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Review

Recent Advances in $C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$ Bond Formation through Cathodic Reactions: Reductive and Convergent Paired Electrolyses

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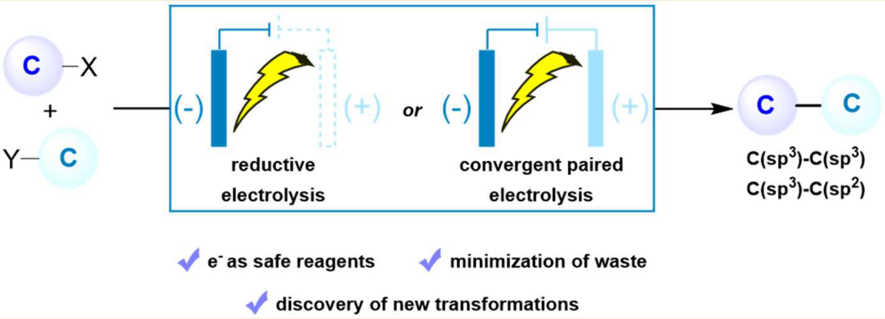

ABSTRACT: The formation of $C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$ bonds is one of the major research goals of synthetic chemists. Electrochemistry is commonly considered to be an appealing means to drive redox reactions in a safe and sustainable fashion and has been utilized for C−C bond-forming reactions. Compared to anodic oxidative methods, which have been extensively explored, cathodic processes are much less investigated, whereas it can pave the way to alternative retrosynthetic disconnections of target molecules and to the discovery of new transformations. This review provides an overview on the recent achievements in the construction of $C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$ bonds via cathodic reactions since 2017. It includes electrochemical reductions and convergent paired electrolyses.

KEYWORDS: *electrosynthesis, electrochemical synthesis, C−C bond formation, electroreduction, convergent paired electrolysis, cathodic reaction, carbon-centered radical, electrocatalysis*

1. INTRODUCTION

$C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$ bonds are inherently omnipresent in most natural and synthetic organic molecules, rendering their formation a central task in organic synthesis. In recent decades, intensive efforts have been devoted to develop efficient C−C bond formation, among which radical-based transformations offer a powerful alternative approach to the traditional polar reactions. In this context, electrochemistry has recently gained renewed interest as a safe and environmentally friendly technique to generate carbon-centered radicals. By carefully controlling the amount of charge and the cell potential, substrates or catalysts can be selectively activated to prohibit unwanted side reactions such as overoxidations or over-reductions that can easily occur with more classical chemical reaction conditions.[1−6] In electrosynthesis, three different approaches can be distinguished: (i) net oxidative anodic electrolysis whereby hydrogen evolution is the most frequent counter-reaction; (ii) net reductive cathodic electrolysis whereby a sacrificial reductant (typically a simple amine, the anode itself, or in few cases the solvent) is oxidized to counterbalance the process; (iii) redox neutral paired electrolysis during which two desirable half-reactions are taking place at both electrodes. As such, in each case, the use of hazardous or difficult to handle redox reagents is avoided. Compared to electro-oxidative methods, electrochemical synthesis employing a cathode material as the working electrode remains relatively less studied.[7] However, several successful approaches have recently been accomplished for the building of $C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$ bonds through cathodic reductions, allowing significant improvement of the previously established procedures as well as the discovery of new transformations. Although electrochemical organic synthesis was comprehensively surveyed by Baran et al. in 2017,[1] this review describes recent

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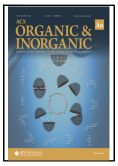


advances in C(sp^3)−C(sp^3) and C(sp^3)−C(sp^2) bond-forming reactions through cathodic transformations that have been reported since July 2017. It covers cathodic reductive processes as well as convergent paired electrolyses, whereby both cathode and anode materials are working electrodes. To aid the reader, electrochemical parameters—including cell type (divided or undivided), mode of electrolysis (constant current CCE or constant potential CPE electrolysis), and electrode compositions—are graphically depicted (Figure 1a). For instance, Figure 1b (left) displays a constant current electrolysis performed in an undivided cell with a carbone cathode and a magnesium anode, whereas Figure 1b (right) corresponds to a constant potential electrolysis in a divided cell with two platinum electrodes. In agreement with the proposed mechanism, a color code is employed to distinguish each fragments of the products. As such, turquoise, pink, and purple are utilized for the reactants that undergo a single-electron transfer (SET) reduction, a SET oxidation, and the attack of either a radical or a carbanion, respectively. Orange color is used for other reactants in multicomponent reactions. For example, in Figure 1c (left), radical R$^{1\bullet}$ **II** is produced at the cathode by SET reduction of reagent **I** and adds to the alkene **III** to form the purposed C−C bond. A second SET reduction of the resulting radical **IV** furnished anion **V**, which reacts with the electrophile E$^+$. As such, R^1 is drawn in turquoise, the alkene **III** in purple, and the electrophile E$^+$ in orange. Conversely, in Figure 1c (right), radicals R$^{1\bullet}$ **II** is formed at the cathode by SET reduction of reagent **I**, whereas radical R^2 **VIII** is generated at the anode by SET oxidation of reagent **VII**. Radicals **II** and **VIII** combine to form the C−C bond and yield product **IX**. As such, R^1 and R^2 are drawn in turquoise and pink, respectively. C(sp^3)−C(sp^3) and C(sp^3)−C(sp^2) bond-forming processes are discussed sequentially, and each part is divided according to the initial electrolytic event that has enabled the generation of either a C(sp^3) radical, carbanion, or radical anion.

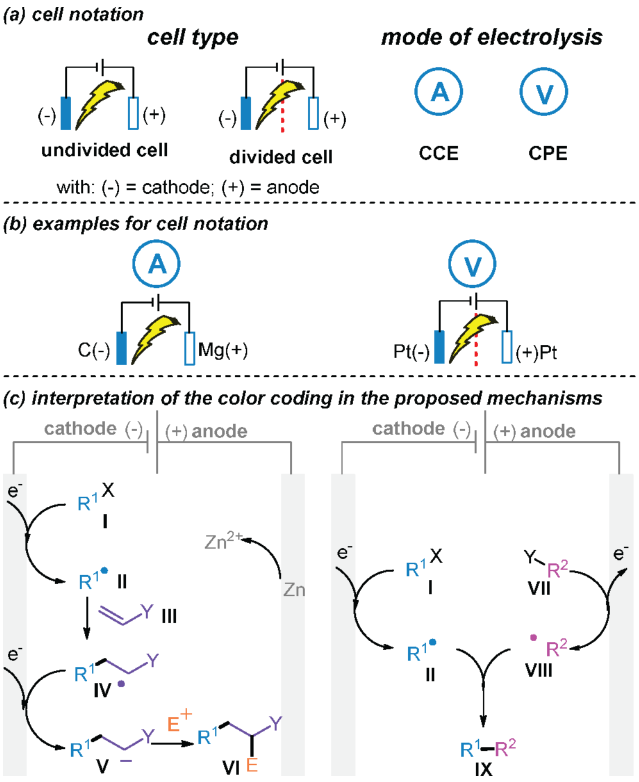


Figure 1. Cell notation and interpretation of the color coding used in the proposed mechanisms.

2. C(sp^3)−C(sp^3) BOND FORMATION

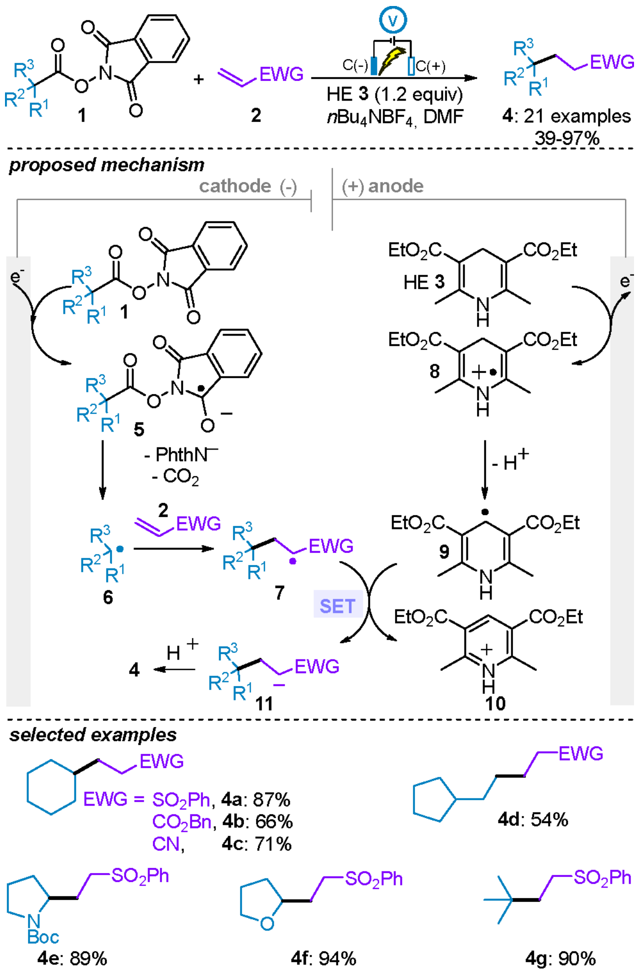
2.1. Reductive Decarboxylative Process

Carboxylic acids are ubiquitous in natural products and constitute therefore an ideal source of versatile C(sp^3)-centered radicals with structural diversity upon decarboxylative processes. Oxidative decarboxylation of aliphatic acids on platinum anodes is a well-known electrochemical transformation (Kolbe electrolysis) wherein the resulting alkyl radicals dimerize (homocoupling) to form a new C−C bond.[8] Even though heterodimerizations between two different carboxylic acids (mixed Kolbe electrolysis) or radical cyclizations have been reported,[9,10] the synthetic potential of the alkyl radical for the construction of C(sp^3)−C(sp^3) bonds was not fully leveraged in such oxidative conditions. Recently, the electroreductive decarboxylation of redox-active *N*-hydroxyphthalimide (NHP)[11] esters became a complementary method to produce alkyl radicals. While primary alkyl iodides and bromides exhibit two-electron reduction at −2.3 and −2.6 V vs SCE in DMF, respectively,[12,13] NHP esters derived from primary carboxylic esters feature single-electron reduction potential at −1.6 V vs SCE in DMF.[7] As such, the desired alkyl radical can be generated under relatively mild reaction conditions upon a rapid N−O fragmentation/decarboxylation sequence. In 2020, Wang et al. reported a decarboxylative Giese-type reaction between NHP esters **1** and various Michael esters **2** under constant potential electrolysis in an undivided cell using two inexpensive graphite electrodes.[14,15] A stoichiometric amount of the reductant Hantzsch ester (HE) **3** was necessary to reduce the cell potential, thus minimizing side reactions. The reaction conditions tolerated a wide range of NHP esters derived from primary, secondary, and tertiary carboxylic acids and various Michael acceptors such as vinyl sulfones and *α*,*β*-unsaturated ketones, esters, and amides. As depicted in Scheme 1, mechanistic investigations suggested that the transformation was initiated by cathodic reduction of NHP ester **1** to form the radical anion **5**. After a fragmentation/decarboxylation sequence, the resulting alkyl radical **6** underwent Giese-type addition to the Michael acceptor **2** and generated radical **7**. Meanwhile, anodic oxidation of the HE **3** furnished radical cation **8**. Subsequent deprotonation would trigger SET between **9** and **7** followed by protonation of anion **11** to yield the desired product **4**.

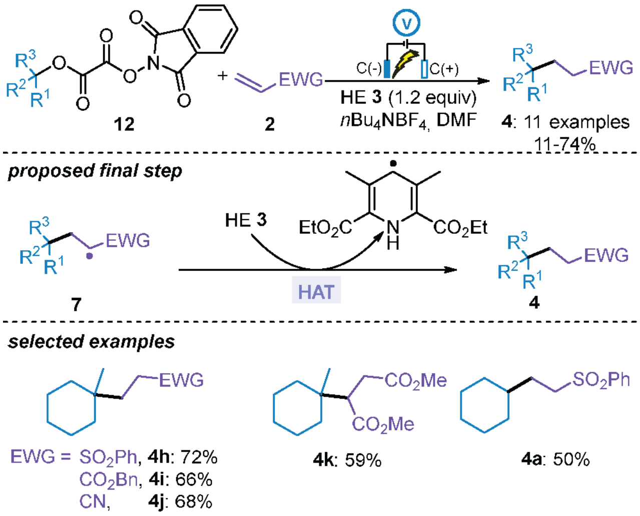
Interestingly, this transformation has been extended to the deoxygenative fragmentation of *N*-phthalimidoyl oxalates **12** derived from secondary and tertiary alcohols (Scheme 2). Herein, a hydrogen atom transfer (HAT) between in situ generated radical **7** and HE **3** was suggested at the end of the proposed mechanism.[15]

Recently, Baran, Blackmond, and Reisman et al. disclosed the radical coupling between redox active NHP esters **13** derived from primary carboxylic acids and aldehydes **14**.[16] Notably, only a catalytic loading of CrCl$_3$ was employed contrary to a previous chemical transformation which required 4 equiv of toxic chrome reagents.[17] This electrochemical reaction took place in an undivided cell using am inexpensive Al-based sacrificial anode and a Ni-foam cathode. Scheme 3 displays the proposed mechanism supported by a combination of detailed kinetic investigations, cyclic voltammetry, and UV−visible spectroelec-

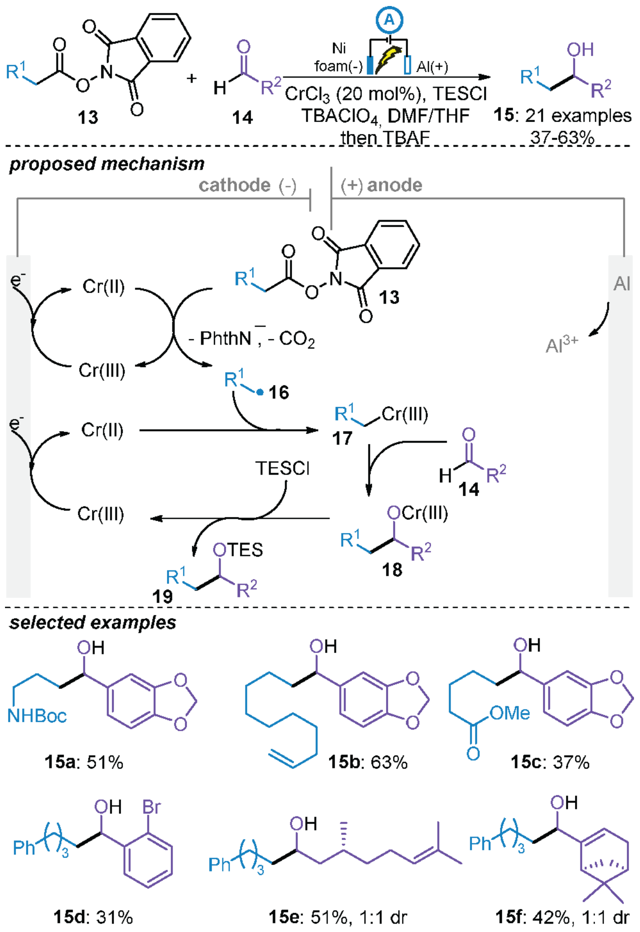
Scheme 1. Electroreductive Decarboxylative Giese-Type Reaction



Scheme 2. Electroreductive Deoxygenative Giese-Type Reaction



Scheme 3. Electroreductive Radical Coupling between NHP Esters and Aldehydes



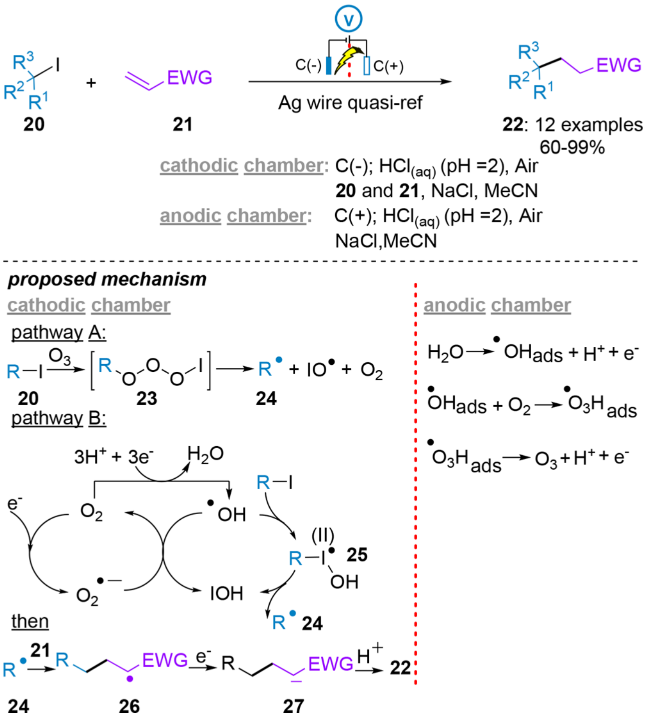
trochemistry. Cr(III) was initially reduced at the cathode to produce Cr(II) which in turn reduced NHP ester **13** to furnish alkyl radical **16**. Coordination with Cr(II) followed by addition to the aldehyde **14** gave rise to Cr alkoxide species **18**. Subsequent transmetalation with oxophilic triethylsilyl chloride (TESCl) regenerated Cr(III) catalyst and delivered protected aldols **19** in moderate to good yields. Aromatic as well as aliphatic aldehydes were well-tolerated.

