Disfavored ring formation: 5-endo-trig Cyclizations are achieved in 2-trifluoromethyl-1-alkenes with a nucleophilic nitrogen, oxygen, sulfur, or carbon atom via (i) intramolecular $\text{S}_{\text{N}}2$' reaction with loss of a fluoride ion or (ii) intramolecular nucleophilic addition to the vinylic group.
A New Class of Substrates for Nucleophilic 5-endo-trig Cyclization, 2-Trifluoromethyl-1-alkenes: Synthesis of Five-Membered Hetero- and Carbocycles Bearing Fluorinated One-Carbon Units

Junji Ichikawa,*[a] Yu Iwai,[b] Ryo Nadano,[b] Takashi Mori,[b] and Masahiro Ikeda[a]

The present work is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

Abstract: Disfavored 5-endo-trig cyclizations are achieved in 2-trifluoromethyl-1-alkenes with a nucleophilic nitrogen, oxygen, sulfur, or carbon atom via (i) intramolecular SN2 reaction with loss of a fluoride ion or (ii) intramolecular nucleophilic addition to the vinylic group. This reaction manifold provides a versatile method for the synthesis of indolines, indoles, pyrrolidines, tetrahydrofurans, 2,3-dihydrobenzo[b]thiophenes, tetrahydrothiophenes, and cyclopentanes bearing a fluorinated one-carbon unit such as a difluoromethylene, difluoromethyl, or trifluoromethyl group.

Keywords: 5-endo-trig cyclization, fluorine, heterocycles, carbocycles, synthetic methods

Introduction

The 5-endo-trig cyclization has long been considered to be a geometrically disfavored process according to Baldwin’s rules.1 Reported examples of this disfavored ring closure are classified into three categories: nucleophile-driven,2,3 electrophile-driven,4 and radical-initiated cyclizations.5 Among these, nucleophile-driven 5-endo-trig cyclizations have rarely been observed in synthetic chemistry, compared with the two other types of cyclization.

In our recent studies, we have accomplished the normally disfavored nucleophilic 5-endo-trig cyclizations with 1,1-difluoro-1-alkene substrates (2,2-difluorovinyl compounds) bearing a functional group such as NHTs, OH, SH, or CH2I (Scheme 1a).2 Deprotonation or lithium–iodine exchange of these groups generates N-, O-, S-, and C-nucleophiles, which successfully undergo a vinylic addition–elimination (SnV) process to construct five-membered ring-fluorinated heterocycles and carbocycles such as indoles, 2-pyrrolines, benzo[b]furans, 2,3-dihydrofurans, benzo[b]thiophenes, 2,3-dihydrothiophenes, and cyclopentenes. Such unique reactivities of 1,1-difluoro-1-alkenes are presumably the result of (i) the highly polarized C=C double bond, which allows the initial five-membered ring formation by electrostatic attraction of the positive CF2 carbon for the nucleophiles, and (ii) the subsequent elimination of fluoride ion, which suppresses the reverse ring opening.

(b) 1-(Trifluoromethyl)vinyl compounds

Scheme 1. Nucleophilic 5-endo-trig Cyclization of Fluoroalkenes.

Among fluoroalkenes, 2-trifluoromethyl-1-alkenes are also known to possess an interesting reactivity in nucleophilic reaction, resulting from (i) the highly electrophilic double bond with a strong electron-withdrawing CF3 group and (ii) the good leaving group ability of allylic fluorine atoms. The nucleophilic reaction of 2-trifluoromethyl-1-alkene substrates [1-(trifluoromethyl)vinyl compounds] proceeds with the accompanying elimination of an allylic fluoride (Sn2'-type process), which provides a potential method for the preparation of 1,1-difluoro-1-alkenes.6 We have recently conducted the Sn2'-type reaction with nitrogen and carbon...
nucleophiles in an intramolecular fashion to construct six-membered rings. Furthermore, we have observed them to undergo addition and substitution in the presence and absence of a proton source, respectively. These reactions readily provided quinoline and isoquinoline derivatives bearing a CF3, CHF2, or =CF2 group under mild reaction conditions.7

Such a high reactivity of 1-(trifluoromethyl)vinyl moieties prompted us to examine the geometrically disfavored 5-endo-trig cyclization, which might allow the development of a new synthetic route to five-membered ring systems bearing fluorinated one-carbon units (Scheme 1b). Indeed, the presence of nucleophilic centers on the position β to the 1-(trifluoromethyl)vinyl group might lead to either an intramolecular S_N2-type process or an addition reaction, depending on the conditions, and thus deliver five-membered cycles.

