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Rapid Access to Benzoxaphospholes and Their Spiro Analogues by a Three-Component Coupling Involving Arynes, Phosphines, and Activated Ketones

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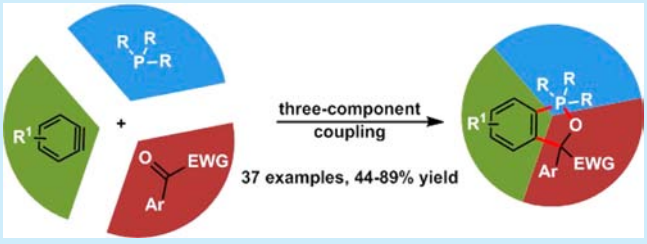
Supporting Information

ABSTRACT: An operationally simple multicomponent coupling involving in situ generated arynes from 2-(trimethylsilyl)aryl triflates, phosphines, and various acyclic and cyclic activated carbonyl compounds has been developed. The reaction proceeds via a formal [3 + 2] cycloaddition mode giving access to differently substituted (spiro)benzoxaphosphole derivatives in moderate to good yields. Mild reaction conditions, a broad scope, and the possibility of varying all the three-components are the notable features of the present reaction.



The rich and fascinating chemistry of multicomponent coupling (MCC) involving arynes has evoked considerable interest, as this method allows a rapid and straightforward access to 1,2-disubstituted benzene derivatives having molecular complexity and structural diversity.[1] The underlying principle of many of the transition-metal-free aryne MCCs involves the addition of nucleophiles devoid of acidic hydrogen atoms to the in situ formed arynes leading to the generation of nucleophilic aryl anion intermediates, which is subsequently intercepted by suitable electrophiles (Figure 1).[2] If the nucleophile and electrophile are not part of the same molecule, this process culminates in a unique three-component coupling. Nucleophiles such as isocyanides,[3] amines,[4] imines,[5] N-heterocycles,[6] and solvents including THF,[3b] DMF,[7] and DMSO[8] can invoke the generation of an aryl anion intermediate. The third component used includes carbonyl compounds including carbon dioxide,[3a,4c,9] activated imines,[3j] and activated alkynes.[3f]

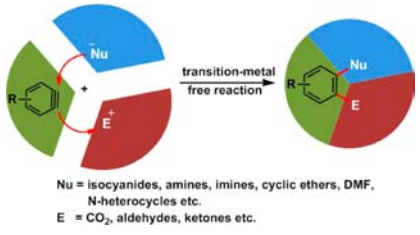
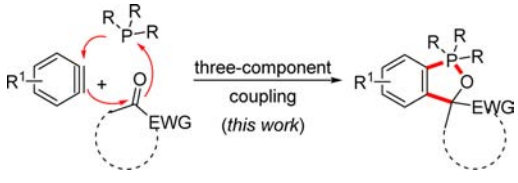


Figure 1. Aryne multicomponent coupling.

We have recently demonstrated the utility of N-heterocycles in aryne MCCs leading to the synthesis of structurally diverse nitrogen heterocycles.[10] Interestingly, however, the use of phosphines as a nucleophilic trigger in aryne MCCs has received only limited attention.[11] This is rather surprising as the synthetic utility of phosphines in nucleophilic catalysis has emerged as one of the powerful methods for the transition-metal-free access to various hetero- and carbocycles.[12] Despite the widespread application of nucleophilic phosphine catalysis, the reactions where phosphines are incorporated into the final product are relatively few.[13] In the pursuit to synthesize benzannulated phosphorus heterocycles, we have very recently demonstrated the aryne MCCs with phosphines, where aldehydes were used as the electrophilic third component.[14] Our continued efforts in aryne MCCs have revealed that the reaction is not limited to aldehydes but is instead applicable to various cyclic and acyclic carbonyl compounds. Herein, we report the mild and efficient phosphine-triggered aryne three-component reaction using activated acyclic ketones as the third component resulting in the synthesis of functionalized benzoxaphospholes in moderate to good yields (Scheme 1). In addition, the results of our studies using activated cyclic ketones such as *N*-substituted isatins leading to the formation of spirobenzoxaphospholes are also demonstrated.

