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Catalytic Ketyl-Olefin Cyclizations Enabled by Proton-Coupled Electron Transfer

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Supporting Information

ABSTRACT: Concerted proton-coupled electron transfer is a key mechanism of substrate activation in biological redox catalysis. However, its applications in organic synthesis remain largely unexplored. Herein, we report the development of a new catalytic protocol for ketyl-olefin coupling and present evidence to support concerted proton-coupled electron transfer being the operative mechanism of ketyl formation. Notably, reaction outcomes were correctly predicted by a simple thermodynamic formalism relating the oxidation potentials and pK_a values of specific Brønsted acid/reductant combinations to their capacity to act jointly as a formal hydrogen atom donor.

Proton-exchange reactions can exert a profound influence on the rates and thermodynamics of associated electron transfers.[1] The significance of these effects is evident in the critical roles that proton-coupled electron transfers (PCET) play in processes as diverse and essential as photosynthetic water oxidation, ribonucleotide reduction, aerobic respiration, and enzymatic C−H bond oxidation.[2] Much current research in PCET reactivity is focused on the advantages afforded by concerted transfer pathways, wherein independent electrons and protons are simultaneously exchanged in a single elementary step. The energetic coupling enforced by a shared transition state allows a favorable driving force associated with one exchange event to compensate for unfavorable energetics in the other without requiring the generation of an intermediate (Figure 1).[3] The more favorable driving forces that result are often complemented by diminished activation barriers,[4] allowing concerted PCET to proceed more rapidly than either competing sequential transfer pathway.

While these kinetic advantages are now widely recognized, concerted PCET[5] has rarely been invoked as a mechanism of substrate activation in organic synthesis.[6] Yet, its potential to function in this capacity is uncommonly broad. Many organic functionalities exhibit large changes in pK_a upon undergoing one-electron oxidation or reduction.[7] As such, coordinating a favorable proton transfer to occur in concert with electron transfer can enable redox reagents with potentials far less energetic than those of their substrates to be successfully employed. This attribute makes concerted PCET activation particularly attractive for applications in photoredox catalysis.[8] Many synthetically valuable radical classes remain inaccessible using these technologies, as the potentials required for their generation are unattainable using established catalyst systems, or the necessary electron-transfer events are too slow to be operative within the lifetime of a given catalyst excited state. In principle, the rate accelerations afforded by concerted PCET may provide a general solution to both of these limitations and provide opportunities to significantly expand the scope of substrates amenable to use in these platforms.[9]

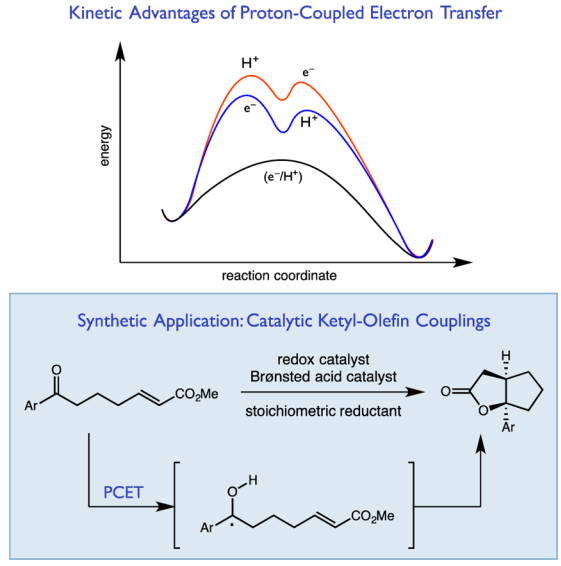

Figure 1. Energetic advantages of concerted PCET and application to catalytic ketyl formation.

Herein we demonstrate the feasibility of concerted PCET activation in organic synthesis in the context of a new catalytic protocol for ketyl-olefin coupling (Figure 1). Ketyls are versatile synthetic intermediates derived from the one-electron reduction of carbonyl compounds that play a key role in numerous important bond-forming and bond-breaking processes.[10] However, the strongly negative potentials required to generate ketyls by electron transfer places practical limits on the scope of viable redox partners, and to date only a handful of catalytic ketyl-olefin coupling chemistries have been developed.[11] We anticipated that the large change in basicity (>17 pK_a units in H_2O)[12,13] attendant to one electron reduction would make ketones attractive candidates for concerted PCET activation and presents an opportunity to develop catalytic ketyl chemistries that employ comparatively mild outer sphere reductants in combination with a catalytic proton donor.