Five-membered heterocycles and carbocycles constitute important classes of compounds in pharmaceuticals, agrochemicals, materials, and catalysts. In these fields of science, the introduction of a fluorine atom or fluorocarbon substituents has come into wide use as one of the most efficient methods for modification of biological activity as well as of physical and chemical properties.8 Among fluorocarbon substituents, fluorinated one-carbon units (CF3, CHF2, =CF2, and CH2F) are quite attractive:9 (i) the incorporation of a trifluoromethyl (CF3) group into organic molecules increases biological activity as well as of physical and chemical properties.8 Among fluorocarbon substituents, fluorinated one-carbon units (CF3, CHF2, =CF2, and CH2F) are quite attractive:9 (i) the incorporation of a trifluoromethyl (CF3) group into organic molecules increases lipophilicity and affects electron density,10 (ii) a difluoromethyl (CHF2) group has hydrogen bond donor ability without nucleophilicity and with high lipophilicity,11 which makes it a special mimic of a hydroxy group,12 and (iii) a difluoromethylene (=CF2) group acts as a reactive site towards nucleophiles13 and a potential isostere of carbonyl groups,14 and provides a CHF2 group via its reduction.15 Nevertheless, synthetic methods for heterocycles and carbocycles with these fluorinated one-carbon units are limited and remain to be developed.

The preliminary results of the 5-endo-trig cyclizations of 1-(trifluoromethyl)vinyl compounds have been briefly reported in our previous communication, where we focused on those with intramolecular nitrogen nucleophiles.16 Combining the results of those obtained with other nucleophiles such as oxygen, sulfur, and carbon resulted in this full account of our studies on the 5-endo-trig cyclizations of 1-(trifluoromethyl)vinyl compounds, yielding difluoromethylene-, difluoromethyl-, and trifluoromethyl-substituted indoline, indole, pyrrolidine, tetrahdrofuran, benzo[b]thiophene, tetrahydrothiophene, and cyclopentanone derivatives.

Results and Discussion

Preparation of the Cyclization Precursors

We first selected α-(trifluoromethyl)styrenes bearing a nucleophilic nitrogen or sulfur at the o-position as 2-trifluoromethyl-1-alkene substrates for 5-endo-trig cyclization, because of the previously reported favorable effect of a 1-aryl group in 1-(trifluoromethyl)vinyl compounds undergoing S_N2 reaction.6,8 2-(3,3,3-Trifluoroprop-1-en-2-yl)-substituted anilines 1 were prepared by the palladium-catalyzed coupling reaction of o-iodoaniline with (3,3,3-trifluoroprop-1-en-2-yl)boronic acid, obtained from the magnesium-mediated Barbier-type reaction of 2-bromo-3,3,3-trifluoropropene with trimethyl borate, following a literature procedure.7a,17 Sulfonylation of the amino group of 1 gave anilides 2 (Scheme 2). Introduction of an S-functionality was effected via diazotization of the amino group. Treatment of 1a with i-AmONO and CF3CO2H, followed by the addition of sodium thioacetate, gave thiophenol ester 3 (Scheme 3).

![Scheme 2. Preparation of 2-(3,3,3-Trifluoroprop-1-en-2-yl) Sulfonylanilides.](image)

![Scheme 3. Preparation of o-(3,3,3-Trifluoroprop-1-en-2-yl) Thiophenol Ester.](image)

In addition, we designed nonconjugated substrates lacking a phenylene tether, 3-(trifluoromethyl)homoallyl sulfonamides, alcohols, thiols, and malonic acid derivatives, as second-type precursors of hetero- and carbocycles. Two methods were employed for the construction of these skeletons: (i) addition of 2-trifluoromethyl-substituted allylsilane to aldehydes18 and (ii) ring opening of oxiranes with 1-trifluoromethyl-substituted vinyl lithium,19 prepared by treatment of 2-bromo-3,3,3-trifluoropropene with n-BuLi, both of which provided 3-(trifluoromethyl)homoallyl alcohols 4. The Mitsunobu reaction of 4 with BocNHTs,20 followed by deprotection of the Boc group afforded the cyclization precursors 5 (Scheme 4). 3-(Trifluoromethyl)homoallyl alcohol 4a was also adopted as a cyclization precursor featuring a nucleophilic oxygen. α-Alkylated ketones 6, prepared from 4 via oxidation and alkylation, were reduced to give homoallyl alcohols 7 bearing 2,2-dialkyl substituents (Scheme 5). S-[3-(Trifluoromethyl)homoallyl] thiocetates 8 were prepared by the Mitsunobu reaction of homoallyl alcohols 4.20 Treatment with AcSH, DEAD, and PPh3 afforded 8a,b in moderate yields (Scheme 6).

