Enzyme-Like Hydroxylation of Aliphatic C–H Bonds From an Isolable Co-Oxo Complex

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ABSTRACT: Selective hydroxylation of aliphatic C–H bonds remains a challenging but broadly useful transformation. Nature has evolved systems that excel at this reaction, exemplified by cytochrome P450 enzymes which use an iron-oxo intermediate to activate aliphatic C–H bonds with \( k_1 > 1400 \text{ s}^{-1} \) at 4 °C. Many synthetic catalysts have been inspired by these enzymes and are similarly proposed to use transition metal-oxo intermediates. However, most examples of well-characterized transition metal-oxo species are not capable of reacting with strong, aliphatic C–H bonds, resulting in a lack of understanding of what factors facilitate this reactivity. Here, we report the isolation and characterization of a new terminal CoIII-oxo complex, PhB(AdIm)3CoIIIO. Upon oxidation a transient CoIV-oxo intermediate is generated that is capable of hydroxylating aliphatic C–H bonds with an extrapolated \( k_1 \) for C–H activation \( >130 \text{ s}^{-1} \) at 4 °C, comparable to values observed in cytochrome P450 enzymes. Experimental thermodynamic values and DFT analysis demonstrate that although the initial C–H activation step in this reaction is endergonic, the overall reaction is driven by an extremely exergonic radical rebound step, similar to what has been proposed in cytochrome P450 enzymes. The rapid C–H hydroxylation reactivity displayed in this well-defined system provides insight into how hydroxylation is accomplished by biological systems and similarly potent synthetic oxidants.

INTRODUCTION

Direct C–H activation and hydroxylation of unactivated aliphatic bonds is a challenging but powerful transformation for the efficient synthesis of complex organic molecules and pharmaceuticals, many of which have oxygenated functionalities.1,2 Nature has evolved enzymatic systems that rapidly and selectively hydroxylate aliphatic C–H bonds.3,4 An archetypal example is CYP119, a cytochrome P450 enzyme that hydroxylates the C–H bonds in fatty acids (BDE ~ 101 kcal/mol) with second order rate constants as large as \( 10^4-10^7 \text{ M}^{-1}\text{s}^{-1} \) at 4 °C.5–7 The remarkable reactivity of this system has motivated intense efforts to understand what factors underpin its activity. A recent analysis of the thermodynamics of this system shows that the initial C–H activation step is uphill, but extremely fast rates are enabled by a highly favorable rebound to the in situ generated carbon radical.7–9

In addition to biological systems, there has been concerted effort in discovering catalysts that mediate C–H hydroxylation reactivity in a synthetic context.10–16 Many of these systems invoke transition metal-oxo intermediates,14,15,17–20 and selectivity is noted to be greater in systems that have an extremely fast rebound step that avoids long-lived radical intermediates that can engage in side reactions.15,18,19 In parallel, there has been significant interest in the detailed study of C–H activation by isolable, well-characterized transition metal-oxo complexes in order to better understand what factors govern the reactivity of enzymatic and synthetic catalysts. However, in most of these cases the activation of strong bonds, such as aliphatic C–H bonds, is rarely observed or slow, in direct contrast to the rates of C–H oxidation by P450s. This muted reactivity with strong C–H bonds by well-defined systems is often attributed to free energy considerations. These relatively stable transition metal-oxo intermediates frequently have BDFE O–H < BDE C–H which, as illustrated by the Bell-Evans-Polanyi relationship and extensive literature precedent, results in inhibited reactivity.21–24 The dichotomy of stabilization at the expense of reactivity results in a scarcity of metal-oxo complexes that activate strong C–H bonds where the thermodynamics are known with fidelity,25–33 and in these limited examples the rates of reaction are slow when BDE C–H > BDFE O–H.30–32 In particular, late transition metal-oxo complexes, which are frequently invoked as potent oxidants, have not displayed this reactivity from well-characterized examples.34–36 The activation of strong tert-butyl C–H bonds in Co complexes has been observed, but hydroxyl radicals are invoked in these reactions and it’s unclear whether this reactivity stems from bona fide metal-oxo intermediates.26,25,28 Gas phase C–H activation of cyclohexane (BDE = 99.5 kcal/mol) by a transient CoIV-oxo complex has been reported, but the relevant reaction free energies are unknown.27 Thus, while it has been proposed that endergonic C–H activation followed by exergonic rebound is central to selective catalysis by both molecular and enzymatic systems, examples of well-characterized transition metal-oxo systems where these steps can be studied are rare.

We recently reported the C–H activation reactivity of an isolable CoIII-oxo complex which displays unusual kinetic trends. As expected, the comparatively low BDFE O–H of this system resulted in no reactivity with strong C–H bonds.36 Additionally, no evidence for oxygenated products arising from rebound was observed. We rationalized that a CoIV
oxidation state would provide a more potent oxidant for strong C–H bonds. Furthermore, rebound to produce oxygenated products might be facilitated by the more favorable generation of a CoIII complex as opposed to a CoI product. However, oxidation of the previously reported PhB(BuIm)3CoIIIO results in intractable mixtures of products. Therefore, we decided to pursue a CoIV oxidation state with a bulkier and more donating ligand featuring adamantyl (Ad) groups to support an oxidized metal center, protect the reactive Co–O unit, and inhibit side reactions.37

Here, we show that 1 e− oxidation of an Ad-substituted terminal CoIII-oxo complex results in a more active oxidant which activates aliphatic C–H bonds with subsequent rebound. C–H activation proceeds through a transient and highly reactive CoIII-oxo intermediate. This unusual high valent late transition metal-oxo species can nonetheless be observed spectroscopically. Detailed characterization of the thermodynamics of this system shows an endergonic initial C–H activation step. Nonetheless, this reaction is exceptionally fast, with a first order rate constant >103 M−1s−1, comparable to those measured for P450 enzymes. Computational analysis supports that these fast rates are driven by extremely favorable rebound, which parallels and supports mechanistic proposals for enzymatic hydroxylations. These results provide detailed experimental validation on how unfavorable C–H activation can be facilitated by favorable radical rebound.

RESULTS AND DISCUSSION

Synthesis and Characterization of Complexes 1-4

We began our pursuit of a more active oxidant by synthesizing the CoIII-oxo complex, PhB(AdIm)3CoIIIO (4, PhB(AdIm)= tris(1-adamantyl-imidazol-2-ylidene)phenyl borate), and the relevant precursors analogously to our previously reported system (Scheme 1).38 Deprotonation of [PhB(AdImH)3][OTf]2 with 3.05 equivalents of lithium diisopropylamide followed by addition of 1 equivalent of CoCl2 results in the formation of PhB(AdIm)3CoIIICl (1) which can be isolated as a bright blue solid in 78% yield. Thorough characterization including NMR and EPR spectroscopies confirm the assignment and purity of this S = 3/2, pseudo-tetrahedral chloride complex (See SI). Single crystal X-ray diffraction (SXRD) reveals that the Co–Cl and Co–C bond lengths in the first coordination sphere (Figure 1, Table S3) are slightly shorter than those observed in the analogous complex with tert-butyl (Bu) substituents on the ligand.39 This observation is consistent with the stronger donation from the Ad substituents.

