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Carbon-fluorine bond cleavage in C₆F₅X arenes by carbonyl-stabilized phosphorus ylides. Synthesis of Ph₃P:C(C₆F₄X-₄)R (X=CN or NO₂). Crystal and molecular structure of Ph₃P:C(C₆F₄C...

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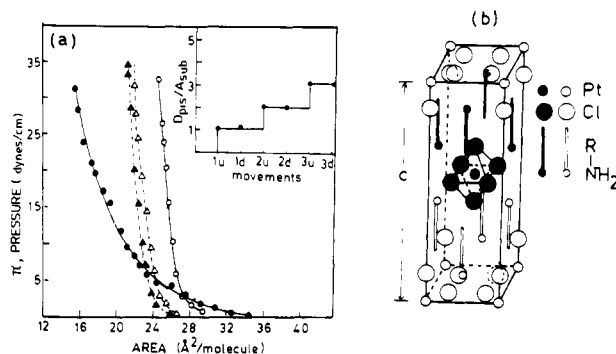


Figure 1. (a) π - A isotherms of *n*-octadecylamine monolayers at the air-water interface (solid line, pH = 4.0; dashed line, pH = 9.0) in the presence (filled points) or absence (open points) of H_2PtCl_6 in the aqueous subphase. Inset shows the displacement of oleic acid piston (D_{pis}) per unit area of substrate (A_{sub}) during the n th upward (nu) and downward (nd) movements. (b) Proposed unit cell structure of the Langmuir-Blodgett film deposited on the substrate (filled circles correspond to one deposition during an upward dip).

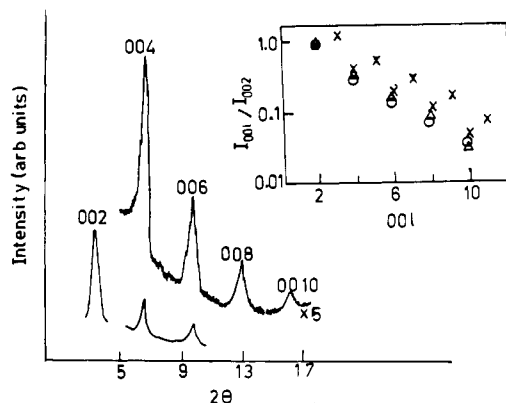


Figure 2. X-ray diffraction pattern of the LB film after 31 dips. Inset: The ratio of the X-ray diffraction intensities, I_{00l}/I_{002} , as measured (triangles) is compared with that calculated (circles) for the cell proposed in Figure 1b. The characteristic "odd-even" intensity oscillation of the 00 l reflections of a typical Langmuir-Blodgett film of lead arachidate is also shown (crosses) for comparison.

the 00 l reflections match well with those experimentally observed (shown in the inset of Figure 2) for the z coordinates given below:

$$\begin{aligned} & \text{Pt}_{0.5}\text{Cl}_2\text{-Cl-NH}_3\text{-(CH}_2)_n \\ & z = 0, 0.096, 0.098, 0.098 + n(0.046) \quad (n = 1-18) \\ & (\text{CH}_2)_n \quad \text{-NH}_3\text{-Cl-Pt}_{0.5}\text{Cl}_2 \\ & z = 0.098 + n(0.046) \quad (n = 0-17), 0.926, 0.904, 1.00 \end{aligned}$$

Any model involving a disordered arrangement of bilayers with the hydrocarbon chains resting on top of another would necessarily give rise to a ~ 54 -Å separation between the planes in which the 00 l reflections with $l = \text{odd}$ would be present. We propose that in the upward movement the $(\text{R-NH}_3)_2\text{PtCl}_6$ bilayer is incorporated with the PtCl_6 unit attached to the substrate. There is very little net deposition in the downward movement.

The multilayer films are not patchy as they do not show any Si from the substrate in X-ray photoelectron spectra (VG ESCA-3 spectrometer, unmonochromatized Al K α radiation). Of interest to us is the location of the $[\text{PtCl}_6]^{2-}$ unit. The ratio I_{30}/I_{70} of the Pt 4f as well as Cl 2p intensities at the two tilt angles of 30° (I_{30}) and 70° (I_{70}) (with respect to the plane of the surface) from such multilayer films is nearly 0.30 in both cases. In terms of the discrete layer model developed by us,⁵ a value of $I_{30}/I_{70} = 0.30$ -0.40 signals the location of the species at a depth equivalent to the length of one hydrocarbon chain from the surface. The N 1s spectrum⁶ shows two features. One of these is a shoulder

