Tetrahedron 67 (2011) 3887–3903

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An effective synthetic route to *ortho*-difluoromethyl arylphosphophosphonates: studies on the reactivity of phosphorus- and fluorine-containing functions

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ARTICLE INFO

Article history:
Received 9 February 2011
Received in revised form 19 March 2011
Accepted 22 March 2011
Available online 30 March 2011

Keywords:
Cyclization
Aromatization
Alkynes
Arylphosphonates
Regioselectivity

ABSTRACT

Herein, we report a new and convenient methodology for the synthesis of *ortho*-XCF_2 arylphosphonates via Diels–Alder reaction of selected 1,3-butadienes with $XCF_2{-}{\equiv}{-}P(O)(OEt)_2$, followed by the aromatization of the cyclic vinylphosphonates obtained using the $KMnO_4/Al_2O_3$ system. The reactivity of *ortho*-XCF_2 arylphosphonates was then examined to give the respective dichlorides that were converted to the corresponding phosphonic acids, phosphine oxides or a carboxylic acid (upon hydrolysis of the CF_2Br group). When *ortho*-XCF_2 arylphosphonates (X=Br) were treated with Zn/CuBr and an electrophile, the dimeric product ArCF=CFAr was isolated only. The lithiation of the CF_2H group (X=H) allowed however to obtain products of nucleophilic substitution with various electrophiles.

1. Introduction

For many years, the participation of organic phosphates in various enzymatic processes in living systems has been known.[1] These compounds have found practical application in medicine,[2] agriculture,[3] industry[4] and organic synthesis.[5] The incorporation of fluorinated substituents into such molecules dramatically alters their physical, chemical and biological properties.[6] Recently, there has been a growing interest in the synthesis of fluorine-containing arylphosphonates. Some of these compounds have found widespread use as effective additives in acrylic elastomer compositions (**A**),[7a] as photostabilizers in polymer composites (**B**)[7b] or as building blocks towards the synthesis of catalysts for ethylene polymerization (**C**).[7c] Moreover, their benzimidazole derivatives show high biological activity towards AMP-protein kinase, useful for diabetes prevention (**D**) (Fig. 1).[7d] Their applications as herbicides, plant-growth regulators,[7e] as well as monomers for synthesis of fluorescent semiconductive polymers,[7f] for fireproof and crosslinking agents[7g] or for photovoltaic cells[7h] have been also established.

The majority of the known methods for the synthesis of perfluoroarylphosphonates is based up on catalytic, thermal or organometallic substitution of an appropriate (perfluoroalkyl)aryl halide with a phosphorus-containing reagent (Fig. 2). While several methods have been developed for this purpose, none is available for the synthesis of arylphosphonates, bearing partially fluorinated groups, such as CF_2H,[8a] CF_2Cl[8b,c] and CF_2Br.[8d,e] In the case of trifluoromethylated *para*- or *meta*-aryl halides, the Michaelis-Becker reaction with dialkyl phosphites proceeds smoothly in the presence of $Pd(PPh_3)_4/Et_3N$[9a,b] or $Pd(OAc)_2/i\text{-}Pr_2NEt$.[9c] To produce polyfluorinated aromatic compounds, an example of a non-catalytic reaction with dialkyl phosphites has been described, however, this method has met with only limited success due to the very low yield of the target products.[9d] Other possible synthetic routes for these compounds could be the catalytic Arbuzov reaction between aryl

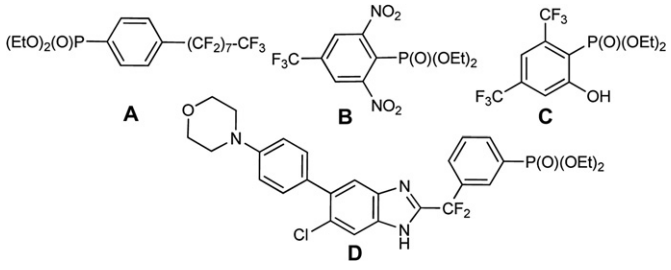

Fig. 1. Some fluorine-containing arylphosphonates with practical application.

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doi:10.1016/j.tet.2011.03.076

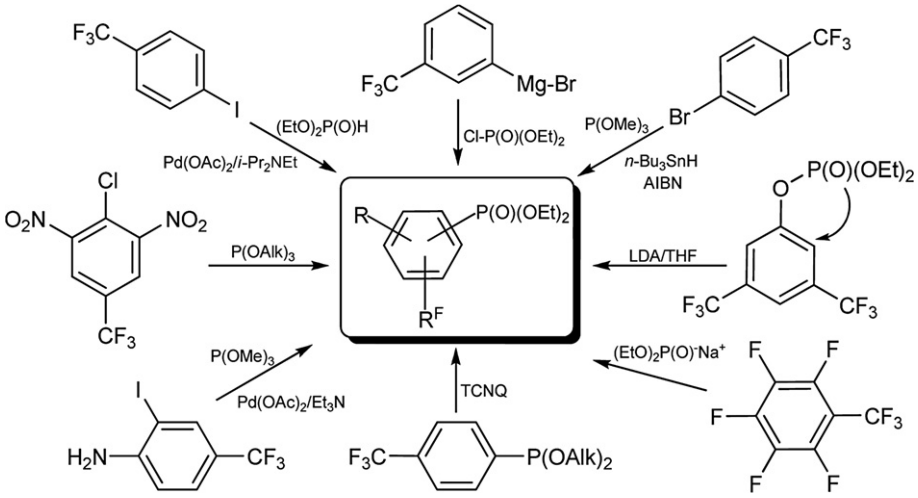


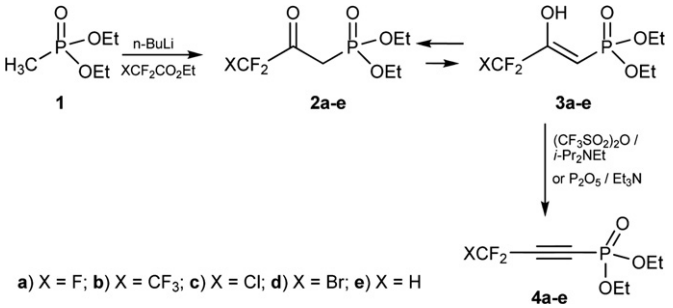
Fig. 2. General methods for the preparation of CF_3-substituted arylphosphonates.

halides and trialkyl phosphites, that proceeds in the presence of $NiCl_2$[10a] and $Pd(OAc)_2/PPh_3$,[10b] or under radical initiation,[10c] with non-activated aryl halides. With activated aryl halides, bearing strong electron-withdrawing groups, e.g., $-NO_2$[10d] or $-F$,[10e] this reaction occurs exclusively upon heating, however requiring very harsh reaction conditions. In some cases, *para*- or *meta*-arylphosphonates could be obtained by the oxidation of the corresponding phosphonites using tetracyanoquinodimethane (TCNQ)[10f] or NO_2.[10g]

In contrast to *para*- and *meta*-derivatives, methods for the preparation of *ortho*-fluorine-containing arylphosphonates have been rarely studied and only recently Heinicke et al. demonstrated for the first time the synthesis of these class of compounds.[7c] Nevertheless, this method including *ortho*-lithiation of 3,5-bis(trifluoromethyl) arylphosphonates with subsequent migration of the phosphoryl group in *ortho*-position to CF_3-moiety (anionic phospho-Fries rearrangement), allows us to obtain hydroxyphosphonates only and is limited by the availability of starting materials.[7c] In our previous work, we have successfully demonstrated the synthesis of some 1,4-cyclohexadienyl-1,2-perfluoroalkylphosphonates via Diels–Alder reaction of perfluoroacetylenephosphonates ($R^F-\equiv-P(O)(OEt)_2$) bearing only inert and highly electron-withdrawing substituents, such as CF_3 and C_2F_5. In addition, no other transformations of the obtained adducts were performed.[11] For such reasons, we propose herein a new and effective method for the synthesis of *ortho*-XCF_2 arylphosphonates, including the formation of six-membered rings and *ortho* substitution of fluorine and phosphorus functions via diene synthesis starting from XCF_2-acetylenephosphonates and subsequent aromatization of the corresponding carbocyclic adducts. Further functionalization of phosphonate and fluorine functions of these novel arenes upon treatment with some nucleophilic and metalloorganic reagents was also investigated.

2. Results and discussion

A convenient method for the synthesis of some perfluoroacetylenephosphonates with CF_3 and C_2F_5 substituents has been reported before based on the lithiation of dialkyl methylphosphonate using *n*-BuLi or LDA and subsequent reaction of the pregenerated $LiCH_2P(O)(OAlk)_2$ with fluorinated ethyl or methyl alkanoates to give the corresponding keto–enol mixtures,[12a–f] which were dehydrated subsequently.[12f,g] A similar methodology was reported for preparing the $ClCF_2$-acetylenephosphonate **4c**, however without full characterization of the targeted product.[12e] On the other hand, the synthetic route to other XCF_2-acetylenephosphonates (X=Br, H) has not been reported beforehand. In this work, we used the aforementioned method, but with some essential improvements that included the use of strictly 1 equiv of *n*-BuLi, the decrease of the temperature of the addition of lithiated methylphosphonate **1** to the fluoroalkanoate to −90 to −100 °C and azeotropic drying of the crude product in boiling benzene, that finally produced a mixture of β-ketophosphonate/enol **2**:**3** in almost quantitative yield (93–98%) and sufficiently pure to be used in the next step without purification. When carrying out the dehydration process of this mixture using the $(CF_3SO_2)_2O/i\text{-}Pr_2NEt$ system at −40 °C and extending the reaction time up to 6–7 h (Method A), alkynephosphonates **4a**–**e** were obtained in excellent yields 82–95% (Scheme 1).



Scheme 1. Synthetic strategy to fluorine-containing alkynephosphonates **4a**–**e**.

An important factor influencing the dehydration process of the ketone/enol **2**:**3** mixture was the amount of base (*i*-Pr_2NEt). In general, an increased amount of the base from 3.6[12f,g] to 5.5 equiv improved the yield and purity of the targeted alkynes **4a**–**e** (Table 1). Acetylenes **4a**–**e** could be also successfully obtained via the dehydration of enols **3a**–**e** using P_2O_5/Et_3N in CH_2Cl_2 at −20 °C (Method B). However, the best results were only achieved using a large excess of the base (up to 6.5 equiv for alkyne **4d**).

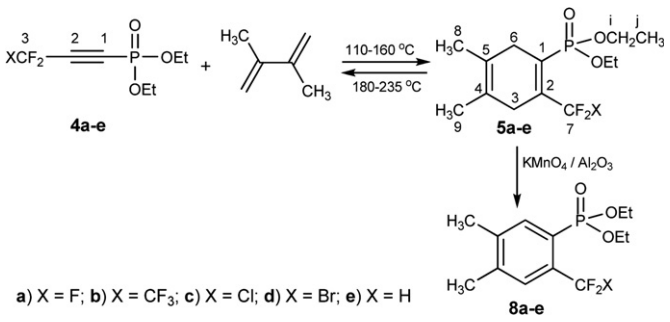
As is already known, the construction of six-membered carbocyclic rings in the classical form of the Diels–Alder reaction could be realized according to the following scheme: (diene–donor)–(acetylene–acceptor).[13] Some cycloadditions of alkynes bearing perfluoroalkyl[14] or dialkyl phosphonate[15] substituents, with 1,3-alkadienes were previously described in the literature. However, there is only one example involving alkynes possessing difluoromethylene, halodifluoromethylene functions[14d,e] and both perfluoroalkyl- and phosphonate[11] groups in such reactions.

Table 1
Synthesis of fluorine-containing alkynephosphonates through the dehydration of a β-ketophosphonate/enol mixture (**2**:**3**)

Substrate ratio[a] (**2**:**3**, mol %)	X	*i*-Pr_2NEt[b] (equiv)	Et_3N[c] (equiv)	Yield[d] (%)	Bp[e] (°C)
2a:**3a** (81:19)[f]	F	4.0	4.5	95/70 (**4a**)	35
2b:**3b** (69:31)	CF_3	4.0	4.5	92/67 (**4b**)	41
2c:**3c** (93:7)[g]	Cl	5.0	6.0	85/65 (**4c**)	56
2d:**3d** (94:6)	Br	5.5	6.5	82/60 (**4d**)	64
2e:**3e** (93:7)	H	4.5	5.0	88/68 (**4e**)	71

[a] According to ^{31}P, ^{19}F and ^{1}H NMR analysis in $CDCl_3$.
[b] For $(CF_3SO_2)_2O$ (1 equiv)/*i*-Pr_2NEt (*x* equiv) system, Method A.
[c] For (1 equiv) P_2O_5/Et_3N (*x* equiv) system, Method B.
[d] Isolated yield, Method A/Method B.
[e] At 0.1 mmHg.
[f] 86:14 (mol %).[12e]
[g] 78:22 (mol %).[12e]

Similarly to perfluoroacetylenephosphonates **4a**–**b** difluorinated alkynephosphonates **4c**–**e** reacted also smoothly with donor 1,3-alkadienes, such as 2,3-dimethyl-1,3-butadiene or isoprene, and formed the corresponding cyclohexo-1,4-dienyl-1-phosphonates **5c**–**e**, **6e** and **7e** in excellent yields (90–98%) (Scheme 2).



Scheme 2. Synthesis of carbocyclic phosphonates **5a**–**e** via Diels–Alder reaction and their aromatization to **8a**–**e**.

This reaction was conducted at 110–160 °C for 1.5–3 h using 10–15 mol % excess of 1,3-alkadiene, anhydrous toluene as solvent and 0.001 mol % of BHT as polymerization inhibitor. We also observed a significant reactivity decrease of the halodifluoroalkyne phosphonates **4c**,**d** (X=Cl, Br) towards 2,3-dimethyl-1,3-butadiene, compared to their perfluoroalkyl counterparts **4a**,**b** (X=F, CF_3). Alkynephosphonate **4e** (X=H) was even a less active dienophile and fully reacted with 15 mol % excess of 2,3-dimethyl-1,3-butadiene for 2.5 h at 150 °C and with isoprene at 160 °C for 3 h, respectively (Table 2). This could be best explained by the weaker electron-withdrawing effect of CF_2X groups of **4c**,**d** (X=Cl, Br) and **4e** (X=H) in comparison to perfluoroacetylenephosphonates **4a**,**b** (X=F, CF_3).

Table 2
Fluorine-containing alkynylphosphonates in Diels–Alder reaction: synthesis of carbocyclic adducts **5a**–**e**

Cycloadduct(s)	Reaction conditions			Yield[b] (%)
	Temperature (°C)	Duration (h)	1,3-Diene[a] (equiv)	
5a	110	0.5	1.05	97
5b	115	0.5	1.1	95
5c	125	1.5	1.1	98
5d	140	2.0	1.15	96
5e	150	2.5	1.15	93
6e+**7e** (59:41)[c]	160	3.0	1.15	90

[a] For alkyne **4a**–**e** (1 equiv):1,3-alkadiene system (*x* equiv).
[b] Isolated yields.
[c] Ratio of isomers (mol %), according to ^{31}P, ^{19}F and ^{1}H NMR data.

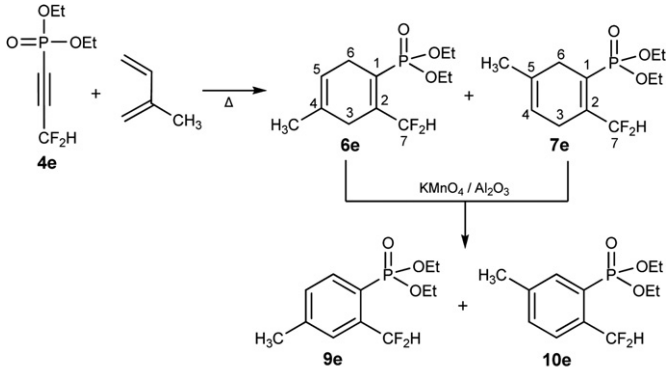
Generally, we observed that the use of higher temperatures (up to 160–165 °C) and reduced reaction time (up to 2–2.5 h) gave better results (Table 3). On the other hand, the temperature elevation during the diene synthesis was limited by the thermal stability of the final adducts **5c**–**e**, **6e** and **7e** that underwent *retro*-Diels–Alder reaction above 180 °C. This process was additionally monitored by the ^{31}P and ^{19}F NMR for the system (alkyne **4d**)/(adduct **5d**). It was found that at temperatures up to 170 °C adduct **5d** is stable. However, upon heating the reaction mixture above 180 °C, the *retro*-Diels–Alder reaction occurred (Table 3).

Table 3
Screening Diels- and *retro*-Diels–Alder reaction conditions for **4d**–**5d**

Entry	Temperature (°C)	Duration (h)	Composition of reaction mixture[a] (% mol)		
			4d	**5d**	Other[b]
1	120	10	0	80	20
2	140	2	0	96	4
3	160	5	0	92	8
4	180	2	15	77	8
5	200	1.5	55	32	13
6	235	0.5	73	0	27

[a] Due to ^{31}P NMR data.
[b] Decomposition products of **4d** (^{31}P NMR δ 3.6, 8.1, 32.5, 54.5) and a mixture of isomeric 1,3-cyclohexadienes (^{31}P NMR δ ~14.9–15.1).

The regioselectivity of such Diels–Alder cycloadditions was investigated by reacting diethyl 3,3-difluoroprop-1-ynylphosphonate **4e** with unsymmetrical 2-substituted-1,3-dienes, such as isoprene. This reaction proceeded under harsh conditions (Table 2) giving a mixture of 4-methyl- and 5-methyl-substituted (2-difluorocyclohexa-1,4-dien-1-yl) phosphonates **6e** and **7e** (Scheme 3).



Scheme 3. Regioselectivity of Diels–Alder reactions: synthesis of adducts **6e**, **7e** and their aromatization to **9e**, **10e**.

The predominant formation of isomer **6e** corresponded to the polarization of the parent compounds[16] and provided evidence for the electronic control of the reaction. The ratio of regioisomers (**6e** and **7e**), according to ^{31}P, ^{19}F and ^{1}H NMR spectra, was found to be 59:41 mol %, respectively. It should be however noted, that isomers **6e** and **7e** cannot be resolved using physical methods. Hence, their structure was established, taking into account the characteristic patterns of C^3, C^6 and C^4, C^5 signals for regioisomers **6e** and **7e** in the ^{13}C NMR spectra and respective data of previously reported examples.[11]

It is known, that cyclohexa-1,4-dienes serve as convenient synthons in the preparation of the corresponding substituted aromatic systems.[17a] In some cases, where the elimination of CO_2,[17b,c] CO[17d,e] or C_2H_4[17f] is possible, the aromatization usually occurs upon heating. Otherwise, for aromatization the use of oxidizing[14a,18a–c]

agents and catalytic dehydrohalogenation[18d,e] is required. In this work, $KMnO_4/Al_2O_3$ system was used for the oxidative dehydrogenation of novel XCF_2-containing cyclohexa-1,4-dienylphosphonates **5a**–**e**, **6e** and **7e** to obtain the *ortho*-XCF_2 arylphosphonates **8a**–**e**, **9e** and **10e** (Schemes 2 and 3). The best results were obtained upon mixing the substrates in dry acetone under an inert atmosphere at −20 to 5 °C. The reagent was added in portions (0.1 equiv each) until the complete disappearance of signals of carbocyclic phosphonates **5a**–**e**, **6e** and **7e** at ~15 ppm in the ^{31}P spectra, and simultaneous appearance of new ones at 17–18 ppm, attributable to arylphosphonates **8a**–**e**, **9e** and **10e**. Our studies have shown that an excess of potassium permanganate was also necessary. The temperature and the reaction time required for the complete conversion of substrates **5a**–**e**, **6e** and **7e**, were depending on the structure of adducts and on the electron-withdrawing properties of CF_2X groups (Table 4). In general, 4,5-dimethyl-1,2-disubstituted cyclohexadienes **5a**–**e** show markedly higher susceptibility for aromatization compared with 4- or 5-metyl derivatives **6e** and **7e**. The position of substituents had little effect on the aromatization process and similar reactivity has been observed for isomers **6e** and **7e**. During the reaction course, the product ratio **9e**:**10e** (61:39 mol %) did not change and was similar to that of the starting mixture **6e**:**7e** (59:41 mol %).

Table 4
The synthesis of *ortho*-CF_2 arylphosphonates by aromatization of the corresponding carbocyclic adducts **5a**–**e**, **6e** and **7e**

Arene(s)	Aromatization conditions			Yield[b] (%)
	$KMnO_4$[a] (equiv)	Duration (h)	Temperature (°C)	
8a	2.0	3.0	−20	96
8b	2.0	3.5	−15	94
8c	2.05	5.0	−5	87
8d	2.05	6.0	0	85
8e	2.1	6.5	0	80
9e+**10e** (61:39)[c]	2.6	10.0	15	60

[a] Per potassium permanganate for cyclohexa-1,4-diene **5a**–**e**, **6e** and **7e** system (1 equiv)/$KMnO_4/Al_2O_3$ (1:1 weight ratio).
[b] Isolated yield.
[c] Ratio of isomers (mol %), according to ^{31}P, ^{19}F and ^{1}H NMR data.

