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A Reproducible and High-yielding Cerium-mediated Route to α,α-Difluoro-β-ketophosphonates.

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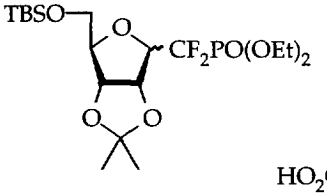
Abstract: The addition of diethyldifluoromethylphosphonate to LDA containing cerium(III) chloride in THF generates an organometallic nucleophile that reacts efficiently with esters and DMF (1,2-addition) affording moderate to good yields of adducts, and extending considerably the range of compounds available containing the difluoromethylenephosphonate group.

The mimicry of reactive phosphate esters has become an established and profitable tactic in the design of biologically-active compounds with useful properties. Methylene, fluoromethylene and difluoromethylene-phosphonates have been prepared as non-hydrolysable analogues of compounds (or their direct precursors) including glycosyl phosphates (such as **1**),[1] nucleoside 5'-phosphates **2**,[2] protected phosphoamino acids tyrosine[3] **3** and serine[4] **4**, and dihydroxyacetone phosphate **5**.[5]



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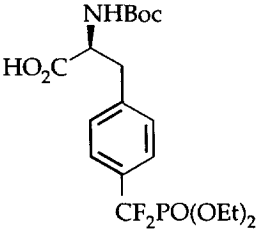

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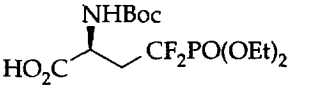

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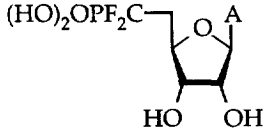

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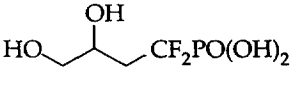


5

In two cases,[3,6] all three analogues have been prepared and compared to the parent phosphate esters; indeed comparisons of this type have led to the development of vigorous controversy as to which is the "best" analogue.[7] In some cases, for example with inhibitors of bacterial Phospholipase C, the methylene and difluoromethylene phosphonates appeared to be equipotent,[8] whereas hexapeptide ligands for protein tyrosine kinase SH-2 domains containing **3** were considerably more effective than methylene or fluoromethylene congeners.[3] A molecular recognition issue clearly exists, but currently, one of the major limitations to useful

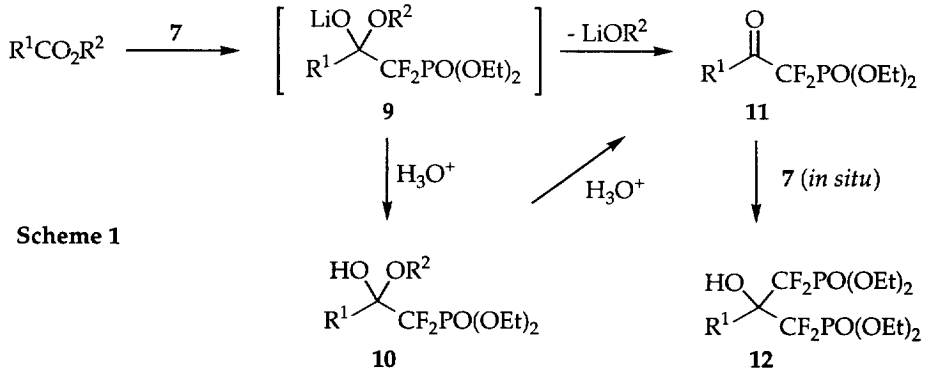
discourse has been the scope of the synthetic methodology available. The difluoromethylenphosphonate group can be attached to primary (CH_2) centres with some facility,[9] but the development of secondary centres bearing the phosphate mimic has remained problematic,[10] particularly within complex molecules, so that analogues of many important phosphorylated sugars, cyclitols and nucleosides have remained inaccessible.[11] The problem hinges around the relatively restricted nucleophilicity of lithiodifluoromethylene phosphonates such as **7** and serious problems of reproducibility of some of the procedures reported in the literature.

$HF_2CPO(OEt)_2$ $XF_2CPO(OEt)_2$

6 **7**, X = Li;
8, X = ZnBr.

