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Mechanistic Insight into the Copper-Catalyzed Phosphorylation of Terminal Alkynes: A Combined Theoretical and Experimental Study

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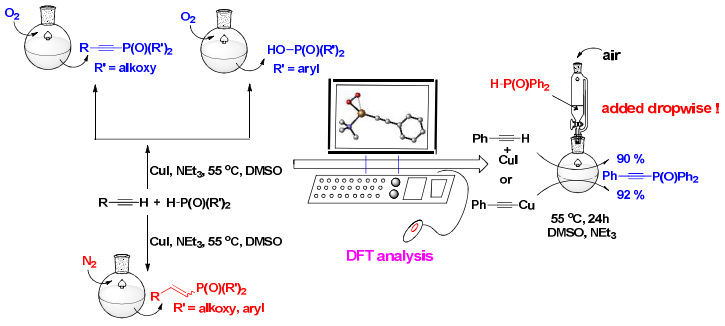


Abstract: The reaction mechanism of copper-catalyzed phosphorylation of terminal alkynes under different conditions has been investigated experimentally and theoretically. The important role of dioxygen has been elucidated, including the formation of η^1-superoxocopper (II), η^2-superoxocopper (III), μ-η^2:η^2-peroxodicopper (II) and bis(μ-oxo)-dicopper (III). More importantly, the proton transfer

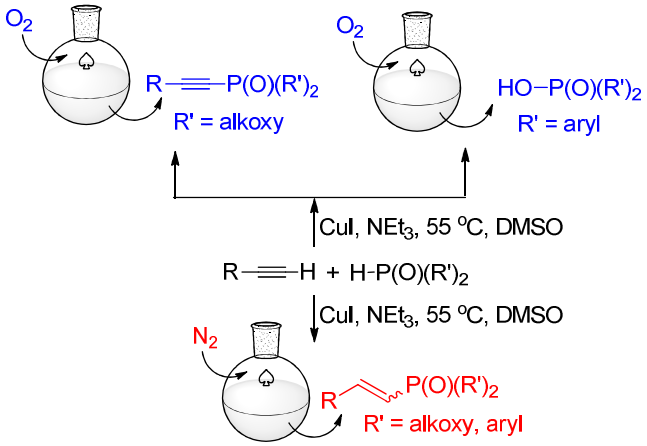
from dialkyl phosphonates (in the form of phosphite) to the bridging oxygen atom entails the migration of the deprotonated phosphonates into the terminal alkyne, leading to the formation of a C−P bond with an activation barrier of only 1.8 kcal/mol. In addition, a particularly stable, six-centered dicopper (I) species was located with the migration of both the $Ph_2P(O)$ groups from the copper to the oxygen atom of bis(μ-oxo)-bridge, explaining experimental observation that secondary phosphine oxides could be oxidized to the phosphinic acid. Thus, the diphenylphosphine oxide was added to the reaction mixture dropwise to minimize the concentration during the reaction course. Gratifyingly, it is almost quantitative to generate the coupling product when the reaction was completed.

1. Introduction

Organophosphorus compounds play a crucial role in pharmaceutical and agrochemical industries. The presence of phosphoryl group often significantly improves the hydrophilicity and bioavailability.[1] Particularly, alkynyl- and alkenyl-phosphorus compounds, containing an extremely versatile multiple bond, can readily undergo nucleophilic addition to give bifunctional adducts.[2] Some of them are successfully used as the precursors of biologically active molecules.[3]

In the past ten years, a number of other metal-catalyzed oxidative couplings using dioxygen have successfully been applied to the construction of structurally sophisticated compounds.[4] For example, Stahl and co-workers reported copper-catalyzed chemoselective aerobic oxidation of alcohols[4a,b] and functionalization of an arene C−H bond.[4c] Dioxygen is undoubtedly the most environmentally benign and abundant oxidant because only water is produced as a byproduct.[5] Recently, we reported a copper-catalyzed aerobic oxidative cross-coupling of dialkyl phosphonates with terminal alkynes to provide a variety of alkynylphosphorus compounds.[6a] It is very interesting to note that alkynylphosphonates (Scheme 1, top, R' = alkoxy) were formed in high yields with the presence of

oxygen while alkenylphosphorus (Scheme 1, bottom, R' = alkoxy or aryl) compounds were generated under nitrogen.[6] Unfortunately, diaryl phosphine oxides were found to be unsuitable coupling partner since they could be oxidized to the phosphinic acid (Scheme 1, top, R' = aryl).[6a] Although copper-catalyzed oxidative couplings have attracted more and more attention,[5] the mechanism, e.g., the role of dioxygen has not been well understood.[5,7] Here, our continued interest in organophosphorus chemistry and reaction mechanisms[8] prompted us to investigate the detailed catalytic steps both experimentally and theoretically to probe the origin of the different behavior summarized in Scheme 1. Benefiting from the theoretical findings, diphenylphosphine oxide was added dropwise to the reaction mixture under air, leading to the diphenyl alkynylphosphine oxide in excellent yield.



Scheme 1. Copper-catalyzed phosphorylation of terminal alkynes under oxygen or nirtrogen.

2. Computational Details

Optimizations of structures with frequency calculations were performed with the Gaussian 03 software package.[9a] Density functional theory (DFT) method B3LYP[10] which has been chosen in several mechanistic studies on Cu-catalyzed reactions,[11] with a mixed basis set employing D95v(d)[12] for C, H, N, O and LANL2DZ[13] for P, I, Cu was used. Polarization functions were added for P (ξ_d = 0.387), I (ξ_d = 0.289) and Cu (ξ_f = 3.525).[14] Transition states with only one imaginary frequency were examined by

