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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.

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 K_is 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 non-peptidyl 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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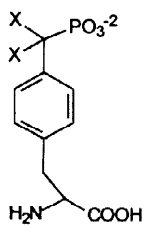
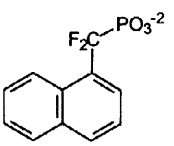
As part of our program to create potent, non-peptidyl inhibitors of PTPs, it was necessary to synthesize a wide variety of aryl(α,α,-difluoromethylenephosphonates). Until fairly recently, aryl(α,α-difluoromethylenephosphonates) have been synthesized via diethylaminosulfurtrifluoride (DAST) fluorination 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 desirable. We have recently demonstrated that naphthyl(α,α-difluoromethylenephosphonates) can be prepared by electrophilic fluorination of α-carbanions of naphthyl(methylphosphonates) using N-fluorobenzenesulfonimide (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(α,α-difluoromethylenephosphonates).



1, X = F (F_2Pmp)
2, X = H



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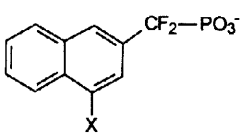


4, X = H
5, X = OH

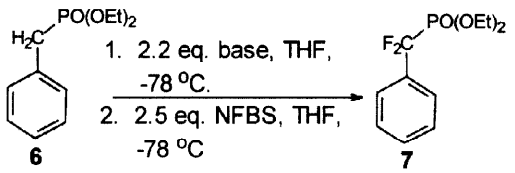
RESULTS AND DISCUSSION

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(α,α,-difluoromethylenephosphonates) 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 reported[10] that very poor yields (10-20%) of non-benzylic α,α-difluorophosphonates 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 non-benzylic 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.

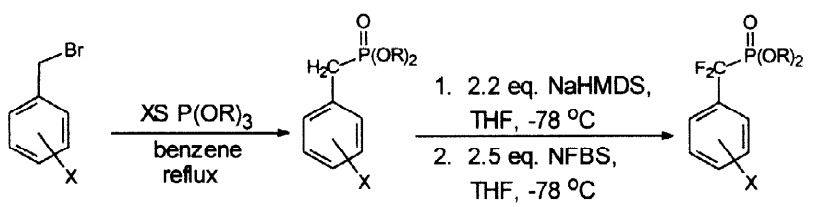
Table 1. Effect of base on the electrophilic fluorination of **6** with NFBS



6 **7**

Base	% Yield of **7**
KDA	39
LDA	33
NaHMDS	79
KHMDS	51
LiHMDS	29

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-

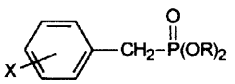
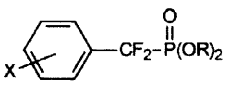


X = H, ester, ether, bromo, keto, phenyl, nitro
R = Me or Et

Scheme 1

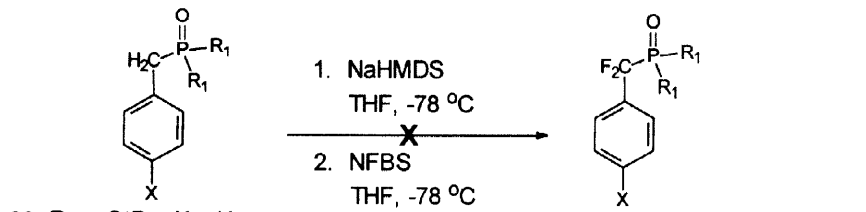
ates to electrophilic fluorination conditions (2.2 eq. NaHMDS, -78 °C in THF, followed by 2.5 eq. NFBS) a wide variety of aryl(difluoromethylenephosphonate) derivatives (**20-31**, Table 2) were obtained in reasonable to good yields. An array of both electron-rich and electron-poor functional groups 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

Table 2. Electrophilic Fluorination of Benzylic Phosphonates with NFBS

Substrate	Product	% Yield
		
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*-$CH_2O(CH_2)_2TMS$, R = Me	**31**, X = *m*-$CH_2O(CH_2)_2TMS$, R = Me	79

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 benzoylphosphonate[11] 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



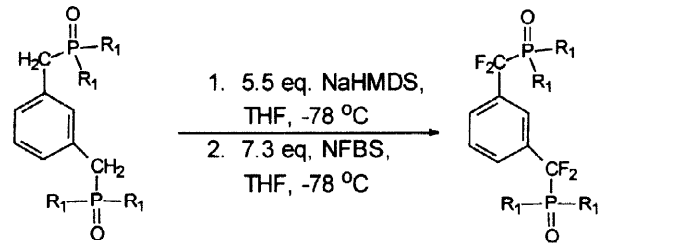
32, R_1 = OtBu, X = H
33, R_1 = OMe, X = CH_2COOBn
34, R_1 = OMe, X = CH_2COOH
35, R_1 = OMe, X = $CH_2PO(OMe)_2$

36, R_1 = OtBu, X = H
37, R_1 = OMe, X = CH_2COOBn
38, R_1 = OMe, X = CH_2COOH
39, R_1 = OMe, X = $CF_2PO(OMe)_2$

Scheme 2

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

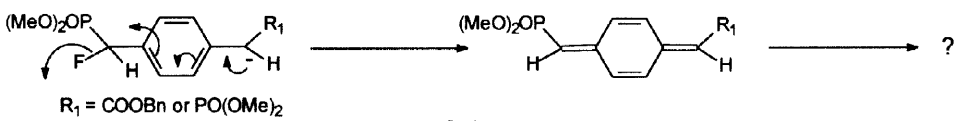


40, R_1 = OMe
41, R_1 = OEt

42, R_1 = OMe (46%)
43, R_1 = OEt (74%)

