Article

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Articles

Synthesis of Non-Peptidyl α,α-Difluoromethylenephosphonic Acids on a Soluble Polymer Support

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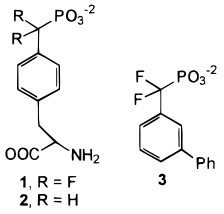
The polymer-supported syntheses of a series of biaryl derivatives bearing the α,α-difluoromethylenephosphonic acid group is reported. Non-cross-linked polystyrene (NCPS) was used as the support which enabled the reactions to be carried out under homogeneous conditions and reactions to be followed using conventional ^{19}F NMR. Synthesis of the biaryl phosphonic acids was initiated by attaching mono-ethyl esters of α,α-difluorophosphonic acids **11** and **12** to 3% alkylhydroxy-modified NCPS via a phosphate ester linkage. Suzuki reaction conditions were developed which allowed for the formation of a series of polymer-bound biaryl phosphonates at ambient temperature. Removal of phosphonic acids from the support and cleavage of the ethyl protecting group was achieved in a single step using TMSI or TMSBr. Yields of the phosphonic acids ranged from 43 to 89% and, in most cases, were obtained in a purity (96−99%), after cleavage from the support, that was sufficient for biological screening.

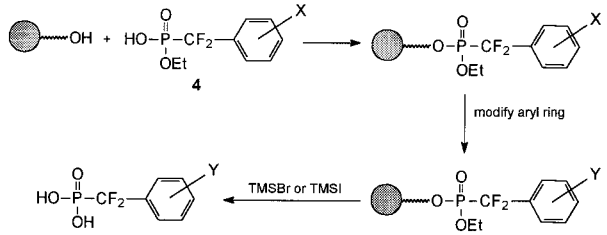
Introduction

Recently, there has been tremendous interest in the development of inhibitors of protein tyrosine phosphatases (PTPs).[1,2] PTPs are enzymes that catalyze the hydrolysis of phosphate groups from phosphotyrosine residue in proteins.[3] Interest in developing inhibitors of these enzymes stems from the recent discoveries that these enzymes are essential for the regulation of a wide variety of crucial cellular processes such as cell growth factor signaling, insulin signaling, fuel metabolism, and cytokine signaling to name but a few.[3,4] Much of the work on the development of reversible PTP inhibitors has focused on incorporating non-hydrolyzable phosphotyrosine mimetics into peptidyl PTP substrates.[1] One mimetic that has proven to particularly effective is the α,α-difluoromethylenephosphonic acid (DFMP) moiety. For example, certain peptides bearing difluoromethylenephosphonyl phenylalanine (F_2Pmp, **1**) are nanomolar inhibitors of PTP1B and can bind up to 2×10^3 times better than the analogous peptide bearing methylenephosphonyl phenylalanine **2**.[1a,c] However, in general, peptide-based inhibitors



make for poor therapeutics due to inadequate bioavailability.

Scheme 1



Consequently, we,[2e−g] as well as other groups,[2a−d,h−j] have begun examining non-peptidyl compounds as PTP inhibitors. Preliminary studies in our group[2e,f] and others[2a,b,d,h−j] have shown that even simple aryl derivatives bearing the DFMP group can be relatively good inhibitors of PTPs. For example, we have found that the *m*-biphenyl DFMP **3** is a good inhibitor of PTP1B (K_i of 17 μM) and is 17-fold more potent that just phenyl DFMP.[2e] As part of our program to prepare non-peptidyl inhibitors of PTPs, we became interested in developing polymer-supported methodologies that would allow for the rapid synthesis of aromatics bearing the DFMP group.[5] The specific methodology we wished to develop is outlined in Scheme 1. An appropriately functionalized aryl α,α-difluoromethylenephosphonic acid **4** is attached to a hydroxy-modified polymer support via a phosphate ester linkage. After further functionalization of the aryl ring, removal of the ethyl protecting group and cleavage of the phosphonic acid from the support would be accomplished in a single step using TMSBr or TMSI. We wished to use a "liquid phase"[6] approach in which the reactions are carried out on a "soluble" polymer in a homogeneous solution. This

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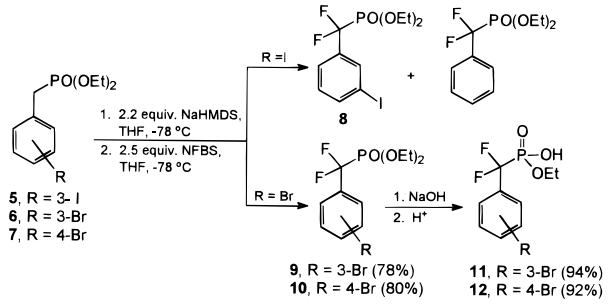
Scheme 2

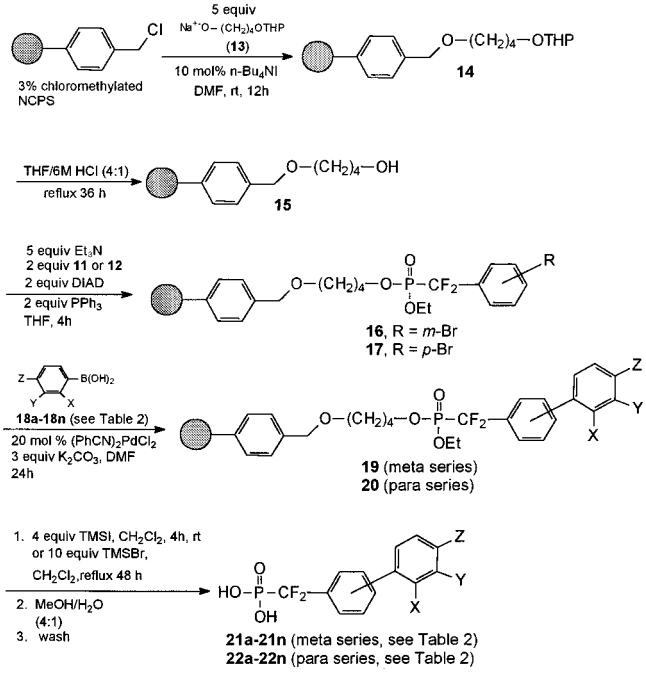


approach has certain advantages over the more common conventional solid phase methodologies such as faster reaction rates[7] and facile monitoring of the reaction using conventional solution NMR. In our case, all chemical transformations on the polymer support could be monitored by ^{19}F NMR. ^{19}F NMR is a particularly attractive method for monitoring the reactions since ^{19}F is a sensitive nucleus and has a very broad frequency range.[8] Consequently, chemical transformations even fairly remote from the fluorines would result in a change in the ^{19}F NMR chemical shift. To ascertain if this would be a feasible approach for synthesizing DFMP-bearing compounds, we chose to prepare a series of biaryl DFMP's using a Suzuki reaction, a reaction that has been used extensively in polymer-supported syntheses,[9] as a model reaction for aryl functionalization. Here we report this is indeed a very powerful approach for the rapid construction of this class of compound.

