Copper-catalyzed addition of H-phosphine oxides to alkynes forming alkenylphosphine oxides†

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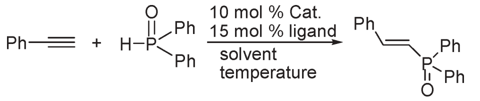
We have developed efficient copper-catalyzed additions of P(O)H compounds to alkynes, and the reactions provided the regio- and stereoselective E-alkenylphosphine oxides under catalysis of the commercially available and inexpensive copper catalyst system CuI/ethylenediamine. This finding is the first example of copper-catalyzed hydrophosphinylation of alkynes to synthesize alkenylphosphine oxides.

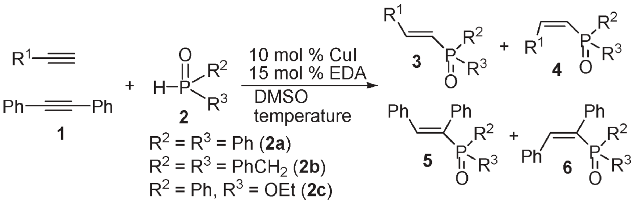
Transition metal-catalyzed addition of a heteroatom compound to a carbon-carbon unsaturated bond is one of the most straightforward ways for the preparation of heteroatom compounds, which have wide applications in organic synthesis and industrial processes.[1] Preparation of alkenylphosphine oxides has attracted much attention for their important roles. For example, they are used as biological active compounds[2] and the key intermediates for the preparation of the palladium ligand.[3] Nucleophiles of amines,[4] phosphines[5] and carbanion species[6] readily add to the olefinic bond in alkenylphosphine oxides to give useful bifunctional adducts, which allow further synthetic elaboration, so it is necessary to develop convenient and efficient approaches to alkenylphosphine oxides. Several efficient methods for metal-catalyzed synthesis of alkenylphosphine oxides have recently been developed including palladium,[7] nickel,[8] rhodium,[9] ytterbium-imine complex-catalyzed[10] additions of P(O)H compounds to alkynes. Here, we report a more convenient and inexpensive copper-catalyzed method for the synthesis of alkenylphosphine oxides.



(1)

We first chose phenylacetylene and diphenylphosphine oxide as the model substrates to optimize the catalysis conditions (eqn (1)), including optimization of the copper catalysts, ligands and solvents in the hydrophosphinylations as shown in Table 1. Only traced amount of product was obtained in the absence of ligand (entry 1) or in the presence of 2,2′-dipyridyl (entries 2 and 3) using CuI as the catalyst. However, when proline or pipecolinic acid was added to the reaction system, the reaction yields were greatly improved (entries 4–8). Solvents also influenced the progress of the reaction, toluene or THF gave mild reaction yield (entries 4 and 5), and ethanol is a bad solvent (entry 18). A good-yielded adduct was obtained when DMSO was used as the solvent.

CuI/*N*,*N*′-dimethylethylenediamine showed mild catalytic efficiency (entry 9). Various primary diamines were also attempted as ligands of CuI, they all showed good catalytic activity, most interestingly, CuI/ethylenediamine (EDA) almost gave a quantitatively transformed yield in DMSO at 60 °C in 3 h, (entry 14) and a 70%-yielded product was formed at room temperature in 18 h (entry 15). The catalytic efficiency of the diamine ligands depends on the electronic effect and steric hinderance. For example, 1,2-diaminocyclohexane, with higher electronic density, gave a higher yield than *o*-phenylenediamine (compare entries 11 and 13), and ethylenediamine with smaller steric hinderance displayed higher efficiency (compare entries 9 and 14). Several copper salts, CuI, CuBr and $CuSO_4$ (entries 14–17), were tested in the addition reactions using DMSO as the solvent, ethylenediamine as the ligand, and the results showed that CuI was the best catalyst. After the optimization process of solvents, ligands and catalysts, we decided that the following addition reactions were carried out in our standard conditions, 10 mol% CuI as the catalyst, 15 mol% ethylenediamine as the ligand relative to P(O)H compound, DMSO as the solvent.



(2)

The scope of the copper-catalyzed addition reaction of P(O)H compounds to alkynes was explored under our standard addition conditions (eqn (2)). As shown in Table 2, the coupling reactions were performed quite well for all the substrates examined, and the desired alkenylphosphine oxides were obtained in good to excellent yields. The data indicated that the yields depended primarily upon the electronic and steric properties of the P(O)H compounds and alkynes. Terminal aromatic alkynes showed better reactivity than terminal aliphatic ones, for example, reaction of diphenylphosphine oxide with phenylacetylene at 60 °C for 3 h provided a 99%

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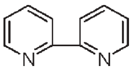
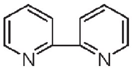
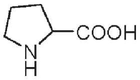
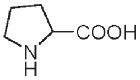
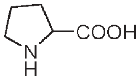
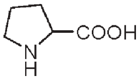
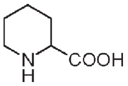
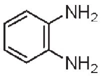
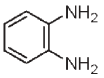
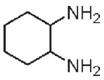
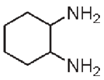
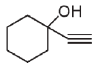
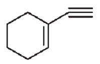
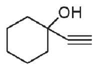
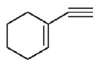
† Electronic supplementary information (ESI) available: Experimental, procedure for copper-catalyzed additions of P(O)H compounds to alkynes, characterization data for compounds **3**–**5**, references, and ^1H, ^{13}C and ^{31}P NMR spectra of compounds **3**–**5**. See DOI: 10.1039/b613416e