Scheme 3

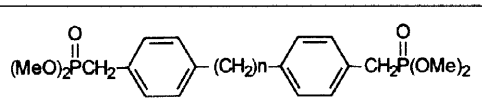
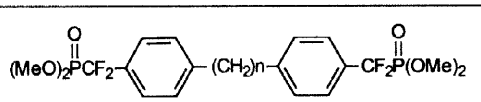
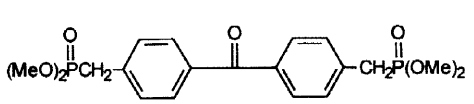
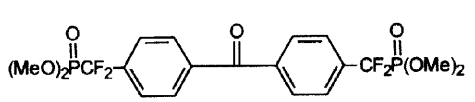
tetrafluoro compounds **42** and **43** in reasonable to good yields (Scheme 3). These results suggest that lack of formation of **37-39** may be due to the elimination of fluorine from the initially formed monofluorinated products, as shown in Scheme 4, yielding the methide derivative which may undergo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



Scheme 4

As mentioned above and in our earlier study,[9] bis(α,α,-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
		
44, n = 0	**48**, n = 0	21
45, n = 1	**49**, n = 1	16
46, n = 4	**50**, n = 4	64
 **47**	 **51**	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(α,α-difluoromethylenephosphonates) 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-difluoromethylenephosphonate 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. ^{1}H, ^{31}P and ^{19}F NMR spectra were recorded on a Varian 200-Gemini NMR machine at approximately 200 MHz, 80 MHz and 188 MHz respectively. ^{13}C 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 $CDCl_3$ as solvent and all ionic (ammonium salts) were run using D_2O as solvent unless stated otherwise. For ^{1}H spectra run in $CDCl_3$, chemical shifts (δ) are reported in parts per million relative to the internal standard tetramethylsilane (TMS). For ^{1}H spectra run in D_2O, chemical shifts (δ) are reported in parts per million relative to the residual HDO peak at δ 4.68. For ^{13}C spectra run in $CDCl_3$, chemical shifts are reported in parts per million relative to the $CDCl_3$ residual carbons (δ 77.0 for the central peak). For ^{13}C spectra run in D_2O, chemical shifts are reported in parts per million relative to the CH_3 peak 3(trimethylsilyl)-1-propanesulfonic acid (external). For ^{31}P NMR spectra, chemical shifts are reported in parts per million relative to 85 % phosphoric acid (external). For ^{19}F 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] **44-46**[14] 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 CCl_4.[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 CH_2Cl_2 (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). ^{1}H NMR: δ 8.06 (d, J = 8.1 Hz, 2H, aryl), 7.43 (m, 7H, aryl), 5.38 (s, 2H, OCH_2), 4.50 (s, 2H, $BrCH_2$); ^{13}C 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, OCH_2), 32.1 (s, $BrCH_2$); EIMS: *m/z* 306 ($M^+\{^{81}Br\}$, 19 %), 199 ($M^+\{^{81}Br\}$ -OCH_2Ph, 70 %), 91 ($M^+\{^{81}Br\}$ - $OOCPhCH_2Br$, 100 %), 304 ($M^+\{^{79}Br\}$, 19 %), 197 ($M^+\{^{79}Br\}$ - OCH_2Ph, 69 %), 91 ($M^+\{^{79}Br\}$ - $OOCPhCH_2Br$, 100 %); HRMS(EI): calcd for $C_{15}H_{13}O_2Br$ (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. ^{1}H NMR: δ 7.33 (m, 9H, aryl), 5.14 (s, 2H, OCH_2), 4.49 (s, 2H, $BrCH_2$), 3.67 (s, 2H, CH_2); ^{13}C 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, OCH_2), 40.9 (s, CH_2), 33.1 (s, $BrCH_2$); EIMS: *m/z* 320 ($M^+\{^{81}Br\}$, 4%) 239 (M^+ - $^{81/79}Br$, 76 %), 185 ($M^+\{^{81}Br\}$ - $OOCCH_2Ph$, 24 %), 91 (M^+ - $OOCCH_2PhCH_2Br$, 100 %), 318 ($M^+\{^{79}Br\}$, 4%), 183 ($M^+\{^{79}Br\}$ – $OOCCH_2Ph$, 26 %); HRMS(EI): calcd for $C_{16}H_{15}O_2Br$ (M^+) *m/z* 320.0235 & 318.0255, found 320.0247 & 318.0270.

