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Direct Access to Allenylphosphine Oxides via a Metal Free Coupling of Propargylic Substrates with P(O)H Compounds

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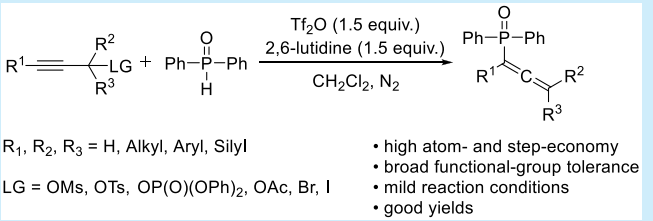
Supporting Information

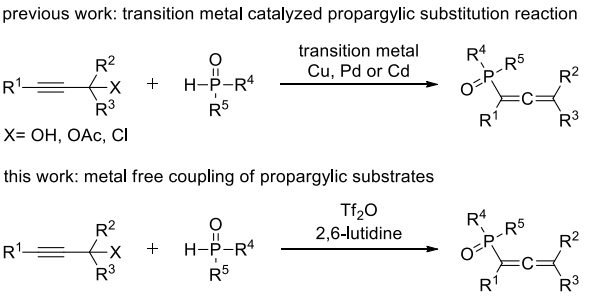
ABSTRACT: A direct and convenient approach for the coupling of propargylic substrates with diphenylphosphine oxide in the presence of Tf_2O and 2,6-lutidine has been developed. The method provides a general approach for the construction of attractive allenylphosphoryl skeletons with high atom and step economy under metal free conditions.



Organophosphorus compounds have found widespread application in organic synthesis and material chemistry,[1] and they are privileged frameworks in biological and medicinal chemistry.[2] Allene motifs, which have two π-orbitals perpendicular to each other, have attracted a tremendous amount of attention recently.[3] Among them, phosphoryl allenes are versatile reagents that are widely used in organic synthesis.[4] For example, phosphoryl allenes can be transformed into functionalized olefins,[4d,j,k,5] chiral organophosphorus compounds,[4b,c] and phosphorus-containing heterocyclic drugs.[4f,g,6] In addition, some allenylphosphine oxides have good bioactive ability.[7]

As such, this is significant for the construction of phosphorylated allenes. Traditionally, these compounds were prepared through the Horner−Mark [2,3] rearrangement reaction discovered in 1962.[8] It is a general approach for the synthesis of phosphorylated allenes.[9] However, this process requires the previous preparation of a rearrangement precursor and the use of phosphorus chlorides that are unstable and hazardous. Recently, substitution reactions of propargylic substrates with P(O)H compounds catalyzed by a transition metal affording allenylphosphoryl moieties have been reported (Scheme 1). Stawinski et al. developed a Pd(0)-catalyzed substitution reaction of propargylic substrates with H-phosphonate diesters for the preparation of allenylphosphonates.[10] In 2016, Zhao et al. reported a method for the synthesis of allenylphosphoryl compounds via a Cu-catalyzed coupling of propargylic alcohols with diphenylphosphine oxide.[11] This provides a new method for the construction of a C−P bond via an S_N1-type reaction. Han et al. realized the preparation of phosphoryl allenes directly using copper as the catalyst[12] and described a coupling reaction of propargyl alcohols with diarylphosphine oxides catalyzed by $CdCl_2$ in 2017.[13] However, the use of precious metals is usually necessary for efficient catalytic conversion, which limits the substrate scope and the actual application of these methods.

Scheme 1. Synthetic Methods for Allenylphosphoryl Compounds



Recently, Miura and Hirano reported a strategy for the generation of phosphenium cations from secondary phosphine oxides promoted by Tf_2O. The phosphenium cations have high electrophilicity and reactivity and could be used for phosphinative cyclization,[1j] [3+2] cycloaddition[14] with alkynes, and the preparation of dibenzophospholes.[15] We are interested in the reactivity of the phosphenium cations generated *in situ* with propargylic substrates and report our results on the coupling of propargylic substrates with diphenylphosphine oxide to afford allenylphosphine oxides (Scheme 1).

We initially studied the coupling reaction with 3-(trimethylsilyl)prop-2-yn-1-ylmethanesulfonate (**1a**) and diphenylphosphine oxide (**2a**). Gratifyingly, with the treatment of 2,6-lutidine and Tf_2O under a N_2 atmosphere, the desired

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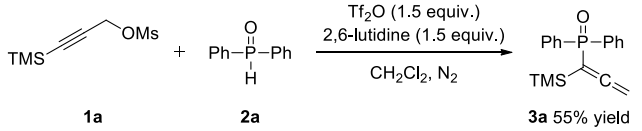
product allenylphosphoryl compound **3a** was obtained in 55% yield (Scheme 2).

