Anodic Cyclizations, Densely Functionalized Synthetic Building Blocks, and the Importance of Recent Mechanistic Observations

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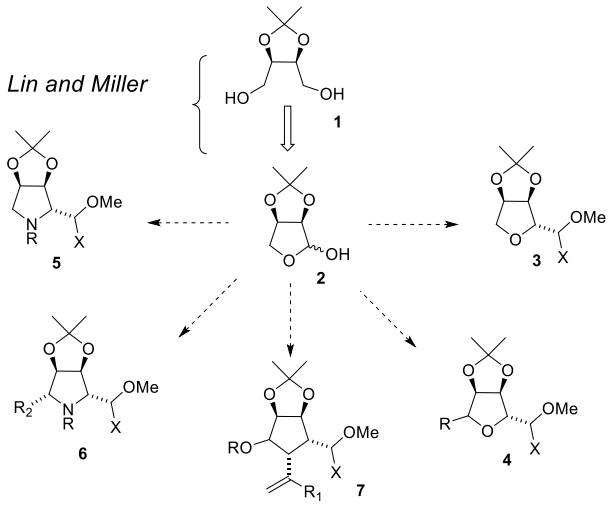
Abstract: Anodic cyclization reactions can provide a versatile method for converting newly obtained chiral lactols to densely funtionalized cyclic building blocks. The method works by first converting the lactol into an electron-rich olefin and then oxidatively generating a radical cation that is trapped by a nucleophile. Historically, such reactions have benefited from the use of less polar radical cations when the trapping nucleophile is a heteroatom and more polar radical cations when the reaction forms C-C bonds. This forced one to optimize underperforming reactions by resynthesizing the substrate. Here we show that by taking advantage of methods that serve to drive a reversible initial cyclization reaction toward the product this dichotomy and need to manipulate the substrate can be avoided. Two such methods were utilized, a faster second oxidation step and a mediated electrolysis. Both led to successful cyclizations using a polar radical cation and heteroatom nucleophiles.

Introduction

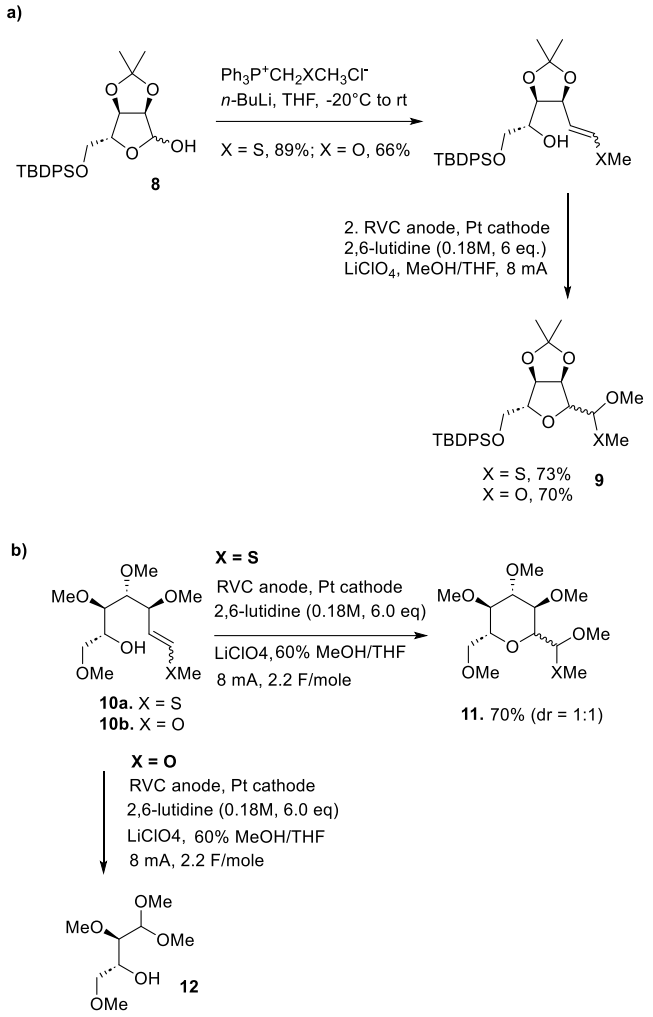
Recently, Lin and Miller published an intriguing method for the desymmetrization of prochiral diols that affords rapid access to chiral lactols and lactones.[1] The products from the reaction have the potential to serve as functionalized synthetic building blocks. For example, the lactol intermediates synthesized appear to be excellent substrates for setting up oxidative cyclization reactions that would convert these starting materials into densely functionalized C-glycoside derivatives, highly substituted pyrrolidine and proline derivatives, and functionalized carbocycles (Scheme 1). In this plan, the chiral lactol would first be converted into an electron-rich olefin with a Wittig reaction and then be subjected to an anodic cyclization reaction.[2-8] Since anodic cyclization reactions are compatible with a variety of nucleophiles, the same approach could be used to convert a single lactol substrate into a family of cyclic products.



Scheme 1. A plan for diversifying the structure of a lactol.

The proposed chemistry would take advantage of lessons learned while making C-glycoside derivatives from sugar derivatives (Scheme 2).[9] Those lesson showed that while some cyclizations (Scheme 2a) were compatible with the use of either an enol ether derived radical cation or a vinylsulfide derived radical cation, many others like the reactions shown in Scheme 2b were not. In those cases, the yield of product obtained from the reaction was dependent on the nature of the radical cation used. Cyclization reactions that form carbon-heteroatom bonds benefited from the use of a less polar radical cation and reactions leading to C-C bond formation benefited from the use of a more polar radical cation.[3,9] The oxidation of **10a** led to a less polar vinylsulfide derived radical cation and a successful cyclization and the generation of **11**. The oxidation of **10b** led to a more polar enol ether derived radical cation and decomposition of the sugar backbone prior to cyclization to form **12** plus other fragmentation products. Conversely, rings that involved the trapping of a radical cation with an allylsilane group (the approach that would be used to construct **7** in Scheme 1) required the use of either an enol ether or N,O-ketene acetal derived radical cation.[4] These observations were rationalized by arguing that the best reactions (as defined by the highest

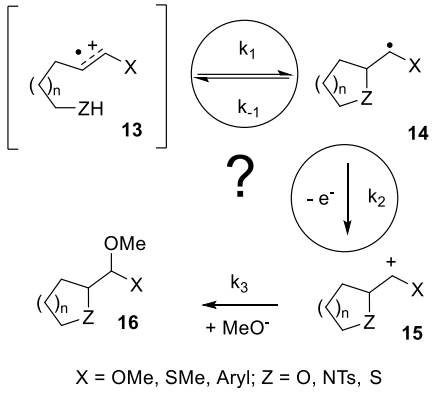
yield of product obtained) proceeded through a more rapid first cyclization step (Scheme 3). But how accurate



Scheme 2. a) Prior anodic cyclizations leading to furanose C-glycosides. b) Prior anodic cyclizations leading to pyranose C-glycosides and the role of radical cation polarity.

is that assessment and how general were the observations made? Does using an anodic cyclization to accomplish the chemistry proposed in Scheme 1 require the selective choice of a radical cation, or based upon the reaction shown in Scheme 2a would this simply not matter? The answer to this mechanistic question was essential if intermediate **2** was to be converted into a correct oxidation substrate.

