# Synthesis of $(\alpha, \alpha$ -Difluoropropargyl)phosphonates via Aldehyde-to-Alkyne Homologation

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**Supporting Information** 



**ABSTRACT:** An efficient synthetic methodology to a series of novel alkynes bearing a difluoromethylenephosphonate function via a Corey–Fuchs-type sequence starting from (diethoxyphosphoryl)difluoroacetic aldehyde is described. Dehydrobromination of the intermediate (3,3-dibromodifluoroallyl)phosphonate with potassium *tert*-butoxide gave rise to the corresponding bromoalkyne, whereas upon treatment with lithium base, the generation of ((diethoxyphosphoryl)difluoropropynyl)lithium has been achieved for the first time. The synthetic potential of this lithium reagent was further demonstrated by its reactions with selected electrophiles such as aldehydes, ketones, triflates, chlorophosphines, and chlorosilanes, leading to the corresponding propargyl phosphonates in good to excellent yields. However, in the case, of sterically hindered aldehydes, ( $\alpha$ -fluoroallenyl)phosphonates were the solely isolated products.

# 1. INTRODUCTION

The interest in the synthesis and application of gemdifluoromethylenephosphates (DFMP) as phosphate mimics is unquestionable. The electronic and structural similarities of the  $C-CF_2-P$  moiety in DFMP to the C-O-P group in phosphates are attractive. In addition, the relative resistance of fluorinated phosphates to metabolic transformations has great potential.<sup>1</sup> Indeed, the importance of difluoromethylenephosphonates as phosphate analogues and enzyme inhibitors has been well established, and they are still of interest in biochemical and pharmaceutical investigations. Recently, the applications of DFMP derivatives in the treatment of infections, inflammations, and respiratory, dermatological, autoimmune diseases (TLR modulators),<sup>2</sup> in psychotic, anxiety, and movement disorders and/or neurological disorders (PDE10 inhibitors),<sup>3</sup> as antidiabetic agents (PTP 1B inhibitors),<sup>4</sup> as targets for cancer chemotherapy (IMPDH and Stat inhibitors),<sup>5</sup> as agonists for purinergic receptors,<sup>6</sup> and as gene expression inhibitors' have been established. Considering these benefits, numerous synthetic methodologies have been investigated for the introduction of the difluoromethylenephosphonate function into a variety of organic compounds.<sup>1d,8</sup>

Despite the unique biological and physical properties imparted by the  $CF_2P(O)(OR)_2$  group, and the obvious versatility of alkynes as valuable scaffolds for more functional

molecules,<sup>9</sup> the attachment of the difluoromethylenephosphonato function onto unsaturated sp carbon centers still remains a nontrivial synthetic problem. Moreover, relatively few reports involving their preparations have appeared in the literature citations to date. The first one, reported by Hammond, involves the Pfitzner-Moffatt oxidation of diethyl  $\alpha$ -hydroxyalkynephosphonate, prepared by the nucleophilic attack of diethyl phosphite on the corresponding aldehyde, followed by the DAST fluorination of the resulting  $\alpha$ -ketophosphonate.<sup>10</sup> Further approaches included the one-pot Shibuya-Yokomatsu type coupling of  $(EtO)_2P(O)CF_2ZnBr$  with the appropriate 1-haloalkynes in the presence of copper(I) halide,<sup>11</sup> nucleophilic substitution of TIPS-difluoropropargyl bromide with diethyl phosphite,<sup>12</sup> electrophilic fluorination of TIPS-propargyl phosphonate using N-fluorobenzenesulfonimide (NFSI), followed by its additional functionalization upon treatment with water or benzaldehyde in the presence of (tetrabutylammonium fluoride) TBAF,<sup>13a</sup> and the copper-mediated oxidative crosscoupling reaction of terminal alkynes with  $\alpha$ -silyldifluorome-thylphosphonates<sup>13b</sup> (Scheme 1). It should be noted, however, that these strategies have been generally restricted by the choice of substrates, the requirement of multiple steps, or the use of

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# Scheme 1. Previous Synthetic Routes to $(\alpha, \alpha$ -Difluoropropargyl)phosphonates



reagents of limited stability, which could hamper their synthetic application.

As an alternative approach to obtaining (difluoropropargyl)phosphonates, we were interested in an aldehyde-to-alkyne homologation process, commonly known as the Ramirez-Corey-Fuchs reaction. In its classical form, this high-yielding two-step procedure involves the transformation of an aldehyde to the homologated dibromoalkene (Ramirez olefination),<sup>14a</sup> followed by the base-promoted, in situ formation of lithium acetylide, whose hydrolysis or treatment with an electrophile furnishes the corresponding terminal or internal acetylenic compound.14b As a result of the high compatibility of a wide range of aldehydes as well as various electrophiles, this method has been widely applied recently, using nonfluorinated substrates in their original or modified form.<sup>15</sup> With this in mind, we report herein the first general application of the aldehyde-to-alkyne procedure in the synthesis of a new class of  $(\alpha, \alpha$ -difluoropropargyl)phosphonates, as well as the generation of ((diethoxyphosphoryl)difluoropropargyl)lithium from (diethoxyphosphoryl)difluoroacetic aldehyde. Systematic investigations on the reactivity of the difluoropropargyl carbanion toward selected electrophiles are also discussed.

# 2. RESULTS AND DISCUSSION

Initially, our attention was focused on finding an appropriate method for the synthesis of the key substrate, (diethoxyphosphoryl)difluoroacetic aldehyde (3). Preliminary results of Percy et al. indicated that compound 3 could be obtained by reacting the lithium salt of diethyl difluoromethylenephosphonate (1) with *N*,*N*-dimethylformamide (DMF) at -78 °C, prior to an

aqueous workup.<sup>16</sup> However, the authors isolated only a masked form of an aldehyde (dihydrate 2) in 80% yield and no details on the preparation and characterization of the desired aldehyde 3 have been reported. We thus re-examined this synthetic procedure and found that after distillation of the dihydrate 2 over phosphorus pentoxide under an inert atmosphere, the corresponding aldehyde was formed in good yield (Scheme 2).

According to the reported procedure for the Ramirez olefination,<sup>17</sup> we attempted to prepare the corresponding dibromo(difluoroallyl)phosphonate 4 starting from 3. To our delight, the slow addition of 3 to a  $CH_2Cl_2$  solution of tetrabromomethane and triphenylphosphine at 0 °C resulted in a total consumption of 3 and quantitative conversion into *gem*-dibromo(difluoroallyl)phosphonate (4) upon mixing the suspension for 1 h at ambient temperature (Scheme 3). Further workup and purification by distillation in vacuo furnished the expected dibromide 4 in very good yield.

We have further studied the appropriate conditions leading to HBr elimination on compound 4. We speculated that the increased acidity of the vinylic hydrogen of 4, arising from the proximity of the strong electron-withdrawing  $CF_2P(O)(OEt)_2$ group, would facilitate the dehydrobromination process.