at a binding energy of 400 eV characteristic of NH_2 groups, and there is a prominent peak at ~ 403 eV characteristic of NH_3^+ groups. The NH_3^+ component of the N 1s spectrum also behaves in the same manner. The Pt, Cl, and N at this level are in the ratio of nearly 1:6:2 (after normalizing for the scattering cross sections). The intensities of two prominent C 1s lines and the N 1s line at ~ 400 eV relative to platinum increase at low takeoff angles ($I_{30}/I_{70} = 1.0$ -1.3), showing that they are on top of the platinum layer. A prominent signal from the O 1s region typical of bound water is only at the surface since it is not seen in the infrared spectrum. Results of detailed studies on the C 1s and N 1s XPS spectra as well as infrared spectroscopic studies are to be presented in another communication.

C-F Bond Cleavage in $\text{C}_6\text{F}_5\text{X}$ Arenes by Carbonyl-Stabilized Phosphorus Ylides. Synthesis of $\text{Ph}_3\text{P}=\text{C}(\text{C}_6\text{F}_4\text{X-4})\text{R}$ ($\text{X} = \text{CN}$ or NO_2). Crystal and Molecular Structure of $\text{Ph}_3\text{P}=\text{C}(\text{C}_6\text{F}_4\text{CN-4})\text{CO}_2\text{Et}$

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Some examples of C-F bond cleavage in fluoroarenes $\text{C}_6\text{F}_5\text{X}$, especially those containing electron-withdrawing substituents X such as CN or NO_2 , have been reported in the literature.¹⁻⁸ This cleavage always occurs following the attack on the arene by a strong nucleophile [amines,¹ X^- ($\text{X} = \text{Cl}, \text{Br}, \text{I}$),² CN^- , MeO^- ,³ OH^- ,⁴ $\text{CF}_3\text{CH}_2\text{O}^-$,⁵ $\text{C}_6\text{H}_5\text{NNH}$,⁶ $\text{Ph}_2\text{PCH}_2\text{P}(\text{=NSiMe}_3)\text{Ph}_2$,⁷ or N_3^- .⁸ Most of these reactions require energetic conditions and give the para-substituted products. A para F-C bond cleavage has been suggested to account for the polymerization of $(\text{C}_6\text{F}_5)_2\text{Me}_2\text{P}=\text{CH}_2$.^{9a} Here we report the first unambiguous examples of C-F bond cleavage in fluoroarenes by phosphorus ylides. An additional noteworthy feature of these reactions is that they occur at room temperature in spite of the weak nucleophilic character of the ylides studied. Some ortho-F-substitution reactions have been described as the result of intramolecular heteroatom (such as Pt¹⁰ or N¹¹) assisted processes.

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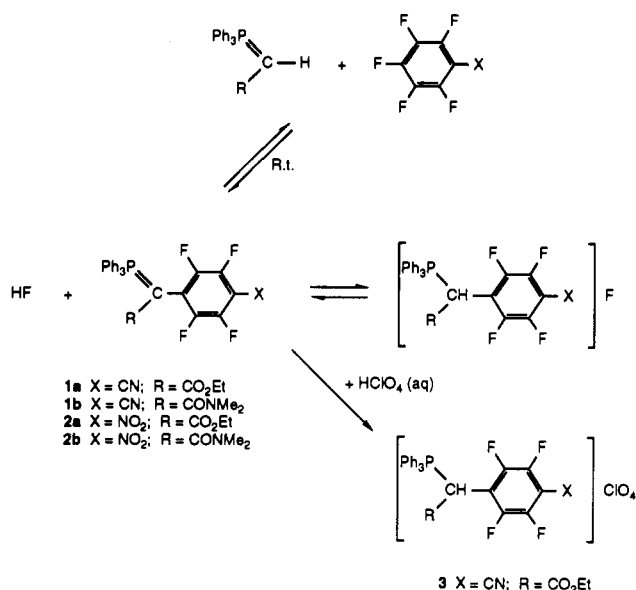
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Scheme I. Synthesis of 1-3



Although we are aware of the existence of only three compounds in which a polyfluoroaryl group is attached to the methylene moiety, most of the reported phosphorus ylides have not been isolated and very few have been characterized by X-ray crystallography.⁹ We report here the synthesis, isolation, and characterization of four such compounds, in addition to the crystal structure of one of the ylides.

