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Highly Regio- and Stereoselective Diels–Alder Cycloaddition of Difluoro(methylene)cyclopropanes

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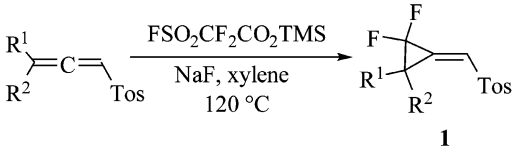
The Diels–Alder reactions of difluoro(methylene)cyclopropanes (F_2MCPs) with cyclic dienes are described. These cycloaddition reactions exhibited complete regioselectivity and high *endo*-stereoselectivity. The obtained cycloadducts underwent a retro-Diels–Alder reaction to give the original dienophiles and dienes when heated, reflecting the reversible Diels–Alder reactivity of F_2MCPs.

Introduction

Methylenecyclopropane derivatives (MCPs) have served as useful synthetic intermediates in organic chemistry over the last decade.[1] The attractive feature of these compounds is their surprising stability, accompanied by a high level of angular strain. This confers on them remarkable chemical reactivity, allowing them to undergo such processes as cycloadditions and ring-opening reactions.[2] The introduction of fluorine onto the ring of such methylenecyclopropanes would have profound effects on their chemical reactivities and physicochemical properties, due to the strongly electron-withdrawing effect of fluorine. However, the synthesis of these fluorinated analogues,[3] such as difluoro(methylene)cyclopropanes (F_2MCPs), is very difficult. Recently, we found that F_2MCPs could be readily prepared from the direct difluorocyclopropanation of allenes, using $FSO_2CF_2CO_2SiMe_3$ as the difluorocarbene precursor (Scheme 1). It was shown that these F_2MCPs could undergo a variety of reactions both at the double bond and on the difluorocyclopropane ring, demonstrating very different reactivity from the nonfluorinated analogues (MCPs).[4] These interesting results prompted us to investigate further the chemical reactivity of F_2MCPs.

The Diels–Alder reaction is among the most fundamental and useful synthetic processes for the construction of numerous complex molecular architectures. A fascinating aspect of the Diels–Alder reaction is its regio- and stereoselectivity.[5] For example, highly *endo*-selective Diels–Alder cycloaddition reactions have been employed as the key step for the total synthesis of many natural products.[6] In the case of F_2MCPs, Dolbier has found that their Diels–Alder reactivity was dramatically increased by the geminal allylic fluorines, preferentially affording CF_2-*endo* products.[1a–1c,3a] The carbon–carbon double bond present in F_2MCPs **1** might exhibit a much stronger electrophilic character than that of Dolbier's F_2MCPs, because F_2MCPs **1** contain an electron-withdrawing sulfonyl group as well as the two geminal allylic fluorines, leading to lower LUMO energies. As a consequence, they would be expected to be good dienophiles in the Diels–Alder reaction.



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Scheme 1. Synthesis of difluoro(methylene)cyclopropanes (for R^1, R^2 see Table 2).

Results and Discussion

Diels–Alder Reaction of F_2MCPs with Cyclic Dienes

To examine this dienophilic nature, we investigated the Diels–Alder reaction of F_2MCPs **1** and the retro-Diels–Alder reaction of the corresponding cycloadducts. Unusually high regio- and Tos-*endo* stereoselectivity was observed in the Diels–Alder reaction of **1** with cyclic dienes, which is contrary to Dolbier's results. At elevated temperature, **1** could be regenerated from the cycloreversion reaction of the Diels–Alder adducts. Herein, we describe these preliminary results, which could provide a good understanding of the stability and reactivity of F_2MCPs.

It is well known that the yield and stereochemistry of the Diels–Alder reaction are strictly dependent on the reaction conditions.[7] Therefore, significant efforts were made to

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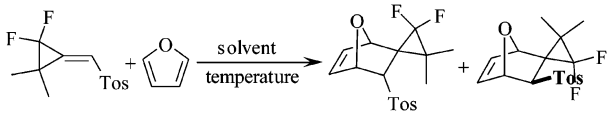
screen the reaction conditions for optimized yield and stereoselectivity. F_2MCPs **1** were prepared according to our previous report with a slight modification.[4] Furan was first used as the diene. It was found that solvent and temperature have a significant effect. Good results were obtained when the reaction was performed in ether at 50 °C with a large excess of furan (Table 1, entry 9). This cycloaddition showed a strong preference for the *endo* product.

