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Transition metal-promoted reactions of diarylphosphine oxides as a synthetic method for organophosphorus heterocyclic compounds

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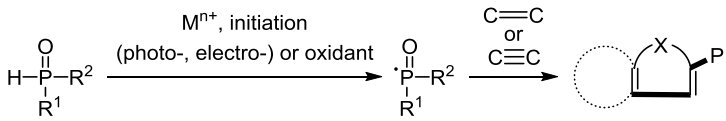


The present work considers main achievements and modern trends in methods of synthesis of organophosphorus heterocyclic compounds through mainly radical phosphorylation of the C(sp^2)–H bonds of unsaturated compounds catalyzed by metal salts and complexes. It also summarizes new ways of obtaining both phosphorous cycles (P-cycles) and heterocycles with another heteroatom (N, O, etc.) containing an external organophosphorus substituent. The most important and promising areas of recent years including the synthesis of 1-benzophospholes, arylphosphonates, phosphines, and phosphine oxides are highlighted. The reactions of phosphorylation/cyclization with acetylene, 2-isocyanobiphenyl, alkynoates, and olefins are analyzed. The assumed mechanisms and intermediates in the reactions of formation of the C–P bond are considered. New 1-benzophosphole oxides possessing photochromic, fluorescent, and some other optical properties are described. The work draws attention to the potential of this intensively developed direction of the organoelemental chemistry in last 5 years.

Keywords: alkene, alkyne, metal, radical, cyclization, phosphorylation.

Organophosphorus compounds with the P–C bond are widely used in medicinal chemistry, biochemistry, photoelectric materials, construction of the phosphine-substituted ligands for catalysis and organic synthesis.[1–8] In this regard, the development of new, more convenient, effective, and atom-economical, primarily catalytic methods of carbon–phosphorus bond formation is of considerable interest for the modern synthetic organoelemental chemistry. Recently, with the development of radical chemistry, $HP(=O)R^1R^2$ has gradually become an ideal radical precursor.[9–11] Since the phosphorus radical exhibits high reactivity in relation to unsaturated bonds, it provides an alternative method for construction of the C–P bond.

The phosphorylation/cyclization process can be successfully used for the synthesis of practically important phosphorylated cyclic compounds; this direction has been actively developed in recent years. Oxidative radical aromatic cyclization avoids using functionalized aromatic ring substrates or expensive transition metals, and the reaction conditions could be mild, which allows for excellent functional groups compatibility. The synthesis of heterocyclic compounds containing a phosphorus atom in both cyclic fragment and its substituents by using metal catalysts through functionalization of alkenes or alkynes, which is accompanied by simultaneous C–H substitution and cyclization, is actively developed, and some examples have been considered in the reviews.[8,12] New cascade reactions initiated by addition of the P-centered radicals to alkenes and alkynes can lead to the formation of a heterocycle. Both the phosphorus cycle (P-cycle) and heterocycle with another heteroatom (N, O, etc.) containing an external organophosphorus substituent can be obtained depending on the nature of the reagent with multiple bonds and reaction conditions.

This review consists of two parts and describes new achievements over the last five years in transition metal-catalyzed phosphorylation/cyclization reactions as a synthetic way to phosphorus-containing heterocycles (P-cycle and N- or O-cycles, respectively). Usually the synthetic significance of these cascade reactions is associated with high reactivity of the vinyl radicals formed at the first stage, which can be captured through rapid cyclization or addition to other π-systems. Nevertheless, there are difficulties in implementing such reactions. Both H-phosphonates and H-phosphine oxides are in equilibrium with the corresponding phosphinous acids and tend to form a P-bound phosphinous acid complex in the presence of a late transition metal.[8] Thus, the metal catalyst binds to the

existing phosphorus rather than to the much less coordinative C–H bond, which inhibits the C–H activation step.[13–15] This review will focus on the successful reactions between unsaturated compounds and P-centered radicals originating from P–H compounds by highlighting the specificity of reactions and, where possible, the mechanistic considerations.

Synthesis of P-heterocycles

Phosphorus-containing heterocycles have been of great interest for synthetic chemists over the last few years because of their wide applications in organic synthesis, medicinal chemistry, and materials science.[16–20] Among them, 1-benzophosphole derivatives, the phosphorus-containing π-conjugated compounds, have attracted significant attention as promising organic optoelectronic materials due to their unique physical and photoelectric properties.[21–29]

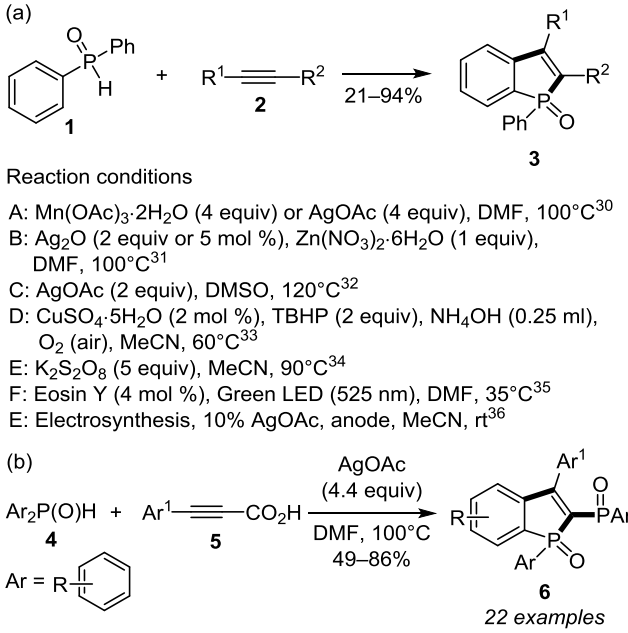
In 2013, Satoh and coworkers developed a novel Ag(I)- or Mn(III)-mediated dehydrogenative annulation of diphenylphosphine oxide (**1**) with alkynes **2** for the synthesis of 1-benzophosphole oxide derivatives **3** (Scheme 1, a) and demonstrated the only example of the reaction using a related phosphorus-substituted alkyne leading to the 2-phosphino-1-benzophosphole product.[30] But this method needed prior preparation of alkynylphosphonates through the transition metal-catalyzed coupling or the reaction of $(RO)_2P(O)Cl$ with Li or Mg acetylides under harsh reaction conditions.

At almost the same time, Ag(I)-mediated synthesis of compounds **3** was reported by Duan[31] and Ackermann.[32] In these two reactions, noble Ag salts or Mn salt are used in excess (2–4 equiv), which is wasteful and expensive. In 2016, Zhao has successfully developed a facile method for the preparation of compounds **3** only by using 2 mol % $CuSO_4·5H_2O$ as the catalyst which is inexpensive and environmentally friendly.[33] Moreover, phosphorylation/cyclization process in oxidative metal-free conditions using $K_2S_2O_8$[34] and photocatalytic method[35] for the synthesis of compounds **3** was successfully developed by Zhao and Lakhdar groups, respectively (Scheme 1, a). In this reaction, an unusual aryl migration of the P atom was observed occurring upon the C–P bond cleavage and formation of a new C–P bond proceeding as a radical process.

