Phosphate esters as "tunable" reagents in organic synthesis†

Stefano Protti and Maurizio Fagnoni*

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The essential role phosphates have in biochemistry has no parallel in man-made chemistry, where the poor reactivity of these esters towards nucleophilic substitution makes more reactive substrates such as halides and sulfonates preferred. Nevertheless, phosphates are acquiring an increasing role in organic synthesis as long as new activation modes become available. These include metal catalysis and photochemistry (the latter effective with benzyl and aryl derivatives) that may turn the present limitation into a promising opportunity by devising convenient tunable reactions.

1. Introduction

Phosphates (and pyrophosphates) are the most abundant esters in living organisms, forming the polar moiety of amphipathic biomolecules such as phospholipids and the connecting bridge between nucleoside units in nucleic acids. Phosphorylations have a key role in energy exchange *via* the ATP hydrolysis (through the activation of the sodium–potassium pump in the membrane cells, Fig. 1(a)). The key role of these esters is due on one hand to their ionic nature, imparted by the free OH (O^-) group and to the fact that the thermodynamic tendency towards hydrolysis is combined with a remarkable kinetic stability under physiological conditions,[1,2] so that cleavage occurs only under enzyme catalysis. These characteristics explain why nature chose phosphates for holding together the genetic code (Fig. 1(b)),[3] but also why these derivatives are a poor choice in nucleophilic substitutions in solution, where the advantage of having a leaving group 'tunable' by complexation to enzymes is lost, and the limited reactivity is a stumbling block.

Hydrolysis of alkyl phosphates involve cleavage of either the O–P bond (path *a*, Fig. 2) or the C–O bond (path *b*), depending both on the structure of the (poly)alkyl phosphates and on the pH of the solution.[4] Generally, monoalkyl esters are hydrolyzed exclusively or predominantly through O–P bond cleavage, although lowering the pH increases the proportion of C–O cleavage, which is preferred in dialkyl phosphates. Trimethyl phosphate has been reported to undergo exclusively P–O cleavage under basic conditions, and C–O cleavage at low pH.[5]

One may wonder whether there is a way of taking advantage of the stability of phosphates and of the possibility of tuning the reactivity by means of a suitable activation also in man-made chemistry,[6] in particular with reference to the most important process in synthesis, *viz*. substitution by a carbon-nucleophile (Nu, see Fig. 2) for making a C–C bond (path *c*, yielding NuR).

The idea that activation modes alternative to enzyme catalysis could be employed for improving the reactivity of phosphate esters in organic synthesis provided the stimulus for the present contribution. In the following, the application of phosphates in organic synthesis is discussed (mainly with

Department of Organic Chemistry, University of Pavia, Via Taramelli 10, 27100 Pavia, Italy. E-mail: fagnoni@unipv.it; Fax: 0039-0382-987323; Tel: 0039-0382-987316

† To the memory of Benedetta Guizzardi, who greatly contributed to the renaissance of phenyl cation chemistry.

Stefano Protti studied chemistry at the University of Pavia (Italy), graduated in 2003 and completed his PhD in 2006 which focused on photochemical arylation reactions via *phenyl cations. He moved in 2007 to LASIR laboratory (Lille), where he worked on the photoreactivity of flavonoids. Currently, he has returned to Pavia, where he is pursuing work on the chemistry of photogenerated phenyl cations.*

Maurizio Fagnoni, graduated in Pavia with a thesis on the synthetic applications of photo-SET reactions working also at the University of Muenster on the photochemistry of cyclopropyl ketones. He then worked at Istituto Ronzoni (Milan) on the synthesis of peptidomimetics and functionalized chitosans. He is currently an associate professor at the University of Pavia focusing on widening the scope of photocatalysis and phenyl cation chemistry.

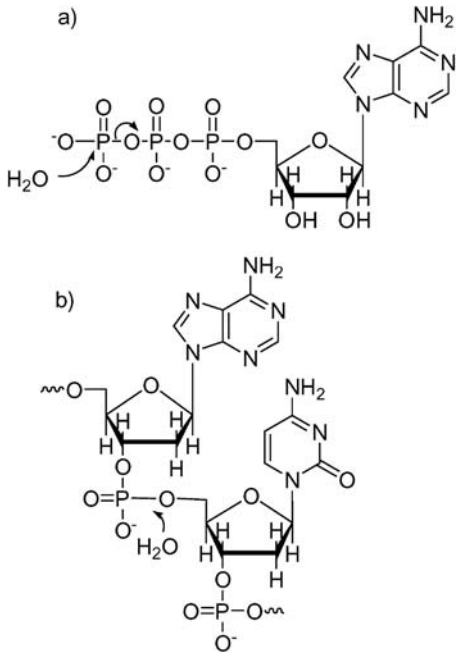


Fig. 1

regard to the formation of C–C bonds), attempting, where possible, to highlight the differences with respect of the much more largely used halides or sulfonates.

2. Reactions of sp^3-phosphates

Allyl (pyro)phosphate esters have been long known to be involved in biosynthetic reactions initiated by a nucleophilic attack. Typically, C–C bonds are formed *via* a S_N1 mechanism starting from the dimethylallyl diphosphate isoprene unit. Likewise, elaborated terpenoid and steroid structures are formed *via* a geranyl diphosphate intermediate.[7]

On the other hand, enzymes are sparsely used in the activation of allyl phosphates for synthetic applications. The alkylation of L-tryptophan at C(4) by dimethylallyl diphosphate catalyzed by the dimethylallyltryptophan synthase (a prenyltransferase) is a representative example.[8] At any rate, allyl phosphates undergo a clean S_N2 reaction only when reacting with soft bases (*e.g.* PhS^-, CN^-, I^-).[9] On the contrary, the reaction with allyl diphenyl phosphates with hard bases such as sodium methoxide or phenyllithium leads either to a complex end mixture or to an attack onto the phosphorus atom.[9] However, treatment of neryl and geranyl (or allyl diphenyl) phosphates with Grignard reagents leads to regio- and stereospecific S_N2 reaction with no loss of optical purity.[10,11] Thus, although simple aliphatic phosphates show a limited reactivity, activated analogues such as allyl or benzyl (see later) derivatives undergo some useful substitution reactions. This is apparent in transition metal catalyzed processes that greatly widen the application of allyl phosphates in organic synthesis.

As an example, allyl phosphates underwent a clean S_N2' reaction with Grignard reagents in the presence of 10% mol Cu(I). In this way, the sex pheromone of African Monarch and the naturally occurring geraniol have been synthesized.[12] The catalyst played a crucial role in directing the reaction towards

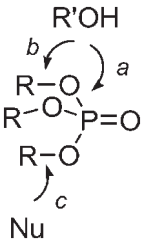
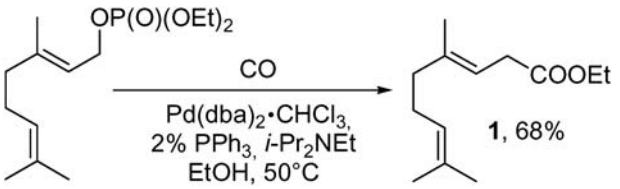