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Research Design. The success of these efforts was predicated on correctly evaluating the feasibility of ketyl formation under the action of specific combinations of one-electron redox catalysts and Brønsted acids. We expected that the reduction potentials of typical ketones ($E_{1/2}^{red}$ = −2.48 V vs Fc for acetophenone)[14] should render them inert to all but the most strongly reducing photocatalysts. Similarly, ketones are weakly basic (pK_a in MeCN = −0.1 for acetophenone), requiring strong acids to generate any meaningful concentration of protio-oxocarbenium ions.[15] However, we anticipated that the joint action of acids and reductants with pK_as and potentials far removed from these values could facilitate efficient ketyl formation through a concerted PCET manifold.

The selection of which acids and reductants to employ could be assessed in quantitative terms by considering an energetic analogy between PCET and related hydrogen atom transfer (HAT) processes. As in HAT, the thermodynamics of a PCET reaction can be described by the difference in bond dissociation free energies (BDFEs) between two bonds undergoing exchange. While no bond in the acid-reductant pair is cleaved homolytically, Mayer and co-workers recently proposed that an energy thermodynamically equivalent to a BDFE may be calculated for any acid/reductant pair from the pK_as and redox potentials of its constituents as well as a constant term that accounts for proton reduction (Figure 2).[7,16] This formalism, which finds its basis in

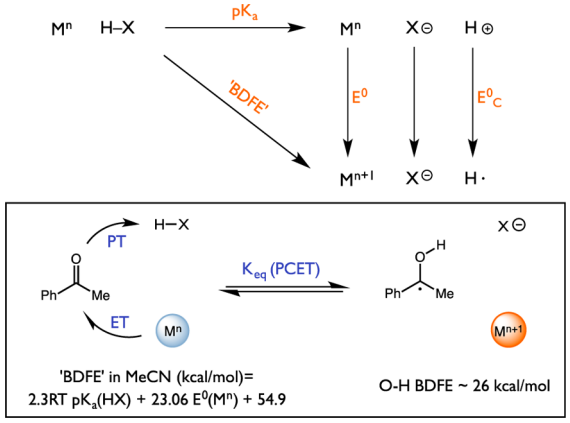
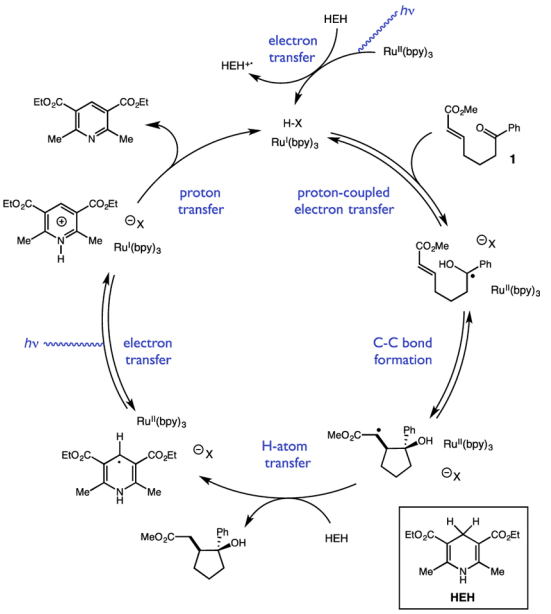


Figure 2. Thermodynamic cycle for determination of formal BDFE values and application to ketyl PCET.

the classical bond strength calculations popularized by Bordwell,[17] allows the thermodynamics of any proposed PCET event to be readily evaluated by comparing the formal BDFE ('BDFE') of a given acid/reductant pair to the strength of the new bond formed in the transfer event. For ketyl formation, CBS-QB3 calculations provided a BDFE for the O−H bond in the acetophenone ketyl of 26 kcal/mol. We reasoned that at formal BDFE values approaching the strength of the ketyl O−H bond, concerted PCET may become kinetically feasible, and subsequent ketyl reactivity might be observed.[18]

