Structure−Reactivity Relationships in Oxidative Carbon−Carbon Bond Forming Reactions: A Mild and Efficient Approach to Stereoselective Syntheses of 2,6-Disubstituted Tetrahydropyrones

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Abstract: Homobenzylic ethers with pendent enol acetate nucleophiles undergo highly efficient cleavage reactions followed by 6-*endo* cyclizations to form 2,6-disubstituted tetrahydropyrones with excellent stereocontrol at room temperature in the presence of the mild oxidant ceric ammonium nitrate. Cyclizations proceed through either stabilized or nonstabilized oxocarbenium ions. Structure−reactivity relationships are presented to provide a predictive guide for the design of radical cation cleavage processes. Unique sequences for preparing cyclization substrates based on stereoselective Lewis acid mediated acetal openings have been developed for the synthesis of complex substrates that are suitable for applications to the synthesis of biologically active natural products.

Introduction

Single electron oxidation presents an intriguing alternative to Lewis acid activation for imparting electrophilic character to molecules. In addition to the often orthogonal chemoselectivity patterns of redox reactions relative to acid−base interactions, the radical cations that form from single electron oxidation can react through unique pathways that are inaccessible to standard cationic intermediates (Figure 1).[1] For example, radical cations that are formed by the single electron oxidation of electron rich alkenes react with nucleophiles to provide a radical-containing product that can either engage in further bond formation or undergo oxidation to form a cation. An alternative reaction pathway for radical cations is mesolytic cleavage to form a radical fragment and a cationic fragment. This method most commonly sacrifices a group that is introduced into a molecule to facilitate selective oxidation and fragmentation, termed by Yoshida[2] as the electroauxiliary, for the desirable capacity to generate electrophiles under nonacidic conditions.

The extent to which oxidative cleavage reactions can be applied to complex molecule synthesis strongly depends on oxidation chemoselectivity (the propensity for electroauxiliary oxidation in preference to other functional groups in the molecule) and the susceptibility of the intermediate radical cation toward fragmentation. Both of these factors can be manipulated rationally by knowing the oxidation potentials of all functional groups in a molecule and by understanding the relationship between structure and fragmentation proclivity. The effects of
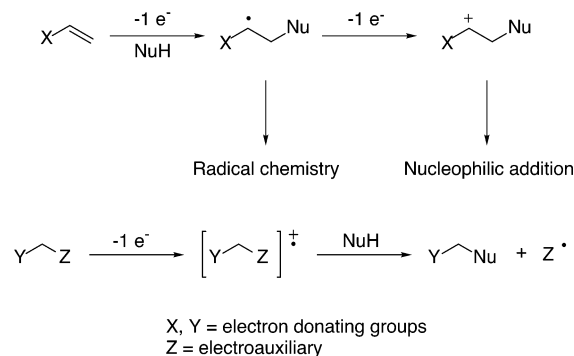

Figure 1. Common reaction pathways for radical cations.

essentially all functional groups on molecular oxidation potentials have been compiled in reference guides to aid chemoselectivity analyses.[3] The penchant of a particular bond in a radical cation to fragment, as defined by its bond dissociation energy (BDE(RC)), can be estimated from a thermodynamic perspective by knowing the oxidation potential of the substrate (E_{pa}(S)), the bond dissociation energy of that bond in the substrate (BDE(S)),[4] and the oxidation potential of the radical that corresponds to the electrophilic fragment (E_{pa}(E))[5] through the relationship (eq 1) that is derived in Figure 2. Several useful design principles can be gleaned from eq 1. For example, weakening a particular bond through substitution or strain inclusion will enhance its tendency to fragment upon oxidation.[6]

(1) For reviews of radical cation reactivity patterns, see: (a) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550. (b) Baciocchi, E.; Bietti, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000**, *33*, 243. (c) Schmittel, M.; Ghorai, M. K. In *Electron Transfer in Chemistry*; Balzani, V., Ed.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2.

(2) Yoshida, J.-i.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2589.

(3) Reed, R. C.; Wightman, R. M. In *Encyclopedia of Electrochemistry of the Elements*; Bard, A. J., Ed.; Marcel Dekker: New York, 1984; Vol. 15.

(4) For excellent tabulations of bond dissociation energies in organic molecules, see: (a) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255. (b) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493.

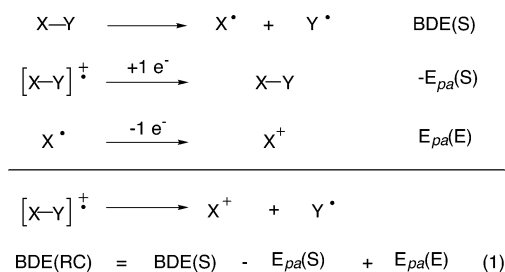(5) Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 132.

Figure 2. Thermodynamics of mesolytic bond cleavage processes in radical cations.
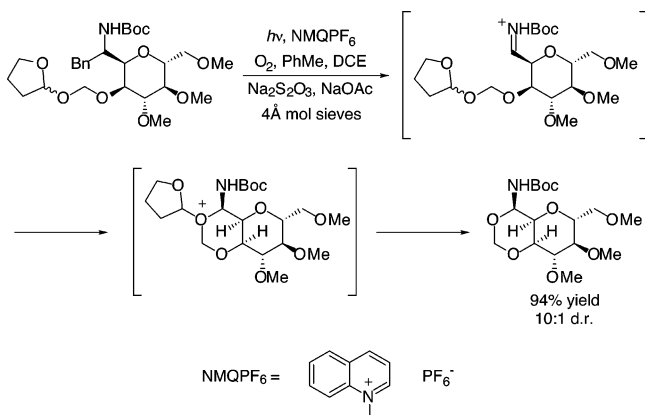

Figure 3. ETIC through formation of a carbon−oxygen bond.