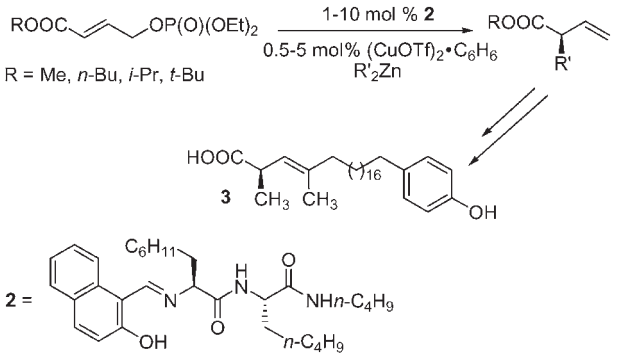
Fig. 2

the S_N2 or the S_N2' path, Fe and Ni based catalysts (*e.g.* $Fe(acac)_3$, $NiBr_2$) favoring the former and CuCN·2LiCl the latter one.[13] The reaction of *n*-BuMgI with the phosphate ester of 4-phenoxybut-2-en-1-ol in the presence of chiral arenethiolate-copper(I) complex resulted in an efficient S_N2' alkylation but with a poor enantiomeric excess (10%) if compared to that obtained with the analogous acetate ester (34% ee).[14] Moreover, the phosphate ester leaving group was found superior when compared to chloride or mesylate ester in the reaction of secondary allylic phosphates with prenyl Grignard reagent (CuCN·2LiCl as the catalyst). As a result, a highly S_N2'-, (*E*)- and antiselective alkylation has been found in the synthesis of (*E*,*E*)-farnesol derivatives.[15] Palladium(0) species have been known since 25 years as effective catalysts for the addition of carbon (*e.g.* malonate anions) and nitrogen (*e.g.* amines) nucleophiles onto allyl diethyl phosphates, resulting in a S_N2' reaction.[16] As an example, the diethyl phosphate ester of trifluoromethylated allylic alcohols smoothly reacted with malonate anions under Pd catalysis.[17] A mixture of S_N2 and S_N2' products (the latter preferred) were obtained instead in the alkylation of (*E*)-2-hexenyl diethyl phosphate with diethyl sodiomalonate catalyzed by $[Ir(COD)Cl]_2$.[18] In contrast, allyl sulfonates did not require any catalyst for the malonate substitution *via* a S_N2 mechanism.[19] Moreover, palladium(0)-catalyzed reactions of allyl phosphates with sodium azide was an easy entry to allyl azides, in turn versatile synthetic intermediates as 1,3-dipoles and for the stereoselective preparation of allylamines.[20] Pd catalysis was also effective in the alkoxycarbonylation of allyl phosphates under CO (1 atm) at 50 °C, an efficient path toward the synthesis of the corresponding β,γ-unsaturated esters. The carbonylation occurred at the least substituted allylic positions with inversion of configuration. Carbonylation of the (*E*)-geranyl phosphate gave ethyl ester of (*E*)-homogeranic acid **1**, stereoselectively (Scheme 1).[21]

Allyl phosphates have been successfully employed in the enantioselective Cu(I) catalyzed reactions with organozinc reagents in the presence of suitable chiral ligands,[22–27] such as pyridyl or amino acid-derived Schiff bases or phosphoramidites. As an example, pyridyl Schiff bases promoted the alkylzinc reagents addition onto allylic phosphates (> 78% ee) leading to



Scheme 1

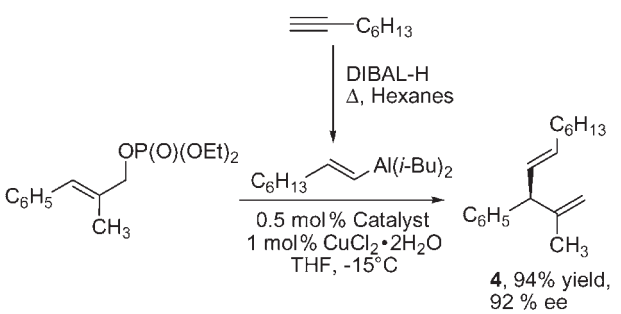


Scheme 2

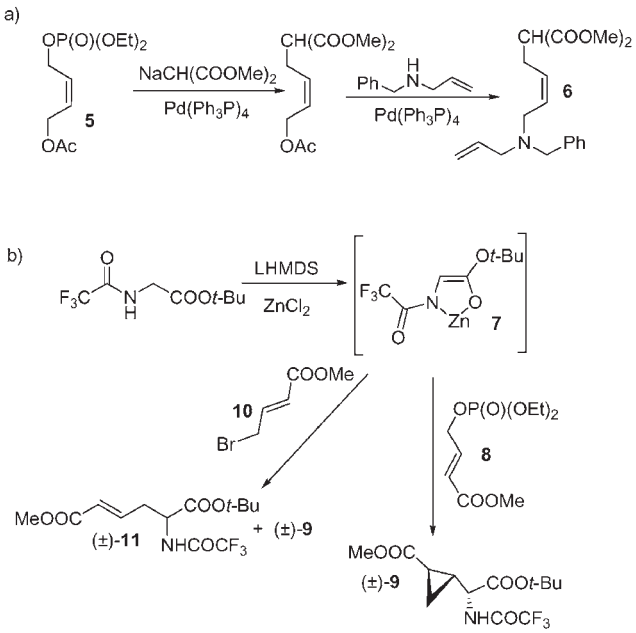
the asymmetric formation of quaternary carbon centers when starting from trisubstituted olefins. The fish deterrent, (−)-sporochnol, has been thus prepared in this way in 82% overall yield.[23] A catalytic and enantioselective desymmetrization of five-, six- and seven-membered *meso*-cyclic allylic bis-diethyl phosphates has been accomplished *via* alkylation with organozinc reagents in the presence of catalytic amounts of $(CuOTf)_2 \cdot C_6H_6$.[25,26] Allylic alkylations of unsaturated esters allowed the synthesis of synthetically versatile α-alkyl-β,γ-unsaturated carbonyls in the optically enriched form. Indeed, the Cu-catalyzed asymmetric alkylation (using the chiral dipeptide **2**) has been used in a concise convergent total synthesis of (*R*)-(−)-elenic acid **3**, a topoisomerase II inhibitor (Scheme 2).[22]

Various complexes containing *N*-heterocyclic carbene (NHC) ligands were successfully used as catalysts. Thus, a highly chemo- and enantioselective Cu-catalyzed alkylation of allyl phosphates with alkylzinc reagents has been reported.[28] These ligands were also used in the preparation of highly effective Ru- and Cu-based complexes that catalyzed enantioselective allylic alkylations.[29] Methylation (by Me_2Zn) of an allyl phosphate by using copper NHC-based complexes was employed in the synthesis of siphonariid metabolite (+)-baconipyrone C (the unnatural enantiomer)[30] and of alkyl-substituted allylsilanes in high enantiomeric purity.[31] Recently Hoveyda and co-workers developed a one-pot, gram-scale synthesis of 1,4-dienes (*e.g.* **4**) by catalytic asymmetric S_N2' reaction *via* addition of *in situ* prepared vinylaluminium reagents (by treatment of terminal alkynes with DIBAL-H) onto allyl phosphates resulting in a Cu-catalyzed three component reaction without the need to resort to the glovebox techniques (Scheme 3).[32]

Two representative examples illustrate the peculiar reactivity of the phosphate group in allyl phosphates. In the



Scheme 3



Scheme 4

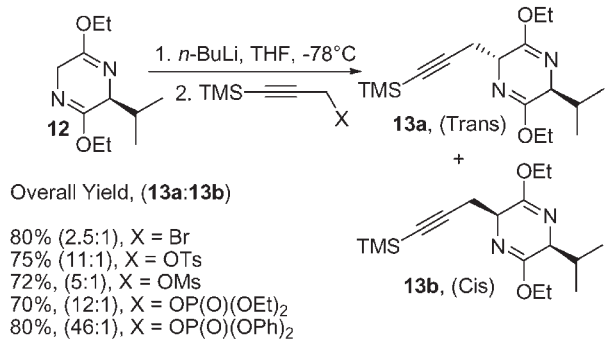
first case (*Z*)-4-acetoxybut-2-enyl diethyl phosphate (**5**) underwent a sequential alkylation (*via* substitution of the phosphate group by the malonate anion) and amination (*via* substitution of the less reactive acetate ester by a secondary amine) under Pd catalysis forming **6** (Scheme 4(a)).[16]

In the second case, the synthesis of cyclic amino acid (±)-**9** was possible because of the lack of reactivity of the phosphate group in (*E*)-but-2-enoate **8** in the reaction with the chelated zinc enolate **7** (Scheme 4(b)). Thus, a Michael addition rather than a nucleophilic substitution took place followed by the formation of the three-membered ring *via* phosphate ester elimination.[33] Interestingly, under the same conditions, the highly reactive allyl bromide (**10**) gave a mixture of (±)-**9** and (±)-**11** rather than a clean reaction.[33]

Noteworthy, the reaction of allyl phosphates with an organochromium(III) reagent (Bu_5CrLi_2) generated the corresponding allylchromium derivatives that acted as nucleophiles toward a variety of electrophiles such as carbonyl compounds and imines affording the corresponding adducts in high yields.[34]

Propargyl phosphates exhibited a similar reactivity. An interesting application of these phosphates was in the reaction with the Schöllkopf chiral auxiliary (**12**) under strongly basic conditions.[35,36] The product stereoselectivity strongly depended on the bulkiness of the nucleofugal group, diphenyl phosphate giving the best results (see Scheme 5). The resulting products (**13**) were smoothly converted into substituted tryptophans by Pd-catalyzed heteroannulation with iodoanilines.