Table 1. Optimization of conditions for Diels–Alder reaction of F_2MCPs with furan.[a]



1a *endo* **2a** *exo* **2a'**

Entry	Solvent	Temp. [°C]	Time [h]	% Yield[a]	*endo*/*exo*[b] (tosyl)
1	none	50	24	0	–
2	none	120	10	84	75:25
3	chloroform	120	10	60	67:33
4	chloroform	50	24	59	90:10
5	acetone	50	24	48	91:9
6	methanol	50	24	47	91:9
7	benzene	50	30	0	–
8	petroleum ether	50	30	49	92:8
9	diethyl ether	50	24	90	88:12
10	[BMIm][PF_6]	50	20	99	93:7

[a] Isolated yield based on F_2MCP. [b] Determined by ^{19}F NMR and HPLC.

It was reported that *endo* selectivity could be greatly improved when the Diels–Alder reaction was performed in ionic liquid, although the mechanism behind the ionic liquid's impact on the reaction is not well understood.[8] As an extension of our interest in ionic liquid chemistry,[9] we investigated the Diels–Alder reaction of F_2MCPs in ionic liquid. It was found that a further improvement of yield and *endo* selectivity was obtained when the reaction was carried out in a commonly used ionic liquid (butylmethylimidazolium hexafluorophosphate, [BMIm][PF_6]), giving a 93:7 (*endo*/*exo*) mixture of diastereomers in almost quantitative yield (Table 1, entry 10). The ionic liquid could be recovered and reused after extraction with diethyl ether. The mixture of *endo*/*exo* isomers could not be separated by normal column chromatography because of their very similar polarities. Fortunately, the pure major *endo* isomer **2a** was easily obtained after recrystallization. The structure of **2a** was confirmed by single-crystal X-ray analysis. As shown in Figure 1, the tosyl group is below the six-membered ring and on the opposite side than the CF_2 group. The oxygen bridge and the CF_2 group are on the same side of the molecule.

With the optimized reaction conditions in hand, we then examined this [4+2] cycloaddition with other F_2MCPs in [BMIm][PF_6]. It can be seen that the introduction of bulky cyclohexyl or ethyl groups into the cyclopropane ring resulted in slightly lower yield and stereoselectivity (Table 2, entries 1–2).

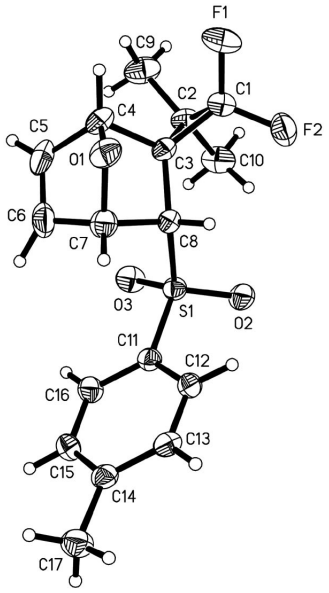
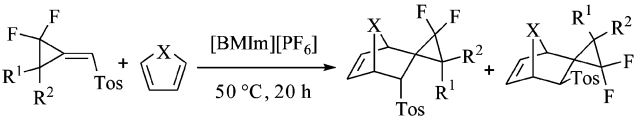


Figure 1. Crystal structure of cycloadduct **2a**.

Table 2. Diels–Alder reaction of F_2MCPs with symmetrical dienes.



1a-1c *endo* **2b-2f** *exo* **2b'-2f'**

Entry	R^1	R^2	X	Product	% Yield[a]	*endo*/*exo* (tosyl)[b]
1	–$(CH_2)_5$–		O	**2b**	96	90:10
2	CH_3CH_2	CH_3CH_2	O	**2c**	75	75:25
3	CH_3	CH_3	CH_2	**2d**	99	> 99:1
4	–$(CH_2)_5$–		CH_2	**2e**	96	> 99:1
5	CH_3CH_2	CH_3CH_2	CH_2	**2f**	47	> 99:1

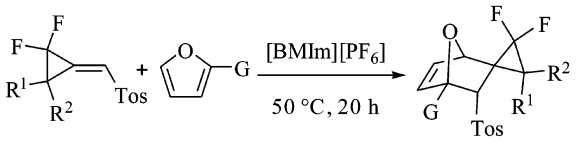
[a] Isolated yield based on F_2MCP. [b] Determined by ^{19}F NMR and HPLC.

