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Facile Synthesis of Aryl(difluoromethyl)phosphonates through CuBr-Mediated Cross Coupling Reactions of [(Diethoxyphosphinyl)difluoromethyl]zinc Bromide with Aryl Iodides

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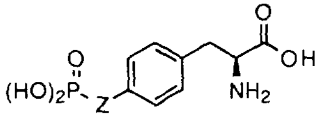
Abstract: The CuBr-promoted coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide **6** with aryl iodides in either DMF or DMA was examined to give a series of aryl(difluoromethyl)phosphonates. The coupling reaction was applicable to the selective synthesis of α,α-difluoro-4-iodobenzylphosphonate **11e**, a useful intermediate for the preparation of F_2Pmp. 1-[(Diethylphosphono)difluoromethyl]naphthalene **15** and the regioisomer **16** were obtained in high yields from 1- and 2-iodonaphthalene, respectively. The phosphonate **16** was transformed to the free acid **4a**, a low molecular-mass inhibitor of protein phosphatases. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

There is currently considerable interest in (difluoromethylene)phosphonates as hydrolytically stable analogues of naturally occurring phosphate esters, since they mimic accurately the parental phosphates in their isosteric and isopolar properties.[1] Although the concept of (difluoromethylene)phosphonates as analogues of phosphate esters has been extensively argued,[2] this replacement has provided several natural product analogues with significant activities.[3] Among the various (difluromethylene)phosphonate mimics, the compounds in which the (difluoromethylene)phosphonate moiety is incorporated with an aromatic ring, such as aryl(difluoromethyl)phosphonates, are of special interest. Burke has described the synthesis of (phosphonodifluoromethyl)phenylalanine (F_2Pmp) **2**[4] as an analogue of phosphotyrosine (pTyr) **1**, and its incorporation within a hexapeptide conferred inhibitory activity for protein-phosphotyrosine phosphatases (PTPases).[5] This demonstrates the potential utility of aryl(difluoromethyl)phosphonates as valuable pharmacological tools for studying cellular signal transduction and for therapeutic intervention. Moreover, structure-activity studies of a series of aryl(difluoromethyl)phosphonates showed that the 1- and 2-substituted naphthyl(difluoromethyl)phosphonates **3** and **4**, the simplified analogues of pTyr, still exhibited binding affinity to the catalytic sites of PTPases, and had good inhibitory potencies toward PTP-1B and the serine/threonine phosphatase PP-2A.[6]



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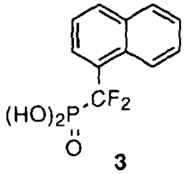
2: Z=CF_2



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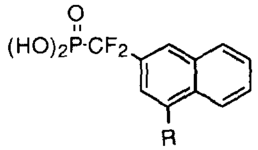
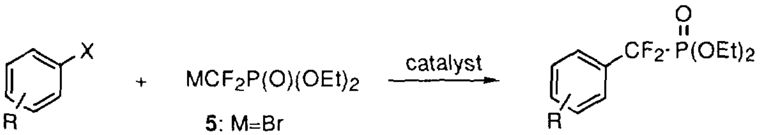


4a: R=H
b: R=OH

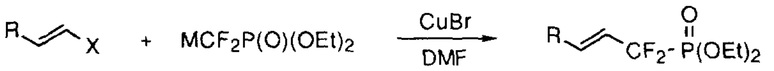
The aryl(difluoromethyl)phosphonates have been conventionally synthesized by a method that involves the preparation of hydrolytically unstable benzilic α-oxophosphonates, followed by the fluorination with (diethylamido)sulfur trifluoride (DAST).[4,6] However, the preparation of aryl(difluoromethyl)phosphonates on multi-gram scales through this method is rather difficult, due to the requirement of a large excess of expensive DAST as well as to the unpredictable exothermic reaction.[7] Thus, the development of DAST-free methods is required for the facile preparation of aryl(difluoromethyl)phosphonates on multi-gram scales.[7] From the methodological point of view, a cross coupling reaction between aryl halides and metalated dialkyl difluoromethylphosphonates catalyzed by transition metal complexes or salts would be desirable (Eq. 1). However, such direct carbon–carbon bond formation has not been extensively studied.[8]



