

ELECTROCHEMISTRY

A molecular mediator for reductive concerted proton-electron transfers via electrocatalysis

Matthew J. Chalkley*[†], Pablo Garrido-Barros*, Jonas C. Peters[‡]

Electrocatalytic approaches to the activation of unsaturated substrates via reductive concerted proton-electron transfer (CPET) must overcome competing, often kinetically dominant hydrogen evolution. We introduce the design of a molecular mediator for electrochemically triggered reductive CPET through the synthetic integration of a Brønsted acid and a redox mediator. Cathodic reduction at the cobaltocenium redox mediator substantially weakens the homolytic nitrogen-hydrogen bond strength of a Brønsted acidic anilinium tethered to one of the cyclopentadienyl rings. The electrochemically generated molecular mediator is demonstrated to transform a model substrate, acetophenone, to its corresponding neutral α -radical via a rate-determining CPET.

There has been a recent surge of interest in applying electrochemistry as a tool for synthetic organic chemistry (1), with the ultimate aim of harnessing renewably sourced electricity for the more sustainable synthesis of value-added organic products (2). Redox mediators, which enable indirect electrochemical transformations of organic substrates, may improve selectivity and prevent electrode passivation by avoiding the formation of reactive intermediates (e.g., radical anions or cations) directly at the electrode surface (3). Although electrochemical transformations that involve initial electron transfer (ET) and subsequent proton transfer (PT) are highly useful (e.g., electrochemical Birch reductions or electrochemical adiponitrile synthesis) (4, 5), the applied bias needed is substantially higher than that which would be required were the initial step a concerted proton-electron transfer (CPET). Illustrating this point is the fact that oxidative approaches to electrocatalytic CPET (eCPET) strategies based on nitroxyl radicals notably lower onset potentials compared with ET-PT approaches (6, 7).

Reductive (electro)catalytic CPET of an unsaturated substrate requires the formation of an X-H bond (where X is CR₂, NR, or O) that is homolytically weak because of the concomitantly formed α -radical [BDFE_{X-H} = 20 to 40 kcal mol⁻¹ (BDFE, bond dissociation free energy); Fig. 1A]. An additional challenge is that the competing hydrogen evolution reaction (HER) is thermodynamically favorable ($\Delta G_{\text{HER}} = -20$ to -60 kcal mol⁻¹, where ΔG is Gibbs free energy). Thus, to be competent for CPET, the mediator must facilitate the rapid

colocalization of a proton and an electron that are sufficiently reactive to form the target X-H bond while kinetically suppressing the formation of H₂. If this could be achieved, a CPET mediator would provide electrochemical means to access valuable, neutral radical intermediates. Such intermediates are synthetically versatile in the context of chemical and photochemical methodologies for reductive CPET transformations (8–10). Against this backdrop, we report a molecular mediator that is capable of facilitating reductive eCPET.

CPET donors that are sufficiently reactive to reduce unsaturated substrates can be generated through the coordination-induced weakening of an O-H bond—for example, by pairing SmI₂ with a polar protic solvent (Fig. 1B) (11). Relatedly, the formation of a homolytically weak and hence reactive Fe-H bond has been invoked to explain the CPET reactivity observed upon combining silanes (Si-H) with an iron alkoxide (Fe-OR) (12). An attractive photochemical approach to triggering a CPET step in challenging reductions has also been demonstrated by pairing an acid with a strong photoreductant (Fig. 1C) (13). Although these strategies are synthetically useful, each of them relies on the inclusion of a stoichiometric reductant (Sm^{II}, a silane, and an amine, respectively); their adaptation to eCPET, in which the cathode is the ultimate source of reducing equivalents, has not proven straightforward. Thus, we set out to develop a method of forming strong CPET donors suited to electrochemical activation. Herein, we demonstrate that the synthetic integration of a Brønsted acid and a redox mediator facilitates reduction-induced bond weakening to enable controlled, reductive eCPET at a cathode in the presence of excess acid. Synthetic integration of the Brønsted acid, dimethylanilinium, and the redox mediator, cobaltocenium, proved key both to attenuating HER and to

facilitating CPET to a model acetophenone substrate.