Treatment of complex 1 with 3 equivalents of NaOH in tetrahydrofuran (THF) produces the CoIV-hydroxide complex PhB(AdIm)3CoIIIOH as a bright violet powder in 57% yield (2, Scheme 1, See SI). Cyclic voltammetry of 2 collected in THF shows a quasi-reversible couple at −440 mV vs. Fc/Fc+ (Fc = ferrocene). This couple is substantially more negative than that observed for the tBu-substituted system (−230 mV vs. Fc/Fc+) suggesting that this compound is more easily oxidized, as expected from the stronger donation of the Ad-substituents. Consistently, the SXRD structure of 2 (Figure 1, Table S3) also displays shorter Co–O and Co–C bonds.38

Oxidation of 2 with 1 equivalent of FcBF4 in THF at −35 °C affords the diamagnetic CoIV-hydroxide complex, [PhB(AdIm)3CoIIIOH][BF4] (3, Scheme 1), as a bright green species. Similarly to our previously reported system,38 3 is thermally unstable. Nonetheless, it is long-lived enough at −35 °C for characterization by low temperature NMR and UV-visible (UV-vis) spectroscopies which reveal a diagnostic O–H resonance (Figure S7) and a strong absorbance at 718 nm (Figure S26), respectively. Single crystals of 3 can also be obtained by layering in situ generated solutions of 3 in THF under cold pentane and allowing them to diffuse at −35 °C. The SXRD structure of 3 (Figure 1) displays a distortion away from pseudo-tetrahedral symmetry, similar to that observed in the ‘Bu-substituted complex.38,40

Deprotonation of complex 3 should result in the formation of the desired CoIII-oxo complex. However, use of the previous base hexamethyldisilazide38 (HMDS) results in impure mixtures of 2 and a new species, PhB(AdIm)3CoIIIO (4). We hypothesized this was due to slow deprotonation from the steric hindrance between HMDS and the Ad

![Scheme 1. Synthesis of Complexes 1-4](image)

**Figure 1.** Crystal structures of complexes 1-4. Thermal ellipsoids are shown at 50% probability. All H–atoms besides those bound to O are omitted for clarity. Counterions and solvent molecules except for the Et2O hydrogen-bonding to the O–H in 3 are also omitted.
groups, which allowed for competitive reduction of 3 by HMDS. Indeed, switching to a sterically less encumbered and less reducing base in the form of potassium tert-butoxide (KOBu) enables the isolation of the pure terminal oxo complex 4 as dark purple crystals in variable yields (22–55%, Scheme 1). Complex 4 is diamagnetic and has been thoroughly characterized by a variety of techniques including IR spectroscopy (See SI) and SXRD (Figure 1). Comparison of the IR spectra of as synthesized 4 and its 18O-isotopologue reveals a Co–O vibration at 807 cm–1 which shifts to 775 cm–1 upon labeling, as expected from a simple harmonic oscillator approximation (Figure S42). This stretching frequency is consistent with a strong Co–O multiple bond. Additionally, a short Co–O bond length of 1.655(3) Å is observed in the SXRD structure (Figure 1), also consistent with a strong multiple bond.41

A more detailed discussion comparing 4 and the tBu-substituted CoIII-oxo complex is warranted. Initial comparison of the Co–C bond lengths in these two complexes shows that on average, the Co–C bond lengths are ~0.02 Å shorter in 4 (Table 1). This is again consistent with the increased donation of the Ad-substituted ligand. Additionally, the Co–O bond length is observed to be ~0.03 Å shorter in 4 than PhB(tBuIm)3CoIIO (Table 1). This could suggest a stronger Co–O bond in 4. However, IR spectroscopic data and density functional theory (DFT) analysis of the Co–O bonding in these two complexes suggests this is not the case. The Co–O stretching frequency in 4 is 807 cm–1, compared to 815 cm–1 in PhB(tBuIm)3CoIIO (Table 1). This difference in stretching frequency corresponds to a bond length difference of only ~0.005 Å according to a Badger’s Law analysis, which is approximately the error in the SXRD bond lengths. The similarity in Co–O stretching frequencies is more consistent with a comparable Co–O bond length between the two complexes. DFT analysis further supports this similarity. The DFT predicted Co–O bond lengths and stretching frequencies are very similar (Table 1) and the computed delocalization index41 (DI, a measure of the covalent bond order) is identical for both bonds (Table 1). Together, the DFT analysis and IR spectroscopic data support an almost identical bonding interaction between Co and O in complex 4 and PhB(tBuIm)3CoIIO despite the slightly different Co–O stretching frequencies. The observed shorter bond length in the crystal structure of 4 may reasonably be attributed to crystal packing effects instead of a stronger Co–O bond.

Despite the similarity of the Co–O bonds, there are notable differences in key thermodynamic parameters between these two systems.45 Measurement of the CoIII-hydroxide/CoIII-oxo redox potential and the pK_a for deprotonation of the CoIII-hydroxide complex in each case (Equation 1, Scheme S1, C is the standard reduction potential of H^+/H in a particular solvent).45,46 Examining the values reported in Table 1, it is evident that the Ad-substituted system is ~200 mV less oxidizing than the tBu-substituted system, but is ~3 pK_a units more basic once the experimentally measured values are extrapolated to DMSO for more direct comparison. This results in a ~2 kcal/mol stronger O–H bond in 2 than in PhB(tBuIm)3CoIIOH. Therefore, we might expect 4 to be a slightly more potent H–atom abstractor. Additionally, the contributions to the BDFEO–H are more imbalanced in the Ad-substituted system than in the tBu-substituted system. We might reasonably expect 4 to activate C–H bonds more asynchronously than was previously shown for PhB(tBuIm)3CoIIO due to a more imbalanced transition state.36

BDFEO–H = 1.37pK_a + 23.06E1/2 + C   \hspace{1cm} (1)

**Oxidation of Complex 4**

To initially explore the oxidation of 4, a cyclic voltammogram (CV) was collected in THF (Figure S48). This shows an irreversible oxidation feature near 0 V vs Fc/Fc+. Closer examination of this feature reveals an initial shoulder with a peak potential Ep,sh = −0.12 V vs Fc/Fc’ that appears before the main feature with Ep = +0.085 V vs Fc/Fc’. We hypothesized that these features could correspond to an initial oxidation to a putative CoIV-oxo intermediate (4ox) followed by a rapid chemical step to produce a second intermediate that could be further oxidized at a similar potential.

The initial oxidation seen by CV should reasonably produce a CoIV-oxo intermediate that could engage in C–H activation reactivity to produce 3 as the metal-containing product. Therefore, we sought to characterize the BDFEO–H in 3. Using Ep,sh as the upper bound for the true value of the 4/4ox redox potential and the pK_a of 3 (Table 1, Equation 1, Scheme S2), we can calculate an upper bound for the BDFEO–H in 3 of 94 kcal/mol. This is ~7 kcal/mol stronger of an O–H bond than that in 2. As predicted, oxidation to produce a putative CoIV-oxo intermediate results in a species that has a greater driving force for H–atom abstraction. This high BDFEO–H, and the commensurately high reactivity of this putative CoIV intermediate, could explain the irreversibility observed in the CV collected at room temperature. Nonetheless, related species with comparable BDFEO–H values have
been observed and characterized previously at low temperatures, so we pursued the low-temperature oxidation of to investigate possible intermediates as well as C–H oxidation reactivity.

We initially monitored these reactions by UV-vis spectroscopy in THF at –80 °C. Addition of 1 equivalent of FcBF₄ to a solution of 4 results in a very rapid (complete within <3 minutes) and relatively clean transformation to a new spectrum with absorbances at 434 nm, 478 nm, 534 nm, and 708 nm (Figure S26). This resulting spectrum does not change appreciably until warming above 0 °C. The absorbance at 708 nm is similar to the diagnostic 718 nm band observed in the UV-vis spectrum of 3 (Figure S23). This suggests that instead of observing 4ox as a discrete intermediate, 3 is produced by rapid C–H activation by 4ox.

