Coupling Reactions

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Selective P–P and P–O–P Bond Formations through Copper-Catalyzed Aerobic Oxidative Dehydrogenative Couplings of H-Phosphonates

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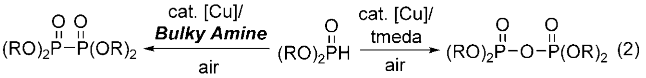
Demands for efficient phosphorus-element bond-forming reactions to prepare structurally sophisticated phosphorus compounds that are not readily available by classical methods have stimulated studies on new phosphorus bond-forming reactions by transition-metal catalysis.[1] While catalytic C–P bond-forming reactions through couplings of P–H bonds with organohalides or additions of P–H bonds to C–C unsaturated bonds are well known,[1] similar phosphorus–heteroatom bond-forming reactions (E–P formations) are limited [Eq. (1)].[2,3]

$$\mathrm{C{-}P} \xleftarrow[\text{coupling or addition}]{\text{C-P formation}\quad [M]} \mathrm{P{-}H} \xrightarrow[\text{E = heteroatom}]{\text{E-P formation}\quad [M]} \mathrm{E{-}P} \qquad (1)$$

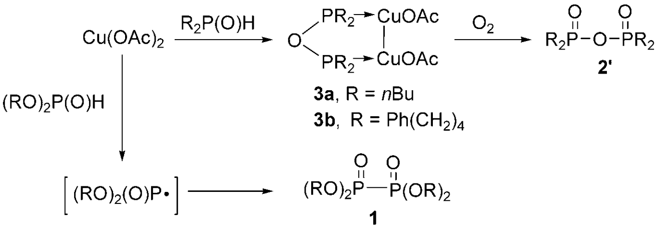
Herein we disclose the first copper-catalyzed P–P and P–O–P bond-forming reactions. By slightly changing the reaction conditions, copper can efficiently catalyze an aerobic oxidative dehydrogenative coupling of H-phosphonate to selectively produce hypophosphate **1** and pyrophosphate **2** in high yields [Eq. (2)].



$$\underset{\mathbf{1}}{(RO)_2P(O){-}P(O)(OR)_2} \xleftarrow[\text{air}]{\text{cat. [Cu]/ } \textbf{\textit{Bulky Amine}}} (RO)_2P(O)H \xrightarrow[\text{air}]{\text{cat. [Cu]/ tmeda}} \underset{\mathbf{2}}{(RO)_2P(O){-}O{-}P(O)(OR)_2} \qquad (2)$$

Traditional methods for the preparation of **1**[4] and **2**[5] are through nucleophilic substitution reactions of $(RO)_2P(O)Cl$ with alkali-metal salts such as $NaOP(OR)_2$ and $NaOP(O)(OR)_2$, which suffer from drawbacks such as low yields, tedious procedures, and lack of functionality tolerance. This is particularly true for the preparation of hypophosphates **1**, since $(RO)_2P(O)Cl$ reacts with $NaOP(OR)_2$ to give a complicated mixture.[4] Phosphorus compounds having P(O)–P(O)[6] and P(O)–O–P(O) linkages are of interest as biologically active substances. The antitumor activity of hypophosphoric acid analogues **1** was noted,[6c] and a lot of biologically important compounds, such as ADP and ATP, contain P(O)–O–P(O) linkages.

We discovered this new catalytic reaction during a study on the possible coordination of $Z_2P(O)H$ (Z = R or OR) to copper complexes.[7] $Z_2P(O)H$ exists in equilibrium with a trivalent $Z_2P(OH)$, which can coordinate to a variety of metals.[7c] Very unexpectedly, we found that a slight change of the substituent Z could lead to the selective generation of both a P–O–P compound **2′** and a P–P compound **1** from a stoichiometric reaction of $Z_2P(O)H$ with copper(II) acetate (Scheme 1).



Scheme 1. Stoichiometric reactions of $Cu(OAc)_2$ with $R_2P(O)H$ and $(RO)_2P(O)H$ affording **2′** and **1**, respectively.