Before pursuing synthetic integration of reductant and acid toward a CPET mediator, we explored the efficacy of pairing Cp₂Co⁺⁰ with an anilinium acid independently. Related approaches have proven effective in net oxidative eCPET reactions by pairing ferrocenium/ferrocene (Fc⁺⁰) as a one-electron oxidant and an alkoxide (e.g., MeO⁻) as a proton acceptor (14). Furthermore, we have recently established that a strong CPET donor can be generated in situ through the protonation of a Cp (or Cp^{*}) ligand of cobaltocenes (15, 16), and studies by our laboratory and others have suggested that cobaltocenes can act as redox mediators in the electrocatalytic reductive protonation of small molecules such as N₂ or CO₂ (17, 18). Nonetheless, with parent cobaltocenes, protonation at carbon is needed to generate the CPET reagent, a step that should be slow because of the substantial reorganization required (sp² to sp³) (19). Also, this protonation step transforms the Cp (or Cp^{*}) ligand, a σ - and π -donor, into a π -accepting diene ligand. This, in turn, anodically shifts the reduction potential (E°) (16, 20), thereby leading to rapid ET and, ultimately, facile and undesired HER.

To underscore these points, cyclic voltammograms (CVs) at 10 mV s⁻¹ of cobaltocenium ([Cp₂Co]⁺) in the presence of 100 mM 4-cyanoanilinium ([^{4-CN}PhNH₃]⁺), in a 200 mM tetrabutylammonium hexafluorophosphate ([TBA][PF₆]) solution of dimethoxyethane (DME), feature an irreversible wave consistent with electrocatalytic HER (see supplementary materials, section 8, for detailed discussion). An increase in current intensity upon increasing the [Cp₂Co]⁺ concentration, while maintaining constant acid concentration, demonstrates that the HER mechanism is first order in [Cp₂Co]⁺ (fig. S24). Alternatively, holding the [Cp₂Co]⁺ concentration constant and increasing that of the [^{4-CN}PhNH₃]⁺ shows that HER is also first order in [^{4-CN}PhNH₃]⁺ (fig. S25). CVs acquired at 100 mV s⁻¹ show partial reversibility at the Co^{III/II} couple (-1.33 V versus Fc⁺⁰), which suggests a buildup of Cp₂Co during the electrocatalysis (fig. S22). These data are consistent with a rate-determining protonation of Cp₂Co, which suggests that the ring-protonated species, [(Cp)Co(η^4 -C₅H₆)]⁺—which would be a strong CPET donor [BDFE_{C-H} of 33.8 kcal mol⁻¹; calculated by density functional theory (DFT); see supplementary materials]—is present only in low concentration. Thus, we anticipate that HER does not involve bimolecular combination of [(Cp)Co(η^4 -C₅H₆)]⁺, but likely proceeds through rapid reduction [$\Delta G(\text{ET}) = -23$ kcal mol⁻¹] to form (Cp)Co(η^4 -C₅H₆) and subsequent protonation to release H₂ and [Cp₂Co]⁺ (Fig. 2A). As [(Cp)Co(η^4 -C₅H₆)]⁺ is both slow to form and rapid

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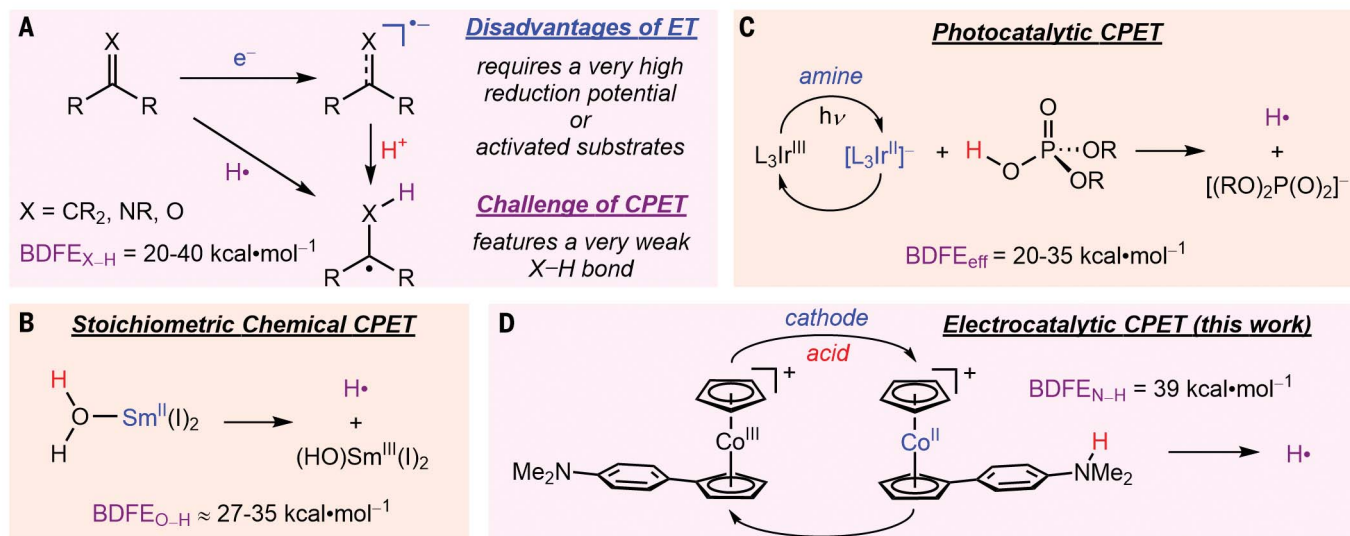