Results and Discussion

Syntheses of Monophosphonic Acids. For our studies, multigram quantities of either the iodo or bromo substituted phosphonic acids **4** (X = Br or I) were required. Iodo arenes undergo Suzuki couplings more readily than their bromo counterparts. However, the large scale synthesis of the iodo derivatives proved to be impractical for a number of reasons. Burke and co-workers have reported the synthesis of diethyl-[(4-iodophenyl)(difluoro)methyl]phosphonate in 60% yield by reacting the corresponding α-ketophosphonate with 5 equiv of DAST.[10] However, other researchers have recently reported that this reaction can explode upon scale-up.[11] In addition, the requirement of 5 equiv of DAST makes this procedure prohibitively expensive. We have recently reported that aryl DFMPs can be constructed by electrophilic fluorination of α-carbanions of benzyl phosphonates using *N*-fluorobenzene sulfonimide (NFSI) as fluorinating agent.[12] We attempted to use this procedure for preparing the iodoarene **8** by subjecting diethyl 3-iodobenzylphosphonate (**5**) to a solution of 2.2 equiv of NaHMDS in THF followed by electrophilic fluorination of the resulting carbanions using 2.5 equiv of NFSI (Scheme 2). However, significant loss of iodine occurred during the electrophilic fluorination, resulting in low yields and the product being contaminated with the noniodinated material which we could not remove. Nonetheless, in contrast to the iodo derivative, both the 3-bromo and 4-bromo arenes **9** and **10** were readily obtained in good yield (78−80%) from benzyl phosphonates **6** and **7** using the electrophilic fluorination procedure (Scheme 2). Diesters **9** and **10** were converted into the monoesters **11** and **12** in excellent yields by basic hydrolysis followed by acidification. Since multigram quantities of **11** and **12** were readily obtained, it was decided to develop all of the Suzuki chemistry using these bromo derivatives.

Scheme 3



Polymer Synthesis and Loading. Poly(ethylene glycol) (PEG) is perhaps the most commonly used support for liquid-phase organic synthesis (LPOS).[6] However, we chose not to use PEG since we were concerned about the stability of this polymer to some of our reaction conditions (such as TMSI or TMSBr). Therefore, non-cross-linked polystyrene (NCPS) was used as the polymer support. NCPS is soluble in polar aprotic solvents such as THF, CH_2Cl_2, $CHCl_3$, EtOAc, DMF, and benzene but insoluble in highly polar protic solvents such as MeOH or EtOH. Thus, the NCPS-supported reactions can be carried out under homogeneous conditions in a wide range of solvents and then rapidly purified by precipitating out the polymer in MeOH or EtOH followed by filtration. NCPS has been employed for the polymer-supported synthesis of peptides, oligonucleotide, and oligosaccharides[6] and has recently been employed by Janda and co-workers for the polymer-supported total synthesis of prostaglandins E_2 and $F_{2\alpha}$[13] and by Enholm for the preparation of polymer-bound stannane reagents.[14]

Functionalized NCPS was prepared in which a linear spacer separates the polystyrene from the site of attachment of the phosphonic acid (Scheme 3). Thus, 3% chloromethylated NCPS[13b,15] was reacted with 5 equiv of the sodium salt of the monoprotected diol **13** in the presence of a catalytic amount of n-Bu_4NI in DMF at room temperature for 12 h. The DMF was removed, the crude polymer was dissolved in CH_2Cl_2, washed with brine, and concentrated. This concentrated solution was added slowly to a solution of cold MeOH/H_2O (4:1) to give pure **14**. Ninety-six percent of the functionalized polymer was recovered. The hydroxy-modified polymer **15** was obtained by refluxing **14** in a solution of THF/6 M HCl (4:1) for 36 h. In this case, pure **15** was

obtained simply by adding the crude reaction mixture directly to cold MeOH/H_2O (4:1) (95% recovery of polymer). ^{1}H NMR analysis of the above crude reaction mixtures indicated that each reaction proceeded in quantitative yields and that the yield of pure polymer product was reduced only by the small loss of polymer that occurred during the precipitation and filtration process.

Two approaches for attaching phosphonic acid **11** and **12** to polymer **15** were considered. One was to convert **11** and **12** to the acid chlorides and then react this with polymer **15**. The other was to attach the phosphonic acid directly to **15** via a Mitsunobu reaction.[16a−c] We chose to use a Mitsunobu reaction since the phosphonic acids could be used directly without prior conversion to the acid chloride, and this reaction is known to proceed in high yields under very mild conditions and has been used very successfully for solid phase peptidylphosphonate synthesis.[17] Using the Mitsunobu conditions developed by Campbell and co-workers[16c] in which the alcohol is the limiting reagent (2 equiv of phosphonic acid, 2 equiv of DIAD, 2 equiv of $P(Ph)_3$, 5 equiv of Et_3N, 1 equiv of **15**, in THF at room temperature), we found that **11** and **12** could be attached to **15** to give the polymer-supported phosphonates **16** and **17** in quantitative yields in just 4 h as judged by ^{1}H NMR and ^{19}F NMR (Scheme 3). Pure **16** and **17** were obtained by adding the crude reaction mixture to a solution of cold MeOH/H_2O (4:1) (96% recovery of polymer). Only a single polymer-bound species was detected by both ^{1}H and ^{19}F NMR.

Suzuki Couplings. Ideally, we wished to perform the Suzuki reactions at room temperature and with readily available reagents and catalysts. A number of reports describing room temperature Suzuki couplings on aryl bromides have appeared in the literature.[18a−d,19] However, these procedures[18a−d] require either toxic and/or expensive additives (TlOH)[18a−c] or solvents (EtOH) that were incompatible with the homogeneous conditions that we desired for the reaction.[18d] Nevertheless, we first attempted the coupling of model diester **9** with phenylboronic acid using the conditions developed by Campi et al.[18d] (5 mol % $Pd(OAc)_2$, 1 equiv of boronic acid, and either $Ba(OH)_2$, K_2CO_3, or Na_2CO_3, except degassed DMF was used as solvent instead of degassed aqueous EtOH). The reaction was monitored by ^{19}F NMR. Although this reaction yielded the desired biaryl product, the reaction was slow and only 25% complete after 24 h. In order to have the reaction go to completion within 24 h at room temperature, we found that, in addition to increasing the amount of boronic acid (3 equiv), the amount of catalyst had to be increased to 20 mol %. Under these conditions, the biaryl product was obtained in quantitative yields and no other products were detected. To determine if other catalysts were more effective than $Pd(OAc)_2$, 12 reactions were set up, each of which contained 20 mol % of a different Pd catalyst, 1 equiv of **9**, 3 equiv of phenyl boronic acid, 3 equiv of solid K_2CO_3, and DMF as solvent, and the reactions were monitored by ^{19}F NMR. The results of this study are shown in Table 1. Under these conditions, it was found that complete conversion of **9** to biaryl product could be accomplished at room temperature within 24 h using either $PdCl_2$, $Pd(OAc)_2$, or $(PhCN)_2PdCl_2$ as catalysts, with the $(PhCN)_2PdCl_2$-catalyzed reaction being slightly faster (complete with 21 h). Lowering the catalyst loading to less than 20 mol % with any of these three catalysts resulted in incomplete reaction after 24 h. The phosphine-bearing catalysts that we employed for these studies did not go to completion within 24 h.[20] This is consistent with the results of Campi et al.[19d] who also found that high yields of biaryl product can be obtained at ambient temperature when palladium catalysts not involving phosphine ligands are employed.[20] Further studies with these three catalysts indicated that other solvents that are compatible with NCPS (benzene, toluene, THF, DME) were less effective than DMF and organic bases, such as Et_3N, were less effective than K_2CO_3.

