A new strategy to efficiently cleave and form C–H bonds using proton-coupled electron transfer

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Oxidative activation and reductive formation of C–H bonds are crucial in many chemical, industrial, and biological processes. Reported here is a new strategy for these transformations, using a form of proton-coupled electron transfer (PCET): intermolecular electron transfer coupled to intramolecular proton transfer with an appropriately placed cofactor. In a fluorenyl-benzoate, the positioned carboxylate facilitates rapid cleavage of a benzylic C–H bond upon reaction with even weak 1e⁻ oxidants, for example, decamethylferrocenium. Mechanistic studies establish that the proton and electron transfer to disparate sites in a single concerted kinetic step, via multi-site concerted proton-electron transfer. This work represents a new elementary reaction step available to C–H bonds. This strategy is extended to reductive formation of C–H bonds in two systems. Molecular design considerations and possible utility in synthetic and enzymatic systems are discussed.

INTRODUCTION

The selective functionalization of carbon-hydrogen (C–H) bonds under mild conditions has long been an area of intense investigation in organic synthesis, industrial chemistry, and biochemistry (1, 2). C–H bonds are typically non-polar with low acidity and high bond strengths and are therefore difficult to activate. The dominant mechanism for cleavage of unactivated C–H bonds, from combustion to enzymatic oxidations, is hydrogen atom transfer (HAT), a subset of proton-coupled electron transfer (PCET): intermolecular electron transfer coupled to intramolecular proton transfer with an appropriately placed cofactor. In a fluorenyl-benzoate, the positioned carboxylate facilitates rapid cleavage of a benzylic C–H bond upon reaction with even weak 1e⁻ oxidants, for example, decamethylferrocenium. Mechanistic studies establish that the proton and electron transfer to disparate sites in a single concerted kinetic step, via multi-site concerted proton-electron transfer. This work represents a new elementary reaction step available to C–H bonds. This strategy is extended to reductive formation of C–H bonds in two systems. Molecular design considerations and possible utility in synthetic and enzymatic systems are discussed.

RESULTS AND DISCUSSION

The present work was started with density functional theory (DFT) calculations to identify candidates for oxidative MS-CPET with a base positioned near a relatively weak C–H bond. The calculated thermochemistries indicated that electronic isolation of the redox and basic sites should allow for MS-CPET oxidation at very mild potentials relative to simple ET in the same system. MS-CPET avoids high-energy intermediates that bear formal charge on the carbon, providing a thermodynamic bias favoring the concerted pathway. These calculations identified the fluorenyl-benzoate compound 1⁻ (Fig. 2A) as a prime candidate be-

cause steric interactions between the rigid fluorene and the benzoate keep the rings nearly perpendicular and position the base near the weak benzylic C–H bond. Both 2-(9-fluorenyl)benzoic acid (1H) and its para-carboxy isomer were prepared using palladium-catalyzed cross couplings. 1⁻ was generated in situ in acetonitrile (MeCN) using 1 eq of a base such as tetrabutylammonium hydroxide (TBAOH) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Nuclear magnetic resonance (NMR) spectra and other characterization support the structure and conformation for 1⁻ shown (for synthetic, experimental, and computational details, see Materials and Methods and the Supplementary Materials).

The reaction of 1⁻ with 2 eq of a 1e⁻ outersphere oxidant and an additional equivalent of base rapidly gave quantitative conversion to the reduced oxidant and a new product, 2. Compound 2 was identified by NMR, infrared (IR), and high-resolution mass spectroscopies (HR-MS) as the known lactone (Fig. 2B and the Supplementary Materials). A range of aminium (NA₃) and ferrocenium (Fc⁺) oxidants, with 1e⁻
potentials ($E_{ox}$) spanning 1.15 V, were found to quantitatively convert $1^-\text{ to } 2$ (Table 1). In contrast, even the strongest oxidant in the series failed to oxidize $1\text{H}$ or the para-carboxy isomer of $1^-$, indicating that the presence and positioning of the base are crucial for the transformation.