Lowering the oxidation potential of a molecule, however, inhibits oxidative cleavage.[7] Finally, lowering the oxidation potential of the electrophilic fragment (usually by increasing the stability of the cationic fragment) promotes cleavage.[8] Also of note is that eq 1 accurately predicts that the cationic fragment from the cleavage reaction will arise from the radical that has the lower oxidation potential.

In consideration of the great potential of oxidative fragmentation reactions in new reaction design for molecular synthesis, we have been studying mesolytic cleavage reactions of homobenzylic ether and amide radical cations to form oxocarbenium[9] and acyliminium ions,[10] respectively.[11] In particular, we have used this reaction to initiate cyclization reactions that form a variety of heterocyclic systems (Figure 3). These studies have exemplified the utility of forming electrophiles under oxidative conditions by showing that acid-sensitive groups such as epoxides and acetals can be incorporated in cyclization substrates and can even be used as nucleophiles[12] and that labile functionality such as the amido trioxadecalin ring system can be prepared in excellent yield.[13]

Applications of this method to carbon−carbon bond formation, however, are complicated by the oxidation of common
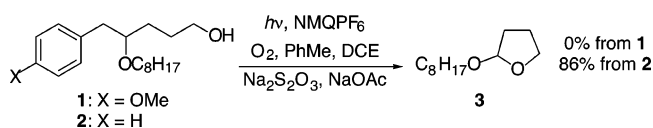

Figure 4. Effects of altering the arene oxidation potential on cyclization efficiency.

carbon-centered nucleophilic groups in preference to the arene. To illustrate, the oxidation potentials of enol silanes are approximately 1.3 V,[14] whereas the oxidation potentials of monoalkylarenes are approximately 2.3 V.[15] The importance of devising new carbon−carbon bond forming processes and our desire to test the viability of using eq 1 in designing substrates that expand the repertoire of electron transfer initiated cyclization (ETIC) reactions led us to initiate a program directed toward utilizing carbon-based nucleophiles. Herein we present a full account of our studies in this area.[16] In particular, we outline our initial work to validate eq 1 in substrate design, our development of a ground-state variant of the reaction using the mild oxidant ceric ammonium nitrate, the application of this method to the synthesis of simple carbocyclic systems, and the use of the process in preparing complex disubstituted tetrahydropyrans with exceptional efficiency and stereocontrol.[17]

Substrate Design and Initial Studies

Achieving the desired chemoselectivity for carbon−carbon bond formation in these processes requires the arene oxidation potential to be lower than that of the nucleophilic group. To determine the effects of altering the arene oxidation potential on fragmentation efficiency we prepared **1** (Figure 4), an analogue of previously studied cyclization precursor **2** that differs only in the inclusion of a *p*-methoxy group in the arene. The *p*-methoxy group was predicted, based upon literature analogy,[18] to lower the oxidation potential of **1** by approximately 0.6 V relative to **2**. Since benzylic bond strength has been shown to be affected only minimally by arene substitution[19] the addition of the *p*-methoxy group is predicted by eq 1 to strengthen the benzylic carbon−carbon bond by approximately 14 kcal/mol.[20] Exposing **1** to our standard aerobic cyclization conditions resulted in a quantitative recovery of starting material while **2** was an excellent participant in ETIC chemistry, providing tetrahydrofuranyl ether **3** in 86% yield. These experiments suggested that bond dissociation or cyclization rather than electron transfer is the rate determining step in the process and demonstrated that eq 1 can be used to predict the propensity of this class of molecules to fragment and cyclize.

According to eq 1 the bond strengthening effects conferred by lowering the oxidation potential can be mitigated by lowering the bond dissociation energy of the benzylic carbon−carbon bond in the substrate. We devised two strategies to accomplish this task (Figure 5). Our initial strategy envisioned substrates

(6) (a) Dinnocenzo, J. P.; Simpson, T. R.; Zuilhof, H.; Todd, W. P.; Heinrich, T. *J. Am. Chem. Soc.* **1997**, *119*, 987. (b) Dinnocenzo, J. P.; Zuilhof, H.; Lieberman, D. R.; Simpson, T. R.; McKetchney, M. W. *J. Am. Chem. Soc.* **1997**, *119*, 994. (c) Herbertz, T.; Roth, H. D. *J. Org. Chem.* **1999**, *64*, 3708.
(7) (a) Dockery, K. P.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Todd, W. P. *J. Am. Chem. Soc.* **1997**, *119*, 1876. (b) Arnold, D. R.; Du, X.; Chen, J. *Can. J. Chem.* **1995**, *73*, 307.
(8) Freccero, M.; Pratt, A.; Albini, A.; Long, C. *J. Am. Chem. Soc.* **1998**, *120*, 284.
(9) Kumar, V. S.; Floreancig, P. E. *J. Am. Chem. Soc.* **2001**, *123*, 3842.
(10) Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 3443.
(11) The directionality of the mesolytic cleavage is consistent with alkoxyalkyl and amidoalkyl radicals having significantly lower oxidation potentials than benzyl radicals (ref 5).
(12) Kumar, V. S.; Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 2849.
(13) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 1495.

