoline-Directed Dehydrogenative Dimerization Reaction

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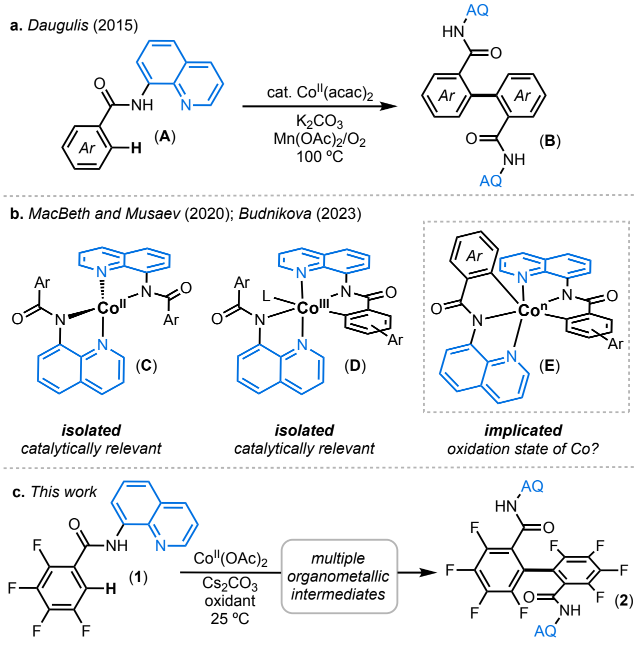
ABSTRACT: This communication describes structure and reactivity studies of cyclometalated cobalt complexes formed during the dehydrogenative dimerization of 2,3,4,5-tetrafluoro-*N*-(quinolin-8-yl)benzamide. This substrate undergoes cyclometalation at $Co(OAc)_2$ to form an NNC cobalt(II) pincer complex. Single-electron oxidation with AgOAc results in a cobalt(III) intermediate that undergoes a second directed $C(sp^2)$–H activation to yield a bis-cyclometalated octahedral cobalt(III) product. This cobalt(III) species is inert to thermal carbon–carbon bond-forming reductive elimination upon heating at 160 ºC for 48 h. However, treatment with ferrocenium oxidants at room temperature results in oxidatively-induced carbon–carbon coupling via a putative cobalt(IV) intermediate.

Over the past decade, cobalt salts have emerged as (pre)catalysts for a variety of directed C–H bond functionalization reactions.[1] Research in this area was spurred by Daugulis' seminal report of the $Co(OAc)_2$-catalyzed aminoquinoline-directed C–H annulation of arene substrates.[2] Following this work, Co-catalyzed C–H functionalization reactions have been developed using a wide variety of other directing groups, types of C–H bonds, and oxidants/functionalization reactions.[2-5]

Catalysis studies in this area have been complemented by mechanistic work aimed at identifying key organometallic intermediates.[6] Numerous cyclometalated cobalt(III) complexes have been isolated and characterized, and their catalytic relevance has been established in both carbon–carbon and carbon–heteroatom bond-forming reactions.[7–13] However, despite this progress, there are still many unresolved mechanistic questions. For example, while nearly all of these transformations involve cobalt(II) (pre)catalysts, it remains unclear whether cobalt(II) centers can participate in the C–H activation step. Furthermore, while many mono-cyclometalated cobalt(III) complexes have been isolated, the organometallic intermediates that follow these species on the catalytic cycle have largely proven undetectable.[9,11,14–16] Finally, in many cases, it has not been established whether the bond-forming step occurs from cobalt(III) or a higher valent cobalt(IV) intermediate.