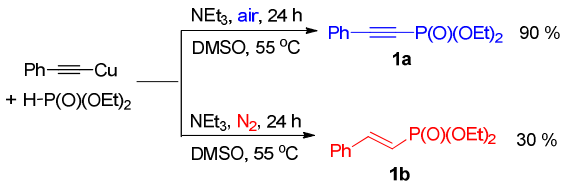
vibrational analysis and then submitted to intrinsic reaction coordinate (IRC) calculations to ensure that such structures are indeed connecting two minima. Energies in solution (DMSO) have been calculated via the Gaussian 09 program[9b] by means of single point calculations (IEF-PCM method with the Bondi radii)[15] with the same method using SDD[16] pseudo-potential for the I, Cu and the extended 6-311++G(2d,p)[17] basis set for the other atoms. The gas-phase geometry was used for all of the solution phase calculations. A similar treatment was also used in many recent computational studies.[18] Dispersion corrections were computed for the optimized geometries using the DFT-D3 package of Grimme[19] with the corresponding B3LYP-D functional. The free energy correction from frequency calculation and dispersion correction was added to the single-point energy to obtain the free energy in solution. All the solution-phase free energies reported herein correspond to the reference state of 1 mol/L, 298 K. In the calculations, the model substrates $(NMe_3)_2CuI$, dimethyl phosphonate, phenylacetylene and dioxygen were chosen. Relative free energies in solution (DMSO) are employed to analyze the reaction mechanism. A comparison of some relative energy values of the reaction mechanism obtained with the model substrates ($(NMe_3)_2CuI$ and dimethyl phosphonate) and the real substrates ($(NEt_3)_2CuI$, diethyl phosphonate) was provided in the Supporting Information. The results showed that the energies in the rate-determining steps do not differ significantly. For example, using the model substrates, the energies of **TS3** (relative to **IN6**) and **TS9** (relative to **IN16**) are 9.3 and 34.1 kcal/mol, respectively. Using the real substrates, the relative energies are 8.6 and 32.8 kcal/mol, respectively. In addition, considering that the B3LYP functional is problematic in treating some transition-metal systems, we evaluated the effects of density functional in this study. The results show that different DFT methods provide a consistent energy profile (for details see the Supporting Information). Optimized structures were visualized by the CYLview program[20] and provided in the

Supporting Information.

3. Results and Discussion

3.1 Cu-catalyzed dioxygen-triggered phosphorylation

Under air or nitrogen, phenylacetylene (0.3 mmol) and $(EtO)_2P(O)H$ (0.25 mmol) were added to a mixture of CuI (0.025 mmol) and NEt_3 (0.05 mmol) in DMSO to immediately give a yellow suspension, clearly demonstrating (phenylethynyl)copper was formed.[21] Thus, the reaction may start when alkyne and a base react with the copper catalyst, generating alkynylcopper reagent. To examine our hypothesis, we treated (phenylethynyl)copper (0.3 mmol), NEt_3 (0.6 mmol) and $(EtO)_2P(O)H$ (0.25 mmol) in DMSO without the presence of CuI at 55 ^oC for 24 h (Scheme 2). Gratifyingly, the corresponding diethyl (phenylethynyl)phosphonate (**1a**) and diethyl styrylphosphonate (**1b**) were formed under air and nitrogen, respectively.[22]



Scheme 2. Phosphorylation of (phenylethynyl)copper.

The catalytic cycle of the Cu-catalyzed dioxygen-triggered phosphorylation of terminal alkynes, including the free energies for all the species, is depicted in Figure 1, in which the Cu atoms have been color-coded to indicate the different oxidation state. Cu (I) is labelled by black, Cu (II) by blue and Cu (III) by red. (Phenylethynyl)copper complex **IN1** (3.3 kcal/mol) is initially formed through a base-mediated ligand exchange process. Subsequently, dioxygen in the triplet state toward **IN1** leads to the formation of the η^1-superoxocopper (II) intermediate **IN3** (triplet, 7.2 kcal/mol) via a low barrier transition state **TS1** (8.4 kcal/mol). Mulliken spin densities for **IN3** are mainly localized in the O_2 part (1.53), indicating the oxidation state of Cu center is +2. Interestingly, the Cu−O1 and Cu−O2 distances

are 1.981 and 2.232 Å in triplet state **IN3**, respectively, while they are quite short in singlet state **IN4** (1.868 and 1.873 Å, 16.2 kcal/mol) (Figure 2). This process (**IN3→IN4**) is expected to require low activation energies.[5,23] When another **IN1** or **IN2** comes, a μ-η^2:η^2-peroxodicopper (II) intermediate **IN6** is formed with a positive energy of 17.3 kcal/mol via a three-membered transition state **TS2** (20.5 kcal/mol).

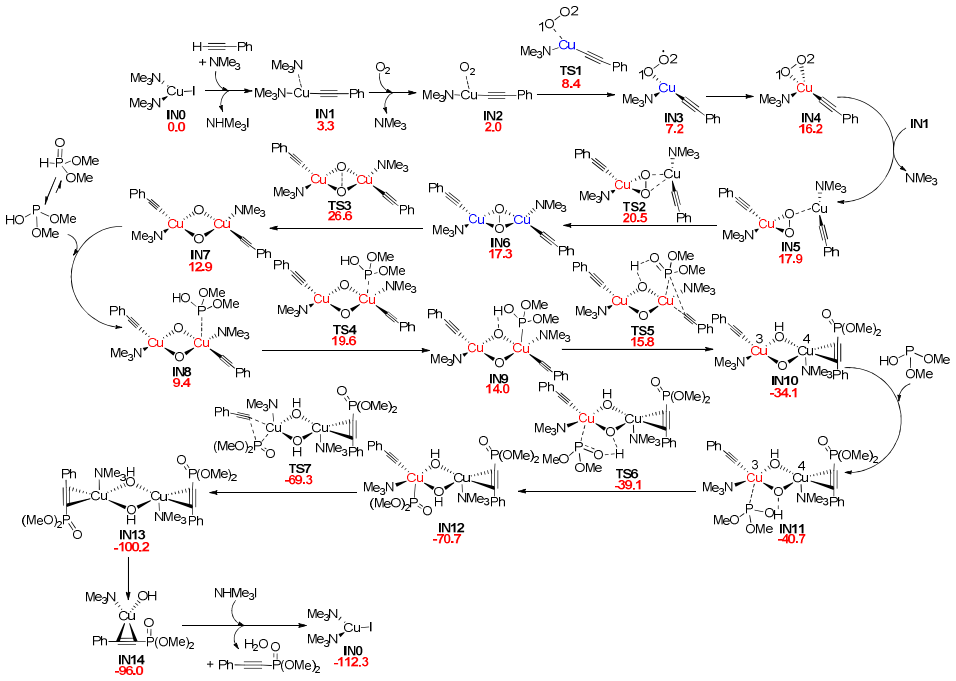
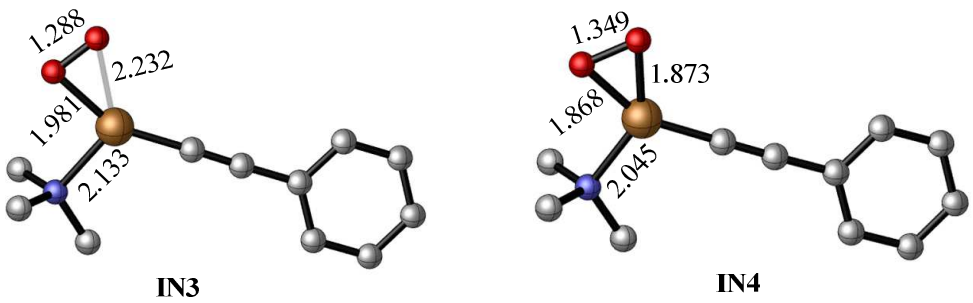


Figure 1. Free energy profile for copper-catalyzed dioxygen-triggered phosphorylation of terminal alkynes. The values are given in kcal/mol.

