Communication

Metal-Free Electrophilic Phosphination/Cyclization of Alkynes

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Metal-Free Electrophilic Phosphination/Cyclization of Alkynes

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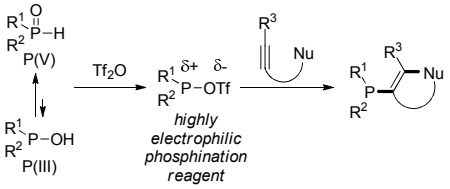
Supporting Information Placeholder

ABSTRACT: A metal-free electrophilic phosphination reaction has been developed. Electrophilic phosphorus species generated in situ from secondary phosphine oxides and Tf_2O smoothly couples with alkynes possessing pendant nucleophiles to afford corresponding phosphinated cyclization products in good yield. Preliminary NMR studies show that phosphirenium species may be involved as an intermediate of the cyclization reaction.

Organophosphorus compounds are now broadly utilized as building blocks of bioactive molecules, functional materials, and ligands for transition metals.[1] The C(sp^2)-P bond formation is one of the most important and fundamental reactions for the synthesis of these organophosphorus compounds. The classical synthetic approaches to form a C(sp^2)-P bond are the reaction of halophosphine electrophiles with organometallic carbon nucleophiles such as organolithium and Grignard reagents and the transition-metal catalyzed cross-coupling reactions of phosphines with C(sp^2)-(pseudo)halides.[1a,b,2] These methodologies, however, often suffer from low functional group compatibility and long step preparation of the coupling precursors. A number of metal-promoted direct C-P coupling reactions have recently been reported, while still they remain underdeveloped.[3,4] An alternative way for the formation of the C(sp^2)-P bond is the Friedel-Crafts-type electrophilic phosphination reaction (phospha-Friedel-Crafts: PFC reaction).[5] This process was already known in 1870's as the reaction of benzene with PCl_3 in the presence of $AlCl_3$.[5a] However, this kind of transformation is usually conducted under harsh conditions in the presence of a stoichiometric amount of Lewis acid such as $AlCl_3$. Additionally, the reactant halophosphines are toxic and air- and moisture-sensitive, which hampers application in complex molecular synthesis. Therefore PFC reaction has been less utilized in modern organic synthesis.

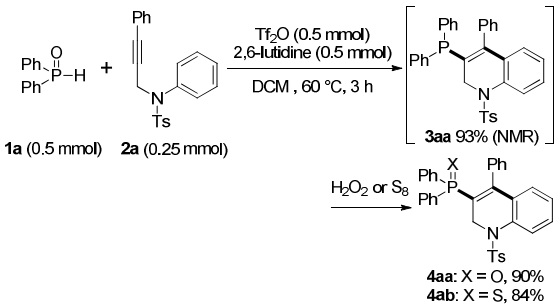
Recently, metal-free electrophilic C-heteroatom bond forming reactions have attracted attention as environmentally-friendly and unique alternatives to the metal-mediated processes.[6] The metal-free C-B,[7] C-N,[8] C-Si[9], and C-S[10] bond formations have been achieved. Herein, we report a metal-free electrophilic phosphination of alkynes. Compared to the above successful bond forming processes, there are a few reports of the metal-free intermolecular electrophilic C-P bond forming reaction.[11] A working hypothesis is depicted in Figure 1. Secondary phosphine oxides are basically stable and readily available phosphorus(V) compounds. It is known that they are in equilibrium with P(III) forms (hydroxyphosphines) in a solution.[1a,12] We envisioned that if this hydroxyl group could be replaced with TfO group upon treatment with Tf_2O, a highly electrophilic phosphorus species would be generated and utilized for PFC reactions under metal-free conditions.[13] As a design of the reaction, we selected an electrophilic cyclization of nucleophile-tethered alkynes. Thus, the formed phosphorus electrophile may activate such an alkyne to trigger subsequent cyclization with the pendant nucleophile part.

