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Electrolytic Partial Fluorination of Organic Compounds. 83. Anodic Fluorination of *N*-Substituted Pyrroles and Its Synthetic Applications to *gem*-Difluorinated Heterocyclic Compounds

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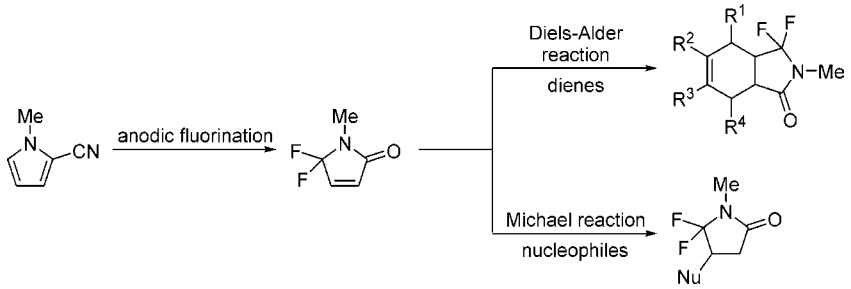

Anodic fluorination of *N*-substituted pyrroles was carried out in MeCN containing supporting fluoride salts such as Et_3N-nHF ($n = 2-5$) and $Et_4NF-4HF$ with use of platinum electrodes under constant current conditions. Anodic fluorination of *N*-methyl- and *N*-*p*-tosylpyrroles having an electron-withdrawing cyano group proceeded smoothly to provide the corresponding fluorinated products in moderate to excellent yields, while anodic fluorination of *N*-methylpyrrole devoid of an electron-withdrawing cyano group did not take place and a polymeric product was formed at the anode surface. In sharp contrast to the cases of *N*-methylpyrroles, even *N*-*p*-tosylpyrrole devoid of an electron-withdrawing cyano group underwent anodic fluorination efficiently. Diels−Alder reaction of 5,5-difluoro-1-methyl-3-pyrrolin-2-one (**2e**) derived from anodic fluorination of 2-cyano-1-methylpyrrole (**2a**) with various dienes was carried out to provide the cycloaddition products in excellent yields. Furthermore, Michael reaction of **2e** with various nucleophiles was also successfully carried out to provide the Michael addition products in good to excellent yields.

Introduction

Fluorine-containing heterocyclic compounds have attracted much interest because of their unique chemical, physical, and biological activities.[1] In particular, fluorine-containing five-membered heteroaromatic compounds, such as fluoropyrroles, fluorothiophenes, and fluorofurans, are useful precursors of various biologically active compounds and conducting polymers. Direct selective fluorination is the most ideal method for the preparation of these compounds from the viewpoint of atom economy. However, it generally requires special equipment and techniques because many fluorinating reagents are usually explosive, toxic, unstable, or hygroscopic.[2] In addition, although the chemical fluorination of five-membered heteroaromatic compounds has been attempted, the yields and selectivity were extremely low in all cases.[3] On the other hand, recently, much attention has also been paid to pharmaceuticals and agricultural chemicals containing a *gem*-difluoromethylene unit because it is isopolar and isosteric with an ether oxygen.[4] There are two complementary approaches to such an important unit. One is

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the substitution of a carbonyl or an active methylene group by various fluorinating reagents derived from fluorine gas,[5] and the other is the use of *gem*-difluoromethylene-containing building blocks.[6] The former approach cannot be applied to complex molecules because of the low selectivity of fluorinating reagents such as SF_4 and diethylaminosulfur trifluoride (DAST). Instead, the latter approach is mainly employed despite the limited availability of *gem*-difluoromethylene-containing building blocks.

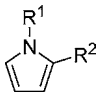
Recently, electrochemical fluorination has been shown to be a useful alternative method for selective direct fluorination because the electrochemical fluorination can be carried out under mild and safe conditions with relatively simple equipment. Therefore, there have been many reports on anodic fluorination of organic compounds such as organosulfur, organonitrogen, and heterocyclic compounds.[7] However, there have been few reports on anodic fluorination of heteroaromatic compounds. On the other hand, we found that electron-withdrawing groups promoted the anodic fluorination of heteroatom compounds.[8] With these facts in mind, we attempted anodic fluorination of *N*-substituted pyrroles and its synthetic applications to *gem*-difluorinated heterocyclic compounds. The results are reported and discussed in this paper.

Results and Discussion

At first, the oxidation potentials of *N*-methyl- and *N*-*p*-tosylpyrrole (**1a**, **3a**) and their 2-cyano derivatives **2a** and **4a** were measured. As shown in Table 1, the oxidation potential of **2a** having a strongly electron-withdrawing cyano group was much higher compared with that of **1a** devoid of an electron-withdrawing cyano group. The oxidation potential of **4a** having a strongly electron-withdrawing cyano group was also much higher compared with that of **3a** devoid of an electron-withdrawing cyano group. Interestingly, **2a** and **3a** have similar oxidation potentials.