Scheme 3. Preparation of Diethyl (3,3-Dibromo-1,1difluoroallyl)phosphonate (4)

$$(EtO)_2P(O)CF_2 \xrightarrow{O} H \xrightarrow{CBr_4, PPh_3} Br \xrightarrow{CF_2P(O)(OEt)_2} Br \xrightarrow{4 (85\%)}$$

# Table 1. Dehydrobromination of 4 under Various Conditions

	Br C	F <sub>2</sub> P(O)(OEt) <sub>2</sub> Base (1 equiv.)			
	Br	Solvent, Condition	$\rightarrow$ Br $\rightarrow$ CF <sub>2</sub> P(O)(OEt)	$_{2}$ + = CF <sub>2</sub> P(O)(OEt) <sub>2</sub>	
	4	-HBr	5	11a	
entry	base	solvent	conditions	yield <sup><math>a</math></sup> of 5 (%)	yield <sup><math>a</math></sup> of <b>11a</b> (%)
1	TEA	Et <sub>2</sub> O	0 °C to room temp	Ь	
2	DIPEA	Et <sub>2</sub> O	0 °C to room temp	Ь	
3	DBU	DMSO	0 °C to room temp	59	36
4	DBU	CH <sub>3</sub> CN	0 °C to room temp	53	30
5	DBU	$CH_2Cl_2$	0 °C to room temp	25	19
6	DBU	THF	0 °C to room temp	49	18
7	NaHMDS	THF	−78 °C to room temp	62	38
8	LDA	THF	−78 °C to room temp	63	37
9	KO <sup>t</sup> Bu	THF	-20 °C to room temp	<b>96</b> <sup>c</sup>	
<sup><i>a</i></sup> Yield determined by <sup>19</sup> F NMR analysis. <sup><i>b</i></sup> Starting material was recovered. <sup><i>c</i></sup> Isolated yield.					

Scheme 4.	Suggested	Mechanism	for the	Formation	of P-F	Derivative 1	)



Therefore, various bases, solvents, and temperatures were examined in depth. Table 1 summarizes a screening of the various reaction conditions for the dehydrobromination of compound 4. Among the variety of bases, non-nucleophilic tertiary amines such as triethylamine (TEA) and N,Ndiisopropyl-N-ethylamine (DIPEA) were shown not to be sufficiently strong to promote the dehydrobromination process, and only starting materials were recovered (Table 1, entries 1 and 2). Better results were obtained when a stronger base, 1,8diazabicyclo [5.4.0] undec-7-ene (DBU), was used. It is wellknown that bicyclic amidines such as DBU serve as powerful reagents in organic chemistry and have been extensively applied to dehydrohalogation in organic synthesis under mild conditions. However, its basicity depends strongly on the solvent used and decreases in the order DMSO > DMF >  $CH_3CN \gg THF.^{18a,b}$  Indeed, upon treating dibromo olefin 4 with 1 equiv of DBU dissolved in DMSO, CH<sub>3</sub>CN, CH<sub>2</sub>Cl<sub>2</sub>, or THF and stirring the resulting mixture for a further 1 h at 0 °C, the <sup>19</sup>F NMR analysis indicated the formation of the desired 1bromoalkyne 5 (Table 1, entries 3–5, respectively). Depending on the polarity of the solvent, the corresponding bromoalkyne 5 was obtained in moderate to good yields (Table 1, entries 3-6). As predicted, the highest yield of the desired product 5 was achieved in the solvent of highest polarity (DMSO) and the lowest yield in the solvent of lowest polarity (THF). In all cases the dehydrobromination of 4 was accompanied by the additional formation of the terminal alkyne 11a ( $\delta_{\rm F}$  –98.6 ppm,  ${}^{2}J_{FP} = 104.4$  Hz,  ${}^{3}J_{FH} = 5.8$  Hz) as well as phosphofluoridate **D** (approximately 5%,  $\delta_{\rm F}$  -80.8 ppm,  ${}^{1}J_{\rm FP}$ = 979.8 Hz) as a result of a nucleophilic substitution of the fluoride anion on phosphorus center. The formation of a fluoride anion could be explained as follows. Under the existing basic conditions, difluoropropargylphosphonate 11a would undergo deprotonation to give a resonance-stabilized allenylpropargyl anions A and B. We speculated that  $F^-$  eliminated from A could then cleave the  $CF_2$ -P bond of 5 and 11a to form phosphofluoridate D and the other byproducts C and E (Scheme 4).

Therefore, we looked for a base more selective than DBU for the preparation of **5**. Attempts to perform this process using sodium bis(trimethylsilyl)amide (NaHMDS) or lithium diisopropylamide (LDA) in dry THF gave better yields of the expected bromoalkyne **5**. However, the formation of a terminal alkyne as a byproduct was still observed during the reaction. Changing the base to the weaker potassium *tert*butoxide (KO<sup>t</sup>Bu) promoted the dehydrobromination process remarkably well, giving cleanly and selectively the bromoalkyne **5** in excellent yield (Table 1, entry 9). Moreover, no P–CF<sub>2</sub> cleavage was surveyed during this process, in contrast to the case for DBU. Compound **5** possesses a bromoalkyne moiety suitable for various cross-coupling reactions.<sup>18c,d</sup>

We next examined the potential of vinyl dibromide **4** as a (diethoxyphosphoryl)difluoropropynyl anion precursor and its reactivity toward selected electrophiles. To the best of our knowledge, there are no literature citations containing the generation of ((diethoxyphosphoryl)difluoropropynyl)lithium (**6**) or functionalization of this synthon. To date, only TIPS–difluoropropargylphosphonate has been described as a source of carbanion in a TBAF-mediated preparation of terminal difluoropropargylphosphonate **11a** and  $\gamma$ -substituted hydroxy difluorophosphonate **7a**.<sup>13a</sup>

In order to find a viable method for the generation of ((diethoxyphosphoryl)difluoropropynyl)lithium 6, we first examined the behavior of dibromo olefin 4 upon treatment with common lithium bases such as*n*-BuLi,*t*-BuLi, and LDA at <math>-78 °C, followed by the addition of a representative electrophile, in this case benzaldehyde. After quenching with

# Table 2. Screening of Various Bases for Alkynylation of Benzaldehyde



Scheme 5. Plausible Mechanism for the in Situ Generation of ((Diethoxyphosphoryl)difluoropropynyl)lithium 6 using Various Bases and Product Distribution after Addition of Benzaldehyde





	BrCF <sub>2</sub> P(O)(OEt); Br	2 LDA (2.1 equiv) THF temp.	$ \left[ \text{Li} - \text{CF}_2 P(O)(OEt)_2 \right] - \frac{D_2 C}{6} $	$D \longrightarrow D \longrightarrow CF_2P(O)(OEt)_2 + F$	
			$ \begin{array}{c} H \\ \rightarrow \\ D \\ G \end{array} \begin{array}{c} F \\ + \\ P(O)(OEt)_2 \end{array} + \begin{array}{c} FP(O)(OEt)_2 \\ D \\ D \end{array} \right) $	$(t)_2 \stackrel{+}{\longrightarrow} LiF \stackrel{+}{\longrightarrow} \stackrel{H}{\longrightarrow} C \stackrel{F}{\longrightarrow} Li$	
			+ C	ligomers	
entry	temp (°C)	yield (%) of $\mathbf{F}^a$	yield (%) of $\mathbf{G}^a$	yield (%) of $\mathbf{D}^a$	yield (%) of $\mathbf{H}^{a}$
1	-78	99			
2	-40	99			
3	-20	99			
4	0	91	8		
5	10	16	78	6	
6	20		93	4	2
Determined by	<sup>19</sup> F NMR analysis.				

PhCHO, the product distribution was analyzed by <sup>19</sup>F NMR spectroscopy and the results are given in Table 2.

