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Communication

Divergent intramolecular reactions between phosphines and alkynes

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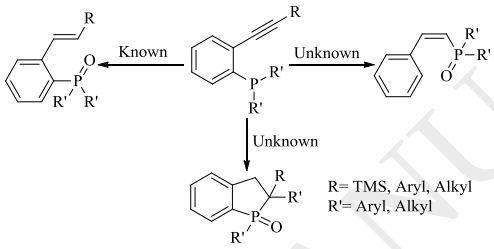
Graphical Abstract



The unexpected divergent reactions of phosphine tethered alkyne in protic solvent with the presence of base were reported. This provided facile syntheses of (*Z*)-alkenylphosphine oxides and phospholane oxides.

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ABSTRACT

A divergent intramolecular reaction of phosphine tethered alkyne in protic solvent was developed. This provided a novel and simple access to a large variety of (Z)-alkenylphosphine oxides and phospholane oxides. Our preliminary studies suggested that these divergent reactions are closely related to the reaction condition and molecular structure. A possible mechanism of C-P bond cleavage of a pentacoordinated hydroxyphosphorane intermediate was proposed.

The carbon-carbon triple bond appears to be extremely versatile due to its ability to undergo a wide variety of transformations for applications in medical chemistry, agrochemistry, and material chemistry [1]. There are numerous publications dealing with the synthetic applications of the C≡C bond [2].

Very recently, much attention has been paid to the synthesis of various important organophosphorus derivatives through phosphination or phosphorylation of carbon-carbon triple bond [3-5]. Among these useful transformations, the generation of active phosphorus species *via* selective C-P cleavage is a challenging topic. Transition-metal-catalyzed C-P bond cleavage plays an important role in the synthetic applications of diverse organophosphorus moieties [6]. Herein, we would like to report a rare example of the synthesis of *Z*-alkenylphosphine oxides and phospholane oxides *via* C−P bond cleavage in protic solvent.

During our explorations of the reaction with phosphine tethered alkyne [4], we tried to synthesize a terminal alkyne **2** from **1a** by removing the trimethylsilyl (TMS) group. Interestingly, after **1a** was stirred with K_2CO_3 (1 equiv.) at room temperature in a mixture of MeOH/DCM, an (*Z*)-alkenylphosphine oxide **3a** was isolated, while the desired terminal alkyne **2** was not detected (Table 1, entry 1). Similar result was observed with Cs_2CO_3 (entry 2). Absence of base resulted in no conversion of **1a** (entry 3). Increasing the amount of K_2CO_3 (entry 4) or the reaction

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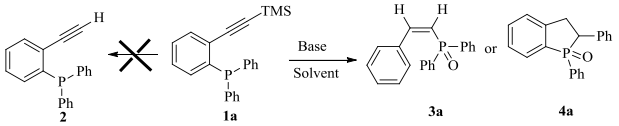
temperature (entry 5) did not improve the yield of the reaction. We were pleased to observe the transformation of **1a** even with a catalytic amount of K_2CO_3 (5 mol%, entry 7). When the mixture of H_2O/DMSO was used as solvent, the conversion of **1a** proceeded very slowly in the presence of a catalytic amount of K_2CO_3. Surprisingly, phospholane oxide **4a** was obtained as major product and only trace amount of **3a** was observed (entry 8). Such phospholane could potentially be used as ligand [7] and organocatalyst [8] in organic synthesis, which is difficult to obtain by other methods [9]. The reaction efficiency could be increased at elevated temperature (entry 9). Higher amount of base did not improve the reaction efficiency (entry 10). The yield of **4a** could be further improved by using KOTMS as the catalyst. (See more details in the Supporting information.)

