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Phosphorylation of C–H bonds of aromatic compounds using metals and metal complexes

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Key achievements and current trends in the development of methods for phosphorylation of aromatic C–H bonds catalyzed by metal salts and complexes are considered. The most important and promising approaches of the last decade, including those concerning the synthesis and properties of arylphosphonates, are distinguished. Methods for the introduction of a phosphonate group into non-activated and functionally substituted aromatic compounds and heteroaromatic molecules and phosphorylation–cyclization reactions involving acetylenes, 2-isocyanobiphenyls and alkynoates are analyzed. The possibilities of ligand-directed phosphorylation of compounds with aromatic C–H bonds and presumed mechanisms and intermediates in the C–P bond formation reactions are considered. The potential of this extensively developing research trend in organic and organoelement chemistry is highlighted.
The bibliography includes 263 references.

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I. Introduction

Carbon–phosphorus bond formation catalyzed by transition metals is considered to be an important route to phosphorus compounds of various types, namely, phosphonates, phosphinates, phosphine oxides, phosphines, *etc*. Many of these compouds are widely used in the organic synthesis,[1–6] medicinal chemistry,[7–9] some of them show biological activity,[10,11] are used in the chemistry of materials[12–14] or as universal ligands in catalytic reactions.[15–19]

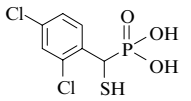
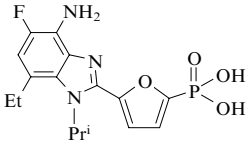
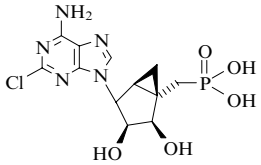
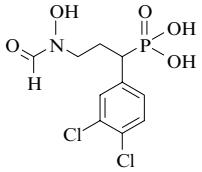
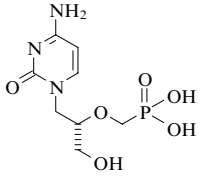
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Phosphorus-containing moieties, such as phosphonic acid residue $RP(O)(OH)_2$, are a part of numerous structurally diverse molecules of natural compounds involved in different biological proccesses. Phosphonic acid moieties are also present in many potential pharmaceutical agents having anticancer, antibacterial or antiviral activity including anti-HIV agents. The presence of the phosphonic acid moiety in a molecule provides unique binding interactions with the biological target due to its trigonal-pyramidal geometry, multichelating properties and possible dual functioning both as a proton acceptor and donor at physiological pH.

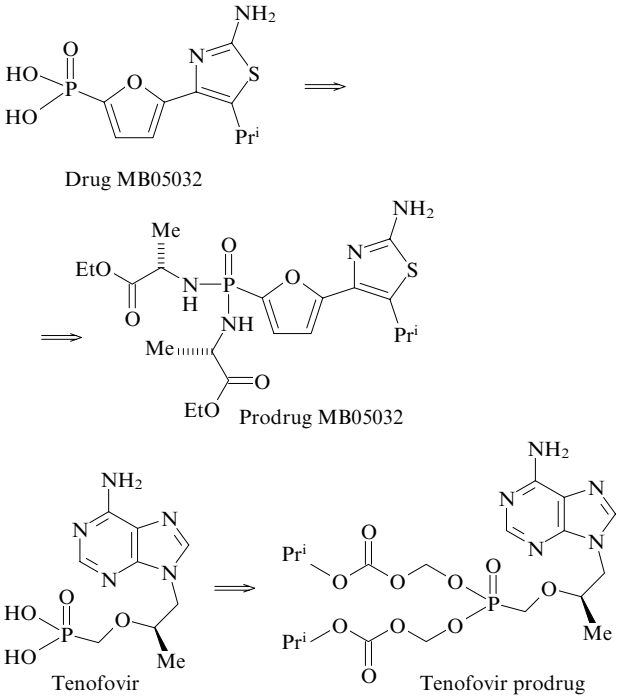
As compared with phosphorus compounds comprising reactive N–P, S–P or O–P bonds, phosphonates are more valuable reagents due to higher stability of the C–P bond against hydrolysis, thermal decomposition and photolysis.[20] The application of phosphorus-containing moieties, mainly, phosphonic acid derivatives, for development of pharmaceutical agents proved to be very successful in many cases. In the past decade, novel drugs for treatment of various diseases such as diabetes,[21,22] asthma,[23] inflammatory disorders,[24–26] heart failure,[27] cancer,[21,28–30] malaria[31] and AIDS[32] were discovered. A number of

Table 1. Examples of potential pharmaceutical agents containing a phosphonic acid residue.

Structure	Biological target and function	Disease	Ref.
	metal-β-lactamase inhibitor	for co-treatment with antibiotics	26
	5′-adenosine monophosphate inhibition	diabetes mellitus type II	22
	receptor P2X activation	heart failure	27
	inhibitor of *Plasmodium falciparum*	malaria	31
	chain-terminating agent at DNA polymerase (reverse transcriptase) level	viral infections (papillomavirus, poxviruses, polyomaviruses, *etc*.)	33, 34

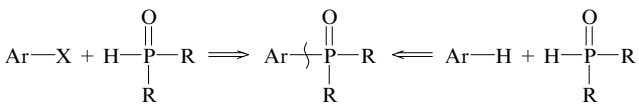
examples are given in Table 1. When a candidate drug showed low bioavailability, the synthetic strategy for preparing a prodrug bearing the phosphonic acid moiety was developed (Scheme 1).[33,35] Thus, phosphonic acid diamide MB06322 is a prodrug of fructose 1,6-bisphosphatase inhibitor MB05032,[34,36] and phosphonic acid diester is the prodrug for Tenofovir developed for the therapy of HIV infection.[37] Two enzymes are needed to release MB05032 from its prodrug MB06322.

Scheme 1



In view of the synthetic value of arylphosphonates, the development of methods for C–P bond construction is of ongoing interest.[16,38–42] Conventional methods for the C–P bond formation are based on the reaction of organometallic reagents with electrophilic P-reagents, *e.g.* $Ph_2P(O)Cl$. Starting with the pioneering study of Hirao *et al*.[43] published in 1981, the transition metal-catalyzed cross-coupling of aryl halides,[44–51] triflates,[52] tosylates,[53] diazonium salts[54] and boronic acids[55–57] with dialkyl H-phosphonates became an available and useful tool for the $C(sp^2)$–P bond formation (Scheme 2).

Scheme 2



X = I, Br, Cl, $B(OH)_2$, *etc*.

In recent years, studies and interest have been focused on the transiton metal-catalyzed C–H-phosphorylation and radical aromatic phosphorylation, which provide a direct and atom-economic approach to P-substituted arenes (see Scheme 2) and are detailed in the present review. However, it should be noted that in most studies, organic halides are used as aromatic substrates, while the examples of the C–H bond substitution with the hydrogen atom being the leaving group are far fewer. In reviews devoted to the metal-catalyzed C–P bond formation published in recent years,[16, 17, 58] virtually no consideration is given to aromatic C–H bond phosphorylation. Catalytic methods, the role of which is of particular importance for green chemistry, came into active development rather recently.

The regularly held ACS GCI Pharmaceutical Round-Table with participation of reputable organizations such as the ACS Green Chemistry Institute (USA),[59] world top pharmaceutical corporations (Amgen, AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Cubist Pharmaceuticals, Eli Lilly and Company, F Hoffman-La Roche, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, *etc.*) and American Chemical Society has placed a particular emphasis on the topicality and good prospects of the search for environmentally acceptable methods of C–H activation of aromatic compounds including aromatic C–H bond phosphorylation.[59, 60] Direct functionalization of C–H bonds provides the most efficient path of transformation of molecules, which makes it highly attractive.[61–75] Although a wide range of such reactions have now been accomplished, including those catalyzed by transition metals, the number of examples of successful formation of the carbon–phosphorus bonds is moderate.

A major challenge in accomplishing the C–H substitution, in partucular, that with P-nucleophiles, is presumably the necessity to use an oxidant in the reductive elimination step and, furthermore, a separate screening is required for each pair of substrates. A difficulty of the catalytic chemistry involving Pd^{II}/Pd^{IV} compounds is that the co-oxidants used are either expensive (silver or other metal salts) or hard-to-separate from the reaction mixture (organic oxidants with high molecular mass), and, furthermore, all of them are insufficiently selective. In recent decades, studies dealing with transition metal-catalyzed functionalization of inert C–H bonds have been extended.[61–79]

The studies in homogeneous catalysis in which transition metals catalyze C–H functionalization may be generally subdivided into two trends. They reflect different approaches and aims and consequently have different tasks and possibilities. One approach implies reactions of completely unfunctionalized aromatic and aliphatic hydrocarbons (primary functionalization). The substrates are nonpolar and hydrophobic and, therefore, they weakly interact with polar metal-containing particles. To overcome this weak metal affinity and trigger metal-mediated C–H cleavage, hydrocarbon substrates are often used in a large excess (*e.g.* as solvents). Since the primary functionalization requires highly reactive metal particles, it is often difficult to achieve a control over chemoselectivity and avoid excessive functionalization.

The second approach to C–H-functionalization suggests the use of a substrate already bearing one (or more) functionalities and is reffered to as 'further functionalization'. One of the advantages of this approach is that the existing functionality (or functionalities) may be used to chelate metal catalyst, which finally occupies the position necessary for the selective cleavage of the C–H bond. The pre-coordination may overcome the inert nature of the C–H bonds, increasing the effective concentration of the substrate, so that there is no need to apply it as a solvent. From the synthetic viewpoint, it is desirable to use a functional group inherent in the substrate, so as to avoid the excessive steps of introduction and removal of the external directing group. Thus, the amplification of a molecule may be accomplished in one step through stereo- and site-selective introduction of another functionality. Although the reactivity also presents a serious challenge (as for the primary functionalization), functionalization strategies are generally different. In the further functionalization, the main task is the search for novel reactions proceeding with a predictable selectivity involving particular substrates bearing several functions and common structural fragments.

Many transition metals, including Pd, are involved in stoichiometric ligand-directed processses of C–H-activation (known also as cyclometallation reactions); however, for phosphorylation, this strategy is not very often used. Except for the general problems inherent in C–H functionalization, substitution of phosphorus-containing groups for hydrogen is faced with additional difficulties, which often negate all the efforts of researchers. They are associated with low reactivity of substrates, difficulties in understanding the mechanism, challenges of the reductive elimination from the intermediate σ^H-adducts obtained from P-nucleophiles, strong coordination ability of phosphorus reagents deactivating the catalyst. Direct C–H phosphorylation presents an attractive example of novel atom-economy and synthetically promising trend in modern organic and organoelement chemistry. In Russia, the obvious leaders in the field of C–H functionalization are research groups of Academicians V N Charushin and O N Chupakhin.[80–83]

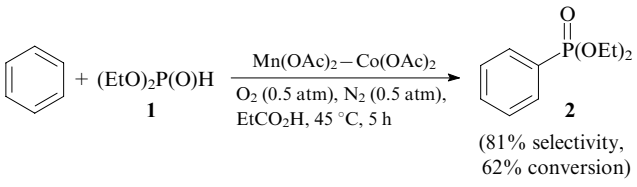
This review presents a discussion of the results of recent investigations of $C(sp^2)$–H bond phosphorylation involving metal salts and their complexes concerning primarily aromatic compounds, since the metal-catalyzed synthesis of phosphorus-containing alkenes and alkynes was detailed and summarized in recent reviews.[16, 17, 60] Particular attention was given to the investigations of the last five years. Since publications dealing with most of reactions described here are related to this period, studying of reaction mechanisms is in the early stage and in many instances, only tentative conclusions are provided. This hampers categorization of the data in terms of reaction mechanisms. In most cases, radical phosphorylation pathway is proposed (for benzenes, heterocyclic substrates, coumarins, *etc.*). However, often, especially for reactions involving directing groups (phenylpyridines, benzamides bearing 8-aminoquinoline moiety as a bidentate directing group), experimental data rather attest to a nonradical, more complex process, presumably involving metals in high oxidation states (Pd^{III}, Cu^{III}). In the present review, particular attention is focused on the elucidation of mechanisms of phosphorylation of each group of substrates by the catalytic systems chosen for them, as this knowledge allows one to predict the reactivity of novel substrates and perform the targeted choice of catalysts for the functionalization of various C–H compounds.

II. Phosphorylation of benzene and substituted benzenes

Dialkyl arylphosphonates are important intermediates in the synthesis of pesticides and biologically active compounds.[1,2,84,85] Several known synthetic approaches to dialkyl arylphosphonates have already beed recognized as classical. Among them, the most common choice is the Michaelis–Arbuzov reaction.[86–89] Photolysis of iodobenzenes in the presence of trialkyl phosphates affords arylphosphonates in good yields.[90,91] Jason and Fields[92] reported a free-radical phosphonation of naphthalene with diethyl H-phosphonate using *tert*-butyl peroxide as a radical initiator. Chemical phosphonation of arenes was accomplished under the action of $(NH_4)_2[Ce(NO_3)_6]$ (CAN, see Ref. 93) or $Na_2S_2O_8$ and $AgNO_3$.[94]

In 2006, Ishii and co-workers[95] proposed a catalytic $Mn^{II}-Co^{II}-O_2$ redox system for the phosphonation of benzene (or substituted benzenes) with dialkyl H-phosphonates, such as $(EtO)_2P(O)H$ (**1**), under mild conditions (Scheme 3). This is the first example of successful phosphonation of benzene with dialkyl H-phosphonate *via* a radical catalytic process.

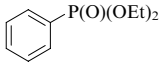
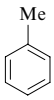
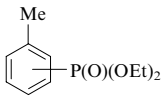
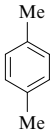
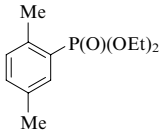
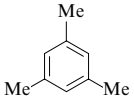
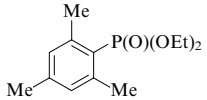
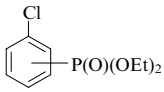
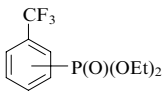
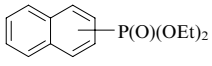
Scheme 3



Optimal phosphonation conditions have been found. The reaction of benzene (2 mmol) with diethyl H-phosphonate (**1**) (6 mmol) in the presence of $Mn(OAc)_2$ (5 mol.%) and $Co(OAc)_2$ (1 mol.%) under O_2 (0.5 atm) and N_2 (0.5 atm) atmosphere in propionic acid at 45 °C for 5 h affords diethyl phenylphosphonate (**2**) with a selectivity of 81% and a small amount of disubstituted product (9%). The yield of product **2** decreased significantly in the absence of $Co(OAc)_2$ in the catalytic system, and the absence of $Mn(OAc)_2$ resulted in no phosphonation at all. The same reaction under argon (1 atm) resulted in the recovery of the starting phosphite **1**. However, phosphonate **2** was obtained with a high selectivity (89%) in air, though the conversion of benzene was low (38%). At the same time, in a pure oxygen (1 atm), the selectivity of the reaction was noticeably lower. Optimal temperature was in the range of 45–60 °C, with no reaction at 25 °C.[95]

The addition of AcOK promotes the benzene phosphonation with phosphite **1**; therefore, the amounts of $Mn(OAc)_2$ and $Co(OAc)_2$ can be reduced. Surprisingly, the addition of AcOK induces the reaction even at room temperature to give phosphonate **2** with a selectivity of 92% though with a low conversion (25%). With radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) (0.1 mmol, 5 mol.%), there was no reaction. This fact implies that the phosphonation proceeds by a radical mechanism. Like diethyl H-phosphonate (**1**), dimethyl H-phosphonate (**3**) also reacted with benzene to give dimethyl phenylphosphonate with a selectivity of 87% at a benzene conversion of 68%, but diisopropyl H-phosphonate was less reactive than compound **1**, affording diiso-

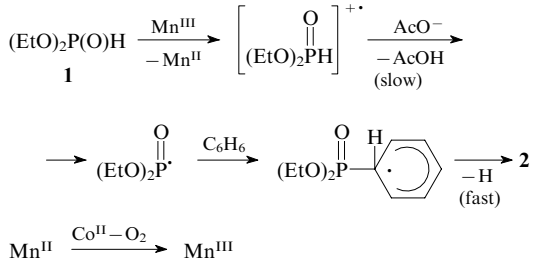
Table 2. Phosphonation of benzene and substituted benzenes with diethyl phosphite in the presence of $Mn(OAc)_2-Co(OAc)_2-O_2$ catalytic system.[95]

Substrate	Solvent	Time /h	Conversion (%)	Product	Selectivity (%)
	$EtCO_2H$	5	62		81
	AcOH	3	56		90 (*ortho* : *meta* : : *para* = 59 : 24 : 17)
	AcOH	5	58		90
	$EtCO_2H$	15	59		82
	$EtCO_2H$	15	69		80
	AcOH	15	71		89
	AcOH	15	56		89 (α : β = 87 : 13)

propyl phenylphosphonate with a selectivity of 83% at a benzene conversion of 30%. Relying on this data, reactions of various substituted benzenes with diethyl H-phosphonate were carried out under the chosen conditions (Table 2). In reactions with toluene, *p*-xylene, mesitylene, chlorobenzene, trifluorobenzene and naphthalene, reasonably good selectivity and conversion values were attained. Naphthalene was phosphonated with diethyl H-phosphonate to give a mixture of diethyl naphthylphosphonate regioisomers in 87 : 13 isomer ratio (see Table 2).[95]

In order to elucidate the pathway of this phosphonation rection, the authors used a 1 : 1 mixture of benzene and deuterated benzene and studied its reaction with diethyl H-phosphonate under the same conditions as in Scheme 3.[95] The products **2** and **2**-D_5 formed in ~1 : 1 ratio and no isotope effect was observed in the reaction. This demonstrates that the loss of the hydrogen atom or a proton from the benzene molecule is not the rate-limiting step. The fact that the addition of a weak base (AcOK) considerably accelerates the reaction indicates that proton elimination may involve AcO^- and occur in the subsequent reaction steps. A reaction mechanism comprising H^+ elimination under the action of AcO^- from the diethyl phosphonate radical cation generated through a Mn^{III} mediated single-electron oxidation of diethyl H-phosphonate **1** was proposed (Scheme 4).

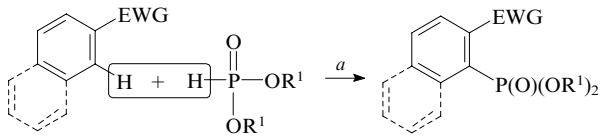
Scheme 4



Thus, catalytic phosphonation of arenes with dialkyl H-phosphonates follows a radical mechanism involving the $Mn^{II}-Co^{II}-O_2$ redox system. This method provides a simple approach to arylphosphonates, which were hitherto elusive; however, it has a drawback of low regioselectivity.[95]

Phosphorylated benzene derivatives bearing electron-withdrawing or electron-donating substituents in the ring are of special interest due to a wide range of practically valuable properties. Therefore, direct phosphorylation of such derivatives presents a special subject of investigations. Thus, just recently, in 2013, a highly effective regioselective $Ag^I-K_2S_2O_8$-catalyzed phosphonation of aromatic substrates bearing electron-withdrawing groups (EWG) was developed by Cheng's research group.[96] This reaction smoothly proceeds for *N*,*N*-dialkylbenzamides, *N*,*N*-dialkylbenzenesulfonamides and nitrobenzene. The method is suitable for a wide range of substrates and proposes a simple design of C–P bonds (Scheme 5).

Scheme 5

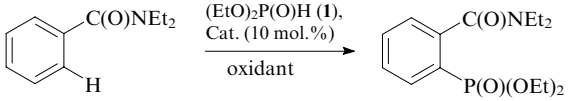


EWG = $C(O)NR^2_2$ (R^2 = Me, Et, Pr^n, Pr^i, Bu^n), $SO_2NR^3_2$ [R^3 = Me, Et, Bu^n; R^3-R^3 = $(CH_2)_2O(CH_2)_2$], NO_2, NHAc;
(*a*) Ag_2SO_4 (10 mol.%), $K_2S_2O_8$ (3.0 equiv.), MeCN–H_2O (1 : 1), 70–90 °C

To recall the history, back in 1985, Effenberger and Kottmann[94] reported the formation of C–P bonds *via* arene coupling with diethyl H-phosphonate using $Na_2S_2O_8$ and $AgNO_3$. However, only arenes with electron-donating groups (EDG) were suitable for this reaction. In 2006, Zhang and co-workers[97] succeeded in developing noncatalytic cross-coupling reactions between heteroarenes and dialkyl H-phosphonates using $Mn(OAc)_3$ as an oxidant. It is noteworthy that these transition metal-catalyzed phosphonation reactions of arenes accompanied by dehydrogenation proceed mainly for arenes bearing electron-donating groups. However, before the study of Cheng and co-workers,[96] there were no reported cross-couplings of dialkyl H-phosphonates with arene substrates bearing strong electron-withdrawing groups such as n-alkyl-substituted amides, *N*,*N*-dialkylbenzenesulfonamides and nitro groups. Thus, the progress of this synthetic strategy was highly desirable.

In relation to model substrates, *N*,*N*-diethylbenzamide and diethyl H-phosphonate (**1**), the authors studied the effect of catalyst, oxidant and solvent nature on the efficacy of the cross-coupling reaction in question (Table 3).[96] The yield of the C–H phosphorylation product was found to substantially increase when Ag^I compounds were used as catalysts (see Table 3, runs 4–7). Other metal salts such as

Table 3. Optimization of phosphonation conditions.[96]



5

Run	Catalyst (10 mol.%)	Oxidant	Solvent	Time /h	Yield (%)
1	$Pd(OAc)_2$	$K_2S_2O_8$	MeCN	10	15
2	CuI	$K_2S_2O_8$	MeCN	24	10
3	$FeCl_2$	$K_2S_2O_8$	MeCN	24	5
4	Ag_2SO_4	$K_2S_2O_8$	MeCN	24	41
5	Ag_2CO_3	$K_2S_2O_8$	MeCN	24	28
6	Ag_2O	$K_2S_2O_8$	MeCN	24	19
7	AgOAc	$K_2S_2O_8$	MeCN	24	32
8	Ag_2SO_4	$K_2S_2O_8$	MeCN–H_2O	24	81
9	Ag_2SO_4 (see [a])	$K_2S_2O_8$	MeCN–H_2O	1	64
10	Ag_2SO_4 (see [b])	$K_2S_2O_8$	MeCN–H_2O	1	81
11	Ag_2SO_4	$K_2S_2O_8$	MeCN–H_2O	10	73
12	Ag_2SO_4	TBHP	MeCN–H_2O	4	traces
13	Ag_2SO_4	$PhI(OAc)_2$	MeCN–H_2O	4	"
14	Ag_2SO_4	DTBP	MeCN–H_2O	4	"
15	Ag_2SO_4	$K_2S_2O_8$	CH_2Cl_2–H_2O	24	47
16	$AgNO_3$	$K_2S_2O_8$	CH_2Cl_2–H_2O	1	76
17	$Mn(OAc)_3$	–	AcOH	24	traces
18	$Mn(OAc)_2$	$Co(OAc)_2$	AcOH	24	"

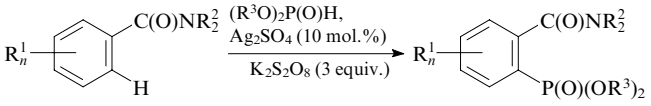
[a] 5 mol.%; [b] 20 mol.%.

