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Communication

Alkynylphosphine Oxide Synthesis

Room-Temperature Alkynylation of Phosphine Oxides with Copper Acetylides: Practical Synthesis of Alkynylphosphine Oxides

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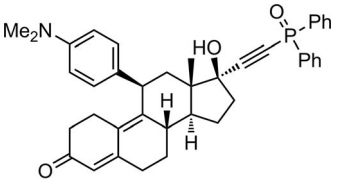
Abstract: An efficient procedure for the synthesis of alkynylphosphine oxides based on the oxidative alkynylation of secondary phosphine oxides with copper acetylides was developed. Activation with molecular oxygen in the presence of either a mixture of 1,2-dimethylimidazole and triethylamine or *N*-methylimidazole alone enabled the formal umpolung of the poorly nucleophilic copper acetylides, which were coupled with phosphine oxides under remarkably mild conditions. Notable features of this procedure are the availability of the starting materials, its user-friendliness, and its mild conditions, which allow the synthesis of complex alkynylphosphine oxides.

Introduction

Heterosubstituted alkynes have been known for decades, and their chemistry has recently been extensively reinvestigated owing to the development of remarkably efficient and robust methods for their synthesis.[1] The renaissance of the chemistry of nitrogen-substituted alkynes is quite representative of this evolution, and the development of general processes for their synthesis has clearly had a dramatic impact on their use as building blocks in chemical synthesis.[2] A similar trend was recently observed with oxygen/sulfur-substituted alkynes, the chemistry of which has also been recently invigorated.[3] In sharp contrast, less attention has been paid to their phosphorus analogues, despite their strong potential as precursors of a wide range of phosphorus-containing molecules.[4] Besides the classical routes to phosphorus-substituted alkynes that are mostly based on elimination reactions from the corresponding vinylic halide/pseudohalide derivatives or the reaction of a metal acetylide with a halophosphine or a derivative, efficient alternatives based on metal-mediated reactions have been recently reported and offer efficient and attractive alternative synthetic routes.

In this context, we recently reported that a wide range of nucleophiles could be efficiently alkynylated by reaction with readily available copper acetylides under oxidative conditions. This method provides a straightforward entry to a series of acetylene derivatives including ynamides, ynimines, trifluoromethylated alkynes, and alkynylarenes as well as alkynylphosphonates and alkynylphosphine–boranes.[5] Motivated by the efficiency of these reactions and their attractiveness, we next decided to study the alkynylation of secondary phosphine oxides: results from these studies are reported in this manuscript.

Besides further expanding the synthetic usefulness of the oxidative alkynylation with copper acetylides, our main motivation lied in the fact that this reaction might provide a valuable and user-friendly entry to alkynylphosphine oxides, useful building blocks with chemistry that is clearly underrated. They have indeed been shown over the years to be suitable starting materials for a number of transformations including, to cite a few, conjugate addition,[6] hydrophosphinylation,[7] and [4+2],[8] [3+2],[9] and [2+2+2][10] cycloaddition reactions. The phosphine oxide moiety was also recently shown to be an efficient protecting group for terminal alkynes.[11] The alkynylphosphine oxide moiety can, in addition, be found in molecules from the pharmaceutical industry such as in progesterone receptor antagonist **1** (Figure 1).[12]



1 (progesterone receptor antagonist, *Johnson & Johnson*)

Figure 1. Example of the use of alkynylphosphine oxides in medicinal chemistry.

