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Direct nucleophilic functionalization of C(sp^2) – H-bonds in arenes and hetarenes by electrochemical methods

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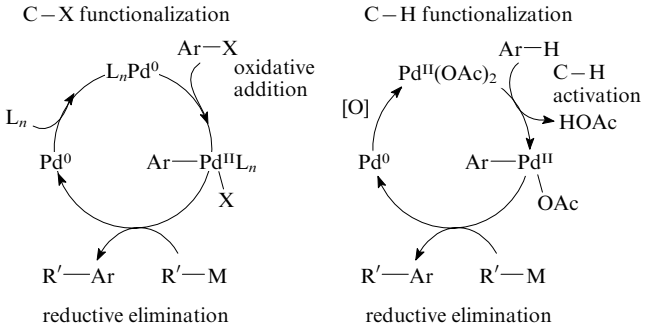
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Abstract. The data on the main electrochemical methods and approaches used for the direct functionalization of the C(sp^2) – H-bond proceeding *via* the mechanisms of nucleophilic substitution of hydrogen (S_N^H-reaction) are classified and summarized. The important features of preparative electrochemical processes are considered. A special emphasis is placed on the synthetic potential of the discussed transformations. The bibliography includes 133 references.

I. Introduction

The 1970s witnessed the triumphant progress of a novel synthetic methodology of arene and hetarene functionalization based on transition metal-catalyzed cross-coupling reactions. These reactions became an integral part of the modern organic synthesis.[1] The most well-known cross-couplings include the Heck, Negishi, Suzuki, Buchwald — Hartwig, Kumada, Sonogashira and Stille reactions,[2] based mainly on the interactions of alkyl and aryl halides (C – X-functionalization) with organometallic reagents *via* the formation of complexes with transition metals (R′M) (Scheme 1). They have found wide use in laboratory and industrial syntheses due to mild reaction conditions, a wide range of functionalities used as well as a high chemoselectivity. Despite all merits of the cross-coupling reactions, one cannot but mention certain drawbacks such as side reactions with the catalyst, homocatalysis, the need for an additional introduction of leaving groups (mainly halides) into reactants, the need to remove catalysts and auxiliary ligands from the reaction mixture. All this restricts the application of this type of reactions. The use of metal-catalyzed cross-coupling reactions for direct functionalization of the C – H-bond (see Scheme 1) allows one to do without halides; however, this does not eliminate all the problems typical of metal- catalyzed reactions.[3]

Scheme 1

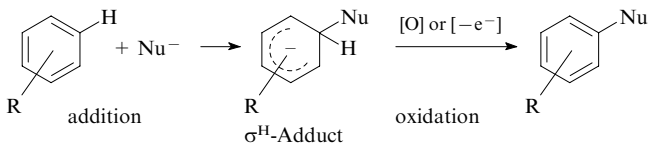


Aromatic nucleophilic substitution (S_N^HAr) of hydrogen without metal catalysis presents an alternative method of functionalization of arenes and hetarenes that does not require halides or complex and expensive catalysts.[4 – 8] According to the presently accepted concepts (Scheme 2), addition of a nucleophile to a substrate yields a key S_N^H reaction intermediate — σ^H-adduct. The next step is adduct aromatization accompanied by formal removal of the hydride ion. There are several ways to abstract the 'hydride-labile' hydrogen,[9, 10] but most attractive is oxidative aromatization $S_N^H(AO)$ (addition – oxidation).[11, 12] Another mechanism, addition – elimination $S_N^H(AE)$, of hydrogen removal from σ^H-adducts is also known but it requires participation of auxiliary groups and is beyond the scope of the present review.

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Scheme 2



R is electron-withdrawing group, Nu^- is nucleophile

Oxidation may be performed both by chemical reagents and electrochemically. The chemical S_N^H(AO) process is often performed as a three-component synthesis, *i.e.* the oxidant is introduced into a system simultaneously with the reaction partners. Naturally, in doing so, consideration must be given to ability of reactants to be oxidized, primarily, of the nucleophile and sometimes also of the substrate, which cannot help affecting the reaction outcome. For the σ^H-adduct, in turn, it is difficult and often even impossible to estimate the oxidation potential as a measure of the substance ability to donate electrons. Therefore, one has to choose the oxidant being guided by the experience, intuition, certain empirical rules, which allow only limited judgement on the oxidant suitability.[4,13] Several prerequisites for a successive performance of the oxidative aromatization may be outlined. For an oxidation-resistant nucleophilic species participating in the reaction, despite the higher concentration of the starting compounds, it is the σ^H-adduct that will be oxidized, giving the desired outcome. Alternatively, highly reactive starting compounds and conditions are used, which produce a high concentration of the σ^H-adduct, and then the starting compounds are not affected by the oxidant. And the most challenging approach is the application of selective oxidants capable of oxidizing the σ^H-adduct without reacting with the nucleophile.

As shown in Scheme 1, characteristic of catalytic C–X and C–H functionalizations are oxidative and reductive steps, and this defines their resemblance with electrochemical processes the essence of which are redox transformations.

A trend in the development of the modern chemistry is switching from traditional methods of organic synthesis to electrochemical processes.[14] By using electrochemical procedures in the aromatic substitution of hydrogen, one can determine the redox potentials of both reactants and intermediates, which provides an approach to more sensible and rational choice of the oxidant. Moreover, electrochemical data may be helpful in elucidating the mechanism of formation of by-products, particularly dimers, which are detected in some cases in S_N^H reactions. The application of electrosynthesis in known and novel S_N^H reactions may improve the atomic efficiency, prevent losses, eliminate the need for a wide range of auxiliary materials and finally decrease the technogenic burden on the environment. This is extremely important, as the contemporary world and the trends for sustainable development force chemical industry to improve the environmental safety[15] and to comply with the requirements of green chemistry.[16,17] Nobel Prize Laureate R Noyori named this 'practical elegance of chemical synthesis',[18] implying that a chemical synthesis must be intellectually logical and technically effective.

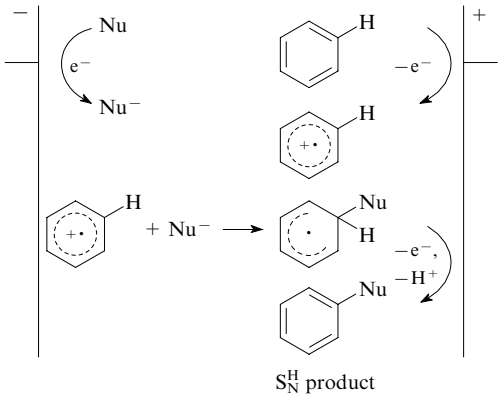
In 1979, Seebach[19] introduced the idea of polarity inversion (Umpolung) into the chemical literature as a method of improving the reactivity of substances. Although this concept is rather common in the organic chemistry, in the electrochemical literature the term 'Umpolung' found practically no use. Here it should be emphasized that the polarity inversion, reflecting the essence of the electrode transformation, is a key step in the electrochemical functionalization of π-excessive compounds.[12,20]

Three basic ways of performing electrochemical nucleophilic substitution of hydrogen may be pointed out: anode activation of the substrate, cathode geneartion of a nucleophilic species, oxidation of the σ^H- adduct.

In the case of the anode activation, the substrate undergoes single-electron transformation to a radical cation, which can add the nucleophile to form a radical intermediate. The latter is then further oxidized yielding the S_N^H product. The cathode activation of a neutral molecule converts it to a more nucleophilic anion, thus promoting the formation of the σ^H-adduct.

The simultaneous occurrence of these transformations together with oxidation of the σ^H-adduct in an undivided cell (Baizer paired electrosynthesis)† might be an ideal process (Scheme 3).

Scheme 3



Scientific communities of leading world powers including Russia made a considerable contribution to the development of the views on the mechanisms and regularities of electron transfer, generation of reactive intermediates and their behaviour under experiment conditions, kinetics and thermodynamics of the reactions, electrode transformations and electrosynthesis of organic compounds.

Presently, research groups engaged in electrochemical aspects of the C(sp^2)–H-bond functionalization have been formed in Spain, Russia and France. However, the history of this problem was started back in the 1950–1960s with the beginning of extensive investigations of hydroxylation, alkoxylation and pyridination of aromatic systems, which were called anodic substitution reactions. These investigations connected with the names of Weinberg, Eberson, Nyberg, Yoshida, Savéan, Swenton and a large variety of other prominent scientists made the most considerable progress in the 1970–1980. A wide range of studies on the electrochemical functionalization of aromatic compounds including acetoxylation, arylation, cyanation, alkylation, *etc.* were performed, being reflected in a series of reviews and monographs. For example, the monograph of Yoshida[21] published in 1984 is devoted to anodic functionaliza-

† *Organic Electrochemistry, An Introduction and a Guide* (Ed. H Lund, M M Baizer) (New York: Marcel Dekker, 1991)

tion of arenes occurring, *via* the formation of radical cations. Some chapters of Torii s monograph are also related to this problem.[22] Finally, the reactions of anodic substitution form a permanent section of the multi-authored monograph 'Organic Electrochemistry'; its fourth edition,[23] comprising 32 chapters written by 29 authors, was published in 2001.

Since 2000, the research group of Gallardo from the Autonomous University of Barcelona has been systematically exploring the electrooxidation of various σ^H-adducts as intermediates in S_N^H reactions of nitroarenes. At the same period of time, investigations of metal-catalyzed cross-coupling reactions with hydrogen replacement began, also employing electrochemical procedures and methods. In 2002, reviews of Budnikova,[24] Magdesieva and Butin[25] were published where data on the application of electrochemically generated metal complex catalysts in the organic synthesis were classified and summarized. Much attention was given to the redox activation of transition metal complexes being the first step of a wide range of cross-coupling reactions. A review[26] published in 2008 summarized the electrochemical aspects of metal-catalyzed reactions. In 2011, a review[12] analyzing data on the mechanisms of anodic substitution reactions in aromatic systems was published. A rational approach considering the ease of nucleophile oxidation *vs.* arene oxidation was used to distinguish two groups of reactions differing in the mechanism of realization, namely, those involving nucleophiles that are either more or less prone to oxidation than arenes; and comparison of the regularities of electrochemical and chemical substitution reactions led to the conclusion that anodic substitution of hydrogen is a universal type of S_N^H reactions.

The aim of the present review is to summarize the data concerning electrochemical methods and procedures used in the direct functionalization of the C(sp^2)–H-bond in arenes and hetarenes. The emphasis is on the matters of synthetic value, preparative possibilities, advantages and limitations of some electrochemical synthetic approaches to the compounds the synthesis of which by usual chemical methods is impossible, experimentally difficult or has environmental restrictions.

An attempt has been made in this review to reflect and classify the main trends and tendencies in the electrochemistry of nucleophilic cross-coupling reactions accompanied by direct functionalization of the C–H-bond, to consider the generation of reactive species from the substrate and the nucleophile under various conditions, to determine their electrochemical characteristics, electrooxidation of σ^H-adducts, and procedures of electrosynthesis. Most of the discussed papers were published during the last 10–15 years, earlier articles are cited only as required.

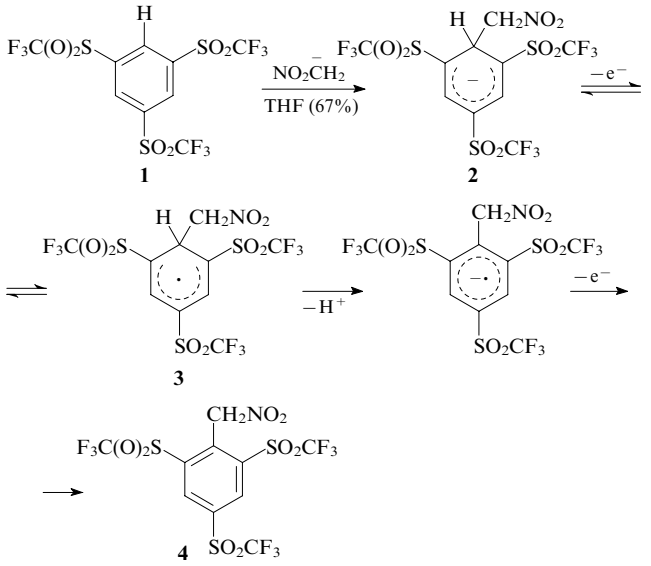
II. Formation of C–X-bonds (X = C, N, O, P, S, Hal)

1. The C–C-bond

a. Alkylation

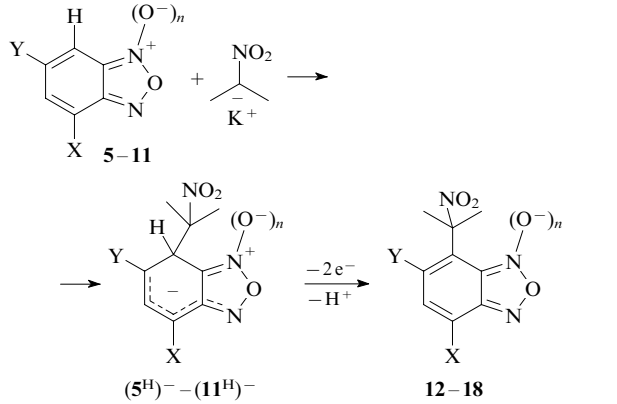
In one of the first reports on the electrochemical study of S_N^HAr alkylation, the nitromethane anion generated by addition of a base served as the nucleophile while the substrate was 1,3,5-tris(trifluorosulfonyl)benzene (**1**), an analogue of 1,3,5-trinitrobenzene. Basing on the data of rotating ring-disk electrode in acetonitrile medium, a possible mechanism of this process was proposed (Scheme 4).[27] It suggests the initial formation of anionic σ^H-adducts **2** with a conversion of 67%. The limiting step of their electrooxidation is transfer of the first electron yielding radical species **3**. The subsequent transformation of the latter into the radical anion is accompanied by proton elimination, which was detected experimentally for the first time as a kinetically independent species. During the final step, the second proton is eliminated to form compound **4**.

Scheme 4



A paper of Terrier and co-workers,[28] a well-known specialist in aromatic nucleophilic substitution, describes the reaction of the potassium salt of 2-nitropropane with nitrobenzofuroxans **5**–**10** and nitrobenzofurazane **11**, yielding products **12**–**18** (Scheme 5).

Scheme 5



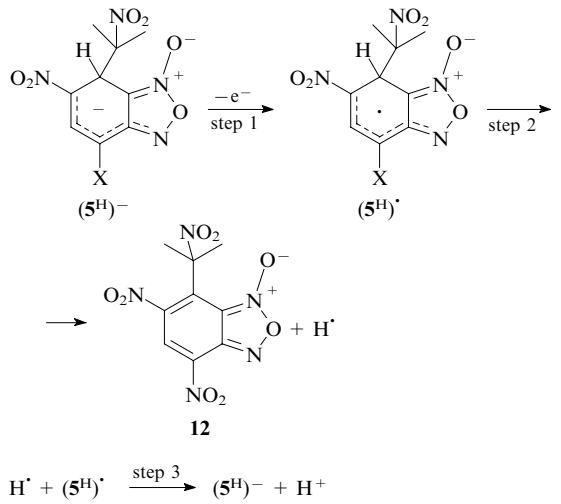
Compounds	X	Y	*n*	E_{ox} σ^H-adduct /V
5, **12**	NO_2	NO_2	1	1.16
6, **13**	NO_2	H	1	0.59
7, **14**	NO_2	SO_2CF_3	1	1.33
8, **15**	NO_2	CF_3	1	0.94
9, **16**	NO_2	CN	1	0.96
10, **17**	CF_3	NO_2	1	0.91
11, **18**	NO_2	H	0	0.48

In the course of the reaction, the σ^H-adducts are formed as the corresponding potassium salts in nearly quantitative

yields. They were characterized by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry (ESI) and X-ray diffraction analysis.[29] Scheme 5 presents the oxidation potentials (E_{ox}) for σ^H-adducts $(\mathbf{5}^H)^-$–$(\mathbf{11}^H)^-$ *vs* the saturated calomel electrode (SCE) in acetonitrile (supporting electrolyte 0.1 M $Bu^n_4NBF_4$). Note that the introduction of an additional electron-withdrawing group or groups having stronger electron-withdrawing properties results in a considerable stabilization of the σ^H-adducts and makes them more stable against electrooxidation. The same is observed for the chemical aromatization. For example, dinitrobenzofuroxane adduct $(\mathbf{5}^H)^-$ is oxidized at a 0.56 V more positive potential than the corresponding monosubstituted adduct $(\mathbf{6}^H)^-$. Meanwhile, the replacement of one nitro group in compound **7** by a trifluoromethylsulfonyl group increases the oxidation potential of the corresponding σ^H-adduct up to 1.33 V.