We also found, that an increased electron-withdrawing ability of CF_2X groups influenced the efficiency and selectivity of the aromatization of cyclohexadienes **5a**–**e**. As summarized in Table 4, in the case of X=F and CF_3 (**5a**,**b**) the appropriate *ortho*-fluorinated arylphosphonates **8a**,**b** were produced in almost quantitative yields when using a stoichiometric amount of the oxidizing agent (Table 4). Due to the lower reactivity of **5c**,**d** (X=Cl, Br), compounds **8c**,**d** were obtained in lower yields even after temperature elevation and reaction time extension (Table 4). For compound **5e** with X=H, the ability for the aromatization and selectivity of the process was significantly lower as shown by an 80% loss of yield for benzene **8e** by the need to use a large excess of $KMnO_4$ (Table 4). It should be however noted, that using $KMnO_4$ for aromatization without Al_2O_3, lower yields of the desired products (30–40%), higher consumption of $KMnO_4$ (up to 3.5 equiv) and the formation of larger amounts of resinous by-products were observed. The effectiveness of aromatization for **5a** was also examined with other reagents using different systems known from the literature for other carbocyclic systems, such as DDQ in dichloromethane,[18a] 2,3,4,5-tetrachlorobenzo-1,4-quinone in toluene,[14a] activated MnO_2 in 1,4-dioxane,[18c] NCS in methylacetate[18e] and KOH in 1,4-dioxane.[14c] The best results (Table 5) were obtained using DDQ and 2,3,5,6-tetrachloro-*p*-benzoquinone (*p*-chloranil), giving rise to arene **8a** in 60–50% yield (Table 5, entries 1 and 2). However due to the formation of by-products and corresponding hydroquinones, obtained from the reduction of DDQ and 2,3,4,5-tetrachlorobenzo-1,4-quinone, chromatographic methods of isolation were essential for isolation and purification of product **8a**, preventing us from using this system on a preparative scale. Taking *N*-chlorosuccinimide (NCS) for the preparation of **8a** was also ineffective as a result of a competitive double bond isomerization in the carbocyclic framework of **5a** and their subsequent polychlorination.

Table 5
Other systems used for dehydrogenation of carbocyclic adduct **5a** to form arene **8a**

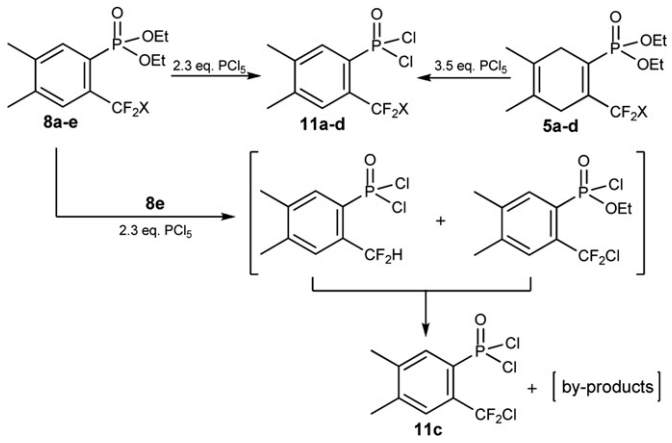
Entry	Reagents, aromatization conditions and purification method[a]	Yield of **8a**[b] (%)
1	DDQ (1.5 equiv), CH_2Cl_2, 4 h, 25 °C, flash column chromatography.	60
2	*p*-Chloranil (2.0 equiv), toluene, 12 h, 100 °C, column chromatography.	50
3	NCS (1.1 equiv), methyl acetate, 5 h, 90 °C, column chromatography.	28
4	Activated MnO_2 (25.0 equiv), 1,4-dioxane, 24 h, 101 °C, column chromatography.	15
5	Powdered KOH (2.0 equiv), 1,4-dioxane, 24 h–few min, 5–101 °C.	0

[a] Based on known literature procedures[14a,c,18a–e] and per 1 equiv of **5a**.
[b] Isolated yield of **8a** with ≥95 mol % purity.

In addition, product **8a** was isolated after column chromatography in 28% yield (Table 5, entry 3). Similarly, activated MnO_2 showed low activity and selectivity in the dehydration of **5a** to **8a** resulting in a conversion less than 50 mol % of **5a**. Hence, arylphosphonate **8a** was isolated with only 15% yield (Table 5, entry 4). An approach to dehydrate cyclohexa-1,4-diene phosphonate **5a** with a suspension of KOH in 1,4-dioxane, did not lead to the desired product **8a**. Monitoring the reaction mixture by ^{31}P and ^{19}F NMR showed no significant difference in spectral pattern upon mixing at 5 °C to ambient temperature within 24 h although, heating the KOH suspension to 50 °C led to noticeable decomposition of substrate **5a** that proceeded fully within few minutes in refluxing 1,4-dioxane (not even traces of **8a** were detected) (Table 5, entry 5). Summarizing the results of testing various oxidizing–dehydration systems (Tables 4 and 5) it could be deduced, that for the aromatization of cyclohexa-1,4-diene phosphonates **5a**–**e**, **6e** and **7e**, which is a key step in the synthesis of the corresponding *ortho*-XCF_2 arylphosphonates **8a**–**e**, **9e** and **10e**, the use of $KMnO_4$ passivated with dehydrated Al_2O_3 gave optimum results. In contrast to other reagents checked, $KMnO_4/Al_2O_3$ in dry acetone is a mild and very selective oxidizing agent for fluorine and phosphorus-containing carbocycles **5a**–**e**, **6e** and **7e**, even at low temperatures.

In the next part of this work, we demonstrate the synthetic utility of novel *ortho*-XCF_2 arylphosphonates **8a**–**e**, **9e** and **10e** by the modification and functionalization of phosphorus and fluorine-containing moieties to access various phosphorus-containing arenes, which were not previously available. The functionalization of a phosphonate group could be best achieved by the replacement of the alkoxy groups with halogens[19a], e.g., chlorine or bromine, in the first step, followed by the addition of a nucleophile. Dichlorophosphonates are usually obtained by treating the appropriate phosphonic or thiophosphonic acid and their alkyl esters with $SOCl_2$,[19b,c] oxalyl chloride[19d] and seldom with PCl_5[19e] in the presence (or absence) of activators, such as DMF, pyridine or *N*-formylpiperidine.

During our investigations we observed, that diethyl arylphosphonates **8a**–**d** underwent chlorination easily using a PCl_5–$POCl_3$ mixture forming the corresponding *ortho*-XCF_2 arylphosphonic dichlorides **11a**–**d** in good to excellent yields (85–94%) (Scheme 4). The optimal reaction conditions were achieved with the ratio of 2.3 equiv PCl_5, 2.1 equiv $POCl_3$ and 1.0 equiv of **8a**–**d** (Method C).



a) X = F; b) X = CF_3; c) X = Cl; d) X = Br; e) X = H

Scheme 4. Chlorination of diethyl phosphonates **8a**–**e** with PCl_5–$POCl_3$: synthesis of arylphosphonic dichlorides **11a**–**d**.

Phosphonic dichlorides **11a**–**d** could also be produced via direct chlorination of cyclohexa-1,4-dienylphosphonates **5a**–**d** (1.0 equiv) with phosphorus pentachloride (3.5 equiv) in the presence of phosphorus oxychloride (3.0 equiv) (Method D). However for this process rather harsh reaction conditions were required (10–12 h at 106 °C) to give arenes **11a**–**d** with significantly lower yield (Table 6, entries 1–4).

Table 6
The synthesis of *ortho*-XCF_2 arylphosphonic dichlorides from phosphonates **8a**–**e** with PCl_5–$POCl_3$

Entry	Starting arylphosphonate	Product	Yield[a] (%)		Bp[b] (°C)
			Method C	Method D[c]	
1	**8a** or **5a**	**11a**	94	40	99
2	**8b** or **5b**	**11b**	93	32	108
3	**8c** or **5c**	**11c**	87	37	135
4	**8d** or **5d**	**11d**	85	30	142
5	**8e**	**11c**	25	—	135

[a] Isolated yield with ≥95% purity.
[b] At 0.1 mmHg.
[c] After three distillations.

Chlorination of phosphonates **8e**, **9e** and **10e** with PCl_5/$POCl_3$ resulted in the chlorination of the CF_2H moiety, instead of the formation of the expected phosphonic dichlorides. In the case of **8e**, we isolated product **11c** in 25% yield as the sole product (Scheme 4, Table 6, entry 5). The treatment of isomeric arylphosphonates **9e**+**10e** with PCl_5/$POCl_3$ led to the decomposition of the HCF_2 group and to the formation of a non-separable mixture of chlorinated products. Interestingly, upon treatment of **8a** and **8c** with PCl_5/$POCl_3$ (Method D) in the presence of a small amount of $FeCl_3$ (<0.01%), a monochlorination of α-methyl groups of the benzene ring occurred (Fig. 3) to give compounds **11a**′+**11a**″ and **11c**′+**11c**″ as a mixture of regioisomers in a 1:1 (mol) ratio with 20% and 15% yield, respectively, according to the ^{1}H NMR data. The isolation of **11a**′, **11a**″ and **11c**′, **11c**″, as well as the separation from the major product **11a** and **11c**, was not possible due to formation of a three-component azeotropic system **11a**:**11a**′:**11a**″ with 60:20:20 mol % and **11c**:**11c**′:**11c**″ with 70:15:15 mol %, with no change in the ratio even after repeated fractional distillation. However, the significant difference in the ^{1}H, ^{31}P, ^{19}F NMR and MS characteristics for **11a**, **11a**′ and **11a**″ (as well as for **11c**, **11c**′ and **11c**″) allowed us to determine the structure of these by-products.

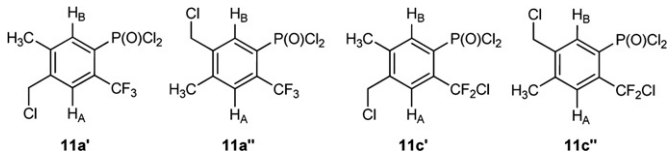
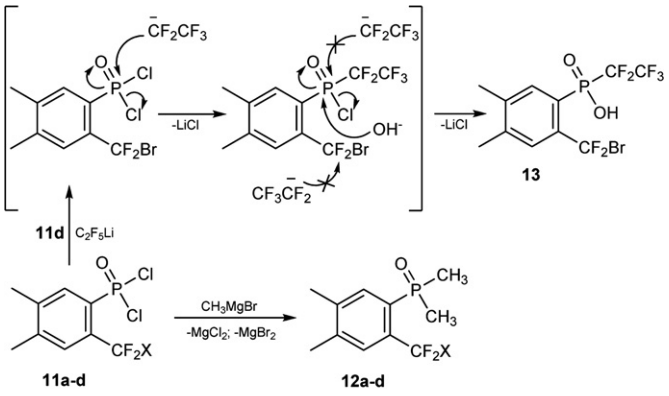


Fig. 3. α-Chloromethyl-containing by-products from the reaction of arylphosphonates **11a**, **11c** with PCl_5–$POCl_3$ in the presence of $FeCl_3$.

In the ^{1}H NMR spectra of **11a**′,**c**′ and **11a**″,**c**″ typical singlets[19f] of *o*-Ar–CH_2Cl and *o*-Ar–CH_3 at ~4.7 and ~2.6 ppm and doublets from protons H_A and H_B at ~7.75 ppm with $^4J_{HP}$ ~8.8 Hz and ~8.3 ppm with $^3J_{HP}$ ~20.5 Hz for isomers **11a**′,**c**′ and at ~7.9 ppm ($^4J_{HP}$ ~8.8 Hz) and ~8.2 ppm ($^3J_{HP}$ ~20.5 Hz) for isomers **11a**″,**c**″ could be distinguished. In the MS spectra, peaks from molecular ions from $[M]^+$ of **11a**′+**11a**″ (*m*/*e*=324) and **11c**′+**11c**″ (*m*/*e*=340) were also observed. It should be noted that this phenomenon has not been previously described in the literature and the mechanism for their formation is not completely clear.

Reactions of phosphorus dichlorides with various nucleophiles allowed us to modify the phosphorus function.[20a] Metalloorganic reagents, such as lithioorganic[20b,c] or Grignard reagents[20d,e] offer an broad access to phosphine oxides[21a] or tertiary phosphines,[21b,c] that serve as valuable ligands in metallocomplex synthesis.[21d–f] At the same time, these transformations using fluorinated organometallic reagents have never been explored. As a part of our studies designed to examine the utility of *ortho*-XCF_2 arylphosphonic dichlorides, we have found that compounds **11a**–**d** reacted smoothly in a solution of dry THF with 2.1 equiv of Grignard reagent, e.g., methylmagnesium bromide, at −30 °C to give appropriate *ortho*-XCF_2 phenyl(dimethyl)-phosphine oxides **12a**–**d** in good yields (51–78%) (Scheme 5).

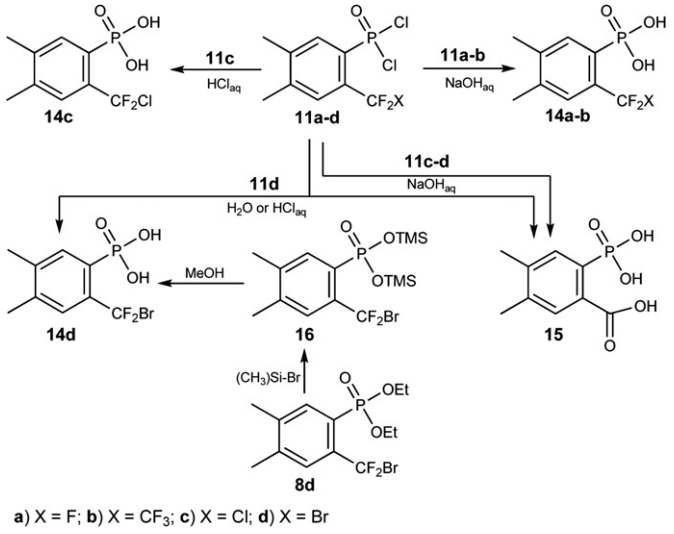


a) X = F; b) X = CF_3; c) X = Cl; d) X = Br

Scheme 5. Reaction of arylphosphonic dichlorides **11a**–**d** with metallorganic reagents: synthesis of phosphine oxides **12a**–**d** and phosphinic acid **13**.

Screening of the reaction conditions and spectral analysis of the crude product showed no significant influence of the CF_2X-function onto the reactivity of the dichlorophosphonic group. Similarly, reactions with **11a**–**c** were carried out under standard conditions and gave similar results, namely high regioselectivity and comparable yields of phosphine oxides **12a**–**c** (75, 73 and 78%). However, in the case of **11d** this reaction did not take place selectively and oligomeric autocondensated by-products (approx. 15%) were obtained and determined as broad multiplets from δ 52 to 61 in the ^{31}P and at −44 to −46 in ^{19}F NMR spectra. In the mass spectrum a group of molecular ions with *m*/*e*=600–850 was also observed. These oligomeric by-products contained some fragments of substrate **11d** (*ortho*-xylene, phosphonate and CF_2Br units) what could be deduced from their subsequent defragmentation probably explaining the ability of the CF_2Br group to form organometallic intermediates[22a,b] and to undergo various coupling reactions[22c] as well as hydrolysis (Scheme 6). As a result, phosphine oxide **12d** was isolated with only moderate 51% yield. To examine the possibility of selective substitution at phosphorus with *C*-nucleophiles in CF_2Br-containing compounds **11d**, the reaction with poor nucleophilic

and highly selective species [C_2F_5Li],[22d] generated in situ from *n*-BuLi and C_2F_5H, was carried out. This process was conducted in anhydrous THF at −78 °C using 1.1, 2.3 or 3.2 equiv of [C_2F_5Li], prior to hydrolysis with 10% HCl. Interestingly, in all cases, a sole product of monosubstitution at phosphorus atom of **11d** was formed (Scheme 5). This process occurred smoothly, without any formation of other by-products and allowed us to obtain arylphosphonic acid **13** in 85% yield (Scheme 5). Substitution of chlorine proceeded probably via an addition–elimination mechanism[22e] already known for phosphonic dichlorides (Scheme 5) however its high selectivity upon treatment with [C_2F_5Li] could be best explained by the steric factors of CF_2Br and C_2F_5 groups. To the best of our knowledge, only one previous example of an effective introduction of two isopropyl groups onto phosphorus in Ar–P(O)Cl_2 has been described.[22f] In the case of [C_2F_5Li], low nucleophilicity of the carbanion and enhanced electrophilicity after addition of a first equivalent of C_2F_5Li and elimination of Cl^- prevented the phosphorus centre from subsequent addition due to the presence of the sterically demanding CF_2Br group in *ortho*-position. In a similar manner, the stability of this moiety upon the reaction conditions could be explained. Nevertheless, the spectral analysis revealed interesting features. In the ^1H NMR spectra of compounds **12a**–**d**, a characteristic doublet of triplets (quartets) was detected from CH_3–P(O) group at 2.0 ppm with $^2J_{HP}$ ~14 Hz and $^6J_{HF}$ ~2 Hz.



a) X = F; **b**) X = CF_3; **c**) X = Cl; **d**) X = Br

Scheme 6. Hydrolysis of arylphosphonic dichlorides **11a**–**d**: synthesis of phosphonic acids **14a**–**d**.

In the ^{13}C NMR, a doublet of triplets (quartets) for methyl group carbons directly attached to phosphorus was observed at ~18.5 ppm with $^1J_{CP}$ ~75 Hz and $^5J_{CF}$ ~5 Hz. Similar coupling constants ($^6J_{FH}$ ~2 Hz) were recorded in multiplets from **12a**–**d** in the ^{19}F NMR spectra. The existence of spin–spin couplings between proton and carbon nuclei of Me–P and fluorines from the Ar–XCF_2 moiety and anomalous large coupling constants ($^6J_{HF}$, $^5J_{CF}$) indicated the through-space character of these interactions. This hypothesis was confirmed by the analysis of the ^{19}F NMR spectrum of compound **13** (Fig. 4). As presented, the CF_2Br group connected to phosphorus is detected as a doublet of triplets at −124.6 ppm with $^2J_{FP}$ 88.3 Hz what is in agreement with the ^{31}P NMR data (δ: t, 24.4, $^2J_{PF}$=88.3 Hz), and $^6J_{FF}$=13.8 Hz. On the other hand, the *ortho*-$BrCF_2$ group is observed as a triplet at −42.8 ppm with a coupling constant of $^6J_{FF}$=13.8 Hz while $^4J_{FP}$ from phosphorus is not observed. This phenomenon confirms strongly intramolecular electron–spatial interactions in structures of **12a**–**d**,**13** attracting special attention to further studies on *ortho*-XCF_2 arylphosphonic compounds.

Another synthetic modification of the dichlorophosphonic moiety, is its hydrolysis,[23a,b] also considered as a nucleophilic substitution at phosphorus. This reaction usually takes place under mild conditions[23a] and has found widespread application due to the fact that the products of hydrolysis—phosphonic acids—play an important role in modern medicine,[23c] agriculture[23d] and technology.[23e] On the other hand, perfluoroalkyl groups attached to the aromatic ring undergo hydrolysis *only* if an acidic proton (e.g., OH, SH and NH) is located in an *ortho*-position to fluorinated substituent.[23f,g] Moreover, there is a lack of literature protocols considering the hydrolysis of XCF_2-aromatic compounds, where X=Cl or Br. For these reasons, hydrolysis of *ortho*-XCF_2 arylphosphonic dichlorides **11a**–**d** has been carried out under basic (5% aq NaOH), acidic (10% HCl) and neutral conditions (Scheme 6).

For compounds **11a**–**d**, aqueous acetonitrile (70–90%) was used. The full conversion of starting materials was determined by the complete homogenization of the reaction mixture. Results of these studies have shown that perfluoro-substituted phosphonic dichlorides **11a**,**b** easily and selectively undergo hydrolysis at pH 1–12 with the formation of the corresponding *ortho*-XCF_2 arylphosphonic acids **14a**,**b** in good yields (75–80%) (Scheme 6). The prolongated reaction time was however necessary for **11b** due to its poorer solubility compared to **11a**, and for **11a**,**b** under acidic conditions in contrast to the reaction under basic conditions, which did not provide to the loss of yield. Furthermore, no decomposition of difluoroalkyl groups has occurred. In contrast, CF_2Cl (**11c**) and particularly CF_2Br (**11d**) groups proved to be moisture and pH sensitive. Hence, under basic conditions the hydrolysis of P(O)Cl_2 groups for **11c**,**d** proceeded smoothly (Table 7), simultaneously with the hydrolysis of CF_2X-moiety, which at pH=12 run quantitatively within 0.5 h and produced 4,5-dimethyl-2-phosphonobenzoic acid **15** in 95% yield (Scheme 6).