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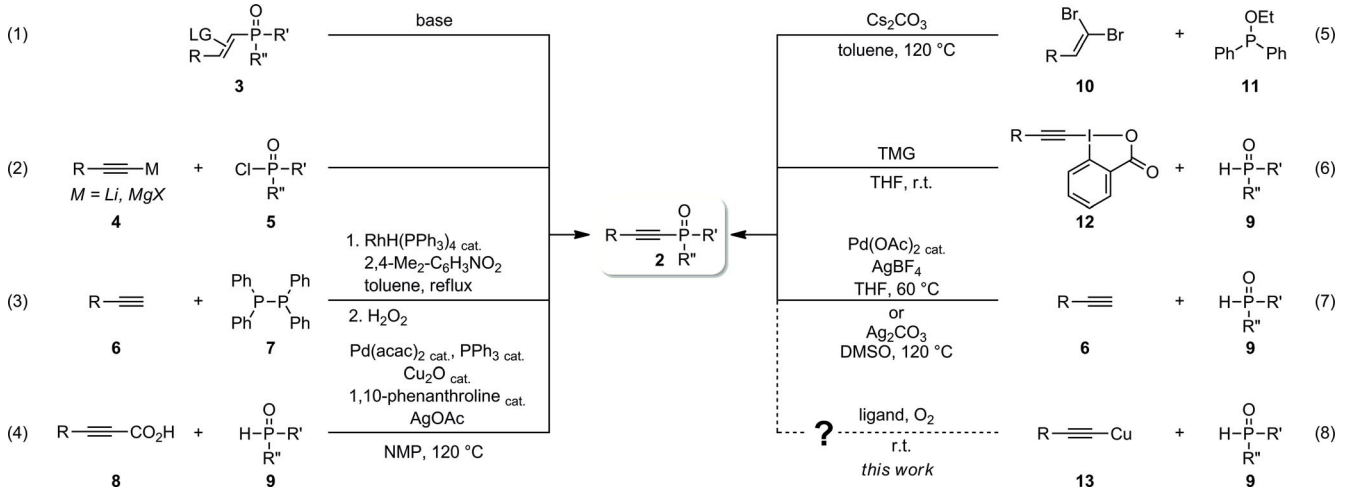

Scheme 1. Classical [equations (1) and (2)], recently reported [equations (3)–(7)], and proposed routes to alkynylphosphine oxides; acac = acetylacetone, NMP = *N*-methylpyrrolidone, TMG = 1,1,3,3-tetramethylguanidine.

Whereas their usefulness need not be further demonstrated, the synthesis of alkynylphosphine oxides is, however, still not always a trivial task and can be hampered by the stability, toxicity, and availability of the reagents needed or simply by the reaction conditions required that are not always compatible with various functional groups. These problems, frequently met with classical syntheses of alkynylphosphine oxides **2** that rely on elimination from halogenated alkenylphosphine oxides **3** [Scheme 1, (1)] or reaction of metal acetylides **4** with electrophilic chlorophosphine oxides **5** [Scheme 1, (2)], have been – at least partially – addressed with some recently reported improved procedures.

Indeed, various research groups have tried to tackle this problem, and this resulted in the development of new routes to alkynylphosphine oxides **2**. They include the rhodium-catalyzed cross-coupling of terminal alkynes **6** with tetraphenylbiphosphine (**7**) followed by oxidation of the intermediate alkynylphosphine [Scheme 1, (3)],[13] the copper/palladium co-catalyzed decarboxylative cross-coupling of phosphine oxides **9** with propiolic acids **8** [Scheme 1, (4)],[14] and the cesium carbonate promoted reaction of ethyl diphenylphosphinite (**11**) with *gem*-dibromoalkenes **10** [Scheme 1, (5)].[15] Although these procedures undoubtedly enable the preparation of alkynylphosphine oxides **2** through unconventional strategies, they still suffer from major limitations such as low substrate scope, limited availability of the starting materials required, and/or harsh reaction conditions. Major breakthroughs in this area were only reported in 2014 and 2015 by the Waser, Chen/Han, and Gao/Lei groups, who developed general routes to alkynylphosphine oxides on the basis of the alkynylation of phosphine oxides **9** with ethynylbenziodoxolone (EBX) reagents **12** at room temperature [Scheme 1, (6)][16] and with terminal alkynes **6** in the presence of a palladium catalyst or a stoichiometric amount of silver carbonate [Scheme 1, (7)].[17] On the basis of these results and limitations remaining for the synthesis of alkynylphosphine oxides, we decided to study an alternate route based on the oxidative alkynylation of secondary phosphine oxides **9** with bench-stable copper acetylides **13** [Scheme 1, (8)].[18] The results of these studies are reported herein.

