CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200700324

A New Class of Substrates for Nucleophilic 5-*endo*-trig Cyclization, 2-Trifluoromethyl-1-alkenes: Synthesis of Five-Membered Hetero- and Carbocycles That Bear Fluorinated One-Carbon Units

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

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

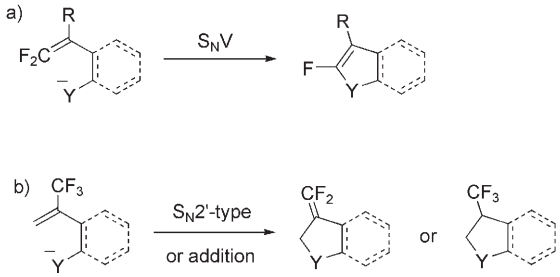
Abstract: Disfavored 5-*endo*-trig cyclizations were achieved in 2-trifluoromethyl-1-alkenes with a nucleophilic nitrogen, oxygen, sulfur, or carbon atom through 1) intramolecular S_N2' reaction with loss of a fluoride ion or 2) intramolecular nucleophilic addition to the vinylic group. This reaction manifold provides a versatile method for the synthesis of indolines, indoles, pyrrolidines, tetrahydrofurans, 2,3-dihydrobenzo[*b*]thiophenes, tetrahydrothiophenes, and cyclopentanes that bear a fluorinated one-carbon unit such as a difluoromethylene, difluoromethyl, or trifluoromethyl group.

Keywords: carbocycles · cyclization · fluorine · heterocycles · synthetic methods

Introduction

5-*endo*-trig Cyclization has long been considered to be a geometrically disfavored process according to the Baldwin 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 been more rarely observed in synthetic chemistry than the other two types of cyclization.

In our recent studies, we accomplished the normally disfavored nucleophilic 5-*endo*-trig cyclizations with 1,1-difluoro-1-alkene substrates (2,2-difluorovinylic compounds) that bear a functional group such as NHTs, OH, SH, or CH_2I (Scheme 1a; Ts = *p*-toluenesulfonyl).[2] Deprotonation or lithium–iodine exchange of these groups generates N, O, S, or C nucleophiles, which successfully undergo a vinylic addition–elimination (S_NV) 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 1) the highly polarized C=C double bond, which allows the initial formation of the five-membered ring by electrostatic attraction of the nucleophiles to the positive CF_2 carbon atom, and 2) the subsequent elimination of fluoride ion, which suppresses the reverse ring opening.



Scheme 1. Nucleophilic 5-*endo*-trig cyclization of fluoroalkenes. a) 2,2-Difluorovinylic compounds. b) 1-(Trifluoromethyl)vinyl compounds.

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Among fluoroalkenes, 2-trifluoromethyl-1-alkenes are also known to have interesting reactivity in nucleophilic reactions, which results from 1) the highly electrophilic double bond with a strong electron-withdrawing CF_3 group, and 2) the good ability of allylic fluorine atoms to act as a leaving group. The nucleophilic reaction of 2-trifluoromethyl-1-alkene substrates (1-(trifluoromethyl)vinyl compounds) proceeds with the accompanying elimination of an allylic fluorine atom (S_N2'-type process), which provides a potential method for the preparation of 1,1-difluoro-1-alkenes.[6] We recently conducted the S_N2'-type reaction with nitrogen and carbon nucleophiles in an intramolecular manner to construct six-membered rings. Furthermore, we observed that these trifluoroalkenes undergo addition and substitution in the presence and absence of a proton source, respectively. These reactions readily provided quinoline and isoquinoline derivatives bearing a CF_3, CHF_2, or $=CF_2$ group under mild reaction conditions.[7]

The high reactivity of the 1-(trifluoromethyl)vinyl moiety 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 an important class of compounds in pharmaceuticals, agrochemicals, materials, and catalysis. In these fields of science, the introduction of a fluorine atom or fluorocarbon substituent has come into wide use as one of the most efficient methods for modification of biological activity as well as physical and chemical properties.[8] Among fluorocarbon substituents, fluorinated one-carbon units (CF_3, CHF_2, $=CF_2$, and CH_2F) are quite attractive[9] because 1) the incorporation of a trifluoromethyl (CF_3) group into organic molecules increases lipophilicity and affects electron density,[10] 2) the difluoromethyl (CHF_2) group is a hydrogen-bond donor without nucleophilicity and with high lipophilicity,[11] which makes it a special mimic of a hydroxy group,[12] and 3) the difluoromethylene ($=CF_2$) group acts as a reactive site towards nucleophiles[13] and as a potential isostere of carbonyl groups,[14] and provides a CHF_2 group through its reduction.[15] Nevertheless, synthetic methods for heterocycles and carbocycles with these fluorinated one-carbon units are limited and remain to be developed.

Preliminary results of the 5-*endo*-trig cyclizations of 1-(trifluoromethyl)vinyl compounds were briefly reported in our previous communication, in which we focused on those with intramolecular nitrogen nucleophiles.[16] The combination of 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 to yield difluoromethylene-, difluoromethyl-, and trifluoromethyl-substituted indoline, indole, pyrrolidine, tetrahydrofuran, benzo[*b*]thiophene, tetrahydrothiophene, and cyclopentane derivatives.

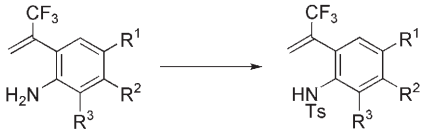
Abstract in Japanese:

分子内に窒素、酸素、硫黄、炭素求核種を有する 2-トリフルオロメチル-1-アルケンにおいて、これまで困難とされてきた求核的 5-*endo*-trig 環化を達成した。この 5 員環形成反応は、1) フッ化物イオンの脱離を伴う分子内 S_N2' 反応、もしくは 2) ビニル基への分子内求核付加を経て進行する。これら一連の反応により、ジフルオロメチレン基、ジフルオロメチル基、トリフルオロメチル基のような含フッ素 1 炭素ユニットを有するインドリン、インドール、ピロリジン、テトラヒドロフラン、2,3-ジヒドロベンゾ[*b*]チオフェン、テトラヒドロチオフェン、およびシクロペンタンを合成することができる。

Results and Discussion

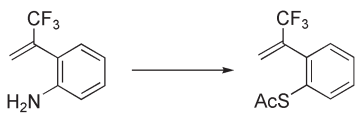
Preparation of the Cyclization Precursors

We first selected α-(trifluoromethyl)styrenes that bear a nucleophilic nitrogen or sulfur atom at the *ortho* 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 the S_N2' reaction.[6b] 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, which was obtained from the magnesium-mediated Barbier-type reaction of 2-bromo-3,3,3-trifluoropropene with trimethyl borate by following a literature procedure.[7a,17] Sulfonylation of the amine group of **1** gave anilides **2** (Scheme 2). Introduction of an S functionality was effected by diazotization of the amine group. Treatment of **1a** with *i*AmONO and CF_3CO_2H followed by the addition of sodium thioacetate gave thiophenol ester **3** (Scheme 3).



1a: R^1 = H, R^2 = H, R^3 = H — **2a** 84%
1b: R^1 = Me, R^2 = H, R^3 = H — **2b** 87%
1c: R^1 = H, R^2 = Cl, R^3 = H — **2c** 92%

Scheme 2. Preparation of 2′-(3,3,3-trifluoroprop-1-en-2-yl) sulfonanilides **2**. Reagents and conditions: TsCl (1.2 equiv), DMAP (0.1 equiv), 0 °C to room temperature, 12 h, pyridine. DMAP = 4-dimethylaminopyridine.



1a — **3** 31%

Scheme 3. Preparation of 2-(3,3,3-trifluoroprop-1-en-2-yl) thiophenol ester **3**. Reagents and conditions: TFA (2.0 equiv), *i*AmONO (2.0 equiv), 0 °C, 0.5 h, MeCN. Am = amyl, TFA = trifluoroacetic acid.

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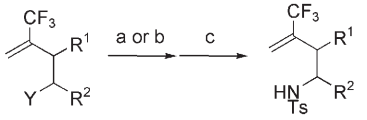
Furthermore, we designed nonconjugated substrates that lack a phenylene tether, 3-(trifluoromethyl)homoallyl sulfonamides, alcohols, thiols, and malonic acid derivatives, as second-type precursors of hetero- and carbocycles. Two methods were employed for the construction of these skeletons: 1) addition of 2-trifluoromethyl-substituted allyl silane to aldehydes[18] and 2) ring opening of oxiranes with 1-trifluoromethyl-substituted vinyllithium,[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 removal of the Boc group afforded the cyclization precursors **5** (Scheme 4). 3-(Trifluoromethyl)homoallyl alcohol **4a** was

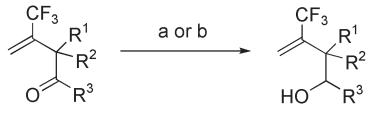


4a: R^1 = H, R^2 = Ph, Y = OH — **5a** 89%
4b: R^1 = H, R^2 = C_6H_4-4-Br, Y = OH — **5b** 65%
4c: R^1 = H, R^2 = 2-furyl, Y = OH — **5c** 29%
4d: R^1 = H, R^2 = *n*-C_6H_{13}, Y = OH — **5d** 61%
4e: R^1 = Ph, R^2 = H, Y = OH — **5e** 64%
4f: R^1 = H, R^2 = H, Y = OTs — **5f** 81%

Scheme 4. Preparation of *N*-[3-(trifluoromethyl)homoallyl] sulfonamides **5**. Reagents and conditions: a) PPh_3 (1.5 equiv), DEAD (1.5 equiv), BocNHTs (1.3 equiv), room temperature, 6 h, THF (for **4a–e**); b) NaH (1.3 equiv), BocNHTs (1.4 equiv), 90 °C, 4 h, DMF (for **4f**); c) TFA (10 equiv), room temperature, 10 h, CH_2Cl_2. Boc = *tert*-butoxycarbonyl, DEAD = diethyl azodicarboxylate, DMF = *N*,*N*-dimethylformamide.

