

Synthesis of Aryl(DifluoromethylenePhosphonates) via Electrophilic Fluorination of α-Carbanions of Benzylic Phosphonates with N-Fluorobenzenesulfonimide.

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Abstract: The electrophilic fluorination of a wide variety of benzylic phosphonates with N-fluorobenzenesulfonimide has been examined. The fluorination reaction proceeds well in the presence of an array of functional groups such as nitro, bromo, ketone, ester, phenyl and ether groups. Phenyl and biphenyl derivatives containing two α , α -difluoromethylenephosphonate groups can also be prepared. This procedure is compatible with methyl or ethyl phosphonate esters but not with t-butyl esters or with benzylic phosphonates containing an additional benzylic moiety at the *para*-position. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

There are now numerous examples in which the substitution of phosphate groups, in natural and unnatural products, with α, α -difluoromethylenephosphonate moieties results in a significant enhancement of their biological properties.¹ Perhaps one of the most striking examples of this phenomenon is the inhibition of protein tyrosine phosphatases (PTPs) with peptides containing the non-hydrolyzable phosphotyrosine mimetic, (phosphonodifluoromethyl)phenylalanine, 1^{2a-d} PTPs are enzymes that catalyze the removal of phosphate groups from phosphotyrosine residues in peptides and proteins. They are key participants in kinase-dependent signal transduction pathways and are essential for the regulation of a wide variety of crucial cellular processes.³⁻⁵ Certain peptides bearing 1 are, in some instances, over 1000-fold more potent inhibitors of selected PTPs than the same peptides bearing the non-fluorinated analogue, 2, and exhibit Kis in the nanomolar region.^{2a-d} This phenomenon is not limited to peptidyl inhibitors. Naphthyl derivatives, 3-5, also retain binding affinity for certain PTPs in contrast to their non-fluorinated counterparts which are not inhibitors. However, they are not highly selective, inhibiting the serine/threonine phosphatase PP2A as well, and are approximately 1000-fold less potent than the peptidyl inhibitors.^{6a,b} Nevertheless, these results are significant in that they demonstrate the potential of aryl(difluoromethylenephosphonyl) derivatives as nonpeptidyl inhibitors of PTPs. Such species are highly desirable as tools for in vivo studies on signal transduction pathways and as potential therapeutics.

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As part of our program to create potent, non-peptidyl inhibitors of PTPs, it was necessary to synthesize a wide variety of $aryl(\alpha, \alpha, -diffuoromethylenephosphonates)$. Until fairly recently, $aryl(\alpha,\alpha)$ difluoromethylenephosphonates) have been synthesized via diethylaminosulfurtrifluoride (DAST) fluorination of the corresponding α -ketophosphonates.^{7,8} However, this procedure requires a large excess (5-15 equivalents) of expensive DAST and, when performed on a multigram scale, can sometimes react explosively.^{8a} In addition, the α -ketophosphonate precursors can sometimes be unstable and difficult to synthesize.⁹ Consequently, an alternative procedure for synthesizing this class of compounds is highly We have recently demonstrated that naphthyl(α,α -difluoromethylenephosphonates) can be desirable. prepared by electrophilic fluorination of α -carbanions of naphthyl(methylphosphonates) using Nfluorobenzenesulfonimide (NFBS).⁹ Here, we examine the scope of this reaction and report that this methodology can be extended to produce a wide variety of $aryl(\alpha,\alpha-diffuoromethylenephosphonates)$.



RESULTS AND DISCUSSION

In 1991, Differding and coworkers reported that non-benzylic phosphonates could be fluorinated at the α -position in moderate to good yields via electrophilic fluorination using NFBS.¹⁰ This fluorination was accomplished via a two step procedure in which 1.3-2.5 eq. of potassium diisopropylamide (KDA) was used to remove an α -proton at -78 °C in THF, followed by the addition of 1.3-2.5 eq. of NFBS to form the α -monofluorophosphonates. The α -monofluorophosphonates were purified and then subjected to the same procedure at < -85 °C to form the α , α -difluorophosphonates in overall yields of 29-36% (from non-fluorinated starting material). On the basis of these studies we reasoned that this methodology could be adapted to synthesize aryl(α , α ,-difluoromethylenephosphonates).

We were specifically interested in developing an electrophilic fluorination procedure that would allow for the construction of $aryl(\alpha,\alpha,-diffuoromethylenephosphonates)$ in a single step. Employing diethyl benzylphosphonate 6 as a model substrate, the fluorination reaction was performed in a single step by the addition of 6 to 2.2eq. of KDA at -78 °C in THF, followed by the addition of 2.5 eq. of NFBS. Although Differding reported¹⁰ that very poor yields (10-20%) of non-benzylic α,α -diffuorophosphonates were obtained via a one-step procedure, we found that this was not the case with 6 and the desired difluorinated material 7 could be obtained in a 39% yield. This yield is comparable to the yields obtained by Differding with nonbenzylic phosphonates using a two-step procedure. In an effort to improve the yield, the fluorination reaction was performed with a variety of bases (Table 1) using the one-pot procedure. Consistent with Differding's original report,¹⁰ the yield depended strongly on the nature of the cation, with lithium counterions giving the lowest yields. However, the yield could be improved from 39% to 51% using potassium hexamethyldisilazide (KHMDS) as opposed to KDA and was further improved to 79% using sodium hexamethyldisilazide (NaHMDS). Performing the reaction with NaHMDS in two steps or at temperatures below -78 °C did not improve the yield.

H ₂ C ^{$PO(OEI)_2$} 1. 2.2 eq. ba -78 °C. 2. 2.5 eq. NF	se, THF, F2C PO(OEt)2 BS, THF,
6 -78 °C	7
Base	% Yield of 7
KDA	39
LDA	33
NaHMDS	79
KHMDS	51
LiHMDS	29

Table 1. Effect of base on the electrophilic fluorination of 6 with NFBS

To explore the scope and applicability of this method to the synthesis of other aryl(difluoromethylenephosphonates), a wide variety of substituted benzyl phosphonates (8-19, Table 2) were prepared. This was accomplished via an Arbuzov reaction between trimethyl or triethyl phosphite and benzylic bromides or chlorides which were either commercially available or could be prepared in a single step by bromination of commercially available toluene derivatives (Scheme 1). Upon subjecting these phosphon-



ates to electrophilic fluorination conditions (2.2 eq. NaHMDS, -78 °C in THF, followed by 2.5 eq. NFBS) a wide variety of aryl(difluoromethylenephosphonate) derivatives (20-31, Table 2) were obtained in reasonable to good yields. An array of both electron-rich and electron-poor functional groups can be tolerated such as ester, ether, nitro, bromo, phenyl, and keto. There was a decrease in yield of the *ortho*-phenyl derivative 30 (46%) compared to the *meta*-phenyl 29 and *para*-phenyl 28 derivatives (60% and 59% respectively). This decrease in yield can be attributed to the increased steric demands of the *ortho*-substituted phosphonate

Substrate	Product	% Yield
	x CF2-P(OR)2	
8, $X = H$, $R = Me$	20 , $X = H$, $R = Me$	63
9 , $X = p$ -NO ₂ , $R = Me$	21 , $X = p$ -NO ₂ , $R = Me$	74
10 , $X = p$ -NO ₂ , $R = Et$	22 , $X = p$ -NO ₂ , $R = Et$	82
11, $X = p$ -Br, $R = Me$	23 , $X = p$ -Br, $R = Me$	79
12 , $X = p$ -Br, $R = Et$	24 , $X = p$ -Br, $R = Et$	81
13, $X = p$ -COOBn, $R = Me$	25 , $X = p$ -COOBn, $R = Me$	72
14, $X = p$ -OMe, $R = Me$	26 , $X = p$ -OMe, $R = Me$	80
15 , $X = p$ -COPh, $R = Et$	27, $X = p$ -COPh, $R = Et$	70
16 , $X = p$ -Ph, $R = Me$	28 , $X = p$ -Ph, $R = Me$	59
17, $X = m$ -Ph, $R = Me$	29 , $X = m$ -Ph, $R = Me$	60
18 , $X = o$ -Ph, $R = Me$	30 , $X = o$ -Ph, $R = Me$	46
19 , $X = m$ -CH ₂ O(CH ₂) ₂ TMS, $R = Me$	31, $X = m$ -CH ₂ O(CH ₂) ₂ TMS, $R = Me$	79

Table 2. Electrophilic Fluorination of Benzylic Phosphonates with NFBS

compared to the *meta-* and *para-substituted* phosphonates. However, this effect is relatively modest (13-14%), suggesting that the reaction is not overly sensitive to bulky substituents at the *ortho* position. In general, slightly better yields were obtained using the ethyl phosphonate esters, though in most instances good yields were obtained using both methyl and ethyl phosphonates. To compare the electrophilic fluorination procedure to the DAST methodology,^{7c} 7 and 20 were prepared by DAST fluorination (5 eq., neat) of dimethyl and diethyl benzoylphosphonate¹¹ using the procedure described by Burke *et al.*^{7c} Using this procedure, 7 and 20 were obtained in yields of 40-45% and 38% respectively with purification sometimes requiring several columns. In contrast, the methodology described here afforded 7 and 20 in yields of 79% and 63% respectively, with facile purification (usually requiring a single flash column). Thus, the electrophilic fluorination procedure is superior, in terms of yield, compared to the DAST procedure when using methyl or ethyl-protected phosphonates. However, it should be pointed out that the electrophilic fluorination procedure

is not applicable to t-butyl-protected phosphonates. Burke and coworkers have prepared the t-butyl-protected derivative **36** in 79% yield by DAST fluorination of the corresponding α -keto-phosphonate.^{7a} Attempts to synthesize this compound from **32** (Scheme 2) using the electrophilic fluorination procedure were unsuccessful. This is consistent with the results of Burke and coworkers who were unable to convert the α -monofluorophosphonate derivative of **32** (obtained by DAST fluorination of the α -hydroxy phosphonate derivative) to **36** using NFBS.^{7a} One possible explanation for this decrease in yield is the greater steric demands of the t-butyl groups compared to methyl and ethyl groups and, as a result, other side reactions may predominate such as elimination of the phosphate and formation of isobutylene. The yields obtained using the



electrophilic fluorination procedure compare favorably with the cross-coupling procedure recently developed by Burton and Qiu.^{8b} For example, these workers prepared 7 in an 80% yield via copper halide-promoted cross-coupling of (diethoxyphosphonyl)difluoromethylcadmium reagent with iodobenzene.^{8b} 7 was prepared in 79% yield (Table 1) using electrophilic fluorination although the yield drops to 63% with the methyl ester (**20**, Table 2). The methyl esters have not been reported using the cross-coupling procedure.

Fluorination of benzylic phosphonates that contained a benzylic moiety at the *para* position using NFBS were unsuccessful. For example, selective fluorination of phosphonate **33** (Scheme 2), which contains a benzylic carbon ester *para* to the phosphonate, was attempted since the fluorination of benzylic carbon esters proceeds very poorly using NaHMDS as base.¹² However, neither the desired product nor any material arising from mono or di-fluorination of both the phosphonate and carbon ester methylene units could be isolated and only unidentified decomposition products were obtained. Selective fluorination of the phosphonate **34** in the presence of the unprotected acid was also attempted using 3.3 eq. NaHMDS and 2.5 eq. NFBS, reasoning that initial formation of the carboxylate anion would favor deprotonation of the methylene unit next to the phosphonate. However, once again, only unidentified decomposition products were obtained. Similarly, attempts to construct the tetrafluoro bisphosphonate **39** using 5.5 eq. NaHMDS and 7.3 eq. NFBS also failed. On the other hand, fluorination of the 1,3-derivatives **40** and **41** under the same conditions yielded the



tetrafluoro compounds 42 and 43 in reasonable to good yields (Scheme 3). These results suggest that lack of formation of 37-39 may be due to the elimination of fluorine from the initially formed monofluorinated products, as shown in Scheme 4, yielding the methide derivative which may undergo further reaction. The 1,3 derivatives (40 and 41) are unable to undergo this elimination reaction.



