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Synthesis and substitution reactions of β-alkoxyvinyl bromodifluoromethyl ketones

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ABSTRACT

β-Alkoxyvinyl bromodifluoromethyl ketones **1a**, **1b** and **1c** were synthesized by the reaction of bromodifluoroacetic anhydride with appropriate vinyl ethers in high yields. The acyclic enone **1a** reacted with amines to give the corresponding β-aminovinyl bromodifluoromethyl ketones **2** in good yields. The reaction of **1a** with electrophilic reagent ICl yielded α-iodoenone **4**. The substitution reaction of the cyclic enones **1b** and **1c** with thio-nucleophiles gave the corresponding difluoromethylene thioethers **6**. The three-component reactions of **2** with primary amines and formaldehyde gave multifunctional 1,2,3,4-tetrahydropyrimidine **3** in moderate yields.

1. Introduction

The ability of fluorine atom to enhance biological and therapeutic activities of organic compounds has led to widespread interest in selective introduction of fluorine atom and fluoroalkyl groups into organic molecules [1–3], especially those heterocyclic compounds which have potential biological activities. Recently, the introduction of the difluoromethylene moiety into organic compounds has been proved to be attractive due to the potential biological properties of such molecules [4–6]. This group has been recognized as an isopolar–isosteric replacement for oxygen. In searching for new CF_2-containing reactive synthetic intermediates [7], we found that β-alkoxyvinyl trifluoromethyl ketones have been widely used as intermediates in heterocyclic synthesis [8–10], but the reaction of the β-alkoxyvinyl bromodifluoromethyl ketones were poorly investigated [11]. Such bromodifluoromethyl synthons **1** may take place the same kind reactions of β-alkoxyvinyl trifluoromethyl ketones, e.g., 1,2-nucleophilic Aldol reaction and 1,4-Michael addition; electrophilic addition in double bond, but the different radical addition and different kind substitution (nucleophilic with SET or halophilic) reaction in the carbon–bromide bond (Fig. 1) were still unknown. Herein we would like to report our recent research of the reactions of **1** as *gem*-difluorinated synthons with some typical nucleophilic and electrophilic reagents, together with their further chemical transformations, especially the $S_{RN}1$ reactions of **1** with thio-nucleophiles.

2. Results and discussion

β-Ethyloxyvinyl bromodifluoromethyl ketone **1a** was easily prepared by the procedure of Hojo et al. [12] from bromodifluoroacetic anhydride and ethyl vinyl ether in 80% yield (Scheme 1 and entry 1 in Table 1,). Similarly the cyclic enones **1b** and **1c** were readily prepared [12,13] by Friedel–Crafts acylation of dihydrofuran and dihydropyran in 95% and 99% yields, respectively (Table 1, entries 2 and 3).

The use of β-dialkylamino-α,β-unsaturated trifluoromethyl ketones [14,15] in the synthesis of fluorine-containing heterocycles [16] were recently reported. Liu also reported the three-component reaction of fluorine-containing enaminoketones or 3-fluoroalkylanilinoacrylic acid esters with primary amines and formaldehyde [17]. β-Aminovinyl bromodifluoromethyl ketones **2** were prepared from enone **1a** in good to excellent yields (Scheme 2 and Table 2) for their further transformation.

N-Monosubstituted enaminones **2a** and **2b** existed predominantly in a *Z*-configuration (*cis*-position between the bromodifluoroacetyl and the amino groups) due to hydrogen bonding in

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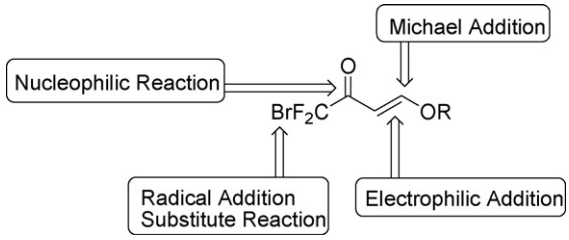
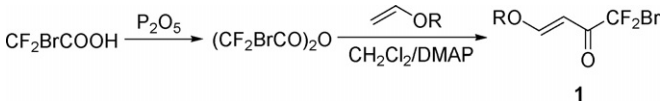
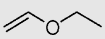
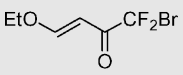
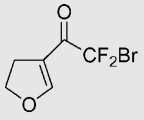
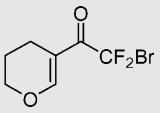


Fig. 1. The reactivity of β-alkoxyvinyl bromodifluoromethyl ketones.



