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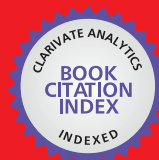
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C-H Activation/Functionalization via Metalla-Electrocatalysis

Guilherme M. Martins, Najoua Sbei, Geórgia C. Zimmer and Nisar Ahmed

Abstract

In conventional methods, C−H activations are largely involved in the use of stoichiometric amounts of toxic and expensive metal & chemical oxidants, conceding the overall sustainable nature. Meanwhile, undesired byproducts are generated, that is problematic in the scale up process. However, electrochemical C−H activation via catalyst control strategy using metals as mediators (instead electrochemical substrate control strategy) has been identified as a more efficient strategy toward selective functionalizations. Thus, indirect electrolysis makes the potential range more pleasant, and less side reactions can occur. Herein, we summarize the metalla-electrocatalysis process for activations of inert C−H bonds and functionalization. These Metalla-electrocatalyzed C−H bond functionalizations are presented in term of C−C and C−X (X = O, N, P and halogens) bonds formation. The electrooxidative C−H transformations in the presence of metal catalysts are described by better chemoselectivities with broad tolerance of sensitive functionalities. Moreover, in the future to enhance sustainability and green chemistry concerns, integration of metalla-electrocatalysis with flow and photochemistry will enable safe and efficient scale-up and may even improve reaction times, kinetics and yields.

Keywords: metalla-electrocatalysis, C−H bonds activation, catalyst control strategy, mediators, atom and step economy

1. Introduction

The direct functionalization of C−H bonds provides a powerful synthetic pathway for selective C−C and carbon−heteroatom (C−X) bond formation, thus improving atom- and step economy as well as rationalization of chemical synthesis [1, 2]. In the field of conventional C−H activation, prefunctionalization of substrates, generally high temperatures, acidic conditions and/or the use of stoichiometric oxidants (such as a peroxide, a hypervalent iodine) are required due to the high bond dissociation energies, unreactive molecular orbital profiles, low acidities, and ubiquitous nature of the C−H bonds [3, 4]. The stoichiometric amount of reagents/oxidants affect the product's selectivity, additionally the formation of by-products result in overall low turnover of the reaction. Electrochemical C−H functionalization has advantages as this process avoids prefunctionalization of substrates and offering the direct transformation of a simple substrate to a complex and valuable molecule [5]. However, for C−H functionalization, still need a high oxidation potential for selective C−H bonds activation compared

to organic solvents and common functional groups. To overcome this problem, indirect electrolysis via catalysts control strategy (mediators such as redox metal catalysts) is beneficial, makes the potential range more pleasant and has control over selectivity at mild conditions that is not observed through classical catalyst control strategy [6, 7]. From the 90's, great progress was observed in the evolution of reactions involving control of regioselectivity and enantioselectivity. Much of this merit was achieved by the evolution of catalysts based on high-performance transition metals. Derivatives of organic halides, triflates and several other leaving groups are still applied in reactions of aryl alkylations (Friedel-Crafts) and in cross-coupling reactions with several organometallic reagents. In addition, alkenes are also good substrates for aryl alkylation, alkenylation, or for cross-coupling reactions catalyzed by transition metals, using the corresponding halides or correlated substrates. However, most of the known transition metal catalysts do not meet all the requirements of modern developments, and often the biggest limitation is low efficiency and high costs to obtain efficient ligands. Faced with this challenge, there is an increasing use of new technologies applied concurrently to these catalytic systems, making transition metal catalysts more efficient and cleaner, enabling new mechanistic routes [8]. Additionally, the use of electrochemistry concomitant with the chemistry of transition metals offers a powerful strategy, since it avoids the use of external redox additives [9].

Electrocatalysis is a field of electrochemistry that has been gaining great growth in recent years due to the several advantages. In indirect electrosynthetic reactions, the exchange of electrons occurs between a mediator and the organic substrate. Therefore, by varying the applied current or voltage of the power source, the oxidation or reduction capacity of the electrochemical system can be manipulated, this being a great advantage in the method. Likewise, the redox mediator alters the applied potential required for electron transfer, making the potential range more pleasant, and fewer side reactions can occur, avoiding overoxidation, dimerization, parallel reactions or electrode passivation (**Figure 1**). In addition, electrocatalysis deals with the development for energy storage, solar fuels, fuel cells, and also other electrochemical devices with charge transfer reactions interfacial control [10].

Whereas the redox potentials and the selectivity of the reaction can be controlled by changing the ligand of the mediators of the complex transition metals. With the use of electrochemistry this process can become more selective, due to the possibility of controlling the electrical potential of the reaction
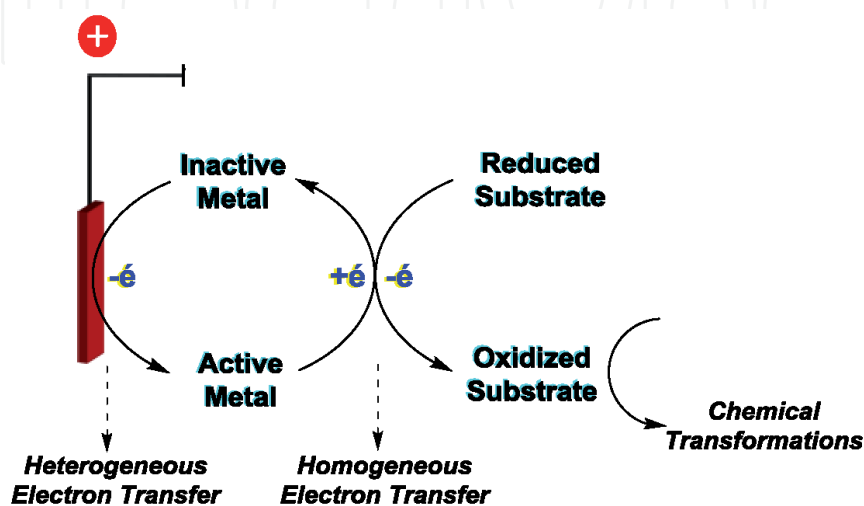

Figure 1.
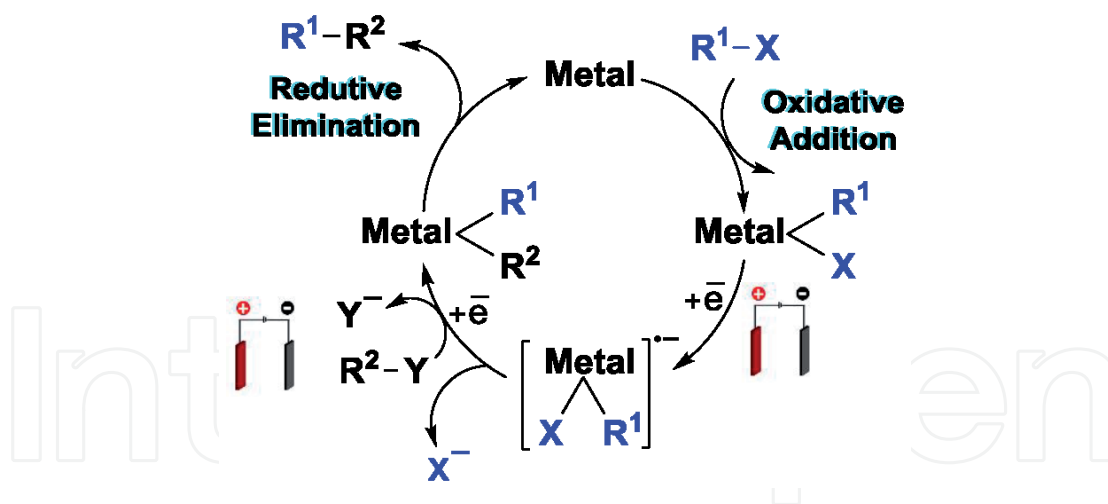*General illustration of indirect anodic transformation.*

Figure 2.
General mechanism for cross-coupling reactions with transition metal mediator.

Figure 3.
Cell notations.

medium by changing the voltage (V) or the electric current (A) through the energy source (**Figure 2**) [11].

Considering this, we have prepared an overview of the recent metalla-electrocatalysis process for activation/functionalization of inert C−H bonds. The perspective and limitations together with mechanistic discussions will be presented.

To offer an easy interpretation of the different catalytic systems discussed here, we will use a standardized notation, differentiating the divided cell from the undivided cell, as well as if the reaction follows via constant current or constant potential (**Figure 3**). Additionally, the different types of electrodes will be added along with other details, offering a better experience for the reader.

2. C-C bond formation

The possibility of extending an organic structure through the formation of new C-C bonds is essential for medicinal chemistry, synthesis of natural products, materials chemistry and even agrochemical synthesis, among others [12–14]. Synthetic methodologies via carbometallation have been intensively developing in recent decades, and group **8–11** metals stand out in these transformations [15].

