Nucleophilic 5-*endo-trig* Cyclization of 2-(Trifluoromethyl)allylic Metal Enolates and Enamides: Synthesis of Tetrahydrofurans and Pyrrolidines Bearing *exo*-Difluoromethylene Units

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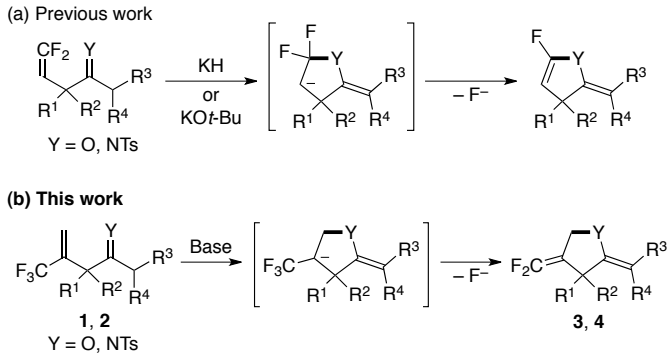
ABSTRACT

Ketones and imines bearing a 2-(trifluoromethyl)allylic moiety successfully underwent nucleophilic 5-*endo-trig* cyclization via their metal enolates and enamides. *O*- or *N*-Cyclization proceeded exclusively in each case to afford the corresponding five-membered heterocycles with both *exo*-difluoromethylene and *exo*-alkylidene units. On treatment with potassium hexamethyldisilazide (KHMDS) or lithium diisopropylamide (LDA), 2-(trifluoromethyl)allylic ketones or imines provided the corresponding tetrahydrofurans or pyrrolidines bearing a *Z*-alkylidene group with perfect or substantial stereoselectivity, respectively.

1. Introduction

Fluoroalkenes constitute a class of versatile compounds not only in synthetic chemistry, but also in pharmaceutical, agricultural, and materials sciences.[1] Among their uses, they serve as key building blocks for synthesizing fluorine-containing compounds via addition–elimination process.[2–4] Because of their electron-deficiency, fluoroalkenes are successfully subjected to nucleophilic substitution. By utilizing the reactivity of fluoroalkenes, we developed methods for cyclizing 1,1-difluoro-1-alkenes and 2-(trifluoromethyl)-1-alkenes, which were directed toward constructing fluorine-containing hetero- and carbocycles.[3,4] For example, 1,1-difluoro-1-alkenes bearing oxygen, nitrogen, sulfur, and carbon nucleophilic sites underwent intramolecular cyclization through nucleophilic vinylic substitution (S_NV) to afford ring-fluorinated cyclic compounds. Similarly, cyclization of 2-trifluoromethyl-1-alkenes proceeded through S_N2'-type reactions to afford difluoromethylene- or difluoromethyl-bearing hetero- and carbocycles. Although transformation of trifluoromethyl groups often causes complete defluorination (cleavage of all three C–F bonds), this protocol enables single C–F bond activation of CF_3 groups.[5,6]

We already demonstrated that the high reactivity of fluoroalkenes induced not only 6-*endo-trig* cyclization but also 5-*endo-trig* cyclization,[3,4,7,8] which is disfavored according to Baldwin's rules.[9–12] During the course of our studies, we recently reported nucleophilic 5-*endo-trig* cyclization of 3,3-difluoroallylic ketones and imines (Scheme 1a).[13] Selective *O*- and *N*-cyclizations proceeded successfully despite the extra steric constraint associated with the planarity of intermediary metal enolates and enamides, which afforded 2-alkylidene-2,3-dihydrofurans and -dihydropyrroles, respectively. As a further challenge, we investigated nucleophilic cyclization of 2-(trifluoromethyl)allylic ketones **1** and imines **2**, in which the difluorovinyl groups of 3,3-difluoroallylic ketones and imines were replaced with the (trifluoromethyl)vinyl group. Consequently, we accomplished 5-*endo-trig* *O*- and *N*-cyclizations of intermediary metal enolates and enamides bearing 2-(trifluoromethyl)allylic groups, which led to the synthesis of *exo*-difluoromethylene-bearing tetrahydrofurans **3** and pyrrolidines **4**, respectively (Scheme 1b).



Scheme 1. Nucleophilic 5-*endo-trig* cyclization of ketones and imines bearing fluoroalkene units

2. Results and discussion

2.1. Preparation of 2-(trifluoromethyl)allylic ketones and imines

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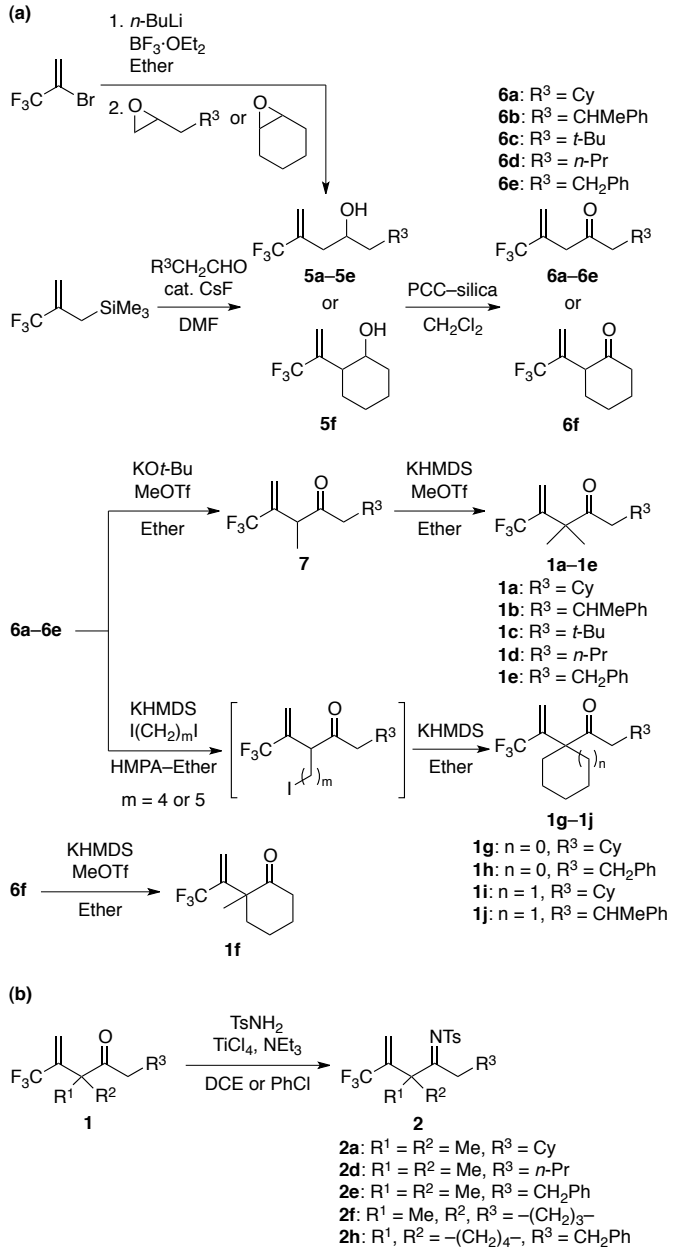


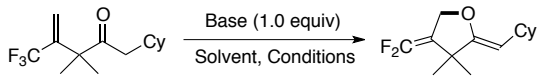
Scheme 2. Preparation of (a) 2-(trifluoromethyl)allylic ketones **1** and (b) 2-(trifluoromethyl)allylic imines **2**

2-(Trifluoromethyl)allylic ketones **1** were obtained through the preparation of (trifluoromethyl)homoallylic alcohols **5**: (i) ring-opening of epoxides with (trifluoromethyl)vinyllithium[14] or (ii) allylation of aldehydes with trimethyl[(trifluoromethyl)allyl]silane (Scheme 2a).[8,15] Alcohols **5** were oxidized with pyridinium chlorochromate (PCC) on silica gel to afford the corresponding ketones **6**. Subsequent stepwise dimethylation by methyl trifluoromethanesulfonate and appropriate bases afforded 2-(trifluoromethyl)allylic ketones **1a**–**1e** bearing two methyl groups. 2-(Trifluoromethyl)allylic ketones **1g**–**1j** with a cycloalkane moiety were prepared via stepwise dialkylation using diiodoalkanes. 2-(Trifluoromethyl)allylic ketone **1f** bearing a cyclohexanone framework is also obtained via methylation of 2-(3,3,3-trifluoroprop-1-en-2-yl)cyclohexan-1-one (**6f**, Scheme 2a). Additionally, on treatment with *p*-toluenesulfonamide in the presence of $TiCl_4$ and triethylamine, ketones **1** afforded 2-(trifluoromethyl)allylic imines **2** (Scheme 2b). Imination of **1f** afforded a mixture of imine **2f** and its enamine form (not shown), which was used for the following 5-*endo-trig* cyclization as it is.

2.2. Cyclization of 2-(trifluoromethyl)allylic ketones

We initially sought suitable conditions for 5-*endo-trig* cyclization of 2-(trifluoromethyl)allylic ketones **1** using ketone **1a** as a model compound (Table 1). When potassium hydride, lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LiHMDS), and sodium hexamethyldisilazide (NaHMDS) were employed as bases in tetrahydrofuran (THF), cyclized products were hardly obtained (Table 1, Entries 1–4). In contrast, on treatment with potassium hexamethyldisilazide (KHMDS) in THF, *O*-cyclization proceeded exclusively in a 5-*endo-trig* fashion to afford tetrahydrofuran **3a** bearing two alkylidene units in 56% yield (Table 1, Entry 5). To improve the yield of **3a**, several other solvents such as diglyme, toluene, and *N*,*N*-dimethylformamide (DMF) were examined (Table 1, Entries 6–9). Among these, DMF was found to be the most effective, affording **3a** in 83% yield (Table 1, Entry 9). Other bases were much less effective even in DMF than KHMDS (Table 1, Entries 10–15).

Table 1. Screening of conditions for 5-*endo-trig* cyclization of **1a**



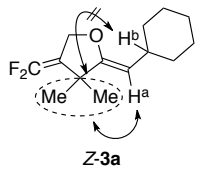
1a **3a**

Entry	Base	Solvent	Conditions	Yield %[a]
1	KH	THF	reflux, 2 h	N.D.[b]
2	LDA	THF	reflux, 2 h	N.D.[b]
3	LiHMDS	THF	reflux, 4 h	N.D.[b]
4	NaHMDS	THF	reflux, 4 h	2
5	KHMDS	THF	reflux, 4 h	56
6	KHMDS	1,4-Dioxane	reflux, 8 h	76
7	KHMDS	Diglyme	reflux, 4 h	39
8	KHMDS	Toluene	reflux, 2 h	20
9	KHMDS	DMF	110 °C, 1 h	83
10	KH	DMF	110 °C, 2 h	17
11	NaH	DMF	110 °C, 2 h	N.D.[b]
12	KO*t*-Bu	DMF	110 °C, 2 h	N.D.[b]
13	LDA	DMF	110 °C, 2 h	N.D.[b]
14	LiHMDS	DMF	110 °C, 2 h	N.D.[b]
15	NaHMDS	DMF	110 °C, 2 h	N.D.[b]

[a]Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard. [b]N.D. = Not detected.

