XX

Electrochemically Initiated Radical Reactions

Martin A. Bohn, Anna Paul and Gerhard Hilt

Fachbereich Chemie, Hans-Meerwein-Straße, Philipps-Universität Marburg, Marburg, Germany

1 INTRODUCTION

Electrochemical transformations can, in principle, be considered. "Green Chemistry" because oxidation and reduction reactions are initiated by electron transfer from the substrate to the electrode or vice versa.[1] Therefore, the redox process is not associated with an additional reagent that has to be added in stoichiometric amounts and, consequently, the spent redox reagent does not have to be removed. These reagents are often toxic transition-metal complexes, the avoidance of which is most favorable from an environmental standpoint. In addition, electrochemical reactions can be controlled by the current passed through the solution through the current density at the electrode surface (galvanostatic conditions), or the applied redox potential which can be controlled in a three-electrode setup utilizing a reference electrode as internal standard. Another factor that controls the reaction is whether the electrochemical reaction is performed in an undivided cell or the anode and cathode compartments are separated by a diaphragm. In general, the less complex the electrochemical setup, the easier it is for nonelectrochemists to reproduce such transformations. In the simplest setup, two electrodes are immersed in the solution in a beaker-type cell and power is supplied by a commercial battery. The choice of the electrode materials, solvents, and supporting electrolyte also play an important role, and specific choices might be needed for optimal results. Finally, the redox process can be performed directly at the electrode surface or, in cases where the eletron transfer is hindered in whatever fashion, indirect electrolysis strategies utilizing a redox catalyst (mediator) can be applied. For detailed introduction to the theory, instrumentation, and various direct and indirect electrochemical applications, the reader is directed to the several reviews and comprehensive textbooks that are available.[2–14]

Nevertheless, electrochemical conversions have an enormous advantage in that the redox potential can be adjusted to the needs of the individual starting material so that even small differences in the redox potential of the functional groups can be differentiated. Accordingly, electron-rich materials can be converted into radical cations upon abstraction of an electron at the anode, while electron-deficient starting materials can be reduced at the cathode to the corresponding radical anions. Once these radical cation/anion intermediates are formed near the electrode surface, in the so-called Helmholtz layer, either a follow-up reaction will occur or in some cases the intermediates undergo further redox processes to generate the corresponding cations or anions, respectively. In this article, we focus on the chemistry associated with radical cations or radical anions, as well as neutral radical species. Of particular interest are those electrochemical transformations published in the time frame from circa 1997 until 2010 that have generated new carbon–carbon bonds or led to the introduction of functional groups.

Encyclopedia of Radicals in Chemistry, Biology and Materials. Edited by Chryssostomos Chatgilialoglu and Armido Studer.
 ISBN: 978-0-470-97125-3.

2 ANODIC PROCESSES

2.1 Intramolecular Anodic Coupling of Electron-Rich Double Bonds to Nucleophiles

Anodic electrochemical transformations have proven to be an effective method for the oxidation of electron-rich functional groups such as enol ethers **1**. Thereby, the reactivity of the enol ether **1** is altered and reactions are initiated under umpolung of the initial reactivity. The oxidation of the enol ether **1** by one-electron oxidation generates a radical cation intermediate such as **2**, which can be trapped with a nucleophile in an intermolecular fashion to form carbon–heteroatom bonds or carbon–carbon bonds (Scheme 1). This transformation affords cyclic intermediates after the bond formation process such as **3**, and a subsequent second oxidation step occurs to generate cationic intermediates such as **4** which are quenched by the solvent (YH) to obtain the final product **5**.

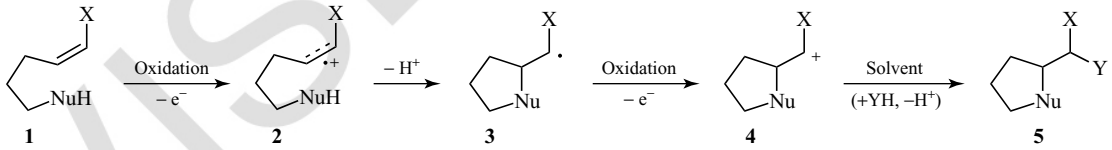
Such anodic processes have been initiated by the oxidation of enol ethers, N,O- or S,S-ketene acetals, and electron-rich aromatic rings. Simple olefins, enol ethers, allyl- and vinylsilanes, electron-rich aryl rings, alcohols, amides, and sulfonamides have been explored as internal nucleophiles for the formation of carbon–heteroatom and carbon–carbon bonds.[15,16]

2.2 Oxidation of Enol Ethers

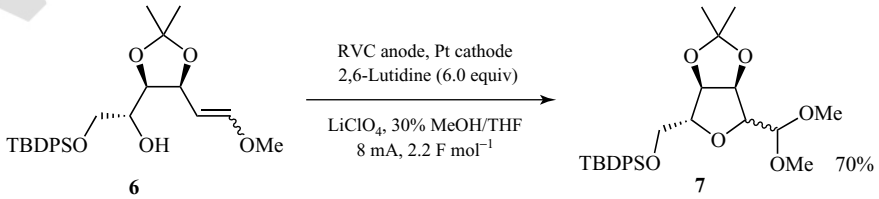
Recent applications of the electrochemical oxidation of enol ethers under current-controlled conditions to the corresponding radical cation intermediates have been reported by Moeller and coworkers. This versatile method was used for the synthesis of various carbocyclic systems either as studies in methodology or for the diversity-oriented synthesis of new carbon–carbon bonds. Various applications of electrochemical oxidation reactions utilizing enol ethers, as an example of an oxidizable electron-rich functionality, have been described as key steps in the synthesis of natural products. Out of the many applications, a selected example of electrochemical activation of an enol ethers is shown in Scheme 2.[17] The electrochemical oxidation is performed on a reticulated vitreous carbon (RVC) electrode at relatively low current (8 mA), and a total amount of 2.2 F mol^{-1} of electricity is passed through the solution.

The synthesis of *C*-glycosides was accomplished from enol ethers such as **6** in a current-controlled electrolysis to afford **7** in good yields as a mixture of diastereomers (Scheme 2). Nevertheless, the stereochemistry of the substrate and the choice of the protecting groups (PGs) applied play important roles, which have not been solved for all combinations.

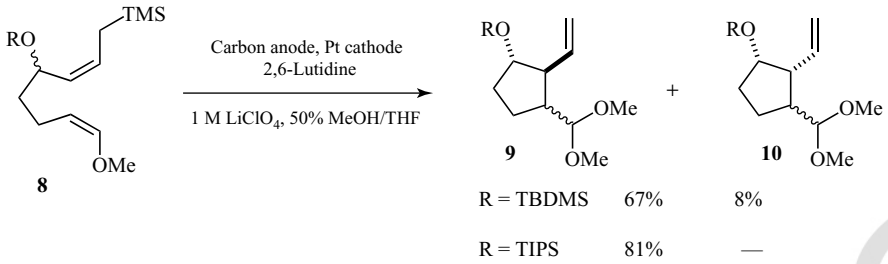
The electrochemical oxidation of enol ethers was also applied in cases where an allyl silane was utilized to react as the electrophlic component.[16] It became obvious that the choice of silyl PGs



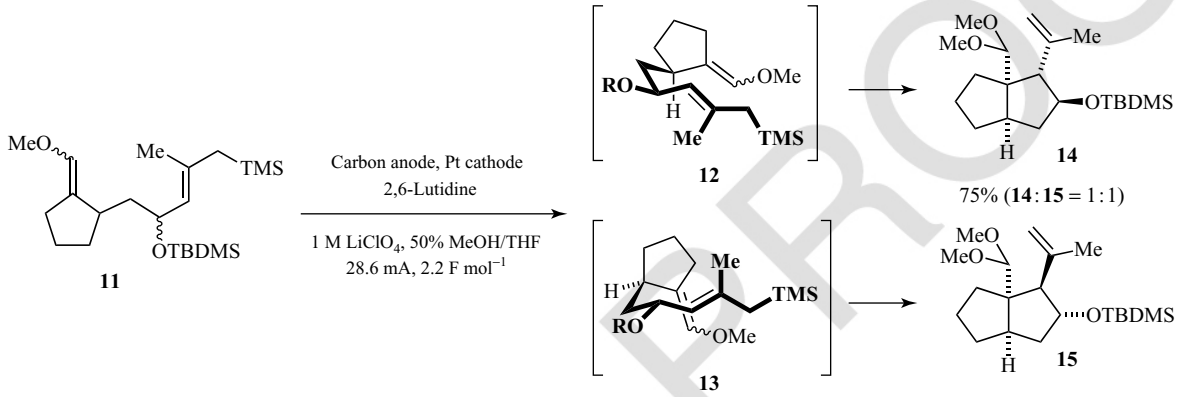
Scheme 1 Intramolecular cyclization by electrochemical umpolung of the starting material.



Scheme 2 Tetrahydrofuran synthesis by electrochemical oxidation of an alcohol bearing enol ether.



Scheme 3 Cyclopentane synthesis by electrochemical oxidation of an allylsilane-bearing enol ether.



Scheme 4 Diastereoselectivity of the radical cation cyclization of polysubstituted starting materials.

on oxygen functionalities in **8** that do not directly react in the electrochemical conversion is crucial for the control of the products formed. In the case illustrated in Scheme 3, the diastereoselectivity is best controlled by a triisopropylsilyl (TIPS) PG to form **9** exclusively, while the *t*-butyldimethylsiloxy (TBDMS) PG led to the formation of the additional diastereomer **10**.

For the synthesis of bicyclic products such as **14** and **15**, the use of the racemic **11** led to the formation of only two of the possible four diastereomers. This stereocontrol is explained by reactive conformers **12** and **13**, which exhibit the lowest barrier for the desired cyclization via their corresponding radical cations (Scheme 4).[18]

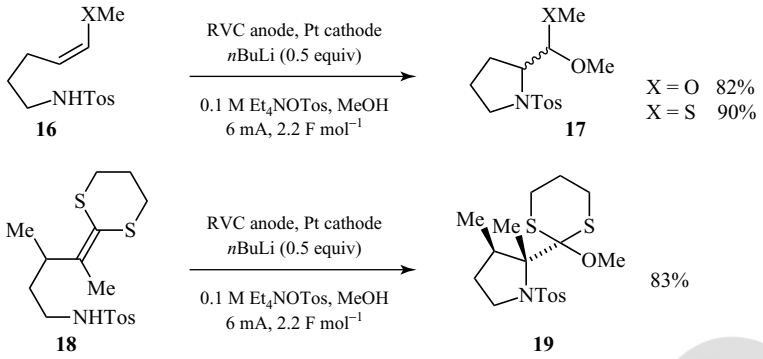
Accordingly, the OTBDMS as well as the biologically important isopropenyl group were introduced with good diastereocontrol, as only the two trans isomers **14** and **15** could be detected.

The Moeller group also reported the use of nitrogen-based functional groups as trapping agents for the intramolecular cyclization of appropriate alkenyl amines such as **16** and **18** (Scheme 5). When the enol ether moieties in **16** or **18** were oxidized at low current densities, the cyclization led predominantly to the five-membered proline-type products such as **17** and **19**. Also, excellent results were obtained when thioenol ethers (X = S) were applied in this reaction under basic conditions.[19]

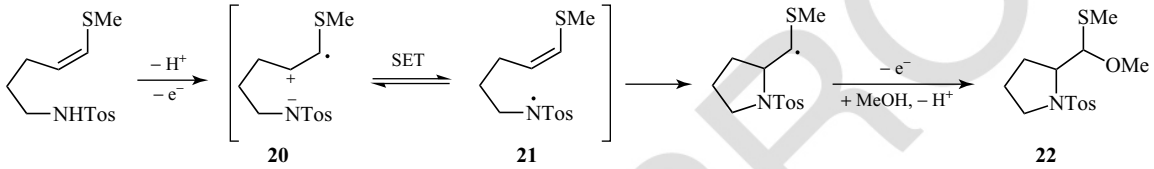
The deprotonation of the sulfonamides **16** and **18** proved to be of advantage for the cyclization process, reducing the tendency to eliminate methanol from the primary cyclization product but also enabling the equilibrium between **20** and **21** by single-electron transfer (SET) (Scheme 6), from which the 5-*endo*-trig-cyclization toward the product rationalizes the formation of the five-membered products **22**.

2.3 Oxidation of Ketene Dithio- and N,O-Acetals

The anodic oxidation of ketene dithioacetals was investigated by Moeller for the synthesis of new carbon–carbon bonds when two electron-rich olefins



Scheme 5 Pyrrolidine formation by electrochemical oxidation of an amine-bearing electron-rich olefins.

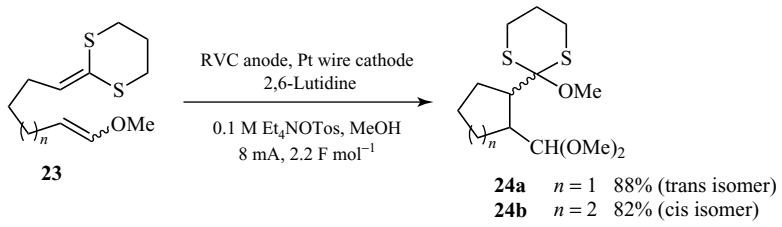


Scheme 6 Mechanism of the radical-cation-initiated cyclization of amine-bearing thioenol ether.

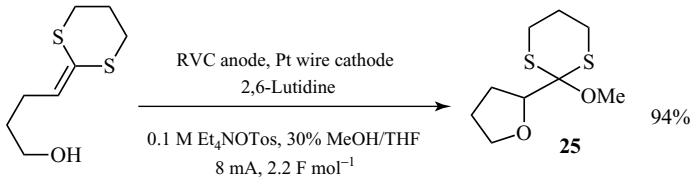
are reacted with each other. The redox potential is expected to be an important issue in these reactions. Electrochemical methods are well suited to discriminate between two functional groups that differ only marginally in their electronic nature. The potential is either controlled by applying an additional reference electrode (potentiostatic electrolysis), or the current density in galvanostatic electrolysis is set to a low value. In the latter case, the low current density at the working electrode will select the starting material (or the functional group), which has the lowest redox potential as long as the diffusion of the starting material is not the limiting factor.

For this purpose, the two ketene dithioacetals **23** and **24** were synthesized and electrolyzed on an RVC anode at a constant current of 8.0 mA until 2.2 F mol^{-1} passed through the solution (Scheme 7).[20] The two reactions gave excellent results in terms of chemical yields, and the five- and six-membered rings were formed in the absence of the all-too-often-needed Thorpe–Ingold effect. It is interesting to note that the two reactions gave different types of diastereomers upon cyclization.

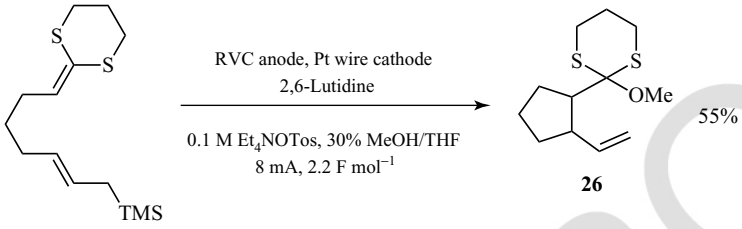
While the five-membered ring product **24a** gave the trans isomer, the cyclization to the cyclohexane derivative **24b** produced the cis isomer exclusively. This finding is in strong contrast to earlier reports concerning coupling reactions of two enol–ether-type double bonds.[21] In these cases, the corresponding cyclization products were formed in a nearly 1 : 1 ratio of the cis/trans isomers. Moeller also reported the trapping of the radical cation generated from the oxidation of the



Scheme 7 Cyclization of a ketene dithio-acetal-bearing enol ether.



Scheme 8 Tetrahydrofuran synthesis of an alcohol-bearing ketene dithio-acetal.

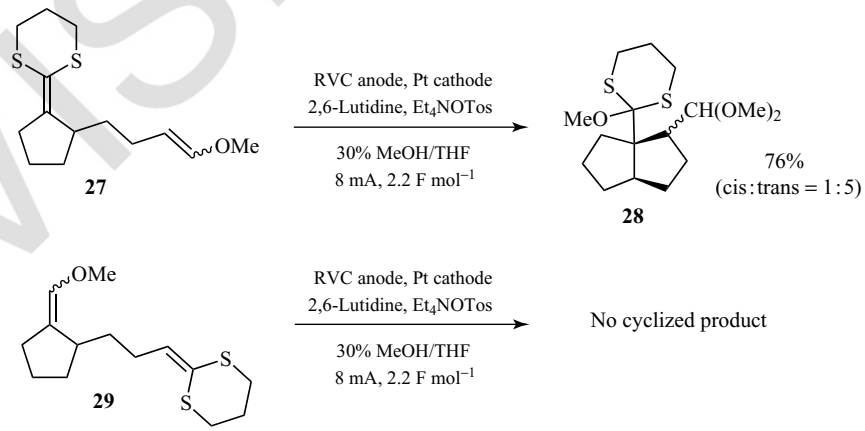


Scheme 9 Cyclopentane synthesis of an allylsilane-bearing ketene dithio-acetal.

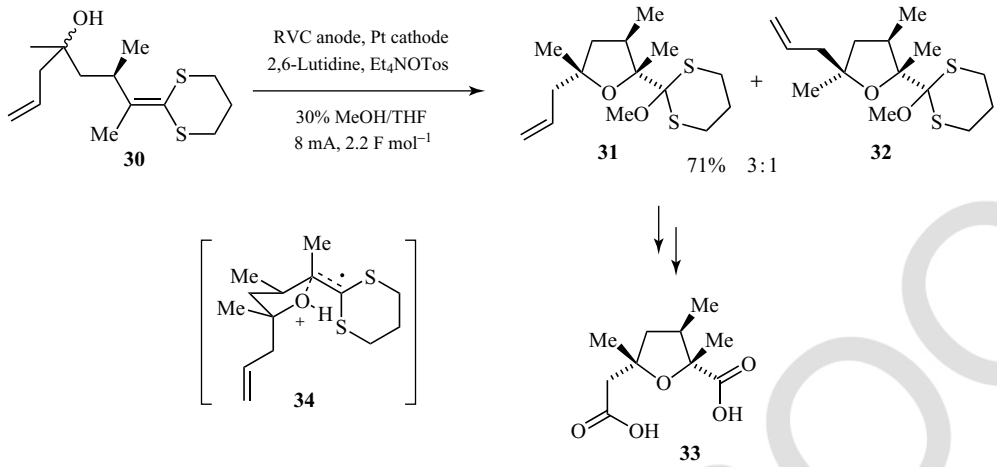
ketene dithioacetal subunit by oxygen nucleophiles. In these cases, tetrahydrofuran (THF) as well as tetrahydropyran derivatives[22] were obtained in excellent yields and additional substituents were well accepted for the formation of the THF derivative **25** in excellent yields as a single product (Scheme 8).[20]

In this context, the direct formation of lactones was realized when amides were utilized as nucleophilic groups in similar cyclization reactions.[23] In addition, an intramolecular cyclization utilizing an allyl silane functionality could be performed for the formation of a new carbon–carbon bond as well, and product **26** was generated in acceptable 55% yield as a mixture of diastereomers (Scheme 9).[20]

In a very interesting cross-experiment, Moeller described the cyclization of the two ketene dithioacetals **27** and **29** (Scheme 10).[24] Ketene dithioacetal **27** gave the desired bicyclic product **28** with a good yield of 76% and an acceptable diastereoselectivity trans:cis = 5 : 1. The radical-type cyclization is not hindered by the steric bulkiness on the carbon bearing the radical functionality. On the other hand, the corresponding regioisomeric starting material **29** did not result in an oxidative cyclization. In this case, the steric hindrance of the internal carbon of the olefin being attacked by the radical has a strong effect on cyclization.



Scheme 10 Cross experiments for cyclization reactions of ketene dithio-acetal-bearing enol ethers.



Scheme 11 Diastereoselective formation of tetrahydrofurans for the synthesis of (+)-nemorensic acid.

Moeller also noted that these cyclization reactions were dependent on the nature of the trapping group. An alkene will react as a "radical-like" nucleophile with the radical cation. When alcohol nucleophiles are used, the observed behavior is different. In these cases, the radical cation intermediates originating either from the oxidation of a ketene dithioacetal or from the oxidation of an alkyl enol ether exhibit "cation-like" reactivity.

This observation eventually led to the design of a ketene dithioacetal starting material which was used for the synthesis of (+)-nemorensic acid (**33**). In this case, the starting material **30** was converted under oxidative conditions in an undivided cell at a constant current of 8.0 mA using 2.0 F mol^{-1} (Scheme 11).[25]

In the key step of the synthesis, the alcohol group trapped the radical cation intermediate **34**, while the allyl group in **30** did not react but remained available as a masked carboxylic acid functionality. The two diastereomers utilized for the electrochemical reaction were transformed with excellent stereocontrol via the transition state **34** to the desired products **31**, while **32** was formed from an analogous epimeric transition state. Finally, the natural product **33** was obtained from **31** in three more steps realizing the synthesis of (+)-nemorensic acid in only 11 steps, with the electrochemical conversion as key transformation.