At pH ≤7, the CF_2Cl group was quite resistant to water. When 10% HCl/CH_3CN was used, the hydrolysis of the dichlorophosphonic group of **11c** proceeded within 2.5 h and the corresponding phosphonic acid **14c** was isolated in 85% yield (Table 7). In addition, our efforts showed that phosphonic acid **14d** cannot be obtained upon selective hydrolysis of **11d**. Therefore, compound **14d** was synthesized using TMS–Br.[24] In the first step diethyl phosphonate **8d** was converted into the corresponding silyl phosphonic ester **16**, followed by methanolysis giving the desired acid in a 65% overall yield (Scheme 6). The above-mentioned experiments showed that the ability of the CF_2X-moiety to undergo hydrolysis decreases in the order: $CF_2Br > CF_2Cl >> CF_3 \approx C_2F_5$. Mechanistically, the key step in the hydrolysis of the CF_2X group should be the formation of intermediate **14d^{IV}**,[25a] that spontaneously undergoes defragmentation with the elimination of HF to give **14d^{V}**[25b] and after the subsequent addition–elimination and protonation of **14d^{VI}** provides the acid **15** (Fig. 5).

However the mechanism of the [CF_2OH] formation of the intermediate **14d^{IV}**, as well as hydrolysis of CF_2X-containing compounds, is not yet clear.[25c] For some vinyl difluoromethyl bromides, the mechanism includes 1,4-dehydrobromination (CF_2X–=–→ CF_2=–=) with the formation of an intermediate of quinoid type, prior to the addition of water to the *gem*-difluorovinyl derivative has been reported.[25d] Although for compound **14d** this explanation seems to be rather weak since it requires the dehydration of a benzene ring in the 6-position using 5% aq NaOH with the destruction of aromaticity, that is, thermodynamically unfavourable and was not confirmed experimentally. From this perspective, we propose an alternative route involving a single electron transfer chain process ($S_{RN}1$) that has been already proved for some perfluoroalkyl iodides[25e] and is in agreement with our experimental data (Fig. 5).

As well as the reactivity in 1994 Burton et al. for the first time reported the synthesis of organometallic reagents from aromatic-CF_2Br, such as CF_2–Cd, CF_2–Cd–CF_2 and CF2-Cu.[26a] Later, other reagents with In,[26b] Zn,[26c] and Mg[26d] were also obtained and their further reactions with electrophiles were investigated.[26b–d] An interesting example of the application of Zn, Cu and Al derivates of *para*-bis[CF_2Br(Cl)] benzene has been described, which includes

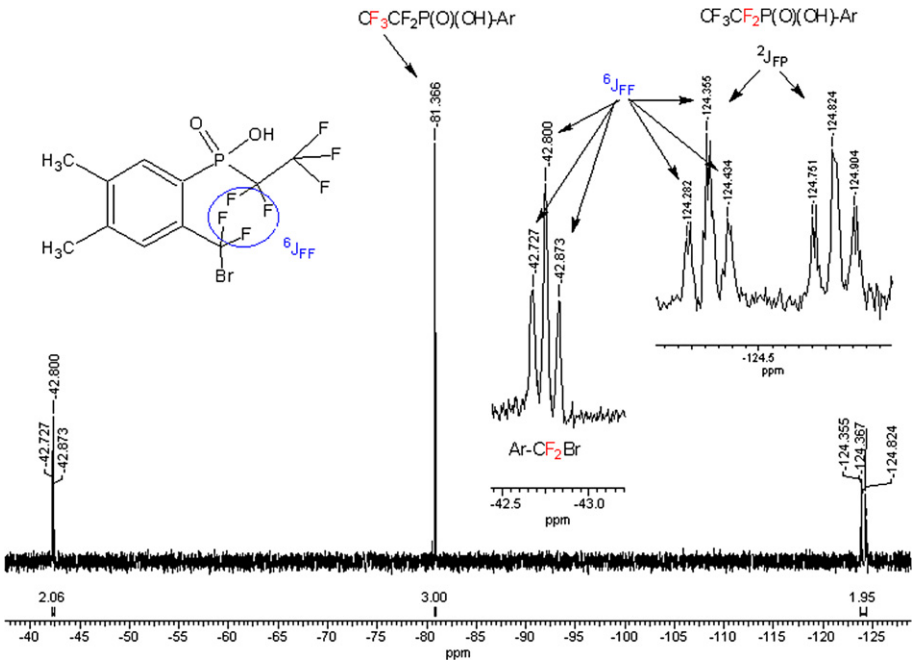


Fig. 4. ^{19}F NMR spectrum of 2-[bromo(difluoro)methyl]-4,5-dimethyl phenyl(pentafluoroethyl)phosphinic acid **13**.

Table 7
Screening the reaction conditions for the hydrolysis of arylphosphonic dichlorides **11a**–**d** at pH 1–12

Entry	Starting phosphonic dichloride	Spectral yield of target product by (conditions) (%)[a]			Target product
		Basic[b]	Acidic[c]	Neutral[d]	
1	**11a**	98	95	96	**14a**
2	**11b**	100	97	98	**14b**
3	**11c**	0	95	90	**14c**
4	**11d**	0	10[e]	~5[f]	**14d**

[a] Due to ^{31}P and ^{19}F NMR analysis.
[b] 5% aq NaOH–CH_3CN (30%:70%), rt, 0.5 h.
[c] 10% aq HCl–CH_3CN (20%:80%), rt, 2.5 h.
[d] H_2O–CH_3CN (10%:90%), rt, 1 h.
[e] In the presence of 70 mol % of **15**.
[f] In the presence of 90 mol % of **15**.

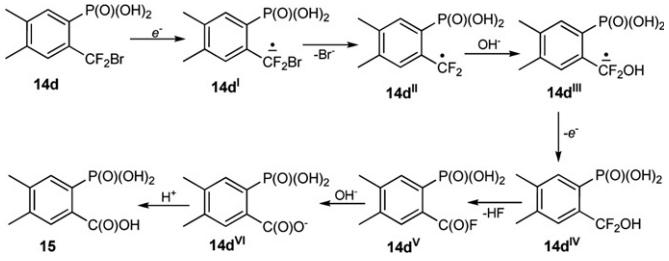
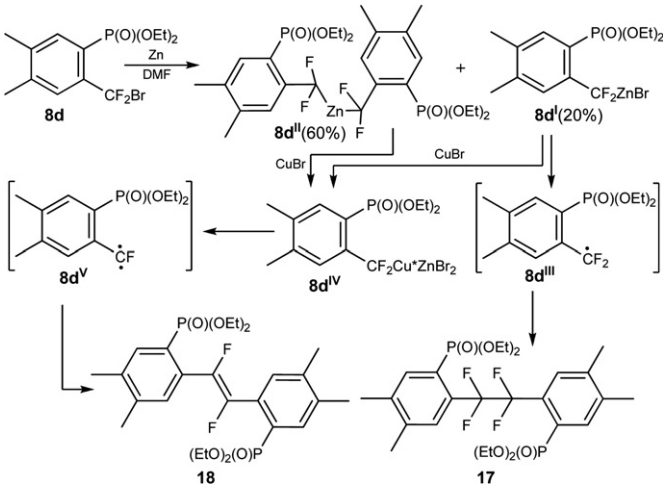


Fig. 5. Probable mechanism for hydrolysis of CF_2Br-moiety of arylphosphonic acid **14d**.

di-, tri- and tetramerization to give industrially important cyclophanes, macrocyclic systems formed from Ar–CF_2–CF_2–Ar units.[27a,b] However, it should be noted that these reactions proceed often with low selectivity and yield. There are also no examples of aromatic CF_2Br(Cl)-arene bearing other EWG-groups, such as carbonyl- or phosphonic-substituents in the literature. To prove the reactivity of the CF_2Br-benzyl moiety in the presence of an *ortho*-phosphonic substituent, diethyl 2-[bromo(difluoro)methyl]-4,5-dimethylphenylphosphonate **8d** was studied in the reaction with acid-washed zinc to produce the corresponding organozinc reagent. This experiment showed that arylphosphonate **8d** gave a mixture of CF_2ZnBr **8d^{I}** and Ar–CF_2ZnCF_2–Ar **8d^{II}** at rt in dry DMF with an 80% overall yield (Scheme 7).

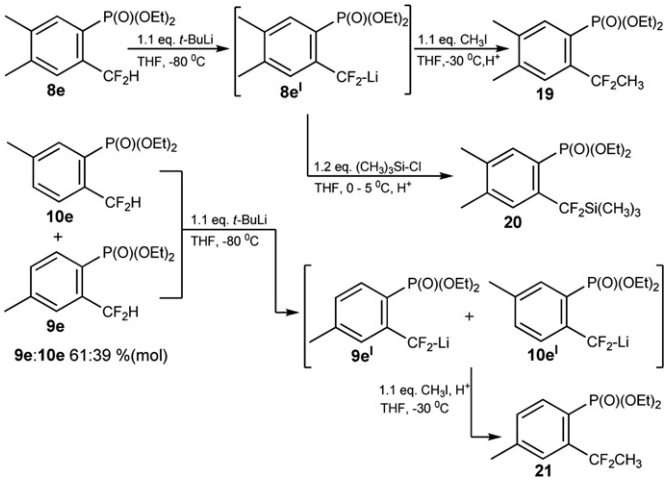


Scheme 7. Synthesis of Zn- and Cu-derivatives of **8d**: reaction pathway to dimers **17** and **18**.

This reaction was observed to proceed exothermically for 3 h and gave additionally small amounts (~4 mol %) of CF_2H-phosphonate **8e**, as a result of the hydrolysis of organozinc reagents **8d^{I}** and **8d^{II}**[26a] according to ^{19}F NMR (doublet at −105.4 ppm with $^{2}J_{FH}$ 55.6 Hz). Reagents **8d^{I}** and **8d^{II}** were identified in a DMF solution by ^{19}F NMR spectroscopy as singlets at δ −92.2 and singlet at δ −91.7 in a 3:1 ratio, in agreement with other analogues.[26a,27c] As it has been known, difluoromethylene zinc bromides form stable solutions[28a] and their dimerization occur only under harsh conditions.[28b] However, in the case of **8d** and Zn, immediately after the completion of reaction, the ^{19}F and ^{31}P NMR analysis showed the existence of dimer **17** (δ_F −95.3, δ_F 22.8) and m/e=582 for $[M]^+$ at MS(EI) in 10% NMR yield (Scheme 7). The dimer **17** is possibly formed as a by-product, simultaneously with **8d^{I}** and **8d^{II}** resulting from the thermal decomposition of **8d^{I}** to give the difluoromethyl radical[27c] **8d^{III}**, which subsequently dimerizes to form **17d**. This synchronic route could be best explained by the observation that the filtrated solution of **8d^{I}**, **8d^{II}** and **17** may be stored without significant changes up to 24 h at rt while the ratio of **8d^{I}**, **8d^{II}** and **17** (3:1:0.5) remains unchanged. The obtained organozinc

reagents in their active form[26a] **8d^{I}**, proved to be very weak nucleophiles. Their reactivity was examined in reactions with MeI, allyl bromide, benzaldehyde and trimethylsilyl chloride at temperatures ranging from 20 to 100 °C. Only allyl bromide and TMS–Cl gave the desired products of substitution (δ_F −91.4 and −85) in traces (3–5 mol %). This decreased nucleophilicity of the organozinc derivative[26a,b] could be best explained by the strong electron-withdrawing properties of the dialkylphosphonic moiety and two fluorine atoms directly connected to the carboanionic centre. Even lower reactivity with electrophiles has been observed for the organocopper reagent ($CF_2Cu\cdots ZnBr_2$) **8d^{IV}**, obtained by the addition of Cu(I)Br to the solution of (**8d^{I}**+**8d^{II}**) at −30 °C.[26a] Although, at this temperature in the presence or absence of an electrophile (allylbromide, benzaldehyde or trimethylsilyl chloride), a fast and spontaneous dimerization of the organocopper reagent occurred with the formation of difluorstilbene **18** in very good 80% NMR yield (Scheme 7). Moreover, the ^{19}F, ^{31}P and ^{1}H NMR analysis of the crude product did not show any substitution products with the concentration of the dimer **17** not changing (~10%). This means that the second electron chain decomposition of **8d^{IV}** with the predominant formation of fluorocarbene[27c] **8d^{V}** occurred and finally gave the conjugated **18**, which was isolated in 71% yield (Scheme 7). Probably, the steric factor of *ortho*-phosphonate groups played also an important role in the dimerization, promoting more the compact, coplanar *trans*-stilbene **18** (Fig. 6). A similar dimerization process of aromatic CF_2-organocuprates has never been reported and was only mentioned in the Zn-mediated preparation of cyclophanes.[28c] The structure of difluorostilbene **18** was determined by the ^{1}H, ^{31}P, ^{19}F, ^{13}C NMR, MS(EI), HRMS and additionally confirmed by X-ray analysis (Fig. 6).[29]

Another method for the functionalization of the CF_2-moiety included the lithiation of HCF_2 group with the formation of the difluoromethyl carbanion and its further interactions with various electrophilic reagents.[30a] To the best of our knowledge, in a series of difluoromethyl arenes this process is generally not known and only few trials can be found in the literature. In these procedures, *n*-BuLi was used as a base however due to the low acidity of Ar–CF_2H moiety, the reaction proceeded only via nucleophilic substitution of aromatic halogen[30b] or the lithiation was observed to occur to the *para*-position of benzene ring.[30c] Here we first demonstrated the synthetic utility of *ortho*-CF_2H groups of arylphosphonate **8e**, **9e** and **10e** in reactions with various strong organic bases and the application of in situ generated difluorocarbanions in reactions with some electrophiles. During our studies we found that *ortho*-fluorine-containing arylphosphonate **8e**, **9e** and **10e** could be easily deprotonated by *t*-BuLi in THF to give the corresponding difluorocarbanions **8e^{I}**, **9e^{I}** and **10e^{I}** (Scheme 8). The thermal stability of **8e^{I}**, **9e^{I}**+**10e^{I}** was tested by rapid hydrolysis of solutions of **8e^{I}**, **9e^{I}** and **10e^{I}** with 10% HCl at −70, −40, 0 and 15 °C and subsequent analysis of the reaction mixture by the ^{19}F and ^{31}P NMR. These experiments have shown that carbanions **8e^{I}**, **9e^{I}** and **10e^{I}** are stable at ambient temperature up to 0–5 °C and gave only starting **8e**, **9e** and **10e** after hydrolysis. Although at 10–15 °C, these carbanions decomposed with the elimination of F^-, the phosphonic group and the aromatic framework. The reactivity of carbanions **8e^{I}**, **9e^{I}** and **10e^{I}** was highly selective. Thus, difluorocarbanion **8e^{I}**, obtained from **8e** reacts smoothly with methyl iodide at −30 °C to give substitution product **19** in 74% yield (Scheme 8).



Scheme 8. Lithiation of CF_2H moiety of compounds **8e**, **9e**, **10e** and their reaction with MeI and trimethylsilyl chloride: synthesis of arylphosphonates **19**–**21**.

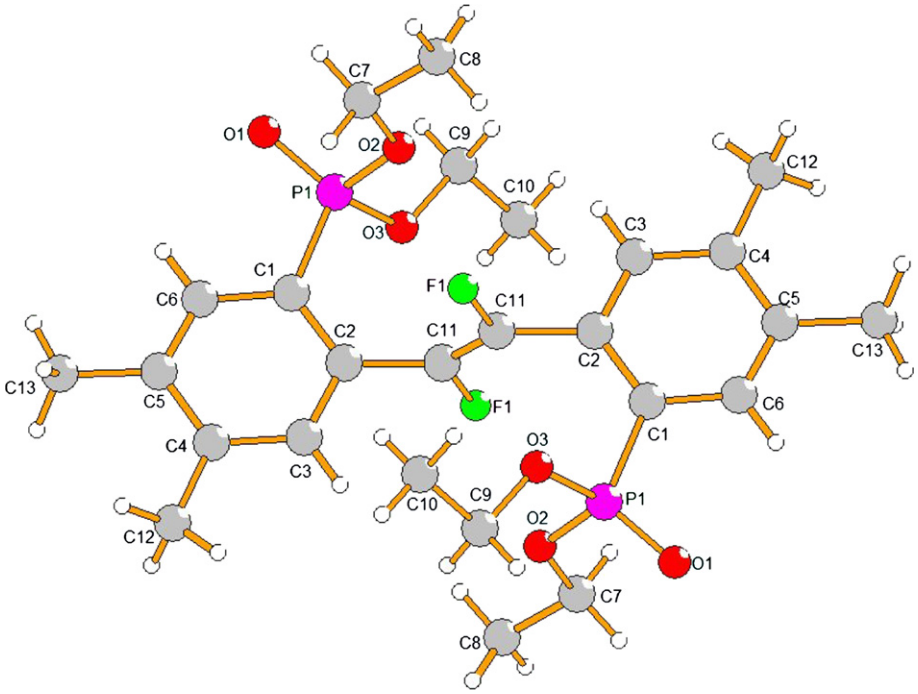


Fig. 6. ORTEP diagram of the single-crystal X-ray structure of compound **18**.

A significantly lower reactivity of carbanion **8e^{I}** was observed in reaction with trimethylsilyl chloride. Therefore, the final product **20** was isolated in 50% yield. Monitoring the progress of the reaction by ^{19}F and ^{31}P NMR showed that prolonging the reaction time (up to 6–8 h) does not influence the product yield **20** but only increases the concentration of decomposition products of **8e^{I}** (signals at ~−138, −160 ppm in the ^{19}F NMR and at ~32, −2 ppm in the ^{31}P NMR). The substitution of allyl and benzyl bromides and final products were obtained in traces. When highly electrophilic carbonyl compounds, such as *para*-fluorbenzaldehyde or difluorophosgene were reacted with **8e^{I}**, the expected products were not formed even in traces and only starting material **8e** was recovered. When the mixture of regioisomers **9e** and **10e** (61:39 mol %) was lithiated with *t*-BuLi followed by the addition of 1.1 equiv of MeI at −25 °C within 4 h and hydrolysis with 10% HCl, the ^{19}F and ^{31}P NMR spectra showed ~80% conversion of diethyl 2-(difluoromethyl)-4-methylphenyl-phosphonate **9e** and the formation of the corresponding substituted 4-methylphenylphosphonate **21** in 73% (45% overall) yield. Interestingly, the starting 5-methyl regioisomer **10e** was recovered after reaction and remaining unchanged in the same proportion (35 mol %). After purification by column chromatography, diethyl 2-(1,1-difluoroethyl)-4-methylphenylphosphonate **21** was isolated in 62% (38% overall) yield and substrate **10e** was recovered in 27% yield. The reason for such low reactivity of 5-methyl carbanion **10e^{I}** in comparison to 4-methyl **9e^{I}** is not yet clear but the general reactivity of **8e^{I}**, **9e^{I}** is probably associated with the strong EWG-effect of *ortho*-phosphonic moiety, that increases the acidity of the CF_2H group and facilitates deprotonation of this unit. On the other hand, it deactivates and stabilizes the negative charge through delocalization and hence determines the high regiospecificity and thermal stability of carbanions **9e^{I}** and **10e^{I}**. In order to optimize the reaction conditions and check the effectiveness of other bases, the reaction of **8e** with MeI was carried out using various metalating agents. The results are summarized in Table 8. As observed, only a very strong and sterically hindered base, such as *t*-BuLi is sufficiently powerful to generate the carbanion, especially in dry THF (Table 8, entries 1 and 2). *n*-BuLi is basic enough to deprotonate the CF_2H moiety but is also sufficiently nucleophilic for the substitution on tetrahedral phosphorus, leading to the formation of an unidentified mixture of phosphine oxides and phosphinic esters (^{31}P NMR, δ ~46–50 and δ ~40–43) and significantly reducing the yield of targeted **19** (Table 8, entries 3).

Other bases such, as (LDA, $LiN(SiMe_3)_2$), were too weak to deprotonate the CF_2H group thus the equilibrium **8e**+LDA⇆**8e^{I}**+*N*,*N*-diisopropylamine was strongly shifted to the left. Whereas in the case of LDA, product **19** was isolated in 10% yield, for $LiN(SiMe_3)_2$ was detected spectroscopically only in traces (Table 8, entries 4 and 5).

Table 8
Examination of some metalating systems for **8e** after treatment with MeI and hydrolysis to arylphosphonate **19**

Entry	Metallating system and reaction conditions[a]	Yield[b] (%)
1	*t*-BuLi (1.1 equiv), THF, −80 to −30 °C, 3 h	74
2	*t*-BuLi (1.1 equiv), Ether, −80 to −20 °C, 4 h	60
3	*n*-BuLi (1.05 equiv), THF, −100 to −25 °C, 3 h	21
4	LDA (1.1 equiv), THF, −70 to 0 °C, 5 h	10
5	$LiN(SiMe_3)_2$ (1.15 equiv), THF, −50 to 10 °C, 5 h	Trace

[a] For 1.0 equiv of **8e**, and further addition of 1.1 equiv of MeI followed by hydrolysis with 10% HCl.
[b] Isolated yield of compound **19**.

