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Nucleophilic difluoromethylation and difluoromethylenation of aldehydes and ketones using diethyl difluoromethylphosphonate

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ABSTRACT

New methodology for difluoromethylation and difluoromethylenation of aldehydes and ketones based on nucleophilic fluorination using diethyl difluoromethylphosphonate (**1**) was developed.

1. Introduction

There is a growing interest in the development of new methodologies for the introduction of fluorine containing groups such as CF_3, CF_2H, and CF_2 into organic compounds due to their potential use in material science, pharmaceutical, and agrochemical industries.[1] Trifluoromethylations have been extensively studied and many efficient and selective methods are now available[2] (e.g., nucleophilic trifluoromethylation with $TMSCF_3$).[3]

In contrast to trifluoromethylation, methods for the analogous direct difluoromethylation and difluoromethylenation are just emerging. A number of geminal difluoromethylated compounds display unique biological activities such as enzyme inhibition[4] and therefore they are valued targets in rational drug design.[5] New synthetic methods for the convenient and efficient preparation of geminal difluoromethylated molecules will expedite their development.

Radical[6] or nucleophilic[7] difluoromethylation has been achieved using organoselenium precursors. Sulfur containing reagents[8] were developed for electrophilic,[9] radical,[10] or nucleophilic difluoromethylation.[11] Difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) can act as not only $[CF_2H]^-$ but also a $[CF_2]^{2-}$ equivalent.[12] $PhSCF_2TMS$ served as a difluoromethylene radical anion synthon $[CF_2]^{\bullet -}$.[13]

Fluorinated phosphonates have been recognized as non-hydrolyzable mimics of phosphates in numerous applications.[14] Diethyl difluoromethylphosphonate (**1**) has been used for nucleophilic introduction of difluoromethylphosphonate moiety by a base deprotonation and reaction with various electrophiles including carbonyl compounds,[15,16] imines,[17] carboxylic acid esters,[18,19] and chlorides,[20] unsaturated compounds[21] and triflates.[22]

Recently, in a preliminary study, we have identified the phosphonate **1** as a source of $[CF_2H]^-$ and $[CF_2]^{2-}$ moieties.[23] In this report, we have utilized phosphonate **1** as a versatile synthon for nucleophilic difluoromethylation and difluoromethylenation of aldehydes and ketones and disclose optimized reaction conditions for these transformations. The products of these reactions are difluoromethyl containing alcohols and 2,2-difluoro-1,3-diols. The later compounds have been previously prepared by nucleophilic difluoromethylation using difluoromethyl phenyl sulfone[12] or sulfoxide[24] giving mostly *anti* diols and electrophilic fluorination of 1,3-dicarbonyl compounds followed by reduction.[25] Asymmetric reduction with moderate enantioselectivity was also achieved.[26]

2. Results and discussion

Phosphonates **3** were prepared as a versatile intermediate using a modified procedure starting from diethyl difluoromethylphosphonate (**1**)[27] and carbonyl compounds **2** in the presence of LDA as a base (Table 1). The reaction is efficient and gives good yields for a range of aldehydes and ketones. With

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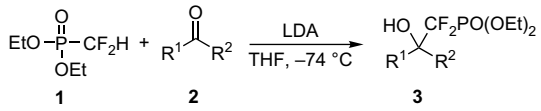
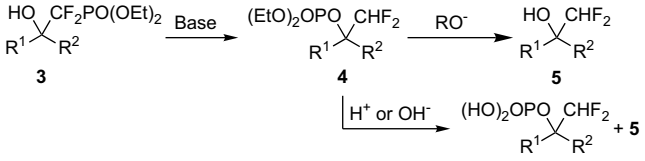
Table 1
Preparation of phosphonates **3** from diethyl difluoromethylphosphonate (**1**) with carbonyl compounds **2**[a]



Entry		R^1	R^2	t (h)	Product	Yield (%)
1	**2a**	Ph	H	0.7	**3a**	93
2	**2b**	4-ClC_6H_4	H	0.7	**3b**	84
3	**2c**	4-$Me_2NC_6H_4$	H	4	**3c**	70
4	**2d**	(*E*)-PhCH=CH	H	0.7	**3d**	78
5	**2e**	$Ph(CH_2)_2$	H	2	**3e**	81
6	**2f**	1-Naphthyl	H	0.7	**3f**	93
7	**2g**	Me	Me	2	**3g**	80
8	**2h**	Ph	Me	2	**3h**	76
9	**2i**	Ph	Ph	6	**3i**	60
10	**2j**	$-(CH_2)_5-$		4	**3j**	89
11	**2k**	$-(CH_2)_3CH=CH-$		4	**3k**	91

[a] Reaction conditions: **1** (1 equiv), LDA (1.05 equiv), THF, −74 °C, 30 min; **2** (1.3 equiv), 0.7–6 h; 0 °C, 10 min.

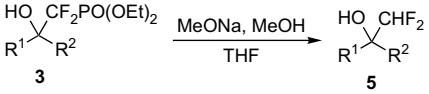
benzophenone (**2i**) the product **3i** was isolated in only 60% yield (entry 9); under the basic reaction conditions some product was transformed to the corresponding phosphate **4i** (Scheme 1).



Scheme 1.

Phosphonates **3** rearrange to phosphates **4** under various basic conditions (Scheme 1).[15] Thus, **3a** reacts with potassium carbonate at room temperature, sodium dimsyl or *t*-BuOK at −50 °C (using DMF as a solvent in all cases) to give phosphate **4a**.[23] Hydrolysis of **4a** to difluoromethyl alcohol **5a** could be performed using $LiOH\cdot H_2O$ in refluxing ethanol, but the conversion to **5a** reaches only 20–30%. A more efficient procedure is the methanolysis with MeONa in methanol,[29] which furnishes the product **5a** in quantitative yield. Pleasingly, the two-step reaction can be carried out in one pot using simple reaction conditions: an excess of MeONa in methanol at room temperature to slightly elevated temperature in THF as a solvent. Our results are highlighted in Table 2. Isolated yields of difluoromethylated alcohols **5** were excellent except for **5k** (entry 7). In this case mostly formation of phosphate **4k** was observed (increasing the amount of base was not helpful).

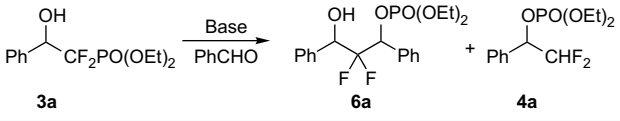
Table 2
Preparation of difluoromethyl alcohols **5** from phosphonates **3**[a]



Entry		R^1	R^2	MeONa (equiv)	T (°C)	t (h)	Product	Yield (%)
1	**3a**	Ph	H	1.5	rt	1	**5a**	83
2	**3b**	4-ClC_6H_4	H	1.5	rt	1	**5b**	96
3	**3e**	$Ph(CH_2)_2$	H	2	30	2	**5e**	90
4	**3f**	1-Naphthyl	H	2	30	1	**5f**	95
5	**3h**	Ph	Me	4	40	1	**5h**	82
6	**3i**	Ph	Ph	2	rt	1	**5i**	86
7	**3k**	$-(CH_2)_3CH=CH-$		2	rt	3	**5k**	35

[a] Reaction conditions: **3** (1 equiv), MeONa (1.5–4 equiv) in MeOH (4 M solution), THF, rt–40 °C, 1–3 h.

Table 3
Optimization of the reaction conditions for the preparation of difluoromethyl phosphate **6a** from phosphonate **3a**[a]



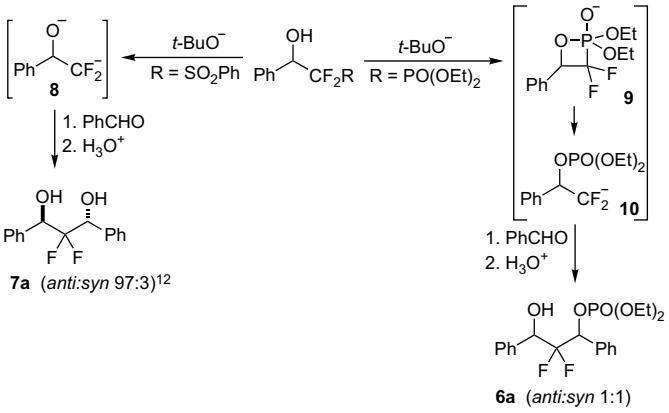
Entry	Base (equiv)	Solvent	T (°C)	t (min)	Product conversion (%)	
					6a	**4a**
1	TMS_2NLi (2)	DMF	−60	30	0	0
2	MeONa (4)	DMF	−50	30	0	75
3	NaH (4)	DMF	−50	30	12	77
4	*t*-BuOK (4)	THF	−60	60	20	0
5	*t*-BuOK (4)	DMF	−10	10	36	0
6	*t*-BuOK (4)	DMF	−50	10	95	0
7	*t*-BuOK (4)	DMF	−65	10	92	0
8	*t*-BuOK (2)	DMF	−65	10	86	0
9	*t*-BuOK (2)	DMF	−65	40	100	0
10	*t*-BuOK (1)	DMF	−65	40	52	0

[a] Reaction conditions: **3a** (1 equiv), PhCHO (2 equiv), base.

The presented methodology provides a simple and practical route toward nucleophilic introduction of difluoromethyl group into aldehydes and ketones. In the process the P–CF_2 bond of phosphonate **3** is cleaved and the generated difluoromethyl anion is quenched with the protic solvent to give the difluoromethyl functionality.