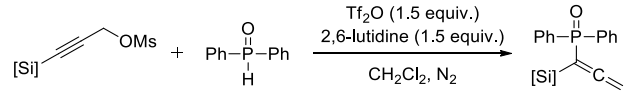
Scheme 2. Direct Coupling of 3-(Trimethylsilyl)prop-2-yn-1-yl Methanesulfonate (1a) with $Ph_2P(O)H$ (2a) in the Presence of 2,6-Lutidine and Tf_2O



1a **2a** **3a** 55% yield

Then, we screened the scope of 3-silylprop-2-yn-1-yl methanesulfonate, and the representative results are summarized in Table 1. Furthermore, the reactions proceeded readily, producing the desired allenylphosphine oxides with TES, TBS, TIPS, and $SiMe_2Ph$ silyl groups (Table 1, entries 2–5, respectively).

Table 1. Direct Coupling of 3-Silylprop-2-yn-1-yl Methanesulfonate (1) with $Ph_2P(O)H$ (2a) Using Various Silyl Substituents[a]



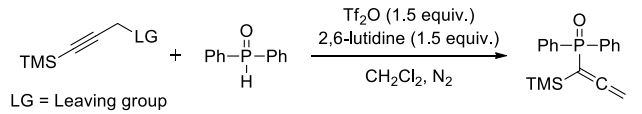
1 **2a** **3**

entry	[Si]	product	yield[b] (%)
1	TMS (**1a**)	**3a**	65
2	TES (**1b**)	**3b**	88[c]
3	TBS (**1c**)	**3c**	79
4	TIPS (**1d**)	**3d**	70
5	$SiMe_2Ph$ (**1e**)	**3e**	73

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), Tf_2O (0.3 mmol), 2,6-lutidine (0.3 mmol), CH_2Cl_2 (2 mL), at room temperature for 2 h under a N_2 atmosphere. [b]Yield of the isolated product. [c]The leaving group of Br took the place of OMs.

We next evaluated the leaving groups (LG) of the alkynes (Table 2). When the leaving group used OTs in place of OMs, allenylphosphine oxide **3a** was acquired in 70% yield. Other leaving groups, such as OAc, $OP(O)(OPh)_2$, and bromine, were suitable, and diphenyl[1-(trimethylsilyl)propa-1,2-dien-1-yl]phosphine oxide (**3a**) was obtained with substrates bearing these leaving groups.

Table 2. Scope of the Leaving Groups of Alkynes[a]



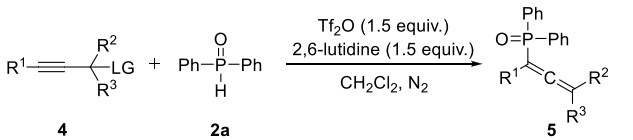
1 **2a** **3a**

entry	LG	product	yield[b] (%)
1	OTs (**1f**)	**3a**	70
2	OAc (**1g**)	**3a**	68
3	$OP(O)(OPh)_2$ (**1h**)	**3a**	65
4	Br (**1i**)	**3a**	72

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), Tf_2O (0.3 mmol), 2,6-lutidine (0.3 mmol), CH_2Cl_2 (2 mL), at room temperature for 2 h under a N_2 atmosphere. [b]Yield of the isolated product.