As mentioned above and in our earlier study,⁹ $bis(\alpha, \alpha, -difluoromethylenephosphonyl)$ phenyl and naphthyl derivatives can be obtained by electrophilic fluorination of the corresponding bisphosphonates using 5.5 eq. NaHMDS and 7.3 eq. NFBS. We have now found that this procedure can be extended to the preparation of the bis(difluoromethylenephosphonyl) biphenyl and benzophenone derivatives (Table 3).

 Table 3. Electrophilic Fluorination of Diphenyl Bis-Phosphonates with NFBS

Substrate	Product	% Yield
0 (MeO)2 ^P CH2-(CH2)n-(CH2)n-CH2 ^P (OMe)2		
44, n = 0	48 , n = 0	21
45 , n = 1	49 , n = 1	16
46 , n = 4	50 , n = 4	64
	(MeO) ₂ PCF ₂ -	28

When the phenyl rings of the bis(phosphonate) substrates were directly attached to one another (44) or were separated by a single methylene unit (45), the yields of bis(difluoromethylenephosphonate) products (48 and 49) were very low (21% and 16%). In the case of 48, the low yield may be due to partial elimination of fluorine from the initially formed monofluorinated product via a mechanism similar to that postulated for compounds 37-39. A similar phenomenon may be occurring with 49 by removal of a proton on the methylene unit separating the two rings. However, no product arising from fluorination of the methylene bridge was isolated. The benzophenone bisphosphonate 47 could be fluorinated to produce the bis(difluoromethylenephosphonyl) benzophenone derivative 51 but in only a 28 % yield. This is not a significantly greater yield than that obtained for 49 and is considerably poorer than that obtained for the mono(difluoromethylenephosphonyl) benzophenone derivative 27. Compound 47 cannot undergo an elimination reaction which suggests that the low yields obtained for 49 may not be due to deprotonation of the methylene followed by elimination of fluorine. To examine whether the distance in between the two phenyl rings makes a difference in yield, the biphenyl derivative 46 was prepared in which the two phenyl rings were separated by 4 methylene units, and was subjected to the fluorination conditions. Here the yield increases to a respectable 64 %, which is very similar to the yield obtained for the monophenyl derivative 20. Thus, it appears that by increasing the distance between the phenyl rings, the yield of the fluorination reaction increases significantly. However, we are unable to offer an explanation for this phenomenon.

For inhibition studies with PTPs, the methyl or ethyl protecting groups were removed from selected α,α difluoromethylenephosphonates (20, 21, 23, 25, 27-30, 48-51). This was accomplished using trimethylsilylbromide (TMSBr) in methylene chloride to form the silyl esters followed by the addition of an aqueous solution of ammonium bicarbonate. Removal of the organic layer followed by repeated lyophilizations yielded the α,α -difluoromethylenephosphonic acids as their ammonium salts in near quantitative yields (see Experimental, compounds 52-63).

CONCLUSION

In conclusion, we have demonstrated that a wide variety of $aryl(\alpha,\alpha-diffuoromethylenephosphonates)$ can be synthesized in a one pot procedure from the corresponding phosphonates via electrophilic fluorination with NFBS. The fluorination reaction proceeds well in the presence of an array of functional groups such as nitro, bromo, ketone, ester, phenyl and ether groups. Phenyl and biphenyl derivatives containing two α,α -diffuoromethylenephosphonate groups can also be prepared. This procedure is compatible with methyl or ethyl phosphonate esters but not with t-butyl ester or with benzylic phosphonates containing an additional benzylic moiety at the *para*-position. Conversion of the phosphonate esters to their ammonium salts could be readily accomplished using TMSBr and aqueous ammonium bicarbonate. Evaluation of the ammonium salts as inhibitors of PTPs is in progress.

EXPERIMENTAL

General. Unless otherwise noted, all starting materials were obtained from commercial suppliers (Aldrich or Lancaster) and were used without further purification. Tetrahydrofuran (THF) and diethylether (ether) were distilled from sodium/benzophenone ketyl under argon. Dichloromethane was distilled from calcium hydride under argon. DMF was distilled under reduced pressure from calcium hydride and stored over 4-A sieves under argon. Reactions involving moisture sensitive reagents were executed under an inert atmosphere of dry argon. Flash chromatography was performed using silica gel 60 (Toronto Research Chemicals, 230-400 mesh ASTM). Melting points were obtained on a Electrothermal Inc. melting point apparatus and are uncorrected. ¹H, ³¹P and ¹⁹F NMR spectra were recorded on a Varian 200-Gemini NMR machine at approximately 200 MHz, 80 MHz and 188 MHz respectively. ¹³C spectra were recorded on a Varian-500 NMR or Varian-400 NMR machine at 125 MHz and 100 MHz respectively unless stated otherwise. The NMR's of all non-ionic compounds were run using CDCl₃ as solvent and all ionic (ammonium salts) were run using D₂O as solvent unless stated otherwise. For ¹H spectra run in CDCl₃, chemical shifts (δ) are reported in parts per million relative to the internal standard tetramethylsilane (TMS). For ¹H spectra run in D₂O, chemical shifts (δ) are reported in parts per million relative to the residual HDO peak at δ 4.68. For ¹³C spectra run in CDCl₃, chemical shifts are reported in parts per million relative to the CDCl₃ residual carbons (§ 77.0 for the central peak). For ¹³C spectra run in D₂O, chemical shifts are reported in parts per million relative to the CH₃ peak 3(trimethylsilyl)-1-propanesulfonic acid (external). For ³¹P NMR spectra, chemical shifts are reported in parts per million relative to 85 % phosphoric acid (external). For ¹⁹F NMR, chemical shifts are reported in parts per million relative to trifluoroacetic acid (external). Electron impact (EI) and fast atom bombardment (FAB, negative ion) mass spectra were obtained on a Micromass 70-S-250 mass spectrometer.

Preparation of Benzyl Bromides.

For compounds 8-12, 16, 34, 35, 40 and 41, the benzylic bromide precursors were obtained from commercial sources. For compound 14, the commercially available benzyl chloride derivative was used. For compounds 18,¹³ 44-46¹⁴ and 47,¹⁵ the benzylic bromide precursors were prepared via literature procedures. Benzylic bromide precursors to compounds 15,¹⁶ and 17,¹⁷ were prepared via bromination of 4-methylbenzophenone and 3-methylbiphenyl respectively using NBS/benzoylperoxide in CCl4.¹⁸ The benzylbromide precursors to compounds 13, 19 and 33 were prepared as described below:

4-Bromomethylbenzoic acid benzyl ester (precursor to 13). Freshly distilled benzyl alcohol (1 eq., 0.48 mL), N,N-dimethyl-4-aminopyridine (0.1 eq., 0.057 g), and dicyclohexylcarbodiimide (DCC, 1 eq., 0.96 g)

were added to a stirring solution of 4-bromomethyl benzoic acid (1.0 g, 4.65 mmol) dissolved in anhydrous CH₂Cl₂ (25 mL). Formation of dicyclohexylurea as a precipitate was evident almost immediately after the addition of DCC. Reaction was stirred for 5 min, filtered, and concentrated by rotary evaporation. The crude product was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:2, $R_f = 0.6$) to give the ester as a white solid (1.12 g, 74 % yield, mp 60-62 °C). ¹H NMR: δ 8.06 (d, J = 8.1 Hz, 2H, aryl), 7.43 (m, 7H, aryl), 5.38 (s, 2H, OCH₂), 4.50 (s, 2H, BrCH₂); ¹³C NMR: δ 165.7 (s, CO), {142.6, 135.8, 130.1, 130.0, 128.9, 128.5, 128.2, 128.1 (s, aryl)}, 66.7 (s, OCH₂), 32.1 (s, BrCH₂); EIMS: *m/z* 306 (M⁺{⁸¹Br}, 19 %), 199 (M⁺{⁸¹Br} - OCH₂Ph, 69 %), 91 (M⁺{⁷⁹Br} - OOCPhCH₂Br, 100 %); HRMS(EI): calcd for C₁₅H₁₃O₂Br (M⁺) *m/z* 306.0078 & 304.0099, found 306.0074 & 304.0097.

(4-Bromomethylphenyl)acetic acid benzyl ester (precursor to 33). This was prepared in a manner similar to that described for 4-bromomethylbenzoic acid benzyl ester starting from commercially available (4-bromomethylphenyl)acetic acid. Purified using silica gel chromatography (hexane/EtOAc, 4:1, $R_f = 0.6$), white solid, mp 59-61 °C, 88 % yield. ¹H NMR: δ 7.33 (m, 9H, aryl), 5.14 (s, 2H, OCH₂), 4.49 (s, 2H, BrCH₂), 3.67 (s, 2H, CH₂); ¹³C NMR: δ 170.9 (s, CO), {136.6, 135.7, 134.1, 129.7, 129.2, 128.5, 128.2, 128.1 (s, aryl)}, 66.6 (s, OCH₂), 40.9 (s, CH₂), 33.1 (s, BrCH₂); EIMS: *m/z* 320 (M⁺{⁸¹Br}, 4%) 239 (M⁺ - ^{81/79}Br, 76 %), 185 (M⁺{⁸¹Br} - OOCCH₂Ph, 24 %), 91 (M⁺ - OOCCH₂PhCH₂Br, 100 %), 318 (M⁺{⁷⁹Br}}, 4%), 183 (M⁺{⁷⁹Br} - OOCCH₂Ph, 26 %); HRMS(EI): calcd for C₁₆H₁₅O₂Br (M⁺) *m/z* 320.0235 & 318.0255, found 320.0247 & 318.0270.

l-Bromomethyl-3-(2-trimethylsilylethoxymethyl)benzene (precursor to 19). To dry THF (30 mL) containing NaH (0.50 g, 20.80 mmol, 1.74 eq.) was added via syringe 2-trimethylsilylethanol (1.5 mL, 12.0 mmol, 1.0 eq.). After the solution was stirred for 1.5 h, α , α '-dibromo-*m*-xylene (3.20 g, 12.1 mmol, 1.01 eq.) in THF (30 mL) was added. The mixture was stirred under reflux for 50 h. Water (50 mL) was added gradually followed by methylene chloride (3 x 50 mL). The organic layer was separated, washed with brine and dried (MgSO₄). Removal of the solvent gave an oil which was subjected to silica gel chromatography (CH₂Cl₂/hexane, 2:3, R_f = 0.4) to give the starting material (0.19 g) and the product (1.97 g, 57% yield based on the reacted starting material). ¹H NMR: δ 7.38 (m, 1H, aryl), 7.29 (m, 3H, aryl), 4.50 and 4.49 (two s, 4H, CH₂Br and ArCH₂O), 3.60 (t, J = 8.3 Hz, 2H, OCH₂CSi), 1.01 (t, J = 8.3 Hz, 2H, CH₂Si), 0.02 (s, 9H, SiCH₃); ¹³C NMR: δ {139.8, 137.9, 128.7, 128.03, 127.96, 127.5 (s, aryl)}, 72.0 (s, ArCH₂O), 67.9 (s, OCH₂CSi), 33.3 (s, CH₂Br), 18.4 (s, CH₂Si), -1.27 (s, SiCH₃); EIMS: *m/z* 257 ((M⁺ + 1H) - 3(CH₃), 62 %), 258 ((M⁺ + 2H) - 3(CH₃), 12 %), 259 ((M⁺ + 3H) - 3(CH₃), 63 %); HRMS(EI): calcd for C₁₀H₁₄BrOSi ((M⁺ + 1H) - 3(CH₃)) *m/z* 256.9997, found 256.9998.