*1-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 ($MgSO_4$). Removal of the solvent gave an oil which was subjected to silica gel chromatography (CH_2Cl_2/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). ^{1}H NMR: δ 7.38 (m, 1H, aryl), 7.29 (m, 3H, aryl), 4.50 and 4.49 (two s, 4H, CH_2Br and $ArC\underline{H}_2O$), 3.60 (t, J = 8.3 Hz, 2H, OCH_2CSi), 1.01 (t, J = 8.3 Hz, 2H, CH_2Si), 0.02 (s, 9H, $SiCH_3$); ^{13}C NMR: δ {139.8, 137.9, 128.7, 128.03, 127.96, 127.5 (s, aryl)}, 72.0 (s, $Ar\underline{C}H_2O$), 67.9 (s, $O\underline{C}H_2CSi$), 33.3 (s, CH_2Br), 18.4 (s, CH_2Si), -1.27 (s, $SiCH_3$); EIMS: *m/z* 257 ((M^+ + 1H) - 3(CH_3), 62 %), 258 ((M^+ + 2H) – 3(CH_3), 12 %), 259 ((M^+ + 3H) – 3(CH_3), 63 %); HRMS(EI): calcd for $C_{10}H_{14}BrOSi$ ((M^+ + 1H) - 3(CH_3)) *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/$CHCl_3$ 2:98, R_f = 0.4), clear, colorless oil, 89% yield. ^{1}H NMR: δ 3.17 (d, J_{HP} = 21.6 Hz, 2H, CH_2), 3.69 (d, J_{HP} = 10.6 Hz, 6H, 2(CH_3)), 7.30 (m, 5H, aryl); ^{31}P NMR: δ 26.65; ^{13}C NMR: δ 32.6 (d, J_{CP} = 137.6 Hz, CH_2), 52.5 (d, J_{CP} = 6.6 Hz, 2(CH_3)), 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 $C_9H_{13}PO_3$ (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. ^{1}H 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(CH_3)), 3.25 (d, J_{HP} = 22.3 Hz, 2H, CH_2); ^{31}P NMR: δ 24.51; ^{13}C 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(CH_3)), 32.9 (d, J_{CP} = 137.2 Hz, CH_2); EIMS: *m/z* 245 (M^+, 25 %), 228 (M^+ - OH, 100 %); HRMS (EI) calcd for $C_9H_{12}PNO_5$ (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. ^{1}H 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(OCH_2)), 3.22 (d, J_{HP} = 22.3 Hz, 2H, CH_2P), 1.23 (t, J = 7.2 Hz, 6H, 2(CH_3)); ^{31}P NMR: δ 21.90; ^{13}C 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(OCH_2)), 33.7 (d, J_{CP} = 137.6 Hz, CH_2P), 16.1 (d, J_{CP} = 5.8 Hz, 2(CH_3)); EIMS: *m/z* 274 (MH^+, 100 %), 137 (MH^+ - $PO(OEt)_2$, 54 %); HRMS(EI): calcd for $C_{11}H_{16}O_5NP$ (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. ^{1}H 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(CH_3)), 3.10 (d, J_{HP} = 21.9 Hz, 2H, CH_2P); ^{31}P NMR: δ 25.73; ^{13}C NMR: δ {131.4, 131.1, 130.2, 120.8 (s, aryl)}, 52.7 (d, J_{CP} = 6.6 Hz, 2(CH_3)), 32.1 (d, J_{CP} = 138.4 Hz, CH_2P); EIMS: *m/z* 280 ($M^+\{^{81}Br\}$, 58 %), 171 ($M^+\{^{81}Br\}$ - $PO(OMe)_2$, 94 %), 278 ($M^+\{^{79}Br\}$, 58 %), 169 ($M^+\{^{79}Br\}$ - $PO(OMe)_2$, 100 %); HRMS(EI): calcd for $C_9H_{12}O_3BrP$ (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. ^{1}H 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(OCH_2)), 3.09 (d, J_{HP} = 20.5 Hz, 2H, CH_2P), 1.25 (t, J = 7.3 Hz, 6H, 2(CH_3)); ^{31}P NMR: δ 23.22; ^{13}C 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(OCH_2)), 33.2 (d, J_{CP} = 138.4 Hz, CH_2P), 16.2 (d, J_{CP} = 5.8 Hz, 2(CH_3)); EIMS: *m/z* 308 ($M^+\{^{81}Br\}$, 24 %), 171 ($M^+\{^{81}Br\}$ - $PO(OEt)_2$, 100 %), 306 ($M^+\{^{79}Br\}$, 24 %), 169 ($M^+\{^{79}Br\}$ - $PO(OEt)_2$, 97 %); HRMS(EI): calcd for $C_{11}H_{16}O_3BrP$ (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. ^{1}H NMR: δ 8.02 (d, J = 8.1 Hz, 2H, aryl), 7.38 (m, 7H, aryl), 5.35 (s, 2H, OCH_2), 3.66 (d, J_{HP} = 10.6 Hz, 6H, 2(CH_3)), 3.21 (d, J_{HP} = 22.4 Hz, 2H, CH_2P); ^{31}P NMR: δ 25.43; ^{13}C 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, CH_2), 52.8 (d, J_{CP} = 6.6 Hz, 2(CH_3)), 32.4 (d, J_{CP} = 137.7 Hz, CH_2P); EIMS: *m/z* 334 (M^+, 6 %), 227 (M^+ - OCH_2Ph, 100 %), 91 (M^+ - $OOCPhCH_2PO(OMe)_2$, 59 %); HRMS(EI): calcd for $C_{17}H_{19}O_5P$ (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. ^{1}H NMR: δ 7.74 (m, 4H, aryl), 7.43 (m, 5H, aryl), 4.02 (m, 4H, 2(OCH_2)), 3.20 (d, J_{HP} = 22.4 Hz, 2H, CH_2P), 1.24 (t, J = 6.9 Hz, 6H, 2(CH_3)); ^{31}P NMR: δ 23.00; ^{13}C 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(OCH_2)), 33.7 (d, J_{CP} = 137.7 Hz, CH_2P), 16.1 (d, J_{CP} = 6.6 Hz, 2(CH_3)); EIMS: *m/z* 332 (M^+, 57 %), 222 (M^+ - 110, 100 %), 195 (M^+ - $PO(OEt)_2$, 30 %); HRMS(EI): calcd for $C_{18}H_{21}O_4P$ (M^+) *m/z* 332.1177, found 332.1172.

