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Recent Advances in the Electrochemical Reduction of Substrates Involving N–O Bonds

Tom Wirtanen,[a] Eduardo Rodrigo,[a] and Siegfried R. Waldvogel[a,*]

[a] Department Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweg 10–14, 55128 Mainz, Germany
Fax: (+49)-6131-39-26777; phone: (+49)-6131-39-26069; e-mail: waldvogel@uni-mainz.de (homepage: www.aksw.uni-mainz.de)

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Abstract: In this review, the versatile and rich chemistry for the electrochemical reduction of substrates involving N–O bonds is surveyed. By the cathodic treatment of nitro, nitroso and other oxygenated organic nitrogen substrates, versatile and reactive intermediates are formed which can be subsequently converted to high value-added products. In many examples, nitrogen heterocycles are selectively formed, but, also depending on the electrolytic conditions, free oximes, nitrones, amines and other entities can be obtained as well. The recent decades have witnessed two major advances – (i) going directly to more complex target molecules and (ii) conducting the electrolyses in much simpler set-ups. Both improvements make the cathodic access of the target compounds much more practical and scalable.

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Keywords: electrochemistry; heterocycles; nitrogen; oxygen; reduction

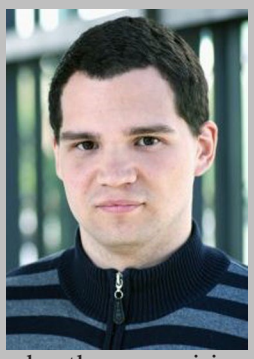
1 Introduction

Chemistry, the *central science*, has always played a pivotal role in the progress of mankind. In particular, recent proceedings in synthetic chemistry have and continue to supply society with, for example, new pharmaceuticals and advanced materials. Today, one of the most urgent and pressing questions asked of synthetic chemists is, how to transition towards more environmentally friendly and less energy-intensive chemical processes, which in turn can help to reduce in unison CO_2 emissions and the expense of the synthesis.[1] Also, the use of critical elements has to be avoided and consequently alternatives to reductions employing various metal powders are highly desired.

In this respect, electro-organic synthesis can be considered as a pinnacle of sustainability.[2] A sole inexpensive electric current replaces expensive and sometimes toxic chemical reducing agents and oxidants.[3] In addition to reducing reagent waste tremendously, electrochemical processes are controllable and safe to conduct as they can be switched-off anytime and thermal runaway reactions are not possible.[4] Within this paradigm, oxidative electrochemical transformations have recently received a lot of attention whereas, reductive electrochemical synthesis to high value-added compounds was less prominent.[5] It is noteworthy that using electricity does not make a process 'green', since excess of supporting electrolyte, critical elements in mediators, and sacrificial electrodes have to be avoided.[6]

Electroreduction of functional groups containing N–O bonds, i.e., nitro compounds, oximes, nitrones, etc., is a highly powerful strategy for organic synthesis. In contrast to other electroreducible groups such as halogens, the follow-up chemistry of N–O reductions after the first electron transfer is much richer and diverse. For example, both nucleophilic and elec-

Tom Wirtanen received his B.Sc. in chemistry in 2010 and M.Sc. in organic chemistry in 2012 from the University of Helsinki. He visited in 2012 Prof. Dr. Jose A. Lopez-Sanchez at the University of Liverpool and finished his Ph.D. in 2018 at the University of Helsinki under supervision of Dr. Juho Helaja. Since 2019, he has been working as a post-doctoral researcher at the Johannes Gutenberg University Mainz in the group of Prof. Dr. Siegfried R. Waldvogel focusing on reductive electrosynthesis.



Eduardo Rodrigo obtained his B.Sc. in chemistry in 2009 and his M.Sc. in organic chemistry in 2011 from the University Autónoma of Madrid. In 2014, he was a visitor at the University of Jyväskylä, Finland (Prof. Dr. Petri M. Pihko). He finished his Ph.D. in 2016 at the University Autónoma of Madrid in the field of organocatalysis under the supervision of Dr. M. Belen Cid. Until 2019, he worked as a post-doctoral researcher at the Johannes Gutenberg University Mainz in the group of Prof. Dr. Siegfried R. Waldvogel, in the field of organic electrosynthesis. Currently, he is working at Abbvie in Ludwigshafen am Rhein (Germany).

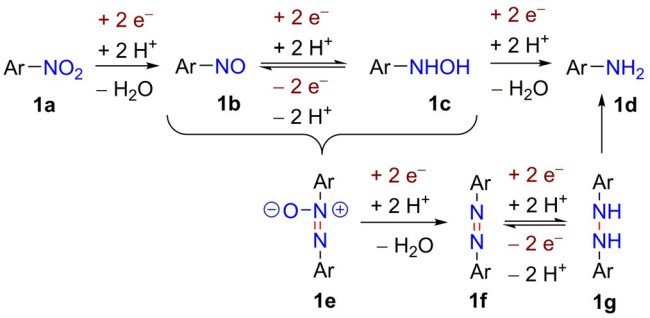
Siegfried R. Waldvogel studied chemistry in Konstanz and received his Ph.D. in 1996 from the University of Bochum/Max-Planck-Institute for Coal Research with Prof. Dr. M. T. Reetz as supervisor. After post-doctoral research at the Scripps Research Institute in La Jolla, California (Prof. Dr. J. Rebek, jr.), he started his own research career in 1998 with a habilitation at the University of Münster. In 2004, he moved to the University of Bonn as professor for organic chemistry. In 2010, he became full professor at the Johannes Gutenberg University Mainz. His major research interest is currently organic electrosynthesis ranging from screening techniques, novel transformations to scale-up. In 2018 he co-founded the start-up ESy-labs GmbH which is also dealing with electrosynthesis

trophilic nitrogen centers can be easily generated by a variation of the reaction conditions. From an economic point of view, many precursors are widely available from commercial sources and some of them (e.g., nitroarenes) are generally more inexpensive and less toxic than their reduced analogues. Furthermore, if they are not commercially available, they can be easily prepared by well-established methods in a few steps.[7] Moreover, the reductions are usually chemoselective in the presence of more than one electron-accepting group (electrophores) that could compete with the N–O reduction. All these points combined make the cathodic reductions of N–O bonds a very robust strategy with a lot of different applications and possibilities. The goal of this review is to survey the recent advances in electrochemical N–O bond reductions that have been published approximately during the last two decades. Occasionally, older references are cited as well. By focusing strongly on synthesis, we aim for portraying an up-to-date picture of the field that complements existing reviews written on the subject.[8]

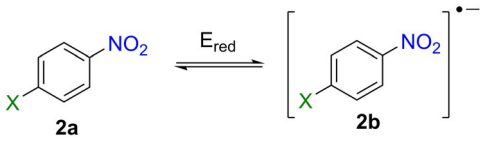
2 Nitro Derivatives

The nitroaryl electroreduction played a very important role at the beginning of the 20th century and eventually led to a significant increase in the understanding of organic electrochemical phenomena.[8a]

Reducing nitroaryls (**1a**, Scheme 1) with electricity can yield nitroso compounds (**1b**), hydroxylamines (**1c**) and anilines (**1d**) as products. As the nitroso group is more easily reducible than the nitro group, obtaining nitroso derivatives by directly reducing a nitro group is difficult and it requires, for example, specific electrode materials.[9] In contrast, hydroxylamines usually form straight from the nitro reduction.



Scheme 1. Reduction of aryl nitro compounds and possible reaction pathways (selection).



X	E_{red}	X	E_{red}
NO_2	–0.674 V	Cl	–1.030 V
CN	–0.846 V	H	–1.110 V
CO(H)	–0.874 V	CH_3	–1.165 V
COMe	–0.910 V	OCH_3	–1.233 V
CF_3	–0.920 V	NH_2	–1.309 V

Scheme 2. One-electron reduction potentials for *para*-substituted nitrobenzene derivatives. Values determined at 25 °C, in CH_3CN with Bu_4NPF_6 [0.2 M] as a supporting electrolyte from CV *vs.* FcH/FcH^+ (scan rate = 100 mV s^{-1}) and recalculated (+0.382 V) *vs.* SCE.[16] Working electrode = glassy carbon.

