Electrochemical Phosphorylation of Organic Molecules

Najoua Sbei,[a] Guilherme M. Martins,[b, c] Bahareh Shirinfar,[d] and Nisar Ahmed*[b]

Abstract: Organophosphorus chemistry is a broad field with multi-dimensional applications in research area of organic, biology, drug design and agrochemicals. Conventional methods have been adopted extensively to access phosphorylated compounds that rely on the use of toxic, moisture sensitive phosphorylating agents and occur in the presence of oxidants, catalysts, as well as high temperatures and harsh conditions are required for complete transformations. However, recent progress has been made for phosphorylation reactions using electricity to introduce green and sustainable synthetic procedures. These reactions can be performed at mild conditions and proceed with excellent atom economy. Herein, we targeted electrochemical phosphorylation reactions with generation of new bonds such as $C(sp^3)$ —P, $C(sp^2)$ —P, O–P, N–P, S–P and Se–P. This review is aimed to offer an overview of recent developments in the synthetic methodology to easy access of organophosphorus compounds using electrochemistry.

Keywords: Electrifying synthesis, Green phosphorylation reactions, Atom economy, Organic electrochemistry, Organophosphorus chemistry

1. Introduction

Functionalized compounds containing phosphorus act as important intermediates in organic synthesis, with applications in medicinal chemistry, agrochemistry, material chemistry, flame retardant, ligands in synthetic chemistry, and it further suggests that they played an important role in the emergence of life on Earth, such as phosphates.[1–8] Considering this, the development of new strategies for obtaining new P–C and P–heteroatom bonds is of great interest, expanding the application possibilities. Generally, the most common paths for the construction of P–C and P–X (X=N, O, S and Se) bonds proceed by the nucleophilic substitution of toxic halides with ROH/RSX,[9] Friedel-Crafts reaction,[10] Michaelis-Arbuzov reaction[11] and also with the use of organometallic and a phosphine.[12] Likewise, phosphorus reagents can be applied as nucleophilic species for the formation of new bonds, starting for example from dialkyl- or diaryl-phosphine oxides, phosphonates esters, hypophosphite, phosphines, phosphine-borane, among others.[13–16] In general, these strategies can follow a direct phosphorylation in heterocycles, involving the cross-coupling between halides or alcohols of aryl or alkyl, and can also proceed to phospha-aldol, phospha-Michael or phospha-Mannich reactions. A second strategy can be considered, involving the formation of heterocyclic rings. These reactions can be subdivided into reactions with or without C–P bond formation, and recently an interesting review described by Zou and co-workers summarized the recent progress in this field, discussing the reaction mechanisms in detail.[17]

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Due to the need to develop procedures with an intrinsic character of sustainability and green chemistry, several modern methodologies for the phosphorylation of organic molecules have already been explored, such as the use of photoredox catalysis,[18] microwave irradiation,[19,20] flow-based technologies,[11,21] ultrasonication systems,[22,23] among others. However, the replacement of redox chemicals by direct application of electricity is one of the most innovative options for chemical processes. Considering this, the electrochemistry in organic synthesis emerges as an eco-friendly alternative, based on simple electron transfers from the electrode to the substrate or mediator. While conventional synthetic methods generally occur under high temperatures or pressures, using external oxidants and often in a long reaction time, in electrochemistry this can be avoided, providing energy savings.[24,25] With the variation of voltage or electrical current, the oxidation or reduction capacity of the electrochemical system is manipulated, allowing the control of the reaction selectivity.

Considering the common principles of electrolysis, electrosynthesis in organic chemistry is carried out in electrolytic circuits, generally equipped with two electrodes, where two half-reactions will occur: an oxidation and a reduction reaction. The reactional solution, in which the electrodes are immersed, needs to be conductive of electric current, and to obtain this property, an electrolyte is usually added, whose function is to conduct the electrical current from the anode to the cathode. Additionally, electrochemical cells can be

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chemistry and molecular recognition of biomolecules.

Guilherme M. Martins obtained his Ph.D in 2019 with the group of Prof. Claudio Silveira (UFSM, Santa Maria – Brazil). He performed an internship in electrosynthesis with Prof. Thomas Wirth and Prof. Nisar Ahmed in 2017 (Cardiff University, Cardiff – UK). In 2019 conducted his postdoctoral research with the group of Prof. Claus Jacob (Universität des Saarlandes, Saarbrücken – Germany). He is currently conducting postdoctoral research on electrosynthesis with the group of Prof. Antonio L. Braga and Prof. Samuel R. Mendes (UFSC, Florianópolis – Brazil).

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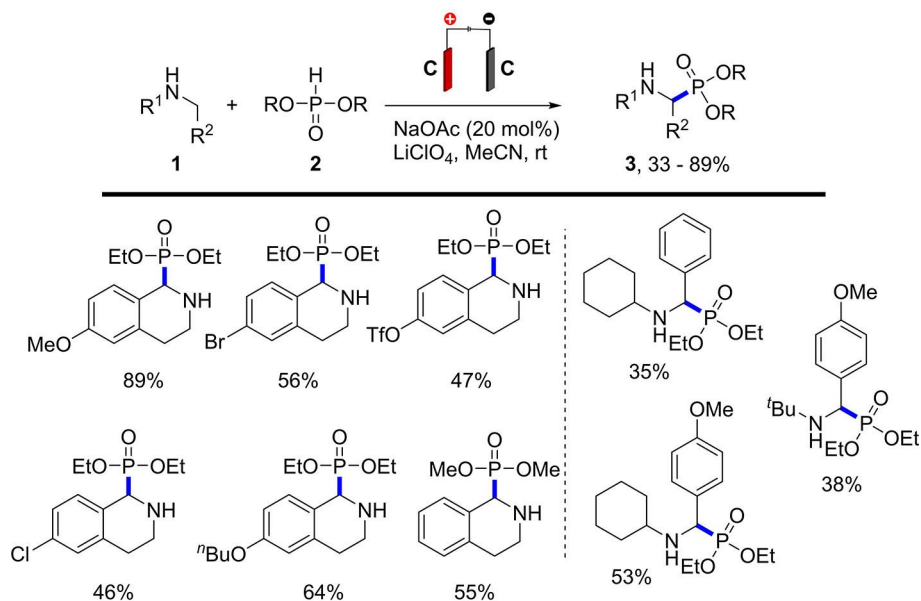
Scheme 1. Electrochemical C–H phosphorylation of a secondary amine with dialkyl phosphite.
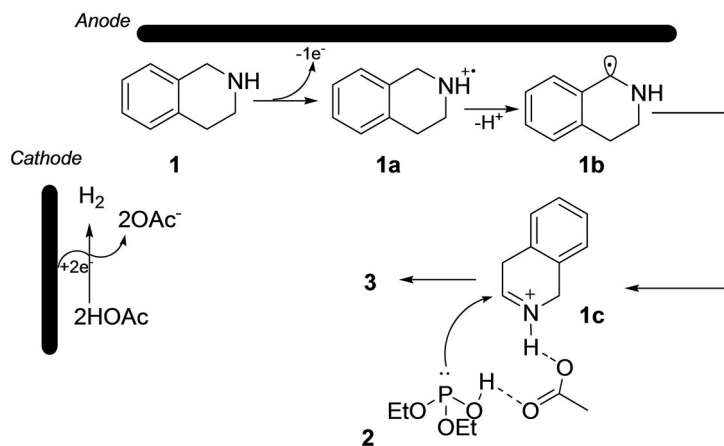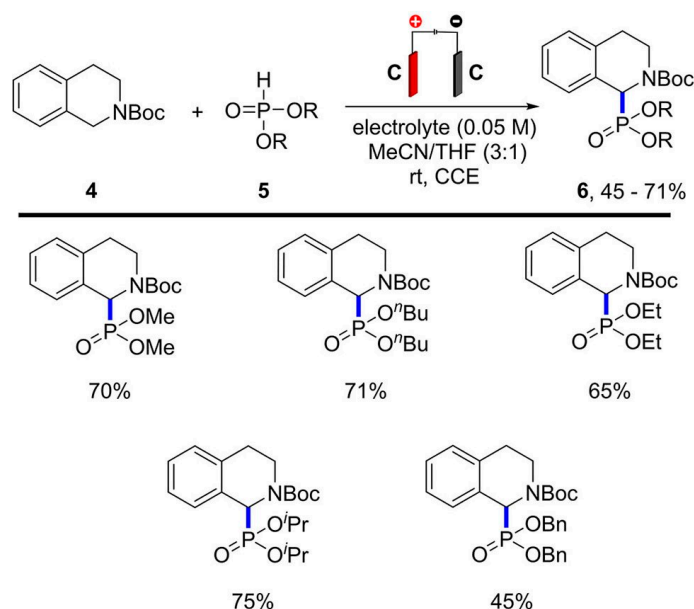

Scheme 2. Plausible mechanism for electrochemical C–H phosphorylation of secondary amine with dialkylphosphite.

assembled in two ways: divided and undivided cells. In the case of divided cells, the anode and cathode electrodes are equipped in different vessels, separated by an ion-exchange membrane or salt bridge that allows the transfer of certain dissolved ions and therefore, the two half-reactions occur separately.[26] The undivided cells, the anode and cathode electrodes are in the same vessel. In general, the reactions can be carried out under constant current (galvanostatic) or with constant potential (potentiostatic). Considering that the potential and the current cannot be controlled at the same time, evaluating which is the best condition can be part of the challenge when assembling an electrolytic cell.[24]

Very recently, we published important review articles, addressing the advantages of using electrolysis for organic reactions of alkene difunctionalizations,[27] alkyne functionalizations,[28] annulation reactions[29] and electrochemical chalcogen (S/Se) functionalizations,[30] and a search on these subjects is recommended for a deep understanding and updating of the main reactions in the field of organic electrosynthesis.

This review provides an overview on the electrochemical phosphorylation of organic molecules. Emphasis is placed on methodology development and mechanistic insight and aims to provide inspiration for future synthetic applications in the field of electrosynthesis in organic chemistry.

Scheme 3. Electrochemical synthesis of α-aminophosphanates.
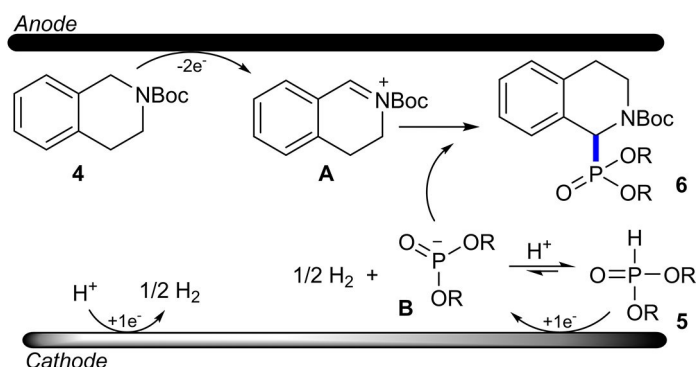
Scheme 4. Plausible mechanism for electrochemical synthesis of α-aminophosphanates.