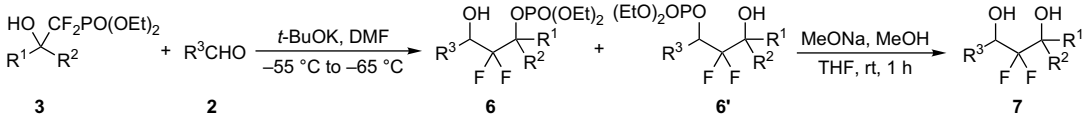
Next, we examined the reaction in a non-protic solvent with the aim of synthetically using the generated difluoromethyl anion for reaction with a second electrophile. Therefore, we turned our attention to a reaction of phosphonate **3a** with benzaldehyde in the presence of a base. We found that while in the presence of sodium methoxide or sodium hydride the main product is phosphate **4a**, the presence of *t*-BuOK in DMF led to the formation of the difluoromethylene containing phosphate **6a**. The results of the optimization of the type and amount of base, reaction time, and temperature are presented in Table 3.

Quantitative formation of the desired product **6a** was achieved using 2 equiv of *t*-BuOK in DMF at −65 °C (entry 9). Under these conditions, the product **6a** was formed as a 1:1 mixture of isomers *syn* and *anti*. *syn* and *anti* isomers of **6a** were identified by NMR (e.g., in ^{19}F NMR of *syn* two signals can be observed: ddd and dd, while *anti* shows one distorted triplet). Additionally methanolysis of *anti*-**6a** gives known *anti*-**7a** (vide infra). The observed low diastereoselectivity in the formation of **6a** is in sharp contrast to the observation made by one of us in a difluoromethylenation using difluoromethyl phenyl sulfone, where the product 2,2-



Scheme 2.

Table 4
Preparation of phosphates **6** and diols **7** from phosphonates **3**



3 **2** **6** **6'** **7**

Entry		R^1	R^2		R^3	t (h)	Phosphate yield (%)[a] **6**+**6′**	**6**:**6′**	Diol yield (%)[b] **7**	Diol yield (%)[c] **7**
1	**3a**	Ph	H	**2a**	Ph	0.7	46 (*anti*)+46 (*syn*)	—	80 (*anti*); 80 (*syn*)	45 (*anti*)+44 (*syn*)
2	**3b**	4-ClC_6H_4	H	**2b**	4-ClC_6H_4	0.7	43 (*anti*)+42 (*syn*)	—	79 (*anti*); 95 (*syn*)	45 (*anti*)+46 (*syn*)
3	**3b**	4-ClC_6H_4	H	**2l**	4-$MeOC_6H_4$	2	83 (*anti*+*syn*)	8:1	81 (*anti*+*syn*)	81 (*anti*+*syn*)
4	**3g**	Me	Me	**2b**	4-ClC_6H_4	2	42	10:1	80	—
5	**3j**	–$(CH_2)_5$–		**2b**	4-ClC_6H_4	2	58	2.45:1	83	—

[a] Reaction conditions: **3** (1 equiv), *t*-BuOK (2 equiv), **2** (2 equiv), DMF, −55 °C to −65 °C, 0.7–2 h.
[b] Yield of diols **7** prepared from phosphates **6**. Reaction conditions: **6** (1 equiv), MeONa (1 equiv) in MeOH (4 M solution), THF, rt, 1 h.
[c] Yield of diols **7** prepared from phosphonates **3** using one pot procedure.

difluoro-1,3-diphenylpropane-1,3-diol (**7a**) was obtained as mostly *anti* isomer with a d.r. of 97:3.[12] In this special case the high d.r. was interpreted by a charge–charge repulsion effect between the reactive dianion species **8** and developing charge during the product (diolate) formation. In our case, the reaction probably proceeds through the anion **10** formed from the intermediate **9** (Scheme 2).

Using the optimized conditions, we have synthesized phosphates **6** on preparative scale starting from different phosphonates **3** and carbonyl compounds **2**. The results are presented in Table 4. Phosphonate **3a** reacted with benzaldehyde (**2a**) in the presence of *t*-BuOK in DMF to give a mixture of phosphates **6a** in total yield of 92%. The *syn* and *anti* isomers of **6a** were easily separated using flash chromatography and each isomer was converted to diol **7a** in very good yields. The removal of the phosphate moiety from **6** deserves some comment. Aqueous alkaline conditions (e.g., 5 equiv $LiOH\cdot H_2O$, in ethanol) gave a maximum conversion of 30% (60 °C, 2 h) and various modifications of the conditions (amount of base, temperature, time) did not improve the result. The use of a diluted methanol solution of sodium methoxide (0.1–10 equiv) afforded maximum of 50% conversion as determined using GC–MS. Finally, we found that the amount of the protic solvent should be kept to minimum. The quantitative formation of diol **7a** was achieved employing 4 M methanolic solution of MeONa (1 equiv) in THF.

This methodology allowed the preparation of other phosphates **6** and diols **7** in very good yields by the reaction of phosphonates derived from aldehydes with aromatic aldehydes (Table 4, entries 1–3). However, the presence of strong base precluded reaction with enolizable aldehydes such as **2e** or *n*-heptanal. The reaction of phosphonate derived from ketones (such as **3g** or **3j**) with aldehydes was possible, but gave only moderate yields of phosphates **6** (entries 4 and 5) probably due to steric bulk of the nucleophilic difluoromethyl anion. In all cases, the crude reaction mixture contained phosphates **6** as a mixture of diastereomers in equal amounts. In the case of non-symmetrical products (entries 3–5) some rearrangement of the phosphate group was observed giving rise to isomeric mixture of phosphates **6** and **6′** (on methanolysis both isomers give the same diol compound). Employing ketones as electrophiles did not lead to any products **6** but only to phosphates **4** (e.g., **3a** with acetone, acetophenone, or benzophenone, **3b** with trifluoromethyl phenyl ketone, **3c** with cyclohexanone, **3g** with acetophenone).

Results presented in Table 4 show that the isolation of intermediate phosphates **6** is not necessary. Diols **7** were obtained from phosphonates **3** with better yields using one pot procedure. This modification represents real improvement because it eliminates one isolation step.[28]

3. Conclusions

In summary, we have utilized diethyl difluoromethylphosphonate (**1**) for $[CF_2H]^-$ and $[CF_2]^{2-}$ transfer in nucleophilic reactions with carbonyl compounds. A simple one step procedure was developed for the preparation of difluoromethyl alcohols **5** from phosphonates **3**. The same starting compounds can be also used for the preparation of *gem*-difluoro-1,3-diols **7** either with the isolation of intermediate phosphates **6** or in one pot reaction.

4. Experimental section

4.1. General

NMR spectra (^1H, ^{13}C, ^{19}F, $^{31}P\{^1H\}$) were measured on a 400 MHz or 500 MHz instrument using $CDCl_3$ or CD_3OD as solvents. The chemical shifts (δ) are reported in parts per million (ppm) relative to Me_4Si (0 ppm, for ^1H NMR), residual $CHCl_3$ peak (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR), residual CD_2HOD peak (3.31 ppm for ^1H NMR and 49.05 ppm for ^{13}C NMR), internal $CFCl_3$ (0 ppm for ^{19}F NMR), and external H_3PO_4 in water (0 ppm for ^{31}P NMR). GC–MS spectra were recorded using a gas chromatograph coupled with a quadrupole mass selective electron impact (EI) detector. High resolution mass spectra (HRMS) were recorded using electrospray (ESI) or electron impact (EI) ionization. Infrared spectra were measured on a FTIR instrument as a KBr discs, chloroform solutions or films. Solvents (DMF, THF, and methanol) were dried using activated molecular sieves (3 Å). Reactions were done under atmosphere of dry argon. All chemicals were used as received. The product purifications were performed by column chromatography using silica gel 60. Yields refer to isolated material judged to be >95% pure by ^1H NMR spectroscopy and GC–MS analysis.

4.2. General procedure for the preparation of phosphonates 3

A solution of *n*-BuLi (8.6 mL, 1.5 M, 12.84 mmol) in cyclohexane was added dropwise to a stirred solution of *i*-Pr_2NH (1.80 mL, 12.84 mmol) in THF (30 mL) cooled to 0 °C. The mixture was stirred at 0 °C for 20 min and then cooled to −74 °C. A solution of diethyl difluoromethylphosphonate (**1**) (2.3 g, 12.23 mmol) in THF (8 mL) was added dropwise, followed by stirring at this temperature for 30 min. A solution of carbonyl compound **2** (15.9 mmol) in THF (5 mL) was added, the mixture was stirred for appropriate time at −74 °C before being warmed up to 0 °C over 10 min. Saturated aqueous solution of NH_4Cl (20 mL) was added, the product was extracted into ethyl acetate or diethyl ether (4×40 mL). The combined organic extract was washed with saturated NaCl solution

(10 mL), dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified on silica gel to yield phosphonate **3**.

4.2.1. Diethyl 1,1-difluoro-2-hydroxy-2-phenylethylphosphonate (**3a**)[15a]

White solid (3.35 g, 93%). Chromatography 35–50% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.25; mp 74–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.5 Hz, CH_3), 1.32 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.4 Hz, CH_3), 4.15–4.28 (m, 5H, 2×CH_2, OH), 5.08–5.16 (m, 1H, CH), 7.33–7.40 (m, 3H, Ph), 7.47–7.51 (m, 2H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.1–16.2 (m), 64.8–65.1 (m), 73.0–73.6 (m), 114.3–121.7 (m), 128.0, 128.1, 128.7, 134.9–135.0 (m); ^{19}F NMR (470 MHz, $CDCl_3$) δ −125.5 (ddd, 1F, $^2J_{FF}$=304.9 Hz, $^2J_{FP}$=104.9 Hz, $^3J_{FH}$=20.3 Hz), −114.9 (ddd, $^2J_{FF}$=304.9 Hz, $^2J_{FP}$=100.2 Hz, $^3J_{FH}$=6.4 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 6.95 (dd, $^2J_{PF}$=104.9, 100.2 Hz); FTIR (KBr, ν_{max} cm^{-1}) 3336 (s), 1493 (w), 1254 (s), 1172 (m), 1103 (m), 1068 (s), 1015 (s), 730 (m), 701 (m); GC–MS (EI) m/z 77 (20%), 107 (20), 109 (20), 132 (100), 133 (20), 140 (20), 160 (30), 161 (70), 188 (80), 221 (10), 294 (M^+, 15); HRMS (ESI^+) calculated for $C_{12}H_{18}F_2O_4P$: 295.0911, found: 295.0918.