Special spectroelectrochemical methods (that allow measuring the spectra in the UV and visible range in the vicinity of the gold electrode during the oxidation potential measurement) were used to study the oxidation of σ^H-adducts and to propose the most possible oxidation mechanism (Scheme 6).

Scheme 6



a

$2(\mathbf{5}^H)^- - 2e^- \longrightarrow 2(\mathbf{5}^H)^\bullet$

$(\mathbf{5}^H)^\bullet \longrightarrow \mathbf{12} + H^\bullet$

$(\mathbf{5}^H)^\bullet + H^\bullet \longrightarrow (\mathbf{5}^H)^- + H^+$

$(\mathbf{5}^H)^- - 2e^- \longrightarrow \mathbf{12} + H^+$

b

$2(\mathbf{5}^H)^- - 2e^- \longrightarrow 2(\mathbf{5}^H)^\bullet$

$(\mathbf{5}^H)^\bullet \rightleftharpoons (\mathbf{12})^{-\bullet} + H^+$

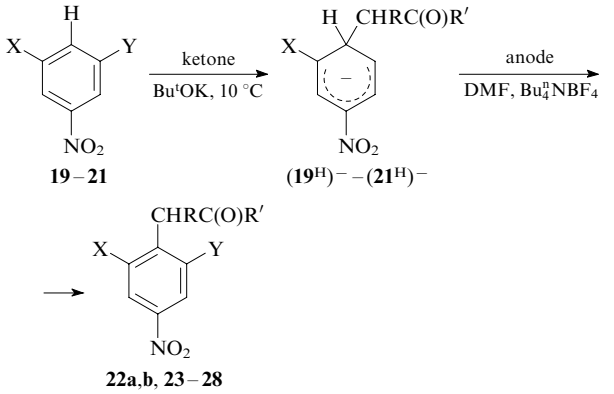
$(\mathbf{5}^H)^\bullet + (\mathbf{12})^{-\bullet} \longrightarrow (\mathbf{5}^H)^- + \mathbf{12}$

$(\mathbf{5}^H)^- - 2e^- \longrightarrow \mathbf{12} + H^+$

The proposed mechanism of this process was characterized by three steps considered in relation to compound $(\mathbf{5}^H)^-$ (see Scheme 6). The paths *a* and *b* in this Scheme are kinetically equivalent but mechanism *b* is unlikely since radical anion $(\mathbf{12})^{-\bullet}$ can be easily protonated, thus increasing the significance of the reverse reaction. At the first step, the anionic adduct $(\mathbf{5}^H)^-$ loses an electron to form the radical $(\mathbf{5}^H)^\bullet$; at the second step, the C–H-bond is cleaved yielding the final product **12** and a hydrogen atom ($H^\bullet$). The third step comprises the oxidation of the hydrogen atom with the radical $(\mathbf{5}^H)^\bullet$, which is probably the strongest oxidant in the system under consideration. At this step, the anion $(\mathbf{5}^H)^-$ is formed and the proton (H^+) is released. Thus, the overall reaction may be written as $(\mathbf{5}^H)^- - 2e^- \rightarrow \mathbf{12} + H^+$ [also, it is possible to write equations $(\mathbf{5}^H)^- \rightarrow \mathbf{12} + 2e^- + H^+$ or $(\mathbf{5}^H)^- - 2e^- - H^+ \rightarrow \mathbf{12}$].

In 2002, an actively working group of Spanish scientists accomplished the synthesis of nitroaromatic ketones **22**–**28** by the anodic alkylation of nitrobenzenes **19**–**21**.[30,31] Acetone, acetophenone and methyl ethyl ketone served as alkylation agents (Scheme 7).

Scheme 7



X = Y = H (**19**, **22a**,**b**, **23**); X = NO_2, Y = H (**20**, **24**, **25**, **26**); X = Y = NO_2 (**21**, **27**, **28**)

Product	R	R′	Product	R	R′
22a	Me	Me	**25**	Me	Me
22b	H	Et	**26**	H	Ph
23	H	Ph	**27**	H	Me
24	H	Me	**28**	H	Et

The intermediate σ^H-adducts were generated chemically by adding ButOK to the nitroarene–methyl ketone–DMF–$Bu^n_4NBF_4$ system under nitrogen. The oxidation potentials of the σ^H-adducts formed were measured by cyclic voltammetry on the glassy carbon electrode *vs*. SCE. Electrolysis of this solution on graphite electrodes gives the corresponding S^H_N-products in good preparative yields (Table 1). This method presents an available, easy and environmentally friendly synthetic route to nitroaromatic ketones. Compared to the chemical synthesis[32] the above method is more advantageous as it does not require the use of chemical oxidants, prevents side reactions and provides

Table 1. Oxidation potentials of σ^H-adducts of compounds **19**–**21** on a glassy carbon electrode *vs*. SCE and yields of the S^H_N-reaction products.[30,31]

Starting compound	Ketone	E_{ox} of the σ^H-adduct /V	Products	Yield
19	MeC(O)Et	0.07	**22a** + **22b**	60
	MeC(O)Et	0.03	**22c** [a]	20
	MeC(O)Ph	0.05	**23**	90
20	MeC(O)Me	0.47	**24**	90 [b]
	MeC(O)Et	0.51	**25**	91
	MeC(O)Ph	0.56	**26**	85
21	MeC(O)Me	0.91	**27**	60
	MeC(O)Et	0.91	**28**	70

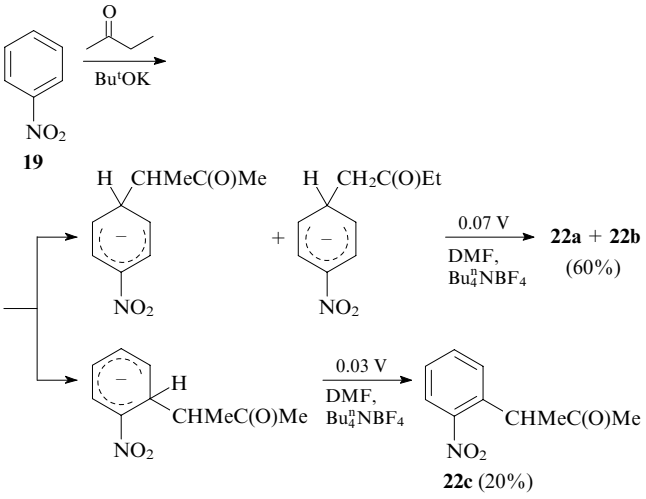
[a] The product of *ortho*-substitution (see Scheme 8). [b] The yield in the chemical reaction is 67% (see Ref. 32).

much higher yields of the desired products. The application of the electrochemical method makes it possible to determine the σ^H-adduct oxidation potential in every particular case and thus to accomplish their selective oxidation. All the above as well as the easy isolation of the products **22**–**28** contribute to the process efficiency.

Note that the increase in the number of electron-withdrawing groups on going from 1,3-dinitrobenzene (**20**) to 1,3,5-trinitrobenzene (**21**) results in the rise of the oxidation potential of the intermediate σ^H-adduct and, at the same time, in the decrease in the yield of the desired oxidation product down to 60%–70% compared to 90% for 1,3-dinitrobenzene derivatives. According to the cyclic voltammetry data, the conversion of dinitrobenzene **20** upon the formation of the key intermediate of the nucleophilic addition $(\mathbf{20}^H)^-$ is close to 100%, whereas the conversion of trinitrobenzene **21** upon the formation of $(\mathbf{21}^H)^-$ is only 70%–80%. It is the authors' opinion that this fact is associated with the steric effect but the possibility of side reactions of intermediates is not denied.

Noteworthy are the data on electrooxidation of nitrobenzene (**19**) and butan-2-one on a graphite electrode in DMF in the presence of Bu^tOK and supporting $Bu^n_4NBF_4$ (Scheme 8).[31] With the oxidation potential being equal to 0.07 V, the products of *para*-substitution 2**2a** and **22b** are formed in 60% yield, while at 0.03 V nucleophilic substitution of hydrogen in the *ortho*-position takes place to afford product **22c**. It should be noted that this example is illustrative of new prospects of electrochemical control over the regioselectivity of nucleophilic substitution of the hydrogen atom.

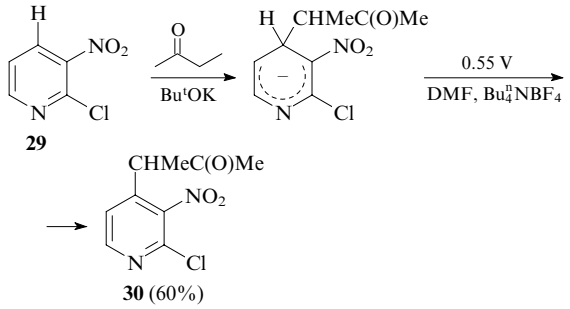
Scheme 8



Of no less interest is the non-classical behaviour of 3-nitro-2-chloropyridine (**29**) in the presence of butan-2-one under the same electrolysis conditions (Scheme 9).[31]

The only product formed in the electrochemical alkylation of chloronitropyridine **29** with methyl ethyl ketone is 3-(2-chloro-3-nitro-4-pyridyl)butan-2-one (**30**), while the product of chlorine atom replacement was not detected. Thus, the nucleophilic attack proceeds regioselectively at the vacant 4-position of the pyridine ring with displacement of the hydrogen atom, while the chlorine atom in the doubly activated 2-position is not affected. Development of such electrochemical methods for selective introduction of various alkyl ketone moieties into aromatic compounds

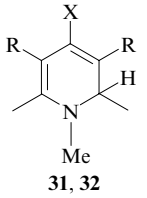
Scheme 9



increases the functionalization index of (het)arenes and may be promising for the industrial application.

Particular attention is drawn to electrochemical investigations of the heterocyclic σ^H-adducts due to the biological importance of such objects. For radical cations generated through the oxidation of 4-substituted 3,5-diacetyl-1,2,6-trimethyl-1,2-dihydropyridines **31** and 4-substituted 1,2,6-trimethyl-3,5-diethoxycarbonyl-1,2-dihydropyridines **32** in acetonitrile at −40 °C, EPR spectra were recorded and their hyperfine structure was analyzed.[33] The oxidation potential and electron distribution were shown to be significantly influenced by the inductive effect of substituents in the 3- and 5-positions of the heterocyclic system. Thus, for diacetyl derivatives **31** the oxidation potential $E_{1/2}$ falls in the range 0.35–0.39 V, and for the compounds **32** it is 0.41–0.44 V.

Structures **31**, **32**



X = 4-MeC_6H_4, Ph, 4-$MeOC_6H_4$;
R = Ac (**31**), CO_2Et (**32**)

Subsequently, the method of rotating ring-disk electrode in protic and aprotic media was used[34,35] for thorough investigation of 1,4-dihydropyridines in their electrooxidation on the disk electrode and electroreduction of the products formed on the ring electrode. During the oxidation of N-unsubstituted 1,4-dihydropyridines on disk or ring electrode, a reduction wave of protonated pyridine forms rather than of neutral molecules was detected (Scheme 10). Analysis of possible ways of the formation of pyridinium salts in the process suggests that upon oxidation, neutral pyridine molecules (Py) are formed initially and, during the transfer from the disk to ring electrode, they are tranformed to be detected as cations.

Scheme 10

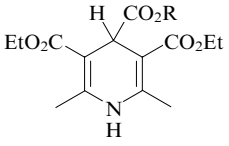
$$PyH_2 - 2e^- - 2H^+ \longrightarrow Py$$

$$PyH_2 - 2e^- - H^+ \longrightarrow PyH^+$$

$$PyRH - 2e^- - H^+ \longrightarrow PyR^+$$

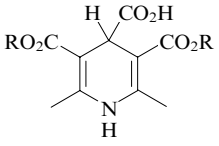
The oxidation was also found to proceed either with the retention or with elimination of the 4-substitutent. Thus, in the case of 4-alkoxy-substituted compounds **33**, the substitutent in 4-position is mainly retained; carboxyl derivatives **34** generally lose this substituent, and the corresponding 4-carbamoyl derivatives **35** afford the products of both types upon oxidation.

Structures **33**–**35**



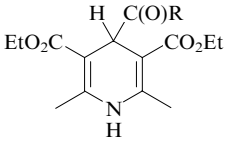
33

R = Me, Et, Pr^i, Bu^t



34

R = Me, Et, Pr^n, Pr^i

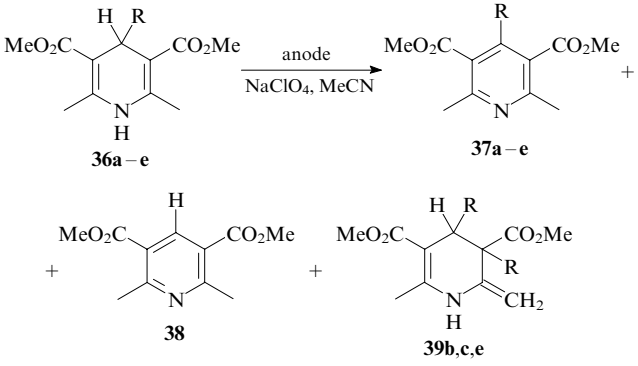


35

R = NH_2, NHMe, NMe_2, NEt_2

Preparative electrooxidation of 4-alkyl-substituted 1,4-dihydropyridines **36a**–**e** was performed in a divided cell on a platinum electrode at the potential 1.2 V *vs.* SCE. in acetonitrile (Scheme 11).[36]

Scheme 11



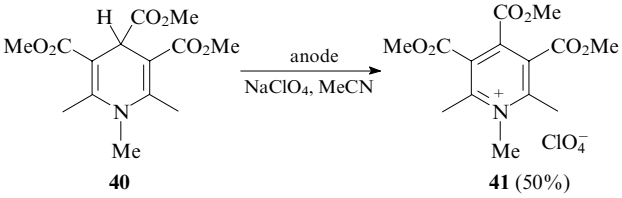
36a–**e** **37a**–**e** **38** **39b,c,e**

Compounds **36**, **37**, **39**	R	Yield (%)		
		37	**38**	**39**
a	Me	95.7	–	–
b	Et	18.5	61.1	12.9
c	Pr^n	46.6	27.3	19.4
d	Pr^i	–	92.8	–
e	Bu^i	36.7	46.1	7.5

The electrolysis of compound **36a** gives a single S_N^H product (**37a**). At the same time, upon electrolysis of compounds **36b**,**c**,**e**, side products **39b**,**c**,**e** are formed along with the products of substitution **37b**,**c**,**e** and dealkylation **38** (see Scheme 11). In turn, the oxidation of compound **36d** is destructive, affording product **38** in 92.8% yield, which is consistent with literature data on the chemical oxidation of dihydropyridines.[37,38] An attempt to optimize the electrooxidation process by adding a base (pyridine) was successful only in part. Indeed, oxidation of compounds **36b**,**c**,**e** gave no side products, but the yield of S_N^H products did not increase either. However, switching from acetonitrile to pyridine in the electrolysis of dihydropyridine **36d** gave the desired product **37d** in 25% yield.