To evaluate the correspondence between formal bond strengths and reaction outcomes, we studied the intramolecular cyclization of ketone **1** using the photoredox catalyst Ru(bpy)$_3$(BAr^F)$_2$ in the presence of various Brønsted acids. We envisioned a catalytic cycle (Scheme 1) initiated by excitation of the ruthenium photocatalyst with 450 nm light. The resulting excited state ($^*E_{1/2}^{red}$ = 0.39 V vs Fc)[19] would be reduced by Hantzsch dihydropyridine (HEH) ($E_{1/2}^{ox}$ = 0.51 V vs Fc)[20] to generate the more strongly reducing Ru^I(bpy)$_3$ ($E_{1/2}^{ox}$ = −1.71 V

Scheme 1. Proposed Catalytic Cycle



vs Fc) and the radical cation HEH$^{+\bullet}$. Concurrently, the Brønsted acid catalyst could be expected to reversibly form a hydrogen-bonded complex with the ketone substrate. Concerted PCET would follow, with electron transfer from the redox catalyst occurring concomitantly with proton transfer to the ketone oxygen along the hydrogen-bond coordinate to generate a neutral ketyl intermediate. This radical would add conjugately to the pendant acrylate to form a new carbocyclic ring and an α-carbonyl radical. Hydrogen atom transfer from HEH to this intermediate would generate the desired closed shell product. The oxidized HEH radical would then regenerate the active form of the acid/reductant donor pair through electron- and proton-transfer events with the excited state of the redox catalyst and the conjugate base of the Brønsted acid.

Optimization and Results. In accord with our thermodynamic analysis, visible light irradiation of a THF solution containing ketone **1** in the presence of 2 mol % Ru(bpy)$_3$(BAr^F)$_2$ and HEH resulted in no conversion. (Table 1, entry 1). Similarly, inclusion of Brønsted acids whose pK_a values, in combination with the Ru(I) reductant, did not furnish formal BDFEs approaching those of the ketyl O−H bond was similarly ineffective (Table 1, entries 2−4). However, addition of 5 mol % diphenyl phosphoric acid (pK_a in MeCN ∼ 13, 'BDFE' = 33 kcal/mol)[21] resulted in full conversion of the ketone starting material and produced the desired cyclization products **2** and **3** as a 4.6:1 mixture in 78% overall yield in 4 h at room temperature (Table 1, entry 5). Other combinations utilizing more strongly reducing redox agents or stronger Brønsted acids were uniformly successful (Table 1, entries 6−8). Notably, when more strongly reducing catalysts were employed, Brønsted acids that previously failed to activate **1** toward PCET were found to be effective, in accord with formal BDFEs commensurate with that of the O−H bond of the ketyl intermediate (Table 1, entry 9).[22] An evaluation of alternative stoichiometric hydrogen atom donors established that the selectivity for the lactone product **2** could be improved to 10:1 when 2-phenyl-dihydrobenzothaizoline (BT) was employed in place of HEH (Table 1, entry 10). This suggests that C−C bond formation may be reversible in these reactions

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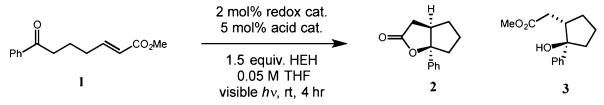
Table 1. Optimization of the Ketyl-Olefin Coupling[a]



1 2 3

entry	acid catalyst	redox catalyst	'BDFE'	% yield	2:3
1	none	$Ru(bpy)_3(BAr^F)_2$	–	0	–
2	BzOH	$Ru(bpy)_3(BAr^F)_2$	45	0	–
3	$NEt_3{\cdot}HBF_4$	$Ru(bpy)_3(BAr^F)_2$	41	0	–
4	lutidine·HBF_4	$Ru(bpy)_3(BAr^F)_2$	35	0	–
5	$(PhO)_2PO_2H$	$Ru(bpy)_3(BAr^F)_2$	33	78	4.6:1
6	*p*TSA	$Ru(bpy)_3(BAr^F)_2$	27	74	4.3:1
7	$(PhO)_2PO_2H$	$Ir(ppy)_2(dtbpy)PF_6$	29	93	4.8:1
8	$(PhO)_2PO_2H$	*fac*-$Ir(ppy)_3$	24	92	4.8:1
9	lutidine·HBF_4	$Ir(ppy)_2(dtbpy)PF_6$	31	74	4.9:1
10[b]	$(PhO)_2PO_2H$	$Ru(bpy)_3(BAr^F)_2$	33	89	10:1