(Eq. 1)

5: M=Br
6: M=BrZn
7: M=BrCd

Recently, we have shown that the coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide **6**[9] and alkenyl halides in dimethylformamide (DMF) in the presence of CuBr is a facile method for the stereospecific introduction of the (difluoromethylene)phosphonate moiety onto the SP^2-carbon, to give the (α,α-difluoroallyl)phosphonates **9** in good yield (Eq. 2).[10] The (α,α-difluoroallyl)phosphonates **9** were proved to be formed by a cross coupling reaction of the organocopper species **8**, formed by the transmetalation of **6** with CuBr, and alkenyl halides.[10] As an extension of the previous work, we have pursued the CuBr-mediated coupling reaction of aryl iodides with **6**, generated from diethyl bromodifluoromethylphosphonate **5** and zinc in either DMF or dimethylacetamide (DMA). During the investigation, Burton reported the CuCl-mediated cross coupling reaction of aryl iodides with the cadmium reagent **7**.[8] The report from Burton prompts us to disclose our own efforts in this field.



(Eq. 2)

R=Ph, $THPOCH_2$ etc.
X=I or Br

6: M=BrZn
8: M=$Br_2Zn\cdot Cu$

9

RESULTS AND DISCUSSION

At first, we examined the possibility of the CuBr-catalyzed coupling reaction of **6** with iodobenzene under a variety of conditions (Table 1). The zinc reagent **6**, prepared from the bromide **5** and zinc powder in DMF, was transmetalated with a stoichiometric amount of CuBr, according to the method reported previously.[10] Then, the resulting organocopper species **8** was treated with iodobenzene at 25 °C for 24 h. While the reaction was found to proceed with the expected coupling product **11a**, the yield (33%) was low under the conditions (entry 1). The yield was not improved by elevating the reaction temperature, due to the thermal instability of the organocopper species **8** in DMF (entry 2).[10] Then, the effects of solvents and ultrasound[11] on this coupling reaction were examined (entries 3-6). While *N*-methyl-2-pyrroridinone (NMP) was ineffective for the improvement of the yield (entry 4), the coupling yield was found to increase to 51% with the reaction in DMA (entry 3). Although the reaction in DMF under ultrasound irradiation did not improve the coupling yield (entries 1 *vs* 5), an increased yield (60%) was obtained when the reaction was carried out in DMA for 24 h under ultrasound irradiation (entries 3 *vs* 6).

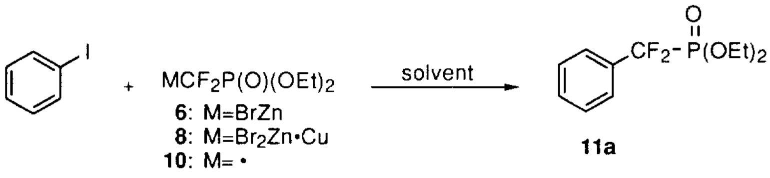


Table 1. CuBr-promoted coupling reaction of **6** with iodobenzene

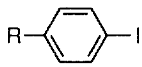
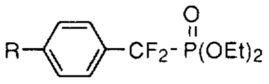
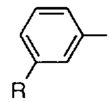
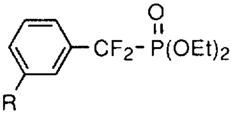
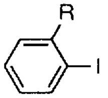
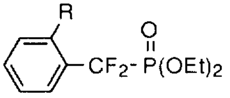
Entry	Condition[a]	Time, h	**11a** Yield, %
1	DMF / 25 °C	24	33
2	DMF / 80 °C	18	3
3	DMA / 25 °C	24	51
4	NMP / 25 °C	24	27
5	DMF / ultrasound / 25 °C	24	33
6	DMA / ultrasound / 25 °C	24	60

[a] Two equivalents of **6** and CuBr were utilized for all reactions.