Complicating this picture further were more recent studies that have shown the initial cyclization step (k_1/k_{-1}) shown in Scheme 3 to be reversible and the second oxidation step (k_2) in the mechanism to be important for generating product in high yield.[10] So, were the initial suggestions about reaction rate being the governing factor in the cyclizations described above correct, and does one really need to change the radical cation intermediate (**13**) in order to improve the yield of a problematic cyclization? Ideally, oxidative cyclization reactions could be optimized without a need to change the substrate. The chemistry proposed in Scheme 1 provided a perfect backdrop for addressing these questions, and we report herein that the proposed anodic cyclization reactions are indeed reversible, and that the yield of a problematic reaction can be optimized not only by changing the substrate and the nature of the radical cation, but also by altering the electrolysis conditions to help drive equilibrium towards the cyclic product. The chemistry highlights why it can be important to reoptimize reaction conditions for examples affording lower yields in substrate scope studies. The effort can shed important insight into the factors that control product formation and alter conclusions about the compatibility of a substrate with the electrochemical reaction.

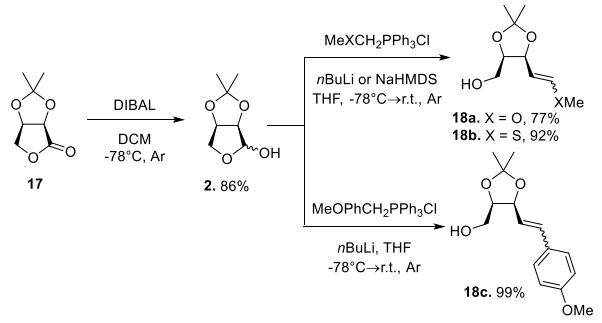


Scheme 3. A mechanistic model for anodic cyclization reactions with a heteroatom nucleophile.

Results and Discussion

Initial Studies Generating Tetrahydrofuran Derivatives:

To begin, a series of three substrates (**18a-c**) were assembled to target products from family **3** in Scheme 1. For these studies, the substrates were synthesized from the commercially available (−)-2,3-*O*-isopropylidene-D-erythronolactone. The lactone was reduced to the corresponding lactol **2**, and then a Wittig reaction was used to assemble the electrolysis substrates (Scheme 4). The methoxy enol ether substrate **18a** was synthesized by treating the lactol with the ylide derived from methoxymethyl triphenylphosphonium chloride. In a similar manner substrates containing a vinyl sulfide moiety for the anodic oxidation (**18b**) and an electron rich styrene moiety for the oxidation (**18c**) were prepared.

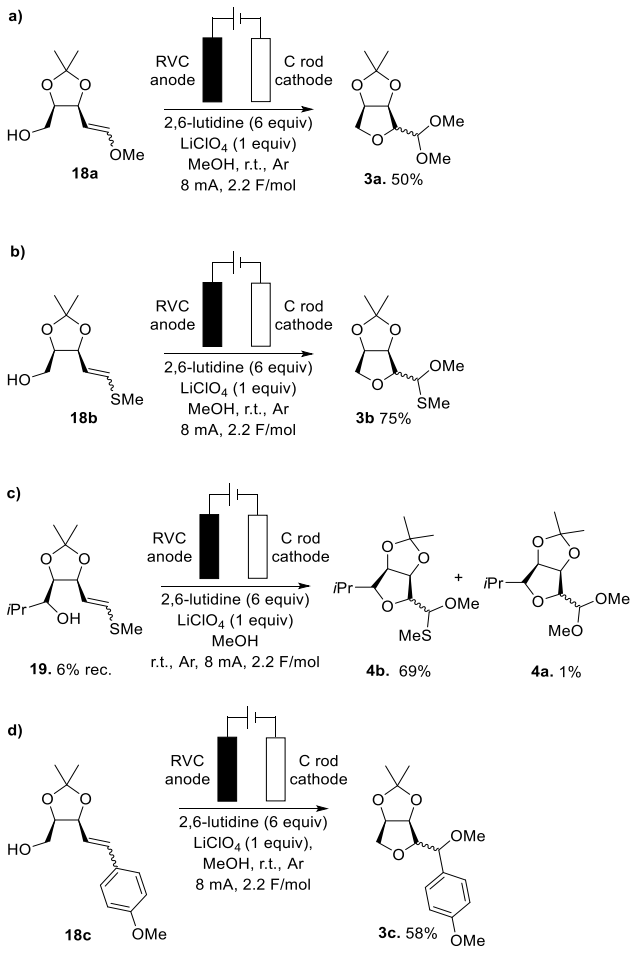


Scheme 4. Synthesis of Substrates

With the initial substrates in hand, the electrolysis reactions were examined beginning with substrate **18a**. In this experiment (Scheme 5a), the substrate was oxidized at a reticulated vitreous carbon (RVC) anode using a carbon-rod for a cathode, methanol as the solvent, lithium perchlorate as the electrolyte, 2,6-lutidine as a proton scavenger, and a constant current of 8 mA until a total of 2.2 F/mole of charge had been passed. For the most part, the reactions were conducted using the electrolysis conditions optimized for the cyclization of C-glycoside precursors (Scheme 2). The reactions used a low current density to avoid dimerization or polymerization of the highly reactive radical cation intermediate (the reactions are not sensitive to small changes in the current density with reactions utilizing 1-20 mA of current on the RVC anode not leading to significant changes in yield), a carbon rod cathode for convenience (the hydrogen evolution reaction at the cathode occurs readily with either a Pt or carbon cathode and there is nothing else in the reaction soluton susceptible to reduction at the cathode), and 2,6-lutidine as a base to make ensure that acid does not build up at the surface of the anode. Like all such electrolysis reactions, the overall reaction is pH neutral. So, the base is only present to shuttle protons away from the anode. 2.6-Lutidine is used because due to sterics it is non-nucleophilic and does not undergo oxidation at the anode. The reactions throughout this effort were monitored by TLC and the number of F/mole passed through the cell reflect the total charge needed for the reactions to reach completion. In the current examples, the electrolysis reactions were conducted in pure methanol instead of the MeOH/THF mixtures that were previously used[9] in order to provide faster trapping of the cation following the second oxidation step. The $LiClO_4$ electrolyte was used in order to ensure solubility of the polar sugar in the double layer.[9a] 2,6-Lutidine was used so that the region of the solution close to the anode would not become too acidic and lead to decomposition of the acid-sensitive substrate. Even with these precautions, the reaction did not go as well as the reaction shown in Scheme 2, and only a 50% isolated yield of the desired cyclic product **3a** could be obtained. The reaction produced multiple unidentified products in a fashion analogous to the oxidation of substrate **10b**. In addition, the formed acetal product was volatile, an observation that contributed to the lower isolated yield obtained. The use of THF as a cosolvent had no effect on the reaction. Clearly, the presence of the sidechain at position 5 of the lactol ring in substrate **8** (Scheme 2) had aided that particular cyclization when the enol ether derived radical cation was utilized. But that example was a "special case". Reactions forming other C-glycosides do not behave in the same manner, and the conditions used for the oxidation of **8** are not optimal even for related substrates like **18a**.