2.2. SET Reduction of Alkyl Halides

Alkyl halides stand out as another important source of alkyl radicals via SET reduction. However, the direct electrolysis of alkyl halides requires highly reducing potentials that could lead to undesired side reactions. As such, indirect processes have been recently developed.

Wilden et al. have described a Giese-type addition of alkyl iodides **20** to activated alkenes **21** under constant potential electrolysis in a divided cell at mildly reducing potential (−1.0 V vs Ag quasi-reference electrode) in a buffered acidic semi-aqueous solvent system.[18] Water and—intriguingly—a catalytic amount of molecular oxygen were essential for the success of this reductive transformation. Primary, secondary, and tertiary alkyl iodides were well-tolerated. However, poor yield was achieved with alkyl bromides. Mechanistic studies identified in situ generated hydroxyl radical and ozone as mediators to generate the C(sp^3) radicals **24** from alkyl iodides **20**. The reaction was initiated by the oxidation of water in the anodic chamber to the hydroxyl radical, which in turn reacted with molecular oxygen to generate ozone. The latter slowly diffused in the cathodic chamber to activate the alkyl iodide **20** via unstable trioxide intermediate **23** that subsequently fragments into the corresponding alkyl radical **24**, $IO^•$ radical, and molecular oxygen. Under the slightly acidic and aerobic conditions, a second pathway produced even more alkyl radicals **24** via two interlocking cycles and the generation of unstable I(II) species **25** from hydroxyl radical OH$^•$. Addition of nucleophilic radical **24** to activated alkenes **21** generated radical **26** which underwent cathodic SET reduction and protonation to deliver the desired product **22** (Scheme 4).[19]

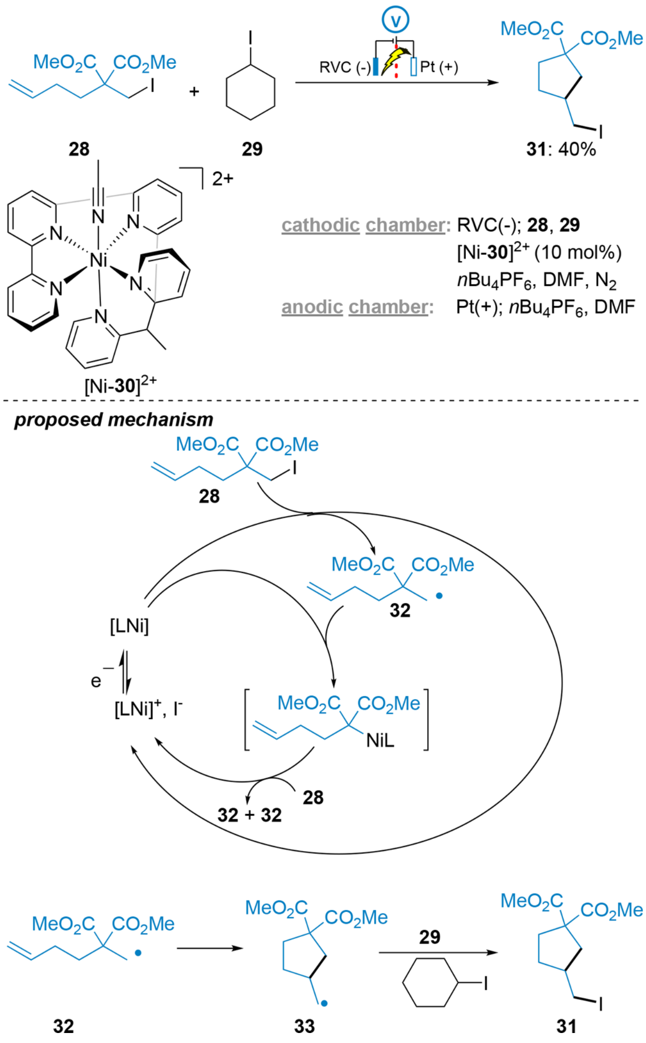
Scheme 4. Reactive Oxygen Species-Mediated Electroreductive Giese-Type Addition of Alkyl Iodides to Electron-Deficient Alkenes



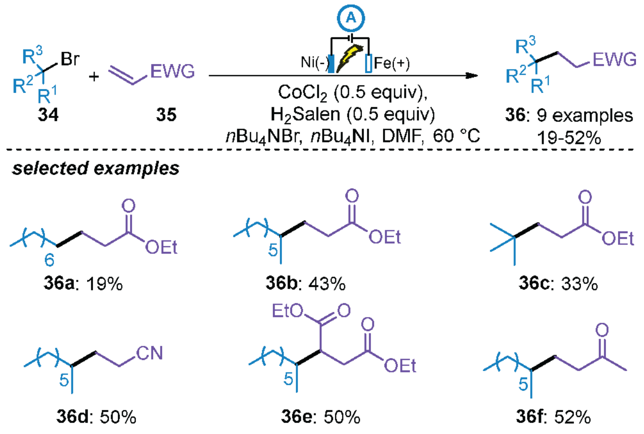
Ni complexes can be employed as electrocatalysts.[20] For instance, recently, Toste and Chang et al. have shown that the new Ni complex **30** featuring a redox-active pentapyridine ligand could activate alkyl iodide **28** toward the synthesis of cyclopentane **31** in the presence of the halogen atom donor **29**.[21] Based on synthetic, electroanalytical, and computational studies, it was proposed that the electroactive reduced Ni complex has its excess spin delocalized throughout the π-system of the redox-active ligand, allowing the activation of the alkyl iodide **29** via outer-sphere electron transfer. The resulting alkyl radical **32** rapidly recombined with the Ni complex to form the [LNi(R)] species. The latter reduced another equivalent of **28** to regenerate the Ni$^+$ complex and form radical **32**. Subsequent cyclization and trapping by **29** produced iodo-containing cyclopentane **31** (Scheme 5).

Condon et al. published an electrocatalytic reductive Giese-type addition of simple alkyl bromides **34** to activated alkenes **35** with low to moderate yields using an in situ generated cobalt–Salen complex as the catalyst.[22] The reaction was performed under simple reaction conditions using constant current electrolysis in an undivided cell with a cheap nickel grid cathode and an iron-based sacrificial anode. The test of other sacrificial anodes resulted in lower yields, indicating a putative role of in situ generated iron salts. Better yields were obtained with the secondary and tertiary alkyl bromides compared to the primary ones (Scheme 6).

Scheme 5. Ni-Electrocatalyzed Reductive Cyclization

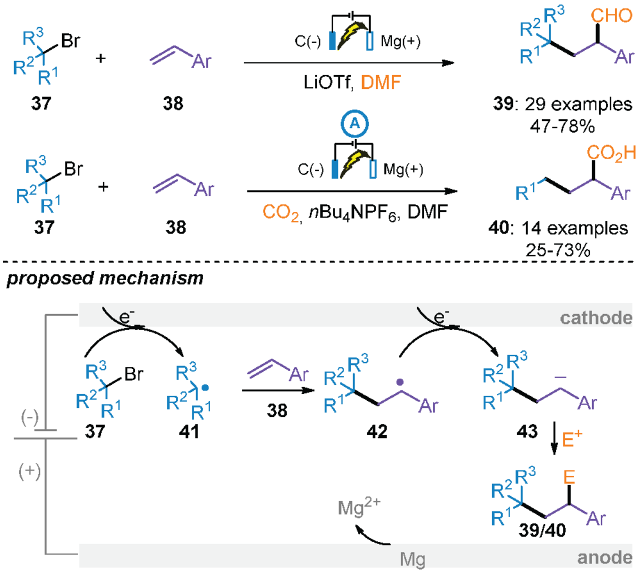


Scheme 6. Co-Electrocatalyzed Reductive Giese-Type Addition of Alkyl Bromides to Activated Alkenes



The intermolecular electrochemical difunctionalization of alkenes is an elegant method to access molecular complexity in a rapid and sustainable fashion. Most of the previous methods rely on electro-oxidative processes.[23−25] The development of electroreductive transformations appears as an attractive means to allow different functionalizations. In 2020, Lin et al. established an elegant electroreductive regioselective carboformylation and carbocarboxylation of styrene derivatives using secondary and tertiary alkyl bromides **37** as alkyl radical precursors and cheap dimethylformamide and carbon dioxide as electrophiles.[26] A simple undivided cell was employed with carbon graphite cathode and Mg-based sacrificial anode under constant current electrolysis. Cyclic voltammetry analysis and control experiments suggested a radical/polar crossover mechanism wherein SET reduction of alkyl bromide **37** delivered an alkyl radical **41** which then added regioselectively to the alkene **38**. Subsequent reduction of the resulting radical **42** to anion **43** followed by addition to the electrophile delivered the dicarbofunctionalized adducts **39**/**40** in good yields. It is also worth noting that this strategy has been extended to the anti-Markovnikov hydroalkylation of alkenes using acetonitrile as proton source (Scheme 7).

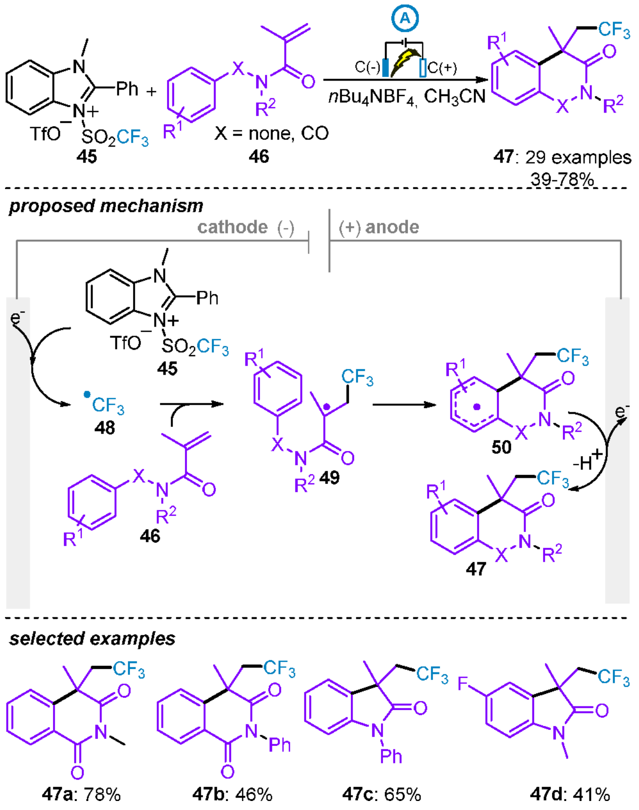
Scheme 7. Electroreductive Carboformylation and Carbocarboxylation of Alkenes



2.3. Generation of Fluoroalkyl Radicals

The incorporation of a trifluoromethyl group onto target molecules can dramatically impact their physical, chemical, and biological properties. Electrochemistry represents an appealing approach to introduce such a group.[27] While most of the electrochemical methods utilized an oxidative process with CF_3SO_2Na (Langlois reagent) as trifluoromethyl reagent,[28] the trifluoromethylation involving cathodic processes for $C(sp^3)-C(sp^3)$ bond formation has been only recently described. Wang et al. reported on the use of IMDN-SO_2CF_3 **45** for the cathodic generation of a trifluoromethyl radical.[29] This approach enabled the synthesis of trifluoromethyl-containing isoquinoline-1,3-diones and oxindoles **47** via a redox-neutral trifluoromethylation/cyclization sequence of activated alkenes **46**. The proposed mechanism started with the SET reduction of **45** followed by the regioselective addition of the resulting trifluoromethyl radical **48** to the alkene **46.** Further radical cyclization on the aromatic ring followed by anodic oxidation and deprotonation provided the desired functionalized heterocycles **47** through a linear paired electrolysis (Scheme 8).

Scheme 8. Electrochemical Construction of Trifluoromethyl-Containing Heterocycles with IMDN-SO_2CF_3



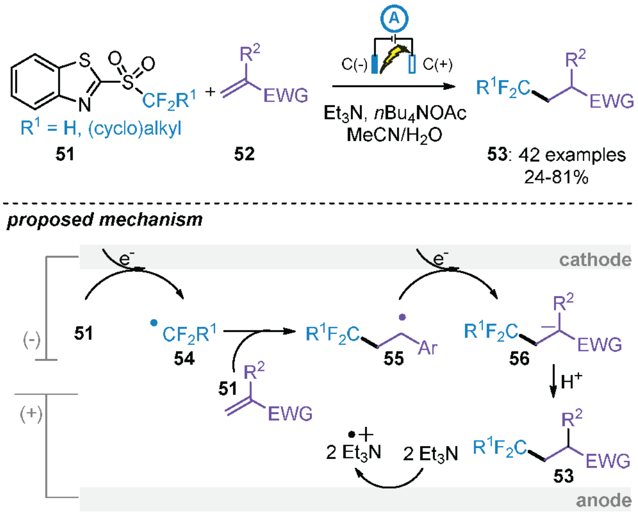
Very recently, Hu et al. developed an electrochemical hydrodifluoroalkylation of conjugated alkenes **52** by cathodic reduction of difluoroalkyl sulfones **51**.[30] The reaction took place in an undivided cell under simple constant current electrolysis using cheap carbon graphite electrodes in the presence of triethylamine. Difluoromethyl radical as well as various difluoroalkyl radicals could be efficiently introduced to provide the difluoroalkyl-containing compounds in moderate to high yields. Control experiments supported a radical/polar crossover mechanism. As such, difluoroalkyl radical **54** was initially generated at the cathode and regioselectively added to the alkene **52** to form the new radical **55**. A subsequent SET reduction and protonation yielded the target product **53**. The oxidation of triethylamine at the cathode counterbalanced the overall process (Scheme 9).