From **IN6**, a bis(μ-oxo)-dicopper (III) complex **IN7** (12.9 kcal/mol) is located through a four-centered transition state **TS3** with a one electron transfer from each Cu (II) to the peroxo group. The activation energy is computed to be 9.3 kcal/mol. The O−O bond distances in **IN6** (peroxo) and **IN7** (oxo) are 1.429 and 2.313 Å, respectively, in line with the experimental observations (1.42 and 2.32 Å for similar species).[23c]



IN3 **IN4**

Figure 2. Structures (Å) of singlet **IN3** and triplet **IN4**. Hydrogen atoms are omitted for clarity.

It is well-known that a tautomeric equilibrium of dialkyl phosphonates or secondary phosphine oxides in the solution exists between a normal tetracoordinated form and an "active" tricoordinated one.[24] Both dialkyl phosphonates and secondary phosphine oxides favor the tetracoordinated form. The formation of phosphorus−metal bond is the driving force for the tautomerization. Actually, a phosphite copper (III) complex **IN9** (14.0 kcal/mol) could be located when dimethyl phosphonate via the form of the dimethyl hydrogen phosphite coordinates to **IN7**. Very interestingly, a more stable intermediate **IN10** (-34.1 kcal/mol) formed through **TS5** with an activation energy of 1.8 kcal/mol only is featured by not only a proton transfer from P−O−H to Cu−O_2−Cu, but also a spontaneous P−C bond formation, which could subsequently generate a more stable intermediate **IN11** (-40.7 kcal/mol) via a hydrogen bond-like interaction of a second dimethyl hydrogen phosphite. It is important to note that several Cu_2O_2 species are proposed as a mix-valence Cu(III)/Cu(I) core.[25] Indeed, in **IN10**, the Cu3−OH bond (1.851 Å) is quite shorter than Cu4−OH bond (2.386 Å), clearly indicating Cu4−OH bond is a weak coordinate bond so that the oxidation states of Cu3 and Cu4 are +3 and +1, respectively, which is similar to other Cu(III)/Cu(I) species.

Subsequently, a five-membered transition state **TS6** appears to be only 1.6 kcal/mol with respect to **IN11**, leading to the formation of a more stable species **IN12** (-70.7 kcal/mol). From **IN12**, a three-centered transition state **TS7** is located with the activation energy of 1.4 kcal/mol. In **TS7**, the

Cu−C, Cu−P and C−P bond lengths are 1.863, 2.314 and 2.446 Å, respectively. In comparison with our previous study on the C−P bond formation step using palladium (II)[8a] or nickel (II)[2i, 8e, i] catalyst, this C−P bond is quite long, indicating that Cu (III) species is a potential useful catalyst for the transformation.

Then the dinuclear intermediate **IN13** breaks up into two monomeric copper (I) species **IN14**. Finally, the ligand exchange gives the desired product and complete the catalytic cycle by regenerating **IN0** (-112.3 kcal/mol) as a catalytically active species. Comparing each step of copper-catalyzed dioxygen-triggered phosphorylation, one could conclude that cleaving the O−O bond is the overall rate-limiting step. The barrier is 26.6 kcal/mol with respect to the catalyst resting state **IN0**, in excellent agreement with the experimental observations that this reaction was performed at 55 ^{o}C.[26]

3.2 Cu-catalyzed dioxygen-free phosphorylation

Under the similar conditions, alkenylphosphorus compounds were generated under nitrogen (Schemes 1 and 2).[6] As shown in Figure 3, this catalytic cycle includes four basic steps: ligand exchange, proton transfer, nucleophilic addition and catalyst recycling. Our calculations showed that the addition step is the most energy-demanding. The activation barrier is computed to be 34.1 kcal/mol, which is much higher than that of dioxygen-triggered process. Although the regeneration of the catalytically active species **IN0** is exoergic of -39.4 kcal/mol, it is much less than that of dioxygen-triggered process (-112.3 kcal/mol). Thus, dioxygen-free phosphorylation is not favorable both kinetically and thermodynamically. Indeed, only 30 % *E*-diethyl styrylphosphonate was obtained after 24 h, along with the 70 % unchanged reactant (Scheme 2).

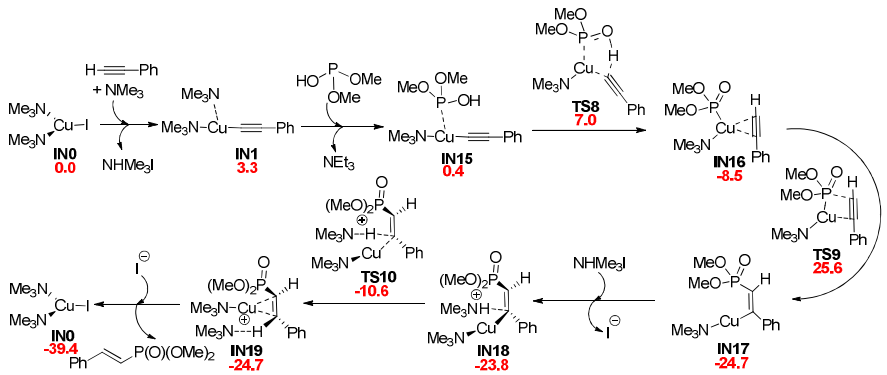
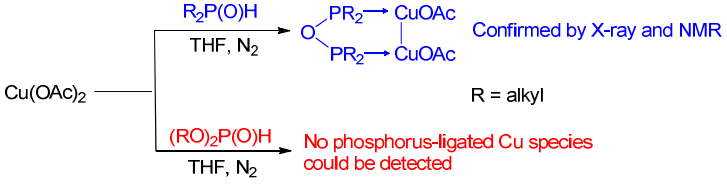


Figure 3. Free energy profile for copper-catalyzed phosphorylation of terminal alkynes under nitrogen. The values are given in kcal/mol.