It is important to mention that the hydroxylamines are very prone to oxidation and they form readily the $2e^-/2H^+$ redox-pair with the corresponding nitroso system. This is one of the reasons why the final reduction to the aniline is difficult and why divided cells are often mandatory to obtain anilines or nitroso compounds on a preparative scale. Moreover, nitroso intermediates and hydroxylamines can condense to afford azoxybenzenes (**1e**), which can be subsequently electroreduced to azobenzenes (**1f**), or further to hydrazobenzenes (**1g**). Also, azobenzenes and hydrazobenzenes form reversible $2e^-/2H^+$ redox-pairs. Furthermore, hydrazobenzenes can be electroreduced to anilines under acidic or basic conditions,[10] but in the former, rearrangement to 1,1-biphenyl-4,4′-diamines competes and complicates the scenery of electroreduction. This might lead to rather complex product mixtures.

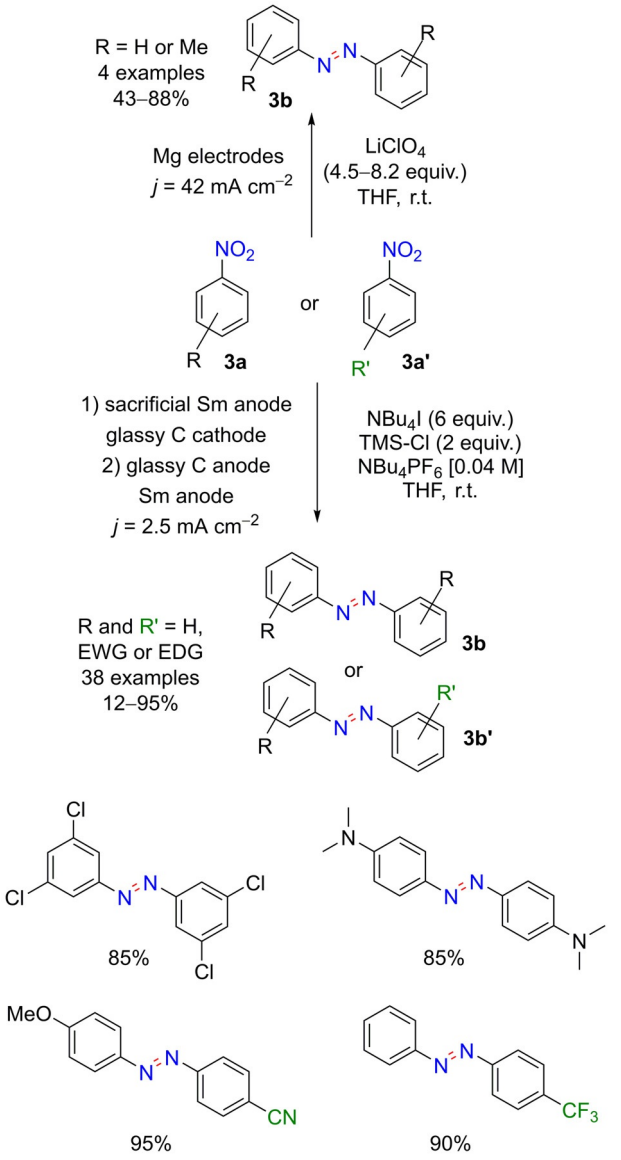
The reduction potentials of nitroarenes may vary a lot, since they depend on the solvent, pH, electrode, electrocatalyst, and the nature of the substituents at the aryl ring. For instance, potentials for reducing the nitrobenzene to phenylhydroxylamine in an EtOH/H_2O solution vary from −0.255 V (pH 1) up to −0.810 V (pH 13) *vs.* SCE.[11] Furthermore, also the hydroxylamine/nitroso half-wave potentials ($E_{1/2}$) shift to more negative values with increasing pH.[12,13]

Conradie and co-workers measured the one-electron reduction potentials of different *para*-substituted nitrobenzenes (**2a**, Scheme 2) to nitrobenzene radical anions (**2b**) in CH_3CN at a glassy carbon cathode.[14] The more electron-releasing the functional group is, the more negative is the reduction potential. Furthermore, they determined that reduction potentials had an excellent correlation with LUMO energies that were obtained by DFT calculations.

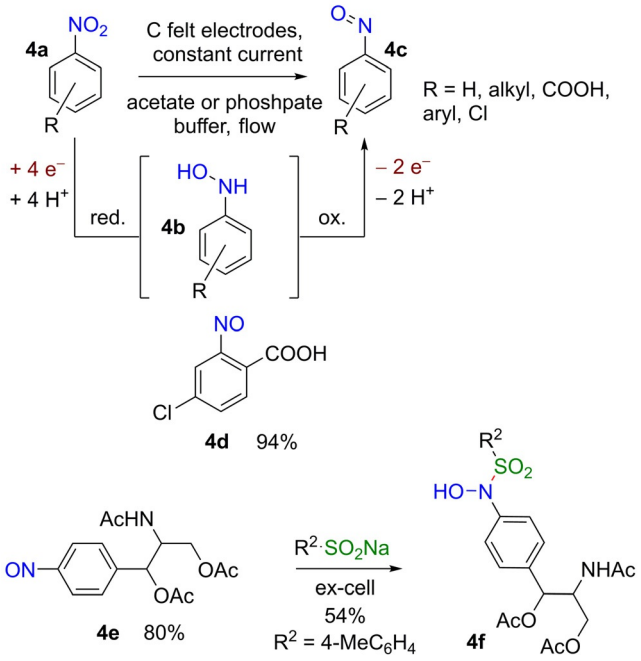
2.1 Intermolecular Reactions

Kim and co-workers used different nitrobenzenes (Scheme 3, **3a**) to synthesize selectively symmetrical azobenzenes (**3b**). Partially sacrificial Mg electrodes (< 5% erosion) were used under galvanostatic conditions (Scheme 3, *upper part*).[15] Interestingly, alternating the polarity of electrodes at an interval range of 30–60 s led to a smaller erosion of Mg electrodes. Noteworthy, the alternation of electric polarity sacrifices both electrodes. Although a narrow scope was presented, they could use high current densities and avoid aniline formation. Years later, Mellah carried out the same reaction, using SmI_2 as a reagent that was electrogenerated from Sm anode and an excess of Bu_4NI as additive (Scheme 3, **3b′**, *lower part*).[17] They reported both catalytic and stoichiometric conditions for the synthesis of azobenzenes. In the stoichiometric protocol, 4 equiv. of SmI_2 are electrogenerated, whereas in the catalytic protocol, 10 mol% of SmI_2 are prepared. The key aspect that allowed the catalytic reaction to proceed was to swap the polarity of the electrodes after SmI_2 generation. This, in the presence of 2 equiv. of TMS-Cl, allowed the electroregeneration of Sm(II) from Sm(III) at the Sm cathode. They could even obtain in some cases unsymmetrical azobenzenes. In both reports, the reactions proceed through the formation of the intermediate azoxybenzenes, which are subsequently reduced to the azobenzenes.

Moinet and co-workers devised a strategy for generating nitroso compounds by first reducing nitroarenes (Scheme 4, **4a**) to hydroxylamines (**4b**) that were in the next step re-oxidized to nitroso compounds (**4c**). For this purpose, they employed a flow cell in a galvanostatic mode using two consecutive porous graphite felt electrodes of opposite polarities.[18,19] This ensures that the nitroso compound cannot form a redox-pair with hydroxylamine that could lead to



Scheme 3. Electrosynthesis of symmetrical and non-symmetrical azobenzenes.

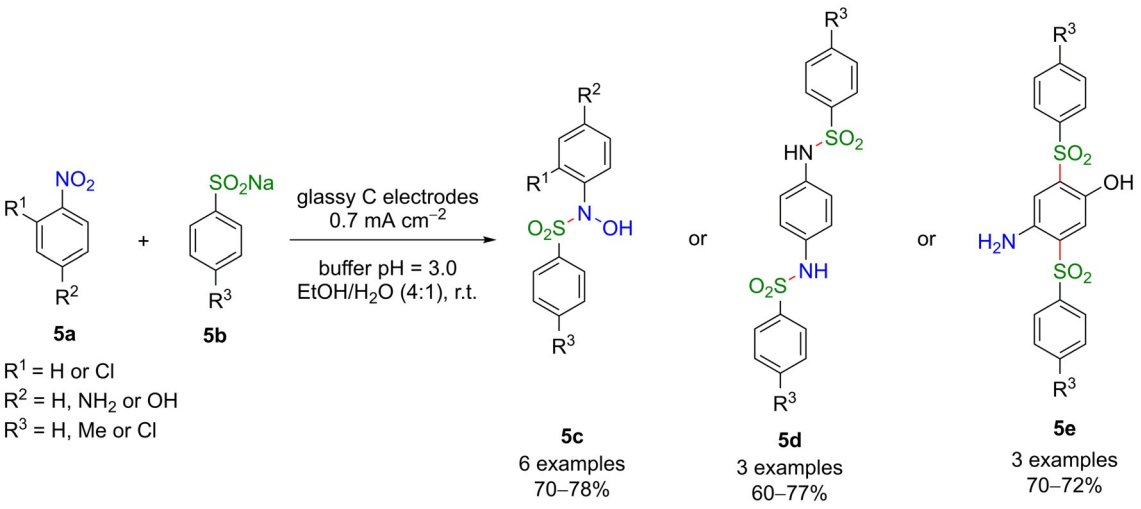


Scheme 4. Selected examples of using "redox-flow" for generating nitroso groups for the formation of various derivatives.