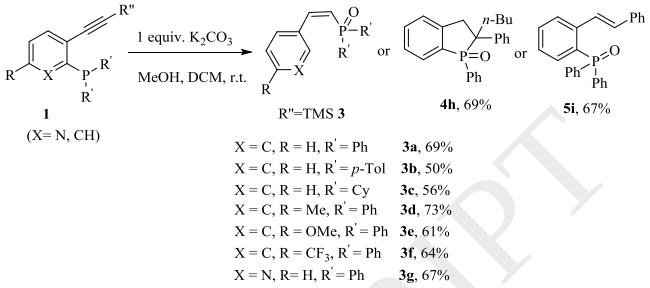
Table 1
Optimizations of the reaction conditions.[a]



Entry	Base (equiv.)	Solvent	T (°C)	Time (h)	Yield (%)	
					3a	**4a**
1	K_2CO_3 (1)	MeOH/DCM	25	8	69	-
2	Cs_2CO_3 (1)	MeOH/DCM	25	7	63	-
3	-	MeOH/DCM	25	6	-	-
4	K_2CO_3 (2)	MeOH/DCM	25	8	68	-
5	K_2CO_3 (1)	MeOH/DCM	50	6	63	-
6	K_2CO_3 (0.5)	MeOH/DCM	25	9	64	-
7	K_2CO_3 (0.05)	MeOH/DCM	25	8	60	-
8	K_2CO_3 (0.05)	H_2O/DMSO	25	38	trace	46
9	K_2CO_3 (0.05)	H_2O/DMSO	70	8	trace	53
10	K_2CO_3 (1)	H_2O/DMSO	70	8	trace	49
11	KOTMS (0.05)	H_2O/DMSO	70	6	trace	58

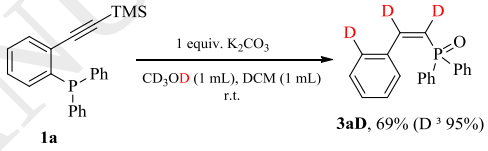
[a] Reaction conditions: **1a** (1mmol) in DCM (2 mL)/ MeOH (2 mL) or DMSO (4 mL) / H_2O (0.3 mL) under N_2 atmosphere.

Encouraged by these unexpected results, we decided to investigate the synthetic applications of these base-promoted transformations of phosphine tethered alkynes in protic solvent. Our initial studies focused on the K_2CO_3 promoted transformation of phosphine tethered alkynes **1** in the mixture of MeOH/DCM. The reaction proved to be robust and versatile and allowed the synthesis of a broad range of (*Z*)-alkenylphosphine oxides **3** (Scheme 1). Both aryl-(**3a**, **b**) and alkyl-(**3c**) substituted phophine oxides were well tolerated. Next, products with various substituted anchors were synthesized in modest to good yields, indicating that the reactions are essentially independent of the electronic properties of the anchors (**3d**, **e**: electron-donating Me and OMe; **3f**: electron-withdrawing CF_3). When the reaction was performed with a pyridine derivative **1g**, **3g** was isolated in 67% yield. To demonstrate the synthetic value of our newly developed reaction, the TMS group was replaced by a phenyl group. However, an alkyne reduced product **5i** was obtained, which is in accordance with the reported results [10]. When *n*-butyl substituted **1h** was used, phospholane oxide **4h** was isolated as major product and a trace amount of unknown mixture of organophosphorus compounds was also observed. These results indicated the presence of TMS group is crucial to the formation of (Z)-alkenylphosphine oxides.



Scheme 1. The reaction of phosphine tethered alkyne in the presence of K_2CO_3. Reaction conditions: **1** (2 mmol), K_2CO_3 (2 mmol) in DCM (4 mL) and MeOH (4 mL), N_2, room temperature, 6-9 h, isolated yield.

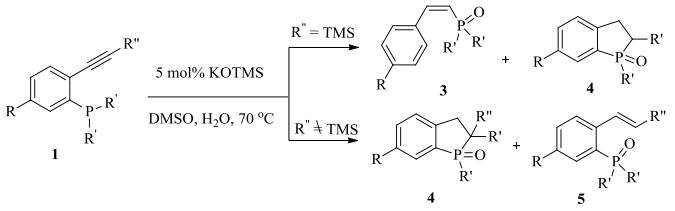
To be noticed, when the control reaction of **1a** was performed in the deuterated solvent, d^4-methanol/DCM, poly-deuterated product **3aD** (D≥95%) was furnished (Scheme 2).



