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Anodic Cyclizations, Seven-Membered Rings, and the Choice of Radical Cation vs. Radical Pathways

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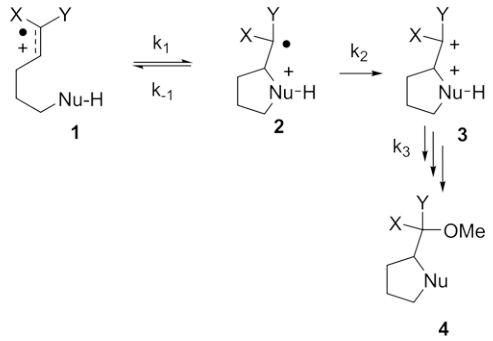
While many steps in an oxidative cyclization reaction can be important, it is the cyclization step itself that plays the central role. If this step does not proceed well, then optimization of the rest of the sequence is futile. We report here that the key to the cyclization is channeling the reaction down the correct pathway. Some reactions require the use of an radical pathway and some require the use of a radical cation pathway. An example of each is provided along with a strategy for accessing both pathways using a common intermediate.

Background and Originality Content

Electroorganic synthesis offers a number of unique opportunities for the construction of complex molecules.[1] These opportunities range from a chance to conduct chemical reactions in more sustainable ways, to unique transformations that combine electrochemical methods with the development of new catalysts, to new umpolung reactions that allow for existing functional groups to be used in new ways. As part of this later group, we have been particularly interested in anodic transformations that allow for electron-rich olefins to be trapped by nucleophiles (Scheme 1).[2] The reactions proceed through a highly reactive

Scheme 1. Mechanistic model for the anodic olefin coupling reaction



radical cation intermediate (**1**), and they can be used to make fused, bridge, and spirocyclic ring skeletons, tetrasubstituted carbons, and a variety of heterocycles.[3]

While a number of issues can arise during an oxidative cyclization reaction ranging from the need to rapidly remove a second electron following the cyclization and elimination reactions leading to overoxidation of the product,[2] the initial cyclization from **1** to **2** always plays the central role in the success of the overall process. If this step in the mechanism does not proceed well, then there is no chance for a successful reaction outcome. The key to this first step being successful is providing the very reactive intermediates generated at the anode with a productive reaction pathway. Radical cation intermediates like **1** are not stable. If the anticipated cyclization reaction is too slow, then the reaction will quickly lead to undesired products from elimination and/or polymerization reactions.

These observations have led to two approaches to channeling oxidative cyclizations down a productive reaction pathway; one that takes advantage of the radical cation intermediate and a second that immediately traps the radical cation and channels the reaction down an radical pathway (Figure 1).

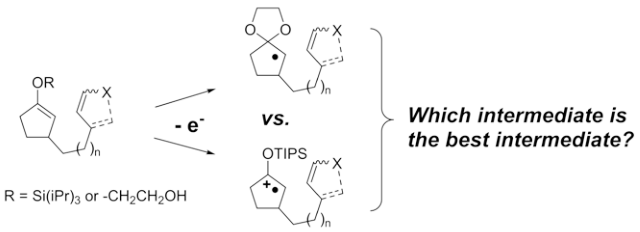


Figure 1 Two possible pathways for a radical cation initiated oxidative cyclization.

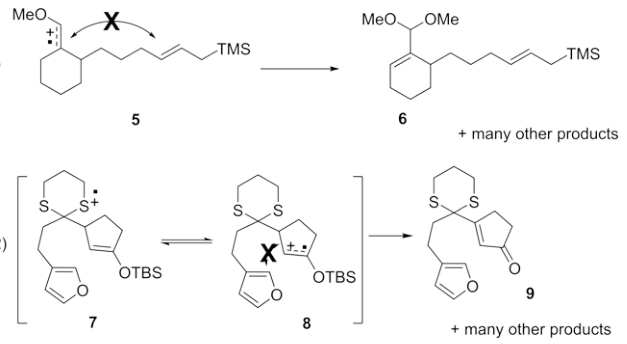
The work highlighted below provides the backdrop needed for determining which of the two pathways one might want to choose when designing an oxidative cyclization and the methodology needed to access either pathway within a given synthetic scheme.

Results and Discussion

The need for the two reaction pathways can be seen by considering the two failed anodic cyclization reactions Two

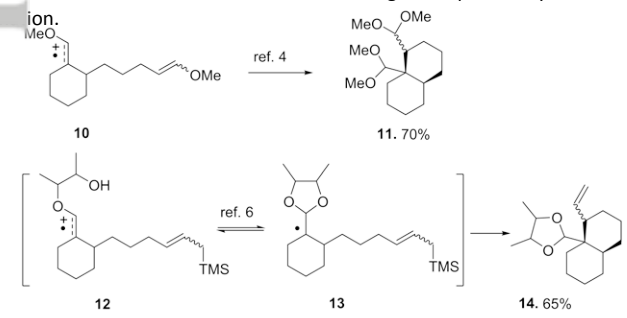
examples of such a situation are shown in Scheme 2. In the first of these reactions, an enol ether was oxidized to form a radical cation that was then to be trapped by an allylsilane to simultaneously form a six-membered ring and a quaternary carbon. However, the cyclization was too slow and the reaction led to both elimination products derived from the radical cation prior to the cyclization and polymerization.[4] None of the desired cyclization product was observed. In the second reaction, it was hoped that the oxidative cyclization would afford a seven-membered ring product.[5] However, once again the cyclization was too slow and the reaction led to the same types of elimination and polymerization products along with only 9% of the desired reaction.

Scheme 2. Unsuccessful cyclization reactions



In these situations, one can either accelerate the desired cyclization or slow down the undesired side reactions. Both approaches can work well. For example (Scheme 3, equation 1), the generation of a six-membered ring and a quaternary carbon can be accomplished with the use of a more reactive trapping group like a second enol ether.[4] Of course, this changes the nature of product leading to a bisacetal, and in turn a new synthetic challenge of having to differentiate the two ends of the cyclization. An alternative approach that slowed the elimination and polymerization reactions originating from the radical cation might circumvent this added complexity. For example, the second

Scheme 3. Alternatives to six-membered ring and quaternary carbon cation.