Results and Discussion

With this goal in mind, the feasibility and the optimization of the reaction was first addressed by using oct-1-ynylcopper (**13a**) with diphenylphosphine oxide (**9a**) as model substrates. We initially chose to use 3 equiv. of the latter to minimize the Glaser–Hay dimerization of the former, which would give **14**, and selected, for practical reasons, oxygen as the oxidant at room temperature for 15 h: selected results from this optimization step are shown in Figure 2. On the basis of the influence of the solvent on both the oxidative alkynylation of heteronucleophiles[5] and the equilibrium between the tautomeric pentavalent $P^{V}\sigma^{4}\lambda^{5}$ and trivalent $P^{III}\sigma^{3}\lambda^{3}$ forms, we naturally chose first to evaluate the influence of the nature of the solvent on our model system (Figure 2, step A). The efficiency of representative solvents including THF, toluene, dioxane, dichloromethane, and DMF was evaluated with *N*-methylimidazole (NMI, 2 equiv.), which was arbitrarily chosen as the ligand. To our pleasure, we observed the formation of the desired alkynylphosphine oxide **2a** upon using dichloromethane or DMF, although it was obtained in rather modest yields (14 %). Given that phosphine oxides are, in general, more soluble in DMF than in dichloromethane, we moved to the next step of the optimization with DMF as the solvent. We next screened a series of six different nitrogen ligands, which were selected on the basis of our experience with copper acetylides (Figure 2, step B). Whereas bidentate ligands such as *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine (TMEDA), 2,2′-bipyridine, and 1,10-phenanthroline, used in a 1:1 ratio with respect to the copper acetylide, were totally inefficient or displayed only little efficiency to promote the oxidative alkynylation, the use of 2 equiv. of a monodentate ligand was found to be more efficient and 1,2-dimethylimidazole (DMI) turned out to be the ligand of choice. Evaluation of the optimal amount of this ligand surpris-

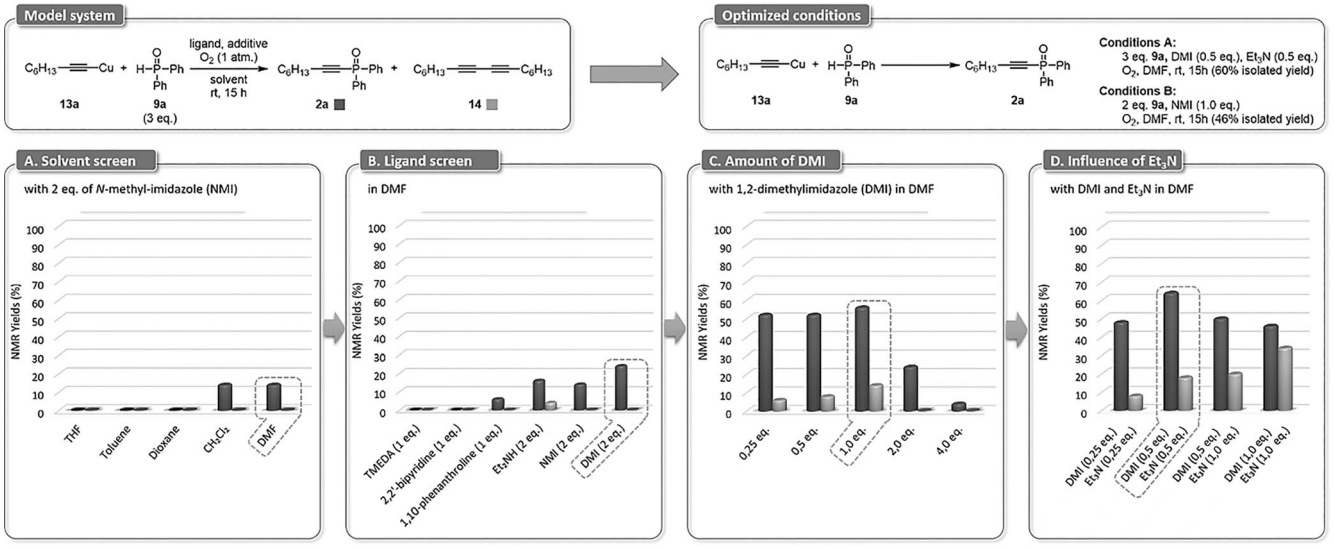

Figure 2. Optimization of the oxidative alkynylation of diphenylphosphine oxide with oct-1-ynylcopper, yields were determined by analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy with the use of diphenylmethane as an internal standard.

