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An improved preparation of α-fluorinated propargylphosphonates and the solid phase synthesis of α-hydroxy-γ-TIPS propargylphosphonate ester

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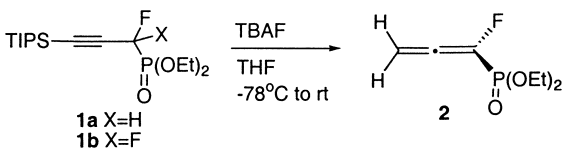
Abstract

Diethyl-3-triisopropylsilyl-1-propynephosphonate was fluorinated using NFSI to give the corresponding monofluoroderivative in good yield. The synthesis of diethyl-1,1-difluoro-3-triisopropylsilylpropynephosphonate was efficiently achieved following Burton's methodology using CuCl/Cd to promote the coupling reaction of diethyl bromodifluoromethylphosphonate with the corresponding alkynyl iodide. Although the solid phase synthesis of α-hydroxy-γ-TIPS propargylphosphonate ester was carried out successfully, its fluorination — using DAST — failed.

Keywords: Fluorophosphonates; Solid-phase synthesis; α-Hydroxyphosphonates

1. Introduction

Selective fluorine substitution, either through fluorinating agents [1] (other reviews include [2,3], for a selected sample of new reagents used in nucleophilic fluorination see [4,5]) or building blocks (see [6]) modifies the physico-chemical and physiological properties of organic molecules (see [7]). α-Fluoroalkylphosphonates, in which the bridging C–O–P phosphate bond has been replaced with either a C–CFH–P or a C–CF_2–P bond, is a case in point. These compounds are important resources for the study of biological phosphate mimics and other therapeutic applications (e.g. [8–13]). It was our postulate that a fluorinated propargylic scaffold, such as **1a**,**b**, is uniquely equipped for the preparation of β,γ-unsaturated-α-fluorinated phosphonates, as well as other conjugated fluoroorganic molecules [14]. Tetrabutylammonium fluoride (TBAF) deprotection of the silyl group in **1a** yields allene **2** through an allenyl-propargyl resonance stabilized anion (Eq. (1)).



1a X=H
1b X=F

(1)

The allene moiety present in **2** has been used as template in the stereoselective synthesis of α-fluoro-γ-amino-α,β-unsaturated phosphonates and (*Z*)-α-fluoroenaminophosphonates, whereas the Diels–Alder cycloaddition of **2** with dienes furnished exocyclic vinylfluorophosphonates [15]. Because of its synthetic importance, various synthetic alternatives to **1a** and its difluoro derivative **1b** have been developed and will be presented in this paper. The synthesis of polymer-bound hydroxypropargyl phosphonate **17a** has been accomplished and is also reported herein.

2. Results and discussion

2.1. The synthesis of TIPS-α-fluoropropargyl phosphonate 1a

Triisopropyl (TIPS) propargyl fluorophosphonate **1a** was obtained from the commercially available propargyl alcohol using a procedure described previously by us [14]: deprotonation of propargyl alcohol **3** with two equivalent of ethylmagnesium bromide formed the acetylide ion which was treated with TIPS chloride to provide **4**. Dess–Martin oxidation of alcohol **4** to the corresponding aldehyde **5** followed by phosphorylation with diethyl phosphite in the presence of KF·2H_2O furnished hydroxyphosphonate **6**. Fluorination was performed using diethylaminosulfur trifluoride (DAST) to obtain **1a** in 27.5% overall yield for the

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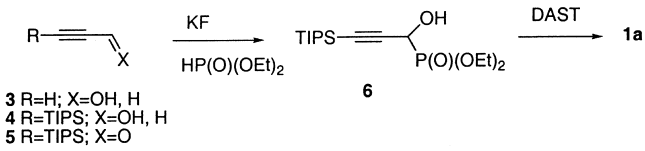
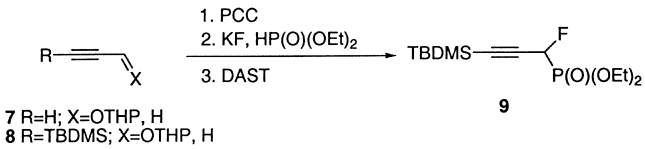
four steps (Eq. (2)).



