Modern Strategies in Electroorganic Synthesis

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Contents

Jun-ichi Yoshida was born in Osaka, Japan in 1952. He graduated from Kyoto University in 1975, where he received his doctor's degree under the supervision of Prof. Makoto Kumada in 1981. In 1979 Yoshida joined the faculty at Kyoto Institute of Technology as an assistant professor. In the meantime, he visited University of Wisconsin during 1982−1983, where he joined the research group of Prof. B. M. Trost. In 1985 he moved to Osaka City University, where he was promoted to an associate professor in 1992. In 1994 he was appointed as a full professor of Kyoto University. His research interests include integrated organic synthesis on the basis of reactive intermediates, organic electron transfer reactions, organometallic reactions, and microreactors. Awards: the Progress Award of Synthetic Organic Chemistry, Japan (1987), the Chemical Society of Japan Award for Creative Work (2001), Nagoya Silver Medal of Organic Chemistry (2006), and Humboldt Research Award (2007).

Kazuhide Kataoka was born in Okayama in 1977 and received his Ph.D. in 2005 under the direction of Professor J. Nokami from Okayama university of science. Thereafter, he moved to JST Innovation Plaza, Kyoto. His main research interests are electroorganic chemistry.

1. Introduction

Electron transfer is one of the most important processes in organic chemistry, and many organic reactions are driven by electron-transfer processes.[1] In an electron-transfer process, one electron is added to or removed from a substrate molecule. Such an electron transfer is reversible only when the resulting species is stable under those conditions. In other cases, an electron transfer triggers subsequent chemical processes, such as bond dissociation and bond formation.

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Roberto Horcajada studied the Degree in Chemistry at the University of Alcala de Henares in Spain, where he briefly collaborated with Prof. Barba in the field of organic electrochemistry. Then he moved to the Queen Mary University of London for his Ph.D. under the supervision of Prof. James H. P. Utley and Dr. Peter B. Wyatt in the field of Electrogenerated Chiral Bases. After a short period at the Institute of biotechnology with Prof. Elisabeth H. Hall, he joined the Department of Synthetic Chemistry and Biological Chemistry of the University of Kyoto with Prof. Jun-ichi Yoshida for two years to develop, among other research projects, parts of the present work. He is currently working at the Barcelona based company IUCT as International Projects Coordinator, managing several multimillion Euro projects.

Aiichiro Nagaki was born in Osaka, Japan, in 1973. He received his Ph.D. in 2005 from Kyoto University under the supervision of Professor Jun-ichi Yoshida. He worked with Professor Hiroaki Suga, Tokyo University, for one year as a postdoctoral fellow. In 2006, he became an assistant professor of Kyoto University and joined the research group of Professor Jun-ichi Yoshida. In 2005, he received the Bulletin Chemical Society of Japan Award in Synthetic Organic Chemistry, Japan. His current research interests are organic synthesis, electroorganic synthesis, and microreactor synthesis.

In organic synthesis, electron-transfer-driven reactions have been widely used for various transformations, although their potential has not yet been fully utilized. Among several methods for electron-transfer-driven reactions, the electrochemical method serves as a straightforward and powerful method. In fact, various carbon−carbon bond formations and functional group transformations can be accomplished by the electrochemical method. For example, the Kolbe reaction[2] that involves the oxidation of carboxylate anions at an anode has been known for many years and still serves as a powerful tool for carbon−carbon bond formation in organic synthesis. In the Kolbe reaction, the initial electron transfer followed by the elimination of CO_2 generates carbon free radicals, which homocouple to make a new carbon−carbon bond. It is noteworthy that the electrochemical method serves as an excellent method for the generation of reactive species under mild conditions. In fact, radical cations and radical anions can be generated by electrochemical electron-transfer reactions of neutral organic compounds. Carbocations, carbon free radicals, and carbanions can also be generated by subsequent bond-dissociation or bond-forming processes. These reactive carbon species are utilized in various synthetic transformations, especially carbon−carbon bond formations. Oxidation and reduction of functional groups are also important transformations in organic synthesis, and the electrochemical method serves as "greener" procedures for such transformations. Therefore, electroorganic synthesis[3,4] has received significant research interest from both academia and industry.

Because modern applications of traditional electrochemical methods have been recently reviewed,[5] this article will provide an outline of principles and applications of new methods for effecting organic electrochemical reactions that have been developed in recent decades.

2. Background

While extensive work has been done to control the selectivity of traditional chemical methods, less work has been aimed at electrochemical methods. It is important to note that reactivity control of substrates at the molecular level has been rather neglected, although a full repertoire of methods for such control has been developed. For example, directing groups that coordinate metal centers and guide the course of reactions are very popular in organometallic synthesis,[6] but a similar approach has not been widely used in electrochemical synthesis. This is an important gap because the electrochemical reaction offers unique challenges that cannot always be solved using methods employed in traditional chemical reactions. These challenges should involve controlling both the selectivity of electron transfer and the subsequent formation of reactive intermediates at the molecular level.

A variety of new reaction media and separation methods such as solid-phase synthesis[7] and strategic separation[8] have been developed in modern organic synthesis. The use of similar methods may open new possibilities of organic electrochemical synthesis, although a simple combination of a polar organic solvent and an ionic supporting electrolyte has been commonly used in conventional organic electrochemistry.

In modern organic synthesis, low temperatures and anhydrous conditions are often employed to conduct reactions in a highly selective manner. However, it has been considered that electrochemical reactions should be conducted at around room temperature and that the presence of moisture is inevitable, although this is not the case any more if we choose an appropriate solvent/electrolyte system. The choice of appropriate devices for electrolysis is also important, because cell conductivity and mass transfer on the surface of the electrode are crucial for efficiency and selectivity of electrochemical reactions. Such issues might be a barrier to applications of the electrochemical method in organic synthesis.

However, extensive studies have been carried out recently to solve such problems, and many different types of strategies have been reported in the literature. Such strategies, which will be discussed in the following sections, open up new possibilities for electroorganic synthesis.

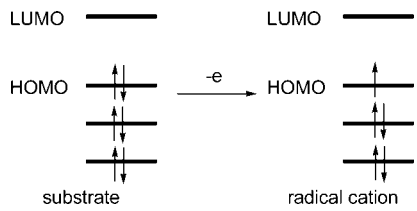


Figure 1. Molecular-orbital diagram for electron transfer.

3. Intramolecular Control

Methods using functional groups that control the reactivity of substrate molecules and reaction pathways are often used in organic synthesis. They are quite effective for driving otherwise difficult reactions and controlling reaction pathways to obtain the desired products selectively. Recently, a few methods for such intramolecular control have also been developed in electroorganic synthesis, which will be discussed in this section.

In electrochemical processes, the tendency of the substrates to undergo electron transfer is represented by their oxidation and reduction potentials. The electron-transfer process is more favorable when the oxidation potential is less positive and the reduction potential is less negative. In order to achieve electron-transfer-driven reactions selectively, the following two points should be considered.

(1) Electron transfer should occur selectively at the position that is needed for the subsequent chemical process.

(2) The subsequent chemical process should occur selectively to cleave the specific bond or make a bond in the specific position.

From the viewpoints of synthetic efficiency and atom economy, the external control, in principle, should be better than the internal approach, but effective and general external methods that enable electron transfer and subsequent chemical processes in a highly selective manner have not yet been developed in electroorganic synthesis. Therefore, we focus only on the intramolecular approaches that use functional groups and templates to guide and facilitate highly selective electroorganic reactions.

3.1. Electroauxiliaries

One of the most straightforward ways for the intramolecular control of electron-transfer-driven reactions is the introduction of a functional group that promotes the electron transfer in a more selective and predictable manner. Such a functional group is called an electroauxiliary (EA).[9] EAs make the electron-transfer process more favorable. Therefore, the oxidation potential becomes less positive or the reduction potential becomes less negative. Another important role of EAs is the control of subsequent chemical processes. In the case that there are several reaction pathways for the reactive species generated by the electron transfer, the EA may facilitate one of them to give a desired product in high selectivity.

This section deals with a brief outline of the principles of EAs and their applications in synthetic electroorganic reactions. Only the EAs for oxidative electron transfer are discussed here, because synthetic applications of EAs in reductive reactions are rather rare.[10]

From a molecular orbital point of view, the oxidation process can be explained by electron transfer from the highest occupied molecular orbital (HOMO) of a substrate (Figure 1). Therefore, an increase in the HOMO level is the most straightforward method for activating the substrate toward oxidation.

In the case where many substrates are susceptible to oxidation, the selectivity of the oxidation process depends on the difference between the HOMO levels of the substrates. The selectivity is higher when the difference between the HOMO levels is greater. If the HOMO levels are very close to each other, however, it is difficult to oxidize one of the substrates without affecting the other. When the substrate that we wish to oxidize has a lower HOMO level than that of the other species, it is, in principle, impossible to accomplish selective oxidation of the substrate. In this case, selective increase of the HOMO level of the substrate that we wish to oxidize by the introduction of an EA serves as a powerful method for accomplishing the desired selective oxidation.

In the case where several sites are susceptible to oxidation in a single molecule, a similar argument can be applied, and the use of an EA to activate a particular functional group that we wish to oxidize is effective for selective oxidation.

Another important issue that we must consider is the stabilization of a radical cation generated by one-electron oxidation of the substrate. The rate of electron transfer depends on the height of the energy barrier. Because the electron-transfer is normally endothermic, stabilization of the radical cation, the energy of which is close to the transition state according to the Bell−Evans−Polanyi principle, usually facilitates the electron transfer. Therefore, functional groups that stabilize the radical cation may act as EAs.

There are several types of EAs based on different principles. The choice of EA depends on the nature of the substrate and reagent.

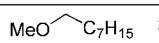
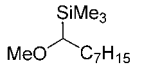
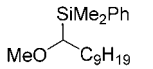
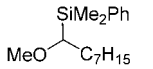
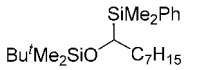
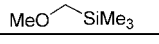
3.1.1. Principles of Electroauxiliaries

3.1.1.1. Electroauxiliaries Based on Molecular Orbital Interaction. The orbital interaction is quite effective for producing activation by increasing the HOMO level. In principle, the interaction of the HOMO with a high energy filled orbital increases its energy level. For example, the energy level of a C−Si σ orbital is usually much higher than that of C−H and C−C σ orbitals. Therefore, the C−Si σ orbital interacts effectively with a nonbonding orbital of heteroatoms such as N, O, and S, which are often the HOMOs of heteroatom compounds (σ−n interaction). The interaction of the C−Si σ orbital is also effective for raising the energy level of π-systems ($\sigma-\pi$ interaction). Stabilization of the radical cations by molecular orbital interaction is also important.

$\sigma-n$ Interactions. The introduction of a silyl group in an α-position to an oxygen atom significantly decreases the oxidation potentials (E) of ethers (Table 1). The oxidation potentials of α-silyl ethers are much lower than those of the parent ethers.[11,12] The nature of the substituents on silicon has some influence on the oxidation potential, although the magnitude is not particularly large.[13]

The decrease in the oxidation potentials by the introduction of a silyl group can be explained in terms of an overlap between the C−Si σ orbital and the nonbonding 2p orbital of O in the neutral molecule. Two new MOs are formed as the result of such an interaction: the orbital produced by the bonding interaction has a lower energy than the original orbitals, and the orbital produced by the antibonding interaction has a higher energy, as shown in Figure 2 (the principle of orbital interaction). The latter orbital becomes the HOMO

Table 1. Oxidation Potentials of Silicon-Substituted Ethers and Related Compounds

compound	E(V)
	>2.50
	1.72
	1.60
	1.72
	1.92
	1.90

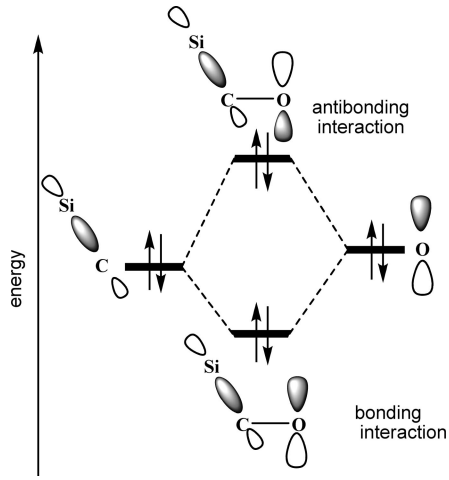


Figure 2. Interaction between the C−Si σ orbital and the nonbonding 2p orbital of an oxygen atom in the neutral molecule.

of the α-silyl ether. This means that the HOMO level of an α-silyl ether is higher than that of the corresponding simple ether, where the nonbonding 2p orbital of O is the HOMO. In other words, the interaction with a neighboring C−Si σ orbital increases the HOMO level of an ether, which in turn favors the electron transfer.

The decrease in the oxidation potential can also be explained in terms of stabilization of the radical cation, which is produced by the electron transfer. The filled C−Si σ orbital interacts with the half-filled 2p orbital of O to produce two new orbitals, as shown in Figure 3. The orbital produced by the bonding interaction has two electrons, and that produced by the nonbonding interaction has one electron. This means that two electrons are stabilized and one electron is destabilized and that the interaction causes a net stabilization of the radical cation.

It is also important to note that such an orbital interaction in the radical cation weakens the C−Si bond. Therefore, the C−Si bond in the radical cation is cleaved selectively in the subsequent chemical process (Scheme 1). The carbon radical thus generated is further oxidized to give a carbocation stabilized by the neighboring oxygen, which reacts with a nucleophile to give the product. Thus, the silyl group controls the fate of the radical cation.

A C−Si σ orbital can also interact with a neighboring nonbonding 2p orbital of nitrogen, raising the HOMO level to decrease the oxidation potential (Table 2).[14,15]

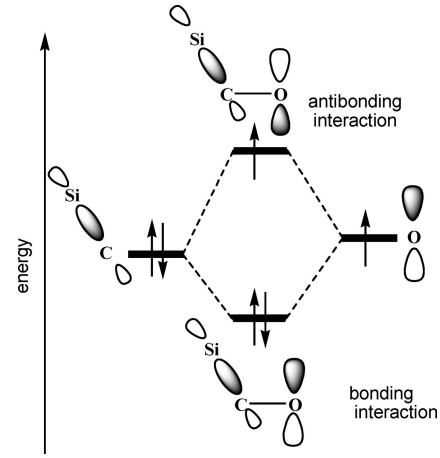


Figure 3. Interaction between the C−Si σ orbital and the half-filled 2p orbital of an oxygen atom in a radical cation.

Scheme 1

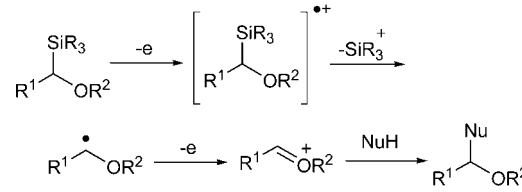
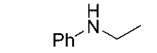
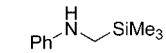
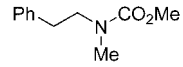
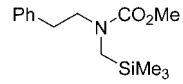
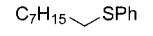
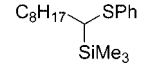


Table 2. Oxidation Potentials of Amines, Carbamates, and Sulfides

compound	E(V)
	0.59
	0.44
	1.95
	1.45
	1.20
	1.10

Silyl groups are also effective in decreasing the oxidation potentials of sulfides, although the magnitude is not large. α-Silyl sulfides have an oxidation potential about 0.1 V lower than that of the parent sulfides.[16] The small effect of the silyl group seems to be attributed to a weaker orbital interaction because of the larger energy difference between the 3p orbital of the S and the C−Si σ orbital. In general, the effectiveness of the silyl groups as electroauxiliaries for the oxidation of heteroatom compounds varies in the order O > N > S.

The oxidation potentials can be tuned by changing the groups on silicon (Table 3), although the effect is not very large.[17]

Germyl[18] and stannyl[19] groups also serve as electroauxiliaries for oxidation of heteroatom compounds. In addition, the oxidation potentials of stannyl-substituted heteroatom compounds are lower than those of the corresponding silyl-substituted compounds. For example, the difference between the oxidation potentials of α-trimethylsilyl ethers and those of α-tributylstannyl ethers is about 0.4−0.7 V (Table 4).

Table 3. Oxidation Potentials of α-Silyl Carbamates and Sulfides with Various Substituents on Silicon

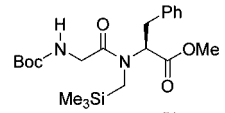
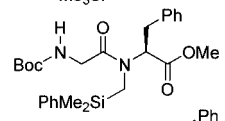
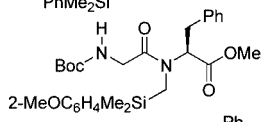
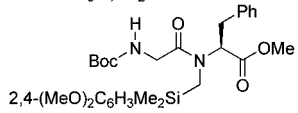
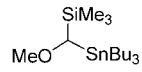
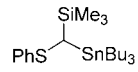
compound	E(V)	compound	E(V)
	1.63	PhS–SiMe$_3$	1.17
		PhS–SiMe$_2$H	1.17
	1.67	PhS–SiMe$_2$C$_{10}$H$_{21}$	1.18
		PhS–SiMe$_2$F	1.27
	1.64		
	1.38		

Table 4. Oxidation Potentials of α-Silyl-α-Stannyl Ethers and Thioethers

compound	E(V)	compound	E(V)
MeO–SiMe$_3$	1.60	PhS–SiMe$_3$	1.12
MeO–SnBu$_3$	0.91	PhS–SnBu$_3$	0.69
	0.90		0.62

Glass and co-workers reported that the introduction of a stannyl group at an α-position in sulfides significantly decreases the oxidation potentials.[20,21] In the case of a silyl group, the high energy level of the 3p orbital of S does not allow a strong interaction with the C−Si σ orbital. However, in the stannyl case, the C−Sn σ orbital of higher energy can effectively interact with the 3p orbital of S, with a concomitant increase in the HOMO level. The C−Sn bond is selectively cleaved in the thus-generated radical cation, and therefore, the stannyl group also controls the reaction pathway.

The oxidation potentials of compounds containing both Si and Sn on the same carbon are very similar to those of compounds having only Sn, as outlined in Table 4.[22,23]

In contrast, the introduction of two silyl groups at the α-position(s) to a heteroatom causes a further decrease in the oxidation potential, as outlined in Table 5.[24]

The oxidation potentials of substituted 1,3-benzodithioles[25] also depend strongly on the number of silyl groups in the 2-position. The introduction of the second silyl group causes a decrease of 0.18 V in the oxidation potential. A similar effect is observed for distannyl compounds.

$\sigma-\pi$ Interactions. It is well-known that the ionization potential decreases when a silyl group is introduced in allylic or benzylic positions.[26] Similar to the $\sigma-$n interaction, the increase in the HOMO level by the orbital interaction is responsible (the $\sigma-\pi$ interaction). Another explanation is that the interaction of a half-filled π orbital with the C−Si σ bond causes a net stabilization of one electron in the radical cation. Such an interaction weakens the C−Si bond, and therefore, the C−Si bond is cleaved selectively after the electron transfer. A similar effect is also observed for stannyl groups.

Table 5. Oxidation Potentials of Carbamates, Ethers, and Thioethers Having Two Silyl Groups

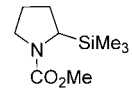
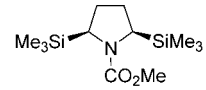
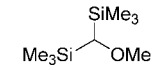
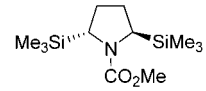
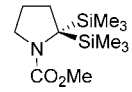
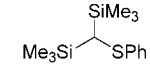
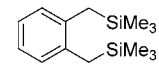
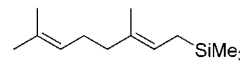
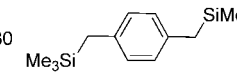
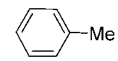
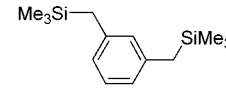
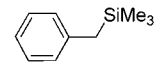
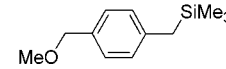
compound	E(V)	compound	E(V)
	1.23	Me$_3$Si–OMe	1.58
	1.13		1.25
	1.10	Me$_3$Si–SPh	1.17
	1.09		1.09

Table 6. Oxidation Potentials of Allylsilanes and Benzylsilanes

compound	E(V)	compound	E(V)
	1.85		1.13
	1.30		1.06
	1.98		1.12
	1.38		1.12

As shown in Table 6, the oxidation potentials of allylic and benzylic silanes are less positive than those of the parent olefins and aromatic compounds.[27–29]

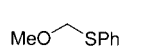
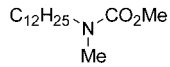
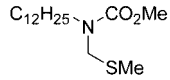
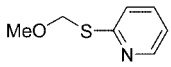
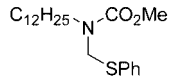
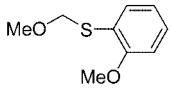
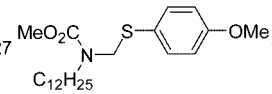
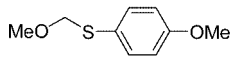
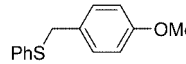
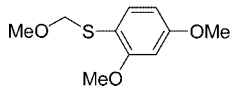
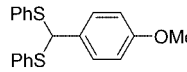
Fry and co-workers pointed out that homobenzylsilane derivatives also have low oxidation potentials, presumably because of the γ-effect of silyl groups.[30] Therefore, the silyl group serves as an EA for oxidation of the homobenzylic position.

