Journal of Fluorine Chemistry 130 (2009) 974–978

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

One-pot synthesis of 4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-lactones by Reformatsky reaction

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ARTICLE INFO

Article history:
Received 9 March 2009
Received in revised form 24 July 2009
Accepted 24 July 2009
Available online 3 August 2009

Keywords:
Reformatsky reaction
Zinc
Cuprous chloride
gem-Difluoromethylenated δ-lactones

ABSTRACT

In th presence of zinc and a catalytic amount of cuprous chloride, ethyl 4-bromo-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)butanoate **1** reacted with carbonyl compounds to give the *gem*-difluoromethylenated 2-(triphenylphosphoranylidene)-δ-lactones **4** in moderate to high yields.

1. Introduction

δ-Lactone is structural element commonly found in a large number of natural products and biologically active compounds [1]. Introduction of fluorine atoms or fluorinated groups into lactone can greatly change the biological activity which has attracted many attentions in recent years. Among the fluorine-modified compounds, *gem*-difluoromethylene moiety (CF_2) has been proved to be a key structural unit in many fluorinated compounds of biological and pharmaceutical significance [2]. This group has been suggested by Blackburn as an isopolar and isosteric substituent for oxygen [3] and its utilization is one of the strategies for the modification of biologically active compounds. For example, 2′-deoxy-2′,2′-difluorocytidine (gemcitabine) has been approved as a drug for solid tumor treatment [4]. There are two kind methods to introduce the difluoromethylene group, such as direct *gem*-difluorination and difluoromethylenation. So far, the Refromatsky reaction of halogeno-difluoromethylated compounds is the most common approach in the construction of molecules derived from CF_2-synthons [5,6]. The resultant α,α-difluorinated β-hydroxy carbonyl compounds are valuable intermediates and can be employed in the synthesis of the lactones containing difluoromethylene moiety [7]. Although there are other synthetic methods of difluoromethylene-lactones in the literatures [8,9], the most advantageous and direct method is to utilize the Refromatsky reaction to prepare such kind of δ-lactones [10,11]. In this paper, we wish to describe our results of the one-pot reaction of ethyl 4-bromo-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)butanoate **1** with carbonyl compounds to give the difluoromethylenated valerolactones.

2. Results and discussion

As shown in Scheme 1, ethyl 4-bromo-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)butanoate **1** was easily prepared by the same procedure of Hamper [12] from the reaction of bromodifluoroacetic anhydride [13] with readily available phosphonium salt in 85% yield.

When **1** was treated with benzaldehyde in the presence of acid-washed zinc dust in diethyl ether [6] or THF at room temperature, no reaction occurred (entries 1 and 2, Table 1). While the reaction was conducted in refluxing THF, the addition product **3a** was formed and the difluoromethylenated valerolactone **4a** was obtained on a prolonged reaction time (entry 3, Table 1). The effects of solvent, temperature, reaction time and the ratio of cuprous chloride on the reaction of **1** with benzaldehyde **2a** (Scheme 2) were briefly investigated and the results are summarized in Table 1. Some literatures have demonstrated that zinc metal could be activated in situ by simple treatment with a

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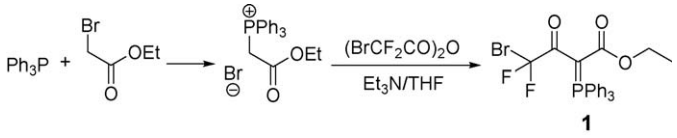
doi:10.1016/j.jfluchem.2009.07.018



Scheme 1.

Table 1
Optimization of reaction conditions for the Reformatsky reaction of **1** with benzaldehyde (see Scheme 2).

Entry	CuCl (equiv.)	Slovent	Temperature	Time (h)	Results
1	0.3	Ether	0 °C–r.t.	2	–[a]
2	–	THF	r.t.	18	–[a]
3	–	THF	Reflux	40	**3a** and **4a**
4	0.3	THF	Reflux	10	**1** and **3a**
5	0.3	THF	Reflux	16	**1**, **3a** and **4a**
6	0.3	THF[b]	Reflux	40	**4a**, 45%[c]
7	0.3	THF	Reflux	40	**4a**, 66%
8	1	THF	Reflux	40	**4a**, 67%
9	**0.3**	**Dioxane**	**Reflux**	**27**	**4a, 66%**
10	0.3	Toluene	Reflux	27	**4a**, 48%[c]

[a] Addition product **3a** or **4a** was not detected.
[b] THF was not dried.
[c] Byproduct $HCF_2COC(PPh_3)CO_2Et$ was isolated.

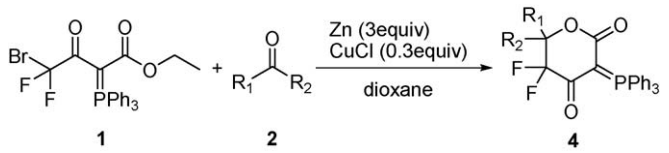
Table 2
Reactions of **1** with aldehydes or ketones.

