Published in final edited form as:

Tetrahedron. 2009 December 26; 65(52): 10830–10836. doi:10.1016/j.tet.2009.10.088.

Mechanistic Analysis of Oxidative C–H Cleavages Using Inter- and Intramolecular Kinetic Isotope Effects

Hyung Hoon Jung and Paul E. Floreancig

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

Abstract

A series of monodeuterated benzylic and allylic ethers were subjected to oxidative carbon–hydrogen bond cleavage to determine the impact of structural variation on intramolecular kinetic isotope effects in DDQ-mediated cyclization reactions. These values are compared to the corresponding intermolecular kinetic isotope effects that were accessed through subjecting mixtures of non-deuterated and dideuterated substrates to the reaction conditions. The results indicate that carbon–hydrogen bond cleavage is rate determining and that a radical cation is most likely a key intermediate in the reaction mechanism.

1. Introduction

Oxygen-containing heterocycles are present in numerous biologically active compounds, making these structures the focus of intensive reaction development studies.¹ These units are often prepared through variations on the Prins reaction, in which ring formation occurs via intramolecular additions of carbon nucleophiles to oxocarbenium ions.² These processes often require the use of strongly acidic conditions to initiate ionization, thereby limiting functional group compatibility. We have been actively pursuing a program that utilizes oxidative carbon–carbon bond cleavage reactions to form oxocarbenium ions in an effort to enhance functional group tolerance.³ Recently we reported⁴ that cyclization reactions can be initiated by forming oxocarbenium ions through DDQ-mediated oxidative carbon–hydrogen bond activation from benzylic and allylic ethers (Scheme 1). The development of this promising method would be facilitated by a greater understanding of the mechanistic nuances of the individual steps of the process. We have initiated studies that are directed

© 2009 Elsevier Science. All rights reserved

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

toward elucidating the details of the carbon–hydrogen bond activation step. In this manuscript we report our findings from inter- and intramolecular kinetic isotope effect studies and present evidence for the formation of a radical cation intermediate prior to hydrogen atom abstraction en route to the oxocarbenium ion intermediate.

2. Results and Discussion

2.1. Background

Three mechanisms have been postulated for the generation of stabilized carbocations through DDQ-mediated oxidation (Scheme 2). The most direct pathway proceeds through a one step hydride transfer to DDQ.⁵ The other two pathways proceed through an initial electron transfer to form the radical cation of the substrate and the radical anion of DDQ. The oxocarbenium ion can then be accessed through hydrogen atom abstraction or proton abstraction followed by a second electron transfer. Bordwell postulated⁶ that proton transfer should be favored over hydrogen atom transfer for radical cations in solution based on the highly favorable proton solvation energy, though this analysis does not discuss the role that a quinone radical anion would play in partitioning the pathways. Baciocchi provided solvent-dependent spectroscopic evidence⁷ for both hydrogen atom transfer and proton transfer in photoinitiated oxidations of diarylmethanes by tetrachloroquinone.

We initiated a series of intermolecular and intramolecular kinetic isotope effect studies on several benzylic and allylic ether substrates (Scheme 3) to study the mechanism of carbocation formation in these reactions. Intramolecular kinetic effects are used to determine the preference for cleaving a C–H bond when a C–D bond is present in the same methylene group. Intermolecular kinetic isotope effects measure the rate difference between substrates that contain a reactive CH₂ group relative to substrates that contain a CD₂ group at the corresponding position.

Comparisons of intermolecular and intramolecular kinetic isotope effects have been used to provide evidence for the formation of a reactive intermediate as a rate determining step prior to bond cleavage.⁸ In this study, rate determining electron transfer would not necessarily diminish the kinetic isotope effect in the intramolecular experiments because the C–H and C–D bond strengths would still be different in a putative radical cation intermediate. Isotope effects would significantly lessen if electron transfer were rate determining in the intermolecular experiments, however (Scheme 4). The radical cations from the H₂ and D₂ substrates are expected to form in approximately identical concentrations because of their similar oxidation potentials, and the rate of bond cleavage would not be isotope dependent because this step would have a lower energetic barrier than return electron transfer. Intermolecular kinetic isotope effects would be approximately equal to intramolecular kinetic isotope effects if electron transfer were not rate determining since equilibration of the radical cations would occur prior to bond cleavage.

2.2. Substrate design and synthesis

The substrates in this study were selected to cover a wide range of reactivities in the oxidative cyclization reactions (Scheme 5).^{4a} We prepared benzylic ethers that undergo oxidative cyclization quickly (*p*-methoxybenzyl ether **1**), moderately quickly (*p*-methylbenzyl ether **2**), and slowly (benzyl ether **3**), with reactivity paralleling the ease of substrate oxidation. We also prepared ether **4** in which the cyclization proceeds at a moderate rate despite the low substrate oxidation potential. Highly reactive allylic ether **5** and relatively unreactive allylic ether **6** were also prepared. While our prior work utilized substrates that contain branched ethers, we employed unbranched ether groups to circumvent the possibility of a kinetic resolution in the carbon–hydrogen bond activation

step. Compounds **1-5** were prepared (eq 1) through standard Williamson ether syntheses between the non-, mono-, and dideuterated benzylic or allylic bromides and the sodium alkoxide of 3-butyn-1-ol followed by ruthenium catalyzed enol acetate formation.⁹ Compound **6** was prepared (eq 2) through the Lewis acid-mediated reaction between the allylic alcohol and the trichloroacetimidate of butynol to avoid the possibility of label scrambling through an S_N2' reaction. The products of the oxidative cyclizations were tetrahydropyrones **7-12**.