Preparation of Phosphonates

Phosphonate 6 was purchased from Aldrich Chemical Co. Phosphonates 14, ¹⁹ 35, ²⁰ 40^{20} and 41^{21} were prepared by literature procedures. All other phosphonates, with the exception of 32, were prepared via an Arbuzov reaction with trimethyl or triethyl phosphite using the general procedure described below.

General procedure for the Preparation of Phosphonates. The benzylic halide was added to trimethyl- or triethylphosphite (10-15 eq.) or to a solution of trimethyl- or triethylphosphite (10-15 eq.) in an equal volume of benzene and heated to reflux for 6-18 hours. The reaction was cooled and then benzene and/or unreacted phosphite and dimethyl methylphosphonate or diethyl ethylphosphonate (formed during the reaction) were removed by vacuum distillation. The phosphonates were obtained in pure form by subjecting the residue to silica gel chromatography or by recrystallization.

Dimethyl benzylphosphonate (8).²² Purified using silica gel chromatography (MeOH/CHCl₃ 2:98, $R_f = 0.4$), clear, colorless oil, 89% yield. ¹H NMR: $\delta 3.17$ (d, $J_{HP} = 21.6$ Hz, 2H, CH₂), 3.69 (d, $J_{HP} = 10.6$ Hz, 6H, 2(CH₃)), 7.30 (m, 5H, aryl); ³¹P NMR: $\delta 26.65$; ¹³C NMR: $\delta 32.6$ (d, $J_{CP} = 137.6$ Hz, CH₂), 52.5 (d, $J_{CP} = 6.6$ Hz, 2(CH₃)), 126.7 (d, $J_{CP} = 3.7$ Hz, aryl), 128.3 (d, $J_{CP} = 2.2$ Hz, aryl), 129.4 (d, $J_{CP} = 6.6$ Hz, aryl), 131.1 (d, $J_{CP} = 9.5$ Hz, aryl); EIMS: *m*/z 200 (M⁺, 45 %), 91 (M⁺ - PO(OMe)₂, 100 %); HRMS(EI): calcd for C₉H₁₃PO₃ (M⁺) *m*/z 200.0602, found 200.0607.

Dimethyl 4-nitrobenzylphosphonate (9). Purified by recrystallization from carbon tetrachloride. Pale yellow solid, mp 64-66 °C, 79% yield. ¹H NMR: δ 8.14 (d, J = 8.5 Hz, 2H, aryl), 7.44 (dd, J = 8.8 Hz, 2.2 Hz, 2H, aryl), 3.71 (d, J_{HP} = 11.0 Hz, 6H, 2(CH₃)), 3.25 (d, J_{HP} = 22.3 Hz, 2H, CH₂); ³¹P NMR: δ 24.51; ¹³C NMR: δ 147.1 (s, aryl), 139.4 (d, J_{CP} = 9.2 Hz, aryl), 130.5 (d, J_{CP} = 7.3 Hz, aryl), 123 (s, aryl), 52.8 (d, J_{CP} = 5.5 Hz, 2(CH₃)), 32.9 (d, J_{CP} = 137.2 Hz, CH₂); EIMS: *m/z* 245 (M⁺, 25 %), 228 (M⁺ - OH, 100 %); HRMS (EI) calcd for C₉H₁₂PNO₅ (M⁺) *m/z*, 245.0453, found 245.0449.

Diethyl 4-nitrobenzylphosphonate (10). Purified using silica gel chromatography (EtOAc, $R_f = 0.4$), yellow oil, 94 % yield. ¹H NMR: δ 8.14 (d, J = 8.4 Hz, 2H, aryl), 7.44 (dd, J = 8.6 Hz, 2.4 Hz, 2H, aryl), 4.03 (m, 4H, 2(OCH₂)), 3.22 (d, J_{HP} = 22.3 Hz, 2H, CH₂P), 1.23 (t, J = 7.2 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 21.90; ¹³C NMR: δ 146.8 (s, aryl), 139.7 (d, J_{CP} = 8.8 Hz, aryl), 130.5 (d, J_{CP} = 6.6 Hz, aryl), 123.5 (s, aryl), 62.2 (d, J_{CP} = 7.3 Hz, 2(OCH₂)), 33.7 (d, J_{CP} = 137.6 Hz, CH₂P), 16.1 (d, J_{CP} = 5.8 Hz, 2(CH₃)); EIMS: *m/z* 274 (MH⁺, 100 %), 137 (MH⁺ - PO(OEt)₂, 54 %); HRMS(EI): calcd for C₁₁H₁₆O₅NP (M⁺) *m/z* 273.0766, found 277.0766.

*Dimethyl 4-bromobenzylphosphonate (11).*²³ Purified using silica gel chromatography (EtOAc, $R_f = 0.3$), white solid, mp 56-58 °C, 98 % yield. ¹H NMR: δ 7.43 (d, J = 8.8 Hz, 2H, aryl), 7.16 (dd, J = 8.5 Hz, 2.6 Hz, 2H, aryl), 3.67 (d, J_{HP} = 10.6 Hz, 6H, 2(CH₃)), 3.10 (d, J_{HP} = 21.9 Hz, 2H, CH₂P); ³¹P NMR: δ 25.73; ¹³C NMR: δ {131.4, 131.1, 130.2, 120.8 (s, aryl)}, 52.7 (d, J_{CP} = 6.6 Hz, 2(CH₃)), 32.1 (d, J_{CP} = 138.4 Hz, CH₂P); EIMS: *m/z* 280 (M⁺{⁸¹Br}, 58 %), 171 (M⁺{⁸¹Br} - PO(OMe)₂, 94 %), 278 (M⁺{⁷⁹Br}, 58 %), 169 (M⁺{⁷⁹Br} - PO(OMe)₂, 100 %); HRMS(EI): calcd for C₉H₁₂O₃BrP (M⁺) *m/z* 279.9687 & 277.9707, found 279.9702 & 277.9721.

Diethyl 4-bromobenzylphosphonate (12).²⁴ Purified using silica gel chromatography (EtOAc/hexane, 1:1, $R_f = 0.3$), colorless oil, 92 % yield. ¹H NMR: δ 7.44 (d, J = 8.8 Hz, 2H, aryl), 7.18 (d, J = 8.8 Hz, 2H, aryl), 4.02 (m, 4H, 2(OCH₂)), 3.09 (d, $J_{HP} = 20.5$ Hz, 2H, CH₂P), 1.25 (t, J = 7.3 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 23.22; ¹³C NMR: δ 131.5 (d, $J_{CP} = 2.9$ Hz, aryl), 131.3 (d, $J_{CP} = 6.6$ Hz, aryl), 130.7 (d, $J_{CP} = 8.7$ Hz, aryl), 120.8 (d, $J_{CP} = 5.1$ Hz, aryl), 62.1 (d, $J_{CP} = 6.6$ Hz, 2(OCH₂)), 33.2 (d, $J_{CP} = 138.4$ Hz, CH₂P), 16.2 (d, $J_{CP} = 5.8$ Hz, 2(CH₃)); EIMS: *m/z* 308 (M⁺{⁸¹Br}, 24 %), 171 (M⁺{⁸¹Br} - PO(OEt)₂, 100 %), 306 (M⁺{⁷⁹Br}, 24 %), 169 (M⁺{⁷⁹Br} - PO(OEt)₂, 97 %); HRMS(EI): calcd for C₁₁H₁₆O₃BrP (M⁺) *m/z* 306.0020, found 306.0015.

Dimethyl 4-carbobenzyloxybenzylphosphonate (13). Purified using silica gel chromatography (EtOAc/hexane, 9:1, $R_f = 0.3$), white solid, mp 66-68 °C, 86 % yield. ¹H NMR: δ 8.02 (d, J = 8.1 Hz, 2H, aryl), 7.38 (m, 7H, aryl), 5.35 (s, 2H, OCH₂), 3.66 (d, J_{HP} = 10.6 Hz, 6H, 2(CH₃)), 3.21 (d, J_{HP} = 22.4 Hz, 2H, CH₂P); ³¹P NMR: δ 25.43; ¹³C NMR: δ 165.9 (s, CO), 136.8 (d, J_{CP} = 8.7 Hz, aryl), 135.9 (s, aryl), 129.8 (d, J_{CP} = 2.9 Hz, aryl), 129.6 (d, J_{CP} = 6.6 Hz, aryl), 128.8 (d, J_{CP} = 3.7 Hz, aryl), {128.4, 128.1, 128.0 (s, aryl)}, 66.5 (s, CH₂), 52.8 (d, J_{CP} = 6.6 Hz, 2(CH₃)), 32.4 (d, J_{CP} = 137.7 Hz, CH₂P); EIMS: *m*/z 334 (M⁺, 6 %), 227 (M⁺ - OCH₂Ph, 100 %), 91 (M⁺ - OOCPhCH₂PO(OMe)₂, 59 %); HRMS(EI): calcd for C₁₇H₁₉O₅P (M⁺) *m*/z 334.0970, found 334.0984.

Diethyl 4-benzoylbenzylphosphonate (15).²⁵ Purified using silica gel chromatography (EtOAc/hexane, 7:3, R_f = 0.3), pale yellow oil, 79 % yield. ¹H NMR: δ 7.74 (m, 4H, aryl), 7.43 (m, 5H, aryl), 4.02 (m, 4H, 2(OCH₂)), 3.20 (d, J_{HP} = 22.4 Hz, 2H, CH₂P), 1.24 (t, J = 6.9 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 23.00; ¹³C NMR: δ 195.8 (s, CO), 137.3 (s, aryl), 136.5 (d, J_{CP} = 9.5 Hz, aryl), 135.8 (d, J_{CP} = 3.7 Hz, aryl), 132.1 (s, aryl), 130.0 (d, J_{CP} = 2.9 Hz, aryl), 129.6 (s, aryl), 129.5 (d, J_{CP} = 6.6 Hz, aryl), 128.0 (s, aryl), 62.0 (d, J_{CP} = 6.6 Hz, 2(OCH₂)), 33.7 (d, J_{CP} = 137.7 Hz, CH₂P), 16.1 (d, J_{CP} = 6.6 Hz, 2(CH₃)); EIMS: *m/z* 332 (M⁺, 57 %), 222 (M⁺ - 110, 100 %), 195 (M⁺ - PO(OEt)₂, 30 %); HRMS(EI): calcd for C₁₈H₂₁O₄P (M⁺) *m/z* 332.1177, found 332.1172. *Dimethyl 4-phenylbenzylphosphonate (16).* Purified using silica gel chromatography (MeOH/CHCl₃ 1:99, $R_f = 0.3$), white solid, mp 68-70°C, 90% yield. ¹H NMR: δ 3.22 (d, J = 21.7 Hz, 2H, CH₂), 3.71 (d, J_{HP} = 10.6 Hz, 6H, 2(CH₃)), 7.50 (m, 9H, aryl); ³¹P NMR: δ 26.60; ¹³C NMR: δ 32.44 (d, J_{CP} = 138.6 Hz, CH₂), 52.9 (d, J_{CP} = 6.9 Hz, 2(CH₃)), 126.9 (s, aryl), 127.3 (m, aryl), 128.7 (s, aryl), 130.0 (d, J_{CP} = 6.8 Hz, aryl), 130.1 (d, J_{CP} = 9.8 Hz, aryl), 139.8 (d, J_{CP} = 3.9 Hz, aryl), 140.5 (s, aryl); EIMS *m/z* 276 (M⁺, 44 %), 167 (M⁺ - PO(OMe)₂, 100 %); HRMS(EI): calcd for C₁₅H₁₇O₃P (M⁺) *m/z* 276.0915, found 276.0922.