The reaction of C₆F₅X (X = CN, NO₂) with carbonyl-stabilized phosphorus ylides Ph₃P=CHC(O)R (R = OEt, NMe₂) (diethyl ether, room temperature, 16–72 h) produces mixtures containing the new ylides Ph₃P=C(C₆F₄X-4)C(O)R [X = CN; R = OEt (1a), NMe₂ (1b)]¹² (see Scheme I) and the corresponding phosphonium fluorides or hydrogen difluorides (identified by IR and NMR spectra) or pure ylides Ph₃P=C(C₆F₄X-4)C(O)R [X = NO₂; R = OEt (2a), NMe₂ (2b)].¹² Because HF must form along with the ylides in the substitution reaction, the phosphonium salts are in acid-base equilibrium with both reagents. The isolation of pure 2a,b from the reaction mixture probably arises from displacement of this equilibrium when HF is removed upon concentration. Although the ylide/phosphonium salt mixtures, obtained when X = CN, cannot be separated, they can be converted into the pure ylides or into phosphonium salts by being treated with Na₂CO₃ or HClO₄(aq), respectively.

Only in the case of the reaction between the most nucleophilic ylide¹³ and the most electrophilic arene,¹⁴ which gives 2b, can a 1:1 molar ratio be used. In the other cases an excess of the pentafluoroarene must be used in order to avoid contamination with the starting ylides. In the case of 1a, for example, 35% of the starting ylide remains unreacted after 16 h at room temperature when the reaction is carried out in a 1:1 molar ratio. Other experiences show that less nucleophilic ylides, e.g., Ph₃P=CHC(O)R [R = Me, Ph],¹³ do not react with C₆F₅CN; nor do pentafluoroarenes containing less-electron-withdrawing substituents, C₆F₅X [X = C(O)Me, H, Br, or MeO], react with Ph₃P=CHCO₂Et. This is in accordance with the free energy data

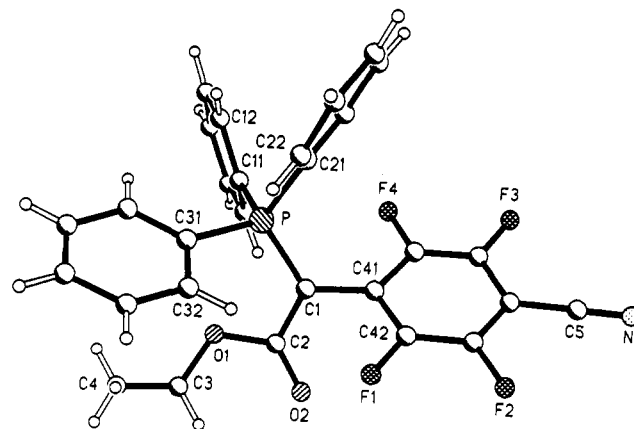


Figure 1. The structure of 1a showing the atom-labeling scheme. Selected bond distances (Å) and angles (deg): C(1)–P, 1.722 (3); C(1)–C(2), 1.441 (4); C(1)–C(41), 1.473 (4); C(2)–O(2), 1.222 (3); C(2)–O(1), 1.365 (4); C(44)–C(5), 1.434 (5); C(5)–N, 1.146 (5); P–C(1)–C(41), 122.9 (2); C(41)–C(1)–C(2), 116.5 (2); C(2)–C(1)–P, 120.6 (2); C(1)–C(2)–O(2), 126.4 (3); C(1)–C(2)–O(1), 110.8 (2).

obtained for the fluoride affinity of C₆F₅X, which follow the sequence for the X substituents $-\Delta G^\circ(\text{NO}_2) > -\Delta G^\circ(\text{CN}) > -\Delta G^\circ[\text{C}(\text{O})\text{Me}] > -\Delta G^\circ(\text{H})$.¹⁴ All the above data suggest that the reactions leading to 1 or 2 are normal nucleophilic substitution reactions.

The isolation of the phosphorus ylides 1 and 2 (yields are in the 55–88% range) in the presence of HF proves the strong acidic character of the phosphonium salts, arising from the electro-negative character of both the polyfluoroaryl and R groups. The corresponding weak basic character of the ylides explains their great thermal and hydrolytic stability, which allows their isolation and storage in the air. The ylide 1a reacts with HClO₄(aq) in CH₂Cl₂ to give [Ph₃PCH(C₆F₄CN-4)CO₂Et]ClO₄ (3).¹² Its IR and NMR spectral data confirm the presence of the phosphonium cation in the mixture obtained from the reaction that leads to 1a.