To determine the configuration of the cyclohexylmethylidene unit of tetrahydrofuran **3a**, which was obtained as a single isomer, nuclear Overhauser effect (NOE) experiments were conducted. A significant correlation was observed between the vinylic proton (H^a in Figure 1) and the protons of the two methyl groups on the tetrahydrofuran ring, while no NOE correlation was detected between the allylic proton (H^b in Figure 1) and the methyl protons. Therefore, the stereochemistry of **3a** was determined to be *Z*. This might be due to steric repulsion between the methyl groups and the cyclohexane ring, which induces selective formation of *Z*-enolates and subsequent cyclization with retention of configuration. This selectivity is the same as for 5-*endo-trig*

cyclization of 3,3-difluoroallylic ketones, which solely produces dihydrofurans bearing *Z*-alkylidene units.[13]

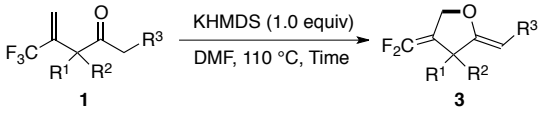


Z-**3a**

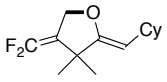
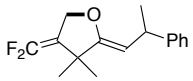
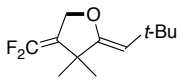
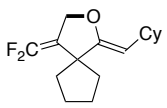
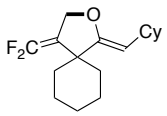
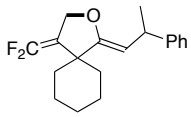
Figure 1. Determination of stereochemistry of **3a** by NOE experiments

With the optimal conditions established, the scope and limitations of the 5-*endo-trig* cyclization of (trifluoromethyl)allylic ketones **1** were investigated (Table 2). Although **3a** partially decomposed upon silica gel column chromatography, **3a** was isolated in 53% yield (Table 2, Entry 1). In general, cyclization of substrates bearing a tertiary or quaternary carbon atom at the β-position of the carbonyl group proceeded efficiently. Dimethylated substrates **1b** and **1c** bearing 1-phehylethyl and *tert*-butyl groups at the carbon α to the carbonyl group underwent 5-*endo-trig* cyclization to afford the corresponding tetrahydrofurans **3b** and **3c** in 29% and 61% isolated yields, respectively (Table 2, Entries 2 and 3), whereas much lower efficiency was observed in cyclization of phenethyl ketone **1e** (not shown). Ketones **1g** and **1i**–**1j** bearing a cyclopentane or a cyclohexane ring at the allylic position were also applicable to 5-*endo-trig* cyclization, affording spirocyclic products **3g**, **3i**, and **3j** bearing a tertiary carbon atom at the outside allylic position in good to high isolated yields (Table 2, Entries 4–6). Cyclohexane-bearing substrate **1i** underwent cyclization more efficiently than cyclopentane-bearing substrate **1g**, presumably because a cyclohexane ring is more sterically demanding than a cyclopentane ring, and thus rather promoted cyclization by bringing the oxygen atom closer to the alkene moiety (Table 2, Entry 4 vs Entry 5).

Table 2. Synthesis of tetrahydrofurans **3** bearing an *exo*-difluoromethylene unit



1 **3**

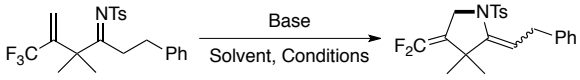
Entry	Time h	**3**		Yield %[a]
1	1		**3a**	53 (83)
2	1		**3b**	29
3	2		**3c**	61 (72)
4	1		**3g**	43
5	1		**3i**	66
6	1		**3j**	71

[a]Isolated yield. Yield determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard is shown in parentheses.

2.3. Cyclization of 2-(trifluoromethyl)allylic imines

We next examined 5-*endo-trig* cyclization of 2-(trifluoromethyl)allylic imines **2** using imine **2e** as a model compound (Table 3). Although no cyclization occurred when treating **2e** with potassium hydride in THF (Table 3, Entry 1), using DMF as a solvent afforded the corresponding pyrrolidine **4e** in 77% yield as an *E*/*Z* mixture (Table 3, Entry 2). Several other bases were then examined in DMF (Table 3, Entries 3–5). Among these bases, LDA and KHMDS exhibited greater efficiency at 110 °C to afford **4e** in 86% and 93% yields with 23/77 and 26/74 *E*/*Z* ratios, respectively (Table 3, Entries 5 and 6).

Table 3. Screening of conditions for 5-*endo-trig* cyclization of **2e**



2e **4e**

Entry	Base (equiv)	Solvent	Conditions	Yield % (*E*/*Z*)[a]
1	KH (2.0)	THF	reflux, 8 h	N.D.[b]
2	KH (1.0)	DMF	110 °C, 2 h	77 (23/77)
3	NaH (1.0)	DMF	110 °C, 5 h	81 (23/77)
4	KO*t*-Bu (2.0)	DMF	110 °C, 2 h	65 (15/85)
5	LDA (1.0)	DMF	110 °C, 5 h	86 (23/77)
6	KHMDS (1.0)	DMF	110 °C, 2 h	93 (26/74)

[a]Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard. [b]N.D. = Not detected.

The stereochemistry of pyrrolidine **4e**, which was obtained as an *E*/*Z* mixture, was determined by NOE experiments as with tetrahydrofuran **3a**. The major isomer exhibited correlation between the vinylic proton (H^a in Figure 2) and the protons of the two methyl groups on the pyrrolidine ring, whereas the minor product exhibited correlation between the allylic proton (H^b in Figure 2) and the methyl protons. These observations suggested that the major and minor products were *Z*- and *E*-isomers of **4e**, respectively. This is in stark contrast to the 5-*endo-trig* cyclization of 3,3-difluoroallylic imines, which afforded *E*-alkylidene dihydropyrroles as major products (*E*/*Z* = >99/<1–79/21).[13b] With 3,3-difluoroallylic imines, *Z*-enamides were initially formed, which caused the tosyl group on the nitrogen atom to face the difluoroalkene unit due to steric repulsion and retarded the cyclization. Thus, *E*-enamides, formed by stereoinversion, underwent cyclization. However, in the current reaction, cyclization proceeded from initially formed *Z*-enamides, probably because of the high reactivity of the (trifluoromethyl)alkene unit.

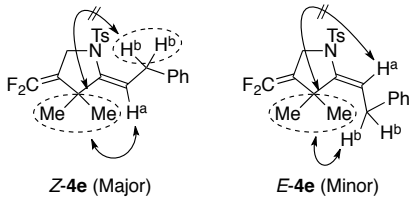
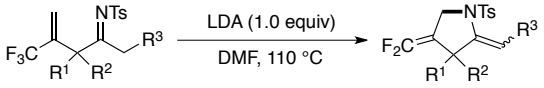
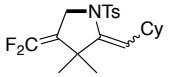
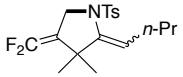
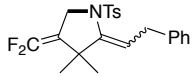
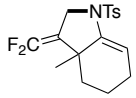
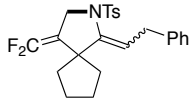


Figure 2. Determination of stereochemistry of **4e** by NOE experiments

Cyclization of several 2-(trifluoromethyl)allylic imines **2** was then investigated using LDA as a base, because it provided satisfying efficiency at lower cost than KHMDS (Table 4). Imines **2a**, **2d**, and **2e** bearing secondary and primary alkyl groups successfully underwent *N*-selective 5-*endo-trig* cyclization to afford the corresponding pyrrolidines **4a**, **4d**, and **4e** in 71%, 84%, and 76% yields, respectively (Table 4, Entries 1–3). Cyclization of a mixture of imine **2f** and its enamine form efficiently proceeded to afford indole derivative **4f** in 93% yield as a sole product (Table 4, Entry 4). Nitrogen-containing spirocyclic compound **4h** was obtained in 85% yield from imine **2h** bearing a cyclopentane moiety at the allylic position (Table 4, Entry 5).

Table 4. Synthesis of pyrrolidines **4** bearing an *exo*-difluoromethylene unit



Entry	Time h	4		Yield %[a] (*E*/*Z*)[b]
1	2		**4a**	71 (32/68)
2	2		**4d**	84 (23/77)
3	5		**4e**	76 (24/76)
4	2		**4f**	93 (N.A.)[c]
5	2		**4h**	85 (18/82)

[a]Isolated yield. [b]Diastereomer ratio was determined by ^{19}F NMR measurement. [c]N.A. = Not applicable.

3. Conclusion

In summary, we have demonstrated nucleophilic 5-*endo-trig* cyclization of 2-(trifluoromethyl)allylic ketones and imines via their metal enolates and enamides. In both cases, carbon–heteroatom bonds were formed during cyclization to afford five-membered heterocycles with two *exo*-alkylidene units including a *gem*-difluoromethylene group. It is noteworthy that single C–F bond activation of the trifluoromethyl group was successfully effected to install two fluorine atoms in the products. The fluorine-containing tetrahydrofurans and pyrrolidines thus obtained would serve as constituents of bioactive pharmaceuticals and agrochemicals.[1]

4. Experimental section

4.1. General information

The ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance 500, a JEOL ECS-400, a JEOL ECZ-400S, or a JEOL EX-270 spectrometer. Chemical shift values are given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ = 0.00 ppm), $CDCl_3$ (for ^{13}C NMR: δ = 77.0 ppm), and C_6F_6 (for ^{19}F NMR: δ = 0.00 ppm). IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV, a JEOL JMS-T100CS, a JEOL JMS-SX-102A, or a Waters UPLC spectrometer. Elemental analyses were performed with a Yanaco MT-3 CHN Coder apparatus at the Elemental Analysis Laboratory, Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba.

Column chromatography and preparative thin-layer chromatography were conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc. for column chromatography and Wakogel B-5F, Wako Pure Chemical Industries for PTLC). All the reactions were conducted under argon or nitrogen.

N,*N*-Dimethylformamide (DMF), tetrahydrofuran (THF), and diethyl ether were purified with a solvent-purification system (GlassContour) equipped with columns of activated alumina and supported-copper catalyst (Q-5) before use. *N*,*N*,*N*′,*N*′,*N*″,*N*″-Hexamethylphosphoric triamide (HMPA) was distilled from CaH_2, and stored over activated molecular sieves 4A. Preparation of 1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (**6e**) and 4,4-dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (**1e**) was conducted according to literature procedures.[8b] Unless otherwise noted, materials were obtained from commercial sources and used directly without further purification.

