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Insertion of Arynes into P–O Bonds: One-Step Simultaneous Construction of C–P and C–O Bonds

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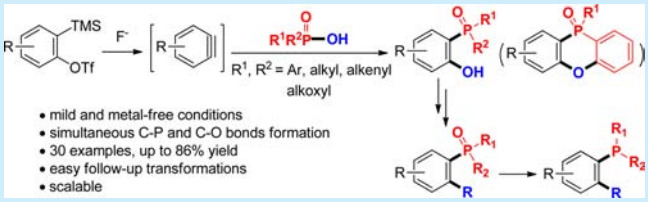
Supporting Information

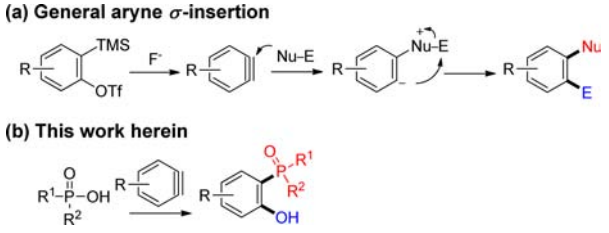
ABSTRACT: The insertion of arynes into P–O bonds for the preparation of *o*-hydroxy-substituted arylphosphine oxides, -phosphinates, and -phosphonates is described. This novel reaction leads to the simultaneous formation of C–P and C–O bonds in one step with good yields and regioselectivities under mild and transition-metal-free conditions. The easy follow-up transformations of the resulting *o*-hydroxyl group extend these reactions to the facile construction of other *ortho*-substituted arylphosphorus compounds.



Organophosphorus compounds have a broad spectrum of applications. In particular, arylphosphorus compounds are extremely useful in organic synthesis,[1] material chemistry,[2] and medicinal chemistry.[3] Although alkylphosphorus compounds could be synthesized easily via the classical Arbuzov reaction,[4] the synthesis of arylphosphorus compounds poses a major challenge, and the existing methods often require expensive transition metals and harsh reaction conditions, such as Pd/Cu/Ni-catalyzed Arbuzov[5] or Hirao reactions.[5a,6] Therefore, the development of new methods for the preparation of arylphosphorus compounds is of importance. In particular, a step-economic difunctionalization reaction that enables simultaneous introduction of phosphorus-containing and other functional groups into one single aryl framework is practically desired.

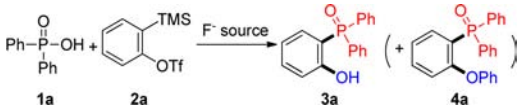
Arynes are highly reactive intermediates and have been widely used in organic synthesis.[7] The insertion of arynes into σ bonds (Scheme 1a) is one of the most common reaction mode of arynes, which enables two functional groups to be introduced simultaneously at the *ortho* positions of the aromatic rings.[8] Some insertion involving σ-bonds linking a variety of atoms (C–C,[8b,9] C–O,[10] C–N,[11] C–P,[12] P–H,[13] P–N,[14] P–Sn,[15] etc.) has been reported. As a continuation of our interest in the aryne field,[16] we envisioned a novel transformation involving the insertion of arynes into P–O bonds of organophosphorus acids to access various *o*-hydroxy-substituted arylphosphorus compounds (Scheme 1b). To the best of our knowledge, the insertion of arynes into P–O bonds has not been explored. Moreover, the newly formed phenolic hydroxyl group in these reactions could be directly modified or transformed into other useful functional groups.

Scheme 1. Aryne σ-Insertion Reactions



To verify our hypothesis, we initially examined the reaction with diphenylphosphinic acid **1a** and β-trimethylsilyl triflate **2a** (Table 1). The reaction with 3.0 equiv of **2a** and 5.0 equiv of CsF in CH_3CN was attempted first (Table 1, entry 1). The expected insertion of aryne into the P–O bond indeed occurred. However, it was compound **4a** instead of the desired

Table 1. Optimization of Reaction Conditions[a]



entry	2a (equiv)	F⁻ (equiv)	solvent	yield[b] (%) 3a	4a
1	3.0	CsF (5.0)	CH_3CN[c]	0	65
2	1.3	CsF (2.6)	CH_3CN	12	42
3	1.3	KF (2.6)[d]	THF	38	11
4	1.3	TBAF (2.6)	THF	35	9
5	1.5	TBAT (2.5)	THF	57	0
6	1.5	TBAT (2.5)	THF	71[e]	0

[a]All reactions were carried out on a 0.2 mmol scale in 8.0 mL of solvent at 25 °C unless otherwise specified. [b]Isolated yields. [c]CH_3CN (4.0 mL). [d]2.0 equiv of 18-crown-6 ether as an additive. [e]The reaction was conducted at 60 °C.