We sought to interrogate these questions in the context of the Co-catalyzed dehydrogenative dimerization reactions (Scheme 1). This transformation was originally demonstrated by Daugulis, who used $Co(acac)_2$ as a catalyst for dimerizing **A** to form **B** (Scheme 1a).[17] Subsequent mechanistic work led to the isolation of cobalt(II) coordination complex **C** and the cobalt(III) metallacycle **D** (Scheme 1b).[9,14] Furthermore, a combination of computational and cyclic voltammetry studies implicated an octahedral bis-cyclometalated complex (**E**) as the intermediate that undergoes C–C bond-forming reductive elimination to release product **B**.[9,14] However, intermediate **E** has not been detected, and the oxidation state of Co in this species (+3 versus +4) has not been definitively established.

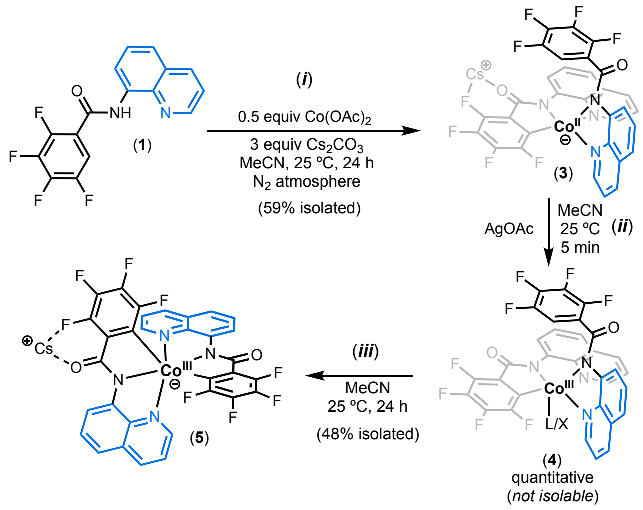


Scheme 1. (a) Co-catalyzed oxidative dimerization of **1**.[17] (b) Isolated and implicated intermediates.[9,14] (c) This work.

In this communication, we leverage a fluorinated substrate, 2,3,4,5-tetrafluoro-*N*-(quinolin-8-yl)benzamide **1**, to study organometallic intermediates in the dehydrogenative dimerization of **1** to form **2** (Scheme 1c). We show that the aminoquinoline-directed cyclometalation of **1** proceeds at both cobalt(II) and cobalt(III) centers, and we isolate a bis-cyclometalated cobalt(III) intermediate (analogue of **E**). Finally, we demonstrate that this cobalt(III) species is inert towards direct reductive elimination up to 160 ºC for >24 h but that it undergoes oxidatively-induced C–C coupling to form **2** at room temperature via a putative cobalt(IV) intermediate.

Initial studies focused on the reaction of **1** with 0.5 equiv $Co(OAc)_2$ and 3 equiv of Cs_2CO_3 under a nitrogen atmosphere

(Scheme 2, *i*). These conditions mimic those employed in Co-catalyzed directed dimerization reactions (albeit without an exogeneous oxidant).[9,10,14,17,18] They are also closely analogous to those reported for the cyclometalation of **1** at copper(II) and nickel(II) centers.[19,20] The reaction was monitored by ^{19}F NMR spectroscopy, and several paramagnetic intermediates were detected (see Figure S1). However, after 24 h at 25 °C, these converged to a single major cobalt product that was isolated as a red solid. Its ^{19}F NMR spectrum shows 4 broad resonances between -140 and -160 ppm, consistent with a paramagnetic species. Similarly, the ^{1}H NMR spectrum shows several low-intensity broad resonances between 24 and -6 ppm. Based on literature reports, we initially hypothesized that this was a cobalt(II) coordination complex directly analogous to **C**.[9,14] However, the X-ray crystal structure (Figure 1a) shows that, instead, it is the anionic cyclometalated cobalt(II) complex **3**. A second equivalent of **1** serves as an LX donor ligand at the pseudo-square pyramidal ($\tau = 0.02$) cobalt(II) center,[19] and the negative charge at cobalt is balanced by a cesium cation. The Co–C bond length of 1.9394 Å is ~0.2 Å longer than that in reported cobalt(III) complexes with analogous coordination environments.[7,9,12–14,21–24] This distance is between that observed in the copper(II) and nickel(II) analogues of **1**, which have M–C bond lengths of 2.002 Å and 1.916 Å, respectively.[19,20] Overall, this represents the first demonstrated example of AQ-directed cyclometalation at a cobalt(II) center.



