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Electrochemical Enabled Cascade Phosphorylation of N–H/O–H/S–H Bonds with P–H Compounds: An Efficient Access to P(O)–X Bonds

Ruige Wang, Xiaojuan Dong, Yonghong Zhang, Bin Wang, Yu Xia, Ablimit Abdukader, Fei Xue, Weiwei Jin,* and Chenjiang Liu*

Abstract: An electrochemical three component cascade phosphorylation reaction of various heteroatoms-containing nucleophiles including carbazoles, phenols, alcohols, and thiols with Ph_2PH has been established. Electricity is used as the "traceless" oxidant and water and air are utilized as the "green" oxygen source. All kinds of structurally diverse organophosphorus compounds with P(O)–N/P(O)–O/P(O)–S bonds are assembled in moderate to excellent yields (three categories of phosphorylation products, 50 examples, up to 97% yield). A tentative free radical course is put forward to rationalize the reaction procedure.

Introduction

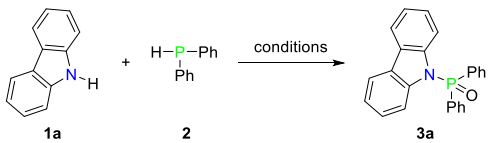
Organophosphorus derivatives, especially the compounds with P(O)–X (X = N, O, S) bonds, are a class of important substructures due to their distinct chemical and biological characteristics. Actually, they have been widely used in synthetic chemistry, organic optoelectronic material, pharmaceutical industry, and biological science.[1] Therefore, a great deal of effort has been devoted to develop potent methods for the formation of these kinds of phosphorus-containing compounds. Traditionally, phosphorylation of nucleophilic heteroatom-containing substrates, such as amines, alcohols, and thiols, with RP(O)–Cl is one of the most extensively adopted strategies to form P(O)–X bonds.[2] As well, transition-metal catalyzed cross-coupling reactions,[3] oxidative dehydrogenative phosphorylation reactions under metal-free conditions,[4] Atherton-Todd-type reactions using in situ generated RP(O)–Cl,[5] and others[6] are also reliable and well-established phosphorylation routes. In spite of this, some obvious shortages including the use of stoichiometric oxidants, toxic CCl_4, expensive transition metal catalysts, and harsh reaction conditions remain to be solved.[2-6,7] Moreover, the heavy metal residue which comes from the involvement of transition metal catalysts will hamper the further application of organophosphorus products in medical and biological research.

In recent years, phosphorus radicals initiated organic reactions have emerged as a powerful and popular tool for the preparation of organophosphorus compounds in synthetic chemistry.[8] In this regard, visible-light enabled photoredox catalysis, which employing transition metal complexes or non-metallic organic dyes as photosensitizers, has demonstrated its potential to form P(O)–C and P(O)–X bonds mainly through the P-centered radicals involved phosphorylation procedures.[9] In addition, since organic electrosynthesis conforms to the intrinsic requirement of green chemistry, it has welcomed its second spring and developed into an alternative to thermal and photo initiated radical chemistry in the past few years.[10] With regard to the construction of P(O)–C,[11] P(O)–N,[12] P(O)–O,[13] and P(O)–S[14,13c] bonds via electrochemical triggered two component radical cross coupling phosphorylation reactions, some recent progress has been well demonstrated in the literature. Although some impressive achievements have been made in this aspect, it is still highly desirable to develop more diverse synthetic routes from readily available chemical feedstocks.

Multicomponent cascade reaction, which can convert multiple substrates into one product in a single step with minimized post-treatment manipulation, has been extensively applied in high throughput drug screening and the synthesis of organic small molecule compound libraries.[15] Recently, organic electrooxidation with water, which generated O_2 in situ through the electrolytic water process as the oxygen source, has received increasing attention from organic chemists due to its safety compared to the direct use of potential explosive molecular oxygen.[16] Herein, as a continuation to our long interest in aerobic oxidation[17] and electrochemical heteroatom-heteroatom cross coupling hydrogen evolution reaction,[12a] we display our research on the electrochemical cascade phosphorylation with P–H compounds using trace water in the reaction medium and air as the oxygen sources to construct P(O)–N/P(O)–O/P(O)–S bonds.