(14) Rathore, R.; Kochi, J. K. *Tetrahedron Lett.* **1994**, *35*, 8577.
(15) Howell, J. O.; Goncalves, J. M.; Amatore, C.; Klasinc, L.; Wightman, R. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 3968.
(16) For a preliminary account of a portion of this work, see: Seiders, J. R., II.; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406.
(17) For other oxidative approaches to tetrahydropyran structures, see: (a) Yoshida, J.-i.; Ishichi, Y.; Isoe, S. *J. Am. Chem. Soc.* **1992**, *114*, 7594. (b) Yoshida, J.-i.; Sugawara, M.; Kise, N. *Tetrahedron Lett.* **1996**, *37*, 3157. (c) Chen, C.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 3252.
(18) Reference 3, p 85.
(19) Wayner, D. D. M.; Sim, B. A.; Dannenberg, J. J. *J. Org. Chem.* **1991**, *56*, 4853.
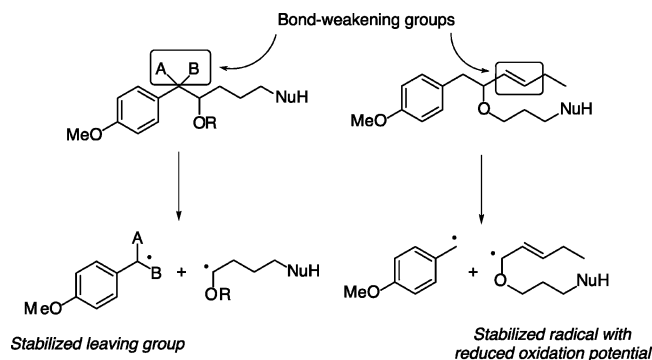(20) One volt is approximately 23 kcal/mol.

Figure 5. Structural alterations to promote bond cleavage.

Table 1. Substituent Effects in ETIC Reactions

a For the syntheses of these substrates, see the Supporting Information of ref 15. *b* Conditions A: Substrate, NMQPF$_6$ (2.5 mol %), $h\nu$ (medium-pressure mercury lamp, Pyrex filtration), gentle aeration, NaOAc, 1,2-dichloroethane, toluene (3.5:1). Conditions B: Substrate, CAN (2.2 eq), NaHCO$_3$, 1,2-dichloroethane, CH$_3$CN (4:1), room temp. *c* Yields refer to isolated, purified products.

that contain substituents at the benzylic position to stabilize the benzyl radical (bond-weakening groups), such as phenyl, vinyl, or alkyl groups. This approach allows for *exo*-cyclizations that are analogous to those that were the subject of our initial studies. The alternative design places a vinyl group at the homobenzylic position to facilitate fragmentation. The nucleophile is then appended through an ether linkage to the homobenzylic oxygen atom, ultimately leading to *endo*-cyclizations.

The validity of these designs was demonstrated through a series of cyclization reactions that again employed a pendent hydroxyl group as the nucleophile (Table 1). This study demonstrated that substituting the benzylic position with a single phenyl or vinyl group or two methyl groups (entries 1–3) restored the reactivity of the system. The benefit of lowering the oxidation potential of the system was manifested through the use of the mild ground state oxidant ceric ammonium nitrate (CAN) to initiate the cyclization (entry 3, conditions B). Although less effective than the photochemical oxidation conditions for this substrate class, possibly due to the weak Lewis acidity of the Ce(III) that forms upon electron transfer, the technical facility of the reaction conditions and nonreliance upon a photochemical reactor make this oxidant quite attractive for future applications. Moreover the new *endo*-variant of the cyclization (entry 4) proved to be quite efficient, significantly

broadening the scope of potential products that can be accessed through this method.

An interesting aspect of these reactions is that, although each of the structural alterations to weaken the benzylic bond were effective in promoting fragmentation, none of these changes should fully compensate for the bond-strengthening effect of the *p*-methoxy group. A potential explanation for the success of these cyclizations is that the concentrations of transiently formed radical cations, a critical factor in the kinetics of reactions that proceed through rate determining bond cleavages, is expected to be higher when the oxidation potential of the substrate is lowered. Alternatively or additionally, the benzylic substituents could favor a reactive conformation that enhances the alignment of the relevant carbon–carbon bond with the π-system of the arene,[8] thereby improving fragmentation potential through a stereoelectronic effect.[21]

Upon establishing the requisite reactivity of the aromatic portion of the substrates, we turned our attention to the selection of appropriate carbon-centered nucleophiles. Although appending the methoxy group significantly lowers the oxidation potential of the arene, enol silanes and alkyl enol ethers would still be expected to undergo preferential and undesired oxidation. Therefore, we explored a series of nucleophiles that, while still possessing sufficient nucleophilicity, are less prone to oxidation. Results of cyclizations employing allylsilane, silylallene, propargylsilane, trisubstituted alkene, and enol acetate nucleophiles are shown in Table 2. With the exception of the cyclization of the weakly nucleophilic[22] propargylsilane (entry 4) these reactions proceeded in good to excellent yields through an extremely simple experimental protocol when CAN was utilized as the oxidant.[23] Most reactions proceeded within a few minutes at either ambient or slightly elevated temperature. Carbon–carbon bond formation through an *endo*-cyclization was also extremely efficient (Entry 6). Photoinitiated oxidations proved to be generally less efficient and, in certain cases, quite inefficient. We attribute this trend to Ce(IV) being a much milder[24] and, therefore, more selective oxidant than the radical cation of toluene, the relevant oxidant in the photooxidation. An exception to this was observed in the cascade cyclization shown in Entry 5.