Entry	**2**	R_1	R_2	Product **4**	Yield (%)[a]
1	**2a**	Ph	H	**4a**	66
2	**2b**	4-$CH_3C_6H_4$	H	**4b**	56
3	**2c**	4-$OCH_3C_6H_4$	H	**4c**	63
4	**2d**	4-BrC_6H_4	H	**4d**	80
5	**2e**	4-ClC_6H_4	H	**4e**	64
6	**2f**	2-ClC_6H_4	H	**4f**	70
7	**2g**	4-$NO_2C_6H_4$	H	**4g**	–
8	**2h**	4-CNC_6H_4	H	**4h**	85
9	**2i**	$(CH_3)_2CH$	H	**4i**	75
10	**2j**	PhCH=CH	H	**4j**	47
11	**2k**	CH_2=CH	H	**4k**	31
12	**2l**	Ph	CH_3	**4l**	56[b]
13	**2m**	4-$CH_3C_6H_4$	CH_3	**4m**	54[b]

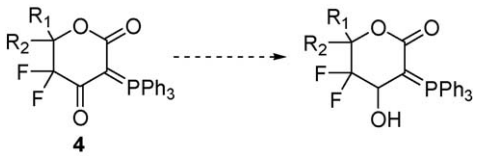
[a] Isolated yields based on **1**.
[b] 10–20% of $HCF_2COC(PPh_3)CO_2Et$ was isolated.

small quantity of cuprous chloride [14]. From the results shown in entries 3 and 7 in our experiments, 0.3 equiv. of cuprous chloride could really accelerate the formation of difluoromethylenated valerolactone **4a**. However, increasing the ratio of CuCl could not improve the yield efficiently (entry 8, Table 1). When **1** reacted with **2a** in the presence of zinc dust (3.0 equiv.) and cuprous chloride (0.3 equiv.) in refluxing anhydrous dioxane for 27 h, the expected difluoromethylenated valerolactone **4a** was obtained in one-pot in 66% yield (entry 9, Table 1). The yields were decreased in wet THF and toluene due to the formation of byproduct $HCF_2COC(PPh_3)CO_2Et$ (entries 6 and 10, Table 1).

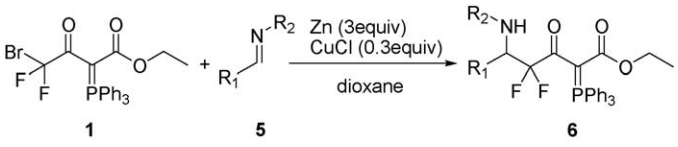
With the optimized reaction conditions in hand, we further investigated the Reformatsky reactions of **1** with a variety of aromatic aldehydes (entries 1–8, Table 2), aliphatic alkyl aldehydes (entry 9, Table 2) and aromatic ketones (entries 12 and 13, Table 2) in the presence of both acid-washed zinc dust (3 equiv.) and a



Scheme 3.



Scheme 4.

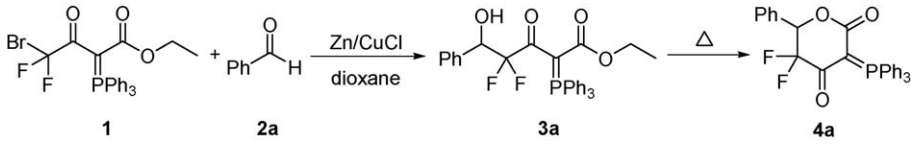


Scheme 5.

catalytic amount of copper (I) chloride (0.3 equiv.) in refluxing dioxane, affording **4** in good yields (Scheme 3). Various substituents on the phenyl ring, either electron-withdrawing or electron-donating groups, such as cyano, chloro, bromo, methyl, methoxy, etc., could be tolerated and had little effect on the yields except for *p*-nitrobenzaldehyde which gave no product under various conditions [15]. Under similar conditions, the reaction also proceeded with α,β-unsaturated aldehydes, such as acrolein and cinnamaldehyde in moderate yields (entries 10 and 11, Table 2).

Shen reported that fluorinated (dicarbonylmethylene) triphenylphosphoranes were stable and unreactive toward aldehydes or ketones due to the strong electron-withdrawing effect of the two carbonyl groups, but they reacted with a variety of Grignard reagents and lithium reagents to give corresponding α,β-unsaturated esters through the protonation and elimination of triphenylphosphine oxide [16,17]. We conducted the reaction of **4** with excess amount of benzaldehyde, no reaction occurred. Unfortunately, the reaction of **4** with n-butyl lithium also failed to give α,β-unsaturated lactone while the lactone ring of **4** was decomposed. Meanwhile we failed to reduce the β-carbonyl of lactone **4** when $NaBH_4$ or $NaBH_4$ with Lewis acids were used as reducing agents (Scheme 4). And **4** was decomposed if $LiAlH_4$ was used.