Dimethyl 3-phenylbenzylphosphonate (17). Purified using silica gel chromatography (EtOAc/hexane 3:1, $R_f = 0.3$), white solid, mp 46-48 °C, 81 % yield. ¹H NMR: δ 7.44 (m, 9H, aryl), 3.70 (d, $J_{HP} = 10.6$ Hz, 6H, 2(CH₃)), 3.24 (d, $J_{HP} = 21.6$ Hz, 2H, CH₂); ³¹P NMR: δ 26.52; ¹³C NMR: δ 141.5 (s, aryl), 140.7 (s, aryl), 131.7 (d, $J_{CP} = 8.7$ Hz, aryl), 128.9 (d, $J_{CP} = 2.9$ Hz, aryl), 128.6 (s, aryl), 128.4 (t, $J_{CP} = 6.3$ Hz, aryl), 127.3 (s, aryl), 127.0 (s, aryl), 125.7 (d, $J_{CP} = 3.6$ Hz, aryl), 52.8 (d, $J_{CP} = 6.6$ Hz, 2(CH₃)), 32.8 (d, $J_{CP} = 138.4$ Hz, CH₂P); EIMS: *m/z* 276 (M⁺, 100 %), 167 (M⁺ - PO(OMe)₂, 87 %); HRMS(EI): calcd for C₁₅H₁₇O₃P (M⁺) *m/z* 276.0915, found 276.0918.

Dimethyl 2-phenylbenzylphosphonate (18). Purified using silica gel chromatography (EtOAc/hexane 3:1, $R_f = 0.3$), pale yellow oil, 86 % yield. ¹H NMR: δ 7.41 (m, 9H, aryl), 3.57 (d, $J_{HP} = 11.0$ Hz, 6H, 2(CH₃)), 3.21 (d, $J_{HP} = 22.0$ Hz, 2H, CH₂); ³¹P NMR: δ 27.09; ¹³C NMR: δ 142.4 (d, $J_{CP} = 8.8$ Hz, aryl), 140.9 (s, aryl), 130.3 (d, $J_{CP} = 4.4$ Hz, aryl), 129.3 (s, aryl), 128.6 (d, $J_{CP} = 8.8$ Hz, aryl), 128.1 (s, aryl), 127.3 (d, $J_{CP} = 2.9$ Hz, aryl), 127.0 (s, aryl), 126.8 (d, $J_{CP} = 3.6$ Hz, aryl), 52.4 (d, $J_{CP} = 6.6$ Hz, 2(CH₃)), 29.2 (d, $J_{CP} = 138.4$ Hz, CH₂P); EIMS: m/z 276 (M⁺, 99 %), 167 (M⁺ - PO(OMe)₂, 70 %), 165 (M⁺ - 111, 100%); HRMS(EI): calcd for C₁₅H₁₇O₃P (M⁺) m/z 276.0915, found 276.0910.

Dimethyl 3-(2-trimethylsilylethoxymethyl)benzylphosphonate (19). This was prepared by the general procedure described above using 1-bromomethyl-3-(2-trimethylsilylethoxymethyl)benzene in neat trimethyl phosphite (15 eq.) with the exception being that it was heated to 80 °C for 3 days. Purification was accomplished using silica gel chromatography (EtOAc, $R_f = 0.5$), yellow oil, 96 %. ¹H NMR: δ 7.25 (m, 4H, Ar), 4.47 (s, 2H, ArCH₂O), 3.67 (d, J_{HP} = 10.6 Hz, 6H, OCH₃), 3.57 (t, J = 8.3 Hz, 2H, OCH₂C), 3.17 (d, J_{HP} = 22.0 Hz, 2H, CH₂P), 0.99 (t, J = 8.30 Hz, 2H, OCCH₂), 0.03 (s, 9H, SiMe); ³¹P NMR: δ 26.62; ¹³C NMR: δ 139.4 (s, aryl), 131.4 (d, J_{CP} = 7.4 Hz, aryl), 128.8 (s, aryl), 128.7 (s, aryl), 128.5 (d, J_{CP} = 5.5 Hz, aryl), 126.0 (s, aryl), 72.1 (s, ArCH₂O), 67.6 (s, CH₂CH₂Si), 52.53 (d, J_{CP} = 5.5 Hz, CH₃OP), 18.20 (s, CH₂Si), -1.42 (s, SiCH₃); EIMS: *m/z* 287 ((M⁺ + 2H) – 3(CH₃), 67 %), 288 ((M⁺ + 3H) – 3(CH₃), 20 %), 301 ((M⁺ + 1H) - 2(CH₃), 37 %), 315 (M⁺ - CH₃, 8 %); HRMS(EI): calcd for C₁₄H₂₄O₄PSi (M⁺ - CH₃) *m/z* 315.1182, found 315.1171.

Di-t-butyl benzylphosphonate (32). To a stirred suspension of NaH (7.02 mmol, 0.21 g of an 80% dispersion NaH in oil, 1.2 eq.) in dry THF (23 mL) at 0 °C was added a solution of di-tert-butyl phosphite (7.02 mmol, 1.36 g, 1.2 eq.) in dry THF (23 mL) over 5 minutes. After stirring for 30 minutes at 0°C, a solution of benzyl bromide (5.92 mmol, 1.0 g, 1.0 eq.) in dry THF (5 mL) was added over a period of 1 minute. The reaction was allowed to come to room temperature and was stirred for 90 minutes. The reaction was cooled in an ice bath and then quenched by adding cold water dropwise. The resulting clear and colorless solution was transferred to a separatory funnel, and the reaction flask was rinsed with water and CHCl₃. The aqueous layer was extracted with CHCl₃ (3 x 50 mL) and the organic layer was washed with saturated brine and dried (MgSO₄). Upon evaporation of the solvent, the desired product was purified using silica gel chromatography (hexane/EtOAc, 1:1, $R_f = 0.5$), clear, colorless oil, 50 % yield. ¹H NMR: δ 1.37 (s, 18H, CH₃), 2.99 (d, $J_{HP} = 21.2$ Hz, 2H, CH₂), 7.20 (m, 5H, aryl); ³¹P NMR: δ 15.85; ¹³C NMR (50.3 MHz): δ 30.7 (s, C(<u>C</u>H₃)₃), 38.1 (d, $J_{CP} = 142.7$ Hz, CH₂), 82.0 (s, <u>C</u>(CH₃)₃), 126.3 (s, aryl), 128.1 (s, aryl), 129.9 (s, aryl); EIMS: *m*/z 284 (M⁺, 4 %), 173 (M⁺ - 111, 100 %); HRMS(EI): calcd for C₁₅H₂₅PO₃ (M⁺) *m*/z 284.1541, found 284.1534.

4-[(Dimethylphosphono)methyl]phenylacetic acid benzyl ester (33). Purified using silica gel chromatography (EtOAc/hexane, 9:1, $R_f = 0.3$), colorless oil, 91 % yield. ¹H NMR: δ 7.28 (s, 4H aryl), 7.22 (s, 5H, aryl), 5.13 (s, 2H, OCH₂Ph), 3.66 (d, J = 10.3 Hz, 8H, CH₂CO and 2(CH₃)), 3.11 (d, J_{HP} = 21.9 Hz, 2H, CH₂P); ³¹P NMR: δ 26.67; ¹³C NMR: δ 170.9 (s, CO), 135.6 (s, aryl), 132.4 (d, J_{CP} = 4.4 Hz, aryl), 129.9 (d, J_{CP} = 8.8 Hz, aryl), 129.7 (d, J_{CP} = 6.6 Hz, aryl), 129.3 (d, J_{CP} = 2.9 Hz, aryl), {128.3, 128.0, 127.9 (s, aryl)}, 66.3 (s, BnCH₂), 52.6 (d, J_{CP} = 6.6 Hz, 2(CH₃)), 40.7 (s, CH₂), 32.2 (d, J_{CP} = 138.4 Hz, CH₂P); EIMS: *m/z* 348 (M⁺, 19 %), 213 (M⁺ - OOCCH₂Ph, 100 %); HRMS(EI): calcd for C₁₈H₂₁O₅P (M⁺) *m/z* 348.1127, found 348.1128.

4-[(Dimethylphosphono)methyl]phenylacetic acid (34). A mixture of 33 (175 mg, 0.5 mmol) and approximately 10 mg of 10 % Pd/C, in ethyl acetate (10 mL), was stirred for 15 h under H₂ (1 atm.). The mixture was filtered through celite and concentrated by rotary evaporation to give 101 mg (78 % yield, mp 111-113 °C) of 34 as a white solid. No further purification was necessary. ¹H NMR: δ 7.24 (s, 4H, aryl), 3.67 (d, J_{HP} = 11.7 Hz, 6H, 2(CH₃)), 3.61 (s, 2H, CH₂CO), 3.16 (d, J_{HP} = 21.9 Hz, 2H, CH₂); ³¹P NMR: δ 27.14; ¹³C NMR: δ 174.8 (s, CO), 132.9 (d, J_{CP} = 3.7 Hz, aryl), 129.7 (d, J_{CP} = 6.6 Hz, aryl), 129.5 (d, J_{CP} = 3.7 Hz, aryl), 129.4 (s, aryl), 53.0 (d, J_{CP} = 6.6 Hz, 2(CH₃)), 40.7 (s, <u>CH₂CO</u>), 32.1 (d, J_{CP} = 139.1 Hz, CH₂P); EIMS:²⁶ *m/z* 258 (M⁺, 5%), 272 (M⁺ + CH₃, 9 %), 214 (M⁺ - CO₂, 99%), 149 (M⁺ - PO(OMe)₂, 55 %); HRMS(EI): calcd for C₁₁H₁₅O₅P (M⁺) *m/z* 258.0657, found 258.0657. 4,4'-Bis[(dimethylphosphono)methyl]biphenyl (44). Purified using silica gel chromatography (MeOH/CHCl₃, 2:98, $R_f = 0.3$), white solid, mp 128-130°C, 47% yield. ¹H NMR: δ 3.21 (d, $J_{HP} = 21.6$, 4H, 2(CH₂)), 3.71 (d, $J_{HP} = 10.6$ Hz, 12H, 4(CH₃)), 7.37 (dd, J = 8.0 Hz, 2.4 Hz, 4H, aryl), 7.54 (d, J = 7.7 Hz, 4H, aryl); ³¹P NMR: δ 26.56; ¹³C NMR: δ 32.5 (d, $J_{CP} = 138.6$ Hz, 2(CH₂)), 52.9 (d, $J_{CP} = 6.9$ Hz, 4(CH₃)), 127.1 (s, aryl), 130.0 (d, $J_{CP} = 6.8$ Hz, aryl), 130.2 (d, $J_{CP} = 9.8$ Hz, aryl), 139.23 (s, aryl); EIMS *m*/z 398 (M⁺, 76%), 289 (M⁺ - PO(OMe)₂, 100%); HRMS(EI): calcd for C₁₈H₂₄P₂O₆ (M⁺) *m*/z 398.1048, found 398.1055.