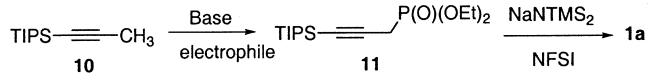
(2)

The *tert*-butyldimethylsilyl derivative **9** was prepared from propargyl alcohol using a slight variation from the protocol described above. Tetrahydropyranyl (THP) protection of propargyl alcohol was followed by alkylation using *tert*-butyldimethylsilyl (TBDMS) chloride. Deprotection and PCC oxidation gave the corresponding aldehyde which was then phosphorylated and fluorinated using the same conditions as for **1a** (Eq. (3)). The overall yield for this six-step sequence was only 8%.



(3)

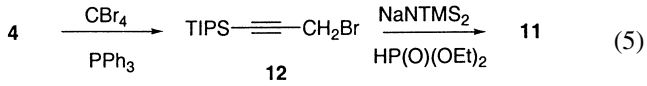
Because the lowest yielding step in the above syntheses was the fluorination with DAST, we varied the solvent, temperature and the rate of addition of DAST, but none of these changes improved the yield. Other fluorinating agents (Deoxo-Fluor™, SelectFluor™, Ishikawa's reagent) did not improve the yield of the fluorination step significantly. In all cases, the yield never rose above 40%. An alternate approach was sought using an electrophilic fluorinating agent, namely, *N*-fluorobenzenesulfonimide (NFSI) (Eq. (4)). The advantage of this route is that it shortened the synthesis of **1a** (two steps instead of four) because the TIPS-containing precursor **10** is commercially available. Although the NFSI fluorination step was more efficient (63% versus 41% using DAST), the phosphorylation of **10** was very inefficient (15–25%) (Eq. (4)). To improve the yield of the phosphorylation step, we modified the base, temperature, order of addition and employed various auxiliary agents (see Table 1).



(4)

None of the conditions shown in Table 1, including replacing the diethyl chlorophosphate with diethyl chlorophosphite (entries 9 and 10), improved the yield of the phosphorylation reaction.

The disappointingly low yields, partially attributed to the poor electrophilicity of phosphorus, prompted us to consider a nucleophilic phosphorus reagent. Thus, TIPS propargyl alcohol **4** was first converted into the corresponding bromide **12** using CBr_4 in 80%. The bromide was then displaced with the anion of diethyl phosphite [16] to give **11** in 78% yield (Eq. (5)). NFSI fluorination of **11** furnished **1** in 63%, bringing to three the total number of steps for this sequence and an overall yield of 39%.



(5)

Very recently, Burton and coworkers utilized $(EtO)_2$-P(O)CFHBr in a one-step preparation of propargylic α-fluorophosphonates from the corresponding propargyl halide [17]. Their protocol — if applied to our system — should shorten significantly the synthesis of **1a**.

2.2. The synthesis of TIPS-α,α,-difluoropropargyl phosphonate **1b**

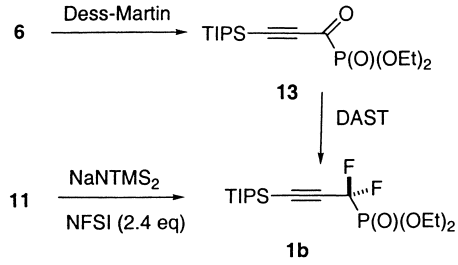
Oxidation of α-hydroxypropargyl phosphonate **6** using Dess–Martin conditions [18] (59%) followed by addition of excess DAST yielded the corresponding α,α-difluorophosphonate **1b** in 30% yield (Scheme 1). This fluorination step was carried out more efficiently by deprotonation of **11** with

Table 1
Phosphorylation of **10**

Entry	**10** → **11**	Yield **11**[a]
1	*n*-BuLi, TEDA, THF, −20°C, 6 h, addition of $ClP(O)(OEt)_2$	15%
2	*n*-BuLi, *t*-BuOK, THF, −50°C, addition of $ClP(O)(OEt)_2$	28%
3	*n*-BuLi, THF, −80°C, 15 min, addition of $ClP(O)(OEt)_2$ (1.5 eq)	25%
4	*n*-BuLi, THF, −20°C, 15 min, inverse addition of $ClP(O)(OEt)_2$ (5 eq)	25%
5	*n*-BuLi, THF, −20°C, 15 min, very slow addition of $ClP(O)(OEt)_2$ (1.25 h)	26%
6	*n*-BuLi, THF, −20°C, 15 min, add $CeCl_3$, stir 1 h, addition of $ClP(O)(OEt)_2$ (1.0 eq)	15%[b]
7	*n*-BuLi, THF, −20°C, 15 min, add HMPA, stir 15 min, addition of $ClP(O)(OEt)_2$ at −75°C	20%
8	*n*-BuLi, THF, −20°C, 30 min, addition of $ClP(O)(OEt)_2$ (1.5 eq), at −20°C, reflux 1 h	28%
9	*n*-BuLi, *t*-BuOK, THF, −50°C, addition of $ClP(OEt)_2$	No reaction
10	*n*-BuLi, THF, −20°C, 30 min, addition of $ClP(OEt)_2$, reflux 4 h	No reaction