4.2.2. Diethyl 2-(4-chlorophenyl)-1,1-difluoro-2-hydroxyethylphosphonate (**3b**)

White solid (1.29 g, 84%). Chromatography 35–50% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.40; mp 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.38 (m, 6H, 2×CH_3), 4.17–4.31 (m, 4H, 2×CH_2), 5.05–5.12 (m, 1H, CH), 7.34–7.37 (m, 2H, $C_{Ar}H$), 7.41–7.43 (m, 2H, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.2–16.3 (m), 65.0–65.3 (m), 72.5–73.1 (m), 114.0–121.4 (m), 128.3, 129.5, 133.3–133.4 (m), 134.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.0 (ddd, 1F, $^2J_{FF}$=305.2 Hz, $^2J_{FP}$=104.8 Hz, $^3J_{FH}$=20.2 Hz), −115.0 (ddd, $^2J_{FF}$=305.2 Hz, $^2J_{FP}$=99.0 Hz, $^3J_{FH}$=5.6 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 7.23 (dd, $^2J_{PF}$=104.8, 99.0 Hz); FTIR (KBr, ν_{max} cm^{-1}) 3315 (s), 1492 (m), 1250 (m), 1174 (m), 1048 (s), 1020 (s), 783 (m); GC–MS (EI) m/z 77 (20%), 132 (100), 160 (30), 161 (70), 188 (85), 255 (10), 328 (M^+, 10); HRMS (ESI^+) calculated for $C_{12}H_{17}F_2O_4PCl$: 329.0521, found: 329.0530.

4.2.3. Diethyl 2-(4-(dimethylamino)phenyl)-1,1-difluoro-2-hydroxyethylphosphonate (**3c**)[29]

Yellow solid (470 mg, 70%). Chromatography 30–60% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.12; mp 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31–1.35 (m, 6H, 2×CH_3), 2.95 (s, 6H, NMe_2), 3.61 (br s, 1H, OH), 4.18–4.29 (m, 4H, 2×CH_2), 4.98–5.04 (m, 1H, CH), 6.72 (d, 2H, $^3J_{HH}$=8.7 Hz, $C_{Ar}H$), 7.33 (d, 2H, $^3J_{HH}$=8.7 Hz, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.2–16.3 (m), 40.5, 64.6–64.9 (m), 73.0–73.6 (m), 112.0, 114.4–122.3 (m), 129.0, 150.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −125.6 (ddd, 1F, $^2J_{FF}$=303.4 Hz, $^2J_{FP}$=106.2 Hz, $^3J_{FH}$=20.2 Hz), −115.2 (ddd, $^2J_{FF}$=303.4 Hz, $^2J_{FP}$=100.9 Hz, $^3J_{FH}$=6.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 7.90 (dd, $^2J_{PF}$=106.2, 100.9 Hz); FTIR (KBr, ν_{max} cm^{-1}) 3336 (s), 2808 (w), 1613 (s), 1523 (s), 1257 (s), 1178 (m), 1165 (m), 1084 (m), 1057 (s), 1025 (s), 786 (m); GC–MS (EI) m/z 150 (100%), 182 (15), 183 (15), 337 (M^+, 10); HRMS (ESI^+) calculated for $C_{14}H_{23}F_2NO_4P$: 338.1333, found: 338.1342.

4.2.4. (E)-Diethyl 1,1-difluoro-2-hydroxy-4-phenylbut-3-enylphosphonate (**3d**)[16b]

Colorless oil (475 mg, 78%). Chromatography 30–50% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32–1.40 (m, 6H, 2×CH_3), 3.47 (br s, 1H, OH), 4.22–4.35 (m, 4H, 2×CH_2), 4.64–4.74 (m, 1H, CHOH), 6.29 (dd, 1H, $^3J_{HH}$=16.0, 6.2 Hz, =CHCH), 6.83 (dd, 1H, $^3J_{HH}$=16.0 Hz, $^4J_{HH}$=1.0 Hz, PhCH=), 7.25–7.29 (m, 1H, Ph), 7.31–7.35 (m, 2H, Ph), 7.41–7.44 (m, 2H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.3–16.4 (m), 65.0 (d, $^2J_{CP}$=6.8 Hz), 72.6–73.2 (m), 114.6–119.9 (m), 122.1 (m), 126.8, 128.2, 128.6, 135.0, 136.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −123.6 (ddd, 1F, $^2J_{FF}$=304.6 Hz, $^2J_{FP}$=102.0 Hz, $^3J_{FH}$=16.3 Hz), −116.5 (ddd, 1F, $^2J_{FF}$=304.6 Hz, $^2J_{FP}$=102.0 Hz, $^3J_{FH}$=8.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 7.25 (t, $^2J_{PF}$=102.0 Hz); GC–MS (EI) m/z 55 (18%), 77 (20), 103 (16), 115 (42), 133 (100), 146 (15), 161 (83), 188 (83), 320 (M^+, 15); HRMS (ESI^+) calculated for $C_{14}H_{20}F_2O_4P$: 321.1067, found: 321.1065.

4.2.5. Diethyl 1,1-difluoro-2-hydroxy-4-phenylbutylphosphonate (**3e**)[30]

Colorless oil (561 mg, 81%). Chromatography 20–40% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.16. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, 6H, $^3J_{HH}$=7.1 Hz, 2×CH_3), 1.94–2.04 (m, 3H, PhCH_2, OH), 2.68–2.76 (m, 1H, CH_aH$_b$CH), 2.91–2.98 (m, 1H, CH$_a$$H_b$CH), 3.90–4.01 (m, 1H, C$H$), 4.23–4.33 (m, 4H, 2×C$H_2$), 7.18–7.23 (m, 3H, Ph), 7.27–7.31 (m, 2H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.3 (d, $^3J_{CP}$=5.6 Hz), 30.3, 31.2, 64.8–64.9 (m), 70.4–71.0 (m), 115.4–122.7 (m), 126.0, 128.4, 128.5, 141.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −125.9 (ddd, 1F, $^2J_{FF}$=304.1 Hz, $^2J_{FP}$=105.2 Hz, $^3J_{FH}$=18.3 Hz), −117.7 (ddd, $^2J_{FF}$=304.1 Hz, $^2J_{FP}$=101.4 Hz, $^3J_{FH}$=7.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 7.59 (dd, $^2J_{PF}$=105.2, 101.4 Hz); FTIR (film, ν_{max} cm^{-1}) 3368 (s), 1604 (m), 1497 (m), 1254 (s), 1165 (s), 1057 (s), 1020 (s), 752 (m), 701 (m); GC–MS (EI) m/z 65 (30%), 91 (100), 111 (40), 132 (50), 138 (90), 161 (50), 166 (60), 188 (30), 198 (30), 284 (20), 322 (M^+, 50); HRMS (ESI^+) calculated for $C_{14}H_{22}F_2O_4P$: 323.1224, found: 323.1234.

4.2.6. Diethyl 1,1-difluoro-2-hydroxy-2-(naphthalen-1-yl)ethylphosphonate (**3f**)

White solid (604 mg, 93%). Chromatography 20–40% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.20; mp 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.6 Hz, CH_3), 1.34 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.6 Hz, CH_3), 4.20–4.32 (m, 4H, 2×CH_2), 6.04–6.11 (m, 1H, CH), 7.47–7.56 (m, 3H, $C_{Ar}H$), 7.86–7.89 (m, 3H, $C_{Ar}H$), 8.07–8.09 (m, 1H, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.2–16.3 (m), 64.8–65.2 (m), 68.7–69.4 (m), 114.8–122.2 (m), 123.5, 125.1, 125.4, 126.2, 126.9, 128.7, 129.3, 131.0–131.1 (m), 131.7, 133.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.1 (ddd, 1F, $^2J_{FF}$=305.6 Hz, $^2J_{FP}$=106.3 Hz, $^3J_{FH}$=21.4 Hz), −113.5 (dd, $^2J_{FF}$=305.6 Hz, $^2J_{FP}$=99.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 7.69 (dd, $^2J_{PF}$=106.3, 99.8 Hz); FTIR (KBr, ν_{max} cm^{-1}) 3318 (s), 1598 (w), 1513 (w), 1252 (m), 1177 (m), 1063 (s), 1029 (s), 799 (m), 789 (m); GC–MS (EI) m/z 127 (35%), 126 (40), 129 (50), 131 (75), 157 (40), 160 (30), 161 (70), 170 (30), 188 (100), 189 (20), 190 (30), 344 (M^+, 40); HRMS (ESI^+) calculated for $C_{16}H_{20}F_2O_4P$: 345.1067, found: 345.1074.

4.2.7. Diethyl 1,1-difluoro-2-hydroxy-2-methylpropylphosphonate (**3g**)

Colorless oil (374 mg, 80%). Chromatography 25–50% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.35. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (m, 12H, 4×CH_3), 4.26–4.34 (m, 4H, 2×CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.3 (d, $^3J_{CP}$=5.7 Hz, CH_2CH_3), 23.2–23.2 (m, Me_2C), 64.9 (d, $^2J_{CP}$=7.1 Hz, CH_2), 72.9 (dt, $^2J_{CF}$=22.3 Hz, $^2J_{CP}$=14.4 Hz, COH), 120.0 (dt, $^1J_{CF}$=270.8 Hz, $^1J_{CP}$=201.0 Hz, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ −119.7 (d, $^2J_{FP}$=105.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 7.84 (t, $^2J_{PF}$=105.2 Hz); FTIR (film, ν_{max} cm^{-1}) 3392 (s), 1261 (s), 1165 (m), 1059 (s), 1024 (s); GC–MS (EI) m/z 43 (12%), 65 (15), 81 (15), 132 (100), 161 (65), 175 (28), 188 (45); HRMS (ESI^+) calculated for $C_8H_{18}F_2O_4P$: 247.0911, found: 247.0918.

