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Multicomponent reactions involving phosphines, arynes and aldehydes†

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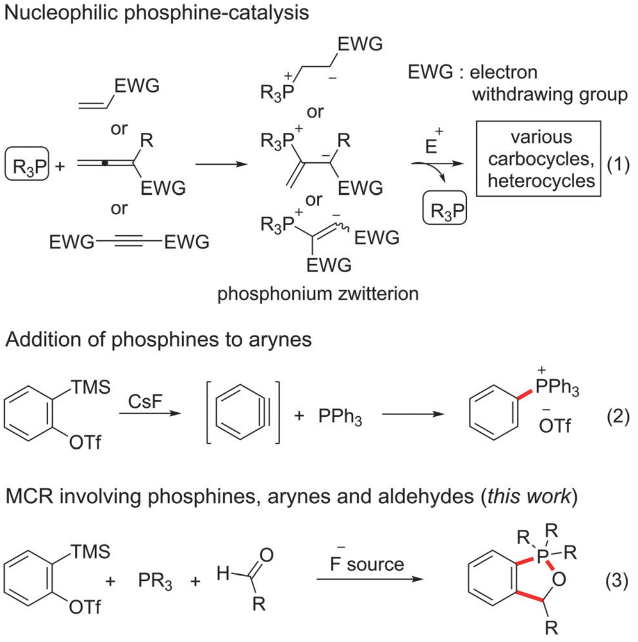
Although nucleophilic phosphine-catalysis is a powerful tool for the construction of various carbocycles and heterocycles, the reactions in which phosphines are incorporated into the final product are rare, and the reports on phosphine addition to highly electrophilic arynes are scarce. Herein, we report the phosphine triggered multicomponent reaction of arynes and aldehydes, which takes place *via* the formal [3+2] cycloaddition of an initially generated 1,3-phosphonium zwitterion from phosphines and arynes with aldehydes. The reaction resulted in the formation of a diverse range of stable pentacovalent phosphoranes in good yields based on the benzooxaphosphole system.

Nucleophilic phosphine-catalysis is one of the powerful synthetic strategies for the synthesis of various carbocycles and heterocycles.[1] The underlying principle of many of these reactions is the initial generation of a phosphonium zwitterion by the nucleophilic addition of phosphines to activated olefins (alkenes, alkynes, and allenes), which is subsequently intercepted with diverse electrophiles allowing access to cyclic, bicyclic or polycyclic compounds (Scheme 1, eqn (1)).[2] In addition, phosphines can mediate organic transformations, where this nucleophilic trigger is ejected out in the end as phosphine oxide.[3] Interestingly, however, the utility of the phosphine as a substrate, which is incorporated into the final product thus constituting multicomponent reactions (MCRs), is not well-explored compared to nucleophilic phosphine catalysis.[4,5] Moreover, despite the widespread application of the phosphine-activated olefin zwitterion in organic reactions, the analogous zwitterion generated from phosphines and highly electrophilic arynes[6] has received only scant attention. The addition of phosphines to arynes leading to the formation of the phosphonium salt *via* the phosphine–aryne zwitterion was first uncovered by Wittig,[7] and the scope of this reaction was expanded recently by Jugé and co-workers[8] by generating arynes from 2-(trimethylsilyl)aryl triflates by the fluoride-induced 1,2-elimination (eqn (2)).[9] Surprisingly, however, the synthetic potential of phosphine–aryne zwitterions in MCRs, to the best of our knowledge, is unknown. Herein, we demonstrate a mild and efficient three-component coupling reaction of phosphines, arynes and aldehydes proceeding *via* a [3+2] cycloaddition pathway leading to the straightforward synthesis of benzooxaphosphole derivatives in good yields (eqn (3)).[10]



Scheme 1 Addition of phosphines to activated olefins.