2.3. Isotope effect determination

Intramolecular kinetic isotope effect studies were conducted by exposing monodeuterated substrates to DDQ and 2,6-dichloropyridine, while intermolecular kinetic isotope effect studies were conducted by exposing 1:1 mixtures of nondeuterated and dideuterated substrates to the reaction conditions. The reactions were taken to approximately 10% conversion to avoid interpretation errors that could arise from product oxidation in the intramolecular series and from selective starting material depletion in the intermolecular series. Kinetic isotope effects were determined by comparing the intensities of ^1H NMR (500 MHz) signals from the benzylic or allylic hydrogens in the products to reference signals.

Values for intra- and intermolecular kinetic isotope effects are shown in Table 1. The magnitudes of the kinetic isotope effects were largest with the more reactive substrates **1**, **2**, **4**, and **5**. Intra- and intermolecular effects were reasonably consistent for each substrate.

2.4. Discussion

Several aspects of these data merit further comment. All substrates showed a kinetic isotope effect, indicating that carbon–hydrogen bond cleavage is involved in the rate determining step. The similar values between the intra- and intermolecular KIE's in all examples confirm that reactive intermediate formation prior to carbon–hydrogen cleavage is not the rate determining step.

The magnitudes of the values for rapidly reacting substrates **1**, **2**, **4**, and **5** are at or above the theoretically maximum value of 6.5 for primary KIE's at room temperature. Secondary KIE's are also possible for these reactions since bond cleavage results in a change of hybridization at the benzylic or allylic position. Secondary KIE values would be >1 when D is retained after cleavage and <1 when H is retained, indicating that primary and secondary effects are synergistic for intramolecular experiments and are antagonistic for intermolecular experiments. The generally close agreement between the intra- and intermolecular KIE values indicates that secondary KIE's are minimal and do not contribute to the large observed values. The largest KIE values are consistent with a modest contribution from tunneling in the transition states.

The magnitude of the KIE values correlate to substrate reactivity, with compounds that react quickly showing large effects and compounds that react slowly showing small effects. This indicates that bond cleavage is more difficult for substrates that react most quickly, in contrast to the result that would be expected for a one-step hydride transfer process. The result is consistent, however, with an electron transfer mechanism. Substrates with lower oxidation potentials, upon single electron oxidation, will form less reactive radical cations than substrates with high oxidation potentials (Figure 1). This phenomenon can be explained by equation 3¹⁰ in which $\text{BDE}(\text{RC})$ is the bond dissociation energy of the cleaving bond in the radical radical cation, $\text{BDE}(\text{S})$ is the bond dissociation energy of this bond in the neutral substrate, $E_{pa}(\text{S})$ is the oxidation potential of the substrate, and $E_{pa}(\text{E}^\bullet)$ is the oxidation potential of the radical from the fragment that becomes the carbocation in the cleavage step.

Thus lowering the oxidation potential of the substrate¹¹ by appending electron donating groups increases the bond dissociation energy of the scissile carbon–hydrogen bond. While these results strongly suggest the presence of an intermediate radical ion pair, a concern for the electron transfer mechanism lies in the considerably unfavorable thermodynamics of electron transfer between the substrates in this study and DDQ. Kochi, however, has reported¹² that rates for electron transfer and carbon–hydrogen bond cleavage for quinone/arene mixtures are substantially faster than predicted values based on Rehm-Weller¹³ considerations, particularly for endergonic transformations, due to the formation of an encounter complex that promotes inner sphere electron transfer.

The high rates of reactions for compounds that have low oxidation potentials appear to contrast the high KIE values for these substrates. These observations can be reconciled by considering the rate equation for cation formation that would arise from the proposed mechanism in Scheme 5. In this relationship (eq 4) the rate of cation formation depends on the rate constant for hydrogen atom transfer k , the concentration of the radical cation [RC], and the concentration of the DDQ radical anion [RA]. While the values of k are expected to be smaller for substrates with low oxidation potentials than for substrates with high oxidation potentials, the concentrations of the radical cations and the radical anions would be higher. The higher concentrations for these species overwhelm the smaller values of k and lead to faster reactions.

$$\text{Rate} = k [\text{RC}] [\text{RA}] \quad (4)$$

While these data provide compelling evidence for an electron transfer pathway, determining whether the bond cleavage results from hydrogen atom abstraction to form the cation directly or from deprotonation, with carbocation formation arising from subsequent radical oxidation, remains a difficult issue to resolve. Baciocchi's studies⁷ of diarylmethane oxidation by tetrachloroquinone are instructive in this regard. This work showed that hydrogen atom abstraction should be favored on thermodynamic grounds, but that the pathway could be perturbed by solvent polarity. Polar solvents promote direct hydrogen atom transfer while non-polar solvents promote deprotonation through destabilizing the negative charge on the quinone radical anion. According to Eq 1 our substrates should be more prone to undergo direct cation formation than those in the Baciocchi study because alkoxy groups lower the oxidation potential of alkyl radicals more than aryl groups.¹⁴ Moreover the negative charge of the radical anion of DDQ will be stabilized by the cyano groups to a greater degree than the corresponding charge in the radical anion of tetrachloroquinone, thereby lessening its capacity for deprotonation. Thus we postulate that these reactions proceed through hydrogen atom abstraction to form the oxocarbenium ions directly, as shown in Scheme 6.

3. Summary and conclusions

We have shown that cyclization reactions that proceed through oxidative carbon–hydrogen bond activation exhibit moderate to large $k_{\text{H}}/k_{\text{D}}$ kinetic isotope effects. This result is consistent with bond cleavage occurring in the rate determining step. The magnitudes of the effects were consistent when determined by intramolecular and intermolecular processes, confirming that the formation of a reactive intermediate prior to bond cleavage is not rate determining. KIE values were largest for substrates that have low oxidation potentials and react quickly. This behavior suggests the intermediacy of radical cation intermediates in which the bond dissociation energies for allylic and benzylic carbon–hydrogen bonds are highest when substrate oxidation potentials are low. The higher reaction rates for substrates that form stable radical cations with stronger carbon–hydrogen bonds must be attributed to

the higher concentrations of reactive intermediates. Literature analogy indicates that these reactions most likely proceed through hydrogen atom abstraction from the radical cation to form oxocarbenium ions directly.