Next, anodic fluorination of **1a**−**4a** was carried out with various supporting fluoride salts in acetonitrile (MeCN). As show in Table 2, anodic fluorination of **1a** did not take place at all and a polymeric product was formed at the anode surface regardless of supporting fluoride salts (entries 1 and 2). On the other hand, anodic fluorination of **2a** proceeded smoothly to provide the fluorinated products **2c**, **2d**, and **2e** depending on the supporting fluoride salts (entries 3−5). Anodic fluorination of **3a** was also carried out to provide the corresponding difluorinated product **3b** in excellent yield (entry 6). Interestingly, anodic fluorination of **3a** proceeded smoothly despite an absence of a substituent at the 2-position. From these results of anodic fluorination of **1a**−**3a**, anodic fluorination of *N*-substituted pyrroles seems to be greatly affected not by steric hindrance at the 2-position but by the reactivity of the cation radical intermediates derived from one-electron oxidation of *N*-substituted pyrroles. Furthermore, anodic fluorination of **4a** with Et_4NF−4HF took place to provide the corresponding difluorinated product **4b** in high yield. On the other hand, **4b** was obtained in moderate yields with use of Et_3N−3HF and Et_3N−5HF, because the oxidation potential of **4a** (E_p^{ox} = 2.56 V vs SCE) is much higher compared with those of Et_3N−3HF (E_d^{ox} = 2.0 V vs SCE) and Et_3N−5HF (E_d^{ox} = 2.4 V vs SCE).

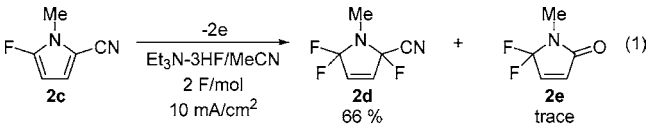
TABLE 1. Oxidation Potentials of *N*-Substituted Pyrroles

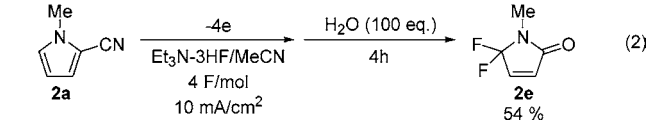


	R^1	R^2	E_p^{ox} (V vs SCE)[a]
1a	Me	H	1.40
2a	Me	CN	1.95
3a	Ts	H	1.96
4a	Ts	CN	2.56

[a] Oxidation potentials (E_p^{ox}) of **1a**−**4a** (0.01 M) were measured in 0.1 M n-Bu_4NBF_4/MeCN, recorded at a Pt disk electrode (ϕ = 8 mm). The scan rate was 100 mV s^{-1}.

To learn about the reaction mechanism, in the case of **2a**, the relationship between the electricity and the yields of the fluorinated products **2c** and **2d** was investigated in Et_3N−3HF/MeCN. As shown in Figure 1, the maximum yield of **2c** was obtained at 2 F/mol, and then the yield decreased with the amount of electricity. On the other hand, the yield of **2d** increased linearly to 65% yield with the amount of electricity. This near-linear formation of **2d** and the course of the yield of **2c** suggest that **2d** is formed via **2c**. Then, the oxidation potential of **2c** was measured. The oxidation potential of **2c** (E_p^{ox} = 1.90 V vs SCE) was slightly lower compared with that of **2a** (E_p^{ox} = 1.95 V vs SCE) because of the resonance effect of the fluorine atom of **2c**. These facts indicate that the further oxidation of **2c** gives **2d** after **2c** is once formed during the electrolysis. Then, anodic fluorination of **2c** was investigated. As shown in eq 1,





anodic fluorination of **2c** in Et_3N−3HF/MeCN was carried out to provide the fluorinated product **2d** in good yield. Thus, it was clarified that **2d** is generated from **2c**. Furthermore, to clarify the oxygen source of **2e**, excess amounts of water were added to the electrolytic solution after the electrolysis of **2a** in

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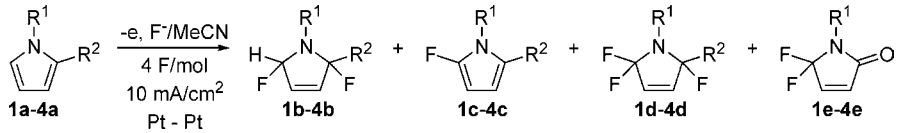
TABLE 2. Anodic Fluorination of *N*-Substituted Pyrroles



entry	substrate	R^1	R^2	supporting electrolyte (1 M)	yield (%)[a] 1b−4b	1c−4c	1d−4d	1e−4e
1[b]	**1a**	Me	H	Et_3N−3HF	0	0	0	0
2[b]	**1a**	Me	H	Et_4NF−4HF	0	0	0	0
3	**2a**	Me	CN	Et_3N−2HF	0	20 (19)[c]	32	trace
4	**2a**	Me	CN	Et_3N−3HF	0	5	65	3
5	**2a**	Me	CN	Et_3N−5HF	0	0	5	54 (51)
6	**3a**	Ts	H	Et_3N−3HF	93 [34/66][d]	0	0	0
7	**4a**	Ts	CN	Et_3N−3HF	48 [46/54]	0	0	0
8	**4a**	Ts	CN	Et_3N−5HF	49 [43/57]	0	0	0
9	**4a**	Ts	CN	Et_4NF−4HF	80(55) [45/55]	0	0	0