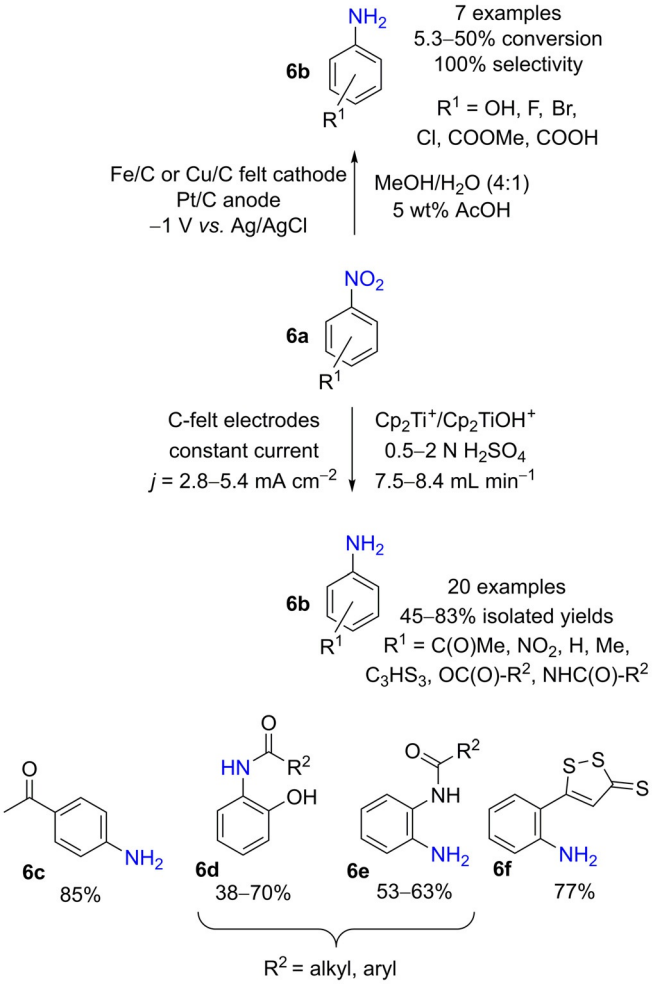
the formation of azoxy compounds and lower the yields. With this protocol, they could isolate several nitroso derivatives of arenes,[19] 4-nitrosophenyl-substituted *meso*-porphyrin derivatives,[20] 2-nitrosobenzoic acids (**4d**),[21] ferrocene nitrosoaryl derivatives,[22] and nitroso derivatives of *para*-nitrophenylserinols (**4e**).[23] In some cases, they reacted the obtained nitroso derivates with sodium *para*-toluenesulfinate which, in an ex-cell process afforded, for example, the corresponding *N*-sulfonylated phenylhydroxylamine derivatives of serinol derivatives (**4f**). Reactions that resulted in cyclized products during the electrolysis or in an ex-cell process are discussed in detail in Section 2.2.

The idea of synthesizing *N*-sulfonylated phenylhydroxylamines (Scheme 5, **5c**) was expanded and improved some years later by the group of Nematollahi. They mixed nitrobenzene derivatives (**5a**) and sodium salts of arylsulfinic acids (**5b**) during the electrolysis and carried out the reduction also under constant current conditions.[12] Different types of *N*-sulfonated phenylhydroxylamines, but also sulfonamides (**5d**) and arylsulfones (**5e**) were obtained, depending on the nature of the starting nitro compound and its substitution pattern as displayed in Scheme 5. Later, they applied the same strategy using similar reaction conditions for the synthesis of *N*-sulfonylated derivatives, but this time starting from dinitrobenzenes.[13] Instead of using constant current, in this report, they controlled the potential that allowed the selective synthesis of either *N*-hydroxy-*N*-(4-nitrophenyl) or *N*-(4-amino-3-(phenylsulfonyl)phenyl) benzenesulfonamide derivatives.

Moinet and co-workers showed that by continuously electroregenerating the redox mediator Cp_2Ti^+/Cp_2TiOH^+ in an aqueous-organic biphasic system, nitroarenes (Scheme 6, **6a**, *lower part*) can be efficiently reduced straight to anilines (**6b**). In their system, Cp_2TiOH^+ in an aqueous layer is regenerated to Cp_2Ti^+ in a flow-cell that operates under constant current conditions. The actual reduction of nitroarene to aniline takes place in dichloromethane or toluene in an ex-cell process with 45–83% yields.[24] The reduction was proposed to proceed through an inner-sphere mechanism. Interestingly, the reduction tolerates other oxygen-containing functional groups such as ketones (**6c**) and also sulfur-containing dithiole-3-thione



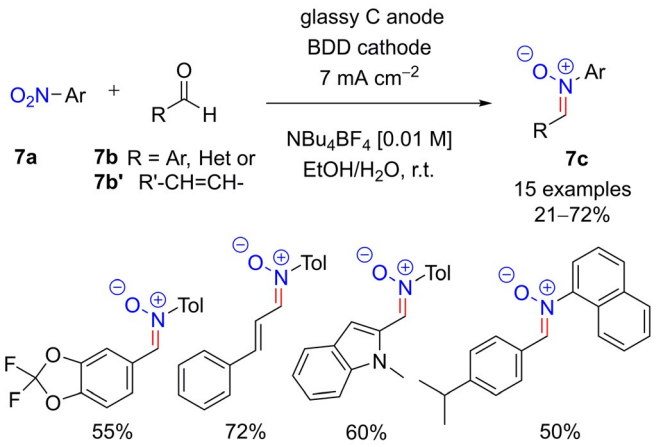
Scheme 5. Electrosynthesis of *N*-sulfonylated phenylhydroxylamines, sulfonamides, and aryl sulfones from nitrobenzenes.



Scheme 6. Electroreduction of aryl nitro compounds to anilines using flow electrolysis cells.

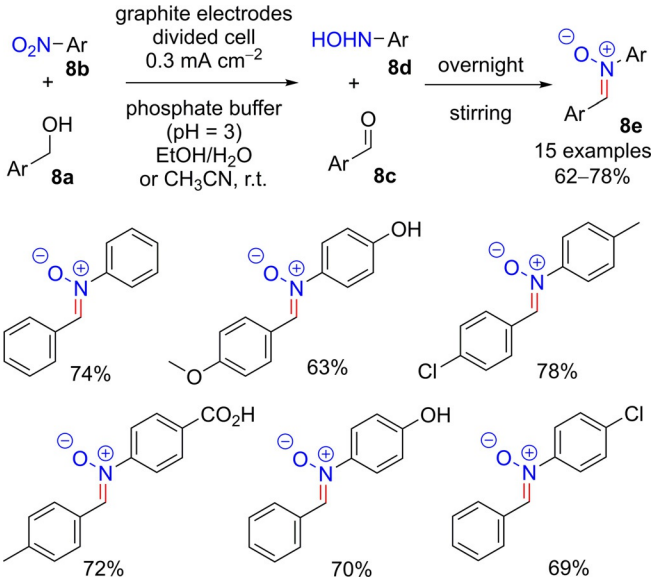
as a substituent (**6f**).[25] Furthermore, they could later reduce *ortho*-substituted derivatives such nitroaryl esters, carbonates, amides, and carbamates which resulted in anilines (**6e**) but also in some cases in rearranged products (**6d**).[26] Moreover, Gultyai and coworkers used $TiCl_3$ as a redox mediator in the electroreduction of 1-ethyl-4-nitro-3-cyanopyrazole to 1-ethyl-4-amino-3-cyanopyrazole in a divided cell with a lead cathode.[27] Recently, nitroarene reduction has also been studied in a divided cell under potentiostatic control using a flow cell in the absence of a mediator (Scheme 6, *upper part*).[28] Noteworthy, an electrochemical potential in a flow cell has a limited meaning, since a potential distribution forms over the path of the flow cell due to substrate depletion, etc. However, in this reduction, Fe/C or Cu/C felt cathodes are used. They are prepared by immobilizing an appropriate metal salt to a slightly air oxidized carbon with an incipient wetness method. Conversions were in the range of 5–50%, but the selectivity of the reactions in all cases was reported to be high as 100%. The authors calculated that by scaling, >500 kg/y production should be easily achievable.