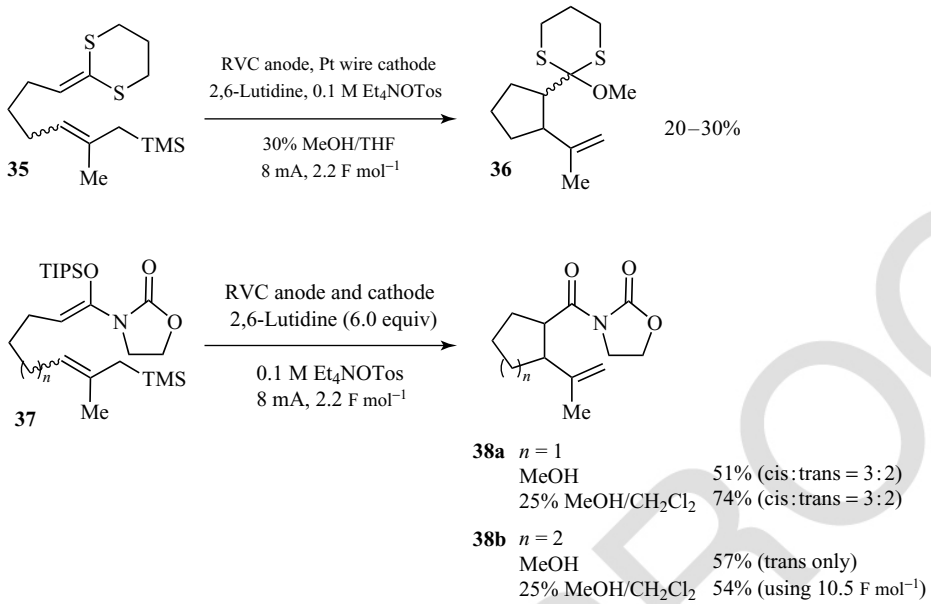
Another interesting application concerning ketene N,O-acetals was the anodic oxidation reaction observed when an intramolecular allyl trimethylsilane subunit was utilized as the radical acceptor.[26] A comparison of different cyclization precursors led to the conclusion that the presence of a single additional methyl substituent such as in the starting material **35** decreased the yield dramatically compared to the pure allylic system so that only 20–30% of **36** could be obtained (Scheme 12). When ketene N,O-acetals such as **37** were applied, good yields of up to 74% for the similar cyclization product **38a** were obtained as a nearly 1 : 1 mixture of diastereomers. The corresponding product **38b** was generated exclusively as the trans isomer in a lower yield of 57%.

Although the diastereoselectivity of this process is only moderate at best for products of type **38a**, the possibility for further optimization using (chiral) modification of the oxazolidinone substituents seems possible, opening the way to controlling the absolute stereochemistry of cyclization products of this type.

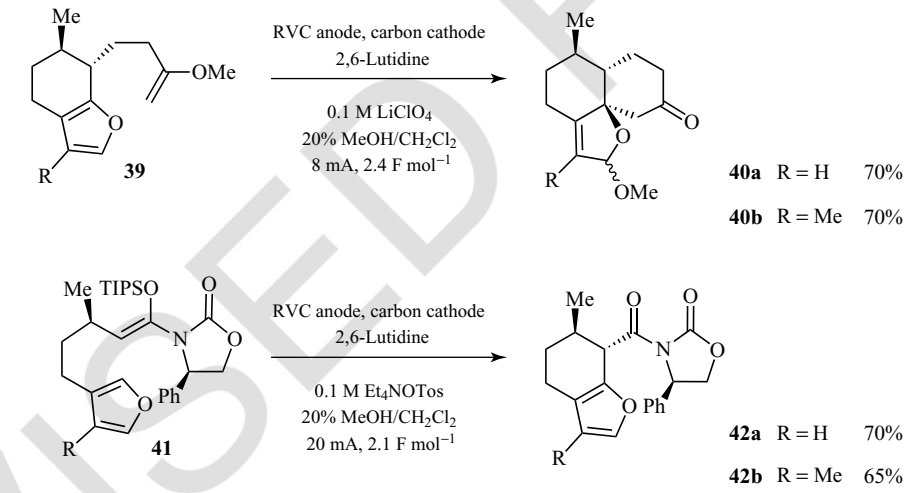
2.4 Oxidation of Electron-Rich Aromatic Rings

The electrochemical oxidation of electron-rich aromatic subunits can be used for the intramolecular cyclization of the intermediate radical cations. In particular, furan derivatives were utilized by Moeller and Wright for the synthesis of bicyclic and tricyclic derivatives.

In studies on the the usefulness of this method, furan derivatives were investigated that were



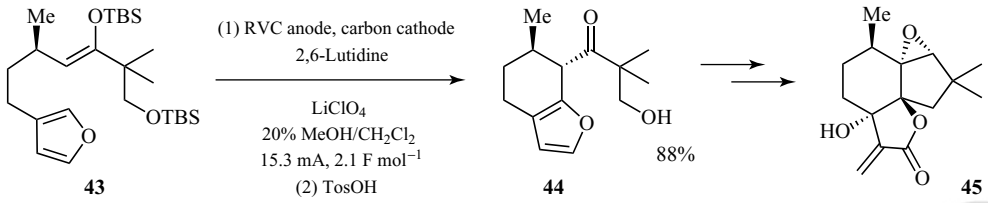
Scheme 12 Comparison between cyclizations of ketene dithio-acetal or ketene N,O-acetals in electrochemically initiated cyclizations.



Scheme 13 Electrochemically initiated cyclization of enol ether-bearing furan derivatives.

functionalized with enol ethers such as **39** as well as ketene N,O-acetals such as **41** to optimize the cyclization process (Scheme 13).[27,28] Both enol ether functional groups are well suited to act as the radical acceptor, and the radical cation generated by the electrochemical oxidation of the furan subunit initiates the cyclization. The tricyclic derivatives **40a** and **40b**, as well as the bicyclic product **42**, are generated in good yields as single isomers.

The synthesis of the tricyclic product **40** generated by the anodic oxidation of **39** at low current densities is a promising example of a transformation toward the synthesis of complex molecules. These selected examples illustrate that the electrochemical oxidation of electron-rich aromatic rings under controlled conditions utilizing low current densities (<20 mA) is a well-suited method to initiate such reactions.



Scheme 14 Electrochemically initiated cyclization of enol ether-bearing furan derivatives for the synthesis of (−)-alliacol A.

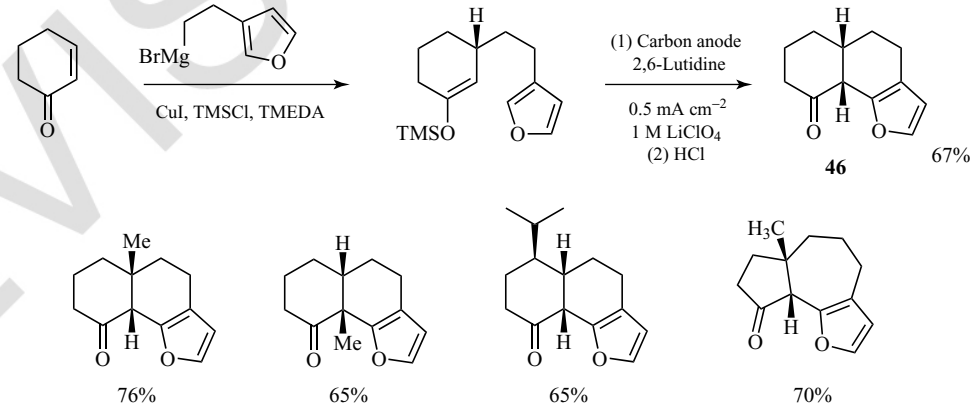
The application of the anodic oxidation of enol ethers as the key step in natural products synthesis was exemplified in the synthesis of linalool[29] and (−)-alliacol A (**45**).[30,31] For the synthesis of (−)-alliacol A, the electrochemical oxidation of the intermediate **43** (Scheme 14) was used for the formation of the six-membered ring in **44** found in the natural products. The product **44** was isolated in an excellent yield of 88% over two steps and, after a number of further steps, (−)-alliacol A **45** was obtained.

This application also illustrates that electrochemical methods are well suited for activating functional groups based only on their lowest oxidation potential once current-controlled methodologies are applied. Other functional groups are not affected, as the higher redox potentials required are not reached. Once the chemoselective activation of the furan has been realized, the intramolecular cyclization is the major reaction pathway to form the desired products.

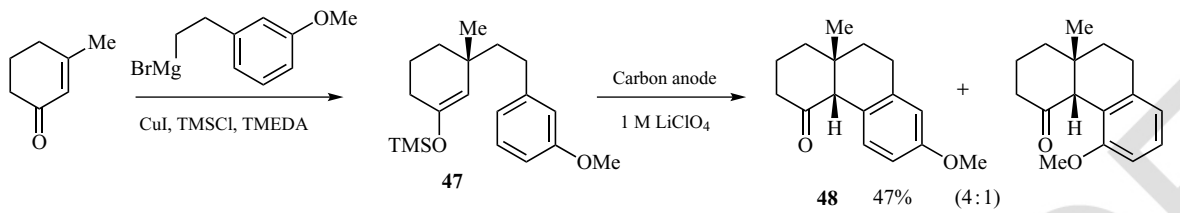
The Wright group also applied furan derivatives for the synthesis of tricyclic products utilizing silyl enol ethers as radical acceptor functionalities. The two-step process consists of a copper-initiated 1,4-addition of a suitable Grignard reagent onto an α,β-unsaturated ketone (Scheme 15), followed by electrochemical cyclization and acidic workup to generate tricyclic products such as **46**.[32] For this sequence, good yields of the desired products were also obtained when quarternary centers were formed and the ring size was altered depending on the α,β-unsaturated ketone or the Grignard reagent utilized, as shown in the additional examples.

Mechanistic studies revealed that the electrochemical transformation leads to the formation of the radical cation intermediate from the silyl enol ether functionality based on the lower redox potential of this group ($E_{1/2} = \sim 0.85$ V) compared to the furan ring system ($E_{1/2} = \sim 1.31$ V).

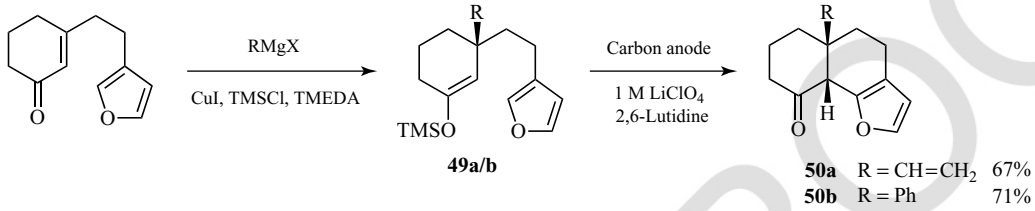
Interestingly, Wright also extended the application of the electrochemical generation of radical cations with the use of anisole-type starting materials. In a key investigation, **47** was generated as before by a copper-catalyzed 1,4-addition and then converted to product **48** by electrochemical oxidation in methanol (Scheme 16).[33]



Scheme 15 Electrochemically initiated cyclization of enol ether-bearing furan derivatives for the synthesis of tricyclic products.



Scheme 16 Electrochemically initiated cyclization of enol ether-bearing anisole derivatives for the synthesis of tricyclic products.



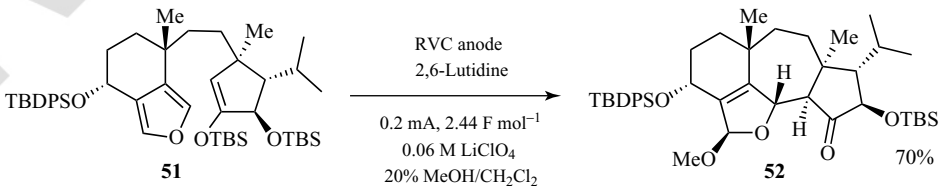
Scheme 17 Cyclization of enol ether-bearing furan derivatives for the synthesis of tricyclic products containing functionalized quarternary centers.

Also, more complex quarternary-carbon-bearing derivatives such as **50a/b** were obtained when the copper-catalyzed 1,4-addition was performed with furan derivatives such as **49a/b** (Scheme 17). The electrochemical generation of the radical cation led to the desired product of type **50** in good yield.

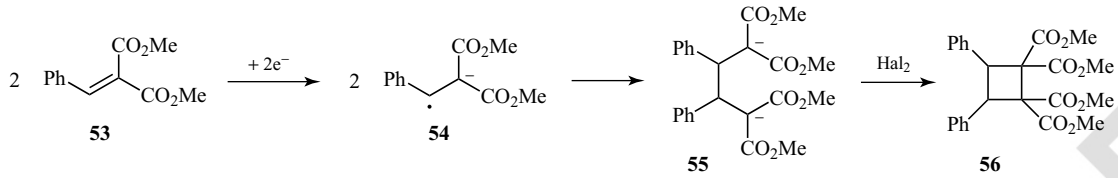
An application of this method on a somewhat more sophisticated level of molecular complexity was reported by Trauner for the assembly of the carbocyclic skeleton of the guanacastepenes.[34] The polyfunctionalized starting material **51** was utilized for the electrochemical key step of the reaction sequence to afford the desired intramolecular carbon–carbon bond formation (Scheme 18). The product **52** was isolated in 70% yield via a diastereoselective cyclization and an approach toward the natural product class of tetracyclic guanacastepene derivatives could be realized.

2.5 Synthesis of Four-Membered Rings

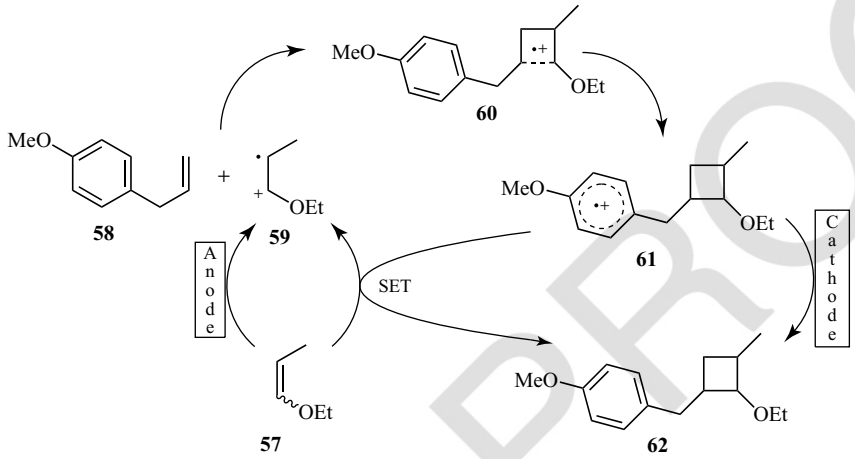
The electrochemically initiated formation of four-membered ring systems starting from alkylidenmalonates can be realized in an undivided cell in terms of a paired electrolysis where processes at both electrodes are used for the generation of the product.[35] In these reactions, the cathodic reduction of the alkylidenmalonate **53** generates the radical anion intermediates **54**, which undergo radical dimerization to form the dianion intermediate **55** (Scheme 19). From here, several reaction pathways are accessible, resulting in a mixture of the products formed. Nevertheless, when the electrolysis is performed in an undivided cell with sodium bromide or sodium iodide as the supporting electrolyte, anodic oxidation of the halide generates the corresponding Hal_2, which reacts with the dianion leading to the formation of the cyclobutane derivatives of type **56**.



Scheme 18 Electrochemical transformation as key step in the synthesis of the guanacastepenes skeleton.



Scheme 19 Cyclobutane synthesis via a paired electrolysis of Knoevenagel adducts.



Scheme 20 Mechanism of the electrocatalytic intermolecular cyclobutane formation.

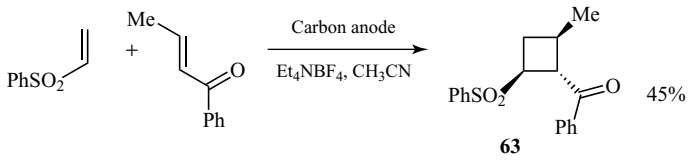
On the other hand, the formation of four-membered ring systems by electrochemical oxidation of electron-rich enol ethers was realized by Chiba in an intermolecular cross-cyclization using two different starting materials.[36] The enol ether **57** is electrochemically oxidized on the basis of the less positive redox potential compared to the allyl benzene derivative **58** (Scheme 20). The umpolung of the reactivity of the enol ether radical cation **59** allows the reaction with the allyl benzene derivative to proceed in a regioselective fashion leading to intermediate **60**. This intermediate reacts as an oxidizing agent on the aromatic substituent to form the more stable radical cation **61** for the formation of the four-membered ring system. The back-electron transfer leading to the final product **62** takes place either on the cathode in an undivided cell or in homogeneous solution utilizing the enol ether starting material **57** as electron donor. Thereby, an electrocatalytic process can be realized in which the process is not stoichiometric in the current passed through the solution so that only a catalytic amount of electricity is sufficient to achieve complete conversion of the starting materials under ideal circumstances.

Similar processes have been utilized in the past for the formation of four-membered ring systems with phenyl vinyl sulfones as starting materials in terms of a homo-cyclization.[37,38] Recently, Felton described the cross-cyclization of phenyl vinyl sulfone in the presence of α,β-unsaturated ketones for the regio- and diastereselective formation of cyclobutane derivatives such as **63** in moderate yields of up to 45% along with a number of side products (Scheme 21).[39]

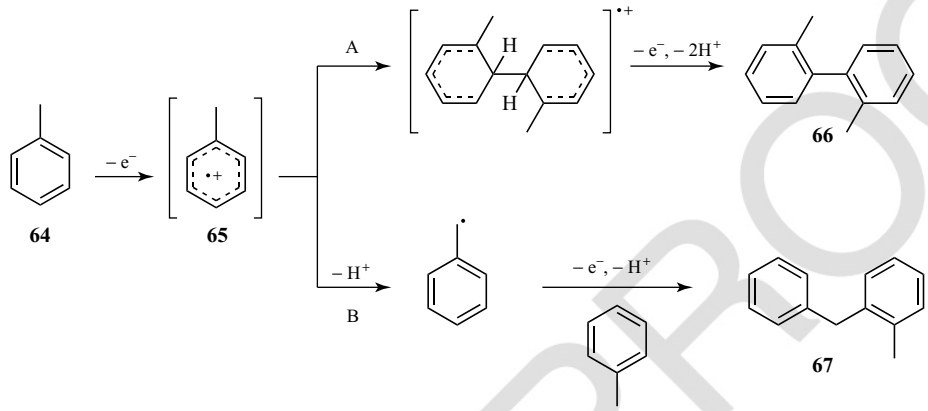
Nevertheless, in combination with a suitable second starting material, similar inter- and intramolecular cyclization reactions initiated by electrochemical oxidation of double bonds seem to be worth investigating in the future.

2.6 Synthesis of Biarylcompounds

Anodically generated radical cations of alkyl-substituted arenes such as **64** can follow two different reaction pathways.[40] Biaryl **66** is formed



Scheme 21 Intermolecular formation of a polyfunctionalized cyclobutane derivative.



Scheme 22 Reaction pathways of the anodically generated radical cation derived from alkylbenzenes.

when the radical cation **65** reacts with the starting compound (Scheme 22, path **A**), whereas deprotonation leads to a benzyl radical which undergoes an electrophilic aromatic substitution after being reoxidized to the cation generating a diphenylmethane compound **67** (path **B**). A major factor influencing this selectivity is the choice of solvent since, in nucleophilic solvents, the biaryl is generated as the main product, whereas the electrolysis in nonnucleophilic and therefore less basic solvents leads to the side-chain reaction forming diphenylmethanes of type **67**. The latter conversion is synthetically more valuable and therefore applied in industrial processes. Additional by-products, quinone-derivatives for example, can occur depending on the reaction medium. Therefore, the anodic coupling of alkyl-substituted benzenes is not the effective method for the synthesis of biaryl compounds compared to the well-established transition-metal-mediated coupling reactions.

Works of Nyberg[41–43] in the early 1970s showed that the homo-coupling products of alkyl-substituted benzenes such as **68** and **69** can be obtained in moderate to good yields using carbon or platinum electrodes and a tetrafluoroborate as the supporting

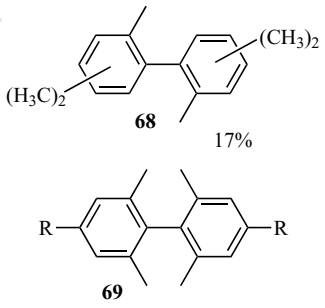
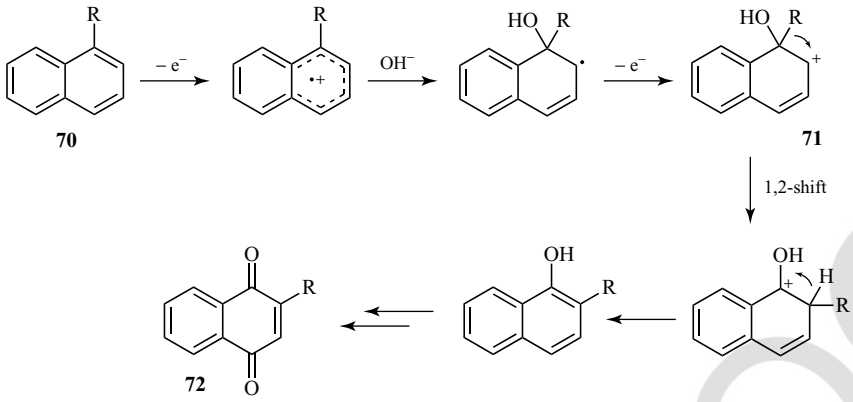


Figure 1 Biaryls formed via anodic oxidation according to the procedure of Nyberg.

electrolyte (Figure 1). The solvents utilized for these conversions are acetonitrile or nitromethane.

The electrolysis of naphthalene and alkylnaphthalenes such as **70** in acetone–water leads to binaphthyls under similar conditions when the substrates are not substituted in 1-position; otherwise, the respective naphthoquinone **72** is formed via further oxidation of the radical intermediate to the cation **71** and a 1,2-shift of the alkyl-substituent in 1-position (Scheme 23).[44,45]



Scheme 23 Formation of naphthoquinones after electrolysis of 1-alkyl-substituted naphthalenes.