The time course of reactions of $1^-$ was followed optically using stopped-flow techniques, monitoring the disappearance of the colored oxidants ($\leq 10^{-3} \text{ M}$) in the presence of excess $1^-$. The reactions are rapid at ambient temperatures, reaching completion in a few milliseconds to seconds. The second-order rate constants ($k_{\text{MS-CPET}}$) span 4.5 orders of magnitude and increase with the strength of the oxidant (Table 1). The use of oxidants with different $E_{ox}$ values changes the ET portion of the driving force of the MS-CPET reactions. The logarithms of the rate constants [log($k_{\text{MS-CPET}}$)] correlate linearly with the differences in driving forces, here described using changes in the equilibrium constants, $\Delta$log($k_{\text{MS-CPET}}$) (Fig. 2D). We use $\Delta$log($k_{\text{MS-CPET}}$) because the absolute values are not well known, but the changes are directly given by the changes in $E_{ox}$ as the substrate is the same for all of the reactions. As discussed below, we estimate that the reaction with FeCp$_2^{*+}$ is close to isoeergic ($\Delta G_{\text{MS-CPET}} = 0$), so Fig. 2D sets $\Delta$log($k_{\text{MS-CPET}}$) = 0 for this oxidant. H/D kinetic isotope effects (KIEs) were measured for a number of oxidants using $1^-\text{d}_1$, selectively deuterated at the 9-position of the fluorene (see Materials and Methods). The primary KIEs range from 1.6 to ~4.5 and increase with increasing $k_{\text{MS-CPET}}$ (Fig. 2D), that is, for reactions using stronger oxidants.

The mechanism of the C–H bond cleavage in $1^-$ could start with initial PT, ET, or MS-CPET (Fig. 3) (8, 9). However, the dependence of $k_{\text{MS-CPET}}$ on both the strength of the oxidant and H/D substitution implicates both ET and PT occurring in the rate-limiting step. The dependence of $k_{\text{MS-CPET}}$ on $E_{ox}$ (Table 1) rules out initial rate-limiting PT, while the slope of that dependence (<1) rules out pre-equilibrium ET. The primary H/D KIEs rule out initial rate-limiting ET, while the variation of the KIEs with oxidant argues against pre-equilibrium ET or PT pathways. Pre-equilibrium PT is ruled out by the lack of H/D exchange in solutions of $1^-\text{d}_1$ with excess CH$_3$OH (section S4.2 and fig. S7). In addition, thermochemical analyses (section S4) show that the PT and ET intermediates are too high in energy to be involved. Together, these results are only consistent with C–H bond oxidation occurring by initial rate-limiting MS-CPET formation of the radical $1^-$ (Fig. 2B). This intermediate rapidly undergoes oxidative deprotonation and cyclization to form the observed product, 2. This is the first demonstration of MS-CPET as an elementary reaction step of C–H bonds (Fig. 1C).

The linear correlation of rate versus thermodynamic driving force [($\Delta$log($k_{\text{MS-CPET}}$)/$\Delta$log($k_{\text{MS-CPET}}$) in Fig. 2D] is typical of PCET reactions. This indicates that MS-CPET is rate-limiting throughout the 1.15-V range in driving force studied here. The shallow slope for the C–H bond oxidations of only 0.21 ± 0.01, however, is quite unusual. This slope, the Brønsted $\alpha$, is much lower than the ~0.5 typically observed for reactions at polar O–H or N–H bonds (4, 5, 7) and for HAT reactions of C–H bonds (3). A possible explanation is that the transition state for MS-CPET involves concerted but asynchronous transfer of the proton and electron; specifically, that the transition states for these reactions could have more PT or bond breaking character. Such “asymmetric” or “imbalanced” transition states where electronic redistribution (in this case, ET) lags behind proton movement have long been invoked as a characteristic of PT reactions at carbon centers (13). Alternatively, the shallow slope could be an indication of electronically nonadiabatic PT, another consequence of the lack of strong, classical hydrogen bonding interactions in these C–H systems (14). Studies to probe the origin of this shallow dependence are underway.