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When the reaction was carried out with 2.1 equiv of *n*-BuLi at -78 °C, followed by trapping with an electrophile, the alkyne 7a was formed in good yield (Table 2, entry 1). However, a partial decomposition of the lithium reagent to fluoroallene 8 in 40% yield occurred. By lowering the temperature to -100 °C, we were able to slightly suppress the decomposition of the lithium reagent, which inevitably occurs using *n*-BuLi as a base (59% of 7a). On the other hand, the treatment of a solution of dibromoalkene 4 with 2.1 equiv of the more basic and sterically

hindered *t*-BuLi at -78 °C and 1 equiv of benzaldehyde resulted in the formation of fluoroallenylphosphonate **8** in 34% yield (59% of 7a). Taking into consideration the obtained results, we then attempted to generate ((diethoxyphosphoryl)-difluoropropynyl)lithium (6) using a base milder than *n*-BuLi or *t*-BuLi, such as LDA. In a typical reaction, a solution of 2.1 equiv of LDA was added to the stirred solution of dibromoalkene **4** in THF at -78 °C, giving subsequent capture by an electrophile (PhCHO) of the anionic species generated in situ. The mixture was warmed to ambient temperature over 1 h and conveniently monitored by <sup>19</sup>F NMR spectroscopy,

## Scheme 6. Proposed Decomposition Pathway of Lithium Reagent 6







## <sup>a</sup>Isolated yield.

which clearly indicated the selective formation of the desired product 7a in nearly quantitative yield (Table 2, entry 3). A plausible explanation for the product distribution upon treatment with different bases could be best explained by the initial formation of the thermally unstable vinyllithium Int-A (Scheme 5). Depending on the base used, two competing reaction pathways could be speculated. When the reactions were carried out with stronger bases such as *n*-BuLi and *t*-BuLi at -78 °C, partial decomposition of unstable **Int-A** took place as a consequence of lithium fluoride elimination via a concerted E2 or E1cB mechanism<sup>19</sup> and the formation of fluoroallenyl-phosphonate **8** as a byproduct was detected (Scheme 5, path A). In contrast, using a milder base such as LDA, rapid construction of a triple bond would be afforded by loss of

# Scheme 7. Plausible Mechanism of the Formation of ( $\alpha$ -Fluoroallenyl)phosphonate 9b



Table 5. Reactions of in Situ Prepared 6 with Selected Ketones



<sup>*a*</sup>Isolated yield.

# Table 6. Reaction of Lithium Reagent 6 with Other Electrophiles

	Br CF <sub>2</sub> P(O)(OEt) <sub>2</sub>	$\frac{1. \text{LDA } (2.1 \text{ equiv}), \text{ THF, -78 °C}}{2 \text{ F.x}}  \text{E} = \text{CF}_2 P(O)(OEt)_2$			
	Br <b>4</b>	3. H <sub>3</sub> O <sup>+</sup>	11		
Entry	Е	Х	Product	Yield (%) <sup>a</sup>	
1	Н	ОН	HCF <sub>2</sub> P(O)(OEt) <sub>2</sub>	98 <sup>13a</sup>	
			11a		
2	(CH <sub>3</sub> ) <sub>3</sub> Si	CI	(H <sub>3</sub> C) <sub>3</sub> SiCF <sub>2</sub> P(O)(OEt) <sub>2</sub>	98	
			11b		
3	<sup>t</sup> Bu(CH <sub>3</sub> ) <sub>2</sub> Si	CI	<sup>t</sup> Bu(H <sub>3</sub> C) <sub>2</sub> Si CF <sub>2</sub> P(O)(OEt) <sub>2</sub>	60	
			11c		
4	$Ph_2P$	CI	Ph <sub>2</sub> PCF <sub>2</sub> P(O)(OEt) <sub>2</sub>	89	
			11d		
5	<sup>'</sup> PrPCI	CI	<sup>/</sup> PrP <del>(</del> CF <sub>2</sub> P(O)(OEt) <sub>2</sub> ) <sub>2</sub>	58	
			11e		
6	$(Et_2N)_2P$	CI	$(Et_2N)_2P$ — $CF_2P(O)(OEt)_2$	$0^{b}$	
			11f		
7	Me	OTf	H <sub>3</sub> CCF <sub>2</sub> P(O)(OEt) <sub>2</sub>	93°	
			11g		

"Isolated yield. <sup>b</sup>Terminal alkyne 11a was obtained after aqueous workup. <sup>c</sup>A stoichiometric amount of HMPA was added as an additive.

lithium bromide in a first step, followed by the lithium–halogen exchange (Scheme 5, path B). Since the treatment of vinyl dibromide 4 with various bases resulted in different product distributions in the same solvent (THF), the aggregation state of RLi species might also affect the reaction course significantly.<sup>20</sup>

It should also be noted that efforts to isolate ((diethoxyphosphoryl)difluoropropynyl)lithium (6) were unsuccessful. Additional information concerning the stability of the lithium reagent was therefore obtained by quenching the dibromoalkene 4/LDA mixture with D<sub>2</sub>O at various temperatures. The product distribution was then conveniently monitored by <sup>19</sup>F NMR spectroscopy, which revealed that the reagent obtained in this fashion is stable when held below 0 °C and decomposes above this temperature. The decomposition process of 6 could be observed by a gradual loss of the doublet associated with product F at -99.0 ppm and the concomitant development of a singlet at  $\delta_{\rm F}$  -183 (LiF), a doublet at  $\delta_{\rm F}$  -160 (G), a doublet at  $\delta_{\rm F}$  -81 (D), and a doublet at  $\delta_{\rm F}$  -167 (H) (Table 3).

Due to the thermal instability of **6** at above 0 °C,  $\beta$ elimination of lithium fluoride from the carbanion **6** is assumed and leads to the formation of compound **B**. This fluoride anion formed in situ could then cleave the carbon-phosphorus bond of **B** to furnish fluoroallene **H** and phosphofluoridate **D** (Scheme 6).

With the optimized reaction conditions established, the reactivity of in situ generated ((diethoxyphosphoryl)difluoropropynyl)lithium (6) toward selected electrophiles was continuously investigated. Initially, we turned our attention to screening various aldehydes under the conditions given in Table 3. A wide range of aromatic aldehydes were suitable for this transformation, regardless of the electronic effects of substituents attached to the aromatic ring (Table 4, entries 1– 7). However, these aldehydes highly affected the stability of the final products 7a-g. In the case of benzaldehyde (entry 1) and its derivatives bearing an electron-donating methoxy group in ortho, meta, and para positions (entries 2-4), the desired propargyl alcohols 7a,b,d,f were obtained and isolated in excellent yields after purification by column chromatography. Aldehydes containing electron-withdrawing substituents such as o-chloro-, m-chloro-, and p-nitrobenzaldehyde after treatment with lithium reagent 6 also produced the desired propargyl alcohols in excellent yield: 7c (92%), 7e (95%), and 7g (91%), respectively (according to the <sup>19</sup>F and <sup>31</sup>P NMR analysis of the crude reaction mixture). However, their isolation was rather cumbersome, since they decomposed during the purification process to an oligomeric material that contained fragments of CF<sub>2</sub>H,  $\alpha$ -fluoroallenyl, and 1,1-difluoroallylphosphonate groups. Therefore, we were not able to isolate and fully characterize compounds 7c,e,g. In the same manner, the linear aliphatic aldehyde 1-heptanal underwent an addition reaction to give the corresponding alcohol 7h in very good yield (entry 5). On the other hand, branched aldehydes such as 2methylpropanal (entry 6) and pivalaldehyde (entry 7), upon treatment with pregenerated carbanion 6, followed by an aqueous hydrolysis at -40 °C, selectively produced allenic alcohols 9a,b as a 1:1 mixture of diastereoisomers.

This unexpected selectivity of the propargylic reagent **6** in  $S_E 2'$  addition to a prochiral aldehyde possessing bulky substituents could be dependent on the geometrical preferences of substrates upon orientation in the transition state **C** to avoid the steric repulsion between reagents (elimination of a fluoride anion after capture of **6** with an aldehyde) (Scheme 7, path A). It may also be a result of a thermodynamic preference of a propargyl anion to isomerize into the unsymmetrical allenyl species **Int-B** under the reaction conditions used, prior to the addition to a sp<sup>2</sup> carbon atom of an aldehyde to form

homoallenyl alcohol 9b as a mixture of diastereoisomers (Scheme 7, path B).