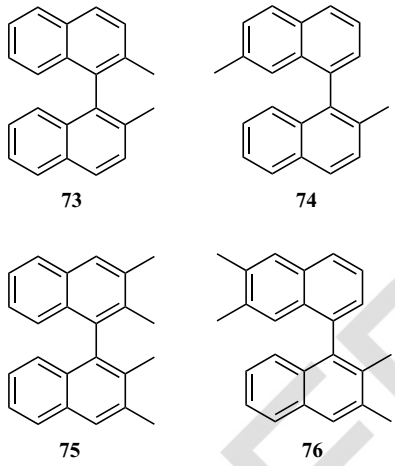
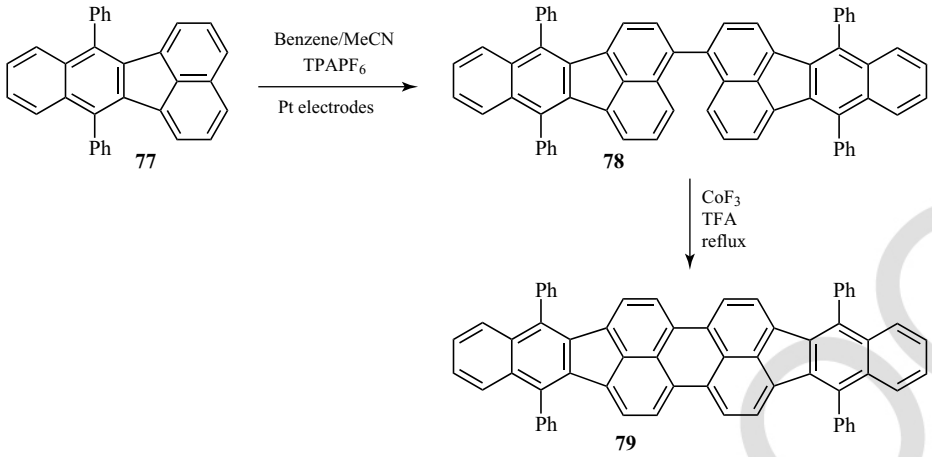


Figure 2 Structures determined by NMR of the isolated binaphthyls (no yield given).

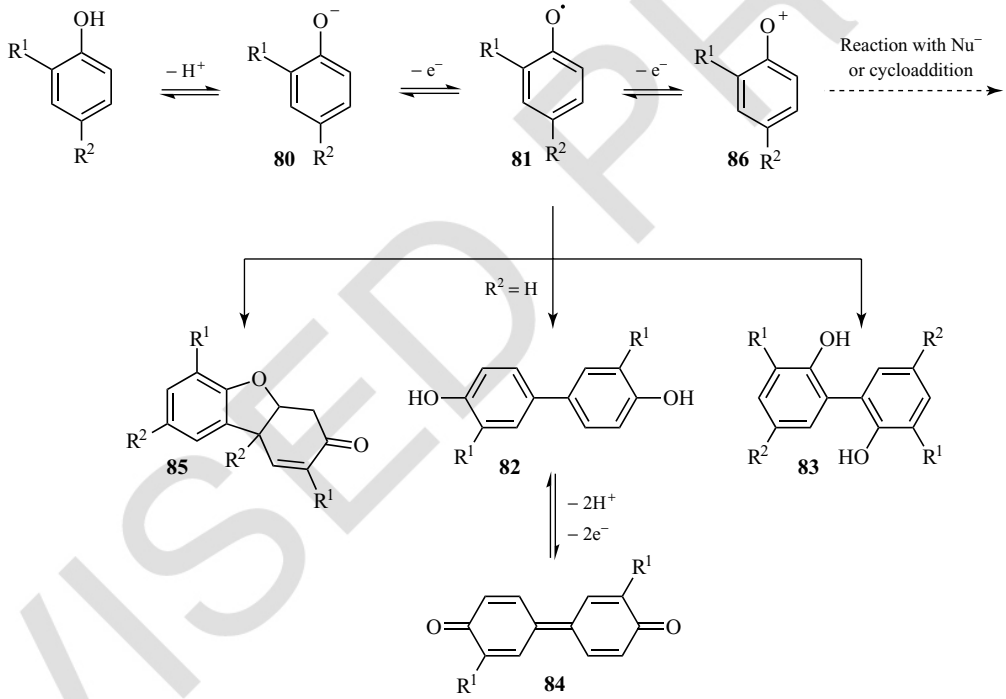
The conversion of 2-methylnaphthalene leads to four regioisomers of the binaphthyl, which were isolated in a 20 : 10 : 1.5 : 1 ratio as detected by gas chromatography-mass spectrometry (GC-MS). The structures of the two major isomers **73/74** and **75/76** obtained from the conversions of 2-methylnaphthalene and 2,3-dimethylnaphthalene were resolved using nuclear magnetic resonance (NMR) techniques (Figure 2). Since a preparative separation of the other isomers was not possible, their probable structures were derived from molecular orbital calculations whereby the most reactive positions of the substrate were determined.

The bulk electrolysis of fluoranthene **77** toward the perylene derivative **78** was accomplished by Bard[46] to investigate the electrochemical properties and chemoluminescence of the radical cation generated from **77**. The process affords the formation of two carbon–carbon bonds of which the first one is intermolecular and the second one intramolecular. It was observed by means of cyclovoltammetry that the intramolecular bond formation is reversible and occurs very slowly; therefore, the direct synthesis of the perylene **79** was not performed electrochemically in preparative scales. The biaryl compound **78** was obtained in 24% yield and the second bond formation is afforded by a chemical oxidation agent (Scheme 24).

Phenol and its derivatives represent appropriate substrates for electrochemical conversions because of the electron-donating and therefore radical-stabilizing nature of the hydroxyl substituent. The anodic coupling is mostly carried out under basic conditions to obtain phenolate **80** as an intermediate, which is then oxidized to the phenoxy radical **81** (Scheme 25).[40] Common bases for this purpose are alkali hydroxides, Et_4NOH, or 2,6-lutidine. The phenoxy radicals form dimers either by carbon–carbon or carbon–oxygen bond formation leading to a variety of isomers when the substrate is an unsubstituted phenol. The main isomer is normally the para–para product **82**; but when this position is blocked by a substituent, the coupling reaction takes place at the ortho position to form product **83** (Scheme 25).[40] Under convenient conditions, further oxidation to a diphenoquinone species **84** takes place; therefore the desired biaryl compound **82** must be regenerated via a subsequent reduction step.



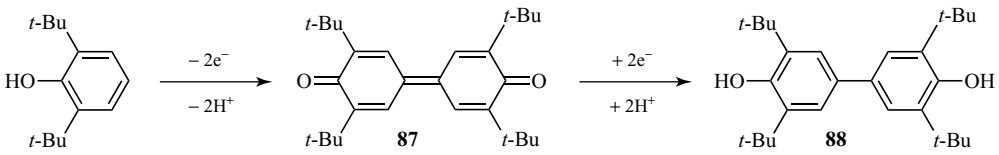
Scheme 24 Synthesis of a perylene derivative by electrolysis and chemical oxidation of fluoranthene.



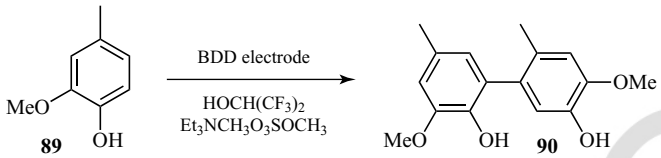
Scheme 25 Reaction pathways of the phenoxy radical.

The ortho–para coupling is followed by an intramolecular Michael addition, generating the Pummerer ketone **85**. When the radical recombination toward the coupling products is slow, the phenoxy radical is further oxidized to the cation **86**, which can react with a nucleophile or form cycloaddition products.

The selectivity between carbon–carbon and carbon–oxygen coupling of the phenoxy radical is determined by the steric and electronic properties of the substituents.[5] Investigation of the oxidation of phenols by Nonhebel[47] suggests that the minimization of repulsion between the oxygen atoms of the combining radicals plays an important role



Scheme 26 Anodic oxidation of 2,6-di-*tert*-butylphenol.



Scheme 27 Anodic homo-coupling of 4-methylguaiacol.

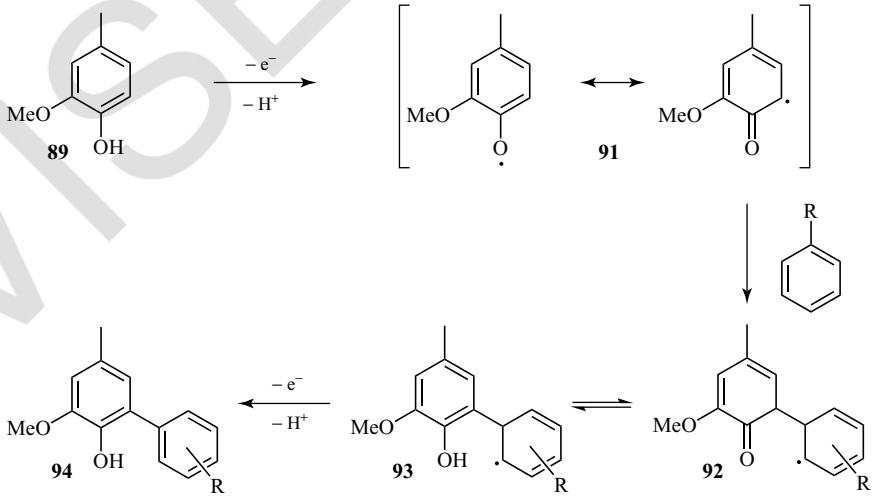
for the regioselectivity. When this minimization is not possible because of bulky substituents, the carbon–oxygen coupling represents the favored pathway.

The homo-coupling of 2,6-di-*tert*-butylphenol with $LiClO_4$ as electrolyte in MeOH in an undivided cell (Scheme 26) was investigated by Schäfer[48] and Torii *et al*.[49] and led to diphenoquinone **87** as the major product.

For the synthesis of the desired biphenol **88** in excellent yields, the electrolysis was performed via subsequent reduction of the initially formed diphenoquinone **87** by changing the current direction in a divided cell. Another solution is a paired electrolysis consisting of the oxidation of the starting material in the anode cell and the simultaneous reduction of the generated diphenoquinone in the cathode cell.

An unusual anodic coupling of a substituted phenol was found by Waldvogel: oxidation of 4-methylguaiacol (**89**) employing boron-doped diamond (BDD) electrodes led to the ortho–meta coupled product **90** instead of the expected ortho coupling (Scheme 27).[50]

The electrolysis was performed in hexafluoroisopropanol whose specific role has not yet been established, but in the absence of hexafluoroisopropanol the conversion does not proceed. However, the fluorinated alcohol is capable of stabilizing radicals because of its nonnucleophilic and protic nature. The reaction requires no additional base, and



Scheme 28 Mechanism of the anodic cross-coupling.

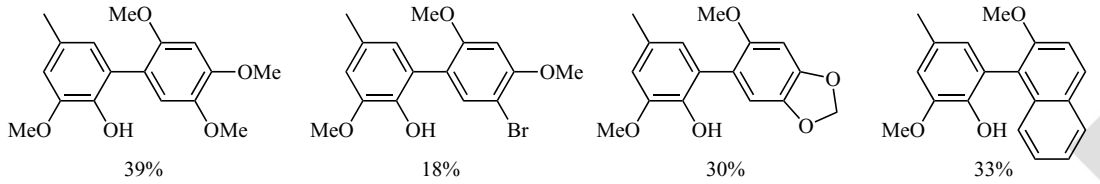
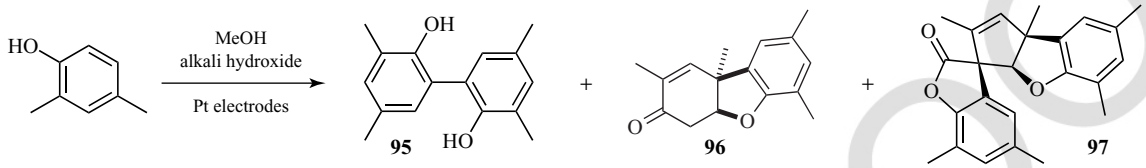


Figure 3 Hetero-coupling products of 4-methylguaiacol and arylethers.



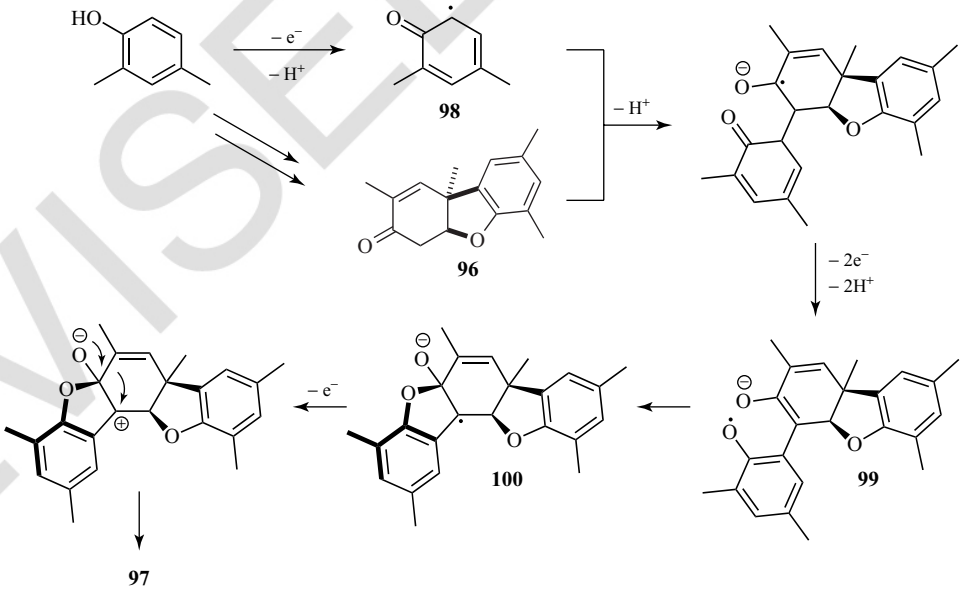
Scheme 29 Products of the anodic oxidation of 4,6-dimethylphenol.

generates no phenolate prior to the electron transfer at the anode. After this oxidation of **89**, the acidity of the phenol species is increased; thus deprotonation occurs immediately to the radical **91** (Scheme 28).

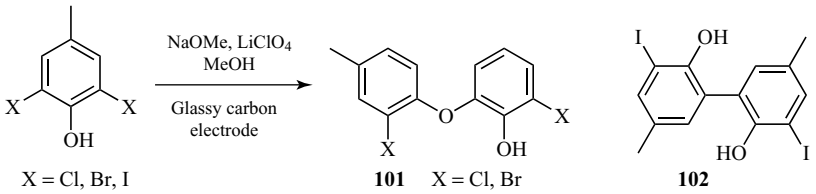
The following electrophilic attack takes place at the most electron-rich position of the coupling partner to form **92**. Tautomerization to **93** and a further oxidation step afford the desired product such as **94**. The reaction can also be performed as a cross-coupling of phenol **89** with several arylethers in moderate yields (Figure 3).

When 4,6-dimethylphenol was exposed to anodic oxidation by Waldvogel, the pentacyclic spirolactone **97** was generated as a single diastereomer alongside the biaryl coupling product **95** and the Pummerer ketone **96** (Scheme 29).[51] The spirolactone **97** represents a trimer of the starting material formed via three dehydrodimerization steps.

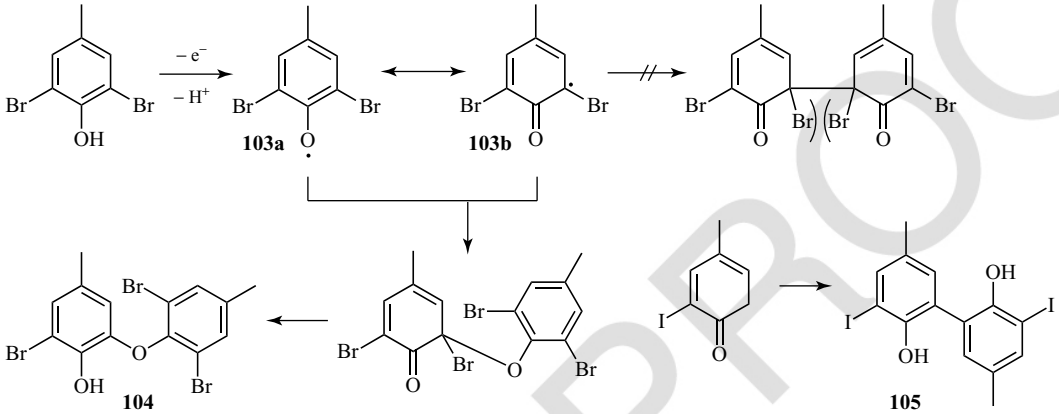
As the reaction is performed in basic media, the formation of **97** begins with an electrophilic attack of the phenoxy radical **98** on the enolate of the Pummerer ketone **96** (Scheme 30). Further oxidation



Scheme 30 Proposed mechanism of spirolactone formation.



Scheme 31 Electrolysis of 2,6-dihalogenated phenols.



Scheme 32 Mechanism of the anodic coupling of 2,6-dihalogenated phenols.

generates the radical anion **99**, which undergoes cyclization to intermediate **100**. Another SET is followed by a Meerwein rearrangement, leading to spirolactone **97**.

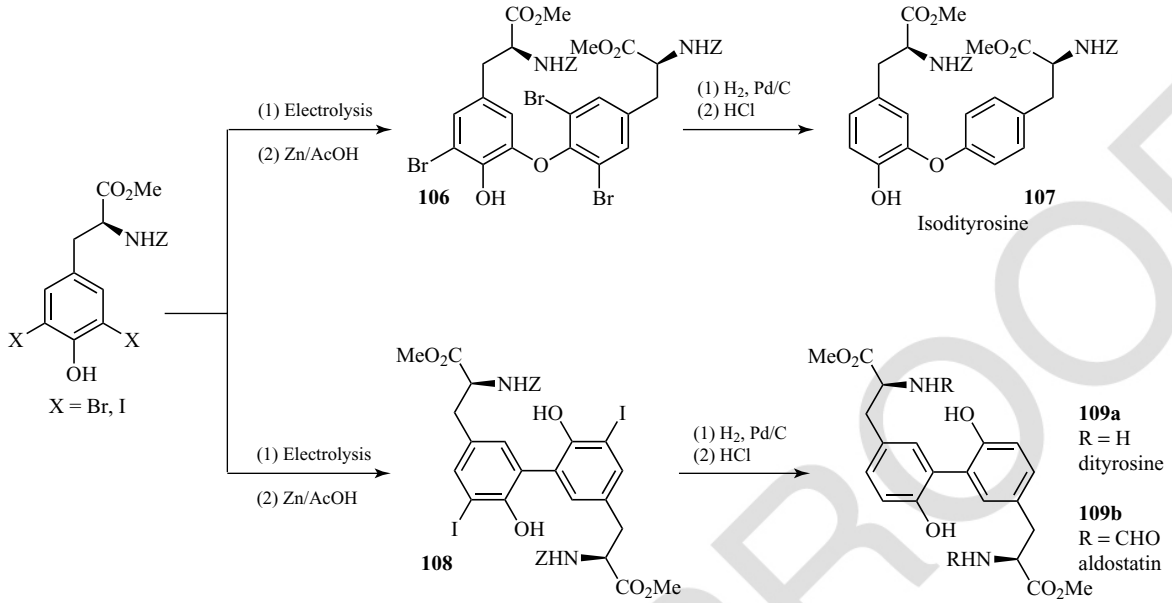
The anodic oxidation of ortho–ortho′ dihalogenated phenols accomplished by Nishiyama[52] generates the ortho-substituted diarylether (**101**) or the biaryl compound (**102**) depending on the halogen substituent (Scheme 31). While the biaryls are obtained from diiodophenols, the analog chlorine and bromine compounds provide the diarylethers, which represent the building blocks for the isodityrosine class natural products. In case of monohalogenated phenols, the reaction leads to the same products, but the selectivity is independent of the type of halogen atoms. The steric demand of the adjacent substituents is the only factor of consequence.[53]

The oxidation of the dihalogenated phenol initially leads to a phenoxy radical with the unpaired electron localized either at the oxygen atom (**103a**) or one of the halogen-substituted carbons (**103b**) (Scheme 32). According to density functional theory (DFT) studies, the oxygen-localized radical resonance structure is always preferred, but the preference is, in agreement with the experimental results, higher for the dichloro and dibromo system than for the diiodo system.[52]

A homo-coupling of the bromine-substituted carbon-localized radical **103b** is in any case improbable because of the repulsion of the bromine atoms; therefore, the carbon–oxygen coupling pathway toward the diarylether **104** is favored. In the case of iodine, the biaryl product **105** is formed after cleavage of one halogen substituent via a nonradical mechanism.

Starting from halogenated L-tyrosine derivatives, the diarylether coupling product of the dibromo derivative **106** was obtained in 45% yield and could be converted into isodityrosine (**107**) in two steps (Scheme 33).[54,55] By changing the halogen substituents to iodine, the same anodic oxidation created the biaryl compound **108** in 28% yield, a precursor of dityrosine **109a**, and its *N*-formylated derivative aldostatin **109b** which is an aldose reductase inhibitor.[52]

The electrooxidative coupling of arylethers to biaryl compounds such as **111** occurs in combination of two radical cations and is more selective than the coupling of the corresponding



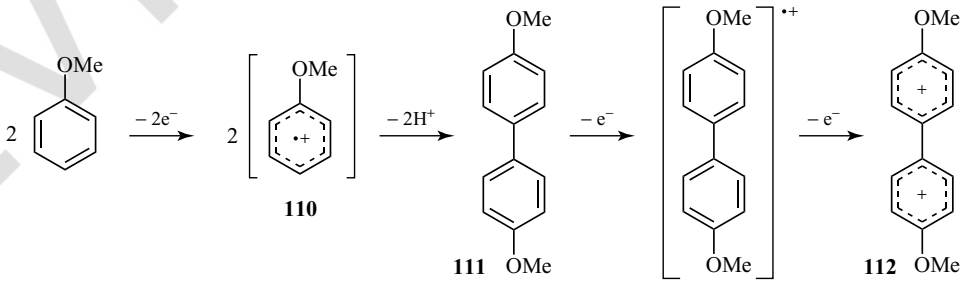
Scheme 33 Application of the coupling of 2,6-dihalogenated phenols for the syntheses of dityrosine-class natural products.

phenols because of the protected hydroxyl functionality which makes the side reaction toward diarylethers impossible (Scheme 34). Furthermore, the ortho coupling and quinone by-products are less readily formed. However, the initially formed radical cations **110** are highly sensitive to the attack of nucleophiles present in the reaction medium; hence water-free conditions are required. The conversions are usually performed in dichloromethane (DCM) or acetonitrile in combination with trifluoroacetic acid (TFA) to lower the nucleophilicity. The over-oxidized dicationic biaryl species **112** is more stable under acid conditions, thus avoiding further reactions to unwanted by-products.