In these coupling reactions, a stoichiometric amount of CuBr was necessary to induce a good yield. The reaction of **6** with iodobenzene, in the presence of a catalytic amount (25 *mol%* relative to **6**) of CuBr in DMA under the sonicated conditions, gave the coupling product in a 21% yield. The results suggest that the coupling reaction does not involve a catalytic cycle with CuBr. Since the coupling reaction between **6** and the alkenyl halides proceeded with catalytic amounts of CuBr under similar conditions, [10] the mechanism of the present coupling reaction differs from that of the coupling reaction with alkenyl halides. The previous investigation shows that the copper species **8** in DMF is prone to decompose to the [(diethoxyphosphinyl)difluoromethyl] radical **10**;[10] therefore, the coupling reaction may involve a single electron transfer process *via* **10**. However, a clear understanding of the the coupling reaction mechanism must await further experimentation.

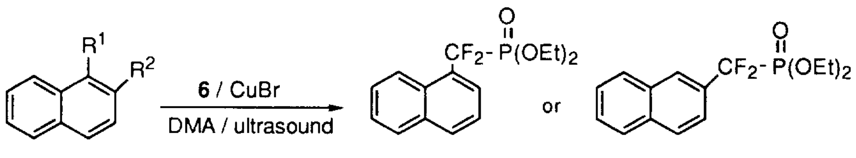
Next, on the basis of these results, several substituted iodobenzenes were coupled with **6** under a variety of conditions, in order to explore the scope and applicability of the method. The results of this exploratory study are summarized in Table 2. The coupling reactions with iodobenzenes possessing an electron withdrawing substituent, such as methyl iodobenzoates, gave higher yields than the coupling reactions of iodotoluene and its α-acethoxy derivatives under the same conditions (entries 1, 7, 10 *vs* 3, 9, 12). While the coupling yields of the reactions with the *p*- and *m*-iodobenzoates were modest (entries 3 and 9), an excellent yield was observed with the reaction of *o*-iodobenzoate (entry 12). With the halo-substituted iodobenzenes, such as 1-chloro-4-iodobenzene, the reaction selectively gave the product coupled at the iodide carbon (entry 4). It is noteworthy that the coupling reaction with 1,4-diiodobenzene gave preferentially α,α-difluoro-4-iodobenzylphosphonate **11e**, a valuable intermediate for the synthesis of protective variants of F$_2$Pmp **2**[4c] (entries 5 and 6). Treatment of 1,4-diiodobenzene with 2 equiv. of **6** in the presence of 2 equiv. of CuBr in DMF for 16 h gave **11e** in a 37% yield, along with the bis-coupling product **12** (9% yield) as a byproduct (entry 5). The yield of **11e** increased to 52%, upon conducting the reaction in DMA for 24 h (entry 6). Since the CuCl-promoted coupling reaction of excess cadmium reagent **7** with 1,4-diiodobenzene gave the bis-coupling product **12** without the formation of **11e** as reported by Burton,[8] the results obtained from the coupling reaction between **6** and 1,4-diiodobenzene clearly show the features of our coupling reaction.

Table 2 CuBr-promoted coupling reaction of **6** with substituted iodobenzenes

Entry	ArI	Condition[a]	Time / h	ArCF$_2$P(O)(OEt)$_2$ (Yield, %)
				
1	R=Me	A	23	**11b** R=Me (17)
2	R=Me	B	18	**11b** (64)
3	R=CO$_2$Me	A	15	**11c** R=CO$_2$Me (51)
4	R=Cl	A	150	**11d** R=Cl (42)
5	R=I	A	16	**11e** R=I (37) **12** R=CF$_2$P(O)(OEt)$_2$ (9)
6	R=I	C	24	**11e** (52) **12** (26)
				
7	R=CH$_2$OAc	A	24	**11f** R=CH$_2$OAc (37)
8	R=CH$_2$OAc	B	7	**11f** (54)
9	R=CO$_2$Me	A	24	**11g** R=CO$_2$Me (52)
				
10	R=CH$_2$OAc	A	24	**11h** R=CH$_2$OAc (42)
11	R=CH$_2$OAc	B	7	**11h** (51)
12	R=CO$_2$Me	A	24	**11i** R=CO$_2$Me (99)

[a] All reactions were carried out at room temperature; condition A: DMF, CuBr (2 equiv.), **6** (2 equiv.); condition B: DMA, CuBr (2 equiv.), **6** (2 equiv.), ultrasound; condition C: DMA, CuBr (2 equiv.), **6** (2 equiv.).