For example, the original publication in the area by Kondo and Obayashi[12] described the generation of **7** from **6** and the reaction with carbonyl electrophiles, leading ultimately to the formation of 1,1-difluoroalkenes. The method is extremely sensitive to minute variations in experimental conditions and quality of the organolithium reagent used to perform the metallation, prompting Piettre[13] and Savignac[14] to develop significant improvements in independent studies. Other workers notably the groups of Burton and Shibuya, have described the preparation of other organometallic reagents. For example, zinc[15] and cadmium[16] phosphonates which undergo copper catalysed reactions with electrophiles have been described. We became interested in developing a new method for the synthesis of difluorinated ketophosphonates, compounds of potential biological use[17] and intermediates with some synthetic potential. In this paper, we wish to report in full our studies concerning the cerium-mediated addition reactions of the lithiophosphonate to carboxylic ester electrophiles.[18]

The effect of cerium(III) salts on the reactivity of organolithium reagents and lithium amide bases has been described extensively in the literature.[19] We reasoned that the cerium salt might be capable of interacting strongly with the tetrahedral intermediates formed upon the addition of the metallated phosphonate to carbonyl electrophiles, in particular, carboxylic esters. By assisting the nucleophilic addition and maybe preventing the collapse of tetrahedral intermediate **9** to β-phosphonoketone compound **11** *in situ*, or preventing phosphoryl transfer reactions,[12,13] the cerium additive could simplify considerably the reaction sequence opening an efficient route to α,α-difluoro-β-ketophosphonates (**Scheme 1**).

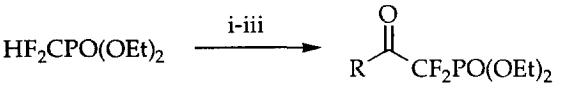


Scheme 1

Work up would then decompose hemiketal **10** and the formation of double addition product **12** would be avoided.[20]

We were concerned that the anticipated high electrophilicity of **11** would result in the formation of significant amounts of **12**. The established literature route to compounds of this type involves the copper catalysed reaction of **8** with acid chlorides.[15] A significant disadvantage of this method lies in the requirement of the use of an acid chloride electrophile, limiting the range of other functional groups that can be present. More recently in a significant advance and to our great surprise, Berkowitz and co-workers[21] described the addition of **7** to methyl esters as a direct route to α,α-difluoro-β-ketophosphonates; in our hands, the reaction of **7** with *ethyl* esters gave at best moderate yields of the desired ketophosphonates, even with very simple electrophiles like ethyl benzoate, and was very sensitive to the quality of the alkyllithium reagent used to prepare the LDA; when the *n*-butyllithium contained appreciable amounts of lithium hydroxide or oxide, very poor yields were obtained. Yields also declined in the presence of added lithium bromide. However, running the reaction in the presence of cerium(III) chloride offered a number of advantages.

The cerium-mediated method (**Scheme 2**) used ethyl ester electrophiles, short reaction times (typically 1 hour) and reproducibly high yields of products uncontaminated by side products. **Table 1** shows the range of compounds prepared using this method. The key step involves the addition of dried solid cerium(III) chloride to a solution of freshly-prepared LDA in THF at -78 °C. After one hour, the ester electrophile could be added directly (without pre-cooling).[22] A work up with aqueous hydrochloric acid completed the sequence.



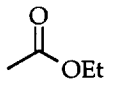
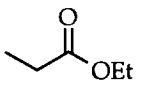
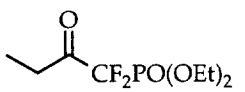
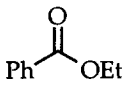
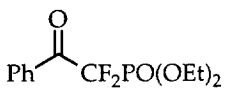
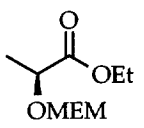
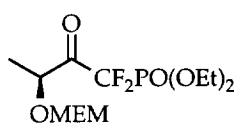
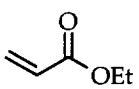
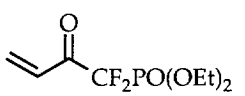
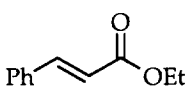
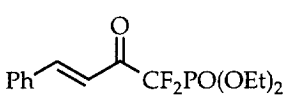
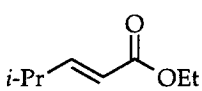
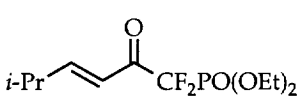
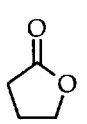
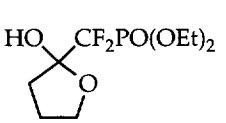
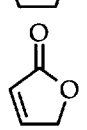
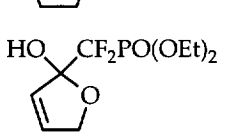
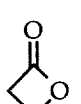
6 **11**

Scheme 2. Reagents and Conditions: i, 1.0 LDA, $CeCl_3$, THF, -78 °C; ii, RCO_2Et; iii, $HCl_{(aq)}$.