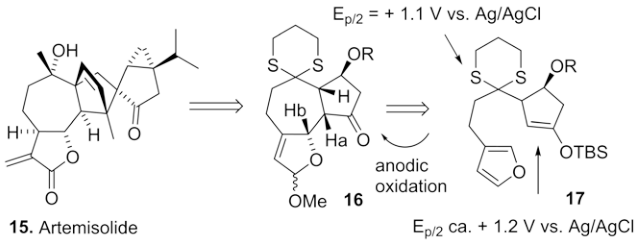


approach illustrated in Scheme 3 trapped the initial enol ether derived radical cation intermediate with an alcohol nucleophile to generate a radical intermediate.[6] The radical intermediate could no longer undergo proton elimination-derived side reactions but could still undergo the desired cyclization. The result was an radical reaction that led to the desired cyclized product in good yield. Clearly, the oxidative cyclization reaction was compatible with the use of an allylsilane trapping group and the combined formation of a six-membered ring and a quaternary carbon if the reaction was channeled down a productive "oxidative cyclization type" pathway.

The observation made in Scheme 3 suggested that perhaps all of the previously problematic anodic cyclizations might benefit from a similar radical type approach. This suggestion was particularly intriguing in connection with the failed seven-membered ring forming reaction shown in Scheme 2, equation 2.

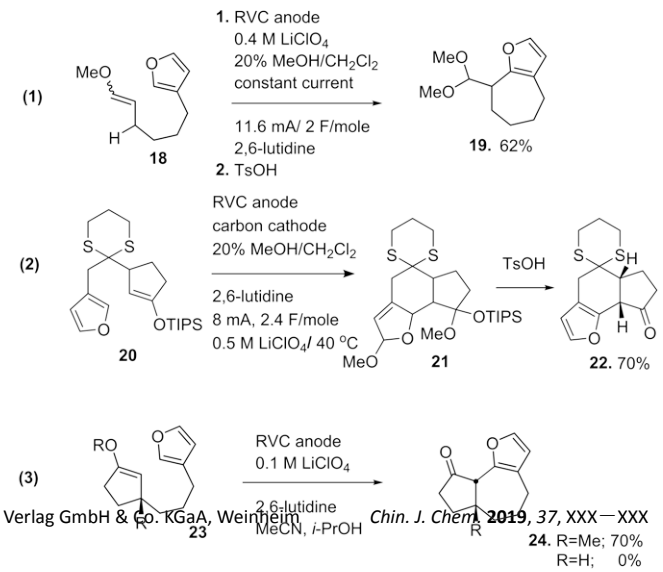
The formation of a seven-membered ring from the oxidative coupling of an enol ether and a furan was being investigated as part of a larger effort to target the synthesis of artemisolide (Scheme 4).[7,8] One of the goals of this effort was to illustrate the synthetic utility of an anodic cyclization controlled by the Curtin-Hammett Principle.[9] The key was to be an initial oxidation of the dithioketal in **17** that would occur preferentially to the less electron-rich enol ether and furan groups needed for the cyclization. An intramolecular electron transfer from the enol ether to the radical cation of the dithioketal would lead to the reversible generation of the enol ether radical cation needed for the cyclization. The cyclization would then drain the equilibrium toward the desired product **16**. The result would be a product functionalized at every carbon necessary for achieving the final total synthesis.

Scheme 4. Retrosynthesis of artemisolide.



Three previous studies (Scheme 5) led to this proposed strategy. The first was an anodic olefin coupling reaction between an enol ether radical cation and a furan ring that demonstrated that the base reaction was compatible with the formation of a seven-membered ring.[10] In the chemistry that supported this finding, the

Scheme 5. Preliminary studies

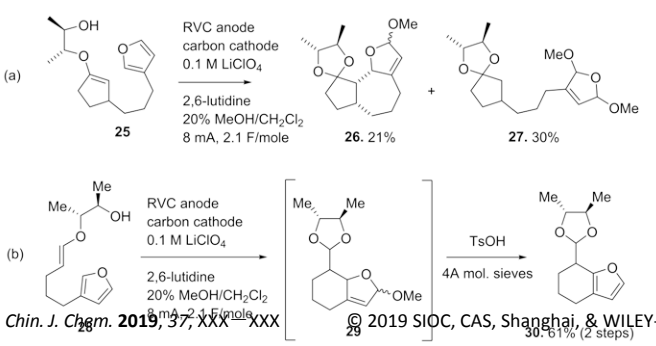


chain between the enol ether and the furan was extended to a point where no coupling between the two groups could occur. In that example, the enol ether was oxidized and the furan was recovered intact, a clear indication that the initial oxidation occurred at the enol ether. In the second study, the proposed Curtin-Hammett controlled cyclization was used for the generation of a six-membered ring. Clearly, the initial oxidation of the dithioketal followed by electron-transfer from the enol ether worked well, and the reaction proceeded as planned when the cyclization was fast enough. The third example from the work of Sperry and Wright (Scheme 5c) provided a note of caution.[11] In their efforts, they demonstrated that the formation of a seven membered ring only occurred when a methyl group was placed on the allylic carbon of the enol ether. This was required to accelerate the reaction. A similar observation was made by the Trauner group in their synthesis of guanacastepene.[12] When this methyl group was not present, the reaction led to no cyclized product. In our hands, the substrate without the methyl group led to the enol ether radical cation derived elimination and polymerization types of products typical of a slow cyclization. We hoped that in substrate **17** (Scheme 4) the ketal would provide a rate acceleration that was sufficient to favor the cyclization and avoid these issues without the inclusion of a methyl group that would not be compatible with the synthesis of artemisolide.

As shown in Scheme 2, equation 2, this was clearly not the case. In comparison with the successful cyclization shown in Scheme 5a, it appeared that in radical cation **7** the optimized overlap between the proton on the allylic carbon and the enol ether derived radical cation accelerated the rate of the elimination reaction relative to the cyclization. The presence of the dithioketal was not sufficient to overcome this problem.