Recently, we have developed a novel MCR involving N-heterocycles, arynes and N-substituted isatins. Using (iso)quinoline

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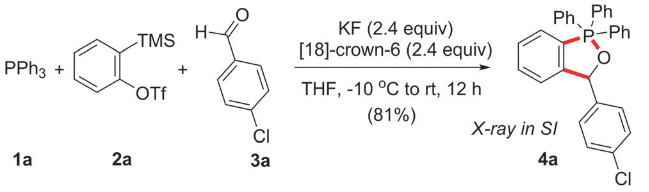
† Electronic supplementary information (ESI) available: Detailed experimental procedures; single crystal X-ray data of **4a**, **10**, & **13**, mechanistic experiments; and characterization data of all compounds. CCDC 1001501, 1001503 and 1001504. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc05420b

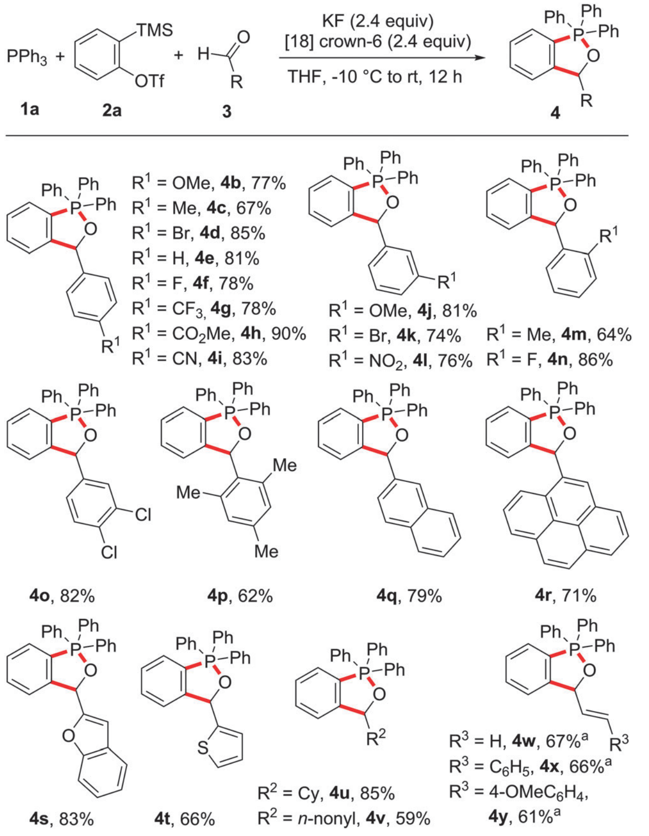


Scheme 2 MCR involving triphenylphosphines, arynes and aldehydes.

as the nucleophilic trigger, the reaction furnished spirooxazino (iso)quinoline derivatives and the utility of pyridine as the nucleophile resulted in the formation of indolin-2-one derivatives.[11] Encouraged by these results, the present study commenced by treating triphenylphosphine **1a** and 4-chlorobenzaldehyde **3a** with the aryne generated from 2-(trimethylsilyl)aryl triflate **2a**[9] using KF and [18] crown-6. Pleasingly, a facile reaction took place resulting in the formation of benzooxaphosphole derivative **4a** in 81% yield (Scheme 2).[12]

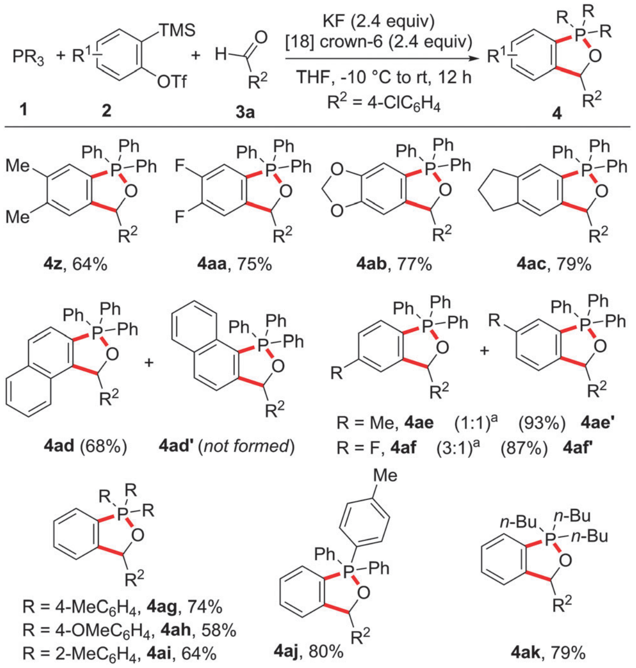
The structure of **4a** was confirmed by single-crystal X-ray analysis.[13] It is important to note that functionalized organophosphorus compounds found potential application in various areas including pharmaceuticals, agrochemicals, materials chemistry and in catalysis.[14]