Palladium-catalyzed C-H cross-coupling reactions are known to be powerful tool to build new C-C bonds. Considering this, Mei and co-workers reported a C(sp^2)-H coupling of ketoximes **1** with organoboron **2** or α-ketoacid **3** reagents catalyzed by Pd, using electrical current instead of external oxidants (**Figure 4**) [16]. In an H-type divided cell, with two platinum electrodes and a Nafion 117 membrane at 60°C,
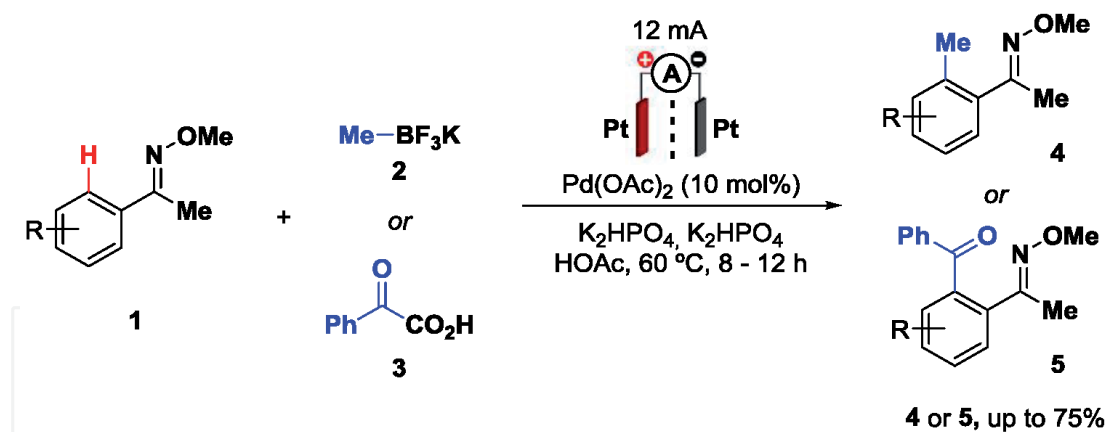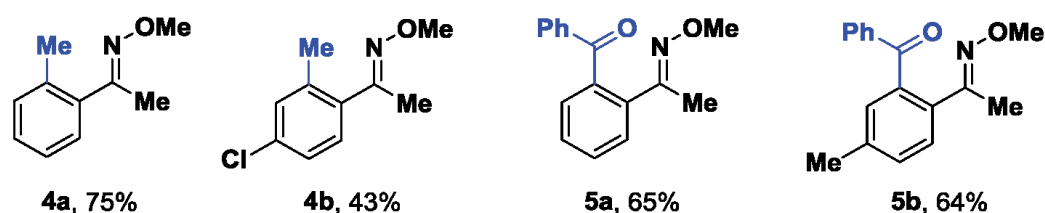
Figure 4.
C(sp²)-H coupling catalyzed by Pd of ketoximes with organoboron or α-ketoacid reagents.

several substituted oxime ethers were applied, and the corresponding methylated **4** and acylated **5** products were obtained, with yields of up to 75% isolated.

Considering experimental results, the authors suggest a mechanism for $C(sp^2)$-H methylation via electrochemical oxidation (**Figure 5**). Initially, the palladium catalyst coordinates with a nitrogen atom, approaching the ortho-C–H bond, activating the $C(sp^2)$-H bond to form the palladacycle. Transmetallation with $MeBF_3K$ under anodic oxidation conditions can provide Pd(III) or Pd(IV), which followed by reductive elimination, delivers the methylated product **4**, regenerating the Pd(II) species. The authors do not rule out the possibility of alkylation going via Pd(II)/Pd(0). It is worth mentioning that the cyclic voltammogram of palladacycle revealed an oxidation wave at 1.21 V *vs* Ag/AgCl, suggesting that the anode can oxidize the aryl palladium(II) intermediate to a high-valued Pd(III) or Pd(IV) species.

Asymmetric catalysis has valuable applications in the synthesis of useful compounds. A greater understanding of the mechanisms involved contributes to expanding its scope, as well as the use of new technologies, which should offer new insights. Ackermann and co-workers reported the very first asymmetric metalla-electrocatalyzed C-H activation [17]. With the aid of a transient directing group (TDG) using graphite felt and platinum electrodes, pallada-electrocatalysis was obtained in high enantioselectivities under moderate reaction conditions, providing the synthesis of highly enantiomerically-enriched biaryls axially chiral scaffolds **9** (**Figure 6**). Likewise, vinyl phosphonate, vinyl sulfone and cholesterol derivatives have increased the versatility of the method. Mechanistic experiments and computation studies provided important insights into the intermediates and the catalyst's path of action with the TDG. Kinetic studies with isotopically labeled substrates suggest that the activation of C-H is the determining step of the reaction.

C-centered radical cyclization under electrochemical conditions has been used to obtain cyclic structures. These radicals are highly reactive and attractive in organic synthesis, and has received attention. Pan and co-workers reported an electrosynthesis of functionalized 1-naphthols using alkynes and 1,3-dicarbonyl compounds by (4 + 2)
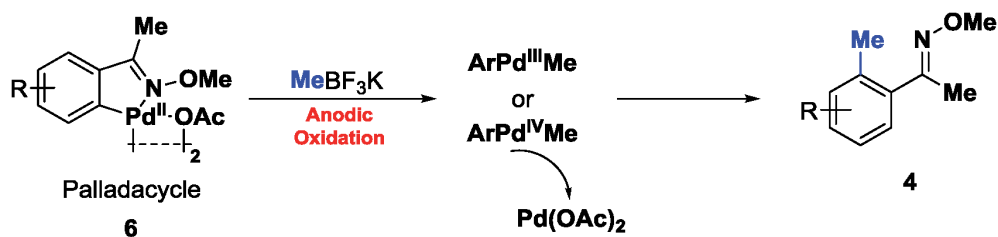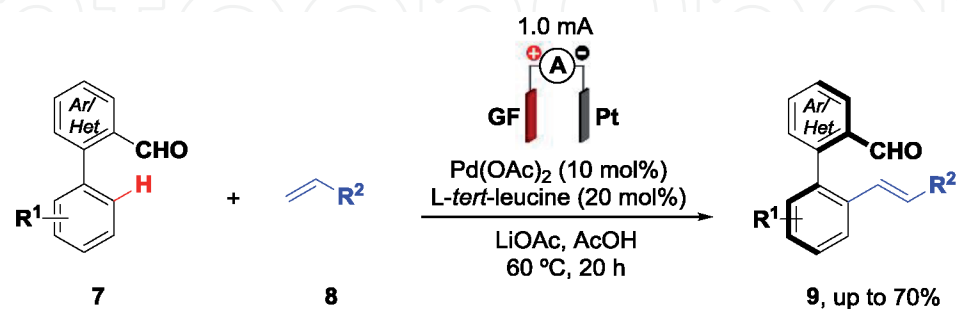
Figure 5.
Representative mechanism for C(sp²)-H coupling catalyzed by Pd of ketoximes with organoboron reagent.
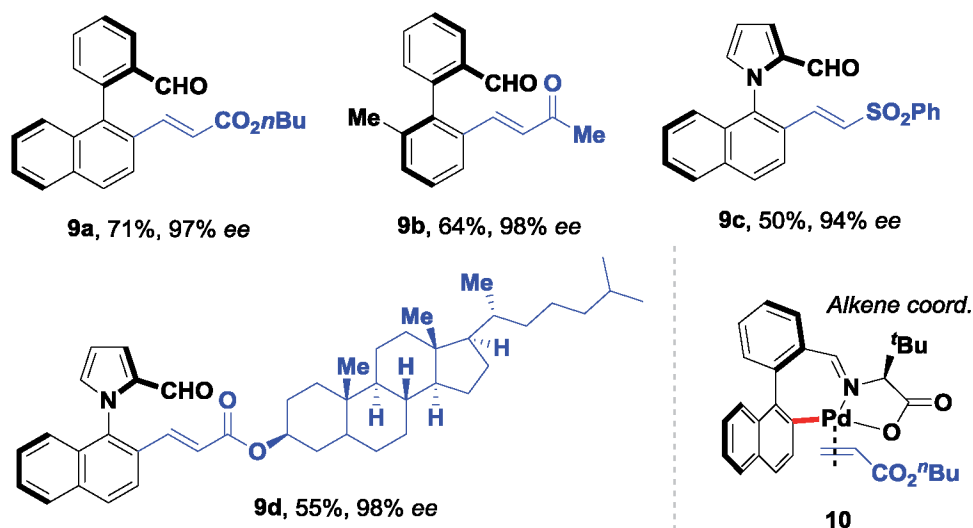

Figure 6.
Asymmetric metalla-electrocatalyzed C-H activation for the synthesis of axially enantioenriched biaryl and heterobiaryl.