2.4. SET Reduction of Ketones

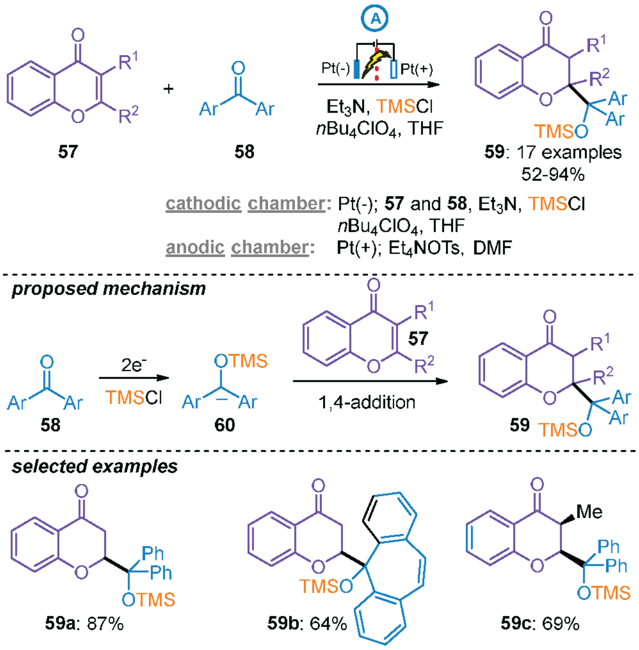
Electrochemical reduction of ketones is a powerful tool to generate ketyl radicals which might undergo further reduction to the corresponding carbanions and nucleophilic addition, direct radical addition, or dimerization depending on the reaction conditions. It constitutes therefore a highly attractive synthetic method for $C(sp^3)-C(sp^3)$ bond formation.

In 2019, Kise et al. published a C2-functionalization of chromones **57** via an electroreductive coupling of various diaryl ketones **58** in the presence of an excess of trimethylsilyl chloride in a divided cell under constant current electrolysis.[31] Moderate to high yields were achieved. However, no reaction took place with electron-rich 4,4′-dimethoxybenzophenone as the partner due to its higher reduction potential (absolute value) in comparison to that of the chromone. Based on cyclic voltammetry analysis, the authors proposed a mechanism, as depicted in Scheme 10. The reaction was initiated by two consecutive SET reductions of diaryl ketone **58** in the presence of trimethylsilyl chloride to generate carbanion **60**. Subsequent

Scheme 9. Electroreductive Hydrodifluoroalkylation of Conjugated Alkenes



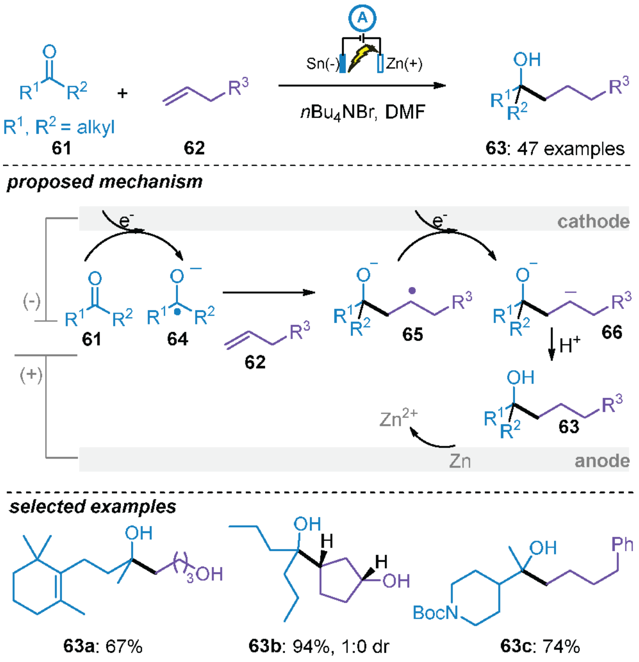
Scheme 10. C2-Functionalization of Chromones



nucleophilic conjugate addition to the chromone **57** delivered 2-substituted chromone **59**. Interestingly, the functionalization of 3-methylchromone and 3-arylchromone produced selectively the *cis*-adducts (Scheme 10). Soon after, the authors extended this procedure to the C2-functionalizations of 4-quinolones.[32]

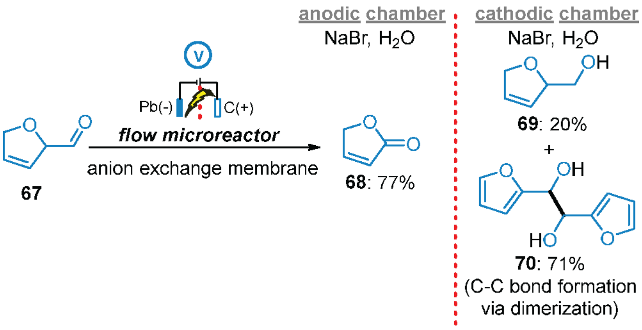
Baran and Minteer et al. reported an electroreductive coupling between aliphatic ketones **61** and unactivated alkenes **62** for the synthesis of tertiary alcohols **63** in good yields.[33] The electrolysis was performed in an undivided cell using a zinc-based sacrificial anode and tin cathode. According to kinetic studies and voltammetry analysis, the transformation was initiated by SET reduction of the ketone **61** to form the ketyl radical anion **64**, which underwent nucleophilic addition of the alkene **62**. This step would be facilitated by the binding of the reactants to the tin cathode. A second SET reduction to dianion **66** followed by protonation formed the tertiary alcohol **63**. The authors highlighted the importance of the sacrificial Zn anode which would facilitate the SET events by providing Zn^{2+} (Scheme 11).

Scheme 11. Electroreductive Coupling between Ketones and Unactivated Alkenes



One year later, Noël et al. described a divergent paired electrochemical transformation of furfural **67** allowing simultaneously the access to 2(5*H*)-furanone **68** in the anodic chamber and furfuryl alcohol **69** and mostly hydrofuroin **70** in the cathodic part. Interestingly, the electrolysis was performed in water in a divided-cell flow microreactor (Scheme 12).[34]

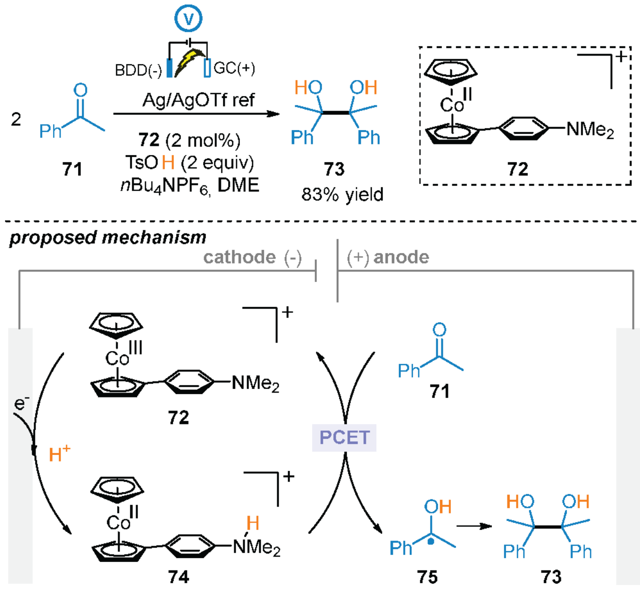
Scheme 12. Divergent Paired Electrolysis of Furfural



Peters et al. designed an electrocatalyst **72** comprising a redox cobaltocene and a tethered Brønsted base to enable the reductive pinacol coupling of acetophenone **71**. The electrolysis was performed at a constant current potential using boron-doped diamond working electrode. In the presence of a Brønsted acid, the electrocatalyst favored a proton-coupled electron transfer (PCET) event leading to the neutral radical **75**. In contrast, a direct reduction on the electrode in the absence of this electrocatalyst required a higher bias, resulting in adsorption and passivation issues and furnished the desired pinacol product **73** in lower yield. Also of note, a simple cobaltocene electrocatalyst was totally inefficient to deliver the pinacol product due to the competing hydrogen evolution reaction.

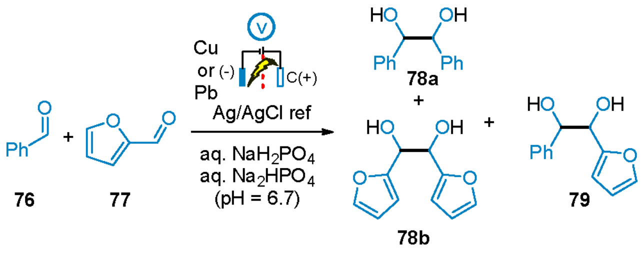
Such observations underpinned the crucial role of both the cobaltocene electrocatalyst and the tethered Brønsted base (Scheme 13).[35]

Scheme 13. Electrocatalytic Reductive Pinacol Coupling of Acetophenone



Recently, Zhang et al. investigated the electroreductive pinacol coupling of aromatic carbonyl compounds and found that carbon fiber paper was optimal as the working electrode.[36] Xu et al. studied the electroreductive cross-coupling of benzaldehyde **76** and furfural **77** on Cu and Pb surfaces. They demonstrated that Cu featured a higher selectivity for cross-coupling product **79** (heterodimerization), whereas Pb favored furfural coupling **78b** (homodimerization). This difference of selectivity was explained by a much stronger adsorption of benzaldehyde on Pb compared to furfural (Scheme 14).[37]

Scheme 14. Electroreductive Cross-Coupling of Furfural and Benzaldehyde



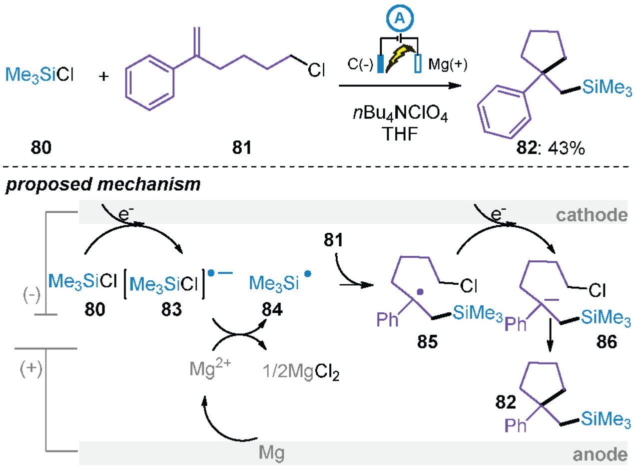
2.5. SET Reduction of Alkenes

Alkenes feature very negative reduction potential, making it difficult to generate the corresponding radical anion. The electrohydrodimerization of acrylonitrile ($E_p \approx -2$ V in H_2O vs SCE)[38] to produce adiponitrile, a precursor of Nylon-6,6, is one of the most well-known industrial synthetic electrochemical transformation. Optimizing such a process by identifying the key factors influencing the selectivity toward adiponitrile is worth studying. Ramachandran et al. developed a mathematical model to elucidate the optimal concentration, voltage, and current as long as the effect of mass transfer coefficients between electrolyte and electrodes.[39] Modestino et al. used a systematic approach to study such parameters.[40] Their investigations have shown that the selectivity of the process toward the formation of adiponitrile was governed by mass transport. Indeed, the formation of propionitrile as the byproduct is favored at high current densities when the reactant concentration in the electrical double layer (EDL) is low. On the other hand, oligomers are formed at low current densities when the reactant concentration in the EDL is high. As such, maintaining intermediate concentration of reactants in the EDL at high current densities is key to enhance the performance of this process. To do so, Modestino et al. combined pulsed electrolysis with artificial intelligence.[41] With pulsed organic electrosynthesis, the composition of the EDL is periodically renewed, enabling an effective process at high current densities, and the diffusion and migration rates of reactants, products, electrolytes, and intermediates are better controlled. Such techniques improved the selectivity by 325% and adiponitrile production rate by 30%.

2.6. Regioselective Radical Silylation of an Alkene

The addition of a radical to an alkene generates a C(sp^3) radical primed for further transformations. Radical silylation of alkenes is a reliable strategy to produce valuable organosilicon molecules with various potential applications in materials science and medicinal chemistry. In this context, Lin et al. developed an elegant new synthetic way to generate silyl radicals via the electroreduction of chlorosilanes **80**.[42] They originally applied this strategy to the vicinal disilylation of alkenes and further extended it to the cyclization of styrene **81** bearing a tethered leaving group, allowing the formation of a C(sp^3)−C(sp^3) bond by a tandem process. The electrolysis was performed in an undivided cell using a graphite working electrode and a Mg-based sacrificial anode under constant current electrolysis in THF. Mechanistic studies suggested that the reaction was initiated by SET reduction of chlorosilane **80**, which would be facilitated by magnesium salts arising from the oxidation of the sacrificial anode. Subsequent regioselective addition to the alkene **81** enabled the construction of a Si−C bond and the generation of C(sp^3) radical **85**. A second SET reduction followed by intramolecular nucleophilic substitution delivered the silylated pentacycle **82** in moderate yield (Scheme 15).

Scheme 15. Tandem Si−C and C−C Bond Formation via Cathodic Generation of Trimethylsilyl Radical

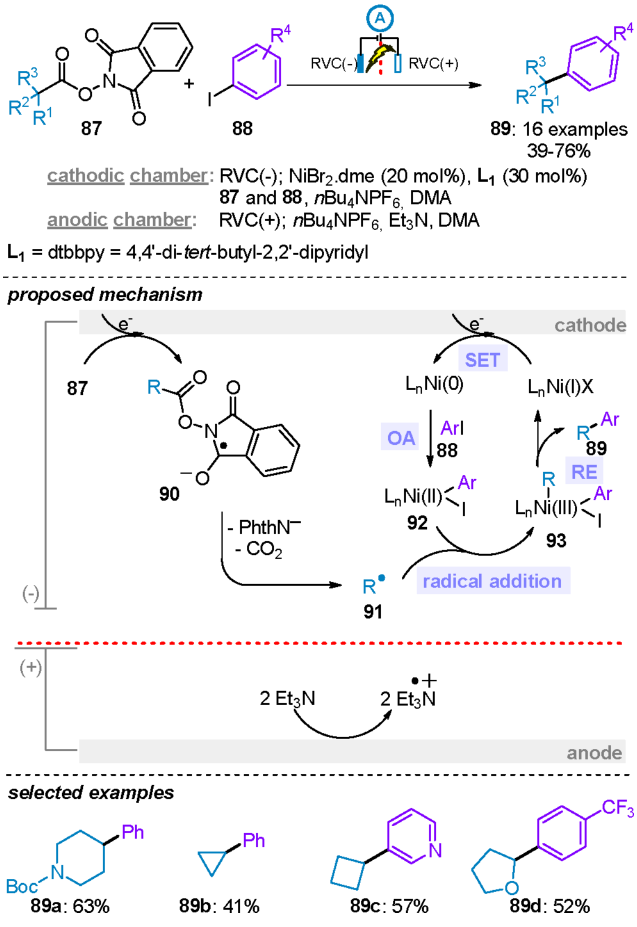


3. C(sp^3)−C(sp^2) BOND FORMATION

3.1. Reductive Decarboxylative Process

The transition-metal-catalyzed electrochemical process is an efficient method for constructing C(sp^3)−C(sp^2) bonds. In 2018, Bio et al. developed a Ni-catalyzed electroreductive coupling between NHP esters **87** and aryl iodides **88**, enabling the formation of a new C(sp^3)−C(sp^2) bond.[43] According to the authors, the matching between the reduction potentials of the electrocatalyst and the reactants allowed both the direct decarboxylative cathodic reduction of NHP esters **87** to the corresponding C(sp^3) radical **91** and the reduction of Ni(I) to Ni(0). Subsequent oxidative addition of the aryl halide **88** and interception of the alkyl radical **91** afforded Ni(III) complex **93**. Further reductive elimination delivered the coupling product **89** and closed the catalytic cycle. Triethylamine was employed as a sacrificial reductant, and a divided cell was required to prevent the anodic oxidation of in situ generated low-valent Ni species. Improved performances were achieved under continuous flow conditions, allowing an easy scale-up (Scheme 16). One year later, Loren et al. designed a similar transformation during which NHP esters are in situ generated from the corresponding carboxylic esters by premixing with tetramethyluronium hexafluorophosphate. Using a Zn-based sacrificial anode, their procedure had the advantage to employ a simple undivided cell.[44]

