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Conjugate Addition Reactions of a (Diethoxyphosphinoyl)difluoromethyl Anion Equivalent to Acyclic and Cyclic Vinyl Sulfones.

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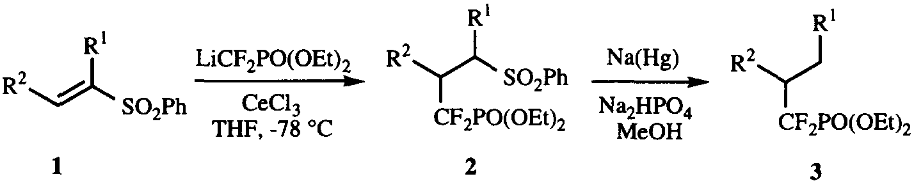
Abstract:Cerium-mediated conjugate additions of (diethoxyphosphinoyl)difluoromethyllithium to cyclic vinyl sulfones proceeded smoothly; reduction afforded the products of formal alkylation, attaching the difluoromethylene phosphonate group to a secondary carbon atom. With acyclic vinyl sulfones, the addition was considerably less efficient and deprotonation competed with addition. Addition failed completely in the absence of cerium(III) chloride. © 1997 Elsevier Science Ltd.

Interest is growing in the development of general methods that allow the synthesis of compounds which contain the difluoromethylene phosphonate group within a functionalised array. Most of the existing methods use a (diethoxyphosphinoyl)difluoromethylmetal reagent in carbon-carbon bond forming reactions.[1] The lithium congener deployed recently by Piettre[2,3] and Berkowitz[4] reacts effectively with hard carbonyl electrophiles in a number of useful reactions. The zinc reagent described originally by the Burton group in Iowa has been used in copper-catalysed coupling reactions with a range of aryl and vinyl halides by the Shibuya group,[5,6] expanding considerably the range of available targets.

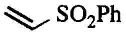
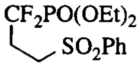
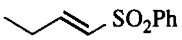
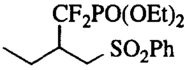
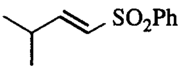
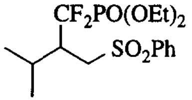
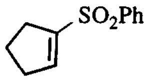
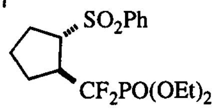
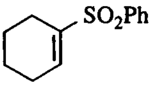
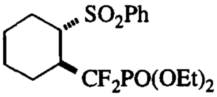
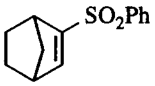
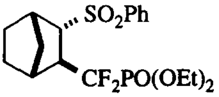
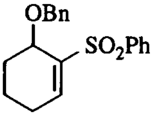
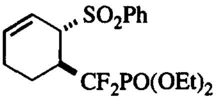
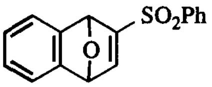
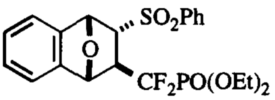
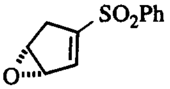
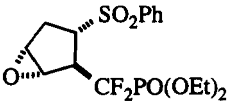
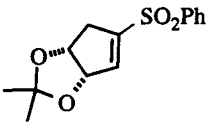
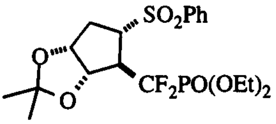
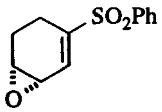
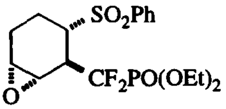
We have shown that the presence of cerium(III) chloride allowed conjugate addition reactions with nitroalkenes,[7,8] and smooth reactions with carboxylic acid esters.[9] In the search for chemistry that was synthetically equivalent to alkylation of the title compound,[10,11] we examined cerium-mediated conjugate additions to acyclic and cyclic vinyl sulfones (**Scheme 1**).[12] These reactions were attractive because of the possibility of mild reductive cleavage of the C-SO_2Ph bond, and because both the acyclic and cyclic substrates were extremely easy to prepare.



Scheme 1

The results are summarised in **Table 1**. Addition failed completely in the absence of the lanthanide salt and the low yields in the acylic series are notable;[13] the yields failed to improve even when an excess (5 equivalents) of the nucleophile were employed. When the reaction with **1b** was quenched with CH_3OD, we obtained deuterated product and recovered α-deuterated **1b** indicating that deprotonation competed with addition. Presumably, the still lower yield for **1c** arises from the greater steric bulk of the β-substituent. We were more successful using cyclic substrates which were prepared following the procedure of Hopkins and Fuchs,[14] in which phenyl sulfenyl chloride is generated *in situ*, except for **1g** and **1j-l** for which the chlorosulfenylation step was performed using freshly-distilled phenyl sulfenyl chloride.[15]

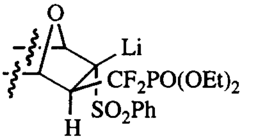
Table 1. Conjugate additions to Vinyl Sulfones

Electrophile		Adduct		Yield (%)
	**1a**		**2a**	47
	**1b**		**2b**	20
	**1c**		**2c**	5
	**1d**		**2d**	63[a]
	**1e**		**2e**	65[a]
	**1f**		**2f**	59[a]
	**1g**		**2g**	43[a]
	**1h**		**2h**	63[a]
	**1j**		**2j**	53[a]
	**1k**		**2k**	61[a]
	**1l**		**2l**	65[a]

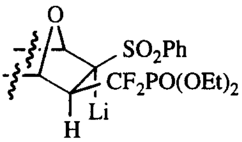
[a] Only one diastereoisomer (racemic modification) could be detected.