Having established optimized conditions for this aryne MCR triggered by phosphines, we then evaluated the scope of the benzooxaphosphole synthesis (Scheme 3). A series of aromatic aldehydes having electron-releasing or -withdrawing groups at the 4-position of the benzene ring underwent smooth cyclization allowing the synthesis of benzooxaphosphole derivatives in 67–90% yield (**4b–4i**). Moreover, substitution at the 3-position as well as the 2-position is well-tolerated leading to the formation of the desired products in good yield (**4j–4n**). The reaction of PPh_3 and arynes with disubstituted aldehydes worked well (**4o**), and even the sterically hindered 2,4,6-trimethyl benzaldehyde afforded the expected product **4p** in 62% yield. In addition, 2-naphthaldehyde and pyrene carboxaldehyde are efficient substrates, and the corresponding products were formed in good yield (**4q** and **4r**). Furthermore, heterocyclic aldehydes, branched and linear aliphatic aldehydes, and α,β-unsaturated aldehydes underwent efficient annulation reactions thereby significantly expanding the scope of this reaction (**4s–4y**). It is noteworthy that the reaction of PPh_3 and arynes with acrolein afforded the target product **4w** in 67% yield.

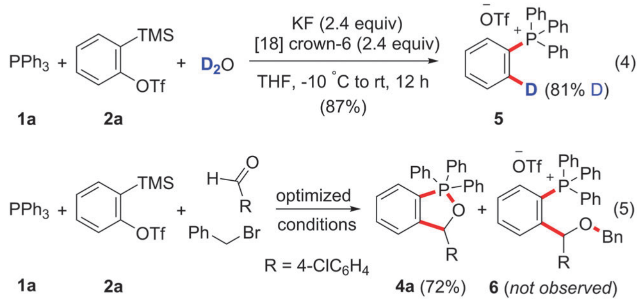


Scheme 3 MCR involving phosphines, arynes and aldehydes: scope of aldehydes. General conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), **3** (0.75 mmol), KF (1.2 mmol), [18] crown-6 (1.2 mmol), THF (3.0 mL) at −10 °C to rt for 12 h. Yields of isolated products are given. [a] The reaction mixture is stirred for 24 h.

Next, we examined the scope of the aryne annulation reaction with substituted arynes and phosphines (Scheme 4). A series of electronically dissimilar 4,5-disubstituted symmetrical arynes readily furnished the benzooxaphospholes **4z–4ac** in good yields. Interestingly, the reaction of PPh_3 and aldehydes with the unsymmetrical naphthalyne afforded the single regioisomer **4ad** in 68% yield (no detectable amount of **4ad′**). This may be attributed to the selective addition of PPh_3 to the least hindered position of naphthalyne. Additionally, the reaction using 4-methylbenzyne and 4-fluorobenzyne resulted in the formation of an inseparable mixture of regioisomers in



Scheme 4 Scope of arynes and phosphines. General conditions: **1** (0.5 mmol), **2** (0.6 mmol), **3a** (0.75 mmol), KF (1.2 mmol), [18] crown-6 (1.2 mmol), THF (3.0 mL) at −10 °C to rt for 12 h. Yields of isolated products are given. [a] Regioisomer ratio determined by ^1H NMR analysis of the crude reaction mixture.

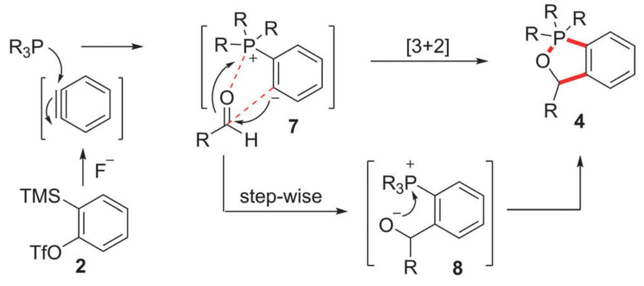


Scheme 5 Mechanistic experiments.

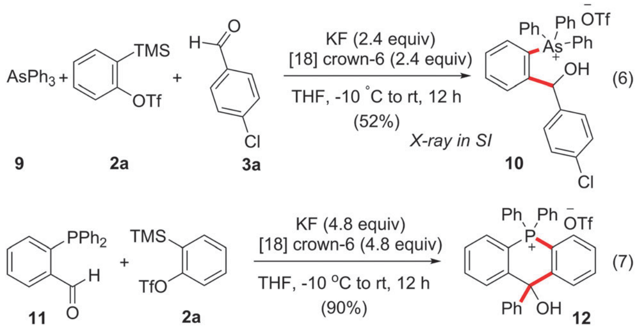
93% and 87% yields respectively. Moreover, several aromatic phosphines are well tolerated under the present reaction conditions furnishing the benzooxaphospholes in good yields (**4ag–4aj**).[15] Furthermore, aliphatic phosphines also underwent smooth annulation producing product **4ak** in 79% yield, thus demonstrating the versatile nature of these aryne MCRs.