C–Sn and C–N bonds were also formed in this way. Thus, a general method for the synthesis of optically active propargylstannanes (and (*Z*)-allylstannanes from them) was developed *via* the reaction of R_3SnCl with optically active secondary propargyl phosphates mediated by a titanium based catalyst.[37] Furthermore, copper(I)-catalyzed aminations (with secondary amines) of propargyl phosphates proceeded under mild reaction conditions to afford biologically important propargylamines.[38] Efficient electrophilic addition onto propargyl



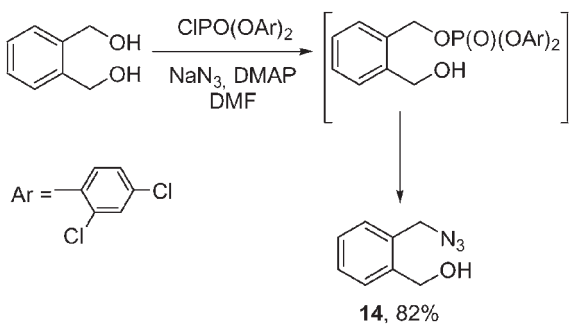
Scheme 5

phosphates mediated by Pd(0) and SmI_2 in THF followed by phosphate elimination was used for the synthesis of allenes in a regioselectivity higher than that observed when using propargyl acetates.[39] 2,3-Allenyl phosphates were likewise suitable substrates for the palladium-catalyzed asymmetric amination or imidation reactions.[40]

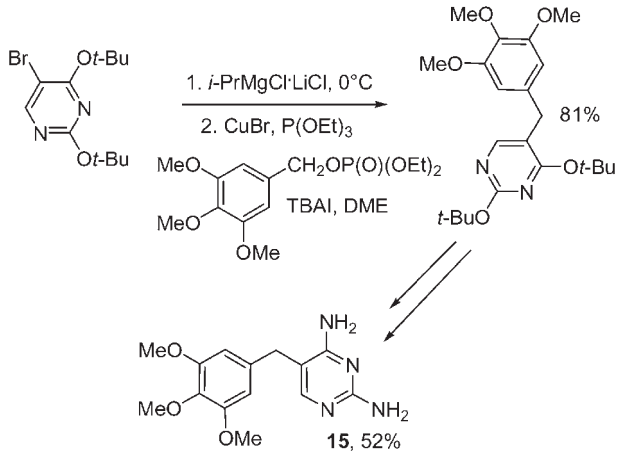
Benzyl phosphates, contrary to benzyl sulfonates,[41–43] were not reported to react either with cyanide ions or intermolecularly with other carbon nucleophiles such as malonate anion. An intramolecular nucleophilic substitution by the anion from a nitrile or by a *tert*-butyl ester enolate onto a benzyl phosphate, however, offered an interesting way for the formation of five-membered rings, as in the asymmetric synthesis of *N*-*tert*-butyl disubstituted pyrrolidines[44] and in building cyclopentane rings bearing three consecutive chiral centers.[45] The phosphate leaving group was chosen in this case due to its lower reactivity toward nucleophiles at the phosphorus center. The usefulness of phosphate chemistry in organic functional group transformation was demonstrated in the one-pot procedure for the efficient preparation of benzyl (*e.g.* **14**) and alkyl azides from alkanols using bis(2,4-dichlorophenyl) phosphate as a good leaving group for the OH activation (Scheme 6).[46]

Benzyl phosphotriesters were converted into the corresponding benzyl iodides under mild, Brønsted-neutral conditions by using iodotrimethylsilane and, contrary to what observed with other alkyl and aryl phosphotriesters, no dealkylation of the ester occurred.[47]

Benzyl phosphates have only recently been used for cross-coupling reactions. Thus, the Suzuki reaction with arylboronic acids[48] allowed the synthesis of unsymmetrical diarylmethanes in excellent yields, though it required a high temperature and



Scheme 6



Scheme 7

the use of a Pd based catalyst, triphenylphosphine and an excess of a base. Grignard reagents could be used in place of organoboranes in cross-coupling reactions under Cu(I) catalysis forming again diarylmethanes, an example being the synthesis of bactericide trimethoprim (**15**, Scheme 7).[49]

Benzylic manganese reagents formed by the oxidative addition of the highly active manganese to benzylic phosphates have been used in the reaction with a variety of electrophiles in the absence of any transition-metal catalyst. Accordingly, the reaction with benzoyl chloride afforded the corresponding benzyl phenyl ketones in a satisfying yield.[50]

Importantly, the photochemical activation of benzyl phosphates required milder conditions,[51] and convenient photoremovable protecting groups for biological applications have been devised on this basis, *e.g.* *o*-nitrobenzyl phosphates.[52] As an example, irradiation of a *caged* ATP (**16**, Fig. 3) *viz* the protected ATP having a photoactive ligand resulted in the generation of free ATP.[53] This procedure avoids the harsh chemical treatment otherwise required, *i.e.* reduction, β-elimination, acid or base hydrolysis that are incompatible with biological systems.

The *o*-nitro group is not a prerequisite for photoremovable groups, since benzyl phosphates were found to be smoothly photocleaved (mainly by a heterolytic cleavage of the C–OP bond when unsubstituted)[51,54] in alcoholic solvent. In some cases the phosphates showed a leaving group ability five orders of magnitude higher with respect to the corresponding acetates.[54] Furthermore, benzoin phosphates have been exploited for the synthesis of 2-phenylbenzo[*a*]furan **17** upon irradiation in either benzene or in methanolic solution,[55] involving a

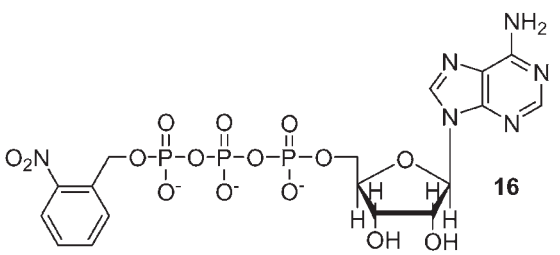
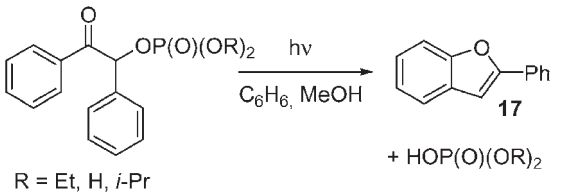
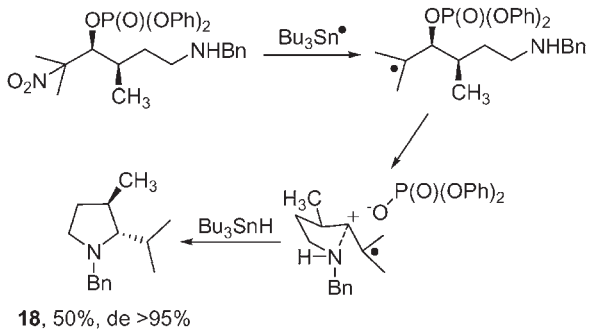


Fig. 3



Scheme 8



Scheme 9

rearrangement of the triplet state cation formed by the heterolytic cleavage of the C–O bond (Scheme 8).[56]

Elimination of the phosphate group took place also as a consequence of the homolytic cleavage of a group in α. This mechanism may actually be involved in the phosphate anion loss from α-oxy-β-phosphatoxy radicals such as those formed by hydrogen-atom abstraction from the DNA sugars,[57] and exploited for the stereoselective synthesis of trisubstituted *N*-benzyl pyrrolidines (**18**, Scheme 9).[58]

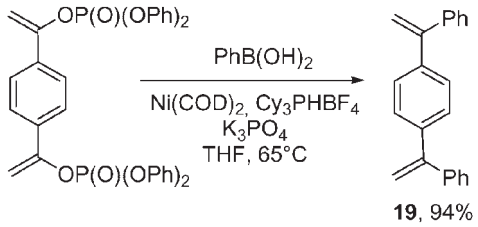
An analogous enol ether radical cation/phosphate anion pair was formed starting from glucose-derived α-phosphatoxy phenylselenides by treatment with tributyltin hydride and AIBN. A smooth highly diastereoselective radical cyclization onto a pendant *O*-allyl chain took place in this case.[59]

To summarize, C–C bond formation *via* sp^3 phosphates applies only to *activated substrates* (allyl, propargyl, benzyl derivatives), and then under metal catalysis or harsh conditions, even if niche applications have been found.