Dimethyl 4-phenylbenzylphosphonate (16). Purified using silica gel chromatography (MeOH/$CHCl_3$ 1:99, R_f = 0.3), white solid, mp 68-70°C, 90% yield. ^{1}H NMR: δ 3.22 (d, J = 21.7 Hz, 2H, CH_2), 3.71 (d, J_{HP} = 10.6 Hz, 6H, 2(CH_3)), 7.50 (m, 9H, aryl); ^{31}P NMR: δ 26.60; ^{13}C NMR: δ 32.44 (d, J_{CP} = 138.6 Hz, CH_2), 52.9 (d, J_{CP} = 6.9 Hz, 2(CH_3)), 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 $C_{15}H_{17}O_3P$ (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. ^{1}H NMR: δ 7.44 (m, 9H, aryl), 3.70 (d, J_{HP} = 10.6 Hz, 6H, 2(CH_3)), 3.24 (d, J_{HP} = 21.6 Hz, 2H, CH_2); ^{31}P NMR: δ 26.52; ^{13}C 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(CH_3)), 32.8 (d, J_{CP} = 138.4 Hz, CH_2P); EIMS: *m/z* 276 (M^+, 100 %), 167 (M^+ - $PO(OMe)_2$, 87 %); HRMS(EI): calcd for $C_{15}H_{17}O_3P$ (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. ^{1}H NMR: δ 7.41 (m, 9H, aryl), 3.57 (d, J_{HP} = 11.0 Hz, 6H, 2(CH_3)), 3.21 (d, J_{HP} = 22.0 Hz, 2H, CH_2); ^{31}P NMR: δ 27.09; ^{13}C 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(CH_3)), 29.2 (d, J_{CP} = 138.4 Hz, CH_2P); EIMS: *m/z* 276 (M^+, 99 %), 167 (M^+ - $PO(OMe)_2$, 70 %), 165 (M^+ - 111, 100%); HRMS(EI): calcd for $C_{15}H_{17}O_3P$ (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 %. ^{1}H NMR: δ 7.25 (m, 4H, Ar), 4.47 (s, 2H, Ar$\underline{C}H_2$O), 3.67 (d, J_{HP} = 10.6 Hz, 6H, OCH_3), 3.57 (t, J = 8.3 Hz, 2H, OCH_2C), 3.17 (d, J_{HP} = 22.0 Hz, 2H, CH_2P), 0.99 (t, J = 8.30 Hz, 2H, $OCCH_2$), 0.03 (s, 9H, SiMe); ^{31}P NMR: δ 26.62; ^{13}C 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, Ar$\underline{C}H_2$O), 67.6 (s, $\underline{C}H_2CH_2Si$), 52.53 (d, J_{CP} = 5.5 Hz, CH_3OP), 18.20 (s, CH_2Si), -1.42 (s, $SiCH_3$); EIMS: *m/z* 287 ((M^+ + 2H) – 3(CH_3), 67 %), 288 ((M^+ + 3H) – 3(CH_3), 20 %), 301 ((M^+ + 1H) - 2(CH_3), 37 %), 315 (M^+ - CH_3, 8 %); HRMS(EI): calcd for $C_{14}H_{24}O_4PSi$ (M^+ - CH_3) *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 $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ (3 x 50 mL) and the organic layer was washed with saturated brine and dried ($MgSO_4$). 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. ^{1}H NMR: δ 1.37 (s, 18H, CH_3), 2.99 (d, J_{HP} = 21.2 Hz, 2H, CH_2), 7.20 (m, 5H, aryl); ^{31}P NMR: δ 15.85; ^{13}C NMR (50.3 MHz): δ 30.7 (s, $C(\underline{C}H_3)_3$), 38.1 (d, J_{CP} = 142.7 Hz, CH_2), 82.0 (s, $\underline{C}(CH_3)_3$), 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 $C_{15}H_{25}PO_3$ (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. ^{1}H NMR: δ 7.28 (s, 4H aryl), 7.22 (s, 5H, aryl), 5.13 (s, 2H, OCH_2Ph), 3.66 (d, J = 10.3 Hz, 8H, CH_2CO and $2(CH_3)$), 3.11 (d, J_{HP} = 21.9 Hz, 2H, CH_2P); ^{31}P NMR: δ 26.67; ^{13}C 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, $BnCH_2$), 52.6 (d, J_{CP} = 6.6 Hz, $2(CH_3)$), 40.7 (s, CH_2), 32.2 (d, J_{CP} = 138.4 Hz, CH_2P); EIMS: *m/z* 348 (M^+, 19 %), 213 (M^+ - $OOCCH_2Ph$, 100 %); HRMS(EI): calcd for $C_{18}H_{21}O_5P$ (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 H_2 (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. ^{1}H NMR: δ 7.24 (s, 4H, aryl), 3.67 (d, J_{HP} = 11.7 Hz, 6H, $2(CH_3)$), 3.61 (s, 2H, CH_2CO), 3.16 (d, J_{HP} = 21.9 Hz, 2H, CH_2); ^{31}P NMR: δ 27.14; ^{13}C 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, $2(CH_3)$), 40.7 (s, $\underline{C}H_2CO$), 32.1 (d, J_{CP} = 139.1 Hz, CH_2P); EIMS:[26] *m/z* 258 (M^+, 5%), 272 (M^+ + CH_3, 9 %), 214 (M^+ - CO_2, 99%), 149 (M^+ - $PO(OMe)_2$, 55 %); HRMS(EI): calcd for $C_{11}H_{15}O_5P$ (M^+) *m/z* 258.0657, found 258.0657.

4,4'-Bis[(dimethylphosphono)methyl]biphenyl ***(44).*** Purified using silica gel chromatography ($MeOH/CHCl_3$, 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, $2(CH_2)$), 3.71 (d, J_{HP} = 10.6 Hz, 12H, $4(CH_3)$), 7.37 (dd, J = 8.0 Hz, 2.4 Hz, 4H, aryl), 7.54 (d, J = 7.7 Hz, 4H, aryl); ^{31}P NMR: δ 26.56; ^{13}C NMR: δ 32.5 (d, J_{CP} = 138.6 Hz, $2(CH_2)$), 52.9 (d, J_{CP} = 6.9 Hz, $4(CH_3)$), 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 $C_{18}H_{24}P_2O_6$ (M^+) *m/z* 398.1048, found 398.1055.