CuI and $FeCl_2$ proved to be far less active catalysts under the same conditions (runs 2 and 3). Subsequently, various oxidants including *tert*-butyl hydroperoxide (TBHP), $PhI(OAc)_2$ and di-*tert*-butyl peroxide (DTBP) (see Table 3, runs 12–14) were also studied, but the expected product was not obtained. Thus, $K_2S_2O_8$ was shown to play a crucial role in the said C–P coupling reaction.

Interestingly, the target product **5** is formed in high yield (81%) with Ag_2SO_4 (10 mol.%) and $K_2S_2O_8$ (3.0 equiv.) in MeCN–H_2O (1 : 1; see Table 3, run 8). This product was also obtained in 47% yield in CH_2Cl_2–H_2O (1 : 1; run 15). When Ag_2SO_4 was added in amounts of 5 mol.% and 20 mol.%, phosphonate **5** was isolated in 64% and 81% yields, respectively (runs 9 and 10). In the case of catalysis by $AgNO_3$, the phosphorylation product was obtained in 76% yield in CH_2Cl_2–H_2O (1 : 1; run 16). In the presence of $Mn(OAc)_2$–$Co(OAc)_2$ and $Mn(OAc)_3$ as catalysts, only a minor amount of the product is formed (runs 17 and 18). Thus, the optimal conditions for regioselective C–P bond formation are as follows: Ag_2SO_4 catalyst (10 mol.%), $K_2S_2O_8$ (3.0 equiv.) as an oxidant and a MeCN–H_2O (1 : 1) mixture as a solvent at 90 °C.[96]

To evaluate the synthetic potential of the reaction, a variety of *N*,*N*-dialkylbenzamides were chosen as substrates for phosphonation (Scheme 6).[96] Under standard conditions, the products were obtained in reasonably high yields. It should be noted that the presence of electron-donating groups and most of electron-withdrawing groups in the aromatic ring does not hamper the C–P coupling reaction; however, in the case of electron-donating substituents, the yields are higher. Using *N*,*N*-diethyl-2-naphthamide as a substrate, only moderate yield (55%) was attained, while replacement of the chlorine atom substituent by bromine improves slightly the substrate reactivity in the phosphonation reaction. In addition to diethyl H-phosphonate, dimethyl, diisopropyl and di-n-butyl H-phosphonates are effective.[96]

Scheme 6

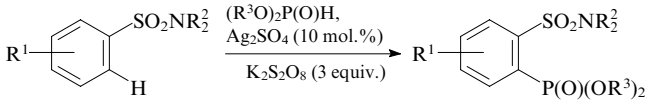


R^1_n	NR^2_2	R^3	Yield (%)	R^1_n	NR^2_2	R^3	Yield (%)
H	NEt_2	Et	77	4-Me	NEt_2	Et	80
H	NMe_2	Et	73	4-Cl	NEt_2	Et	61
H	NPr^i_2	Et	79	4-Br	NEt_2	Et	64
H	NPr^n_2	Et	82	H	NEt_2	Bu^n	79
H	NBu^n_2	Et	72	H	NEt_2	Me	81
H	morpho-lino	Et	H	H	NEt_2	Pr^i	80
				3,4-benzo	NEt_2	Et	55

The authors[96] have also examined the scope of the C–P coupling reaction by changing the directing groups and substrates. As illustrated in Scheme 7, *N*,*N*-dialkylbenzenesulfonamides readily react with dialkyl H-phosphonates to form the C–P bond with high regioselectivity in moderate to good yields (59%–82%).

Under identical conditions, *N*-phenylacetamide and nitrobenzene react with diethyl H-phosphonate to afford

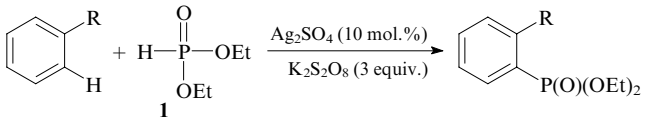
Scheme 7



R^1	NR^2_2	R^3	Yield (%)	R^1	NR^2_2	R^3	Yield (%)
4-Me	NEt_2	Et	69	H	NBu^n_2	Et	79
4-MeO	NEt_2	Et	75	H	NBu^n_2	Bu	76
H	NEt_2	Me	67	H	NMe_2	Et	75
H	NEt_2	Pr^i	78	4-Me	morpho-lino	Et	59
H	NPr^n_2	Et	82				

the corresponding phosphonation product in a moderate yield (Scheme 8).[96]

Scheme 8

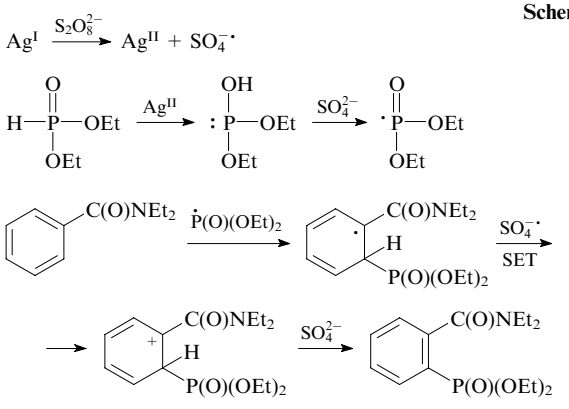


R = NHAc (1 h, 54% yield); NO_2 (12 h, 50%)

The proposed mechanism of regioselective C–P bond formation is shown in Scheme 9. The addition of the radical scavenger (2,2,6,6-tetramethylpiperidine *N*-oxide, TEMPO) to the system comprising *N*,*N*-diethylbenzamide and diethyl H-phosphonate results in a sharp decrease in the reaction rate and product yield under standard coupling conditions, thus indicating a free radical process. According to several previous reports and experimental data, Cheng and co-workers [96] suggested that Ag^I salt and the persulfate anion form an unstable Ag^{II} compound reacting subsequently with diethyl H-phosphonate to generate an intermediate radical cation. After proton elimination, the latter may give a free phosphonyl radical. A key step is the addition of the radical to *N*,*N*-diethylbenzamide to form unconfirmed intermediates; finally, deprotonation results in the target product of the C–H-phosphorylation.[96]

Thus, Cheng and co-workers succeeded in developing a highly regioselective Ag^I salt-catalyzed dehydrogenation–cross-coupling reaction for the direct phosphonation of

Scheme 9



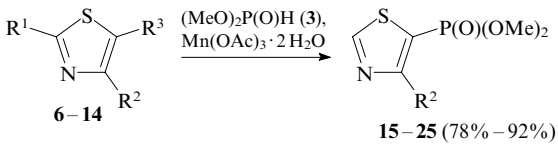
SET is single electron transfer

arenes bearing an electron-withdrawing group.[96] A variety of products may be synthesized using Ag_2SO_4 as a catalyst and $K_2S_2O_8$ as an oxidant. This method has a broad synthetic scope and provides a relatively convenient formation of the C–P bonds.

III. Phosphorylation of heterocyclic aromatic compounds

Zhang and co-workers[97] suggested a new method for direct phosphonation of thiazoles, furans and pyrroles. The reactions of heteroaromatic compounds (particularly, thiazoles **6**–**14**) with dimethyl or diethyl H-phosphonates and $Mn(OAc)_3 \cdot 2H_2O$ as a catalyst under mild conditions were found to afford phosphonates (including compounds **15**–**25**) in high yields and with a good regioselectivity (Scheme 10, Table 4). This work appeared nearly simultaneously with the study of Ishii and co-workers,[95] which is considered to be the first example of phosphonation of aromatic (but not heteroaromatic) compounds using the $Mn(OAc)_2-Co(OAc)_2-O_2$ redox system. In their method, the researchers cited used 2,4-dimethylthiazole (**6**) as a model compound. The optimized phosphonation procedure is as follows: compound **6** (2 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (6 mmol) are added to a solution of dimethyl H-phosphonate (**3**) (4 mmol) in 10 ml of AcOH. Then the mixture is maintained at 80 °C, the reaction being completed in 3 h. The general procedure of phosphonylation was employed for the reactions of 4-methyl-2-ethylthiazole (**7**) and 2-methyl-4-phenylthiazole (**8**) (see Table 4). The corresponding products were obtained in 90% and 87% yields. The reaction with 2-methoxythiazole (**9**) was used to estimate the regioselectivity. Surprisingly, phosphonation of 2-methoxythiazole proceeded regioselectively to position 5 in a yield of up to 90% (see Table 4, run 4). The reactions with 2-ethoxythiazole (**10**) and 2-acetylthiazole (**11**) also afford single products.[97]

Scheme 10



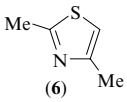
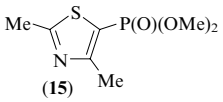
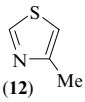
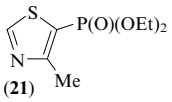
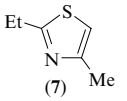
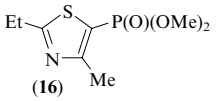
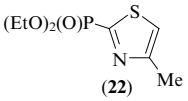
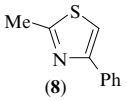
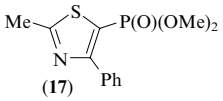
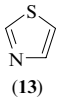
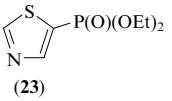
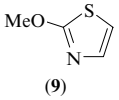
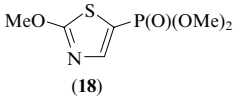
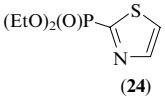
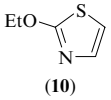
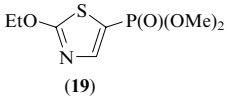
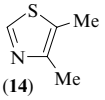
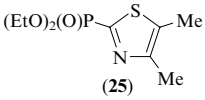
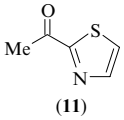
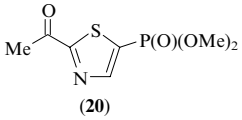
R^1 = H, Me, Et, MeO, EtO, Ac; R^2 = H, Me, Ph; R^3 = H, Me

The regioselectivity of phosphonation was tested on several thiazoles. The reaction with 4-methylthiazole (**12**) gave 5-phosphonated compound **21** as the a major product in 80% yield along with minor 2-phosphonated product **22** (9%) (see Table 4, run 7). For thiazole (**13**), 5- and 2-phosphonation products **23** and **24** were obtained in a 10 : 78 ratio (run 8). With 4,5-dimethylthiazole (**14**) as a substrate, phosphonation proceeded readily to give compound **25** in 83% yield (run 9).[97]

A possible reaction mechanism is presented in Scheme 11, which explains the regioselective phosphonation of thiazoles. Dimethyl H-phosphonate exists as two tautomers (**A** and **B**). The reaction of $Mn(OAc)_3$ with tautomer **A** affords the phosphonyl radical **26**.[97] This radical may attack the thiazole ring at position 4 or 5. In compound **27**, the radical site is adjacent to the imine nitrogen atom, *i.e.*, it has a more stable position than this site in compound **28**, which is adjacent to the sulfur atom. The formation of radical **27** is more advantageous and results in 5-phosphonated thiazoles **18**–**20** after oxidation with air or Mn^{III} to restore the ring aromaticity.[97]

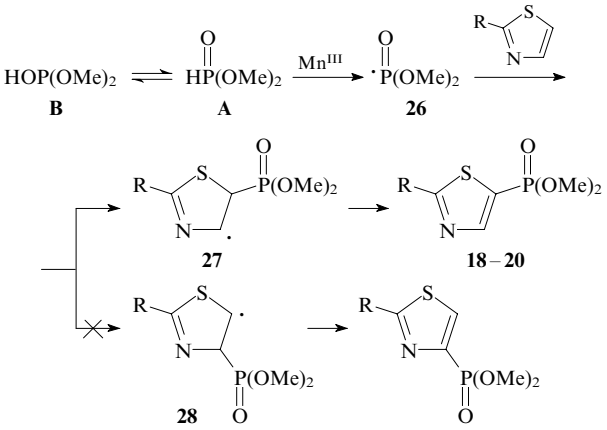
The results obtained for reaction with unsubstituted thiazole (see Table 4, run 8) demonstrate that position 2 of

Table 4. Phosphorylation of thiazoles.[97]

Run	Substrate	Product	Yield (%)	Run	Substrate	Product	Yield (%)
1	 (**6**)	 (**15**)	92	7	 (**12**)	 (**21**)	80
2	 (**7**)	 (**16**)	90			 (**22**)	9
3	 (**8**)	 (**17**)	87	8	 (**13**)	 (**23**)	10
4	 (**9**)	 (**18**)	90			 (**24**)	78
5	 (**10**)	 (**19**)	89	9	 (**14**)	 (**25**)	83
6	 (**11**)	 (**20**)	88				

the ring is most reactive towards phosphonation. The next most reactive is position 5, whereas position 4 is the least active. Interestingly, phosphonation products were not detected on functionalization of unsubstituted thiazole (**13**).

Scheme 11



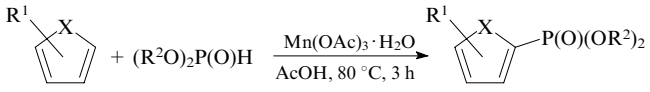
To examine the scope and regioselectivity of phosphonation, different heterocyclic substrates such as furans and pyrroles **29**–**35** were also utilized. Under the above mentioned general conditions, the reaction of 2-formylfuran (**29**) gives a single product **36** in 95% yield (Table 5, run 1). Similarly, starting from 2-substituted furans **30**–**32**, products of 5-phosphonation **37**–**39** were obtained in 86%–89% yields (runs 2–4). In contrast to 2-substituted furans, 3-substituted furans **33** and **34** react with diethyl H-phosphonate to give only 2,3-disubstituted furans **40** and **41** in 84%–89% yields (runs 5 and 6). Finally, 2-acetyl-1-methylpyrrole (**35**) affords a single 5-phosphonated product **42** in 91% yield (run 7).[97]

Thus, independently of the first case of direct phosphonation of aromatic compounds presented by Ishii's resewch group,[95] Zhang and co-workers[97] developed a simple but very effective method of phosphonation of heteroaromatic compounds including various thiazoles, furans and pyrroles. The reaction are carried out under mild conditions using dimethyl or diethyl H-phosphonate and $Mn(OAc)_3 \cdot H_2O$ as the reactants. The method is characterized by a broad synthetic scope and, what is more important, the process is regioselective.[97]

Recently, Huang's group[98] proposed another catalytic system for the phosphorylation of heteroaromatic compounds. The authors pioneered in performing dehydrogenation–cross-coupling reaction for substituted furans, thiophene, thiazole and pyrrole **12**, **29**, **30**, **35** and **43** and dialkyl H-phosphonates **1** and **3** catalyzed by silver derivatives to obtain the corresponding phosphonated products **36**, **37**, **42** and **44**–**48** in yileds of up to 89% and good regioselectivity. Moreover, an unparalleled combination of different pyridines and dialkyl H-phosphonates with $AgNO_3$ as a catalyst and $K_2S_2O_8$ as an oxidant was used followed by the reduction with $Na_2S_2O_3$ to obtain the target pyridine and quinoline phosphonates in satisfactory yields and good regioselectivity (Scheme 12).

Initially, to study and optimize the reaction conditions, 2-acetylfuran (**30**) and diethyl H-phosphonate (**1**) were chosen as model compounds.

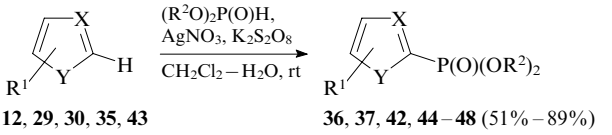
Table 5. Phosphonation of furans and pyrroles.[97]



29–**35** **35**–**42**

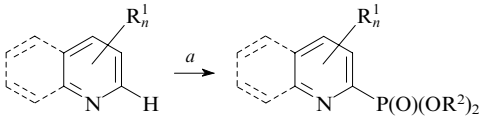
Run	Substrate	Product	Yield (%)
1	OHC, O (**29**)	OHC, O, P(O)(OMe)2 (**36**)	95
2	Me, O, O (**30**)	Me, O, O, P(O)(OMe)2 (**37**)	89
3	Pr^{i}O, O (**31**)	Pr^{i}O, O, P(O)(OMe)2 (**38**)	87
4	Me, O, O, O (**32**)	Me, O, O, O, P(O)(OMe)2 (**39**)	86
5	O, CHO (**33**)	O, P(O)(OEt)2, CHO (**40**)	84
6	O, OEt, O (**34**)	O, P(O)(OEt)2, OEt, O (**41**)	89
7	Me, N, Me, O (**35**)	Me, N, Me, O, P(O)(OMe)2 (**42**)	91

Scheme 12



12, **29**, **30**, **35**, **43** **36**, **37**, **42**, **44**–**48** (51%–89%)

X = CH, Y = O: R^1 = 2-Ac, 2-CHO; X = CH, Y = S, R^1 = H; Y = NMe, R^1 = 2-Ac; X = N, Y = S, R^1 = 4-Me



(53%–89%)

R^1_n = H, 2-Me, 2-Et, 4-Me, 2-NH_2; R^2 = Et, Me;
(*a*) 1) $(R^2O)_2P(O)H$, $AgNO_3$, $K_2S_2O_8$, $CH_2Cl_2-H_2O$, rt; 2) $Na_2S_2O_3$

The effective catalyst and oxidant system (Ag_2CO_3 and $K_2S_2O_8$, respectively) chosen by the authors can be considered as a fortune, resulting in the successful cross-coupling in a mixed solvent ($CH_2Cl_2-H_2O$) to give the desired

Table 6. Dehydrogenation–cross-coupling reaction between 2-acetylfuran (**30**) and diethyl phosphite.[98]

Run	Catalyst	Oxidant (equiv.)	Solvent	Yield (%)
1	Ag_2CO_3	$K_2S_2O_8$ (4)	$CH_2Cl_2-H_2O$	81
2	AgOAc	$K_2S_2O_8$ (4)	$CH_2Cl_2-H_2O$	69
3	Ag_2O	$K_2S_2O_8$ (4)	$CH_2Cl_2-H_2O$	63
4	$AgNO_3$	$K_2S_2O_8$ (4)	$CH_2Cl_2-H_2O$	89
5	CAN	$K_2S_2O_8$ (4)	$CH_2Cl_2-H_2O$	traces
6	SmI_2	$K_2S_2O_8$ (4)	$CH_2Cl_2-H_2O$	"
7	$AgNO_3$	H_2O_2 (4)	$CH_2Cl_2-H_2O$	0
8	$AgNO_3$	MnO_2 (4)	$CH_2Cl_2-H_2O$	traces
9	$AgNO_3$	TBHP	$CH_2Cl_2-H_2O$	0
10	$AgNO_3$	DTBP	$CH_2Cl_2-H_2O$	0
11	$AgNO_3$	$K_2S_2O_8$ (4)	$MeCN-H_2O$	traces
12	$AgNO_3$	$K_2S_2O_8$ (4)	$DMF-H_2O$	"
13	$AgNO_3$	$K_2S_2O_8$ (4)	$acetone-H_2O$	79
14	$AgNO_3$	$K_2S_2O_8$ (3)	$CH_2Cl_2-H_2O$	85
15	$AgNO_3$	$K_2S_2O_8$ (2)	$CH_2Cl_2-H_2O$	76

5-acetylfuran-2-ylphosphonate (**44**) in 81% yield and no isomeric 5-acetylfuran-3-ylphosphonate (Table 6, run 1).[98]

Only some oxidants were found to be active in these transformations.[98] Among silver salts, $AgNO_3$ proved to be the best, affording product **44** in 89% yield (see Table 6, run 4). Other oxidants such as H_2O_2, MnO_2, TBHP, DTBP were not effective (runs 7–10). The nature of solvent is also of vital importance in this reaction. Using $MeCN-H_2O$, $DMF-H_2O$ and $EtOH-H_2O$ mixtures resulted in trace amounts of product **44**, while the $acetone-H_2O$ mixture provided a moderate yield (runs 11–13). However, the method proposed requires a large, at least four-fold, excess of the oxidant; otherwise, the yields decrease (runs 14 and 15).[98]

Thus, the optimal reaction conditions are as follows: $AgNO_3$ catalyst (20 mol.%), $K_2S_2O_8$ as an oxidant, mixed solvent $CH_2Cl_2-H_2O$, room temperature.[98] Under the optimal conditions, the synthetic scope of the cross-coupling reaction between five-membered heteroarenes **12**, **29**, **30**, **35** and **43** and dialkyl H-phosphonates **1** and **3** was examined. The experiments demonstrated that 2-acetylfuran (**30**) readily reacts with dialkyl H-phosphonates **1** and **3** to give 2-furylphosphonates **44** and **37** in high yields and with good regioselectivity (Table 7, runs 1, 2). Furan-2-carbaldehyde (**29**) also proved to be an effective substrate, the product **36** being obtained in a good yield (run 3). Thiophene (**43**) reacts with dialkyl H-phosphonates **1** and **3**, but the yields of 2-thienylphosphonates **45** and **46** are relatively low (runs 4 and 5).[98] Meanwhile, thiazole **12** furnished 2-thiazolylphosphonate **47** in a good yield (run 6). Similarly to furan **30**, pyrrole **35** also undergoes coupling resulting in pyrrolylphosphonates **42** and **48** in good yields and with good regioselectivity (runs 7 and 8).[98]

The researchers cited[98] were able to scale-up the process, the target 2-furylphosphonate being obtained in 88% yield as in the small-scale reaction. The reaction was carried out at room temperature without the necessity of strict absence of water and oxygen. Thus, this approach to heteroarylphosphonates will probably have an industrial application.

The procedure of Huang also proved to be effective for the phosphorylation of pyridine and its derivatives **49**–**53**, as well as quinoline (**54**).[98] However, under the above conditions being optimal for the five-membered arenes, the target 2-pyridylphosphonate is obtained in lower yield (Table 8, run 1). A minor amount of 2-pyridylphosphonate *N*-oxide is formed as a side product.