Scheme 2. Deuterated experiment.

After screening the scope of (*Z*)-alkenylphosphine oxide, we moved our attention to the KOTMS catalyzed reaction of phosphine tethered alkynes **1** (Table 2). It is noteworthy that the complexity may arise with the TMS substituted alkynes (R" = TMS), since the selectivity of the reactions are highly reliable on the substituents on phosphorus and the electronic effect of the aryl anchor. The diphenylphosphine derivative **1a** gave the cyclized product **4a** as major product (entry 1), while (*Z*)-alkenylphosphine oxide **3c** was obtained selectively in the case of the dialkyl substituted phosphine **1c** (entry 2). When R" is TMS, the product will be either **3** or **4** (entries 1-5). The effect of R on anchored aryl group is elusive. When R is neutral H or Me, the formation of cyclized product **4** was favored (entries 1, 3). When R is electron-donating OMe or electron-withdrawing CF_3, (Z)-alkenylphosphine oxides were isolated as major products (entries 4, 5). When R" is aryl or alkyl group, the reactions gave **4** and/or **5** (entries 6-11). When R" is electron neutral or rich aryl group, the formation of cyclized product **4** was preferred (entries 6, 7). The structure of **4k** was unambiguously established by X-ray crystallographic analysis (Fig. 1) (CCDC 1892220). The formation of **5** was preferred with electron deficient derivatives (entries 8, 9). The structure of **5m** (CCDC 1892217) was confirmed by X-ray analysis (Fig. 1). The reaction of n-butyl substituted (R" = *n*-Bu) **1h** gave cyclized **4h**, but the reaction of bulky alkyl substituted (R" = *t*-Bu) **1n** provided **5n**.

Table 2
The reaction of phosphine tethered alkyne with a catalytic amount of KOTMS.[a]



Entry	Substrate	R	R'	R'	Yield (%)[b]		
					3	**4**	**5**
1	**1a**	H	Ph	TMS	trace	**4a** (58)	-
2	**1c**	H	Cy	TMS	**3c** (41)	-	-
3	**1d**	Me	Ph	TMS	**3d** (11)	**4d** (43)	-
4	**1e**	OMe	Ph	TMS	**3e** (67)	trace	-
5	**1f**	CF_3	Ph	TMS	**3f** (64)	trace	-
6	**1j**	H	Ph	*p*-MeO-C_6H_4	-	**4j** (64)	trace
7	**1k**	H	Ph	*p*-Tol	-	**4k** (56)	**5k** (23)
8	**1l**	H	Ph	*p*-F-C_6H_4	-	trace	**5l** (58)
9	**1m**	H	Ph	*p*-CF_3-C_6H_4	-	trace	**5m** (75)
10	**1h**	H	Ph	*n*-Bu	-	**4h** (61)	trace
11	**1n**	H	Ph	*t*-Bu	-	trace	**5n** (69)

[a] Reaction conditions: **1** (1 mmol), KOTMS (5 mol %) in H_2O (0.3 mL) and DMSO (2 mL), N_2, 70 °C, 6-8 h.
[b] Isolated yield.

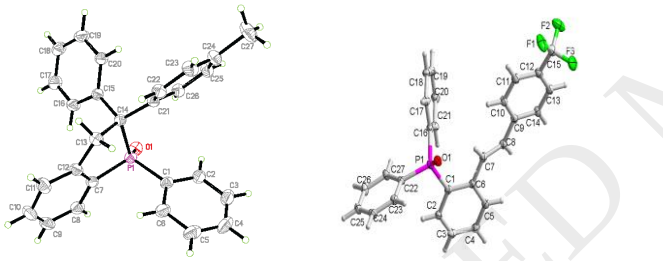
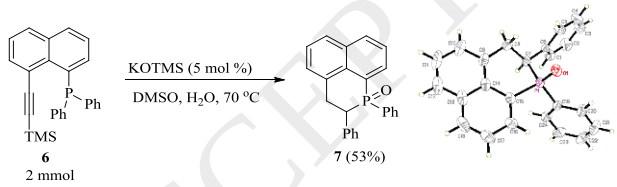