3-(Trifluoromethyl)homoallyl-substituted malonate and malononitrile 10 and 11 were prepared for carbocycle synthesis. Conjugate addition of 2-(trifluoromethyl)allylsilane18 to diethyl...
Synthesis of Indolines and Indoles Bearing Fluorinated One-Carbon Units

We first examined the reaction of sulfonanilides 2 as precursors of indolines. The cyclization of 2a was attempted by treatment with 1.2 equiv of NaH in several solvents. While the reaction in THF or 1,4-dioxane gave no cyclized products, the use of DMF successfully promoted the desired 5-endo-trig cyclization via an S_N2 reaction to afford 3-(difluoromethylene)indoline 12a in 84% yield (Scheme 8). On the other hand, a similar reaction of 2a conducted in the presence of a proton source was expected to afford the addition product, 3-(trifluoromethyl)indoline 13a. The cyclization was examined by employing DBU instead of NaH as a base, where the sulfonamide NH group of 2a and/or DBU•+ acted as a proton donor. Whereas 1 equiv of DBU gave 3-(trifluoromethyl)indoline 13a only in 18% yield, 0.3 equiv of DBU surprisingly improved the yield of 13a to 81% (Scheme 8). When this reaction was monitored by ^19F NMR after heating at 80 °C for 2 h, the formation of 12a and 13a was observed. The mixture, when heated at 120 °C, finally gave rise to 13a. These facts indicate that DBU•+ acted as an HF source, which transformed 12a to the trifluoromethylated indoline 13a during the reaction.

These two types of 5-endo-trig products, the S_N2 and the addition products, were obtained from other sulfonanilides 2b,c bearing a methyl or a chlorine group on the benzene ring. The corresponding o-nitrobenzenesulfonamides (nosylamides) also underwent these reactions, albeit slightly less effectively. Thus, indolines 12 and 13 bearing a difluoromethylene or trifluoromethyl group were selectively obtained from common substrates 2 by choosing the base and the reaction conditions (Scheme 8).

Derivatization of indoline 12a was examined in order to synthesize indoles bearing fluorinated one-carbon units. An attempted double bond isomerization leading to aromatization of 12a failed under acidic (camphor sulfonic acid) and basic (DBU) conditions. We then tried addition of electrophiles (XY) such as IF, Br_2, and HI to the exocyclic double bond of 12a. Subsequent elimination of HX including an H at the 2-position from the adducts would allow the desired aromatization (Scheme 9). When 12a was treated with 2.4 equiv of N-iodosuccinimide (NIS) and 2.5 equiv of Et_3N•3HF, addition of IF followed by elimination of HI readily
occurred to give 3-(trifluoromethyl)indole 14 in 90% yield. Similarly, treatment of 12a with 1.3 equiv of Br2 gave 3-(bromodifluoromethyl)indole 15 in 96% yield. Furthermore, when HI [generated from NaI (1.6 equiv), TMSCl (1.6 equiv), and H2O (0.8 equiv)27] was added to 12a, 3-(difluoromethyl)indole 16 was obtained in 96% yield.28 While the opposite regioselectivity in the HI addition of 12a would be kinetically favorable because of the cation-stabilizing effect of fluorine,29 the addition product with that regiochemistry underwent elimination of HI to regenerate 12a. Consequently, the synthesis of indoles 14–16 with a variety of fluorinated one-carbon units is readily accomplished from a common starting material, 12a.

Scheme 9. Synthesis of Indoles 14–16 Bearing Fluorinated One-Carbon Units. Reagents and conditions: (a) NIS (2.4 equiv), Et3N•3HF (2.5 equiv), –10 °C, 2 h, CH2Cl2. (b) Br2 (1.3 equiv), rt, 3 h, CCl4. (c) NaI (1.6 equiv), TMSCl (1.6 equiv), H2O (0.8 equiv), rt, 10 h, CH3CN.

**Synthesis of 2,3-Dihydrobenzo[b]thiophenes Bearing Fluorinated One-Carbon Units**

As a further example of the intramolecular cyclization, we examined a sulfur nucleophile, although 5-endo-trig cyclizations with sulfur nucleophiles are not a disfavored process by Baldwin’s rules because of the large atom size of sulfur.1 A solution of a thiophenolate, generated in situ by treatment of thiophenol ester 3 with 1.1 equiv of potassium tert-butoxide (KOH-Bu) in THF, was heated at reflux to afford 3-difluoromethylene-2,3-dihydrobenzothiophene 17 in 65% yield (Scheme 10). The intramolecular addition process of the sulfur nucleophile under protic conditions was also examined. On treatment of 3 with 1.1 equiv of K2CO3 in MeOH, the desired 3-trifluoromethyl-2,3-dihydrobenzothiophene 18 was obtained in 61% yield (Scheme 10).20 These cyclizations of sulfur nucleophiles proceeded under milder conditions than those required for nitrogen nucleophiles.