[a] Determined by ^{19}F NMR spectroscopy. [b] A polymeric product was formed at the anode surface. [c] Isolated yield in parentheses. [d] Ratio of cis/trans isomers.

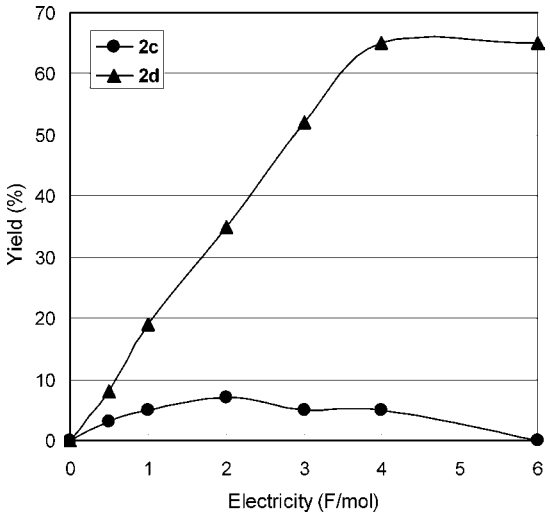


FIGURE 1. Relationship between the electricity and the yields of **2c** and **2d** in Et_3N−3HF/MeCN.

Et_3N−3HF/MeCN (eq 2). The reaction mixture was stirred for 4 h to give the difluorinated product **2e** in 54% yield (ca. 83% yield from **2d** in consideration of entry 4 in Table 2). This result clearly indicates that **2d** was readily hydrolyzed to form **2e** efficiently. Therefore, **2d** is a precursor to **2e**. Thus, the oxygen source of **2e** is water contaminated in the fluoride salts, and there seems to be more water contamination in Et_3N−5HF.

In consideration of these results, a possible reaction mechanism was proposed as shown in Scheme 1. At first, one-electron oxidation of a substrate gives the corresponding cation radical intermediate **A**. Then, in the case of **1a**, anodic polymerization proceeds via the radical coupling reaction of **A**.[9] On the other hand, in the cases of **2a**, **3a**, and **4a**, anodic fluorination takes place to provide the corresponding difluorinated product via a conventional ECEC process. Therefore, interestingly, electron-withdrawing *p*-tosyl and cyano groups promote anodic fluorination of pyrroles, while they suppress highly efficiently anodic polymerization. The reaction pathway seems to greatly depend not on steric hindrance at the 2-position but on the reactivity of the cation radical intermediate **A**, because anodic fluorination of **3a** devoid of a substituent at the 2-position proceeded smoothly (entry 6 in Table 2). The difluorinated product **2b** derived from **2a** eliminates a fluoride anion rapidly due to the absence of an electron-withdrawing group on the nitrogen atom to provide **2c**. Then, since **2c** is more easily oxidized than **2a**, the trifluorinated product **2d** is preferentially formed by the further oxidation of **2c** once formed during the electrolysis. On the other hand, it also seems to be possible to form **2d** by the further oxidation of **2b**; however, the further oxidation of **3b** and **4b** did not take place at all. Therefore, **2d** is formed from **2c**. Then, the trifluorinated product **2d** reacts rapidly with water to give the difluorinated product **2e**.

The difluorinated product **2e** derived from **2a** has both a biologically interesting *gem*-difluoromethylene unit and an activated olefin in the heterocyclic ring. Therefore, it is expected that **2e** becomes a useful building block having a *gem*-difluoromethylene unit. Then, at first, the Diels−Alder reaction of **2e** as a dienophile with various dienes was investigated. Several examples of the Diels−Alder reaction are shown in Table 3. **2e** reacted with open-chain dienes such as isoprene (**5a**) and 2,3-dimethyl-1,3-butadiene (**6a**) under reflux in toluene to afford the corresponding cycloaddition products **5b** and **5c** in excellent yield as a regioisomeric mixture and **6b** in quantitative yield, respectively (entries 1 and 2). The Diels−Alder reaction of **2e** with cyclic dienes such as cyclopentadiene (**7a**), cyclohexadiene (**8a**), and furan (**9a**) also proceeded smoothly to provide the cycloaddition products **7b**, **8b**, and **9b** in quantitative yields with endo selectivities (entries 3−5). From these results, it was found that **2e** is a highly useful dienophile having a *gem*-difluoromethylene unit in the Diels−Alder reaction.