To obtain more details on the selectivity of ((diethoxyphosphoryl)difluoropropargyl)lithium (6), we next applied our procedure to various acyclic, cyclic, aromatic, and  $\alpha_{\beta}$ unsaturated ketones. Interestingly, ketones regardless of their steric and electronic properties underwent the addition of the lithium reagent smoothly, providing access to tertiary propargyl alcohols 10a-h in excellent yields (Table 5). In contrast to the case for aromatic aldehydes, acetophenones bearing electrondonating (entry 6) or electron-withdrawing (entry 7) groups attached to the aromatic ring also participated in alkynyl addition, giving rise to products 10e,g, respectively, in very good yields. Moreover, these compounds were easily purified by column chromatography without any decomposition. When a sterically hindered ketone such as diisopropyl ketone was used as an electrophile, an excellent isolated product yield was afforded and no obvious influence of steric factors on the distribution of the reaction product was observed (entry 2). In addition, we also attempted the reaction of 6 with the  $\alpha_{\beta}$ unsaturated ketone cyclohexenone, which gave only the product of 1,2-nuclephilic addition to the carbonyl group and no Michael addition adducts were formed under the reaction conditions, even in the presence of additives such as hexamethylphosphortriamide (HMPA) and cerium chloride, which have been known to promote Michael addition toward conjugated carbonyl compounds in the case of difluorinated lithium reagents (Table 5, entry 4).<sup>21</sup>

In our quest for a viable route to the synthesis of novel ( $\alpha_{,\alpha}$ difluoropropargyl)phosphonates, we extended our method to other electrophiles to gain further information concerning the selectivity of the lithium reagent 6. From our results in Table 6, it is seen that the (diethoxyphosphoryl)difluoropropynyl anion of 6 reacts readily in the usual manner with a limited range of electrophilic centers to afford the respective CF<sub>2</sub>P(O)(OEt)<sub>2</sub>containing alkynes, typically in good to very good yields. These include mostly phosphorus and silyl chlorides (Table 6, entries 2-7) as well as organic triflates (entries 8 and 9). Moreover, the hydrolysis of the lithium acetylide at -40 °C furnished the terminal propargylphosphonate 11a in near-quantitative yield (Table 6, entry 1). Smooth and quantitative conversion of 6 into the silvl derivative 11b was also detected when trimethylsilyl chloride (TMSCl) was used as an electrophilic source (Table 6, entry 2), whereas a lower yield of the expected difluoropropargyl phosphonate 11c was obtained in the case of tert-butyldimethylsilyl chloride (TBDMSCl) as a result of the steric bulkiness of a tert-butyl group in proximity to an electrophilic center (Table 6, entry 3). Bearing in mind the high susceptibility of the phosphorus-halogen linkage to nucleophilic displacement, chlorophosphines were also examined as substrates in the reaction with lithium acetylide 6 to furnish the corresponding propargylphosphonates 11d-f. In this series, however, a significant substituent electronic effect occurred: the more electron-deficient the chlorophosphines, the higher the conversions. Therefore, the highest conversion of substrates was observed in the case of electron-deficient diphenylchlorophosphine (Table 6, entry 4), whereas no satisfactory results were obtained in an attempt with bis(diethylamino)chlorophosphine. Only the terminal alkyne 11a was isolated as the sole product after aqueous workup (Table 6, entry 6). In our further attempt, it was also found that lithium reagent 6 afforded a good yield of bis(propargylphosphonate) 11e when 1 equiv of dichloro(isopropyl)phosphine was used as an

electrophilic source under standard reaction conditions (Table 6, entry 5).

Finally, we examined the ability of organic triflates to undergo nucleophilic displacement with preformed ((diethoxy-phosphoryl)difluoropropynyl)lithium 6. Unfortunately, no significant product derived from nucleophilic substitution of methyl triflate with 6 was detected in the reaction mixture. However, we tweaked the synthetic procedure and found that upon generation of the anion 6 from dibromide 4 (1 equiv) with LDA (2.1 equiv) in the presence of a stoichiometric amount of lithium-complexing reagent, such as hexamethyl-phosphortriamide (HMPA, 1 equiv), at -78 °C, followed by the addition of methyl triflate, the displacement reaction proceeded in excellent yield. The effect of a polar cosolvent (HMPA) on the subsequent reactions of the organolithium reagents, e.g., increasing rates of S<sub>N</sub>2 reactions, has already been described elsewhere.<sup>22</sup>

It should also be noted that other electrophiles such as iodomethane, dimethyl sulfate, benzoyl chloride, ethyl benzoate, benzyl chloride, and oxiranes were examined under the same reaction conditions, but no addition or substitution products were obtained, even in the presence of lithium-complexing reagents such as HMPA, TMEDA, and Lewis acids. The terminal alkyne **11a** was mostly obtained after an aqueous workup. The problem may be in the relatively weak nucleophilicity of lithium reagent **6**, caused by the presence of strongly electron-withdrawing difluoromethylene as well as phosphonate groups that affects its nucleophilicity. Therefore, anion **6** was observed only to react with very good electrophiles.

In each case, the formation of the (diethoxyphosphoryl)difluoropropynyl function was confirmed by the presence of a doublet resonance in the <sup>19</sup>F NMR spectrum in the region of -97 to -99 ppm with the typical coupling constant  ${}^{1}J_{\rm FP} \approx 105$ Hz (with respect to  $CFCl_3$ ). This is characteristic of an alkynic  $CF_2P(O)(OEt)_2$  group. Additional confirmation of the alkynic  $CF_2P(O)(OEt)_2$  was supported by <sup>13</sup>C NMR spectroscopy, in which  $CF_2P(O)(OEt)_2$  was clearly resolved as a triplet of doublets in the region of 109 ppm with coupling constants  $J_{CF}$ = 253 Hz and  $J_{CP}$  = 229 Hz, respectively. Two further triplet of doublets and doublet of triplets resonances, corresponding to the carbon nuclei  $C_{sp} \alpha$  and  $\beta$  to  $CF_2$  group, were observed at  $\delta_{\rm C}$  71 ( $J_{\rm CF}$  = 33.8,  $J_{\rm CP}$  = 17.2 Hz) and 98 ppm ( $J_{\rm CF}$  = 7.8,  $J_{\rm CP}$  = 6.7 Hz), respectively. For compound 10g (S isomer) additional information was acquired from single X-ray diffraction studies. This represents the first crystallographic structure of any (diethoxyphosphoryl)difluoropropargyl compound (Figure 1; see the Supporting Information).<sup>2</sup>

# 3. CONCLUSIONS

A novel and efficient strategy for the synthesis of a class of  $(\alpha, \alpha$ difluoropropargyl)phosphonates via modification of the Corey–Fuchs methodology starting from (diethoxyphosphoryl)difluoroacetic aldehyde<sup>25</sup> has been described. By the action of appropriate bases on the intermediate 3,3-dibromo-1,1-difluoroalkene, the synthesis of bromoalkyne and the generation of (diethoxyphosphoryl)difluoromethyllithium have been achieved for the first time. This anion reacted readily with a limited range of electrophiles such as aldehydes, ketones, chlorophosphines, trialkylsilyl chlorides, and organic triflates to furnish the corresponding CF<sub>2</sub>P(O)(OEt)<sub>2</sub>-containing alkynes in excellent yield. When aldehydes with sterically demanding substituents were reacted with the anion generated



Figure 1. Solid-state molecular structure of compound 10g (H atoms are omitted for clarity).

in situ, respective fluoroallenyl alcohols were isolated. Detailed investigations on the stability of the pregenerated anion, as well as mechanistic considerations including the reactivity of the preformed lithium acetylide, were also discussed in this paper.

