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Journal of Fluorine Chemistry 127 (2006) 1195-1203

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# A facile synthesis of 4-gem-difluoromethylene $\beta$ -lactam and its derivatives from BrCF<sub>2</sub>CF<sub>2</sub>Br

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Received 7 April 2006; received in revised form 29 May 2006; accepted 30 May 2006 Available online 15 June 2006

#### Abstract

4-Bromodifluoromethyl  $\beta$ -lactams 2 are prepared from the commercial available BrCF<sub>2</sub>CF<sub>2</sub>Br in overall five-step reaction procedure. Under the radical reaction conditions (Bu<sub>3</sub>SnH/AIBN), compound 2 reacted with alkenes affording to the corresponding addition product difluoromethylene  $\beta$ -lactams 7. In the absence of alkenes, it can be converted into the corresponding difluoromethyl  $\beta$ -lactam 6 in almost quantitative yield. Furthermore, allylic stannic reagent Bu<sub>3</sub>SnCH<sub>2</sub>CH=CH<sub>2</sub> reacted with 2 under the same reaction conditions gave the allylic addition product 8.

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Keywords: Bromodifluoromethyl; Difluomethyl; Difluoromethylene; β-Lactam; Free radical

# 1. Introduction

The field of fluoroorganic chemistry has grown tremendously in recent years, and fluorochemicals have permeated nearly every aspect of our daily lives [1]. Incorporation of fluorine atoms into an organic molecule sometimes adds an unexpected quality to organic molecules [1]. It led to the discovery of potent medicinal agents and development of original methods of preparation [2]. Among them, gem-difluoro compounds have been the subject of an important area of research as the  $CF_2/CH_2$  transposition has been recognized as a valuable tool in the blockage of metabolic processes. Replacement of various functional groups by a gemdifluoromethylene group has generated potent transition-statetype inhibitors [3]. The preparation of *gem*-difluoromethylene substituted molecules falls broadly into two classes. The first involves direct *gem*-difluorination, [4] and the second draws from the construction of molecules derived from  $CF_2$ -synthons. BrCF<sub>2</sub>-containing building blocks are one of the most used and important origins of the *gem*-difluoromethylene.  $\beta$ -Lactams are very important structures existing widely in various antibiotics and natural products [5]. A series of methodologies to prepare this structure have been established [6].  $\alpha$ -Gem-difluoromethylene lactam can be easily prepared from the reaction of ethyl bromodifluoroacetate and imines. 4-Gem-difluoro-methylene lactams, to our knowledge, however, do not be synthesized up to now.

### 2. Results and discussion

Following we report a facile method to synthesize this kind of 4-gem-difluoromethylene lactams 1 from the commercial available BrCF<sub>2</sub>CF<sub>2</sub>Br.

The 4-gem-difluoromethylene containing lactams 1 can be synthesized from the corresponding  $\gamma$ -bromo-difluoromethyl lactam 2 through the radical initiation reactions, as delineated in Scheme 1. Intramolecular cyclizations of the  $\beta$ -amino ester 3 can afford to the BrCF<sub>2</sub>-containing  $\beta$ -lactams 2. Dehydrofluorination of the ester 5, followed by substituion of the fluorine with amines, and reduction of the imines by NaBH<sub>4</sub> will give the  $\beta$ -amino ester 3. The ester 5 can be prepared from

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<sup>0022-1139/\$ –</sup> see front matter  $\bigcirc$  2006 Elsevier B.V. All rights reserved. doi:10.1016/j.jfluchem.2006.05.024



the commercial available  $BrCF_2CF_2Br$  in a two-step procedure [7].

Synthesis efforts towards 1 commenced with reaction of  $BrCF_2CF_2Br$  and ethyl vinyl ether giving ester 5 over two steps after the reported procedure (Scheme 2) [7].

Dehydrohalogenation of **5** with  $Et_3N$  in refluxing  $CH_2Cl_2$ , followed by substitution of the fluorine with the aromatic amines give the desired imines **4** together with its tautomer enamine **4**'. NaBH<sub>4</sub> in EtOH can easily reduce these two tautomers at room temperature in good yields. Except the desired reduced product amines, two byproducts, **3a**' and **3b**', are also isolated (Scheme 3).

As we all know,  $\beta$ -lactams can be efficiently synthesized from the corresponding  $\beta$ -amino esters through the nucleophilic reaction in the presence of Grignard's reagent [8]. Ring closures of the  $\beta$ -amino esters **3** using methylmagnesium bromide to deprive the hydrogen on the nitrogen atom smoothly lead to the desired BrCF<sub>2</sub>-containing  $\beta$ -lactams in good yields, respectively (Scheme 4).

Their structures were further determined by spectrum methods and elemental analysis, while the compound **2b** was also further confirmed by X-ray diffraction (Fig. 1).

It is interesting that the  $\beta$ -lactam ring, methoxyl and phenyl ring are nearly coplanar, the torsion angle is only 5°. We early reported that there exist halogen-bonding interactions between the carbonyl oxygen atom and the bromine atom on the bromodifluoromethyl [9]. Therefore, we also want to know if there are similar halogen bonding interactions between the bromine atom and the amide oxygen atom in the structure of **2b**. However, no intermolecular halogen bonding interactions but

Reagent and conditions: i, Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, NaHCO<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>OH, 45°C; ii, Caro's acid;

Scheme 2.



Scheme 3.