It was reported that the Reformatsky reactions of halodifluoroacetate with aldimines and chiral 1,3-oxazolidines usually gave difluorinated β-lactams [18–21]. However, the similar reactions of 4-bromo-4,4-difluoroacetoacetate with aldimines and ketimines were reported to give complicated results [22]. We found that the Reformatsky-imine addition reaction of **1** with a series of aromatic aldimines provided the correspondent amines **6** in low yields and the δ-lactams were not detected under the above reaction conditions (Scheme 5), possibly due to the weak of reactivity of



Scheme 2.

Table 3
Reactions of **1** with aldimines.

Entry	5	R_1	R_2	Product	Yield (%)[a,b]
1	**5a**	Ph	Ph	**6a**	30
2	**5b**	4-ClC_6H_4	Ph	**6b**	23
3	**5c**	2-$OCH_3C_6H_4$	Ph	**6c**	–
4	**5d**	4-CNC_6H_4	Ph	**6d**	25
5	**5e**	Ph	4-$OCH_3C_6H_4$	**6e**	15
6	**5f**	Ph	2-ClC_6H_4	**6f**	–
7	**5g**	Ph	4-$CF_3C_6H_4$	**6g**	–

[a] Isolated yields of pure compounds based on **1**.
[b] Most product was $HCF_2COC(PPh_3)CO_2Et$.

the corresponding aldimines. Most of the reactant **1** was reduced to $HCF_2COC(PPh_3)CO_2Et$. No addition products were either detected (entries 3 and 6, Table 3) because of the much lower reactivities of sterically bulky **5c** and **5f**.

3. Conclusions

In summary, we have described an efficient one-pot synthesis of 4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactones by the Reformatsky reactions of ethyl 4-bromo-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)butanoate **1** with carbonyl compounds in the presence of zinc and a catalytic amount of cuprous chloride. The preparation of ethyl 4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-5-aminopentanoates **6** by the Reformatsky-imine addition reactions of **1** with aldimines promoted by zinc-cuprous chloride was also resulted.

4. Experimental

All melting points were uncorrected. IR spectra were measured on a Nicolet Magna IR-550 spectrometer using potassium bromide pellet. High resolution mass spectra were carried out on a Finnigan GC-MS-4021 spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125.8 MHz) spectra were recorded on a Bruker AC-500 spectrometer with Me_4Si as internal standard. ^{19}F NMR spectra were obtained on Bruker AC-500 (470 MHz) spectrometer in $CDCl_3$ with $CFCl_3$ as external standard, downfield shifts being designated as negative. All chemical shifts (δ) are expressed in ppm, coupling constants (J) are given in Hz. Anhydrous THF was dried and freshly distilled from sodium wire. All other reagents were purified before use according to the standard methods.

4.1. Procedure for the preparation of ethyl 4-bromo-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)butanoate

A slurry of (carbethoxymethyl)-triphenylphosphonium bromide (21.5 g, 50 mmol) in 100 mL of anhydrous THF was cooled in an ice-water bath and treated with triethylamine (15 mL, 110 mmol). After being stirred for 30 min, the mixture was treated dropwise with bromodifluoroacetic anhydride (18.25 g, 55 mmol) and allowed to stir for 2 h. The mixture was filtered, the precipitates were washed three times with cold THF, and the filtrate was concentrated in vacuum to afford a yellow oily residue. Trituration of the residue with 60 mL of water afforded a crystalline product, which was collected, washed with water, and dried in vacuum to afford 21.5 g (85%) of a cream colored solid. An analytical sample of **1**, a white needle solid, was obtained by recrystallization from methanol–water.

4.1.1. Ethyl 4-bromo-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)butanoate (1)

White needle solid, mp 121–122 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72–7.65 (6H, m), 7.61–7.57 (3H, m), 7.52–7.47 (6H, m), 3.80 (2H, q, J = 7.2 Hz), 0.88 (3H, t, J = 7.2 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −55.89 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 177.6 ($^2J_{CF}$ = 20 Hz), 166.4 ($^2J_{CP}$ = 13 Hz), 134.0 ($^3J_{CP}$ = 10 Hz), 133.1, 129.6 ($^3J_{CP}$ = 13 Hz), 125.0 ($^1J_{CP}$ = 94 Hz), 116.0 (CF_2, $^1J_{CF}$ = 318 Hz, $^3J_{CP}$ = 14 Hz), 68.7 ($^1J_{CP}$ = 111 Hz), 60.7, 14.3. EI-MS (m/z) 506 (M^++2, 2), 504 (M^+, 2), 461 (3), 459 (3), 375 (100), 347 (9), 262 (44), 183 (37). IR (cm^{-1}, KBr) 1689, 1586, 1569, 690. HRMS calcd for $C_{24}H_{20}BrF_2O_3P$: 504.0302, found 504.0301.