annulation of C-centered radical [18]. The reactions were carried out in an undivided cell in the presence of Cp_2Fe as a catalyst in THF/EtOH at a constant potential of 1.15 V vs. Ag/AgCl with NaOEt (30 mol%), during 2 h at 100°C (**Figure 7**). In general, good yield were obtained for compounds with the electron-donating or electron-withdrawing substituents, up to 84%. According to the control experiments, radical intermediates are involved and with absence of Cp_2Fe the product was obtained with reduced yield, that is, direct electrolysis results in lower yields. Based on this and cyclic voltammetry experiments, a possible mechanism was proposed (**Figure 8**). Under electrochemical conditions, it is necessary to form the conjugate base **14** to react with Cp_2Fe due the oxidation potential of intermediate **14** is slightly lower than Cp_2Fe. The ethoxy ion was formed from cathodic reduction and reacts with the compound **1a** to form the intermediate **14**. Meanwhile, at the anode, Cp_2Fe is oxidized to Cp_2Fe^+, which can be oxidized to intermediate **14** to conduct the single-electron transfer, generating a C-radical intermediate **15**. The radical intermediate **15** react with compound **12** to give
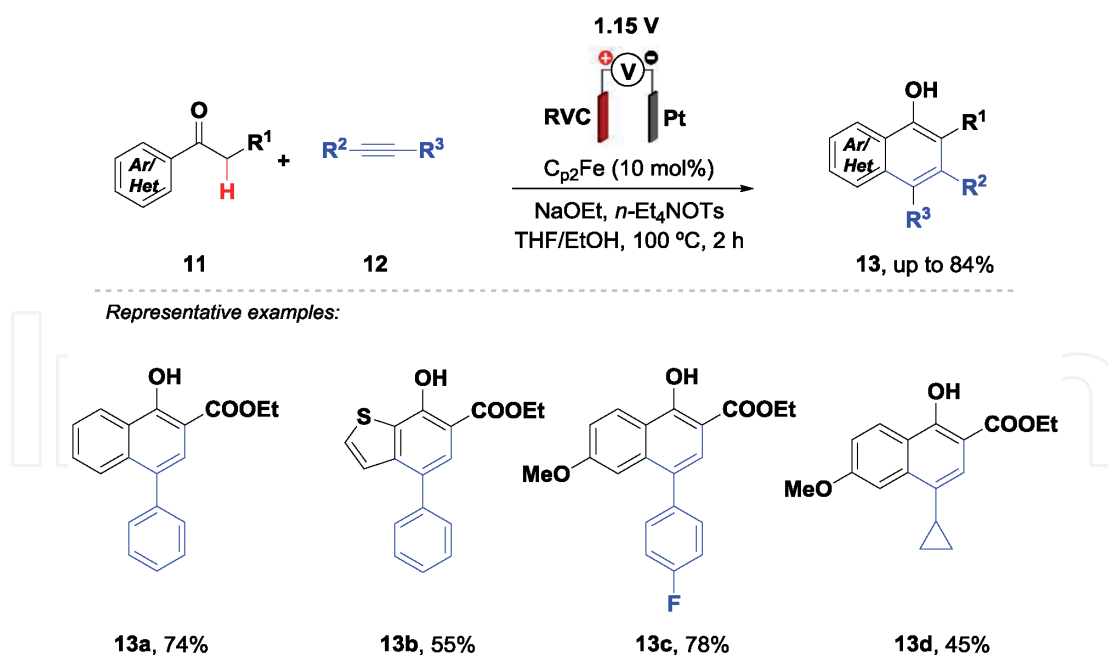
Figure 7.
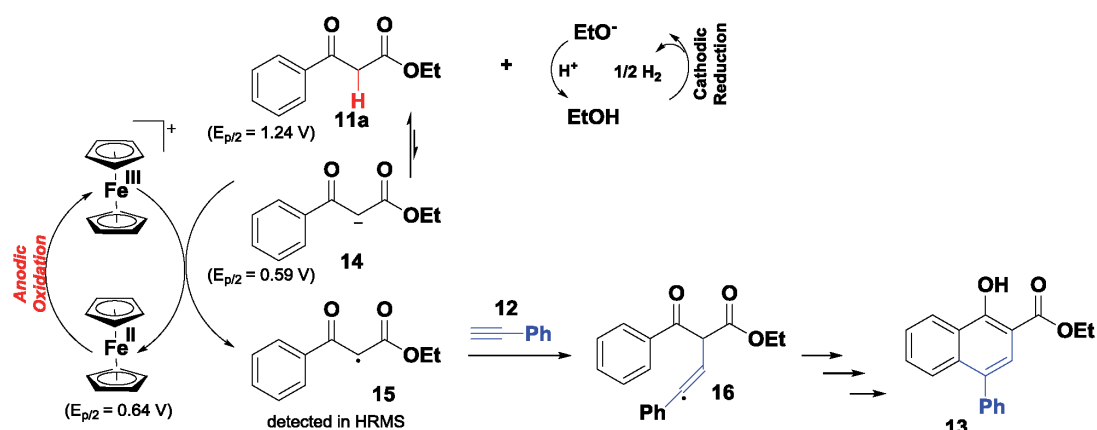*Electrochemical intermolecular annulation of alkyne with 1,3-dicarbonyl.*

Figure 8.
Proposed mechanism for electrosynthesis of functionalized 1-naphtols.

intermediate **16**. From this point an intramolecular cyclization occur leading to obtain the product **13**.

Ackermann and co-workers reported an electrooxidative C-C alkenylation performed by rhodium(III) catalysis [19]. This reaction proceeded with ample scope and excellent levels of chemo- and position selectivities within an organometallic C-C activation manifold. The reactions were carried out in an undivided cell, in a constant current at 4.0 mA using $[Cp^*RhCl_2]_2$ as catalyst, in combination with a platinum plate cathode and a reticulated vitreous carbon (RVC) at anode, along with KOAc as additive in H_2O at 100°C (**Figure 9**). According to the examination of leaving group substitution pattern, tertiary and secondary alcohols bearing either aryl or alkyl groups led the product **19**. Contrarily, a primary alcohol did not deliver the desired product, illustrating the importance of the acidic functionality for inducing the C-C cleavage. This methodology revealed to be a position-selective rhodium-catalyzed C-C activation of 1,2,3-trisubstituted arenes **17**. Mechanism analysis showed that C-C activation occurred significantly faster as compared to corresponding C−H activation. Furthermore, the presence of molecular hydrogen
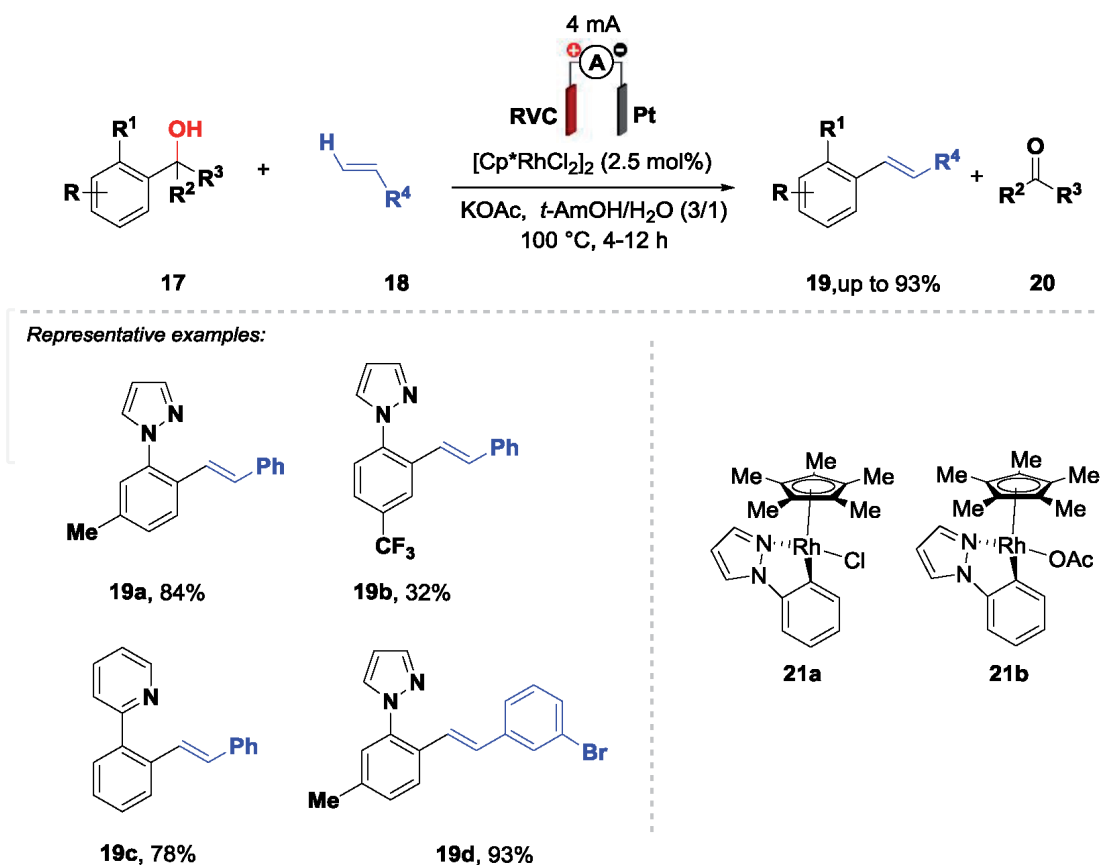
Figure 9.
Eletrochemical C−C alkenylation by rhodium(III) catalysis.
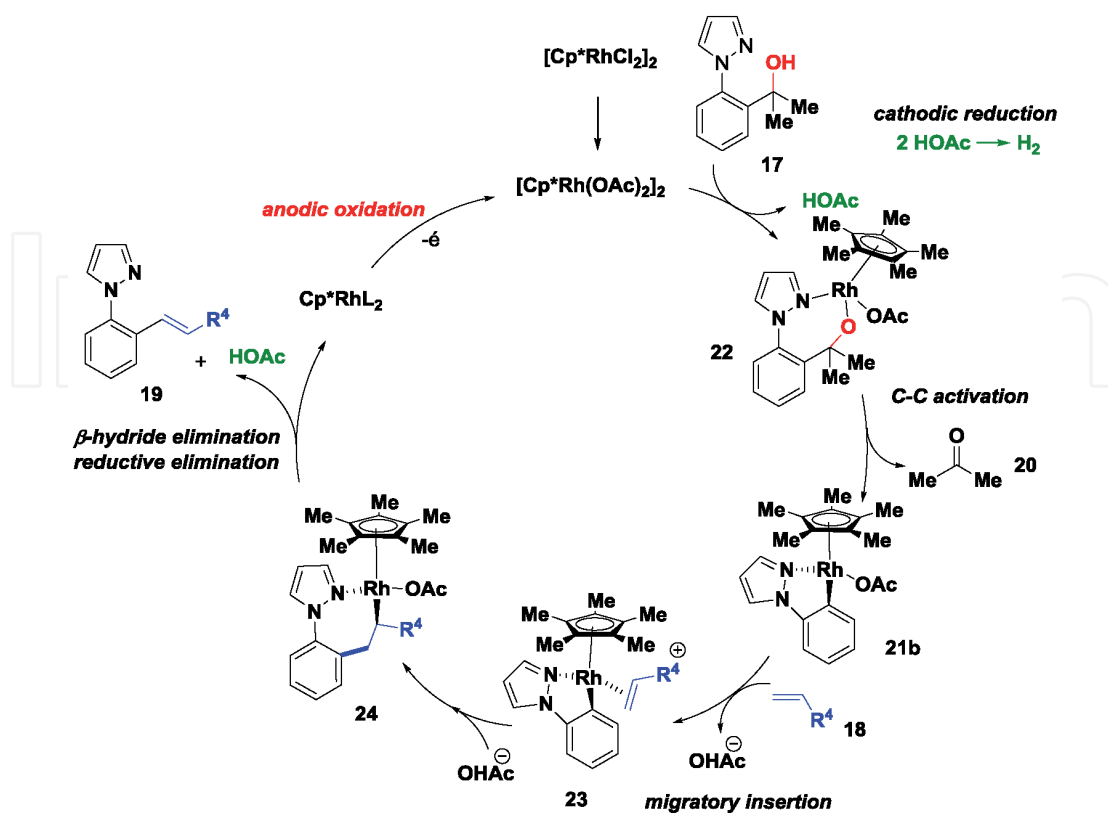