Finally, this coupling reaction was applied to the synthesis of protecting variants of the naphthyl(difluoromethyl)phosphonic acids **3** and **4a**.[6a,c] Treatment of **6** with the iodonaphthalenes **13** and **14**[12] in DMA for 14 h under sonicated conditions gave the phosphonates **15** and **16** in 85% and 79% yields, respectively. Deprotection of **16** in the usual manner [1) TMSBr / CH_2Cl_2, 2) MeOH] afforded **4a**, a low molecular-mass inhibitor of protein phosphatases,[6c] in a 67% yield. The previous synthesis of **4a** required a 4-step sequence from 2-formylnaphthalene, for a 12% yield.[6a] Therefore, the efficacy of the present coupling reaction with iodonaphthalenes is apparent.



13: R^1=I, R^2=H
14: R^1=H, R^2=I

15 Yield: 85%

16 Yield: 79%

CONCLUSION

In conclusion, we have developed a DAST-free route for the synthesis of aryl(difluoromethyl)phosphonates, using the Cu(I)-mediated cross coupling reaction of [(diethoxyphosphinyl)-difluoromethyl]zinc bromide **6** and aryl iodides. This method offers some distinct advantages over the conventional one using the DAST reagent, such as simplicity, safety, and low cost.

EXPERIMENTAL

General. All reactions were carried out under nitrogen atmospheres, unless otherwise specified. The sonicated reactions were carried out under ultrasound irradiation generated by an ultrasonic cleaner (Iuchi VS-100, 100 W, 50 KHz). NMR data were recorded in $CDCl_3$ unless otherwise specified. ^1H NMR data were obtained on a Bruker AM 400 (400 MHz) or a Varian Gemini 300 (300 MHz). The chemical shift data for each signal are given in units of δ relative to TMS, $CHCl_3$ (δ.7.26), or DMSO (δ 2.50). ^{13}C NMR (100 MHz) and ^{31}P NMR (160 MHz) were taken on a Bruker AM 400 with broad-band ^1H decoupling. The chemical shifts of ^{13}C are reported relative to $CDCl_3$ (δ 77.0) or DMSO-d_6 (δ 39.7). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4. ^{19}F NMR spectra (Bruker AM 400, 376 MHz) were measured using benzotrifluoride (BTF) as an internal reference. IR spectra were recorded as film or KBr disc on a Perkin-Elmer 1710 FTIR spectrometer. Mass spectra were measured on a Hitachi M-80 or a VG Auto Spec spectrometer.

General Procedure for the CuBr-mediated coupling reaction between aryl iodides and 6. To a stirred suspension of Zn dust (390 mg, 6 mmol) in dry DMF (3 mL) was slowly added a solution of **5** (1.60 g, 6 mmol) in DMF (3 mL). During the addition, an exothermic reaction occurred. The addition was controlled so that the internal temperature was maintained at 50-60 °C. After the addition was completed, the solution was stirred at room temperature for an additional 3 h, and then CuBr (860 mg, 6 mmol) was added in one portion. The mixture was stirred at the same temperature for 30 min to give the organocopper reagent **8** in DMF. Aryl iodide (3 mmol) in DMF (1 mL) was added dropwise at room temperature (exothermic reaction occurred). After being stirred under the conditions indicated in Tables 1 and 2, the mixture was portioned between water and ether. The biphasic mixture was passed through Celite, and was extracted with Et_2O. The extract was washed with brine, and dried over $MgSO_4$. The volatile component of the extracts was removed *in vacuo*, and the residue was chromatographed on silica gel to give the aryl(difluoromethyl)phosphonates

11a-i and the bis-phosphonate **12** (a product from the reaction with 1,4-diiodobenzene) as oils. The same procedure was applied when DMA and NMP were utilized in place of DMF. The elution solvent and physical data for **11a-i** and **12** are as follows.