4.2. Reformatsky addition reactions of 1 with aldehydes and ketones; typical procedure

A solution of benzaldehyde (117 mg, 1.1 mmol) and **1** (505 mg, 1 mmol) in anhydrous dioxane (1 mL) was added dropwise to a heterogeneous solution of acid-washed zinc dust (196 mg, 3.0 mmol) and CuCl (30 mg, 0.3 mmol) in anhydrous dioxane (2 mL). The reaction mixture was stirred under reflux for 27 h. Then saturated NH_4Cl (5 mL) was added. Excess zinc was removed by suction filtration and washed with EtOAc (10 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), the organic layers were combined and washed with water, brine, then dried over Na_2SO_4. After evaporation of the solvents, the residue was chromatographed on silica gel eluting with PE-EtOAc, 3:1 to give **4a** (321 mg) in 66% yield.

4.2.1. 5-Phenyl-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (4a)

White spumy solid, mp 81–82 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72–7.62 (8H, m), 7.56–7.51 (8H, m), 7.42–7.39 (4H, m), 5.60 (1H, dd, J = 18 Hz, J = 7 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −122.8 (1F, dd, J_{F-F} = 282 Hz, J_{F-H} = 17 Hz), −123.5 (1F, d, J_{F-F} = 282 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 179.6, 166.7 ($^2J_{CP}$ = 11 Hz), 134.5 ($^3J_{CP}$ = 10 Hz), 133.8, 129.7 ($^3J_{CP}$ = 13 Hz), 128.9, 128.8, 123.1 ($^1J_{CP}$ = 93 Hz), 109.6 (CF_2, $^1J_{CF}$ = 254 Hz, $^3J_{CP}$ = 14 Hz), 69.6 ($^1J_{CP}$ = 111 Hz). EI-MS (m/z) 486 (M^+, 25), 349 (34), 301 (100), 183 (15). IR (cm^{-1}, KBr) 1690, 1628, 691. HRMS calcd for $C_{29}H_{21}F_2O_3P$: 486.1196, found 486.1197.

4.2.2. 5-p-Tolyl-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (4b)

White solid, mp 217–219 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60–7.30 (17H, m), 7.08 (2H, d, J = 7.9 Hz), 5.48 (1H, dd, J = 16 Hz, J = 9 Hz), 2.23 (3H, s). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −122.7 (1F, dd, J_{F-F} = 277 Hz, J_{F-H} = 14 Hz), −123.4 (1F, d, J_{F-F} = 277 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 179.4 ($^2J_{CF}$ = 13 Hz), 166.5 ($^2J_{CP}$ = 11 Hz), 139.5, 134.3 ($^3J_{CP}$ = 10 Hz), 133.6, 129.5 ($^3J_{CP}$ = 13 Hz), 129.0, 128.5, 122.9 ($^1J_{CP}$ = 93 Hz), 109.6 (CF_2, $^1J_{CF}$ = 254 Hz, $^3J_{CP}$ = 14 Hz), 69.5 ($^1J_{CP}$ = 111 Hz), 21.7. EI-MS (m/z) 500 (M^+, 13), 349 (14), 301 (100), 183 (12). IR (cm^{-1}, KBr) 1690, 1628, 691. HRMS calcd for $C_{30}H_{23}F_2O_3P$: 500.1353, found 500.1353.

4.2.3. 5-(4-Methoxyphenyl)-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (4c)

White spumy solid, mp 199–201 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80–7.42 (17H, m), 6.91 (2H, d, J = 8.7 Hz), 5.56 (1H, dd, J = 17.6 Hz, J = 7.5 Hz), 3.77 (3H, s). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −122.0 (1F, dd, J_{F-F} = 277 Hz, J_{F-H} = 14 Hz), −122.6 (1F, d, J_{F-F} = 277 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 179.6 ($^2J_{CF}$ = 25 Hz, $^2J_{CP}$ = 5 Hz), 166.7 ($^2J_{CP}$ = 11 Hz), 163.1, 160.9, 134.3 ($^3J_{CP}$ = 10.4 Hz), 133.7, 131.4, 130.1, 129.7, 129.6 ($^3J_{CP}$ = 13 Hz), 127.5, 123.9, 122.9 ($^1J_{CP}$ = 93 Hz), 114.2, 109.7 (CF_2, $^1J_{CF}$ = 253 Hz, $^3J_{CP}$ = 14 Hz), 102.2, 69.5 ($^1J_{CP}$ = 111 Hz), 55.8. EI-MS (m/z) 516 (M^+, 8), 472 (11), 301 (100), 183 (11). IR (cm^{-1}, KBr) 1698, 1625, 1584, 1256, 1177, 1077, 690. HRMS calcd for $C_{30}H_{23}F_2O_4P$: 516.1302, found 516.1301.