The Waldvogel group has also used the reduction of the nitro moiety (Scheme 7, **7a**) in order to synthesize nitrones (**7c**) with a very simple electrochemical set-up. Under galvanostatic conditions in an undivided cell, several aryl nitro derivatives could be reduced in the presence of enals (**7b′**) and aromatic aldehydes (**7b**) to yield directly nitrones. The nitro group is reduced to the corresponding hydroxylamine, undergoing *in situ* condensation with the aldehyde. Noteworthy is the use of green conditions: $EtOH/H_2O$ is used as a solvent mixture, electrodes are carbon-based and the reduction was performed for the first time in the absence of metals.[29] When the reaction was scaled up to an ordinary 200 mL beaker-type cell, 2.5 g of nitrone were obtained by a very simple to conduct protocol.



Scheme 7. Metal-free electrochemical method for the formation of nitrones from nitro derivatives. BDD = boron-doped diamond.

Finally, another nitrone (Scheme 8, **8e**) synthesis using electrochemistry in a divided cell was published. In this case, benzylic alcohols (**8a**) and aryl nitro groups (**8b**) are used as starting materials in a parallel-type electrosynthesis.[30] In the anodic compartment, benzylic alcohols are oxidized to aldehydes (**8c**) and in the cathodic half-cell, nitro derivatives are reduced to hydroxylamines (**8d**). Once the electrolysis is completed, the contents of both chambers are mixed and stirred overnight to yield nitrones. Low current densities were needed for the process to obtain good yields. (Scheme 8).

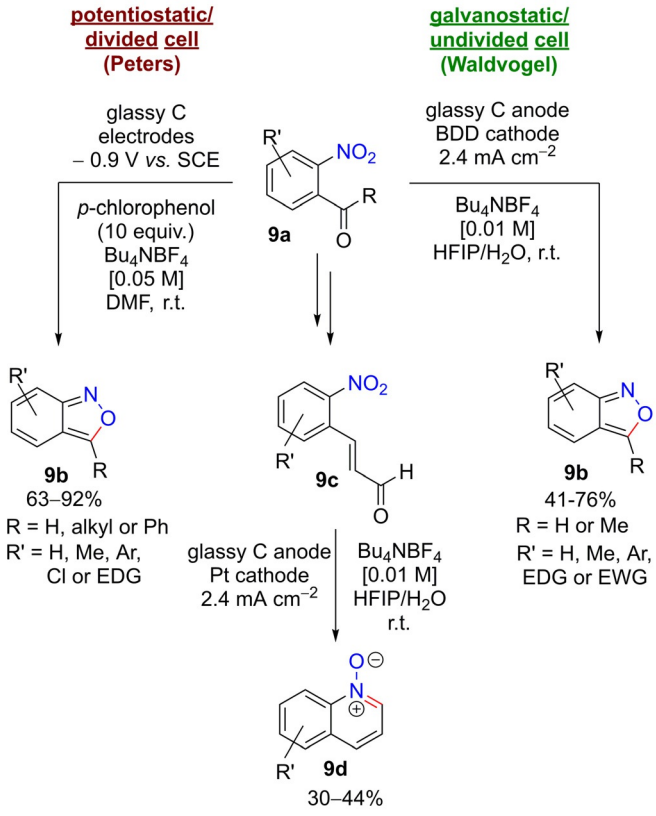


Scheme 8. Metal-free and electrochemical method for the formation of nitrones from nitro derivatives.

2.2 Intramolecular Reactions: Synthesis of Heterocycles

The presence of the nitro moiety at different positions within larger molecules has allowed the electrochemical synthesis of several nitrogen-containing heterocycles.

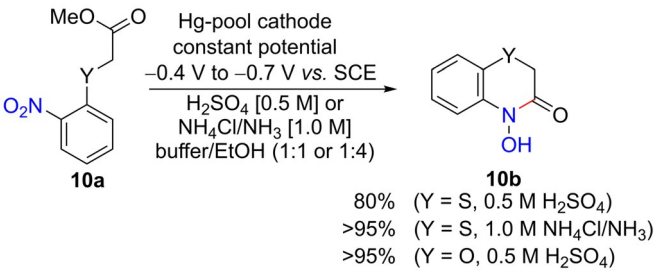
Regarding the previous electrolytic transformation in which a synthesis of nitrones *via* hydroxylamine formation was performed, an analogous intramolecular version of the procedure was described that allowed access to different types of heterocycles. Although the reduction of 2-nitrobenzaldehydes was known electrochemically with sacrificial lead cathodes,[31] very recently the groups of both Peters and Waldvogel have described protocols for the synthesis of 2,1-benzoxazoles (Scheme 9, **9b**). Referring to the report of Peters, the reaction is performed under potentiostatic conditions and in a divided cell, using 4-chlorophenol (10 equiv.) as an additive (Scheme 9, *left side*).[32] No scale for this electrosynthesis was reported. In the second case, galvanostatic conditions in an undivided cell were described by Waldvogel and coworkers (Scheme 9, *right side*). The latter approach avoids the use of malodorous additives and also allowed the synthesis of quinoline *N*-oxides (**9d**, Scheme 9, *middle*), offering an alternative to obtain



Scheme 9. Electrosynthesis of 2,1-benziosxazoles and quinoline *N*-oxides.

two different heterocycles from one common starting point. In addition, the important electron-withdrawing groups were introduced to the scope of this reaction for the first time. The practical nature of this protocol was demonstrated by scale-up of the whole electrosynthesis.[33]

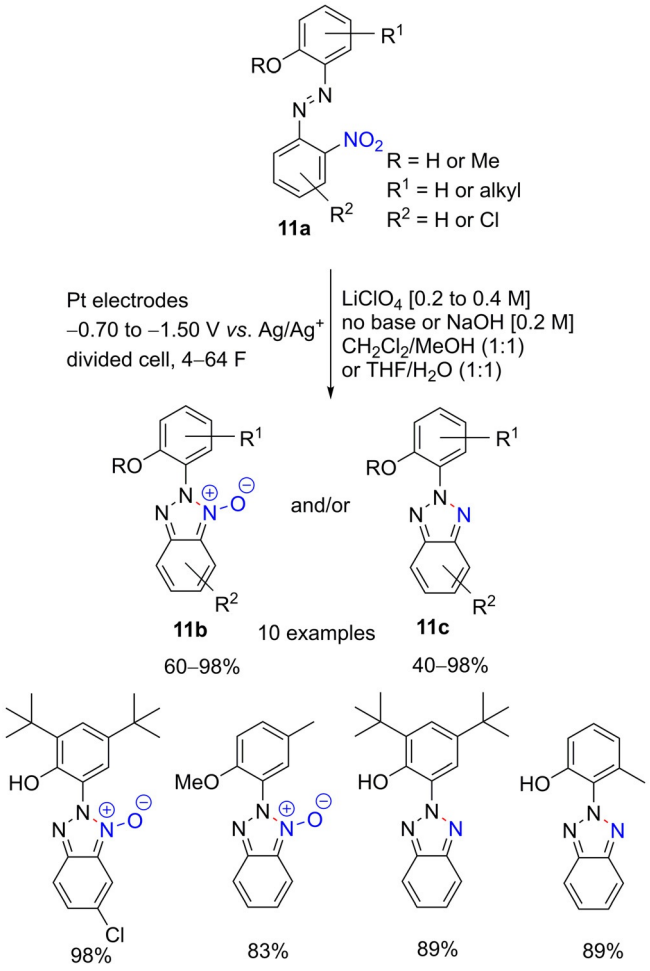
Several research groups have focused on the synthesis of 2*H*-4-hydroxy-1,4-benzoxazin-3-one (Scheme 10, **10b**) and 2*H*-4-hydroxy-1,4-benzthiazin-3-one from *ortho*-nitrophenoxyacetic acid and 2-(*ortho*-nitrophenylthio)acetic acid or from their methyl esters (**10a**). Early controlled potential attempts with free carboxylic acids using Hg cathodes in an HCl electrolyte in divided cells resulted only in deoxygenated 7-chloro derivatives in 70–71% yields.[34] Instead, 2*H*-4-hydroxy-1,4-benzthiazin-3-one could be obtained in an 80% yield when the electrolysis was carried out in a mixture of sulfuric acid (0.5 M) and ethanol (1:4 v/v) in a divided cell using a mercury pool cathode under potentiostatic control.[35] However, in this case, 20% of 7-ethoxy derivative was formed as a by-product. Finally, substituting 0.5 M H_2SO_4 for 1.0 M NH_4Cl/NH_3 gave rise to 2*H*-4-hydroxy-1,4-benzthiazin-3-one in quantitative yield.[36] Similarly, 2*H*-4-hydroxy-1,4-benzoxazin-3-one was obtained from a mixture of sulfuric acid (0.5 M) and ethanol (1:1 v/v) in quantitative yield.[37] All electrolysis reactions proceeded through hydroxylamine intermediates.