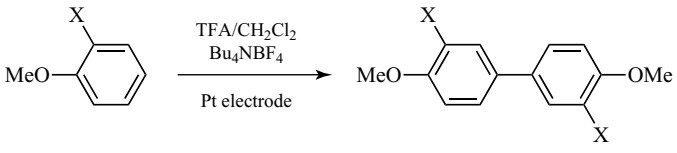
A frequently used electrolyte is Bu_4NBF_4 as in the synthesis of biaryls such as **113a** starting from 1,2-dimethoxybenzene by Parker (Scheme 35). The respective coupling of *ortho*-bromanisole to **113b** was accomplished under the same conditions.[56]

A methoxy-substituted triphenylene derivative **114** was obtained in 60% yield by mixed electrolysis of anisole and veratrol (Scheme 36).[57]

Functionalized triphenylene cores, which represent receptors for the binding of alkylated oxopurines[58] such as caffeine, were synthesized by Waldvogel under similar conditions (Scheme 37).[59] The coupling of chiral spiroketals derived from catechol affords two diastereomers of the triphenylene

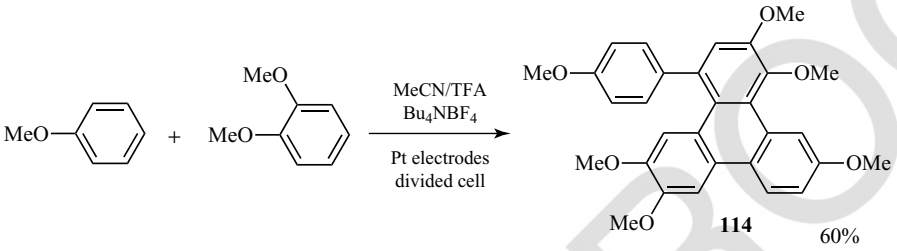


Scheme 34 Biaryl synthesis via anodic coupling of arylethers.



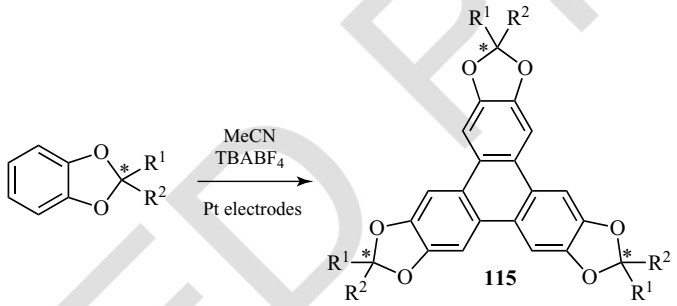
113a X = OMe 86%
113b X = Br 43%

Scheme 35 Conversion of arylethers.



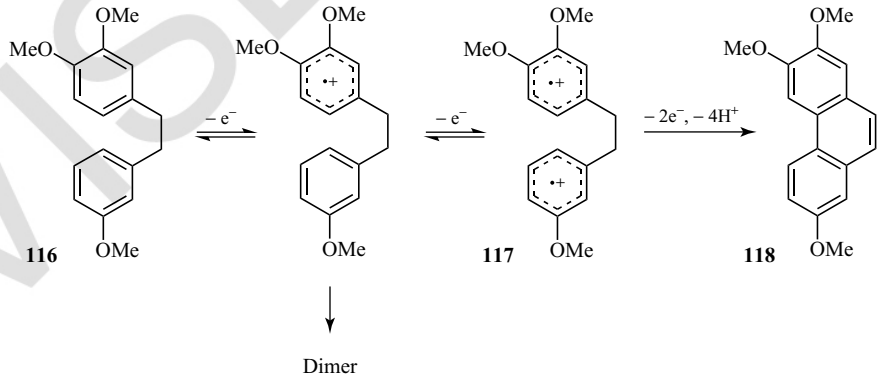
114 60%

Scheme 36 Synthesis of a triphenylene core by electrolysis of anisole and veratrol.

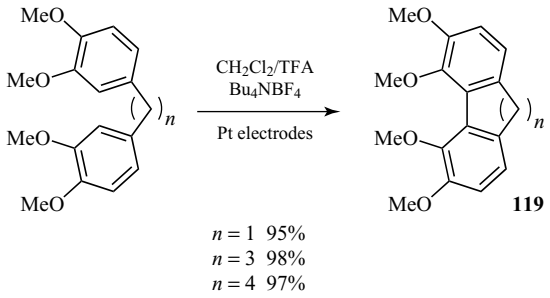


115

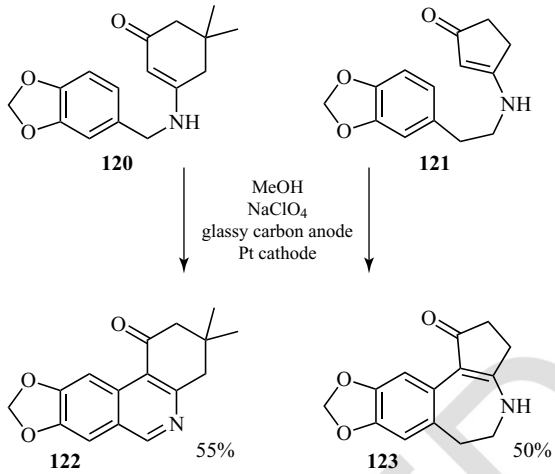
Scheme 37 Coupling of chiral spiroketals toward functionalized triphenylene cores.



Scheme 38 Formation of a methoxylated phenanthrene.



Scheme 39 Intramolecular coupling of methoxylated diphenylalkanes.



Scheme 40 Synthesis of isoquinolines and benzazepines.

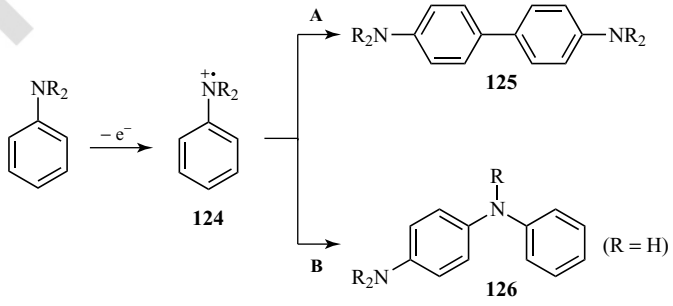
product **115**. These electron-rich donors are able to host electron-deficient guest molecules showing C_3 symmetry.[60] An intramolecular electrochemical coupling reaction for the synthesis of alkyl-bridged biphenyls of type **116** was accomplished by Parker (Scheme 38).[61–63] The formation of a diradical species **117** is necessary for this conversion to proceed toward the intramolecular product **118**; otherwise, the dimer of the substrate will be formed.

The six-membered ring resulting from the diphenylethane **116** is further oxidized to the corresponding phenanthrene **118** at higher potentials (Scheme 38).[61] Under typical conditions, five-, seven-, and eight-membered rings (**119**) derived from methoxylated diphenylalkenes were obtained in excellent yields (Scheme 39).

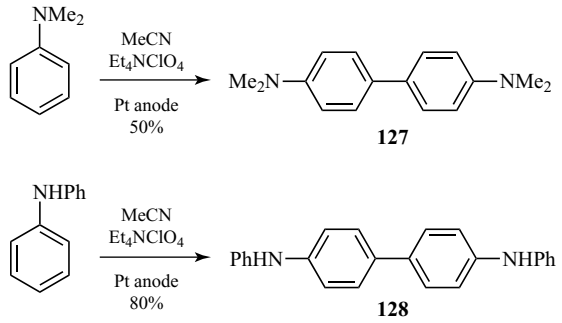
Isoquinolines and benzazepines of types **122** and **123** were obtained via intramolecular cyclization at the anode by Schäfer (Scheme 40).[64] The conversion of the alkyl-linked aryl enaminones **120/121** was performed in MeOH with $NaClO_4$ as the supporting electrolyte. The products **122/123** could be isolated in good yields and represent building blocks in the syntheses of alkaloid natural products.

The electrochemical reaction of arylamines toward biaryl compounds of type **125** proceeds in analogy to the conversion of arylethers starting with the generation of a radical cation **124** (Scheme 41). The synthesis of the benzidines **125** resulting from carbon–carbon coupling (path **A**) is accompanied by the formation of diphenylamines **126** (path **B**) when utilizing primary or secondary arylamines.

The selectivity strongly depends on steric factors since the biaryl product of type **125** is favored in the presence of bulky alkyl substituents R, but the product ratio is also determined by substrate concentration, current density, and pH of the solution.[65] In dilute solutions at high current densities and low pH values, the benzidine compound is the major product, whereas the opposite conditions predominantly lead to the diphenylamine. The electrolysis is usually carried out in acetonitrile with Et_4NClO_4 as the supporting electrolyte.[40] Under these conditions, the



Scheme 41 Electrochemical conversion of dialkylanilines.



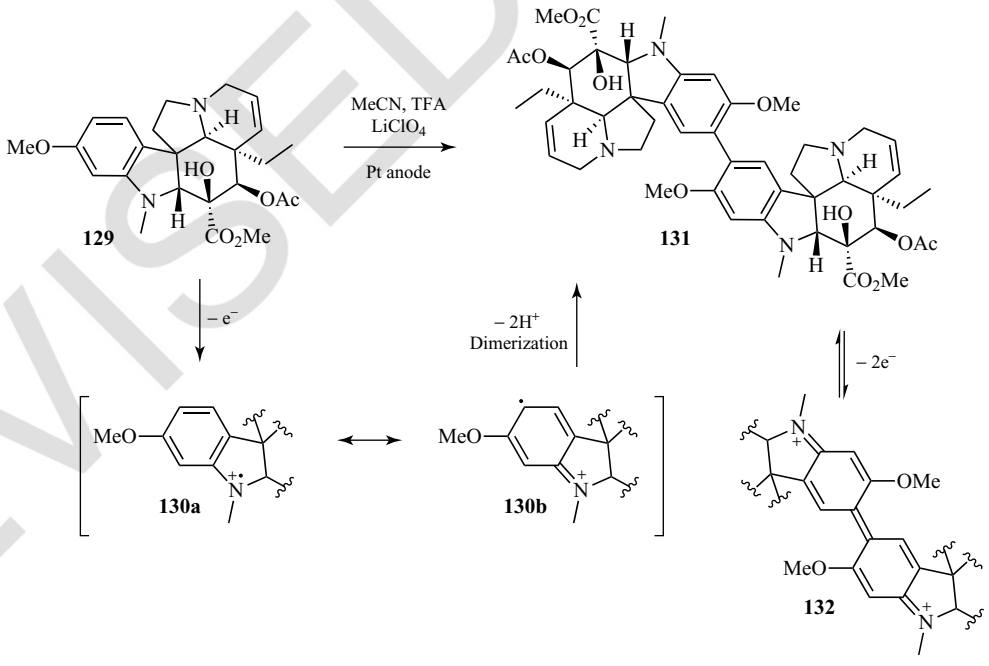
Scheme 42 Homo-coupling of aniline derivatives toward biaryl compounds.

homo-coupling of *N*,*N*-dimethylaniline was accomplished by Hand and Nelson[66] in moderate to good yields to produce **127**, while the respective coupling of diphenylamine yielding 80% of benzidine **128** was performed by Cauquis (Scheme 42).[67]

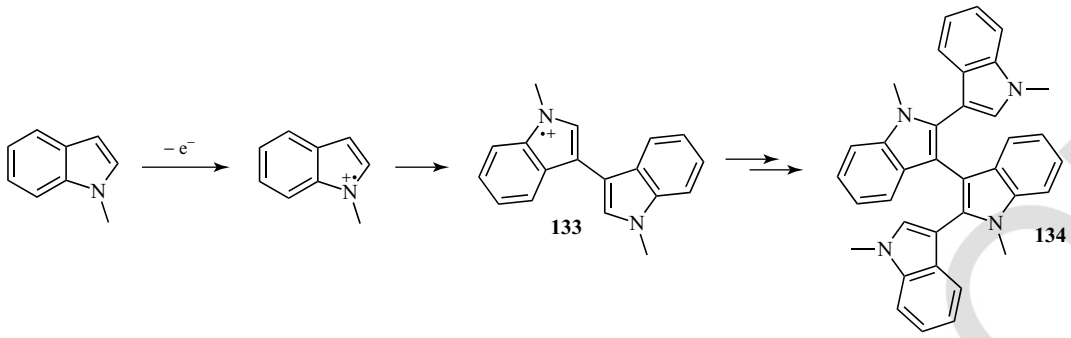
An oxidation–reduction sequence for the synthesis of 10,10′-bisvindoline (**131**) was presented by Tabakovic (Scheme 43).[68] The synthesis was carried out in a divided cell in MeCN with $LiClO_4$ and additional TFA in the anode cell, where at first the bis-indole alkaloid vindoline **129** was oxidized to the radical cation **130a/b**. This intermediate is stabilized by several resonance structures and dimerizes to the product **131**. On account of further oxidation to the dication **132**, changing the current direction after full conversion is required to obtain the desired product in 60% yield.

The application of unsubstituted indoles in anodic oxidation leads to polymers linked at 2 and 3 positions. Polyindoles represent electroconductive materials, which have evoked interest in the field of sensors. Investigations by Berlin *et al*.[69] have shown the initial formation of a 3,3′-coupled dimer **133** for the oxidation of 1-methylindole in acetonitrile. Further electrolysis generates the tetramer **134** (Scheme 44).

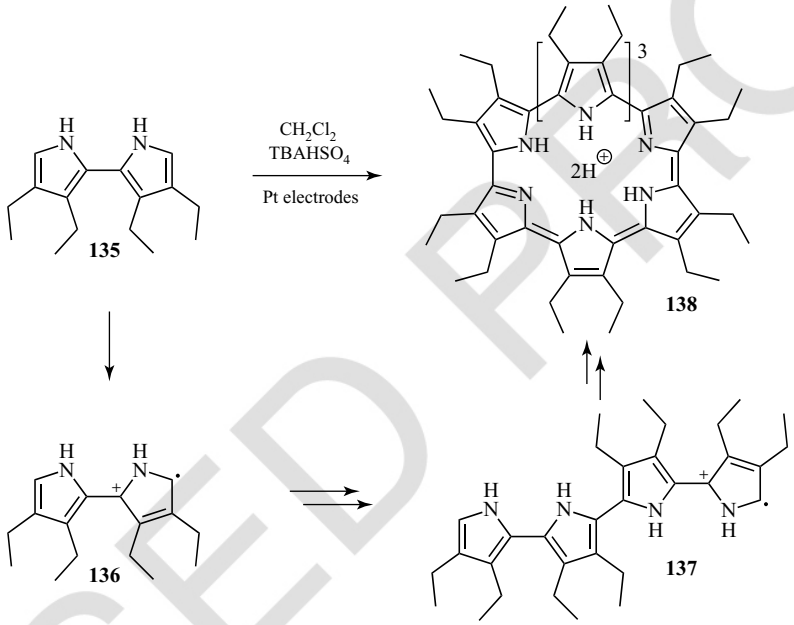
Sessler recently succeeded in synthesizing cyclo[8]pyrrole **138** electrochemically from tetraethyldipyrrole **135** (Scheme 45).[70] They found that the conversion strongly depends on the size of counter anion of the ammonium salt applied as the supporting electrolyte. The yield ranges from 0% with tetrabutylammoniumfluoride (TBAF) and almost 70% with tetrabutylammoniumdihydrogensulfate ($TBAHSO_4$). This is explained by templating effects of the anion during the polypyrrole formation, which leads to stabilization of the



Scheme 43 Dimerization of vindoline.



Scheme 44 Electrochemical generation of an indole tetramer.



Scheme 45 Synthesis of cyclo[8]pyrrole.

linear intermediates such as **136** and **137**. However, when the anion is too basic, deprotonation might occur leading to side-product formation.

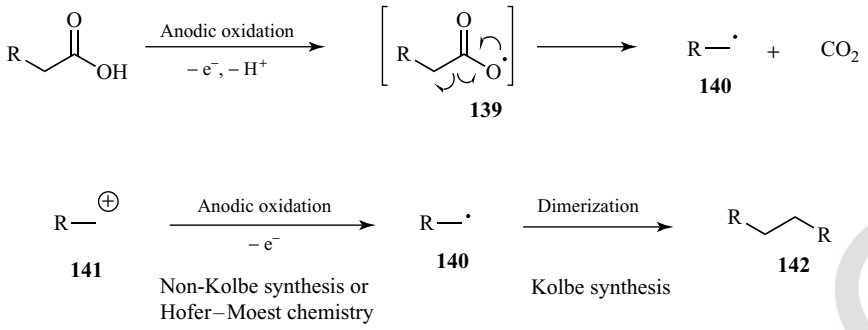
The conversion starts with the anodic generation of a radical cation (**136**), which undergoes dimerization to **137** after being deprotonated. Further oxidation and deprotonation leads to the tetramer and its cyclization to cyclo[8]pyrrole **138**.

2.7 Kolbe Electrolysis

The dimerization of two sp^3-carbon-centered radicals generated by electrochemical one-electron oxidation of the homologous carboxylic acid is generally known as *Kolbe synthesis* (Scheme 46).

The short-lived intermediate acyloxy radicals **139** rapidly decarboxylate, leading to aliphatic radicals of type **140**. If two free radicals combine, the desired Kolbe dimer is obtained. The most commonly encountered side reaction results from a second oxidation process, resulting in the formation of the corresponding carbocation **141**, which, being itself an unstable intermediate, generally reacts with any present nucleophile. This process is known as *non-Kolbe synthesis* or the *Hofer–Moest reaction*.

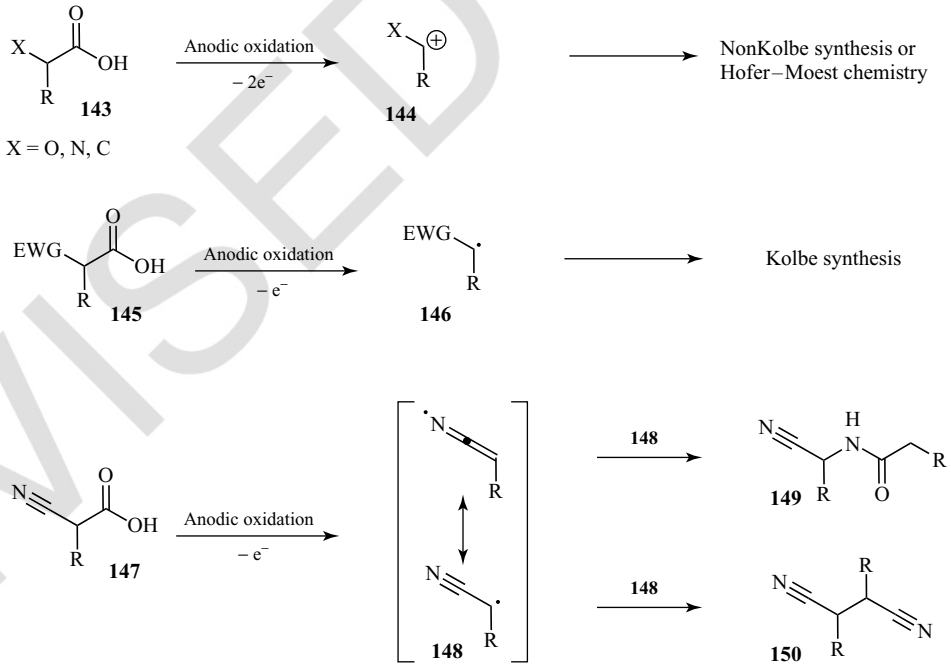
The conditions leading to the preference of Kolbe synthesis over Hofer–Moest chemistry are well



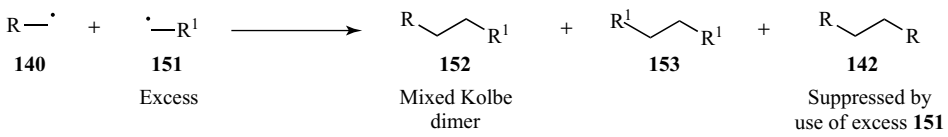
Scheme 46 Electrochemical generation of acyloxy radicals **139** with subsequent decarboxylation giving sp^3 carbon radicals **140** and their reactions.

understood: polar/protic solvents (mainly methanol), platinum anodic electrode, weakly acidic pH (easily achieved by the addition of up to 30 mol% of alkali alkoxides, thus regulating pH and generating the supporting electrolytes *in situ*), and high current densities are the conditions commonly used.

