Frustrated Lewis Pairs

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Developing Phospha-Stork Chemistry Induced by a Borane Lewis Acid**

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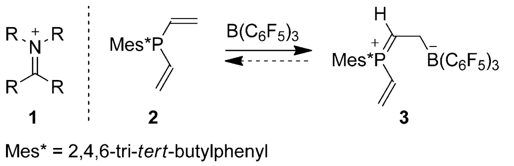
Abstract: *Bulky vinyl phosphanes undergo carbon–carbon coupling with aryl aldehydes with the help of the Lewis acid $B(C_6F_5)_3$ to give isolable methylene phosphonium products. Dimesityl(vinyl)phosphane undergoes a phospha-Stork reaction with bulky enones efficiently catalyzed by $B(C_6F_5)_3$ to eventually yield the corresponding substituted cyclobutane products.*

The carbon–carbon coupling reaction of enamines with various electrophiles (the Stork reaction) is of great synthetic importance.[1,2] A great variety of organic carbonyl reagents react with enamines in stoichiometric or even catalytic reactions to make a number of interesting target molecules easily available.[3,4] Iminium ions **1** (Scheme 1) play an important role as substituents in these reactions.[5]



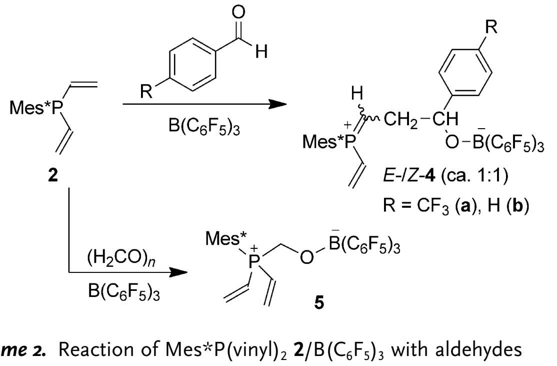
Scheme 1. The iminium cation and a methylene phosphonium zwitterion in frustrated Lewis pair chemistry.

Vinyl phosphanes are the heavy analogues of the enamines. They could in principle undergo a phospha-Stork reaction, for example upon treatment with a reactive aldehyde and ketone in the presence of a suitable Lewis acid. However, there are two apparently obvious adverse issues that seem to have prevented the development of the phosphorus analogue of typical enamine chemistry. The first is the high tendency of most phosphane Lewis bases to form strong adducts with Lewis acids and many other electrophiles. The second is that methylene phosphonium chemistry is much less developed than iminium ion chemistry, although a few $R_2P^+{=}CR_2$ examples with rather bulky substituents were isolated and amply characterized.[6,7]

Both these critical issues can be addressed and possibly overcome by frustrated Lewis pair chemistry.[8] Employing sufficiently bulky vinyl phosphanes has successfully prevented neutralizing adduct formation with strong Lewis acids such as $B(C_6F_5)_3$, and we have recently shown that borane attack at the ene–phosphane β-carbon atom can take place instead. In this way we have prepared a few examples of zwitterionic methylene phosphonium systems that are stable (or at least observable) under conditions of thermodynamic control. The formation of **3** from **2** and $B(C_6F_5)_3$ is a typical example (Scheme 1).[7]

We have now made use of these previous observations by reacting suitable vinyl phosphanes with selected organic carbonyl compounds in the presence of $B(C_6F_5)_3$ and found that this has apparently opened a viable route toward developing stoichiometric and catalytic variants of the phospha-Stork reaction.

We first reacted the very bulky 2,4,6-tri-*tert*-butylphenyl substituted divinyl phosphane substrate **2** with *p*-trifluoromethylbenzaldehyde and the Lewis acid $B(C_6F_5)_3$ in a circa 1:1:1 molar ratio. The reaction quickly went to completion at room temperature to give a 57:43 ratio of the *Z*- and *E*-configured carbon–carbon coupling products **4a** (Scheme 2). Crystallization from the product mixture obtained on a preparative scale eventually gave single crystals of the *Z*-**4a** product isomer (isolated in 30% yield) that allowed its characterization by X-ray diffraction. The X-ray crystal structure analysis has confirmed that the carbonyl coupling reaction induced by the Lewis acid had taken place. The compound *Z*-**4a** contains the newly formed C4−C5 carbon–carbon single bond (1.562(4) Å). The $B(C_6F_5)_3$ moiety is found attached at the former aldehyde carbonyl oxygen atom (O1−B1 1.488(4) Å, angle C5-O1-B1 120.9(2)°). The reaction has resulted in the formation of the substituted methylene phosphonium subunit. It contains the bulky supermesityl



Scheme 2. Reaction of Mes*P(vinyl)$_2$ **2**/$B(C_6F_5)_3$ with aldehydes (Mes* = 2,4,6-tri-*tert*-butylphenyl).