We turned to low temperature NMR spectroscopy to provide further insight into the products of this reaction. A solution of FcBF₄ in CD₃CN was mixed with a solution of 4 in THF-d₈ at –35 °C and allowed to react for ~15 minutes before a ¹H NMR spectrum was collected at –30 °C. No paramagnetic species are observed, precluding non-integer spin 4ox as a likely component in this reaction mixture. On the other hand, some amount of 3 was produced in this reaction as indicated by a set of ¹H NMR features (blue highlighted peaks in Figure 2A) that match those observed for independently prepared 3. Interestingly, the observation of the diagnostic O–H resonance at 10.60 ppm indicates that solvent C–H activation is not the source of that H–atom, since this experiment was carried out in deuterated solvent. The ¹H NMR spectrum also shows there is another species in solution (red highlighted peaks in Figure 2A, 5) that is highly asymmetric, resulting in each imidazol-2-yldene arm being inequivalent to each other and giving rise to 6 separate Im–H resonances. The observation of these asymmetric signals is consistent with C–H activation of the Ad group on one arm of the ligand (Scheme 2A), putatively by 4ox.

While 3 decays at room temperature (see above), the new diamagnetic species 5 is thermally stable which allowed for detailed 1D and 2D NMR spectroscopic characterization (See SI). Based on these results, complex 5 can be assigned as the chiral Co³⁺-alkoxide product, [PhB(t⁴Ad)₆(t⁴AdIm)Co³⁺][BF₄] (Scheme 2B). The formulation of 5 is just one H–atom away from the expected Co⁰ product (4reb, Scheme 2A) that might be expected as a result of C–H activation of an Ad group by 4ox followed by rebound.
to form a C–O bond. We propose that this net H–atom is lost to form 5 via in situ oxidation of 4reb by Fc⁺ with subsequent proton transfer to 4 (Scheme 2B). This explains the observation of 3 as a product in this reaction mixture which should be formed in a 1:1 molar ratio with 5. Indeed, integration of the 1H NMR spectrum reveals ratios consistent with this mechanistic proposal (Figure 2A). The resonance at 6.94 ppm corresponds to 1 Im–H in asymmetric 5 while the resonance at 7.29 ppm corresponds to 3 Im–H in symmetric 3. As expected for a 1:1 molar ratio of 5:3, these resonances integrate in a 1:3 ratio.

The overall reaction shown in Scheme 2 should result in a maximum 50% yield of 5 relative to the Fc formed during the reaction. Indeed, this yield is observed in 1H NMR spectra collected of solutions warmed to room temperature after oxidation. Additional support for the proposed formation of 5 from 4reb shown in Scheme 2B comes from experiments carried out with the addition of 2 equivalents of FcBF₄ to 4 in the presence of 1 equivalent of KO·Bu. When this reaction is monitored by UV-vis spectroscopy at ~80 °C, the growth of a strong absorbance near 700 nm, diagnostic for the presence of 3 in solution, is dramatically attenuated (Figure S32). Additionally, monitoring this reaction by 1H NMR spectroscopy at ~35 °C shows very little 3 as assayed by the diagnostic O–H resonance (Figure S21). Analysis of these solutions by 1H NMR spectroscopy after the reaction has been warmed to room temperature shows that the yield of 5 relative to Fc is increased to ~90% (Figure S20).

Complex 5 was therefore synthesized in bulk using 2 equivalents of FcBF₄ and 1 equivalent of KO·Bu and isolated in 64% yield. This compound has been thoroughly characterized, including by elemental analysis (See Experimental and SI). The assignment of 5 was also confirmed by X-ray diffraction data collected on single crystals of the ion-exchanged BAR₄⁺ salt (BAR₄⁺ = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate, see Experimental) grown from an Et₂O solution layered under pentane (Figure 2B). Due to complicated disorder of the O–atom over multiple positions, the data quality is only suitable to confirm the connectivity of the atoms in 5. Nonetheless, the Co–O–C unit is clearly observed and the presence of a single BAR₄⁺ ion supports a CoIV complex with an alkoxide ligand. Taken together, these observations support the formation of the terminal product 5 from rapid intramolecular C–H activation by 4ox and subsequent rebound to form 4reb followed by the intermolecular reactivity shown in Scheme 2.

Observation of the CoIV Intermediate 4ox

The reaction mechanism shown in Scheme 2A invokes a key CoIV-oxo intermediate. Such high-valent Co complexes are quite rare although they have been invoked as reactive intermediates. 27,28,34,35,47,48 While there is one example of a spectroscopically characterized terminal CoIV-oxo species, it does not engage in the activation of aliphatic C–H bonds. 35 Therefore, we set out to observe any transient CoIV complex in order to support the proposed agency of 4ox. We first monitored addition of FcBF₄ to solutions of 4 by UV-vis spectroscopy at temperatures lower than ~80 °C in the hopes of slowing down the reaction enough to observe 4ox. However, no evidence for an intermediate is discernible in the UV-vis spectra of reactions carried out in THF at ~105 °C or in 2-MeTHF at ~130 °C (See SI). We turned to EPR spectroscopy in the hopes of observing an S = 1/2 signal in solutions prepared by mixing FcBF₄ and 4 at low temperatures (~105 °C in THF or ~130 °C in 2-MeTHF) followed by freezing in liquid nitrogen. However, no S = 1/2 signal consistent with a CoIV intermediate can be observed in these experiments.

C–H activation reactions mediated by transition metal-oxo and hydroxide complexes frequently have large deuterium kinetic isotope effects (KIEs), especially at low temperatures. 26,49,50 Furthermore, deuteration of reactive C–H groups on ligands has previously enabled the characterization of transient oxo intermediates. 31 Therefore, we reasoned that we would be able to observe 4ox by slowing down the reaction through deuteration of the Ad groups on the ligand in 4. This was achieved on a small scale starting from adamantane-d₁₆. The starting material for the first step of the ligand synthesis, 31 1-bromo adamantane-d₁₆, was synthesized by refluxing adamantane in bromine for 3 hours. 52 After work up, 1-bromo adamantane-d₁₆ was isolated in 73% yield. With this material in hand, 1-(adamantyl-d₁₃)-imidazole and PhB(Ad-d₁₅)OTf were made following the reported procedures for the synthesis of the prototype compounds. 31 Finally, following the procedures reported here (See Experimental), the compounds 1-d₁₅, 2-d₁₅, and 4-d₁₅ were made. Unfortunately, after this lengthy synthetic route, the obtained 4-d₁₅ was contaminated with a 29% impurity of 2-d₁₅ as determined by 1H NMR spectroscopy. Fortunately, this impurity can be easily accounted for during subsequent analysis of the reactions as described below.

Oxidation of 4-d₁₅ with FcBF₄ in THF-d₈ at ~105 °C was initially followed by UV-vis spectroscopy (Figure S33). After collection of an initial spectrum, 1 equivalent of FcBF₄ was injected into the cuvette and a spectrum was collected beginning ~5 seconds after injection. Additional spectra were collected every 45 seconds. Examination of the spectra >900 nm shows immediate consumption of 4-d₁₅ upon addition of oxidant, as evidenced by the disappearance of the trailing absorbance from 4-d₁₅ in the first scan after injection, followed by no further changes over time. This is in contrast to the oxidation of 4, where only ~1/2 of 4 is consumed immediately after injection of FcBF₄, as the other 1/2 equivalent of FcBF₄ is consumed by the rapidly produced 4reb. A slower disappearance of the additional 1/2 equivalent of 4 occurs during the putative proton transfer step, consistent with the mechanism shown in Scheme 2. Thus, for the oxidation of 4-d₁₅, it is likely that all oxidation equivalents are consumed in the generation of 4ox-d₁₅ without any convolution from the immediate formation of 4reb or 5. After spectral decomposition to remove features from the small amount of 3-d₁₅ generated from the 2-d₁₅ impurity, we observe a spectrum with features at 492 nm, 552 nm, and 616 nm (Figure S34). This spectrum displays generally good agreement with the spectrum predicted by TD-DFT calculations carried out on 4ox (Figure S34), even considering the limited accuracy of computational methods in predicting such spectra. 32 This correlation supports that we are indeed observing this proposed CoIV intermediate.