Figure 1. A Working Hypothesis of This Study



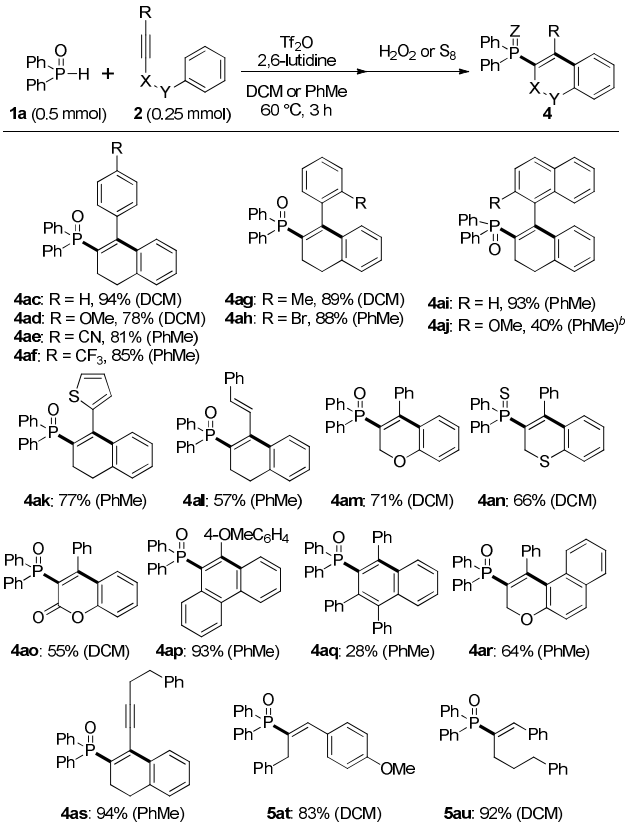
With the above hypothesis, we commenced optimization of the electrophilic phosphinative cyclization of alkyne **2a** using diphenylphosphine oxide (**1a**) (Scheme 1). To our delight, treatment of **1a** (0.5 mmol) with **2a** (0.25 mmol) in the presence of 2,6-lutidine (0.5 mmol) and Tf_2O (0.5 mmol) in DCM (2 mL) at 60 °C for 3 h in a schlenk tube afforded phosphinative cyclization product **3aa** in 93 % NMR yield (see the Supporting Information (SI) for detailed optimization studies). For an ease of handling, the phosphine was isolated as phosphine oxide **4aa** (90%) or sulfide **4ab** (84%) after treatment with H_2O_2 or S_8, respectively.

Scheme 1. Electrophilic Phosphination/Cyclization Reaction of 1a with 2a



Under the conditions in Scheme 1, we next examined the scope of alkynes. Representative products are summarized in Table 2. In some cases, better results were obtained in toluene. In addition to propargyl amide **2a**, simple methylene-tethered arylalkynes possessing both electron-donating and withdrawing-groups at ortho- (**2c-2f**) or para-positions (**2g** and **2h**) smoothly reacted with **1a** to afford corresponding coupling products **4ac-4ah**. Furthermore, this methodology was applied to synthesize 1,1-binaphthyl type phosphines,[14] MOP analogues **4ai** and **4aj** were formed in synthetically useful yields. In addition, not only benzene ring, but also thiophene (**4ak**), and conjugated enyne (**4al**) could be employed without any difficulties.

Table 1. Scope of Alkynes 2[a]

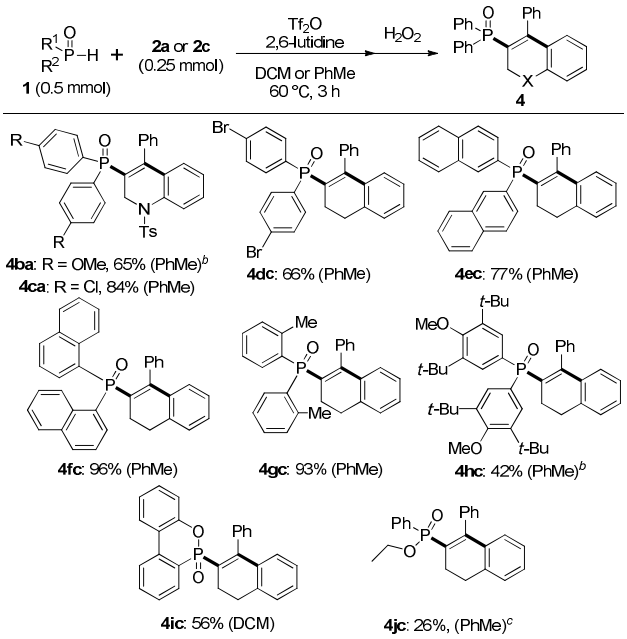


[a] Reaction conditions: 1) **1a** (0.5 mmol), **2** (0.25 mmol), Tf_2O (0.5 mmol), 2,6-lutidine (0.5 mmol) in DCM or PhMe (2 mL) at 60 °C under N_2 for 3 h; 2) H_2O_2 or S_8 workup. Isolated yields are shown based on the amount of **2**. [b] Reaction for 12 h.