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(Mes*, 2,4,6-tri-*tert*-butylphenyl) substituent at phosphorus (P1−C11 1.796(3) Å). The remaining P-vinyl unit features a P−C(sp^2) single bond (P1−C1 1.770(3) Å, C1−C2 1.296(5) Å). The adjacent P1−C3 linkage is much shorter at 1.629(3) Å; it is a P=C double bond,[6,7] and the C3−C4 linkage (1.468(4) Å) is in the carbon–carbon single bond range. The coordination geometry at phosphorus is planar-three-coordinate (ΣP1^{CCC} = 360.0°). The P1-C3-C4 angle in *Z*-**4a** is 127.6(2)° (see Figure 1).

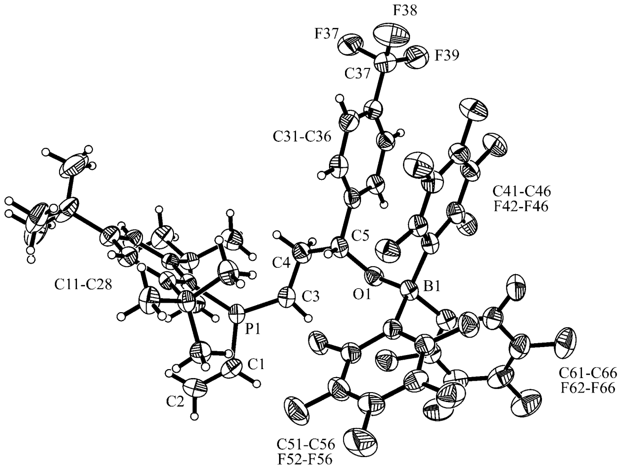


Figure 1. A view of the molecular structure of the methylene phosphonium product *Z*-**4a**, formed by a phospha-Stork reaction (ellipsoids are set at 30% probability).[14]

The typical NMR data were directly obtained from the *Z*-**4a**/*E*-**4a** mixture without workup. Compound *Z*-**4** shows the methylene phosphonium C3–H resonances at δ 8.83 (^{1}H) and 151.3 (^{13}C, $^1J_{PC}$ = 130 Hz) and heteronuclear NMR resonances at δ 137.6 (^{31}P) and δ −2.9 (^{11}B) (*E*-**4a**: δ 7.72/δ 150.2 ($^1J_{PC}$ = 127.9 Hz)([P]=CH), δ 143.7 (^{31}P)). We have also carried out the analogous C−C coupling reaction of the ene–phosphane **2** and B(C$_6$F$_5$)$_3$ with benzaldehyde to give a temperature-dependent mixture of compound **2** and *Z*-/*E*-**4b** (for details, see the Supporting Information).

It cannot be taken for granted that the presence of one very bulky substituent such as the Mes* group in **6** is sufficient to always direct the reaction with a reactive carbonyl compounds toward the phospha-Stork reaction. A typical example is the reaction of Mes*P(vinyl)$_2$ (**2**) with paraformaldehyde in the presence of B(C$_6$F$_5$)$_3$. From the reaction mixture, we isolated the conventional product **5**, formed by addition of the phosphane nucleophile to the B(C$_6$F$_5$)$_3$ activated aldehyde (Scheme 2). The X-ray crystal structure analysis showed that the phosphane/borane system had acted as a P/B pair and added across the formaldehyde carbonyl functionality. A new phosphorus carbon σ-bond was formed (P1−C5 1.835(2) Å), the pair of vinyl groups at P1 had been left untouched, and the borane was found attached at oxygen (O1−B1 1.482(2) Å, C5−O1 1.382(2) Å, angles P1-C5-O1 107.7(1)°, C5-O1-B1 120.2(1)°; Figure 2).