2. Electrochemically Induced Phosphorylation Reactions

2.1. C(sp³)–P Bond Formation

Tertiary and secondary amine are the most interesting substrates for the C(sp³)–P bond formation. In 2019, Ding's group[31] reported a simple approach for an electrochemical C–H phosphorylation of unprotected secondary amine **1** with phosphonate derivatives **2**. Employing carboxylate salts as a catalyst under controlled potential led to the desired product **3** in moderate to good yields (scheme 1). The aromatic group with electron-donating and electron-withdrawing were well tolerated in this methodology. Graphite felt carbon was used both as anode and cathode during the electrolysis. The authors

suggest that the cascade of reactions begins with anodic oxidation of amine **1** to generate **1b**, after losing one radical proton, which after further oxidation, gives **1c**. The phosphite **2** was then catalyzed by sodium acetate, attacks intermediate **1c** to provide the desired compound **3** (scheme 2).

In addition to unprotected amine, Léonel and co-workers[32] proved recently that the protected amine could be applied for the synthesis of α-aminophosphanates **6** (scheme 3). With N-carbamates tetrahydroisoquinoline **4** and phosphonate derivatives **5**, different α-aminophosphanates **6** were obtained in good yields. The reaction was performed in an undivided cell at constant current, using graphite electrodes plates both as anode and cathode. Scheme 4 shows a proposed mechanism of the electrochemical phosphorylation of protected amine **4**. The reaction starts with an anodic oxidation of
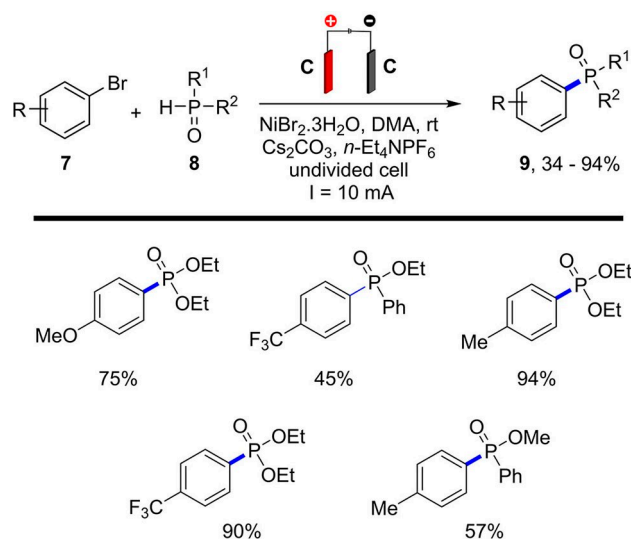
Scheme 5. Nickel- catalyzed electrochemical synthesis of arylphosphinates.

tertiary amine to generate cation intermediate **A**. Simultaneously, on the cathode, the reduction of dialkyl phosphite gives the intermediate anion **B**, which subsequently attacks the intermediate **A** to provide the desired product **6**.
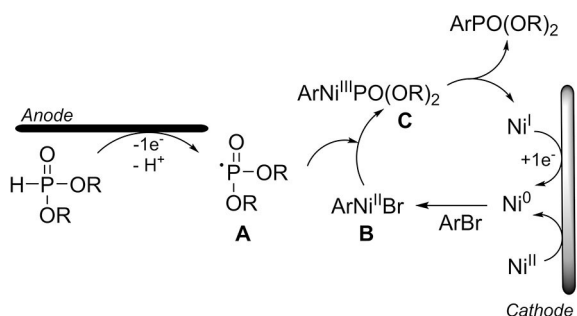
2.2. C(sp^2)–P Bond Formation

In the last years, there is an expanded number of electrochemical reactions for C(sp^2)–P bond formation. The

phosphorylation of aryl halogen, hydrazones and arenes is the main method to generate C(sp^2)–P bond. In 2019, Xiang's group[33] reported an interesting Ni-catalyzed electrochemical method for C(sp^2)–P functionalization. Different aryl bromides **7**, dialkylphosphite, ethyl phenyl phosphinate and diphenyl phosphine oxide **8** could afford a large family of desired product **9** in excellent yields (scheme 5). The electrolysis proceeded in an undivided cell at constant of current 10 mA, using carbon plates as electrodes. Based on this methodology, Leonel's group[34] reported recently in 2020 a new synthetic approach to achieve the electrosynthesis of arylphosphinates **9** and vinylphosphinates **11** (scheme 6). Under mild condition, using NiBr$_2$ as a mediator, the combination of aryl or vinyl bromide with phosphinates derivatives **8**, affords a broad scope of the desired product in good yields. The reaction was conducted in an undivided cell at room temperature with iron/nickel (64/36) anode and nickel as a cathode. As an improvement of the electro C(sp^2)–P formation, the authors suggested the following plausible mechanism (scheme 7). The anodic oxidation of phosphites substrates leads to the radical **A**; on the cathode, the reduction of Ni^{II} generates Ni^0, which reacts with aryl bromide to form intermediate **B**, the coordination between intermediate **A** and **B** gives Ni^{III} complex **C**, whose subsequent reductive elimination leads to the desired product (**9, 11**) and Ni^I species.

Still talking about the phosphorylation of aryl halide, two methods that we cited previously were based on the use of metal catalyst as NiBr$_2$. In 2019, Wang groups[35] proved a
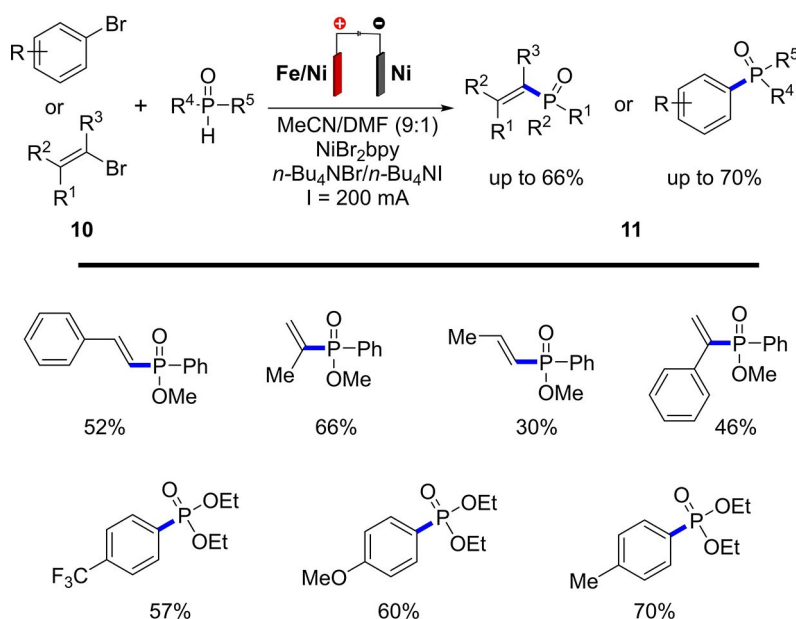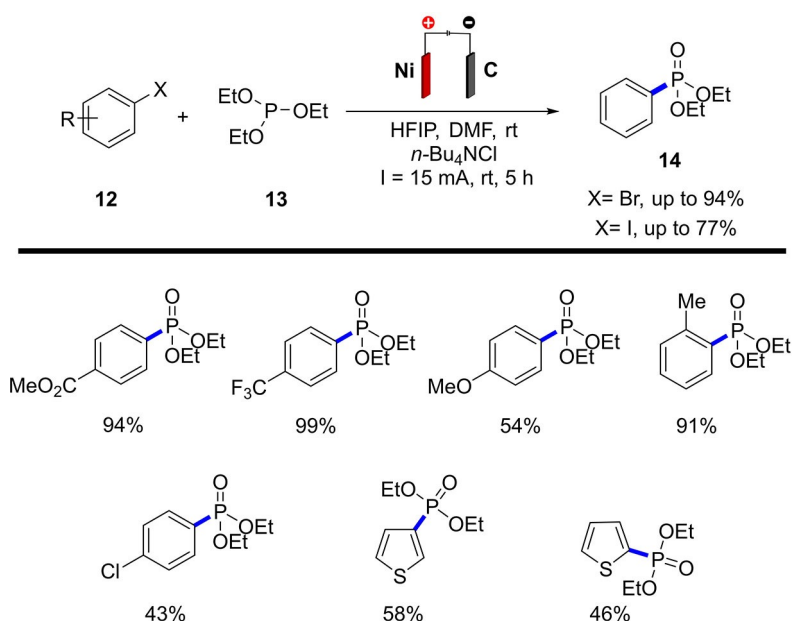

Scheme 6. Nickel- catalyzed electrochemical synthesis of arylphosphinates and vinylphosphinates.
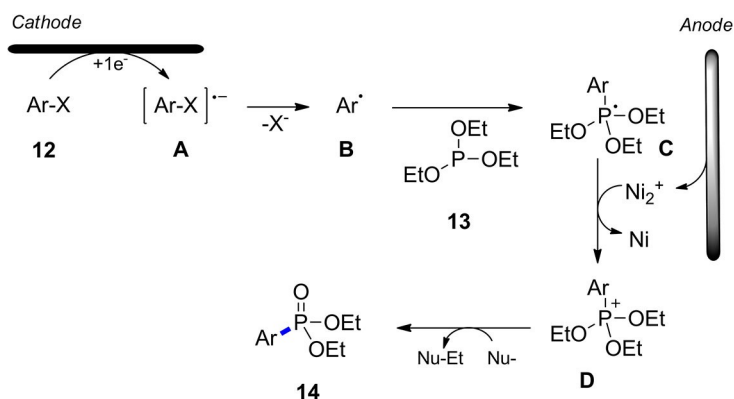
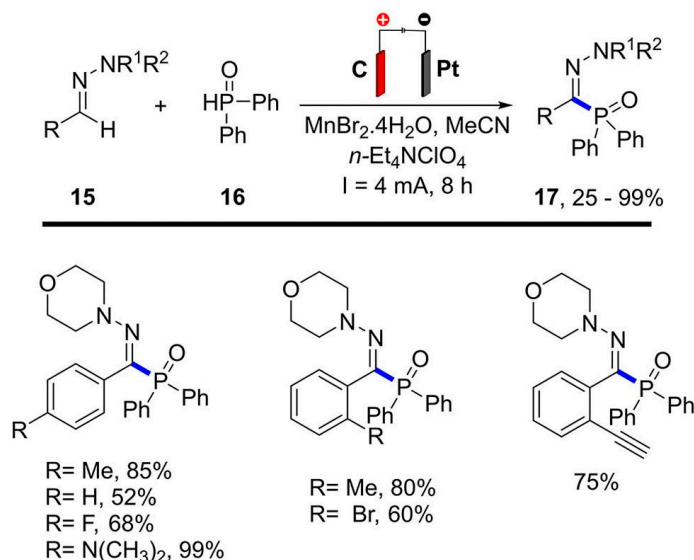**Scheme 7.** Plausible mechanism for electrochemical synthesis of arylphosphinates and vinylphosphinates.