Figure 10.
Proposed catalytic cycle for the rhodium-electrocatalysed C−C alkenylation.

as byproduct was confirmed by gas-chromatographic headspace analysis. The previously prepared complex **21a-b** showed to be a competent catalyst, proving the organometallic nature of the electro-oxidative C−C alkenylation. The cyclic voltammetry experiments showed clearly a ligand exchange, forming [Cp*Rh(OAc)$_2$]$_2$. The proposed reoxidation of rhodium(I) species to regenerate the catalytically competent rhodium(III) was explored with the well-defined Cp*Rh(I) complex [Cp*Rh(cod)]. This complex was shown to be easily oxidized at Ep = −0.16 V versus Fc$^{+/0}$. Based on this study a plausible catalytic cycle for the rhodium-electrocatalyzed C-C alkenylation was proposed (**Figure 10**).

Mo and co-workers reported a general electrochemical strategy for the combined trifluoromethylation/C(sp^2)−H functionalization using Langlois' reagent as the CF$_3$ source [20]. The reactions were carried out an undivided cell using MnBr$_2$ as the mediator, H$_3$PO$_4$ as the sacrificial oxidant, Pt as the electrodes with a constant electric current of 10 mA for 6 h (**Figure 11**).

The mechanism study by cyclic voltammetry showed that combination of MnBr$_2$ and CF$_3$SO$_2$Na exhibits a quasi-reversible anodic CV feature at 0.83 V, that was attributed to the Mn^{II}/Mn^{III} redox couple of the CF$_3$-bond complex. When the reagent was added in mixture of MnBr$_2$ and CF$_3$SO$_2$Na, it was observed the presence of two irreversible anodic waves of 0.94 and 1.59 V, which correspond to the formation of the putative Mn^{III}-CF$_3$ and the single electron oxidation leading to the final product. Summarizing, the Mn^{III}-CF$_3$ species is produced by anodic oxidation of Mn^{II} in the presence of Langlois reagent. After, Mn-assisted delivery of CF$_3$• to the olefin forming a carbon radical. Subsequently, the aromatic ring radical is

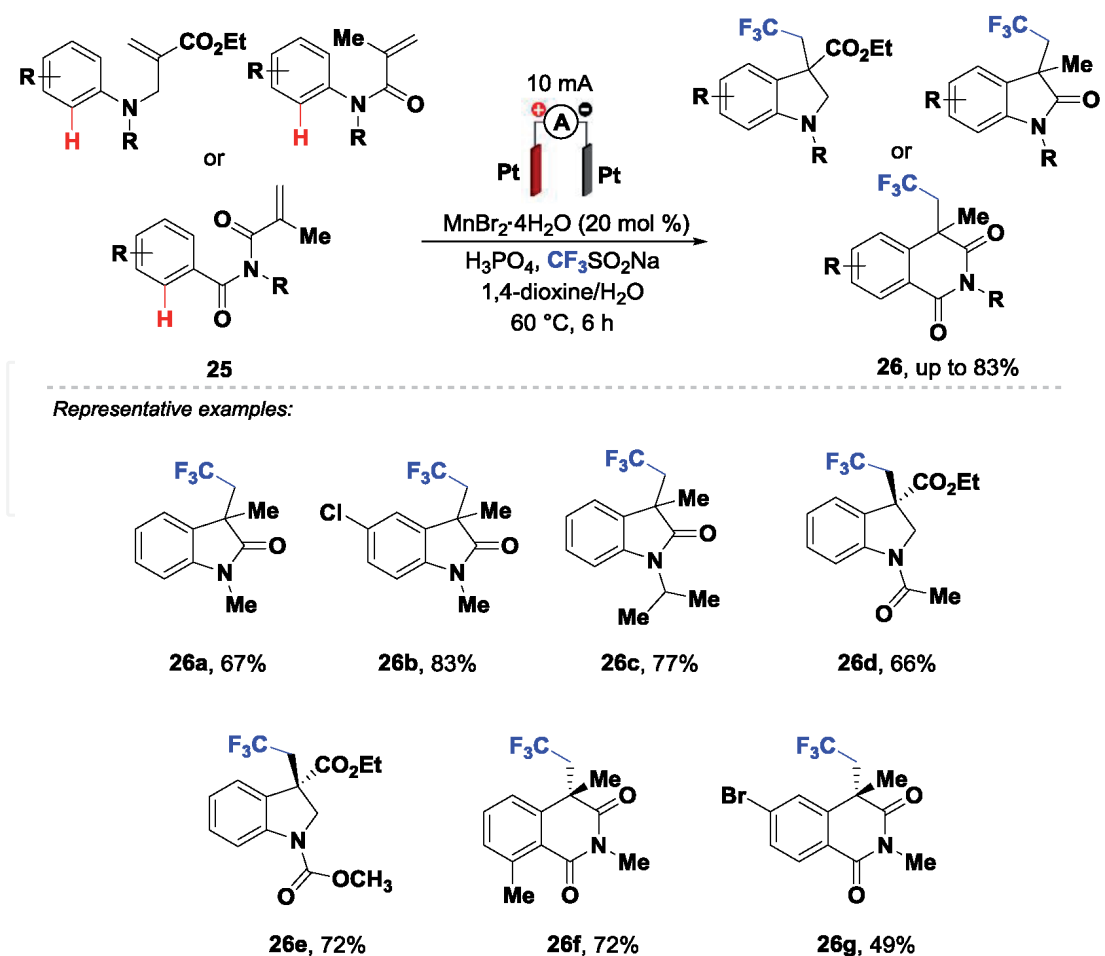**Figure 11.**
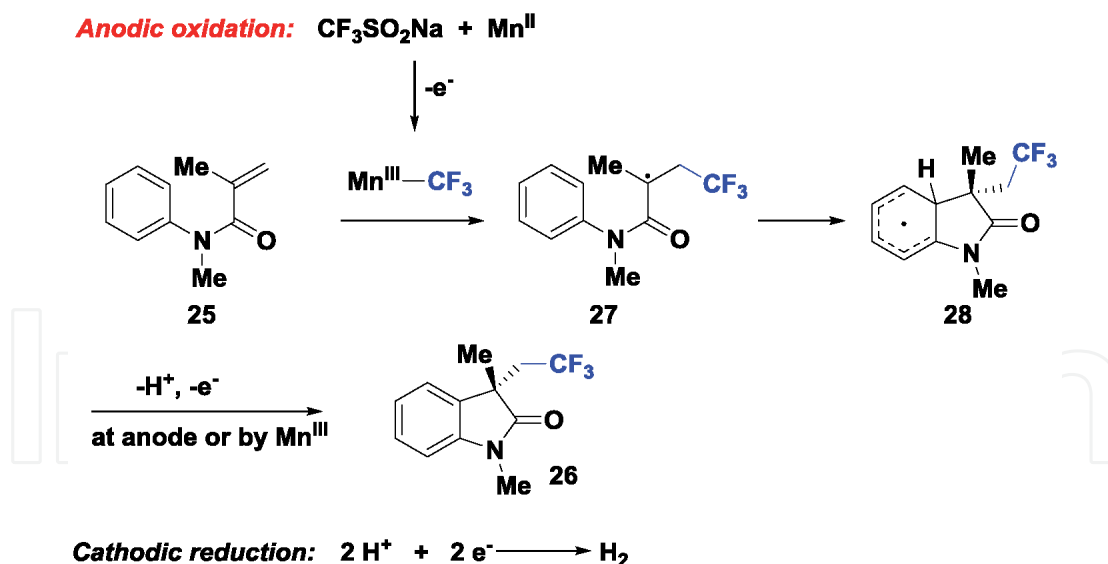*Oxidant-free electrochemical trifluoromethylation-initiated radical oxidative cyclization.*

Figure 12.
Proposed mechanism for trifluoromethylation/C(sp²)−H functionalization.

formed and following by either anode or Mn^{III}-mediated oxidation, then product **26** was obtained (**Figure 12**).

3. C-X (X = O, N, P, halogen) bond formation

The organic molecules with C-N, C-P, C-O, and C-Cl bond play an important role in the biological application, such as drug synthesis, agrochemicals, etc. [21–24]. Therefore, the new synthetic strategies to form a carbon-heteroatom bond have been made in the developments of various electrochemical methods based on metal-catalysis such as Pd, Co, Mn, Ag, and Rh. In this context, Lei and co-workers reported a C-H/N-H coupling catalyzed by Pd to synthesize of pyrido[1,2-*a*] benzimidazole [25]. Under the mild condition, different N-phenylpyridin-2-amine could afford the desired product in yields of up to 99% (**Figure 13**). The reaction was performed in an undivided cell equipped with a carbon plate as anode and a Fe plate as a cathode, under a constant current, using the system CH$_3$CN/LiClO$_4$ as a solvent/electrolyte.

