

Catalytic Ring-Opening of Cyclic Alcohols Enabled by PCET Activation of Strong O–H Bonds

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S Supporting Information

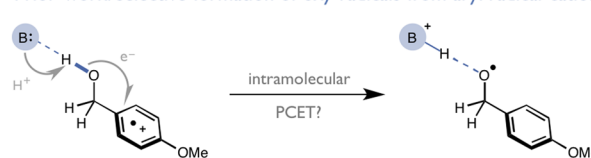
ABSTRACT: We report a new photocatalytic protocol for the redox-neutral isomerization of cyclic alcohols to linear ketones via C–C bond scission. Mechanistic studies demonstrate that key alkoxy radical intermediates in this reaction are generated via the direct homolytic activation of alcohol O–H bonds in an unusual intramolecular PCET process, wherein the electron travels to a proximal radical cation in concert with proton transfer to a weak Brønsted base. Effective bond strength considerations are shown to accurately forecast the feasibility of alkoxy radical generation with a given oxidant/base pair.

Alkoxy radicals are versatile synthetic intermediates, enabling both H-atom abstraction from unfunctionalized alkanes and the cleavage of adjacent C–C bonds via β -scission.^{1,2} In principle, alkoxy radicals can be accessed via direct hydrogen atom transfer from the hydroxyl groups of aliphatic alcohols. However, the pronounced homolytic stability of these bonds (O–H BDFEs \approx 105 kcal/mol) presents a challenge to the design of such schemes, and general catalytic methods for the selective homolysis of alcohol O–H bonds are currently unknown.³

Our group has recently become interested in an alternative approach to the homolytic activation of strong bonds based on proton-coupled electron transfer (PCET).⁴ In oxidative PCET reactions, a one-electron oxidant and a Brønsted base function together to remove a proton and an electron from a substrate in a concerted elementary step. As the oxidant and base can be varied independently, the thermochemistry of PCET processes can be rationally modulated over a wide range of energies to facilitate the homolytic cleavage of strong bonds that cannot be activated using conventional H-atom transfer catalysts.⁵ With respect to alcohol PCET reactivity, we were intrigued by elegant spectroscopic studies from Bacchioici, Bietti, and Steenken, who demonstrated that the O–H bonds of alcohols adjacent to arene radical cations undergo selective deprotonation at near diffusion-controlled rates with modest driving forces to furnish discrete alkoxy radical intermediates (Figure 1).⁶ While the precise mechanism of the intramolecular charge transfer event was not delineated in these studies, the authors suggested that concerted PCET may play a role.

Here we provide support for this hypothesis in the context of a novel catalytic method for the isomerization of cyclic aryl alkanols to linear ketones. This redox-neutral process is mediated by a key alkoxy radical intermediate that is generated through an unusual intramolecular PCET event between a tertiary hydroxyl

Prior work: Selective formation of oxy-radicals from aryl radical cations



Synthetic application: redox-neutral isomerization of cyclic alcohols

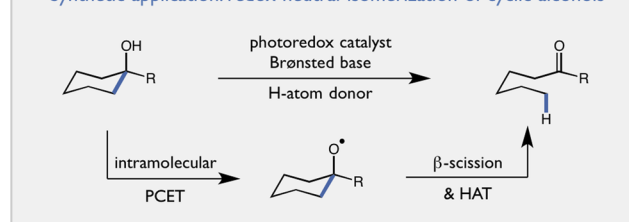


Figure 1. Catalytic ring-opening of cyclic alcohols via PCET.

group and a proximal radical cation in the presence of a weak Brønsted base (Figure 1). Notably, this protocol allows alkoxy radical generation from alcohols that are spatially removed from the arene radical cation, providing a means to selectively cleave distal C–C bonds. This reaction represents a rare example of catalytic alcohol O–H homolysis⁷ and may provide new opportunities for the strategic use of C–C bond cleavage transforms in synthesis. The design, scope, and preliminary mechanistic evaluation of this process are presented herein.