new and efficient free catalyst formation of C(sp²)–P bond (scheme 8). Aryl iodide **12** with a wide range of functional groups could be tolerated to form the desired products with moderate to excellent yields up to 99%. Aryl bromide was also tested, but less yield of desired products was obtained up to 77%, the authors suggest that it could be explained by the easy cleavage of C–I bond than C–Br. The reaction was conducted in an undivided cell, under a constant current of 25 mA, Ni plate anode, graphite cathode, using the mixture of CH₃CN and HFIP as solvent at room temperature. As an improvement, the author suggests the following mechanism (scheme 9). The reaction begins with the reduction of aryl halides **12** leading the radical anion **A**. Further elimination of X⁻ gives the radical **B** which reacts with substrate **13** to give
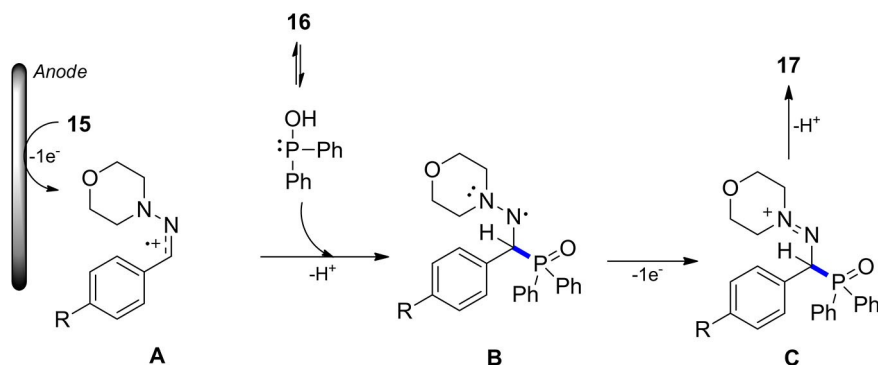

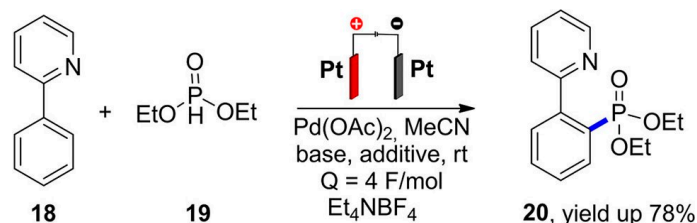**Scheme 8.** Electrochemical synthesis of arylphosphinates.

Scheme 9. Plausible mechanism for the electrochemical synthesis of arylphosphinates.

Scheme 10. Electrochemical synthesis of α-iminophosphine.

Scheme 11. Plausible mechanism for synthesis of α-iminophosphine.
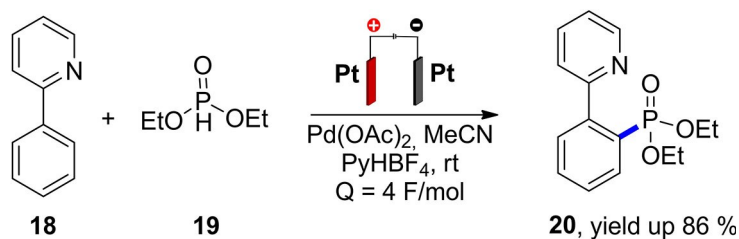

Scheme 12. Electrochemical phosphonation of phenyl pyridine.

intermediate **C**. The cation Ni^{2+} produced by Ni-anode oxidise radical **C** to form the cation intermediate **D** which gives after losing ethyl group the desired product **14**.

Independently of aryl halide, aldehyde hydrazine **15** was also used as a substrate for electrochemical phosphorylation by diphenylphosphine oxide **16** (scheme 10). This methodology

was reported by Roan's group[36] in 2020. α-iminophosphine **17** oxides were formed in excellent yields with a wide range of different functional groups such as OMe, CN, SMe, CF$_3$ etc. The results showed that high yields were obtained when the electrolyte n-Et$_4$NClO$_4$ and small catalytic amount of MnBr$_2$·2H$_2$O were used. The electrolysis was carried out in an

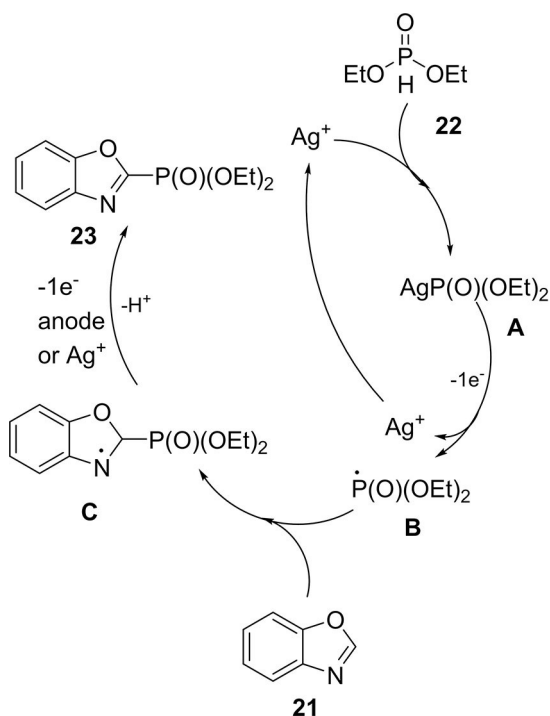**Scheme 13.** Electrochemical phosphonation of phenyl pyridine.
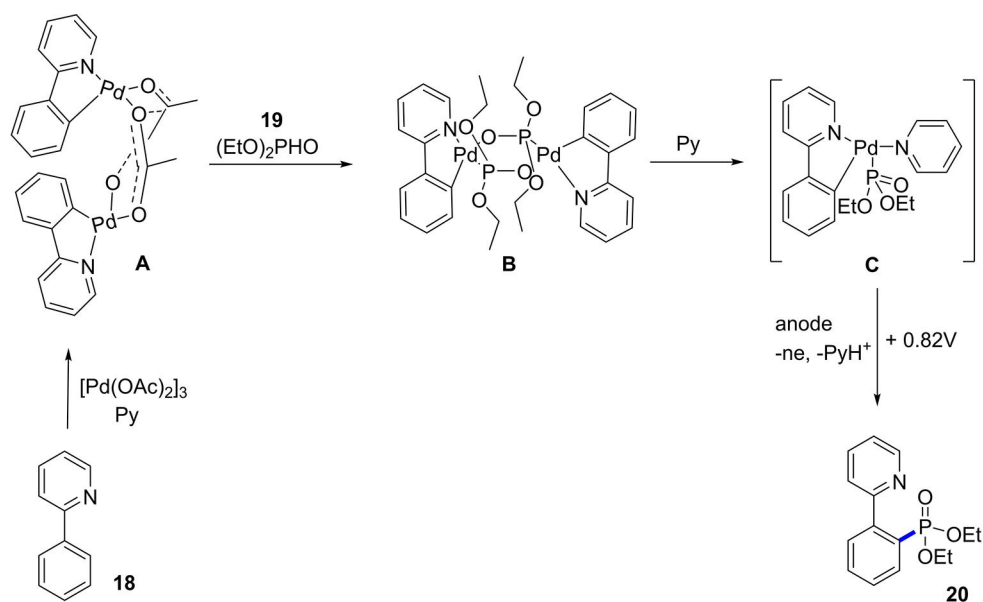
Scheme 14. Plausible mechanism for electrochemical phosphonation of phenyl pyridine.
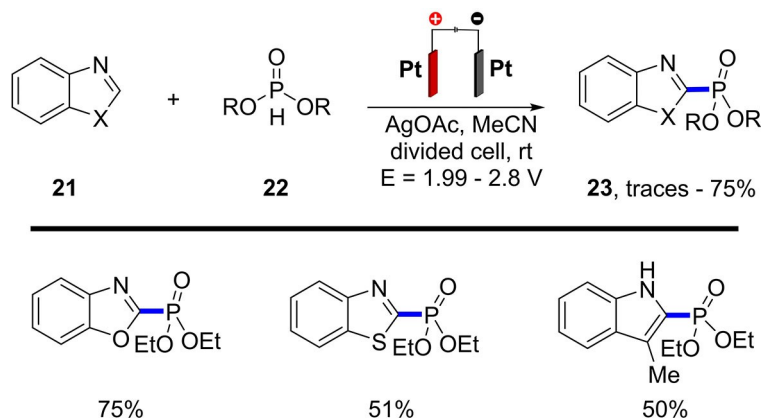
Scheme 15. Electrochemical synthesis of azole dialkylphosphonates.

undivided cell at a constant current of 4 mA in acetonitrile, using graphite as anode and platinum plate as cathode. The proposed mechanism in scheme 11 shows that the reaction

starts at the anode. The oxidation of substrate **15** leads to the intermediate **A**, which reacts with **16** to form the intermediate **B**. This latter is oxidized on the anode to form the
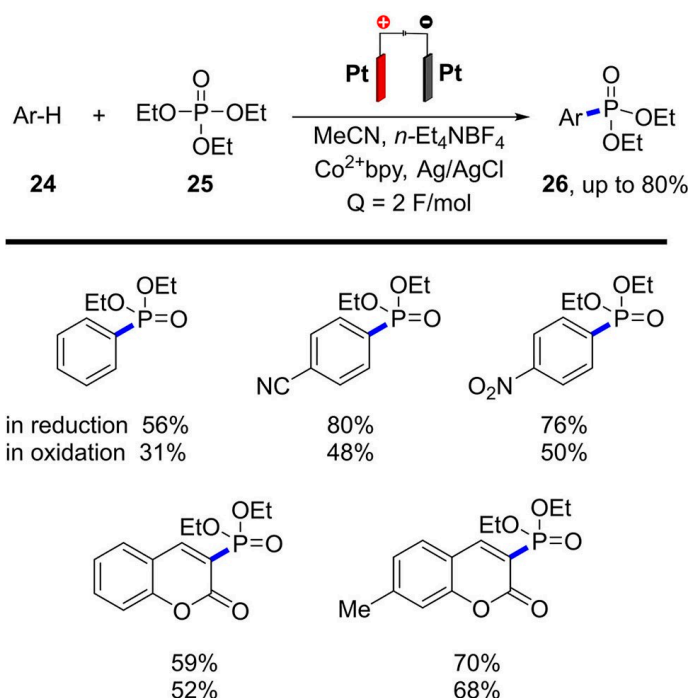
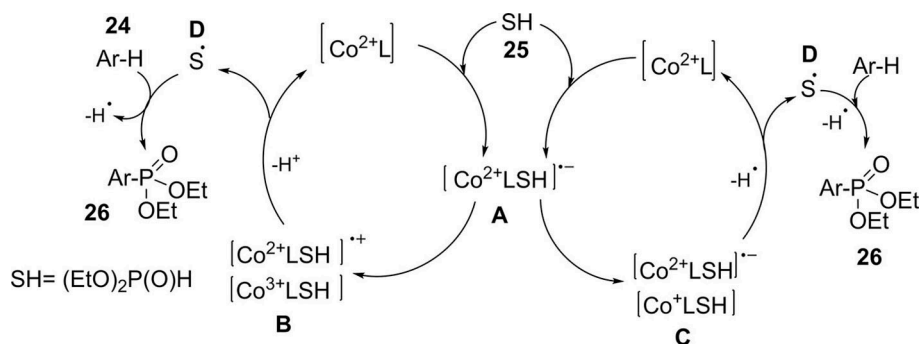**Scheme 16.** Plausible mechanism for electrochemical synthesis of azole dialkylphosphonates.

intermediate **C**, followed by losing one proton, leading the desired product **17**.