3.3 Oxidation of secondary phosphine oxides and dialkyl phosphonates

Unfortunately, secondary phosphine oxide such as $Ph_2P(O)H$ did not provide the oxidative coupling product under similar reaction conditions. Only $Ph_2P(O)OH$ was detected in the crude mixture.[6a] Drawing inspiration from our experience in organophosphorus chemistry, we found the copper catalyst is susceptible to secondary phosphine oxides rather than dialkyl phosphonates (Scheme 3).[8j] Actually, the energy of the HOMO in tricoordinated Ph_2POH is 0.02 eV higher than that in $(MeO)_2POH$, thus Ph_2POH is more nucleophilic. The energy of the LUMO in $(MeO)_2POH$ is 0.03 eV, whereas that in Ph_2POH is −0.03 eV, indicating Ph_2POH is also a better candidate for enhancing back-donation from the Cu center.[27] Hence, we presume that tricoordinated phosphine could strongly bind to the Cu center using its lone electron pair, inhibiting the *in situ* formation of alkynylcopper, instead, forming the phosphine copper complex, where the phosphorus center (III) might be easily oxidized by dioxygen.



Scheme 3. Previous study of coordination ability using secondary phosphine oxides and dialkyl phosphonates (R = alkyl).

A possible mechanism is proposed based on the above analysis (Figure 4). A more stable intermediate **IN20** (-5.7 kcal/mol) is formed via a ligand replacement process. In a similar way, after two steps, a μ-η^2:η^2-peroxodicopper (II) complex **IN22** is located to be -8.7 kcal/mol. Very interestingly, once cleaving the O−O bond in **IN22**, no bis(μ-oxo)-dicopper (III) complex could be located. Instead, a very stable six-centered dicopper (I) species **IN23** (-155.7 kcal/mol) is located with the migration of both the $Ph_2P(O)$ groups from the copper to the oxygen atoms of bis(μ-oxo)-bridge. Note that this process is much exergonic, because the transition state (**TS11**) appears with a one electron transfer from each Cu to the peroxo group so that the oxidation states of Cu have been increased to +3. However, the corresponding dicopper (III) species is not stable enough to be found, indicating that in this case the $Ph_2P(III)(O)$ group is very easily oxidized to the $Ph_2P(V)(O)O$ group, in line with the experimental observations that only the oxidized product (phosphinic acid) was detected.

Since a side product $(i\text{-PrO})_2P(O)OH$ was detectable in 3% yield,[6a] we next turned our attention to the oxidation of H-phosphonates (See the Supporting Information for details). Our calculation results show that the formation of intermediates **IN21'** (8.3 kcal/mol) is unfavorable than that of **IN3** (7.2 kcal/mol). Although the energy difference is not significant, the (phenylethynyl)copper complex is regarded as a slightly soluble coordination polymer with strong π-bonding between metal and the acetylenes,[28] promoting a forward shift in the chemical equilibrium to **IN3**.

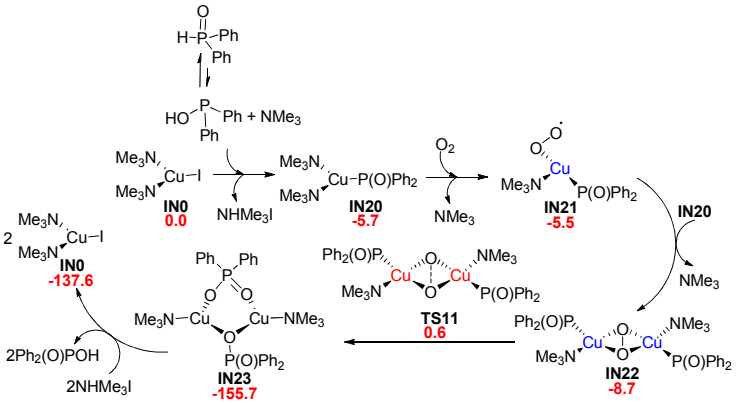


Figure 4. Free energy profile for the formation of $Ph_2P(O)OH$. The values are given in kcal/mol.

3.4 Synthesis of diphenyl alkynylphosphine oxides

On the basis of above calculation results, once the tricoordinated phosphine binds to the Cu center, the *in situ* formation of alkynylcopper might be inhibited. In addition, the phosphine was readily oxidized by the dioxygen with only 9.3 kcal/mol activation energy (**IN22→TS11**). To avoid this problem, we first investigated the coupling step of terminal alkynes and secondary phosphine oxides (See the Supporting Information for details). The results showed that the P−C bond formations are quite facile (activation barriers are 1.9 and 5.3 kcal/mol for **TS5'** and **TS6'**). More importantly, the key η^1-superoxocopper (II) intermediates **IN3** (7.2 kcal/mol, Figure 1) and **IN21** (-5.5 kcal/mol, Figure 4) may control the chemical selectivity, leading to the coupling product and oxidation product, respectively. Thus, we directly treated (phenylethynyl)copper (0.3 mmol), NEt_3 (0.05 mmol) and $Ph_2P(O)H$ (0.25 mmol) in DMSO under air without the presence of CuI at 60 ^oC for 24 h. However, the desired coupled product diphenyl(phenylethynyl)phosphine oxide was detected only 78 % NMR yield, along with the 22% oxidized product $Ph_2P(O)OH$. Presumably, the deprotonated alkyne of alkynylcopper complex may be protonated and followed by replacement of the more nucleophilic phosphine. Thus, two strategies for preparation of diphenyl alkynylphosphine oxide were designed (Figure 5). The diphenylphosphine oxide in DMSO was added to the reaction mixture dropwise so that the concentration of it is minimized during the reaction course. Surprisingly, it is almost quantitative to generate the coupled product diphenyl(phenylethynyl)phosphine oxide (**1c**) and only a trace amount of oxidized byproduct could be detected when the reaction finished (less than 3 % by ^{31}P NMR).