4.2.8. Diethyl 1,1-difluoro-2-hydroxy-2-phenylpropylphosphonate (**3h**)

Colorless oil (443 mg, 76%). Chromatography 20–40% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.7 Hz, CH_3CH_2), 1.37 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.7 Hz, CH_3CH_2), 1.71–1.72 (m, 3H, CH_3C), 3.53–3.63 (m, 1H, CH_aH$_b$), 3.80–3.89 (m, 1H, CH_aH$_b$), 4.23–4.32 (m, 2H, 2×CH$_a$$H_b$), 4.50 (br s, 1H, O$H$), 7.29–7.39 (m, 3H, Ph), 7.57–7.59 (m,

2H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.9 (d, $^3J_{CP}$=5.9 Hz, CH_3CH_2), 16.3 (d, $^3J_{CP}$=5.6 Hz, CH_3CH_2), 23.1 (CH_3C), 64.4 (d, $^2J_{CP}$=7.1 Hz, CH_2), 65.1 (d, $^2J_{CP}$=7.1 Hz, CH_2), 75.9 (dt, $^2J_{CF}$=21.6 Hz, $^2J_{CP}$=14.3 Hz, COH), 115.3–122.8 (m), 126.6, 127.9, 140.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −118.0 (dd, 1F, $^2J_{FF}$=301.9 Hz, $^2J_{FP}$=106.7 Hz), −117.1 (dd, 1F, $^2J_{FF}$=301.9 Hz, $^2J_{FP}$=100.4 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 7.80 (dd, $^2J_{PF}$=106.7, 100.4 Hz); FTIR ($CHCl_3$, ν_{max} cm^{-1}) 3598 (m), 3436 (s), 1603 (w), 1496 (m), 1449 (m), 1395 (m), 1249 (s), 1164 (m), 1132 (s), 1076 (s), 1061 (s), 1031 (s); GC–MS (EI) *m*/*z* 43 (35%), 77 (20), 105 (15), 121 (45), 132 (100), 161 (90), 188 (95), 308 (M^+, 10); HRMS (ESI^+) calculated for $C_{13}H_{20}F_2O_4P$: 309.1067, found: 309.1073.

4.2.9. Diethyl 1,1-difluoro-2-hydroxy-2,2-diphenylethylphosphonate (**3i**)

Colorless oil (719 mg, 60%). Chromatography 17–20% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.39 (m, 6H, 2×CH_3), 3.91–4.11 (m, 4H, 2×CH_2), 5.33 (br s, 1H, O*H*), 7.46–7.54 (m, 6H, Ph), 7.81–7.83 (m, 4H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.1 (d, $^3J_{CP}$=5.8 Hz, CH_3), 64.8 (d, $^2J_{CP}$=7.0 Hz, CH_2), 79.0 (dt, $^2J_{CF}$=20.6 Hz, $^2J_{CP}$=15.1 Hz, COH), 119.2 (dt, $^1J_{CF}$=276.2 Hz, $^1J_{CP}$=200.7 Hz, CF_2), 127.5, 127.8, 127.9, 139.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −111.7 (d, $^2J_{FP}$=102.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 8.24 (t, $^2J_{PF}$=102.8 Hz); FTIR (film, ν_{max} cm^{-1}) 3380 (s), 1495 (m), 1450 (m), 1245 (s), 1163 (s), 1152 (s), 1072 (s), 1056 (s), 1031 (s), 725 (m), 699 (m); GC–MS (EI) *m*/*z* 77 (20%), 105 (40), 132 (30), 165 (30), 183 (100), 216 (30); HRMS (ESI^+) calculated for $C_{18}H_{21}F_2O_4PNa$: 393.1043, found: 393.1040.

4.2.10. Diethyl difluoro(1-hydroxycyclohexyl)-methylphosphonate (**3j**)[29]

White solid (1.032 g, 89%). Chromatography 15–40% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.31; mp 50–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, 6H, $^3J_{HH}$=7.1 Hz, 2×CH_2CH_3), 1.49–1.67 (m, 8H, 4×CH_2), 1.84–1.87 (m, 2H, CH_2), 2.82 (br s, 1H, O*H*), 4.24–4.32 (m, 4H, 2×CH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.3, 16.3, 20.4, 25.3, 29.6–29.7 (m), 64.8, 64.8, 73.9 (dt, $^2J_{CF}$=21.0 Hz, $^2J_{CP}$=13.5 Hz, COH), 120.3 (dt, $^1J_{CF}$=270.9 Hz, $^1J_{CP}$=200.4 Hz, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ −121.8 (d, $^2J_{FP}$=106.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 8.03 (t, $^2J_{PF}$=106.2 Hz); FTIR (KBr, ν_{max} cm^{-1}) 3356 (s), 1251 (s), 1159 (m), 1056 (s), 1019 (s); GC–MS (EI) *m*/*z* 81 (30%), 109 (20), 132 (100), 133 (25), 160 (30), 161 (80), 188 (100), 215 (10), 243 (15), 266 (M^+−F, 15); HRMS (ESI^+) calculated for $C_{11}H_{22}F_2O_4P$: 287.1224, found: 287.1230.

4.2.11. Diethyl difluoro(1-hydroxycyclohex-2-enyl)methylphosphonate (**3k**)

Colorless oil (1.09 g, 91%). Chromatography 40–60% Et_2O/hexanes; R_f (60% Et_2O/hexanes) 0.33. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 6H, 2×CH_3), 1.73–2.13 (m, 6H, 3×CH_2), 3.17 (br s, 1H, O*H*), 4.25–4.35 (m, 4H, 2×CH_2CH_3), 5.88–5.91 (m, 1H, C*H*=CH), 6.09–6.13 (m, 1H, CH=C*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.3, 16.3, 17.4, 24.9, 29.4, 64.7–65.0 (m), 72.0 (dt, $^2J_{CF}$=21.9 Hz, $^2J_{CP}$=14.4 Hz, COH), 120.1 (dt, $^1J_{CF}$=271.0 Hz, $^1J_{CP}$=201.7 Hz, CF_2), 123.9–124.0 (m), 135.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −119.8 (dd, 1F, $^2J_{FF}$=302.8 Hz, $^2J_{FP}$=105.3 Hz), −119.1 (dd, 1F, $^2J_{FF}$=302.8 Hz, $^2J_{FP}$=103.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.24 (dd, $^2J_{PF}$=105.3, 103.9 Hz); FTIR (film, ν_{max} cm^{-1}) 3364 (s), 1652 (w), 1254 (s), 1162 (m), 1048 (s), 1017 (s), 736 (m); GC–MS (EI) *m*/*z* 79 (20%), 97 (80), 109 (20), 132 (100), 133 (25), 160 (35), 161 (80), 188 (90); HRMS (ESI^+) calculated for $C_{11}H_{20}F_2O_4P$: 285.1067, found: 285.1062.

4.3. General procedure for the preparation of difluoromethyl alcohols 5

A solution of sodium methoxide (0.19 mL, 4 M, 0.75 mmol) in methanol was added to a solution of phosphonate **3** (0.5 mmol) in THF (8 mL). The mixture was stirred at rt to 40 °C for 1–3 h followed by the addition of saturated solution of NH_4Cl (10 mL). The product was extracted into ethyl acetate or dichloromethane (4×15 mL). The combined organic extract was washed with saturated NaCl solution (6 mL), dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified on silica gel to yield difluoromethyl alcohol **5**.

4.3.1. 2,2-Difluoro-1-phenylethanol (**5a**)[11c]

Colorless oil (66 mg, 83%). Chromatography 15% Et_2O/hexanes; R_f (20% EtOAc/hexanes) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (br s, 1H, O*H*), 4.81 (ddd, 1H, $^3J_{HF}$=10.8, 9.5 Hz, $^3J_{HH}$=4.7 Hz, C*H*), 5.77 (dt, 1H, $^2J_{HF}$=55.8 Hz, $^3J_{HH}$=4.7 Hz, CF_2H), 7.38–7.43 (m, 5H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 73.6 (t, $^2J_{CF}$=24.5 Hz, *C*H), 115.8 (t, $^1J_{CF}$=245.4 Hz, CF_2), 127.1, 128.6, 129.0, 135.8 (t, $^3J_{CF}$=3.2 Hz, C_{Ar}CH); ^{19}F NMR (470 MHz, $CDCl_3$) δ −128.4 (ddd, 1F, $^2J_{FF}$=284.1 Hz, $^2J_{FH}$=55.8 Hz, $^3J_{FH}$=10.8 Hz), −127.7 (ddd, 1F, $^2J_{FF}$=284.1 Hz, $^2J_{FH}$=55.8 Hz, $^3J_{FH}$=9.5 Hz); FTIR (film, ν_{max} cm^{-1}) 3401 (s), 1607 (w), 1497 (m), 1456 (m), 1139 (m), 1121 (m), 1071 (s), 1028 (m), 701 (s); GC–MS (EI) *m*/*z* 51 (20%), 77 (50), 79 (70), 107 (100), 158 (M^+, 20); HRMS (EI) calculated for $C_8H_8F_2O$: 158.0543, found: 158.0548.