Scheme 2. (i) Cyclometalation of **1** at cobalt(II) to form **3**. (ii) Oxidation of **3** with AgOAc for form **4**. (iii) Cyclometalation of **4** to afford **5**.

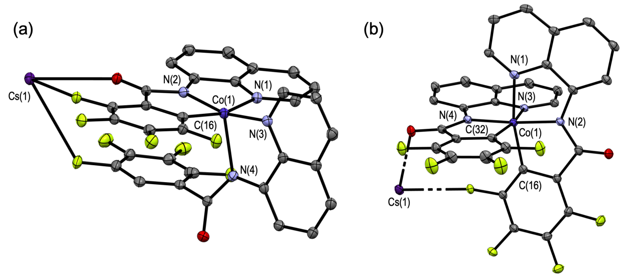


Figure 1. ORTEP diagrams of (a) **3** and (b) **5**. Thermal ellipsoids drawn at 25% probability. Hydrogen atoms and solvent molecules omitted for clarity. Selected bond lengths for **3** (Å): Co(1)–C(16) 1.939, Co(1)–N(1) 1.978, Co(1)–N(2) 1.902, Co(1)–N(3) 1.939, Co(1)–N(4) 2.177. Selected bond lengths for **5** (Å): Co(1)–C(16) 1.924, Co(1)–C(32) 1.920, Co(1)–N(1) 1.987, Co(1)–N(2) 1.907, Co(1)–N(3) 1.988, Co(1)–N(4) 1.902.

Cyclic voltammetry (CV) was next conducted to interrogate the oxidation of cobalt(II) complex **3** in MeCN/NBu$_4$PF$_6$ (Figure 2, light blue). At a scan rate of 100 mV/s, the CV of **3** shows two quasi reversible oxidations with $E_{1/2}$ of approximately -0.85 V and 0.54 V versus Ag/Ag$^+$ (Figure 2). We assign these as Co$^{II/III}$ and Co$^{III/IV}$ couples, respectively.

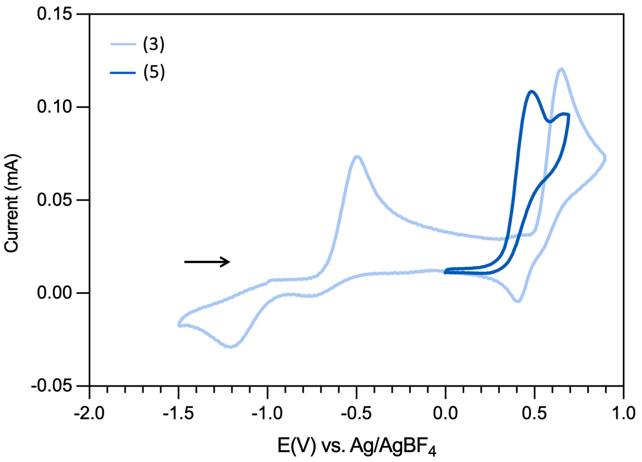


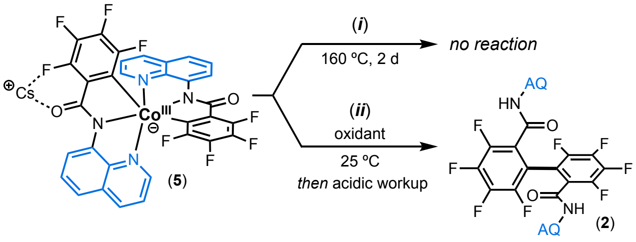
Figure 2. Cyclic voltammograms of cobalt(II) complex **3** (light blue) and cobalt(III) complex **5** (dark blue). Conditions: 4-6 mM solution of [Co] in 0.1 M NBu$_4$PF$_6$ in CH$_3$CN; scan rate of 100 mV/s.