The Pd-catalyzed electrochemical phosphonation of phenyl pyridine **18** has been described by Budnikova group[37] in 2015. The reaction was performed in a divided cell at a constant voltage in acetonitrile using platinum plates, both as anode and cathode (scheme 12). However, this method presented the need of bases and additives such as NaOAc/ benzoquinoline and lutidine/bpy, in addition to that, it has a limited yield (up to 78%). For this reason, recently, the same scientific[38] group tried to modify and optimize their method to get an excellent yield up to 86% (scheme 13). The electrolysis was carried out in a divided cell at constant voltage in acetonitrile, using platinum plats as electrodes. The reaction proceeds between phenyl pyridine **18** and ethyl phosphonate **19** in the presence of pyridine for 1.25 hours at 25 °C under argon atmosphere. Scheme 14 demonstrates the plausible mechanism for this reaction. At the start phenyl pyridine coordinates with $[Pd(OAc)_2]_3$ to lead intermediate **A**, which after further addition of $(EtO)_2PHO$ gives the cyclic intermediate **B**. This later under the effect of pyridine leads intermediate **C**. Finally, the oxidation of **C** at the anode provides the final product **20**.

In view of the remarkable interest of Budnikova group[39] in the reaction of $C(sp^2)-P$ bond such as the phosphorylation of pyridine mediated by $Ni(BF_4)bpy$ and $CoCl_2bpy$,[40] Mn-mediated phosphorylation of coumarins[41] and the phospho-

Scheme 17. Electrochemical synthesis of arylphosphinates.

Scheme 18. Plausible mechanism for electrochemical synthesis of arylphosphinates derivatives.
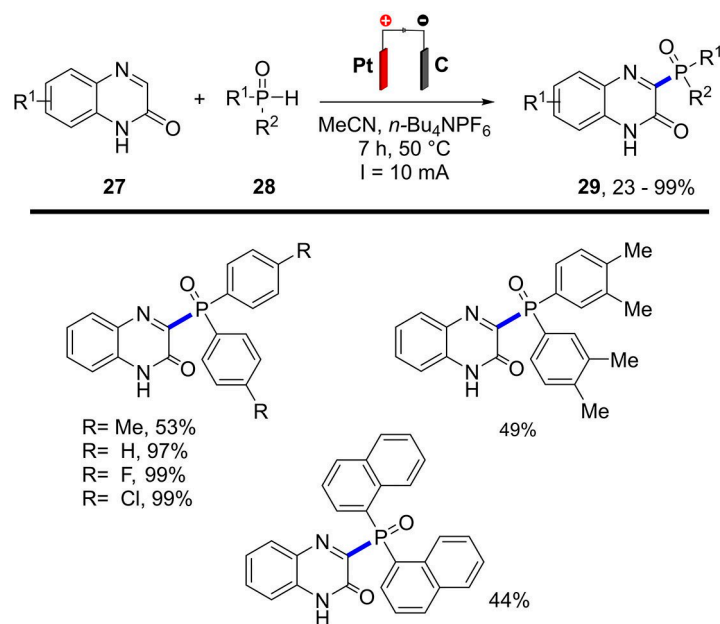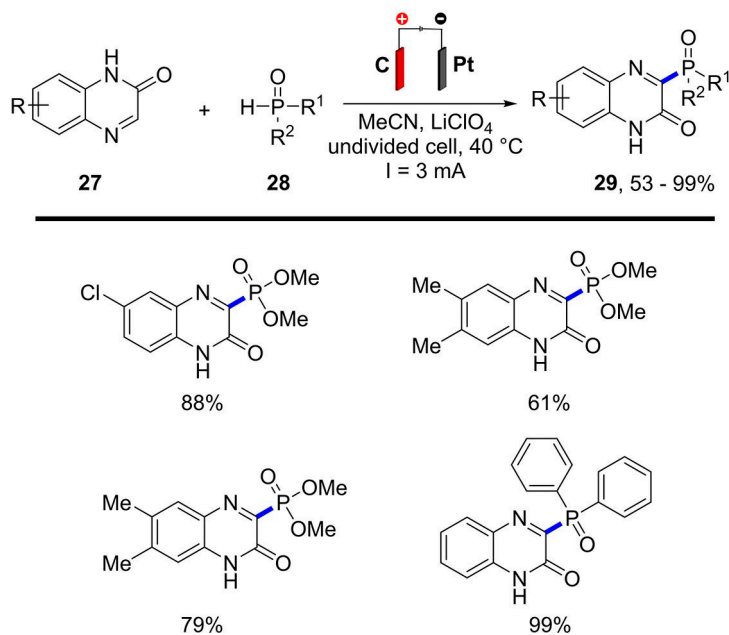

Scheme 19. Electrochemical synthesis of phosphonated quinaxolin-2-(1H)-one.

nation of caffeine in the presence of metal catalyst.[42] The group also reported an efficient approach to a range azole dialkyl phosphonates.[43] By using silver as a catalyst for the electrochemical transformation, different substituted azole **21** and dialkyl-*H*-phosphonates **22** could afford the desired products **23** in good yields up to 75 % (scheme 15). The electrolysis was carried out in divided cell at oxidation potential, using acetonitrile as solvent. The optimal yields were obtained by the combination of AgOAc and Na₃PO₄ as additives. Scheme 16 shows a proposed mechanism of this methodology. The reaction starts with the reaction of dialkyl-*H*-phosphonate and silver (I) cation leading intermediate **A**, which after oxidation leads radical intermediate **B**. Then Azole derivatives reacts with **B** to give radical **C**. This latter, after

losing hydrogen cation and an electron leads to the desired products **23**.

More recently, the same group achieved an elegant approach for the electrochemical phosphorylated aromatic compounds,[44] by using cobalt complex as a catalyst for the electrochemical oxidative or reductive reactions. Different diethyl phosphonates **25** and aryl derivatives **24** (scheme 17) could afford the desired products **26** with yield up to 80 % if the reaction was carried out in reductive condition and up to 68 % in oxidative condition. The electrolysis proceeds under controlled potential (E = −0.3 V vs FC⁺/FC) in divided cell. Platinum electrodes were used both as anode and cathode.

A mechanistic elucidation in scheme 18 shows that Co²⁺ precursors coordinate with diethyl-H-phosphonate **25** to give complex **A**, which after further oxidation (or reduction) leads

Scheme 20. Electrochemical synthesis of phosphonate quinaxolin-2-(1H)-one.
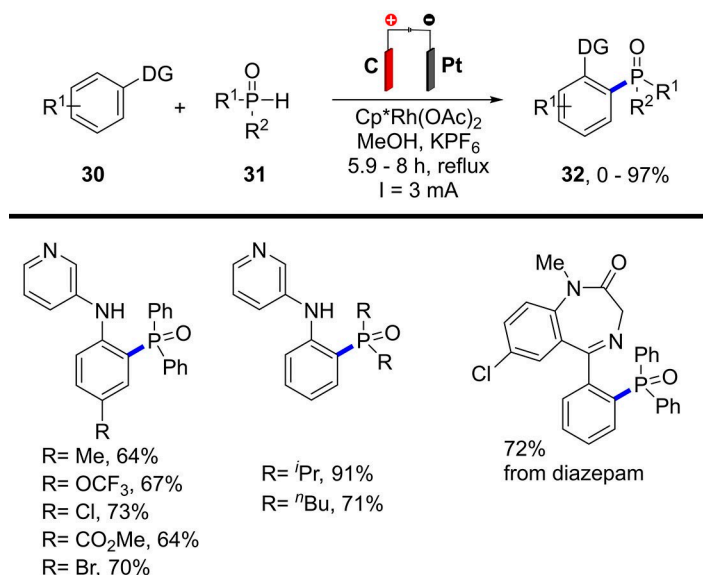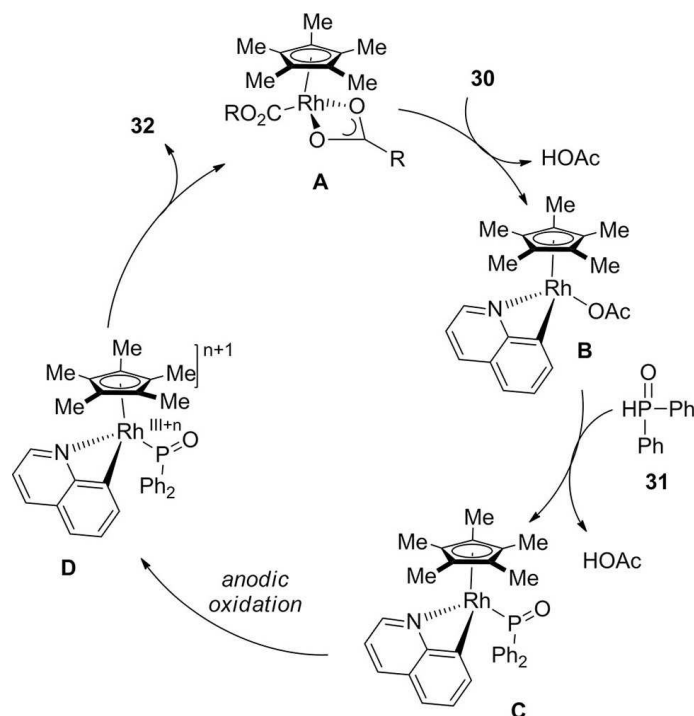

**Scheme 21.** Rh(III)- catalyzed electrochemical phosphorylation of aryl substrates.

intermediate **B** (or **C**). This latter gives after proton elimination radical intermediate **D**. finally, the insertion of **24** leads to final products **26**.