3. Conclusions

In this work, we have demonstrated a new methodology towards the synthesis of *ortho*-XCF_2-containing arylphosphonates that includes the following steps: (i) synthesis of β-ketophosphonates **2a**–**e** and 2-hydroxyprop-1-enylphosphonates **3a**–**e** and their subsequent dehydration with the formation of CF_2X-containing alkynephosphonates **4a**–**e**. (ii) The formation of six-membered cyclic systems based on the Diels–Alder cycloaddition of alkynephosphonates **4a**–**e** with some classical 1,3-alkadienes (2,3-dimethyl-1,3-butadiene and isoprene). (iii) Aromatization of the obtained *ortho*-XCF_2 cyclohexa-1,4-dienylphosphonates **5a**–**e**, **6e** and **7e** using $KMnO_4/Al_2O_3$ and synthesis of targeted arylphosphonates **8a**–**e**, **9e** and **10e** with excellent yield. The synthetic utility of these compounds has been examined identifying possible routes of their subsequent modification that includes reactivity studies of phosphorus and fluorine-containing groups in some reactions by their functionalization: (iv) the dialkyl phosphonate group has been activated via its transformation into dichlorides **11a**–**d**, which were further treated with metallorganic reagents to give appropriate phosphine oxides **12a**–**d** or phosphinic acid **13**, and their hydrolysis gave arylphosphonic acids **14a**–**d**. (v) In the case of chloro- and bromodifluoromethyl compounds the hydrolysis of fluorinated group to *ortho*-phosphonobenzoic acid **15** under mild conditions was firstly reported and by generating novel organozinc and copper reagents and their dimerization product, *E*-(bis)aryl-difluorostilbene **18** was obtained. For the first time the successful lithiation of difluoromethyl moiety directly connected to aromatic ring was performed and based on *ortho*-difluoromethyl arylphosphonates **8e** and **9e** and **10e**, novel $ArCF_2R$ **19**–**21** derivatives were obtained. Applying the aforementioned strategies, a series of novel fluorine- and phosphorus-containing aromatic compounds were synthesized possibly serving as promising synthons for new materials,[7g,h] bioactive substances[7d,e] and reagents in organic chemistry.[7g]

4. Experimental section

4.1. General

All reagents were obtained from commercial suppliers and were used without further purification. All solvents used in reactions were freshly distilled from appropriate drying agents before use. THF was distilled from sodium/benzophenone immediately before use. Zinc was activated by washing four times with 1% HCl and subsequently with water, acetone and diethyl ether. All other reagents were recrystallized or distilled as necessary. All glassware was oven-dried at 140 °C, and reactions were performed under an atmosphere of dry nitrogen. Analytical TLCs were performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished using UV light or spraying by $Ce(SO_4)_2$ solution in 5% H_2SO_4. Column chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. NMR spectra were obtained on a Bruker DPX-200 spectrometer operating at 200.13 MHz for ^{1}H(TMS), 188.31 MHz for ^{19}F ($CFCl_3$), 80.99 MHz for ^{31}P (H_3PO_4), 50.32 MHz ^{13}C (TMS) and recorded at 25 °C. Chemical shifts (δ) are reported in parts per million and coupling constants (J) in Hertz. ^{13}C NMR and ^{31}P NMR spectra were broadband decoupled from hydrogen nuclei. MS and HRMS spectra were obtained on a Varian MAT CH7A instrument at 70 eV.

*4.1.1. Diethyl 3,3,3-trifluoro-2-oxopropylphosphonate (**2a**).* *n*-BuLi (2.5 M solution in *n*-hexane, 0.15 mol) was added at −100 °C to dry THF (240 mL). Subsequently diethyl methylphosphonate **1**[31] (22.8 g, 0.15 mol) was added dropwise and the mixture was stirred for 1 h at −95 °C. Next, ethyl trifluoroacetate (21.3 g, 0.15 mol) was added slowly and the solution was kept for 1 h below −90 °C. Then, the mixture was warmed to −20 °C, followed by the addition of 6 N HCl (40 mL). After warming to rt both layers were separated water phase was extracted with diethyl ether (2×100 mL, 3×75 mL)

and organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting mixture was dissolved in dry benzene (250 mL) and refluxed with a Dean–Stark trap until complete removal of water. The evaporation of benzene under reduced pressure yielded yellowish oil **2a** (in mixture with **3a**). Yield (together with isomer **3a**) 36.5 g (98%); content 81 mol %, bp 58–60 °C (0.1 mmHg). ^{1}H, ^{13}C, ^{31}P, ^{19}F NMR and MS (HRMS) data are consistent with the literature.[12a–d]

*4.1.2. Diethyl 3,3,3-trifluoro-2-hydroxyprop-1-enylphosphonate (**3a**).* In mixture with **2a**; content 19 mol %. ^{1}H NMR (200 MHz, $CDCl_3$): δ=11.39 (br s, 1H, OH), 4.92 (d, $^2J_{H,P}$=8.3 Hz, 1H, C=C–H), 3.96–4.15 (m, 4H, O–CH_2), 1.23 (t, $^3J_{H,H}$=7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=160.1 (qd, $^2J_{C,F}$=31.8 Hz, $^2J_{C,P}$=2.9 Hz, 1C, 2-C), 118.6 (qd, $^1J_{C,F}$=275.5 Hz, $^3J_{C,P}$=26.0 Hz, 1C, CF_3), 84.9 (d, $^1J_{C,P}$=183.0 Hz, 1C, 1-C), 62.9 (d, $^2J_{C,P}$=5.8 Hz, 2C, i-C), 16.0 (d, $^3J_{C,P}$=5.8 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=23.3 (q, $^4J_{P,F}$=2.5 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−76.1 (br s, 3F, CF_3) ppm.

*4.1.3. Diethyl 3,3,4,4,4-pentafluoro-2-oxobutylphosphonate (**2b**)[12b].* Prepared similarly to **2a** from **1** (19.8 g, 0.13 mol), *n*-BuLi (2.5 M solution in *n*-hexane, 0.13 mol) and ethyl pentafluoropropanoate (25.1 g, 0.13 mol). In mixture with **3b**; yield (together with isomer **3b**) 36.8 g (95%); content 69 mol %, bp 64–65 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.07–4.21 (m, 4H, O–CH_2), 3.38 (d, $^2J_{H,P}$=22.5 Hz, 2H, P–CH_2), 1.30 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=186.6 (td, $^2J_{C,F}$=28.5 Hz, $^2J_{C,P}$=8.1 Hz, 1C, 2-C), 118.0 (qt, $^1J_{C,F}$=286.6 Hz, $^2J_{C,F}$=34.1 Hz, 1C, CF_3), 106.7 (tqd, $^1J_{C,F}$=268.0 Hz, $^2J_{C,F}$=38.5 Hz, $^3J_{C,P}$=4.3 Hz, 1C, CF_2), 63.7 (d, $^2J_{C,P}$=6.8 Hz, 2C, i-C), 37.1 (d, $^1J_{C,P}$=133.4 Hz, 1C, 1-C), 16.4 (d, $^3J_{C,P}$=6.2 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=16.9 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−123.6 (s, 2F, CF_2), −83.0 (s, 3F, CF_3) ppm.

*4.1.4. Diethyl 3,3,4,4,4-pentafluoro-2-hydroxybut-1-enylphosphonate (**3b**).* In mixture with **2b**; content 31 mol %. ^{1}H NMR (200 MHz, $CDCl_3$): δ=11.55 (br s, 1H, OH), 5.04 (d, $^2J_{H,P}$=8.8 Hz, 1H, C=C–H), 4.01–4.13 (m, 4H, O–CH_2), 1.28 (t, $^3J_{H,H}$=6.8 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=161.1 (td, $^2J_{C,F}$=27.0 Hz, $^2J_{C,P}$=3.7 Hz, 1C, 2-C), 120.9 (tqd, $^1J_{C,F}$=283.2 Hz, $^2J_{C,F}$=37.5 Hz, $^3J_{C,P}$=2.8 Hz, 1C, CF_2), 118.6 (qt, $^1J_{C,F}$=282.8 Hz, $^2J_{C,F}$=30.4 Hz, 1C, CF_3), 86.5 (dt, $^1J_{C,P}$=181.7 Hz, $^3J_{C,F}$=4.7 Hz, 1C, 1-C), 63.4 (d, $^2J_{C,P}$=5.0 Hz, 2C, i-C), 16.3 (d, $^3J_{C,P}$=5.9 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=23.2 (t, $^4J_{P,F}$=2.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−123.9 (s, 2F, CF_2), −84.7 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=298 (2) $[M]^+$, 271 (9), 253 (2) $[M-OEt]^+$, 243 (32), 225 (18), 179 (100) $[M-C_2F_5]^+$, 151 (38), 137 (8) $[P(O)(OEt)_2]^+$, 123 (97). HRMS (EI) for $C_8H_{12}F_5O_4P$ $[M]^+$ calcd 298.0393; found 298.0388.

*4.1.5. Diethyl 3-chloro-3,3-difluoro-2-oxopropylphosphonate (**2c**).* Prepared similarly to **2a** from **1** (19.7 g, 0.13 mol), *n*-BuLi (2.5 M solution in *n*-hexane, 0.13 mol) and ethyl chloro(difluoro)acetate (20.0 g, 0.13 mol). In mixture with **3c**; yield (together with isomer **3c**) 33.0 g (96%); content 93 mol %, bp 68–69 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.04–4.19 (m, 4H, O–CH_2), 3.33 (d, $^2J_{H,P}$=21.5 Hz, 2H, P–CH_2), 1.28 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=183.9 (td, $^2J_{C,F}$=31.6 Hz, $^2J_{C,P}$=7.5 Hz, 1C, 2-C), 119.6 (td, $^1J_{C,F}$=305.2 Hz, $^3J_{C,P}$=5.6 Hz, 1C, CF_2Cl), 63.6 (d, $^2J_{C,P}$=6.8 Hz, 2C, i-C), 35.3 (d, $^1J_{C,P}$=134.0 Hz, 1C, 1-C), 16.5 (d, $^3J_{C,P}$=6.3 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=17.4 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−69.5 (s, 2F, CF_2Cl) ppm.

*4.1.6. Diethyl 3-chloro-3,3-difluoro-2-hydroxyprop-1-enylphosphonate (**3c**).* In mixture with **2c**; content 7 mol %. ^{1}H NMR (200 MHz, $CDCl_3$): δ=11.51 (br s, 1H, OH), 4.90 (d, $^2J_{H,P}$=9.2 Hz, 1H, C=C–H), 4.05–4.20 (m, 4H, O–CH_2), 1.27 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=164.2 (td, $^2J_{C,F}$=29.8 Hz, $^2J_{C,P}$=3.7 Hz, 1C, 2-C), 116.7 (td, $^1J_{C,F}$=292.9 Hz, $^3J_{C,P}$=14.7 Hz, 1C, CF_2Cl), 82.3 (dt, $^1J_{C,P}$=181.1 Hz, $^3J_{C,F}$=3.1 Hz, 1C, 1-C), 63.3 (d, $^2J_{C,P}$=6.2 Hz, 2C, i-C), 16.5 (d, $^3J_{C,P}$=6.1 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=23.9 (br s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−63.7 (br s, 2F, CF_2Cl) ppm. MS (EI, 70 eV): *m*/*z* (%)=264 (8) $[M]^+$, 237 (50), 235 (21) $[M-Et]^+$, 229 (10) $[M-Cl]^+$, 179 (100) $[M-CF_2Cl]^+$, 151 (33) $[M-C(O)CF_2Cl]^+$, 137 (14) $[P(O)(OEt)_2]^+$. HRMS (EI) for $C_7H_{12}ClF_2O_4P$ $[M]^+$ calcd 264.0130; found 264.0129.

*4.1.7. Diethyl 3-bromo-3,3-difluoro-2-oxopropylphosphonate (**2d**).* Prepared similarly to **2a** from **1** (15.2 g, 0.1 mol), *n*-BuLi (2.5 M solution in *n*-hexane, 0.1 mol) and ethyl bromo(difluoro)acetate (30.0 g, 0.1 mol). In mixture with **3d**; yield (together with isomer **3d**) 28.7 g (93%); content 94 mol %, bp 84–86 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.06–4.20 (m, 4H, O–CH_2), 3.37 (d, $^2J_{H,P}$=21.7 Hz, 2H, P–CH_2), 1.31 (td, $^3J_{H,H}$=6.8 Hz, $^4J_{H,P}$=2.0 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=184.0 (td, $^2J_{C,F}$=28.5 Hz, $^2J_{C,P}$=7.4 Hz, 1C, 2-C), 113.7 (td, $^1J_{C,F}$=319.5 Hz, $^3J_{C,P}$=6.2 Hz, 1C, CF_2Br), 63.5 (d, $^2J_{C,P}$=6.7 Hz, 2C, i-C), 34.8 (d, $^1J_{C,P}$=134.6 Hz, 1C, 1-C), 16.6 (d, $^3J_{C,P}$=6.2 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=17.5 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−66.3 (s, 2F, CF_2Br) ppm.

*4.1.8. Diethyl 3-bromo-3,3-difluoro-2-hydroxyprop-1-enylphosphonate (**3d**).* In mixture with **2d**; content 6 mol %. ^{1}H NMR (200 MHz, $CDCl_3$): δ=11.53 (br s, 1H, OH), 4.89 (d, $^2J_{H,P}$=8.8 Hz, 1H, C=C–H), 4.07–4.21 (m, 4H, O–CH_2), 1.30 (td, $^3J_{H,H}$=7.0 Hz, $^4J_{H,P}$=1.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=165.1 (td, $^2J_{C,F}$=28.2 Hz, $^2J_{C,P}$=4.3 Hz, 1C, 2-C), 124.8 (td, $^1J_{C,F}$=314.8 Hz, $^3J_{C,P}$=20.2 Hz, 1C, CF_2Br), 81.4 (dt, $^1J_{C,P}$=182.4 Hz, $^3J_{C,F}$=3.7 Hz, 1C, 1-C), 63.2 (d, $^2J_{C,P}$=6.2 Hz, 2C, i-C), 16.5 (d, $^3J_{C,P}$=6.5 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=23.8 (br s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−59.5 (d, $^4J_{F,P}$=2.3 Hz, 2F, CF_2Br) ppm. MS (CI, positive): *m*/*z* (%)=309 (48) $[M+H]^+$, 282 (12), 248 (100), 231 (48), 196 (20), 179 (18) $[M+H-CF_2Br]^+$. MS (CI, negative): *m*/*z* (%)=307 (29) $[M-H]^-$, 228 (9) $[M-H-Br]^-$, 224 (16), 210 (100). HRMS (CI) for $C_7H_{12}BrF_2O_4P$ $[M]^+$ calcd 307.9625; found 307.9644; for $C_7H_{12}F_2O_4P$ $[M-Br]^+$ calcd 229.0441; found 229.0442.

*4.1.9. Diethyl 3,3-difluoro-2-oxopropylphosphonate (**2e**)[12f].* Prepared similarly to **2a** from **1** (22.8 g, 0.15 mol), *n*-BuLi (2.5 M solution in *n*-hexane, 0.15 mol) and ethyl difluoroacetate (18.6 g, 0.15 mol). In mixture with **3e**; yield (together with isomer **3e**) 33.5 g (97%); content 93 mol %, bp 70–72 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=5.85 (t, $^2J_{H,F}$=53.8 Hz, 1H, CF_2–H), 4.02–4.17 (m, 4H, O–CH_2), 3.27 (dt, $^2J_{H,P}$=22.5 Hz, $^4J_{H,F}$=1.2 Hz, 2H, P–CH_2), 1.27 (td, $^3J_{H,H}$=7.1 Hz, $^4J_{H,P}$=0.8 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=191.2 (td, $^2J_{C,F}$=19.3 Hz, $^2J_{C,P}$=7.7 Hz, 1C, 2-C), 108.9 (td, $^1J_{C,F}$=251.4 Hz, $^3J_{C,P}$=2.8 Hz, 1C, CF_2H), 62.6 (d, $^2J_{C,P}$=6.4 Hz, 2C, i-C), 36.4 (d, $^1J_{C,P}$=130.1 Hz, 1C, 1-C), 15.8 (d, $^3J_{C,P}$=4.3 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=18.3 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−129.6 (d, $^2J_{F,H}$=54.3 Hz, 2F, CF_2H) ppm.

*4.1.10. Diethyl 3,3-difluoro-2-hydroxyprop-1-enylphosphonate (**3e**).* In mixture with **2e**; content 7 mol %. ^{1}H NMR (200 MHz, $CDCl_3$): δ=11.18 (br s, 1H, OH), 5.81 (t, $^2J_{H,F}$=53.6 Hz, 1H, CF_2–H), 4.80 (d, $^2J_{H,P}$=10.3 Hz, 1H, C=C–H), 3.97–4.11 (m, 4H, O–CH_2), 1.26 (t, $^3J_{H,H}$=7.1 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=165.2 (td, $^2J_{C,F}$=25.1 Hz, $^2J_{C,P}$=2.9 Hz, 1C, 2-C), 109.6 (td, $^1J_{C,F}$=241.8 Hz, $^3J_{C,P}$=22.2 Hz, 1C, CF_2H), 82.1 (dt, $^1J_{C,P}$=182.1 Hz, $^3J_{C,F}$=4.8 Hz, 1C, 1-C), 62.3 (d, $^2J_{C,P}$=5.4 Hz, 2C, i-C), 15.9 (d, $^3J_{C,P}$=5.6 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=24.9 (t, $^4J_{P,F}$=1.4 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−126.5 (dd, $^2J_{F,H}$=54.7 Hz, $^4J_{F,P}$=1.3 Hz, 2F, CF_2H) ppm. MS (EI, 70 eV): *m*/*z* (%)=230 (5) $[M]^+$, 179 (100) $[M-CF_2H]^+$, 151 (30) $[M-C(O)CF_2H]^+$, 137 (20) $[P(O)(OEt)_2]^+$, 123

(65), 109 (50). HRMS (EI) for $C_7H_{13}F_2O_4P$ $[M]^+$ calcd 230.0520; found 230.0519.

*4.1.11. Diethyl 3,3,3-trifluoroprop-1-ynylphosphonate (**4a**). Method A*: *N,N*-Diisopropylethylamine (62.0 g, 0.48 mol) was added quickly under nitrogen to a solution of ketone–enol **2a**:**3a** (24.8 g, 0.1 mol) mixture in dry methylene chloride (180 mL) cooled to −45 °C. The resulting solution was stirred at this temperature for 10 min and trifluoromethanesulfonic anhydride (33.9 g, 0.12 mol) was then added dropwise at −40 °C. The suspension was kept for 7 h at −40 °C and then 2 h at 5–7 °C. The reaction mixture was diluted with anhydrous ether (1000 mL) and left overnight at −30 °C. The resulting precipitate was filtered off and washed with cold diethyl ether (3×75 mL). Then, the filtrate was washed with diluted solution of HCl (1×500 mL 1%, 3×300 mL 3%), organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure to give crude product, which was distilled under reduced pressure yielding 21.9 g (95%) of pure **4a** as a colourless oil.

