**The Phospha-Bora-Wittig Reaction**

Andryj M. Borys, Ella F. Rice, Gary S. Nichol, Michael J. Cowley*

School of Chemistry, The University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ

**ABSTRACT:** Here, we report the phospha-bora-Wittig reaction for the direct preparation of phosphaalkenes from aldehydes, ketones, esters, or amides. The transient phosphaborene Mes*P=BNR₂ reacts with carbonyl compounds to form 1,2,3-phosphaboroaxetanes, analogues of oxaphosphetane intermediates in the classical Wittig reaction. 1,2,3-phosphaboroaxetanes undergo thermal or Lewis acid/base-promoted cycloreversion, yielding phosphaalkenes. Experimental and density functional theory studies reveal far-reaching similarities between classical and phospha-bora-Wittig reactions.

Phosphaalkenes are closely related to alkenes. The similar electronegativity of carbon and phosphorus makes C=P π bonds structurally and chemically similar to alkenes, albeit with narrower HOMO-LUMO gaps as a result of the weaker 2p-3p π bond. Because the replacement of C=C with C=P units alters frontier orbital energies without significantly polarizing the π-system, phosphaalkenes are attractive building blocks for main-group π-conjugated molecules and materials. Their advance from laboratory curiosity to accessible and synthetic access to their analogues of excited similar to the Wittig reaction, the latter is less well developed and understood. Few mechanistic studies have been made. Furthermore, the reported 'phospha-Wittig' reagents can be unstable or challenging to prepare. Phosphinidene transfer reactions are generally limited to aldehydes or activated carbonyl compounds. A widely-applicable method of preparing phosphaalkenes directly from a range of carbonyl compounds remains desirable.

![Figure 1. a) Key Examples of Phospha-Wittig Reagents; b) This Work](image)

- **a) Key Examples of Phospha-Wittig Reagents**

1. \( \text{(CO)}_2W\text{Ph} \rightarrow \text{PhOEt} \)
2. \( \text{Mes*} \)
3. \( \text{Ar} \)

**Mathey (1988)**

**Stephan (1995)**

**Protaśiewicz (1998)**

- **b) This Work**

\[ (\text{Mes*})_3\text{P}=\text{BNR}_2 \rightarrow \text{Mes*} \text{P}=\text{BNR}_2 \]

\[ X \rightarrow \text{Mes*} \text{P}=\text{BNR}_2 \]

\[ X = \text{H}, \text{alkyl}, \text{aryl}, \text{alkoxy}, \text{amino} \]

---

**Figure 1. a) Selected phospha-Wittig reagents; b) the phospha-bora-Wittig reaction reported here.**

We have recently demonstrated that transient phosphaborenes \( [\text{Mes*P}=\text{BNR}_2] \) (Mes* = 2,4,6-tri-tert-butylphenyl; NR₂ = 2,2,6,6-tetramethylpiperidine) can be accessed in solution and subsequently trapped by unsaturated compounds including phenylacetylene to give the corresponding formal [2+2] cycloaddition product. In 1986, Nöth reported that transient methyleneboranes \( [\text{R}=\text{C}=\text{BNR}'] \) undergo a Wittig-type reaction with ketones to give the corresponding alkenes. Considering the isoelectronic relationship between CR₂ and PR, and the reported reactivity of phosphinoboranes R₂PB(R')₂ with C=O bonds, we suspected that that phosphoborenes might be used to prepare phosphaalkenes. Here, we report the development of the 'phospha-bora-Wittig' reaction (Figure 1b). Using the stabilizing Mes* substituent at P, we demonstrate the synthesis of known and novel phosphaalkenes directly from a wide range of carbonyl compounds including ketones, aldehydes, esters and amides. We show that the reaction proceeds by a stepwise cycloaddition/cycloreversion mechanism, analogous to that considered operative in the classical Wittig reaction.

