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Facile [2,3]-Rearrangements of Difluoroallylic Alcohols with C-P and C-S Bond Formation.

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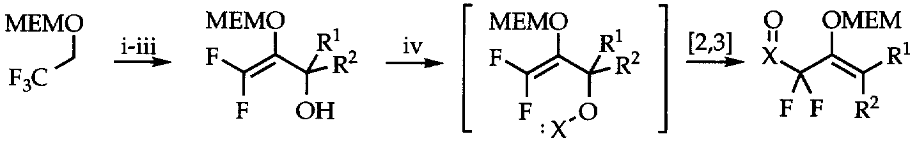
Abstract: Primary, secondary and tertiary difluoroallylic alcohols underwent facile [2,3]-rearrangement upon treatment with phenylsulfenyl chloride or chlorodiphenylphosphine, to the corresponding sulfoxides and phosphine oxides. In the primary cases, the rearrangement was considerably slower, while in the tertiary cases, S_N2' chlorination reactions competed to a significant extent. Heating the sulfoxide products with triethyl phosphite failed to induce conversion back to the allylic alcohols, consistent with the strong preference of the CF_2 centre for the sp^3 hybridisation state. Copyright © 1996 Elsevier Science Ltd

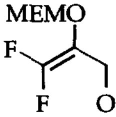
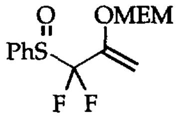
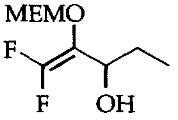
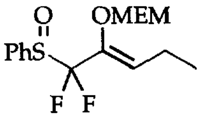
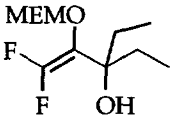
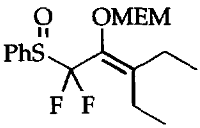
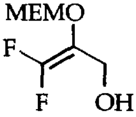
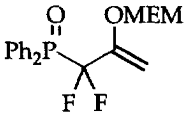
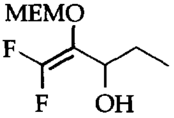
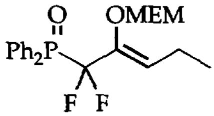
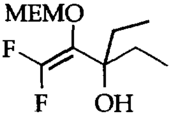
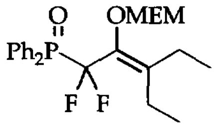
The reversible sulfenate to sulfoxide (Mislow-Evans) rearrangement has found a number of applications in synthetic organic chemistry.[1] Analogous [2,3]-rearrangements involving phosphorus are also known, including phosphite to phosphonate (Arbuzov), and phosphinate to phosphine oxide rearrangements, though the range of examples is quite narrow. For example, propargyl alcohols rearrange under mild conditions to afford allenic phosphine oxides and phosphonates.[2] However, only electron deficient *allylic* alcohols[3] rearranged at low temperature. The rearrangement therefore appears to be facilitated by the presence of a low energy LUMO in the allylic component, close in energy to the non-bonded (lone pair) electrons on the second row atom. While α,α-difluoromethylenephosphonic acid derivatives are well known as phosphate ester mimics,[4] α,α-difluoro-sulfoxides or -sulfones are relatively unusual compounds.[5] Consistent with our interest in the chemistry of mono- and di-fluoroallylic alcohols and their transposition through sigmatropic rearrangement reactions,[6] we have examined facile [2,3]-rearrangements leading to CF_2-S and CF_2-P bond formation (**Scheme 1**).[7]



Scheme 1. Reagents and Conditions: i, 2.0 LDA, THF, -78 °C, inverse addition; ii, R^1COR^2 then warm to -30 °C; iii, NH_4Cl, MeOH; iv, XCl, Et_3N, CH_2Cl_2 (X = PhS or Ph_2P).

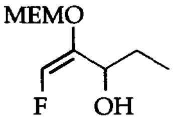
As our allylic alcohols showed high reactivity in the [2,3]-Wittig rearrangement,[8] we reasoned that their high electrophilicity should render them reactive under these [2,3]-rearrangement conditions allowing us to obtain some unusual products. **Table 1** summarises our results.

Table 1

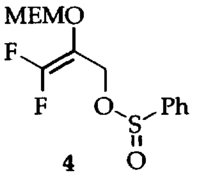
XCl	Alcohol		[2,3]-Product		%Yield
PhSCl		**1a**		**2a**	72
		**1b**		**2b**	64
		**1c**		**2c**	25
Ph_2PCl		**1a**		**6a**	52[a]
		**1b**		**6b**	40
		**1c**		**6c**	35[a]

[a]DMAP (0.1 equivalents) was added in these cases.

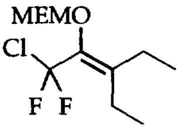
Treatment of **1a**, prepared using our published procedure[9] with freshly-distilled phenyl sulfenyl chloride[10] led to the rapid formation of a single product, shown to be sulfoxide **2a** by spectroscopic methods, in high yield. Less substituted alcohol **1b** exhibited the same behaviour though we also isolated sulfinate ester **4** in this case,[11] together with the sulfoxide **2b**. However, tertiary alcohol **1c** afforded a low yield of sulfoxide **2c** (25 %) and a significant proportion of chlorodifluoromethyl enol acetal **5**. Monofluoroalcohol **1d**[6] decomposed under these reaction conditions. The Evans-Mislow rearrangement failed to occur when **2a** was heated with triethylphosphite in methanol for extended periods,[12] consistent with the strong thermodynamic preference for the CF_2 group to be sp^3 hybridised.[13]



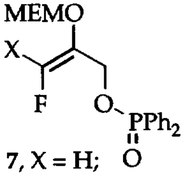
1d



4



5



7, X = H; **8**, X = F.