Our synthetic studies examined the catalytic isomerization of alcohol **1** to ketone **2** using a ternary catalyst system comprising a visible light photoredox catalyst, a Brønsted base, and a thiol hydrogen atom donor (Figure 2). We anticipated a catalytic cycle wherein oxidation of the electron-rich arene by the excited state of the redox catalyst would furnish a transient radical cation. An intramolecular PCET reaction would follow (*vide infra*) in which deprotonation of the hydroxyl group by the Brønsted base catalyst occurs in concert with one-electron reduction of the radical cation to provide the key alkoxy radical intermediate. It is well-known that alkoxy radicals substantially weaken adjacent C–C bonds,⁸ enabling favorable ring-opening to generate an aryl ketone and a distal alkyl radical. A catalytic H atom donor, such as thiophenol, could then intercept and reduce the nascent alkyl radical,^{9,10} affording a linear ketone product. Reduction of the resulting thiyl by the reduced state of the photocatalyst and protonation by the conjugate acid of the Brønsted base would complete the catalytic cycle.

Received: June 23, 2016

Published: August 12, 2016

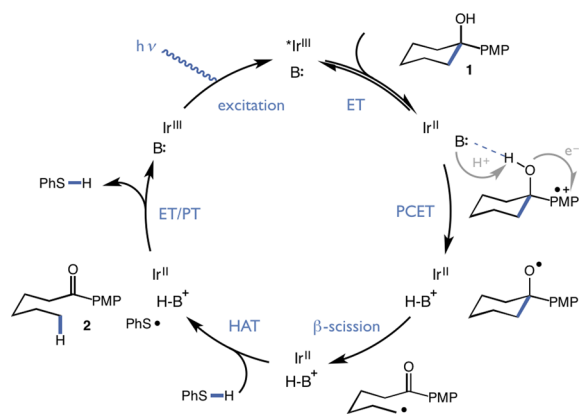


Figure 2. Proposed catalytic cycle.

Gratifyingly, we found that when **1** ($E_{p/2} = 1.22$ V vs Fc/Fc^+) was exposed to sufficiently oxidizing Ir photocatalysts under blue light irradiation in the presence of thiophenol and a number of weak Brønsted bases, ring-opened product **2** was observed (entries 1–7, Table 1). The most oxidizing catalyst evaluated in the series, $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{S},\text{S}'\text{-d}(\text{CF}_3)\text{bpy})](\text{PF}_6)$ (**C**) ($*E_{1/2} = 1.30$ V vs Fc/Fc^+), proved optimal, while collidine was found to be the most efficient proton acceptor (entry 3). Up to 91% yield of **2** was observed when 3 equiv of collidine was used; however, lower base loadings were also effective (entries 3, 8, 9). Control experiments run in the absence of light, photocatalyst, or Brønsted base provided essentially no product. Reactions excluding thiophenol produced **2** in 50% yield, presumably due to HAT from the benzylic C–H bonds of collidine to the alkyl radical. The use of CD_2Cl_2 solvent did not result in deuterium incorporation.

With these optimized conditions, we evaluated the scope of the isomerization process. On preparative scale the model reaction was successful, furnishing ketone **2** in 89% yield. We also observed that numerous other ring sizes could be accommodated (3–8) (Table 2) suggesting that ring strain is not a prerequisite for efficient bond scission.¹¹ In unsymmetrical ring systems, high selectivities were observed for bond scissions that eject the more stable radical intermediate (9–12, 14). Moreover, this selectivity was also manifested in β -substituted substrates such as that leading to **13**, which demonstrated 8.5:1 selectivity for cleavage to form a neopentyl radical. Importantly, successful cleavage to

form **18** demonstrates that the electron-rich PMP group need not reside on the same carbon as the alcohol. Additionally, this ring-opening strategy can be applied toward more complex cyclic and bicyclic structures such as **15**, **16**, and **17** without compromising proximal stereocenters. Complex natural product-derived substrates such as hecogenin analogue **19** were also successful. Notably, while the substrate leading to **19** exhibits two distinct hydroxyl groups, β -scission occurs exclusively on the alcohol proximal to the PMP-group.