Scheme 16. Ni-Catalyzed Electroreductive Cross-Coupling between NHP Esters and Aryl Iodides

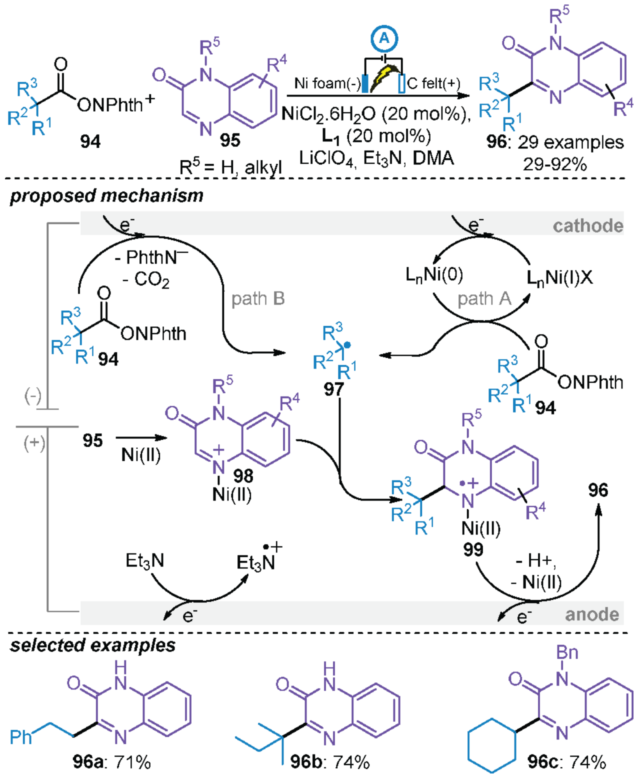


cathodic chamber: RVC(-); $NiBr_2$.dme (20 mol%), L_1 (30 mol%)
87 and 88, nBu_4NPF_6, DMA
anodic chamber: RVC(+); nBu_4NPF_6, Et_3N, DMA
L_1 = dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl

Minisci-type reaction is an efficient method for the formation of C(sp^3)−C(sp^2) bonds, through radical addition of nucleophilic carbon radicals on electron-deficient azacycles.

In 2019, Zeng et al. published a Ni-catalyzed redox-neutral cross-coupling between NHP esters **94** and quinaxolin-2-ones **95**. A Ni(II) complex was used as the electrocatalyst in an undivided cell with a carbon felt anode and a nickel foam cathode. Contrary to the work reported above, the authors proposed here that the Ni(II) species would promote the indirect reduction of NHP esters **94** to generate the alkyl radical **97** (path A). The latter would add to quinaxolinone **95** via complex **98**. Subsequent deprotonation and oxidation would lead to functionalized quinaxolinone **96** and release the electrocatalyst. An alternative mechanism involving the direct reduction of NHP esters **94** was also proposed (path B). Oxidation of triethylamine took place at the anode (Scheme 17).[45] Afterward, Wang et al. reported a similar transformation under electrocatalyst- and triethylamine-free reaction conditions in an undivided cell with two graphite electrodes.[46]

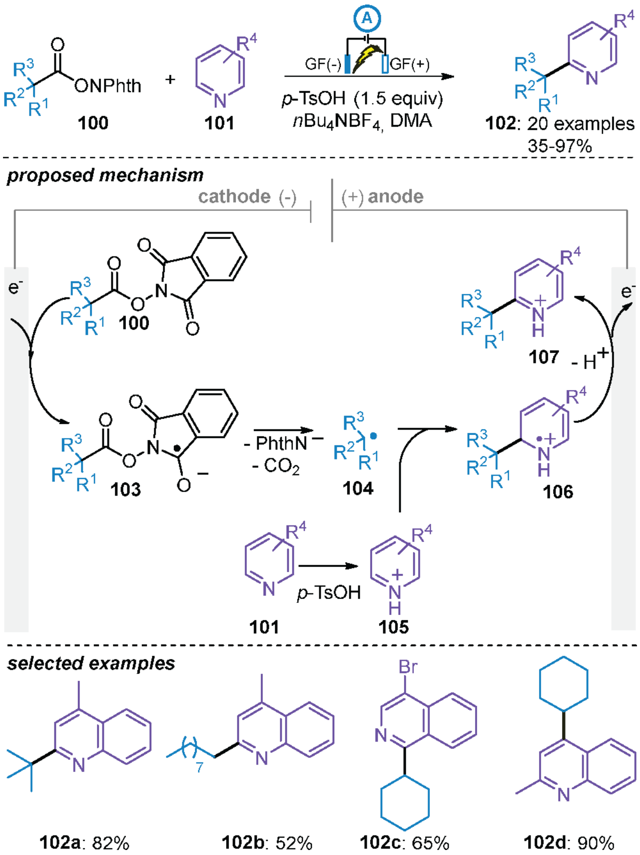
Scheme 17. Ni-Catalyzed Electroreductive Cross-Coupling between NHP Esters and Quinaxolinones



$NiCl_2.6H_2O$ (20 mol%),
L_1 (20 mol%)
$LiClO_4$, Et_3N, DMA

In 2019, Lei et al. explored an electrochemical decarboxylative Minisci-type alkylation of azaarenes **101** using NHP esters **100** as alkyl radical precursors, providing the corresponding functionalized heterocycles **102** in moderate to high yields.[47] The electrolysis was performed in an undivided cell employing two simple graphite felt electrodes and *p*-toluene sulfonic acid as an acidic additive. Based on cyclic voltammetry and RPE experiments, the authors suggested a mechanism involving a linear paired electrolysis. As depicted in Scheme 15, the transformation started by the direct cathodic decarboxylative generation of alkyl radicals **103** from NHP esters **100**. Subsequent regioselective radical addition to protonated azacycles **105** furnished radical cation **106**, which underwent deprotonation and anodic oxidation to deliver the desired products **102** (Scheme 18).

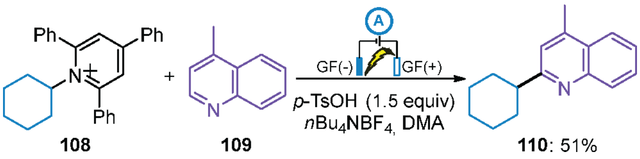
Scheme 18. Electrochemical Decarboxylative Minisci-Type Alkylation of Azaarenes with NHP Esters



3.2. Reductive Deaminative Process

During their investigations on electrochemical Minisci-type reaction, Lei et al. employed the Katritzky *N*-cyclohexylpyridinium salt **108** as the alkyl radical precursor for the C2-functionalization of 4-methylquinoline **109** through a cathodic deaminative process (Scheme 19).[48]

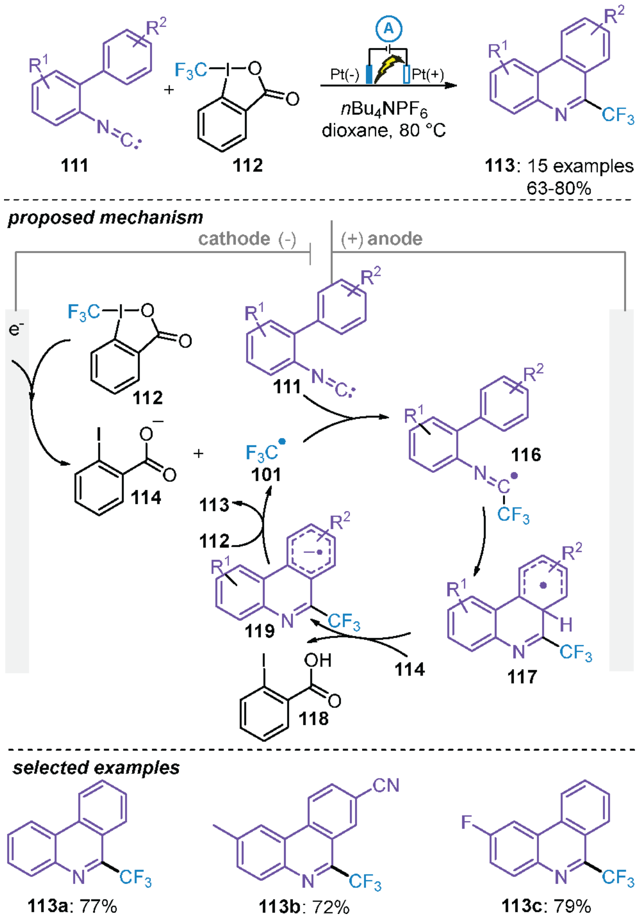
Scheme 19. Electrochemical Deaminative Minisci-Type Alkylation of Quinoline 109 with Kratrizky Salt 108



3.3. Generation of Fluoroalkyl Radicals

In 2018, Studer et al. disclosed a radical trifluoromethylation of isonitriles **111** to build CF_3-containing phenanthridine **113**.[48] The reaction was initiated by the cathodic reduction of Togni reagent **112** to form trifluoromethyl radical **115**. After radical addition to isonitrile **111** and cyclization, the resulting cyclohexadienyl radical **117** is deprotonated by in situ generated *ortho*-iodobenzoate **114**, leading to radical anion **119**. The latter would be a sufficient oxidant species to enable SET, with Togni reagent **112** delivering the desired heterocycle **113** and another trifluoromethyl radical **115**. As such, this radical chain mechanism allowed the transformation to proceed with a catalytic amount of electric charge (0.075*F*) (Scheme 20).

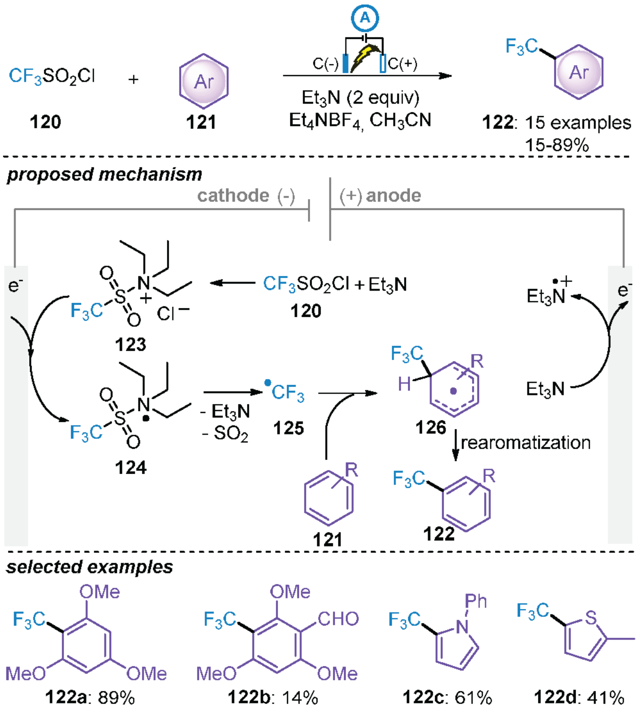
Scheme 20. Electroreduction of Togni Reagent-Initiated Trifluoromethylation of Isonitrile



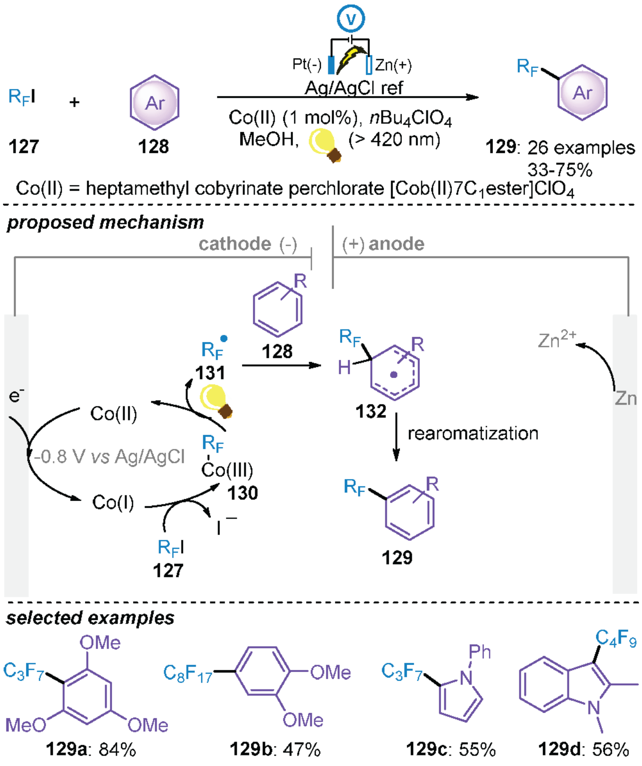
In 2019, Kappe and Cantillo et al. explored an electroreductive approach for the radical trifluoromethylation of electron-rich (hetero)cycles using readily available triflyl chloride **120** and triethylamine in an undivided cell with two cheap carbon graphite electrodes. Based on NMR experiments and density functional theory (DFT) calculations, the authors suggested that the trifluoromethyl radical **125** was formed upon SET cathodic reduction of in situ generated triflyltriethylammonium complex **123**. Subsequent addition to aromatic cycle **121** formed radical **126**, which rearomatized via either hydrogen atom abstraction or SET oxidation/deprotonation processes to yield the CF_3-containing aromatic cycles **122** in modest to good yields. Interestingly, this cathodic event enabled the electrochemical trifluoromethylation of compounds, which would be difficult to achieve under an oxidative procedure with thiacycles or substrates bearing aldehydes (Scheme 21).[49] In 2020, Luo and Nguyen et al. established an alternated current electrolysis for the trifluoromethylation of (hetero)arenes with triflyl chloride in the presence of an inorganic base.[50]

Hisaeda et al. employed a vitamin B_{12} derivative as a cobalt-based electrocatalyst for the cathodic perfluoalkylation of electron-rich (hetero)arenes **128** with cheap perfluoroalkyl iodides **127** under visible light irradiation. The electrolysis was performed in an undivided cell equipped with a reference

