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A Conjugate Addition/Sulfoxide Elimination Route to Allylic Difluorophosphonates

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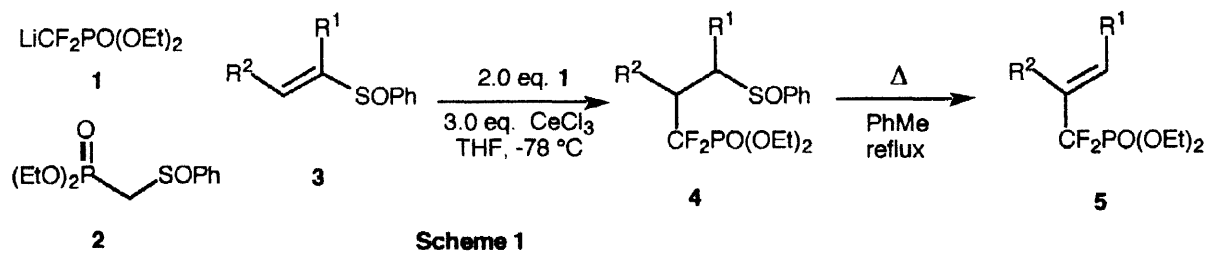
Abstract:

Cerium-mediated conjugate additions of (diethoxyphosphinoyl) difluoromethyllithium to cyclic vinyl sulfoxides proceeded smoothly; thermal sulfoxide elimination afforded the products of formal vinylation, attaching the difluoromethylenephosphonato group to an alkenyl carbon atom. With acyclic vinyl sulfoxides, the addition occurred in moderate to poor yield. Addition failed completely in the absence of cerium(III) chloride, and was facilitated by an excess of the reagent.

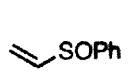
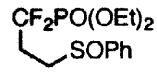
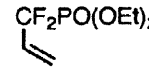
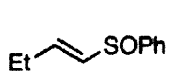
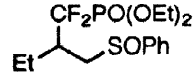
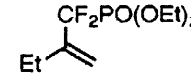
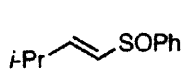
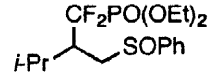
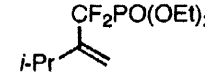
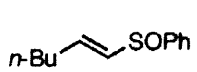
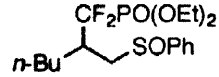
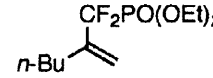
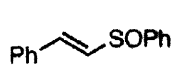
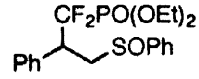
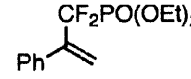
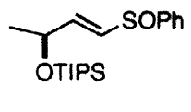
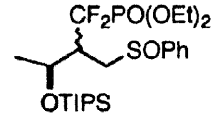
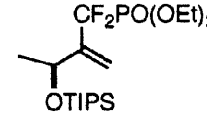
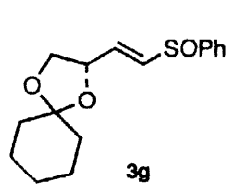
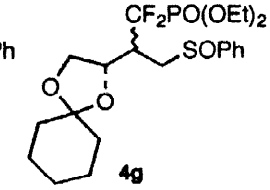
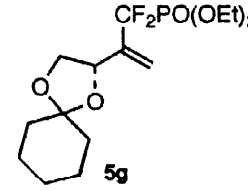
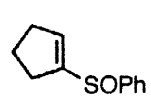
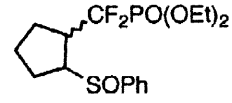
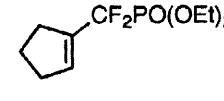
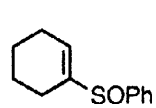
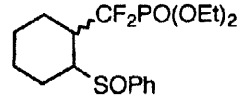
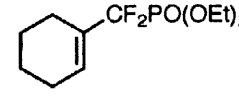
Interest is growing in the development of general methods that allow the synthesis of compounds in which the difluoromethylenephosphonato group is borne within a functionalised array.[1-3] For example, the Shibuya group has developed copper(I) bromide catalysed coupling of [(diethoxyphosphinyl)-difluoromethyl]zinc bromide to alkenyl iodides, and a related addition across alkynes.[4] This will become a valuable method for the synthesis of analogues of phosphate containing natural products[5,6] and has already found direct application in the design and syntheses of potential PNP inhibitors.[7] Free radical addition of diethyl iododifluoromethylphosphonate to terminal alkynes has also been described by Li and Chen,[8] though the starting materials are less accessible. Recently, we reported our findings on the cerium-mediated conjugate additions of [(diethoxyphosphinyl)difluoromethyl]lithium **1** to acyclic and cyclic vinyl sulfones.[9] The reaction proceeded smoothly with cyclic vinyl sulfones but failed with all but the simplest acyclic congeners. Nevertheless, the cyclic products underwent reductive desulfonation to afford the products of formal alkylation of the lithiophosphonate. We decided to explore the behaviour of vinyl sulfoxides under similar conditions (**Scheme 1**).