It has been recently demonstrated that the silver-catalyzed reaction of C–H/P–H functionalization with alkynes can be realized under electrocatalytic oxidative conditions.[36,37] This approach allows directly to obtain 1-benzophosphole oxides in high yield under mild conditions (room temperature) and low loading of the silver catalyst. In this case, the usual excess of oxidant and high temperature are not required, which is obviously more efficient compared with the previously discussed techniques.[30–35,38] The reaction takes place under action of Ag(II) resulting from oxidation of Ag(I) (10%) catalyst at the anode. The mechanism of this process requires further research.

Recently, the Zhao group described the synthesis of compound **6** through silver-mediated cascade decarboxylative coupling and annulation reaction of arylpropiolic acids **5** with diarylphosphine oxides **4** *via* sequential decarboxylative C–P cross coupling and C–H/P–H functionalization (Scheme 1, b).[38]

Scheme 1. Synthesis of 1-benzophosphole oxide derivatives

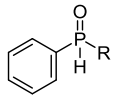
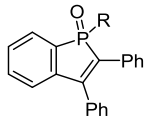
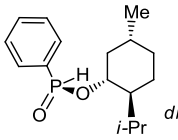
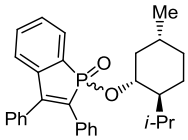
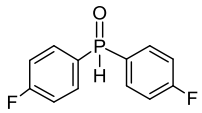
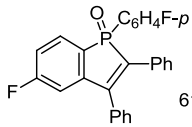
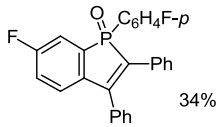
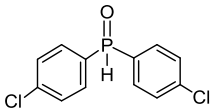
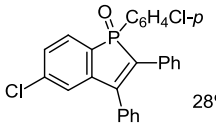
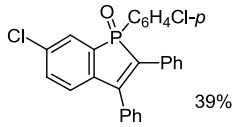
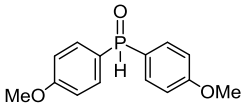
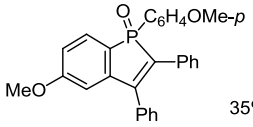
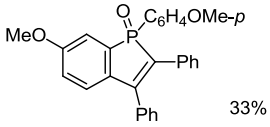
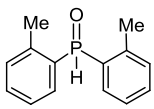
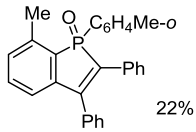
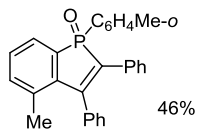
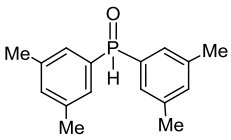
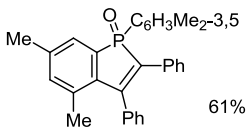
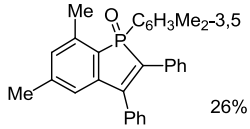


The conditions of synthetic reactions leading to phospholes **3** or **6** were carefully optimized, and the selected catalysts and oxidants were shown to allow preparation of these products with yields from 60[32] to 94%.[31] With the optimized conditions in hand, the current method was applied for various substrates, and the results obtained by Duan are shown in Table 1 as an example.[31]

Monophenylphosphine oxides bearing various substituted groups, such as *tert*-butyl, cyclohexyl, and ethoxy, can be coupled with diphenylacetylene to afford the corresponding products in moderate to good yields (Table 1, entries 1−4). An optically pure phenylphosphinate containing a (–)-menthol moiety can also be converted to the phosphorus heterocycle, albeit with obvious epimerization at the phosphorus atom (entry 5). In addition, phosphine oxides having various electron-rich or electron-poor substituted aryl groups were examined in the reaction with diphenylacetylene, which produced mixtures of regioisomers (entries 6–10). It was suggested that an aryl migration takes place involving a C−P bond cleavage and a new C−P bond formation process, which has not been reported and discussed in details before Duan's publication.[31]

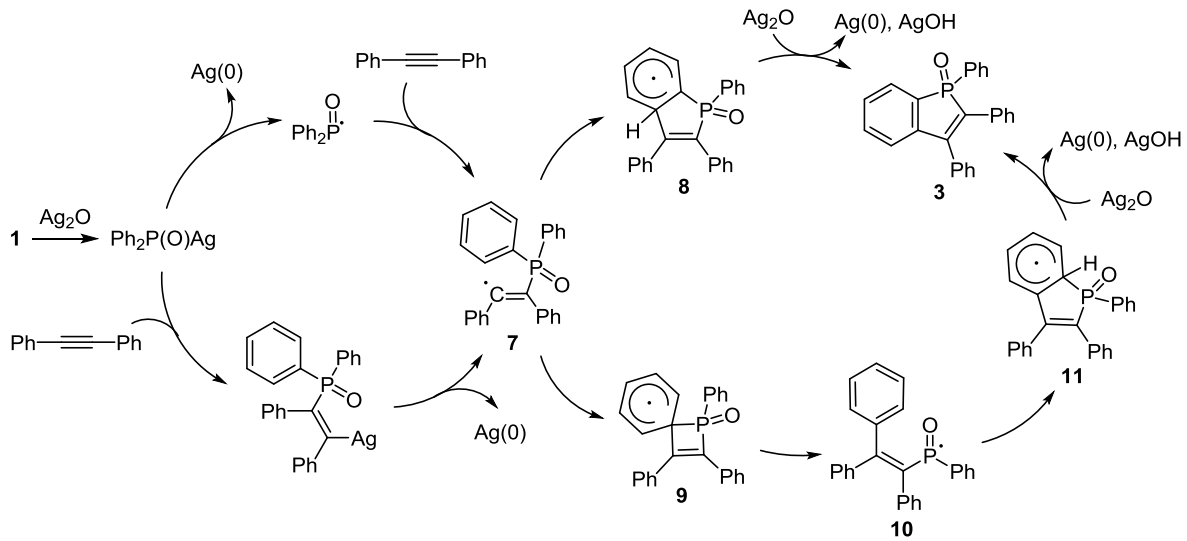
To obtain more insights into the mechanism of the current reaction, a series of experiments were conducted. Given that aryl migration is often observed in radical reactions, Duan proposed a tentative mechanism for the current system (Scheme 2).[31] First, a phosphorus radical is generated from silver diphenylphosphine oxide, and then the radical addition to the alkyne affords alkenyl radical **7**. Alternatively, radical **7** also might be generated through the addition of silver diphenylphosphine oxide to alkyne,

Table 1. Silver-mediated oxidative cyclization of phosphine oxides with diphenylacetylene*

Entry	Phosphine oxide	Product/Yield, %
1–4		 R = Ph (94%) R = *t*-Bu (76%) R = Cy (42%) R = OEt (60%)
5	 *dr* 99:1	 40%, *dr* 63/37
6		 61%  34%
7		 28%  39%
8		 35%  33%
9		 22%  46%
10		 61%  26%

* Reaction conditions: Ag_2O (2 equiv), DMF, 100°C.

