Recent Progress in the Selective Functionalization of P(O)-OH Bonds

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Abstract

As we all know, organic phosphorus compounds have high application values in chemical industries. Compared with the traditional phosphorylation reagents with P-X (X = Cl, Br, I) and P-H bonds, P(O)-OH bond containing compounds are a stable, environmentally friendly, and inexpensive phosphorylation reagent. However, in recent years, there have been few studies on the selective functionalization of P(O)-OH bonds for the fabrication of P-C and P-Z bonds. In general, the four-coordinated P(O)-OH compound has reached the coordination saturation due to its phosphorus atom center, and it cannot evolve the phosphorus coordination center through intra-molecular tautomerization; but the weak coordination effects between the P=O bond and the transition metals can be utilized to activate the P(O)-OH bonds. This review highlights the most important recent contributions toward the selective functionalization of P(O)-OH bonds via cyclization/cross coupling/esterification reactions using transition metals or small organic molecules as the catalyst.

Introduction

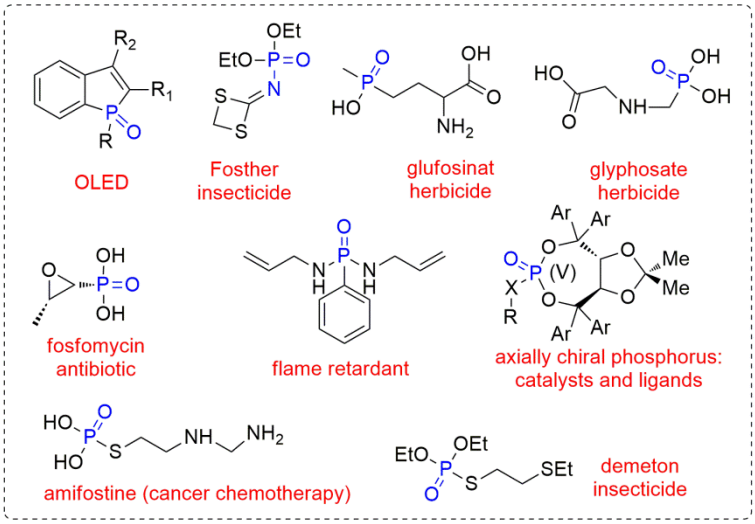


Fig.1 Application of organic phosphorus compounds.

Organic phosphorus compounds are widely used in organic synthesis, medicinal chemistry, agricultural chemistry, materials chemistry, coordination chemistry and other fields due to their unique biological activities.[1-9] For example, π-conjugated phosphate molecules are widely used in the area of organic light-emitting diodes (OLEDs) and photovoltaic cells.[10] Phosphoramidates are used as Fosthirtn insecticides.[11] Fosfomycin is an

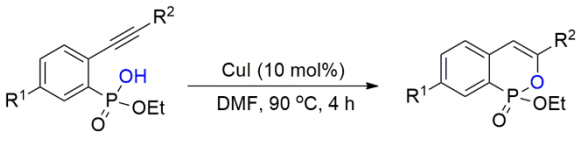
antibiotic used clinically, and glyphosate and glufosinate are widely used as herbicides.[12] Phosphonamide is an important intermediate and precursor for the synthesis of flame retardants.[13] Chiral phosphine molecules can be adopted as catalysts and ligands and play a vital role in asymmetric catalytic reactions.[14] Phosphorothioate can also be used as anticancer drugs and insecticides (**Fig. 1**).[15]

Traditional protocols for the synthsis of phosphates/phosphites/phosphonates/phosphine oxides mostly employed P-H/P-X/$P(OR)_3$ reagents as the raw materials. However, in the related reports, the authors used P(O)-OH bonds as the starting materials for the synthesis of these compounds. It is because the P(O)-OH bonds are stable and less reactive than the P-H/P-X/$P(OR)_3$ reagents. The general activation and functionalization method for P(O)-OH bonds is to convert them into a highly active and toxic P(O)-Cl compounds under the chlorination of thionyl chloride, and then introduced a nucleophilic reagent (alcohol, phenol, etc.) for the generation of the corresponding phosphorylation products. To avoid the adoption of toxic reagents and air/moisture sensitive reagents, it is gradually the case to employ P(O)-OH bonds as the direct phosphorylation reagents for the synthesis of organophosphorus compounds.

In continuation of our recent works on the selective activation and functionalization of P(O)-OH bonds, herein we will summarize the recent developments in the synthesis of phosphates/phosphites/phosphonates/phosphine oxides through the cyclization/cross-coupling/esterification reactions of P(O)-OH bonds with C-H/C-X/C-Z bonds. Transition metal-catalyzed/mediated reactions are discussed first, and then transition-metal-free activation will be covered at the end of this review. It should be pointed out that we have not discussed the chlorination of P(O)-OH bonds, because it is a well-known reaction in organophosphorus chemistry.

Transition metal catalysis

Transition metal-catalyzed intermolecular/intramolecular cyclization reaction of alkynes with nucleophiles (*e.g.*, N-H, O-H, S-H) near the carbon-carbon triple bond has sttracted great interest in organic synthesis, and various heterocycles can be efficiently constructed in an economical manner. In 2003, Ding et al. firstly investigated the Cu-catalyzed intramolecular cyclization reaction of P-OH bonds with cabon-carbon triple bonds for the generation of phosphaisocoumarins with pharmaceutical activity (**Scheme 1**).[16] This method can be adopted to a variety of 2-ethynylaryl hydrogen phosphonates, and also has the good functional group tolerance, resulting in the corresponding cyclization products with satisfactory yields. It is worth noting that the solvent with Lewis base site (i.e. DMF) and the weak coordination effect of P=O bond with copper ion was the key factor in the synergistic activation of the P(O)-OH bond.



1

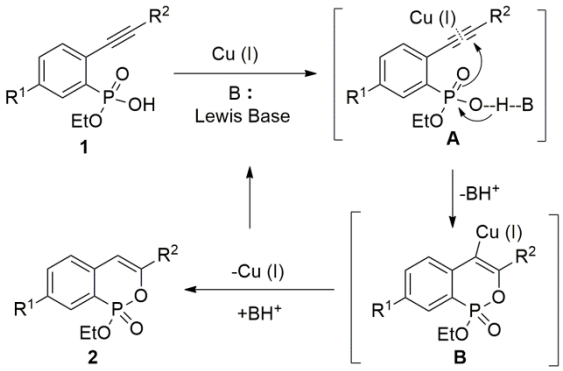
2
12 examples
62%- 92% yields

R^1 = H, R^2 = C_6H_5, 80%
R^1 = H, R^2 = *n*-Bu, 79%
R^1 = Cl, R^2 = *n*-Bu, 75%
R^1 = Cl, R^2 = C_6H_5, 83%
R^1 = Cl, R^2 = *p*-$CH_3CH_2C_6H_4$, 92%
R^1 = Cl, R^2 = *p*-$NO_2C_6H_4$, 63%
R^1 = Cl, R^2 = CH_2OH, 62%
R^1 = Cl, R^2 = CH_2OCH_3, 74%
R^1 = Cl, R^2 = H, 55%
R^1 = Cl, R^2 = cyclopropyl, 71%
R^1 = Cl, R^2 = C_6H_5, 88%
R^1 = Cl, R^2 = *p*-$CH_3CH_2C_6H_4$, 60%

Scheme 1 Copper-catalyzed intramolecular cyclization of 2-ethynylaryl hydrogen phosphonates.

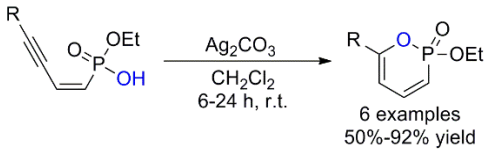
Ding and coworkers have discussed a reasonable reaction mechanism in **Scheme 2**. Firstly, the corresponding

π complex **A** could be generated directly through the coordination of the carbon-carbon triple bond of **1** with CuI and the hydrogen bond between the P-OH bond and C=O bonds with the Lewis base. Then, the transition state **B** would be generated *in-situ* via the intramolecular regio-selective nucleophilic attack of the P-OH bond to the alkynyl substituent. With the reduction elimination reaction and the protonation reaction, the cyclization target product **2** was formed, and the released CuI was recycled as the active species to the reaction.



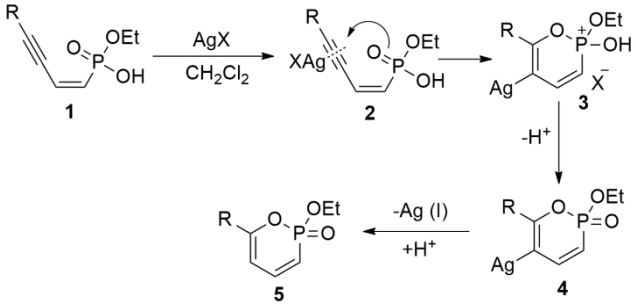
Scheme 2 Possible mechanism: Cu-catalyzed intermolecular cyclization of 2-alkynyl phosphinic acids.

In 2005, Ding et al. further investigated the silver-catalyzed intramolecular annulation of (Z)-2-alken-4-ynylphosphonic acids in CH_2Cl_2.[17] It should be pointed out that the intramolecular cyclization reaction of this type of P(O)-OH compounds was firstly reported by this group, and the corresponding oxaphosphorin 2-oxides were obtained with good yields and excellent regioselectivity at room temperature (**Scheme 3**). In addition, the synthesized cyclization products are important phosphorus heterocyclic compounds with potential antimicrobial applications. Compared to the previous work, dichloromethane was used as the solvent for the reaction instead of the adoption of a solvent with Lewis basicity.



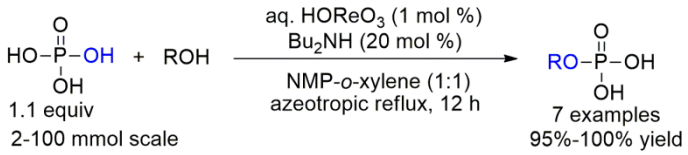
Scheme 3 Synthesis of phosphorus heterocycles via silver catalysis.

The possible mechanism for the Ag-mediated intramolecular annulation of (Z)-2-alken-4-ynylphosphonic acids is illustrated in **Scheme 4**. The carbon-carbon triple bond was activated through the reaction of the electron-rich alkynyl moiety in **1** with silver ion, forming the reaction intermediate **2**. Simutaneously, the intermediate **3** was generated via the intramolecular annulation reaction of the P=O bond with the alkynyl unit in the transitional state **2**. In the presence of H^+, the transition state **4** and the target product **5** could be formed with the release of HX and Ag(I), which acted as the catalytic species in the reaction.