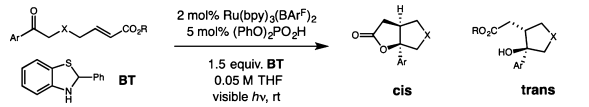
[a]Yields and isomeric ratios were determined by GC analysis of crude reaction mixtures relative to calibrated internal standards. Visible light irradiation was provided by 26 W fluorescent lamps. Formal BDFE values ('BDFE') calculated using the thermodynamic cycle presented in Figure 2 from pK_a and potential data in MeCN. For details, see Supporting Information. [b]BT used in place of HEH.

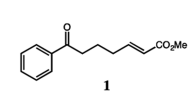
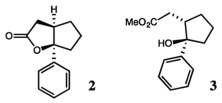
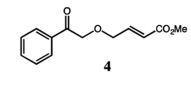
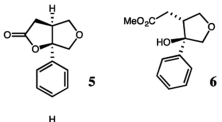
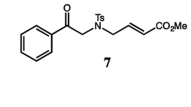
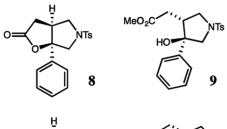
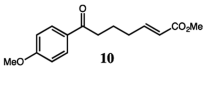
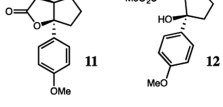
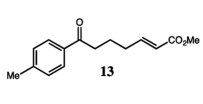
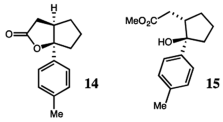
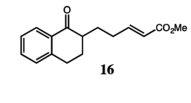
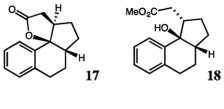
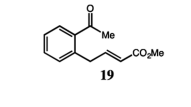
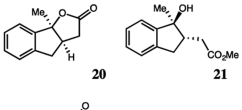
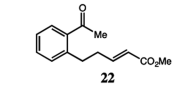
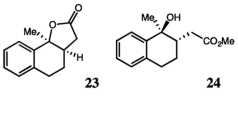
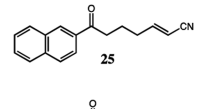
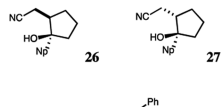
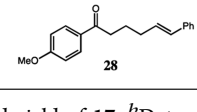
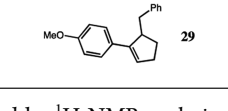
and that the diastereoselectivity is determined, at least in part, by the relative rates of the HAT steps.

Having established effective conditions for the cyclization of **1**, we next investigated the scope and generality of this protocol. On a preparative scale, model substrate **1** cyclized to produce **2** and **3** in a combined 73% isolated yield as an 11:1 mixture of diastereomers (Table 2, entry 1). Incorporation of α-oxygen and α-nitrogen substituents was well-tolerated, providing 2,3-disubstituted tetrahydrofuran (**5** and **6**) and pyrrolidine products (**8** and **9**) in good yields (Table 2, entries 2 and 3). Ketones **10** and **13**, whose reduction potentials are nearly 900 mV more negative than the oxidation potential of the active Ru(I) catalyst, were also found to be viable substrates (Table 2, entries 4 and 5).[13] Alkyl branching α to the carbonyl was tolerated, as demonstrated by the successful cyclization of a tetralone-derived substrate to produce fused polycyclic product **17** in high diastereoselectivity (Table 2, entry 6). An *ortho*-substituted acetophenone derivative **19** provided cyclized products in 96% yield as a 2:1 mixture of diastereomers favoring the lactone product **20** (Table 2, entry 7). The six-membered analogue **22** was also found to be a viable substrate, though it cyclized with poor diastereoselectivity (Table 2, entry 8). Acrylonitrile **25** was also cyclized under these conditions, furnishing γ-hydroxy nitrile product **26** (Table 2, entry 9). Lastly, it was found that these conditions could enable ketyl additions to styrenyl acceptors, such as **28**, resulting in the formation of dehydrated product **29** in good yield (Table 2, entry 10). Notably, for the acrylate substrates, this protocol provides selective access to the *cis*-fused bicyclic lactone products, which are generally the minor diastereomeric products observed when these and similar substrates are cyclized under the action of SmI_2.[23]