The room temperature Suzuki reaction conditions (DMF, 3 equiv of boronic acid, 3 equiv of K_2CO_3, 20 mol % $(PhCN)_2PdCl_2$) worked out in solution with model ester **9** worked equally well with polymer-bound aryl bromides **16** and **17**. Thus, a variety of boronic acids (Table 2) were coupled to **16** and **17** at room temperature, yielding a series of polymer-bound biaryl derivatives of type **18** and **19**. Each reaction was followed by ^{19}F NMR.[21] For those boronic acids

Table 1. Effect of Catalyst on the Room Temperature Suzuki Cross-Coupling Reactions[a] of **9** with $PhB(OH)_2$

entry	catalyst	percent conversion[b] (%)
1	$Pd(dppe)_2Cl_2$	48
2	Pd(acac)	3
3	Pd_2dba_3	53
4	$PdCl_2$	100
5	$(Ph_3P)_2PdCl_2$	46
6	$(Et_3P)_2PdCl_2$	29
7	$PdCl_2$dppf	75
8	Pd_2dba_3	76
9	$Pd(OAc)_2$	100
10	$Pd(dppe)_2$	39
11	$Pd(PPh_3)_4$	7
12	$(PhCN)_2PdCl_2$	100

[a] 1 equiv of **9**, 3 equiv of $PhB(OH)_2$, 3 equiv of K_2CO_3, 20 mol % catalyst in DMF for 24 h at room temperature. [b] Percent conversion of **9** into biaryl product as determined by ^{19}F NMR.

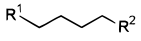
Table 2. Yields and Purities of Biaryl Phosphonic Acids after Cleavage from **19** or **20**

boronic acid	biaryl product	yield[a] (purity)[b]	biaryl product	yield[a] (purity)[b]
18a, X = Y = Z = H	**21a**	82 (97)	**22a**	89 (98)
18b, X = Y = H, Z = Ph	**21b**	83 (91)	**22b**	61 (96)[d]
18c, X = H, Y = Z = CH=CH−CH=CH[c]	**21c**	77 (98)	**22c**	64 (97)
18d, X = Me, Y = Z = H	**21d**	71 (98)	**22d**	67 (98)
18e, X = Y = H, Z = Me	**21e**	70 (99)	**22e**	66 (99)
18f, X = Y = H, Z = Et	**21f**	72 (99)	**22f**	75 (96)
18 g, X = Y = H, Z = *t*-Bu	**21g**	81 (99)	**22g**	64 (98)
18h, X = Y = H, Z = MeC(O)	**21h**	69 (80)	**22h**	90 (91)
18i, X = Z = H, Y = CF_3	**21i**	68 (97)	**22i**	54 (97)
18j, X = Y = H, Z = CF_3	**21j**	43 (99)	**22j**	74 (98)
18k, X = Z = H, Y = F	**21k**	66 (98)	**22k**	81 (98)
18l, X = Y = H, Z = F	**21l**	75 (98)	**22l**	75 (99)
18m, X = Y = H, Z = Cl	**21m**	72 (99)	**22m**	75 (99)
18n, X = H, Y = Cl, Z = F	**21n**	75 (96)	**22n**	77 (96)

[a] Yields are calculated starting from **15**. [b] Determined by NMR and HPLC. The lowest value obtained by these methods is reported. [c] 2-Naphthyl boronic acid. [d] The amount of material obtained corresponded to a 61% yield. However, due to solubility problems, the purity of this compound was determined by HPLC only.

that contained electron withdrawing groups, (*p*-trifluoromethyl, *p*-fluoro), the reaction was 100% complete within 3−6 h. For boronic acids bearing electron donating groups (*p*-methyl, *p*-ethyl, *p*-*tert*-butyl), quantitative conversion required 24 h. The reaction with *o*-methylbenzene boronic acid was also complete within 24 h, indicating that the reaction is not strongly effected by steric factors although this may not be the case if substituents larger than a methyl group are present at the ortho position. After removal of the palladium catalyst, pure polymer-bound biaryl product was obtained by adding the crude reaction mixture directly to cold MeOH/H_2O (4:1). No loss of the phosphonate from the support occurred during the reaction or during the workup as determined by ^{19}F NMR of the filtrate of the precipitated polymer. It was found that, when working with small amounts of polymer (500 mg or less), recovery of the polymer-bound products from the filter was more difficult, and in several cases, less than 95% of the polymer was recovered. Thus, although the above Suzuki couplings were quantitative in most cases (only a single polymer-bound species was evident by ^{19}F NMR), the amount of recovered polymer varied from 85 to 95%.

Removal from the Support. The phosphonic acids were removed from the support and deprotected in a single step by reacting the polymer-bound biaryls with 4 equiv of TMSI in CH_2Cl_2 at room temperature for 4 h. TMSBr could also be used; however, this required a 48 h reflux in CH_2Cl_2. The resulting TMS phosphonate esters were converted to the free acids by adding a CH_2Cl_2 solution of the crude reaction mixture to MeOH/H_2O (4:1) followed by stirring for 12 h. Filtration followed by concentration of the filtrate yielded the phosphonic acids (**21a**−**21n** and **22a**−**22n**). ^1H NMR analysis of the concentrated filtrate indicated that the product was contaminated with small amounts of polymer as well as what appeared to be small quantities of alkyl halides of type **23** which resulted from cleavage of the spacer



23, R^1 = OH or OTMS
R^2 = I or Br

arm from the polymer during the TMSI or TMSBr reaction. Thus, the crude filtrate was dissolved in 0.1 N NaOH and washed with CH_2Cl_2. The solution was then acidified to pH ∼0.5, and the phosphonic acid was extracted with diethyl ether and the ether layer concentrated. The residue was dissolved in an aqueous solution containing 2.5 equiv of NH_4HCO_3 and then repeatedly lyophilized to give the desired phosphonic acids as their ammonium salts in 43−89% yield starting from **15**. ^1H NMR analysis of the concentrated ether layer before conversion to the ammonium salts showed no traces of contaminating linker arm or polymer. Indeed, NMR (^1H, ^{19}F, and ^{31}P) and HPLC analysis of the ammonium salts indicated that the majority of the biaryl products were obtained in *remarkably high purity with 21 of the 28 compounds being 97% pure or better. Three of the other seven acids were obtained in 96% purity. Most of the acids could be used directly for biological screening*[22] *without any further purification.* However, three of the acids required further purification by HPLC before biological testing: the *m*-triphenyl derivative **21b** (91% pure by HPLC), and the two acetyl derivatives **21h** (80% pure by HPLC) and **22h** (91% pure by HPLC). In addition, biaryl derivative **22b** proved to be insoluble in organic and aqueous solutions, and its purity could only be determined by HPLC (96% pure) and could not be evaluated for biological activity.