Fig. 2. Kinetics of the oxidation of $1^-$ with various oxidants. (A) Computed structure of $1^-$ indicating PT (red arrow) to a benzoate oxygen. Nontransferring protons omitted for clarity. (B) C–H bond oxidation in compound $1^-\text{ forms } 1^-$, which is further oxidized to 2. (C) overlaid optical spectra over time, from a stopped-flow instrument, showing the disappearance of the oxidant N(ArOMe)$_2^{*+}$ in the presence of excess $1^-; \text{ the inset shows the exponential decay of the absorbance at 716 nm.}$ (D) Plot of log($k_{\text{MS-CPET}}$) versus $\Delta$log($k_{\text{MS-CPET}}$) including $k_d$ for ammonium (●) and ferrocenium oxidants (○) and $k_2$ (●). $\Delta$log($k_{\text{MS-CPET}}$) = $\Delta$($E_{ox}$)/2.303RT; the top axis shows $E_{ox}$. The fit lines have unitless slopes of 2.1 ± 0.01 ($k_d$) and 0.17 ± 0.02 ($k_2$). Thermochemical estimates (section S4) indicate that $\Delta G_{\text{MS-CPET}} \approx 0$ for the reaction with FeCp$_2^{*+}$, so that point was set to $\Delta$log($k_{\text{MS-CPET}}$) = 0.
It is striking that $1^-$ is oxidized to 2 with the very mild oxidant decamethylferrocenium (FeCp$_2^+$, $E_{ox} = −0.48$ V; Table 1). This reaction was, however, predicted to be favorable based on the established thermochemistry of using an oxidant/base pair to remove $\text{H}^+$ from an X–H bond (9). For HAT reactions, the driving force is equal to the difference in homolytic bond dissociation free energies (BDFE). For MS-CPET reactions, Waidmann et al. (15) defined an “effective BDFE" for combinations of oxidants and bases (Eq. 1; $\Delta G^o$ = oxidant, $B^*$ = base). BDFE$_{eff}$ is calculated from the pK$_a$ of the conjugate acid, the standard reduction potential ($E^o$) of the reduct cofactor, and the H$^+/\text{H}$ standard reduction potential, C$_{G, red}$ (Eq. 2; $C_{G,red} = 54.9$ kcal mol$^{-1}$ referenced to FeCp$^{2+}$ in MeCN). The overall free energy change for an MS-CPET reaction ($\Delta G_{MS-CPET}$) is then given by the difference between this BDFE$_{eff}$ and the BDFE of the bond being cleaved (Eq. 3).

$$A + BH \rightarrow A^+ + B^- + \text{H}^+$$

$$\Delta G^o = \text{BDFE}_{eff} (A + BH^+)$$

$$\text{BDFE}_{eff} (A + BH^+) = 1.37pK_a (B^-) + 23.1E^o (A^+ / 0) + C_{G, red}$$

$$\Delta G_{MS-CPET} = \text{BDFE}(XH) − \text{BDFE}_{eff} (A + BH^+)$$

Using Eq. 2, the combination of FeCp$_2^+$ and benzoate in MeCN is thermodynamically capable of cleaving a C–H bond with BDFE = 73 kcal mol$^{-1}$. This value is within the range of the estimated C–H BDFE in $1^−$ of 74±2 kcal mol$^{-1}$ based on values for related fluorenyl analogs (section S4.1) (9, 16). Thus, the MS-CPET step for $1^−$ + FeCp$_2^+$ is predicted to be roughly thermoneutral, logK$_{MS-CPET} \approx 0$. This analysis also explains why the weaker oxidant cobaltocene (CoCp$_2$) does not react with $1^−$ (Table 1). As stated above, neither the acid form 1H nor the para-carboxy isomer of $1^−$ is oxidized by even the strongest oxidant in the series, N(Ar$_3$)$_2H^+$ (Table 1; $E_{ox} = +0.67$ V). The ability of very mild oxidants to accomplish this MS-CPET reaction arises from the strong coupling of pK$_a$ and reduct state in 1, which is common in C–H bonds (9). Thus, milder potentials and reagents relative to those required for simple ET will be a common feature of MS-CPET in other C–H systems, suggesting utility of this new strategy for C–H functionalization in natural product, medicinal, and fine-chemical synthesis applications (1).

The computational screen that identified $1^−$ also led us to the commercially available dyes rhodamine B (3a) and 2-(1-phenylvinyl)benzoic acid (5) as likely candidates for reductive MS-CPET reactivity (Fig. 4, A and B). By analogy with the oxidation system above, each bears an appropriately placed carboxylic acid proton donor that, in conjunction with an 1$^e$ reduced reductant, could form a new C–H bond via MS-CPET. Our DFT calculations showed that 5 and the 1$^e$ reduced form of 3a (3b) have low-energy conformers with the carboxylic acid proton positioned near the bond-forming carbon and displaying weak OH...π interactions (section S1.3). Treating 3a with 2 eq of the reductant decamethylcobaltocene (CoCp$_2$) in C$_3$D$_3$N rapidly yields 2 eq of CoCp$_2^+$ and quantitative formation of the reduced leuco-rhodamine B (4), which bears a new C–H bond at the 9-position of the xanthene ring (Fig. 4A). Compound 5 was prepared directly from 2-carboxybenzophenone by a Wittig reaction (see Materials and Methods). Reaction of 5 with 1 eq of CoCp$_2$ in benzene gave 30% stoichiometric yield of the known hydroxgenated product (6), readily identified by its 1$^H$ NMR spectrum (Fig. S5). These reactions of 3$^a$ and 5 indicate that C–H bonds can also be formed using separated proton and electron donors.