We initially investigated the reaction of diphosphadiboretane with benzophenone. Heating 1 with two equivalents of benzophenone. Heating 1 with two equivalents of benzophenone in C₆D₆ at 80 °C resulted in consumption of all...
starting materials and the emergence of new resonances at δ 15.4 and 38.6 in the $^{31}$P and $^{11}$B NMR spectra respectively. X-ray diffraction experiments on crystalline product confirmed the identity of the formal [2+2] cycloaddition product as 2a (Figure 2). 2a is analogous to the oxazaboretidines obtained from the reaction of iminoboranes with ketones and aldehydes.\textsuperscript{27} No evidence of the [4+2] cycloaddition product of 1 and benzophenone was observed spectroscopically\textsuperscript{.}\textsuperscript{28} However, addition of AlBr$_3$ (1 equivalent) immediately converted 2a-e into their corresponding phosphaalkenes 3a-e. The major initial boron-containing by-product resonates at δ 20.0 in the $^{11}$B NMR spectrum. Subsequent addition of pyridine (to sequester AlBr$_3$) led to the replacement of this signal with one at δ 22.3, which we assign to [R$_3$NBO].\textsuperscript{22} Al(III) halides promote the intramolecular decomposition of Mes*-substituted phosphaalkenes.\textsuperscript{30} We did not observe such reactivity except with super-stoichiometric (to 2a-e) quantities of AlBr$_3$. A preference for AlBr$_3$ complexation of [R$_3$NBO], (consistent with the $^{11}$B NMR signal at δ 20.0) over coordination to phosphaalkenes is thus likely. Conversion of 2a-e to phosphaalkenes could also be achieved with sub-stoichiometric quantities of AlBr$_3$, or N-heterocyclic carbene (see SI).

Phosphaalkenes 3a-e are conveniently prepared in one pot from 1 and the corresponding ketone or aldehyde. After formation of the 1,2,3-phosphaboroaxetanes 2a-e (80 °C, 2 hours), AlBr$_3$ addition affords known and novel phosphaalkenes 3a-e in good purity and yield (Figure 2a, 53-95%). Fluorenylidene phosphaalkenes (e.g. 3c) are promising components for organic materials based on their optoelectronic and redox properties.\textsuperscript{31–35}

Figure 2. a) Preparation of 1,2,3-phosphaboroaxetanes 2a-e and their subsequent conversion into phosphaalkenes 3a-e. (Mes* = 2,4,6-tri-tert-butylphenyl; NR$_2$ = 2,2,6,6-tetramethylpiperidino). b) Structure of 2a, thermal ellipsoids at 50% probability and hydrogen atoms omitted.

Diphosphadiboretane 1 also reacts cleanly with acetonitrile, forming the dimethyl 1,2,3-phosphaboroaxetane, 2b. In contrast (to P=B), N=B bonds react with the enol tautomer of acetonitrile by 1,2 addition.\textsuperscript{29} 9-fluorenol, isobutyaldehyde, or benzaldehyde also react with 1, forming 2c-2e. Aldehyde-derived 2d/2e have stereogenic P and C centers in their central PBCO ring. Only one of the expected two pairs of diastereomers of 2d/2e was observed spectroscopically; either 2d and 2e are formed stereospecifically, or inversion at phosphorus is facile. 2a-e were characterized by NMR spectroscopy and single-crystal X-ray diffraction (see SI).

1,2,3-phosphaboroaxetanes 2a-e are reminiscent of the four-membered oxetane intermediates in the classical Wittig reaction.\textsuperscript{30} We thus considered that their conversion into phosphaalkenes may be possible. Elimination of the O=BNR$_2$ fragment and its subsequent oligomerization would provide a thermodynamic incentive through B–O bond formation. The likelihood of such an elimination appears increased upon examination of the structures of 2a-e. For example, the structure of 2a (Figure 1b) reveals a planar, strained, central PBCO ring. The internal angles at C1 (92.07°(8)$^\circ$) and B1 (94.10°(9)$^\circ$) are particularly narrow. The NR$_2$ substituent at B1 is oriented to allow B=N π-bonding, leading to the short B1–N1 distance (1.410(2) Å).

We did not observe thermal elimination of phosphaalkenes from the 1,2,3-phosphaboroaxetanes 2a-e, even at elevated temperatures. However, addition of AlBr$_3$ (1 equivalent) immediately converted 2a-e into their corresponding phosphaalkenes 3a-e. The major initial boron-containing by-product resonates at δ 20.0 in the $^{11}$B NMR spectrum. Subsequent addition of pyridine (to sequester AlBr$_3$) led to the replacement of this signal with one at δ 22.3, which we assign to [R$_3$NBO].\textsuperscript{22} Al(III) halides promote the intramolecular decomposition of Mes*-substituted phosphaalkenes.\textsuperscript{30} We did not observe such reactivity except with super-stoichiometric (to 2a-e) quantities of AlBr$_3$. A preference for AlBr$_3$ complexation of [R$_3$NBO], (consistent with the $^{11}$B NMR signal at δ 20.0) over coordination to phosphaalkenes is thus likely. Conversion of 2a-e to phosphaalkenes could also be achieved with sub-stoichiometric quantities of AlBr$_3$, or N-heterocyclic carbene (see SI).