The preparation of the "dried" cerium(III) chloride requires some comment; commercial cerium(III) chloride develops polymeric oxides upon storage so some literature procedures recommend Soxhlet extraction into THF before use. Also the salt has low solubility in THF and the early procedures "digest" the salt into THF by lengthy periods of stirring before the addition of the Grignard or organolithium reagent.[23] More recently, sonication has been used to accelerate the solution process.[24] We simply pre-ground the commercial heptahydrate, heated the material to *ca.* 200 °C *in vacuo* repeatedly over 2 hours and allowed the material to cool under an atmosphere of argon. We believe that the lanthanide salt is *effectively* anhydrous; if one mole equivalent (or more) of water is retained *in available form*,[25] we would expect to observe the formation of one equivalent of **6** from the reaction, *yet **6** was absent in quantity from the crude reaction mixtures*. The reaction accepted a range of substrates, including simple aliphatic and aromatic esters. A protected hydroxyl at the α-position was tolerated though the extent to which racemisation had occurred was not determined.

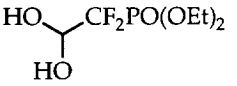
When ethyl acrylate was used as the electrophile, 1,4-addition competed with ketoester formation, and yields of both regioproducts were modest; however, the presence of a substituent (Ph or *i*-Pr) at the β-position of the alkenoate restored both the 1,2-selectivity and the yield.

Table 1. Reaction of 7 with ester and lactone electrophiles.

Electrophile	Product		Yield[a] (%)
		**11a**	61
		**11b**	88
		**11c**	81
		**11d**	68
			20[b]
		**11e**	57
		**11f**	71
		**11g**	76
		**11h**	14[b]
	(-)[c]		(-)

[a]Yields refer to isolated yields of pure (>98% by GC) products.
[b]An inseparable 1:1 mixture of 1,2- and 1,4-adducts was isolated.
[c]Complex mixture of (>10) products.

With butyrolactone, the 1,2-addition product could not be ring opened beyond the hemiketal stage. An inseparable mixture of 1,2- and 1,4-products was isolated in poor (31%) yield from the reaction with 5(2*H*)-furanone. Several attempts to open strained β-propiolactone led to the formation of multiple (>10) products, even at -100 °C and the reaction failed completely with *N,N*-dimethylacrylamide.However, with DMF,[26] an electrophile which fails[27] to yield useful products when exposed to **7**, we obtained an interesting result. After acid work-up, the hydrate **12** of the aldehyde product was obtained in excellent (80%) scaleable yield.[28] The hydrate could be purified by column chromatography and careful Kugelrohr distillation from phosphorus pentoxide afforded the aldehyde. However, this material rehydrated extremely rapidly on contact with air and complete characterisation was impossible.



12

With *N,N*-dimethylacetamide, we were unable to isolate either the methyl ketone or the corresponding hydrate due to poor conversion (even after extended reaction times) and difficulties with purification (preventing the full characterisation of the reaction products) though the acetyl phosphonate was available from the cerium-mediated reaction with ethyl acetate. Clearly the replacement of a hydrogen atom by a methyl group has a critical effect on the rate of nucleophilic addition. With ethyl propiolate, deprotonation of the alkyne occurred and none of the adduct was formed, indicating that the so-called cerium reagent still displays appreciable basicity.

In conclusion, we recommend this method as a direct, reproducible and high yielding approach to useful and interesting ketophosphonates.

Acknowledgement

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EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC-300 (300.13 and 75.47 MHz respectively) and Bruker AMX-400 (400.14 and 100.6 MHz respectively) spectrometers. All spectra were recorded relative to tetramethylsilane as the internal standard. ^{19}F-NMR spectra and ^{31}P-NMR spectra were recorded on a Bruker AC-300 (282.41 and 121.5 MHz respectively) or a Jeol GX-90 (84 MHz for ^{19}F) spectrometer relative to chlorotrifluoromethane and *ortho*-phosphoric acid as the internal standards. ^{13}C NMR spectra were recorded using the PENDANT pulse sequence unless stated otherwise. Mass spectra were recorded on a VG Prospec mass spectrometer. Chemical ionisation (CI^+) methods used ammonia as the reactant gas. Microanalyses were performed at the University of Sheffield (fluorine analysis could not be obtained). For TLC, precoated aluminium-backed silica gel plates were supplied by E. Merck, A.G. Darmstadt, Germany (Silica gel 60 F_{254}, thickness 0.2 mm). Potassium permanganate staining was employed for visualisation,

unless stated otherwise. Column chromatography was performed using silica gel (E. Merck A. G. Kieselgel 60, Art. 9385). Column fractions were collected and monitored by thin layer chromatography.

Gas chromatographic analyses were carried out on a Carlo-Erba 8000 series chromatograph. The chromatograph was fitted with a wall-coated fused silica capillary column, type DB-5 (50 m). Infra red spectra were obtained from a Perkin Elmer 1600 series FTIR spectrophotometer, in the region 4000-625 cm^{-1}. The samples were run as films.