These overall results encouraged us to investigate whether vinyl phosphanes with substituents less bulky than the extreme 2,4,6-tri-*tert*-butylphenyl group might undergo phospha-Stork reactions with suitable carbonyl compounds. First we looked at a 1:1 dimesityl(vinyl)phosphane **6**[9]/B(C$_6$F$_5$)$_3$ mixture in CD$_2$Cl$_2$ by NMR spectroscopy at variable temperature and found that there seemed to be an equilibrium with the zwitterionic methylene phosphonium product (**7**) favoring the latter with decreasing temperature. The B−C addition product **7** shows a ^{11}B NMR signal at 213 K at δ −13.3 and a characteristic ^{31}P NMR resonance at δ 105.6. The **6** + B(C$_6$F$_5$)$_3$ $\rightleftarrows$ **7** equilibrium was ca 1:4 at 213 K and 7:93 at 183 K in CD$_2$Cl$_2$ (by ^{31}P NMR spectroscopy).

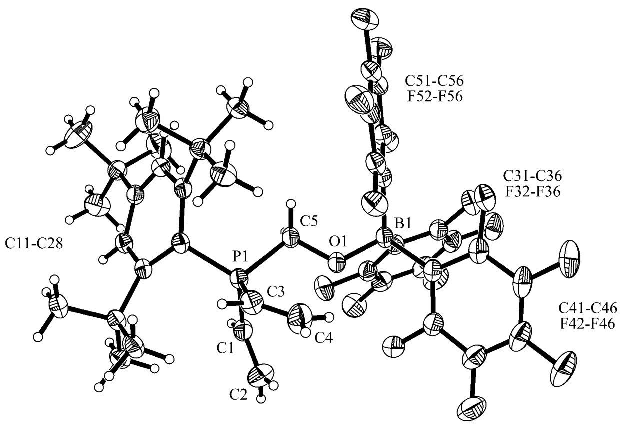
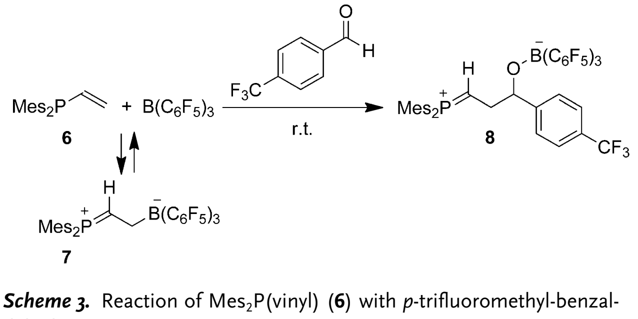


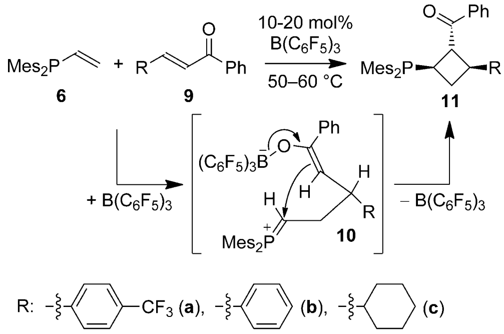
Figure 2. A view of the molecular structure of the conventional addition product **5** of the P/B FLP **2**/B(C$_6$F$_5$)$_3$ to formaldehyde (ellipsoids are set at 30% probability).[14]

The **6** + B(C$_6$F$_5$)$_3$ mixture reacted with *p*-trifluoromethylbenzaldehyde to give the ene–phosphane carbonyl addition product **8** (Scheme 3). Compound **8** shows the typical ^{31}P NMR resonance of a substituted methylene phosphonium cation at δ 124.8 with a corresponding [P]=CH ^{13}C NMR signal at δ 162.5 ($^1J_{PC}$ = 116 Hz). The system shows a typical ^{1}H NMR pattern of the [P]=CH−CH$_2$−CH moiety (8.46 ([P]=CH), 5.02 (CHO), 3.35/2.77 (CH$_2$)), with a negligible $^2J_{PH}$ coupling constant (for details and views of the NMR spectra, see the Supporting Information).