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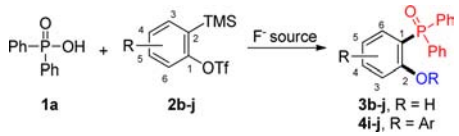
3a that was obtained in 65% yield. This could be explained by the further reaction of **3a** with another equivalent of benzyne generated in situ. To optimize the formation of **3a**, the effects of solvent, fluoride source, temperature, and stoichiometry were carefully studied (entries 2−6). Considering the basicity of fluoride source and enhanced nucleophilicity of the phenolic hydroxyl group under basic conditions, TBAT (tetrabutylammonium difluorotriphenylsilicate) with weaker basicity[17] was chosen as the fluoride source to suppress the further reaction of **3a**. Under the optimized conditions, **3a** was obtained in 71% yield (entry 6). The same reaction on a larger scale (**1a**, 600 mg, 2.75 mmol) also provided **3a** in a similar yield.

To understand the scope of the novel transformation, a wide range of *β*-trimethylsilyl triflates **2b−j** were then examined with diphenylphosphinic acid **1a**, and the results are summarized in Table 2. All of the reactions for aryne precursors with electron-donating groups led to the formation of the desired products in good yields of 77−86% (Table 2, entries 1−5, 8, and 10), which were slightly higher than the yield for unsubstituted benzyne precursor **2a**. The positions and amounts of electron-donating groups did not affect yields significantly, and even the steric hindrance of 3- and/or 6-substituted groups had no influence on yields (entries 1, 2, and 5). Lower yields were observed in the reactions with 4,5-difluorobenzyne precursor **2g** bearing strong electron-withdrawing groups (entry 6) and naphthalyne precursor **2h** (entry 7). It was noteworthy that the reactions with asymmetric 3-methoxy- or 3,5-dimethoxybenzyne precursors (entries 1 and 2) exhibited excellent regioselectivity at the *meta* position, which was consistent with the reported selectivity.[18] The structure of **3b** was unequivocally confirmed by single-crystal X-ray analysis (Figure 1).[19] Under the conditions of CsF in CH_3CN, excess benzyne precursors could lead to further reaction of the resulting phenol with benzyne, as indicated by the formation of compounds **4i** and **4j** (entries 9 and 11). This could be utilized to transform phenolic hydroxyl groups to expand its potential applications.

In order to further gauge the scope and generality of the reaction, a series of organophosphorus acids **1b−n** were reacted with *β*-trimethylsilyl triflate **2a** under the optimized reaction conditions (Table 3). For the phosphinic acids bearing aryl groups, *para* electron-donating groups on aryl groups did not influence the yields apparently (Table 3, entries 1 and 2). However, *para* or *ortho* strong electron-withdrawing groups on aryl groups reduced the yields greatly, which might result from the reduced nucleophilicity of the phosphinic acids (entries 3−5). For phosphinic acid **1f**, in the presence of K_2CO_3, the phenolate anion formed in situ could continue to undergo a nucleophilic aromatic substitution to give **4o** along with the departure of fluoride ion. This provides a novel route to synthesize benzofused phosphacycles in a cascade fashion (entry 6), which usually possess unique physical properties and draw much attention.[20] For the phosphinic acids bearing alkyl or alkenyl groups, all reactions could lead to the desired products in good yields (entries 7−12). The insertion of arynes into P−O bonds of phosphonate **1m** (entry 14) and phosphate **1n** (entry 16) was also explored, which provided the desired products in good yields under the same conditions as for phosphinic acids. For different kinds of organophosphorus acids, an excess of benzyne precursor **2a** could lead to further reaction of the resulting phenol, for example, the formation of **4u** (entry 13), **4v** (entry 15), and **4w** (entry 17).