Further studies, including the application of novel  $(\alpha, \alpha$ difluoropropargyl)phosphonates as building blocks in the synthesis of more complex molecules, will be reported in due course.

#### 4. EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under an atmosphere of dry argon. THF was freshly distilled from sodium benzophenone ketyl. Reagents, obtained from commercial sources, were used without further purification. All other reagents were distilled or recrystallized, if necessary. Diethyl difluoromethylphosphonate (1) was prepared according to the known procedure.<sup>24</sup> Column chromatography was performed using silica gel 60 (230-400 mesh ASTM) and TLCs using silica gel 60 F254. Visualization was achieved by UV light or by spraying with  $Ce(SO_4)_2$  solution in 5% H<sub>2</sub>SO<sub>4</sub>. <sup>1</sup>H (400 MHz), <sup>13</sup>C (100 MHz), <sup>19</sup>F (376 MHz), and <sup>31</sup>P NMR (161 MHz) spectra were measured on a 400 MHz spectrometer at room temperature using 5 mm tubes. TMS was the internal standard in <sup>1</sup>H NMR; CFCl<sub>3</sub> was used as a reference for <sup>19</sup>F NMR and 85% H<sub>3</sub>PO<sub>4</sub> in <sup>31</sup>P NMR. Chemical shifts ( $\delta$ ) are reported in ppm and coupling constants (J) in Hz. <sup>31</sup>P NMR spectra were broadband decoupled from hydrogen nuclei. High-resolution mass spectra were recorded on an ESI-Qq-TOF mass spectrometer. Melting points are uncorrected.

(Diethoxyphosphoryl)difluoroacetic Aldehyde (3). To a solution of LDA (41 mL, 2.0 M solution in THF/n-heptane/ ethylbenzene) in dry THF at -78 °C was added freshly dried cerium(III) chloride (21 g, 82 mmol) in one portion. The resulting suspension was stirred vigorously at -78 °C for 20 min. Diethyl difluoromethylphosphonate (1; 15 g, 80 mmol) was added dropwise over 15 min, and the mixture was stirred for 1 h. Freshly distilled N,Ndimethylformamide (6.2 mL, 6 g, 82 mmol) was slowly added to the pale yellow-orange suspension, and after the mixture was stirred for 1 h further, aqueous hydrochloric acid was added until complete dissolution of cerium salts and the solution was warmed to room temperature. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine, dried over MgSO4, and concentrated in vacuo. The residue was distilled over phosphorus pentoxide to afford the desired aldehyde 3 (11.0 g, 65%) as a colorless oil: bp 74-77 °C/0.1 mmHg; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.34 (t, J = 7.1 Hz, 6H), 4.27 (quint, J = 7.1 Hz, 4H), 9.54 (dt,  $J_{\rm HF} = J_{\rm HP} = 3.7$  Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  16.3 (d, J =5.1 Hz), 65.6 (d, J = 6.7 Hz), 112.2 (td, J = 269.3, 192.7 Hz), 187.9 (td, J = 29.7, 14.4 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376 MHz)  $\delta$  –123.6 (dd, J = 96.8, 3.4 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 161 MHz)  $\delta$  3.1 (t, *J* = 96.8 Hz); HRMS (ESI) calcd for  $[M + H]^+$  C<sub>6</sub>H<sub>12</sub>F<sub>2</sub>O<sub>4</sub>P 217.0441, found 217.0448.

Diethyl 3,3-Dibromo-1,1-difluoroallylphosphonate (4). To a solution of triphenylphosphine (19.9 g, 76 mmol) in dry dichloromethane (130 mL) at 0 °C was added carbon tetrabromide (12.7 g, 38 mmol) in one portion. The resulting mixture was stirred for 20 min, and then (diethoxyphosphoryl)difluoroacetic aldehyde (3; 7.8 g, 36 mmol) was added slowly via syringe. After it was stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature. Pentane (200 mL) was then added to the resulting mixture, and the precipitate that formed was then filtered off. The filtrate was concentrated in vacuo, and cyclohexane was added to the residue. The precipitate was filtered off, the filtrate was concentrated by rotary evaporation, and the crude product was distilled, yielding vinyl dibromide 4 (11.4 g, 85%) as a colorless oil (bp 98-100 °C/0.1 mmHg): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.37 (t, J = 7.1 Hz, 6H), 4.11–4.41 (m, 4H), 6.78 (td, J =13.3, 2.2 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  16.5 (d, J = 5.2 Hz), 65.2 (d, J = 6.8 Hz), 98.8 (dt, J = 9.3, 9.2 Hz), 115.6 (td, J = 263.7 Hz, 221.9 Hz), 128.4 (td, J = 23.7, 14.4 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376 MHz)  $\delta$  –108.1 (dd, J = 108.8, 13.3 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 161 MHz)  $\delta$  4.9 (t, J = 108.4 Hz); HRMS (ESI) calcd for  $[M + Na]^+$ C<sub>7</sub>H<sub>11</sub>Br<sub>2</sub>F<sub>2</sub>NaO<sub>3</sub>P 392.8660, found 392.8673.

**Diethyl (3-Bromo-1,1-difluoroprop-2-yn-1-yl)phosphonate** (5). To a mixture of vinyl dibromide 4 (1 g, 2.7 mmol) in dry THF (10 mL) at -20 °C was slowly added a solution of potassium *tert*butoxide (0.3 g, 2.7 mmol) in THF (2 mL). The resulting mixture was stirred for 1 h at room temperature, prior to hydrolysis with water (5 mL) and extraction with diethyl ether. After evaporation of the solvent, the crude product was purified by flash column chromatography, with *n*-pentane–ethyl acetate as eluent: colorless oil (890 mg, 96%); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.38 (t, *J* = 7.1 Hz, 6H), 4.20–4.41 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  16.4 (d, *J* = 4.8 Hz), 56.6 (td, *J* = 10.1, 8.4 Hz), 65.7 (d, *J* = 6.7 Hz), 70.6 (td, *J* = 35.5, 18.2 Hz), 109.1 (td, *J* = 253.1, 229.1 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376 MHz)  $\delta$  –96.8 (d, *J* = 105.5 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 161 MHz)  $\delta$  3.4 (t, *J* = 105.5 Hz); HRMS (ESI) calcd for [M + Na]<sup>+</sup> C<sub>7</sub>H<sub>10</sub>BrF<sub>2</sub>NaO<sub>3</sub>P 312.9416, found 312.9420.

General Procedure for the Synthesis of  $\alpha,\alpha$ -Difluoropropargylphosphonates (7a–h, 10a–h, and 11a–g). To a solution of dibromide (500 mg, 1.4 mmol, 1 equiv) in dry THF (30 mL) at -78 °C was slowly added LDA (6.8 mL, 2 M solution in THF/*n*-heptane/ ethylbenzene, 2.5 equiv). The resulting mixture was stirred at this temperature for 5 min, and then an appropriate electrophile (1 equiv) was added. After the mixture was stirred for 30 min, it was quenched with 3 M HCl (10 mL). After the organic layer was separated, the additional extraction with diethyl ether was repeated twice. The solvent was evaporated, and the crude product was purified by column chromatography with *n*-pentane–ethyl acetate as eluent.