3.1.1.2. Electroauxiliaries Based on High Energy Level Nonbonding Orbitals. The introduction of an arylthio (ArS) group at an α-position of an ether causes a significant decrease in the oxidation potential (Table 7).[31] In contrast, the oxidation potential of an α-ArS ether is slightly more positive than that of the corresponding simple sulfide (ArSR).[32] This means that the orbital interaction is not responsible for the decrease of the oxidation potential upon introducing an ArS group to ethers. The introduction of an ArS group at the α-position of carbamates also decreases their oxidation potentials.[33–35]

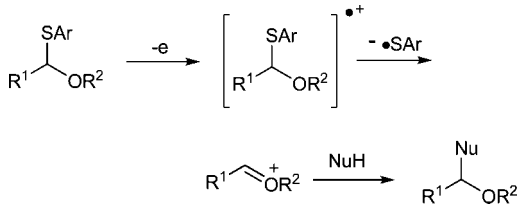
Another important point is that the oxidation of α-ArS-substituted heteroatom compounds leads to the selective cleavage of the C−S bond to give a cation stabilized by the heteroatom, which reacts with a nucleophile to give a product. Therefore, the function of the ArS group is quite similar to that of silyl and stannyl groups. Therefore, it is reasonable to consider that the ArS group serves as an EA.

The mechanism of the oxidation of ArS-substituted heteroatom compounds, however, seems to be different from that for the silyl and stannyl cases. The electron transfer of α-ArS-substituted ethers and carbamates seems to take place from the nonbonding orbital of S, the energy level of which

Table 7. Oxidation Potentials of Organosulfur Compounds

Compound	E(V)	Compound	E(V)
	1.40		1.92
	1.24		1.24
	1.78		1.37
	1.27		1.13
	1.18		1.05
	1.00		0.95

Scheme 2



is much higher than those of O and N. In the thus-generated radical cation, the C−S σ orbital is perpendicular to the half-filled 3p orbital of S. However, the generation of a positive charge on S significantly weakens the C−S bond, which eventually collapses to give a carbocation and ArS radical (Scheme 2). Nucleophilic attack on the carbocation then gives the product.

One of the advantages of the ArS group as an EA is the easy tuning of the activity by changing the substituent on the aryl group. For example, the introduction of electrodonating groups on the aryl group such as a methoxy group causes a decrease in the oxidation potential, as depicted in Table 7.

Other chalcogen atoms such as Se and Te also serve as electroauxiliaries. For example, the introduction of ArSe and ArTe on the anomeric carbon of glycosides facilitates the electron transfer.[36]

3.1.1.3. Electroauxiliaries Based on Intramolecular Coordination. Oxidative electron transfer in solution is generally assisted by the stabilization of the resulting radical cation by the coordination of solvent molecules or ions that are present in the solution. However, if a substrate molecule has a specific coordinating site to stabilize the developing charge, the electron transfer should be assisted by intramolecular coordination (Figure 4). Such coordination is also expected to facilitate subsequent chemical processes such as fragmentation.

The oxidation of tetraalkylstannanes having a coordinating group at a suitable position serves as a good example of this concept.[37] The intramolecular coordination stabilizes the radical cation of Sn and, therefore, makes the electron transfer easy. As a result, the oxidation potentials of such compounds are lower than that of the parent compound (Table 8).

The pyridyl group is also effective as a coordinating group for the oxidation of compounds containing heteroatoms such

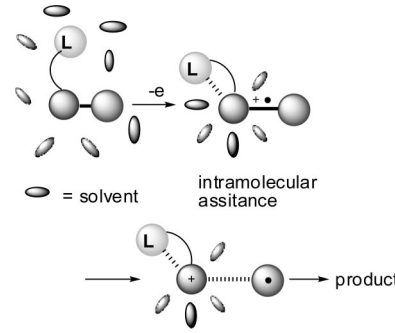


Figure 4. Oxidative electron transfer in solution and stabilization of a radical cation by intramolecular coordination of a suitable functional group (L).

Table 8. Oxidation Potentials of Organostannanes Having a Coordinating Group

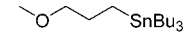
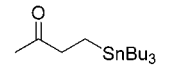
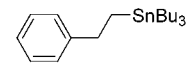
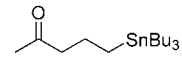
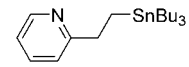
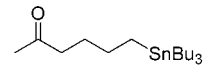
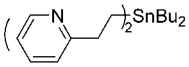
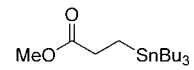
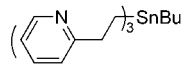
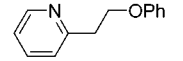
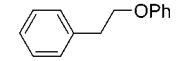
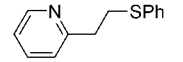
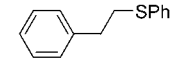
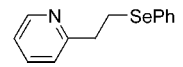
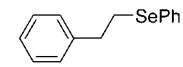
compound	E(V)	compound	E(V)
$SnBu_4$	1.67		1.42
	1.41		1.50
	1.55		1.14
	1.61		1.03
	1.48		0.92

Table 9. Oxidation Potentials of 2-PyCH$_2$CH$_2$YPh and PhCH$_2$CH$_2$YPh (Y = O, S, Se)

compound	E(V)	compound	E(V)
	1.32		1.58
	1.12		1.21
	0.99		1.05

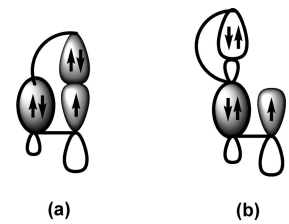


Figure 5. Two types of cooperative effects of orbital interaction and coordination in a radical cation.

as O, S, and Se.[38] As shown in Table 9, 2-(2-pyridyl)ethyl substituted ethers, sulfides, and selenides have lower oxidation potentials than the corresponding 2-phenylethyl derivatives.

3.1.1.4. Combination of Different Principles. A combination of the orbital interaction and intramolecular coordination is effective for controlling the oxidation potential and the reaction pathway. This combination can be performed in two ways in terms of the stabilization of the radical cation, as depicted in Figure 5: (a) two filled orbitals may interact with the singly occupied molecular orbital (SOMO), or (b) the SOMO may interact with a filled orbital that has another interaction with another filled orbital from the back.

Table 10. Oxidation Potentials of Sulfides Having Silyl and/or Pyridyl Groups

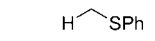
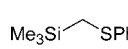
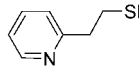
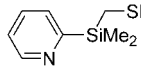
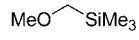
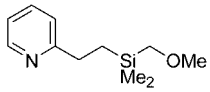
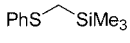
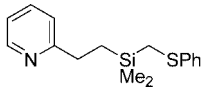
compound	E (V)
	1.21
	1.12
	1.12
	1.07

Table 11. Oxidation Potentials of α-Silyl Ethers and Sulfides with and without a Pyridyl Group

compound	Ep (V)
	1.58
	1.36
	1.12
	0.93

Examples of the interaction depicted in Figure 5a are outlined in Table 10. As has already been noted in the previous sections, the introduction of a silyl group in the α-position of a sulfide causes a decrease in the oxidation potential. Intramolecular assistance by pyridyl coordination to S also causes a decrease in the oxidation potential. The two effects work simultaneously, producing a further decrease in the oxidation potential, although the extent of the effect is small.[15]

The orbital interaction shown in Figure 5b is demonstrated by the examples shown in Table 11. The substitution of a methyl group on Si by a 2-pyridylethyl group causes a decrease in the oxidation potential.[39] This is an indication that both the $\sigma-$n interaction and the intramolecular coordination work simultaneously.[38]

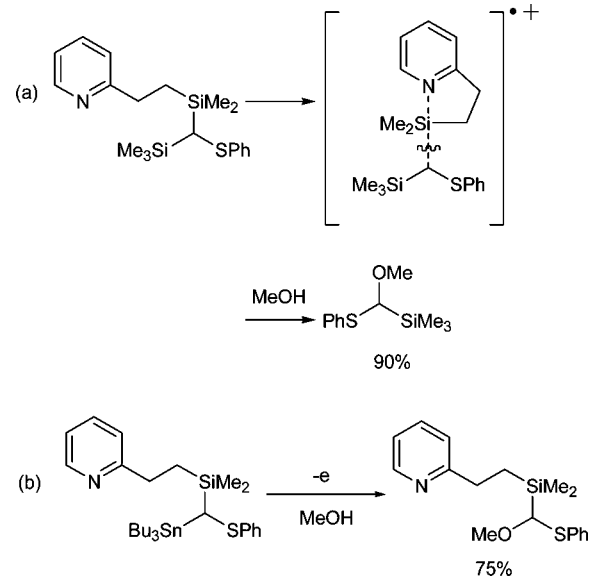
The anodic methoxylation shown in Scheme 3 is interesting. In the competition between the (2-pyridylethyl)silyl group and the trimethylsilyl group, the former group selectively reacts to give the product (Scheme 3a). However, in the case of competition between the (2-pyridylethyl)silyl group and the tributylstannyl group, the latter group reacts selectively (Scheme 3b). Therefore, the strength of these groups as electroauxiliaries can be ordered as Bu_3Sn > $Py(CH_2)_2Me_2Si$ > Me_3Si.

3.1.2. Applications of Electroauxiliaries

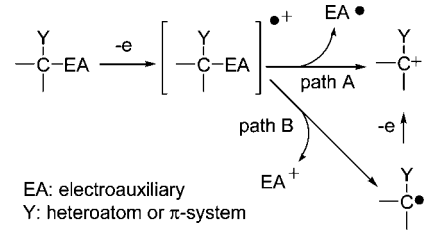
Anodic oxidation of organic compounds containing a heteroatom or a π-system having an EA results in a selective C−EA bond cleavage. This process leads to the selective formation of a carbocation via either path A or B depending on the nature of the EA (Scheme 4). The carbocation thus obtained reacts with various nucleophiles to give the desired products. Examples of such selective electron-transfer-driven reactions are shown in the following sections.

3.1.2.1. Oxidation of Heteroatom Compounds. Anodic oxidation serves as a powerful method for synthesizing various organic compounds containing heteroatoms such as nitrogen with interesting functions and biological activities.[40] The concept of an electroauxiliary serves as a powerful tool for such transformations.

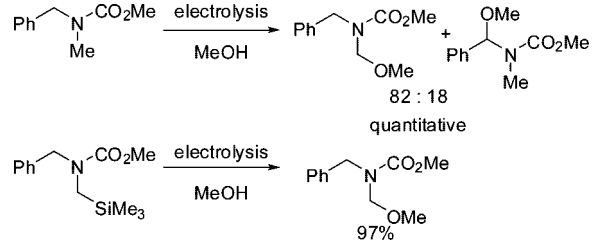
Scheme 3



Scheme 4



Scheme 5

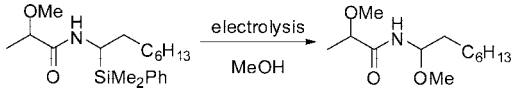


3.1.2.1.1. Oxidation of Nitrogen-Containing Compounds. It is well-known that *N*-acyliminium ions are generated by anodic oxidation of carbamates. The use of electroauxiliaries is advantageous in enhancing both the reactivity and selectivity of this reaction. For example, electrochemical methoxylation of unsymmetrically substituted carbamates usually leads to formation of a mixture of two regioisomeric products, as shown in Scheme 5.[41] However, Yoshida and co-workers found that the introduction of a silyl group as an EA controlled the reaction pathway to bias the formation of the desired product.[15]

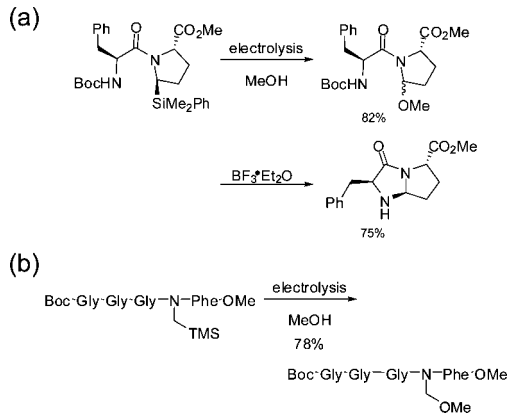
The reaction using an $SiMe_2Ph$ group as an EA has also been reported by Kamada and Oku (Scheme 6).[42]

The concept of an electroauxiliary has been effectively used to construct functionalized peptidomimetics.[43,17a] For example, Moeller and co-workers have reported that a dipeptide analogue containing the $SiMe_2Ph$ group can be electrochemically oxidized in high yields to form the desired

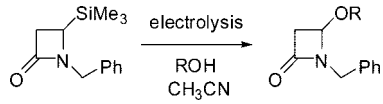
Scheme 6



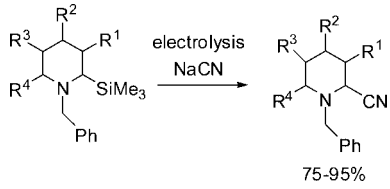
Scheme 7



Scheme 8



Scheme 9



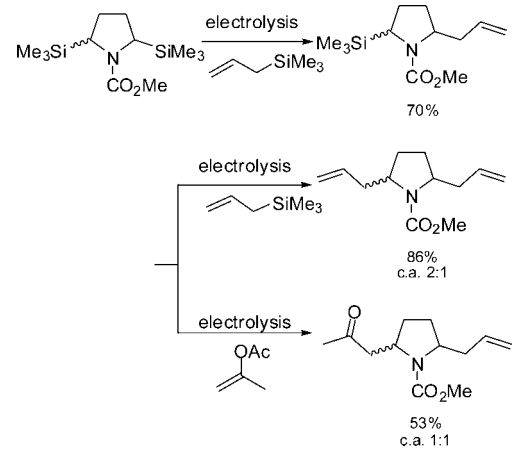
methoxylated product, which is allowed to react with $BF_3 \cdot OEt_2$ to obtain the bicyclic compound in the subsequent step (Scheme 7a). This technique was also used to functionalize a large peptide derivative (Scheme 7b). The electrochemical oxidation led to selective methoxylation of the tetrapeptide at the position to which the silyl group was attached.

Suda and co-workers reported that the silyl group was also effective for regioselective functionalization of β-lactams by anodic oxidation (Scheme 8). An alkoxyl group is selectively introduced on the carbon to which the silyl group has been attached, whereas the benzylic carbon is oxidized in the absence of the silyl group.[44] The ArS group also serves as an effective EA for the selective oxidation of the β-lactam ring.[45]

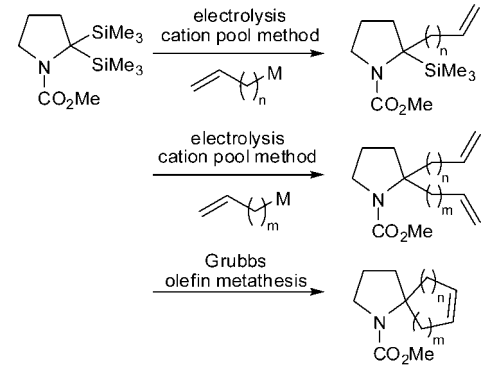
Cyanide anion is also effective as a nucleophile in electroauxiliary-assisted electrochemical oxidation of nitrogen-containing compounds. For example, the anodic oxidation of cyclic α-silyl amines in the presence of sodium cyanide gives rise to effective cyanation under mild conditions (Scheme 9).[46] The control of the reaction pathway by the silyl group is demonstrated by the fact that methoxylation occurs selectively in the cyclohexane ring.

The effective use of two EAs is demonstrated by the reaction of *N*-methoxycarbonyl pyrrolidines having two silyl groups.[24] The oxidation of α,α′-bis(trimethylsilyl)-*N*-methoxycarbonylpyrrolidine in the presence of an allylsilane leads to monoallylated product in good yield. In the subsequent step, the remaining silyl group can be used as an EA to introduce a second nucleophile (Scheme 10).

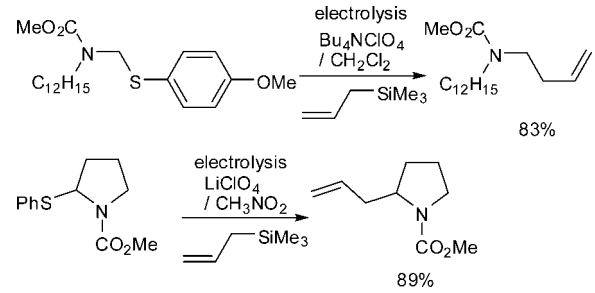
Scheme 10



Scheme 11



Scheme 12

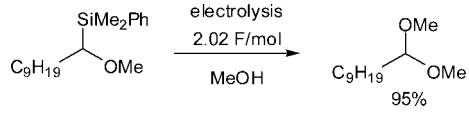


The effective use of two EAs on the same carbon has also been demonstrated by the following example based on the cation-pool method (*vide infra*).[24] With the aid of two silyl groups, two substituents containing a carbon−carbon double bond are introduced sequentially, and the product thus obtained is subjected to ring-closing metathesis. The transformation serves as a useful route to spiro compounds (Scheme 11).

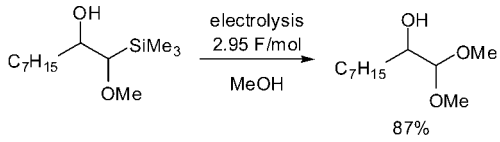
The use of more powerful EAs expands the scope of nucleophiles. For example, the use of an ArS group as an EA enables the *in situ* use of allylsilanes as nucleophiles. Thus, ArS-substituted carbamates can be anodically oxidized in the presence of allyltrimethylsilane to give the corresponding allylated products directly, as outlined in Scheme 12.[33,34]

3.1.2.1.2. Oxidation of Oxygen-Containing Compounds. Aliphatic ethers are usually difficult to oxidize because their oxidation potentials are very high. The use of an EA enables the anodic oxidation of aliphatic ethers under mild conditions. For example, the anodic oxidation of α-silyl ethers in an alcohol as solvent leads to the formation of acetals via

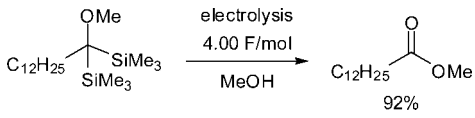
Scheme 13



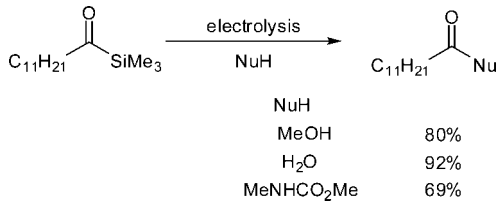
Scheme 14



Scheme 15



Scheme 16



selective C−Si bond cleavage (Scheme 13).[11,47] The anodic oxidation of a β-hydroxy-α-silyl ether is interesting, because the oxidation of β-hydroxyethers without a silyl group usually leads to carbon−carbon bond cleavage. However, the C−Si bond is cleaved selectively without affecting the C−C bond (Scheme 14).[48]

Similarly, a disilyl ether is oxidized in methanol to give the corresponding ester by four-electron oxidation (Scheme 15). The corresponding orthoester is not obtained, presumably because it is spontaneously hydrolyzed to the ester *in situ*.

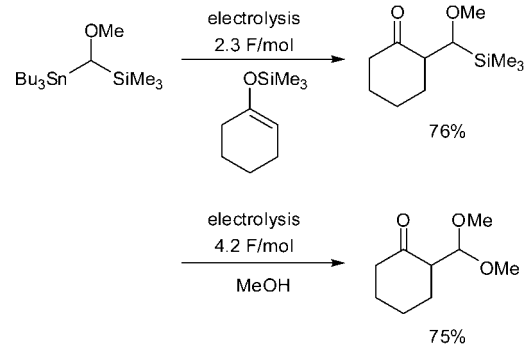
The silyl group serves as an EA for the oxidation of carbonyl compounds.[49] The oxidation potentials of silyl-substituted carbonyl compounds (acylsilane) are less positive than those of the parent compounds. The interaction between the nonbonding orbital of O and the C−Si σ orbital is responsible, as indicated by molecular orbital calculations. These compounds can be anodically oxidized in the presence of alcohols, water, and amines to give esters, acids, and amides, respectively (Scheme 16).

Similar to the carbamate cases, α-stannyl- and ArS-substituted ethers have lower oxidation potentials than those of α-silyl ethers. Therefore, carbon−carbon bond formation using carbon nucleophiles such as allylsilanes can be achieved.

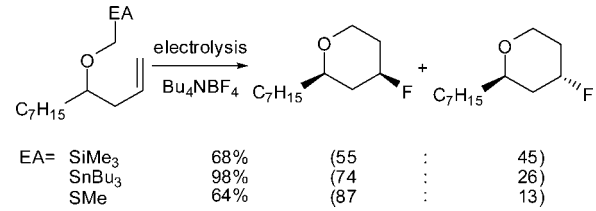
Sequential introduction of two different nucleophiles can be achieved using two EAs.[23] For example, anodic oxidation of an α-silyl-α-stannyl ether in the presence of a silyl enol ether as a nucleophile gives a γ-carbonyl-α-silyl ether, which can be further oxidized in methanol to give the corresponding acetal (Scheme 17).