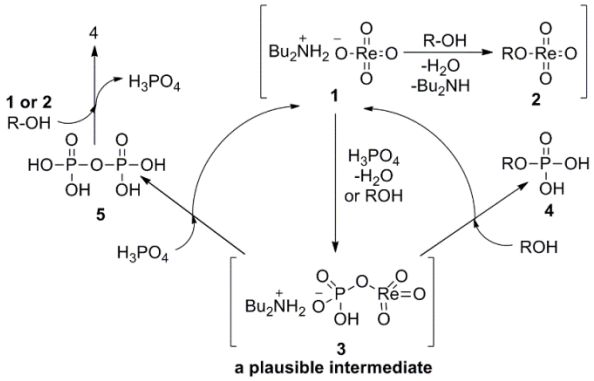
Scheme 4 Possible mechanism: Ag-mediated intramolecular annulation of (Z)-2-alken-4-ynylphosphonic acids.

Phosphate monoesters are important intermediates in functional materials and medicinal chemistry and many other fields. From the view of economy and green chemistry, the direct catalytic esterification of equimolar amounts of P-OH bond containing compounds and alcohol is very important for the production of the corresponding monoesters, because water is the only side product for the reaction. In general, the direct condensation of P(O)-OH bond with alcohol is more difficult than C(O)-OH bond due to its stronger acidity. In 2007, Ishihara et al. disclosed the Re-catalyzed direct dehydration condensation reaction of H_3PO_4 with alcohols for the prepartion of its corresponding monoesters.[18] This work used oxorhenium(VII) complexes as the catalyst, which is considered to be of low toxicity (**Scheme 5**). In addition, the present condensation reaction could also be performed in a large scale. Thus, it is an effective method for the generation of phosphate monoesters in laboratory and industry.



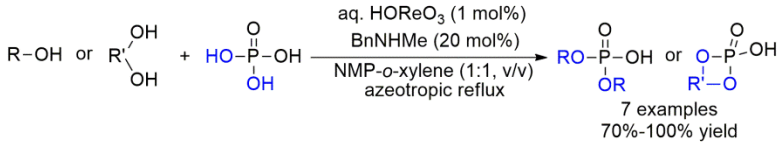
Scheme 5 Re-catalyzed dehydration condensation of H_3PO_4 with alcohols.

Scheme 6 describes the plausible reaction path for the Re-catalyzed dehydration condensation of H_3PO_4 with alcohols. Initially, perrhenic acid amonium salt **1** could be transformed to alkyl perrhenate **2** under a refluxing condition. Then, phosphoric acids reacted with compound **1** or **2** to form the reaction intermediate **3**. Due to the fact that the acidity of $HReO_4$ (pK_a = -1.25) is higher than that of H_3PO_4 (pK_{a1} = 2.1), the nucleophilic substitution reaction of alcohol on the phosphorus atom takes place preferentially to generate the phosphate monoester **4**. Due to the stronger acidity of phosphate monoesters and phosphodiesters than phosphoric acid, the transformation process of **1** or **2** with H_3PO_4 is prior to the phosphoric acid monoester **4**. Therefore, the phosphoric acid monoester was selectively generated by the condensation of this reaction. On the other hand, the active substance **3** can react with the P-OH bond directly in H_3PO_4 to generate pyrophosphoric acid **5,** which could afford the phosphate monoesters **4** easily through the reaction of alcohols.



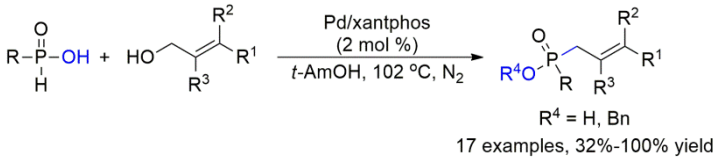
Scheme 6 Plausible mechanism: Re-catalyzed dehydration condensation of H_3PO_4 with alcohols.

In 2008, they further studied the selective synthesis of phosphodiester through the Re-catalyzed dehydration condensation of H_3PO_4 with two equivalents of alcohols.[19] This transformation is particularly effective for the generation of cyclic phosphodiester (**Scheme 7**). It is worth noting that the combination of perrhenic acid with BnNHMe could activate the P(O)-OH bond effectively. The molecular interaction effect between perrhenic acid and *N*-methyl-1-phenylmethanamine is the key procedure to stabilize the intermediate and promote the dehydration condensation.



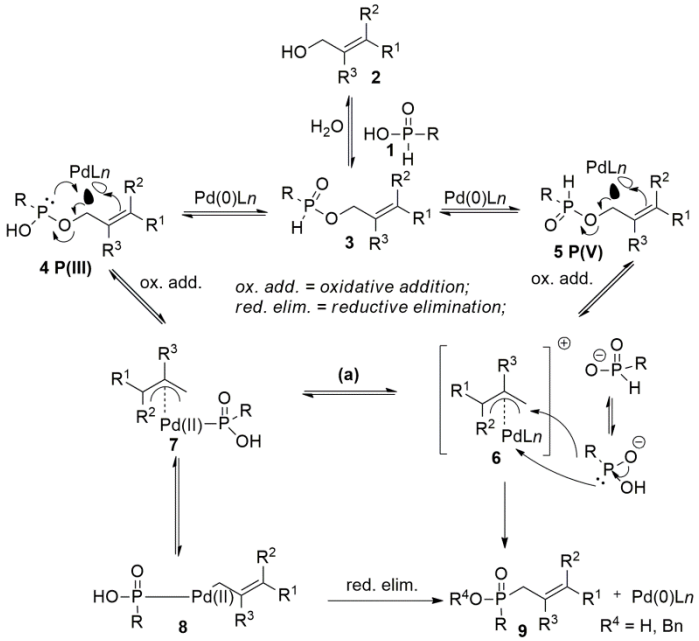
Scheme 7 Rhenium-catalyzed selective synthesis of phosphodiester from phosphoric acid and alcohols.

In 2008, Montchamp et al. described a facile and regioselective allylation of *H*-phosphinic acids with allylic alcohols by palladium catalysis in a protonic solvent, where powdered 3A molecular sieves are crucial to gain the satisfactory yields and reduce the generation of phenylphosphonic acid (**Scheme 8**).[20] Due to the corresponding products functionalized with an allylic moiety, which are considered as the potentially important units for the production of functionalized organophosphorus compounds. In most cases, this method has good functional group tolerance towards the substrates and the desired allylation products were synthesized with satisfactory yields.



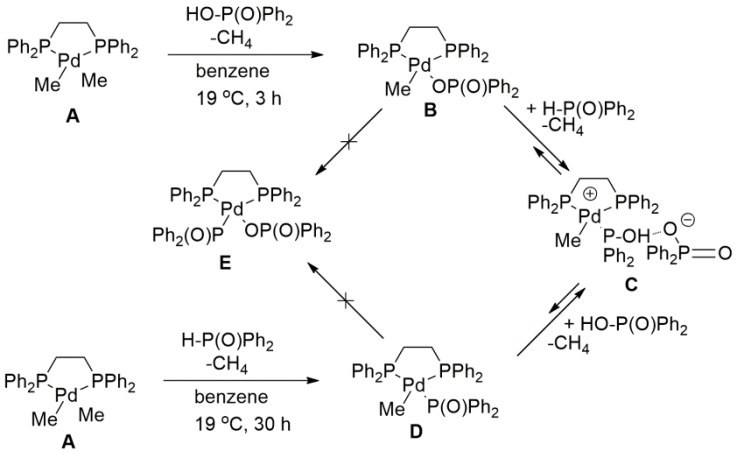
Scheme 8 Regioselective allylation of H-phosphinic acids with allylic alcohols by palladium catalysis.

Scheme 9 describes the possible mechanism for the regioselective allylation of *H*-phosphinic acids with allylic alcohols by palladium catalysis. Firstly, olefin compound **2** reacted with *H*-hypophosphorous compound **1** to form hypophosphite **3**. Compound **3** was attacked by Pd to form transition state **5** (P(V)), or compound **3** isomerizes to a tri-coordinated P compound. After being attacked by Pd, transition state **4** (P(III)) was formed. The oxidative addition of Pd occurred in **4** or **5** to form the π-allyl palladium intermediate **7** or **6**. Finally, the final product **9** was generated through the reductive elimination. The released Pd catalyst was regenarated and reused to the next catalytic cycle .



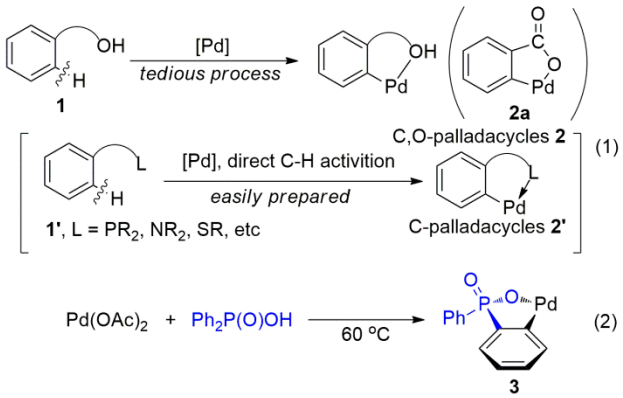
Scheme 9 Plausible mechanism: regioselective allylation of H-phosphinic acids with allylic alcohols by palladium catalysis.

In 2011, Tanaka et al. found that the P(O)-H bond can undergo the addition reaction efficiently to a alkynyl unit in the presence of a palladium chelated phosphine-bronsted acid (P(O)-OH) complex.[21] It is worth noting that negative results were obtained when the reaction adopted monodentate phosphine ligands or was carried out without the introduction of a bronsted acid. **Scheme 10** describes the ligand exchange reaction of diphenylphosphinic acid and diphenylphosphorus oxide with $Me_2Pd(dppe)$. **B** could be generated in a quantitative yield through the reaction of $Me_2Pd(dppe)$ (**A**) with diphenylphosphinic acid in benzene at 19 °C for 3 hours. Due to the excellent coordination ability of diphenylphosphine oxide than diphenylphosphinic acid, **C** was synthesized as the major product. Similarly, diphenylphosphine oxide could react with **A** easily to afford **D**. With the addition of diphenylphosphinic acid, and **C** was formed rapidly via the intermolecular hydrogen bond interaction instead of the generation of **E**.



Scheme 10 Ligand exchange reaction of $Me_2Pd(dppe)$ with $Ph_2P(O)$-H and $Ph_2P(O)$-OH.

