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Oxidative Cyclization Reactions: Controlling the Course of a Radical Cation-Derived Reaction with the Use of a Second Nucleophile**

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The oxidative generation of reactive radical cation intermediates can serve as a powerful tool for the construction of new ring systems.[1,2] For example, substrates with electronrich olefins can be oxidized to generate radical cations that trigger cyclizations with a variety of electron-rich groups.[3] Enol ethers, vinylsulfides, ketene derivatives, electron-rich aryl rings, and styrenes have all been oxidized to form radical cations, whereas enol ethers, allyl and vinylsilanes, aryl rings, styrenes, alcohols, amides, sulfonamides, and amines have all been used to trap the radical cation. The reactions have led to the synthesis of fused and bicyclic ring skeletons and are often compatible with the formation of tetrasubstituted carbons. In addition, they have served to help us gain a better understanding of radical cation intermediates.[4]

However, not all oxidative cyclizations work well. Radical cations are very reactive intermediates. If a cyclization reaction is too slow, then alternative pathways compete. Two examples are shown in Scheme 1. In both examples, a slow cyclization reaction led to side reactions involving an elimination step after formation of the radical cation.[5, 6] This type of “cationic” decomposition of the radical cation is common in anodic reactions that fail.

The failure of reactions like those highlighted in Scheme 1 suggests that an alternative strategy is needed that will allow for oxidative cyclization reactions to be accomplished when they involve slower ring formation. To do so requires that one slows down the competitive “cationic” decomposition pathways while pushing the intermediate toward the

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desired cyclization. We report here that this can be accomplished with the use of a second intramolecular nucleophile for trapping the radical cation.

The basic idea is a simple one. It is illustrated in Scheme 2 as a potential solution to the first problematic cyclization shown in Scheme 1. In this oxidative cyclization, the radical cation (**2**) would initially be trapped by an alcohol nucleophile to make a five-membered ring acetal (**3**). The five-membered ring cyclization between an enol ether radical cation and an alcohol-trapping group is known to be very fast, a situation that should reduce the chance for competing elimination reactions.[4,7]

The result of the initial cyclization would be the formation of a radical intermediate that could then go on to complete the desired cyclization while avoiding the unwanted elimination reaction. Oxidation of a second electron and elimination of the silyl group would then complete the formation of product (**4**).

Work on the project was started by first establishing the feasibility of the general plan. To this end, substrate **5** was synthesized and exposed to the anodic oxidation reaction (Scheme 3).[8] The oxidative cyclization was conducted in an undivided cell with the use of a reticulated vitreous carbon (RVC) anode, a carbon-rod cathode, 2,6-lutidine as a proton scavenger, a 0.1 M $LiClO_4$ in 20% $MeOH/CH_2Cl_2$ electrolyte solution, and a constant current of 8 mA. The reaction was allowed to proceed until 2.1 $Fmol^{-1}$ of charge had been passed through the cell. Initially, the reaction led to a mixture of two main products (both a mixture of stereoisomers): the expected cyclic acetal product **6** and a mixed acetal product **7** that was derived from **6**. The mixed acetal was converted back to the cyclic acetal with toluenesulfonic acid and 4 Å molecular sieves to afford an 82% isolated yield of the desired **6** from substrate **5**.

Clearly, inclusion of the second nucleophile did not interfere with the success of the electrolysis in any way. But did the reaction really lead to a radical intermediate like that proposed in Scheme 2?

Insight into this question was gained by examining the intermolecular trapping reaction illustrated in Scheme 4. The oxidation was conducted using identical electrolysis conditions to the reaction shown in Scheme 3 and led to the formation of four products in an overall yield of 65%. The products were a mixture of molecules that contained either a five-membered ring acetal or a mixed acetal derived from methanol opening of the five-membered ring cyclic acetal.

The formation of product **12** was consistent with an initial cyclization to form a five-membered ring acetal derivative analogous to intermediate **3** in Scheme 2 followed by hydrogen atom abstraction from solvent by the radical left at the β-carbon of the radical cation. The possibility that the product was derived from a simple methanolysis of the starting material was ruled out because of the success of the oxidation shown in Scheme 3. Substrates **5** and **8** were oxidized using identical reaction conditions. It is highly unlikely that one reaction led to methanolysis of the substrate and the other did not. Instead, it is more likely that both reactions led to the same radical intermediate. In one case (substrate **5**),

that intermediate was presented with an efficient intramolecular trapping group. The result was a high yield of cyclization. In the other case (substrate **8**), no intramolecular trapping group was present. In the absence of a fast cyclization, the reaction led to a competition between hydrogen atom abstraction and the formation of product **12** and oxidation of the radical leading to the formation of a cation. Formation of the cation led to products **9**, **10**, and **11**.

