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Decarboxylative cross-coupling reactions for P(O)–C bond formation

Akram Hosseinian,^{*a} Fatemeh Alsadat Hosseini Nasab,^b Sheida Ahmadi,^c Zahra Rahmani^d and Esmail Vessally^{id}^c

Phosphorus-containing compounds are one of the most important classes of organic compounds, which have wide applications in organic chemistry, medicinal chemistry, agricultural chemistry, and materials chemistry. In particular, organophosphorus compounds bearing a P(O)–C bond have attracted significant attention in recent decades due to their widespread biological and pharmacological activities. In this review, we will highlight the most important developments in the construction of P(O)–C bonds through decarboxylative C–P cross-coupling reactions. The literature has been surveyed from 2011 to May 2018.

1. Introduction

Organophosphorus compounds are among the most important classes of organic compounds, which are diversely found in natural products,¹ pharmaceutical drugs,² insecticides,³ and ligands.⁴ In particular, P(O)–C bond-containing compounds have attracted significant attention of medicinal chemists and pharmacologists in recent years owing to their broad spectrum of pharmacological profiles.⁵ Several currently marketed drugs contain this important structural unit, which is used for the treatment of various kinds of diseases. For example (Fig. 1),

fosinopril **1** with the brand name Monopril is a phosphinate-containing angiotensin-converting enzyme inhibitor marketed worldwide for the treatment of hypertension (high blood pressure) and some types of chronic heart failures.⁶ Adefovir **2**, with trade names Preveon and Hepsera, is a promising antiviral drug that is used to treat chronic hepatitis B; the drug works by blocking reverse transcriptase, an enzyme crucial for the hepatitis B virus to reproduce in the body.⁷ Alendronic acid **3** (Fosamax) is a bisphosphonate drug used to treat osteoporosis and several other bone diseases.⁸ As a consequence, the construction of P(O)–C bonds is an essential issue and has gained much attention from the research community interested in chemical synthesis.

The most general and straightforward methods for the construction of P(O)–C bonds involve either C–P cross-coupling of organic halides or triflates with P(O)H compounds (Fig. 2, route a)⁹ or direct dehydrogenative C–P cross-coupling between

^aSchool of Engineering Science, College of Engineering, University of Tehran, P. O. Box 11365-4563, Tehran, Iran. E-mail: hosseinian@ut.ac.ir

^bDepartment of Chemistry, Hormozgan University, P. O. Box 3995, Bandar Abbas, Iran

^cPayame Noor University, Department of Chemistry, 19395-4697 Tehran, Iran

^dDepartment of Chemistry, Tabriz Branch, Islamic Azad University, Tabriz, Iran



Akram Hosseinian was born in Ahar, Iran, in 1973. She received her B.S. degree in Pure Chemistry from University of Tehran, Iran, and her M.S. degree in Inorganic Chemistry from Tarbiat Modares University, Tehran, Iran, in 2000 under the supervision of Prof. A. R. Mahjoub. She completed her PhD degree in 2007 under the supervision of Prof. A. R. Mahjoub. Now she is working at University of Tehran

as an Associate Professor. Her research interests include inorganic and organic synthesis and new methodologies in nanomaterial synthesis.



Fatemeh Alsadat Hosseini Nasab was born in Sirjan, Kerman, Iran, in 1980. She received her B.S. degree in Pure Chemistry from University of Shahid Bahonar, Kerman, Iran, and her M.S. degree in Organic Chemistry from Shahid Bahonar University, Kerman, Iran, in 2006 under the supervision of Dr M. Eslami. Now, she is working at Hormozgan University of Bandar Abbas as an

Instructor. Her research interests include organic synthesis and new nanochemistry.



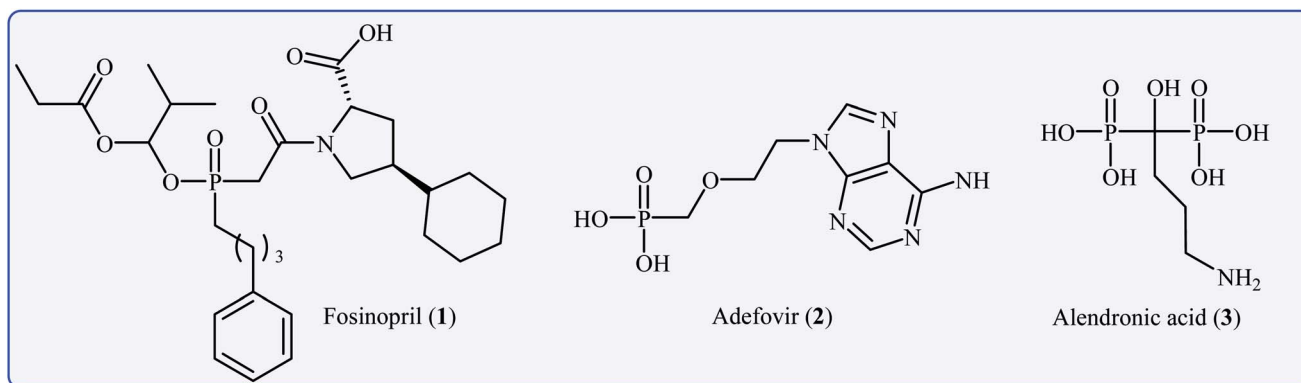


Fig. 1 Selected examples of drugs containing a P(O)–C bond.

R–H compounds and P(O)H compounds (Fig. 2, route b).¹⁰ However, each of these methods suffer from various inherent drawbacks, and the most important of these drawbacks are as



Sheida Ahmadi was born in Miyaneh, Iran. She has received her B.S. degree in Applied Chemistry from Islamic Azad University, Tehran, Iran, in 1997, and her M.S. degree in inorganic chemistry from Shahid Bahonar University, Kerman, Iran, in 2007 under the supervision of Prof. S. J. Fatemi. She received her PhD degree in 2017 under the supervision of Prof. M. Hakimi in Payam Noor University, Tehran,

Iran. Now, she is working at Payame Noor University of Tehran as an Assistant Professor. Her research interests include inorganic polymers, synthesis of inorganic complexes and bioinorganic chemistry.



Zahra Rahmani was born in Takab, Iran, in 1985. She received her B.S. degree in Applied Chemistry from University of Urmia, Iran, and her M.S. degree in Organic Chemistry from Payam Noor University, Zanjan, Iran, in 2012 under the supervision of Prof. E. Vessally. She is currently a PhD student in Organic Chemistry under the supervision of Prof. E. Vessalli in Islamic Azad University, Tabriz,

Iran. Her doctoral thesis examines the interaction of boron nitride and aluminum nitride nanostructures with some sulfonamide drugs. Now, she is working at Zarshuran Gold Company of Takab as a Laboratory Supervisor.

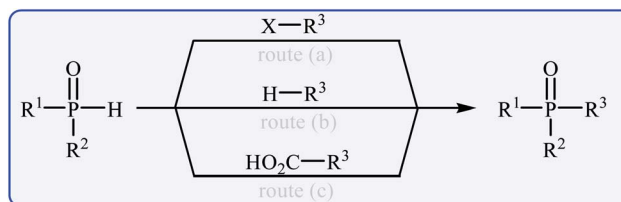


Fig. 2 C–P cross-coupling routes for the formation of P(O)–C bond.

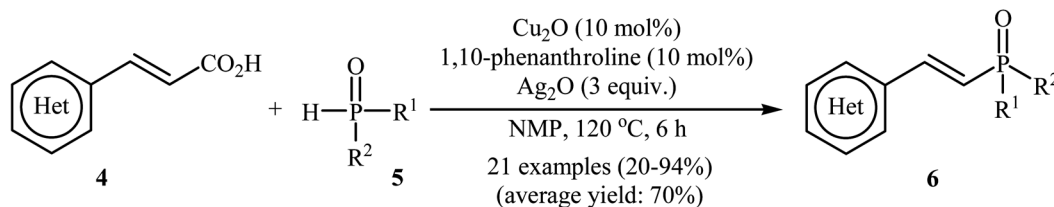
follows: (i) most of the organic halides are environmentally toxic and liberate hazardous halogen by-products; (ii) triflates are unstable, expensive, and liberate potentially genotoxic triflic acid;¹¹ and (iii) the selective activation of a specific C–H bond poses a particular challenge.¹² An alternative and efficient protocol for the formation of P(O)–C bonds involves decarboxylative C–P cross-coupling between carboxylic acids and P(O)H compounds (Fig. 2, route c). To the best of our knowledge, a comprehensive review on decarboxylative C–P cross-coupling reactions has not been reported in the literature so far. In continuation of our recently published reviews on metal-catalyzed cross-coupling reactions¹³ and the green synthesis



Esmail Vessally was born in Sharabiyan, Sarab, Iran, in 1973. He received his B.S. degree in Pure Chemistry from University of Tabriz, Tabriz, Iran, and his M.S. degree in Organic Chemistry from Tehran University, Tehran, Iran, in 1999 under the supervision of Prof. H. Pir-elahi. He completed his PhD degree in 2005 under the supervision of Prof. M. Z. Kassae. Now, he is working at Payame

Noor University as a full Professor of Organic Chemistry. His research interests include theoretical organic chemistry, new methodologies in organic synthesis and spectral studies of organic compounds.