Thermochemical and mechanistic analyses of these reductive systems are more complicated than those for 1$^−$ above and will be described in future reports. However, preliminary analyses implicate MS-CPET mechanisms in each case. For the reduction of 5 in benzene, for example, initial ET from CoCp$_2$ is very unlikely based on reduction potentials in more polar solvents. In tetrahydrofuran (THF), $E^o$ has been determined for Ph$_2$C=CH$_2$ to be $−3.08$ V versus FeCp$_2^{2+}$ (17, 18). Since $E^0(\text{CoCp}_2^+) = −1.95$ V (19), initial ET would be very endoergic, $−1.1$ eV.
Similarly, although $pK_a$ values are not available, PT from the carboxylic acid in 5 to the alkene appears to be very unlikely, especially as it would form a zwitterion in low-polarity benzene. In addition, DFT studies indicate that this carboxylate-carbocation zwitterion would very rapidly collapse to the much more stable lactone (see Supplementary Materials), a rearrangement that is not observed in solutions of 5.

The methyl C–H bond formed in 5 is vicinal to a radical center and therefore is quite weak. Its BDFE is roughly estimated as 46 kcal mol$^{-1}$.

Fig. 4. Reductive MS-CPET to form C–H bonds. (A) Reduction of rhodamine B (3$^+$) with CoCp$^*_2$; (B) Reduction of an alkene with CoCp$^*_2$. "AH" is an additional equivalent of 5. (C) The trans-selective alkene reduction of protochlorophyllide by DPOR occurs via long-distance ET from an iron-sulfur cluster ≥10 Å away from the substrate. Short-range PT occurs from the propionic acid side chain and a proximal aspartic acid (Asp$^{274}$). (D) Crystal structure of DPOR active site, showing the Fe$_4$S$_4$ redox cofactor and heme-derived substrate; PT from the propionic acid side chain to the C$^{17}$=C$^{18}$ bond is indicated with an arrow. Figure made using VMD (Visual Molecular Dynamics) and adapted from Muraki et al. (20). ADP, adenosine 5′-diphosphate; ATP, adenosine 5′-triphosphate.
from the heat of hydrogenation of Ph2C==CH2 and the BDFE of Ph2CH–H (section S4.1). Application of Eq. 2 indicates that the combination of CoCp*2 and benzoic acid in MeCN has BDFEΔf = 40 kcal mol⁻¹. These estimates predict a ΔG° MS-CPET of ca. −6 kcal mol⁻¹, indicating that the reaction with CoCp*2 is thermodynamically feasible. A related analysis for the C–H bond forming step in the reduction of 3* (the second step in Fig. 4A) is given in the Supplementary Materials.

The low yield of 6 from 5 is due in part to the competing reaction of CoCp*2 with the carboxylic acid proton (fig. S5). Such reductant/acid incompatibilities, and parallel oxidant/base incompatibilities, are common competing pathways to MS-CPET. Oxidants, for example, are electron-deficient and therefore often react with electron-rich, nucleophilic phases. These reagent incompatibilities are a limitation that must be mitigated in MS–CPET chemistry (6, 15).

The computational screen that identified 1†, 3†, and 5 examined (i) structural features to properly place the transferring proton and (ii) the thermodynamic bias toward CPET over stepwise pathways. While the importance of the latter is known for MS-CPET reactions of O–H and N–H bonds (6), the unique feature of 1†, 3†, and 5 is the preorganization of the PT coordinate in the absence of classical hydrogen bonding. In each case, the proton acceptor or donor is positioned near the C–H bond or proton-accepting carbon, or it has an energetically accessible conformation with that positioning (section S1). The proton acceptor/donor positioning is accomplished primarily by steric effects in these systems. However, electronic effects such as weak nonclassical hydrogen bonding can also play a role, particularly in reductive systems where the acidic proton can interact with the electron-accepting π system. In essence, the proton prepositioning makes the C–H bond reactions resemble well-known MS-CPET reactions of polar O–H and N–H bonds in which the hydrogen bond creates the PT alignment needed for MS-CPET.