In addition to *p*-methoxyphenyl, a number of arenes can be accommodated as the initial site of oxidation, including benzofuran (**20**), benzothiophene (**21**), naphthalene (**22**), and phenanthrene (**23**). Furthermore, the reaction conditions can be used to extrude free alkyl radical fragments from linear alcohols (**24–26**). Again, high selectivities were observed for bond cleavages to form the more stabilized radical leaving group. Lastly, we found that fluorine-, chlorine-, and bromine-atom donors could all be readily incorporated into the catalytic cycle in place of the thiol catalyst to produce distally halogenated ketones **27**, **28**, and **29**. With respect to limitations, this protocol is unsuccessful with arenes that cannot be oxidized by **C** (such as the simple phenyl analogue of **1**), as well as nonaryl tertiary alkyl carbinols. Efforts to address these constraints are ongoing.

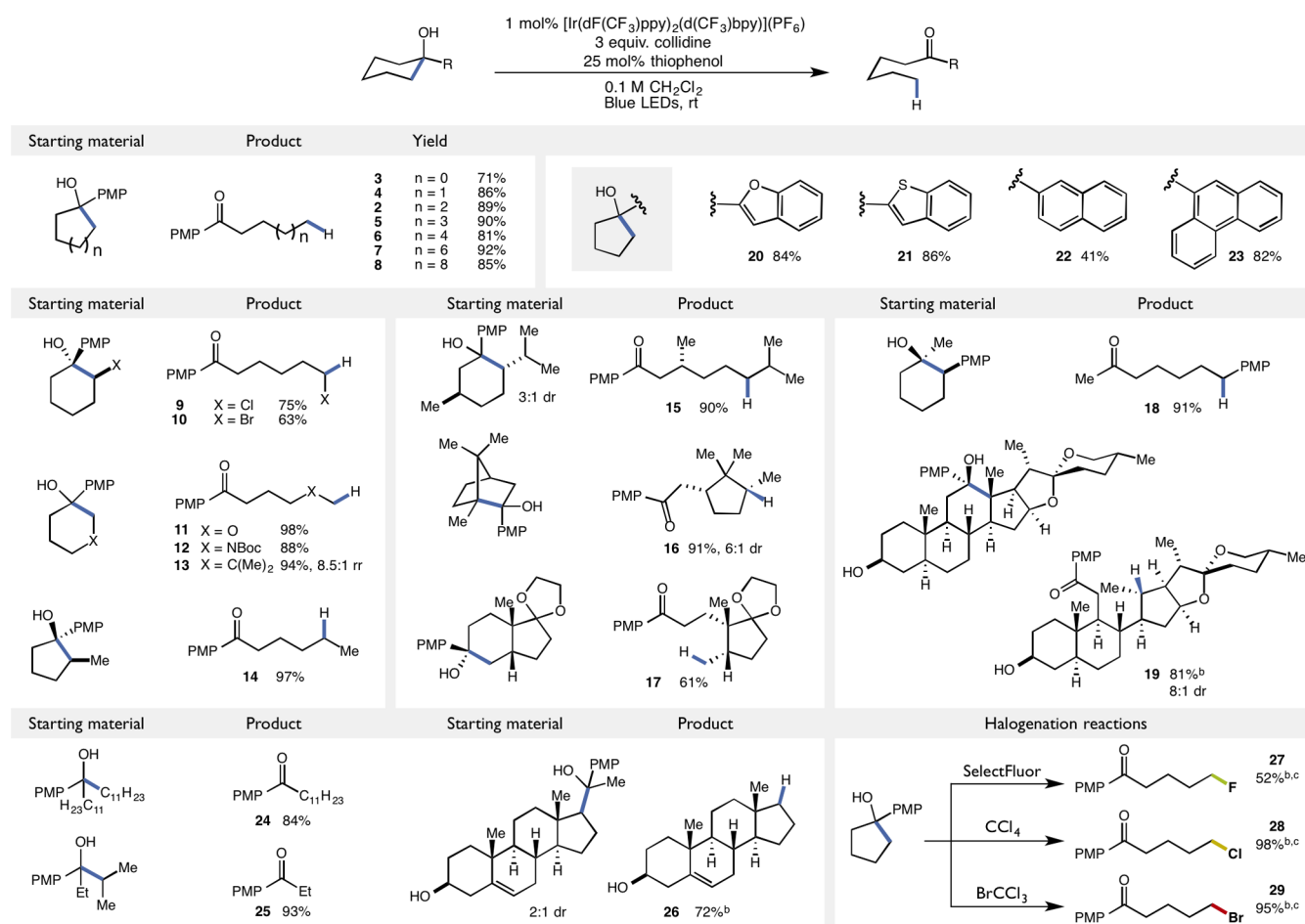
In addition to these synthetic studies, we have also examined the initial steps of the proposed catalytic cycle. With respect to the first electron transfer event, Stern–Volmer analysis revealed that the excited state of iridium catalyst **C** is efficiently quenched by admixtures of collidine and the cyclooctyl analogue of **1** in CH_2Cl_2 at rt. Independently varying the concentrations of these two components revealed a first order dependence on the concentration of alcohol and a zero order dependence on the concentration of collidine, suggesting that direct arene oxidation, rather than O–H PCET, is the dominant mechanism of excited state charge transfer. Based on potential difference this excited state ET reaction is exergonic by ~ 90 mV.