Scheme 10. Synthesis of 3-Difluoromethylene and 3-Trifluoromethyl 2,3-Dihydrobenzo[b]thiophenes 17 and 18. Reagents and conditions: (a) KOt-Bu (1.1 equiv), reflux, 2 h, THF. (b) K2CO3 (1.1 equiv), reflux, 1 h, MeOH.

**Synthesis of Pyrrolidines Bearing Fluorinated One-Carbon Units**

Substrates 2 and 3 have a benzene ring tethering the nucleophilic heteroatom and the 1-(trifluoromethyl)vinyl group, which could allow a 6a-electrocyclization process to operate. To rule out the possibility of the 6a-electrocyclization mechanism and to broaden the scope for these types of 5-endo-trig cyclizations, we investigated the reaction of a nonconjugated system, N-[3-(trifluoromethyl)homoallyl] sulfonamides 5 bearing a two-sp3 carbon tether. Whereas the 1-(trifluoromethyl)vinyl system without a 1-aryl group is known to possess a reduced SN2' reactivity,68 we expected activation of the substrates by conducting the reactions in an intramolecular fashion.

Treatment of 5a with 1.3 equiv of NaH in DMF successfully promoted a similar cyclization to afford 4-(difluoromethylene)pyrrolidine 19a in 91% yield (Scheme 11).15,16,31 In contrast, the intermolecular reaction of 5-phenyl-2-(trifluoromethyl)pent-1-ene with 4-methyl-N-propylenesulfonamide gave only 2% yield of the corresponding SN2' product under similar reaction conditions. These results clearly indicate that (i) the reactions proceed via the nucleophilic 5-endo-trig cyclization, not via the electrocyclization, and (ii) substrate 5a preserves good SN2' reactivity due to the intramolecular nature of the reaction. We further examined the intramolecular SN2' reaction of several other N-[3-(trifluoromethyl)homoallyl] sulfonamides 5b–e bearing a 1-aryl, 1-alkyl, or 2-aryl group, and 1,2-unsubstituted homoallyl sulfonamide 5f. The reactions afforded good to excellent yields of the desired 4-difluoromethylene-substituted pyrrolidines 19b–f.

Cyclization of 5 in the presence of a proton source was attempted for the synthesis of (trifluoromethyl)pyrrolidines. In contrast to (trifluoromethyl)indoline synthesis, treatment of 5a with DBU in DMF promoted the SN2' reaction and not the addition reaction. When the reaction was conducted with 5 equiv of KOH in ethylene glycol or ethylene glycol–THF (10:1), the desired addition product, 4-(trifluoromethyl)pyrrolidine 20a, was obtained in 85% yield with high 2,4-trans selectivity (trans : cis = 92 : 8) (Scheme 11).15,16,32 We conducted the intramolecular addition reaction of other sulfonamides 5b–e, which afforded good to high yields of the desired 4-(trifluoromethyl)pyrrolidines 20b–e with 2,4-trans selectivity (20b–d)33 or 3,4-trans selectivity (20e).34 Under the cyclization conditions, neither the cis nor the trans isomer of 20b underwent cis/trans isomerization, which indicates that the ratios represent the kinetic selectivity of the cyclization.
when conducted in sigmatropic rearrangement. The reaction of however, gave a complex mixture presumably due to 3,3-
products. Thus, we examined substrates its intramolecular dehydration without accompanying cyclized
reaction, leading to 4-difluoromethylene-substituted tetrahydrofurans 21a–c in high yields (Scheme 12). 36 The 1-styryl-
substituted substrate 7d [R₁ = R² = Me, R³ = CH=CHPh(E)], however, gave a complex mixture presumably due to 3,3-
sigmatropic rearrangement. The reaction of 7a with KOH-Bu, even when conducted in t-BuOH, gave 21a as well as 4-
-(trifluoromethyl)tetrahydrofuran.

Synthesis of Tetrahydrofurans Bearing a Difluoromethylene Group

We then focused on the construction of oxygen heterocycles. An attempted Sn²-type cyclization of homoallyl alcohol 4a resulted in its intramolecular dehydration without accompanying cyclized products. Thus, we examined substrates 7 bearing two alkyl groups at the allylic position to prevent dehydration and to take advantage of the gem-dialkyl effect in cyclization.35 On treatment with KOH-Bu in THF at 70 °C, homoallyl alcohols 7a–e underwent an Sn²-type reaction, leading to 4-difluoromethylene-substituted tetrahydrofurans 21a–e in high yields (Scheme 12).36 The 1-styryl-
substituted substrate 7d [R₁ = R² = Me, R³ = CH=CHPh(E)], however, gave a complex mixture presumably due to 3,3-
sigmatropic rearrangement. The reaction of 7a with KOH-Bu, even when conducted in t-BuOH, gave 21a as well as 4-
-(trifluoromethyl)tetrahydrofuran.