Results and discussion

Table 1. Optimization of reaction conditions.[a]



1a 2 3a

Entry	Variation from the standard conditions	Yield (%)[b]
1	none	85
2	without TBAI	n.r.

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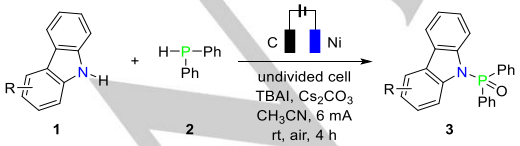
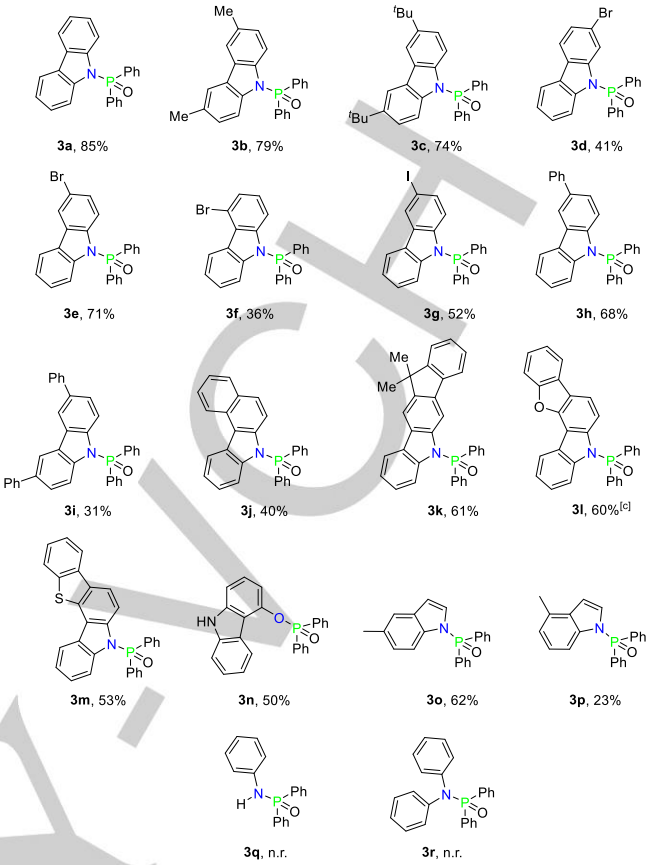
3	DMMI	65
4	$^{n}Bu_4NPF_6$	54
5	KBr	47
6	without Cs_2CO_3	24
7	without current	17
8	CH_3OH	67
9	DMSO	trace
10	DMF	n.r.
11	8 mA	51
12	4 mA	57
13	under N_2	49
14	under O_2	20
15	dry CH_3CN	16

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), TBAI (0.2 mmol), Cs_2CO_3 (0.2 mmol), CH_3CN (4.0 mL), C anode, Ni cathode, constant current = 6 mA, 4 h, room temperature, under air, undivided cell, reactions performed using ElectraSyn 2.0. [b] Isolated yields. n.r. = no reaction. DMMI = 1.3-dimethyllimidazolium.

Our studies were started by investigating reaction conditions, carbazole (**1a**) and diphenylphosphine (**2**) were selected as the model substrates for optimization studies (Table 1, see the Supporting Information (SI) for details, Table S1-S7). Screening revealed that in an undivided cell, using TBAI as the electrolyte, Cs_2CO_3 as the base and acetonitrile as the solvent, combined with the use of C anode and Ni cathode with a constant current of 6 mA after 4 hours in the ambient atmosphere, resulted in the highest yield of the desired product **3a** at room temperature (entry 1). Compared to our previous report on electrochemical direct cross coupling hydrogen evolution reaction between carbazole and diphenylphosphine oxide,[12a] the isolated yield of target product **3a** in this three component cascade reaction was enhanced obviously (from 71% to 85%). TBAI was found to be essential for this phosphorylation reaction (entry 2), other electrolytes, such as DMMI, $^{n}Bu_4NPF_6$, and KBr, showed the relative poor performances (entries 3-5). Cs_2CO_3 and electrical current were also necessary for this reaction on the basis of control experiments (entries 6 and 7). The use of eco-friendly CH_3OH as the solvent produced satisfied result as well (entry 8). While, only trace product **3a** could be detected in DMSO and the model reaction even did not work in DMF (entries 9 and 10). Increasing or decreasing the current intensity provided lower product yields (entries 11 and 12). Moreover, when the reaction was performed under a N_2 or O_2 atmosphere, the decrease in the yields of product **3a** was observed (entries 13 and 14). Finally, using dry acetonitrile as the reaction medium also obviously reduced the yield of **3a** (entry 15). The above results demonstrate that water is primarily split to generate O_2, which serves as the main oxygen source.

