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Tuning Reactivity and Chemoselectivity in Electron Transfer Initiated Cyclization Reactions: Applications to Carbon−Carbon Bond Formation

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When properly substituted, organic radical cations undergo mesolytic cleavage reactions to form radical fragments and cationic fragments.[1] Generating electrophiles through this process nicely complements acid-mediated functional group activation due to the orthogonal chemoselectivity of acid−base interactions relative to electron transfer reactions, the most common method of preparing radical cations.[2] Studies that define the relationship between a functional group's oxidation potential and the propensity of its radical cation to fragment will significantly aid in the development of new and selective transformations based on oxidative cleavage. We recently reported a photoinduced electron transfer initiated heterocycle synthesis (Figure 1)[3] that proceeds through mesolytic carbon−carbon σ-bond cleavages of homobenzylic ethers or amides to form benzyl radicals and oxocarbenium or acyliminium ions, respectively, under essentially neutral reaction conditions. Initial attempts to form carbocycles through this process by utilizing electron-rich olefins as nucleophiles were unsuccessful, however, due to the preferential oxidation of the olefin over the arene. In this communication, we illustrate that a simple mathematical model aids in designing substrates that retain the reactivity of the parent series while undergoing arene oxidation with enhanced selectivity. We use this relationship to broaden the applicability of the method to include electron-rich olefins as nucleophiles. We also show that, by lowering the oxidation potential of the arene, ceric ammonium nitrate can initiate cyclizations under nonphotochemical conditions.

To establish a relationship between the oxidation potential of alkylarenes and the reactivity of their radical cations, we compared the reactions of homobenzylic ether **1a** with those of its more readily oxidized[2] *p*-methoxy-substituted analogue **1b** (Figure 2). While **1a** undergoes rapid cyclization to form **2** when irradiated (medium-pressure mercury lamp, Pyrex filter) in the presence of *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$) under aerobic conditions,[4] **1b** fails to react. These results can be explained by eq 1,[5] in which BDE(RC) defines the mesolytic bond dissociation energy of the radical cation, BDE(S) defines the homolytic bond dissociation energy of the same bond in the neutral substrate, E_{pa}(S) defines the oxidation potential of the substrate, and E_{pa}(E) defines the oxidation potential of the radical corresponding to the fragment that ultimately becomes the electrophile (the alkoxyalkyl radical in the present case).[6] Thus, lowering the oxidation potential of a cyclization substrate strengthens the benzylic carbon−carbon bond and suppresses cyclization despite the increased facility of radical cation formation.[7]

$$\mathrm{BDE(RC)} = \mathrm{BDE(S)} - E_{pa}(\mathrm{S}) + E_{pa}(\mathrm{E}) \qquad (1)$$

In addition to forecasting the inverse relationship between oxidation potential and radical ion reactivity, eq 1 also suggests that lowering BDE(S) should facilitate radical cation cleavage. Thus, cyclization substrates can be rationally designed to retain the high reactivity of the parent system while undergoing single electron

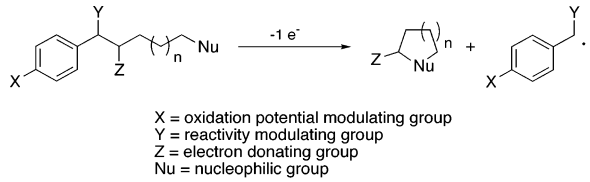

Figure 1. General representation of ETIC reactions.

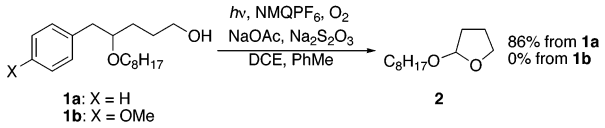

Figure 2. Effect of altering the arene oxidation potential on radical cation reactivity.

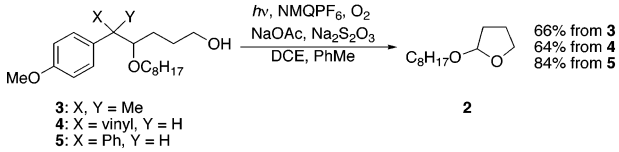

Figure 3. Reactivity recovery through selective bond-weakening.

oxidation with greater selectivity.[8] To test this hypothesis, we prepared several analogues of **1b**, in which the relevant carbon−carbon bonds were weakened by adding radical-stabilizing groups at the benzylic position,[9] and subjected them to our standard cyclization conditions (Figure 3). While all substitutions at the benzylic center enhanced reactivity relative to **1b**, phenyl substitution provided an exceptional rate enhancement, with substrate **5** displaying reactivity that essentially matches that of **1a**.[10] The benefits of lowering the oxidation potential of the substrate are manifested through the successful employment of ceric ammonium nitrate,[11] a mild oxidant that is unreactive toward **1a**, to initiate the cyclization of **5** to **2** in 45% yield under nonphotochemical conditions.