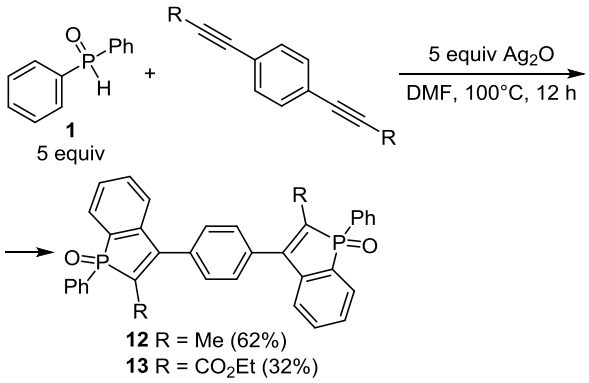
Scheme 2. Mechanism of 1-benzophosphole formation from phosphine oxide **1** and diphenylacetylene[31]



followed by a silver-induced formation of an alkenyl radical. Next, the intramolecular addition of alkenyl radical **7** to the aryl ring at the *ortho* position to the phosphorus atom followed by the oxidation of the cyclic radical **8** with Ag_2O and the removal of a proton afford phosphorus heterocycle **3**. For the formation of the aryl migration product, alkenyl radical **7** attacks the aryl ring at the *ipso* position followed by the C−P bond cleavage, furnishing a phosphorus radical **10**. Subsequently, radical phosphination of the aryl group that lies at the *cis* position to the phosphorus atom affords cyclic radical **11** which in the presence of Ag_2O as the oxidant affords the phosphorus heterocycle with the migrated aryl group.[31] It is noteworthy that the addition of 2 equiv of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical scavenger completely suppressed the reaction, thus indicating the reaction likely to proceed by single electron transfer processes.[32,38]

The reactions of diynes with diphenylphosphine oxide were conducted for the one-step synthesis of the bis-(1-benzophosphole oxides) (Scheme 3), which has been suggested to have potential applications in organic electronics. In addition, the absorption/emission spectra of the obtained 1-benzophosphole oxides **12** and **13** were recorded in CH_2Cl_2, and both compounds showed blue fluorescence with 0.6−14.5% quantum yields.[31]

Scheme 3. Synthesis of bis(1-benzophosphole oxides)



With continuous interest in the design of various photochromic materials, it was envisioned that the direct attachment of two thienyl rings onto the phosphole ring would offer a strategy to optimize the photochromic performance of the system.[39] Thus, photochromic 1-benzophosphole oxides were prepared by silver-mediated dehydrogenative annulation of phenyl hydrophosphine oxides and diarylacetylenes,[30,31] whereas the photochromic 1-benzophosphole derivatives were prepared by functionalization of the phosphorus center, using a modified version of a literature procedure for the synthesis of phosphole derivatives[21,40,41] (Fig. 1).

In 2016, a new regioselective synthetic methodology for 1-benzophosphole derivatives has been developed by Satoh and Miura group.[42] Thus, a series of functionalized 1-benzophosphole oxides **15** could be synthesized in a semi-one-pot manner *via* Rh(III)-catalyzed C−H alkenylation of arylthiophosphinamides **14** with alkynes followed by

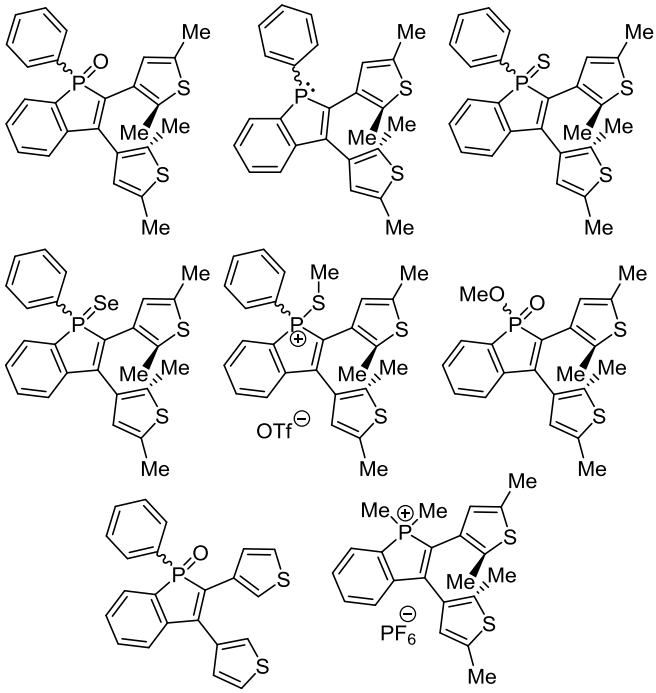
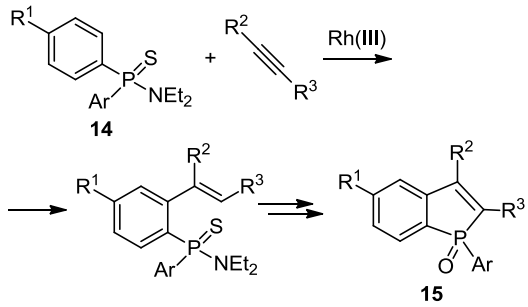


Figure 1. Chemical structures of some photochromic 1-benzophosphole derivatives.

formal phospha-Friedel–Crafts cyclization (Scheme 4). Optical properties including absolute fluorescent quantum yields determined by using an integrating sphere system showed relatively strong fluorescence in a range of 446 to 519 nm and remarkably, a blue-shifted emission in a high quantum yield (420 nm, Φ_F 0.9).[42]

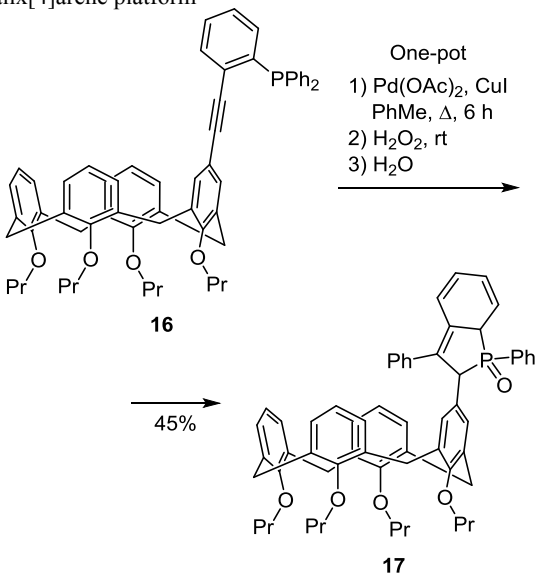
Scheme 4. Regioselective synthesis of 1-benzophosphole oxides by semi-one-pot protocol[42]



The effects of counter anions, P-substituents, and solvents on the optical and photophysical properties of 2-phenyl-1-benzophospholium salts in solution were investigated recently.[43] It was demonstrated that 2-aryl-1-benzophospholium salts would be promising scaffolds for developing new phosphole-based ionic fluorophores that are capable of responding to external stimuli such as anionic species and solvents.