Fortunately, the approach previously taken for less optimal cyclizations proved effective here as well (Scheme 5b,c). When substrate **18b** having a vinylsulfide initiating group was submitted to the oxidation reaction using conditions identical to those used for the oxidation of **18a**, the yield of cyclic product **3b** obtained improved to 75%. Because the reactions generated a mixed acetal product, the reaction did lead to the generation of three major diastereomers in a ratio of 1.3/1/3.6. The diastereomers could not be separated, but from a synthetic standpoint this was not considered to be important since deprotection of the mixed acetal would lead to an aldehyde moiety. Epimerization would then place the aldehyde on the convex face of the bicyclic ring alleviating any issue with the initial formation of diastereomers. The use of the vinylsulfide was compatible with the addition of steric bulk to the secondary alcohol (Scheme 5c). In this case, the oxidation of substrate **19** afforded a 69% yield of the desired product **4b** (the mixed acetal) along with 6% of the recovered starting material and 1% of the dimethoxy acetal **4a** that was formed from over-oxidation of **4b**.

The reactions were also compatible with the formation of aryl containing C-glycosides derived from the oxidation of styrene groups (Scheme 5d). The oxidation of **18c** did afford a lower yield of the cyclic product **3c** (58%) relative to the reaction with the vinylsulfide substrates.

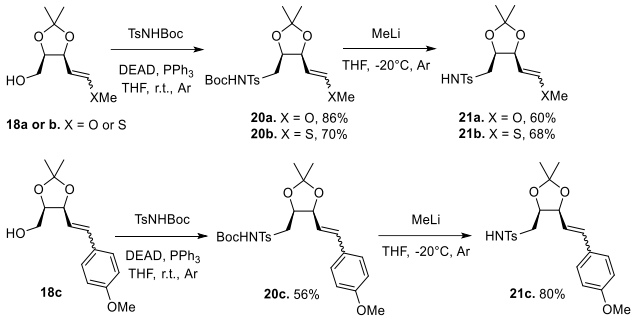


Scheme 5. a) Baseline study showing moderate yield with an enol ether substrate and the original reaction conditions. b) Improvement with the use of a vinylsulfide and a less polar radical cation. c) Compatibility of the reactions with steric bulk by the nucleophile. d) Compatibility of the reaction with an electron-rich styrene.

These initial studies indicated that while the conditions developed for the previous cyclization shown in Scheme 2 were not optimal, the desired cyclization could be improved by changing the nature of the radical cation with a less polar radical cation favoring the cyclization. As with prior anodic cyclizations, this observation was initially attributed to the rate of the cyclization reaction.

Anodic Cyclizations and the Formation Pyrrolidine Derivatives:

The chemistry outlined in Scheme 1 also suggested that densely functionalized pyrrolidine rings would be accessible through an anodic cyclization strategy. To this end, substrates **18a-c** were converted to sulfonamide-based substrates **21a-c** with the use of a Mitsunobu

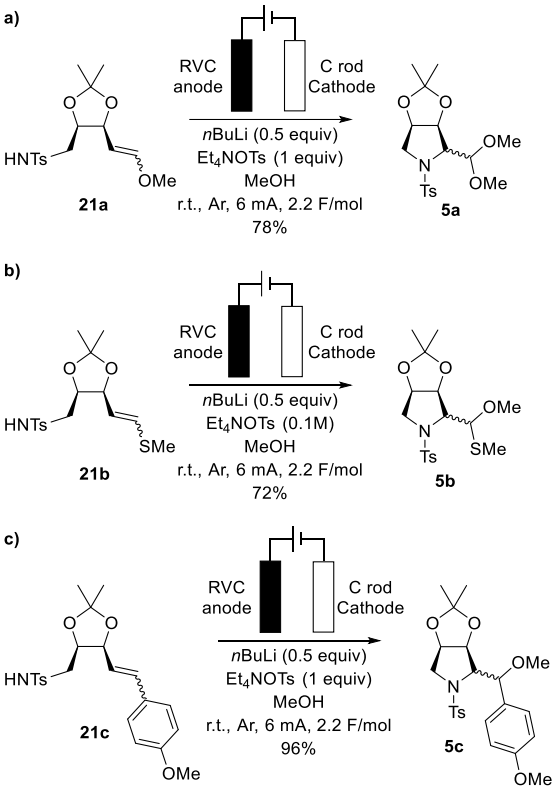


Scheme 6. Synthesis of Sulfonamide Substrates

reaction followed by deprotection of the *t*-Boc protecting group that was used to lower the pKa of the N-based nucleophile for the Mitsunobu reaction (Scheme 6).[11]

The electrolysis reactions with substrates **21a-c** were run using an RVC anode along with a C-rod cathode (Scheme 7). *n*-BuLi was added to the reaction along with methanol solvent in order to generate lithium methoxide *in situ*. Since the reaction is conducted in an undivided cell with methoxide generated at the cathode from a hydrogen evolution reaction, the initial basic pH is retained throughout the reaction. The more basic electrolysis reaction enables deprotonation of the sulfonamide and subsequent oxidation of the anion to form a N-radical. The N-radical can then undergo the cyclization reaction with the electron-rich double bond, followed by the second oxidation step and formation of the product.[2] While an electron transfer from the electron-rich olefin to the N-radical can lead to generation of an olefin radical cation,[12] the oxidation potential of the nitrogen anion to form the N-radical is lower than that of the electron-rich olefin, indicating that formation of the olefin radical cation is uphill in energy. Hence, the change in mechanism using the more basic conditions leading to the anion would minimize the amount of the olefin radical cation present and hence minimize the decomposition of the sugar-based substrate that the radical cation can trigger.