Scheme 1

0040-4039/98/$ - see front matter
PII: S0040-4039(98)02000-0

Table 1. Conjugate additions to Vinyl Sulfoxides

Electrophile	Adduct[a]	Yield (%)	Alkene[b]	Yield (%)
 **3a**	 **4a**	52	 **5a**	75
 **3b**	 **4b**	73	 **5b**	77
 **3c**	 **4c**	55	 **5c**	62
 **3d**	 **4d**	40	 **5d**	54
 **3e**	 **4e**	23	 **5e**	61
 **3f**	 **4f**	15	 **5f**	44
 **3g**	 **4g**	17	 **5g**	53
 **3h**	 **4h**	71	 **5h**	76
 **3j**	 **4j**	75	 **5j**	75

[a]All possible diastereoisomers were detected. [b]Only one regiosomer was detected in each case.

Acyclic vinyl sulfoxides **3b-g** (except **3a** which was available commercially) were prepared as mixtures of *E* and *Z* diastereoisomers from the reaction of **2** with aldehydes under the mild conditions described for alkenoate synthesis by Rathke, and modified by us for the synthesis of a difluorophosphonate-containing vinyl sulfone dienophile.[10] Cyclic vinyl sulfoxides **3h** and **3j** were prepared by addition of PhSCl to the alkenes followed by careful oxidation and

elimination.[11] The lithiophosphonate was prepared in the presence of cerium(III) chloride as described previously;[12] addition of **3h** and **3j** afforded conjugate adducts **4h** and **4j** as mixtures of diastereoisomers in 71% and 75% yield respectively after the usual acid work up. We made no attempt to unravel the stereochemical outcome of the addition reaction; instead, after the removal of non-conjugate addition products, the mixtures were taken up in toluene and heated affording alkenes **5h** and **5j** in 76% and 75% respectively after 18 hours at reflux. The additions failed completely in the absence of the lanthanide reagent.

Adding **3b** to the lithiophosphonate/cerium(III) chloride mixture afforded adduct **4b** in 50% yield as a complex mixture of stereoisomers after mild acidic work up.[13] The yield for the addition to the corresponding sulfone was only 25%; conceivably, the higher addition yield reflects a lower rate of deprotonation, consistent with the weaker acidifying power of the sulfinyl group. However, in the presence of two equivalents of the lithiophosphonate and three equivalents of the lanthanide reagent, **4b** was obtained in 73% isolated yield. One possible explanation for this result would involve Lewis acid mediation of the addition by the highly oxophilic lanthanide reagent. Reaction yields only increased when the third equivalent of lanthanide reagent was present, suggesting that the first two equivalents are complexed tightly to (or have reacted with) the lithiophosphonate nucleophile. We were not able to find examples of Lewis-acid mediated addition reactions to vinyl sulfoxides[14] though catalysis of cycloaddition reactions of alkynyl sulfoxides has been reported by Lee and co-workers.[15] Steric hindrance (**4f** and **4g**) and electronic deactivation (**4e**) took their toll of the isolated yield in preliminary experiments though again, the comparison with the corresponding sulfonyl analogues is interesting (5% and 0% addition to the analogues of **4d** and **4e** respectively). All the stereoisomeric mixtures of adducts underwent sulfoxide elimination[16] under the conditions described previously to afford the alkenyl products **5a-5g** in moderate to good yields.

Products **5a-g** represent useful complements to the alkyne adducts described by Shibuya *et al.*, and Lin and Chen in which the difluorophosphonate group occupies the terminal or chain end position. Our efforts to optimise and apply these methods will continue.

Acknowledgements

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References and Notes

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[9] Blades K, Lapotre D, Percy JM. Tetrahedron Lett.1997; 38: 5895-5898.

[10] Blades K, Lequeux TP, Percy JM. Chem. Commun.1996;1457-1458. The method was based on the following: Rathke MW, Nowak M. J. Org. Chem. 1985;50;2624-2626. Commercial diethyl (phenylthio)methylphosphonate was oxidised to **2** (1.0 eq. *m*CPBA, DCM, 10 min) then treated with an aldehyde (1.1 eq.) and triethylamine (1.1 eq.) in THF containing LiBr (1.1 eq.) at 0 °C for 18 hours to afford *E/Z* mixtures of vinyl sulfoxides in good yields (65-80%).

[11] Based on the method of Hopkins PB, Fuchs PL J. Org. Chem.1978;43:1208-1207. Phenylsulfenyl chloride was generated *in situ* and reacted with the alkenes in quantitative yield (DCM, rt) within 10 mins. The *trans*-chloro phenylsulfides were oxidised with *m*CPBA (1.0 eq., DCM, 10 min) then refluxed with DBU (2.0 eq. $CHCl_3$, 5 days).

[12] Blades K, Lequeux TP, Percy JM. Tetrahedron 1997; 53: 10623-10632.