*4.2. 1-Cyclohexyl-4-(trifluoromethyl)pent-4-en-2-ol (**5a**)*

To a diethyl ether (106 mL) solution of 2-bromo-3,3,3-trifluoroprop-1-ene (5.00 mL, 48.0 mmol) and $BF_3{\cdot}OEt_2$ (4.00 mL, 31.9 mmol) was added dropwise a diethyl ether (21 mL) solution of *n*-BuLi (1.47 M in hexane, 32.6 mL, 47.9 mmol) at –100 °C. After stirring at –100 °C for 15 min, a diethyl ether (21 mL) solution of 2-(cyclohexylmethyl)oxirane (4.48 g, 31.9 mmol) was added dropwise to the mixture. After stirring at –100 °C for 15 min, the mixture was warmed to room temperature. After stirring at room temperature for another 12 h, the reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with ethyl acetate three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (hexane/ethyl acetate = 5/1) to give **5a** (4.42 g, 59%) as a colorless oil; [Found: C, 61.07; H, 8.21. $C_{12}H_{19}F_3O$ requires C, 61.00; H, 8.11%]; IR (neat) ν 3375, 2924, 2854, 1448, 1348, 1167, 1122, 1032, 945 cm^{-1}; ^{1}H NMR (500 MHz, $CDC1_3$) δ 0.83–0.92 (m, 1H), 0.92–1.01 (m, 1H), 1.10–1.22 (m, 1H), 1.22–1.35 (m, 3H), 1.36–1.55 (m, 3H), 1.64–1.74 (m, 4H), 1.77–1.84 (m, 1H), 2.29 (dd, J = 14.9, 8.4 Hz, 1H), 2.39 (dd, J = 14.9, 3.8 Hz, 1H), 3.90–3.97 (m, 1H), 5.48 (q, J_{HF} = 1.2 Hz, 1H), 5.80 (q, J_{HF} = 1.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.1, 26.3, 26.5, 32.7, 34.0, 34.1, 38.7, 45.0, 66.6, 120.9 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 274 Hz), 135.2 (q, J_{CF} = 30 Hz); ^{19}F NMR (470 MHz, $CDC1_3$) δ 93.5 (br s, 3F).

*4.3. 6,6-Dimethyl-2-(trifluoromethyl)hept-1-en-4-ol (**5c**)*

Compound **5c** was prepared by the method described for **5a** using 2-bromo-3,3,3-trifluoroprop-1-ene (1.10 mL, 10.6 mmol) and 2-neopentyloxirane (769 mg, 6.74 mmol). Purification by column chromatography (hexane/ethyl acetate = 5/1) gave **5c** (801 mg, 57%) as a colorless oil; [Found: C, 56.88; H, 8.19. $C_{10}H_{17}F_3O$ requires C, 57.13; H, 8.15%]; IR (neat) ν 3396, 2956, 2871, 1365, 1346, 1165, 1117, 945, 874, 580 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.39–1.42 (m, 2H), 1.52 (br s, 1H), 2.31 (dd, J = 14.8, 8.5 Hz, 1H), 2.36 (dd, J = 14.8, 4.6 Hz, 1H), 3.93–3.99 (m, 1H), 5.47 (br s, 1H), 5.80 (q, J_{HF} = 1.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 30.0, 30.3, 40.1, 50.6, 66.9, 121.1 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 274 Hz), 135.2 (q, J_{CF} = 29 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ 93.6 (br s, 3F).

*4.4. 2-(3,3,3-Trifluoroprop-1-en-2-yl)cyclohexan-1-ol (**5f**)*

Compound **5f** was prepared by the method described for **5a** using 2-bromo-3,3,3-trifluoroprop-1-ene (12.4 mL, 119 mmol) and 7-oxabicyclo[4.1.0]heptane (8.01 g, 81.6 mmol). Purification by column chromatography (hexane/ethyl acetate = 4/1) gave **5f** (8.48 g, 54%) as a colorless oil; IR (neat) ν 3404, 2933, 2860, 1450, 1346, 1296, 1163, 1113, 1063, 937 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22–1.34 (m, 4H), 1.69–1.72 (m, 1H), 1.78–1.82 (m, 1H), 1.92–1.94 (m, 1H), 2.02 (br s, 1H), 2.07–2.10 (m, 1H), 2.11–2.16 (m, 1H), 3.57–3.62 (m, 1H), 5.49 (br s, 1H), 5.85 (q, J_{HF} = 1.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.7, 25.7, 33.0, 34.9, 47.1, 72.6, 118.5 (q, J_{CF} = 6 Hz), 123.8 (q, J_{CF} = 274 Hz), 140.8 (q, J_{CF} = 29 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ 94.0 (br s, 3F); HRMS (FAB): MH^+, found 195.0977. $C_9H_{14}F_3O$ requires 195.0997.

*4.5. 1-Cyclohexyl-4-(trifluoromethyl)pent-4-en-2-one (**6a**)*

To a dichloromethane (45 mL) suspension of pyridinium chlorochromate (4.98 g, 23.1 mmol) and silica gel (5.02 g) was added alcohol **5a** (3.56 g, 15.1 mmol). After stirring at room temperature for 13 h, the mixture was filtered through a pad of Celite (diethyl ether). After the solvent was removed under reduced pressure, the residue was purified by column chromatography (hexane/ethyl acetate = 10/1) to give **6a** (3.21 g, 91%) as a colorless oil; [Found: C, 61.35; H, 7.49. $C_{12}H_{17}F_3O$ requires C, 61.53; H, 7.31%]; IR (neat) ν 2925, 2854, 1722, 1450, 1412, 1356, 1306, 1173, 1124, 949, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87–0.97 (m, 2H), 1.08–1.18 (m, 1H), 1.22–1.32 (m, 2H), 1.62–1.72 (m, 5H), 1.80–1.89 (m, 1H), 2.36 (d, J = 6.9 Hz, 2H). 3.25 (br s, 2H), 5.50 (q, J_{HF} = 1.2 Hz, 1H), 5.91 (q, J_{HF} = 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.0, 26.3, 33.0, 33.6, 43.5, 50.2, 122.6 (q, J_{CF} = 6 Hz), 123.1 (q, J_{CF} = 274 Hz), 131.4 (q, J_{CF} = 31 Hz), 204.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ 92.7 (br s, 3F).

*4.6. 6,6-Dimethyl-2-(trifluoromethyl)hept-1-en-4-one (**6c**)*

Compound **6c** was prepared by the method described for **6a** using alcohol **5c** (740 mg, 3.52 mmol). Purification by column chromatography (hexane/ethyl acetate = 5/1) gave **6c** (564 mg, 77%) as a colorless oil; [Found: C, 57.60; H, 7.42. $C_{10}H_{15}F_3O$ requires C, 57.68; H, 7.26%]; IR (neat) ν 2958, 2871, 1662, 1468, 1414, 1356, 1300, 1171, 1119, 949, 598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9H), 2.39 (s, 2H), 3.26 (s, 2H), 5.48 (q, J_{HF} = 1.1 Hz, 1H), 5.91 (q, J_{HF} = 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.5, 31.0, 44.9, 54.6, 122.7 (q, J_{CF} = 6 Hz), 123.1 (q, J_{CF} = 274 Hz), 131.4 (q, J_{CF} = 31 Hz), 204.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ 92.7 (br s, 3F).

*4.7. 2-(3,3,3-Trifluoroprop-1-en-2-yl)cyclohexan-1-one (**6f**)*

Compound **6f** was prepared by the method described for **6a** using alcohol **5f** (1.21 g, 6.22 mmol). Purification by column chromatography (hexane/ethyl acetate = 5/1) gave **6f** (978 mg, 82%) as a colorless oil; IR (neat) ν 2939, 2870, 1720, 1334, 1297, 1240, 1171, 1120, 945 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.69–1.84 (m, 3H), 1.93–2.03 (m, 1H), 2.12–2.19 (m, 1H), 2.20–2.27 (m, 1H), 2.38–2.46 (m, 1H), 2.48–2.54 (m, 1H), 3.28 (dd, J = 12.0, 5.0, Hz, 1H), 5.44 (br s, 1H), 5.98 (q, J_{HF} = 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.4, 27.9, 34.3, 42.2, 51.1, 121.2 (q, J_{CF} = 6 Hz), 123.4 (q, J_{CF} = 274 Hz), 135.9 (q, J_{CF} = 30 Hz), 207.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ 93.5 (br s, 3F); HRMS (EI): MH^+, found 192.0767. $C_9H_{11}F_3O$ requires 192.0762.

*4.8. 1-Cyclohexyl-3-methyl-4-(trifluoromethyl)pent-4-en-2-one (**7a**)*

To a diethyl ether (60 mL) solution of ketone **6a** (2.83 g, 12.1 mmol) was added potassium *tert*-butoxide (1.54 g, 13.7 mmol) at –78 °C. After stirring at –78 °C for 1 h, methyl trifluoromethanesulfonate (2.00 mL, 17.7 mmol) was added to the mixture. After stirring at –78 °C for 20 min, the mixture was warmed to room temperature and stirred for another 11 h. The reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with ethyl acetate three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (hexane/ethyl acetate = 10/1) to give **7a** (2.83 g, 95%) as a colorless oil; [Found: C, 62.92; H, 7.94. $C_{13}H_{19}F_3O$ requires C, 62.89; H, 7.71%]; IR (neat) ν 2927, 2854, 1720, 1450, 1306, 1284, 1174, 1124, 951 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.82–0.96 (m, 2H), 1.07–1.17 (m, 1H), 1.21–1.32 (m, 2H), 1.27 (d, J = 7.1 Hz, 3H), 1.60–1.71 (m, 5H), 1.79–1.88 (m, 1H), 2.30–2.39 (m, 2H), 3.39 (q, J = 7.1 Hz, 1H), 5.46 (br s, 1H), 5.89 (q, J_{HF} = 1.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.8, 26.00, 26.05, 26.2, 32.9, 33.1, 33.3, 45.8, 48.9, 120.2 (q, J_{CF} = 6 Hz), 123.4 (q, J_{CF} = 274 Hz), 137.7 (q, J_{CF} = 30 Hz), 208.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ 93.2 (br s, 3F).

*4.9. 3,6,6-Trimethyl-2-(trifluoromethyl)hept-1-en-4-one (**7c**)*

Compound **7c** was prepared by the method described for **7a** using ketone **6c** (1.36 g, 6.53 mmol) and methyl trifluoromethanesulfonate (1.10 mL, 9.72 mmol). Purification by column chromatography (pentane/ethyl acetate = 20/1) gave **7c** (1.25 g, 86%) as a colorless oil; [Found: C, 59.38; H, 7.72. $C_{11}H_{17}F_3O$ requires C, 59.45; H, 7.71%]; IR (neat) ν 2956, 2871, 1720, 1466, 1304, 1273, 1171, 1119, 1082, 951 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.26 (d, J = 7.0 Hz, 3H), 2.35 (d, J = 16.1 Hz, 1H), 2.40 (d, J = 16.1 Hz, 1H), 3.37 (q, J = 7.0 Hz, 1H), 5.44 (q, J_{HF} = 0.5 Hz, 1H), 5.85 (q, J_{HF} = 0.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.7, 29.5, 30.8, 46.6, 53.5, 120.2 (q, J_{CF} = 6 Hz), 123.4 (q, J_{CF} = 274 Hz), 137.9 (q, J_{CF} = 30 Hz), 207.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 93.1 (br s, 3F).