Accordingly, reactions originating from the oxidation of enol ether and vinylsulfide substrates (**21a** and**21b**) behaved in a similar fashion. In both cases, the electrolysis was conducted with a constant current of 6 mA until 2.2 F/mol of charge was passed, a scenario that led to complete conversion of the starting material. The yield of the reaction originating from oxidation of the enol ether substrate **21a** was 78%. The yield of the cyclization originating from oxidation of the vinylsulfide substrate was 72%, and the reaction utilizing the styrene based coupling partner for the sulfonamide group (**21c**) was a surprisingly high 96%. The yield obtained for product **5c** did make us wonder about the stability of the acetal groups in products **5a** and **5b** since in those cases the proton-NMR of the crude reaction product appeared equally clean.



Scheme 7. a) The compatibility of the parent reaction with a sulfonamide trapping group. b) C-N bond formation with a less polar radical cation. c) Compatibility of C-N bond formation with the use of a styrene based radical cation.

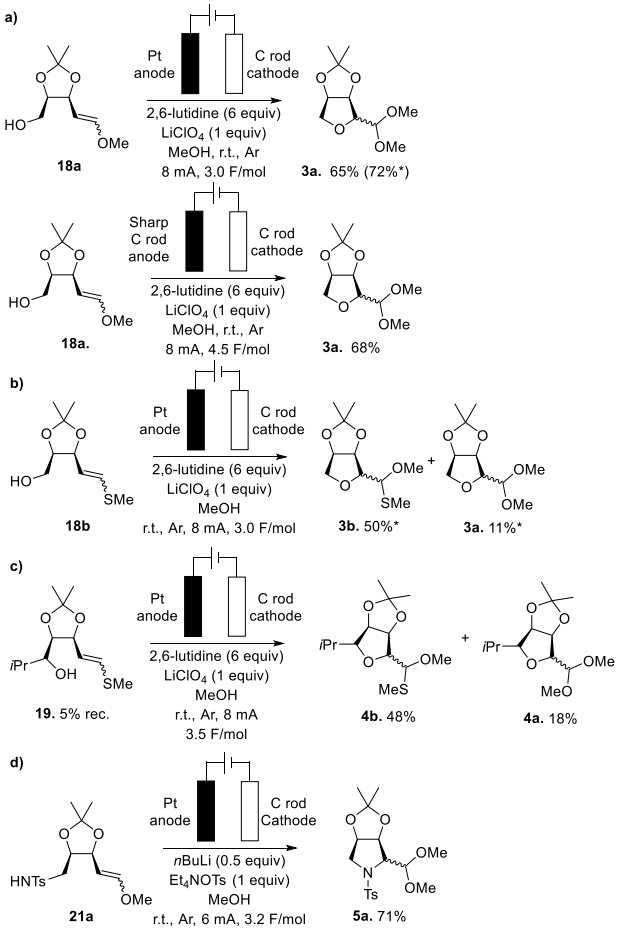
A Closer Look at the Electrolysis:

While these studies demonstrated that the original approach to thinking about the reactions was compatible with making predictions about the reactions and the proper selection of a radical cation, the question remained as to whether the reactions being studied were really being controlled by the cyclization rate as originally described (k_1 in Scheme 3) or if they were reversible and governed at least in part by the second oxidation step (k_2 in Scheme 3) required for the transformation. In this mechanism, computational studies suggested that deprotonation of the alcohol nucleophile occurred during the cyclization prior to the formation of cyclic intermediate **14** .[12] To probe this issue, a closer look at the cyclization originating from **18a** was undertaken. As a reminder, it was suggested based on earlier work that the radical cation derived from oxidation of the enol ether in

this case was not stable and led to fragmentation of the sugar backbone.[9a] If this were the case, then the issue with the oxidation of substrate **18a** was either that the cyclization reaction was slower than the reactions derived from oxidation of the less polar radical cations leading to more fragmentation and lower yields of cyclic product *or* that the cyclization reaction itself was fast but reversible. In the second case, a fast, reversible cyclization followed by a slow second oxidation step would lead to a higher concentration of the initial uncyclized radical cation and more decomposition of the sugar backbone. For this second possibility, a change in the reaction that pulled the equilibrium toward the cyclic product would lead to a decrease in the amount of the uncyclized radical cation intermediate present, less fragmentation of the sugar backbone, and a higher yield of the desired product. There are two options for shifting the initial equilibrium to the cyclic product. The first would be to increase the rate of the second oxidation step shown in Scheme 3, Because the cyclization product cannot reopen after removal of the second electron to form a dication intermediate. The second method to stop the cyclic product from reopening would be to trap the cyclic radical intermediate (**15** in Scheme 3) following the cyclization.

To test the effect of a shift in equilibrium, the rate of the second oxidation step was accelerated first. This was accomplished with the use of either a Pt-anode or a sharpened carbon rod anode while maintaining the same current for the electrolysis (Scheme 8a). Since either electrode would have a lower surface area than an RVC-anode, this change raised the current density at the electrode surface. In a constant-current electrolysis, higher current density requires more substrate to be at the electrode surface. If that demand is not met, then the working potential of the electrode increases and both the initial oxidation reaction and any subsequent oxidation – namely k_2 – are accelerated. We have shown using competition studies that this change leads to the formation of kinetic products from an electrolysis reaction.[12] For substrate **18a**, the change to a Pt-anode raised the yield of the overall process from the 50% obtained with the RVC anode to 65% isolated yield (72% by NMR), a value that was not significantly different than the yield of the cyclization obtained with the less polar vinylsulfide-derived radical cation. When these conditions were scaled to 376 mg (2mmol) of substrate, the cyclization afforded a 58% isolated yield of product.

Alternatively, when the reaction was conducted with a sharpened carbon rod as the anode, the isolated yield of product obtained from the reaction was 68%. The current efficiency of this reaction did drop, and the electrolysis required 4.5F/mol of charge to reach completion. The loss of current efficiency was not a surprise because a higher working potential at the anode would lead to a less selective oxidation and afford some oxidation of the solvent. What was clear from both the reaction employing the Pt-anode and the one employing the sharpened carbon rod anode is that the yield of the cyclization is not solely dependent on the rate of the cyclization step, as the rate of the cyclization step in the mechanism would be similar irrespective of the electrode surface. The reaction instead benefited from a faster second oxidation step and driving the initial reversible cyclization toward the cyclic product.



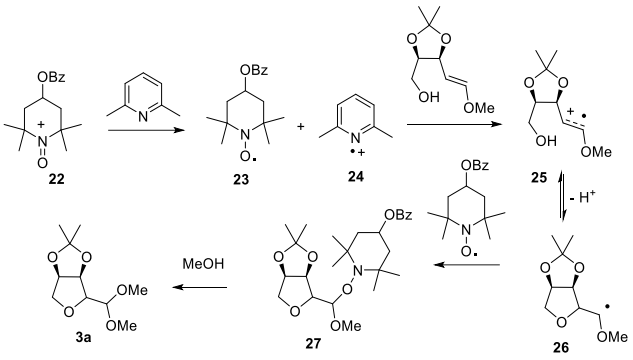
Scheme 8. a) Using surface area and current density to optimize radical cation reactions derived from an enol ether. b) The use of higher current density and a vinyl sulfide; evidence of higher oxidation potential. c) Illustrating the generality of the conclusion. d) Higher current density and C-N bond formation. * Yields were determined by NMR.