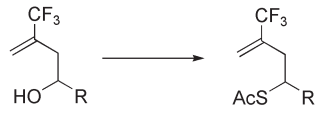
also adopted as a cyclization precursor that features a nucleophilic oxygen atom. α-Alkylated ketones **6**, prepared from **4** by oxidation and alkylation, were reduced to give homoallyl alcohols **7**, which bear 2,2-dialkyl substituents (Scheme 5). *S*-[3-(Trifluoromethyl)homoallyl] thioacetates **8** were prepared by the Mitsunobu reaction of homoallyl alcohols **4**.[20] Treatment with AcSH, DEAD, and PPh_3 afforded **8a** and **8b** 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)allylsilane[18] to diethyl benzylidenemalonate **9** and a modified Mitsunobu reaction[21] of **4a** with malononitrile gave **10** and **11**, respectively (Scheme 7).



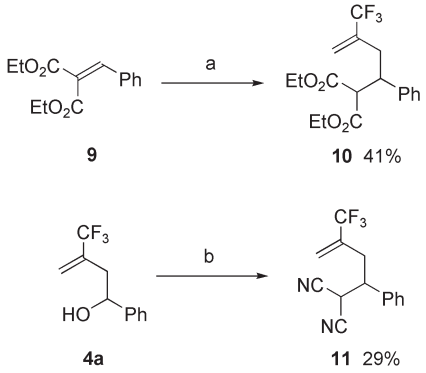
6a: R^1 = Me, R^2 = Me, R^3 = Ph — **7a** 87%
6b: R^1, R^2 = -$(CH_2)_4$-, R^3 = Ph — **7b** 86%
6c: R^1 = Me, R^2 = Me, R^3 = $(CH_2)_2C_6H_5$ — **7c** 83%
6d: R^1 = Me, R^2 = Me, R^3 = CH=CHPh (*E*) — **7d** 77%

Scheme 5. Preparation of 3-(trifluoromethyl)homoallyl alcohols **7**. Reagents and conditions: a) $NaBH_4$ (1.5 equiv), reflux, 3–4 h, EtOH (for **6a–c**); b) $CeCl_3$ (1.0 equiv), $NaBH_4$ (1.0 equiv), 0 °C, 3 h, MeOH (for **6d**).



4a: R = Ph — **8a** 34%
4d: R = *n*-C_6H_{13} — **8b** 51%

Scheme 6. Preparation of *S*-[3-(trifluoromethyl)homoallyl] thioacetates **8**. Reagents and conditions: PPh_3 (2.0 equiv), DEAD (2.0 equiv), AcSH (1.5 equiv), 0 °C, 12 h, THF.

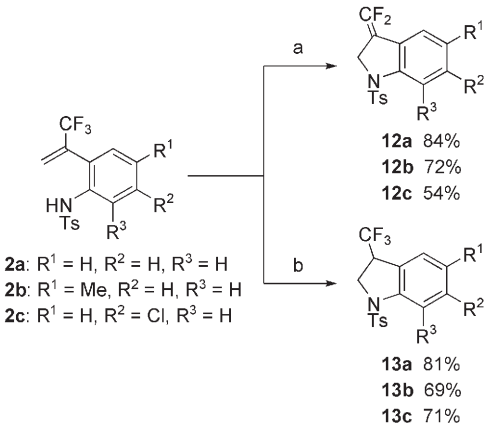


Scheme 7. Preparation of 3-(trifluoromethyl)homoallyl-substituted malonate and malononitrile **10** and **11**. Reagents and conditions: a) CH_2=C-$(CF_3)CH_2Si(CH_3)_3$ (1.0 equiv), TBAF (0.12 equiv), 4-Å molecular sieves, room temperature, 12 h, THF; b) nBu_3P=CHCN (1.5 equiv), malononitrile (1.5 equiv), room temperature, 24 h, benzene. TBAF = tetra-*n*-butylammonium fluoride.

Synthesis of Indolines and Indoles That Bear 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 equivalents of NaH in several solvents. Whereas the reaction in THF or 1,4-dioxane gave no cyclized products, the use of DMF successfully promoted the desired 5-*endo*-trig cyclization by an S_N2' reaction to afford 3-(difluoromethylene)indoline **12a** in 84% yield (Scheme 8).[16,22] 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**.[16,23,24] The cyclization was examined by employing DBU instead of NaH as a base, whereby the sulfonamide NH group of **2a** and/or DBU·H^+ acts as a proton donor. Whereas 1 equivalent of DBU gave 3-(trifluoromethyl)indoline **13a** in only 18% yield, 0.3 equivalents of DBU surprisingly improved the yield of **13a** to 81% (Scheme 8). When this reaction was monitored by ^{19}F NMR spectroscopy after heating at 80 °C for 2 h, formation of **12a** and **13a** was observed. The mixture, when heated at 120 °C, finally gave rise to **13a**. These observations indicate that DBU·HF acted as an HF source, which transformed **12a** into the trifluoromethylated indoline **13a** during the reaction.

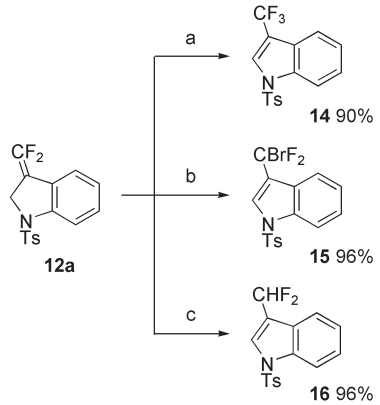
These two types of 5-*endo*-trig products, the S_N2' and the addition products, were also obtained from sulfonamides **2b** and **2c**, which bear a methyl or a chlorine group on the ben-



Scheme 8. Synthesis of 3-difluoromethylene and 3-trifluoromethyl indolines **12** and **13**. Reagents and conditions: a) NaH (1.2 equiv), 80 °C, 5–7 h, DMF; b) DBU (0.3 equiv), 120 °C, 0.5–1 h, DMF. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

zene ring. The corresponding *o*-nitrobenzenesulfonamides (nosylamides)[25] also underwent these reactions, albeit slightly less effectively. Thus, indolines **12** and **13** with 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 to synthesize indoles that bear fluorinated one-carbon units. An attempted double-bond isomerization leading to aromatization of **12a** failed under acidic (camphor sulfonic acid) and basic (DBU) conditions.[22] 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 atom at the 2-position from the adducts, would allow the desired aromatization (Scheme 9). When **12a** was treated with 2.4 equivalents of NIS and 2.5 equivalents of $Et_3N{\cdot}3HF$,[26] addition of IF followed by elimination of HI readily occurred to give 3-(trifluoromethyl)indole **14** in 90% yield.

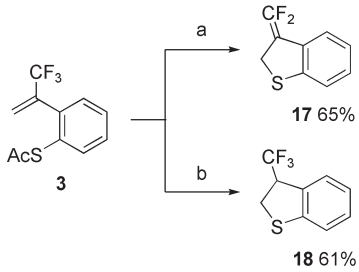


Scheme 9. Synthesis of indoles **14**–**16** with fluorinated one-carbon units. Reagents and conditions: a) NIS (2.4 equiv), $Et_3N{\cdot}3HF$ (2.5 equiv), −10 °C, 2 h, CH_2Cl_2; b) Br_2 (1.3 equiv), room temperature, 3 h, CCl_4; c) NaI (1.6 equiv), TMSCl (1.6 equiv), H_2O (0.8 equiv), room temperature, 10 h, CH_3CN. NIS = *N*-iodosuccinimide, TMS = trimethylsilyl.

Similarly, treatment of **12a** with 1.3 equivalents of Br_2 gave 3-(bromodifluoromethyl)indole **15** in 96% yield. Furthermore, when HI (generated from NaI (1.6 equiv), TMSCl (1.6 equiv), and H_2O (0.8 equiv))[27] was added to **12a**, 3-(difluoromethyl)indole **16** was obtained in 96% yield.[28] Whereas the opposite regioselectivity in the HI addition of **12a** would be kinetically favorable because of the α-cation-stabilizing effect of fluorine,[29] the addition product from that regiochemistry underwent elimination of HI to regenerate **12a**. Consequently, the synthesis of indoles **14**–**16** with a variety of fluorinated one-carbon units was readily accomplished from a common starting material, **12a**.

Synthesis of 2,3-Dihydrobenzo[*b*]thiophenes That Bear 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 the Baldwin rules because of the large atomic size of sulfur.[1] A solution of a thiophenolate, generated in situ by treatment of thiophenol ester **3** with 1.1 equivalents of potassium *tert*-butoxide (KO*t*Bu) in THF, was heated at reflux to afford 3-difluoromethylene-2,3-dihydrobenzothiophene **17** in 65% yield (Scheme 10). The intramolecular addition



Scheme 10. Synthesis of 3-difluoromethylene and 3-trifluoromethyl 2,3-dihydrobenzo[*b*]thiophenes **17** and **18**. Reagents and conditions: a) KO*t*Bu (1.1 equiv), reflux, 2 h, THF; b) K_2CO_3 (1.1 equiv), reflux, 1 h, MeOH.

process of the sulfur nucleophile under protic conditions was also examined. On treatment of **3** with 1.1 equivalents of K_2CO_3 in MeOH, the desired 3-trifluoromethyl-2,3-dihydrobenzothiophene **18** was obtained in 61% yield (Scheme 10).[30] These cyclizations of sulfur nucleophiles proceeded under milder conditions than those required for nitrogen nucleophiles.

Synthesis of Pyrrolidines That Bear Fluorinated One-Carbon Units

Substrates **2** and **3** have a benzene ring that tethers the nucleophilic heteroatom and the 1-(trifluoromethyl)vinyl group, which could allow a 6π-electrocyclization process to operate. To rule out the possibility of the 6π-electrocyclization mechanism and to broaden the scope for these types of

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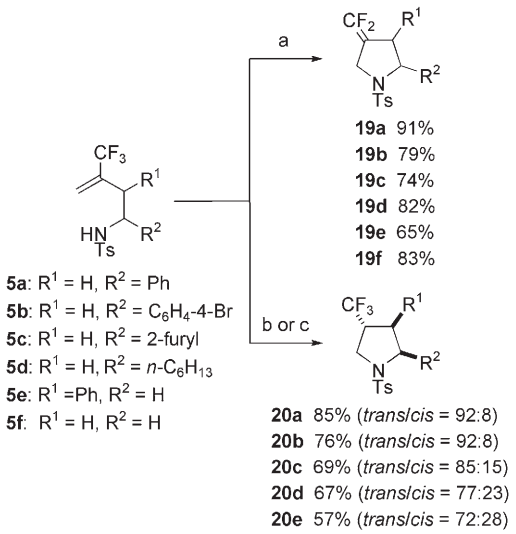
5-*endo*-trig cyclizations, we investigated the reaction of a nonconjugated system, *N*-[3-(trifluoromethyl)homoallyl] sulfonamides **5** that bear a tether of two C(sp^3) atoms. Whereas the 1-(trifluoromethyl)vinyl system without a 1-aryl group is known to have decreased S_N2' reactivity,[6b] we expected activation of the substrates by conducting the reactions in an intramolecular manner.