Scheme 1. Utility of Phosphines in Aryne MCCs



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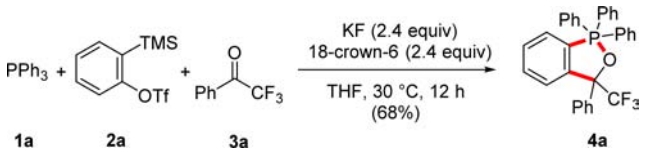
The present study was initiated by treating triphenylphosphine (**1a**) and 2,2,2-trifluoro-1-phenylethan-1-one (**3a**) with the aryne generated *in situ* from 2-(trimethylsilyl)aryl triflate (**2a**)[15] using KF and 18-crown-6. Under these conditions, a facile reaction occurred leading to the formation of the benzoxaphosphole derivative **4a** in 68% yield (Scheme 2). Notably, 2-fold excesses of KF and 18-crown-6 were needed

Scheme 2. Three-Component Coupling Involving Phosphine, Aryne, and Trifluoroacetophenone



for the satisfactory yield of **4a**, and other fluoride sources such as CsF (used in CH_3CN as solvent) and tetrabutyl ammonium fluoride (TBAF) furnished a lesser yield of **4a**. The product **4a** was crystallized from CH_2Cl_2, and its structure was unequivocally confirmed by single-crystal X-ray analysis (Figure 2).[16] It may be mentioned that compounds containing the

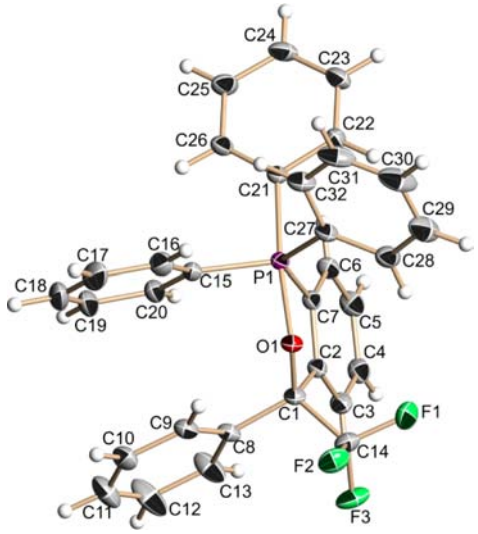
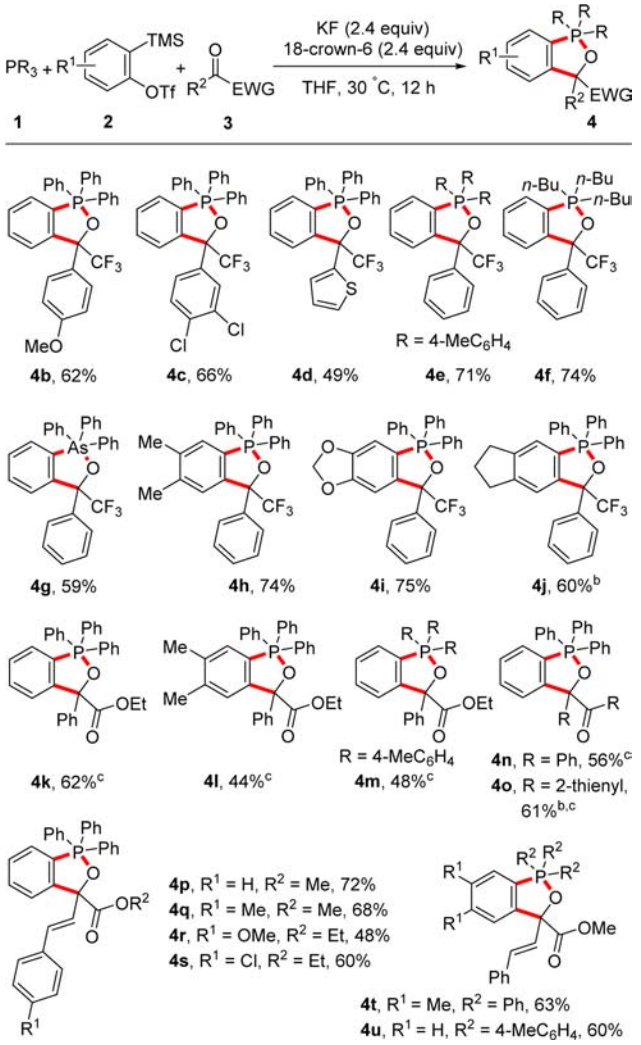


Figure 2. Crystal structure of **4a** (thermal ellipsoids are shown with 50% probability).

trifluoromethyl moiety have pharmaceutical relevance,[17] and the products incorporating the benzoxaphosphole core as well as the trifluoromethyl group is anticipated to have potential biological properties.