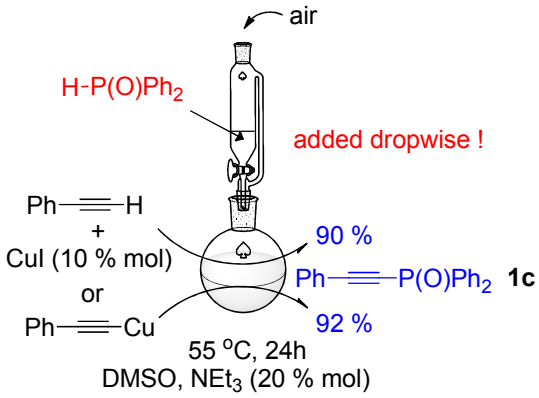


Figure 5. Two strategies for preparation of diphenyl alkynylphosphine oxide.

4. Conclusion

We have investigated the mechanism of Cu-catalyzed phosphorylation of terminal alkynes both experimentally and theoretically. The important role of dioxygen has been been elucidated. The dioxygen-triggered and dioxygen-free phosphorylation processes start with ligand replacement of initial catalyst $(NMe_3)_2CuI$ to yield the alkynylcopper. In the former process, the dioxygen is activated by Cu (I) species, forming η^1-superoxocopper (II), η^2-superoxocopper (III), μ-η^2:η^2-peroxodicopper (II) and bis(μ-oxo)-dicopper (III). Then the proton transfer from phosphite to the bridging oxygen atom leads to the formation of a P−C bond. In the latter process, only Cu (I) species can be located without the presence of any oxidants. The nucleophilic addition is the rate-limiting step with an activation barrier of 34.1 kcal/mol. Importantly, we found that secondary phosphine oxides is easily oxidized by dioxygen because the copper catalyst is susceptible to secondary phosphine oxides rather than dialkyl phosphonates. Further calculations confirm this hypothesis. Therefore, the diphenyl phosphine oxides were added dropwise to the reaction mixture to minimize the concentration during the reaction course, leading to almost quantitative generation of the coupling product. Our findings can serve as a benchmark for other similar Cu-catalyzed dioxygen-triggered reactions, which may open a new avenue to the design of more efficient cross-coupling reactions.

5. Experimental Section

General Information.

^{31}P, ^{1}H, and ^{13}C NMR spectra were measured on 400 M spectrometers. ^{1}H NMR and ^{13}C NMR were recorded using tetramethylsilane (TMS) in the solvent $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm) and 85% H_3PO_4 as external standard for ^{31}P NMR. All coupling constants (J values) were reported in hertz (Hz).

Diethyl (phenylethynyl)phosphonate (**1a**, CAS No.: 3450-67-7). A vial containing (phenylethynyl)copper (49.2 mg, 0.3 mmol), NEt_3 (60.6 mg, 0.6 mmol), $(EtO)_2P(O)H$ (34.5 mg , 0.25 mmol) and DMSO (3.0 mL) was stired at 55 ^{o}C under air for 24 hours. The solvent was evaporated under vacuum. The residue was then purified by flash chromatography (hexane/ethyl acetate = 2:1) to yield the desired diethyl (phenylethynyl)phosphonate (**1a**)[29] as a powder (54 mg, 90 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56-7.54 (m, 2H), 7.46-7.42 (m, 1H), 7.38-7.34 (m, 2H), 4.25-4.18 (m, 4H), 1.41-1.37 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6 (d, J_{C-P} = 2.6 Hz), 130.6, 128.5, 119.5 (d, J_{C-P} = 5.8 Hz), 99.0 (d, J_{C-P} = 53.6 Hz), 76.9 (d, J_{C-P} = 297.2 Hz), 63.2 (d, J_{C-P} = 5.5 Hz), 16.1 (d, J_{C-P} = 7.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ -6.4. MS (ESI) *m/z*: Calcd. for $C_{12}H_{15}O_3PNa^+$: 261.1, Found: 261.1.

(E)-Diethyl styrylphosphonate (**1b**, CAS No.: 20408-33-7). A vial containing (phenylethynyl)copper (49.2 mg, 0.3 mmol), NEt_3 (60.6 mg, 0.6 mmol), $(EtO)_2P(O)H$ (34.5 mg , 0.25 mmol) and DMSO (3.0 mL) was stired at 55 ^{o}C under nitrogen for 24 hours. The solvent was evaporated under vacuum. The residue was then purified by flash chromatography (hexane/ethyl acetate = 2:1) to yield the desired (E)-diethyl styrylphosphonate (**1b**)[30] as a powder (18 mg, 30 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.37 (m, 6H), 6.30-6.21 (t, J = 17.5 Hz, 1H), 4.17-4.09 (m, 4H), 1.37-1.34 (t, J = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7 (d, J_{C-P} = 6.5 Hz), 141.0 (d, J_{C-P} = 23.3 Hz), 130.2, 128.9, 127.7, 114.5 (d, J_{C-P} = 199.2 Hz), 61.8 (d, J_{C-P} = 5.4 Hz), 16.4 (d, J_{C-P} = 6.4 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz) δ 19.6. MS (ESI) *m/z*: Calcd. for $C_{12}H_{17}O_3PNa^+$: 263.1, found: 263.1.

Diphenyl(phenylethynyl)phosphine oxide (**1c**, CAS No.: 7608-18-6). (i) A vial containing CuI (7.5 mg, 0.04 mmol), NEt_3 (8.1 mg, 0.08 mmol), phenylacetylene (49.0 mg, 0.48 mmol) and DMSO (2.0 mL) was stired at 55 ^{o}C under air for 4 hours. Then diphenylphosphine oxide (81 mg, 0.4 mmol) in DMSO (2.0 mL) was added dropwise during 20 hours. The solvent was evaporated under vacuum. The residue was then purified by flash chromatography (hexane/ethyl acetate = 1:1) to yield the desired diphenyl alkynylphosphine oxide (**1c**)[31] as a powder (109 mg, 90 %). (ii) A vial containing (phenylethynyl)copper (78.7 mg, 0.48 mmol), NEt_3 (8.1 mg, 0.08 mmol) and DMSO (2.0 mL) was stired at 55 ^{o}C under air for 4 hours. Then diphenylphosphine oxide (81 mg, 0.4 mmol) in DMSO (2.0 mL) was added dropwise during 20 hours. It was purified by the same procedure described above, providing diphenyl alkynylphosphine oxide (**1c**) (111 mg, 92 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90-7.85 (m, 4H), 7.58-7.40 (m, 9H), 7.34-7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 132.5 (d, J_{C-P} = 1.8 Hz), 132.3 (d, J_{C-P} = 2.8 Hz), 131.0 (d, J_{C-P} = 11.4 Hz), 130.7, 128.6, 128.6, 120.0 (d, J_{C-P} = 4.7 Hz), 105.6 (d, J_{C-P} = 30.0 Hz), 83.2 (d, J_{C-P} = 170.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 8.5. MS (ESI) *m/z*: Calcd. for $C_{20}H_{15}OPNa^+$: 325.1, Found: 325.1.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H, ^{13}C NMR and ^{31}P NMR spectra for compounds **1a**, **1b** and **1c**, the 3D structures and