*4.2.4. 5-(4-Bromophenyl)-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (**4d**)*

White spumy solid, mp 86–87 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73–7.62 (9H, m), 7.56–7.51 (8H, m), 7.45 (2H, d, J = 8.4 Hz), 5.58 (1H, dd, J = 21 Hz, J = 3.4 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −122.6 (1F, dd, J_{F-F} = 277 Hz, J_{F-H} = 19 Hz), −123.8 (1F, d, J_{F-F} = 277 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 179.2 ($^2J_{CF}$ = 29 Hz), 166.4 ($^2J_{CP}$ = 11 Hz), 134.5 ($^3J_{CP}$ = 10 Hz), 133.9, 132.1, 131.1, 130.5, 129.8 ($^3J_{CP}$ = 13 Hz), 124.1, 122.9 ($^1J_{CP}$ = 93 Hz), 109.6 (CF_2, $^1J_{CF}$ = 254 Hz, $^3J_{CP}$ = 14 Hz), 69.8 ($^1J_{CP}$ = 111 Hz). EI-MS (*m*/*z*) 566 (M^++2, 11), 564 (M^+, 11), 349 (16), 301 (100), 183 (10). IR (cm^{-1}, KBr) 1691, 1629, 1075, 691. HRMS calcd for $C_{29}H_{20}BrF_2O_3P$: 564.0302, found 564.0303.

*4.2.5. 5-(4-Chlorophenyl)-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (**4e**)*

White solid, mp 190–191 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71–7.47 (17H, m), 7.34 (2H, d, J = 8.3 Hz), 5.59 (1H, d, J = 21 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −122.5 (1F, dd, J_{F-F} = 282 Hz, J_{F-H} = 23.5 Hz), −123.7 (1F, d, J_{F-F} = 277 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 179.1 ($^2J_{CF}$ = 20 Hz), 166.2 ($^2J_{CP}$ = 11 Hz), 135.7, 134.3 ($^3J_{CP}$ = 10.3 Hz), 133.8, 130.5, 130.1, 129.7 ($^3J_{CP}$ = 13 Hz), 129.0, 122.7 ($^1J_{CP}$ = 93 Hz), 109.4 (CF_2, $^1J_{CF}$ = 253 Hz, $^3J_{CP}$ = 17 Hz), 69.7 ($^1J_{CP}$ = 111 Hz). EI-MS (*m*/*z*) 522 (M^++2, 7), 520 (M^+, 17), 301 (100), 183 (11). IR (cm^{-1}, KBr) 1703, 1621, 1078, 687. HRMS calcd for $C_{29}H_{20}ClF_2O_3P$: 520.0807, found 520.0808.

*4.2.6. 5-(2-Chlorophenyl)-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (**4f**)*

White spumy solid, mp 104–105 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82–7.52 (17H, m), 7.43–7.31 (2H, m), 6.22 (1H, d, J = 23.7 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −121.5 (1F, dd, J_{F-F} = 282 Hz, J_{F-H} = 23.5 Hz), −126.0 (1F, d, J_{F-F} = 277 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 179.3 ($^2J_{CF}$ = 25 Hz), 166.6 ($^2J_{CP}$ = 11 Hz), 134.4 ($^3J_{CP}$ = 10.4 Hz), 133.7, 131.3, 131.0, 129.9, 129.6 ($^3J_{CP}$ = 13 Hz), 127.3, 122.8 ($^1J_{CP}$ = 93 Hz), 109.8 (CF_2, $^1J_{CF}$ = 253 Hz, $^3J_{CP}$ = 17 Hz), 69.4 ($^1J_{CP}$ = 111 Hz). EI-MS (*m*/*z*) 522 (M^++2, 1), 520 (M^+, 3), 485 (100), 301 (90), 183 (11). IR (cm^{-1}, KBr) 3062, 2984, 1695, 1633, 1043, 691. HRMS calcd for $C_{29}H_{20}ClF_2O_3P$: 520.0807, found 520.0807.

*4.2.7. 4-(3,3-Difluoro-4,6-dioxo-3-(triphenylphoranylidene)tetrahydro-2H-pyran-2-yl)benzonitrile (**4 h**)*

White spumy solid, mp 218–219 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72–7.51 (19H, m), 5.65 (1H, d, J = 23 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −121.0 (1F, dd, J_{F-F} = 277 Hz, J_{F-H} = 23.5 Hz), −123.2 (1F, d, J_{F-F} = 282 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 178.8 ($^2J_{CF}$ = 25 Hz), 165.9 ($^2J_{CP}$ = 11 Hz), 137.1, 134.4 ($^3J_{CP}$ = 10.3 Hz), 133.9, 132.6, 129.7 ($^3J_{CP}$ = 13 Hz), 129.4, 122.6 ($^1J_{CP}$ = 93 Hz), 119.0, 113.7, 109.2 (CF_2, $^1J_{CF}$ = 251 Hz, $^3J_{CP}$ = 14 Hz), 69.8 ($^1J_{CP}$ = 111 Hz). EI-MS (*m*/*z*) 511 (M^+, 39), 301 (100), 183 (13). IR (cm^{-1}, KBr) 2920, 2225, 1685, 1639, 691. HRMS calcd for $C_{30}H_{20}F_2NO_3P$: 511.1149, found 511.1150.

