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Ambient Temperature Hydrophosphination of Internal, Unactivated Alkynes and Allenyl Phosphineoxides with Phosphine Borane Complexes

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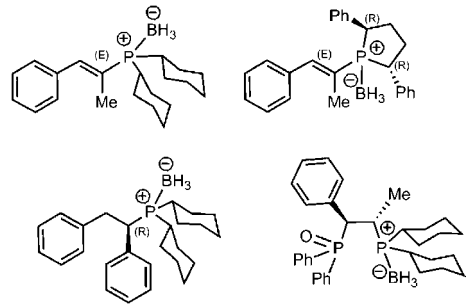
ABSTRACT



Phosphine boranes have been found to hydrophosphinate internal, unactivated alkynes at room temperature under basic conditions without the need for catalysts or radical initiators. The use of air-sensitive secondary phosphines is avoided in this facile process. Broad scope in both the phosphine borane and alkyne partners leads to excellent diversity in the phosphine products. Asymmetric hydrogenation of these species then provides one of the shortest possible routes to chiral monodentate phosphines. Hydrophosphination of allenyl phosphine oxides under similar conditions followed by hydrogenation of the exomethylene moiety yields a wide variety of bis-phosphine derivatives.

We have recently reported on the use of BIPI 153, a novel P−N ligand capable of carrying out asymmetric hydrogenations with near-perfect enantioselectivity.[1] The key C−P bond-forming reaction in the synthesis of this chiral ligand is an S_NAr reaction between fluoroimidazoline **1** and a phosphine borane (Figure 1). As part of a continuing investigation of conformational restriction in these ligands, we prepared alkynyl fluoroimidazoline **2** and subjected it to our standard S_NAr conditions. To our surprise, no trace of the expected product was found; rather, a vinylphosphine borane **3** (Scheme 1) was generated via regiospecific hydrophosphination of the internal alkyne.[2] The regiochemistry and stereochemistry of **3** were easily established through the application of two successive heteronuclear NOE (HOESY) experiments with ^{19}F and ^{31}P, respectively.[3] It was quickly determined that neither the fluorine or imidazoline moieties

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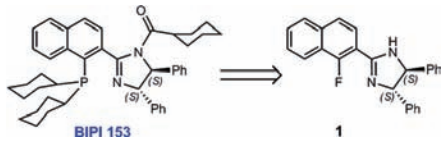
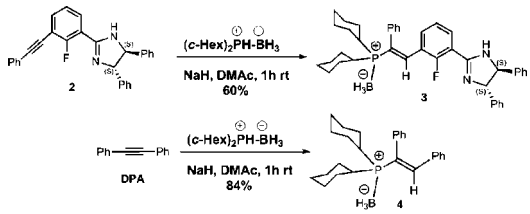


Figure 1. BIPI 153 and S_NAr substrate.

were required for reactivity, as diphenylacetylene gave the product of internal hydrophosphination **4** under the same conditions (Scheme 1).

Scheme 1. Alkyne Hydrophosphinations

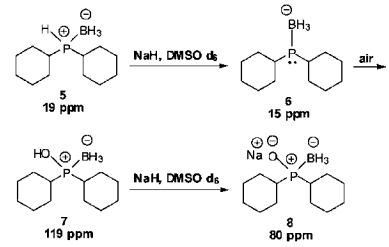


The addition of free secondary phosphines to alkynes has been known for more than 40 years[4] and continues to be a method used for the synthesis of vinyl phosphines.[4d] Hydrophosphination of alkynes with secondary phosphines has also been accomplished with catalysis by various transition metals,[5] and silylphosphines have been similarly utilized.[6a] From the point of view of process safety and raw material handling, however, the ability to utilize an air-stable phosphine borane[6b] in a process rather than a pyrophoric free phosphine confers an enormous advantage. All of the hydrophosphinations described here proceed without the need for catalysis or the use of pyrophoric materials, and can even be performed with *catalytic* base.[6c] Here the presumed vinyl anion intermediate likely deprotonates the phosphine borane starting material.

Phosphine boranes have been added to *terminal* alkynes under thermal[7a] and palladium-catalyzed[7b] conditions, yet additions to internal, unactivated alkynes of the current work have not been previously reported. Secondary phosphine oxides have also been utilized for the hydrophosphination of alkynes using both thermal[4e] and metal-catalyzed[8a,b] methods, as have *H*-phosphinates,[8c] yet these of course require a subsequent reduction to yield the desired phosphines.