With the inability to use this approach to accelerate the cyclization, we turned our attention toward slowing the elimination reaction. It was against this backdrop that substrate **25** (Scheme 6a) was synthesized and submitted to the anodic oxidation reaction. We hoped to use the successful strategy employed to make **14** to once again avoid the elimination of a proton from the radical cation intermediate and in so doing buy time for the desired cyclization. The two methyl groups were added to the enol ether in order to improve the solubility of the substrate. The attempt was partially successful.

Scheme 6. The radical pathway.

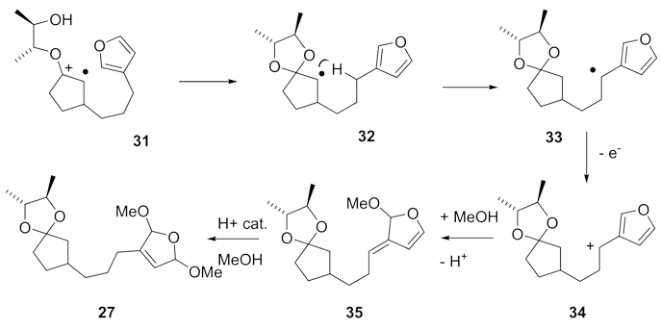


The reaction did lead to a low yield of the desired cyclic product **26**. However, the major product observed (**27**) arose from oxidation of the furan ring. The two products were unstable and could not be isolated in decent yields. So, the crude reaction was analyzed by proton NMR and the yields for the two products obtained with the use of coumarin as an internal standard. Changes in the electrolyte, solvent, nature of the base, etc. either led to no change in the reaction, a drop in current efficiency (recovered starting material), or in the cases where tetraethylammonium tosylate was used as the electrolyte the generation of elimination products from the enol ether radical cation.

In these reactions, the formation of a furan oxidation product (**27**) was puzzling. As pointed out above, previous studies had clearly demonstrated that an enol ether will oxidize in the presence of a furan ring even when it is less electron-rich than the enol ether in substrate **25**.[10] In addition, the oxidation leading to radical cation **8** in Scheme 2b had not led to any furan oxidation product. Finally, the reaction to form a six-membered ring originating from the oxidation of substrate **28** (Scheme 6, equation b) led nicely to the desired product without any evidence for the furan oxidation.[6] This last reaction ruled out any suggestion of an initial proton induced cyclization of the enol ether in the substrate to form the cyclic ketal prior to the oxidation. Such a side reaction would not depend on the size of the ring being generated. Furthermore, the ratio of the two products generated in the attempt to make a seven membered ring did not depend on the pH of the reaction, another observation that was inconsistent with decomposition of the enol ether prior to the oxidation.

In light of these observations, it seems more likely that the desired radical for the radical cyclization led to a hydrogen atom abstraction as shown in Scheme 7. This H-atom abstraction

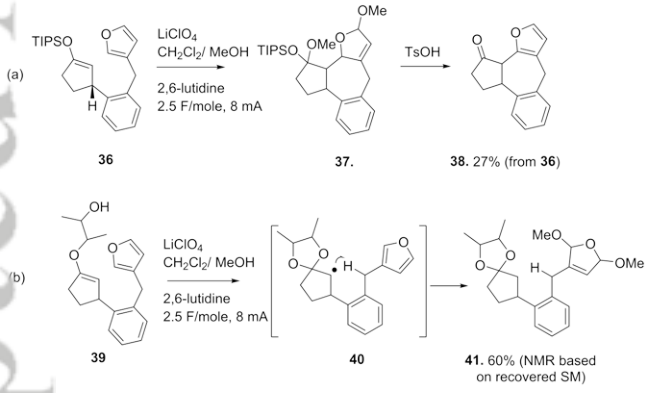
Scheme 7. H-atom abstraction mechanism.



followed by a second oxidation, methanol trapping, and then methanolysis of the resulting diene ether would lead to the oxidized furan product **27** in a manner consistent with previous observations about the selectivity of the oxidation and stability of the enol ether. In this mechanism, the trapping of oxonium **34** would occur in a kinetic 1,2-type manner. Alternatively, radical **33** could undergo an intermolecular hydrogen abstraction followed by oxidation of the resulting furan to form **27**. While this possibility would require a 4 electron oxidation and the competitive oxidation of radical **33** at the anode is expected to be fast, the low mass balance of the reaction makes it impossible to rule this pathway. Either way, the occurrence of the intramolecular H-atom abstraction should not have been a surprise.[13] However, it caught us off guard because of the success of the cyclization shown in Scheme 5, equation 1. In fact, no other anodic olefin coupling reaction conducted to date has led to a similar competitive H-atom abstraction. Could it be that radical cation intermediates do not abstract H-atoms?

Either way, it was clear that a different approach to solving the seven-membered ring problem was needed. This refocused our efforts on a method to accelerate the cyclization reaction relative to the unwanted side reactions and led to the design of two new substrates (Scheme 8). In these substrates, a phenyl ring was

Scheme 8. Radical cation vs. radical pathways and seven-membered rings.



inserted as a conformational constraint into the tether between the two coupling partners in order to accelerate the cyclization reaction. The phenyl ring might also accelerate the hydrogen atom abstraction and the elimination of a proton from alpha to the enol ether radical cation. However, it was hoped that the presence of the phenyl ring would accelerate the cyclization in a manner that overcame either of those side reactions. The two substrates gave us an opportunity to determine whether it was better to push the reaction down a radical-cation pathway (Scheme 8a) or an radical pathway (Scheme 8b).

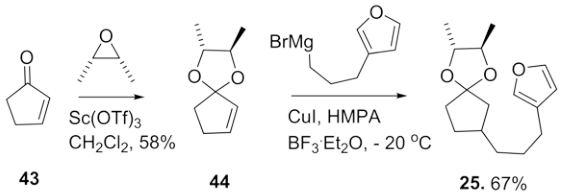
The cyclization reaction originating from the oxidation of **36** was partially successful and led to a low yield of the desired product. The reaction appeared to lead to the types of polymerization products that have previously been associated with the elimination of a proton from the carbon alpha to the enol ether radical cation. No evidence was obtained for the H-atom abstraction and the resulting furan oxidation.