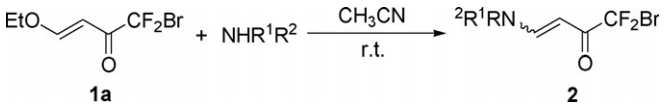
Scheme 1.

Table 1
The preparation of β-alkoxyvinyl bromodifluoromethyl ketones **1**.

Entry	Substance	Product	Yield (%)
1		 **1a** (**1a**)	80
2		 **1b** (**1b**)	95
3		 **1c** (**1c**)	99

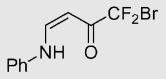
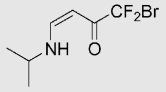
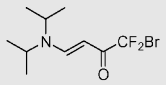
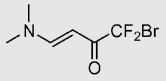
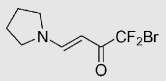
C═O···HN, which were shown by the coupling constant across the double bond on ^{1}H NMR spectra. It is well-known that the $^3J_{trans}$ value in 1,2-substituted ethylenic compounds is always larger than the $^3J_{cis}$ value. For instance, the characteristic features of the ^{1}H NMR in $CDCl_3$ spectra of **2b** were the appearances of doublets centered at 5.32 ppm and 7.23 ppm with $^3J_{H-H}$ = 7.1 Hz for 3-H and 4-H protons, respectively, indicating the *cis* configuration of the vicinal two hydrogen atoms. The *trans* configuration of the *N*,*N*-dimethylenaminone **2d** was also based on the appearances of doublets centered at 5.25 ppm and 7.85 ppm with $^3J_{H-H}$ = 12.2 Hz in the ^{1}H NMR spectra

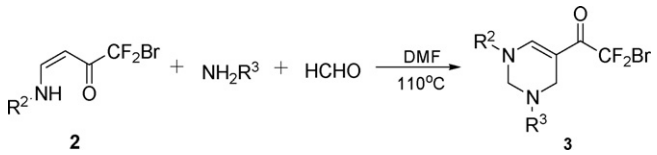
The three-component reaction of *N*-monosubstituted enaminoketones **2a** and **2b** with primary amines and formaldehyde were proceeded in DMF at 110 °C with a mole ratio of 1:3:6.5



Scheme 2.

Table 2
The reaction of β-ethyloxyvinyl bromodifluoromethyl ketone **1a** with amines.

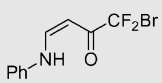
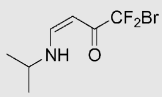
Entry	R^1	R^2	Product	Yield (%)
1	H	Ph	 **2a** (**2a**)	75
2	H	i-Pr	 **2b** (**2b**)	100
3	i-Pr	i-Pr	 **2c** (**2c**)	86
4	CH_3	CH_3	 **2d** (**2d**)	91
5			 **2e** (**2e**)	93

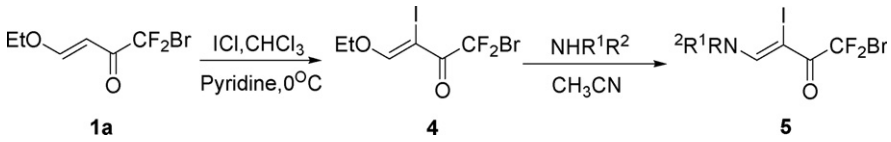


Scheme 3.

(**2**:primary amines:HCHO) (Scheme 3) according to the reference optimum condition [17]. As shown in Table 3, aliphatic primary amines reacted readily with **2a**, **2b** and formaldehyde to give multifunctional 1,2,3,4-tetrahydropyrimidine **3** in moderate yields. It were found that the length and bulkiness of the carbon chain in primary amines had little influence on the reaction. The

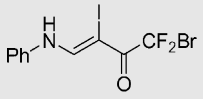
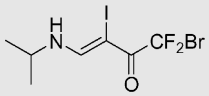
Table 3
The reaction of *N*-monosubstituted enaminoketones **2** with primary amines and formaldehyde.