4. Experimental Section

4.1. General experimental

Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 300 MHz and 75 MHz, respectively or at 500 MHz and 125 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^1H NMR: $\text{CDCl}_3 = 7.26$ ppm, for ^{13}C NMR: $\text{CDCl}_3 = 77.23$. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2 . Methylene chloride was distilled under N_2 from CaH_2 . 1,2-dichloroethane was dried over 4Å molecular sieves. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32–63 60 Å silica gel. Sodium borodeuteride and lithium aluminum deuteride were purchased from Sigma-Aldrich. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as purchased for chromatography. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

4.2. Method for determining intramolecular kinetic isotope effects

To a 0.1 M solution of the d_1 -ether substrate (1.0 equiv) and 2,6-dichloropyridine (0.2 equiv) in anhydrous 1,2-dichloroethane was added powdered 4Å molecular sieves (2 mass equiv). In case of the allylic ether substrate, LiClO_4 (0.1 equiv) was added. The mixture was stirred at room temperature for 15 minutes, and then DDQ (0.1 equiv) was added in one portion. The resulting reaction mixture was stirred at room temperature for 24 h. The crude solution was directly purified by flash chromatography, and a mixture of non- (d_0) and monodeuterated (d_1) products was separated from the starting substrate. The product ratio of d_1 to d_0 was calculated by acquiring a ^1H NMR spectrum (500 MHz, pulse delay time = 10 sec) and comparing the intensities of the signals from the benzylic or allylic hydrogen to a signal from a hydrogen that was unaffected by the reaction.

4.3. Method for determining intermolecular kinetic isotope effects

To a 0.1 M solution of the ether substrates- d_0 (0.5 equiv) and - d_2 (0.5 equiv), and 2,6-dichloropyridine (0.2 equiv) in anhydrous 1,2-dichloroethane was added powdered 4Å molecular sieves (2 mass equiv). In case of the allylic ether substrates, LiClO_4 (0.1 equiv) was added. The mixture was stirred at room temperature for 15 minutes, and then DDQ (0.1 equiv) was added in one portion. The resulting reaction mixture was stirred at room temperature for 24 h. The crude solution was directly purified by flash chromatography, and a mixture of non- (d_0) and monodeuterated (d_1) products was separated from the starting substrate. The product ratio of d_1 to d_0 was calculated by acquiring a ^1H NMR spectrum (500 MHz, pulse delay time = 10 sec) and comparing the intensities of the signals from the benzylic or allylic hydrogen to a signal from a hydrogen that was unaffected by the reaction.

4.4. General method for preparing benzylic substrates

To a solution of the benzylic bromide (1.0 equiv) and 3-butyn-1-ol (1.2 equiv) in DMF was added sodium hydride (60% dispersion in mineral oil, 1.5 equiv) at 0 °C. The reaction mixture was stirred at room temperature for approximately 2–3 h and quenched with water at 0 °C. The organic fraction was extracted with EtOAc, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude material was filtered through a short pad of silica gel with EtOAc/hexanes (1:4) as the eluent to afford the homopropargylic benzylic ether as a colorless oil (>90% yield).

To a mixture of [Ru(*p*-cymene)Cl₂]₂ (0.01 equiv), tri(2-furyl)phosphine (0.02 equiv), Na₂CO₃ (0.5 equiv) and 1-decyne (0.3 equiv) in toluene was added acetic acid (5.0 equiv). The brown mixture was stirred at 80 °C until the reaction color changed to green (*ca.* 2–4 h), then was cooled to room temperature. A solution of homopropargylic benzylic ether (1.0 equiv) in toluene was added. The resulting mixture was stirred at 80 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified via flash column chromatography to afford the benzylic ether substrate as a colorless oil (>70% yield).

4.4.1. 4-(4-Methoxybenzyloxy)but-1-en-2-yl acetate (1)—¹H NMR (500 MHz, CDCl₃): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.80 (s, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.57 (t, *J* = 6.5 Hz, 2H), 2.53 (t, *J* = 6.5 Hz, 2H), 2.10 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.1, 159.2, 153.5, 130.3, 129.3, 113.8, 102.8, 72.6, 66.7, 55.3, 33.9, 21.0; IR (neat): 3003, 2936, 2862, 1754, 1667, 1612, 1513, 1369, 1249, 1215, 1181, 1098, 1032, 822 cm⁻¹; HRMS (EI) *m/z* calcd. for C₁₄H₁₈O₄ (M)⁺ 250.1205, found 250.1192.

4.4.2. 4-(4-Methoxybenzyloxy)but-1-en-2-yl acetate (1-d₁)—¹H NMR (500 MHz, CDCl₃): δ 7.26 (dm, *J* = 8.5 Hz, 2H), 6.88 (dm, *J* = 8.5 Hz, 2H), 4.80 (s, 2H), 4.43 (s, 1H), 3.80 (s, 3H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.10 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.0, 159.2, 153.5, 130.3, 129.3, 113.8, 102.7, 72.2 (t, 1:1:1, ²*J*(¹³C, ²H) = 22 Hz), 66.7, 55.3, 33.9, 21.0; IR (neat): 3002, 2932, 2862, 2120, 1755, 1667, 1612, 1513, 1370, 1247, 1183, 1101, 1032, 881, 822 cm⁻¹; HRMS (ESI) *m/z* calcd. for C₁₄H₁₇DO₄Na (M+Na)⁺ 274.1166, found 274.1167.

