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Unprecedented Synthesis of Alkynylphosphine-boranes through Room-Temperature Oxidative Alkynylation

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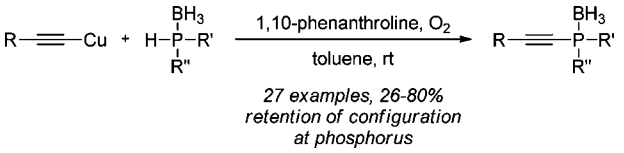
ABSTRACT



An original and user-friendly synthesis of alkynylphosphine-boranes, useful building blocks in organic synthesis, based on an oxidative P-alkynylation reaction with readily available copper acetylides is reported. The ability of a secondary phosphine protected with a borane to undergo oxidative coupling without oxidation of the P-moiety is demonstrated for the first time. The reaction, which proceeds at room temperature, is applicable to the preparation of enantioenriched and structurally complex alkynylphosphine-boranes.

Heterosubstituted alkynes are among the most useful and versatile building blocks in organic synthesis with applications in medicinal chemistry or material science.[1−3] The rich and diverse chemistry of the alkynyl function allows for the introduction of a broad array of functionalities into organic molecules. Taking advantage of the strong polarization of the triple bond resulting from the presence of the heteroatom, heterosubstituted alkynes have been extensively used for the design of remarkably efficient and highly regio- and stereoselective transformations. In addition, the development of intramolecular reactions from these heterosubstituted alkynes enabled the emergence of new paradigms in heterocyclic chemistry.

While nitrogen-substituted alkynes (ynamines and ynamides)[1] and oxygen/sulfur-substituted acetylenes (alkynyl(thio)ethers)[2] have been extensively studied during the past decade, the chemistry of their phosphorus analogues, and especially alkynylphosphines and alkynylphosphine-boranes, have been far less investigated.[3] They however represent a class of heterosubstituted alkynes which holds great potential for the development of metal-catalyzed reactions, as demonstrated recently by the groups of Imamoto and Sawamura who used them as efficient ligands in asymmetric rhodium-catalyzed hydrogenation and conjugated addition reactions,[4] asymmetric palladium-catalyzed alkylative ring-opening reactions,[4] and gold-catalyzed cyclization of acetylenic β-ketoesters

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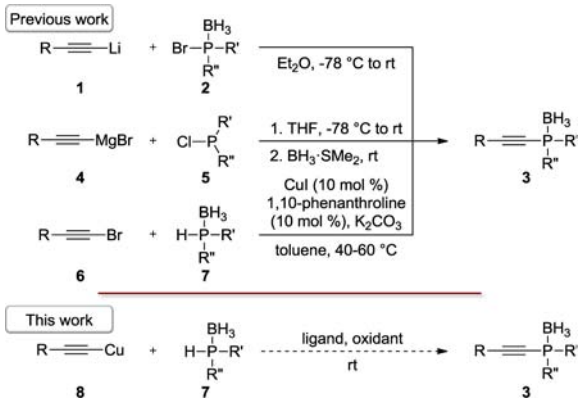
or acetylenic silyl enol ethers.[5] Alkynylphosphine-boranes have also been used as substrates in regio- and stereoselective carbocuprations and hydroaluminations, reactions that further demonstrated their potential in organic synthesis.[6b]

As for most classes of heterosubstituted alkynes, difficulties associated with their synthesis have considerably hampered their full development. Most existing routes suffer from limitations in terms of yields, scope, and reaction conditions when they do not rely on the use of toxic or nonpractical reagents. Indeed, alkynylphosphine-boranes **3**, stable precursors of alkynylphosphines, are typically prepared by the reaction between bromophosphine-boranes **2** and lithium acetylides **1**[4] or by borane complexation of alkynylphosphines, *in situ* generated from chlorophosphines **5** and acetylenic Grignard reagents **4** (Scheme 1).[6] More recently, **3** have been shown to be conveniently prepared by a copper-catalyzed direct alkynylation of secondary phosphine-boranes **7** with bromoalkynes **6**.[7] Catalytic protocols based on the use of terminal alkynes and nickel or copper complexes were also proposed recently for the synthesis of alkynylphosphines[8a,b] and alkynylphosphonates.[8c]

Scheme 1. Previously Reported Syntheses of Alkynylphosphine-boranes and Strategy Based on Copper Acetylides



In continuation of our studies on the development of new syntheses of heterosubstituted alkynes[7,9] and on the use of readily available and bench-stable copper acetylides for the alkynylation of heteronucleophiles under mild conditions,[10] we envisioned that alkynylphosphine-boranes **3** could be obtained by reacting secondary phosphine-boranes **7** with stable, readily available copper acetylides **8** in the presence of a chelating ligand and an oxidant (Scheme 1).[11] The well-known high sensitivity of phosphines toward oxidation motivated our choice of using their borane complexes.[12] Provided that the oxidative transfer of the alkynyl group from copper to phosphorus from alkynylcopper **8** is faster than their dimerization and the oxidation of **7**, this would offer a useful and user-friendly entry to alkynylphosphine-boranes **3** under mild conditions.