The subsequent experiments have shown that the addition of 4 equiv. of $Na_2S_2O_3$ to the reaction mixture after the coupling markedly increases the yield of the target product,[98] *i.e.* increasing the yield of the phosphonated pyridines requires one more step of reduction in the presence of $Na_2S_2O_3$, which thus becomes a part of the one-pot coupling reaction. A number of substituted pyridines **50**–**53** and quinoline (**54**) were tested in the coupling reaction. It was demonstrated that using $AgNO_3$ as a

Table 7. Dehydrogenation–cross-coupling reaction between five-membered heteroaromatic compounds and dialkyl H-phosphonates (see Scheme 12).[98]

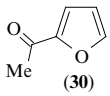
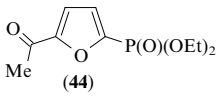
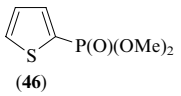
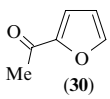
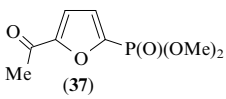
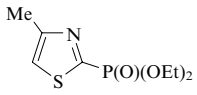
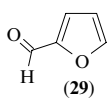
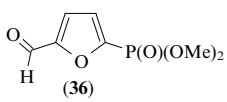
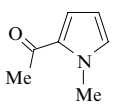
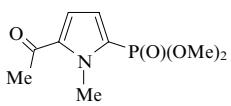
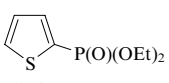
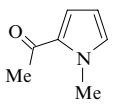
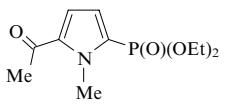
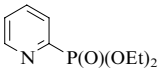
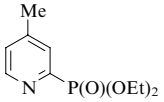
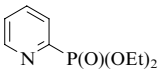
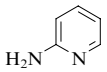
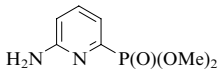
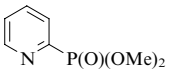
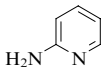
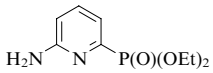
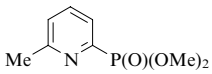
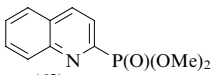
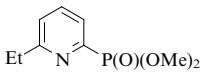
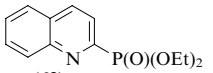
Run	Substrate	Product	Time /h	Yield (%)	Run	Substrate	Product	Time /h	Yield (%)
1	 (**30**)	 (**44**)	6	89	5	 (**43**)	 (**46**)	8	61
2	 (**30**)	 (**37**)	6	87	6	 (**12**)	 (**47**)	6	81
3	 (**29**)	 (**36**)	6	83	7	 (**35**)	 (**42**)	10	83
4	 (**43**)	 (**45**)	8	51	8	 (**35**)	 (**48**)	10	85

Table 8. Silver salt-catalyzed coupling reaction of pyridines and quinoline with dialkyl H-phosphonates (see Scheme 12).[98]

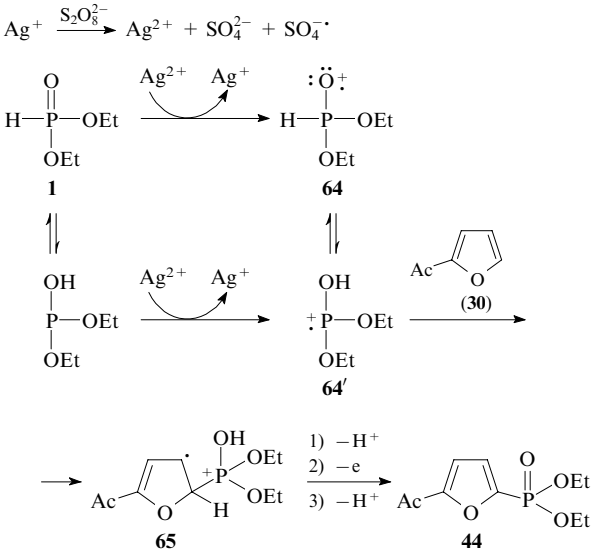
Run	Heterocycle	Product	Time /h	Yield (%)	Run	Heterocycle	Product	Time /h	Yield (%)
1	 (**49**)	 (**55**)	6	58 [a]	6	 (**52**)	 (**59**)	6	78
2	 (**49**)	 (**55**)	6	81	7	 (**53**)	 (**60**)	10	55
3	 (**49**)	 (**56**)	0.25	68	8	 (**53**)	 (**61**)	10	70
4	 (**50**)	 (**57**)	0.25	61	9	 (**54**)	 (**62**)	8	53
5	 (**51**)	 (**58**)	0.25	71	10	 (**54**)	 (**63**)	8	55

[a] Without $Na_2S_2O_3$.

catalyst and $K_2S_2O_8$ as an oxidant, the coupling reaction with dialkyl H-phosphonates can be smoothly carried out under mild conditions for various pyridines to give the desired 2-pyridyl- and 2-quinolylphosphonates **55**–**63** in 53%–78% yields and good regioselectivity (runs 2–10).[98]

If a radical scavenger (TEMPO) is added to the reaction mixture, the dehydrogenation–cross-coupling reaction between acetylfuran **30** and diethyl H-phosphonate does not proceed. This result demonstrates[98] that the reaction may follow a radical mechanism, probably similar to that proposed by Effenberger and Kottmann[94] (Scheme 13).

Scheme 13



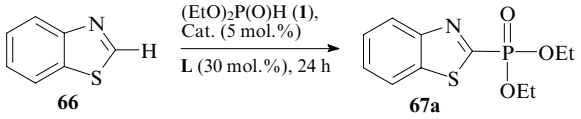
First, silver(I) is oxidized by peroxodisulfate to give silver(II). Then, diethyl H-phosphonate (**1**) loses an electron under the action of Ag^{II} yielding radical cations **64** and **64′**. Electrophilic addition of the latter to furan **30** yields intermediate **65**, which may successively lose a proton, an electron and one more proton, to afford the target 2-furylphosphonate **44**.[98]

Thus, the procedure proposed by Huang and co-workers[98] enables one to carry out phosphorylation of substituted furans, thiophenes, thiazoles and pyrroles with dialkyl H-phosphonates under mild conditions in yields of up to 89% and with good regioselectivity. Furthermore, one may consider the phosphorylation of pyridines using $AgNO_3$ as a catalyst and $K_2S_2O_8$ as an oxidant in a $CH_2Cl_2-H_2O$ mixture followed by reduction with $Na_2S_2O_3$ affording the desired 2-pyridylphosphonates in satisfactory yields and good regioselectivity to be a great success.

Li and co-workers[99] were the first to report direct Pd-catalyzed phosphorylation of azoles with dialkyl H-phosphonates. This method comprises oxidative cleavage of C–H and P(O)–H bonds and represents an atom-effective alternative to the classical ArX phosphorylation. The process follows a mechanism based on the Pd^{II}/Pd^{IV} redox transformation without addition of a base or an acid. Over the last decade, scientists have paid efforts to direct C(2)–H-functionalization of azoles to obtain 2-substituted azoles. Effective methods of their arylation,[100–102] alkynylation,[103,104] alkylation,[105–107] carboxylation,[108] carbonylation[109] and amination[110–113] were developed. Nevertheless, prior to the Li's group research, no mention was made concerning transition metal-catalyzed direct 2-phosphonation of azoles.

Li and co-workers[99] optimized the conditions by using the model oxidative phosphonation of benzothiazole (**66**) with diethyl H-phosphonate (**1**) (Table 9). The reaction proceeded slowly but afforded a single C(2)-phosphonated product **67a** (see Table 9, run 1) when carried out in MeCN

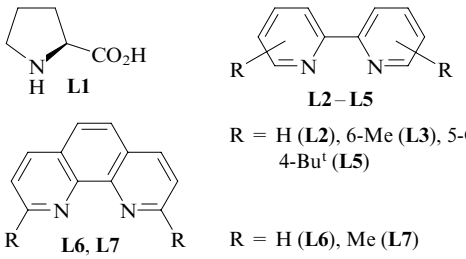
Table 9. Optimization of the reaction conditions between benzothiazole and diethyl H-phosphonate.[99]



Run	Catalyst [a]	Ligand	Oxidant	Yield (%)
1	$Pd(OAc)_2$	–	$K_2S_2O_8$	12
2	$Pd(OAc)_2$	–	–	0
3	$Pd(OAc)_2$	**L1**	$K_2S_2O_8$	56
4 [b]	$Pd(OAc)_2$	**L1**	$K_2S_2O_8$	56
5	$PdCl_2$	**L1**	$K_2S_2O_8$	27
6	$Pd(tfa)_2$	**L1**	$K_2S_2O_8$	47
7	$PdCl_2(cod)$	**L1**	$K_2S_2O_8$	47
8 [c]	$Pd(OAc)_2$	**L1**	$K_2S_2O_8$	56
9 [d]	$Pd(OAc)_2$	**L1**	$K_2S_2O_8$	10
10 [e]	$Pd(OAc)_2$	**L1**	$K_2S_2O_8$	38
11 [f]	$Pd(OAc)_2$	**L1**	$K_2S_2O_8$	26
12 [g]	$Pd(OAc)_2$	**L1**	$K_2S_2O_8$	55
13	$Pd(OAc)_2$	**L2**	$K_2S_2O_8$	48
14	$Pd(OAc)_2$	**L3**	$K_2S_2O_8$	54
15	$Pd(OAc)_2$	**L4**	$K_2S_2O_8$	34
16	$Pd(OAc)_2$	**L5**	$K_2S_2O_8$	23
17	$Pd(OAc)_2$	**L6**	$K_2S_2O_8$	41
18	$Pd(OAc)_2$	**L7**	$K_2S_2O_8$	55

[a] tfa is trifluoroacetate, cod is cycloocta-1,5-diene; [b] 50 mol.% **L1**; [c] under Ar atmosphere; [d] under O_2 atmosphere; [e] at 80 °C; [f] at 120 °C; [g] for 30 h.

Structures L1-L7



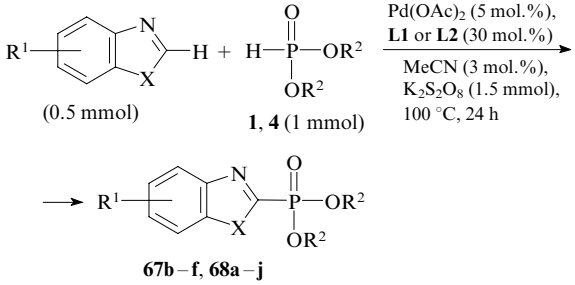
under the catalysis of 5 mol.% of $Pd(OAc)_2$ in the presence of $K_2S_2O_8$ at 100 °C. In 2007, Fu and co-workers [114] reported that proline (**L1**) is suitable as a ligand to improve the efficiency of copper-catalyzed addition of H-phosphine oxide to alkynes. The authors [99] have found that adding the ligand **L1** significantly increases the yield of the desired product **67a** (from 12% to 56%, run 3); however, an increase in the amount of ligand **L1** (up to 50 mol.%) has no effect on the catalytic properties (run 4). Replacement of $Pd(OAc)_2$ by the other Pd compounds such as $PdCl_2$, $Pd(tfa)_2$ or $PdCl_2(cod)$ resulted in a slight decrease in the product yield (runs 5–7). It may be assumed that the nature of Pd-catalyst counter ions is not critical for the catalytic efficacy contrary to the Pd-catalyzed phosphonation *via* cross-coupling between aryl halides and dialkyl H-phosphonate.[115]

Carrying out the experiments in an argon atmosphere instead of air resulted in the same yield of product **67a**; however, in a pure oxygen the phosphonation rate slowed down dramatically (the yield was as low as 10%) (see Table 9, runs 8 and 9). The yield of the target product was maximum at 100 °C (runs 10 and 11). Although phosphonation was not completed in 24 h, prolonging the reaction time up to 30 h did not improve the outcome (run 12).[99]

The oxidative C(2)–H-phosphonation of thiazole **66** with diethyl H-phosphonate gives a very low yield of product **67a** (5%) in the presence of a very broad range of organic or inorganic oxidants except for $K_2S_2O_8$, which was recognized to be the most effective among the oxidants tested. Among the solvents used, the best result was shown by MeCN. The increase in the reaction efficacy with some other amino acids and bidentate N-ligands (**L2**–**L7**) (runs 13–18) was also studied. The use of ligands **L3** and **L7** was found to give compound **67a** in roughly the same yields as proline, but the latter was recornized as the optimal ligand in the direct phosphonation of benzothiazole derivatives with dialkyl H-phosphonates as being far less expensive and more available.[99]

The researchers cited [99] have examined the range of possible substrates in a model reaction under optimized conditions [5 mol.% of $Pd(OAc)_2$–**L1**, $K_2S_2O_8$, MeCN, 100 °C] (Scheme 14). Benzothiazole bearing the 6-Me substituent gives a lower yield of **67b** (41%) than unsubstituted benzothiazole (56%). Introduction of the chlorine atom into the same position increases slightly its capability for phosphonation (57% yield of **67c**). Upon replacement of diethyl H-phosphonate by more hindered and electron-donating diisopropyl H-phosphonate (**4**), the unsubstiuted benzothiazole and its derivatives reacted smoothly affording the target products **67d**–**f** in higher yields (45%–70%) as compared with the corresponding phosphonation with phosphite **1**.

Scheme 14

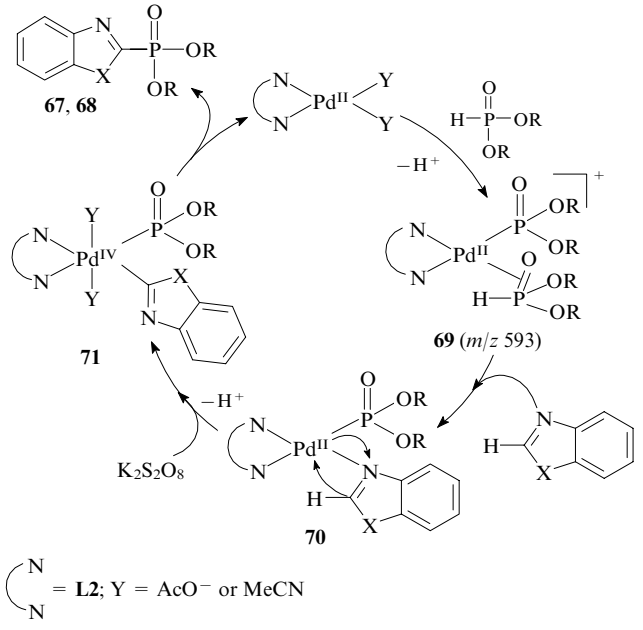


Compound	X	R^1	R^2	Yield (%)
67b	S	6-Me	Et	41
67c	S	6-Cl	Et	57
67d	S	H	Pr^i	64
67e	S	6-Me	Pr^i	45
67f	S	6-Cl	Pr^i	70
68a	O	H	Et	55
68b	O	5-Me	Et	62
68c	O	5-Bu^t	Et	68
68d	O	6-Me	Et	60
68e	O	5-Cl	Et	61
68f	O	H	Pr^i	63
68g	O	5-Me	Pr^i	67
68h	O	5-Bu^t	Pr^i	83
68i	O	5-Cl	Pr^i	74
68j	O	6-Me	Pr^i	65

Surprisingly, the reaction with benzoxazole (X = O) gave **68a** in a yield as low as 15%.[99] The repeated optimization of the reaction conditions showed that ligands **L2** and **L3** are more advantageous for benzoxazole phosphonation. Moreover, this process was found to be very oxygen- and even air-sensitive. With ligand **L2** and under argon atmosphere, phosphonation of benzoxazole proceeds readily to afford product **68a** in a moderate yield, while introduction of an electron-withdrawing group in the benzene ring results in an increase in the yields of **68b–d**. 5-Chloro derivative gives a similar yield of **68e**, and replacement of diethyl H-phosphonate (**1**) by diisopropyl H-phosphonate (**4**) increases the yields of heterocyclic phosphonates from moderate to good (products **68f–j**, 63%–83%). Other aromatic substrates such as *N*-methylbenzimidazole and *N*-methylindole were also used in the reaction but gave no products of direct phosphonation.[99]

The mechanism of Pd-catalyzed phosphonation of aryl halides with dialkyl H-phosphonate was thorougly studied by Stawinski and co-workers[45,115,116] and by Stockland and co-workers.[117] To elucidate the mechanism of this novel C–P bond formation reaction, Li and co-workers[99] performed first the phosphonation in the presence of TEMPO and obtained phosphonate **67a** in a yield similar to that in the model reaction without TEMPO. This fact suggested that the oxidative phosphonation under consideration is not necessarily a radical process. pH measurements in the reaction mixture in the beginning (4.5) and upon completion of the reaction (2.5) showed that some quantity of H^+ ions was released into a solution upon cleavage of C–H and P(O)–H bonds. To get more information concerning the Pd-catalyst species involved in the catalytic cycle, the phosphonation reaction of compounds **66** and **4** was monitored using electrospray ionization mass spectrometry (ESI-MS), which was successfully applied to study a variety of Pd-catalyzed reactions.[55,118,119] In the ESI-MS spectrum of the reaction mixture, the authors found two types of monocationic Pd species in the reaction mixture out of which cation **69** predominated (Scheme 15).[99] Previously, it was assumed that Pd^{II}-catalyzed oxidation reactions generally proceed through a Pd^{II}/Pd^0 catalytic cycle in the presence of an oxidant such as benzoquinone, O_2 or $CuCl_2$.[120,121] However, all these oxidants were inactive in the said phosphonation process and, hence, it was suggested that the reaction involves a Pd^{II}/Pd^{IV} catalytic cycle rather than Pd^{II}/Pd^0 (see Ref. 76).

Scheme 15

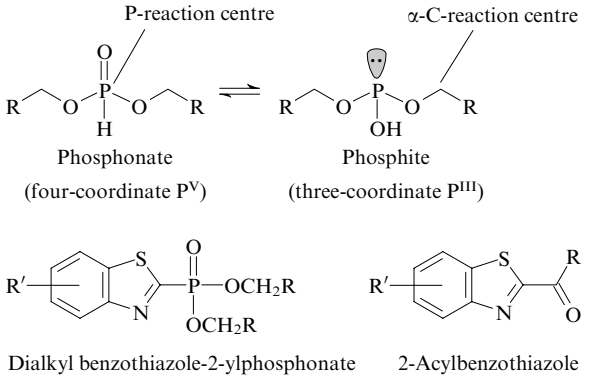


Considering these results and results of other similar studies[76,120,121] a possible catalytic cycle was proposed[99] (see Scheme 15). The reaction is initiated by the nucleophilic coordination of phosphite to Pd^{II} to form a monocationic palladium complex **69**, which further coordinates to azole after dissociation of one (or two) phosphite molecules to give one more Pd^{II} complex **70**. Its subsequent deprotonation and rearrangement occur in the presence of $K_2S_2O_8$ yielding finally Pd^{IV} intermediate **71**, which undergoes reductive elimination affording phosphonate **67** or **68**.[99]

Thus, Li and co-workers[99] were the first to propose highly regioselective palladium-catalyzed oxidative phosphonation of azoles with dialkyl H-phosphonates without using additional bases or acids. Such transformation presents an atom-economic alternative to traditional phosphonation of ArX, which requires pre-functionalized aromatic substrates and a stoichiometric amount of a base. The reactions give various 2-phosphonated azoles in moderate and good yields.

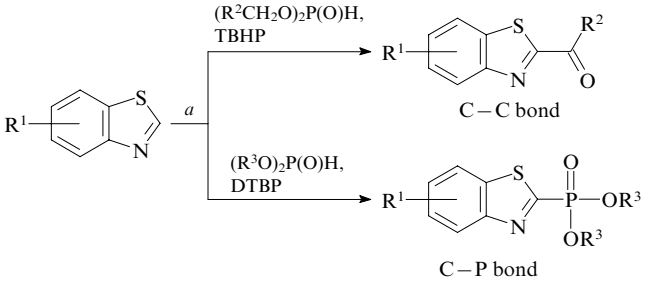
Y-F Zhao and co-workers[122] found that depending on the nature of the peroxide oxidant, the reaction between benzothiazoles and H-phosphonates may give different products. Finally, two synthetic approaches to two types of valuable benzothiazole derivatives, namely, 2-acylbenzothiazoles and dialkylbenzothiazol-2-ylphosphonates, under mild conditions and without metal participation were developed. Although this study[122] does not fall exactly into the subject of the present review because C–H-phosphorylation proceeds without metals or their complexes, nevertheless, it is worth mentioning as a novel interesting approach to the products of P–C coupling under oxidative conditions. H-Phosphonate $(RO)_2P(O)H$ exists in equilibrium with its tautomeric dialkyl phosphite form $(RO)_2POH$. *tert*-Butyl hydroperoxide promotes the formation of α-carbon-centred phosphite radicals, whereas di-*tert*-butyl peroxide generates phosphorus-centred phosphonate radicals (Scheme 16).

Scheme 16



The two radical types result in the formation of two reaction processes, namely, direct C(2)-acylation of benzothiazoles and C(2)-phosphonation of benzothiazoles (Scheme 17).[122]

Scheme 17



R^1 = H, Me, OMe, Cl, Br, NO_2; R^2, R^3 = Alk;
(*a*) MeCN, 80 °C, 24 h

IV. Synthesis of phosphorylated coumarins

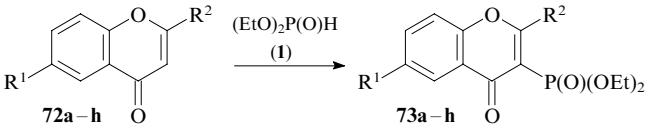
Coumarins the skeleton of which is present in a variety of natural compounds and also forms a part of molecules possessing biological activity [123–132] or of fluorescence dyes,[133–138] have lately attracted a substantial attention of scientists. Particularly, a number of 3-phosphorylated coumarins were found to exhibit cytotoxicity towards certain human leukemia cells as well as high alkylation ability.[139] Previously, 3-phosphorylated coumarins were generally obtained *via* the Arbuzov or Knoevenagel reaction.[140–146] These methods are based on multistep consecutive reactions, they do not comply with the atom-economy principles and, therefore, they are low efficient. To our knowledge, until recently, there was only a single paper by Zhang's group [147] that discussed the radical phosphonation of coumarins requiring a stoichiometric amount of $Mn(OAc)_3 \cdot 2H_2O$ (3 equiv.) and an aliphatic acid as a solvent.