Intramolecular carbon−carbon bond formation has also been achieved by the anodic oxidation of molecules containing an EA and a tethered olefin (Scheme 18).[31,50] Fluoride ion derived from BF_4^- is introduced to the cyclized cation. It is noteworthy that the *cis*:*trans* ratio depends on the nature

Scheme 17

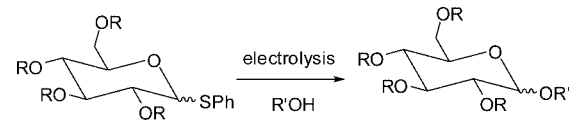


Scheme 18

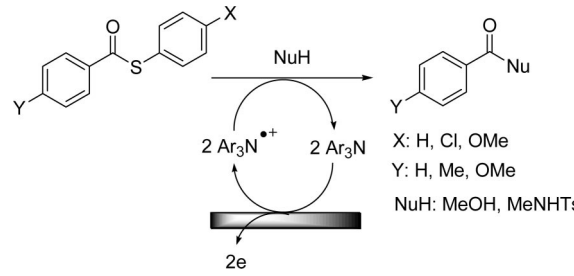


EA=					
$SiMe_3$	68%	(55	:	45)
$SnBu_3$	98%	(74	:	26)
SMe	64%	(87	:	13)

Scheme 19



Scheme 20



of the EA. Cathodically generated Br^- can also be used as a nucleophile to give cyclized bromine-containing compounds.[51]

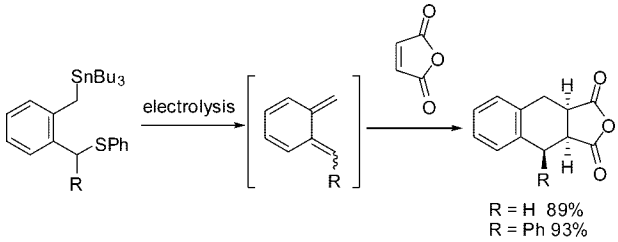
The concept of electroauxiliary has proved to be useful for electrochemical glycosylation reactions. For example, the electrochemical methoxylation of ArS-substituted glucose proceeds smoothly, as shown in Scheme 19.[52] The C−S bond is cleaved selectively and an alkoxyl group is introduced to the anomeric carbon. Disaccharide synthesis is also achieved by anodic oxidation using ArS as an EA.[53–56]

Anodic oxidation of ArTe- and ArSe-substituted glycosides takes place similarly, with cleavage of the C−Te or C−Se bond and introduction of an alkoxyl group on the anomeric carbon.[57]

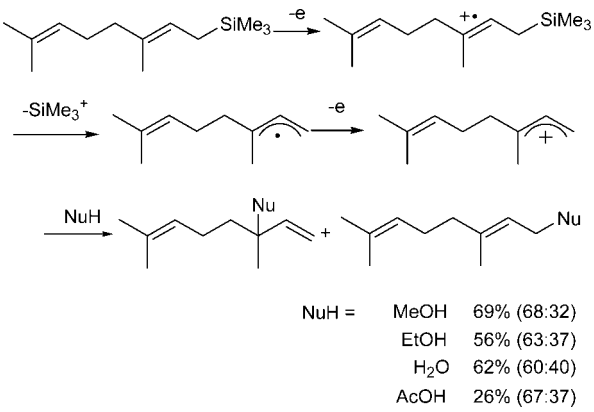
ArS groups also serve as EAs for the oxidation of carbonyl compounds. Fuchigami and co-workers reported that the arylthiobenzoates could be oxidized to cleave the C−S bond by triarylamine-mediated anodic oxidation (Scheme 20).[58] The use of ArS for the anodic oxidation of tosylhydrazone is also effective, and the corresponding nitrile is obtained in good yield.

3.1.2.1.3. Oxidation of Other Heteroatom Compounds. The anodic oxidation of α-silyl sulfides also proceeds smoothly to cleave the C−Si bond.[16,27,59] The use of an alcohol as a

Scheme 21



Scheme 22



nucleophile leads to the formation of the corresponding α-alkoxy sulfide. Because the ArS group serves as an EA for the oxidation of ethers, the second oxidation subsequently takes place to cleave the C−S bond to give an acetal as a product. Similarly, the anodic oxidation of α,α-disilyl sulfides gives the corresponding esters.[47]

Chiba and co-workers developed an interesting method for the generation of *o*-quinodimethanes using a stannyl group as an EA (Scheme 21).[60] The C−Sn bond is cleaved selectively in the radical cation intermediate. The *o*-quinodimethanes thus generated are effectively trapped with dienophiles to give the corresponding cycloadducts.

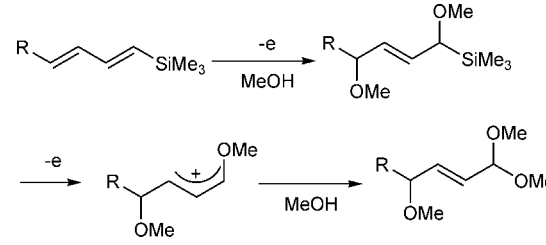
3.1.2.2. Oxidation of π-Systems. Anodic reactions serve as powerful methods for the oxidation of π-systems such as olefins and aromatic compounds.[61] The concept of electroauxiliary is also effective for this type of reaction.

3.1.2.2.1. Oxidation of Allylic Positions. A silyl group serves as an effective EA for allylic oxidation of olefins, as demonstrated by the example shown in Scheme 22.[27,29] The electron transfer takes place only for the allylsilane moiety without affecting the other carbon−carbon double bond, because the silyl group activates the neighboring carbon−carbon double bond. In the radical cation thus generated, the C−Si bond is cleaved selectively without affecting other allylic C−H bonds to generate the corresponding allylic radical, which is further oxidized to give the allylic cation. The attack of a nucleophile such as an alcohol, water, or acetic acid gives the final product as a mixture of two regioisomers.

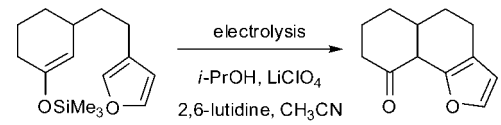
The anodic oxidation of 1,3-dienes is interesting (Scheme 23).[62] The initial two-electron oxidation gives a silyl-substituted dimethoxylated compound. The second two-electron oxidation takes place selectively with the aid of the silyl group as an EA, which controls the regiochemistry of the allyl cation formation. The third methoxy group is introduced selectively on the carbon bearing the oxygen atom, which stabilizes the neighboring cationic center.

The anodic oxidation of silyl enol ethers is also interesting, because a silyl group can be considered as an EA for the

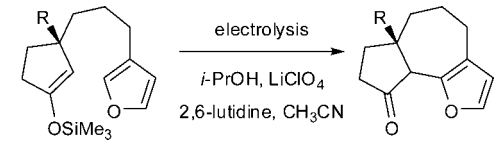
Scheme 23



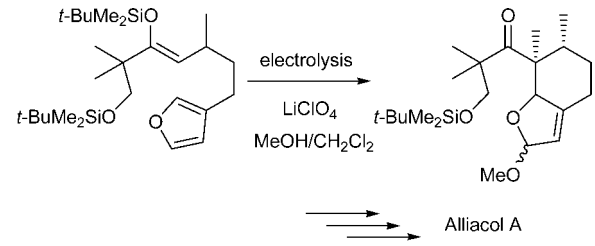
Scheme 24



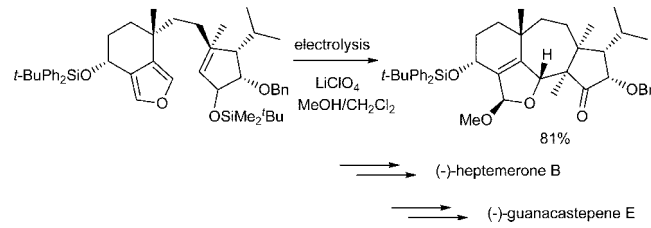
Scheme 25



Scheme 26



Scheme 27



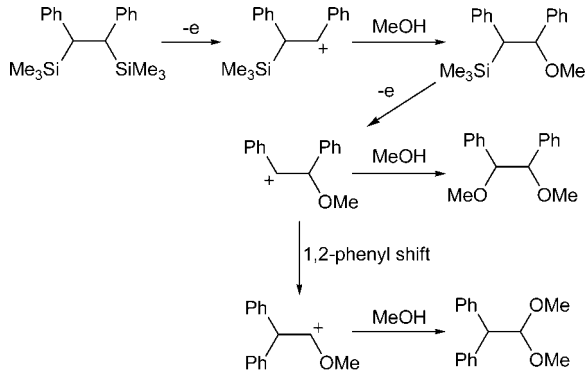
oxidation of enols. An intramolecular anodic coupling of a silyl enol ether with a furan ring takes place smoothly with O−Si bond cleavage, and this provides an excellent method for synthesizing carbon ring skeletons. For example, Wright and co-workers reported the anodic coupling of a furan derivative and a silyl enol ether to form a six-membered ring (Scheme 24) and a seven-membered ring (Scheme 25).[63]

Moeller et al. also used an intramolecular anodic coupling of a furan and a silyl enol ether to develop a novel route to a tricyclic natural product, alliacol A (Scheme 26).[64–66]

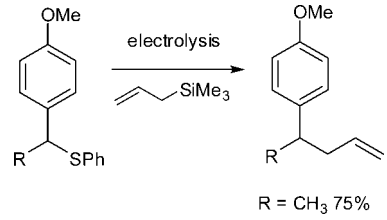
Trauner et al. also reported that an intramolecular anodic coupling of a silyl enol ether and a furan ring provides an excellent method for synthesizing the unnatural enantiomer of the neodolastane diterpenoids (−)-heptemerone B and (−)-guanacastepene E (Scheme 27).[67]

3.1.2.2.2. Oxidation of the Benzylic Position. The silyl group is also effective for the oxidation of the benzylic position.[27–29] Fry and co-workers reported the anodic oxidation of 1,2-biphenyl-1,2-bis(trimethylsilyl)ethane, which serves as a vicinal dication synthon (Scheme 28).[68] Anodic oxidation in methanol led to the formation of a mixture of

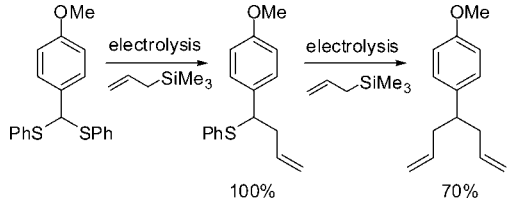
Scheme 28



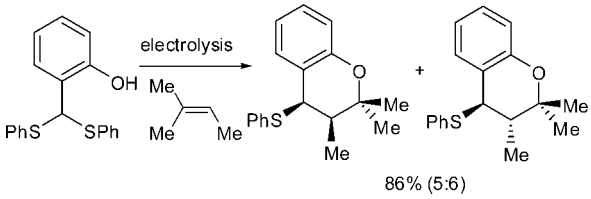
Scheme 29



Scheme 30



Scheme 31



the 1,2-dimethoxylated product (65%) and the acetal (35%), which was produced via a 1,2-phenyl shift in the monomethoxylated cation. The 1,2-phenyl shift can be avoided by the use of aryl groups with electrodonating groups such as the *p*-methoxyphenyl group.

ArS groups are also effective as EAs for the oxidation of π-systems. The anodic oxidation of benzylic sulfides in the presence of allylsilanes takes place smoothly, giving rise to selective C−S bond cleavage and introduction of an allyl group on the benzylic carbon. (Scheme 29).[35]

This type of reaction may have many synthetic applications. For example, bis(phenylthio) compounds can be used for sequential introduction of two nucleophiles (Scheme 30). In addition, the anodic oxidation of a bis(phenylthio) compound leads to a heterodiene that undergoes a hetero-Diels−Alder reaction with an alkene (Scheme 31).

The use of an ArS group as an EA is effective for paired electrolysis.[69] Chiba and co-workers reported that the anodic oxidation of ArS-substituted alkylbenzenes led to the formation of the corresponding benzylic cation, which reacted with nitromethyl anion generated by deprotonation of nitromethane (solvent) using a cathodically generated base (Figure 6).[70]

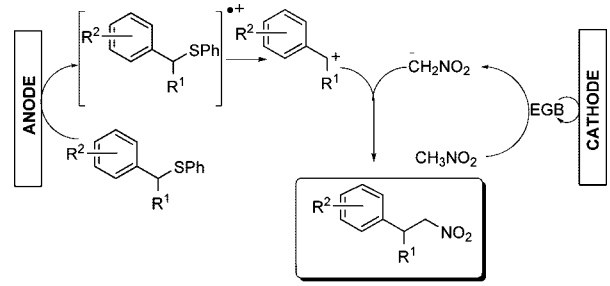
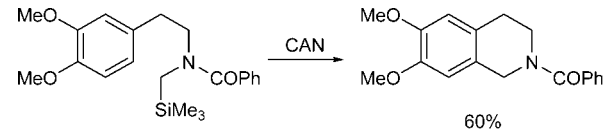
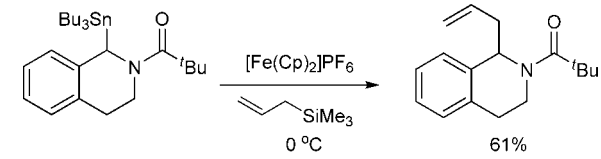


Figure 6. Paired electrochemical nitroalkylation of benzylsulfides.

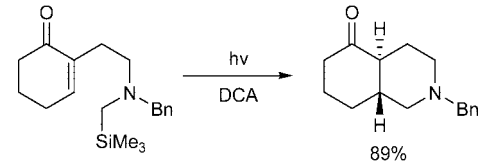
Scheme 32



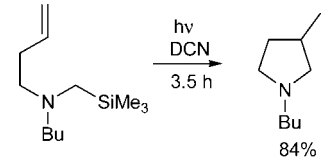
Scheme 33



Scheme 34



Scheme 35



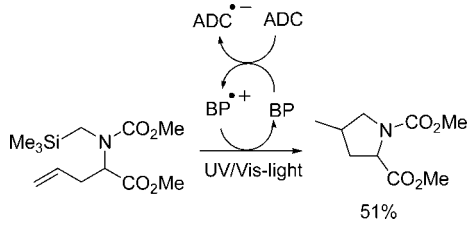
3.1.3. Electroauxiliaries for Chemical and Photochemical Reactions

It is important to note that the concept of electroauxiliary is applicable not only for electrochemical reactions but also for other types of electron-transfer-driven reactions, such as chemical electron-transfer reactions[71] and photoinduced electron-transfer reactions.[72]

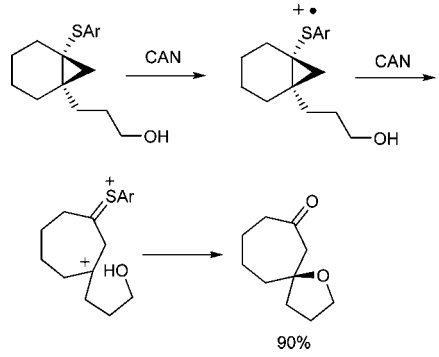
We will touch briefly on some examples here, although there are many other examples. Mariano et al. reported the use of a silyl group as an EA for ceric ammonium nitrate (CAN)-mediated oxidative cyclization involving an *N*-acyliminium ion (Scheme 32).[73] Narasaka et al. reported that a stannyl group is also effective as an EA for chemical oxidation to generate an *N*-acyliminium ion, which is trapped by allyltrimethylsilane (Scheme 33).[74] In this case, $[Fe(Cp)_2]PF_6$ is used as an oxidant.

The concept of an EA is also effective for photochemical reactions. Mariano et al. reported photoinduced carbon−carbon bond formation controlled by a silyl group as an EA (Scheme 34).[75] Pandey et al. (Scheme 35)[76] and Steckhan et al. (Scheme 36)[77] also reported silyl-group-assisted photoelectron-transfer reactions, independently.

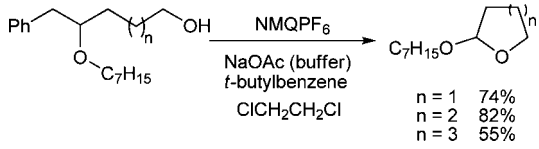
Scheme 36



Scheme 37



Scheme 38



Iwata et al. reported that an arylthio group is effective as an EA for chemical oxidation.[78] In the example shown in Scheme 37, the initial electron transfer takes place from S. Opening of the three-membered ring then occurs to generate the corresponding carbocation, which is trapped intramolecularly by a hydroxyl group to give the final product.

A substituted benzyl group is also effective as an EA. Floreancig et al. developed excellent photoinduced electron transfer-mediated cyclization reactions based on this concept (Scheme 38).[79] The carbon−carbon bond is selectively cleaved to generate the carbocation stabilized by the alkoxyl group.

The examples shown in this section demonstrate how the electrochemical methods fit in nicely with chemical and photochemical methods and speak well for the potential of the concept of an EA in organic synthesis.

3.2. Template-Directed Methods

Generally, an intramolecular reaction is more favorable than the intermolecular counterpart because of a lesser demand in the decrease of entropy. Therefore, intramolecularization[80] of reactions has attracted significant research interest from the viewpoints of both efficiency and selectivity.[81]

Template-directed reactions, which are good examples of intramolecularization, serve as powerful methods for the construction of compounds that are otherwise difficult to synthesize. This approach has also been used in the field of electroorganic synthesis (Figure 7). The anodic oxidation of phenols serves as a powerful method for the synthesis of bioactive compounds,[82] and Waldvogel and co-workers reported that the selective anodic coupling of phenols could be achieved using a boron template (Scheme 39).[83] In the

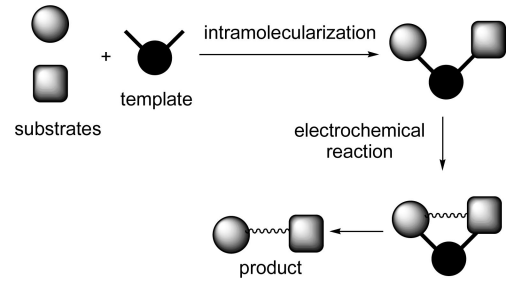
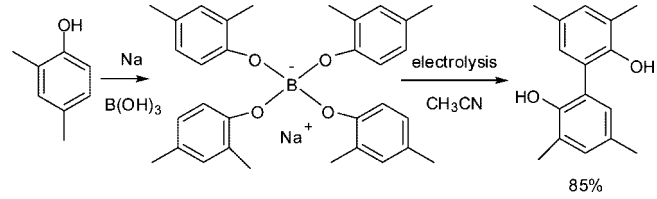
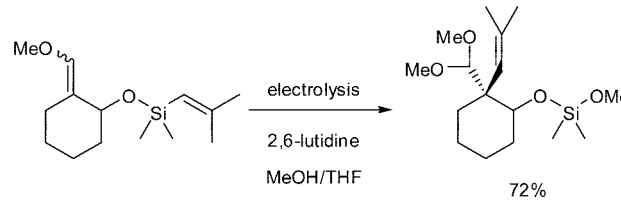


Figure 7. Template-directed electroorganic synthesis.

Scheme 39



Scheme 40



first step, a tetraphenoxyborate is prepared by the reaction of a phenol and $B(OH)_3$ with Na in THF. In the second step, the anodic oxidation is carried out to obtain the ortho−ortho coupled product selectively.

Moeller et al. reported that silicon tethers could be used to effect oxidative coupling reactions.[84] Oxidation of an enol ether followed by electrophilic-type cyclization leads to the formation of a five-membered ring intermediate, which gives the final coupling product (Scheme 40).

4. Reaction Media

Reaction media such as solvents and supporting electrolytes play important roles in the control of electrochemical reactions, because they serve as an environment for molecular events such as electron transfer and subsequent chemical processes. Therefore, electrochemical reactions in nonconventional organic solvents have received significant research interest. For example, Matsumura and co-workers reported that fluorine-containing solvents such as trifluoroethanol[85] exhibited interesting features in the anodic oxidation of organic compounds. Nishiguchi and co-workers also reported interesting anodic oxidation reactions using trifluoroacetic acid.[86] New reaction media such as ionic liquid and supercritical fluids can also be used for organic electrochemical reactions. Another important factor in the electrochemical environment is the supporting electrolyte. In this section, recent developments in reaction media including solvents and supporting electrolyte are discussed.

4.1. Ionic Liquid

Ionic liquids, salts that form a stable fluid at or near room temperature, have received significant research interest as environmentally benign reaction media. Ionic liquids are expected to replace hazardous and volatile organic solvents.

Table 12. Physical and Electrochemical Properties of Ionic Liquids (25 °C)

ionic liquid		density (g/cm^3)	viscosity (mPa·s)	conductivity (mS/cm)	potential window (V vs Li^+/Li[c]) E_{red}	E_{ox}
[emim][AlCl$_4$]	8	1.29	18	22.6	1.0	5.5
[emim][$H_{2.3}F_{3.3}$]	−9.0	1.14	5	10.0	1.5	5.3
[emim][BF$_4$]	11	1.24	43	13.0	1.0	5.5
[emim][CF_3CO_2]	−14	1.29[b]	35[b]	9.6[a]	1.0[d]	4.6[d]
[emim][CH_3SO_2]	39	1.25	160	2.7	1.3[d]	4.9[d]
[emim][CF_3SO_2]	−10	1.38	43	9.3	1.0	5.3
[emim][$(CF_3SO_2)_2N$]	−15	1.52[b]	28	8.4	1.0	5.7
[emim][$(C_2F_5SO_2)_2N$]	−1		61	3.4	0.9	5.8
[emim][$(CF_3SO_2)_3C$]	39		181	1.7	1.0	6.0

[a] 20 °C. [b] 22 °C. [c] GC (glassy carbon), 1 mA·cm^{-2}, 20 mV·s^{-2}. [d] Pt, 50 mV ·s^{-1}, emim = 1-ethyl-3-methydazolium.