The syntheses of 1 and 2 involve cleavage of C–F and C–H bonds and formation of HF and one C–C bond. The enthalpy change for this reaction can be estimated¹⁵ as $\Delta H = \Delta H(\text{F–H}) + \Delta H(\text{C–C}) - \Delta H(\text{C–H}) - \Delta H(\text{C–F}) = (-570 - 376 + 400 + 474) \text{ kJ mol}^{-1} = -72 \text{ kJ mol}^{-1}$. Therefore, formation of HF seems to be the driving force of these reactions.

Phosphorus ylides are reagents of great interest in olefin synthesis (Wittig reaction).^{16–18} Surprisingly, there is only one general method for the synthesis of ylides, that is, deprotonation of phosphonium salts. However, some examples of substitution reactions of the type Ph₃P=CHR + XR' → Ph₃P=CRR' + XH where X = Cl, Br, SR'', or R''O and R' = R''C(O), CO₂R'', CH₂CN, or CH₂CH=CH₂ (R'' is an alkyl or aryl group) have been described.¹⁶ As far as we are aware there is no previous report of such a process in which a C–F bond is involved.

The IR spectra of new ylides show the band assignable to $\nu(\text{CO})$ at 1630–1535 cm⁻¹. The shift to higher frequencies (5–30 cm⁻¹) with respect to the parent ylides Ph₃P=CHC(O)R¹³ can be explained by the greater electron-withdrawing ability of the C₆F₄X-4 (X = CN, NO₂) groups compared to the H atom. For the same reason, the methine proton resonance in the ¹H NMR spectrum of the phosphonium salt 3 is shifted to low field by 1.1 ppm with respect to the methylene resonance in the spectrum of [Ph₃PCH₂CO₂Et]ClO₄. As expected, the IR spectrum of the phosphonium salt 3 shows the $\nu(\text{CO})$ band shifted to higher frequencies (100 cm⁻¹) when compared to that for 1a.

The ¹⁹F NMR spectra of 1–3 exhibit two multiplets in the region of 133–139 ppm corresponding to an AA'BB' system. The

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^1H NMR spectra of the ylides **1b** and **2b** show that both methyls are equivalent, suggesting that the $\pi(\text{CN})$ bond order is small enough to allow rotation of the NMe_2 group. The same is observed in the spectra of the parent $\text{Ph}_3\text{P}=\text{CHC}(\text{O})\text{NMe}_2$ species.^{13b}

The crystal structure of **1a**¹⁹ was solved at -95°C and is shown in Figure 1. The coplanarity of the atoms P, C(41), C(1), C(2), O(1), O(2) (within 0.04 Å) and the rotation of the $\text{C}_6\text{F}_4\text{CN}$ ring by 59° out of this plane show that a delocalization of electron density affects mainly the O—C—C—P bonding arrangement. This effect is clearly shown by the P—C(1) bond distance [1.722 (3) Å], which is, as expected, somewhat shorter than the standard $\text{C}_{\text{sp}^2}(\text{Ar})\text{—PR}_3$ bond distance [1.793 Å²⁰], but longer than in non-carbonyl ylides such as $\text{Ph}_3\text{P}=\text{CH}_2$ [1.697 (8), 1.688 (3) Å].²¹ However, only marginal shortening of the C(1)—C(2) bond [1.441 (4) Å vs mean value of 1.460 Å for a C=C—C(O)R bond²⁰] and lengthening of the C(2)—O(2) bond [1.222 (3) Å vs mean value of 1.199 Å for a C=C—CO₂R²⁰] are evident.

This study proves that para-C—F bond cleavage in $\text{C}_6\text{F}_4\text{X}$ (X = CN, NO₂) is easily achieved by the weak nucleophiles $\text{Ph}_3\text{P}=\text{CHC}(\text{O})\text{R}$ (R = OEt, NMe₂).

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Supplementary Material Available: Experimental information and data on compounds **1–3** and structure determination summary, data collection, solution and refinement and tables of atomic coordinates, bond lengths and angles, anisotropic displacement coefficients, and H-atom coordinates for **1a** (10 pages); listing of observed and calculated structure factors for **1a** (16 pages). Ordering information is given on any current masthead page.

(19) Crystal data for **1b**: pale yellow prism, $0.65 \times 0.35 \times 0.25$ mm, monoclinic, space group $P2_1/c$, $T = -95^\circ\text{C}$, $a = 15.217$ (4) Å, $b = 9.306$ (2) Å, $c = 18.465$ (4) Å, $\beta = 111.27$ (2) $^\circ$, $V = 2436.8$ (10) Å³, $Z = 4$. The structure was solved by direct methods and refined to $R = 0.043$, $wR = 0.047$ for 2895 reflections $> 4\sigma(F)$ to $2\sigma_{\text{max}}$ 50° (Mo K α , $\lambda = 0.71069$ Å).

