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Copper-Catalyzed Aerobic Oxidative Coupling of Terminal Alkynes with *H*-Phosphonates Leading to Alkynylphosphonates

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The increasing importance of phosphorus compounds in organic synthesis, materials, and biology demands new, efficient phosphorus−element bond-forming reactions for the construction of structurally sophisticated phosphorus compounds that are not readily available by classic methods. This has stimulated extensive studies of C−P bond-forming reactions via transition-metal catalysis through either couplings with organohalides or additions to unsaturated C−C bonds.[1,2] Herein we disclose *a new methodology for catalytically constructing C−P bonds* (oxidative coupling): an aerobic oxidative coupling of terminal alkynes with *H*-phosphonates that is efficiently catalyzed by Cu to generate alkynylphosphonates in high yields (eq 1).

$$\underset{\mathbf{1}}{(R'O)_2P(O)H} + \underset{\mathbf{2}}{\equiv\!\!-R} \xrightarrow{\text{cat CuI, Air}} \underset{\mathbf{3}}{(R'O)_2P(O)\!-\!\!\equiv\!\!-R} + H_2O \quad (1)$$

This new reaction was accidently found during work on optimizing our Cu(I)-catalyzed hydrophosphorylation of alkynes,[2a] which gives alkenylphosphorus compounds under nitrogen but remarkably produced alkynylphosphorus compounds when air was introduced. Alkynylphosphonates are extremely versatile reagents for the preparation of highly functional phosphorus compounds through conjugate-addition reactions, metallacycle formation, and unique cycloadditions.[3,4] Some alkynylphosphonates are also biologically active.[5] These compounds can be prepared by a few methods, the most frequently employed of which is the reaction using the hazardous chemical $(RO)_2P(O)Cl$ with Li or Mg acetylides, which suffers from a lack of functionality tolerance.[4] Copper-catalyzed oxidative homodimerization of terminal alkynes to generate 1,3-diynes (the Glaser reaction)[6] is a well-known reaction. However, similar heterocoupling of a terminal alkyne with a H-heteroatom compound is rare,[7] and to the best of our knowledge, there is no precedent for similar air-induced C−P bond-forming reactions.[8]

Under dry air, phenylacetylene (**1a**, 0.6 mmol) and $(i\text{-PrO})_2P(O)H$ (**2a**, 0.5 mmol) were added to a mixture of CuI (0.05 mmol) and K_2CO_3 (0.05 mmol) in DMSO to immediately generate a yellow suspension. The mixture was heated at 50 °C overnight, and all of the insoluble materials disappeared to produce a clear yellow solution in which a 91% yield of $(i\text{-PrO})_2P(O)C{\equiv}CPh$ (**3a**) was formed, as determined by ^{31}P NMR spectroscopy. Side products detectable in this reaction were $(i\text{-PrO})_2P(O)OH$ (3%), $[(i\text{-PrO})_2P(O)]_2O$ (2%), and $(PhC{\equiv}C)_2$ (10% as determined by GC).

A screening of the catalysts showed that copper(I) halides and copper acetate were good catalysts for this reaction, whereas $CuCl_2$ gave only a trace amount of **3a**. Catalysts (10 mol %) and corresponding yields of **3a** were as follows: CuBr, 87%; CuCl, 92%; Cu_2O, 7%; $CuCl_2$, 4%; and $Cu(OAc)_2 \cdot H_2O$, 94%. Other metal salts, such as AgI, $NiCl_2$, $PdCl_2$, $Pd(OAc)_2$, and $FeCl_3$, did not or only sluggishly catalyzed this reaction. Besides K_2CO_3, other bases could also be used to give good yields of **3a**: Cs_2CO_3, 91%; Et_2NH, 96%; and Et_3N, 93%. Solvents also highly affected this reaction. Although DMF could also give a good yield of **3a**, MeCN, THF, dioxane, CH_2Cl_2, and toluene produced only a trace amount of the product.

As demonstrated in Table 1, this new copper-catalyzed aerobic oxidative coupling of terminal alkynes with *H*-phosphonates is a highly general and practically useful method for the preparation of alkynylphosphonates. Thus, both an aromatic alkyne (run 1) and an aliphatic alkyne (run 2) gave the corresponding oxidative coupling products in high yields. A variety of functionalities, such as hydroxyl, alkoxyl, carboxyl, carbonyl, cyano, chloro, amino, carbamoyl, and sulfonamido groups, were all tolerated under the reaction conditions, and the corresponding oxidative coupling products were obtained in high yields. An enyne substrate (run 11) and the bioactive 19-norethindrone having a reactive enone unit (run 16) could also be used in the reaction to give the desired alkynylphosphonates selectively without damaging the other functionalities. An alkyne bearing an electron-withdrawing group (ethyl propiolate, run 12) was also a good substrate for this oxidative coupling reaction. In regard to the *H*-phosphonates, in addition to **2a**, diethyl (**2b**), dibutyl (**2c**), and dibenzyl phosphate (**2d**) all could be used as the substrate, generating the corresponding alkynylphosphonates in high yields. It was particularly noteworthy that when the highly functionalized hydrogen phosphonate **2e**, a nucleotide analogue that shows unique biological activity,[9] was used as the substrate (run 19), the acetylido group was readily introduced to phosphorus selectively, clearly demonstrating the great potential of this new methodology to allow access to highly functionalized targets. Hydrogen isopropyl phenylphosphinate **2f** could also be used as the substrate to give the products in high yield (run 20). However, under similar reaction conditions, secondary phosphine oxide $Ph_2P(O)H$ did not afford the oxidative coupling product at all.[10]