We established a single experimental protocol for the hydrophosphinations and applied it to all substrates. We used the conditions previously optimized for the S_NAr reaction, namely NaH (60% in oil, untreated) in DMAc at ambient temperature. A finding of considerable practical importance was made during the course of this work which led to a key modification for the reaction protocol. We discovered that phosphine borane anions such as those prepared here will oxidize in air to phosphinous acid boranes. These organophosphorus species have been previously described, prepared by reduction of secondary phosphine oxides with borane.[9] This oxidation has been achieved with N_2O,[10] yet we are unaware of any reports describing this air oxidation. Scheme 2 shows the chemical shifts of all relevant species as

Scheme 2. Oxidation and NMR Shifts



determined by ^{31}P NMR spectroscopy. Under the basic conditions of the hydrophosphination (and the ligand S_NAr reactions), the anion (**8**) of the phosphinous acid borane is ultimately formed. We therefore changed our experimental protocol: The phosphine borane, alkyne, and DMAc were first charged to the reactor, and then argon or nitrogen was bubbled beneath the solution surface for 15 min prior to the addition of NaH, which initiates the hydrophosphination. This serves to remove dissolved oxygen and allowed us to reduce the phosphine borane charge from 2 equiv to 1.2 equiv. This

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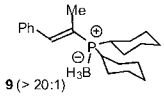
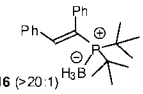
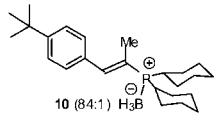
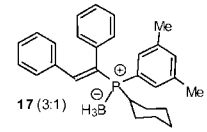
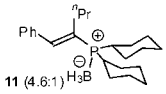
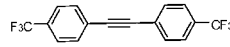
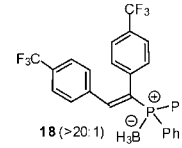
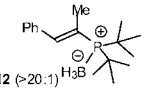
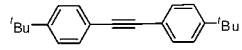
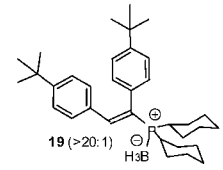
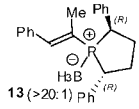
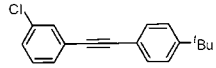
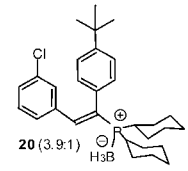
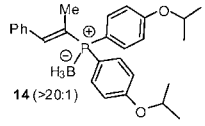
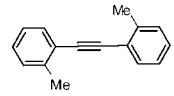
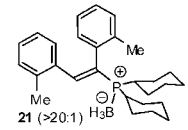
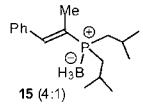
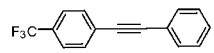
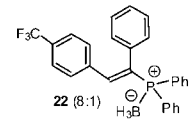
Table 1. Hydrophosphination of Internal Alkynes*

alkyne	time (h)	yd (%)[a]	product (*E*:*Z*)[b]	alkyne	time (h)	yd (%)[a]	product (*E*:*Z*)[b]
	1	85	 **9** (> 20:1)		36	88[d]	 **16** (>20:1)
	6	76	 **10** (84:1)		24	80[c]	 **17** (3:1)
	4	83	 **11** (4.6:1)		0.3	98[d]	 **18** (>20:1)
	36	84	 **12** (>20:1)		1	87	 **19** (>20:1)
	16	59	 **13** (>20:1)		1	81	 **20** (3.9:1)
	36	78[c]	 **14** (>20:1)		24	99[d]	 **21** (>20:1)
	0.50	79	 **15** (4:1)		0.8	67[d]	 **22** (8:1)

* All reactions at rt. All reactions with 1 equiv of alkyne, 1.2 equiv of phosphine borane, 1.2 equiv of 60% NaH/oil, in DMAc, unless otherwise noted. Average concentrations: [0.47 M] (PB), [0.35 M] (alkyne). [a] Isolated yield (*E* + *Z*) after crystallization and/or chromatography. [b] Overall *E*/*Z* ratio after purification. [c] 1.5 equiv of phosphine borane used. [d] 2.0 equiv of phosphine borane used.

phosphine borane anion oxidation is also the explanation behind the unusual stoichiometric requirements for the original ligand S_NAr reaction previously noted.[1a]

With the experimental procedure thus established, we set out to determine the scope with respect to both the secondary phosphine borane and the internal alkyne. The results obtained using eight different alkynes and seven different phosphine boranes are shown in Table 1.

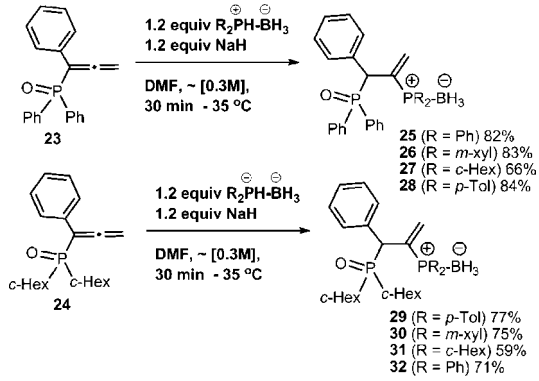
Phenylalkylalkynes were found to react with a variety of phosphine boranes at room temperature, furnishing products **9**−**13**. The sterically demanding di-*tert*-butyl- and *m*-xylylphosphine boranes reacted readily, as did diphenyl phospholane phosphine borane (**12** and **13**). In general, mixtures of *E* and *Z* olefins were obtained, with the *E* by far the major (or exclusive) isomer formed.