Scheme 21. Cathodic Trifluoromethylation of (Hetero)arenes with Triflyl Chloride



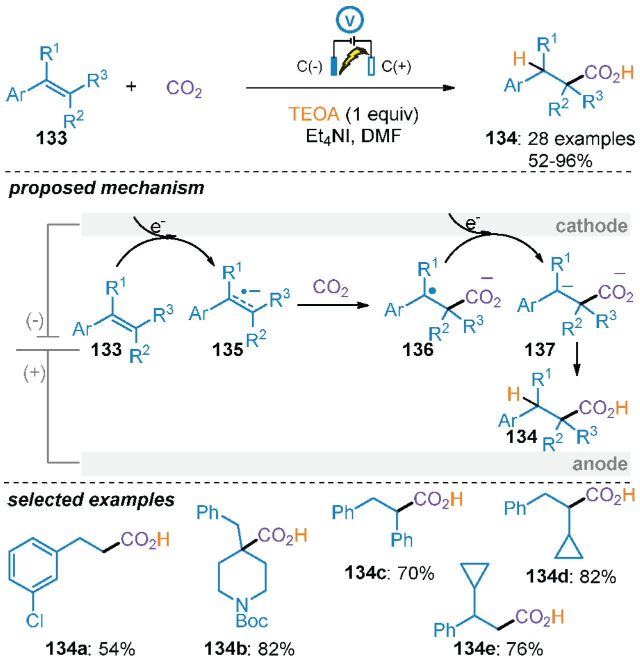
Scheme 22. Co-Electrocatalyzed Perfluoroalkylation of Arenes with Perfluoroalkyl Iodides under Light Irradiation



electrode to fix the potential at −0.8 V vs Ag/AgCl. Herein, Co(II) was initially reduced to Co(I) species. The latter underwent oxidative addition of perfluoroalkyl iodides **127** to form Co(III)−R_F complex **130** and subsequently produce perfluoroalkyl radical upon visible light irradiation. Further radical addition to the arene and rearomatization delivered the target functionalized product. A very low catalyst loading was employed, but the slow addition of a large excess of perfluoroalkyl reagent (9 equiv) was required (Scheme 22).[51]

3.4. SET Reduction of Alkenes

Scheme 23. Electroreductive Hydrocarboxylation of Styrenes

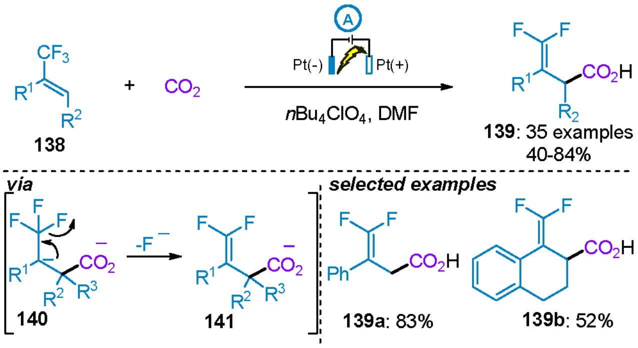


Alkenes have emerged as an attractive source of alkyl radical anion through an electrochemical reductive process in cross-coupling with CO_2 as the electrophile. Recently, Buckley and Malkov et al. reported an electrosynthetic highly regioselective hydroxycarboxylation of styrenes **133**, giving rise to *β*-carboxylation products **134** (Scheme 23).[52,53] The electrolysis proceeded in a simple undivided cell under constant current using carbon electrodes and triethanolamine (TEOA) as a proton source. This protocol is compatible with a wide range of substrates including mono-, di-, and trisubstituted alkenes. Based on cyclic voltammetry and control experiments, the proposed mechanism involved an electrochemical chemical electrochemical chemical process with adsorption of the alkene **133** on the cathode, followed by SET reduction to the corresponding radical anion **135**, subsequent carboxylation to regioselectively form the C−C bond by favoring the formation of benzylic radical **136**, and further SET reduction and protonation. However, due to the small difference of reduction potential between carbon dioxide and styrene ($E_{1/2} = -2.21$ V and −2.58 V vs SCE in DMF, respectively), an alternative mechanism involving the direct reduction of carbon dioxide to the corresponding radical anion $^{\bullet}CO_2^-$ and subsequent addition to the styrene to form the common intermediate **136** could not be ruled out (Scheme 20). This procedure has been subsequently applied to the selective *α*,*δ*-hydrocarboxylation of conjugated dienes[53] and to the selective *β*-carboxylation of *α*,*β*-unsaturated esters.[54]

Wang and Zhang et al. reported the electrochemical *β*-carboxylation of *α*,*β*-unsaturated ketones using silica nanowires as the working electrode under light irradiation. This specific electrode would absorb light energy to reduce the consumption of electrical energy and enhance the reaction efficiency.[55]

Zhou et al. developed a regioselective defluorinative/carboxylation of α-trifluoromethyl alkenes **138** under constant current electrolysis with two platinum electrodes.[56] Herein, the anion **140** resulting from the second cathodic SET reduction underwent rapid fluoride elimination via an E1CB-type mechanism instead of protonation leading to valuable *gem*-difluoroalkenes **139** in good yields. Notably, a wide range of α-CF_3 alkenes **138** could be efficiently employed, including those with α-aryl/alkyl/alkynyl substituents and trisubstituted alkenes (Scheme 24).

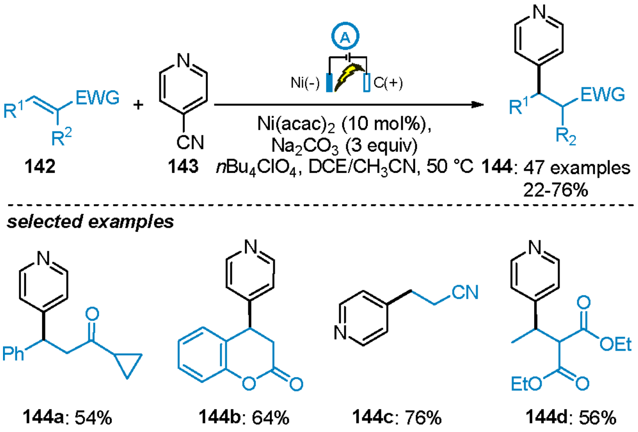
Scheme 24. Electroreductive Carboxylation of α-CF_3 Alkenes for the Synthesis of *gem*-Difluoroalkenes



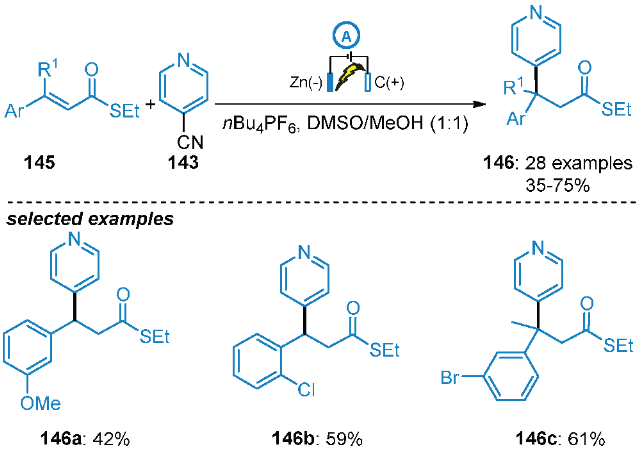
Cyanopyridines are often used as partners in a radical−radical coupling reaction to access pyridines, which are found in a broad variety of biologically active molecules. Findlater et al. described an efficient regioselective hydropyridylation of electron-deficient alkenes **142** with 4-cyanopyridine **143**.[57] This electroreductive decyanative alkylation reaction was facilitated by a catalytic amount of $Ni(acac)_2$. The authors suggested two putative mechanisms involving the initial reduction of the Michael acceptor to the corresponding radical anion followed by either radical addition to Ni-activated 4-cyanopyridine or radical cross-coupling with in situ generated 4-cyanopyridyl radical anion (Scheme 25).

Very recently, Jiang and Xu et al. employed α,β-unsaturated thioesters **145** as electron-deficient alkenes for a similar hydropyridylation reaction under Ni-free electrolysis. Interestingly, β-aryl-β-alkyl-substituted thioesters were compatible substrates, allowing the construction of quaternary carbons α to pyridines. Contrary to the work described above, cyclic voltammetry experiments strongly supported the cathodic reduction of both reaction partners **145** and **143** and further radical combination. The oxidation of dimethylsulfoxide (DMSO) was suggested to be the counter-reaction occurring at the anode (Scheme 26).[58]

Scheme 25. Electroreductive Hydropyridylation of Electron-Deficient Alkenes



Scheme 26. Electroreductive Hydropyridylation of α,β-Unsaturated Alkenes

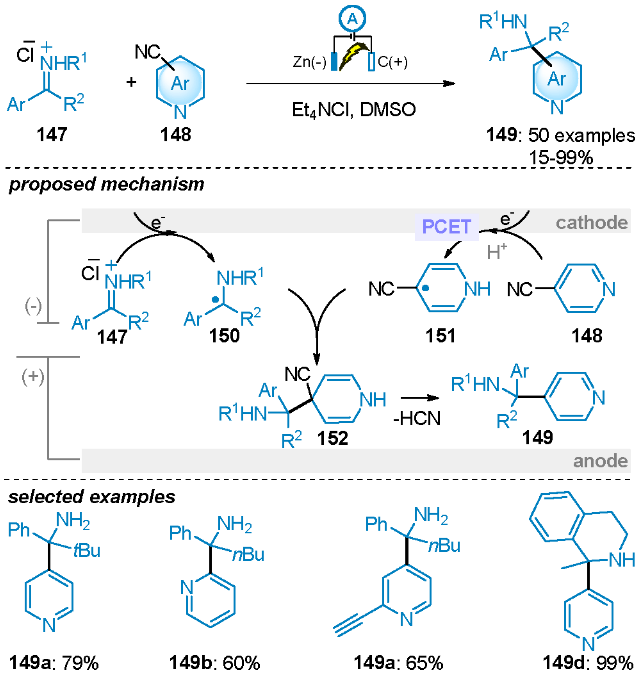


3.5. SET Reduction of C═X Bonds (X = O, NR)

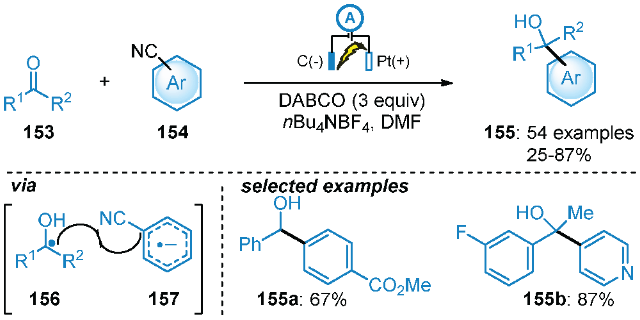
Rovis and Lehnherr et al. demonstrated an elegant electrosynthetic access to quaternary carbon centers bearing a challenging primary or secondary amino group.[59] Their approach relied on the reductive coupling between iminium salts **147** and cyanoazaarenes **148**. A simple undivided cell was employed under constant current electrolysis. A zinc-based cathode featuring a high overpotential for hydrogen evolution was employed to preclude the loss of H^+. Cyclic voltammetry analyses and DFT calculations supported a mechanism involving cathodic generation of both transient α-amino radical **150** from iminium **147** via a SET reduction and persistent neutral radical **151** from cyanoazaarene **148** via a PCET event. Further radical cross-coupling afforded the *ipso*-substituted products **149** with moderate to excellent yields. The PCET process allowed a better matching between the reduction potential of both reactive partners but imposed unavoidably the use of N-heterocycles (Scheme 27).

Similarly, an electroreductive coupling between carbonyl compounds **153** and cyano(aza)arenes **154** has been disclosed by Xia and Yang et al.[60] Aromatic and aliphatic aldehydes as well as aromatic ketones were suitable substrates for this *ipso*-substitution transformation, delivering the corresponding secondary and tertiary alcohols **155** in high yields. DABCO was employed as a sacrificial reductant. Herein, the higher reduction potential (absolute value) of the carbonyl compounds compared to that of the iminium salts matched more easily with those of the cyano(hetero)arenes. As such, unlike Rovis's work, a PCET process was not required and a radical−radical cross-coupling between cathodically generated transient ketyl radical **156** and persistent radical anion **157** was proposed. Accordingly, azaarenes were not mandatory, making electron-poor hydrocarbon-based cyanoarenes, such as 1,4-dicyanobenzene, additional successful coupling partners (Scheme 28). A similar coupling between ketones or aldehydes and 1,4-dicyanoarenes was demonstrated by Findlater, Zhang, and Xu et al. The latter

Scheme 27. Electroreductive Coupling between Iminium Salts and Cyanoazaarenes



Scheme 28. Electroreductive Coupling between Carbonyl Compounds and Cyano(aza)arenes

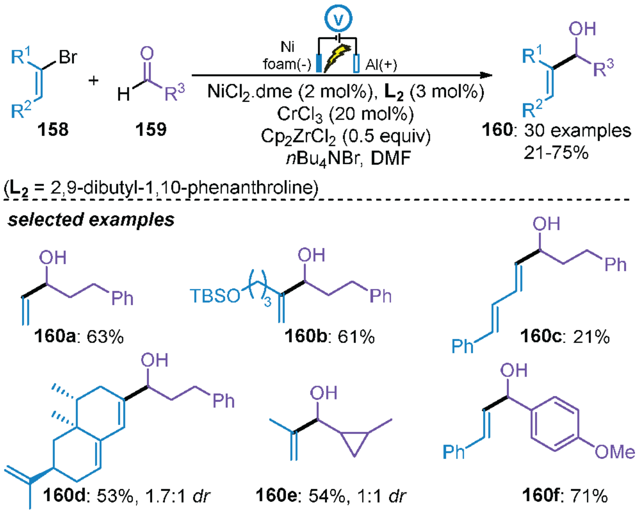


proposed an alternative mechanism involving reduction of the 1,4-dicyanoarene to the corresponding radical anion **157** with further nucleophilic addition to the aldehyde, second SET reduction, and decyanation.[61]

3.6. Generation of a Vinyl Organometallic Species and Further Addition to Aldehydes

Recently, Baran, Blackmond, and Reisman et al. developed a new electrochemical Nozaki−Hiyama−Kishi (NHK) reaction between vinyl halides **158** and aldehydes **159**.[16] The cathodic reduction of Cr(III) avoids the use of superstoichiometric amount of reducing agents, which are traditionally required to render this transformation catalytic in Cr. Although early electrochemical NHK couplings exhibited limited substrate scope (only one example of aliphatic aldehyde) and issues due to difficult setup and the use of expensive electrodes,[62−64] this new protocol features operationally simple reaction conditions: undivided cell, cheap Al-based sacrificial anode, and Ni-foam cathode and potentiostatic electrolysis without a reference electrode. Choosing Cp_2ZrCl_2 as the oxophilic additive to trap the alkoxide at this end of the catalytic cycle was key for the success of this transformation. A broad substrate scope was demonstrated with aromatic as well as aliphatic aldehydes using a catalytic amount of $NiCl_2$ and $CrCl_2$. Also noteworthy is an asymmetric version of this transformation using a chiral ligand (Scheme 29).