Thus, a mixture of $nBu_2P(O)H$ (0.15 mmol) and $Cu(OAc)_2$ (0.1 mmol) was dissolved in [D$_8$]THF (0.5 mL) at room temperature under nitrogen. After 2 h, two new signals at $\delta = 55.7$ ppm and 122.6 ppm were observed by ^{31}P NMR spectroscopy (the integration ratio of the two signals = $^1/_2$). The signal at $\delta = 55.7$ ppm was assigned to $nBu_2P(O)OH$ by comparing with an authentic sample, while the signal at $\delta = 122.6$ ppm was assigned to **3a** as described below.[8] Complex **3a** is extremely air sensitive. On contact with air, **3a** immediately changes from colorless to blue, and phosphinic acid anhydride **2′** was formed.

Although crystals suitable for X-ray analysis were not obtained from **3a**, by changing the substituent R from *n*Bu to $Ph(CH_2)_4$, air- and moisture-sensitive colorless crystals of **3b**[9] suitable for X-ray analysis were obtained in 56% yield (Figure 1). Compound **3b** is a copper(I) carboxylate complex having an interesting tetranuclear structure.[10] A novel $R_2P{-}O{-}PR_2$ unit, formally generated by the dehydration of two

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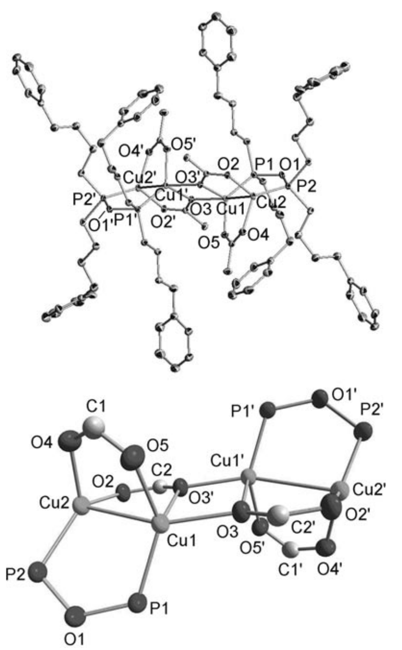
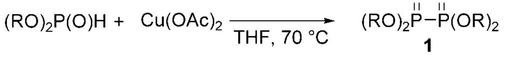


Figure 1. Top: Molecular structure of **3b** at 20% probability (hydrogen atoms omitted for clarity). Bottom: View of core with substituent R omitted. Selected bond lengths [Å] and angles [°]: Cu1–Cu2 2.6809(6), Cu1–P1 2.1467(8), Cu1–O5 2.004(2), Cu1–O3 2.1291(18), Cu1–O3′ 2.1643(18), Cu2–O2 1.983(2), Cu2–O4 2.014(2), Cu2–P2 2.1438(9), O1–P2 1.639(2), O1–P1 1.649(2), O3-Cu1 2.1643(18); P1-Cu1-Cu2 85.42(3), P2-Cu2-Cu1 97.28(3), P1-O1-P2 123.35(12), O1-P1-Cu1 118.37(8), O1-P2-Cu2 108.57(8), O2-Cu2-Cu1 90.85(5), O4-Cu2-Cu1 84.75(6), O5-Cu1-Cu2 81.41(6), O3-Cu1-Cu2 153.99(5), O3′-Cu1-Cu2 75.00(5), P1-Cu1-Cu2 85.42(3), O3-Cu1-O3′ 80.14(7), Cu1-O3-Cu1′ 99.86(7).

$R_2P(O)H$ units, chelates a pair of copper(I) atoms, which are further linked into a dimer by intermolecular copper–oxygen interactions. The Cu1–Cu2 length (2.6809(6) Å) is significantly shorter than the sum of their van der Waals radii (2.80 Å),[11] indicating the existence of a Cu^I–Cu^I interaction.