3. Reactions of sp^2-phosphates

3.1 Reactions of vinyl (enol)-phosphates

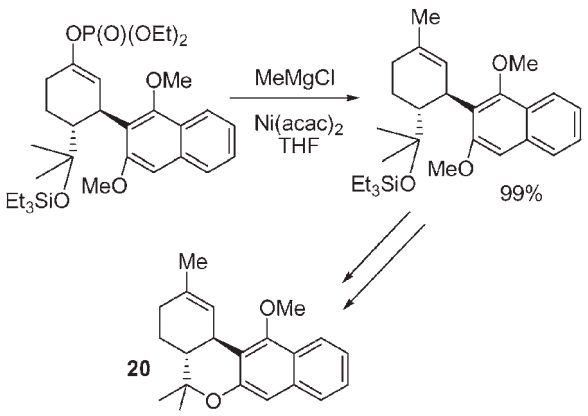
As for enol phosphates, an important case in nature is the reaction of the phosphoenolpyruvate with shikimic acid 3-phosphate (an oxygen based nucleophile) in the shikimate pathway.[7] In the laboratory, vinyl (or enol) phosphates are versatile substrates for cross-coupling reactions mediated by Pd(0) and Ni(0) such as Suzuki, Stille, Sonogashira, Negishi and Kumada reactions. Moreover, the phosphate moiety can be easily converted into a variety of functional groups. These reactions have been applied in total syntheses, particularly for building heterocyclic rings. In this case there is a clear advantage because the high stability of vinyl phosphates make them a robust and less expensive alternative to triflates (or iodides) and in some cases they proved to perform better with an easier work up. Thus, vinyl phosphates, easily accessed from the corresponding ketones, underwent nickel(0) catalyzed cross-coupling reactions with a variety of arylboronic acids to give aryl-substituted alkenes.[60–62] As an example, 1,1-diarylalkenes (*e.g.* **19**), a class of biologically active compounds, were easily synthesized in yields up to 99% by Suzuki–Miyaura cross-coupling of 1-arylalkenyl phosphates by using $Ni(COD)_2$ and ligand Cy_3PHBF_4 (Scheme 10).[61] 4-Substituted tetrahydropyridines have been obtained from *N*-Boc-4-piperidone *via* Pd-mediated coupling of the corresponding vinyl phosphate with phenyl boronic acids.[62]



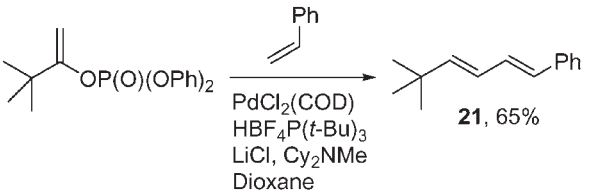
Scheme 10

Cross-coupling with alkyl and aryl Grignard reagents has been similarly obtained under nickel, palladium and iron catalysis.[62–66] Representative examples are the synthesis of allylsilanes, important models for the study of biomimetic cyclizations, through a nickel mediated cross-coupling reaction between a vinyl phosphate and a trimethylsilylmethylmagnesium halide[63,64] and the substitution of a methyl for the phosphate group by using MeMgCl in the presence of $Ni(acac)_2$ in THF at room temperature, a step in the synthesis of tetrahydrocannabinols (**20**, Scheme 11).[65]

Further examples included a useful one-pot protocol for the conversion of enolizable ketones to alkylated or arylated olefins by Pd-catalyzed cross-coupling of *in situ*-generated enol phosphate intermediates with Grignard reagents;[66] the synthesis of 4-substituted coumarins (by using organozinc reagents, since the α,β-unsaturated lactone moiety in the starting vinyl phosphate did not tolerate either organocuprates or Grignard reagents);[67] the alkylation by organoaluminium reagents under $Pd(PPh_3)_4$ catalysis;[68,69] the synthesis of substituted gem-difluoro olefins from the corresponding difluoroketones *via* reaction of the vinyl phosphate intermediates with organocuprates (*e.g.* Bu_2CuLi).[70] The Pd-mediated Heck reaction of some vinyl phosphates with styrene or 4-vinylpiridine occurred with attending isomerisation to give a diene (*e.g.* **21** in Scheme 12).[71,72]



Scheme 11



Scheme 12

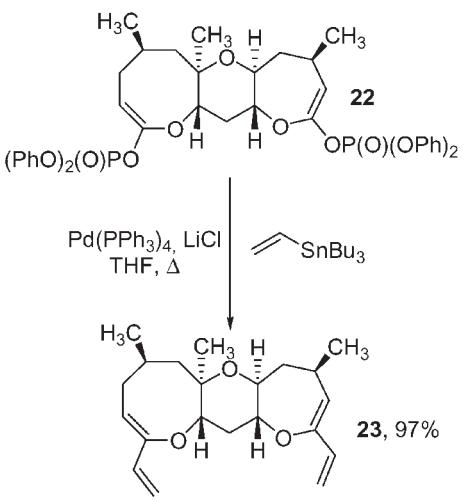
Moreover, conversion of a vinyl phosphate to the corresponding α,β-unsaturated ester was obtained in 76% yield by a Pd(0)-catalyzed carbonylation reaction and the product used in the preparation of ciguatoxin derivatives.[73]

Dienyl phosphates have been similarly employed, in particular for Kumada coupling, but the yields were lower than with the corresponding triflates especially under copper(I)-catalysis,[74] although nickel-catalysts were effective for obtaining 2-substituted-1,3-dienes by coupling with aryl and *n*-alkyl Grignard reagents.[75–77]

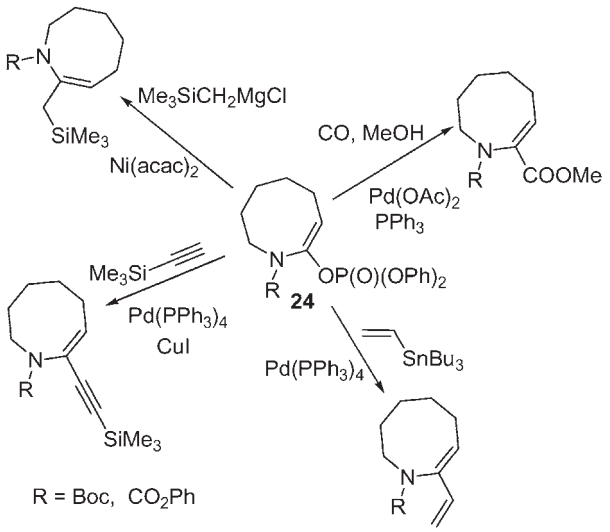
Cyclic ketene acetal phosphates have as yet found a limited application, although they appear to enjoy some advantage with respect to the expensive and unstable triflates, often characterized by low yields, both in the formation and in the coupling yield. However, phosphate **22** gave **23**, an intermediate in the total synthesis of brevetoxin A, in 97% yield under $Pd(PPh_3)_4$ catalysis[78] (Scheme 13) and the cross-coupling of 5,6-dihydro-4*H*-pyran-2-yl phosphate ester with alkoxydienylboronates gave a conjugated alkoxytriene.[79]

Recently, Nicolaou introduced ketene aminal phosphates as an interesting alternative to sulfonates for the construction of nitrogen-containing heterocycles including enantiomerically enriched cyclic amino acids. These phosphates were found in most cases to be more versatile and convenient with respect to the corresponding triflates, since the latter were rather unstable and were available only through a cumbersome syntheses employing rather expensive triflating reagents. Ketene aminal phosphates (*e.g.* **24**) underwent cross-coupling reactions with organoaluminium, -tin, -zinc and -magnesium reagents as illustrated in Scheme 14.[80]

Applications included the synthesis of chiral non-racemic trifluoromethyl substituted piperidines and decahydroquinolines,[81]



Scheme 13

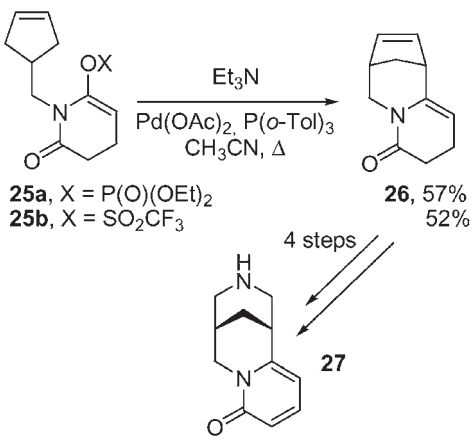


Scheme 14

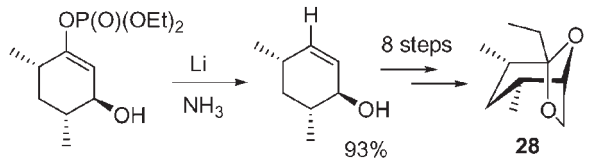
the efficient preparation of *N*-(*o*-bromophenyl)enecarbamates, precursors for the synthesis of 2-substituted indoles and indolines,[82] and of 3-substituted-4*H*-1,4-benzoxazines,[83] in all cases under palladium catalysis. Moreover, an intramolecular Heck cyclization of phosphate **25a** was the key step in the formation of the bridged tricyclic intermediate **26** that was used for the synthesis of racemic (±)-cytisine **27** in a few steps.[84] Interestingly, **26** was formed from the phosphate **25a** in the same yield as from the triflate **25b** (Scheme 15).