Based on our experimental results and related literatures,[10,14] the proposed mechanism for the transformation is shown in

Table 2. Scope of Aryne Precursor Substrates[a]



entry	aryne precursor	product	yield[b] (%)
1	**2b**; R = 3-OMe	**3b**; R = 6-OMe	83
2	**2c**; R = 3,5-$(OMe)_2$	**3c**; R = 4,6-$(OMe)_2$	78
3	**2d**; R = 4,5-$(OMe)_2$	**3d**; R = 4,5-$(OMe)_2$	77
4	**2e**; R = 4,5-$(Me)_2$	**3e**; R = 4,5-$(Me)_2$	82
5	**2f**; R = 3,6-$(Me)_2$	**3f**; R = 3,6-$(Me)_2$	85
6	**2g**; R = 4,5-$(F)_2$	**3g**; R = 4,5-$(F)_2$	54
7	**2h**	**3h**	65
8	**2i**	**3i**	86
9		**4i**	66[c]
10	**2j**	**3j**	83
11		**4j**	66[d]

[a] **1a** (0.2 mmol), **2** (0.3 mmol), TBAT (0.5 mmol), THF (8.0 mL), 60 °C, 6 h. [b] Isolated yields. [c] **1a** (0.2 mmol), **2i** (0.6 mmol), KF (1.6 mmol), 18-crown-6 (0.8 mmol), dioxane (4.0 mL), 60 °C, 8 h. [d] **1a** (0.2 mmol), **2j** (0.6 mmol), CsF (1.0 mmol), CH_3CN (4.0 mL), 60 °C, 8 h.

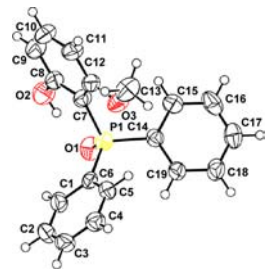


Figure 1. Crystal structure of **3b**.

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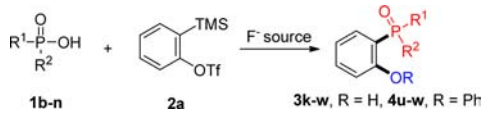
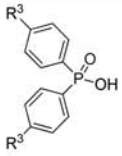
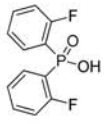
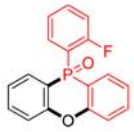
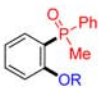
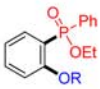
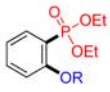
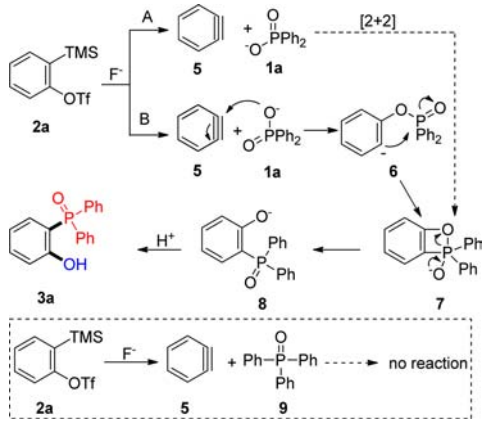
Table 3. Scope of Organophosphorus Acid Substrates[a]



entry	organophosphorus acid	product	yield[b] (%)
			
1	**1b**, R^3 = OMe	**3k**, R^3 = OMe	70
2	**1c**, R^3 = Me	**3l**, R^3 = Me	72
3	**1d**, R^3 = F	**3m**, R^3 = F	42
4	**1e**, R^3 = CF_3	**3n**, R^3 = CF_3	40
			
5	**1f**	**3o**	40
			
6		**4o**	41[c]
			
7	**1g**, R^1 = *i*-propyl	**3p**, R^1 = *i*-propyl	68
8	**1h**, R^1 = *n*-pentyl	**3q**, R^1 = *n*-pentyl	72
9	**1i**, R^1 = cyclopentyl	**3r**, R^1 = cyclopentyl	65
10	**1j**, R^1 = benzyl	**3s**, R^1 = benzyl	68
11	**1k**, R^1 = vinyl	**3t**, R^1 = vinyl	60
			