Table 1	
The data for the hydrogen bonding interactions for compound <b>2b</b>	

Hydrogen bonding	Distance (Å)	Angle (°)	
$C(10)-H(7)\cdots F(2)$ (intramolecular)	2.438	136.13	
$C(3)-H(2)\cdots Br(1)$ (intramolecular)	2.932	107.09	
$C(6)-H(4)\cdots O(1)$ (intramolecular)	2.486	123.71	
$C(7)-H(5)\cdots O(1)$ (intermolecular)	2.495	155.98	

intramolecular hydrogen bondings was found (Fig. 1). The distances and angles of the hydrogen bonding interactions in the compound 2b are listed in Table 1. There are weak hydrogen bonding interactions between the hydrogen atoms on the phenyl ring and fluorine and oxygen atoms. Furthermore, there also exist close intramolecular Br. . . H contacts, which forming fivemembered ring, although the hydrogen bonding interaction is rather weak according to its contacting distance and angle (2.932 Å, 107.09). To the best of our knowledge, there are few examples that the hydrogen on methylene or methyl involved in a hydrogen bond [10]. It was also found from the packing diagram of **2b** that the hydrogen atom H(5) on the phenyl ring involved in the intermolecular hydrogen bonding interactions to the amide oxygen atom O(1) (Fig. 1b). The intermolecular hydrogen bonding interactions dimerize two molecules to form a 10-atom constituted cavity (Fig. 1b).

With the BrCF<sub>2</sub>-containing  $\beta$ -lactam **2** in hand, we then explored its further chemical transformation.  $\beta$ -Lactam **2** is a useful fluorinated synthetic building block to synthesize CF<sub>2</sub>-containing  $\beta$ -lactams through the radical reaction conditions to break the C–Br bond.

It is well know that Bu<sub>3</sub>SnH/AIBN is the most used free radical initiating system. Therefore, we initially explored



Bu<sub>3</sub>SnH/AIBN involved the radical cleavage of the C–Br bond in the BrCF<sub>2</sub>-containing  $\beta$ -lactam **2**. Treatment of **2b** with Bu<sub>3</sub>SnH/AIBN in refluxing benzene at 80 °C for 8 h gave only trace of diffuoromethyl  $\beta$ -lactam **6**. Raising the temperature did not enhance the yield obviously. Further experimental tries turned out that it was inert to the other free radical initiating conditions, such as CrCl<sub>3</sub>/Fe, Cp<sub>2</sub>TiCl/Fe, NaS<sub>2</sub>O<sub>4</sub>/NaHCO<sub>3</sub>, CuCl/ethanolamine and Pd [11], etc. (Scheme 5).

Hu reported that the BrCF<sub>2</sub>-moiety is fairy stable when it was not activated by the  $\alpha$ -substituted electron-withdrawing group, such as C=C double bonds, carbonyl, etc. [10]. It is difficult to break the C–Br bond using the common radical initiating reagents. It was consisted with our experimental results. Hu developed a method, in which the unactivated CF<sub>2</sub>Br-containing compounds could react with alkenes to give the adducts promoted by Co(III)/Zn system [12]. However, the catalyst Co(III)/Zn is difficult to avail.

As mentioned above,  $Bu_3SnH/AIBN$  is one of the most classical and efficient radical initiating systems in the field of radical reaction of the halogen compounds and alkenes. Uneyama reported that  $Bu_3SnH/AIBN$  could mediate the radical cleavage of the C–Br bond of the unactivated  $CF_2Br$ moiety in a pressed sealed-tube [13]. Under the similar reaction conditions, the starting material **2b** was completely disappearing overnight at 110 °C in a sealed tube when  $Bu_3SnH/AIBN$ 



Fig. 1. The X-ray structure of 2b.



Scheme 7.

Table 2 The reaction of **2b** and alkenes initiated by Bu<sub>3</sub>SnH and AIBN<sup>a</sup>

Entry	$CH_2 = CHR (R =)$	Products	Yield (%) <sup>b</sup> of products
1	c	6	98
2	COOEt	7a/6	36/64
3	COOMe	7b/6	44/53
4	CN	7c/6	38/62
5	COCH <sub>3</sub>	7d/6	48/21
6	OEt	7f/6	17/50
7	Ph	7e/6	77/0
8	d	8/6	25/31

<sup>a</sup> All reaction were run in a sealed tube at 110  $^{\circ}$ C overnight using benzene as the solvent.

<sup>b</sup> Isolated yield.

<sup>c</sup> No alkenes were added.

<sup>d</sup> Using Bu<sub>3</sub>SnCH<sub>2</sub>CH=CH<sub>2</sub> in stead of alkenes and Bu<sub>3</sub>SnH.

was used to initiate the reaction and benzene as the solvent. The reduction product 6 was isolated in almost quantitative yield (Scheme 6).

Promotion by the above success, we further explore its addition reactions with kinds of alkenes. Experiments results showed that  $\beta$ -lactams 2 could react with both electron rich and poor alkenes. But in most cases, the reduction product **6** was obtained as the major product. It was inevitable to form the undesired reduced byproduct **6**, even under strict water-free conditions (Table 2).