[13] Typical procedure: **Preparation of 4a**

LDA was generated *via* the slow addition of *n*-butyllithium (3.10 ml of a 1.8 M solution in hexanes) to di*iso*propylamine (0.82 ml, 5.83 mmol) in THF (15 ml) at -78 °C, under dry nitrogen. After stirring for 1 hour at -78 °C, anhydrous cerium(III) chloride (1.30 g, 5.30 mmol), which had been dried by periodic heating to 200 °C under reduced pressure (0.1 mmHg), was added rapidly to the mixture, to afford a white suspension. The reaction was stirred for a futher 45 minutes at -78 °C. Diethyl (difluoromethyl)phosphonate (0.83 ml, 5.30 mmol) was added dropwise over a 15 minute period to the reaction to afford a pale orange solution. The reaction was stirred at -78 °C for a further 60 minutes, then phenyl vinyl sulfoxide (0.80 g, 5.30 mmol) was added slowly. The reaction was allowed to stir for 60 minutes before being quenched with saturated ammonium chloride solution (10 ml) at -78 °C. The mixture was extracted with diethyl ether (4 x 20 ml) and the combined organic extracts were dried ($MgSO_4$). The solvent was removed *in vacuo* to afford a yellow oil. Purification by column chromatography (R_f = 0.10, 40% ethyl acetate in 40-60 petroleum ether) afforded the conjugate adduct **4a** (0.85 g, 47%). (Found : C, 45.84; H, 5.53%. Calcd for $C_{13}H_{19}F_2O_4PS$: C, 45.88; H, 5.59%); δ_H (300 MHz; $CDCl_3$) 7.64-7.18 (m, 5H), 4.34-4.06 (m, 4H,), 3.20-3.07 (m, 1H), 2.92-2.78 (m, 1H,), 2.67-2.35 (m, 1H), 2.28-2.03 (m, 1H), 1.38-1.19 (m, 6H); δ_C (75 MHz; $CDCl_3$) 142.6, 131.3, 129.4, 123.9, 119.7 (dt, $^1J_{C-P}$ 216. 5 Hz, $^1J_{C-F}$ 260.5 Hz), 64.7, 47.6, 26.3 (dt, $^2J_{C-P}$ 15.8 Hz, $^2J_{C-F}$ 22.1 Hz), 16.3; δ_F (282 MHz; $CDCl_3$) -111.1-(-111.2) (m, 1F), -111.4-(-111.6) (m, 1F); δ_P (121 MHz; $CDCl_3$) 6.3 (t, $^2J_{P-F}$ 105.9 Hz); m/z (Electrospray) 379 (15%, $M+[K]^+$), 363 (100%, $M+[Na]^+$). Satisfactory NMR and HRM Spectra were obtained for all other (chromatographically pure) new compounds.

[14] Though additions of carbonyl-stabilised carbanions to vinyl sulfoxides appear to be relatively common, we found few examples of additions of less stabilised organometallic species such as cuprates. For one example, see Takaki K., Maeda T., Ishikawa M. J. Org. Chem. 1989;54:58-62 Reactions of more activated species such as (arylsulfinyl)cycloalkenones are summarised in Perlmutter P. Conjugate addition reactions in organic synthesis. Oxford: Pergamon Press, 1992:170-172.

[15] Lee AWM, Chan WH, Ji FY, Poon WH. J. Chem. Res. (S). 1995:368-369; Lee AWM, Chan WH. Top. Curr. Chem. 1997:190;103-129.

[16] Typical procedure:**Preparation of 5c**

Adduct **4c** (0.533 g, 1.45 mmol) was dissolved in toluene (10.0 ml) and the reaction was refluxed for 24 hours to afford a dark solution. The solution was concentrated *in vacuo* and purified by flash column chromatography (R_f = 0.47, 40% ethyl acetate in 40-60 petroleum ether) to afford **5c** as a clear oil (0.200 g, 54%). (Found : C, 47.04; H, 7.41%. Calcd for $C_{10}H_{19}F_2O_3P$: C, 46.88; H, 7.42%); δ_H (300 MHz, $CDCl_3$) 5.59 (s, 1H), 5.38 (s, 1H), 4.30-4.14 (m, 4H,), 2.71-2.60 (m, 1H), 1.33 (t, 6H, $^3J_{H-H}$ 7.4 Hz), 1.09 (d, 6H, $^3J_{H-H}$ 6.6 Hz); δ_C (75 MHz; $CDCl_3$) 148.5 (dt, $^2J_{C-P}$ 12.4 Hz, $^2J_{C-F}$ 17.5 Hz), 119.0 (dt, $^1J_{C-P}$ 215.9 Hz, $^1J_{C-F}$ 262.8 Hz), 117.4 (dt, $^3J_{C-P}$ 5.1 Hz, $^3J_{C-F}$ 10.1 Hz), 64.3, 28.0, 23.4, 16.2; δ_F (282 MHz, $CDCl_3$) -109.6 (d, $^2J_{F-P}$ 115.2 Hz); δ_P (121 MHz, $CDCl_3$) 6.9 (t, $^2J_{P-F}$ 115.2 Hz); m/z (CI) 274 (35%, $M+[NH_4]^+$), 257 (100%, M+1). Satisfactory NMR and HRM Spectra were obtained for all other (chromatographically pure) new compounds.