Entry		R^2	R^3	Product	Yield (%)
1	 **2a** (**2a**)	Ph	i-Pr	(**3a**)	49
2		Ph	t-Bu	(**3b**)	48
3		Ph	Ph		Complex
4	 **2b** (**2b**)	i-Pr	i-Pr	(**3c**)	35
5		i-Pr	t-Bu	(**3d**)	33
6		i-Pr	Ph		Complex



Scheme 4.

Table 4
The reaction of α-iodoenone (**4**) with amines.

Entry	R^1	R^2	Product	Yield (%)
1	H	Ph	 **5a** (**5a**)	62
2	H	i-Pr	 **5b** (**5b**)	63
3	CH_3	CH_3	(**5d**)	Decomposed

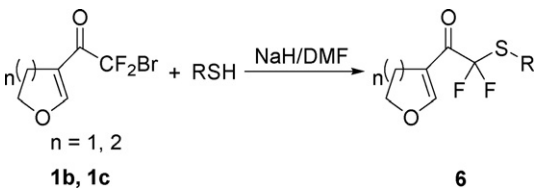
reaction yield of aromatic enaminoketones **2a** was higher than that of aliphatic enaminoketones **2b**. However, in case of aniline, the reactions were very complicated and no expected cyclic products were obtained (Table 3, entries 3 and 6).

The reactions of enone **1a** with electrophiles were scarcely investigated [18]. We found the reaction of **1a** with iodine underwent very slowly. However, the reaction of much more electrophilic iodine monochloride were effective in the introduction of the iodine atom to the α-position to the carbonyl group of enone **1a**. The addition of ICl to enone **1a** in the presence of one equivalent of pyridine at low temperature gave the corresponding α-iodoenone **4** in the isolated yield of 50% with the conversion of 66% (Scheme 4).

Iodoenone **4** showed the similar reactivity of enone **1a**. The reaction of enone **4** with amines produced the corresponding enaminones **5a** and **5b** in 62–63% yields (Table 4, entries 1 and 2). The dimethylamino substituted enaminone **5d** was not stable and decomposed (Table 4, entry 3).

The *Z*-configuration was observed in the α-iodoenaminone **5**. For example, the chemical shift of the NH proton of **5b** was observed at 5.91 ppm. The isomer with *trans*-disposed bromodifluoroacetyl and amino group becomes more stable presumably because of steric bulk of the α-halogeno substituent [18].

It was assumed that the CF_2Br group of β-alkoxyvinyl bromodifluoromethyl ketones would be reactive with sulfur nucleophiles [19–21]. In fact, in the presence of NaH, the reactions of cyclic enones **1b** and **1c** with thiolates in dimethylformamide were rapid and exothermic, completed within 30 min, to give the



Scheme 5.

Table 5
Reactions of acyclic enone (**1a**), cyclic enones (**1b**) and (**1c**) with thiolates.

Entry	Substance	Thiolate	Product	Yield (%)
1	(**1a**)	C_6H_4SH		Complex
2	(**1b**)	4-ClC_6H_4SH	(**6a**)	75
3	(**1b**)	4-$CH_3C_6H_4SH$	(**6b**)	75
4	(**1c**)	4-ClC_6H_4SH	(**6c**)	78
5	(**1c**)	4-$CH_3C_6H_4SH$	(**6d**)	80

corresponding difluoromethylene thioethers **6**. The isolated yields varied from 75% to 80% (Scheme 5 and Table 5). The displacement of bromide from the CF_2Br group was considered by an $S_{RN}1$ mechanism [20] involving a SET chain process. Unfortunately, the attempted reaction of **1a** with sodium thiolate led to decomposition and none of the desired product could be isolated (Table 5, entry 1).

