Carbophosphinylation of Arynes with Cyanomethyldiphenylphosphine Oxide

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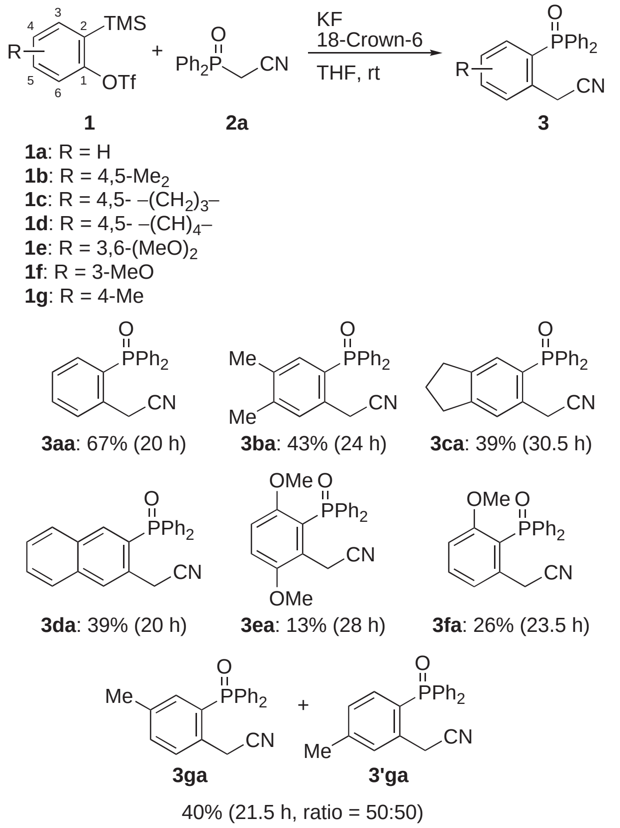
A methylene–phosphorus σ-bond of cyanomethyldiphenylphosphine oxide was found to add across a carbon–carbon triple bond of arynes, leading to the simultaneous introduction of cyanomethyl and diphenylphosphinyl moieties into 1,2-positions of the aromatic skeletons.

Addition reactions of an element–element σ-bond across a triple bond of arynes have attracted considerable attention as a general and potent method for simultaneous introduction of two elements into the adjacent positions of the aromatic skeletons, resulting in the formation of diverse polysubstituted arenes, which are otherwise difficult to prepare.[1,2] In particular, the additions of a carbon–element σ-bond would have high synthetic significance, since the reactions are inevitably accompanied by construction of carbon framework through carbon–carbon bond forming processes.[3] Recently, we have disclosed that a carbon–carbon σ-bond of β-dicarbonyl[4,5] or α-cyanocarbonyl[6] compounds readily add to arynes, demonstrating that two carbon–carbon σ-bonds are formed in one step. Since then, we have been studying the reactions of arynes with active methylene compounds containing other electron-withdrawing groups, and have found that cyanomethyldiphenylphosphine oxide adds to arynes at its methylene–phosphorus moiety solely. Herein, we report on the carbophosphinylation of arynes, in which carbon–carbon and carbon–phosphorus bonds are generated all at once (Eq 1).[7]

(1)

First, we examined the reaction of in situ-prepared benzyne (from **1a** and KF/18-Crown-6)[8] with cyanomethyldiphenylphosphine oxide (**2a**) in THF at room temperature, and observed that insertion of benzyne into the methylene–phosphorus σ-bond took place smoothly to afford diphenyl[2-(cyanomethyl)-phenyl]phosphine oxide (**3aa**) in 67% yield (Scheme 1).[9] Such substituted arynes as 4,5-dimethylbenzyne (from **1b**), 4,5-trimethylenebenzyne (from **1c**), or 2,3-naphthalyne (from **1d**) also took part in the reaction, offering the respective carbophosphinylation products (**3ba**–**3da**) in moderate yields. In marked contrast, the reaction of 3,6-dimethoxybenzyne (from **1e**) became sluggish, probably owing to the steric congestion around the triple bond. An unsymmetrical aryne, 3-methoxybenzyne (from **1f**), underwent the addition of **2a** as well to produce **3fa** exclusively, which holds the diphenylphosphinyl moiety at the *ortho* position of the methoxy group.[10] The intermediacy of an aryne in the present reaction has been confirmed by the reaction of 4-methylbenzyne (from **1g**), where a mixture of regioisomeric products (**3ga** and **3′ga**) was obtained in equal ratio.[11,12]

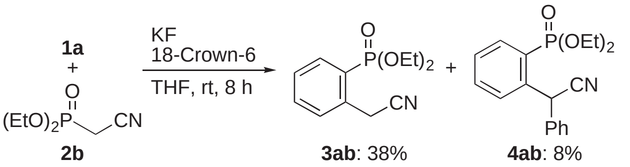
The reaction is also applicable to cyanomethylphosphonate **2b** to furnish a 38% yield of **3ab** with the formation of 2:1 coupling product **4ab**, bearing the second benzyne-derived phenyl moiety at the benzylic position (Scheme 2).