In the latest investigations of Harrowfield,[44,45] conical calix[4]arene receptor **17** with a 1-benzophosphole oxide chromophore grafted to its upper rim was obtained in six steps by starting from 5-bromo-25,26,27,28-tetrapropyl-

Scheme 5. Synthesis of phosphole oxide from phosphane on calix[4]arene platform[44,45]

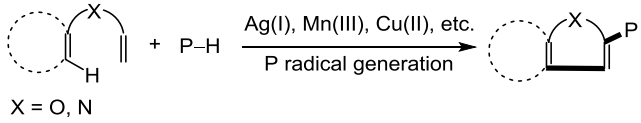


oxycalix[4]arene (Scheme 5). The route involved the synthesis of calixarene intermediate **16** that bears the 2-(diphenylphosphinyl)phenylethynyl substituent connected to the calixarene wider rim. Under Pd(II)/Cu(I) cocatalysis, mixed phosphane-alkyne when heated at 120°C underwent P–Ph bond cleavage followed by attack of the phosphorus atom on the carbon–carbon triple bond. The resulting calixarene-phosphole was then oxidized to form the corresponding phosphole oxide, which luminesces strongly under UV irradiation.[44]

Synthesis of N- or O-heterocycles bearing organophosphorus substituent

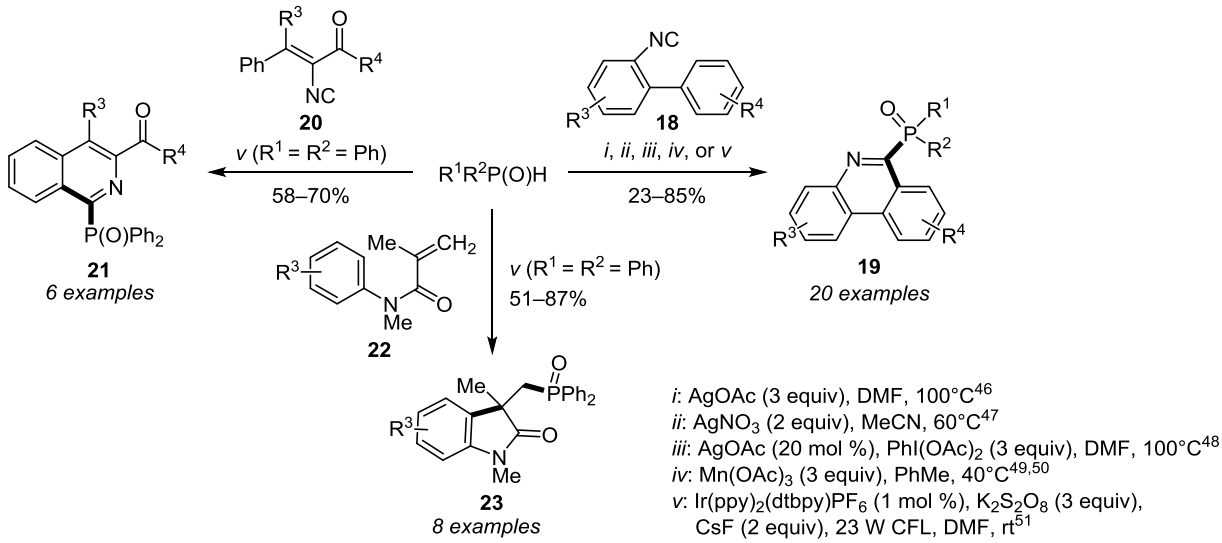
Radical cascade reactions involving attachment of the oxidatively generated P-centered radical to the unsaturated fragment (alkene, alkyne, isonitrile functions, etc.) and the subsequent homolytic aromatic substitution appears to be a new effective way to construct various complex heteroaromatic systems, the aromatic ring being created through phosphorylation (Scheme 6). All reactions involve affordable and cheap compounds, diorganophosphine oxides, as a phosphorus reagent and P-centered radical precursor. Therefore, the following cascade schemes of C–P bond formation and heterocyclization all start from $R^1R^2P(O)H$ and include a variety of new reactions of compounds with double or triple bonds that are capable of trapping P radicals.

Scheme 6. Radical cascade phosphorylation/cyclization reactions

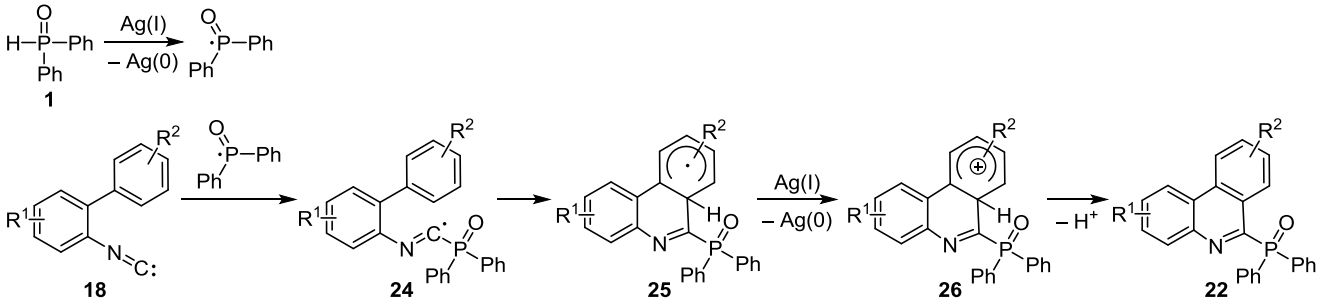


In 2014, the groups of Studer,[46] Yang,[47] Wang,[48] Wu,[49] and Zhao[50] independently described new approaches toward phenanthridines phosphorylated at position 6 based on easily obtained 2-isocyanobiphenyls and P radical precursors. Studer reported a reaction of AgOAc-mediated P-centered radical addition to aryl isocyanides **18** (Scheme 7) followed by cyclization of imidoyl radical and deprotonation for the synthesis of 6-phosphinoylated phenanthridines **19**.[46] A similar work was also reported by the Yang group by using 2 equiv of $AgNO_3$.[47] Moreover, the Wang group reported a Ag(I)-catalyzed process to promote the reaction using $PhI(OAc)_2$ as oxidant.[48] $Mn(OAc)_3$ (3 equiv) as oxidant was proposed for this synthesis by Wu[49] and Zhao.[50] In 2016, Lu discovered an effective photoredox tandem phosphorylation/cyclization reaction of diphenylphosphine oxide with three types of radical acceptors, biphenyl isocyanides **18**, vinyl isocyanides **20**, *N*-arylacrylamides **22**, yielding $P(O)Ph_2$-containing phenanthridines **19**, isoquinolines **21**, and indolin-2-ones **23**, respectively, by formation of both C−P and C−C bonds (Scheme 7).[51] [Ir-$(ppy)_2$(dtbpy)]PF_6 (1 mol %) was used as the catalyst and $K_2S_2O_8$ as the oxidant. A series of functional groups can be tolerated at room temperature.