*4.10. 3-Methyl-2-(trifluoromethyl)oct-1-en-4-one (**7d**)*

To a diethyl ether (125 mL) solution of 2-bromo-3,3,3-trifluoroprop-1-ene (7.76 mL, 74.1 mmol) and $BF_3{\cdot}OEt_2$ (6.23 mL, 50.5 mmol) was added dropwise a diethyl ether (50 mL) solution of *n*-BuLi (2.64 M in hexane, 27.2 mL, 71.9 mmol) at –110 °C. After stirring at –110 °C for 15 min, a diethyl ether (25 mL) solution of 2-butyloxirane (5.00 g, 49.9 mmol) was added dropwise to the mixture. After stirring at –110 °C for 15 min, the mixture was warmed to –60 °C. After stirring at –60 °C for another 10 min, the reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with diethyl ether three times. The combined organic

extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (heptane/ethyl acetate = 5/1) to give a crude mixture (3.44 g) including 2-(trifluoromethyl)oct-1-en-4-ol (**5d**) as a pale yellow oil.

To a dichloromethane (30 mL) suspension of pyridinium chlorochromate (6.07 g, 28.2 mmol) and silica gel (6.07 g) was added the obtained crude mixture. After stirring at room temperature for 39 h, the mixture was filtered through a pad of Celite (dichloromethane). After the solvent was removed under reduced pressure, the residue was purified by column chromatography (heptane/ethyl acetate = 4/1) to give a crude mixture (2.19 g) including 2-(trifluoromethyl)oct-1-en-4-one (**6d**) as a pale yellow oil.

To a diethyl ether (46 mL) solution of the obtained crude mixture was added potassium *tert*-butoxide (1.14 g, 10.2 mmol) at –78 °C. After stirring at –78 °C for 30 min, methyl trifluoromethanesulfonate (1.62 mL, 14.3 mmol) was added to the mixture. After stirring at –78 °C for 20 min, the mixture was warmed to room temperature and stirred for another 22 h. The reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with diethyl ether three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (heptane/ethyl acetate = 10/1) to give **7d** (1.12 g, 11%) as a yellow oil; IR (neat) ν 2962, 2877, 1722, 1458, 1412, 1342, 1304, 1173, 1124, 953, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H), 1.24–1.34 (m, 2H), 1.29 (d, J = 7.2 Hz, 3H), 1.51–1.60 (m, 2H), 2.40–2.56 (m, 2H), 3.43 (q, J = 7.2 Hz, 1H), 5.47 (br s, 1H), 5.87 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 16.7, 22.1, 25.7, 40.8, 45.4, 120.1 (q, J_{CF} = 6 Hz), 123.4 (q, J_{CF} = 274 Hz), 137.9 (q, J_{CF} = 30 Hz), 208.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ 93.2 (br s, 3F); HRMS (EI): M^+, found 208.1078. $C_{10}H_{15}F_3O$ requires 208.1075.

*4.11. 1-Cyclohexyl-3,3-dimethyl-4-(trifluoromethyl)pent-4-en-2-one (**1a**)*

To a diethyl ether (37 mL) solution of ketone **7a** (1.00 g, 4.03 mmol) was added dropwise a toluene solution of potassium hexamethyldisilazide (0.50 M, 11.3 mL, 5.6 mmol) at –100 °C. After stirring at –90 °C for 30 min, methyl trifluoromethanesulfonate (0.70 mL, 6.2 mmol) was added to the mixture at –100 °C. After stirring for 10 min at –100 °C, the reaction mixture was warmed to room temperature and stirred for another 16 h. The reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with diethyl ether three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (heptane/ethyl acetate = 5/1) to give **1a** (959 mg, 91%) as a colorless liquid; [Found: C, 64.21; H, 7.98. $C_{14}H_{21}F_3O$ requires C, 64.10; H, 8.07%]; IR (neat) ν 2924, 2852, 1716, 1450, 1327, 1178, 1126, 1097, 1038, 949 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.79–0.88 (m, 2H), 1.06–1.16 (m, 1H), 1.22–1.36 (m, 2H), 1.32 (s, 6H), 1.60–1.69 (m, 5H), 1.81–1.90 (m, 1H), 2.26 (d, J = 6.7 Hz, 2H), 5.61 (q, J_{HF} = 0.6 Hz, 1H), 5.93 (q, J_{HF} = 1.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.7, 26.1, 26.2, 33.0, 33.1, 44.3, 50.5, 120.7 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 142.7 (q, J_{CF} = 28 Hz), 209.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.3 (br s, 3F).

*4.12. 3,3,6,6-Tetramethyl-2-(trifluoromethyl)hept-1-en-4-one (**1c**)*

Compound **1c** was prepared by the method described for **1a** using ketone **7c** (1.17 g, 5.26 mmol) and methyl trifluoromethanesulfonate (0.89 mL, 7.9 mmol). Purification by column chromatography (pentane/ethyl acetate = 20/1) gave **1c** (1.01 g, 81%) as a colorless liquid; [Found: C, 60.78; H, 7.91. $C_{12}H_{19}F_3O$ requires C, 61.00; H, 8.11%]; IR (neat) ν 2956, 2871, 1718, 1365, 1327, 1124, 1097, 1051, 951, 910, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.31 (s, 6H), 2.31 (s, 2H), 5.61 (br s, 1H), 5.92 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.8, 29.4, 30.3, 48.3, 51.0, 120.6 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 142.9 (q, J_{CF} = 28 Hz), 209.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.4 (br s, 3F).

*4.13. 3,3-Dimethyl-2-(trifluoromethyl)oct-1-en-4-one (**1d**)*

Compound **1d** was prepared by the method described for **1a** using ketone **7d** (895 mg, 4.30 mmol) and methyl trifluoromethanesulfonate (0.75 mL, 6.6 mmol). Purification by column chromatography (heptane/ethyl acetate = 5/1) gave **1d** (618 mg, 65%) as a pale yellow oil; IR (neat) ν 2962, 2875, 1716, 1466, 1410, 1327, 1178, 1130, 1101, 914, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3H), 1.24–1.31 (m, 2H), 1.33 (s, 6H) 1.49–1.56 (m, 2H), 2.40 (t, J = 7.4 Hz, 2H), 5.62 (br s, 1H), 5.94 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.2, 23.8, 26.0, 36.4, 50.5, 120.6 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 142.7 (q, J_{CF} = 28 Hz), 210.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.1 (br s, 3F); HRMS (EI): M^+, found 222.1228. $C_{11}H_{17}F_3O$ requires 222.1231.

*4.14. 2-Methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)cyclohexan-1-one (**1f**)*

Compound **1f** was prepared by the method described for **1a** using ketone **6f** (986 mg, 5.13 mmol) and methyl trifluoromethanesulfonate (0.87 mL, 7.7 mmol). Purification by column chromatography (hexane/ethyl acetate = 5/1) gave **1f** (535 mg, 51%) as a colorless oil; [Found: C, 58.20; H, 6.49. $C_{10}H_{13}F_3O$ requires C, 58.25; H, 6.35%]; IR (neat) ν 2945, 2871, 1716, 1319, 1174, 1124, 957, 912, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.59–1.66 (m, 1H), 1.69–1.77 (m, 1H), 1.77–1.86 (m, 2H), 1.91–2.00 (m, 1H), 2.32–2.38 (m, 1H), 2.39–2.45 (m, 1H), 2.49–2.56 (m, 1H), 5.58 (q, J_{HF} = 1.1 Hz, 1H), 5.95 (q, J_{HF} = 1.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 24.3, 27.6, 38.2, 39.4, 52.6, 121.1 (q, J_{CF} = 6 Hz), 121.5 (q, J_{CF} = 275 Hz), 141.0 (q, J_{CF} = 28 Hz), 211.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ 101.2 (br s, 3F).

*4.15. 3,3-Dimethyl-6-phenyl-2-(trifluoromethyl)hept-1-en-4-one (**1b**)*

To a DMF (7.5 mL) suspension of 3-phenylbutanal (1.00 g, 6.74 mmol), cesium fluoride (249 mg, 1.64 mmol), and molecular sieves 4A (220 mg) was added a DMF (7.5 mL) solution of trimethyl[(trifluoromethyl)allyl]silane (1.31 g, 7.19 mmol). After stirring at room temperature for 26 h, the reaction was quenched with an aqueous HCl solution (1 M). The organic materials were extracted with diethyl ether three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (heptane/ethyl acetate = 3/1) to give a crude mixture (594 mg) including 6-phenyl-2-(trifluoromethyl)hept-1-en-4-ol (**5b**) as a pale yellow oil.

To a dichloromethane (6.9 mL) solution of the obtained crude mixture were added pyridinium chlorochromate (756 mg, 3.51 mmol) and silica gel (756 mg). After stirring at room temperature for 19 h, the mixture was filtered through a pad of Celite (dichloromethane). After the solvent was removed under reduced

pressure, the residue was purified by column chromatography (pentane/diethyl ether = 6/1) to give a crude mixture (548 mg) including 6-phenyl-2-(trifluoromethyl)hept-1-en-4-one (**6b**) as a pale yellow oil.

To a diethyl ether (12 mL) solution of the obtained crude mixture was added potassium *tert*-butoxide (264 mg, 2.35 mmol) at –78 °C. After stirring at –78 °C for 1 h, methyl trifluoromethanesulfonate (0.37 mL, 3.3 mmol) was added to the mixture. After stirring at –78 °C for 20 min, the mixture was warmed to room temperature and stirred for another 23 h. The reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with diethyl ether three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (heptane/ethyl acetate = 6/1) to give a crude mixture (552 mg) including 3-methyl-6-phenyl-2-(trifluoromethyl)hept-1-en-4-one (**7b**) as a pale yellow oil.

To a diethyl ether (14 mL) solution of the obtained crude mixture was added dropwise a toluene solution of potassium hexamethyldisilazide (0.50 M, 3.16 mL, 1.6 mmol) at –100 °C. After stirring at –100 °C for 30 min, methyl trifluoromethanesulfonate (0.18 mL, 1.6 mmol) was added to the mixture at –100 °C. After stirring for 10 min at –100 °C, the reaction mixture was warmed to room temperature and stirred for another 14 h. The reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with diethyl ether three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by preparative thin-layer chromatography (heptane/ethyl acetate = 8/1) to give **1b** (352 mg, 18%) as a pale yellow oil; [Found: C, 67.51; H, 6.77. $C_{16}H_{19}F_3O$ requires C, 67.59; H, 6.74%]; IR (neat) ν 2972, 1716, 1454, 1327, 1173, 1113, 953, 760, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.23 (d, J = 7.2 Hz, 3H), 1.28 (s, 3H), 2.61 (dd, J = 17.6, 7.6 Hz, 1H), 2.71 (dd, J = 17.6, 6.4 Hz, 1H), 3.31–3.40 (m, 1H), 5.48 (q, J_{HF} = 0.8 Hz, 1H), 5.88 (q, J_{HF} = 0.8 Hz, 1H), 7.16–7.20 (m, 3H), 7.26–7.30 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 23.4, 23.6, 34.8, 45.6, 50.4, 120.9 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 277 Hz), 126.2, 126.9, 128.4, 142.3 (q, J_{CF} = 27 Hz), 146.4, 208.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.3 (br s, 3F).