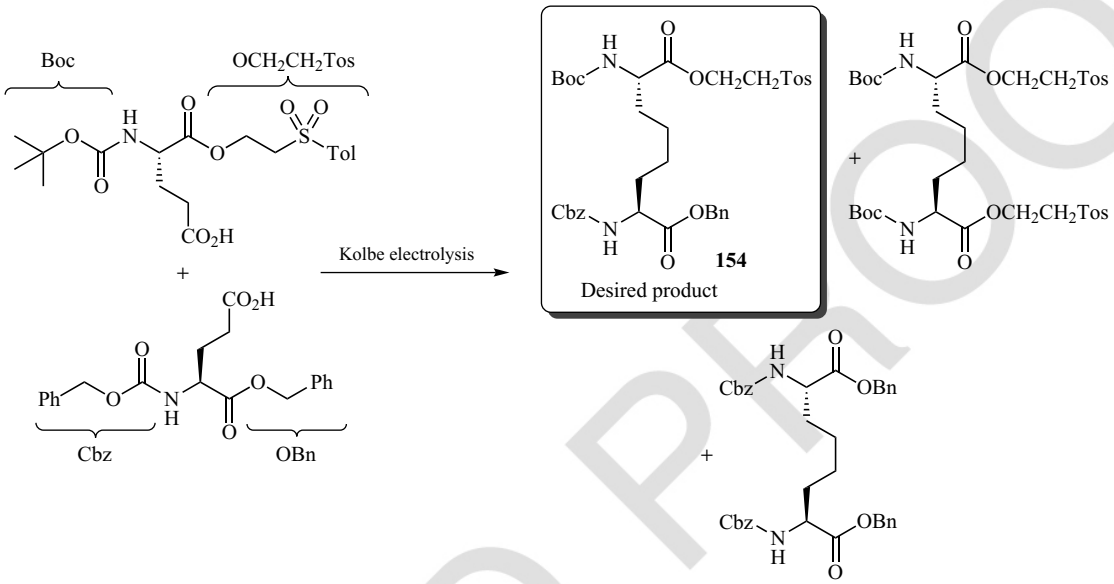
The success of the Kolbe dimerization depends strongly on the substrate applied. Substituents in α-position, which stabilize cations, lead to Hofer–Moest products via **144** (Scheme 47). As such, tertiary (and to a lesser extent secondary) carboxylic as well as α-hydroxy or α-amino acids are generally not convertible to the required radical species **140**. Electron-withdrawing substituents in the α-position, on the other hand, strongly favor the formation of radical species **146** and thus lead to the desired dimeric Kolbe products. Notable exceptions are α-nitrilo acids, which give radical **148** upon oxidation. Dimerization can proceed through both of the shown mesomeric forms, leading to a



Scheme 47 Effect of the substrate substitution pattern on the outcome of the electrolysis of carboxylic acids (EWG: electron-withdrawing group).



Scheme 48 Reaction of two different substrates under Kolbe conditions.



Scheme 49 Example of separable mixtures of dimers of orthogonally protected diaminodicarboxylic acids based on the applied protecting groups.

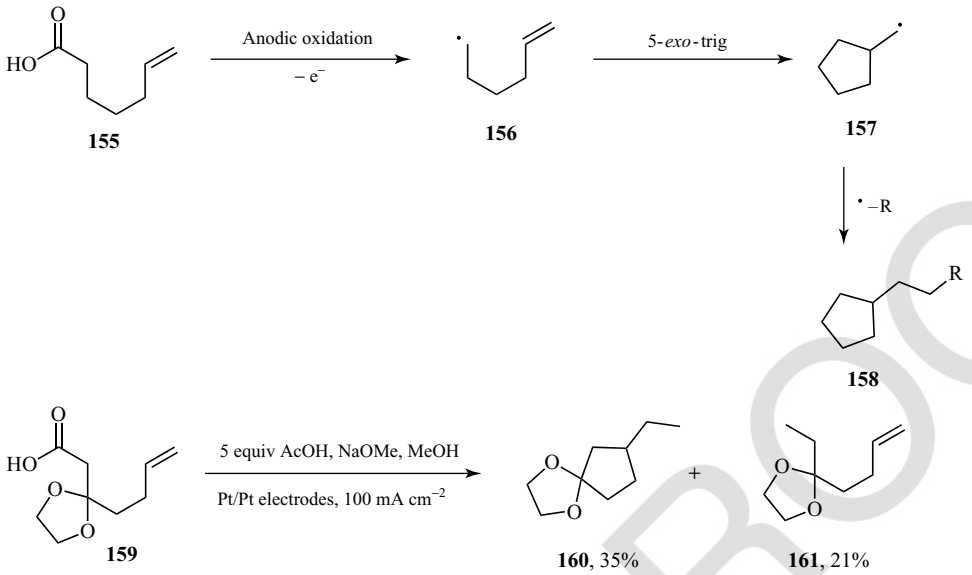
mixture of products **149** (Ritter-type reactivity) and **150**.

Yields for Kolbe dimerizations of substrates with hindering α-substituents are generally below 25–30%, although some new approaches offer the possibility of improvement (sono-emulsions for example).[71]

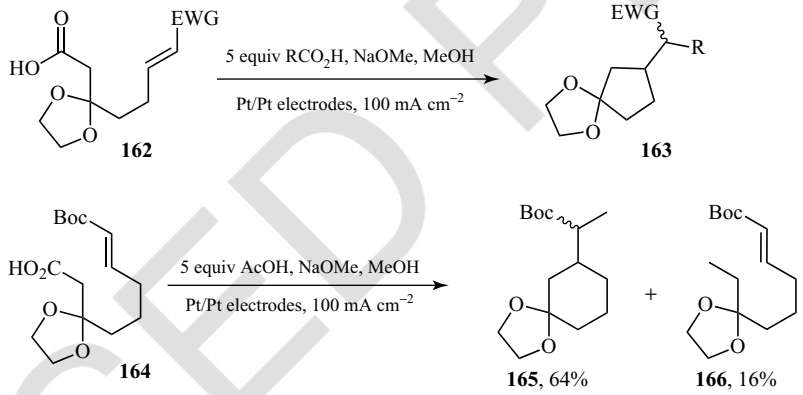
The rather indiscriminating reactivity pattern of the radical intermediates **140** and **151** leads to statistical mixtures of products (**152**, **153**, and **142**) when two different acids are applied (Scheme 48). Unless the acids in question are of greatly different polarity and/or molecular structure, separation of these mixtures is usually not readily attainable. However, when one of the acids (usually the less expensive one) is used in excess, the formation of one of the symmetrical dimers (**142** in Scheme 48) is suppressed, greatly simplifying the purification of the desired unsymmetrical mixed Kolbe dimer. Some work has been carried out utilizing differently protected glutamic and aspartic acids in the synthesis of orthogonally protected diaminodicarboxylic acids where both starting materials are present in 1 : 1 ratio (Scheme 49).[72]

While no solution to the low yields of this scenario is presented (12–16% of the desired mixed dimers **154** are obtained), utilizing Boc (*tert*-butyloxycarbonyl)/EtTos (ethyl tolyl sulfone) on one glutamic acid and Cbz (carboxybenzyl)/Bn (benzyl) on the other generally leads to mixtures that are separable by column chromatography based on the greatly different polarity of the protected diaminodicarboxylic acids (Scheme 49).

The applicability of the Kolbe reaction in the formation of numerous substance classes (1,ω-diesters, long-chain hydrocarbons, etc.)[73] and natural products[74–76] has a long and proven track record, which has been discussed elsewhere. Two recent works, however, have extended the range of applicability of this venerable reaction.



Scheme 50 Radical cyclization initiated by Kolbe electrolysis.

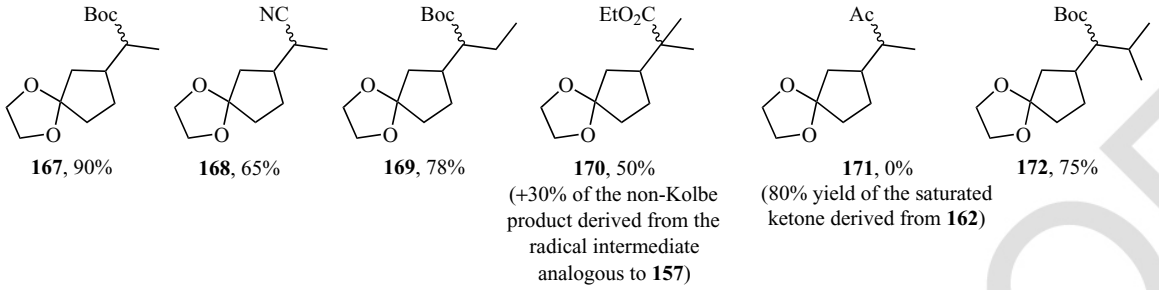


Scheme 51 Effect of an electron-withdrawing group (EWG) on the radical cyclization of ε-unsaturated carboxylic acids.

Building on the pioneering work of Schäfer[77–79] regarding the radical cyclization of ε-(**155**, **159** in Scheme 50) and ζ-unsaturated carboxylic acids to five- and six-membered rings, respectively, Lebreux has shown that the yield of the cyclization product is greatly increased, compared to the almost 1 : 1 ratio of cyclized (**160**) to linear (**161**) product obtained for a terminal olefin, when the double bond is electron deficient (Scheme 50).[80]

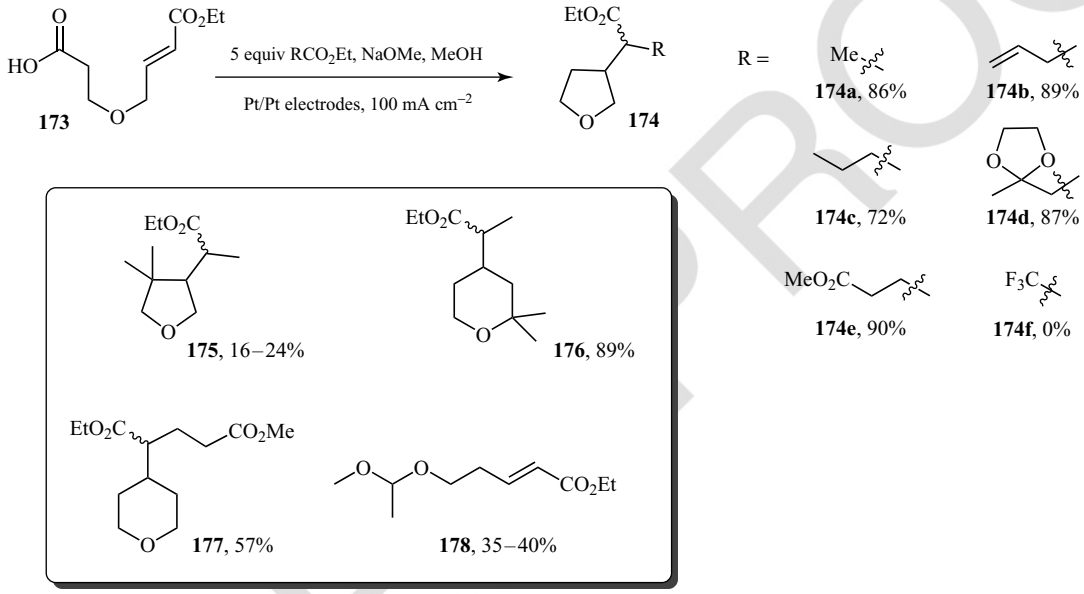
Both the 5-*exo*-trig and 6-*exo*-trig cyclizations, leading to cyclopentanes (**163**) and hexanes (**165**), readily occur under these conditions (Scheme 51), although the 6-*exo*-trig cyclization does appear to be somewhat slower, as a small amount of linear product **166** was obtained.

The nature of the electron-withdrawing group (EWG) is not unimportant: unbranched α,β-unsaturated esters smoothly give the product in excellent yield (**167**, Figure 4), while α-methyl unsaturated esters already give a mixture of cyclized (**170**) and cyclization/Hofer–Moest tandem product derived from an intermediate presumably analogous to **157**. Nitriles predominantly lead to **168** and, while no mention of alternative products is made, it appears plausible that side reactions deriving from radical intermediates of type **148** might play



167, 90% **168**, 65% **169**, 78% **170**, 50% (+30% of the non-Kolbe product derived from the radical intermediate analogous to **157**) **171**, 0% (80% yield of the saturated ketone derived from **162**) **172**, 75%

Figure 4 Products obtained from the 5-*exo*-trig cyclization presented in Scheme 51.



173 **174** **174a**, 86% **174b**, 89% **174c**, 72% **174d**, 87% **174e**, 90% **174f**, 0% **175**, 16–24% **176**, 89% **177**, 57% **178**, 35–40%

Scheme 52 Synthesis of tetrahydrofuran and tetrahydropyran derivatives via electrochemically initiated radical cyclizations.

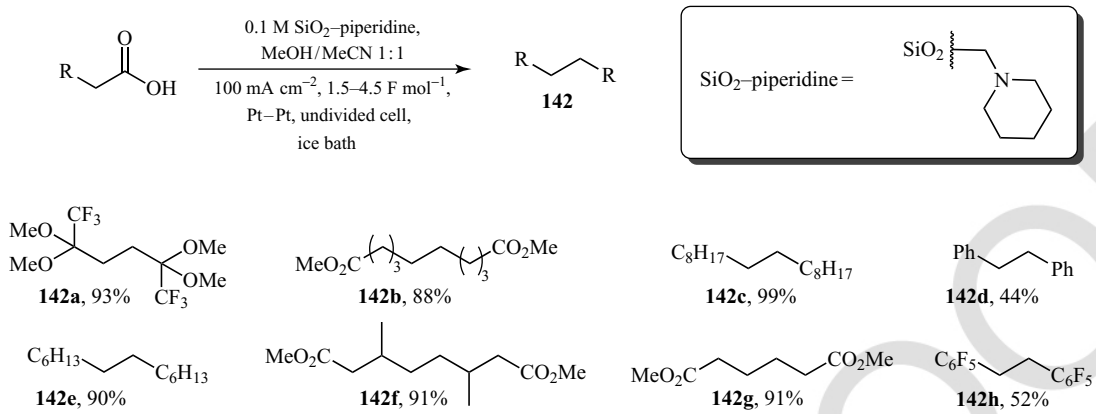
a role in the lower yield. Unsaturated ketones do not appear to be substrates in this conversion, as the cathodic reduction of the α,β-double bond completely dominates (**171**, Figure 4).

The application of electron-deficient olefins and the universal use of the Thorpe–Ingold effect enable the reported increase in yields and selectivities with respect to the desired cyclization reactions.

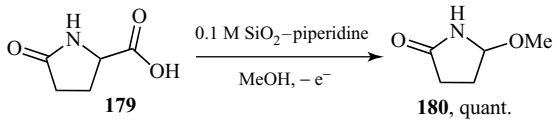
Besides acetic acid, propanoic and isobutyric acids were also applied as co-acids, both leading to the desired products in good yields (**169** and **172** respectively, Figure 4).

Ethers of type **173** could also be applied (Scheme 52), permitting the generation of THF derivatives with a wide range of functionalities derived from various co-acids (**174a–e**). Only the electron-poor trifluoroacetic acid proved to be unreactive (**174f**). Products of the type **175** were obtained only in poor yields, presumably because of steric congestion of the intermediate radical, as no further products were reported. Tetrahydropyran derivatives are accessible in excellent yields (**176**) when a gem-dimethyl substitution pattern is applied. Without the dimethyl moiety, the obtained yield is reduced (**177**), coupled with the generation of a further linear product **178** possibly originating in a rearrangement of either a radical or carbocationic intermediate.

The classical application of the Kolbe reaction is the dimerization of primary carboxylic acids leading to the decarboxylated dimer (refer to Scheme 46). While the reaction generally proceeds smoothly,



Scheme 53 Kolbe dimerization of primary aliphatic carboxylic acids utilizing SiO_2 gel-supported piperidine.



Scheme 54 Influence of α-heteroatoms on the outcome of the electrolysis of carboxylic acids.

yields of significantly lower than 50% are the norm.

Recent work by Fuchigami has increased the yield that can be expected for the dimerization.[81] This was achieved by the application of silica–gel-bound piperidine as the base, with the resulting ammonium carboxylate pair serving as the supporting electrolyte, in methanol/acetonitrile 1 : 1. Interestingly, no Ritter-type side reactions derived from the attack by the generated radicals on the nitrile functionality of the co-solvent were reported.

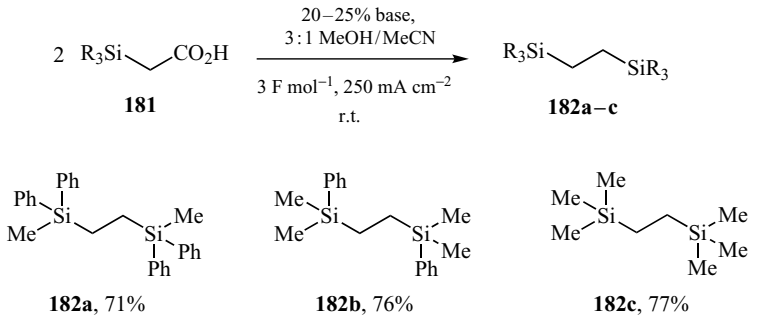
Using this new methodology, excellent to quantitative yields were obtained in the cases that favor generation of the radical (**140**) over the cationic (**141**) intermediate (Scheme 53). Purification was reported to be greatly simplified: filtration and removal of the solvent were usually the only tasks required to allow isolation of pure product. The silica-bound piperidine proved to be recyclable; up to 10 cycles were reported without loss of activity.

The general limits of the Kolbe reaction do, however, still apply. Benzylic radical intermediates, generated from 2-aryl acetic acids, lead to the formation of a significant amount of Hofer–Moest products and thus lower yields of the desired dimer (**142 d** and **142 h**). The dimerization yields are nevertheless still higher for these substrates than usually obtained when using the original procedure. Following this trend, the same authors have also reported that heteroatoms in α-position as in **179** to the newly formed radical intermediate lead exclusively to the generation of the carbocationic species, so that non-Kolbe products such as **180** are the only species observed (Scheme 54).[82]

The higher yields obtainable with the silica-bound piperidine bring the yield into synthetically interesting ranges. Should the mixed Kolbe reaction be equally amenable to this strategy, it stands to reason that renewed attention will be directed at this venerable transformation.

Shtelman and Becker recently reported the successful synthesis of 1,2-bissilyl ethanes (**182a–c**, Scheme 55) from the corresponding α-silyl carboxylic acids (**181**, Scheme 55).[83] Part of the interest for this project was derived from the uncertain influence of the α-silyl group on the outcome of the Kolbe reaction. The authors note that competing electronic influences of the Si–C bonds (α/β-Si effect) might lead to unexpected results for these α-silyl acids. Should the cationic intermediate be preferred, substantially lower yields are to be expected. The results indicate that radical formation is indeed the preferred pathway, as good yields are obtained, after optimization, for the three examined silyl groups (Scheme 55).

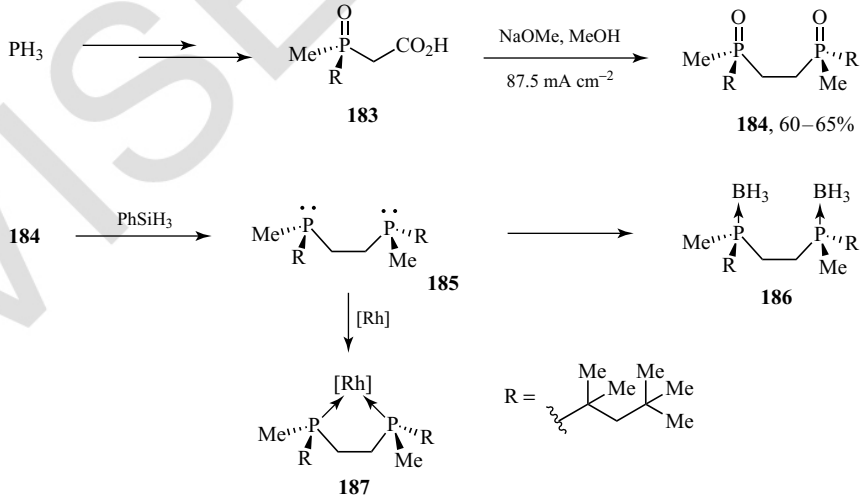
It was found that the standard Kolbe conditions did not lead to successful conversion of the starting materials. When the amount of base (the preferred base was 3 N KOH) applied was increased to 20%, the yield responded favorably, leading the



Scheme 55 Electrochemical dimerization of α-silyl acetic acids.

authors to the conclusion that the weaker pK_a of the α-silyl acetic acids (5.22 vs 4.75) was to blame for the initial failure. Higher current densities (200–250 mA cm^{-2}), room temperature, and a 3 : 1 MeOH/MeCN mixture were further identified as optimal parameters. Electricity consumptions of over 3 F mol^{-1} were also found to be detrimental.

Kolbe electrolysis has also been used by Sugiya and Nohira to generate P-chiral bisphosphine compounds via the intermediate P-chiral phosphinoyl carboxylic acids (Scheme 56).[84,85] Starting from phosphine, the key racemic phospinoyl carboxylic acid intermediate is obtained after several steps. Optical resolution by fractional crystallization using (−)-(*S*)-1-phenylethylamine as the resolving agent gave the desired chiral compounds (**183**). Standard Kolbe conditions permitted the synthesis of the P-chiral bisphospine oxides (**184**) in 60–65%, isolated yield from which the bisphosphines (**185**) were liberated by reduction with phenyl silane. The expected side products of the Kolbe reaction account for the nonquantitative yield and could be isolated, showing varying amounts of Hofer–Moest, disproportionation (where possible), and esterification products. The absolute configuration was confirmed by conversion of **185** into bisphosphine–borane complexes (**186**) and by comparing with available literature for optical rotation values. The bisphosphino ethane **185** was used as a chiral ligand, with rhodium giving chiral complexes of type **187**. This complex was tested in the hydrogenation of α-(acylamino)acrylic derivatives. The corresponding saturated compounds showed good to excellent entantiomeric excesses, proving the worth of



Scheme 56 Generation of P-chiral bisphosphino ligands with Kolbe electrolysis as the key step.

this type of P-chiral chelating ligand in asymmetric catalysis. Higher homologs of the bisphosphino compounds are also accessible.