1,1'-Bis[4-((dimethylphosphono)methyl)benzene]methane (45). Purified using silica gel chromatography (MeOH/CHCl₃, 5:95, $R_f = 0.3$), yellow oil, 76% yield. ¹H NMR: δ 3.13 (d, $J_{HP} = 21.6$ Hz, 4H, 2(CH₂P)), 3.67 (d, $J_{HP} = 11.0$ Hz, 12H, 4(CH₃)), 3.93 (s, 2H, ArCH₂Ar), 7.20 (m, 8H, aryl); ³¹P NMR: δ 26.79; ¹³C NMR: δ 32.3 (d, $J_{CP} = 138.6$ Hz, 2(CH₂P)), 41.0 (s, ArCH₂Ar), 52.8 (d, $J_{CP} = 6.8$ Hz, 4(CH₃)), 128.8 (d, $J_{CP} = 9.8$ Hz, aryl), 129.1 (s, aryl), 129.7 (d, $J_{CP} = 6.8$ Hz, aryl), 139.6 (s, aryl); EIMS: *m/z* 412 (M⁺, 100 %), 303 (M⁺ - PO(OMe)₂, 38 %), 194 (M⁺ - 2(PO(OMe)₂), 16 %), 193 (M⁺ - 219, 65 %); HRMS(EI): calcd for C₁₉H₂₆P₂O₆ (M⁺) *m/z* 412.1205, found 412.1216.

1,4'-Bis[4-((dimethylphosphono)methyl)benzene]butane (46). Purified using silica gel chromatography (MeOH/CHCl₃, 2:98, R_f = 0.3), white solid, mp 88-90°C, 69% yield. ¹H NMR: δ 1.63 (m, 4H, CH₂CH₂CH₂CH₂), 2.60 (bt, 4H, 2(ArCH₂)), 3.13 (d, J_{HP} = 21.2 Hz, 4H, 2(CH₂P)), 3.66 (d, J_{HP} = 11.0 Hz, 12H, 4(CH₃)), 7.15 (m, 8H, aryl); ³¹P NMR: δ 26.90; ¹³C NMR: δ 30.9 (s, 2(CH₂)), 31.9 (d, J_{CP} = 138.6 Hz, 2(CH₂P)), 35.3 (s, 2(ArCH₂)), 52.8 (d, J_{CP} = 6.8 Hz, 4(CH₃)), 128.3 (d, J_{CP} = 8.8 Hz, aryl), 128.7 (d, J_{CP} = 2.9 Hz, aryl), 129.5 (d, J_{CP} = 6.9 Hz, aryl), 141.2 (d, J_{CP} = 3.9 Hz, aryl); EIMS *m*/z 454 (M⁺, 100 %), 227 (M⁺ - (CH₂)₂PhCH₂PO(OMe)₂, 66 %); HRMS(EI): calcd for C₂₂H₃₂P₂O₆ (M⁺) *m*/z 454.1674, found 454.1684.

4,4'-Bis[(dimethylphosphono)methyl]benzophenone (47). Purified using silica gel chromatography (MeOH/CHCl₃, 0.5:9.5, $R_f = 0.2$), white solid, mp 91-93 °C, 61 % yield. ¹H NMR: δ 7.76 (d, J = 8.5 Hz, 4H aryl), 7.43 (d, J = 2.2 Hz, 4H, aryl), 3.71 (d, J_{HP} = 11.0 Hz, 12H, 4(CH₃)), 3.25 (d, J_{HP} = 22.0 Hz, 4H, 2(CH₂)); ³¹P NMR: δ 25.48; ¹³C NMR: δ 195.3 (s, CO), 136.1 (d, J_{CP} = 9.5 Hz, aryl), 135.9 (d, J_{CP} = 2.9 Hz, aryl), 130.1 (d, J_{CP} = 2.9 Hz, aryl), 129.4 (d, J_{CP} = 6.6 Hz, aryl), 52.7 (d, J_{CP} = 6.6 Hz, 4(CH₃)), 32.7 (d, J_{CP} = 137.7 Hz, 2(CH₂)); EIMS: *m/z* 426 (M⁺, 55 %), 317 (M⁺ - PO(OMe)₂, 21 %), 227 (M⁺ - PhCH₂PO(OMe)₂, 100 %); HRMS(EI): calcd for C₁₉H₂₄O₇P₂ (M⁺) *m/z* 426.0997, found 426.0986.

Preparation of α, α -Difluoromethylenephosphonates

With the exception of 31, all fluorination reactions were performed as described below.

General Procedure for the Preparation of α, α -Difluoromethylenephosphonates. To a solution of NaHMDS (Aldrich, 1.0 M in THF, 2.2 eq.) in dry THF (approximately 0.4 mL NaHMDS/mL THF) at -78 °C was added a solution of the benzylic phosphonates (1.0 eq.) in dry THF (approximately 15-20 mL THF/mmol phosphonate) over a period of 2 minutes. The resulting orange to dark red solution (sometimes a suspension forms) was stirred for 1 h at -78 °C. A solution of NFBS (Aldrich, 2.5 eq.) in dry THF (approximately 2-4 mL THF/mmol NFBS) was added over a period of two minutes, during which time the solution (suspension becomes a solution) turned from dark red or orange to yellow-brown. After addition, the solution was stirred for 1-2 hours and then allowed to warm to -30 °C during which time a precipitate formed. The reaction was quenched with 0.01 N HCl and the resulting solution (precipitate dissolves) was extracted with EtOAc. The organics were combined and washed with 5 % NaHCO₃, brine, dried (MgSO₄) and concentrated by rotary evaporation to give a yellow oil which was purified via flash chromatography. For the formation of bis-difluoromethylenephosphonate derivatives, **42**, **43** and **48-51**, 5.5 eq. NaHMDS and 7.3 eq. NFBS were used.

[(Diethylphosphono)difluoromethyl]benzene (7). Purified using silica gel chromatography (EtOAc/hexane, 3:2, $R_f = 0.5$), colorless oil, 79 % yield. ¹H NMR: δ 7.64 (m, 2H, aryl), 7.48 (m, 2H, aryl), 4.18 (m, 4H, 2(CH₂)), 1.43 (t, J = 7.1 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 4.36 (t, J_{PF} = 116.0 Hz); ¹⁹F NMR: δ -32.6 (d, J_{FP} = 116.0 Hz); ¹³C NMR: δ 132.5 (td, J_{CF} = 21.9 Hz, J_{CP} = 13.9 Hz, aryl), 130.6 (s, aryl), 128.3 (s, aryl), 126.1 (td, J_{CF} = 7.3 Hz, J_{CP} = 2.2 Hz, aryl), 117.9 (td, J_{CF} = 262.3 Hz, J_{CP} = 218.2 Hz, CF₂), 64.7 (d, J_{CP} = 7.4 Hz, 2(CH₂)), 16.2 (d, J_{CP} = 5.8 Hz, 2(CH₃)); EIMS: *m*/z 264 (M⁺, 20 %), 127 (M⁺ – PO(OEt)₂, 100 %); HRMS(EI): calcd for C₁₀H₁₃O₄F₂P (M⁺) *m*/z 264.0727, found 264.0726.

[(Dimethylphosphono)difluoromethyl]benzene (20). Purified using silica gel chromatography (hexane/EtOAc, 7:3, $R_f = 0.3$), colorless oil, 63% yield. ¹H NMR: δ 3.78 (d, $J_{HP} = 10.6$ Hz, 6H, 2(CH₃)), 7.50 (m, 5H, aryl); ³¹P NMR: δ 6.52 (t, $J_{PF} = 116.7$ Hz); ¹⁹F NMR: δ -31.6 (d, $J_{FP} = 116.7$ Hz); ¹³C NMR: δ 54.92 (m, OCH₃), 118.3 (td, $J_{CF} = 263.4$, $J_{CP} = 218.8$ Hz, CF₂P), 126.1 (td, $J_{CF} = 6.8$ Hz, $J_{CP} = 2.4$ Hz, aryl), 128.5 (bs, aryl), 130.9 (d, $J_{CP} = 1.4$ Hz), 132.3 (td, $J_{CF} = 22.0$ Hz, $J_{CP} = 13.9$ Hz, aryl); EIMS: *m/z* 236 (M⁺, 14 %), 127 (M⁺ - PO(OMe)₂, 100 %); HRMS(EI) calcd for C₉H₁₁F₂PO₃ (M⁺) *m/z* 236.0414, found 236.0424.

4-[(Dimethylphosphono)difluoromethyl]nitrobenzene (21). Purified using silica gel chromatography (EtOAc/hexane, 1:1, $R_f = 0.5$), pale yellow solid, 74 % yield. ¹H NMR: δ 8.05 (d, J = 8.4 Hz, 2H, aryl), 7.82 (d, J = 7.7 Hz, 2H, aryl), 3.89 (d, J_{HP} = 10.7 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 5.37 (t, J_{PF} ~ 110 Hz); ¹⁹F NMR: δ -32.7 (d, J_{FP} ~ 110 Hz); ¹³C NMR: δ 149.4 (s, aryl), 138.4 (td, J_{CF} = 22.7 Hz, J_{CP} = 13.9 Hz, aryl), 127.5 (td, J_{CF} = 6.6 Hz, J_{CP} = 2.2 Hz, aryl), 123.6 (s, aryl), 117.3 (td, J_{CF} = 265.0 Hz, J_{CP} = 217.0 Hz, CF₂), 55.2 (d, J_{CP} = 6.6 Hz, 2(CH₃)); EIMS: *m*/z 281 (M⁺, 18 %), 171 (M⁺ - PO(OMe)₂, 33 %) 109 (M⁺ - 172, 100%); HRMS(EI): calcd for C₁₀H₁₃O₄F₂P (M⁺) *m*/z 281.0264, found 266.0274.

4-[(Diethylphosphono)difluoromethyl]nitrobenzene (22). Purified using silica gel chromatography (EtOAc/hexane, 2:3, $R_f = 0.4$), off-white solid, mp 51-53 °C, 82 % yield. ¹H NMR: δ 8.32 (d, J = 9.1 Hz, 2H, aryl), 7.82 (d, J = 8.5 Hz, 2H, aryl), 4.25 (m, 4H, 2(OCH₂)), 1.35 (t, J_{HP} = 6.9 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 3.08 (t, J_{PF} ~ 110 Hz); ¹⁹F NMR: δ -33.5 (d, J_{FP} ~ 110 Hz); ¹³C NMR: δ 149.2 (s, aryl), 138.8 (td, J_{CF} = 22.1 Hz, J_{CP} = 13.4 Hz, aryl), 127.6 (td, J_{CF} = 6.7 Hz, J_{CP} = 1.9 Hz, aryl), 123.5 (s, aryl), 117.1 (td, J_{CF} = 264.2 Hz, J_{CP} = 216.0 Hz, CF₂), 65.1 (d, J_{CP} = 6.7 Hz, 2(CH₂)), 16.2 (d, J_{CP} = 4.8 Hz, 2(CH₃)); EIMS: *m/z* 310 (MH⁺, 7 %), 173 (MH⁺ - PO(OEt)₂, 10 %), 109 (MH⁺ - 201, 100 %); HRMS(EI): calcd for C₁₁H₁₄NO₅F₂P (M⁺) *m/z* 309.0578, found 309.0577.