Treatment of **5a** with 1.3 equivalents 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



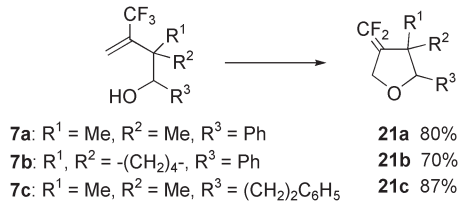
Scheme 11. Synthesis of 4-difluoromethylene and 4-trifluoromethyl pyrrolidines **19** and **20**. Reagents and conditions: a) NaH (1.3 equiv), 120–130 °C, 0.5–4 h, DMF; b) KOH (5 equiv), 130 °C, 20 h, $(CH_2OH)_2$ (for **20a–c** and **20e**); c) KOH (5 equiv), 130 °C, 20 h, $(CH_2OH)_2$/THF (10:1) (for **20d**).

of 5-phenyl-2-(trifluoromethyl)pent-1-ene with 4-methyl-*N*-propylbenzenesulfonamide gave only 2% yield of the corresponding S_N2' product under similar reaction conditions. These results clearly indicate that 1) the reactions proceed by nucleophilic 5-*endo*-trig cyclization and not by electrocyclization, and 2) substrate **5a** preserves good S_N2' reactivity owing to the intramolecular nature of the reaction. We further examined the intramolecular S_N2' reaction of several other *N*-[3-(trifluoromethyl)homoallyl] sulfonamides **5b–e**, which bear 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 the synthesis of (trifluoromethyl)indolines, treatment of **5a** with DBU in DMF promoted the S_N2' reaction instead of the addition reaction. When the reaction was conducted with 5 equivalents 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* (**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.

Synthesis of Tetrahydrofurans That Bear a Difluoromethylene Group

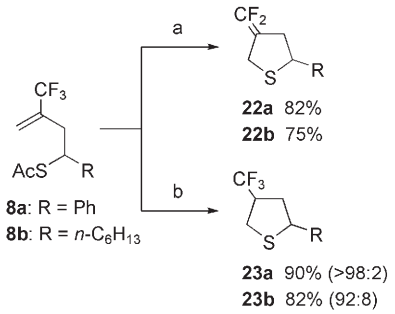
We then focused on the construction of oxygen heterocycles. An attempted S_N2'-type cyclization of homoallyl alcohol **4a** resulted in its intramolecular dehydration without accompanying cyclized products. Thus, we examined substrates **7** with two alkyl groups at the allylic position to prevent dehydration and to take advantage of the *gem*-dialkyl effect in cyclization.[35] On treatment with KO*t*Bu in THF at 70 °C, homoallyl alcohols **7a–c** underwent an S_N2'-type reaction to lead to 4-difluoromethylene-substituted tetrahydrofurans **21a–c** in high yields (Scheme 12).[36] The 1-styryl-substituted substrate **7d** ($R^1 = R^2 = Me$, $R^3 = CH{=}CHPh$-(*E*)), however, gave a complex mixture, presumably owing to 3,3-sigmatropic rearrangement. The reaction of **7a** with KO*t*Bu, even when conducted in *t*BuOH, gave **21a** as well as 4-(trifluoromethyl)tetrahydrofuran.



Scheme 12. Synthesis of 4-difluoromethylene tetrahydrofurans **21**. Reagents and conditions: KO*t*Bu (1.3 equiv), 70 °C, 2.5–6 h, THF.

Synthesis of Tetrahydrothiophenes That Bear Fluorinated One-Carbon Units

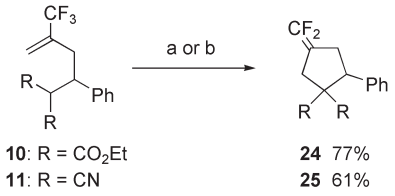
A sulfur nucleophile was employed in the cyclizations for the construction of the tetrahydrothiophene ring. Treatment of thioacetates **8a** and **8b** with 1.3 equivalents of NaOMe in DMF generated the corresponding thiolate, which underwent an S_N2'-type reaction to afford 4-(difluoromethylene)-tetrahydrothiophenes **22a** and **22b** in 82 and 75% yield, respectively (Scheme 13).[37] The addition reaction of **8a** and **8b** was also readily effected on treatment with 1.1 equivalents of K_2CO_3 in MeOH as a proton source (Scheme 13). The desired 4-(trifluoromethyl)tetrahydrothiophenes **23a** and **23b** were obtained in 90 and 82% yield, respectively.[38]



Scheme 13. Synthesis of 4-difluoromethylene and 4-trifluoromethyl tetrahydrothiophenes **22** and **23**. Reagents and conditions: a) NaOMe (1.3 equiv), 100 °C, 10–15 h, DMF; b) K_2CO_3 (1.1 equiv), reflux, 1–2 h, MeOH.

Synthesis of Cyclopentanes That Bear 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 equivalents of NaH in DMF, the S_N2'-type cyclization proceeded successfully to give difluoromethylene-substituted cyclopentanes **24** and **25** in 77 and 61 % yield, respectively (Scheme 14).[39]



Scheme 14. Synthesis of difluoromethylene cyclopentanes **24** and **25**. Reagents and conditions: a) KH (1.6 equiv), 110 °C, 3 h, DMF (for **10**); b) NaH (1.3 equiv), 100 °C, 3 h, DMF (for **11**).

Conclusions

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 concept of intramolecular substitution and addition, provide a high-yielding process for a variety of five-membered heterocycles and carbocycles. The resulting indolines, indoles, pyrrolidines, tetrahydrofurans, 2,3-dihydrobenzo[*b*]thiophenes, tetrahydrothiophenes, and cyclopentanes that bear fluorinated one-carbon units (=CF_2, CF_3, CHF_2, and $CBrF_2$) have so far not been very accessible, despite their increasing and potential utility as agrochemicals, pharmaceuticals, and other materials. The concept of intramolecular substitution and addition opens the way to these fluorinated cyclic compounds.

Experimental Section

General

IR spectra were recorded by the ATR (attenuated total reflectance) method. NMR spectra were recorded in $CDCl_3$ at 500 (^{1}H NMR), 126 (^{13}C NMR), and 470 MHz (^{19}F NMR). Chemical-shift values are given in ppm relative to internal Me_4Si (^{1}H NMR: $\delta = 0.00$ ppm), $CDCl_3$ (^{13}C NMR: $\delta = 77.0$ ppm), and C_6F_6 (^{19}F NMR: $\delta_F = 0.0$ ppm). Column chromatography and preparative thin-layer chromatography (PTLC) were performed on silica gel. All reactions were conducted under argon. Toluene, DMF, CH_2Cl_2, THF, and diethyl ether (Et_2O) were dried by passing over a column of activated alumina (A-2, Purity) followed by a column of Q-5 scavenger (Engelhard). MeOH, ethane-1,2-diol, and EtOH were distilled from Na and stored over 3-Å molecular sieves. Acetonitrile (CH_3CN) was distilled from P_2O_5 and then from CaH_2, and stored over 3-Å molecular sieves. Pyridine was distilled from KOH and stored over 4-Å molecular sieves. Benzene was distilled to remove water azeotropically and stored over 4-Å molecular sieves. 2-(3,3,3-Trifluoroprop-1-en-2-yl)aniline (**1**),[17] [2-(trifluoromethyl)prop-2-en-1-yl]trimethylsilane,[18] 3-(trifluoromethyl)homoallyl alcohols **4**,[18,19] *tert*-butyl *N*-(4-methylbenzenesulfonyl)carbamate,[40] methyl trifluoromathanesulfonate,[41] and cyano(tributylphosphaniumyl)methanide (Bu_3P=CHCN)[21] were prepared according to the literature.

Syntheses

2: TsCl (0.6 mmol) and a catalytic amount of DMAP (0.1 mmol) was added to a solution of **1** (0.5 mmol) in pyridine (2.5 mL) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. The reaction was quenched with phosphate buffer (pH 7, 10 mL). The organic materials were extracted with EtOAc (3×10 mL). The combined extracts were washed with aqueous HCl (10 mL) and brine (10 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by PTLC to give 4-methyl-*N*-[2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl]benzenesulfonamides **2**.

2a: 4-Methyl-*N*-[2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl]benzenesulfonamide: Colorless crystals, yield 84 %. IR (neat): $\tilde{\nu}$ = 3282, 1495, 1412, 1346, 1188, 1130, 916, 812, 771, 669 cm^{-1}; ^{1}H NMR: $\delta = 2.38$ (s, 3H), 5.07 (q, $J_{H,F} = 1.4$ Hz, 1H), 6.07 (q, $J_{H,F} = 1.4$ Hz, 1H), 6.42 (br s, 1H), 7.10–7.12 (m, 2H), 7.23 (d, $J = 8.3$ Hz, 2H), 7.32–7.36 (m, 1H), 7.64 (d, $J = 8.3$ Hz, 2H), 7.66 ppm (d, $J = 8.4$ Hz, 1H); ^{13}C NMR: $\delta = 21.5$, 121.1, 122.4 (q, $J_{C,F} = 274$ Hz), 124.6, 124.9, 125.5 (q, $J_{C,F} = 5$ Hz), 127.3, 129.6, 130.2, 130.5, 134.6 (q, $J_{C,F} = 32$ Hz), 134.8, 136.1, 144.2 ppm; ^{19}F NMR: δ_F = 94.4 ppm (br s); elemental analysis: calcd (%) for $C_{16}H_{14}F_3NO_2S$: C 56.30, H 4.13, N 4.10; found: C 56.49, H 4.29, N 3.97.