Phosphaalkenes 3a-e are conveniently prepared in one pot from 1 and the corresponding ketone or aldehyde. After formation of the 1,2,3-phosphaboroaxetanes 2a-e (80 °C, 2 hours), AlBr$_3$ addition affords known and novel phosphaalkenes 3a-e in good purity and yield (Figure 2a, 53-95%). Fluorenylidene phosphaalkenes (e.g. 3c) are promising components for organic materials based on their optoelectronic and redox properties.\textsuperscript{31–35}

Figure 3. Synthesis of phosphaalkenes 4a-c directly from esters and amides. (Mes* = 2,4,6-tri-tert-butylphenyl; NR$_2$ = 2,2,6,6-tetramethylpiperidino).

When diphosphadiboretane 1 was reacted with esters in place of ketones/aldehydes, direct conversion to the 2-alkoxy-phosphaalkene products occurred (Figure 3). For example, the reaction of 1 and ethyl acetate led to the new phosphaalkene 4a as a mixture (22:78) of E and Z isomers, identified by signals in the $^{31}$P{^1}H NMR spectrum at δ 120.1 and 104.4. $^{11}$B NMR spectroscopy revealed the formation of [R$_3$NBO],\textsuperscript{36} indicated by a resonance at δ 28.1, which we confirmed crystallographically. Monitoring the reaction of 1 and ethyl acetate by NMR spectroscopy revealed that it proceeds through a transient 1,2,3-phosphaboroaxetane intermediate: signals at δ –115.7 ($^{31}$P{^1}H) and δ 39.0 ($^{11}$B) are consistent with those for 2a-e (Figure S1). We extended the reaction of esters with 1 to α-pyrones to afford the exocyclic phosphaalkene 4b as a mixture (58:42) of E and Z isomers. We also prepared the known 2-aminophosphalkene 4c\textsuperscript{37} from 1 and N,N-dimethylacetamide. Phosphaalkenes 4a-c were easily isolated in high purity and yield (70-91%).
We used density functional theory calculations (M06-2X/def2svp) to probe the mechanism of the reaction of I with carbonyl compounds. The first step in the reaction pathway (Figure 4) is the dissociation of I into the monomeric phosphaborene INT-1.  

Phosphaborenes have orthogonal P=B and B=N π systems and can exhibit both nucleophilic (at P) and electrophilic (at B) reactivity. For the initial interaction with acetone, we thus considered i) formation of a betaine-like intermediate by attack of P at the carbonyl carbon, and ii) interaction of the carbonyl oxygen atom with boron. We could not locate betaine-type structures as minima. Instead, phosphaborene INT-1 and acetone react via TS1acetone (+20.07 kcal mol\(^{-1}\)) to form acetone adduct INT-2acetone (+20.10 kcal mol\(^{-1}\)).

Coordination of acetone to boron in INT-2acetone increases electrophilicity at the carbonyl carbon (C–O distance: 1.24 Å vs acetone, 1.20 Å). As a result, intramolecular attack of the phosphorus center at the carbonyl carbon occurs via the very early transition state TS2acetone (+22.32 kcal mol\(^{-1}\)), closing the 4-membered ring. The resulting isolable phosphaborene 2b is substantially stable relative to its precursors (−22.42 kcal mol\(^{-1}\)).

Phosphaborene INT-1 and acetamide follow an alternative pathway. Attempts to optimize acetamide counterparts of adduct INT-2acetone minimized only to INT-1 and acetamide. INT-1 and acetamide instead react by cycloaddition through TS2acetamide (+12.08 kcal mol\(^{-1}\)) to form the phosphaborene P(R)-C(S)-5c (−7.36 kcal mol\(^{-1}\)). The amino-phosphaboraoxetane 5c can exist as two pairs of diastereomers due to stereogenic P and C centers in the 4-membered ring. P(R)-C(S)-5c is less stable than its diastereomer P(S)-C(S)-5c relative to 0.5 I + acetamide (+0.99 vs −7.36 vs kcal mol\(^{-1}\)). We could not locate transition states leading to P(S)-C(S)-5c from INT-1 + acetamide; inspection of TS2acetamide reveals that inversion of either P or C centers would generate an unfavorable 1,2 steric interaction between Mes and NMe2 groups. Experimental insight into the stereochemistry of the intermediates 5c is limited by the ready interconversion of E and Z-phosphaalkenes.

Close inspection of the geometry of TS2acetone and TS2acetamide reveals that they adopt markedly different structures (Table S8). TS2acetone is highly puckered (P–B–O–C torsion = 48.8°) with a much more fully formed B–O than P–C bond (B–O distance 1.561 vs 2a 1.386 Å [−13%]; P–C 3.015 vs 1.921 Å [−57%]). In contrast, TS2acetamide has the developing P–C and B–O bonds form synchronously (B–O: 2.055 vs 1.393 Å [−48%]; P–C: 2.947 vs 1.974 Å [−49%]). The developing PBCO ring is much flatter (P–B–O–C torsion = −24.2°).