Oxidations to **1j-l** were performed using standard methods. Conjugate additions proceeded from the less hindered face of the alkene in moderate though useful yields affording *trans* products (presumably) in all cases.[16] Presumably, the cyclic vinyl sulfones are less acidic because the conformation required for deprotonation in which the scissile C-H bond is co-axial with the p-orbitals of the π-bond is more difficult to attain in the constrained systems.

The additions to **1g** and **1j-l** are attractive because they indicate that highly functionalised systems may be accessible using this chemistry. The reactions of **1g** and **1h** are related and deserve comment. Conjugate addition sets the stage for C-O bond cleavage, a reaction employed to effect by Plumet *inter alia* in *de novo* syntheses of various cyclitols.[17-19] There are mechanistic ambiguities in these transformations and at this stage, we are not able to distinguish between elimination/addition and addition/elimination (followed by isomerisation) mechanisms for the formation of **1g**. In **1h**, *cis*-addition from the less hindered top face sets up an sp^3 type carbanion **4** on the upper face which cannot invert rapidly to **5** because of the eclipsing interaction which would develop between the two bulky groups. Elimination must then occur through an unfavourable *syn*-coplanar stereoelectronic arrangement.[20]

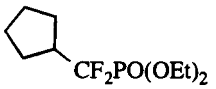


4

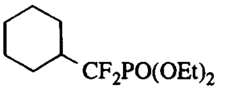


5

The preparation of **2a** from **1a** is representative. Dried[21] solid cerium(III) chloride (1.0 equiv.) was added to freshly-prepared LDA (1.05 equiv., *ca.* 0.3 M in THF) at -78 °C. After stirring for 45 minutes at -78 °C, diethyl(difluoromethyl)phosphonate (1.0 equiv.) 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 sulfone (1.0 equiv.) was added slowly. The reaction was allowed to stir for 1 hour before being quenched with saturated ammonium chloride (10 ml) at -78 °C. Extractive work up followed by column chromatography afforded the conjugate adduct.[22]



3d



3e

3f

Amalgam reduction was performed at a substrate concentration of 0.1 M in methanol[23] (5% Na(Hg), 5.0 equivalents) containing Na$_2$HPO$_4$ (7.0 equivalents) at room temperature, proceeding smoothly[24] for **2d-2f** to afford useful yields of **3d-3f** (67, 65 and 73% respectively) suggesting that extremely general formal alkylation chemistry is available. We are exploring applications of this chemistry for the construction of analogues of phosphocyclitols.

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20. Eliminative ring openings of 7-oxabicyclo[2.2.1]heptanyl systems *via* sulfonyl-stabilised carbanions are relatively rare. An highly optimised case was described by Plumet and co-workers; see Acena, J. L.; Arjona, O.; Delapradilla, R. F.; Plumet, J.; Viso, A. *J. Org. Chem.*, **1992**, *57*, 1945-1946. Jung and Truc described an anomalous reaction pathway in the context of a similar reaction that looked straightforward; Jung, M. E.; Truc, V. C. *Tetrahedron Lett.*, **1988**, *29*, 6059-6062. For an overview of ring opening reactions of related substrates, see Woo, S., Keay, B. A. *Synthesis*, **1996**, 669-686.
21. The issue of dryness (or otherwise) of the lanthanide salt is contentious and has been discussed; see Blades, K.; Percy, J.M., Lequeux, T.P. *Tetrahedron*, **1997**, in press.
22. All compounds were purified by flash column chromatography and characterised by ^{1}H, ^{19}F, ^{13}C, and ^{31}P NMR and HRMS.
    Data for **2a**: $R_f = 0.3$, 40% ethyl acetate/40-60 petroleum ether; Found : C, 43.59; H, 5.41. Calcd for $C_{13}H_{19}O_5F_2PS$: C, 43.82; H, 5.33%; δ_H (300 MHz; $CDCl_3$) 7.87 (d, 2H, $^3J_{H-H}$ 7.7 Hz), 7.63 (t, 1H, $^3J_{H-H}$ 7.7 Hz), 7.53 (t, 2H, $^3J_{H-H}$ 7.7 Hz), 4.25-4.10 (m, 4H), 3.36-3.23 (m, 2H), 2.57-2.32 (m, 2H), 1.28 (t, 6H, $^3J_{H-H}$ 7.5 Hz); δ_C (75 MHz; $CDCl_3$) 138.5, 134.3, 129.6, 128.1, 119.0 (dt, $^1J_{C-P}$ 216.9 Hz, $^1J_{C-F}$ 261.3 Hz), 64.9, 48.8, 28.0 (dt, $^2J_{C-P}$ 16.7 Hz, $^2J_{C-F}$ 19.1 Hz), 16.5; δ_F (282 MHz; $CDCl_3$) -111.8 (dt, $^2J_{F-P}$ 104.3 Hz, $^2J_{F-H}$ 18.3 Hz); δ_P (121 MHz; $CDCl_3$) 5.9 (t, $^2J_{P-F}$ 104.3 Hz); m/z (CI) 374 (85%, $M+[NH_4]^+$), 357 (100%, M+1).
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24. Desulfonations should be monitored carefully by TLC; the lability of the C-P bond under basic conditions can lead to product decomposition at extended reaction times. In the cases of **2d** and **2e**, reduction was complete within 2 hours. To date, desulfonations of other conjugate adducts have not been attempted.

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