Scheme 3. Reaction of Mes$_2$P(vinyl) (**6**) with *p*-trifluoromethyl-benzaldehyde.

Carbon–carbon coupling with α,β-unsaturated carbonyl groups is one of the most important variants of the Stork reaction.[2] Therefore, we have reacted the ene–phosphane **6** with the non-enolizable substituted conjugated enone **9a** in the presence of catalytic amount of the B(C$_6$F$_5$)$_3$ Lewis acid



Scheme 4. Diastereoselective C–C bond formation of Mes$_2$P(vinyl) (**6**) with conjugated enones **9** catalyzed by B(C$_6$F$_5$)$_3$.

(Scheme 4). In this case, we chose catalytic conditions from the beginning. The reaction between **6** and **9a** proceeded cleanly at 50 °C in the presence of 10 mol % of the B(C$_6$F$_5$)$_3$ catalyst. Workup including chromatographic purification eventually gave the product **11a** in 80 % yield. Apparently, the ene–phosphane had attacked the β-position of the B(C$_6$F$_5$)$_3$ activated enone as a carbon nucleophile. The likely intermediate **10a** consequently contained an enolate nucleophile with the reactive methylene phosphonium carbon electrophile in close proximity. Subsequent internal C–C bond formation then took place with formation of the final four-membered carbocyclic framework of product **11a**.[10] Concomitant cleavage of the B(C$_6$F$_5$)$_3$ Lewis acid catalyst eventually gave the observed product of the phospha-Stork reaction and closed the catalytic cycle.

The product **11a** was characterized by X-ray diffraction (crystals were obtained from CH$_2$Cl$_2$ by solvent evaporation). The X-ray crystal structure analysis has confirmed the formation of the phosphanyl substituted cyclobutane derivative by the catalytic carbon–carbon coupling sequence. The central C$_4$ ring is slightly puckered. It contains the Mes$_2$P and the aryl substituent in *cis*-1,3-position. The C(O)Ph functional group is oriented *trans* to the phosphanyl group (Figure 3).

Compound **11a** shows the ^{13}C NMR carbonyl resonance at δ 198.4 and the ^{13}C NMR signals of the central cyclobutane unit at δ 52.4 (CH, $^2J_{PC} = 13.1$ Hz), 43.8 (CH$^{[Ar]}$, $^3J_{PC} = 15.6$ Hz), 34.1 (CH$_2$, $^2J_{PC} = 22.2$ Hz) and 29.9 (PCH, $^1J_{PC} = 22.2$ Hz). Compound **11a** shows a ^{31}P NMR resonance at δ −11.1 (for further details, see the Supporting Information).

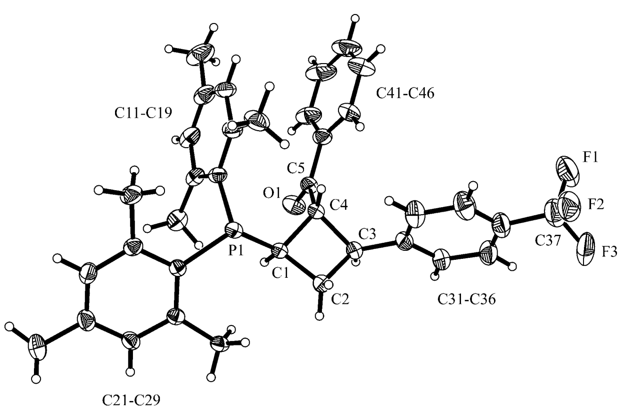


Figure 3. Molecular structure of the product **11a** (ellipsoids are set at 30% probability). Selected bond lengths [Å] and angles [°]: P1–C1 1.861(3), C5–O1 1.216(4), ΣP1^{CCC} 311.4, C4-C1-C2 88.5(2), C1-C2-C3 88.7(2), C2-C3-C4 88.6(2), C3-C4-C1 87.6(2).[14]

The phenyl-substituted product **11b** was prepared analogously from Mes$_2$P(vinyl) (**6**) and chalcone **9b** in a B(C$_6$F$_5$)$_3$ (10 mol %) catalyzed phospha-Stork reaction at 60 °C. Compound **11b** was isolated in 61 % yield, and we have also prepared the analogous cyclohexyl substituted derivative **11c** starting from the phosphane **6** and the conjugated enone **9c** (for details, see the Supporting Information.)

