Electron Transfer Initiated Cyclizations: Cyclic Acetal Synthesis through Carbon−Carbon σ-Bond Activation

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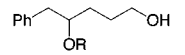
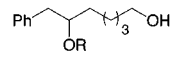
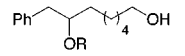
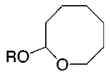
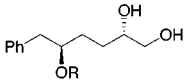
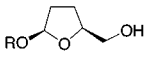
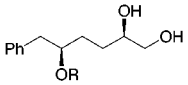
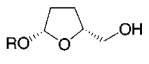
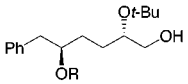
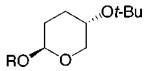
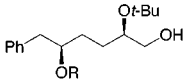
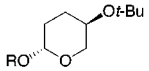
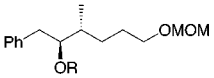
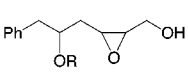
Selective and transient activations of normally unreactive functional groups are potentially quite useful processes in the design of new synthetic transformations.[1] The stability of carbon−carbon σ-bonds and the wealth of methods available for their construction suggest that devising methods for carbon−carbon bond activation could create novel strategic opportunities in organic synthesis. In this context we have initiated an investigation of cyclization reactions involving the transient conversion of homobenzylic ethers into potent electrophiles through single electron oxidation.[2] This communication details the development of electron transfer initiated cyclization (ETIC) reactions, the use of this method to synthesize several cyclic acetals, a mechanistic study of the process, and a new approach to anomeric stereocontrol in furanose and pyranose synthesis.

Carbon−carbon bond cleaving reactions of homobenzylic ether radical cations have been the focus of extensive mechanistic studies.[3] The benzylic carbon−carbon bonds of these highly reactive species are significantly weakened, allowing for benzyl radical displacement by a variety of poor nucleophiles. The following criteria highlight the advantages of employing this unique method of carbon−carbon bond activation in the design of a new cyclization reaction (Scheme 1): (1) the generally inert nature of the benzyl group facilitates substrate synthesis, (2) the reaction conditions (*hν*, single electron acceptor) are essentially neutral, allowing for the inclusion of acid- or base-sensitive functionality in cyclization substrates, (3) the oxidation potential of the substrate, and therefore the chemoselectivity of the oxidation, can be altered in a rational manner by introducing substituents onto the arene,[4] (4) the reactivity of the system can be tuned by introducing substituents at the benzylic position,[5] and (5) the highly electrophilic nature of these radical cations should allow a wide variety of nucleophiles to be employed in the reaction.

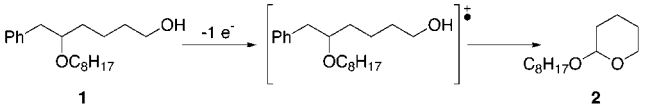
Attempts to initiate ETIC reactions utilizing homobenzylic ether substrates with a variation of Arnold's conditions[3a] (1,4-dicyanobenzene, CH_3CN, Pyrex filtered irradiation, medium-pressure mercury lamp) resulted in little or no product formation. We hypothesized that rapid regeneration of starting material by return electron transfer from the dicyanobenzene radical anion to the substrate radical cation was the source of cyclization inefficiency. To slow this unproductive process we initiated the cyclization with cation-sensitized electron transfer,[6] an effective method for increasing the lifetimes of radical cations even in nonpolar solvents.[7] Irradiation of **1** (Scheme 1) in the presence of the sensitizer *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$), solid NaOAc (buffer), and *tert*-butylbenzene (cosensitizer) in 1,2-dichloroethane dramatically increased the efficiency of the reaction, *providing a 92% yield of* ***2*** *in only 20 min.*

Table 1. ETIC Reactions with Various Substrates[a]

Entry	Substrate[b]	Product	Yield (%)	D.R.[c]
1			74	-
2			82	-
3			55	-
4			74	10:1[d]
5			92	1.2:1[d]
6			84	1.7:1
7			82	1.1:1
8			67[e]	1.4:1
9[f]			78[g]	2.6:1

[a] Reaction conditions: *hν*, *N*-methylquinolinium tetrafluoroborate (1−2 equiv), NaOAc, DCE, *tert*-butylbenzene (4:1). [b] R = *n*-octyl. [c] Diastereomeric ratio. The major diastereomer is represented by the structure in the Product column. Stereochemical assignments were based on ^{1}H NMR coupling constants except where noted. [d] Stereochemistry was determined by NOE analysis. [e] Yield at 88% conversion. [f] The relative stereochemistry of the starting material and the products was not determined. [g] Yield at 91% conversion.