The use of mild redox cofactors and the acid/base positioning described above are ubiquitous characteristics of enzymatic catalysis, so it is very likely that biology utilizes MS-CPET to manipulate C–H bonds. One probable example is the trans-selective hydrogenation of the C=C=O double bond in a heme-derived substrate by dark-oxidized, highly oxidized, and semiquinone forms of heme (21). This reaction is similar to the hydrogenation of 5 above. Given the potential thermodynamic and kinetic benefits of MS-CPET, it is likely that this mechanism is operative in many enzymatic catalysts and will prove valuable in organic and inorganic syntheses.

The systems reported here show that C–H bonds can be cleaved and formed via MS-CPET using separated acid/base and redox cofactors. The rapid oxidations of 1† even under mild conditions at very low driving forces suggest that this approach will be applicable to stronger C–H bonds important in a range of synthetic and biological systems. This work extends MS-CPET beyond examples with O–H and N–H bonds by utilizing substrate structure to properly position the transferring proton. This positioning takes the place of the strong hydrogen bonds that are critical for MS-CPET at polar bonds. Thus, this work shows the requirements and opportunities for this new elementary reaction step for C–H bonds.

MATERIALS AND METHODS
Experimental design
To investigate a new mechanism for transformations of C–H chemical bonds, molecules were synthesized and characterized and their reactions with various chemical reagents were studied using spectroscopic and kinetic measurements.

Reagents, spectroscopy, and electrochemistry
Reagents were typically purchased from Sigma-Aldrich, Alfa Aesar, or Acros and used as received. DBU and TBAOH (as a 1.0 M solution in MeOH) were purchased from Alfa Aesar. Solvents were obtained from Fisher and deuterated solvents were obtained from Cambridge Isotope Laboratories. Deuterated solvents were dried over molecular sieves before use. n-Butyllithium (1.6 M solution in hexanes) was obtained from Acros. Methyl 2- and 4-bromobenzoate were obtained from Sigma-Aldrich. Fluorene and 2-benzoylbenzoic acid were purchased from Eastman. Methyltriphenylphosphonium bromide, potassium tert-butoxide, and rhodamine B were purchased from Acros. [CoCp2]PF6 was purchased from Strem Chemicals. All oxidants used were hexafluorophosphates (PF6−) salts. Aminium (7) and ferrocenium (4) oxidants were prepared as described previously. CoCp*2 was purchased from Sigma-Aldrich and purified before use by dissolving the metalloocene in a minimal amount of pentane, filtering, and concentrating the filtrate in vacuo in a N2-filled dry box.

NMR samples following MS-CPET reactions were prepared in a N2-filled glovebox using degassed solvents dried over activated 4 Å molecular sieves NMR spectra were collected on Agilent DD2 400, DD2 500, or DD2 600 MHz spectrometers. Representative NMR spectra are found in the Supplementary Materials (figs. S3 to S5). IR spectra (fig. S6) were collected in a N2-filled glovebox on a Bruker Alpha FT-IR spectrometer in a cell using CaF2 windows.

Oxidant E1/2 values for all aminium oxidants were taken from Rhile et al. (7). E1/2 for FeCp*2+ was taken from Connelly et al. (18).

Cyclic voltammograms of CoCp2 and FeCpCp* were taken in a N2-filled glovebox using a three-electrode setup in MeCN with 0.1 M tetra-n-butylammonium hexafluorophosphate (TBAPF6) as the supporting electrolyte. The working electrode was glassy carbon, and the auxiliary electrode was a Pt electrode. A silver wire pseudoreference was used. The silver wire was polished and placed in a capillary containing 0.1 M TBAPF6 in MeCN and separated from solution with a Vycor tip. Scans were internally referenced to ferrocene (FeCp*0). The concentrations of CoCp2, FeCpCp*, and FeCp2 were each ca. 1 mM. Where appropriate, literature E° values were corrected to FeCp*0 reference using (18) or (21).