Table 2. Substrate scope of phosphorylation of carbazoles.[a,b]

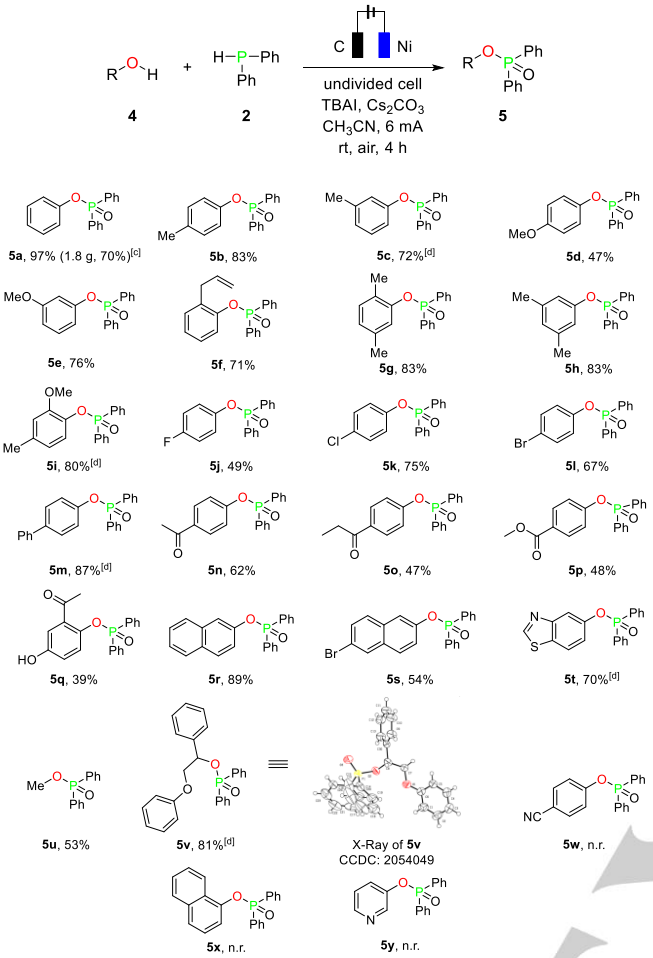




[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), TBAI (0.2 mmol), Cs_2CO_3 (0.2 mmol), CH_3CN (4.0 mL), C anode, Ni cathode, constant current = 6 mA, 4 h, room temperature, under air, undivided cell, reactions performed using ElectraSyn 2.0. [b] Isolated yields. [c] Reaction time = 5 h.

With the optimized reaction conditions in hand, we next investigated the scope of carbazoles in this electrochemical cascade phosphorylation reaction (Table 2). A range of substituted carbazoles could be smoothly converted into their corresponding phosphorylation products in moderate to good yields under optimal conditions. To our satisfaction, carbazoles substituted with electron donating alkyl groups (3,6-di-Me and 3,6-di-^{t}Bu) behaved better reactivities in this system than in our previous two component CCHE reaction,[12a] generating the corresponding products **3b** and **3c** in 79% and 74% yields, respectively. Halogen substituents (Br and I) at a different position in the phenyl ring of carbazoles were well tolerated (**3d-g**). Moreover, carbazole derivatives with a large conjugate system afforded the target products **3h-m** in 31-68% yields. When the substrate 9*H*-carbazol-4-ol which simultaneously containing two possible reaction sites was exposed to the standard conditions, only the direct O–H/P–H cross coupling product **3n** was obtained in 50% yield, while leaving the N–H bond intact. This demonstrates that O–H bond behaves better reaction activity than N–H bond in this catalytic system. When 5-methyl-1*H*-indole and 4-methyl-1*H*-indole were introduced as the reactants, their desired phosphorylation products **3o** and **3p** were formed in 62% and 23% yields, respectively. However, under standard conditions, primary amine (aniline) and secondary amine (diphenylamine) failed to give the desired products (**3q-r**).