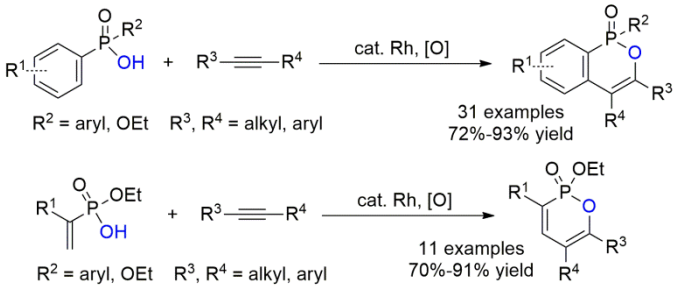
In 2011, Han et al. prepared a new oxapalladacycle **3** via the direct palladation of $Ph_2P(O)$-OH with $Pd(OAc)_2$ (**Scheme 11**).[22] Palladacycle is recognized as a novel catalyst in transition-metal catalysis and an active intermediate in C-H bond activation as well as cascade transformation. In addition, oxapalladacycles (**2**) with C-Pd and O-Pd bonds are the key intermediates related to the C-O coupling reaction and selective functionalization of aryl carboxylic acids. In this work, the oxapalladacycle **3** can effectively promote the Markovnikov-type addition reaction of Z-H bonds (S-H, P-H and alkynyl-H) with alkynes.



Scheme 11 Synthesis of oxapalladacycle from diphenylphosphinic acid.

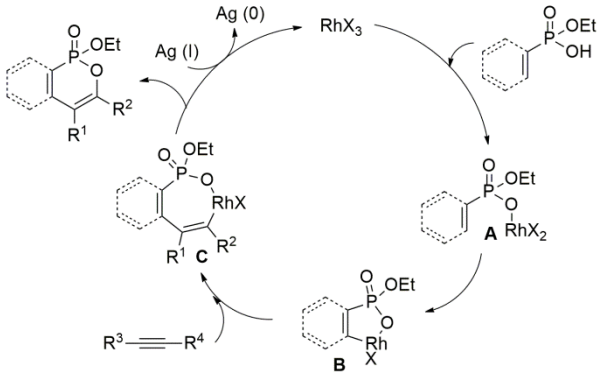
In 2013, Lee et al. investigated the intermolecular annulation of alkynes with diarylphosphinic acids and arylphosphonic acid monoester via rhodium catalysis, where a wide range of arylphosphonic monoesters and diarylphosphinic acids were used, affording the expected annulation products in satisfactory yields.[23] Moreover,

the adoption of alkenylphosphonic monoesters successfully yielded the phosphorus 2-pyrones via oxidative annulations reaction with a carbon-carbon triple bond. The control experiments showed that the C-H bond metalation reaction is irreversible, which is considered as a key rate-determining step for the reaction (**Scheme 12**).



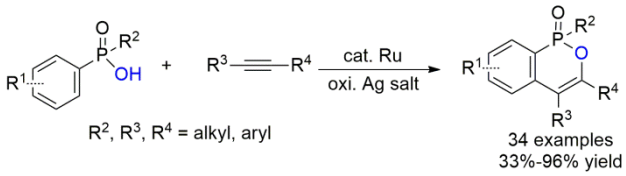
Scheme 12 Rh-catalyzed intermolecular annulation of P-OH bonds with alkynes.

Scheme 13 reveals a possible mechanism for the Rh-catalyzed intermolecular annulation of diarylphosphinic acids and arylphosphonic acid monoester with alkynes. First, the rhodium(III) phosphonate **A** was formed through the substitution reaction of phosphonic monoester with RhX_3. The oxidative addition process occurred in A via the *o*-metalation for the generation of rhodacycle transition state **B**. In the presence of alkyne, the insertion reaction of alkyne and the corresponding reductive elimination processes could yield the cyclization products. Rhodium(III) catalyst was regenerated by the oxidation of silver salt, and reused for the next catalytic cycle.



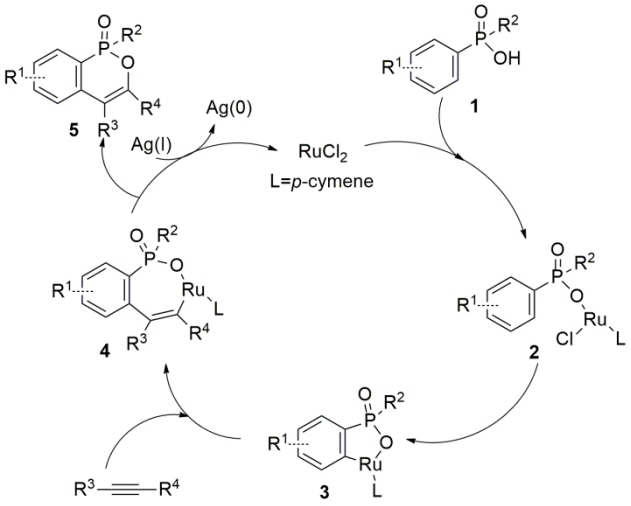
Scheme 13 Plausible mechanism: Rh-catalyzed intermolecular annulation of P-OH bonds with alkynes.

Encouraged by their previous results, Lee et al. further disclosed an effective and cost-effective ruthenium-catalyzed intermolecular annulation of P-OH bonds with alkynyl units under aerobic conditions, where hydrogen phosphonic esters and arylphosphinic acids were employed as the starting materials (**Scheme 14**).[24] This method used $[RuCl_2(p\text{-cymene})]_2$ and potassium hexafluorophosphate as the catalysts and silver salt as an oxidant. A series of P-OH bonds, diarylacetylenes, dialkylacetylenes, and alkylarylacetylenes were scoped for the reaction, and the expected phosphaisocoumarins were synthesized under the optimized conditions with satisfactory yields. Interestingly, the compound bearing a carboxylic and P(O)-OH moieties could be efficiently cyclized with hex-3-yne to give the product having both isocoumarin and phosphaisocoumarin moieties. The correspondng competition experiments indicate that the substituent insensibility in alkynes has no obvious influence for the oxidative cyclization processes.



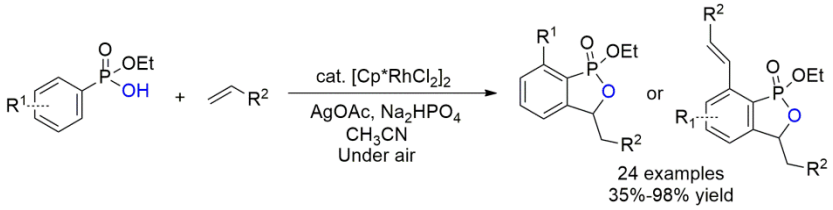
Scheme 14 Ruthenium-catalyzed intermolecular annulation of P-OH bonds with alkynes.

As shown in **Scheme 15**, Lee et al. discussed the possible catalytic cycle for the reaction. Firstly, P(O)-OH compound **1** was coordinated with $RuLCl_2$ after deprotonation to yield the ruthenium phosphonate **2**. Then, the ortho metalation occurred in **2** with the generation of a five-membered ring transition state **3**. Due to the stronger coordination ability of ruthenium with alkynyl moiety, the insertion product **4** was formed rapidly via the reaction of intermediate **3** with alkyne. Finally, the cyclization target product **5** was synthesized via the reductive elimination. The released ruthenium catalyst was regenerated by silver salt and reused in the next catalytic cycle.



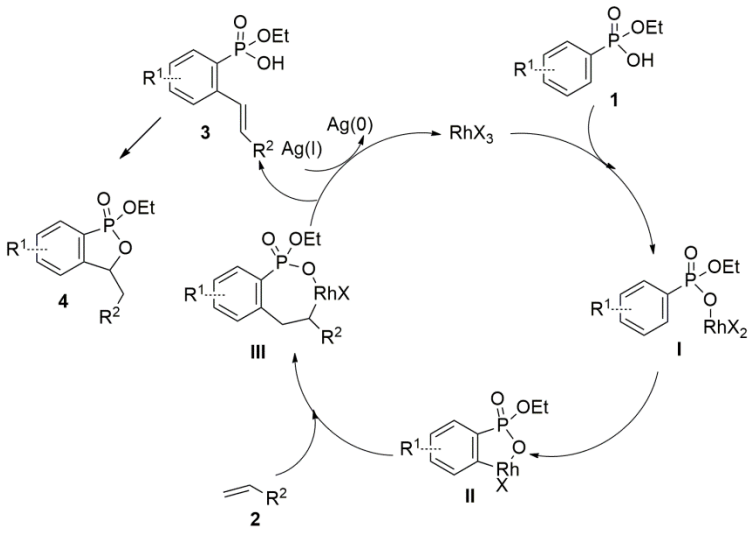
Scheme 15 Possible mechanism: ruthenium-catalyzed intermolecular annulation of P-OH bonds with alkynes.

Under aerobic conditions, the Rh-catalyzed alkenylation and an intramolecular oxy-Michael reaction for the preparation of benzoxaphosphole 1-oxides were investigated by Lee's group. Arylphosphonic acid monoesters and alkenes were adopted as the substrates, AgOAc and Na_2HPO_4 were used as the additives to increase the selectivity and yield for the reaction, and the target cyclized products were obtained with moderate to excellent yields (**Scheme 16**).[25] When arylphosphonic acid monoesters have a substituent at the *para*-position of the aryl ring, the 7-alkenylated benzoxaphosphole 1-oxides could be synthesized selectively through the tandem dialkenylation and an oxy-Michael reaction.



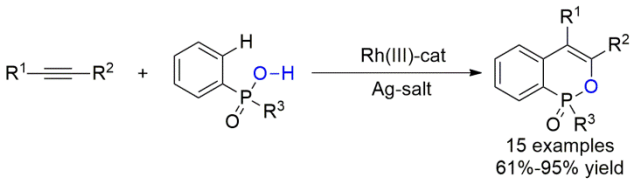
Scheme 16 Rh-catalyzed alkenylation and intramolecular oxy-Michael reaction of P-OH bonds with alkenes.

As illustrated in **Scheme 17**, they have discussed the possible catalytic cycle for the reaction. Firstly, the reaction is initiated by the coordination reaction of arylphosphonic acid monoester **1** with Cp*RhX_2 to form the rhodium phosphonate **I**, and then the *ortho*-metalation took place in **I** with the production of a rhodacycle intermediate **II**. Followed by the olefin insertion, β-hydride elimination and reductive elimilation, the *o*-alkenylated arylphosphonic acid monoethyl ester **3** was synthesized *in-situ* from **III**, which could undergo the oxy-Michael reaction to obtain the final target product **4**.