Tetrahydrofuran was dried by refluxing with sodium metal and benzophenone under dry nitrogen, until a deep purple colour persisted. The solvent was then collected by syringe as required. Cerium(III) chloride heptahydrate (99%, #22,893-1) was purchased from the Aldrich Chemical Company and used without further purification. Dimethyl formamide and diisopropylamine were distilled from calcium hydride and stored over fresh calcium hydride under nitrogen. All electrophiles were purchased from the Aldrich Chemical Company and distilled before use, or prepared freshly by literature procedures. Ethyl lactate was converted to the MEM ether following the protocol of Massad and co-workers.[29]

Ketophosphonate products could be stored for extended periods in the freezer. All products were purified to >98% purity by Kugelrohr distillation or flash column chromatography and analysed immediately.

Typical Procedure: Preparation of (**11a**).

n-Butyllithium (4.0 ml of 1.4 M solution in hexane, 5.6 mmol) was added dropwise to a cold (-78 °C) solution of diisopropylamine (0.80 ml, 5.7 mmol) in dry THF (15 ml). The solution was warmed to 0 °C for 10 minutes under dry nitrogen then recooled to -78 °C; freshly-dried (see text) cerium(III) chloride (1.30 g, 5.3 mmol) was added then in one portion. The resulting suspension was stirred vigorously at -78 °C for 20 minutes. Diethyl difluoromethane phosphonate (1.0 g, 5.3 mmol) was added dropwise over 15 minutes and the mixture was stirred for 1 hour. Ethyl acetate (0.82 ml, 5.8 mmol) was added slowly to the pale yellow-orange suspension and after stirring for one hour further, aqueous hydrochloric acid (3N, 5.0 ml) was added and the mixture was stirred and warmed to room temperature over a further 20 minutes. The aqueous layer was extracted with dichloromethane (10 ml) and the combined organic layers were washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Kugelrohr distillation of the crude product afforded pure *ketophosphonate* **11a** (0.86 g, 61%) as a clear oil, b.p. 65-75 °C/0.1 mmHg; δ_H(300 MHz, $CDCl_3$) 4.29-4.11 (4H, *m*, -OC*H*$_2$CH$_3$), 2.31 (3H, *s*, C*H*$_3$CO), 1.24 (6H, *t*, $^3J_{H\text{-}H}$ 7.0, -OCH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 196 (*dt*, $^2J_{C\text{-}P}$ 14.6, $^2J_{C\text{-}F}$ 24.15,*C*O), 112.2 (*dt*, $^1J_{C\text{-}P}$ 195.8, $^1J_{C\text{-}F}$ 269.6, *C*F$_2$), 65.1 (*d* , $^2J_{C\text{-}P}$ 6.3, -O*C*H$_2$CH$_3$), 25.2 (*C*H$_3$CO), 16.1 (*d*, $^3J_{C\text{-}P}$ 5.2, -OCH$_2$*C*H$_3$); δ_F(282 MHz, $CDCl_3$) -118.2 (*d*, $^2J_{F\text{-}P}$ 96.7); δ_P(121 MHz; $CDCl_3$) 3.3 (*t*, $^2J_{P\text{-}F}$ 96.7); *m/z* 248 ($M+NH_4^+$, 65), 231 ($M+H^+$, 100), 213 (15); νmax (Film) 1760 (C=O), 1290 (P=O) cm^{-1}. HRMS calculated for $[C_7H_{17}NF_2O_4P]^+$ 248.086010, found 248.086328.

Preparation of (**11b**).

Following the general experimental procedure, using ethyl propionate (0.61 ml, 5.3 mmol) as electrophile, followed by Kugelrohr distillation afforded **11b** (1.15 g, 88%) as a colourless oil, b.p. 50-55 °C/0.1 mmHg; (Found: C, 39.48; H, 6.09. Calc. for $C_8H_{15}F_2O_4P$: C, 39.35; H, 6.19%); δ_H(300 MHz, $CDCl_3$) 4.27-4.09 (4H, *m*, -OC*H*$_2$CH$_3$), 2.55 (2H, *q*, $^3J_{H\text{-}H}$ 7.0, -OCC*H*$_2$CH$_3$), 1.20 (6H, *t*, $^3J_{H\text{-}H}$ 7.0, -OCH$_2$C*H*$_3$), 0.95 (3H, *t*, $^3J_{H\text{-}H}$ 7.0, -OCCH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 199.1 (*dt*, $^2J_{C\text{-}P}$ 14.2, $^2J_{C\text{-}F}$ 23.1, *C*O), 113.2 (*dt*, $^1J_{C\text{-}P}$ 195.0, $^1J_{C\text{-}F}$ 273.3, *C*F$_2$), 65.1 (*d*, $^2J_{C\text{-}P}$ 6.5, -O*C*H$_2$CH$_3$), 30.8 (-OC*C*H$_2$CH$_3$), 15.9 (*d*, $^3J_{C\text{-}P}$ 5.0,