Scheme 29. Electrocatalytic NHK Reaction

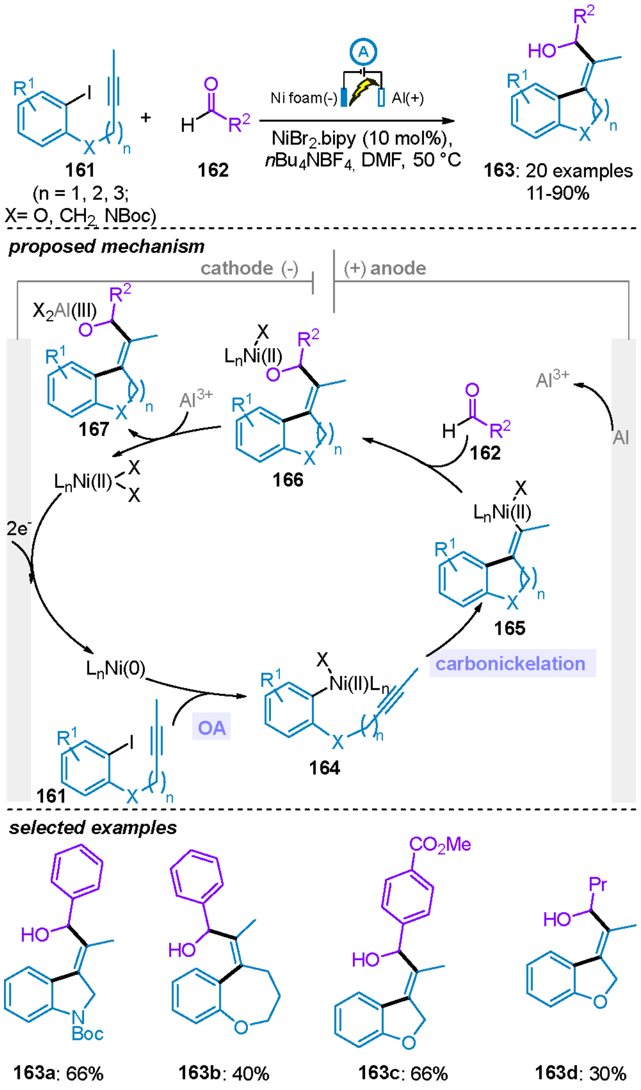


Durandetti et al. have developed a nickel-catalyzed electroreductive intramolecular carbometalation of alkynes **161** and subsequent reaction with aldehydes **162**.[65] This domino process formed consecutively a $C(sp^2)-C(sp^2)$ bond and a $C(sp^2)-C(sp^3)$ bond to furnish various functionalized dihydrobenzofurans, (iso)chromans, indoles, and indanes **163** in good yields. The electrolysis was performed in an undivided cell with cheap nickel foam cathode and a sacrificial aluminum anode under constant current. Cyclic voltammetry studies supported the initial two-electron reduction of Ni(II) catalyst to Ni(0). Subsequent oxidative addition of the aryl iodide **161** and stereoselective 5-*exo*-dig cyclization produced the vinylnickel species **165**. Final addition to the aldehyde **162** and transmetalation with anodically generated Al(III) furnished the aluminum alkoxide species **167** and closed the nickel catalytic cycle (Scheme 30).

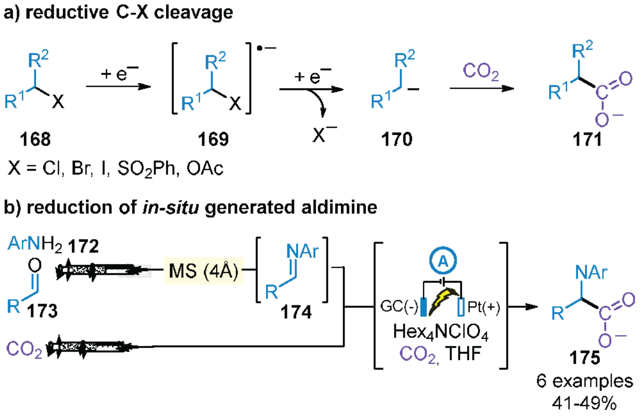
3.7. Two Consecutive SET Reductions for the Generation of a Carbanion or a Nucleophilic Organometallic Species and Further Carboxylation

As mentioned above (see section 3.4), the use of carbon dioxide as a C1 source for the direct access to carboxylic acid is a very appealing approach. Various procedures have recently been established or improved for the carboxylation of cathodically generated carbanion intermediates **170** via two consecutive SET reductions of the substrate **168** and C−X bond cleavage.[66] In some cases, the competitive SET reduction of carbon dioxide could take place at the cathode, resulting in the need of excess electricity or an alternative mechanism. In 2018, He et al. developed a core−shell structured silver nanowire/nitrogen-doped carbon electrocatalyst for the electrocarboxylation of organic bromides.[67] In 2018, Senboku et al. reported the synthesis of mandelic acid derivatives through the electrocarboxylation of the corresponding benzal diacetates.[68] Recently, the same authors described the synthesis of *N*-Boc-α-amino acids in an electroreductive C−S bond cleavage of the *N*-Boc-α-aminosulfones/carboxylation sequence in DMF with a platinum plate cathode and a magnesium rod anode.[69] In 2020,

Scheme 30. Intramolecular Carbonickelation of Alkynes and Subsequent Reaction with Aldehydes



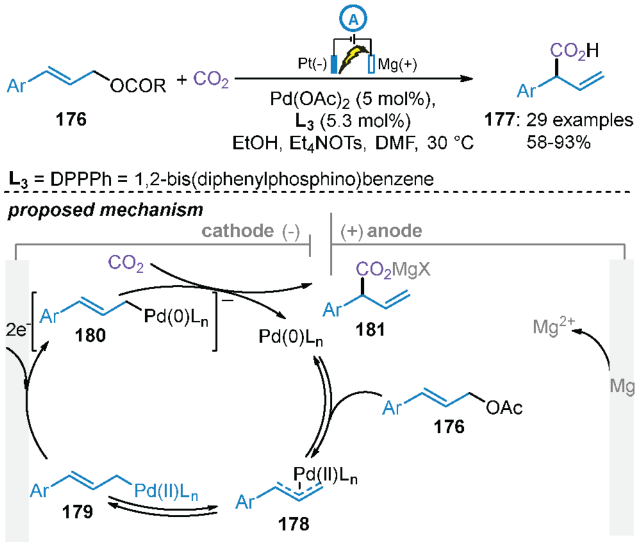
Scheme 31. Two Consecutive SET Electroreductions and Subsequent Carboxylations



Guirado et al. reported the synthesis of Ibuprofen and Naproxen via the electrocarboxylation of the corresponding benzyl chlorides. They used an ionic liquid as the solvent/electrolyte system and a silver cathode to decrease the reduction potential value of the organic halide.[70,71] Very recently, Manthiram et al. employed anhydrous magnesium bromide as a source of Mg^{2+} cations to inhibit the nucleophilicity of the obtained carboxylate salts, allowing the electrocarboxylation of various benzylic and aliphatic halides to take place with a platinum anode instead of a sacrificial anode (Scheme 31a).[72] Also of note, Senboku et al. utilized a continuous flow system to succeed in the electroreductive carboxylation of in situ generated *N*-aryl aldimines **174**, giving rise to *N*-aryl-α-amino acids **175** in moderate to high yields (Scheme 31b).[73]

In 2018, Mei et al. reported an efficient Pd-catalyzed electroreductive carboxylation of allylic esters **176** under constant current electrolysis, giving rise to α-aryl carboxylic acids **177** with good yields and regioselectivity. A simple undivided cell was used with platinum cathode and magnesium-based sacrificial anode. Cyclic voltammetry measurements supported an initial oxidative addition of allylic ester **176** to in situ generated Pd(0) to form cationic π-allyl Pd(II) complex **178**. The latter equilibrated to the favored branched η^1-allyl Pd(II) species **179**, which underwent two cathodic SET reductive events. The resulting nucleophilic Pd(0) species **180** reacted with carbon dioxide to deliver magnesium carboxylate **181** to regenerate Pd(0). The addition of 1 equiv of ethanol was essential for the success of this transformation, but its role was not elucidated. Remarkably, an asymmetric variant was proposed with up to 67% ee using a chiral phosphine (Scheme 32).[74] In 2020, Ackermann et al. reported a similar elegant carboxylation of allylic chloride using earth-abundant Co(II) electrocatalyst with good yields and low to moderate regioselectivity. A Co(III)/Co(I) catalytic cycle was proposed.[75]

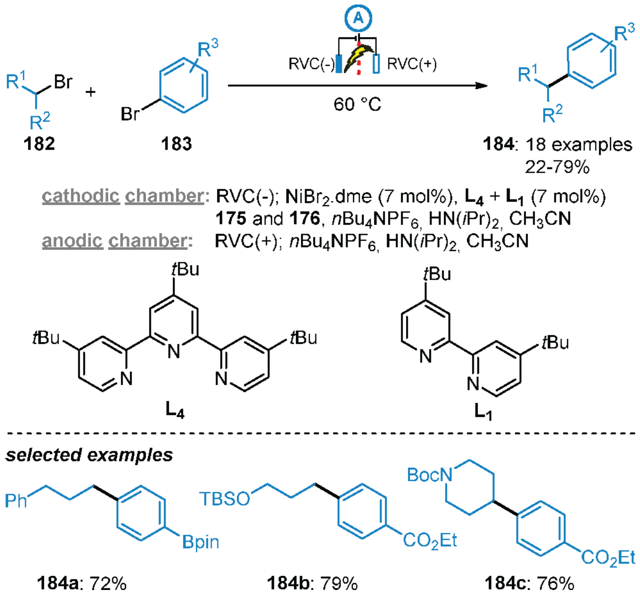
Scheme 32. Pd-Catalyzed Electroreductive Carboxylation of Allylic Esters



3.8. Ni-Electrocatalyzed Alkylation of $C(sp^2)$ Centers with Alkyl Halides

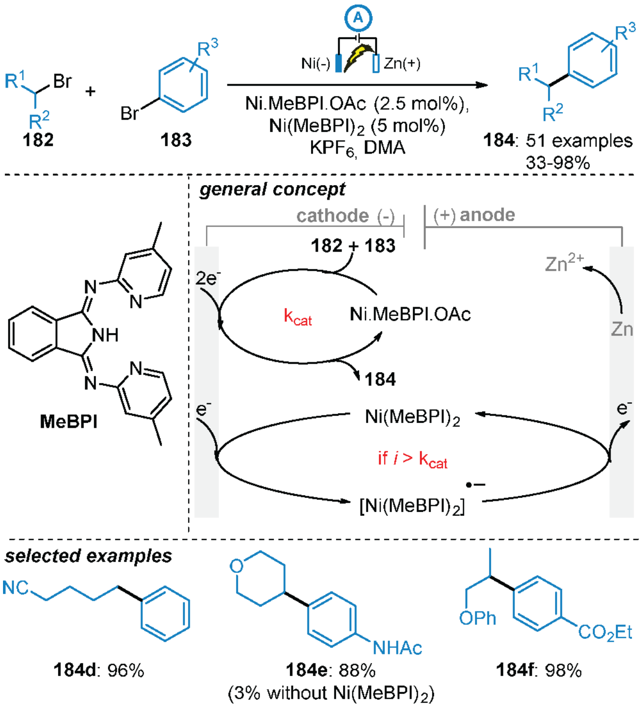
Ni-electrocatalyzed cross-electrophile coupling represents an attractive strategy for the formation of $C(sp^2)-C(sp^3)$ bonds.[76,77] In 2019, Hansen et al. reported a Ni-catalyzed reductive cross-coupling of aryl bromides **183** with alkyl bromides **182**.[78] The electrolysis was conducted in acetonitrile in a divided cell with reticulated vitreous carbon (RVC) electrodes. In contrast with their previous work, simple diisopropylamine was employed as an organic sacrificial reductant instead of a zinc-based sacrificial anode.[79] With careful adjustments of the charge (3.3*F*) and the catalyst loading (7 mol %), yields up to 80% could be achieved at high current (50 mA) with short reaction times on large scales. Importantly, a combination of two ligands was crucial for the success, but the optimal ratio was substrate-dependent (Scheme 33).

Scheme 33. Ni-Electrocatalyzed Reductive Cross-Coupling of Aryl Bromides with Alkyl Bromides in Acetonitrile



In 2020, Sevov et al. investigated the same reaction and discovered an electrocatalytic system which was operationally simple (electrolysis at room temperature in an undivided cell), demonstrably scalable (>17 g), and exhibited a broad substrate scope including primary and challenging secondary alkyl bromides with high to excellent yields.[80] The salient feature of this new procedure is the use of Ni complex Ni·MeBPI·OAc, featuring a tridentate ligand MeBPI in combination with the redox shuttle Ni(MeBPI)$_2$, which served as an overcharge protector of the active Ni catalytic species. Indeed, intensive cyclic voltammetry analyses and evaluation of the reactivity of isolated organometallic complexes revealed that over-reduction of the on-cycle active Ni catalyst species occurred at a potential ($E = -2.0$ V vs Fc/Fc$^+$) which was only 100 mV higher (absolute value) than the potential required to initiate the cross-coupling ($E = -1.9$ V vs Fc$^+$/Fc). In a constant current electrolysis, this reductive degradation of the catalyst was overcome thanks to the redox shuttle Ni(MeBPI)$_2$ that could short circuit the electrochemical cell by carrying the electrons from the cathode to the anode when the rate of reduction (current density *i*) was becoming superior to the rate of cross-coupling (k_{cat}) (Scheme 34).

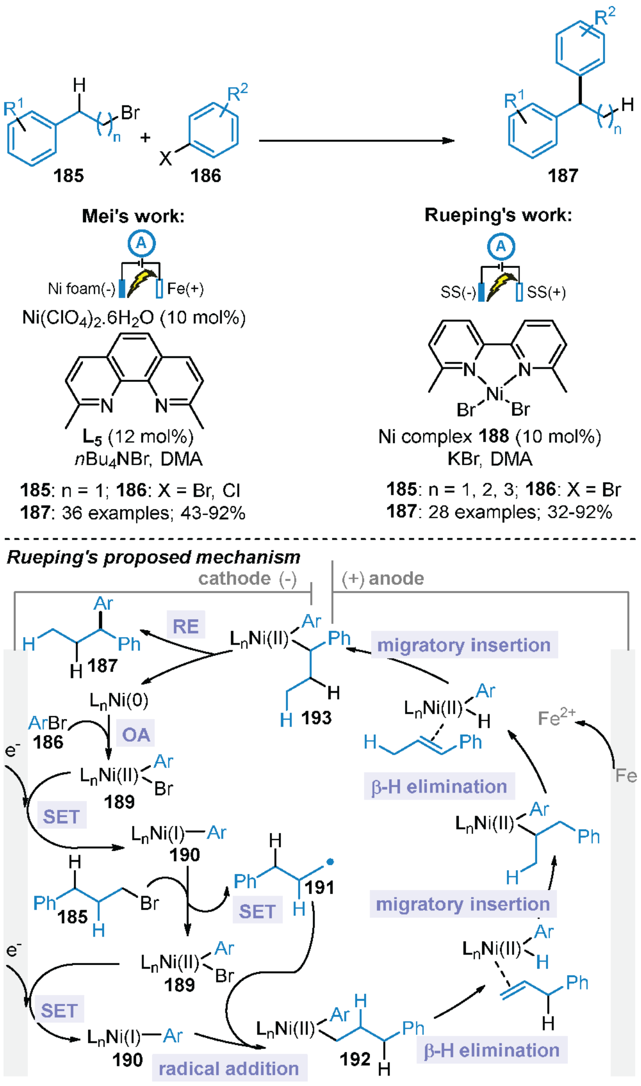
Scheme 34. Ni-Electrocatalyzed Reductive Cross-Coupling of Aryl Bromides with Alkyl Bromide in the Presence of an Overcharge Protector