Table 13. Conductivity of Poly(hydrogen fluoride) Salts

poly(hydrogen fluoride) salt	conductivity (mS/cm)
$Me_4NF·4HF$	197.6
$Et_4NF·4HF$	99.2
$Pr^n{}_4NF·4HF$	33.6
$Bu^n{}_4NF·4HF$	9.7
$Me_3N·3HF$	32.8

Their advantages include minuscule vapor pressure, nonflammability, high polarity, and relative inertness. They can be recovered and reused after reactions, although there are some practical problems associated with these processes. In particular, ionic liquids show relatively wide potential windows and high conductivity. Ionic liquids themselves play the role of supporting electrolyte, and therefore, electrolyses can be conducted without any intentionally added supporting electrolyte.

4.1.1. Electrochemical Properties of Ionic Liquids

Most ionic liquids consist of bulky organic cations such as *N,N*-dialkylimidazolium, *N*-alkylpyridinium, quaternary ammonium, quaternary phosphonium, and common weakly coordinating anions such as $AlCl_4^-$, BF_4^-, PF_6^-, $CF_3SO_3^-$ (TfO^-), $(CF_3SO_3)_2N^-$ (Tf_2N^-), and $(H_nF_{n+1})^-$. Some ionic liquids, such as *N,N*-dialkylimidazolium salts, show excellent conductivity. The conductivity of imidazolium ions decreases with an increase in the length of the alkyl chain on nitrogen because their viscosity increases with increasing chain length. The absence of a substituent on nitrogen decreases conductivity because the viscosity increases as a result of hydrophilic interactions. Thus, ethylmethylimidazolium (emim) salts show the maximum conductivity among the series.[87] Physical and electrochemical properties of emim salts with various counteranions are listed in Table 12.

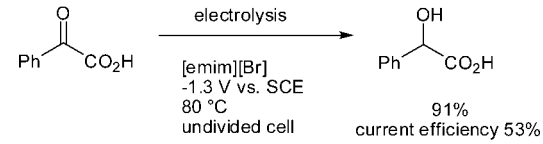
Poly(hydrogen fluoride) salts (both imidazolium and ammonium), which mainly consist of amine or ammonium fluoride and hydrogen fluoride, show good conductivity because of their low viscosity (Table 13).[88]

Hapiot and co-workers have reported that the kinetics of the heterogeneous electron transfer are considerably slower in imidazolium and quaternary ammonium bis(trifluoromethylsulfonyl)imide compared with that observed in conventional organic solvents.[89]

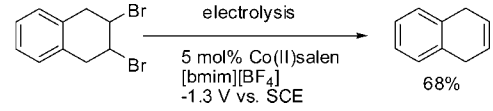
4.1.2. Electrochemical Reactions in Ionic Liquids

4.1.2.1. Simple Reduction. Simple electrochemical reduction of carbonyl compounds and organic halides can be achieved in ionic liquids. For example, electrochemical reduction of benzoylformic acid in [emim][Br] gives mandelic acid in 91% yield (Scheme 41).[90]

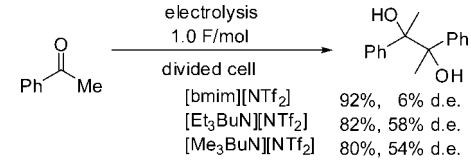
Scheme 41



Scheme 42



Scheme 43



Electroreductive dehalogenation of organic dihalides has been conducted using a Co(II)salen complex in [bmim][BF_4] (bmim = 1-benzyl-3-methylimidazolium) (Scheme 42).[91] The catalyst/solvent system can be readily recycled with little loss of reactivity.

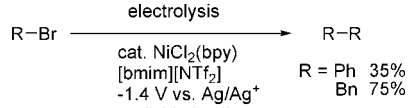
4.1.2.2. Electroreductive Coupling. Cathodic reduction of benzaldehyde in [bmpyr][NTf_2] (bmpyr = 1-butyl-1-methylpyrrolidinium) leads to dimerization. Extensive kinetic studies by Doherty and Brooks revealed that the dimerization rate constant (1.4×10^4 mol^{-1} dm^3 s^{-1}) is strongly affected by the use of ionic liquids.[92]

Electroreductive coupling of acetophenone in ionic liquids gives the corresponding pinacol as a mixture of diastereomers (Scheme 43).[93] During the reaction, the dimerization step is considerably accelerated by stabilization of a radical anion intermediate because of favorable interaction with the cationic component of the ionic liquids. The diastereoselectivity is also affected by the use of ionic liquids.

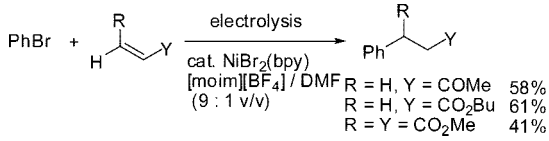
Peters and co-workers studied the catalytic behavior of Ni(I)salen in [bmim][BF_4] using cyclic voltammetry. Ni(I)salen serves as a catalyst for the cleavage of carbon−halogen bonds in iodoethane and 1,1,2-trichlorotrifluoroethane (Freon 113).[94]

The electroreductive coupling of organic halides has been studied in ionic liquids. Organic halides such as bromobenzene and benzyl bromide homocouple in the presence of an Ni(II) complex catalyst in [bmim][NTf_2] (Scheme 44).[95]

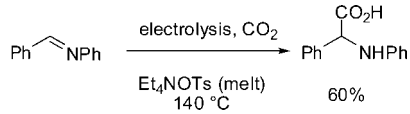
Scheme 44



Scheme 45



Scheme 46



Ionic liquids such as [moim][BF_4] (moim = 1-methyl-3-octylimidazolium) are not efficient enough as electrolytes for the homocoupling, presumably because of their high viscosity, which would limit the ion mobility. However, good conductivity can be attained by the use of 5−10% v/v of a cosolvent such as DMF.[96] The Ni-catalyzed electroreductive coupling of organic halides with activated olefins has also been developed using DMF as a cosolvent (Scheme 45).[96]

These examples demonstrate that metal-catalyzed electrosynthesis can be successfully achieved to give the corresponding C−C bond formation products in ionic liquids, showing that electrochemistry, homogeneous catalysis, and ionic liquids can be combined to achieve environmentally friendly reactions.

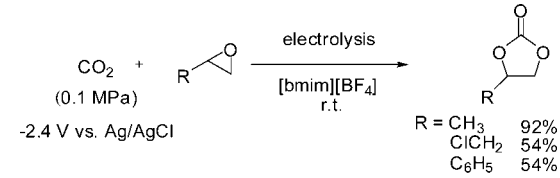
4.1.2.3. Electroreductive Carboxylation. One of the earliest examples of electrolysis in ionic liquids was the use of quaternary ammonium salts such as [Et_4N][OTs] as both supporting electrolyte and solvent. Et_4NOTs is solid at room temperature, but it is liquid at 140 °C. At this temperature, it dissolves a variety of organic compounds and exhibits good conductivity (1×10^{-2} S/cm) and a broad potential window.[97] The electroreductive carboxylation of benzalaniline to give α-phenylglycine can be achieved using [Et_4N][OTs] (Scheme 46).

The use of ionic liquids as reaction media in the electrocatalytic cycloaddition of carbon dioxide to epoxides to give cyclic carbonates has been reported.[98] CO_2 is reduced at approximately −2.4 V vs Ag/AgCl (copper cathode), generating an anion radical of CO_2. This species is unstable in the absence of a substrate. However, this anion radical reacts rapidly with epoxides to give the desired cyclic carbonates by donating an electron to another CO_2 molecule. Duñach et al. also reported the electrochemical reaction of epoxides with CO_2 in the presence of a nickel complex to afford the corresponding cyclic carbonates under mild conditions.[99] In the present case, however, the use of a volatile organic solvent and a heavy metal catalyst is not necessary to conduct this useful reaction.

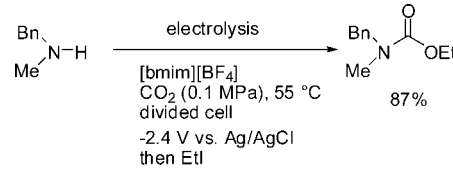
For the reaction of CO_2 with propylene oxide, epichlorohydrin, and styrene oxide, the use of [bmim][BF_4] led to 54−92% yields, with the best current efficiency being 87% (Scheme 47). When [bmim][BF_4] was replaced with [emim][BF_4], [bpy][BF_4] (bpy: butylpyridinium), or [bmim][PF_6], the conversion decreased.

Electrochemical synthesis of carbamates can also be accomplished under similar conditions.[100] The electrolysis

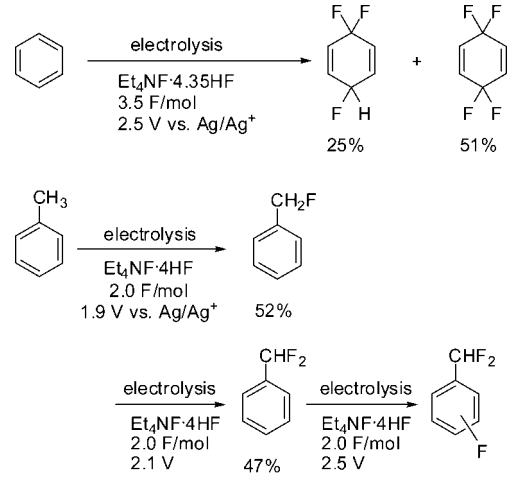
Scheme 47



Scheme 48



Scheme 49



of a solution of CO_2 and an amine in [bmim][BF_4] followed by the addition of EtI as an alkylating agent gave the corresponding carbamate in 87% yield (Scheme 48).

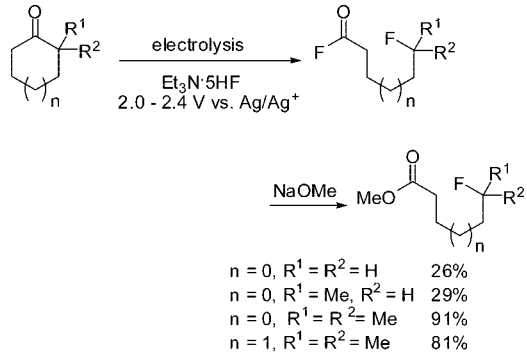
4.1.2.4. Electrochemical Partial Fluorination. Electrochemical partial fluorination of organic compounds has been the subject of intensive study.[101,102] The conventional electrochemical fluorination has been carried out in organic solvents containing fluoride salts such as $Et_3N \cdot 3HF$ and $Et_4NF \cdot 3HF$.[103] The method suffers from a limitation caused by the relatively low oxidation potentials of $Et_3N \cdot 3HF$/MeCN and $Et_4NF \cdot 3HF$ (2 V vs Ag/Ag^+).

A dramatic improvement in the stability of fluoride salts toward oxidation was achieved using $R_4N \cdot mHF$: R = Me, Et, *n*-Pr; $m > 3.5$) and $Et_3N \cdot 5HF$ (3 V vs Ag/Ag^+). These salts can be used as both reaction media and supporting electrolytes for the electrochemical fluorination of aromatic compounds (Scheme 49).[88]

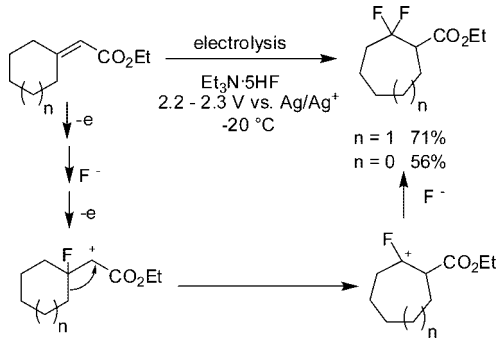
Yoneda and co-workers reported that electrochemical fluorination of aliphatic aldehydes and cyclic ketones could also be conducted in $Et_3N \cdot 5HF$.[104] The selective cleavage of the bond between the carbonyl carbon and the substituted α-carbon in cyclic ketones takes place to give fluoroacyl fluorides, which are readily converted to the corresponding fluorocarboxylic esters by subsequent alcoholysis (Scheme 50).

Electrochemically induced fluorinative ring expansion of cycloalkylideneacetates to give β,β-difluorocycloalkanecarboxylic esters has also been developed.[105] The following mechanism has been suggested. The radical cation species generated by one-electron oxidation of the substrate followed

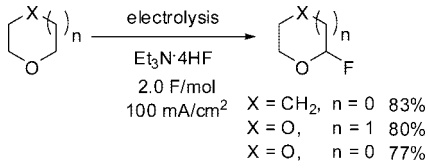
Scheme 50



Scheme 51



Scheme 52



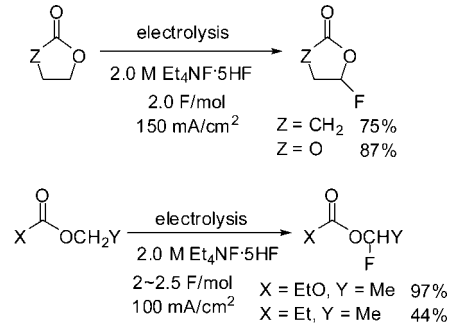
by fluorination with $Et_3N \cdot 5HF$ gives a fluoroalkyl radical intermediate. The subsequent oxidation and rearrangement of the cationic intermediate results in the generation of the more stable cation, which gives the desired products by attack of the fluoride ion (Scheme 51).

It is noteworthy that these electrochemical fluorination reactions can be achieved under mild conditions using simple equipment. Hazardous reagents, which are usually necessary in chemical fluorination, are not necessary. However, electrochemical fluorination of compounds containing oxygen functionalities such as ethers, lactones, carbonates, and esters was not successful (12−28% yields in $Et_3N \cdot 4HF$ as a solvent), because their oxidation potentials are relatively close to those of fluoride ionic liquids such as $Et_3N \cdot 4HF$. However, it has been shown that electrochemical fluorination of such compounds can be successfully carried out by a decrease in the ratio of $Et_3N \cdot 4HF$ to substrate (1.5−1.7 equiv of F^- to 1 equiv of substrate) to avoid simultaneous oxidation of $Et_3N \cdot 4HF$.[40d,106] For example, fluorination of tetrahydrofuran, 1,4-dioxane, and 1,3-dioxolane was achieved in the presence of 2.4 equiv of $Et_4NF \cdot 4HF$, as shown in Scheme 52.

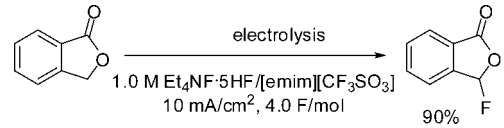
Fuchigami and co-workers extensively studied partial fluorination using these systems.[106a,b] For example, electrochemical fluorination of both cyclic and acyclic lactones and ethylene carbonates can also be carried out to obtain the corresponding fluorine-containing compounds (Scheme 53).

Electrochemical fluorination of phthalides is also problematic because of their high oxidation potential (2.86 V vs SCE). However, fluorination can be achieved effectively using $[emim][CF_3SO_3]$ as reaction medium and $Et_3N \cdot 5HF$ as both electrolyte and fluorine source (Scheme 54).[106b]

Scheme 53



Scheme 54



Scheme 55

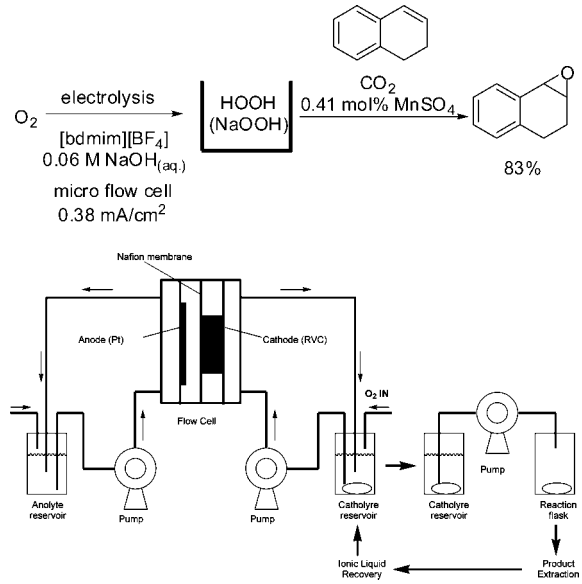
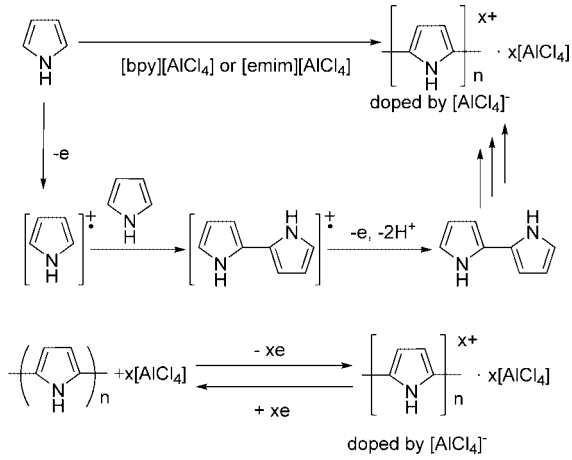


Figure 8. Schematic diagram of H_2O_2 electrogeneration in an ionic liquid for catalytic epoxidation.

ArS groups are effective as EAs for anodic fluorination in ionic liquids.[107] The C−S bond is cleaved selectively, and fluoride ion is introduced to the carbon.

4.1.2.5. Electrochemical Epoxidation of Olefins. A practical method involving electrochemical generation of H_2O_2 in ionic liquid has been developed.[108] H_2O_2 is currently attracting attention as a green oxidant because it leaves no hazardous byproducts, only oxygen and water, after reaction. However, the conventional method of H_2O_2 production (the anthraquinone process) involves the use of large amounts of organic solvents. Weidner et al. showed that the stable superoxide ion could be electrochemically generated from O_2 in ionic liquids such as $[bmim][PF_6]$.[109] Based on this reaction, Chan et al. developed a useful process involving electrosynthesis of H_2O_2 in ionic liquids followed by *in situ* epoxidation of alkenes in the presence of a manganese catalyst (Scheme 55 and Figure 8).[108b]

Scheme 56



4.1.2.6. Other Electrochemical Reactions in Ionic Liquid. Nédélec and co-workers reported TEMPO-mediated oxidation of alcohols to carbonyl compounds in ionic liquid medium.[110] TEMPO diffusion currents are suppressed relative to acetonitrile solvent, because of the high viscosity. However, the presence of a substrate and base reagent (2,6-lutidine) significantly reduces the viscosity, improving the performance.

4.1.3. Electrochemical Polymerization in Ionic Liquid

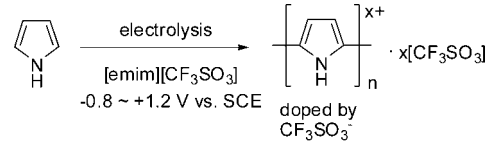
The π-conjugated polymers such as polyacetylene, polyarenes, polyaniline, polypyrrole, and polythiophene as conductive materials have received considerable attention in recent years.[111] Electrochemical synthesis of these conductive polymers takes advantage of the fact that the anion component of the electrolyte can be introduced to the polymer as a doping agent to improve conductivity. The use of ionic liquids as electrolytes, doping agents, and practical recycling media for electrochemical polymerization has also been studied.

An early investigation was carried out in chloroaluminate ionic liquids such as [emim][$AlCl_4$]. For example, polypyrrole film can be prepared in [bpy][$AlCl_4$], and the electrochemical analysis of such a film appears to be more facile than that of polypyrrole films prepared in a conventional solvent system, such as acetonitrile (Scheme 56).[112] The electrochemical synthesis and analysis of π-conjugated polymers such as polyarenes,[113] polythiophene,[114] and polyaniline[115] have also been achieved in chloroaluminate ionic liquids.

However, the use of chloroaluminate ionic liquids is problematic because their handling requires a special apparatus because of their inherent moisture sensitivity. The application to film synthesis has been limited by the low stability of chloroaluminate ionic liquids as doping agents and supporting electrolytes.

A dramatic improvement has been achieved using *N*,*N*-dialkylimidazolium ionic liquids having stable counteranions such as BF_4^-, PF_6^-, and $CF_3SO_3^-$, which exhibit air and moisture stability.[116–118] For example, electrochemical polymerization of pyrrole can be conducted using [emim][CF_3SO_3] (Scheme 57).[116a] This method enables better control of the morphological structure of the film formed on the anode, and improvements in the polymerization rate, electrochemical capacity, and conductivity. After simple removal (extraction) of the remaining pyrrole monomer,

Scheme 57



[emim][CF_3SO_3] can be reused without significant loss of reactivity for the polymerization.