Table 3. Substrate scope of phosphorylation of phenols and alcohols.[a,b]

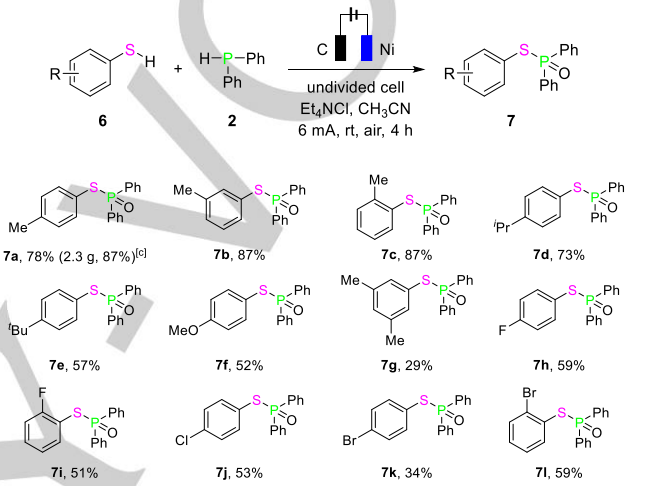


[a] Reaction conditions: **4** (0.2 mmol), **2** (0.3 mmol), TBAI (0.2 mmol), Cs_2CO_3 (0.2 mmol), CH_3CN (4.0 mL), C anode, Ni cathode, constant current = 6 mA, 4 h, room temperature, under air, undivided cell, reactions performed using ElectraSyn 2.0. [b] Isolated yields. [c] Gram-scale synthesis. Reaction conditions: **4a** (6.0 mmol), **2** (9.0 mmol), TBAI (6.0 mmol), Cs_2CO_3 (6.0 mmol), CH_3CN (30 mL), C anode, Ni cathode, constant current = 18 mA, 24 h, room temperature, under air, undivided cell. [d] Reaction time = 3 h.

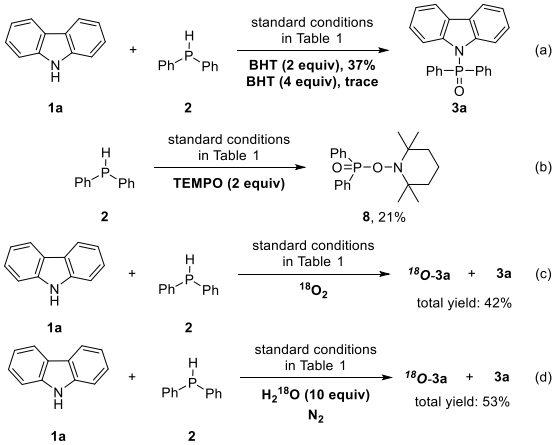
Inspired by the result of chemoselective formation of product **3n**, a series of coupling partners with various O–H bonds were subsequently examined (Table 3). To our delight, various phenols under the same reaction conditions shown in Table 2 were effectively converted into desired products in high yields up to 97%. Various electron-neutral, electro-rich, and electro-deficient phenols were employed to deliver the corresponding products **5a**-**q** in moderate to excellent yields (39-97%). Additionally, aromatic and heterocyclic rings condensed phenols were also suitable starting materials, the desired phosphonate products were constructed with moderate to high yields (**5r**-**t**). Finally, aliphatic alcohol phosphorylation products **5u** and **5v** were also easily prepared from corresponding methanol and benzenemethanol by this method. And the structure of **5v** was further characterized by X-ray diffraction of single crystal (CCDC 2054049). But 4-cyanophenol, 1-naphthalenol, and pyridin-3-ol failed to give the corresponding products (**5w**-**y**).

Finally, we successfully extended this electrooxidation system to various aryl thiols under slightly changed base-free conditions using Et_4NCl as the electrolyte (see SI for details, Table S8), obtaining the corresponding thiophosphates in good yields (29-87%, Table 4). Generally, the electron rich thiols achieved much better yields and no obvious steric effect was observed. Aryl thiol attached the electro-donating groups (Me, ^{i}Pr, ^{t}Bu, and OMe) at the *ortho*-, *meta*-, and/or *para*- positions of the phenyl ring resulted in the respective products in moderate to good yields (**7a**-**g**). Halogen (F, Cl, and Br) substituents were well tolerated in the reaction system (**7h**-**l**). Furthermore, under the optimal conditions the model reaction in Table 3 could be easily scaled up and assembled the target product **5a** in 70% yield (1.8 g). Similarly, a gram-scale reaction between thiophenol and diphenylphosphine under optimal conditions led to the product **7a** in 87% yield (2.3 g, Table 4). These indicate that the potential of this protocol for the practical utilities in organic synthesis.