As an improvement of this transformation, the authors suggest a mechanism for C-H/N-H coupling reaction catalyzed by Pd(II) via electrochemical oxidation (**Figure 14**). Initially, Pd(II) coordinates with a nitrogen atom of substrate **29** to form the intermediate **31**, which gives the complex intermediate **32** after electrophilic deprotonation. The latter then underwent a reductive elimination process to provide the desired product **30** and Pd(0). Finally, Pd(0) oxidized at the anode to be recovered to Pd(II).

Cobalt-catalyzed C-H cross-coupling reactions are known to be a strong implement to build new C-N bonds [26]. In this context, Lei and co-workers reported a C(sp²)-H coupling catalyzed by Co of quinoline amide **32** with secondary amine **33** (**Figure 15**) [27]. Under a constant current of 10 mA, a large family of desired product **34** was obtained in moderate to good yields up to 74%. The reaction proceeds in a divided cell equipped with a carbon plate as an anode in acetonitrile and a Ni plate cathode in methanol. Independently from Lei group, Ackermann group [28] also reported the Co-catalyzed electrooxidative reaction of amides derivatives **35** and a secondary amine **36** (**Figure 16**). The authors achieved the best results in an undivided cell equipped with an RVC and Pt as the anode/cathode system,
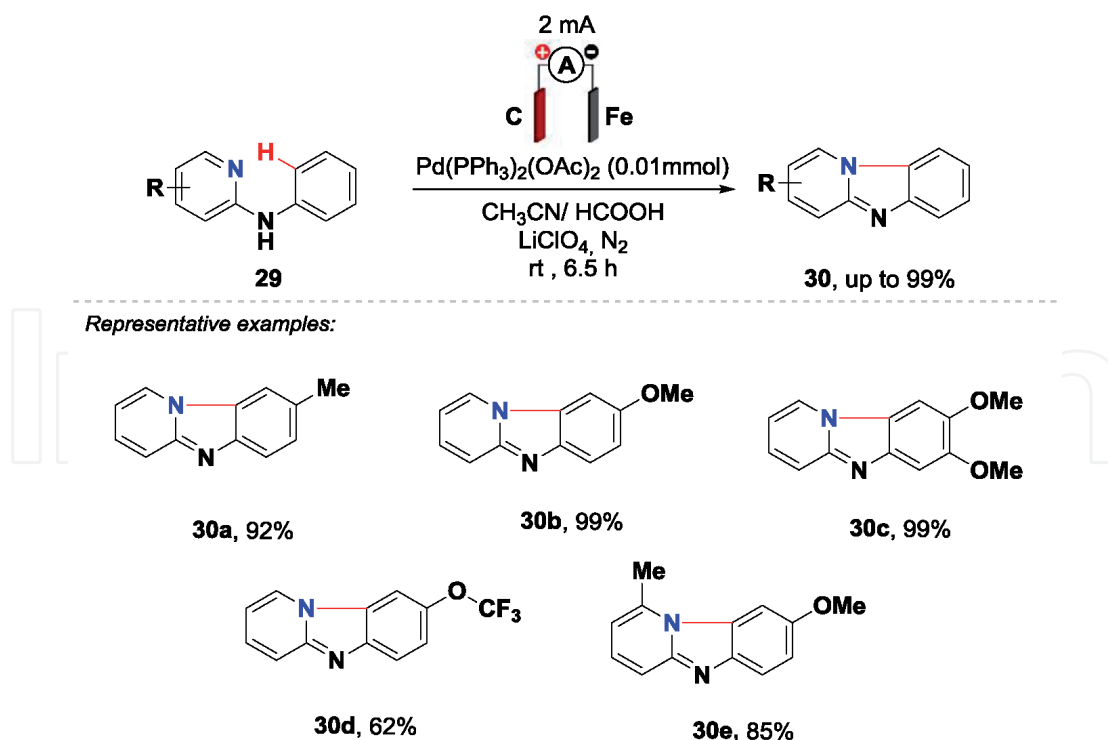
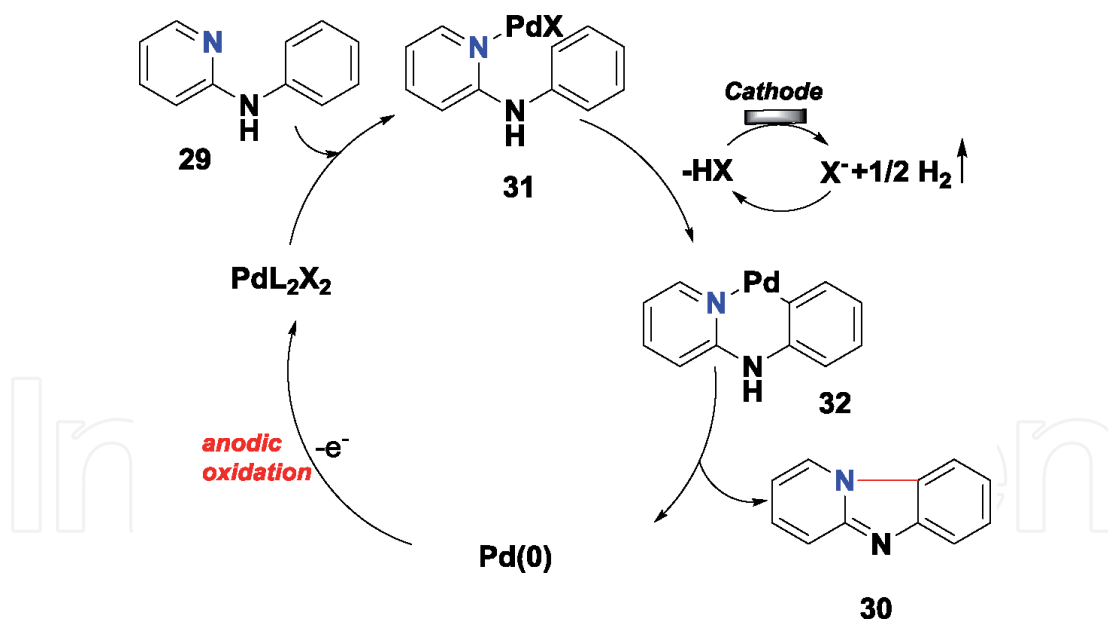**Figure 13.**
Pd-catalyzed C-N bond formation.

Figure 14.
A plausible mechanism for C(sp²)-H coupling catalyzed by Pd of N-phenylpyridin-2-amine.

at a constant current of 2.5 mA. The desired products **37** were formed in excellent yields of up to 83%.

As an improvement of this methodology, the authors suggest a plausible mechanism (**Figure 17**). In the path I: Co(II) is oxidized at the anode to give Co(III); which coordinates with N-(quinolin-8-yl)benzamide **35** to form Co(III)-species **39**. In the Path II: Co(II) coordinated to N-(quinolin-8-yl)benzamide **35** to get Co(II)-complex **38**, in the presence of a base. This Co(II)- species **38** is oxidized at the anode to provide Co(III)-species **39**. Then, C−H activation took place by the base,
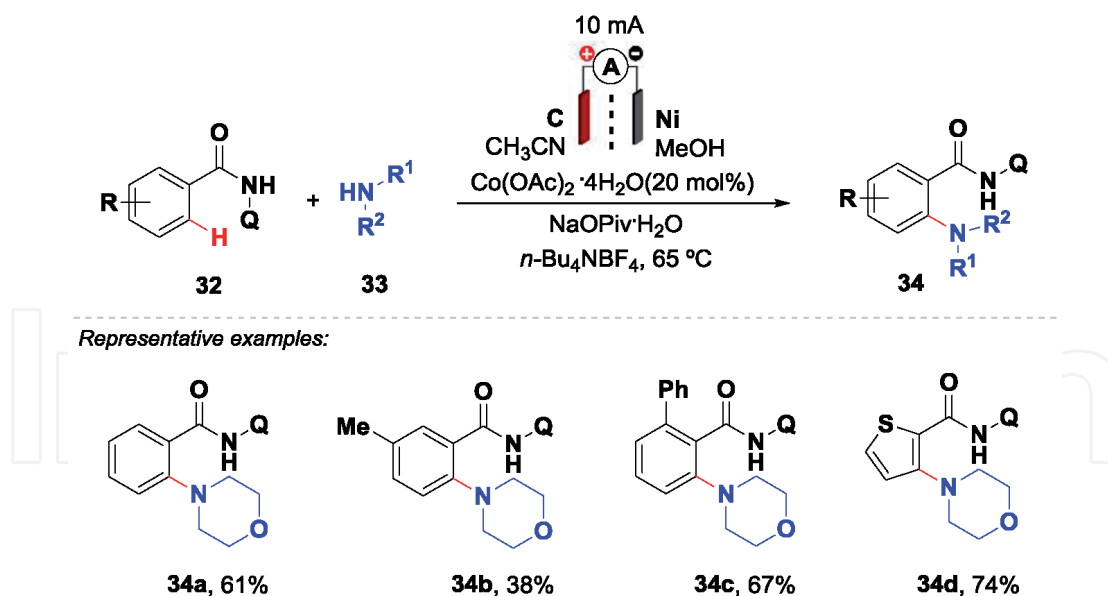
Figure 15.
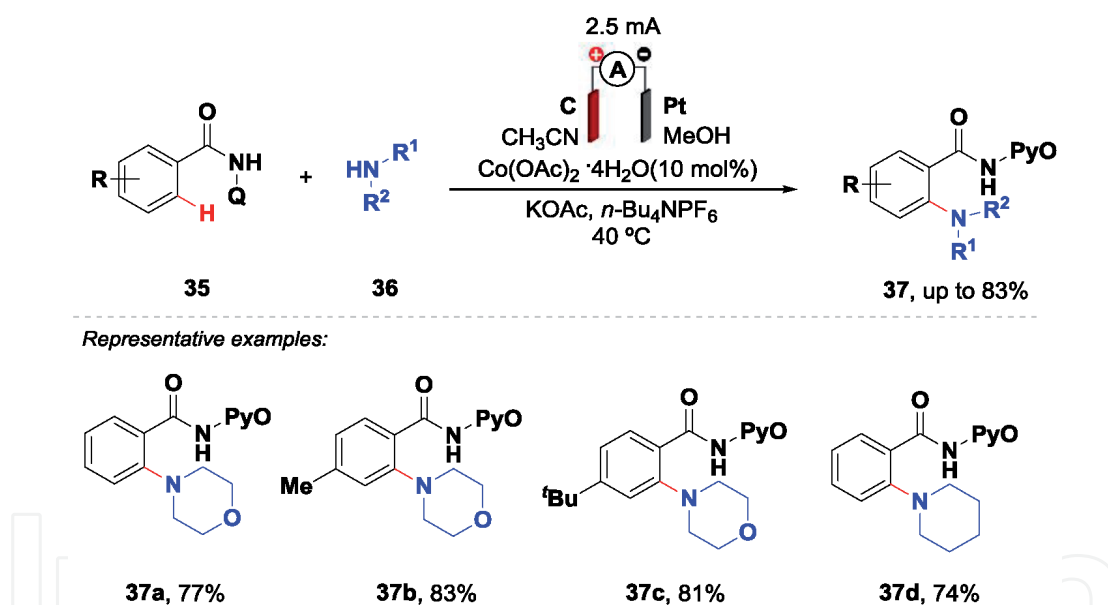*Co-catalyzed C-N bond formation.*