Diethyl α,α-Difluorobenzylphosphonate 11a. Eluted with hexane:EtOAc=10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.60 (2H, m), 7.53-7.42 (3H, m), 4.33-4.09 (4H, m), 1.31 (6H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6 (dt, J_{CP}= 14.0 Hz, J_{CF}= 21.6 Hz), 130.7, 128.4, 126.2 (t, J_{CF}= 5.7 Hz), 118.0 (dt, J_{CP}= 216.8 Hz, J_{CF}= 261.4 Hz), 64.7 (d, J_{CP}= 6.5 Hz), 16.2 (d, J_{CP}= 5.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -45.7 (d, J_{PF}= 116.1 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 6.15 (t, J_{PF}= 116.1 Hz); IR (film) 1273, 1046, 1020 cm^{-1}; EIMS m/z 265 (M^++1), 264 (M^+), 127 (M^+-$(EtO)_2P$=O). Anal. Calcd for $C_{11}H_{15}\ O_3F_2P$: C, 50.01, H, 5.72. Found: 49.78, H, 5.76.

Diethyl α,α-Difluoro-4-methylbenzylphosphonate 11b. Eluted with hexane:EtOAc=10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (2H, d, J = 7.6 Hz), 7.25 (2H, d, J = 7.6 Hz), 4.28-4.06 (4H, m), 2.39 (3H, s), 1.31 (6H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 129.7 (dt, J_{CP}= 14.0 Hz, J_{CF}= 22.1 Hz), 129.1, 126.1 (t, J_{CF}= 5.5 Hz), 118.2 (dt, J_{CP}= 217.8 Hz, J_{CF}= 261.3 Hz), 64.6 (d, J_{CP}= 6.8 Hz), 21.3, 16.3 (d, J_{CP}= 5.2 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ -45.2 (d, J_{PF}= 117.3 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 6.32 (t, J_{PF}= 117.3 Hz); IR (film) 1272, 1046, 1020 cm^{-1}; EIMS *m/z* 279 (M^++1), 278 (M^+), 141 (M^+–$(EtO)_2P$=O). Anal. Calcd for $C_{12}H_{17}\ O_3F_2P$: C, 51.80; H, 6.16. Found: C, 51.60; H, 6.12.

Diethyl α,α-Difluoro-4-(methoxycarbonyl)benzylphosphonate 11c. Eluted with hexane:EtOAc =10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (2H, d, J = 8.1 Hz), 7.70 (2H, d, J = 8.1 Hz), 4.35-4.12 (4H, m), 3.94 (3H, s), 1.32 (6H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 137.0 (dt, J_{CP}= 14.2 Hz, J_{CF}= 21.7 Hz), 132.4, 129.6, 126.4 (t, J_{CF}= 5.7 Hz), 117.7 (dt, J_{CP}= 215.1 Hz, J_{CF}= 262.0 Hz), 64.9 (d, J_{CP}= 6.4 Hz), 52.4, 16.3 (d, J_{CP}= 5.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -47.7 (d, J_{PF}= 117.0 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 5.55 (t, J_{PF}= 117.0 Hz); IR (film) 1730, 1280, 1019 cm^{-1}; EIMS *m/z* 322 (M^+), 291 (M^+-OMe), 185 (M^+-$(EtO)_2P$=O). Anal. Calcd for $C_{13}H_{17}O_5F_2P$: C, 48.46; H, 5.31. Found: C, 48.14; H, 5.31.

Diethyl α,α-Difluoro-4-chlorobenzylphosphonate 11d. Eluted with hexane:EtOAc=20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, J = 8.0 Hz), 7.43 (2H, d, J = 8.0 Hz), 4.36-4.12 (4H, m), 1.32 (6H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 131.2 (dt, J_{CP}= 13.3 Hz, J_{CF}= 5.7 Hz), 128.8, 127.7 (t, J_{CF}= 5.7 Hz), 117.7 (dt, J_{CP}= 217.3Hz, J_{CF}= 262.0 Hz), 64.8 (d, J_{CP}= 6.8 Hz), 16.3 (d, J_{CP}= 5.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -45.7 (d, J_{PF}= 114.5 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 5.71 (t, J_{PF}= 114.5 Hz); IR (film) 1274, 1018 cm^{-1}; EIMS *m/z* 299 (M^++1), 298 (M^+), 161 (M^+-$(EtO)_2P$=O). HRMS m/z calcd for $C_{11}H_{14}O_3ClF_2P$ (M^+): 298.0337. Found: 298.0341.