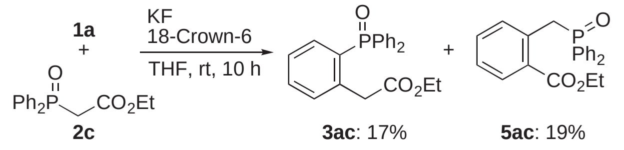
Scheme 1.

In contrast to the cases with **2a** or **2b**, the reaction of benzyne with ethyl (diphenylphosphinyl)acetate (**2c**) occurred at both methylene–phosphorus and methylene–carbonyl bonds, giving **3ac** and **5ac** in almost equal ratio (Scheme 3).

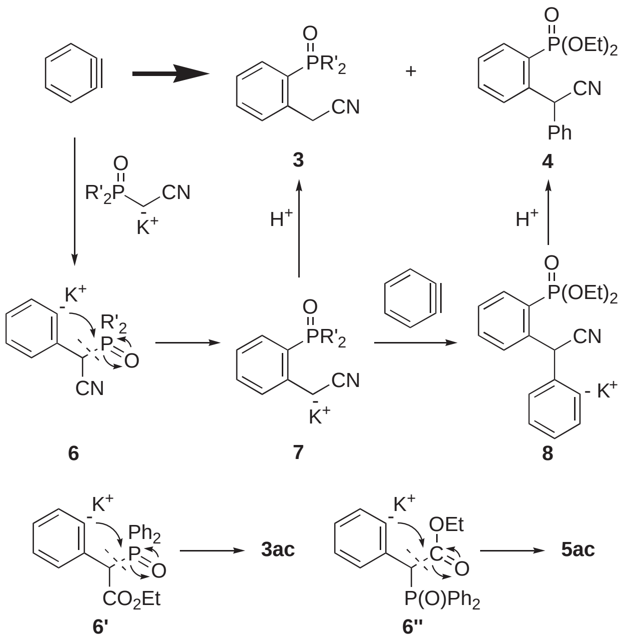
The present reaction would be triggered by a nucleophilic attack of an in situ-generated anionic species to an aryne to form **6** as depicted in Scheme 4.[13] Subsequent intramolecular nucleophilic substitution at a phosphorus moiety of **6** produces benzyl anion **7**, which further reacts with a proton or a second aryne to afford **3** or **4**, respectively. The perfect regioselectivity observed in the reaction of 3-methoxybenzyne can be rationally explained



Scheme 2.



Scheme 3.



Scheme 4.

by a steric and/or electron-withdrawing effect of the methoxy group, both of which favor the nucleophilic attack at *m*-position of the substituent. In the case of 4-methylbenzyne, steric and electronic differences around the triple bond would be negligible, and thus, an equal addition to the both ends takes place, leading to the formation of a mixture of regioisomers. On the other hand, the generation of **3ac** and **5ac** in the reaction with **2c** would be ascribable to the synchronous nucleophilic substitution at the phosphorus (**6′**) and the carbonyl (**6″**) moieties.[14]

In conclusion, we have disclosed a carbon–phosphorus σ-bond addition reaction to arynes, which enables direct and simultaneous introduction of carbon and phosphorus functional groups into the adjacent positions of the aromatic skeletons. Further studies on the improvement of the yield as well as on expansion of the reaction scope are in progress.

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References and Notes

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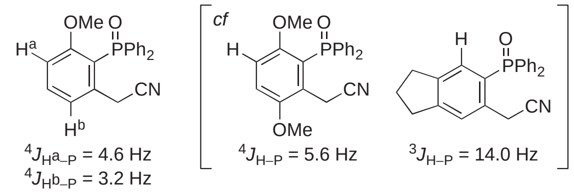
9 To a THF solution (1.0 mL) of **1** (0.40 mmol), **2a** (0.20 mmol), and 18-Crown-6 (0.212 g, 0.80 mmol) was added KF (0.047 g, 0.80 mmol), and the reaction mixture was stirred at room temperature for the time specified in Scheme 1. The mixture was diluted with ethyl acetate, washed with brine and concentrated. The residue was purified by GPC to give the corresponding product.

10 Configuration of **3fa** was determined based on coupling constants between aromatic proton and phosphorus as follows.



11 A significant amount of **2a** was recovered in the reactions with low product yields (51% in the reaction using **1e**, for example), and trace amounts of unidentified by-products were observed.

12 In the present reaction, consumption of aryne precursors was considerably slower than that in the reactions using β-dicarbonyl or α-cyanocarbonyl compounds, which resulted in the prolonged reaction time, although the reasons for this are unclear.

13 For a review on the nucleophilic couplings with arynes, see: S. V. Kessar, "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Flemming, Pergamon Press, Oxford (1991), Vol. 4, pp 483–515.

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