In summary, we have prepared a series of biaryl DFMP derivatives using a liquid phase methodology. The approach described here is particularly powerful since it allows for the direct monitoring of the polymer-supported reactions using conventional ^{19}F NMR. In addition, the overall process is rapid and relatively straightforward. The majority of the biaryl products obtained after cleavage from the support did not require any further purification for biological evaluation. The approach outlined here for the polymer-supported synthesis of aryl DFMP derivatives may also find use for the rapid development of DFMP-bearing inhibitors of other enzymes besides PTPs.

Experimental Section

General. Boronic acids were purchased from Lancaster Synthesis Inc. (Windham, NH). All other reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI). ^1H NMR, ^{19}F NMR, and ^{31}P NMR spectra were recorded on a Varian Gemini-200 or Varian-300 spectrophotometer. All ^{31}P NMR spectra were proton decoupled, and chemical shifts are reported in parts per million relative to 85% phosphoric acid (external). Chemical shifts for ^{19}F NMR spectra are reported in parts per million (ppm) relative to trifluoroacetic acid (external standard). Electrospray mass spectra were obtained using a Micromass Platform mass spectrometer. Electron impact (EI) were obtained on a Micromass 70-S-250 mass spectrometer. Analytical and preparative HPLC was performed using a Waters LC 4000 system equipped with a Vydac 218TP54 analytical C-18 reverse phase column or a Vydac 218TP1022 semipreparative reverse phase column and a Waters 486 tunable absorbance detector set at 254 nM. For both analytical and preparative HPLC, the following mobile phase gradient system was used (solvent A: acetonitrile; solvent B: water with 0.1% TFA modifier): 0 min: 10% A; 6 min: 10% A; 16 min: 100% A; 26 min: 100% A; 36 min: 10% A; 51 min: 10% A.

Diethyl (3-Iodobenzyl)phosphonate (5). 3-Iodobenzyl bromide (2 g, 6.74 mmol, 1 equiv) and triethyl phosphite (5.84 mL, 5.6 g, 33.7 mmol, 5 equiv) were combined in benzene (2 mL). The reaction was refluxed for 16 h. The solvent and excess triethyl phosphite was removed in vacuo. Column chromatography (1:1 hexane/EtOAc, $R_f = 0.3$) of the crude residue yielded **5** as a yellow oil (2.31 g, 97%): ^1H NMR ($CDCl_3$) δ 7.57 (2H, m, Ar−H), 7.25 (1H, d, J = 5.9 Hz, Ar−H), 7.00 (1H, t, J = 8.1 Hz, Ar−H), 4.00 (4H, m, CH_2), 3.04 (2H, d, J = 21.9 Hz), 1.22 (6H, t, J = 7.4 Hz, CH_3); ^{31}P NMR ($CDCl_3$) δ 3.36; ^{13}C NMR ($CDCl_3$) δ 138.64 (d), 135.89 (d), 134.22 (d), 130.02 (d), 129.00 (d), 94.05 (d), 62.13 (d), 33.36 (d, J_{CP} = 138.2 Hz), 16.27 (d); MS *m*/*z* (relative intensity) 354 (100), 217 (97), 227 (50); HRMS calcd for $C_{11}H_{16}O_3PI$ 353.9882, found 353.9879.

Diethyl (3-Bromobenzyl)phosphonate (6). To a solution of 3-bromobenzyl bromide (25.0 g, 100 mmol, 1 equiv) in

benzene (50 mL) was added triethyl phosphite (85.7 mL, 83.1 g, 500 mmol, 5 equiv), and the mixture refluxed for 16 h. Solvent was removed, and **6** was obtained as a pure colorless oil by vacuum distillation (29.1 g, 95%): bp 70 °C, 0.050 mm; ^{1}H NMR ($CDCl_3$) δ 7.40 (2H, m, Ar−H), 7.21 (2H, m, Ar−H), 4.04 (4H, m, CH_2), 3.11 (2H, d, J = 20.5 Hz, CH_2), 1.26 (6H, t, J = 7.3 Hz, CH_3); ^{31}P NMR ($CDCl_3$) δ 23.28; ^{13}C NMR ($CDCl_3$) δ 134.31 (d), 132.71 (d), 129.83, 128.35 (d), 122.37, 62.06 (d), 33.55 (d, J_{CP} = 139.1 Hz), 16.18 (d); MS *m*/*z* (relative intensity) 109 (100), 169 (73), 306 (49); HRMS calcd for $C_{11}H_{16}O_3PBr$ 306.0020, found 306.0014.

Diethyl (4-Bromobenzyl)phosphonate (7). Compound **6** was prepared from 4-bromobenzyl bromide in the same manner as described for **6**. Column chromatography (1:1 hexane/EtOAc, R_f = 0.5) of the crude residue yielded pure **7** as a colorless oil in 95% yield: ^{1}H NMR ($CDCl_3$) δ 7.43 (2H, d, J = 8.1 Hz, Ar−H), 7.17 (2H, t, J = 8.1 Hz, Ar−H), 4.00 (4H, m, CH_2), 3.08 (2H, d, J = 21.9 Hz, CH_2), 1.25 (6H, t, J = 7.3 Hz, CH_3); ^{31}P NMR ($CDCl_3$) δ 23.19; ^{13}C NMR ($CDCl_3$) δ 131.56, 131.50, 131.47, 131.34, 130.88 (d), 120.81 (d), 62.10 (d), 33.27 (d, J_{CP} = 138.2 Hz), 16.29 (d); MS *m*/*z* (relative intensity) 169 (100), 109 (90), 306 (49); HRMS calcd for $C_{11}H_{16}O_3PBr$ 306.0020, found 306.0011.