Next, the Michael reaction of **2e** with various nucleophiles was also investigated. Several examples of the Michael reaction are listed in Table 4. In every case, the reactions proceeded smoothly in the presence of Bu_4NF at room temperature to provide the corresponding Michael addition products in good

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SCHEME 1. Reaction mechanism

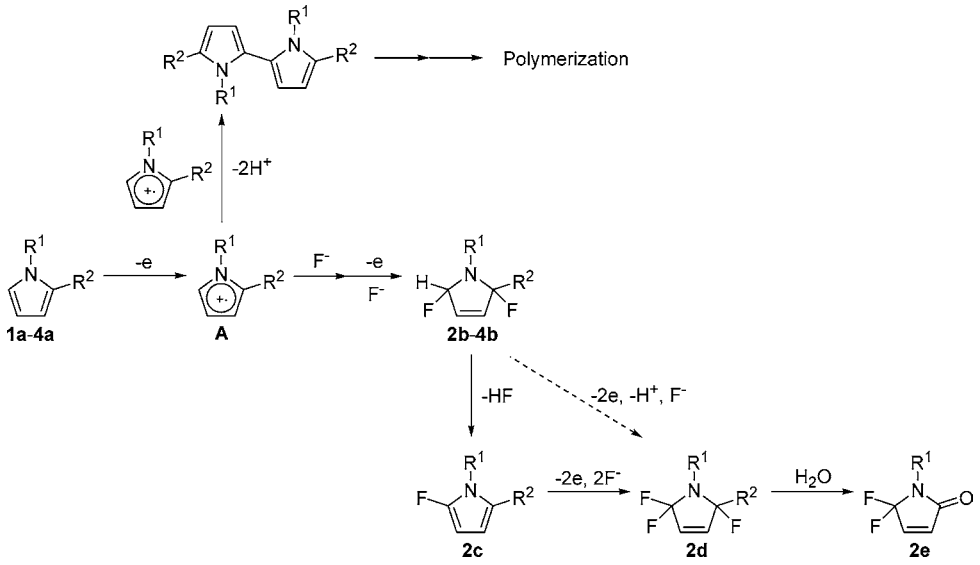
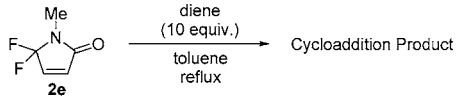


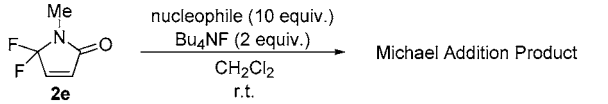
TABLE 3. Diels−Alder Reaction of 2e with Various Dienes



entry	diene	time (d)	product	yield (%)[a]
1	**5a**	1.5	**5b** / **5c**	98 (96)[b] [**5b**/**5c**=2/1][c]
2	**6a**	1	**6b**	quant. (98)
3	**7a**	0.5	**7b**	quant. (97) (*endo* only)
4	**8a**	1	**8b**	98 (96) (*endo* only)
5	**9a**	1.5	**9b**	quant. (98) (*endo*/*exo*=2/1)

[a] Determined by ^{19}F NMR Spectroscopy. [b] Isolated yield in parentheses. [c] Regioisomeric ratio.

TABLE 4. Michael Reaction of 2e with Various Nucleophiles



entry	nuclephile	time (d)	product	yield (%)[a]
1	**10a**	0.5	**10b**	quant. (97)[b]
2	**11a**	0.25	**11b**	quant. (95)
3	**12a**	2	**12b**	85 (80)
4	**13a**	1	**13b**	quant. (90)
5	**14a**	1.5	**14b**	96 (75)

[a] Determined by ^{19}F NMR Spectroscopy. [b] Isolated yield in parentheses.

to quantitative yields. Thus, it was found that **2e** is also valuable in the Michael reaction.

Conclusion

We have successfully carried out the anodic fluorination of pyrroles having electron-withdrawing groups at 1- and/or 2-positions to provide some corresponding fluorinated products. On the other hand, anodic fluorination of *N*-methylpyrrole devoid of an electron-withdrawing group did not take place at all and a polymeric product was formed at the anode surface. The reaction pathway greatly depended on the reactivity of cation radical intermediates derived from one-electron oxidation

of *N*-substituted pyrroles. Anodic fluorination of 2-cyano-1-methylpyrrole (**2a**) in Et_3N-5HF/MeCN gave 5,5-difluoro-1-methyl-3-pyrrolin-2-one (**2e**) having a biologically interesting *gem*-difluoromethylene unit and an activated olefin in the heterocyclic ring in moderate yield. The Diels−Alder reaction of **2e** with various dienes proceeded smoothly to provide the corresponding cycloaddition products in excellent yields. Furthermore, the Michael reaction of **2e** with various nucleophiles also took place to provide the corresponding Michael addition products in good to excellent yields. Therefore, it was found that **2e** derived from anodic fluorination of **2a** is a highly useful building block having a *gem*-difluoromethylene unit in the Diels−Alder reaction and Michael reaction.