Why is TS2acetamide substantially lower in energy than TS2acetone? We ascribe this to two factors: i) the synchronous formation of P–C and B–O bonds in TS2acetamide proceeds with a lesser decrease in B–N π-bonding as the P=B=N angle is distorted from away from linear in TS2−2 (160° vs 129°); ii) The more planar P–B–C–O ring in TS2acetamide enables the formation of C–H⋯O hydrogen bonds between the amide oxygen and the methyl groups of the tetramethyipiperidine substituent at boron. The C–H⋯O distances, angles, and C=O⋯H angles in TS2acetamide (2.2–2.3 Å, 125–130°, and 135–145°, Table S10) are ideal for interactions of this kind, whereas those in the puckered TS2acetone are not (Table S9). Such interactions can amount to as much as 4 kcal mol\(^{-1}\) with optimum geometry.

The second barrier, for the cycloreversion of phosphaborenetanes 2b/5c to phosphaalkenes and transient [R2NBO] is much higher for 2b than it is for 5c (+38.77 vs +13.02 kcal mol\(^{-1}\)). The high energy of TS3acetone (+16.35 kcal mol\(^{-1}\)) is consistent
with the observed thermal stability of 2b, which requires the addition of AlBr₃ to promote cycloreversion.

Examination of the structures of TS-3 reveal their asynchronous character: in both cases, compared to precursors 2a/5c, substantial C–O bond elongation (+51%, +55%) is observed with only minimal P–B elongation (+14, +4 %, Table S11). This behavior strongly suggests that the lower energy of TS-3_acetamide vs TS-3_acetone can be attributed in part to stabilization of the developing positive charge at the carbon center by its NMe₂ substituent. Alkoxyl substituents can be expected to fulfill the same π-donor role, which explains the differing fates in reactions of 1 with amides/esters and ketones/aldehydes. Similarly, we propose that AlBr₃ coordination to 2a-e lowers the energy of TS-3_acetone by polarizing the C–O (and thus the forming C–P) bonds.

Our studies reveal deep and far-reaching mechanistic similarities between the reactions of 1 and carbonyl compounds and the Wittig reaction. We thus propose the term ‘phospha-bora-Wittig’ to describe phosphaalkene-forming reactions of phosphaboren es with carbonyl compounds. In the Wittig reaction, the nature of transition states for cycladdition between ylide (Ph₂P=CHR) and carbonyl compound are subtly influenced by factors including 1,2 and 1,3 steric interactions, dipole/dipole interactions, and C=O–H hydrogen bonds.25–27 Interactions play a role in the formation of 5c, though the importance of 1,3 interactions is negated by the two-coordinate nature of the P/B centers. CH hydrogen bonding in TS-3 is also observed.

We also note the similarity to borata-Wittig reactions of borata-alkenes, [R=C=BR₂] with carbonyl compounds.22,44–48

The classical Wittig reaction is limited in scope for esters/amides, generally requiring careful substrate modification to counteract the effect of the OR and NR₂ substituents.49 This limitation is absent in the reactions of 1 with esters or amides. We ascribe this to the greater electrophilicity of the boron in RP=BR vs C=O. On this basis, and considering the close relationship between CR₂ and :PR, we wish to propose here that reagents of the type R=C=NR₂ may prove practical and general bora-Wittig reagents for the formation of alkynes from simple amides and esters.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Synthetic procedures, NMR spectra, and computational details (PDF)

AUTHOR INFORMATION

Michael J. Cowley
michael.cowley@ed.ac.uk
EaStCHEM School of Chemistry, University of Edinburgh
Joseph Black Building, David Brewster Road, Edinburgh EH9 3FJ, United Kingdom: orcid.org/0000-0003-0664-2891.

Author Contributions

AMB conceived the study and co-wrote the manuscript. AMB and EFR carried out experimental work. GSN performed crystallography. MJC designed and coordinated the research programme, performed DFT studies, and co-wrote the manuscript. All authors have given approval to the final version of the manuscript.

Funding Sources

ERC-2016-STG-716315

ACKNOWLEDGMENT

MJC wishes to thank Dr Stephen Thomas for helpful discussions during this work. This project has received funding from the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation programme (grant agreement no. ERC-2016-STG-716315).