In 2019, Hu and co-workers[45] reported a new synthetic approach to achieve the electrochemical formation of C(sp²)–P bond from quinaxolin-2-(1*H*)-one (scheme 19). Electrolyzing quinaxolin-2-(1*H*)-one **27** with diaryl phosphine oxides **28** in an undivided cell at constant current in acetonitrile using *n*-

Bu₄NBF₆ as electrolytes, leads to phosphonated quinaxolin-2-(1*H*)-one **29** in moderate to good yield. The combination of platinum as anode and graphite as cathode gives the optimal results. The aromatic group with electron-donating and electron-withdrowing were tolerated in this methodology with yield up 99 %. However, 3,4-disubstituted diaryl phenyl oxide, naphtyl and heteroaryl-substituted also could be tolerated in this result but low yields were obtained. This methodology was
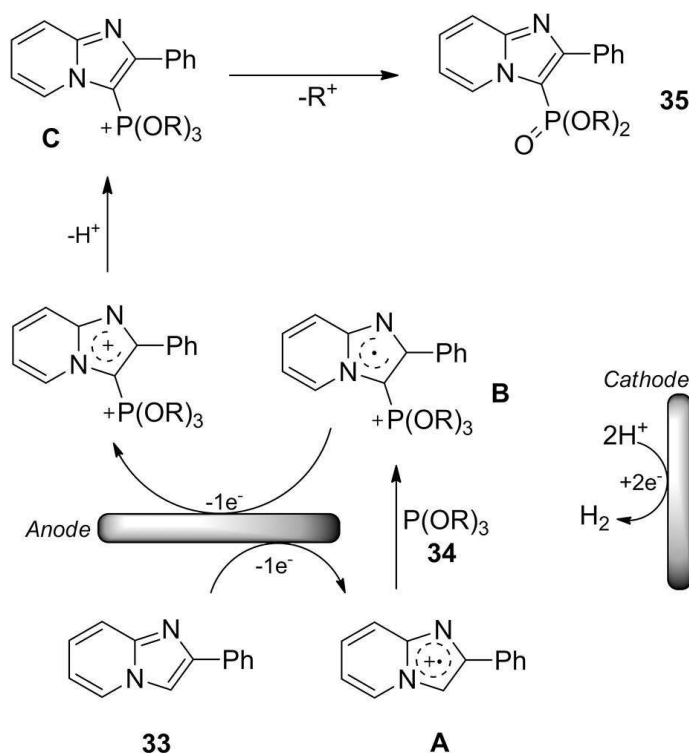
Scheme 22. Plausible mechanism for Rh(III)- catalyzed electrochemical phosphorylation of aryl substrates
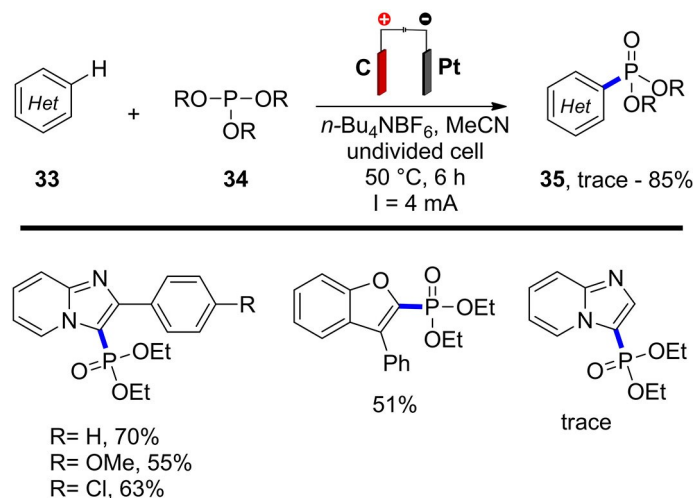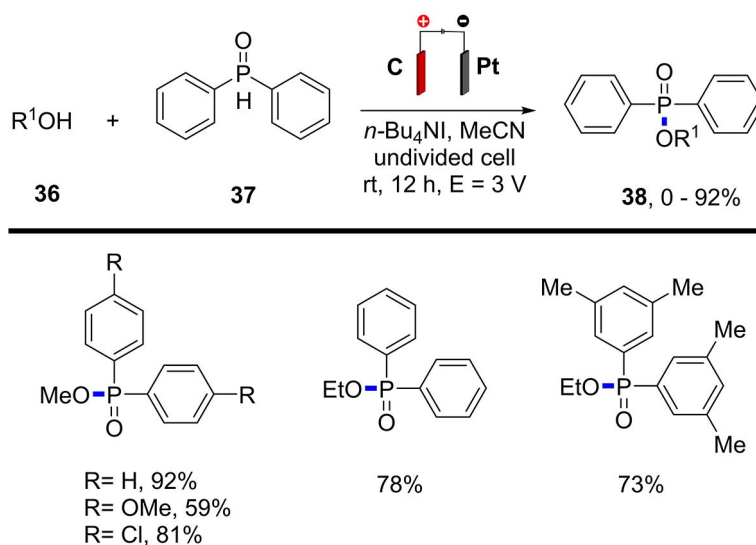

Scheme 23. Electrochemical C-H phosphonylation of imidazo[1,2-a]pyridine.

extended by Sun's group in the same year.[46] In addition to diaryl phenyl oxide, the authors preceded the reaction with alkylphosphonate such as dimethyl phosphonate, diethyl phosphonate, etc. The desired products were obtained with yield up to 99 %. The authors proved that the same procedure could be applied for C(sp³)–H phosphonylation of xanthenes (scheme 20), moreover, only few examples has been developed and the final products formed with moderate yields (50 % to

79 %). The electrolysis proceeds in an undivided cell equipped with platinum as cathode and graphite as the anode. The electrochemical reaction commences with anodic oxidation of substrates **27** to give the radical cation **A**, which reacts with **B** to form the intermediate **C**. Then the radical **C** reacts with the protonated quinaxolin-2-(1*H*)-one giving the isolable intermediate **D**, which then after further oxidation and deprotonation leading the final products **29**.
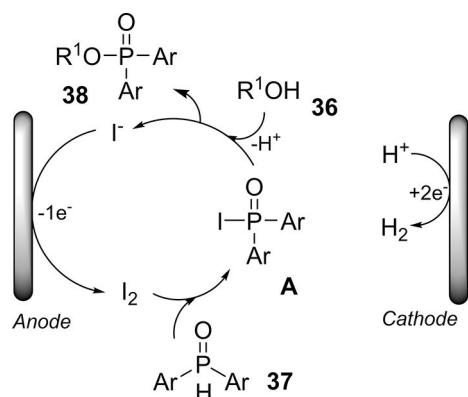
Scheme 24. Plausible mechanism for electrochemical C–H phosphonylation of imidazo[1,2-a]pyridine.

Scheme 25. Electrochemical dehydrogenative phosphorylation of alcohols.

Xu and co-workers[47] reported in 2019 an efficient method for the electro-catalyzed phosphorylation of aryl substrates **30** by rhodium (III) (scheme 21). A graphite rod as anode and platinum plates as cathode were used for the electrolysis. Different substituted of *N*-(2-pyridyl)aniline **30** and diphenyl

phosphine oxide **31** could afford the desired product **32** in good yields. Moreover, lower efficiency of reaction was obtained with unsubstituted *N*-(2-pyridyl)aniline or Br-substituted and diethylphosphine oxides. The electrolysis proceeds in an undivided cell, under reflux in methanol at constant

Scheme 26. Plausible mechanism for electrochemical dehydrogenative phosphorylation of alcohols.

current. Scheme 22 shows a possible mechanism of the transformation. The reaction begins with C–H activation in phenylpyridine **30** by the catalyst **A** to lead intermediate **B**. The further insertion of diphenylphosphine oxide **31** gives **C**. This later undergoes anodic oxidation forming to products **32**, regenerating the active complex A.

Lei and co-workers[48] reported the electrochemical oxidative C–H phosphonylation of phenyl imidazo[1,2-*a*]pyridine and 2-thiophenyl imidazo[1,2-*a*]pyridine **33** by triethyl

phosphite **34** (scheme 23). This transformation, could afford a vast scope of desired products **35** in moderate to good yield. The substituted substrates with electron-rich and electron-deficient could be tolerated in this synthesis. However, with unsubstituted imidazo[1,2-*a*]pyridine only trace amount of desired product was obtained; the authors explain this result by the high oxidative potential of imidazo[1,2-*a*]pyridine which is not easily oxidized. The reaction was carried out in an undivided cell, equipped with carbon rod anode and platinum plate cathode at a constant current in acetonitrile at 50 °C. The authors also proved that the same procedure could be applied for C(sp^3)–H phosphonylation of xanthenes and *N*-methyl-9, 10-dihydroacridine, the final products were formed with good yields up to 88%. Mechanistic elucidation in scheme 24 shows that initially starts the substrates **33** oxidized at the anode to lead the radical intermediate **A**, which than reacts with P(OR)$_3$ **34** to provide intermediate **B**. This latter after further oxidation and dehydrogenation result in the construction of intermediate **C**. Then the dialkylation of **C** gives the final compound **35**. Meantime, on the cathode proton were reduced to form H$_2$.
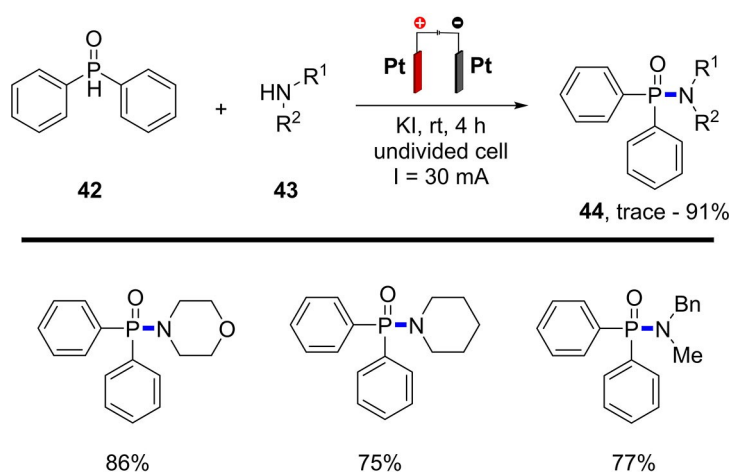
2.3. O–P Bond Formation