We additionally looked at this reaction by EPR spectroscopy. Fortunately, any 3-d₁₅, which is diamagnetic, that
would be generated from the $2\cdot d_{5s}$ impurity will be silent by EPR spectroscopy, preventing any signal convolution as was seen in UV-vis spectroscopy. Preparation of samples at $-105^\circ \text{C}$ in THF-$d_8$ followed by immediate freezing in liquid nitrogen and collection of data within 5 minutes at 15 K reveals a unique $S = 1/2$ signal (Figure 3). Simulation of this signal gives $g$-values of 2.0439, 2.0238, and 2.0218. There is also a B-line pattern arising from coupling to the $I = 7/2$ $^{59}\text{Co}$ nucleus. This pattern can be simulated with hyperfine coupling constants of $A = 16.6, 76.2$, and $-0.2$ MHz. These simulated parameters are consistent with an $S = 1/2$ Co complex, as proposed for this $d^3$ CoV-Oxo species. These parameters are also in line with those that have been reported previously for other $S = 1/2$ Co$^{IV}$ complexes. In particular, $4\cdot d_{45}$ displays relatively small hyperfine coupling constants that are more similar to those reported for spin delocalized systems than those reported for systems where the spin is highly localized on the $^{59}\text{Co}$ nucleus. This, in addition to the $g$-values near 2, suggests that there is likely a significant amount of O-centered spin density in $4\cdot d_{45}$. IBO analysis predicts a population of 0.44 spins on O,$^{60,61}$ consistent with this hypothesis. Regardless, the UV-vis and EPR spectroscopic data for the oxidation of $4\cdot d_{45}$ support the presence of $4\cdot ox$ as an intermediate in the reaction outlined in Scheme 2.

Analysis of C–H Activation by $4\cdot ox$

While the above data from reactions with $4\cdot d_{45}$ support the agency of $4\cdot ox$ in this system, the fleeting nature of this and other intermediates invoked in Scheme 2A, namely $4\cdot rad$ and $4\cdot reb$, prompted us to use density functional theory calculations to optimize these possible intermediates and analyze the free energies of this proposed mechanism (Figure 4). These calculations reveal that the initial C–H activation step to produce $4\cdot rad$ is endergonic with $\Delta G = +3.3$ kcal/mol. This result agrees with our experimentally determined thermodynamics; we calculate an upper bound for the BDE$_{\text{OE-OH}}$ in 3 as 94 kcal/mol (see above), and the BDE$_{\text{C-H}}$ for the CH$_2$ groups in free adamantane is 98.5 kcal/mol.$^{62}$ Using these as good approximations for the C–H bond broken and the O–H bond formed to give the intermediate $4\cdot rad$, we would estimate that $\Delta G = +4.5$ kcal/mol for C–H activation.

Despite this initial endergonic step, productive reactivity does occur to form 5, presumably through the intermediate $4\cdot reb$. This must be driven by a favorable secondary reaction, since ground state thermodynamics would predict that for a reaction with $\Delta G > 0$, any equilibrium would heavily favor the reactants in the first step. Indeed, this idea is supported by the very exergonic secondary reaction predicted by DFT to produce $4\cdot reb$ from $4\cdot rad$ (Figure 4) with $\Delta G = -42$ kcal/mol. This second step only has a barrier of 1.1 kcal/mol from $4\cdot rad$ and would be expected to proceed very rapidly whenever $4\cdot rad$ is formed. This combination of a very exergonic step
with almost no barrier likely contributes to favoring formation of \( \text{4}_{\text{oxy}} \) and ultimately the observed product \( \text{5} \).

We can contrast this result to the analogous Co\( ^{\text{III}} \) system (complex 4) which does not engage in this reactivity. Samples of 4 are stable at \(-35^\circ\text{C}\) for weeks and can be handled at room temperature over hours, while all attempts at isolating \( \text{4}_{\text{oxy}} \) result in rapid formation of 5. DFT analysis of the same reaction coordinate for the Co\( ^{\text{III}} \) system (Figure S50) reveals that the initial C–H activation step is now 17 kcal/mol uphill from 4 while the rebound step to produce a Co\( ^{\text{I}} \) complex is only 19 kcal/mol downhill from the Co\( ^{\text{II}} \) intermediate (See SI). Not only is there less driving force for rebound in this system, but the formation of a Co\( ^{\text{I}} \) complex is essentially thermoneutral from the starting complex 4. This highlights that by oxidizing to a formally Co\( ^{\text{IV}} \) oxidation state, we are able to engage in more difficult reactivity by a) utilizing a stronger oxidant to enable the initial C–H activation step and b) driving the overall reaction with an extremely favorable secondary rebound step, which is not accessible for a Co\( ^{\text{III}} \) starting material.

We also sought to contextualize the rate of C–H activation by \( \text{4}_{\text{oxy}} \) by comparing to other examples in the literature. Most isolable transition metal-oxo (or related) complexes that engage in uphill reactivity do so at very slow rates.\(^{30,31,46} \) In contrast, cytochrome P450 enzymes are known to react with the strong C–H bonds in fatty acids with second order rate constants on the order of \( 10^4-10^7 \text{ M}^{-1}\text{s}^{-1} \) and a first order rate constant for C–H activation after substrate is bound has been estimated at \( >1400 \text{ s}^{-1} \) at \( 4^\circ\text{C} \).\(^5 \) We note that care must be taken in comparing the rate constants of these bimolecular reactions in synthetic examples with enzymatic reactions. Nonetheless, we set out to estimate the first order rate constant for C–H activation by \( \text{4}_{\text{oxy}} \) in order to see how the present system compares to one of the most kinetically active oxidants known.

Given our inability to isolate \( \text{4}_{\text{oxy}} \) upon oxidation of 4, we are unable to directly measure the rate constant for C–H activation. However, the rapid kinetics of the reaction necessitate that the rate of C–H activation must be greater than the rate of oxidation of 4 by FcBF\(_4\). Therefore, in order to provide a lower bound on the rate of C–H activation by \( \text{4}_{\text{oxy}} \), we estimated the rate of oxidation of 4 by the method of initial rates.\(^{61} \) Unfortunately, the rate of this reaction is at the limit of measurable rates for our experimental apparatus, so we were only able to provide a lower bound for the rate constant for oxidation (See Experimental and SI). Nonetheless, we estimated the lower bound of the second order rate constant for oxidation of 4 by FcBF\(_4\) as \( 440\pm50 \text{ M}^{-1}\text{s}^{-1} \) at \(-80^\circ\text{C} \). We carried out this analysis at two additional temperature, \(-105^\circ\text{C} \) and \(-40^\circ\text{C} \), in order to estimate the second order rate constant at \( 4^\circ\text{C} \) for direct comparison to P450. This analysis gives us a lower bound on the second order rate constant for oxidation of \( 1.1(6)\times10^3 \text{ M}^{-1}\text{s}^{-1} \) at \( 4^\circ\text{C} \). To convert this oxidation rate constant to a C–H activation rate constant, we used our assumption that the rate of C–H activation by \( \text{4}_{\text{oxy}} \) is greater than the rate of oxidation at any point during the reaction. If we assume that an upper bound for the maximum buildup of \( \text{4}_{\text{oxy}} \) is 1% of initial concentration of 4, then we can use this lower bound for \( k_c \) to determine a lower bound for the first order rate constant for C–H activation by \( \text{4}_{\text{oxy}} \) as \( 1.3(7)\times10^2 \text{ s}^{-1} \) at \( 4^\circ\text{C} \) (See Experimental, Equation 12).