Synthesis of Tetrahydrothiophenes Bearing Fluorinated One-
Carbon Units

A sulfur nucleophile was employed in the cyclizations for the construction of the tetrahydrothiophene ring. Treatment of thioacetates 8a,b with 1.3 equiv of NaOMe in DMF generated the corresponding thiolate, which underwent an Sn²-type reaction to
afford 4-(difluoromethylene)tetrahydrothiophenes 22a,b in 82% and 75% yield, respectively (Scheme 13).37 The addition reaction of 8a,b was also readily effected on treatment with 1.1 equiv of K₂CO₃ in MeOH as a proton source (Scheme 13). The desired 4-
(trifluoromethyl)tetrahydrothiophenes 23a,b were obtained in 90% and 82% yield, respectively.38

Synthesis of Cyclopentanes Bearing a Difluoromethylene Group

Having accomplished heterocycle synthesis, we turned our attention to the 5-endo-trig cyclization of 1-(trifluoromethyl)vinyl compounds with carbon nucleophiles, which would allow the construction of five-membered carbocycles with a fluorinated one-carbon unit. When 3-(trifluoromethyl)homoallyl-substituted malonate and malononitrile 10 and 11 were treated with 1.3 equiv of NaH in DMF, the Sn²-type cyclization successfully proceeded to give difluoromethylene-substituted cyclopentanes 24 and 25 in 77% and 61% yield, respectively (Scheme 14).39

In conclusion, we have found that the 1-(trifluoromethyl)vinyl system with a nucleophilic moiety constitutes a new class of compounds that undergoes the normally disfavored 5-endo-trig cyclization. These ‘anti-Baldwin’ results, based on the intramolecular substitution and addition concept, provide a high-yielding process for a variety of five-membered heterocycles and carbocycles. The resulting indolines, indoles, pyrrolidines, tetrahydrofurans, and tetrahydrothiophenes, have so far been less accessible, despite their increasing and potential utility as agrochemicals, pharmaceuticals, and other materials. The
Methyl-3-(trifluoromethyl)but-3-en-1-one (26): To a solution of 3-(trifluoromethyl)but-3-en-1-one (4,362 mg) in CH2Cl2 (20 mL) was added TFA (1.5 mL, 20 mmol) at rt. After the mixture was stirred for 1 h, the reaction was quenched with aqueous Na2CO3 (20 mL), and organic materials were extracted with CH2Cl2 (15 mL). After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 27.

4-Methyl-N-[1-phenyl-3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamide (5a): Colorless crystals; yield 89%; m.p. 289, 306, 316, 329, 342, 359, 362, 363, 371, 392, 405, 415, 425, 1325, 1159, 1120, 912 cm−1; 1H NMR: δ = 2.37 (3H, s), 5.68 (1H, d, J = 15.3 Hz, 7.8 Hz), 4.49 (1H, ddd, J = 7.3, 7.8, 7.3, 11.5 Hz, 491 (1H, br. s), 5.39 (1H, s), 5.50 (1H, s), 5.82 (2H, t, J = 7.1 Hz, 7.1 Hz); 13C NMR: δ = 15.1, 80.2, 103.9, 118.8, 121.2, 127.9, 128.1, 130.6, 137.8, 137.9 (q, J = 33 Hz), 138.2, 139.3; 13F NMR: δ = −95.1 (br s); HRMS (FAB): calculated for C14H12F3N2O2S [M + H]+ 376.0386, found 376.0381.

5-N-(3-Chloro-3,3,3-trifluoroprop-2-en-2-yl)-4-methylbenzenesulfonamide (2e): Colorless crystals; yield 92%; IR (neat): 3388, 3282, 1597, 1493, 1388, 1324, 1113, 1120, 1092 cm−1; 1H NMR: δ = 2.40 (3H, s), 5.15 (1H, q, J = 1.2 Hz, 6.1 Hz), 6.12 (1H, d, J = 1.2 Hz, 6.6 Hz) 6.68 (1H, br s), 7.04 (1H, d, J = 8.3 Hz, 7.08) (1H, d, J = 8.3 Hz, 7.08), 7.27 (2H, d, J = 8.3 Hz, 7.67) 7.76 (2H, d, J = 8.3 Hz, 7.76) 7.76 (2H, d, J = 8.3 Hz, 7.76) Hz; 13C NMR: δ = 21.5, 126.6, 122.1 (q, J = 32 Hz), 125.0, 125.5 (q, J = 55 Hz), 125.7, 123.8, 129.6, 130.8, 139.2, 131.7 (q, J = 132 Hz), 135.8, 136.0, 136.1, 144.6; 19F NMR: δ = −94.3 (br s); HRMS (FAB): calculated for C13H9ClF4NO2S+ (M + H)2 379.0386, found 379.0381.