The detailed reaction mechanism remains to be clarified. However, it is reasonable to assume that this Cu-catalyzed aerobic oxidative coupling should proceed via a mechanism similar to that of the Glaser reaction,[6] which is widely used in the synthesis of diynes but mechanistically is still not well-understood (Scheme 1). The participation of a copper acetylide **4** is evident, since its formation as a precipitate was observed at the very beginning of the reaction; it remained insoluble during the reaction, but completely disappeared at the end of the reaction. Indeed, **4** did

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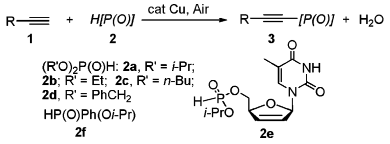
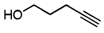
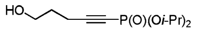
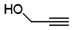
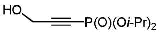
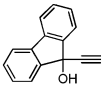
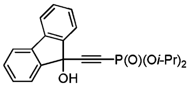
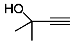
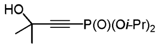
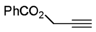
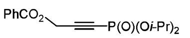
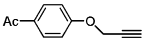
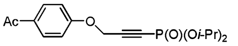
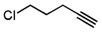
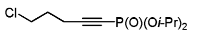
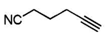
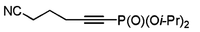
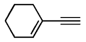
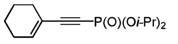
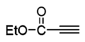
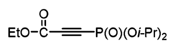
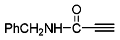
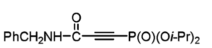
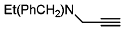
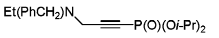
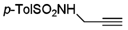
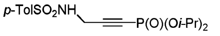
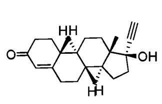
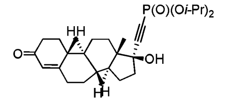
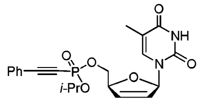
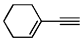
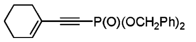
Table 1. Copper-Catalyzed Aerobic Oxidative Coupling of Terminal Alkynes with H−P(O) Compounds[a]

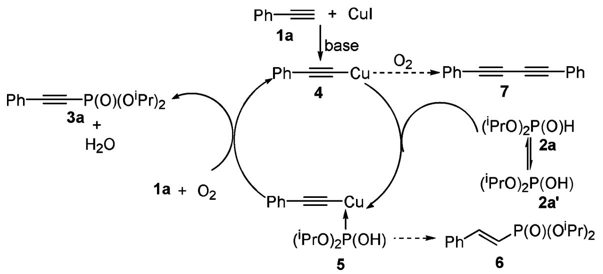


run	alkyne **1**	product **3**	% yield[b]
1	Ph—≡	Ph—≡—P(O)(O*i*-Pr)$_2$	93 (83)[c]
2	*n*-Bu—≡	*n*-Bu—≡—P(O)(O*i*-Pr)$_2$	85 (72)[c]
3			93 (81)[c]
4			95 (83)[d]
5			97 (88)[d]
6			98 (82)[c]
7			98 (87)[c]
8			87 (78)[c]
9			94 (82)[c]
10			99 (88)[c]
11			93 (82)[d]
12			98 (82)[d]
13			94 (85)[c]
14			93 (84)[e]
15			97 (83)[d]
16			98 (90)[g]
17	Ph—≡	Ph—≡—P(O)(OEt)$_2$	83 (74)[c]
18		Ph—≡—P(O)(O*n*-Bu)$_2$	89 (81)[c]
19			90 (81)[c,h]
20		Ph—≡—P(O)Ph(O*i*-Pr)	99 (87)[f]
21			94 (75)[e]

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), Cu catalyst (0.05 mmol), base (0.1 mmol), DMSO (1 mL), 55 °C, overnight under dry air. [b] Determined by ^{31}P NMR. Yields are based on the amount of **2** used. Yields in parentheses are isolated yields after column chromatography on silica. [c] CuI catalyst, Et$_3$N base. [d] CuI catalyst, Et$_2$NH base. [e] Cu(OAc)$_2$·H$_2$O catalyst, Et$_3$N base. [f] Cu(OAc)$_2$□H$_2$O catalyst, 50 °C. [g] Using **1** (0.3 mmol), **2** (0.45 mmol), CuI (0.03 mmol), and Et$_3$N (0.06 mmol). [h] At 55 °C for 32 h.

react with **2a** under air to give **3a** and **7** in 44% and 56% yields, respectively (0.1 mmol each of **4** and **2a**, DMSO, 55 °C, 24 h). In addition, **4** also catalyzed the oxidative coupling reaction to generate **3a** in 85% yield (5 mol % **4**, 5 mol % Et$_3$N, DMSO, 55 °C, 24 h). Interestingly, when the reaction of **4** with **2a** was conducted under nitrogen, **3a** could not be detected, Instead, an addition product **6** was obtained in 41% yield, in agreement with the results for Cu-catalyzed H−P(O) bond additions to alkynes.[2a] The coordination of **2a** (in the form of the trivalent phosphite **2a′**) to **4**, giving **5**, should be also reasonable.[2b] In addition, this coordination must take place before the interaction of **4** with oxygen in order to prevent the homodimerization to give **7**. However, details of the mechanism, such as reactive Cu−O$_2$ intermediates,[11] are not clear at present. Mechanistic studies and applications of this new methodology to other heteroatom compounds are the subjects of future studies.

Scheme 1. Proposed Reaction Path



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Supporting Information Available: Characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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