Diethyl (1,1-difluoro-4-hydroxy-4-phenylbut-2-yn-1-yl)phosphonate (**7a**): yellow oil (421 mg, 98%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.34 (t, *J* = 7.1 Hz, 6H), 3.1 (bs, 1H), 4.22–4.31 (m, 4H), 5.08 (s, 1H), 7.21–7.29 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 16.4 (d, *J* = 5.4 Hz), 65.8 (d, *J* = 6.7 Hz), 69.6 (td, *J* = 2.0, 1.1 Hz), 74.0 (td, *J* = 33.9, 17.4 Hz), 96.3 (dt, *J* = 7.6, 6.9 Hz), 109.3 (td, *J* = 253.1, 229.1 Hz), 124.8, 128.1, 128.5, 150.1; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –98.2 (d, *J* = 104.5 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>) δ 3.9 (t, *J* = 105.6 Hz); HRMS (ESI) calcd for  $[M + H]^+ C_{14}H_{17}F_2O_4P$ 318.0832, found 318.0838. The observed data were in accord with those reported in the literature.<sup>13a</sup>

Diethyl (1,1-difluoro-4-hydroxy-4-(2-methoxyphenyl)but-2-yn-1yl)phosphonate (**7b**): colorless oil (440 mg, 94%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.29 (t, *J* = 7.1 Hz, 6H), 3.83 (s, 3H), 4.12–4.29 (m, 4H), 5.74 (s, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1H), 7.2–7.21 (m, 1H), 7.47 (dd, *J* = 7.5, 1.7 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.3 (d, *J* = 5.5 Hz), 55.6, 60.1, 65.7 (d, *J* = 6.3 Hz), 74.4 (td, *J* = 33.8, 17.4 Hz), 92.9 (dt, *J* = 7.6, 6.7 Hz), 110.9 (td, *J* = 253.2, 229.5 Hz), 120.9, 127.2, 127.8, 130.1, 156.6; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  –97.5 (dd, *J* = 106.7, 5.0 Hz); <sup>31</sup>P NMR (161 MHz,

CDCl<sub>3</sub>)  $\delta$  3.7 (t, J = 106.6 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>1</sub>;H<sub>19</sub>F<sub>2</sub>O<sub>5</sub>P 349.1016, found 349.1021.

Diethyl (1,1-difluoro-4-hydroxy-4-(3-methoxyphenyl)but-2-yn-1yl)phosphonate (**7d**): colorless oil (430 mg, 93%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.29 (t, *J* = 7.1 Hz, 6H), 3.83 (s, 3H), 4.18–4.30 (m, 4H), 4.69 (bs, 1H), 5.49 (s, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1H), 7.2–7.21 (m, 1H), 7.47 (dd, *J* = 7.5, 1.7 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.3 (d, *J* = 5.5 Hz), 55.3, 63.7, 65.9 (d, *J* = 6.3 Hz), 75.3 (td, *J* = 33.8, 17.4 Hz), 93.0 (dt, *J* = 7.6, 6.7 Hz), 108.7 (td, *J* = 253.2, 229.5 Hz), 114.4, 118.9, 129.8, 140.5, 159.8; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  –97.9 (dd, *J* = 106.7, 4.9 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  3.7 (t, *J* = 106.2 Hz); HRMS (ESI): calcd for [M + H]<sup>+</sup> C<sub>15</sub>H<sub>19</sub>F<sub>2</sub>O<sub>5</sub>P 349.1010, found 349.1012.

Diethyl (1,1-difluoro-4-hydroxy-4-(4-methoxyphenyl)but-2-yn-1yl)phosphonate (**7f**): colorless oil (451 mg, 97%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.34 (td, *J* = 7.1, 1.4 Hz, 6H), 3.79 (s, 3H), 4.21–4.34 (m, 4H), 5.48 (td, *J* = 4.8, 2.2 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.4 (d, *J* = 5.5 Hz), 55.4, 63.6, 65.8 (d, *J* = 6.3 Hz), 75.5 (td, *J* = 33.8, 17.4 Hz), 93.1 (dt, *J* = 7.6, 6.7 Hz), 106.4 (td, *J* = 253.2, 229.5 Hz), 114.4, 128.2, 131.2, 159.9; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -97.9 (dd, *J* = 106.0, 4.9 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  3.9 (t, *J* = 106.2 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>15</sub>H<sub>19</sub>F<sub>2</sub>O<sub>5</sub>P 349.1010, found 349.1015.

Diethyl (1,1-difluoro-4-hydroxydec-2-yn-1-yl)phosphonate (**7h**): colorless oil (382 mg, 93%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.87 (t, *J* = 6.6 Hz, 3H), 1.28–1.33 (m, 6H), 1.39 (t, *J* = 7.1 Hz, 6H), 1.41–1.47 (m, 2H), 3.00 (bs, 1H), 1.68–1.81 (m, 2H), 4.18–4.30 (m, 4H), 4.47 (tt, *J* = 6.7, 2.2 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  14.1, 16.3 (d, *J* = 5.5 Hz), 22.6, 24.9, 28.9, 31.7, 36.9, 62.0, 55.3, 65.6 (d, *J* = 6.7 Hz), 65.7 (d, *J* = 6.7 Hz), 74.3 (dt, *J* = 17.4, 16.3 Hz), 93.0 (dt, *J* = 7.6, 6.7 Hz), 108.6 (td, *J* = 253.2, 229.5 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -97.3 (dd, *J* = 106.7, 4.9 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  3.9 (t, *J* = 106.6 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>12</sub>H<sub>26</sub>F<sub>2</sub>O<sub>4</sub>P 303.1536, found 303.1540.

Diethyl (1,1-difluoro-4-hydroxy-4-methylpent-2-yn-1-yl)phosphonate (**10a**): colorless oil (357 mg, 98%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.28 (t, *J* = 7.1 Hz, 6H), 1.43 (s, 6H), 4.17–4.26 (m, 4H), 4.65 (bs, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.2 (d, *J* = 5.5 Hz), 30.3, 64.4, 65.7 (d, *J* = 6.7 Hz), 71.2 (td, *J* = 33.8, 17.2 Hz), 97.8 (dt, *J* = 7.6, 6.7 Hz), 108.9 (td, *J* = 253.2, 229.5 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -97.4 (d, *J* = 106.9 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  3.7 (t, *J* = 107.4 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>10</sub>H<sub>18</sub>F<sub>2</sub>O<sub>4</sub>P 271.0905, found 271.0908.

Diethyl (1,1-difluoro-4-hydroxy-4-isopropyl-5-methylhex-2-yn-1yl)phosphonate (10b): colorless oil (405 mg, 92%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.94 (d, J = 6.8 Hz, 6H), 0.97 (d, J = 6.8 Hz, 6H), 1.32 (t, J = 6.8 Hz, 6H), 1.92 (sept, J = 6.8 Hz, 2H), 2.89 (bs, 1H), 4.25 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.1, 16.4 (d, J = 5.8 Hz), 17.8, 34.3, 65.3 (d, J = 6.7 Hz), 75.1 (td, J = 34.5, 16.3 Hz), 94.9 (dt, J = 7.6, 6.7 Hz), 109.0 (td, J = 252.1, 230.1 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -96.8 (d, J = 108.4 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  4.1 (t, J = 109.4 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>14</sub>H<sub>26</sub>F<sub>2</sub>O<sub>4</sub>P 327.1536, found 327.1538.