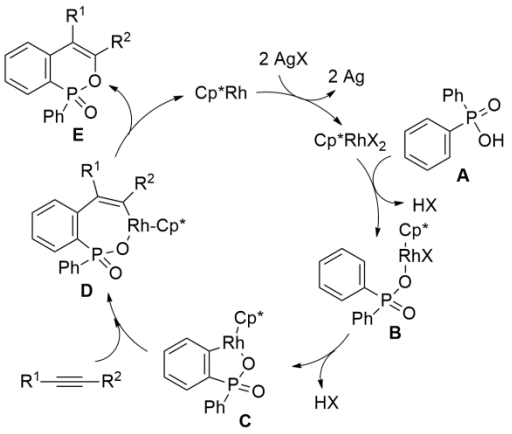
Scheme 17 Possible mechanism: Rh-catalyzed alkenylation and intramolecular oxy-Michael reaction of P-OH bonds with alkenes.

In 2013, Miura et al. reported the Rh-catalyzed oxidative cyclization reaction through the aryl C-H bond activation by the direction of a phosphinoxy groups, where the phosphaisocoumarins could be synthesized directly via the reaction of P-OH bond in arylphosphonic acids with alkynes. In this reaction, $[Cp^*Rh(MeCN)_3][SbF_6]_2$ was used as the catalyst and silver acetate was adopted as the oxidant. It is worth noting that 4 mol% catalyst can promote the reaction efficiently and produce the target cyclization product in 95% yield (**Scheme 18**).[26] Moreover, the reaction of P-H bond with alkyl acrylates could also be performed efficiently for the production of the *ortho*-alkenylated products.



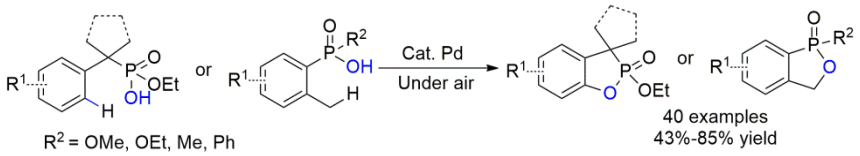
Scheme 18 Rh-catalyzed cyclization of P-OH bonds with alkynes.

The proposed mechanism in this work is similar to the reaction mechanism in Lee's work.[23-24] As shown in **Scheme 19**, P-OH bond in **A** first coordinated with rhodium(III) catalyst to give the rhodium(III) phosphonate **B**. Then, the *o*-metalation of **B** yielded a five-membered ring transition state **C**. In the presence of an alkyne, the insertion reaction occurred with the generation of a seven-membered ring intermediate **D**. Finally, the catalytic cycle was ended by the reductive elimination of Rh(I) species. The Rh(III) species was regenerated from Rh(I) via the oxidation of Ag(I) for the next catalytic cycle.



Scheme 19 Possible mechanism for the Rh-catalyzed cyclization of P-OH bonds with alkynes.

As presented in **Scheme 20**, Lee et al. disclosed an efficient protocol for the production of benzoxaphosphole oxides from phosphinic/phosphonic acid derivatives through a C-H activation/C-O bond formation process under oxidative aerobic conditions by palladium catalysis.[27] (Diacetoxyiodo)benzene was employed as an efficient oxidant for the regeneration of Pd(II) to Pd(IV) in the reaction. The functional group tolerance for the phosphonic/phosphinic acid derivatives in this transformation is very good, and the desired cyclization products of benzoxaphosphole 2-oxides were synthesized in satisfactory yields. The possible mechanism for this transformation has not been explained by the authors, but the kinetic isotope effect (KIE) experimental results proved that the *sp*^{2} C-H bond activation at the *ortho*-position of arylphosphonate is the rate-limiting step for the reaction.

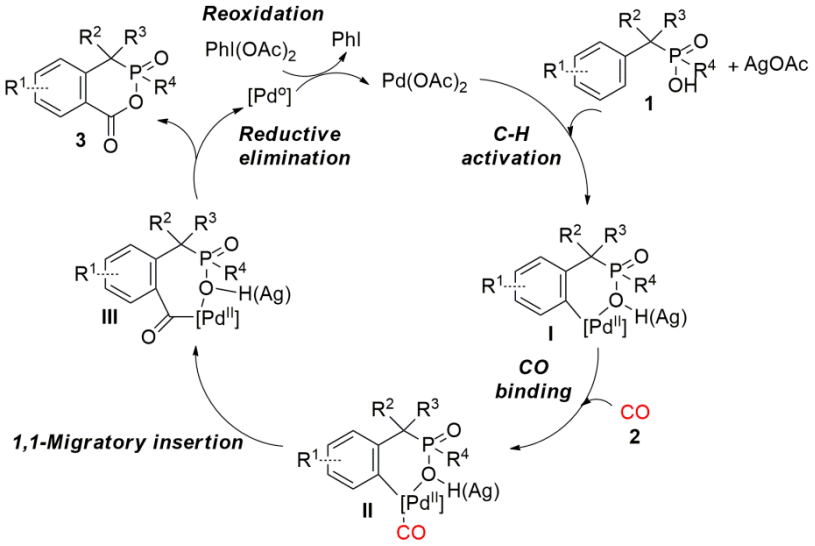


Scheme 20 Palladium-catalyzed oxidative aerobic C-H activation/C-O bond formation of phosphonic/phosphinic acid derivatives.

In 2014, Lee et al. investigated the selective carbonylation/annulation of arylphosphonic and arylphosphinic acids with carbon monoxide for the generation of oxaphosphorinanone oxides by palladium catalysis. (**Scheme 21**).[28] The phosphaannulation products are novel phosphorus heterocyclic scaffolds. (Diacetoxyiodo)benzene served as the oxidant and silver acetate was adopted as the suitable base for this reaction. It should be noted that the existence of a functional group located in the α-positions of ethyl group for the substrates could influence the carbonylation process obviously. However, the introduction of two functional groups at the α-position of ethyl hydrogen benzylphosphonates could promote the carbonylation process efficiently.

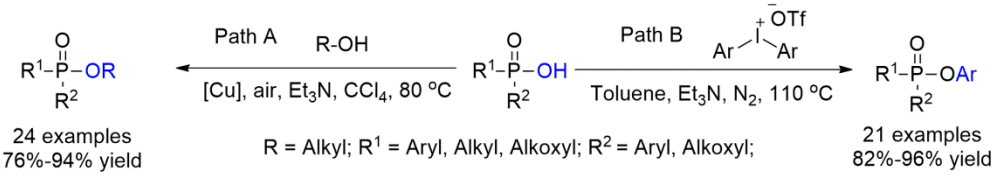
Scheme 21 Palladium-catalyzed selective carbonylation/annulation of arylphosphonic and arylphosphinic acids with carbon monoxide.

As described in **Scheme 22**, the reaction initiated by the coordination of the hydroxyl group in P(O)-OH of compound **1** with the palladium salt, providing the Pd(II) phosphonate and phosphinate **I**. The palladacycle intermediate I was produced in-situ via the intramolecular ortho-metalation. Followed by the CO bonding of carbon monoxide and 1,1-migratory insertion, the corresponding carbonylated products were generated via the reductive elimilation. The Pd(0) species was regenerated by $PhI(OAc)_2$ and reused in the reaction.



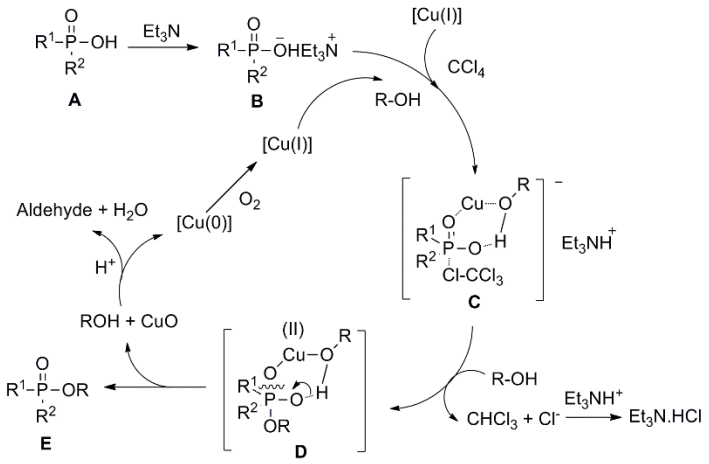
Scheme 22 Plausible mechanism for the carbonylation/annulation process.

In 2015, Yin et al. established an efficient esterification protocol for P-OH bonds with alcohols under aerobic oxidative reaction conditions by copper catalysis.[29] It is worth noting that the adoption of carbon tetrachloride was essential for the present esterification reaction, and the coordination effect of P=O bond with copper ions and the deprotonation of the organic base triethylamine can efficiently activate the P(O)-OH bond and promote aerobic-oxidative esterification of alcohols. In addition, with the assistance of an organic base, the selective arylation of the P-OH bonds with hypervalent diaryliodonium trifluoromethanesulfonate can be effectively realized under mild conditions (**Scheme 22**). Various alkyl functionalized organophosphorus compounds from basic raw materials were produced in satisfactory yields through these divergent methods.



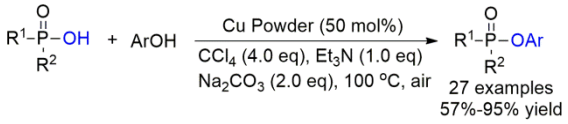
Scheme 23 Selective arylation and esterification of P-OH bonds.

As shown in **Scheme 24**, Yin et al. have proposed a reasonable catalytic cycle for the esterification of P-OH bonds with alcohols by copper catalysis. Firstly, P(O)-OH bond (**A**) combined with triethyl amine to form the corresponding ammonium salt **B**. Through the reaction of **B** with CCl_4, the transition state **C** was formed via the coordination reaction of **B** with copper ion and alcohol. In addition, another one molecule of alcohol attacked **C**, forming a six-membered ring intermediate **D**, followed by the release of $CHCl_3$ and Cl^-. Finally, the esterified product **E** was synthesized via the elimination of copper oxide and alcohol. The copper oxide was readily reduced by alcohol, and then oxidized by oxygen to afford the Cu(I) species with a high catalytic activity.

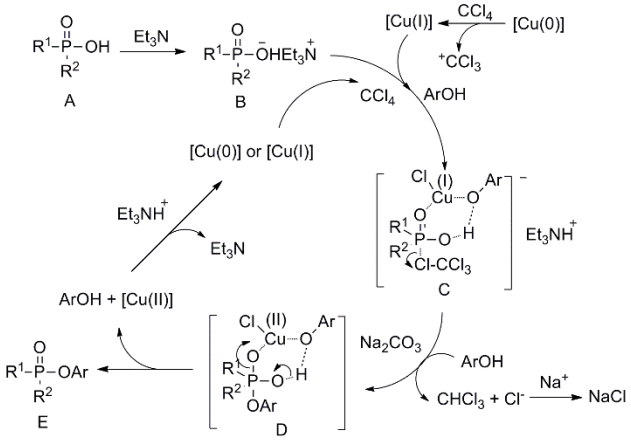


Scheme 24 Possible mechanism for the selective arylation and esterification of P-OH bonds.