The Co$^{II/III}$ redox potential indicates that silver(I) salts should be capable of oxidizing **3** to **4**. Indeed, the treatment of **3** with AgOAc resulted in an instantaneous color change from dark red to green accompanied by the formation of a silver mirror. Analysis of the crude reaction mixture by ^{19}F NMR spectroscopy showed the formation of a diamagnetic intermediate with 8 distinct ^{19}F NMR resonances (Figure S2). Based on these spectroscopic data, the established precedent for related species,[7,9,10,12–14,21–25] and the observed reactivity of this intermediate (*vide infra*), we assign this as the mono-cyclometalated cobalt(III) complex **4** (Scheme 2, *ii*). [Notably, there could be either an acetate ligand or an equivalent of acetonitrile coordinated in the sixth coordination site of this complex, as indicated by L/X in Scheme 2.]

Attempts to isolate **4** were hampered by its low stability. Over 24 h at room temperature in MeCN, **4** was completely consumed to form a new diamagnetic complex, **5**. Product **5** has higher symmetry than **4**, as indicated by the presence of four distinct fluorine environments and a single aminoquinoline environment (as established by ^{19}F and ^{1}H NMR spectroscopy, respectively). We also noted that this complex does not show a resonance for a C–H bond on the fluoroaryl ring, which typically appears between 6.5 and 7 ppm by ^{1}H NMR spectroscopy. Overall, these data led us to propose that **5** was a bis-cyclometalated cobalt(III) species analogous to **E** (Scheme 2, *iii*).[26]

X-ray quality crystals of **5** were obtained by slow diffusion of pentanes into a THF solution. The ORTEP structure is show in Figure 1b, and it confirms that **5** is an anionic octahedral bis-cyclometalated cobalt(III) complex. The average Co–C bond distance in **4** is 1.922 Å, which is ~0.017 Å shorter than that in cobalt(II) complex **3** but very similar to Co–C bond distances in related cobalt(III) metallacycles.[7,9,12–14,21–24] The negative charge at cobalt is again balanced by a cesium cation that has close interactions with C=O (Cs---O = 3.110 Å) and a fluorine of the cyclometalated aryl group (Cs---F = 2.926 Å). Complex **5** was further characterized by HRMS and elemental analysis. To our knowledge, this is the first example of an isolated cobalt(III) complex featuring two cyclometalated aminoquinoline ligands.

Heating a DMSO solution of **5** at 160 ºC for 2 days resulted in no reaction, with nearly quantitative recovery of the cobalt(III) starting material (Scheme 3, *i* and Figure S3).[27] This indicates a high activation barrier for direct C–C bond-forming reductive elimination from the cobalt(III) center and thus provides strong evidence against a $Co^{III/I}$ pathway for the oxidative dimerization of **1**.



Scheme 3. C–C coupling from **5**: (i) direct and (ii) oxidatively-induced.

The CV of **5** in MeCN shows an irreversible oxidation with an onset potential of ~0.3 V versus Ag/Ag$^+$ (Figure 2, dark blue). This $Co^{III/IV}$ couple is shifted negative (by ~170 mV) relative to that of the neutral mono-cyclometalated complex **4**, as would be expected for a more electron-rich anionic cobalt(III) species. Additionally, no return wave is observed following the oxidation of **5**, suggesting that the transient cobalt(IV) product undergoes a chemical reaction on the timescale of the CV experiment. We hypothesized that this reactivity was likely C–C bond-forming reductive elimination from cobalt(IV) to release **2**.