Our early studies employed octyl ethers as inert groups that increase molecular weight and aid product isolation. In the interest of preparing compounds that can be more useful in subsequent transformations, we also studied ether groups that can be removed more readily than alkyl ethers. We observed that benzyl ethers (Entry 7) and allyl ethers (data not shown) participate in cyclization reactions, albeit with slightly diminished efficiency relative to alkyl ethers. The TBDMS ether (Entry 8), however, provided only a low yield of the cyclization product upon exposure to CAN with aldehydes comprising the majority of the products. We postulate that the electrofugacity of silyl ethers results in a kinetic preference for their departure

(21) (a) Perrott. A. L.; de Lisjer, H. J. P.; Arnold, D. R. *Can. J. Chem.* **1997**, *75*, 384. (b) Perrott, A. L.; Arnold, D. R. *Can. J. Chem.* **1992**, *70*, 272.
(22) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375.
(23) CAN that is used without purification provides variable results. We have found that a single purification provides a reagent that can be used for months without loss of activity. For the purification of CAN, see: Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, U.K., 1996; p 376.
(24) The redox potential of CAN in CH$_3$CN has recently been reported to be 550 mV vs Ag/AgNO$_3$ or 0.97 V vs SCE. Zhang, Y.; Flowers, R. A., II. *J. Org. Chem.* **2003**, *68*, 4560.

Table 2. Carbon−Carbon Bond Formation in ETIC Reactions

Entry	Substrate[a]	Product	Conditions[b]	Yield (%)[c]
1[d]	**10**	**11**	A	50
			B	71
2	**12**	**13**	A	75
			B	94
3[e]	**14**	**15**	A	13
			B	91
4	**16**	**17**	B	47
5	**18**	**19**	A	49
			B	32
6	**20**	**21**	B	91
7[e]	**22**	**23**	B	66
8[e]	**24**	**25**	B	<10

[a] For the syntheses of these substrates, see the Supporting Information of ref 15. R = PhCH(*p*-OMe)Ph. [b] Conditions A: Substrate, NMQPF$_6$ (2.5 mol %), *hν* (medium-pressure mercury lamp, Pyrex filtration), gentle aeration, NaOAc, 1,2-dichloroethane, toluene (3.5:1). Conditions B: Substrate, CAN (2.2 eq), NaHCO$_3$, 1,2-dichloroethane, CH$_3$CN (4:1), room temp. to 40 °C. [c] Yields refer to isolated, purified products. [d] Products isolated as a 1.7:1 ratio of diastereomers. [e] Reaction provided a 1.2:1 (trans: cis) ratio of diastereomers.
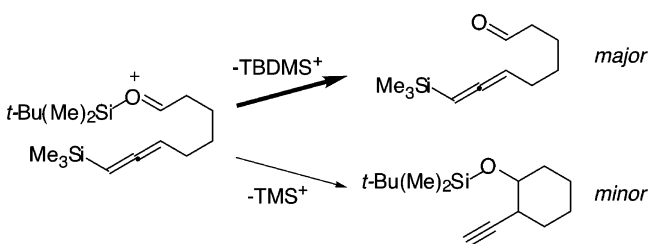

Figure 6. Silyl group loss from oxocarbenium ion.

rather than intramolecular nucleophilic attack upon intermediate oxocarbenium ion formation (Figure 6).[25] Thus, efficient cyclizations require homobenzylic ethers that cannot rapidly decompose to form a stable carbocation.

Oxidant Selection and Oxidation Mechanism

The efficiency and procedural simplicity of using CAN in these cyclizations led us to undertake a brief study of other ground-state oxidants as bond cleaving agents in order to probe the range of potential reagents and to garner information regarding the mechanistic details of the electron transfer.

DDQ (2,3-dichloro-4,5-dicyanoquinone) is a common reagent for oxidative cleavage of *p*-methoxybenzyl ethers. Exposing **7**
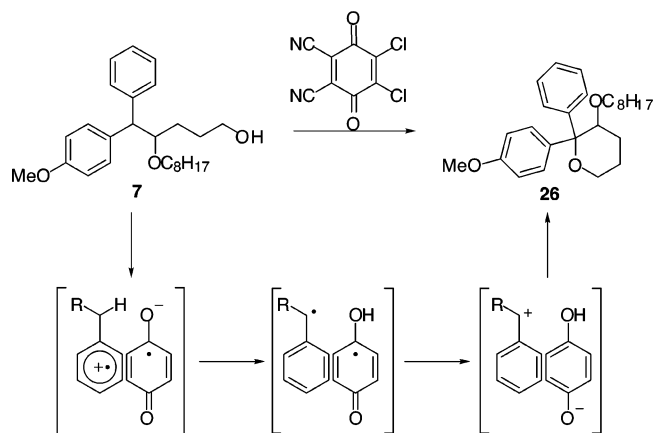
Figure 7. Carbon−hydrogen bond activation using DDQ. Substituents have been omitted for clarity.

to DDQ resulted in the consumption of starting material within 3 h. The product of this reaction, however, did not arise from the expected carbon−carbon bond cleavage pathway but rather from carbon−hydrogen bond activation to form cyclic ether **26** as a mixture of diastereomers (Figure 7). The mechanistic basis for this change in reactivity resides in the nature of the initial products of the electron transfer. Nonhindered arenes have been shown to form complexes with quinones prior to electron transfer,[26] ensuring proximity between the resulting radical ions. Benzylic carbon−hydrogen bonds in alkylarene radical cations are highly acidic[15] and, in the presence of the proximal basic oxygen atoms of the quinone radical anion, can readily be cleaved to form benzyl radicals. Further oxidation of the benzyl radical forms a carbocation that reacts with the pendent hydroxyl group to yield the observed tetrahydropyran. This pseudo unimolecular proton-transfer mechanism contrasts the photochemical and CAN conditions in which bimolecular proton-transfer cannot compete with carbon−carbon bond cleavage, even when 2,6-lutidine is used as a soluble base.