-OCH_2CH_3), 6.1 (-$OCCH_2CH_3$); δ_F(84 MHz, $CDCl_3$) -118.5 (*d*, $^2J_{F-P}$ 94.6); δ_P(36 MHz, $CDCl_3$) 3.2 (*t*, $^2J_{P-F}$ 94.6); *m/z* 262 ($M+NH_4^+$, 90), 245 ($M+H^+$, 100%), 208 (40), 206 (50), 168 (15), 52 (15); νmax (Film) 1742 (C=O), 1280 (P=O) cm^{-1}.

Preparation of (**11c**).

Following the above experimental procedure, using ethyl benzoate (0.85 ml, 5.3 mmol) as electrophile, and followed by Kugelrohr distillation afforded **11c** (1.25 g, 81%) as a clear oil, b.p. 140-150 °C/0.1 mmHg; (Found: C, 49.35; H, 5.13. Calc. for $C_{12}H_{15}F_2O_4P$: C, 49.32; H, 5.17%); δ_H(300 MHz, $CDCl_3$) 8.10 (2H, *d*, $^3J_{H-H}$ 8.0, *o*-Ph), 7.60 (1H, *t*, $^3J_{H-H}$ 8.0, *p*-Ph), 7.45 (2H, *dd*, $^3J_{H-H}$ 8.0, $^3J_{H-H}$ 8, *m*-Ph), 4.37-4.21 (4H, *m*, -OCH_2CH_3), 1.45 (6H, *t*, $^3J_{H-H}$ 6.5, -OCH_2CH_3); δ_C(75 MHz, $CDCl_3$) 187.9 (*dt*, $^2J_{C-P}$ 15.3, $^2J_{C-F}$ 24.1, *CO*), 134.7, 132.0, 130.3, 128.6 (*Ph*), 114.9 (*dt*, $^1J_{C-P}$ 200.4, $^1J_{C-F}$ 275.7, CF_2), 65.3 (*d*, $^2J_{C-P}$ 6.7, -OCH_2CH_3), 16.2 (*d*, $^3J_{C-P}$ 5.6, -OCH_2CH_3); δ_F(84 MHz, $CDCl_3$) -110.5 (*d*, $^2J_{F-P}$ 95.2); δ_P(36 MHz, $CDCl_3$) 3.4 (*t*, $^2J_{P-F}$ 95.2, *PO*); *m/z* 310 ($M+NH_4^+$, 7), 293 ($M+H^+$, 8%), 282 (60), 264 (35), 246 (15), 228 (10), 156 (100), 138 (32), 120 (35), 105 (22), 94 (7), 78 (7), 60 (8); νmax (Film), 1696 (C=O), 1290 (P=O) cm^{-1}.

Preparation of (**11d**).

Following the general experimental procedure, ethyl 2-[(methoxyethoxy)-methyloxy] propanoate[29] (1.10 g, 5.3 mmol) was used as the electrophile. Flash column chromatography (60% ethyl acetate in hexane) of the crude product afforded **11d** (1.25 g, 68%) as a clear oil; δ_H(300 MHz, $CDCl_3$) 4.58-4.45 (3H, *m*, -OCH_2O, -$OCH(CH_3)CO$), 4.19-4.06 (4H, *m*, -OCH_2CH_3), 3.48-3.41 (2H, *m*, -OCH_2CH_2O-), 3.30-3.24 (2H, *m*, -OCH_2CH_2O-), 3.15 (3H, *s*, -OCH_3), 1.20 (3H, *d*, $^3J_{H-H}$ 7.5, CH_3), 1.15 (6H, *t*, $^3J_{H-H}$ 7, -OCH_2CH_3); δ_C(75 MHz, $CDCl_3$) 198.4 (*dt*, $^2J_{C-P}$ 13.0, $^2J_{C-F}$ 23.2, *CO*), 113.3 (*dt*, $^1J_{C-P}$ 197.4, $^1J_{C-F}$ 275.7, CF_2), 98.4 (-OCH_2O-), 73.4 (-$OCH(CH_3)CO$), 71.3 (-OCH_2CH_2O-), 67.2 (-OCH_2CH_2O-), 65.2 (*d*, $^2J_{C-P}$ 6.7, -OCH_2CH_3), 58.6 (-OCH_3), 17.1 (CH_3), 16.2 (*d*, $^3J_{C-P}$ 5.4, -OCH_2CH_3); δ_F(84 MHz, $CDCl_3$) -117.5 (*d*, $^2J_{F-P}$ 95.2); δ_P(36 MHz, $CDCl_3$) 2.9 (*t*, $^2J_{P-F}$ 95.2); *m/z* 366 ($M+NH_4^+$, 30), 349 ($M+H^+$, 27%), 273 (68), 262 (15), 226(10), 196 (35), 209 (30), 174 (20), 156 (17), 108 (15), 94 (100), 52 (50), 44 (54); HRMS calculated for $[C_{12}H_{24}F_2O_7P]^+$ 349.122773, found 349.123122.