Surprisingly, a different product was obtained when H-phosphonate $(RO)_2P(O)H$ was employed as the substrate. Thus, when $R_2P(O)H$ was replaced by $(RO)_2P(O)H$, a similar copper complex could not be observed at all. Instead, the exclusive formation of **1** took place [Eq. (3)]. For example, $[(i\text{PrO})_2P(O)]_2$ from dehydrogenative coupling (24 h, 18% yield) was observed upon mixing a stoichiometric mixture of $(i\text{PrO})_2P(O)H$ with $Cu(OAc)_2$ in THF. Compound $[(i\text{PrO})_2P(O)]_2$ was obtained quantitatively upon further heating at 70 °C for 4 h [Eq. (3)].[12] Under similar stoichiometric reaction conditions, other H-phosphonates also efficiently reacted with $Cu(OAc)_2$ to give the corresponding dehydrogenetive coupling products **1** in high yields (yields of isolated products: R = Et 90%; R = *n*Bu 92%; R = $nC_{12}H_{25}$ 91%; R = *i*Pr 93%; R = CH_2Ph 94%; R = $-CH_2C(Me_2)CH_2-$ 90%).

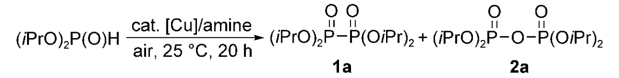


$$(RO)_2P(O)H + Cu(OAc)_2 \xrightarrow[\text{THF, 70 °C}]{} (RO)_2\overset{O}{\overset{\|}{P}}-\overset{O}{\overset{\|}{P}}(OR)_2 \qquad (3)$$

1

Stimulated by the above results of the stoichiometric reactions of $Z_2P(O)H$ with copper(II) acetate, we thought that a catalytic reaction to selectively generate **1** and **2** should be possible. This indeed proved to be the case. After an extensive screening of the reaction conditions, we found that the oxidative dehydrogenative coupling of $(RO)_2P(O)H$ does take place efficiently with a catalytic amount of copper under air. Moreover, it can produce both the P–P hypophosphate **1a** and the P–O–P pyrophosphate **2a** highly selectively by changing the reaction conditions only slightly (Table 1).[13]

Table 1: Copper-catalyzed aerobic oxidative dehydrocoupling of $(i\text{PrO})_2P(O)H$ leading to hypophosphate **1a** and pyrophosphate **2a**.[a]



$$(i\text{PrO})_2P(O)H \xrightarrow[\text{air, 25 °C, 20 h}]{\text{cat. [Cu]/amine}} (i\text{PrO})_2\overset{O}{\overset{\|}{P}}-\overset{O}{\overset{\|}{P}}(Oi\text{Pr})_2 + (i\text{PrO})_2\overset{O}{\overset{\|}{P}}-O-\overset{O}{\overset{\|}{P}}(Oi\text{Pr})_2$$

1a **2a**

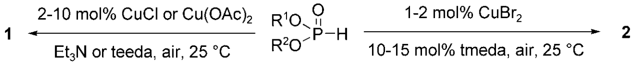
Run	[Cu] [mol%]	Amine [mol%]	Yield (**1a**/**2a**) [%][b]
1	$Cu(OAc)_2$ (2)	Et_3N[c]	98/trace (32/1)[d]
2[e]	CuCl (5)	Et_3N (20)	17/6
3[e]		$i\text{Pr}_2NH$ (20)	9/15
4[e]		$(t\text{BuNHCH}_2)_2$ (10)	16/42
5[e]		2,2′-bipyridyl (10)	2/44
6[e]		tmeda (10)	11/49
7[e]		teeda[f] (10)	71/28
8[g]	CuCl (10)	teeda (20)	**97/2**
9[e,h]	CuCl (2)	tmeda (200)	**2/97**
10[e]	$CuBr_2$ (1)	tmeda (10)	**0/99**

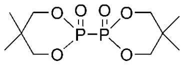
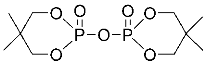
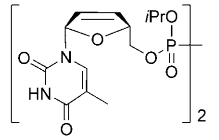
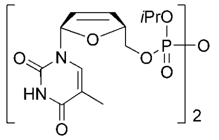
[a] $(i\text{PrO})_2P(O)H$ (1 mmol), copper compound, and amine under air for 20 h, unless otherwise noted. [b] Determined by GC. [c] 0.2 mL Et_3N was used; reaction time 4 h. [d] 50 μL of water was added. [e] Conducted in acetone (1 mL). [f] teeda = $Et_2NCH_2CH_2NEt_2$. [g] Neat, 1.5 h. [h] 3 h.