Diethyl α,α-Difluoro-4-iodobenzylphosphonate 11e. Eluted with hexane:EtOAc=10:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 7.9 Hz), 7.34 (2H, d, J = 7.9 Hz), 4.32-4.08 (4H, m), 1.32 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 132.3 (dt, J_{CP}= 14.2 Hz, J_{CF}= 22.2 Hz), 127.9 (t, J_{CF} = 5.6 Hz), 117.7 (dt, J_{CP} = 217.0 Hz, J_{CF} = 261.8 Hz), 97.5, 64.8 (d, J_{CP}= 6.8 Hz), 16.3 (d, J_{CP}= 4.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -47.5 (d, J_{PF}= 113.3 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 5.55 (t, J_{PF}= 113.3 Hz); IR (film) 1270, 1020 cm^{-1}; EIMS *m/z* 390 (M^+), 253 (M^+-$(EtO)_2P$=O). Anal. Calcd for $C_{11}H_{14}O_3F_2IP$: C, 33.87; H, 3.62. Found: C, 34.02; H, 3.68.

Diethyl α,α-Difluoro-3-(acethoxymethyl)benzylphosphonate 11f. Eluted with hexane:EtOAc =5:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.53 (2H, m), 7.52-7.41 (2H, m), 5.14 (2H, s), 4.38-4.04 (4H, m), 2.11 (3H, s), 1.32 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 136.4, 132.9 (dt, J_{CP}= 13.8 Hz, J_{CF}= 22.1 Hz), 130.3, 128.6, 126.0 (t, J_{CF}= 6.2 Hz), 125.7 (t, J_{CF}= 6.2 Hz), 117.8 (dt, J_{CP}= 218.2, J_{CF} = 263.3 Hz), 65.5, 64.7 (d, J_{CP}= 6.9 Hz), 20.7, 16.2 (d, J_{CP}= 5.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -45.6 (d, J_{PF}= 114.5 Hz), ^{31}P NMR (160 MHz, $CDCl_3$) δ 5.87 (t, J_{PF}= 114.5 Hz); IR (film) 1744, 1271, 1024 cm^{-1}; EIMS *m/z* 336 (M^+), 293 (M^+–CH_3CO), 156; HRMS *m/z* calcd for $C_{14}H_{19}O_5F_2P$ (M^+): 336.0938. Found: 336.0937.

Diethyl α,α-Difluoro-3-(methoxycarbonyl)benzylphosphonate 11g. Eluted with hexane:EtOAc =10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, s), 8.17 (1H, d, J = 7.8 Hz), 7.82 (1H, d, J = 7.8 Hz), 7.55 (1H, t, J = 7.8 Hz), 4.32-4.08 (4H, m), 3.94 (3H, s), 1.33 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.1, 133.2 (dt, J_{CP}= 13.5, 22.6 Hz), 131.8, 130.6 (t, J_{CF} = 5.6 Hz), 128.6, 127.3 (2 carbons), 117.6 (dt, J_{CP} = 216.8 Hz, 261.9 Hz), 64.9 (d, J_{CP} = 6.4 Hz), 52.3, 16.2 (d, J_{CP} = 4.8 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ -46.0 (d, J_{PF} = 114.9 Hz); ^{31}P NMR (160 MHz, CDCl$_3$) δ 5.61 (t, J_{PF} = 114.9 Hz); IR (film) 1729, 1306, 1274, 1230, 1022 cm^{-1}; EIMS *m/z* 322 (M$^+$), 291 (M$^+$-OMe), 185 (M$^+$-(EtO)$_2$P=O); HRMS *m/z* calcd for $C_{13}H_{17}O_5F_2P$: 322.0782. Found: 322.0780.