For comparison, none of the desired product was isolated from the reaction forced down the oxidative cyclization pathway (substrate **39**). While there was some evidence for cyclization in the proton NMR of the crude reaction product, the reaction was very messy, the current efficiency of the reaction was poor, and the major product generated was the product derived from a hydrogen atom abstraction reaction.

Of the two reaction pathways, it was clear that the reaction channeled down the radical cation pathway (substrate **36**) held the best chance for success because the use of the radical cation intermediate did avoid the H-atom abstraction reaction. At this point, we do not know if this observation is an inherent property of the radical cation or if the more electron-poor radical cation simply favors a reaction with the more electron-rich furan ring. As mentioned earlier, no previous anodic olefin coupling reactions involving a radical cation has led to a H-atom abstraction. However, each of those reactions involved coupling to an electron-rich olefin. Either say, the conclusion reached indicate that one cannot simply channel a reaction down an radical pathway to overcome a slow radical cation based cyclization. While for the specific examples shown there is still work to do to either accelerate the cyclization to avoid the competitive elimination from the radical cation or block that elimination, the use of a radical cation based pathway holds the best chance for a successful seven-membered ring cyclization.

At the same time, it is also clear that in situations such as the one shown in Scheme 3 the best course of action is the use of the radical pathway. With this in mind, it is important to take note that both families of substrates are made from the same starting materials. The silyl enol ether substrates are typically made by a cuprate addition to an enone followed by trapping of the enolate with a silylating agent.[11,12] As illustrated in Scheme 9, the ene diol substrates can be made from the same cuprate and enone starting material by first converting the enone into a cyclic acetal.[14] In using the same overall synthetic sequence to produce both types of substrate, both the radical cation and radical pathways can be accessed within a given synthetic sequence.

Scheme 9. Substrate synthesis.

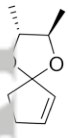


Conclusions

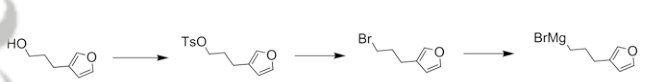
While the optimization of an anodic cyclization reaction can involve a series of steps including a need to accelerate a second oxidation step or avoid eliminations from a cyclized product that lead to overoxidation,[2] all of the reactions require the initial cyclization to proceed well. The success of that step is dependent on the proper choice of the reactive intermediate involved. There

are times like the formation of six membered rings and quaternary carbons where channeling the reaction down an radical pathway and away from a radical cation based cyclization is essential.[6] There are also times, seven-membered ring formation, that the use of the radical cation intermediate is essential. The key to identifying which processes is best appears to be the possibility of an intramolecular H-atom transfer. When an intramolecular H-atom abstraction can occur, the use of a radical cation intermediate is essential. While this is important to know for the design of the oxidative cyclization, the need to choose between the reactive intermediates does not require a change to a larger synthetic strategy that takes advantage of the desired umpolung reaction. Both the radical and radical cation pathways can be accessed using the same overall synthetic approach. The requirement for one intermediate over the other only influences the manner in which the step forming the oxidation substrate is performed. Hence, both pathways are equally viable.

Experimental



(2,3-dimethyl-1,4-dioxaspiro[4.4]non-6-ene: To a solution of 2-cyclopenten-1-one (1.0 mL, 12.0 mmol) in CH_2Cl_2 (10 mL) was added Na_2SO_4 (0.36 g). A solution of cis-epoxybutane (3.1 mL, 36 mmol) in CH_2Cl_2 (10 mL) was added dropwise very slowly overnight via syring pump. Triethylamine (1.5 mL) was then added, and the reaction was diluted with ether. The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude epoxide was purified via chromatography on basic alumina (eluting with 5:1 hexanes:ether) to give ketal product as a colorless liquid (1.622 g, 7.0 mmol) in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$) 6.08 (dt, J = 5.7 Hz, 1H), 5.72 (dt, J = 5.7 Hz, 1H), 3.70-3.57, (m, 4H), 2.75-2.37 (m, 2H), 2.12-2.07 (m, 2H), 1.28 (d, J = 2.1 Hz, 3H), 1.26 (d, J = 2.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 136.3, 131.7, 119.3, 78.6, 78.2, 35.5, 29.4, 16.9, 16.6; IR (neat, KBr) 2997, 2931, 2878, 2250, [illegible] cm^{-1}; ESI HRMS *m/z* $(M+Na)^+$ calcd 177.0881, obsd 177.0886.



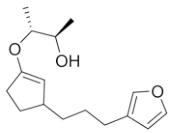
Grignard reagent stock solution:

The furanyl alcohol was synthesized according to the procedure given in Mihelcic, J.; Moeller, K.D. *J Am. Chem. Soc.* **2004**, *126*, 9106.

To the alcohol (2.1346 g, 16.8 mmol) in CH_2Cl_2 (85 mL) was added DMAP (2.67 g, 21.8 mmol) followed by tosyl chloride (3.94 g, 20.7 mmol) and the reaction stirred overnight. The reaction mixture was diluted with ether and washed with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ether, and the organic washes were dried over Na_2SO_4 and concentrated *in vacuo*.

The crude tosylate was then taken up in acetone (5.5 mL) and LiBr added (0.26 g). The reaction was refluxed for 4 hr, then cooled to 0°C. Water was added, the layers separated, and the aqueous layer extracted with ether. The organic washes were dried over Na_2SO_4 and concentrated *in vacuo*. The crude bromide was purified via silica gel chromatography (eluting with 10:1 hexanes:ether) to give bromide product (1.9938 g, 10.6 mmol) in 63% yield over 2 steps. The spectral data for this bromide matched that previously reported.