3. Conclusions

β-Ethyloxyvinyl bromodifluoromethyl enone **1a**, cyclic enones **1b** and **1c** were prepared in high yields. Acyclic enone **1a** reacted with amines to give β-aminovinyl bromodifluoromethyl ketones **2**. Meanwhile, the reaction of enone **1a** with electrophilic reagent ICl gave α-iodoenone **4**, which was also able to be converted to the corresponding enaminones **5**. The preparations of difluoromethylene thioethers **6** in good yields were realized by the substitute reaction of the cyclic enones **1b**, **1c** with thiolates. It provided an effective method for the synthesis of multifunctional 1,2,3,4-tetrahydropyrimidines **3** through the three-component reactions of **2** with primary amines and formaldehyde.

4. Experimental

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. ^1H NMR (500 MHz) and ^{13}C (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.

4.1. General procedure for the preparation of β-alkoxyvinyl bromodifluoromethyl ketones

To a stirred solution of 4-dimethylaminopyridine (10 mg) and bromodifluoroacetic anhydride (10 mmol) which was prepared according to a previously reported procedure [22] in dichloromethane (15 ml), ethyl vinyl ether (12 mmol) was added dropwise at −10 °C. The reaction mixture was stirred for 10 h at 0 °C, allowed to warm to room temperature and the solvent was evaporated in vacuo. The reaction mixture was poured into sodium bicarbonate solution (the deep violet color changed to the yellow color), the two phases were separated and the organic phase was washed with water, dried over anhydrous sodium sulfate. The

solvent was evaporated in vacuo to give the crude compound **1** as a light yellow oil.

*4.1.1. 2-Bromo-1-(4,5-dihydrofuran-3-yl)-2,2-difluoroethanone (**1b**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (1H, t, J = 1.6 Hz), 4.7 (2H, t, J = 9.8 Hz), 3.0 (2H, t, J = 9.8 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −59.1 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 178.8 (t, J = 27.4 Hz), 164.0 (t, J = 7.0 Hz), 114.4 (t, J = 317.6 Hz), 112.6, 74.4, 27.9. IR (cm^{-1}, KBr): 2929, 1779, 1670, 1594, 1151, 818. EI-MS (m/z): 228 (M + 2$^+$, 6), 226 (M$^+$, 6), 97 (100). HRMS calcd for $C_6H_5O_2F_2Br$: 225.9441, found: 225.9441.

*4.1.2. 2-Bromo-1-(5,6-dihydro-4H-pyran-3-yl)-2,2-difluoroethanone (**1c**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.0 (1H, s), 4.2 (2H, t, J = 5.3 Hz), 2.35 (2H, t, J = 6.3 Hz), 1.99–1.94 (2H, m). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −55.9 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 181.4 (t, J = 25.2 Hz), 162.8 (t, J = 6.9 Hz), 114.4 (t, J = 318.9 Hz), 109.8, 68.3, 21.3, 19.0. IR (cm^{-1}, KBr): 2960, 1678, 1609, 1236, 960. EI-MS (m/z): 242 (M + 2$^+$, 3), 240 (M$^+$, 3), 111 (100), 83 (24). HRMS calcd for $C_7H_7O_2F_2Br$: 239.9597, found: 239.9597.

4.2. General procedure for the synthesis of enaminones

$PhNH_2$ (5 mmol) was added dropwise to the solution of enone **1a** (4 mmol) in acetonitrile (10 ml) under stirring at 0 °C. The mixture was stirred at room temperature for 10 h to complete the reaction, then the mixture was treated with about 30 ml of water and extracted with 3 × 20 ml of ether. The combined organic layer was washed with saturated brine solution and dried over anhydrous sodium sulfate. After evaporation of ether, the crude product was subjected to column chromatography to give the pure product **2a**.