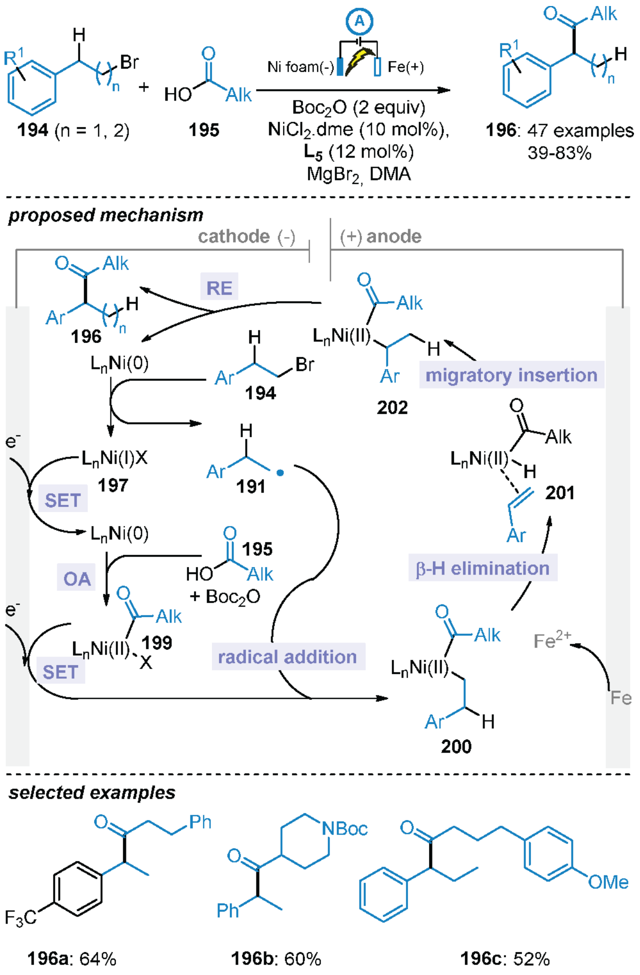
Mei et al. and Rueping et al. independently developed a Ni-catalyzed electroreductive coupling between aryl halides **186** and alkyl bromides **185**, whereby a chain-walking process took place. After the formation of the Ni(II)(alkyl)(aryl) complex, an iterative *β*-hydride elimination, migratory insertion, and reductive elimination afforded products in good yields and excellent regioselectivity.[81,82] The electrolyses were performed under mild reaction conditions in an undivided cell. The two methyl groups at the *ortho* position on the ligands were critical to achieve the desired regioselectivity. The two research groups suggested a Ni(0)/Ni(II) catalytic cycle in which Ni(0) species underwent oxidative addition of aryl halide **186**. According to Rueping et al., the resulting Ni(II) intermediate **189** was reduced at the cathode. SET between the Ni(I)−Ar complex **190** and alkyl bromide **185** generated the corresponding primary alkyl radical **191** and re-formed Ni(II) intermediate **189**. Upon a second SET cathodic event, the trapping of radical **191** by the Ni(I)−Ar complex **190** afforded Ni(II)(alkyl)(aryl) complex **192**. Iterative *β*-H elimination/migratory insertion sequences took place until the thermodynamically more stable branched benzylic Ni(II) complex **193** was attained. Final reductive elimination eventually led to the desired 1,1-diarylalkanes **187** and regenerated the active Ni(0) species (Scheme 35).

Subsequently, Mei et al. harnessed such a chain-walking process for the electroreductive cross-coupling of alkyl bromides **194** and in situ generated alkyl anhydrides to access to dialkyl ketones **196** in good yields and high regioselectivity. A control experiment with a stoichiometric amount of Ni(cod)$_2$ indicated a putative Ni(0) species as the active catalyst. Based on cyclic voltammetry measurements, the proposed mechanism involved the oxidative addition of in situ generated anhydride to Ni(0) to form acyl Ni(II) complex **199**. Upon cathodic SET reduction, trapping of alkyl radical **198** led to Ni(II) complex **200**. Subsequent *β*-H elimination, migratory insertion, and reductive elimination yielded dialkyl ketones **196** and the active Ni(0) complex. The latter reduced the alkyl bromide **194** to generate the alkyl radical **198**. A second SET cathodic reduction regenerated the active Ni(0) catalyst species. It is worth mentioning that addition of magnesium salts was critical to the success of this transformation, probably facilitating the oxidative addition of alkyl anhydride (Scheme 36).[83]

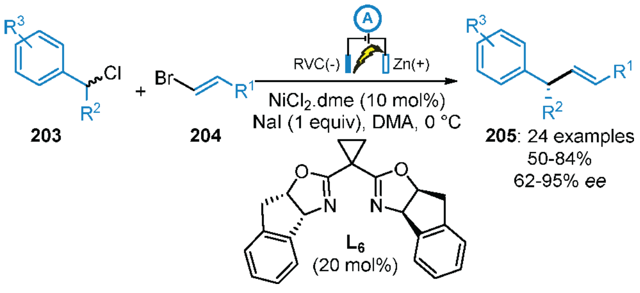
Scheme 35. Ni-Catalyzed Reductive Cross-Coupling of Alkyl Bromides to Aryl Halides



Scheme 36. Ni-Catalyzed Reductive Cross-Coupling of Alkyl Bromides to In Situ Generated Alkyl Anhydrides



Scheme 37. Ni-Catalyzed Asymmetric Electroreductive Alkenylation of Benzyl Chlorides



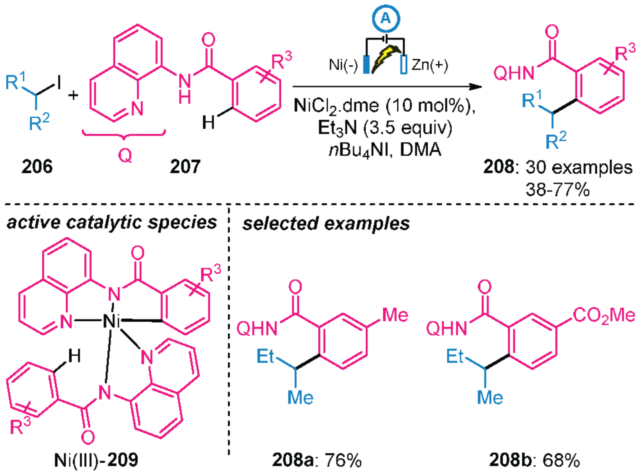
In 2019, Reisman et al. proposed an electrochemical variant to their previously reported enantioselective Ni-catalyzed reductive cross-coupling of alkenyl bromide **204** and benzyl chloride **203**.[84,85] Using the chiral Box ligand $\mathbf{L_6}$, high yields and excellent enantioselectivities were achieved in an undivided cell equipped with a RVC cathode and a zinc-based sacrificial anode. Sodium iodide, which was used as an additive to increase reaction efficiency under the chemical approach, herein played the role of the electrolyte. Such transformation constitutes one of the rare examples of asymmetric electrocatalysis proceeding with high selectivity (Scheme 37).[86−89]

In 2020, Ackermann et al. reported a Ni-catalyzed redox-neutral *ortho*-C−H alkylation of benzamide derivative **207** using 8-aminoquinoline as the bidentate directing group.[90] While conventional chemical approaches of nickel-catalyzed C−H activation required high reaction temperatures and strong bases,[91] this electrochemical cross-coupling was achieved at room temperature with triethylamine as a mild base in an undivided cell using a zinc-based sacrificial anode. Both primary and secondary alkyl iodides **206** could be employed as alkylating agents. Mechanistic studies revealed Ni(III) complex **209** as an active catalytic species in the presence of electricity. A Ni(III/II/I) catalytic cycle was therefore hypothesized involving two SET cathodic reductions (Scheme 38).

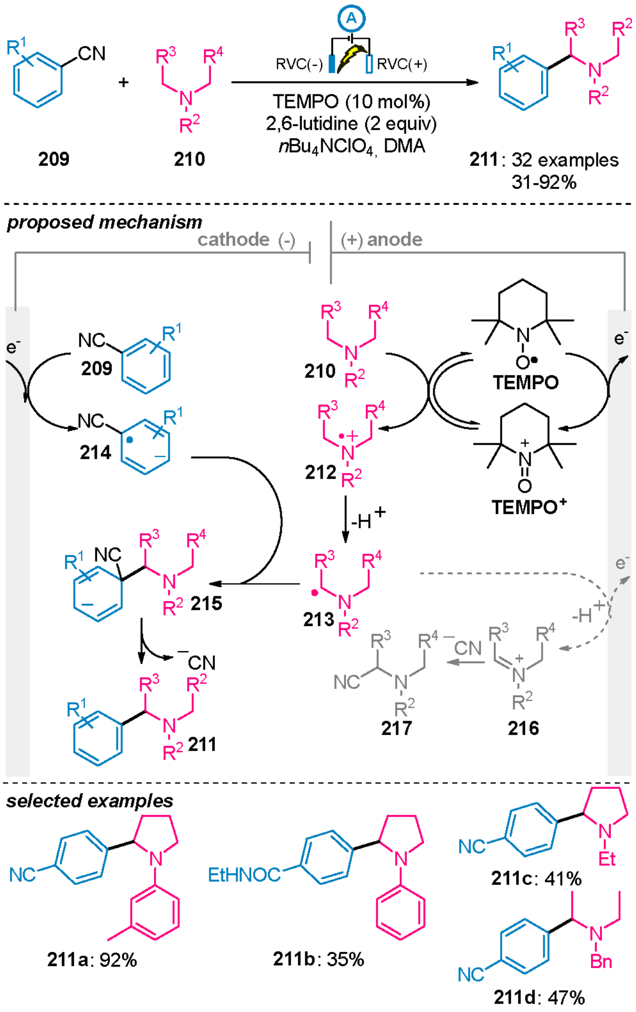
3.9. Convergent Paired Electrolysis

Except for the few cases of linear paired electrolyses (see Schemes 8, 17, and 18) or divergent paired electrolysis (Scheme 12), in most of the examples discussed above, the reaction of interest occurs only at the cathode, while a sacrificial oxidation reaction has to take place at the anode to fulfill electron neutrality. As waste is therefore produced, the overall sustainability and practicability of these processes are not optimal. In contrast, in convergent paired electrolysis, both anodic and cathodic events generate intermediates which react

Scheme 38. Ni-Electrocatalyzed Redox-Neutral *ortho*-C−H Alkylation of 8-Aminoquinoline



Scheme 39. Electrochemical Redox-Neutral α-Amino C(sp^3) Arylation



with each other to yield the product. Although very appealing, this redox-neutral approach implies several challenges that need to be leveraged to achieve the desired transformation over side reactions. Most importantly, it requires (i) properly matching the reaction rate of anodic oxidation and cathodic reduction and (ii) ensuring an effective mass transfer of reactive intermediates from the surface of the electrodes to the bulk solution. To succeed in the formation of a C(sp^3)−C(sp^2) bond via convergent paired electrolysis, two general strategies have recently emerged involving the anodic generation of a C(sp^3) radical and subsequent combination with (i) a cathodically produced persistent aryl radical anion or (ii) a Ni(II)ArX complex.

3.9.1. Combination with a Cathodically Produced Persistent Radical Anion.

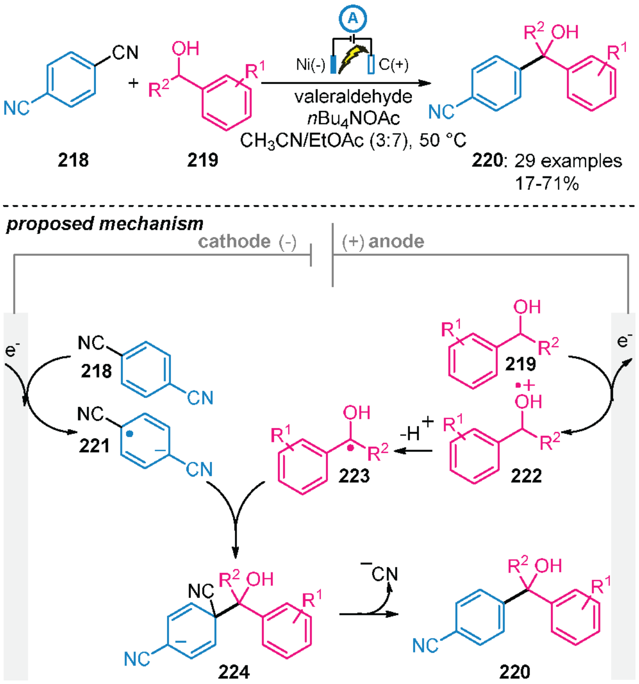
In 2019, Ye et al. accomplished an electrochemical redox neutral α-arylation of tertiary amines **210** with benzonitriles **209**.[92] Using TEMPO as electrocatalyst in the presence of 2,6-lutidine, this C(sp^3)−H bond functionalization proceeded under constant current electrolysis with two RVC electrodes. The best yields were obtained with tertiary arylamines bearing electron-donating groups on the aromatic ring, while electron-withdrawing substituents were not tolerated. Interestingly, the arylation reactions of cyclic tertiary aliphatic amines took place regioselectively at the cyclic position. Cyanoheteroarenes, such as 1,4-dicyanopyridines, were not compatible. From a mechanistic point of view, SET anodic oxidation of TEMPO afforded TEMPO$^+$ which in turn oxidized tertiary amines **203** to form α-amino radical **212** in the presence of 2,6-lutidine. Meanwhile, persistent radical anion **214** was generated at the cathode via SET reduction of benzonitrile **209**. Subsequent radical cross-coupling delivered the *ipso*-substitution product **211** upon elimination of cyanide anion and aromatization. α-Cyanation byproduct **217** was also obtained in a small amount with over anodic oxidation of radical **213** to iminium **216**. It is worth mentioning that an electrolysis on a 10 mmol scale was performed with a three-electrode system, RVC(+)|RVC(−)|RVC(+), to increase the concentration of an α-amino radical at the anode and the collision frequency of anodic and cathodic radicals (Scheme 39). A similar transformation was realized by Mo and Lu et al. in the absence of TEMPO by employing an engineered microfluidic cell (μRN-eChem) equipped with two glassy carbon electrodes.[93]

In their continuous effort to develop electrochemical access to diaryl methanol derivatives (see section 3.5), Findlater, Zhang, and Xu et al. disclosed an electrochemical α-arylation of benzylic alcohols **219** with 1,4-dicyanobenzene **218** using a graphite anode and a nickel cathode.[61] Primary and secondary alcohols could be employed, albeit with lower yields in the latter case. Cyclic voltammetry analyses provided evidence of both anodic oxidation of benzylic alcohol **219** and cathodic reduction of 1,4-dicyanobenzene **218**, leading to ketyl radicals **223** and radical anion **221**, respectively. Further radical cross-coupling gave rise to intermediate **224** and eventually to the *ipso*-substitution product **220** upon spontaneous decyanation. This C(sp^3)−H bond functionalization was performed in the presence of valeraldehyde to trap the toxic cyanide anion (Scheme 40).

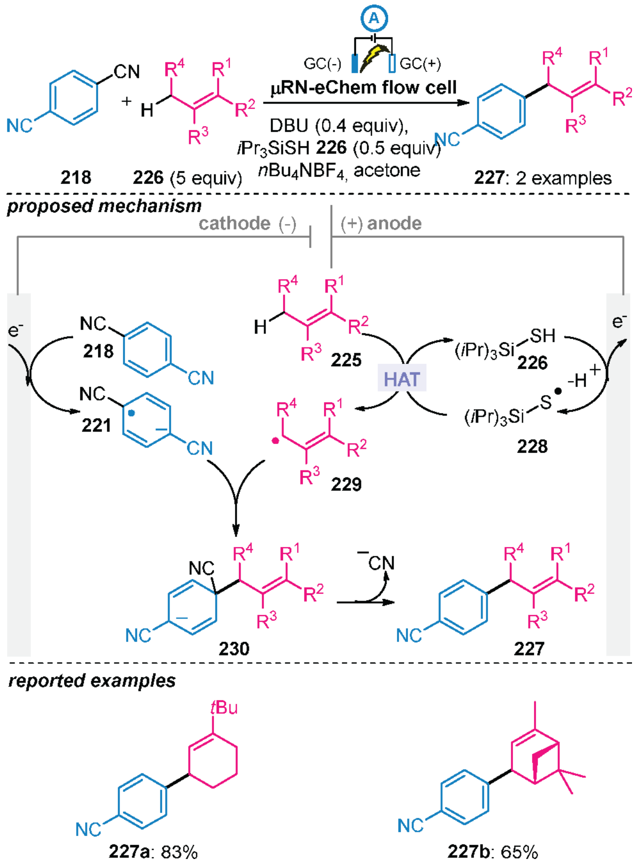
An elegant thiol-catalyzed allylic C(sp^3)−H arylation of alkenes **225** with 1,4-dicyanobenzene **218** was demonstrated by Mo et al. by taking advantage of their μRN-eChem flow cell.[93] Anodic oxidation of triisopropylsilanethiol catalyst **226** generated electrophilic thiyl radical **228** which regioselectively abstracted a hydrogen atom at the allylic position of alkene **226**. The resulting allylic radical **229** coupled with cathodically generated persistent radical anion **221** to build the C(sp^2)−C(sp^3) bond upon *ipso*-substitution (Scheme 41).