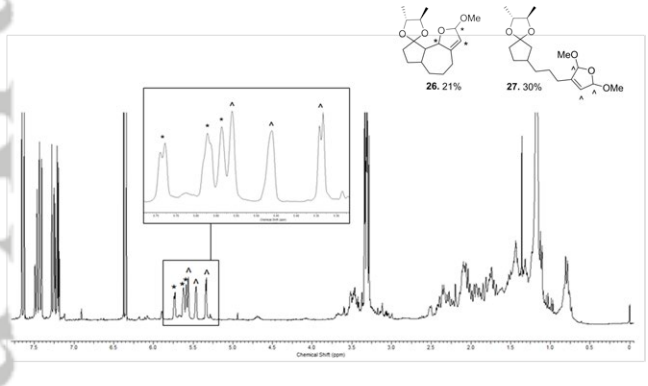
To make a stock solution of the Grignard reagent: To dried magnesium powder (1.3 g) under argon in dry THF (5 mL) was added bromide (0.9444 g, 5.0 mmol) in THF (2 mL) dropwise over 1 hr. The reaction was stirred another hour, diluted with THF (3 mL), and stirred another hour. The grey solution was then cannulated off the excess magnesium into a separate flask. The Grignard stock solution was titrated using a menthol with a small amount of 1,10-phenanthroline in THF until a slight pink color persisted. These stock solutions typically yielded a 0.3-0.4 M Grignard solution.



3-({3-[3-(furan-3-yl)propyl]cyclopent-1-en-1-yl}oxy)butan-2-ol: A solution of 0.3-0.4 M in THF stock Grignard solution (3.0 mL) and HMPA (0.46 mL, 2.6 mmol) was sonicated for 10 minutes. The mixture was cooled to -20°C and freshly purified CuI (0.12 g, 0.63 mmol) was added. The solution was stirred at -20°C for 30 min. A solution of 2,3-dimethyl-1,4-dioxaspiro[4.4]non-6-ene (0.0872 g, 0.57 mmol) in THF (0.3 mL) was then added, followed by dropwise addition of BF_3-Et_2O (0.07 mL, 0.57 mmol) at -20°C. The reaction was stirred at -20°C for 3 hr. 2,6-lutidine (0.15 mL, 1.3 mmol) was then added at -20°C. The reaction mixture was warmed to room temperature, quenched with cold saturated aqueous $NaHCO_3$, and diluted with ether. The layers were separated and the organic layer washed twice with saturated aqueous $NaHCO_3$. The aqueous layer was then extracted once with ether. The combined organic layers were washed with 0.1 M EDTA solution at pH 8 until the washes no longer showed any blue/green coloration. The organic layer was then washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude enol ether was purified via silica gel chromatography (packed with 1.5% NEt_3, eluting with 5:1 hexanes:ether) to give enol ether product (0.0997 g, 0.38 mmol) as a colorless to pale yellow oil in 67% yield, along with some amount of 2,6-lutidine mixed in. ^{1}H NMR (300 MHz, $CDCl_3$) 7.34 (s, 1H), 7.21 (s, 1H), 6.26 (s, 1H), 4.45 (s with fine coupling, 1H), 3.79 (septet, J = 6 Hz, 1H), 3.69 (septet of d, J = 6, 3 Hz, 1H), 2.74-2.59 (m, 1H), 2.46-2.22 (m, 4H), 2.10-1.96 (m, 1H), 1.66-1.46 (m, 2H), 1.46-1.23 (m, 3H), 1.21-1.14 (m, 6H) ^{13}C NMR

(75 MHz, $CDCl_3$) 142.6, 138.7, 125.2, 111.0, 110.0, 99.43, 99.39, 79.4, 70.5, 70.4, 42.1, 42.0, 37.2, 37.1, 31.79, 31.76, 28.1, 27.9, 25.0, 18.3, 15.1, 15.0 ; IR (neat, KBr) 3434, 2975, 2924, 2858, 1642 cm^{-1}

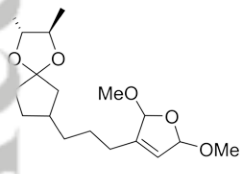
General Procedure for the Electrolyses:
In a flame-dried three-neck round bottom flask, the substrate was dissolved in an anhydrous 20% MeOH/CH_2Cl_2 solution (0.025 M, 1.0 equiv.) with 2,6-lutidine (10.0 equiv.) and $LiClO_4$ (0.1 M) electrolyte. The reaction flask was equipped with a reticulated vitreous carbon anode (100 PPI) and a carbon rod cathode. The reaction was cooled to -78°C. A constant current of 8.0 mA was passed through the solution. Upon completion (as monitored by TLC), the solution was allowed to warm to room temperature, diluted with ether and then washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was chromatographed through a silica gel column (using Sorbtech Premium Rf silica gel, slurry packed using



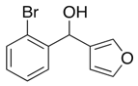
1% triethylamine in hexane/ether).

Crude ^{1}H NMR for the electrolysis of susbstrate 25 with coumarin as an internal standard – Shown above. (In this case, the suspected cyclized product could not be isolated in its pure form. Its identity was confirmed by conversion to the corresponding furan derivative. The proton NMR for the furan product is included in the supporting information along with a more easily characterized analog missing the methyls on the cyclic ketal.):

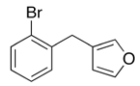
Spectral data for the hydrogen atom abstraction byproduct.



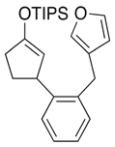
7-(3-(2,5-dimethoxy-2,5-dihydrofuran-3-yl)propyl)-2,3-dimethyl-1,4-dioxaspiro[4.4]nonane: ^{1}H NMR (300 MHz, $CDCl_3$) 5.64 (s, 1H), 5.53 (s, 1H), 5.41 (s, 1H), 3.62-3.49 (m, 2H), 3.41 (s, 3H), 3.38 (s, 3H), 2.44 (t, J = 7.4 Hz, 1H), 2.28-1.68 (m, 6H), 1.64-1.30 (m, 6H), 1.30-1.18 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 145.6, 123.6, 107.8, 106.9, 78.3, 76.6, 54.2, 53.7, 44.5, 38.0, 37.8, 37.6, 37.3, 35.8, 35.6, 30.5, 29.7, 26.6, 25.8, 17.2, 17.0, 16.9; IR (neat, KBr) 2966, 2929, 2867, 1740, 1673 cm^{-1}; ESI HRMS *m/z* $(M+Na)^+$ calcd 349.1985, obsd 349.1982.