4.4.3. 4-(4-Methoxybenzyloxy)but-1-en-2-yl acetate (1-d₂)—¹H NMR (500 MHz, CDCl₃): δ 7.26 (dm, *J* = 8.5 Hz, 2H), 6.88 (dm, *J* = 8.5 Hz, 2H), 4.80 (s, 2H), 3.80 (s, 3H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.10 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.1, 159.2, 153.5, 130.1, 129.3, 113.8, 102.8, 66.6, 55.3, 33.9, 21.0; IR (neat): 3003, 2957, 2862, 2165, 2061, 1754, 1667, 1612, 1513, 1370, 1255, 1183, 1104, 1030, 879, 801 cm⁻¹; HRMS (ESI) *m/z* calcd. for C₁₄H₁₆D₂O₄Na (M+Na)⁺ 275.1228, found 275.1271.

4.4.4. 4-(4-Methylbenzyloxy)but-1-en-2-yl acetate (2)—¹H NMR (500 MHz, CDCl₃): δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 4.80 (s, 2H), 4.48 (s, 2H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 2.34 (s, 3H), 2.10 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.1, 153.5, 137.3, 135.1, 129.0, 127.8, 102.7, 72.8, 66.9, 33.9, 21.1, 21.0; IR (neat): 3021, 2923, 2862, 1755, 1667, 1368, 1214, 1183, 1100, 1020, 881, 804 cm⁻¹; HRMS (EI) *m/z* calcd. for C₁₄H₁₈O₃ (M)⁺ 234.1256, found 234.1261.

4.4.5. 4-(4-Methylbenzyloxy)but-1-en-2-yl acetate (2-d₁)—¹H NMR (500 MHz, CDCl₃): δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 4.80 (sm, 2H), 4.46 (s, 1H), 3.57 (t, *J* = 6.5 Hz, 2H), 2.53 (t, *J* = 6.5 Hz, 2H), 2.34 (s, 3H), 2.10 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.0, 153.5, 137.3, 135.1, 129.0, 127.8, 102.7, 72.5 (t, 1:1:1, ²*J*(¹³C, ²H) = 22 Hz), 66.9, 34.0, 21.1, 21.0; IR (neat): 3022, 2923, 2865, 2121, 1756, 1667, 1370,

1185, 1104, 1020, 881, 794 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{14}\text{H}_{17}\text{DO}_3$ (M)⁺ 235.1319, found 235.1323.

4.4.6. 4-(4-Methylbenzyloxy)but-1-en-2-yl acetate (2-d₂)—¹H NMR (500 MHz, CDCl_3): δ 7.23 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.81 (s, 2H), 3.57 (t, J = 6.5 Hz, 2H), 2.53 (t, J = 6.5 Hz, 2H), 2.34 (s, 3H), 2.10 (s, 3H); ¹³C NMR (75 MHz, CDCl_3): δ 169.0, 153.5, 137.3, 135.0, 129.0, 127.8, 102.7, 66.8, 34.0, 21.1, 21.0; IR (neat): 3022, 2923, 2863, 2167, 2064, 1755, 1667, 1370, 1216, 1186, 1107, 1020, 880, 780 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{14}\text{H}_{16}\text{D}_2\text{O}_3$ (M)⁺ 236.1381, found 236.1377.

4.4.7. 4-(Benzyloxy)but-1-en-2-yl acetate (3)—¹H NMR (500 MHz, CDCl_3): δ 7.33 (sm, 4H), 7.28 (m, 1H), 4.81 (s, 2H), 4.52 (s, 2H), 3.60 (t, J = 6.5 Hz, 2H), 2.55 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H); ¹³C NMR (75 MHz, CDCl_3): δ 169.1, 153.4, 138.2, 128.4, 127.7, 127.6, 102.9, 73.0, 67.0, 33.9, 21.0; IR (neat): 3031, 2862, 1755, 1667, 1369, 1214, 1184, 1103, 1020, 739 cm^{-1} ; HRMS (ESI) m/z calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$)⁺ 243.0997, found 243.1127.

4.4.8. 4-(Benzyloxy)but-1-en-2-yl acetate (3-d₁)—¹H NMR (500 MHz, CDCl_3): δ 7.34 (sm, 4H), 7.28 (m, 1H), 4.81 (sm, 2H), 4.50 (s, 1H), 3.59 (t, J = 6.5 Hz, 2H), 2.55 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H); ¹³C NMR (75 MHz, CDCl_3): δ 169.0, 153.5, 138.2, 128.4, 127.7, 127.6, 102.8, 72.6 (t, 1:1:1, $^2J(^{13}\text{C}, ^2\text{H})$ = 22 Hz), 67.0, 34.0, 21.0; IR (neat): 3062, 3029, 2865, 2120, 1755, 1667, 1369, 1215, 1184, 1107, 1021, 880, 727 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{13}\text{H}_{15}\text{D}_1\text{O}_3$ (M)⁺ 221.1162, found 221.1169.

4.4.9. 4-(Benzyloxy)but-1-en-2-yl acetate (3-d₂)—¹H NMR (500 MHz, CDCl_3): δ 7.34 (sm, 4H), 7.28 (m, 1H), 4.81 (sm, 2H), 3.59 (t, J = 6.5 Hz, 2H), 2.55 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H); ¹³C NMR (75 MHz, CDCl_3): δ 169.1, 153.4, 138.0, 128.4, 127.7, 127.6, 102.9, 66.9, 33.9, 21.0; IR (neat): 3028, 2863, 2168, 2063, 1755, 1667, 1370, 1217, 1185, 1111, 1021, 882, 721 cm^{-1} ; HRMS (ESI) m/z calcd. for $\text{C}_{13}\text{H}_{14}\text{D}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$)⁺ 245.1123, found 245.1348.