Preparation of (**11e**).

Following the general experimental procedure, ethyl *trans*-cinnamate (0.89 ml, 5.3 mmol) was used as the electrophile. Column chromatography (30% ethyl acetate in hexane) of the crude product afforded **11e** (0.960 g, 57%) as a yellow oil (R_f 0.38); (Found: C, 52.98; H, 5.42. Calc. for $C_{14}H_{17}F_2O_4P$: C, 52.83; H, 5.38%); δ_H(300 MHz, $CDCl_3$) 7.85 (1H, *d*, $^3J_{H-H}$ 15.3, H_b), 7.67-7.58 (2H, *m*, *Ph*), 7.50-7.36 (3H, *m*, *Ph*), 7.15 (1H, *d*, $^3J_{H-H}$ 15.3, H_a), 4.36-4.25 (4H, *m*, -OCH_2CH_3), 1.35 (6H, *t*, $^3J_{H-H}$ 7.0, -OCH_2CH_3); δ_C(75 MHz, $CDCl_3$) 186.6 (*dt*, $^2J_{C-P}$ 14.3, $^2J_{C-F}$ 23.4, *CO*), 148.0 (C_b), 133.8, 131.8, 129.2, 129.0 (*Ph*), 118.3 (C_a), 116.7 (*dt*, $^1J_{C-P}$ 195, $^1J_{C-F}$ 274, CF_2), 65.3 (*d*, $^2J_{C-P}$ 6.5, -OCH_2CH_3), 16.3 (*d*, $^3J_{C-P}$ 5.5, -OCH_2CH_3); δ_F(84 MHz, $CDCl_3$) -118.7 (*d*, $^2J_{F-P}$ 98.6); δ_P(36 MHz, $CDCl_3$) 3.5 (*t*, $^2J_{P-F}$ 98.6); *m/z* 336 ($M+NH_4^+$, 52), 319 ($M+H^+$, 100%), 301 (17), 283 (25), 147 (12), 139 (10), 131 (52), 106 (15), 100 (15), 52 (17).

Preparation of (**11f**).

Following the general experimental procedure, ethyl 4-methylpent-2-enoate (0.753 g, 5.3 mmol) was used as the electrophile. Column chromatography (25% ethyl acetate in hexane) of the crude product afforded **11e** (0.960 g, 71%) as a yellow oil; (Found: C, 52.98; H, 5.42. Calc. for $C_{14}H_{17}O_4F_2P$: C, 52.83; H, 5.38%); δ_H(300 MHz, $CDCl_3$) 7.15 (1H, *dd*, $^3J_{H\text{-}H}$ 6, $^3J_{H\text{-}H}$ 15.0, *Hb*), 6.50 (1H, *dd*, $^4J_{H\text{-}H}$ 1.3, $^3J_{H\text{-}H}$ 15.0, *Ha*), 4.31-4.23 (4H, *m*, -OC*H*$_2$CH$_3$), 2.56-2.42 (1H, *m*, C*H*(CH$_3$)$_2$), 1.30 (6H, *t*, $^3J_{H\text{-}H}$ 7.0, -OCH$_2$C*H*$_3$), 1.05 (6H, *d*, $^3J_{H\text{-}H}$ 7.5, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 187.0 (*dt*, $^2J_{C\text{-}P}$ 14.8, $^2J_{C\text{-}F}$ 24.0, *C*O), 160.1 (*C*H=CHCO), 119.8 (CH=*C*HCO), 114.0 (*dt*, $^1J_{C\text{-}P}$ 187, $^1J_{C\text{-}F}$ 273, *C*F$_2$), 65.3 (*d*, $^2J_{C\text{-}P}$ 6.5, -O*C*H$_2$CH$_3$), 31.7 (*C*(CH$_3$)$_2$), 20.8 (*C*H$_3$) 20.6 (*C*H$_3$), 16.3 (*d*, $^3J_{C\text{-}P}$ 5.5, -OCH$_2$*C*H$_3$); δ_F(84 MHz, $CDCl_3$) -118.7 (*d*, $^2J_{F\text{-}P}$ 99.3); δ_P(36 MHz, $CDCl_3$) 3.4 (*t*, $^2J_{P\text{-}F}$ 99.3); *m/z* 302 (M+NH$_4^+$, 55), 285 (M+H$^+$, 100%), 97 (38), 58 (13), 44 (36).