12	**1l**	**3u**, R = H	65
13		**4u**, R = Ph	42[d]
			
14	**1m**	**3v**, R = H	64
15		**4v**, R = Ph	53[d]
			
16	**1n**	**3w**, R = H	57
17		**4w**, R = Ph	47[d]

[a] **1** (0.2 mmol), **2a** (0.3 mmol), TBAT (0.5 mmol), THF (8.0 mL), 60 °C, 6 h. [b] Isolated yields. [c] **1f** (0.2 mmol), **2a** (0.3 mmol), TBAT (0.5 mmol), K_2CO_3 (0.6 mmol), THF (8.0 mL), 60 °C, 24 h. [d] **1l**, **1m** or **1n** (0.2 mmol), **2a** (0.6 mmol), CsF (1.0 mmol), CH_3CN (4.0 mL), 60 °C, 8 h.

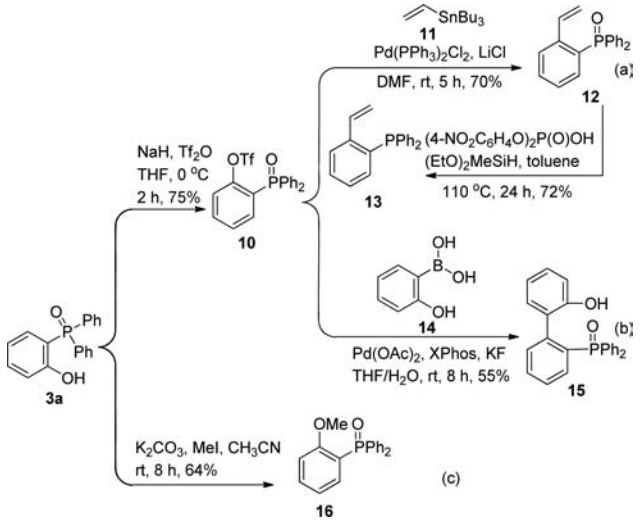
Scheme 2. Proposed Mechanism for the Insertion of Benzyne into P−O Bond



Scheme 2. Theoretically, two pathways could possibly lead to the desired product **3a**. In pathway A, benzyne **5** generated in situ reacts with the P═O bond in **1a** through concerted [2 + 2] cycloaddition to form intermediate **7** in one step, which could rearrange to **3a**. In pathway B, the oxygen anion attacks benzyne **5** to form aryl anion intermediate **6**, which undergoes an anionic Fries rearrangement through **7** to produce **3a**. Although it was reported that P═N and P═S bonds could react with arynes through a similar process to pathway A,[21] we found the P═O bond in triphenylphosphine oxide **9** did not react with benzyne under the optimized conditions, which supported pathway B for our reaction to some extent. Moreover, considering the stronger nucleophilicity of the oxygen anion than the oxygen atom of P═O bond, pathway B might be a plausible process.

To illustrate the synthetic utility of this novel transformation, the follow-up chemistries on **3a** were investigated (Scheme 3). Considering the importance of *ortho*-substituted arylphosphorus compounds, we transformed phenol **3a** into triflate **10**, which could be easily employed for various transition-metal-catalyzed coupling reactions. For example, the respective transformations of triflate **10** into olefin **12** and biphenyl **15**

Scheme 3. Follow-up Chemistry[a]



[a] Yields were not optimized.

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by Stille and Suzuki couplings could lead to alternative routes to tertiary phosphine **13**[22] and a series of phosphine−oxazoline derivatives,[23] which are examples of useful ancillary ligands in homogeneous catalysis. Other transformations involved the methylation of phenolic hydroxyl group leading to compound **16** and subsequent nucleophilic aromatic substitution to produce chiral aminophosphine ligands[24] or easy modification to access kinds of functionalized compounds.[25]

In summary, a novel strategy for the simultaneous construction of C−P and C−O bonds to synthesize *o*-hydroxy-substituted arylphosphorus compounds was developed. This scalable transformation proceeded via the insertion of arynes into P−O bonds under mild and transition-metal-free conditions. The resulting products, as well as a series of follow-up chemistries, provided novel synthetic routes for *ortho*-substituted arylphosphorus compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03283.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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