*4.2.8. 4,4-Difluoro-5-isopropyl-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (**4i**)*

White spumy solid, mp 59–60 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68–7.46 (15H, m), 4.30 (1H, d, J = 27 Hz), 2.33 (1H, td, J = 13.3 Hz, J = 6.6 Hz), 1.14 (6H, t, J = 6.8 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −120.1 (1F, d, J_{F-F} = 277 Hz), −122.3 (1F, dd, J_{F-F} = 282 Hz, J_{F-H} = 24 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 179.9 ($^2J_{CF}$ = 25 Hz, $^2J_{CP}$ = 4.4 Hz), 168.0 ($^2J_{CP}$ = 11 Hz), 134.3 ($^3J_{CP}$ = 10.4 Hz), 133.7, 129.7 ($^3J_{CP}$ = 13 Hz), 122.6 ($^1J_{CP}$ = 93 Hz), 111.1 (CF_2, $^1J_{CF}$ = 250 Hz, $^3J_{CP}$ = 7 Hz), 70.1 ($^1J_{CP}$ = 111 Hz), 27.5, 19.8, 18.9. EI-MS (*m*/*z*) 452 (M^+, 6), 410 (100), 301 (51), 183 (14). IR (cm^{-1}, KBr) 1686, 1622, 690. HRMS calcd for $C_{26}H_{23}F_2O_3P$: 452.1353, found 452.1353.

*4.2.9. (E)-4,4-Difluoro-5-styryl-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (**4j**)*

White spumy solid, mp 69–71 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74–7.27 (20H, m), 6.96 (1H, d, J = 16 Hz), 6.40 (1H, dd, J = 16 Hz, J = 5.8 Hz), 5.24 (1H, dt, J = 16.6 Hz, J = 5 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −119.9 (1F, d, J_{F-F} = 277 Hz), −124.5 (1F, dd, J_{F-F} = 277 Hz, J_{F-H} = 14 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 179.3 ($^2J_{CF}$ = 25 Hz), 166.3 ($^2J_{CP}$ = 11 Hz), 136.8, 134.5 ($^3J_{CP}$ = 10.3 Hz), 133.8, 129.7 ($^3J_{CP}$ = 13 Hz), 129.4, 129.2, 127.6, 123.1 ($^1J_{CP}$ = 93 Hz), 119.4, 110.1 (CF_2, $^1J_{CF}$ = 253 Hz, $^3J_{CP}$ = 17 Hz), 69.8 ($^1J_{CP}$ = 111.5 Hz). EI-MS (*m*/*z*) 512 (M^+, 3), 375 (100), 301 (33), 183 (11). IR (cm^{-1}, KBr) 1689, 1626, 691. HRMS calcd for $C_{31}H_{23}F_2O_3P$: 512.1353, found 512.1353.

*4.2.10. 4,4-Difluoro-5-vinyl-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (**4k**)*

White spumy solid, mp 158–159 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69–7.47 (15H, m), 6.08–6.00 (1H, m), 5.66 (1H, d, J = 17.3 Hz), 5.52 (1H, d, J = 10.7 Hz), 5.03 (1H, dt, J = 18 Hz, J = 5 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −120.1 (1F, d, J_{F-F} = 277 Hz), −123.5 (1F, dd, J_{F-F} = 277 Hz, J_{F-H} = 14 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 178.3 ($^2J_{CF}$ = 25 Hz, $^2J_{CP}$ = 5 Hz), 165.5 ($^2J_{CP}$ = 11 Hz), 133.7 ($^3J_{CP}$ = 10.4 Hz), 133.1, 129.0 ($^3J_{CP}$ = 13 Hz), 127.8, 122.3 ($^1J_{CP}$ = 93 Hz), 121.7, 109.1 (CF_2, $^1J_{CF}$ = 268 Hz, $^3J_{CP}$ = 14 Hz), 69.0 ($^1J_{CP}$ = 111.6 Hz). EI-MS (*m*/*z*) 436 (M^+, 18), 349 (55), 301 (100), 183 (20). IR (cm^{-1}, KBr) 1689, 1622, 688. HRMS calcd for $C_{25}H_{19}F_2O_3P$: 436.1040, found 436.1040.