Scheme 10. Electrosynthesis of 2*H*-4-hydroxy-1,4-benzoxazin-3-one and 2*H*-4-hydroxy-1,4-benzthiazin-3-one.

In addition, Trazza and co-workers were able to synthesize benzimidazoles and benzimidazole *N*-oxides from *ortho*-nitroanilides with a mercury pool cathode in divided cells with a constant potential.[38] Later on, they also electroreduced *N*-benzyl-*N*-nitrosoanthranilic acids to 3*H*-1-benzyl-1,2-dihydroindazol-3-one with similar conditions.[39]

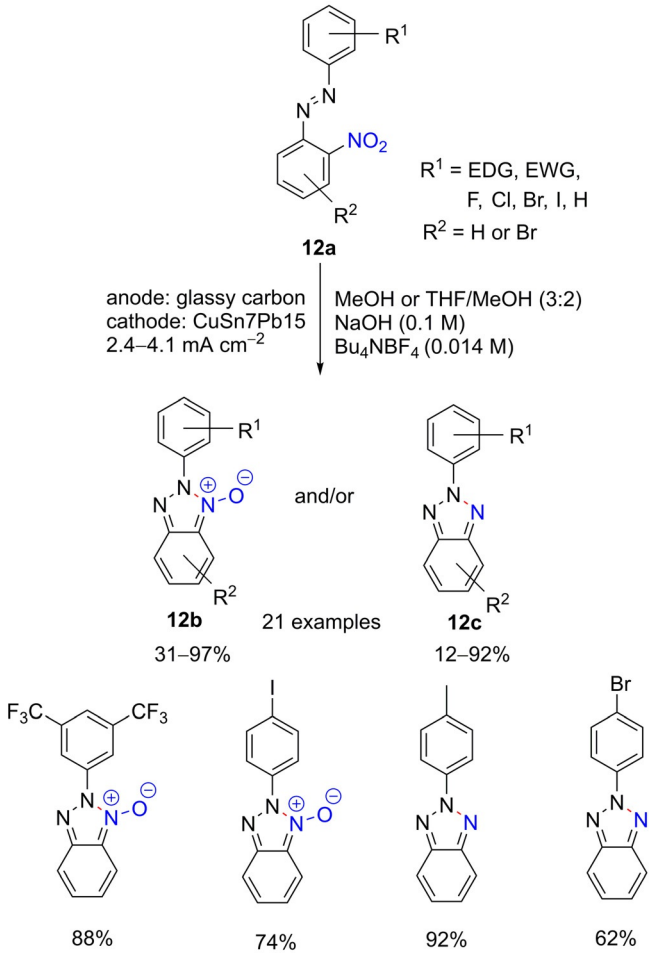
At the beginning of the century, Kim and co-workers synthesized electrochemically 2*H*-2-arylbenzo[*d*]-1,2,3-triazoles (Scheme 11, **11c**) and their corresponding *N*-oxides (**11b**) from 2-nitrophenylazo derivatives (**11a**).[40] Using the potentiostatic mode and a divided cell, the conditions varied a lot depending on the substituents at the aryl rings, which were limited to some specific functional groups, with low current efficiencies. However, the synthesis of the triazole could be modulated, in some examples, by adding NaOH to the reaction mixture.



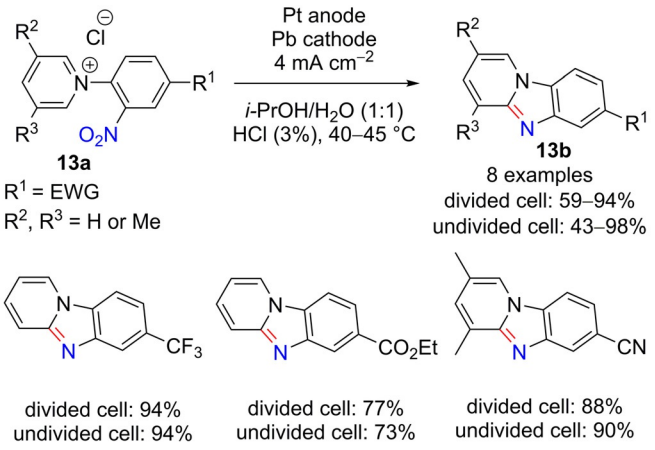
Scheme 11. Formation of 2-aryl-2*H*-benzo[*d*]-1,2,3-triazoles and their corresponding *N*-oxides under potentiostatic conditions.

Most recently, Waldvogel and co-workers demonstrated that both 2*H*-2-arylbenzo[*d*]-1,2,3-triazoles (Scheme 12, **12c**) and their *N*-oxides (**12b**) are accessible in a very simple undivided cell under galvanostatic conditions with a leaded bronze cathode from **12a**.[41] In this protocol, the Bu_4NBF_4 as supporting electrolyte could be omitted. The key to this simple electrotransformation is the use of leaded bronzes which can be considered as a significantly more stable alternative to lead cathodes.[42,43,44]

The group of Gultyai has also employed reduction of the nitro group for the synthesis of heterocycles. They published a methodology for the formation of pyrido[1,2-*a*]benzimidazoles (Scheme 13, **13b**) by reducing a nitro group (**13a**) electrochemically.[45] Firstly, *ortho*-chloronitrobenzenes reacted with pyridine



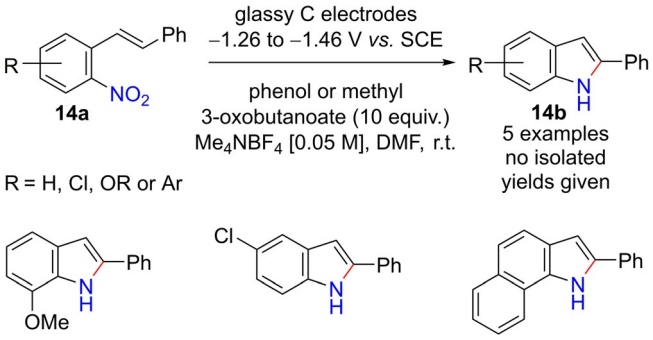
Scheme 12. Selective formation of 2-aryl-2*H*-benzo[*d*]-1,2,3-triazoles and their corresponding *N*-oxides under constant current conditions.



Scheme 13. Formation of pyrido[1,2-*a*]benzimidazoles using electrical current.

derivatives to obtain the Zincke-type precursors for this reaction. After reductive transformation of the nitro group into hydroxylamine, pyrido[1,2-*a*]benzimidazoles were obtained by an attack of the N atom to the pyridine ring and elimination of water. They utilized Pb as a cathode under constant current conditions, with a small amount of acid that serves as a proton donor, improves conductivity, and promotes the water elimination. Both divided and undivided cells proved to be valid for the reaction, with similar yields in both set-ups. This might be rationalized by the cationic nature of the substrates. The reaction and some examples are displayed in Scheme 13. Later, they showed that by using $SnCl_2$ as a redox mediator the current density can be increased which leads to shorter reaction times.[46] It is noteworthy that Zincke salts can be prepared by electrosynthetic approaches as well.[47]

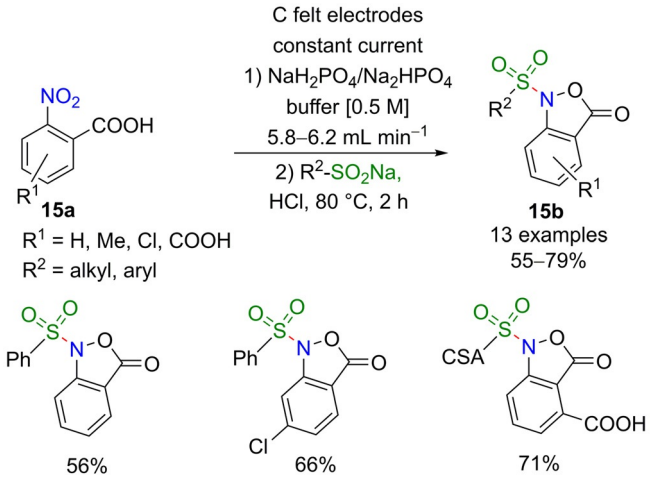
There is another example, which was carried out by the group of Peters. Different *otho*-nitrostyrenes (Scheme 13, **14a**) were reduced to substituted 1*H*-indoles (**14b**).[48] A proton donor was demonstrated to be useful for the final conversion to the indole, since the reduction is much more difficult in its absence (Scheme 14). The authors reported the experimental conditions and the isolation of some of the indoles, but unfortunately not their yields. Representative examples are also depicted in Scheme 14.