*4.16. 3-Phenyl-1-[1-(3,3,3-trifluoroprop-1-en-2-yl)cyclopentyl]propan-1-one (**1h**)*

To a diethyl ether (8.3 mL) solution of ketone **6e** (391 mg, 1.61 mmol) was dropwise added a toluene solution of potassium hexamethyldisilazide (0.50 M, 3.40 mL, 1.7 mmol) at –78 °C. After strirring at 0 °C for 10 min, the mixture was added to a diethyl ether (8.3 mL) solution of 1,4-diiodobutane (0.43 mL, 3.3 mmol) and hexamethylphosphoramide (2.7 mL) at –78 °C. The mixture was warmed to room temperature. After stirring for 7 h, the reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with ethyl acetate three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (hexane/ethyl acetate = 10/1) to give a crude mixture (372 mg) including 8-iodo-1-phenyl-4-(3,3,3-trifluoroprop-1-en-2-yl)octan-3-one as a colorless oil.

To a diethyl ether (3.1 mL) solution of the obtained crude mixture was added dropwise a toluene solution of potassium hexamethyldisilazide (0.50 M, 1.30 mL, 0.65 mmol) at –78 °C. After stirring at –78 °C for 5 min, the mixture was warmed to room temperature and stirred for another 4 h. The reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with ethyl acetate three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (hexane/ethyl acetate = 10/1) to give **1h** (257 mg, 54%) as a colorless oil; [Found: C, 69.05; H, 6.46. $C_{17}H_{19}F_3O$ requires C, 68.90; H, 6.46%]; IR (neat) ν 2960, 1712, 1454, 1323, 1167, 1120, 748, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.49–1.58 (m, 2H), 1.59–1.67 (m, 2H), 1.68–1.76 (m, 2H), 2.12–2.18 (m, 2H), 2.70 (t, J = 7.8 Hz, 2H), 2.86 (t, J = 7.8 Hz, 2H), 5.59 (q, J_{HF} = 1.0 Hz, 1H), 5.89 (q, J_{HF} = 1.0 Hz, 1H), 7.14–7.18 (m, 2H), 7.18–7.21 (m, 1H), 7.24–7.29 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.2, 30.3, 33.2, 38.9, 62.5, 120.7 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 276 Hz), 126.1, 128.39, 128.43, 140.9 (q, J_{CF} = 28 Hz), 141.1, 207.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ 99.4 (br s, 3F).

*4.17. 2-Cyclohexyl-1-[1-(3,3,3-trifluoroprop-1-en-2-yl)cyclopentyl]ethan-1-one (**1g**)*

Compound **1g** was prepared by the method described for **1h** using ketone **6a** (500 mg, 2.13 mmol) and 1,4-diiodobutane (0.57 mL, 4.3 mmol). Purification by column chromatography (heptane/ethyl acetate = 20/1) gave **1g** (456 mg, 74%) as a colorless liquid; [Found: C, 66.65; H, 7.99. $C_{16}H_{23}F_3O$ requires C, 66.65; H, 8.04%]; IR (neat) ν 2924, 2852, 1448, 1410, 1323, 1167, 1120, 945, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78–0.88 (m, 2H), 1.05–1.16 (m, 1H), 1.21–1.32 (m, 2H), 1.57–1.78 (m, 11H), 1.79–1.90 (m, 1H), 2.18–2.22 (m, 2H), 2.26 (d, J = 6.4 Hz, 2H), 5.64 (q, J_{HF} = 1.2 Hz, 1H), 5.92 (q, J_{HF} = 0.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.3, 26.1, 26.3, 33.0, 33.1, 33.2, 44.5, 62.6, 120.6 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 141.2 (q, J_{CF} = 28 Hz), 207.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 99.7 (br s, 3F).

*4.18. 2-Cyclohexyl-1-[1-(3,3,3-trifluoroprop-1-en-2-yl)cyclohexyl]ethan-1-one (**1i**)*

Compound **1i** was prepared by the method described for **1h** using ketone **6a** (500 mg, 2.13 mmol) and 1,5-diiodopentane (0.63 mL, 4.3 mmol). Purification by column chromatography (heptane/ethyl acetate = 20/1) gave **1i** (548 mg, 85%) as a pale yellow oil; [Found: C, 67.42; H, 8.27. $C_{17}H_{25}F_3O$ requires C, 67.53; H, 8.33%]; IR (neat) ν 2924, 2854, 1714, 1448, 1317, 1282, 1161, 1120, 951, 901, 741, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77–0.87 (m, 2H), 1.06–1.15 (m, 1H), 1.19–1.32 (m, 2H), 1.39–1.45 (m, 2H), 1.49–1.55 (m, 4H), 1.61–1.67 (m, 5H), 1.75–1.89 (m, 3H), 1.93–2.00 (m, 2H), 2.23 (d, J = 6.4 Hz, 2H), 5.64 (q, J_{HF} = 1.2 Hz, 1H), 6.08 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.2, 25.7, 26.1, 26.3, 31.6, 32.9, 33.1, 44.3, 54.8, 123.0 (q, J_{CF} = 6 Hz), 123.7 (q, J_{CF} = 277 Hz), 140.3 (q, J_{CF} = 27 Hz), 209.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.0 (br s, 3F).

*4.19. 3-Phenyl-1-[1-(3,3,3-trifluoroprop-1-en-2-yl)cyclohexyl]butan-1-one (**1j**)*

Compound **1j** was prepared by the method described for **1h** using ketone **6b** (410 mg, 1.60 mmol) and 1,5-diiodopentane (0.48 mL, 3.2 mmol). Purification by column chromatography (heptane/ethyl acetate = 10/1) gave **1j** (392 mg, 76%) as a pale yellow oil; IR (neat) ν 2866, 1712, 1454, 1317, 1161, 1122, 760, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.8 Hz, 3H), 1.30–1.54 (m, 6H), 1.66–1.87 (m, 3H), 1.96–2.02 (m, 1H), 2.59 (dd, J = 17.8, 7.8 Hz, 1H), 2.69 (dd, J = 17.8, 6.2 Hz, 1H), 3.35 (dqd, J = 7.8, 6.8, 6.2 Hz, 1H), 5.47 (q, J_{HF} = 1.6 Hz, 1H), 5.98 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 22.1, 22.2, 25.6, 31.3, 31.7, 34.6, 45.6, 54.7, 123.2 (q, J_{CF} = 6 Hz), 123.6 (q,

J_{CF} = 277 Hz), 126.2, 127.0, 128.4, 139.9 (q, J_{CF} = 27 Hz), 146.5, 208.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.0 (br s, 3F); HRMS (EI): M^+, found 324.1710. $C_{19}H_{23}F_3O$ requires 324.1701.

*4.20. N-[3,3-Dimethyl-2-(trifluoromethyl)oct-1-en-4-ylidene]-4-methylbenzenesulfonamide (**2d**)*

To a 1,2-dichloroethane (15 mL) solution of ketone **1d** (335 mg, 1.51 mmol) and 4-methylbenzenesulfonamide (313 mg, 1.83 mmol) was added triethylamine (0.32 mL, 2.3 mmol) at 0 °C. After stirring at 0 °C for 5 min, $TiCl_4$ (0.33 mL, 3.0 mmol) was added dropwise to the mixture at 0 °C. After the mixture was refluxed for 36 h, the reaction was quenched with phosphate buffer (pH 7) at room temperature. The reaction mixture was filtered through a pad of Celite. The organic materials were extracted with dichloromethane three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (pentane/diethyl ether = 5/1) to give **2d** (210 mg, 37%) as a colorless crystal; IR (neat) ν 2960, 2918, 1616, 1321, 1157, 1124, 1090, 908, 731, 667, 559 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.36 (s, 6H), 1.39–1.48 (m, 2H), 1.71–1.78 (m, 2H), 2.43 (s, 3H), 2.77–2.81 (m, 2H), 5.59 (br s, 1H), 5.92 (br s, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.5, 21.6, 23.6, 25.1, 31.2, 33.6, 49.7, 121.2 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 277 Hz), 126.9, 129.3, 138.4, 142.7 (q, J_{CF} = 28 Hz), 143.4, 192.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.6 (br s, 3F); HRMS (ESI+): MNa^+, found 398.1377. $C_{18}H_{24}F_3NNaO_2S$ requires 398.1378.

*4.21. N-[1-Cyclohexyl-3,3-dimethyl-4-(trifluoromethyl)pent-4-en-2-ylidene]-4-methylbenzenesulfonamide (**2a**)*

Compound **2a** was prepared by the method described for **2d** using ketone **1a** (303 mg, 1.15 mmol) and 4-methylbenzenesulfonamide (237 mg, 1.38 mmol). Purification by column chromatography (hexane/ethyl acetate = 10/1) gave **2a** (81 mg, 17%) as a colorless crystal; IR (neat) ν 2929, 2854, 1616, 1321, 1157, 1126, 1090, 814, 739, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01–1.11 (m, 1H), 1.11–1.19 (m, 1H), 1.24–1.32 (m, 2H), 1.36 (s, 6H), 1.62–1.68 (m, 1H), 1.70–1.79 (m, 5H), 2.08–2.18 (m, 1H), 2.43 (s, 3H), 2.74 (d, J = 7.5 Hz, 2H), 5.56 (br s, 1H), 5.87 (br s, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 25.4, 26.0, 26.4, 33.7, 38.0, 41.4, 49.6, 121.0 (q, J_{CF} = 6 Hz), 123.6 (q, J_{CF} = 277 Hz), 126.9, 129.3, 138.6, 143.19 (q, J_{CF} = 27 Hz), 143.21, 192.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ 101.1 (br s, 3F); HRMS (ESI+): MNa^+, found 438.1700. $C_{21}H_{29}F_3NNaO_2S$ requires 438.1691.