2b: 4-Methyl-*N*-[4-methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl]benzenesulfonamide: Colorless crystals, yield 87 %. IR (neat): $\tilde{\nu}$ = 3286, 1601, 1496, 1392, 1342, 1161, 1132, 904, 727 cm^{-1}; ^{1}H NMR: $\delta = 2.28$ (s, 3H), 2.38 (s, 3H), 4.97 (q, $J_{H,F} = 1.2$ Hz, 1H), 6.00 (q, $J_{H,F} = 1.2$ Hz, 1H), 6.45 (s, 1H), 6.91 (s, 1H), 7.14 (d, $J = 8.4$ Hz, 1H), 7.22 (d, $J = 8.3$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.61 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR: $\delta = 20.6$, 21.4, 122.0, 122.4 (q, $J_{C,F} = 274$ Hz), 125.2 (q, $J_{C,F} = 5$ Hz), 125.5, 127.3, 129.6, 130.8, 130.9, 132.1, 134.7 (q, $J_{C,F} = 32$ Hz), 134.8, 136.3, 144.0 ppm; ^{19}F NMR: $\delta_F = 94.6$ ppm (br s); elemental analysis: calcd (%) for $C_{17}H_{16}F_3NO_2S$: C 57.46, H 4.54, N 3.94; found: C 57.42, H 4.78, N 3.69.

2c: *N*-[5-Chloro-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl]-4-methylbenzenesulfonamide: Colorless crystals, yield 92 %. IR (neat): $\tilde{\nu}$ = 3388, 3282, 1597, 1493, 1389, 1342, 1163, 1122, 1092 cm^{-1}; ^{1}H NMR: $\delta = 2.40$ (s, 3H), 5.15 (q, $J_{H,F} = 1.2$ Hz, 1H), 6.12 (q, $J_{H,F} = 1.2$ Hz, 1H), 6.68 (br s, 1H), 7.04 (d, $J = 8.3$ Hz, 1H), 7.08 (dd, $J = 8.3$, 1.9 Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.70 ppm (d, $J = 1.9$ Hz, 1H); ^{13}C NMR: $\delta = 21.5$, 120.6, 122.1 (q, $J_{C,F} = 274$ Hz), 122.6, 124.6, 126.3 (q, $J_{C,F} = 5$ Hz), 127.3, 129.8, 131.4, 133.7 (q, $J_{C,F} = 32$ Hz), 135.6, 136.0, 136.1, 144.6 ppm; ^{19}F NMR: $\delta_F = 94.3$ ppm (br s); HRMS (FAB): *m/z* calcd for $C_{16}H_{14}ClF_3NO_2S$: 376.0386 $[M+H]^+$; found: 376.0381.

3: TFA (0.43 mL, 5.6 mmol) and *i*AmONO (0.75 mL, 5.6 mmol) were added to a solution of 2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (**1a**; 522 mg, 2.79 mmol) in CH_3CN (8 mL) at 0 °C. The reaction mixture was

stirred for 0.5 h. The solution was treated with AcSNa (prepared from AcSH (0.60 mL, 8.4 mmol) and NaH (60% dispersion in mineral oil; 335 mg, 8.4 mmol) in DMF (5 mL) at 0 °C) and stirred for 3 h at room temperature. The reaction was quenched with phosphate buffer (pH 7, 10 mL). The mixture was filtered through celite, and the organic materials were extracted with Et_2O (3×15 mL). After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc = 10:1) to give *S*-[2-(3,3,3-trifluoroprop-1-en-2-yl)-phenyl] ethanethioate (**3**; 214 mg, 31%) as a pale-yellow liquid. IR (neat): $\tilde{\nu}$ = 1705, 1473, 1402, 1346, 1171, 1111, 1093, 906, 729 cm^{-1}; ^1H NMR: δ = 2.38 (s, 3H), 5.52 (s, 1H), 6.06 (s, 1H), 7.36–7.38 (m, 1H), 7.43–7.45 (m, 2H), 7.51–7.53 ppm (m, 1H); ^{13}C NMR: δ = 30.0, 122.6 (q, $J_{C,F}$ = 274 Hz), 123.5 (q, $J_{C,F}$ = 5 Hz), 128.1, 129.6, 129.8, 130.7, 136.8, 137.2 (q, $J_{C,F}$ = 33 Hz), 138.2, 193.4 ppm; ^{19}F NMR: δ_F = 95.1 (br s); HRMS (FAB): *m/z* calcd for $C_{11}H_{10}F_3OS$: 247.0404 $[M+H]^+$; found: 247.0415.

5: DEAD (40% in toluene; 1.36 mL, 4.0 mmol) was added to a solution of 3-(trifluoromethyl)but-3-en-1-ol (**4**; 2.0 mmol), PPh_3 (1.05 g, 4.00 mmol), and *tert*-butyl *N*-(4-methylbenzenesulfonyl)carbamate (814 mg, 3.00 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give *tert*-butyl *N*-(4-methylbenzenesulfonyl)-*N*-[3-(trifluoromethyl)but-3-en-1-yl]-carbamate. TFA (15 mmol) was added to a solution of *tert*-butyl *N*-(4-methylbenzenesulfonyl)-*N*-[3-(trifluoromethyl)but-3-en-1-yl]carbamate (1.5 mmol) in CH_2Cl_2 (15 mL) at room temperature. The reaction mixture was stirred at room temperature for 10 h. The reaction was quenched with aqueous Na_2CO_3 (20 mL), and the organic materials were extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 4-methyl-*N*-[3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamides **5**.

5a: 4-Methyl-*N*-[1-phenyl-3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamide: Colorless crystals, yield 89%. M.p.: 78–80 °C; IR (neat): $\tilde{\nu}$ = 3269, 3064, 3030, 2927, 1456, 1325, 1159, 1120, 912 cm^{-1}; ^1H NMR: δ = 2.37 (s, 3H), 2.58 (dd, J = 15.3, 7.2 Hz, 1H), 2.71 (dd, J = 15.3, 7.8 Hz, 1H), 4.49 (ddd, J = 7.8, 7.3, 7.2 Hz, 1H), 4.91 (br s, 1H), 5.19 (s, 1H), 5.63 (s, 1H), 7.02–7.04 (m, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.17–7.19 (m, 3H), 7.54 ppm (d, J = 8.2 Hz, 2H); ^{13}C NMR: δ = 21.4, 37.6, 56.5, 121.9 (q, $J_{C,F}$ = 5 Hz), 123.3 (q, $J_{C,F}$ = 272 Hz), 126.6, 127.1, 127.8, 128.6, 129.3, 133.4 (q, $J_{C,F}$ = 30 Hz), 137.2, 139.5, 143.2 ppm; ^{19}F NMR: δ_F = 93.4 ppm (br s); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79; found: C 58.56, H 5.08, N 3.80.

5b: *N*-[1-(4-Bromophenyl)-3-(trifluoromethyl)but-3-en-1-yl]-4-methylbenzenesulfonamide: Colorless crystals, yield 65%. M.p.: 131–133 °C; IR (neat): $\tilde{\nu}$ = 3263, 3066, 3030, 2924, 2872, 1489, 1321, 1155, 1117, 953 cm^{-1}; ^1H NMR: δ = 2.39 (s, 3H), 2.49 (dd, J = 15.2, 7.2 Hz, 1H), 2.64 (dd, J = 15.2, 8.0 Hz, 1H), 4.46 (ddd, J = 8.0, 7.6, 7.2 Hz, 1H), 5.21 (s, 1H), 5.61 (s, 1H), 5.91 (br s, 1H), 6.90 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.50 ppm (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.4, 37.4, 55.9, 121.6, 122.3 (q, $J_{C,F}$ = 6 Hz), 123.2 (q, $J_{C,F}$ = 272 Hz), 127.0, 128.4, 129.4, 131.5, 133.0 (q, $J_{C,F}$ = 30 Hz), 136.9, 138.4, 143.6 ppm; ^{19}F NMR: δ_F = 93.5 ppm (br s); elemental analysis: calcd (%) for $C_{18}H_{17}BrF_3NO_2S$: C 48.23, H 3.82, N 3.12; found: C 48.14, H 3.77, N 2.89.

5c: *N*-[1-(Furan-2-yl)-3-(trifluoromethyl)but-3-en-1-yl]-4-methylbenzenesulfonamide: Colorless crystals, yield 29%. IR (neat): $\tilde{\nu}$ = 3269, 1599, 1326, 1157, 1114, 1011, 949 cm^{-1}; ^1H NMR: δ = 2.38 (s, 3H), 2.66 (dd, J = 15.1, 8.0 Hz, 1H), 2.70 (dd, J = 15.1, 7.5 Hz, 1H), 4.61 (ddd, J = 8.6, 8.0, 7.5 Hz, 1H), 5.24 (s, 1H), 5.32 (d, J = 8.6 Hz, 1H), 5.64 (s, 1H), 5.92 (d, J = 3.2 Hz, 1H), 6.10 (dd, J = 3.2, 1.8 Hz, 1H), 7.16 (d, J = 1.8 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.61 ppm (d, J = 8.1 Hz, 2H); ^{13}C NMR: δ = 21.4, 35.0, 50.2, 107.8, 110.0, 121.9 (q, $J_{C,F}$ = 6 Hz), 123.3 (q, $J_{C,F}$ = 272 Hz), 127.0, 129.4, 132.1 (q, $J_{C,F}$ = 30 Hz), 137.3, 142.1, 143.3, 151.2 ppm; ^{19}F NMR: δ_F = 93.4 ppm (br s); HRMS (FAB): *m/z* calcd for $C_{16}H_{17}F_3NO_3S$: 360.0881 $[M+H]^+$; found: 360.0878.