Prompted by the good reactivity of F_2MCPs with furan, we then extended our study to the Diels–Alder reaction of F_2MCPs with cyclopentadiene. Much to our surprise, these reactions proceeded with unusually high *endo* diastereoselectivity, giving almost pure cycloadducts with *endo*-configuration (Table 2, entries 3–5).

Reaction of an unsymmetrical dienophile with an unsymmetrical diene can give rise to two regioisomeric adducts. In order to explore the regioselectivity of F_2MCPs in Diels–Alder reaction, we extended our investigation to the reaction of F_2MCPs with unsymmetrical dienes like 2-substituted furans. Much to our delight, all of these Diels–Alder reactions of F_2MCPs with 2-substituted furans were completely regio- and *endo*-stereoselective, giving the corresponding cycloadducts as a single diastereoisomer (Table 3). The regio- and *endo*-diastereoselectivity of the cycloadducts was established through single-crystal X-ray

structure determination of **2j** (Figure 2). As shown in Figure 2, the substituent on the bridge carbon and the tosyl group are present on the same side of the molecule.

Table 3. Diels–Alder reaction of F_2MCPs with unsymmetrical dienes.



1a-1c **2g-2n**

Entry	R^1	R^2	G	Product	% Yield[a]
1	CH_3	CH_3	CH_3	**2g**	83
2		$-(CH_2)_5-$	CH_3	**2h**	81
3	CH_3CH_2	CH_3CH_2	CH_3	**2i**	48
4	CH_3	CH_3	CH_2OH	**2j**	72
5		$-(CH_2)_5-$	CH_2OH	**2k**	75
6	CH_3CH_2	CH_3CH_2	CH_2OH	**2l**	48
7	CH_3	CH_3	CH_2OCH_3	**2m**	44
8		$-(CH_2)_5-$	CH_2OCH_3	**2n**	63

[a] All yields refer to analytically pure compounds.

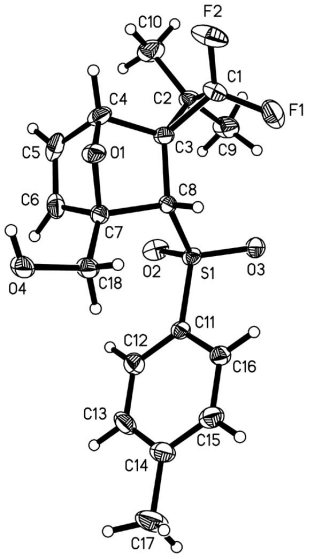


Figure 2. Crystal structure of cycloadduct **2j**.

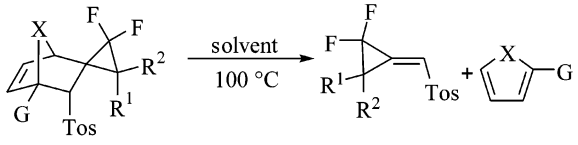
Compared with the symmetrical dienes described above (Table 2), the yields were lower for these 2-substituted furans (Table 3), which indicated that this Diels–Alder reaction is very sensitive to the steric influence of the substituents attached to the reactants.

Retro-Diels–Alder Reaction of the Cycloadducts

It is well known that the Diels–Alder reaction has been frequently used as a method for protection of a double bond because the alkene moiety can be regenerated through a thermal retro-Diels–Alder reaction.[10] However, if the cycloadducts are too labile, the Diels–Alder adducts may become difficult to handle; and if they are too stable, the cycloreversion may not occur. Therefore the retro-Diels–Alder reaction could demonstrate the relative stability of the cycloadducts, which further reveals the corresponding reactivity of the dienophiles and dienes. In order to gain more insight into the properties of these highly strained difluoro(methylene)cyclopropanes, the thermal stability of these Diels–Alder cycloadducts was thus investigated.

Although the above adducts **2a**–**n** were all stable at room temperature for long periods of time, compound **2a** underwent a retrodiene decomposition when it was heated in [BMIm][PF_6] at 100 °C for 14 h, giving the parent compound **1a** in 34% yield (Table 4, entry 1). Changing the solvent to benzene or *tert*-butyl alcohol resulted in a higher cycloreversion (Table 4, entries 2–3). The corresponding dienophile **1a** could be obtained almost quantitatively when **2g** was subjected to the same reaction conditions as above (Table 4, entry 5). Nevertheless, the cycloadduct **2d** remained intact under those reaction conditions (Table 4, entry 6), which indicated that the cyclopentadiene moiety in **2d** was difficult to cleave under thermal cycloreversion reaction conditions. This is in agreement with the previous observation that furan adducts are more reactive than cyclopentadienes toward the retro-Diels–Alder reaction.[11]

Table 4. Selected examples of the retro-Diels–Alder reaction.