This first order rate constant is large and comparable to that reported for C–H activation by cytochrome P450 enzymes, \( \sim10^3 \text{ s}^{-1} \) at \( 4^\circ\text{C} \). This large rate constant is also consistent with the relatively low energy of the transition state predicted by DFT (Figure 4). In fact, this system has many parallels to the proposed factors that enable the remarkable reactivity of P450. It has been recently argued that the reactivity of P450 is enabled by a thermodynamically favorable rebound immediately following unfavorable C–H activation, exactly the scenario at play in this Co-based system.\(^7 \) These similarities suggest that the C–H activation exhibited by the terminal metal-oxo \( \text{4}_{\text{oxy}} \) is biomimetic, and that the strategy of enabling uphill C–H activation with a rapid and favorable rebound step can be general across synthetic and natural systems.

**CONCLUSIONS**

We have isolated and characterized a new terminal Co\( ^{\text{III}} \)-oxo complex. Oxidation of this complex results in an unusual and highly reactive Co\( ^{\text{IV}} \)-oxo intermediate which rapidly activates a C–H bond on the ligand. While this initial C–H activation step is endergonic, an extremely favorable rebound step to form a C–O bond enables the overall reactivity. This mechanistic scenario has been confirmed by the isolation and characterization of the chiral Co\( ^{\text{III}} \)-alkoxide compound 5 as well as spectroscopic characterization of the deuterated intermediate \( \text{4}_{\text{oxy}} \text{-d}_{28} \). DFT calculated reaction energetics as well as spectroscopic parameters also support this picture.

Efforts to measure the kinetics of C–H activation provide a lower bound for the first order rate constant for C–H activation of \( 130 \text{ s}^{-1} \), a value comparable to the \( 1400 \text{ s}^{-1} \) value determined for C–H activation by compound 1 in P450 enzymes.\(^3 \) Thus, by oxidizing a terminal Co\( ^{\text{III}} \)-oxo complex, we are able to generate a hydroxylating intermediate that is capable of activating strong C–H bonds with similar rate constants and mechanistic features to enzymatic systems. These studies constitute one of the few well-characterized examples of activation of strong C–H bonds by a transition metal-oxo complex. In particular, this well-defined system, where we can measure and determine thermodynamic parameters, validates the proposed importance of rebound in enzymatic and synthetic catalysts.

**EXPERIMENTAL SECTION**

**Materials and Instrumentation.** All manipulations were performed under a dry nitrogen atmosphere using either standard Schlenk techniques or in an mBraun Unilab Pro glovebox unless otherwise stated. All chemicals were obtained from commercial sources and used as received unless otherwise stated. Adamantane-d_{28} was purchased from CDN Isotopes and used as received. Solvents were dried on a solvent purification system from Pure Process Technologies before storing over 4 Å molecular sieves under N2. Tetrahydrofuran (THF), THF-d_{6} and diethyl ether (Et\(_2\)O) were stirred over NaK alloy and passed through a column of activated alumina prior to storing over 4 Å sieves under N2. PhB\((\text{Me})_2\text{OTf}_2 \) and NaBAR\(_4\) were prepared according to previously reported procedures.\(^{37,64} \) [HMTBD][BF\(_4\)] was
Synthesis of 1-bromoadamantane-\(d_{15}\). This compound was synthesized following a previously reported procedure.\(^{32}\) A 50 mL round bottom flask equipped with a stir bar was charged with 2.0 g (13 mmol) of adamantane-\(d_{15}\) and 5.0 mL of \(\text{Br}_2\) (97 mmol). After reflux condenser was added and loosely capped with a septum equipped with a vent needle. The mixture was heated to reflux (~60 °C) for 3 h before being cooled to room temperature. The mixture was diluted with \(\text{CCl}_4\) (20 mL) and transferred to a separatory funnel. The solution was washed with saturated sodium bisulfite (NaHSO\(_3\)) solution in 10 mL portions until the Br\(_2\) color was gone. CAUTION: Lots of heat and gas is released during this step. Take appropriate safety precautions. The now pale yellow \(\text{CCl}_4\) solution was washed twice with \(\text{H}_2\text{O}\) before drying over \(\text{MgSO}_4\) and filtering to give a clear yellow solution. The solvent was removed \textit{in vacuo} and the residue recrystallized from MeOH to give pure 1-bromoadamantane-\(d_{15}\) in 73% yield (2.21 g, 9.5 mmol). \(^1\text{H}\) NMR (CDCl\(_3\), 76.8 MHz): \(\delta\) 2.33 (6\(\text{H}\)), 2.06 (3\(\text{H}\)), 1.68 (6\(\text{H}\)).

Synthesis of 1-(adamantyl-\(d_{15}\))-imidazole. This compound was synthesized analogously to 1-adamantylimidazole.\(^{37}\) A 100 mL Schlenk tube with a Kontes valve was charged with 2.21 g (9.5 mmol) 1-bromoadamantane-\(d_{15}\), 2.6 g (38 mmol) imidazole, 2.0 mL toluene, and a stir bar. The Schlenk tube was sealed and heated to 150 °C behind a blast shield for 36 hours. CAUTION: Explosion hazard due to heating above the boiling point of toluene in a sealed vessel. After the reaction, the mixture was allowed to cool to room temperature before being unsealed and mixed with 50 mL of 1 M KOH. Dichloromethane (DCM, 50 mL) was added and the mixture transferred to a separatory funnel. The DCM layer was collected, dried over \(\text{MgSO}_4\), filtered and down to a brown, sticky residue. Extraction into hot hexanes and removal of the solvent \textit{in vacuo} afforded 1-(adamantyl-\(d_{15}\))-imidazole in 55% yield (1.12 g, 5.2 mmol). \(^1\text{H}\) NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.63 (1\(\text{H}\), Im-\(H\)), 2.06 (2\(\text{H}\), Im-\(H\)). \(^1\text{H}\) NMR (CDCl\(_3\), 76.8 MHz): \(\delta\) 2.19 (3\(\text{H}\), Ad-\(d_{-2-H}\)), 2.05 (6\(\text{H}\), Ad-\(d_{-2-H}\)), 1.70 (6\(\text{H}\), Ad-\(d_{-2-H}\)).

Synthesis of PhB(Ad-\(d_{15}\)-ImH)\(_3\).OTf\(_2\). This compound was synthesized analogously to PhB(Ad\(_{15}\)-ImH)\(_3\).OTf\(_2\).\(^{37}\) Toluene (7 mL), PhBCl\(_2\) (240 μL, 1.8 mmol), 1-(adamantyl-\(d_{15}\))-imidazole (1.2 g, 5.5 mmol), and TMSCOTf (670 μL, 3.6 mmol) were combined in a 50 mL round bottom Schlenk flask. The flask was equipped with a reflux condenser under active N\(_2\) flow and the heterogeneous mixture was heated to 100 °C overnight before being allowed to cool to room temperature. The solvent was decanted and the solid dissolved in boiling DCM. This solution was stored at ~35 °C until pure PhB(Ad-\(d_{15}\)-ImH)\(_3\).OTf\(_2\) crystallized as a white solid (714 mg, 0.69 mmol, 37% yield). \(^1\text{H}\) NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.30 (3\(\text{H}\), Im-\(H\)), 7.42 (6\(\text{H}\), Im-\(H\), Ph-\(H\)), 7.27 (3\(\text{H}\), Im-\(H\)), 7.23 (2\(\text{H}\), Ph-\(H\)). \(^1\text{H}\) NMR (CDCl\(_3\), 76.8 MHz): \(\delta\) 2.16 (br, 27\(\text{H}\), Ad-\(d_{-2-H}\)), 1.68 (18\(\text{H}\), Ad-\(d_{-2-H}\)).