Experimental Section

General Procedure for Anodic Fluorination. Anodic fluorination of **1a**, **2a**, **3a**, **4a**, and **2c** (1 mmol) was carried out with platinum plate electrodes (2 × 2 cm^2) in MeCN (10 mL) containing a fluoride salt (1 M), using an undivided cell at room temperature. Constant current (10 mA cm^{-2}) was applied. The conversion of a starting material was monitored by TLC. After the charge was passed (4 F mol^{-1}) until the starting material was consumed, the electrolytic solution was passed through a short column of silica gel eluting with $CHCl_3$ to remove the fluoride salt. The eluent was evaporated under vacuum. Then, the yields of the fluorinated products **2c**−**e**, **3b**, and **4b** were calculated by means of ^{19}F NMR by using a known amount of monofluorobenzene as an internal standard. After that, **2c**, **2e**, **3b**, and **4b** were isolated by liquid chromatography eluting with MeCN to give the pure fluorinated products.

2-Cyano-5-fluoro-1-methylpyrrole (2c): ^1H NMR (270 MHz, $CDCl_3$) δ 6.66 (m, 1H), 5.60 (m, 1H), 3.62 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 148.2 (d, J = 267.2 Hz), 129.3 (d, J = 4.5 Hz), 117.9 (d, J = 3.9 Hz), 113.3, 88.3 (d, J = 11.7 Hz), 30.1 (d, J = 1.7 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −54.5 (m); MS (*m*/*z*) 124 (M^+), 109, 84; HRMS calcd for $C_6H_5N_2F$ 124.0437, found 124.0443.

2,5,5-Trifluoro-1-methyl-3-pyrrolin-2-carbonitrile (2d): ^{19}F NMR (254 MHz, $CDCl_3$) δ −2.5 (dd, J = 205.3, 18.5 Hz), −11.3 (dd, J = 205.3, 27.7 Hz), −30.4 (dd, 27.7, 18.5 Hz); MS (*m*/*z*) 162 (M^+).

5,5-Difluoro-1-methyl-3-pyrrolin-2-one (2e): FTIR (KBr) ν_{max} 3445 (br), 3096, 1705, 1441, 1389, 1256, 1107, 1053, 941, 831, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.92 (d, J = 5.8 Hz, 1H), 6.30 (d, J = 5.8 Hz, 1H), 2.94 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.6, 138.0 (t, J = 27.4 Hz), 130.2 (t, J = 3.9 Hz), 122.3 (t, J = 243.7), 22.8; ^{19}F NMR (254 MHz, $CDCl_3$) δ −23.6 (s); MS (*m*/*z*) 133 (M^+), 106, 84; HRMS calcd for $C_5H_5F_2NO$ 133.0339, found 133.0335.

2,5-Difluoro-1-*p*-tosyl-3-pyrroline (3b): *cis*-**3b**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.48 (dd, J = 50.0, 24.0 Hz, 2H), 6.24 (s, 2H), 2.44 (s, 3H); ^{19}F NMR (254 MHz, $CDCl_3$) δ −57.1 (dd, J = 50.0, 24.0 Hz); MS (*m*/*z*) 259 (M^+), 155, 109, 91, 65, 51; HRMS calcd for $C_{11}H_{11}F_2NO_2S$ 259.0479, found 259.0477. *trans*-**3b**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.85 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.50 (dd, J = 50.8, 32.3 Hz, 2H), 6.28 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 144.4, 137.2, 131.6 (dd, J = 14.0, 13.4 Hz), 129.6, 127.1, 98.8 (dd, J = 224.1, 8.4 Hz), 21.7; ^{19}F NMR (254 MHz, $CDCl_3$) δ −51.1 (dd, J = 50.8, 32.3 Hz); MS (*m*/*z*) 259 (M^+), 155, 109, 91, 65, 51; HRMS calcd for $C_{11}H_{11}F_2NO_2S$ 259.0479, found 259.0484.