Due to the strong electron-withdrawing properties of the fluorine atoms, the difluoromethylene radical derived from **2b** should be highly reactive. There existed two competitive reactions as to the radical generated from **2b**, addition to alkenes to lead to the difluorinemethylene  $\beta$ -lactams **7**, and directly depriving the hydrogen atom on Bu<sub>3</sub>SnH to produce the reduced product **6**. In all cases, product **6** was isolated as the main product except in the case of styrene as the reactant, in which no reduced product was detected and the addition product **7e** was obtained as the sole product in 77% yield. We cannot account for this finding at this time (Table 2, entries 1–7). Bu<sub>3</sub>SnCH<sub>2</sub>CH=CH<sub>2</sub> was often used as an allylic reagent to

induce allyl into the organic molecules through radical reactions initiated by AIBN. When  $Bu_3SnCH_2CH=CH_2$  was used to react with **2b** under the same reaction conditions, desired allylic addition product **8** was obtained in 25%, together with the reduction product **6** in 30% (Table 2, entry 8) (Scheme 7).

#### 3. Conclusions

In summary, diffuoromethylene containing  $\beta$ -lactams 2 are prepared started from the commercial available BrCF<sub>2</sub>CF<sub>2</sub>Br in overall five-step reaction procedure. The compound 2 is a useful fluorinated synthetic building block to synthesize CF<sub>2</sub>containing  $\beta$ -lactams through the radical reaction conditions to break the C-Br bond. Although the difluoromethylene containing  $\beta$ -lactams 2 is relative stable molecule to the common radical reaction conditions, it still can react with alkenes under the radical reaction conditions (Bu<sub>3</sub>SnH/AIBN) in the sealed tube giving the desired addition product in moderate to good yields. And in the absence of alkenes, under the same reaction conditions, 4-bromodifluoromethyl Blactams 2b can be reduced to the corresponding difluoromethyl  $\beta$ -lactam 6 in nearly quantitative yield. Furthermore, allylic stannic reagent Bu<sub>3</sub>SnCH<sub>2</sub>CH=CH<sub>2</sub> reacted with 2 under the same reaction conditions gave the allylic addition product 8.

### 4. Experimental

Melting points were measured in Temp-Melt apparatus and were uncorrected. NMR spectra were taken at 300 MHz (for <sup>1</sup>H NMR), 75.3 MHz (for <sup>13</sup>C NMR) and 282 MHz (for <sup>19</sup>F NMR) in CDCl<sub>3</sub> with Me<sub>4</sub>Si and CFCl<sub>3</sub> (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained using an FTIR spectrometer and only major peaks are reported in cm<sup>-1</sup>. Mass spectra were recorded by the EI method. Thin-layer chromatography was performed on pre-coated silica gel 60 F254 analytical plates.

#### 4.1. Typical procedure for preparation of 4 and 4'

A mixture of 5 mmol of 2,2-dihydropolyfluoroalkante, 7.5 mmol of aniline, 15 mmol Et<sub>3</sub>N and 5 ml CH<sub>3</sub>CN was stirred at 70 °C for 6 h. The mixture was then neutralized with aqueous of 1N HCl solution and extracted with ether. The ethereal layer was washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent, the residue was purified by column chromatography using ether and ethyl acetate as the eluant to give the mixture of enamine and imine.

4.2. 4-Bromo-4,4-difluoro-3-(4-methoxy-phenylamino)but-2-enoic acid ethyl ester (4b)



The product, a pale yellow solid, was isolated in 60% (yield); mp: 36–37 °C; (Found: C, 44.68; H, 4.19; N, 3.89. Calc. for C<sub>13</sub>H<sub>14</sub>O<sub>3</sub>BrF<sub>2</sub>N: C, 44.70; H, 4.01; N, 4.01%);  $v_{max}$  (KBr)/cm<sup>-1</sup> 3246, 3183, 2981, 2964, 2934, 2839, 1903, 1665, 1620, 1518, 1270, 1197, 1167, 1139, 1111;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 9.70 (s, 1H), 7.20 (d, J = 8.4, 2H), 6.89–6.85 (m, 2H), 5.26 (m, 1H), 4.21 (q, 2H, J = 7.2), 3.82 (s, 3H), 1.32 (t, 3H);  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 14.3, 55.4, 60.0, 85.6, 113.2, 113.8 (t,  $J_{\rm CF} = 349.2$ ), 129.3, 130.6, 153.4 (t,  $J_{\rm CF} = 22.7$ ), 158.5, 169.8;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) –48.1 (s, 2F); MS (EI): m/z (%) = 349 ( $M^+$ , 27), 303 (29), 174 (100), 146 (15), 122 (3), 77 (7).

# 4.3. 4-Bromo-4,4-difluoro-3-(4-methoxy-phenylimino)butyric acid ethyl ester (4b')



The product, a yellow oil, was isolated in 35% (yield); [Found (HRMS): 349.0126,  $C_{13}H_{14}O_3BrF_2N$  requires 349,0125];  $\nu_{max}$  (neat)/cm<sup>-1</sup> 2983, 2838, 1739, 1669, 1605, 1580, 1505, 1297, 1247, 1197, 1136;  $\delta_{H}$  (in CDCl<sub>3</sub>) 6.89 (s, 4H), 4.15 (q, J = 6.9, 2H), 3.78 (s, 3H), 3.53 (s, 3H), 1.24 (t, J = 6.9, 2H);  $\delta_{C}$  (in CDCl<sub>3</sub>) 14.0, 33.8, 55.4, 62.0, 114.4, 116.7(t,  $J_{CF} = 307.8$ ), 120.7, 139.6, 156.1 (t,  $J_{CF} = 24.7$ ), 157.3, 166.7;  $\delta_{F}$  (in CDCl<sub>3</sub>) -55.9 (s, 2F); MS (EI): m/z (%) = 349 ( $M^+$ , 18), 262 (2), 242 (2), 220 (100), 174 (20), 77 (7).