Method B: To a suspension of P_2O_5 (15.6 g, 0.11 mol) in 200 mL of anhydrous methylene chloride cooled to −20 to −25 °C under dry nitrogen atmosphere at vigorous stirring was added dropwise a solution of ketone–enol mixture **2a**:**3a** (24.8 g, 0.1 mol) and triethylamine (50.1 g, 0.5 mol) in 100 mL of anhydrous methylene chloride maintaining the reaction mixture temperature below −20 °C. The suspension was stirred for 6 h at this temperature and then 2 h at the temperature 5–7 °C. Then the reaction mixture was diluted with anhydrous ether (1000 mL) and left overnight at −30 °C. The product was isolated according to *Method A* yielding 16.1 g (70%) of **4a**. Bp 34–36 °C (0.1 mmHg). ^{1}H, ^{13}C, ^{31}P, ^{19}F NMR and MS (HRMS) data are consistent with the literature.[11]

*4.1.12. Diethyl 3,3,4,4,4-pentafluorobut-1-ynylphosphonate (**4b**).* Prepared similarly to **4a** from **2b**:**3b** (23.9 g, 0.08 mol), *N,N*-diisopropylethylamine (51.7 g, 0.4 mol) and trifluoromethanesulfonic anhydride (27.1 g, 0.1 mol); yield 20.6 g (92%) (Method A) or from **2b**:**3b** (29.8 g, 0.1 mol), triethylamine (50.1 g, 0.5 mol), phosphorus pentoxide (15.6 g, 0.11 mol); yield 18.8 g (67%) (Method B), bp 40–41 °C (0.1 mmHg). ^{1}H, ^{13}C, ^{31}P, ^{19}F NMR and MS (HRMS) data are consistent with the literature.[11]

*4.1.13. Diethyl 3-chloro-3,3-difluoroprop-1-ynylphosphonate (**4c**).* Prepared similarly to **4a** from **2c**:**3c** (15.9 g, 0.06 mol), *N,N*-diisopropylethylamine (45.2 g, 0.35 mol) and trifluoromethanesulfonic anhydride (20.3 g, 0.07 mol); yield 12.6 g (85%) (Method A) or from **2c**:**3c** (26.5 g, 0.1 mol), triethylamine (66.8 g, 0.7 mol), phosphorus pentoxide (15.6 g, 0.11 mol); yield 16.0 g (65%) (Method B), bp 56–57 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.08–4.23 (m, 4H, O–CH_2), 1.33 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=112.7 (td, $^1J_{C,F}$=279.1 Hz, $^3J_{C,P}$=5.6 Hz, 1C, CF_2Cl), 85.7 (td, $^2J_{C,F}$=46.5 Hz, $^2J_{C,P}$=44.1 Hz, 1C, 2-C), 78.7 (dt, $^1J_{C,P}$=277.9 Hz, $^3J_{C,F}$=5.0 Hz, 1C, 1-C), 64.8 (d, $^2J_{C,P}$=6.2 Hz, 2C, i-C), 16.3 (d, $^3J_{C,P}$=6.2 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=−9.7 (t, $^4J_{P,F}$=5.1 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−41.7 (d, $^4J_{F,P}$=5.1 Hz, 2F, CF_2Cl) ppm. MS (EI, 70 eV): *m*/*z* (%)=211 (21) $[M-Cl]^+$, 191 (90), 183 (100), 173 (42), 109 (20) $[M-P(O)(OEt)_2]^+$. MS (CI, positive): *m*/*z* (%)=247 (100) $[M+H]^+$. MS (CI, negative): *m*/*z* (%)=281 (10) $[M+Cl]^-$, 217 (100) $[M-Et]^-$, 182 (60). HRMS (EI) for $C_7H_{10}F_2O_3P$ $[M-Cl]^+$ calcd 211.0336; found 211.0335.

*4.1.14. Diethyl 3-bromo-3,3-difluoroprop-1-ynylphosphonate (**4d**).* Prepared similarly to **4a** from **2d**:**3d** (37.1 g, 0.12 mol), *N,N*-diisopropylethylamine (99.5 g, 0.77 mol) and trifluoromethanesulfonic anhydride (40.6 g, 0.14 mol); yield 28.6 g (82%) (Method A) or from **2d**:**3d** (30.9 g, 0.1 mol), triethylamine (72.3 g, 0.72 mol) and phosphorus pentoxide (15.6 g, 0.11 mol); yield 21.0 g (60%) (Method B), bp 64–66 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.08–4.24 (m, 4H, O–CH_2), 1.34 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=100.8 (td, $^1J_{C,F}$=292.2 Hz, $^3J_{C,P}$=6.2 Hz, 1C, CF_2Br), 86.6 (dt, $^2J_{C,P}$=47.1 Hz, $^2J_{C,F}$=39.7 Hz, 1C, 2-C), 79.9 (dt, $^1J_{C,P}$=277.3 Hz, $^3J_{C,F}$=5.6 Hz, 1C, 1-C), 64.8 (d, $^2J_{C,P}$=5.6 Hz, 2C, i-C), 16.4 (d, $^3J_{C,P}$=6.8 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=−9.6 (t, $^4J_{P,F}$=4.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−38.8 (d, $^4J_{F,P}$=3.9 Hz, 2F, CF_2Br) ppm. MS (EI, 70 eV): *m*/*z* (%)=289 (8) $[M-H]^+$, 235 (19), 211 (15) $[M-Br]^+$, 183 (100), 139 (30), 103 (28). HRMS (EI) for $C_7H_9BrF_2O_3P$ $[M-H]^+$ calcd 288.9441; found 288.9440.

*4.1.15. Diethyl 3,3-difluoroprop-1-ynylphosphonate (**4e**).* Prepared similarly to **4a** from **2e**:**3e** (18.4 g, 0.08 mol), *N,N*-diisopropylethylamine (58.2 g, 0.45 mol) and trifluoromethanesulfonic anhydride (27.1 g, 0.1 mol); yield 14.9 g (88%) (Method A) or from **2e:3e** (23.0 g, 0.1 mol), triethylamine (55.7 g, 0.55 mol) and phosphorus pentoxide (15.6 g, 0.11 mol); yield 14.4 g (68%) (Method B), bp 71–72 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.23 (td, $^2J_{H,F}$=53.1 Hz, $^4J_{H,P}$=2.2 Hz, 1H, CF_2–H), 4.07–4.22 (m, 4H, O–CH_2), 1.33 (t, $^3J_{H,H}$=7.1 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=103.1 (td, $^1J_{C,F}$=235.7 Hz, $^3J_{C,P}$=5.0 Hz, 1C, CF_2H), 87.8 (dt, $^2J_{C,P}$=47.3 Hz, $^2J_{C,F}$=34.6 Hz, 1C, 2-C), 78.8 (dt, $^1J_{C,P}$=281.3 Hz, $^3J_{C,F}$=6.8 Hz, 1C, 1-C), 64.5 (d, $^2J_{C,P}$=5.6 Hz, 2C, i-C), 16.3 (d, $^3J_{C,P}$=6.8 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=−8.9 (t, $^4J_{P,F}$=6.4 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−111.4 (dd, $^1J_{F,H}$=53.1 Hz, $^4J_{F,P}$=6.5 Hz, 2F, CF_2H) ppm. MS (EI, 70 eV): *m*/*z* (%)=211 (22) $[M-H]^+$, 185 (60), 164 (40), 157 (100), 139 (58). HRMS (EI) for $C_7H_{10}F_2O_3P$ $[M-H]^+$ calcd 211.0336; found 211.0337.

*4.1.16. Diethyl 4,5-dimethyl-2-(trifluoromethyl)cyclohexa-1,4-dien-1-ylphosphonate (**5a**).* To a dry ampoule flushed with nitrogen and charged with dry toluene (50 mL) were added: acetylenephosphonate **4a** (20.7 g, 0.09 mol), 2,3-dimethyl-1,3-butadiene (7.8 g, 0.095 mol) and small amount (20–25 mg, ca. 0.001 mol %) of 2,6-di-*tert*-butyl-*p*-cresol (BHT). The ampoule was sealed and heated at the temperature 110 °C for 0.5 h. Then all volatiles were removed under reduced pressure and the residue was dried overnight under vacuum yielding 27.3 g (97%) of **5a**, which can be additionally purified by distillation in a vacuum. Yellowish oil; bp 84–86 °C (0.1 mmHg). ^{1}H, ^{13}C, ^{31}P, ^{19}F NMR and MS (HRMS) data are consistent with the literature.[11]

*4.1.17. Diethyl 4,5-dimethyl-2-(pentafluoroethyl)cyclohexa-1,4-dien-1-ylphosphonate (**5b**).* Prepared similarly to **5a** from **4b** (19.6 g, 0.07 mol), 2,3-dimethyl-1,3-butadiene (6.3 g, 77 mmol) at 115 °C for 0.5 h; yield 24.1 g (95%) as a yellowish oil, bp 89–91 °C (0.1 mmHg). ^{1}H, ^{13}C, ^{31}P, ^{19}F NMR and MS (HRMS) data are consistent with the literature.[11]

*4.1.18. Diethyl 2-[chloro(difluoro)methyl]-4,5-dimethylcyclohexa-1,4-dien-1-ylphosphonate (**5c**).* Prepared similarly to **5a** from **4c** (22.2 g, 0.09 mol), 2,3-dimethyl-1,3-butadiene (8.1 g, 0.1 mol) at 125 °C for 1.5 h; yield 29.0 g (98%) as a yellowish oil, bp 95–97 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.06–4.22 (m, 4H, O–CH_2), 2.96–3.01 (m, 4H, CH_2), 1.65 (s, 6H, CH_3), 1.33 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=141.6 (td, $^2J_{C,F}$=25.4 Hz, $^2J_{C,P}$=3.7 Hz, 1C, 2-C), 128.2 (dt, $^1J_{C,P}$=179.3 Hz, $^3J_{C,F}$=2.5 Hz, 1C, 1-C), 125.2 (td, $^1J_{C,F}$=292.8 Hz, $^3J_{C,P}$=9.9 Hz, 1C, 7-C), 121.2 (t, $^4J_{C,F}$=1.2 Hz, 1C, 4-C), 122.4 (d, $^3J_{C,P}$=9.9 Hz, 1C, 5-C), 62.8 (d, $^2J_{C,P}$=6.2 Hz, 2C, i-C), 37.5 (d, $^2J_{C,P}$=8.7 Hz, 1C, 6-C), 33.6 (dt, $^3J_{C,P}$=13.0 Hz, $^3J_{C,F}$=3.7 Hz, 1C, 3-C), 18.1 (d, $^4J_{C,P}$=1.2 Hz, 1C, 8-C), 16.7 (d, $^3J_{C,P}$=6.8 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=15.2 (t, $^4J_{P,F}$=3.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−51.5 (br s, 2F, CF_2Cl) ppm. MS (EI, 70 eV): *m*/*z* (%)=327 (4) $[M-H]^+$, 291 (100) $[M-Cl-H_2]^+$, 263 (40), 35 (79), 215 (81), 201 (21). HRMS (EI) for $C_{13}H_{18}F_2O_3P$ $[M-Cl-H_2]^+$ 291.0961; found 291.0962.

*4.1.19. Diethyl 2-[bromo(difluoro)methyl]-4,5-dimethylcyclohexa-1,4-dien-1-ylphosphonate (**5d**).* Prepared similarly to **5a** from **4d**

(23.3 g, 0.08 mol), 2,3-dimethyl-1,3-butadiene (7.6 g, 0.092 mol) at 140 °C for 2.0 h; yield 28.7 g (96%) as a yellowish oil, bp 110–112 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.04–4.18 (m, 4H, O–CH_2), 2.95 (br s, 4H, CH_2), 1.65 (s, 6H, CH_3), 1.34 (t, $^3J_{H,H}$=6.8 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=142.8 (td, $^2J_{C,F}$=22.3 Hz, $^2J_{C,P}$=3.7 Hz, 1C, 2-C), 127.5 (dt, $^1J_{C,P}$=179.4 Hz, $^3J_{C,F}$=2.4 Hz, 1C, 1-C), 122.4 (d, $^3J_{C,P}$=9.9 Hz, 1C, 5-C), 121.1 (t, $^4J_{C,F}$=1.2 Hz, 1C, 4-C), 117.5 (td, $^1J_{C,F}$=306.4 Hz, $^3J_{C,P}$=9.9 Hz, 1C, 7-C), 62.8 (d, $^2J_{C,P}$=6.2 Hz, 2C, i-C), 37.5 (d, $^2J_{C,P}$=8.7 Hz, 1C, 6-C), 33.5 (dt, $^3J_{C,P}$=12.4 Hz, $^3J_{C,F}$=3.7 Hz, 1C, 3-C), 18.3 (s, 1C, 9-C), 18.1 (d, $^4J_{C,P}$=1.2 Hz, 1C, 8-C), 16.7 (d, $^3J_{C,P}$=6.2 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=15.3 (t, $^4J_{P,F}$=3.2 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–46.4 (s, 2F, CF_2Br) ppm. MS (EI, 70 eV): *m*/*z* (%)=293 (100) $[M-Br]^+$, 237 (55), 235 (31) $[M-H-P(O)(OEt)_2]^+$, 215 (46). MS (CI, positive): *m*/*z* (%)=373 (100) $[M+H]^+$, 293 (72), 237 (10) $[M-P(O)(OEt)_2+H]^+$. HRMS (EI) for $C_{13}H_{20}F_2O_3P$ $[M-Br]^+$ calcd 293.1118; found 293.1110.

*4.1.20. Diethyl 2-(difluoromethyl)-4,5-dimethylcyclohexa-1,4-dien-1-ylphosphonate (**5e**).* Prepared similarly to **5a** from **4e** (21.2 g, 0.1 mol), 2,3-dimethyl-1,3-butadiene (9.4 g, 0.115 mol) at 150 °C for 2.5 h; yield 27.4 g (93%) as a yellowish oil, bp 98–100 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.41 (t, $^2J_{H,F}$=55.3 Hz, 1H, CF_2–H), 3.92–4.12 (m, 4H, O–CH_2), 2.80 (s, 4H, CH_2), 1.60 (br s, 6H, CH_3), 1.26 (t, $^3J_{H,H}$=7.1 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=143.7 (td, $^2J_{C,F}$=24.2 Hz, $^2J_{C,P}$=9.3 Hz, 1C, 2-C), 128.3 (dt, $^1J_{C,P}$=175.2 Hz, $^3J_{C,F}$=8.9 Hz, 1C, 1-C), 121.9 (d, $^3J_{C,P}$=9.9 Hz, 1C, 5-C), 121.8 (d, $^4J_{C,P}$=2.2 Hz, 1C, 4-C), 112.1 (td, $^1J_{C,F}$=234.5 Hz, $^3J_{C,P}$=7.8 Hz, 1C, 7-C), 62.3 (d, $^2J_{C,P}$=5.9 Hz, 2C, i-C), 35.2 (d, $^2J_{C,P}$=7.8 Hz, 1C, 6-C), 29.9 (dt, $^3J_{C,P}$=14.9 Hz, $^3J_{C,F}$=3.4 Hz, 1C, 3-C), 18.3 (d, $^5J_{C,P}$=1.2 Hz, 1C, 9-C), 18.2 (d, $^4J_{C,P}$=1.2 Hz, 1C, 8-C), 16.5 (d, $^3J_{C,P}$=6.2 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=16.7 (t, $^4J_{P,F}$=5.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–121.7 (dd, $^2J_{F,H}$=55.4 Hz, $^4J_{F,P}$=4.8 Hz, 2F, CF_2H) ppm. MS (EI, 70 eV): *m*/*z* (%)=293 (10) $[M-H]^+$, 273 (100), 245 (16), 217 (20), 197 (45). HRMS (EI) for $C_{13}H_{20}F_2O_3P$ $[M-H]^+$ calcd 293.1118; found 293.1105.

*4.1.21. Diethyl 2-(difluoromethyl)-4-methylcyclohexa-1,4-dien-1-ylphosphonate (**6e**).* Prepared similarly to **5a** from **4e** (19.1 g, 90 mmol), 2-methyl-1,3-butadiene (7.1 g, 104 mmol) at 160 °C for 3.0 h; in mixture with **7e**; yield (together with isomer **7e**) 22.7 g (90%) as a yellowish oil; content 59 mol %, bp 95–96 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.46 (t, $^2J_{H,F}$=55.5 Hz, 1H, CF_2–H), 5.34–5.36 (m, 1H, C=C–H), 3.94–4.12 (m, 4H, O–CH_2), 2.80 (s, 2H, CH_2), 2.85–2.93 (m, 2H, CH_2), 1.65 (br s, 6H, CH_3), 1.26 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=143.3 (td, $^2J_{C,F}$=23.9 Hz, $^2J_{C,P}$=9.6 Hz, 1C, 2-C), 129.9 (d, $^4J_{C,P}$=1.6 Hz, 1C, 4-C), 128.2 (dt, $^1J_{C,P}$=175.8 Hz, $^3J_{C,F}$=9.0 Hz, 1C, 1-C), 117.0 (d, $^3J_{C,P}$=10.2 Hz, 1C, 5-C), 112.2 (td, $^1J_{C,F}$=234.2 Hz, $^3J_{C,P}$=8.1 Hz, 1C, 7-C), 62.4 (d, $^2J_{C,P}$=5.3 Hz, 2C, i-C), 29.6 (d, $^2J_{C,P}$=7.4 Hz, 1C, 6-C), 27.9 (dt, $^3J_{C,P}$=14.9 Hz, $^3J_{C,F}$=3.7 Hz, 1C, 3-C), 22.9 (d, $^5J_{C,P}$=1.6 Hz, 1C, 9-C), 16.5 (d, $^3J_{C,P}$=6.5 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=16.9 (t, $^4J_{P,F}$=5.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–122.1 (dd, $^2J_{F,H}$=55.2 Hz, $^4J_{F,P}$=3.9 Hz, 2F, CF_2H) ppm.

*4.1.22. Diethyl 2-(difluoromethyl)-5-methylcyclohexa-1,4-dien-1-ylphosphonate (**7e**).* In mixture with **6e**; content 41 mol %. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.44 (t, $^2J_{H,F}$=55.5 Hz, 1H, CF_2–H), 5.33–5.35 (m, 1H, C=C–H), 3.95–4.14 (m, 4H, O–CH_2), 2.75 (s, 2H, CH_2), 2.87–2.95 (m, 2H, CH_2), 1.65 (br s, 6H, CH_3), 1.27 (t, $^3J_{H,H}$=7.1 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=143.5 (td, $^2J_{C,F}$=24.5 Hz, $^2J_{C,P}$=8.9 Hz, 1C, 2-C), 128.1 (dt, $^1J_{C,P}$=175.2 Hz, $^3J_{C,F}$=8.7 Hz, 1C, 1-C), 130.0 (d, $^3J_{C,P}$=9.6 Hz, 1C, 5-C), 116.8 (d, $^4J_{C,P}$=2.2 Hz, 1C, 4-C), 112.1 (td, $^1J_{C,F}$=233.8 Hz, $^3J_{C,P}$=7.8 Hz, 1C, 7-C), 62.4 (d, $^2J_{C,P}$=5.6 Hz, 2C, i-C), 33.1 (d, $^2J_{C,P}$=7.4 Hz, 1C, 6-C), 24.4 (dt, $^3J_{C,P}$=14.6 Hz, $^3J_{C,F}$=3.7 Hz, 1C, 3-C), 22.8 (d, $^4J_{C,P}$=1.6 Hz, 1C, 8-C), 16.6 (d, $^3J_{C,P}$=6.2 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=16.7 (t, $^4J_{P,F}$=4.9 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–121.7 (dd, $^2J_{F,H}$=55.6 Hz, $^4J_{F,P}$=4.7 Hz, 2F, CF_2H) ppm. MS (EI, 70 eV): *m*/*z* (%)=279 (5) $[M-H]^+$, 259 (100) $[M-H_2F]^+$, 231 (25), 203 (30), 183 (35), 123 (40) $[M-HF-P(O)(OEt)_2]^+$. HRMS (EI) for $C_{12}H_{18}F_2O_3P$ $[M-H]^+$ calcd 279.0962; found 279.0949; for $C_{12}H_{17}FO_3P$ $[M-H_2F]^+$ calcd 259.0899; found 259.0892.

*4.1.23. Diethyl 4,5-dimethyl-2-(trifluoromethyl)phenylphosphonate (**8a**).* To a suspension of $KMnO_4/Al_2O_3$ (49.3 g, 156 mmol) in dry acetone (350 mL) a solution of adduct **5a** (24.3 g, 78 mmol) in dry acetone (250 mL) was added dropwise at –20 °C over 1.5 h under vigorous stirring. Afterwards, the mixture was left for 3 h at the same temperature and warm up to rt. The precipitate was filtered off and washed with a hot acetone (3×200 mL). Combined filtrates were filtered through a 10–15 cm layer of Celite®, concentrated and dried under vacuum yielding 23.2 g (96%) of **8a** as a colourless oil, bp 118–119 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.98 (d, $^3J_{H,P}$=15.7 Hz, 1H, Ar–H), 7.53 (d, $^4J_{H,P}$=5.9 Hz, 1H, Ar–H), 4.04–4.18 (m, 4H, O–CH_2), 2.33 (s, 6H, Ar–CH_3), 1.30 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=142.1 (d, $^4J_{C,P}$=3.1 Hz, 1C, 4-C), 140.8 (dq, $^2J_{C,P}$=14.3 Hz, $^4J_{C,F}$=1.2 Hz, 1C, 6-C), 137.9 (d, $^3J_{C,P}$=8.7 Hz, 1C, 5-C), 130.0 (qd, $^2J_{C,F}$=32.2 Hz, $^2J_{C,P}$=6.8 Hz, 1C, 2-C), 129.1 (dq, $^3J_{C,P}$=12.1 Hz, $^3J_{C,F}$=5.9 Hz, 1C, 3-C), 124.0 (dq, $^1J_{C,P}$=185.5 Hz, $^3J_{C,F}$=1.6 Hz, 1C, 1-C), 123.9 (qd, $^1J_{C,F}$=273.6 Hz, $^3J_{C,P}$=4.3 Hz, 1C, 7-C), 62.8 (d, $^2J_{C,P}$=5.6 Hz, 2C, i-C), 20.2 (d, $^4J_{C,P}$=1.2 Hz, 1C, 8-C), 19.9 (s, 1C, 9-C), 16.5 (d, $^3J_{C,P}$=6.8 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=17.0 (q, $^4J_{P,F}$=1.5 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–59.7 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=310 (42) $[M]^+$, 254 (100), 231 (25), 205 (15). HRMS (EI) for $C_{13}H_{18}F_3O_3P$ $[M]^+$ calcd 310.0946; found 310.0938.