Fig. 1. Strategies for reductive CPET reactions. (A) Stepwise (ET-PT) and concerted (CPET) routes to the formation of a neutral α -radical intermediate, featuring a homolytically weak X-H bond, from an unsaturated substrate (e.g., alkene, imine, or ketone). (B) Coordination-induced weakening of an O-H bond by Sm₂, activating H₂O for reductive CPET transformations of unsaturated substrates (11). (C) Photocatalytic reductive

CPET via the pairing of an acid with a potent photoreductant (e.g., L = phenylpyridine) generated from a sacrificial amine reductant and light. eff, effective; h ν , photons. (D) The approach introduced in this work, in which a redox mediator (cobaltocenium/cobaltocene) is synthetically integrated with a Brønsted acid/base (anilinium/aniline), so as to promote CPET to a substrate and disfavor H₂ evolution.

to consume, it is likely unsuitable as a CPET mediator under electrocatalytic conditions (vide infra).

Appending an aniline-derived Brønsted base to cobaltocenium can serve to accelerate the rate of protonation (due to minimal reorganization at nitrogen) and to insulate the Co^{III/II} redox couple, as the immediate coordination sphere at cobalt remains unchanged. To accomplish this, we followed the synthetic protocol outlined in Fig. 2B. The target, aniline-modified cobaltocene, (Cp)₂Co(Cp^N) (where Cp^N is 4-*N,N*-dimethylanilinecyclopentadienyl), can be isolated in pure form, as can its oxidized Co^{III} salt, [(Cp)₂Co(Cp^N)]⁺[OTf]⁻. The latter can be readily protonated to provide [(Cp)₂Co(Cp^{NH})]²⁺[OTf]₂⁻ (where Cp^{NH} is 4-*N,N*-dimethylaniliniumcyclopentadienyl). The highly reactive CPET donor, [(Cp)₂Co(Cp^{NH})]⁺, can be generated in situ through either the low-temperature reduction of [(Cp)₂Co(Cp^{NH})]²⁺[OTf]₂⁻ or the low-temperature protonation of (Cp)₂Co(Cp^N), as evidenced by optical spectroscopy and freeze-quench electron paramagnetic resonance spectroscopy (figs. S12 and S15). It can also be generated electrochemically (vide infra). The data are consistent with the conclusion that the Cp₂Co core is maintained throughout, with the proton residing on the appended aniline (Fig. 2B).