5d: 4-Methyl-*N*-[2-(trifluoromethyl)dec-1-en-4-yl]benzenesulfonamide: Colorless crystals, yield 61%. M.p.: 65–67 °C; IR (neat): $\tilde{\nu}$ = 3276, 3020, 2956, 2929, 2860, 1217, 1159, 1120 cm^{-1}; ^1H NMR: δ = 0.84 (t, J = 7.1 Hz, 3H), 1.02–1.32 (m, 9H), 1.42–1.50 (m, 1H), 2.26 (dd, J = 14.9, 7.3 Hz, 1H), 2.37 (dd, J = 14.9, 6.6 Hz, 1H), 2.42 (s, 3H), 3.37–3.44 (m, 1H), 4.29 (br s, 1H), 5.33 (s, 1H), 5.66 (s, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.74 ppm (d, J = 8.3 Hz, 2H); ^{13}C NMR: δ = 14.0, 21.4, 22.4, 24.9, 28.7, 31.5, 34.3, 36.0, 52.4, 121.3 (q, $J_{C,F}$ = 6 Hz), 123.2 (q, $J_{C,F}$ = 272 Hz), 127.0, 129.5, 134.3 (q, $J_{C,F}$ = 29 Hz), 137.9, 143.3 ppm; ^{19}F NMR: δ_F = 93.6 ppm (br s); elemental analysis: calcd (%) for $C_{18}H_{26}F_3NO_2S$: C 57.27, H 6.94, N 3.71; found: C 57.03, H 7.20, N 3.59.

5e: 4-Methyl-*N*-[2-phenyl-3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamide: Colorless crystals, yield 64%. M.p.: 108–110 °C; IR (neat): $\tilde{\nu}$ = 3282, 3032, 1417, 1325, 1159, 1124, 1093 cm^{-1}; ^1H NMR: δ = 2.44 (s, 3H), 3.27 (ddd, J = 13.1, 8.1, 5.3 Hz, 1H), 3.46 (ddd, J = 13.1, 7.4, 7.1 Hz, 1H), 3.62 (dd, J = 8.1, 7.4 Hz, 1H), 4.51 (dd, J = 7.1, 5.3 Hz, 1H), 5.45 (q, $J_{H,F}$ = 1.0 Hz, 1H), 5.90 (q, $J_{H,F}$ = 1.0 Hz, 1H), 7.07 (d, J = 8.1 Hz, 2H), 7.25–7.32 (s, 5H), 7.68 ppm (d, J = 8.1 Hz, 2H); ^{13}C NMR: δ = 21.5, 44.6, 46.2, 119.9 (q, $J_{C,F}$ = 6 Hz), 123.2 (q, $J_{C,F}$ = 275 Hz), 127.0, 127.8, 127.8, 129.0, 129.8, 136.6, 137.5, 138.4 (q, $J_{C,F}$ = 29 Hz), 143.7 ppm; ^{19}F NMR: δ_F = 94.5 (br s); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79; found: C 58.72, H 5.05, N 3.54.

5f: NaH (55% dispersion in mineral oil; 97 mg, 2.2 mmol) was added to a solution of 3-(trifluoromethyl)but-3-en-1-yl 4-methylbenzenesulfonate (**4f**; 506 mg, 1.72 mmol) and *tert*-butyl *N*-(4-methylbenzenesulfonyl)carbamate (661 mg, 2.44 mmol) in DMF (10 mL) at 0 °C. After being stirred at that temperature for 0.5 h, the reaction mixture was heated at 90 °C for 4 h. The reaction was quenched with phosphate buffer (pH 7, 20 mL), and the organic materials were extracted with EtOAc (3×20 mL). The combined extracts were washed with brine (20 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, crude *tert*-butyl (4-methylbenzenesulfonyl)-*N*-[3-(trifluoromethyl)but-3-en-1-yl]carbamate (715 mg) was obtained. TFA (1.5 mL, 20 mmol) was added to a solution of crude *tert*-butyl *N*-(4-methylbenzenesulfonyl)-*N*-[3-(trifluoromethyl)but-3-en-1-yl]carbamate (715 mg) in CH_2Cl_2 (20 mL) at room temperature. After the mixture was stirred for 6 h, the reaction was quenched with aqueous $NaHCO_3$ (40 mL). The organic materials were extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with brine (20 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc = 2:1) to give 4-methyl-*N*-[3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamide (**5f**; 408 mg, 81%) as colorless crystals. M.p.: 54–55 °C; IR (neat): $\tilde{\nu}$ = 3263, 1427, 1315, 1153, 1117, 945, 928, 814 cm^{-1}; ^1H NMR: δ = 2.42 (t, J = 6.9 Hz, 2H), 2.44 (s, 3H), 3.14 (dt, J = 6.9, 6.9 Hz, 2H), 4.50 (br s, 1H), 5.37 (q, $J_{H,F}$ = 1.3 Hz, 1H), 5.76 (q, $J_{H,F}$ = 1.4 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.75 ppm (d, J = 8.1 Hz, 2H); ^{13}C NMR: δ = 21.5, 30.2, 41.0, 120.9 (q, $J_{C,F}$ = 6 Hz), 123.3 (q, $J_{C,F}$ = 274 Hz), 127.0, 129.8, 134.4 (q, $J_{C,F}$ = 30 Hz), 136.7, 143.7 ppm; ^{19}F NMR: δ_F = 93.3 ppm (br s); elemental analysis: calcd (%) for $C_{12}H_{14}F_3NO_2S$: C 49.14, H 4.81, N 4.78; found: C 49.27, H 4.96, N 4.59.

26: 1-Phenyl-3-(trifluoromethyl)but-3-en-1-ol (**4a**; 13.9 g, 64.4 mmol) was added to a mixture of pyridinium chlorochromate (38.4 g, 178 mmol) and silica gel (38.4 g) in CH_2Cl_2 (350 mL). The reaction mixture was stirred for 2 h at room temperature and then diluted with Et_2O. The solid materials were removed by filtration through a short column of florisil. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc = 4:1) to give 1-phenyl-3-(trifluoromethyl)but-3-en-1-one (**26**; 12.2 g, 88%) as colorless crystals. IR (neat): $\tilde{\nu}$ = 3062, 1689, 1414, 1358, 1323, 1169, 1115, 1005, 949, 754, 688 cm^{-1}; ^1H NMR: δ = 3.85 (s, 2H), 5.51 (br s, 1H), 5.95 (br s, 1H), 7.48 (dd, J = 7.7, 7.7 Hz, 2H), 7.60 (t, J = 7.7 Hz, 1H), 7.96 ppm (d, J = 7.7 Hz, 2H); ^{13}C NMR: δ = 38.7, 122.6 (q, $J_{C,F}$ = 6 Hz), 123.1 (q, $J_{C,F}$ = 272 Hz), 128.3, 128.7, 131.8 (q, $J_{C,F}$ = 31 Hz), 133.5, 135.9, 194.8 ppm; ^{19}F NMR: δ_F = 92.9 ppm (br s); elemental analysis: calcd (%) for $C_{11}H_9F_3O$: C 61.68, H 4.24; found: C 61.75, H 4.39.

27: A solution of potassium hexamethyldisilazide (KHMDS, 0.56 M in toluene; 4.1 mL, 2.3 mmol) was added dropwise to a solution of **26** (500 mg, 2.33 mmol) in Et_2O (20 mL), and the reaction mixture was stirred for 40 min at −78 °C. Methyl trifluoromethanesulfonate (0.26 mL, 2.3 mmol) was added at that temperature, and the mixture was allowed to warm to room temperature. After the mixture was stirred for 6 h, the reaction was

quenched with phosphate buffer (pH 7, 20 mL), and the organic materials were extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (10 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by PTLC (hexane/EtOAc=4:1) to give 2-methyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one (**27**; 429 mg, 81%) as a colorless liquid. IR (neat): $\tilde{\nu}$=2987, 2943, 1687, 1273, 1219, 1169, 1115, 962, 704, 687 cm^{-1}; ^1H NMR: δ=1.42 (d, J=6.8 Hz, 3H), 4.36 (q, J=6.8 Hz, 1H), 5.52 (br s, 1H), 5.87 (br s, 1H), 7.47 (dd, J=7.2, 7.2 Hz, 2H), 7.58 (t, J=7.2 Hz, 1H), 7.90 ppm (d, J=7.2 Hz, 2H); ^{13}C NMR: δ=17.8, 40.2, 120.7 (q, $J_{C,F}$=6 Hz), 123.5 (q, $J_{C,F}$=272 Hz), 128.4, 128.7, 133.3, 135.5, 137.9 (q, $J_{C,F}$=30 Hz), 198.5 ppm; ^{19}F NMR: δ_F=94.0 ppm (br s); elemental analysis: calcd (%) for $C_{12}H_{11}F_3O$: C 63.16, H 4.86; found: C 63.13, H 5.05.

6a: A solution of KHMDS (0.56 M in toluene; 1.6 mL, 0.90 mmol) was added dropwise to a solution of **27** (205 mg, 0.90 mmol) in Et_2O (10 mL), and the reaction mixture was stirred for 1 h at −78 °C. Methyl trifluoromethanesulfonate (0.11 mL, 0.90 mmol) was added at that temperature, and the mixture was allowed to warm to room temperature. After the mixture was stirred for 12 h, the reaction was quenched with phosphate buffer (pH 7, 10 mL), and the organic materials were extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (10 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=5:1) to give 2,2-dimethyl-1-phenyl-3-(trifluoromethyl)-but-3-en-1-one (**6a**; 110 mg, 51%) as a colorless liquid. IR (neat): $\tilde{\nu}$= 2987, 1684, 1323, 1246, 1178, 1119, 1092, 972, 719, 690 cm^{-1}; ^1H NMR: δ=1.53 (s, 6H), 5.60 (br s, 1H), 5.93 (br s, 1H), 7.38 (dd, J=8.0, 8.0 Hz, 2H), 7.48 (t, J=8.0 Hz, 1H), 7.85 ppm (d, J=8.0 Hz, 2H); ^{13}C NMR: δ= 26.4, 49.8, 120.4 (q, $J_{C,F}$=6 Hz), 123.6 (q, $J_{C,F}$=276 Hz), 128.1, 129.2, 132.1, 135.6, 143.5 (q, $J_{C,F}$=27 Hz), 200.8 ppm; ^{19}F NMR: δ_F=100.3 ppm (br s); elemental analysis: calcd (%) for $C_{13}H_{13}F_3O$: C 64.46, H 5.41; found: C 64.25, H 5.58.