The electrochemical quaternization of 1,2,6-trimethyl-3,4,5-trimethoxycarbonyl-1,4 dihydropyridine (**40**) in the anode compartment of the divided cell furnished the corresponding product **41** in a yield not exceeding 50% and comparable with the results of chemical oxidation (Scheme 12).[39]

Scheme 12



40 **41** (50%)

The electrochemical process of pyrocatechol **42**–**45** functionalization by various ketones **46**–**49** was successively accomplished (Scheme 13).[40,41] Polycyclic pyrocatechol derivatives **50**–**63** are potential HIV inhibitors and their electrosynthesis is attractive because it can do without toxic reagents. In acetonitrile in the presence of acetate or phosphate buffer (pH 6) as an electrolyte on a graphite electrode, the above pyrocatechols react with the corresponding aryl ketones to afford the desired products in 20%–82% yields. In the authors' opinion, the reaction mechanism involves the initial anodic oxidation of pyrocatechols **42**–**45** to quinones. At the next step, nucleophilic Michael addition and subsequent aromatization of the intermediates giving the products **50**–**63** take place.

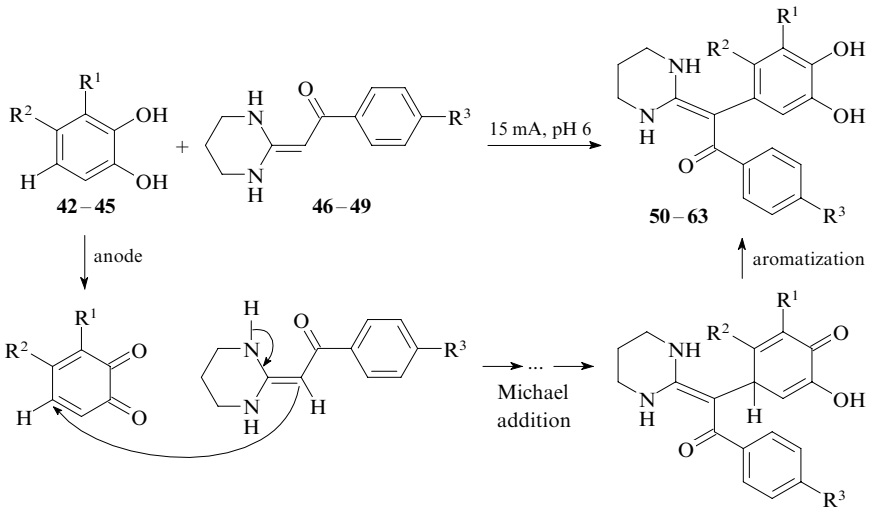
Alkylation of nitroarenes using organometallic compounds (RM: R = Me, Et, Bu^n; M = Li, MgHal) and tetramethylammonium tetrabutylborate yields stable σ^H-adducts,[10,42] which can be chemically oxidized with Br_2, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), $KMnO_4$ to give the target alkylation–dehydration products but often in low yields and with a problematic isolation process.[43]

More convenient is the electrochemical alkylation of nitroarenes[44,45] using Bu^{n}MgCl or Bu^{n}Li as 'alkylating' agents. The process is based on the exhaustive electrooxidation of the corresponding σ^H-adducts in DMF or THF on a graphite electrode and affords the products of S_N^H reactions in acceptable yields (30%–80%) (Schemes 14 and 15). Electrolysis allows one to avoid the use of additional chemical reagents thus significantly facilitating the isolation of the target products. This procedure was used to prepare products **64**–**69** from nitrobenzenes **19**–**21**, and derivatives **70**–**72** were thus converted to **73**–**75**.

The application of Bu^{n}MgCl proved to be more attractive compared to Bu^{n}Li, in view of the process selectivity. Thus, in the reactions of nitroarenes **19** and **20** with Bu^{n}MgCl, disubstituted products **65** and **68** are formed in low yields if at all (see Scheme 14).

It was also reported[44] that when Li and Mg organic compounds are used for the alkylation of 1,3,5-trinitrobenzene (**21**), the products of nucleophilic substitution are not detected, whereas electrolysis using $Me_4NBBu_4^n$ furnishes compound **69** in 79% yield. It should be specially noted that the only outcome of a similar alkylation of 2,4,6-trinitrochlorobenzene (**72**) is replacement of the hydrogen atom (see Scheme 15) rather than the chlorine atom. At the first glance, this is in contradiction with classical concepts of nucleophilic aromatic substitution.

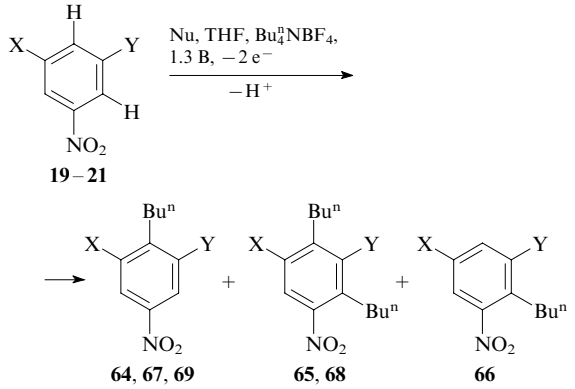
Scheme 13



R^1 = H: R^2 = Bu^t (**42**), Me (**43**), CH=CHCO$_2$H (**44**); R^1 = OMe, R^2 = H (**45**); R^3 = Cl (**46**), H (**47**), Me (**48**), OMe (**49**)

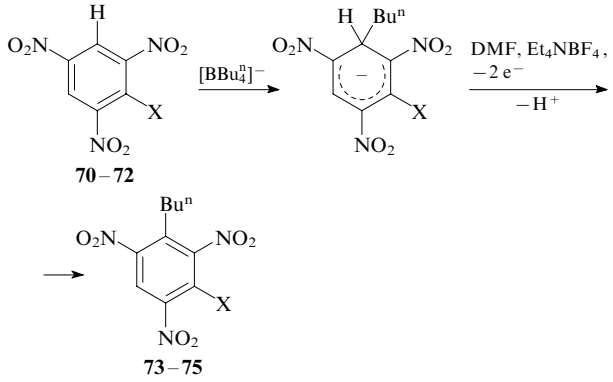
Substrate	Nucleophile	Product	Yield (%)	Substrate	Nucleophile	Product	Yield (%)	Substrate	Nucleophile	Product	Yield (%)
42	**46**	**50**	27	**42**	**48**	**55**	39	**44**	**47**	**60**	20
43	**46**	**51**	79	**42**	**49**	**56**	46	**44**	**48**	**61**	76
44	**46**	**52**	32	**43**	**47**	**57**	49	**44**	**49**	**62**	25
45	**46**	**53**	54	**43**	**48**	**58**	82	**45**	**48**	**63**	59
42	**47**	**54**	68	**43**	**49**	**59**	40				

Scheme 14



Substrate	Nucleophile	Product	Yield (%)
19	Bu^nLi	**64**	41
		65	47
	Bu^nMgCl	**64**	40
		65	10
		66	35
20	Bu^nLi	**67**	43
		68	30
	Bu^nMgCl	**67**	36
	$Me_4NBBu_4^n$	**68**	30
21	$Me_4NBBu_4^n$	**69**	79

Scheme 15



X = OMe (**70**, **73**), Me (**71**, **74**), Cl (**72**, **75**)

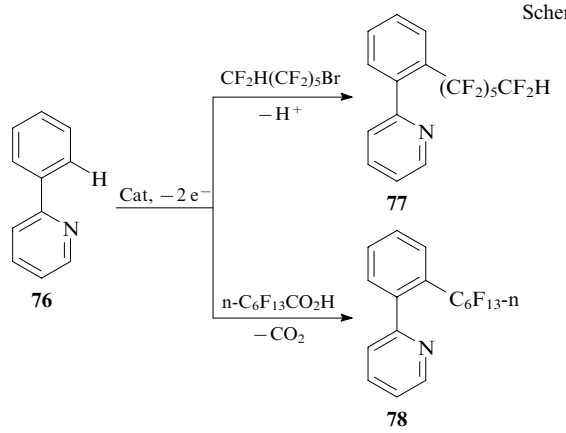
Substrate	E_{ox} of the σ^H-adduct /V [a]	Product	Yield (%)
70	0.91	**73**	70
71	0.89	**74**	35
72	0.94	**75**	48

[a] The oxidation potential was determined by cyclic voltammetry with a graphite disk electrode in DMF in 0.1 M Et_4NBF_4 supporting electrolyte.

An innovation in the direct functionalization of the C–H-bond combining metal catalysis with electrosynthesis is the recent example of fluoroalkylation of 2-phenylpyridine (**76**) affording products **77** and **78** (Scheme 16).[46]

More available nickel complex catalyst was shown (see Scheme 16) to be more effective than palladium catalysts. The electrolysis was performed at the potential 1.3 V (Ag/AgCl), corresponding to the transition Ni^{II}/Ni^{III}. The mechanisms of these catalytic and electrochemical trans-

Scheme 16



PhPhy is 2-phenylpyridine

Catalyst (Cat)	Yield (%)	
	77	**78**
$[Ni(bipy)_3]^{2+}$	62	85
$Pd(PhPy)_2(OAc)_2$	30	81
$Pd(OAc)_2$	10	18

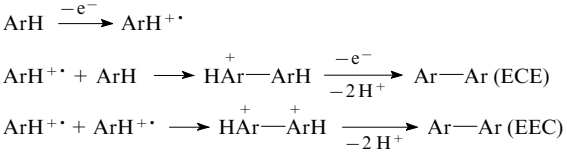
formations, which are obviously of interest, are not discussed in the article.

b. Arylation

Biaryls and bihetaryls are structural moieties of a wide range of compounds that are of pharmaceutical and technological value. The latest advances in the area of metal-catalyzed cross-coupling reactions have significantly increased the availability of such derivatives. However, it should be noted that purification of the products from metals, particularly from palladium, is often a special and challenging task in the chemistry of biaryls.Therefore, the interest in the direct activation of C–H-bonds is well evident.[47]

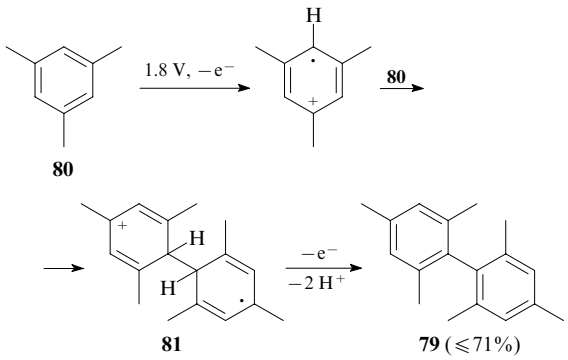
Investigations of electrodimerization processes of anilines, polymethylbenzenes, naphthalenes, anthracenes, certain phenols and anisoles resulting in the corresponding symmetric biaryls were intensively conducted mostly in the 1970–1980s and were summarized in, *e.g.*, the monographs.[21,23] The existence of two basic mechanisms of the electrodimerization was proposed. The first mechanism (ECE) consists in the electrophilic reaction of the radical cation (the product of the primary oxidation of a neutral molecule) with the starting arene as with a nucleophile, and the second one (EEC) involves the reaction of two similar radical cations with each other (Scheme 17).‡ In any case, the basis of these transformations is the anodic activation of a substrate to radical cation.[48]

Scheme 17



Since the interaction of two radical cations is thermodynamically less favourable, the ECE mechanism appears to be preferable in many cases. This is the mechanism according to which dimesityl **79** is presumably formed from mesitylene **80** on a platinum anode in $CH_2Cl_2/Bu^n_4NBF_4$ (Scheme 18). The sequence of proton and electron abstraction steps from intermediate **81** was not discussed.

Scheme 18



One can draw analogy between the electrochemical C–C-bond formation of two aryl moieties and chemical redox processes in the reactions of hydroxy- and amino-arylation of *N*-alkylazinium cations in which the electron

‡ In ECE and EEC designations, the symbol E denotes the electrochemical step, and the symbol C denotes the chemical step.

Scheme 19

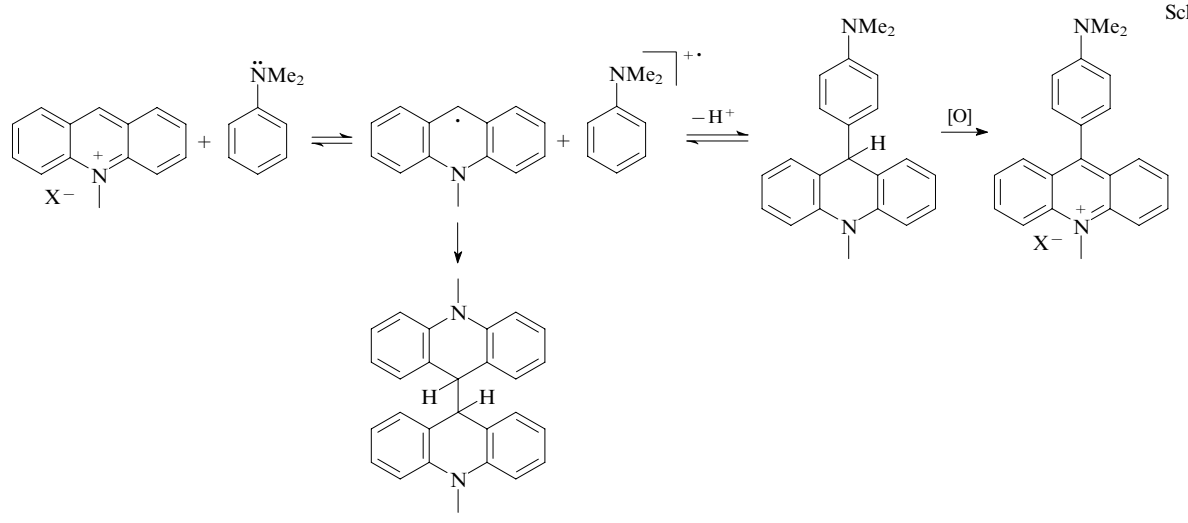
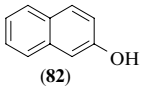
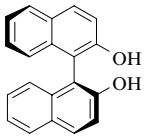
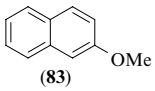
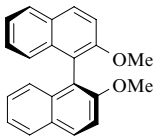


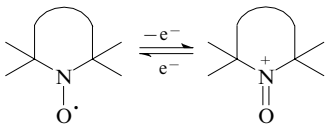
Table 2. Enantioselective electrocatalytic coupling of naphthalene derivatives on a graphite electrode modified with 4-amino-2,2,6,6-tetramethylpiperidin-1-oxyl, in 0.2 M $NaClO_4$ in MeCN.[52]

Substrate	Product	Current yield (%)	Yield (%)	*ee* (%)
 (**82**)	 (**84**)	88.8	93.6	99.5
 (**83**)	 (**85**)	91.0	92.3	93.6

transfer from arylamine (or phenol) to the azinium cation followed by coupling of radical species also results in the generation of biaryl structures with the side formation of dimers (Scheme 19).[49]

Among the most promising trends in modern organic chemistry is asymmetric synthesis, although examples of electrochemically induced processes are few. One of them may be the oxidative coupling of methylquinones,[50] 2-naphthol (**82**) and 2-methoxynaphthalene (**83**) to give the corresponding binaphthyls **84** and **85** in a >90% yield (Table 2).[51] The process was performed under electrolysis conditions at a controlled potential of 0.6 V on a graphite anode modified with an aminoxyl radical on a polymer film. The presence of (−)-sparteine chiral base results in enantioselective coupling giving high yields of *S*-dimers with optical purity of >90%.[52] The enantioselectivity of the electrocatalyzed process is probably due to the formation of a chiral intermediate complex upon the interaction of the substrate, sparteine and the aminoxyl radical,[53] the mediator forming a unique redox system (Scheme 20).