To test this challenging hypothesis, dicyclohexylphosphine-borane **7a** and octynylcopper **8a** were chosen as model substrates for the optimization step. Among all possible oxidants, oxygen was chosen for obvious practical reasons, and to minimize the dimerization of **8a**, 2 equiv of **7a** were used. Toluene was selected as the solvent in order to avoid a possible competitive decomplexation of both phosphine-boranes **7a** and **3a**, known to occur with coordinating and/or basic solvents.[7a] For the same reason, strongly chelating and basic ligands such as diamines were discarded from this study and the efficiency of an excess of various imidazole- or pyridine-type mono- or bidendate conjugated *N*-ligands to promote the alkynylation at room temperature without any additional base was evaluated (Figure 1).[13]

While 2,2′-bipyridine was surprisingly inefficient to activate the copper acetylide in the presence of oxygen, all other *N*-ligands were found to be suitable promoters, with various efficiencies however. Indeed, while the use of pyridine and 1-methyl-imidazole resulted in the formation of the desired alkynylphosphine-borane **3a** as the major product, neither the homodimerization of the starting copper acetylide **8a** leading to **10** nor the deborylation/oxidation yielding considerable amounts of alkynylphosphine oxide **9** could be suppressed. The former could be avoided with the more electron-rich 1,2-dimethylimidazole, but the use of this ligand still resulted in 22% of **9**. Gratifyingly, switching to 1,10-phenanthroline resulted in the clean formation of alkynylphosphine-borane **3a**, which could be isolated in 75% yield, together with traces of diyne **10** (2%) and phosphine oxide **9** (5%). In an effort to further optimize the reaction conditions, we next evaluated the

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(13) Preliminary experiments using 2 equiv of monodentate *N*-ligands or 1 equiv of bidentate *N*,*N*-ligands resulted in clean reactions but low yields, presumably due to *in situ* borane decomplexation and coordination of the resulting alkynylphosphine to copper(II) salts. Excess ligand would allow trapping the copper salts and avoid decomplexation.

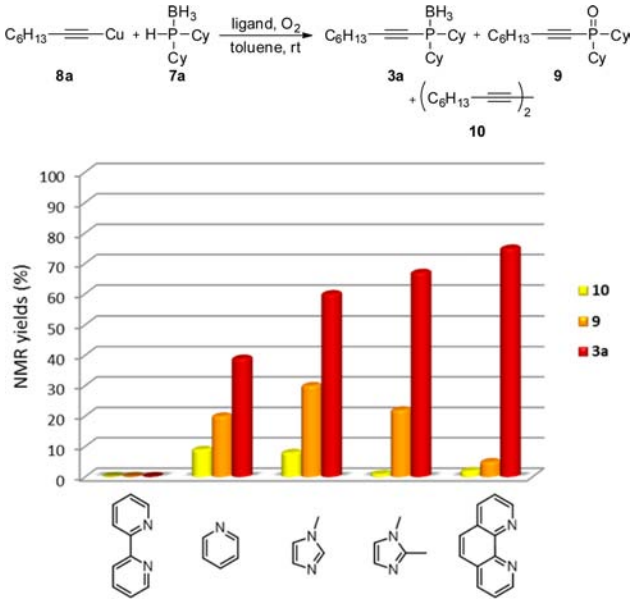


Figure 1. Compared efficiency of N-ligands for the alkynylation of dicyclohexylphosphine-borane. Standard conditions: 0.12 mmol of **8a**, 0.24 mmol of **7a**, 0.6 mmol (if bidentate) or 1.2 mmol (if monodentate) of ligand, 1 atm of O_2, 0.3 mL of toluene, rt, 8 h.

possibility of decreasing the amount of phosphine-borane. By using 1.5 equiv instead of 2, the isolated yield of **3a** (70%) was minimally affected: thus a 1:1.5 ratio between reagents **8** and **7** was kept for the scope and limitation studies.