As an ongoing investigation on the selective functionalization of P-OH bonds, Yin et al. established a facile protocal for the selective esterification of P-OH bonds with phenols through copper catalysis.[30] It is a simple way to synthesize *O*-arylated phosphoric/phosphinic acid derivatives from basic phenols (**Scheme 25**). The introduction of carbon tetrachloride and triethyl amine was essential for the catalytic cycle to get the desired products, but the amount of Cu powder was higher than 50 mol%. It is worth noting that different kinds of phenols or phosphoric and phosphinic acids are well tolerated in this protocol, yielding the corresponding products in moderate to good yields. However, when 2-hydroxy-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide was adopted as the substrate, the esterification product was not generated during the reaction. This problem may be attributed to the unstable property for the five membered cyclic phosphoric acid, which could undergo the decomposition reaction by CCl_4 under the present reaction conditions.



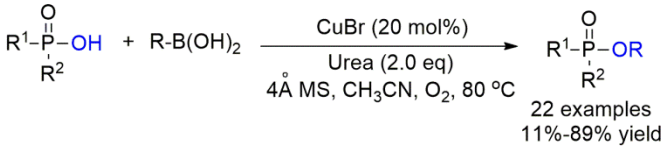
Scheme 25 Selective phosphorylation of phenols with P(O)-OH compounds by copper catalysis.



Scheme 26 Possible mechanism for the selective phosphorylation of phenols with P(O)-OH compounds by copper catalysis.

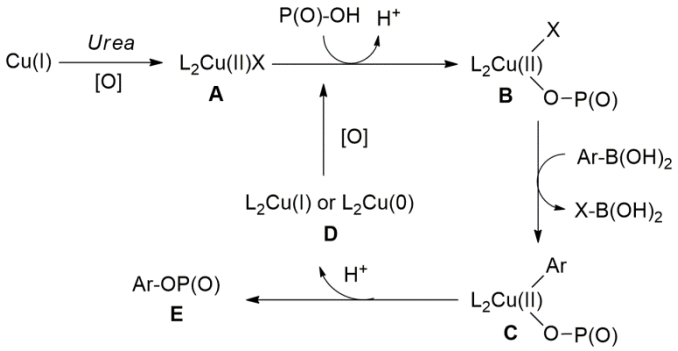
The possible mechanism for the selective phosphorylation of phenols with P-OH bonds by copper catalysis was described in **Scheme 26**. At the initial stage of the reaction, P-OH bond in **A** first combined with triethyl amine to produce the intermediate **B**. In addition, copper powder could be oxidized easily by carbon tetrachloride to afford the corresponding copper salt(I). Then **B** coordinated with copper ion(I) and phenol simultaneously, thus yielding the key intermediate **C**. Moreover, the Cu(II) coordinated intermediate **D** was formed through the attack of phenol to **C**, followed by the release of chloroform and Cl^-. Finally, the reaction was completed via the tautomerization of P-O to P=O bond, and the regenerated Cu or Cu(I) species was reused for the next reaction.

In 2017, we have reported the oxidative cross-coupling of P-OH bonds with arylboronic acid through copper catalysis under Chan-Lam reaction conditions (**Scheme 27**).[31] It was the first time for realizing the generation of O-aryl phosphinic/phosphoric acid derivatives through the direct cross-coupling of P-OH bonds with arylboronic acids. Different from the traditional cross-coupling reactions, the introduction of ligands showed negative results to the catalytic system. This defect may be attributed to the fact that these ligands have the stronger coordination abilities than P(O)-OH bonds with copper salts, which could interrupt the process of the catalytic cycle. Moreover, the use of 4 Å molecular sieve (MS) and urea was crucial for the reaction to increase the yield of the reaction.



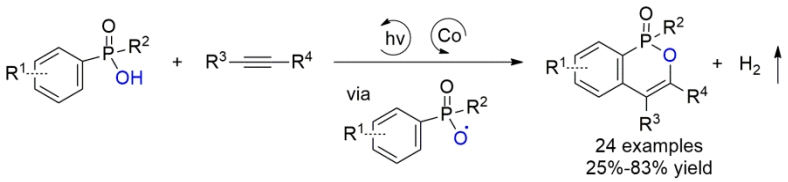
Scheme 27 Cross-coupling of P-OH bonds with arylboronic acids by copper catalysis.

Scheme 28 outlines a possible mechanism for this reaction. At the initial stage of the reaction, copper ion(I) was oxidized by O_2 to Cu(II), and then underwent coordination reaction with urea to give the copper salt **A**. In addition, the ligand exchange reaction occurred between A and P-OH bond to form the intermediate **B**. Simutaneously, through the reaction of **B** with arylboronic acids, the transition state **C** was synthsized with the elimilation of $B(OH)_2^-$ and X. The reaction was ended through the reductive elimination reaction, the corresponding coupling product **E** was formed, and the regenerated Cu(I) or Cu(0) was reused as the catalytically active substances to the reaction.



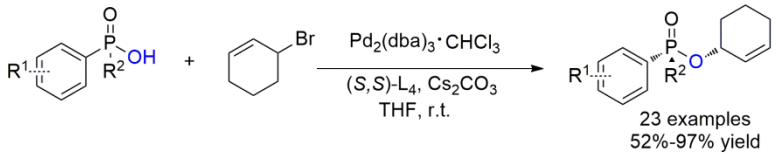
Scheme 28 Possible mechanism for the cross-coupling of P-OH bonds with arylboronic acids by copper catalysis.

In 2019, Shi et al. developed the direct phosphinyloxy radical addition/cyclization cascade reaction of arylphosphinic/arylphosphonic acid derivatives with carbon-carbon triple bonds for the preparation of phosphaisocoumarins through the assistance of visible-light photoredox catalysis.[32] In this catalytic system, acridinium photosensitizer and cobaloxime proton-reducing catalyst were employed as a bifunctional catalytic system for the radical addition and cyclization cascade reaction (**Scheme 29**). As compared to the previous works, this protocol avoids the introduction of oxidant, and also has a wide substrate range under mild conditions.



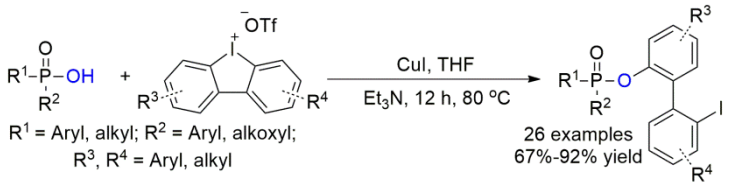
Scheme 29 Visible-light-induced annulation of arylphosphonic/arylphosphinic acid derivatives with alkynes.

In 2019, Trost et al. discovered that in the presence of (+)-(11S,12S)bis[2′-(diphenylphosphino)benzamido]-9,10-dihydro-9,10-ethanoanthracene, the desymmetrization of arylphosphinic acids through the selective allylic alkylation of P-OH bonds with allylic halides by palladium catalysis under mild reaction conditions, and it was a rapid access to the functionalized P‑chiral optically active phosphinates with high enantio- and diastereoselectivity (**Scheme 30**).[33] These optically active phosphinates can easily be transformed to the corresponding phosphine oxides through the nucleophilic substitution reaction. It should be noted that the high steric hindrance at the phosphorus atom could increase the diastereoselectivity for the reaction.



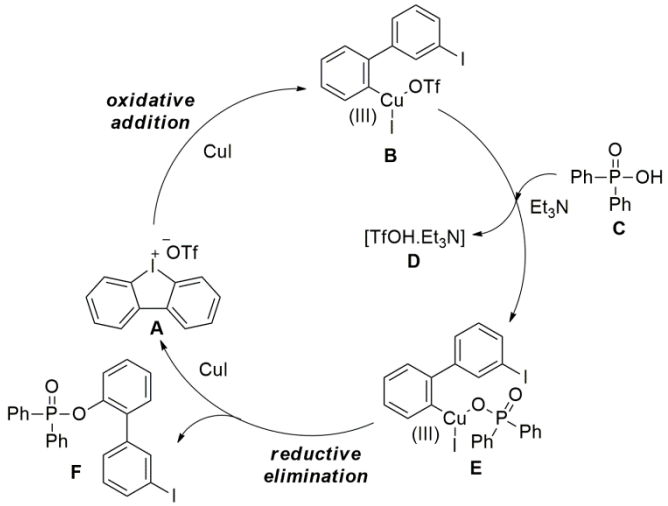
Scheme 30 Synthesis of optically active phosphinates through the palladium-catalyzed desymmetrization coupling of P-OH bonds with allylic halides.

Although we have realized the selective arylation of P-OH bonds with linear hypervalent diaryliodonium salts, a stoichiometric amount of iodobenzene was released during the reaction. Very recently, we disclosed the Cu-catalyzed selective diarylation of P-OH bonds with cyclic hypervalent diaryliodonium salts (**Scheme 31**).[34] The corresponding phosphinic/phosphoric acids and symmetric cyclic hypervalent diaryliodonium salts are well tolerated in this transformation. Valuable 2'-iodo-substituted biaryl phosphinates were generated with moderate to good yields, which could be further converted into various structural units for the production of biologically active organophosphorus compounds, drugs and functional materials. On the contrary, the electron-withdrawing aryl substituents are transferred efficiently than the electron-donating aryl substituents in the selective diarylation of P-OH bonds with unsymmetric cyclic hypervalent diaryliodonium salts.



Scheme 31 Selective diarylation of P-OH bonds by copper catalysis.

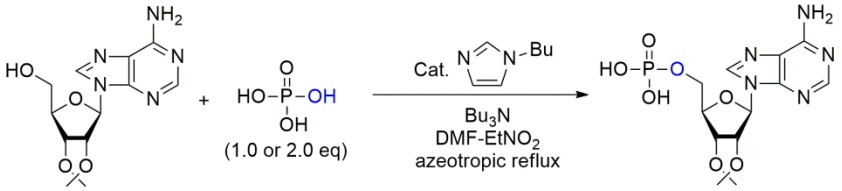
As shown in **Scheme 32**, we have proposed a possible reaction mechanism for the reaction. Firstly, oxidative addition occurred between cyclic hypervalent diaryliodonium salt (**A**) and CuI to yield the Cu(III) intermediate **B**. Through the aid of a base, phosphinic/phosphoeic acid **C** could easily undergo the ion exchange reaction with TfOH to yield the transition state **E**. Finally, the catalytic cycle was accomplished by the reductive elimination accompanied with the recovery of CuI as the catalyst during the reaction.