Ar = Ph, 2-naphthyl, 2-furyl, 4-Me-C₆H₄, 4-OMe-C₆H₄, 4-F-C₆H₄, 4-Cl-C₆H₄, 4-CN-C₆H₄, 3-Me-C₆H₄, 3-OMe-C₆H₄, 3-Br-C₆H₄, 2-Me-C₆H₄, 2,4-Cl₂-C₆H₃, 2,5-OMe₂-C₆H₃, 3,4-Me₂-C₆H₃, 3,5-OMe₂-C₆H₃, 3,4-OCH₂O-C₆H₃
 R¹ = Ph, OEt, O^tPr
 R² = Ph, O^tPr

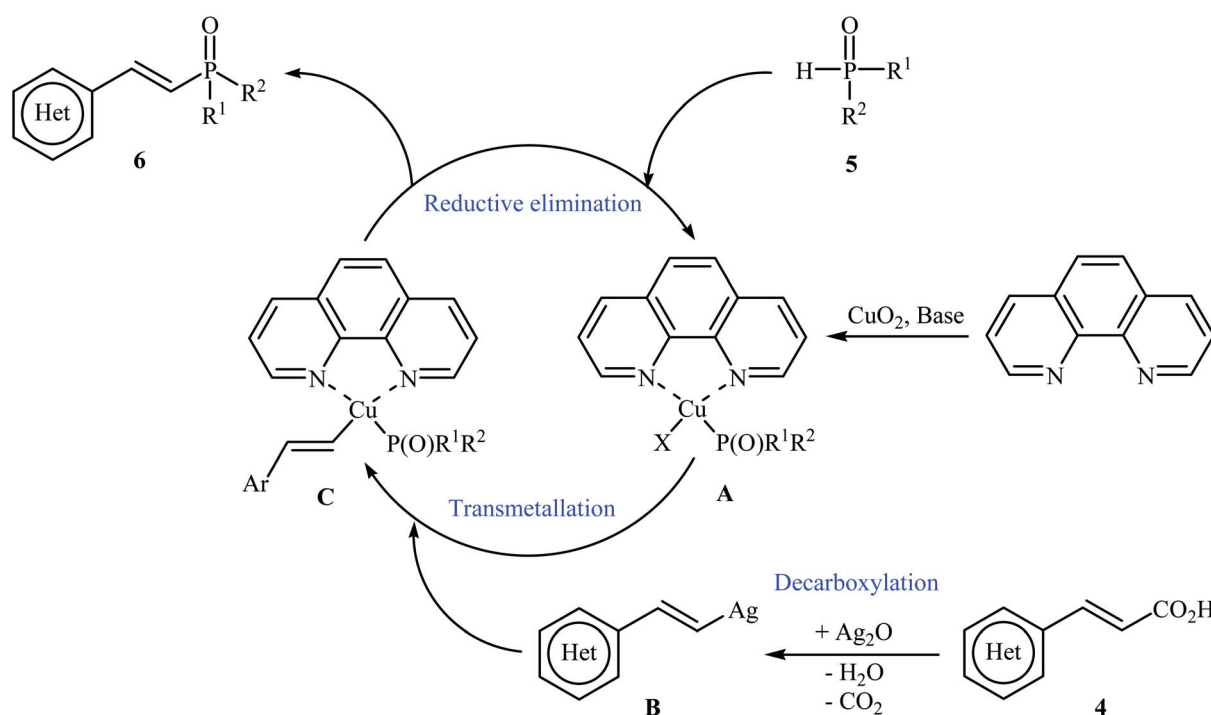
Scheme 1 Cu-catalyzed decarboxylative coupling reactions of alkenyl acids with P(O)H compounds developed by Hu and co-workers.

field,¹⁴ in this review, we will highlight the most important developments of decarboxylative C–P cross-coupling reactions from 2011 to May 2018. It is worth mentioning that a special emphasis is placed on the mechanistic aspects of the reactions.

2. Coupling of alkenyl acids with P(O)H compounds

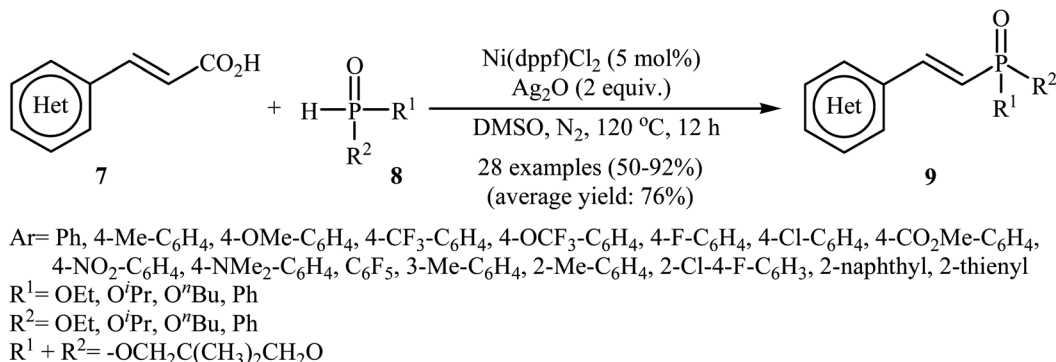
The first synthesis of alkenylphosphorus compounds through transition-metal-catalyzed decarboxylative coupling reactions of alkenyl acids with P(O)H compounds was reported by Hu and co-workers in 2011;¹⁵ they treated various cinnamic acids **4** with hydrogen phosphoryl compounds **5** in the presence of 10 mol% of low-cost, commercially-available Cu₂O as the catalyst, 10 mol% of 1,10-phenanthroline as the ligand and 3.0 equiv. of Ag₂O as the additive in NMP. The reactions were carried out at

120 °C for 6 h and provided the expected alkenylphosphorus compounds **6** in moderate to excellent yields (Scheme 1). It should be mentioned that all three kinds of P(O)–H compounds (H-phosphinates, H-phosphonates, and secondary phosphine oxides) were applicable to this coupling reaction. The decreasing order of the reactivities of hydrogen phosphoryl compounds with cinnamic acids under these reaction conditions was secondary phosphine oxides > H-phosphinates > H-phosphonates. Interestingly, the electronic character of the substituents in the phenyl ring periphery of cinnamic acids had negligible effect on the rate of the reaction. However, steric hindrance led to lower yields. A plausible mechanism that explains this transformation is depicted in Scheme 2. Initially, P(O)–H compound **5** reacted with the copper/phen catalyst to form the intermediate **A**. Meanwhile, the reaction of alkenyl acids **4** with Ag₂O produced intermediate **B** through a decarboxylation process. This intermediate **B** upon transmetalation



Scheme 2 Mechanistic proposal for the formation of alkenylphosphorus compounds **6**.





Scheme 3 Ni-catalyzed decarboxylative coupling of alkenyl acids **7** with P(O)-H compounds **8**.

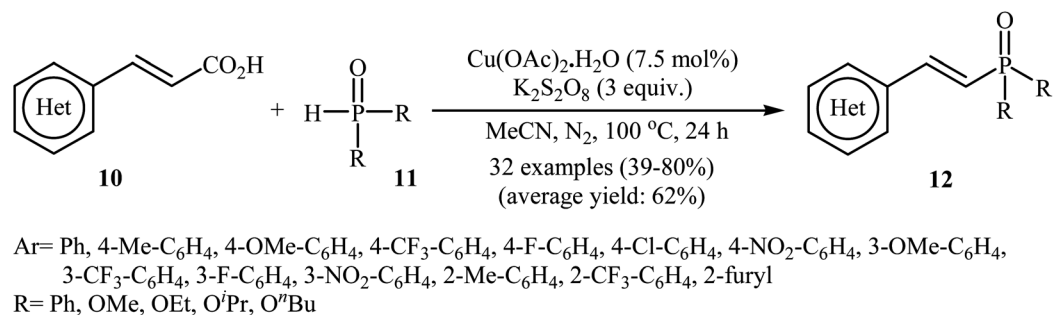
into intermediate **A** formed the organocopper intermediate **C**. Finally, reductive elimination of intermediate **C** afforded the observed alkenylphosphorus compounds **6** along with the initial copper species.

Next, Gao's group demonstrated for the first time the usefulness of nickel catalysts for decarboxylative coupling of alkenyl acids with P(O)-H compounds.¹⁶ Thus, in the presence of Ni(dppf)Cl₂ as the catalyst and Ag₂O as the additive in DMSO at 120 °C, coupling of cinnamic acids **7** with hydrogen phosphonyl compounds **8** afforded the corresponding (*E*)-1-alkenylphosphorus compounds **9** in moderate to high yields (Scheme 3). A variety of sensitive functional groups including NO₂, NMe₂, CO₂Me, OMe, CF₃, F, and Cl were tolerated by the reaction conditions employed. This made further derivatization of the products possible. It is noted that other nickel catalysts such as Ni(OAc)₂, Ni(acac)₂, NiBr₂, and NiCl₂ also promoted this coupling reaction; however, lower yields were observed. Based on density functional theory (DFT) calculations and experimental data, the authors found that in this coupling reaction, the phosphine ligand exhibited better catalytic performance than the nitrogen ligand in the reductive elimination step owing to stronger nucleophilicity and larger size.