Cartesian coordinates for all the species, free energy profiles for oxidation step of dimethyl phosphonate and coupling step of diphenylphosphine oxide. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Reference:

1. Selected recent publications: (a) Queffélec, C.; Petit, M.; Janvier, P.; Knight, D. A.; Bujoli, B., *Chem. Rev.* **2012,** *112*, 3777-3807. (b) Demmer, C. S.; Krogsgaard-Larsen, N.; Bunch, L., *Chem. Rev.* **2011**, *111*, 7981-8006. (c) Gao, J.; Ju, K.-S.; Yu, X.; Velásquez, J. E.; Mukherjee, S.; Lee, J.; Zhao, C.; Evans, B. S.; Doroghazi, J. R.; Metcalf, W. W.; van der Donk, W. A., *Angew. Chem. Int. Ed.* **2014**, *53*, 1334-1337. (d) Leung, C. Y.; Park, J.; De Schutter, J. W.; Sebag, M.; Berghuis, A. M.; Tsantrizos, Y. S. *J. Med. Chem.* **2013**, *56*, 7939−7950. (e) Bastidas, A. C.; Deal, M. S.; Steichen, J. M.; Guo, Y.; Wu, J.; Taylor, S. S., *J. Am. Chem. Soc.* **2013**, *135*, 4788-4798.

2. Selected recent publications: (a) Sajna, K. V.; Srinivas, V.; Kumara Swamy, K. C., *Adv. Synth. Catal.* **2010**, *352*, 3069-3081. (b) Li, X.; Hu, G.; Luo, P.; Tang, G.; Gao, Y.; Xu, P.; Zhao, Y., *Adv. Synth. Catal.* **2012**, *354*, 2427-2432. (c) Cockburn, N.; Karimi, E.; Tam, W., *J. Org. Chem.* **2009**, *74*, 5762-5765. (d) Kettles, T. J.; Cockburn, N.; Tam, W., *J. Org. Chem.* **2011**, *76*, 6951-6957. (e) Lecerclé, D.; Sawicki, M.; Taran, F., *Org. Lett.* **2006**, *8*, 4283-4285. (f) Ben-Valid, S.; Quntar, A. A. A.; Srebnik, M., *J. Org. Chem.* **2005**, *70*, 3554-3559. (g) Mo, J.; Kang, D.; Eom, D.; Kim, S. H.; Lee, P. H., *Org. Lett.* **2012**, *15*, 26-29. (h) Quntar, A. A. A.; Baum, O.; Shibli, A.; Dembitsky, V. M.; Srebnik, M., *Angew. Chem. Int. Ed.* **2003**, *42*, 4777-4779. (i) Liu, L.; Wang, Y.; Zeng, Z.; Xu, P.; Gao, Y.; Yin, Y.; Zhao, Y., *Adv. Synth. Catal.* **2013**, *355*, 659-666. (j) Kondoh, A.; Yorimitsu, H.; Oshima, K., *Org. Lett.* **2010**, *12*, 1476-1479. (k) Hara, K.; Park, S.-Y.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M., *Chem. Asian J.* **2008**, *3*, 1500-1504.

3. (a) Van derpoorten, K.; Migaud, M. E., *Org. Lett.* **2004**, *6*, 3461-3464. (b) Nicolaou, K. C.; Maligres, P.; Shin, J.; De Leon, E.; Rideout, D., *J. Am. Chem. Soc.* **1990**, *112*, 7825-7826. (c)

Haynes, R. K.; Loughlin, W. A.; Hambley, T. W., *J. Org. Chem.* **1991**, *56*, 5785-5790. (d) Li, X.; Zhang, D.; Pang, H.; Shen, F.; Fu, H.; Jiang, Y.; Zhao, Y., *Org. Lett.* **2005**, *7*, 4919-4922.

4. Selected recent publications: (a) Steves, J. E.; Stahl, S. S., *J. Am. Chem. Soc.* **2013**, *135*, 15742-15745. (b) Hoover, J. M.; Stahl, S. S., *J. Am. Chem. Soc.* **2011**, *133*, 16901-16910. (c) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S., *J. Am. Chem. Soc.* **2010**, *132*, 12068-12073. (d) Stowers, K. J.; Kubota, A.; Sanford, M. S., *Chem. Sci.* **2012**, *3*, 3192-3195. (e) Ratnikov, M. O.; Xu, X.; Doyle, M. P., *J. Am. Chem. Soc.* **2013**, *135*, 9475-9479. (f) Pun, D.; Diao, T.; Stahl, S. S., *J. Am. Chem. Soc.* **2013**, *135*, 8213-8221. (g) Tsukamoto, D.; Shiraishi, Y.; Sugano, Y.; Ichikawa, S.; Tanaka, S.; Hirai, T., *J. Am. Chem. Soc.* **2012**, *134*, 6309-6315. (h) Sonobe, T.; Oisaki, K.; Kanai, M., *Chem. Sci.* **2012**, *3*, 3249-3255. (i) Volla, C. M. R.; Bäckvall, J.-E., *Angew. Chem. Int. Ed.* **2013**, *52*, 14209-14213. (j) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780-1824. (k) Hamada, T.; Ye, X.; Stahl, S. S., *J. Am. Chem. Soc.* **2008**, *130*, 833-835. (l) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N., *Chem. Soc. Rev.* **2012**, *41*, 3381-3430.

5. (a) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C., *Chem. Rev.* **2013**, *113*, 6234-6458. (b) Zhang, C.; Tang, C.; Jiao, N., *Chem. Soc. Rev.* **2012**, *41*, 3464-3484. (c) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S., *Angew. Chem. Int. Ed.* **2011**, *50*, 11062-11087.