With a mechanistic premise in place, the scope of the reactions was examined (Scheme 5). Three trapping groups were selected for this study: an enol ether because the coupling reaction would afford a chance to make a bis-acetal product with the ends differentiated, a furan because furans are synthetically very useful coupling partners for oxidative cyclization reactions,[9] and a second alcohol because we wondered if an intramolecular alcohol trapping group might channel a reaction like the one shown in Scheme 4 to a single product.

In each case, the electrolysis conditions were identical to those used previously, and in each case the cyclization proceeded nicely. In the first reaction [Scheme 5, Eq. (1)], the oxidative cyclization led to an 85% yield of a product having two distinct acetal groups. The acyclic acetal was then converted in 85% yield to an aldehyde affording the new ring with the two ends of the oxidative cyclization clearly differentiated. The second cyclization [Scheme 5, Eq. (2)] showed the compatibility of the approach with the use of a furan coupling partner. As in the earlier reaction with substrate **5**, the cyclization led to a mixture of cyclic and acyclic acetal products. The furan was oxidized and trapped with methanol as we have seen in all previous furan-based cyclizations.[9] The use of toluenesulfonic acid and 4 Å molecular sieves again converted the mixture to the desired cyclic acetal, while simultaneously regenerating the aromatic furan ring.

The oxidative cyclizations resulting from substrates **18 a** and **18b** were interesting since one might anticipate that the formation of a radical intermediate like **20** (Figure 1) would preclude formation of the second ring and lead to hydrogen atom abstraction products like **12** above. However, unlike the trapping of an enol ether derived radical cation to form a carbon-carbon bond that has been shown to give rise to kinetic product formation,[10] the alcohol trapping of an enol ether radical cation has been shown to be reversible.[4a] Hence, the formation of **20** can reverse, regenerating the original radical cation **19** and giving rise to an opportunity to equilibrate acetal **20** with cyclic ether **21**.[11] The alternative cyclization to form **21** would be a relatively fast pathway when compared to the decomposition pathways available to the intermolecular trapping reaction (Scheme 4). The formation of cyclic ether **21** would place the radical next to an oxygen, a scenario that would dramatically lower its oxidation potential and give rise to formation of the bicyclic product. If the oxidation is slower than the equilibration between **20** and **21**, then product formation would be governed by the Curtin–Hammett Principle.[6] This turned out to be the case, and the reactions proved to be compatible with the formation of both five- and a six-membered ring ether products in good yield (Scheme 5).

Next, attention was turned toward a demonstration that the method would allow us to overcome the problems encountered earlier with slow cyclization reactions. For this reason, substrate **22** (Scheme 6) was synthesized.[8] This substrate was selected so that the new

method could be directly compared with a previous cyclization that had failed [Scheme 1, Eq. (1)].

Oxidation of **22** using the conditions employed for the cyclizations in Schemes 3 and 5 led to a small amount of slightly impure product (ca. 10%) along with general decomposition of the starting material. The result was encouraging because oxidation of the methoxy enol ether substrate under similar conditions led to none of the desired product. The presence of the second nucleophile in **22** did indeed push the reaction toward the desired direction.

Changing to reaction conditions used for the initial failed cyclization attempts with the methoxy enol ether substrate (K_2CO_3, 0.5$_M$ $LiClO_4$ in 50% MeOH/THF) led to an increased yield (ca. 25%).[5a] However, the isolated product was again slightly impure and decomposition of starting material was still observed.