## 4.3.1. General procedure for the preparation of the 2amino acetate **3**

A dry flask, 100 ml, 2-necked, fitted with a refluxed condenser, gas inlet, and magnetic stirrer, was charged with

3 mmol of the mixture of enamine and imines 4 and 4', 228 mg (6 mmol) of NaBH<sub>4</sub>, and 30 ml of ethanol. The mixture was stirred under nitrogen atmosphere in ice water bath until TLC indicated the disappearance of the compounds 4 and 4'. The mixture was washed with water and extracted with  $CH_2Cl_2$ . The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel.

# 4.4. 4-Bromo-4,4-difluoro-3-phenylamino-butyric acid ethyl ester (**3a**)



The product, a pale yellow solid, was isolated in 60% (yield); mp: 19–20 °C; [Found (HRMS): 321.0175,  $C_{12}H_{14}O_2BrF_2N$  requires 321.0261];  $\nu_{max}$  (KBr)/cm<sup>-1</sup> 3387, 1733, 1604, 1515, 1499, 1278, 1263, 1182, 1110;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 7.11–7.06 (m, 2H), 6.72–6.61 (m, 3H), 4.51–4.38 (m, 1H), 4.00 (q, J = 7.2, 2H), 3.86 (d, J = 9.0, 1H), 2.81 (1H, A part of a AB-d system,  $J = 4.2, J_{AB} = 15.6$ ), 2.51 (1H, B part of a AB-d system,  $J = 9.3, J_{AB} = 15.6$ ), 1.06 (3H, J = 7.2, t);  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 13.0, 35.7, 59.0 (t,  $J_{\rm CF} = 23.3$ ), 60.3, 113.1, 118.4, 124.2 (t,  $J_{\rm CF} = 312.6$ ), 128.3, 144.7, 168.3;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) –53.2 (1F, A part of a AB-d system,  $J = 8.5, J_{AB} = 161.6$ ), -53.5 (1F, B part of a AB-d system,  $J = 5.9, J_{BA} = 161.6$ ); MS (EI): m/z (%) = 321 ( $M^+$ , 17), 192 (100), 104 (62), 77 (19).

4.5. 4,4-Difluoro-3-phenylamino-butyric acid ethyl ester (3a')



The product, a pale yellow oil, was isolated in 11% (yield); [Found (EI): 223.1012,  $C_{12}H_{15}O_2F_2N$  requires 223.1009];  $\nu_{max}$ (neat)/cm<sup>-1</sup> 3390, 2984, 1732, 1604, 1514, 1499, 1377, 1284, 1258, 1189, 1141;  $\delta_H$  (in CDCl<sub>3</sub>) 7.16–7.09 (m, 2H), 6.72–6.60 (m, 3H), 5.84 (dt, J = 2.4,  $J_{AB} = 56.1$ , 1H,), 4.17–4.12 (m, 1H), 4.05 (q, J = 7.2, 2H,), 3.86 (d, J = 10.2, 1H), 2.65 (1H, A part of a AB-d system, J = 7.9,  $J_{AB} = 15.9$ ), 2.51 (1H, B part of a AB-d system, J = 7.2,  $J_{AB} = 15.9$ ), 1.16 (t, J = 7.2, 3H);  $\delta_C$  (in CDCl<sub>3</sub>) 13.2, 32.4, 51.7 (t,  $J_{CF} = 23.0$ ), 60.2, 112.9, 114.1 (t,  $J_{CF} = 246.4$ ),118.1, 128.6, 145.0, 169.8;  $\delta_F$  (in CDCl<sub>3</sub>) -125.5 (1F, A part of a AB-d system, J = 7.9,  $J_{AB} = 282.0$ ), -130.3 (1F, B part of a AB-d system, J = 9.6,  $J_{BA} = 282.0$ ); MS (EI): m/z (%) = 243 ( $M^+$ , 55), 192 (100), 156 (62), 118 (32), 104 (95), 77 (32).





The product, a colorless solid, was isolated in 90% (yield); mp: 36–8 °C; (Found: C, 44.52; H, 4.50; N, 3.90. Calc. for  $C_{13}H_{16}O_3BrF_2N$ : C, 44.19; H, 4.50; N, 4.00%);  $\nu_{max}$  (KBr)/ cm<sup>-1</sup> 3368, 3006, 2961, 2937, 1721, 1623, 1532, 1510, 1285, 1252, 1192, 1180, 1100;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 6.82–6.73 (m, 4H), 4.14 (q, *J* = 7.2, 2H), 3.76 (s, 3H), 3.67 (d, *J* = 8.4, 2H), 2.91 (1H, A part of a AB-d system, *J* = 3.9, *J*<sub>AB</sub> = 15.6), 2.61 (1H, B part of a AB-d system, *J* = 9.5, *J*<sub>BA</sub> = 15.6), 1.24 (t, *J* = 7.2, 3H), 1.03 (br, 1H);  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 14.1, 36.8, 55.6, 61.3, 61.4 (t, *J*<sub>CF</sub> = 22.9), 114.8, 115.9, 125.5 (t, *J*<sub>CF</sub> = 313.0), 139.6, 153.4, 169.5;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) -53.4 (s); MS (EI): *m/z* (%) = 353 (*M*<sup>+</sup>, 23), 222 (100), 148 (50), 134 (42), 77 (9).