N-[3-Chloro-(E)-3,3,3-trifluoroprop-2-en-2-yl]benzenesulfonamide (1): To a solution of 3-(E)-3,3,3-trifluoroprop-2-en-2-yl)aniline (130 mg) in CH2Cl2 (5 mL) was added TFA (1.5 mL, 20 mmol) at rt. After the mixture was stirred for 1 h, the reaction was quenched with aqueous Na2CO3 (20 mL), and organic materials were extracted with CH2Cl2 (15 mL). After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 27.

Preparation of 4-methyl-1-[1-phenyl-3-(trifluoromethyl)but-3-en-2-yl]benzenesulfonamide (5b): To a solution of 3-(4-methylbenzenesulfonyl)-3-tert-butyl(2-hexyl)benzenesulfonamide (408 mg, 81%) as colorless crystals. m.p. 65–67 °C; IR (neat): 3425, 3062, 1689, 1414, 1277, 1250 cm−1; 1H NMR: δ = 1.34 (3H, t, J = 6 Hz, 1.34 Hz), 1.42–1.45 (9H, m), 1.50–1.53 (3H, m), 1.93–1.96 (2H, m), 7.07 (2H, d, J = 8.3 Hz, 7.07 Hz), 7.10 (2H, d, J = 8.3 Hz, 7.10 Hz). 13C NMR: δ = 21.4, 50.7, 50.9, 59.3, 61.7, 123.1, 128.5, 129.2, 138.6; 13F NMR: δ = −152.1 (q, J = 19 Hz, 152.1 Hz), 137.9, 144.3; 19F NMR: 𝜑 = −93.6 (br s); elemental analysis: calculated (%) for C19H19F3NO2S: C 57.45, H 4.94, N 3.79; found: C 57.37, H 4.92, N 3.84.