1,1'-Bis[4-((dimethylphosphono)methyl)benzene]methane ***(45).*** Purified using silica gel chromatography ($MeOH/CHCl_3$, 5:95, R_f = 0.3), yellow oil, 76% yield. ^1H NMR: δ 3.13 (d, J_{HP} = 21.6 Hz, 4H, $2(CH_2P)$), 3.67 (d, J_{HP} = 11.0 Hz, 12H, $4(CH_3)$), 3.93 (s, 2H, $ArCH_2Ar$), 7.20 (m, 8H, aryl); ^{31}P NMR: δ 26.79; ^{13}C NMR: δ 32.3 (d, J_{CP} = 138.6 Hz, $2(CH_2P)$), 41.0 (s, $ArCH_2Ar$), 52.8 (d, J_{CP} = 6.8 Hz, $4(CH_3)$), 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 $C_{19}H_{26}P_2O_6$ (M^+) *m/z* 412.1205, found 412.1216.

1,4'-Bis[4-((dimethylphosphono)methyl)benzene]butane ***(46).*** Purified using silica gel chromatography ($MeOH/CHCl_3$, 2:98, R_f = 0.3), white solid, mp 88-90°C, 69% yield. ^1H NMR: δ 1.63 (m, 4H, $CH_2C\underline{H_2}C\underline{H_2}CH_2$), 2.60 (bt, 4H, $2(ArCH_2)$), 3.13 (d, J_{HP} = 21.2 Hz, 4H, $2(CH_2P)$), 3.66 (d, J_{HP} = 11.0 Hz, 12H, $4(CH_3)$), 7.15 (m, 8H, aryl); ^{31}P NMR: δ 26.90; ^{13}C NMR: δ 30.9 (s, $2(CH_2)$), 31.9 (d, J_{CP} = 138.6 Hz, $2(CH_2P)$), 35.3 (s, $2(ArCH_2)$), 52.8 (d, J_{CP} = 6.8 Hz, $4(CH_3)$), 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^+ - $(CH_2)_2PhCH_2PO(OMe)_2$, 66 %); HRMS(EI): calcd for $C_{22}H_{32}P_2O_6$ (M^+) *m/z* 454.1674, found 454.1684.

4,4'-Bis[(dimethylphosphono)methyl]benzophenone ***(47).*** Purified using silica gel chromatography ($MeOH/CHCl_3$, 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, $4(CH_3)$), 3.25 (d, J_{HP} = 22.0 Hz, 4H, $2(CH_2)$); ^{31}P NMR: δ 25.48; ^{13}C 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, $4(CH_3)$), 32.7 (d, J_{CP} = 137.7 Hz, $2(CH_2)$); EIMS: *m/z* 426 (M^+, 55 %), 317 (M^+ - $PO(OMe)_2$, 21 %), 227 (M^+ - $PhCH_2PO(OMe)_2$, 100 %); HRMS(EI): calcd for $C_{19}H_{24}O_7P_2$ (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 % $NaHCO_3$, brine, dried ($MgSO_4$) 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. ^{1}H NMR: δ 7.64 (m, 2H, aryl), 7.48 (m, 2H, aryl), 4.18 (m, 4H, 2(CH_2)), 1.43 (t, J = 7.1 Hz, 6H, 2(CH_3)); ^{31}P NMR: δ 4.36 (t, J_{PF} = 116.0 Hz); ^{19}F NMR: δ -32.6 (d, J_{FP} = 116.0 Hz); ^{13}C 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, CF_2), 64.7 (d, J_{CP} = 7.4 Hz, 2(CH_2)), 16.2 (d, J_{CP} = 5.8 Hz, 2(CH_3)); EIMS: *m/z* 264 (M^+, 20 %), 127 (M^+ – $PO(OEt)_2$, 100 %); HRMS(EI): calcd for $C_{10}H_{13}O_4F_2P$ (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. ^{1}H NMR: δ 3.78 (d, J_{HP} = 10.6 Hz, 6H, 2(CH_3)), 7.50 (m, 5H, aryl); ^{31}P NMR: δ 6.52 (t, J_{PF} = 116.7 Hz); ^{19}F NMR: δ -31.6 (d, J_{FP} = 116.7 Hz); ^{13}C NMR: δ 54.92 (m, OCH_3), 118.3 (td, J_{CF} = 263.4, J_{CP} = 218.8 Hz, CF_2P), 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 $C_9H_{11}F_2PO_3$ (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. ^{1}H 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(CH_3)); ^{31}P NMR: δ 5.37 (t, J_{PF} ~ 110 Hz); ^{19}F NMR: δ -32.7 (d, J_{FP} ~ 110 Hz); ^{13}C 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, CF_2), 55.2 (d, J_{CP} = 6.6 Hz, 2(CH_3)); EIMS: *m/z* 281 (M^+, 18 %), 171 (M^+ – $PO(OMe)_2$, 33 %) 109 (M^+ - 172, 100%); HRMS(EI): calcd for $C_{10}H_{13}O_4F_2P$ (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. ^{1}H 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(OCH_2)), 1.35 (t, J_{HP} = 6.9 Hz, 6H, 2(CH_3)); ^{31}P NMR: δ 3.08 (t, J_{PF} ~ 110 Hz); ^{19}F NMR: δ -33.5 (d, J_{FP} ~ 110 Hz); ^{13}C 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, CF_2), 65.1 (d, J_{CP} = 6.7 Hz, 2(CH_2)), 16.2 (d, J_{CP} = 4.8 Hz, 2(CH_3)); EIMS: *m/z* 310 (MH^+, 7 %), 173 (MH^+ - $PO(OEt)_2$, 10 %), 109 (MH^+ - 201, 100 %); HRMS(EI): calcd for $C_{11}H_{14}NO_5F_2P$ (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. ^{1}H 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(CH_3)); ^{31}P NMR: δ 6.02 (t, J_{PF} ~ 116 Hz); ^{19}F NMR: δ -32.1 (d, J_{FP} ~ 116 Hz); ^{13}C 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, CF_2), 54.8 (d, J_{CP} = 6.6 Hz, 2(CH_3)); EIMS: *m/z* 316 ($M^+\{^{81}Br\}$, 18 %), 207 ($M^+\{^{81}Br\}$ - $PO(OMe)_2$, 99 %), 314 ($M^+\{^{79}Br\}$, 19 %), 205 ($M^+\{^{79}Br\}$ - $PO(OMe)_2$, 100 %); HRMS(EI): calcd for $C_9H_{10}O_3F_2BrP$ (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. ^{1}H 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(CH_2)), 1.33 (t, J_{HP} = 7.4 Hz, 6H, 2(CH_3)); ^{31}P NMR: δ 3.73 (t, J_{PF} = 114.5 Hz); ^{19}F NMR: δ -32.6 (d, J_{FP} = 114.5 Hz); ^{13}C 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, CF_2), 64.7 (d, J_{CP} = 6.6 Hz, 2(CH_2)), 16.2 (d, J_{CP} = 5.8 Hz, 2(CH_3)); EIMS: *m/z* 344 ($M^+\{^{81}Br\}$, 11 %), 207 ($M^+\{^{81}Br\}$ - $PO(OEt)_2$, 93 %), 109 ($M^+\{^{81}Br\}$ - 235, 100 %), 342 ($M^+\{^{79}Br\}$, 11 %), 205 ($M^+\{^{79}Br\}$ - $PO(OEt)_2$, 96 %), 109 ($M^+\{^{79}Br\}$ - 233, 100 %); HRMS(EI): calcd for $C_{11}H_{14}O_3F_2BrP$ *m/z* 341.9832, (M^+ $\{^{79}Br\}$) 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. ^{1}H 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, OCH_2), 3.84 (d, J_{HP} = 10.6 Hz, 6H, 2(CH_3)); ^{31}P NMR: δ 6.01 (t, J_{PF} = 112.9 Hz); ^{19}F NMR: δ -32.5 (d, J_{PF} = 112.9 Hz); ^{13}C 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, CF_2), 67.1 (s, CH_2), 55.0 (d, J_{CP} = 5.9 Hz, 2(CH_3)); EIMS: *m/z* 370 (M^+, 5 %), 263 (M^+ -