Diethyl Difluoro(3-bromophenyl)methylphosphonate (9). A solution of **6** (5.7 g, 18.6 mmol, 1 equiv) in dry THF (40 mL) was cooled to −78 °C. NaHMDS (1 M in THF, 41.0 mL, 41.0 mmol, 2.2 equiv) was added dropwise over 5 min. The solution was stirred for 1 h, and NFSi (13.4 g, 43.0 mmol, 2.3 equiv) dissolved in dry THF (40 mL) was added dropwise to the reaction mixture. The reaction was allowed to react at −78 °C for 1 h and then quenched with water (250 mL). Solvent was removed under reduced pressure and the aqueous layer extracted with CH_2Cl_2 (4 × 100 mL), dried ($MgSO_4$), and concentrated leaving a yellow oil. Column chromatography (CH_2Cl_2, R_f = 0.5) of the crude residue yielded pure **9** as a yellow oil (4.95 g, 78%): ^{1}H NMR ($CDCl_3$) δ 7.74 (1H, s, Ar−H), 7.52 (2H, t, J = 8.8 Hz, Ar−H), 7.33 (1H, t, J = 8.1 Hz, Ar−H), 4.19 (4H, m, CH_2), 1.32 (6H, t, J = 7.3 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −33.18 (d, J_{FP} = 114.5 Hz); ^{31}P NMR ($CDCl_3$) δ 3.68 (t, J_{PF} = 113.7 Hz); ^{13}C NMR ($CDCl_3$) δ 135.05 (br dt), 133.80, 129.90, 129.37 (br t), 124.99 (br t), 122.41, 117.20 (dt, J_{CF} = 264.5 Hz, J_{CP} = 217.8 Hz), 64.74 (d), 16.16 (d); MS *m*/*z* (relative intensity) 109 (100), 205 (54), 342 (25); HRMS calcd for $C_{11}H_{14}O_3F_2PBr$ 341.9832, found 341.9846.

Diethyl Difluoro(4-bromophenyl)methylphosphonate (10). Compound **10** was prepared from **7** in a same manner as described for **9**. Column chromatography (9.8:0.2 CH_2Cl_2/EtOAc) of the crude residue yielded pure **10** as a yellow oil in 80% yield: ^{1}H NMR ($CDCl_3$) δ 7.60 (2H, d, J = 7.3 Hz, Ar−H), 7.49 (2H, d, J = 8.8 Hz, Ar−H), 4.21 (4H, m, CH_2), 1.33 (6H, t, J = 7.4 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −32.86 (d, J_{FP} = 115.9 Hz); ^{31}P NMR ($CDCl_3$) δ 3.58 (t, J_{PF} = 115.2 Hz); ^{13}C NMR ($CDCl_3$) δ 131.67, 127.96 (br t), 125.41, 117.72 (dt, J_{CF} = 263.5 Hz, J_{CP} = 218.7 Hz), 64.70 (d), 16.19 (d); MS *m*/*z* (relative intensity) 205 (100), 109 (71), 342 (39); HRMS calcd for $C_{11}H_{14}O_3F_2PBr$ 341.9832, found 341.9828.

Ethyl Hydrogen [(3-Bromophenyl)(difluoro)methyl]-phosphonate (11). To a suspension of **9** (4.72 g, 13.8 mmol, 1 equiv) in H_2O (36 mL) was added a solution of NaOH (10 M, 2.3 mL, 23.4 mmol, 1.7 equiv). The reaction was stirred at 55 °C for 4 h until it became homogeneous. After cooling to room temperature, the crude reaction was washed with ether (2 × 50 mL). The aqueous layer was acidified to pH 0.5−1.0 with 6 M HCl, extracted with CH_2Cl_2 (4 × 100 mL), dried ($MgSO_4$) and concentrated to give pure **11** as a pale yellow oil which solidified upon standing as a waxy solid (4.08 g, 94%): mp 50 °C; ^{1}H NMR ($CDCl_3$) δ 10.86 (1H, s, OH), 7.70 (1H, s, Ar−H), 7.62 (1H, d, J = 7.3 Hz, Ar−H), 7.50 (1H, d, J = 8.7 Hz, Ar−H), 7.33 (1H, t, J = 8.1 Hz, Ar−H), 4.16 (2H, m, CH_2), 1.32 (3H, t, J = 7.3 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −33.83 (d, J_{FP} = 119.1 Hz); ^{31}P NMR ($CDCl_3$) δ 3.75 (t, J_{PF} = 118.3 Hz); ^{13}C NMR ($CDCl_3$) δ 134.71 (br dt) 133.89, 129.90, 129.44 (br dt), 125.07 (br dt), 122.42, 116.84 (dt, J_{CF} = 262.6 Hz, J_{CP} = 224.2 Hz), 65.36 (d), 16.07 (d); MS *m*/*z* (relative intensity) 205 (100), 314 (37), 109 (20); HRMS calcd for $C_9H_{10}O_3F_2PBr$ 313.9519, found 313.9517.

Ethyl Hydrogen [(4-Bromophenyl)(difluoro)methyl]-phosphonate (12). Compound **12** was prepared from **10** in the same manner as described for **11**. Pure **12** was obtained without further purification as a pale yellow oil, which solidified on standing as a waxy solid in 92% yield: mp 58 °C; ^{1}H NMR ($CDCl_3$) δ 11.61 (1H, s, OH), 7.58 (2H, d, J = 8.1 Hz, Ar−H), 7.42 (2H, d, J = 8.1 Hz, Ar−H), 4.12 (2H, m, CH_2), 1.31 (3H, t, J = 7.0 Hz, CH_3); ^{19}F NMR ($CDCl_3$) ??-34.38 (d, J_{FP} = 119.0 Hz); ^{31}P NMR ($CDCl_3$) ??3.60 (t, J_{PF} = 119.8 Hz); ^{13}C NMR ($CDCl_3$) δ 131.69, 128.03, 125.52, 117.42 (dt, J_{CF} = 262.6 Hz, J_{CP} = 224.7 Hz), 65.32 (d), 16.13 (d); MS *m*/*z* (relative intensity) 205 (100), 126 (37), 314 (26); HRMS calcd for $C_9H_{10}O_3F_2PBr$ 313.9519, found 313.9523.

Coupling of 13 to 3% Chloromethylated NCPS (14). To a suspension of sodium hydride (0.48 g, 20 mmol, 5 equiv) in dry DMF (60 mL) was added **13**,[23] (3.5 g, 20 mmol, 5 equiv) and the mixture was stirred at 0 °C for 2 h. Then 3% chloromethylated non-cross-linked polystyrene (NCPS, 0.3 mmol/g, 10 g, 4 mmol, 1 equiv)[13b] and n-Bu_4NI (0.148 g, 0.40 mmol, 0.10 equiv) were added, and the mixture was stirred at room temperature for 12 h. The DMF was removed in vacuo, and the resulting crude polymer was dissolved in CH_2Cl_2 (100 mL), washed with brine (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (60 mL) and added dropwise to a solution of cold H_2O/MeOH (600 mL, 1:4). The precipitate was collected by filtration, washed with cold H_2O/MeOH (150 mL, 1:4), and vacuum-dried to give **14** as a white fluffy solid (9.7 g, 96% polymer recovered). No other polymer-bound species were detected by ^{1}H NMR. ^{1}H NMR ($CDCl_3$) δ 4.65 (1H, br s, O−CH−O), 4.45 (2H, br s, Ar−CH_2), 3.85 (2H, br s, CH_2−O−THP) 3.5 (4H, br s, O−CH_2−CH_2−). Signals in the range of 7.3−6.2 and 2.3−1.2 overlap with that of the NCPS. Consequently, ^{1}H NMR assignments were not attempted for any signals which fell in these two regions for this or any subsequent polymer-bound species described below.