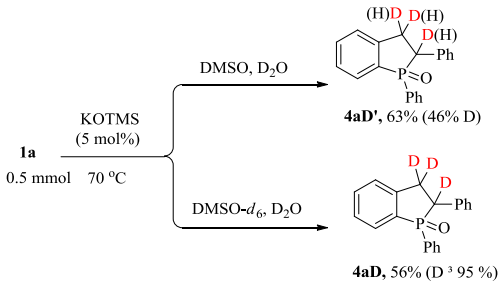
Fig. 1. The crystal structures of **4k** and **5m**.



Scheme 3. Synthesis of phosphahexacycle **7** (CCDC 1892219)

The KOTMS catalyzed cascaded phosphination, aryl migration and protonation were used to synthesize a new fused phosphahexacycle **7** (Scheme 3).

To understand the reaction mechanism, the control and deuterium-labeling experiments were performed (Scheme 4). Partial deuterated product **4aD'** was obtained in D_2O/DMSO. The deuterated product **4aD** (D ≥ 95 %) was isolated when reaction was performed in D_2O/DMSO-d_6. These results indicated the importance of both H_2O and DMSO in this tandem process.



Scheme 4. Control and deuterated experiments.

On the basis of the literatures [11] and control experiments, a plausible reaction mechanism is proposed and outlined in Fig. 2. The reaction starts with an intramolecular nucleophilic attack of the alkynyl group by phosphine to form zwiterionic **8** [10]. Subsequently, hydrolysis of **8** by the protic solvent to generate pentacoordinated hydroxyphosphorane **9**, followed by the decompositon of **9** to give the tertiary phosphine oxide **3** or **5**. Upon the removal of the hydroxyl proton from **9**, a concerted aryl migration process gives **11** [12], which provides phospholane oxide **4** after hydrolysis.

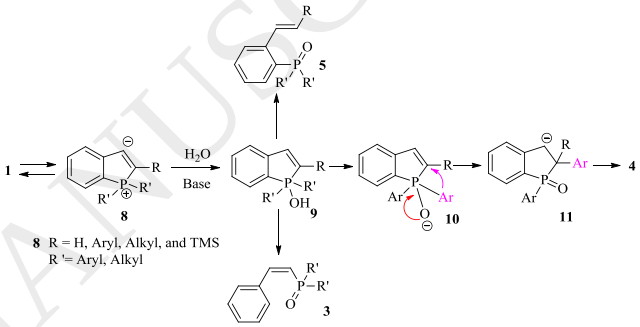


Fig. 2. The proposed mechanism.

In summary, a divergent reaction of phosphine tethered alkyne in protic solvent has been realized. Our preliminary studies suggest that these divergent reactions are closely related to the reaction condition and molecular structure. In the presence of K_2CO_3, the TMS substituted alkynes were converted into (*Z*)-alkenylphosphine oxides in the mixture of MeOH and DCM. The reaction pathways in the mixture of H_2O and DMSO with a catalytic amount of KOTMS are complicated. The divergences are dependent on the electronic nature of aryl anchor, the substituents on alkyne and phosphine: When TMS substituted alkynes were used, the alkylphosphines gave (*Z*)-alkenylphosphine oxides selectively. Arylphophines with electron neutral anchors produced phospholane oxides as major products, which are difficult to access by other methods. Arylphophines with electron-rich or deficient anchor preferred the formation of (*Z*)-alkenylphosphine oxides. When aryl substituted alkynes were used, the electron-rich aryl substituents favored the formation of phospholane oxides while the electron-deficient ones favored the alkenylphosphine oxide products. Placement of primary alkyl group on the end of alkyne allows for the selective formation of phospholane oxide. But the bulky alkyl substituted alkyne gives the alkenylphosphine oxide. Further efforts on the understanding the rules governing the selective transformations of phosphine tethered alkynes as well as the synthetic applications of these transformations are underway in our laboratory.

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