In a related investigation, Tang and Wang along with their co-workers found that the treatment of alkenyl acids **10** with P(O)-H compounds **11** (phosphine oxides and H-phosphonates) in the presence of Cu(OAc)₂·H₂O/K₂S₂O₈/MeCN combination as a catalytic system afforded the corresponding (*E*)-1-alkenylphosphorus compounds **12** in moderate to high yields with excellent stereoselectivities (Scheme 4).¹⁷ Some important

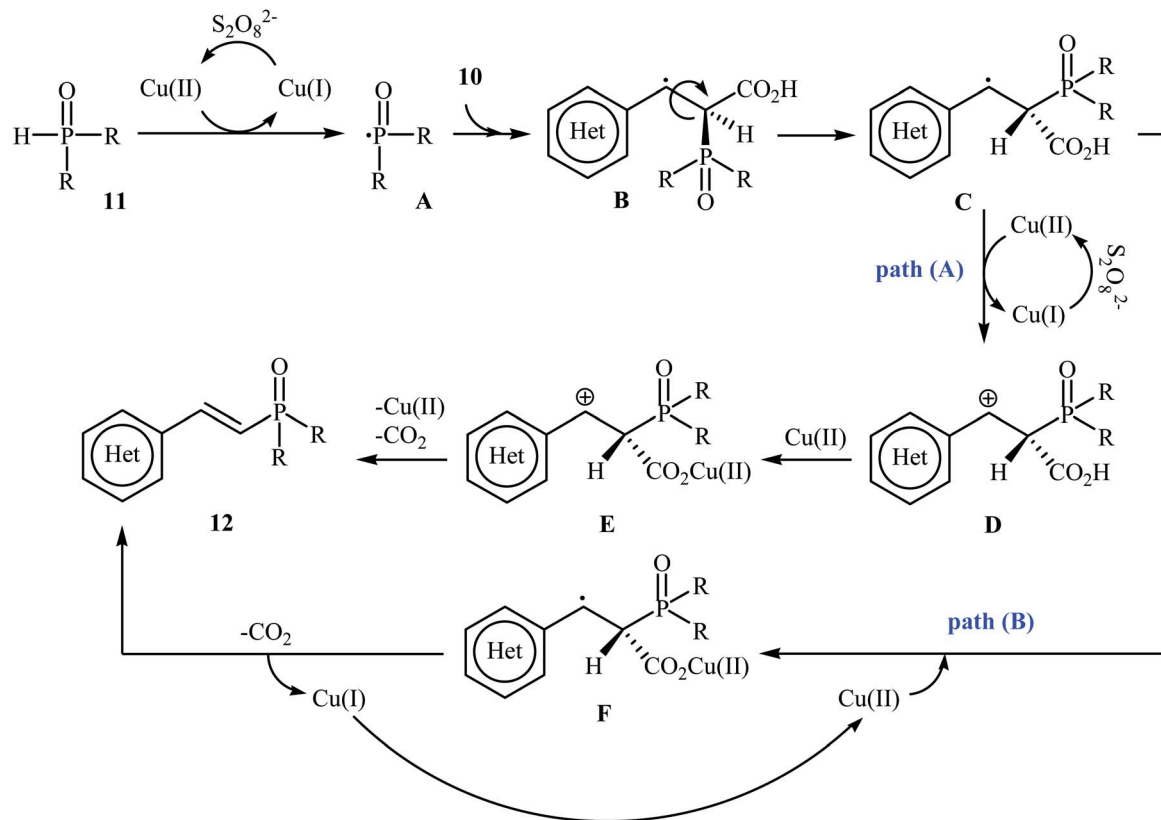
points regarding the reactions are listed below: (i) aliphatic alkenyl acids failed to enter the reaction; (ii) depending on the electronic effects of the substituents on the aryl ring of cinnamic acids, substrates with electron-donating groups gave higher yields than those with electron-withdrawing groups; and (iii) phosphine oxides gave lower yields of desired products compared with H-phosphonates. It is noteworthy that this catalytic system was also successfully applied in the cross-coupling of various P(O)-H compounds with styrenes and β-nitrostyrene. A plausible mechanism for this transformation starts with the formation of the phosphonyl radical **A** by oxidation of the starting phosphonate **11** with *in situ* generated Cu^{II} species [Cu(CH₃CN)_{*n*}]²⁺; its nucleophilic attack on the alkenyl acid **10** led to the formation of radical **B**, which could be converted into a more stable conformation **C**. Next, the oxidation of this intermediate **C** by the Cu^{II} species gave the carbocation intermediate **D**, which finally afforded the final product by a ligand-exchange-decarboxylation sequence (path A). In another possibility (path B), intermediate **C** gave complex **D** through ligand exchange, followed by decarboxylation to afford the corresponding (*E*)-1-alkenylphosphorus product (Scheme 5).

Very recently, Liu and co-workers described efficient transition-metal-free phosphorylation of alkenyl acid derivatives with P(O)H compounds *via* radical-promoted decarboxylation under mild conditions.¹⁸ They carefully tested several oxidants, bases, additives and solvents, and the system of TBPB/K₂HPO₄/KI/DMSO was found to be superior. Under optimized conditions, various aromatic and heteroaromatic alkenyl acids **13**, including those exhibiting substitution on the C=C bond,



Scheme 4 Tang-Wang's synthesis of (*E*)-1-alkenylphosphorus compounds **12**.





Scheme 5 Mechanistic proposal for the reactions in Scheme 4.

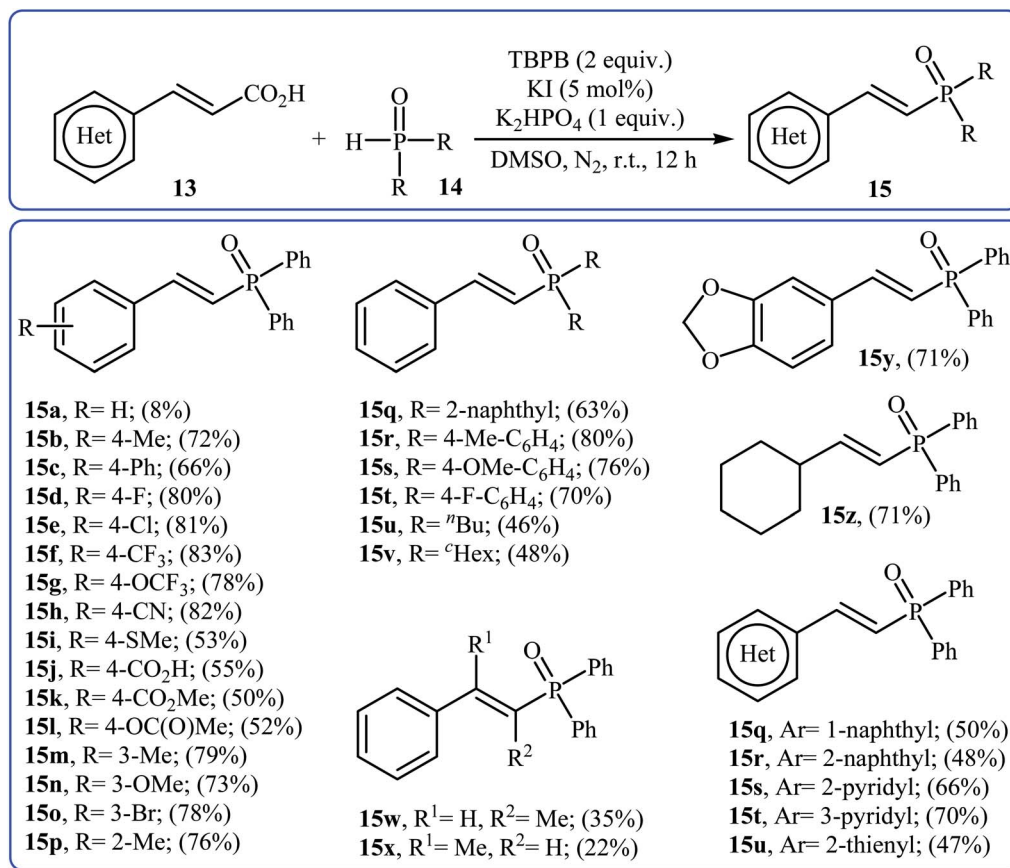
and symmetrical secondary phosphine oxides **14** reacted to give good yields of the corresponding products **15** (Scheme 6). In addition to mild reaction conditions and excellent functional group tolerance (F, Cl, Br, CN, CO₂H, CO₂Me, OCOMe, OMe, and SMe), the major advantage of this method is the formation of (*E*)-1-alkenylphosphorus compounds **15** on a gram-scale. The authors also showed the application of this procedure for the high yielding syntheses of the estrone derivative **17**, a steroidal progestin used in clinic, with estrogenic activity (Scheme 7). They assumed that the mechanism of this coupling reaction involved the initial formation of *tert*-butoxyl and benzoyloxyl radicals *via* decomposition of TBPB, which was promoted with the assistance of iodide anions. Next, the abstraction of a hydrogen atom from H(O)PR¹R² **14** by a *tert*-butoxyl or benzoyloxyl radical afforded the phosphorus radical **A**, which underwent radical addition to the cinnamic acid anion **B** (generated from the reaction of the starting acid **13** with a base) to provide the radical intermediate **C**. Finally, decarboxylation of intermediate **C** followed by single-electron oxidation of the radical anion afforded the expected products **15** (Scheme 8).

3. Coupling of alkynyl acids with P(O)H compounds

In 2011, Liang and Yang along with their co-workers reported the first example of decarboxylative C–P cross-coupling of alkynyl acids with P(O)H compounds.¹⁵ They showed that

electron-rich alkynyl acids **18** underwent rapid C–P cross-coupling with various hydrogen phosphoryl compounds **19** in the presence of Cu₂O/Pd(acac)₂/1,10-phenanthroline/PPh₃/AgOAc combination as a catalytic system in NMP at 120 °C. The corresponding alkynylphosphorus compounds **20** were obtained in moderate to high yields (Scheme 9). The reaction is noteworthy since both alkyl and aryl alkynyl carboxylic acids and all three kinds of P(O)–H compounds were tolerated. It was noted that the presence of both copper and palladium catalysts is essential in this reaction; unsatisfactory yields of the expected products were obtained in the absence of any of these catalysts. The proposed mechanism by the authors is illustrated in Scheme 10. First, a Cu^I–phosphine-complex **A** was formed *via* the reaction of P(O)H compound **19** with the copper/phen catalyst. In parallel, decarboxylation of alkynyl acid **18** by silver gave alkynyl–silver species **B**. The *in situ* generated Pd^{II} complex (by oxidation of Pd⁰ with silver) transmetalated with the alkynyl–silver species **B** to generate the alkynyl–palladium intermediate **C**. The transmetalation of this highly active intermediate **C** with the Cu^{II}-complex **A** then gave the intermediate **D**. Finally, reductive elimination of intermediate **D** resulted in the formation of the expected alkynylphosphorus compounds **20**. Later, Gao's group showed that alkynyl phosphonate derivatives were also formed from the corresponding alkynyl acids and diisopropyl phosphonate by a simple process employing Ni(NO₃)₂·6H₂O as the catalyst and Ag₂CO₃ as the oxidant in DMSO at 100 °C. However, the yields of the desired products were low (36–45% for three examples).¹⁶



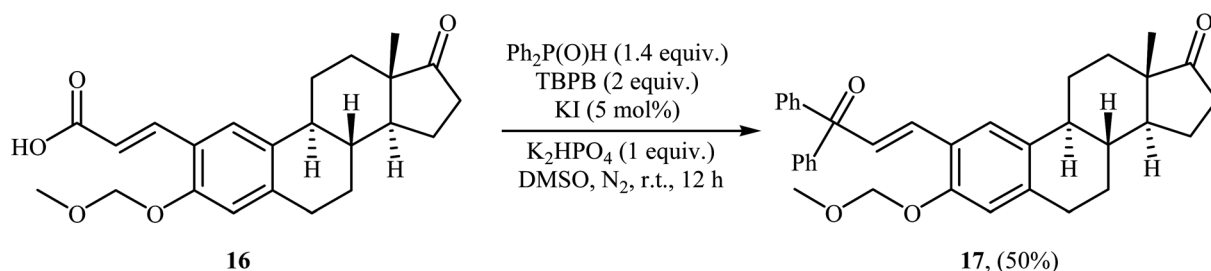


Scheme 6 Transition-metal-free phosphorylation of alkenyl acid derivatives with P(O)H compounds reported by Liu.