The O–P bond formation from alcohol derivatives is the most attractive method. In 2019, a new approach for electro-
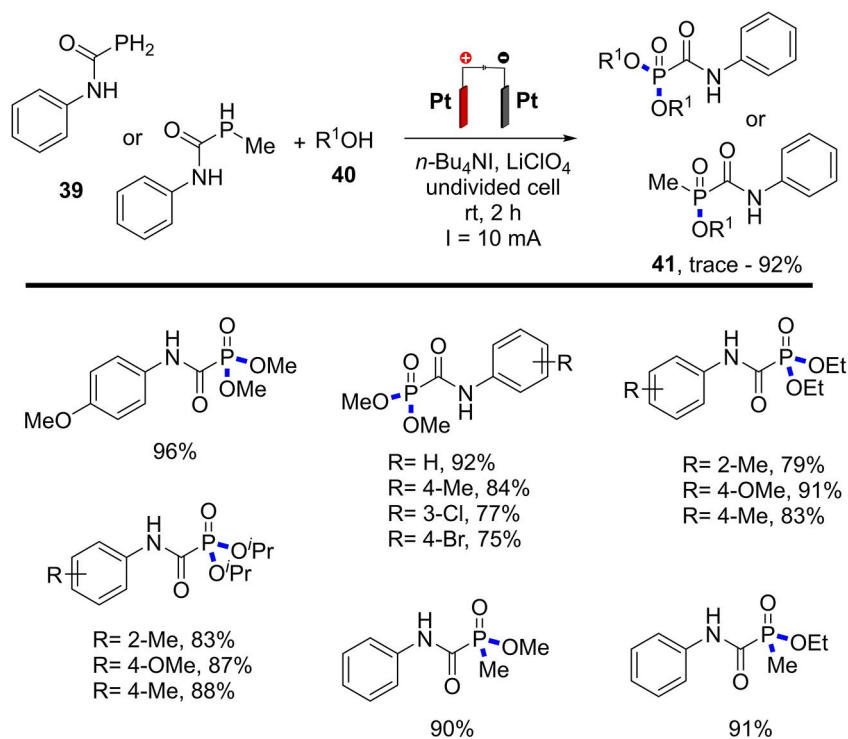
Scheme 27. Electrosynthesis of carbamoylphosphonates.
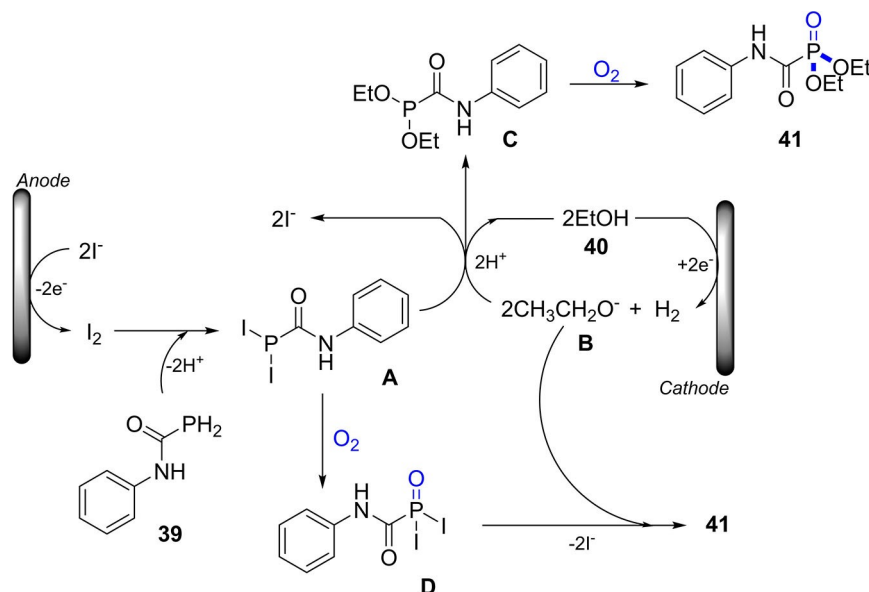
Scheme 28. Plausible mechanism for electrosynthesis of carbamoylphosphonates.
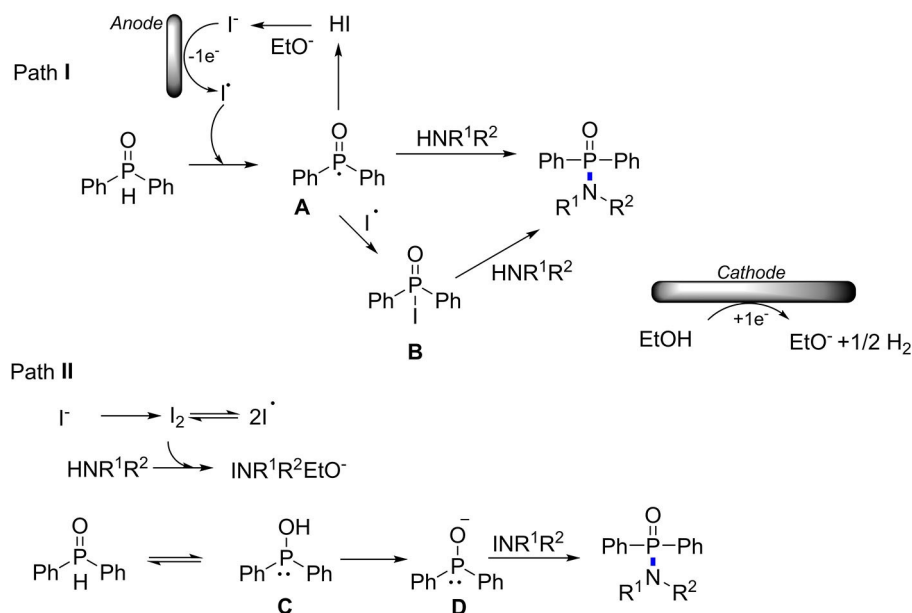

**Scheme 29.** Electrosynthesis of substituted phosphonic amides.

chemical dehydrogenative phosphorylation of alcohols was developed by Tang's group.[49] Alike, Han and co-workers[50] developed the synthesis of organophosphinate **38** by the cross dehyrogenative-coupling reaction between phosphines oxides **37** and alcohols **36** (scheme 25). The reaction was conducted in an undivided cell in the presence of *n*-Bu₄NI both as catalyst and electrolyte, under constant current in acetonitrole. The proposed mechanism implies that the reaction starts with anodic oxidation of iodide to molecular iodine, which produces iodation of H-phosphite **37** to provide intermediate **A**. Subsequently, the alcohols **36** reacts with intermediate **A** to

provide the final product **38** after elimination of iodine anion and one proton (scheme 26).

Recently, Quan and co-workers[51] reported an efficient *n*-Bu₄NI-catalyzed electrosynthesis of carbamoylphosphonates **41**, starting from phosphoramides **39** and alcohols **40** (scheme 27). Using platinum plates as electrodes, large scope of the final product was formed in good to excellent yields up to 96%. The reaction proceeds in an undivided cell at a constant current. In this transformation, the alcohol reacts as a solvent and a substrate. Scheme 28 describes the plausible mechanism as an improvement for this transformation. The reaction begins with anodic oxidation of iodide to lead

Scheme 30. Plausible mechanism for electrosynthesis of substituted phosphonic amides.
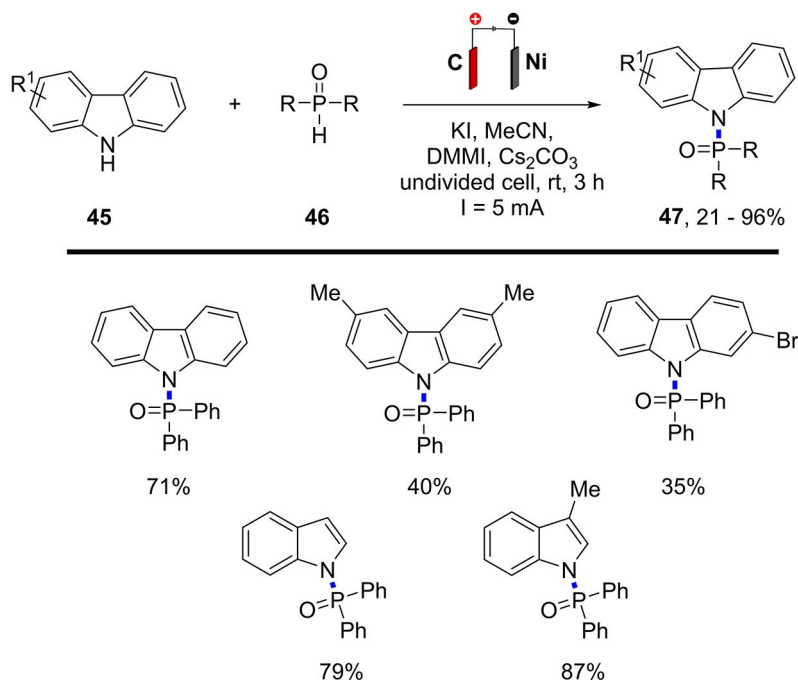
Scheme 31. Electrochemical phosphonation of carbazoles and indoles.

molecule I$_2$, which reacts with **39** to produce the intermediate **A**. Then, the electrogenerated ethoxy anion **B** produced on the cathode attacks intermediate **A** to give intermediate **C**. Then further oxidation of **C** by O$_2$ in air leading the final product **41**. In pathway II, **A** can be oxidized by O$_2$ to give intermediate **D**, which reacts with an electrogenerated ethoxy anion to produce the final products.
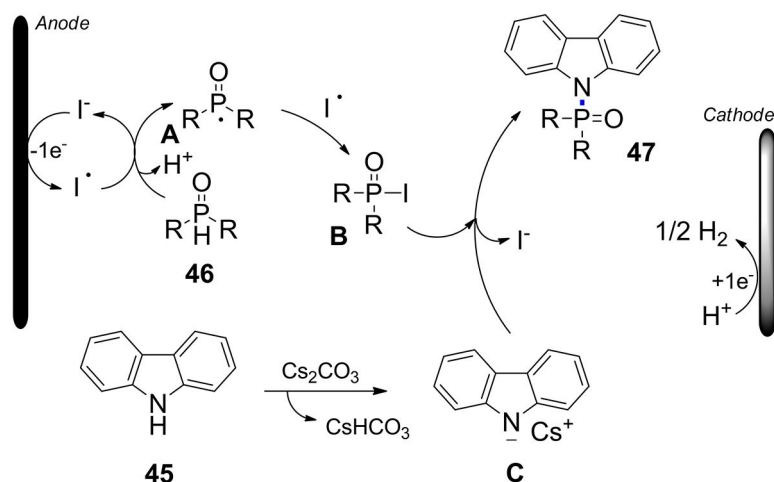
Scheme 32. Plausible mechanism for electrochemical phosphonation of carbazoles and indoles.
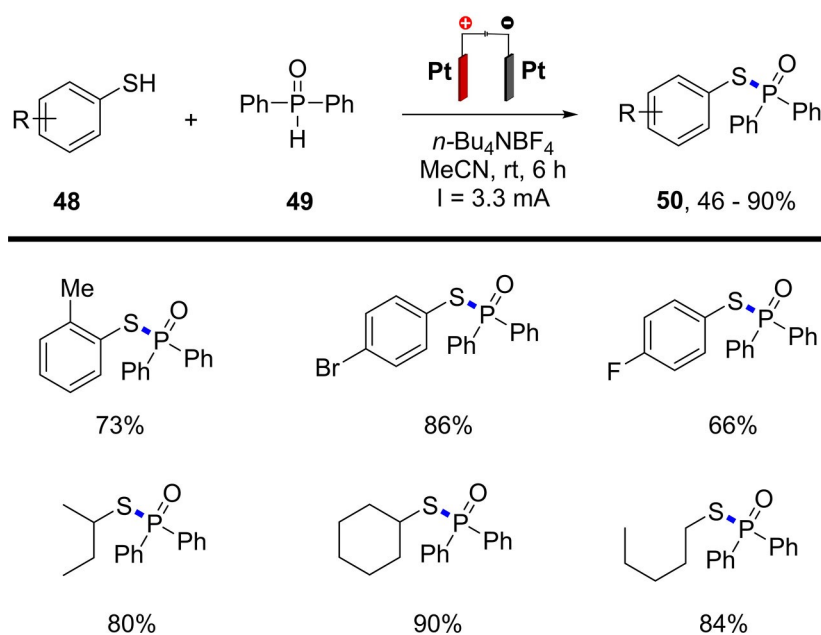
Scheme 33. Electrosynthesis of organothiophosphates.