The anodic cyclization resulting from substrate **22** could be optimized by dropping the temperature for the reaction to −78 °C (Scheme 6). Under these conditions, a 65% yield of the desired cyclic product could be obtained. The isolated stereoisomers of the product were assigned as having a cis ring fusion based upon analogy to the earlier reactions that coupled two enol ethers.[5a]

The temperature of the reaction was dropped because the initial oxidation led to, along with the small amount of product, an unidentifiable mixture of elimination and polymer byproducts that we have come to recognize as the hallmarks of radical cation decomposition. As mentioned earlier, we have shown that the alcohol trapping of a radical cation intermediate can be reversible.[4a] If this is the case for the oxidation of **22**, then intermediates **2** and **3** (Scheme 2) would be in equilibrium with each other. In this way, the presence of the second nucleophile would reduce the effective concentration of radical cation **2**, but it would still be present. Subsequent radical cation decomposition would be slowed but not completely avoided. Fortunately, the same studies that showed alcohol-trapping reactions to be reversible also showed them to be exothermic. The reactions could be driven to the cyclic product with lower temperature.[4a] In the same manner, we hoped that lowering the temperature for the oxidation of **22** would push the alcohol trapping reaction toward the formation of cyclic intermediate **3**, reduce the concentration of the radical cation, and more effectively channel the reaction toward the radical cyclization pathway. This turned out to be the case, and lowering the temperature of the reaction did dramatically improve the cleanliness of the transformation.

The success of the cyclization originating from the oxidation of **22** relative to the reaction that originated from the nearly identical methoxy enol ether substrate [Scheme 1, Eq. (1)] further supports the suggestion that the cyclization reaction involves radical **3** and helps to rule out an alternative mechanism where a second oxidation step converts radical **3** to a cation prior to the cyclization reaction. While it is certainly possible that a second oxidation step occurs prior to the cyclization, it is unlikely that a radical cation intermediate with cationic character at the (β-carbon of the enol ether would lead to cation-based elimination reactions [Scheme 1, Eq. (1)] and no cyclization while the formation of a full cation at the same (β-carbon would lead to the complete opposite selectivity.

In conclusion, we have found that trapping both ends of an enol ether radical cation is an effective tool for completing oxidative cyclization reactions. The chemistry expands the utility of enol ether—enol ether coupling reactions by differentiating the ends of the cyclization, is compatible with the use of a variety of trapping groups, and provides a method to accomplish previously unsuccessful cyclizations.

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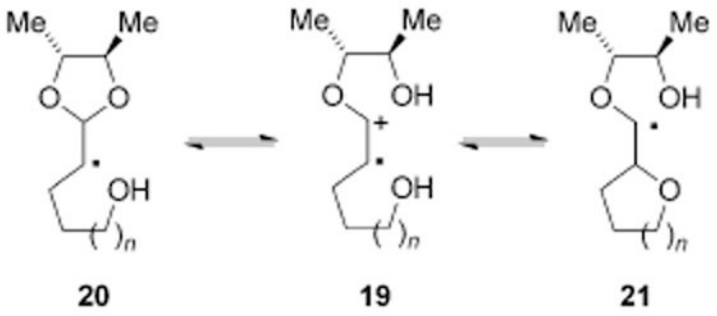
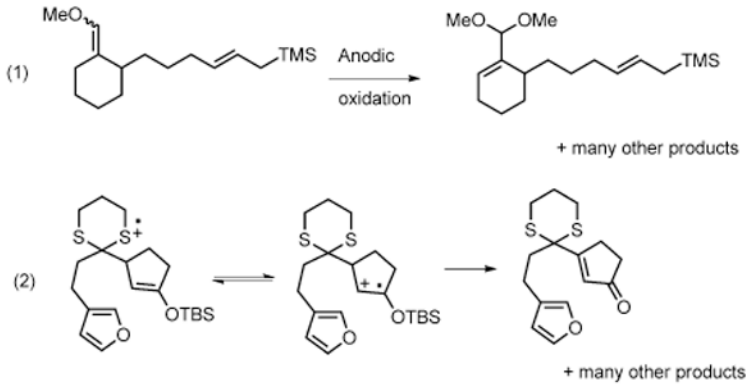
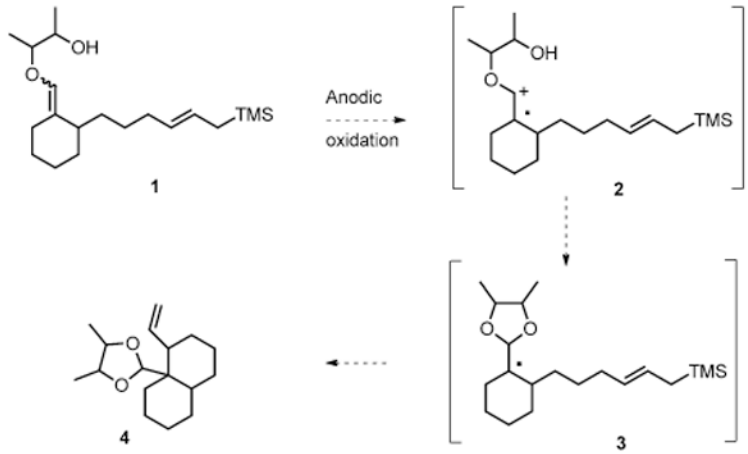