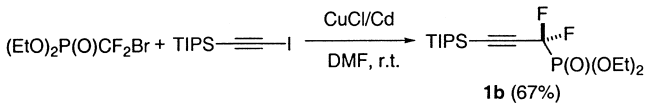
[a] For all reactions, the only other product found in the reaction was unreacted starting material.
[b] The major product of the reaction was TIPS–C≡C–CH_2–O–P(O)$(OEt)_2$ (36%).

2.2 equivalents of $NaN(TMS)_2$ followed by treatment with NFSI (2.4 equivalents) to give **1b** in 79% yield.



Scheme 1

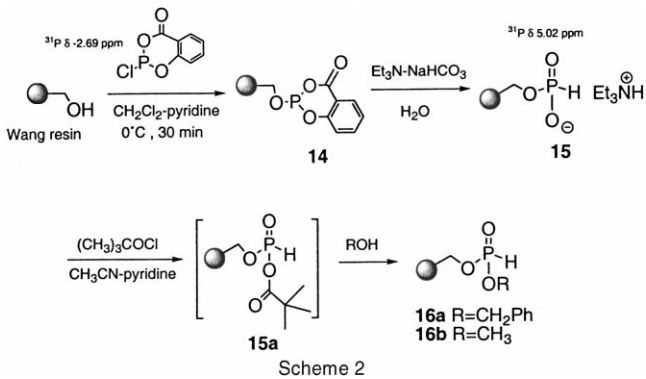
In pursuit of a shorter and more efficient way to **1b**, we turned our attention to the Burton's CuCl/Cd-promoted coupling reaction [19] of the readily available diethyl bromodifluoromethyl phosphonate with 1-iodo-3-TIPS ethyne, which we postulated as a suitable alternative coupling partner to Burton's aryl iodide. To our satisfaction, this protocol proved very successful (Eq. (6)).



(6)

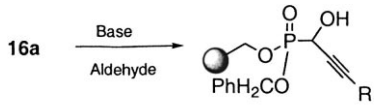
2.3. The solid phase synthesis of TIPS-α-hydroxypropargyl phosphonate **17**

The solid phase syntheses of organic compounds play an important role in combinatorial chemistry [20]. If the phosphoryl group in our fluorinated propargyl building block could be linked to a polymer support it could permit the solid-phase synthesis via HWE of fluoroenynes and fluoroenediynes (on conjugated enynes and enediynes see [21,22]). With this goal in mind we prepared **14** and salt **15** following the procedure developed by Mjalli and Cao [23]. Reaction of **15** with pivaloyl chloride provided the intermediate **15a** which was not isolated but completely converted to the desired product **16a** using benzyl alcohol (^{31}P NMR δ 8.4 ppm) (Scheme 2).



Scheme 2

When methanol replaced benzyl alcohol, two signals were observed in the ^{31}P NMR spectrum: δ 7.1 ppm, corresponding to **16b**, and δ 12.8 ppm, presumed to belong to **16a**. We decided to continue the synthesis using the benzyl ester as this reaction was more efficient than with methanol. Mjalli and Cao have reported that when **16b** was treated with a series of alkyl and aryl aldehydes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the corresponding α-hydroxyalkyl- or α-hydroxy-aryl phosphonates were obtained in satisfactory yield. Using their conditions in the reaction of **16a** with **5** and 2-octynal, we obtained the desired **17a** and **17b**, respectively, (Eq. (7)) albeit in low yields (entries 1 and 2 in Table 2).