Bisvinylphosphates have been also employed for the Pd-catalyzed (under Suzuki and Stille conditions) preparation of a 1,4-oxazine ring[85,86] as well as of 2,6-disubstituted dihydropyridines.[87,88]

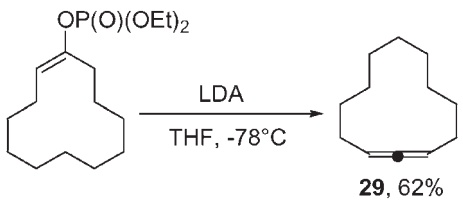
Among applications not involving the formation of a C–C bond, one should mention the conversion of vinyl diethyl phosphate esters into vinylstannanes under photostimulation in liquid ammonia in the presence of triorganostannyl anions (*via* a $S_{RN}1$ mechanism)[89] and the reduction to alkenes under Birch conditions (alkali metals in liquid ammonia),[90,91] an effective method for ketone–olefin conversion that was applied for the total synthesis of (±)-α-multistriatin **28** (Scheme 16).[92] Titanium trichloride was also used as the reducing agent in the synthesis of alkenes and dienes in a high yield (up to 100%).[93]



Scheme 15



Scheme 16



Scheme 17

On the other hand, vinyl chlorides and bromides were accessible by the reaction of vinyl phosphates with $Ph_3P{\cdot}Cl_2$ and $Ph_3P{\cdot}Br_2$, respectively, in MeCN at room temperature.[94]

Treatment of vinyl phosphates with a strong base (*e.g.* LDA) at a low temperature (≤ -78 °C) caused β-elimination to give terminal acetylenes,[95] as in the preparation of 1-ethynyl ethers by treating a ketene acetal phosphate (obtained from the corresponding acetate) with *t*-BuLi at −100 °C in pentane.[96] With substituted vinyl phosphates, elimination gave an allene rather than an internal alkyne if deprotonation of the least substituted carbon was kinetically preferred, a fact exploited for the preparation of macrocyclic allenes (*e.g.* **29**), as shown in Scheme 17.[97] In contrast, the same reaction carried out by using the corresponding vinyl triflate gave cyclododecyne in 95% yield.[97]

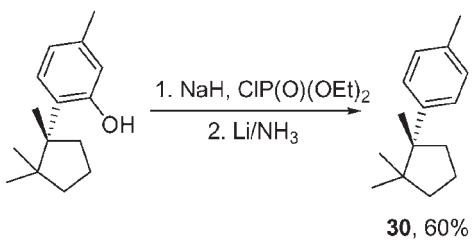
3.2 Reactions of aryl phosphates

Unlike vinylphosphates, the synthetic application of arylphosphates has received only sparse attention and at present they rarely are a significant alternative to other Ar–X derivatives for the formation of Ar–C bonds *via* cross-coupling reactions under metal catalysis. Bromides, iodides and sulfonate esters are currently used for this purpose, although extension to other leaving groups has been tested. Recently, the less reactive but cheaper aryl chlorides have been successfully employed,[98] although a high arylation yield was obtained only through non-trivial experimental procedures and with the use of a large amount of auxiliary materials (ligand, inorganic base), which made such methods not environment-friendly. Moreover, successful applications were mainly limited to electron-poor aryl chlorides and to a high reaction temperature (at least 80 °C) unless a strong nucleophile was used (*e.g.* a Grignard reagent). Milder conditions were attained under Ni(0) catalysts as recently reported.[99] Aryl fluorides have also been used either with strong nucleophiles (*e.g.* Grignard reagents) or when the aromatic ring was activated by a strong electron-withdrawing substituent.[100] Aromatic diazonium salts may be alternative substrates in palladium-catalyzed cross-coupling reactions, but the limited stability of most of these salts at room temperature is a serious drawback.[101] Esters are attractive substrates, as they are smoothly obtained from largely available phenols, but triflates, the most reactive derivatives of this class are quite expensive and sometimes unstable. Other sulfonate esters such as mesylates,[102] and tosylates[103–105] (easily handled as crystalline solids) have been recently introduced, but these exhibited a lower reactivity.[99,106] It may be noted that methoxy groups too could act as the leaving groups in some cases.[107,108] Aryl phosphate derivatives are less prone to catalytic activation than vinyl derivatives. This, coupled with the poor tendency of the Ar–OP bond to oxidative addition to the metal centre (*e.g.* by Pd or Ni)[109] means that aryl phosphates have been rarely used in aryl–carbon bond formation. As a matter of fact, Skrydstrup *et al.* demonstrated, at least for Heck reactions, that phenyl (but also vinyl) phosphates lie at the lower hand of the reactivity scale among groups involved in the oxidative insertion step (I > OTf = Br > Cl > $OP(O)(OPh)_2$).[72] Furthermore, the $ArS_{RN}1$ reaction *via* radical anion appears not to apply to phosphates, at least for Ar–C bond formation. Thus, the treatment of phenyl diethyl phosphate with the acetone enolate in liquid ammonia gave only traces (4%) of the phenylacetone.[110] Furthermore, using an aryl phosphate bearing a more reactive substituent, such as a bromide, underwent the exclusive reaction of the latter group, with the phosphate acting as an effective protecting group of the phenol function.[111] Nevertheless, phosphate substitution with Ar–Y bond (Y = H, N, Sn) formation occurred under $ArS_{RN}1$ conditions. Indeed, a useful procedure for the reduction of phenols involved treatment of the corresponding aryl phosphates with alkali metals in liquid ammonia or with sodium naphthalene in THF,[112] as applied in the synthesis of naturally occurring derivatives such as (+)-cuparene (**30**, a sesquiterpene)[113] (Scheme 18) (−)-*trans*- and (+)-*cis*-calamenene[114] and of tetrahydrocannabinol analogues.[115]

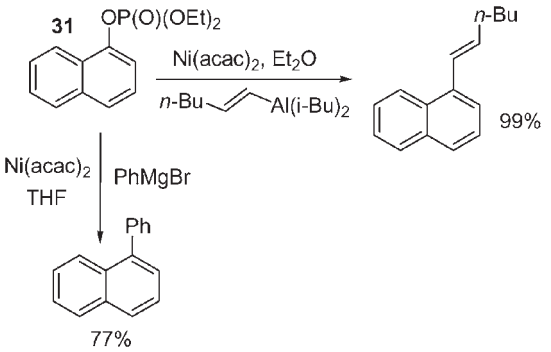
Reductive amination was obtained in the conversion of the diethyl phosphate ester of 2,6-dimethylphenol to the corresponding aniline in liquid ammonia in the presence of K/KNH_2.[116] An $ArS_{RN}1$ reaction was also applied in the synthesis of various arylstannanes (50–100% yield) *via* the photostimulated reaction of sodium triorganostannides (Me_3SnNa or Ph_3SnNa) with aryl diethyl phosphate esters.[111]

To our knowledge, metal-mediated cross-coupling involving an aryl phosphate has been reported only under Ni catalysis in a couple of cases up to now. This was first reported by Kumada in 1981 and was based on a Ni mediated reaction between alkyl naphthyl (**31**) or phenyl phosphates and highly reactive Grignard or organoaluminium reagents[117] (Scheme 19).

In both cases at least three equiv. of the organometallic species were required.[118–120] A further application was reported



Scheme 18



Scheme 19

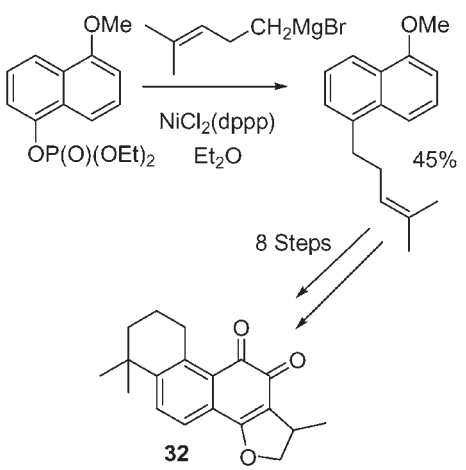
for the synthesis of compounds of pharmaceutical significance including (±)-cryptotanshinone (**32**, Scheme 20).[119,120]

Aryl phosphonates have been used with some success in place of the phosphates,[121] but are obtained through more elaborate and expensive syntheses and, as observed by Steel,[109] with these compounds the activation of the Ph-P bond competes with that of the Ph–O bond. At any rate, aryl (or vinyl)[122] phosphonates, just as the phosphates, did not react in the presence of a more reactive group such as a bromide.

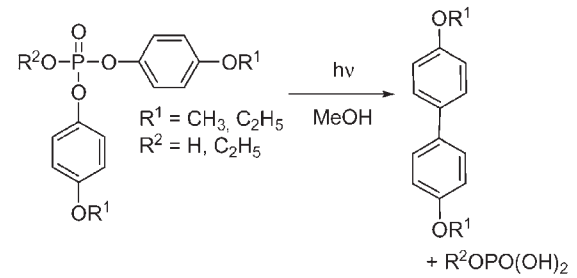
Importantly, the limitations of the transition-metal activation of the Ar–OP bonds have been overcome by having recourse to light-induced reactions.