Removal of THP Group from 14 (15). Polymer **14** (4 g, 1.2 mmol) was dissolved in a mixture of THF/6 M HCl (30 mL, 4:1) and refluxed for 36 h. The reaction mixture was added to a cold solution of H_2O/methanol (250 mL, 1:4). The resulting precipitate was collected by filtration, washed with cold H_2O/methanol (100 mL, 1:4), and dried under high vacuum to give polymer **15** as a white solid (3.9 g, 95% recovery of polymer): ^{1}H NMR ($CDCl_3$) δ 4.47 (2H, br s, Ar−CH_2−O), 3.68 (2H, br s, C*H*$_2$OH), 3.51 (2H, br s, −O−C*H*$_2$−CH_2−). The loading was determined to 0.3 mmol/g as determined using NMR methods similar to that described in ref 13b.

Attachment of 11 and 12 to Polymer 15 (16 and 17). To a solution of **11** or **12** (2 equiv), triphenyl phosphine (2 equiv), and DIAD (diisopropylazidodicarboxylate, 2 equiv) in dry THF (5 mL) was added a solution of polymer **15** (∼1 equiv of free hydroxyl group) and triethylamine (5 equiv) in dry THF (25 mL). The mixture was stirred at room temperature for 4 h and then added dropwise to a solution of cold H_2O/methanol (300 mL, 1:4) which resulted in the precipitation of the polymer. The precipitate was collected by filtration and dried under high vacuum which yielded polymer **16** or **17** as a white powder (96% recovery of polymer): Polymer **16**: ^{1}H NMR ($CDCl_3$) δ 4.43 (2H, br s, Ar−CH_2−O), 4.25 (4H, br m, CH_2−O−P), 3.47 (2H, br s, O−CH_2); ^{19}F NMR ($CDCl_3$) δ −32.29 (d, J_{FP} = 112.9 Hz). Polymer **17**: ^{1}H NMR ($CDCl_3$) δ 4.45 (2H, br s, Ar−CH_2−O), 4.23 (4H, br m, CH_2−O−P), 3.49 (2H, br s, O−CH_2); ^{19}F NMR ($CDCl_3$) δ −32.51 (d, J_{FP} = 116 Hz).

General Method for Suzuki Cross-Coupling on Polymers 16 and 17 (General Structure 19 and 22). Polymers **16** or **17** (400−500 mg, ∼1 equiv polymer-bound aryl bromide), arylboronic acid (**18a**−**18n**, 3 equiv), K_2CO_3 (3 equiv), H_2O (10 equiv), and $(C_6H_5CN)_2PdCl_2$ (0.2 equiv) were placed in a round-bottom flask flushed with argon and were dissolved in DMF (3 mL) that had been deoxygenated via three freeze−pump−thaw cycles. Then 400 μL of the reaction mixture was withdrawn and placed in an argon flushed NMR tube, which was attached to a 180° shaker. The reaction progress was monitored via ^{19}F NMR until 100% conversion was observed. The reaction mixture was transferred to microcentrifuge tubes and centrifuged (∼15 min in an Eppendorf microcentrifuge) to remove the palladium catalyst. The supernatant was concentrated, dissolved in CH_2Cl_2 (3 mL), and added to a solution of cold H_2O/methanol (30 mL, 1:4). The precipitated polymers of type **19** and **20** were collected by filtration. Percent recovery of **19** and **20** varied from 85 to 95%. Only a single polymer-bound species was evident by ^{19}F NMR. In general, the ^{19}F NMR chemical shift of polymers bearing the biaryl products differed by about 1−2 ppm from that of starting polymers **16** and **17.**

General Method for Cleaving the Phosphonic Acids from Polymers of Type 19 and 20 (21a−21n, 22a−22n). To a solution of the polymer-bound biaryl derivatives of type **19** and **20** (∼400−500 mg, ∼1 equiv of polymer-bound phosphonate) in dry CH_2Cl_2 (3 mL) was added TMSI (4 equiv) or TMSBr (10 equiv). The reaction was stirred for 3 h (TMSI) or refluxed for 48 h (TMSBr). The crude reaction mixture was concentrated in vacuo, and the residue was subjected to high vacuum for several hours. The residue was dissolved in CH_2Cl_2 (2.5 mL) and added dropwise to a solution of H_2O/methanol (25 mL, 1:4) and stirred for 12 h. The suspension was filtered, and the filtrate was concentrated in vacuo. To remove trace amounts of polymer and other organic impurities, the following wash procedure was performed. The crude reaction product was dissolved in a NaOH solution (9 mL, 0.1 M solution) and washed with CH_2Cl_2 (3 × 8 mL). The solution was acidified to pH 0.5−1.0 with 5 N HCl, extracted into diethyl ether (5 × 10 mL), and concentrated to give the phosphonic acid products. The phosphonic acids were dissolved in an aqueous solution (2 mL) containing NH_4HCO_3 (2.5 equiv). The solution was frozen and then lyophilized. The lyophilization procedure was repeated until a constant weight was obtained. This yielded the phosphonic acids as white to slightly off-white ammonium salts. See Table 2 for yields and purities.

(3-Phenylphenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21a). Yield: 69.6 (mg/g); ^{1}H NMR (D_2O) δ 7.38−7.86 (9H, br m, Ar−H); ^{19}F NMR (D_2O) δ −27.77 (d, J_{FP} = 93.1 Hz); ^{31}P NMR (D_2O) δ 5.39 (t, J_{PF} = 93.9 Hz); ESMS *m*/*z* (relative intensity) 283 (100). HPLC retention time = 16.4 min. Purity: 97% (HPLC).

(3-(4′-Biphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21b). Yield: 98.2 (mg/g); ^{1}H NMR (D_2O) δ 7.52−7.94 (13H, br m, Ar−H); ^{19}F NMR (D_2O) δ −27.84 (d, J_{FP} = 94.6 Hz); ^{31}P NMR (D_2O) δ 5.32 (t, J_{PF} = 94.6 Hz); ESMS *m*/*z* (relative intensity) 359 (100). HPLC retention time = 18.0 min. Purity: 91% (HPLC).

(3-(2′-Naphthyl)phenyl)(difluoro)methylphosphonic Acid (21c). Yield: 85.2 (mg/g); ^{1}H NMR (D_2O) δ 7.56−8.27 (11H, br m, Ar−H); ^{19}F NMR (D_2O) δ −27.90 (d, J_{FP} = 97.7 Hz); ^{31}P NMR (D_2O) δ 5.32 (t, J_{PF} = 95.4 Hz); ESMS *m*/*z* (relative intensity) 333 (100). HPLC retention time = 17.3 min. Purity: 99% (HPLC).

(3-(2′-Methylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21d). Yield: 70.9 (mg/g); ^{1}H NMR (D_2O) δ 7.41−7.68 (8H, br m, Ar−H), 2.32 (3H, s, CH_3); ^{19}F NMR (D_2O) δ −27.44 (d, J_{FP} = 94.7 Hz); ^{31}P NMR (D_2O) δ 5.39 (t, J_{PF} = 93.9 Hz); ESMS *m*/*z* (relative intensity) 297 (100). HPLC retention time = 16.8 min. Purity: 98% (HPLC).