6b: A solution of KHMDS (0.50 M in toluene; 12.6 mL, 6.3 mmol) was added dropwise to a solution of **4a** (1.29 g, 6.0 mmol) in Et_2O (30 mL) at −78 °C. The reaction mixture was stirred for 10 min at 0 °C and then transferred to a solution of 1,4-diiodobutane (4.7 mL, 36 mmol) and hexamethylphosphoric triamide (HMPA; 10 mL) in Et_2O (30 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with phosphate buffer (pH 7, 30 mL), and the organic materials were extracted with EtOAc (3× 10 mL). The combined extracts were washed with brine (10 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc= 20:1→5:1) to give a mixture of phenyl[1-(3,3,3-trifluoroprop-1-en-2-yl)cyclopentyl]methanone (**6b**) and 2-(4-iodobutyl)-1-phenyl-3-(trifluoromethyl)but-3-en-1-one (1.82 g) as a colorless liquid. A solution of KHMDS (0.50 M in toluene; 7.22 mL, 3.6 mmol) was added dropwise to a solution of the mixture (1.43 g) in Et_2O (30 mL) at −78 °C. The reaction mixture was stirred for 5 min at −78 °C and then allowed to warm to room temperature. After the mixture was stirred for 4 h, the reaction was quenched with phosphate buffer (pH 7, 30 mL), and then organic materials were extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (10 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=20:1) to give **6b** (0.90 g, 67% over 2 steps) as a colorless liquid. IR (neat): $\tilde{\nu}$=2958, 2925, 2854, 1684, 1317, 1234, 1167, 1126 cm^{-1}; ^1H NMR: δ=1.56–1.64 (m, 2H), 1.67–1.76 (m, 2H), 2.02 (ddd, J=13.0, 6.5, 6.5 Hz, 2H), 2.46 (ddd, J=13.0, 6.5, 6.5 Hz, 2H), 5.55 (q, $J_{H,F}$=1.0 Hz, 1H), 5.87 (q, $J_{H,F}$=0.9 Hz, 1H), 7.38 (dd, J=7.5, 7.5 Hz, 2H), 7.48 (t, J=7.5 Hz, 1H), 7.88 ppm (d, J=7.5 Hz, 2H); ^{13}C NMR: δ= 24.3, 35.9, 60.7, 119.9 (q, $J_{C,F}$=6 Hz), 123.6 (q, $J_{C,F}$=277 Hz), 128.1, 129.5, 132.2, 135.4, 142.1 (q, $J_{C,F}$=27 Hz), 199.2 ppm; ^{19}F NMR: δ_F=99.9 ppm (br s); HRMS (FAB): m/z calcd for $C_{15}H_{16}F_3O$: 269.1153 $[M+H]^+$; found: 269.1178.

28: 1-Phenyl-5-(trifluoromethyl)hex-5-en-3-ol (10.3 g, 42.2 mmol) was added to a mixture of pyridinium chlorochromate (13.6 g, 63.2 mmol) and silica gel (14 g) in dichloromethane (126 mL). The reaction mixture was stirred for 12 h at room temperature and then diluted with Et_2O. The solid materials were removed by filtration through celite. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/Et_2O=5:1) to give 1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (**28**; 9.81 g, 96%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3030, 2927, 1722, 1604, 1496, 1456, 1412, 1363, 1308, 1169, 1113, 950, 748, 698 cm^{-1}; ^1H NMR: δ=2.82 (t, J=7.6 Hz, 2H), 2.92 (t, J=7.6 Hz, 2H), 3.25 (s, 2H), 5.45 (q, $J_{H,F}$=1.1 Hz, 1H), 5.89 (q, $J_{H,F}$=1.5 Hz, 1H), 7.17–7.22 (m, 3H), 7.29 ppm (dd, J=7.6, 7.6 Hz, 2H); ^{13}C NMR: δ=29.5, 43.2, 43.9, 122.7 (q, $J_{C,F}$=6 Hz), 123.0 (q, $J_{C,F}$=274 Hz), 126.2, 128.3, 128.5, 131.3 (q, $J_{C,F}$=31 Hz), 140.5, 204.2 ppm; ^{19}F NMR: δ_F=92.7 ppm (br s); elemental analysis: calcd (%) for $C_{13}H_{13}F_3O$: C 64.46, H 5.41; found: C 64.68, H 5.60.

29: A solution of KHMDS (0.70 M in toluene; 59.6 mL, 41.7 mmol) was added dropwise to a solution of **28** (9.81 g, 40.5 mmol) in Et_2O (200 mL) at −78 °C, and the reaction mixture was stirred for 1 h at that temperature. Methyl trilfluoromethanesulfonate (9.2 mL, 81 mmol) was added, and the mixture was stirred for 15 min. After being allowed to warm to room temperature, the reaction mixture was stirred for 12 h. The reaction was quenched with phosphate buffer (pH 7, 50 mL), and the organic materials were extracted with EtOAc (3×30 mL). The combined extracts were washed with brine (30 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=20:1) to give 4-methyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (**29**; 9.74 g, 94%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3030, 2983, 2941, 1720, 1604, 1496, 1454, 1415, 1304, 1277, 1171, 1115, 953, 748, 698 cm^{-1}; ^1H NMR: δ=1.25 (d, J=7.0 Hz, 3H), 2.71–2.78 (m, 1H), 2.81–2.90 (m, 3H), 3.37 (q, J=7.0 Hz, 1H), 5.35 (s, 1H), 5.80 (s, 1H), 7.15–7.20 (m, 3H), 7.27 ppm (dd, J=7.5, 7.5 Hz, 2H); ^{13}C NMR: δ=16.5, 29.7, 42.6, 45.7, 120.3 (q, $J_{C,F}$=6 Hz), 123.4 (q, $J_{C,F}$=274 Hz), 126.1, 128.3, 128.4, 137.6 (q, $J_{C,F}$=30 Hz), 140.7, 207.3 ppm; ^{19}F NMR: δ_F=93.3 ppm (br s); elemental analysis: calcd (%) for $C_{14}H_{15}F_3O$: C 65.62, H 5.90; found: C 65.84, H 6.13.

6c: A solution of KHMDS (0.70 M in toluene; 33.5 mL, 23.4 mmol) was added dropwise to a solution of **29** (5.72 g, 22.3 mmol) in Et_2O (200 mL) at −105 °C, and the reaction mixture was stirred for 30 min at −90 °C. Methyl trifluoromethanesulfonate (5.05 mL, 44.6 mmol) was added at −105 °C, and the mixture was stirred for 10 min at that temperature. After being allowed to warm to room temperature, the mixture was stirred for 2 h. The reaction was quenched with phosphate buffer (pH 7, 30 mL), and the organic materials were extracted with EtOAc (3× 30 mL). The combined extracts were washed with brine (30 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc= 20:1) to give 4,4-dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-one (**6c**; 4.38 g, 73%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3028, 2983, 2941, 1716, 1454, 1325, 1176, 1126, 1099, 953 cm^{-1}; ^1H NMR: δ=1.31 (s, 6H), 2.73 (t, J=7.6 Hz, 2H), 2.89 (t, J=7.6 Hz, 2H), 5.56 (s, 1H), 5.91 (s, 1H), 7.19 (d, J=7.5 Hz, 2H), 7.20 (t, J=7.5 Hz, 1H), 7.29 ppm (dd, J=7.5, 7.5 Hz, 2H); ^{13}C NMR: δ=23.5, 30.1, 38.7, 50.4, 120.8 (q, $J_{C,F}$=6 Hz), 123.7 (q, $J_{C,F}$=277 Hz), 126.0, 128.3, 128.4, 141.0, 142.4 (q, $J_{C,F}$=28 Hz), 209.1 ppm; ^{19}F NMR: δ_F=100.3 ppm (br s); HRMS (FAB): m/z calcd for $C_{15}H_{18}F_3O$: 271.1310 $[M+H]^+$; found: 271.1281.

6d: A solution of KHMDS (0.50 M in toluene; 21.1 mL, 10.5 mmol) was added dropwise to a solution of **6c** (2.71 g, 10 mmol) at −78 °C, and the reaction mixture was stirred for 10 min at 0 °C. Trimethylsilyl chloride (2.6 mL, 20.1 mmol) was added at −78 °C, and the mixture was stirred for 15 min. After being allowed to warm to room temperature, the reaction was quenched with phosphate buffer (pH 7, 50 mL), and the organic materials were extracted with EtOAc (3×30 mL). The combined extracts were washed with brine (30 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude silyl enolate was obtained as a pale-brown liquid. The crude product was then dissolved in CH_3CN (20 mL), and the solution was added to a solution of $Pd(OAc)_2$ (2.9 g, 13 mmol) in CH_3CN (20 mL) at room temperature. After the mixture was stirred for 12 h at room temperature, Et_2O (50 mL) was added, and the solid materials were removed through celite. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=20:1→5:1) to give 4,4-dimethyl-1-

phenyl-5-(trifluoromethyl)hexa-1,5-dien-3-one (**6d**; 1.91 g, 71%) as a colorless liquid. IR (neat): $\tilde{\nu}$=2983, 2941, 1689, 1610, 1323, 1176, 1120, 1099, 1053, 982, 953 cm^{-1}; ^{1}H NMR: δ=1.42 (s, 6H), 5.68 (s, 1H), 6.00 (s, 1H), 6.91 (d, J=15.7 Hz, 1H), 7.37–7.38 (m, 3H), 7.53 (dd, J=3.2, 3.2 Hz, 2H), 7.72 ppm (d, J=15.7 Hz, 1H); ^{13}C NMR: δ=23.8, 49.8, 120.2, 121.0 (q, $J_{C,F}$=6 Hz), 123.7 (q, $J_{C,F}$=277 Hz), 128.4, 128.8, 130.5, 134.5, 142.8 (q, $J_{C,F}$=28 Hz), 143.7, 198.6 ppm; ^{19}F NMR: δ_F=100.2 (br s); elemental analysis: calcd (%) for $C_{15}H_{15}F_3O$: C 67.16, H 5.64; found: C 67.23, H 5.81.