# 4.7. 4-Bromo-4,4-difluoro-3-(4-methoxy-phenylamino)butan-1-ol (**3b**')



The product, a brown solid, was isolated in 9.0% (yield); mp: 74–76 °C; (Found: C, 43.00; H, 4.40; N, 4.50. Calc. for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>BrF<sub>2</sub>N: C, 42.72; H, 4.50; N, 4.50%);  $\nu_{max}$  (KBr)/ cm<sup>-1</sup> 3457, 3340, 2968, 2912, 2893, 2838, 1619, 1512, 1261, 1238, 1104;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 6.83–6.70 (m, 4H), 4.10–4.00 (br, 1H), 3.86–3.84 (br, 2H), 3.76 (s, 3H), 3.54 (d, J = 9.6, 2H), 2.26–2.16 (m, 1H), 2.04 (b, 1H), 1.78–1.67 (m, 1H);  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 33.7, 55.7, 58.9, 61.5 (t,  $J_{\rm CF} = 22.2$ ), 114.9, 115.6, 127.0 (t,  $J_{\rm CF} = 314.1$ ), 140.3, 153.2;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) –52.3 (m, 2F); MS (EI): *m/z* (%) = 309 (*M*<sup>+</sup>, 19), 180 (100), 162 (24), 134 (21), 107 (7).

Typical procedure for the preparation of  $\beta$ -lactams 2: To a dry ice-acetone cooled flask, charged with 16.5 mmol amine 3 and 33 ml dry THF, was added dropwise 5.5 ml CH<sub>3</sub>MgBr ether solution (3 mol/l). After the reaction was completed monitored by the use of TLC, saturated NH<sub>4</sub>Cl solution was added. Then it was extracted with ether, the organic phase was dried over MgSO<sub>4</sub>, purified with flash chromatography on silica gel.

# 4.8. 4-(Bromo-difluoro-methyl)-1-phenyl-azetidin-2-one (2a)



The product, a colorless needle crystal, was isolated in 74% (yield); mp: 84–86 °C; [Found (EI): 274.9755,  $C_{10}H_8OBrF_2N$  requires 274.9757];  $\nu_{max}$  (KBr)/cm<sup>-1</sup> 3095, 2987, 1764, 1599, 1502, 1459, 1418, 1375, 1352, 1294, 1260, 1218, 1202, 1127, 1095;  $\delta_H$  (in CDCl<sub>3</sub>) 7.45–7.16 (m, 5H), 4.65 (dq, J = 3.4, 5.8, 12.6, 1H), 3.40 (1H, A part of a AB-d system,  $J = 5.7, J_{AB} = 15.6$ ), 3.18 (1H, B part of a AB-d system,  $J = 2.4, J_{AB} = 15.6$ );  $\delta_C$  (in CDCl<sub>3</sub>) 40.7, 57.0 (t,  $J_{CF} = 24.5$ ), 117.7, 122.4 (t,  $J_{CF} = 307.8$ ), 125.2, 129.2, 136.6, 162.6;  $\delta_F$  (in CDCl<sub>3</sub>) –50.7 (1F, A part of a AB system, J = 164.7), –57.7 (1F, B part of a AB-d system, J = 164.7); MS (EI): m/z (%) = 275 ( $M^+$ , 22), 146 (8), 119 (34), 104 (100), 77 (79).

4.9. 4-(Bromo-difluoro-methyl)-1-(4-methoxy-phenyl)azetidin-2-one (2b)



BrCF<sub>2</sub>

The product, a pale yellow solid, was isolated in 82% (yield); mp: 100–101 °C; (Found: C, 43.25; H, 3.33; N, 4.44. Calc. for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>BrF<sub>2</sub>N: C, 43.28; H, 3.28; N, 4.59%);  $\nu_{max}$  (KBr)/cm<sup>-1</sup> 2953, 1747, 1588, 1516, 1385, 1300, 1241, 1183, 1120, 1026;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 7.36–7.31 (m, 2H), 6.91–6.85 (m, 2H), 4.61–4.53 (m, 1H), 3.79 (s, 3H), 3.33 (1H, A part of a AB-d system, J = 5.4,  $J_{\rm AB} = 15.0$ );  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 40.6, 55.5, 57.4 (t,  $J_{\rm CF} = 26.1$ ), 114.4, 119.8, 122.5 (t,  $J_{\rm CF} = 308.2$ ), 129.8, 157.1, 162.4;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) –50.8 (1F, A part of a AB-d system, J = 172.3), -57.7 (1F, B part of a AB-d system, J = 14.4,  $J_{\rm BA} = 172.3$ ); MS (EI): m/z (%) = 307 ( $M^+$  + 2, 35), 305 ( $M^+$ , 35), 184 (89), 149 (33), 134 (100), 77 (48).