This homemade μRN-eChem flow cell was also applied to the electrochemical decarboxylative and decyanative cross-coupling

Scheme 40. Electrochemical Redox-Neutral α-Arylation of Benzylic Alcohols

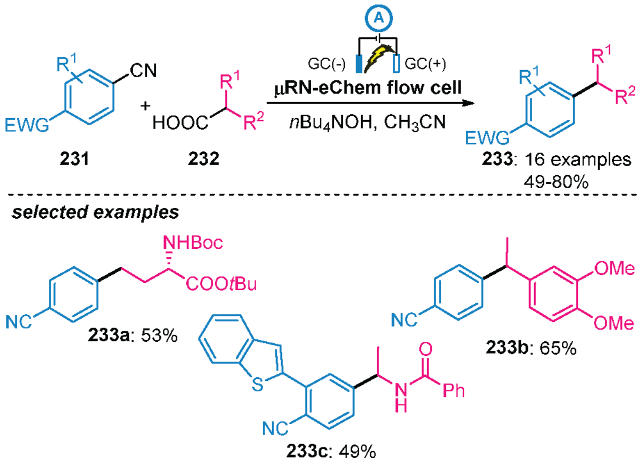


Scheme 41. Thiol-Electrocatalyzed Redox-Neutral Allylic C−H Arylation



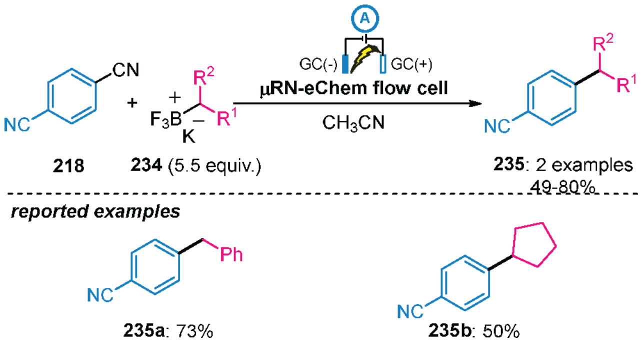
between carboxylic acids **232** and electron-poor cyanobenzenes **231**.[94] Six equivalents of carboxylic acids were necessary to obtain high yields. Tetrabutyl ammonium hydroxide was employed as a base to generate the carboxylate salts. As such, the reaction medium was sufficiently conductive, making an additional electrolyte unnecessary. The transformation involved the concomitant anodic generation of an alkyl radical via oxidative decarboxylation of carboxylate salts and cathodic generation of a persistent aromatic radical anion via SET reduction of **231** and further radical combination. Such a convergent paired electrolysis precluded the preactivation of carboxylic acids under the form of redox-active esters. Primary and secondary alkyl radicals reacted smoothly, but no example was reported with the tertiary ones (Scheme 42).

Scheme 42. Electrochemical Redox-Neutral Decarboxylative Arylation of Carboxylic Acids



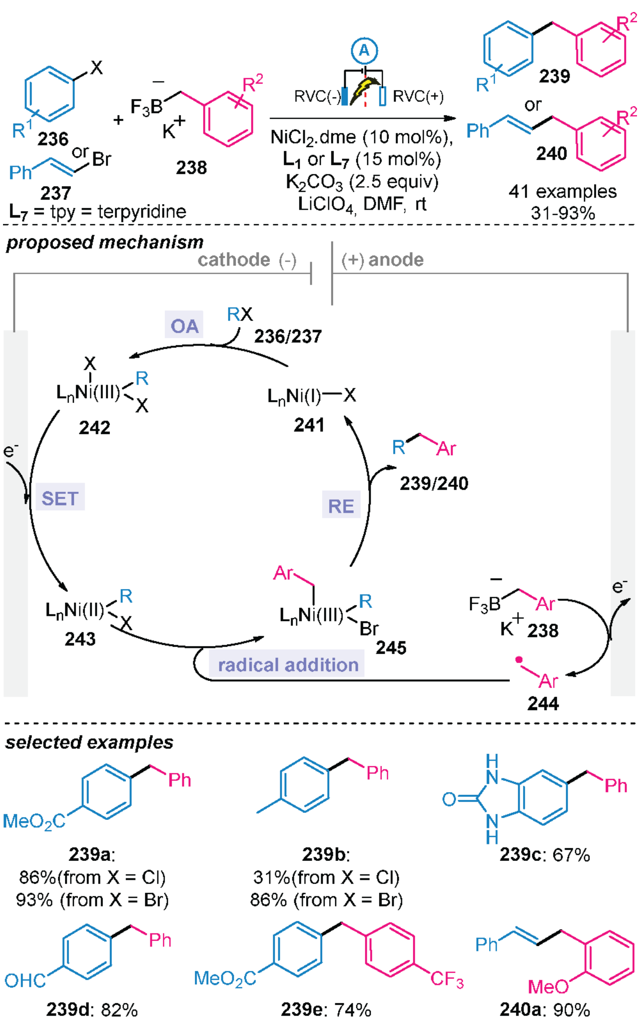
A last application of this electrochemical flow cell involved the deboronative arylation of organic trifluoroborate salts **234** with 1,4-dicyanobenzene **218**.[94] In a similar process as the decarboxylative arylation reaction mentioned above, an alkyl radical was generated at the anode upon SET oxidation of **234** and further deboronation (Scheme 43).

Scheme 43. Electrochemical Redox-Neutral Deboronative Arylation of Organic Trifluoroborate Salts with 1,4-Dicyanobenzene



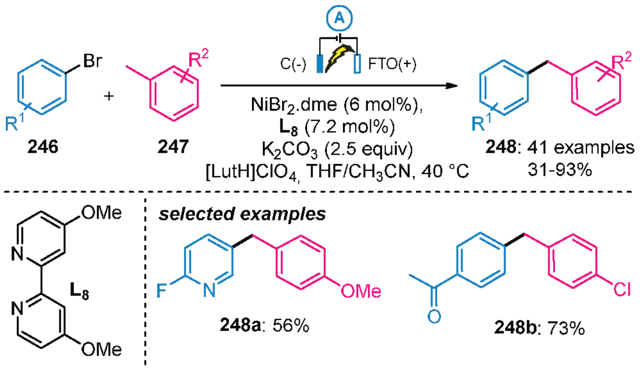
3.9.2. Combination with a Cathodically Produced Ni(II)ArX Complex. Liu et al. reported a Ni-catalyzed electrochemical cross-coupling of benzyltrifluoroborate salts **238** with (hetero)aryl bromides or chloride **236** and β-bromostyrene **237**. Two RVC electrodes were utilized under galvanostatic electrolysis.[95] Remarkably, electron-rich and electron-poor substituents were well-tolerated on the aromatic rings of both **236** and **238**. Mechanistically, cyclic voltammetry analysis ruled out a Ni(I)/Ni(0) redox couple at the cathode. The catalytic active Ni(I) species **241** would more likely undergo oxidative addition of the organic halide **236**/**237** to provide Ni(III) complex **242**. Concomitant cathodic SET reduction of the latter and anodic SET deboronative oxidation of **238** afforded Ni(II) complex **243** and benzylic radical **244**, respectively. Subsequent radical combination and reductive elimination of the resulting high valent Ni(III) species **245** delivered the cross-coupling products **239**/**240** and recovered the active catalytic Ni(I) species (Scheme 44).

Scheme 44. Ni-Electrocatalyzed Redox-Neutral Cross-Coupling of Organic Trifluoroborate Salts with Organic Halides



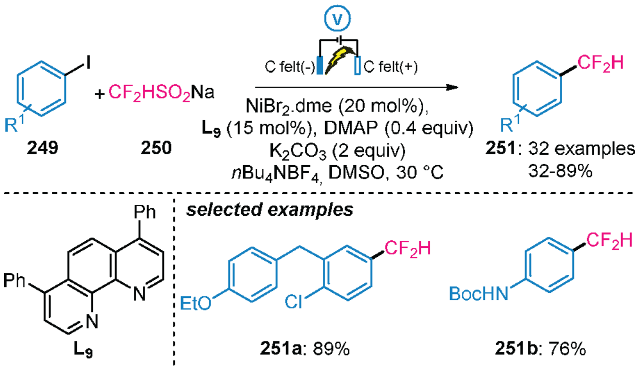
In 2020, Hu et al. established a Ni-catalyzed electrochemical redox-neutral cross-coupling between toluene derivatives **247** and (hetero)aryl bromides **246**.[95,96] This attractive benzylic C(sp^3)−H arylation proceeded under mild constant current electrolysis but required a specific fluorine-doped tin oxide-coated glass anode. Electron-rich as well as electron-poor aryl bromides **246** were suitable coupling partners for this transformation. However, a large excess of toluene derivatives **247** was necessary to achieve high yields (typically 3 equiv of 4-methylanisole and 10 equiv of other less electron-rich partners). Cyclic voltammetry measurements and control experiments supported the anodic generation of a benzylic radical. The latter was introduced in the nickel catalytic cycle similarly to Liu's work (see Scheme 44) (Scheme 45).

Scheme 45. Ni-Electrocatalyzed Redox Neutral Cross-Coupling of Toluene Derivatives with Aryl Bromides



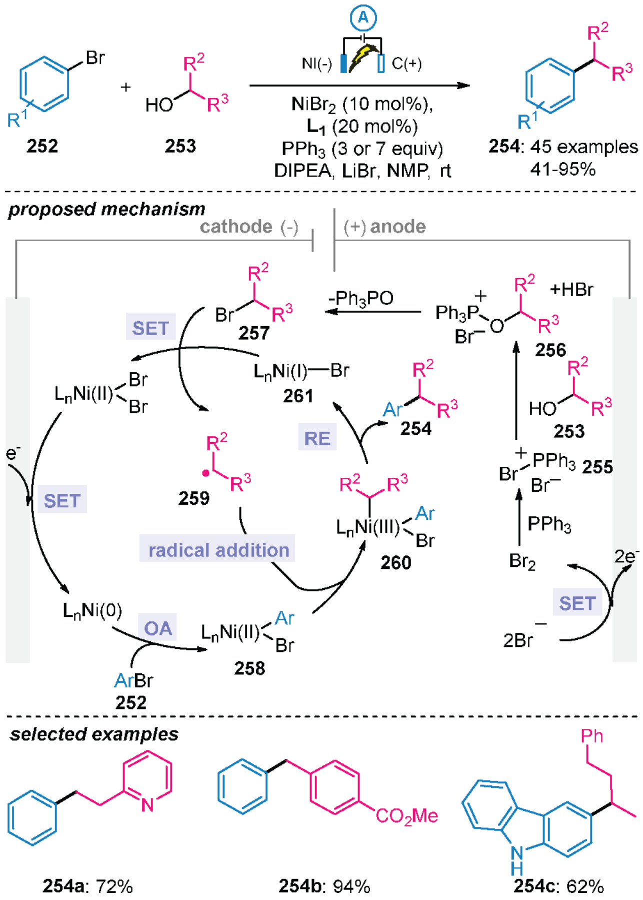
In the same vein, Zhang and Wang et al. have very recently developed a nickel-catalyzed electrochemical difluoromethylation of aryl iodides **249** by employing sodium difluoromethanesulfinate **250** as source of fluoroalkyl radicals with simple graphite felt electrodes in DMSO. Phenanthroline derivative $\mathbf{L_9}$ was the best ligand in the presence of dimethylamino pyridine (DMAP). Moderate to good yields were obtained but no reaction occurred with aryl bromides. It is worth mentioning that this procedure could be extended to the monofluoromethylation of aryl iodides (Scheme 46).[97]

Scheme 46. Ni-Electrocatalyzed Redox-Neutral Difluoromethylation of Aryl Iodides



Very recently, Li et al. have developed an elegant electrochemical dehydroxylative coupling of primary and secondary alcohols **253** with aryl bromides **252** under Ni(II) catalysis.[98] The electrolysis was performed under constant current with cheap graphite anode and nickel foam cathode in NMP/LiBr as the solvent electrolyte system in the presence of an excess of triphenylphosphine. Control experiments and analysis of reaction byproducts provided evidence for the in situ generation of alkyl bromides **257**. Accordingly, two consecutive SET oxidations of bromide anion would occurred first at the anode to generate Br_2 which would be trapped by the triphenylphosphine to form bromotriphenylphosphonium salt **255**. Further reaction with alcohol **253** would produce the alkyl bromide **257** via the intermediate **256** (Appel-type reaction). Subsequently, at the cathode, the coupling with aryl bromide **252** under Ni(II) electrocatalysis formed the C(sp^2)−C(sp^3) bond, in agreement with Hansen's and Sevov's works (see section 3.8).[78−80] More specifically, the authors proposed the electrochemical generation of low-valent Ni(0) species via two SET reductions of $NiBr_2$. Oxidative addition of aryl bromide **252** and combination with alkyl radical **259** gave rise to Ni(III) complex **260**. Subsequent reductive elimination afforded the coupling product **254** and Ni(I) complex **261**. The latter further reduced alkyl bromide **257** to produce the alkyl radical **259** and to regenerate the Ni(II) catalyst. A stoichiometric amount of DIPEA was required to neutralize the in situ generated HBr (Scheme 47).

Scheme 47. Ni-Electrocatalyzed Redox-Neutral Dehydroxylative Coupling of Alcohol with Aryl Bromide



4. CONCLUSION

Important achievements have been recently accomplished in electrochemical cathodic processes for the formation of $C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$. Electroreductive transformations as well as convergent paired electrolysis have been performed under mild reaction conditions, enabling a great step toward green and sustainable chemistry. Such successes have been possible thanks to intensive mechanistic studies, the development of electrocatalytic systems, and the amelioration of electrolytic setups such as electrode materials.[82] The use of flow cell systems has also greatly contributed to these recent accomplishments. Indeed, by shortening the distance between the anode and cathode, such engineering minimizes the Ohmic drop and increases mass transfer, allowing therefore the application of higher currents, the reduction of the concentration of supporting electrolytes, and an easier scale-up.[99,100] Additionally, the recent standardization of apparatus either in batch[101,102] or flow cells[103−105] should accelerate the recourse to the electrosynthesis in both academic and industrial research. However, despite significant advances, unconquered challenges still need to be met to access more complex molecules. The design of cascade reactions and the combination with photocatalytic processes[106,107] are examples of avenues worth exploring. Moreover, the "holy grail" in the formation of C−C bonds is the control of the enantioselectivity. Rare examples of catalytic asymmetric electroreductive processes have been reported to date and much more development in the highly challenging enantioselective electrochemical cathodic reactions has to be accomplished. We hope that this review will stimulate further progress in this exciting area of electrochemical C−C bond-forming reactions through cathodic transformations.

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Notes

The authors declare no competing financial interest.

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