

Synthesis of Z-Alkenyl Phosphorus Compounds through Hydroalumination and Carbocupration of Alkynyl Precursors

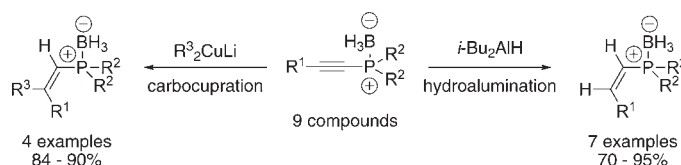
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ABSTRACT



The stereocontrolled synthesis of Z-alkenylphosphine–borane complexes is easily accomplished via the hydroalumination or carbocupration of alkynyl precursors. Z/E ratios are generally higher than 95/5. These reactions are stereocomplementary to our olefination approach.

Organophosphorus compounds are key synthetic intermediates, especially for the preparation of phosphine ligands. Among them, conjugated alkenyl phosphorus derivatives are of particular interest since the carbon–carbon double bond can be functionalized further. A variety of methods have been reported for the preparation

of alkenyl phosphines, their borane complexes, and their oxides.¹ These include metal-catalyzed cross-coupling, olefin metathesis, and hydrophosphination and related reactions. The wealth of literature references is an indication of the intense activity in this field.¹ Similarly, a plethora of methods exists to prepare variously substituted alkenyl phosphonates.²

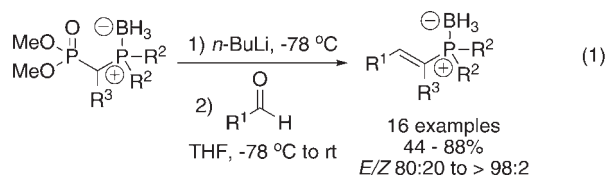
Recently, we reported a simple and general method to access a variety of alkenylphosphorus compounds via carbonyl olefination with mixed 1,1-bisphosphorus reagents.³

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The reaction proceeds with high *E*-stereoselectivity (typically >98:2, eq 1). However, attempts at accessing *Z*-isomers through the modification of the reagents were unsuccessful. In terms of methodology, stereoselectivity is critically important, and the ability to prepare either stereoisomer highly desirable. We therefore set out to develop a stereocomplementary approach, and we are now disclosing a successful and general solution to this problem.



Our approach parallels chemistry that was developed for alkynyl phosphonates, in significant part the fruit of Srebnik's efforts.⁴ The first step was therefore to prepare alkynylphosphine–borane complexes. Very few compounds of this type have been reported previously, none of which are phosphonite–borane complexes.⁵ Unsurprisingly, deprotonation of a terminal alkyne followed by reaction with a chlorophosphine and complexation with borane delivered good yields of products (Table 1).

Table 1. Preparation of alkynylphosphine–Borane Complexes^a

entry	R ¹	R ²	product	isolated yield (%)
1	<i>n</i> -hexyl	EtO	1	50
2	phenyl	EtO	2	86
3	3-chloropropyl	EtO	3	73
4	H	EtO	4	75 ^b
5	<i>n</i> -hexyl	Ph	5	76
6	3-chloropropyl	Ph	6	73
7	H	Ph	7	58 ^b
8	<i>n</i> -hexyl	<i>i</i> -Pr	8	84
9	phenyl	<i>i</i> -Pr	9	94

^aFor experimental details, see the Supporting Information. ^bPrepared from commercially available ethynylmagnesium bromide.

(4) For example, see: (a) Sinelnikove, Y.; Rubinstein, A.; Srebnik, M.; Al Quntar, A. A. *Tetrahedron Lett.* **2009**, *50*, 867. (b) Quntar, A. A.; Rosenthal, D.; Srebnik, M. *Tetrahedron* **2006**, *62*, 5995. (c) Al-Quntar, A. A.; Srebnik, M. *J. Organomet. Chem.* **2005**, *690*, 2504. (d) Ben-Valid, S.; Quntar, A. A.; Srebnik, M. *J. Org. Chem.* **2005**, *70*, 3554. (e) Rochdi, A.; Taourirte, M.; Lazrek, H. B.; Barascut, J. L.; Imbach, J. L. *Molecules* **2000**, *5*, 1139. (f) Cristau, H.-J.; Pirat, J.-L.; Drag, M.; Kafarski, P. *Tetrahedron Lett.* **2000**, *41*, 9781. Reviews: (g) Iorga, B.; Eymery, F.; Carmichael, D.; Savignac, P. *Eur. J. Org. Chem.* **2000**, 3103. (h) Minami, T.; Okauchi, T.; Kouno, R. *Synthesis* **2001**, 349.