4.3.2. 2,2-Difluoro-1-(4-chlorophenyl)ethanol (**5b**)

Colorless oil (123 mg, 96%). Chromatography 10–30% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.76. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (br s, 1H, O*H*), 4.82 (ddd, 1H, $^3J_{HF}$=10.5, 9.5 Hz, $^3J_{HH}$=4.7 Hz, C*H*), 5.73 (dt, 1H, $^2J_{HF}$=56.0 Hz, $^3J_{HH}$=4.7 Hz, CF_2H), 7.33–7.43 (m, 4H, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 73.0 (t, $^2J_{CF}$=24.7 Hz, *C*H), 115.5 (t, $^1J_{CF}$=245.7 Hz, CF_2), 128.4, 128.9, 134.1 (t, $^3J_{CF}$=3.2 Hz, C_{Ar}CH), 134.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ −128.5 (ddd, 1F, $^2J_{FF}$=285.2 Hz, $^2J_{FH}$=56.0 Hz, $^3J_{FH}$=9.5 Hz), −127.8 (ddd, 1F, $^2J_{FF}$=285.2, $^2J_{FH}$=56.0 Hz, $^3J_{FH}$=10.5 Hz); FTIR ($CHCl_3$, ν_{max} cm^{-1}) 3609 (s), 1602 (m), 1496 (s), 1090 (s), 1079 (s), 1054 (s); GC–MS (EI) *m*/*z* 51 (15%), 77 (85), 113 (25), 141 (100), 192 (M^+, 15); HRMS (EI) calculated for $C_8H_6ClF_2O$: 191.0070, found: 191.0076.

4.3.3. 1,1-Difluoro-4-phenylbutan-2-ol (**5e**)[11f]

Colorless oil (62 mg, 90%). Chromatography 10–15% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.79. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81–2.00 (m, 2H, PhCH_2), 2.10 (d, 1H, $^3J_{HH}$=5.1 Hz, O*H*), 2.72–2.79 (m, 1H, CH_aH_bCH), 2.88–2.95 (m, 1H, CH_aH_bCH), 3.69–3.80 (m, 1H, C*H*OH), 5.63 (dt, 1H, $^2J_{HF}$=56.1 Hz, $^3J_{HH}$=4.2 Hz, CF_2H), 7.21–7.24 (m, 3H, Ph), 7.30–7.34 (m, 2H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 30.9, 31.4 (t, $^3J_{CF}$=3.2 Hz, CH_2CH), 70.2 (t, $^2J_{CF}$=23.3 Hz, *C*H), 116.3 (t, $^1J_{CF}$=243.7 Hz, CF_2), 126.2, 128.4, 128.5, 140.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −130.1 (dd, $^2J_{FH}$=56.1 Hz, $^3J_{FH}$=10.7 Hz); FTIR (film, ν_{max} cm^{-1}) 3401 (s), 1604 (m), 1497 (m), 1455 (m), 1139 (s), 1063 (s), 751 (s), 700 (s); GC–MS (EI) *m*/*z* 51 (10%), 65 (15), 77 (15), 91 (100), 92 (40), 105 (25), 117 (60), 168 (10), 186 (M^+, 40); HRMS (EI) calculated for $C_{10}H_{12}F_2O$: 186.0856, found: 186.0852.

4.3.4. 2,2-Difluoro-1-(naphthalen-1-yl)ethanol (**5f**)

Colorless oil (89 mg, 95%). Chromatography 15% EtOAc/hexanes; R_f (20% EtOAc/hexanes) 0.47. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (d, 1H, $^3J_{HH}$=4.0 Hz, O*H*), 5.57–5.64 (m, 1H, C*H*), 6.02 (ddd, 1H, $^2J_{HF}$=56.4, 55.1 Hz, $^3J_{HH}$=4.6 Hz, CF_2H), 7.49–7.59 (m, 3H, $C_{Ar}H$), 7.70–7.71 (m, 1H, $C_{Ar}H$), 7.86–7.93 (m, 2H, $C_{Ar}H$), 8.05–8.07 (m, 2H, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 70.4 (dd, $^2J_{CF}$=26.1, 23.2 Hz, *C*H), 115.8 (dd, $^1J_{CF}$=246.4, 245.3 Hz, CF_2), 122.8, 125.1, 125.2, 125.8, 126.6, 128.9, 129.5, 130.9, 131.6–131.7 (m), 133.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −127.5 (ddd, 1F, $^2J_{FF}$=282.7 Hz, $^2J_{FH}$=56.4 Hz, $^3J_{FH}$=12.5 Hz), −125.8 (ddd, 1F, $^2J_{FF}$=282.7 Hz, $^2J_{FH}$=55.1 Hz, $^3J_{FH}$=7.2 Hz); FTIR (film, ν_{max} cm^{-1}) 3401 (s), 1599 (m), 1513 (m), 1172 (m), 1139 (m), 1118 (m), 1068 (s), 779 (s); GC–MS (EI) *m*/*z* 127 (40%), 128 (55), 129 (100), 157 (90), 208 (M^+, 50); HRMS (EI) calculated for $C_{12}H_{10}F_2O$: 208.0699, found: 208.0703.

*4.3.5. 1,1-Difluoro-2-phenylpropan-2-ol (**5h**)*

Colorless oil (120 mg, 82%). Chromatography 20–40% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (t, 3H, ^3J=1.6 Hz, CH_3), 2.27 (br s, 1H, OH), 5.73 (dd, 1H, $^2J_{HF}$=56.9, 56.0 Hz, CF_2H), 7.32–7.42 (m, 3H, Ph), 7.51–7.53 (m, 2H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.3 (t, $^3J_{CF}$=2.5 Hz, CH_3), 74.2 (t, $^2J_{CF}$=22.0 Hz, COH), 116.9 (t, $^1J_{CF}$=249.2 Hz, CF_2), 125.7, 128.1, 128.4, 140.2–140.3 (m); ^{19}F NMR (470 MHz, $CDCl_3$) δ −131.1 (dd, $^2J_{FF}$=276.3 Hz, $^2J_{FH}$=56.9 Hz), −130.1 (dd, $^2J_{FF}$=276.3 Hz, $^2J_{FH}$=56.0 Hz); FTIR ($CHCl_3$, ν_{max} cm^{-1}) 3598 (s), 3471 (m), 1604 (w), 1497 (m), 1449 (s), 1387 (m), 1098 (s), 1074 (s), 1052 (s), 1029 (s); GC–MS (EI) *m*/*z* 43 (80%), 51 (20), 77 (22), 109 (15), 121 (100); HRMS (EI) calculated for $C_9H_{10}F_2O$: 172.0700, found: 172.0697.

*4.3.6. 2,2-Difluoro-1,1-diphenylethanol (**5i**)[31]*

Colorless oil (131 mg, 86%). Chromatography 10% EtOAc/hexanes; R_f (20% EtOAc/hexanes) 0.68. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (br s, 1H, OH), 6.26 (t, 1H, $^2J_{HF}$=55.1 Hz, CF_2H), 7.34–7.42 (m, 6H, Ph), 7.49–7.52 (m, 4H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 78.0 (t, $^2J_{CF}$=21.1 Hz, COH), 116.8 (t, $^1J_{CF}$=250.3 Hz, CF_2), 127.0, 128.2, 128.3, 140.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −128.1 (d, $^2J_{FH}$=55.1 Hz); FTIR (film, ν_{max} cm^{-1}) 3551 (s), 3468 (s), 1601 (m), 1495 (s), 1450 (s), 1073 (s), 1049 (s), 760 (s), 721 (s); GC–MS (EI) *m*/*z* 51 (10%), 77 (40), 105 (80), 183 (100), 184 (14); HRMS (ESI$^+$) calculated for $C_{14}H_{12}F_2ONa$: 257.0754, found: 257.0745.

*4.3.7. 1-(Difluoromethyl)cyclohex-2-enol (**5k**)*

Colorless liquid (89 mg, 35%). Chromatography 20% Et_2O/hexanes; R_f (20% Et_2O/hexanes) 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68–1.79 (m, 4H, 2×CH_2), 1.96–2.14 (m, 3H, CH_2, OH), 5.56 (t, 1H, $^2J_{HF}$=56.3 Hz, CF_2H), 5.64–5.67 (m, 1H, CH=CH), 6.09–6.13 (m, 1H, CH=CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4, 25.0, 29.2 (t, $^5J_{CF}$=2.3 Hz, CH_2CH=), 69.8 (t, $^2J_{CF}$=21.2 Hz, COH), 117.0 (t, $^1J_{CF}$=247.5 Hz, CF_2), 124.0 (t, $^3J_{CF}$=3.5 Hz), 135.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −133.3 (dd, $^2J_{FF}$=278.3 Hz, $^2J_{FH}$=56.3 Hz), −132.6 (dd, $^2J_{FF}$=278.3 Hz, $^2J_{FH}$=56.3 Hz); FTIR (film, ν_{max} cm^{-1}) 3592 (m), 3401 (s), 3033 (m), 1652 (m), 1070 (s), 989 (m), 734 (m); GC–MS (EI) *m*/*z* 41 (10%), 51 (15), 79 (20), 97 (100); HRMS (EI) calculated for $C_7H_{10}F_2O$: 148.0700, found: 148.0707.

4.4. General procedure for the preparation of phosphates 6

A solution of *t*-BuOK (224.4 mg, 2 mmol) in DMF (3 mL) was added dropwise to a stirred solution of phosphonate **3** (1 mmol) and carbonyl compound **2** (2 mmol) in DMF (3 mL) cooled to −65 °C. The mixture was stirred at −55 °C to −65 °C for appropriate time and then aqueous solution of NH_4Cl (8 mL) was added, the product was extracted into ethyl acetate or dichloromethane (3×15 mL). The combined organic extract was washed with saturated NaCl solution (7 mL), dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified on silica gel to yield phosphate **6**.