In 2014, Li and co-workers reported that the combination of $Cu(OAc)_2 \cdot H_2O$ /1,10-phenanthroline could efficiently catalyze the decarboxylative cross-coupling of alkynyl acids **21** with dialkyl H-phosphonates **22** under relatively mild conditions in the most significant green solvent water (Scheme 11).¹⁹ Various aryl alkynyl acids and several dialkyl H-phosphonates were well tolerated in this catalytic system with moderate to high yields (40–88%). However, alkyl alkynyl acids failed to participate in this reaction. Interestingly, other copper salts [e.g., $CuCl_2$, $Cu(OTf)_2$, and $CuSO_4 \cdot 5H_2O$] were also found to promote the reaction albeit with reduced efficiencies. According to the mechanism proposed by the authors (Scheme 12), this reaction consists of the following key steps: (i) initial formation of active copper(II) intermediate **A** via coordination of 1,10-phenanthroline to $Cu(OAc)_2$; (ii) ligand exchange between intermediate **A**

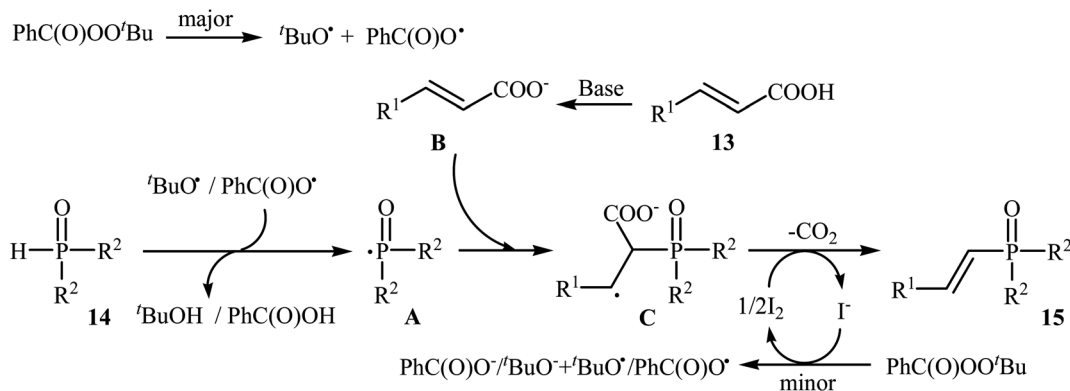
and alkynyl acid **21** to afford the copper(II) intermediate **B**; (iii) decarboxylative reaction of intermediate **B** to give the copper(II) intermediate **C**; (iv) reaction of the intermediate **C** with a phosphonate anion (generated from H-phosphonate **22** and K_3PO_4) to form the copper(II) intermediate **D** and (v) reductive elimination of intermediate **D** to give the desired products **23**.

At almost the same time, Hu, Gao, and Zhao demonstrated elegant and innovative copper-catalyzed decarboxylative cross-coupling of alkynyl acids with hydrogen phosphonyl compounds for the formation of alkenylphosphorus compounds.²⁰ Thus, in the presence of a catalytic amount of $CuCl$ (10 mol%) in DMF under nitrogen atmosphere, cross-coupling of aryl alkynyl acids **24** with H-phosphine oxides **25** afforded the corresponding (*E*)-alkenylphosphine oxide derivatives **26** in moderate to almost quantitative yields (Scheme 13).

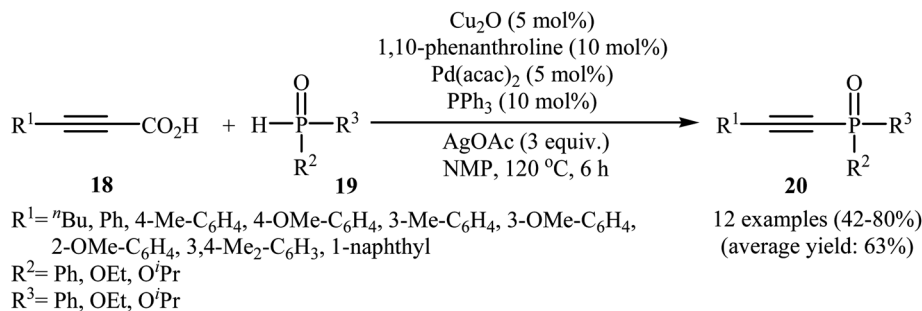


Scheme 7 Synthesis of estrone derivative **17** through a decarboxylative C–P cross-coupling reaction.





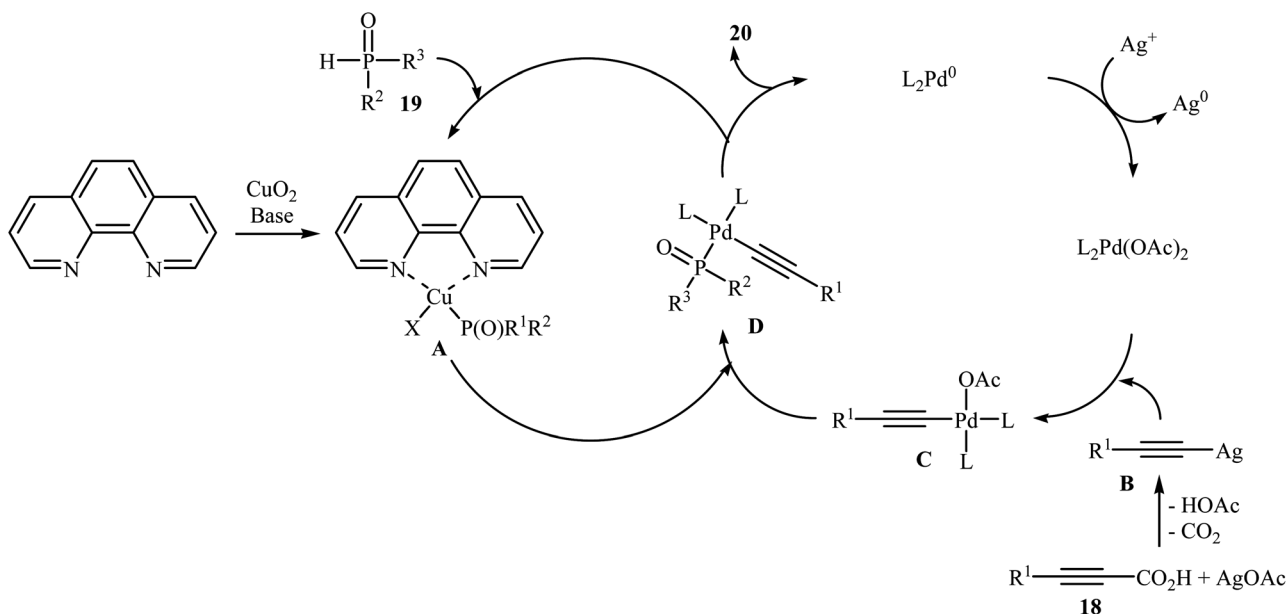
Scheme 8 Mechanism that accounts for the formation of (*E*)-1-alkenylphosphorus compounds 15.



Scheme 9 Cu/Pd-catalyzed decarboxylative C–P cross-coupling of alkynyl acids 18 with P(O)H compounds 19.