*4.2.1. (Z)-1-Bromo-1,1-difluoro-4-(phenylamino)but-3-en-2-one (**2a**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 11.7 (1H, br), 7.70–7.65 (1H, m), 7.4 (2H, t, J = 8.0 Hz), 7.2 (1H, t, J = 7.9 Hz), 7.13 (2H, d, J = 7.7 Hz), 5.64 (1H, d, J = 7.5 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −61.8 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 182.4 (t, J = 25.6 Hz), 150.3, 139.5, 130.6, 126.3, 118.0, 115.5 (t, J = 317.8 Hz), 88.9. IR (cm^{-1}, KBr): 3248, 1606, 1565, 1300, 1137, 751. EI-MS (m/z): 277 (M + 2$^+$, 20), 275 (M$^+$, 20), 146 (100). HRMS calcd for $C_{10}H_8ONF_2Br$: 274.9757, found: 274.9758.

*4.2.2. (Z)-1-Bromo-1,1-difluoro-4-(isopropylamino)but-3-en-2-one (**2b**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.1 (1H, br), 7.23 (1H, q, J = 7.1 Hz), 5.32 (1H, d, J = 7.1 Hz), 3.65–3.57 (1H, m), 1.32 (6H, d, J = 6.6 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −60.6 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 180.7 (t, J = 24.7 Hz), 156.6, 116.2 (t, J = 318.1 Hz), 85.2, 51.8, 23.9. IR (cm^{-1}, KBr): 3270, 2977, 1644, 1587, 1139, 1072, 875. EI-MS (m/z): 243 (M + 2$^+$, 16), 241 (M$^+$, 16), 112 (100), 70 (33). HRMS calcd for $C_7H_{10}ONF_2Br$: 240.9914, found: 240.9914.

*4.2.3. (E)-1-Bromo-4-(diisopropylamino)-1,1-difluorobut-3-en-2-one (**2c**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (1H, d, J = 12.4 Hz), 5.35 (1H, d, J = 12.4 Hz), 3.96–3.89 (1H, m), 3.66–3.60 (1H, m), 1.24 (6H, d, J = 6.8 Hz), 1.21 (6H, d, J = 6.8 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −61.0 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 180.1 (t, J = 23.7 Hz), 152.6, 117.1 (t, J = 320.2 Hz), 85.8, 51.0, 49.8, 24.2, 20.2. IR (cm^{-1}, KBr): 3451, 2985, 1563, 1308, 935. EI-MS (m/z): 285 (M + 2$^+$, 15), 283 (M$^+$, 15), 204 (43), 154 (100). HRMS calcd for $C_{10}H_{16}ONF_2Br$: 283.0383, found: 283.0383.

*4.2.4. (E)-1-Bromo-4-(dimethylamino)-1,1-difluorobut-3-en-2-one (**2d**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 (1H, d, J = 12.2 Hz), 5.25 (1H, d, J = 12.2 Hz), 3.24 (3H, s), 2.98 (3H, s). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −61.4 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 180.0 (t, J = 23.9 Hz), 157.5, 116.7 (t, J = 320.2 Hz), 86.0, 46.2, 38.1. IR (cm^{-1}, KBr): 3447, 2925, 1657, 1585, 1070, 868, 682. EI-MS (m/z): 229 (M + 2$^+$, 23), 227 (M$^+$, 23), 98 (100). HRMS calcd for $C_6H_8ONF_2Br$: 226.9757, found: 226.9757.

*4.2.5. (E)-1-Bromo-1,1-difluoro-4-(pyrrolidin-1-yl)but-3-en-2-one (**2e**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (1H, d, J = 12.2 Hz), 5.22 (1H, d, J = 12.2 Hz), 3.62 (2H, t, J = 6.8 Hz), 3.32 (2H, t, J = 7.0 Hz), 2.11–2.05 (2H, m), 2.03–1.95 (2H, m). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −61.2 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 179.9 (t, J = 23.9 Hz), 153.3, 116.8 (t, J = 320.2 Hz), 86.9, 53.7, 48.1, 25.7 7, 25.5. IR (cm^{-1}, KBr): 2924, 2876, 1662, 1579, 1266, 1077, 939, 863. EI-MS (m/z): 255 (M + 2$^+$, 8), 253 (M$^+$, 8), 174 (12), 124 (100). HRMS calcd for $C_8H_{10}ONF_2Br$: 252.9914, found: 252.9915.