*4.2.11. 5-Methyl-5-phenyl-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (**4l**)*

White solid, mp 200–202 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69–7.37 (20H, m), 1.84 (3H, s). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −114.8 (1F, d, J_{F-F} = 268 Hz), −124.0 (1F, d, J_{F-F} = 272 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 179.0 ($^2J_{CF}$ = 25 Hz, $^2J_{CP}$ = 5 Hz), 165.9 ($^2J_{CP}$ = 11 Hz), 140.4, 134.2 ($^3J_{CP}$ = 10 Hz), 133.5, 129.5 ($^3J_{CP}$ = 12.6 Hz), 129.1, 126.4, 122.9 ($^1J_{CP}$ = 93 Hz), 109.2 (CF_2, $^1J_{CF}$ = 244 Hz, $^3J_{CP}$ = 12 Hz), 69.5 ($^1J_{CP}$ = 114 Hz), 22.9. EI-MS (*m*/*z*) 500 (M^+, 20), 349 (28), 301 (100), 183 (12). IR (cm^{-1}, KBr) 1687, 1628, 689. HRMS calcd for $C_{30}H_{23}F_2O_3P$: 500.1353, found 500.1353.

*4.2.12. 5-Methyl-5-p-tolyl-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-δ-valerolactone (**4m**)*

White solid, mp 215–217 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61–7.30 (17H, m), 7.13 (2H, d, J = 8 Hz), 2.33 (3H, s), 1.75 (3H, s). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −115.2 (1F, d, J_{F-F} = 268 Hz), −124.0 (1F, d, J_{F-F} = 268 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 177.6 ($^2J_{CF}$ = 25 Hz, $^2J_{CP}$ = 5 Hz), 164.5 ($^2J_{CP}$ = 11 Hz), 136.9, 135.8, 132.7 ($^3J_{CP}$ = 10 Hz), 128.1, 127.8 ($^3J_{CP}$ = 12.8 Hz), 124.9, 121.5 ($^1J_{CP}$ = 93.5 Hz), 110.5 (CF_2, $^1J_{CF}$ = 255 Hz, $^3J_{CP}$ = 14 Hz), 67.7 ($^1J_{CP}$ = 114 Hz), 21.3, 20.1. EI-MS (*m*/*z*) 514 (M^+, 17), 349 (13), 301 (100), 183 (10). IR (cm^{-1}, KBr) 1686, 1625, 690. HRMS calcd for $C_{31}H_{25}F_2O_3P$: 514.1509, found 514.1510.

*4.3. Reformatsky imine addition reactions of **1** with aldimines; typical procedure*

A solution of benzylideneaniline (199 mg, 1.1 mmol) and **1** (505 mg, 1 mmol) in anhydrous dioxane (1 mL) was added dropwise to a heterogeneous solution of acid-washed zinc dust (196 mg, 3.0 mmol) and CuCl (30 mg, 0.3 mmol) in anhydrous dioxane (2 mL). The reaction mixture was stirred under reflux for 27 h. Then saturated NH_4Cl (5 mL) was added. Excess zinc was removed by suction filtration and washed with EtOAc (10 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), the organic layers were combined and washed with water and brine, then dried over Na_2SO_4. After evaporation of

the solvents, the residue was chromatographed on silica gel eluting with PE-EtOAc (3:1) to give **6a** (182 mg) in 30% yield.

*4.3.1. Ethyl 4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-5-phenyl-5-(phenyl-amino)pentanoate (**6a**)*

White solid, mp 207–208 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61–7.27 (20H, m), 7.15 (2H, t, J = 7.6 Hz), 6.71–6.67 (3H, m), 5.72 (1H, dd, J = 16 Hz, J = 9 Hz), 3.73–3.69 (2H, m), 0.74 (3H, t, J = 7.2 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −104.7 (1F, d, J_{F-F} = 244 Hz), −118.2 (1F, dd, J_{F-F} = 244 Hz, J_{F-H} = 24 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 183.9 ($^2J_{CF}$ = 25 Hz), 165.9 ($^2J_{CP}$ = 13 Hz), 145.5, 135.1, 132.1 ($^3J_{CP}$ = 10 Hz), 131.0, 128.2, 127.8 ($^3J_{CP}$ = 13 Hz), 127.1, 126.8, 123.8 ($^1J_{CP}$ = 94 Hz), 116.2, 116.4 (CF_2, $^1J_{CF}$ = 318 Hz), 112.1, 69.8 ($^1J_{CP}$ = 110 Hz), 58.8, 58.4 ($^2J_{CF}$ = 23 Hz), 12.5. EI-MS (m/z) 607 (M^+, 4), 552 (40), 375 (100), 182 (48). IR (cm^{-1}, KBr) 3305, 1681, 1558, 1110, 691. HRMS calcd for $C_{37}H_{32}F_2NO_3P$: 607.2088, found 607.2089.