Entry	R^1	R^2	X	G	Solvent	Time [h]	Product	% Yield[a]
1	CH_3	CH_3	O	H	[BMIm][PF_6]	14	**1a**	34
2	CH_3	CH_3	O	H	C_6H_6	8	**1a**	55
3	CH_3	CH_3	O	H	*t*BuOH	8	**1a**	57
4		$-(CH_2)_5-$	O	H	*t*BuOH	8	**1b**	79
5	CH_3	CH_3	O	CH_3	*t*BuOH	8	**1a**	99
6	CH_3	CH_3	CH_2	H	*t*BuOH	8	–	–

[a] Isolated yields.

Conclusions

In summary, we have successfully developed a fully regio- and *endo*-selective Diels–Alder reaction of F_2MCPs. This complete regio- and *endo*-selectivity might result from a combination of multiple factors including the olefin structure, solvent effects, steric interactions, electrostatic forces, hydrogen bonds, etc. The corresponding cycloadducts undergo an efficient retro-Diels–Alder reaction under mild conditions to release the F_2MCPs. These features provide new understanding of the relative stability and reactivity of F_2MCPs with high ring strain. We are currently exploiting structural effects on this peculiar reactivity and other chemical conversions of F_2MCPs, which will be reported in due course.

Experimental Section

General: Melting points were uncorrected. ^{1}H NMR spectra were recorded with a Bruker AM 300 (300 MHz) spectrometer with TMS as an internal standard (negative for upfield). ^{19}F NMR spectra were recorded with a Bruker AM 300 (282 MHz) with $CFCl_3$ as an external standard (negative for upfield). ^{13}C NMR spectra were recorded with a Bruker AM 300 (75 MHz) spectrometer with $CDCl_3$ as an internal standard (negative for upfield).The solvent for NMR measurement was $CDCl_3$, which was purchased from Cambridge Isotope Laboratories, Aldrich or Acros. MS and HRMS were recorded with a Hewlett–Packard HP-5989A spectrometer and a Finnigan MAT-8483 mass spectrometer. Elemental analyses were obtained with a Perkin–Elmer 2400 Series II Elemental Analyzer. Infrared spectra were measured with a Perkin–Elmer 983 spectrometer. TLC analysis was performed on silica gel plates, column chromatography over silica gel (mesh 300–400), both obtained from Qingdao Ocean Chemicals. All solvents were purified by standard methods. $FSO_2CF_2COOSiMe_3$ (TFDA),[12] sulfonyl allenes,[13] and [BMIm][PF_6][14] were prepared as described in the literature. All commercially available reagents and chemicals were purchased from Aldrich, Acros or Alfa Aesar.

Typical Procedure for the Addition of Difluorocarbene to Allenes 1a–c: The allene 1-methyl-4-(3-methylbuta-1,2-dienylsulfonyl)benzene (2 g, 9.2 mmol), NaF (38 mg, 10 mol-%) and xylene (20 mL) were placed under N_2 in a three-necked flask fitted with a magnetic stirring bar and a pressure-equalizing dropping funnel. After the mixture was heated to 120 °C (oil bath), TFDA (5.75 g, 2.5 equiv.) diluted in xylene (5 mL) was added dropwise over a period of about 1 h. The mixture was then stirred for an additional 1 h to ensure that the substrate was consumed. After cooling the mixture to room temperature, the solvent was removed under reduced pressure. The residual product was purified by chromatography on a silica gel column (petroleum ether/ethyl acetate, 10:1) to yield **1a**, 2.1 g (85% based on allene), solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (t, J = 1.5 Hz, 6 H), 2.46 (s, 3 H), 7.00 (s, 1 H), 7.37 (d, J = 8.1 Hz, 2 H), 7.80 (d, J = 8.1 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –138.7 (s, 2 F) ppm.

1b: The TFDA was added dropwise to the reaction without being diluted. Yield 64%, solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34–1.44 (m, 3 H), 1.68–1.90 (m, 5 H), 1.96–2.08 (m, 2 H), 2.46 (s, 3 H), 6.95 (s, 1 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.76 (d, J = 8.4 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –140.4 (s, 2 F) ppm.