The N-H BDFE of the CPET donor [(Cp)₂Co(Cp^{NH})]⁺ is of central interest. To assess BDFEs, it is typical to measure the thermochemistry of the stepwise ET-PT or PT-ET pathways in a solvent (Eq. 1). Although DME is well suited

to the study of reductive protonations, it lacks a well-defined pK_a scale (where K_a is the acid dissociation constant) and C_G value, a solvent-dependent thermodynamic constant to account for the energy required to form H• from H⁺ and e⁻, both of which are required to assess Eq. 1. Thus, as is common in non-aqueous thermochemistry, we performed our thermochemical measurements in acetonitrile [C_G in acetonitrile (MeCN) is 54.9 kcal mol⁻¹]. The relevant BDFE values are likely similar to those in DME, as BDFEs typically vary little with solvent (21). The CV of [(Cp)₂Co(Cp^N)]⁺ in MeCN reveals both a reversible reduction at -1.35 V versus Fc⁺⁰ and a reversible oxidation at 0.52 V versus Fc⁺⁰. The former is assigned to the Co^{III/II} couple on the basis of its similarity to that of parent cobaltocenium, and the latter is assigned to an N-centered oxidation on the basis of its similarity to the oxidation of parent *N,N*-dimethylaniline (0.38 V versus Fc⁺⁰) (22). An oxidation event for the aniline-protonated [(Cp)₂Co(Cp^{NH})]²⁺ species is not observed; a reversible reduction (Co^{III/II}) is observed at -1.21 V versus Fc⁺⁰. The pK_a of [(Cp)₂Co(Cp^{NH})]²⁺ was assessed through equilibration experiments with aniline bases of known pK_a's probed by means of ¹H nuclear magnetic resonance (NMR) spectroscopy in MeCN-*d*₃. The resultant pK_a of 8.62 ± 0.02 can be compared with 11.4 for parent *N,N*-dimethylanilinium (23). This establishes that the [Cp₂Co]⁺ serves as an electron-withdrawing substituent on the aniline ring.

$$\text{BDFE} = 1.37 \times \text{p}K_{\text{a}} + 23.06 \times E^{\circ} + C_{\text{G}} \quad (1)$$

With these data and Eq. 1, the BDFE_{N-H} of [(Cp)₂Co(Cp^{NH})]²⁺ is predicted to be 79 kcal mol⁻¹. This value agrees very well with the BDFE_{N-H} of *N,N*-dimethylanilinium (79 kcal mol⁻¹). However, reduction of Co^{III} to the Co^{II} state substantially lowers the strength of the remote N-H bond by 40 kcal mol⁻¹. This reduction-induced bond weakening contrasts with previously studied examples, where a one-electron change in oxidation state lowered an X-H BDFE by ~10 to 15 kcal mol⁻¹ (24, 25). In these previous examples, the X-H bond was strongly electronically coupled to the redox site. By contrast, the remote redox effect that we observe with [(Cp)₂Co(Cp^{NH})]^{2+/+} is in line with the effective BDFE postulate, which holds that Eq. 1 predicts the strength of a hypothetical H• donor formed by a separated acid and reductant. The effective BDFE predicted for the pairing of the two parent subunits, *N,N*-dimethylanilinium and Cp₂Co, is 40 kcal mol⁻¹, which is in good agreement with the experimentally determined BDFE_{N-H} for our synthetically integrated system (39 kcal mol⁻¹; Fig. 2C). Nevertheless, the thermodynamic equivalence between the independent reagent pair and the synthetically integrated construct does not imply kinetic equivalence. We next show that synthetic integration of the acid and reductant into a single molecule shifts the behavior of the system from undesired HER toward productive eCPET reactivity with substrate.

