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Synthetic Applications of Anodic Electrochemistry

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The manuscript is dedicated in memory of Professor Eberhard Steckhan—12 September 1943–10 February 2000

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1. Introduction and Background

Anodic electrochemistry can provide a powerful means for making and modifying organic molecules.[1] The advantages of this technique lie in its utility for selectively oxidizing functional groups, generating highly reactive intermediates, and reversing the polarity of nucleophiles. Because anodic processes utilize neutral reaction conditions and allow for wide variations in oxidation potential, many of these transformations are unique to electrochemistry. Therefore, the use of anodic oxidation reactions to complement existing methodology can open entirely new strategies for the synthesis of complex molecules. For this reason, this review will highlight a number of anodic reactions in order to provide synthetic chemists with an overview of the types of transformations that are available for use in the future.

Many chemists not familiar with electrochemistry are put off by the technique because of a feeling that it is complicated and requires the use of specialized equipment. This feeling is exacerbated by summaries of electrochemical reactions that describe a variety of reaction setups and electrochemical equipment that are not common to most synthetic laboratories. However, utilizing an electrochemical reaction for synthesis does not need to be difficult. With even a basic understanding of electrochemistry, many reaction setups can be simplified so that a transformation of interest can be attempted using a simple battery as a power supply and glassware common to any synthetic laboratory.[2]

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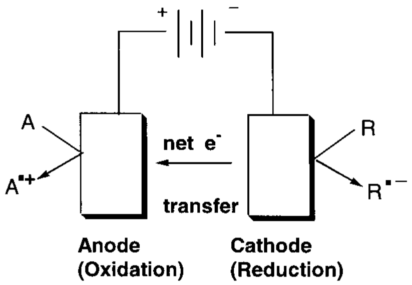


Constant Current -- potential varies
Controlled Potential -- current varies

Anode materials: **Carbon or Platinum**
Solvents: **MeOH, AcOH, CH_3CN, CH_2Cl_2**
THF, H_2O
Electrolytes: **Et_4NOTs, $LiClO_4$, Bu_4NBF_4,**
Bu_4NPF_6

Scheme 1.

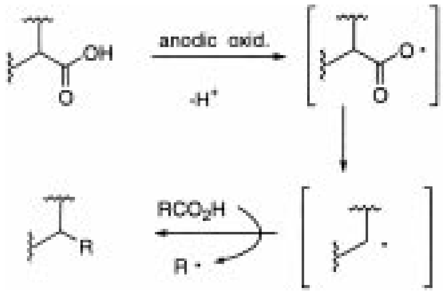
For that reason, a *very* brief overview of electrochemistry is provided below. In most cases, an understanding of even this very simplistic view of electrochemistry is sufficient for beginning to successfully pursue the reactions that are outlined in the review that follows.[3]

To begin, all electrochemical reactions utilize an electrical circuit that has been broken. On each side of the break is added an electrode (Scheme 1). The two electrodes are then inserted into a solution that contains a substrate, an electrolyte (which provides counterions for the reactive intermediates generated at the electrode surfaces), and a solvent. For an organic reaction, the solvents of choice include methanol, THF, dichloromethane, and acetonitrile, while common electrolytes include lithium perchlorate, tetraethylammonium tosylate, tetrabutylammonium tetrafluoroborate, etc. Following insertion of the electrodes into the solution, a voltage is applied across the gap between the electrodes. This initiates two separate processes. At one electrode (the anode), molecules are oxidized leading to a transfer of electrons from the reaction mixture to the electrode. At the other electrode (the cathode), molecules are reduced leading to a transfer of electrons from the electrode to the reaction mixture. The net result of these two processes is the transfer of electrons from the cathode to the anode. This electron transfer completes the circuit and allows current to flow through the cell.

Electrochemical reactions can be controlled in one of two ways. The first method is referred to as a ‘constant current’ reaction. In a constant current reaction, the flow of current through the electrochemical cell is held at a constant value while the potentials of the electrodes are allowed to vary. Once the current for the reaction is set, the potential of the anode climbs until it reaches a value sufficient for oxidizing the species in solution with the lowest oxidation potential. The potential then stabilizes and the species in solution is oxidized at a rate consistent with the current flow required by the cell. When the first reactive species is consumed, the potential of the electrode climbs until a second species with a higher oxidation potential is found. The potential of the electrode then stabilizes at this second potential and the rate of oxidation of the second species proceeds in a fashion again consistent with the current flow set for the cell. This process repeats until either the solvent is oxidized or the current is turned off. At the cathode, an equivalent reduction process takes place. The advantage of a constant current reaction is that the reaction setup is very simple, and for this reason constant current reactions are very common. The disadvantage is that the selectivity of the initial oxidation reaction decreases as the first substrate is consumed and the potential at the electrode begins to climb. In many cases, the lack of selectivity associated with a constant current reaction is not a problem. For example, if no other electroactive species exists in solution and the reaction product oxidizes at a potential much greater than that of the starting material, then constant current reactions can be pushed to greater than 90% completion. Even in cases where selectivity is an issue, constant current reactions can often be run to greater than 60% conversion without interference from the competing processes. As mentioned above, the potential at an electrode in a constant current reaction remains constant so long as sufficient starting material is present to satisfy the demands of the preset current. While this scenario holds, the selectivity of the initial reaction is not lost.

In cases where the need for selectivity is an issue, a ‘controlled potential’ electrolysis can be used. In these reactions, a reference electrode is added to the reaction and the potential of the working electrode (the electrode at which the desired process occurs) held constant relative to the reference.[4] For an anodic reaction, these conditions ensure that only substrates having an oxidation potential equal to or lower than that set for the anode will be oxidized. The reactions are highly selective, and since the potential of the electrode can not climb as the substrate is consumed, the selectivity is maintained for the entire course of the reaction. However, there is a price to pay for this selectivity. As the concentration of the initial substrate drops the current for the reaction decreases. For this reason, it can be time consuming to push a controlled potential electrolysis to completion. In addition, controlled potential electrolyses do require the use of a third electrode and a potentiostat for fixing the potential of the working electrode relative to the reference. This leads to a more complicated reaction setup. However, the availability of commercial power supplies, potentiostats, and reference electrodes does make such setups readily accessible.[5]

Because all electrochemical reactions involve two processes, the reactions at both electrodes need to be considered. While the reaction that occurs at the auxiliary electrode (the cathode for an oxidation reaction) is often not directly involved in generating the desired product, it can play an important role in defining the overall reaction conditions for the process. For example, electrochemical oxidations often produce acid as a byproduct at the anode. In such reactions, alcohol solvents are commonly utilized so that the reduction at the cathode will produce hydrogen gas and two equivalents of an alkoxide. The alkoxide reacts with



Scheme 2.

the acid generated at the anode and preserves the neutrality of the electrolysis cell. Reactions of this type benefit from the use of an undivided cell where the anode and cathode are not separated. Typical undivided cells include vials, beakers, and round bottom flasks.

While undivided cells are used with regularity, reactions do arise where the product generated at the auxiliary electrode either interferes with the desired process or reacts with the primary product of interest. Problems of this nature are solved by using a divided cell.[5] In a divided cell, a partition is placed between the anode and the cathode so that the two half-reactions of the electrolysis remain separate. Both constant current reactions and controlled potential reactions can be run using either undivided or divided cells.

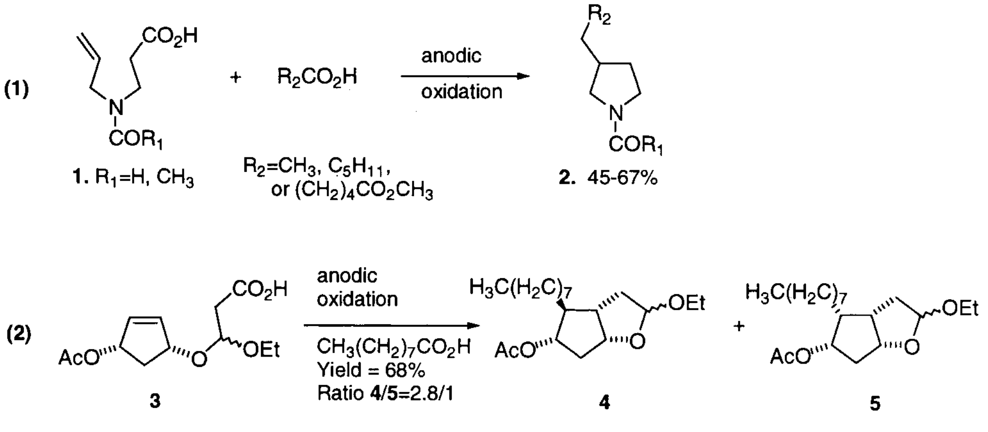
For the anodic oxidation reactions discussed in this review, the primary reaction of interest occurs at the anode. Normally, anodic reactions fall into one of three categories; elimination and fragmentation reactions, coupling reactions that trap the initial reactive intermediates generated at the anode, and reactions that generate reactive reagents. The reaction summary that follows is organized along these three lines.

2. Elimination and Fragmentation Reactions

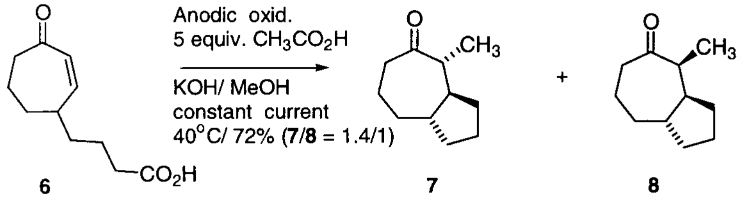
2.1. Kolbe and non-Kolbe oxidations of carboxylic acids

Arguably the best known anodic oxidation reaction is the Kolbe electrolysis. The Kolbe electrolysis leads to the oxidative decarboxylation of a carboxylic acid and the generation of a radical intermediate (Scheme 2). The radical generated then couples to a second radical generated from a second acid. Both intermolecular and intramolecular coupling reactions are known. Because of the success of these reactions, the Kolbe electrolysis has been extensively reviewed.[6] However, a number of recent examples deserve attention. Schäfer and coworkers have used the Kolbe electrolysis as a method for synthesizing heterocycles (Scheme 3). In these reactions, the initially generated radical added to an olefin within the molecule prior to trapping the radical from a second carboxylic acid.[7,8] The reactions illustrated the power of the Kolbe electrolysis for forming both the new heterocycle and two new carbon–carbon bonds in good yield. A similar reaction has been used to synthesize perhydroazulenes (Scheme 4).[9] Finally, the Kolbe electrolysis has recently been used to couple dimethylcitrate starting materials and to synthesize fatty acids (Scheme 5).[10]

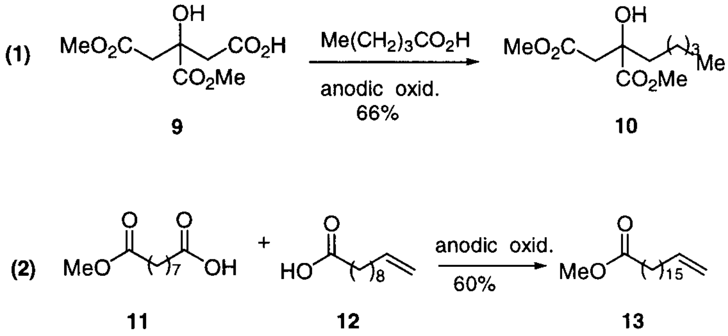
While the Kolbe electrolysis is perhaps best known for generating radicals, the nature of the substrate can dramatically alter whether radical or cation intermediates are generated during the reactions.[6] Cation intermediates are derived from carboxylic acids having alpha heteroatoms.



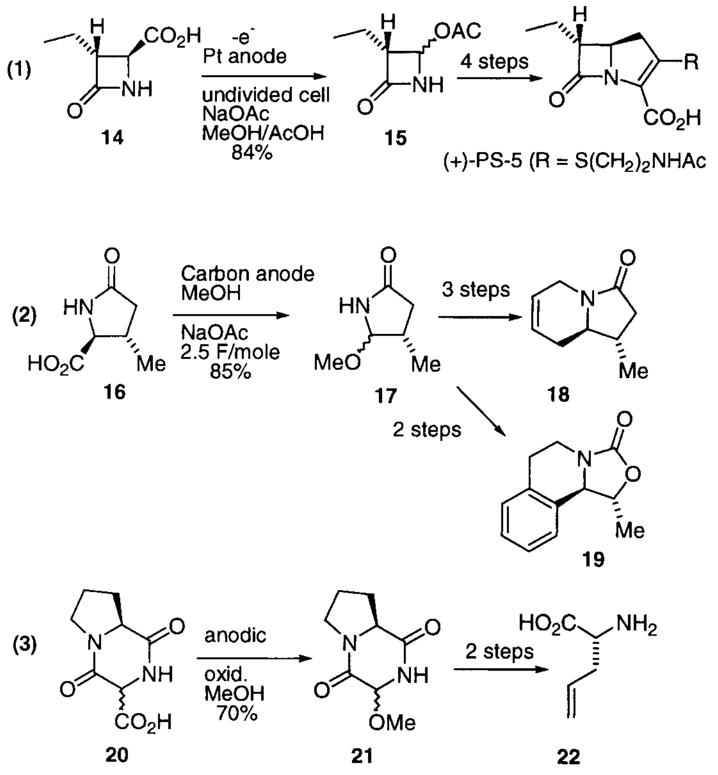
Scheme 3.



Scheme 4.



Scheme 5.



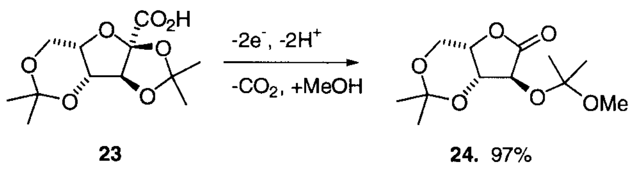
Scheme 6.