Zhang's group found that manganese(III) acetate can effectively generate phosphonyl radicals, which react with benzene,[148] heteroarenes such as thiazoles and furans [97] and substituted styrenes bearing electron-withdrawing groups to give products phosphorylated at the vinyl group.[149] They also react with 1,3-diarylpropynones affording phosphonated indenones.[150] The authors also found that phosphinoyl radical [*e.g.* $Ph_2(O)P^{\bullet}$] can react with 5-arylpent-2-enoates yielding *trans*-disubstituted tetrahydronaphtalenes.[151] Using their experience, the group of Zhang succeeded in developing phosphonation of flavone and coumarin.[147]

Development of effective methods of introduction of phosphorus-containing moiety into flavones and coumarins is of current concern since it should result in the production of a variety of novel compounds promising for the biological studies. To the best of our knowledge, prior to Zhang's studies only several phosphorylated flavones and coumarins have been obtained through a multistep synthesis.[40, 139–144, 146, 152–154]

Zhang and co-workers [147] found that the phosphonyl radical generated in the reaction between manganese(III) acetate and diethyl H-phosphonate adds selectively to flavones **72a–h** and coumarins at position 3 to afford phosphonated products in moderate and good yields. Flavone **72a** was used in a model reaction. To optimize manganese(III)-catalyzed phosphonation reaction, the solvent, reactant ratio, temperature and reaction time were varied. Solvent screening (acetic acid, ethanol, methanol, acetonitrile) showed ethanol to be the best solvent.[147] The most suitable reactant ratio **72a** : **1** : $Mn(OAc)_3$ was 1 : 2 : 3. Using < 2 equiv. of $Mn(OAc)_3$ resulted in low yields of the product, while the addition of 3 equiv. in three portions gave the best results. The reaction temperature ranged from 20 to 80 °C and the reaction time was varied from 60 to 120 min. There was nearly no reaction at the temperature below 60 °C. Under optimized conditions [**72a** : **1** : $Mn(OAc)_3$ = 1 : 2 : 3, ethanol, 80 °C, 90 min], a phosphorylated product **73a** was obtained in 44% yield (Scheme 18).

Scheme 18



Compounds **72**, **73**	R^1	R^2	Conversion (%)	Yield (%)
a	H	Ph	75	44
b	H	4-$MeOC_6H_4$	78	46
c	H	2-Th	75	62
d	H	4-BrC_6H_4	82	68
e	H	3-BrC_6H_4	79	58
f	H	4-$O_2NC_6H_4$	72	47
g	H	2,3-$(OCH_2O)C_6H_3$	76	45
h	Cl	Ph	71	42

Th is thienyl.

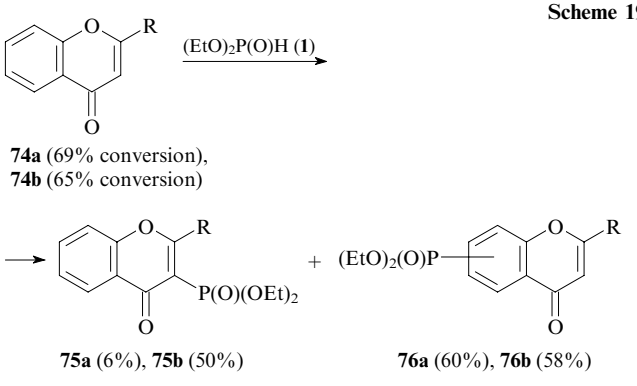
To examine the scope and limitations of this method, a number of flavone analogues were utilized. Aromatic substituents in position 2 of 4*H*-chromen-4-ones **72a–h** did not change significantly the yields of products **73a–h** (see Scheme 18).[147] The isolated yields of phosphorylated products **73a–h** were 20%–30% lower that the conversion. Since no noticeable amounts of side products were isolated, some compounds were apparently lost during chromatographic purification.[147]

It was found that the reactants are consumed incompletely under the above conditions even over a long reaction time. The authors suggested that this may result from the steric hindrance due to the 2-phenyl group of flavone.[147] To check this hypothesis, 2-methyl-4*H*-chromen-4-one (**74a**), unsubstituted chromen-4-one (**74b**) and its 2-styryl derivative **74c** were used as substrates, furnishing products **75a–c**, **76a**,**b**, **77** (Scheme 19).

The phosphonation was proved to proceed predominanty into the benzene ring rather than the expected position 3. 2-Styryl-substituted chromone **74c** transformed into a mixture of products phosphonated in position 3 and in the vinyl group in 1 : 1.6 ratio. No phosphonation of the benzene ring was observed (see Scheme 19).[147]

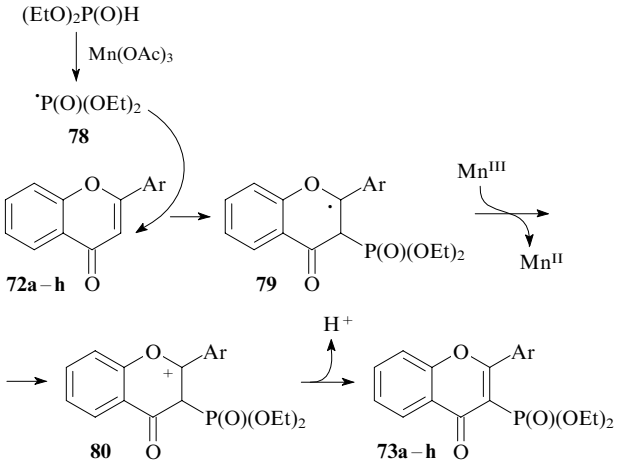
The phenyl group in position 2 is responsible for the regioselectivity of the reaction of phosphonyl radicals with 4*H*-chromen-4-ones.[147] A mechanism explaining these transformations was suggested (Scheme 20). Phosphonyl radical **78**, generated in the reaction of manganese(III) acetate with diethyl H-phosphonate, attacks position 3 of flavones **72a–h** yielding benzyl radicals **79**. The latter are subsequently oxidized by manganese(III) acetate to give

Scheme 19



carbocations **80**, which are deprotonated affording the products **73a–h**.[147]

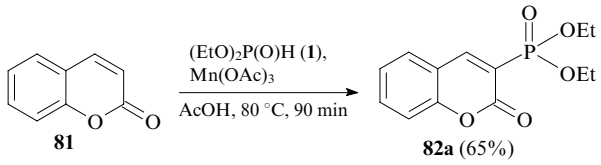
Scheme 20



There are two competing reaction pathways for the phosphonyl radical to react with compounds **74a**,**b**. The attack on the benzene ring is preferred over the attack on position 3 of 4*H*-chromen-4-one, since the latter process does not produce the stable benzyl radical. The reaction of compound **74c** also has two competing pathways. Product **77** is formed *via* the major pathway as it is formed from the benzyl radical intermediate.[147]

Zhang and co-workers[147] suggested coumarins to be more suitable substrates for the phosphonation because they do not comprise aryl groups in position 2, which created steric hindrance, as opposed to flavones, and they are able to generate stable benzyl radical after addition of the phosphonyl radical at position 3. The reaction of coumarin (**81**) with diethyl phoshite actually gave 3-phosphonated coumarin **82a** in 65% yield (Scheme 21), which is higher than that for 3-phosphonyl flavone **73a** (see Scheme 18). The outcomes of the reaction for a number of coumarins attest that substituents both in the benzene ring and in position 4 have no substantial effect on the product yield.[147]

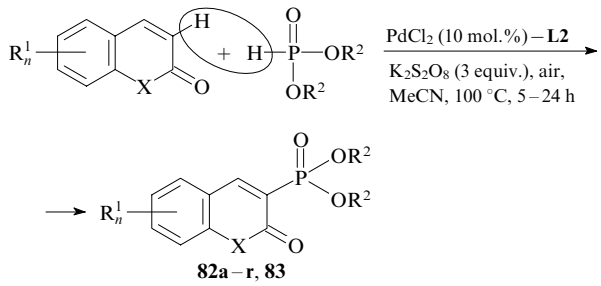
Scheme 21



Thus, Zhang's group[147] pioneered in developing an effective method for direct phosphonation of flavones and coumarins. The reactions of phosphonyl radical generated under the action of manganese(III) acetate proceed regioselectively ine position 3 of flavones and coumarins. This convenient and selective procedure increases the synthetic attractiveness of free radical phosphonation of heteroaromatic compounds.

A novel Pd^{II}-catalyzed dehydrogenation–cross-coupling reaction of coumarins and their aza-analogues with dialkyl phoshites was developed in 2013 by the research group of Wu[155] with the aim to obtain the corresponding 3-phosphonated products **82a–r**, **83** in moderate to good yields with high selectivity (Scheme 22).

Scheme 22



Compound	X	R^1_n	R^2	Yield (%)
82a	O	H	Et	48
82b	O	H	Me	44
82c	O	H	Pr^i	56
82d	O	H	Bu^n	47
82e	O	H	Bu^s	59
82f	O	H	Bu^i	51
82g	O	6-Me	Et	46
82h	O	6-Me	Pr^i	52
82i	O	7-OMe	Et	64
82j	O	7-OMe	Pr^i	74
82k	O	6-OMe	Et	57
82l	O	6-OMe	Pr^i	63
82m	O	6,7-$(OMe)_2$	Et	60
82n	O	6,7-$(OMe)_2$	Pr^i	67
82o	O	7-OBn	Et	59
82p	O	7-OBn	Pr^i	63
82q	O	7-OH	Pr^i	34
82r	O	6-CHO	Pr^i	27
83	NMe	H	Pr^i	47

The authors started optimization of the reaction conditions for coumarin (2*H*-chromen-2-one, **81**) and diethyl H-phosphonate (**1**) using 10 mol.% $Pd(OAc)_2$ and $K_2S_2O_8$ in MeCN at 100 °C for 24 h.[155] Phosphonation occurred in position 3 of the coumarin nucleus with high regioselectivity and in a relatively low but encouraging isolated yield (21%) (Table 10, run 1). When 2,2′-bipyridine (**L2**) was introduced into the reaction system as a ligand, the yield increased up to 46% (run 2). Then a number of commercially available transition metal salts ($PdCl_2$, CuBr, CuI) were tested with ligand **L2**, but they did not show better catalytic activity except for $PdCl_2$, being as active as $Pd(OAc)_2$ (runs 2 and 3).[155] Among the organic and inorganic oxidants tested, $K_2S_2O_8$ was the best (runs 4–7); however, it should be taken in at least three-fold excess relative to coumarin; otherwise, the product yield is decreased (run 4). Organic oxidants such as *p*-benzoquinone (BQ) and TBHP may hamper this catalytic process (runs 6, 7). Certain other bidentate N-ligands (**L6**–**L8**) and amino acids (**L9**) did not improve the results (runs 8–12). Though the ligand X-phos (**L10**) provided a similar yield as 2,2′-bipyridine, the latter was considered to be the optimal ligand for this reaction taking into account the demands of green chemistry and cost-effectiveness (see Table 10, runs 2 and 12). Testing of various solvents (DMF, THF, dioxane, toluene) demonstrated a considerable solvent effect on the yield, MeCN being the solvent of choice.[155] The increase in the amount of $PdCl_2$ up to 20 mol.% did not increase the yield of phosphonate **82a** (see Table 10, run 15). However, upon addition of a larger amount of diethyl H-phosphonate to this system, the reaction product is formed in a lower yield (run 16), apparently, due to strong coordinating ability of the phosphorus-containing reagent.[155] The problems of C–H phosphonation associated with the strong coordinating ability of the P-reagents involved in the coupling reaction have been mentioned in many studies.[95, 98, 99, 156–161]

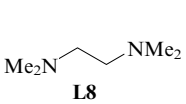
Table 10. Optimization of the reaction condidions between coumarin and diethyl phosphite.[155]

81 (0.5 mmol) + **1** (1 mmol) $\xrightarrow[\text{ligand, oxidant, 24 h}]{\text{Cat. (10 mol.\%)}}$ **82a**

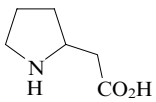
Run	Catalyst	Ligand	Oxidant	Yield (%)
1	$Pd(OAc)_2$	–	$K_2S_2O_8$	21
2	$Pd(OAc)_2$	**L2**	$K_2S_2O_8$	46
3	$PdCl_2$	**L2**	$K_2S_2O_8$	46
4[a]	$PdCl_2$	**L2**	$K_2S_2O_8$	38
5[b]	$PdCl_2$	**L2**	$K_2S_2O_8$	48
6	$PdCl_2$	**L2**	BQ	0
7	$PdCl_2$	**L2**	TBHP	0
8	$PdCl_2$	**L6**	$K_2S_2O_8$	27
9	$PdCl_2$	**L7**	$K_2S_2O_8$	26
10	$PdCl_2$	**L8**	$K_2S_2O_8$	28
11	$PdCl_2$	**L9**	$K_2S_2O_8$	38
12	$PdCl_2$	**L10**	$K_2S_2O_8$	46
13[c]	$PdCl_2$	**L2**	$K_2S_2O_8$	46
14[d]	$PdCl_2$	**L2**	$K_2S_2O_8$	45
15[e]	$PdCl_2$	**L2**	$K_2S_2O_8$	33
16[f]	$PdCl_2$	**L2**	$K_2S_2O_8$	38

[a] 2 equiv. $K_2S_2O_8$; [b] 4 equiv. $K_2S_2O_8$, in all other cases, 3 equiv.; [c] 20 mol.% $PdCl_2$; [d] 60 mol.% $PdCl_2$; [d] 12 h; [f] 1.5 mmol of **1**.

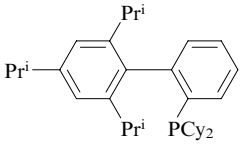
Structures L8–L10



L8



L9



L10 (Cy is cyclohexyl)

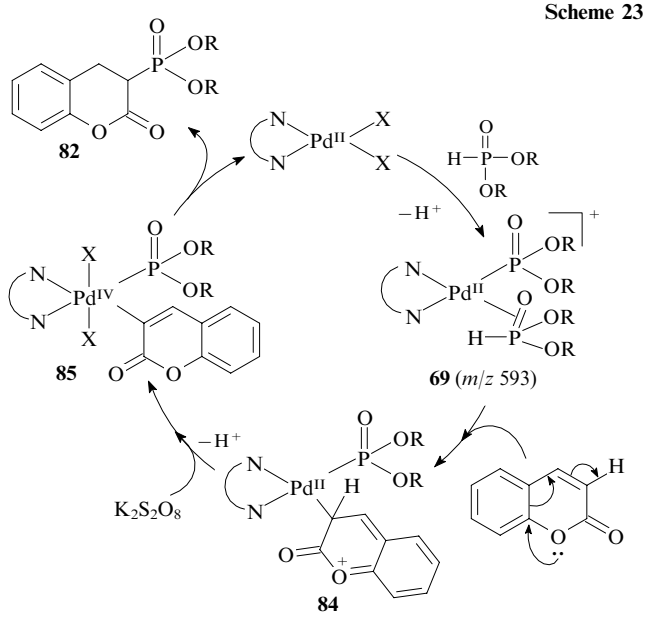
Having chosen the optimal conditions, Huang and coworkers[155] examined the range of possible substrates, namely, dialkyl H-phosphonates and coumarins (see Scheme 22). It was found that a number of coumarin derivatives undergoes dehydrogenation–phosphonation in moderate and good yields with high regioselectivity. The reactions between the tested dialkyl H-phosphonates and coumarins proceed smoothly under the optimized conditions to give products (**82a**–**r**, **83**) in moderate yields. Diisopropyl- and di-*sec*-butyl H-phosphonates were established to be the best partners for coumarin phosphonation. Coumarins bearing electron-donating substituents generally give higher yields than their analogues with electron-withdrawing groups. Coumarin derivatives with a methyl group in position 6 give lower yields of phosphonates **82g**,**h** (46% and 52%) than unsubstituted coumarin (**82a**,**c**, 48% and 56%).[155] Reaction yields from moderate to good ones (57%–74%) have been gained for coumarins comprising electron-donating substituents (OMe, OEt, OBn) in position 7 (phosphonates **82i**–**p**), the reaction being faster in these cases. Moreover, the novel phosphonation system proved to tolerate OH and CHO groups, though the yields of products **82q**,**r** decreased. It should be noted that this procedure was successfully used in the reaction with 1-methyl-2-quinolinone, the product **83** being obtained in 47% yield.[155] This compound acts as a human immunodeficiency virus (HIV-1) inhibitor and a novel antibacterial agent.[162, 163]

To study the process mechanism, TEMPO (1 equiv.) was added to the reaction system comprising coumarin and diethyl H-phosphonate. Product **82a** was obtained in 37% yield similar to the yield in the model reaction without TEMPO. This result demonstrates that the reaction can occur by a non-radical mechanism. The reaction between coumarin and phosphite **4** was monitored by ESI-MS. As was to be expected, palladium cation complexes **69** (m/z 593) were detected in the reaction mixture (Scheme 23). The possible mechanism of the cross-coupling reaction accompanied by dehydrogenation was proposed (see Scheme 23).[155]

The reaction starts with nucleophilic coordination of phosphite to Pd^{II} affording the monocationic palladium intermediate **69**. Due to higher nucleophilicity of position 3 of coumarin, the electrophilic palladation of the latter results in a different palladium complex **84**. This is followed by oxidation–dehydrogenation in the presence of $K_2S_2O_8$ generating Pd^{IV} species **85**. The subsequent reductive elimination furnishes 3-phosphonated coumarin and Pd^{II} species, which return to the catalytic cycle. Thus, the protocol of Wu and co-workers[155] gives rise to 3-phosphonated coumarins in moderate and good yields with a high regioselectivity by the palladium complex-catalyzed reaction.

Phosphorylated coumarins may by synthesized through phosphorylation–cyclization of alkynoates. Several exam-

Scheme 23



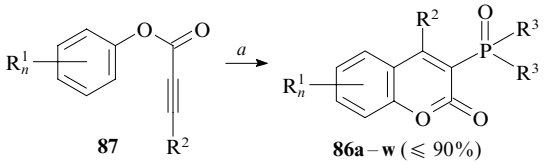
ples of cascade reactions are described, initiated by addition of P-centred radicals to alkynes.[150,164–167] Their synthetic value is generally related to high reactivity of vinyl radicals formed in this step, which may be captured through fast cyclization or addition to other π-systems. Presently, the development of efficient P-radical tandem methods attracts considerable attention since they provide a promising alternative for designing complex organophosphorus structures. In 2014, Wu's research group[168] suggested using Ag_2CO_3-catalyzed tandem process of alkyne double functionalization comprising radical phosphonation and C–H-functionalization to synthesize various 3-phosphonated coumarins in moderate and good yields and with high regioselectivity (Scheme 24). For the first time, a catalytic amount of cheap and nontoxic silver salt was used in a domino-reaction resulting in the C–P and C–C bond formation.

Wu and co-workers[168] assumed that silver can catalyze P-radical addition to alkynoates and accomplish a direct cyclization to give the corresponding phosphonated coumarins as potential pharmaceutical agents.[139,169] Thus, a domino method for the synthesis of coumarin 3-phosphonate derivatives through sequential silver-catalyzed radical reaction between aryl alkynoates and dialkyl H-phosphonates resulting in the C–P and C–C bond formation was proposed.[168]

First, the tandem radical phosphonation–cyclization of phenyl alkynoate with diethyl H-phosphonate (**1**) was studied in the presence of 1 equiv. of $AgNO_3$ in MeCN at 100 °C for 12 h; as a result, the target product **86a** was isolated in 23% yield. Optimization of conditions showed that most advantageous was the use of Ag_2CO_3 with $Mg(NO_3)_2$ additive, molecular sieves 4 Å and elevated temperature (100 °C) in acetonitrile. Furthermore, in a control experiment, it was found that $Mg(NO_3)_2$ by itself did not facilitate this reaction.[168]

The radical phosphonation–cyclization method under optimal conditions was applied to various substrates (see Scheme 24).[168] The reaction can also proceed with various dialkyl H-phosphonates to produce the corresponding

Scheme 24



R^2 = Ar, Alk; (*a*) $R^3_2P(O)H$, Ag_2CO_3 (10 mol.%), $Mg(NO_3)_2 \cdot 6H_2O$, air, MS 4 Å, MeCN, 100 °C, 12 h; MS are molecular sieves

Compounds **86**	R^1_n	R^2	R^3	Yield (%)
a	H	Ph	OEt	80
b	H	Ph	OMe	70
c	H	Ph	OBu^i	90
d	H	Ph	Ph	80
e	6-Me	Ph	OEt	85
f	6-Bu^t	Ph	OEt	85
g	5,7-Me_2	Ph	OEt	71
h	6-OMe	Ph	OEt	57
i	6-OPh	Ph	OEt	69
j	6-F	Ph	OEt	68
k	6-Cl	Ph	OEt	68
l	6-Br	Ph	OEt	64
m	6-CF_3	Ph	OEt	47
n	8-Me	Ph	OEt	0
o + **o′**	6-Cl,7-Me + 6-Cl,5-Me	Ph	OEt	81 (1.2 : 1)
p + **p′**	5-Me + 7-Me	Ph	OEt	73 (1.5 : 1)
q	7-OMe	Ph	OEt	78
r	H	4-$MeOC_6H_4$	OEt	71
s	H	4-MeC_6H_4	OEt	70
t	H	2-MeC_6H_4	OEt	77
u	H	4-ClC_6H_4	OEt	73
v	H	3-Cl,4-FC_6H_4	OEt	66
w	H	n-C_5H_{11}	OEt	31

products **86a–c** in good yields. As expected, diphenylphosphine oxide also proved to be a suitable P-radical precursor in this transformation and the target product **86d** was isolated in 80% yield. Studying different alkynoates under optimized reaction conditions showed that various aryl 3-phenylpropiolates bearing *para*- and *meta*-substituents in the phenoxy group readily cyclize to give the corresponding coumarins **86e–l** in moderate and good yields. For a strongly electron-withdrawing substituent (CF_3) in the phenoxy group, the yield of the corresponding product **86m** was as low as 47%. A methyl group in the *ortho*-position of the phenoxy substituent hampers the formation of the expected product **86n** even under the optimal reaction conditions.