*4.1.24. Diethyl 4,5-dimethyl-2-(pentafluoroethyl)phenylphosphonate (**8b**).* Prepared similarly to **8a** from **5b** (26.1 g, 72 mmol), $KMnO_4/Al_2O_3$ reagent (45.5 g, 144 mmol) at –15 °C for 3.5 h; yield 24.4 g (94%) as a colourless oil, bp 121–122 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.05 (d, $^3J_{H,P}$=14.7 Hz, 1H, Ar–H), 7.39 (d, $^4J_{H,P}$=5.9 Hz, 1H, Ar–H), 3.97–4.17 (m, 4H, O–CH_2), 2.30 (s, 6H, Ar–CH_3), 1.26 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=141.9 (d, $^4J_{C,P}$=2.8 Hz, 1C, 4-C), 140.9 (d, $^2J_{C,P}$=14.3 Hz, 1C, 6-C), 138.1 (d, $^3J_{C,P}$=8.1 Hz, 1C, 5-C), 131.0 (dtq, $^3J_{C,P}$=12.4 Hz, $^3J_{C,F}$=7.5 Hz, $^4J_{C,F}$=1.9 Hz, 1C, 3-C), 128.5 (td, $^2J_{C,F}$=24.2 Hz, $^2J_{C,P}$=6.2 Hz, 1C, 2-C), 125.3 (dt, $^1J_{C,P}$=187.3 Hz, $^3J_{C,F}$=1.9 Hz, 1C, 1-C), 119.5 (qt, $^1J_{C,F}$=287.2 Hz, $^2J_{C,F}$=39.1 Hz, 1C, CF_3), 114.1 (tqd, $^1J_{C,F}$=256.2 Hz, $^2J_{C,F}$=38.5 Hz, $^3J_{C,P}$=3.7 Hz, 1C, 7-C), 62.8 (d, $^2J_{C,P}$=6.2 Hz, 2C, i-C), 20.1 (d, $^4J_{C,P}$=1.2 Hz, 1C, 8-C), 19.9 (s, 1C, 9-C), 16.5 (d, $^3J_{C,P}$=6.2 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=17.5 (t, $^4J_{P,F}$=2.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–108.1 (s, 2F, CF_2), –84.3 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=360 (26) $[M]^+$, 304 (50), 288 (43), 241 (100), 213 (40). HRMS (EI) for $C_{14}H_{18}F_5O_3P$ $[M]^+$ calcd 360.0914; found 360.0903.

*4.1.25. Diethyl 2-[chloro(difluoro)methyl]-4,5-dimethylphenylphosphonate (**8c**).* Prepared similarly to **8a** from **5c** (29.6 g, 90 mmol), $KMnO_4/Al_2O_3$ (58.3 g, 185 mmol) at –5 °C for 5 h; yield 25.6 g (87%) as a yellowish oil, bp 134–135 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.98 (d, $^3J_{H,P}$=15.7 Hz, 1H, Ar–H), 7.53 (d, $^4J_{H,P}$=6.9 Hz, 1H, Ar–H), 4.05–4.27 (m, 4H, O–CH_2), 2.35 (s, 6H, Ar–CH_3), 1.35 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=142.3 (d, $^4J_{C,P}$=3.1 Hz, 1C, 4-C), 140.3 (dt, $^2J_{C,P}$=14.0 Hz, $^4J_{C,F}$=0.9 Hz, 1C, 6-C), 137.7 (d, $^3J_{C,P}$=8.1 Hz, 1C, 5-C), 136.3 (td, $^2J_{C,F}$=27.3 Hz, $^2J_{C,P}$=6.8 Hz, 1C, 2-C), 128.7 (dt, $^3J_{C,P}$=12.2 Hz, $^3J_{C,F}$=7.1 Hz, 1C, 3-C), 126.0 (td, $^1J_{C,F}$=292.2 Hz, $^3J_{C,P}$=4.3 Hz, 1C, 7-C), 122.5 (dt, $^1J_{C,P}$=186.7 Hz, $^3J_{C,F}$=1.9 Hz, 1C, 1-C), 62.9 (d, $^2J_{C,P}$=6.2 Hz, 2C, i-C), 20.3 (d, $^4J_{C,P}$=1.2 Hz, 1C, 8-C), 19.9 (s, 1C, 9-C), 16.7 (d, $^3J_{C,P}$=6.8 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=17.3 (t, $^4J_{P,F}$=2.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–46.9 (s, 2F, CF_2Cl) ppm. MS (EI, 70 eV):

m/*z* (%)=326 (18) $[M]^+$, 241 (100) $[M-CF_2Cl]^+$, 235 (82), 215 (90), 187 (20). HRMS (EI) for $C_{13}H_{18}ClF_2O_3P$ $[M]^+$ calcd 326.0650; found 326.0650.

*4.1.26. Diethyl 2-[bromo(difluoro)methyl]-4,5-dimethylphenylphosphonate (**8d**).* Prepared similarly to **8a** from **5d** (31.4 g, 84 mmol), $KMnO_4/Al_2O_3$ reagent (54.4 g, 172 mmol) at 0–5 °C for 6 h; yield 26.5 g (85%) as a yellow-orange oil, bp 143–145 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.94 (d, $^3J_{H,P}$=15.7 Hz, 1H, Ar–H), 7.49 (d, $^4J_{H,P}$=5.9 Hz, 1H, Ar–H), 4.05–4.26 (m, 4H, O–CH_2), 2.32 (s, 6H, Ar–CH_3), 1.33 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=142.3 (d, $^4J_{C,P}$=3.1 Hz, 1C, 4-C), 140.4 (d, $^2J_{C,P}$=14.1 Hz, 1C, 6-C), 138.1 (td, $^2J_{C,F}$=24.2 Hz, $^2J_{C,P}$=6.5 Hz, 1C, 2-C), 137.5 (d, $^3J_{C,P}$=8.1 Hz, 1C, 5-C), 128.6 (dt, $^3J_{C,P}$=12.1 Hz, $^3J_{C,F}$=6.9 Hz, 1C, 3-C), 121.8 (dt, $^1J_{C,P}$=187.3 Hz, $^3J_{C,F}$=1.9 Hz, 1C, 1-C), 117.4 (td, $^1J_{C,F}$=305.8 Hz, $^3J_{C,P}$=4.3 Hz, 1C, 7-C), 62.9 (d, $^2J_{C,P}$=5.6 Hz, 2C, i-C), 20.3 (d, $^4J_{C,P}$=1.2 Hz, 1C, 8-C), 19.9 (s, 1C, 9-C), 16.7 (d, $^3J_{C,P}$=6.2 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=17.3 (t, $^4J_{P,F}$=2.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–41.6 (s, 2F, CF_2Br) ppm. MS (EI, 70 eV): *m*/*z* (%)=291 (75) $[M-Br]^+$, 254 (42), 241 (45), 235 (80), 215 (100). HRMS (EI) for $C_{13}H_{18}F_2O_3P$ $[M-Br]^+$ calcd 291.0962; found 291.0942.

*4.1.27. Diethyl 2-(difluoromethyl)-4,5-dimethylphenylphosphonate (**8e**).* Prepared similarly to **8a** from **5e** (14.7 g, 50 mmol), $KMnO_4/Al_2O_3$ reagent (33.2 g, 105 mmol) at 0–5 °C for 6.5 h; yield 11.7 g (80%) as a yellowish oil, bp 115–117 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.63 (d, $^3J_{H,P}$=14.4 Hz, 1H, Ar–H), 7.48 (d, $^4J_{H,P}$=4.9 Hz, 1H, Ar–H), 7.21 (t, $^2J_{H,F}$=55.0 Hz, 1H, CF_2–H), 3.88–4.11 (m, 4H, O–CH_2), 2.22 (s, 6H, Ar–CH_3), 1.20 (t, $^3J_{H,H}$=7.1 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=142.7 (d, $^4J_{C,P}$=3.1 Hz, 1C, 4-C), 139.7 (dt, $^2J_{C,P}$=14.3 Hz, $^4J_{C,F}$=1.9 Hz, 1C, 6-C), 135.1 (d, $^3J_{C,P}$=8.9 Hz, 1C, 5-C), 135.0 (td, $^2J_{C,F}$=22.6 Hz, $^2J_{C,P}$=9.3 Hz, 1C, 2-C), 127.8 (dt, $^3J_{C,P}$=13.6 Hz, $^3J_{C,F}$=5.6 Hz, 1C, 3-C), 123.5 (dt, $^1J_{C,P}$=183.6 Hz, $^3J_{C,F}$=6.5 Hz, 1C, 1-C), 112.7 (td, $^1J_{C,F}$=236.3 Hz, $^3J_{C,P}$=3.1 Hz, 1C, 7-C), 62.6 (d, $^2J_{C,P}$=5.3 Hz, 2C, i-C), 20.2 (d, $^4J_{C,P}$=0.9 Hz, 1C, 8-C), 19.8 (s, 1C, 9-C), 16.5 (d, $^3J_{C,P}$=6.5 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=18.4 (t, $^4J_{P,F}$=2.5 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–110.8 (d, $^2J_{F,H}$=55.1 Hz, 2F, CF_2H) ppm. MS (EI, 70 eV): *m*/*z* (%)=292 (100) $[M]^+$, 241 (70) $[M-CF_2H]^+$, 224 (40), 199 (90), 183 (60). HRMS (EI) for $C_{13}H_{19}F_2O_3P$ $[M]^+$ calcd 292.1040; found 292.1033.

*4.1.28. Diethyl 2-(difluoromethyl)-4-methylphenylphosphonate (**9e**).* Prepared similarly to **8a** from **6e**:**7e** (16.8 g, 60 mmol), $KMnO_4/Al_2O_3$ reagent (49.3 g, 156 mmol) at 10–15 °C for 10 h; purified by distillation in vacuo using Vigreux column; in mixture with **10e**; yield (together with isomer **10e**) 10.0 g (60%) as a yellowish oil; content 61 mol %, bp 110–112 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.93 (dd, $^3J_{H,P}$=14.2 Hz, $^3J_{H,H}$=7.9 Hz, 1H, Ar–H), 7.64 (d, $^4J_{H,P}$=5.4 Hz, 1H, Ar–H), 7.40 (dd, $^3J_{H,H}$=8.0 Hz, $^4J_{H,P}$=4.7 Hz, 1H, Ar–H), 7.31 (t, $^2J_{H,F}$=54.8 Hz, 1H, CF_2–H), 4.02–4.18 (m, 4H, O–CH_2), 2.38 (s, 3H, Ar–CH_3), 1.25 (t, $^3J_{H,H}$=7.1 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=144.0 (dt, $^4J_{C,P}$=3.1 Hz, $^4J_{C,F}$=0.9 Hz, 1C, 4-C), 137.5 (td, $^2J_{C,F}$=22.6 Hz, $^2J_{C,P}$=9.9 Hz, 1C, 2-C), 134.0 (d, $^3J_{C,P}$=8.7 Hz, 1C, 5-C), 131.2 (dt, $^2J_{C,P}$=14.6 Hz, $^4J_{C,F}$=1.8 Hz, 1C, 6-C), 127.0 (dt, $^3J_{C,P}$=13.7 Hz, $^3J_{C,F}$=6.2 Hz, 1C, 3-C), 123.7 (dt, $^1J_{C,P}$=184.5 Hz, $^3J_{C,F}$=6.2 Hz, 1C, 1-C), 112.4 (td, $^1J_{C,F}$=236.6 Hz, $^3J_{C,P}$=3.7 Hz, 1C, 7-C), 62.6 (d, $^2J_{C,P}$=5.6 Hz, 2C, i-C), 21.3 (d, $^5J_{C,P}$=0.6 Hz, 1C, 9-C), 16.3 (d, $^3J_{C,P}$=6.5 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=18.0 (t, $^4J_{P,F}$=2.6 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–111.6 (dd, $^2J_{F,H}$=55.2 Hz, $^4J_{F,P}$=2.3 Hz, 2F, CF_2H) ppm.

*4.1.29. Diethyl 2-(difluoromethyl)-5-methylphenylphosphonate (**10e**).* In mixture with **9e**; content 39 mol %. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.67 (d, $^3J_{H,H}$=8.2 Hz, 1H, Ar–H), 7.64 (d, $^3J_{H,P}$=14.7 Hz, 1H, Ar–H), 7.59 (dd, $^3J_{H,H}$=8.3 Hz, $^4J_{H,P}$=5.0 Hz, 1H, Ar–H), 7.28 (t, $^2J_{H,F}$=54.5 Hz, 1H, CF_2–H), 3.94–4.12 (m, 4H, O–CH_2), 2.37 (s, 3H, Ar–CH_3), 1.26 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=140.9 (dt, $^2J_{C,P}$=14.0 Hz, $^4J_{C,F}$=1.8 Hz, 1C, 6-C), 134.7 (td, $^2J_{C,F}$=23.3 Hz, $^2J_{C,P}$=9.9 Hz, 1C, 2-C), 134.4 (d, $^3J_{C,P}$=8.7 Hz, 1C, 5-C), 133.8 (dt, $^4J_{C,P}$=2.8 Hz, $^4J_{C,F}$=0.8 Hz, 1C, 4-C), 126.7 (dt, $^1J_{C,P}$=180.8 Hz, $^3J_{C,F}$=5.6 Hz, 1C, 1-C), 126.5 (dt, $^3J_{C,P}$=13.6 Hz, $^3J_{C,F}$=5.9 Hz, 1C, 3-C), 112.5 (td, $^1J_{C,F}$=236.4 Hz, $^3J_{C,P}$=3.4 Hz, 1C, 7-C), 62.7 (d, $^2J_{C,P}$=5.4 Hz, 2C, i-C), 21.7 (d, $^4J_{C,P}$=1.6 Hz, 1C, 8-C), 16.3 (d, $^3J_{C,P}$=6.5 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=17.9 (t, $^4J_{P,F}$=2.5 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–110.9 (dd, $^2J_{F,H}$=54.7 Hz, $^4J_{F,P}$=2.4 Hz, 2F, CF_2H) ppm. MS (EI, 70 eV): *m*/*z* (%)=277 (30) $[M-H]^+$, 227 (95) $[M-CF_2H]^+$, 222 (80), 185 (100), 169 (60). HRMS (EI) for $C_{12}H_{16}F_2O_3P$ $[M-H]^+$ calcd 277.0805; found 277.0807.

*4.1.30. 4,5-Dimethyl-2-(trifluoromethyl)phenylphosphonic dichloride (**11a**).* To arylphosphonate **8a** (5.52 g, 17.8 mmol) freshly distilled phosphorus oxychloride (3.5 mL, 37.4 mmol) was added and the mixture was cooled to 0 °C. Then, phosphorus pentachloride (8.52 g, 40.9 mmol) was added in small portions and the mixture was stirred under reflux for 4 h (Method C). The excess of phosphorus oxychloride was removed under reduced pressure and the resulting crude product was distilled in a vacuum yielding 4.9 g (94%) of **11a** as a yellowish oil, bp 98–100 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.10 (d, $^3J_{H,P}$=20.6 Hz, 1H, Ar–H), 7.67 (d, $^4J_{H,P}$=8.8 Hz, 1H, Ar–H), 2.44 (s, 6H, Ar–CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=145.6 (d, $^4J_{C,P}$=3.7 Hz, 1C, 4-C), 141.9 (d, $^2J_{C,P}$=16.8 Hz, 1C, 6-C), 136.8 (d, $^3J_{C,P}$=11.8 Hz, 1C, 5-C), 130.1 (dq, $^3J_{C,P}$=14.3 Hz, $^3J_{C,F}$=5.6 Hz, 1C, 3-C), 129.4 (dq, $^1J_{C,P}$=152.0 Hz, $^3J_{C,F}$=1.2 Hz, 1C, 1-C), 129.2 (qd, $^2J_{C,F}$=33.5 Hz, $^2J_{C,P}$=9.3 Hz, 1C, 2-C), 123.4 (qd, $^1J_{C,F}$=274.2 Hz, $^3J_{C,P}$=5.0 Hz, 1C, 7-C), 20.5 (d, $^4J_{C,P}$=1.9 Hz, 1C, 8-C), 20.3 (s, 1C, 9-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=32.7 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–57.2 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=290 (100) $[M]^+$, 270 (22) $[M-HF]^+$, 255 (40) $[M-Cl]^+$, 170 (43). HRMS (EI) for $C_9H_8Cl_2F_3OP$ $[M]^+$ calcd 289.9642; found 289.9646.

*4.1.31. 4,5-Dimethyl-2-(perfluoroethyl)phenylphosphonic dichloride (**11b**).* Prepared similarly to **11a** from **8b** (4.94 g, 13.7 mmol), $POCl_3$ (2.7 mL, 28.8 mmol) and PCl_5 (6.56 g, 31.5 mmol); yield 4.4 g (93%) as a yellowish solid, mp 49 °C, bp 108–110 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.21 (d, $^3J_{H,P}$=20.5 Hz, 1H, Ar–H), 7.56 (d, $^4J_{H,P}$=9.3 Hz, 1H, Ar–H), 2.44 (s, 6H, Ar–CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=144.9 (d, $^4J_{C,P}$=4.3 Hz, 1C, 4-C), 142.2 (dt, $^2J_{C,P}$=16.8 Hz, $^4J_{C,F}$=1.2 Hz, 1C, 6-C), 136.6 (d, $^3J_{C,P}$=11.8 Hz, 1C, 5-C), 131.9 (dtq, $^3J_{C,P}$=14.3 Hz, $^3J_{C,F}$=8.1 Hz, $^4J_{C,F}$=1.9 Hz, 1C, 3-C), 127.6 (td, $^2J_{C,F}$=24.8 Hz, $^2J_{C,P}$=8.7 Hz, 1C, 2-C), 130.7 (d, $^1J_{C,P}$=151.4 Hz, 1C, 1-C), 119.3 (qt, $^1J_{C,F}$=287.2 Hz, $^2J_{C,F}$=39.1 Hz, 1C, CF_3), 114.1 (tqd, $^1J_{C,F}$=257.4 Hz, $^2J_{C,F}$=39.1 Hz, $^3J_{C,P}$=3.7 Hz, 1C, 7-C), 20.4 (d, $^4J_{C,P}$=1.9 Hz, 1C, 8-C), 20.3 (s, 1C, 9-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=33.6 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=–104.4 (s, 2F, CF_2), –83.5 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=340 (65) $[M]^+$, 305 (15) $[M-Cl]^+$, 271 (100), 167 (18), 103 (10). HRMS (EI) for $C_{10}H_8Cl_2F_5OP$ $[M]^+$ calcd 339.9610; found 339.9610.

*4.1.32. 2-[Chloro(difluoro)methyl]-4,5-dimethylphenylphosphonic dichloride (**11c**).* Prepared similarly to **11a** from **8c** (4.05 g, 12.4 mmol), $POCl_3$ (2.4 mL, 26.0 mmol) and PCl_5 (5.94 g, 28.5 mmol); yield 3.3 g (87%) as a yellowish solid, mp 64 °C, bp 134–135 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.09 (d, $^3J_{H,P}$=20.6 Hz, 1H, Ar–H), 7.64 (d, $^4J_{H,P}$=8.8 Hz, 1H, Ar–H), 2.43 (s, 6H, Ar–CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=145.2 (d, $^4J_{C,P}$=3.7 Hz, 1C, 4-C), 141.4 (dt, $^2J_{C,P}$=16.8 Hz, $^4J_{C,F}$=1.2 Hz, 1C, 6-C), 135.9 (d, $^3J_{C,P}$=11.8 Hz, 1C, 5-C), 135.5 (td, $^2J_{C,F}$=27.9 Hz, $^2J_{C,P}$=9.3 Hz, 1C, 2-C), 129.6 (dt, $^3J_{C,P}$=14.3 Hz, $^3J_{C,F}$=6.5 Hz, 1C, 3-C), 127.8 (dt, $^1J_{C,P}$=153.2 Hz, $^3J_{C,F}$=1.4 Hz, 1C, C-1), 125.3 (td, $^1J_{C,F}$=290.9 Hz,

$^{3}J_{C,P}$=4.3 Hz, 1C, 7-C), 20.5 (d, $^{4}J_{C,P}$=1.3 Hz, 1C, 8-C), 20.2 (s, 1C, 9-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=33.3 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−44.8 (s, 2F, CF_2Cl) ppm. MS (EI, 70 eV): *m*/*z* (%)=306 (13) $[M]^+$, 273 (60), 271 (100) $[M-Cl]^+$, 167 (15). HRMS (EI) for $C_9H_8Cl_3F_2OP$ $[M]^+$ calcd 305.9346; found 305.9340.