OCH_2Ph, 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, OCH_3 and $2(POCH_3)$); ^{31}P NMR: δ 6.78 (t, J_{PF} = 120.6 Hz); ^{19}F NMR: δ -30.4 (d, J = 120.6 Hz); ^{13}C 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, CF_2), 55.3 (s, $ArOCH_3$), 54.8 (d, J_{CP} = 7.4, $2(POCH_3)$); EIMS: *m/z* 266 (M^+, 10 %), 157 (M^+ – $PO(OMe)_2$, 100 %); HRMS(EI): calcd for $C_{10}H_{13}O_4F_2P$ (M^+) *m/z* 266.0519, found 266.0511.

4-[(Diethylphosphono)difluoromethyl]benzophenone (27). Purified using silica gel chromatography (EtOAc/CH_2Cl_2, 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, $2(CH_2)$), 1.31 (t, J_{HP} = 6.9 Hz, 6H, $2(CH_3)$); ^{31}P NMR: δ 3.69 (t, J_{PF} = 113.7 Hz); ^{19}F NMR: δ -32.9 (d, J_{FP} = 113.7 Hz); ^{13}C 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, CF_2), 64.8 (d, J_{CP} = 7.3 Hz, $2(CH_2)$), 16.1 (d, J_{CP} = 5.9 Hz, $2(CH_3)$); EIMS: *m/z* 368 (M^+, 100 %), 231 (M^+ - $PO(OEt)_2$, 96 %); HRMS(EI): calcd for $C_{18}H_{19}O_4F_2P$ (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, $2(CH_3)$), 7.60 (m, 9H, aryl); ^{31}P NMR: δ 6.64 (t, J_{PF} ~ 117 Hz); ^{19}F NMR: δ -31.3 (d, J_{FP} ~ 117 Hz); ^{13}C NMR: δ 54.9 (d, J_{CP} = 6.6 Hz, $2(CH_3)$), 118.3 (td, J_{CF} = 263.4, J_{CP} = 219.4 Hz, CF_2), 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 $C_{15}H_{15}F_2O_3P$ (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, $2(CH_3)$); ^{31}P NMR: δ 6.60 (t, J_{PF} ~ 117 Hz); ^{19}F NMR: δ -31.4 (d, J_{FP} ~ 117 Hz); ^{13}C 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, CF_2), 54.8 (d, J_{CP} = 6.6 Hz, $2(CH_3)$); EIMS: *m/z* 312 (M^+, 39 %), 203 (M^+ - $PO(OMe)_2$, 100 %), 183 (M^+ - 129, 20 %); HRMS(EI): calcd for $C_{15}H_{15}O_3F_2P$ (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. ^{1}H NMR: δ 7.50 (m, 9H, aryl), 3.73 (d, J = 10.2 Hz, 6H, 2(CH_3)); ^{31}P NMR: δ 6.49 (t, J_{PF} ~ 117.5 Hz); ^{19}F NMR: δ -22.0 (d, J_{FP} ~ 117.5 Hz); ^{13}C 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(CH_3)); EIMS: *m/z* 312 (M^+, 37 %), 203 (M^+ - $PO(OMe)_2$, 76 %), 183 (M^+ - 129, 100 %); HRMS(EI): calcd for $C_{15}H_{15}O_3F_2P$ (M^+) *m/z* 312.0727, found 312.0740.