Table 1 Copper-catalyzed addition of diphenylphosphine oxide to phenylacetylene: optimization of the catalysis conditions[a]

Entry	Ligand	Cat.	Solvent	Conditions	Yield (%)
1	No ligand	CuI	Toluene	90 °C 24 h	Trace
2		CuI	Toluene	90 °C 12 h	Trace
3		CuI	DMSO	90 °C 12 h	Trace
4		CuI	Toluene	80 °C 12 h	55[b] (45)[c]
5		CuI	THF	80 °C 12 h	50[b] (40)[c]
6		CuI	DMSO	60 °C 10 h	80[b] (70)[c]
7		CuI	DMSO	80 °C 10 h	99[b] (88)[c]
8		CuI	DMSO	60 °C 9 h	83[b] (72)[c]
9		CuI	DMSO	60 °C 12 h	50[b]
10		CuI	DMSO	60 °C 3 h	30[b]
11		CuI	DMSO	60 °C 10 h	85[b] (75)[c]
12		CuI	DMSO	60 °C 3 h	32[b]
13		CuI	DMSO	60 °C 10 h	95[b] (80)[c]
14		CuI	DMSO	60 °C 3 h	99[b] (90)[c]
15		CuI	DMSO	25 °C 18 h	70[b] (62)[c]
16		CuBr	DMSO	25 °C 18 h	65[b] (58)[c]
17		$CuSO_4$	DMSO	60 °C 3 h	16[b]
18		CuI	EtOH	60 °C 3 h	Trace

[a] Reaction conditions: diphenylphosphine oxide (0.5 mmol), phenylacetylene (0.75 mmol), solvent (1.0 mL), CuI catalyst (0.05 mmol), ligand (0.075 mmol) under N_2. [b] Determined reaction yield by ^{31}P NMR (other possible isomers were not determined). [c] Isolated yield.

Table 2 Copper-catalyzed hydrophosphinylation of various alkynes[a]

Entry	1	2	Conditions	Products	Yield (%)
1	Ph—≡	**2a**	60 °C, 3 h	**3a**	99[b] (90)[c] (>99)[d]
2	n-C_6H_{13}—≡	**2a**	90 °C, 12 h	**3b/4b**	75[b] (67)[c] (85 : 15)[d]
3		**2a**	60 °C, 9 h	**3c/4c**	85[b] (75)[c] (90 : 10)[d]
4		**2a**	60 °C, 10 h	**3d**	70[b] (65)[c] (>99)[d]
5	Ph—≡	**2b**	60 °C, 18 h	**3e**	76[b] (66)[c] (>99)[d]
6	n-C_6H_{13}—≡	**2b**	90 °C, 18 h	**3f**	86[b] (72)[c] (>99)[d]
7		**2b**	60 °C, 18 h	**3g**	75[b] (64)[c] (>99)[d]
8		**2b**	60 °C, 18 h	**3h**	70[b] (61)[c] (>99)[d]
9	Ph—≡	**2c**	90 °C, 10 h	**3i**	82[b] (70)[c] (>99)[d]
10	Ph—≡—Ph	**2a**	60 °C, 3 h	**5a**	trace
11	Ph—≡—Ph	**2a**	100 °C, 18 h	**5a**	68[b] (60)[c] (>99)[d]
12	Ph—≡—Ph	**2b**	100 °C, 12 h	**5b**	88[b] (79)[c] (>99)[d]

[a] Reaction conditions: phosphine oxide (0.5 mmol), alkyne (0.75 mmol), CuI (0.05 mmol), ethylenediamine (EDA) (0.075 mmol) in DMSO (1 mL) under N_2. [b] Determined reaction yield by ^{31}P NMR. [c] Isolated yield. [d] Ratio (**3** : **4** or **5** : **6**) of isomers.

reaction yield (entry 1), however, 1-octyne showed lower reactivity under the same conditions, when reaction temperature was raised to 90 °C, and reaction time was elongated to 12 h, a 75% reaction yield was provided (entry 2). The result showed that alkynes containing electron-withdrawing group could provide higher yields than ones containing electron-donating group. Diphenylphosphine oxide displayed higher reactivity than dibenzylphosphine oxide using terminal alkynes as partners, however, the contrary result appeared using internal alkyne diphenylacetylene as the partner. The internal alkyne showed weaker activity than the terminal alkynes (entries 10–12). Additionally, the functional groups in alkynes, such as OH (entries 3 and 7) and the carbon–carbon double bond (entries 4 and 8), did not led to the side products, so the results showed that the addition reactions were of tolerance of functional groups. Interestingly, all addition reactions of P(O)H compounds to alkynes showed the regio- and stereoselectivities, terminal alkynes mainly afforded the *anti*-Markovnikov adducts by the regioselective addition of the phosphorus atom at the terminal carbon of the triple bond. The structures of the adducts were confirmed by ^{1}H, ^{13}C, ^{31}P NMR spectroscopy and spectroscopic data of the known compounds (see the supporting information†).

In conclusion, we have developed efficient copper-catalyzed additions of P(O)H compounds to alkynes, and the reactions provided the regio- and stereoselective *E*-alkenylphosphine oxides under catalysis of commercially available and inexpensive copper catalyst system. This finding is the first example of copper-catalyzed hydrophosphinylation of alkynes to synthesize alkenylphosphine oxides, and further mechanistic investigation and synthetic applications of this finding and extensions to other heteroatom compounds are now in progress.

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