Scheme 20

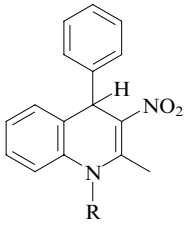


The synthesis of asymmetric biaryls is of special interest not only because of the practical value of these compounds,[54, 55] but also due to difficulties faced by their synthesis by chemical methods related to the need of prefunctionalization using leaving groups and toxic catalysts based on transition metals.[56, 57] Organic electrosynthesis with direct activation of the C–H-bond proves to be an attractive alternative for the synthesis of biaryls. Extending this approach to the synthesis of asymmetric biaryls has limitations caused by low selectivity of the process due to competition between the cross-coupling and homo-coupling reactions,[58] though the development of novel materials may overcome these drawbacks. The use of a boron-doped diamond electrode (BDD)[59] gave a good result in the cross-coupling reaction between phenols and arenes (Scheme 21).[60]

Electrolysis of a solution of phenol, arene and a supporing electrolyte in a $(CF_3)_2CHOH$–MeOH mixture using a BDD anode and a nickel cathode afforded the desired products in acceptable yields (see Scheme 21). It is suggested that MeOH acts as a mediator of the electron transfer between the phenol and the anode, while the fluorinated solvent stabilizes the radicals formed, resulting finally in a quite satisfactory selectivity of the cross-coupling reaction. Particularly noteworthy is the formation of compounds **99** and **100**, since unlike the metal-catalyzed cross-coupling reactions where a halogen atom is the leaving group, in this instance, it is possible to retain the halogen atom. Thus, nowadays, this approach represents an elegant and convenient process of direct arylation of the $C(sp^2)$–H-bond.

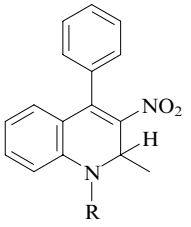
On the other hand, asymmetric biaryls may be obtained through the electrochemical oxidation of the chemically synthesized σ^H-adducts. Such σ^H-adducts comprising a heterocyclic moiety have been thoroughly examined by the methods of classical polarography, cyclic voltammetry, EPR spectroscopy and the method of rotating ring-disk electrode. Of special attention is the fact that the N-methylated derivative of 1,4-dihydroquinoline **102b** (E_{ox} = 0.80 V) is oxidized much more easily than the corresponding N-unsubstituted derivative **102a** (E_{ox} = 1.37 V).[61] Moreover, 1,4-dihydroquinolines **102** are more easily oxidized than 1,2-dihydroquinolines **103** (the difference in the potentials is 350 mV), which is in good agreement with the results for electrooxidation of 1,4-dihydropyridines and 1,2-dihydropyridines.[62]

Structures **102**, **103**



102a,**b**

R = H (**a**), Me (**b**)

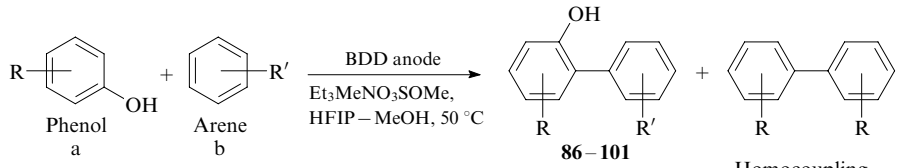


103a,**b**

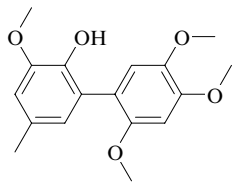
R = Me (**a**), Et (**b**)

Noteworthy is the series of studies[63–65] aimed at the investigation of a wide range of derivatives of 1,4-dihydropyridine **104a**–**o** and **105**a–**l**, which are of special interest as potential antioxidants distinguished by cardiovascular and hepatoprotective activities. The oxidation potentials of the σ^H-adducts of these compounds are given. Voltammet-

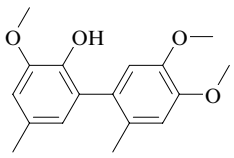
Scheme 21



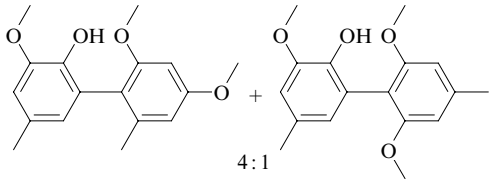
HFIP = $(CF_3)_2CHOH$



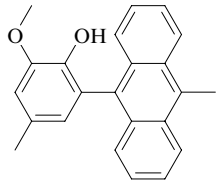
86 (69%, ab : bb > 100 : 1)



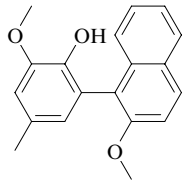
87 (6%, ab : bb > 100 : 1)



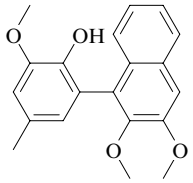
88 + **89** (37%, ab : bb > 100 : 1)



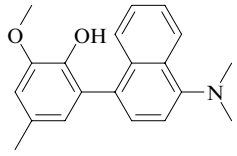
90 (25%, ab : bb > 100 : 1)



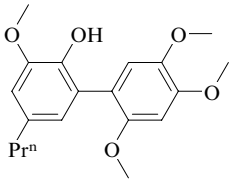
91 (42%, ab : bb > 100 : 1)



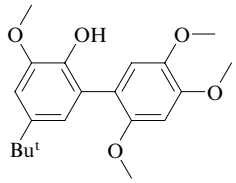
92 (12%, ab : bb > 100 : 1)



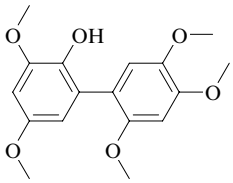
93 (12%, ab : bb > 33 : 1)



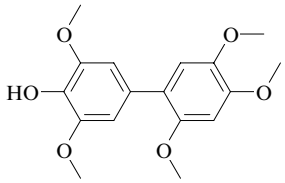
94 (38%, ab : bb > 17 : 1)



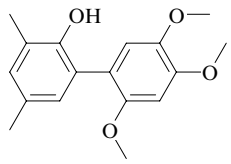
95 (60%, ab : bb > 43 : 1)



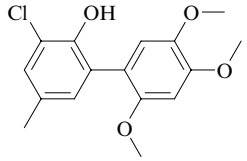
96 (24%, ab : bb > 100 : 1)



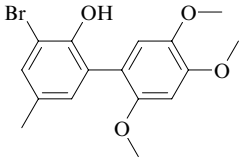
97 (62%, ab : bb > 100 : 1)



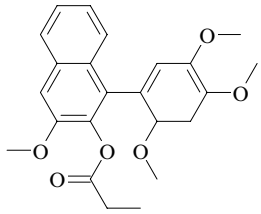
98 (11%, ab : bb > 4.5 : 1)



99 (31%, ab : bb > 1 : 1)



100 (17%, ab : bb > 1 : 1.5)



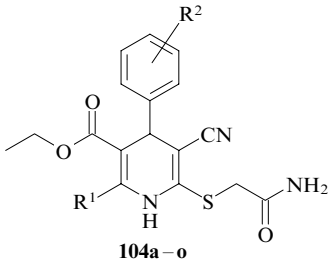
101 (20%, ab : bb > 3 : 1)

Electrolysis conditions: 50 °C, current density 2.8 mA cm^{-2}, quantity of charge 2 *F* per mol of phenol, phenol : arene ratio = 1 : 3, supporting electrolyte Et_3MeNO_3SOMe

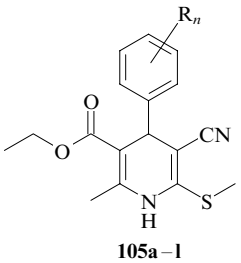
ric measurements were performed in anhydrous acetonitrile with 0.1 M $Bu^n_4NPF_6$ as a supporting electrolyte on a rotating ring-disk electrode and a fixed glassy carbon electrode. All potentials were measured *vs.* 0.1 N $Ag/AgNO_3$ reference electrode. The data on the relative ease of the reduction of these structures are of importance for the quantitative estimation of their proneness to oxidation during the targeted search for biologically active compounds.

Analysis of the presented data demonstrates that the oxidation potentials of compounds **104a–j** are of little sensitivity to the change in electron-donating properties of a substituent in the phenyl ring located in the 4-position of the 1,4-dihydropyridine ring. Replacing the electron-donating 4-OMe substituent (compound **104c**) by a strong electron acceptor 4-NO_2 (compound **104b**) increases the electrooxidation potential by only 60 mV. The same replacement of substituents in 2-methylthio-1,4-dihydropyridines shifts the oxidation potential to the anodic region by 110 mV (compounds **105c** and **105i**). On the other hand, if one compares derivatives bearing the same R^2 substituent among compounds **104a–o**, in all instances the increase in the electron-withdrawing properties of R^1 shifts the electrooxidation potential towards more positive values. Moreover, all 2-carbamoylmethylthio-1,4-dihydropyridines **104a–j** examined are oxidized more easily than the corresponding 2-methylthio-1,4-dihydropyridines **105**. This fact is not consistent with the ideas of the effect of donor or acceptor properties of a substitutent on the electrooxidation potentials of the starting compounds, since the carbamoyl group of the substituent in the 2-position of the 1,4-dihydropyridine ring possesses electron-withdrawing properties and should hamper the electron abstraction during the

Structures **104**, **105**



104a–o



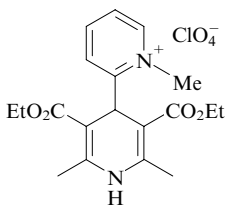
105a–l

Compound **104**	R^1	R^2	E_{ox} /V	Compound **105**	R_n	E_{ox} /V
a	Me	H	1.26	**a**	H	1.32
b	Me	4-NO_2	1.28	**b**	4-OH	1.32
c	Me	4-OMe	1.22	**c**	4-OMe	1.33
d	Me	4-OH	1.23	**d**	2-OMe	1.28
e	Me	2-OMe	1.18	**e**	4-Cl	1.42
f	Me	4-Cl	1.28	**f**	3-Cl	1.42
g	Me	3-Cl	1.27	**g**	2-Cl	1.36
h	Me	2-Cl	1.28	**h**	2,4-Cl_2	1.40
i	Me	3-NO_2	1.29	**i**	4-NO_2	1.44
j	Me	4-CN	1.28	**j**	3-NO_2	1.42
k	Ph	H	1.32	**k**	4-CN	1.42
l	Ph	4-NO_2	1.37	**l**	3-CN	1.39
m	Ph	4-OMe	1.36			
n	4-$O_2NC_6H_4$	4-NO_2	1.45			
o	4-$O_2NC_6H_4$	4-OMe	1.42			

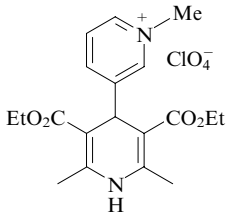
electrochemical process. The answer to this question came from analysis of X-ray diffraction data. It turned out that compound **104f** has an intramolecular hydrogen bond between the proton at the nitrogen atom of the heterocycle and the oxygen atom of the carbamoyl group, whereas there is no such bond in compound **105e**. This fact apparently accounts for the ease of electrooxidation of compound **104f**.

The studies of 1,4-dihydropyridines are not limited only to electroanalytical methods. Indeed, preparative oxidation of 1,4-dihydropyridines bearing a 4-pyridinium substituent (compounds **106**–**108**) in the anodic compartment of a divided cell was reported.[66,67] Electrolysis was performed in acetonitrile in the presence of 0.1 M $NaClO_4$ on a platinum electrode with controlled potential. Contrary to the chemical oxidation, the electrooxidation affords a single product, that is, the corresponding bipyridinium salt (Scheme 22). Unfortunately, the authors restricted themselves to stating this fact without presenting the yields of the desired electrolysis products.

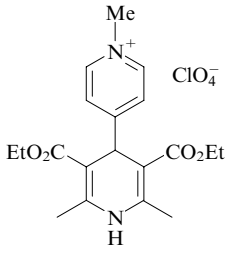
Structures **106**–**108**



106 (1.5 V)

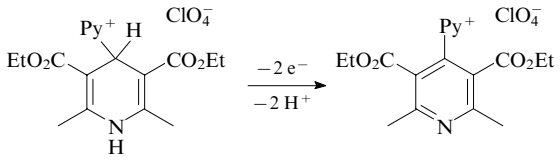


107 (1.27 V)



108 (1.27 V)

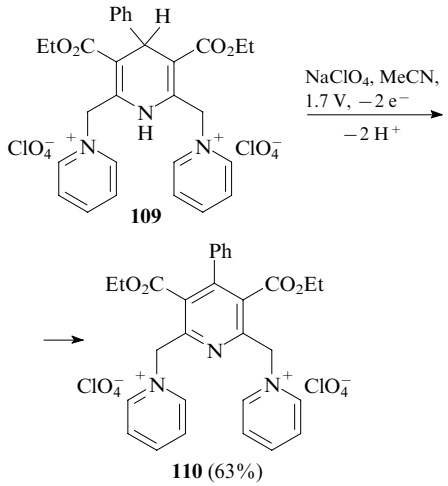
Scheme 22



Py^+ is *N*-methylpyridinio-2(3,4)-yl

Another example of electrooxidation of 1,4-dihydropyridines opens up a new possibility[68] to obtain cationic derivatives of pyridine which may be applied in the genetic therapy research as model compounds for the gene delivery agents. Controlled-potential electrolysis of compound **109** on a platinum electrode in the anode compartment of a divided cell (Scheme 23) furnished compound **110** in 63% yield, which is comparable with the results of chemical oxidation.

Scheme 23



109

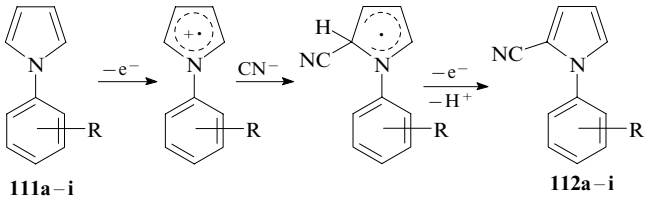
110 (63%)

c. Cyanation

Electrochemical cyanation of aromatic systems is among the best studied electrochemical processes of nucleophilic aromatic hydrogen substitution. This is probably related to a set of useful properties of the target products as well as with the relative resistance of the cyanide ion against oxidation and its high nucleophilicity. The investigation that started back in the 1960s provided extensive information concerning the anodic cyanation of various aromatic compounds (benzenes, anilines, anthracenes, furans, thiophenes, pyrroles, indoles), which was repeatedly summarized.[21,23]

Furthermore, anodic cyanation remains topical nowadays as well. Thus, as a development of Yoshida's work,[21] successful electrochemical cyanation of a series of 1-arylpyrroles **111a**–**i** was reported[69] (Scheme 24).