Lowering the oxidation potential of the arene also allows a much broader range of nucleophiles to be employed in this process. The capacity of several electron-rich olefins to serve as nucleophiles in carbocyclization reactions is shown in Table 1.[12] Cyclizations proceed with allylsilanes, allenylsilanes, and enol acetates (entries 1−3). Using trisubstituted olefins as the nucleophile (entry 4) creates new possibilities for initiating oxidative cascade cyclization reactions.[13] For most of the carbocyclization reactions, nonphotochemical Ce(IV)-mediated conditions[14,15] proved to be superior to photochemical conditions. These reactions are essentially instantaneous at moderate temperatures.

An improvement in the atom economy[16] of the reaction can be envisioned through incorporating the bond-activating group into the product instead of the leaving group. This can be accomplished by placing an olefin at the homobenzylic position and appending the nucleophilic group onto the ether linkage (Figure 4). We tested

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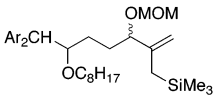
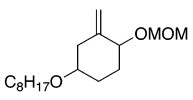
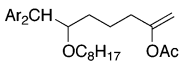
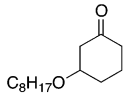
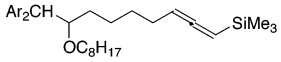
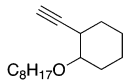
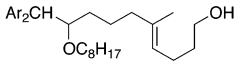
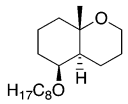
Table 1. Carbon Nucleophiles in ETIC Reactions[a]

Entry	Substrate[b,c]	Product	Yield (%)[d]
1[e]	 **6**	 **7**	71
2	 **8**	 **9**	94
3[f]	 **10**	 **11**	91
4[g]	 **12**	 **13**	49

[a] Reaction conditions: 2.5 equiv of CAN in CH_3CN was added to a suspension of the substrate, $NaHCO_3$, and 4 Å molecular sieves in DCE at 45 °C (entries 1−3). [b] Ar_2CH = *p*-MeOPhC(H)Ph. [c] See the Supporting Information for substrate syntheses. [d] Isolated yields of purified products. [e] Product was isolated as a 3:2 mixture of diastereomers. [f] Product was isolated as a 1:1 mixture of diastereomers after a Bu_4NF workup. [g] Photochemical conditions were employed. Stereochemistry was assigned by analyzing ^1H NMR coupling constants.

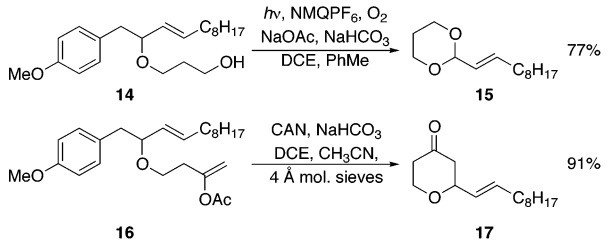


Figure 4. Placement of the bond-weakening group in the product fragment.

this strategy by subjecting **14** to our photochemical conditions. As predicted, we observed the smooth production of acetal **15**. Ce(IV)-mediated cyclization resulted in acetal hydrolysis, presumably due to the mild Lewis-acidity of Ce(III).[11] Notably, this design also accommodates carbon nucleophiles, with enol acetate **16** undergoing cyclization under Ce(IV)-mediated conditions to form tetrahydropyrone **17** in 91% yield.

In summary, we have shown that the facility of carbon−carbon bond cleavage reactions for alkylarene radical cations correlates with expected trends for the oxidation potentials of the substrates, with diminished reactivity being observed at lower oxidation potentials. A simple relationship between the arene's oxidation potential and the bond dissociation energy of the benzylic carbon−carbon bond has been exploited to design substrates that can be oxidized under mild conditions while still undergoing efficient mesolytic cleavage reactions. This strategy allows electron-rich olefins to be used in ETIC reactions that are initiated by Ce(IV) under nonphotochemical conditions. An alternate substrate design further validates the utility of eq 1 in substrate design and allows for the inclusion of the bond-activating substituent in the product, thereby improving the atom economy of the process. The ability to utilize the interplay between oxidation potential and bond dissociation energies is expected to be extremely valuable in the design of new radical ion fragmentation processes for unique synthesis and materials applications.

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Supporting Information Available: Synthetic schemes for all cyclization substrates. Experimental procedures and characterization for all cyclization reactions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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