Electropolymerization of benzene was achieved using ionic liquids based on $AlCl_3$ in 1993.[119] More recently, Endres and co-workers reported the electropolymerization of benzene in modern air- and water-stable ionic liquids.[120]

4.2. Solid-Supported Electrolytes

To provide sufficient electrical conductivity to solvents for electrolysis, the use of a supporting electrolyte is essential under conventional conditions. For organic electrolysis, tetraalkylammonium salts such as Et_4NOTs and Bu_4NBF_4 are often used because of their good solubility in organic solvents. However, good solubility causes a problem of separation of products from the supporting electrolyte after electrolysis. Column chromatography is often necessary for such a purpose. It is also important to note that recycling of supporting electrolytes is important from the viewpoints of cost and wastes in industrial applications. However, recycling of tetraalkylammonium salts also requires a lot of energy and is expensive. To solve such problems, insoluble polymer-supported electrolytes have been developed.

Ogumi and co-workers have developed solid polymer electrolytes (SPE) technology that enables electrochemical reactions in the absence of a conductive fluid containing supporting electrolyte.[121] This technology is very important for fuel cells, e.g., in the proton exchange (or polymer electrolyte) membrane fuel cell (PEMFC) and in the direct methanol fuel cell (DMFC). The benefits of this technology include the omission of steps for separation and recycling of a supporting electrolyte and the suppression of side reactions with such additives.

Jorissen and Tallec reported independently that ion-exchange membranes could function as solid polymer electrolytes in nonconductive liquids.[122,123] The principle of SPE technology using ion-exchange membranes is demonstrated in Figure 9. The electrochemical reactions take place at the interfaces between the ion-exchange membrane and electrocatalytically active layers of porous electrodes. In the case of a cation-exchange membrane, H^+ ions, which are formed by the anodic reaction, migrate with their solvation shell through the membrane and are usually reduced to hydrogen gas at the cathode. Therefore, the cation-exchange membrane works like immobilized sulfuric acid.

SPE technology enabled the anodic methoxylation of *N*,*N*-dimethylformamide (DMF) in nonaqueous solution.[122] Various other alkoxylation reactions were carried out with similar success. The alkoxylation of furan and *N*-alkylamides also takes place in the SPE process. On the other hand, the methoxylation of *p*-methoxytoluene, which receives significant interest in industry, required an unacceptably high cell voltage. However, long-term stable operation could be achieved using a combination of the following methods: (1) optimized membrane preparation, first in DMF and additionally in the cell fluid, (2) use of DMF as cosolvent, (3) boiling of the cell fluid in the anode chamber to avoid polymer deposition on the anode, and (4) addition of very small

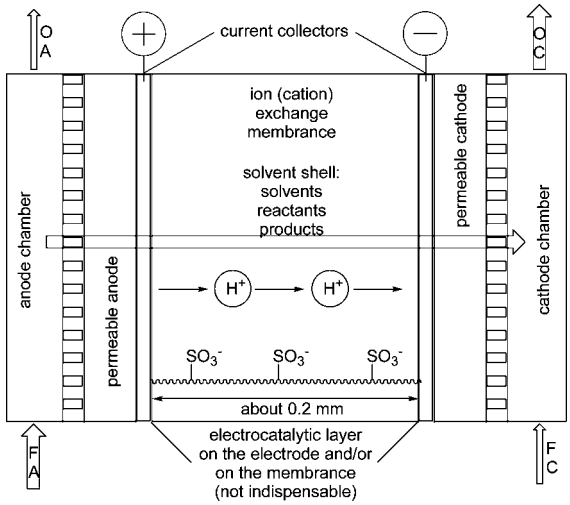
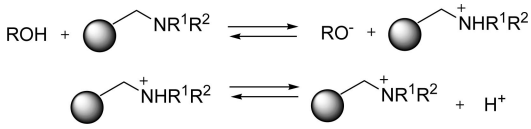


Figure 9. Scheme of an SPE cell with cation-exchange membranes.

Scheme 58



amounts of sulfuric acid (2% of the usual quantity as supporting electrolyte).[122]

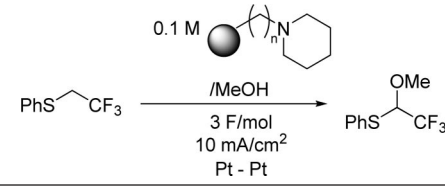
Tajima, Fuchigami, and co-workers have developed a novel environmentally friendly electrolytic system using protic organic solvents and recyclable solid-supported bases.[124] In general, solid-supported bases are electrochemically inactive at the electrode surface because electron transfer between two solids is very difficult.[125] For example, polystyrene-supported piperidine is not oxidized in 0.1 M Bu_4NBF_4/acetonitrile at all, even under stirring, whereas soluble *N*-methylpiperidine is easily oxidized at ca. 1.3 V vs SCE. This means that solid-supported bases are not oxidized at the electrode surface. On the other hand, the cyclic voltammogram of polystyrene-supported piperidine in MeOH gave an oxidation wave because of MeO^- at ca. 1.0 V vs SCE and a reduction current for H^+. Therefore, methanol seems to dissociate into methoxide anions and protons with the aid of a solid-supported base. The thus-generated protons may serve as carriers of electronic charge (Scheme 58).

The anodic methoxylation of phenyl-2,2,2-trifluoroethyl sulfide was carried out using various solid-supported bases. Although the use of conventional polystyrene-supported piperidine gave the methoxylated product in low yield, porous polystyrene-supported piperidine and silica gel-supported piperidine were found to be quite effective, and the methoxylated product was obtained in excellent yields (Table 14). The efficiency of the reaction increases with the basicity of the base attached on the solid support (piperidine 76%, pyridine 52%, and imidazole 51%).

In addition, the methoxylated products and the solid-supported bases can be easily separated by simple filtration (Figure 10). Therefore, the desired methoxylated products can be readily isolated simply by concentration of the filtrates. The separated and recovered solid-supported bases can be reused several times for electrolysis.

The method was successfully applied for anodic methoxylation of carbamates, furans, phenols, and dimethoxybenzene, as shown in Table 15. However, attempts to oxidize 4-*tert*-butyltoluene and toluene were unsuccessful because of the high oxidation potentials of such compounds.

Table 14. Anodic Methoxylation of Phenyl-2,2,2-trifluoroethyl Sulfide Using Various Solid-Supported Piperidines



solid	*n*	yield (%)
polystyrene	1	39
porous polystyrene	2	92
silica gel	3	76

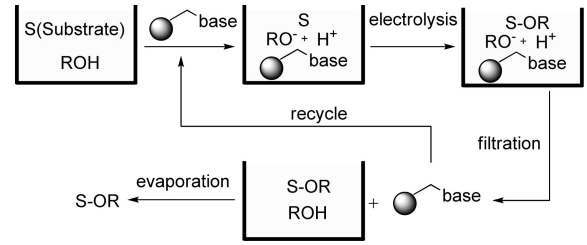
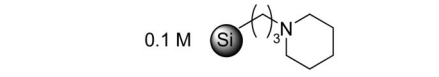
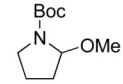
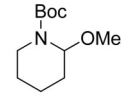
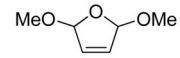
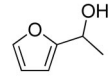
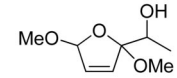
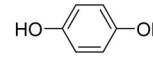
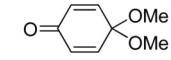
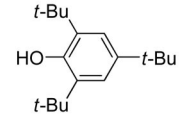
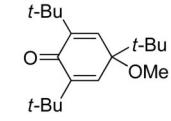
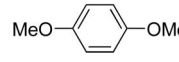
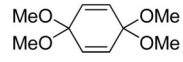


Figure 10. Experimental procedure for electrolysis using a solid-supported base.

Table 15. Anodic Methoxylation of Various Compounds Using Solid-Supported Piperidine

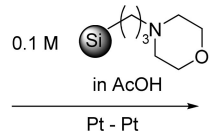


substrate	product	yield(%)
		94
		98
		78 (cis:trans 1:1)
		96
		94
		91
		88

Anodic acetoxylation of phenyl-2,2,2-trifluoroethyl sulfide, dimethoxybenzene, phenols, and methoxytoluene can also be performed in the presence of a solid-supported base using acetic acid/acetonitrile (1:1) as a protic organic solvent (Table 16).

Silica gel-supported piperidine is also effective for electrolysis of carbamates, *N*-acylated alanines, and *p*-methox-

Table 16. Anodic Acetoxylation of Various Compounds Using Solid-Supported Morpholine



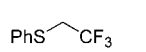
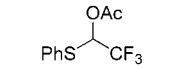
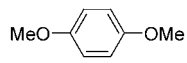
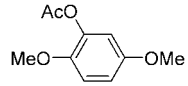
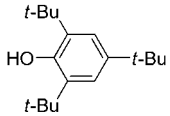
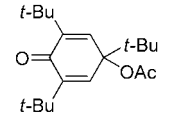
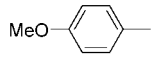
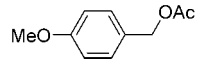
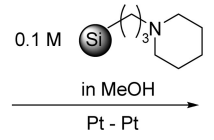
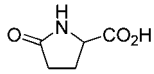
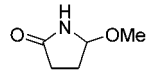
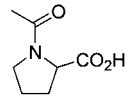
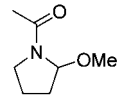
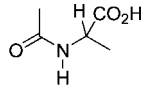
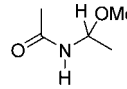
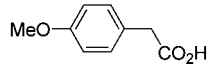
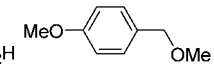
substrate	product	yield(%)
		72
		91
		95
		72

Table 17. Electrolysis of Various Carboxylic Acids Using Silica Gel-Supported Piperidine



substrate	product	yield(%)
		quant
		98
		quant
		96

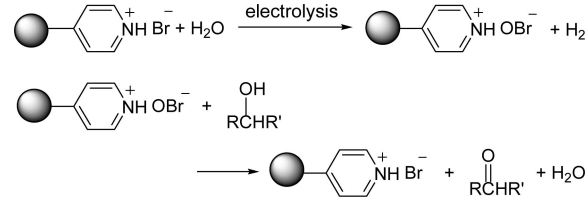
yphenylacetic acid using methanol as a protic organic solvent, and the corresponding methoxylated products are obtained in excellent yields, as shown in Table 17.

4.3. Solid-Supported Mediators

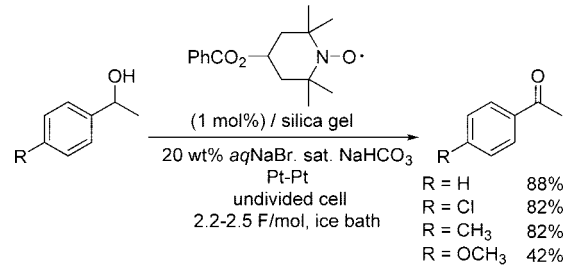
In electrochemical reactions, electron transfer usually takes place at the electrode surface. However, the reactions can also be conducted based on indirect electron transfer using mediators. Recently, various solid-supported mediators have been developed, and they serve as powerful methods for electroorganic synthesis. Yoshida, Kawabata, and co-workers developed a cross-linked poly-4-vinylpyridine hydrobromide system, which mediates the oxidation of alcohols to ketones (Scheme 59).[126] The method can also be applied to electrochemical epoxidation of alkenes, oxidation of sulfides to sulfoxides, and side-chain oxidation of alkylbenzenes. Further study using a similar polymeric system has also been reported by Zupan.[127]

N-Oxyl-mediated electrochemical oxidation has been studied extensively.[128] Recently, Tanaka and co-workers developed an *N*-oxyl-mediated reaction using an aqueous

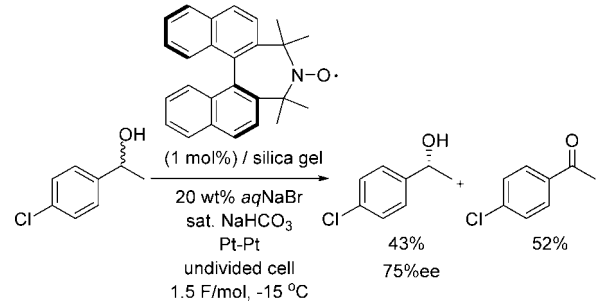
Scheme 59



Scheme 60



Scheme 61



silica gel disperse system (Scheme 60).[129] The oxidation of alcohols can be achieved without using organic solvent. The dispersed system offers many advantages over its solution-phase counterpart, including ease of product separation from the reaction mixture, minimizing of waste disposal, and recycling of reagents or catalysts.

Oxidation of 1,4-diols and 1,5-diols also proceeds smoothly to afford the corresponding γ-lactones and δ-lactones, respectively.

Kinetic resolution of a *sec*-alcohol with an optically active *N*-oxyl was achieved using a similar silica gel disperse electrolysis system to afford the corresponding ketone in 52% yield. The starting alcohol was recovered in 43% yield (75% ee) (Scheme 61).

The same system can also be applied to enantioselective oxidation of a *meso*-1,4-diol to obtain the corresponding optically active lactone in 89% yield (74% ee).

For isolation of products and recovery of *N*-oxyl catalyst, the silica gel disperse system needs processes including filtration, extraction of silica gel with acetone, evaporation, and short-column chromatography. To simplify these processes, *N*-oxyl-immobilized silica gel was prepared as an easily recyclable catalyst (Scheme 62).[130]

The reactions are carried out using the disperse system consisting of *N*-oxyl-immobilized silica gel, NaBr, aqueous NaOCl generated by anodic oxidation of aqueous NaCl, and/or a buffer solution ($NaHCO_3$) without using organic solvents. This method is effective for the oxidation of aromatic and aliphatic alcohols. In addition, the *N*-oxyl-immobilized silica gel can be easily separated by filtration and reused repeatedly, after washing with acetone, for the oxidation processes. The initial catalytic activity of the

Scheme 62

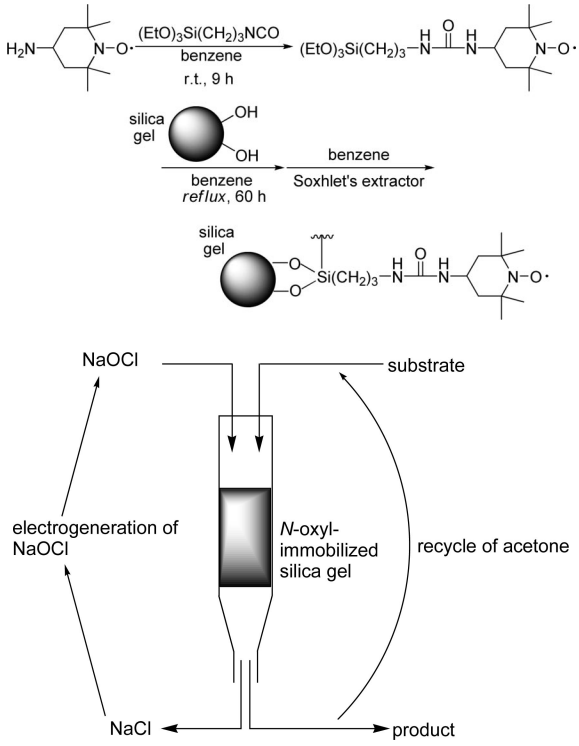
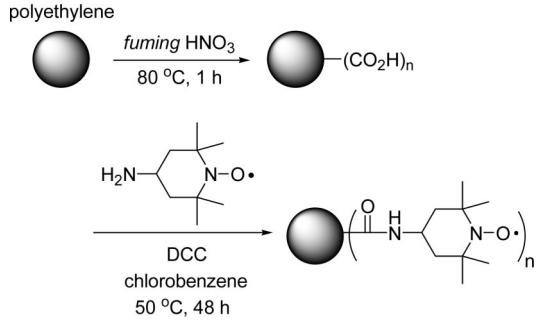


Figure 11. Preparation of *N*-oxyl-immobilized silica gel.

Scheme 63



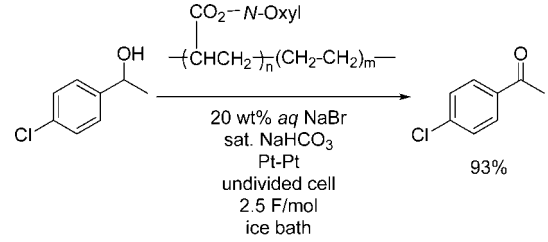
N-oxyl moiety on the silica gel remains intact at least 10 times. Moreover, a packed column containing *N*-oxyl-immobilized silica gel enables a continuous-flow system for the oxidation of alcohols. The operation is very simple: (1) loading of an alcohol, (2) passing of aqueous NaOCl generated by electrolysis of aqueous NaCl, and (3) eluting the product with acetone, as shown in Figure 11.

N-Oxyl can also be immobilized on polyethylene particles, the surface of which is functionalized with fuming HNO_3, as shown in Scheme 63, with the immobilized system being effective for the anodic oxidation of alcohols.[131]

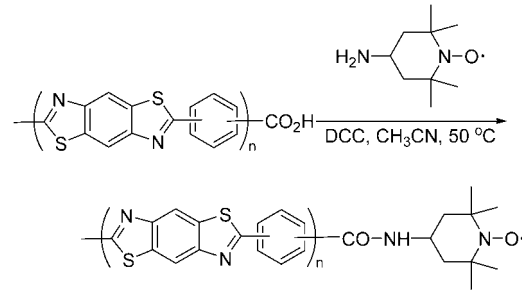
N-Oxyl can be immobilized on ethylene−acrylic acid copolymer particles as well, and the immobilized system can be used as a disperse phase for the anodic oxidation of alcohols in water (Scheme 64).[132]

N-Oxyl-immobilized poly(*p*-phenylene benzobisthiazole) network polymer particles (PBZTNT-*N*-Oxyl) shown in Scheme 65 have also been developed. The polymer is effective for the anodic oxidation of alcohols to afford the corresponding ketones, aldehydes, and/or carboxylic acids.[133]

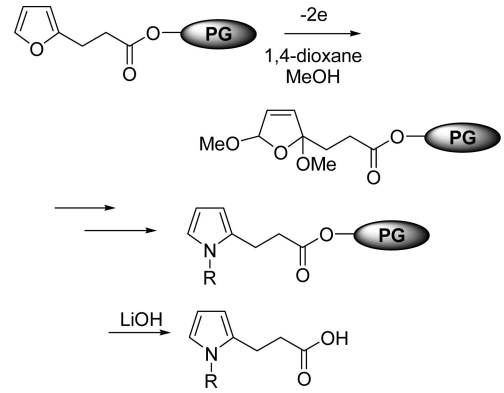
Scheme 64



Scheme 65



Scheme 66



4.4. Supported Substrate−Product Capture

Synthesis using solid-supported substrates is advantageous because of easy separation of products, which are bound to the solid. However, the use of solid-supported substrates is not effective for electrochemical reactions, because electron transfer between the solid electrode and a solid-supported substrate is very difficult. Recently, however, interesting methods have been developed, in which the electrolysis can be conducted under homogeneous traditional conditions yet the products can still be easily separated from the reaction media by simple operations.

Harrg, Breinbauer, and co-workers have developed a soluble-polymer-assisted synthesis involving an electrochemical reaction as a key step (Scheme 66).[134] Dendritic polyglycerol (PG) is used as a high-loading support. Electrolysis of the polymer-bound furan is performed in 1,4-dioxane/MeOH under homogeneous conditions. After several subsequent transformations, the product bound to the polymer is purified via dialysis. Then the product is cleaved off from the polymer by treatment with LiOH.

Chiba and co-workers constructed biphasic, thermomorphic liquid−liquid separation systems that can be achieved by moderate thermocontrol in the practical range 25−55 °C using the $LiClO_4/CH_3NO_2$ system (1:4) and cyclohexane (Figure 12).[135] The $LiClO_4$/nitrile/cycloalkane system has also been developed.[136]

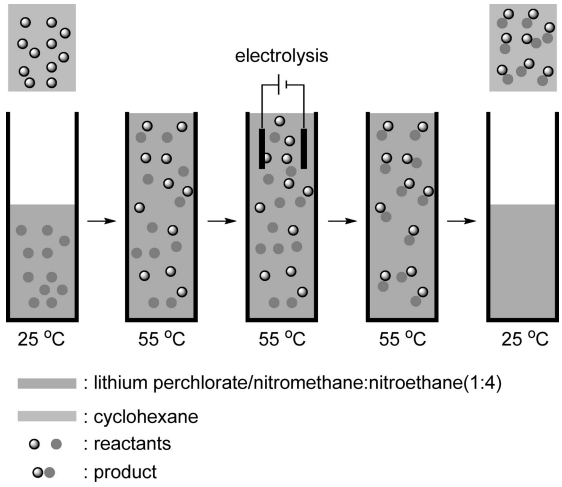
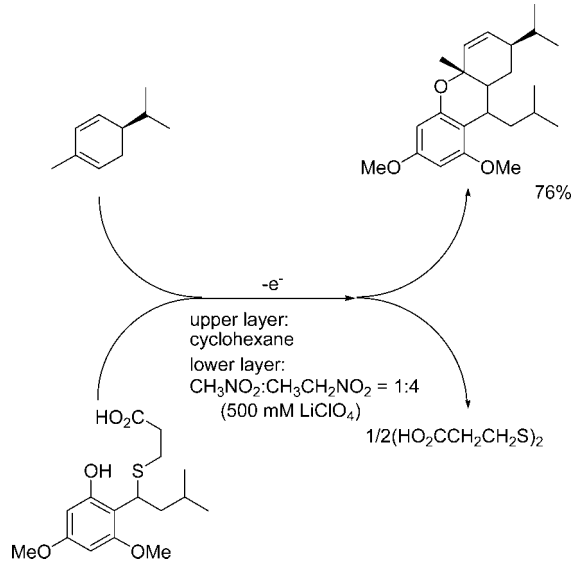


Figure 12. Thermomorphic biphasic electrolytic reaction system.