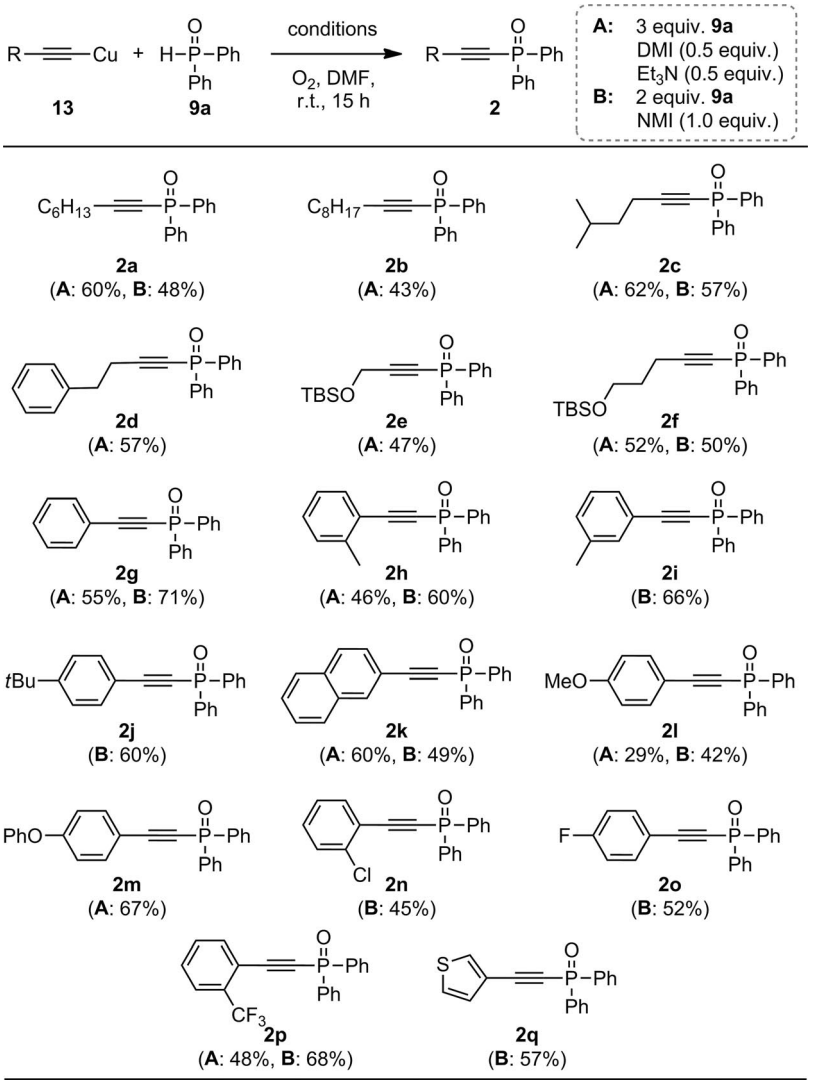

Figure 3. Scope and limitations studies: alkynylation of diphenylphosphine oxide with representative copper acetylides; TBS = *tert*-butyldimethylsilyl.

ingly revealed that the use of 1 equiv. was superior than 2 equiv. (Figure 2, step C) and led to the formation of the expected alkynylphosphine oxide **2a** in 56 % yield, as determined by NMR spectroscopy. Further analysis of the influence of various additives finally revealed a synergistic effect between DMI and triethylamine and the use of 0.5 equiv. of each was found to be efficient, which yielded **2a** in 64 % yield (determined by NMR spectroscopy); it was isolated in 60 % yield (Figure 2, step D). The optimized conditions (conditions A), therefore, rely on the use of 3 equiv. of the phosphine oxide in combination with 0.5 equiv. of both DMI and triethylamine under an atmosphere of oxygen in DMF at room temperature for 15 h. In an attempt to reduce the amount of the starting phosphine oxide, which could be critical in the case of either expensive or complex phosphine oxides, we performed a second round of optimization (data not shown), which led to alternative conditions (conditions B) involving 2 equiv. of the starting phosphine oxide and 1 equiv. of NMI.