4.3. General procedure for the synthesis of 1,2,3,4-tetrahydropyrimidines

To a solution of enaminone **2a** (1 mmol) in DMF (5 ml), were added primary amines (3 mmol) and 37% formaldehyde (6.5 mmol). The mixture was stirred at 110 °C for 2–5 h (monitored by TLC or ^{19}F NMR). After completion of the reaction, the mixture was cooled to room temperature, diluted with water and extracted with Et_2O. The organic layer was washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by flash chromatography on silica gel.

*4.3.1. 2-Bromo-2,2-difluoro-1-(3-isopropyl-1-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone (**3a**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (1H, s), 7.27 (2H, t, J = 7.9 Hz), 6.96 (3H, t, J = 7.9 Hz), 4.69 (2H, s), 4.22 (2H, s), 3.55–3.48 (1H, m), 1.18 (6H, d, J = 6.7 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz): δ −52.6 (2F, s); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 176.7 (t, J = 23.7 Hz), 149.4, 148.7, 130.0, 122.4, 119.1, 115.7 (t, J = 318.9 Hz), 64.8, 56.4, 46.1, 21.8; IR (cm^{-1}, KBr): 2975, 1585, 1129, 694; EI-MS (m/z): 360 (M + 2$^+$, 13), 358 (M$^+$, 13), 279 (100), 105 (44); HRMS calcd for $C_{15}H_{17}O_2N_2F_2Br$: 358.0492, found: 358.0492.

*4.3.2. 2-Bromo-1-(3-tert-butyl-1-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroethanone (**3b**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.04 (1H, s), 7.34–6.98 (5H, m), 4.57 (2H, s), 3.68 (2H, s), 1.14 (9H, s); ^{19}F NMR ($CDCl_3$, 470 MHz): δ −53.9 (2F, s); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 176.3 (t, J = 23.7 Hz), 145.8, 142.4, 129.0, 124.8, 118.6, 113.5 (t, J = 318.8 Hz), 62.6, 54.6, 41.0, 26.1; IR (cm^{-1}, KBr): 2975, 1578, 1149, 757, 695; EI-MS (m/z): 374 (M + 2)$^+$, 11), 372 (M$^+$, 11), 293 (100), 208 (88), 104 (56); HRMS calcd for $C_{16}H_{19}ON_2F_2Br$: 372.0649, found: 372.0649.

*4.3.3. 2-Bromo-1-(1,3-diisopropyl-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroethanone (**3c**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (1H, s), 4.14 (2H, s), 3.64 (2H, s), 3.62–3.54 (1H, m), 2.96–2.88 (1H, m), 1.32 (6H, d, J = 6.7 Hz), 1.16 (6H, d, J = 6.4 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz): δ −52.3 (2F, s); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 174.9 (t, J = 23.4 Hz), 147.2, 114.2 (t, J = 319.1 Hz), 96.9, 61.6, 54.7, 49.8, 43.3, 20.2, 19.2; IR (cm^{-1}, KBr): 2974, 1586, 1134, 690; EI-MS (m/z): 326 (M + 2$^+$, 6), 324 (M$^+$, 6), 245 (100), 174 (26), 124 (26); HRMS calcd for $C_{12}H_{19}ON_2F_2Br$: 324.0649, found: 324.0648.

*4.3.4. 2-Bromo-1-(3-tert-butyl-1-isopropyl-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroethanone (**3d**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (1H, s), 3.99 (2H, s), 3.61–3.54 (1H, m), 3.52 (2H, s), 1.26 (6H, d, J = 6.0 Hz), 1.16 (9H, s); ^{19}F NMR ($CDCl_3$, 470 MHz): δ −52.5 (2F, s); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 174.7 (t, J = 23.6 Hz), 147.1, 114.1 (t, J = 318.8 Hz), 98.5, 59.1, 55.0, 54.3, 41.3, 25.5, 20.2; IR (cm^{-1}, KBr): 2973, 1586, 1131, 689; EI-MS (m/z): 340 ($M + 2^+$, 6), 338 (M^+, 6), 259 (100), 203 (32), 124 (25), 70 (50); HRMS calcd for $C_{13}H_{21}ON_2F_2Br$: 338.0805, found: 338.0805.