(2-Bromophenyl)(furan-3-yl)methanol: To a solution of 3-bromo furan (5.23 g, 36 mmol, 1.1 eq) in THF (40 mL) at -78 °C was added n-BuLi (14.2 mL of a 1.6 *M* solution in hexane, 1.2 eq) in a dropwise fashion. After 30min, 2-bromobenzaldehyde (3.66 mL, 32 mmol) in 15 mL THF was added in dropwise. The reaction mixture was allowed to warm to room temperature and then stirred overnight. The reaction was then quenched with a saturated aqueous solution of NH_4Cl and most of THF solvent removed under reduced pressure. The residue was diluted with water and DCM, and the aqueous layer extracted with three times with dichloromethane (DCM). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was chromatographed through silica gel using 20% ethyl acetate in hexane as eluent to give 7.0 g of product (87% yield). The NMR data matched the previously published data (Hartman, G. D.; Halczenko, W.; Phillips, B. T.; *J. Org. Chem.* **1986**, *51*, 142).



3-(2-Bromobenzyl)furan:

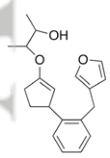


To a solution of NaI (5.55 g, 37 mmol, 4.5 eq) in acetonitrile (100 mL) at 0 °C, was added TMSCl (4.73 mL, 37 mmol, 4.5 eq) in a dropwise fashion. The reaction was stirred at 0 °C for 15min before adding **57** (2.08 g, 8.2 mmol, 1 eq) in 50 mL of CH_3CN dropwise over 1h at 0 °C. The reaction was then quenched with NaOH (2*M*). The resulting aqueous layer was extracted two times with Et_2O. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was chromatographed through silica gel with hexane as eluent to give 2.0 g of product (85% yield). The NMR data again matched the previously reported data (Hartman, G. D.; Halczenko, W.; Phillips, B. T.; *J. Org. Chem.* **1986**, *51*, 142).

A procedure for making phenyl bromide Grignard:
Mg ribbon (4 g, freshly sanded, freshly cut) was placed in 50 mL flask. The flask was flame dried and then cooled to room temperature. THF (12 mL) was added to the flask and the mixture

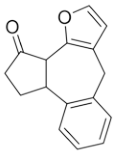
sonicated for 15 min. The starting bromide (8.5 mmol) was dissolved in 8 mL of THF. The subsequent additions were made using a Sage Instruments Syringe Pump (Model number 341B). In stage one, 2 mL of the bromide solution was added to the flask with the syringe pump at a rate of 8 mL/min. A heat gun was then used to initiate a reflux. In a second stage, the remaining 6 mL of bromide solution was added to the flask at a rate of 2 mL/min while the reaction was heated with a hot plate. In the third stage of the reaction, the result mixture was refluxed for 5h. A dark red solution was obtained.

A procedure for titration of phenyl bromide Grignard:
A 5 mL flask was flame dried and placed under argon with the use of a balloon. To this flask was added 14.5 mg of menthol along with ½ a spatula of 1,10-phenanthroline to be used as an indicator. Methanol solvent (0.5 mL) was then used to dissolve the solid. To this mixture was added the Grignard-reagent in a dropwise fashion. Upon addition, a milky white solid was formed. After 0.54 mL of the Grignard-reagent was added, the mixture became a clear, dark red solution. The titration indicated that the Grignard-reagent had a concentration of 0.18 *M*. This concentration varied due to a loss of solvent during the preparation of the Grignard and activation of the bromide.



3-((3-(2-(Furan-3-ylmethyl)phenyl)cyclopent-1-en-1-yl)oxy)butan-2-ol: To a freshly made Grignard solution (0.69 *M*, 2mL) at 0 °C was added freshly recrystallized CuI (50 mg). The mixture was stirred at room temperature for 30 min until a dark red suspension was formed. The mixture was then cooled to -78 °C. To this solution was added the unsaturated ketal (synthesized above) (154 mg, 1.0 mmol, 1 eq) in 1 mL of THF in a dropwise fashion. Following the addition, BF_3-Et_2O (0.04 mL, 1 mmol, 1 eq) was added and then the reaction stirred for 5 h. To the resulting solution was added 2,6-lutidine (0.6 mL). The reaction was then quenched with a saturated aqueous $NaHCO_3$ solution. The reaction was washed with EDTA solution (pH=8, 0.1 *M*) until no blue color remained. The layers were separated, and the aqueous layer was washed with ether three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was chromatographed on silica gel (20% EtOAc in hexane, packed with 1% TEA) to give 148 mg of **43a** and 2,6-lutidine (2:1 ratio of products by proton NMR). The reaction afforded a 28% yield of the desired product and 28% of the recovered acetal starting material. Due to acid sensitivity, the product was carried on to the electrolysis without further purification. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.47 (t, J = 7.7 Hz, 1.79H), 7.41 – 7.03 (m, 6H), 6.97 (d, J = 7.6 Hz, 2.98H), 6.23 (d, J = 2.3 Hz, 1H), 4.49 (t, J = 1.8 Hz, 1H), 4.26 – 4.11 (m, 1H), 3.98 – 3.69 (m, 4H), 2.50 – 2.24 (m, 4H), 1.35 – 1.14 (m, 6H).