Figure 16.
Co-catalyzed C-N bond formation.

and Co(III)-species **39** was attacked by **36** to form Co(III)-species **40**, followed by reductive elimination of Co(III)-complex **40** to release the desired product and Co(I) species. Finally, Co(I) species was reoxidized to Co(II) at the anode to complete the whole catalytic cycle of Co.

The Mn-catalyzed formation of the C-Cl bond was reported by Chen and co-workers (**Figure 18**) [29]. Electrolyzing styrene derivatives **42** in the presence of O$_2$ gas and MgCl$_2$ at a constant current afford a large family of desired products **43** in very good yields. The reaction proceeds in an undivided cell equipped with a carbon rod both as anode and cathode, using the system Acetone-DCM/LiClO$_4$ as a solvent/electrolyte, for 12 h (**Figure 18**).

A mechanistic elucidation in **Figure 19** shows that first, Mn(II)Cl oxidized at the anode providing Mn(III)Cl species. Then styrene derivatives **42** reacts with Mn(III)
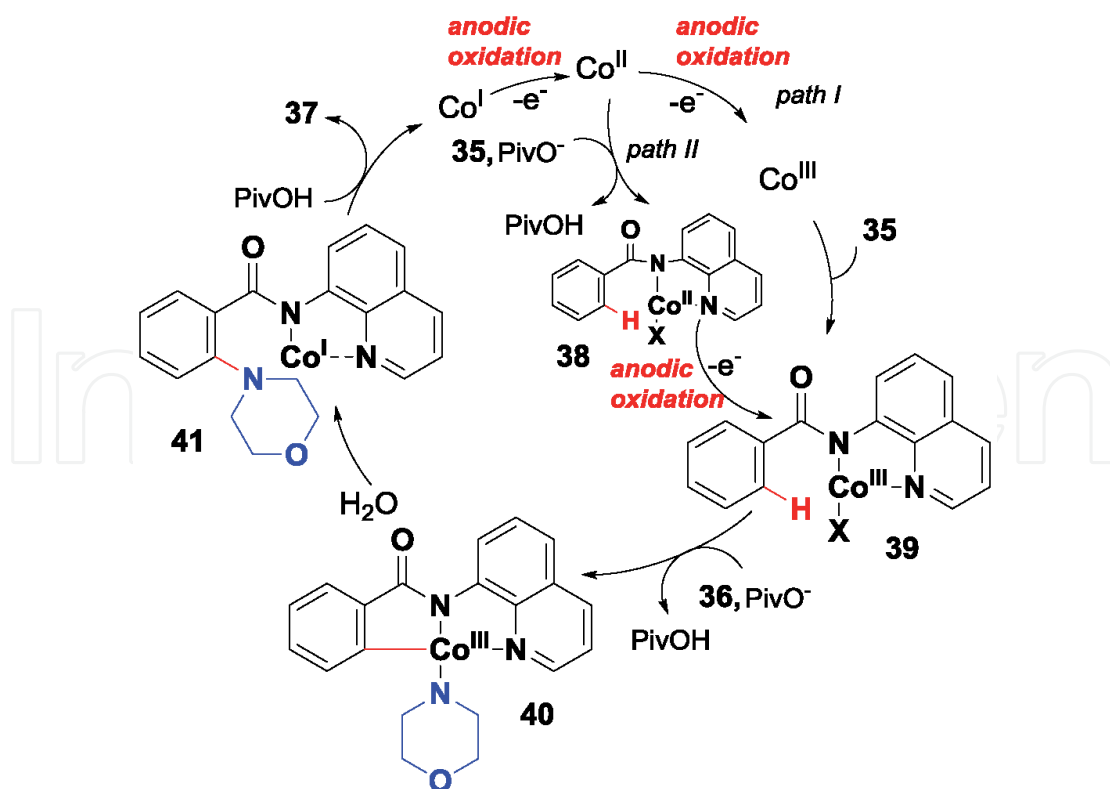
Figure 17.
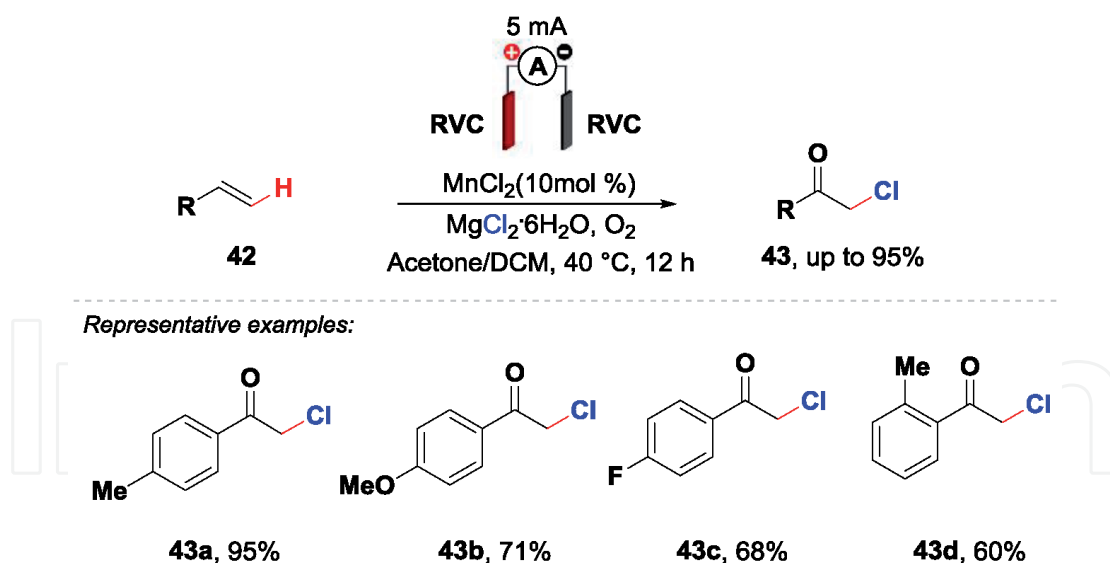*A plausible mechanism for C-N bond formation by Co-catalysis.*

Figure 18.
Mn-catalyzed C-Cl bond formation.

Cl to provide intermediate **44**. At the same time, at the cathode, the reduction of O_2 gives the radical superoxide ion which easily reacts with **44** to generate intermediate **45**. This later decomposes to form compound **46**. After further oxidation of **46**, the desired products **43** was formed.

Budnikova and co-workers reported an efficient approach of Ag-catalyzed reaction to a range azole dialkyl phosphonates derivatives **49** [30]. Under mild conditions, different substituted azole **47** and dialkyl-*H*-phosphonates **48** afford the final products **49** in moderate to good yields up to 75% (**Figure 20**).
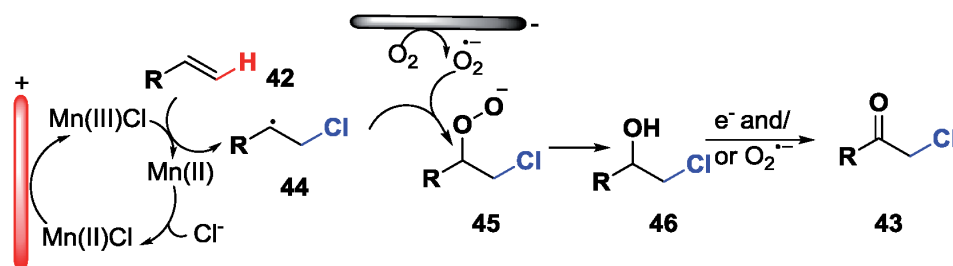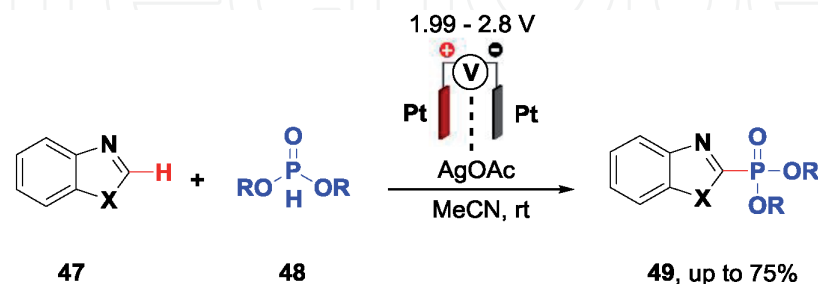
Figure 19.
A plausible mechanism for C-Cl bond formation by Mn-Catalysis.
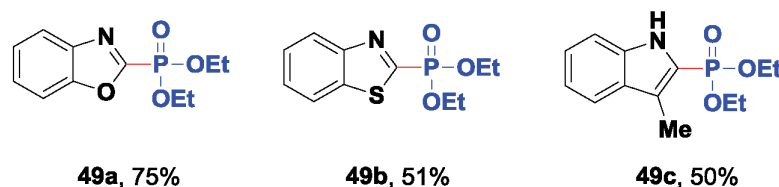

Figure 20.
Ag-catalyzed C-P bond formation.