4.4. Procedure for preparation of Iodoenone

To the stirred solution of enone **1a** (19 mmol) in 5 ml $CHCl_3$ was added a solution of ICl (19 mmol) in 3 ml $CHCl_3$ at 0 °C. After 1 h pyridine (21 mmol) was added to the reaction mixture with stirring at 0 °C. The reaction mixture was stirred for 1–2 h at 20 °C, then water (50 ml) was added, the water phase was extracted with hexane (3 × 10 ml). The combined organic layers were dried by $MgSO_4$ and the slovent was evaporated in vacuo to give the crude compound **4** as red oil.

*4.4.1. (Z)-1-Bromo-4-ethoxy-1,1-difluoro-3-iodobut-3-en-2-one (**4**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (1H, s), 4.44 (2H, q, J = 7.1 Hz), 1.5 (3H, t, J = 7.1 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −54.5 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 177.6 (t, J = 26.3 Hz), 169.1 (t, J = 6.7 Hz), 112.0 (t, J = 319.1 Hz), 75.1, 73.6, 16.1. IR (cm^{-1}, KBr): 2985, 1686, 1598, 1234, 933, 869. EI-MS (m/z): 356 ($M + 2^+$, 15), 354 (M^+, 15), 225 (100), 197 (93). HRMS calcd for $C_6H_6O_2F_2BrI$: 353.8564, found: 353.8564.

4.5. General procedure for the synthesis of α-iodoenaminones

$PhNH_2$ (8 mmol) was added dropwise to the solution of iodoenone **4** (4 mmol) in acetonitrile (10 ml) under stirring at 0 °C. The mixture was stirred at room temperature for 10 h to complete the reaction, then the mixture was treated with about 30 ml of water and extracted with 3 × 20 ml of ether. The combined organic layer was washed with saturated brine solution and dried over anhydrous sodium sulfate. After evaporation of ether, the crude product was subjected to column chromatography to give the pure product **5a**.

*4.5.1. (Z)-1-Bromo-1,1-difluoro-3-iodo-4-(phenylamino)but-3-en-2-one (**5a**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.08 (1H, d, J = 13.6 Hz), 7.6 (1H, br), 7.33 (2H, t, J = 7.9 Hz), 7.14 (1H, t, J = 7.4 Hz), 7.05 (2H, d, J = 8.2 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −52.6 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 174.3 (t, J = 25.0 Hz), 147.3 (t, J = 6.7 Hz), 137.3, 129.2, 124.8, 116.7, 110.3 (t, J = 319.6 Hz), 70.6. IR (cm^{-1}, KBr): 3292, 1584, 1144, 935. EI-MS (m/z): 403 ($M + 2^+$, 18), 401 (M^+, 18), 272 (100), 146 (26). HRMS calcd for $C_{10}H_7ONF_2BrI$: 400.8724, found: 400.8725.

*4.5.2. (Z)-1-Bromo-1,1-difluoro-3-iodo-4-(isopropylamino)but-3-en-2-one (**5b**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 (1H, d, J = 14.1 Hz), 5.91 (1H, br), 3.88–3.75 (1H, m), 1.39 (6H, d, J = 6.6 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −52.0 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 175.0 (t, J = 24.7 Hz), 154.0, 112.3 (t, J = 318.1 Hz), 67.8, 51.3, 24.2. IR (cm^{-1}, KBr): 3289, 2976, 1603, 1136, 909. EI-MS (m/z): 369 ($M + 2^+$, 18), 367 (M^+, 18), 238 (100), 196 (28). HRMS calcd for $C_{10}H_7ONF_2BrI$: 366.8880, found: 366.8880.

4.6. General procedure for $S_{RN}1$ reactions of cyclic enones

To the stirred suspension of NaH (2 mmol) in dry DMF (5 ml), benzenethiol (1.5 mmol) was added dropwise at 0 °C. Hydrogen gas was evolved and the flask became warm. After stirring for 15 min, a clear solution was obtained. Then cyclic enone (1 mmol) **1b** was added all at once, and the solution was allowed to stir at 0 °C for 30 min. The reaction mixture was poured into 10 ml of water, and the mixture was extracted with $CHCl_3$ (3 × 10 ml). The combined organic layer was washed with 30 ml water to remove the DMF, then dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure. The resulting oil was purified by flash column chromatography on silica gel.