As a linker of substrate, ether (**4am**), thioether (**4an**), ester (**4ao**), arene (**4ap**), or alkene (**4aq**) was also viable. The reaction of 2-naphthyl ether **2r** formed **4ar** selectively cyclized at the C1 position, which may be dominated by electronic effect. Interestingly, the reaction of 1,8-diphenylocta-3,5-diyne (**2s**) selectively formed 1:1 coupling product **4as**. It should be noted that when the alkyne has a shorter or longer methylene linker (**2t**, **2u**), the cyclization did not occur and hydrophosphinylated product **5at** or **5au** was instead obtained (see below for the detailed pathway to **5at** and **5au**). Additionally, attempts to apply terminal alkynes and dialkyl alkynes such as 4-phenyl-1-butyne and 1-phenyl-4-cyclopropyl-3-butyne remained unsuccessful.

We subsequently investigated scope of phosphine oxides **1** (Table 2). 4,4'-Disubstituted diphenylphosphine oxides **1b-d** reacted with **2a** or **2c** to afford the corresponding coupling products **4ba**, **4ca**, and **4dc**. The present system was tolerated with sterically demanding **1e**, **1f**, and **1g** (**4ec**, **4fc**, **4gc**). In the case of substrates possessing electron-donating groups **1b** and **1h** (and **2j** in Table 1 as well), longer reaction time (12 h) was required for completion (**4ba**, **4hc**). The hydrophosphinylated products corresponding to **5** in Table 1 were formed when the reaction was quenched in 3 h. This result may imply participation of a phosphirenium intermediate (vide infra). Pleasingly, the electrophilic phosphination was also compatible with phosphinate esters **1i** and **1j** albeit in moderate yields (**4ic**, **4jc**). In the case of **4jc**, addition of 2,6-lutidine gave a complicated mixture while the reason is unclear at present. Unfortunately, the present methodology was not applicable to dialkylphosphine oxides (e.g. dicyclohexyl- and diisopropyl phosphine oxides) and phosphites (e.g. diphenylphosphite, not shown).

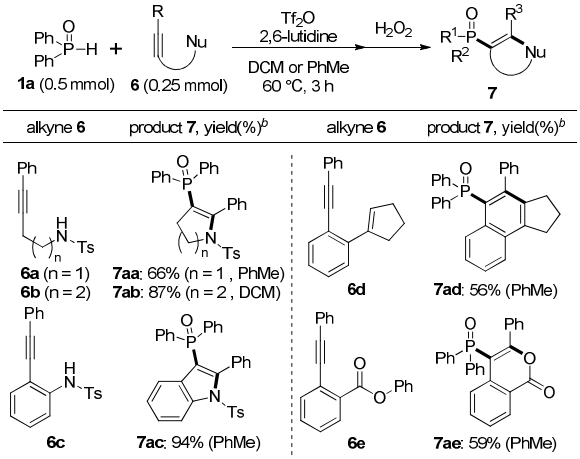
Table 2. Scope of Phosphine Oxides 1[a]



[a] Reaction conditions: 1) **1** (0.5 mmol), **2a** or **2c** (0.25 mmol), Tf_2O (0.5 mmol), 2,6-lutidine (0.5 mmol) in DCM or PhMe (2 mL) at 60 °C under N_2 for 3 h; 2) H_2O_2 or S_8 workup. Isolated yields are shown based on the amount of **2**. [b] Reaction time for 12 h. [c] Reaction was conducted without 2,6-lutidine.

We also explored nucleophiles other than the aromatic ring (Table 3). When, tosylamides **6a-c** were employed under identical conditions, the corresponding nitrogen heterocycles dihydropyrrole **7aa**, tetrahydropyridine **7ab**, and indole **7ac** were formed. The successful formation of five-membered ring (**7aa** and **7ac**) was a sharp contrast to the case of arene nucleophile (**5at** in Table 1), while exclusive 6-*endo-dig* product **7ab** was observed in the reaction of **6b**. Furthermore, an alkene could also be employed as the nucleophile. Thus, the reaction of **1a** with **6d** afforded **7ad** in an acceptable yield. It was somehow surprising that phenyl 2-(phenylethynyl)benzoate **6e** underwent the phosphinative cyclization to form isocoumarin scaffold **7ae** in 59% yield, in which the ester oxygen atom served as the nucleophile.