4.4.10. 4-(3,5-Dimethoxybenzyloxy)but-1-en-2-yl acetate (4)—¹H NMR (300 MHz, CDCl_3): δ 6.50 (d, J = 2.4 Hz, 2H), 6.38 (t, J = 2.4 Hz, 1H), 4.81 (sm, 2H), 4.47 (s, 2H), 3.79 (s, 6H), 3.58 (t, J = 6.3 Hz, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.11 (s, 3H); ¹³C NMR (75 MHz, CDCl_3): δ 169.1, 160.9, 153.4, 140.6, 105.3, 102.9, 99.6, 72.9, 67.0, 55.3, 33.9, 21.0; IR (neat): 2939, 2841, 1754, 1598, 1463, 1367, 1206, 1156, 1106, 835 cm^{-1} ; HRMS (ESI) m/z calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_5\text{Na}$ ($\text{M}+\text{Na}$)⁺ 303.1208, found 303.1182.

4.4.11. 4-(3,5-Dimethoxybenzyloxy)but-1-en-2-yl acetate (4-d₁)—¹H NMR (300 MHz, CDCl_3): δ 6.50 (d, J = 2.4 Hz, 2H), 6.38 (t, J = 2.4 Hz, 1H), 4.81 (sm, 2H), 4.44 (s, 1H), 3.79 (s, 6H), 3.58 (t, J = 6.3 Hz, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.11 (s, 3H); ¹³C NMR (75 MHz, CDCl_3): δ 169.1, 160.9, 153.4, 140.6, 105.3, 102.9, 99.7, 72.6 (t, 1:1:1, $^2J(^{13}\text{C}, ^2\text{H})$ = 22 Hz), 66.9, 55.3, 33.9, 21.0; IR (neat): 3001, 2940, 2868, 2840, 2121, 1754, 1667, 1598, 1462, 1350, 1206, 1155, 1109, 1063, 1021, 883, 833 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{15}\text{H}_{19}\text{DO}_5\text{Na}$ (M)⁺ 281.1373, found 281.1363.

4.4.12. 4-(3,5-Dimethoxybenzyloxy)but-1-en-2-yl acetate (4-d₂)—¹H NMR (300 MHz, CDCl_3): δ 6.50 (d, J = 2.4 Hz, 2H), 6.38 (t, J = 2.4 Hz, 1H), 4.82 (sm, 2H), 3.79 (s, 6H), 3.58 (t, J = 6.3 Hz, 2H), 2.54 (t, J = 6.3 Hz, 2H), 2.11 (s, 3H); ¹³C NMR (75 MHz, CDCl_3): δ 169.1, 160.8, 153.4, 140.5, 105.3, 102.9, 99.6, 66.8, 55.3, 33.9, 21.0; IR (neat): 3001, 2941, 2864, 2840, 2170, 2068, 1753, 1598, 1428, 1369, 1156, 1112, 1063, 882, 831 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{15}\text{H}_{18}\text{D}_2\text{O}_5\text{Na}$ (M) 282.1436, found 282.1432.

4.4.13. (E)-4-(2-Methyltridec-2-enyloxy)but-1-en-2-yl acetate (5)—¹H NMR (500 MHz, CDCl₃): δ 5.38 (t, *J* = 7.0 Hz, 1H), 4.78 (s, 1H), 4.77 (s, 1H), 3.83 (s, 2H), 3.46 (t, *J* = 7.0 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.11 (s, 3H), 2.00 (q, *J* = 7.0 Hz, 2H), 1.61 (s, 3H), 1.35–1.29 (m, 2H), 1.29–1.20 (brs, 14H), 0.86 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 168.9, 153.6, 131.8, 128.6, 102.5, 77.0, 66.3, 33.9, 31.8, 29.6, 29.5, 29.4, 29.30, 29.27, 27.6, 22.6, 20.9, 14.0, 13.7; IR (neat): 2924, 2854, 1760, 1667, 1464, 1369, 1213, 1185, 1093, 1019, 871 cm⁻¹; HRMS (EI) *m/z* calcd. for C₂₀H₃₆O₃ (M)⁺ 324.2664, found 324.2673.

4.4.14. (E)-4-(2-Methyltridec-2-enyloxy)but-1-en-2-yl acetate (5-d₁)—¹H NMR (500 MHz, CDCl₃): δ 5.39 (t, *J* = 7.0 Hz, 1H), 4.80 (s, 1H), 4.79 (s, 1H), 3.82 (s, 1H), 3.47 (t, *J* = 7.0 Hz, 2H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.13 (s, 3H), 2.02 (q, *J* = 7.0 Hz, 2H), 1.63 (s, 3H), 1.35–1.29 (m, 2H), 1.29–1.20 (brs, 14H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.1, 153.7, 131.8, 128.7, 102.6, 76.7 (t, 1:1:1, ²*J*(¹³C, ²H) = 21 Hz), 66.3, 34.0, 31.9, 29.6, 29.54, 29.50, 29.4, 29.3, 27.7, 22.7, 21.0, 14.1, 13.8; IR (neat): 2924, 2855, 2130, 1759, 1668, 1464, 1369, 1215, 1186, 1102, 1020, 873 cm⁻¹; HRMS (EI) *m/z* calcd. for C₂₀H₃₅DO₃ (M)⁺ 325.2727, found 325.2719.