*4.4.1. anti-2,2-Difluoro-3-hydroxy-1,3-diphenylpropyl diethyl phosphate (anti-**6a**)*

White gummy solid (184 mg, 46%). Chromatography 20–70% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3), 1.40 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3), 3.82–4.02 (m, 2H, CH_2), 4.12–4.30 (m, 2H, CH_2), 5.16–5.23 (m, 1H, CH), 5.30 (d, 1H, $^3J_{HH}$=5.9 Hz, OH), 5.76–5.85 (m, 1H, CH), 7.30–7.40 (m, 6H, Ph), 7.46–7.51 (m, 4H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.7 (d, $^3J_{CP}$=6.7 Hz, CH_3), 16.0 (d, $^3J_{CP}$=6.7 Hz, CH_3), 65.0 (d, $^2J_{CP}$=13.1 Hz, CH_2), 65.1 (d, $^2J_{CP}$=13.1 Hz, CH_2), 70.8 (dd, $^2J_{CF}$=28.7, 26.6 Hz, $CHOH$), 75.0–75.7 (m, CH), 119.1 (dt, $^1J_{CF}$=254.0 Hz, $^3J_{CP}$=7.4 Hz, CF_2), 127.9, 128.0, 128.1, 128.2, 128.3, 129.3, 132.5 (d, $^3J_{CF}$=3.2 Hz, CCH), 135.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −122.4 to −122.3 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.24 (s); FTIR (film, ν_{max} cm^{-1}) 3339 (s), 1496 (m), 1456 (m), 1254 (s), 1166 (s), 1038 (s), 1025 (s), 745 (m), 718 (m), 699 (s); GC–MS (EI) *m*/*z* 77 (10%), 105 (10), 140 (100), 141 (10), 274 (15); HRMS (ESI$^+$) calculated for $C_{19}H_{24}F_2O_5P$: 401.1329, found: 401.1320.

*4.4.2. syn-2,2-Difluoro-3-hydroxy-1,3-diphenylpropyl diethyl phosphate (syn-**6a**)*

White solid (185 mg, 46%). Chromatography 20–70% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.10; mp 74–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3), 1.23 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3), 3.66–3.81 (m, 2H, CH_2), 3.95–4.12 (m, 2H, CH_2), 4.35 (d, 1H, $^3J_{HH}$=5.2 Hz, OH), 4.47–4.54 (m, 1H, CHOH), 5.96–6.04 (m, 1H, CHOP), 7.29–7.31 (m, 3H, Ph), 7.34–7.38 (m, 2H, Ph), 7.41–7.44 (m, 3H, Ph), 7.64–7.66 (m, 2H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.6 (d, $^3J_{CP}$=7.2 Hz, CH_3), 15.8 (d, $^3J_{CP}$=7.2 Hz, CH_3), 63.8 (d, $^2J_{CP}$=5.8 Hz, CH_2), 64.1 (d, $^2J_{CP}$=5.8 Hz, CH_2), 72.3 (dd, $^2J_{CF}$=30.3, 23.7 Hz, $CHOH$), 77.7–78.2 (m, CH), 119.7 (ddd, $^1J_{CF}$=257.0, 250.9 Hz, $^3J_{CP}$=7.0 Hz, CF_2), 127.9, 128.0, 128.4, 128.5, 128.6, 129.4, 133.8–133.9 (m), 136.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −123.9 (ddd, 1F, $^2J_{FF}$=250.7 Hz, $^3J_{FH}$=19.0, 6.3 Hz), −122.9 (dd, $^2J_{FF}$=250.7 Hz, $^3J_{FH}$=16.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −1.56 (s); FTIR (KBr, ν_{max} cm^{-1}) 3314 (s), 1495 (w), 1246 (m), 1163 (m), 1045 (s), 1021 (m), 721 (m), 701 (m); GC–MS (EI) *m*/*z* 77 (10%), 79 (10), 105 (10), 108 (10), 140 (100), 141 (10), 155 (15), 226 (10), 274 (15); HRMS (ESI$^+$) calculated for $C_{19}H_{24}F_2O_5P$: 401.1329, found: 401.1313.

*4.4.3. 1,3-Bis(4-chlorophenyl)-2,2-difluoro-3-hydroxypropyl diethyl phosphate (anti-**6b**)*

Colorless oil (123 mg, 43%). Chromatography CH_2Cl_2/hexanes/EtOAc 20:20:1; R_f (CH_2Cl_2/hexanes/EtOAc) 0.33. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.0 Hz, CH_3), 1.41 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3), 3.85–4.05 (m, 2H, CH_2), 4.16–4.31 (m, 2H, CH_2), 5.11–5.19 (ddd, 1H, $^3J_{HF}$=17.9, 12.1 Hz, $^3J_{HH}$=5.9 Hz, CHOH), 5.46 (d, 1H, $^3J_{HH}$=5.9 Hz, OH), 5.71–5.80 (m, 1H, CHOP), 7.31–7.43 (m, 8H, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.8 (d, $^3J_{CP}$=6.6 Hz, CH_3), 16.0 (d, $^3J_{CP}$=6.7 Hz, CH_3), 65.1 (d, $^2J_{CP}$=6.4 Hz, CH_2), 65.3 (d, $^2J_{CP}$=6.2 Hz, CH_2), 70.1 (dd, $^2J_{CF}$=27.8, 27.4 Hz, $CHOH$), 74.2–74.9 (m, CH), 118.9 (dt, $^1J_{CF}$=254.1 Hz, $^3J_{CP}$=7.2 Hz, CF_2), 128.1, 128.5, 129.3, 129.6, 131.0 (d, $^3J_{CF}$=3.3 Hz, CCH), 134.0, 134.2, 135.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −122.5 to −122.4 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.43 (s); FTIR (film, ν_{max} cm^{-1}) 3328 (m), 1599 (w), 1581 (w), 1493 (m), 1256 (m), 1164 (m), 1033 (s), 1014 (s), 804 (m), 766 (m); GC–MS (EI) *m*/*z* 77 (10%), 139 (12), 141 (10), 155 (10), 174 (100), 176 (40); HRMS (ESI$^+$) calculated for $C_{19}H_{21}Cl_2F_2NaO_5P$: 491.0364, found: 491.0363.

*4.4.4. 1,3-Bis(4-chlorophenyl)-2,2-difluoro-3-hydroxypropyl diethyl phosphate (syn-**6b**)*

White solid (120 mg, 42%). Chromatography 30–50% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.25; mp 109–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3), 1.27 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3), 3.70–3.84 (m, 2H, CH_2), 3.99–4.13 (m, 2H, CH_2), 4.44–4.49 (m, 1H, CHOH), 4.61 (br s, 1H, OH), 5.99 (ddd, 1H, $^3J_{HF}$=16.8, 6.2 Hz, $^3J_{HP}$=9.8 Hz, CHOP), 7.27–7.32 (m, 4H, $C_{Ar}H$), 7.40–7.43 (m, 2H, $C_{Ar}H$), 7.59 (d, 2H, J=8.4 Hz, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.7 (d, $^3J_{CP}$=7.0 Hz, CH_3), 15.9 (d, $^3J_{CP}$=7.1 Hz, CH_3), 64.1 (d, $^2J_{CP}$=6.0 Hz, CH_2), 64.5 (d, $^2J_{CP}$=5.9 Hz, CH_2), 71.9 (dd, $^2J_{CF}$=30.8, 23.8 Hz, CH), 116.8–121.9 (m, CF_2), 128.3, 128.8, 129.4, 130.0, 132.2 (dd, $^3J_{CF}$=5.4, 2.2 Hz, CCH), 134.5, 134.7, 135.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −124.1 (ddd, 1F, $^2J_{FF}$=252.0 Hz, $^3J_{FH}$=19.7, 6.2 Hz), −122.5 (dd, 1F, $^2J_{FF}$=252.0 Hz, $^3J_{FH}$=16.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −1.64 (s); FTIR (KBr, ν_{max} cm^{-1}) 3290 (s), 1601 (w), 1581 (w), 1493 (m), 1260 (s), 1166 (m), 1049 (s), 1033 (s), 1015 (s), 802 (w), 764 (m); GC–MS (EI) *m*/*z* 77 (12%), 139 (15), 141

(13), 155 (25), 174 (100), 176 (30); HRMS (ESI^+) calculated for $C_{19}H_{21}Cl_2F_2NaO_5P$: 491.0364, found: 491.0363.

4.4.5. 1-(4-Chlorophenyl)-2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)propyl diethyl phosphate (**6bl**); 3-(4-chlorophenyl)-2,2-difluoro-3-hydroxy-1-(4-methoxyphenyl)propyl diethyl phosphate (**6′bl**)

Ratio (8:1); colorless liquid (225 mg, 83%). Chromatography 20–70% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.10. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.0 Hz, CH_3), 1.12 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.0 Hz, CH_3), 1.25 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.0 Hz, CH_3), 1.38 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.0 Hz, CH_3), 3.71–4.25 (m, 14H, 4×CH_2, 2×OMe), 4.44–4.51 (m, 1H), 4.56–4.59 (m, 1H), 5.10–5.17 (m, 1H, CH), 5.49 (d, 1H, $^3J_{HH}$=5.8 Hz, OH), 5.67–5.76 (m, 1H, CH), 5.87–5.96 (m, 1H, CH), 6.87–6.94 (m, 4H, $C_{Ar}H$), 7.28–7.32 (m, 6H, $C_{Ar}H$), 7.36–7.42 (m, 4H, $C_{Ar}H$), 7.53–7.56 (m, 2H, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.7 (d, $^3J_{CP}$=7.0 Hz, CH_3), 15.7 (d, $^3J_{CP}$=6.7 Hz, CH_3), 15.8 (d, $^3J_{CP}$=7.0 Hz, CH_3), 16.0 (d, $^3J_{CP}$=6.7 Hz, CH_3), 55.2, 55.2, 63.8 (d, $^2J_{CP}$=5.7 Hz, CH_2), 64.2, (d, $^2J_{CP}$=6.0 Hz, CH_2), 64.9 (d, $^2J_{CP}$=6.4 Hz, CH_2), 65.0 (d, $^2J_{CP}$=6.2 Hz, CH_2), 70.3 (dd, $^2J_{CF}$=28.1, 27.6 Hz, CH), 71.8 (dd, $^2J_{CF}$=23.7, 30.3 Hz, CH), 74.7–75.4 (m), 77.1–77.8 (m), 113.7, 113.9, 116.6–122.2 (m), 128.0, 128.1, 129.3, 129.4, 129.7, 130.0, 134.0, 134.3, 134.9, 160.3, 160.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −124.0 (ddd, 1F, $^2J_{FF}$=251.0 Hz, $^3J_{FH}$=19.5, 6.0 Hz, *syn*), −122.8 (dd, 1F, $^2J_{FF}$=251.0 Hz, $^3J_{FH}$=19.5 Hz, *syn*), −122.3 (dd, 2F, $^3J_{FH}$=12.4, 11.5 Hz, *anti*); ^{31}P NMR (162 MHz, $CDCl_3$) δ −1.49 (s, P′, *syn*), −1.41 (s, P, *syn*), −0.02 (s, P′, *anti*), 0.20 (s, P, *anti*); FTIR (film, ν_{max} cm^{-1}) 3320 (s), 2840 (m), 1614 (s), 1587 (m), 1516 (s), 1492 (m), 1253 (s), 1178 (m), 1164 (m), 1031 (s), 808 (m); GC–MS (EI) *m*/*z* 77 (10%), 111 (10), 119 (10), 127 (20), 135 (40), 136 (40), 139 (20), 155 (25), 170 (25), 174 (100), 175 (10), 176 (40); HRMS (ESI^+) calculated for $C_{20}H_{24}ClF_2O_6PNa$: 487.0865, found: 487.0873.