Thus, a mixture of $(i\text{PrO})_2P(O)H$ and $Cu(OAc)_2$ (2 mol%) in Et_3N under air was stirred at room temperature for 4 h to afford the P–P coupling product **1a** almost quantitatively (less than 0.1% yield of the P–O–P coupling product **2a**, Table 1, run 1). The use of Et_3N in the reaction is essential for this reaction. In the absence of Et_3N, only a trace amount of the coupling products could be obtained. This coupling reaction can be carried out in solvents such as acetone, THF, and EtOAc to give **1a** in high yields. However, since the copper catalyst was hydrolyzed to the catalytically inactive $Cu(OH)_2$ (see below), addition of water lowered the yields of the products. For example, when 50 μL of H_2O was added, only 32% yield of **1a** was obtained after 20 h (run 1). With the exception of $Cu(OH)_2$, which hardly catalyzes the reaction, a variety of Cu^{II} or Cu^I compounds can serve as good catalysts for this coupling reaction to give high yields of the products. It was noted that both the efficiency of the catalysts and the selectivity of the products are dramatically affected by the amine used. Thus, a screening on amines using CuCl (Table 1, runs 2–9) revealed that bidentate amines are suitable compounds for the copper-catalyzed reactions. Moreover, while *N,N,N′,N′*-tetramethylethylenediamine (tmeda) prefers the formation of **2a** (Table 1, run 6), a bulky *N,N,N′,N′*-tetraethylethylenediamine (teeda) leads to a reverse in the selectivity to the products favoring the formation of **1a** (Table 1, run 7). Further efforts on the optimization of the reactions[13] established the best conditions for the selective generation of both **1a** and **2a**. Thus, **1a** can be produced in 97 % yield with greater than 97 % selectivity by using a catalyst CuCl/teeda (Table 1, run 8), while **2a** can be obtained in 97 % yield with greater than 97 % selectivity by replacing tmeda with teeda (Table 1, run 9), or by using $CuBr_2$/tmeda as the catalyst to produce a quantitative yield of **2a** (Table 1, run 10).[13]

This catalytic dehydrogenative coupling reaction can be applied to other H-phosphonates to produce the corresponding P–P compounds **1** and the P–O–P compounds **2** in high yields with high selectivity (Table 2). An analogue of a nucleotide that shows unique biological activity (run 7)[14] could also be used to give the corresponding P–P and P–O–P products in high yields, demonstrating clearly the high potential of the current method to allow access to highly functionalized targets.

Table 2: Copper-catalyzed selective aerobic oxidative couplings of H-phosphonates affording hypophosphates **1** and pyrophosphates **2**.[a]