1c: The reaction temperature was 110 °C. Yield 50%, solid, m.p. 82–84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.6 Hz 3 H), 1.66–1.83 (m, 5 H), 1.60–2.09 (m, 2 H), 2.46 (s, 3 H), 7.03 (s, 1 H), 7.35–7.38 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 8.0 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –138.7 (s, 2 F) ppm. IR (film): $\tilde{\nu}$ = 3065, 2979, 2946, 1922, 1805, 1596, 1458, 1339, 1320, 1182, 1154 cm^{-1}. MS (ESI): m/z = 301.2 [M + H$^+$]. $C_{15}H_{18}F_2O_2S$ (300.10): calcd. C 59.98, H 6.04, F 12.65; found C 59.86, H 6.08, F 12.80.

General Procedure for Diels–Alder Reaction of Compounds 1 with Furan and Other Dienes: A sample containing **1a** (50 mg, 0.184 mmol), furan (0.05 mL, >3 equiv.) and [BMIm][PF_6] (0.5 mL) was stirred in a 5-mL sealed tube at 50 °C for 20 h. The homogeneous phase was extracted several times with diethyl ether (5 mL), until TLC showed that no additional compound could be extracted from the IL system. The diethyl ether was removed and the residue was purified by chromatography (petroleum ether/ethyl acetate, 8:1). The pure *endo* product was obtained by recrystallization to yield **2a**, 62 mg (99%), solid, m.p. 190–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 3 H), 1.49 (s, 3 H), 2.49 (s, 3 H), 4.18 (d, J = 4 Hz 1 H), 4.45 (d, J = 4 Hz, 1 H), 4.84 (s, 1 H), 6.54 (d, J = 6 Hz, 1 H), 6.72 (d, J = 6 Hz, 1 H), 7.42 (d, J = 7.1 Hz, 2 H), 7.77 (d, J = 7.1 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –141.0 (d, J = 150 Hz, 1 F), –149.3 (d, J = 150 Hz 1 F) ppm. IR (film): $\tilde{\nu}$ = 3018, 2976, 2954, 2936, 1944, 1832, 1597, 1495, 1475, 1438, 1324, 1315, 1308, 1292, 1189, 1183, 1156, 1143, 1087 cm^{-1}. MS (ESI): m/z = 358.0 [M + NH_4^+]. $C_{17}H_{18}F_2O_3S$ (340.09): calcd. C 59.99, H 5.33, F 11.16; found C 60.00, H 5.28, F 11.04.

2b: Yield 58 mg (96%), solid, m.p. 162–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.50 (m, 3 H), 1.52–1.83 (m, 6 H), 2.36 (d, J = 13 Hz, 1 H), 2.48 (s, 3 H), 4.16 (d, J = 5.5 Hz, 1 H), 4.42 (d, J = 5.5 Hz 1 H), 5.00 (s, 1 H), 6.50 (d, J = 5.5 Hz, 1 H), 6.67 (d, J = 5.5 Hz, 1 H), 7.40–7.43 (d, J = 8.0 Hz, 2 H), 7.77 (d, J = 8.0 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –142.0 (d, J = 150 Hz, 1 F), –149.8 (dd, J = 150, J = 6.1 Hz 1 F) ppm. IR (film): $\tilde{\nu}$ = 3012, 2944, 2926, 2856, 1598, 1496, 1465, 1454, 1442, 1324, 1309, 1295, 1193, 1163, 1143, 1113, 1107, 1087, 1043 cm^{-1}. MS (ESI): m/z = 398.2 [M + NH_4^+]. $C_{20}H_{22}F_2O_3S$ (380.12): calcd. C 63.14, H 5.83, F 9.99; found C 63.22, H 5.86, F 9.77.

2c: Yield 46 mg (75%), solid, m.p. 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92–1.04 (m, 6 H), 1.30–1.50 (m, 1 H), 1.78–2.10 (m, 3 H), 2.48 (s, 3 H), 4.19 (d, J = 4.1 Hz, 1 H), 4.54 (d, J = 4.1 Hz, 1 H), 4.90 (s, 1 H), 6.53 (d, J = 5.3 Hz, 1 H), 6.68 (d, J = 5.5 Hz, 1 H), 7.41 (d, J = 8.1 Hz, 2 H), 7.77 (d, J = 8.2 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –141.7 (d, J = 154 Hz, 1 F), –148.8 (d, J = 158 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3094, 3035, 2980, 2945, 2884, 1942, 1595, 1471, 1449, 1328, 1320, 1293, 1263, 1186, 1164, 1145, 1116, 1090, 1046, 1027 cm^{-1}. MS (ESI): m/z = 386.4 [M + NH_4^+]. $C_{19}H_{22}F_2O_3S$ (368.1): calcd. C 61.94, H 6.02, F 10.31; found C 61.75, H 6.06, F 10.36.