(7)

17a R=TIPS ^{31}P δ 18.9 ppm
17b R=C_5H_{11} ^{31}P δ 16.4 ppm

Based on our previous results (e.g. see Eqs. (2) and (3)), we replaced DBU with KF. Thus, when **16a** was treated with $KF{\cdot}2H_2O$ and TIPS-propargyl aldehyde, **17a** was obtained in very good yield according to the ^{31}P NMR spectrum of the crude product (entry 3). To our surprise, under the same reaction conditions, 2-octynal did not react at all (entry 4). The fluorination of **17a** with either DAST or Deoxo-Fluor™ was attempted with no success. The resulting crude mixture showed a new ^{19}F NMR doublet at δ −72 ppm ($^1J_{PF}$ = 676 Hz) which we regarded as an indication that a P–F bond had been formed.[1] No other fluorination attempts were carried out.

3. Experimental

All glassware was dried in flame or in an oven at 120° prior to use. All experiments were conducted under an atmosphere of dry argon. Commercial reagents were used without further purification. Solvents were dried as follows: methylene chloride and toluene were distilled from CaH_2. THF was distilled from Na/benzopheonone. All the reactions were monitored using one of the following techniques: TLC, GC-MS, ^{19}F and ^{31}P NMR. Analytical TLC was performed using Alltech polygram Sil G/UV_{254} precoated plates. Column chromatography utilized silica gel, 230–400 mesh (Lagand Chemical Co. Inc.). ^1H, ^{13}C, ^{19}F, ^{31}P NMR spectra were recorded in $CDCl_3$ at 300, 133, 282, 121 MHz, respectively. ^{19}F NMR spectra are referenced against external $CFCl_3$, ^{31}P NMR spectra against 85% H_3PO_4. ^{19}F and ^{31}P NMR spectra were broad-band decoupled from hydrogen nuclei. Melting points are not corrected. All NMR spectra were recorded on a Bruker AC-300 NMR spectrometer at ambient temperature. IR spectra were recorded on Perkin-Elmer 1310 or Bruker Vector 22 FT-IR Spectrophotometers. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

[1] The coupling constant of in P–F bonds is approximately 552–1441 Hz.

Table 2
Addition of **17a** to propargyl aldehydes

Entry	Base	Aldehyde	Conditions	**18**
1	DBU (3 eq) (1 M in CH_3CN)	**5**	RT, 30 min	30%
2		2-Octynal	RT, overnight	30%
3	KF.2H_2O(5 eq) (1 M in CH_3CN)	**5**	RT, overnight	85%
4		2-Octynal	RT, overnight	No reaction

3.1. 1-Triisopropylsilyl-3-bromopropyne **12**

To a solution of TIPS-propargyl alcohol (1.0554 g, 4.97 mmol) and carbon tetrabromide (2.0907 g, 6.30 mmol) in dichloromethane (7.5 ml) at 0°C was added triphenylphosphine (2.0071 g, 7.65 mmol) in small portions during 1.5 h. After the addition, the solvent was removed under vacuum, ether was added (10 ml) and the solids were filtrated through a short plug of Celite. The solids were washed with ether (3 × 5 ml) and the combined ethereal solution was concentrated under vacuum. The residue was taken up in hexanes and filtrated through a short plug of silica gel to give, after removal of the solvent, 1.099 g (80%) of **12**, homogeneous by TLC: ^{1}H NMR δ 1.07 (s, 21H), 3.95 (s, 2H).

3.2. Diethyl-3-triisopropylsilyl-1-propynephosphonate **11** *from* **10**

To a cold solution (−20°C) of commercially available **10** (25.59 g, 0.130 mol) in THF (250 ml) was added *n*-BuLi (81.44 ml of a 1.6 M solution in hexane, 0.130 mol). After 15 min, diethylchlorophosphate (18.86 ml, 97%, 0.130 mol) was added dropwise at −20°C. After the addition was completed, the reaction mixture was allowed to warm up to room temperature, then refluxed for 1 h. The reaction was poured into saturated NH_4Cl (250 ml) and extracted with ether (3 × 100 ml). The combined ethereal extracts were dried ($MgSO_4$) and concentrated in vacuo. Fractional distillation furnished **11** (11.05 g, 25%) bp 120–128°C/0.2 Torr, and unreacted **10** (13.20 g, 52%) bp 44–46°C/0.2 Torr.