The phosphorus variant of the Stork reaction provides a simple synthetic entry to potentially useful functionalized new phosphane ligands for transition-metal chemistry and catalysis.[11] We have planned to apply compounds **11** as building blocks for the synthesis of new frustrated P/B Lewis pairs, for example by Wittig olefination followed by hydroboration with Piers' borane [HB(C$_6$F$_5$)$_2$],[12] and we have successfully carried out the first steps into this direction (for details, see the Supporting Information).

Our study has shown that the phosphorus analogues of enamine Stork chemistry can be realized. Care is taken to prevent the vinyl phosphanes from forming simple adducts with the necessary Lewis acid or with strongly electrophilic carbonyl reagents. The typical features of frustrated Lewis pair chemistry have been found to achieve that aim perfectly. This has allowed us to open a pathway to ene–phosphane analogues of typical enamine chemistry and thereby will help developing a phospha-Stork chemistry. Frustrated Lewis pair chemistry seems to continue being helpful in the disclosure of new reaction types.[8b,c,13]

Experimental Section

11a: Mes$_2$P(vinyl) (**6**; 315.0 mg, 0.106 mmol), the enone **9a** (294.2 mg, 0.106 mmol, 1 equiv), and B(C$_6$F$_5$)$_3$ (51.2 mg, 0.010 mmol, 0.1 equiv) were mixed in CD$_2$Cl$_2$ (ca. 1.5 mL). The reaction mixture was then transferred into an NMR tube, which was sealed and placed in an autoclave filled with CH$_2$Cl$_2$. After heating the autoclave at 50 °C for 24 h, the reaction mixture was purified by column chromatography (alumina; pentane/triethylamine 98:2) to give compound **11a** (485 mg, 80 %) as an oil. Crystals suitable for the X-ray single crystal structure analysis were obtained from a solution of compound **11a** in CH$_2$Cl$_2$ at room temperature. Elemental analysis calcd. for C$_{35}$H$_{36}$F$_3$P: C 75.51, H 6.34; found: C 75.14, H 6.18. IR (KBr): C=O: 1674 cm^{-1}. ^{1}H NMR (600 MHz, 299 K, [D$_2$]dichloromethane): $\delta = 7.56$ (m, 2H, *m*-Ar), 7.40 (m, 1H, *p*-Ph$^{C=O}$), 7.31 (m, 2H, *o*-Ar), 7.22 (m, 1H, *o*-Ph$^{C=O}$), 7.18 (m, 1H, *m*-Ph$^{C=O}$), 6.78 (dm, $^4J_{PH} = 2.1$ Hz, 2H, *m*-Mes^a), 6.37 (dm, $^4J_{PH} = 1.8$ Hz, 2H, *m*-Mes^b), 4.45 (m, $^2J_{PH} = 4.1$ Hz, 1H, PCH), 3.72 (dt, $^3J_{PH} = 12.7$ Hz, $^3J_{HH} \approx {}^3J_{HH} \approx 9.1$ Hz, 1H, CH), 3.54 (dt, $^3J_{HH} \approx 9.3$ Hz, $^3J_{HH} \approx {}^3J_{HH} \approx 9.1$ Hz, 1H, CH^{Ar}), 2.92 (m, $^3J_{PH} = 5.0$ Hz), 2.59 (dm, $^3J_{PH} = 13.4$ Hz, $^2J_{HH} = 11.1$ Hz)(each 1H, CH$_2$), 2.28 (s, 6H, *o*-CH$_3^b$), 2.24 (s, 3H, *p*-CH$_3^a$), 2.20 (s, 6H, *o*-CH$_3^a$), 1.87 (s, 3H, *p*-CH$_3^b$). ^{19}F NMR (564 MHz): $\delta = -62.7$ ($\nu_{1/2} \approx 4$ Hz). ^{31}P{^{1}H} NMR (243 MHz): $\delta = -11.1$ ($\nu_{1/2} \approx 5$ Hz).

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[14] CCDC 1008912 (*Z*-**4a**), CCDC 1008913 (**5**), and CCDC 1008914 (**11a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.