*4.22. N-[4,4-Dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-ylidene]-4-methylbenzenesulfonamide (**2e**)*

Compound **2e** was prepared by the method described for **2d** using ketone **1e** (620 mg, 2.29 mmol) and 4-methylbenzenesulfonamide (392 mg, 2.29 mmol). Purification by column chromatography (hexane/ethyl acetate = 5/1) gave **2e** (534 mg, 55%) as a colorless oil; [Found: C, 62.53; H, 5.83; N, 3.25. $C_{22}H_{24}F_3NO_2S$ requires C, 62.39; H, 5.71; N, 3.31%]; IR (neat) ν 2985, 2946, 1770, 1616, 1456, 1412, 1321, 1240, 1157, 1126, 1090, 816, 741, 675, 552 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 6H), 2.44 (s, 3H), 3.09 (s, 4H), 5.61 (q, J_{HF} = 1.2 Hz, 1H), 5.95 (q, J_{HF} = 1.1 Hz, 1H), 7.20–7.33 (m, 7H), 7.87 (d, J = 8.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 25.0, 35.0, 36.0, 49.8, 121.5 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 277 Hz), 126.5, 127.0, 128.3, 128.6, 129.4, 138.2, 140.5, 142.5 (q, J_{CF} = 28 Hz), 143.6, 191.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.7 (br s, 3F).

*4.23. 4-Methyl-N-[2-Methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)cyclohexylidene]benzenesulfonamide (**2f**)*

Compound **2f** was prepared by the method described for **2d** using ketone **1f** (414 mg, 2.01 mmol) and 4-methylbenzenesulfonamide (344 mg, 2.01 mmol). Purification by column chromatography (hexane/ethyl acetate = 5/1) gave a 1:1 mixture of **2f** and its enamine form (587 mg, 81%) as a white solid; [(1:1 mixture) Found: C, 56.48; H, 5.60; N, 3.70. $C_{17}H_{20}F_3NO_2S$ requires C, 56.81; H, 5.61; N, 3.90%]; IR (neat) ν (1:1 mixture) 3290, 2939, 1622, 1408, 1323, 1157, 1128, 1090, 814, 739, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (1:1 mixture) 1.08 (q, J_{HF} = 1.6 Hz, 1.5H), 1.30 (s, 1.5H), 1.32–1.41 (m, 0.5H), 1.42–1.47 (m, 0.5H), 1.47–1.55 (m, 0.5H), 1.62–1.89 (m, 2.5H), 1.95–2.02 (m, 0.5H), 2.02–2.06 (m, 1H), 2.36–2.42 (m, 0.5H), 2.436 (s, 1.5H), 2.442 (s, 1.5H), 2.79 (ddd, J = 14.2, 10.6, 5.0 Hz, 0.5H), 3.43 (ddd, J = 14.2, 5.6, 4.0 Hz, 0.5H), 5.32 (q, J_{HF} = 1.9 Hz, 0.5H), 5.46 (br s, 0.5H), 5.52–5.53 (m, 0.5H), 5.83 (dd, J = 4.2, 4.2 Hz, 0.5H), 5.85 (q, J_{HF} = 1.2 Hz, 0.5H), 5.92–5.93 (m, 0.5H), 7.29–7.31 (m, 1H), 7.31–7.33 (m, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (1:1 mixture) 17.2, 21.4, 21.6, 23.0, 24.1, 26.2, 27.9, 33.7, 36.7, 39.0, 42.0, 50.5, 113.9, 121.6 (q, J_{CF} = 13 Hz), 123.3 (q, J_{CF} = 14 Hz), 123.6 (q, J_{CF} = 277 Hz), 123.8 (q, J_{CF} = 277 Hz), 126.9, 127.5, 129.3, 129.5, 134.3, 136.6, 138.5, 140.7 (q, J_{CF} = 26 Hz), 142.3 (q, J_{CF} = 27 Hz), 143.4, 143.9, 193.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ (1:1 mixture) 101.0 (br s, 1.5F), 101.4 (br s, 1.5F).

*4.24. 4-Methyl-N-{3-phenyl-1-[1-(3,3,3-trifluoroprop-1-en-2-yl)cyclopentyl]propylidene}benzenesulfonamide (**2h**)*

Compound **2h** was prepared by the method described for **2d** using ketone **1h** (500 mg, 1.69 mmol) and 4-methylbenzenesulfonamide (289 mg, 1.69 mmol). Purification by column chromatography (hexane/ethyl acetate = 5/1) gave **2h** (232 mg, 31%) as a colorless crystal; IR (neat) ν 2960, 1616, 1456, 1319, 1159, 1128, 1092, 912, 814, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55–1.69 (m, 4H), 1.77–1.85 (m, 2H), 2.18–2.24 (m, 2H), 2.45 (s, 3H), 3.02–3.11 (m, 4H), 5.68 (br s, 1H), 6.01 (br s, 1H), 7.20–7.24 (m, 1H), 7.28–7.31 (m, 4H), 7.33 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 22.6, 34.3, 35.0, 36.1, 61.8, 121.9 (q, J_{CF} = 6 Hz), 123.5 (q, J_{CF} = 277 Hz), 126.5, 127.0, 128.3, 128.6, 129.4, 138.2, 140.60 (q, J_{CF} = 28 Hz), 140.63, 143.6, 188.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.0 (br s, 3F); HRMS (ESI+): MNa^+, found 472.1538. $C_{24}H_{26}F_3NNaO_2S$ requires 472.1534.

*4.25. (Z)-2-(Cyclohexylmethylene)-4-(difluoromethylene)-3,3-dimethyltetrahydrofuran (**3a**)*

To a DMF (1.7 mL) solution of ketone **1a** (44 mg, 0.17 mmol) was added a toluene solution of KHMDS (0.50 M, 0.33 mL, 0.17 mmol) at 0 °C. After stirring at 110 °C for 1 h, the reaction was quenched with phosphate buffer (pH 7) at room temperature. The organic materials were extracted with diethyl ether three times. The combined organic extracts were washed with water and brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (pentane/diethyl ether = 10/1) to give **3a** (21 mg, 53%) as a colorless oil; [Found: C, 69.37; H, 8.34. $C_{14}H_{20}F_2O$ requires C, 69.40; H, 8.32%]; IR (neat) ν 2924, 2850, 1772, 1689, 1448, 1271, 1244, 1057, 1016, 928, 889, 789, 594, 540 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95–1.08 (m, 2H), 1.10–1.20 (m, 1H), 1.22–1.36 (m, 2H), 1.32 (s, 6H), 1.59–1.73 (m, 5H), 2.25–2.35 (m, 1H), 4.07 (d, J = 8.5 Hz, 1H), 4.61 (dd, J_{HF} = 3.0, 3.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.1, 26.2, 27.3, 33.8, 34.3, 41.0, 66.0 (d, J_{CF} = 4 Hz), 96.0 (dd, J_{CF} = 19, 19 Hz), 101.8,

149.0 (dd, J_{CF} = 287, 284 Hz), 161.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 68.1 (d, J_{FF} = 63 Hz, 1F), 76.2 (d, J_{FF} = 63 Hz, 1F).

*4.26. (Z)-4-(Difluoromethylene)-3,3-dimethyl-2-(2-phenylpropylidene)tetrahydrofuran (**3b**)*

Tetrahydrofuran **3b** was synthesized by the method described for **3a** using ketone **1b** (52 mg, 0.18 mmol). Purification by preparative thin-layer chromatography (heptane/ethyl acetate = 15/1) gave **3b** (14 mg, 29%) as a colorless oil; [Found: C, 72.60; H, 6.97. $C_{16}H_{18}F_2O$ requires C, 72.71; H, 6.86%]; IR (neat) ν 2968, 2873, 1772, 1689, 1456, 1375, 1257, 1230, 1045, 1007, 758, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 6.8 Hz, 3H), 1.32 (s, 3H), 1.37 (s, 3H), 3.84 (dq, J = 9.2, 6.8 Hz, 1H), 4.39 (d, J = 9.2 Hz, 1H), 4.61 (ddd, J = 12.2 Hz, J_{HF} = 3.4, 3.4 Hz, 1H), 4.65 (ddd, J = 12.2 Hz, J_{HF} = 3.4, 3.4 Hz, 1H), 7.14–7.18 (m, 1H), 7.22–7.30 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.7, 27.1, 27.2, 35.1, 41.3 (dd, J_{CF} = 3, 3 Hz), 66.2 (d, J_{CF} = 4 Hz), 95.9 (dd, J_{CF} = 19, 19 Hz), 100.9, 125.6, 126.8, 128.2, 147.5, 149.0 (dd, J_{CF} = 287, 284 Hz), 162.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ 68.3 (d, J_{FF} = 63 Hz, 1F), 76.4 (d, J_{FF} = 63 Hz, 1F).

*4.27. (Z)-4-(Difluoromethylene)-2-(2,2-dimethylpropylidene)-3,3-dimethyltetrahydrofuran (**3c**)*

Tetrahydrofuran **3c** was synthesized by the method described for **3a** using ketone **1c** (82 mg, 0.35 mmol). Purification by column chromatography (pentane/diethyl ether = 10/1) gave **3c** (46 mg, 61%) as a colorless oil; [Found: C, 66.67; H, 8.27. $C_{12}H_{18}F_2O$ requires C, 66.64; H, 8.39%]; IR (neat) ν 2954, 2868, 1772, 1684, 1458, 1362, 1284, 1242, 1081, 1041, 1012, 951, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.30 (s, 6H), 4.12 (s, 1H), 4.60 (dd, J_{HF} = 3.4, 3.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.5, 30.6, 30.8, 42.0, 66.1 (d, J_{CF} = 5 Hz), 95.7 (dd, J_{CF} = 20, 19 Hz), 105.7, 149.0 (dd, J_{CF} = 287, 283 Hz), 161.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ 68.5 (d, J_{FF} = 65 Hz, 1F), 76.7 (d, J_{FF} = 65 Hz, 1F).

*4.28. (Z)-1-(Cyclohexylmethylene)-4-(difluoromethylene)-2-oxaspiro[4.4]nonane (**3g**)*

Tetrahydrofuran **3g** was synthesized by the method described for **3a** using ketone **1g** (106 mg, 0.37 mmol). Purification by column chromatography (heptane/ethyl acetate = 100/1) gave **3g** (43 mg, 43%) as a colorless oil; [Found: C, 71.70; H, 8.29. $C_{16}H_{22}F_2O$ requires C, 71.61; H, 8.26%]; IR (neat) ν 2922, 2850, 1770, 1684, 1448, 1373, 1259, 1234, 1207, 1092, 1034, 947, 889, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96–1.05 (m, 2H), 1.11–1.20 (m, 1H), 1.25–1.35 (m, 2H), 1.60–1.78 (m, 9H), 1.81–1.88 (m, 2H), 1.94–2.01 (m, 2H), 2.27–2.35 (m, 1H), 4.08 (d, J = 8.8 Hz, 1H), 4.60 (dd, J_{HF} = 3.4, 3.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.9, 26.1, 26.2, 33.8, 34.4, 40.0 (d, J_{CF} = 2 Hz), 50.9 (dd, J_{CF} = 3, 3 Hz), 66.5 (d, J_{CF} = 4 Hz), 96.9 (dd, J_{CF} = 19, 19 Hz), 102.1, 148.8 (dd, J_{CF} = 286, 283 Hz), 162.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ 68.4 (d, J_{FF} = 64 Hz, 1F), 75.4 (d, J_{FF} = 64 Hz, 1F).