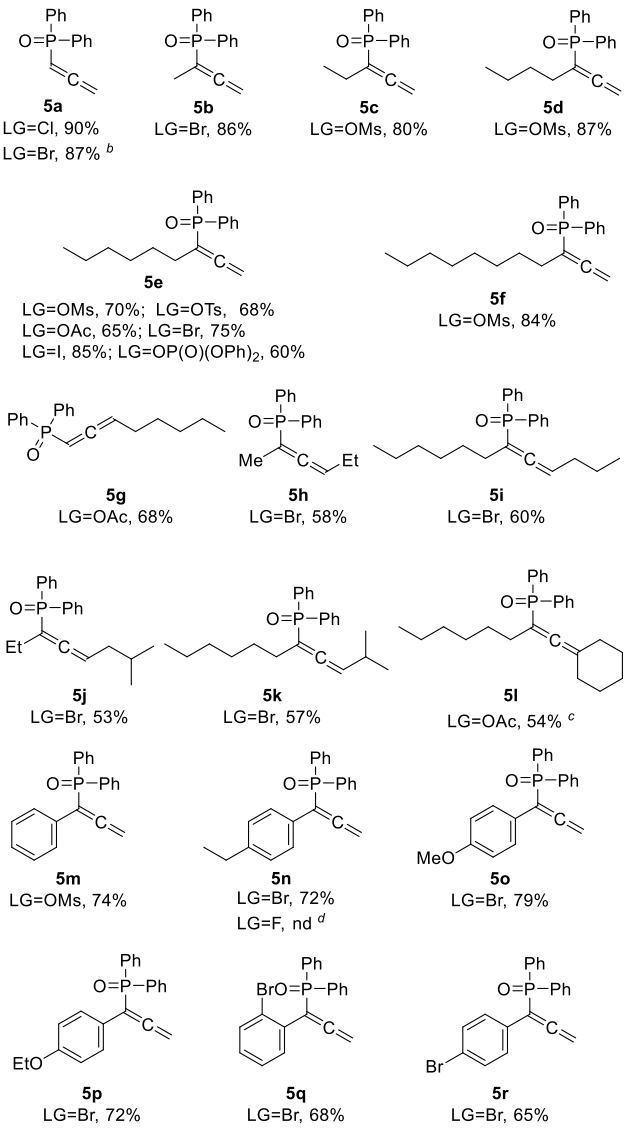
Then, we screened the scope of alkynes (Scheme 3). For R^1 = alkyl, the reactions proceeded smoothly to afford the corresponding allenylphosphine oxides in decent yields (**5a–5l**). The numbers of carbon atoms in the substituents have less influence on the reaction (**5a–5f**). When LG = I, the reaction proceeds readily, producing the allene product (**5e**) in 85% yield.

Scheme 3. Coupling of Propargylic Substrates with $Ph_2P(O)H$ (2a)[a]



4 **2a** **5**

R_1, R_2, R_3 = H, Alkyl, Aryl LG = OMs, OTs, $OP(O)(OPh)_2$, OAc, Br, I



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), Tf_2O (0.3 mmol), 2,6-lutidine (0.3 mmol), CH_2Cl_2 (2 mL), at room temperature for 2 h under a N_2 atmosphere. [b]On a 2 g scale. [c]Byproduct of phosphonyl 1,3-diene (**5l'**) obtained in 14% yield. [d]nd, not detected.

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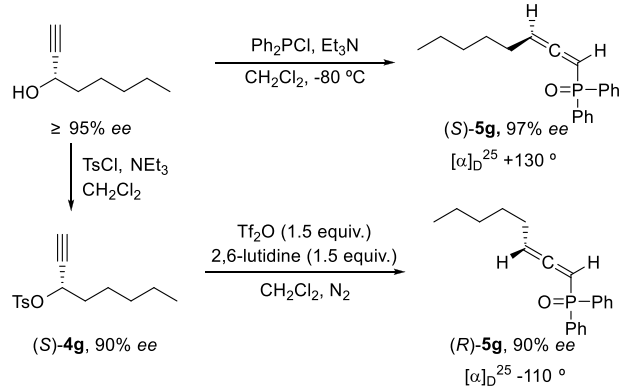
Substrates with R^2 or $R^3 \neq H$ reacted to a diminished extent in the coupling reaction (**5h**−**5k**), with the generation of a phosphonyl 1,3-diene byproduct. While substrates with R^2 and $R^3 \neq H$ also reacted, the phosphonyl 1,3-diene byproduct was formed even more readily. For example, the reaction of 1-(oct-1-yn-1-yl)cyclohexyl acetate (**4l**) resulted in both allenylphosphine oxide (**5l**) and phosphonyl 1,3-diene (**5l'**) (see the Supporting Information for details).

When R = aryl, the desired allenylphosphonates **5m**−**5r** were isolated in 65−79% yields, and the electronic effect of the substituents on the aryl ring has no effect on the coupling reaction. The reactions with substrates with electron-donating or electron-withdrawing groups on the benzene ring could proceed in moderate yields. Moreover, the reaction was not sensitive to the position of the substituents on the aryl rings (**5q** and **5r**). When the substrate with a fluoride leaving group (**4n'**; LG = F) was subjected to the reaction, the desired product (**5n**) was not detected. To test the scalability of the protocol, scale-up synthesis of **5a** on a gram scale was carried out. The reaction of 3-bromopropyne on a 2 g scale afforded **5a** in 87% yield.