2.8 Aminoxyl Radical-Mediated Reactions

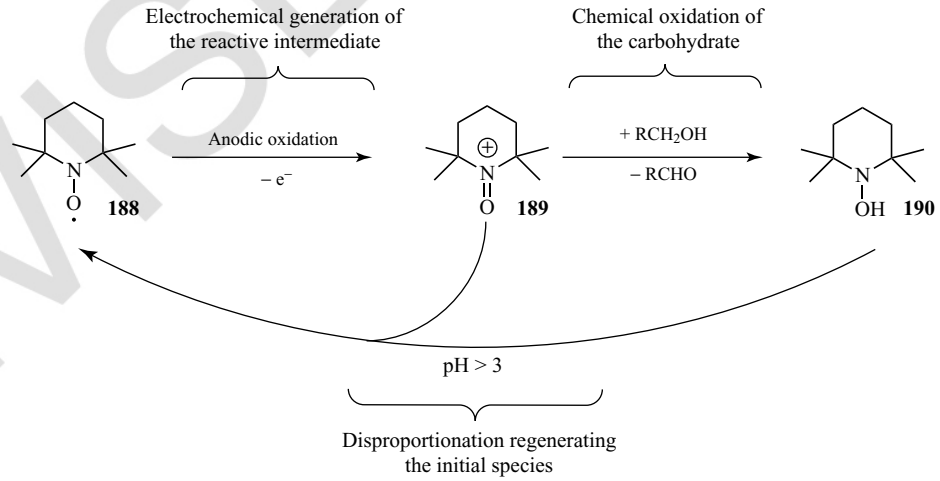
The electrochemical generation of radicals from various precursor molecules permits the rapid and selective functionalization or defunctionalization of molecular scaffolds. Many of these processes involve radical species only transiently or as noncritical intermediates. While these reactions are in and of themselves fascinating, they do not fall under the scope of this brief overview and as such we point to the original publications themselves for those interested in further information.[86–98]

One of these fields of work which should nonetheless be highlighted is the regeneration of reactive intermediates in the catalytic application of stable N,O radical species (see **Nitroxides in Synthetic Radical Chemistry**, Volume 2). This approach underlines the synthetic utility of radical chemistry in general and the unique opportunities afforded by the appropriate use of electrochemistry. TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl, **188**) is the most prominent of this class of stabile radicals and numerous uses are known; stoichiometric quantities of this species are often required, but the addition of an oxidant to regenerate the active species **189** and thus allow catalytic turnover with regard to TEMPO are also common. In this context, Schäfer has applied catalytic amounts of TEMPO as a mediator in the selective electrochemical oxidation of carbohydrates to the respective uronic acids.[99,100]

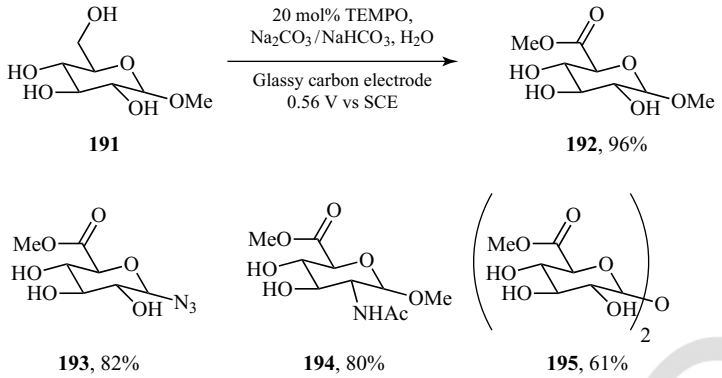
TEMPO is electrochemically converted to the actual chemical oxidant: the nitrosonium cation **189**. After the target oxidation itself is carried out, hydroxylamine **190** reacts with another equivalent of **189** to regenerate TEMPO itself, thus closing the catalytic cycle. The electrochemically generated species (**189**) is not just the key oxidant but also crucial for the regeneration of the catalyst. A wide range of carbohydrates such as **191** were reacted under the reported reaction conditions, a small excerpt of which (**192**–**195**) is shown in Scheme 58.

A range of functionalities is tolerated, and in general the yields are good to excellent. The nitrosonium cation **189** can evidently discriminate handily between the primary and secondary hydroxy functionalities, thus permitting selective oxidation. One of the key limitations of this method is that the anomeric center must be protected.

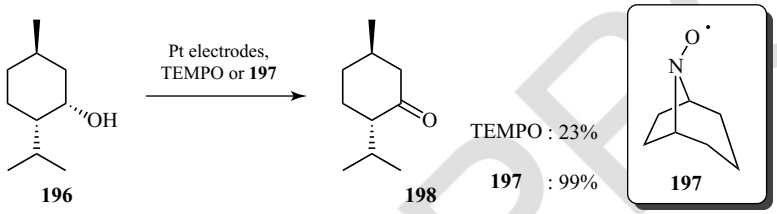
Demizu *et al*. carried out further tests with different stable *N*-oxyl radicals, here azabi- and tricyclic systems, which owe their stability to Bredt's rule.[101] The nitrosonium cations (equivalent to **189**, Scheme 57) were successfully applied in the oxidation of primary and secondary alcohols to aldehydes and ketones. In many cases, such as the oxidation of menthol (**196**) to **198** mediated by **197** in Scheme 59, the alternative *N*-oxyl radicals lead to significantly higher yields than TEMPO.



Scheme 57 Role of TEMPO in the electrochemical oxidation of carbohydrates.



Scheme 58 Examples of the uronic acids accessible via the TEMPO-mediated electrochemical oxidation of carbohydrates.



Scheme 59 Electrochemical oxidation of menthol mediated by azabicyclic *N*-oxyl radical **197**.

2.9 Halide-Mediated Reactions

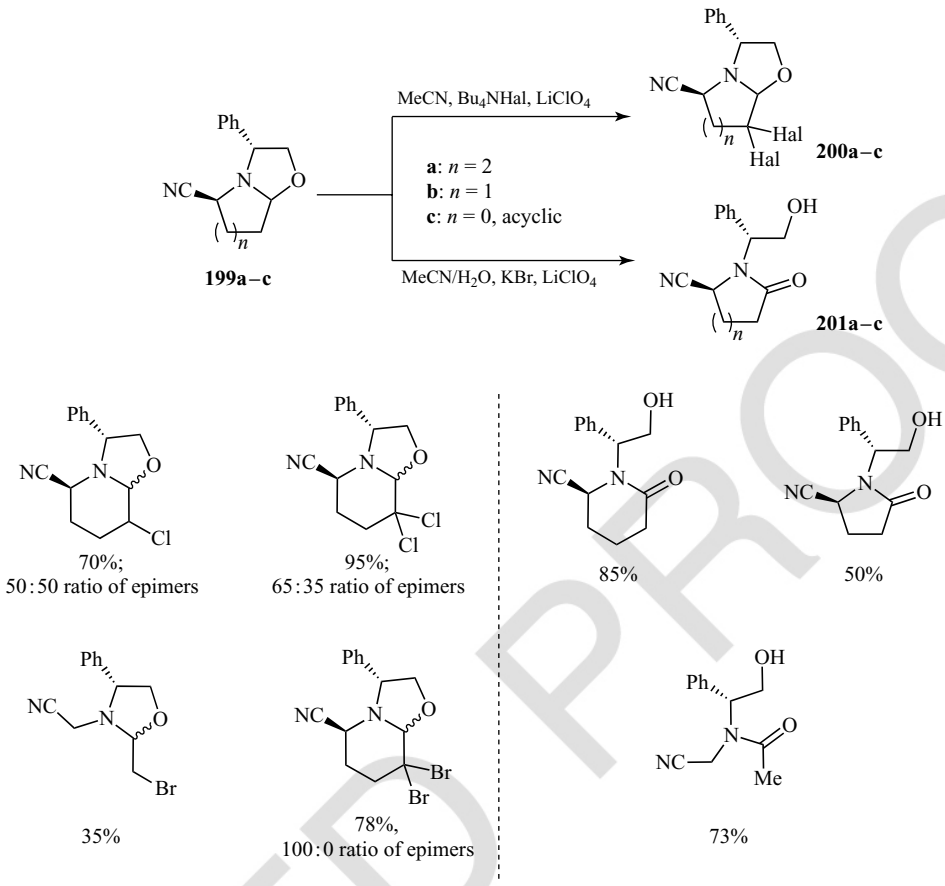
The opening of carbocycles and subsequent derivatization of the thus obtained radical intermediates is a strategy that shows promise. Royer's group has published work on the anodic oxidation of *N*-cyanomethyloxazolidines of type **199** (Scheme 60). They have observed that, in the presence of halogenides (Cl^- and Br^-), which are presumed to act as mediators in the course of the reaction as well as the halogenating agents, a gem-dihalogenated product **200** is observed, while in the presence of water products of type **201** are obtained.[102]

A general feature of these reactions is that the presence of at least traces of bromide is essential to obtain high yields and rates of reaction. The authors provide mechanistic evidence pointing toward the crucial role of the trihalogenide anions, which are generated *in situ* following electrochemical oxidation of the simple halogenides to the elemental halogens, for successful conversion of the starting material (Scheme 61). The proposed hypothesis argues that tribromide is the superior electron transfer agent and thus critical to the success of the conversion of **202** to **207**. The bromination is believed to proceed from **204a/b** to the iminium cation **205**, which is then in equilibrium with the bicyclic intermediate **206**. Repetition of this sequence leads to the dihalogenated product **207**. Fluoride was not able to mediate the oxidation, in accordance with its high oxidation potential. The use of iodide was not reported.

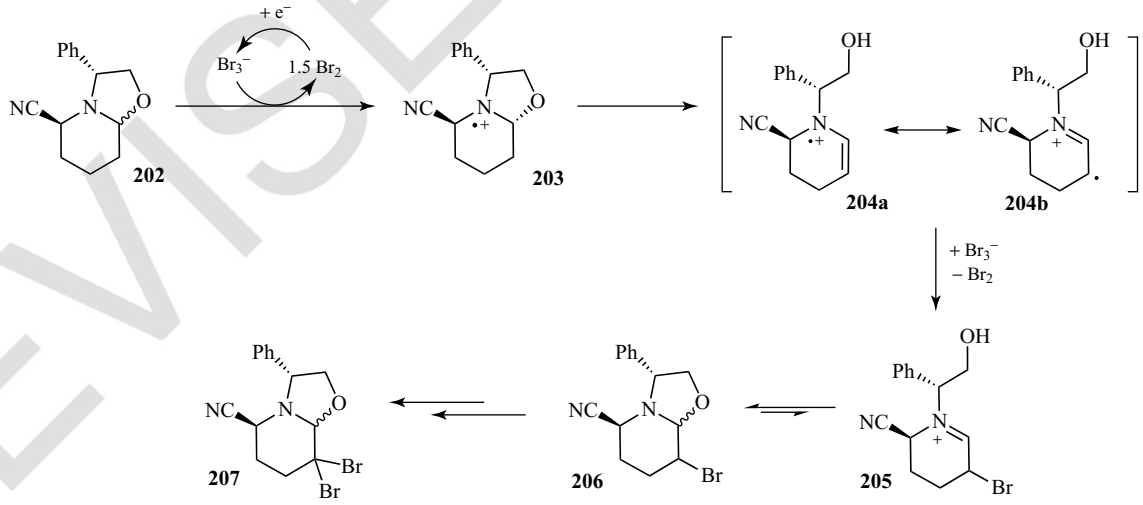
When vinyl ethers are added and lithium perchlorate is used as the supporting electrolyte, the result is the expansion of the ring system to the cyclization product **208** (Scheme 62).[103] A similar mechanism is postulated, with the addition of the unsaturated ether to intermediate **209** as the key step.

2.10 Functional Group Exchange Reactions

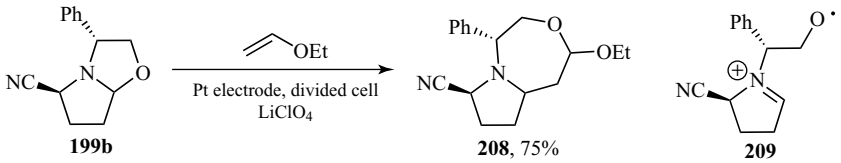
Le Gall presented a case where the selective fragmentation of an electrochemically generated radical was exploited to deliver a valuable compound. They report that, upon anodic oxidation of N-substituted α-silyl piperidines of type **210** in the presence of a cyanide source, exclusive exchange of the silyl group for cyanide to generate products of type **211** is observed.[104]



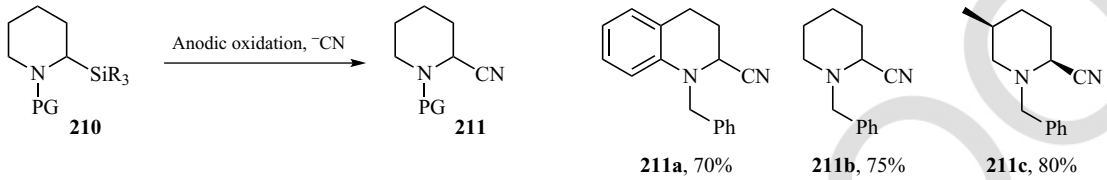
Scheme 60 Electrochemical functionalization of oxazolidines **199a–c**.



Scheme 61 Postulated mechanism for the electrochemical functionalization of **202**.



Scheme 62 Electrochemical ring expansion of oxazolidines with vinyl ethers.



Scheme 63 Exchange of silyl for nitrile functionality in piperidine derivatives (PG: protecting group).

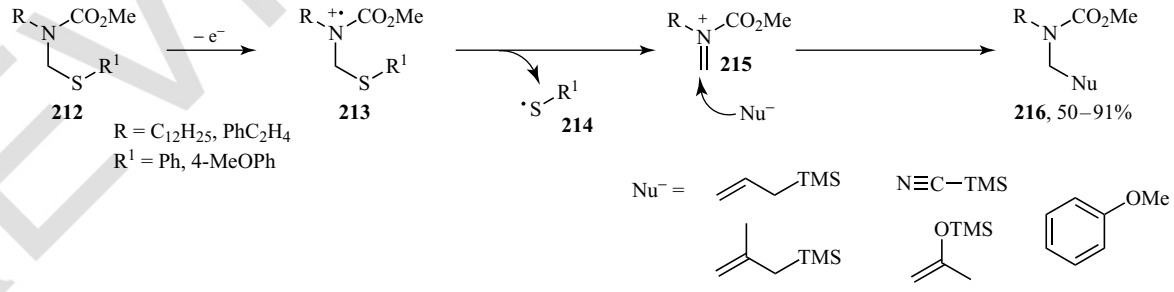
The mechanism is postulated to proceed via a preliminary N-centered radical cation derived from **210**, which leads to exclusive fragmentation of the α-C–Si bond. This generates a secondary C-centered radical which is subjected to a second oxidation step leading to an intermediate iminium ion, which is then attacked by cyanide to yield the α-nitrile amine products of type **211**. The nitrile group always assumes an axial orientation in the piperidine ring. The authors offer an explanation based on the stereoelectronics of the intermediate iminium cation. The rationale is broadly identical with the concept of an anomeric effect as derived from carbohydrate chemistry.

A common problem when subjecting tertiary or secondary amines to anodic oxidation is the lack of specificity with respect to which the α-bond fragments to generate the iminium cation. A novel solution was presented by Yoshida's group.[105] They determined that the C–S bond of a N,S-acetal (**212**) functions as an electrochemically activated breaking point (Scheme 64). The thus-derived iminium cation **215** can be subsequently derivatized by nucleophilic attack to yield product **216**.

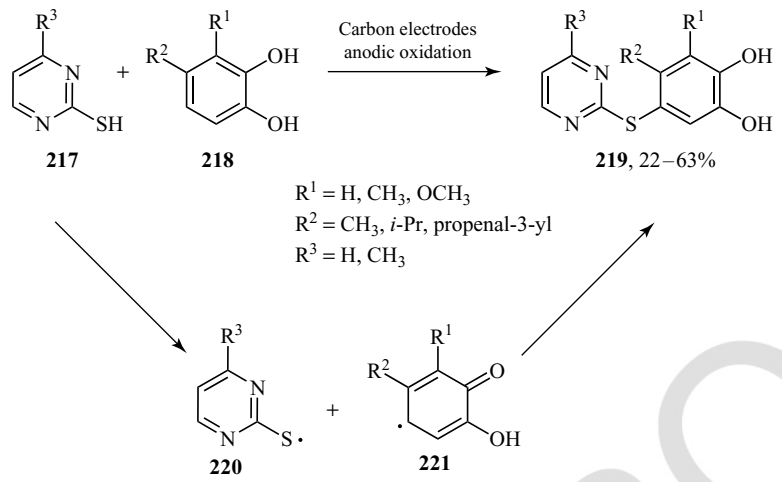
The first step is the oxidation of the carbamate nitrogen in **212** to generate the radical cation **213**. Despite a second α-position being available for fragmentation, the α-C–S bond is selectively cleaved, freeing an S-centered radical **214** (which reacts with a second equivalent to generate a disulfide) and the electrophilic iminium cation **215**. Various carbon nucleophiles were tested, and good to excellent yields of the corresponding products of type **216** were reported.

2.11 Coupling Reactions Initiated by Anodic Oxidation

The coupling of substituted catechols (**218**) and aromatic thiols (**217**) via electrochemical oxidation of both substrates was achieved by Becker



Scheme 64 Electrochemical functionalization of α-thio carbamates with carbon nucleophiles.



Scheme 65 Oxidative electrochemical formation of thioethers.

(Scheme 65).[106] While the desired thioethers of type **219** were obtained in poor to acceptable yields, the products do show a relatively high degree of functionality and are reported as intermediates of interest for materials and biological applications.

Although the mechanism of this transformation has not yet been elucidated, the authors speculate that the coupling might take place via the reaction of two separate electrochemically generated radical intermediates, **220** and **221**, which then combine to give the product upon re-aromatization.

3 CATHODIC PROCESSES

3.1 Cyclizations Induced by Reduction of Carbonyl Groups

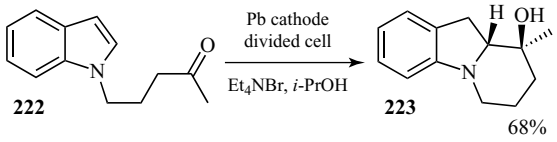
The reduction of carbonyl groups by SmI_2 is a very versatile method for the initiation of cyclization reactions of suitable starting materials utilizing 2 equiv of the reducing agent (see **Organic Synthesis Using Samarium Diiodide**, Volume 2). In order to reduce waste and to be able to continuously adjust the redox potential for each individual starting material, electrochemical reduction would be the method of choice. Recent applications in such cyclization reactions have been reported by Kise for the generation of mono- and bicyclic products starting from ketones and oximes. As acceptor functionalities, imides,[107] indole derivatives,[108] and esters,[109] were used.

Of particular interest are those reactions that involve heteroaromatic scaffolds such as the indole derivative shown in Scheme 66.[108] The electrochemically initiated reaction of indole derivative **222** generates the tricyclic product **223** in good yield of 68% in an undivided cell (divided cell; 65% yield), which is comparable to the yield obtained for the chemical method utilizing SmI_2 as reductand (73%).

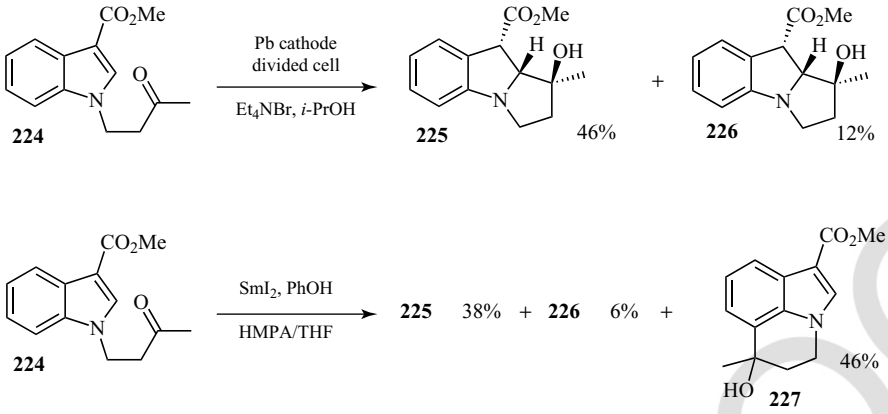
The electrochemical method allows the formation of the product **225** in moderate yield (46%) with three adjacent chiral carbon atoms with reasonable diastereoselectivity (Scheme 23). Interestingly, the corresponding SmI_2-initiated reaction from **224** led to a different distribution of products. In this case, **225** was generated alongside 6% of **226**, but the tricyclic derivative **227** was also isolated and identified as yet another cyclization product.

In the case of the ester-functionalized starting material **224**, cyclovoltammetry indicated that the reduction is more likely to proceed at the

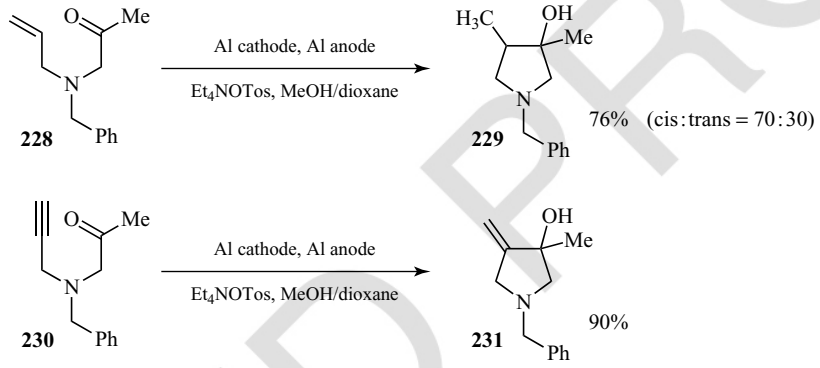
rad025



Scheme 66 Reductive cyclization of a ketone-bearing indole derivative.



Scheme 67 Comparison of the electrochemical and chemical reductive cyclization of a ketone-containing indole derivative.



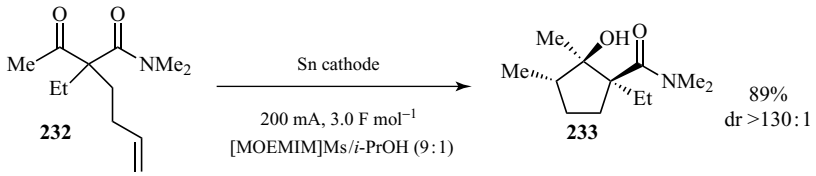
Scheme 68 Reductive cyclization of a ketone-bearing alkene and alkyne derivative.