2d: Yield 63 mg (99%), solid, m.p. 182–184 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 3 H), 1.32 (d, J = 13.8 Hz 1 H), 1.45 (s, 3 H), 2.39 (s, 3 H), 2.85 (s, 2 H), 3.95 (s, 2 H), 6.17 (d, J = 6.3 Hz, 1 H), 6.43 (d, J = 6.3 Hz, 1 H), 7.39 (d, J = 7.5 Hz, 2 H), 7.77 (d, J = 7.2 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –139.5 (d, J = 147 Hz 1 F), –150.4 (d, J = 148 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3069, 3022, 3003, 2956, 2929, 1598, 1482, 1432, 1322, 1288, 1276, 1187, 1168, 1146, 1089, 1060 cm^{-1}. MS (ESI): m/z = 356.3 [M + NH_4^+]. $C_{18}H_{20}F_2O_2S$ (338.12): calcd. C 63.88, H 5.96, F 11.23; found C 63.77, H 5.85, F 11.50.

2e: Yield 62 mg (96%), solid, m.p. 169–171 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.75 (m, 12 H), 2.38 (d, J = 12.7 Hz, 1 H), 2.41 (s, 3 H), 2.93 (s, 1 H), 3.96 (s, 1 H), 6.10 (m, 1 H), 6.31 (m, 1 H), 7.31–7.33 (d, J = 8.1 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, CDCl3): δ = –140.1 (dd, J = 150, J = 4.2 Hz, 1 F), –150.1 (dd, J = 154, J = 6.5 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3068, 3008, 2926, 2853, 1654, 1467, 1453, 1321, 1274, 1257, 1184, 1158, 1143, 1128, 1094, 1053 cm^{-1}. MS (ESI): m/z = 396.4 [M + NH_4^+]. $C_{21}H_{24}F_2O_2S$ (378.2): calcd. C 66.64, H 6.39, F 10.04; found C 66.28, H 6.60, F 10.08.

2f: Yield 41 mg (47%), solid, m.p. 151–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92–1.04 (m, 6 H), 1.30–1.55 (m, 3 H), 1.88–1.95 (m, 1 H), 2.00–2.04 (br., 2 H), 2.47 (s, 3 H), 2.57 (s, 1 H), 2.97 (d, J = 2.7 Hz 1 H), 4.07 (d, J = 2.4 Hz 1 H), 6.13 (m, 1 H), 6.38–6.39 (m, 1 H), 7.37 (d, J = 7.8 Hz, 2 H), 7.77 (d, J = 7.8 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –141.5 (d, J = 147 Hz 1 F), –149.8 (d, J = 147 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3072, 3057, 2907, 2936, 2877, 1940, 1838, 1598, 1460, 1438, 1332, 1318, 1302, 1290, 1182, 1159, 1144, 1126, 1087, 1054 cm^{-1}. MS (ESI): m/z = 384.4 [M + NH_4^+]. $C_{20}H_{24}F_2O_3S$ (366.15): calcd. C 65.55, H 6.60, F 10.37; found C 65.44, H 6.64, F 10.44.

2g: Yield 83%, solid, m.p. 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 3 H), 1.28 (s, 3 H), 1.37 (s, 1 H), 2.45 (s, 3 H), 3.87 (d, J = 1.2 Hz 1 H), 4.75 (s, 1 H), 6.48 (d, J = 5.9 Hz 1 H), 6.66 (dd, J = 5.6, J = 1.2 Hz 1 H), 7.38 (d, J = 8.3 Hz, 2 H), 7.78 (d, J = 8.2 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –141.0 (d, J = 148 Hz 1 F), –150.2 (d, J = 148 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 18.3 (d, J_{FC} = 5.7 Hz), 18.5, 18.9, 19.0 (d, J_{FC} = 7.3 Hz), 21.7, 36.0 (m, 1 C), 45.3 (m, 1 C), 72.3, 80.1 (d, J_{FC} = 8.9 Hz), 89.7, 114.6 (m, 1 C), 128.3, 130.0, 135.8, 138.0 (138.02, 138.06, 2 C), 145.1 ppm. IR (film): $\tilde{\nu}$ = 3026, 2970, 1597, 1471, 1435, 1391, 1319, 1303, 1293, 1262, 1207, 1143, 1111, 1187, 1007 cm^{-1}. MS (ESI): m/z = 377.2 [M + Na$^+$]. $C_{18}H_{20}F_2O_3S$: calcd. C 61.00, H 5.91; found C 60.51, H 5.91. HRMS (ESI) calcd. for $C_{18}H_{20}F_2O_3S$ H$^+$: 355.1174; found 355.1180.