Scheme 67



The electrolysis was carried out under homogeneous conditions at 55 °C. After the electrolysis was complete, cooling of the reaction mixture to 25 °C gave rise to separation of the mixture into two phases. Therefore, the product could be easily separated from the electrolyte, which could be reused for the next cycle of the reaction. An application of the method for a cycloaddition reaction based on the anodic oxidation of benzylic sulfide is shown in Scheme 67.

Thermosensitive micromicelle-like particles have been developed for reversible capture of electrogenerated *N*-acyliminium ions (Figure 13).[137] The thiol-containing amphiphilic maleimide forms microparticles with eicosane in acetonitrile. The anodic oxidation of *N*-acetylpyrrolidine is then carried out in microparticle dispersion in $LiClO_4$/CH_3NO_2 at 0 °C. The unstable *N*-acyliminium ions that are generated are captured by the thiol groups, which are bound to the particles. After the electrolysis, the microparticles can be separated easily by centrifugal separation. The captured *N*-acyliminium ions can also be released from the particles by warming to the melting point of eicosane (45 °C). The resulting solution is then subjected to anodic oxidation in the presence of allyltrimethylsilane to obtain the allylated product.

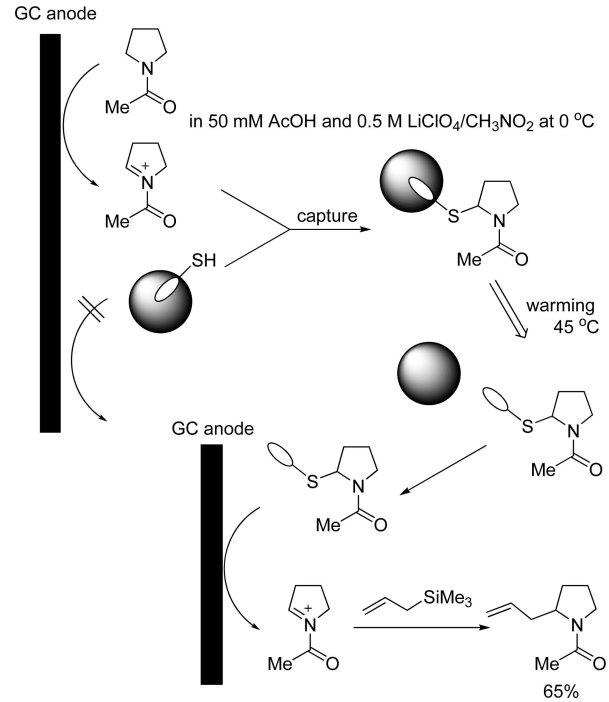
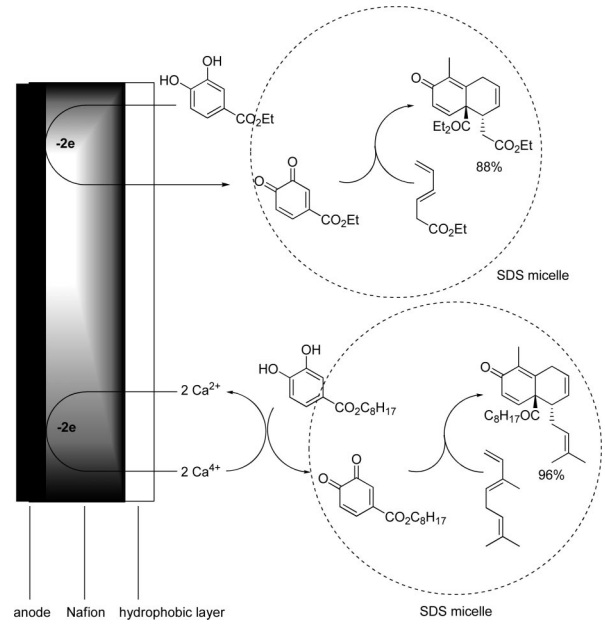


Figure 13. Releasable capture of acetyl pyrrolidine by the micellar electrolyte solution.

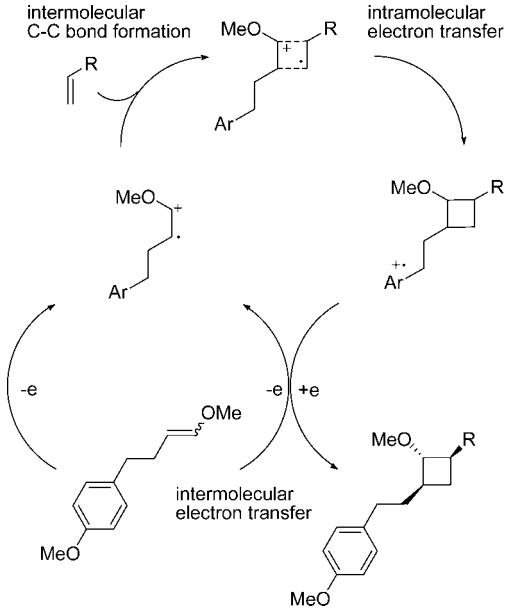
Scheme 68



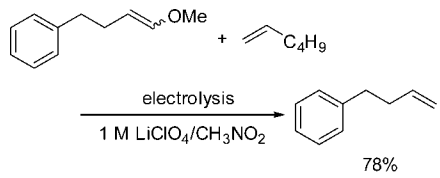
It is well-known that the anodic oxidation of *N*-acetylpyrrolidine in the presence of allyltrimethylsilane leads to preferential oxidation of the latter. This is because the oxidation potential of allyltrimethylsilane is lower than that of *N*-acetylpyrrolidine. The method involving captured *N*-acyliminium ions solves this problem (see also section 5.2).

The micellar system is also effective for the capture of electrochemically generated unstable quinines.[138] The sodium dodecyl sulfate (SDS) micellar system, which might prevent the decomposition of quinines, serves as a good environment for the Diels−Alder reaction with dienes (Scheme 68).

Scheme 69



Scheme 70



4.5. A Unique Electrolyte/Solvent System

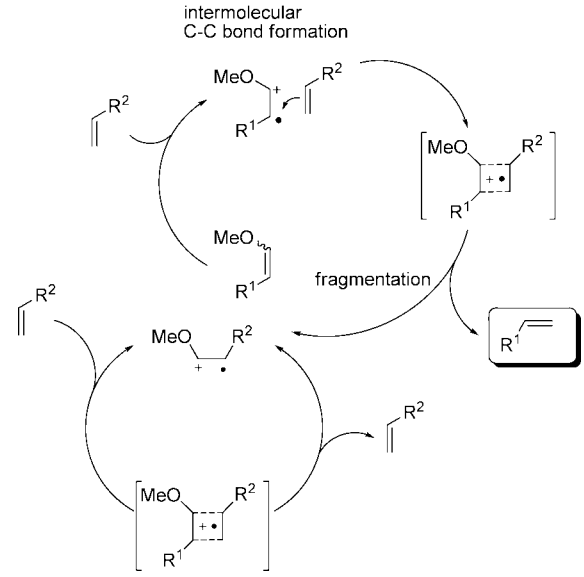
Some solvent/electrolyte systems serve as a special reaction environment for electrolysis. For example, a system consisting of $LiClO_4$ and CH_3NO_2 exhibits remarkable features for electroorganic synthesis, as demonstrated by Chiba and co-workers.

Electrolysis in the $LiClO_4/CH_3NO_2$ system triggers intermolecular formal [2 + 2] cycloaddition of electron-rich olefins.[139] For example, the anodic oxidation of an enol ether that bears a *p*-methoxyphenyl group in the presence of an olefin led to the formation of the corresponding [2 + 2] cycloadduct in 88% yield (Scheme 69). Electrocatalytic [2 + 2] cycloaddition of activated enyloxybenzene with alkenes can also be accomplished.[140] A methoxyphenyl group in enol ethers seems to serve as an intramolecular electron donor to form the cyclobutane ring, and this intermolecular olefin coupling seems to be facilitated in the $LiClO_4/CH_3NO_2$ system.

The reaction of a substrate containing a phenyl group instead of a *p*-methoxyphenyl group led to the formation of the cross-metathesis product (Scheme 70).[141] The success of the reaction also seems to be attributed to a unique property of the $LiClO_4/CH_3NO_2$ system. The reaction can be extended to a combination of simple alkyl enol ethers and alkenes.

The mechanism shown in Scheme 71 has been suggested. The initial anodic oxidation of an enol ether followed by reaction with an alkene results in the formation of a cyclobutane radical cation as a key intermediate. The cyclobutane radical cation that is formed undergoes a fragmentation reaction to give a cross-metathesis product and a radical cation of the enol ether.

Scheme 71



5. Reaction Conditions

Reaction conditions are sometimes crucial for the success of electrochemical reactions. Electrochemical reactions for organic synthesis have usually been carried out at or near room temperature. However, recent progress in electrochemical reactors enables us to perform electrochemical reactions under high-temperature and/or high-pressure conditions.[142] Such high-temperature and high-pressure technology led to the use of supercritical fluids as reaction media for organic electrochemical synthesis. It is also noteworthy that electrolysis can be conducted at very low temperatures, which enable us to generate and accumulate unstable reactive species.

5.1. Supercritical Fluids

A method for conducting electrochemical reactions under high-temperature−high-pressure conditions has been developed, and this technique enables us to use supercritical fluids as reaction media.

Supercritical fluids have attracted significant research interest as efficient reaction media. In particular, supercritical carbon dioxide ($scCO_2$) has significant potential as an environmentally benign solvent. $scCO_2$ might replace hazardous organic solvents because it is nontoxic, inexpensive, miscible with organic compounds, and nonflammable. In addition, $scCO_2$ can be recovered and reused after the reaction. It is also noteworthy that supercritical conditions for CO_2 can be readily attained (T_c = 31 °C, P_c = 7.3 MPa).[143]

5.1.1. Electrochemical Properties of $scCO_2$

Early experimental studies on electrolysis in $scCO_2$ by Silvestre and co-workers showed that carbon dioxide is poorly conducting under supercritical conditions.[144] It was found, however, that the use of a small amount of water as cosolvent led to sufficient conductivity and that the voltammetry of ferrocene in $scCO_2$ containing tetrahexylammonium hexafluorophosphate could be achieved by the addition of water.[145] Voltammetric studies in $scCO_2$ were also carried out for *p*-benzoquinone and anthracene.[146]

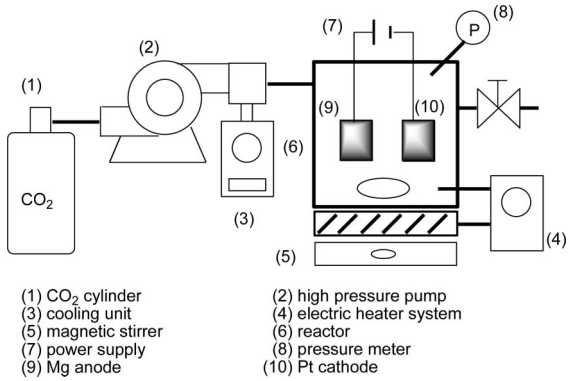
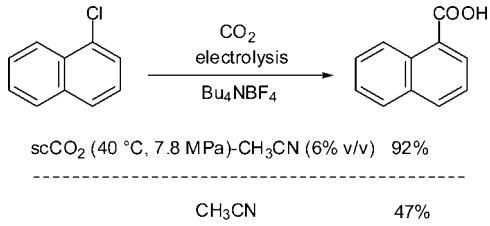


Figure 14. Apparatus for electroreductive carboxylation in $scCO_2$.

Scheme 72



5.1.2. Electroreductive Carboxylation in $scCO_2$

The utilization of carbon dioxide as a carbon source is an important subject in modern organic chemistry in view of its abundance and the environmental aspects. Electrochemical fixation of carbon dioxide into organic substrates has been studied extensively.[147] The use of a sacrificial anode such as magnesium or aluminum in DMF is quite effective.

The first attempt at electrolysis in $scCO_2$ was not successful. Although many nonpolar organic compounds are soluble in $scCO_2$, highly polar compounds such as supporting electrolytes are not very soluble because $scCO_2$ is relatively nonpolar. Limited solubility prevents the potential of $scCO_2$ for use in a broad range of applications. However, successful electrochemical carboxylations in $scCO_2$ have been achieved by Senboku and Tokuda by adding a small amount of cosolvent such as acetonitrile.[148] The apparatus for the electroreductive carboxylation in $scCO_2$ is shown in Figure 14.

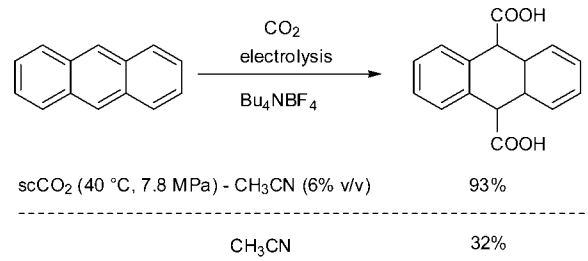
The electrochemical carboxylation of 1-chloronaphthalene in $scCO_2$ gives aryl naphthalene-1-carboxylic acid in 92% yield; although a similar carboxylation in CH_3CN containing atmospheric pressure of CO_2 gives the product only in 47% yield (Scheme 72).[148a–c] Higher yields in $scCO_2$ in comparison with those in CH_3CN seem to be attributed to faster diffusion in the supercritical fluid than in normal liquids.

Electrochemical carboxylation of anthracene in $scCO_2$ affords *trans*-1,4-dihydroanthracene-1,4-dicarboxylic acid in 93% yield, although similar carboxylation in CH_3CN containing atmospheric pressure of CO_2 affords the product only in 32% yield (Scheme 73).[148d] Faster diffusion in supercritical fluids than in normal liquids seems to be responsible for the higher yield.

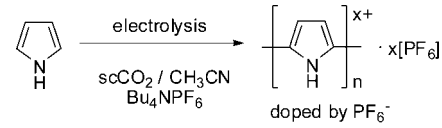
5.1.3. Electrochemical Polymerization in $scCO_2$

The use of $scCO_2$ in electrochemical polymerization has attracted significant research interest, because it is well-known that carbon dioxide penetrates into polymeric materials and often reduces interchain interactions. Recently,

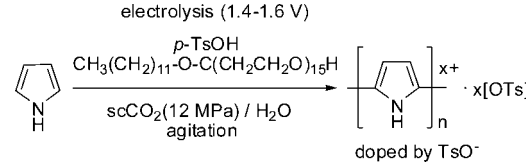
Scheme 73



Scheme 74



Scheme 75



homogeneous $scCO_2$/cosolvent systems have been applied to electrochemical polymerization. For example, electrochemical polymerization of pyrrole to form polypyrrole film was successfully achieved in the $scCO_2$/acetonitrile system (Scheme 74).[149]

It has been reported that the $scCO_2$/water emulsion system is also effective for electrochemical polymerization of pyrrole to form polypyrrole film (Scheme 75).[150]

Electropolymerization of pyrrole and thiophene in $scCHF_3$ has also been reported.[151]

5.2. The Cation-Pool Method

Carrying out electrolysis on a preparative scale at low temperatures, such as −78 °C, was considered difficult, probably because of the high viscosity of the solutions, which in turn inhibits the movement of ions carrying the electric charge. However, recent progress in organic electrochemistry enables us to carry out electrolysis on a preparative scale at such low temperatures. This technique opens a new possibility for organic electrochemistry, especially the generation and accumulation of reactive intermediates such as organic cations.

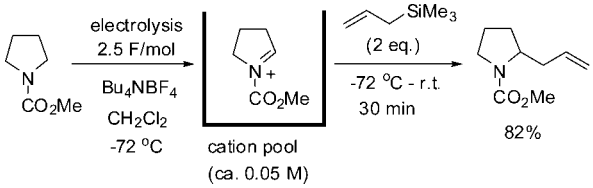
Based on a low-temperature electrolysis technique, Yoshida, Suga, and co-workers developed a method for generation and accumulation of highly reactive carbocations in the absence of a nucleophile; this method is called the cation-pool method.[152]

After generation and accumulation of the cation, a suitable nucleophile such as an organic or organometallic compound is added to the cation pool to accomplish the desired reaction. The method has been successfully applied to the generation and reactions of *N*-acyliminium ions, alkoxycarbenium ions, and diarylcarbenium ions.

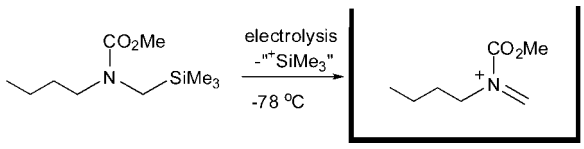
5.2.1. Generation of N-Acyliminium Ion Pools

N-Acyliminium ions[153] are useful intermediates in the synthesis of a variety of nitrogen-containing compounds. It is well-known that the anodic oxidation of carbamates leads

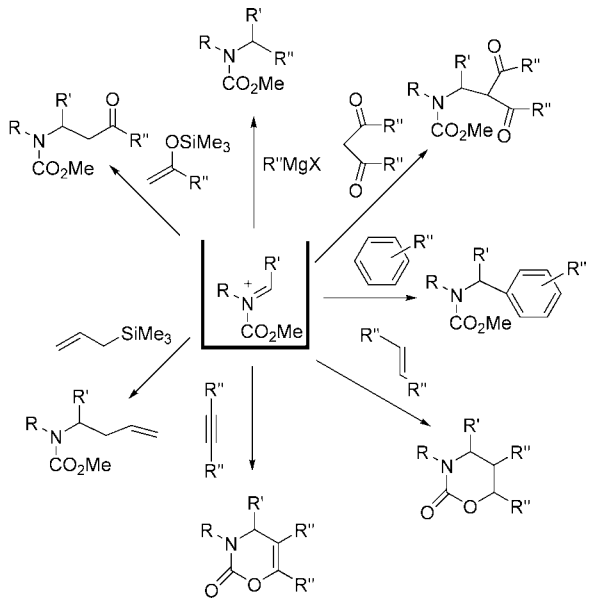
Scheme 76



Scheme 77



Scheme 78



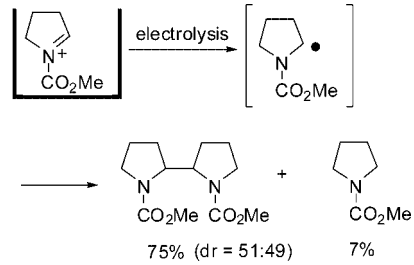
to the formation of *N*-acyliminium ions.[154] It should be noted that *N*-acyliminium ions, which do not have a stabilizing group, had been considered to be only transient intermediates until the cation-pool method was developed. Therefore, *N*-acyliminium ions are trapped *in situ*, although only compounds with high oxidation potentials, such as methanol and cyanide ion, can be used as nucleophiles.

A cation pool of an *N*-acyliminium ion can be generated and accumulated by low-temperature (−70 to −80 °C) electrolysis of a carbamate in Bu_4NBF_4/CH_2Cl_2 (Scheme 76).[155] Accumulation of the *N*-acyliminium ion as a single species can be confirmed by NMR analysis.[156] FTIR spectroscopy is also effective for characterization.[157] In the next step, the addition of a nucleophile such as allyltrimethylsilane to the solution affords the desired product in good yield. It is noteworthy that compounds that are more easily oxidized than carbamates can also be used as nucleophiles.

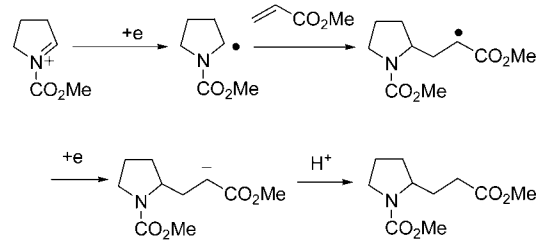
The use of a silyl group as an EA was found to be quite effective for the cation-pool method. The following example demonstrates effective regiochemical control by the silyl group in the generation of an *N*-acyliminium ion (Scheme 77).

N-Acyliminium ion pools react with various carbon nucleophiles, as summarized in Scheme 78. For example, allylsilanes, silyl enol ethers, Grignard reagents, and 1,3-dicarbonyl compounds serve as good nucleophiles.[158]

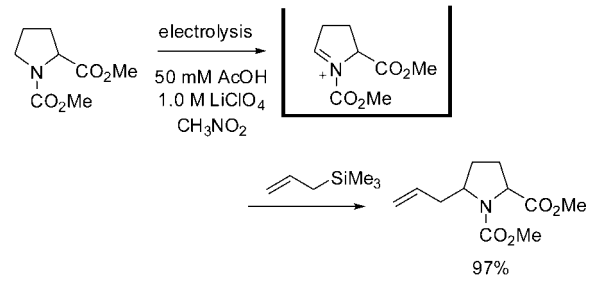
Scheme 79



Scheme 80



Scheme 81



Friedel−Crafts-type alkylation with aromatic and heteroaromatic compounds,[159] [4 + 2] cycloaddition with alkenes and alkynes,[160] carbohydroxylation reactions with alkenes and alkynes,[161] and three-component coupling with olefins and allylsilanes,[162] have also been developed. *N*-Acyliminium ion pools also serve as effective initiators of carbocationic polymerization of vinyl ethers using microflow systems.[163]

The electrochemical reduction of an *N*-acyliminium ion pool gives the corresponding homocoupled product (Scheme 79), indicating the formation of the carbon radical by one-electron reduction.[164]

The radical generated by the reduction of an *N*-acyliminium ion pool can be trapped using an electron-deficient olefin such as an acrylate ester. A mechanism involving radical addition to an electron-deficient olefin followed by one-electron reduction to give a carbanion, which is trapped by a proton, has been suggested (Scheme 80).