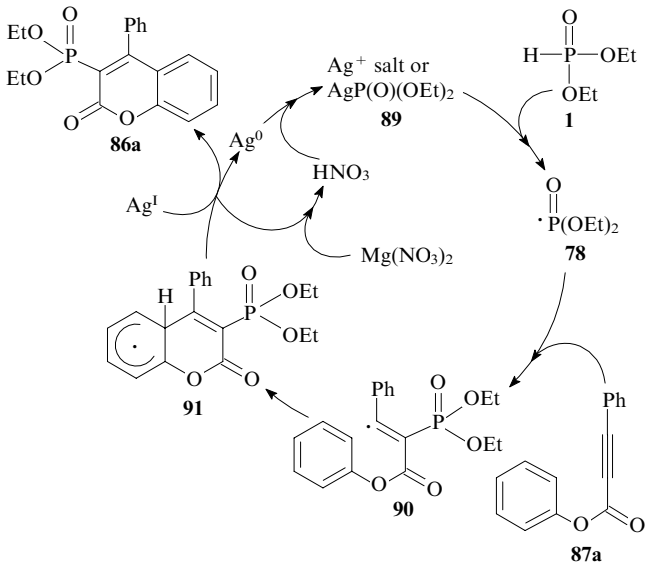
To study the regioselectivity of the cascade reaction discovered, *meta*-substituted aryl alkynoates were synthesized and successfully transformed into the corresponding products in good yields. Whereas phosphonates **86o,o′** and **86p,p′** were formed as mixtures of two isomers, the formation of product **86q** in high yield was fully regiocontrolled. These results demonstrate that the cyclization preferably involves the position most distant from the *meta*-substituent. An estimation of the effects of functional groups in the alkynyl moiety showed that all substrates readily react being converted to the corresponding products in good yields irrespective of the presence of an electron-

donating or electron-withdrawing substituent (phosphonates **86r–v**). Even phenyl oct-2-ynoate is suitable for this reaction, showing a moderate yield of the product **86w**.[168]

To elucidate the transformation mechanism, a set of control experiments were performed. The reaction is completely arrested in the presence of 1.0 equiv. of TEMPO as a radical scavenger. This is in agreement with a radical mechanism hypothesis. If alkynoate **87a** (R^1_n = H, R^2 = Ph) is introduced into the reaction under standard conditions without phosphite **1**, no C–H functionalization occurred and the cyclization product, 4-phenylcoumarin (**88**), was not detected.[168]

Thus, the authors concluded that the first step is phosphonation involving Ag_2CO_3. When a stoichiometric amount of the complex $AgP(O)Ph_2$ was used, no transformation of the substrate **87a** was observed both in the presence of Ag_2CO_3 and without it. The results demonstrated that (i) $AgP(O)Ph_2$ cannot be added to alkynoate **87a** to form silver particles, (ii) P-radicals are reactive intermediates in this process. Nevertheless, in the presence of a catalytic amount of $AgP(O)Ph_2$, substrate **87a** readily reacts with diethyl H-phosphonate affording phosphonate **86a** in 70% yield. This confirms the generation of P-radicals from dialkyl-H-phosphonates oxidized by Ag_2CO_3 or $AgP(O)Ph_2$. For further understanding of the catalytic cycle of carbon atom phosphorylation, intra- and intermolecular kinetic isotope effects (KIE) were investigated (intramolecular $k_H/k_D = 1.27$ and intermolecular $k_H/k_D = 1.07$), indicating that C–H bond cleavage in the phenoxy ring was not the rate-limiting step.[168] Based on these results, a mechanism was proposed comprising a radical type catalytic cycle (Scheme 25).[168] First, P-radical **78** is generated from diethyl H-phosphonate (**1**) under the action of Ag_2CO_3 or intermediate **89**. Then the selective addition of the P-radical to the α-position of the C–O bond in **87a** yields alkenyl radical **90** stabilized by the phenyl group. This radical cyclizes to give intermediate **91**. Then a single-electron transfer from intermediate **91** to Ag^I releases product **86a** together with HNO_3 and Ag^0. In the presence of HNO_3, Ag^0 is oxidized to Ag^I.

Scheme 25



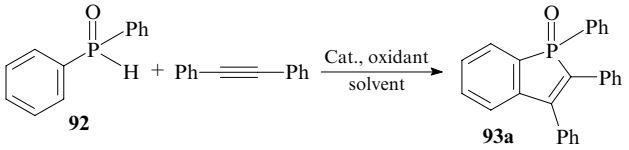
Thus, the research group of Wu[168] proposed a novel approach to the synthesis of 3-phosphonated coumarins from readily synthetically accessible alkynoates and commercially available H-phosphonates as P-radical precursors. Various 3-phosphonated coumarins were synthesized with high resioselectivity and in moderate to good yields. In the catalyzed phosphonation of the carbon atom of alkynoates, cheap and nontoxic silver salts were utilized.

V. Oxidative cyclization of phosphine oxides with acetylenes as a route to benzo[*b*]phosphole oxides

Organophosphorus heterocyclic compounds have extensive application in organic synthesis, medicinal chemistry and material chemistry.[18, 19, 170] Among these compounds, benzo[*b*]phospholes have recently attracted particular attention due to their valuable physical and optical properties suitable for the design of new optoelectrochemical materials.[171, 172] Most of the reported synthetic routes to benzo[*b*]phospholes start from the synthesis of *ortho*-halo-substituted arylalkynes followed by a multistep phosphonation and cyclization.[173–176] Development of novel effective approaches to benzo[*b*]phospholes is very attractive and is nowadays an important trend in the chemistry of organophosphorus compounds.

However, only few studies are devoted to the synthesis of P-containing heterocycles by C–H functionaliza-

Table 11. Oxidative cyclization of diphenylphosphine oxide with diphenylacetylene in the presence of silver and other metal compounds.[180]



Run [a]	Catalyst (mol.%) [b]	Oxidant (equiv.) [c]	Solvent [d]	Yield (%)
1	Cp^*RhCl_2 (2.5)	Ag_2CO_3 (3.0)	DMF	85
2	$Pd(OAc)_2$ (5)	Ag_2CO_3 (3.0)	DMF	77
3	–	Ag_2CO_3 (3.0)	DMF	70
4	–	Ag_2O (2.0)	DMF	85
5	–	$AgNO_3$ (4.0)	DMF	62
6	–	AgOAc (6.0)	DMF	85
7	–	AgOTf (6.0)	DMF	0
8	–	$Cu(OAc)_2$ (2.0)	DMF	0
9	–	$FeCl_3$ (4.0)	DMF	0
10	–	Ag_2O (1.5)	DMF	94
11	–	Ag_2O (1.5)	MeCN	89
12	–	Ag_2O (1.5)	dioxane	23
13	–	Ag_2O (1.5)	PhMe	21
14	–	Ag_2O (1.5)	dichloroethane	22
15	–	Ag_2O (1.5)	t-AmylOH	32
16	–	Ag_2O (1.5)	AcOH	74
17	Ag_2O (20)	$NaBrO_3$ (1.5)	DMF	22
18	Ag_2O (20)	CAN (2.0)	DMF	23
19	Ag_2O (20)	1 atm O_2	DMF	0

[a] Amount of **92**: 2.5 equiv. (runs 1–7), 2.0 equiv. (runs 8, 9), 1.5 equiv. (runs 10–19); 120 °C, 1 h (runs 1–9), 100 °C, 8 h (runs 10–19); [b] $Cp^* = \eta^5$-C_5Me_5; the dash means no catalyst; [c] Tf = CF_3SO_2; [d] t-AmylOH is *tert*-amyl alcohol.

tion.[98, 99, 157, 177–179] Recently, an interesting publication appeared[180] describing a silver-mediated CH–PH functionalization of disubstituted phosphine oxides with alkynes with the aim to synthesize benzo[*b*]phosphole oxides by a direct convenient procedure and in a high yield. In this reaction, an unusual aryl migration of the P-atom was observed occurring upon the C–P bond cleavage and formation of a new C–P bond proceeding as a radical process.

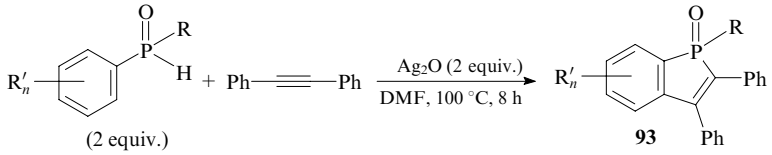
Duan and Chen[180] have found that diphenylphosphine oxide (**92**) enters the transition metal-catalyzed reaction with diphenylacetylene. A tentative intention of the authors was to use the coordination ability of phosphorus towards transition metals for the formation and functionalization of possible intermediate metallacycles *via ortho*-C–H-activation.[64, 181–184] Using Rh- or Pd-catalysts in the presence of Ag_2CO_3 as an oxidant facilitates somewhat the transformation to produce the desired P-heterocycle **93a** in a good yield (Table 11, runs 1 and 2).[180] In addition, a test showed the reaction to be initiated only in the presence of Ag_2CO_3 (run 3). Search for the optimal conditions revealed that the use of Ag_2O gave the best results (runs 3–7) [other oxidants such as copper acetate or ferric chloride were inactive (runs 8 and 9)] with dimethylformamide being the solvent of choice (runs 10–16). Finally, attempts to use catalytic amounts of Ag_2O with stoichiometric amounts of oxidants (sodium bromate, CAN and O_2) failed (runs 17–19).[180]

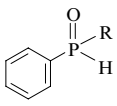
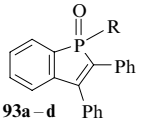
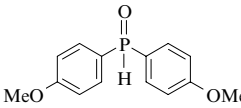
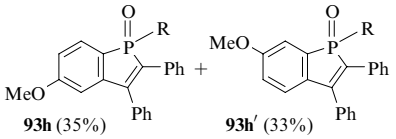
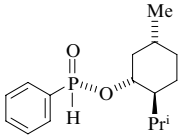
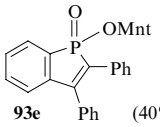
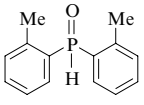
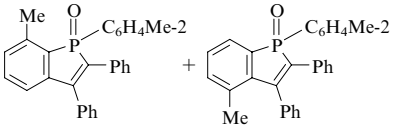
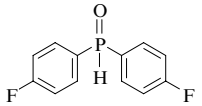
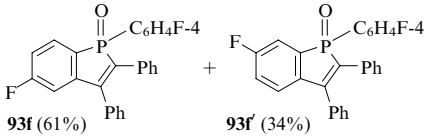
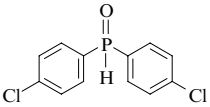
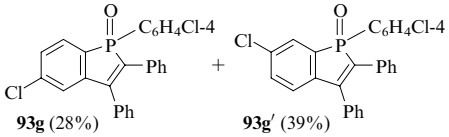
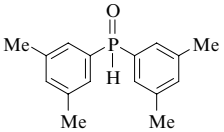
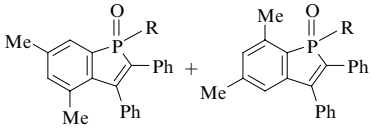
The method was applied to various substrates under the chosen optimal conditions (Table 12).[180] Phenylphosphine oxides bearing different substituents (Bu^t, Cy, EtO) can couple with diphenylacetylene giving the corresponding products **93b–d** in moderate to good yields. Optically pure phenylphosphinate having (–)-menthyl (Mnt) moiety can also be transformed to P-heterocycle **93e**, though with an evident loss of the enantiomeric excess. Also, aromatic phosphines bearing electron-donating and -withdrawing substitutents were investigated. Along with the desired products, a number of other compounds formed *via* aryl migration at the phosphorus atom were obtained (**93f′–93j′**). This aryl migration occurs through the C–P bond cleavage and formation of a new C–P bond; this reaction was unknown[185–188] before this publication of Chen and Duan.[180]

Reactions of diphenylphosphine oxide with various disubstituted alkynes were studied (Scheme 26).[180] Both diaryl- and dialkyl-substituted alkynes readily react with diphenylphosphine oxide (**92**) producing products **94a**,**b** in high yields. In the unsymmetrically substituted alkynes, the phosphorus atom occupies a sterically less hindered position (products **94c–e**). Moreover, ethyl-3-phenylpropiolate and 3-phenylpropionitrile are also suitable reagents able to extend the scope of the method (products **94f**,**g**). Chen and Duan[180] applied the interesting approach proposed by Yang and co-workers[178] to regenerate the active Ag^I catalyst from Ag^0 by oxidation with metal nitrates. Study of a number of nitrates showed that 1 equiv. of zinc nitrate with 5 mol.% of Ag_2O favours the coupling reaction of phosphine oxides with alkynes to produce P-heterocycles in moderate to good yields (see Scheme 26).[180]

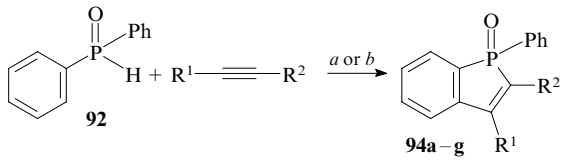
To get a deeper insight into the mechanism of this reaction, a set of special experiments was performed. First, competing reactions of diphenylphosphine oxide (**92**) with

Table 12. Silver oxide-catalyzed oxidative cyclization of phosphine oxides with diphenylacetylene.[180]



Phosphine oxide	Products (yield)	Phosphine oxide	Products (yield)
	 **93a–d** R = Ph (**a**, 94%), Bu^t (**b**, 76%), Cy (**c**, 42%), OEt (**d**, 60%)		 **93h** (35%) **93h′** (33%) R = 4-MeOC$_6$H$_4$
 (*dr* = 99 : 1)	 **93e** (40%, *dr* = 63 : 37)		 **93i** (22%) **93i′** (46%)
	 **93f** (61%) **93f′** (34%)		
	 **93g** (28%) **93g′** (39%)		 **93j** (61%) **93j′** (26%) R = 3,5-Me$_2$C$_6$H$_3$

Scheme 26



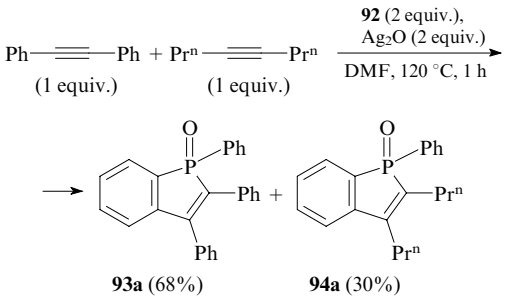
(*a*) Ag_2O (2 equiv.); (*b*) Ag_2O (5 mol.%), $Zn(NO_3)_2 \cdot 6H_2O$ (1 equiv.)

Compound **94**	R^1	R^2	Yield (%)	
			method *a*	method *b*
a	Pr^n	Pr^n	78	46
b	4-FC_6H_4	4-FC_6H_4	85	56
c	Ph	Pr^n	76	63
d	Ph	Me	81	62
e	4-FC_6H_4	Me	69	40
f	Ph	CO_2Et	82	52
g	Ph	CN	43	11

diphenylacetylene and dipropylacetylene were studied. The results showed that diphenylacetylene reacts with phosphine oxide faster than dipropylacetylene (Scheme 27).[180]

This may be caused by higher electron defficiency of PhC≡CPh. As regards aryl migration, phosphine oxides bearing two different aryl substitutents were considered. The compounds with phenyl and 4-fluorophenyl groups at the phosphorus atom proved to react at similar rates, while those with 4-methoxyphenyl group react a little slower (Scheme 28). The kinetic isotope effect was studied using the reaction of deuterated diphenylphosphine oxide with PhC≡CPh, and the ratio $k_H/k_D = 1.05$ was found. This result showed that the C–H bond cleavage in the aromatic ring of phosphine oxide is not the rate-limiting step.[180]

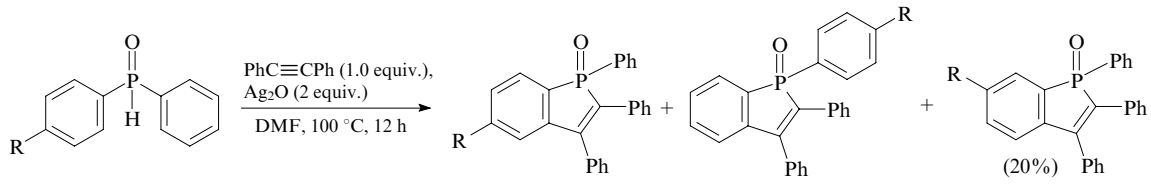
Scheme 27



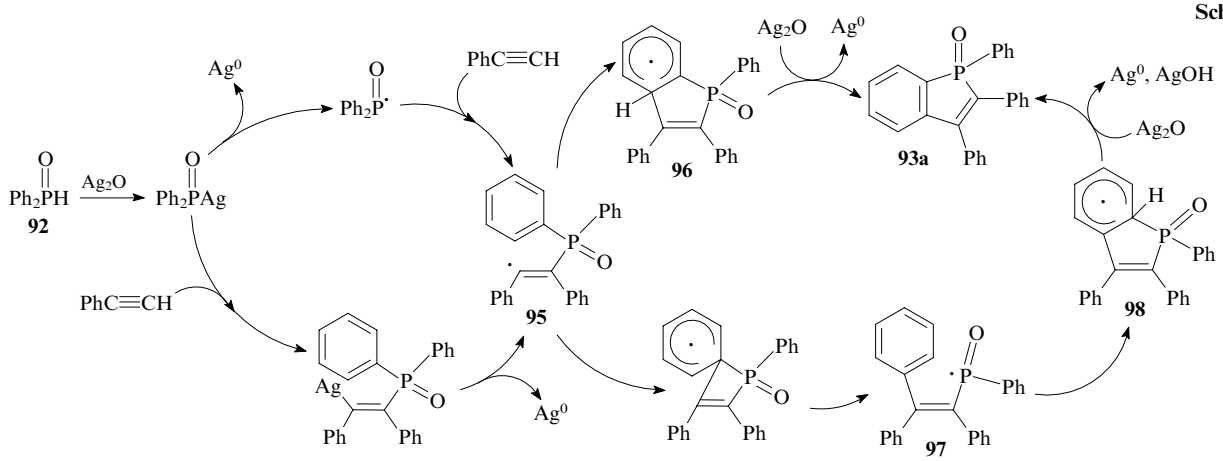
Since aryl migration often occurs in radical reactions, the authors[180] suggested a possible mechanism for the process under discussion (Scheme 29). In the first step, the P-radical is generated from the silver diphenylphosphine oxide and then the radical adds to phenylacetylene to furnish alkenyl radical **95**. Alternatively, radical **95** may be obtained through an addition of silver diphenylphosphine oxide to an alkyne followed by the silver-induced formation of an alkenyl radical. The next step is intramolecular addition of the alkenyl radical **95** to the *ortho*-position of the aryl moiety (relative to the phosphorus atom), which is followed by Ag_2O oxidation and removal of a proton to obtain P-heterocycle **93a** (*via* intermediate **96**). The aryl migration product is formed upon the attack of alkenyl radical **95** on the aryl moiety, particularly on the carbon atom directly bonded to phosphorus; subsequently, C–P bond cleavage results in the generation of P-radical **97**. And finally, radical phosphinylation of the aryl group located in the *cis*-position relative to the phosphorus atom in the presence of Ag_2O as an oxidant yields the P-heterocycle with migration of the aryl group (*via* intermediate **98**).[180]

For the purpose of further detailing of this mechanism, compounds **99** and **100** were obtained and investigated under the conditions of radical cyclization and the reaction

Scheme 28

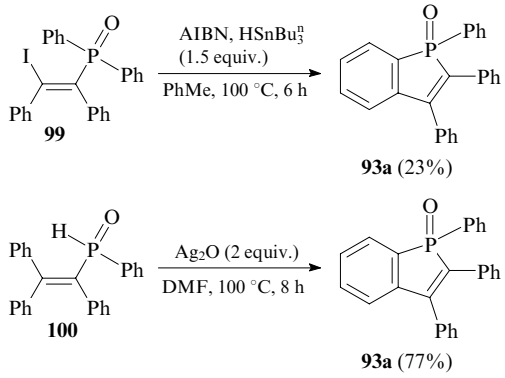


Scheme 29



under consideration, respectively.[180] The same P-heterocycle **93a** was obtained in both cases (Scheme 30).

Scheme 30

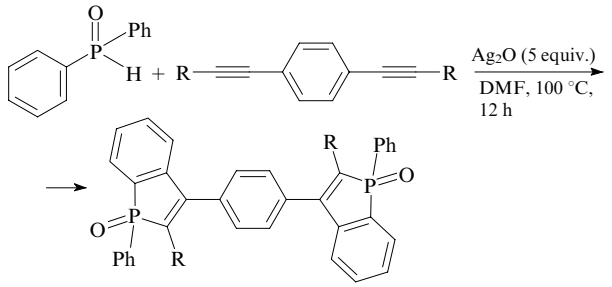


AIBN is α,α′-azobis(isobutyronitrile)

These results demonstrate that the radical process is suitable for both pathways, namely, **95** → **96** → **93a** and **98** → **93a**. Moreover, P-centred radicals may be obtained through reaction of disubstituted phosphine oxides with $Mn(OAc)_3$, *i.e.*, the transformation under investigation proceeds with $Mn(OAc)_3$ as an oxidant. Two types of benzo[*b*]phosphole oxides were isolated in good yields; this was accompanied by the aryl migration (Scheme 31), providing additional evidence for the mechanism outlined in Scheme 29.[180]

The efficacy of this method was shown in a single-step synthesis of bis(benzo[*b*]posphole oxides) (Scheme 32), which may find application in the organic electronics.

Scheme 32



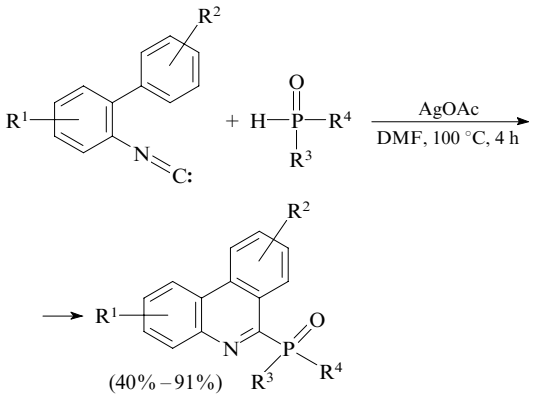
R = Me (62%), CO_2Et (32%)

Absorption and emission spectra of the benzo[*b*]phosphole oxides in CH_2Cl_2 were measured; all of these compounds were found to exhibit blue fluorescence with quantum efficiencies of 0.6%–14.5%. Thus, Duan and co-workers[180] described silver-mediated oxidative reaction of a C–H,P–H-functionalization of disubstituted phosphine oxides with internal alkynes producing benzo[*b*]phosphole oxides in high yields. An unusual aryl migration–cyclization at the phosphorus atom, occurring by a radical pathway as discussed above, was found.

VI. Phosphorylation of 2-isobenzocyanobiphenyls

In 2014, research groups of Studer[189] and Wu[190] independently described approaches to 6-phosphorylated phenanthridines from readily synthetically accessible 2-isocyanobiphenyls and commercially available P-radical precursors. In this case, radical cascade reaction comprises addition of a P-centred radical generated in the oxidative process to the isonitrile group followed by a homolytic aromatic substitution. A number of 6-phosphorylated phenanthridines were obtained in moderate to high yields. Contrary to methods of direct phosphorylation of aromatic compounds, which are now under vigorous research, in the above approach, the aromatic nucleus is formed upon the accompanying phosphorylation (Scheme 33).[189]

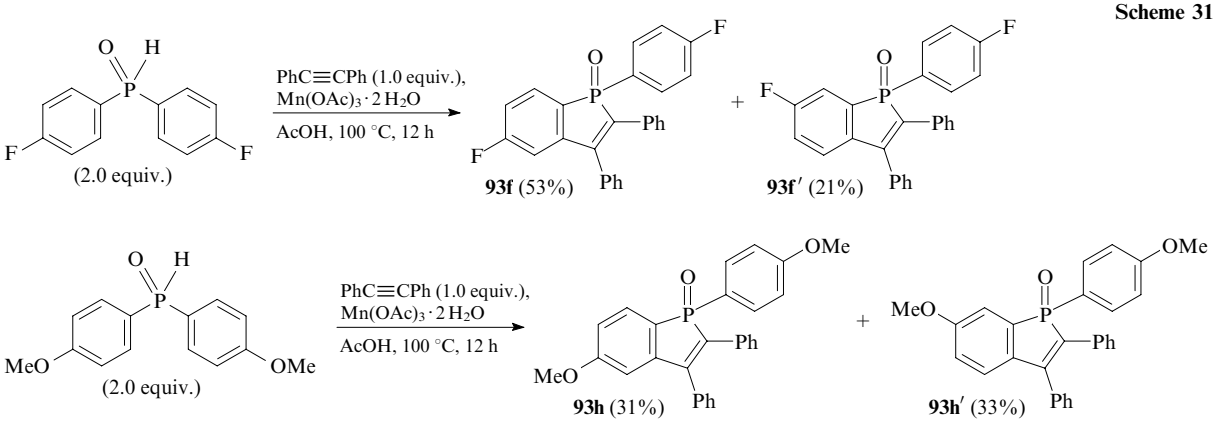
Scheme 33



C–P and C–C bond formation

R^1 = 2-Me, 2-F, *etc.*; R^2 = H, 8-Me, 8-Bu^t, 8-OMe, 8-Cl, 8-Ph, 8-CN, *etc.*; R^3, R^4 = Ph, OEt

Scheme 31



In recent years, aromatic isonitriles have attracted particular attention of scientists as radical acceptors in cascade reactions giving rise to heteroarenes.[191–195] The ingenuity and significance of the approach proposed by Studer's research group are, first, in the fact that arylisonitriles have not hitherto been employed as P-radical acceptors in cascade reactions. Second, in contrast to arene phosphorylation being intensively studied in which the C–P bond is commonly formed with retention of the aromatic ring, the phosphorylation in the above reaction is accompanied by the arene formation. Therefore, this approach does not face the regioselectivity problems, which arise in the direct CH-phosphorylation of arenes. Finally, contrary to the known methods in which the reaction involves formation of only the C–P bond, the process discussed now involves the formation of the C–P bond along with the C–C bond.