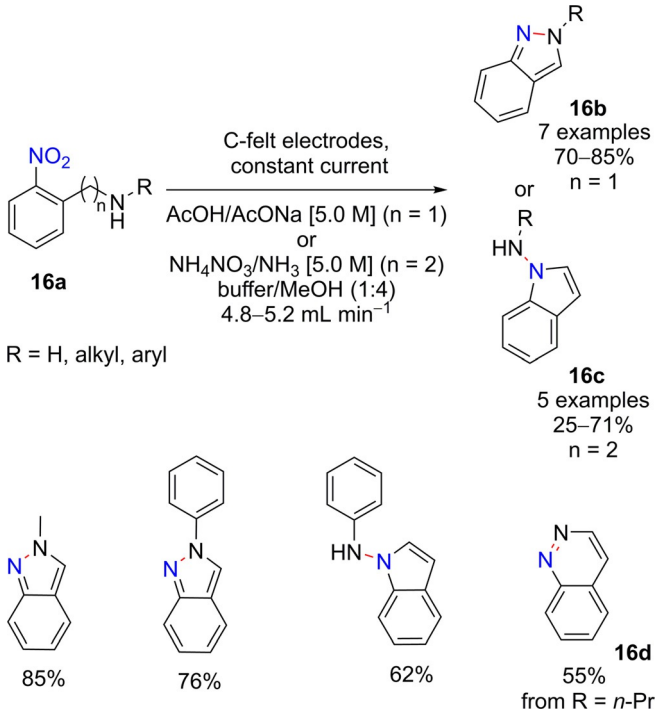
Scheme 14. Intramolecular cyclization for the electrosynthesis of some 1*H*-indoles.

Moinet and co-workers used their "redox-flow" method for reducing nitroarenes to nitroso compounds in such a way that the intermediates cyclize either directly or in an ex-cell process to afford different heterocycles. For example, they synthesized sulfonyl-2,1-benzisoxazol-3(1*H*)-ones (Scheme 15, **15b**) from 2-nitrobenzoic acid derivatives (**15a**).[21] In this reaction, a nitro group is reduced to the corresponding nitroso compound that then reacts with an alkyl- or arylsulfinate salt to generate *N*-alkyl- or *N*-arylsulfonylhydroxylamines. These intermediates cyclize to the end products in an ex-cell process at 80 °C in 2 h.

When 2-nitrobenzylamines (Scheme 16, **16a**) are used as substrates under the "redox-flow" conditions, 2-substituted 1*H*-indazoles (**16b**) are obtained in 70–



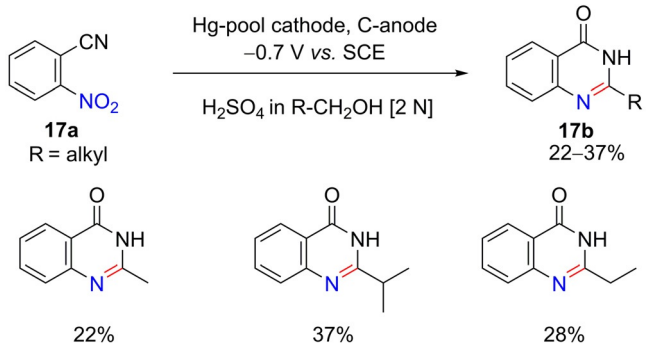
Scheme 15. Synthesis of sulfonyl-2,1-benzisoxazol-3(1*H*)-ones from 2-nitrobenzoic acid. CSA = (1*S*)-(+)-10-camphorsulfonic acid.



Scheme 16. Intramolecular cyclization for the electrosynthesis of 1*H*-indazoles and 1-aminoindoles.

85% yields.[49] The reaction was found to tolerate both alkyl and aryl substituents at the N-2 position. In contrast, when 2-(*ortho*-nitrophenyl)ethylamines are used as starting materials, the electroreduction produces 1-aminoindoles (**16c**) in 25–71% yields.[50] Interestingly, also 1,4-dihydrocinnoline (55%) and cinnoline (**16d**, 55%) were obtained with certain substrates.

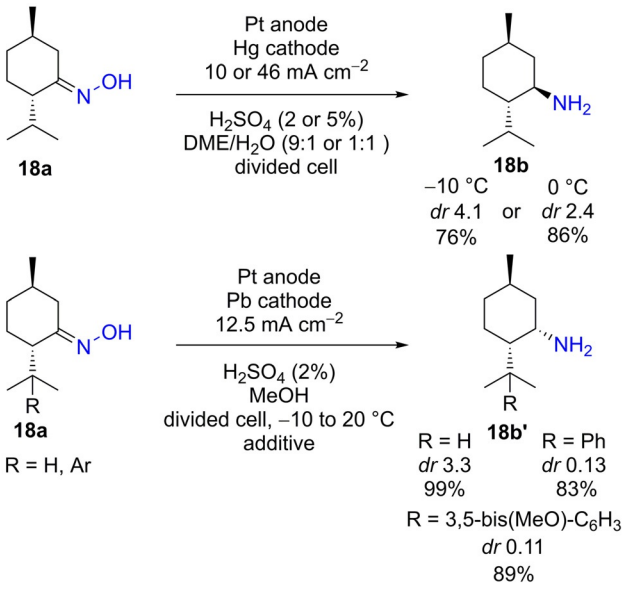
2-Nitrobenzonitriles (Scheme 17, **17a**) have been converted to 3*H*-2-alkyl-4-quinazolinones (**17b**) using a mercury pool cathode and carbon anode in an undivided cell under potentiostatic control.[51] In the reaction, an alcoholic solvent is oxidized at the anode to an aldehyde that eventually reacts with a hydroxylamine intermediate that is produced at the cathode from the reduction of 2-nitrobenzonitrile.



Scheme 17. Intramolecular cyclization of 2-nitrobenzonitriles.

3 Oximes

The oxime is another common functional group that contains an N–O bond. Oximes can be reduced with a total of four electrons to the corresponding amines as there are two reducible groups: the C=N double bond, which would need two electrons, and the bond between the oxygen and the nitrogen, which would need another two. As in the case of the nitro moiety, different electrochemical studies were carried out, noticing a different behavior in aprotic and protic solvents. In protic media, reduction to the imines occurs first. Indeed, oximes are most reliably reduced in acidic media.[52] In terms of synthetic usefulness, oximes were employed by Waldvogel and co-workers for a stereodivergent electrochemical formation of optically pure menthylamines (Scheme 18, **18b**, **18b′**).[53] Taking advantage of the chirality of the starting molecule (**18a**), the oxime could be reduced to the amine, proving that the cathode material has an influence on the selectivity and the obtained diastereomer (R = H). In addition, both diastereoisomers could be later separated by taking advantage of the different solubilities of the hydrochloric salts in *t*-BuOMe. Years later, bulkier oximes were tested (R = Ar), affording better results, when applying the same methodology.[54] In all of the examples, galvanostatic conditions in divided cells were applied. In order to enhance energy and current efficiency, specific supporting electrolytes were added in small amounts to the acidic media which tremendously suppressed cathode corrosion of the lead and parasitic hydrogen evolution.[55] Other cathodic materials with a high overpotential for hydrogen evolution but stability towards