Consideration of both the yield and the current efficiency of the reaction led to the choice of a Pt-anode for the subsequent mechanistic studies. Along those lines, the use of a Pt-anode and a higher current density did not improve the yield of reactions originating from the oxidation of a vinylsulfide substrate (Scheme 8b and 8c). This was not a surprise since the oxidation of a thioether happens at a low potential. Hence, the oxidation of cyclic radical **14** in Scheme 3 (Z=SMe) is expected to happen more readily even with the lower current densities associated with an RVC-anode. The formation of significant amounts of over-oxidation product (the dimethoxy-acetal) from the electrolysis of substrates **18b** and **19** was consistent with use of the Pt-anode leading to a higher working potential at the anode and a less selective reaction relative to the electrolysis using the RVC anode

(Scheme 5). Hence, from a synthetic perspective one would select an RVC anode for the oxidation of a vinylsulfide substrate and readily avoid the overoxidation.

When a Pt-anode was used for the oxidation of sulfonamide substrate **21a**, a 71% isolated yield of the cyclic product was obtained (Scheme 8d). This yield was only slightly lower than that obtained when the RVC anode was used (Scheme 7a). It appeared in this case that the cyclization reaction originating from the N-radical did not benefit from a faster second oxidation step. This observation was again consistent with a mechanism that did not involve significant concentrations of an olefin radical cation intermediate. Without the presence of such an intermediate, decomposition of the sugar backbone would be slow and there would be no need to push the cyclization to completion.

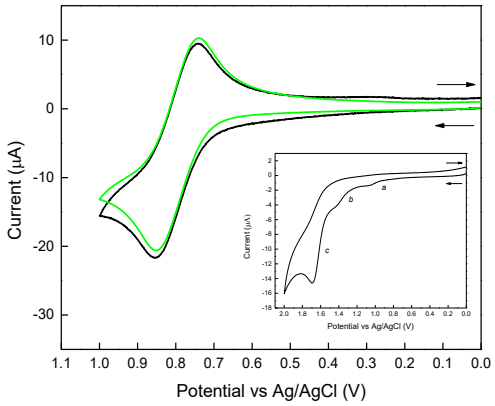
The second method for driving the reversible cyclization reaction toward the cyclic product (trapping the cyclic radical intermediate) also proved effective. To this end, the oxidative cyclization reaction was attempted using a mediated electrolysis that involved both 2,6-lutidine base and 4-OH-TEMPO benzoate. While we initially thought to mediate the reactions using the TEMPO-derivative,[13] cyclic voltammetry and preparative reaction studies were more consistent with the reactions proceeding through an initial oxidation of the 2,6-lutidine which then led to oxidation of the substrate to form radical cation **25** (Scheme 9). It is very possible that **23** and **24** form a complex that does the subsequent oxidation reaction,[14] but that detail would not lead to a change in the overall mechanism. A subsequent cyclization reaction would afford cyclic radical **26** that would in turn be trapped by the 4-OH-TEMPO benzoate to afford an intermediate that leads to the desired product **3a** in methanol solvent. Computational studies have suggested that deprotonation of the alcohol occurs in the transition state of the cyclization.[12]



Scheme 9. Proposed mechanism for the 4-OH-TEMPO benzoate and 2,6-lutidine mediated oxidative cyclization.

As mentioned, cyclic voltammetry (CV) studies and preparative control experiments were both consistent with this mechanistic paradigm (Figure 1). Shown in Figure 1a are the CVs for 4-OH-TEMPO benzoate, a mixture of 4-OH-TEMPO benzoate and substrate **18a**, and the CV for substrate **18a** (insert). The CV for **18a** was obtained separately because its electrode kinetics are much slower than the mediator. Hence, a very high concentration of substrate **18a** was required in order to obtain a reasonable CV wave. The CV for **18a** does show a minor

a)



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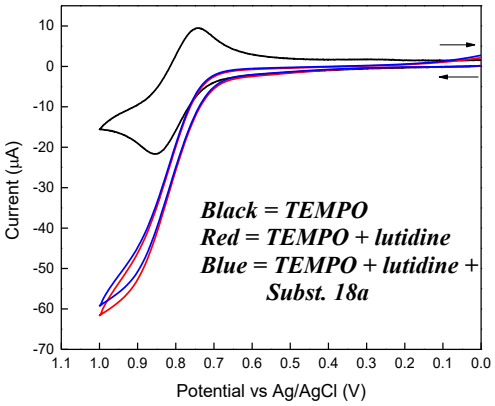
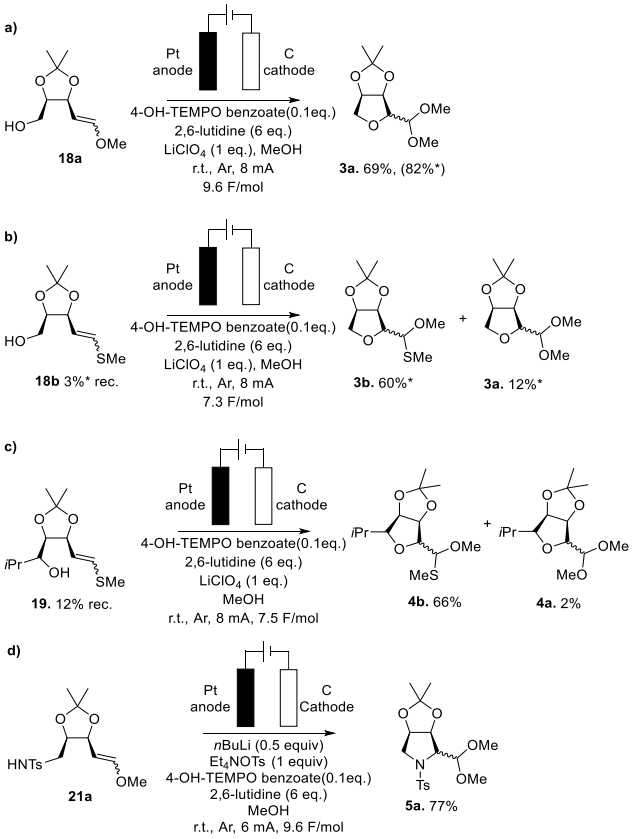