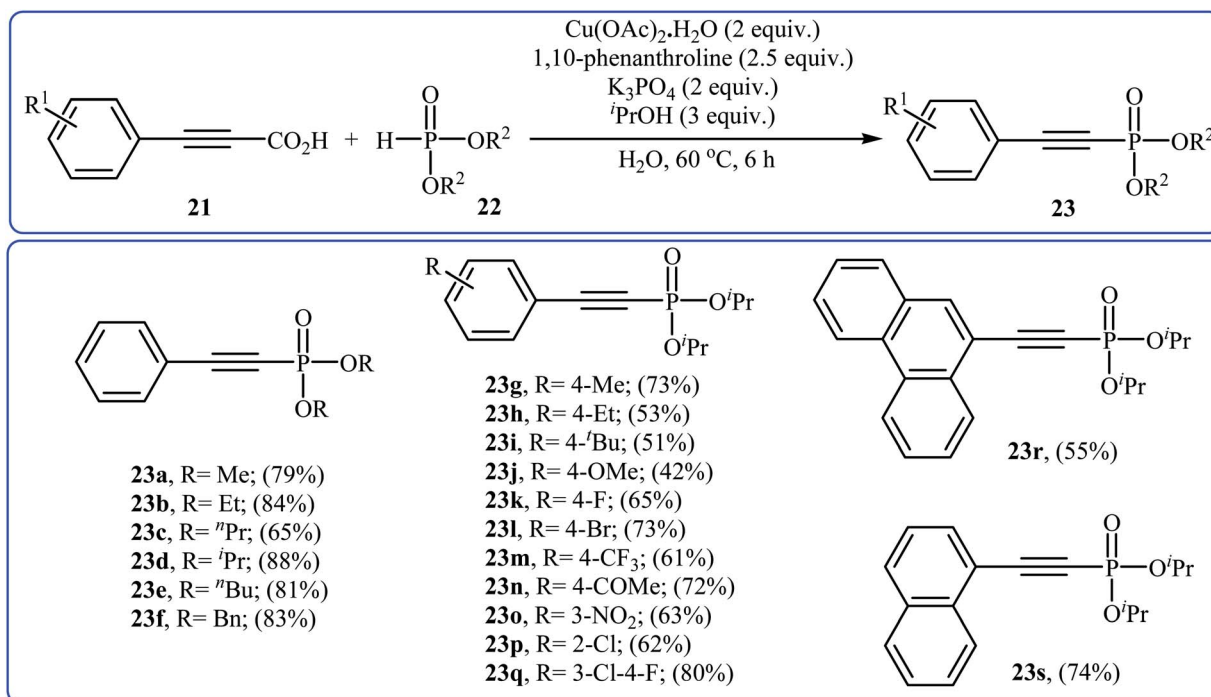
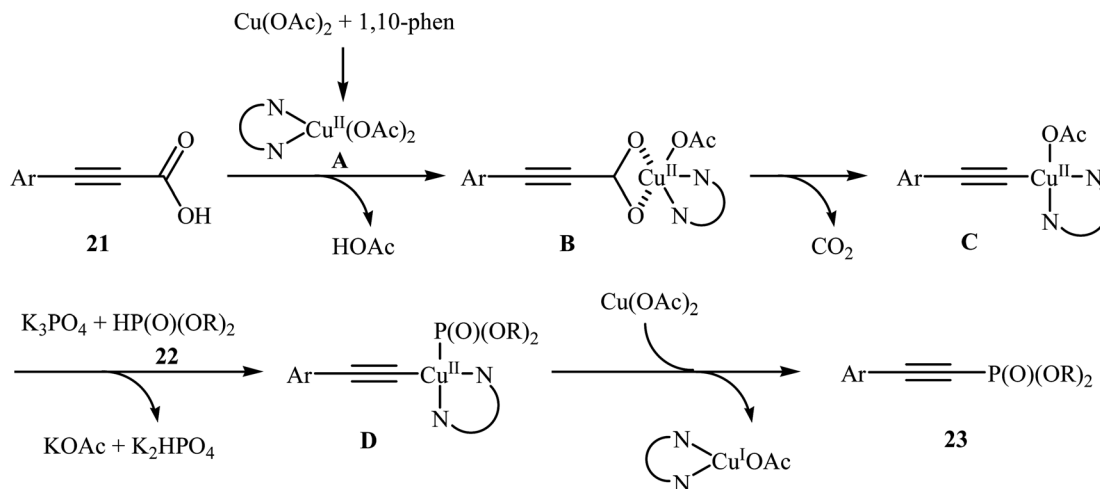
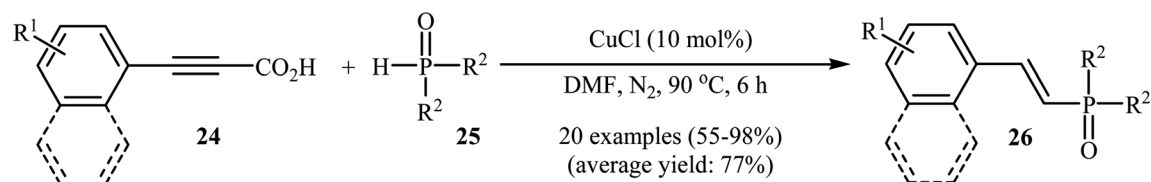
The reaction could also be conducted successfully on a gram scale. However, the reaction did not give good yields with alkyl and heteroaryl alkynyl acids. The proposed mechanism of the reaction by the authors is depicted in Scheme 14. It consists of the following key steps: (i) initial formation of the alkynyl copper intermediate A *via* decarboxylation of alkynyl acid 24 with CuCl and the generation of one molecule of CO₂ and one

molecule of HCl at the same time; (ii) coordination of P(O)H compound 25 (in the form of trivalent phosphine oxide 25') to the intermediate A to form the intermediate B; (iii) migration of a proton from the oxygen atom to the C sp atom in the intermediate B to give a three-membered-ring transition state C; (iv) conversion of intermediate C (in the form of four-centered transition state C') to a thermodynamically more stable



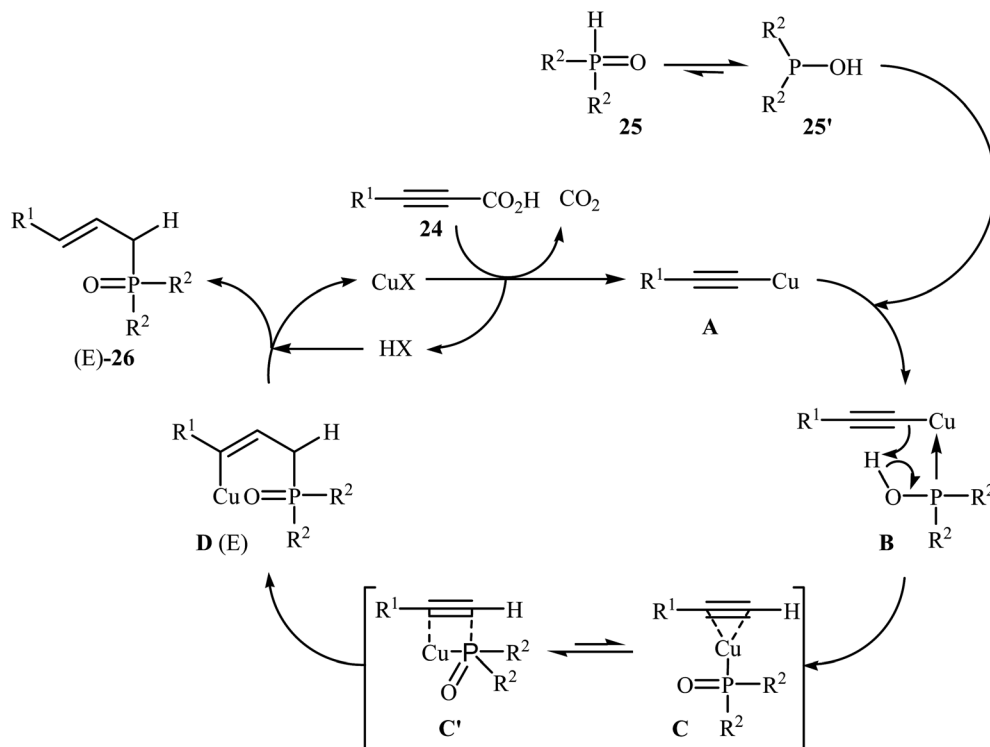
Scheme 10 Mechanism proposed to explain the synthesis of alkenylphosphorus compounds 20.



Scheme 11 Decarboxylative cross-coupling of alkynyl acids **21** with dialkyl H-phosphonates **22** mediated by $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$.Scheme 12 Proposed mechanistic pathways for the formation of alkyne phosphonates **23**.

$\text{R}^1 = \text{H}, 4\text{-Me}, 4\text{-OMe}, 4\text{-CF}_3, 4\text{-OCF}_3, 4\text{-F}, 4\text{-Cl}, 4\text{-Br}, 4\text{-I}, 4\text{-CN}, 4\text{-NO}_2, 4\text{-COMe}, 4\text{-CO}_2\text{H}, 4\text{-CO}_2\text{Et}, 3\text{-Me}, 3\text{-CF}_3, 2\text{-Me}$
 $\text{R}^2 = \text{Ph}, {}^n\text{C}_5\text{H}_{11}, 4\text{-Me-C}_6\text{H}_4$

Scheme 13 Cu-catalyzed decarboxylative cross-coupling of alkynyl acids **24** with H-phosphine oxides **25** for the stereoselective synthesis of (*E*)-alkenylphosphine oxides **26**.

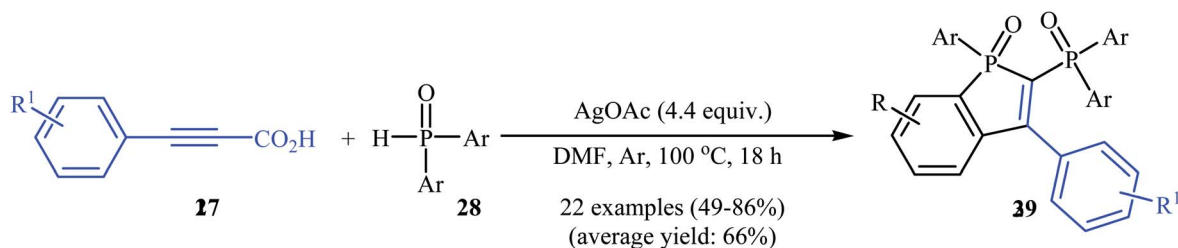


Scheme 14 Mechanistic explanation of the synthesis of (*E*)-alkenylphosphine oxide derivatives **26**.

alkenyl copper intermediate **D** with the *E* configuration; and (v) protonolysis of intermediate **D** with alkyne acid **24** or HCl to generate the desired product **26**.