Scheme 24



111a–i **112a–i**

Compounds **111**, **112**	R	E_{ox}/V	E/V [a]	Yield of **112** (%)
a	H	1.48	1.3	77
b	2-Me	1.46	1.3	83
c	3-Me	1.51	1.3	83
d	4-Me	1.45	1.2	80
e	4-OMe	1.36	1.2	84
f	2-Cl	1.51	1.4	85
g	3-Cl	1.50	1.4	81
h	4-Cl	1.53	1.4	76
i	4-F	1.50	1.3	81

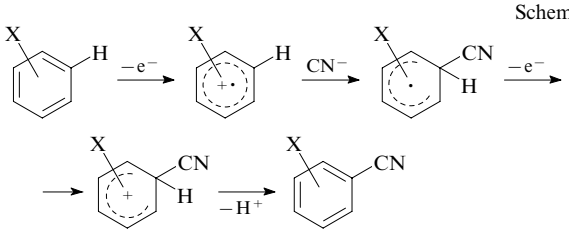
[a] E is the potential of electrolysis *vs.* SCE.

Electrolysis was performed in a divided cell on platinum electrodes in a methanol and sodium cyanide medium. Passing $3F$ of charge resulted in the formation of the corresponding nitriles **112a–i** in good yields. The advantages of the process comprise convenient reaction conditions, low cost and high purity of the products.

The behaviour of the anodic cyanation is often described by the ECE mechanism based on the initial generation of radical cations of the substrate (Scheme 25).

However, involvement of the EEC_rC_p mechanism proposed by Swenton to describe the processes of arene methoxylation is also possible (see Section II.3 and Scheme 39 therein). This mechanism is most probable for cyanation in the galvanostatic electrolysis or in the electrolysis that has to be conducted at high anodic potentials

Scheme 25

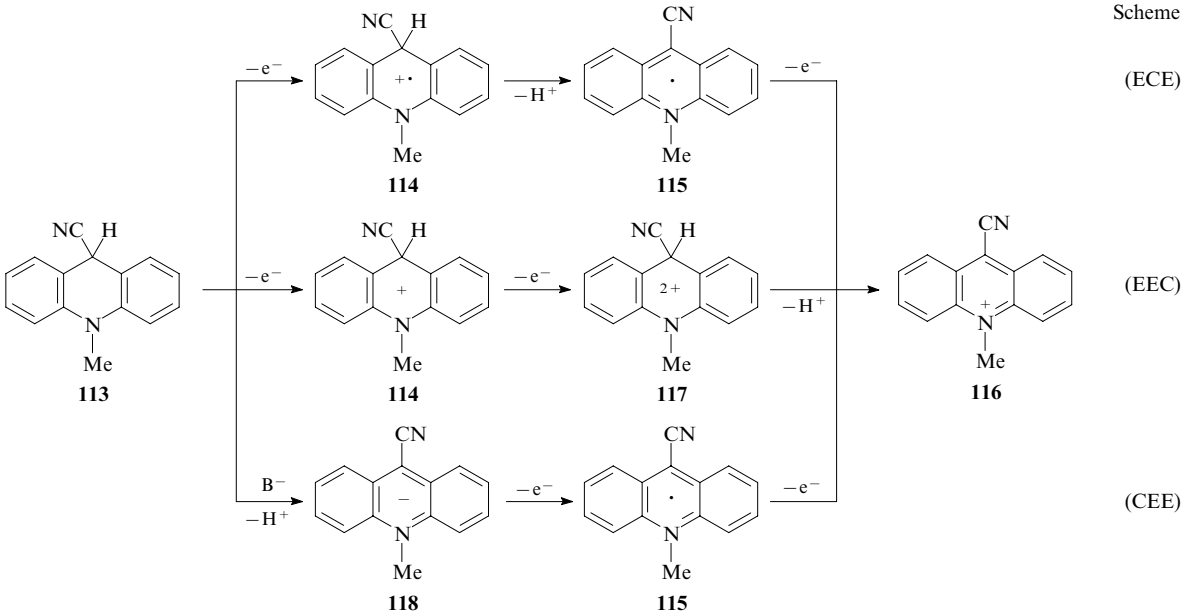


(under conditions of co-oxidation of arene and cyanide ion), as at lower potentials the process does not take place.[21]

Another approach to electrochemical cyanation makes use of the fact that the cyanide ion as a nucleophile is able to form neutral or anionic σ^H-adducts with certain aromatic substrates, and the subsequent electrooxidation of the σ^H-adducts affords S_N^H products.

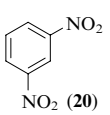
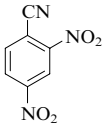
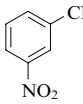
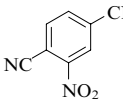
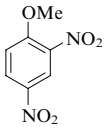
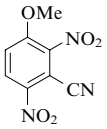
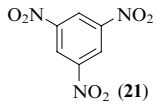
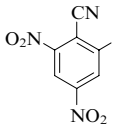
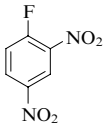
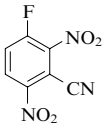
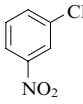
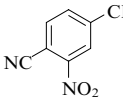
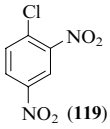
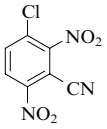
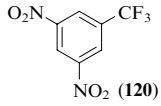
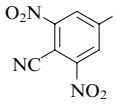
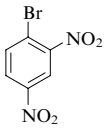
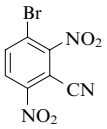
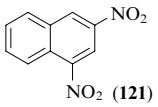
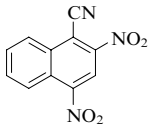
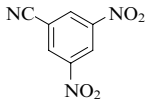
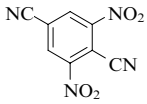
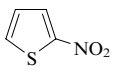
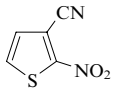
The mechanisms of oxidation of σ^H-adducts of the dihydroazine series have been investigated by Sosonkin and co-workers.[70–73] Considering the data from the rotating ring-disk electrode method and using oxidation of 9-cyanoacridane **113** as an example, three oxidation schemes were proposed (Scheme 26). The most probable is the following sequence of elementary steps: the transfer of the first electron yields an unstable radical cation **114**, which transforms to acridinyl radical **115** upon proton abstraction. Radical **115** is oxidized to give the corresponding acridinium cation **116**. Cyanoacridane radical cations **114** may also undergo further oxidation affording dications **117** followed by proton abstraction and realization of the EEC mechanism. Moreover, initial abstraction of a proton from acridane **113** was shown to be possible even under the action of weak bases, furnishing anion **118**, which undergoes single-electron oxidation to afford stable radical **115**. The subsequent oxidation of the latter gives the final reaction product **116** according to the CEE mechanism. By the rotating ring-disk electrode method, the formation of all the above intermediate compounds was detected. Thus, it was demonstrated that depending on the stability of species, ECE, EEC or CEE schemes are possible, representing in total the cleavage of the C–H-bond with a formal abstraction of a hydride ion.

Scheme 26



B is base

Table 3. Cyclic voltammetry data and results of anodic oxidation of the σ^H-adducts formed in the nucleophilic reaction of the cyanide ion with a variety of nitrobenzenes in a 0.1 M $Bu^n_4NBF_4$ solution in DMF.[74]

Substrate	E_{ox} σ^H-adduct /V	Product	Yield (%)	Substrate	E_{ox} σ^H-adduct /V	Product	Yield (%)
	0.59		48		0.65		45
	0.61		15		1.04		60
	0.56		8		0.58		35
	0.59		7		1.03		43
	0.59		6		0.64		35
	0.92		40		0.62		35

In 2001, Gallardo's group published an article[74] concerned with electrochemical cyanation of nitroarenes. A rather wide range of nitroaromatic substrates was examined, reacting with the cyanide ion in DMF under inert atmosphere to give σ^H-adducts. The oxidation potentials of these adducts *vs.* SCE were determined using cyclic voltammetry. In studies of the regularities of σ^H-adduct oxidation, preference is given to the ECE mechanism proposed earlier by Sosonkin and co-workers[75] The subsequent exhaustive electrolysis on a graphite electrode with the oxidation potential being 100 mV higher than the peak potential (E_{ox} + 100 mV) affords the target products in yields of up to 60% (Table 3). The main advantages of the electrochemical cyanation are the environmental compatibility and high atomic efficiency. Mild conditions of the electrochemical synthesis provide for retaining the halide atoms (including the fluorine atom) in the S^H_N reaction products.

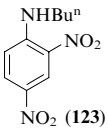
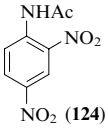
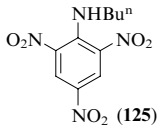
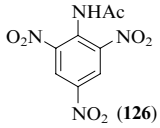
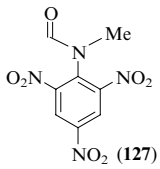
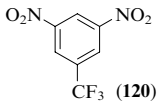
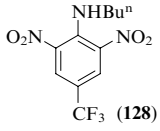
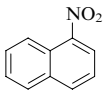
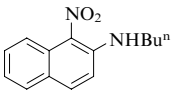
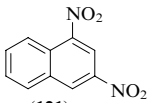
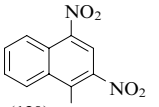
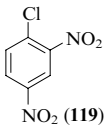
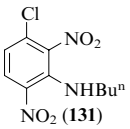
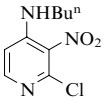
2. The C–N-bond

Examination of published data has shown that the electro-induced S^H_N processes of amination of aromatic compounds are poorly known as opposed to the chemical ones. This is apparently due to the lower C–N-bond strength compared to the C–C-bond strength and, accordingly, the lower stability of the σ^H-adducts, which hampers the anodic aromatization process. In this connection, the data of relatively recent studies are of undoubtful interest. Table 4 summarizes the results of the electrochemical oxidation of intermediates formed in the reactions of nitroaromatic compounds **20**, **21**, **29** and **119**–**122** with N-nucleophiles. The group of nitroaromatic substrates is confined to a dozen of compounds including nitrobenzenes, nitronaphthalenes, nitropyridine. Butylamine, acetamide[76] and *N*-methylformamide[77] serve as N-nucleophiles. The σ^H-adducts under investigation were obtained directly in the electrochemical cell by addition of the corresponding nucleophile to a nitroarene dissolved in a supporing electrolyte (DMF solution of $Bu^n_4NBF_4$) under nitrogen. The oxidation potentials thereof on a glassy carbon electrode were measured *vs.* SCE. Electrolysis of such solutions at the oxidation potentials of the σ^H-adducts was conducted on a graphite electrode.This gave products **123**–**132**.

The authors used cyclic voltammetry as an analytical tool to detect the species present in the reaction mixture and to measure their concentrations. For example, with a considerable excess of the amine, only the oxidation peaks of the resulting σ^H-adduct were detected, while the reduction peaks of the starting nitroarene disappeared, suggesting complete conversion of the latter. The advantages of this method were demonstrated by the example of compounds **119** and **121**. Thus, for dinitronaphthalene **121**, a 16-fold excess of an amine was added until the conversion of the substrate to the σ^H-adduct was complete. As a result, in the subsequent oxidation, the yield of compound **130** reached 84% compared to 15% for product **131**.

The analytical possibility of cyclic voltammetry has also been used to estimate the effect of bases, which improve the efficiency of the σ^H-adduct formation step. The best results were achieved using Bu^tOK, which is oxidized at a relatively high potential, and this does not interfere with the experi-

Table 4. Results of electrolysis of the σ^H-adducts formed in the reaction of nitroaromatic compounds with N-nucleophiles in 0.1 M $Bu^n_4NBF_4$ in DMF.[76, 77]

Substrate	Nucleophile (ratio substrate : nucleophile : base)	E_{ox} σ^H-adduct /V	S^H_N-Product	Yield (%)
20	Bu^nNH_2 (1 : 10 : 0)	0.62	 (**123**)	30
	Bu^nNH_2 + Bu^tOK (1 : 5 : 2)	0.62		49
	$AcNH_2$ + Bu^tOK	0.60	 (**124**)	55
21	Bu^nNH_2 (1 : 3 : 0)	1.12	 (**125**)	30
	$AcNH_2$ + Bu^tOK (1 : 5 : 2)	1.15	 (**126**)	66
	MeNHCHO	1.12	 (**127**)	76 [a]
 (**120**)	Bu^nNH_2 (1 : 6 : 0)	1.18	 (**128**)	34
 (**122**)	Bu^nNH_2 + Bu^tOK (1 : 5 : 2)	0.38	 (**129**)	15
 (**121**)	Bu^nNH_2 (1 : 16 : 0)	0.80	 (**130**)	84
 (**119**)	Bu^nNH_2 (1 : 2 : 0)	1.12	 (**131**)	15
29	Bu^nNH_2 + Bu^tOK (1 : 5 : 1)	0.49	 (**132**)	30

[a] Yield for the electrolysis procedure based on the cathodic activation of the substrate (Scheme 27).[77]

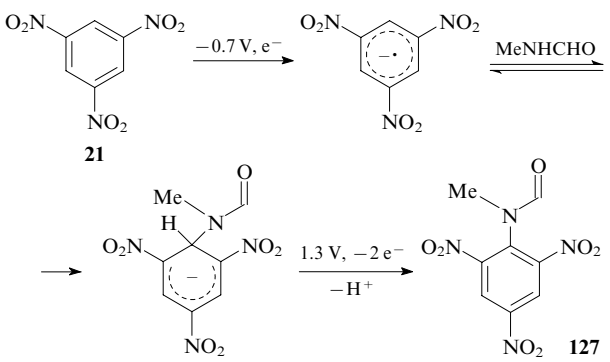
ments. Generally, the presence of a base increases significantly the yield of the desired products in all cases of introduction of amine or amide group in an arene. For example, in reaction of dinitrobenzene **20** with butylamine, the yield increased from 30% to 49%. This is a good result, as this added no complexity to the experimental procedure.

As the number of electron-withdrawing groups in the substrates increases, the stability and the oxidation potentials of the corresponding σ^H-adducts rise; this may have a considerable influence on the process behaviour, the experimental conditions being of great importance. For example, in a series of compounds **20**, **21** and **120**, the stability of the corresponding σ^H-adducts is expected to increase; however

in experiments without addition of a base (see above and Table 4), this did not markedly change the yield of the desired products **123**, **125** and **128**. On the contrary, acetamidation of trinitrobenzene **21** in the presence of a base proceeds in 66% yield, while in a similar reaction of dinitrobenzene, the yield of the desired product is only 55%.

Relatively high yield of product **127** upon the electrochemical introduction of the *N*-methylformamide moiety into trinitrobenzene **21** is caused by the application of a different electrosynthesis strategy. In this case, the first step is the cathodic activation of a substrate. The next step comprises the formation of the σ^H-adduct followed by its electrooxidation with aromatization (Scheme 27).

Scheme 27



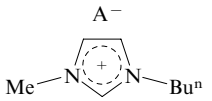
Thus, in the first stage, a solution of trinitrobenzene **21** in *N*-methylformamide in $Bu^n_4NBF_4$ supporting electrolyte was electrolyzed at −0.7 V (the reduction potential of trinitrobenzene **21** E_{red} = −0.53 V) by passing 1 *F* of charge (considering a single-electron process). The formation of the σ^H-adduct with an oxidation potential of 1.12 V was detected by voltammetry. The subsequent exhaustive electrolysis at 1.3 V resulted in S_N^H product **127** in ~80% yield. Conducting an electrochemical reaction in this way proved to be more effective compared to the electrolysis at 1.12 V where the yield of product **127** was not higher than 20%.[77]

The amination of 2,4-dinitrochlorobenzene (**119**) and 3-nitro-2-chloropyridine (**29**) demonstrates important advantages of the electrochemical approach in S_N^HAr reactions. In this case, a good leaving group (chlorine atom) is located in the activated positions of the aromatic ring, and at the potential of 1.35 V the classical displacement of the chlorine atom takes place ($S_N^{ipso}Ar$). However, reducing the controlled potential of the electrolysis to values at which only the σ^H-adduct is oxidized resulted in selective displacement of hydrogen (S_N^HAr) with retention of the chlorine atom (see Table 4).