4-[(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 ($MgSO_4$) 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 ^{19}F 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. ^{1}H NMR: δ 7.50 (m, 4H, aryl), 4.51 (s, 2H, ArCH_2O), 3.85 (d, J_{HP} = 10.6 Hz,, 2H, OCH_3), 3.58 (t, J = 8.3 Hz, 2H, OCH_2C), 0.99 (t, J = 8.3 Hz, 2H, CH_2Si), 0.01 (s, 9H, $SiCH_3$); ^{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_{CP} = 219.0 Hz, CF_2), 71.7 (PhCH_2O), 67.8 (OCH_2CSi), 54.6 (d, J_{CP} = 7.3 Hz, OCH_3), 18.2 (CH_2Si), -1.5 ($SiCH_3$); EIMS: *m/z* 351 (M^+ - CH_3, 8 %), 337 (M^+ - 2CH_3 + 1H, 12%), 323 (M^+ - 3(CH_3) + 2H, 37%); HRMS(EI): calcd for $C_{14}H_{22}F_2O_4PSi$ (M^+ - CH_3) *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. ^{1}H NMR: δ 7.75 (m, 4H, aryl), 3.80 (m, 12H, 4(CH_3)); ^{31}P NMR: δ 5.83 (t, J_{PF} ~ 115 Hz); ^{19}F NMR: δ -32.2 (d, J_{FP} ~ 115 Hz); ^{13}C 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(CF_2)), 55.0 (d, J_{CP} = 6.6 Hz, CH_3); EIMS: *m/z* 394 (M^+, 10 %), 285 (M^+ – $PO(OMe)_2$, 100 %); HRMS(EI): calcd for $C_{12}H_{16}O_6F_4P_2$ (M^+) *m/z* 394.0358, found 450.0365.

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

4(CH_2)), 1.28 (t, J = 6.9 Hz, 12H, 4(CH_3)); ^{31}P NMR: δ 3.66 (t, J_{PF} = 115.5 Hz); ^{19}F NMR: δ -33.0 (d, J_{FP} = 115.5 Hz); ^{13}C 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(CF_2)), 64.8 (d, J_{CP} = 6.6 Hz, 4(CH_2)), 16.2 (d, J_{CP} = 5.8 Hz, 4(CH_3)); EIMS: *m/z* 451 (MH^+, 35 %), 313 (MH^+ – $PO(OEt)_2$, 100 %); HRMS(EI): calcd for $C_{16}H_{24}O_6F_4P_2$ (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. ^{1}H NMR: δ 3.85 (d, J_{HP} = 10.6 Hz, 12H, 4(CH_3)), 7.69 (m, 8H, aryl); ^{31}P NMR: δ 6.41 (t, J_{PF} = 116.7 Hz); ^{19}F NMR: δ -31.8 (d, J_{FP} = 116.7 Hz); ^{13}C NMR: δ 55.0 (d, J_{CP} = 6.8 Hz, 4(CH_3)), 118.2 (td, J_{CF} = 262.8 Hz, J_{CP} = 218.9 Hz, 2(CF_2)), 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 $C_{18}H_{20}F_4O_6P_2$ (M^+) *m/z* 470.0671, found 470.0678.

1,1'-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. ^{1}H NMR: δ 3.83 (d, J_{HP} = 10.3 Hz, 12H, 4(CH_3)), 4.06 (s, 2H, CH_2), 7.27 (d, J = 8.1 Hz, 4H, aryl), 7.55 (d, J = 8.1 Hz, 4H, aryl); ^{31}P NMR: δ 6.58 (t, J_{PF} ~ 117 Hz); ^{19}F NMR: δ -31.4 (d, J_{FP} ~ 117 Hz); ^{13}C NMR: δ 41.4 (s, CH_2), 54.9 (d, J_{CP} = 6.9 Hz, 4(CH_3)), 118.1 (td, J_{CF} = 262.5, J_{CP} = 219.6 Hz, 2(CF_2)), 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 $C_{19}H_{22}F_4O_6P_2$ (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. ^{1}H NMR: δ 1.66 (bs, 4H, CH_2), 2.67 (bt, 4H, CH_2), 3.82 (d, J_{HP} = 10.2 Hz, 12H, 4(CH_3)), 7.25 (d, J = 7.4 Hz, 4H, aryl), 7.52 (d, J = 7.3 Hz, 4H, aryl); ^{31}P NMR: δ 6.75 (t, J_{PF} = 118.3 Hz); ^{19}F NMR: δ -31.0 (d, J_{FP} = 118.3 Hz); ^{13}C NMR: δ 30.7 (s, 2(CH_2)), 35.5 (s, 2(CH_2)), 54.8 (d, J_{CP} = 7.4 Hz, 4(CH_3)), 118.3 (td, J_{CF} = 262.9 Hz, J_{CP} = 219.7 Hz, 2(CF_2)), 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 $C_{22}H_{28}F_4O_6P_2$ (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. ^{1}H 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(CH_3)); ^{31}P NMR: δ 5.89 (t, J_{PF} ~

113 Hz); ^{19}F NMR: δ -32.4 (d, J_{FP} ~ 113 Hz); ^{13}C 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(CF_2)), 55.1 (d, J_{CP} = 6.7 Hz, 4(CH_3)); EIMS: *m/z* 498 (M^+, 41 %), 389 (M^+ - $PO(OMe)_2$, 100 %) 280 (M^+ - 2(-$PO(OMe)_2$), 6 %); HRMS(EI): calcd for $C_{19}H_{20}O_7F_4P_2$ (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 CH_2Cl_2 (approximately 1 mL CH_2Cl_2/0.1 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 CH_2Cl_2 (approximately 1 mL CH_2Cl_2/0.1 mmol phosphonate) and a solution of NH_4HCO_3 (2 equivalents per silyl ester moiety) in water (approximately 15 mL water/gram NH_4HCO_3) was added. The biphasic mixture was stirred vigorously for 30-60 minutes and the CH_2Cl_2 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); ^{31}P NMR: δ 5.83 (t, J_{PF} = 91.6 Hz); ^{19}F NMR: δ -27.5 (d, J_{FP} = 93.8 Hz); ^{13}C NMR: δ 137.2 (btd, aryl), 130.4 (s, aryl), 129.0 (s, aryl), 126.7 (bt, aryl), 122.8 (td, CF_2); 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); ^{31}P NMR: δ 4.81 (t, J_{PF} ~ 89 Hz); ^{19}F NMR: δ -32.7 (d, J_{FP} ~ 89 Hz); ^{13}C 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, CF_2); 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); ^{31}P NMR: δ

5.43 (bt); ^{19}F NMR: δ -28.0 (d, J_{FP} = 91.5 Hz); ^{13}C 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, CF_2), FABMS: *m/z* 285 (M^{-2} + $1H^+$, 99%).