Recently, the same research team reported an interesting silver-mediated cascade decarboxylative C–P cross-coupling and annulation reaction of alkyne acids **27** with diarylphosphine oxides **28** to form structurally sophisticated 2-phosphinobenzo[*b*]phosphole oxide frameworks **29** (Scheme 15).²¹ The reaction was performed under an argon atmosphere using AgOAc as the oxidant in DMF; it tolerated a number of functional groups (*e.g.*, OMe, OCF₃, F, Cl, Br, CN, CHO, COMe, CO₂H, and CO₂Et) and generally provided highly substituted 2-phosphinobenzo[*b*]phosphole oxides **29** in moderate to high yields. According to mechanistic studies, this reaction proceeded through the formation of an arylolefinyl silver intermediate **A** from the decarboxylative reaction of alkyne acid **27** and AgOAc under heat, following the coordination of this intermediate **A**

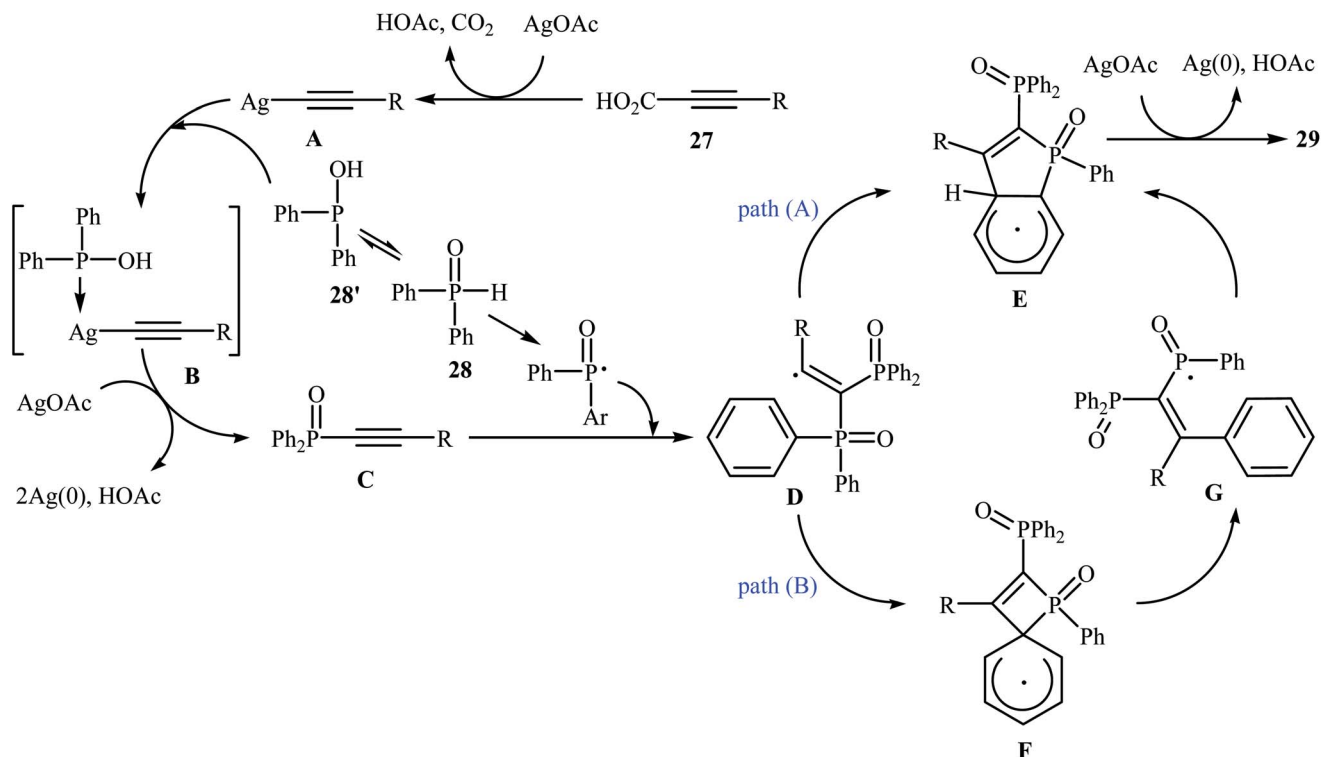
(in the form of the trivalent phosphine oxide **28'**) to give the intermediate **B**, which then underwent silver-mediated oxidative cross-coupling to produce the critical intermediate **C** via two single-electron oxidations. Subsequently, the addition of the diphenylphosphonyl radical (generated from **28**) to the intermediate **C** afforded the alkenyl radical intermediate **D**, which underwent intramolecular addition to the phenyl ring at the *ortho* position of the phosphorus atom to afford the intermediate **E**. Then, the oxidation of this intermediate by AgOAc along with the removal of a proton led to the final product **29**. In another possibility, the alkenyl radical **D** attacked the phenyl ring at the carbon position directly attached to the phosphorus atom to form the intermediate **F**, followed by C–P bond cleavage to give the phosphorus radical **G**. Next, the addition of **G** to the phenyl ring generated the intermediate **E**, which after oxidation, afforded 2-phosphinobenzo[*b*]phosphole oxide frameworks **29** (Scheme 16).



$R^1 = H, 4\text{-Me}, 4\text{-}^t\text{Bu}, 4\text{-Ph}, 4\text{-CF}_3, 4\text{-OMe}, 4\text{-OCF}_3, 4\text{-F}, 4\text{-Cl}, 4\text{-Br}, 4\text{-CN}, 4\text{-CHO}, 4\text{-COMe}, 4\text{-CO}_2\text{H}, 3,5\text{-Me}_2, 3,5\text{-F}_2, 3,5\text{-Cl}_2$
 $Ar = Ph, 4\text{-Me-C}_6\text{H}_4, 4\text{-Cl-C}_6\text{H}_4, 2\text{-Me-C}_6\text{H}_4$

Scheme 15 Ag-mediated cascade reaction of arylpropionic acids **27** with diarylphosphine oxides **28** developed by Gao.





Scheme 16 Mechanistic proposal for the reaction in Scheme 14.

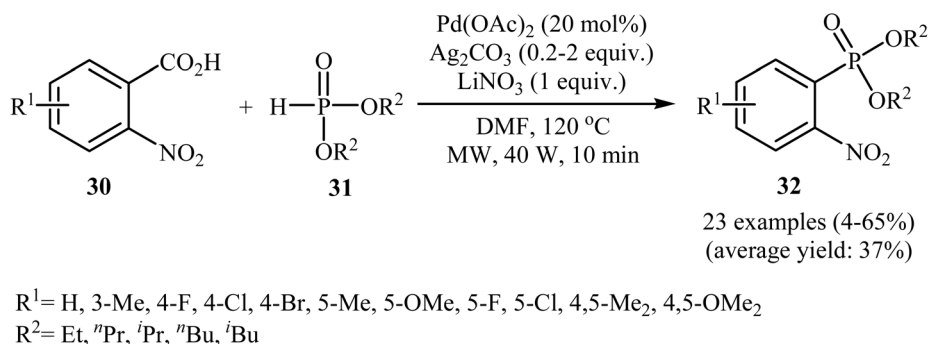
4. Coupling of benzoic acids with P(O)H compounds

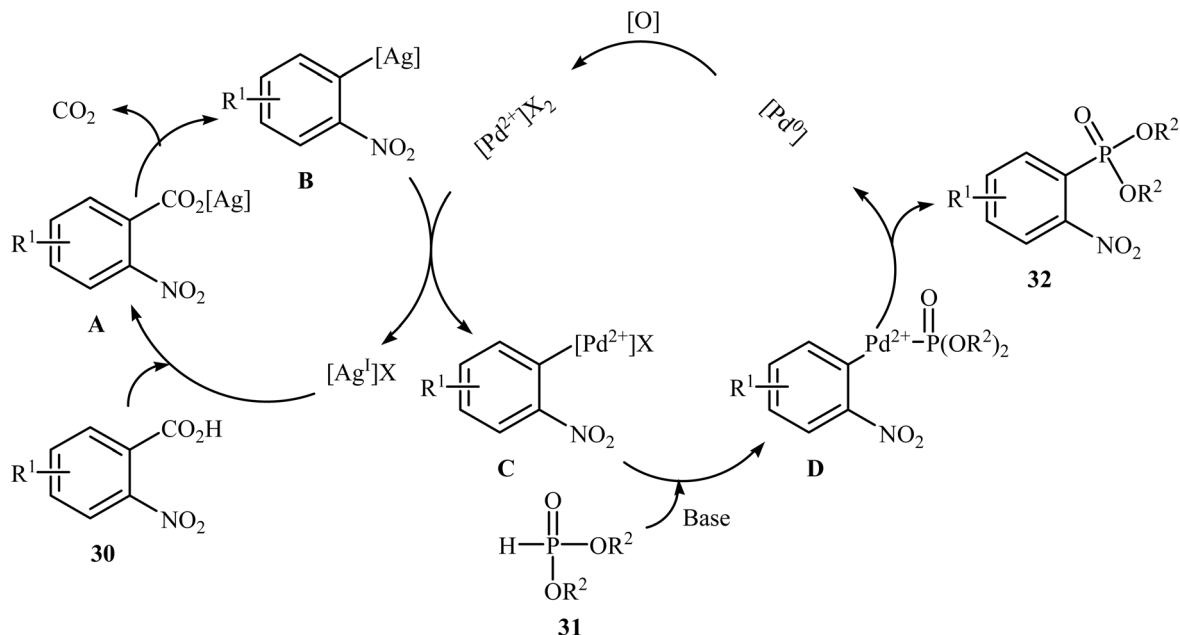
Decarboxylative C–P cross-coupling of benzoic acids with P(O)H compounds has been scarcely studied; in fact, only one example of such a reaction has been reported so far. In this report, Xiao and co-workers showed that the treatment of *ortho*-nitrobenzoic acids **30** with H-phosphonates **31** in the presence of a bimetallic palladium/silver catalytic system [Pd(OAc)₂/Ag₂CO₃] in DMF resulted in the formation of functionalized aryl phosphonates **32** in low to good yields (Scheme 17).²² However, *meta*- and *para*-substituted benzoic acids were inert to this coupling reaction. The results showed that the reaction was not very efficient and general since it had a number of limitations and exceptions. Thus, the development of a novel and efficient catalytic system that improves the efficiency of this interesting coupling reaction is highly desirable. According to the mechanism proposed by

the authors (Scheme 18), this reaction starts with the reaction of silver salt with benzoic acid **30**, leading to the formation of the silver benzoate species **A**. Subsequently, decarboxylation of this intermediate yields an aryl-Ag species **B**; its transmetalation with Pd²⁺X₂ forms an aryl-Pd intermediate **C** along with regeneration of the Ag⁺ salt. Next, ligand exchange of intermediate **C** with H-phosphonate **31** generates the Pd²⁺ complex **D**. Finally, reductive elimination of **D** affords the observed phosphonation product **32** and Pd⁰. Pd⁰ is then oxidized to Pd²⁺ to close the catalytic cycle.