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Our laboratory has been involved in developing the chemistry of phosphonite–borane complexes^{3,6} because these have proved useful as protected *H*-phosphinate equivalents. Therefore, alkyne **1** containing this functional group was first selected as starting material for conversion to the *Z*-olefin. Initially, reduction of **1** was attempted using Lindlar-type hydrogenation conditions.^{4f} However, these reactions were sluggish, gave a mixture of products, including some oxidation to the phosphonate, and the stereoselectivity was low (*Z/E* ~ 80:20). As a result, we turned our attention to uncatalyzed hydroalumination,⁷ specifically with diisobutylaluminum hydride (*i*-Bu₂AlH, DIBAL-H) since it is an inexpensive and easily handled reagent. Additionally, hydrometalation can also provide an alkenyl metal intermediate suitable for further elaboration. For example, Negishi and others have developed the hydroalumination (and carboalumination) of alkynes (both catalyzed and uncatalyzed) followed by cross-coupling as a powerful tool for the regio- and stereocontrolled synthesis of alkenes.⁸

Table 2 summarizes the results of hydroalumination/hydrolysis. Minor adjustments in stoichiometry, temperature, and reaction time led to excellent results. Only styrene compounds gave a slightly eroded *Z*-stereoselectivity (entries 2 and 7), while other alkynyl substrates gave rise to an essentially stereospecific reduction.

Table 2. *Z*-Alkenylphosphine–Boranes from Hydroalumination of Alkynyl Precursors^a

entry	alkyne	<i>n</i> equiv	time (h) (°C)	product	<i>Z/E</i> ratio	isolated yield (%)
1a	1	1.2	24 (rt)	10	>99:1	80
1b	1	1.2	2 (50)			81
2	2	2	4 (50)	11	95:5	70
3	3	1.2	24 (rt)	12	>99:1	95
4	5	2	4 (50)	13	>99:1	83 ^b
5	6	2	4 (50)	14	>99:1	93
6	8	2	4 (50)	15	>99:1	90
7	9	2	15 (50)	16	86:14	89

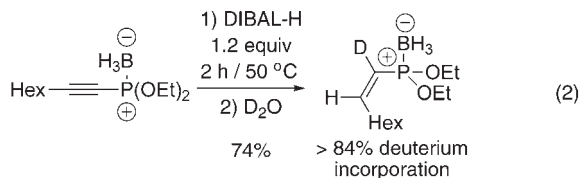
^aFor experimental details, see the Supporting Information. ^bKnown compound; see ref 10.

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As expected, the reaction proceeds through conjugate reduction. Deuterolysis following Table 2, entry 1, provided **10-d₁** in 74% yield, with the deuterium exclusively in the α -position of the phosphorus atom, and incorporation higher than 84% (eq 1). Unfortunately, preliminary experiments to functionalize the intermediate alkenylaluminum with other electrophiles were not very successful, but this will be investigated more fully in forthcoming studies.



Interestingly, the DIBAL-H mediated hydroalumination of an alkyne phosphonate diester (HexC≡CP(O)(OEt)₂) gave the known *E*-alkenyl stereoisomer^{2c} (>99:1), regardless of reaction time or temperature (69% isolated yield). It should be noted that the only example we could find of an alkenyl phosphonate synthesis involving hydroalumination is based on 1-octyne hydroalumination (DIBAL-H, cat. Cp₂ZrCl₂) followed by trapping with diethyl chlorophosphate to yield the *E*-alkenyl phosphonate (72% yield).⁹ On the other hand, hydroalumination of **2** with LiAlH₄ (0.5 equiv, rt, 4 h) gave mainly the corresponding *E*-alkenyl product (*E*-**11**) in 85% NMR yield (*E/Z* 87:13). Because this stereoselectivity was lower than in our olefination approach (*E/Z* > 98:2),³ this was not pursued further, but this result still indicates the possibility of preparing either alkenyl isomer through stereodivergent hydroalumination with the selection of the aluminum hydride reagent.