4.4.15. (E)-4-(2-Methyltridec-2-enyloxy)but-1-en-2-yl acetate (5-d₂)—¹H NMR (500 MHz, CDCl₃): δ 5.39 (t, *J* = 7.0 Hz, 1H), 4.80 (s, 1H), 4.79 (s, 1H), 3.47 (t, *J* = 7.0 Hz, 2H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.13 (s, 3H), 2.02 (q, *J* = 7.0 Hz, 2H), 1.63 (s, 3H), 1.35–1.29 (m, 2H), 1.29–1.20 (brs, 14H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.0, 153.7, 131.8, 128.8, 102.6, 66.2, 34.0, 31.9, 29.6, 29.54, 29.50, 29.4, 29.3, 27.7, 22.7, 21.0, 14.1, 13.7; IR (neat): 2925, 2854, 2166, 2061, 1760, 1667, 1464, 1370, 1215, 1186, 1106, 1020, 876 cm⁻¹; HRMS (EI) *m/z* calcd. for C₂₀H₃₄D₂O₃ (M)⁺ 326.2790, found 326.2785.

4.4.16. 4-(2-Methylenetridecyloxy)but-1-en-2-yl acetate (6)—¹H NMR (500 MHz, CDCl₃): δ 4.98 (s, 1H), 4.88 (s, 1H), 4.80 (s, 1H), 4.79 (sm, 1H), 3.90 (s, 2H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.13 (s, 3H), 2.03 (t, *J* = 7.5 Hz, 2H), 1.43 (p, *J* = 7.5 Hz, 2H), 1.33–1.22 (brs, 16H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.1, 153.5, 146.3, 111.1, 102.8, 73.9, 66.9, 34.0, 33.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 22.7, 21.0, 14.1; IR (neat): 2925, 2854, 2060, 1760, 1667, 1464, 1369, 1213, 1185, 1103, 1019, 900 cm⁻¹; HRMS (EI) *m/z* calcd. for C₂₀H₃₄D₂ (M)⁺ 324.2664, found 324.2665.

4.4.17. 4-(2-Methylenetridecyloxy)but-1-en-2-yl acetate (6- d₁)—¹H NMR (500 MHz, CDCl₃): δ 4.98 (s, 1H), 4.88 (s, 1H), 4.81 (s, 1H), 4.79 (sm, 1H), 3.88 (s, 1H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.51 (t, *J* = 6.5 Hz, 2H), 2.14 (s, 3H), 2.03 (t, *J* = 7.5 Hz, 2H), 1.43 (p, *J* = 7.5 Hz, 2H), 1.33–1.22 (brs, 16H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.1, 153.5, 146.2, 111.2, 102.8, 73.5 (t, 1:1:1, ²*J*(¹³C, ²H) = 21 Hz), 66.8, 33.9, 33.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 22.7, 21.0, 14.1; IR (neat): 2925, 2854, 2135, 1759, 1667, 1464, 1370, 1215, 1186, 1107, 1020, 898 cm⁻¹; HRMS (EI) *m/z* calcd. for C₂₀H₃₅DO₃ (M)⁺ 325.2727, found 325.2738.

4.4.18. 4-(2-Methylenetridecyloxy)but-1-en-2-yl acetate (6- d₂)—¹H NMR (500 MHz, CDCl₃): δ 4.98 (s, 1H), 4.88 (s, 1H), 4.80 (s, 1H), 4.79 (sm, 1H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.51 (t, *J* = 6.5 Hz, 2H), 2.13 (s, 3H), 2.03 (t, *J* = 7.5 Hz, 2H), 1.43 (p, *J* = 7.5 Hz, 2H), 1.33–1.22 (brs, 16H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.1, 153.6, 146.2, 111.3, 102.8, 66.8, 34.0, 33.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 22.7, 21.0, 14.1; IR (neat): 2925, 2854, 2170, 2065, 1758, 1668, 1464, 1370, 1216, 1186, 1109, 1020, 875 cm⁻¹; HRMS (EI) *m/z* calcd. for C₂₀H₃₄D₂O₃ (M)⁺ 326.2790, found 326.2785.

4.4.19. 2-(4-Methoxyphenyl)dihydro-2H-pyran-4(3H)-one (7)—¹H NMR (500 MHz, CDCl₃): δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.60 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.40 (ddd, *J* = 11.5, 7.5, 1.5 Hz, 1H), 3.83 (td, *J* = 11.5, 2.5 Hz, 1H), 3.81 (s, 3H), 2.75–2.68 (m, 2H), 2.65–2.59 (m, 1H), 2.42 (dm, *J* = 14.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 206.5, 159.5, 132.7, 127.1, 114.0, 79.5, 66.6, 55.3, 49.8, 42.2; IR (neat): 2964, 2935, 2839, 1718, 1613, 1514, 1369, 1249, 1032, 831 cm⁻¹; HRMS (EI) *m/z* calcd. for C₁₂H₁₄O₃ (M)⁺ 206.0943, found 206.0940.

4.4.20. 2-p-Tolyldihydro-2H-pyran-4(3H)-one (8)—¹H NMR (500 MHz, CDCl₃): δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.61 (dd, *J* = 9.0, 5.5 Hz, 1H), 4.42 (ddd, *J* = 11.5, 7.5, 1.5 Hz, 1H), 3.83 (td, *J* = 11.5, 3.0 Hz, 1H), 2.72 (ddd, *J* = 14.5, 9.5, 7.5 Hz, 1H), 2.64 (m, 2H), 2.43 (dm, *J* = 14.5 Hz, 1H), 2.35 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 206.4, 137.9, 137.7, 129.3, 125.7, 79.8, 66.7, 49.9, 42.2, 21.1; IR (neat): 2965, 2922, 2855, 1720, 1516, 1370, 1315, 1247, 1167, 1073, 805 cm⁻¹; HRMS (EI) *m/z* calcd. for C₁₂H₁₄O₂ (M)⁺ 190.0994, found 190.0986.