To determine whether the subsequent charge transfer event between the arene radical cation and the O–H bond proceeds via stepwise PT/ET or concerted PCET, we evaluated the C–C cleavage reactivity of a series of substrates with an increasing number of methylene groups between the alcohol and the arene (Figure 3). This line of inquiry was guided by the assumption that the $\text{p}K_a$ of the scissile O–H bond should rapidly increase as a function of increasing distance from the radical cation, ultimately approaching that of an isolated tertiary alcohol (~ 40 in

Table 1. Reaction Optimization^a

entry	photocatalyst	base	yield (%)
1	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})](\text{PF}_6)$ (A)	collidine	0
2	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})](\text{PF}_6)$ (B)	collidine	9
3	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{S},\text{S}'\text{-d}(\text{CF}_3)\text{bpy})](\text{PF}_6)$ (C)	collidine	79
4	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{S},\text{S}'\text{-d}(\text{CF}_3)\text{bpy})](\text{PF}_6)$ (C)	pyridine	6
5	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{S},\text{S}'\text{-d}(\text{CF}_3)\text{bpy})](\text{PF}_6)$ (C)	TBA ⁺ (PhO) ₂ POO [−]	4
6	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{S},\text{S}'\text{-d}(\text{CF}_3)\text{bpy})](\text{PF}_6)$ (C)	TBA ⁺ CF ₃ COO [−]	48
7	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{S},\text{S}'\text{-d}(\text{CF}_3)\text{bpy})](\text{PF}_6)$ (C)	TBA ⁺ PhCOO [−]	8
8	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{S},\text{S}'\text{-d}(\text{CF}_3)\text{bpy})](\text{PF}_6)$ (C)	collidine (2 equiv)	83
9	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{S},\text{S}'\text{-d}(\text{CF}_3)\text{bpy})](\text{PF}_6)$ (C)	collidine (3 equiv)	91

^aOptimization reactions were performed on a 0.05 mmol scale. Yields determined by ¹H NMR analysis of the crude reaction mixtures. Structures and potential data for all photocatalysts are included in the SI.

Table 2. Substrate Scope^a

^aReactions run on 1.0 mmol scale. Reported yields are for isolated and purified material and are the average of two experiments. Diastereomeric ratios were determined by ¹H NMR or GC analysis of the crude reaction mixtures. ^b0.5 mmol scale. ^cFor experimental details of halogenations, see SI.

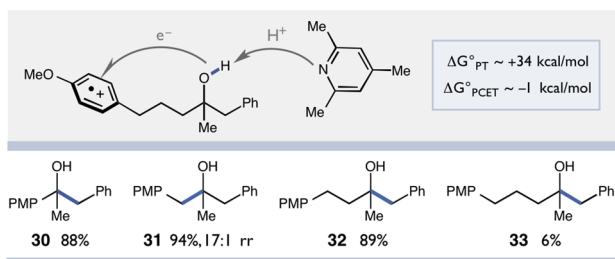


Figure 3. Distal C–C bonds cleaved via long-range PCET.