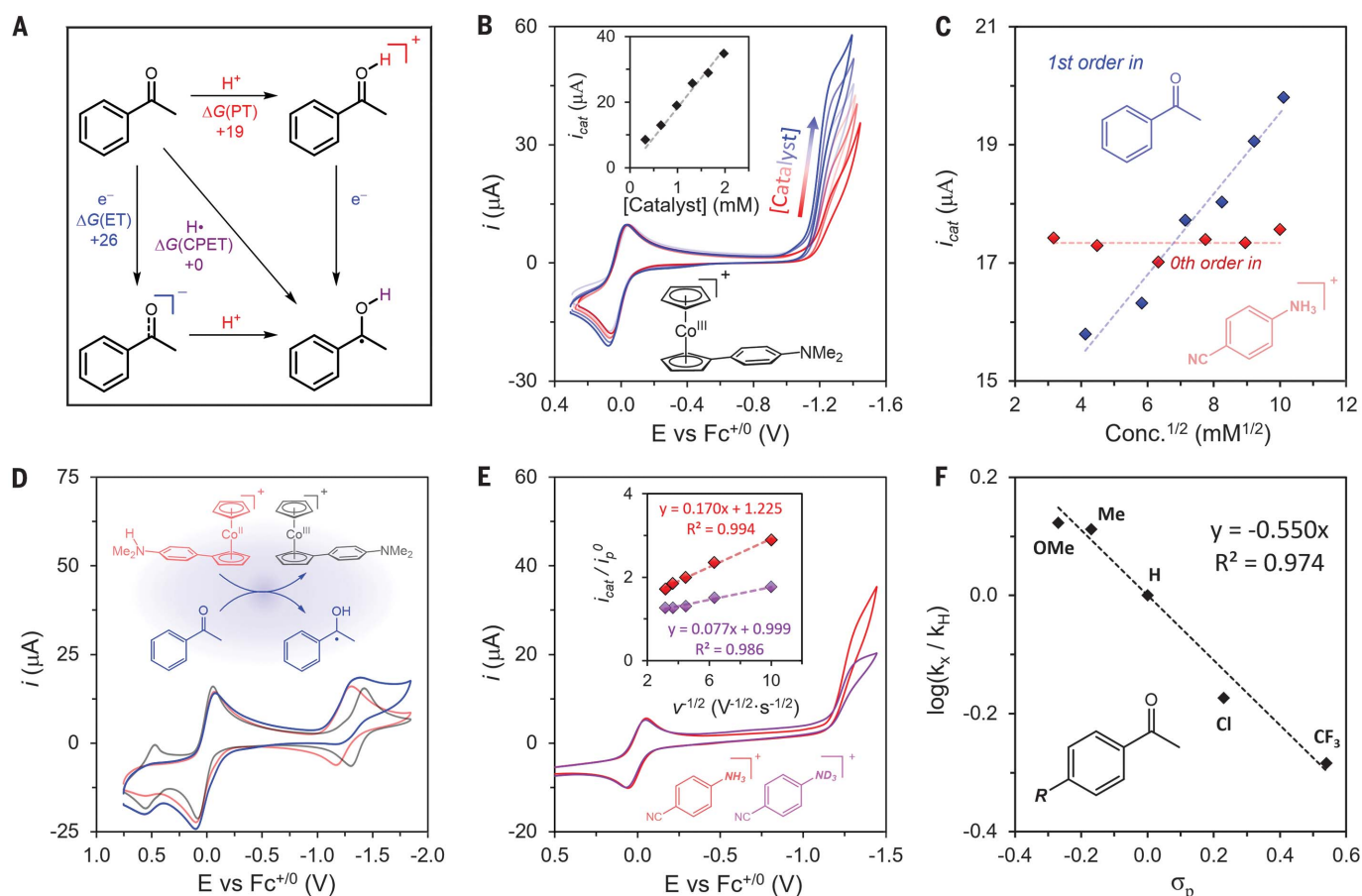


Fig. 3. Mechanistic details of electrocatalytic reductive CPET. (A) DFT calculated ΔG (in kilocalories per mole) for initial ET, PT, and CPET from $[(\text{Cp})\text{Co}(\text{Cp}^{\text{NH}})]^+$ to acetophenone. (B) CVs showing the increase in current with increasing concentration of $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^+$, with an inset demonstrating the first order dependence of CPET on Co concentration. (C) Plot of the catalytic current (i_{cat}) for CPET with respect to the square root of the concentration (Conc.) of acetophenone (blue) and $[\text{4-CNPhNH}_3]^+$ (red) showing a first order and zeroth order dependence, respectively (eqs. S5 to

S7). (D) Demonstration of the redox couple of $[(\text{Cp})\text{Co}(\text{Cp}^{\text{NH}})]^{2+/+}$ (red) and $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^{+/0}$ (gray), and a CV of $[(\text{Cp})\text{Co}(\text{Cp}^{\text{NH}})]^{2+}$ in the presence of acetophenone (blue). (E) Comparison of CVs taken at 10 mV s^{-1} with $[\text{4-CNPhNH}_3]^+$ (red) and $[\text{4-CNPhND}_3]^+$ (purple). The inset shows the plot used to determine the corresponding rates for evaluation of the KIE, where i_p^0 is the current intensity of the one electron reduction for $[(\text{Cp})\text{Co}(\text{Cp}^{\text{NH}})]^{2+/+}$ and v is the scan rate. R^2 , coefficient of determination. (F) Hammett plot for the CPET reaction with 4-substituted acetophenones against the σ_p parameter.