*4.3.2. Ethyl 5-(4-chlorophenyl)-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-5-(phenyl-amino)pentanoate (**6b**)*

White solid, mp 220–221 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60–7.24 (19H, m), 7.16 (2H, t, J = 7.8 Hz), 6.71 (1H, t, J = 7.3 Hz), 6.65 (2H, d, J = 8 Hz), 5.81 (1H, s), 5.71 (1H, d, J = 23 Hz), 3.72–3.65 (2H, m), 0.71 (3H, t, J = 7.1 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −104.9 (1F, d, J_{F-F} = 244 Hz), −118.0 (1F, dd, J_{F-F} = 244 Hz, J_{F-H} = 24 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 183.6 ($^2J_{CF}$ = 25 Hz), 168.7 ($^2J_{CP}$ = 13 Hz), 148.0, 136.5, 135.4, 134.8 ($^3J_{CP}$ = 10 Hz), 133.8, 131.9, 131.0, 130.5 ($^3J_{CP}$ = 13 Hz), 130.1, 126.4 ($^1J_{CP}$ = 94 Hz), 119.2, 118.8 (CF_2, $^1J_{CF}$ = 318 Hz), 114.8, 72.6 ($^1J_{CP}$ = 109 Hz), 61.6, 60.7 ($^2J_{CF}$ = 23 Hz), 15.2. EI-MS (m/z) 643 (M^++2, 2), 641 (M^+, 5), 586 (46), 375 (100), 183 (25). IR (cm^{-1}, KBr) 3314, 1673, 1560, 1104, 1050, 690. HRMS calcd for $C_{37}H_{31}ClF_2NO_3P$: 641.1698, found 641.1699.

*4.3.3. Ethyl 5-(4-cyanophenyl)-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)-5-(phenyl-amino)pentanoate (**6d**)*

White solid, mp 241–242 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63–7.26 (19H, m), 7.1 (2H, t, J = 7.4 Hz), 6.66 (1H, t, J = 7.3 Hz), 6.53 (2H, d, J = 7.7 Hz), 5.82 (1H, s), 5.70 (1H, d, J = 23 Hz), 3.61 (2H, q, J = 7.1 Hz), 0.63 (3H, t, J = 7.1 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −104.4 (1F, d, J_{F-F} = 249 Hz), −117.8 (1F, dd, J_{F-F} = 249 Hz, J_{F-H} = 24 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 182.2 ($^2J_{CF}$ = 25 Hz), 166.0 ($^2J_{CP}$ = 12 Hz), 144.9, 141.0, 132.1 ($^3J_{CP}$ = 10 Hz), 130.9, 128.6, 127.8 ($^3J_{CP}$ = 9.3 Hz), 123.7 ($^1J_{CP}$ = 94 Hz), 117.9, 112.1, 110.8, 107.6 (CF_2, $^1J_{CF}$ = 318 Hz), 69.6 ($^1J_{CP}$ = 109 Hz), 58.9, 58.4 ($^2J_{CF}$ = 28 Hz), 12.5. EI-MS (m/z) 632 (M^+, 3), 577 (96), 375 (100). IR (cm^{-1}, KBr) 3310, 1669, 1563, 1103, 1047, 691. HRMS calcd for $C_{38}H_{31}F_2N_2O_3P$: 632.2040, found 632.2017.

*4.3.4. Ethyl 4,4-difluoro-5-(4-methoxyphenyl-amino)-3-oxo-2-(triphenylphosphoranylidene)-5-phenylpentanoate (**6e**)*

White solid, mp 129–130 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63–7.27 (21H, m), 6.76 (1H, d, J = 8.9 Hz), 6.63 (2H, d, J = 8.9 Hz), 5.71 (1H, d, J = 23 Hz), 5.38 (1H, s), 3.73 (3H, s), 3.61 (2H, q, J = 7.2 Hz), 0.74 (3H, t, J = 7.2 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ −105.2 (1F, d, J_{F-F} = 244 Hz), −118.3 (1F, dd, J_{F-F} = 244 Hz, J_{F-H} = 24 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 183.6 ($^2J_{CF}$ = 25 Hz), 167.0 ($^2J_{CP}$ = 13 Hz), 151.9, 140.7, 136.3, 133.1 ($^3J_{CP}$ = 10 Hz), 132.0, 128.8 ($^3J_{CP}$ = 13 Hz), 127.8, 125.3, 124.6, 114.6 ($^1J_{CP}$ = 75 Hz), 108.7 (CF_2, $^1J_{CF}$ = 318 Hz), 70.2 ($^1J_{CP}$ = 109 Hz), 60.3 ($^2J_{CF}$ = 23 Hz), 59.8, 59.1, 13.6. EI-MS (m/z) 637 (M^+, 1), 375 (100), 183 (10). IR (cm^{-1}, KBr) 1671, 1590, 1105, 1045, 690. HRMS calcd for $C_{38}H_{34}F_2NO_4P$: 637.2194, found 637.2194.

Acknowledgement

The authors thank the National Natural Science Foundation of China (NNSFC) (no. 20672034) for financial support.

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