Other metal based oxidants such as (phen)$_3$Fe(PF$_6$)$_3$ (phen = 1,10-phenanthroline) and CTAN ((Bu$_4$N)$_2$Ce(NO$_3$)$_6$) failed to initiate reactions with **7** or **18**. These results, although initially unexpected based on the essentially equivalent redox potentials of these oxidants and CAN,[24,27] can be reconciled by invoking an inner sphere electron-transfer mechanism[28] to initiate bond cleavage. The kinetics of inner sphere processes[29] are dependent upon the formation of a complex between the substrate and oxidant prior to electron transfer. Although any explanation of these results at this time must be considered speculative, we postulate that bulky tetrabutylammonium ions in CTAN disfavor association between Ce(IV) and the arene relative to the smaller ammonium ions in CAN. Extensive evidence has established that (phen)$_3$Fe(PF$_6$)$_3$ reacts exclusively through outer sphere pathways,[30] providing further substantiation for our postulate of an inner sphere process being the relevant pathway in cleavage reactions that proceed with ground-state oxidants.

(25) A similar phenomenon was recently observed in oxidative oxocarbenium ion formation through carbon−hydrogen bond activation. Ying, B.-P.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y.-C. *Org. Lett.* **2004**, *6*, 1523.
(26) Hubig, S. M.; Rathore, R.; Kochi, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 617.
(27) Wong, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 5593.
(28) For an excellent study of inner sphere electron transfer in metal-arene complexes, see: Lau, W.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 6720.
(29) Kochi, J. K. *Acc. Chem. Res.* **1992**, *25*, 39.
(30) Rollick, K. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 1319.
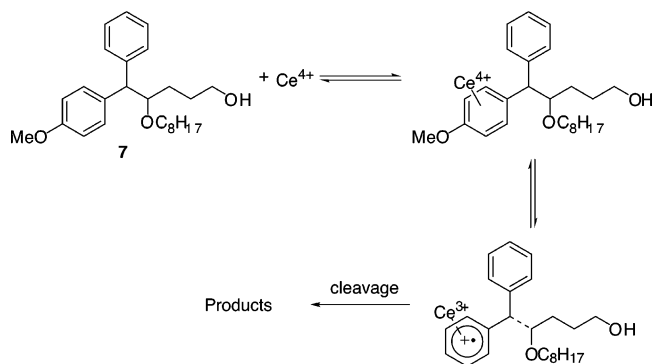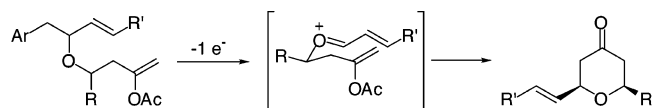
Figure 8. Inner sphere electron transfer.

Figure 9. Diastereocontrol in *endo*-ETIC reactions.
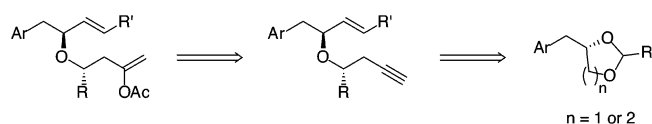

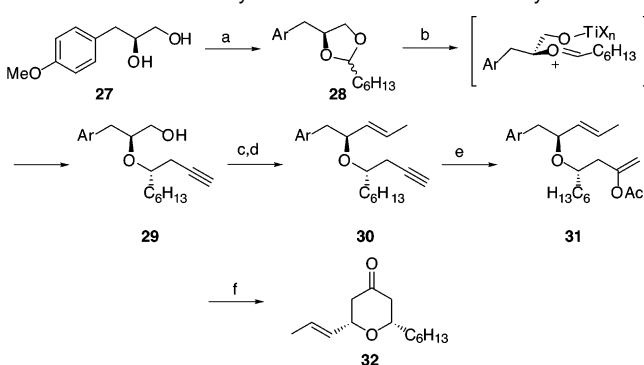**Figure 10.** Retrosynthesis of cyclization substrates.

Based on predicted oxidation potentials of the substrates of approximately 1.6 V and the reduction potential of CAN in organic solvent being 0.9 V, electron transfer in these reactions is a significantly endergonic process. Kochi has shown[31] that endergonic electron transfer events can initiate arene radical cation deprotonation reactions, provided that subsequent reactions are sufficiently rapid and thermodynamically favorable. The success in ETIC processes, by analogy, results from energetically propitious nucleophilic additions to intermediate oxocarbenium ions driving the unfavorable electron transfer and bond cleavage equilibria toward the final products.

Stereoselective Cyclizations

As shown in Table 2, entries 2 and 3, cyclizations that proceed through *exo*-additions to oxocarbenium ions display poor stereocontrol. Superior stereocontrol is expected for the 6-*endo*-pathway due to its strong preference for chair transition states[32] and an (*E*)-configuration for the oxocarbenium ion.[33] In consideration of the presence of 2,4,6-trisubstituted tetrahydropyrans in numerous biologically active natural products,[34] and of the efficient reactivity of the enol acetate in the *endo*-cyclization, we initiated a program directed toward oxidative syntheses of *syn*-2,6-disubstituted tetrahydropyrones (Figure 9).