Scheme 1. Electron Transfer Initiated Cyclization



1 **2**

To explore the scope of this method a series of substrates were prepared and subjected to sensitized electron-transfer conditions (Table 1).[8]

This method has proven to be effective for accessing a range of medium-sized rings (entries 2−3). The efficiency of the cyclizations to form seven- and eight-membered rings is remark-

(1) *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999.

(2) For a review of single electron oxidation in organic synthesis, see: Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550.

(3) (a) Arnold, D. R.; Lamont, L. J. *Can. J. Chem.* **1989**, *67*, 2119. (b) Perrott, A. L.; Arnold, D. R. *Can. J. Chem.* **1992**, *70*, 272. (c) Arnold, D. R.; Du, X.; Chen, J. *Can. J. Chem.* **1995**, *73*, 307. (d) Perrott, A. L.; de Lisjer, H. J. P.; Arnold, D. R. *Can. J. Chem.* **1997**, *75*, 384. (e) Baciocchi, E.; Bietti, M.; Putignani, L.; Steenken, S. *J. Am. Chem. Soc.* **1996**, *118*, 5952. (f) Baciocchi, E.; Bietti, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000**, *33*, 243. (g) Chen, L.; Farahat, M. S.; Gan, H.; Farid, S.; Whitten, D. G. *J. Am. Chem. Soc.* **1995**, *117*, 6398. (h) Freccero, M.; Pratt, A.; Albini, A.; Long, C. *J. Am. Chem. Soc.* **1998**, *120*, 284.

(4) Howell, J. O.; Goncalves, J. M.; Amatore, C.; Klasinc, L.; Wightman, R. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 3968.

(5) Popielarz, R.; Arnold, D. R. *J. Am. Chem. Soc.* **1990**, *112*, 3068.

(6) Majima, T.; Pac, C.; Nakasone, A.; Sakurai, H. *J. Am. Chem. Soc.* **1981**, *103*, 4499.

(7) (a) Todd, W. P.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R. *J. Am. Chem. Soc.* **1991**, *113*, 3601. (b) Dockery, K. P.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Todd, W. P. *J. Am. Chem. Soc.* **1997**, *119*, 1876.

(8) All new compounds have been characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS. See the Supporting Information for details.

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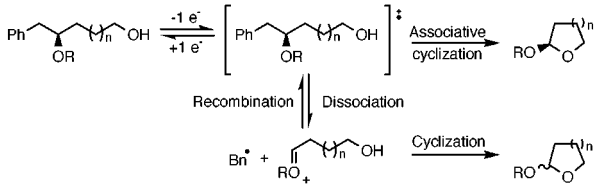


Figure 1. Proposed mechanistic pathways.

able given the absence of conformational constraints in the substrates.[9] Attempts to prepare small, strained rings were not successful. In a direct competition, the formation of furanose structures is preferred relative to the formation of pyranose structures (entries 4 and 5). Protection of the secondary hydroxyl as a bulky *tert*-butyl ether reverses this selectivity (entries 6 and 7). Alkoxyalkyl ethers can also serve as the nucleophilic group in the reaction (entry 8). In this example, oxonium ion dealkylation follows cyclization. The compatability of the sensitive epoxy alcohol (entry 9) with the reaction conditions demonstrates that strong acid is not produced in this procedure.

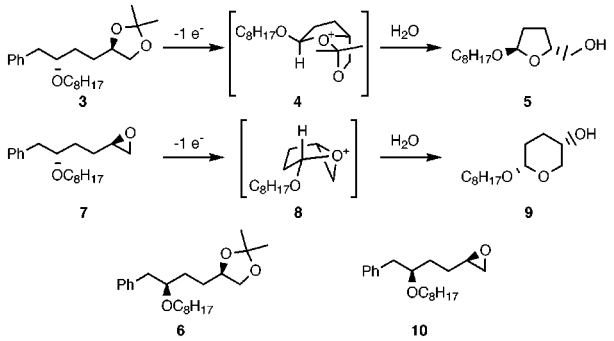
An analysis of the results in Table 1 led us to propose the mechanistic scheme for the process shown in Figure 1. A reversible and essentially isoenergetic electron transfer from the substrate to the radical cation of *tert*-butylbenzene (generated from electron transfer to the photoexcited *N*-methylquinolinium ion) yields the substrate radical cation. The substrate radical cation can cyclize through two pathways: an associative S_N2-type pathway leading to stereochemical inversion at the electrophilic center or a dissociative, stereorandom S_N1-type pathway.