With the optimized conditions in hand, we next moved to evaluate the scope of this reaction. Toward this goal, a variety of copper acetylides **8**[10a] were reacted with dicyclohexylphosphine-borane **7a** using these optimized reaction conditions (Figure 2). A variety of dicyclohexyl(alkynyl)-phosphine-boranes **3a**–**s** could be obtained by simply treating a solution of dicyclohexylphosphine-borane **7a** with the appropriate copper acetylide **8** in the presence of an excess of 1,10-phenanthroline (5 equiv) under an atmosphere of oxygen at rt for 8 h. The corresponding alkynylphosphine-boranes **3** were obtained in fair-to-good yields, regardless of the nature of the substituent of the starting copper acetylide **8**. Indeed, alkyl- (**3a**-**f**), carboxy- (**3h**), vinyl- (**3i**), or aryl- (**3j**–**s**) substituted alkynylphosphine derivatives could be obtained with similar efficiencies, except when starting from a copper acetylide containing an unprotected alcohol which failed to give the corresponding alkynylated product **3g**. In the case of aryl-substituted copper acetylides, the nature and position of the substituents had little effect on the outcome of the reaction. Compared to the alkynylation with bromoalkynes, it ought to be mentioned that this procedure is especially convenient, from a practical point of view, for the synthesis of alkynylphosphine-boranes substituted with small chains (such as **3c**, **3d**, or **3i**), the bromoalkynes that would be required for their synthesis, being highly volatile and strongly lachrymator.

The reaction scope was also investigated with respect to the phosphorus-nucleophile using octynylcopper **8a** and

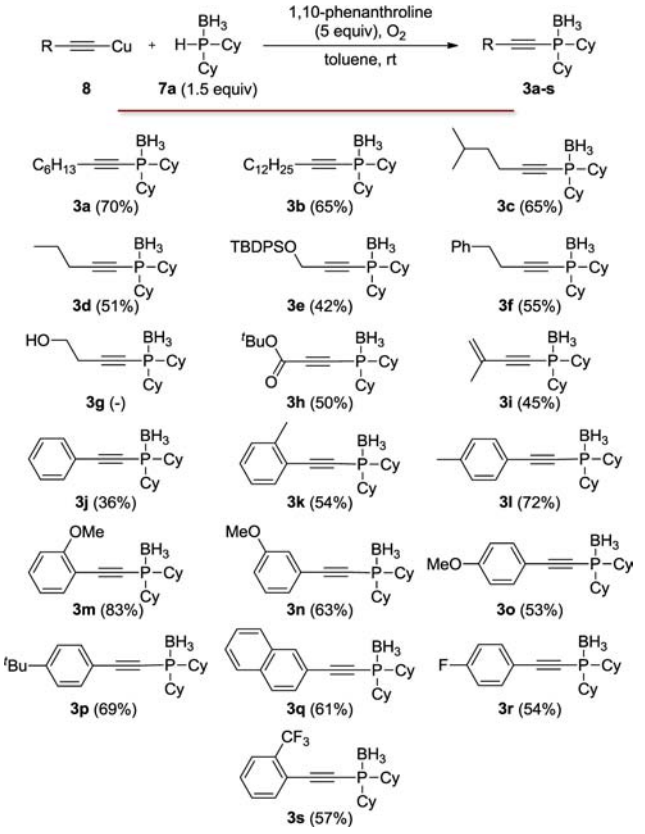


Figure 2. Oxidative alkynylation of dicyclohexylphosphine-borane with representative copper acetylides.

various phosphine-boranes **7** (Figure 3). While the nature of the copper acetylide was found to have little influence on the outcome of the reaction, a marked difference in reactivity was observed with the various phosphine-boranes evaluated. Steric hindrance strongly affected the reaction, with bulky substituents on **7** favoring the dimerization of octynylcopper **8a**. While an isopropyl group was tolerated on the starting phosphine borane, with the resulting alkynylphosphine-borane **3u** being obtained in 70% yield, the presence of one (**3w**) or two (**3x**) *tert*-butyl

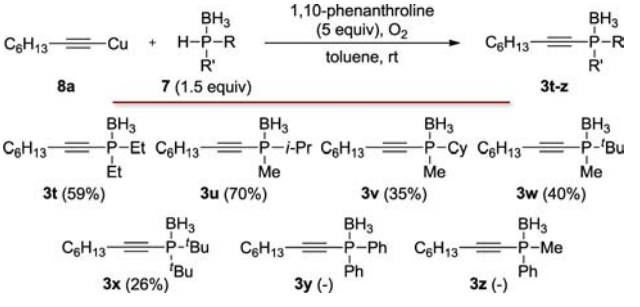
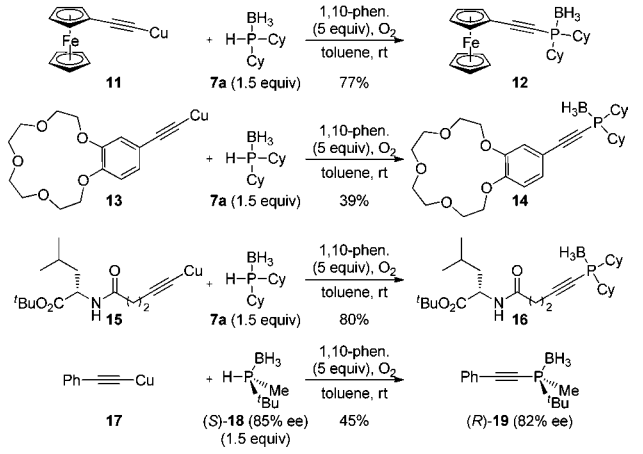