For example, the Kolbe electrolysis of α-amino acids leads to the generation of *N*-acyliminim ions (Scheme 6, reaction (1)).[11] In the first example illustrated, the product from the oxidation (**15**) was used as a key intermediate in the asymmetric synthesis of the bicyclic β-lactam (+)-PS-5. A similar reaction has been used to convert amino acid derivatives into electrophiles for use as chiral building blocks (Scheme 6, reaction (2)).[12] Similarly, the oxidation of **20** afforded the chiral cationic glycine equivalent **21** (Scheme 6, reaction (3)).[13]

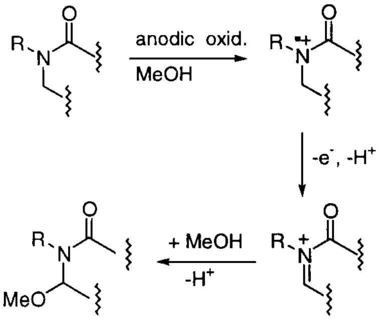
In a related reaction, carboxylic acids having alpha oxygens are known to lead to oxonium ions.[14] This reaction has been used to convert compound **23** (an intermediate in the technical synthesis of vitamin C into the much less readily accessible L-xylonolactone **24** (Scheme 7).[10] Lactone **24** can be converted into L-xylo-C-glycosides.

2.2. Oxidations of amides

Another anodic oxidation reaction well known to many synthetic organic chemists involves the direct oxidation of an amide nitrogen to form an *N*-acyliminium ion (Scheme 8). A comprehensive review on this reaction has appeared.[15] Since the appearance of that review, the anodic amide oxidation reaction has continued to be effectively utilized for the synthesis of complex organic molecules. This work falls into three main groups; the construction of building



Scheme 7.



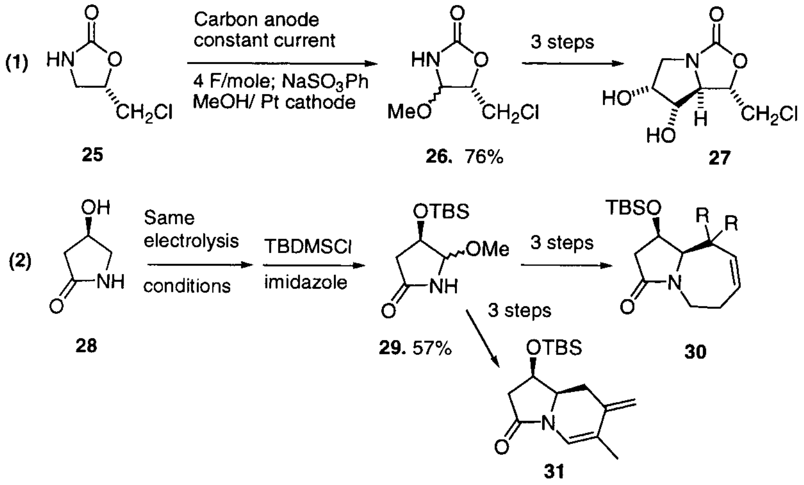
Scheme 8.

blocks for asymmetric synthesis, the synthesis of natural products, and the synthesis of constrained peptidomimetics. In keeping with the overall goal of this review to provide a 'flavor' of the synthesis that can be done using anodic electrochemistry, a sampling of these reactions is highlighted here.

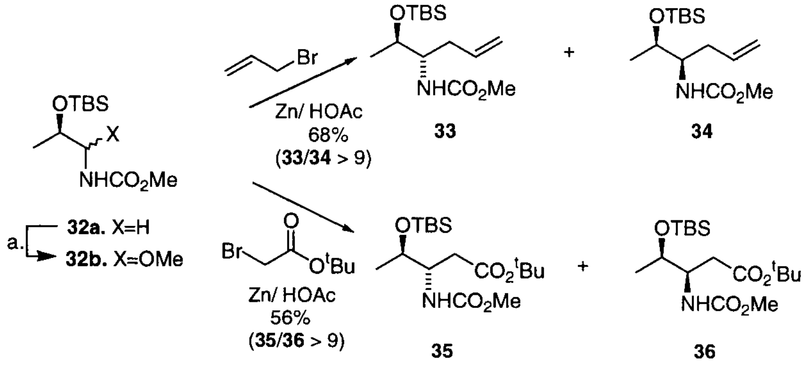
Steckhan and coworkers have taken advantage of amide oxidations in order to generate chiral building blocks for synthesis (Scheme 9).[16] In each case illustrated, the oxidation reaction was used to make an *N*-α-methoxy amide that was stable and could be stored for future use. The oxidation of **25** is representative of this family of reactions.[16a] This reaction was conducted using constant current conditions and was used to generate twelve grams of product. For those new to electrochemistry, the '4 F/mol' term listed as part of the reagents indicates that four moles of electrons were utilized for every mole of substrate. Since the oxidation required the removal of two electrons per molecule, 4 F/mol indicates that twice the theoretically required current was utilized. The methoxylated amide obtained was used to generate precursors of pyrrolidine azasugar derivatives (**27**).[17] Using the same conditions, substrate **28** was oxidized to generate the methoxylated amide **29** on a five gram scale.[16b] Compound **29** was used as a precursor to a series of bicyclic lactam intermediates **30** and **31**.[18]

In a related set of reactions, Kise and coworkers demonstrated that organozinc reagents could be added to electrochemically derived *N*-acyliminium ions. These reactions were used to synthesize β-amino acid derivatives (Scheme 10).[19]

Matsumura and coworkers demonstrated that *N*-acyliminium ions can serve as electrophiles in asymmetric alkylation reactions (Scheme 11).[20] In this case, the methoxycarbamate of a series of cyclic amines was oxidized in order to generate *N*-α-methoxy amides which were then

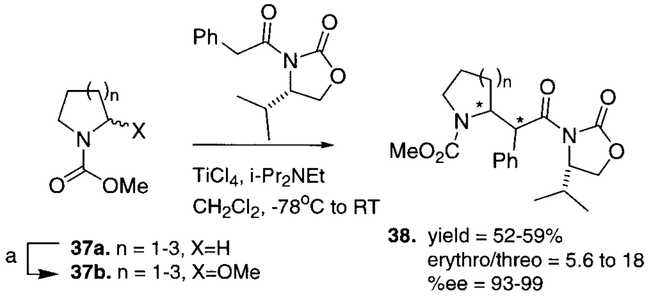


Scheme 9.



Reagents: a) Carbon anode, MeOH, Et_4NOTs, 2.0 F/mole, 62%

Scheme 10.



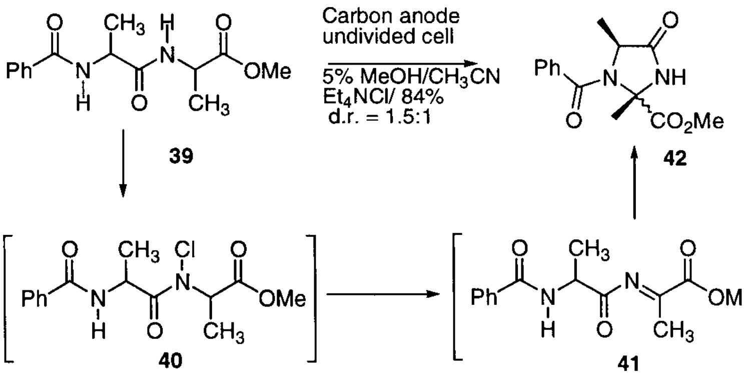
Reagents: a) Carbon anode, MeOH, Et_4NBF_4, 2.3 F/mole, 85% (n=2)

Scheme 11.

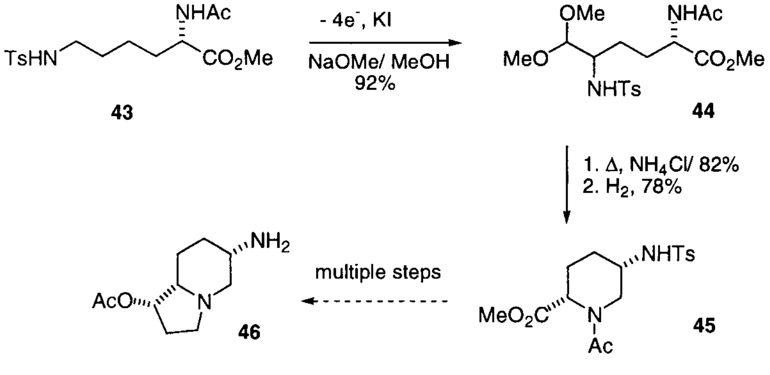
treated with chiral enolate equivalents. The reactions resulted in the formation of enantiomerically enriched methylphenidate precursors (**38**).

In addition to direct oxidations, indirect oxidations of amides have proven useful for synthesizing chiral building blocks. These reactions employ a halogen electrolyte that is oxidized at the anode surface to form a reactive 'X^+' species. The X^+ intermediate then reacts with the amide nitrogen. A subsequent elimination reaction generates the desired *N*-acyliminium ion. Reactions of this type have been used to functionalize amino acid derivatives (Scheme 12),[21] as well as to initiate oxidation-rearrangement sequences for building bicyclic amines (Scheme 13).[22] In this example, the initial oxidation of **43** led to the formation of an enamine which then underwent a subsequent oxidation to form an alkoxy aziridine intermediate. Trapping with methanol afforded product **44**.

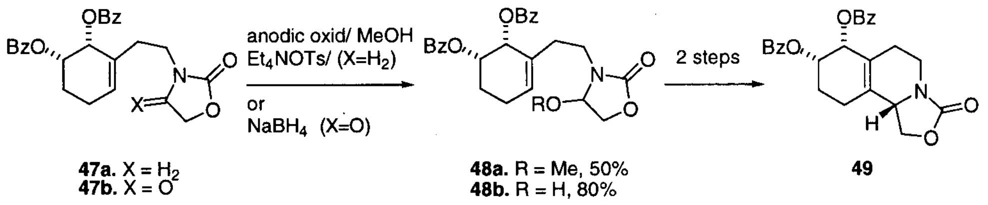
Both of the previous cases illustrate how anodic amide oxidations can be used to selectively functionalize molecules containing a nitrogen. This ability to add functionality to carbons alpha to a nitrogen has proven to be a powerful tool for synthesizing both natural products and peptidomimetics. In a pair of recent examples, Hudlicky and coworkers have used an anodic amide oxidation reaction in the synthesis of octahydroisoquinoline and azathymine derivatives. For the synthesis of octahydroisoquinolines (Scheme 14),[23] an electrochemical route to the *N*-α-alkoxyamide (**48a**) was used in order to provide a complementary route to a reductive route to **48b** originating from imide **47b**. The yield of the *N*-α-alkoxyamide was not



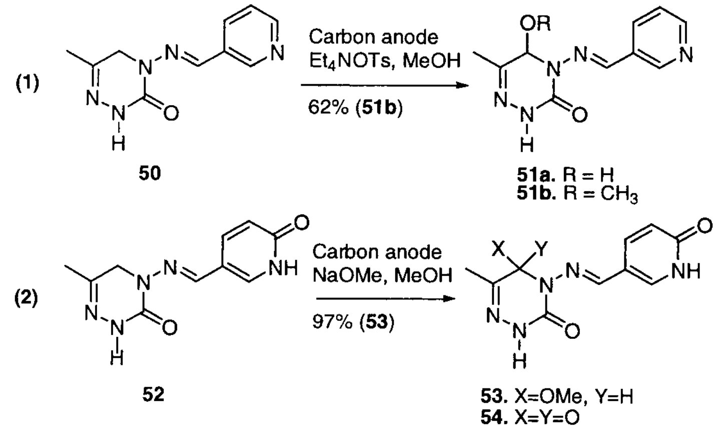
Scheme 12.



Scheme 13.



Scheme 14.



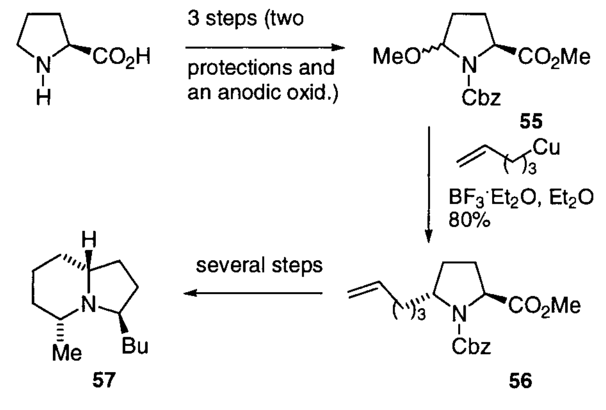
Scheme 15.

as high for the oxidation route (50%) as it was for the reductive route (80%). However, the use of the oxidation did allow flexibility in terms of when the alkoxy functionality was introduced into the molecule and did avoid the use of base sensitive intermediates like imide **47b**.

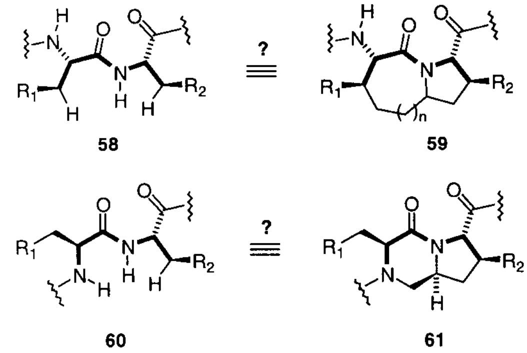
For the synthesis of the azathymine derivatives, Hudlicky and coworkers utilized an anodic amide oxidation in order to circumvent problems with an anionic oxygenation reaction (Scheme 15).[24] When compound **50** was treated with *sec*-butyllithium followed by treatment with oxygen, a 10–35% yield of the hydroxylated product **51a** was obtained. The reaction could not be run safely on a large scale, and the authors recommend against performing it on more than 2 mmol of material. On the other hand, the anodic oxidation of **50** led nicely to a 62% isolated yield of the methoxylated product **51b**. This reaction could be run on a 20 g scale. In a similar experiment, the anionic oxygenation of **52** failed to produce the desired hydroxylated product. For comparison, the anodic oxidation on a small scale led to a 97% yield (721 mg) of the methoxylated product **53**. For larger scale reactions, it was important to force the transformation to completion because the starting material was difficult to remove from the product. On the other hand, the overoxidized product **54** could be separated from the desired product by recrystallization. With this in mind, large scale reactions of **52** (10–15 g) were pushed to a point where they led to 45–50% yields of the desired product along with 25% of the overoxidized **54**.

The functionalization of proline has been used to synthesize natural products from the indolizidine alkaloid family.[25] To this end, Lhommet and coworkers utilized an anodic oxidation reaction to form the methoxylated carbamate **55** (Scheme 16). The conversion of L-proline to **55** required three steps (two protections and the oxidation) and proceeded in a 69% overall yield. The methoxylated amide was then treated with a cuprate reagent in the presence of $BF_3{\cdot}Et_2O$ in order to produce compound **56** which was then converted into the desired indolizidine ring system using several steps. The keys to this transformation were a Wacker oxidation to generate a methyl ketone and then a subsequent intramolecular reductive amination reaction.