Diethyl (1,1-difluoro-3-(1-hydroxycyclohexyl)prop-2-yn-1-yl)phosphonate (**10c**): yellow oil (385 mg, 92%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.17–1.25 (m, 1H), 1.34 (t, *J* = 6.8 Hz, 6H), 1.44– 1.68 (m, 9H), 1.89–1.93 (m, 2H), 4.22–4.34 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.4 (d, *J* = 5.8 Hz), 22.9, 25.0, 38.9, 65.7 (d, *J* = 6.7 Hz), 68.2, 73.5 (td, *J* = 33.4, 16.5 Hz), 97.1 (dt, *J* = 7.6, 6.7 Hz), 109.1 (td, *J* = 253.1, 230.0 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  –97.2 (d, *J* = 106.9 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  4.0 (t, *J* = 107.4 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>13</sub>H<sub>22</sub>F<sub>2</sub>O<sub>4</sub>P 311.1223, found 311.1228.

Diethyl (1,1-difluoro-3-(1-hydroxycyclohex-2-en-1-yl)prop-2-yn-1-yl)phosphonate (10d): yellow oil (383 mg, 92%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.36 (t, *J* = 6.8 Hz, 6H), 1.72–1.78 (m, 2H), 1.86–1.92 (m, 1H), 1.99–2.07 (m, 3H), 4.11 (bs, 1H), 4.25–4.33 (m, 4H), 5.71 (dt, *J* = 9.9, 1.9 Hz, 1H), 5.85 (dt, *J* = 9.9, 3.7 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.4 (d, *J* = 5.8 Hz), 18.6, 24.6, 36.8, 64.9 (td, *J* = 2.0, 1.0 Hz), 65.8 (d, *J* = 6.7 Hz), 72.9 (td, *J* = 33.6, 17.3 Hz), 96.7

(dt, J = 7.6, 6.7 Hz), 108.8 (td, J = 253.1, 230.0 Hz), 128.9, 130.9; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  –97.3 (d, J = 106.9 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  3.9 (t, J = 108.4 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>13</sub>H<sub>20</sub>F<sub>2</sub>O<sub>4</sub>P 309.1067, found 309.1071.

Diethyl (1, 1-difluoro-4-hydroxy-4-phenylpent-2-yn-1-yl)phosphonate (**10e**): yellow oil (384 mg, 92%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.32 (dt, *J* = 7.1, 6.7 Hz, 6H), 1.77 (s, 3H), 4.21–4.27 (m, 4H), 4.48 (bs, 1H), 7.25–7.36 (m, 3H), 7.57 (dd, *J* = 7.6, 1.2 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 16.4 (d, *J* = 5.4 Hz), 32.5, 65.8 (d, *J* = 6.7 Hz), 69.5 (td, *J* = 2.0, 1.1 Hz), 74.1 (td, *J* = 33.9, 17.4 Hz), 96.3 (dt, *J* = 7.6, 6.9 Hz), 109.1 (td, *J* = 253.1, 229.1 Hz), 124.9, 128.0, 128.5, 143.9; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –97.7 (d, *J* = 106.5 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>) δ 3.8 (t, *J* = 105.6 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>15</sub>H<sub>20</sub>F<sub>2</sub>O<sub>4</sub>P 333.1067, found 333.1069.

Diethyl (1,1-difluoro-4-hydroxy-4-(4-methoxyphenyl)pent-2-yn-1-yl)phosphonate (10f): colorless oil (450 mg, 92%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.32 (dt, *J* = 7.3, 6.8 Hz, 6H), 1.75 (s, 3H), 3.77 (s, 3H), 4.22–4.29 (m, 4H), 4.30 (s, 1H), 6.8 (d, *J* = 9.2 Hz, 2H), 7.5 (d, *J* = 8.7 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.4 (d, *J* = 5.8 Hz), 32.3, 55.4, 65.8 (d, *J* = 6.7 Hz), 69.2, 73.9 (td, *J* = 33.6, 17.3 Hz), 96.4 (dt, *J* = 7.6, 6.7 Hz), 109.1 (td, *J* = 253.1, 229.1 Hz), 113.7, 126.2, 136.1, 159.4; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  –96.8 (d, *J* = 109.0 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  4.1 (t, *J* = 109.0 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>16</sub>H<sub>22</sub>F<sub>2</sub>O<sub>3</sub>P 363.1173, found 363.1180.

Diethyl (1,1-difluoro-4-hydroxy-4-(4-nitrophenyl)pent-2-yn-1-yl)phosphonate (**10g**): colorless crystals (490 mg, 96%), mp 64–67 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.3 (dt, *J* = 10.1, 6.8 Hz, 6H), 1.8 (s, 3H), 4.2 (m, 4H), 4.9 (bs, 1H), 7.8 (d, *J* = 8.7 Hz, 2H), 8.2 (d, *J* = 8.7 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.4 (d, *J* = 3.8 Hz), 32.7, 65.9 (d, *J* = 6.7 Hz), 69.1, 74.8 (td, *J* = 33.6, 17.3 Hz), 94.7 (dt, *J* = 7.6, 6.7 Hz), 109.0 (td, *J* = 253.1, 229.1 Hz), 123.8, 126.1, 147.7, 150.1; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  –98.5 (d, *J* = 105.5 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  3.6 (t, *J* = 105.6 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>15</sub>H<sub>19</sub>F<sub>2</sub>NO<sub>6</sub>P 378.0918, found 378.0919.

Diethyl (1,1,5,5,5-pentafluoro-4-hydroxy-4-phenylpent-2-yn-1yl)phosphonate (10h): colorless oil (479 mg, 92%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.33 (dt, J = 10.9, 6.8 Hz, 6H), 4.20–4.2 (m, 4H), 6.16 (s, 1H), 7.38–7.40 (m, 3H), 7.70 (dd, J = 5.5, 3.5 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.2 (d, J = 5.6 Hz), 66.0 (d, J = 6.7 Hz), 66.1 (d, J = 6.7 Hz), 73.1 (m, 2C), 88.2 (dt, J = 7.6, 6.8 Hz), 108.2 (td, J = 253.0, 228.9 Hz), 122.5 (q, J = 285.0 Hz), 127.2, 128.4, 129.8, 134.4; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  –79.6 (s, 3F), –99.5 (d, J = 104.1 Hz, 2F); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  2.9 (t, J = 103.7 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>15</sub>H<sub>17</sub>F<sub>5</sub>O<sub>4</sub>P 387.0784, found 387.0788.

Diethyl (1,1-difluoroprop –2-yn-1-yl)phosphonate (11a): yellowish oil (92%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.26 (t, *J* = 7.1 Hz, 6H), 3.15 (td, *J* = 6.1, 3.1 Hz, 1H), 4.14–4.24 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 16.2 (d, *J* = 5.8 Hz), 65.6 (d, *J* = 6.7 Hz), 73.0 (td, *J* = 33.6, 17.3 Hz), 80.7 (dt, *J* = 7.7, 6.7 Hz), 107.3 (td, *J* = 253.0, 228.1 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -99.1 (d, *J* = 104.1 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>) δ 3.5 (t, *J* = 103.7 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>7</sub>H<sub>12</sub>F<sub>2</sub>O<sub>3</sub>P 213.0492, found 213.0494. The observed data were in accord with those reported in the literature.<sup>13a</sup>

Diethyl 1,1-difluoro-3-(trimethylsilyl)prop-2-ynylphosphonate (11b): colorless oil (353 mg, 92%); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  0.21 (s, 9H), 1.37 (dt, *J* = 7.1, 0.7 Hz, 6H), 4.25–4.34 (m, 4H), <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  –0.8, 16.4 (d, *J* = 4.8 Hz), 65.5 (d, *J* = 6.6 Hz), 93.2 (td, *J* = 31.6, 16.3 Hz), 99.2 (dt, *J* = 5.6 Hz), 108.3 (td, *J* = 253.1, 228.1 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376 MHz)  $\delta$  –96.7 (d, *J* = 110.3 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 161 MHz)  $\delta$  3.8 (t, *J* = 106.2 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>10</sub>H<sub>20</sub>F<sub>2</sub>O<sub>3</sub>PSi 285.0882, found 285.0889.