Although the above examples demonstrate the main advantages of the electrochemical functionalization of arene derivatives, a particular drawback is the use of organic polar solvents and supporing electrolytes. In this regard the use of ionic liquids, acting both as a solvent and as an electrolyte, presents a promising approach. The application of ionic liquids is attractive also due to their high conductivity and electrochemical stability in oxidation processes (from 0 to 1.7 V *vs*. calomel reference electrode).[78]

As has been shown in a recent study,[79] the use of the ionic liquids **133**–**136** significantly improves the characteristics of the electrochemical functionalization of nitroarenes. For example, replacing the solvent and the supporting electrolyte in the amination of compound **20** by ionic liquid **136** increases the yield of 1-n-butylamino-2,4-dinitrobenzene (**123**) up to 94% (see Table 4).

Structures **133**–**136**

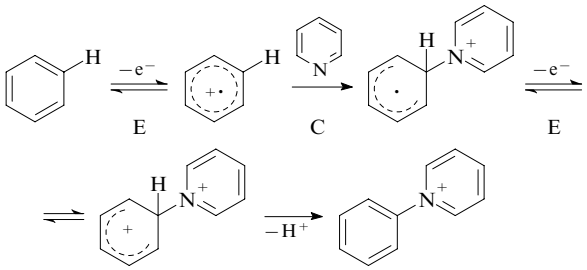


133–**136**

$A^- = BF_4^-$ (**133**), PF_6^- (**134**), $(CF_3SO_2)_2N^-$ (**135**), AcO^- (**136**)

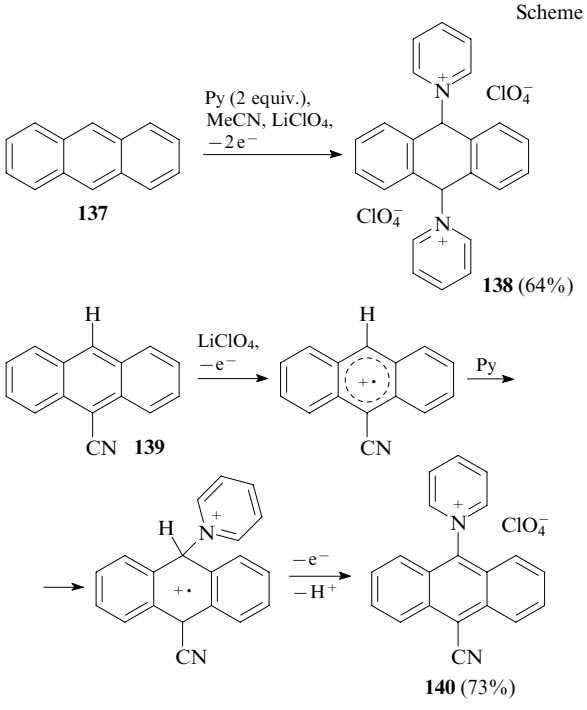
Another important type of modification of aromatic structures is the introduction of N-heteroaromatic moieties. The use of pyridine as N-nucleophile is rather popular in the electrochemical S_N^Hreactions. The aromatic substitution of hydrogen in anthracene by pyridine was mentioned as early as in the classical publication of Lund.[80] Relying on the voltammetric data, a possible ECE mechanism of this process was suggested comprising an electron transfer at the first step and formation of a radical cation of the substrate, the chemical reaction of the radical cation with a nucleophile and generation of a radical cation adduct followed by its further oxidation with proton release (or with attack by the second nucleophile) (Scheme 28).[81]

Scheme 28



The radical cations electrochemically generated from anthracene, 9-substituted anthracene, benzo[*a*]pyrene, perylene and thianthrene react with pyridine and substituted pyridines in aprotic solvents according to the above mechanism. For unsubstituted anthracene (**137**), the anodic

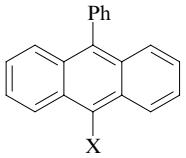
Scheme 29



reaction affords a relatively stable bis-addition product, namely 9,10-dipyridinio-9,10-dihydroanthracene perchlorate (**138**). Note that passing of $2F$ of charge (per mol of arene) through a cell containing the supporting electrolyte, 9-cyanoanthracene (**139**) and pyridine yields S_N^H product **140**, 9-pyridinio-10-cyanoanthracene perchlorate (Scheme 29).[82, 83]

Nowadays the fact that an attack of the *ipso*-position of halogen-substituted anthracenes is less favourable than the attack of the unsubstituted position C(sp^2)–H is no longer surprising, since halogen atoms demonstrate steric effect and bear a δ^- charge. As a result, the kinetically controlled product is the σ^H-adduct rather that the σ^{Cl}-adduct. As for the oxidative aromatization step, here again the preferable

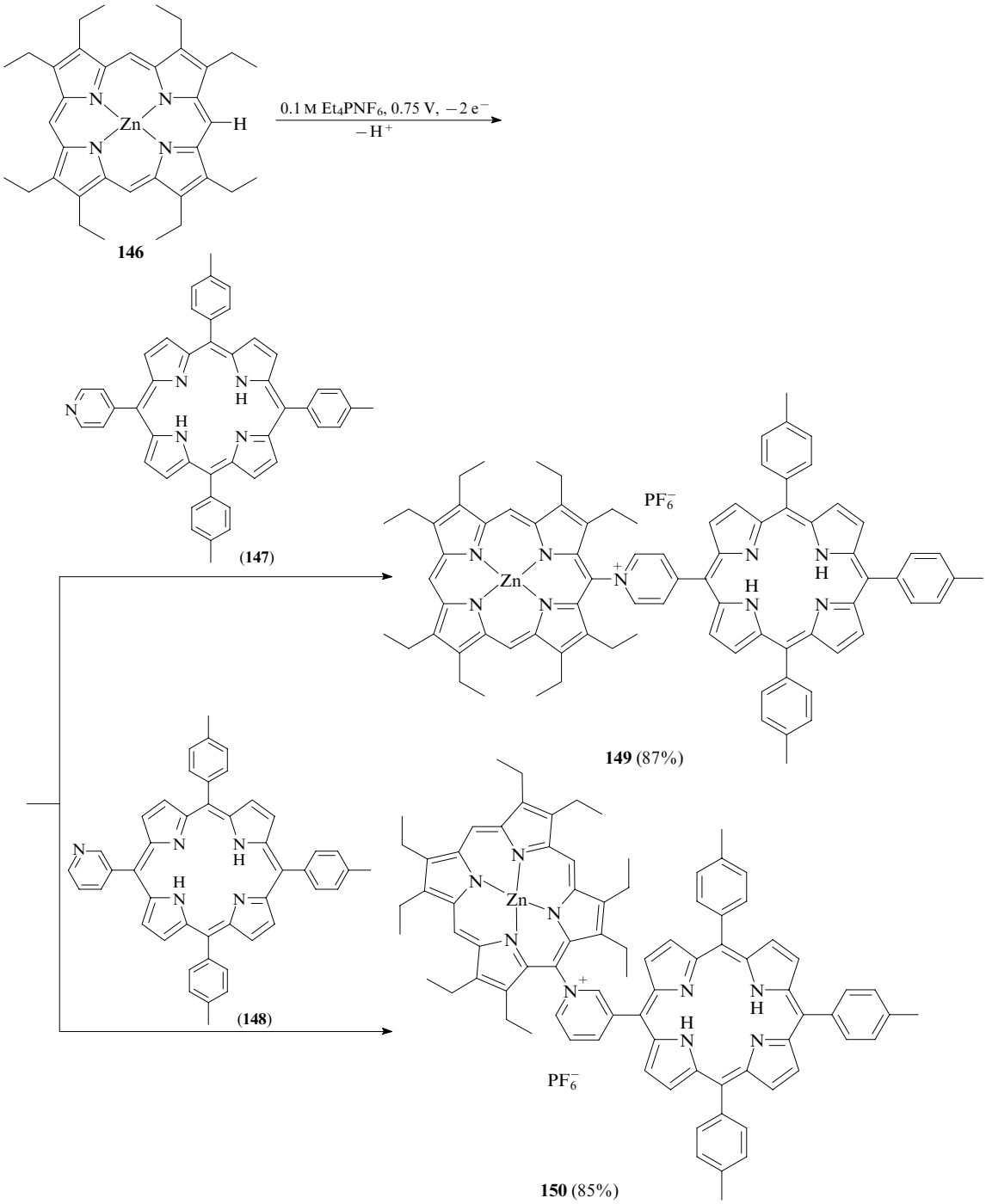
Structures **141**–**145**



141–**145**

Compound	X	E_{ox}/V	Compound	X	E_{ox}/V
141	H	0.85	**144**	Br	0.94
142	F	0.88	**145**	I	0.93
143	Cl	0.91			

Scheme 30

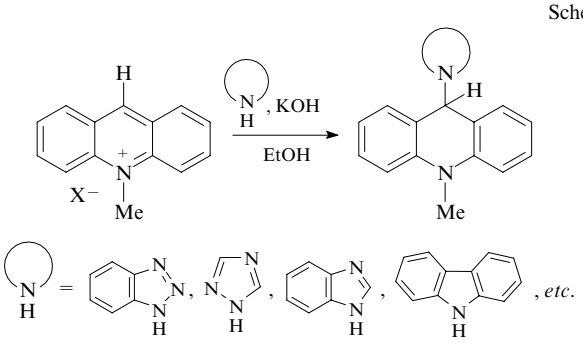


position belongs to the σ^H-adducts. Measurements of the oxidation potentials have been conducted on platinum electrodes in $MeCN-LiClO_4$ system *vs.* $Ag/AgNO_3$ reference electrode using linear and cyclic voltammetry methods. Relatively low oxidation potential of 9-phenylanthracene (**141**) confirms the preference of displacement of the hydrogen atom compared to halogens in reaction of 9-phenyl-10-X-anthracenes **141**–**145** with pyridine.[84]

The application of electrosynthesis in the S_N^H strategy proved to be effective for porphyrins the optical and redox properties of which attract attention of scientists, since these compounds are vital for biochemical processes.[85,86] The authors performed the synthesis of two isomeric porphyrin dimers (Scheme 30). The radical cation generated at the potential of 0.75 V from the zinc complex with β-octaethylporphyrin (**146**) reacts with the nucleophilic pyridine moiety of another porphyrin molecule **147** or **148**. The subsequent electron and proton abstraction affords the 'dimer' **149** or **150** in 87% or 85% yield, respectively.[87]

The σ^H-adducts formed in the reaction of NH-heterocycles with the 10-methylacridinium cation were studied[88] (Scheme 31). Their structures were confirmed by a number of methods including X-ray diffraction analysis, while their oxidation potentials were measured using cyclic voltammetry. Quantum chemical calculations of the HOMO energies have shown that the oxidation potential varies in parallel with the change in the HOMO energy and also depends on some structural characteristics of the compounds under investigation. It can be suggested that development of this approach would allow estimating the stability and the oxidation potentials of the σ^H-adducts to be synthesized using quantum chemical calculations; this, in turn, will provide a more proper choice of the strategy of their synthesis and the choice of the oxidant for the aromatization.

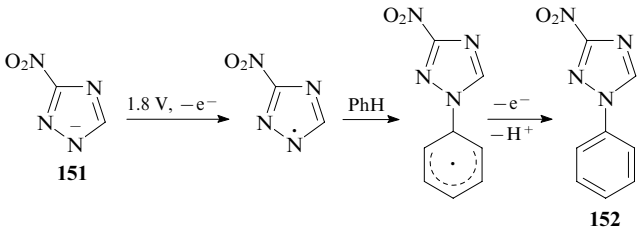
Scheme 31



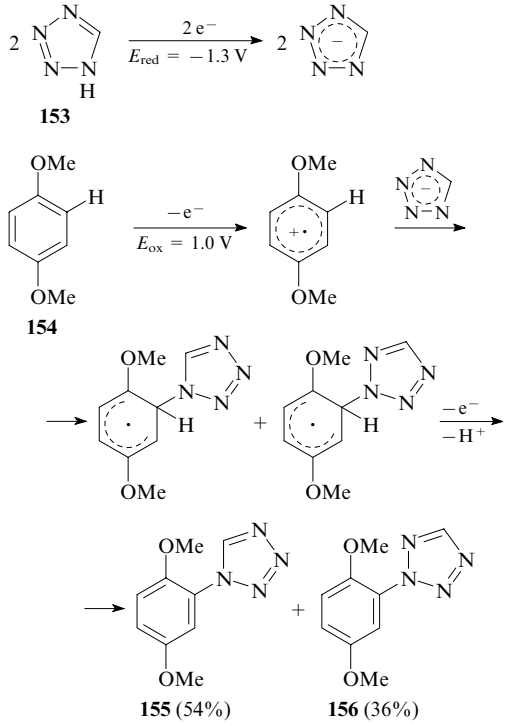
One more example of S_N^H reactions that are accomplished electrochemically is the introduction of azole moieties into the aromatic substrates. The first studies of arene azolation were performed in 1988.[89] It was found that during the potentiostatic electrolysis ($E = 1.8$ V) of tetramethylammonium 3-nitro-1,2,4-triazolate (**151**) in the anode compartment of a divided cell (platinum electrode, 0.2 M $LiClO_4$ solution in MeCN) in the presence of 10 vol.% of benzene, 3-nitro-1-phenyl-1,2,4-triazole (**152**) is formed in 25% yield along with two possible isomers thereof in the total yield of ~3% (Scheme 32).

These investigations were further continued in publications[90–92] devoted to the electrosynthesis in an undivided cell with the simultaneous activation of both the reagent and the substrate (paired electrosynthesis). Under these conditions, the functionalization of di- and trimethoxybenzenes was performed by introducing 1*H*-tetrazole (**153**), 1,2,4-triazole and 5-phenyl-1*H*-tetrazole residues. Electrolysis of the azole–arene equimolar mixture **154** using platinum electrodes and 0.1 M $Bu_4^nNClO_4$ in acetonitrile produced a mixture of moderate quantities of S_N^H products **155** and **156**; replacing the supporting electrolyte by the tetrazole tetrabutylammonium salt caused the total yield of the isomeric products to increase up to 88% (Scheme 33).[90–92]

Scheme 32

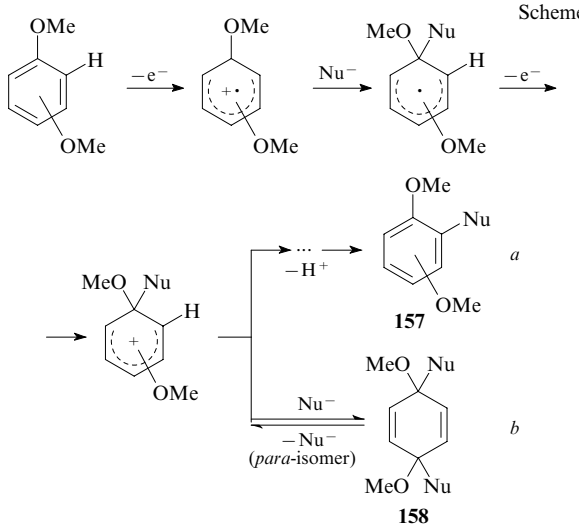


Scheme 33



Subsequently, the set of azoles was extended and the introduction of pyrazole, 3,5-methylpyrazole, 4-nitropyrazole, triazole, 3-nitro-1,2,4-triazole and tetrazole residues into the aromatic substrate (1,4-, 1,3- and 1,2-dimethoxybenzenes) was performed. In doing so, the corresponding S_N^H products were formed in the current and substance yields of up to 60%.[93–97] Detailed study of the regularities of these reactions has shown that according to the ECE mechanism (Scheme 34), the initially formed *ipso*-arenonium cation rearranges according to the *cine*-substitution mechanism to give the corresponding *ortho*-substituted cation, which is stabilized through proton elimination to give the product of *ortho*-substitution **157**. In the case of *p*-dimethoxybenzene, this process in competitive with the reverse addition of the second nucleophile yielding the *ipso*-bis-addition product **158**. As this takes place, product **158** may transform into the *ortho*-substituted product **157** during the electrolysis. The

Scheme 34

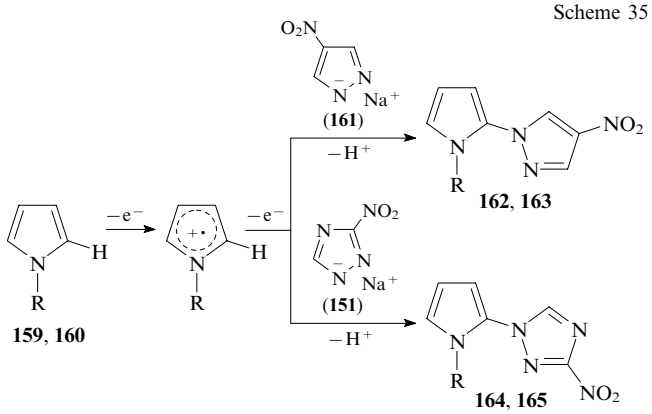


Substrate is *o*-, *m*- or *p*-dimethoxybenzene, Nu is azolate ion

competing processes *a* and *b* were established to be catalyzed by the addition of acids.