4-[(Dimethylphosphono)difluoromethyl]bromobenzene (23). Purified using silica gel chromatography (EtOAc/hexane, 3:7, $R_f = 0.3$), colorless oil, 79 % yield. ¹H NMR: δ 7.60 (d, J = 8.8 Hz, 2H, aryl), 7.48 (d, J = 8.5 Hz, 2H, aryl), 3.83 (d, J_{HP} = 10.6 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 6.02 (t, J_{PF} ~ 116 Hz); ¹⁹F NMR: δ -32.1 (d, J_{FP} ~ 116 Hz); ¹³C NMR: δ 131.7 (s, aryl), 131.5 (m, aryl), 127.7 (td, J_{CF} = 6.6 Hz, J_{CP} = 2.2 Hz, aryl), 125.5 (s, aryl), 117.7 (td, J_{CF} = 263.4 Hz, J_{CP} = 219.2 Hz, CF₂), 54.8 (d, J_{CP} = 6.6 Hz, 2(CH₃)); EIMS: m/z 316 (M⁺{⁸¹Br}, 18 %), 207 (M⁺{⁸¹Br} - PO(OMe)₂, 99 %), 314 (M⁺{⁷⁹Br}, 19 %), 205 (M⁺{⁷⁹Br} - PO(OMe)₂, 100 %); HRMS(EI): calcd for C₉H₁₀O₃F₂BrP (M⁺) m/z 315.9499 & 313.9519, found 315.9511 & 313.9533.

4-[(Diethylphosphono)difluoromethyl]bromobenzene (24). Purified using silica gel chromatography (EtOAc/hexane, 3:7, $R_f = 0.5$), pale yellow oil, 80 % yield. ¹H NMR: δ 7.60 (d, J = 8.8 Hz, 2H, aryl), 7.49 (d, J = 7.3 Hz, 2H, aryl), 4.21 (m, 4H, 2(CH₂)), 1.33 (t, J_{HP} = 7.4 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 3.73 (t, J_{PF} = 114.5 Hz); ¹⁹F NMR: δ -32.6 (d, J_{FP} = 114.5 Hz); ¹³C NMR: δ 131.6 (s, aryl), 131.5 (m, aryl), 127.8 (td, J_{CF} = 6.8 Hz, J_{CP} = 2.2 Hz, aryl), 125.3 (d, J = 2.2 Hz, aryl), 117.6 (td, J_{CF} = 263.5 Hz, J_{CP} = 218.5 Hz, CF₂), 64.7 (d, J_{CP} = 6.6 Hz, 2(CH₂)), 16.2 (d, J_{CP} = 5.8 Hz, 2(CH₃)); EIMS: *m*/z 344 (M⁺{⁸¹Br}, 11 %), 207 (M⁺{⁸¹Br} - PO(OEt)₂, 93 %), 109 (M⁺{⁸¹Br} - 235, 100 %), 342 (M⁺{⁷⁹Br}, 11 %), 205 (M⁺{⁷⁹Br} - PO(OEt)₂, 96 %), 109 (M⁺{⁷⁹Br} - 233, 100 %); HRMS(EI): calcd for C₁₁H₁₄O₃F₂BrP *m*/z 341.9832, (M⁺ {⁷⁹Br}) found 341.9819.

Benzyl 4-[(dimethylphosphono)difluoromethyl]benzoate (25). Purified using silica gel chromatography (EtOAc/hexane, 2:3, $R_f = 0.6$), colorless oil, 72 % yield. ¹H NMR: δ 8.17 (d, J = 8.0 Hz, 2H, aryl), 7.70 (d, J = 8.4 Hz, 2H, aryl), 7.40 (m, 5H aryl), 5.39 (s, 2H, OCH₂), 3.84 (d, J_{HP} = 10.6 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 6.01 (t, J_{PF} = 112.9 Hz); ¹⁹F NMR: δ -32.5 (d, J_{PF} = 112.9 Hz); ¹³C NMR: δ 165.4 (s, CO), 137.7 (m, aryl), {135.6, 132.4, 129.8, 128.6, 128.4, 128.2 (s, aryl)}, 126.3 (t, J_{CF} = 5.8 Hz, aryl), 117.6 (td, J_{CF} = 264.0 Hz, J_{CP} = 216.9 Hz, CF₂), 67.1 (s, CH₂), 55.0 (d, J_{CP} = 5.9 Hz, 2(CH₃)); EIMS: *m*/z 370 (M⁺, 5 %), 263 (M⁺ -

OCH₂Ph, 100 %), 261 (M⁺ - PO(OMe)₂, 29 %); HRMS(EI): calcd for $C_{17}H_{17}O_5F_2P$ (M⁺) *m/z* 370.0782, found 370.0782.

4-[(Dimethylphosphono)difluoromethyl]methoxybenzene (26). Purified using silica gel chromatography (EtOAc/hexane, 1:1, $R_f = 0.45$), colorless oil, 80 % yield. ¹H NMR: δ 7.51 (d, J = 8.1 Hz, 2H, aryl), 6.92 (d, J = 8.7 Hz, 2H, aryl), 3.76 (d, 9H, OCH₃ and 2(POCH₃)); ³¹P NMR: δ 6.78 (t, J_{PF} = 120.6 Hz); ¹⁹F NMR: δ -30.4 (d, J = 120.6 Hz); ¹³C NMR: δ 161.5 (s, aryl), 127.6 (td, J_{CF} = 6.6 Hz, J_{CP} = 1.2 Hz, aryl), 124.3 (td, J_{CF} = 22.7 Hz, J_{CP} = 13.9 Hz, aryl), 118.3 (td, J_{CF} = 263.7 Hz, J_{CP} = 221.9, CF₂), 55.3 (s, ArOCH₃), 54.8 (d, J_{CP} = 7.4, 2(POCH₃)); EIMS: *m*/z 266 (M⁺, 10 %), 157 (M⁺ – PO(OMe)₂, 100 %); HRMS(EI): calcd for C₁₀H₁₃O₄F₂P (M⁺) *m*/z 266.0519, found 266.0511.

4-[(Diethylphosphono)difluoromethyl]benzophenone (27). Purified using silica gel chromatography (EtOAc/CH₂Cl₂, 0.5:9.5, R_f = 0.7), colorless oil, 70 % yield. ¹H NMR: δ 7.81 (m, 6H, aryl), 7.53 (m, 3H, aryl), 4.21 (m, 4H, 2(CH₂)), 1.31 (t, J_{HP} = 6.9 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 3.69 (t, J_{PF} = 113.7 Hz); ¹⁹F NMR: δ -32.9 (d, J_{FP} = 113.7 Hz); ¹³C NMR: δ 195.6 (s, CO), 139.6 (s, aryl), 136.8 (s, aryl), 136.2 (td, J_{CF} = 21.8 Hz, J_{CP} = 13.7 Hz, aryl), {132.7, 129.9, 129.7, 128.3 (s, aryl)}, 126.2 (t, J_{CF} = 6.6 Hz, aryl), 117.6 (td, J_{CF} = 263.8 Hz, J_{CP} = 217.3 Hz, CF₂), 64.8 (d, J_{CP} = 7.3 Hz, 2(CH₂)), 16.1 (d, J_{CP} = 5.9 Hz, 2(CH₃)); EIMS: *m*/z 368 (M⁺, 100 %), 231 (M⁺ - PO(OEt)₂, 96 %); HRMS(EI): calcd for C₁₈H₁₉O₄F₂P (M⁺) *m*/z 368.0989, found 368.0978.

4-[4-((Dimethylphosphono)difluoromethyl)phenyl]benzene (28). Purified using silica gel chromatography (hexane/EtOAc 7:3, R_f = 0.3), white solid, mp 75-78°C, 59% yield. ¹H NMR: δ 3.87 (d, J_{HP} = 10.2 Hz, 6H, 2(CH₃)), 7.60 (m, 9H, aryl); ³¹P NMR: δ 6.64 (t, J_{PF} ~ 117 Hz); ¹⁹F NMR: δ -31.3 (d, J_{FP} ~ 117 Hz); ¹³C NMR: δ 54.9 (d, J_{CP} = 6.6 Hz, 2(CH₃)), 118.3 (td, J_{CF} = 263.4, J_{CP} = 219.4 Hz, CF₂), 126.6 (td, J_{CF} = 6.6 Hz, J_{CP} = 2.2 Hz, aryl), 127.3 (broad dd, aryl), 128.0 (s, aryl), 128.9 (s, aryl), 131.2 (td, aryl), 140.0 (s, aryl), 143.8 (d, J_{CP} = 2.2 Hz, aryl); EIMS: *m/z* 312 (M⁺, 19 %), 203 (M⁺ - PO(OMe)₂, 100 %); HRMS(EI): calcd for C₁₅H₁₅F₂O₃P (M⁺) *m/z* 312.0727, found 312.0730.

3-[4-((Dimethylphosphono)difluoromethyl)phenyl]benzene (29). Purified using silica gel chromatography (EtOAc/hexane, 1:1, R_f = 0.5) colorless oil, 60 % yield. ¹H NMR: δ 7.61 (m, 9H, aryl), 3.86 (d, J_{HP} = 10.2 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 6.60 (t, J_{PF} ~ 117 Hz); ¹⁹F NMR: δ -31.4 (d, J_{FP} ~ 117 Hz); ¹³C NMR: δ 141.7 (s, aryl), 140.0 (s, aryl), 133.0 (td, J_{CF} = 22.0 Hz, J_{CP} = 13.9 Hz, aryl), {129.6, 129.0, 128.9, 127.8, 127.2 (s, aryl)}, 124.8 (m, aryl), 118.2 (td, J_{CF} = 263.6 Hz, J_{CP} = 218.2 Hz, CF₂), 54.8 (d, J_{CP} = 6.6 Hz, 2(CH₃)); EIMS: m/z 312 (M⁺, 39 %), 203 (M⁺ - PO(OMe)₂, 100 %), 183 (M⁺ - 129, 20 %); HRMS(EI): calcd for C₁₅H₁₅O₃F₂P (M⁺) m/z 312.0727, found 312.0744.

2-[4-((Dimethylphosphono)difluoromethyl)phenyl]benzene (30). Purified using silica gel chromatography (EtOAc/hexane, 1:1, $R_f = 0.5$), colorless oil, 46 % yield. ¹H NMR: δ 7.50 (m, 9H, aryl), 3.73 (d, J = 10.2 Hz, 6H, 2(CH₃)); ³¹P NMR: δ 6.49 (t, $J_{PF} \sim 117.5$ Hz); ¹⁹F NMR: δ -22.0 (d, $J_{FP} \sim 117.5$ Hz); ¹³C NMR: δ 141.7 (m, aryl), {141.1, 132.7, 130.2, 129.4 (s, aryl)}, 128.0 (bt, aryl), {127.3, 127.1, 127.0 (s, aryl)}, 119.6 (td, $J_{CF} = 265.3$ Hz, $J_{CP} = 218.5$ Hz, CF_2), 54.8 (d, $J_{CP} = 6.6$ Hz, 2(CH₃)); EIMS: *m/z* 312 (M⁺, 37 %), 203 (M⁺ - PO(OMe)₂, 76 %), 183 (M⁺ - 129, 100 %); HRMS(EI): calcd for C₁₅H₁₅O₃F₂P (M⁺) *m/z* 312.0727, found 312.0740.