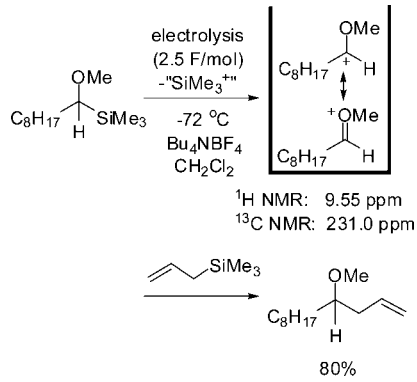
Recently, radical addition to an *N*-acyliminium ion pool has also been reported.[165]

Use of the $LiClO_4/CH_3NO_2$ system enables the generation and accumulation of *N*-acyliminium ions by electrolysis in an undivided cell at 0 °C (Scheme 81).[166] The *N*-acyliminium ions that are generated react with nucleophiles such as thiophenol and allyltrimethylsilane to give the desired products.

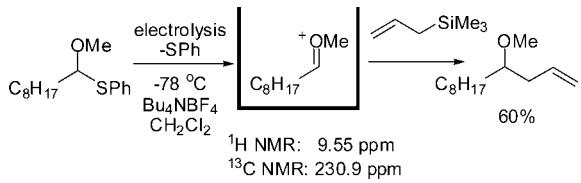
5.2.2. Generation of Alkoxycarbenium Ion Pools

Low-temperature electrolysis is also effective for the generation and accumulation of alkoxycarbenium ions, which are important reactive intermediates in modern organic synthesis.[167] In this case, the use of an EA is essential

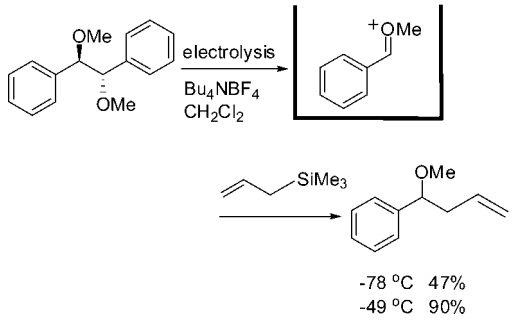
Scheme 82



Scheme 83



Scheme 84



because oxidation potentials of ethers, especially aliphatic ethers, are very positive and they are difficult to oxidize. Therefore, α-silyl-substituted ethers are used for electrochemical generation of alkoxycarbenium ion pools, which can be well characterized by NMR (Scheme 82).[168] A study of thermal stability indicates that an alkoxycarbenium ion is stable at temperatures below approximately −50 °C. Above this temperature, it decomposes. Alkoxycarbenium ion pools react with various carbon nucleophiles such as substituted allylsilanes and enol silyl ethers to give the corresponding coupling products in good yields.

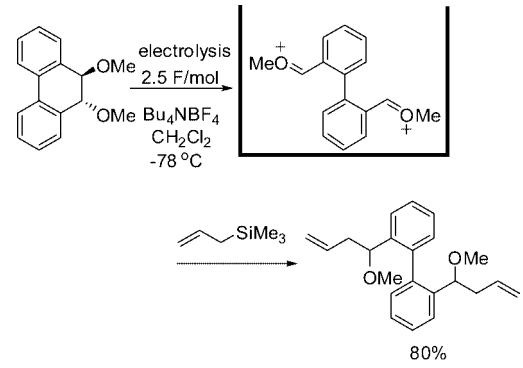
Alkoxycarbenium ion pools can also be generated using an ArS group as an EA (Scheme 83).[54]

The present method can be applied to disaccharide synthesis, although the glycosyl cation was not detected.[54] The nature of the reactive intermediate is not clear at present. It is also noteworthy that the use of Bu_4NOTf as a supporting electrolyte gave rise to the formation of glycosyl triflates, which can be well characterized by NMR.[55]

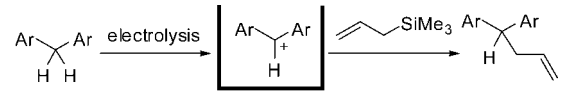
Oxidative C−C bond dissociation is also effective for alkoxycarbenium ion pool generation.[169] Thus, low-temperature electrochemical oxidation of 1,2-dimethoxy-1,2-diphenylethane leads to the formation of an alkoxybenzyl cation pool (Scheme 84).

The C−C bond dissociation approach is advantageous for generation of dication pools.[170] Thus, low-temperature electrochemical oxidation of the cyclic compound shown in Scheme 85 leads to generation and accumulation of the

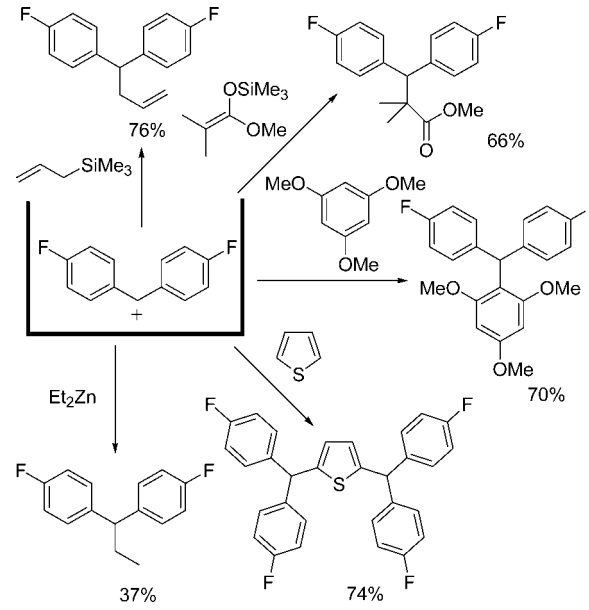
Scheme 85



Scheme 86



Scheme 87



corresponding dication, the ^{13}C NMR spectrum of which indicates that the two cationic centers are equivalent.[169] The addition of allyltrimethylsilane to the solution gives the corresponding diallylated compound in 80% yield.

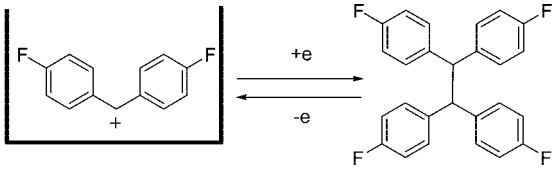
5.2.3. Generation of Diarylcarbenium Ion Pools

Low-temperature electrolysis of diarylmethanes leads to the formation of diarylcarbenium ion pools, although the efficiency of the reaction strongly depends on the nature and location of the substituents on the aryl group (Scheme 86).[171]

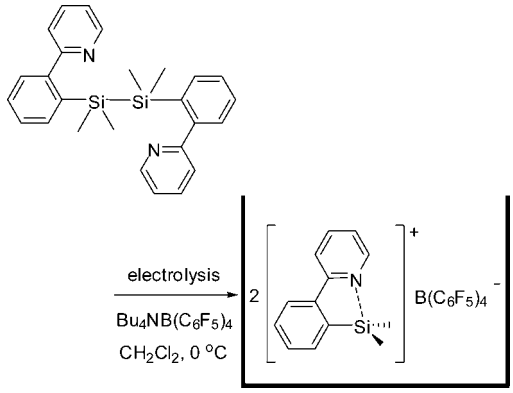
As summarized in Scheme 87, the diarylcarbenium ion pool reacts with various nucleophiles, including allylsilanes and ketene silyl acetals. Friedel−Crafts-type reactions with aromatic and heteroaromatic compounds also take place smoothly.

The reductive coupling of the diarylcarbenium ion can be accomplished by low-temperature electrochemical reduction (Scheme 88). The homocoupled product that is obtained can be oxidized by low-temperature electrolysis to regenerate the diarylcarbenium ion pool.

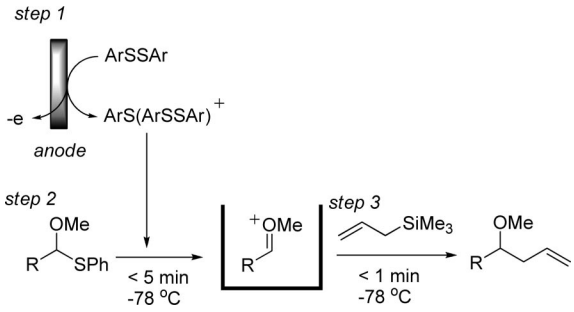
Scheme 88



Scheme 89



Scheme 90



5.2.4. Generation of Other Cation Pools

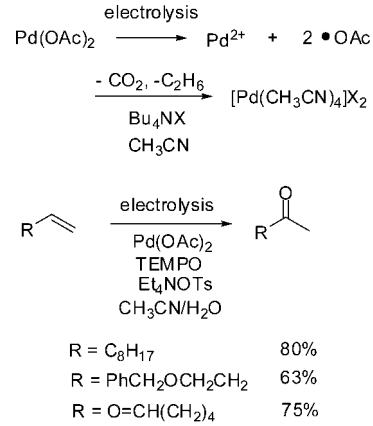
Cations of other elements can also be generated and accumulated by the cation-pool method. For example, a donor-stabilized organosilicon cation was generated by electrochemical oxidative Si−Si bond dissociation and accumulated in the solution (Scheme 89).[172]

$ArS(ArSSAr)^{+}$[173] can be generated and accumulated by the low-temperature electrolysis of ArSSAr (Scheme 90).[174] This cation pool was found to be quite effective for the generation of alkoxycarbenium ion pools from α-ArS-substituted ethers. The reaction is complete within 5 min at −78 °C. The alkoxycarbenium ion pool that is obtained exhibits similar stability and reactivity to that obtained with the direct electrochemical method.

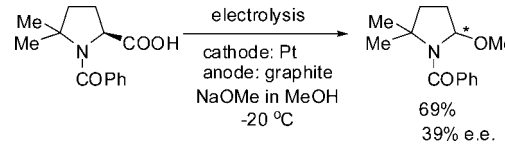
Miller and co-workers reported that the anodic oxidation of I_2 in acetonitrile gave "CH_3CNI^{+}" (equivalent of I^{+}) and that this species reacted with aromatic compounds to give the corresponding aromatic iodides.[175] Romakhin and co-workers reported the IR spectrum of "CH_3CNI^{+}", which did not show any absorption resulting from the vibration of the CN triple bond.[176] The species has been recently characterized by CSI-MS, which exhibited signals due to CH_3CNI^{+} and $(CH_3CN)_2I^{+}$.[177]

Recently, Mitsudo and Tanaka reported that the generation and accumulation of cationic palladium complexes with weakly coordinating anions has been achieved by the electrochemical oxidation of $Pd(OAc)_2$ in CH_3CN. Bu_4NBF_4, Bu_4NPF_6, and Bu_4NClO_4 are effective as supporting electrolytes (Scheme 91).[178] A mechanism involving oxidation of the acetate anion of $Pd(OAc)_2$ to the acetoxy radical has been suggested. Based on this information, *N*-oxyl/Pd double-mediatory electrochemical Wacker-type oxidation of alkenes to ketones has been developed.

Scheme 91



Scheme 92



6. Electrochemical Devices

The outcome of an electrochemical reaction strongly depends on the nature of the reaction devices used. The electrode material plays a crucial role in many electrochemical reactions. The shape and size of the cell also play important roles. Sometimes the use of extra energies such as ultrasound affects the efficiency and selectivity. This section focuses on recent developments in the hardware of electroorganic synthesis.

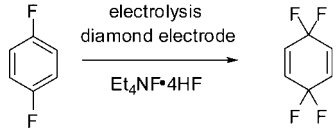
6.1. Electrode Materials

It is well-known that the choice of electrode materials is often crucial for the success of electrochemical reactions. Sometimes, a change in the electrode material alters the reaction pathway. For example, the use of a graphite electrode is crucial for chiral memory in the anodic oxidation of *N*-acyl-α-amino acids (Scheme 92).[179] Strong interaction between the *N*-acyliminium ion intermediate and a graphite electrode seems to be responsible. The use of platinum and glassy carbon electrodes resulted in complete racemization.

It is well-known that the use of reactive metals such as Mg and Al as sacrificial electrodes serves as a powerful method for electrochemical reduction. Recent progress in sacrificial Mg electrode technology includes the synthesis of polysilanes with ordered sequences[180] and silylene−germylene copolymers[181] using Mg electrodes developed by Kashimura, Ishifune, and co-workers. Double C-acylation[182] and C-carboxylation[183] of olefins using Zn electrodes developed by Nishiguchi, Maekawa, and co-workers are also interesting. It is also noteworthy that sacrificial sulfur−graphite electrodes containing reactive polysulfide anions have been developed and used in electroorganic synthesis.[184]

Various interesting modified electrodes have been developed and used for electroorganic synthesis, although only a

Scheme 93



limited number of examples are listed here. A crown ether-modified Pt electrode containing alkali metal ions has been developed by Ishifune, Kashimura, and co-workers, and this electrode is useful for paired electrolysis to conduct coupling of an ester with tetrahydrofuran.[185] Introduction of a hydroxyl group on the surface of carbon using an electrogenerated NO_3 radical is also interesting.[186] With the aid of the hydroxyl groups, various functional groups can be introduced on the surface of carbon electrodes, which can be utilized for electroorganic synthesis. Maeda, Ohmori, and co-workers developed a method of surface modification of carbon electrodes using anodic oxidation in the presence of alcohols.[187]

Cathodic reduction of diazonium salts developed by Savéant et al. is one of the most reliable methods for the modification of electrodes.[188] Fry and co-workers reported the introduction of triarylamine onto the surface of a graphite electrode by diazotization of an aminotriarylamine followed by electrochemical reduction.[189] Bélanger and co-workers reported the modification of glassy carbon and gold electrodes by electrochemical reduction of diazonium cations generated *in situ* in aqueous medium.[190] Simonet and Peters reported an electrochemically formed iodide-modified Pt electrode for the reduction of alkyl halides.[191]

Noncovalent modification of electrodes has also been extensively studied. For example, Osa, Kashiwagi, Anzai, Bobbit, and co-workers reported that a Pt electrode covered with poly(acrylic acid) containing optically active *N*-oxyl was quite effective for asymmetric oxidation of alcohols.[192] Nonaka et al. reported the use of hydrophobic PTFE composite-plated Pt anodes for Kolbe electrolysis.[193] It is also interesting to note that the PTFE-fiber-coated electrode is quite effective for electrochemical generation of quinines and subsequent Diels−Alder reactions.[194]

Recently, new electrode materials have been developed and are being used for electroorganic synthesis. For example, the chemical inertness and physical strength of diamond attracts significant attention from electrochemists as an electrode material. In fact, boron-doped diamond has a wide potential window and can be used for various electrochemical reactions.[195] Boron-doped diamond thin-film electrodes are used for the anodic fluorination of 1,4-difluorobenzene in neat $Et_4NF•4HF$ (Scheme 93).[196] The cyclic voltammogram obtained with Pt and highly ordered pyrolytic graphite exhibited waves associated with the formation of an adsorbed oxygen or platinum oxide layer and the intercalation of fluoride ion. However, the voltammogram obtained for diamond consisted essentially of a wave attributable to the fluorination of 1,4-difluorobenzene in the same sweep range. This observation indicates a wide potential window and high chemical/electrochemical stability for the diamond electrode.

6.2. Ultrasound and Centrifugal Fields

The use of ultrasound in chemical synthesis has attracted significant research interest. In homogeneous solution, the mass-transport process is suggested to be accelerated by ultrasound because of macroscopic streaming[197] and microscopic cavitation.[198]

The effect of ultrasound on homogeneous electrolysis processes such as Kolbe electrolysis has been studied by Nonaka, Atobe, and co-workers.[199,200] It is interesting to note that a characteristic change in the distribution from one-electron to two-electron oxidation products was observed together with a faster conversion under ultrasound conditions, although the detailed mechanism is not clear at present.[201]

Ultrasound enhances electroorganic reactions in emulsion systems.[202] For example, Kolbe electrolysis was found to be enhanced by ultrasound under biphasic conditions.[203] A clean and highly efficient process at Pt electrodes with formation of "one-electron oxidation" products is produced selectively, in marked contrast to processes in monophasic media. A dynamically modified electrode surface, at which hydrophobic products are immediately "trapped" via partitioning into a nonpolar organic phase and transported away into the emulsion system, seems to be responsible. Polycrystalline boron-doped diamond electrodes, which might minimize the surface erosion induced by ultrasound, can also be used for the reaction. The type and yield of products obtained at diamond electrodes are essentially identical to those observed at Pt electrodes. Ultrasonication is also used for electropolymerization of pyrrole[204] and ethylenedioxythiophene.[205]

Electrolysis in centrifugal fields has also been studied using an electrochemical cell in a centrifuge tube.[206] Studies on electrochemical copolymerization of aromatic compounds such as aniline and *o*-aminobenzonitrile revealed that the copolymerization ratio could be controlled by the applied gravitational force.

6.3. Electrochemical Microflow Systems

Recently, microflow systems have received significant research interest from both academia and industry.[207] Microflow systems are expected to serve as a much better reaction environment than conventional macrobatch reactors by virtue of the inherent advantages of microspace, such as small size and large surface-to-volume ratio. In electroorganic synthesis, the use of a microflow reactor serves as a solution to the problems of conventional macrobatch electrochemical reactors, such as difficulty in mass transfer on the surface of the electrodes and high ohmic drop between the electrodes.[208] Various types of electrochemical microflow reactors have also been developed, in the field of electrophoresis,[209,210] electrochemical analytic studies,[211] and electrogenerated chemiluminescence.[212,213]

A microflow electrochemical reactor having a plate-to-plate electrode configuration mounted in a nonconducting housing has been developed by Löwe and co-workers.[214,215] The working electrode and the counterelectrode are separated using a 75 μm-thick polyimide foil between them, as shown in Figure 15.

The reactor was used for the anodic oxidation of *p*-methoxytoluene to give *p*-methoxybenzaldehyde dimethyl acetal. The efficiency (98%) was higher than that of the conventional macrobatch industrial processes (85%) (Scheme 94).[216]

A ceramic microflow electrochemical reactor has also been developed. The anodic oxidation of furans in methanol using H_2SO_4 as the supporting electrolyte was carried out, and the effect of the residence time was investigated by mass spectrometry analysis, but the amount of electricity and the yield of the product were not indicated (Scheme 95).[217]

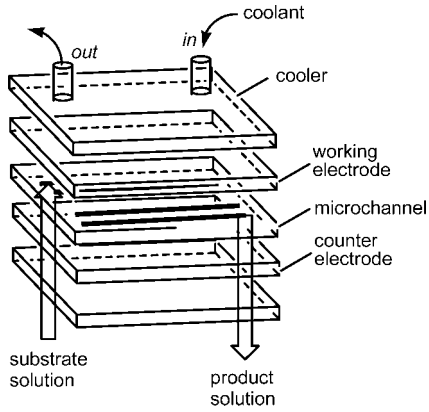
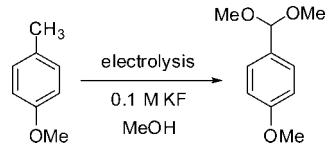


Figure 15. Schematic view of a microflow electrochemical reactor having a plate-to-plate electrode configuration.

Scheme 94



Scheme 95

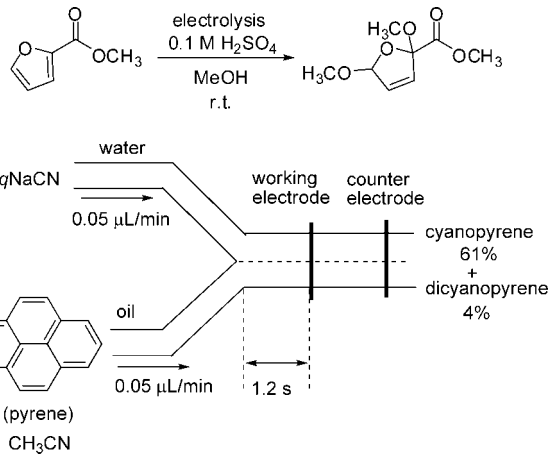


Figure 16. Cyanation of pyrene in an electrochemical microchip reactor.

A polymer microchip having a microchannel (100 μm width $\times$ 20 μm depth) integrated with electrodes[218–220] has been developed and applied to the anodic oxidation of pyrene in the presence of NaCN by Kitamura and co-workers.[221,222] An acetonitrile solution of pyrene containing Bu_4NClO_4 and an aqueous NaCN solution were introduced into the microchannel (Figure 16), and 1-cyanopyrene was produced in 61% yield under the optimum conditions. The overoxidation to form 1,3-dicyanopyrene could be suppressed using the microflow system. In the macrobatch electrolysis, 1,3-dicyanopyrene was produced in 14% yield, but its yield decreased to 4% in the microchip reactor.