Scheme 32 Possible mechanism for the selective diarylation of P-OH bonds by copper catalysis.

Transition-metal-free activation

In 2005, Ishihara et al. studied the selective dehydration condensation of H_3PO_4 by one equimolar amount of alcohol, where *N*-alkylimidazole and 4-(*N*-hexyl-*N*-methyl)pyridine was used as the combined catalyst for the reaction.[35] Owing to the low solubility of H_3PO_4 in organic solvent, lipophilic tertiary amines were introduced to the reaction to resolve this problem. On the other hand, the amino substituents were protonated by H_3PO_4 during the reaction to give the ammonium salts, which could prevent the dehydration condensation of amino groups with H_3PO_4 under the optimized reaction conditions (**Scheme 33**).

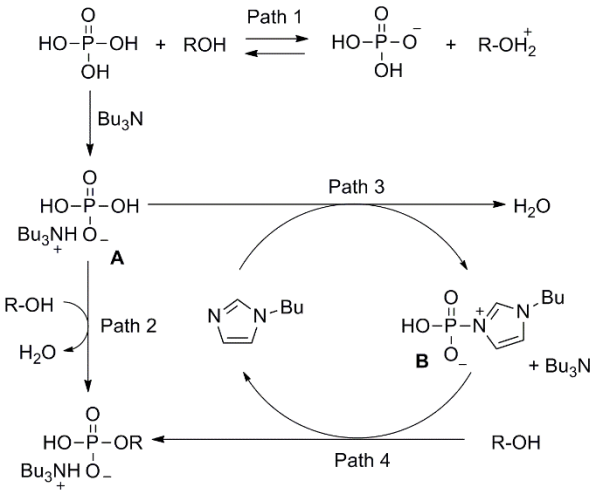


Scheme 33 Base-catalyzed selective dehydration condensation of H_3PO_4 with alcohol.

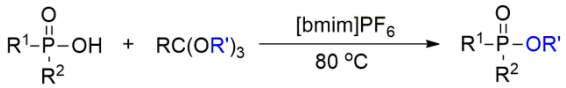
Scheme 34 describes the possible mechanism of this dehydration condensation reaction. When the reaction proceeded without the addition of tributyl amine, the alcohol was protonated by H_3PO_4 partially, which could reduce the yield of the reaction (Path 1). With the introduction of a tertiary amine to the reaction, the ammonium phosphate **A** was generated rapidly due to its stronger acidity. However, compound **A** still has two hydroxyl substituents that can be esterified, and could react with alcohols to synthesize the phosphoric acid monoesters in moderate yields (Path 2). On the other hand, nucleophilic base can react with **A** directly to form the active intermediate **B** (Path 3), and it is believed that B could react with alcohols efficiently to produce the phosphate monoester (Path 4).

Recently, Togo et al. disclosed a controllable and convenient method for the selective esterification of phosphonic/phosphinic acids with trialkyl orthoacetate under mild conditions, where ionic liquid was used as a recyclable solvent.[36] It should be noted that after optimization of the solvent effects for the reaction, [bmim]BF_4 and [bmim]Cl showed negative results for the reaction, and [bmim]PF_6 was proved to be the best solvent for the reaction. However, the loss of ionic liquids is the deficiency of this system. After the fourth regeneration, only 30% of [bmim]PF_6 was recovered. It was deduced that [bmim]PF_6 was partly extracted by benzylphenylphosphinate

ester during the regeneration process (**Scheme 35**).

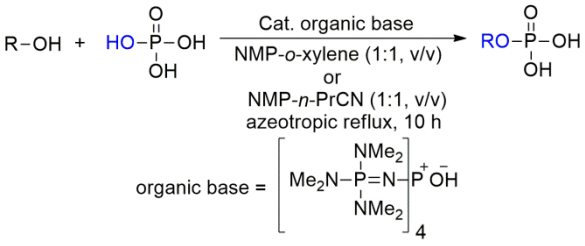


Scheme 34 Possible mechanism for the base-catalyzed selective dehydration condensation of H_3PO_4 with alcohol.



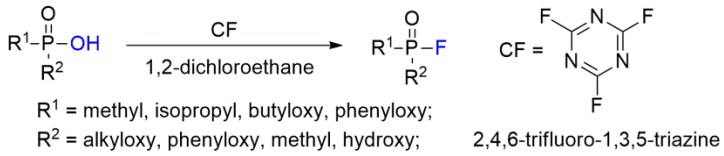
Scheme 35 Esterification of P-OH bonds with trialkyl orthoacetate.

Although Ishihara et al. have reported a catalytic amount of nucleophilic bases catalyzed the direct esterification of H_3PO_4 with alcohols, the reaction was not a true catalytic process, because it still required the exhaustion of one equivalent of trialkylamine. Very recently, they have found that 1 mol% of perrhenic acid could catalyze the condensation of H_3PO_4 with alcohols efficiently. However, due to the fact that oxorhenium(VII) compounds are very expensive, which limited the application for this transformation. From the view of economy and green chemistry, the direct esterification of H_3PO_4 with one equimolar amount of alcohols can allow the generation of the mono-esterificated derivatives for phosphoric acid. Thus, they have further investigated the dehydrative condensation of H_3PO_4 with alcohols through the catalysis of a phosphazenium cation (**Scheme 36**).[37] Different from the previous works, this transformation could be easily adopted for the large production of octadecyl dihydrogen phosphate in a 100 mmol scale, yielding the condensation product in 93% yield.



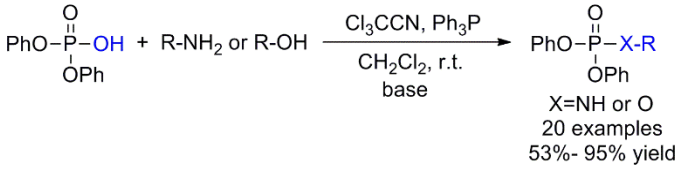
Scheme 36 Dehydrative condensation of H_3PO_4 with alcohols by phosphazenium cation catalysis.

The traditional methods for the production of phosphorus fluoridates generally employed the halogen exchange process of phosphoryl chlorides with a fluoride ion, but the phosphoryl chlorides are very reactive and toxic, and phosphoric acids are often generated in a considerable yield with water during the reaction. In 2010, Wärme et al. found a new way for the conversion of phosphinic/phosphoric acids to phosphoryl fluorides, cyanuric acid fluoride was selected as the efficient fluorination reagent in this reaction (**Scheme 37**).[38] Cyanuric acid was formed as the byproduct, which could be easily separated from the mixture by filtration.



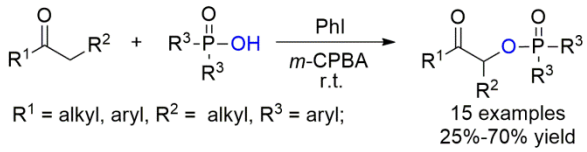
Scheme 37 Selective fluoration of P-OH bonds by cyanuric fluoride.

In 2011, Jang et al. used Cl_3CCN/Ph_3P as the efficient chlorination reagent for the selective amidation and esterification of P-OH bonds with alcohols and amines. Although this transformation could be operated under mild reaction conditions within a short time, the molar ratio of $Cl_3CCN/Ph_3P/Et_3N$ used was higher than 3:2:3 (**Scheme 38**).[39] In view of green chemistry and economy, this protocol is not suitable for the selective functionalization of P-OH bonds. The author did not mention the reaction mechanism in this work.

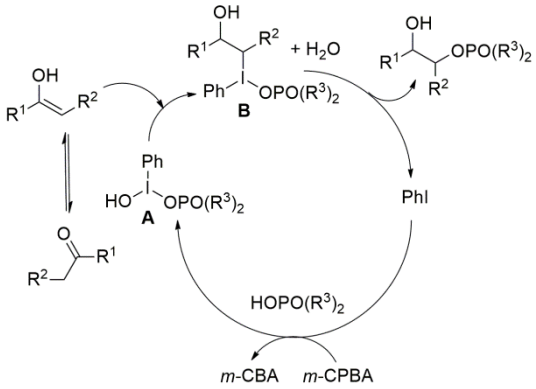


Scheme 38 Selective esterification and amidation of P-OH bonds with amines and alcohols using Cl_3CCN/Ph_3P.

In 2012, Yan et al. found an effective protocol for the preparation of α-phosphorylated ketones (**Scheme 39**).[40] Iodobenzene was adopted as a recyclable intermediate and *m*-CPBA (*m*-chloroperoxybenzoic acid) was chosen as the oxidant. It is notable that the α-phosphoryloxylation of ketones could be easily carried out at room temperature in CH_3CN. In most cases, ketones with electron-poor substituents in aryl rings yielded the target products with satisfactory yields; while the electron-rich substituents in aryl rings gave the negative results. However, cyclic ketones (cyclohexanone, cyclopentanone) cannot be tolerated in the reaction, and the expected products were not detected after the reaction.



Scheme 39 Selective α-phosphoryloxylation of ketones with P(O)-OH bonds.

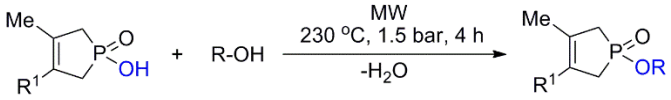


Scheme 40 Possible mechanism for the selective α-phosphoryloxylation of ketones with P-OH bonds.

Scheme 40 describes the possible mechanism for the iodobenzene/*m*-CPBA induced α-sp^3 C-H bond

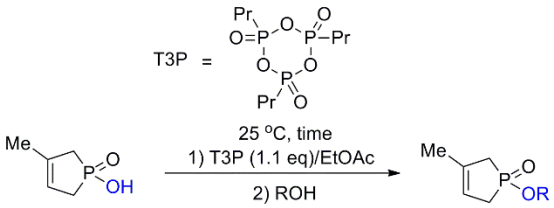
phosphorylation of ketones. Firstly, P-OH bond could react with iodobenzene and *m*-CPBA rapidly to afford the high-valent iodine reagent **A**. In addition, the enol compounds were generated in-situ via the tautomerization of ketones, which can react with **A** directly to form the transition state **B**. After the reductive elimilation, the keto phosphate was obtained. Iodobenzene was recovered and reused for the reaction.

Due to the high values of activation enthalpy of phosphinic acid, it is well known that it can hardly be esterified by alcohols under the traditional heating conditions. In 2012, Keglevich et al. discovered the microwave-assisted esterification of P-OH bonds with alcohols in cyclic phosphinic acids (**Scheme 41**).[41] The kinetic data obtained by the authors through thermodynamics or high-level quantum chemical calculations proved that the esterification of P-OH bonds in cyclic phosphinic acids under traditional thermal conditions was not feasible. Under the present reaction conditions, various novel cyclic phosphinates were produced with satisfactory yields via this MW-assisted protocol.