*4.6.1. 2-(4-Chlorophenylthio)-1-(4,5-dihydrofuran-3-yl)-2,2-difluoroethanone (**6a**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 (1H, s), 7.55 (2H, d, J = 8.5 Hz), 7.38 (2H, d, J = 8.5 Hz), 4.62 (2H, t, J = 9.8 Hz), 2.93 (2H, t, J = 9.8 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −78.4 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 182.8 (t, J = 27.6 Hz), 165.0 (t, J = 7.5 Hz), 139.6, 135.0, 131.2, 125.5 (t, J = 290.2 Hz), 125.4, 115.9, 75.2, 28.9. IR (cm^{-1}, KBr): 3085, 1647, 1574, 1180, 1074, 822. EI-MS (m/z): 292 ($M + 2^+$, 2), 290 (M^+, 5), 97 (100). HRMS calcd for $C_{12}H_9O_2ClF_2S$: 289.9980, found: 289.9980.

*4.6.2. 1-(4,5-Dihydrofuran-3-yl)-2,2-difluoro-2-(p-tolylthio)ethanone (**6b**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52 (1H, s), 7.42 (2H, d, J = 8.0 Hz), 7.13 (2H, d, J = 8.0 Hz), 4.53 (2H, t, J = 9.7 Hz), 2.84 (2H, t, J = 9.7 Hz), 2.31 (3H, s). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −79.5 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 180.5 (t, J = 27.6 Hz), 162.2 (t, J = 7.2 Hz), 139.8, 135.8, 129.0, 122.7 (t, J = 290.0 Hz), 120.6, 113.4, 72.4, 26.3, 20.3. IR (cm^{-1}, KBr): 3084, 1651, 1578, 1136, 1072, 814. EI-MS (m/z): 270 (M^+, 17), 97 (100). HRMS calcd for $C_{13}H_{12}O_2F_2S$: 270.0526, found: 270.0526.

*4.6.3. 2-(4-Chlorophenylthio)-1-(5,6-dihydro-4H-pyran-3-yl)-2,2-difluoroethanone (**6c**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (1H, s), 7.47 (2H, d, J = 8.5 Hz), 7.29 (2H, d, J = 8.5 Hz), 4.08 (2H, t, J = 5.3 Hz), 2.22 (2H, t, J = 6.3 Hz), 1.88–1.82 (2H, m). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −74.3 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 182.9 (t, J = 27.2 Hz), 161.5 (t, J = 7.4 Hz), 136.9, 135.9, 128.4, 123.5 (t, J = 291.4 Hz), 123.0, 110.4, 66.6, 19.8, 17.3. IR (cm^{-1}, KBr): 2959, 1653, 1591, 1075, 817. EI-MS (m/z): 306 ($M + 2^+$, 1), 304 (M^+, 2), 111 (100). HRMS calcd for $C_{13}H_{11}O_2ClF_2S$: 304.0136, found: 304.0132.

*4.6.4. 1-(5,6-Dihydro-4H-pyran-3-yl)-2,2-difluoro-2-(p-tolylthio)ethanone (**6d**)*

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (1H, s), 7.42 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz), 4.08 (2H, t, J = 5.3 Hz), 2.3 (3H, s), 2.22 (2H, t, J = 6.3 Hz), 1.87–1.82 (2H, m). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −75.4 (2F, s). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 183.3 (t, J = 27.2 Hz), 161.4 (t, J = 7.2 Hz), 139.7, 135.7, 128.9, 123.3 (t, J = 290.0 Hz), 120.8, 110.6, 66.5, 20.3, 19.8, 17.3. IR (cm^{-1}, KBr): 2966, 1652, 1588, 1070, 832. EI-MS (m/z): 284 (M^+, 12), 111 (100). HRMS calcd for $C_{14}H_{14}O_2F_2S$: 284.0683, found: 284.0683.

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