To shed light on the mechanism of this annulation reaction, the following experiments were carried out. The reaction of PPh_3 and arynes in the presence of D_2O afforded the phosphonium salt **5** in 87% yield with 81% deuterium incorporation at the 2-position of the ring (Scheme 5, eqn (4)). This indicates the initial formation of the zwitterionic intermediate from PPh_3 and arynes, which is quenched by D_2O leading to **5**. Moreover, performing the reaction under optimized conditions in the presence of benzyl bromide resulted in the formation of the MCR product **4a** in 72% yield (eqn (5)). No observation of benzyl incorporated product **6** (92% benzyl bromide was recovered) indicates the preference of benzooxaphosphole formation over the corresponding phosphonium alkoxide zwitterion form.[16]

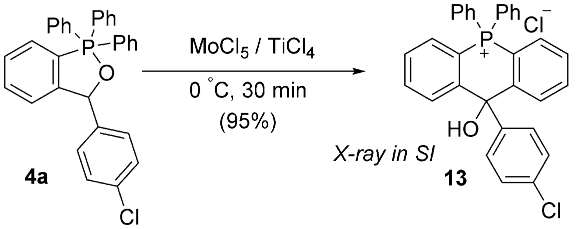
Based on these experiments, a tentative mechanism of the reaction can be delineated as follows (Scheme 6). The reaction proceeds *via* the nucleophilic attack of phosphine on the aryne derived from **2** generating the 1,3-zwitterionic intermediate **7**. It is likely that the 1,3-dipole **7** can undergo a formal [3+2] cycloaddition reaction with the electrophilic carbonyl group of aldehydes resulting in the formation of the benzooxaphosphole **4**. The desired product formation can also be rationalized by a step-wise mechanism proceeding through the alkoxide intermediate **8**, which cyclizes to afford **4**.



Scheme 6 Plausible mechanism of the reaction.



Scheme 7 Reaction using triphenylarsine and the attempted intramolecular reaction.



Scheme 8 Mo-mediated oxidative coupling.

Additionally, when triphenylarsine **9** was used as the nucleophilic trigger instead of PPh_3, the expected annulation reaction did not take place. Interestingly, this reaction afforded the arsonium triflate **10** in 52% yield (Scheme 7, eqn (6)). The structure of **10** was confirmed by single crystal X-ray analysis.[13] Furthermore, we have studied the intramolecular version of this reaction. Treatment of phosphanyl benzaldehyde **11** with arynes resulted in the formation of the phosphonium salt **12** in 90% yield, presumably *via* the *C*-arylation of the alkoxide intermediate instead of the cyclization to form the bicyclic benzooxaphosphole derivative (eqn (7)).[17] In addition, the formation of **12** sheds light on a rather non-concerted nature of the aryne annulation reactions triggered by phosphines.

The synthetic potential of the benzooxaphosphole derivative was demonstrated by the mild Mo-mediated conversion of **4a** to diphenyl dihydroacridophosphonium salt **13** (Scheme 8). The reaction proceeds *via* the P–O bond-cleavage of benzooxaphosphole **4a** followed by a unique oxidative coupling mediated by Mo leading to the formation of **13**.[18] The reaction involves both aryl C–H and benzylic C–H bond-activation processes. The structure of **13** was confirmed by single crystal X-ray analysis.[13]

In conclusion, we have developed the transition-metal-free MCR involving phosphines, arynes and aldehydes leading to the generation of stable pentacovalent phosphoranes based on the benzooxaphosphole system.[19] The reaction proceeds *via* the initial generation of a 1,3-zwitterionic intermediate from phosphines and arynes, which undergoes a formal [3+2] cycloaddition with aldehydes allowing the synthesis of phosphorus heterocycles. The compatibility with a wide range of functional groups, ease of variation of all the three components, mild reaction conditions, and high yield of products are the noteworthy features of this reaction. Further studies on expanding the scope of this reaction with various electrophiles are in progress.

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