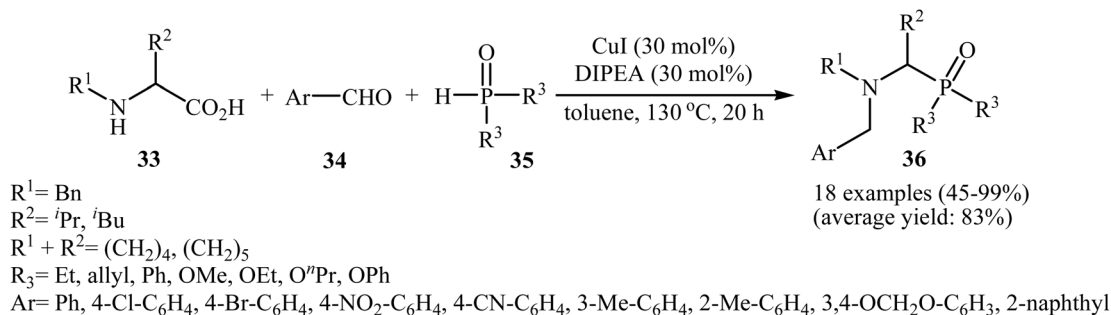
5. Coupling of amino acids with P(O)H compounds

After the pioneering study by Hu and co-workers on decarboxylative coupling of *N*-benzyl-protected proline with diphenylphosphine oxide employing CuCl as the catalyst,¹⁵ the first

Scheme 17 Pd/Ag-catalyzed decarboxylative C–P coupling of *o*-nitrobenzoic acids **30** with H-phosphonates **31**.



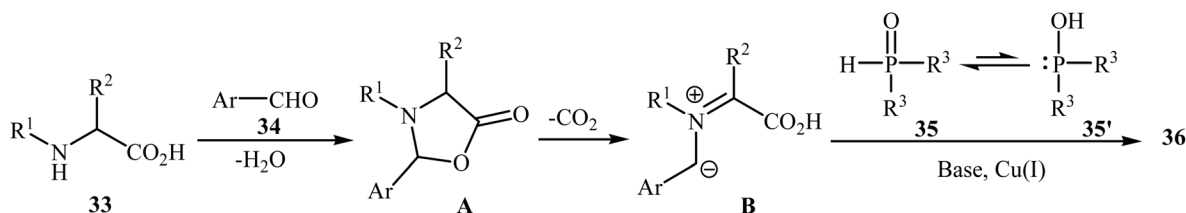
Scheme 18 Plausible mechanism for the formation of aryl phosphonates 32.

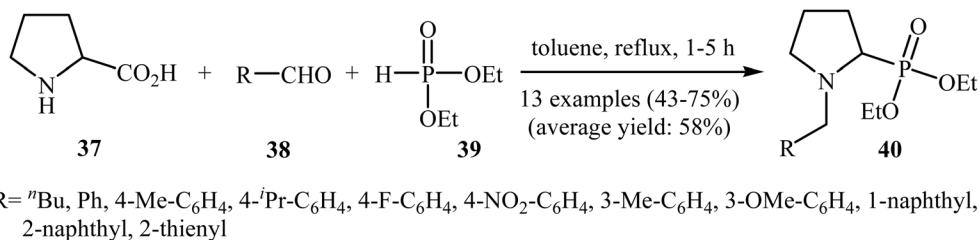
Scheme 19 Cu-catalyzed three-component decarboxylative coupling of natural α -amino acids **33** with aromatic aldehydes **34** and P(O)H compounds **35**.

general report on the synthesis of biologically important tertiary amino phosphorus compounds **36** through three-component decarboxylative coupling of natural α -amino acids **33** with aromatic aldehydes **34** and P(O)H compounds **35** was published in 2011 by Yang *et al.*²³ They carefully studied the effects of reaction variables such as catalyst, additive, solvent, and temperature and found that performing the reaction in toluene at 130 °C using CuI/DIPEA (*N,N*-diisopropylethylamine) combination as the catalytic system was the optimum reaction condition. Various α -amino acids, H-phosphonates, secondary phosphine oxides, and both electron-poor and electron-rich aldehydes reacted well under the optimized reaction

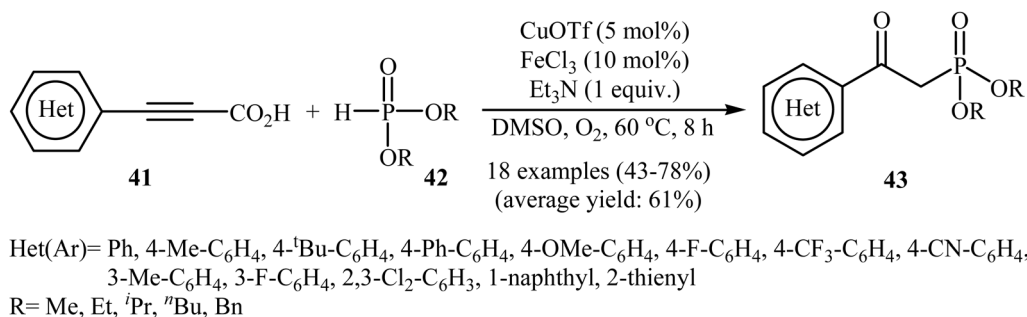
conditions to produce the corresponding tertiary amino phosphorus compounds **36** in moderate to quantitative yields (Scheme 19). The proposed mechanism by the authors is depicted in Scheme 20. First, an oxazolidin-5-one intermediate **A** was formed *via* condensation of an α -amino acid **33** with an aldehyde **34**; this intermediate underwent decarboxylation to generate the azomethine ylide **B**. Finally, the addition of P(O)H compound **35** (in the form of the trivalent phosphine oxide **3'**) to this dipole **B** gave the expected product **36**.

In a closely related investigation, Kaboudin's group showed that many *N*-benzyl-2-(di(ethyl)phosphoryl)pyrrolidine derivatives **40** were successfully formed from the reaction of proline **37**

Scheme 20 Mechanism that accounts for the formation of tertiary amino phosphorus compounds **36**.



Scheme 21 Kaboudin's synthesis of *N*-benzyl-2-(di(ethyl)phosphoryl)pyrrolidine derivatives **40**.



Scheme 22 Oxidative decarboxylative coupling of alkynyl acids **41** with P(O)H compounds **42** developed by Song.

with aldehydes **38** and diethyl phosphite **39** in the absence of any transition metal catalyst by simple heating in toluene (Scheme 21).²⁴ Various aromatic, heteroaromatic, and aliphatic aldehydes were used to establish the general applicability of the method. The results demonstrated that the aromatic aldehydes afforded better yields compared to the aliphatic aldehydes. However, *ortho*-substituted benzaldehydes failed to enter this reaction.

6. Oxidative decarboxylative coupling of carboxylic acids with P(O)H compounds

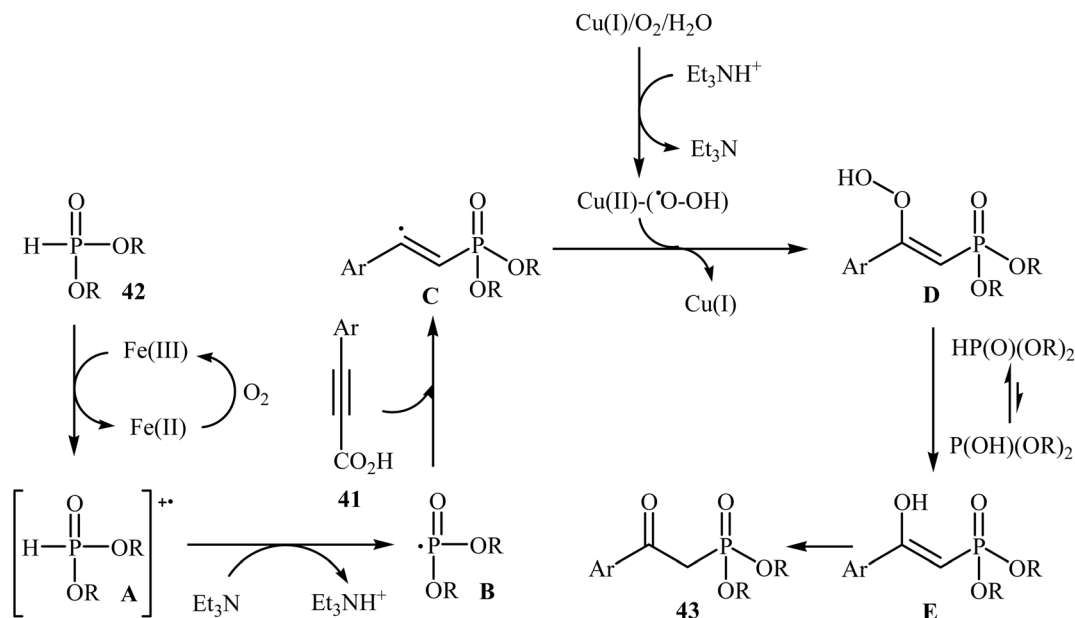
6.1. Alkynyl acids

The possibility of metal-catalyzed oxidative decarboxylative coupling of alkynyl acids with P(O)H compounds was first demonstrated by Song and his research team in 2015,²⁵ and they synthesized a series of β -ketophosphonates **43** from the reaction of propiolate acids **41** with H-phosphonates **42** in the presence of only 5 mol% of CuOTf as the catalyst, 10 mol% of FeCl₃ as the co-catalyst, and 1.0 equiv. of Et₃N as the base in DMSO under oxygen atmosphere (balloon). This Cu/Fe-cocatalyzed reaction tolerated both aryl as well as heteroaryl alkynyl acids and various symmetrical H-phosphonates and provided β -ketophosphonates **43** in fair to good yields (Scheme 22). However, aliphatic alkynyl acids did not function well under these reaction conditions. It should be mentioned that this catalytic system was also successfully applied in the oxyphosphorylation of terminal alkynes with P(O)H compounds. The mechanistic pathway of this oxidative decarboxylative coupling reaction is shown in Scheme 23, and it involved the initial formation of the dialkyl phosphonate cation radical **A** through the transfer of