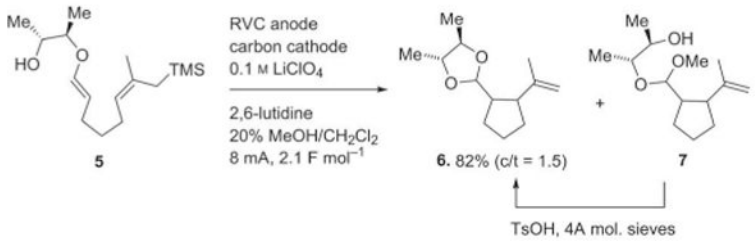
Figure 1.
A potential equilibration of intermediates.



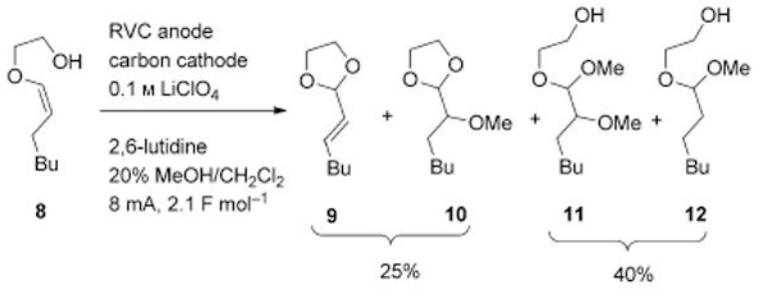
Scheme 1.
Failed anodic cyclization reactions.



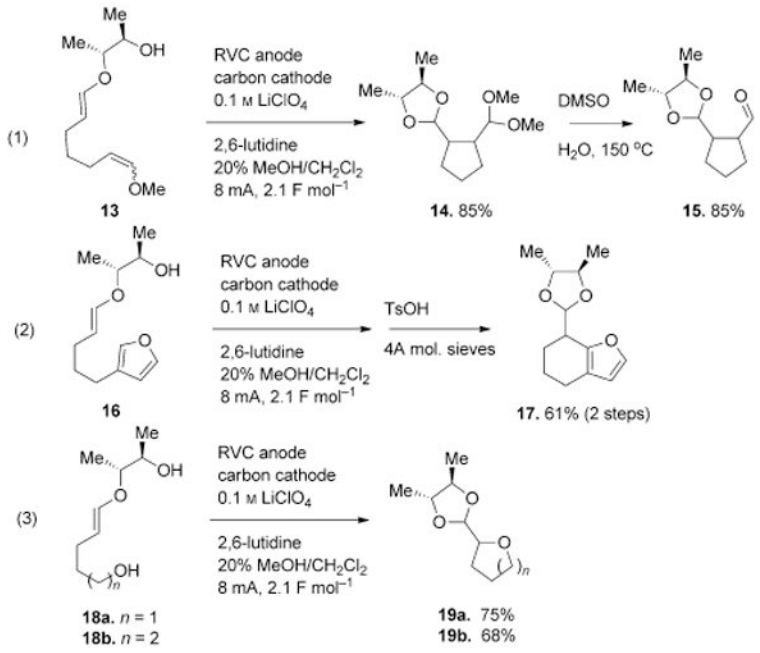
Scheme 2.
A plan for avoiding elimination reactions.



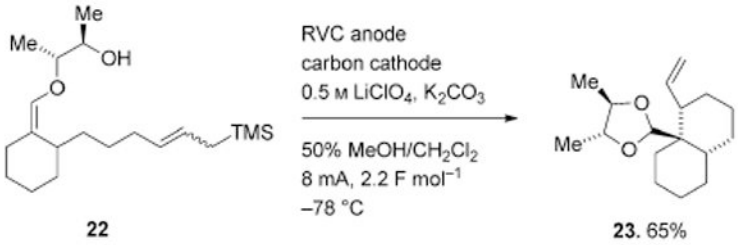
Scheme 3.
The initial experiment.



Scheme 4.
Intermolecular trapping.



Scheme 5.
The compatibility of the cyclization with alternative trapping groups.



22 **23.** 65%

Scheme 6.
Application to a prior failed cyclization.