concentration and a square root increase in the substrate concentration (i.e., $[\text{acetophenone}]^{1/2}$). Thus, by systematically varying the concentration of the reaction components, we can use the changes observed in the catalytic current to determine that the CPET reaction is first order in cobalt, first order in acetophenone, and zeroth order in acid (Fig. 3, B and C). To determine whether the acetophenone reacts with $[(\text{Cp})\text{Co}(\text{Cp}^{\text{NH}})]^{2+/+}$ rather than $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^{+/0}$, we studied the influence of acetophenone on the electrochemical behavior in the absence of acid (figs. S36 to S39). CVs of $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^+$ were unperturbed, whereas those of $[(\text{Cp})\text{Co}(\text{Cp}^{\text{NH}})]^{2+}$ became irreversible with an additional reduction event observed at the $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^{+/0}$ redox couple. These data establish the consumption of $[(\text{Cp})\text{Co}(\text{Cp}^{\text{NH}})]^+$ by a net proton and electron transfer to acetophenone, followed

by the reduction of the resulting $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^+$ product (Fig. 3D).

To establish the concerted nature of the proton-electron transfer in the rate-determining step, the kinetic isotope effect (KIE) of the catalysis was determined by comparing the catalytic current at different scan rates in experiments using either $[\text{4-CNPhNH}_3]^+$ or $[\text{4-CNPhND}_3]^+$ (Fig. 3E). The observed KIE of 4.9 ± 0.7 is larger than that observed for both chemical and photochemical CPET reactions with ketones: SmI_2 and H_2O have a KIE of ~ 2 (27), and $\text{Ir}(\text{phenylpyridine})_3$ and $(\text{PhO})_2\text{P}(\text{O})\text{OH}$ have KIEs between 1.2 and 3 (13). Thus, the collective data are fully consistent with a rate-determining reductive CPET from $[(\text{Cp})\text{Co}(\text{Cp}^{\text{NH}})]^+$ to acetophenone to form its neutral α -radical.

The kinetics of eCPET for a series of para-substituted acetophenones $[\text{4-RPh}(\text{C})\text{O}]\text{Me}$, where

R is CF_3 , Cl, H, Me, or OMe] was also studied. A Hammett plot against σ_p (28) reveals a linear relationship with a modest negative slope ($\rho = -0.50 \pm 0.04$; Fig. 3F). This observation suggests a slight buildup of positive charge on the acetophenone unit in the transition state (TS) and may be consistent with an asynchronous CPET reaction in which the TS involves slightly more proton-transfer than electron-transfer character (29, 30). Although these observations warrant further study, the relative rate of reactivity with 2-pentanone—which has a similar basicity to acetophenone ($\Delta pK_a^{\text{calc}} = -0.6$) but forms an α -radical with a homolytically much weaker O-H bond ($\text{BDFE}_{\text{calc}} = 28 \text{ kcal mol}^{-1}$) than that formed by acetophenone—clearly illustrates the overall CPET nature of the transformation. Indeed, 2-pentanone reacts an order of magnitude more slowly than acetophenone ($0.31 \pm 0.09 \text{ s}^{-1}$ versus $4.6 \pm$

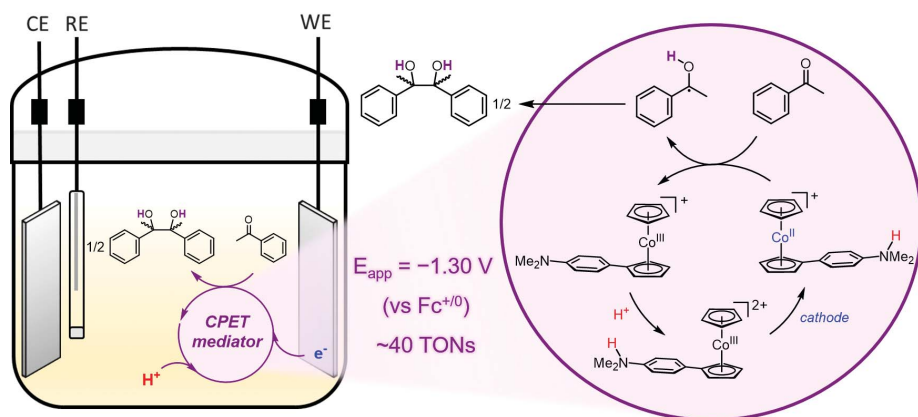


Fig. 4. Overall reaction. (Left) Schematic of an electrochemical setup for the reduction of acetophenone via eCPET. CE, counter electrode; RE, reference electrode; WE, working electrode. (Right) Atomistic mechanism for eCPET of acetophenone mediated by $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^+$. E_{app} , applied potential.