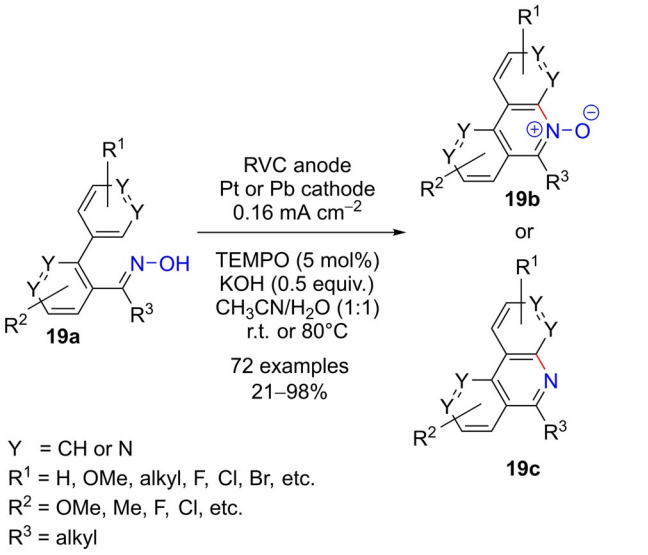


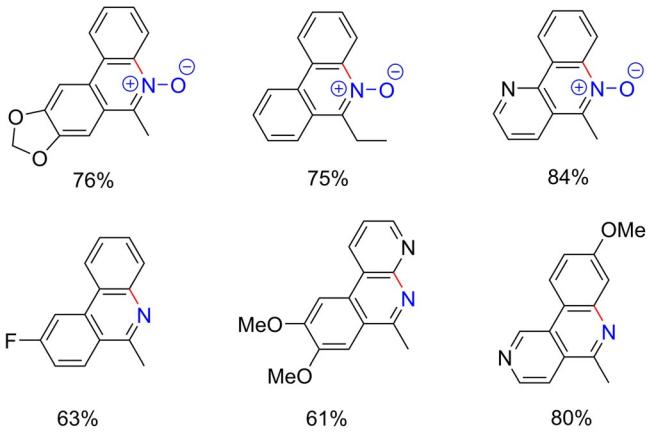
Scheme 18. Electroreduction of oximes to chiral amines. In the lower part, the stereoselectivity with R = Ar is inverted.

cathodic corrosion like BDD have been investigated as well, but they show poorer performance.[56]

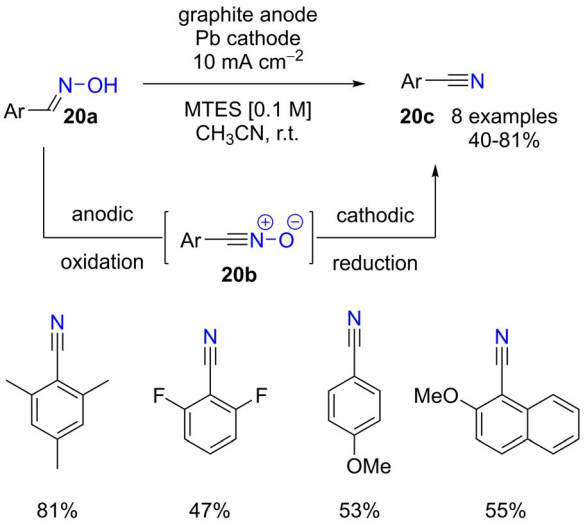
Oximes can also be partially reduced in a two-electron process. Xu and co-workers applied this concept in the synthesis of polycyclic nitrogen heteroaromatic compounds (Scheme 19, **19c**) and their corresponding *N*-oxides (**19b**), through electrochemical C–H functionalization of biaryl ketoximes (**19a**).[57] Undivided cells were employed under galvanostatic conditions at very low current densities. However, the most important feature was the influence of the cathodic material on the reaction outcome. Using Pt, the reaction stopped at the formation of the *N*-oxide, whereas when Pb was employed, N–O bond cleavage occurred, yielding the nitrogen-containing heteroaromatic molecules. The scale-up of the electrolysis could be conducted up to a decagram scale.

Finally, another aspect that aromatic oximes (aldoximes) present is that they not only can be reduced but also oxidized to the corresponding nitrile oxides. Nitrile oxides are usually used as valuable components for 1,3-dipolar cycloadditions, but cleavage of the N–O bond is also possible. This consecutive paired process was first described by Shono et al. They claimed to employ chloronium species as mediators.[58] However, moderate yield and fairly low current efficiencies indicate other electrolytic processes. Indeed, in our hands, the major reactivity observed was the massive Pt corrosion. By means of contemporary screening techniques, more effective, cheaper, and stable electrodes were identified. This domino oxidation–reduction sequence was conducted by Waldvogel and co-workers to transform aldoximes (Scheme 20, **20a**) into nitriles (**20c**). Initially, the oxime was oxidized at



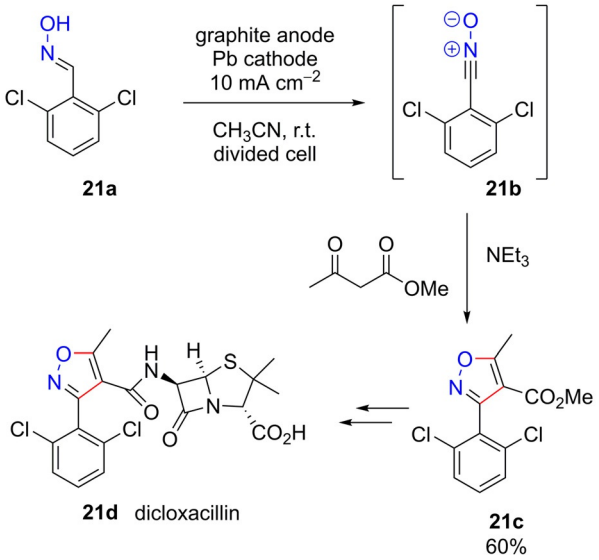


Scheme 19. Electrochemical C–H functionalization of biarylketoximes for the formation of polycyclic heteroaromatic nitrogen compounds.



Scheme 20. Redox domino process for the transformation of oximes into nitrile derivatives. MTES = methyltriethylammonium methyl sulfate.

the graphite anode to nitrile oxide (**20b**) that was immediately reduced to the stable nitrile moiety at the Pb cathode. Galvanostatic conditions and an undivided cell were utilized.[59] Later, a flow version of this transformation was developed, both in undivided and divided cells.[43] In the flow electrolysis cell, leaded bronze (15% Pb) was applied since this material behaves chemically similar to Pb but exhibits significantly enhanced mechanical stability.[44] In the narrow gap cells, the electrolysis to nitriles was conducted in an acetonitrile-water mixture without the necessity of supporting electrolytes. In particular for haloaldoximes, this resulted in significantly higher yields (62%) compared to the batch-type approach (41%). When going for the nitrile oxide, a separator must be employed and the use of an additional supporting electrolyte is indispensable. The formal synthesis of dicloxacillin (Scheme 21, **21d**), a penicillin derivative, was conducted, whereby the isoxazole (**21c**) building block was synthesized from 2,4-dichlorobenzaldoxime (**21a**) *via* dehydration to its nitrile-oxide (**21b**) that underwent a 1,3-dipolar cycloaddition in 60% yield.[43]

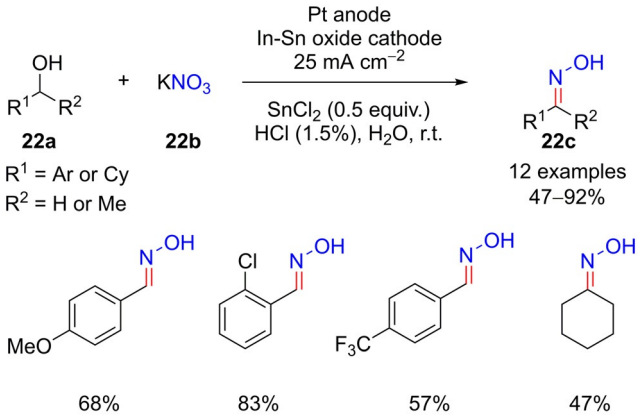


Scheme 21. Process for the transformation of oximes into nitrile oxides and subsequent formal synthesis of dicloxacillin.