With this set of two optimized reaction conditions, we next moved to the study of the scope of the oxidative alkynylation. We therefore first evaluated the reactivity of a set of representative copper acetylides **13** for the alkynylation of diphenylphosphine oxide (**9a**). Bench-stable polymeric reagents **13** were readily prepared by simple reaction of the corresponding terminal alkynes with copper iodide in aqueous ammonia and ethanol or in the presence of potassium carbonate in DMF followed by simple filtration of **13**, which precipitated from the reaction mixtures.[5a] Results from these scope and limitation studies, shown in Figure 3, clearly show that the oxidative alkynylation of diphenylphosphine oxide is fairly general and yields the corresponding alkynylphosphine oxides **2** in fair-to-good yields, even if the dimerization of the starting acetylides could not be totally suppressed in all cases. The dimers could, in general, be easily separated from the desired products, which were obtained regardless of the electronic and steric properties of the substituents on the starting copper acetylides. Indeed, alkyl-substituted (see products **2a**–**f**) and (hetero)aryl-substituted (see products **2g**–**q**) alkynylphosphine oxides were readily obtained at room temperature. In the latter cases, the substitution pattern and the electron-withdrawing/donating effect of the aryl substituent did not have a pronounced effect on the outcome of the reaction, even if a general trend for the reactivity of the starting copper acetylide could not be easily drawn from these experiments, which might be due to different polymeric structures. Notably, primary silyl ethers such as **2e** and **2f** were compatible with the reaction conditions. The two sets of reaction conditions (A and B) were found to be quite complementary, and the first one was slightly superior if starting from alkyl-substituted copper acetylides, whereas the second one was superior if an aryl-substituted copper acetylide was used for the oxidative alkynylation.

After extensively studying the reactivity of diphenylphosphine oxide under our optimized conditions, we next moved to the reactivity of a set of representative phosphine oxides possessing two or one aryl substituent or no aryl substituent at all, as such substituents could potentially strongly impact the efficiency of the oxidative alkynylation owing to strong modifications of both the pK_a and the coordination properties. As shown by the results collected in Figure 4, we were delighted to note that all classes of phosphine oxides performed relatively well under our reaction conditions. The presence of an aryl bromide in the starting phosphine oxide, yielding **2r**, was in addition well tolerated and no side products resulting from competitive Castro–Stephens alkynylation were observed.[19] In

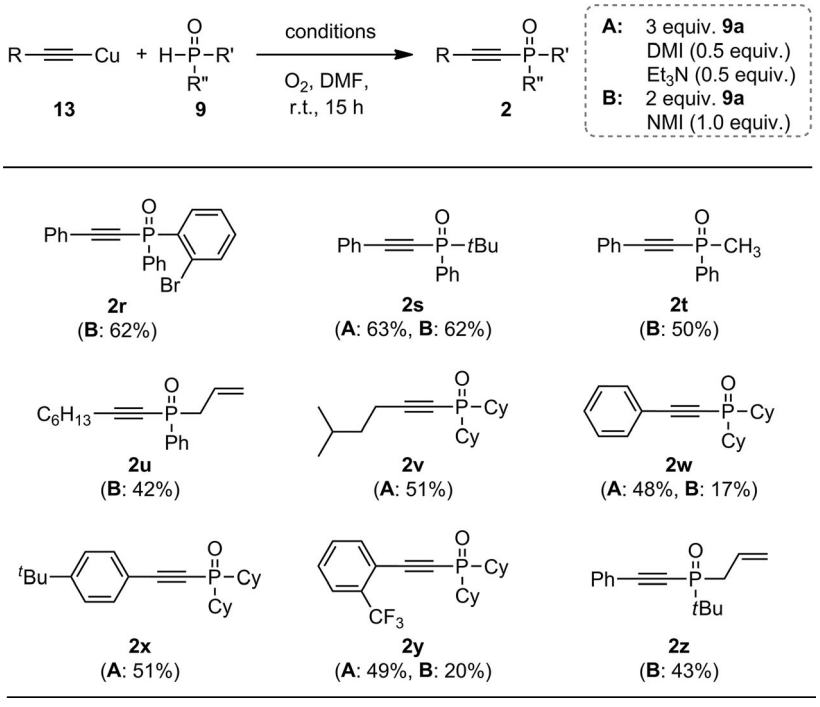

Figure 4. Scope and limitations studies: alkynylation of representative phosphine oxides with copper acetylides; Cy = cyclohexyl.

this case, a trace amount of an alkenylphosphine oxide resulting from competitive addition of the phosphine oxide across the triple bond was observed.[18,20] *P*-Aryl,*P*-alkyl as well as *P*,*P*-dialkyl phosphine oxides also gave corresponding alkynylation products **2s**–**u** and **2v**–**z**, even in the presence of a bulky *tert*-butyl group, which often blocks the reactivity of phosphorus nucleophiles in cross-coupling reactions, and sensitive allylic positions. In the case of two different substituents on starting alkynylphosphine oxide **9** (R′ ≠ R″), it ought to be mentioned that conditions B, which rely on the use of 2 equiv. of the starting phosphine oxide rather than 3 equiv., are probably more appropriate.