Synthesis of 1. To a suspension of 5.0 g (5.0 mmol) of PhB(Ad\(_{15}\)-ImH)\(_3\).OTf\(_2\) in 100 mL THF at ~78 °C was added 3.05 equivalents of LDA (15.4 mmol, prepared in situ from a 1:1 mixture of n-BuLi and HN(\(t\text{Pr}\))\(_2\) in 25 mL THF at ~78 °C). This heterogeneous mixture was allowed to stir at ~78 °C for 1.5 h until the mixture became homogeneous and yellow-pink in color. Solid CoCl\(_2\) (650 mg, 5.5 mmol) was added and the reaction allowed to warm to room temperature with stirring overnight. The solution was pumped down and dried at ~75 °C to ensure complete removal of THF. The blue residue was dissolved in DCM and filtered through Celite to remove LiCl and LiOTf salts. This solution was pumped down and washed with THF. A bright blue solid was collected by filtration and dried to give 1 in 78% yield (3.1 g, 3.9 mmol). Single crystals suitable for X-ray diffraction were grown from a toluene solution of 1 layered under pentane at ~35 °C and had a toluene molecule in the unit cell. \(^1\text{H}\) NMR (CDCl\(_3\), 400 MHz): \(\delta\) 9.27 (3\(\text{H}\), Im-\(H\)), 3.69 (3\(\text{H}\), Im-\(H\)), 12.92 (18\(\text{H}\), Ad-\(H\)), 5.55 (1\(\text{H}\), Ph-\(H\)), 5.42 (9\(\text{H}\), Ad-\(H\)), 5.13 (2\(\text{H}\), Ph-\(H\)), 4.25 (9\(\text{H}\), Ad-\(H\)), 1.80 (2\(\text{H}\), Ph-\(H\)), 0.72 (9\(\text{H}\), Ad-\(H\)). \(^1\text{C}\) NMR (CDCl\(_3\), 100 MHz): \(\delta\) 199.3, 130.6, 128.3, 125.9, 123.8, 112.5, 57.3, 32.5. \(^{11}\text{B}\) NMR (CDCl\(_3\), 128 MHz): \(\delta\) 68.8, \(\mu\text{eB}\) (CD\(_2\)Cl\(_2\)): 43.2 B.M. IR (KBr, cm\(^{-1}\)): 3145 (w), 3070 (w), 3033 (s), 2908 (s), 2853 (s), 1549 (w), 1477 (w), 1453 (m), 1387 (m), 1375 (w), 1359 (m), 1309 (m), 1273 (s), 1240 (w), 1159 (s), 1119 (m), 1103 (m), 1076 (w), 1016 (s), 938 (w), 895 (w), 879 (m), 834 (m), 816 (m), 804 (m), 786 (s), 771 (w), 736 (sh), 725 (sh), 712 (s), 681 (s). UV-vis, nm in THF (\(\epsilon\), M\(^{-1}\) cm\(^{-1}\)): 584 (514), 616 (774), 674 (1007). Anal. Calc. for C\(_{5}\)H\(_{5}\)BClCoN\(_{6}\) (674 (1007)). Anal. Calc. for C\(_{5}\)H\(_{5}\)BClCoN\(_{6}\) (674 (1007)).
at −35 °C. 1H NMR (CD₃CN, 400 MHz): δ 91.32 (3H, Im-H), 44.94 (3H, Im-H), 8.27 (2H, Ph-H), 7.60 (2H, Ph-H), 7.52 (1H, Ph-H), 5.16 (18H, Ad-H), 4.35 (9H, Ad-H), 4.00 (9H, Ad-H), 1.24 (9H, Ad-H). 13C NMR (CD₃CN, 100 MHz): δ 222.1, 139.8, 129.6, 128.3, 126.9, 105.7, 55.3, 39.5. 11B NMR (CD₃CN, 128 MHz): δ 127.3. μeff (C₆D₆): 4.22 B.M. IR (KBr, cm⁻¹): 3173 (w), 3134 (w), 3042 (w), 2906 (s), 2850 (s), 1616 (br), 1534 (br), 1477 (w), 1453 (m), 1433 (w), 1386 (m), 1359 (m), 1329 (m), 129.6, 128.3, 126.9, 105.7, 55.3, 39.5. 11B NMR (CD₃CN, 128 MHz): δ –1.2. UV-vis, nm in THF: ε 458 (1267), 636 (sh, 503), 718 (898).

Synthesis of 2-d₄₅. Isotopically labeled 2 was synthesized following the above procedure, substituting 1-d₄₅ for 1. The purity of 2-d₄₅ was confirmed by 1H NMR spectroscopy.

Synthesis of 2-18O. Isotopically labeled 2 was synthesized following the above procedure, substituting Na¹⁸OH for natural abundance NaOH. The purity of 2-18O was confirmed via 1H NMR spectroscopy.

Synthesis of 3. A solution of 2 in 2.0 mL of THF (25 mg, 33 μmol) was cooled to −35 °C before FcBF₄ (8.9 mg, 33 μmol) was cooled to −35 °C. A solution of FcBF₄ (22 mg, 78 μmol) in 0.5 mL MeCN was added to result in a color change to red-purple. The reaction was allowed to stir for ~15 minutes at −50 °C before pumping down at room temperature. The red residue was triturated with pentane before being washed with Et₂O to remove Fc. The remaining solid was dissolved in MeCN and layered under Et₂O at −35 °C to give pure 3 as a red powder (43 mg, 50 μmol, 64% yield). 1H NMR (CD₃CN, 400 MHz): δ 7.78 (2H, Ph-H), 7.55 (3H, Ph-H), 7.53 (1H, Im-H), 7.46 (1H, Im-H), 7.37 (2H, Im-H), 7.31 (1H, Im-H), 6.87 (1H, Im-H), 3.78 (1H, Ad-H), 2.62 (3H, Ad-H), 2.53 (1H, Ad-H), 2.46 (6H, Ad-H), 2.37 (3H, Ad-H), 2.30 (7H, Ad-H), 2.22 (1H, Ad-H), 2.00 (1H, Ad-H), 1.89-1.76 (16H, Ad-H), 1.72 (3H, Ad-H), 1.60 (1H, Ad-H), 1.47 (1H, Ad-H). 13C NMR (CD₃CN, 100 MHz): δ 134.6, 129.7, 129.5, 127.8, 126.7, 126.5, 123.8, 122.5, 121.4, 80.5, 65.2, 59.5, 59.2, 46.4, 45.7, 43.0, 40.9, 40.0, 37.1, 36.5, 36.3, 36.2, 36.0, 35.7, 31.2, 30.7, 30.5, 30.3, 30.2, 29.9. 11B NMR (CD₃CN, 128 MHz): δ −6.12. 19F NMR (CD₃CN, 471 MHz): δ −151.9. IR (KBr, cm⁻¹): 3173 (w), 3134 (m), 2906 (s), 2852 (s), 1626 (br), 1542 (m), 1450 (m), 1430 (s), 1409 (m), 1380 (m), 1363 (w), 1339 (m), 1306 (m), 1248 (m), 1219 (m), 1192 (s), 1172 (m), 1105 (s), 1062 (s), 1029 (s), 933 (m), 903 (w), 891 (s), 832 (s), 816 (w), 801 (w), 785 (m), 764 (m), 725 (s), 697 (s). UV-vis, nm in MeCN (ε, M⁻¹cm⁻¹): 406 (sh, 799), 492 (736), 526 (695), 648 (sh, 174). Anal. Calc. for C₄₅H₅₆BCoN₆O: C 70.35, H 7.33, N 10.89.