Cross-coupling of a series of five-membered heterocycles was accomplished[98] (Scheme 35). In the anodic compartment of the divided cell at the oxidation potentials of *N*-methylpyrrole (**159**) (1.3 V *vs.* SCE) and *N*-phenylpyrrole (**160**) (1.5 V) in the presence of the corresponding azolate ions **161** and **151**, hitherto unknown pyrrolylazoles **162**–**165** were obtained.

Scheme 35

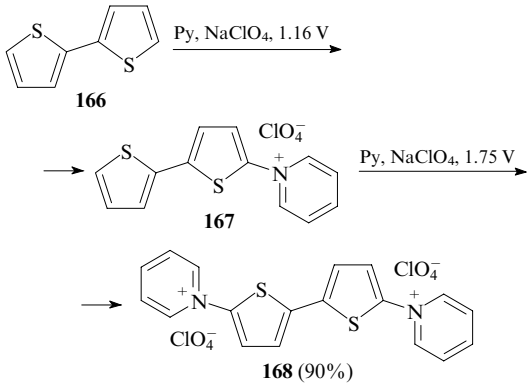


Compound	R	Yield (%)	Compound	R	Yield (%)
159	Me		**163**	Ph	28
160	Ph		**164**	Me	20
162	Me	43	**165**	Ph	28

The interest in the development of the electrochemical S_N^H strategy for the synthesis of *N*-arylazoles is caused by their structural identity with a wide range of biologically active substances exhibiting, *e.g.*, antifungal[99] or antiinflammatory[100] activity.

A preparative electrochemical pyridination of 2,2′-bithiophene (**166**) has been reported;[101] varying the electrolysis potential resulted in the selective formation of monosubstituted (**167**) or disubstituted (**168**) products (Scheme 36). This example demonstrates a rather frequently encountered possibility of electrochemical control over aromatic substitution of hydrogen. The target compounds may be useful as mediators in electrochemistry, coordination chemistry and photochemistry,[102] including the construction of different types of molecular electronic devices.

Scheme 36

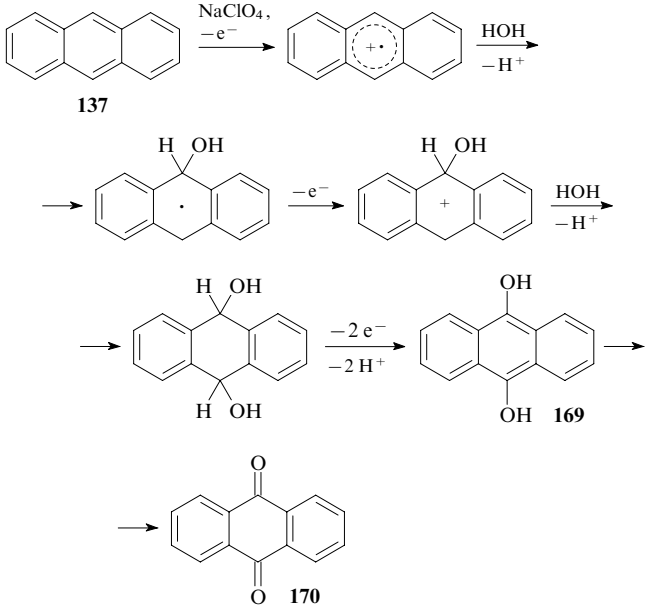


3. The C–O-bond

a. Hydroxylation

Water and hydroxide anion are the simplest and the most readily available nucleophiles. Studies of hydroxylation of aromatic systems have not received extensive development; they were mainly performed in the mid-20th century and were analyzed in a monograph.[21] Therefore, we shall restrict our consideration to a few examples only. Thus, electrochemical oxidation of anthracene (**137**) in a galvanostatic mode at a current intensity of 100 mA in acetonitrile affords a radical cation, which reacts with water to yield 9,10-dihydroxyanthracene (**169**) (Scheme 37).[103, 104] Unfortunately, these studies moving forward to the efficient synthesis of anthraquinone (**170**), were not continued. This is probably due to a low yield of anthraquinone and side processes giving polymerization products.

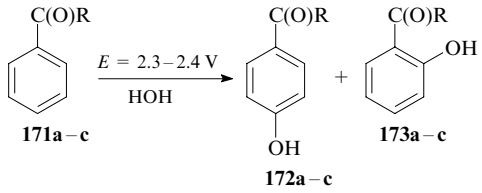
Scheme 37



The anodic hydroxylation of acetophenone, benzoic acid and its ethyl ester (compounds **171a**–**c**) was performed; the reaction involved the *ortho*-and *para*-positions relative to the carbonyl group and yielded isomeric products **172a**–**c** and **173a**–**c** (Scheme 38).[105] The process was conducted in a mixture of CH_2Cl_2–CF_3CO_2H (2 : 1) with

0.1 M Et_4NBF_4 as a supporting electrolyte; the oxidation potentials were measured *vs.* an $Ag/AgNO_3$ electrode.

Scheme 38

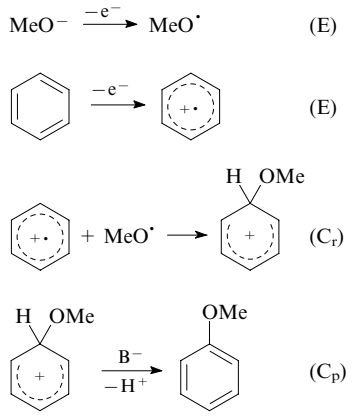


Compounds **171–173**	R	E_{ox}/V	Yield (%)	
			172	**173**
a	Me	2.4	< 5	85
b	OEt	2.3	19	43
c	OH	2.3	20	55

b. Alkoxylation

These transformations are mainly represented in the electrochemical literature by methoxylation reactions. The studies in this area of functionalization of aromatic systems started as early as in the 1950s. Anodic alkoxylation of furans, benzothiophenes, pyrroles, pyridines, phenols, anisoles and naphthalenes conducted on platinum or graphite electrodes in methanol proceeds according to the S_N^H pattern (Scheme 39), where the key step is generation of the corresponding arene radical cation.[12, 21, 23]

Scheme 39

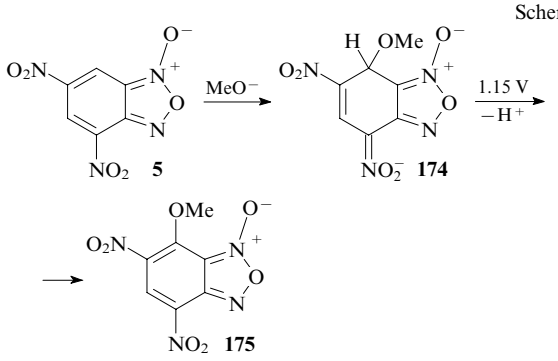


To describe such reactions, Swenton[106] proposed the EEC_rC_p mechanism (see Scheme 39). The first two letters 'E' denote electrochemical steps of the formation of radical and radical cation species, while C_r and C_p designate the subsequent chemical steps involving radical and polar intermediates, respectively.

In 2001 Terrier and co-workers[28] considered the possibility of electrochemical S_N^H methoxylation based on the chemical pre-generation of the σ^H-adduct. The stable σ^H-adduct **174** of 4,6-dinitrobenzofuroxan (**5**) was studied by cyclic voltammetry. The oxidation of the adduct in methanol on a platinum anode yields the S_N^HAr product **175**. Unfortunately, the yield of the product **175** is not given in the article (Scheme 40).

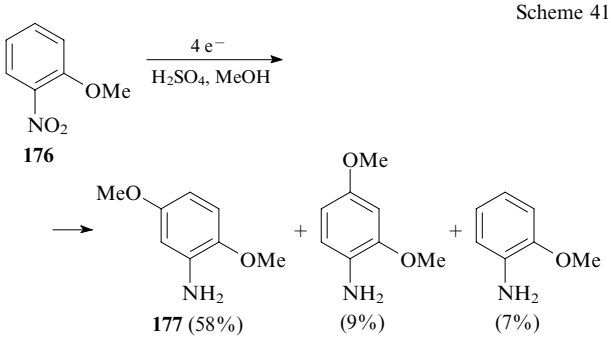
An interesting fact was found in the electroreduction of 2-nitroanisole (**176**) in a 1 M solution of H_2SO_4 in MeOH.[107] The galvanostatic electrolysis (10 mA cm^{-2}) of

Scheme 40



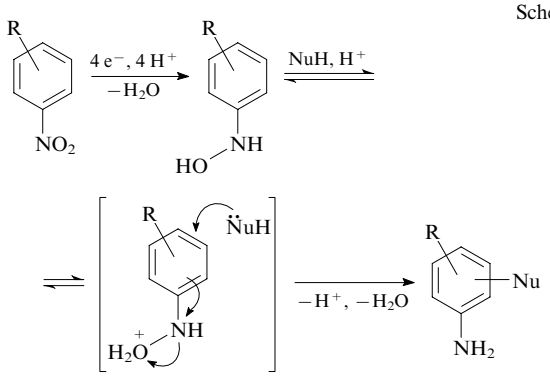
2-nitroanisole on a mercury cathode gave predominantly the product of methoxylation **177** in the *meta*-position relative to the amino group (Scheme 41).

Scheme 41



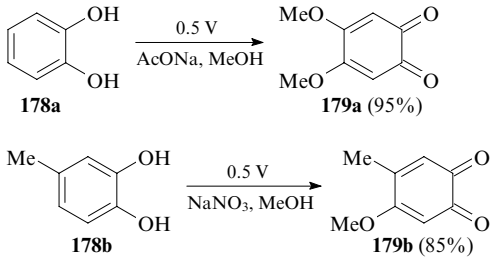
The proposed mechanism of the process is shown in Scheme 42.

Scheme 42



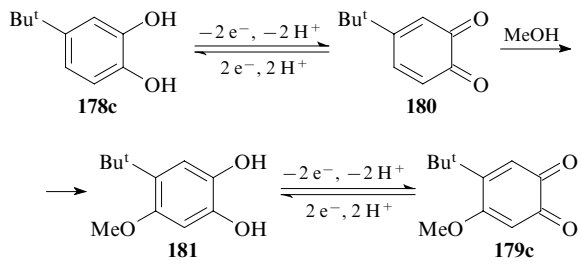
The electrochemical oxidation of pyrocatechol (**178a**) and 4-methylpyrocatechol (**178b**) in methanol was studied using cyclic voltammetry and preparative controlled potential electrolysis.[108] The electrolysis in the anodic compartment of a divided cell on a graphite electrode afforded methoxylated products of oxidation **179a** and **179b** in yields of 95% and 85%, respectively (Scheme 43).

Scheme 43



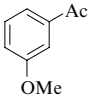
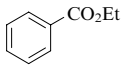
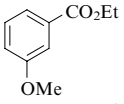
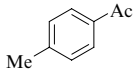
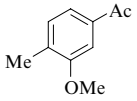
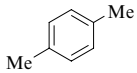
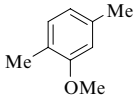
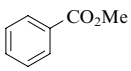
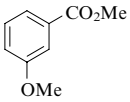
A study of oxidation of pyrocatechols by cyclic voltammetry at various pH values in mehtanol and ethanol [109] resulted in elucidation of the alkoxylation mechanism as illustrated in Scheme 44 by the example of pyrocatechol **178c**.[110, 111] The transfer of two electrons at the first step results in generation of *o*-quinone **180**, which is subjected to nucleophilic attack of methanol yielding intermediate **181**. The latter is immediately oxidized further, losing protons and giving rise to the final product **179c**. It should be noted that intermediate **181** is oxidized more readily compared to the starting pyrocatechol **178c** due to the presence of electron-donating methoxy group.

Scheme 44



Finally, note the results of a relatively recent study [112] where the electrochemical methoxylation of several aromatic compounds has been successfully performed (Table 5). Electrolysis was conducted at room temperature in an undivided cell on platinum electrodes in a methanol solution of KOH. This example demonstrates a novel synthetic procedure of alkoxy group introduction, which is easy to use and safe.

Table 5. Results of the electrochemical methoxylation of arenes.[112]

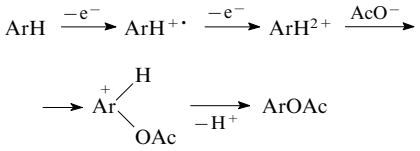
Compounds	E/V [a]	Product	Yield (%)
 (**171a**)	1.90		86
 (**171b**)	1.80		92
	1.70		95
	1.95		85
	2.10		88

[a] Electrolysis potential *vs*. SCE.

c. Acetoxylation

A high stability of the acetate anion (AcO^-) makes it a suitable model for the investigation of the S_N^H reactions of aromatics.[12, 21, 23] The anodic oxidation of a variety of aromatic and alkylaromatic substrates in acetic acid in the presence of sodium acetate was shown to give the acetoxylation products in moderate yields. Despite the numerous attempts to examine the mechanism of acetoxylation, this issue is still obscure.[21] For example, one proposed mechanism is based on the step of generation of arene dication (Scheme 45),[113] whereas the other studies suggest [12] that a mechanism involving the interaction of the intermediate arene radical cation with the acetate ion followed by the formation of an unstable σ^H-adduct is more probable.