Scheme 7. Phosphorylation/cyclization reactions



Scheme 8. Reaction of P-centered radicals with isocyanides



This process allows convenient and direct access to three types of phosphorylated N-heterocycles in moderate to excellent yields.

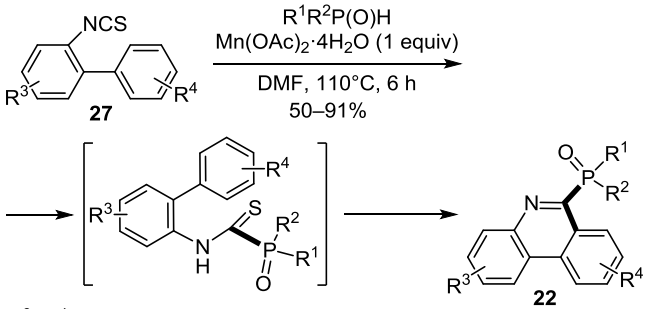
The originality and significance of the proposed synthetic routes lie in the fact that, firstly, the aryl isocyanides have not been previously used as P radical acceptors in cascade reactions. Secondly, unlike the intensely studied phosphorylation of arenes, in which the formation of the C–P bond typically preserves the benzene ring, the discussed reactions include phosphorylation with formation of fused arenes. Therefore, these approaches often do not have problems of regiochemistry that can be observed in the reactions of direct C–H phosphorylation of arenes. Finally, in contrast to the known methods, in which the reaction takes place through the transformation with the formation of a single C–P bond, this process involves the formation of the C–P bond along with a C–C bond.

A radical mechanism of this process was proposed (Scheme 8). The reaction is triggered by oxidation of phosphine oxide **1** by Ag(I) salt; the corresponding P-centered radical and Ag(0) are generated. Adding the P radical to the isocyanide function of compound **18** gives imidoyl radical **24**, which is undergoing cyclization while generating cyclohexadienyl radical **25**. Then the latter is oxidized by the Ag(I) salt, giving cyclohexadienyl cation **26** through transfer of one electron. Finally, deprotonation of cation **26** gives product **22**.[46]

Phenanthridine nucleus is an important structural fragment, which is present in many natural products with different biological activity.[52,53] It can therefore be expected that the proposed methods will be applied in the synthesis of biologically active compounds.

A novel Mn(II)-promoted tandem phosphorylation/cyclization reaction of 2-biaryl isothiocyanates **27** with phosphine oxides was described in 2017 by Li group (Scheme 9).[54] This is the first general method to synthesize 6-phosphorylated phenanthridines from 2-biaryl isothiocyanates. The approach is featured by no need for an oxidant, low loading of P reagent, easy operation, and tolerance toward different substituents. The authors suggested that unlike all the previously discussed reactions, the formation of 6-phosphorylated phenanthridines **22** is carried out in an ionic, not radical path. So, the proposed ionic mechanism includes the unusual intramolecular cyclization of the intermediate in the presence of Mn(II) affording the transient compound, which rapidly eliminates H_2S to provide the final product **22**. The reason that cyclization could take

Scheme 9. Synthesis of 6-phosphorylated phenanthridines from isothiocyanates

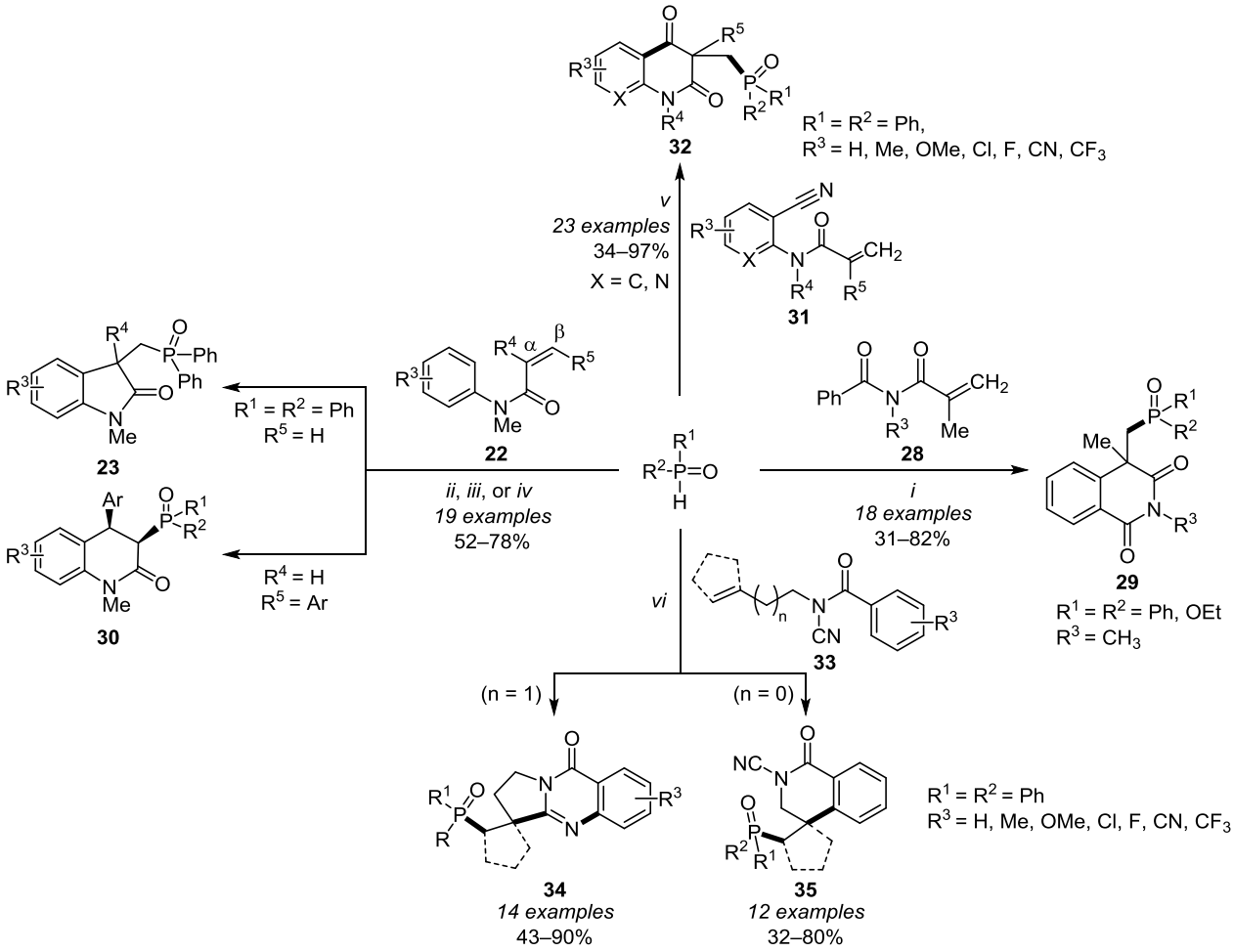


place is probably due to the high electronegativity of the P-substituted thioamide. However, the mechanism proposed by the authors requires further confirmation and justification. This environmentally benign strategy is expected to become a useful alternative for the synthesis of 6-phosphorylated phenanthridine derivatives.