Ion Exchange to Produce 5-BArF₄. A solution of 15 mg (18 μmol) NaBArF₄ in 1.2 mL Et₂O was added to 15 mg (18 μmol) of solid 5. The mixture was allowed to stir until all of the red solid had dissolved into solution. This solution was filtered to remove NaBArF₄ and layered under pentane at −35 °C to afford single crystals of 5-BArF₄ suitable for X-ray diffraction.

Cyclic Voltammetry. For cyclic voltammetry experiments, 5.0 mL of a 3 mM solution of the complex of interest were prepared in THF. Tetrabutylammonium hexafluorophosphate (TBAPF₆) was used as the supporting electrolyte at a concentration of 0.1 M. A glassy carbon electrode with a 3 mm diameter was used as the working electrode with a platinum wire as the counter electrode. A silver wire was used as the reference electrode and referenced to the FeC/Fc⁺
couple. Cyclic voltammograms were collected at a standard scan rate of 100 mV/s.

**Procedure for Determining the pKₐ of 3.** The pKₐ of 3 was determined by titrating 4 with [HMTBD][BF₄]. The titration of 4 with [HMTBD][BF₄] was monitored by ⁱH NMR spectroscopy. As the product of the reaction, 3, is unstable above ~35 °C, the samples were prepared and stored cold and the spectra were collected at ~35 °C. Spectra were collected on three separate samples for each amount of acid added. To prepare a typical sample, 0.25 mL of a 10 mM solution of hexamethyldisiloxane (TMS₂O) in THF-δ was added as an internal standard followed by addition of varying volumes of a 25 mM solution of [HMTBD][BF₄] in THF-δ to reach 0.75, 1.0, or 1.5 equivalents of added acid relative to 4. Finally, the samples were diluted with THF-δ to reach a total volume of 0.50 mL and initial concentrations of 5 mM 4, 5 mM TMS₂O, and 3.75–7.5 mM [HMTBD][BF₄]. It was discovered upon collecting the spectra that all species in solution (3, 4, [HMTBD][BF₄], and MTBD) were in rapid equilibrium resulting in the appearance of coalesced peaks in the ⁱH NMR spectra. The ratios of the concentrations of 3:4 and [HMTBD][BF₄]:MTBD were determined according to Equations 2–4. The peaks used for analysis were an Im-H peak and two Ad-H peaks for 3/4 and the methyl protons of MTBD/[HMTBD][BF₄] (Table S1). From this data the equilibrium constant for the reaction shown in Equation 5, K_eq, was calculated and the values obtained from each 3/4 peak averaged. In THF, these species exist as ion pairs in solution so the calculated equilibrium constant is for those ion pairs, not the true pKₐ values. Using Equations 6 and 7,⁴³ we can calculate ΔpKₐ relative to the pKₐ of [HMTBD]⁺ (18.0 in THF)⁴³ using the methods described in Reference ⁴² to estimate K_eq values (Table S2). Finally, the relationship shown in Equation 8 was used to calculate the pKₐ of 3.

\[
\delta_{obs} = \delta_A x_A + \delta_B x_B
\]  

\[
\frac{[3]}{[4]} = \frac{\delta_{obs} - \delta_4}{\delta_3 - \delta_{obs}}
\]  

\[
\frac{[\text{HMTBD}]}{[\text{HMTBD}^+]} = \frac{\delta_{\text{HMTBD}^+} - \delta_{obs}}{\delta_{obs} - \delta_{\text{HMTBD}}}
\]  

\[
K_{eq} = \frac{[3][\text{HMTBD}^+]}{[4][\text{HMTBD}^+]}
\]  

\[
\Delta pK_{ip} = \log \left( K_{eq} \right)
\]  

\[
\Delta pK_a = \Delta pK_{ip} - \log \left( \frac{K_{3,\text{HMTBD}^+}}{K_{4,3}} \right)
\]  

\[
\Delta pK_a = pK_{a,3} - pK_{a,\text{HMTBD}^+}
\]

**Procedure for Oxidation of 4 in the Presence of Base Monitored by UV-vis Spectroscopy.** In the glovebox, 2.0 mL of a 1.25 mM solution of 4 in THF was transferred to a standard 1 cm cuvette and sealed with a puncturable cap. The cuvette was then transferred to the cryostat and cooled to the desired temperature (~80 °C, ~−80 °C, or ~−105 °C). After an initial scan, 50 μL of a 50 mM solution (1 equivalent) of FcBF₄ in 2:1 THF/MeCN was injected into the cuvette. The reaction was monitored by collecting spectra every 45 seconds until the spectrum stopped changing.

**Procedure for Determining the pKₐ of 3.** The pKₐ of 3 was determined by titrating 4 with [HMTBD][BF₄]. The titration of 4 with [HMTBD][BF₄] was monitored by ⁱH NMR spectroscopy. As the product of the reaction, 3, is unstable above ~35 °C, the samples were prepared and stored cold and the spectra were collected at ~35 °C. Spectra were collected on three separate samples for each amount of acid added. To prepare a typical sample, 0.25 mL of a 10 mM solution of hexamethyldisiloxane (TMS₂O) in THF-δ was added as an internal standard followed by addition of varying volumes of a 25 mM solution of [HMTBD][BF₄] in THF-δ to reach 0.75, 1.0, or 1.5 equivalents of added acid relative to 4. Finally, the samples were diluted with THF-δ to reach a total volume of 0.50 mL and initial concentrations of 5 mM 4, 5 mM TMS₂O, and 3.75–7.5 mM [HMTBD][BF₄]. It was discovered upon collecting the spectra that all species in solution (3, 4, [HMTBD][BF₄], and MTBD) were in rapid equilibrium resulting in the appearance of coalesced peaks in the ⁱH NMR spectra. The ratios of the concentrations of 3:4 and [HMTBD][BF₄]:MTBD were determined according to Equations 2–4. The peaks used for analysis were an Im-H peak and two Ad-H peaks for 3/4 and the methyl protons of MTBD/[HMTBD][BF₄] (Table S1). From this data the equilibrium constant for the reaction shown in Equation 5, K_eq, was calculated and the values obtained from each 3/4 peak averaged. In THF, these species exist as ion pairs in solution so the calculated equilibrium constant is for those ion pairs, not the true pKₐ values. Using Equations 6 and 7,⁴³ we can calculate ΔpKₐ relative to the pKₐ of [HMTBD]⁺ (18.0 in THF)⁴³ using the methods described in Reference ⁴² to estimate K_eq values (Table S2). Finally, the relationship shown in Equation 8 was used to calculate the pKₐ of 3.