Many reactions have been applied to the functionalization of alkyne phosphonates,⁴ and therefore, several might be expected to be successful on our alkyne compounds. We chose to focus on carbocupration.¹⁰ With alkyne phosphonates, few literature precedents exist.¹¹ We found that standard cuprates (R₂CuLi) give the best results, as opposed to the RMgX/CuX (5:1) system.

Table 3 summarizes the carbocupration results. In all cases, good stereoselectivity was observed. Iodolysis of the intermediate organocopper could also be achieved in good yield to provide tetrasubstituted iodide **18** highly stereoselectively (entry 2). Other electrophilic trapping reactions, as well as metal-catalyzed cross-coupling of compounds like **18**, will be studied in the future, since the ability to prepare tetrasubstituted phosphine–borane complexes in a regio- and stereocontrolled manner is important.

As mentioned previously, phosphonite–boranes are of particular interest to us because they are potential precursors

Table 3. Carbocupration of Alkynephosphine–Boranes^a

entry	alkyne	product	Z/E ratio	isolated yield (%)	
1	2		17	96:4	84
2	2		18	1:99	72
3	2		19	94:6	88
4	4		20	>99:1	90
5	4		21	>99:1	90

^aFor experimental details, see the Supporting Information.

to *Z*-alkenyl-*H*-phosphinates, compounds which were only available through the palladium-catalyzed cross-coupling of *Z*-alkenyl halides.¹² Therefore, compounds **10–12** and **17** were deprotected using refluxing ethanol (Table 4).¹³ The corresponding *H*-phosphinate esters **22–25** were obtained in high yield, although once again, the stereoselectivity for the styrene case (entry 2) was problematic, and in fact, *E*-**23** was the major product. Although we initially had hoped that compound **12** would undergo in situ decomplexation/Arbuzov to form the corresponding heterocycle (2,3-dihydrophosphorinanic acid ethyl ester), this reaction did not take place in useful yields.

Even trisubstituted **17** could be deprotected without any significant isomerization. Since these stereoisomers are difficult to obtain, as our metal-catalyzed hydrophosphinylation of terminal alkynes only provides the *E*-alkenyl-*H*-phosphinates,¹⁴ the present methodology significantly expands the scope of accessible *H*-phosphinates. Even if the reaction times are long for deprotection with EtOH the reaction mixtures were very clean, and other methods either failed (HBF₄) or gave complex mixtures

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Table 4. Deprotection of the Phosphonite–Boranes^a

entry	alkene	product	<i>Z/E</i> ratio	isolated yield (%)
1	10	22	>99:1	77
2	11	23	47:53	77
3	12	24	>99:1	91
4	17	25	>99:1	83

^aFor experimental details, see the Supporting Information.

(amines).¹⁵ The stereocontrolled access to phosphine–borane complexes is also important due to these compounds' role in ligand synthesis.

In conclusion, we have developed a simple and general method to access alkenyl phosphine–borane complexes stereoselectively. In combination with our olefination approach, a wide variety of substituted alkenylphosphorus compounds is now readily accessible. Furthermore, the preparation of *Z*-alkenyl-*H*-phosphinates is significant

because those compounds have only been available through cross-coupling reactions requiring relatively rare *Z*-alkenyl halides. Considering the broad importance of alkenyl phosphorus derivatives, the preparation of alkenyl metal intermediates (for example, through carboalumination or carbomagnesiation) and their functionalization will be investigated in future work, in order to access tri- and tetra-substituted products. The availability of these alkenyl phosphorus compounds also opens up possibilities to study their reactivity in reactions involving the carbon–carbon double bond to include asymmetric transformations. Unlike chemistry based on alkynyl- and alkenylphosphonates, which is now a rather mature area of research, the one corresponding to phosphine–borane complexes holds much untapped synthetic potential to be unleashed for future development.

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Supporting Information Available. Representative experimental procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.