*4.29. (Z)-1-(Cyclohexylmethylene)-4-(difluoromethylene)-2-oxaspiro[4.5]decane (**3i**)*

Tetrahydrofuran **3i** was synthesized by the method described for **3a** using ketone **1i** (103 mg, 0.34 mmol). Purification by column chromatography (heptane/ethyl acetate = 100/1) gave **3i** (63 mg, 66%) as a colorless oil; [Found: C, 72.41; H, 8.45. $C_{17}H_{24}F_2O$ requires C, 72.31; H, 8.57%]; IR (neat) ν 2922, 2850, 1765, 1684, 1448, 1255, 1080, 1038, 997, 887, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99–1.12 (m, 2H), 1.14–1.21 (m, 1H), 1.26–1.32 (m, 2H), 1.34–1.54 (m, 1H), 1.57–1.78 (m, 14H), 2.30–2.38 (m, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.54 (dd, J_{HF} = 3.2, 3.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.06, 22.08, 25.1, 26.1, 26.3, 33.9, 34.1, 34.6, 44.5 (dd, J_{CF} = 3, 3 Hz), 65.9 (d, J_{CF} = 4 Hz), 96.2 (dd, J_{CF} = 20, 17 Hz), 105.6, 149.2 (dd, J_{CF} = 288, 282 Hz), 160.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ 71.1 (d, J_{FF} = 64 Hz, 1F), 77.0 (d, J_{FF} = 64 Hz, 1F).

*4.30. (Z)-4-(Difluoromethylene)-1-(2-phenylpropylidene)-2-oxaspiro[4.5]decane (**3j**)*

Tetrahydrofuran **3j** was synthesized by the method described for **3a** using ketone **1j** (104 mg, 0.32 mmol). Purification by preparative thin-layer chromatography (heptane/ethyl acetate = 15/1) gave **3j** (69 mg, 71%) as a pale yellow oil; [Found: C, 74.94; H, 7.37. $C_{19}H_{22}F_2O$ requires C, 74.97; H, 7.29%]; IR (neat) ν 2929, 2871, 1765, 1684, 1450, 1250, 1076, 997, 879, 758, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, J = 6.8 Hz, 3H), 1.36–1.81 (m, 10H), 3.89 (dq, J = 9.1, 6.8 Hz, 1H), 4.54 (ddd, J = 12.0 Hz, J_{HF} = 3.2, 3.2 Hz, 1H), 4.58 (ddd, J = 12.0 Hz, J_{HF} = 3.2, 3.2 Hz, 1H), 4.69 (d, J = 9.1 Hz, 1H), 7.14–7.19 (m, 1H), 7.26–7.33 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.10, 22.10, 22.9, 25.1, 33.98, 34.04, 35.5, 44.7, 66.0 (d, J_{CF} = 4 Hz), 96.1 (dd, J_{CF} = 19, 17 Hz), 104.6, 125.6, 126.8, 128.2, 147.6, 149.2 (dd, J_{CF} = 289, 282 Hz), 160.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ 71.4 (d, J_{FF} = 63 Hz, 1F), 77.3 (d, J_{FF} = 63 Hz, 1F).

*4.31. 2-(Cyclohexylmethylene)-4-(difluoromethylene)-3,3-dimethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (**4a**)*

To a DMF (2.1 mL) solution of imine **2a** (43 mg, 0.10 mmol) in was added LDA (1.0 M in THF, 0.10 mL, 0.10 mmol) at 0 °C. After stirring at 110 °C for 2 h, the reaction was quenched with phosphate buffer (pH 7) at 0 °C. The organic materials were extracted with diethyl ether three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by preparative thin-layer chromatography (pentane/diethyl ether = 10/1) to give **4a** (29 mg, 71%, *E*/*Z* = 32/68) as a white solid; IR (neat) ν 2925, 2850, 1768, 1448, 1360, 1277, 1240, 1163, 1043, 895, 843, 814, 717, 665, 582, 544 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (major) 0.95–1.05 (m, 2H), 0.99 (s, 6H), 1.12–1.22 (m, 1H), 1.25–1.34 (m, 2H), 1.63–1.73 (m, 3H), 1.75–1.81 (m, 2H), 2.43 (s, 3H), 2.67–2.75 (m, 1H), 4.19 (dd, J_{HF} = 3.2, 3.2 Hz, 2H), 4.95 (d, J = 10.2 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H); δ (minor) 1.05 (s, 6H), 1.12–1.29 (m, 5H), 1.57–1.78 (m, 5H), 2.22–2.31 (m, 1H), 2.42 (s, 3H), 4.35 (dd, J_{HF} = 3.4, 3.4 Hz, 2H), 5.67 (d, J = 11.4 Hz, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (major) 21.5, 25.7, 26.1, 27.1, 32.9, 33.5, 37.3, 48.2, 94.0 (dd, J_{CF} = 19, 19 Hz), 120.6, 127.6, 129.5, 136.5, 142.7, 143.9, 149.6 (dd, J_{CF} = 290, 281 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (major) 69.1 (d, J_{FF} = 61 Hz, 1F), 76.2 (d, J_{FF} = 61 Hz, 1F); δ (minor) 70.2 (d, J_{FF} = 60 Hz, 1F), 76.5 (d, J_{FF} = 60 Hz, 1F); HRMS (ESI+): MNa^+, found 418.1635. $C_{21}H_{27}F_2NNaO_2S$ requires 418.1628.

*4.32. 2-Butylidene-4-(difluoromethylene)-3,3-dimethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (**4d**)*

Pyrrolidine **4d** was synthesized by the method described for **4a** using imine **2d** (47 mg, 0.13 mmol). Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) gave **4d** (38 mg, 84%, *E*/*Z* = 23/77) as a white solid; IR (neat) ν 2929, 2873, 1770, 1730, 1464, 1334, 1290, 1252, 1163, 1090, 1045, 814, 667, 544 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (major) 0.92 (t, J = 7.1 Hz, 3H), 1.04 (s, 6H), 1.37–1.45 (m, 2H), 2.31–2.37 (m, 2H), 2.43 (s, 3H), 4.18 (dd, J_{HF} = 3.2, 3.2 Hz, 2H), 5.14 (t, J = 7.0 Hz, 1H), 7.30 (d, J = 7.9 Hz, 2H), 7.73 (d, J = 7.9 Hz, 2H); δ (minor) 0.93 (t, J = 7.1 Hz, 3H), 1.09 (s, 6H), 1.37–

1.45 (m, 2H), 2.08–2.14 (m, 2H), 2.44 (s, 3H), 4.34 (dd, J_{HF} = 3.4, 3.4 Hz, 2H), 5.77 (t, J = 8.0 Hz, 1H), 7.28–7.30 (m, 2H), 7.68 (d, J = 8.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (major) 13.9, 21.5, 22.3, 24.0, 26.0, 36.6, 48.3 (d, J_{CF} = 3 Hz), 90.9 (d, J_{CF} = 14 Hz), 127.2, 129.8, 136.1, 143.8, 157.5 (dd, J_{CF} = 280, 280 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (major) 69.3 (d, J_{FF} = 61 Hz, 1F), 76.3 (d, J_{FF} = 61 Hz, 1F); δ (minor) 70.1 (d, J_{FF} = 60 Hz, 1F), 76.5 (d, J_{FF} = 60 Hz, 1F); HRMS (ESI+): MNa^+, found 378.1320. $C_{18}H_{23}F_2NNaO_2S$ requires 378.1315.

*4.33. 4-(Difluoromethylene)-3,3-dimethyl-2-(2-phenylethylidene)-1-(4-methylbenzenesulfonyl)pyrrolidine (**4e**)*

Pyrrolidine **4e** was synthesized by the method described for **4a** using imine **2e** (41 mg, 0.097 mmol). Purification by preparative thin-layer chromatography (pentane/diethyl ether = 5/1) gave **4e** (30 mg, 76%, *E*/*Z* = 24/76) as a white solid; [Found: C, 65.53; H, 5.96; N, 3.28. $C_{22}H_{23}F_2NO_2S$ requires C, 65.49; H, 5.75; N, 3.47%]; IR (neat) ν 2979, 2927, 1728, 1714, 1454, 1331, 1290, 1252, 1161, 1090, 1057, 814, 700, 667, 552 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (major) 1.07 (s, 6H), 2.43 (s, 3H), 3.74 (d, J = 6.9 Hz, 2H), 4.23 (dd, J_{HF} = 3.2, 3.2 Hz, 2H), 5.34 (t, J = 6.9 Hz, 1H), 7.19–7.22 (m, 3H), 7.29–7.36 (m, 4H), 7.76 (d, J = 8.3 Hz, 2H); δ (minor) 1.21 (s, 6H), 2.42 (s, 3H), 3.50 (d, J = 8.3 Hz, 2H), 4.40 (dd, J_{HF} = 3.3, 3.3 Hz, 2H), 5.92 (t, J = 8.3 Hz, 1H), 7.12 (d, J = 7.4 Hz, 2H), 7.19–7.22 (m, 3H), 7.29–7.36 (m, 2H), 7.59 (d, J = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (major) 21.6, 27.0, 35.5, 43.3 (dd, J_{CF} = 3, 3 Hz), 48.2 (d, J_{CF} = 5 Hz), 93.8 (dd, J_{CF} = 22, 19 Hz), 118.3, 126.0, 127.8, 128.42, 128.42, 129.7, 136.1, 141.2, 144.3, 145.4, 149.8 (dd, J_{CF} = 288, 284 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (major) 69.6 (d, J_{FF} = 60 Hz, 1F), 76.6 (d, J_{FF} = 60 Hz, 1F); δ (minor) 70.7 (d, J_{FF} = 60 Hz, 1F), 76.9 (d, J_{FF} = 60 Hz, 1F).

*4.34. 3-(Difluoromethylene)-3a-methyl-1-(4-methylbenzenesulfonyl)-2,3,3a,4,5,6-hexahydro-1H-indole (**4f**)*

Pyrrolidine **4f** was synthesized by the method described for **4a** using a mixture of imine **2f** and its enamine form (60 mg, 0.17 mmol). Purification by preparative thin-layer chromatography (pentane/diethyl ether = 10/1) gave **4f** (52 mg, 93%) as a white solid; IR (neat) ν 2941, 1776, 1682, 1599, 1454, 1362, 1282, 1165, 1092, 814, 669, 544 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60 (s, 3H), 1.50–1.59 (m, 2H), 1.68–1.70 (m, 1H), 1.93–1.95 (m, 1H), 2.09–2.17 (m, 2H), 2.41 (s, 3H), 4.05 (ddd, J = 13.2, 4.7, 3.3 Hz, 1H), 4.20 (dd, J = 13.2, 3.0 Hz, 1H), 5.70 (t, J = 3.8 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.2, 21.5, 23.1, 23.5 (d, J_{CF} = 2 Hz), 31.6 (d, J_{CF} = 4 Hz), 40.5 (dd, J_{CF} = 3, 3 Hz), 46.5 (d, J_{CF} = 5 Hz), 92.4 (dd, J_{CF} = 23, 18 Hz), 107.9, 127.2, 129.5, 134.6, 141.0, 144.0, 149.9 (dd, J_{CF} = 287, 286 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ 70.5 (dt, J = 60, 4 Hz, 1F), 75.6 (d, J = 60 Hz, 1F); HRMS (ESI+): MNa^+, found 362.1006. $C_{17}H_{19}F_2NNaO_2S$ requires 362.1002.