\[
\delta_{obs} = \delta_A x_A + \delta_B x_B
\]  

\[
\frac{[3]}{[4]} = \frac{\delta_{obs} - \delta_4}{\delta_3 - \delta_{obs}}
\]  

\[
\frac{[\text{HMTBD}]}{[\text{HMTBD}^+]} = \frac{\delta_{\text{HMTBD}^+} - \delta_{obs}}{\delta_{obs} - \delta_{\text{HMTBD}}}
\]  

\[
K_{eq} = \frac{[3][\text{HMTBD}^+]}{[4][\text{HMTBD}^+]}
\]  

\[
\Delta pK_{ip} = \log \left( K_{eq} \right)
\]  

\[
\Delta pK_a = \Delta pK_{ip} - \log \left( \frac{K_{3,\text{HMTBD}^+}}{K_{4,3}} \right)
\]  

\[
\Delta pK_a = pK_{a,3} - pK_{a,\text{HMTBD}^+}
\]
inspection of an anomalous spike in the absorbance data) at 
−40 °C, −80 °C, and −105 °C, respectively. A linear fit of the 
first 30% of the concentration versus time profile gave an 
“initial rate” for the reaction (Figures S32–S34). Typically, 
initial rates are performed on the first 5% of the reaction, 
but mixing limitations precluded this analysis in our case. 
Therefore, this “initial rate” is an underestimation of the 
true rate. Nonetheless, we can use this “initial rate” and the 
initial concentrations of 4 and FcBF₄ to calculate a lower 
bound on the second order rate constant, k₂, for this reaction 
at a given temperature (Equation 9). A linear fit of a plot of 
ln(k₂/T) versus 1/T allows for the extrapolation of this 
lower bound k₂ to other temperatures (Figure S35). Assum-
ing Equation 10 is true, conversion of this lower bound k₂ 
value to a lower bound first order rate constant, k, for C–H 
activation by 4ox was done using Equations 9 and 11 to give 
Equation 12, which was evaluated assuming 1% of initial 4 
had been converted into 4ox. This percentage was chosen 
with the following justification: a reasonable lower bound 
for the concentration of 4ox observable by EPR spectroscopy 
is 1% of the initial concentration of 4. Since we never ob-
served 4ox by EPR, that puts an upper bound on the concen-
tration of 4ox as 1% of the initial concentration of 4. Assum-
ing that during this initial “1%” build-up of 4ox there is no 
loss of 4ox, we can evaluate Equation 12 below with [4] = 

\[
\text{Rate}_{\text{ox}} = \frac{-d[4]}{dt} = k₂ \cdot [4] \cdot [\text{FcBF}_4] 
\] (9)

\[
\text{Rate}_{\text{C–H act}} > \text{Rate}_{\text{ox}} 
\] (10)

\[
\text{Rate}_{\text{C–H act}} = \frac{-d[4^{\text{ox}}]}{dt} = k \cdot [4^{\text{ox}}] 
\] (11)

\[k \cdot [4^{\text{ox}}] > k₂ \cdot [4] \cdot [\text{FcBF}_4] \] (12)

Procedure for Oxidation of 4-d₄₅ Monitored by UV-vis 
Spectroscopy. In the glovebox, 2.0 mL of a solution of 4-d₄₅ 
(contaminated with 29% 2-d₄₅) in THF (1.25 mM total Co 
concentration) was transferred to a standard 1 cm cuvette 
and sealed with a puncturable cap. The cuvette was then 
transferred to the cryostat and cooled to the desired tem-
perature −105 °C. After an initial scan, 50 μL of a 50 mM so-
lution (1 equivalent relative to total Co) of FcBF₄ in 2:1 
THF/MeCN was injected into the cuvette. The reaction was 
monitored by collecting spectra every 45 seconds until the 
spectrum stopped changing. The spectrum of 4ox-d₄₅ was 
revealed by subtracting off 29% of the spectrum of 3-d₄₅ ex-
pected to form from oxidation of the 2-d₄₅ contaminant.

Procedure for Oxidation of 4-d₄₅ Monitored by EPR 
Spectroscopy. In the glovebox, 150 μL of a solution of 4-d₄₅ 
(contaminated with 29% 2-d₄₅) in THF-d₆ (10 mM total Co 
concentration) was transferred to an EPR tube and sealed 
with a puncturable septum. The tube was removed from the 
glovebox and cooled in an ethanol/liquid nitrogen bath 
which can reach temperatures as low as −116 °C. After cool-
ing (during which the solution stayed liquid), 15 μL of a 100 
mM solution (1 equivalent relative to total Co) of FcBF₄ in 
CD₃CN was injected through the septum. The solutions were 
mixed as rapidly and completely as possible before freezing 
in liquid nitrogen. An EPR spectrum was collected at 15 K 
within ~5 minutes of freezing the sample. Any 3-d₄₅ ex-
pected to form from oxidation of the 2-d₄₅ contaminant 
would be silent (S = 0) by EPR spectroscopy and therefore 
not convolute the spectrum. The EPR spectrum was simu-
lated using the simulation software package in the program 
SpinCount.⁶⁶

Computational Methods. All DFT calculations were per-
formed in ORCA 5.0.0 using the O3LYP functional with def-
gital grid settings.⁶⁷–⁷⁰ The CPCM continuum polarization 
model with gaussian charges and the dielectric constant 
of THF was included.⁷¹ The basis sets of Weigend and Ahrlich 
were employed: cobalt was given def2-TZVPP; all ligands 
bound to cobalt, the transferring hydrogen, and the carbon 
donating the transferring hydrogen were given def2-TZVPP; 
the secondary hydrogen also bound to the donating carbon 
was given def2-SVP; all other atoms were given def2-
SV(P).⁷²,⁷³⁷² We confirmed the barrier height to C–H activa-
tion was unchanged within 0.1 kcal/mol with respect to 
larger basis sets and integration grids. Frequency calcu-
lations were performed numerically. All minima were 
confirmed to have zero imaginary frequencies and saddle 
points to have exactly one imaginary frequency, excepting 
for a few modes with magnitudes less than 40 cm⁻¹ which 
al so corresponded to rotating adamantyl groups or cyclopenta-
dienyl ligands. Thermodynamic values were computed 
using the QRRHO model of Grimme and coworkers;⁷⁴ spuri-
ous imaginary modes (but not the reactive modes) were in-
cluded to keep a consistent set of normal modes in all free 
energy differences. TD-DFT, population analyses, and Co–O 
bond metrics of 4ox were calculated at the optimized geo-
metry with a slightly different basis set; Co and O were given 
def2-QZVPP, the carbene carbons were given def2-TZVPP, 
and all other atoms given def2-SV(P). TD-DFT was calcu-
lated without frozen core orbitals. The delocalization index, 
which measures the number of electron pairs shared in a 
bond and can serve as an estimate of the bond order,⁷⁵–⁷⁷ 
was calculated in Becke fuzzy atomic space using the Multi-
wfn program.⁷⁸,⁷⁹ Intrinsic atomic populations were calcu-
lated in iboview with exponent 4.⁶⁰,⁶¹

Crystallographic Details. The diffraction data for 3 
were measured at 100 K on a Bruker D8 fixed-chi with 
PILATUS1M (CdTe) pixel array detector (synchrotron radi-
ation, λ = 0.41328 Å (30 KeV)) at the Chem-MatCARS 15-ID-
B beamline at the Advanced Photon Source (Argonne Na-
tional Laboratory). The diffraction data for 1, 2, 4, and 5 
were measured at 100 K on a Bruker D8 VENTURE diffrac-
tometer equipped with a microfocus Mo-target X-ray tube 
(λ = 0.71073 Å) and PHOTON 100 CMOS detector. Data re-
duction and integration were performed with the Bruker 
APEX3 software package (Bruker AXS, version 2017.3-0, 
2018). Data were scaled and corrected for absorption ef-
fects using the multi-scan procedure as implemented in 
SADABS (Bruker AXS, version 2014/5).⁸⁰ The structures 
were solved by SHELXT (Version 2014/5)⁸¹ and refined by 
a full-matrix least-squares procedure using OLEX2 (XL re-
finement program version 2018/1).⁸²,⁸³ Structure solutions 
were performed with the use of standard restraints and 
constraints as implemented in ShelXL. Additional
crystallographic and refinement data can be found in the Supporting Information.

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**Notes**
The authors declare no competing financial interest.

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