For the primary experiments, Studer's group chose a known pathway [189] in which P-centred radicals were formed from P–H-derivatives in the presence of $Mn(OAc)_3$ as an oxidant.[149–151, 196, 197] Radical phosphorylation of a readily synthetically accessible isonitrile **101a** with phosphine oxide **92** in the presence of $Mn(OAc)_3 \cdot 2H_2O$ as an oxidant in acetic acid at 100 °C for 4 h was investigated. The target product **102a** was obtained in 37% yield (Table 13, run 1). Optimization of the radical cascade reaction conditions showed that the product yield may be improved using AgOAc as an oxidant (run 2). Other oxidants which should have generated P-radicals from the corresponding P–H compounds (such as $AgNO_3 - K_2S_2O_8$ and Bu^n_4NI – TBHP) showed no expected result under the given conditions (runs 7 and 8). α,α′-Azobis(isobutyronitrile) as an initiator and oxidant has not provided the desired phosphorylated phenanthridine **102a**, another phenanthridine being formed as the major product upon addition of 2-cyanopropyl radicals (run 9).[189]

Out of solvents, DMF is best suited for this reaction, providing product **102a** in 91% yield (runs 2–4). The yield decreases when 1.5 equiv. of phosphine oxide **92** is used (run 5), and a decrease in the AgOAc amount significantly impairs the results (run 6).[189]

Then, the synthetic scope of the above approach under optimal conditions was investigated. First, substituents in the benzene ring devoid of isonitrile group were varied. It was found that substrates bearing electron-withdrawing or electron-donating substituents in the *para*-position react smoothly and the corresponding products **102b–h** can be isolated in moderate and good yields.[189]

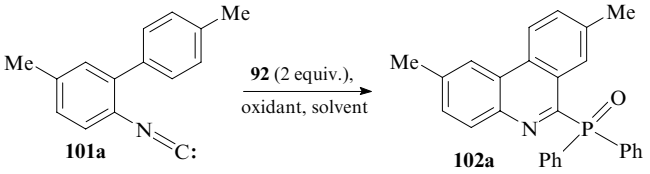
The yields slightly decreased, probably due to the steric factors, but were still quite acceptable for *ortho*-substituted substrates (products **102j,k**). Heteroaromatic substrates such as pyridine are also susceptible to this reaction, the product **102l** being isolated in 63% yield. The regioselectivity of this cascade reaction was studied in relation to *meta*-substituted arylisonitriles, which were successfully transformed into the corresponding products **102m–o** in moderate to good yields.[189]

Phenanthridine **102m** is formed with good regioselectivity (7 : 1 according to ^{31}P NMR data), and the formation of **102n,o** is fully regiocontrolled. The cyclization occurs mainly at the most distant position from the *meta*-substituent (only the major isomer **102m** is shown).

Arylisonitriles having substituents (other than Me) in the arene moiety with an isonitrile group also readily undergo the addition–cyclization reaction affording the corresponding products in moderate to good yields (*e.g.* product **102p**). Ethylphenylphosphinate was also shown to be a suitable precursor of P-radicals for this transformation, and phenanthrydine **102q** was isolated in 85% yield.[189]

The possible reaction mechanism is illustrated in Scheme 34. It is known that P-centred radicals can be obtained from diarylphosphine oxides upon the reaction

Table 13. Radical phosphorylation of isonitrile **101a** under various conditions.[189]

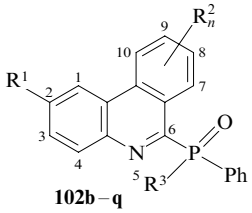


101a **102a**

Run	Oxidant (equiv.)	Solvent	Yield (%)
1	$Mn(OAc)_3 \cdot 2H_2O$ (3)	AcOH	37
2	AgOAc (3)	AcOH	79
3	AgOAc (3)	MeCN	77
4	AgOAc (3)	DMF	91
5[a]	AgOAc (3)	DMF	78
6	AgOAc (2)	DMF	30
7	$AgNO_3$ (0.2) + $K_2S_2O_8$ (3)	DMF	22
8	Bu^n_4NI (0.2) + TBHP (3)	MeCN	12
9	AIBN (1.5)	DMF	0

[a] 1.5 equiv. **92**.

Structures 102b–q

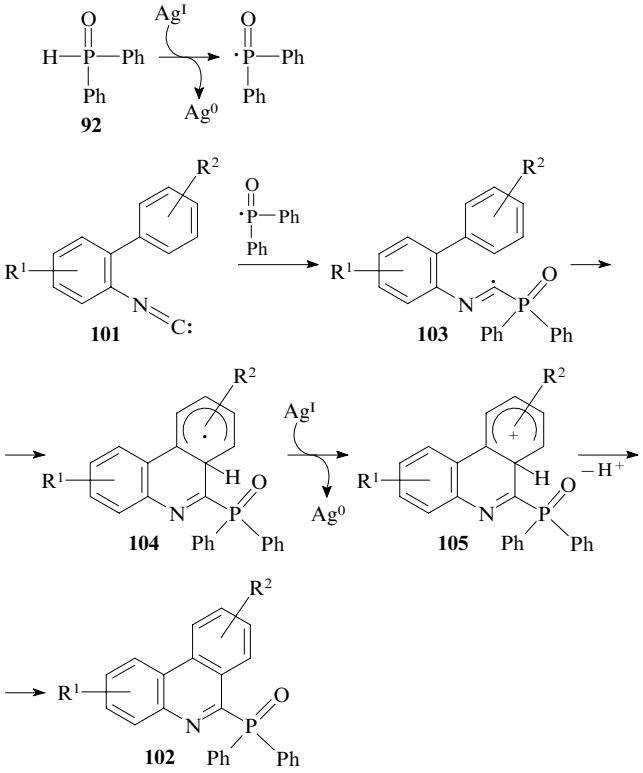


102b–q

Compound **102**	R^1	R^2_n	R^3	Yield (%)
b	Me	H	Ph	63
c	Me	8-Bu^t	Ph	80
d	Me	8-OMe	Ph	64
e	Me	8-Cl	Ph	62
f	Me	8-F	Ph	73
g	Me	8-Ph	Ph	71
h	Me	8-CN	Ph	45
i	Me	benzofuro[2,3-*k*]	Ph	45
j	Me	dibenzo[*j*,*k*]	Ph	56
k	Me	10-Me	Ph	58
l	Me	pyrido[3,4-*j*]	Ph	63
m	Me	9-Me	Ph	70
n	Me	9-Cl	Ph	65
o	Me	8,9-(OCH_2O)	Ph	40
p	F	H	Ph	50
q	Me	8-Me	OEt	85

with oxidants based on the Ag derivatives. Presumably, phosphine oxide **92** is the first to be oxidized with the Ag^I salt to generate the corresponding P-centred radical and Ag^0. It should be noted that the reaction produces a 'silver mirror'. The addition of P-radical to the isonitrile group of substrate **101** yields imidoyl radical **103**, which cyclizes to generate cyclohexadienyl radical **104**. Subsequently, radical **104** is oxidized with the Ag^I salt *via* single electron transfer to cyclohexadienyl radical **105**. Finally, cation **105** is deprotonated to produce product **102**.[189]

Scheme 34



The study of Wu's group[190] is practically identical to the work of Studer's group[189,191] as regards the ideas and the proposed mechanism; however, according to their results, the optimal synthetic conditions are the follows: $Mn(OAc)_3$ (3 equiv.), toluene, heating to 40 °C; this affords the desired product in 80% yield.

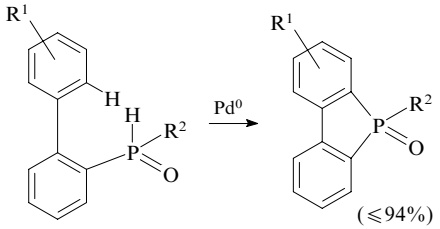
Thus, research groups of Studer[189,191] and Wu[190] proposed a novel approach to 6-phosphorylated phenanthridines from readily synthetically accessible 2-isocyanobiphenyls and commercially available diphenylphosphine oxide as a P-radical precursor. Various 6-phosphorylated phenanthridines were synthesized in moderate to good yields. The phenanthridine nucleus is an important structural moiety present in many natural compounds having diverse biological activities.[198,199] Therefore, the method proposed is expected to be applied to the synthesis of biologically active compounds.

VII. Phosphorylation of phenylpyridine and its derivatives

The ligand-directed phosphorylation using palladium complexes and salts becomes a new trend in the development of the aromatic C–H-bond functionalization. Just recently, Yu and co-workers[179] reported a palladium-catalyzed pyridine (or generally, heterocyclic compound)-directed C–H phosphorylation with the direct use of dialkyl H-phosphonates. This reaction comprises a step of *ortho*-palladation. Both H-phosphonates and diarylphosphine oxides are suitable coupling partners.

Here, it should be mentioned once again that one of the problems retarding the development of novel approaches to the design of the $C(sp^2)$–P bonds using metal complexes is the strong coordination ability of P reagents. Takai and coworkers[157] have successfully evaded this problem using a bound phosphite as both the directing group and the coupling partner and developed a first Pd^0-catalyzed reaction of intramolecular C–H-phosphorylation [Scheme 35, reaction (1)].

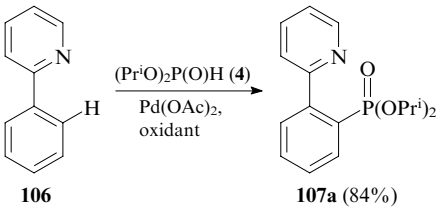
Scheme35



(1)

($\leqslant$94%)

R^1 = H, 3-Me, 4-MeO, 4-Cl; R^2 = Ph, Pr^i, Bu^t

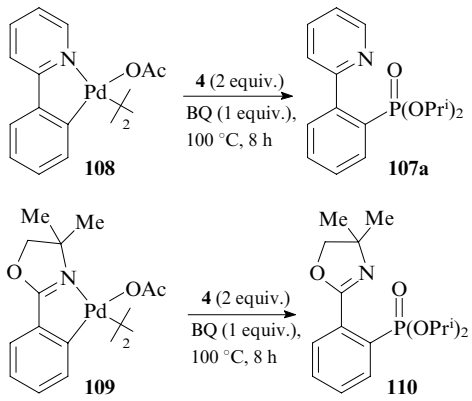


(2)

106 **107a** (84%)

Yu's research group[179] has successfully accomplished intermolecular C–H-phosphorylation of a number of heterocycles [such as, *e.g.* 2-phenylpyridine (**106**) yielding phosphonate **107a** (see Scheme 35, reaction (2)]. Pyridine- and oxazoline-containing phosphonates are potential pre-

Scheme 36



Product	Yield in various solvents (%)			
	MeCN	t-AmylOH	$ClCH_2CH_2Cl$	PhMe
107a	87	91	84	36
110	92	85	85	49

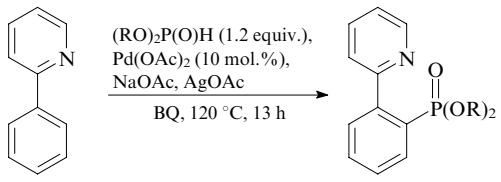
cursors in the synthesis of pharmaceticals[8, 9, 200] and N,P-bidentate ligands.[201] To recognize a possibility of the C–P bond formation from complexes comprising palladaheterocycles and dialkyl H-phosphonates, the authors treated the complexes **108** and **109** with phosphite **4** under various conditions. Mixing the reactants in the presence of 1 equiv. of 1,4-benzoquinone was found to produce desired phosphorylated product **107a** or **110** in moderate to high yield (Scheme 36). It was established that the presence of BQ is critical to the product formation. Presumably, BQ promotes the reductive elimination similar to that observed in the C–H bond coupling with organometallic reagents.[202, 203]

The conditions of this transformation were studied using 2-phenylpyridine (**106**) and phosphite **4** as model substrates. It is not surprising that a one-pot reaction with Pd catalyst gave no desired product.[179] Phosphite coordination to the Pd^{II} catalyst supposedly inhibits the C–H-activation step. Tautomeric equilibrium for H-phosphonates is well known and tricoordinated P atom of phosphite can strongly bind to the Pd^{II}-centre through a lone pair of electrons.[204]

To overcome this problem, dropwise addition of phosphite **4** to the reaction mixture was proposed, so that its concentration throughout the process was minimized.[179]

The chosen reaction conditions, namely, $Pd(OAc)_2$ (10 mol.%) as a catalyst, Ag_2CO_3 as an oxidant and Na_2CO_3 as a base and the dropwise addition of phosphite **4** at 100 °C (Table 14), furnished the desired product; *tert*-amyl alcohol was the solvent of choice (run 5). The reaction is favoured both by a suitable base and an acid (runs 6–9). Whereas K_3PO_4 as a stronger base totally inhibits the reaction (run 10), using NaOAc provides phosphonate **107a** in 69% yield (run 12). Among silver salts, AgOAc shows the best results (up to 79% yield) (run 15).

Scheme 37



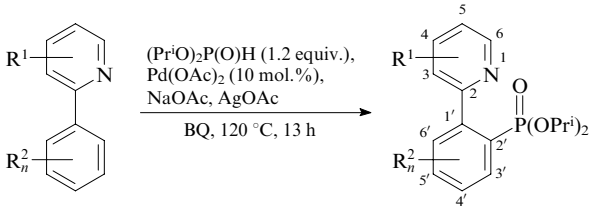
106 **107a–f**

R = Pr^i (**a**, 78%), Et (**b**, 66%), Ph (**c**, 0%), Bn (**d**, traces);
R–R = $CH_2CMe_2CH_2$ (**e**, 51%), CMe_2CMe_2 (**f**, 25%)

$Cu(OAc)_2$ and $K_2S_2O_8$ may also be used as oxidants though less effectively compared to the silver salt (runs 16 and 17). Rising the temperature to 120 °C increases the product yield up to 84% (run 18). For other diaryl H-phosphonates and cyclic H-phosphonates, the yields of phosphonates **107b–f** were lower (Scheme 37).[179]

The possible aromatic substrates entering the C–H-phosphorylation under the optimized conditions were examined (Scheme 38).[179] Aromatic substrates having an electron-donating methyl substituent in *para*- and *meta*-positions produced the expected products **111a**,**b** in yields of 73% and 80%, whereas *ortho*-methyl-substituted arene gave product **111c** in a lower yield (61%) because of a steric effect. Similar tendencies in the yields were observed for MeO-substituted arenes (products **111d–f**). Introduction of a moderately electron-withdrawing Cl atom into the *para*-position of arene does not affect markedly the process, and product **111g** was obtained in 67% yield. However, the presence of Cl atom in the *meta*-position and strong electron-withdrawing groups (F, CF_3, CN or CO_2Me) in the *para*-position decrease the yields of phoshonates **111h–k**,**m** down to 58%, 45%, 42%, 15% and 58%, respectively.[179]

Scheme 38



107a, **111a–r**

R^1 = H: R^2_n = 4′-Me (**a**, 73%), 5′-Me (**b**, 80%), 3′-Me (**c**, 61%), 4′-MeO (**d**, 61%), 5′-MeO (**e**, 70%), 6′-MeO (**f**, 63%), 4′-Cl (**g**, 67%), 5′-Cl (**h**, 58%), 4′-F (**i**, 45%), 4′-F_3C (**j**, 42%), 5′-NC (**k**, 15%), 4′-AcHN (**l**, 61%), 4′-MeO_2C (**m**, 58%), 4′,5′-benzo (**n**, 79%);
R^2_n = H: R^1 = 6-Me (**o**, 66%), 5-MeO (**p**, 73%), 3-Me (**q**, 79%), 3-MeO (**r**, 77%)

The reaction of 2-(2-pyridyl)naphthalene also proceeds readily and with a high selectivity — the β-phosphorylated product **111n** is obtained in 79% yield. Yields from moder-

Table 14. Optimization of the reaction conditions between 2-phenylpyridine and H-phosphonate **4** in the presence of $Pd(OAc)_2$ (10 mol.%) and 1,4-benzoquinone.[179]

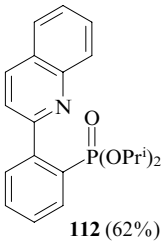
Run	*T*/°C	Base or acid	Oxidant	Solvent	Yield (%)	Run	*T*/°C	Base or acid	Oxidant	Solvent	Yield (%)
1	100	Na_2CO_3	Ag_2CO_3	dichloroethane	19	10	100	K_3PO_4	Ag_2CO_3	t-AmylOH	0
2	100	Na_2CO_3	Ag_2CO_3	MeCN	22	11	100	Natfa	Ag_2CO_3	t-AmylOH	47
3	100	Na_2CO_3	Ag_2CO_3	1,4-dioxane	17	12	100	NaOAc	Ag_2CO_3	t-AmylOH	69
4	100	Na_2CO_3	Ag_2CO_3	PhMe	34	13	100	NaOAc	Ag_3PO_4	t-AmylOH	73
5	100	Na_2CO_3	Ag_2CO_3	t-AmylOH	58	14	100	NaOAc	AgO	t-AmylOH	34
6	100	–	Ag_2CO_3	t-AmylOH	29	15	100	NaOAc	AgOAc	t-AmylOH	79
7	100	PivOH [a]	Ag_2CO_3	t-AmylOH	52	16	100	NaOAc	$Cu(OAc)_2$	t-AmylOH	50
8	100	AcOH	Ag_2CO_3	t-AmylOH	52	17	100	NaOAc	$K_2S_2O_8$	t-AmylOH	44
9	100	$NaHCO_3$	Ag_2CO_3	t-AmylOH	54	18	120	NaOAc	AgOAc	t-AmylOH	84
						19	140	NaOAc	AgOAc	t-AmylOH	72

[a] Piv is pivaloyl.

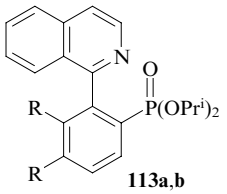
ate to good (66%–79%) were attained in the case of substitution in the pyridine ring (phosphonates **111o–r**).[179]

The method proved to be suitable for the other N-heterocycles. Directed phosphorylation of quinoline and isoquinoline affords the corresponding products **112** and **113a** in yields of 62% and 74%. Steric hindrances decrease the yield of the phosphorylation product **113b** (28%). The procedure[179] is suitable for the synthesis of some useful ligands such as phosphorylated 7,8-benzoquinone **114** (65%). Phosphorylation of 2-phenylpyrimidine produced the corresponding products **115a–c** in 61%–76% yields. The authors also attempted to apply this reaction to obtain PHOX-type ligands [2-(*o*-diphenylphosphinophenyl)oxazolines], but the yield of compound **110** was as low as 40%. 2-Phenylimidazole was also phosphonyled affording phosphonate **116** in 51% yield.[179] The reactions of these phosphonates with ArMgX produce triarylphosphine oxides, which may be readily reduced to give triarylphosphine ligands.