The electrolysis proceeds in a divided cell at a constant voltage, employing AgOAc and Na_3PO_4 as additives and using acetonitrile as solvent. The proposed mechanism of this methodology is described in **Figure 21**. The reaction starts by combining dialkyl-*H*-phosphonate and silver (I) cation leading intermediate **50**, which after oxidation gives the radical intermediate **51**. Then azole derivatives **47** coordinate with **51** to form radical **52**. This latter, after losing hydrogen cation and an electron, leads to the desired product **49**.

Xu and co-workers reported an efficient method for rhodium (III)-electrocatalyzed to form the C-P bond (**Figure 22**) [31]. Using a graphite rod as anode and a platinum plates as a cathode, different substituted *N*-(2-pyridyl) aniline **53** and phosphine oxide **54** could provide the final product **55** in high yields. The electrolysis was performed in an undivided cell, under reflux in methanol at a constant current.

A possible mechanism of this strategy is shown in **Figure 23**. The reaction starts with C-H activation in phenylpyridine **53** by the catalyst **56** to give intermediate **57**. A further insertion of diphenylphosphine oxide **54** gives intermediate **58**. This later undergoes anodic oxidation forming to products **55**, regenerating the active complex **56**.

Strekalova and co-workers developed an elegant approach for Co-catalysed electrochemical formation of the C-P bond [32]. By using cobalt complex as a catalyst, different diethyl phosphonates **61** and aryl derivatives **60** could afford the desired products **62** with yields up to 80% for reductive condition and up to 68%
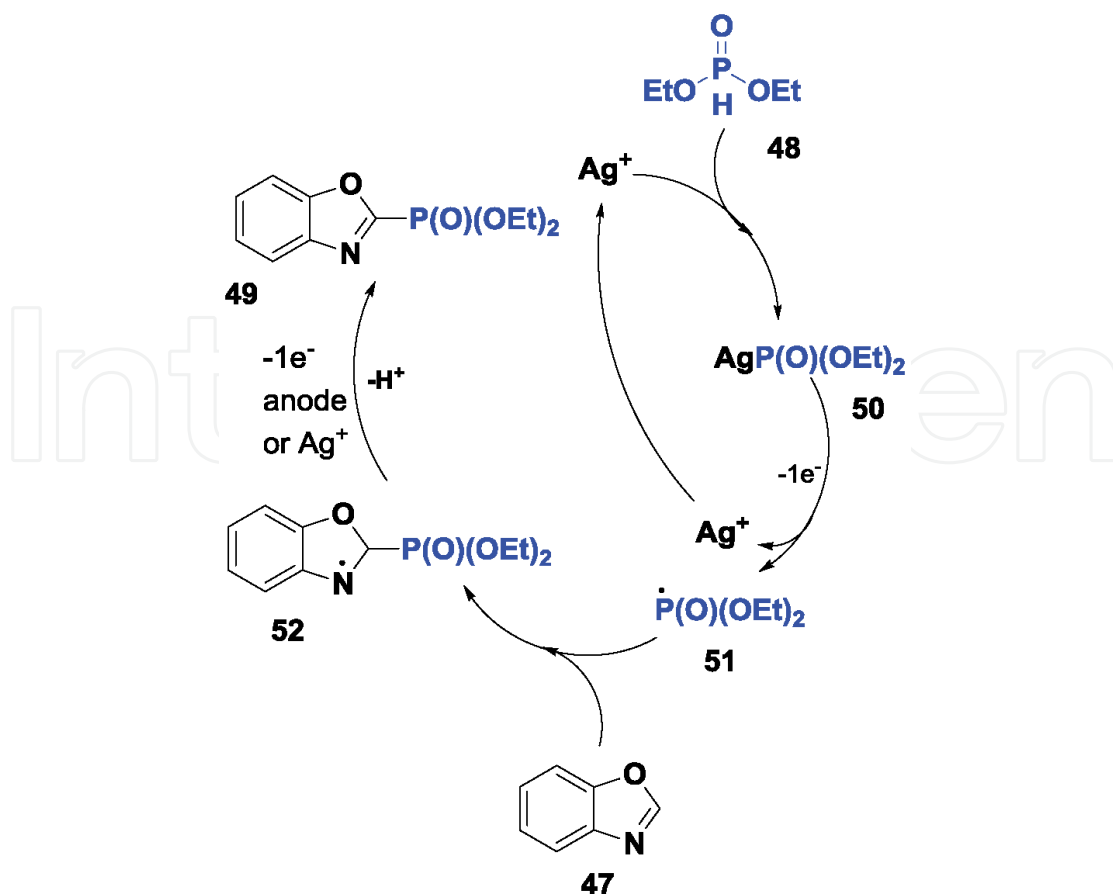
Figure 21.
A plausible mechanism for C-P bond formation by Ag-Catalysis.
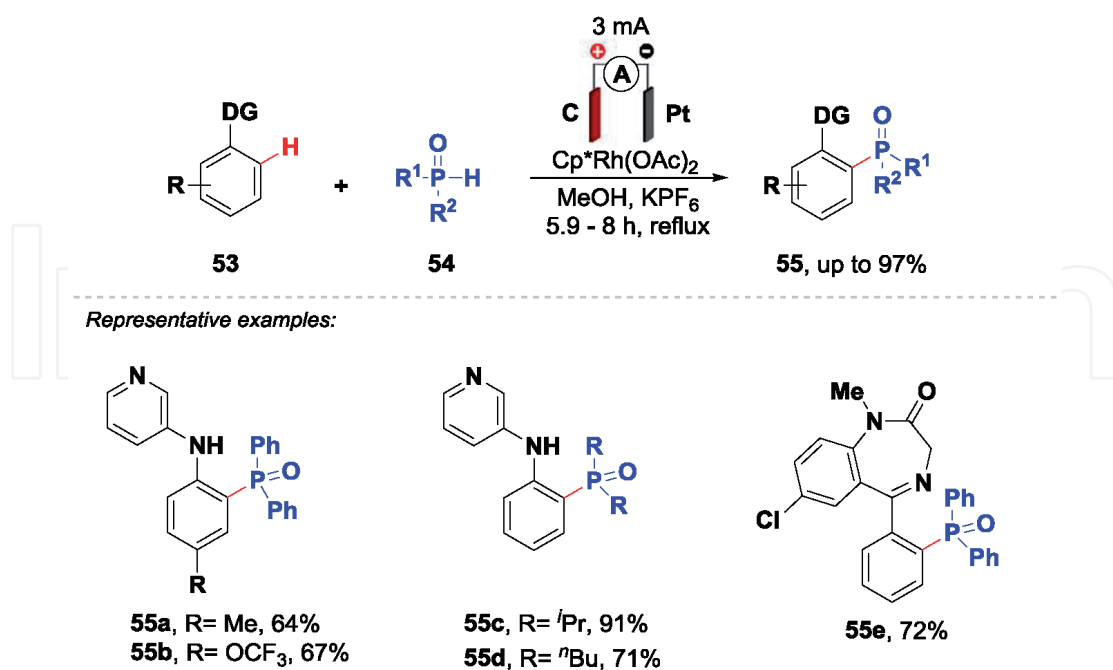

Figure 22.
Rh(III)- catalyzed electrochemical phosphorylation of aryl substrates.