Table 4. Substrate scope of phosphorylation of thiols[a,b]



[a] Reaction conditions: **6** (0.2 mmol), **2** (0.3 mmol), Et_4NCl (0.2 mmol), CH_3CN (4.0 mL), C anode, Ni cathode, constant current = 6 mA, 4 h, room temperature, under air, undivided cell, reactions performed using ElectraSyn 2.0. [b] Isolated yields. [c] Gram-scale synthesis. Reaction conditions: **6a** (8.0 mmol), **2** (12.0 mmol), Et_4NCl (8.0 mmol), CH_3CN (40 mL), C anode, Ni cathode, constant current = 22 mA, 22.5 h, room temperature, under air, undivided cell.



Scheme 1. Control experiments.

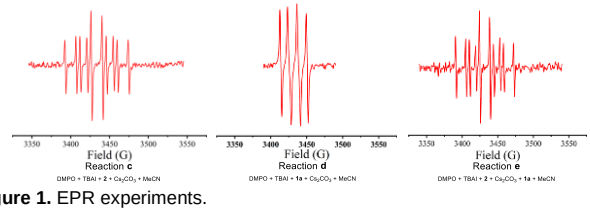
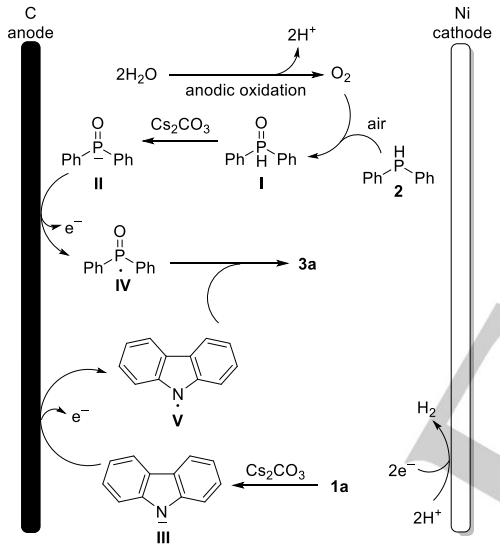


Figure 1. EPR experiments.

Control experiments provide some deep insight into the possible mechanism of this reaction, as shown in Scheme 1. A potential free radical process was supported by the radical trapping experiments employing BHT (2,6-di-*tert*-butyl-4-methylphenol) (Scheme 1a). Similar results were also observed during the phosphorylation of phenol and 4-methylbenzenethiol, only trace products were detected in the presence of 2 equivalent BHT or TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy). And the free radical trapping product **8** was detected by the radical scavenger TEMPO, showing the presence of a phosphorus radical species in this system (Scheme 1b). Electron paramagnetic resonance (EPR) experiments also supported the radical reaction produce, N- and P-centered radicals were detected (Figure 1, see SI for details). The HRMS analysis of the isotope labeling experiments in the presence of $^{18}O_2$ or $H_2{}^{18}O$ confirms that water is the main oxygen source of this catalytic system (Scheme 1c-d). Finally, the evolution of H_2 during this cascade electrochemical reaction route was preliminary monitored by a gas detector (see SI for details, S12, Figure S1).



Scheme 2. Putative mechanism.

Based on our studies and literature reports,[12a,13c] a possible reaction mechanism is proposed, as depicted in Scheme 2. Water is electrolysed at anode to form molecular oxygen and liberate H_2 at cathode, simultaneously. The oxidation of diphenylphosphine **2** with molecular oxygen and/or air to produce diphenylphosphine oxide **I**. Then, with the assistance of Cs_2CO_3, **I** and **1a** are converted into their respective anionic intermediates **II** and **III**, which are both oxidized at anode to give the P-centered radical **IV** and N-centered radical **V**, respectively. The direct cross coupling of these two radicals to deliver the target product **3a**.