Figure 3. Oxidative alkynylation of representative phosphine-boranes with octynylcopper.

Scheme 2. Oxidative Alkynylation of Phosphine-boranes with More Complex Substrates

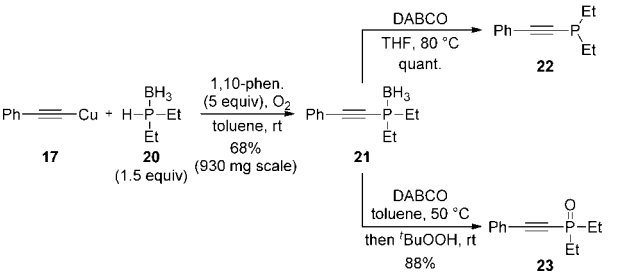


groups had a detrimental effect on the reaction. The bulky alkynylated phosphine-boranes were however formed, although in modest yields, which is quite remarkable since di-*tert*-butylphosphine derivatives are typically poor partners in cross-coupling reactions.[14] The electronic property of phosphine-borane **7** was found to be a crucial parameter, with the presence of one (**3y**) or two (**3z**) aryl groups completely inhibiting the alkynylation.

Compared to other syntheses, a major advantage of our procedure lies in the mildness of the reaction conditions which do not require the use of strongly nucleophilic and basic reagents such as lithium acetylides or heating. Therefore, and to further test our procedure and demonstrate its synthetic utility, the preparation of more complex alkynylphosphine-boranes was briefly investigated. To this end, readily available ferrocene, benzo-15-crown-5 ether, and leucine derived copper acetylides **11**, **13**, and **15** were reacted with dicyclohexylphosphine-borane **7a** under our standard conditions (Scheme 2). Except in the case of **13**, which gave the corresponding alkynylphosphine-borane **14** in a modest 39% yield, **11** and **15** were smoothly transformed to the corresponding alkynylphosphine-boranes **12** and **16** with high efficiency, therefore demonstrating further the synthetic utility of our procedure. The stereochemical outcome of the oxidative alkynylation was also addressed starting from optically enriched phosphine-borane **18** (85% ee).[4] Upon reaction with phenylethynylcopper **17**, a clean alkynylation occurred with retention of configuration, yielding enantiomerically enriched alkynylphosphine-borane **19** (82% ee), with almost no erosion of optical purity.

The scale-up of the reaction and the postfunctionalization of alkynylphosphine-boranes was finally evaluated (Scheme 3). Indeed, we could demonstrate that the reaction is not limited to the small scale (0.24 mmol) used for

Scheme 3. Gram-Scale Synthesis of Alkynylphosphine-boranes and Postfunctionalization



the oxidative cross-coupling reactions described above, as it could be conveniently performed from 1 g of commercially available phenylethynylcopper **17**, yielding the corresponding alkynylphosphine-borane **21** in 68% yield. Further decomplexation with DABCO[15a] in THF under argon then smoothly gave alkynylphosphine **22**, a compound that cannot be efficiently obtained by a direct alkynylation of diethylphosphine which mostly gave pyrophosphate $Et_2P(O)-O-P(O)Et_2$. In addition, decomplexation and subsequent treatment with *tert*-butylhydroperoxide[15b] directly converted **21** into alkynylphosphine oxide **23**.

In conclusion, we have developed an efficient and practical synthesis of alkynylphosphine-boranes, useful building blocks that can be obtained in a simple manner by reaction with readily available copper acetylides in the presence of 1,10-phenanthroline and oxygen at room temperature. The successful use of secondary dialkylphosphine-boranes as coupling partners under oxidative conditions is unprecedented and solves the problem of using highly oxidable secondary phosphines. This should contribute to further extension of the synthetic utility of alkynylphosphine derivatives in organic synthesis and expand the oxidative chemistry of organocopper compounds. Application of this oxidative alkynylation to other nucleophiles is under study and will be reported in due time.

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Supporting Information Available. Experimental procedures, characterization, copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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