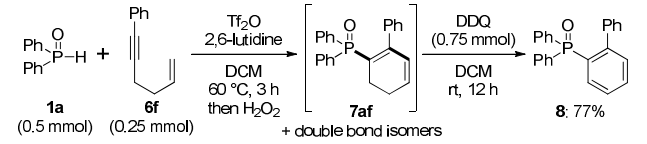
Table 3. Variation of Pendant Nucleophiles[a]



[a] Reaction conditions: 1) **1** (0.5 mmol), **6** (0.25 mmol), Tf_2O (0.5 mmol), 2,6-lutidine (0.5 mmol) in DCM or PhMe (2 mL) at 60 °C under N_2 for 3 h; 2) H_2O_2 work up. Isolated yields are shown based on the amount of **6**.

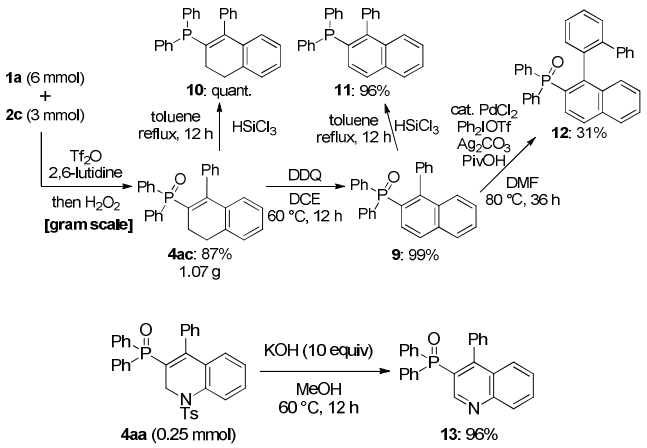
A Buchwald-type biarylphosphines were also accessible by using the present methodology (Scheme 2). For example, the reaction of **1a** with homoallylalkyne **6f** generated dihydrobenzene scaffold **7af** along with its double bond isomers. While inseparable, the mixture was subsequently treated with DDQ at room temperature to give single biarylphosphine oxide **8** in 77% yield.

Scheme 2. Synthesis of Biarylphosphine Oxide 8



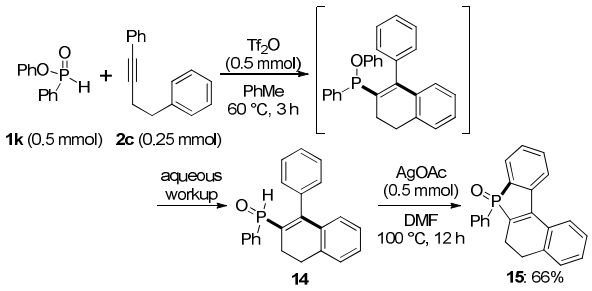
We further demonstrated the utility of this transformation in the ligand synthesis (Scheme 3). The present PFC-type reaction could be conducted on a gram scale; **4ac** was obtained in 87% yield (1.07 g, 3 mmol scale). The DDQ-promoted dehydrogenative aromatization of **4ac** provided biarylphosphine oxide **9** quantitatively. In addition, **4ac** and **9** were reduced with $HSiCl_3$ to the corresponding phosphines **10** and **11**, respectively in excellent yields. Furthermore, **9** could be transformed to polyarylphosphine oxide **12** by a Pd-catalyzed C-H arylation.[15] Isoquinoline-containing biarylphosphine oxide **13** was also synthesized by KOH-promoted dehydrosulfination of **4aa**.

Scheme 3. Synthetic Applications



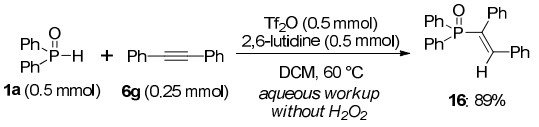
The present system finds an application in the construction of a phosphole framework, which considerably attracted attention in the area of materials chemistry.[16] Upon treatment of **1k** and **2c** with Tf_2O in toluene followed by aqueous workup, secondary phosphine oxide **14** was selectively formed probably via a preformed phenoxyphosphine (Scheme 4). The crude **14** was directly subjected to silver-mediated oxidative radical cyclization conditions,[17] leading to benzo[*b*]phosphole **15** in 66% yield based on the amount of **2c**.