4-f(Dimethylphosphono)difluoromethyl]-3-(2-trimethylsilylethoxymethyl)benzene (31). To a solution containing 18 (0.432 g, 1.31 mmol, 1.0 eq.) in dry THF (15 mL), was added NaHMDS (3 mL, 1.0 M in THF, 3.0 mmol, 2.3 eq.) in THF (10 mL) over a period of 20 minutes at -78°C. The mixture was stirred for 1 h at this temperature and then NFBS (1.03 g, 3.27 mmol, 2.5 eq.) in THF (15 mL) was added over 15 minutes. The mixture was warmed to room temperature and stirred for 2 h. Water (20 mL) was added followed by methylene chloride (3 x 20 mL). The organic layer was separated and dried (MgSO₄) and the solvent was evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:2, $R_f = 0.5$) to yield a colorless oil. NMR analysis of the chromatographed material indicated that a small amount (5-6 % as determined by ¹⁹F NMR) of an unidentified impurity was present (0.41g, 79 % yield of the desired product). We were unable to obtain clean product even after repeated columns. ¹H NMR: δ 7.50 (m, 4H, aryl), 4.51 (s, 2H, ArCH₂O), 3.85 (d, J_{HP} = 10.6 Hz, 2H, OCH₃), 3.58 (t, J = 8.3 Hz, 2H, OCH₂C), 0.99 (t, J = 8.3 Hz, 2H, CH₂Si), 0.01 (s, 9H, SiCH₃); 31 P NMR: δ 6.56 (t, J_{PF} ~ 117 Hz); 19 F NMR: δ -31.6 (d, J_{FP} ~ 117 Hz); 13 C NMR (50.3 MHz): δ 139.7 (s, aryl), 131.1 (td, J_{CF} = 21.9 Hz, J_{CP} = 14.6 Hz, aryl), {129.7, 128.4, 125.2, 125.0, 124.9 (s, aryl)}, 118.2 (td, J_{CF} = 262.6 Hz, J_{CF} = 219.0 Hz, CF₂), 71.7 (Ph<u>C</u>H₂O), 67.8 (O<u>C</u>H₂CSi), 54.6 (d, J_{CP} = 7.3 Hz, OCH₃), 18.2 (CH₂Si), -1.5 (SiCH₃); EIMS: m/z 351 (M⁺ - CH₃, 8 %), 337 (M⁺ - 2CH₃ + 1H, 12%), 323 (M⁺ - 3(CH₃) + 2H, 37%); HRMS(EI): calcd for $C_{14}H_{22}F_2O_4PSi$ (M⁺ - CH₃) m/z 351.0993, found 351.0975.

1,3-Bis[(dimethylphosphono)difluoromethyl]benzene (42). Purified using silica gel chromatography (EtOAc/hexane, 4:1, $R_f = 0.35$), colorless oil, 46 % yield. ¹H NMR: δ 7.75 (m, 4H, aryl), 3.80 (m, 12H, 4(CH₃)); ³¹P NMR: δ 5.83 (t, $J_{PF} \sim 115$ Hz); ¹⁹F NMR: δ -32.2 (d, $J_{FP} \sim 115$ Hz); ¹³C NMR: δ 133.0 (td, $J_{CF} = 22.7$ Hz, $J_{CP} = 15.0$ Hz, aryl), 129.0 (aryl), 128.7 (t, $J_{CF} = 6.6$ Hz, aryl), 123.9 (m, aryl), 117.6 (td, $J_{CF} = 264.4$ Hz, $J_{CP} = 218.2$ Hz, 2(CF₂)), 55.0 (d, $J_{CP} = 6.6$ Hz, CH₃); EIMS: *m/z* 394 (M⁺, 10 %), 285 (M⁺ - PO(OMe)₂, 100 %); HRMS(EI): calcd for C₁₂H₁₆O₆F₄P₂ (M⁺) *m/z* 394.0358, found 450.0365.

l,3-Bis[(diethylphosphono)difluoromethyl]benzene (43). Purified using silica gel chromatography (EtOAc/hexane, 4:1, $R_f = 0.5$), colorless oil, 74 % yield. ¹H NMR: δ 7.75 (m, 4H, aryl), 4.15 (m, 8H,

4(CH₂)), 1.28 (t, J = 6.9 Hz, 12H, 4(CH₃)); ³¹P NMR: δ 3.66 (t, J_{PF} = 115.5 Hz); ¹⁹F NMR: δ -33.0 (d, J_{FP} = 115.5 Hz); ¹³C NMR: δ 133.3 (td, J_{CF} = 22.7 Hz, J_{CP} = 14.7 Hz, aryl), 128.7 (s, aryl), 123.9 (t, J_{CF} = 7.3 Hz, aryl), 117.4 (td, J_{CF} = 263.6 Hz, J_{CP} = 218.2 Hz, 2(CF₂)), 64.8 (d, J_{CP} = 6.6 Hz, 4(CH₂)), 16.2 (d, J_{CP} = 5.8 Hz, 4(CH₃)); EIMS: *m*/z 451 (MH⁺, 35 %), 313 (MH⁺ – PO(OEt)₂, 100 %); HRMS(EI): calcd for C₁₆H₂₄O₆F₄P₂ (M⁺) *m*/z 450.0984, found 450.0990.

4,4'-Bis[(dimethylphosphono)difluoromethyl]biphenyl (48). Purified using silica gel chromatography (hexane/EtOAc, 1:4, $R_f = 0.45$), white crystalline solid, mp 92-94°C, 21% yield. ¹H NMR: δ 3.85 (d, $J_{HP} = 10.6$ Hz, 12H, 4(CH₃)), 7.69 (m, 8H, aryl); ³¹P NMR: δ 6.41 (t, $J_{PF} = 116.7$ Hz); ¹⁹F NMR: δ -31.8 (d, $J_{FP} = 116.7$ Hz); ¹³C NMR: δ 55.0 (d, $J_{CP} = 6.8$ Hz, 4(CH₃)), 118.2 (td, $J_{CF} = 262.8$ Hz, $J_{CP} = 218.9$ Hz, 2(CF₂)), 126.8 (td, $J_{CF} = 3.9$ Hz, $J_{CP} = 2.0$ Hz, aryl), 127.4 (s, aryl), 132.0 (td, $J_{CF} = 22.4$ Hz, $J_{CP} = 13.7$ Hz, aryl), 142.5 (s, aryl); EIMS: m/z 470 (M⁺, 14 %), 361 (M⁺ - PO(OMe)₂, 100 %), 252 (M⁺ - 2(-PO(OMe)₂), 39 %); HRMS(EI): calcd for C₁₈H₂₀F₄O₆P₂ (M⁺) m/z 470.0671, found 470.0678.

l, *l*'-Bis[4-((dimethylphosphono)difluoromethyl)benzene]methane (49). Purified using silica gel chromatography (hexane/EtOAc, 1:4, $R_f = 0.3$), yellow oil, 16.5% yield. ¹H NMR: δ 3.83 (d, $J_{HP} = 10.3$ Hz, 12H, 4(CH₃)), 4.06 (s, 2H, CH₂), 7.27 (d, J = 8.1 Hz, 4H, aryl), 7.55 (d, J = 8.1 Hz, 4H, aryl); ³¹P NMR: δ 6.58 (t, $J_{PF} \sim 117$ Hz); ¹⁹F NMR: δ -31.4 (d, $J_{FP} \sim 117$ Hz); ¹³C NMR: δ 41.4 (s, CH₂), 54.9 (d, $J_{CP} = 6.9$ Hz, 4(CH₃)), 118.1 (td, $J_{CF} = 262.5$, $J_{CP} = 219.6$ Hz, 2(CF₂)), 126.3 (td, $J_{CF} = 6.8$ Hz, $J_{CP} = 2.9$ Hz, aryl), 129.1 (weak td, aryl), 130.4 (weak td, aryl), 143.13 (s, aryl); EIMS *m*/z 484 (M⁺, 14 %), 375 (M⁺ - PO(OMe)₂, 100.0%), 266 (M⁺ - 2(-PO(OMe)₂), 13.0%); HRMS(EI): calcd for C₁₉H₂₂F₄O₆P₂ (M⁺) *m*/z 484.0828, found 484.0804.

1,4 '-*Bis*[4-((dimethylphosphono)difluoromethyl)benzene]butane (50). Purified using silica gel chromatography (hexane/EtOAc, 1:4, $R_f = 0.35$), white solid, mp 99-101°C, 64% yield. ¹H NMR: δ 1.66 (bs, 4H, CH₂), 2.67 (bt, 4H, CH₂), 3.82 (d, $J_{HP} = 10.2$ Hz, 12H, 4(CH₃)), 7.25 (d, J = 7.4 Hz, 4H, aryl), 7.52 (d, J = 7.3 Hz, 4H, aryl); ³¹P NMR: δ 6.75 (t, $J_{PF} = 118.3$ Hz); ¹⁹F NMR: δ -31.0 (d, $J_{FP} = 118.3$ Hz); ¹³C NMR: δ 30.7 (s, 2(CH₂)), 35.5 (s, 2(CH₂)), 54.8 (d, $J_{CP} = 7.4$ Hz, 4(CH₃)), 118.3 (td, $J_{CF} = 262.9$ Hz, $J_{CP} = 219.7$ Hz, 2(CF₂)), 126.1 (td, $J_{CF} = 7.3$ Hz, $J_{CP} = 2.2$ Hz, aryl), 128.6 (s, aryl), 129.9 (td, $J_{CF} = 21.9$ Hz, $J_{CP} = 13.1$ Hz, aryl), 145.5 (s, aryl); EIMS: *m/z* 526 (M⁺, 12 %), 417 (M⁺ - PO(OMe)₂, 13 %), 308 (M⁺ - 2(PO(OMe)₂), 9 %), 93 (M⁺ - 433, 100 %); HRMS(EI): calcd for C₂₂H₂₈F₄O₆P₂ (M⁺) *m/z* 526.1297, found 526.1319.

4,4'-Bis[(dimethylphosphono)difluoromethyl]benzophenone (51). Purified using silica gel chromatography (EtOAc, $R_f = 0.6$), off-white solid, mp 114-116 °C, 28 % yield. ¹H NMR: δ 7.89 (d, J = 8.4 Hz, 4H, aryl), 7.76 (d, J = 8.0 Hz, 4H, aryl), 3.89 (d, J_{HP} = 10.7 Hz, 12H, 4(CH₃)); ³¹P NMR: δ 5.89 (t, J_{PF} ~

113 Hz); ¹⁹F NMR: δ -32.4 (d, J_{FP} ~ 113 Hz); ¹³C NMR: δ 194.9 (s, CO), 139.0 (s, aryl), 136.5 (td, J_{CF} = 22.1 Hz, J_{CP} = 13.4 Hz, aryl), 130.0 (s, aryl), 126.4 (t, J_{CF} = 5.3 Hz, aryl), 117.7 (td, J_{CF} = 263.9 Hz, J_{CP} = 217.8 Hz, 2(CF₂)), 55.1 (d, J_{CP} = 6.7 Hz, 4(CH₃)); EIMS: *m/z* 498 (M⁺, 41 %), 389 (M⁺ - PO(OMe)₂, 100 %) 280 (M⁺ - 2(-PO(OMe)₂), 6 %); HRMS(EI): calcd for C₁₉H₂₀O₇F₄P₂ (M⁺) *m/z* 498.0620, found 498.0601.

Preparation of Ammonium Salts of α , α -Difluoromethylenephosphonic acids.

Deprotection of α, α -difluoromethylenephosphonate esters was accomplished using the general procedure described below.