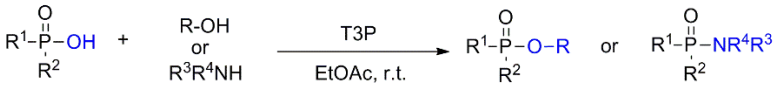


Scheme 41 MW-assisted selective esterification of P-OH bonds in cyclic phosphinic acids.

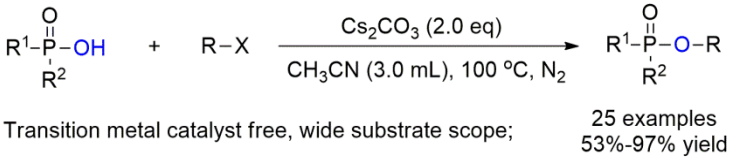
Propylphosphonic anhydride (T3P) is recognized as an effective coupling agent for the dehydration condensation of carboxylic acids with nucleophiles. Keglevich et al. have extended the selective esterification of P-OH bonds in a five-membered ring or linear phosphinic acids with O- and N-nucleophiles by using T3P as the coupling reagent (**Scheme 42, 43**).[43,44] This reaction can be carried out under mild conditions, and also has the excellent functional group tolerance for the nucleophiles. However, the amount of propylphosphonic anhydride used was higher than 1.1 equivalent in this method.



Scheme 42 T3P promoted condensation of cyclic P-OH bonds with alcohols.



Scheme 43 T3P promoted condensation of linear P-OH bonds with O-/N-nucleophiles.

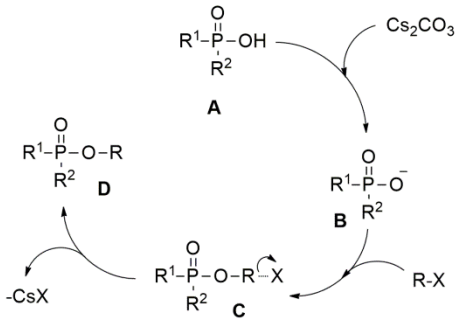


Scheme 44 Base-promoted nucleophilic substitution of P-OH bonds with alkyl halides

In 2014, the base-promoted cross-coupling of P-OH bonds with alkyl halides was investigated by Yin's group (**Scheme 44**).[45] The results proved that CH_3CN was the suitable solvent and Cs_2CO_3 was the optimized base for the reaction. The adoption of aryl chlorides can also afford the corresponding coupling products with satisfactory yields. When iodobenzene was employed, it was difficult to get the coupling product after the reaction. This

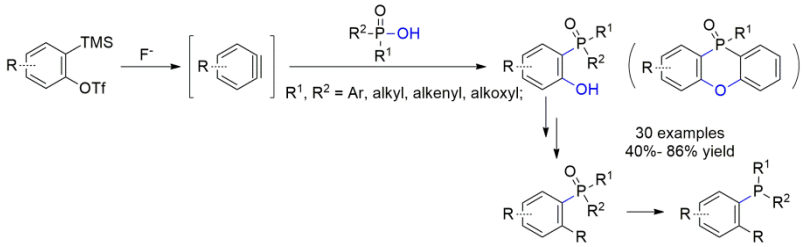
phenomenon may be ascribed to the p-π conjugative effect of the C-I bond in iodobenzene, which does not favor the direct cross-coupling reaction with P-OH bonds in a S_N2 type reaction.

Scheme 45 describes a reasonable mechanism for the base-assisted nucleophilic substitution reaction of P-OH bonds with alkyl halides. Firstly, a stoichiometric amount of an inorganic base Cs_2CO_3 was required to react with P-OH bond in **A** for the generation of the nucleophilic anion **B**. Then, the transition state **C** was formed through the reaction of **B** with R-X. Through the assistance of a base, the C-X bond was broken with the elimilation of CsX, and the expected alkylation product **D** was generated.

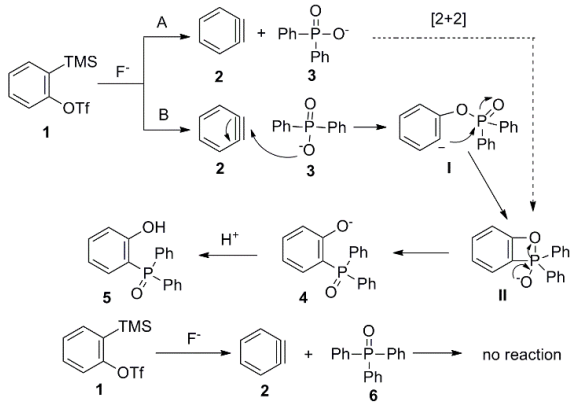


Scheme 45 Possible mechanism for the base-promoted nucleophilic substitution of P-OH bonds with alkyl halides.

In 2016, He et al. disclosed the fluoro ion-induced arene-insertion of P-O bonds with β-trimethylsilyl aryl triflates under transition-metal-free conditions. Compared with previous works, they have firstly realized the preparation of o-hydroxy arylorganophosphorus compounds from P(O)-OH compounds. Interestingly, various functionalized β-trimethylsilyl aryl triflates were tolerated for this reaction, and the *ortho*-hydroxyl group for the products readily underwent the transformations for the construction of other *ortho*-substituted arylphosphorus compounds. The results showed that TBAT (tetrabutylammonium difluorotriphenylsilicate) was the best fluoride source for the reaction due to its weaker basicity (**Scheme 46**).[46]



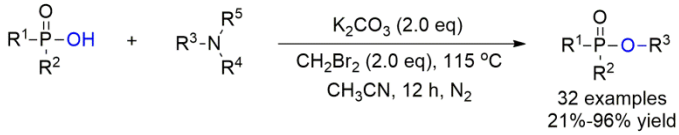
Scheme 46 Fluoro ion-induced arene-insertion of P-O bonds with β-trimethylsilyl aryl triflates.



Scheme 47 Possilbe mechanism for the fluoro ion-induced arene-insertion of P-O bonds with β-trimethylsilyl aryl triflates.

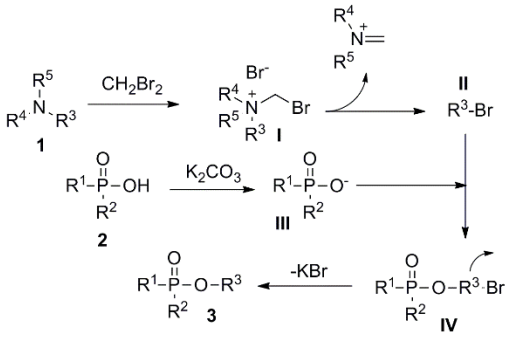
The plausible mechanism for this transformation was described in **Scheme 47**. There are two pathways that may produce the target product **5**. In route A, the in-situ generated benzyne **2** with P=O bond in **3** afforded the intermediate **II** in one step via the [2+2] cycloaddition reaction, and then the rearrangement reaction took place in **II** for the generation of **5**. In route B, the $Ph_2(O)P$-O anion attacked benzyne **2** to give the corresponding phenyl anion intermediate **I**, which could undergo a Fries rearrangement to afford the target product **5**.

In 2016, Yin et al. reported the regioselective alkylation of P-OH bonds with tertary amines via the aid of an inorganic base, and various alkyl-functionalized phosphinates, phosphonates and phosphates were synthesized through the cleavage of C-N bonds (**Scheme 48**).[47] The use of halomethane was essential for the reaction, and CH_2Br_2 was the best additive. It was deduced that the formation of the quaternary ammonium salt was the key step for the alkylation reaction.



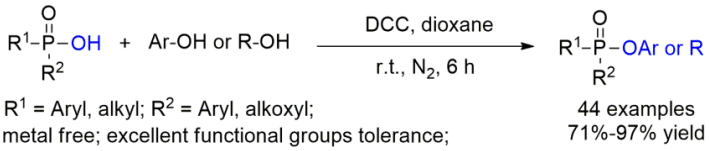
Scheme 48 Base-assisted regioselective alkylation of P-OH bonds with tertary amines.

A reasonable mechanism was described by the authors in **Scheme 49**. Firstly, the quaternary ammonium salt (**I**) was produced in-situ from the reaction of the tertiary amine **1** with CH_2Br_2, which further decomposed to produce bromoalkane (**II**). In the presence of K_2CO_3, the anions (**III**) could be formed in quantitative yields via the deprotonation of P-OH bonds. Intermediate **III** are recognized as the good nucleophiles which can react with bromoalkanes (**II**) easily through the nucleophilic substitution to afford the coupling product **3**.



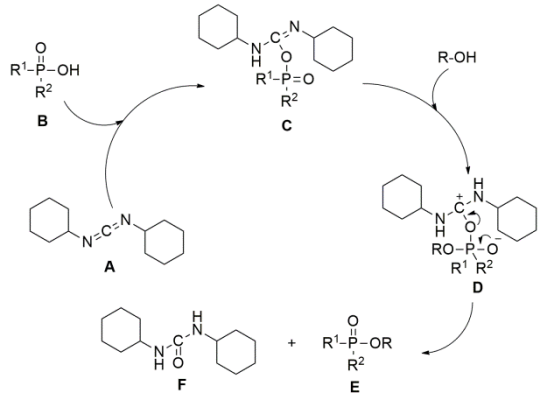
Scheme 49 Possible mechanism for the base-assisted regioselective alkylation of P-OH bonds with tertary amines.

In 2017, we established an effective and controllable way for the functionalization of P-OH bonds with phenols and alcohols to produce the corresponding esterified products. Dicyclohexylcarbodiimide (DCC) was used as the efficient activation reagent for the cleavage of P-OH bond. It should be noted that the transformation of P-OH bonds to P-O-C bonds could be achieved at room temperature within 6 hours, giving a convenient way for the production of phosphonic/phosphinic acid esters from commercially available P-OH bonds under mild conditions (**Scheme 50**).[48]



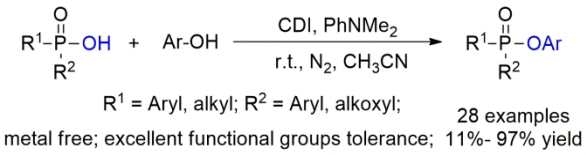
Scheme 50 DCC-promoted selective esterification of P-OH bonds with *O*-nucleophiles.