0.4 s^{-1} , respectively). However, this result does suggest that thermally uphill CPET reactions [$\Delta G(\text{CPET})_{\text{calc}} = +10 \text{ kcal mol}^{-1}$ for 2-pentanone] can proceed, in this case, likely driven by a subsequent irreversible step such as coupling of the α -radical intermediates (vide infra).

Evidence for the generation of the neutral α -radical intermediate is provided by controlled potential coulometry (CPC) experiments and subsequent product analysis. CPC at -1.30 V versus $\text{Fc}^{+/0}$ of $1 \text{ mM } [(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^+$, 50 mM acetophenone, 100 mM tosylic acid, and 200 mM [TBA][PF₆] in DME with a glassy carbon counter electrode, a Ag/AgOTf (5 mM) reference electrode, and a boron doped diamond (BDD) working electrode afforded the pinacol-coupling product 2,3-diphenyl-2,3-butanediol in 83% yield with 11% recovery of remaining acetophenone. We presume that the 2,3-diphenyl-2,3-butanediol forms through the coupling of two neutral α -radicals in a fast step that follows the rate-determining CPET reaction (Fig. 4). Related radical pinacol couplings have previously been observed to occur at essentially diffusion-controlled rates (31). A turnover number (TON) of ~ 40 confirms the electrocatalytic nature of the CPET reaction and compares favorably to TONs demonstrated for oxidative eCPET reactions, which are typically between 5 and 10 (7, 32). The overall Faradaic efficiency (FE) for eCPET is 39%. Most of the remaining current is accounted for in the formation of H₂ (FE = 45%) as a side product; the HER reaction likely begins to dominate at low ketone concentrations. The molecular CPET mediator appears to be stable during the CPC experiment; differential pulse voltammograms at the end of the experiment reveal the expected peaks for $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^+$ at 0.52 and -1.35 V , and x-ray photoelectron spectroscopy does not indicate the deposition of Co on the BDD electrode (fig. S76).

Consistent with our cyclic voltammetry experiments, CPC in the absence of the CPET mediator, $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^+$, also showed some pinacol product but at a much slower rate (10% yield over the same reaction time). Furthermore, none of the starting ketone was recovered in this case. This latter finding suggests that molecular eCPET mediators of the type described here, like redox mediators, may afford benefits compared with transformations that occur directly on the electrode, which can suffer from adsorption and passivation processes. Furthermore, the use of $[\text{Cp}_2\text{Co}]^+$ in the CPC instead of $[(\text{Cp})\text{Co}(\text{Cp}^{\text{N}})]^+$ was ineffective. In this case, the pinacol product yield was even lower than that of the background electrode (5%), and HER was enhanced (66% FE).

Synthetic integration of cobaltocenium and a Brønsted acid provides a molecular CPET mediator that operates via redox-induced bond weakening. This approach stores the chemical capacity of a reductant and an acid within a single molecule to facilitate a bimolecular transition state for CPET to an acceptor molecule. Site isolation of the proton and electron kinetically attenuates the thermally favorable HER reaction, thus allowing for reductive CPET in an electrocatalytic fashion.

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SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/369/6505/850/suppl/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S94
Tables S1 to S44
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Delivering protons with electrons

Many chemical reactions involve concurrent transfer of a proton and an electron. In electrochemical synthesis, this mechanism could prove useful in lowering the energy necessary for cathodic electron transfer alone, but it is hindered by competing direct coupling of the protons and electrons to make hydrogen instead. Chalkley *et al.* now report a molecular mediator consisting of a dimethylaniline base tethered to a cobaltocenium electron acceptor. This construct can deliver both a proton and an electron to a substrate from an acid and a cathode while skirting the hydrogen pathway.

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