Scheme 4. Benzo[*b*]phosphole Synthesis by Sequential Double Annulation



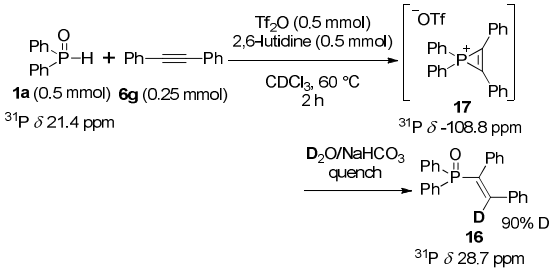
To obtain the mechanistic information, we next attempted the reaction of alkyne without the pendant nucleophile. Treatment of **1a** with simple diphenylacetylene (**6g**) under the standard conditions afforded hydrophosphinylated product **16** in a high yield (Scheme 5). Interestingly, the product was exclusively obtained in the phosphine oxide form even without any oxidative workup.

Scheme 5. Metal-free Hydrophosphinylation of 6g

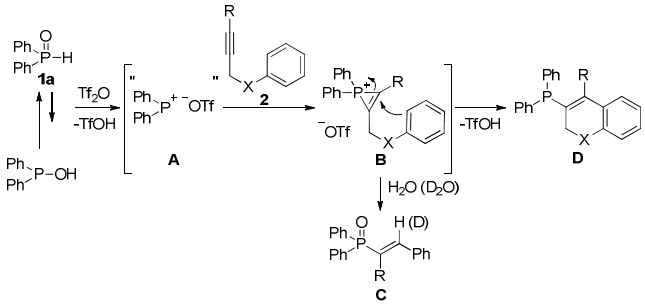


This intriguing result prompted us to carry out *in situ* $^{31}P\{^1H\}$ NMR studies on the reaction in Scheme 5. The phosphine oxide **1a** was treated with **6g** in $CDCl_3$ under the standard conditions and the resulting reaction mixture was monitored by $^{31}P\{^1H\}$ NMR (Scheme 6, see the SI for details). After 2 h, the signal of **1a** (δ 21.4 ppm) disappeared and two singlet signals (δ -108.9 and 42.2 ppm) were observed. The signal at δ 42.2 is corresponding to $Ph_2P(O)Cl$, which could be formed from the phosphenium species Ph_2P^+ through Cl abstraction from $CDCl_3$ and oxidation. On the other hand, the distinctive upshifted signal at δ -108.9 is assigned to phosphirenium species **17**.[18,19] The reaction mixture was then quenched by D_2O and $NaHCO_3$ at room temperature. The vinylphosphine oxide **16** and the starting **1a** were mainly observed in the crude mixture. Furthermore, ^1H and ^2D NMR analyses showed a 90% deuterium incorporation at the β-positon of **16**. It was previously documented that Ph_2PCl underwent [2+1] cycloaddition with diphenylacetylene **6g** in the presence of $AlCl_3$ to form a tetraphenylphosphirenium cation, which was immediately hydrolyzed upon treatment with H_2O to form the same hydrophosphinylated product **16**.[19a]

Scheme 6. In Situ $^{31}P\{^1H\}$ NMR Study of The Reaction of 1a with 6g



Scheme 7. Proposed Mechanism



Based on the preliminary mechanistic studies, we propose a tentative reaction mechanism for the present phosphinative cyclization reaction in Scheme 7. The electrophilic phosphorus species **A**[20] generated from **1a** and Tf_2O undergoes the [2+1] cycloaddition with alkyne **2** to form the phosphirenium cation **B**. The phosphirenium **B** may readily undergo ring-opening hydroly-

sis to form the corresponding hydrophosphinylated product **C** upon aqueous workup. If the alkyne **2** has a pendant aryl moiety as a nucleophile at the appropriate position, the arylative ring-opening of the phosphirenium may occur to form the phosphinative cyclization product **D**. The longer reaction periods with MeO-substituted substrates (**4aj**, **4ba**, **4hc**) were also consistent with the mechanism; its electron-donating nature may stabilize the phosphirenium **B** and delay the subsequent ring-opening event.

In summary, we have developed the metal-free electrophilic phosphinative cyclization reaction of alkynes. The electrophilic phosphination reagent generated *in situ* from secondary diarylphosphine oxides with the Tf_2O/2,6-lutidine system smoothly undergoes the tandem coupling reaction with alkynes to form various phosphine derivatives. The ^{31}P NMR mechanistic studies suggested the intermediacy of phosphirenium species in the reaction medium. Further application of the newly developed metal-free strategy is under investigation in our group.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge via the Internet at http://pubs.acs.org.

Procedures and characterization data

X-ray crystallographic data for **4ar** and **7ae**

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Notes

The authors declare no competing financial interest.

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