Diethyl (3-(tert-butyldimethylsilyl)-1,1-difluoroprop-2-yn-1-yl)phosphonate (11c): colorless oil (405 mg, 92%); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.13 (s, 6H), 0.92 (s, 9H), 1.34 (td, *J* = 7.1, 0.7 Hz, 6H), 4.17–4.36 (m, 4H), <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ –5.3, 16.4 (d, *J* = 5.6 Hz), 16.5, 25.8, 65.3 (d, *J* = 6.6 Hz), 94.0 (td, *J* = 32.1, 16.6 Hz), 98.1 (dt, *J* = 5.9, 5.6 Hz), 108.3 (td, *J* = 253.2, 228.1 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376 MHz) δ –96.8 (d, *J* = 107.2 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 161

MHz)  $\delta$  3.9 (t, J = 107.2 Hz); HRMS (ESI) calcd for  $[M + H]^+$   $C_{13}H_{26}F_2O_3PSi$  327.1357, found 327.1362.

Diethyl (3-(diphenylphosphino)-1,1-difluoroprop-2-yn-1-yl)phosphonate (**11d**): yellow oil (492 mg, 92%); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.29 (td, J = 7.1, 0.8 Hz, 6H), 4.16–4.31 (m, 4H), 7.32– 7.35 (m, 6H), 7.53–7.60 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ 16.4 (d, J = 5.4 Hz), 65.6 (d, J = 6.5 Hz), 92.5 (ddt, J = 35.6, 7.1, 7.0 Hz), 95.8 (td, J = 33.5, 16.8 Hz), 108.8 (td, J = 254.0, 227.3 Hz), 128.9, 129.0, 129.8, 132.8, 133.1; <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376 MHz)  $\delta$ –97.3 (dd, J = 106.4, 10.8 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 161 MHz)  $\delta$  3.8 (td, J = 106.4, 3.1 Hz, 1P), -34.9 (td, J = 9.7, 2.8 Hz, 1P); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>19</sub>H<sub>21</sub>F<sub>2</sub>O<sub>3</sub>P<sub>2</sub> 397.0934, found 397.0939.

Tetraethyl ((isopropylphosphinediyl)bis(1,1-difluoroprop-2-yne-3,1-diyl))bis(phosphonate) (11e): yellow oil (415 mg, 62%); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.28 (d, J = 7.0 Hz, 3H), 1.32 (d, J = 7.0 Hz, 3H), 1.38 (t, J = 7.1 Hz, 12H), 2.27 (sept, J = 7.0 Hz, 1H), 4.26– 4.36 (m, 8H), <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  16.4 (d, J = 5.4 Hz), 19.3 (d, J = 11.6 Hz), 27.8, 65.7 (d, J = 6.7 Hz), 65.8 (d, J = 6.7 Hz), 86.0–86.5 (m), 95.0 (td, J = 33.1, 16.6 Hz), 108.7 (td, J = 252.0, 231.1 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376 MHz)  $\delta$  –98.2 (dd, J = 106.6, 10.2 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 161 MHz)  $\delta$  3.4 (td, J = 104.7, 3.3 Hz, 2P), -51.5 (quint t, J = 9.3, 3.1 Hz, 1P); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>17</sub>H<sub>28</sub>F<sub>4</sub>O<sub>6</sub>P<sub>3</sub> 497.1035, found 497.1037.

Diethyl (1,1-difluorobut-2-yn-1-yl)phosphonate (**11g**): yellow oil (308 mg, 92%); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.30 (t, J = 7.1 Hz, 6H), 1.91 (td, J = 6.3, 3.2 Hz, 3H), 4.17–4.27 (m, 4H), <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  3.8, 16.3 (d, J = 5.4 Hz), 65.3 (d, J = 6.6 Hz), 69.9 (td, J = 33.2, 17.4 Hz), 90.3 (dt, J = 7.7, 6.9 Hz), 108.9 (td, J = 252.0, 231.1 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376 MHz)  $\delta$  –95.8 (dq, J = 108.8, 6.3 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 161 MHz)  $\delta$  4.1 (t, J = 108.6 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>8</sub>H<sub>13</sub>F<sub>2</sub>NaO<sub>3</sub>P 249.0464, found 249.0466.

General Procedure for the Synthesis of ( $\alpha$ -Fluoroallenyl)phosphonates (9a,b). To a solution of dibromide (500 mg, 1.4 mmol, 1 equiv) in dry THF (30 mL) at -78 °C was slowly added LDA (6.8 mL, 2 M solution in THF/*n*-heptane/ethylbenzene 2.5 equiv). The resulting mixture was stirred at this temperature for 5 min, and then 1 equiv of 2-methylpropanal (9a) or pivalaldehyde (9b) was added. After the mixture was stirred for 30 min, it was quenched with 3 M HCl (10 mL). The organic layer was then separated, and the additional extraction with diethyl ether was repeated twice. The solvent was evaporated, and the crude allene was purified by column chromatography with *n*-pentane—ethyl acetate as eluent.

Diethyl (1-fluoro-4-hydroxy-5-methylhexa-1,2-dien-1-yl)phosphonate (**9a**): yellow oil (310 mg, 88%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.69 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.24 (dt, *J* = 7.1, 2.2 Hz, 6H), 1.96–2.16 (m, 1H), 3.38 (bs, 1H), 4.13–4.23 (m, 4H), 4.28 (dd, *J* = 2.1, 1.5 Hz, 1H), 6.45 (dd, *J* = 39.6, 8.6 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  14.9, 16.3 (d, *J* = 5.9 Hz), 19.9, 31.3, 64.3 (d, *J* = 6.0 Hz), 81.3, 116.3 (d, *J* = 26.0 Hz), 159.3 (dd, *J* = 309.4, 224.7 Hz), 198.6 (d, *J* = 13.1 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -103.7 (dd, *J* = 98.7, 39.1 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>)  $\delta$  2.5 (d, *J* = 98.9 Hz); HRMS (ESI) calcd for [M + H]<sup>+</sup> C<sub>11</sub>H<sub>21</sub>FO<sub>4</sub>P 267.1161, found 267.1165.

Diethyl (1-fluoro-4-hydroxy-5,5-dimethylhexa-1,2-dien-1-yl)phosphonate (**9b**): yellow oil (400 mg, 86%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.89 (s, 9H), 1.28 (t, *J* = 7.5 Hz, 6H), 3.65 (bs, 1H), 3.92 (d, *J* = 3.4 Hz, 1H), 4.00–4.25 (m, 4H), 6.57 (dd, *J* = 37.8, 8.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 16.2 (d, *J* = 5.5 Hz), 26.1, 36.1, 64.2 (d, *J* = 5.5 Hz), 84.1 (dd, *J* = 2.1, 1.5 Hz), 117.8 (d, *J* = 26.1 Hz), 157.7 (dd, *J* = 309.3, 225.3 Hz), 199.4 (d, *J* = 12.7 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -107.1 (dd, *J* = 98.7, 37.8 Hz); <sup>31</sup>P NMR (161 MHz, CDCl<sub>3</sub>) δ 2.8 (d, *J* = 98.9 Hz); HRMS (ESI) calcd for  $[M + H]^+$  C<sub>12</sub>H<sub>23</sub>FO<sub>4</sub>P 281.1318, found 281.1322.

# ASSOCIATED CONTENT

#### **S** Supporting Information

A CIF file giving X-ray structural data for compound **10g** and figures giving <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F, and <sup>31</sup>P NMR spectra of the

products. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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