7: Sodium borohydride (84 mg, 2.2 mmol) was added to a solution of 1-substituted 2,2-dialkyl-3-trifluoromethylbut-3-en-1-one **6** (1.45 mmol) in EtOH (14 mL) at room temperature. The reaction mixture was heated at reflux for 3 h, then phosphate buffer (pH 7, 30 mL) was added to quench the reaction. The mixture was extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC (hexane/EtOAc=5:1) to give 2,2-dialkyl-3-(trifluoromethyl)homoallyl alcohol **7**.

7a: 2,2-Dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-ol: Colorless liquid, yield 87%. IR (neat): $\tilde{\nu}$=3464, 3064, 3022, 2987, 2924, 1454, 1321, 1115, 1092, 1039, 949, 727, 702 cm^{-1}; ^{1}H NMR: δ=1.08 (s, 3H), 1.19 (s, 3H), 1.94 (d, J=2.8 Hz, 1H), 4.85 (d, J=2.8 Hz, 1H), 5.49 (q, $J_{H,F}$=1.8 Hz, 1H), 5.92 (q, $J_{H,F}$=1.2 Hz, 1H), 7.23–7.32 ppm (m, 5H); ^{13}C NMR: δ=21.7, 23.8, 43.0, 77.7, 122.0 (q, $J_{C,F}$=7 Hz), 124.4 (q, $J_{C,F}$=277 Hz), 127.5, 127.6, 128.0, 140.2, 143.3 ppm (q, $J_{C,F}$=27 Hz); ^{19}F NMR: δ_F=100.9 ppm (br s); elemental analysis: calcd (%) for $C_{13}H_{15}F_3O$: C 63.93, H 6.19; found: C 64.12, H 6.46.

7b: Phenyl[1-(3,3,3-trifluoroprop-1-en-2-yl)cyclopentyl]methanol: Colorless liquid, yield 86%. IR (neat): $\tilde{\nu}$=3464, 3064, 3032, 2962, 2879, 1454, 1301, 1159, 1115, 1078, 947, 704 cm^{-1}; ^{1}H NMR: δ=1.50–1.59 (m, 4H), 1.78–1.80 (m, 1H), 1.88–1.94 (m, 3H), 2.07 (d, J=3.0 Hz, 1H), 4.87 (d, J=3.0 Hz, 1H), 5.29 (q, $J_{H,F}$=1.5 Hz, 1H), 5.86 (q, $J_{H,F}$=1.2 Hz, 1H), 7.24–7.31 ppm (m, 5H); ^{13}C NMR: δ=22.7, 22.8, 32.1, 32.6, 55.9, 76.6, 123.0 (q, $J_{C,F}$=7 Hz), 124.4 (q, $J_{C,F}$=277 Hz), 127.6, 127.6, 127.7, 141.1, 141.1 ppm (q, $J_{C,F}$=26 Hz); ^{19}F NMR: δ_F=101.8 (br s); HRMS (FAB): m/z calcd for $C_{15}H_{18}F_3O$: 271.1310 $[M+H]^+$; found: 271.1308.

7c: 4,4-Dimethyl-1-phenyl-5-(trifluoromethyl)hex-5-en-3-ol: Colorless liquid, yield 83%. IR (neat): $\tilde{\nu}$=3456, 3028, 2981, 2929, 1319, 1153, 1117, 1092, 949, 748, 698 cm^{-1}; ^{1}H NMR: δ=1.14 (s, 3H), 1.19 (s, 3H), 1.55 (d, J=5.2 Hz, 1H), 1.57–1.64 (m, 1H), 1.74–1.82 (m, 1H), 2.62 (ddd, J=13.6, 10.0, 6.8 Hz, 1H), 2.92 (ddd, J=13.6, 10.4, 5.2 Hz, 1H), 3.69 (dd, J=10.4, 5.2 Hz, 1H), 5.50 (q, $J_{H,F}$=2.2 Hz, 1H), 5.88 (d, $J_{H,F}$=0.8 Hz, 1H), 7.19–7.30 ppm (m, 5H); ^{13}C NMR: δ=22.2, 23.4, 33.4, 33.4, 42.7, 75.5, 121.1 (q, $J_{C,F}$=7 Hz), 124.2 (q, $J_{C,F}$=277 Hz), 125.9, 128.4, 128.4, 142.0, 143.8 ppm (q, $J_{C,F}$=26 Hz); ^{19}F NMR: δ_F=101.3 (br s); HRMS (FAB): m/z calcd for $C_{15}H_{20}F_3O$: 273.1466 $[M+H]^+$; found: 273.1473.

7d: Cerium(III) chloride (140 mg, 0.57 mmol) was added to a solution of **6d** (150 mg, 0.56 mmol) in MeOH (1.3 mL), and the mixture was stirred at room temperature for 0.5 h. Upon cooling the mixture to 0°C, sodium borohydride (21 mg, 0.56 mmol) was added. The reaction mixture was stirred for 3 h, then phosphate buffer (pH 7, 10 mL) was added to quench the reaction. 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 removal of the solvent under reduced pressure, the residue was purified by PTLC (hexane/EtOAc=5:1) to give 4,4-dimethyl-1-phenyl-5-(trifluoromethyl)hexa-1,5-dien-3-ol (**7d**; 117 mg, 77%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3433, 3028, 2983, 2887, 1496, 1408, 1323, 1153, 1115, 1086, 968, 754, 692 cm^{-1}; ^{1}H NMR: δ=1.20 (s, 3H), 1.26 (s, 3H), 1.77 (br d, J=3.0 Hz, 1H), 4.38 (dd, J=6.7, 3.0 Hz, 1H), 5.60 (q, $J_{H,F}$=1.8 Hz, 1H), 5.94 (q, $J_{H,F}$=1.2 Hz, 1H), 6.20 (dd, J=15.9, 6.7 Hz, 1H), 6.62 (d, J=15.9 Hz, 1H), 7.25 (t, J=7.2 Hz, 1H), 7.32 (dd, J=7.8, 7.2 Hz, 2H), 7.38 ppm (d, J=7.8 Hz, 2H); ^{13}C NMR: δ=22.5, 23.4, 42.6, 76.9, 121.6 (q, $J_{C,F}$=7 Hz), 124.3 (q, $J_{C,F}$=277 Hz), 126.5, 127.8, 127.8, 128.6, 132.7, 136.6, 143.3 ppm (q, $J_{C,F}$=28 Hz); ^{19}F NMR: δ_F=101.3 (br s); HRMS (FAB): m/z calcd for $C_{15}H_{18}F_3O$: 271.1310 $[M+H]^+$; found: 271.1334.

8a: DEAD (40% in toluene solution; 3.45 mL, 6.83 mmol) was added to a solution of **4a** (520 mg, 2.41 mmol), PPh_3 (1.90 g, 7.23 mmol), and thioacetic acid (0.345 mL, 3.6 mmol) in THF (15 mL) at −10°C. The reaction mixture was stirred at 0°C for 12 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=50:1) to give *S*-[1-phenyl-3-(trifluoromethyl)but-3-en-1-yl] ethanethioate (**8a**; 224 mg, 34%) as a pale-yellow liquid. IR (neat): $\tilde{\nu}$=3064, 3032, 2929, 1693, 1217, 1169, 1124 cm^{-1}; ^{1}H NMR: δ=2.30 (s, 3H), 2.82 (dd, J=15.8, 8.7 Hz, 1H), 2.87 (dd, J=15.8, 7.2 Hz, 1H), 4.81 (dd, J=8.7, 7.2 Hz, 1H), 5.21 (s, 1H), 5.66 (s, 1H), 7.23–7.33 ppm (m, 5H); ^{13}C NMR: δ=30.3, 35.7, 45.8, 120.9 (q, $J_{C,F}$=6 Hz), 123.4 (q, $J_{C,F}$=272 Hz), 127.7, 127.7, 128.7, 134.6 (q, $J_{C,F}$=30 Hz), 140.1, 194.0 ppm; ^{19}F NMR: δ_F=93.4 ppm (br s); elemental analysis: calcd (%) for $C_{13}H_{13}F_3OS$: C 56.92, H 4.78; found: C 56.89, H 4.90.

8b: DEAD (40% in toluene solution; 3.45 mL, 6.81 mmol) was added to a solution of 2-(trifluoromethyl)dec-1-en-4-ol (**4d**; 540 mg, 2.41 mmol), PPh_3 (1.29 g, 4.90 mmol), and thioacetic acid (258 μL, 3.6 mmol) in THF (15 mL) at −10°C. The reaction mixture was stirred at 0°C for 20 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane) to give *S*-[2-(trifluoromethyl)-dec-1-en-4-yl] ethanethioate (**8b**; 346 mg, 51%) as a pale-yellow liquid. IR (neat): $\tilde{\nu}$=2956, 2929, 2858, 1695, 1458, 1417, 1354, 1319, 1169, 1122, 951 cm^{-1}; ^{1}H NMR: δ=0.87 (t, J=6.5 Hz, 3H), 1.27–1.75 (m, 10H), 2.32 (s, 3H), 2.47 (d, J=7.6 Hz, 2H), 3.66–3.73 (m, 1H), 5.41 (s, 1H), 5.78 ppm (s, 1H); ^{13}C NMR: δ=14.0, 22.5, 26.6, 29.0, 30.7, 31.6, 34.2, 34.9, 42.4, 120.1 (q, $J_{C,F}$=6 Hz), 123.5 (q, $J_{C,F}$=274 Hz), 135.4 (q, $J_{C,F}$=30 Hz), 195.2 ppm; ^{19}F NMR: δ_F=93.3 ppm (br s); HRMS (FAB): m/z calcd for $C_{13}H_{22}F_3OS$: 283.1343 $[M+H]^+$; found: 283.1326.