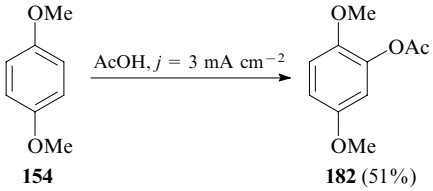
Scheme 45



Generally, the anodic acetylation of aromatic compounds is confined to substrates with oxidation potentials lower than that of acetic acid.[114] The use of trifluoroacetic acid extends the range of aromatic substrates. On the one hand, trifluoroacetic acid may stabilize significantly the radical cation intermediates,[21, 115] and on the other hand, the formation of trifluoroacetoxylation products susceptible to hydrolysis is considered to be an effective approach to phenol derivatives.[21]

Since the mid-1980, investigations of acetoxylation of the aromatic systems have almost ceased; however, recently, a growth of attention to these studies has been observed. An interesting technical solution has been proposed.[116] The authors utilize a continuous-flow thin-layer cell with the electrode spacing of 80 μm, which operates without a supporting electrolyte. Thus, the reaction mixture contains only the substrate and acetic acid. Crucial characteristics for this version of the acetoxylation are the flow rate and the electric current density (j). Thus the acetoxylation of 1,4-dimethoxybenzene (**154**) is performed at j = 3 mA cm^{-2} and solution flow rate of 0.1 ml min^{-1} to give product **182** in 51% yield (Scheme 46).

Scheme 46



Meanwhile, it has been repoted [97] that product **182** can also be obtained in a highly effective manner under 'classical' conditions. Thus, the galvanostatic electrolysis of dimethoxybenzene **154** (I = 200 mA) in an undivided cell on platinum electrodes in dichloromethane in the presence of Et_4NOAc and acetic acid furnished product **182** in 56% yield. The addition of $ZnCl_2$ to the electrolyte increased the yield up to 70%,[117] and with addition of silica gel-immobilized morpholine derivative the yield reached 91%.[118]

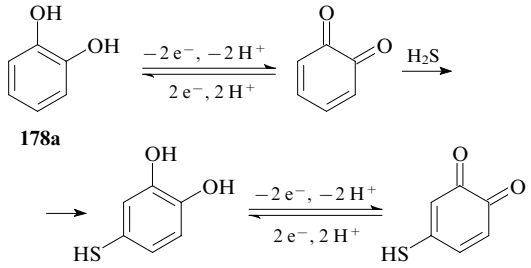
4. The C–P and C–S-bonds

Literature data on electrochemical reactions of nucleophilic aromatic substitution of hydrogen under the action of S- and P-nucleophiles are very limited.

Studies on the electrochemical introduction of S-nucleophiles relates mainly to the investigation of the S_N^H-reac-

tions of quinones. For example, it was proposed to utilize the nucleophilic substitution of hydrogen in the electrochemically activated quinones as an analytical procedure to detect sulfides (Scheme 47).[119] Five structurally and functionally different compounds (pyrocatechol, dopamine, hydroquinone, *p*-aminophenol and *N*,*N*-dimethylphenylene-1,4-diamine) were studied as potential electrochemical indicators for the sulfide analysis in aqueous solutions. All the derivatives are able to be oxidized to give the quinone intermediate, which can undergo the S_N^HAr reaction with sulfides. The analytical signal observed (the oxidation peak of the S_N^H product) is clearly detected by cyclic voltammetry.

Scheme 47

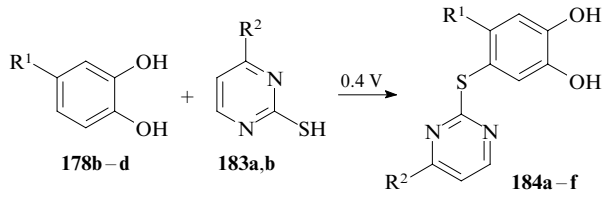


Pyrocatechol derivatives form a large group of compounds of undoubted interest since quinone moieties generated upon the oxidation of catechols form a part of structure of many antitumour drugs such as doxorubicin, daunorubicin, mitomycin C.[120]

The electrochemical oxidation of 4-substituted pyrocatechol derivatives **178b–d** in the presence of 2-sulfanylpyrimidines **183a**,**b** afforded monopyrimidinyl thio-substituted dihydroxybenzenes **184a–f** in good yields (Scheme 48). The electrolysis was carried out at a controlled potential of the graphite electrode in an undivided cell in a 9 : 1 water–acetonitrile mixture containing 0.2 mol litre^{-1} of sodium acetate (pH 6.0).

In the case of oxidation of the unsubstituted pyrocatechol (**178a**) and 3-substituted pyrocatechols **185a**,**b** under similar electrolysis conditions, both monosubstituted

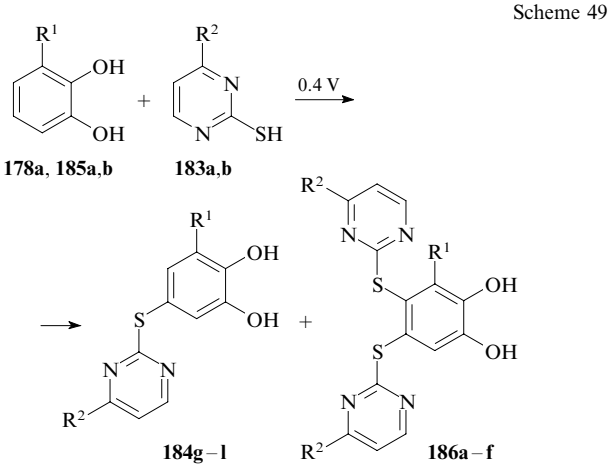
Scheme 48



178: R^1 = Me (**b**), Bu^t (**c**), CH=CHCO$_2$H (**d**);
183: R^2 = H (**a**), Me (**b**)

Compound **184**	R^1	R^2	Yield (%)
a	Me	H	49
b	Bu^t	H	49
c	CH=CHCO$_2$H	H	58
d	Me	Me	57
e	Bu^t	Me	51
f	CH=CHCO$_2$H	Me	63

Scheme 49



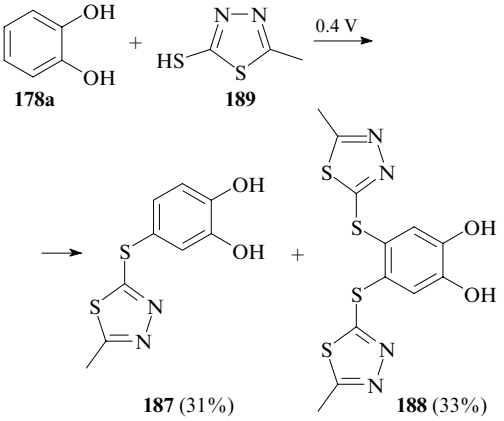
185: R^1 = Me (**a**), OMe (**b**)

Compound	R^1	R^2	Yield (%)	Compound	R^1	R^2	Yield (%)
184g	H	H	41	**184j**	Me	Me	38
186a	H	H	23	**186d**	Me	Me	22
184h	H	Me	40	**184k**	OMe	H	35
186b	H	Me	27	**186e**	OMe	H	24
184i	Me	H	36	**184l**	OMe	Me	53
186c	Me	H	26	**186f**	OMe	Me	25

(**184g–l**) and dipyrimidinylthio-substituted derivatives (**186a–f**) are formed in reasonably good yields (Scheme 49).[121] These compounds are potential anti-HIV drugs; therefore, the electrochemical synthesis thereof seems especially attractive because of its high purity and the absence of side products.

S_N^H Products **187** and **188** of similar structure are formed upon the anodic oxidation of pyrocatechol **178a** in the presence of 5-methyl-1,2,4-thiadiazole-2-thiol (**189**) (Scheme 50).[122]

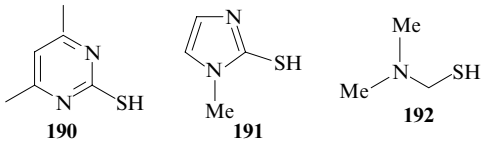
Scheme 50



Electrochemical co-oxidation of pyrocatechols **178a**,**e** [R^1 = H (**a**), CO$_2$H (**e**)] **185a** with nucleophiles **183a**, **190–192** bearing thiol groups has been studied using cyclic voltammetry with variation of the pH and nucleophile concentration. The reaction rate constant was estimated by

comparing the experimental cyclic voltammograms with the results of digital modelling. These investigations demonstrated that the reaction rate constant depends on the nature of substituents in pyrocatechol and on the thiol nucleophilicity.[123]

Structures **190**–**192**



190 **191** **192**

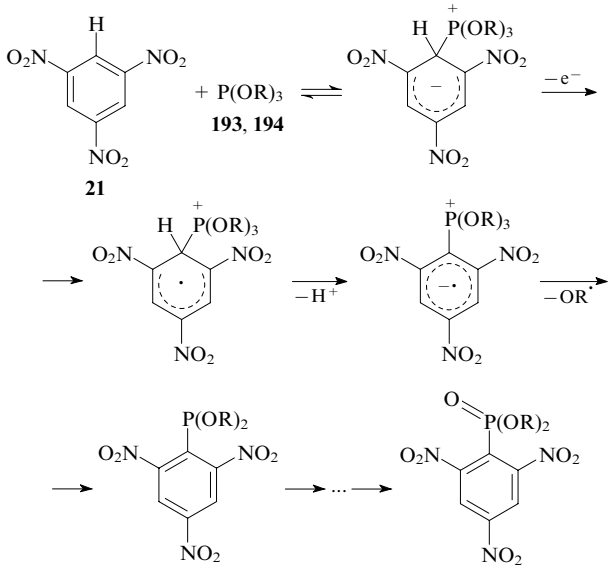
Although, as noted above, the number of studies concerning aromatic nucleophilic substitution of hydrogen with S- and P-nucleophiles is few, having regard to the novelty, topicality and biological orientation of these studies, one can predict with certainty that investigations along this line will be continued.

Recently, the electrochemical version of S_N^H reactions has been applied to obtain organophosphorus compounds which could be useful in such fields as pharmacology, medicine or material science. By now, investigations of the introduction of P-nucleophiles into an aromatic nucleus are limited to an electrochemical method for the synthesis of phosphorus-containing nitroaromatic compounds according to the procedure given below.[124] The corresponding P-nucleophile was added (in some cases together with the Bu^{t}OK base) to a nitroarene solution in DMF containing 0.1 M $Bu_4^nNBF_4$ under inert atmosphere. The potential of the σ^H-adduct thus obtained was determined using cyclic voltammetry *vs.* SCE. Then the solution was subjected to the controlled potential electrolysis (the oxidation potential was adjusted to be 100 mV greater than the measured one) on a graphite anode (Table 6). The steric factor was shown to have a great impact on the yield of the desired product: introduction of bulky nucleophiles significantly decreases the yield of the S_N^H product. In the case of nucleophile attack by trimethyl phosphite (**193**) and triethyl phosphite (**194**), σ^H-adducts are formed; their electrochemical oxidation leads to the Arbuzov rearrangement to afford target compounds **195** and **196** (Scheme 51).

Table 6. Results of the anodic oxidation of σ^H-adducts formed in the reaction of trinitrobenzene **21** with P-nucleophiles [Ar = $C_6H_2(NO_2)_3$-2,4,6].[124]

Nucleophile (ratio of substrate : nucleophile : base)	E_{ox} σ^H-adduct /V	Product	Yield (%)
$HP(O)(OMe)_2$ (1 : 2 : 2)	0.88	$ArP(O)(OMe)_2$ (**195**)	80
$HP(O)(OEt)_2$ (1 : 1 : 1)	0.86	$ArP(O)(OEt)_2$ (**196**)	33
$HP(O)Ph_2$ (1 : 2 : 2)	0.83	$ArP(O)Ph_2$	10
$P(OMe)_3$ (**193**) (1 : 0.25 : 0)	0.88	$ArP(O)(OMe)_2$ (**195**)	14
193 (1 : 200 : 0)	0.88	**195**	68
$P(OEt)_3$ (**194**) (1 : 50 : 0)	0.88	$ArP(O)(OEt)_2$ (**196**)	20

Scheme 51



21 **193**, **194** **195**, **196**

R = Me (**193**), Et (**194**)

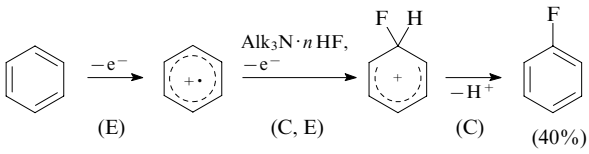
5. The C–Hal-bond

The electrochemical chlorination, bromination and iodination of arenes proceeding with replacement of the hydrogen atom by a halogen are considered in detail in a recent review,[125] saving us from the need to consider and summarize the literature data once again.

The chemical fluorination of aromatic compounds is most commonly performed through diazonium salts according to Schiemann reaction. This process is rather laborious and often also dangerous because of explosiveness of the diazonium salts. In this conection, electrochemical methods of fluorination of aromatic compounds using the strategy of nucleophilic substitution of hydrogen are very topical.

In their pioneering studies, Rozhkov and co-workers [126, 127] showed for the first time that anodic oxidation of aromatic compounds in the presence of tetraalkylaamonium fluorides or hydrogenfluorides is accompanied by fluorination to give fluorine-containing S_N^H products. Based on the data of cyclic voltammetry, the ECEC-mechanism of the process was proposed with the first step (E) corresponding to electron transfer yielding the radical cation of the aromatic substrate. Reaction of the latter with a nucleophile and the oxidation of the radical thus formed (steps C and E) results in the arenonium ion. At the final step (C), the arenonium ion is stabilized giving off a proton. For example, this mechanism is involved in the formation of fluorobenzene in 40% yield upon the oxidation of benzene on a platinum electrode in MeCN (Scheme 52). The ECEC mechanism of the above process is also supported by the fact that the fluoride ion is one of the most oxidation-resistant nucleophiles.

Scheme 52

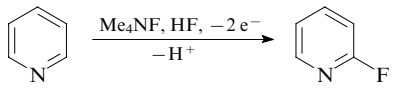


(E) (C, E) (C) (40%)

In succeeding years, the mild fluorination method proposed by Rozhkov was extensively developed. This strategy

was used to fluorinate five- and six-membered heterocycles, *e.g.*, pyridine (Scheme 53).[128]

Scheme 53



(22%)

A short summary of recent advances in the selective electrochemical fluorination with a consideration of the effect of the solvent nature and the procedure of electrolysis used is given in the work of Japanese scientists.[129]

III. Conclusion

The analysis of literature data demonstrates that the electrochemical processes of direct nucleophilic functionalization of C(sp^2)–H-bonds in arenes and hetarenes are widely used and are becoming universal tool in the synthetic organic chemistry.[130, 131] Using these processes, it is possible to improve the atomic efficiency of reactions by refusing the additional introduction of nucleofugal groups and auxiliary reagents and materials. The possibility of quantification of redox potentials of reactants and intermediates offers prospects for the conscious and rational choice of oxidizing agents (or switching to electrochemical processes without using oxidants) and also makes it possible to gain information on the S_N^H mechanism both in chemical and in electrochemical versions. Electron transfer provides activation for both the substrates and the reagents, thus extending considerably the range of arenes and hetarenes suitable for S_N^Hreactions. The possibilities to control the electrochemical process offer prospects for the regiospecific substitution of the C–H-bonds even in the presence of readily leaving groups.

By now, the number of publications on electrosynthesis including cross-coupling reactions based on direct functionalization of the C–H-bond in arenes and hetarenes is still low. However, the latest advances in electrosynthesis with controlled potential or current intensity, new possibilities of chemical and mechanical modification of the electrode materials, application of ionic liquids in the absence of a supporting electrolyte, the use of two-phase systems and improved cell design — all this brings hope that the organic chemistry of anodic and cathodic processes will become more convenient and effective and find more practical use.

Now, more and more often, the decisive role in choosing a process is played by the compliance with the demands of environmental acceptability *i.e.*, the so called green factor.[132, 133] In this context there are strong grounds to believe that electrochemical direct nucleophilic functionalization of the C(sp^2)–H-bonds of aromatic compounds considered in the present review being *per se* atom-economic and environmentally favourable have a real chance to occupy a worthy place in the modern organic synthesis.

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