Figure 1. All CVs were run with a Pt-working electrode, a Pt-auxiliary electrode, a Ag/AgCl reference electrode, and a sweep rate of 100 mV/sec. Figure 1a insert: Cyclic voltammogram of **18a** (50 mM) in an electrolyte of $LiClO_4$ (0.1 M) in MeCN. Peak *a* (unknown minor impurity) $E_{p/2}$ = 1.06 V. Peak *b* (peak for **18a**) $E_{p/2}$ = 1.44 V. Peak *c* (second oxidation wave for **18a** that occurs in the presence of oxygen) $E_{p/2}$ = 1.66 V. a) Black: Cyclic voltammogram of 4-OH-TEMPO benzoate (3 mM) in an electrolyte of $LiClO_4$ (50 mM) in MeOH. Green: Cyclic voltammogram of **18a** (5 mM), 4-OH-TEMPO benzoate (3 mM) in an electrolyte of $LiClO_4$ (50 mM) in MeOH. b) Black: Cyclic voltammogram of 4-OH-TEMPO benzoate (3 mM) in an electrolyte of $LiClO_4$ (50 mM) in MeOH. Red: Cyclic voltammogram of 4-OH-TEMPO benzoate (3 mM), 2,6-lutidine (30mM) in an electrolyte of $LiClO_4$ (50 mM) in MeOH. Blue: Cyclic voltammogram of **18a** (5 mM), 4-OH-TEMPO benzoate (3 mM), 2,6-lutidine (30mM) in an electrolyte of $LiClO_4$ (50 mM) in MeOH.

impurity. There are then two waves for the oxidative cyclization shown in the insert. The first is associated with the initial electron transfer of **18a** to the electrode surface. It is this wave that is enhanced by the addition of base to

the reaction (Figure S2). The second wave appears when oxygen is present in the reaction medium. Our current view is that oxygen either complexes the initial radical cation or the cyclic product and makes the second oxidation step slightly more difficult. Either way, when the substrate was mixed with the mediator there was no evidence for a catalytic current (Figure 1a). The CV is consistent with a selective oxidation of the 4-OH-TEMPO benzoate-mediator in the presence of the substrate since the oxidation of the substrate occurs at a much higher potential, a result that is also consistent with preparative experiments (see below). In Figure 1b, the CV for a mixture of 4-OH-TEMPO benzoate and 2,6-lutidine is shown along with a CV for a mixture of 4-OH-TEMPO benzoate, 2,6-lutidine, and substrate **18a**. In the experiment shown, a catalytic current is observed once 2,6-lutidine is added to the 4-OH-TEMPO benzoate. An identical CV trace is observed when the substrate was added to this mixture. For the CV of 2,6-lutidine, please see the supporting information. While 2,6-lutidine will oxidize with an $E_{p/2}$ of around + 0.55 V vs. Ag/AgCl, it is not efficiently oxidized at an anode due to sterics and hence consumes little to no current at the electrode for the concentrations used in the preparative experiment. The CV data shown in Figure 1 is consistent with a rapid oxidation of 2,6-lutidine by the oxidized 4-OH-TEMPO benzoate, a process consumes all of the current at a potential significantly lower than that required for the direct oxidation of the substrate. The use of $NaHCO_3$ as a base for the in CV-experiment does not lead to a significant catalytic current indicating that the catalytic current observed when 2,6-lutidine is present is not simply the result of a base being present (Figure S6). The lack of a further increase in the catalytic current when **18a** is added to the mixture suggests a slower oxidation of the substrate by the radical cation of 2,6-lutidine that occurs away from the electrode. This observation was consistent with the small currents and slow electrode kinetics observed for the substrate even at the anode.

The suggestion that the 2,6-lutidine radical cation did in fact oxidize substrate **18a** was supported with the use of preparative experiments. When the mediated electrolysis was used for the preparative oxidation of **18a** (Scheme 10a), the product was obtained in a 69% isolated yield. The reaction was very clean and an 82% yield of the product was determined by integration of the proton NMR of the crude reaction mixture against an internal standard. The loss of some product during the isolation was most likely due to the volatility of **3a**. A control experiment that used the 4-OH-TEMPO benzoate mediator but replaced the 2,6-lutidine with $NaHCO_3$ as an alternate base led to a dramatic decrease in the efficiency of the reaction. In this case, 37% of the starting material was recovered with the formation of only a 46% yield of the cyclic product. Clearly, the high yield of cyclic product and efficiency of the reaction illustrated in Scheme 10a was dependent on the presence of 2,6-lutidine. The suggestion that this result was simply a matter of 2,6-lutidine serving as a more effective base during the cyclization reaction was not consistent with this observation and the knowledge that once radical cation 25 is generated an inefficient cyclization leads to lower amounts of product and decomposition; not regeneration of the starting material (Scheme 5a). The radical cation simply does not live long enough to migrate to the cathode. Hence, the higher percent conversion observed for the reaction shown in Scheme 10a relative to the one shown in Scheme 10b reflects a difference in the efficiency with which **18a** is converted to radical cation **25**. That difference is due to the presence of 2,6-lutidine. Of note, while the presence of 2,6-lutidine in the absence of TEMPO does improve the efficiency of the direct oxidation because deprotonation of the alcohol is required for the cyclization,[12] it does not alter the potential at which the direct oxidation of substrate **18a** occurs (Figure S2). This observation is consistent with the cyclization not being concerted with the oxidation step, and it indicates that at the working potential for the indirect electrolysis, radical cation **25** is only generated by the indirect pathway. In this way, all of the data obtained is consistent with the mechanism presented in Scheme 9.



Scheme 10. a) The mediated electrolysis of an enol ether substrate. b) The mediated electrolysis of a vinylsulfide substrate showing overoxidation. c) Illustrating the generality of the conclusion. d) Compatibility of the mediated electrolysis with C-N bond formation. *Yields were determined by NMR.

While the yield of the mediated-reaction was much higher than that obtained from the direct oxidation at an RVC anode (Scheme 5a), the reaction was not as efficient from a current standpoint. The mediated electrolysis

required the passage of 9.6 F/mole in order to reach complete conversion. This result was again consistent with a slow oxidation of **18a** by the 2,6-lutidine radical cation, a reaction that was conducted in an undivided cell where the 2,6-lutidine radical cation could be reduced at the cathode.

The stereochemical outcome of the reaction was identical to the direct oxidation reaction (a 1.5:1 ratio of diastereomers), an observation at least consistent with trapping of the radical following the cyclization. In addition, the overall mass balance for the reaction was higher than that obtained from the direct oxidation at an RVC anode. This observation was also consistent with the 4-OH-TEMPO benzoate driving the reaction toward the cyclic product by trapping the radical intermediate **26**; a situation that would reduce the amount of enol ether derived radical cation in solution and minimize decomposition reactions that originated from this intermediate.