((3-(2-(Furan-3-ylmethyl)phenyl)cyclopent-1-en-1-yl)oxy)triisopropylsilane: A Grignard solution (10 mL, 0.2 *M*) was freshly made using the procedure reported above. To this solution at 0 °C was added CuI (200 mg, 0.5 eq) and HMPA (0.68 mL, 2 eq). The mixture was then stirred at 0 °C for 10 min before the temperature was allowed to slowly climb to room temperature and the reaction stirred for an additional 30 min. The reaction was cooled to -78 °C, and then cyclopent-2-en-1-one (164 mg, 2 mmol) in 3 mL of THF was added to the mixture followed by the addition of TIPSOTf (1.62 mL, 3 eq). The reaction was stirred for 1h before the addition of trimethylamine (1.6 mL, 3 eq). The resulting reaction mixture was allowed to warm to room temperature, 2,6-lutidine (0.21 mL) added, and then the mixure quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the organic layer washed with an EDTA solution (0.1 *M*, pH=8) until no green/blue coloration remained. The aqueous layer was extracted two times with Et_2O, and then the combined organic layers dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A ^{1}H NMR of the crude reaction product was taken, using 2,6-lutidine as internal standard. Integration indicated a 60% NMR yield of the desired enol ether. The crude product was chromatographed on silica gel (using hexane as eluting solvent) to give 114 mg of product (30% yield). ^{1}H NMR (600 MHz, Chloroform-d) δ 7.35 (d, J = 1.8 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.13 (dd, J = 6.4, 1.6 Hz, 2H), 7.08 (s, 1H), 6.23 (d, J = 1.7 Hz, 1H), 4.65 (q, J = 1.8 Hz, 1H), 4.14 (dd, J = 8.5, 6.1, 2.4 Hz, 1H), 3.88 – 3.78 (m, 2H), 2.42 – 2.37 (m, 1H), 2.32 (ddd, J = 13.0, 8.6, 4.9 Hz, 1H), 1.74 (dq, J = 12.0, 6.8, 5.5 Hz, 2H), 1.23 (q, J = 7.4 Hz, 3H), 0.89 (q, J = 8.5, 7.6 Hz, 18H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.87, 143.04, 140.16, 137.00, 134.43, 126.85, 124.25, 124.09, 123.20, 121.88, 108.52, 103.23, 40.50, 31.99, 30.85, 25.79, 19.99, 15.24. Due to acid sensitivity. The reaction was utilized in the electrolysis without further purification.



1,3a,7,11b-tetrahydrobenzo[7,8]azuleno[4,5-b]furan-3(2H)-one: To a three-neck round bottom flask was charged with **36** (0.2 mmol, 1eq), LiClO4 (254 mg, 0.6 M), MeOH/DCM (1:1, 4 mL), 2,6-lutidine (116 mL, 5 eq), the mixture was electrolyzed at 8 mA until 2.5 F/mol current passed. The reaction was then quenched with water. Aqueous layer was extracted with DCM for three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed through silica column using 10% ethyl acetate in hexane as eluent to give 13.0 mg of product (27% yield). ^{1}H NMR (500 MHz, CDCl) δ 7.43 – 7.33 (m, 2H), 7.33 – 7.28 (m, 1H), 7.25 – 7.19 (m, 2H), 6.27 (d, *J* = 1.8 Hz, 1H), 4.14 (dd, *J* = 16.2, 3.2 Hz, 1H), 3.70 – 3.62 (m, 1H), 3.53 (d, *J* = 16.2 Hz, 1H), 3.10 (dd, *J* = 13.6, 2.9 Hz, 1H), 2.77 – 2.68 (m, 1H), 2.52 – 2.40 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.78, 144.64, 141.69, 140.15, 139.28, 128.75, 127.37, 127.25, 124.43, 117.94, 112.10, 54.70, 43.12, 37.92, 31.41, 24.44.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2019xxxxx and includes spectral data for the new compounds synthesized.