2.4. N–P Bond formation

In 2013 Wang and co-workers[52] developed an efficient approach to achieve the cross- coupling reaction between N–H and P–H. Starting from phosphines oxides **42** and amines **43**, a variety of different substituted phosphonic amides **44** were formed in good yields up to 91 % (scheme 29). The authors used KI as a mediator, platinum plates as electrodes with a constant current in an undivided cell for 7 hours. Mechanistic studies (scheme 30) shows that the reaction begins with an anodic oxidation of iodide anion to

give iodine radical (path I), which reacts with **42** to produce intermediate **A** with loosing of HI molecule. Then, amine derivatives **43** reacts with **A** to provide the final product (or it could be generated when iodine radical attacks intermediate **A** to give diphenyl phosphinyl iodide **B**, which could react quickly with **43** and offer the final product). In path II, similar to path **I** the reaction begins with an anodic oxidation of iodide anion to give molecular iodine. Then, I$_2$ reacts with amine **43** to lead the intermediate **C**. Next, the electro-generated ethoxy anion deprotonates intermediate **C** to give
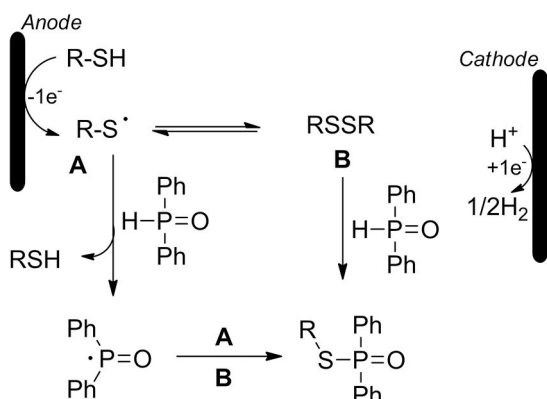
Scheme 34. Plausible mechanism for electrosynthesis of organothiophosphates.

the anion intermediate **D**, which reacts with amine **43** to give the final product.

Recently, Liu and co-workers[53] reported an efficient approach for an electrochemical phosphonation of carbazoles and indoles **45** by P(O)-H compounds **46** using catalytic quantity of DMMI as the redox mediator (scheme 31). A variety of phosphorylation products **47** was formed in moderate to excellent yields. The final products attached to electron-donating such as Me, Me O, CH_2CN, or electron-withdrawing such as Cl, Br, CO_2Me have a good tolerance in this transformation. The electrolysis proceeds in an undivided

cell, equipped with Carbone anode and nickel cathode, at a constant current, containing $DMMI/CH_3CN$ as the electrolyte/solvent in the presence of Cs_2CO_3 a base for 3 h at room temperature. The scheme 32 illustrates the plausible mechanism of the reaction. The process starts by anodic oxidation of iodide anion to give iodide radical, which reacts with **46** to form the intermediate **A**. Further addition of iodide radical to **A** provided intermediate **B**. Meantime, Cs_2CO_3 deprotonate the substrates **45** to generate intermediate anion **C**. Then **C** attacks **B** to lead the final product **47**.

2.5. S–P Bond Formation

Thiols derivatives with aromatic or aliphatic substituted are the most interesting substrates for the formation of S–P bond. In 2013, Zheng and co-workers[54] demonstrated an efficient electrochemical approach for S–P bond formation, starting from thiols derivatives **48** and diphenyl phosphine oxides **49**. The reaction proceeds both in an undivided cell and continuous-flow. The heights results were obtained by the combination of platinum electrodes both as anode and cathode in acetonitrile as a solvent in the presence of n-Bu_4NBF_4 as an electrolyte (scheme 33). Different thiols derivatives could afford a large scope of organothiophosphates **50** in good yields up to 90 %. In addition to thiols derivatives, alcohol substrates were also tolerated in this transformation, and the final products were formed in very good yields. However, only phenyl phosphine oxides were applicable. Scheme 34 illustrates
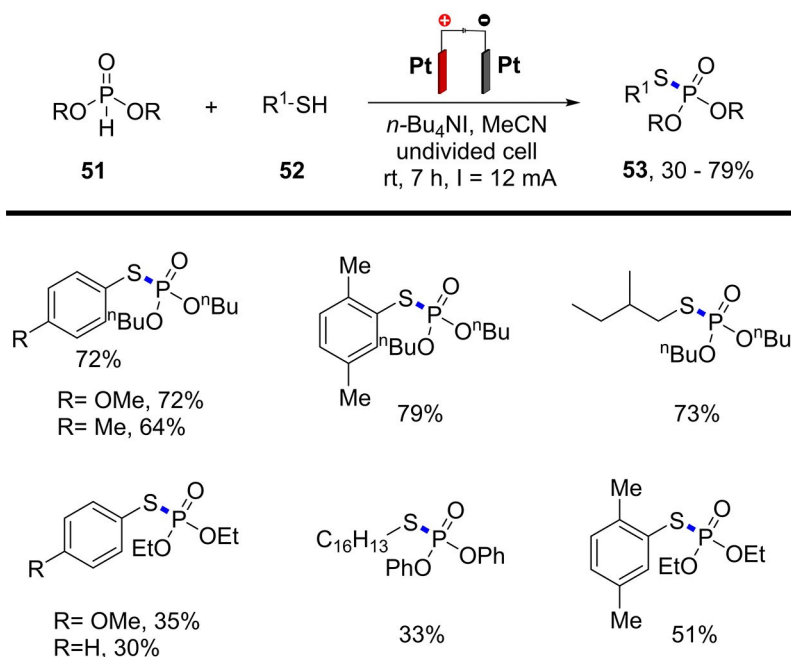
Scheme 35. Electrosynthesis of organothiophosphates derivatives.
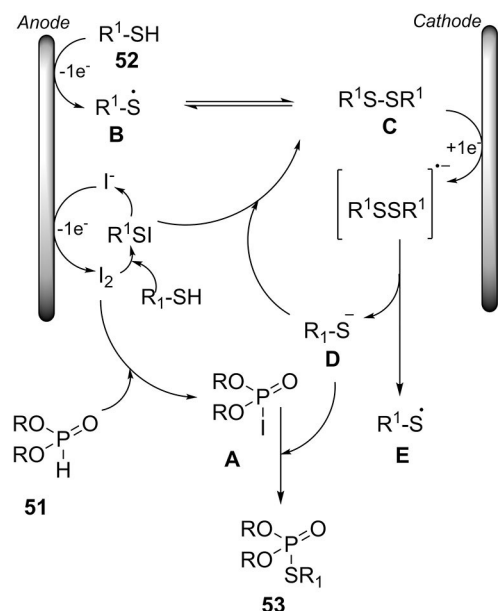
Scheme 36. Plausible mechanism for electrosynthesis of organothiophosphates derivatives.

the plausible mechanism for the reaction. On the anode, the reaction starts by oxidation of thiols **48** to produce radical **A** followed by fast dimerization of sulphur radical to give disulfide **B**. Simultaneously, the phosphorus radicals **C** are formed from **A** by a hydrogen atom transfer. Then the

phosphorus radical **C** reacts easily with **A** or **B** to give the final products **50**.

Recently, this methodology was extended in 2019 by Lee and co-workers.[55] The authors developed an efficient method for $n\text{-Bu}_4\text{NI}$ mediated electrosynthesis of organothiophosphanates **53**. Under mild condition, different phosphinates and thiols could afford the desired product in good to moderate yield (scheme 35). Aryl thiols derivatives well tolerated in this transformation. Di-n-butyl phosphate with arylthiols affords the desired products in moderate to good yield 35–79 %, however, diethylphosphites were also tested providing the corresponding products in moderate yield up 35 %. However, alkylthiols were also evaluated leading products with moderate to good yields (33–73 %). The reaction proceeds in an undivided cell under constant current, platinum plates were used as electrodes and acetonitrile as a solvent in the presence of $n\text{-Bu}_4\text{NI}$ as an electrolyte. Based on control experiments, the authors suggested the following mechanism (scheme 36). The reaction begins with anodic formation of I_2, which oxidize easily both phosphonate and thiol giving respectively, iodophosphate **A** and sulfenyl iodide **B**. On the cathode the reduction of disulfide **C** leads to thiolate anion **D** and thiyl radical **E**, then iodophosphate **A** reacts with thiolate anion **D** providing the desired product **53**.