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A DNA Hairpin as a Target for Antisense Oligonucleotides

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Artificial regulation of gene expression can be achieved by antisense oligonucleotides complementary to part of a messenger RNA.¹ Although RNAs can be written as single strands, self-pairing between adjacent or remote sequences gives rise to double-stranded regions. RNA hairpins will weaken or prevent the binding of an antisense oligomer if its target is sequestered in such a structure.² We propose here a strategy to bind an oligonucleotide to a hairpin without disrupting the structure, via the formation of base triplets.^{3–8} Our suggestion is to form a "double

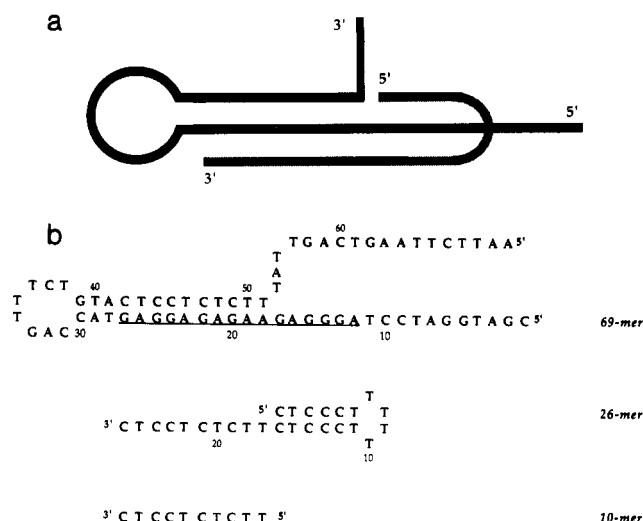


Figure 1. (a) Schematic representation of the double hairpin structure. (b) Sequence of the 69-mer showing the hairpin structure. The 16-purine target sequence is underlined. The sequences of the oligopyrimidine 26-mer and 10-mer are shown at the bottom. The antisense 26-mer is folded to evidence its association with the target 69-mer. Oligodeoxynucleotides were synthesized on an Applied Biosystem synthesizer using phosphoramidite chemistry and were purified by electrophoresis on polyacrylamide gels containing 7 M urea.

hairpin" complex (Figure 1a). The antisense oligomer has two domains: the first one is complementary to the single-stranded sequence at the bottom of the hairpin, and the second one is designed to form a triplex with both the hybridized first domain and the stem of the hairpin.

We investigated this possibility with a 69-mer oligodeoxynucleotide, able to fold into a hairpin, the stem of which comprised 13 base pairs. The 5' strand contained a sequence of 10 purines, and consequently, the 3' strand contained 10 pyrimidines. In addition, a stretch of six purines, 5'AGGGAG, was immediately upstream of the stem, leading to a 16-purine-long sequence that we selected as a target for an antisense 26-mer oligopyrimidine (Figure 1b). We also synthesized a 10-mer complementary to the stem of the hairpin.

Electrophoretic analysis, on a nondenaturing polyacrylamide gel, showed that the 26-mer induced a mobility shift of the 69-mer indicating the association of the two oligomers (not shown). We then probed the double hairpin complex by chemical footprinting. Diethyl pyrocarbonate (DEPC) clearly mapped the stem region,^{5,9} in the 69-mer from G(20) to A(29) (Figure 2a). The addition of the 10-mer did not reveal any significant change; but when the modification of the 69-mer was carried out in the presence of the 26-mer, the reactivity of purines from G(13) to A(19) was reduced, indicating the protection of this sequence by the antisense oligonucleotide (Figure 2a). Surprisingly, the reactivity of A(32) (in the loop) and of the purines on the 3' side of the stem (from A(53) to A(62)) was increased, suggesting an overall conformation change of the 69-mer upon association of the 26-mer.

These conclusions were strengthened by the modification of the 69-mer by dimethyl sulfate (DMS). The addition of the 10-mer decreased the sensitivity to DMS from G(20) to G(27), indicating the formation of the expected 69-mer/10-mer triplex (Figure 2b). In the 69-mer + 26-mer mixture, the reactivity of G(13) to G(27) was reduced almost to 0, demonstrating that both the double-stranded region of the hairpin and the upstream sequence were involved in the binding of the antisense 26-mer. An unexpected hyperreactivity of G(27) was induced by the formation of the double-hairpin structure (Figure 2b). This might reveal the triplex-duplex junction, but such an increased sensitivity was not

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