The stereospecificity observed in entry 4 indicates that this substrate cyclizes predominantly through the associative pathway.[10] The lack of stereospecificity observed in entries 5−8, however, shows that cyclizations of several substrates proceed at least in part through the dissociative pathway. The extent to which cyclizations partition between the associative and dissociative pathways follows expected trends based on substrate structure. Lowering the rate of the associative pathway by employing a weak or bulky nucleophile or generating steric repulsion in the transition state leads to a greater contribution from the dissociative pathway.

When cyclization through the dissociative pathway proceeds slowly the intermediate carbocation can recombine with the benzyl radical to reform the radical cation. Reduction of the radical cation by *tert*-butylbenzene regenerates starting material. The starting material recovered from the cyclization of the particularly slowly reacting ether in entry 9 was a 1:1 mixture of diastereomers, providing evidence for this pathway.

Recognizing that forcing ETIC reactions to proceed through the dissociative pathway results in *transient, chemoselective carbocation formation under neutral conditions* led us to envision opportunities for the design of unique regio- and stereocontrolled reactions. We proposed that single electron oxidation of a homobenzylic ether tethered to a very weakly nucleophilic cyclic ether could provide a bicyclic intermediate in which stereoselecontrol of the nascent anomeric center would be dictated by the energetic preference of bulky substituents for the less sterically hindered face of the ring system (Scheme 2). In support of this

Scheme 2. Stereoselective Cyclizations through Bicyclic Intermediates



proposal, the cyclization of acetonide **3** is consistent with the initial formation of bicycle **4**, with the alkoxy group oriented on the sterically less-encumbered convex face of the bicyclo[3.3.0] ring system. Hydrolytic decomposition of **4** provides dideoxyriboside **5** in 74% yield as an 11:1 mixture of diastereomers, representing a 110-fold reversal in the stereochemical outcome of the reaction relative to the cyclization of the parent diol. The involvement of the dissociative pathway in this reaction was confirmed through the observation that the cyclization of diastereomeric acetonide **6** provided a product mixture identical with that from **3**.

The generation of bicyclic oxonium ions has also been employed for the synthesis of pyranosides (Scheme 2). In this case the outcome of the ETIC reaction of epoxide **7** is consistent with an initial formation of epioxonium ion **8** followed by nucleophilic attack by adventitious water at the more substituted center, forming pyranoside **9** as a >19:1 mixture of diastereomers in 49% yield. In addition to the excellent diastereoselectivity observed in this reaction, the intermediacy of the epioxonium ion suggests that this methodology could be useful for the initiation of polyether cascade cyclizations[11] under neutral conditions. The expected predominance of the dissociative pathway in this reaction was confirmed by the formation of **9** in a 9:1 diastereomeric ratio from epimeric epoxide **10**.

In summary, we have developed a new cyclization reaction that proceeds through an experimentally simple electron-transfer mediated carbon−carbon σ-bond activation pathway. Cyclizations proceed through either an associative or a dissociative mechanism, with the latter providing access to stabilized carbocations under neutral conditions. This approach has been utilized to form bicyclic oxonium ions as intermediates in the diastereoselective construction of furanoside and pyranoside systems, thus leading to a unique strategy for controlling anomeric stereochemistry.

Acknowledgment. This work was supported by the University of Pittsburgh. We thank Dr. Fu-Tian Lin for assistance with stereochemical analyses and Professors Scott Nelson, Ted Cohen, and Craig Wilcox for helpful discussions.

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

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(10) These product ratios could also result from an initial dissociation followed by a rapid cyclization relative to benzyl radical diffusion.

(11) For a review see: Koert, U. *Synthesis* **1995**, 115.