The anodic functionalization of amino acids has also proven to be a very effective tool for constructing bicyclic peptidomimetics.[26] In this work, a series of constrained peptide analogs were designed by replacing spatially close hydrogens in a proposed active peptide conformation with carbon based bridges. This resulted in molecules that fixed both the peptide backbone conformation and the amino acid side



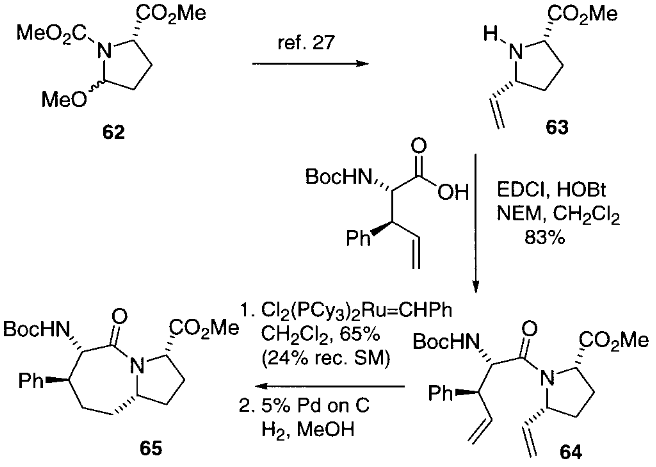
Scheme 16.



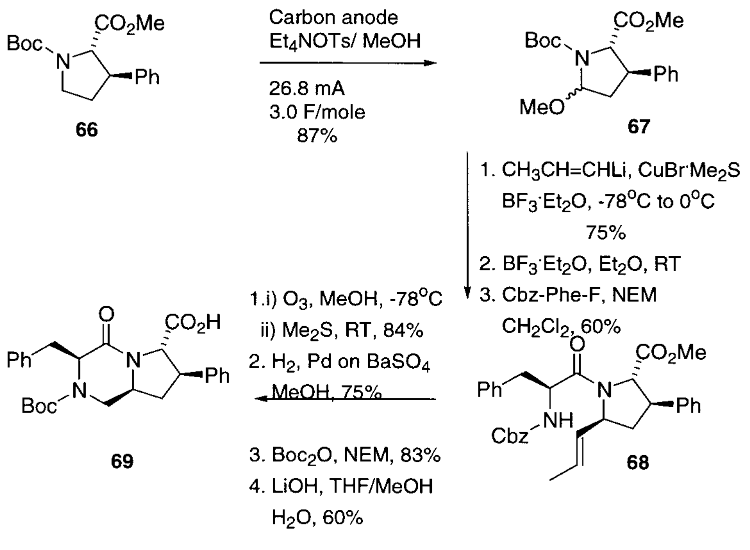
Scheme 17.

chains in place with a polycyclic ring skeleton. Two families of analogs designed in this manner are illustrated in Scheme 17. While constrained peptide mimetics like **59** and **61** are easy to propose, they can be difficult to synthesize. However, the availability of anodic amide oxidations has greatly simplified such efforts. Because the oxidation of an amide allows for the selective functionalization of amino acid derivatives, it enables the synthesis of constrained analogs from starting materials that have the chiral centers in place. For example, consider the synthesis of the constrained amino acid building block outlined in Scheme 18.[26i] In this synthesis, methyl proline was protected as a carbamate and then oxidized at an anode to form starting material **62**. This starting material was converted into a vinyl substituted amino acid derivative **63**[27] which was then coupled to a known carboxylic acid[28] in order to form diene **64**. Olefin metathesis followed by hydrogenation of the double bond resulted in the synthesis of the desired building block **65**. This approach has been used to build a series of constrained analogs for the endocrine hormone TRH which have in turn been used to map the conformational requirement of the TRH endocrine receptor site TRH-R$_1$.[26i]

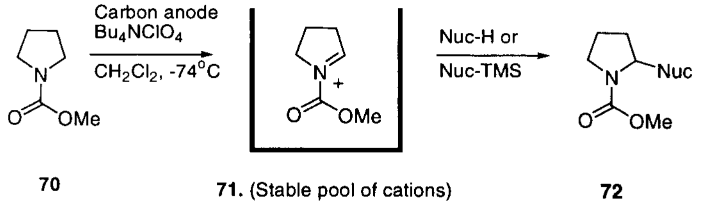
The versatility of this approach to peptidomimetics is illustrated in Scheme 19. In this example, a variation on the approach used above led to the synthesis of a member of the second family of analogs suggested in Scheme 17.[27e,f] The anodic amide oxidation reaction was employed to functionalize phenylsubstituted proline derivative **66**.[29] Once the methoxylated product (**67**) was available, a



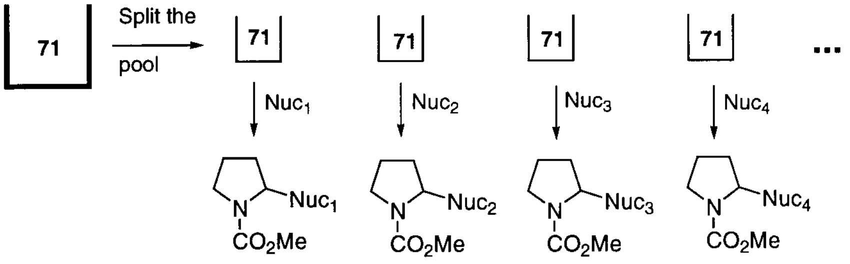
Scheme 18.



Scheme 19.



Scheme 20.



Scheme 21.

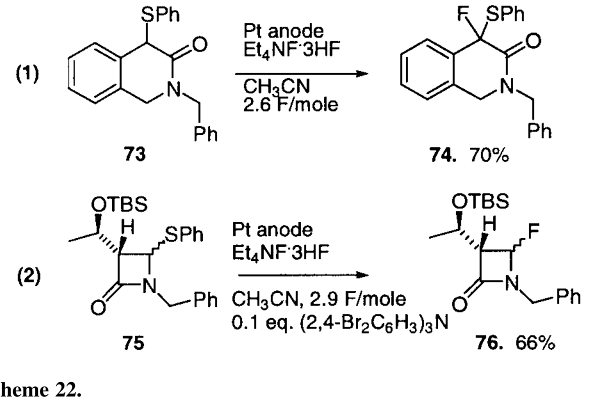
cuprate reagent was used to replace the methoxy group with a vinyl substituent, and then standard peptide chemistry used to build the dipeptide equivalent **68**. An ozonolysis reaction followed by an intramolecular reductive amination led to completion of the bicyclic ring skeleton. The molecule was then converted into peptide building block **69** which was in turn used in the synthesis of a series of constrained substance P analogs.[30]

Recently, Yoshida and coworkers have reported a new use for electrochemical amide oxidations. In this work, the anodic oxidation was used to make a stable 'cation pool' of iminium ions.[31] The cation pool was then trapped with nucleophiles to directly form carbon–carbon bonds (Scheme 20). Two items about this work are particularly interesting. First, the method overcomes synthetic problems that normally complicate the direct trapping of oxidatively generated electrophiles with nucleophiles. Since cationic intermediates are generally not stable to oxidation conditions, the nucleophile for such a reaction needs to be present during the oxidation so that it can trap the electrophile as it is generated. However, most nucleophiles are also sensitive to oxidation. For example, under normal conditions an anodically generated *N*-acyliminium ion can not be trapped directly with an allylsilane nucleophile because allylsilanes have a lower oxidation potential than the amide. For this reason, a procedure is used where the amide is first methoxylated, and then the allylsilane added in a second step that utilizes a Lewis acid in order to remove the methoxy group and regenerate the *N*-acyliminium ion.[27b] Using the cation pool method, the need for methanol trapping and regeneration of the cation with a Lewis acid can be avoided. The oxidation reaction is conducted at low temperature using dichloromethane as the solvent without any nucleophile being present. Under these conditions, the *N*-acyliminium ion is stable. In fact, upon completion of the electrolysis the pool of iminium ions is stable to temperatures up to zero degrees. The reaction is completed by adding a nucleophile to the cation pool. Allylsilanes, 1,3-dicarbonyl equivalents, and electron rich aromatic rings have all been used as nucleophiles for this process. Second, the 'cation pool' method makes available reactive cation intermediates for parallel synthesis approaches to molecular libraries. In this work, the cation pool is split into separate flasks following the electrolysis reaction and then a different nucleophile added to each in order to form a series of products (Scheme 21).

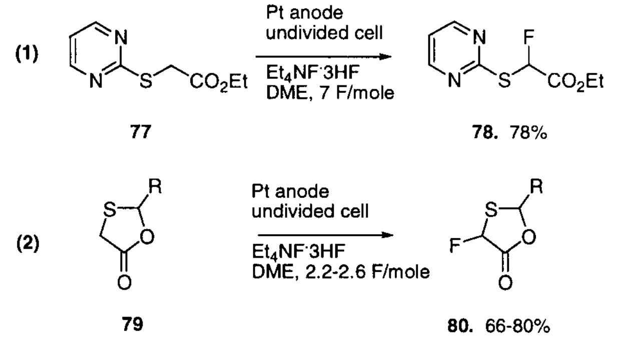
2.3. Oxidation of sulfur

The anodic oxidation of thioethers can also lead to a number of interesting elimination and fragmentation reactions. These reactions usually fall into one of two general types. The first involves the elimination of a proton from the carbon bearing the sulfur and the subsequent introduction of a nucleophile. The second involves a fragmentation reaction that leads to replacement of the sulfur with a nucleophile. A number of useful synthetic methods have been developed using each.

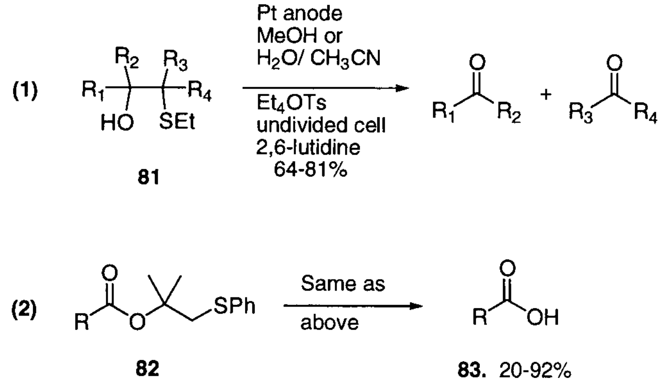
Both reactions have been used by Fuchigami and coworkers to introduce fluoride groups into organic molecules.[32,33] Consider the reactions outlined in Scheme 22. In the first case (reaction (1)),[32b] oxidation of the sulfur led to elimination of a proton from the alpha carbon. A fluoride anion then added to the resulting cation to afford product **74** in a 70% isolated yield. In the second,[32a] the sulfur radical cation



Scheme 22.



Scheme 23.



Scheme 24.

generated from the initial oxidation was lost, an *N*-acyliminium ion generated, and the cation trapped with fluoride. In this case, a triarylamine was used as a mediator for the reaction.[34] The triaryl amine was oxidized at the anode to form a radical cation intermediate which in turn oxidized the sulfide regenerating the original amine. The oxidation of **75** was done this way in order to avoid passivation of the electrode by the liberated sulfur species. The difference in the two pathways (reaction (1) vs. reaction (2)) appears to be a consequence of the group on the carbon to be functionalized. The presence of an electron-withdrawing group in this position encourages elimination of a proton while the presence of a strong electron-donating group leads to cleavage of the carbon–sulfur bond.

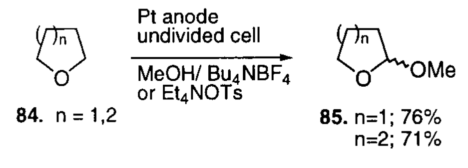
Recently, the elimination pathway has been utilized to introduce fluorides into biologically active molecules. These efforts have led to the partial fluorination of 2-pyrimidyl, 2-pyridyl and 2-quinazolinonyl sulfides (cf. Scheme 23, reaction (1)),[35] as well as 2-substituted 1,3-oxathiolan-5-ones (Scheme 23, reaction (2)).[36]

The oxidation of a sulfide has also been used to initiate the cleavage of carbon–carbon bonds.[37] In these examples, a series of β-hydroxy sulfides were electrolyzed (Scheme 24, reaction (1)). In each case, a pair of carbonyl equivalents were obtained. When methanol was used as the solvent, the reactions led to the formation of dimethoxy ketal and acetal products. The reactions proceeded best when at least one of the two carbons comprising the bond to be cleaved was disubstituted, and either formaldehyde or acetone was liberated as one of the two carbonyl products. In the same paper, a similar reaction was used as a method for deprotecting carboxylic acids under neutral, oxidative conditions (reaction (2)). The yields for this process ranged from 72 to 92%, except for a case with a terminal olefin.

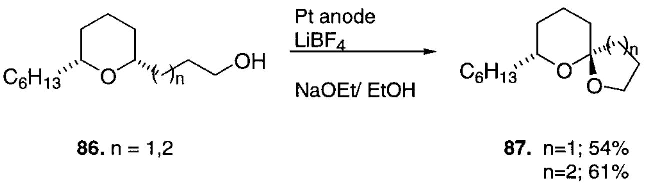
2.4. Oxidation of alcohols and ethers

The electrochemical oxidation of oxygen containing molecules has also been intensively studied. In 1987, Shono and coworkers reported the direct oxidation of cyclic ethers at an anode surface (Scheme 25).[38] Tetrahydrofuran was oxidized to form the cyclic acetal equivalent in a 76% yield, and tetrahydropyran was oxidized to the corresponding cyclic acetal in 71% yield. Substrates having a substituent on one of the ether carbons underwent oxidation at the least hindered position. In a similar fashion, a disubstituted tetrahydropyran has recently been oxidized in order to generate a spirocyclic ketal product (Scheme 26).[39]

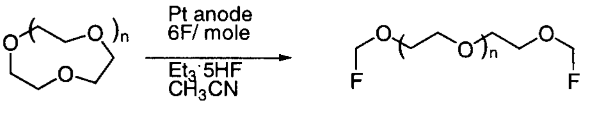
The regioselectivity of the oxidation in this example appeared to be a direct result of the sodium ethoxide added to the reaction. Apparently, the mechanism involved an initial deprotonation of the sidechain alcohol followed by oxidation of the alkoxide. An intramolecular hydrogen atom abstraction followed by a second oxidation reaction then afforded selective formation of one of the two possible cyclic oxonium ions. The reaction was completed by a subsequent cyclization. Reactions leading to both five and six-membered ring ethers were accomplished.