Cyanopyrene could be obtained as the sole product (13.5%) using the microflow electrochemical reactor of different electrode configuration shown in Figure 17. In this configuration, the initial product solution cannot come in contact with the working electrode (the anode).

A microflow electrochemical system serves as a quite effective method for oxidative generation of unstable organic cations at low temperatures (Figure 18). This method is called the cation-flow method.[157] An electrochemical reactor for

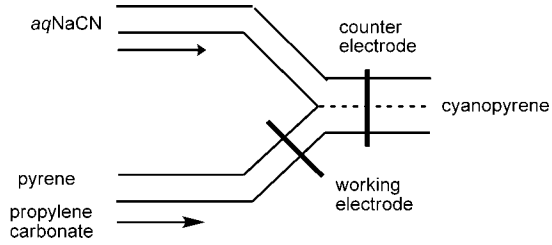


Figure 17. Cyanation reaction of pyrene in a microchannel.

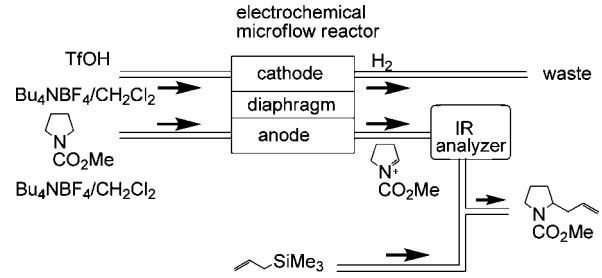
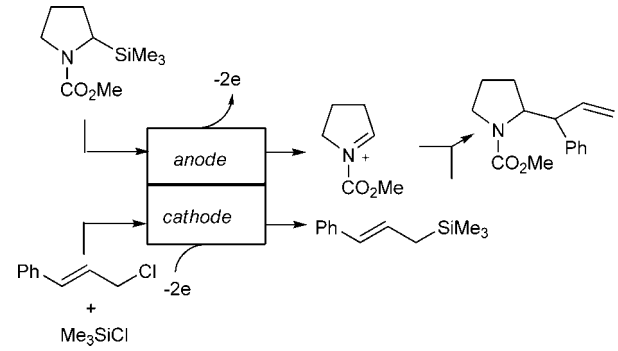


Figure 18. Schematic diagram of the cation-flow system.

Scheme 96



the cation-flow method is equipped with a carbon felt anode and a platinum wire cathode. The anodic chamber and the cathodic chamber are separated by a diaphragm of PTFE membrane. A solution of a cation precursor is introduced to the anodic chamber, and a solution of trifluoromethanesulfonic acid (TfOH) as a proton source is introduced to the cathodic chamber. The reaction can be monitored by inline FTIR spectroscopy (ATR method). The organic cation that is generated is immediately transferred to a vessel in which a nucleophilic reaction takes place to give the desired coupling product.

Paired electrolysis,[223] in which both the anodic oxidation and the cathodic reduction contribute to the formation of the final product(s), is highly advantageous from the viewpoint of efficiency and economy. Thus, a paired microflow electrochemical system has been developed where an organic cation is generated by anodic oxidation and a carbanion equivalent is generated by cathodic reduction; both intermediates are allowed to react to give the corresponding coupling product.[224]

For example, a silyl-substituted carbamate is oxidized at the anode to generate a solution of *N*-acyliminium ion, and cinnamyl chloride is reduced at the cathode in the presence of chlorotrimethylsilane to generate the corresponding allylsilane[225] in the continuous microflow system (Scheme 96). In the next step, the *N*-acyliminium ion is allowed to react with the allylsilane to give the coupling product.

Atobe and Fuchigami reported that the use of parallel laminar flow in a microflow electrochemical reactor enables

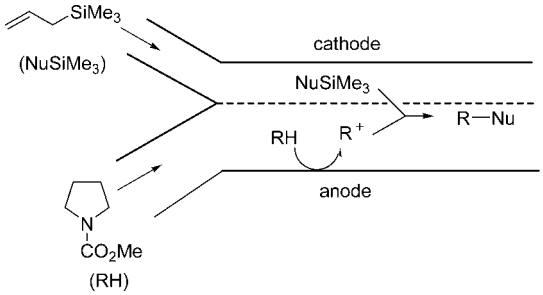


Figure 19. Parallel laminar microflow system for the electrochemical generation and reaction of *N*-acyliminium ion.

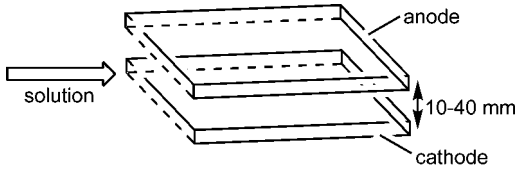


Figure 20. Electrochemical microflow system without added supporting electrolyte.

the effective generation of an *N*-acyliminium ion followed by trapping with an easily oxidizable carbon nucleophile such as allyltrimethylsilane (Figure 19).[226] A solution of a cation precursor and a solution of allyltrimethylsilane are introduced in a parallel manner. The laminar flow prevents the oxidation of allyltrimethylsilane at the anode. Only the precursor is oxidized to generate the *N*-acyliminium ion. The *N*-acyliminium ion that is generated diffuses and reacts with allyltrimethylsilane. Although the efficiency of the process is very low for the Bu_4NBF_4/CH_3CN system, use of the Bu_4NBF_4/TFE (2,2,2-trifluoroethanol) system (59% yield) or ionic liquid (62−91% yield) gave rise to the formation of the desired product.

Electrochemical microflow systems have also received significant research interest from the viewpoint of electrolysis without a supporting electrolyte. Although various electrolyte-free electrochemical systems have been developed,[121–124,227,228] the microflow-system-based approach is attractive because the short distance between the electrodes and the high electrode-surface to reactor-volume are advantageous for conductivity and reaction efficiency.

Marken and co-workers accomplished the electrolysis without intentionally added electrolyte using a simple electrochemical microflow system having a parallel electrode configuration (Figure 20).[229] Two electrodes are placed facing each other at a distance of micrometer order, and a substrate solution flows through the chamber. In this system, the liquid flow and the current flow are perpendicular. A paired electrolysis consisting of one electron oxidation of ferrocene and the two-electron−two-proton reduction of tetraethyl ethylenetetracarboxylate in ethanol was achieved without electrolyte.[230]

The anodic oxidation of furans in methanol can also be carried out without intentionally added electrolyte using a microflow system of parallel electrode configuration. In this case, a glassy carbon anode and a platinum cathode directly face each other at a distance of 80 μm (Figure 21).[231,232] 2,5-Dimethoxy-2,5-dihydrofuran is obtained in 98% yield. The anodic methoxylation and acetoxylation of various organic compounds can also be carried out using this system.

There is another type of microflow system that can be used for electrolyte-free electrolysis (Figure 22).[233] In this system, two carbon fiber electrodes are separated by a spacer (porous

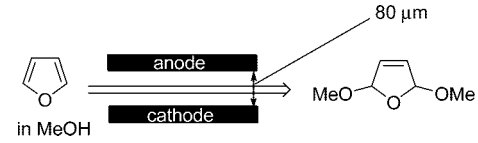


Figure 21. Electrochemical oxidation of furan.

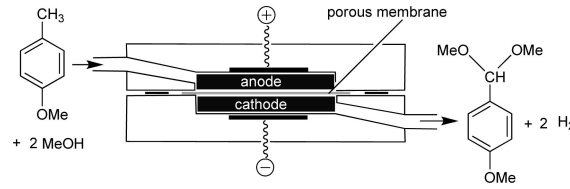


Figure 22. Methoxylation of *N*-methoxycarbonyl pyrrolidine using an electrochemical microflow system without intentionally added electrolyte.

PTFE membrane; pore size, 3 μm; thickness, 75 μm) at a distance of micrometer order. An anodic solution flows through the spacer membrane into the cathodic chamber. The product solution leaves the system from the cathodic chamber. In this system, the electric current flow and the liquid flow are parallel.

Using this electrochemical microflow system, the anodic methoxylation of *p*-methoxytoluene was accomplished effectively without intentionally added electrolyte. The device could also be used for the anodic methoxylation of *N*-methoxycarbonyl pyrrolidine and acenaphthylene.

7. Combinatorial Electrochemical Synthesis

Creation of new molecules having desired functions or activity is the key to the progress of science. Synthetic organic chemistry has contributed to the development of materials science and life science through providing efficient methods and strategies for making useful organic frameworks. Although target-oriented synthesis has been the mainstream approach, the emergence of combinatorial chemistry[234] and diversity-oriented synthesis[235] has changed the way of planning and doing chemical synthesis as a whole. Library-based approaches enable rapid discovery and optimization of molecules having desired functions or activity. In addition, there is a high probability of discovering unexpected functions or activity in these library-based approaches. In this section, we discuss the electrochemical methods for generating molecular diversity.[236]

7.1. Parallel Electrolysis Using a Macrosystem

The use of the electrochemical method for generating molecular diversity has appeared in the literature rather recently. In 2000, Yudin et al. reported a spatially addressable electrolysis platform consisting of a Teflon block with 16 wells and a set of 16 glass vials (Figure 23).[237]

The anodic α-alkoxylation of carbamates and sulfonamides was chosen to test the feasibility of parallel electroorganic synthesis (Scheme 97, Table 18). The constant-current electrochemical oxidation could be conducted in a parallel fashion to obtain the corresponding products in high yields.

The parallel electrolysis using a spatially addressable electrolysis platform could also be applied to electrochemical reduction (Scheme 98).[238] The electroreductive hydrocoupling of aldimines using sacrificial Al anodes gave the corresponding 1,2-diamine derivatives.

The cation-pool method serves as a powerful tool for parallel combinatorial synthesis. A typical example is shown

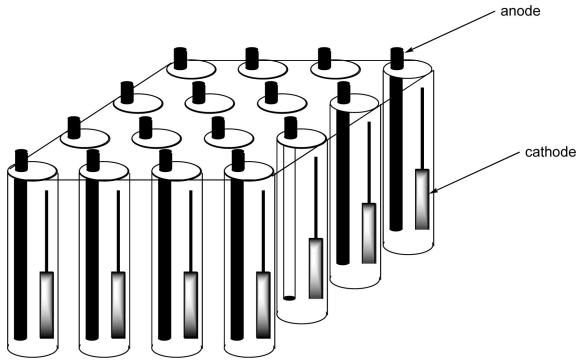


Figure 23. 16-well platform for parallel electrolysis.

Scheme 97

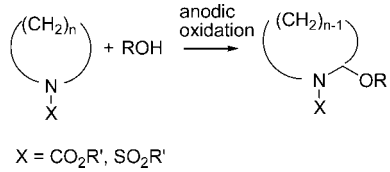
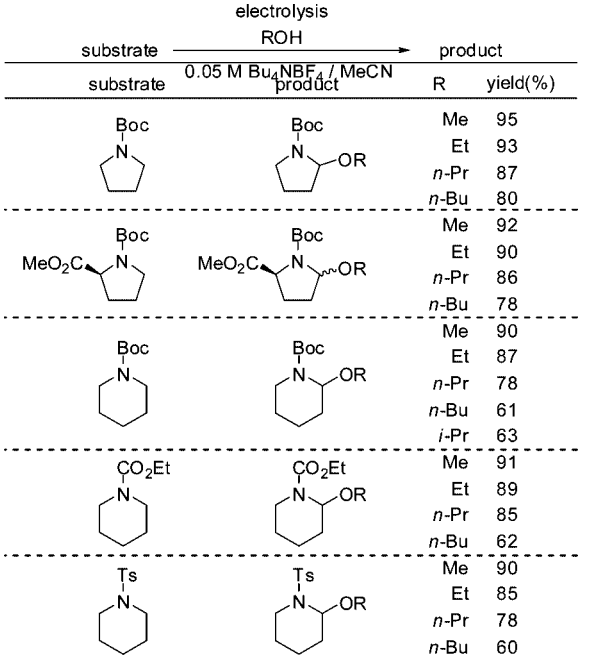
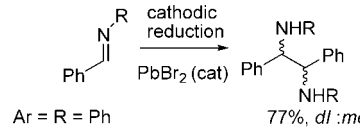


Table 18. Parallel Electrosynthesis of α-Alkoxycarbamates, α-Alkoxyamides, and α-Alkoxysulfonamides Using a Spatially Addressable Electrolysis Platform



Scheme 98



Ar = R = Ph	77%, *dl* :*meso* = 60 : 40
Ar = Ph, R = Ph_2CH	65%, *dl* :*meso* = 99 : 1
Ar = *p*-$MeOC_6H_4$, R = Ph_2CH	57%, *dl* :*meso* = 99 : 1
Ar = *p*-CNC_6H_4, R = Ph_2CH	62%, *dl* :*meso* = 99 : 1
Ar = *o*-FC_6H_4, R = Ph_2CH	67%, *dl* :*meso* = 99 : 1

in Figure 24. A solution of a cation generated by low-temperature electrolysis is divided into several portions. Different nucleophiles are added to each portion to obtain the products of different coupling combinations.

The procedure can be easily automated[239] by a robotic synthesizer equipped with automated syringes and low-temperature reaction vessels. The yields of the products are essentially the same as those obtained by one-pot reactions with manual operation, which are shown in parentheses.

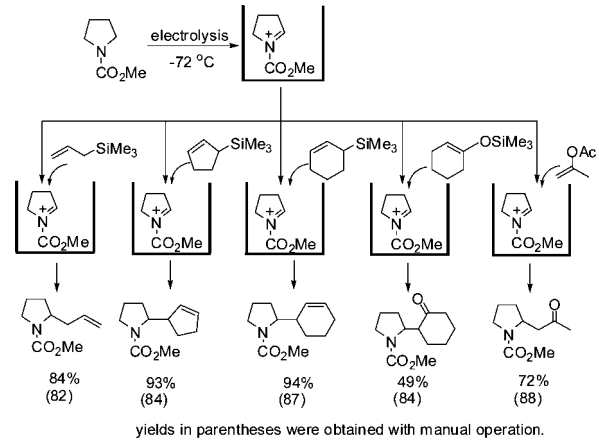


Figure 24. Parallel combinatorial synthesis based on the cation-pool method.

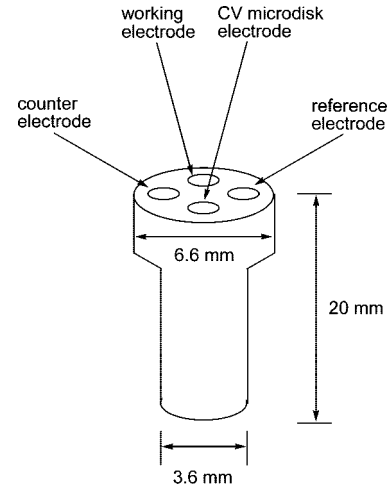


Figure 25. Assembly of the electrode bundle consisting of a PTFE holder.

7.2. Parallel Electrolysis Using a Microsystem

Speiser reported miniaturized combinatorial electroorganic synthesis using a computer-controlled instrument equipped with a well containing microtiter plates (Figure 25).[240] An electrode bundle consisting of a PTFE holder, a working electrode, a CV microdisk, a reference electrode, and a counterelectrode can be moved from well to well automatically. Libraries of iminoquinol ethers and triazolopyridinium ions are generated by potentiostatic electrolysis. Progress of the electrolyses can be monitored by microelectrode steady-state voltammetry.

Moeller et al. developed a microchip-based molecular library construction system using a 1 cm^2 chip having an array of 1024 individually addressable Pt electrodes (Figure 26).[241] The array was coated with a porous hydroxylated polymer membrane. 10-Undecenoic acid moieties were introduced to the hydroxyl groups on the membrane. The Pd-catalyzed Wacker oxidation mediated by the electrochemical oxidation of a triarylamine was performed at selected electrodes to generate the ketones, which were converted to their 2,4-DNP derivatives.

The 2,4-DNP recognition sites at the selected electrodes were treated with a rabbit *anti*-2,4-dinitrophenol antibody

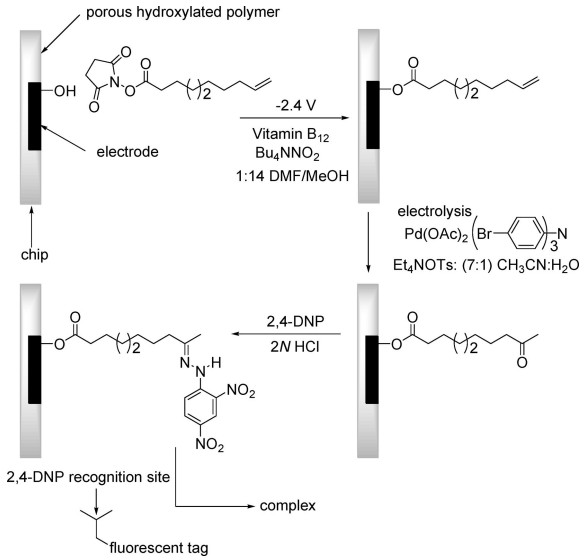


Figure 26. A microchip-based molecular library construction system.

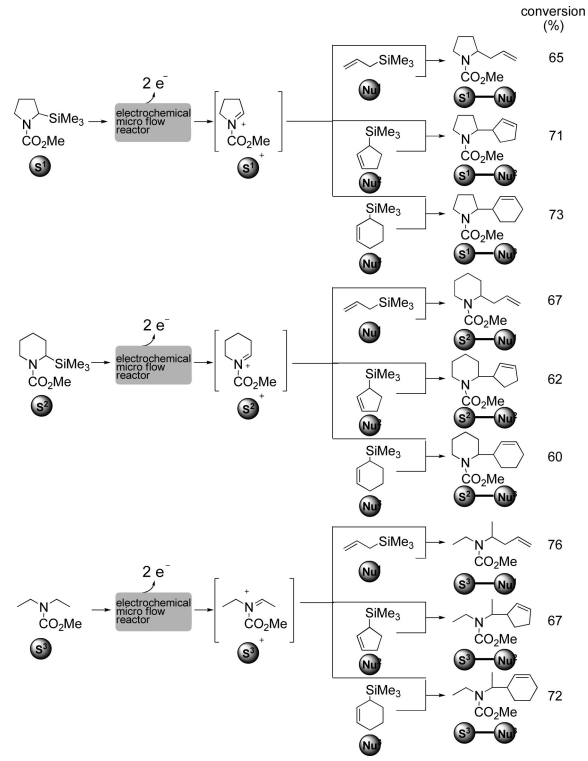


Figure 27. Sequential combinatorial synthesis based on the cation-flow method.

that is conjugated to a fluorescent probe. Imaging using an epifluorescence microscope showed that only the selected electrodes exhibited fluorescence. This experiment proved that the selected electrodes could be selectively modified chemically at will. The success of this system opened the possibility of building addressable libraries on an array of microelectrodes.

This approach has been expanded to other addressable libraries using a mass spectrometry cleavable linker for monitoring reactions.[242] Selective coumarin synthesis and real-time signaling of antibody−coumarin binding based on microchip technology have also been reported.[243]

7.3. Serial Electrolysis Using a Microsystem

The cation-flow method enables sequential combinatorial synthesis by simple flow switching.[157,224] For example, a cation generated from precursor $\mathbf{S}^1$ is allowed to react with nucleophile $\mathbf{Nu}^1$ (Figure 27). Then, a nucleophile is switched to $\mathbf{Nu}^2$, $\mathbf{Nu}^3$, and so on. In the next step, a cation precursor is switched to $\mathbf{S}^2$, and the cation generated from $\mathbf{S}^2$ is allowed to react with nucleophiles $\mathbf{Nu}^1$, $\mathbf{Nu}^2$, and $\mathbf{Nu}^3$ sequentially. Then, a cation precursor is switched to $\mathbf{S}^3$, and a cation generated from $\mathbf{S}^3$ is allowed to react with nucleophiles $\mathbf{Nu}^1$, $\mathbf{Nu}^2$, and $\mathbf{Nu}^3$ sequentially. The potential of this method is demonstrated by the synthesis of nine compounds from three precursors of *N*-acyliminium ions and three allylsilanes. Although parallel syntheses enjoy versatile applications in combinatorial chemistry, this continuous sequential method opens up a new aspect of combinatorial synthesis.

8. Conclusions

The examples shown in this review article demonstrate that a variety of new strategies including intramolecular control, reaction media, reaction conditions, and devices have been developed in electroorganic synthesis. Such strategies enable selective and efficient electron transfer and/or precise control of pathways of subsequent reactions. It is hoped that these strategies provide solutions to the problems of conventional electrochemical processes and serve as powerful methods for conventional and combinatorial organic synthesis in laboratories. It is also noteworthy that the applications of these modern strategies speak well for their potentiality in developing economically advantageous and environmentally benign processes for the industrial production of a variety of chemicals, although only a limited number of organic electrochemical processes have been developed in industry so far. Hopefully, a wide range of strategies based on different principles will be exploited in organic electrochemistry and will work together to meet the great demands for organic synthesis in the future.

9. Acknowledgments

We would like to express our gratitude to Grants-in-Aid for Scientific Research, Practical Application Research (JST Innovation Plaza, Kyoto), and the Project of Development of Microspace and Nanospace Reaction Environment Technology for Functional Materials of NEDO. We also thank the reviewers of the manuscript for their kind suggestions and corrections. We dedicate this paper to the late Professor Yoshihiro Matsumura in honor of his outstanding contributions to organic electrochemistry.

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