4 Other Functionalities

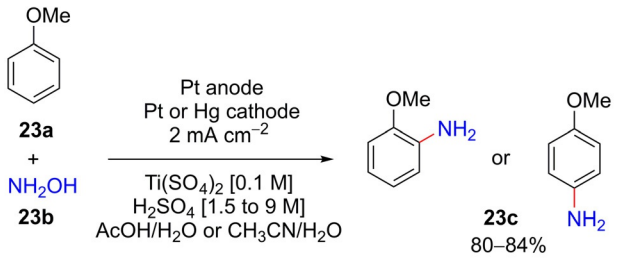
Although nitro and oxime functionalities have been the most prolific groups in the described electrochemical reductions, there are other examples in which molecules containing N–O bonds were also successfully converted in electrochemical synthesis.

Wang and co-workers established a methodology in which nitrate salts (Scheme 22, **22b**) could be reduced to hydroxylamine in order to synthesize benzyl oximes (**22c**).[60] In this case, alcohols (**22a**) were employed as starting materials and $SnCl_2$ was used as a mediator in catalytic amounts (50 mol%). Alcohols were oxidized at the Pt anode, forming carbonyl compounds, while Sn(II) was reduced at the cathode to form Sn(0), which was the species responsible for reduction of the nitrate to the hydroxylamine. Rather high current densities in an undivided cell were used.



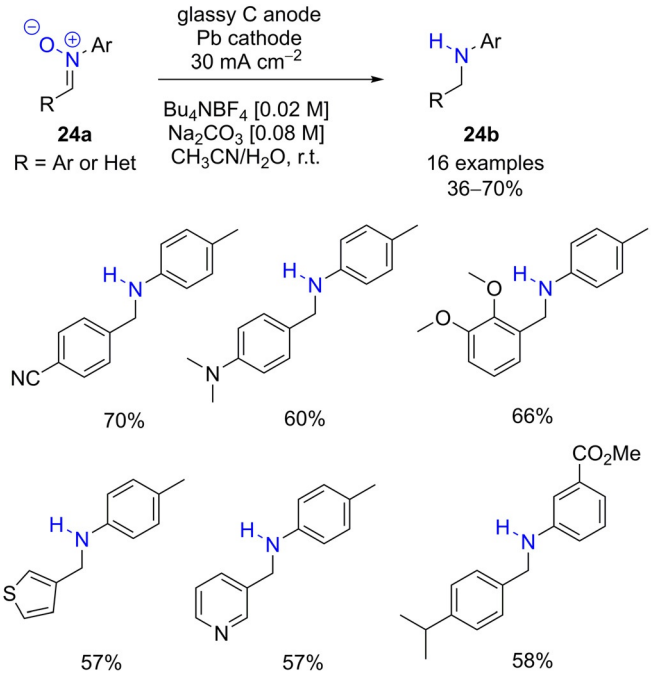
Scheme 22. Formation of oximes from alcohols and potassium nitrate.

Lysitin and co-workers used hydroxylamine (Scheme 23, **23b**) as a reagent for the amination of aromatic compounds.[61] They successfully aminated anisole (**23a**),[61a–i] benzene,[61j–q] chlorobenzene,[61r] and anilines.[61s,t] In all cases, strong acidic conditions were mandatory for the reactions to take place. Galvanostatic conditions and metallic cathodes were employed for the reduction of Ti(IV) salts to Ti(III), which allowed the reduction of hydroxylamine to the ammonium radical cation and subsequently amination of the aromatic ring (**23c**). The current yields of over 100% indicate chain mechanisms in these reactions.



Scheme 23. Amination of anisole with hydroxylamine as the nitrogen source.[61a–c]

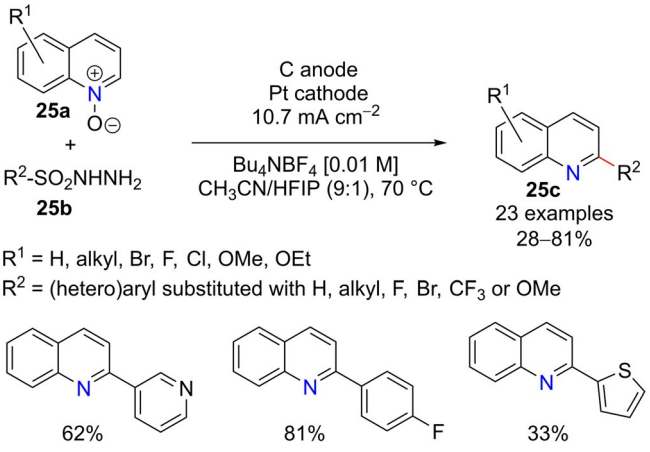
Waldvogel and co-worker described a methodology for the electrosynthesis of amines (Scheme 24, **24b**) starting from nitrones (**24a**). This 4-electron reduction was carried out under constant current conditions in an undivided cell. A broad scope of aromatic and heteroaromatic amines, containing a large variety of



Scheme 24. Electrochemical one-pot reduction of nitrones to amines.

functional groups, was accessible. The utilization of electric current allowed for the first time the avoidance of two different reagents for this reduction, something mandatory if this transformation were performed with classical chemical reagents.[62]

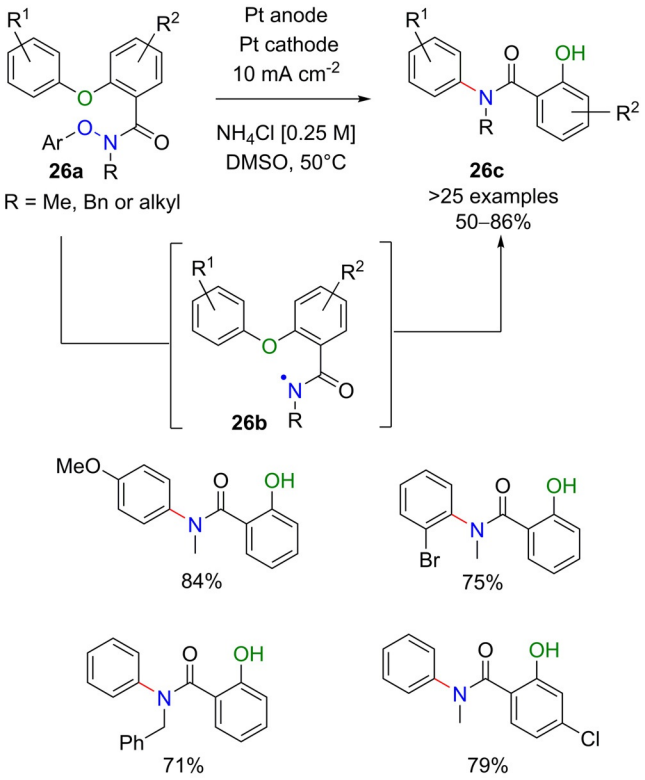
Lei and co-workers recently reported a protocol where quinoline *N*-oxides (Scheme 25, **25a**) are reacted with different aryl radicals to afford C-2 arylated quinolines (**25c**).[63] The radicals are generated by oxidation of arylsulfonylhydrazides (**25b**) and the resulting intermediate containing the N–O bond is then subsequently reduced at the cathode to afford the



Scheme 25. Electrochemical deoxygenative C-2 arylation of quinoline *N*-oxides.

final product. The electrosynthesis was performed with graphite rod anode and Pt plate anode under constant current conditions in a mixture of 9:1 CH_3CN/HFIP at 70 °C. They could synthesize both aryl and heteroaryl derivatives of quinoline *N*-oxides.

Finally, Guo and co-workers reported a radical Smiles rearrangement under galvanostatic conditions in an undivided cell.[64] They generated an intermediate amidyl radical (Scheme 26, **26b**) from the cleavage of the N–O bond of **26a** at the Pt cathode, which led to the final product (**26c**). Various hydroxylamine (**26a**) derivatives bearing different substituents were demonstrated to be suitable in this transformation.



Scheme 26. Radical Smiles rearrangement *via* an intermediate amidyl radical.

5 Conclusions

The recent advances in electrochemical reduction of substrates containing N–O bonds, as reviewed herein, reveal undoubtedly that it is a very robust and versatile strategy for obtaining various kinds of high value-added products. The essence of its synthetic power lies, perhaps, in the fact that by a clever variation of reaction conditions, electrodes, and mediators, the reactivity can be easily controlled for generating intermediates that are not easily obtained otherwise. Lately, the reductive electrochemistry has been overshadowed by the recent successes in oxidative electro-

synthetic methods. In our opinion, research on the reductive protocols and, in particular, those involving N–O bonds, should be regarded as an important part of electrifying organic synthesis. Despite the advances made, new reductive electroconversions are still waiting to be found.

Acknowledgements

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