Scheme 25.



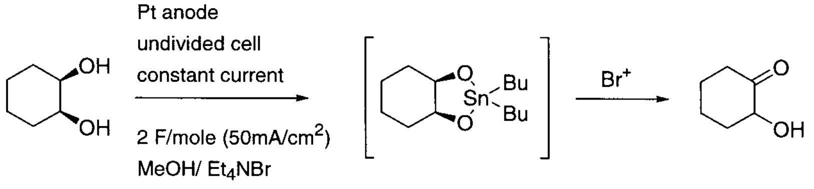
Scheme 26.



88

89. n=3; 90%
n=4; 74%

Scheme 27.

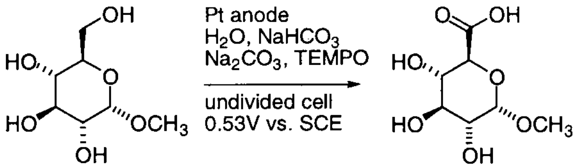


90 **91** **92.** 96%

Scheme 28.

Fuchigami has utilized similar reactions to build fluorinated polyethers.[40] In the reaction outlined in Scheme 27, a crown ether was oxidized in order to fragment a carbon–carbon bond and generate of a pair of oxonium ions. The oxonium ions were both trapped with fluoride to afford a 90% yield of product **89** (when $n = 3$). For the substrate where n=4, the reaction led to a 74% yield of the difluorinated product. While the direct oxidation of ethers can be effective, in many cases the reactions benefit from the use of a mediator. While reactions of this type have been reviewed,[34b] a number of recent examples deserve mention. Matsumura and coworkers have used $Bu_2Sn{=}O$ and electrochemically generated Br^+ to oxidize 1,2-diols to alpha hydroxy ketones (Scheme 28).[41] This reaction could be run in a fashion that was catalytic in both the tin compound and the source of Br^+. This electrochemcial process represented a dramatic improvement over the corresponding two step chemical reaction that required the diol to be converted into the dibutylstannylene (**91**) prior to a brominolysis reaction. This sequence utilized both the tin reagent and the source of Br^+ in stoichiometric amounts.

TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy radical) has also proven to be an effective mediator for the electrochemical oxidation of alcohols. Schäfer and coworkers have demonstrated the use of a TEMPO mediated electrolysis for selectively oxidizing the primary oxygen of a sugar directly to a carboxylic acid.[42] To this end, the primary alcohol of methyl α-D-glucopyranoside (**93**) was oxidized to methyl α-D-glucopyranosiduronic acid in a 96% yield (Scheme 29). The yields for 8 such cases ranged from 52–96%. The reactions also proved compatible with the selective oxidation of primary alcohols in polysaccharides. The reactions were run in a beaker as an undivided cell using controlled potential conditions (SCE reference electrode). A similar electrochemical reaction can be accomplished using a direct electrolysis at a nickel oxide anode.[43]

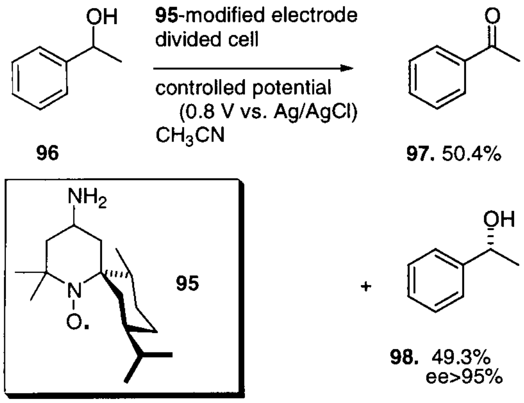


93 **94.** 96%

Scheme 29.

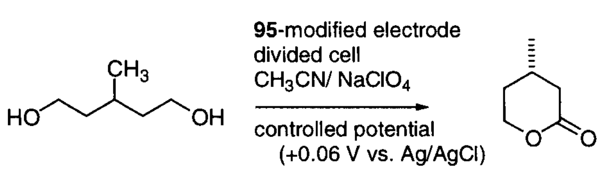
Modified TEMPO derivatives have also been used as mediators for asymmetric oxidation reactions.[44] When the racemic **96** was oxidized with the use of **95** as the mediator, the unreacted alcohol **98** was obtained in a 70%ee. The chiral purity of this process was optimized greatly by utilizing a PPA coating on the anode in order to immobilize the chiral mediator at the electrode surface.[45] Using these conditions, the oxidation of **96** led to recovered **98** in a 95% ee (Scheme 30). Other examples had uniformly high ee's. Using the same conditions (immobilized **95** on an PPA modified electrode) the kinetic resolution of racemic amines was also achieved.[46] Similar ee's for the unreacted starting material were obtained.

Modified anodes have also proven useful for the formation of asymmetric lactones from symmetrical diols. For example, the carbon felt anode modified with **95** was employed to convert diol **99** into the chiral lactone **100**



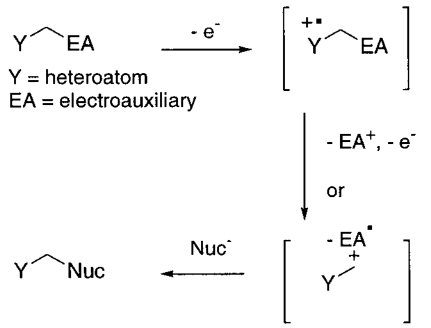
96 **97.** 50.4% **95** **98.** 49.3% ee>95%

Scheme 30.

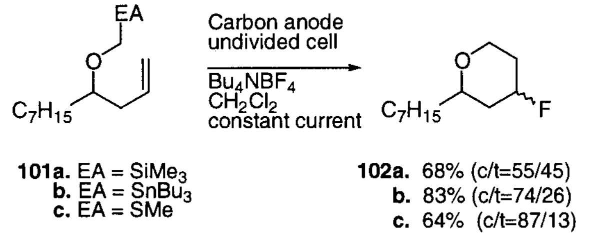


99 **100.** 96% ee = 99%

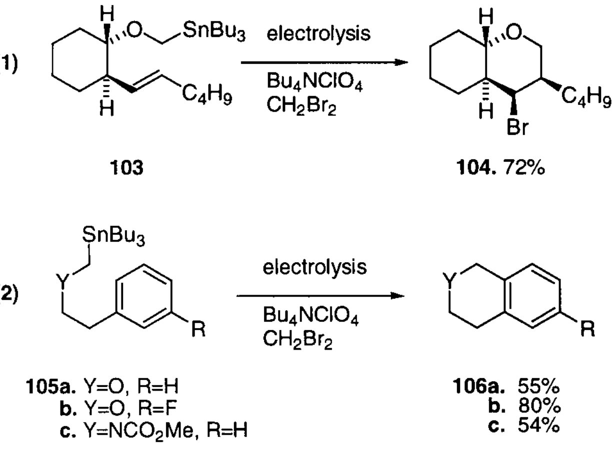
Scheme 31.



Scheme 32.



Scheme 33.



Scheme 34.

(Scheme 31).[47] It has also been reported that similar kinetic resolutions can be accomplished with a TEMPO modified graphite electrode if (−)-sparteine is introduced into the reaction as a chiral additive,[48a] although this result has proven difficult to reproduce.[48b]

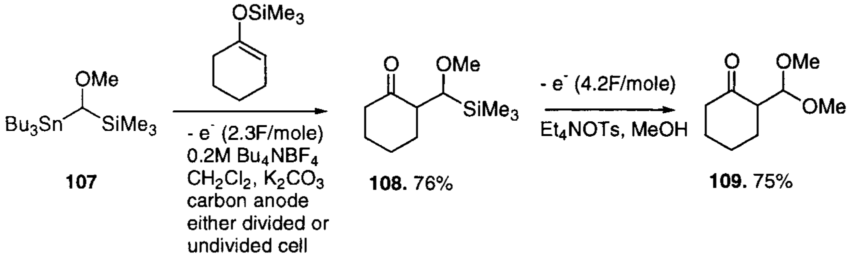
Ethers can also be oxidized at anode surfaces with the aid of an 'electroauxiliary'.[49] An electroauxiliary is a group that is added to a molecule in order to reduce the oxidation potential of the starting material (Scheme 32).[50] The electroauxiliary, which works by donating electron density to the group being oxidized and hence raising the energy of its HOMO, normally serves two main purposes. First, it enables oxidation of the starting material in the presence of a desired nucleophile, and second it lowers the oxidation potential of the starting material relative to the product generated, thus reducing the chance for overoxidation. Sulfur, silicon, tin, and germanium groups have all been used as electroauxiliaries for the oxidation of an oxygen, although it should be noted that the use of sulfur may very well involve initial oxidation of the sulfur group as discussed in Section 2.3.

Scheme 33 illustrates the use of silicon, tin, and sulfur electroauxiliaries for aiding in the initiation of oxidative cyclization reactions.[51]

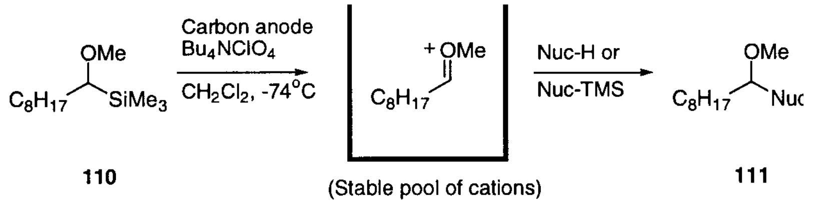
While the trapping of the products **102** with fluoride was potentially useful, the authors were also interested in trapping the products with a more synthetically useful functional group. This was done by incorporating a bromide trapping group into the electrolysis conditions.[52] Initially, the bromide was introduced into the reaction by using Bu_4NBr as the electrolyte. However, this reaction failed because the bromide was oxidized at the anode in preference to the substrate. This problem was avoided by running the reaction in dibromomethane solvent instead of dichloromethane (Scheme 34, reaction (1)). In this way, the bromide ion was generated by reduction of the solvent at the cathode; a technique that led to low concentrations of the bromide and good yields of the desired cyclized product.

The same reaction conditions have been used to initiate Friedel Crafts type cyclizations (Scheme 34, reaction (2)). Both the use of an α-stannyl ether and an α-stannyl amide led to cyclized product. The success of these reactions highlighted the use of electrochemistry for triggering umpolong reactions. Normally, group 14 organometallic compounds serve as nucleophiles, but in the electrolysis reactions illustrated they clearly function as cation synthons.

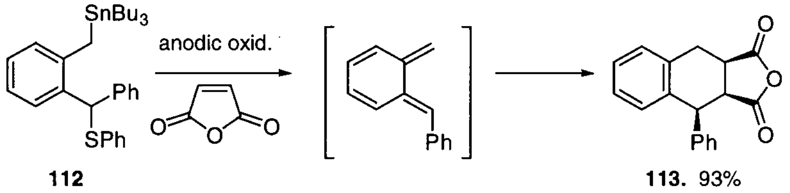
In another interesting set of reactions, Yoshida and coworkers have demonstrated that molecules containing more than one electroauxiliary can undergo selective reactions depending on the relative oxidation potentials of the auxiliaries (Scheme 35).[53] When **107** was oxidized using a constant current for 2.3 F/mol, the tributylstannane group ($E_{(\mathrm{decomp})}=+0.90$ V vs. SCE) was replaced selectively



Scheme 35.



Scheme 36.



Scheme 37.

by a silyl enol ether nucleophile. Oxidation for another 4.2 F/mol then led to removal of the silyl group ($E_{(\mathrm{decomp})}=+1.60$ V vs. SCE) and the addition of a second nucleophile.

Electroauxiliary chemistry has also allowed for the use of oxonium ions in the 'chiral pool' approach to synthesis.[54] As with the previously used *N*-acyliminium ions (Scheme 21), the electrolysis reaction was used to generate a stable 'pool' of cations under neutral conditions. The pool was then be split and various nucleophiles added (Scheme 36). In this example, the anodic oxidation was carried out in Bu_4NBF_4/CH_2Cl_2 at −72°C. The oxonium ions generated were stable and could be characterized by both proton and carbon NMR spectroscopy. The nucleophiles added to the oxonium ion 'cation pools' were allylsilanes, silyl enol ethers, enol acetates, and acetoacetone. The yields of the reactions ranged from 55 to 84%.

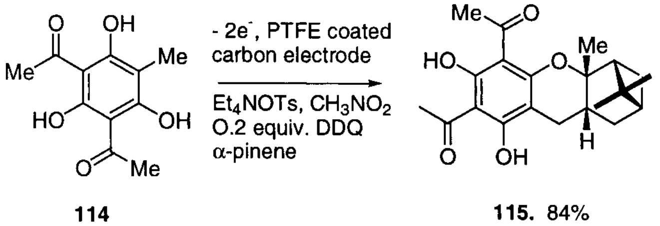
2.5. Elimination and fragmentation reactions involving aromatic rings

Chiba and coworkers have shown that the anodic oxidation of heteroatoms can be used to generate reactive intermediates from aromatic rings. For example, both *o*-quinodimethane and quinomethane intermediates have been synthesized and then used in subsequent Diels–Alder chemistry (Scheme 37).

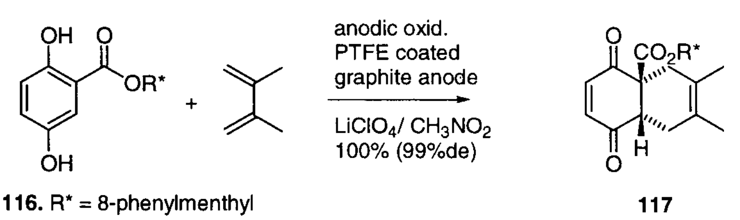
The *o*-quinodimethane intermediate was synthesized by oxidizing substrate **112**.[55] In this case, the reaction was initiated by oxidation of the sulfide followed by a 1,4-elimination reaction of the tributylstannyl group. The oxidations were performed in a 1.0 M lithium perchlorate in nitromethane solution using a glassy carbon anode and a platinum cathode. The reactions were done in the presence of 0.1 M acetic acid and 1.2 equiv. of the dienophile. Both the solvent conditions and the presence of the stannyl group were essential for the successful formation of the cycloaddition product. The reactions did not proceed without the electrolysis reaction.