The photoreactivity of aryl phosphates was first demonstrated by Havinga in 1956 in his study of the photohydrolysis of *m*-nitrodiethylphosphorylbenzene, which opened the path towards photonucleophilic aromatic substitutions.[123] However, synthetic applications involving the formation of Ar–C bonds have only recently emerged. Thus, it has been reported that under UV light irradiation, both triaryl[124,125] and biaryl[126] phosphates and phosphonates underwent an intramolecular formation of Ar–Ar bonds affording the corresponding biaryl derivatives with elimination of the phosphate group (Scheme 21).

A similar formation of Ar–C bond has been reported in the irradiation of alken-1-yl aryl methyl phosphates, where both aryl alkanones and aryl alkenyls were formed in the reaction in various proportion.[127]



Scheme 20

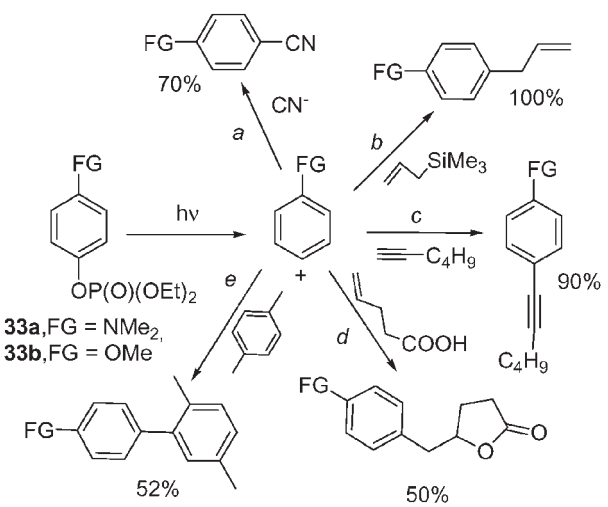


Scheme 21

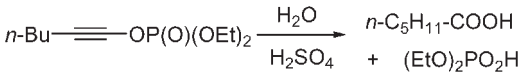
A large scope strategy has been recently developed, which is based on ArS_N1 reaction *via* photogenerated triplet phenyl cations (Scheme 22).[128] Phenyl cations are virtually inaccessible thermally, but are smoothly formed photochemically. Accordingly, the photolysis in polar solvent of aryl diethyl phosphates caused heterolysis of the aryl–oxygen bond and the thus formed phenyl cation reacted with suitable carbon nucleophiles in a chemoselective fashion forming Ar–C bonds under mild conditions.

Scheme 22 summarizes the range of products accessible starting from aryl phosphate *via* the photo-S_N1 reaction. The reactions occurred satisfactorily with aryl phosphates bearing electron-donating substituents (FG = NMe_2 (**33a**) and OMe (**33b**)). As an example, irradiation of aryl phosphates in a cyanide aqueous acetonitrile solution gave the corresponding benzonitriles (Scheme 22, path *a*).[129] Allylaromatics, including bioactive allylphenols, were also obtained in a high yield by reaction with allyltrimethylsilane (path *b*)[130] and alkynyl derivatives through a metal-free Sonogashira reaction with alkynes (path *c*).[131] Moreover, arylation of ω-unsaturated acids afforded benzyl (phenyl) γ- and δ-lactones by tandem formation of Ar–C and C–O bonds (path *d*).[132] Benzene[130,133] and alkyl benzenes (*e.g.* *p*-xylene)[134] were likewise smoothly arylated (path *e*). Importantly, in these reactions neutral π nucleophiles were successfully used rather than carbanions or organoboranes and the synthesis of biaryls occurred *via* a direct H substitution in aromatics.

To summarize, the C=C double bond makes activation of vinyl phosphates by metals much more effective than with



Scheme 22



Scheme 23

unactivated alkyl derivatives, with the aryl phosphates in between.

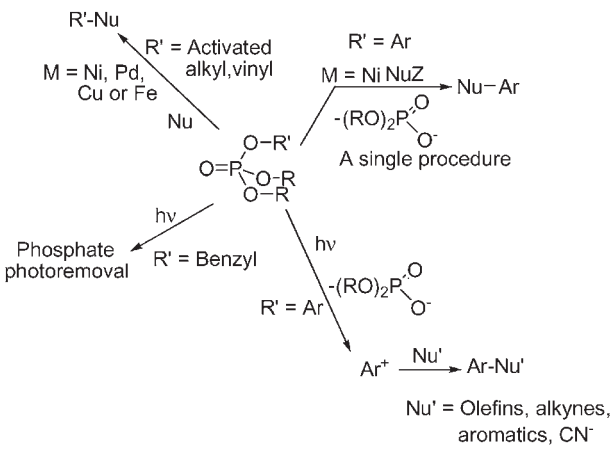
4. Reactions of sp-phosphates

Alkynyl phosphates are considered electron-rich acetylenes. These are promising in medicinal chemistry as potent, novel enzyme inhibitors.[135] At present, their chemistry is limited to aqueous acid hydrolysis forming a carboxylic acid[136] as illustrated in Scheme 23.

5. Conclusions

A survey of the literature confirms the moderate reactivity of phosphate esters in nucleophilic substitutions, where better electrophiles such as sulfonates or halides are generally found by far preferable. The reactivity somewhat varies with the C-hybridization (sp^3, sp^2 or sp). Thus, alkyl phosphates are used for the formation of C–C bonds only when the organic residue R′ is activated (R′ = benzyl or allyl, see Scheme 24), and mostly under harsh conditions. Although the thermal reactions of vinyl phosphates are more varied, these at any rate required metal catalysis (Pd or the more reactive Ni) and in most cases an aggressive nucleophile (*e.g.* an organometallic reagent).

This does not necessarily bar phosphate esters from the group of useful reagents in synthesis, however. A couple of cases of exemplificative types, where other groups are selectively activated, have been mentioned above supporting that the difference of reactivity may be exploited for selective activation. The target is now to devise activation methods that are effective under mild conditions. The very fact of the poor reactivity of phosphates opens the path for catalysis. Actually, substitution occurs only when the C–O bond is weak (allyl or benzyl derivatives) and/or when it is weakened. Thus, selective activation modes have been found not only *via* the enzymes that nature use, but also in solution, by means of



Scheme 24

metal complexation or *photochemical excitation*, with the important difference that the latter mode is effective also with aryl phosphates, poorly reactive under metal catalysis. The seeming limitation may thus develop into an opportunity by allowing a finer tuning of the activation. As an example, the poor reactivity of phosphates should allow using them as a protective group under most usual conditions, to be turned into activating groups when appropriate, through metal (or better photochemical) activation. As for the last point, one may point out that nature found a solution in the use of enzymes under physiological conditions for the activation of the P–O bond in phosphates and formation of a C–O bond, while irradiation (provided that the organic moiety absorbs at a convenient wavelength) smoothly activates the C–O bond for the formation of a C–C bond (see Scheme 24). Thus, aryl phosphates, both electron-rich and electron-poor, are virtually unreactive under metal catalysis but react smoothly upon irradiation. In this case, the phosphate anion is an effective leaving group, contributing to widen the scope of the synthesis *via* phenyl cations. Combined with the easy availability, moderate price and stability, the development of selective activation methods should lead to a more extensive use of phosphate esters.