Diethyl α,α-Difluoro-2-(acethoxymethyl)benzylphosphonate 11h. Eluted with hexane:EtOAc =5:1; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (1H, d, J = 7.8 Hz), 7.56-7.45 (2H, m), 7.44-7.38 (1H, m), 5.42 (2H, s), 4.49-4.06 (4H, m), 2.13 (3H, s), 1.31 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.5, 135.1, 130.9, 130.2 (dt, J_{CP} = 13.6 Hz, J_{CF} = 20.5 Hz), 129.5, 127.8, 127.6, 119.1 (dt, J_{CP} = 215.7 Hz, J_{CF} = 263.0 Hz), 64.8 (d, J_{CP} = 6.5 Hz), 63.4 (t, J_{CF} = 5.7 Hz), 16.2 (d, J_{CP} = 4.4 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ -40.9 (d, J_{PF} = 114.9 Hz); ^{31}P NMR (160 MHz, CDCl$_3$) δ 6.12 (t, J_{PF} = 114.9 Hz); IR film) 1742, 1240, 1040 cm^{-1}; EIMS *m/z* 336 (M$^+$), 293 (M$^+$-Ac); HRMS *m/z* calcd for $C_{14}H_{19}O_5F_2P$ (M$^+$): 336.0938. Found: 336.0923.

Diethyl α,α-Difluoro-2-(methoxycarbonyl)benzylphosphonate 11i. Eluted with hexane:EtOAc =10:1; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (1H, d, J = 6.8 Hz), 7.60-7.47 (3H, m), 4.36-4.06 (4H, m), 3.91 (3H, s), 1.32 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.7, 132.0, 130.5, 130.4-129.7 (m), 128.5, 128.4, 118.1 (dt, J_{CP} = 215.2 Hz, J_{CF} = 263.2 Hz), 64.8 (d, J_{CP} = 6.7 Hz), 52.5, 16.2 (d, J_{CP} = 5.2 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ -38.9 (d, J_{PF} = 109.8 Hz), ^{31}P NMR (160 MHz, CDCl$_3$) δ 5.55 (t, J_{PF} = 109.8 Hz); IR (film) 1739, 1271, 1039 cm^{-1}; EIMS *m/z* 322 (M$^+$), 291 (M$^+$–OMe). Anal. Calcd for $C_{13}H_{17}O_5F_2P$: C, 48.46; H, 5.31. Found: C, 48.16; H, 5.36.

1,4-Bis-[(diethylphosphono)difluoromethyl]benzene 12. Eluted with hexane:EtOAc=1:1; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (4H, s), 4.32-4.07 (8H, m), 1.28 (12H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.2 (dt, J_{CP} = 14.2 Hz, J_{CF} = 22.3 Hz), 126.4, 117.6 (dt, $J_{C\text{-}P}$ = 217.5 Hz, $J_{C\text{-}F}$ = 263.5 Hz), 64.9 (d, J_{CP} = 6.9 Hz), 16.2 (d, J_{CP} = 4.6 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ -46.2 (d, J_{PF}=114.9 Hz); ^{31}P NMR (160 MHz, CDCl$_3$) δ 5.52 (t, J_{PF}=114.9 Hz); EIMS *m/z* 450 (M$^+$), 313 (M$^+$–(EtO)$_2$P=O), 176 (M$^+$–[(EtO)$_2$P=O]$_2$); HRMS *m/z* calcd for $C_{16}H_{24}O_6F_4P_2$ (M$^+$): 450.0984. Found: 450.0976.