An efficient synthesis of molecules bearing both isoquinolinedione motif and phosphonyl group is quite rare. The catalytic phosphorylation/cyclization reactions between methacryloylbenzamides **28** and phosphine oxides (Scheme 10) yield 4-phosphorylisoquinoline-2,4(1*H*,3*H*)-diones **29**, as it was reported by Zhao in 2016.[55] This radical reaction, triggered by TBHP peroxide in the presence of copper salt, $Cu(OTf)_2$, provides a rapid access to a broad spectrum of phosphonated products in moderate to good yields. Moreover, the use of inexpensive Cu(II) catalyst, using readily-prepared methacryloylbenzamides **28** and P(O)H compounds mean that this facile protocol will be attractive for academia and industry.

An efficient protocol for the preparation of diphenylphosphoryl oxindoles **23** was developed by Yang in 2013.[56] Ag-catalyzed cascade addition/cyclization process between *N*-aryl-*N*-methylacrylamides **22** and diorganyl phosphine oxides (Scheme 10). Alternatively, the transformation also could be realized by using visible-light photocatalysis[51] or $K_2S_2O_8$ as oxidant.[57] In these reactions, the P-centered radical was added selectively to the β-position to carbonyl, with the exception in the case of an aryl group as substituent at the β-position to carbonyl, were P-centered radical selectivity added to the α-position to carbonyl and afforded 3,4-disubstituted dihydroquinolin-2(1*H*)-ones **30** through an intermolecular radical addition and an intramolecular cyclization along the 6-*endo*-*trig* pathway.[58]

Scheme 10. Phosphorylation/cyclization of amides



i: $Cu(OTf)_2$ (10 mol %), TBHP (3 equiv), MeCN, 100°C[55]
ii: $AgNO_3$ (5 mol %), $Mg(NO_3)_2 \cdot 6H_2O$ (0.5 equiv), MeCN, 100°C[56,58]
iii: Ir(ppy)(dtbpy)PF_6 (1 mol %), $K_2S_2O_8$ (3 equiv), Cs_2CO_3 (2 equiv), 23 W CFL, DMF, rt[51];
iv: $K_2S_2O_8$ (3 equiv), MeCN, 90°C[57]
v: $CuBr_2$ (10 mol %), $Mg(NO_3)_2 \cdot 6H_2O$ (0.3 equiv), MeCN, 100°C[59]
vi: $AgNO_3$ (1 equiv), MeCN, 80°C[60]

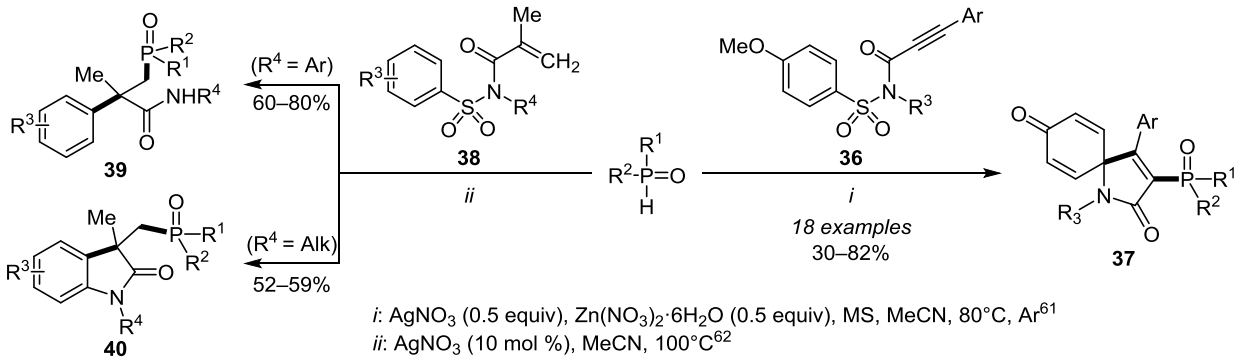
With a nitrile substituent in the aromatic ring of *N*-arylacrylamide **31**, reaction yields phosphorylated quinoline-2,4(1*H*,3*H*)-diones **32**. This result was reported by the Li group, and the reaction was carried out through Cu-catalyzed cascade addition/cyclization where the cyclization was accomplished by an intramolecular addition of the carbon radical to the nitrile.[59] The mechanism of the reaction was proposed where the P-centered radical attacked the C=C double bond to afford the corresponding carbon-centered radical; then imine was formed *via* an intramolecular addition of the alkyl radical to the coordinated nitrile group, and its hydrolysis by H_2O provided the final product **32**.

Moreover, *N*-cyano amides, too, could react with a P-centered radical. A silver(I)-mediated phosphorylation/cyclization radical cascade reaction of *N*-alkenyl-*N*-cyanamides **33** resulting the formation of phosphorylated spirocyclic pyrrolo[2,1-*b*]quinazolinones **34** and dihydroisoquinolinones **35** was reported by Cui.[60] Both terminal and cyclic alkenes **33** were used, and the cyclizations were consistent with the Baldwin's rule. The mechanism of the cascade phosphorylation/cyclization of *N*-cyanamide alkenes was proposed depending on *n* number.