Structures 112–116

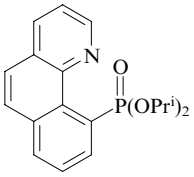


112 (62%)

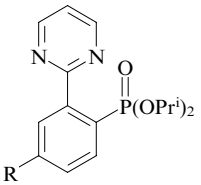


113a,b

R = H (**a**, 74%);
R–R is benzo (**b**, 28%)

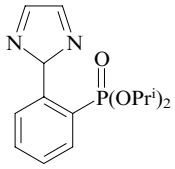


114 (65%)



115a–c

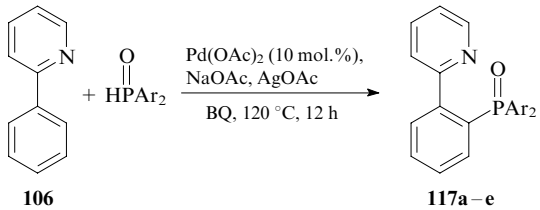
R = H (**a**, 61%), Me (**b**, 69%),
MeO (**c**, 76%)



116 (51%)

It was also demonstrated that various diarylphosphine oxides could act as P-reagents in the coupling under consideration, although under the conditions being studied the target products **117** were produced in moderate yields (Scheme 39).[179]

Scheme 39

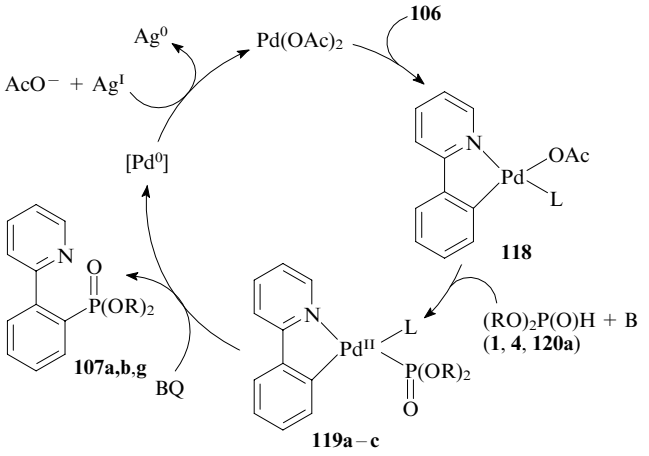


106 **117a–e**

Ar = Ph (**a**, 46%), 2-MeC_6H_4 (**b**, 39%), 3-$F_3CC_6H_4$ (**c**, 48%),
3,5-$Me_2C_6H_3$ (**d**, 46%), 3,5-$(F_3C)_2C_6H_3$ (**e**, 46%)

Being aware that Ag^I-mediated phosphorylation of indoles with H-phosphonates follows a radical pathway,[188] Yu and co-workers[179] performed a control run without Pd-catalyst; however, no reaction was observed. Since palladacycles **108** and **109** were shown to react with phosphite **4** to give phosphorylation products (see Scheme 36), it may be assumed that the process occurs *via* directed palladation followed by coupling with phosphites. CH-Activation of 2-phenylpyridine **106** generates cyclopalladium species **118**, which undergo anionic ligand exchange with the phosphite to form complex **119a–c**. Then, BQ-promoted reductive elimination furnishes the desired phosphorylation product **107**. The Ag^I-based oxidant again oxidizes Pd^0 to Pd^{II}, thus completing the catalytic cycle (Scheme 40). When comparing the course of the redox processses, one can see that this reaction[179] differs from the intramolecular Takai reaction in which Pd^0 inserts into a P–H bond forming P–Pd–H species, which cleave the C–H bonds.[157]

Scheme 40



R = Pr^i (**4**, **119a**, **107a**), Bu^n (**120a**, **119b**, **107g**), Et (**1**, **119c**, **107b**);
B is base

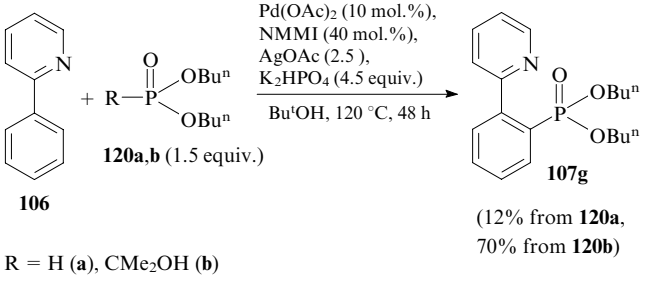
Thus, Pd^{II}-catalyzed intermolecular C–H-activation–phosphorylation reaction was originally developed by Yu and co-workers.[179] They were able to phosphorylate various heterocyclic substrates and obtain N,P-bidentate compounds which are potentially useful ligands for medicinal chemistry and catalysis. This approach was further developed in Pd-catalyzed *ortho*-C(sp^2)–H functionalization reactions promoted by ligands and weakly coordinated directing groups.[205]

The results of an independent study of a similar reaction of 2-arylpyridine phosphonation by Murakami's research group[206] were published in 2013, almost at the same time as the study of Yu and co-workers. They found that hydroxyalkylphosphonate generates an H-phosphonate acting as a masked phosphonylating reagent.[207–209] Treating the reaction mixture with a base[210] preserves the active state of the catalyst. Performing the stepwise stoichiometric reactions allowed the authors to comprehensively describe some details of the mechanism.

Upon treatment of 2-phenylpyridine (**106**) with phosphite **120a** in the presence of palladium(II) acetate (10 mol.%), *N*-methylmaleimide (NMMI, 40 mol.%), silver(I) acetate (2.5 equiv.) and K_2HPO_4 (4.5 equiv.) at 120 °C for 48 h, the product of phosphorylation of *ortho*-C–H-bond **107g** was obtained in the yield of only 12% (Scheme 41).[206] However, when phosphite **120a** was replaced by α-hydroxyalkylphosphonate **120b**, readily obtainable from phosphite **120a** and acetone in a single step, the product **107g** was surprisingly obtained in 70% yield along with a small amount (6%) of diphosphonated product. Thus, α-hydroxyalkylphosphonate **120b** proved to

be more effective phosphonation agent, probably, due to the fact that it gradually generates phosphite **120a**. Other reaction conditions were investigated using phosphite **120b** as a latent phosphonation agent; however, the use of such oxidants as $Cu(OAc)_2$ and Ag_2CO_3, stronger bases (K_3PO_4) and other solvents gave worse results.[206]

Scheme 41

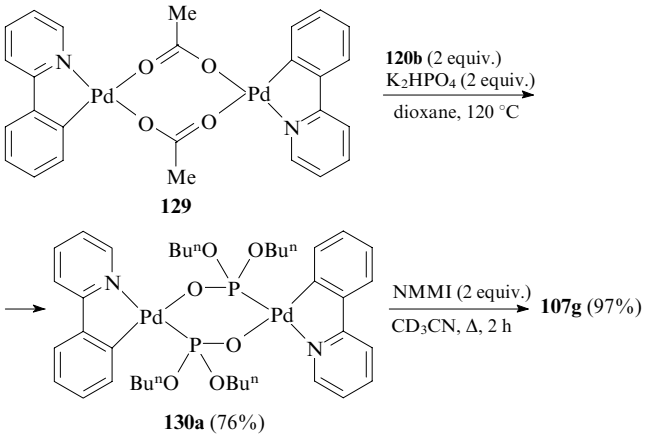


2-Arylpyridines bearing various substitutents were phosphorylated using reagent **120b** to yield phosphonates **121**–**128**. 2-(*o*-Tolyl)pyridine afforded monophosphonated product **121** (66%). The substrate bearing the *meta*-tolyl group was phosphonated selectively into a less sterically hindered position (product **122a**) (82%). Good yields were also attained in the case of MeO and Cl substituents in the phenyl moiety. The latter was replaced with benzothiophene and cycloheptene (products **123** and **124**), and the pyridine ring was changed for quinoline and pyrimidine rings (products **126** and **128**).[206]

The proposed reaction mechanism is illustrated in Scheme 40. Initially, cyclopalladation of substrate **106** with palladium(II) acetate furnishes palladacycle **118**.[211,212] α-Hydroxyphosphonate **120b** gradually releases acetone under the reaction conditions, thus generating a small amount of phosphite **120a**, which reacts with palladacycle **118** with replacement of the acetate ligand at the palladium atom. Palladium(II) complex **119b** undergoes reductive elimination under the action of NMMI. As a result, arylphosphonate **107g** is obtained along with Pd^0 species, which are reoxidized by silver(I) acetate to form Pd^{II}.[213–215]

Murakami and co-workers[206] performed several stoichiometric reactions to confirm the steps constituting the proposed catalytic cycle. Complex **118** was obtained by treating compound **106** with palladium(II) acetate (1.0 equiv.) in MeOH and isolated as dimer **129**. Then a solution of complex **129**, phosphonate **120b** (2.0 equiv.) and K_2HPO_4 (2.2 equiv.) in dioxane was heated at 120 °C (Scheme 42). The acetate ligand in complex **118** was replaced by phosphonate ligand to form complex **119b**, which was isolated as dimer **130a**.[206] In the next step, upon refluxing dimer **130a** in the presence of NMMI (2.0 equiv.), reductive elimination resulted in arylphoshonate **107g** in 97%yield (see Scheme 42). Benzoquinone and maleic anhydride also efficiently induce reductive elimination, while Ph_3P is less active (the product yield is 60% in 48 h). These data attest that electron-withdrawing ligands are essential to facilitate the reductive elimination of arylphosphonate **107g** from palladacycle **119b**.[206]

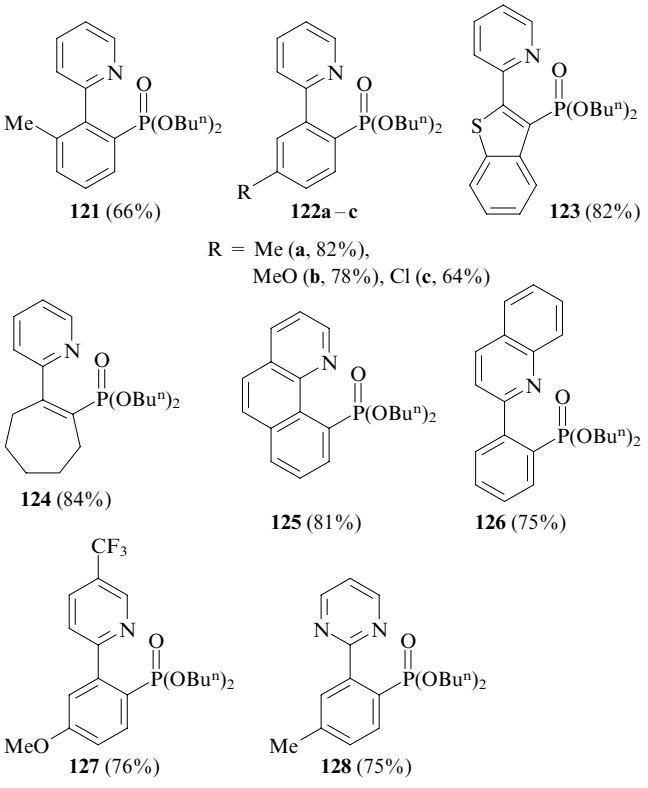
Scheme 42



Recently, an electrochemical version of phosphorylation of phenylpyridine was proposed.[216,217] Electrochemical methods for C–H substitution with phosphorus-containing nucleophiles are very limited. Successful examples of electrochemical reactions have been mainly known so far only for fucntionalization of nitroaromatic substrates.[80,218–223] Ligand-directed substitution at the C–H bond in phenylpyridine, which was earlier employed for acetoxylation and perfluoroalkylation under elecrochemical conditions[224,225] in the presence of palladium(II) acetate, proved to be effective in the case of phosphorylation.[216,217] The introduction of the phosphonate group is based on electrochemical oxidation of a mixture of palladium acetate, phenylpyridine and diethyl H-phosphonate at room temperature, phosphonate **107b** being obtained from substrate **106**.

Intermediate dipalladium cyclic compex **130b** (dimer of **119c** with EtO groups at the P-atom) formed *via* the *ortho*-palladation of phenylpyridine and substitution of phosphonate ions for acetate ions was isolated and studied by X-ray diffraction and for redox properties. Preparative oxidation

Structures 121–128



of complex **130b** affords selectively the product of phosphonation of the phenylpyridine C–H-bond, namely, phosphonate **107b**.[216, 217]

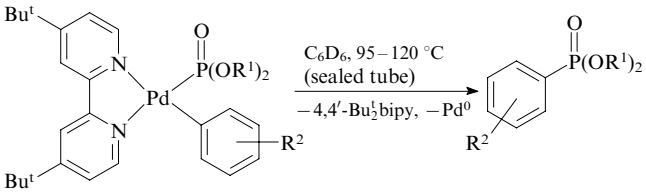
Thus, palladium-catalyzed phosphonation of aromatic $C(sp^2)-H$ bond can be accomplished using the pyridyl moiety as a directing group.

VIII. Arylpalladium compexes as intermediates in the C–P bond formation reactions

Reactions giving carbon–heteroatom bonds, including carbon–phosphorus bonds, are of key importance for the design of a variety of organic molecules. Understanding of electronic and steric effects of particular moieties at particular transformation steps and reaction pathways is critical for the development of highly active catalysts for these processes. Whereas reactions catalyzed by silver, manganese and copper derivatives follow, most often, radical mechanisms (see numerous examples in the present review) for which isolation and identification of intermediates is very difficult, the palladium-catalyzed reactions of P–C bond formation have been studied using a set of synthetic, spectroscopic, crystallographic and calculation techniques. The results of Stockland's research groups[117] are most impressive.

The formation of arylphosphonate from reaction intermediates of the $(4,4'\text{-}Bu^t_2bipy)Pd(Ar)P(O)(OR)_2$ type was investigated (Scheme 43).[226, 227] These compounds were the first isolated four-coordinate arylpalladium complexes comprising a phosphonate moiety, and they were rather resistant against reductive elimination at 25 °C. Studying the conditions necessary for inducing the reductive elimination from the given intermediates provided the idea of a key step of the phosphorus–carbon bond formation in the palladium-catalyzed synthesis of arylphosphonates. Furthermore, the chelating ligand determines the *cis*-positions of the aryl and phosphonate moieties in the Pd complex, therefore, there is no need in izomerization for the reductive elimination from these compounds to proceed.

Scheme 43



R^1 = Alk, Ar; R^2 = EDG, EWG; $4,4'Bu^t_2bipy$ is 4,4′-di-*tert*-butyl-2,2′-bipyridine

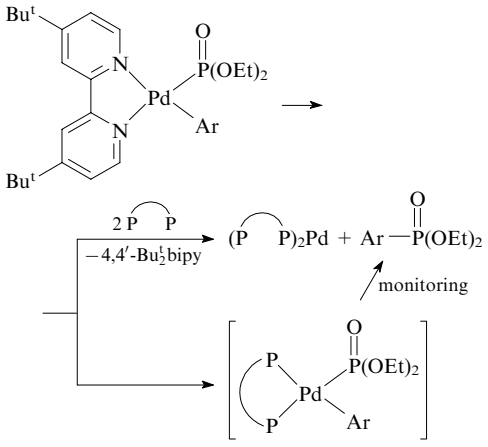
Unlike other reactions of carbon–heteroatom bond formation from Pd^{II} complexes,[228] aryl moieties bonded to a metal and comprising electron-donating groups, promote the elimination process, whereas substituents such as NO_2, Cl and CN (EWG) retard the phosphorus–carbon bond formation. Note that although the use of bipyridine-type ligands promoted the formation, isolation and identification of intermediates, complexes with monodentate or bidentate phosphine donor ligands are still utilized in most of palladium-catalyzed coupling reactions. The potency of diphosphine ligands in promoting the phosphorus–carbon bond formation *via* reductive elimination from intermediates of the type $(diphosphine)Pd(Ar)P(O)(OR)_2$ is of interest for developing more efficient catalysts.

Stockland and co-workers[226, 227, 229, 230] reported that silver phosphonates were convenient precursors of palladium and gold phosphonate species. For example, reaction of $(4,4'\text{-}Bu^t_2bipy)Pd(R)Cl$ with $AgP(O)(OR')_2$ afforded complexes $(4,4'\text{-}Bu^t_2bipy)Pd(R)P(O)(OR')_2$ in high yields. The researchers suggested that treatment of (diphosphine)Pd(R)Cl with silver phosphonate salts would furnish the desired compounds. However, numerous experiments resulted only in decomposition and formation of 'palladium mirrors'.[117] There was a strong need in an alternative method for the generation of diphosphine species $Pd(R)P(O)(OR')_2$. Since diphosphines are generally stronger donors towards the Pd atom compared to bipyridines, an addition of diphosphine to a solution of $(4,4'\text{-}Bu^t_2bipy)Pd(Ar)P(O)(OR')_2$ may cause displacement of the bipyridine ligand and formation of the expected complexes. The use of $(4,4'\text{-}Bu^t_2bipy)Pd(Ph)P(O)(OEt)_2$ as a model system and addition of 1.0 equiv. of $Ph_2P(CH_2)_2PPh_2$ (dppe) (in C_6D_6 solution) resulted in fast and quantitative elimination of bipyridine and generation of $(dppe)Pd(Ph)P(O)(OEt)_2$. Moreover, the ^1H NMR spectrum of this reaction mixture recorded several minutes after the diphosphine addition revealed the presence of $PhP(O)(OEt)_2$. This suggested that elimination from the compounds with a diphosphine ligand proceeds at far lower temperatures compared to bipyridine ligands.[117]

Having developed an efficient procedure for preparing the desired intermediates, Stockland and co-workers[117, 226, 227] synthesized a number of compounds using arylpalladium precursors with the aim to compare the electronic and steric effects in the aryl moiety bonded to a metal. The effects of typical impurities on the elimination reaction were studied;[117] whereas an excess of diphosphine or pyridine had a slight impact on the reaction rate, addition of water retarded the phosphorus–carbon bond formation. Coordination of water moleculs to the complex was observed by spectroscopic and crystallographic techniques.

To investigate the electronic effects caused by introduction of donor or acceptor groups into a metal-bonded aryl moiety and the influence of these groups on the rate of carbon–phosphorus bond formation, the elimination from

Scheme 44



$Ar = C_6H_{5-n}R_n$, P P is diphosphine ligand

(diphosphine)Pd($C_6H_{5-n}R_n$)P(O)(OEt)$_2$ species (R_n = 4-OMe, 4-Me, H, 4-CN, 4-NO_2, 2-Me, 2,6-Me_2) was studied (Scheme 44).[117]

Certain observations and conclusions concerning the elimination process have been made. Aryl groups bearing electron-withdrawing substituents demonstrated lower rates of reductive elimination compared to electron-rich aryl groups. If the reaction involving (dppe)Pd(Ph)P(O)(OEt)$_2$ is taken as a reference, the introduction of the 4-CN-group decreases the reductive elimination rate twofold, whereas the introduction of electron-donating 4-OMe-group significantly increases the reaction rate. These observations correlate with the mechanism involving an intramolecular attack of the metal-bonded *ipso*-carbon atom of the aryl moiety on the P-centre to form a new phosphorus–carbon bond. The presence of an electron-donating group should promote this process, whereas electron-withdrawing groups may slow down the bond formation.[117]

Although Stockland's explanation seems to be attractive, this kinetic model cannot exclude the possibility of concerted reductive elimination.[117] The replacement of dppe by other diphosphine ligands affects significantly the rate of the phosphorus–carbon bond formation. Using $Ph_2P(CH_2)_3PPh_2$ (dppp) as an ancillary ligand resulted in a marked increase in the rates of all elimination reactions. The complexes (dppp)Pd(4-RC_6H_5)P(O)(OEt)$_2$ (R = Me, MeO) undergo elimination at room temperature so rapidly that an adequate rate measurement was impossible. The electronic effect observed in these metal phosphonate systems differs from almost all the other carbon–heteroatom bond formation reactions described earlier for Pd^{II} (see Refs 228 and 231). Works of Hartwig and other researchers have demonstrated that reductive elimination from arylpalladium alkoxides,[232, 233] sulfides[234] and amides[235] comprising Pd^{II} complexes is promoted by the presence of electron-withdrawing groups in the metal-bonded aryl moiety. Although an apparent difference between the phosphonate systems consideted by Stockland and co-workers[117] and the systems involving OR, NR_2 and PR_2 groups consists in the absence of a lone electrons pair on the heteroatom, recent studies have shown that electronic effects observed in the carbon–heteroatom bond formation reactions are caused by σ-chain perturbations while π-contributions are minor.[117] It should also be noted that the rate of reductive elimination of arylphosphine from a diphosphine-bonded palladium phosphide increases upon introduction of an electron-withdrawing group (NO_2) into a metal-bonded aryl moiety.[236] Analysis of the elimination rates (k_{obs}) in relation to the compex comprising the electron neutral phenyl group (k_H) in terms of the Hammett plot is illustrated in Fig. 1. A nearly linear relationship between σ_p and the elimination rate was found ($\rho_I = -2.7$; $R^2 = 0.99$). It is of interest to compare these ρ_I values with similar parameters for the other carbon–heteroatom bond formation reactions. However, the inductive parameter σ provided a poor correlation for the elimination in aryl sulfides and arylamines. Linear correlations were observed when using a parameter representing the resonance effects of substituents (σ_R). The ρ value for the reactions of carbon–carbon bond formation from Pd^{II} complexes may also be compared with the values for the transformations under consideration. It should be noted the the formation of biaryls from palladium(II) compounds proceeds rapidly and this complicates the measurements.[117]

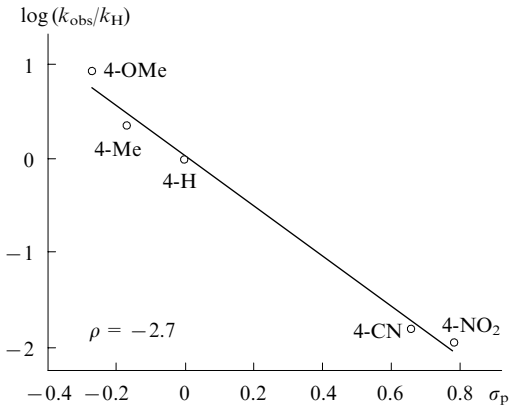


Figure 1. Hammett linear plots for the elimination reaction from (dppe)Pd(4-RC_6H_4)P(O)(OEt)$_2$.[117]

The authors compared the electronic and steric effects of the metal-bonded aryl moieties on the elimination rate taking into account the structure of the diphosphine ligand. The complexes (diphosphine)Pd(Ar)P(O)(OEt)$_2$, where Ar = Ph, 4-NCC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-MeC_6H_4, 2,6-$Me_2C_6H_3$ *etc*., diphosphine = dppe, dppp, were studied. It was found that for dppe complexes, the electronic factor

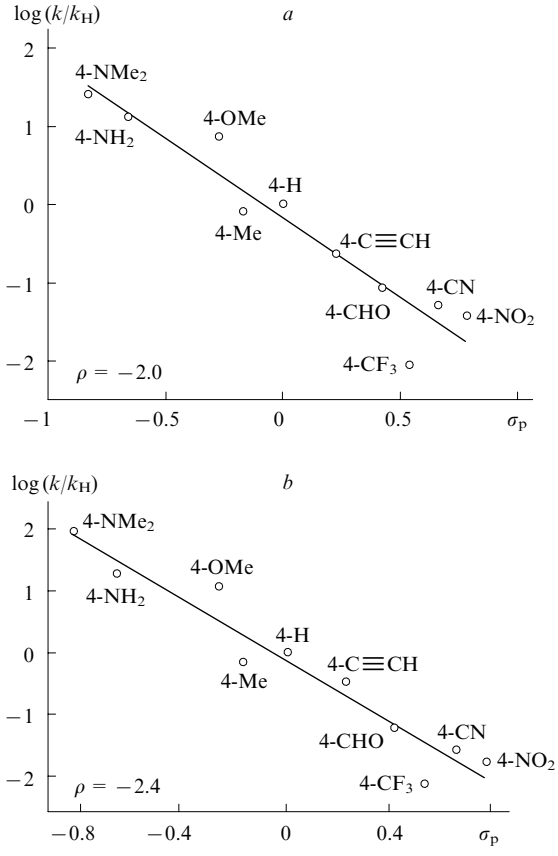


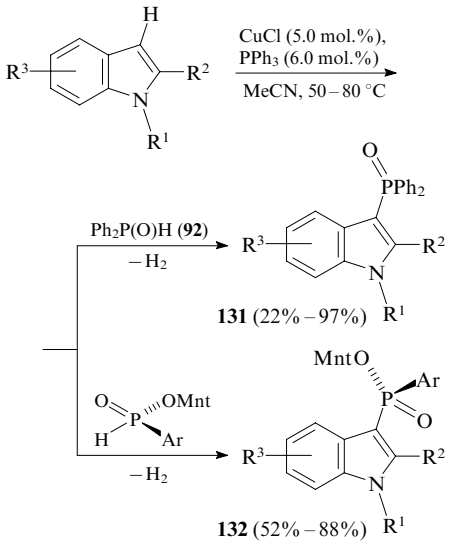
Figure 2. Calculated Hammett plots for the reaction of phosphorus–carbon bond formation upon the reductive elimination from the Pd complex having 4-RC_6H_4ligand.[117]
(*a*) In the gas phase, (*b*) in benzene.

is of critical importance; however as the chain length of the diphosphine ligand increases (replacement of dppe by dppp), the role of steric characteristics of the aryl moiety grows.