α,β-unsaturated subunit rather than at the keto functionality as in **222**. Accordingly, the reduction of the two starting materials generates radical anions at different functional groups based on the redox potential. The chemical reducing agent SmI_2 generated a mixture of products in the presence of hexamethylphosphoramide (HMPA) as cosolvent, while, in the absence of HMPA product **225** was formed in 73% yield.

Nonconjugated enones and ynones were applied by Nishiguchi for the synthesis of functionalized five- and six-membered carbo-, sulfur- and nitrogen-containing heterocycles.[110] The electrolysis was conducted with aluminum electrodes, and the application of enones such as **228** gave the desired products **229** in moderate to good yields (Scheme 68), whereas the electrolysis of the ynone **230** gave the corresponding cyclic allylic alcohol derivatives of type **231** in good to excellent yields.

The application of ionic liquids such as 1-methoxyethyl-3-methylimidazolium mesylate (MOEMIM) as solvent and electrolyte, together with isopropanol as proton donor, was reported by Yadav in the electrochemical reduction of β-ketoesters and β-ketoamides such as **232** (Scheme 69).[111] In these cases, the β-dicarbonyl groups were substituted with an alkyl group and a 1-butenyl substituent at the α-position to supress the formation of enolates. Accordingly, the polysubstituted products such as **233** were formed in good to excellent yields, in good to exclusive diastereselectivities, and with excellent regioselectivities.

The electrochemical reduction of carbon–carbon double bonds can be easily achieved when electron-deficient double bonds are used as starting materials. Accordingly, educts of the Knoevenagel type have a long track of successful applications in



Scheme 69 Reductive cyclization of an alkenyl substituted 1,3-diketone in a ionic liquid.

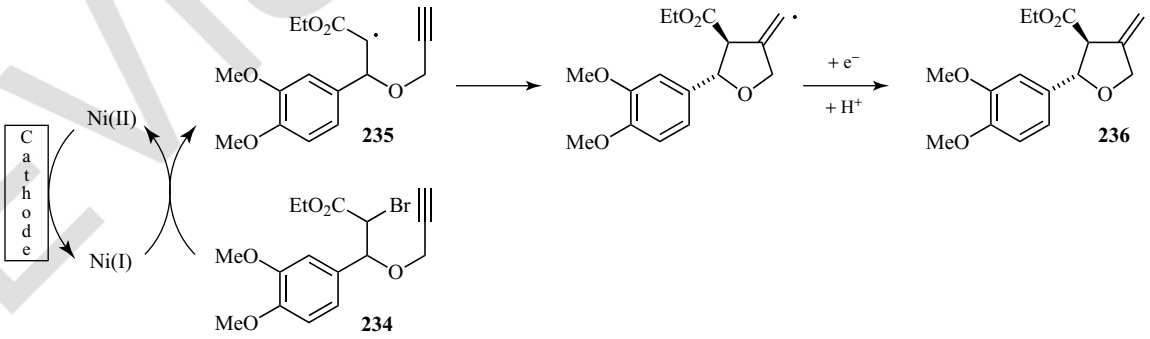
such reactions. In the presence of *in situ* accessible nucleophiles (such as malonates), two successive carbon–carbon bond formations can be realized in a one-step procedure. Thereby, cyclopropanations of Knoevenagel-type starting materials can be realized.[35, 112–120] The reactions are performed in alcoholic solvents utilizing a halide source as the electrochemical mediator, and, therefore, from a mechanistic point of view, such reactions are most likely initiated by an electroreductively generated alkoxide base that deprotonates the malonate-type starting material and the oxidation of the halide, initiating ionic follow-up reactions with the Knoevenagel-type materials applied.

3.2 Nickel-Mediated Reduction of Alkylhalides

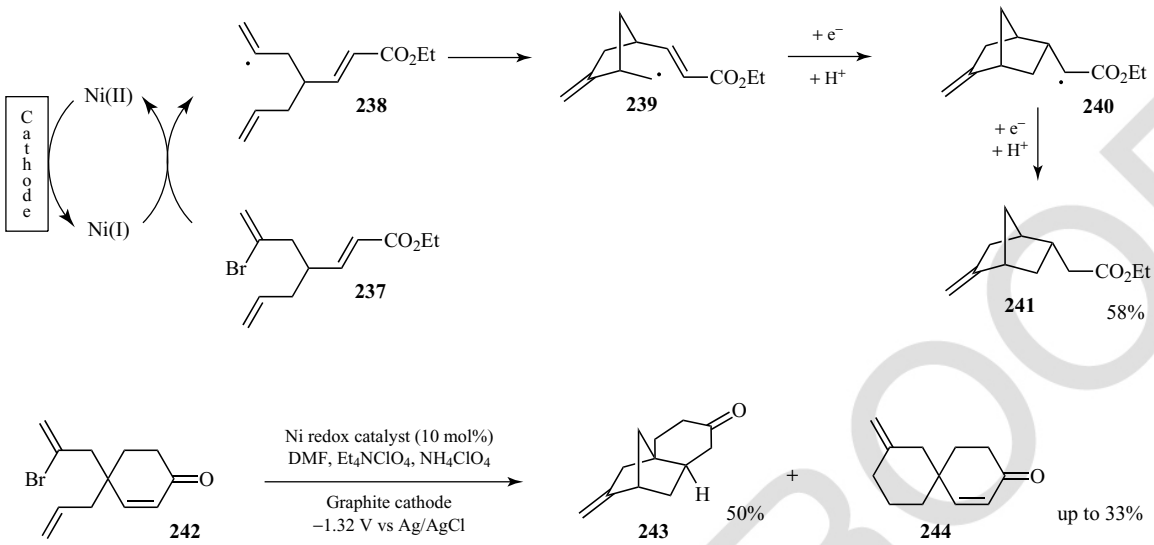
Another type of functional group that is well suited for electrochemical reductions under mild conditions are alkylbromide or alkyliodide derivatives. Being adjacent to ester functionalities, the radical anions such as **235** are stabilized and lead to cyclization reactions with unsaturated groups along the chain (Scheme 70). The electrochemical reduction of such starting materials (e.g., **234**) can be performed directly at the cathode surface with only moderate success,[121] or indirectly utilizing nickel complexes acting as mediators.[122–125] In these latter cases, the desired cyclization product **236** could be obtained in up to quantitative yield, depending on the nickel complex used as the redox catalyst or the substituents present in the starting material.

Consecutive tandem cyclizations have been described by Toyota for the synthesis of norbornene-type structures utilizing vinylbromides such as **237** as starting material under nickel redox catalysis (Scheme 71).[126] The tandem cyclization reaction via intermediates **238**/**239** and **240** led predominantly to the endo-substituted norbornene product **241** in moderate yield. Alongside the norbornene products (**243**) formed from bisallyl-modified cyclic enones (**242**), spiro-bicyclic products such as **244** could also be obtained in moderate yield.

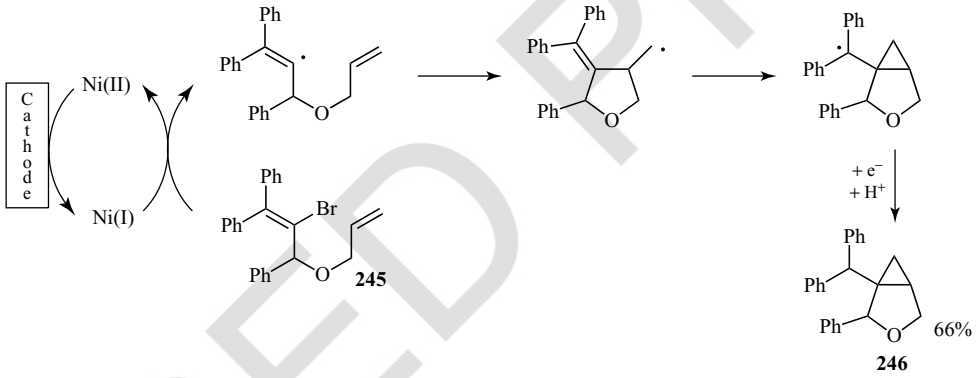
On the other hand, when additional double bonds were not present as in **245**, the formation of bicyclic compounds such as **246** via a tandem cyclization reaction sequence initiated by the reductive carbon–bromine bond cleavage was observed (Scheme 72).[127] In these cases, the Thorpe–Ingold effect seems to have promoted the cyclization; only the appropriately substituted carbocycles or furan- and pyrrolidine-derivatives were investigated.



Scheme 70 Mechanism of the indirect electrochemical nickel-mediated reductive cyclization of a halide-bearing alkyne.



Scheme 71 Mechanism of the indirect electrochemical nickel-mediated reductive tandem cyclization of a halide-bearing polyene.



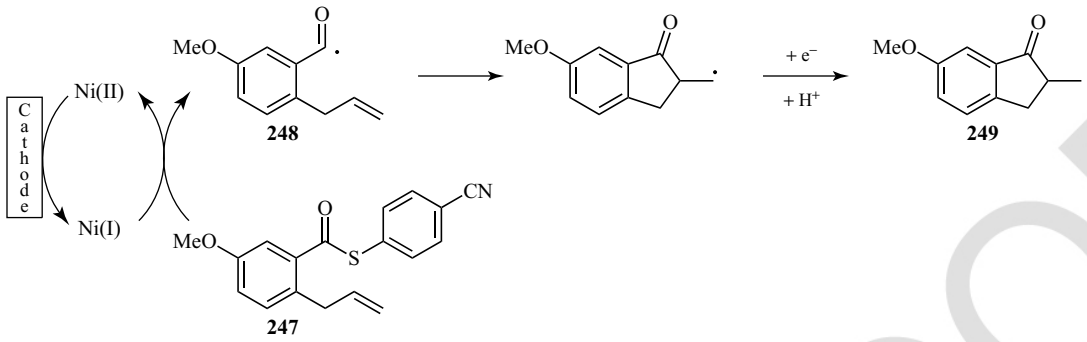
Scheme 72 Mechanism of the indirect electrochemical nickel-mediated cyclopropane formation from a halide-bearing alkene.

Nickel catalysts were also used for the cleavage of the carbon–sulfur bond in thioesters, as was described by Ozaki. In these cases, the thioester functionality in **247** is easily cleaved under reductive conditions. Interestingly, this procedure can be used for the generation of the sulfur-centered radical for the synthesis of sulfur-containing heterocycles[128] as well as for the generation of acyl radicals (**248**) as shown in Scheme 73. In the latter case, the acyl radical **248** led to the formation of the corresponding ketones **249** upon intramolecular addition to a double bond and further reduction and protonation.[129,130]

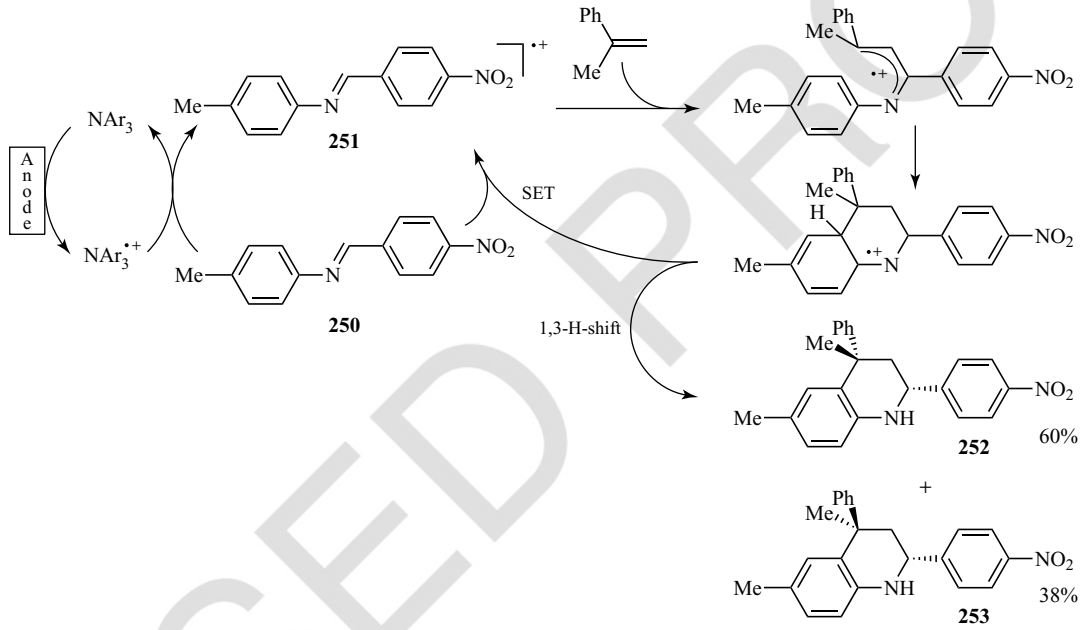
In this context, the further reduction of the sulfur-centered radical to the thiolate anion was utilized by Ozaki for the nucleophilic ring-opening reaction of epoxides to generate 5,7-membered bicyclic sulfur-containing heterocycles in an intramolecular fashion.[131]

Although the application of organic electron-transfer reagents of the triarylamine type is an oxidative indirect electrochemical-initiated reaction, the methodology fits well into the context of indirect electrochemical reactions. Accordingly, triarylamines can be utilized for the electron-transfer-initiated Povarov reaction of aromatic imines with styrene derivatives and dihydrofuran via radical cation intermediates of type **251** (Scheme 74).[132]

The reaction is very dependent on the redox potentials of the starting material **250** and the



Scheme 73 Mechanism of the indirect electrochemical nickel-mediated thioester cleavage for the synthesis of a ketone.

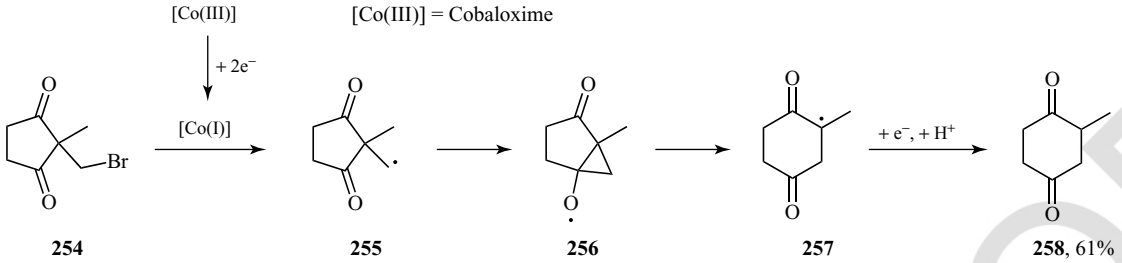


Scheme 74 Mechanism of the indirect electrochemical triarylamine-mediated, oxidatively induced Povarov cyclization.

styrene derivative applied. The reaction takes place only when the oxidation potential of the dienophile is appreciably lower than that of the hetero-diene **250**. Nevertheless, when the redox potentials are well chosen, the cis product **252** and the trans-configured product **253** are formed in excellent combined yield.

Inokuchi reported a cobalt-mediated method leading to cyclohexane-1,4-diones (**258**) in moderate to acceptable yields from cyclopentane-1,3-diones (**254**).[133] Cobaloxime was used as the cobalt source, and the electrochemical generation of a cobalt(I) species permitted the abstraction of bromine from the substrate **254** leading to the primary radical **255** (Scheme 75). The ring-expanded cyclohexane-1,4-dione **258** is thought to result from a formal 1,2-acyl shift (**255** to **257**) via cyclopropane **256** and subsequent reduction to an enolate and protonation.

A further cobalt-mediated transformation of styrene to cyclopropyl benzene has been presented.[134] An electrochemical reduction of vitamin B_{12} (a naturally occurring cobalt–corrin complex) was carried out to generate the reactive Co(I) complex. This reacts with DCM, leading to the chloro methyl radical, which adds to styrene. The benzylic



254 **255** **256** **257** **258**, 61%

Scheme 75 Cobalt-mediated ring expansion of cyclopentane-1,3-diones.

radical thus generated is postulated to be further reduced, and the resulting anion should attack the chlorine-bearing carbon intramolecularly. The desired product cyclopropyl benzene was obtained in quantitative yields. No other substrates were examined, but the work does however hint at the tantalizing prospect of combining biologically derived or inspired molecules with synthetic electrochemistry.

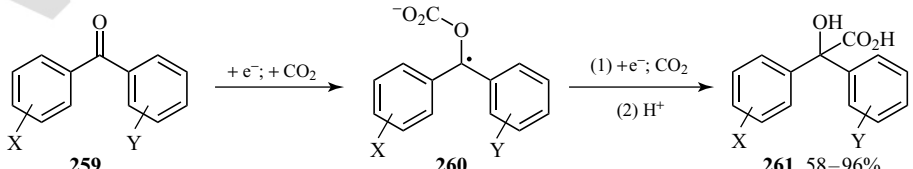
3.3 Coupling Reactions Initiated by Reduction of Ketones

Radical anions generated via cathodic reduction processes are also viable synthetic intermediates. Gennaro and coworkers examined the reactions of radical anions **260** derived from the benzophenone and its halogenated derivatives **259** with CO_2 to afford α-hydroxy carboxylic acids such as **261** (Scheme 76).[135]

Yields of the target α-hydroxy carboxylic acids were generally good to excellent; only in two cases did the yield fall below 80%. The main focus was however on the elucidation of the mechanistic aspects of this transformations. The author's proposed mechanism is outlined in Scheme 76. The reaction is initiated by the reduction of the ketone **259** to the respective ketyl anion radicals, which capture CO_2, leading to formation of the carbonate **260**. A further reduction step leads to a carbanionic intermediate, which itself nucleophilicly attacks CO_2 giving a carbonate/carboxylate intermediate that is transformed to the final α-hydroxy carboxylic acid **261** after acid workup freeing the alcohol functionality by hydrolysis of the carbonate moiety. The key to obtaining high yields, as reported, is deemed to be the presence of CO_2, as the intermediate ketyl radical anions suffer fragmentation of the C–X/Y bonds, precluding the formation of halogenated α-hydroxy carboxylic acids of type **261**.

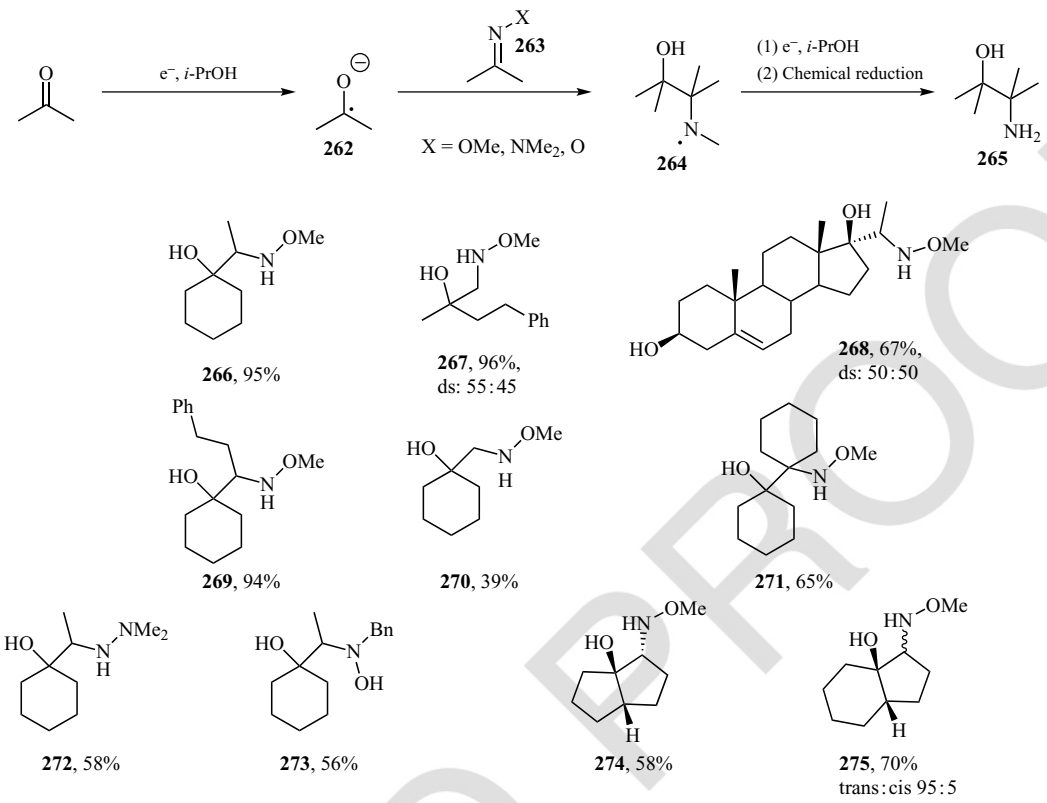
A relatively early report of the reductive coupling of ketones and imine-type compounds was provided by Shono *et al*.[136] Under cathodic conditions, the ketone was reduced to a ketyl radical anion (**262**) which then reacted with the imine derivative (oximes, hydrazones, and nitrones are reported as viable reaction partners) to form the α-amino alcohol compound after chemical reduction (Scheme 77). A wide variety of ketones and nitrogen-containing compounds were reacted, and some examples are presented in Scheme 77 (**266–275**).

Cyclic and acyclic ketones and oximes are suitable substrates for this conversion, with yields



259 **260** **261**, 58–96%

Scheme 76 Reactions of halogenated benzophenones with CO_2 under reductive conditions.



Scheme 77 Reductive coupling of ketones with oximes, hydrazones, and nitrones.

generally in the good to excellent range (see compounds **266**, **267**, **269**–**271**). More complex ketones also react satisfactorily, as shown by the reaction of a steroidal ketone leading to **268**. Hydrazone and nitrone derivatives also lead to the respective β-amino alcohol precursors **272** and **273**, although the yields are lower than in the reactions with the oxime compounds. Intramolecular cyclizations are also amenable to this methodology, as exemplified by **275**. Yields and selectivities for the cyclizations are satisfactory to good.