Mechanistically, the reaction proceeds via the initial generation of a 1,3-zwitterionic intermediate from a phosphine and an aryne, which is subsequently intercepted by the electrophilic carbonyl group of trifluoroacetophenone in a formal [3 + 2] cycloaddition mode leading to the formation of the benzoxaphosphole derivative. With the reaction conditions in hand, we then examined the substrate scope of these phosphine-triggered aryne MCCs (Scheme 3). First, we evaluated various activated acyclic ketones. Interestingly, substituted aromatic trifluoroacetophenones and heterocyclic trifluoromethyl ketones were well-tolerated affording the benzoxaphosphole derivatives in good yields (**4b**–**4d**). Moreover, the phosphine moiety was variable, and even tributylphosphine and triphenylarsine can be used as the nucleophilic trigger providing the desired product in good yields (**4e**–**4g**).[18] The structure of **4g** was unambiguously confirmed by single-crystal X-ray analysis.[16] In addition, symmetrically substituted arynes generated from the corresponding precursors underwent a smooth cyclization reaction with **1a** and **3a** demonstrating the versatility of the present aryne MCCs (**4h**–**4j**). Gratifyingly, an α-ketoester, such as ethyl benzoylformate, and α-diketones, such as benzil and 2,2′-thenil, furnished the target benzoxaphosphole derivatives in moderate to good yields (**4k**–**4o**). Furthermore, α-keto β,γ-unsaturated esters can also be used as the activated ketone component, and the corresponding benzoxaphospholes were isolated in 48–72% yield, thus significantly expanding the scope of the aryne MCCs (**4p**–**4u**). Notably, our preliminary studies showed that unactivated ketones such as aceto- and benzophenone did not afford the desired benzoxaphospholes under the optimized reaction conditions.

Scheme 3. Substrate Scope for the MCC Involving Phosphines, Arynes, and Activated, Acyclic Ketones[a]



[a]General conditions: **1** (0.50 mmol), **2** (0.60 mmol), **3** (0.75 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (3.0 mL) at 30 °C for 12 h. Yields of isolated products are given. [b] The reaction was run on 0.25 mmol scale. [c] The reaction was performed using 1.0 mmol of **2**, 2.0 mmol of KF, and 2.0 mmol of 18-crown-6.

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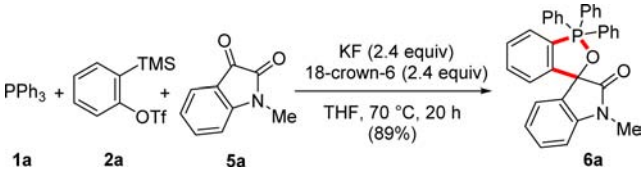
In view of the interesting results obtained using acyclic ketones, we then focused our attention on activated cyclic carbonyl compounds. If successful, this will lead to the synthesis of novel spirocyclic benzoxaphospholes. We began our studies using N-substituted isatins as the third component.[19] Interestingly, the reaction of **1a** with *N*-methyl isatin **5a** and aryne generated from **2a** using KF and 18-crown-6 resulted in the formation of the spirobenzoxaphosphole derivative **6a** in 89% yield (Scheme 4). Notably, this reaction proceeds at a high

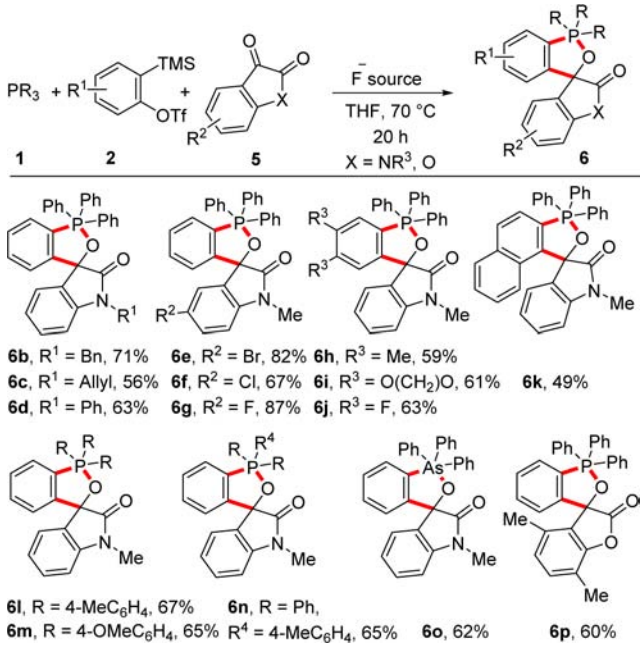
Scheme 4. Three-Component Coupling Involving Phosphine, Aryne, and *N*-Methyl Isatin