3.3. Diethyl-1-fluoro-3-triisopropylsilylpropynephosphonate **1a** *from* **11**

To a solution of **11** (0.1966 g, 0.59 mmol) in THF (5 ml) was added sodium bis(trimethysilyl)amide (0.70 ml, 1 M solution in THF) at −80°C. After the addition, the reaction was warmed up to −50°C over 1 h, then cooled down to −80°C and *N*-fluorobenzenesulfonimide (NFSI, 0.186 g, 0.59 mmol) in THF (3 ml) was added. The reaction mixture was allowed to warm up to room temperature, poured into saturated NH_4Cl (10 ml) and extracted with ether (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was triturated with hexane, filtrated and concentrated. The resulting oil was purified by flash chromatography (hexane/EtOAc = 7:3) to afford **1a** (0.130 g, 63%). ^{1}H NMR δ 1.09 (s, 21H), 1.37 (t, J = 7.1 Hz, 6H), 4.28 (m, 4H), 5.35 (dd, J = 47.0, 12.5 Hz, 1H); ^{19}F NMR δ −196 (d, J = 79 Hz); ^{31}P NMR δ 11.4 (d, J = 79 Hz); IR (neat, NaCl) 2950, 2870, 2180, 1460, 1275, 1060, 1020 and 885 cm^{-1}. Anal. Calcd. for $C_{16}H_{32}FO_3PSi$: C, 54.83; H, 9.20. Found: C, 54.77; H, 9.23%.

3.4. Diethyl-1-oxo-3-triisopropylsilylpropynephosphonate **13**

A solution of **6** (0.60 g, 1.72 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a solution of Dess–Martin periodinane (0.73 g, 1.72 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with H_2O. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc = 8:2) affording **13** (0.35 g, 59%) as a light yellow oil. ^{1}H NMR δ 1.13 (s, 21H), 1.39 (t, J = 7.1 Hz, 6H), 4.29 (m, 4H); ^{31}P NMR δ −3.8; IR (neat, NaCl) ν 2940, 2865, 2160, 1710, 1460, 1385, 1365, 1210, 1030, 885 cm^{-1}; GC-MS *m/z* 317 ($M^+ - 29$, 3), 275 (100), 247 (60), 219 (72), 177 (54), 109 (72), 59 (61). Anal. Calcd. for $C_{16}H_{31}O_4SiP$: C, 55.47; H, 9.02. Found: C, 55.71; H, 9.10%.

3.5. Diethyl-1,1-difluoro-3-triisopropylsilylpropynephosphonate **1b** *from* **13**

A mixture of **13** (0.1038 g, 0.3 mmol) and DAST (0.483 g, 3 mmol) in CH_2Cl_2 (5 ml) was refluxed for 6 h (be careful! DAST can undergo violent decomposition at higher temperatures). The reaction mixture was diluted with CH_2Cl_2 (10 ml), then saturated NH_4Cl (10 ml) was added to the ice-cold solution, the organic layer was separated and the aqueous layer was extracted with ether (2 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a dark red oil. Purification of the crude product by flash chromatography (hexane/EtOAc = 9:1) afforded **1b** (0.0327 g, 30%) as a light yellow oil. ^{1}H NMR δ 1.11 (s, 21H), 1.39 (t, J = 7.0 Hz, 6H), 4.32 (m, 4H); ^{19}F NMR δ −96.8 (d, J = 109 Hz); ^{31}P NMR δ 4.2 (t, J = 109 Hz); IR (neat, NaCl) ν 2950, 2870, 2170, 1465, 1390, 1370, 1280, 1150, 1040, 885, 770 cm^{-1}; GC-MS *m/z* 325 ($M^+ - 43$, 89), 297 (39), 269 (100), 153 (13), 109 (20),

81 (40). Anal. Calcd. for $C_{16}H_{31}O_3F_2SiP$: C, 52.15; H, 8.48. Found: C, 52.22; H, 8.37%.

3.6. Diethyl-1,1-difluoro-3-triisopropylsilylpropynephosphonate **1b** from **11**

To a solution of **11** (0.1261 g, 0.38 mmol) in THF (5 ml) was added sodium bis(trimethylsilyl)amide solution (2.2 eq, 0.834 ml, 1 M in THF) at −60°C. After the solution was stirred at that temperature for 15 min, *N*-fluorobenzenesulfonimide (2.4 eq, 0.287 g) in THF (5 ml) was added dropwise to the reaction, the resulting reaction mixture was warmed up to room temperature slowly. The reaction was quenched with saturated NH_4Cl, the organic layer was separated and the aqueous layer was extracted with ether (3×20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc = 8:2) affording **1b** (0.1107 g, 79%) as a light yellow oil.