Liang reported the reaction of terminally aryl-substituted *N*-[(4-methoxyphenyl)sulfonyl]-*N*-methylprop-2-ynamide **36** with a P-centered radical affording phosphorylated azaspiro-[4.5]decenones **37** *via* a phosphorylation/1,5-aryl migration/desulfonylation/dearomatization process (Scheme 11).[61] For alkenyl-substituted sulfonamides **38**, Nevado,[62] in 2014, proposed a mild and efficient protocol, similar to that by Liang,[61] for the Ag-catalyzed and P-centered radical-mediated tandem addition/cyclization followed by a desulfonylation yielding α-aryl-β-phosphoryl amides **39** or the corresponding indolinones **40**.[62]

$Mn(OAc)_3$-mediated radical oxidative phosphorylation/lactonization of alkenoic acids with terminal and internal alkene bonds under relatively mild conditions yield γ- or δ-lactone phosphonates substituted with phosphorylmethyl

Scheme 11. Phosphorylation/cyclization of sulfonamides



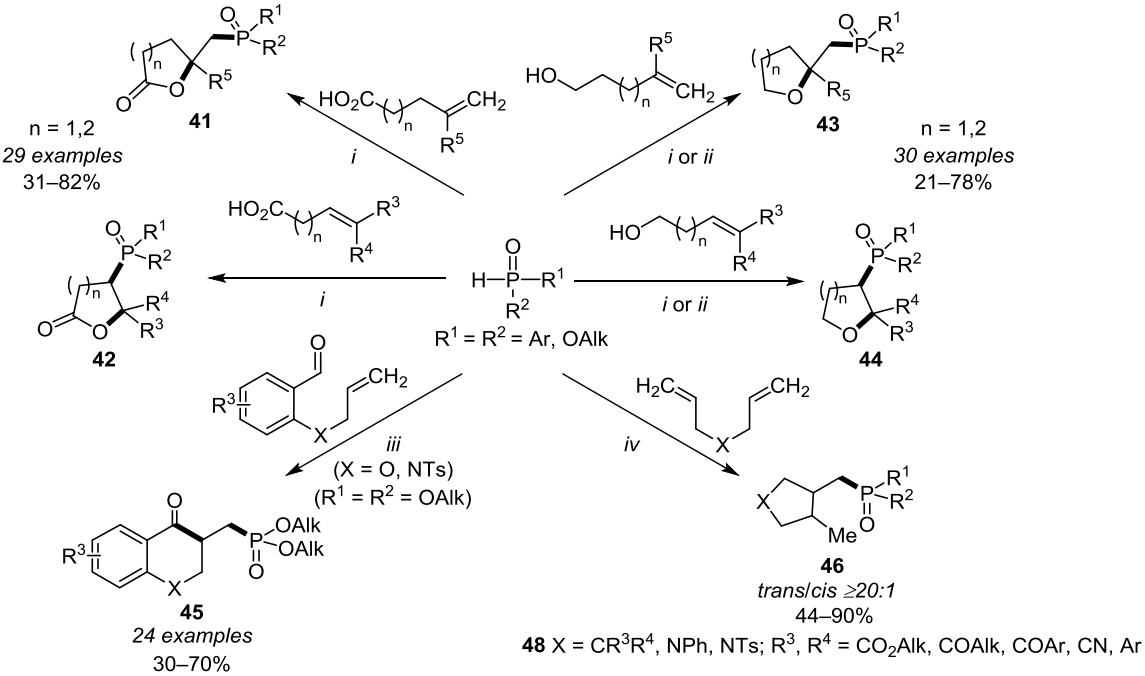
(compounds **41**) and phosphoryl groups (compounds **42**), respectively[63] (Scheme 12). When terminal and internal hydroxyalkenes were used as the substrates, the corresponding β-phosphonotetrahydrofurans or β-phosphonotetrahydropyrans **43**, **44** were obtained in moderate to good yields (Scheme 12).[64] These transformations would provide a new pathway for the formation of lactone rings and cyclic ether rings bearing a phosphono group.

In 2016, the Li group reported the reactions between P(O)H derivatives and 2-(allyloxy)aryl aldehydes for the preparation of phosphorylated chroman-4-ones **45** using silver salt as the catalyst and $K_2S_2O_8$ as the oxidant (Scheme 12).[65] In the proposed reaction mechanism, the catalytic cycle was initiated by generation of acyl and P-centered radicals under the reaction conditions. Then an intramolecular cyclization generates alkyl radical. Finally, the target product **45** was obtained *via* a radical coupling reaction.

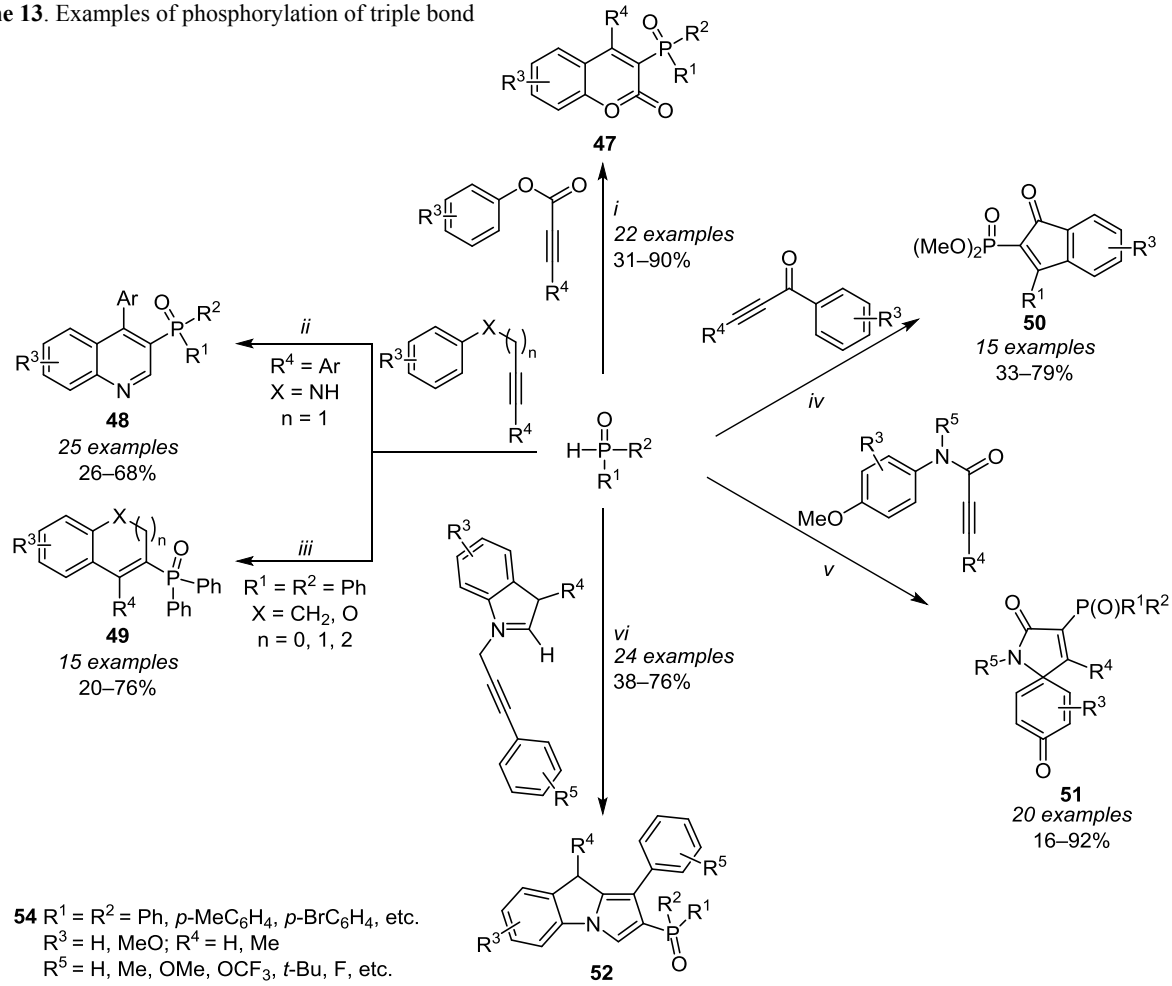
A silver-catalyzed phosphorylation/cyclization radical cascade of 1,6-dienes has been developed.[66] The reaction process involves a one-pot operation described as an auto–tandem catalytic process with a cascading radical cyclization for the construction of C–P and C–C bond with high stereoselectivity (*trans*/*cis* ≥20:1) (Scheme 12). The method also affords an efficient method (up to 90%) for the synthesis of valuable exocyclic phosphine oxides **46** with broad substrate diversity under mild reaction conditions.