Preparation of 1-[(diethylphosphono)difluoromethyl]naphthalene 15. The organocopper reagent **8** was generated in DMA (6 mL) from the bromide **5** (1.60 g, 6 mmol), zinc (390 mg, 6 mmol) and CuBr (860 mg, 6 mmol) as described above. A solution of 1-iodonaphthalene **13** (760 mg, 3 mmol) in DMA (1 mL) was added at room temperature. The mixture was sonicated at 25 °C for 14 h. Usual work up, follwed by chromatograpy on silica gel (hexane:EtOAc=10:1) gave **15** (800 mg, 85%) as an oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.45 (1H, d, J = 8.7 Hz), 7.97 (1H, d, J = 8.1 Hz), 7.88 (1H, d, J = 7.8 Hz), 7.82 (1H, d, J = 7.4 Hz), 7.63-7.50 (3H, m), 4.26-4.03 (4H, m), 1.26 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.0, 132.0, 129.9, 128.5, 126.7, 126.3 (dt, J_{CP} = 3.1 Hz, J_{CF} = 10.7 Hz), 126.1, 126.0 (t, J_{CF} = 4.8 Hz), 124.3, 119.9 (dt, J_{CP} = 216.9 Hz, J_{CF} = 264.1 Hz), 64.7 (d, J_{CP} = 6.5 Hz), 16.2 (d, J_{CP} = 4.9 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ 39.0 (d, J_{PF} = 114.1 Hz); ^{31}P NMR (160 MHz, CDCl$_3$) δ 6.50 (t, J_{PF} = 114.1 Hz); IR (film) 1273, 1023 cm^{-1}; EIMS *m/z* 314 (M$^+$), 177 (M$^+$–(EtO)$_2$P=O). Anal. Calcd for $C_{15}H_{17}O_3F_2P$: C, 57.33; H, 5.45. Found: C, 57.10; H, 5.57.

2-[(Diethylphosphono)difluoromethyl]naphthalene 16. Under the same conditions as described above, 2-iodonaphthalene **14**[12] (760 mg, 3 mmol) gave **16** (740 mg, 79%) as an oil after column chromatography on silica gel (hexane:EtOAc=10:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.14 (1H, s),7.98-7.83 (3H, m), 7.69 (1H, d, J = 8.6 Hz), 7.11-7.50 (2H, m), 4.34-4.08 (4H, m), 1.32 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.1, 132.4, 129.9 (dt, J_{CP} = 13.7 Hz, J_{CF} = 21.9 Hz), 128.7, 128.4, 127.7, 126.7, 126.5 (dt, J_{CP} = 3.1 Hz, J_{CF} = 7.6 Hz), 122.7 (t, J_{CF} = 5.6 Hz), 118.3 (dt, J_{CP} = 218.4 Hz), J_{CF} = 263.3 Hz), 64.8 (d, J_{CP} = 6.6 Hz), 16.3 (d, J_{CP} = 4.9 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ -45.0 (d, J_{PF} = 115.8 Hz); ^{31}P NMR (160 MHz, CDCl$_3$) δ 6.21 (t, J_{PF} = 115.8 Hz);

IR (film) 1275, 1021 cm^{-1}; EIMS *m/z* 314 (M$^+$), 177 (M$^+$-(EtO)$_2$P=O). Anal. Calcd for $C_{15}H_{17}O_3F_2P$: C, 57.33; H, 5.45. Found: C, 57.61; H, 5.50.

1,1-Difluoro-1-(2-naphthyl)methylphosphonic acid 4a. To a stirred solution of **16** (314 mg, 1 mmol) in CH_2Cl_2 (2 mL) was added TMSBr (0.4 mL, 3 mmol), the mixture was stirred at 25 °C for 20 h. The volatile of component of the mixture was evaporated, and the residue was treated with MeOH (2 mL) at 25 °C for 2 h. The solvent was removed *in vacuo* to leave a semi-solid. A crystalline material was collected, and washed with cold $CHCl_3$ to give **4a** (174 mg, 67% yield): mp 110-111 °C, lit.,[6a] mp 111-112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (1H, s), 8.09-7.92 (3H, m), 7.71-7.50 (3H, m), 3.17 (2H,s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 133.7, 132.2, 131.7 (dt, J_{CP} = 12.7 Hz, J_{CF} = 21.7 Hz), 128.8, 128.2, 127.9, 127.7, 127.1, 126.1, 123.5, 119.3 (dt, J_{CP} = 205.3 Hz, J_{CF} = 261.9 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ -46.4 (d, J_{PF} = 106.2 Hz); ^{31}P NMR (160 MHz, DMSO-d_6) δ 7.59 (t, J_{PF} = 106.8 Hz); IR (KBr) 3059, 1107, 1061 cm^{-1}; FABMS *m/z* 259 (MH$^+$), 177 (M$^+$-(HO)$_2$P=O). Anal. Calcd for $C_{11}H_7O_3F_2P \cdot H_2O$: C, 47.84; H, 4.01. Found: C, 47.62; H, 4.17.

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