General procedure for the deprotection of α, α -difluoromethylenephosphonate esters. To a solution of the α, α -difluoromethylenephosphonate ester in dry CH₂Cl₂ (approximately 1 mL CH₂Cl₂/0.1 mmol phosphonate) was added TMSBr (approximately 1.5 equivalents of TMSBr per methyl or ethyl group). The solution was stirred at room temperature for 12 hours (for methyl esters) or at reflux for 36 hours (for ethyl esters). The solution was concentrated and the residue subjected to high vacuum for several hours. The residue was dissolved in CH₂Cl₂ (approximately 1 mL CH₂Cl₂/0.1 mmol phosphonate) and a solution of NH₄HCO₃ (2 equivalents per silyl ester moiety) in water (approximately 15 mL water/gram NH₄HCO₃) was added. The biphasic mixture was stirred vigorously for 30-60 minutes and the CH₂Cl₂ layer removed by rotary evaporation. The aqueous layer was then lyophilized several times (3-4 times) leaving the desired α, α -difluoromethylenephosphonic acids as their ammonium salts (white fluffy powders) in near quantitative yields.

α,α-Difluorobenzylphosphonic acid, ammonium salt (52). Prepared using the general procedure from 20. ¹H NMR: δ 7.62 (m, 2H, aryl), 7.49 (m, 3H, aryl); ³¹P NMR: δ 5.83 (t, $J_{PF} = 91.6$ Hz); ¹⁹F NMR: δ -27.5 (d, $J_{FP} = 93.8$ Hz); ¹³C NMR: δ 137.2 (btd, aryl), 130.4 (s, aryl), 129.0 (s, aryl), 126.7 (bt, aryl), 122.8 (td, CF₂); FABMS: m/z 207 (M⁻² + 1H⁺, 100%).

4-[(Phosphono)difluoromethyl]nitrobenzene, ammonium salt (53). Prepared using the general procedure from 21. ¹H NMR: δ 8.19 (d, J = 8.8 Hz, 2H, aryl), 7.72 (d, J = 8.8 Hz, 2H, aryl); ³¹P NMR: δ 4.81 (t, J_{PF} ~ 89 Hz); ¹⁹F NMR: δ -32.7 (d, J_{FP} ~ 89 Hz); ¹³C NMR: δ 149.4 (s, aryl), 149.7(s, aryl) 145.4 (btd, aryl), 128.7 (s, aryl), 124.2 (s, aryl), 122.9 (td, CF₂); FABMS: m/z 252 (M⁻² + 1H⁺, 99%).

4-[(Phosphono)difluoromethyl]bromobenzene, ammonium salt (54). Prepared using the general procedure from 23. ¹H NMR: δ 7.52 (d, J = 8.4 Hz, 2H, aryl), 7.40 (d, J = 8.4 Hz, 2H, aryl); ³¹P NMR: δ

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5.43 (bt); ¹⁹F NMR: δ -28.0 (d, J_{FP} = 91.5 Hz); ¹³C NMR: δ 136.3 (btd, aryl), 131.9 (s, aryl), 128.6 (t, J_{CF} = 6.9 Hz, aryl), 124.0 (s, aryl) 122.0 (td, CF₂), FABMS: *m/z* 285 (M⁻² + 1H⁺, 99%).

Benzyl 4-[(phosphono)difluoromethyl]benzoate, ammonium salt (55). Prepared using the general procedure from 25. ¹H NMR: δ 7.72 (bs, 2H, aryl), 7.52 (bs, 2H, aryl), 7.03 (bs, 5H, aryl), 4.94 (s, 2H, CH₂); ³¹P NMR: δ 4.69 (t, J_{PF} = 103.8 Hz); ¹⁹F NMR: δ -30.4 (d, J_{FP} = 103.8 Hz); ¹³C NMR: δ 167.8 (s, CO), 139.7 (td, J_{CF} = 22.4 Hz, J_{CP} = 11.8 Hz, aryl), {136.4, 131.8, 130.2, 129.4, 129.1, 128.8 (s, aryl)}, 127.1 (bt, aryl), 120.1 (td, J_{CF} = 260.4 Hz, J_{CP} = 202.1 Hz, CF₂), 67.9 (s, CH₂); FABMS: *m/z* 341 (M⁻² + 1H⁺, 100%).

4-[(Phosphono)difluoromethyl]benzophenone, ammonium salt (56). Prepared using the general procedure from 27. ¹H NMR: δ 7.68 (bs, 7H, aryl), 7.53 (bs, 2H, aryl); ³¹P NMR: δ 5.56 (t, J_{PF} ~ 92 Hz); ¹⁹F NMR: δ -28.5 (d, J_{FP} ~ 92 Hz); ¹³C NMR: δ 201.5 (s, CO), 142.5 (td, J_{CF} = 22.4 Hz, J_{CP} = 11.7 Hz, aryl), {138.5, 137.7, 134.6, 131.3, 130.8, 129.6 (s, aryl)}, 127.1 (t, J_{CF} = 6.6 Hz, aryl), 123.5 (td, J_{CF} = 262.2 Hz, J_{CP} = 180.2 Hz, CF₂); FABMS: *m/z* 311 (M⁻² + 1H⁺, 100%).

4-[4-((Phosphono)difluoromethyl)phenyl]benzene, ammonium salt (57). Prepared using the general procedure from 28. ¹H NMR: δ 7.72 (m, 6H, aryl), 7.50 (m, 3H, aryl); ³¹P NMR: δ 5.84 (bt, $J_{PF} \sim 92$ Hz); ¹⁹F NMR: δ -27.2 (d, $J_{FP} \sim 92$ Hz); ¹³C NMR: δ 142.4 (s, aryl), 141.0 (s, aryl), 136.9 (btd, aryl), 130.1 (s, aryl), 129.0 (s, aryl), 128.1 (s, aryl), 127.6 (bs, aryl), 127.5 (bs, aryl), 123.1 (td, CF₂); FABMS: *m/z* 283 (M⁻² + 1H⁺, 100%).

3-[4-((Phosphono)difluoromethyl)phenyl]benzene, ammonium salt (58). Prepared using the general procedure from 29. ¹H NMR: δ 7.91 (s, 1H, aryl), 7.57 (m, 8H, aryl); ³¹P NMR: δ 5.89 (t, $J_{PF} = 91.5$ Hz); ¹⁹F NMR: δ -27.4 (d, $J_{FP} = 91.5$ Hz); ¹³C NMR: δ 141.2 (d, $J_{CP} = 5.8$ Hz, aryl), 138.4 (td, aryl), {130.1, 129.8, 128.9 128.1 (s, aryl)}, 126.1 (t, $J_{CF} = 6.6$ Hz, aryl), 125.4 (t, $J_{CF} = 6.6$ Hz, aryl), 123.0 (td, CF₂); FABMS: m/z 283 ($M^{-2} + 1H^{+}$, 100%).

2-[4-((Phosphono)difluoromethyl)phenyl]benzene, ammonium salt (59). Prepared using the general procedure from 30. ¹H NMR: δ 7.87 (bs, 1H, aryl), 7.46 (m, 7H, aryl), 7.24 (bs, 1H, aryl); ³¹P NMR: δ 5.38 (t, J_{PF} = 97.6 Hz); ¹⁹F NMR: δ -17.8 (d, J_{FP} = 97.6 Hz); ¹³C NMR: δ {143.4, 141.8, 133.2, 130.6, 130.4 (s, aryl)}, 129.5 (t, J_{CF} = 7.7 Hz, aryl), {128.4, 128.2, 127.9 (s, aryl)}, 123.1 (td, CF₂); FABMS: m/z 283 (M⁻² + 1H⁺, 100%).

4,4'-Bis[(phosphono)difluoromethyl]biphenyl, ammonium salt (60). Prepared using the general procedure from 48. ¹H NMR: δ 7.70 (d, J = 8.8 Hz, 4H, aryl), 7.78 (d, J = 8.4 Hz, 4H, aryl); ³¹P NMR: δ 6.18

(bt); ¹⁹F NMR: δ -27.5 (d, J_{FP} = 93.9 Hz); ¹³C NMR: δ 141.8 (s, aryl), 137.2 (btd, aryl), 127.6 (t, J_{CF} = 6.6 Hz, aryl), 123.1 (td, CF₂); FABMS: *m/z* 413 (M⁻⁴ + 3H⁺, 51%).

Bis[4-((phosphono)difluoromethyl)benzene]methane, ammonium salt (61). Prepared using the general procedure from 49. ¹H NMR: δ 7.50 (d, J = 6.9 Hz, 4H, aryl), 7.32 (d, J = 7.3 Hz, 4H, aryl), 4.02 (s, 2H, CH₂); ³¹P NMR: δ 5.81 (bt); ¹⁹F NMR: δ -27.5 (d, J_{FP} = 94.7 Hz); ¹³C NMR: δ 143.8 (s, aryl), 135.3 (td, J_{CF} = 22.7 Hz, J_{CP} = 11.7 Hz, aryl), 129.4 (s, aryl), 127.1 (bt, J_{CF} = 6.8 Hz, aryl), 122.8 (td, J_{CF} = 262.2 Hz, J_{CP} = 184.5 Hz, CF₂), 41.5 (s, CH₂); FABMS: m/z 427 (M⁻⁴ + 3H⁺, 100%).

1,4'-Bis[4-((phosphono)difluoromethyl) benzene] butane, ammonium salt (62). Prepared using the general procedure from 50. ¹H NMR: δ 7.51 (d, J = 8.0 Hz, 4H, aryl), 7.29 (d, J = 8.0 Hz, 4H, aryl), 2.67 (bt, CH₂), 1.63 (bt, CH₂); ³¹P NMR: δ 6.11 (t, J_{PF} ~ 93.5 Hz); ¹⁹F NMR: δ -27.2 (d, J_{PF} ~ 93.5 Hz); ¹³C NMR: δ 145.6 (s, aryl), 135.0 (btd, aryl), 129.1 (s, aryl), 127.0 (bt, J_{CF} = 6.9 Hz, aryl), 123.0 (td, CF₂), 35.6 (s, CH₂), 31.1 (s, CH₂); FABMS: m/z 469 (M⁻⁴ + 3H⁺, 100%).

4,4'-Bis[(phosphono)difluoromethyl]benzophenone, ammonium salt (63). Prepared using the general procedure from 51. ¹H NMR: δ 7.87 (d, J = 7.3 Hz, 4H, aryl), 7.77 (d, J = 8.8 Hz, 4H, aryl); ³¹P NMR: δ 5.42 (t, J_{PF} ~ 92 Hz); ¹⁹F NMR: δ -28.6 (d, J_{FP} ~ 92 Hz); ¹³C NMR: δ 201.0 (s, CO), 142.2 (td, J_{CF} = 21.9 Hz, J_{CP} = 11.1 Hz, aryl), 138.3 (s, aryl), 130.9 (s, aryl), 127.0 (t, J_{CF} = 6.9 Hz, aryl), 122.2 (td, J_{CF} = 257.8 Hz, J_{CP} = 186.3 Hz, 2(CF₂)); FABMS: *m/z* 441 (M⁻⁴ + 3H⁺, 26%).

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- 26. In addition to the M⁺ peak (and others having a lower m/z) corresponding to a m/z of 258, the EIMS of 34 also showed a significant peak corresponding to a m/z of 272. We believe that this peak corresponds to the methyl ester of 34 and this is supported by a HRMS analysis of this peak. However, we prepared

an authentic sample of the methyl ester of 34 and compared its 1 H, 13 C and 31 P NMR's to those that we obtained for 34 itself and found that our sample of 34 *did not contain any methyl ester or any other contaminant*. These results indicate that 34 undergoes a methyl transfer reaction (probably an intermolecular methyl transfer from the phosphate methyl ester to the carbon acid) in the mass spectrometer itself.