REFERENCES

(1) Mathey, F. Phospha-Organic Chemistry: Panorama and Perspectives. Angew. Chemie Int. Ed. 2003, 42 (14), 1578–1604. https://doi.org/10.1002/anie.200200557.
(2) Baumgartner, T.; Jäkle, F. Main Group Strategies towards Functional Hybrid Materials; Wiley, 2017. https://doi.org/10.1002/9781119235941.
(3) Weber, L. Phosphorus Heterocycles: From Laboratory Curiosities to Ligands in Highly Efficient Catalysts. Angew. Chemie Int. Ed. 2002, 41 (4), 563–572. https://doi.org/10.1002/1021/ja0037733.2020215414.4:563::AID-ANIE563.3.0.CO;2-Q.
(4) Le Floch, P. Phosphaalkene, Phospholyl and Phosphinine Ligands: New Tools in Coordination Chemistry and Catalysis. Coord. Chem. Rev. 2006, 250 (5–6), 627–681. https://doi.org/10.1016/j.ccr.2005.04.032.
(5) Gates, D. P. Expanding the Analogy between P=C and C=C Bonds to Polymer Science. Top. Curr. Chem. 2005, 250, 107–126. https://doi.org/10.1007/b100983.
(6) Bates, J. I.; Dugtal-Tessier, J.; Gates, D. P. Phospha-Organic Chemistry: From Molecules to Polymers. Dalton Trans. 2010, 39 (13), 3151–3159. https://doi.org/10.1039/b918938f.
(7) Becker, G. Mono-substitutionsreaktionen an Substituierten Disilylphosphinen Mit Pivaloylchlorid. Z. Anorg. Allg. Chem. 1976, 421, 242–254. https://doi.org/10.1002/anie.198813821.
(8) Klebch, T. C.; Lourens, R.; Bickelhaupt, F. Synthesis of P-Mesitylideneynylephosphene: A Stable Compound with a Localized P=C Bond. J. Am. Chem. Soc. 1978, 100 (15), 4886–4888. https://doi.org/10.1021/ja00483a041.
(9) Appel, R.; Peters, J.; Westerhaus, A. Phospha-Alkene Durch Thermische, Basen-Oder-Metall-Induzierte Eliminierung. Tetrahedron Lett. 1981, 22 (49), 4957–4960.
(10) Appel, R.; Casset, C.; Immenkamp, M.; Knoch, F. Easy Synthesis of Phosphaalkenes by a Phosphorus- Analogous Isocyane Reaction and an Atypical Crystal Structure of a Tetracarbonyl(Phosphaalkene)Iron Complex. Angew. Chemie Int. Ed. 1984, 23 (11), 895–896. https://doi.org/10.1002/anie.198408951.
(11) Aitken, R. A. 2-Functionalized Alkylidenephosphenes. Sci. Synth. 2005, 22, 565–600.
(12) Marinetti, A.; Mathey, F. A Novel Entry to the PC-Double Bond: The ‘Phospha-Wittig’ Reaction. Angew. Chemie Int. Ed. 1988, 27 (10), 1382–1384. https://doi.org/10.1002/anie.198813821.
(13) Marinetti, A.; Bauer, S.; Ricard, L.; Mathey, F. The ‘Phospha-Wittig’ Reaction: A New Method for Building Phosphorus-Carbon Double and Single Bonds from Carbonyl Compounds. Organometallics 1990, 9 (3), 793–798. https://doi.org/10.1021/om00117a040.
(14) Shah, S.; Protasiewicz, J. D. ‘Phospha-Variations’ on the Themes of Staudinger and Wittig: Phosphorus Analogs of Wittig Reagents. Coord. Chem. Rev. 2000, 210, 181–201.
(15) Brenn, T. L.; Stephan, D. W. Phosphinidene Transfer Reactions of the Terminal Phosphinidene Complex Cp₂Zr(PCH₃=2,4,6-t-Bu)₂(PMe₃). J. Am. Chem. Soc. 1995, 117 (48), 11914–11921. https://doi.org/10.1021/ja90153a013.
(16) Cummins, C. C.; Schroak, R. R.; Davis, W. M. Phosphinidenetetramethylenephosphine Complexes of the Type [(N=NTe=PR) as Phospha-Wittig Reagents. Angew. Chemie Int. Ed. 1993, 32 (5), 756–759. https://doi.org/10.1002/anie.199307561.
(17) Shah, S.; Protasiewicz, J. D. ‘Phospha-Wittig’ Reactions Using Isolable Phosphoranylenephosphines ArP=PR₂ (Ar = 2,6-Mes₂C₆H₃ or 2,4,6-iBu₃C₆H₃). Chem. Commun. 1998, 3, 1585–1586.