6. (a) Gao, Y.; Wang, G.; Chen, L.; Xu, P.; Zhao, Y.; Zhou, Y.; Han, L.-B., *J. Am. Chem. Soc.* **2009**, *131*, 7956-7957. (b) Niu, M.; Fu, H.; Jiang, Y.; Zhao, Y., *Chem. Commun.* **2007**, *43*, 272-274.

7. (a) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S., *J. Am. Chem. Soc.* **2013**, *135*, 9797-9804. (b) Hoover, J. M.; Ryland, B. L.; Stahl, S. S., *J. Am. Chem. Soc.* **2013**, *135*,

2357-2367. (c) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M., *J. Am. Chem. Soc.* **2010**, *132*, 2522-2523. (d) Zhang, C.; Feng, P.; Jiao, N., *J. Am. Chem. Soc.* **2013**, *135*, 15257-15262. (e) Jover, J.; Maseras, F., *Chem. Commun.* **2013**, *49*, 10486-10488. (f) Zhang, G.; Yi, H.; Zhang, G.; Deng, Y.; Bai, R.; Zhang, H.; Miller, J. T.; Kropf, A. J.; Bunel, E. E.; Lei, A., *J. Am. Chem. Soc.* **2014**, *136*, 924-926. (g) Saracini, C.; Liakos, D. G.; Zapata Rivera, J. E.; Neese, F.; Meyer, G. J.; Karlin, K. D., *J. Am. Chem. Soc.* **2014**, *136*, 1260-1263.

8. For carbon-phosphorus bond formations, see: (a) Wang, T.; Sang, S.; Liu, L.; Qiao, H.; Gao, Y.; Zhao, Y., *J. Org. Chem.* **2014**, *79*, 608-617. (b) Gao, Y.; Huang, Z.; Zhuang, R.; Xu, J.; Zhang, P.; Tang, G.; Zhao, Y., *Org. Lett.* **2013**, *15*, 4214-4217. (c) Xu, J.; Zhang, P.; Gao, Y.; Chen, Y.; Tang, G.; Zhao, Y., *J. Org. Chem.* **2013**, *78*, 8176-8183. (d) Zhuang, R.; Xu, J.; Cai, Z.; Tang, G.; Fang, M.; Zhao, Y., *Org. Lett.* **2011**, *13*, 2110-2113. (e) Liu, L.; Lv, Y.; Wu, Y.; Gao, X.; Zeng, Z.; Gao, Y.; Tang, G.; Zhao, Y., *RSC Adv.* **2014**, *4*, 2322-2326. (f) Miao, W.; Gao, Y.; Li, X.; Gao, Y.; Tang, G.; Zhao, Y., *Adv. Synth. Catal.* **2012**, *354*, 2659-2664. (g) Wang, Y.; Gan, J.; Liu, L.; Yuan, H.; Gao, Y.; Liu, Y.; Zhao, Y., *J. Org. Chem.* **2014**, *79*, 3678-3683. (h) Zhao, Z.; Xue, W.; Gao, Y.; Tang, G.; Zhao, Y., *Chem. Asian J.* **2013**, *8*, 713-716. (i) Zhang, X.; Liu, H.; Hu, X.; Tang, G.; Zhu, J.; Zhao, Y., *Org. Lett.* **2011**, *13*, 3478-3481. For phosphorus-phosphorus bond formation, see: (j) Zhou, Y.; Yin, S.; Gao, Y.; Zhao, Y.; Goto, M.; Han, L.-B., *Angew. Chem. Int. Ed.* **2010**, *49*, 6852-6855. For reaction mechanism studies, see: (k) Fan, J.; An, K.; Wang, X.; Zhu, J. *Organometallics* **2013**, *32*, 6271–6276. (l) Huang, C.; Hao, Y.; Zhao, Y.; Zhu, J. *Organometallics,* **2014**, *33*, 817–822. (m) Zhu, C.; Luo, M.; Zhu, Q.; Zhu, J.; Schleyer, P. v. R.; Wu, J.; Lu, X.; Xia, H. *Nat. Commun.* **2014**, *5*, 3265. (n) Zhu, J.; An, K. *Chem. Asian J.* **2013**, *8*, 3147-3151. (o) Liu, L.; Yuan, H.; Fu, T.; Wang, T.; Gao, X.; Zeng,

Z.; Zhu, J.; Zhao, Y., *J. Org. Chem.* **2014**, *79*, 80-87. (p) Liu, L.; Zhang, S.; Chen, H.; Lv, Y.; Zhu, J.; Zhao, Y., *Chem. Asian J.* **2013**, *8*, 2592-2595. (q) Liu, L.; Wu, Y.; Wang, T.; Gao, X.; Zhu, J.; Zhao, Y., *J. Org. Chem.* **2014**, *79*, 5074-5081.

9. (a) Frisch, M. J.; et al. Gaussian 03, Revision E.01; Gaussian, Inc.: Wallingford, CT, 2004. (b) Frisch, M. J.; et al. Gaussian 09, Revision B.01; Gaussian, Inc.: Wallingford, CT, 2010.
10. (a) Lee, C.; Yang, W.; Parr, R. G., *Phys. Rev. B* **1988**, *37*, 785−789. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J., *J. Phys. Chem.* **1994**, *98*, 11623−11627.
11. (a) Zhang, T.; Wang, C.; Liu, S.; Wang, J.-L.; Lin, W., *J. Am. Chem. Soc.* **2014**, *136*, 273-281. (b) Zhang, S.; Çelebi-Ölçüm, N.; Melzer, M. M.; Houk, K. N.; Warren, T. H., *J. Am. Chem. Soc.* **2013**, *135*, 16746-16749. (c) Shanmugam, M.; Wilcoxen, J.; Habel-Rodriguez, D.; Cutsail Iii, G. E.; Kirk, M. L.; Hoffman, B. M.; Hille, R., *J. Am. Chem. Soc.* **2013**, *135*, 17775-17782. (d) Peterson, R. L.; Ginsbach, J. W.; Cowley, R. E.; Qayyum, M. F.; Himes, R. A.; Siegler, M. A.; Moore, C. D.; Hedman, B.; Hodgson, K. O.; Fukuzumi, S.; Solomon, E. I.; Karlin, K. D., *J. Am. Chem. Soc.* **2013**, *135*, 16454-16467. (e) Haack, P.; Kärgel, A.; Greco, C.; Dokic, J.; Braun, B.; Pfaff, F. F.; Mebs, S.; Ray, K.; Limberg, C., *J. Am. Chem. Soc.* **2013**, *135*, 16148-16160. (f) Eberhart, M. S.; Norton, J. R.; Zuzek, A.; Sattler, W.; Ruccolo, S., *J. Am. Chem. Soc.* **2013**, *135*, 17262-17265.
12. Dunning Jr. T. H.; Hay P. J., *in Modern Theoretical Chemistry*, Ed. H. F. Schaefer III, Vol. 3 (Plenum, New York, 1976) 1-28.
13. Wadt, W. R.; Hay, P. J., *J. Chem. Phys.* **1985**, *82*, 284−298.
14. (a) Hollwarth, A.; Bohme, M.; Dapprich, S.; Ehlers, A. W.; Gobbi, A.; Jonas, V.; Kohler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G., *Chem. Phys. Lett.* **1993**, *208*, 237−240. (b) Ehlers,