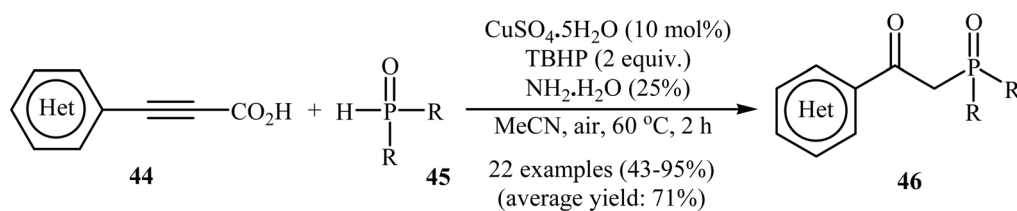
a single electron from iron(II) species to H-phosphonate **42** in the presence of molecular oxygen. Next, deprotonation of this cation radical **A** in the presence of a base gave the dialkyl phosphonyl radical **B**, which then attacked the triple bond of the alkynyl acid **41** to produce the radical intermediate **C**. Subsequently, the reaction of this radical with Cu(II)-(OOH) species (generated from Cu(I) under dioxygen atmosphere) gave the hydroperoxide species **D**. Finally, the removal of oxygen from **D** afforded the observed β -ketophosphonates **43** through the intermediate **E**.

Concurrently, Zhang and co-workers presented efficient copper-catalyzed oxidative decarboxylative coupling of alkynyl acids **44** with H-phosphine oxides **45** to form β -ketophosphine oxide derivatives **46**.²⁶ The results of this investigation revealed that the optimum condition for this reaction was the combination of CuSO₄·5H₂O (10 mol%), TBHP (2 equiv.), and NH₃·H₂O (25%) as the catalytic system using acetonitrile as the solvent at 60 °C. Under optimized conditions, the reaction tolerated various symmetrical and unsymmetrical H-phosphine oxides and a range of aromatic and heteroaromatic alkynyl acids and gave the expected products in moderate to excellent yields (Scheme 24). However, aliphatic alkynyl acids failed to enter the reaction. Mechanistically, this reaction was proposed to be initiated by the formation of *tert*-butoxy and hydroxyl radicals *via* decomposition of TBHP in the presence of Cu(II). Then, the abstraction of a hydrogen atom from H-phosphine oxide **45** by a *tert*-butoxyl radical afforded the phosphorus radical **A**. Meanwhile, the reaction of alkynyl acid **44** with Cu(II) generated a salt of cupric carboxylate **B**. Subsequently, the addition of the phosphorus radical **A** to the α -position of the triple bond of the cupric carboxylate **B** gave the radical intermediate **C**, which was ultimately trapped by a hydroxyl radical to provide the intermediate **D**. The formation of the alkenyl copper

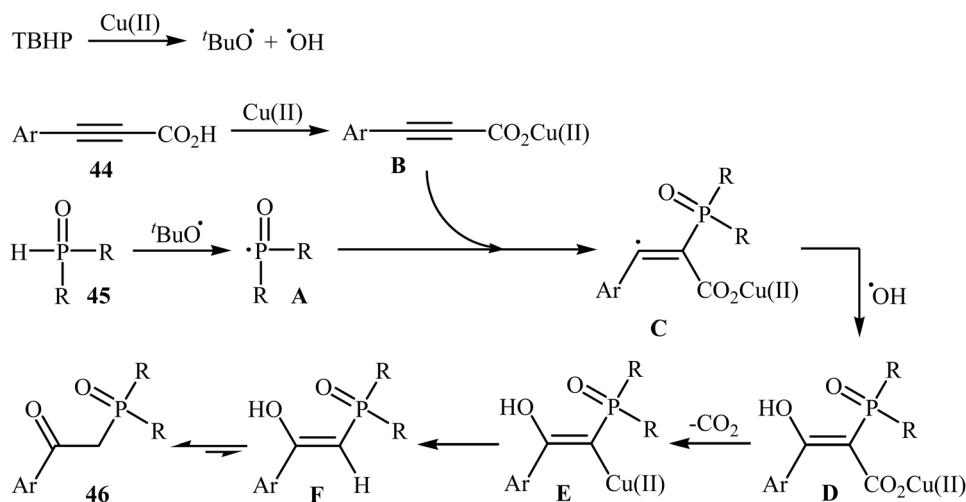




Scheme 23 Mechanistic proposal for the reaction in Scheme 22.



Het(Ar) = Ph, 4-Me-C₆H₄, 4-Ph-C₆H₄, 4-OMe-C₆H₄, 4-OCF₃-C₆H₄, 4-F-C₆H₄, 4-Cl-C₆H₄, 4-Br-C₆H₄, 4-I-C₆H₄, 4-CF₃-C₆H₄, 4-CF₃-C₆H₄, 4-CN-C₆H₄, 4-CO₂Et-C₆H₄, 3-Me-C₆H₄, 3-CF₃-C₆H₄, 3-Br-C₆H₄, 2-Me-C₆H₄, 3,5-Me₂-C₆H₄, 1-naphthyl, 2-thienyl
 R = Ph, 4-Me-C₆H₄, 4-Cl-C₆H₄, 4-Br-C₆H₄

Scheme 24 CuSO₄·5H₂O-catalyzed oxidative decarboxylative coupling of alkynyl acids **44** with H-phosphine oxides **45** into β-ketophosphine oxides **46**.Scheme 25 Plausible mechanism for the formation of β-ketophosphine oxides **46**.

and gave desired products in moderate yields. Moreover, they successfully extended this chemistry to the synthesis of a variety of functionalized β -ketophosphonates *via* a domino Knoevenagel-decarboxylation–oxyphosphorylation sequence from aromatic aldehydes and H-phosphonates.

The synthesis of β -keto phosphorus compounds **52** in good to excellent yields (up to 92%) was also reported by Chen's research team through the oxidative decarboxylative coupling reaction of cinnamic acids **50** with P(O)H compounds **51** by employing $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ as an efficient catalyst and air oxygen as an environmentally benign oxidant (Scheme 27).²⁹ Solvent has a dramatic role in this reaction; among the common solvents (*e.g.*, THF, DCE, DMF, DMSO, MeCN, EtOH, and 1,4-dioxane), acetonitrile was the most effective solvent. Interestingly, the other solvents were completely ineffective. The authors proposed a mechanism for this decarboxylation–oxyphosphorylation reaction in which an acetonitrile-soluble complex $[\text{Cu}(\text{MeCN})_6]^{2+}$ **A**, generated from the copper(II) ion and MeCN, underwent a reaction with air oxygen to form a copper-active-oxygen complex **B**, which then quickly attacked the P(O)H compound **51** to produce the hydroperoxide complex **C** as well as the phosphoryl radical **D**. Subsequently, the addition of radical **D** to cinnamic acid **50** afforded the radical **E**, which in the presence of the hydroperoxide complex **C** yielded a hydroperoxide intermediate **F**. Next, dehydration of this intermediate **F** gave the intermediate **G**. Finally, energetically favorable decarboxylation of intermediate **G** afforded the final products **52** (Scheme 28).

7. Summary and conclusion

Carbon–phosphorus bond construction represents a key step in the synthesis of various medicines, insecticides, ligands, and modified nucleosides and nucleotides. In particular, P(O)–C bond formation reactions have attracted much attention owing to their presence in a number of commercialized drugs such as fosinopril, adefovir, alendronic acid, cidofovir, and brincidofovir. General methods to construct the P(O)–C bond involve transition-metal-catalyzed cross-coupling of organic halides, triflates, or tosylates with P(O)H compounds or the nucleophilic substitution reaction of organometallic reagents with electrophilic P-reagents. Despite significant progress, these methods still suffer from some limitations such as the use of metal reagents, expensive and unstable triflates, environmentally toxic organic halides, and poor tolerance of functional groups. In the last seven years, the decarboxylative C–P cross-coupling reaction between carboxylic acids and P(O)H compounds has emerged as one of the most reliable and robust tools for the construction of P(O)–C bonds.

As illustrated, all three kinds of P(O)–H compounds (H-phosphinates, H-phosphonates, and secondary phosphine oxides) were applicable to this novel coupling reaction. Interestingly, most of the reactions covered in this review could be scaled up to provide multigram quantities of the desired coupling products. These results showed the potential applications of these reactions in industry. Despite all these successes, many challenges still remain to be overcome: (i) the

number of reported examples in this interesting research arena is limited. There is still a further need to study the scope and limitations of this approach for the formation of P(O)–C bonds; (ii) most of the reported decarboxylative C–P cross-coupling reactions are performed at high temperatures; thus, the exploration of milder processes is highly desirable, and (iii) other reactions such as coupling of allylic and benzylic carboxylic acids with various P(O)–H compounds should be explored. We conclude this review by hoping that it will stimulate researchers to carry out further research in this domain.

Conflicts of interest

There are no conflicts to declare.

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