Synthesis

**2-(9H-fluoren-9-yl)benzoic acid (1H)**

Methyl ester precursors for 1H and its para-carboxy isomer, 4-(9H-fluoren-9-yl)benzoic acid, were prepared from fluorene and the appropriate aryl bromide following the procedure of Chen and co-workers (22). The isolated methyl ester (1.252 g, 4.17 mmol) was added to a degassed solution of ethanol (120 ml) and 3 M aqueous KOH (30 ml). This solution was brought to reflux for 25 min, after which the reaction mixture was cooled to room temperature and diluted with 1 M HClaq (100 ml), at which point a precipitate formed. The suspension was cooled in a refrigerator overnight and filtered, and the filtrate was washed with water to yield the product as a white solid (1.107 g, 3.87 mmol). The 1H NMR in CDCl3 matched a previous report (23). 4H NMR (400 MHz, CD3CN) δ (parts per million (ppm)): 6.33 (s, 1H, Fl–9H), 6.39 (d, 1H, 7.23 to 7.34 (m, 6H), 7.42 (td, 2H), 7.90 (d, 2H), 8.03 (d, 1H), 9.77 (carboxylic acid, brs, 1H).

**2-(9D-fluoren-9-yl)benzoic acid (1-d1)***

Following literature precedent (24), 1H (0.143 g, 0.5 mmol) was dissolved in anhydrous THF (15 ml) under an inert atmosphere and...
cooled to −78°C. n-Butyllithium (0.625 ml of 1.6 M solution in hexanes, 1 mmol) was added dropwise, yielding a bright red-orange solution. After stirring for 2 hours, the reaction mixture was allowed to warm to room temperature and was then quenched with D₂O (0.5 ml) and stirred an additional 15 min. The reaction mixture was diluted with water (100 ml) and made acidic with HClₐq and then washed with DCM (3 × 30 ml). The organics were washed with water (2 × 30 ml) and then brine (30 ml) and dried with magnesium sulfate. Removal of solvent yielded a white solid product (0.133 g, 0.46 mmol). High conversion of 1 to 1-d₁ was confirmed by the absence of any detectable peak at δ = 6.39 ppm (in CDCl₃) in the ¹H NMR spectrum.

**4-(9H-fluorene-9-yl)benzoic acid**

This *para*-carboxy isomer of 1H was prepared via the methyl ester (22) under the same conditions used for 1H. The ¹H NMR spectrum in DMSO-d₆ is consistent with a literature report (25). ¹H NMR (400 MHz, CD₂CN) δ (ppm): 9.37 (brs, 1H), 7.91 (dd, 1H), 7.50 (td, 1H), 7.35 (td, 1H) 7.27 (dd, overlapping with solvent), 5.13 (m, 1H), 4.90 (m, 1H).

**Calculations**

Details of the DFT screening calculations can be found in the Supplementary Materials. All calculations were performed using Gaussian 09 (27). Optimized geometries were confirmed to be local minima by vibrational analysis (NIMAG = 0). Computed vibrational frequencies are unscaled. Unless otherwise specified, all calculations were performed using (U)B3LYP/6-31+G(d) with a polarizable continuum model [PCM; (28)] of MeCN solvent. NMR calculations used B3LYP/6-31+G(2d,p)/B3LYP/6-31+G(d), with a PCM of MeCN solvent.

**Kinetics**

Stopped-flow kinetic runs were performed on a single-mixing OLIS RSM-1000 stopped-flow spectrophotometer. The solvent was anaerobic MeCN (Burdick & Jackson low water) that was sparged with argon and plumbed directly into a N₂-filled glovebox. All solutions used for kinetics were prepared in a N₂-filled glovebox and used within an hour of preparation. All measurements were made at 295 ± 2 K. Typically, a solution of oxidant (10⁻² to 10⁻³ M) was reacted with a series of solutions of ¹⁻ generated in situ with tetra-butylammonium hydroxide (1 M in MeOH). MeOH was added to solutions of ¹⁻ such that the [MeOH] was consistent in all solutions. Concentrations of ¹⁻ ranged from ca. 10- to 50-fold molar excess (in reactions using amium iodinates) or ca. 4- to 20-fold molar excess (in reactions using ferrocenium iodinates). Additional information can be found in the Supplementary Materials.

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30. J. W. D. and T. F. M. performed all experimental work and data analysis; each made substantial and complementary contributions to the work. J. W. D., T. F. M., and J. M. M. conceived the approach, designed and performed all DFT calculations, synthesized the substrates, and discovered the MS-CPET reactions of diphenylethylene by a thermally frustrated diethyl ether-BF3 Lewis pair. J. M. M. suggested the project and oversaw the work including direction and scope. J. W. D. and T. F. M. acknowledge financial support from the U.S. NIH (2R01GM50422 to J. M. M.).
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