MeCN).^{5c} In this limiting regime, deprotonation of the hydroxyl by collidine ($pK_a = 15.0$ in MeCN)¹² would be prohibitively endergonic ($\Delta G^\circ \approx +34$ kcal/mol) and unable to compete with charge recombination between the arene radical cation and the reduced Ir(II) state of the photocatalyst ($\Delta G^\circ = -53$ kcal/mol). Conversely, the thermochemistry of concerted PCET is expected to be modestly exergonic ($\Delta G^\circ \approx -1$ kcal/mol) virtually irrespective of the ET distance.¹³ Experimentally, we found that C–C cleavage reactivity was indeed observed for substrates with up to four carbon atoms separating the arene and the alcohol, a remarkable outcome that is strongly suggestive of a concerted PCET mechanism.¹⁴ In addition to their mechanistic significance, these observations suggest interesting synthetic possibilities wherein oxidation at a remote site might be relayed

to a specific hydroxyl group to induce selective cleavage of a distal C–C bond.

Based on the observations above, we also sought to evaluate how reaction outcomes varied as a function of the thermodynamic driving force for the PCET event. As noted by Mayer, the capacity of any given oxidant/base pair to function as a formal H^\bullet acceptor can be quantified as an effective bond strength (“BDFE”) derived from the pK_a and reduction potential of its constituents (see equation in Figure 4).^{4b} In our proposed mechanism, the relevant reduction potential is that of the arene radical cation that serves as an internal oxidant. To examine the relationship between effective BDFEs and reaction outcomes, we evaluated the isomerization reaction for eight substrates bearing different arenes with oxidation potentials spanning a range of ~ 900 mV. In conjunction with four different Brønsted bases, we were able to generate a set of 32 unique combinations with effective bond strengths ranging from 77 to 105 kcal/mol. Remarkably, in all cases wherein the effective BDFE of the oxidant/base combination approaches or exceeds that of the substrate (O–H BDFE ≈ 102 kcal/mol),¹³ the reactions were successful and generated the expected ketone products. However, all combinations with effective BDFEs less than ~ 98 kcal/mol furnished little or no ring-opened products. These energetic correlations provide further support for the notion that

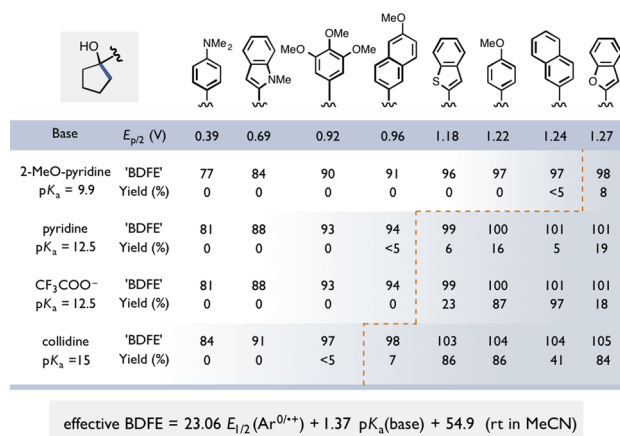


Figure 4. Effective BDFE correlations with reactivity.

simple thermodynamic considerations can be used to accurately forecast the feasibility of a given PCET process.¹⁵

In conclusion, we have developed a new catalytic method for the redox-neutral isomerization of cyclic alkanols to linear ketones that proceeds via C–C bond β -scission. Moreover, this work represents a rare example of alkoxy radical generation via multisite PCET activation of alcohol O–H bonds. Efforts to expand these results to include simple alcohol substrates are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06517.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the NIH (R01 GM113105). R.R.K. is a fellow of the A. P. Sloan Foundation. We thank István Pelczer for help with NMR experiments and Laura Wilson for help with sample purification.

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