Preparation of (**11g**).

Following the above experimental procedure, using γ-butyrolactone (0.48 ml, 5.8 mmol) as the electrophile. Column chromatography (40% ethyl acetate in hexane) of the crude product afforded **11g** (1.10 g, 76%) as a clear oil R_f 0.47; (Found: C, 39.56; H, 6.24. Calc. for $C_9H_{17}O_5F_2P$: C, 39.42; H, 6.20%); δ_H(300 MHz, $CDCl_3$) 4.76 (1H, *Br. s*, -O*H*), 4.24-4.16 (4H, *m* , -OC*H*$_2$CH$_3$), 4.09-4.01 (1H, *m*, C*H*$_a$H$_b$O), 3.90-3.80 (1H, *m*, CH$_a$*H*$_b$O), 2.32-1.78 (4H, *m*, -OC*H*$_2$C*H*$_2$-), 1.24 (6H, *t*, $^3J_{H\text{-}H}$ 7.3, -OCH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 116.2 (*dt*, $^1J_{C\text{-}P}$ 197.8, $^1J_{C\text{-}F}$ 273.7, *C*F$_2$), 104.7 (*dt*, $^2J_{C\text{-}P}$ 12.0, $^2J_{C\text{-}F}$ 27.3, *C*OH), 69.7 (*C*-O), 65.1 (-O*C*H$_2$CH$_3$), 31.8 (-*C*H$_2$COH), 24.5 (-CH$_2$*C*H$_2$CH$_2$-), 16.1 (-OCH$_2$*C*H$_3$); δ_F(282 MHz, $CDCl_3$) -118.7 (1F, *dd*, $^2J_{Fa\text{-}P}$ 100.5, $^2J_{Fa\text{-}Fb}$ 301.4, F$_a$), -121.0 (1F, *dd*, $^2J_{Fb\text{-}P}$ 96.6, $^2J_{Fb\text{-}Fa}$ 301.4, F$_b$); δ_P(121 MHz; $CDCl_3$) 7.4 (*dd*, $^2J_{P\text{-}Fb}$ 96.6, $^2J_{P\text{-}Fa}$ 100.5); *m/z* 292 (M+NH$_4^+$, 10), 274 (M+H$^+$, 50), 257 (45), 206 (20), 139 (40).

Preparation of (**11h**).

Following the above experimental procedure, using 5(*2H*)-furanone (0.37 ml, 5.3 mmol) as the electrophile. Column chromatography (30% ethyl acetate in hexane) of the crude product afforded **11h** and 1,4-adduct as an inseparable mixture of products (0.2 g, 14%) (R_f 0.03); 1,4 adduct + 1,2-adduct (Found: C, 39.82; H, 5.57. Calc. for $C_9H_{15}F_2O_5P$: C, 39.70; H, 5.57%); 1,2-adduct: δ_H(300 MHz, $CDCl_3$) 6.32 (1H, *d*, $^3J_{H\text{-}H}$ 5.9, -CH$_2$CH=C*H*-), 5.81 (1H, *dt*, $^3J_{H\text{-}H}$ 3.0, $^3J_{H\text{-}H}$ 5.9, -CH$_2$C*H*=CH-), 4.87 (1H, *d*, $^2J_{H\text{-}H}$ 18.0, CH$_a$*H*$_b$O), 4.66 (1H, *d*, $^2J_{H\text{-}H}$ 18.0, C*H*$_a$H$_b$O), 4.45 (1H, *s*, -O*H*), 4.41-4.03 (4H, *m*, -OC*H*$_2$CH$_3$), 1.40 (6H, *t*, $^3J_{H\text{-}H}$ 7.30, -OCH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 134.4 (-CH$_2$*C*H=CH-), 123.4 (-CH$_2$CH=*C*H-), 118.2 (*dt*, $^1J_{C\text{-}P}$ 203.3, $^1J_{C\text{-}F}$ 275.1, *C*F$_2$), 109.7 (*dt*, $^2J_{C\text{-}P}$ 9.7, $^2J_{C\text{-}F}$ 20.5, *C*OH), 76.1 (*C*-O), 65.3 (*d*, $^2J_{C\text{-}P}$ 6.3, -O*C*H$_2$CH$_3$), 16.3 (-OCH$_2$*C*H$_3$); δ_F(282 MHz, $CDCl_3$) -118.4 (1F, *dd*, $^2J_{Fa\text{-}Fb}$ 302.3, $^2J_{Fa\text{-}P}$ 98.7, F$_a$), -119.8 (1F, *dd*, $^2J_{Fb\text{-}Fa}$ 300.1, $^2J_{Fb\text{-}P}$ 98.7, F$_b$); δ_P(121 MHz, $CDCl_3$) 7.3 (*t*, 1P, $^2J_{P\text{-}F}$ 98.7, PO); *m/z* (CI) 290 (M+NH$_4^+$, 100), 273 (M$^+$H$^+$, 20), 139 (10).