To examine the stereochemistry of this reaction, an enantioenriched propargylic substrate (*S*)-**4g** (90% ee) was subjected to the coupling reaction under the developed conditions, and allenylphosphine oxide [(*R*)-**5g**] was acquired in 90% ee (Scheme 4). The ee was not decreased compared

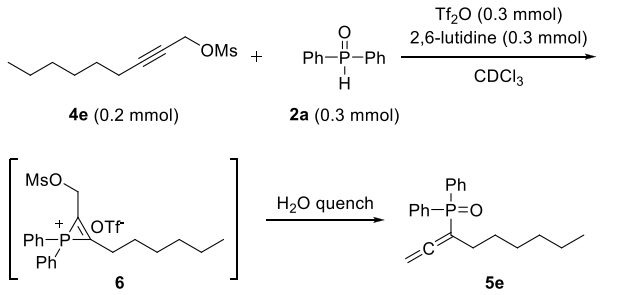
Scheme 4. Stereochemical Synthesis of Allenylphosphoryl Product 5g



with that of (*S*)-**4g**, but the allenylphosphoryl product **5g** prepared from (*S*)-oct-1-yn-3-ol by Horner−Mark [2,3] rearrangement had the opposite configuration, (*S*)-**5g** (Scheme 4).

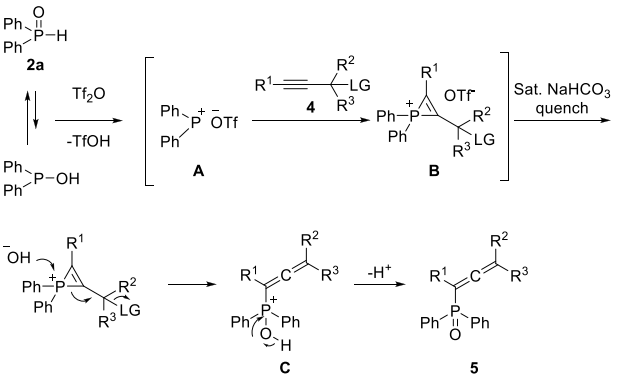
As reported by Miura and Hirano,[1j,14,15] a phosphenium species (Ph_2POTf) would be generated from diphenylphosphine oxide promoted by Tf_2O. The phosphenium species (Ph_2POTf) reacts with the propargylic substrates, yielding allenylphosphonate products. To gain insights into the pathway of the reaction, NMR experiments were carried out using **4e** as the substrate (see the Supporting Information for details). The ^{31}P NMR spectra showed that the signal of phosphine oxide (**2a**) at δ 21.4 disappeared after the treatment with **4e** in $CDCl_3$ under the standard conditions, and a signal at δ −95.7 appeared. The signal at δ −95.7 corresponds to phosphirenium species **6** (Scheme 5). When the reaction was quenched with H_2O, the signal at δ −95.7 disappeared and a new signal at δ 29.5 was observed. The signal at δ 29.5 is assigned to the allenylphosphonate (**5e**).

Scheme 5. ^{31}P NMR Experiments of $Ph_2P(O)H$ (2a) with 4e



On the basis of the ^{31}P NMR studies and previously reported results, we propose a possible mechanism for the coupling reaction of propargylic substrates with $Ph_2P(O)H$ (Scheme 6). When diphenylphosphine oxide (**2a**) was mixed

Scheme 6. Proposed Reaction Mechanism



with trifluoromethanesulfonic anhydride (Tf_2O), a phosphenium species **A** was generated. The phosphenium species **A** could couple with propargylic substrates **4** to form the phosphirenium cation **B**. When the reaction was quenched with a saturated aqueous $NaHCO_3$ solution, a hydroxyl anion would attack the phosphirenium cation **B** and form the intermediate **C**. Then intermediate **C** removed a hydrogen ion, producing allene product **5**.

In summary, a general method for the synthesis of allenylphosphine oxides with propargylic substrates is reported. The phosphirenium species (Ph_2POTf) produced *in situ* from diphenylphosphine oxide promoted by Tf_2O and 2,6-lutidine reacts with propargylic substrates, yielding the allenylphosphonate products. ^{31}P NMR studies suggest that the reaction proceeds via an intermediate of phosphirenium species. The mild reaction conditions, simple operation, good yields, and high step and atom economy make this protocol a valuable method for the preparation of various allenylphosphine oxides. This method could be applied to the construction of (1-silylpropa-1,2-dien-1-yl)phosphine oxides, and their further applications are being investigated by our group.

■ ASSOCIATED CONTENT

Supporting Information

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Representative experimental procedures, characterization data of substrates and products, and NMR spectra (PDF)

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§H.F. and H.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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