This work built on the authors' earlier syntheses of the Euglobal family of natural products that had utilized quinomethane intermediates. In these reactions, the key intermediate was synthesized by a controlled potential oxidation of a phenol starting material (Scheme 38).[56] The oxidation was accomplished with the use of a PTFE-fiber coated electrode along with DDQ as a mediator. The use of the hydrophobic coating on the electrode protected the highly reactive intermediate from the solvent and enhanced the reaction with the hydrophobic dienophile. Earlier cycloaddition reactions had benefited strongly from the use of an electrode coating[57] and the presence of SDS micelles. Both the electrode coating and the micelles provided a hydrophobic environment where the highly reactive quinomethane could interact with the dienophile.

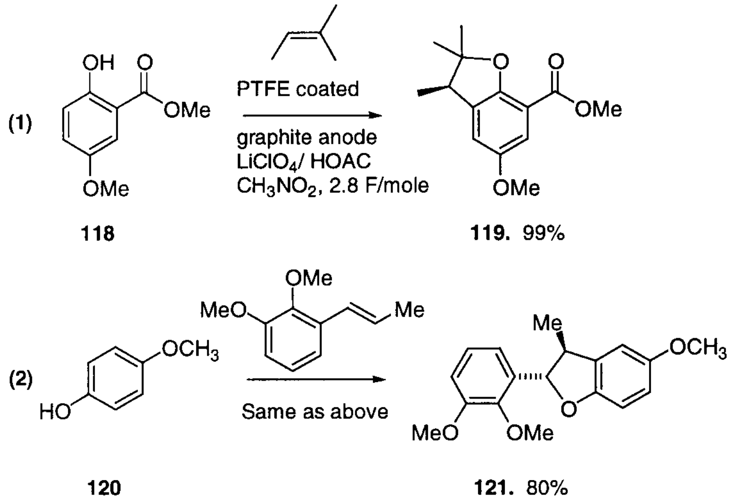
The reactions have also been used to synthesize quinones that serve as dienophiles (Scheme 39).[58] Once again, the controlled potential electrolyses benefited from the use of the PTFE fiber coated electrode. In this case, a highly polar electrolyte solution of 3 M lithium perchlorate in nitromethane was used. The PTFE-fiber was found to significantly accelerate the cycloaddition reaction by again bringing together the hydrophobic quinone and diene



Scheme 38.



Scheme 39.

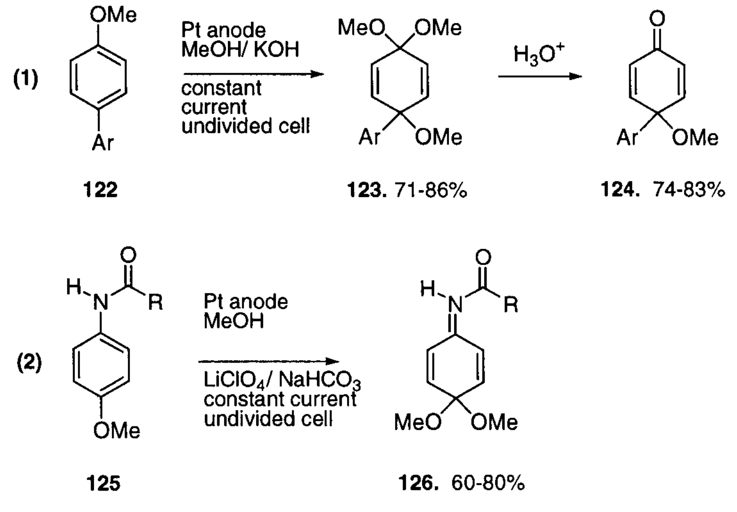


Scheme 40.

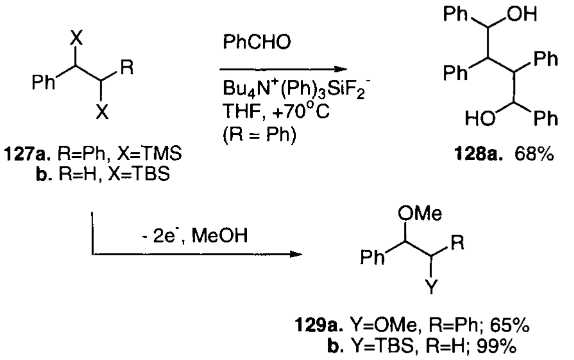
reacting partners. Finally, these reactions could be performed in a stereoselective fashion with the use of a chiral auxiliary.

In a related reaction, Chiba and coworkers demonstrated that the oxidation of hydroquinones can be used to initiate [3+2] cycloaddition reactions (Scheme 40, reaction (1)).[59] In these reactions, a series of olefins were used. The product yields ranged from 60–99%. This work was directly analogs to earlier work by Swenton and coworkers (Scheme 40, reaction (2)).[60] The work by Swenton was part of a large effort to develop the synthetic use of anodic electrochemistry for converting aromatic rings into reactive intermediates for synthesis. This work involved both the conversion of methoxylated aromatic rings to quinone derivatives (Scheme 41, reaction (1)),[61] and the conversion of p-methoxyanilide derivatives into quinone *N*-acylimine ketals (Scheme 41, reaction (2)).[62] Recently, a related effort has explored the compatibility of oxidations involving substrates like **125** with both substituents on the aromatic ring and a variety of protecting groups on the nitrogen. In this work, the quinone imine acetals (**126**) were obtained in yields ranging from 62–97%.[63]

The oxidation of aromatic rings having benzylic silyl groups



Scheme 41.



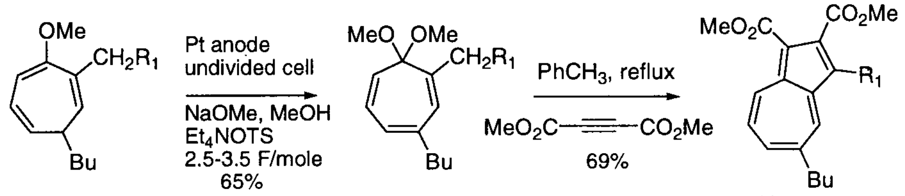
Scheme 42.

has also been used to initiate interesting umpolong reactions (Scheme 42).[64] When **127a** was treated with a source of fluoride followed by an electrophile, the product generated resulted from an electrophilic attack on the benzylic carbon. A variety of electrophiles were used including alkyl halides, aldehydes, acid derivatives, imines and activated olefins. On the other hand, an anodic oxidation of **127a** led to replacement of the silyl groups with methanol as a nucleophile. In unsymmetrical cases like **127b**, the benzylic silane was selectively replaced. In this example, the use of *t*-butyldimethylsilyl groups was needed in place of the trimethylsilyl substituents in order to avoid elimination of the second silyl group from the initially generated benzylic cation.

The oxidation of cycloheptatriene systems also leads to the formation of useful synthetic intermediates.[65] In this case, a series of tropone intermediates were generated. In one interesting example, the oxidation of **130** led to product **131**. When **131** was treated with dimethylacetylenedicarboxylate and heated, it lost the elements of methanol and underwent a cycloaddition reaction to form the bicyclic **132** (Scheme 43).

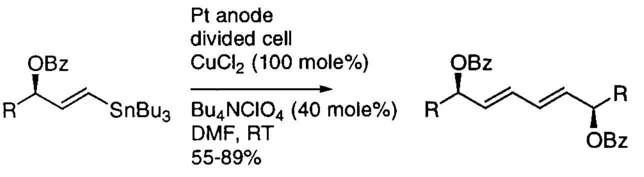
2.6. Oxidations of copper salts

Torii and coworkers have shown that the oxidation of divinyl substituted copper II salts can be used to synthesize symmetrical dienes (Scheme 44).[66] The copper salts were prepared by adding two equivalents of a vinylstannane to $CuCl_2$. Oxidation of the divinyl copper species then led to a reductive elimination of the vinyl groups to form the diene. In the example shown, the reaction was checked for its compatibility with chiral centers at the allylic positions. None of the chirality was lost demonstrating that the reactions were useful for the synthesis optically active 2,4-diene-1,6-diol derivatives. While for the asymmetric example a stoichiometric amount of the copper reagent



130 **131** **132**

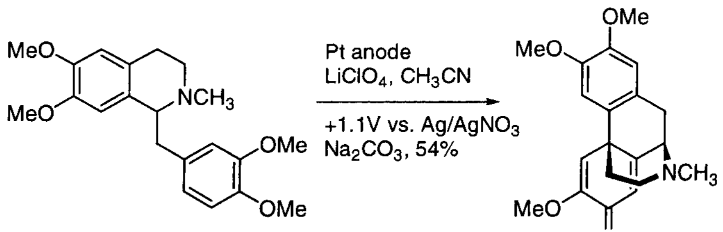
Scheme 43.



133

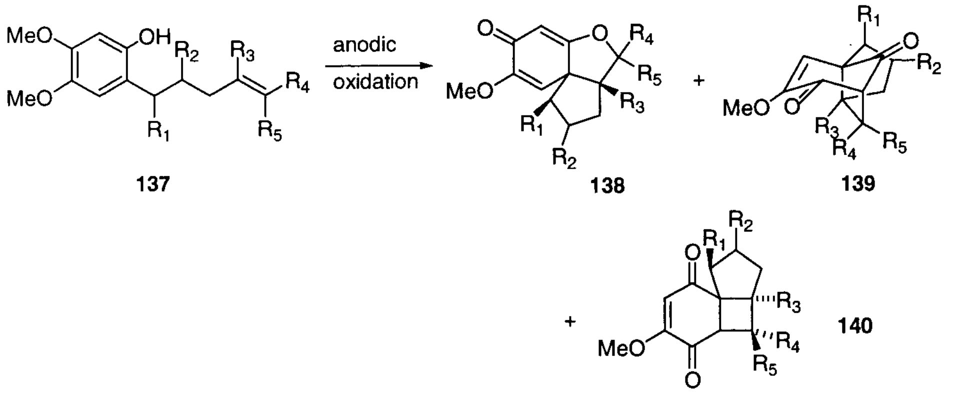
134. R = n-C_5H_{11}, $PhCH_2CH_2$, n-C_8H_{17}, iPr

Scheme 44.



135 **136**

Scheme 45.



Scheme 46.

was used, many of the examples presented used a catalytic amount of the copper II precursor.

3. Coupling Reactions Involving Anodically Generated Intermediates

3.1. Aryl–aryl coupling reactions

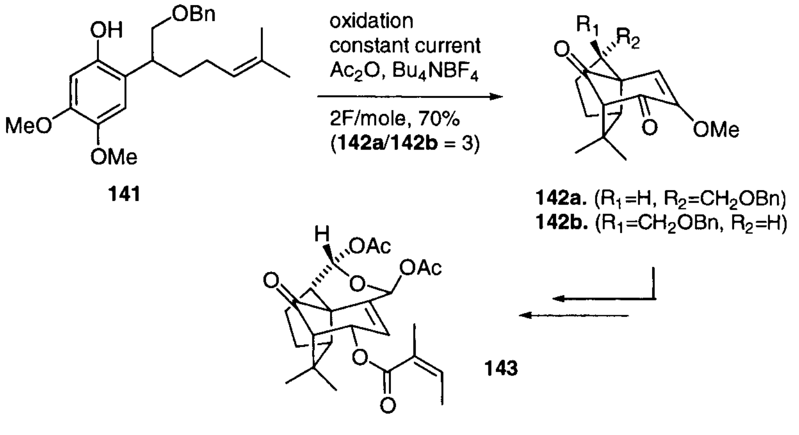
Perhaps the most well-known reaction involving the direct trapping of an intermediate generated at an anode surface is the coupling of two electron-rich aryl rings to form a biphenyl-type ring system. These reactions have been extensively reviewed,[67] and will not be presented in detail here. However, it should be noted that the development of these reactions was very important for the development of anodic electrochemistry as a whole. The syntheses achieved provided an early example of how useful anodic processes could be for constructing polycyclic ring skeletons (Scheme 45),[68] and the chemistry discovered paved the way for much of the work that has followed.

3.2. Aryl–olefin coupling reactions

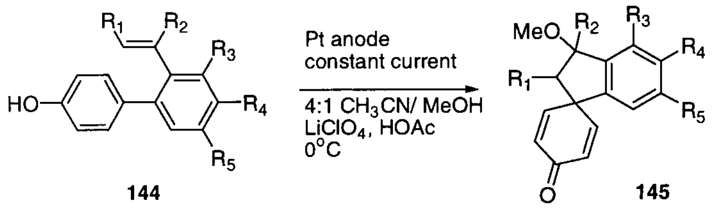
From the standpoint of natural product synthesis, one of the most useful anodic processes has been the coupling of phenols to olefins. This work, pioneered by Yamamura and coworkers, demonstrated that intramolecular coupling reactions between the two groups can lead to three different families of products (Scheme 46).[69] The nature of the product obtained was dependent on both the substitution and stereochemistry of the olefin. For example, if the olefin was substituted with a methyl group in position R_3, then products of type **138** or **140** were formed. Within this group, an 3,4-dimethoxyphenyl substituent in position R_4 led to a product of type **138** while the same group in position R_5 led to the formation of a product of type **140**.[70] If R_3 was a hydrogen, then the products formed were normally of type **139**.[71,72] This also proved true for olefins that did not have the aryl ring on the olefin.[72,73] When an electron-poor olefin was used the reactions formed products of type **140** even without the methyl group in position R_3.[74] The yields for the reactions typically ranged from 40–80%.

Both products of type **139** and **140** have proven to be very useful synthetic intermediates. This work has been reviewed,[75] so a single recent example has been selected as an illustration.[76] In this example, phenol **141** was oxidized at a constant current of 9 mA (2 F/mol) in acetic anhydride containing Bu_4NBF_4 as the supporting electrolyte. A 70% isolated yield of the tricyclic **142a,b** was obtained as a 3:1 mixture of stereoisomers (Scheme 47). The major product (**142a**) was carried forward and eventually used to complete the first synthesis of (±)-acourtia isocedrene (**143**).

Swenton and coworkers have also studied the anodic coupling of phenol and olefin moieties, in this case as a means for making spirocyclic ring skeletons (Scheme 48).[77] The substrates were oxidized at a platinum anode



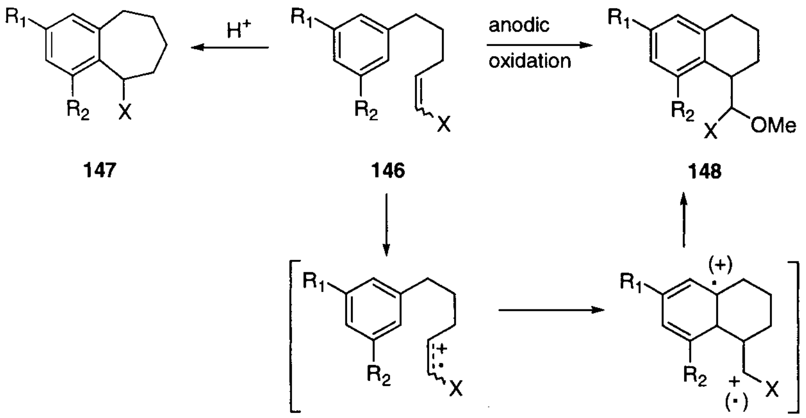
Scheme 47.