Mechanism of ketyl formation. We studied the mechanism of ketyl formation using fluorescence quenching techniques and acetophenone as a model substrate.[24,25] A Stern–Volmer analysis revealed that acetophenone ($E_{1/2}^{red}$ = −2.48 V vs Fc) does not quench the excited state of $Ir(ppy)_3$ ($*E_{1/2}^{ox}$ = −2.11 V vs Fc) in acetonitrile at 25 °C.[26] However, inclusion of diphenyl phosphoric acid resulted in a large decrease in the measured fluorescence. Control experiments confirmed that the phosphoric acid itself does not quench the Ir(III) excited state at the

Table 2. Substrate Scope of the Ketyl-Olefin Coupling[c]



entry	substrate	products	yield (cis:trans)
1			73% 11:1
2			87% 4.8:1
3			80% 3.4:1
4			78% 12:1
5			86% 6:1
6			82%[a] 16:1[b]
7			96% 2:1
8			78% 1.2:1
9			64% 10:1
10			68%

[a]Isolated yield of **17**. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Reactions run on 0.5 mmol scale. Yields and isomeric ratios are for isolated material following chromatography. Visible light irradiation was provided by 26 W fluorescent lamps.

concentrations studied. Variation of the acid and ketone concentrations in these assays revealed that the quenching process exhibits a first-order dependence on each component. Additionally, an isotope effect of 1.22 ± 0.02 was observed in quenching studies conducted with protiated and deuterated diphenyl phosphoric acid. Collectively, these results preclude direct electron transfer from being the mechanism of excited-state quenching.

In principle, the observed rate law is consistent with either a stepwise pathway involving rate-limiting proton transfer followed by fast electron transfer to a protio-oxocarbenium ion or a concerted proton–electron transfer to a hydrogen-bonded

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ketone·acid complex. The former possibility can be discounted by considering the large pK_a difference in MeCN between protonated acetophenone (pK_a = −0.1)[15] and the diphenyl phosphoric acid (pK_a ∼ 13).[21] Taking this free energy difference of +17.9 kcal/mol as the minimal kinetic barrier to proton transfer necessitates a rate constant $<4.6 \times 10^{-1}$ $M^{-1}s^{-1}$. As such, this stepwise mechanism is too slow to be operative within the 1.9 μs lifetime of the Ir(III) excited state.[26]

As both sequential transfer mechanisms can be discounted, the observed rate law suggests that concerted mechanisms are likely operative in ketyl formation. Assuming a BDFE of 26 kcal/mol for the acetophenone ketyl O−H bond, the driving force for concerted transfer with these reagents is −1.9 kcal/mol. Importantly, while these experiments were carried out in MeCN to allow comparisons to established pK_a and potential values, catalytic reactions of **1** and BT under the action of $Ir(ppy)_3$ and diphenyl phosphoric acid in MeCN were viable, delivering the cyclization products in 83% yield as a 5.3:1 mixture of diastereomers.

Analogous fluorescence quenching studies are not possible in the ruthenium-catalyzed reactions due to the more modest reducing abilities of the $Ru^{II}(bpy)_3$ excited state ($^*E_{1/2}^{ox}$ = −1.19 V vs Fc, 'BDFE' = 45 kcal/mol with diphenyl phosphoric acid). However, analysis of the relevant energies required by the stepwise pathways would suggest that concerted PCET is also operative in the catalytic reactions. While direct electron transfer between $Ru^{I}(bpy)_3$ and **1** is endergonic by ∼18 kcal/mol, the driving force for ketyl formation in the analogous PCET mechanism is only +7.0 kcal/mol. This assumption is bolstered by the lack of consumption of **1** under conditions known to generate Ru(I), both in the presence and absence of Brønsted acids of sufficient acidity to quantitatively protonate any transiently generated ketyl radical anion (pK_a ∼20 in MeCN) (Table 1, entries 1−4).

In conclusion, we have developed a new protocol for catalytic ketyl radical chemistry enabled by concerted proton-coupled electron transfer. We anticipate that concerted PCET will prove to be a general mode of catalytic activation and the elements of reaction design described herein will prove successful in their application to other substrate classes and transformations as well.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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