3.7. Preparation of **1b** from triisopropylsilyliodoacetylene

A solution of triisopropylsilylacetylene (5.27 g, 29 mmol) in THF (30 ml) was cooled at −78°C and treated with *n*-BuLi (2.5 M in hexane, 13.9 ml, 1.2 eq). After 30 min stirring at this temperature, a solution of iodine (8.10 g, 1.1 eq) in THF (12 ml) was added via a syringe, which gave a thick white suspension. The mixture was slowly warmed up to room temperature in 2 h and saturated NH_4Cl (20 ml) was added. The resulting homogeneous solution was extracted with EtOAc (30×3 ml), washed with H_2O (30 ml), dried over Na_2SO_4 and concentrated to give a light yellow oil product 8.56 g, 96% yield (GC purity >98%), which was used directly in the next step. To a solution of diethyl bromodifluoromethylphosphonate (147 mg, 0.55 mmol) in dry DMF (3 ml) was added cadmium powder (100 mesh, 68 mg, 1.1 eq). The resulting suspension was stirred at room temperature for 2 h and then copper(I) chloride (38 mg, 0.7 eq) was added, followed by dropwise addition of triisopropylsilyliodoacetylene (102 mg, 0.6 eq), causing an immediate color change from gray to deep red-brown. The mixture was stirred at room temperature for another 2 h. Diethyl ether (20 ml) was added to precipitate the inorganic solid. After work-up (washing with saturated NH_4Cl and H_2O, drying over Na_2SO_4 and solvent removal) the crude product was obtained as a viscous yellow oil, which was further purified by flash chromatography to furnish pure **1b** (82 mg, 67%).

3.8. Synthesis of modified resin **15**

To a suspension of a Wang resin (0.60 g, 1.2 mmol $OH^-\ g^{-1}$) in dry CH_2Cl_2 (6.0 ml) and dry pyridine (3.0 ml) at 0°C, was added a 1.0 M solution of 2-chloro-4*H*-1,3,2-benzo-dioxaphosphorin-4-one (2.16 ml, 3.0 eq) [23]. The reaction mixture was warmed to room temperature and gently stirred for an additional 30 min, subsequently, treated with a cold solution of 1:1 Et_3N–$NaHCO_3$ in H_2O (3.0 ml). The modified resinate was filtered, washed sequentially with H_2O, CH_3CN, CH_2Cl_2 and dried in vacuo over P_2O_5 to afford triethylammonium phosphonate **15** (0.6370 g, 90% estimated). ^{31}P NMR δ 5.02 ppm.

3.9. Synthesis of modified resin **16a**

The salt **15** (0.50 g, ∼0.5 mmol) was treated with 1.0 M solution of benzyl alcohol (2.5 ml, 5 eq) in CH_3CN followed by the addition of 1.0 M pivaloyl chloride (2.5 ml, 5 eq) in 1:1 CH_3CN–pyridine. After stirring at room temperature for 15 min, the mixture was filtered, and washed with dry CH_3CN to afford crude **16a** (0.4962 g, 90% estimated from ^{31}P NMR). ^{31}P NMR δ 8.4 ppm.

3.10. Synthesis of modified resin **17a**

Resin **16a** (0.255 g, 0.25 mmol) was treated with 1.0 M solution of $KF{\cdot}2H_2O$ (1.5 ml, approx. 6 eq) in CH_3CN and 1.0 M solution of **5** (0.75 ml, 3 eq) in CH_3CN. The mixture was stirred at room temperature overnight, and the resulting solid was filtered, and washed sequentially with H_2O, CH_3CN, CH_2Cl_2 to provide **17a** (0.264 g, 85% estimated from ^{31}P NMR). ^{31}P NMR δ 18.9 ppm.

3.11. Synthesis of modified resin **17b**

Resin **16a** (0.264 g, ∼0.25 mmol) was treated with 1.0 M solution of DBU (1.0 ml, 4 eq) in CH_3CN and 1.0 M solution of 2-octynal (1.0 ml, 4 eq) in CH_3CN. The mixture was stirred at room temperature overnight, the resulting solid was filtered, and washed sequentially with H_2O, CH_3CN, CH_2Cl_2 to provide the **17b** (0.240 g, 30% estimated from ^{31}P NMR). ^{31}P NMR δ 16.4 ppm.

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