#### 4.10. X-ray data of 7b

 $C_{11}H_{10}NO_2BrF_2$ : MW = 306.11, triclinic, space group: *P*-1, a = 10.062(4), b = 10.2297(2), c = 5.937(3) Å;  $\alpha =$  $103.81(3)^{\circ}$ ,  $\beta = 95.42(4)^{\circ}$ ,  $\gamma = 87.45(3)^{\circ}$ ; V = 590.6(4)Å3, Z = 2, Dc = 1.721 g/cm,  $F(0 \ 0 \ 0) = 304.00$ . Radiation, Mo K $\alpha$ ( $\lambda = 0.71069$  Å). Crystal dimensions, 0.15 mm  $\times$  0.20 mm  $\times$ 0.30 mm. Intensity data were collected at 293(1) K with a Bruker P4 four-circle diffractometer with graphite monochromator and Mo K $\alpha$  radiation ( $\lambda = 0.71069$  Å). A total of 5696 independent reflection were measured in range  $12.32^{\circ} < 2\theta < 19.99^{\circ}$ . The structure was solved by heavy-atom Patterson methods 2 and expanded using Fourier techniques 3. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement 4 on F2 was based on 1264 observed reflections and 195 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = S ||Fo| - |Fc||/S|Fo| = 0.047,$$
  

$$wR2 = [S(w(Fo^{2} - Fc^{2})^{2})/Sw(Fo^{2})^{2}]^{1/2} = 0.092$$

The standard deviation of an observation of unit weight5 was 0.89. Unit weights were used. Plots of  $Sw(|Fo| - |Fc|)^2$  versus |Fo|, reflection order in data collection, sin q/l and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.60 and  $-0.62 \text{ e}^{-}/\text{Å}^3$ , respectively.

Neutral atom scattering factors were taken from Cromer and Waber6. Anomalous dispersion effects were included in Fcalc7; the values for Df' and Df'' were those of Creagh and McAuley8. The values for the mass attenuation coefficients are those of Creagh and Hubbell9. All calculations were performed using the CrystalStructure, 11 crystallographic software package.

4.11. 4 -Difluoro-methyl-1-(4-methoxy-phenyl)-azetidin-2one (6)



A sealed tube, charged with 153 mg (0.5 mmol) **2b**, Bu<sub>3</sub>SnH (291 mg, 1 mmol), AIBN (16 mg, 0.1 mmol) and benzene (2 ml), was immersed in the oil bath with the temperature maintaining about 110 °C overnight. Cooled to room temperature, the sealed was open, and saturated KF solution (4 ml) was added and stir for another hour an hour. Then the mixture was extracted with ether and dried over MgSO<sub>4</sub>, purified with flash chromatography on silica gel to give the desired product in almost quantitative yield.

The procedure is similar for the preparation 4-gemdifluoromethylene  $\beta$ -lactams when using alkenes to trap the radical.

The product, a colorless solid, was isolated in 98% (yield); mp: 65–67 °C; (Found: C, 58.08; H, 4.98; N, 5.86. Calc. for  $C_{13}H_{16}O_3BrF_2N$ : C, 58.15; H, 4.85; N, 6.17%);  $\nu_{max}$  (KBr)/cm<sup>-1</sup> 3117, 1770, 1345, 1301, 814;  $\delta_H$  (in CDCl<sub>3</sub>) 7.38–7.27 (m, 2H), 6.89–6.86 (m, 2H), 6.03 (td,  $J_1 = 3.9$ ,  $J_2 = 55.2$ , 1H), 4.31(br, 1H), 3.79(s, 3H), 3.28–3.05(m, 2H);  $\delta_C$  (in CDCl<sub>3</sub>) 37.5, 51.3, 55.5 (t,  $J_{CF} = 27.3$ ), 114.4, 114.5 (t,  $J_{CF} = 244.0$ ), 118.7, 130.6, 156.6, 162.9;  $\delta_F$  (in CDCl<sub>3</sub>) – 125.5 (1F, A part of a AB-d system, J = 55.3,  $J_{AB} = 293.6$ ), -123.3 (1F, B part of a AB-d system, J = 54.7,  $J_{BA} = 293.6$ ); MS (EI): m/z (%) = 227 ( $M^+$ , 33), 185 (29), 149 (11), 134 (100), 107 (12), 92 (11), 77 (22).

4.12. Ethyl 4,4-Difluoro-4-[1-(4-methoxy-phenyl)-4-oxoazetidin-2-yl]-butyrate (7a)



The product, a colorless solid, was isolated in 37% (yield); mp: 75-77 °C; (Found: C, 58.73; H, 5.95; N, 4.20. Calc. for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>BrF<sub>2</sub>N: C, 58.71; H, 5.85; N, 4.28%); v<sub>max</sub> (KBr)/ cm<sup>-1</sup> 3490, 2982, 2964, 2938, 1732, 1613, 1517, 1464, 1443, 1386, 1111, 829;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 7.39–7.27 (m, 2H), 6.90–6.86 (m, 2H), 4.39-4.35 (m, 1H), 4.14 (q, J = 7.2, 2H), 3.79 (s, 3H),3.28 (1H, A part of a AB-d system, J = 6.0,  $J_{AB} = 15.3$ ), 3.16(1H, B part of a AB-d system, J = 2.4,  $J_{BA} = 15.3$ ), 2.57  $(2H, t, J = 7.8), 2.29-2.18 \text{ (m, 2H)}, 1.25 \text{ (t, } J = 7.2, 3\text{H}); \delta_{\text{C}} \text{ (in }$ CDCl<sub>3</sub>) 14.1, 26.1 (t,  $J_{CF} = 4.21$ ), 28.3 (t,  $J_{CF} = 23.79$ ), 38.7, 53.9 (t,  $J_{CF} = 30.65$ ), 55.5, 61.0, 114.3, 119.6, 122.5 (t,  $J_{\rm CF} = 244.42$ ), 130.5, 156.7, 163.3, 171.9;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) -105.6 (1F, A part of a AB-d system, J = 252.7), -106.9 (1F, B part of a AB-d system, J = 258.3; MS (EI): m/z (%) = 327 ( $M^+$ , 100), 299 (3), 282 (53), 240 (54), 221 (55), 175 (45.7), 134 (100), 77 (18).