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Notes and references

1 N. H. Williams and P. Wyman, *Chem. Commun*., 2001, 1268.
2 R. Wolfenden, C. Ridgway and G. Young, *J. Am. Chem. Soc*., 1998, **120**, 833.
3 F. H. Westheimer, *Science*, 1987, **235**, 1173.
4 P. G. Loncke and P. J. Berti, *J. Am. Chem. Soc*., 2006, **128**, 6132.
5 F. H. Westheimer, S. Huang and F. Covitz, *J. Am. Chem. Soc*., 1988, **110**, 181.
6 Actually, phosphate anion was not included among the heterolytic nucleofugal leaving groups in a recent review; see: S. D. Lepore and D. Mondal, *Tetrahedron*, 2007, **63**, 5103.
7 P. M. Dewick, *Medicinal Natural Products, a Biosynthetic Approach*, John Wiley & Sons Ltd, Chichester, 2nd edn, 2001.
8 J. C. Gebler, A. B. Woodside and C. D. Poulter, *J. Am. Chem. Soc*., 1992, **114**, 7354.
9 S. Araki, K. Minami and Y. Butsugan, *Bull. Chem. Soc. Jpn*., 1981, **54**, 629.
10 R. C. Haley, J. A. Miller and H. C. S. Wood, *J. Chem. Soc. C*, 1969, **2**, 264.
11 S. Araki, T. Sato and Y. Butsugan, *J. Chem. Soc., Chem. Commun*., 1982, 285.
12 S. Araki and Y. Butsugan, *J. Chem. Soc., Perkin Trans. 1*, 1984, 969.
13 A. Yanagisawa, N. Nomura and H. Yamamoto, *Tetrahedron*, 1994, **50**, 6017.
14 M. van Klaveren, E. S. M. Persson, A. del Villar, D. M. Grove, J.-E. Bäckvall and G. van Koten, *Tetrahedron Lett*., 1995, **36**, 3059.
15 A. Yanagisawa, Y. Noritake, N. Nomura and H. Yamamoto, *Synlett*, 1991, 251.
16 Y. Tanigawa, K. Nishimura, A. Kawasaki and S.-I. Murahashi, *Tetrahedron Lett*., 1982, **23**, 5549.
17 Y. Hanzawa, S. Ishizawa and Y. Kobayashi, *Chem. Pharm. Bull*., 1988, **36**, 4209.
18 R. Takeuchi and M. Kashio, *J. Am. Chem. Soc*., 1998, **120**, 8647.
19 A. J. Pearson and V. P. Ghidu, *J. Org. Chem*., 2004, **69**, 8975.
20 S.-I. Murahashi, Y. Taniguchi, Y. Imada and Y. Tanigawa, *J. Org. Chem*., 1989, **54**, 3292.

21 S.-I. Murahashi, Y. Imada, Y. Taniguchi and S. Higashiura, *J. Org. Chem.*, 1993, **58**, 1538.
22 K. E. Murphy and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, 4690.
23 C. A. Luchaco-Cullis, H. Mizutani, K. E. Murphy and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2001, **40**, 1456.
24 M. A. Kacprzynski and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2004, **126**, 10676.
25 U. Piarulli, C. Claverie, P. Daubos, C. Gennari, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2003, **5**, 4493.
26 U. Piarulli, P. Daubos, C. Claverie, M. Roux and C. Gennari, *Angew. Chem., Int. Ed.*, 2003, **42**, 234.
27 S. Ongeri, U. Piarulli, M. Roux, C. Monti and C. Gennari, *Helv. Chim. Acta*, 2002, **85**, 3388.
28 A. O. Larsen, W. Leu, C. Nieto Oberhuber, J. E. Campbell and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2004, **126**, 11130.
29 J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2005, **127**, 6877.
30 D. G. Gillingham and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2007, **46**, 3860.
31 M. A. Kacprzynski, T. L. May, S. A. Kazane and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2007, **46**, 4554.
32 Y. Lee, K. Akiyama, D. G. Gillingham, M. K. Brown and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2008, **130**, 446.
33 M. Pohlman and U. Kazmaier, *Org. Lett.*, 2003, **5**, 2631.
34 M. Hojo, R. Sakuragi, S. Okabe and A. Hosomi, *Chem. Commun.*, 2001, 357.
35 C. Ma, X. Liu, S. Yu, S. Zhao and J. M. Cook, *Tetrahedron Lett.*, 1999, **40**, 657.
36 C. Ma, S. Yu, X. He, X. Liu and J. M. Cook, *Tetrahedron Lett.*, 2000, **41**, 2781.
37 S. Okamoto, S.-I. Matsuda, D. K. An and F. Sato, *Tetrahedron Lett.*, 2001, **42**, 6323.
38 Y. Imada, M. Yuasa, I. Nakamura and S.-I. Murahashi, *J. Org. Chem.*, 1994, **59**, 2282.
39 C. Mikami, A. Yoshida, S. Matsumoto, F. Feng, Y. Matsumoto, A. Sugino, T. Hanamoto and J. Inanaga, *Tetrahedron Lett.*, 1995, **36**, 907.
40 Y. Imada, M. Nishida, K. Kutsuwa, S.-I. Murahashi and T. Naota, *Org. Lett.*, 2005, **7**, 5837.
41 A. Saito, M. Okada, Y. Nakamura, O. Kitagawa, H. Horikawa and T. Taguchi, *J. Fluorine Chem.*, 2003, **123**, 75.
42 D. Sikazwe, M. L. Bondarev, M. Dukat, J. B. Rangisetty, B. L. Roth and R. A. Glennon, *J. Med. Chem.*, 2006, **49**, 5217.
43 R. V. Hoffman and H.-O. Kim, *Tetrahedron Lett.*, 1993, **34**, 2051.
44 J. Y. L. Chung, R. Cvetovich, J. Amato, J. C. McWilliams, R. Reamer and L. Di Michele, *J. Org. Chem.*, 2005, **70**, 3592.
45 Z. J. Song, M. Zhao, R. Desmond, P. Devine, D. M. Tschaen, R. Tillyer, L. Frey, R. Heid, F. Xu, B. J. Foster, J. Li, R. Reamer, R. Volante, E. J. J. Grabowski, U. H. Dolling, P. J. Reider, S. Okada, Y. Kato and E. Mano, *J. Org. Chem.*, 1999, **64**, 9658.
46 C. Yu, B. Liu and L. Hu, *Org. Lett.*, 2000, **2**, 1959.
47 Q. Zhu and M. S. Tremblay, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 6170.
48 M. McLaughlin, *Org. Lett.*, 2005, **7**, 4875.
49 C. C. Kofink and P. Knochel, *Org. Lett.*, 2006, **8**, 4121.
50 Y. S. Suh, J.-S. Lee, S.-H. Kim and R. D. Rieke, *J. Organomet. Chem.*, 2003, **684**, 20.
51 R. S. Givens and L. W. Kueper III, *Chem. Rev.*, 1993, **93**, 55.
52 A. P. Pelliccioli and J. Wirz, *Photochem. Photobiol. Sci.*, 2002, **1**, 441.
53 *p*-Hydroxyphenacyl ATP can also be used as "caged" ATP, see: R. S. Givens and C.-H. Park, *Tetrahedron Lett.*, 1996, **37**, 6259.
54 D. P. DeCosta, N. Howell, A. L. Pincock, J. A. Pincock and S. Rifai, *J. Org. Chem.*, 2000, **65**, 4698.
55 R. S. Givens and B. Matuszewski, *J. Am. Chem. Soc.*, 1984, **106**, 6860.
56 C. S. Rajesh, R. S. Givens and J. Wirz, *J. Am. Chem. Soc.*, 2000, **122**, 611.
57 D. Crich and X.-S. Mo, *Tetrahedron Lett.*, 1997, **38**, 8169.
58 D. Crich and K. Ranganathan, *J. Am. Chem. Soc.*, 2005, **127**, 9924.
59 D. Crich, D.-H. Suk and S. Sun, *Tetrahedron: Asymmetry*, 2003, **14**, 2861.
60 Y. Nan and Z. Yang, *Tetrahedron Lett.*, 1999, **40**, 3321.
61 A. L. Hansen, J.-P. Ebran, T. M. Gøgsig and T. Skrydstrup, *Chem. Commun.*, 2006, 4137.
62 U. S. Larsen, L. Martiny and M. Begtrup, *Tetrahedron Lett.*, 2005, **46**, 4261.
63 T. Hayashi, T. Fujiwa, Y. Okamoto, Y. Katsuro and M. Kumada, *Synthesis*, 1981, 1001.
64 R. J. Amstrong, F. L. Harris and L. Weiler, *Can. J. Chem.*, 1982, **60**, 673.
65 A. D. William and Y. Kobayashi, *J. Org. Chem.*, 2002, **67**, 8771.
66 J. A. Miller, *Tetrahedron Lett.*, 2002, **43**, 7111.
67 J. Wu and Z. Yang, *J. Org. Chem.*, 2001, **66**, 7875.
68 K. Takai, M. Sato, K. Oshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 108.
69 M. Sato, K. Takai, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1981, **22**, 1609.
70 T. Ishihara, M. Yamana and T. Ando, *Tetrahedron Lett.*, 1983, **24**, 5657.
71 A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby and T. Skrydstrup, *Angew. Chem., Int. Ed.*, 2006, **45**, 3349.
72 J.-P. Ebran, A. L. Hansen, T. M. Gøgsig and T. Skrydstrup, *J. Am. Chem. Soc.*, 2007, **129**, 6931.
73 H. Takakura, M. Sasaki, S. Honda and K. Tachibana, *Org. Lett.*, 2002, **4**, 2771.
74 S. E. Karlström, M. Rönn, A. Thorarensen and J.-E. Bäckvall, *J. Org. Chem.*, 1998, **63**, 2517.
75 A. S. E. Karlström, K. Itami and J.-E. Bäckvall, *J. Org. Chem.*, 1999, **64**, 1745.
76 R. C. Verboom, B. A. Persson and J.-E. Bäckvall, *J. Org. Chem.*, 2004, **69**, 3102.
77 C. Sahlberg, A. Quader and A. Claesson, *Tetrahedron Lett.*, 1983, **24**, 5137.
78 K. C. Nicolaou, G.-Q. Shi, J. L. Gunzner, P. Gärtner and Z. Yang, *J. Am. Chem. Soc.*, 1997, **119**, 5467.
79 E. G. Occhiato, C. Prandi, A. Ferrali, A. Guarna and P. Venturello, *J. Org. Chem.*, 2003, **68**, 9728.
80 K. C. Nicolaou, G.-Q. Shi, K. Namoto and F. Bernal, *Chem. Commun.*, 1998, 1757.
81 J. Jiang, R. J. DeVita, G. A. Doss, M. T. Goulet and M. J. Wyvratt, *J. Am. Chem. Soc.*, 1999, **121**, 593.
82 H. Fuwa and M. Sasaki, *Org. Lett.*, 2007, **9**, 3347.
83 C. Buon, P. Bouyssou and G. Coudert, *Tetrahedron Lett.*, 1999, **40**, 701.
84 J. W. Coe, *Org. Lett.*, 2000, **2**, 4205.
85 E. Claveau, I. Gillaizeau, J. Blu, A. Bruel and G. Coudert, *J. Org. Chem.*, 2007, **72**, 4832.
86 C. Buon, L. Chacun-Lefevre, R. Rabot, P. Bouyssou and G. Coudert, *Tetrahedron*, 2000, **56**, 605.
87 D. Mousset, I. Gillaizeau, A. Sabatié, P. Bouyssou and G. Coudert, *J. Org. Chem.*, 2006, **71**, 5993.
88 D. Mousset, I. Gillaizeau, J. Hassan, F. Lepifre, P. Bouyssou and G. Coudert, *Tetrahedron Lett.*, 2005, **46**, 3703.
89 A. B. Chopa, V. B. Dorn, M. A. Badajoz and M. T. Lockhart, *J. Org. Chem.*, 2004, **69**, 3801.
90 F. Charbonnier, A. Moyano and A. E. Greene, *J. Org. Chem.*, 1987, **52**, 2303.
91 R. E. Ireland and G. Pfister, *Tetrahedron Lett.*, 1969, **10**, 2145.
92 J. P. Marino and H. Abe, *J. Org. Chem.*, 1981, **46**, 5379.
93 S. C. Welch and M. E. Walters, *J. Org. Chem.*, 1978, **43**, 2715.
94 K. Kamei, N. Maeda and T. Tatsuoka, *Tetrahedron Lett.*, 2005, **46**, 229.
95 E.-I. Negishi, A. O. King and W. L. Klima, *J. Org. Chem.*, 1980, **45**, 2526.
96 J. A. Cabezas and A. C Oehlschlager, *J. Org. Chem.*, 1994, **59**, 7523.
97 K. M. Brummond, E. A. Dingess and J. L. Kent, *J. Org. Chem.*, 1996, **61**, 6096.
98 A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176.
99 Z.-Y. Tang, S. Spinella and Q.-S. Hu, *Tetrahedron Lett.*, 2006, **47**, 2427.
100 L. Ackermann, R. Born, J. H. Spatz and D. Meyer, *Angew. Chem., Int. Ed.*, 2005, **44**, 7216.
101 A. Roglans, A. Pla-Quintana and M. Moreno-Manas, *Chem. Rev.*, 2006, **106**, 4622.
102 V. Percec, G. M. Golding, J. Smidrkal and O. Weichold, *J. Org. Chem.*, 2004, **69**, 3447.