1,4 Adduct: δ_H(300 MHz, $CDCl_3$) 4.41-4.03 (4H, *m*, -OC*H*$_2$CH$_3$), 4.17-4.03 (2H, *m*, -C*H*$_2$O-), 3.40-3.21 (1H, *m*, C*H*CF$_2$), 2.81 (1H, *dd*, $^2J_{H\text{-}H}$ 19.0, $^3J_{H\text{-}H}$ 7.3, C*H*$_a$H$_b$CO), 2.69 (1H, *dd*, $^2J_{H\text{-}H}$ 19.0, $^3J_{H\text{-}H}$ 6.2, CH$_a$*H*$_b$CO), 1.40 (6H, *t*, $^3J_{H\text{-}H}$ -OCH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 174.5 (*C*=O), 116.2 (*dt*, $^1J_{C\text{-}P}$ 203.2, $^1J_{C\text{-}F}$ 274.6, *C*F$_2$), 66.0 (-*C*H$_2$O-), 65.3 (d, $^2J_{C\text{-}P}$ 6.3 Hz, -O*C*H$_2$CH$_3$), 39.5 (*dt*, $^2J_{C\text{-}P}$ 16.0, $^2J_{C\text{-}F}$ 21.2

Hz, -*C*HCF$_2$), 27.8 (-*C*H$_2$-), 16.3 (-OCH$_2$*C*H$_3$); δ_F(282 MHz, CDCl$_3$) -117.2 (1F, ddd, $^2J_{Fa-Fb}$ 304.6, $^2J_{Fa-P}$ 103.2, $^3J_{Fa-H}$ 15.3, F$_a$), -119.4 (1F, ddd, $^2J_{Fa-Fb}$ 304.6, $^2J_{Fb-P}$ 103.2, $^3J_{Fb-H}$ 14.4, F$_b$); δ_P(121 MHz, CDCl$_3$) 5.5 (t, $^2J_{P-F}$ 103.2); *m/z* (CI) 290 ($M^+NH_4^+$, 100), 273 ($M+H^+$, 20), 139 (10).

Preparation of (**12**).

Following the general experimental procedure, freshly distilled *N,N*-dimethylformamide (0.41 ml, 5.3 mmol) was added slowly to the pale yellow-orange suspension and the resulting mixture was stirred for a further 1 hour. An aqueous solution of HCl (3N) was added dropwise until complete dissolution of cerium salt and the solution was warmed to room temperature. The aqueous layer was extracted with dichloromethane (2x10 ml) and the combined organic layers were washed (brine) and dried (MgSO4). Column chromatography (60% ethyl acetate in hexane) of the crude product afforded hydrate **12** (1.07 g, 80%) as a clear oil (R_f 0.15); (Found: C, 30.54; H, 5.33. Calc. for $C_6H_{13}F_2O_5P$: C, 30.78 ; H, 5.48%); δ_H(300 MHz, CDCl3) 5.92 (2H, *br. s*, O*H*), 5.20-5.08 (1H, *m*), 4.26-4.15 (4H, *m* -OC*H*$_2$CH$_3$), 1.25 (6H, *t*, $^3J_{H-H}$ 6.5, -OCH$_2$C*H*$_3$) ; δ_C(75 MHz, CDCl3) 116.1 (*dt*, $^1J_{C-P}$ 205.2, $^1J_{C-F}$ 275.4, *C*F$_2$), 88.2 (*dt*, $^2J_{C-P}$ 15.2, $^2J_{C-F}$ 15.2, *C*H(OH)$_2$), 64.8 (d, $^2J_{C-P}$ 6.5, -O*C*H$_2$CH$_3$), 15.8 (d, $^3J_{C-P}$ 5.0, -OCH$_2$*C*H$_3$); δ_F(282 MHz, CDCl$_3$) -124.3 (*dd*, $^2J_{F-H}$ 6.5, $^2J_{F-P}$ 100.7); δ_P(121 MHz, CDCl$_3$) 6.2 (*t*, $^2J_{P-F}$ 100.7)*m/z* 252 ($M+NH_4^+$, 7), 235 ($M+H^+$, 20), 234 (100), 217 (50), 170 (35), 102 (75).

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