4.13. Methyl 4,4-Difluoro-4-[1-(4-methoxy-phenyl)-4-oxoazetidin-2-yl]-butyrate (**7b**)



The product, a colorless solid, was isolated in 44% (yield); mp: 91–93 °C; (Found: C, 57.25; H, 5.57; N, 4.27. Calc. for  $C_{13}H_{16}O_3BrF_2N$ : C, 57.50; H, 5.47; N, 4.47%);  $\nu_{max}$  (KBr)/ cm<sup>-1</sup> 3475, 2947, 2957, 2842, 1755, 1736, 1515, 1448, 1386, 1119, 833;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 7.38–7.27 (m, 2H), 6.89–6.86 (m, 2H), 4.42–4.34 (m, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.25 (1H, A part of a AB-d system, J = 6.3,  $J_{AB} = 15.3$ ), 3.01 (1H, B part of a AB-d system, J = 2.4,  $J_{BA} = 15.3$ ), 2.58 (t, J = 8.1, 2H), 2.33– 2.12 (m, 2H);  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 25.9 (t,  $J_{\rm CF} = 4.06$ ), 28.3 (t,  $J_{\rm CF} = 24.10$ ), 38.7, 52.1, 53.9 (t,  $J_{\rm CF} = 30.12$ ), 55.5, 114.3, 119.6, 122.4 (t,  $J_{\rm CF} = 244.50$ ), 130.5, 156.8, 163.3, 172.3;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) –105.7 (1F, A part of a AB-m system, J = 252.7), -106.7(1F, B part of a AB-d system, J = 226.7); MS (EI): m/z(%) = 313 ( $M^+$ , 100), 282 (11), 207 (20), 175 (14), 134 (90), 77 (9).

4.14. 4,4-Difluoro-4-[1-(4-methoxy-phenyl)-4-oxoazetidin-2-yl]-butyronitrile (7c)



The product, a colorless solid, was isolated in 38% (yield); mp: 83–85 °C; (Found: C, 59.96; H, 5.06; N, 9.97. Calc. for  $C_{13}H_{16}O_3BrF_2N$ : C, 60.00; H, 5.03; N, 10.00%);  $\nu_{max}$  (KBr)/ cm<sup>-1</sup> 3467, 2999, 1759, 1514, 1377, 1256;  $\delta_H$  (in CDCl<sub>3</sub>) 7.36– 7.27 (m, 2H), 6.92–6.87 (m, 2H), 4.47–4.39 (m, 1H), 3.80 (s, 3H), 3.30 (1H, A part of a AB-d system, J = 6.3,  $J_{AB} = 15.6$ ), 3.17 (1H, B part of a AB-d system, J = 1.8,  $J_{BA} = 15.6$ ), 2.62 (t, J = 7.5, 2H), 2.34–2.12 (m, 2H);  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 9.95 (t,  $J_{\rm CF} = 5.7$ ), 29.32 (t,  $J_{\rm CF} = 4.2$ ), 38.64, 53.611 (t,  $J_{\rm CF} = 35.09$ ), 114.5, 118.0, 119.6, 121.4 (t,  $J_{\rm CF} = 245.80$ ), 129.8, 157.0, 162.9;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) –105.3 (1F, A part of a AB-d system,  $J_{\rm AB} = 251.3$ ), -107.7 (1F, B part of a AB-d system,  $J_{\rm BA} = 251.3$ ); MS (EI): m/z (%) = 280 ( $M^+$ , 15), 238 (16), 149 (22), 134 (100), 77 (37), 69 (3).

4.15. 5,5-Difluoro-5-[1-(4-methoxy-phenyl)-azetidin-2-yl]pentan-2-one (7d)



The product, a colorless solid, was isolated in 21% (yield); mp: 122–124 °C; [Found (ES): 297.1193,  $C_{15}H_{17}F_2NO_3$ requires 297.1176];  $\nu_{max}$  (KBr)/cm<sup>-1</sup> 3476, 2969, 2937, 2842, 1742, 1716, 1515, 1380, 841;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 7.37–7.33 (m, 2H), 6.90–6.84 (m, 2H), 4.39–4.32 (m, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.23(1H, A part of a AB-d system, J = 6.0,  $J_{\rm AB} = 15.3$ ), 3.00 (1H, B part of a AB-d system, J = 3.0,  $J_{\rm BA} = 15.3$ ), 2.70 (t, J = 7.2, 2H), 2.22–2.10 (m, 3H);  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 26.8 (t,  $J_{\rm CF} = 23.87$ ), 30.0, 34.8, 38.7, 54.0 (t,  $J_{\rm CF} = 29.52$ ), 55.5, 114.3, 119.6 (t,  $J_{\rm CF} = 244.20$ ), 130.5, 156.7, 163.4, 206.0;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) –105.2 (1F, A part of a AB-d system,  $J_{\rm CF} = 251.3$ ); MS (EI): m/z (%) = 297 ( $M^+$ , 91), 191 (43), 149 (22),134 (100), 77 (15).