Conclusions

In summary, we have developed a safe and efficient methodology for the electrochemical cascade phosphorylation of carbazoles, phenols, alcohols, and thiols with P–H compounds. A series of phosphorylation products containing P(O)–N bonds were constructed in moderate to excellent yields. Control experiments demonstrate that oxygen atom mainly originate from water, thus avoiding perform the reaction in the potential explosive molecular oxygen atmosphere. The protocol features its mild reaction conditions, broad substrate scope, good substituent tolerance, and readily scale up capacity.

Experimental Section

General. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Inova-400 (400, 100 and 160 MHz, respectively) spectrometer. ^{1}H and ^{13}C NMR chemical shifts were determined relative to internal standard TMS at δ 0.0 ppm or $CDCl_3$ ($\delta(^1H)$, 7.26 ppm; $\delta(^{13}C)$, 77.16 ppm) or DMSO-D_6 ($\delta(^1H)$, 2.50 ppm; $\delta(^{13}C)$, 39.52 ppm). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The HRMS analysis was obtained on a Agilent 6540 UHD Q-TOF mass spectrometer. The melting point was recorded on BÜCHI (M-560) and uncorrected. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60 F254 plates and viewed by UV light (254 nm). Column chromatographic purification was performed using 200-300 mesh silica gel. Electrochemical phosphorylation reactions were performed on IKA ElectraSyn 2.0 pro. X-ray single crystal diffraction data were collected on a Bruker D8 VENTURE. H_2 detection experiment was conducted on a ES20B-H_2 gas detector (Shenzhen Eyesky Technology Co., Ltd). Cyclic voltammetry (CV) was carried out on a CHI660E electrochemical workstation (CH Instruments, Ins).

General procedure (taking 3a as an example): Under air, a mixture of carbazole **1a** (33 mg, 0.2 mmol), diphenylphosphine **2** (52 µl, 0.3 mmol), TBAI (74 mg, 0.2 mmol), Cs_2CO_3 (65 mg, 0.2 mmol) and CH_3CN (4.0 mL) were added in an oven-dried undivided bottle (10 mL). The bottle was equipped with graphite rod as the anode and nickel plate as the cathode. The resulting mixture was stirred and electrolyzed at a constant current mode with a constant current 6 mA at ambient temperature for 4 h. When the reaction was finished, the resulting mixture was extracted with EtOAc (3×10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and all the volatiles were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 4:1, v/v) to afford the desired product **3a** as a white solid (62.3 mg, 85% yield).

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Keywords: electrochemistry • phosphorylation • P(O)—X bonds • cross-coupling • hydrogen evolution

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ARTICLE

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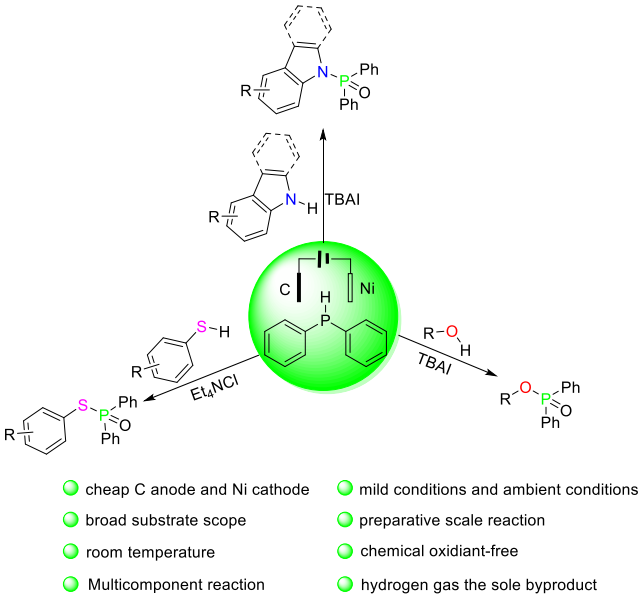
Electrochemical Enabled Cascade Phosphorylation of N–H/O–H/S–H Bonds with P–H Compounds: An Efficient Access to P(O)–X Bonds



An electrochemical enabled three component cascade phosphorylation of carbazoles, phenols, alcohols, and thiols with Ph_2PH has been well developed. A variety of organophosphorus compounds containing P(O)–X (X = N, O, S) bonds are produced in moderate to excellent yields (50 examples, up to 97% yield).