Run	**1**[a,b]	Yield [%][c]	**2**[d,e]	Yield [%][c]
1	$(i\mathrm{PrO})_2\overset{O}{\overset{\|}{P}}-\overset{O}{\overset{\|}{P}}(\mathrm{O}i\mathrm{Pr})_2$	93[a]	$(i\mathrm{PrO})_2\overset{O}{\overset{\|}{P}}-O-\overset{O}{\overset{\|}{P}}(\mathrm{O}i\mathrm{Pr})_2$	99[d]
2	$(n\mathrm{BuO})_2\overset{O}{\overset{\|}{P}}-\overset{O}{\overset{\|}{P}}(\mathrm{O}n\mathrm{Bu})_2$	80[b]	$(n\mathrm{BuO})_2\overset{O}{\overset{\|}{P}}-O-\overset{O}{\overset{\|}{P}}(\mathrm{O}n\mathrm{Bu})_2$	99[d]
3	$(\mathrm{EtO})_2\overset{O}{\overset{\|}{P}}-\overset{O}{\overset{\|}{P}}(\mathrm{OEt})_2$	85[b]	$(\mathrm{EtO})_2\overset{O}{\overset{\|}{P}}-O-\overset{O}{\overset{\|}{P}}(\mathrm{OEt})_2$	99[d]
4	$(n\text{-}C_{12}H_{25}O)_2\overset{O}{\overset{\|}{P}}-\overset{O}{\overset{\|}{P}}(\mathrm{O}n\text{-}C_{12}H_{25})_2$	84[a]	$(n\text{-}C_{12}H_{25}O)_2\overset{O}{\overset{\|}{P}}-O-\overset{O}{\overset{\|}{P}}(\mathrm{O}n\text{-}C_{12}H_{25})_2$	98[e]
6	$(\mathrm{PhCH_2O})_2\overset{O}{\overset{\|}{P}}-\overset{O}{\overset{\|}{P}}(\mathrm{OCH_2Ph})_2$	83[b]	$(\mathrm{PhCH_2O})_2\overset{O}{\overset{\|}{P}}-O-\overset{O}{\overset{\|}{P}}(\mathrm{OCH_2Ph})_2$	90[e]
7		84[b]		96[e]
8		78[b]		91[e]

[a] $Cu(OAc)_2$ (2 mol%), Et_3N (0.2 mL), $(RO)_2P(O)H$ (1 mmol), 4 h. [b] CuCl (10 mol%), teeda (30 mol%), acetone (0.5 mL), $(RO)_2P(O)H$ (1 mmol), 1.5–6 h. [c] Yields of isolated products. [d] $CuBr_2$ (1 mol%), tmeda (10 mol%), acetone (1 mL), $(RO)_2P(O)H$ (1 mmol), 6 h. [e] $CuBr_2$ (2 mol%), tmeda (15 mol%), THF (1 mL), $(RO)_2P(O)H$ (1 mmol), 8–24 h.

By referring to the known copper-mediated coupling reactions in the literature, the formation of the P–P compound **1** was rationalized to take place by the coupling of phosphoryl radical $(RO)_2(O)P$, which was generated by an electron-transfer (ET) process of $(RO)_2P(O)H$ to Cu^{II}.[15,16] In contrast, the reaction via intermediate **3** should be one of the possible ways for the formation of the P–O–P compound **2**. Although detailed mechanistic aspects remained to be clarified, it was rationalized that a bulky amine could retard the intermolecule reaction pathway for the formation of the P–O–P compound **2**, and favor the formation of the P–P compound **1** by couplings of phosphoryl radicals.

In summary, a copper-catalyzed oxidative dehydrocoupling of $(RO)_2P(O)H$ selectively affording P–P and P–O–P compounds was revealed for the first time. We believe that the present work not only provides an efficient and clean method for the selective preparation of hypophosphate **1** and pyrophosphate **2**, but also is highly informative for the design of new copper-catalyzed oxidative coupling reactions.[16] Further studies on the clarification of the reaction mechanism and applications to other substrates are underway.

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Keywords: copper · dehydrogenation · homogeneous catalysis · phosphorus

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[8] The reaction took place as: $3\,R_2P(O)H + 2\,Cu(OAc)_2 \rightarrow \mathbf{3} + R_2P(O)OH + 2\,AcOH$. However, the exact pathway for the formation of **3** is not clear.

[9] CCDC 777312 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[12] No possible intermediates of $(i\mathrm{PrO})_2P(O)H$-ligated Cu species could be detected by ^{31}P NMR spectroscopy. Other products are CuOAc as white precipitate (95 % yield of isolated product) and acetic acid (97 % yield measured by NMR spectroscopy), which accounts for the stoichiometry of the reaction: $2\,(RO)_2P(O)H + 2\,Cu(OAc)_2 \rightarrow \mathbf{1} + 2\,Cu(OAc) + 2\,AcOH$.

[13] For details of the experiments, see the Supporting Information. A separate experiment using isolated **1a** showed that compound **1a** is stable under the reaction conditions for the formation of **2a**, indicating that **2a** was not formed by further oxidation of **1a**.

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