*4.35. 4-(Difluoromethylene)-2-(2-phenylethylidene)-2-(4-methylbenzenesulfonyl)-2-azaspiro[4.4]nonane (**4h**)*

Pyrrolidine **4h** was synthesized by the method described for **4a** using imine **2h** (80 mg, 0.18 mmol). Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) gave **4h** (65 mg, 85%, *E*/*Z* = 18/82) as a white solid; IR (neat) ν 2958, 2877, 1766, 1599, 1452, 1360, 1165, 1090, 814, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (major) 1.59–1.69 (m, 8H), 2.43 (s, 3H), 3.76 (d, J = 6.8 Hz, 2H), 4.20 (br s, 2H), 5.35 (t, J = 6.8 Hz, 1H), 7.16–7.24 (m, 3H), 7.30 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H); δ (minor) 1.59–1.83 (m, 8H), 2.42 (s, 3H), 3.45 (d, J = 8.3 Hz, 2H), 4.32 (br s, 2H), 5.98 (t, J = 8.3 Hz, 1H), 7.15–7.32 (m, 7H), 7.57 (d, J = 7.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (major) 21.6, 25.9, 35.7, 40.2, 48.9 (d, J_{CF} = 4 Hz), 53.6, 95.1 (d, J_{CF} = 18 Hz), 119.3, 126.0, 128.1, 128.4, 128.5, 129.6, 136.0, 141.3, 144.2, 146.6, 149.6 (dd, J_{CF} = 270, 266 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (major) 69.9 (d, J_{FF} = 60 Hz, 1F), 76.2 (d, J_{FF} = 60 Hz, 1F); δ (minor) 70.4 (d, J_{FF} = 59 Hz, 1F), 76.3 (d, J_{FF} = 59 Hz, 1F); HRMS (ESI+): MH^+, found 430.1647. $C_{24}H_{26}F_2NO_2S$ requires 430.1652.

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References and notes

1. (a) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry, Principles and Commercial Applications*, Plenum Press, New York, 1994. (b) Uneyama, K. *Organofluorine Chemistry*, Blackwell Publishing, Oxford, 2006. (c) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Hoboken, 2008. (d) Nenajdenko, V. ed. *Fluorine in Heterocyclic Chemistry vol. 1 and 2*, Springer, Heidelberg, 2014. (e) Vulpetti, A.; Dalvit, C. *Drug Discov. Today* **2012**, *17*, 890–897. (f) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422–518. (g) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16–29. (h) Jeschke, P. *Pest Manag. Sci.* **2010**, *66*, 10–27. (i) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003–1022. (j) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.
2. For reviews on synthetic applications of 1,1-diflluoro-1-alkenes and 2-(trifluoromethyl)-1-alkenes, see: (a) Bonnet-Delpon, D.; Bégué, J.-P.; Lequeux, T.; Ourevitch, M. *Tetrahedron* **1996**, *52*, 59–70. (b) Chelucci, G. *Chem. Rev.* **2012**, *112*, 1344–1462. (c) Unzner, T. A.; Magauer, T. *Tetrahedron Lett.* **2015**, *56*, 877–883. (d) Zhang, X.; Cao, S. *Tetrahedron Lett.* **2017**, *58*, 375–392.
3. For addition–elimination of 1,1-diflluoro-1-alkenes, see: Ichikawa, J. *Chim. Oggi* **2007**, *25(4)*, 54–57.
4. For addition–elimination of 2-(trifluoromethyl)-1-alkenes, see: Ichikawa, J. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1175–1184. See also ref. 3.
5. For a recent review on single activation of CF_3 groups, see: Jaroschik, F. *Chem. Eur. J.* **2018**, *24*, 14572–14582.
6. For recent publications on the single C–F activation of CF_3-alkenes, see: (a) Ichitsuka, T.; Fujita, T.; Ichikawa, J. *ACS Catal.* **2015**, *5*, 5947–5950. (b) Fuchibe, K.; Hatta, H.; Oh, K.; Oki, R.; Ichikawa, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 5890–5893. (c) Meißner, G.; Kretschmar, K.; Braun, T.; Kemnitz, E. *Angew. Chem. Int. Ed.* **2017**, *56*, 16338–16341. (c) Kumar, T.; Massicot, F.; Harakat, D.; Chevreux, S.; Martinez, A.; Bordolinska, K.; Preethalayam, P.; Kokkuvayil Vasu, R.; Behr, J.-B.; Vasse, J.-L.; Jaroschik, F. *Chem. Eur. J.* **2017**, *23*, 16460–16465. (d) Wu, X.; Xie, F.; Gridnev, I. D.; Zhang, W. *Org. Lett.* **2018**, *20*, 1638–1642.
7. (a) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **1997**, 1537–1538. (b) Ichikawa, J.; Fujiwara, M.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **2000**, 1887–1888. (c) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917–1936.
8. (a) Nadano, R.; Iwai, Y.; Mori, T.; Ichikawa, J. *J. Org. Chem.* **2006**, *71*, 8748–8754. (b) Ichikawa, J.; Iwai, Y.; Nadano, R.; Mori, T.; Ikeda, M. *Chem. Asian J.* **2008**, *3*, 393–406.
9. For Baldwin's rules, see: (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736–738.

10. For recent reports on nucleophilic 5-*endo*-*trig* cyclization, see: (a) Tong, K.; Tu, J.; Qi, X.; Wang, M.; Wang, Y.; Fu, H.; Pittman, C. U., Jr.; Zhou, A. *Tetrahedron* **2013**, *69*, 2369–2375. (b) En, D.; Zou, G.-F.; Guo, Y.; Liao, W.-W. *J. Org. Chem.* **2014**, *79*, 4456–4462. (c) Johnston, C. P.; Kothari, A.; Sergeieva, T.; Okovytyy, S. I.; Jackson, K. E.; Paton, R. S.; Smith, M. D. *Nat. Chem.* **2015**, *7*, 171–177. (d) Kapoorr, R.; Singh, S. N.; Tripathi, S.; Yadav. L. D. S. *Synlett* **2015**, *26*, 1201–1206. (e) Sharma, K.; Wolstenhulme, J. R.; Painter, P. P.; Yeo, D.; Grande-Carmona, F.; Johnston, C. P.; Tantillo, D. J.; Smith, M. D. *J. Am. Chem. Soc.* **2015**, *137*, 13414–13424. (f) Williams, B. M.; Trauner, D. *Angew. Chem., Int. Ed.* **2016**, *55*, 2191–2194. (g) Markwell-Heys, A. W.; George, J. H. *Org. Biomol. Chem.* **2016**, *14*, 5546–5549. (h) Xiao, T.; Li, L.; Zhou, L. *J. Org. Chem.* **2016**, *81*, 7908–7916. (i) Zhang, B.; Zhang, X.; Hao, J.; Yang, C. *Org. Lett.* **2017**, *19*, 1780–1783. (j) Hao, J.; Milcent, T.; Retailleau, P.; Soloshonok, V. A.; Ongeri, S.; Crousse, B. *Eur. J. Org. Chem.* **2018**, 3688–3692.
11. For recent reports on radical-driven 5-*endo*-*trig* cyclization, see: (a) Ram, R. N.; Gupta, D. K.; Soni, V. K. *J. Org. Chem.* **2016**, *81*, 1665–1674. (b) Clark, A. J.; Curran, D. P.; Fox, D. J.; Ghelfi, F.; Guy, C. S.; Hay, B.; James, N.; Phillips, J. M.; Roncaglia, F.; Sellars, P. B.; Wilson, P.; Zhang, H. *J. Org. Chem.* **2016**, *81*, 5547–5565. (c) Fava, E.; Nakajima, M.; Tabak, M. B.; Rueping, M. *Green Chem.* **2016**, *18*, 4531–4535. (d) Li, J.; Hao, W.-J.; Zhou, P.; Zhu, Y.-L.; Wang, S.-L.; Tu, S.-J.; Jiang, B. *RSC Adv.* **2017**, *7*, 9693–9703. (e) Jiang, B.; Li, J.; Pan, Y.; Hao, W.; Li, G.; Tu, S. *Chin. J. Chem.* **2017**, *35*, 323–334. (f) Jansana, S.; Coussanes, G.; Diaba, F.; Bonjoch, J. *Eur. J. Org. Chem.* **2017**, 2344–2352. (g) Wang, A.-F.; Hao, W.-J.; Zhu, Y.-L.; Li, G.; Zhou, P.; Tu, S.-J.; Jiang, B. *ACS Omega* **2018**, *3*, 1482–1491.
12. For recent reports on electrophile-driven 5-*endo*-*trig* cyclization, see: (a) Karjalainen, O. K.; Nieger, M.; Koskinen, A. M. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 2551–2554. (b) Singh, P.; Panda, G. *RSC Adv.* **2014**, *4*, 2161–2166. (c) Tata, R. R.; Harmata, M. *J. Org. Chem.* **2015**, *80*, 6839–6845. (d) Fujita, T.; Watabe, Y.; Yamashita, S.; Tanabe, H.; Nojima, T.; Ichikawa, J. *Chem. Lett.* **2016**, *45*, 964–966. (e) Miao, M.; Xu, H.; Luo, Y.; Jin, M.; Chen, Z.; Xu, J.; Ren, H. *Org. Chem. Front.* **2017**, *4*, 1824–1828. (f) Raghavan, S.; Nyalata, S. *Tetrahedron* **2018**, *74*, 1071–1077. (g) Arimitsu, S.; Nakanose, M.; Gima, E. *Tetrahedron Lett.* **2018**, *59*, 887–890.
13. (a) Fujita, T.; Sakoda, K.; Ikeda, M.; Hattori, M.; Ichikawa, J. *Synlett* **2013**, *24*, 57–60. (b) Fujita, T.; Ikeda, M.; Hattori, M.; Sakoda, K.; Ichikawa, J. *Synthesis* **2014**, *46*, 1493–1505.
14. (a) Nadano, R.; Ichikawa, J. *Synthesis* **2006**, 128–132. (b) Nadano, R.; Fuchibe, K.; Ikeda, M.; Takahashi, H.; Ichikawa, J. *Chem. Asian J.* **2010**, *5*, 1875–1883. See also ref. 8a.
15. Yamazaki, T.; Ishikawa, N. *Chem. Lett.* **1984**, *13*, 521–524.