2.6. Se–P Bond Formation

Heteroatom bond to phosphorus moieties with selenium is important chemical construction in organic chemistry because
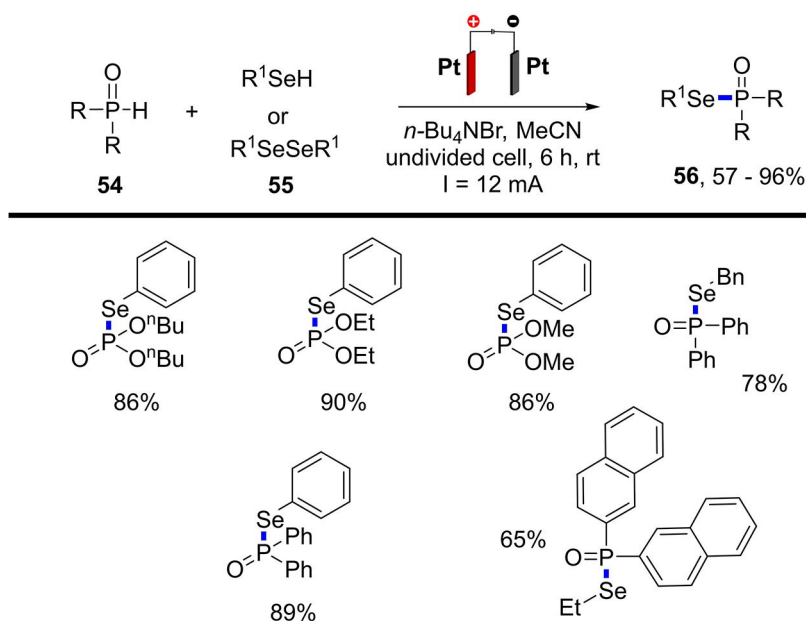
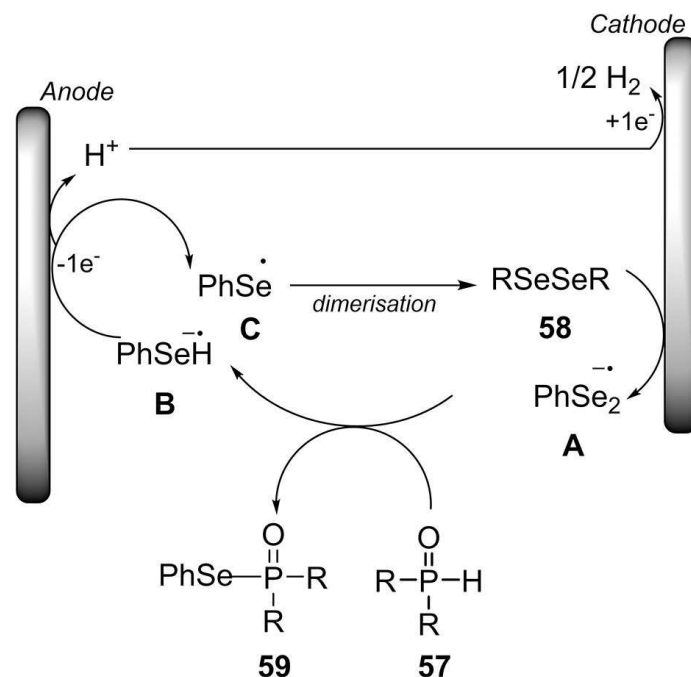**Scheme 37.** Electrosynthesis of organoselenophosphorus derivatives.
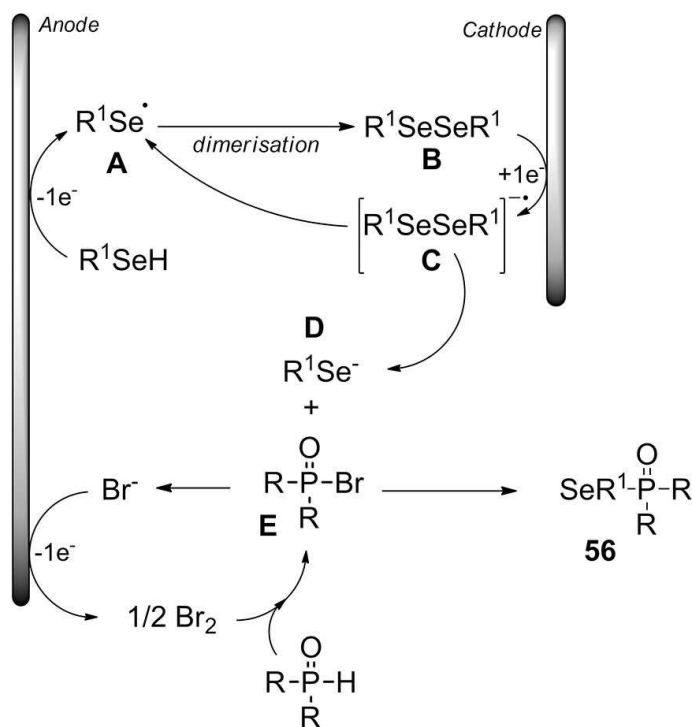
Scheme 38. Plausible mechanism for electrosynthesis of organoselenophosphorus derivatives.

Se–P bond could provide some bioactive molecules. An interesting protocol was reported by Cai and co-workers[56] for the electrochemical formation of Se–P bond. The reaction proceeds between selenols **55** derivatives and phosphonates or phosphines oxides **54** using n-Bu$_4$NBr as the redox mediator (scheme 37). Under mild condition, the electrolysis performed in an undivided cell at constant current 12 mA for 6 h, containing n-Bu$_4$NBr/CH$_3$CN as the electrolyte/solvent and platinum plates as electrodes. The final product **56** was formed smoothly with good to excellent yield. Different phosphonates derivatives well tolerated in this transformation leading the desired product in 84 to 90%. Aryl phosphonate like diphenyl phosphonate give desired compound in 96%. However, with diaryl phosphine low yields were obtained, the authors changed the electrolysis condition, in dichloromethane at 10 mA for 4 h results increasing yield to 87–89%. Moreover, in addition to selenols derivatives, diselenides substrates were also tested, yielding the final products with very good yields. The plausible mechanism in scheme 38 shows that initially, selenol was oxidized at the anode to produce selenium radical **A**, which after dimerization give diselenide **B**. This latter was reduced at the cathode to provide radical anion **C**, which after further decomposition lead **A** and selenium anion **D**. Meantime, the oxidation of Br$^-$ on the anode give Br$_2$, which reacts with substrates **54** to form intermediate **E**. At the end, the condensation of **E** and **D** provides the final product.

In the same year, the group of Wirth[57] demonstrated that automated flow electrochemical reactor was successfully useful
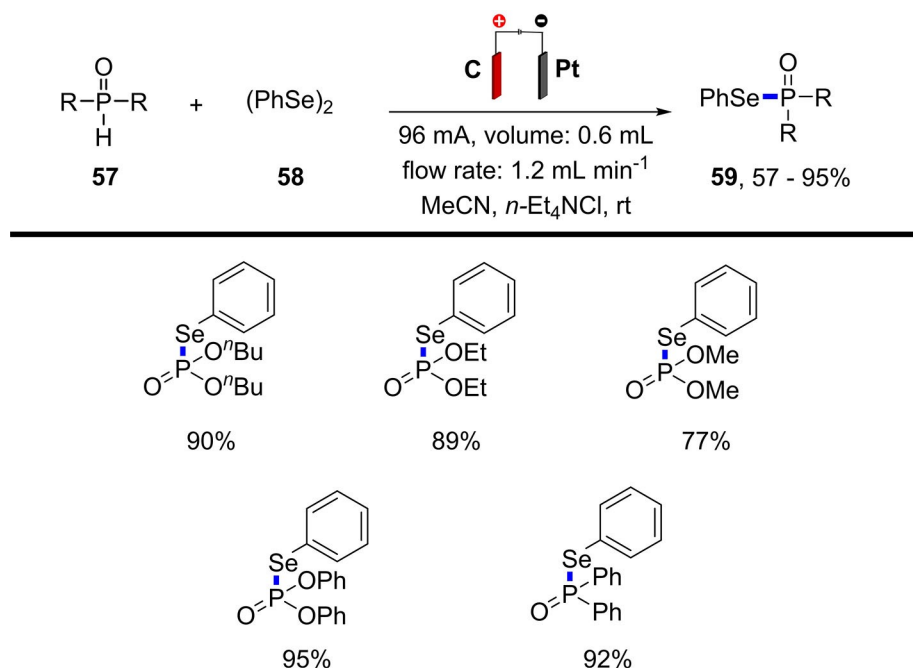
Scheme 39. Electrosynthesis of organoselenophosphorus derivatives.

Scheme 40. Plausible mechanism for electrosynthesis of organoselenophosphorus derivatives.

for the synthesis of organoselenophosphorus (scheme 39). With diphenyl diselenide and phosphites derivatives a large scope of desired compounds was formed in moderate to good yields. The optimal yields were obtained by the combination of graphite anode and platinum cathode in acetonitrile using n-Et$_4$NCl as an electrolyte. Scheme 40 illustrates the possible mechanism for this transformation. The reaction starts on the cathode by the reduction of diselenide leading the radical anion **A**, which forms with phosphite substrates the final product **59** and intermediate **B**. This latter oxidized on the anode to lead the radical **C**, which then dimerizes to produce **58**.

3. Summary and Outlook

As already established that phosphorous containing organic molecules such as polymeric chains of DNA/RNA are playing important role in nature biology. Similar, organophosphorus molecules have significant utility in industry, drug design, agrochemicals, material science and organic chemistry. Therefore, the new synthetic strategies to form phosphorus-carbon or phosphorus-heteroatom bond and enlarge the substrate scope will remain an exciting practice in organic reactions to synthesize organophosphorus compounds of potential applications. In the past, much effort has been made in the developments of various methods based on transition metal-

and organic catalysis to construct organophosphorus compounds. However, this review offers an overview of latest developments to use smart electrochemistry as a source of green tool in synthesis of organophosphorus compounds since it avoids using conventional chemical oxidants and generating reagents waste. Its applications in organophosphorus chemistry would be more sustainable and more attractive.

This review is concentrated on the recent advances of C (sp^3)–P, C(sp^2)–P, O–P, N–P, S–P, and Se–P bond formation reactions promoted by electrochemistry. These electrochemical bond formations are explained in two ways: 1) catalyzed electrochemical reaction by metal or non-metal catalyst 2) catalyst-free reaction (direct oxidation or reduction of substrates). This review demonstrated the efficacy of the electrosynthesis as an excellent, efficient and green way for constructing new bond such as C–P, O–P, N–P, S–P, and Se–P. Even with this progress, still the need to develop the catalyst-free bond process, especially for N–P and O–P bonds. Additionally, there has been made recent progress to access phosphorylated compounds using flow and automated technology [57] that would be an additional step for easy handling of chemicals and less involvement of human, allowing the chemists, at the same time, to apply their expertise to other pressing challenges in their fields.

Acknowledgements

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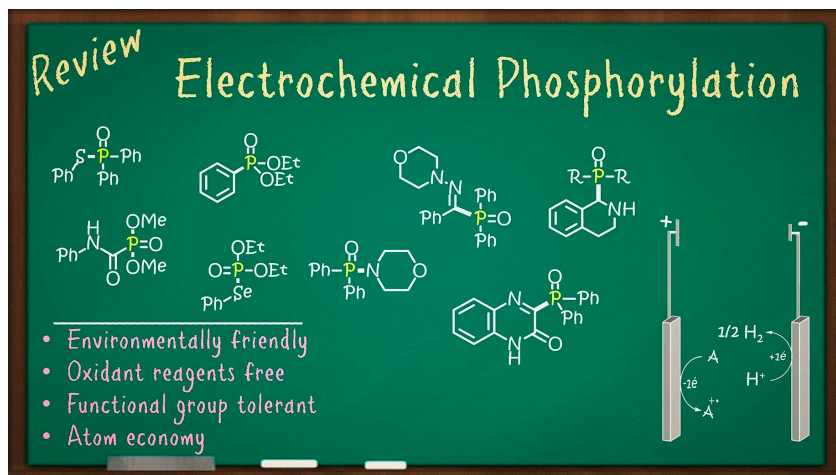
N. Sbei, G. M. Martins, B. Shirinfar, N. Ahmed*

1 – 24

Electrochemical Phosphorylation of Organic Molecules

Herein, electrochemical phosphorylation reactions involving catalyst and catalyst-free conditions, with generation of new bonds such as $C(sp^3)$–P, $C(sp^2)$–P, O–P, N–P, S–P and Se–P have been discussed.