To achieve this objective, we needed to devise a solution to the nontrivial challenge of incorporating an ether linkage between two secondary carbons (Figure 10). We envisioned this unit to arise from Lewis acid-mediated cleavage reactions of cyclic acetals in the presence of a metalloallene. The homo-

(31) Schlesener, C. J.; Amatore, C.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 3567.
(32) (a) Kay, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915. (b) Overman, L. E.; Castaneda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303.
(33) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435.
(34) For examples, see: (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51. (b) Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535. (c) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1996**, *117*, 8126.

Scheme 1. Substrate Synthesis and Stereoselective Cyclization[a]

[a] Reagents and conditions: (a) *n*-Heptanal, *p*-TsOH, benzene, reflux. (b) Allenyltributylstannane, TiCl₄, CH₂Cl₂, -78 °C. (c) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂. (d) Ethyl 1-phenyl-1*H*-tetrazolylsulfone, KHMDS, DME, -60 °C. (e) HOAc, Na₂CO₃, P(Fur)₃, [(*p*-Cymene)RuCl₂]₂, PhMe, 80 °C. (f) CAN, NaHCO₃, DCE, CH₃CN, 80%.

propargylic ethers that arise from this transformation can be converted to enol acetates through metal-catalyzed Markovnikov acetic acid additions. This mild method of forming a stable and easily handled nucleophile from an inexpensive and nontoxic reagent illustrates a highly attractive attribute of utilizing enol acetates in these reactions. Of note in this sequence is that stereogenicity at the homopropargylic (α) center is established relative to the homobenzylic (α′) stereocenter in the acetal opening reaction. Given that the homobenzylic stereocenter is lost during the oxidative cleavage step of the cyclization and reformed during the nucleophilic addition step under the aegis of the α-stereocenter,[35] enantioselective product synthesis is possible from enantiomerically pure acetals if a high degree of diastereoselectivity is achieved in the ring-opening reaction. Extensive studies from several groups[36] have shown that the requisite level of diastereocontrol in these reactions can be attained through careful selection of reaction conditions. Enantiomerically pure acetals are readily available through sequences that proceed through asymmetric olefin dihydroxylation or aldehyde allylation reactions.

Known[37] diol **27**, prepared as a single enantiomer from Sharpless asymmetric dihydroxylation[38] of allylanisole, served as the starting material for the syntheses of our first generation of cyclization substrates (Scheme 1). Condensing **27** with heptanal formed acetal **28** as a 1.7:1 mixture of inseparable diastereomers. Exposing **28** to tributylstannylallene and TiCl₄[39] provided homopropargyl ether **29** *as a single diastereomer* in 84% yield. The remarkable selectivity in this reaction is consistent with a mechanism in which the Lewis acid binds to the less sterically encumbered oxygen to form an oxocarbenium ion that rapidly equilibrates exclusively to the (*E*) configura-

(35) This sequence can be considered as a cationic variant of the self-reproduction of chirality. See: Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.
(36) For lead references, see: (a) Bartlett, P. A.; Johnson, W. S.; Elliot, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (b) Denmark, S. E.; Wilson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258. (c) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. (d) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458. (e) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485. (f) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998.
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(38) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
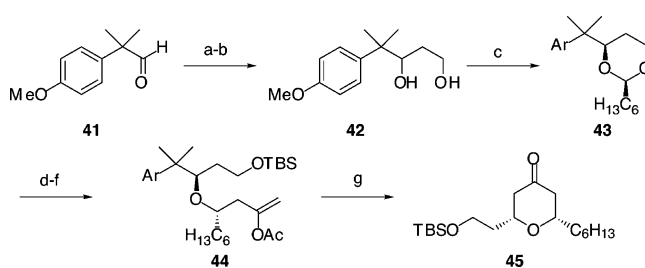(39) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925.

Table 3. Effects of Olefin Substitution on Cyclization Efficiency[a]

Entry	Substrate[b]	Product	Yield (%)[c]
1	**33**	**34**	70
2	**35**	**36**	80
3	**37**	**38**	79
4	**39**	**40**	19

[a] Reactions were conducted by adding a solution of CAN (2−4 eq) in CH_3CN to the substrate (1eq), $NaHCO_3$ (4−9 eq), and powdered 4 Å mol sieves (2 weight eq) in DCE at room temp. [b] See the Supporting Information for the syntheses of these substrates. Ar = *p*-methoxyphenyl. [c] Yields refer to isolated, purified material.

tion.[33] Ion pairing results in the *Si* face of the intermediate being blocked, leading to reaction from the Re-face. To the best of our knowledge, this is the first report of diastereoselective cyclic acetal opening with a stannylallene reagent. Oxidation of the resulting alcohol followed by a Julia-Kocienski olefination[40] yielded **30**, which was converted to enol acetate **31** by a [RuCl2-(*p*-cymene)]2/trifurylphosphine-mediated HOAc addition.[41] Exposing **31** to CAN at room temperature resulted in oxidative cleavage and cyclization to form tetrahydropyrone **32** with complete stereocontrol in 80% yield within 20 min. The selective formation of the 2,6-*syn*-stereoisomer results from a displacement reaction that proceeds with stereochemical retention, consistent with the intermediacy of a discrete oxocarbenium ion.

We prepared several olefinic substrates and subjected them to oxidative cyclization conditions to establish the generality of this method (Table 3). This study demonstrated that olefin geometry is retained through the cyclization (entry 1). Trisubstituted olefins (entry 2) are also effective substrates in this process. Allylic silyl ethers are tolerated in the reaction (entry 3), despite the possibility for a competitive vinylogous pinacol rearrangement following oxocarbenium formation. Interestingly a simple vinyl group (entry 4) does not sufficiently weaken the benzylic carbon−carbon bond to promote cleavage and cyclization, with the alternative reaction pathway of nucleophilic attack by nitrate on the aromatic nucleus to form **40** being the only discernible process. Since olefin substitution has only a small

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(41) (a) Goosen, L. J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706. (b) Neveaux, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1197.