4.4.6. 4-(4-Chlorophenyl)-3,3-difluoro-4-hydroxy-2-methylbutan-2-yl diethyl phosphate (**6gb**); 1-(4-chlorophenyl)-2,2-difluoro-3-hydroxy-3-methylbutyl diethyl phosphate (**6′gb**)

Ratio (10:1); colorless oil (96 mg, 42%). Chromatography 25–60% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (dt, 3H′, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3CH$_2$), 1.30 (dt, 3H′, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.2 Hz, CH_3CH$_2$), 1.35 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3CH$_2$), 1.36 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3CH$_2$), 1.42 (s, 3H′, CH_3), 1.60 (d, 3H, J=1.2 Hz, CH_3), 1.77 (s, 3H, CH_3), 1.87 (s, 3H′, CH_3), 3.19 (br s, 1H′, OH), 3.76–3.86 (m, 2H′, CH_2), 4.04–4.19 (m, 4H, 2H′, CH_2), 4.40 (d, 1H, $^3J_{HH}$=5.1 Hz, OH), 5.11–5.18 (m, 1H, CH), 5.63–5.72 (m, 1H′, CH), 7.31–7.44 (m, 4H, 4H′, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.7 (d, $^3J_{CP}$=6.9 Hz, CH_3CH$_2$), 16.0 (d, $^3J_{CP}$=7.1 Hz, CH_3CH$_2$), 22.7, 23.4, 24.4, 64.1 (d, $^2J_{CP}$=6.3 Hz, CH_2), 64.2 (d, $^2J_{CP}$=5.9 Hz, CH_2), 64.3 (d, $^2J_{CP}$=5.9 Hz, CH_2), 64.6 (d, $^2J_{CP}$=5.9 Hz, CH_2), 71.8 (dd, $^2J_{CF}$=33.5, 23.8 Hz, CH), 84.0–84.7 (m), 119.3 (ddd, $^1J_{CF}$=260.3, 269.9 Hz, $^3J_{CP}$=9.1 Hz, CF_2), 128.1, 128.5, 129.5, 130,0, 132.7, 134.2, 135.3, 135.5 (d, $^3J_{CF}$=1 Hz, CCH); ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.8 (dd, 1F, $^2J_{FF}$=263.9 Hz, $^3J_{FH}$=21.1 Hz), −123.8 (dd, 1F′, $^2J_{FF}$=263.9 Hz, $^3J_{FH}$=16.9 Hz), −114.5 (d, 1F′, $^2J_{FF}$=263.5 Hz), −113.0 (d, 1F, $^2J_{FF}$=263.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −5.17 (s, P), −1.20 (s, P′); FTIR ($CHCl_3$, ν_{max} cm^{-1}) 3595 (m), 3337 (m), 1600 (w), 1494 (m), 1152 (m), 1031 (s); GC–MS (EI) *m*/*z* 77 (25%), 99 (50), 126 (33), 141 (25), 155 (100), 174 (30) (major); 59 (25%), 77 (20), 92 (20), 109 (22), 141 (30), 155 (28), 174 (100), 176 (35), 277 (20) (minor); HRMS (ESI^+) calculated for $C_{15}H_{23}F_2O_5PCl$: 387.0940, found: 387.0937.

4.4.7. 1-(2-(4-Chlorophenyl)-1,1-difluoro-2-hydroxyethyl)-cyclohexyl diethyl phosphate (**6jb**); 1-(4-chlorophenyl)2,2-difluoro-2-(1-hydroxycyclohexyl)ethyl diethyl phosphate (**6′jb**)

Ratio (2.45:1); colorless oil (103 mg, 58%). Chromatography 20–40% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (dt, 3H′, $^3J_{HH}$=6.0 Hz, $^4J_{HP}$=1.1 Hz, CH_3), 1.30 (dt, 3H′, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=1.1 Hz, CH_3), 1.35–1.41 (m, 6H, 2×CH_3), 1.53–2.55 (m, 10H, 10H′, 10×CH_2), 2.81 (s, 1H′, OH), 3.76–3.86 (m, 2H′, CH_2CH$_3$), 4.05–4.22 (m, 4H, 2H′, CH_2CH$_3$), 5.12–5.21 (m, 2H, CH, OH), 5.64–5.72 (m, 1H′, CH), 7.31–7.42 (m, 4H, 4H′, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.7–16.0 (m), 16.0–16.1 (m), 20.6–20.7 (m), 20.8–20.9 (m), 24.6, 25.2, 29.6, 30.4–30.7 (m), 64.2–64.6 (m), 71.7–72.3 (m), 74.2–74.7 (m), 75.3–75.9 (m), 87.6 (dt, $^2J_{CF}$=27.3, $^2J_{CP}$=9.1 Hz, C*O*P), 117.0–122.1 (m), 128.0, 128.4, 129.6, 130.0, 133.0, 134.0, 135.2, 135.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −125.6 (dd, 1F′, $^2J_{FF}$=264.5 Hz, $^3J_{FH}$=16.9 Hz), −124.0 (dd, 1F, $^2J_{FF}$=268.4 Hz, $^3J_{FH}$=22.2 Hz), −116.0. (d, 1F′, $^2J_{FF}$=264.5 Hz), −109.5 (d, 1F, $^2J_{FF}$=268.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −5.58 (s, P), −1.29 (s, P′); FTIR (film, ν_{max} cm^{-1}) 3339 (s), 2984 (m), 2939 (s), 2867 (m), 1599 (w), 1581 (w), 1493 (m), 1452 (m), 1265 (s), 1250 (s), 1090 (s), 1028 (s), 807 (m); GC–MS (EI) *m*/*z* 81 (15%), 99 (15), 141 (25), 155 (20), 174 (100), 176 (30), 149 (40), 151 (12), 277 (10), 308 (7); HRMS (ESI^+) calculated for $C_{18}H_{26}ClF_2O_5PNa$: 449.1067, found: 449.1068.

4.5. General procedure for the preparation of difluoromethyl diols 7 from phosphates 6

A solution sodium methoxide (0.125 mL, 4 M, 0.5 mmol) in methanol was added to a solution of phosphate **6** (0.5 mmol) in THF (4 mL). The mixture was stirred at room temperature for 1 h and then aqueous solution of NH_4Cl (4 mL) was added, the product was extracted into ethyl acetate or dichloromethane (4×15 mL). The combined organic extract was washed with saturated NaCl solution (6 mL), dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified on silica gel to yield difluoromethyl diols **7**.

4.5.1. anti-2,2-Difluoro-1,3-diphenylpropane-1,3-diol (anti-**7a**)[12]

White solid (102 mg, 80%). Chromatography 20–60% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.57; mp 129–131 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 4.88 (br s, 2H, 2×OH), 5.16 (t, 2H, $^3J_{HF}$=12.5 Hz, 2×CH), 7.27–7.35 (m, 6H, Ph), 7.43–7.46 (m, 4H, Ph); ^{13}C NMR (100.6 MHz, CD_3OD) δ 72.9 (t, $^2J_{CF}$=28.1 Hz, CH), 121.9 (t, $^1J_{CF}$=250.7 Hz, CF_2), 128.9, 129.1, 129.4, 139.2; ^{19}F NMR (470 MHz, CD_3OD) δ −121.5 (t, $^3J_{FH}$=12.5 Hz); FTIR (KBr, ν_{max} cm^{-1}) 3460 (s), 3318 (s), 1495 (m), 1456 (m), 1160 (m), 1153 (m), 1042 (s), 1025 (m), 745 (m), 728 (m), 695 (m); GC–MS (EI) *m*/*z* 51 (10%), 77 (30), 79 (30), 105 (15), 107 (30), 140 (100), 141 (15); HRMS (ESI^-) calculated for $C_{15}H_{13}F_2O_2$: 263.0884, found: 263.0872.

4.5.2. syn-2,2-Difluoro-1,3-diphenylpropane-1,3-diol (syn-**7a**)

White solid (105 mg, 80%). Chromatography 20–60% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.41; mp 143–145 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 4.82 (dd, 2H, $^3J_{HF}$=14.1, 11.4 Hz, 2×CH), 4.87 (br s, 2H, 2×OH), 7.30–7.37 (m, 6H, Ph), 7.44–7.46 (m, 4H, Ph); ^{13}C NMR (100.6 MHz, CD_3OD) δ 74.1 (dd, $^2J_{CF}$=26.6, 24.2 Hz, CH), 122.2 (dd, $^1J_{CF}$=255.2, 247.9 Hz, CF_2), 129.0, 129.3, 129.3, 139.2; ^{19}F NMR (470 MHz, CD_3OD) δ −124.8 (dt, 1F, $^2J_{FF}$=250.9 Hz, $^3J_{FH}$=14.1 Hz), −122.8 (dt, 1F, $^2J_{FF}$=250.9 Hz, $^3J_{FH}$=11.4 Hz); FTIR (KBr, ν_{max} cm^{-1}) 3397 (s), 1496 (m), 1457 (m), 1199 (m), 1144 (m), 1060 (s), 1034 (m), 1023 (m), 759 (m), 730 (m), 704 (m); GC–MS (EI) *m*/*z* 77 (25%), 79 (30), 107 (30), 140 (100), 141 (15); HRMS (ESI^-) calculated for $C_{15}H_{13}F_2O_2$: 263.0884, found: 263.0896.