Initial efforts have been reported that combine many of the optimization parameters specific to electrochemical systems, thus enabling new synergistic possibilities of reaction activation. An interesting application of triple activation was reported by Compton, who applied photoactivation, ultrasound emulsification, and electrochemistry to permit a reaction previously not readily attainable.[137]

3.4 Defunctionalization

Defunctionalization of aryl and alkyl halides has been reported by several groups with two broad trends being recognizable: direct defunctionalization through direct electron transfer and subsequent C–Hal bond cleavage; or activation of transition metals or complexes thereof, which then carry out the defunctionalization chemistry. Both the direct defunctionalization at various electrode materials[138–140] and the transition-metal-mediated defunctionalization have been examined from a primarily mechanistic viewpoint, but no particular effort with a methodological/synthetic focus has been reported.[141–144]

4 CONCLUSIONS

The generation of neutral as well as charged radical species can be performed by electrochemical

methods, as shown by many applications in the past and present. The usefulness of electrochemistry for the initiation of relevant organic transformations has been demonstrated in basic transformations such as the formation of carbon–carbon bonds as well as the formation and the cleavage of carbon–heteroatom bonds.

The use of the anode and cathode as mass-free redox reagents will always be of considerable interest in terms of effectiveness and environmental compatibility. Nevertheless, electrochemical methods are still considered as complicated and difficult to master. The examples outlined in this article illustrate that the allocation of time and resources required initially is not futile, as the pay off is most rewarding.

While fundamental questions are still being addressed, evermore sophisticated applications are being and have been developed and applied to the selective activation of functional groups in increasingly complex starting materials. The fact that research groups are willing to apply electrochemical redox processes in the synthesis of complex molecules and do so with success is a remarkable confirmation of the utility of these transformations and a sign of how far this field has developed.

REFERENCES

1. E. Steckhan, T. Arns, W. R. Heineman, *et al*., *Chemosphere*, 2001, **43**, 63–73.
2. K. D. Moeller, *Tetrahedron*, 2000, **56**, 9527–9554.
3. H. Lund, *J. Electrochem. Soc.*, 2002, **149**, 21–33.
4. M. Schmittel and A. Burghart, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2550–2589.
5. S. Quideau, L. Pouységu, and D. Deffieux, *Curr. Org. Chem.*, 2004, **8**, 113–148.
6. D. Pletcher, *Acta Chem. Scand.*, 1999, **53**, 745–750.
7. M. Okimoto and Y. Takahashi, *Curr. Org. Synth.*, 2004, **1**, 233–251.
8. E. Duñach, M. J. Medeiros, and S. Olivero, *New J. Chem.*, 2006, **30**, 1534–1548.
9. J. B. Sperry and D. L. Wright, *Chem. Soc. Rev.*, 2006, **35**, 605–621.
10. H. Lund and O. Hammerich, *Organic Electrochemistry*, Marcel Dekker, New York, 2001.
11. J. Grimshaw, *Electrochemical Reactions and Mechanism in Organic Chemistry*, Elsevier, Amsterdam, 2000.
12. K. Izutsu, *Electrochemistry in Nonaqueous Solutions*, Wiley-VCH Verlag GmbH, Weinheim, 2002.
13. H. Ohno, *Elechtrochemical Aspects of Ionic Liquids*, John Wiley & Sons, Inc, Hoboken, NJ, 2005.
14. R. G. Compton and C. E. Banks, *Understanding Voltammetry*, World Scientific Publishing, Singapore, 2007.
15. F. Tang and K. D. Moeller, *Tetrahedron*, 2009, **65**, 10863–10875.
16. D. A. Frey, J. A. Marx, and K. D. Moeller, *Electrochim. Acta*, 1997, **42**, 1967–1970.
17. G. Xi and K. D. Moeller, *Org. Lett.*, 2010, **12**, 2590–2593.
18. D. A. Frey, S. H. K. Reddy, and K. D. Moeller, *J. Org. Chem.*, 1999, **64**, 2805–2813.
19. H.-C. Xu and K. D. Moeller, *J. Am. Chem. Soc.*, 2008, **130**, 13542–13543.
20. Y. Sun, B. Liu, J. Kao, *et al*., *Org. Lett.*, 2001, **3**, 1729–1732.
21. K. D. Moeller and L. V. Tinao, *J. Am. Chem. Soc.*, 1992, **114**, 1033–1041.
22. S. Duan and K. D. Moeller, *J. Am. Chem. Soc.*, 2002, **124**, 9368–9369.
23. J. D. Brandt and K. D. Moeller, *Org. Lett.*, 2005, **7**, 3553–3556.
24. Y. Sun and K. D. Moeller, *Tetrahedron Lett.*, 2002, **43**, 7159–7161.
25. B. Liu and K. D. Moeller, *Tetrahedron Lett.*, 2001, **42**, 7163–7165.
26. Y.-T. Huang and K. D. Moeller, *Org. Lett.*, 2004, **6**, 4199–4202.
27. H. Wu and K. D. Moeller, *Org. Lett.*, 2007, **9**, 4599–4602.
28. F. Tang and K. D. Moeller, *J. Am. Chem. Soc.*, 2007, **129**, 12414–12415.
29. S. Duan and K. D. Moeller, *Org. Lett.*, 2001, **3**, 2685–2688.
30. J. Mihelcic and K. D. Moeller, *J. Am. Chem. Soc.*, 2004, **126**, 9106–9111.
31. J. Mihelcic and K. D. Moeller, *J. Am. Chem. Soc.*, 2003, **125**, 36–37.
32. J. B. Sperry and D. L. Wright, *Tetrahedron*, 2006, **62**, 6551–6557.
33. C. R. Whitehead, E. H. Sessions, I. Ghiviriga, and D. L. Wright, *Org. Lett.*, 2002, **4**, 3763–3765.
34. C. C. Hughes, A. K. Miller, and D. Trauner, *Org. Lett.*, 2005, **7**, 3425–3428.
35. M. N. Elinson, S. K. Feducovich, A. A. Zakharenkov, *et al*., *Tetrahedron*, 1995, **51**, 5035–5046.
36. Y. Okada, R. Akaba, and K. Chiba, *Tetrahedron Lett.*, 2009, **50**, 5413–5416.
37. J. Delaunay, G. Mabon, A. Orliac, and J. Simonet, *Tetrahedron Lett.*, 1990, **31**, 667–668.
38. J. F. Bergamini, J. Delaunay, P. Hapiot, *et al*., *J. Electroanal. Chem.*, 2004, **569**, 175–184.
39. G. A. N. Felton, *Tetrahedron Lett.*, 2008, **49**, 884–887.
40. H. J. Schäfer, in *Electrolytic Oxidative Coupling in Organic Electrochemistry*, eds. H. Lund and O. Hammerich, Marcel Dekker, New York, 2001, pp. 883–967.
41. K. Nyberg, *Acta Chem. Scand.*, 1971, **25**, 2499–2506.
42. K. Nyberg, *Acta Chem. Scand.*, 1971, **25**, 534–542.
43. K. Nyberg, *Acta Chem. Scand.*, 1971, **25**, 2983–2988.
44. R. E. Sioda, R. B. Frankowska, and E. B. Lesiak, *Monatsh. Chem.*, 2008, **139**, 513–519.
45. G. A. Bhat, M. Periasamy, and M. V. Bhatt, *Tetrahedron Lett.*, 1979, **20**, 3097–3098.
46. J. D. Debad, J. C. Morris, P. Magnus, and A. J. Bard, *J. Org. Chem.*, 1997, **62**, 530–537.
47. D. R. Armstrong, C. Cameron, D. C. Nonhebel, and P. G. Perkins, *J. Chem. Soc., Perkin Trans. 2*, 1983, 587–589.

48. H. J. Schäfer, *Top. Curr. Chem.*, 1987, **142**, 101–129.
49. S. Torii, A. L. Dhimane, Y. Araki, and T. Inokuchi, *Tetrahedron Lett.*, 1989, **30**, 2105–2108.
50. A. Kirste, G. Schnakenburg, F. Stecker, *et al*., *Angew. Chem. Int. Ed.*, 2010, **49**, 971–975.
51. I. M. Malkowsky, C. E. Rommel, K. Wedeking, *et al*., *Eur. J. Org. Chem.*, 2006, 241–245.
52. M. Takahashi, H. Konishi, S. Iida, *et al*., *Tetrahedron*, 1999, **55**, 5295–5302.
53. K. Mori, M. Takahashi, S. Yamamura, and S. Nishiyama, *Tetrahedron*, 2001, **57**, 5527–5532.
54. S. Yamamura and S. Nishiyama, *Synlett*, 2002, 533–543.
55. S. Nishiyama, M. H. Kim, and S. Yamamura, *Tetrahedron Lett.*, 1994, **35**, 8397–8400.
56. A. Ronlán, K. Bechgaard, and V. D. Parker, *Acta Chem. Scand.*, 1973, **27**, 2375–2382.
57. A. Ronlán, B. Aalstad, and V. D. Parker, *Acta Chem. Scand.*, 1982, **36b**, 317–325.
58. S. R. Waldvogel, A. R. Wartini, P. H. Rasmussen, and J. Rebek, *Tetrahedron Lett.*, 1999, **40**, 3515–3517.
59. S. R. Waldvogel and D. Mirk, *Tetrahedron Lett.*, 2000, **41**, 4769–4772.
60. S. R. Waldvogel, R. Fröhlich, and C. A. Schalley, *Angew. Chem. Int. Ed.*, 2000, **39**, 2472–2475.
61. V. D. Parker and A. Ronlán, *J. Am. Chem. Soc.*, 1975, **97**, 4714–4721.
62. A. Ronlán, O. Hammerich, and V. D. Parker, *J. Am. Chem. Soc.*, 1973, **95**, 7132–7138.
63. A. Ronlán and V. D. Parker, *J. Org. Chem.*, 1974, **39**, 1014–1016.
64. W. Eilenberg and H. J. Schäfer, *Tetrahedron Lett.*, 1984, **25**, 5023–5026.
65. R. L. Hand and R. F. Nelson, *J. Am. Chem. Soc.*, 1974, **96**, 850–860.
66. R. Hand and R. F. Nelson, *J. Electrochem. Soc.*, 1970, **117**, 1353–1357.
67. G. Cauquis, J. Cognard, and D. Serve, *Tetrahedron Lett.*, 1971, **12**, 4645–4648.
68. I. Tabakovic and K. Tabakovic, *Tetrahedron Lett.*, 1996, **37**, 3659–3662.
69. A. Berlin, A. Canavesi, G. Schiavon, *et al*., *Tetrahedron*, 1996, **52**, 7947–7960.
70. M. Buda, A. Iordache, C. Bucher, *et al*., *Chem.—Eur. J.*, 2010, **16**, 6810–6819.
71. J. D. Wadhawan, F. Marken, R. G. Compton, *et al*., *Chem. Commun.*, 2001, 87–88.
72. J. Hiebl, H. Kollmann, F. Rovenszky, and K. Winkler, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2963–2966.
73. A. Weiper-Idelmann, M. Kahmen, and H. J. Schäfer, *Acta Chem. Scand.*, 1998, **52**, 672–682.
74. K. Schierle, J. Hopke, M. L. Niedt, *et al*., *Tetrahedron Lett.*, 1996, **48**, 8715–8718.
75. M. J. Steinbauer, F. Östrand, T. E. Bellas, *et al*., *Chemoecology*, 2004, **14**, 217–223.
76. A. Brecht-Forster, J. Fitremann, and P. Renaud, *Hel. Chim. Acta*, 2002, **85**, 3965–3974.
77. R. F. Garwood and B. C. L. Weedon, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2714–2721.
78. J. Weiguny and H. J. Schäfer, *Liebigs Ann. Chem.*, 1994, 235–242.
79. A. Matzeit, H. J. Schäfer, and C. Amatore, *Synthesis*, 1995, 1432–1444.
80. F. Lebreux, F. Buzzo, and I. E. Markó, *Synlett.*, 2008, 2815–2820.
81. H. Kurihara, T. Fuchigami, and T. Tajima, *J. Org. Chem.*, 2008, **73**, 6888–6890.
82. T. Tajima, H. Kurihara, and T. Fuchigami, *J. Am. Chem. Soc.*, 2007, **129**, 6680–6681.
83. A. V. Shtelman and J. Y. Becker, *Electrochim. Acta*, 2009, **54**, 6696–6699.
84. M. Sugiya and H. Nohira, *Chem. Lett.*, 1998, 479.
85. M. Sugiya and H. Nohira, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 705–712.
86. S. Prigent, P. Cauliez, J. Simonet, and D. G. Peters, *Acta Chem. Scand.*, 1999, **53**, 892–900.
87. I. Barba and M. Tornero, *Tetrahedron*, 1997, **53**, 8613–8624.
88. F. Barba, M. G. Quintanilla, and G. Montero, *J. Org. Chem.*, 1995, **60**, 5658–5660.
89. K. Fujimoto, Y. Tokuda, Y. Matsubara, *et al*., *Tetrahedron Lett.*, 1995, **36**, 7483–7486.
90. O. Buriez, J.-Y. Nedelec, and J. Perichon, *J. Electroanal. Chem.*, 2001, **506**, 162–169.
91. H.-C. Xu and K. D. Moeller, *Org. Lett.*, 2010, **12**, 1720–1723.
92. S. Kratschmer, H. J. Schäfer, and R. Frohlich, *J. Electroanal. Chem.*, 2001, **507**, 2–10.
93. C. M. Sanchez-Sanchez, E. Exposito, B. Batanero, *et al*., *Electrochem. Commun.*, 2004, **6**, 595–599.
94. J. Kaminski, M. Pachulska, R. Stolarski, and Z. Kazimierczuk, *Tetrahedron*, 1997, **53**, 2609–2616.
95. K. N. Knust, M. P. Foley, M. S. Mubarak, *et al*., *J. Electroanal. Chem.*, 2010, **638**, 100–108.
96. C. Kaimakliotis and A. J. Fry, *J. Org. Chem.*, 2003, **68**, 9893–9898.
97. L. M. Korotayeva, T. Y. Rubinskaya, E. V. Klimkina, *et al*., *Russ. Chem. Bull.*, 2000, **49**, 2037–2044.
98. M. A. Bohn, G. Hilt, P. Bolze, and C. Gürtler, *ChemSusChem*, 2010, **3**, 823–828.
99. K. Schnatbaum and H. J. Schäfer, *Synthesis*, 1999, **5**, 864–872.
100. M. Schamann and H. J. Schäfer, *Eur. J. Org. Chem.*, 2003, **2**, 351–358.
101. Y. Demizu, H. Shiigi, T. Oda, *et al*., *Tetrahedron Lett.*, 2007, **49**, 48–52.
102. F. Billon-Souquet, T. Martens, and J. Royer, *Tetrahedron*, 1996, **52**, 15127–15136.
103. T. Martens, F. Billon-Souquet, I. Gauthier, and J. Royer, *Tetrahedron Lett.*, 1997, **38**, 4075–4078.
104. E. Le Gall, J.-P. Hurvois, and S. Sinbandhit, *Eur. J. Org. Chem.*, 1999, **10**, 2645–2653.
105. M. Sugawara, K. Mori, and J.-I. Yoshida, *Electrochim. Acta*, 1997, **42**, 1995–2003.
106. C.-C. Zeng, D.-W. Ping, S.-C. Zhang, *et al*., *J. Electroanal. Chem.*, 2008, **622**, 90–96.
107. N. Kise, K. Fukazawa, and T. Sakurai, *Tetrahedron Lett.*, 2010, **51**, 5767–5770.
108. N. Kise, T. Mano, and T. Sakurai, *Org. Lett.*, 2008, **10**, 4617–4620.
109. N. Kise, K. Arimoto, and N. Ueda, *Tetrahedron Lett.*, 2003, **44**, 6281–6284.
110. S. Goda, K. Yamada, Y. Yamamoto, *et al*., *J. Electroanal. Chem.*, 2003, **545**, 129–140.

111. A. K. Yadav, M. Manju, M. Kumar, *et al*., *Tetrahedron Lett.*, 2008, **49**, 5724–5726.
112. M. N. Elinson, S. K. Feducovich, Z. A. Starikova, *et al*., *Tetrahedron*, 2004, **60**, 11743–11749.
113. M. N. Elinson, S. K. Feducovich, A. N. Vereshchagin, *et al*., *Tetrahedron Lett.*, 2006, **47**, 9129–9133.
114. M. N. Elinson, S. K. Feducovich, Z. A. Starikova, *et al*., *Tetrahedron*, 2006, **62**, 3989–3996.
115. M. N. Elinson, S. K. Feducovich, T. A. Zaimovskaya, *et al*., *Russ. Chem. Bull.*, 2005, **54**, 1593–1598.
116. M. N. Elinson, S. K. Feducovich, T. A. Zaimovskaya, *et al*., *Russ. Chem. Bull.*, 2005, **54**, 673–677.
117. M. N. Elinson, S. K. Feducovich, Z. A. Starikova, *et al*., *Tetrahedron Lett.*, 2005, **46**, 6389–6393.
118. M. N. Elinson, S. K. Fedukovich, A. N. Vereshchagin, *et al*., *Russ. Chem. Bull.*, 2003, **52**, 2235–2240.
119. M. N. Elinson, S. K. Fedukovich, T. A. Zaimovskaya, *et al*., *Russ. Chem. Bull.*, 2003, **52**, 2241–2246.
120. M. N. Elinson, S. K. Feducovich, Z. A. Starikova, *et al*., *Tetrahedron Lett.*, 2000, **41**, 4937–4941.
121. A. P. Esteves, D. M. Goken, L. J. Klein, *et al*., *J. Electroanal. Chem.*, 2003, **560**, 161–168.
122. A. P. Esteves, C. S. Neves, M. J. Medeiros, and D. Pletcher, *J. Electroanal. Chem.*, 2008, **614**, 131–138.
123. E. Dunach, A. P. Esteves, M. J. Medeiros, and S. Olivero, *New J. Chem.*, 2005, **29**, 633–636.
124. E. Dunach, A. P. Esteves, A. M. Freitas, *et al*., *Pure Appl. Chem.*, 2001, **73**, 1941–1945.
125. A. P. Esteves, A. M. Freitas, M. J. Medeiros, and D. Pletcher, *J. Electroanal. Chem.*, 2001, **499**, 95–102.
126. M. Toyota, A. Ilangovan, Y. Kashiwagi, and M. Ihara, *Org. Lett.*, 2004, **6**, 3629–3632.
127. S. Ozaki, E. Matsui, J. Waku, and H. Ohmori, *Tetrahedron Lett.*, 1997, **38**, 2705–2708.
128. S. Ozaki, E. Matsui, T. Saiki, *et al*., *Tetrahedron Lett.*, 1998, **39**, 8121–8124.
129. S. Ozaki, M. Adachi, S. Sekiya, and R. Kamikawa, *J. Org. Chem.*, 2003, **68**, 4586–4589.
130. S. Ozaki, H. Yoshinaga, E. Matsui, and M. Adachi, *J. Org. Chem.*, 2001, **66**, 2503–2505.
131. S. Ozaki, E. Matsui, H. Yoshinaga, and S. Kitagawa, *Tetrahedron Lett.*, 2000, **41**, 2621–2624.
132. X. Jia, H. Lin, C. Huo, *et al*., *Synlett*, 2003, 1707–1709.
133. H. Kawafuchi and T. Inokuchi, *Tetrahedron Lett.*, 2002, **43**, 2051–2054.
134. C. K. Njue, B. Nuthakki, A. Vaze, *et al*., *Electrochem. Commun.*, 2001, **3**, 733–736.
135. A. A. Isse, A. Galia, C. Belfiore, *et al*., *J. Electroanal. Chem.*, 2002, **526**, 41–52.
136. T. Shono, N. Kise, T. Fujimoto, *et al*., *J. Org. Chem.*, 1994, **59**, 1730–1740.
137. T. J. Davies, C. E. Banks, B. Nuthakki, *et al*., *Green Chem.*, 2002, **4**, 570–577.
138. V. A. Sauro, D. C. Magri, J. L. Pitters, and M. S. Workentin, *Electrochim. Acta*, 2010, **55**, 5584–5591.
139. A. A. Isse, A. De Giusti, A. Gennaro, *et al*., *Electrochim. Acta*, 2006, **51**, 4956–4964.
140. J. Simonet, *J. Electroanal. Chem.*, 2005, **583**, 34–45.
141. O. Buriez, C. Cannes, J.-Y. Nedelec, and J. Perichon, *J. Electroanal. Chem.*, 2000, **495**, 57–61.
142. O. M. Nikitin, G. V. Gavrilova, and T. V. Magdesieva, *Russ. Chem. Bull.*, 2007, **56**, 1013–1019.
143. A. Gennaro, A. A. Isse, and F. Maran, *J. Electroanal. Chem.*, 2001, **507**, 124–134.
144. M. P. Foley, P. Du, K. J. Griffith, *et al*., *J. Electroanal. Chem.*, 2010, **647**, 194–203.

Please note that the abstract and keywords will not be included in the printed book, but are required for the online presentation of this book which will be published on Wiley's own online publishing platform.

If the abstract and keywords are not present below, please take this opportunity to add them now. The abstract should be a short paragraph upto 200 words in length and keywords between 5 and 10 words.

Abstract: This article reports on the applications of electrochemistry for the generation of radicals as neutral, cationic, and anionic intermediates and their use in preparative reactions for the formation of carbon–carbon and carbon–heteroatom bonds. The focus of this article is on electrochemical oxidation reactions of enol ethers, ketene acetals, and electron-rich aromatic compounds. Furthermore, recent advances in the electrochemically induced synthesis of four-membered ring systems and biaryl compounds are covered. The oxidative carbon–carbon bond formation by Kolbe electrolysis concludes the section dealing with oxidative transformations. The section describing reductive processes consists of indirect electrochemical reduction of alkylhalides and thioesters, as well as the reductive interconversion of functional groups described recently.

Keywords: electrochemistry; radical intermediates; enol ethers; ketene acetals; furanes; Kolbe electrolysis; biphenylenes; indirect electrolysis; nickel redox catalysis; aminoxy radicals; oxidation; reduction