2,5-Difluoro-1-*p*-tosyl-3-pyrrolin-2-carbonitrile (4b): *cis*-**4b**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 6.58 (dd, J = 66.6, 7.4 Hz, 1H), 6.46 (d, J = 5.8 Hz, 1H), 6.31 (d, J = 5.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 145.6, 135.3, 133.7 (dd, J = 15.9, 6.7 Hz), 130.9 (dd, J = 18.7, 6.7 Hz), 129.8, 128.3, 112.0 (d, J = 58.7 Hz), 99.7 (d, J = 210.2 Hz), 95.1 (d, J = 210.7 Hz), 21.8; ^{19}F NMR (254 MHz, $CDCl_3$) δ −23.1 (dd, J = 42.5, 7.4 Hz), −60.3 (dd, J = 66.6, 42.5 Hz); MS (*m*/*z*) 284 (M^+), 155, 109, 91, 65, 51; HRMS calcd for $C_{12}H_{10}F_2N_2O_2S$ 284.0431, found 284.0435. *trans*-**4b**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 6.48 (d, J = 5.8 Hz, 1H), 6.47 (dd, J = 64.6, 18.0 Hz, 1H), 6.34 (d, J = 5.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 145.4, 136.0, 133.4 (dd, J = 17.9, 6.7 Hz), 131.4 (dd, J = 22.4, 8.4 Hz), 129.7, 128.0, 112.0 (dd, J = 58.1, 11.7 Hz), 99.0 (dd, J = 213.5, 6.1 Hz), 94.7 (dd, J = 215.2, 6.1 Hz), 21.7; ^{19}F NMR (254 MHz, $CDCl_3$) δ −20.3 (dd, J = 42.5, 18.0 Hz), −55.1 (dd, J = 64.6, 42.5 Hz); MS (*m*/*z*) 284 (M^+), 155, 109, 91, 65, 51; HRMS calcd for $C_{12}H_{10}F_2N_2O_2S$ 284.0431, found 284.0428.

General Procedure for the Diels−Alder Reaction. The Diels−Alder reaction of **2e** (0.1 mmol) with a diene (1 mmol) was carried out in toluene (5 mL). The reaction mixture was stirred for 0.5−1.5 d under reflux. After the reaction was complete, the reaction mixture was passed through a short column of silica gel eluting with $CHCl_3$. The eluent was evaporated under vacuum. Then, the yields of the cycloaddition products **5b**, **5c**, **6b**, **7b**, **8b**, and **9b** were calculated by means of ^{19}F NMR by using a known amount of monofluorobenzene as an internal standard. After that, **5b**, **5c**, **6b**, **7b**, **8b**, and **9b** were isolated by liquid chromatography eluting with MeCN to give the pure cycloaddition products.

3,3-Difluoro-2,5-dimethyl-2,3,3a,4,7,7a-hexahydroisoindol-1-one (5b): ^1H NMR (270 MHz, $CDCl_3$) δ 5.48 (br s, 1H), 3.01−2.83 (m, 2H), 2.87 (s, 3H), 2.39−2.14 (m, 4H), 1.72 (br s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.6, 134.3, 126.8 (dd, J = 250.4, 247.6 Hz), 118.8, 39.8, 38.5 (dd, J = 26.3, 20.7 Hz), 29.8, 27.4, 23.4, 21.3 (dd, J = 6.7, 2.2 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ −1.0 (dd, J = 185.0, 12.9 Hz), −17.5 (d, J = 185.0 Hz); MS (*m*/*z*) 201(M^+), 186, 181, 152; HRMS calcd for $C_{10}H_{13}F_2NO$ 201.0965, found 201.0962.

3,3-Difluoro-2,6-dimethyl-2,3,3a,4,7,7a-hexahydroisoindol-1-one (5c): ^1H NMR (270 MHz, $CDCl_3$) δ 5.48 (br s, 1H), 3.01−2.83 (m, 2H), 2.87 (s, 3H), 2.39−2.14 (m, 4H), 1.72 (br s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.8, 134.2, 126.8 (dd, J = 250.4, 247.6 Hz), 119.6, 39.4 (dd, J = 25.7, 20.7 Hz), 39.3 (d, J = 1.7 Hz), 25.9 (dd, J = 6.7, 1.7 Hz), 23.8, 23.4, 23.2; ^{19}F NMR (254 MHz, $CDCl_3$) δ −1.3 (dd, J = 185.0, 14.8 Hz), −15.7 (d, J = 185.0 Hz); MS (*m*/*z*) 201(M^+), 186, 170, 152; HRMS calcd for $C_{10}H_{13}F_2NO$ 201.0965, found 201.0961.

3,3-Difluoro-2,5,6-trimethyl-2,3,3a,4,7,7a-hexahydroisoindol-1-one (6b): ^1H NMR (270 MHz, $CDCl_3$) δ 2.94 (m, 2H), 2.85 (s, 3H), 2.38−2.11 (m, 4H), 1.67 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.5, 126.9 (dd, J = 249.8, 247.0 Hz), 126.0, 125.3, 40.5, 39.7 (dd, J = 25.7, 20.1 Hz), 29.5, 27.9 (dd, J = 6.7, 1.7 Hz), 23.8, 19.2, 18.8; ^{19}F NMR (254 MHz, $CDCl_3$) δ 1.0 (dd, J = 186.8, 14.8 Hz), −15.6 (d, J = 186.8 Hz); MS (*m*/*z*) 215(M^+), 200, 195, 152; HRMS calcd for $C_{11}H_{15}F_2NO$ 215.1122, found 215.1117.