Indeed, the treatment of **5** with ferrocenium-based oxidants (2 equiv) yielded the C–C coupled product at room temperature (Table 1). With ferrocenium tetrafluoroborate ($FcBF_4$), this oxidatively-induced reductive elimination was relatively slow, requiring 24 h to afford full conversion and quantitative yield of **2** (following an acidic workup to release the product from cobalt). The stronger oxidant acetylferrocenium triflate (AcFcOTf) afforded full conversion in just 10 min, albeit with a lower yield of **2** (65%) along with several unidentified byproducts.[28] Overall, these results implicate an oxidatively-induced pathway for C–C coupling via a transient cobalt(IV) intermediate.

Table 1. Impact of oxidant on rate and yield of oxidatively-induced reductive elimination from **5** to form **2**

entry	oxidant	time	% conversion	%2
1	AgOAc	24 h	<1	n.d.
2	$FcBF_4$	10 min	55	55
3	$FcBF_4$	1 h	95	95
4	$FcBF_4$	24 h	99	99
5	AcFcOTf	10 min	>99	65

We note that Musaev and MacBeth proposed a direct C–C coupling pathway from an analogue of **5** in thermal reactions of a non-fluorinated aminoquinoline substrate.[9] In contrast, the current work shows that direct reductive elimination from cobalt(III) is not kinetically accessible with fluorinated substrate **2**. Instead, C–C coupling from **5** only proceeds following oxidation to a more reactive cobalt(IV) species. Our proposed pathway is more analogous to those implicated by Budnikova[14] and Ackermann[10] in related electrochemical oxidative dimerization reactions.

In summary, this report demonstrates that the fluorinated substrate 2,3,4,5-tetrafluoro-*N*-(quinolin-8-yl)benzamide (**1**) can be used to detect and isolate previously unknown intermediates in aminoquinoline-directed dehydrogenative dimerization reactions at cobalt. We show that cyclometalation at cobalt(II) acetate proceeds at room temperature under inert atmosphere. The addition of silver(I) acetate to the cobalt(II) pincer product results in rapid oxidation to cobalt(III). The transient cobalt(III) intermediate then undergoes a second cyclometalation to generate octahedral cobalt(III) intermediate **5**. Complexes analogous to **5** have been implicated in Co-catalyzed dehydrogenative coupling reactions but have not been detected to date. **5** proved inert to direct thermal C–C bond forming reductive elimination even after prolonged heating at 160 ºC. However, oxidation with ferrocenium salts led to rapid C–C coupling via a putative cobalt(IV) intermediate. Our ongoing work is focused on leveraging substrate **1** and derivatives thereof to study intermediates in other Co-catalyzed C–H functionalization reactions.

Supporting Information

Experimental procedures, characterization data, NMR spectra, and X-ray crystallographic information are available as Supporting Information for Publication.

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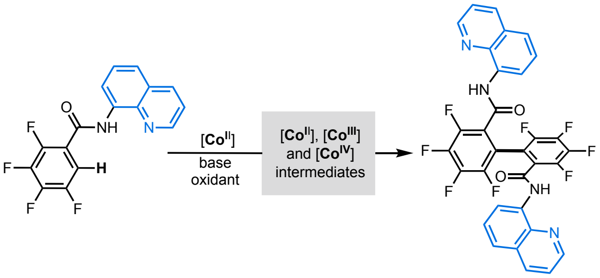
(26) This cyclometalation could be aided by an inner- or outer-sphere acetate base under these conditions. However, we note that AgOTf promotes an analogous oxidation/cyclometalation sequence, suggesting that a base is not required for this transformation.

(27) This reaction was also conducted in the presence of 3 equiv of **1** to more closely resemble catalytic conditions. After heating at 160 °C for 2 d, 96% of the Co(III) starting material remained, and **2** was not observed by ^{19}F NMR.

(28) We have not been able to definitively characterize these by-products, as they are formed in small quantities. They could potentially be different isomers of the dimer, resulting from either C–N coupling between the fluoroarene and the amide fragment, or from C–C coupling between the two aminoquinoline backbones. Similar products have been previously observed by Budnikova et al. (ref. 14) under various oxidizing conditions.

TOC Graphic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