The reasonable mechanism for the selective esterification reaction of P-OH bonds with *O*-nucleophiles was discussed in **Scheme 51**. Firstly, the P-OH bond in compound **B** was attacked by dicyclohexylcarbodiimide (DCC) **A**, affording the nucleophilic type addition product **C**. The intermediate **C** can react with *O*-nucleophiles directly to afford the transition state **D**. Finally, the reaction was completed through the P-O bond cleavage.



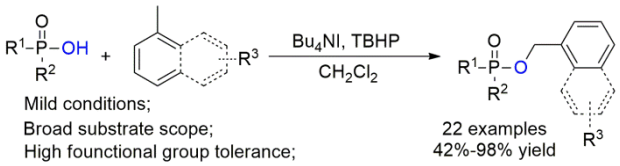
Scheme 51 Possible mechanism for the DCC-promoted selective esterification of P-OH bonds with *O*-nucleophiles.

N, *N*-carbonyldiimidazole (CDI) was also an efficient coupling reagent for the selective esterification of P-OH bonds with phenols (**Scheme 52**).[49] Different from the DCC-activation system, base was required to improve the yield in this reaction, and $PhNMe_2$ was the best additive. It should be noted that the di-esterification reaction can hardly be reached under the present reaction condition. It is deduced that the mono-esterified product bearing an electron-withdrawing group may have a lower redox potential than the substrate, leading to the case that another hydroxyl substituent can hardly be esterified by diphenylphosphinic acid.



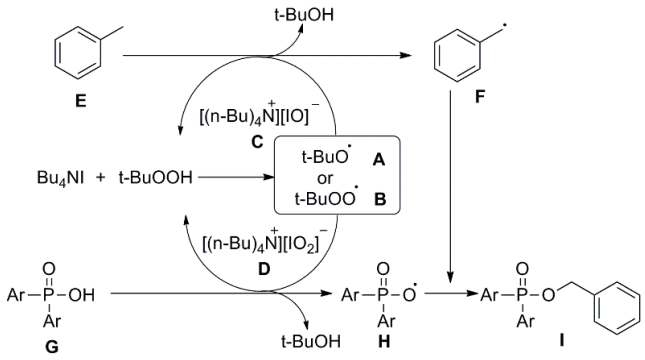
Scheme 52 CDI-promoted selective esterification of P-OH bonds with phenols.

In order to scope with the application of P-OH bonds in cross-dehydrogenative-coupling (CDC) reaction, we found that Bu_4NI could catalyze the CDC type reaction of P-OH bonds with the C(sp^3)-H bonds of methyl group in arenes under aerobic oxidative reaction conditions (**Scheme 53**).[50] The reaction could be effectively performed under mild conditions without the addition of transition metals. This work represented a direct method for preparing valuable phosphinic acid esters from commercially available methyl-substituted arenes and diarylphosphinic acids. In order to avoid the waste of methyl-substituted arenes, dichloromethane was found to be the optimal solvent for the reaction. However, this protocol is only compatible with diarylphosphinic acids and arenes that have a primary C(sp^3)-H, which cannot be extended to $(RO)_2P(O)$-OH type of compounds and phosphoric acid.



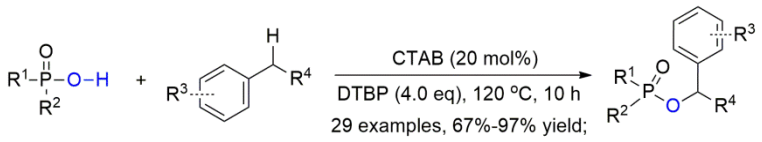
Scheme 53 Bu_4NI-catalyzed CDC reaction of diarylphosphinic acids with methyl-substituted arenes.

Scheme 54 describes the possible catalytic cycle for this transformation. Bu_4NI first reacted with TBHP to form the corresponding radicals **A** and **B** or the oxidation adducts **C** and **D**. In addition, both of the hydrogen atoms of methyl in arenes **E** and diarylphosphinic acids **G** were captured by these intermediates to afford the arylmethylene radical **F** and phosphoroxyl radical **H**. Finally, through the radical coupling of **H** and **F**, the reaction was completed with the generation of product **I**.

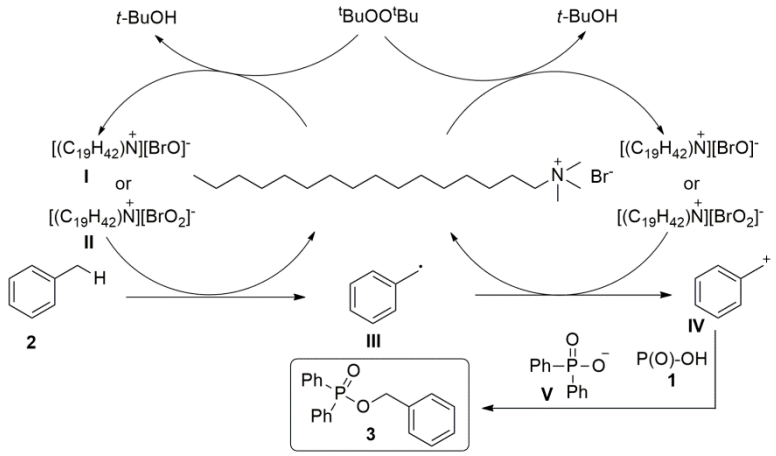


Scheme 54 Possible mechanism for the Bu_4NI-catalyzed CDC reaction of diarylphosphinic acids with methyl-substituted arenes.

In 2019, Yin et al. investigated the cetyltrimethyl ammonium bromide (CTAB) catalyzed CDC type reaction of P-OH bonds with benzyl substitued arenes (**Scheme 55**).[51] A wide range of benzyl substitued arenes and phosphinic/phosphoric acids showed good tolerance for the reaction, yielding the expected CDC coupling products with moderate to excellect yields. Compared with the previous works, they have further extended the substrate class from phosphinic acids to inert phosphoric acids in this work.



Scheme 55 Cetyltrimethyl ammonium bromide catalyzed CDC type reaction of P-OH bonds with benzyl substitued arenes.

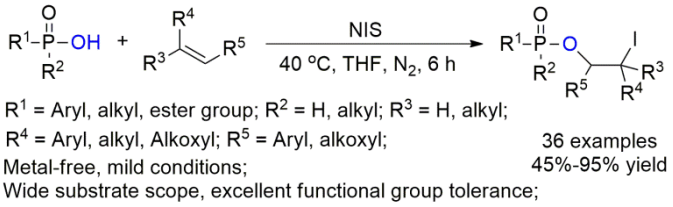


Scheme 56 Possible mechanism for the cetyltrimethyl ammonium bromide catalyzed CDC type reaction of P-OH bonds with benzyl substitued arenes.

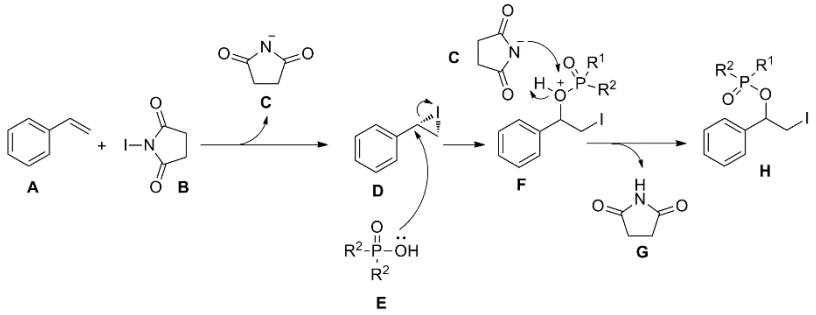
They have also discussed the possible mechanism in **Scheme 56**. Firstly, the oxidation adducts **I** or **II** were

formed through the reaction of CTAB with DTBP, which were the active species that could activate the C(sp^3)-H bonds in methyl-substituted arenes to generate the benzylic radical. In addition, the benzylic radical could be oxidized by **I** or **II** in-situ to generate the benzyl cation **IV**. Finally, the coupling product was formed through the reaction of benzyl cation with P(O)-OH bond.

Very recently, we established a difunctionalization protocol for the regioselective iodonation and phosphoroxylation of alkenes with P-OH bonds under mild conditions, *N*-Iodosuccinimide (NIS) was adopted as an iodination reagent for the activation of carbon-carbon bonds in this method (**Scheme 57**).[52] Various difunctionalized β-iodo-1-ethylphosphinate/phosphonate esters were synthesized with moderate or excellent yields. These iodophosphorylation products could be decorated to diversified units for the production of bioactive organophosphorus compounds, antibiotics and flame retardant materials through the simple modification of iodo atom. It is worth noting that the substituent insensibility in alkenes did not affect the rate-determining step. However, due to the higher pKa value of phosphoric acids than phosphinic acids, phosphinic acids were transformed more efficiently than phosphoric acids in this reaction.



Scheme 57 NIS-promoted regioselective difunctionalization of alkenes with P-OH bonds.



Scheme 58 Possible mechanism for the NIS-promoted regioselective difunctionalization of alkenes with P-OH bonds.

As shown in **Scheme 58**, we proposed a possible mechanism for the reaction. Firstly, the iodonium intermediate **D** was generated in quantitative yields through the reaction of *N*-iodosuccinimide **B** with styrene **A**, pyrrolidine-2,5-dione anion C was released as the byproduct. In the presence of a nucleophile (P-OH bond, **E**), this compound can undergo a ring-opening reaction efficiently with **D**, forming the transition state **F**. Finally, the iodophosphoryloxylation product **H** was synthesized via the deprotonation of **C** with **F**.

CONCLUSIONS AND PERSPECTIVES

In this review, we have highlighted the recent progress for the selective functionalization of P-OH bonds. Through these methods, phosphoric/phosphinic/phosphoric acids can be transformed into a group of widely used organic phosphorus heterocyclic compounds, phosphinates, phosphonates and phosphates. These reactions can be roughly divided into two categories: metal catalysis and transition-metal-free activation. Transition-metal catalysis mostly employed Cu, Pd, Rh, Ru, Ag, and Re as the catalyst for the functionalization of P-OH bonds with the aid of a base or an oxidant. From the perspective of economy and green chemistry, transition-metal-free activation is

more environmentally friendly and feasible, which avoids the adoption of metals and deleterious chemicals, and the reactions could be carried out under mild conditions and are suitable for industrial-scale synthesis.

Nevertheless, the development of a new protocol for the regioselective functionalization of P-OH bonds is still urgently needed. For example, it should become a promising field in the future works to achieve the activation of P-OH bonds with high catalytic efficiency system under mild conditions, especially in the fields of photo-catalysis and electrochemical transition metal catalysis.

ACKNOWLEDGMENTS

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