4.4.21. 2-Phenyldihydro-2H-pyran-4(3H)-one (9)—¹H NMR (500 MHz, CDCl₃): δ 7.38 (brs, 4H), 7.35–7.31 (m, 1H), 4.65 (dd, *J* = 9.0, 5.5 Hz, 1H), 4.44 (ddd, *J* = 11.0, 7.5, 1.5 Hz, 1H), 3.85 (td, *J* = 11.0, 2.5 Hz, 1H), 2.72 (ddd, *J* = 14.5, 12.5, 7.5 Hz, 1H), 2.65 (m, 2H), 2.43 (dm, *J* = 14.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 206.4, 140.6, 128.7, 128.2, 125.7, 79.8, 66.8, 50.0, 42.2; IR (neat): 3032, 2968, 2924, 2857, 1720, 1415, 1370, 1247, 1152, 1075, 756 cm⁻¹; HRMS (EI) *m/z* calcd. for C₁₁H₁₂O₂ (M)⁺ 176.0837, found 176.0841.

4.4.22. 2-(3,5-Dimethoxyphenyl)dihydro-2H-pyran-4(3H)-one (10)—¹H NMR (500 MHz, CDCl₃): δ 6.52 (d, *J* = 2.5 Hz, 2H), 6.41 (t, *J* = 2.5 Hz, 1H), 4.58 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.43 (ddd, *J* = 12.0, 7.5, 2.0 Hz, 1H), 3.82 (m, 1H), 3.80 (s, 6H), 2.71 (ddd, *J* = 14.5, 12.5, 7.5 Hz, 1H), 2.63 (m, 2H), 2.42 (dm, *J* = 14.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 206.1, 161.0, 143.0, 103.5, 100.0, 79.7, 66.7, 55.3, 49.9, 42.1; IR (neat): 2963, 2843, 1717, 1598, 1462, 1430, 1367, 1204, 1155 cm⁻¹; HRMS (EI) *m/z* calcd. for C₁₃H₁₆O₄ (M)⁺ 236.1048, found 236.1058.

4.4.23. (E)-2-(Tridec-2-en-2-yl)dihydro-2H-pyran-4(3H)-one (11)—¹H NMR (500 MHz, CDCl₃): δ 5.46 (td, *J* = 7.0, 1.5 Hz, 1H), 4.29 (ddd, *J* = 11.5, 7.5, 2.0 Hz, 1H), 3.97 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.70 (td, *J* = 11.5, 3.0 Hz, 1H), 2.60 (ddd, *J* = 14.5, 12.0, 7.5 Hz, 1H), 2.53 (dm, *J* = 14.5 Hz, 1H), 2.38 (ddm, *J* = 14.5, 2.5 Hz, 1H), 2.34 (dm, *J* = 14.5 Hz, 1H), 2.03 (td, *J* = 7.0, 4.0 Hz, 1H), 2.02 (td, *J* = 7.0, 3.0 Hz, 1H), 1.68 (s, 3H), 1.38–1.30 (m, 2H), 1.30–1.22 (m, 14 H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 207.2, 133.5, 128.3, 82.9, 66.1, 47.1, 42.2, 31.9, 29.6, 29.5, 29.3, 27.6, 22.7, 14.1, 12.1; IR (neat): 2924, 2854, 1721, 1465, 1371, 1246, 1155, 1078 cm⁻¹; HRMS (EI) *m/z* calcd. for C₁₈H₃₂O (M)⁺ 280.2402, found 280.2411.

4.4.24. 2-(Tridec-1-en-2-yl)dihydro-2H-pyran-4(3H)-one (12)—¹H NMR (500 MHz, CDCl₃): δ 5.07 (s, 1H), 4.95 (s, 1H), 4.30 (dm, *J* = 11.5 Hz, 1H), 4.05 (dd, *J* = 9.5, 4.0 Hz, 1H), 3.71 (td, *J* = 11.5, 3.0 Hz, 1H), 2.61 (ddd, *J* = 14.5, 11.5, 7.0 Hz, 1H), 2.52–2.46 (m, 2H), 2.37 (dm, *J* = 14.5 Hz, 1H), 2.15–2.07 (m, 1H), 2.07–2.00 (m, 1H), 1.50–1.41 (m, 2H), 1.34–1.18 (m, 16H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 206.9, 148.3, 110.8, 80.0, 66.2, 47.2, 42.2, 32.1, 31.9, 29.65, 29.62, 29.59, 29.5, 29.4, 29.3, 27.8, 22.7, 14.1; IR (neat): 2925, 2853, 1722, 1465, 1248, 1154, 1088 cm⁻¹; HRMS (EI) *m/z* calcd. for C₁₈H₃₂O₂ (M)⁺ 280.2402, found 280.2403.

4.4.25. General procedure for the preparation of monodeuterated benzylic bromides—To a solution of the appropriate benzaldehyde (1.0 eq.) in THF at 0 °C was added NaBD₄ (1.0 eq.) in one portion, followed by addition of water (several drops). The reaction mixture was stirred at room temperature for 1–3 h and quenched with water at 0 °C. The resulting mixture was stirred at room temperature overnight and extracted with ether or EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude mixture was dissolved in diethyl ether, followed by addition of phosphorous tribromide (0.5 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 2–3 h and carefully quenched with aqueous saturated NaHCO₃ solution. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

4.4.26. General procedure for the preparation of dideuterated benzylic bromides—To a solution of the appropriate benzoic acid (1.0 eq.) in diethyl ether was added LiAlD₄ (1.0 eq.) in several portions at 0 °C. The reaction mixture was stirred at 0 °C for 1–2 h and then at room temperature overnight. The reaction was quenched with D₂O at 0 °C. Water (H₂O) and EtOAc or ether were added and the organic layer was separated. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude material was dissolved in diethyl ether at 0 °C and phosphorous tribromide (0.5 eq.) was added. The reaction mixture was stirred at room temperature for ca. 2–3 h and was quenched with aqueous saturated NaHCO₃. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Science Foundation (CHE-0139851) and the National Institutes of Health (GM062924) for generous support of this work. We thank Professor Joseph Dinnocenzo (University of Rochester) for bringing the issue of electron transfer kinetics to our attention.