Acknowledgement

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References

1. For reviews see: (a) Sperry, J. B.; Wright D. L. The application of cathodic reductions and anodic oxidations in the synthesis of complex molecules. *Chem. Soc. Rev.* **2006**, *35*, 605-621. (b) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern Strategies in Electroorganic Synthesis. *Chem. Rev.* **2008**, *108*, 2265-2299. (c) Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R. Organic electrosynthesis: a promising green methodology in organic chemistry. *Green Chem.* **2010**, *12*, 2099-2119. (d) Francke, R.; Little, R. D. Redox catalysis in organic electrosynthesis: Basic principles and recent developments. *Chem. Soc. Rev.* **2014**, *43*, 2492-2521. (e) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230-13319. (f) Nutting, J. E.; Rafiee, M.; Stahl, S. S. Tetramethylpiperidine N-Oxyl (TEMPO), Phthalimide N-Oxyl (PINO), and Related N-Oxyl Species: Electrochemical Properties and Their Use in Electrocatalytic Reactions *Chem. Rev.* **2018**, *118*, 4834−4885. (g) Moeller, K. D. Using Physical Organic Chemistry To Shape the Course of Electrochemical Reactions *Chem. Rev.* **2018**, *118*, 4817–4833. (h) Sauermann, N.; Meyer, T. H.; Ackermann, Y. L. Electrocatalytic C-H Activation. *ACS Catalysis.* **2018**, *8*, 7086−7103. (i) Sauer, G. S.; Lin, S. An Electrocatalytic Approach to the Radical Difunctionalization of Alkenes. *ACS Catalysis.* **2018**, *8*, 5175–5187. (j) Möhle, S,; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R. Modern Electrochemiscal Aspects for the Synthesis of Value-Added Organic Products. *Angew. Chem. Int. Ed.* **2018**, *57*, 6018–6041.
2. Feng, G.; Smith, J. A.; Moeller, K. D. Anodic Cyclization Reactions and the Mechanistic Strategies that Enable Optimization. *Acc. Chem. Res.* **2017**, *50*, 2346-2352.
3. For a review of early synthetic efforts please see: Moeller, K. D. Intramolecular Anodic Olefin Coupling Reactions: Using Radical Cation Intermediates to Trigger New Umpolung Reactions. *Synlett. (Invited Account)* **2009**, 1208-1218.
4. (a) Tinao-Wooldridge, L. V.; Moeller, K. D. Hudson, C. M. Intramolecular Anodic Olefin Coupling Reactions: A new Approach to the Synthesis of Angularly Fused, Tricyclic Ketones. *J. Org. Chem.* **1994**, *59*, 2381-2389. (b) For similar results with a bridged bicyclic system see: Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. Anodic Oxidations of Electron-Rich Olefins: Radical Cation Based Approaches to the Synthesis of Bridged Bicyclic Ring Skeletons *Tetrahedron* **2001**, *57*, 5183-5197.
5. Redden, A.; Moeller, K. D. Anodic Coupling Reactions: Exploring the Generality of Curtin-Hammett Controlled Reactions. *Org. Lett.* **2011**, *13*, 1678-1681.
6. Redden, A.; Perkins, R. J.; Moeller, K. D. Oxidative Cyclization Reactions: Controlling the Course of a Radical Cation-Derived Reaction with the Use of a Second Nucleophile. *Angew. Chem. Int. Ed.* **2013**, *52*, 12865-12868.
7. (a) For the isolation of Artemisolide see Dim, J. H.; Kim, H. –K.; Jeon, S. B.; Son, K. –H.; Kim, E. H.; Kang, S. K.; Sung, N. –D.; Kwon, B. –M. New Sesquiterpene-Monoterpene Lactone Artemisolide, Isolated from Artemisia Argyi. . *Tetrahedron Lett.* **2002**, *43*, 6205-6208. (b) For isolation of the related Arteminolides see Lee, S. -H.; Kim, H. -K.; Seo, J. -M.; Kang, H. -M.; Kim, J. H.; Son, K. -H.; Lee, H.; Kwon, B. –M. *J. Org. Chem.* **2002**, *67*, 7670-7675.
8. For synthetic studies targeting the related Arteminolides see (a) Sohn, J. –H. Studies Toward Synthesis of Arteminolides: Intramolecular [5+2] Oxidopyrylium Ion Cycloaddition Reactions with Silicon Tether. *Bull. Korean Chem. Soc.* **2010**, *31*, 1841-1842. (b) Sohn, J. –H. [5+2] Oxidopyrylium Ion Cycloaddition Reaction with Vinylsilane: Construction of Core Structure of Biogenic Intermediates or Arteminolides. *Bull. Korean Chem. Soc.* **2009**, *30*, 2517-2518. (c) Lee, H. –Y.; Sohn, J. –H.; Kim, H. Y. Studies Toward the Synthesis of Arteminolide: [5+5] Cycloaddition Reaction of Allenes with Oxidopyrylium Ions. *Tetrahedron Lett.* **2001**, *42*, 1695-1698.
9. (a) Duan, S.; Moeller, K. D. Anodic Cyclization Reactions: Capitalizing on an Intramolecular Electron Transfer to Trigger the Synthesis of a Key Tetrahydropyran Building Block. *J. Am. Chem. Soc.* **2002**, *124*, 9368-9369. (b) For an intramolecular electron-transfer reaction involving a radical cation and a 4-methoxyphenyl ring as an electron donor, see: Chiba, K.; Miura, T.; Kim, S.; Kitano, Y.; Tada, M. Electrocatalytic Intermolecular Olefin Cross-Coupling by Anodically Induced Formal [2+2] Cycloaddition Between Enol Ethers and Alkenes. *J. Am. Chem. Soc.* **2001**, *123*, 11314-11315. (c) For an early example involving the anodic oxidation of an aromatic ring and an amide as an electron-donor see: Moeller, K. D.; Wang, P. W., Tarazi, S.; Marzabadi, M. R.; Wong, P. L. Anodic Amide Oxidations in the Presence of Electron-Rich Phenyl Rings: Evidence for an Intramolecular Electron-Transfer Mechanism. *J. Org. Chem.* **1991**, *56,* 1058-1067.
10. New, D. G.; Tesfai, Z.; Moeller, K. D. Intramolecular Anodic Olefin Coupling Reactions and the Use of Electron-Rich Aryl Rings. *J. Org. Chem.* **1996**, *61*, 1578-1598.
11. (a) Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Wright D. L. Two-Step Electrochemical Annulation for the Assembly of Polycyclic Systems. *Org. Lett.* **2002**, *4*, 3763-3765. (b) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. Electrooxidative Coupling of Furans and Silyl Enol Ethers: Application to the Synthesis of Annulated Furans. *J. Org. Chem.* **2004**, *69*, 3726-3734. (c) Sperry, J. B.; Wright, D. L. The Gem-Dialkyl Effect in Electron Transfer Reactions: Rapid Synthesis of Seven-Membered Rings Through an Electrochemical Annulation. *J. Am. Chem. Soc.* **2005**, *127*, 8034-8035. (d) Sperry, J. B.; Constanzo, J. R.; Jasinski, J.; Butcher, R. J.; Wright, D. L. Studies on the Diels-Alder Reaction of Annulated Furans: Application to the Synthesis of Substituted Phenanthrenes. *Tetrahedron Lett.* **2005**, *46*, 2789-2793. (e) Sperry, J. B.; Wright, D. L. Annulated Heterocycles Through a Radical-Cation Cyclization: Synthetic and Mechanistic Studies. *Tetrahedron* **2006**, *62*, 6551-6557.

12. Miller, A. K.; Hughes, C. C.; Kennedy-Smith, J. J.; Gradl, S. N.; Trauner, D. Total Synthesis of (-)-Heptemerone B and (-)-Guanacastepene. *J. Am. Chem. Soc.* **2006**, *128*, 17057−17062.
13. For a previous electrochemical example see Audebert, P.; Bekolo, H.; Cossy, J.; Bouzide, A. Electrochemical Evidence for Intramolecular Reactions of the Electrogenerated Cation-Radicals of Some Amidoenamines. *J. Electroanal. Chem.* **1995**, *389*, 215-218.
14. (a) Mioskowski, C.; Manna, S.; Falck, J. R. Reactivity of α,β-Unsaturated Acetals and Ketals Toward Organolithium Reagents in Pentane. *Tetrahedron Lett.* **1984**, *25*, 519-522. (b) Ghribi, A.; Alexakis, A.; Normant, J. F. Reactivity of RCu,BF3 and R2CuLiBF3 Toward Allylic Acetals and Ethers. *Tetrahedron Lett.* **1984**, *25*, 3079-3082.

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Robert J. Perkins, Ruozhu Feng, Qingquan Lu, and Kevin D. Moeller*

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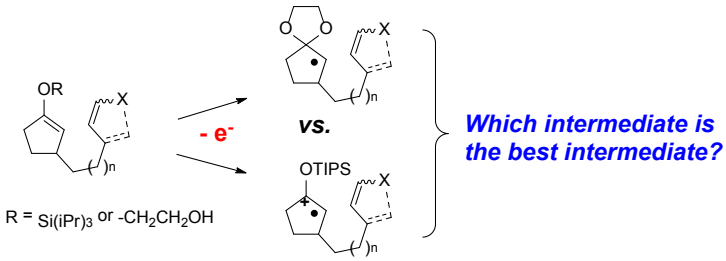

Anodic cyclization reactions can be channeled down one of two main pathways. This manuscript describes when to use each.