Computational investigations of the reductive elimination supported the experimental data. The results of DFT calculations confirmed the conclusion that the mechanism of formation of the P–C bonds is reductive elimination and electron-withdrawing substituents promote the process.[117]

Thus, a number of phosphonate complexes of arylpalladium have been obtained, characterized and examined as key intermediates of the palladium-catalyzed coupling reactions. All the palladium complexes eliminate arylphosphonate species in high yields and under mild conditions. In contrast to almost all other carbon–heteroatom bond formation reactions from palladium(II) complexes, the presence of electron-withdrawing groups in the metal-bonded aryl moiety results in lower rates of the reductive elimination. Using the Hammett equation demonstrated linear plots for σ_p with $\rho_I = -2.7$ (see Fig. 1). Computational study confirmed this experimental observation and also revealed a linear dependence of a relative rate on σ_p with $\rho = -2.4$ for a model system in benzene solution (Fig. 2).[117]

Scheme 45



R^1 = H, Me, *etc.*; R^2 = H, Me, CO_2Et, CO_2Me, 2-Py, *etc.*; R^3 = H, Me; Ar = Ph, *etc.*; Py is pyridyl

IX. Synthesis of 3-phosphoindoles *via* cross-coupling reaction with hydrogen evolution

Generally, novel approaches to direct activation and functionalization of C–H bonds catalyzed by transition metals are based mainly on the oxidative Heck coupling and the Li cross-coupling reaction followed by dehydrogenation, catalytic tandem direct arylation *etc.*[61, 70, 74, 78, 237–242] Although the above transformations were described in terms of the catalytic dehydrogenation–cross-coupling, no hydrogen gas by-product was generally evolved in these reactions. The cause is that the loss of H_2 upon C–C or C–heteroatom bond formation is thermodynamically unfavourable. Furthermore, metal-catalyzed dehydrogenation–coupling usually requires a stoichiometric amount of an oxidant as an external driving force. In the oxidative Heck coupling reactions accompanied by dehydrogenation, a base is also added.

Currently, the development of a transition metal-catalyzed oxidative cross-coupling with direct removal of H_2 presents an important and serious challenge.[243, 244] In 2014, Yang's research group[245] discovered a unique Cu^I-catalyzed cross-coupling reaction proceeding with the removal of hydrogen (H_2) resulting in a stereoselective synthesis of 3-phosphoindoles. This reaction totally obviates the use of an oxidant and a base, falling outside the scope of the dehydrogenation–coupling oxidative reactions; the hydrogen is evolved as the only one by-product. This approach made it possible to synthesize a number of 3-phosphoindoles **131**, **132** (Scheme 45).

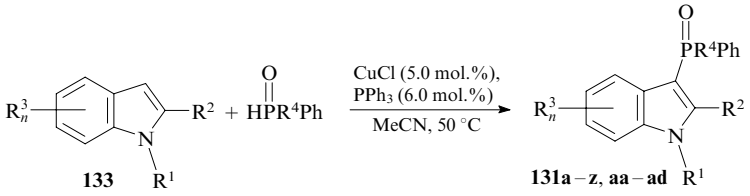
The proposed process has the advantages including the ease of application, mild conditions, possibility of scaling-up (gramme amounts). Indole is an important structural moiety commonly encountered in pharmaceuticals and natural products.[178, 246–251] Therefore, the functionalization of indole *via* C–H-bond activation attracts considerable attention and the transition metal-catalyzed phosphorylation of the indole C–H-bonds with the aim to form C–P bonds is of special interest. 3-Phosphoindoles represent novel second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs), demonstrating an excellent potency *in vitro* agaist wild-type and NNRTI-resistant type of HIV-1.[252–256]

In the primary study,[245] Yang and co-workers chose ethyl *N*-methylindole-2-carboxylate (**133a**) and phosphine oxide $Ph_2P(O)H$ (**92**) as model substrates. A broad screening for catalysts, solvents and temperatures was performed. The optimal reaction conditions were thus found to be as follows: CuCl catalyst (5 mol.%), PPh_3 ligand (6 mol.%) in MeCN; 2 equiv. of indole **133a** (relative to phosphine oxide **92**), 50 °C, argon atmosphere.

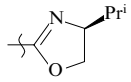
The effects of various functionalities and a range of suitable substrates were examined (Scheme 46). Study of various N-protective groups showed that methyl, ethoxycarbonylmethyl and benzyl derivatives react much better that the NAc derivative (see the yields of products **131a**,**c**–**e**). N-Unsubstituted ethyl indole-2-carboxylate also reacts efficiently, the corresponding products being obtained in high yields (**131b**,**f**).[245]

Steric effects have no appreciable influence: good yields of the products were observed for the substrates having a Me group in position 4, 5, 6 or 7 (phosphonates **131h**–**k**). Studying the electronic effects showed that electron-donating groups improve the reactivity of substrates compared to electron-withdrawing ones. Indeed, for most of products **131l**–**r**, high yields were actually obtained. Other phosphonates such as Ph(EtO)P(O)H also react to give the desired products in moderate yields (for example, **131s**). The given reaction is characterized by a high tolerance to functional groups. When a substituent [*e.g.* Ac, CHO, CN, C(O)NHMe and Ph] is located in position 2 of indole, the reaction proceeds readily with the good yields of the corresponding products (**131t**–**v**,**x**,**y**). However for the groups such as CO_2H, Me or H atom in position 2, the substrates turned out to be practically inactive (phosphonates **131z**,**aa**,**ab**). Heterocyclic groups (*e.g.* pyridyl and oxazolyl) can also serve as substituents suitable for the reaction. In this case, the potential P,N-ligands **131ac**,**ad** are obtained. It is noteworthy that the reaction may be

Scheme 46



Compound **131** [a]	R^1	R^2	R^3_n	Yield (%)	Compound **131** [a]	R^1	R^2	R^3_n	Yield (%)
a	Me	CO_2Et	H	97	**p**	Me	CO_2Et	5-CF_3	81
b	H	CO_2Et	H	93	**q**	Me	CO_2Et	5-OH	61
c	CH_2CO_2Et	CO_2Et	H	78	**r**	Me	CO_2Et	5-Cl, 7-Me	89
d	Bn	CO_2Et	H	80	**s**	Me	CO_2Et	H	69
e	Ac	CO_2Et	H	18	**t**	Me	Ac	H	95
f	H	CO_2Me	H	88	**u**	Me	CHO	H	96
g	Me	CO_2Me	H	91	**v**	Me	CN	H	93
h	Me	CO_2Et	7-Me	90	**w**	H	$C(O)NH_2$	H	22
i	Me	CO_2Et	6-Me	91	**x**	H	C(O)NHMe	H	86
j	Me	CO_2Et	4-Me	89	**y**	H	Ph	H	78
k	Me	CO_2Et	5-Me	91	**z**	H	CO_2H	H	0
l	Me	CO_2Et	5-OMe	96	**aa**	Me	H	H	traces
m	Me	CO_2Et	5-F	87	**ab**	Me	Me	H	0
n	Me	CO_2Et	5-Cl	90	**ac**	Me	2-Py	H	73
o	Me	CO_2Et	5-Br	81	**ad**	Me	see [b]	H	77

[a] For **131s** R^4 = OEt, otherwise R^4 = Ph; [b] R^2 = 

successfully scaled-up with the high product yields being retained.[245]

A special attention was given to the stereoselective synthesis of chiral 3-phosphoindoles. The progress of this stereoselective method is of critical importance for examination of the asymmetric functionalization of C–H-bonds and development of therapeutics against HIV-1.[245] The use of (1*R*,2*S*,5*R*)–(–)-menthol as a reactant in this reaction afforded a chiral (1*S*,2*S*,5*R*)–(–)-menthyl phenylphosphinate (**134**), which was used in the synthesis of chiral 3-phosphoindoles **132a–s** (Scheme 47). The authors identified a wide range of indole derivatives which turned out to be effective substrates in the reaction under consideration.[245]

Chiral 3-phosphoindoles bearing electron-donating or electron-withdrawing substituents in the aromatic ring may be obtained in good yields and with high stereoselectivity. Also, N-unsubstituted indoles with different substituents in position 2 proved to be active substrates and demonstrated stability of the functional groups.[245]

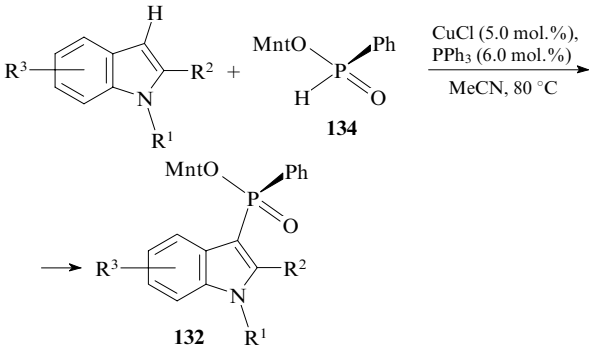
Compound **135** (IDX899), a new second-generation NNRTI, exhibits considerably higher resistance and sufficiently lower toxicity, good adhesion and better pharmacokinetic behaviour compared to NNRTIs of the first generation (Scheme 48).

Compound IDX899 has been approved by the FDA and is currently under phase II clinical trials.[253] To confirm the synthetic value of the method, Yang and co-workers[245] transformed commercially available 5-chloro-1*H*-indole-2-carboxylate into a precursor of IDX899 (compound **132t**) in 56% yield *via* cross-coupling with menthyloxy 5-methyl-3-cyanovinylphenylphosphinate with evolution of hydrogen (H_2). It was suggested[178,199,257–259] that this dehydrogenation–coupling reaction follows a radical mechanism similar to the previously described processes involving $Ph_2P(O)H$.

To establish the mechanism, Yang and co-workers[245] utilized radical scavengers such as cyclohexa-1,4-diene and BHT (2 equiv.). In the presence of these scavengers under usual reaction conditions, product **131a** was obtained in 89% and 94% yields, respectively. These results demonstrate that the transformation can be a non-radical process. Attempts to use TEMPO and 1,1-diphenylethene failed as they caused substrate decomposition. The intermolecular kinetic isotope effect was observed, (k_H/k_D = 1.2) suggesting that cleavage of the C–H bonds occurs after the rate-limiting step.

Basing on the kinetic studies, the authors[245] proposed that the formation of activated L_nCuH species (**136**) is the key step of this process and the evolution of hydrogen is the driving force of the reaction. The assumed mechanism is illustrated in Scheme 49. First, diphenylphosphine oxide reacts with the complex L_nCuCl (L = PPh_3) to form intermediate complex $L_nCuP(O)Ph_2$ (**137**). Then, the latter coordinates to ethyl *N*-methylindole-2-carboxylate (**133a**) affording η^2-complex **138**, which is subsequently converted to η^1-complex **139** *via* insertion. Finally product **131a** is formed upon anti-β-elimination of the hydrogen atom and dissociation, with regeneration of the active catalyst L_nCuH (**136**), which reacts with diphenylphosphine oxide to produce intermediate complex $L_nCuP(O)Ph_2$ (**137**). Hydrogen and HCl are evolved in the catalytic cycle. Thus, Yang and

Scheme 47



Compound **132**	R^1	R^2	R^3	Yield (%)	*dr*
a	Me	CO_2Et	H	88	> 20 : 1
b	H	CO_2Et	H	65	> 20 : 1
c	Me	CO_2Me	H	86	> 20 : 1
d	H	CO_2Me	H	67	> 20 : 1
e	Me	CO_2Et	4-Me	80	> 20 : 1
f	Me	CO_2Et	5-Me	85	> 20 : 1
g	Me	CO_2Et	5-OMe	84	> 20 : 1
h	Me	CO_2Et	5-F	73	> 20 : 1
i	Me	CO_2Et	5-Cl	78	> 20 : 1
j	Me	CO_2Et	5-Br	83	> 20 : 1
k	Me	CO_2Et	5-CF_3	79	> 20 : 1
l	Me	CN	H	79	> 20 : 1
m	Me	C(O)NHMe	H	52	~ 10 : 1
n	Me	C(O)NHOMe	H	73	~ 12 : 1
o	Me	CHO	H	82	~ 18 : 1
p	Me	Ac	H	82	> 20 : 1
q	H	C(O)NHOMe	5-Cl	68	~ 11 : 1
r	H	(*R*)-C(O)NHCHPhMe	H	traces	
s	Me	CHO	5-Cl	76	~ 17 : 1

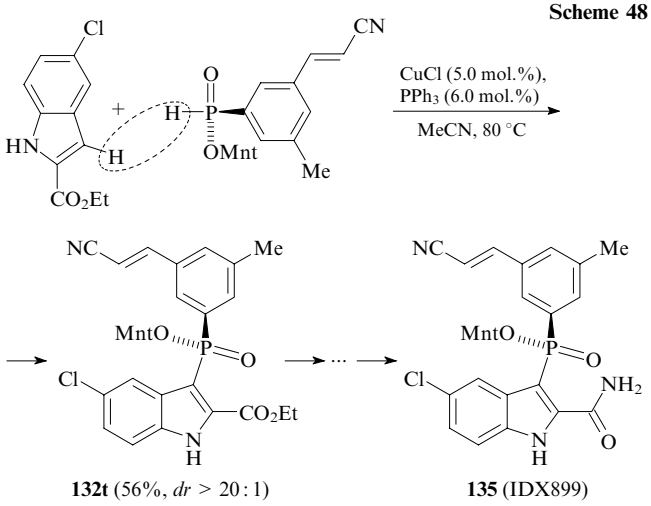
co-workers[245] elaborated a high-yield synthetic procedure to obtain various 3-phosphoindoles by a copper-catalyzed cross-coupling reaction with the evolution of hydrogen.

X. Phosphorylation of benzamides

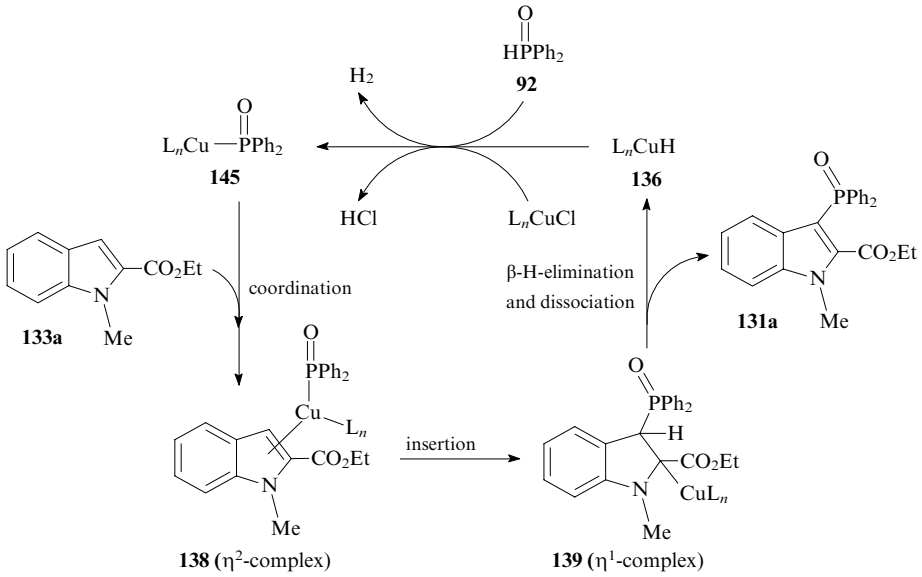
Very recently, Yu and co-workers[260] reported phosphorylation with dialkyl H-phosphonates of *ortho*-C–H bonds in benzamides containing an 8-aminoquinoline moiety as a bidentate directing group (for example, compound **140a**) using a copper catalyst under mild temperature conditions. This method demonstrates a high compatibility of functional groups and selectively affords monosubstituted products (*e.g.*, **141a**) (Scheme 50).

The aplication of Cu-reagents as catalysts for C–H bond activation is especially advantageous because of their low cost and low toxicity. Numerous examples of C–H-bond functionalization reactions using copper catalysts are known; however, not a single intermolecular direct phosphorylation of aromatic C–H-bond was reported before publications of Yu's research group. Using an amide (8-acylaminoquinoline) as a directing group allows one to stabilize the high-valence Cu-intermediates.[261, 262] It was suggested that the 8-aminoquinoline moiety should also favour the *ortho*-phosphonation of C(sp^2)–H-bonds.

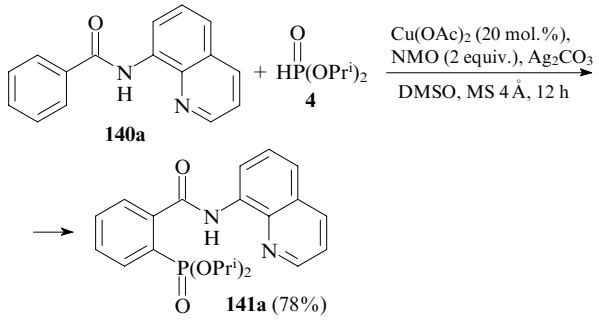
Scheme 48



Scheme 49



Scheme 50

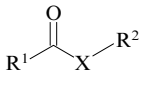


NMO is *N*-methylmorpholine-*N*-oxide

The optimal conditions for the reaction between *N*-(quinoline-8-yl)benzamide (**140a**) and diisopropyl H-phosphonate (**4**) were found to be as follows: $Cu(OAc)_2$ catalyst (20 mol.%), Ag_2CO_3 oxidant, DMSO, 55 °C. Under these conditions, product **141a** was obtained in 78% yield.[260]

The effect of the directing group nature was studied separately (substrates **140b–g**).[260] *N*-Methylamide **140b** showed no reaction with diisopropyl H-phosphonate. Probably, the acidic proton of the NH-group of amide **140a** plays an important role. Unsuccessful attempts to introduce substrates **140c–e** into the reaction provided the conclusion that *N*,*N*-bidentate directing group is of utmost importance for the process to proceed. Furthermore, using *N*-benzylpicolineamide (**140f**) or *N*-(2-methylsulfanylphenyl)benzamide (**140g**) resulted in a trace amounts of the phosphorylation products. Hence, the reaction appeared to be more effective when applying 8-acylaminoquinoline moiety as a directing group.

Structures 140b–g



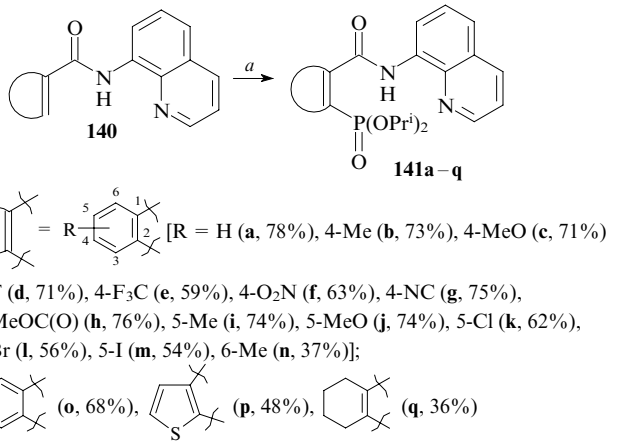
140b–g

Compound **140**	X	R^1	R^2
b	NMe	Ph	8-quinolyl
c	O	Ph	8-quinolyl
d	NH	Ph	1-naphthyl
e	O	Ph	2-pyridylmethyl
f	NH	2-Py	Bn
g	NH	Ph	2-$MeSC_6H_4$

The reaction of benzoic acid quinolylamides with phosphite **4** under optimal reaction conditions to give products **141a–n** was studied (Scheme 51).[260]

Both electron-rich and electron-deficient derivatives of benzoic acid are suitable for the cross-coupling, resulting in products **141b**,**c**,**i**,**j** and **141d–h**,**k–m**, respecrively, in moderate to good yields. In these cases only *ortho*-monophosphorylated products were isolated. Furthermore, the reaction tolerates many functional groups including ether groups (**141c**,**j**), halogen atoms (**141d**,**k–m**), ester (**141h**), nitrile (**141g**) and nitro groups (**141f**). On introducing *meta*-substituted benzamides into the reaction, irrespective of the electronic nature of substitutents, phosphorylation mainly involves the less sterically hindered position (**141i–m**). Also, both five- and six-membered heterocyclic amides are suitable as substrates. Pyridine and thiophene derivatives were transformed into monosubstituted products **141o**,**p** in high yields.[260]

Scheme 51



(*a*) $(Pr^iO)_2P(O)H$ (**4**), $Cu(OAc)_2$ (20 mol.%), NMO (2 equiv.), Ag_2CO_3, DMSO, MS 4 Å, 12 h

The copper-catalyzed direct phosphorylation in question is also applicable to vinyl C–H-bonds (product **141q**). This reaction was scaled up by a factor of ten. Various dialkyl and diaryl H-phosphonates were also studied, the corresponding products being obtained in moderate yields. Apparently, steric and electronic effects of phosphites affect the rate and efficacy of the process. When the coupling P-reagent was replaced by dihexyl H-phosphonate having longer aliphatic chains, the reaction time increased. For diphenyl H-phosphonate, the reaction was totally arrested because of the bulky benzene rings. Finally, diisopropyl H-phosphonate (**4**) turned out to be the best reagent for phosphorylation of *N*-(8-quinolyl)benzamide derivatives.[260]

Taking into account the previous data where Ag^I-catalyzed phosphorylation of indoles[177] and *N*,*N*-diethylbenzamide[96] with dialkyl H-phosphonates followed a radical pathway, a control run in the presence of TEMPO was performed.[260] The addition of TEMPO did not decrease the product yield in the model reaction. In addition, there was no reaction in the absence of Cu catalyst. These results suggest that radicals are not involved in the catalytic phosphorylation cycle. Although the reaction mechanism is not clear as yet, there is a strong possibility that it occurs *via* Cu^{III}-intermediate (a 'silver mirror' and/or silver black were observed after the reaction).[263]

Thus, a method for direct intermolecular C–H-phosphorylation of a non-acidic benzamide *ortho*-C–H bond was elaborated.[260] The reaction utilizes low-cost copper acetate under mild conditions. Moreover, the process yields selectively only monosubstituted products and has high tolerance for functional groups.

* * *

Recently, the ever increasing key role of organophosphorus compounds in various fields of science and practice has stimulated more scientists to dig into this line of research. However, the success can be achieved only with the search for novel approaches to compounds having phosphorus–element, primarily phosphorus–carbon, bonds to avoid considerable amounts of by-products, based on the atom-economic, environmentally friendly, easy-to-perform catalytic processes. The C–H-bond phosphorylation is among such processes. After a certain 'quiet period', in the last 3–4

years, development of novel methods for selective coupling of aromatic C(sp^2)—H-bonds and organophosphorus reagents, represented so far by only dialkyl H-phosphonates and diarylphosphine oxides, to synthesize biologically active compounds and to design various useful materials became an intensively developed area of chemical science. It is hoped that the range of organophosphorus reagents will be extended and the associated challenges and problems will be overcome in the nearest future.

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