5,5-Difluoro-4-methyl-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (7b): *endo*-**7b**: ^1H NMR (270 MHz, $CDCl_3$) δ 6.09 (s, 2H), 3.34−3.10 (m, 4H), 2.73 (s, 3H), 1.66 (d, J = 8.7 Hz), 1.46 (d, J = 8.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 172.8, 134.3, 134.1, 125.3 (dd, J = 248.7, 244.8 Hz), 51.4, 48.8 (t, J = 2.2 Hz), 45.8 (dd, J = 26.3, 20.7 Hz), 44.5, 43.9 (t, J = 2.8 Hz), 23.3; ^{19}F NMR (254 MHz, $CDCl_3$) δ 7.7 (dd, J = 190.5, 16.6 Hz), −13.4 (d, J = 190.5 Hz); MS (*m*/*z*) 199(M^+), 172, 156, 149; HRMS calcd for $C_{10}H_{11}F_2NO$ 199.0809, found 199.0815.

5,5-Difluoro-4-methyl-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-en-3-one (8b): *endo*-**8b**: ^1H NMR (270 MHz, $CDCl_3$) δ 6.13 (m, 2H), 3.09 (m, 1H), 2.99 (m. 1H), 2.85−2.71 (m, 2H), 2.79 (s, 3H), 1.53 (m, 2H), 1.34 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.7, 132.4, 131.3, 126.5 (dd, J = 248.2, 245.4 Hz), 46.6 (t, J = 1.7 Hz), 44.4 (dd, J = 25.7, 20.1 Hz), 31.0, 29.4 (dd, J = 5.0, 2.2 Hz), 23.8, 23.5, 23.0; ^{19}F NMR (254 MHz, $CDCl_3$) δ 7.5 (dd, J = 186.8,

16.6 Hz), −11.7 (d, J = 186.8 Hz); MS (*m*/*z*) 213(M^+), 185, 170, 155; HRMS calcd for $C_{11}H_{13}F_2NO$ 213.0965, found 213.0970.

5,5-Difluoro-4-methyl-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (9b): *endo*-**9b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.45−6.36 (m, 2H), 5.25−5.19 (m, 2H), 3.60−3.52 (m, 1H), 3.41−3.30 (m, 1H), 2.73 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.4, 134.6, 134.4, 123.5 (dd, J = 247.0, 246.0 Hz), 79.4, 78.5 (dd, J = 4.5, 2.2 Hz), 49.2 (t, J = 2.2 Hz), 45.4 (dd, J = 28.5, 21.2 Hz), 23.6; ^{19}F NMR (254 MHz, $CDCl_3$) δ 5.5 (dd, J = 194.2, 14.8 Hz), −13.7 (dt, J = 194.2, 7.4 Hz); MS (*m*/*z*) 201 (M^+), 172, 132, 114, 95; HRMS calcd for $C_9H_9F_2NO_2$ 201.0601, found 201.0588. *exo*-**9b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.53−6.45 (m, 2H), 5.33 (s, 1H), 5.25 (s, 1H), 2.89 (s, 3H), 2.89−2.86 (m, 1H), 2.77−2.72 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.9, 137.2, 135.9, 124.4 (dd, J = 249.3, 246.0 Hz), 80.3, 78.6 (dd, J = 7.3, 3.4 Hz), 49.4, 46.7 (dd, J = 27.9, 22.9 Hz), 24.0; ^{19}F NMR (254 MHz, $CDCl_3$) δ 5.1 (dd, J = 188.7, 14.8 Hz), −14.9 (d, J = 188.7 Hz); MS (*m*/*z*) 201-(M^+), 132, 114, 95; HRMS calcd for $C_9H_9F_2NO_2$ 201.0601, found 201.0601.

General Procedure for the Michael Reaction. Michael reaction of **2e** (0.1 mmol) with a nucleophile (1 mmol) was carried out in CH_2Cl_2 (5 mL) in the presence of Bu_4NF (0.2 mmol). The reaction mixture was stirred for 0.25−2 d at room temperature. After the reaction was complete, the reaction mixture was passed through a short column of silica gel eluting with $CHCl_3$. The eluent was evaporated under vacuum. Then, the yields of the Michael addition products **10b**, **11b**, **12b**, **13b**, and **14b** were calculated by means of ^{19}F NMR by using a known amount of monofluorobenzene as an internal standard. After that, **10b**, **11b**, **12b**, **13b**, and **14b** were isolated by liquid chromatography eluting with MeCN to give the pure Michael addition products.