2h: Yield 81%, solid, m.p. 140–142 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (s, 3 H), 1.19–1.47 (m, 4 H), 1.61–1.94 (m, 6 H), 2.45 (s, 3 H), 3.85 (s, 1 H), 4.81 (s, 1 H), 6.44 (d, J = 5.6 Hz, 1 H), 6.60 (d, J = 5.5 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 2 H), 7.71 (d, J = 7.9 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –142.2 (d, J = 151 Hz, 1 F), –150.0 (dd, J = 152, J = 6.1 Hz 1 F) ppm. IR (film): $\tilde{\nu}$ = 2929, 2856, 1596, 1492, 1442, 1320, 1303, 1191, 1163, 1144, 1118, 1085, 1072, 1003 cm^{-1}. MS (ESI): m/z = 412.0 [M + NH_4^+]. $C_{21}H_{24}F_2O_3S$ (394.14): calcd. C 63.94, H 6.13; found C 64.21, H 6.39.

2i: Yield 48%, solid, m.p. 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (t, J = 7.5 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H), 1.17–1.34 (m, 2 H), 1.38 (s, 3 H), 1.76–2.01 (m, 2 H), 2.40 (s, 3 H), 3.81 (s, 1 H), 4.75 (s, 1 H), 6.51 (d, J = 5.7 Hz, 1 H), 6.57 (d, J = 5.7 Hz, 1 H), 7.30 (d, J = 7.9 Hz, 2 H), 7.65 (d, J = 8.0 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –142.7 (d, J = 152 Hz, 1 F), –149.1 (d, J = 155 Hz, 1 F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.3–9.3 (d, J_{FC} = 2.4 Hz), 10.5, 18.8, 19.9 (d, J_{FC} = 3.8 Hz), 21.7, 21.9–22.0 (d, J_{FC} = 6.6 Hz), 37.3 (m), 46.8 (m), 71.9, 80.0 (d, J_{FC} = 9.8 Hz), 89.6, 115 (t, J_{FC} = 285.5 Hz), 127.9, 129.8, 136.4, 138.6, 138.9, 144.8 ppm. IR (film): $\tilde{\nu}$ = 3026, 2970, 1597, 1471, 1435, 1391, 1319, 1303, 1293, 1262, 1207, 1143, 1111, 1187, 1007 cm^{-1}. MS (ESI): m/z = 405.0[M + Na$^+$]. Anal. HRMS (ESI) calcd. for $C_{20}H_{25}F_2O_3S$ H$^+$: 383.1487; found 383.1490.

2j: Yield 72%, solid, m.p. 157–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3 H), 1.83 (dd, J = 8.4, J = 5.4 Hz, 1 H), 2.45 (s, 3 H), 3.67 (dd, J = 12.7, J = 8.2 Hz, 1 H), 3.78 (dd, J = 12.7, J = 5.4 Hz, 1 H), 3.49 (s, 1 H), 4.84 (s, 1 H), 6.57 (d, J = 5.7 Hz, 1 H), 6.73 (dd, J = 5.7, J = 1.6 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.76 (d, J = 8.1 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –141.0 (d, J = 152 Hz 1 F), –149.7 (dd, J = 150 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3480, 3091, 2995, 2972, 2933, 2916, 1596, 1487, 1465, 1434, 1319, 1307, 1291, 1203, 1189, 1145, 1099, 1089, 1077, 1062, 1054, 1002 cm^{-1}. MS (ESI): m/z = 388.2 [M + NH_4^+]. $C_{18}H_{20}F_2O_4S$ (370.10): calcd. C 58.37, H 5.44; found C 58.36, H 5.23.