To take further advantage of the mildness of the reaction conditions, we next briefly explored the reactivity of more complex and/or sensitive copper acetylides, the use of which could result in the preparation of alkynylphosphine oxides that could be extremely challenging to synthesize with other methods owing either to tedious preparation of the starting materials that would be required or to the reaction conditions themselves in which sensitive functional groups would not be tolerated. Examples of such alkynylphosphine oxides shown in Figure 5, which include epoxide (see product **2aa**), amino acid (see products **2ab** and **2ac**), and steroid (see product **2ad**) derivatives, clearly showcase the potential of the method reported in this manuscript for the preparation of alkynylphosphine oxide derivatives and its potential use in medicinal chemistry.

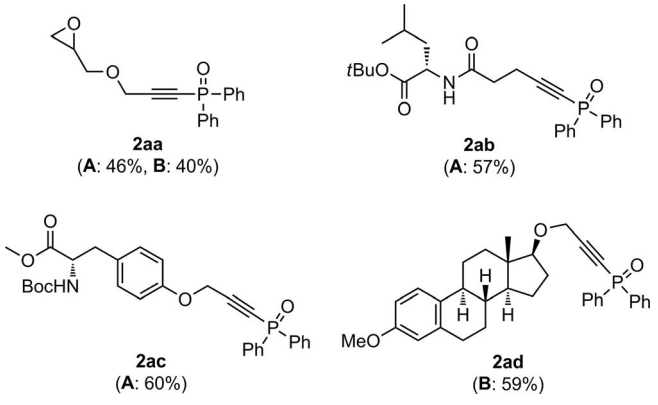

Figure 5. Oxidative alkynylation with complex/sensitive copper acetylides; Boc = *tert*-butoxycarbonyl.

Conclusions

In conclusion, we reported an efficient synthesis of alkynylphosphine oxides under mild conditions from readily available copper acetylides. Upon simple activation with molecular oxygen at room temperature, they were shown to be especially convenient reagents for the alkynylation of secondary phosphine oxides. The mildness of the reaction conditions, the ease of operation, and the availability/stability of copper acetylides, which are readily prepared by cupration of the corresponding terminal alkynes with copper iodide, should render this process quite attractive for the preparation of alkynylphosphine oxides, at least for cases in which an excess amount of the phosphine oxide can be used. As an important closing note, whereas a catalytic version of this reaction based on the direct use of a terminal alkyne in the presence of a copper catalyst might seem more appealing – at least in terms of "atom economy" – the use of a preformed, readily prepared copper acetylide is, in general, much more practical and efficient, as deactivation of the catalyst as a result of chelation of the P-nucleophile is, in addition, an important issue for the formation of C–P bonds relying on the use of copper-based catalytic systems.

Overall, the process reported in this manuscript should contribute to expand further both the usefulness of copper acetylides in synthesis and the chemistry of phosphorus-substituted alkynes.

Experimental Section

General Procedure for the Synthesis of Alkynylphosphine Oxides under Conditions A: A 5 mL round-bottomed flask was successively charged with the secondary phosphine oxide (750 μmol), the alkynylcopper reagent (250 μmol), and DMF (1.0 mL). Triethylamine (20 μL, 125 μmol) and 1,2-dimethylimidazole (10 μL, 125 μmol) were then added, and the resulting mixture was vigorously stirred at room temperature under an oxygen atmosphere (balloon) for 15 h. The mixture was then poured into a 1:1 mixture of saturated ammonium chloride and ammonium hydroxide (25 % aqueous solution). The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The crude residue was finally purified by flash column chromatography (silica gel) to afford the desired alkynylphosphine oxide.

General Procedure for the Synthesis of Alkynylphosphine Oxides under Conditions B: A 2 mL round-bottomed flask was successively charged with the secondary phosphine oxide (500 μmol), the alkynylcopper reagent (250 μmol), and DMF (1.0 mL). *N*-Methylimidazole (20 μL, 250 μmol) was then added, and the resulting mixture was vigorously stirred at room temperature under an oxygen atmosphere (balloon) for 15 h. The blue-green mixture was then poured into a 1:1 mixture of saturated ammonium chloride and ammonium hydroxide (25 % aqueous solution). The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The crude residue was finally purified by flash column chromatography (silica gel) to afford the desired alkynylphosphine oxide.

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Keywords: Synthetic methods · Umpolung · Cross-coupling · Copper · Alkynes · Phosphanes

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