(3-(4′-Methylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21e). Yield: 69.9 (mg/g); ^{1}H NMR (D_2O) δ 7.27−7.84 (8H, br m, Ar−H), 2.31 (3H, s, CH_3); ^{19}F NMR (D_2O) δ −27.47 (d, J_{FP} = 93.1 Hz); ^{31}P NMR (D_2O) δ 5.54 (t, J_{PF} = 92.4 Hz); ESMS *m*/*z* (relative intensity) 297 (100). HPLC retention time = 16.8 min. Purity: 99% (HPLC).

(3-(4′-Ethylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21f). Yield: 74.9 (mg/g); ^{1}H NMR (D_2O) δ 7.11−7.85 (8H, br m, Ar−H), 2.45 (2H, unres m, CH_2), 1.03 (3H, t, J = 7.4 Hz, CH_3); ^{19}F NMR (D_2O) δ −28.41 (d, J_{FP} = 99.2 Hz); ^{31}P NMR (D_2O) δ 5.09 (t, J_{PF} = 98.4 Hz); ESMS *m*/*z* (relative intensity) 311 (100). HPLC retention time = 17.7 min. Purity: 99% (HPLC).

(3-(4′-*tert*-Butylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21g). Yield: 91.1(mg/g);

^{1}H NMR (D_2O) δ 7.58−7.85 (8H, br m, Ar−H), 1.29 (9H, s, CH_3); ^{19}F NMR (D_2O) δ −29.41 (d, J_{FP} = 102.2 Hz); ^{31}P NMR (D_2O) δ 4.75 (t, J_{PF} = 102.3 Hz); ESMS *m*/*z* (relative intensity) 339 (100). HPLC retention time = 18.1 min. Purity: 99% (HPLC).

(3-(4′-Acetylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21h). Yield: 67.3 (mg/g); ^{1}H NMR (D_2O) δ 7.46−7.80 (8H, br m, Ar−H), 2.45 (3H, s, CH_3); ^{19}F NMR (D_2O) δ −29.43 (d, J_{FP} = 102.3 Hz); ^{31}P NMR (D_2O) δ 4.54 (t, J_{PF} = 102.3 Hz); ESMS *m*/*z* (relative intensity) 325 (100). HPLC retention time = 15.8 min. Purity: 80% (HPLC).

(3-(3′-Trifluoromethylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21i). Yield: 78.9 (mg/g); ^{1}H NMR (D_2O) δ 7.50−7.98 (8H, br m, Ar−H); ^{19}F NMR (D_2O) δ 16.16 (s), −27.74 (d, J_{FP} = 93.1 Hz); ^{31}P NMR (D_2O) δ 5.39 (t, J_{PF} = 93.1 Hz); ESMS *m*/*z* (relative intensity) 351 (100). HPLC retention time = 17.4 min. Purity: 100% (HPLC).

(3-(4′-Trifluoromethylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21j). Yield: 49.9 (mg/g); ^{1}H NMR (D_2O) δ 7.58−7.84 (8H, br m, Ar−H); ^{19}F NMR (D_2O) δ 16.29 (s), −28.94 (d, J_{FP} = 100.2 Hz); ^{31}P NMR (D_2O) δ 4.88 (t, J_{PF} = 99.2 Hz); ESMS *m*/*z* (relative intensity) 351 (100). HPLC retention time = 17.5 min. Purity: 99% (HPLC).

(3-(3′-Fluorophenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21k). Yield: 66.7 (mg/g); ^{1}H NMR (D_2O) δ 7.83 (1H, s, Ar−H), 7.40−7.67 (6H, br m, Ar−H), 7.08 (1H, t, J = 5.1 Hz, Ar−H); ^{19}F NMR (D_2O) δ −27.78 (d, J_{FP} = 93.0 Hz), −35.24 (s); ^{31}P NMR (D_2O) δ 5.41 (t, J_{PF} = 93.1 Hz); ESMS *m*/*z* (relative intensity) 301 (100). HPLC retention time = 16.5 min. Purity: 98% (HPLC).

(3-(4′-Fluorophenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21l). Yield: 75.8 (mg/g); ^{1}H NMR (D_2O) δ 7.45−7.80 (7H, br m, Ar−H), 7.15 (1H, t, J = 8.8 Hz, Ar−H); ^{19}F NMR (D_2O) δ −27.72 (d, J_{FP} = 93.1 Hz), −37.51 (s); ^{31}P NMR (D_2O) δ 5.49 (t, J_{PF} = 93.1 Hz); ESMS *m*/*z* (relative intensity) 301 (100). HPLC retention time = 16.4 min. Purity: 96% (HPLC).

(3-(4′-Chlorophenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21m). Yield: 76.2 (mg/g); ^{1}H NMR (D_2O) δ 7.26−7.74 (8H, br m, Ar−H); ^{19}F NMR (D_2O) δ −28.95 (d, J_{FP} = 100.7 Hz); ^{31}P NMR (D_2O) δ 4.86 (t, J_{PF} = 99.2 Hz); ESMS *m*/*z* (relative intensity) 317 (100). HPLC retention time = 16.9 min. Purity: 99% (HPLC).

(3-(3′-Chloro-4′-fluorophenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (21n). Yield: 83.5 (mg/g); ^{1}H NMR (D_2O) δ 7.22−7.74 (6H, br m, Ar−H), 7.18 (1H, t, J = 8.8 Hz, Ar−H); ^{19}F NMR (D_2O) δ −28.18 (d, J_{FP} = 96.1 Hz), −40.45 (s); ^{31}P NMR (D_2O) δ 5.22 (t, J_{PF} = 94.6 Hz); ESMS *m*/*z* (relative intensity) 335 (100). HPLC retention time = 17.0 min. Purity: 96% (HPLC).

(4-Phenylphenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22a). Yield: 85.2 (mg/g); ^{1}H NMR (D_2O) δ 7.69 (6H, s, Ar−H), 7.38−7.52 (3H, br m, Ar−H); ^{19}F NMR (D_2O) δ −27.50 (d, J_{FP} = 94.6 Hz); ^{31}P NMR (D_2O) δ 5.49 (t, J_{PF} = 93.8 Hz); ESMS *m*/*z* (relative intensity) 283 (100). HPLC retention time = 16.3 min. Purity: 98% (HPLC).

(4-(4′-Biphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22b). Yield: 72.3 (mg/g); NMR data could not be obtained due to solubility problems. ESMS *m*/*z* (relative intensity) 359 (100). HPLC retention time = 19.1 min. Purity: 96% (HPLC).

(4-(2′-Naphthyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22c). Yield: 70.8 (mg/g); ^{1}H NMR (D_2O) δ 7.55−8.18 (11H, br m, Ar−H); ^{19}F NMR (D_2O) δ −29.17 (d, J_{FP} = 100.7 Hz); ^{31}P NMR (D_2O) δ 4.81 (t, J_{PF} = 101.5 Hz); ESMS *m*/*z* (relative intensity) 333 (100). HPLC retention time = 17.4 min. Purity: 97% (HPLC).