However, cascade P radical cyclization of 1,6-dienes has so far been rarely reported, possibly because the radical can be trapped or scavenged easily, which would result in poor reaction selectivity. Thus, stereoselective addition of 1,6-dienes accompanied by radical cyclization still has been considered a challenge. To gain more insight into the silver-catalyzed cascade radical cyclization, radical capture experiments were conducted by employing radical inhibitor

Scheme 12. Phosphorylation/cyclization of alkenoic acids, alkenols, and allyl compounds



Scheme 13. Examples of phosphorylation of triple bond



i: Ag_2CO_3 (10 mol %), 4 Å MS, MeCN, 100°C, $Mg(NO_3)_2·6H_2O$ (0.3 equiv)[67]
ii: TBHP (3.5 equiv), DMF, Ar, 60°C[68]
iii: $R^1 = R^2$ = Ph, AcOH, $Mn(OAc)_3·6H_2O$ (3 equiv)[69]
iv: $R^1 = R^2$ = OMe, AcOH, $Mn(OAc)_3·6H_2O$ (3 equiv)[70]
v: $Mg(NO_3)_2·6H_2O$ (0.5 equiv), $AgNO_3$ (10 mol %), MeCN, 100°C, air[71]
vi: Anhydrous $CuSO_4$ (25 mol %), $K_2S_2O_8$ (2.0 equiv), MeCN (2.0 ml), Ar, 60°C, 12 h[72]

TEMPO and 1,1-diphenylethylene. No desired product was obtained when these radical trapping reagents were added in the reaction medium under the standard conditions. Interestingly, the product was obtained in 28% yield when 1 equiv of 1,1-diphenylethylene was added to the reaction. It was speculated that 1,1-diphenylethylene could produce more stable free radical intermediates with the addition of the P-centered radical. These results would reveal that a free radical might be involved in this cyclization. Moreover, when $[Ph_2P(O)Ag]$ instead of Ag_2CO_3 was tested under the optimized reaction conditions the product was obtained in 76% yield. Thus, the first step is phosphorylation with Ag_2CO_3, and the formation of $[Ph_2P(O)Ag]$ intermediate is the key step in this transformation.[66]

Ag(I)-catalyzed tandem phosphorylation/cyclization process to synthesize various 3-phosphonated coumarins **47** from readily prepared alkynoates and H-phosphonates (Scheme 13) was discovered by Wu and coauthors.[67] The appropriate reaction mechanism involved phosphorylation *via* the addition of P radicals, following by radical cyclization/aromatization. The Zhao group developed a metal-free phosphinoylation/cyclization/aromatization method for the synthesis of a series of substituted 3-phosphinoylquinolines **48** from *N*-propargylanilines and H-phosphine oxides. The transformation proceeds smoothly only in the presence of TBHP without using a base, a metal, or an additive (Scheme 13, *ii*).[68] The new synthesis of 2-phosphinoylated 3,4-dihydronaphthalenes **49** through phosphinoyl radical tandem addition/cyclization of 1,4-diarylbutynes was demonstrated by Zhang and Zou groups.[69] This reaction could be further extended for the synthesis of benzo[7]annulene, indene, and 2*H*-chromene (Scheme 13).[69]

2-Phosphonylindenones **50** were synthesized through the reactions between H-phosphonates and 1,3-diarylpropynones.[70] In this protocol, Mn(III)-induced formation of P radicals was followed by their addition to 1,3-diarylpropynones, whereafter cascade cyclization/oxidation/deprotonation processes took place to form the desired products **50** (Scheme 13). The Liang group demonstrated that the reaction of *N*-(*p*-methoxyaryl)propiolamides with

P radicals under silver-catalyzed conditions leads to efficient construction of phosphorylated azadecenones **51** *via* phosphorylation/5-*exo* cyclization/dearomatization processes.[71]

In 2017, Zhu reported a copper-catalyzed tandem radical cyclization of 1-(3-phenylprop-2-yn-1-yl)-1*H*-indole with diphenylphosphine oxides[72] (Scheme 13). C−P bond formation was achieved coupled with C(sp^2)−H functionalization and provided an access to the pyrrolo[1,2-*a*]indole motif and a series of 2-phosphinoyl-9*H*-pyrrolo[1,2-*a*]-indoles **52**. The results showed that both electron-withdrawing and electron-donating functional groups are well tolerated. A gram-scale reaction was performed, generating the product in 65% yield (R^1 = R^2 = Ph, R^3 = R^4 = R^5 = H). For further investigation of the mechanism, some control experiments were carried out. When 1 equiv of TEMPO was added, the reaction ceased and no product was detected. The TEMPO–P(O)Ph_2 adduct was observed by LC-MS and ^{31}P NMR. Meanwhile, the P-centered radical by addition of 2-methyl-2-nitrosopropane, a radical spin trapping agent, was detected by EPR experiment.[72] These experiments have proved the radical mechanism of the process. Thus, a method to synthesize fused indoles was developed, which may be applied in synthetic organic chemistry.

The increasing key role of heterocyclic organophosphorus compounds with phosphorus–carbon bonds in various spheres of science and practice in recent times attracts new researchers in this field. However, success can only be expected in the search for new synthesis techniques excluding significant by-products and based on atom efficient, environmentally friendly, easy to realize catalytic approaches to C–H functionalization.[8,12,73,74]

To sum it up, we can say that the use of catalysis by metals in order to form heterocyclic compounds with P–C bonds revealed the high potential of this method, which allows obtaining a variety of practically important products. The mechanism of phosphorylation/cyclization reactions is usually radical. In some cases, however, ionic paths cannot be excluded. Thus, many recently proposed new approaches and techniques, described in this review, constitute an important practical path of synthesis of valuable phosphorylated products that are potentially important in the pharmaceutical, agrochemical and related industries. They are often the most atom economical, environmentally friendly and correspond to the high demands of modern chemistry.

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