103 A. H. Roy and J. F. Hartwig, *J. Am. Chem. Soc*., 2003, **125**, 8704.
104 H. N. Nguyen, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc*., 2003, **125**, 11818.
105 A. Forstner, A. Leitner, M. Mendez and H. Krause, *J. Am. Chem. Soc*., 2002, **124**, 13856.
106 L. Ackermann and A. Althammer, *Org. Lett*., 2006, **8**, 3457.
107 J. W. Dankwardt, *Angew. Chem., Int. Ed*., 2004, **43**, 2428.
108 F. Kakiuchi, M. Usui, S. Ueno, N. Chatani and S. Murai, *J. Am. Chem. Soc*., 2004, **126**, 2706.
109 I. B. Campbell, J. Guo, E. Jones and P. G. Steel, *Org. Biomol. Chem*., 2004, **2**, 2725.
110 R. A. Rossi and J. F. Bunnett, *J. Am. Chem. Soc*., 1972, **94**, 683.
111 A. B. Chopa, G. F. Silbestri and M. T. Lockhart, *J. Organomet. Chem*., 2005, **690**, 3865.
112 S. J. Shafer, W. D. Closson, J. M. F. van Dijk, O. Piepers and H. M. Buck, *J. Am. Chem. Soc*., 1977, **99**, 5118.
113 C. Fuganti and S. Serra, *J. Org. Chem*., 1999, **64**, 8728.
114 S. Serra and C. Fuganti, *Tetrahedron Lett*., 2005, **46**, 4769.
115 Y. Gareau, C. Dufresne, M. Gallant, C. Rochette, N. Sawyer, D. M. Slipetz, N. Tremblay, P. K. Weech, K. M. Metters and M. Labelle, *Bioorg. Med. Chem. Lett*., 1996, **6**, 189.
116 F. Ohseto, H. Murukami, K. Araki and S. Shinkai, *Tetrahedron Lett*., 1992, **33**, 1217.
117 T. Hayashi, Y. Katsuro, Y. Okamoto and M. Kumada, *Tetrahedron Lett*., 1981, **22**, 4449.
118 M. Tanaka, K.-I. Chiba, M. Okita, T. Kaneko, K. Tagami, S. Hibi, Y. Okamoto, H. Shirota, M. Goto, H. Obaishi, H. Sakurai, Y. Machida and I. Yamatsu, *J. Med. Chem*., 1992, **35**, 4665.
119 W. G. Huang, Y.-Y. Jiang, Q. Li, J. Li, J. Y. Li, W. Lu and J.-C. Cai, *Tetrahedron*, 2005, **61**, 1863.
120 Y.-Y. Jiang, Q. Li, W. Lu and J.-C. Cai, *Tetrahedron Lett*., 2003, **44**, 2073.
121 I. P. Beletskaya, *Pure Appl. Chem*., 2002, **74**, 1327.
122 Y. Kobayashi and A. D. William, *Org. Lett*., 2002, **4** 4241.
123 E. Havinga, R. O. De Jongh and W. Dorst, *Recl. Trav. Chim. Pays-Bas*, 1956, **75**, 378.
124 R. A. Finnegan and J. A. Matson, *J. Am. Chem. Soc*., 1972, **94**, 4780.
125 M. Shi, K. Yamamoto, Y. Okamo and S. Takamuku, *Phosphorus, Sulfur Silicon Relat. Elem*., 1991, **60**, 1.
126 R. A. Finnegan and J. A. Matson, *J. Chem. Soc., Chem. Commun*., 1975, 928.
127 M. Nakamura, Y. Okamoto and S. Takamuku, *Chem. Commun*., 1996, 209.
128 M. Fagnoni and A. Albini, *Acc. Chem. Res*., 2005, **38** 713.
129 V. Dichiarante, M. Fagnoni and A. Albini, *Chem. Commun*., 2006, 3001.
130 M. De Carolis, S. Protti, M. Fagnoni and A. Albini, *Angew. Chem., Int. Ed*., 2005, **44**, 1232.
131 S. Protti, M. Fagnoni and A. Albini, *Angew. Chem., Int. Ed*., 2005, **44**, 5675.
132 S. Protti, M. Fagnoni and A. Albini, *J. Am. Chem. Soc*., 2006, **128**, 10670.
133 V. Dichiarante, D. Dondi, S. Protti, M. Fagnoni and A. Albini, *J. Am. Chem. Soc*., 2007, **129**, 5605. Correction: V. Dichiarante, D. Dondi, S. Protti, M. Fagnoni and A. Albini, *J. Am. Chem. Soc*., 2007, **129**, 11662.
134 V. Dichiarante, M. Fagnoni and A. Albini, *Angew. Chem., Int. Ed*., 2007, **46**, 6495.
135 P. J. Stang, *Acc. Chem. Res*., 1991, **24**, 304.
136 A. D. Allen, T. Kitamura, K. A. Roberts, P. J. Stang and T. T. Tidwell, *J. Am. Chem. Soc*., 1988, **110**, 622.