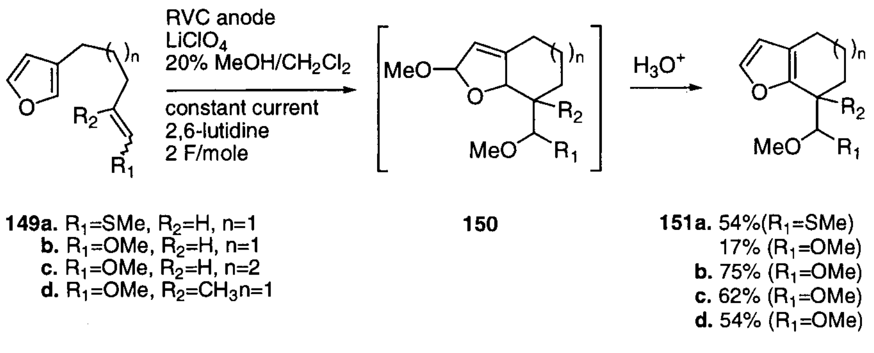
Scheme 48.

using constant current conditions and a $LiClO_4$ in 4:1 CH_3CN/MeOH electrolyte solution. The reactions were run at 0°C in the presence of acetic acid and were most efficient when a substituent was present at position R_2 of the olefin. In these cases, the product was generated in 65–85% yields. The substituent at R_2 was essential for keeping the olefin in a conformation compatible with the cyclization reaction. In the absence of a substituent at R_2 (R_3 also equal to H), sterics favored the conformation of the molecule that placed the olefin close to R_3 and away from the phenol ring. The yield of the reaction fell from the 65–85% range to 16–35%. Evidence that this fall off in the yield was due to conformational factors was gained by placing a methyl group in position R_3 while leaving R_2 as a hydrogen. In this substrate, the steric penalty for placing the olefin next to the phenol was removed because of steric interactions between the olefin and R_3. The cyclization afforded a 70% yield of the desired product. The reactions also benefited from the presence of oxygen substituents in positions R_4 and R_5. This work has been recently reviewed.[75]

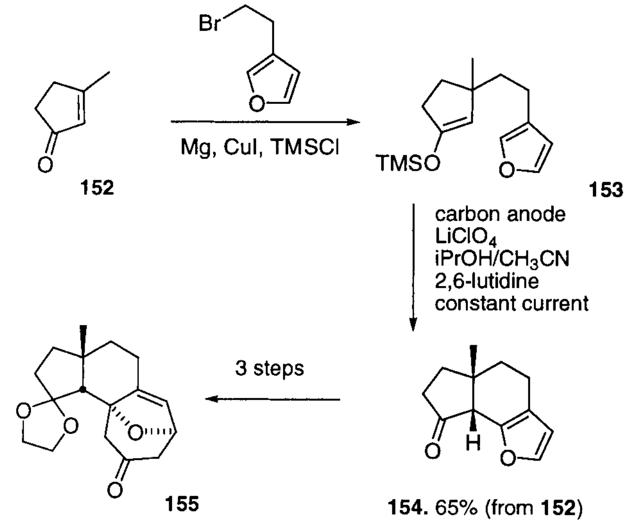
Coupling reactions between electron rich aryl rings and olefins have also been used to synthesize fused bicyclic ring skeletons.[78] These reactions illustrated how an anodic oxidation reaction could be used to reverse the regiochemistry (product **148**) of a Friedel Crafts reaction (product **147**/Scheme 49). This change in regiochemistry was caused by the anodic oxidation reaction reversing the polarity of an electron-rich olefin. These reactions, which have been recently reviewed,[75] benefited from the use of either constant potential electrolysis conditions (R_1=OMe, R_2=H, X=OMe) or the use of a vinyl sulfide as the electron-rich olefin (R_1=R_2=OMe, X=SMe). In both cases, the changes were made in order to avoid overoxidation of the electron-rich aromatic ring in the product. In addition to electron-rich phenyl rings, furan rings, were examined for their ability to participate in the reactions (Scheme 50).[78] To this end, substrates **149** were oxidized using a carbon anode,[79] an undivided cell, and constant current conditions. 2,6-Lutidine was added to the reaction as an acid scavenger to prevent methanolysis of the enol ether at the anode



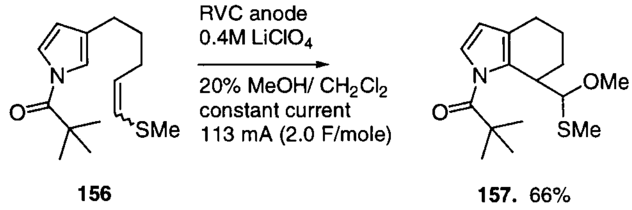
Scheme 49.



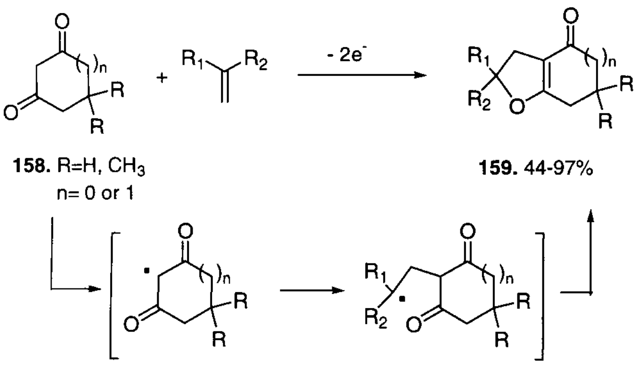
Scheme 50.



Scheme 51.



Scheme 52.

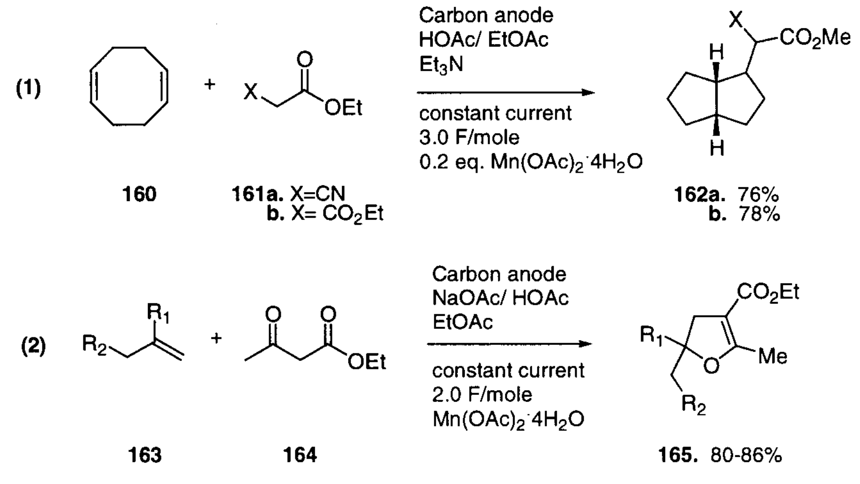


Scheme 53.

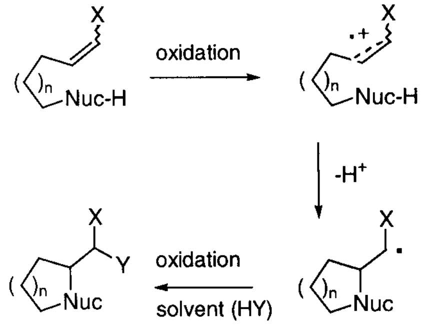
surface. The initial product obtained was derived from trapping of the olefin radical carbon by the furan ring followed by trapping of the subsequent intermediate with methanol. The furan product was obtained by working the reaction up with acid. The reactions were compatible with the use of both enol ether and vinylsulfide initiating groups and the formation of both six- and seven-membered ring products. The generation of six-membered rings proved to be compatible with the formation of a quaternary carbon (**151d**). In addition to the enol ether and vinylsulfide based cases shown, the reactions were compatible with the use of allylsilanes, styrenes, and simple alkyl substituted olefins. In the case of a simple alkyl-substituted olefin, the initial oxidation led to a radical cation of the furan ring demonstrating that the furan ring could serve as either the initiating group or the terminating group for the reactions.

Recently, Wright and coworkers reported the use of a related anodic reaction as part of an oxidative coupling-[4+3] cycloaddition strategy for the synthesis of the cyathin core (**155**, Scheme 51).[80] In this example, a silylenol ether was coupled to a furan ring to form the tricyclic product **154**. The substrate for the electrolysis reaction (**153**) was synthesized with the use of a Michael reaction. The anodic oxidation reaction was performed using a carbon anode, a $LiClO_4$ in 20% *i*PrOH in acetonitrile electrolyte solution, 2,6-lutidine as a proton scavenger, an undivided cell, and constant current conditions. Isopropyl alcohol was used in place of methanol in order to avoid cleavage of the silyl enol ether. Overall, the procedure formed the tricyclic product **154** in a 65% overall yield from 3-methylpentenone. Once **154** was available, the seven-membered ring of the cyathin ring skeleton **155** was constructed in three steps by using the furan ring as a starting material for the [4+3]-cycloaddition.

Pyrrole rings can also be used for the coupling reactions (Scheme 52).[78] Oxidation of **156** at a carbon anode using a 0.4 M $LiClO_4$ in 20% $MeOH/CH_2Cl_2$ electrolyte solution, an undivided cell, and constant current conditions led to a 66% yield of the bicyclic product. In this case, the use of a vinyl sulfide as the initiating group was important for avoiding overoxidation of the pyrrole product.



Scheme 54.



Scheme 55.

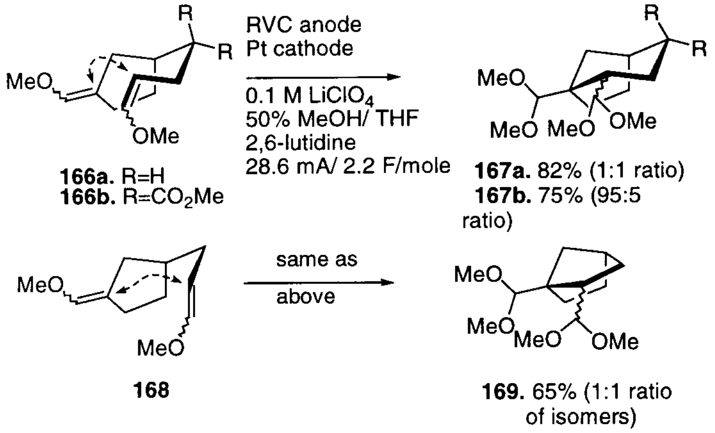
3.3. Oxidations of 1,3-dicarbonyl derivatives

Chemical oxidations of 1,3-dicarbonyl compounds have been studied extensively for their ability to generate radical intermediates and initiate cyclization reactions.[81] Many of these reactions utilize $Mn(OAc)_3$ as the oxidant. Similar oxidative cyclization reactions involving the direct anodic oxidation of acylic 1,3-dicarbonyl compounds have not been reported. However, the direct anodic oxidation of cyclic 1,3-dicarbonyl compounds has been reported (Scheme 53),[82] as well as $Mn(OAc)_3$ (generated from $Mn(OAc)_2{\cdot}H_2O$) mediated electrochemical oxidation of both cyclic and acyclic 1,3-dicarbonyl compounds. Like their chemical counterparts, the mediated reactions have been used to initiate a variety of radical addition and cyclization reactions (cf. Scheme 54).[83] The chemistry has been reviewed elsewhere.[75]

3.4. Intramolecular anodic olefin coupling reactions

The anodic oxidation and subsequent coupling reactions of electro-rich olefins offers a variety of new opportunities for generating carbon–carbon bonds and ring skeletons. As seen with the earlier coupling reactions involving aromatic rings (Schemes 49–52), these reactions reverse the polarity of the electron-rich olefin oxidized; a fact that can allow an enolate equivalent (Scheme 55, X=OR) to be utilized as an electrophile. To date, most of the reactions studied have utilized a second olefin as the nucleophilic group. While the early work in this area has been reviewed,[75] three recent results deserve comment here.