We then examined diphenylacetylene, and vinyl phosphine boranes **14**−**16** were all prepared in good yield from this alkyne. Five additional diarylacetylenes were then examined, providing products **17**−**22**.

We found that the presence of a single electron-withdrawing substituent on a nonsymmetric diarylacetylene was sufficient to give high regiocontrol (**20**, **22**) for the addition. The bis(*o*-tolyl)acetylene was prepared, and it was found to react efficiently with dicyclohexyl phosphine borane to furnish **21** in excellent yield. We carried out this experiment specifically because this substrate was reported[4f] to be unreactive toward a free secondary phosphine. Thus the current protocol not only provides a safer and more convenient experimental method, but also gives access to targets that cannot be prepared by other approaches.

We have also examined the reactivity of allenyl phosphine oxides **23** and **24**, which were each prepared in one step by a well-established propargylic rearrangement reaction.[12] Each of these extremely reactive substrates was hydrophosphinated (Scheme 3) *in minutes* at −35 °C furnishing the mixed

Scheme 3. Synthesis of Bisphosphines

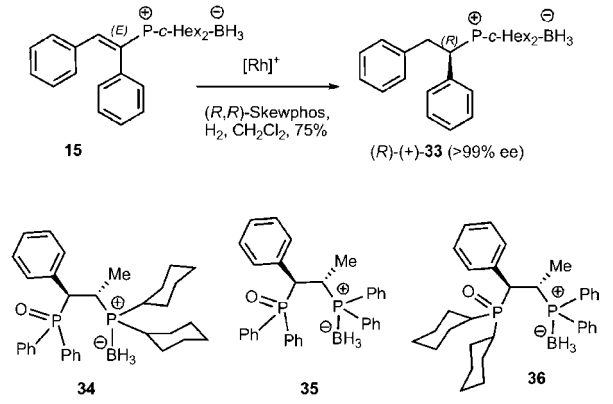


phosphine oxide−phosphine boranes **25**−**32** in good yield. We switched the solvent from DMAc to DMF here to take advantage of the lower freezing point of the latter. Hydrophosphination of allenes with hypophosphorous acids[13] and secondary phosphines[5d] are known. No examples of allene hydrophosphination with phosphine boranes have been previously reported.

These mixed species should be quite valuable synthetically. Deprotection of the phosphine borane would furnish a bis-phosphine monooxide (BPMO), a class of ligands for a variety of metal-catalyzed reactions[14] which have been the subject of several recent reviews.[14a,d] Reduction of the phosphine oxide would yield a bis-phosphine, and these are probably the single most important class of bidentate ligands in all of catalysis.

To demonstrate the utility of these novel phosphine intermediates for the development of a unique family of phosphine ligands for many catalytic processes, we first screened a number of hydrogenation conditions for our vinyl phosphine boranes. A Rh-(*R*,*R*)-Skewphos catalyst system was identified as suitable for olefin reduction without disturbing the phosphine borane (Scheme 4). Applying this hydrogenation to **15** furnished chiral phosphine borane (*R*)-

Scheme 4. Vinylphosphine Functionalizations



(+)−**33** in >99% ee. The synthesis and use of chiral monodentate phosphines has become an extremely active area of recent research with applications to many different types of asymmetric transformations.[15] The hydrophosphination/hydrogenation sequence described here provides one of the shortest possible routes to these targets. Hydrogenation of **27**, **25**, and **32** with tricyclohexylphosphine as ligand furnished bis-phosphines **34**, **35**, and **36**, respectively. In each case, a single species was observed by NMR, showing that the hydrogenations had proceeded with complete control of the relative stereochemistry to give the *trans*-species shown (Scheme 4). Since dialkyl- and diaryl-substitution on phosphorus is tolerated for both the allene synthesis and the hydrophosphination, broad diversity in the substituents on *each* phosphorus atom can be achieved.

In summary, we have discovered that phosphine borane anions will hydrophosphinate internal unactivated alkynes and allenyl phosphine oxides at ambient temperature or below, without the need for catalysts, radical initiators, or microwave heating. The former class of vinylphosphine boranes can be hydrogenated to optically pure monodentate phosphines, while the latter class can be converted stereoselectively to bis-phosphine derivatives. The reactions utilize easily handled and stable phosphine boranes, and show good scope with respect to both the multiple bond electrophile and phosphine borane partners. The creation of chiral monodentate phosphine libraries for screening in asymmetric catalysis as well as performing the allene hydrophosphinations with control of the absolute stereochemistry are under active investigation and will be reported in due course.

Supporting Information Available: Full experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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