4.5.3. anti-1,3-Bis(4-chlorophenyl)-2,2-difluoropropane-1,3-diol (anti-**7b**)[32]

White solid (69 mg, 79%). Chromatography 20–40% EtOAc/hexanes; R_f (33% EtOAc/hexanes) 0.26; mp 149–150 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 4.88 (br s, 2H, 2×OH), 5.19 (t, 2H, $^3J_{HF}$=12.4 Hz, 2×CH), 7.32–7.34 (m, 4H, $C_{Ar}H$), 7.41–7.43 (m, 4H, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, CD_3OD) δ 72.0 (t, $^2J_{CF}$=28.4 Hz, CH), 121.8 (dd, $^1J_{CF}$=250.8, 250.5 Hz, CF_2), 129.0, 130.9, 135.0, 138.1; ^{19}F NMR

(470 MHz, CD_3OD) δ −121.5 (t, $^3J_{FH}$=12.4 Hz); FTIR (KBr, ν_{max} cm^{-1}) 3593 (s), 1596 (w), 1578 (w), 1493 (m), 1090 (s), 1074 (s), 1035 (m), 1016 (m), 795 (s), 756 (s); GC–MS (EI) *m*/*z* 77 (23%), 78 (20), 113 (10), 141 (40), 142 (42), 143 (20), 144 (18), 174 (100), 176 (30). HRMS (ESI^-) calculated for $C_{15}H_{11}Cl_2F_2O_2$: 331.0099, found 331.0101.

4.5.4. *syn*-1,3-Bis(4-chlorophenyl)-2,2-difluoropropane-1,3-diol (*syn*-**7b**)

Viscous oil (81 mg, 95%). Chromatography 20–40% EtOAc/hexanes; R_f (33% EtOAc/hexanes) 0.38. ^1H NMR (400 MHz, CD_3OD) δ 4.81 (dd, 2H, $^3J_{HF}$=13.8, 11.2 Hz, 2×C*H*), 4.88 (br s, 2H, 2×O*H*), 7.34–7.37 (m, 4H, $C_{Ar}H$), 7.43–7.45 (m, 4H, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 73.5 (dd, $^2J_{CF}$=28.8, 24.8 Hz, *C*H), 119.2 (dd, $^1J_{CF}$=256.6, 247.9 Hz, *C*F_2), 128.6, 129.3, 134.3 (d, $^3J_{CF}$=2.7 Hz, *C*CH), 135.0; ^{19}F NMR (470 MHz, CD_3OD) δ −124.5 (dt, 1F, $^2J_{FF}$=251.9 Hz, $^3J_{FH}$=13.8 Hz), −122.2 (dt, 1F, $^2J_{FF}$=251.9 Hz, $^3J_{FH}$=11.2 Hz); FTIR (film, ν_{max} cm^{-1}) 3573 (w), 3387 (m), 1598 (m), 1580 (w), 1493 (s), 1193 (m), 1092 (s), 1060 (s), 1031 (m), 1015 (s), 844 (m), 802 (m), 763 (s); GC–MS (EI) *m*/*z* 77 (50%), 113 (15), 141 (85), 143 (37), 174 (100), 176 (38). HRMS (ESI^-) calculated for $C_{15}H_{11}Cl_2F_2O_2$: 331.0099, found 331.0103.

4.5.5. 1-(4-Chlorophenyl)-2,2-difluoro-3-(4-methoxyphenyl)-propane-1,3-diol (**7bl**)

Colorless thick oil (85 mg, 81%). Chromatography 25–55% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.31. ^1H NMR (400 MHz, CD_3OD) δ 3.77 (s, 3H, O*Me*), 3.78 (s, 3H, O*Me*), 4.73–4.86 (m, 2H, 2×C*H*), 4.88 (br s, 4H, 4×O*H*), 5.08–5.19 (m, 2H, 2×C*H*), 6.86–6.92 (m, 4H, $C_{Ar}H$), 7.31–7.43 (m, 12H, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, CD_3OD) δ 55.7, 55.7, 71.9–72.7 (m), 73.2–74.0 (m), 114.3, 114.5, 119.4–124.7 (m), 128.9, 129.1, 130.5, 130.5, 130.9–131.0 (m), 134.9, 135.1, 138.1–138.2 (m), 161.1, 161.3; ^{19}F NMR (470 MHz, CD_3OD) δ −124.8 (dt, 1F, $^2J_{FF}$=250.8 Hz, $^3J_{FH}$=14.0 Hz, *syn*), −122.8 (dt, 1F, $^2J_{FF}$=250.8 Hz, $^3J_{FH}$=11.2 Hz, *syn*), −121.5 (t, 2F, $^3J_{FH}$=12.4 Hz, *anti*); FTIR (film, ν_{max} cm^{-1}) 3401 (s), 2839 (m), 1613 (s), 1587 (m), 1515 (s), 1493 (m), 1252 (s), 1179 (s), 1067 (s), 1034 (s), 840 (m), 802 (m); GC–MS (EI) *m*/*z* 77 (15%), 94 (10), 109 (10), 137 (100), 170 (10), 174 (10), 328 (5); HRMS (ESI^-) calculated for $C_{16}H_{14}F_2O_3Cl$: 327.0600, found: 327.0602.

4.5.6. 1-(4-Chlorophenyl)-2,2-difluoro-3-methylbutane-1,3-diol (**7gb**)

White solid (50 mg, 80%). Chromatography 25–40% EtOAc/hexanes; R_f (30% EtOAc/hexanes) 0.45; mp 97–99 °C. ^1H NMR (400 MHz, CD_3OD) δ 1.36 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 4.88 (br s, 2H, 2×O*H*), 5.13 (dd, 1H, $^3J_{HF}$=21.4 Hz, $^3J_{HH}$=3.9 Hz, C*H*), 7.33–7.36 (m, 2H, $C_{Ar}H$), 7.43 (d, 2H, *J*=8.4 Hz, $C_{Ar}H$); ^{13}C NMR (100.6 MHz, CD_3OD) δ 24.3, 25.1, 73.3 (dd, $^2J_{CF}$=33.7, 24.0 Hz, *C*H), 74.6 (t, $^2J_{CF}$=26.3 Hz, *C*OH), 122.0 (dd, $^1J_{CF}$=259.1, 247.7 Hz, *C*F_2), 128.9, 131.1, 135.0, 138.6; ^{19}F NMR (470 MHz, CD_3OD) δ −127.8 (dd, 1F, $^2J_{FF}$=260.6 Hz, $^3J_{FH}$=21.4 Hz), −113.2 (d, 1F, $^2J_{FF}$=260.6 Hz); FTIR (KBr, ν_{max} cm^{-1}) 3369 (s), 3247 (s), 1598 (w), 1493 (s), 1409 (m), 1150 (m), 1088 (s), 1072 (s), 780 (s); GC–MS (EI) *m*/*z* 43 (20%), 60 (25), 78 (55), 92 (80), 142 (100), 174 (40); HRMS (ESI^-) calculated for $C_{11}H_{12}ClF_2O_2$: 249.0494, found: 249.0497.

4.5.7. 1-(2-(4-Chlorophenyl)-1,1-difluoro-2-hydroxyethyl)-cyclohexanol (**7jb**)

White solid (48 mg, 83%). Chromatography 20–40% EtOAc/hexanes; R_f (40% EtOAc/hexanes) 0.63; mp 140–142 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.55–1.96 (m, 10H, 5×CH_2), 2.39 (br s, 1H, O*H*), 4.27 (br s, 1H, O*H*), 5.07–5.13 (m, 1H, C*H*), 7.33–7.36 (m, 2H, $C_{Ar}H$), 7.39–7.42 (m, 2H, $C_{Ar}H$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 20.3, 20.7, 25.1, 29.7, 30.7, 72.8 (dd, $^2J_{CF}$=32.9, 24.7 Hz, *C*H), 76.1 (dd, $^2J_{CF}$=26.9, 24.8 Hz, *C*OH), 119.0 (dd, $^1J_{CF}$=258.9, 250.7 Hz, *C*F_2), 128.2, 129.6, 134.4, 134.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −135.2 to −135.1 (m, 1F), −134.6 to −134.5 (m, 1F), −114.8 (s, 1F), −114.2 (s, 1F); FTIR (KBr, ν_{max} cm^{-1}) 3404 (s), 3253 (s), 1598 (w), 1491 (m), 1449 (m), 1414 (m), 1079 (s), 1071 (s), 985 (m), 812 (m); GC–MS (EI) *m*/*z* 77 (40%), 81 (35), 132 (80), 141 (100), 143 (30), 172 (20), 176 (5); HRMS (ESI^-) calculated for $C_{14}H_{16}F_2O_2Cl$: 289.0801, found: 289.0813.

4.6. General procedure for the preparation of difluoromethyl diols 7 from phosphonates 3 (one pot procedure)

A solution of *t*-BuOK (224.4 mg, 2 mmol) in DMF (3 mL) was added dropwise to a stirred solution of phosphonate **3** (1 mmol) and carbonyl compound **2** (2 mmol) in DMF (3 mL) cooled to −65 °C. The mixture was stirred at −55 °C to −65 °C for appropriate time and then at this temperature a solution sodium methoxide (0.25 mL, 4 M, 1 mmol) in methanol was added. The mixture was warmed up to rt and stirred for 1 h. Aqueous solution of NH_4Cl (4 mL) was added, the product was extracted into dichloromethane (4×15 mL). The combined organic extract was washed with saturated NaCl solution (6 mL), dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified on silica gel to yield difluoromethyl diols **7**.

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