Scheme 2. *Endo*-Cyclization through a Nonstabilized Oxocarbenium Ion[a]

[a] Reagents and conditions: (a) Allylmagnesium bromide, THF, -78 °C. (b) O_3, CH_2Cl_2, MeOH, then $NaBH_4$. (c) $C_6H_{13}CHO$, *p*-TsOH, PhMe, reflux. (d) Tributylstannylallene, $TiCl_4$, Ti(O*i*-Pr)4 (3:1), CH_2Cl_2 -78 °C. (e) HOAc, [(*p*-cymene)RuCl2], Fur3P, Na_2CO_3, PhMe. f) TBSCl, imidazole, CH_2Cl_2. (g) CAN, $NaHCO_3$, 4 Å mol sieves, DCE, CH_3CN, room temp., 88%.

effect on allylic bond dissociation energies but significantly lowers the oxidation potentials of allylic radicals,[42] this result highlights the importance of $E_{pa}(E)$ in eq 1.

The generality of the first generation of cyclization substrates is limited by the necessity for a conjugated oxocarbenium ion intermediate. We postulated that this requirement could be overcome by weakening the benzylic carbon−carbon bond by adding methyl groups to the benzylic position. Substrates that were designed to test this hypothesis were prepared from aldehyde **41**[43] (Scheme 2). Allylation followed by ozonolysis and reductive workup provided diol **42**. Although these substrates were synthesized as racemic mixtures, they can readily be prepared in enantiomerically pure form through additions using chiral nucleophilic allylation reagents.[44] Conversion of diol **42** to its acetal followed by Lewis acid mediated ring opening with tributylstannylallene provided homopropargyl ether **43**, again with excellent diastereocontrol. Enol acetate construction and silyl ether formation yielded cyclization substrate **44**. CAN-mediated oxidative cyclization of **44** proceeded smoothly within minutes and with complete stereocontrol at room temperature to provide tetrahydropyrone **45** in 88% yield, demonstrating that the *endo*-cyclization pathway does not require a conjugated oxocarbenium ion intermediate and is well-suited for substrates that have additional activation at the benzylic position.

Further studies on the scope of this cyclization are shown in Table 4. Secondary ether groups do not inhibit the reaction and play no role in the stereoselectivity of the cyclization. In fact, the substrates with the greatest molecular complexity react with the highest efficiency of any compounds we have tested, with yields in excess of 95% in each example. The isolation of single stereoisomers of these compounds shows that stereochemical integrity of the intermediate oxocarbenium ions is not compromised through oxonia-Cope rearrangements.[45] Isolating **47** from

(42) Wayner, D. D. M.; Houman, A. *Acta Chem. Scand.* **1998**, *52*, 377.
(43) Aldehyde **41** can be prepared on multigram scale through a two step sequence consisting of nucleophilic aromatic substitution of *p*-fluoroanisole by isobutyronitrile (Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712) followed by DIBAL reduction.
(44) For reagents that effect highly efficient and enantioselective additions into tertiary aldehydes, see: (a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (b) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (c) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.
(45) Inconsequential oxonia-Cope reactions might occur in these transformations. For examples of stereochemical erosion due to this process in related cyclization reactions, see: (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. D. *Org. Lett.* **2002**, *4*, 577. (b) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815.

Table 4. Scope of Cyclizations with Non-stabilized Oxocarbenium Ions

Entry	Substrate[b]	Product	Yield (%)[c]
1	**46**	**47**	100
2	**48**	**49**	97
3	**50**	**47**	96
4	**51**	**52**	70
5	**53**	**54**	75

[a] Reactions were conducted by adding a solution of CAN (2−4 eq) in CH$_3$CN to the substrate (1eq), NaHCO$_3$ (4−9 eq), and powdered 4 Å mol sieves (2 weight eq) in DCE at room temp. [b] Ar = *p*-methoxyphenyl. [c] Yields refer to isolated, purified material.

the cyclizations of both **46** and **50** demonstrates again that the stereochemistry of the homobenzylic center is irrelevant in the stereochemical outcome of the product. Notably, the functionality in **47** maps well onto the C2−C10 portion of the potent cytotoxic agent leucoscandrolide A.[34a,46] This work also demonstrated that the added reactivity conferred by the benzylic methyl groups promotes bond cleavage and leads to cyclization when the oxocarbenium ion is substituted by a simple vinyl group.

Our attempts to incorporate an allylsilane as nucleophile resulted in the interesting and unexpected formation of allyl nitrate **54** rather than the expected methylene tetrahydropyran. Moreover, this reaction was nearly instantaneous at room temperature. Mariano has shown[17c] that a similar allylsilane in a substrate in which an α-tributylstannyl ether served as a progenitor to an oxocarbenium ion did not undergo oxidation
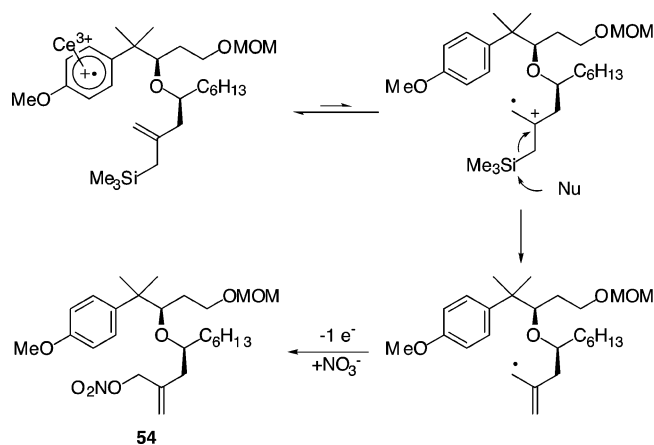
Figure 11. Antenna effect in allylsilane oxidation.