First, the reactions were used to construct bridged bicyclic ring skeletons from both the bicyclo[2.2.1]heptane and bicyclo[3.2.1]octane families (Scheme 56).[84] In all three examples illustrated, the bis enol ether substrate was oxidized at a carbon anode using an undivided cell and constant current conditions along with a 0.1 M $LiClO_4$ in 50% MeOH/THF electrolyte solution and 2,6-lutidine as a proton scavenger. The reaction originating from **166a** led to a 1:1 mixture of stereoisomers, whereas the reaction originating from **166b** led to predominately the product having both dimethoxyacetal groups in equatorial positions. The difference between the two reactions was explained by the presence of a 1,3-diaxial interaction in the pathway leading to the minor product that was only present during the cyclization of **166b** (Scheme 57). In addition to their synthetic value, these reactions provided insight into how cyclic voltammetry data can influence the way in which the reactions are viewed. Initially, it was thought that the lower yield of the product obtained from **168** was due to the strain of the forming bicyclo[2.2.1]heptane ring skeleton causing the rate of the cyclization to be slower. This would allow more time for the radical cation to decompose prior to the cyclization. However, cyclic voltammetry data suggested that the rate of the cyclization originating from **168** was slightly *faster* than the six-membered ring formation originating from **166a**. Evidently, the formation of a six-membered ring slowed the cyclization down more than did the extra strain associated with the bicyclo[2.2.1]heptane



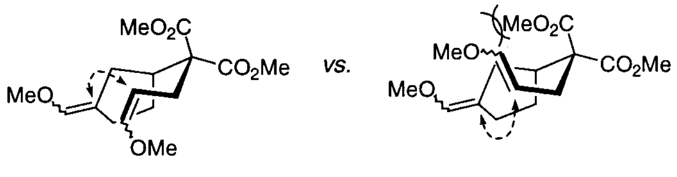
166a. R=H
166b. R=CO_2Me

167a. 82% (1:1 ratio)
167b. 75% (95:5 ratio)

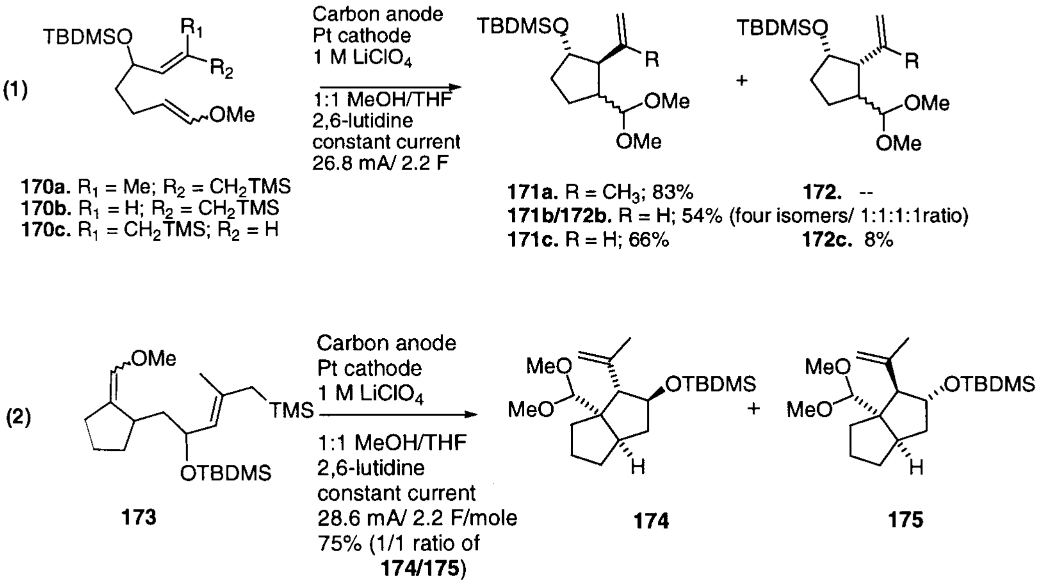
168

169. 65% (1:1 ratio of isomers)

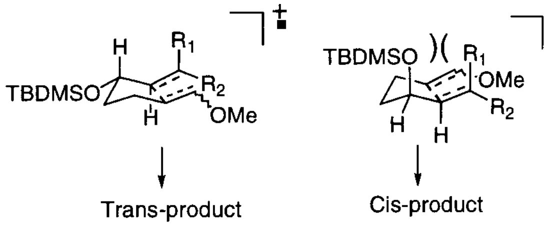
Scheme 56.



Scheme 57.



Scheme 58.



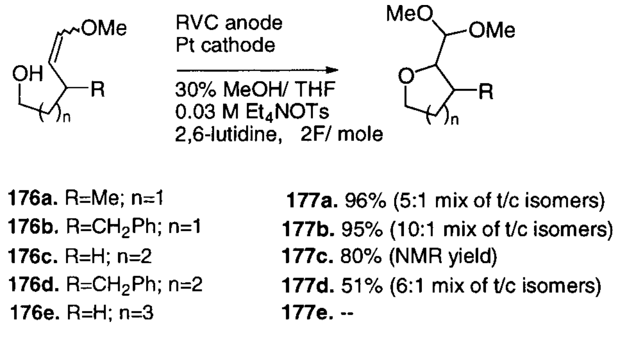
Scheme 59.

skeleton. For this reason, the lower yield obtained for the cyclization originating from **168** was attributed to the instability of the product once it was formed.

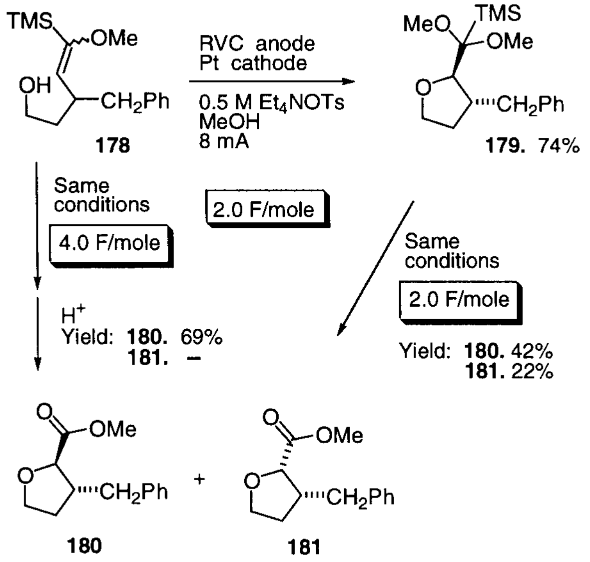
Second, recent studies have shown that intramolecular coupling reactions between enol ether and allylsilane nucleophiles are compatible with the presence of an alkoxy group on the allylic carbon of the allylsilane (Scheme 58).[85] These reactions were of interest because they demonstrated the gentle nature of the cyclization reactions.

Even when challenged to make a quaternary center, the reactions showed no elimination on the allylic alkoxy group. Clearly, the electrolysis reactions could be used to make highly reactive intermediates from very sensitive substrates. In addition, the reactions were of interest because they appeared to be under 'kinetic control'. Previous cyclization reactions using vinylsilane terminating groups were shown to be reversible.[86] Evidence for kinetic control of the reactions shown in Scheme 58 was obtained by examining the distributed allylsilane substrates **170b** and **170c**. In these cases, both substrates afforded the same products. If the reactions were under thermodynamic control, then the products from the two reactions would be formed in the same ratios. If the reactions were under kinetic control, then the differences in the starting materials would be reflected in the transition states for the reactions, and the ratio of the products obtained would be different. In practice, the cyclization reaction originating from **170c** was far more selective than the cyclization originating from **170b** indicating that the reactions were controlled by kinetics. The selectivity observed with substrates **170a** and **170c** was attributed to the major product having the large alkoxy group in a pseudoequatorial position thereby avoiding an $A^{1,3}$-interaction with R_1 (Scheme 59). The *trans*-disubstituted allylsilane substrate (**170b**) did not have a substituent in position R_1 and thereby did not have the possibility for an $A^{1,3}$-interaction in the transition state leading to the minor product. Hence, the lower degree of selectivity.

Finally, anodic coupling reactions have been shown to be compatible with the use of oxygen nucleophiles and the generation of tetrahydrofuran and tetrahydropyran ring systems (Scheme 60).[87] The reactions afforded mainly the *trans* products. At this time, it is not known whether the stereoselectivity was the result of thermodynamic or kinetic controls. These cyclization were of interest because they again provided an interesting example of how an anodic oxidation reaction can be used to reverse the polarity of an enol ether equivalent. This observation was further highlighted when a ketene acetal equivalent was used to initiate the reaction (Scheme 61). In this case, a 4 F/mol oxidation could be used to generate a product where the oxygen nucleophile had been added to the alpha carbon of an ester.



Scheme 60.



Scheme 61.

3.5. Trapping of N-centered radicals and radical cations

While the above reactions generated heterocycles by trapping an anodically generated reactive intermediate with an oxygen nucleophile, an opposite approach has been taken for synthesizing nitrogen containing heterocycles. In these reactions, the anodic oxidation has been used to generate a reactive intermediate from the nitrogen atom. Two main classes of reactions have been studied. In the first, nitrogen based anions have been oxidized to generated nitrogen radicals, and in the second the lone pair of a neutral nitrogen has been oxidized to generate a radical cation intermediate.

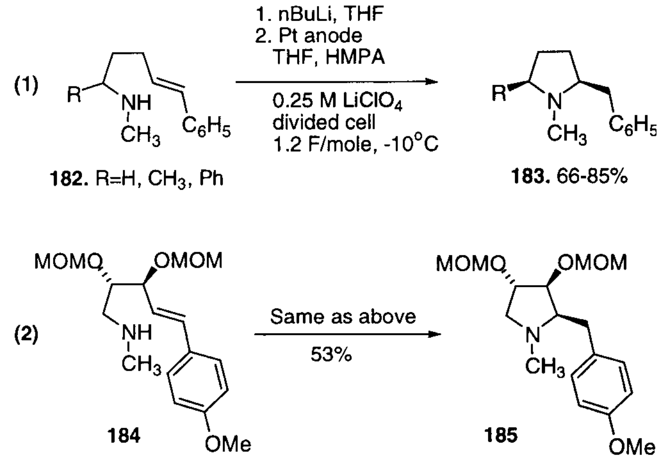
An example of the nitrogen based radical approach is illustrated in Scheme 62.[88] In both examples shown, the amines were treated with *n*-BuLi in order to make the nitrogen anion and then the resulting lithium amide oxidized at a platinum anode using constant current conditions, a divided cell, and a 0.25 M $LiClO_4$ in THF/HMPA (30:1) electrolyte solution. The oxidations were run until 1.2 F/mol was passed. The one-electron oxidation led to the formation of a radical, which following cyclization, abstracted a hydrogen atom from the solvent. The cyclization reactions were both regio- and stereoselective and generated only pyrrolidine products having *cis*-stereochemistry. Finally, the cyclization originating from **184** was performed as part of a total synthesis of (+)-*N*-methylanisomycin, an effort that afforded the natural product in 15 steps and an overall yield of 14%.[88b] Direct oxidation of the amines without prior treatment with *n*-BuLi failed to produce the cyclized product.

The direct oxidation of *N*-methoxy amines did afford cyclic products (Scheme 63), although the yields for cases directly analagous to **182** were not competitive with the earlier lithium amide cyclizations.[88a] However, a related reaction used in the synthesis of an 11-substituted dibenzo[*a*,*d*]-cycloheptenimine derivative proved very successful.[89] On a 1 g scale, a controlled potential electrolysis of **188** using an undivided cell, an SCE reference electrode, a graphite felt anode, a stainless steel cathode, and a 1% $NaBF_4$ in 70/30 THF/H_2O electrolyte solution led to an 85% isolated yield of the product. This reaction was eventually scaled up using a flow cell in order to electrolyze 200 g of the starting material. The yield for the scale up was 75%.

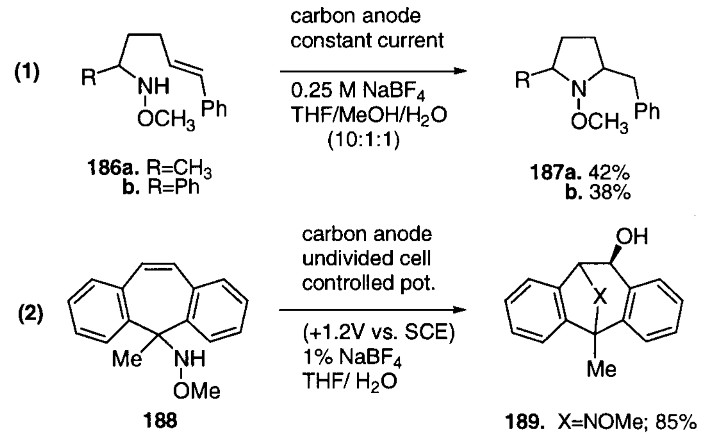
The oxidation of substrate **190** also led to the formation of a nitrogen based heterocycle in high yield (Scheme 64).[90] This reaction was accomplished using a platinum gauze electrode at a controlled potential of +1.8 V vs. Ag/AgCl. The reaction was shown to proceed through an initial oxidation of the amide by placing substituents on the two phenyl rings of the substrate. It was found that substituents in position X did not influence the initial oxidation wave obtained for the substrate, whereas substituents in position Y had a profound influence on the initial oxidation. When Y was an electron withdrawing group, the initial oxidation wave increased in potential indicating a more difficult initial oxidation. The opposite was observed for electron donating substituents.

4. Using the Anode as a Source of Strong Electrophiles, Radicals, and Electrogenerated Acids

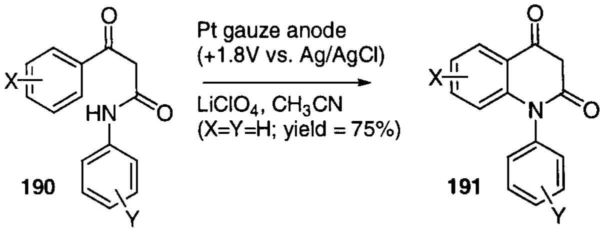
To this point, the reactions examined have all utilized the oxidation reaction to generate a reactive species from a substrate of interest that have then gone on to initiate a



Scheme 62.



Scheme 63.



Scheme 64.

variety of reactions. In this final section, the electrochemical reactions reviewed use the oxidation in order to generate reagents that then act on the substrate. The reactions differ from mediated processes because the reagent becomes part of the product.

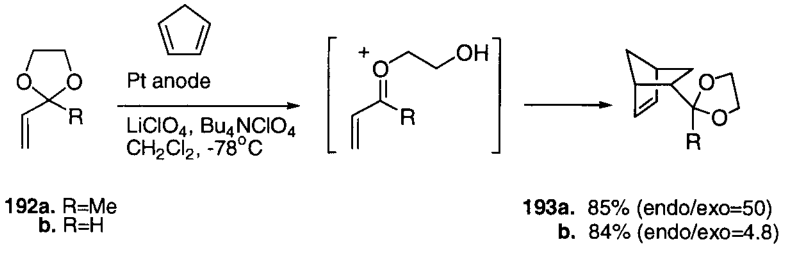
4.1. Electrogenerated acids

The use of electrogenerated acids provides an excellent example of how anodic oxidation can be used to generate reagents and initiate interesting new reactions.[91] Electrogenerated acids are typically formed at an anode as a side product from an oxidation reaction. While the overall electrolysis reaction remains neutral (a base is generated at the cathode), the area surrounding the anode can becomes acidic enough to catalyze reactions. Hence, the electrolysis offers an opportunity to catalyze a reaction with acid while maintaining neutral reaction conditions. Torii and coworkers have exploited this chemistry in their study of Diels–Alder reactions involving α,β-unsaturated enal acetals (Scheme 65).[92] In this case, the electrogenerated acid ($HClO_4$) was generated from a quaternary ammonium perchlorate salt. The reactions proceed through the oxonium ion and led to high levels of *endo* product relative to thermal reactions using the corresponding carbonyl based dienophile. With the electrogenerated acid, the Diels–Alder reaction between the methylvinyl ketone derivative **192a** and cyclopentadiene afforded an 85% yield of a 50/1 ratio of *endo* and *exo* isomers. The *endo*/*exo* ratio for the corresponding thermal Diels–Alder reaction using methylvinyl ketone was approximately 3–3.9/1. In addition, the use of the electrogenerated acid conditions avoided the polymerization problems that often accompany reactions utilizing methylvinylketone. The reaction using the acetal derived from acrolein (**192b**) showed similar improvements, although not to the same extent. In this case, an 84% yield of product was obtained in a 4.8/1 *endo* to *exo* ratio. The corresponding thermal reaction using the aldehyde led to a 2.4–2.9/1 ratio of *endo* and *exo* isomers. Ten such Diels–Alder reactions were reported.