5,5-Difluoro-1-methyl-4-(phenylthio)pyrrolidin-2-one (10b): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.35−7.33 (m, 3H), 4.06−3.93 (m, 1H), 3.07−2.96 (m, 1H), 2.90 (s, 3H), 2.60−2.49 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 169.4, 132.8, 131.7, 129.2, 128.5, 124.8 (dd, J = 251.5, 248.7 Hz), 47.1 (dd, J = 27.4, 24.6 Hz), 36.4 (t, J = 1.1 Hz), 24.1; ^{19}F NMR (254 MHz, $CDCl_3$) δ −3.0 (ddd, J = 183.1, 11.1, 3.7 Hz), −8.7 (ddd, J = 183.1, 7.4, 1.9 Hz); MS (*m*/*z*) 223 (M^+ − HF), 221, 136, 135, 109; HRMS calcd for $C_{11}H_{11}F_2NOS$ 243.0529, found 243.0522.

5,5-Difluoro-1-methyl-4-(4-methoxyphenylthio)pyrrolidin-2-one (11b): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.49 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 3.90−3.81 (m, 1H), 3.81 (s, 3H), 2.99−2.88 (m, 1H), 2.88 (s, 3H), 2.56−2.46 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 169.3, 160.4, 136.4, 128.5, 121.2 (dd, J = 248.7, 240.9 Hz), 114.7, 55.4, 47.9 (dd, J = 26.3, 24.6 Hz), 36.1 (d, J = 2.2 Hz), 24.0; ^{19}F NMR (254 MHz, $CDCl_3$) δ −3.3 (ddd, J = 183.1, 12.9, 3.7 Hz), −8.9 (ddd, J = 183.1, 7.4, 1.9 Hz); MS (*m*/*z*) 253 (M^+ − HF), 251, 151, 139; HRMS calcd for $C_{12}H_{13}F_2NO_2S$ 273.0635, found 273.0634.

4-(4-Ethoxyphenylamino)-5,5-difluoro-1-methylpyrrolidin-2-one (12b): ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.82−6.78 (m, 2H), 6.68−6.65 (m, 2H), 4.39−4.27 (m, 1H), 3.97 (q, J = 7.1 Hz, 2H), 3.69 (br s, 1H), 3.12−3.02 (m, 1H), 2.93 (s, 3H), 2.44−2.34 (m, 1H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 169.6, 152.5, 139.3, 124.7 (dd, J = 254.3, 252.1 Hz), 115.6, 115.3, 64.0, 54.5 (dd, J = 26.8, 21.8 Hz), 37.2, 23.8, 15.0; ^{19}F NMR (254 MHz, $CDCl_3$) δ −7.6 (dd, J = 185.0, 11.1 Hz), −17.3 (dd, J = 185.0, 5.5 Hz); MS (*m*/*z*) 270 (M^+), 250 (M^+ − HF), 221, 207; HRMS calcd for $C_{13}H_{16}F_2N_2O_2$ 270.1180, found 270.1172.

Diethyl 2-(2,2-difluoro-1-methyl-5-oxo-pyrrolidin-3-yl)malonate (13b): ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.30−4.19 (m, 4H), 3.69 (d, J = 9.1 Hz), 3.53−3.36 (m, 1H), 2.92−2.81 (m, 1H), 2.89 (s, 3H), 2.66−2.55 (m, 1H), 1.32−1.25 (m, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.3, 166.6, 166.5, 125.7 (dd, J = 251.0, 249.3 Hz), 62.3, 62.2, 51.2, 39.9 (dd, J = 25.7, 21.8 Hz), 33.4, 23.8, 14.0; ^{19}F NMR (254 MHz, $CDCl_3$) δ −1.5 (ddd, J = 186.8, 12.9, 3.7 Hz), −19.5 (dd, J = 186.8, 7.4 Hz); MS (*m*/*z*) 273 (M^+ − HF), 248, 220, 200, 172, 152, 128; HRMS calcd for $C_{12}H_{17}F_2NO_5$ 293.1075, found 293.1080.

Diethyl 2-(2,2-difluoro-1-methyl-5-oxo-pyrrolidin-3-yl)-2-methylmalonate (14b): ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.29−4.15 (m, 4H), 3.49−3.34 (m, 1H), 2.97−2.77 (m, 2H), 2.88 (s, 3H), 1.61 (s, 3H), 1.30−1.22 (m, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.0, 170.0, 169.4, 126.2 (dd, J = 252.2, 248.7 Hz), 62.2, 61.9, 54.1, 45.4 (dd, J = 25.7, 20.1 Hz), 33.3, 23.7, 19.3, 14.0; ^{19}F NMR (254 MHz, $CDCl_3$) δ 6.2 (ddd, J = 190.5, 15.0, 1.9 Hz), −11.5 (ddd, J = 190.5, 7.4, 1.9 Hz); MS (*m*/*z*) 287 (M^+ − HF), 262, 214, 186, 166, 142, 128; HRMS calcd for $C_{13}H_{19}F_2NO_5$ 307.1231, found 307.1234.

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Supporting Information Available: General experimental details and spectroscopy data. This material is available free of charge via the Internet at http://pubs.acs.org.

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