temperature of 70 °C, with a longer reaction time of 20 h, and the attempted reaction at 30 °C for 12 h resulted in a reduced yield of **6a**.

After establishing the conditions for the synthesis of spirocyclic benzoxaphospholes, we then examined the scope of this spirocyclization reaction (Scheme 5). Alkyl and aryl

Scheme 5. Substrate Scope for the MCC Involving Phosphines, Arynes, and Isatins[a]



[a]General conditions: **1** (0.50 mmol), **2** (0.75 mmol), **5** (0.75 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (4.0 mL) at 70 °C for 20 h. Yields of isolated products are given.

substitutions on the isatin nitrogen are well-tolerated resulting in the formation of the spirobenzoxaphosphole derivatives in moderate to good yields (**6b**–**6d**). Moreover, halogen substitution on the carbocyclic ring of isatin did not disturb the reactivity, and the corresponding products were formed in good yields (**6e**–**6g**). Additionally, electronically different 4,5-disubstituted symmetrical arynes as well as the unsymmetrical naphthalyne underwent the annulation reaction to furnish the desired products (**6h**–**6k**). In the case of compound **6h**, the structure was confirmed by single-crystal X-ray analysis (Figure 3).[16]

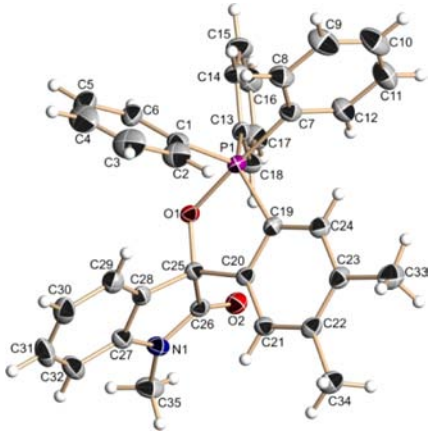


Figure 3. Crystal structure of **6h** (thermal ellipsoids are shown with 50% probability).

Furthermore, substituted triarylphosphines are useful as a nucleophilic trigger in the present annulation reaction (**6l**–**6n**), and triphenylarsine can also be used as the initiator in the present aryne MCC affording the desired product **6o** in 62% yield.[18] Interestingly, the present annulation reaction is not limited to the use of N-substituted isatins as third component, but instead, 4,7-dimethylbenzofuran-2,3-dione can also be used as the third component delivering the expected product **6p** in 60% yield, thus demonstrating the versatility of the present reaction.[20]

In conclusion, we have developed the transition-metal-free MCC involving phosphines, arynes, and activated acyclic and cyclic carbonyl compounds. The reaction resulted in a convenient synthesis of (spiro)benzoxaphospholes in moderate to good yields. Mechanistically, the reaction proceeds via the initial generation of a 1,3-dipolar intermediate from phosphines and arynes, which on interception with carbonyl compounds in a formal [3 + 2] cycloaddition mode afford the synthesis of phosphorus heterocycles. It is noteworthy that the reaction tolerates a broad range of functional groups, and the variation of all three components is possible. In view of the importance of organophosphorus compounds as pharmaceuticals and agrochemicals, the method reported herein is likely to find potential applications. Further studies on related aryne MCCs are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Details on experimental procedures; single crystal X-ray data for **4a**, **4g**, and **6h**; and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) CCDC-1001502 (**4a**), CCDC-1023341 (**4g**), and CCDC-1020395 (**6h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(18) It is interesting to note that the reaction of triphenylarsine with aryne and aldehyde afforded the acyclic arsonium triflate in moderate yield. However, with **3a** and **5a** as the third component, the arsonium triflate formation was not observed. For details, see ref 14.

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(20) It may be noted that preliminary studies showed that the cyclic ketones such as cyclohexanone did not afford the spirobenzoxaphosphole derivative under the present reaction conditions.