The mediated reaction benefited from the use of a Pt-anode rather than an RVC-anode. When an RVC-anode was used for this approach, a 0% yield of the desired cyclic product **3a** was formed along with a 92% of the recovered starting material **18a** when passing 9.6 F/mol of current through the reaction. The use of sharpened carbon rod anode afforded 59% product and 27% recovered starting material indicating that the difference between the electrodes was related to the current density at the anode and not the nature of the surface itself. This observation was consistent with the CV data that did not show an increase in the catalytic current for formation of the 2,6-lutidine radical cation **24** when the substrate was added to the reaction. The oxidation of **18a** by **24** was slow and happened away from the surface of the electrode. Such a slow oxidation would benefit from the higher concentration of the oxidant (**24**) generated from a higher current density. As in the direct electrolysis reactions, the higher current density also meant that the method was not as effective for the cyclization of substrates having a vinylsulfide as the electron-rich olefin. As illustrated in Schemes 10b and 10c, the use of the mediated electrolysis reaction with a vinylsulfide substrate led to over-oxidation of the cyclic product and generation of the dimethoxy-acetal derivative. In the end, the mediated electrolysis conditions were superior for the enol ether-based substrate, but the direct electrolysis conditions on an RVC anode were superior for the vinylsulfide substrates.

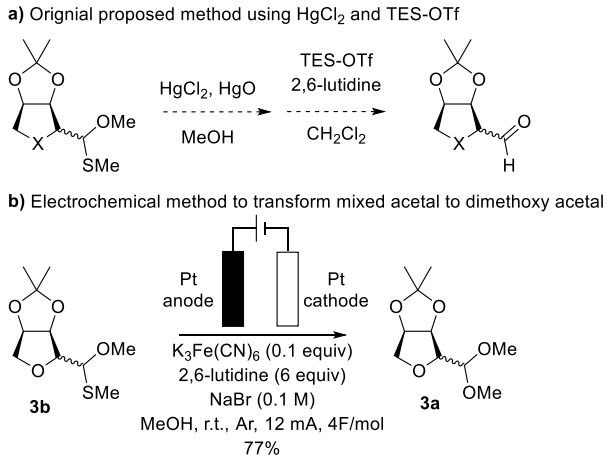
Finally, the use of the mediated electrolysis conditions did not interfere with the generation of a nitrogen-based radical or the subsequent cyclization reaction. As illustrated in Scheme 10d, the mediated electrolysis of substrate **21a** afforded a 77% yield of the desired cyclic product, a yield virtually identical to that obtained from the direct electrolysis (71%).

The success of the mediated reactions does mean that the cyclization chemistry would be compatible with future efforts to develop electrode-surface based approaches to stereochemical control, methods that take advantage of mediated electrolyses.[15]

Both approaches to driving the initial reversible cyclization toward the cyclic product clearly showed that consideration of more recent mechanistic studies of the anodic olefin coupling reaction were important for correcting our earlier view of what was needed to optimize an oxidative cyclization. While reactions that trap radical cations with alcohol nucleophiles do benefit from the use of a less polar radical cation, changing the nature of the radical cation by changing the substrate for the electrolysis was not the only way to overcome a problematic reaction. What happens "downstream" of the cyclization is also critically important, and optimization of those steps in the mechanism can lead to higher product yield *without* a need to resynthesize substrates. The observations also suggested that the "special-case" originating from the oxidation of substrate **8** may well have resulted from the sidechain altering the position of the initial equilibrium. Did the steric bulk associated with the very large t-butlydiphenylsilyl substituent lead to an equilibrium that favored the cyclic product? While we do not have a direct answer to this question, we do know that an explanation of how the sidechain influence the reaction should not focus solely on the rate of the cyclization step.

Deprotection Strategies:

With a general strategy for optimizing cyclization reactions from both enolether and vinylsulfide substrates in place, attention was turned to the selective deprotection of the acetal sidechain obtained in these reactions. Since it initially appeared that the cyclization reactions proceeded in higher yields with the use of a vinylsulfide-derived radical cation (Scheme 5), efforts to deprotect the aldehyde sidechain in the presence of the acid-sensitive acetonide protecting group began with a focus on the mixed acetal product **4a** (Scheme 11). The plan called for



Scheme 11. Initial efforts for deprotection of O,S mixed acetal

conversion of the mixed O,S-acetal to a dimethoxy acetal using a method that we did earlier, and then cleavage of the dimethoxy-acetal in the presence of an acetonide.[16]

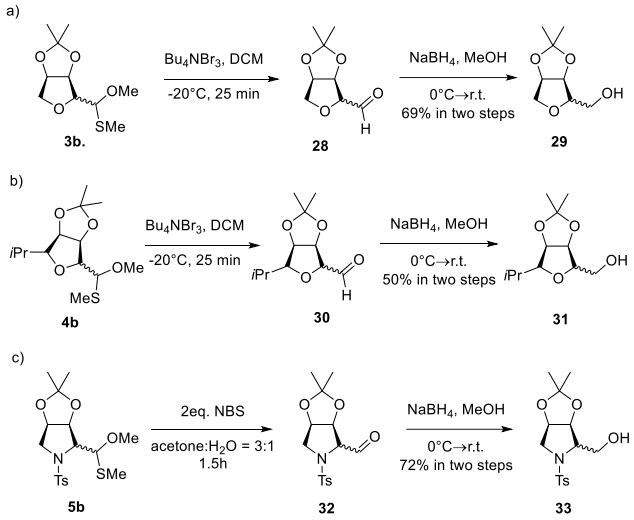
However, the use of that approach was bothersome because in our hands the method for converting the mixed O,S-acetal to the dimethoxy-acetal required the use of stoichiometric mercury. For this reason, we sought a more sustainable method for generation of the dimethoxy acetal from the mixed acetal, and accordingly turned our attention to a mediated electrolysis approach (Scheme 11b). In this reaction, NaBr was used as an electrolyte as well as the mediator. The reaction proceeded through the generation of Br^+ at the anode, bromination of the sulfur atom in the mixed acetal, and then replacement of this group with methoxide. Potassium ferrocyanide served as a Lewis acid that further facilitated the exchange reaction. In this way, a 77% yield of the dimethoxy acetal could be obtained without the use of mercury.

However, cleavage of the dimethoxy acetal to the desired aldehyde proved to be significantly more challenging than expected. The initial conditions tried to capitalize on the use of TES-triflate and 2,6-lutidine in direct analogy to previous efforts.[17] However, in the current case, the reaction led to no conversion of the dimethoxy-acetal to the aldehyde. Efforts using trifluoroacetic acid[18] or potassium ferrocyanide and $LiBF_4$[19] to cleave the dimethoxy-acetal proved to be equally problematic. Each reaction attempted led to complete recovery of the starting material. Only treating the dimethoxy-acetal with concentrate hydrochloric acid (12M) led to any reaction,[18] but while these conditions did consume the starting material, no product aldehyde was obtained.