*4.1.33. 2-[Bromo(difluoro)methyl]-4,5-dimethylphenylphosphonic dichloride (**11d**).* Prepared similarly to **11a** from **8d** (4.68 g, 12.6 mmol), $POCl_3$ (2.5 mL, 26.5 mmol) and PCl_5 (6.04 g, 29.0 mmol); yield 3.8 g (85%), yellowish solid, mp 70 °C, bp 142–144 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.05 (d, $^{3}J_{H,P}$=20.6 Hz, 1H, Ar–H), 7.61 (d, $^{4}J_{H,P}$=8.8 Hz, 1H, Ar–H), 2.42 (s, 6H, Ar–CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=145.2 (d, $^{4}J_{C,P}$=3.7 Hz, 1C, 4-C), 141.4 (d, $^{2}J_{C,P}$=16.1 Hz, 1C, 6-C), 135.9 (d, $^{3}J_{C,P}$=11.8 Hz, 1C, 5-C), 135.6 (td, $^{2}J_{C,F}$=29.2 Hz, $^{2}J_{C,P}$=8.7 Hz, 1C, 2-C), 129.6 (dt, $^{3}J_{C,P}$=14.0 Hz, $^{3}J_{C,F}$=7.1 Hz, 1C, 3-C), 127.8 (dt, $^{1}J_{C,P}$=153.2 Hz, $^{3}J_{C,F}$=2.1 Hz, 1C, 1-C), 125.4 (td, $^{1}J_{C,F}$=290.9 Hz, $^{3}J_{C,P}$=4.4 Hz, 1C, 7-C), 20.5 (d, $^{4}J_{C,P}$=1.9 Hz, 1C, 8-C), 20.2 (s, 1C, 9-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=33.4 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−40.2 (s, 2F, CF_2Br) ppm. MS (EI, 70 eV): *m*/*z* (%)=271 (100) $[M-Br]^+$, 167 (12), 139 (8), 103 (10). HRMS (EI) for $C_9H_8Cl_2F_2OP$ $[M-Br]^+$ calcd 270.9658; found 270.9653.

*4.1.34. [4,5-Dimethyl-2-(trifluoromethyl)phenyl](dimethyl)phosphine oxide (**12a**).* To a solution of phosphonic dichloride **11a** (2.74 g, 9.4 mmol) in a dry THF (65 mL) at −30 °C methylmagnesium bromide (3.2 M solution in THF, 19.8 mmol) was added dropwise, the mixture was stirred for 3 h at −30 °C and left overnight to warm to rt. Next, 10% HCl (15 mL) was added at −30 °C and stirred for 1 h at rt. The water phase was separated, extracted with diethyl ether (3×30 mL), organic layers were combined, dried over $MgSO_4$ and solvent evaporated under reduced pressure giving crude product then was purified by sublimation in vacuo (0.1 mmHg) yielding 1.77 g (75%) of **12a** as a white solid; mp 104 °C, bp 116–117 °C (0.1 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.16 (d, $^{3}J_{H,P}$=13.7 Hz, 1H, Ar–H), 7.58 (d, $^{4}J_{H,P}$=4.9 Hz, 1H, Ar–H), 2.40 (s, 3H, Ar–CH_3), 2.37 (d, $^{5}J_{H,P}$=0.5 Hz, 3H, Ar–CH_3), 1.96 (dq, $^{2}J_{H,P}$=13.7 Hz, $^{6}J_{H,F}$=1.7 Hz, 6H, P–CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=142.3 (d, $^{4}J_{C,P}$=2.5 Hz, 1C, 4-C), 142.1 (dq, $^{2}J_{C,P}$=10.5 Hz, $^{4}J_{C,F}$=1.2 Hz, 1C, 6-C), 136.4 (d, $^{3}J_{C,P}$=6.5 Hz, 1C, 5-C), 129.2 (dq, $^{3}J_{C,P}$=8.7 Hz, $^{3}J_{C,F}$=5.6 Hz, 1C, 3-C), 128.24 (qd, $^{2}J_{C,F}$=31.9 Hz, $^{2}J_{C,P}$=7.4 Hz, 1C, 2-C), 127.8 (dq, $^{1}J_{C,P}$=90.6 Hz, $^{3}J_{C,F}$=1.9 Hz, 1C, 1-C), 124.5 (qd, $^{1}J_{C,F}$=272.9 Hz, $^{3}J_{C,P}$=2.5 Hz, 1C, 7-C), 20.2 (d, $^{4}J_{C,P}$=0.9 Hz, 1C, 8-C), 20.1 (s, 1C, 9-C), 18.7 (dq, $^{1}J_{C,P}$=72.0 Hz, $^{5}J_{C,F}$=3.7 Hz, 2C, i-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=43.9 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−56.9 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=250 (100) $[M]^+$, 235 (20) $[M-CH_3]^+$, 187 (50), 181 (10) $[M-CF_3]^+$. HRMS (EI) for $C_{11}H_{14}F_3OP$ $[M]^+$ calcd 250.0734; found 250.0721.

*4.1.35. [4,5-Dimethyl-2-(pentafluoroethyl)phenyl](dimethyl)phosphine oxide (**12b**).* Prepared similarly to **12a** from **11b** (3.1 g, 9.1 mmol), methylmagnesium bromide (19.1 mmol) in dry THF (70 mL); yield 2.0 g (73%) as a white solid, mp 232 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.14 (d, $^{3}J_{H,P}$=14.2 Hz, 1H, Ar–H), 7.42 (d, $^{4}J_{H,P}$=4.9 Hz, 1H, Ar–H), 2.37 (s, 3H, Ar–CH_3), 2.35 (s, 3H, Ar–CH_3), 2.00 (dt, $^{2}J_{H,P}$=13.2 Hz, $^{6}J_{H,F}$=1.9 Hz, 6H, P–CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=142.7 (d, $^{4}J_{C,P}$=2.0 Hz, 1C, 4-C), 142.5 (dt, $^{2}J_{C,P}$=11.2 Hz, $^{4}J_{C,F}$=1.6 Hz, 1C, 6-C), 136.6 (d, $^{3}J_{C,P}$=7.4 Hz, 1C, 5-C), 131.0 (dt, $^{3}J_{C,P}$=7.8 Hz, $^{3}J_{C,F}$=7.3 Hz, 1C, 3-C), 127.8 (d, $^{1}J_{C,P}$=93.7 Hz, 1C, 1-C), 126.8 (td, $^{2}J_{C,F}$=24.8 Hz, $^{2}J_{C,P}$=6.8 Hz, 1C, 2-C), 119.2 (qt, $^{1}J_{C,F}$=287.2 Hz, $^{2}J_{C,F}$=39.1 Hz, 1C, CF_3), 114.9 (tqd, $^{1}J_{C,F}$=255.0 Hz, $^{2}J_{C,F}$=38.5 Hz, $^{3}J_{C,P}$=1.9 Hz, 1C, 7-C), 20.2 (s, 2C, 8,9-C), 18.8 (dt, $^{1}J_{C,P}$=75.6 Hz, $^{5}J_{C,F}$=5.6 Hz, 2C, i-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=49.1 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−105.6 (s, 2F, CF_2), −84.1 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=300 (100) $[M]^+$, 285 (35) $[M-CH_3]^+$, 215 (10), 181 (30) $[M-C_2F_5]^+$. HRMS (EI) for $C_{12}H_{14}F_5OP$ $[M]^+$ calcd 300.0702; found 300.0700.

*4.1.36. {2-[Chloro(difluoro)methyl]-4,5-dimethylphenyl}(dimethyl) phosphine oxide (**12c**).* Prepared similarly to **12a** from **11c** (3.04 g, 9.9 mmol), methylmagnesium bromide (20.8 mmol) in dry THF (60 mL); yield 2.1 g (78%) as a yellowish solid, mp 175 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.29 (d, $^{3}J_{H,P}$=13.7 Hz, 1H, Ar–H), 7.51 (d, $^{4}J_{H,P}$=4.9 Hz, 1H, Ar–H), 2.35 (s, 3H, Ar–CH_3), 2.32 (s, 3H, Ar–CH_3), 2.07 (dt, $^{2}J_{H,P}$=13.7 Hz, $^{6}J_{H,F}$=1.9 Hz, 6H, P–CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=142.4 (d, $^{4}J_{C,P}$=2.1 Hz, 1C, 4-C), 141.8 (d, $^{2}J_{C,P}$=10.6 Hz, 1C, 6-C), 136.4 (d, $^{3}J_{C,P}$=6.8 Hz, 1C, 5-C), 134.6 (td, $^{2}J_{C,F}$=26.7 Hz, $^{2}J_{C,P}$=8.1 Hz, 1C, 2-C), 129.0 (dt, $^{1}J_{C,P}$=90.6 Hz, $^{3}J_{C,F}$=2.9 Hz, 1C, 1-C), 129.0 (dt, $^{3}J_{C,P}$=8.9 Hz, $^{3}J_{C,F}$=6.4 Hz, 1C, 3-C), 127.7 (td, $^{1}J_{C,F}$=269.2 Hz, $^{3}J_{C,P}$=1.9 Hz, 1C, 7-C), 20.1 (d, $^{4}J_{C,P}$=1.0 Hz, 1C, 8-C), 20.0 (s, 1C, 9-C), 19.3 (dt, $^{1}J_{C,P}$=73.8 Hz, $^{5}J_{C,F}$=5.0 Hz, 2C, i-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=44.3 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−43.9 (s, 2F, CF_2Cl) ppm. MS (EI, 70 eV): *m*/*z* (%)=266 (100) $[M]^+$, 251 (10) $[M-CH_3]^+$, 231 (50) $[M-CH_2Cl]^+$, 215 (30). HRMS (EI) for $C_{11}H_{14}ClF_2OP$ $[M]^+$ calcd 266.0439; found 266.0432.

*4.1.37. {2-[Bromo(difluoro)methyl]-4,5-dimethylphenyl}(dimethyl) phosphine oxide (**12d**).* Prepared similarly to **12a** from **11d** (3.29 g, 9.35 mmol), methylmagnesium bromide (19.6 mmol) in dry THF (55 mL); yield 1.5 g (51%) as a yellow-orange solid, mp 184 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.10 (d, $^{3}J_{H,P}$=13.8 Hz, 1H, Ar–H), 7.98 (d, $^{4}J_{H,P}$=5.1 Hz, 1H, Ar–H), 2.33 (s, 3H, Ar–CH_3), 2.31 (s, 3H, Ar–CH_3), 2.04 (dt, $^{2}J_{H,P}$=14.2 Hz, $^{6}J_{H,F}$=1.6 Hz, 6H, P–CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=142.0 (d, $^{4}J_{C,P}$=3.4 Hz, 1C, 4-C), 141.2 (d, $^{2}J_{C,P}$=10.6 Hz, 1C, 6-C), 136.4 (td, $^{2}J_{C,F}$=24.1 Hz, $^{2}J_{C,P}$=6.7 Hz, 1C, 2-C), 135.8 (d, $^{3}J_{C,P}$=5.9 Hz, 1C, 5-C), 129.8 (dt, $^{1}J_{C,P}$=85.7 Hz, $^{3}J_{C,F}$=2.4 Hz, 1C, 1-C), 128.7 (dt, $^{3}J_{C,P}$=15.4 Hz, $^{3}J_{C,F}$=6.7 Hz, 1C, 3-C), 124.9 (td, $^{1}J_{C,F}$=274.5 Hz, $^{3}J_{C,P}$=3.0 Hz, 1C, 7-C), 20.0 (d, $^{4}J_{C,P}$=1.8 Hz, 1C, 8-C), 19.7 (s, 1C, 9-C), 18.7 (dt, $^{1}J_{C,P}$=73.2 Hz, $^{5}J_{C,F}$=4.7 Hz, 2C, i-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=42.8 (s, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−38.1 (s, 2F, CF_2Br) ppm. MS (EI, 70 eV): *m*/*z* (%)=310 (25) $[M]^+$, 295 (20) $[M-CH_3]^+$, 231 (100) $[M-Br]^+$, 181 (50) $[M-CF_2Br]^+$. HRMS (EI) for $C_{11}H_{14}BrF_2OP$ $[M]^+$ calcd 310.0347; found 310.0342.

*4.1.38. 2-[Bromo(difluoro)methyl]-4,5-dimethylphenyl(pentafluoroethyl) phosphinic acid (**13**).* To a solution of pentafluoroethane (1.61 g, 13.4 mmol) in dry THF (50 mL), cooled to −90 °C, *n*-BuLi (12.9 mmol, 2.5 M solution in hexane) was added dropwise keeping the temperature below −80 °C. The resulting mixture was stirred for 1 h at that temperature and a solution of **11d** (1.97 g, 5.6 mmol) in dry THF (10 mL) was added slowly at −80 °C and stirred at that temperature for 4 h. The reaction was warmed slowly to rt, cooled to −20 °C and 10% HCl (15 mL) was added. Next, water phase was separated and washed with diethyl ether (3×20 mL), organic layers were combined and dried over $MgSO_4$. After removal of volatiles under reduced pressure the crude product was purified by sublimation in vacuum (0.1 mmHg) yielding 2.0 g (85%) of **13** as a white solid; mp 133 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=10.37 (s, 1H, OH), 7.92 (d, $^{3}J_{H,P}$=14.7 Hz, 1H, Ar–H), 7.59 (d, $^{4}J_{H,P}$=5.9 Hz, 1H, Ar–H), 2.42 (s, 3H, Ar–CH_3), 2.40 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=145.1 (d, $^{4}J_{C,P}$=3.1 Hz, 1C, 4-C), 141.0 (d, $^{3}J_{C,P}$=13.8 Hz, 1C, 5-C), 140.0 (td, $^{2}J_{C,F}$=24.5 Hz, $^{2}J_{C,P}$=7.7 Hz, 1C, 2-C), 138.5 (dt, $^{2}J_{C,P}$=7.7 Hz, $^{4}J_{C,F}$=0.7 Hz, 1C, 6-C), 128.5 (dt, $^{3}J_{C,P}$=12.3 Hz, $^{3}J_{C,F}$=7.7 Hz, 1C, 3-C), 118.7 (qtd, $^{1}J_{C,F}$=369.7 Hz, $^{2}J_{C,F}$=49.1 Hz, $^{2}J_{C,P}$=17.3 Hz, 1C, CF_3), 117.1 (dt, $^{1}J_{C,P}$=146.4 Hz, $^{3}J_{C,F}$=2.1 Hz, 1C, C-1), 115.4 (td, $^{1}J_{C,F}$=304.4 Hz, $^{3}J_{C,P}$=2.9 Hz, 1C, C-7), 111.6 (tdq, $^{1}J_{C,F}$=279.4 Hz, $^{1}J_{C,P}$=147.4 Hz, $^{2}J_{C,F}$=39.5 Hz, 1C, P–CF_2), 20.6 (d, $^{4}J_{C,P}$=0.9 Hz, 1C, 8-C), 20.0 (s, 1C, 9-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=24.4 (t, $^{2}J_{P,F}$=88.3 Hz, 1P) ppm. ^{19}F NMR (188 MHz,

$CDCl_3$): δ=−124.6 (dtq, $^2J_{F,P}$=88.3 Hz, $^6J_{F,F}$=13.8 Hz, $^3J_{F,F}$=1.2 Hz, 2F, P−CF_2), −81.4 (s, 3F, CF_3), −42.8 (t, $^6J_{F,F}$=13.8 Hz, 2F, CF_2Br) ppm. MS (EI, 70 eV): *m*/*z* (%)=337 (100) $[M-Br]^+$, 317 (20), 217 (83), 189 (30). MS (CI, negative): *m*/*z* (%)=415 (5) $[M-H]^-$, 336 (100), 235 (20). HRMS (EI) for $C_{11}H_9F_7O_2P$ $[M-Br]^+$ calcd 337.0228; found 337.0223.

*4.1.39. 4,5-Dimethyl-2-(trifluoromethyl)phenylphosphonic acid (**14a**).* The solution of **11a** (0.18 g, 0.62 mmol) in CH_3CN (1 mL) was added dropwise to a mixture of 5% aq solution of NaOH (8 mL) and acetonitrile (18.6 mL) at rt and was stirred for 0.5 h at basic pH. RM was acidified with concentrated HCl to pH 0–1 and the resulting precipitate was filtered off, washed with 1% HCl, dried and recrystallized from 1,4-dioxane/EtOH (3:1) yielding 0.12 g (75%) of **14a** as a white solid; mp 229–228 °C (dec). ^{1}H NMR (200 MHz, DMSO-d_6): δ=7.81 (d, $^3J_{H,P}$=14.7 Hz, 1H, Ar−H), 7.54 (d, $^4J_{H,P}$=4.9 Hz, 1H, Ar−H), 6.78 (br s, 2H, OH), 2.92 (s, 6H, Ar−CH_3) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ=141.1 (d, $^2J_{C,P}$=12.5 Hz, 1C, 6-C), 140.9 (d, $^4J_{C,P}$=2.5 Hz, 1C, 4-C), 136.4 (d, $^3J_{C,P}$=7.5 Hz, 1C, 5-C), 129.0 (qd, $^1J_{C,F}$=305.2 Hz, $^3J_{C,P}$=2.5 Hz, 1C, 7-C), 128.7 (qd, $^2J_{C,F}$=31.6 Hz, $^2J_{C,P}$=6.8 Hz, 1C, 2-C), 128.5 (dq, $^3J_{C,P}$=11.2 Hz, $^3J_{C,F}$=5.6 Hz, 1C, 3-C), 124.8 (dq, $^1J_{C,P}$=187.3 Hz, $^3J_{C,F}$=6.2 Hz, 1C, C-1), 20.1 (s, 1C, 9-C), 20.0 (d, $^4J_{C,P}$=0.9 Hz, 1C, 8-C) ppm. ^{31}P NMR (81 MHz, DMSO-d_6): δ=10.5 (s, 1P) ppm. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−57.5 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=254 (100) $[M]^+$, 234 (17), 190 (22), 170 (30). HRMS (EI) for $C_9H_{10}F_3O_3P$ $[M]^+$ calcd 254.0320; found 254.0315.

*4.1.40. 4,5-Dimethyl-2-(pentafluoroethyl)phenylphosphonic acid (**14b**).* Prepared similarly to **14a** from **11b** (0.24 g, 0.72 mmol), 5% aq solution of NaOH (8.6 mL) in acetonitrile (20.0 mL); yield 0.18 g (80%) as a white solid, mp 206–207 °C (dec) from 1,4-dioxane/EtOH (3:1). ^{1}H NMR (200 MHz, DMSO-d_6): δ=7.91 (d, $^3J_{H,P}$=14.7 Hz, 1H, Ar−H), 7.30 (d, $^4J_{H,P}$=5.9 Hz, 1H, Ar−H), 2.31 (s, 6H, Ar−CH_3) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ=141.5 (d, $^2J_{C,P}$=12.4 Hz, 1C, 6-C), 141.0 (d, $^4J_{C,P}$=2.5 Hz, 1C, 4-C), 136.8 (d, $^3J_{C,P}$=7.5 Hz, 1C, 5-C), 131.3 (dt, $^1J_{C,P}$=178.6 Hz, $^3J_{C,F}$=2.4 Hz, 1C, 1-C), 130.3 (dt, $^3J_{C,P}$=9.8 Hz, $^3J_{C,F}$=8.7 Hz, 1C, 3-C), 126.9 (td, $^2J_{C,F}$=24.2 Hz, $^2J_{C,P}$=6.8 Hz, 1C, 2-C), 119.5 (qt, $^1J_{C,F}$=288.1 Hz, $^2J_{C,F}$=39.5 Hz, 1C, CF_3), 114.4 (tqd, $^1J_{C,F}$=255.3 Hz, $^2J_{C,F}$=37.6 Hz, $^3J_{C,P}$=3.7 Hz, 1C, 7-C), 20.2 (s, 1C, 9-C), 20.0 (br s, 1C, 8-C) ppm. ^{31}P NMR (81 MHz, DMSO-d_6): δ=10.8 (s, 1P) ppm. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−106.2 (s, 2F, CF_2), −83.1 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=304 (80) $[M]^+$, 215 (100), 187 (25), 173 (10). HRMS (EI) for $C_{10}H_{10}F_5O_3P$ $[M]^+$ calcd 304.0288; found 304.0286.