Preparation of 4-methyl-1-[(4-methylbenzenesulfonyl)-3-tert-butyl(2-hexyl)benzenesulfonamide (5f): To a solution of 3-(4-methylbenzenesulfonyl)-3-tert-butyl(2-hexyl)benzenesulfonamide (408 mg, 81%) as colorless crystals. m.p. 57–59 °C; IR (neat): 3425, 3062, 1689, 1414, 1277, 1250 cm−1; 1H NMR: δ = 1.34 (3H, t, J = 6 Hz, 1.34 Hz), 1.42–1.45 (9H, m), 1.50–1.53 (3H, m), 1.93–1.96 (2H, m), 7.07 (2H, d, J = 8.3 Hz, 7.07 Hz), 7.10 (2H, d, J = 8.3 Hz, 7.10 Hz). 13C NMR: δ = 21.4, 50.7, 50.9, 59.3, 61.7, 123.1, 128.5, 129.2, 138.6; 13F NMR: δ = −152.1 (q, J = 19 Hz, 152.1 Hz), 137.9, 144.3; 19F NMR: 𝜑 = −93.6 (br s); elemental analysis: calculated (%) for C19H19F3NO2S: C 57.45, H 4.94, N 3.79; found: C 57.37, H 4.92, N 3.84.
4.1 mL, 23 mmol) dropwise, and the reaction mixture was stirred for 40 min at 78 °C. Methyl trifluoromethanesulfonate (0.20 mL, 2.3 mmol) was added at that temperature, and then the mixture was allowed to warm up to rt. After stirring for 8 h, the reaction mixture was quenched with phosphate buffer (pH 7.0, 20 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), dried over Na2SO4, the solvent was removed under reduced pressure, and the crude product was obtained as a pale brown amorphous solid. The product was purified by preparative thin layer chromatography (hexane-EtOAc, 1:1) to give 6b (0.81 g, 81% yield) as a colorless liquid; yield 87%; IR (neat): 3464, 3064, 3022, 2987, 2924, 1454, 1321, 1115, 1092, 968, 754, 692 cm⁻¹; 1H NMR: δ 6.08 (1H, d, J = 6.7 Hz), 5.68 (1H, s), 6.00 (1H, s), 6.91 (1H, d, J = 5.2 Hz), 5.88 (1H, d, J = 1.2 Hz), 7.23–7.32 (5H, m); 13C NMR: δ 21.7, 23.4, 70.9, 123.5 (q, JCF = 273 Hz), 127.5, 127.6, 126.0, 140.3 (J CF = 273 Hz), 125.4 (q, JCF = 275 Hz), 123.7 (q, JCF = 277 Hz), 123.9, 124.4 (br s), 125.7 (br s); HRMS (FAB): calcd for C15H18F3O3 [M]+ + H²O: 276.1356, found 276.1361. 4-Methyl-1-phenoxy-5-(trifluoromethyl)-hex-5-en-3-one (4c): To a solution of 4-methyl-1-phenoxy-5-(trifluoromethyl)-hex-5-en-3-one (200 mL) was added a solution of KH (67 mg, 2.0 mmol) in MeOH (1.3 mL) at RT (0.5 h). After cooling the mixture to 0 °C, cerium (III) chloride (140 mg, 0.57 mmol) was added. The reaction mixture was stirred for 12 h at RT. After cooling the mixture to 0 °C, cerium (III) chloride (140 mg, 0.57 mmol) was added. After being allowed to warm up to rt, the reaction mixture was quenched with phosphate buffer (pH 7.0, 20 mL), and organic materials were extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over Na2SO4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography (hexane-EtOAc, 1:1) to give 4c (0.17 g, 21% yield) as a colorless liquid. The product was purified by preparative thin layer chromatography (hexane-EtOAc, 1:1) to give 4c (0.17 g, 21% yield) as a colorless liquid. The product was purified by preparative thin layer chromatography (hexane-EtOAc, 1:1) to give 4c (0.17 g, 21% yield) as a colorless liquid.
In a reaction mixture was stirred until 48 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane:EtOAc = 10:1) to give 13c (65 mg, 30%) as a colorless liquid. IR (neat): 3149, 3018, 2924, 1562, 1448, 1372, 1289, 1209, 1134, 1045, 1044, 946 (CH3); HRMS (FAB): m/z 346.0301, 378.0336. 1-tert-Butyl-3,5-difluoro-1H-indoline-2-carbonitrile (14): To a mixture of tert-butyl-3,5-difluoro-1H-indoline-2-carbonitrile (12b) and 60% dispersion of NaH (60 mg) in THF (1 mL) was added a solution of diisocyanatobenzene (1.6 mmol) in THF (1.6 mL) at –20 °C. After 30 min, the reaction was quenched with water and brine, and dried over Na2SO4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (pentane:EtOAc = 20:1) to give 14 (23 mg, 29%) as a colorless liquid. IR (neat): 3070, 3035, 2908, 2260, 2192, 1546, 1348, 1169, 120595 cm–1; 1H NMR: δ 7.45 (1H, d, J = 7.6 Hz), 7.38 (1H, d, J = 7.7 Hz), 7.09 (1H, dd, J = 7.7, 7.7 Hz), 7.68 (1H, d, J = 7.4 Hz), 7.07 (1H, d, J = 7.4 Hz); 13C NMR: δ 132.8, 126.9, 127.9, 127.6, 124.3, 124.2, 114.9, 124.0, 123.4, 123.3, 110.6, 105.0, 75.7 (CH3); HRMS (FAB): m/z 348.0305, 379.0340. 1-(4-Chlorophenyl)-2,2-difluoro-1H-indoline-3-carbonitrile (15): To a solution of 1-(4-chlorophenyl)-2,2-difluoro-1H-indoline-3-carbonitrile (14) (89 mg, 96%) as colorless crystals. IR (neat): 3149, 3018, 2924, 1562, 1448, 1372, 1289, 1209, 1134, 1045, 1044, 946 (CH3); HRMS (FAB) for C17H17F3NO2S (M+Na)+: 376.0381. 1-(4-Chloro-3-fluorophenyl)-2,2-difluoro-1H-indoline-3-carbonitrile (16): To a solution of 1-(4-chloro-3-fluorophenyl)-2,2-difluoro-1H-indoline-3-carbonitrile (15) (12a) (224 mg, 77%) as a colorless liquid. IR (neat): 3149, 3018, 2924, 1562, 1448, 1372, 1289, 1209, 1134, 1045, 1044, 946 (CH3); HRMS (FAB) for C18H17F3NO2S (M+Na)+: 384.0473.
1.3 Hz; \( \text{C} \) NMR: \( \delta = 30.1 \) (1, \( J = 3.3 \) Hz), 94.2 (dd, \( J = 26.2, 26.2 \) Hz), 122.1, 124.0 (dd, \( J = 2, 7 \) Hz), 124.6, 126.3 (dd, \( J = 3, 3 \) Hz), 131.5 (dd, \( J = 3, 3 \) Hz), 142.7 (dd, \( J = 5, 12 \) Hz). 78.4 (1F, \( J = 40, 50 \) Hz) = 55 Hz; elemental analysis: calculated for \( \text{C}_7\text{H}_7\text{F}_2\text{N}_2\text{O}_3\text{S} \): C 52.74, H 4.79, N 3.87.