These attempts at the deprotection suggested that there was no easy way of cleaving the dimethoxy-acetal in the presence of the acetonide, a situation that made a two-step procedure even less attractive. So, attention was turned toward a direct deprotection of the mixed O,S-acetal. The plan was to capitalize on the unique reactivity of the sulfur to afford the aldehyde in the presence of the acetonide. The first attempt to accomplish the transformation took advantage of the electrochemical method illustrated in Scheme 11b but replaced the methanol solvent with water. The reaction did work to some extent leading to a 25% yield (by proton NMR) of the aldehyde, but the yield of aldehyde product could not be optimized beyond this initial result. While undertaking these studies it was determined that the aldehyde product was not stable and decomposed in an NMR tube following isolation.

A non-electrochemical oxidation of the sulfur did ultimately prove successful (Scheme 12a).[20] When the mixed acetal was treated with tetrabutylammonium tribromide (TBATB) the sulfur in the O,S-acetal was selectively oxidized. The oxidized acetal was generated at -20 ℃ in dichloromethane and then quickly quenched by water after 25 min. This led to an aldehyde (**28**) that could be stored at room temperature for 24 hours prior to purification. However, when aldehyde **28** was passed through either silica gel or aluminum oxide it underwent the same decomposition mentioned in the preceding paragraph. For this reason, the crude aldehyde product from the deprotection was immediately reduced with sodium borohydride to form alcohol **29**. The alcohol was stable, and it could be isolated in a 69% yield following the deprotection-reduction sequence. A similar deprotection-reduction sequence starting with the substituted mixed acetal product **4b** led to a 50% yield of the corresponding alcohol **31** (Scheme 12b). The yield of this two-step sequence was not optimized since the reduction was conducted only so the product could be characterized.

While the TBATB deprotection reaction was successful in cleaving the O,S-acetal in **3b** and **4b**, it was not effective with the sulfonamide substrate **5b**. For this substrate, the use of TBATB as the oxidant led to complete recovery of the starting material. Fortunately, an alternative approach that treated the mixed acetal **5b** with *N*-bromosuccinimide (NBS) in acetone/water led to formation of aldehyde **32**.[21] Reduction of the crude aldehyde product with sodium borohydride did lead to alcohol **33** in a 72% isolated yield over the two-step sequence.



Scheme 12. a) Nonelectrochemical method for the deprotection of a O,S mixed acetal. b) Illustrating the compatibility of the method with a more substituted tetrahydrofuran derivative. c) Illustrating the utility of the method with a pyrrole base substrate and the need for a change in the brominating reagent.

In each case, it was clear that the acetal sidechain in the cyclic product could be unmasked selectively setting the stage for use of the cyclic products as starting materials in subsequent synthetic strategies.

Conclusions:

An electrochemical cyclization strategy for the conversion of chiral lactols into functionalized tetrahydrofuran and pyrroline derivatives was examined. It was found that while the exact reaction conditions used in earlier cyclization reactions were not optimal for some substrates in the current study, the overall predictive model developed previously was upheld: problematic

radical cation reactions with heteroatom trapping groups benefited from the use of a less polar radical cation. However, the earlier mechanistic model attributed the success of the reactions utilizing less polar radical cations solely to the rate of the cyclization reaction. We found here that this picture was not entirely accurate. Instead, it is best to consider the radical cation reactions as being reversible cyclization reactions that benefit from reaction conditions that shift the equilibrium toward the cyclic product, a conclusion that aligns with other more recent mechanistic studies. With this knowledge, problematic reactions that involve the coupling of enol ether derived radical cations and alcohol trapping groups can be optimized *without* a need to change the nature of the radical cation intermediate (and hence synthesize a different substrate for the reactions). Instead, the problematic transformations can be optimized by either increasing the rate of the second oxidation step following the cyclization or by taking advantage of a mediated electrolysis that contained a TEMPO-derivative for trapping the radical intermediate generated from the cyclization. Both sets of conditions served to drive the reversible cyclization reaction toward the cyclic product. While these findings meant that one did not need to use a vinylsulfide for optimization of an oxidative cyclization, the use of a vinylsulfide-based substrate did prove to be advantageous in the current reactions because the mixed O,S-acetal generated in the product could be selectively deprotected in the presence of an acetonide protecting group.

The end result of these mechanistic observations was that all of the substrates could be converted to the desired products in good yield if the correct electrolysis conditions were employed. Substrates leading to vinylsulfide derived radical cations proceeded nicely on RVC anodes with low current densities. Substrates leading to enol ether derived radical cations proceeded nicely on either Pt electrodes or low surface area carbon electrodes or with the use of a mediated electrolysis.

These findings do suggest that the use of a standard set of reaction conditions for a variety of substrates can be misleading. Initial studies employing this approach suggested that some substrates were superior electrolysis substrates relative to others. This turned out not to be true when the electrolysis conditions were reoptimized for the problematic substrates based upon mechanistic considerations; a result that highlights the value in revisiting reactions that afford lower yields in a table showing substrate scope. Reoptimization of the reaction conditions for those substrates can help shape our understanding of what truly controls the outcome of the reactions.

Efforts to use the specific cyclization reactions studied here to further probe the reactivity of radical cation intermediates and to further expand the scope of anodic cyclization reactions are underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures for all reactions are provided along with NMR spectra for all compounds and cyclic voltammetry data. This material is available free of charge via the Internet at https://nam10.safelinks.protection.outlook.com/?url=http%3A%2F%2Fpubs.acs.org%2F&data=05%7C02%7Cmoeller%40wustl.edu%7C047f6e4e90a544fed58c08dc01c1c9b4%7C4ccca3b571cd4e6d974b4d9beb96c6d6%7C0%7C0%7C638387179032072877%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=PigV1LLVCHkvmDX14Bx64Kor28zS8VdWVWt9WN18tXI%3D&reserved=0."

Data Availability

The data underlying this study are available in the published article and its Supporting Information.

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Notes

The authors declare no competing financial interests.

Footnote:

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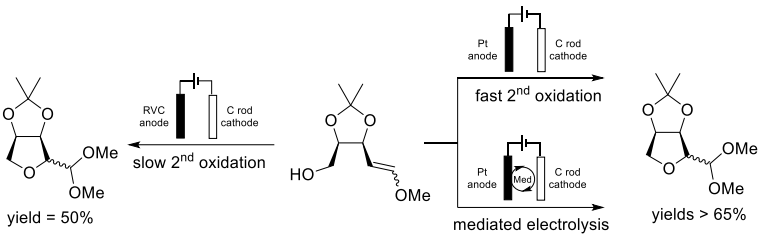
TOC Graphic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