*4.1.41. 2-[Chloro(difluoro)methyl]-4,5-dimethylphenylphosphonic acid (**14c**).* Prepared similarly to **14a** from **11c** (0.18 g, 0.59 mmol), 10% aq HCl (3.5 mL) in acetonitrile (14.0 mL) within 2.5 h; yield 0.14 g (85%) as a white solid, mp 209–210 °C (dec) from benzene/MeOH (6:1). ^{1}H NMR (200 MHz, CD_3CN): δ=7.24 (d, $^3J_{H,P}$=14.6 Hz, 1H, Ar−H), 6.96 (d, $^4J_{H,P}$=4.9 Hz, 1H, Ar−H), 1.74 (s, 3H, Ar−CH_3), 1.72 (s, 3H, Ar−CH_3) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ=140.8 (d, $^4J_{C,P}$=2.9 Hz, 1C, 4-C), 140.3 (d, $^2J_{C,P}$=12.5 Hz, 1C, 6-C), 135.9 (d, $^3J_{C,P}$=7.7 Hz, 1C, 5-C), 134.0 (td, $^2J_{C,F}$=30.6 Hz, $^2J_{C,P}$=10.7 Hz, 1C, 2-C), 131.2 (dt, $^1J_{C,P}$=178.9 Hz, $^3J_{C,F}$=3.4 Hz, 1C, 1-C), 127.8 (dt, $^3J_{C,P}$=10.5 Hz, $^3J_{C,F}$=7.7 Hz, 1C, 3-C), 123.6 (td, $^1J_{C,F}$=293.7 Hz, $^3J_{C,P}$=8.3 Hz, 1C, 7-C), 19.1 (s, 1C, 9-C), 19.0 (d, $^4J_{C,P}$=0.9 Hz, 1C, 8-C) ppm. ^{31}P NMR (81 MHz, CD_3CN): δ=10.7 (s, 1P) ppm. ^{19}F NMR (188 MHz, CD_3CN): δ=−45.0 (s, 2F, CF_2Cl) ppm. MS (EI, 70 eV): *m*/*z* (%)=270 (20) $[M]^+$, 215 (100), 212 (90), 148 (40). HRMS (EI) for $C_9H_{10}ClF_2O_3P$ $[M]^+$ calcd 270.0024; found 270.0025.

*4.1.42. 4,5-Dimethyl-2-phosphonobenzoic acid (**15**).* Prepared similarly to **14a** from **11d** (0.31 g, 0.88 mmol) or **11c** (0.26 g, 0.85 mmol), 5% aq solution of NaOH (10 mL) in acetonitrile (23.0 mL) within 0.5 h; yield 0.19 g (95%) as a white solid, mp 242–244 °C (dec) from 1,4-dioxane/MeOH (5:1). ^{1}H NMR (200 MHz, DMSO-d_6): δ=11.42 (s, 3H, OH), 7.59 (d, $^3J_{H,P}$=21.0 Hz, 1H, Ar−H), 7.56 (s, 1H, Ar−H), 2.27 (s, 6H, Ar−CH_3) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ=169.7 (d, $^3J_{C,P}$=4.8 Hz, 1C, COOH), 140.1 (d, $^4J_{C,P}$=2.9 Hz, 1C, 4-C), 139.7 (d, $^2J_{C,P}$=13.4 Hz, 1C, 6-C), 134.2 (d, $^3J_{C,P}$=8.6 Hz, 1C, 3-C), 133.5 (d, $^3J_{C,P}$=8.6 Hz, 1C, 5-C), 131.4 (d, $^2J_{C,P}$=12.5 Hz, 1C, 2-C), 129.9 (d, $^1J_{C,P}$=178.3 Hz, 1C, 1-C), 19.8 (br s, 1C, 8-C), 19.7 (s, 1C, 9-C) ppm. ^{31}P NMR (81 MHz, DMSO-d_6): δ=13.5 (s, 1P) ppm. MS (EI, 70 eV): *m*/*z* (%)=406 (10) $[2M-3H_2O]^+$, 212 (100) $[M-H_2O]^+$, 148 (50), 132 (95). HRMS (EI) for $C_9H_9O_4P$ $[M-H_2O]^+$ calcd 212.0239; found 212.0233.

*4.1.43. Bis(trimethylsilyl) 2-[bromo(difluoro)methyl]-4,5-dimethylphenylphos-phonate (**16**).* To a solution of **8d** (1.7 g, 4.6 mmol) in dry CH_2Cl_2 (20 mL), trimethylsilyl bromide (1.5 g, 9.7 mmol) was added dropwise at 0 °C; the mixture was stirred for 2 h at this temperature and overnight at rt. Volatiles were evaporated and residue was dried under vacuum (0.1 mmHg) yielding 2.1 g (98%) of **16** as a yellowish, viscous oil; 95 mol % purity. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.96 (d, $^3J_{H,P}$=14.7 Hz, 1H, Ar−H), 7.40 (d, $^4J_{H,P}$=4.9 Hz, 1H, Ar−H), 2.26 (s, 6H, Ar−CH_3), 0.20 (s, 18H, Si−CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=141.3 (s, 1C, 4-C), 140.2 (d, $^2J_{C,P}$=14.3 Hz, 1C, 6-C), 137.2 (td, $^2J_{C,F}$=24.8 Hz, $^2J_{C,P}$=5.9 Hz, 1C, 2-C), 137.0 (d, $^3J_{C,P}$=8.4 Hz, 1C, 5-C), 128.4 (dt, $^3J_{C,P}$=11.2 Hz, $^3J_{C,F}$=6.5 Hz, 1C, 3-C), 125.4 (dt, $^1J_{C,P}$=195.1 Hz, $^3J_{C,F}$=5.6 Hz, 1C, 1-C), 117.8 (td, $^1J_{C,F}$=306.4 Hz, $^3J_{C,P}$=2.4 Hz, 1C, 7-C), 20.2 (s, 1C, 8-C), 19.9 (s, 1C, 9-C), 1.4 (s, 6C, i-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=−1.2 (s, 1P) ppm. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−40.6 (s, 2F, CF_2Br) ppm. MS (EI, 70 eV): *m*/*z* (%)=379 (100) $[M-Br]^+$, 291 (14), 195 (20), 147 (10). HRMS (EI) for $C_{15}H_{26}F_2O_3PSi_2$ $[M-Br]^+$ calcd 379.0544; found 379.0548.

*4.1.44. 2-[Bromo(difluoro)methyl]-4,5-dimethylphenylphosphonic acid (**14d**).* Methanol (20 mL) was added to **16** (2.0 g, 4.4 mmol) at rt and the solution was stirred overnight. After the evaporation of volatiles the resulting solid was washed with dry chloroform (4×3 mL), dried in a vacuum and recrystallized from toluene/EtOH (5:1) yielding 0.92 g (66%) of **14d** as a white solid; mp 197–199 °C (dec). ^{1}H NMR (200 MHz, CD_3OD): δ=7.87 (d, $^3J_{H,P}$=14.7 Hz, 1H, Ar−H), 7.52 (d, $^4J_{H,P}$=5.9 Hz, 1H, Ar−H), 2.34 (s, 6H, Ar−CH_3) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ=142.5 (d, $^4J_{C,P}$=1.9 Hz, 1C, 4-C), 141.3 (d, $^2J_{C,P}$=13.7 Hz, 1C, 6-C), 138.6 (td, $^2J_{C,F}$=24.2 Hz, $^2J_{C,P}$=6.8 Hz, 1C, 2-C), 136.6 (d, $^3J_{C,P}$=8.1 Hz, 1C, 5-C), 128.8 (dt, $^3J_{C,P}$=11.8 Hz, $^3J_{C,F}$=6.8 Hz, 1C, 3-C), 126.1 (dt, $^1J_{C,P}$=187.3 Hz, $^3J_{C,F}$=3.9 Hz, 1C, 1-C), 118.6 (td, $^1J_{C,F}$=304.6 Hz, $^3J_{C,P}$=4.4 Hz, 1C, 7-C), 19.8 (d, $^4J_{C,P}$=0.9 Hz, 1C, 8-C), 19.7 (s, 1C, 9-C) ppm. ^{31}P NMR (81 MHz, CD_3OD): δ=13.8 (s, 1P) ppm. ^{19}F NMR (188 MHz, CD_3OD): δ=−42.1 (s, 2F, CF_2Br) ppm. MS (CI, negative): *m*/*z* (%)=314 (9) $[M]^+$, 236 (26) $[M-Br]^+$, 214 (100), 187 (25). HRMS (CI) for $C_9H_{10}BrF_2O_3P$ $[M]^+$ calcd 313.9519; found 313.9513.

*4.1.45. (E)-Tetraethyl 6,6′-(1,2-difluoroethene-1,2-diyl)bis(3,4-dimethyl-6,1-phenylene)diphosphonate (**18**).* To a suspension of freshly activated Zn powder (0.3 g, 4.56 mmol) in dry DMF (10 mL) a solution of **8d** (1.41 g, 3.8 mmol) in 3 mL dry DMF was added dropwise. The mixture was stirred for 3 h at the temperature not exceeding 40 °C and filtered under nitrogen. The filtrate was added slowly to a solution of CuBr (0.55 g, 3.83 mmol) in a dry DMF (20 mL) at −30 °C. The mixture was stirred for 0.5 h at the same temperature while 2% aq HCl (150 mL) was added under cooling with an ice bath. The resulting mixture was extracted with diethyl ether (4×50 mL), organic layers were combined, dried over $MgSO_4$ and volatiles removed under reduced. The crude product was purified by a recrystallization from a diethyl ether yielding 0.78 g (71%) of **18** as white crystals; mp 137–138 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.87 (d, $^3J_{H,P}$=14.2 Hz, 2H, Ar−H), 7.54 (d, $^4J_{H,P}$=5.4 Hz, 2H, Ar−H), 3.99–4.24 (m, 8H, O−CH_2), 2.35 (s, 12H, Ar−CH_3), 1.31 (t, $^3J_{H,H}$=6.9 Hz, 12H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=147.4 (ddd, $^1J_{C,F}$=297.1 Hz, $^2J_{C,F}$=112.0 Hz, $^3J_{C,P}$=5.3 Hz, 2C, 7,7′-C), 142.1

(dd, $^4J_{C,P}$=3.4 Hz, $^4J_{C,F}$=1.2 Hz, 2C, 4,4′-C), 139.2 (ddd, $^2J_{C,P}$=14.6 Hz, $^4J_{C,P}$=1.2 Hz, $^5J_{C,P}$=1.2 Hz, 2C, 6,6′-C), 136.3 (dd, $^3J_{C,P}$=9.3 Hz, $^5J_{C,P}$=1.0 Hz, 2C, 5,5′-C), 133.5 (ddd, $^3J_{C,P}$=13.3 Hz, $^3J_{C,F}$=2.8 Hz, $^4J_{C,F}$=2.8 Hz, 2C, 3,3′-C), 130.0 (ddd, $^2J_{C,F}$=10.2 Hz, $^3J_{C,F}$=10.2 Hz, $^2J_{C,P}$=8.1 Hz, 2C, 2,2′-C), 125.8 (dd, $^1J_{C,P}$=184.2 Hz, $^3J_{C,F}$=0.9 Hz, 2C, 1,1′-C), 62.5 (d, $^2J_{C,P}$=5.0 Hz, 4C, i,i′-C), 20.3 (d, $^4J_{C,P}$=1.2 Hz, 2C, 8,8′-C), 12.0 (s, 2C, 9,9′-C), 16.7 (d, $^3J_{C,P}$=6.5 Hz, 4C, j,j′-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=18.8 (dd, $^4J_{P,F}$=1.5 Hz, $^5J_{P,F}$=1.5 Hz, 2P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−131.4 (s, 2F, CF=CF) ppm. MS (EI, 70 eV): *m*/*z* (%)=544 (100) $[M]^+$, 448 (20), 392 (18), 269 (15), 216 (10). HRMS (EI) for $C_{26}H_{36}F_2O_6P_2$ $[M]^+$ calcd 544.1955; found 544.1965.

*4.1.46. Diethyl 2-(1,1-difluoroethyl)-4,5-dimethylphenylphosphonate (**19**).* To a solution of **8e** (0.6 g, 2.09 mmol) in dry THF (30 mL) at −80 °C, *t*-BuLi (1.6 M solution in *n*-pentane, 2.26 mmol) was added dropwise and the RM was stirred for 0.5 h at the same temperature. Then, the mixture was allowed to warm up to −30 °C and methyl iodide (0.14 mL, 2.26 mmol) was added dropwise under vigorous stirring. Afterwards, the mixture was left for 3 h at −30 °C and 10% HCl (5 mL) was quickly added. The mixture was warmed to rt and both layers were separated. Water phase was extracted with diethyl ether (3×15 mL), organic layers were combined, dried over $MgSO_4$ and all volatiles were evaporated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/EtOAc; 20:1) yielding 0.46 g (74%) of pure **19** as a colourless oil; R_f=0.24. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.80 (d, $^3J_{H,P}$=14.7 Hz, 1H, Ar−H), 7.39 (d, $^4J_{H,P}$=6.1 Hz, 1H, Ar−H), 4.07–4.25 (m, 4H, O−CH_2), 2.32 (s, 6H, Ar−CH_3), 2.06 (t, $^3J_{H,F}$=18.6 Hz, 3H, CF_2−CH_3), 1.35 (t, $^3J_{H,H}$=6.9 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=141.9 (dt, $^4J_{C,P}$=3.1 Hz, $^4J_{C,F}$=0.7 Hz, 1C, 4-C), 139.5 (td, $^2J_{C,F}$=27.4 Hz, $^2J_{C,P}$=9.6 Hz, 1C, 2-C), 138.2 (dt, $^2J_{C,P}$=14.0 Hz, $^4J_{C,F}$=1.3 Hz, 1C, 6-C), 136.5 (d, $^3J_{C,P}$=8.4 Hz, 1C, 5-C), 128.6 (dt, $^3J_{C,P}$=13.7 Hz, $^3J_{C,F}$=8.8 Hz, 1C, 3-C), 122.9 (td, $^1J_{C,F}$=241.9 Hz, $^3J_{C,P}$=3.7 Hz, 1C, 7-C), 122.8 (dt, $^1J_{C,P}$=187.0 Hz, $^3J_{C,F}$=2.5 Hz, 1C, 1-C), 62.7 (d, $^2J_{C,P}$=5.9 Hz, 2C, i-C), 27.2 (t, $^2J_{C,F}$=28.8 Hz, 1C, CF_2−CH_3), 20.3 (d, $^4J_{C,P}$=1.2 Hz, 1C, 8-C), 19.9 (s, 1C, 9-C), 16.7 (d, $^3J_{C,P}$=6.8 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=18.7 (t, $^4J_{P,F}$=2.6 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−84.6 (qd, $^3J_{F,H}$=18.1 Hz, $^4J_{F,P}$=2.1 Hz, 2F, CF_2CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=306 (10) $[M]^+$, 286 (20) $[M-HF]^+$, 241 (25) $[M-CF_2CH_3]^+$, 213 (100), 130 (30). HRMS (EI) for $C_{14}H_{21}F_2O_3P$ $[M]^+$ calcd 306.1196; found 306.1193.

*4.1.47. Diethyl 2-[difluoro(trimethylsilyl)methyl]-4,5-dimethylphenylphosphonate (**20**).* Prepared similarly to **19** from **8e** (1.13 g, 3.87 mmol), *t*-BuLi (4.26 mmol) and trimethylsilyl chloride (0.5 g, 4.64 mmol) in dry THF (50 mL) at 0–5 °C within 4 h; yield 0.71 g (50%) as a yellowish oil, eluent *n*-hexane/ethylacetate (4:1), R_f=0.2. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.80 (d, $^3J_{H,P}$=14.2 Hz, 1H, Ar−H), 7.18 (d, $^4J_{H,P}$=6.6 Hz, 1H, Ar−H), 4.05–4.23 (m, 4H, O−CH_2), 2.32 (s, 6H, Ar−CH_3), 1.34 (t, $^3J_{H,H}$=7.3 Hz, 6H, CH_3), 0.18 (s, 9H, $SiMe_3$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=141.5 (d, $^4J_{C,P}$=3.1 Hz, 1C, 4-C), 140.2 (td, $^2J_{C,F}$=20.8 Hz, $^2J_{C,P}$=9.3 Hz, 1C, 2-C), 137.4 (dt, $^2J_{C,P}$=14.1 Hz, $^4J_{C,F}$=2.2 Hz, 1C, 6-C), 136.5 (dt, $^3J_{C,P}$=8.4 Hz, $^5J_{C,F}$=0.7 Hz, 1C, 5-C), 128.7 (td, $^1J_{C,F}$=266.7 Hz, $^3J_{C,P}$=2.8 Hz, 1C, 7-C), 128.5 (dt, $^3J_{C,P}$=13.6 Hz, $^3J_{C,F}$=9.6 Hz, 1C, 3-C), 122.5 (dt, $^1J_{C,P}$=188.3 Hz, $^3J_{C,F}$=3.2 Hz, 1C, 1-C), 62.5 (d, $^2J_{C,P}$=6.2 Hz, 2C, i-C), 20.3 (d, $^4J_{C,P}$=0.9 Hz, 1C, 8-C), 19.9 (s, 1C, 9-C), 16.8 (d, $^3J_{C,P}$=6.2 Hz, 2C, j-C), 1.5 (s, 3C, Si−CH_3) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=19.2 (t, $^4J_{P,F}$=3.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−102.8 (s, 2F, CF_2Si) ppm. MS (EI, 70 eV): *m*/*z* (%)=363 (25) $[M-H]^+$, 313 (100) $[M-CF_2H]^+$, 285 (20), 273 (60), 215 (30). HRMS (EI) for $C_{16}H_{26}F_2O_3PSi$ $[M-H]^+$ calcd 363.1357; found 363.1353.

*4.1.48. Diethyl 2-(1,1-difluoroethyl)-4-methylphenylphosphonate (**21**).* Prepared similarly to **19** from **9e**:**10e** (5.0 g, 18.0 mmol, 61:39 mol %), *t*-BuLi (19.8 mmol) and MeI (1.2 mL, 19.8 mmol) in dry THF (220 mL) at −25 °C within 4 h; yield 2.0 g (62%, 38% overall) as a colourless oil, eluent dichloromethane/ethylacetate (15:1), R_f=0.3. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.90 (dd, $^3J_{H,P}$=14.4 Hz, $^3J_{H,H}$=7.9 Hz, 1H, Ar−H), 7.44 (d, $^4J_{H,P}$=6.0 Hz, 1H, Ar−H), 7.27 (dd, $^3J_{H,H}$=7.9 Hz, $^4J_{H,P}$=2.6 Hz, 1H, Ar−H), 4.05–4.24 (m, 4H, O−CH_2), 2.41 (s, 6H, Ar−CH_3), 2.07 (t, $^3J_{H,F}$=18.8 Hz, 3H, CF_2−CH_3), 1.34 (t, $^3J_{H,H}$=7.1 Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=143.2 (dt, $^4J_{C,P}$=3.1 Hz, $^4J_{C,F}$=0.6 Hz, 1C, 4-C), 142.1 (td, $^2J_{C,F}$=27.0 Hz, $^2J_{C,P}$=9.6 Hz, 1C, 2-C), 135.3 (d, $^3J_{C,P}$=7.8 Hz, 1C, 5-C), 130.1 (dt, $^2J_{C,P}$=14.3 Hz, $^4J_{C,F}$=1.2 Hz, 1C, 6-C), 127.9 (dt, $^3J_{C,P}$=13.3 Hz, $^3J_{C,F}$=9.0 Hz, 1C, 3-C), 122.8 (dt, $^1J_{C,P}$=188.6 Hz, $^3J_{C,F}$=2.8 Hz, 1C, 1-C), 122.7 (td, $^1J_{C,F}$=241.8 Hz, $^3J_{C,P}$=3.6 Hz, 1C, 7-C), 62.7 (d, $^2J_{C,P}$=6.2 Hz, 2C, i-C), 27.1 (t, $^2J_{C,F}$=27.9 Hz, 1C, CF_2−CH_3), 21.9 (s, 1C, 8-C), 19.8 (s, 1C, 9-C), 16.7 (d, $^3J_{C,P}$=6.5 Hz, 2C, j-C) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=18.2 (t, $^4J_{P,F}$=2.0 Hz, 1P) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−85.0 (qd, $^3J_{F,H}$=18.5 Hz, $^4J_{F,P}$=2.2 Hz, 2F, CF_2CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%)=291[8] $[M-H]^+$, 272 (22) $[M-HF]^+$, 227 (45) $[M-CF_2CH_3]^+$, 199 (100), 116 (25). HRMS (EI) for $C_{13}H_{18}F_2O_3P$ $[M-H]^+$ calcd 291.0962; found 291.0961.

Acknowledgements

The Deutsche Forschungsgemeinschaft (436 RUS 113/961/0-1) is greatly acknowledged for financial support of this work. We would like also to express our gratitude to Dr. T. Duelcks (University of Bremen) for recording MS and HRMS spectra and to Dr. Romana Pajkert for valuable advices.

Supplementary data

Characterization data includes ^{1}H, ^{13}C, ^{31}P, ^{19}F NMR spectra of all new compounds and X-ray crystal data of **18**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.076. These data include MOL files and InChIKeys of the most important compounds described in this article.

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29. CCDC 776607 contains the supplementary crystallographic data of compound **18**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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