1.4-Bromomethylene (18B): To a solution of 3.07 mg (0.3 mmol) in MeOH (3 mL) was added KCO\(_3\) (52 mg, 0.378 mmol) at rt. After the mixture was heated under reflux for 1 h, phosphorus buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with EtO\(_2\) (10 mL \( \times 3 \)). The combined extracts were washed with water and dried over MgSO\(_4\). After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane to EtOAc 1:1) to give 18B (94 mg, 61%) as a colorless liquid. IR (neat): 3018, 1587, 1461, 1339, 1049, 767 cm\(^{-1}\); 1H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.55 \) (1H, dd, \( J = 10.2, 7.6 \) Hz), 7.35 (1H, dd, \( J = 10.2, 7.6 \) Hz), 6.98, 7.23 (2H, d, \( J = 8.4, 8.4 \) Hz), 3.59 (1H, dd, \( J = 12.0, 9.0 \) Hz), 4.12–4.20 (1H, m), 7.08 (1H, dd, \( J = 7.6, 7.6 \) Hz), 7.21–7.25 (2M, 7.4H, \( J = 7.6, 7.6 \) Hz). \( \text{C} \) NMR: \( \delta = 31.4 \) (q, \( J = 31.4 \) Hz), 51.5 (q, \( J = 31.4 \) Hz), 122.5, 124.6, 126.0 (2M, \( J = 28 \) Hz), 129.5, 132.6, 142.7; \( \text{F} \) NMR: \( \delta = 21.1 \) (1F, \( J = 28 \) Hz), 78.4 (1F, \( J = 40, 50 \) Hz); HRMS (FAB): calculated for \( \text{C}_7\text{H}_7\text{F}_2\text{N}_2\text{O}_3\text{S} \): [M + H\(^+\)]\(^+\) 305.0259, found 305.0259.

Cyclization of 5 under acido philic conditions: To a solution of 5 (1.0 mmol) in DMF (10 mL) was added NaH (60% dispersion in mineral oil, 2g, 1.3 mmol) at 0°C. The reaction mixture was stirred at 0°C for 15 min and then 120°C for 0.5–4 h. After separation of cis- and trans-isomer was achieved by column chromatography (hexane–EtOAc 5:1) to give trans-20b (70%) and cis-20b (6%) as colorless crystals. Organic materials were extracted with EtO\(_2\) (10 mL \( \times 3 \)). The combined extracts were washed with water and dried over Na\(_2\)SO\(_4\). After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 3-trifluoromethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (20b) as a mixture of trans- and cis-isomers.

**31.6: 1H NMR: \( \delta = 91.9 \) (1M, \( J = 8 \) Hz), \( \delta = 91.9 \) (1M, \( J = 8 \) Hz); elemental analysis: calculated for \( \text{C}_7\text{H}_7\text{F}_2\text{N}_2\text{O}_3\text{S} \): C 59.0, H 4.79, N 3.52; found: C 59.0, H 5.19, N 3.73.

- **1H NMR: \( \delta = 91.9 \) (1M, \( J = 8 \) Hz), \( \delta = 91.9 \) (1M, \( J = 8 \) Hz); elemental analysis: calculated for \( \text{C}_7\text{H}_7\text{F}_2\text{N}_2\text{O}_3\text{S} \): C 59.0, H 4.79, N 3.52; found: C 59.0, H 5.19, N 3.73.

- **1H NMR: \( \delta = 91.9 \) (1M, \( J = 8 \) Hz), \( \delta = 91.9 \) (1M, \( J = 8 \) Hz); elemental analysis: calculated for \( \text{C}_7\text{H}_7\text{F}_2\text{N}_2\text{O}_3\text{S} \): C 59.0, H 4.79, N 3.52; found: C 59.0, H 5.19, N 3.73.
4-Difluoromethylene-1-phenyl-2-oxaspiro[4.4]nonane (21b): To a solution of 80 mg (0.08 mmol) in MeOH (3 mL) was added potassium hydride (KH, 15 mg, 0.37 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was heated at reflux for 2 h, phosphate buffer (pH 7, 20 mL) was added to quench the reaction, and organic materials were extracted with EtOAc (20 mL × 3). The combined extracts were washed with brine, and dried over Na2SO4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 230:1) to give 23b (47 mg, 75%) as a colorless liquid. IR (neat): 2956, 2927, 2873, 2856, 1380, 1269, 1161, 1111 cm⁻¹; 1H NMR: δ 7.41 (2H, d, J = 7.4, 7.4 Hz), 7.40 (2H, d, J = 7.4, 7.4 Hz), 7.26 (1H, t, J = 7.3 Hz), 7.33 (2H, d, J = 7.3, 7.3 Hz), 7.38 (2H, d, J = 7.3, 7.3 Hz); 13C NMR: δ 140.2, 142.6, 28.6, 28.8 (d, J = 8 Hz) J = 29.1, 29.1, 31.7, 36.1, 36.4 (dd, J = 2.2, 2.2 Hz), 48.8, 48.9 (dd, J = 21, 21 Hz), 150.4 (dd, J = 283, 283 Hz); 19F NMR: δ 70.6 (1F, dm, J = 56 Hz); elemental analysis: calcd (%) for C14H10F2N2: C 68.85, H 4.13, N 11.37.

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