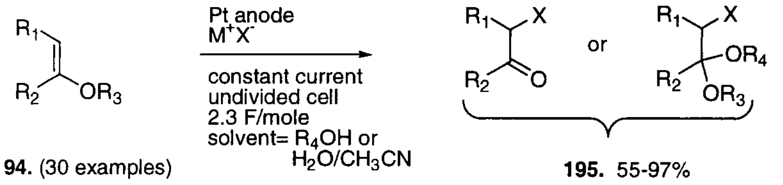
A variety of other reactions have been initiated with electrogenerated acids including the acylation of aromatic rings using acetic anhydride,[93] the opening of epoxides,[91,94] and aldol type condensations.[95]

4.2. Oxidation of halogens

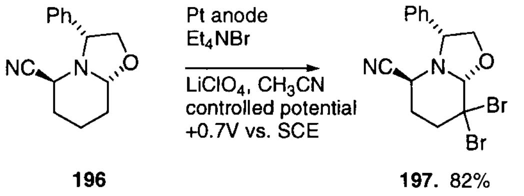
In related reactions, anodes have been used to generate X^+ species for use in halogenation reactions. For example, consider the general reaction illustrated in Scheme 66.[96] In these reactions, bromide, iodide, and chloride ions were oxidized in the presence of a series of enol ethers and enol acetates. The oxidations, which were conducted using constant current electrolysis conditions in an undivided cell, led to halogenation of the enol ether and the temporary formation on an oxonium ion. The oxonium ion was trapped



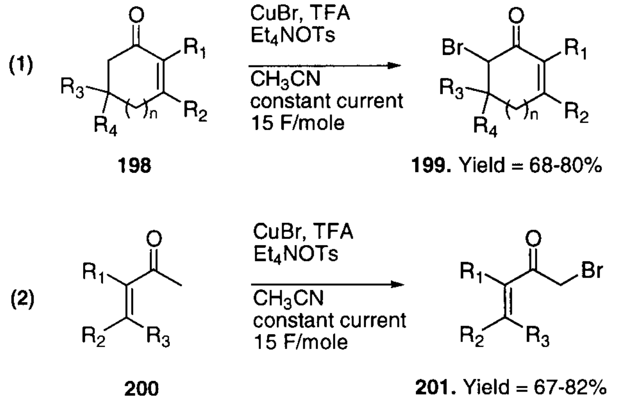
Scheme 65.



Scheme 66.



Scheme 67.



Scheme 68.

either water or alcohol depending on the solvent for the reaction. The solvents used were H_2O/CH_3CN, MeOH, EtOH, PrOH, $CH_2{=}CHCH_2OH$, and $MeOCH_2CH_2OH$. The source of halogen was most often NH_4X, although LiBr, Et_4NBr, NaBr, KBr, and $MgBr_2$ were also used. The yield of the reaction varied from 55–90% for thirty examples.

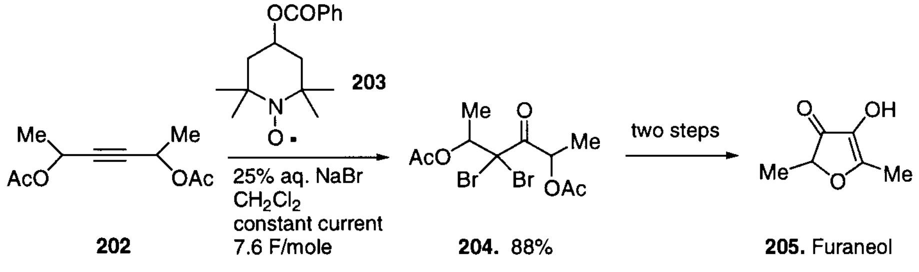
Recently, an electrochemical bromination reaction has been used in the synthesis of polyfunctionalized piperidines (Scheme 67).[97] The selectivity of the reaction was the result of a ring opening reaction that led to the formation of an enamine radical cation. The enamine radical cation then underwent reaction with an oxidized bromide (Br) to generate an α-brominated iminium ion. Elimination of a proton to regenerate the enamine, oxidation to reform the enamine radical cation, and trapping of a second bromine radical led to the inclusion of a second bromide alpha to the iminium ion. Recyclization then generated the final bicyclic product.

Electrolysis reactions have also been used to brominate the α′ position of α,β-unsaturated ketones (Scheme 68).[98] These reactions were accomplished with the use of constant current electrolysis conditions. CuBr as the source for Br^+ (following oxidation), trifluoroacetic acid, a carbon anode, an undivided cell, and a tetraethylammonium tosylate in acetonitrile electrolyte solution. The reactions were dependent on the use of the trifluoroacetic acid. Reactions using other acids or bases did not offer the same selectivity.

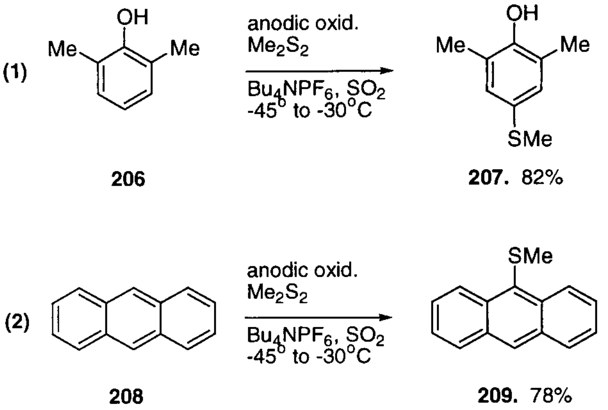
The bromination of acetylenes also proved to be useful (Scheme 69).[99] In these reactions, the oxidation of a solution of 25% aq. NaBr, dichloromethane, *N*-oxylradical **203**, and the acetylene led to the formation of the dibromoketone **204** in a 88% isolated yield. The reactions were run using constant current conditions in an undivided cell with either platinum or glassy carbon electrodes. For the case shown, the product was converted into furaneol (**205**).

4.3. Methylthiation reactions

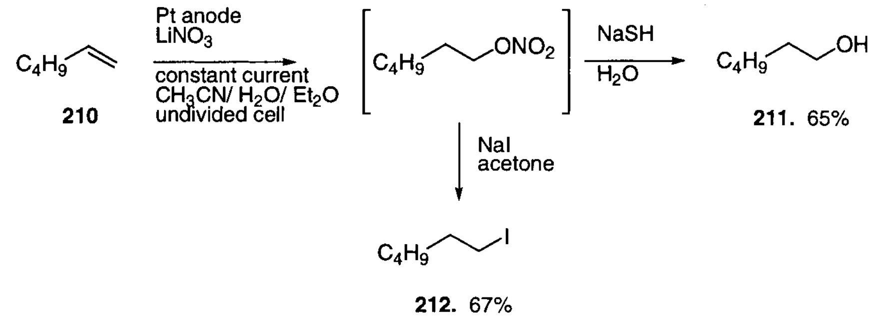
In addition to adding halogens to molecules, anodic electrochemistry has been used to add thiomethyl groups to nucleophiles (Scheme 70).[100] In this work, Me_2S_2 was oxidized in a divided cell using controlled potential conditions with a Ag wire as a reference electrode, a Pt gauze anode, *n*-Bu_4NPF_6 as the electrolyte, and liquid SO_2 as the solvent. The temperature of the reactions was maintained at −45 to −30°C. The reactions were run until 2 F/mol of charge had been passed. An aluminum foil cathode was used. When complete, the solvent was allowed to evaporate, the product taken up in dichloromethane, and then ether added in order to precipitate the electrolyte. The product was then chromatographed.



Scheme 69.



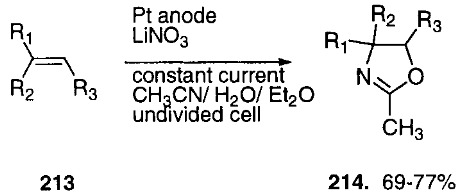
Scheme 70.



Scheme 71.

4.4. Anodic oxidation of NO_3^-

The oxidation of nitrate anions leads to nitrate radicals ($\cdot NO_3$) which in turn add to olefins (Scheme 71).[101] These oxidations were carried out at a Pt anode using constant current conditions, an undivided cell, a mixed MeCN:H_2O:Et_2O (10:2:1) solvent system, and $LiNO_3$ until 8 F/mol of electricity was passed. The nitrate ester products were not stable and were therefore immediately converted to either alcohol or iodide products. The reactions were also compatible with the use of disubstituted olefins such as cyclohexene, cyclooctene, and *trans*-octene. Interestingly, reactions using 1,1-disubstituted olefins led to a product derived from acetonitrile trapping. Using the same conditions outlined above, these reactions afforded oxazole products in good yields (Scheme 72). The proposed mechanism for this transformation suggested that the nitrate radical added to the olefin in order to generate the most substituted radical. Oxidation of the radical would then lead to a tertiary carbonium ion that would in turn be trapped by the acetonitrile solvent. A loss of NO_2^+ would then afford the observed product.



Scheme 72.

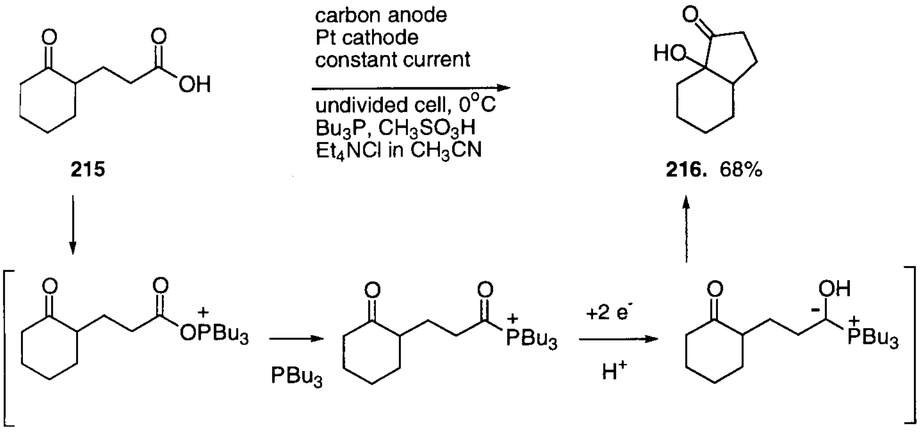
4.5. Anodic oxidation of phosphines

The oxidation of phosphorous compounds has also been used to trigger a number of interesting synthetic reactions. These reactions employ the oxidation reaction to generate a radical cation from a phosphine. The radical cation then traps a nucleophile in solution and undergoes a second oxidation step. Two main reaction pathways follow. Either the product is used as an ylide precursor, or the product is used as a method for converting an oxygen into a leaving group. This work has been recently reviewed.[102] However, one very intriguing aspect of this research provides a nice backdrop for emphasizing its potential importance. Ohmori and coworkers have used anodically generated phosphorous intermediates to set up cathodic reduction reactions (Scheme 73).[103] In this experiment, a carboxylic acid was used as the direct precursor of an acyl anion equivalent. To accomplish this, an undivided cell was used to oxidize either triphenylphosphine or tributylphosphine at a carbon anode in the presence of the acid. The oxidation led to the formation of a phosphorous radical cation which was trapped by the carboxylic acid. A second electron was removed, and the resulting intermediate attacked by a second equivalent of the phosphine in order to generate an acyl phosphonium ion. The acyl phosphonium ion was reduced at the cathode to generate an ylide which then trapped a second carbonyl in an intramolecular reaction. The elimination of phosphine generated the cyclic product, **216**. A number of examples were illustrated. In addition to the formation of five-membered ring product, the reaction was compatible with the formation of a six-membered ring in 44% isolated yield. The reaction was not capable of generating seven-membered rings.

These reactions demonstrated the utility of electrochemistry for initiating reactions not available using more traditional chemical methodology. In this case, the one-pot oxidation–reduction sequence was accomplished because the use of electrochemistry allowed for the spatial separation of a strong oxidant (anode) and a strong reducant (cathode) within the same reaction flask.

5. Conclusions

Anodic electrochemistry provides numerous opportunities for exploring and developing novel synthetic transformations. These opportunities arise because the use of



Scheme 73.

electrochemistry enables a chemist to oxidize molecules at controlled potentials while maintaining neutral conditions. In this way, highly reactive intermediates can be generated and their reactions channeled toward the formation of a desired product. The result is a series of reactions that selectively increase the functionality of molecules and reverse the polarity of known functional groups. Recent applications of anodic electrochemistry to the construction of complex molecules ranging from peptidomimetics to natural products serve to demonstrate that electrochemical synthetic methods are not just novelties, but rather useful synthetic tools that are capable of opening up entirely new strategies for synthesis. While electrochemical techniques are still far from routine, the utility of simple reaction setups and the availability of commercial power supplies, electrodes, and reaction cells means that the majority of electrochemical synthetic methods are available to any chemist willing to pursue them. As the methodology becomes more and more versatile, it hoped that an increasing number of chemists will choose to do so.

Acknowledgements

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4. Typically the controlled potential reactions included in this review have been run with either saturated calomel (SCE) or Ag/AgCl reference electrodes. These electrodes are commercially available from BAS.

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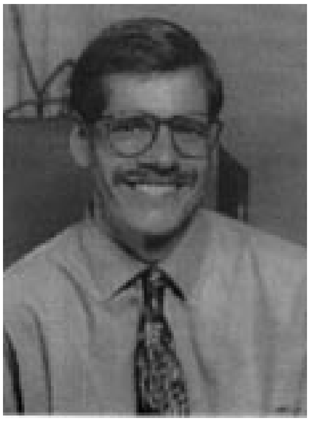
Biographical Sketch



Kevin Moeller was born in Scranton, Pennsylvania in 1958. He received his B.A. degree in chemistry from the University of California, Santa Barbara in 1980 and then his Ph.D. degree from the same institution in 1985 after studying the chemistry of 1,3-diyl trapping reactions with Professor R. Daniel Little. After two years of postdoctoral study with Professor Barry M. Trost at the University of Wisconsin, Madison, he joined the faculty at Washington University in St. Louis in 1987 where he is now Professor of Chemistry. Professor Moeller's research focuses on exploring the use of organic electrochemistry as a tool for organic synthesis. He is married and has two children (a 14-year-old son and a 12-year-old daughter).