References

1. Recent reviews: (a) Larrosa I, Romea P, Urpí F. *Tetrahedron* 2008;64:2683. (b) Clarke PA, Santos S. *Eur. J. Org. Chem* 2006:2045. (c) Nakata T. *Chem. Rev* 2005;105:4314. [PubMed: 16351046] (d) Zeni G, Larock RC. *Chem. Rev* 2004;104:2285. [PubMed: 15137792] (e) Elliot MC. *J. Chem. Soc., Perkin Trans. 1* 2002:2301.
2. For a representative list of recent examples in complex molecule synthesis, see: (a) Wender PA, DeChristopher BA, Schrier AJ. *J. Am. Chem. Soc* 2008;130:6658. [PubMed: 18452292] (b) Seden PT, Charmant JPH, Willis CL. *Org. Lett* 2008;10:1637. [PubMed: 18355075] (c) Custar DW, Zabawa TP, Scheidt KA. *J. Am. Chem. Soc* 2008;130:804. [PubMed: 18161979] (d) Smith AB III, Basu K, Bosanac T. *J. Am. Chem. Soc* 2007;129:14872. [PubMed: 17997560] (e) Van Orden LJ, Patterson BD, Rychnovsky SD. *J. Org. Chem* 2007;72:5784. [PubMed: 17595145] (f) Yadav JS, Reddy MS, Rao PP, Prasad AR. *Synlett* 2007:2049. (g) Sanchez CC, Keck GE. *Org. Lett* 2005;7:3053. [PubMed: 15987203] (h) Aubele DL, Wan S, Floreancig PE. *Angew. Chem., Int. Ed* 2005;44:3485. (i) Overman LE, Pennington LD. *J. Org. Chem* 2003;68:7143. [PubMed: 12968864]
3. (a) Jung HH, Seiders JR II, Floreancig PE. *Angew. Chem., Int. Ed* 2007;46:8464. (b) Floreancig PE. *Synlett* 2007:191. (c) Wang L, Seiders JR II, Floreancig PE. *J. Am. Chem. Soc* 2004;126:12596.

- [PubMed: 15453792] (d) Seiders JR II, Wang L, Floreancig PE. J. Am. Chem. Soc 2003;125:2406. [PubMed: 12603124]
4. (a) Tu W, Floreancig PE. Angew. Chem., Int. Ed 2009;48:4567. (b) Tu W, Liu L, Floreancig PE. Angew. Chem., Int. Ed 2008;47:4184.
5. Trost BM. J. Am. Chem. Soc 1967;89:1847. [PubMed: 6040521]
6. Zhang X-M, Bordwell FG. J. Am. Chem. Soc 1994;116:904.
7. Baciocchi E, Del Giacco T, Elisei F, Lanzalunga O. J. Am. Chem. Soc 1998;120:11800.
8. (a) Anderson DR, Faibish NC, Beak P. J. Am. Chem. Soc 1999;121:7553. (b) Baciocchi E, Gerini MF, Harvey PZ, Lanzalunga O, Prosperi A. J. Chem. Soc., Perkin Trans 2001;2:1512. (c) Shearer J, Zhang CX, Hatcher LQ, Karlin KD. J. Am. Chem. Soc 2003;125:12670. [PubMed: 14558790]
9. (a) Goosen LJ, Paetzold J, Koley D. Chem. Commun 2003:706. (b) Neveaux M, Bruneau C, Dixneuf PH. J. Chem. Soc., Perkin Trans. 1 1991:1197.
10. Popielarz R, Arnold DR. J. Am. Chem. Soc 1990;112:3068.
11. For the determination of arene oxidation potentials, see: (a) Zweig A, Hodgson WG, Jura WH. J. Am. Chem. Soc 1964;86:1684. (b) Merkel PB, Luo P, Dinnocenzo JP, Farid S. J. Org. Chem. ASAP DOI: 10.1021/jo9011267. For alkene oxidation potentials see: Schepp NP, Johnston LJ. J. Am. Chem. Soc 1996;118:2872.
12. Hubig SM, Kochi JK. J. Am. Chem. Soc 1999;121:1688.
13. Rehm D, Weller A. Isr. J. Chem 1970;8:259.
14. (a) Wayner DDM, McPhee DJ, Griller D. J. Am. Chem. Soc 1988;110:132. (b) Fu Y, Liu L, Yu H-Z, Wang Y-M, Guo Q-X. J. Am. Chem. Soc 2006;127:7227. [PubMed: 15884964]

Scheme 1.
Cyclization reactions through oxidative carbon-hydrogen bond activation.

Scheme 2.

Possible mechanisms of oxidative carbocation formation.

Scheme 3.
Intra- and intermolecular kinetic isotope effects.

Scheme 4.

Relative rate constants for intermolecular KIE studies.

Scheme 5. Cyclization substrates, products, and synthetic routes. $n = 0 - 2$.

Figure 1.
Bond strength as a function of radical cation stability.

Scheme 6.
Proposed reaction mechanism.

Table 1

Intra- and intermolecular kinetic isotope effects.

entry	substrate	product	KIE (intra)	KIE (inter)
1	1	7	7.3	6.8
2	2	8	7.4	7.5
3	3	9	1.6	2.8
4	4	10	8.0	7.9
5	5	11	6.5	6.7
6	6	12	1.4	2.0