by CTAN during a 12 h reaction. This difference in reactivity suggests that the arene plays a role in the oxidation of the allylsilane. A proposed mechanism for this process is shown in Figure 11. Based on their expected oxidation potentials, arene oxidation is postulated to occur in preference to allylsilane oxidation.[47] Intramolecular electron transfer to form a low concentration of the allylsilane-centered radical cation, however, proceeds faster than benzylic bond cleavage. Rapid cleavage of the allylsilane bond, presumably with assistance from nucleophilic addition of acetonitrile into silicon,[48] provides an allyl radical that can be further oxidized to yield a cation that reacts with nitrate to form **54**. Antenna effects of this type have been observed by Moeller[49] in electrochemical oxidations of tertiary amides that contain electron rich aromatic rings. Although allylsilane oxidation was surprising based on our previous success with an allylsilane nucleophile (Table 2, entry 1) the difference in reactivity can be explained by the inductive protection of the allylsilane in **10** against oxidation by the allylic ether group. This method of modulating the kinetics of allylsilane oxidation by remote functionality could prove to be quite useful in designing new polarity-inverted transformations that proceed under unexpectedly mild conditions.

Summary and Conclusions

We have demonstrated that the thermodynamic propensity of carbon−carbon bonds in radical cations to cleave into cationic and radical fragments can be predicted by a simple arithmetical relationship that only requires knowledge of the bond dissociation energy of the particular bond in the neutral substrate, the oxidation potential of the substrate, and the oxidation potential of the radical that corresponds to the cationic fragment. This relationship applies most generally when comparing reactions in a particular series, so an understanding of the trends of the relevant oxidation potentials and bond dissociation energies suffices to make accurate predictions regarding the tendency of a radical cation to cleave. This study showed that lowering the oxidation potential of the aromatic ring in homobenzylic ethers by incorporating a methoxy group, a desirable structural

(46) For total and formal syntheses of leucascandrolide A, see: (a) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894. (b) Fettes, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4098. (c) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2006. (d) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670. (e) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343. (f) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641. (g) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3934.

(47) The oxidation potentials of allylsilanes of this general structure can be estimated as being >1.9 V vs SCE. See: Yoshida, J.-i.; Murata, T.; Isoe, S. *Tetrahedron Lett.* **1986**, *27*, 3373.

(48) (a) Todd, W. P.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R. *J. Am. Chem. Soc.* **1991**, *113*, 3601. (b) Ohga, K.; Yoon, U. C.; Mariano, J. P. *J. Org. Chem.* **1984**, *49*, 213.

(49) Moeller, K. D.; Wang, P. O.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058.

change for expanding the range of compatible nucleophiles in these reactions, diminishes the reactivity of the radical cation and precludes the desired cleavage reaction. Cleavage reactivity can be recovered by lowering the bond dissociation energy of the benzylic carbon−carbon bond. This was accomplished by introducing substituents at the benzylic position (stabilizing the radical leaving group) or by introducing unsaturation at the homobenzylic position (stabilizing the cationic group). These structural alterations led to the development of new 6-*exo*- and 6-*endo*-cyclization reactions.

Lowering the oxidation potential of the aromatic ring allows for a significant increase in the functional groups that can be used as nucleophiles in these reactions. Of particular importance are electron-rich alkenes such as allylsilanes, enol acetates, and silylallenes that lead to carbon−carbon bond formation. As with reactions with heteroatom nucleophiles, both 6-*exo*- and 6-*endo*-cyclizations proceed with excellent efficiency, provided that the alkyl group of the homobenzylic ether cannot leave as a stable cation upon oxocarbenium ion formation. An additional benefit to facilitating arene oxidation is the ability to employ the mild ground state oxidant ceric ammonium nitrate to initiate cyclizations, thereby simplifying the reaction setup and increasing the yields of reactions that employ carbon-centered nucleophiles. DDQ, another commonly used ground-state oxidant, provides selective carbon−hydrogen bond activation due to the proximity of the basic oxygen atoms of the quinone radical anion to the acidic benzylic hydrogens after the electron transfer. This complementary reactivity could prove to be useful in designing new benzylic functionalization reactions.

Excellent diastereocontrol can be achieved in these reactions by exploiting the strong tendency of 6-*endo*-cyclizations to proceed through well-defined chairlike transition states. We demonstrated that this method was remarkably efficient for generating *syn*-2,6-disubstituted tetrahydropyranones, useful building blocks in the syntheses of numerous biologically active natural products, within minutes at room temperature. We were able to address the challenging construction of ether linkages between two secondary carbons in the substrates for these reactions by using diastereoselective Lewis acid-mediated acetal opening reactions in the presence of stannylallene reagents. The resulting homopropargylic ethers can readily be converted to enol acetates by ruthenium-catalyzed Markovnikov additions of acetic acid. The mildness and efficiency of the cyclization, the ability to tune reactivity in a rational manner, and the use of acetals as key synthetic intermediates portend well for the applicability of this strategy in the syntheses of complex molecules of biological relevance.

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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