Rearrangements involving phosphine oxides followed a similar pattern. Treatment of **1a** with chlorodiphenylphosphine in dichloromethane at -30 °C led to the isolation of **6a** directly (52%), while **1b** afforded **6b** (40%). Again, chlorination was observed with tertiary alcohol **1c**, concomitant with the formation of **6c** (35%). Monofluoroalcohol **1d** was exposed to the same conditions, but only phosphinate **7** (46%) was isolated, and none of the rearranged material.

Certain features of these rearrangement reactions invite comment. Firstly, though not completely general, the rearrangements proceed smoothly in the primary, and particularly, the secondary cases allowing considerable structural variation to be achieved through the use of different aldehyde electrophiles. The reason for the significant difference in the rate of rearrangement between primary and secondary alcohols is unknown though it suggests that the stabilising effect of the alkyl group on the transposed double bond exerts a favourable (lowering) effect on the barrier for the rearrangement. We propose that oxidation of the phosphorus and sulfur electrophiles, and of the phosphinate and sulfenate intermediates occurs at similar rates, competitive with rearrangement in the case of the primary allylic alcohol. It follows that we were able to suppress the oxidation reactions by degassing the reaction solvent, prior to the addition of the P(III) or S(II) electrophile.[14]

In the case of the tertiary alcohol, the chlorination reaction resembles a low yielding transposition described recently by Sauvêtre[7] except that in our cases, we assume that the chlorination arises from an S_N2' displacement by chloride ion *via* a transition state with significant tertiary allylic cation character. Slow reaction between the hindered tertiary alcohol allows time for oxidation of phosphorus and sulfur electrophiles. We are exploring the rearrangement further as a new and mild approach to the synthesis of mono- and difluoromethylene phosphonates[15] and sulfones of potential biological significance.[16]

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10. In a typical procedure, phenylsulfenyl chloride (1.5 eq.) was added slowly to a solution of the difluoroallylic alcohol (0.1 M in dichloromethane) containing triethylamine (1.2 eq.) at -78 °C. After 1 hour at that temperature, the mixture was allowed to warm to -30 °C (sulfur electrophiles) or room temperature (phosphorus electrophiles) overnight. Sulfoxide and phosphine oxide products were purifed by flash column chromatography after aqueous work-up.
11. Sulfinates have been prepared from sulfenates by oxidation with *m*CPBA; see Bravermann, S.; Duar, Y. *Tetrahedron Lett.*, **1975**, 343. For *sulfinate ester* **4**:- ν_{max} (Film)1758, 1647, 1446 and 1026 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 3.38 (s, 3H), 3.54 (t, 2H, $^3J_{H\text{-}H}$ = 4.5 Hz), 3.76-3.86 (m, 2H), 4.20 (ddd, 1H, $^4J_{H\text{-}F}$ = 3.7 Hz, $^4J_{H\text{-}F}$ = 1.8 Hz, $^2J_{H\text{-}H}$ = 12.6 Hz), 4.62 (ddd, 1H, $^4J_{H\text{-}F}$ = 3.8 Hz, $^4J_{H\text{-}F}$ = 2.6 Hz, $^2J_{H\text{-}H}$ = 12.6 Hz), 4.88 (d, 1H, $^2J_{H\text{-}H}$ = 6.5 Hz), 4.94 (d, 1H, $^2J_{H\text{-}H}$ = 6.5 Hz), 7.51-7.63 (m, 3H), 7.69-7.79 (m, 2H); δ_C (75 MHz; $CDCl_3$) 58.0, 59.0, 68.3, 71.5, 95.8, 111.5 (dd, $^2J_{C\text{-}F}$ = 37.8, 16.2 Hz), 125.3, 129.2, 132.5, 144.2, 155.6 (t, $^1J_{C\text{-}F}$ = 290.9 Hz); δ_F (282 MHz; $CDCl_3$) –105.8 (d, 1F, $^2J_{F\text{-}F}$ = 56.8 Hz), –95.6 (d, 1F, $^2J_{F\text{-}F}$ = 56.8 Hz); m/z (CI, NH_3) 340 (60%, $[M+NH_4]^+$), 323 (17%, $[M+H]^+$), 216 (85), 94 (100), 52 (76), 44 (40); HRMS calcd for $C_{13}H_{20}F_2NO_5S$ ($[M+NH_4]^+$) 340.10303, found 340.10342.
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14. When the reaction of primary allylic alcohol **1b** with chloro diphenylphosphine was run in dry undegassed dichloromethane, oxidised product **8** was isolated in 21% yield. In dichloromethane that had been purged with dry argon, only **6b** was obtained (68%).
15. Initial attempts to phosphitylate with commercial diethyl chlorophosphite failed to afford phosphonate products with or without added DMAP. We are exploring currently other phosphitylating agents.
16. Sulfone-containing peptidomimetics have been described recently: Rivero, R.A.;. Greenlee, W.J.; Patchett, A.A. *Tetrahedron Lett.*, **1991**, *32*, 5263; Jungheim, L.N.; Shepherd, T.A.; Baxter, A.J.; Burgess, J.; Hatch, S.D.; Lubbehusen, P.; Wiskerchen, M.; Muesing, M.A. *J. Med. Chem.*, **1996**, *39*, 96.

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