2k: Yield 75%, solid, m.p. 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.48 (m, 2 H), 1.57–1.88 (m, 8 H), 2.47 (s, 3 H), 3.62–3.70 (dd, J = 12.8, J = 8.3 Hz, 1 H), 3.72–3.82 (dd, J = 12.8, J = 5.3 Hz, 1 H), 3.47 (s, 1 H), 4.91 (s, 1 H), 6.52–6.57 (d, J = 5.8 Hz, 1 H), 6.66–6.70 (dd, J = 5.7, J = 1.5 Hz, 1 H), 7.35–7.39 (d, J = 8.3 Hz, 2 H), 7.74–7.79 (d, J = 8.4 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –143.2–142.7 (d, J = 152 Hz 1 F), –150.3–149.7 (dd, J = 151, J = 5.8 Hz 1 F) ppm. IR (film): $\tilde{\nu}$ = 3545, 3486, 3086, 2977, 2926, 2856, 1923, 1598, 1470, 1457, 1444, 1399, 1312, 1306, 1293, 1192, 1161, 1141, 1086, 1052, 1014 cm^{-1}. MS (ESI): m/z = 428.2 [M + NH_4^+]. $C_{21}H_{24}F_2O_4S$ (410.14): calcd. C 61.45, H 5.89; found C 61.51, H 5.89.

2l: Yield 48%, solid, m.p. 147–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78–0.85 (t, J = 7.1 Hz, 3 H), 0.97–1.04 (t, J = 7.1 Hz, 3 H), 1.28–1.46 (m, 2 H), 1.82–2.07 (m, 3 H), 2.46 (s, 3 H), 3.93–4.10 (m, 2 H), 4.52 (s, 1 H), 4.92 (s, 1 H), 6.65–6.69 (d, J = 5.8 Hz, 1 H), 6.70–6.75 (dd, J = 5.7 Hz, 1 H), 7.33–7.36 (d, J = 7.9 Hz, 2 H), 7.73–7.76 (d, J = 7.5 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –143.8–142.2 (d, J = 150 Hz 1 F), –149.2–148.7 (dd, J = 150, J = 5.4 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3515, 2977, 2881, 1596, 1454, 1319, 1307, 1294, 1183, 1145, 1077, 1053, 1002 cm^{-1}. MS (ESI): m/z = 416.2 [M + NH_4^+]. $C_{20}H_{24}F_2O_4S$ (398.5): calcd. C 60.28, H 6.09, F 9.54; found C 60.22, H 6.39, F 9.72.

2m: Yield 44%, solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 3 H), 1.30 (s, 3 H), 2.47 (s, 3 H), 3.28 (s, 3 H), 3.40 (d, J = 11.4 Hz, 1 H), 3.53 (d, J = 11.4 Hz, 1 H), 4.55 (s, 1 H), 4.84 (s, 1 H), 6.51 (d, J = 5.8 Hz, 1 H), 6.71 (d, J = 6.0 Hz, 1 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.76 (d, J = 8.2 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –141.5 (d, J = 153 Hz 1 F), –150.0 (d, J = 151, J = 6 Hz 1 F) ppm. IR (film): $\tilde{\nu}$ = 2937, 1597, 1469, 1435, 1317, 1305, 1203, 1182, 1145, 1116 cm^{-1}. MS (ESI): m/z = 385.0 [M + H$^+$]. $C_{19}H_{22}F_2O_4S$ (384.12): calcd. C 59.36, H 5.77; found C 59.38, H 5.76.

2n: Yield 63%, solid, m.p. 126–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08–1.39 (br., 4 H), 1.45–1.79 (br., 6 H), 2.40 (s, 3 H), 3.21 (s, 3 H), 3.27 (d, J = 11.5 Hz, 1 H), 3.45 (d, J = 11.5 Hz, 1 H), 4.46 (s, 1 H), 4.83 (s, 1 H), 6.40–6.42 (d, J = 6.1 Hz, 1 H), 6.59 (d, J = 6.0 Hz, 1 H), 7.29 (d, J = 7.9 Hz, 2 H), 7.68 (d, J = 8.4 Hz, 2 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –142.9 (d, J = 152 Hz, 1 F), –149.9 (dd, J = 150, J = 6 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 2930, 2855, 1597, 1471, 1447, 1310, 1307, 1291, 1185, 1160, 1146, 1118, 1085, 1066 cm^{-1}. MS (ESI): m/z = 425.2 [M + H$^+$]. $C_{22}H_{26}F_2O_4S$ (424.15): calcd. C 62.25, H 6.17; found C 62.06, H 6.36.

General Procedure of Retro-Diels–Alder Reaction of Compound 2: A sample containing **2a** (50 mg, 0.147 mmol) and *tert*-butyl alcohol (0.1 mL) was stirred in a 5-mL sealed tube at 100 °C for 8 h. The heating was then stopped and the product was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to yield **1a** (29 mg, 57%).

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