4.16. 2-(3-Ethoxy-1,1-difluoro-propyl)-1-(4-methoxy-phenyl)-azetidine (**7e**)



The product, a pale yellow oil was isolated in 17% (yield); [Found (ES): 299.1287,  $C_{15}H_{19}F_2NO_3$  requires 299.1333];  $\nu_{max}$ (KBr)/cm<sup>-1</sup> 2974, 2877, 1762, 1514, 1382, 1247, 1117;  $\delta_H$  (in CDCl<sub>3</sub>) 7.42–6.90 (m, 2H), 6.90–6.85 (m, 2H), 4.55–4.46 (m, 1H), 3.80 (s, 3H), 3.68–3.60 (m, 2H), 3.54–3.47 (m, 2H), 3.19 (1H, A part of a AB-d system, J = 5.7,  $J_{AB} = 15.6$ ), 3.00 (1H, B part of a AB-d system, J = 3.0,  $J_{BA} = 15.6$ ), 2.27–2.12 (m, 2H), 1.30–1.19 (m, 3H);  $\delta_C$  (in CDCl<sub>3</sub>) 15.06, 29.69, 34.66 (t,  $J_{CF} = 39.61$ ), 38.73 (t,  $J_{CF} = 4.07$ ), 54.02 (t,  $J_{CF} = 28.76$ ), 63.56, 66.58, 114.26, 119.9, 122.5 (t,  $J_{CF} = 244.05$ ), 130.8, 156.7, 163.7;  $\delta_F$  (in CDCl<sub>3</sub>) –103.0 (1F, A part of a AB-d system,  $J_{CF} = 248.4$ ), –106.8 (1F, B part of a AB-d system,  $J_{CF} = 254.4$ ); MS (EI): m/z (%) = 299 ( $M^+$ , 100), 193 (29), 185 (100), 176 (15), 149 (34), 134 (60), 77 (13).

4.17. 2-(1,1-Difluoro-3-phenyl-propyl)-1-(4-methoxy-phenyl)-azetidine (7f)



The product, a colorless solid, was isolated in 76% (yield); mp: 108–110 °C; [Found (ES): 331.1396, C<sub>19</sub>H<sub>19</sub>F<sub>2</sub>NO<sub>2</sub> requires 331.1384];  $\nu_{max}$  (KBr)/cm<sup>-1</sup> 3478, 3026, 2926, 1784, 1513, 1386, 1242, 698;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 7.44–6.90 (m, 9H), 4.41–4.37 (m, 1H), 3.81 (s, 3H), 3.22 (1H, A part of a AB-d system,  $J = 6.0, J_{\rm AB} = 15.3$ ), 3.03 (1H, B part of a AB-d system,  $J = 2.4, J_{\rm BA} = 15.3$ ), 2.91 (t, J = 8.1, 2H), 2.27–2.13 (m, 2H);  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 27.3 (t,  $J_{\rm CF} = 4.59$ ), 35.1 (t,  $J_{\rm CF} = 24.10$ ), 38.7, 54.04 (t,  $J_{\rm CF} = 30.72$ ), 55.5, 114.4, 119.7, 122.7 (t,  $J_{\rm CF} = 196.16$ ), 126.5, 127.7, 128.3, 130.7, 139.9, 156.8, 163.5;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) –105.3 (1F, A part of a AB-d system,  $J_{\rm CF} = 253.0$ ), -106.2 (1F, B part of a AB-d system,  $J_{\rm CF} = 252.4$ ); MS (EI): m/z (%) = 331 ( $M^+$ , 100), 225 (67), 185 (46), 170 (8), 134 (22), 91 (16), 77 (6).

4.18. 4-(1,1-Difluoro-but-3-enyl)-1-(4-methoxy-phenyl)azetidin-2-one (8)



The product, a colorless solid, was isolated in 25% (yield); mp: 52–54 °C; (Found: C, 62.91; H, 5.73; N, 5.23. Calc. for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>BrF<sub>2</sub>N: C, 62.91; H, 5.66; N, 5.24%);  $\nu_{max}$  (KBr)/cm<sup>-1</sup> 3484, 2967, 2957, 2843, 1760, 1512, 1384, 1115, 831;  $\delta_{\rm H}$  (in CDCl<sub>3</sub>) 7.41–7.35 (m, 2H), 6.91–6.86(m, 2H), 5.89(m, 1H), 5.27 (m, 2H), 4.42–4.34 (m, 1H), 3.80 (s, 3H), 3.21 (1H, A part of a AB-d system,  $J = 6.0, J_{AB} = 15.3$ ), 3.03 (1H, B part of a AB-d system,  $J = 2.7, J_{BA} = 15.3$ ), 2.74–2.60 (m, 2H), 2.33-2.12 (m, 2H);  $\delta_{\rm C}$  (in CDCl<sub>3</sub>) 38.2, 38.7 (m), 53.7 (t,  $J_{\rm CF} = 30.35$ ), 55.5, 114.3, 119.8, 121.5, 121.9 (t,  $J_{\rm CF} = 244.8$ ), 127.6, 130.6, 156.8, 163.4;  $\delta_{\rm F}$  (in CDCl<sub>3</sub>) –102.9 (1F, A part of a AB-d system, J = 252.7); MS (EI): m/z (%) = 267 ( $M^+$ , 100), 225 (25), 204 (48), 160 (4), 149 (18), 134 (89), 77 (17).

#### Acknowledgement

The authors thank the National Natural Science Foundation of China (NNSFC) (Nos. 20372077 and 20472106).

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