for oxidative conditions. The electrolysis was carried out under a constant voltage of $-0.3\,V$ vs. Fc^+/Fc in a divided cell, equipped with platinum electrodes both as anode and cathode (**Figure 24**).
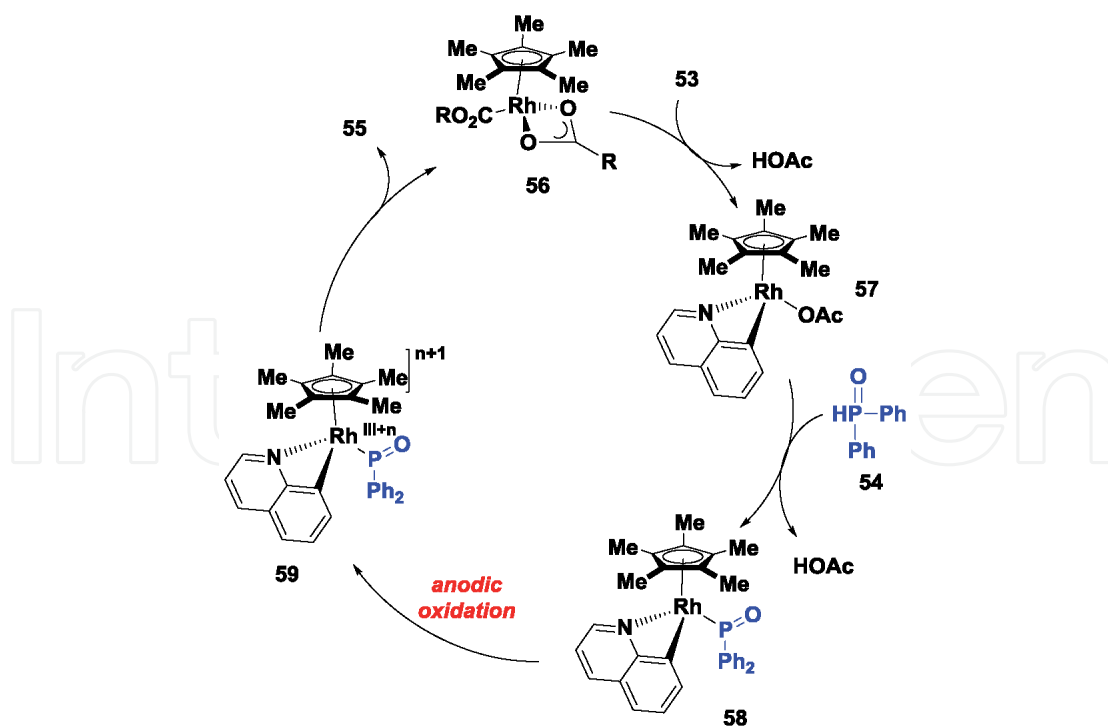
Figure 23.
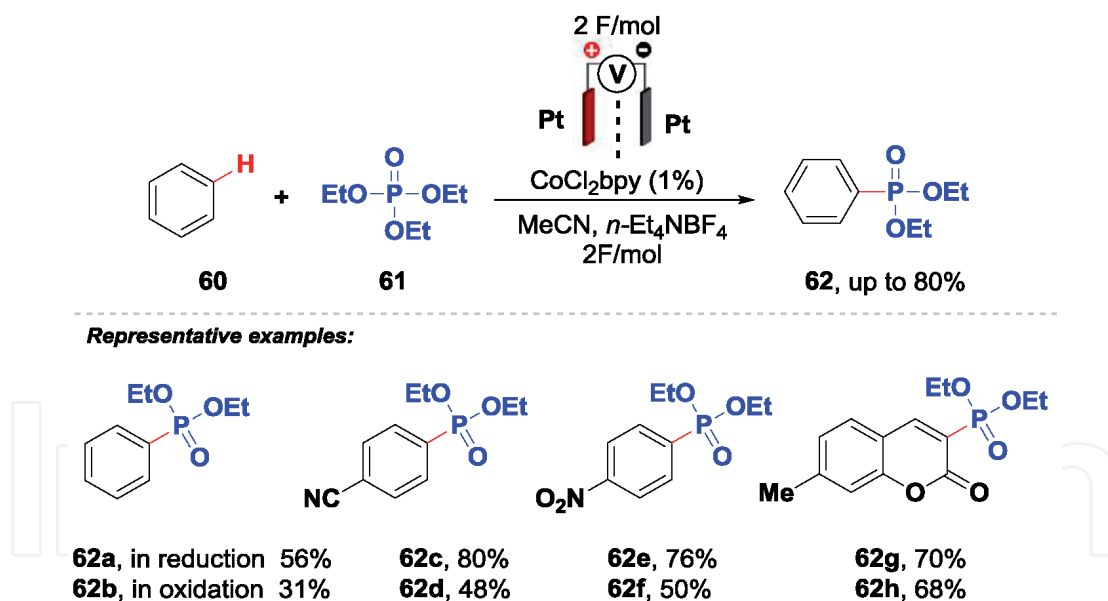*Plausible mechanism for Rh(III)- catalyzed electrochemical phosphorylation of aryl substrates.*

Figure 24.
Co-catalyzed C-P bond formation.

The plausible mechanism (**Figure 25**) shows that at the start, Co²⁺ precursors coordinates with H-phosphonate **61** to give complex intermediate **63**, which after further oxidation (or reduction), leads the intermediate **64** (or **65**). **B** (or **C**) forms after proton elimination a radical intermediate **67**. Then, the insertion of **60** provides the final products **62**.

The C-O bond formation under Co-catalyst was reported by Ackermann group (**Figure 26**) [33]. A variety of amides **68** and primary alcohols **69** were electrolyzing at a constant current of 8 mA as a green oxidant in a simple undivided cell equipped with carbon as anode and a platinum cathode for 6 h, providing the desired product **70** with good yields.
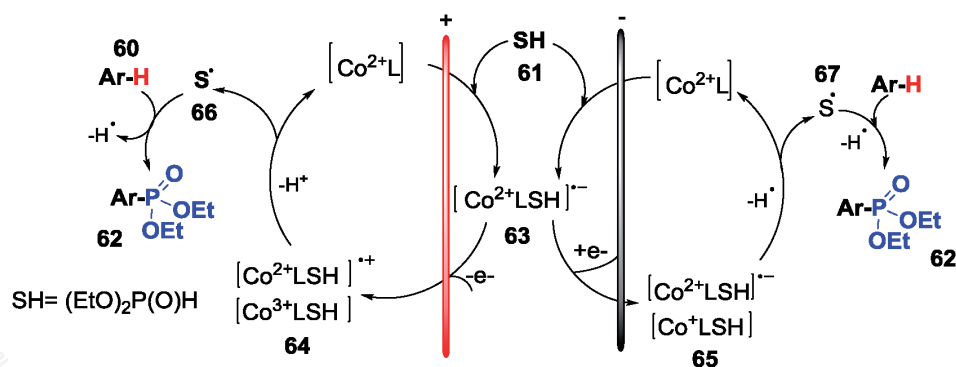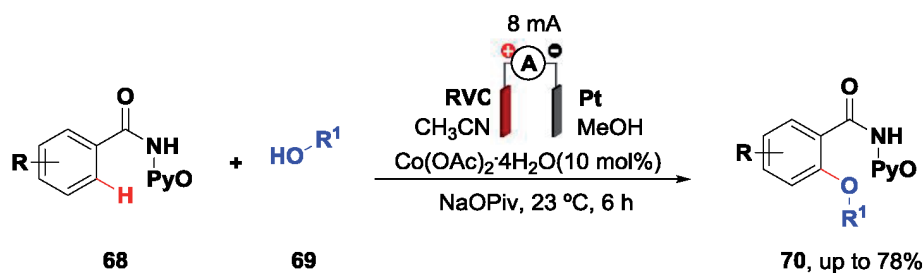
Figure 25.
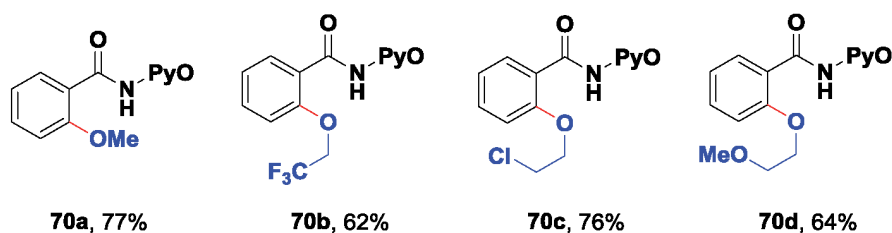*A plausible mechanism for C-P bond formation by Co-Catalysis.*

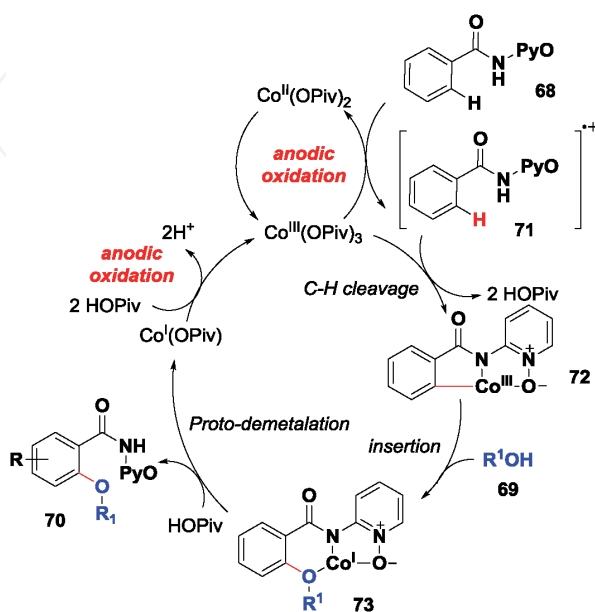**Figure 26.**
Co-catalyzed C-O bond formation.

Figure 27.
A plausible mechanism for C-O bond formation by Co-Catalysis.

Presumably, a catalytic cycle commences with the oxidation of Co^{II} precatalyst at the anode to give a Co^{III} species capable of forming complex **72**. Successive addition of alcohol derivatives leads to complex **73**, which in the presence of HOPiv gives the final product and forms a Co^{I} species. The latter, which is oxidized at the anode, gives a catalytically active Co^{III} species (**Figure 27**).

4. Conclusions

C−H activation/functionalization via metalla-electrocatalysis appears as a valuable tool for organic synthesis. Coupling reactions with hydrogen evolution demonstrate great potential for application in the synthesis of complex molecules. Likewise, electrochemical C−H activation appears to be a greener method, and even more progress is expected in this area of research. However, there are still several challenges, such as the application of other transition metals, the recycling of transition metals and electrolytes, an in-depth study of asymmetric transformations, the application of new ligands, etc. Despite all these challenges, we believe that in the future, the fusion between the transition metal catalysis with electrochemical methods will have a great development, being highly promising for synthetic chemistry, becoming a common tool in all research laboratories.

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Conflict of interest

The authors declare no conflict of interest.

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