A.; Böhme, M.; Dapprich, S.; Gobbi, A.; Höllwarth, A.; Jonas, V.; Köhler, K.; Stegmann, R.; Veldkamp, A.; Frenking, G., *Chem. Phys. Lett.* **1993**, *208*, 111−114.

15. Bondi, A., *J. Phys. Chem.* **1964**, *68*, 441−451.

16. Dolg, M.; Wedig, U.; Stoll, H.; Preuss, H., *J. Chem. Phys.*, **1987**, *86*, 866-72.

17. (a) Krishan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A., *J. Chem. Phys.* **1980**, *72*, 650−654. (b) McLean, A. D.; Chandler, G. S., *J. Chem. Phys.* **1980**, *72*, 5639−5648. (c) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. V. R., *J. Comput. Chem.* **1983**, *4*, 294−301.

18. (a) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N., *J. Am. Chem. Soc.* **2014**, *136*, 344-355. (b) Hong, X.; Trost, B. M.; Houk, K. N., *J. Am. Chem. Soc.* **2013**, *135*, 6588-6600.

19. (a) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H., *J. Chem. Phys.* **2010**, *132*, 154104. (b) Grimme, S., *J. Comput. Chem.* **2006**, *27*, 1787-1799. (c) Grimme, S., *J. Comput. Chem.* **2004**, *25*, 1463-1473.

20. Legault, C. Y. CYLview, 1.0b; Université de Sherbrooke: Sherbrooke, Québec, Canada, 2009; www.cylview.org.

21. A brilliant yellow precipitate of Cu(I) phenylacetylide, see: (a) Shao, C.; Cheng, G.; Su, D.; Xu, J.; Wang, X.; Hu, Y., *Adv. Synth. Catal.* **2010**, *352*, 1587-1592. (b) Cataldo, F.; Ursini, O.; Angelini, G.; Tommasini, M.; Casari, C., *J. Macromol. Sci., Part A: Pure Appl. Chem.*, **2010**, *47*, 739-746.

22. A general synthesis of ynamides and alkynylphosphonates using alkynylcopper reagents was reported recently: Jouvin, K.; Heimburger, J.; Evano, G., *Chem. Sci.* **2012**, *3*, 756-760.

23. (a) Ginsbach, J. W.; Kieber-Emmons, M. T.; Nomoto, R.; Noguchi, A.; Ohnishi, Y.; Solomon, E. I.

Proc. Natl. Acad. Sci. U.S.A. **2012**, *109*, 10793−10797. (b) Fukuzumi, S.; Karlin, K. D. *Coord. Chem. Rev.* **2013**, *257*, 187−195. (c) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Chem. Rev.* **2004**, *104*, 1013−1045. (d) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047−1076. (e) Qayyum, M. F.; Sarangi, R.; Fujisawa, K.; Stack, T. D. P.; Karlin, K. D.; Hodgson, K. O.; Hedman, B.; Solomon, E. I., *J. Am. Chem. Soc.* **2013**, *135*, 17417-17431.

24. (a) Kraszewski, A.; Stawinski, J. *Pure Appl. Chem.* **2007**, *79*, 2217-2227. (b) Shaikh, T. M.; Weng, C.-M.; Hong, F.-E. *Coord. Chem. Rev.* **2012**, *256*, 771-803. (c) Allefeld, N.; Grasse, M.; Ignat'ev, N.; Hoge, B., *Chem. Eur. J.* **2014**, DOI: 10.1002/chem.201402425. (d) The gas-phase free energies of tricoordinated $(MeO)_2POH$ and Ph_2POH are 4.6 and 1.2 kcal/mol higher than those of tetracoordinated $(MeO)_2P(O)H$ and $Ph_2P(O)H$, respectively.

25. For the recent studies of mix-valence copper cores, see: (a) Okubo, T.; Kuwamoto, H.; Kim, K. H.; Hayami, S.; Yamano, A.; Shiro, M.; Maekawa, M.; Kuroda-Sowa, T., *Inorg. Chem.* **2011**, *50*, 2708-2710. (b) Halvagar, M. R.; Solntsev, P. V.; Lim, H.; Hedman, B.; Hodgson, K. O.; Solomon, E. I.; Cramer, C. J.; Tolman, W. B., *J. Am. Chem. Soc.* **2014**, *136*, 7269-7272.

26. We estimate the barrier value from the Eyring equation, i.e., $k = (k_BT/h)\exp(-\Delta G^{\ddagger}/RT)$, where k is rate constant, k_B is Boltzmann's constant, h is Planck's constant, $\Delta G^{\ddagger}$ is the activation free energy, R is the gas constant, and T is the temperature. Assuming the concentration of each reactant is 1 mol/L and the second-order rate constant k of a reaction whose half life is 24 h is 1.2×10^{-5} L/mol • s, we obtain $\Delta G^{\ddagger}$ is 26.7 kcal/mol at 55 °C.

27. Tukov, A. A.; Normand, A. T.; Nechaev, M. S., *Dalton Trans.* **2009**, 7015-7028.

28. Corfield, P. W. R.; Shearer, H. M. M., *Acta Crystallogr.* **1966**, *21*, 957-965.

29. Li, X.; Yang, F.; Wu, Y.; Wu, Y., *Org. Lett.* **2014**, *16*, 992-995.

30. Evano, G.; Tadiparthi, K.; Couty, F., *Chem. Commun.* **2011**, *47*, 179-181.

31. Hu, J.; Zhao, N.; Yang, B.; Wang, G.; Guo, L.-N.; Liang, Y.-M.; Yang, S.-D., *Chem. Eur. J.* **2011**, *17*, 5516-5521.