(4-(2′-Methylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22d). Yield: 66.9 (mg/g); ^{1}H NMR (D_2O) δ 7.26−7.66 (8H, br m, Ar−H), 2.19 (3H, s, CH_3); ^{19}F NMR (D_2O) δ −27.80 (d, J_{FP} = 94.6 Hz); ^{31}P NMR (D_2O) δ 5.43 (t, J_{PF} = 94.7 Hz); ESMS *m*/*z* (relative intensity) 297 (100). HPLC retention time = 16.9 min. Purity: 98% (HPLC).

(4-(4′-Methylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22e). Yield: 65.9 (mg/g); ^{1}H NMR (D_2O) δ 7.60−7.68 (6H, br m, Ar−H), δ 7.33 (2H, d, J = 8.8 Hz, Ar−H), 2.34 (3H, s, CH_3); ^{19}F NMR (D_2O) δ −27.31 (d, J_{FP} = 93.0 Hz); ^{31}P NMR (D_2O) δ 5.78 (t, J_{PF} = 92.3 Hz); ESMS *m*/*z* (relative intensity) 297 (100). HPLC retention time = 17.0 min. Purity: 99% (HPLC).

(4-(4′-Ethylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22f). Yield: 78.1 (mg/g); ^{1}H NMR (D_2O) δ 7.34−7.68 (8H, br m, Ar−H), 2.65 (2H, unres m, CH_2), 1.18 (3H, t, J = 7.4 Hz, CH_3); ^{19}F NMR (D_2O) δ −27.27 (d, J_{FP} = 91.6 Hz); ^{31}P NMR (D_2O) δ 5.60 (t, J_{PF} = 92.4 Hz); ESMS *m*/*z* (relative intensity) 311 (100). HPLC retention time = 17.5 min. Purity: 96% (HPLC).

(4-(4′-*tert*-Butylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22g). Yield: 72.0 (mg/g); ^{1}H NMR (D_2O) δ 7.57−7.74 (8H, br m, Ar−H), 1.30 (9H, s, CH_3); ^{19}F NMR (D_2O) δ −27.78 (d, J_{FP} = 94.6 Hz); ^{31}P NMR (D_2O) δ 5.37 (t, J_{PF} = 94.6 Hz); ESMS *m*/*z* (relative intensity) 339 (100). HPLC retention time = 18.2 min. Purity: 98% (HPLC).

(4-(4′-Acetylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22h). Yield: 97.5 (mg/g); ^{1}H NMR (D_2O) δ 7.74−8.00 (8H, br m, Ar−H), 2.62 (3H, s, CH_3); ^{19}F NMR (D_2O) δ −27.45 (d, J_{FP} = 91.6 Hz); ^{31}P NMR (D_2O) δ 5.66 (t, J_{PF} = 93.1 Hz); ESMS *m*/*z* (relative intensity) 325 (100). HPLC retention time = 15.8 min. Purity: 91% (HPLC).

(4-(3′-Trifluoromethylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22i). Yield: 62.7 (mg/g); ^{1}H NMR (D_2O) δ 7.60−8.00 (8H, br m, Ar−H); ^{19}F NMR (D_2O) δ 16.11 (s), −27.47 (d, J_{FP} = 94.7 Hz); ^{31}P NMR (D_2O) δ 5.54 (unres t); ESMS *m*/*z* (relative intensity) 351 (100). HPLC retention time = 18.7 min. Purity: 97% (HPLC).

(4-(4′-Trifluoromethylphenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22j). Yield: 85.9 (mg/g); ^{1}H NMR (D_2O) δ 7.71−7.85 (8H, br m, Ar−H); ^{19}F NMR (D_2O) δ 16.29 (s), −27.56 (d, J_{FP} = 93.0 Hz); ^{31}P

NMR (D_2O) δ 5.49 (t, J_{PF} = 92.3 Hz); ESMS *m/z* (relative intensity) 351 (100). HPLC retention time = 16.7 min. Purity: 97% (HPLC).

(4-(3′-Fluorophenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22k). Yield: 81.9 (mg/g); ^{1}H NMR (D_2O) δ 7.41−7.69 (7H, br m, Ar−H), 7.11 (1H, t, J = 2.9 Hz, Ar−H); ^{19}F NMR (D_2O) δ −27.59 (d, J_{FP} = 91.5 Hz), −35.23 (s); ^{31}P NMR (D_2O) δ 5.47 (t, J_{PF} = 93.1 Hz); ESMS *m/z* (relative intensity) 301 (100). HPLC retention time = 16.5 min. Purity: 99% (HPLC).

(4-(4′-Fluorophenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22l). Yield: 75.8 (mg/g); ^{1}H NMR (D_2O) δ 7.67 (6H, s, Ar−H), 7.20 (2H, t, J = 8.8 Hz, Ar−H); ^{19}F NMR (D_2O) δ −27.35 (d, J_{FP} = 93.1 Hz), −37.32 (s); ^{31}P NMR (D_2O) δ 5.58 (t, J_{PF} = 93.1 Hz); ESMS *m/z* (relative intensity) 301 (100). HPLC retention time = 16.6 min. Purity: 99% (HPLC).

(4-(4′-Chlorophenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22m). Yield: 79.4 (mg/g); ^{1}H NMR (D_2O) δ 7.39−7.63 (8H, br m, Ar−H); ^{19}F NMR (D_2O) δ −28.35 (d, J_{FP} = 99.2 Hz); ^{31}P NMR (D_2O) δ 5.11 (t, J_{PF} = 97.7 Hz); ESMS *m/z* (relative intensity) 317 (100). HPLC retention time = 17.1 min. Purity: 99% (HPLC).

(4-(3′-Chloro-4′-fluorophenyl)phenyl)(difluoro)methylphosphonic Acid, Ammonium Salt (22n). Yield: 85.9 (mg/g); ^{1}H NMR (D_2O) δ 7.52−7.77 (6H, br m, Ar−H), 7.27 (1H, t, J = 9.6 Hz, Ar−H); ^{19}F NMR (D_2O) δ −27.67 (d, J_{FP} = 93.1 Hz), −40.28 (s); ^{31}P NMR (D_2O) δ 5.43 (t, J_{PF} = 93.9 Hz); ESMS *m/z* (relative intensity) 335 (100). HPLC retention time = 17.4 min. Purity: 98% (HPLC).

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Supporting Information Available. ^{1}H and ^{19}F NMR spectra and HPLC chromatograms of **21a**−**21n** and **22a**−**22n**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(21) ^1H NMR was of little or no use for following these reactions since most of the protons of the biaryl products appear in the aryl region which were obscured by the polymer. In general, the ^{19}F NMR chemical shift of polymers bearing the biaryl products (**19** and **20**) differed by about 1−2 ppm from that of starting polymers **16** and **17.**

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