Benzyl 4-[(phosphono)difluoromethyl]benzoate, ammonium salt ***(55)***. Prepared using the general procedure from **25**. ^{1}H NMR: δ 7.72 (bs, 2H, aryl), 7.52 (bs, 2H, aryl), 7.03 (bs, 5H, aryl), 4.94 (s, 2H, CH_2); ^{31}P NMR: δ 4.69 (t, J_{PF} = 103.8 Hz); ^{19}F NMR: δ -30.4 (d, J_{FP} = 103.8 Hz); ^{13}C 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, CF_2), 67.9 (s, CH_2); FABMS: *m/z* 341 (M^{-2} + $1H^+$, 100%).

4-[(Phosphono)difluoromethyl]benzophenone, ammonium salt ***(56)***. Prepared using the general procedure from **27**. ^{1}H NMR: δ 7.68 (bs, 7H, aryl), 7.53 (bs, 2H, aryl); ^{31}P NMR: δ 5.56 (t, J_{PF} ~ 92 Hz); ^{19}F NMR: δ -28.5 (d, J_{FP} ~ 92 Hz); ^{13}C 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, CF_2); FABMS: *m/z* 311 (M^{-2} + $1H^+$, 100%).

4-[4-((Phosphono)difluoromethyl)phenyl]benzene, ammonium salt ***(57)***. Prepared using the general procedure from **28**. ^{1}H NMR: δ 7.72 (m, 6H, aryl), 7.50 (m, 3H, aryl); ^{31}P NMR: δ 5.84 (bt, J_{PF} ~ 92 Hz); ^{19}F NMR: δ -27.2 (d, J_{FP} ~ 92 Hz); ^{13}C 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, CF_2); FABMS: *m/z* 283 (M^{-2} + $1H^+$, 100%).

3-[4-((Phosphono)difluoromethyl)phenyl]benzene, ammonium salt ***(58)***. Prepared using the general procedure from **29**. ^{1}H NMR: δ 7.91 (s, 1H, aryl), 7.57 (m, 8H, aryl); ^{31}P NMR: δ 5.89 (t, J_{PF} = 91.5 Hz); ^{19}F NMR: δ -27.4 (d, J_{FP} = 91.5 Hz); ^{13}C 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, CF_2); FABMS: *m/z* 283 (M^{-2} + $1H^+$, 100%).

2-[4-((Phosphono)difluoromethyl)phenyl]benzene, ammonium salt ***(59)***. Prepared using the general procedure from **30**. ^{1}H NMR: δ 7.87 (bs, 1H, aryl), 7.46 (m, 7H, aryl), 7.24 (bs, 1H, aryl); ^{31}P NMR: δ 5.38 (t, J_{PF} = 97.6 Hz); ^{19}F NMR: δ -17.8 (d, J_{FP} = 97.6 Hz); ^{13}C 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, CF_2); FABMS: *m/z* 283 (M^{-2} + $1H^+$, 100%).

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

(bt); ^{19}F NMR: δ -27.5 (d, J_{FP} = 93.9 Hz); ^{13}C NMR: δ 141.8 (s, aryl), 137.2 (btd, aryl), 127.6 (t, J_{CF} = 6.6 Hz, aryl), 123.1 (td, CF_2); FABMS: *m/z* 413 (M^{-4} + $3H^+$, 51%).

Bis[4-((phosphono)difluoromethyl)benzene]methane, ammonium salt ***(61)***. Prepared using the general procedure from **49**. ^{1}H NMR: δ 7.50 (d, J = 6.9 Hz, 4H, aryl), 7.32 (d, J = 7.3 Hz, 4H, aryl), 4.02 (s, 2H, CH_2); ^{31}P NMR: δ 5.81 (bt); ^{19}F NMR: δ -27.5 (d, J_{FP} = 94.7 Hz); ^{13}C 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, CF_2), 41.5 (s, CH_2); 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**. ^{1}H NMR: δ 7.51 (d, J = 8.0 Hz, 4H, aryl), 7.29 (d, J = 8.0 Hz, 4H, aryl), 2.67 (bt, CH_2), 1.63 (bt, CH_2); ^{31}P NMR: δ 6.11 (t, J_{PF} ~ 93.5 Hz); ^{19}F NMR: δ -27.2 (d, J_{PF} ~ 93.5 Hz); ^{13}C 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, CF_2), 35.6 (s, CH_2), 31.1 (s, CH_2); FABMS: *m/z* 469 (M^{-4} + $3H^+$, 100%).

4,4'-Bis[(phosphono)difluoromethyl]benzophenone, ammonium salt ***(63)***. Prepared using the general procedure from **51**. ^{1}H NMR: δ 7.87 (d, J = 7.3 Hz, 4H, aryl), 7.77 (d, J = 8.8 Hz, 4H, aryl); ^{31}P NMR: δ 5.42 (t, J_{PF} ~ 92 Hz); ^{19}F NMR: δ -28.6 (d, J_{FP} ~ 92 Hz); ^{13}C 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(CF_2)); 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.