10: A solution of TBAF (1.0 M in THF; 0.69 mL, 0.69 mmol) was added to a mixture of trimethyl[2-(trifluoromethyl)prop-2-en-1-yl]silane (1.06 g, 5.82 mmol), diethyl 2-benzylidenemalonate (**9**; 1.44 g, 5.80 mmol) and 4-Å molecular sieves (1.0 g) in THF (15 mL) at room temperature, and the mixture was stirred for 12 h at room temperature. The reaction was quenched with phosphate buffer (pH 7, 20 mL), and the solid materials were removed through celite. After the organic materials were extracted with EtOAc (3×10 mL), the combined extracts were washed with water (2×10 mL) and brine (10 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (benzene) to give diethyl [1-phenyl-3-(trifluoromethyl)-but-3-en-1-yl]malonate (**10**; 857 mg, 41%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3032, 2983, 2939, 2906, 1749, 1732, 1369, 1219, 1167, 1122 cm^{-1}; ^{1}H NMR: δ=0.96 (t, J=7.2 Hz, 3H), 1.29 (t, J=7.2 Hz, 3H), 2.53 (dd, J=15.0, 10.1 Hz, 1H), 2.73 (dd, J=15.0, 3.2 Hz, 1H), 3.66 (d, J=10.1 Hz, 1H), 3.68 (ddd, J=10.1, 10.1, 3.2 Hz, 1H), 3.90 (q, J=7.1 Hz, 2H), 4.23 (dq, J=10.8, 7.2 Hz, 1H), 4.26 (dq, J=10.8, 7.2 Hz, 1H), 4.96 (s, 1H), 5.51 (s, 1H), 7.19 (dd, J=7.6, 7.6 Hz, 2H), 7.20 (t, J=7.6 Hz, 1H), 7.27 ppm (d, J=7.6 Hz, 2H); ^{13}C NMR: δ=13.6, 13.9, 33.8, 43.7, 58.4, 61.3, 61.7, 120.8 (q, $J_{C,F}$=6 Hz), 123.5 (q, $J_{C,F}$=272 Hz), 127.2, 128.3, 128.5, 134.8 (q, $J_{C,F}$=30 Hz), 139.0, 167.4, 167.9 ppm; ^{19}F NMR: δ_F=93.5 (br s); elemental analysis: calcd (%) for $C_{18}H_{21}F_3O_4$: C 60.33, H 5.91; found: C 60.26, H 6.01.

11: Bu_3P=CHCN (107 mg, 0.44 mmol) was added to a solution of **4a** (64 mg, 0.30 mmol) and malononitrile (28 mg, 0.43 mmol) in benzene (2 mL) at room temperature, and the reaction mixture was stirred at room temperature for 24 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=20:1) to give [1-phenyl-3-(trifluoromethyl)but-3-en-1-yl]propanedinitrile (**11**; 23 mg, 29%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3070, 3035, 2908, 2260, 2192, 1456, 1348, 1169, 1120, 957 cm^{-1}; ^{1}H NMR: δ=2.91 (dd, J=15.1, 8.8 Hz, 1H), 2.98 (dd, J=15.1, 7.0 Hz, 1H), 3.49–3.54 (m, 1H), 3.99 (d, J=5.4 Hz, 1H), 5.35 (s, 1H), 5.79 (s, 1H), 7.35–7.45 ppm (m, 5H); ^{13}C NMR: δ=29.3, 32.8, 44.2, 111.2, 111.3, 123.0 (q, $J_{C,F}$=6 Hz), 123.1 (q, $J_{C,F}$=272 Hz), 127.9, 129.4, 129.4, 133.4 (q, $J_{C,F}$=30 Hz), 135.1 ppm; ^{19}F NMR: δ_F=94.1 (br s); elemental analysis: calcd (%) for $C_{14}H_{11}F_3N_2$: C 63.63, H 4.20, N 10.60; found: C 63.38, H 4.33, N 10.33.

Cyclization of **2** under aprotic conditions: A solution of **2** (2 mmol) in DMF (10 mL) was added to a suspension of NaH (60% dispersion in mineral oil; 104 mg, 2.6 mmol) in DMF (3 mL) at 0°C. The reaction mixture was stirred for 5–7 h at 80°C, then phosphate buffer (pH 7, 20 mL)

was added to quench the reaction. The organic materials were extracted with EtOAc (3×20 mL). The combined extracts were washed with water and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 3-difluoromethylene-1-(4-methylbenzenesulfonyl)indolines **12**.

12a: 3-Difluoromethylene-1-(4-methylbenzenesulfonyl)indoline: Colorless crystals, yield 84%. IR (neat): $\tilde{\nu}$=1760, 1597, 1475, 1464, 1362, 1269, 1169, 812, 752 cm^{-1}; ^1H NMR: δ=2.37 (s, 3H), 4.55 (dd, $J_{H,F}$=4.1, 4.1 Hz, 2H), 7.03 (dd, J=7.5, 7.5 Hz, 1H), 7.22–7.27 (m, 4H), 7.67–7.71 ppm (m, 3H); ^{13}C NMR: δ=21.5, 49.2 (d, $J_{C,F}$=4 Hz), 88.2 (dd, $J_{C,F}$=22, 22 Hz), 114.8, 123.3 (d, $J_{C,F}$=2 Hz), 123.4 (d, $J_{C,F}$=2 Hz), 124.2, 127.2, 129.0, 129.9, 133.5, 142.7 (d, $J_{C,F}$=5 Hz), 144.6, 149.8 ppm (dd, $J_{C,F}$=287, 287 Hz); ^{19}F NMR: δ_F=74.9 (dt, $J_{F,F}$=43 Hz, $J_{F,H}$=4 Hz, 1F), 77.8 ppm (dt, $J_{F,F}$=43 Hz, $J_{F,H}$=4 Hz, 1F); elemental analysis: calcd (%) for $C_{16}H_{13}F_2NO_2S$: C 59.80, H 4.08, N 4.36; found: C 59.96, H 4.25, N 4.18.

12b: 3-Difluoromethylene-5-methyl-1-(4-methylbenzenesulfonyl)indoline: Colorless crystals, yield 72%. IR (neat): $\tilde{\nu}$=2924, 1755, 1475, 1358, 1165, 912, 742 cm^{-1}; ^1H NMR: δ=2.28 (s, 3H), 2.36 (s, 3H), 4.52 (dd, $J_{H,F}$=4.3, 4.3 Hz, 2H), 7.04 (d, J=8.2 Hz, 1H), 7.06 (s, 1H), 7.23 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.2 Hz, 1H), 7.65 ppm (d, J=8.3 Hz, 2H); ^{13}C NMR: δ=20.9, 21.5, 49.4 (d, $J_{C,F}$=3 Hz), 88.3 (dd, $J_{C,F}$=22, 22 Hz), 114.7, 123.7 (d, $J_{C,F}$=9 Hz), 124.3 (dd, $J_{C,F}$=6, 4 Hz), 127.2, 129.7, 129.8, 133.5, 134.0, 140.5, 144.4, 149.6 ppm (dd, $J_{C,F}$=288, 288 Hz); ^{19}F NMR: δ_F=74.6 ppm (dt, $J_{F,F}$=43 Hz, $J_{F,H}$=4 Hz, 1F), 77.5 (dt, $J_{F,F}$=43 Hz, $J_{F,H}$=4 Hz, 1F); elemental analysis: calcd (%) for $C_{17}H_{15}F_2NO_2S$: C 60.88, H 4.51, N 4.18; found: C 60.73, H 4.78, N 3.92.

12c: 6-Chloro-3-difluoromethylene-1-(4-methylbenzenesulfonyl)indoline: Colorless crystals, yield 54%. IR (neat): $\tilde{\nu}$=3020, 2927, 1757, 1597, 1475, 1363, 1215, 1167, 966 cm^{-1}; ^1H NMR: δ=2.36 (s, 3H), 4.52 (dd, $J_{H,F}$=4.3, 4.3 Hz, 2H), 7.04 (d, J=8.2 Hz, 1H), 7.06 (s, 1H), 7.23 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.2 Hz, 1H), 7.65 ppm (d, J=8.3 Hz, 2H); ^{13}C NMR: δ=21.6, 49.6 (d, $J_{C,F}$=3 Hz), 87.6 (dd, $J_{C,F}$=27, 27 Hz), 114.9, 122.8 (dd, $J_{C,F}$=4, 4 Hz), 123.9 (dd, $J_{C,F}$=9, 2 Hz), 124.2, 127.2, 130.0, 133.3, 134.8, 143.6 (d, $J_{C,F}$=5 Hz), 144.9, 149.8 ppm (dd, $J_{C,F}$=289, 289 Hz); ^{19}F NMR: δ_F=75.7 (dt, $J_{F,F}$=41 Hz, $J_{F,H}$=4 Hz, 1F), 78.4 ppm (dt, $J_{F,F}$=41 Hz, $J_{F,H}$=4 Hz, 1F); HRMS (FAB): m/z calcd for $C_{16}H_{13}ClF_2NO_2S$: 356.0324 $[M+H]^+$; found: 356.0332.

Cyclization of **2** under protic conditions: DBU (1.5 mg, 0.010 mmol) was added to a solution of **2** (0.30 mmol) in DMF (3 mL) at room temperature. After the mixture was stirred at 120°C for 0.5–2 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. The organic materials were extracted with Et_2O (3×10 mL). The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 1-(4-methylbenzenesulfonyl)-3-(trifluoromethyl)indolines **13**.

13a: 1-(4-Methylbenzenesulfonyl)-3-(trifluoromethyl)indoline: Colorless crystals, yield 81%. IR (neat): $\tilde{\nu}$=2924, 1597, 1481, 1462, 1360, 1273, 1167, 1124, 1090, 814, 756, 660 cm^{-1}; ^1H NMR: δ=2.37 (s, 3H), 3.82–3.90 (m, 1H), 4.05 (dd, J=11.8, 5.6 Hz, 1H), 4.11 (dd, J=11.8, 10.3 Hz, 1H), 7.05 (dd, J=7.8, 7.8 Hz, 1H), 7.24 (d, J=8.2 Hz, 2H), 7.25 (d, J=7.8 Hz, 1H), 7.34 (dd, J=7.8, 7.8 Hz, 1H), 7.68 (d, J=8.2 Hz, 2H), 7.70 ppm (d, J=7.8 Hz, 1H); ^{13}C NMR: δ=21.5, 44.3 (q, $J_{C,F}$=30 Hz), 49.2 (q, $J_{C,F}$=3 Hz), 114.9, 124.0, 124.3, 125.3 (q, $J_{C,F}$=279 Hz), 126.1, 127.2, 129.8, 130.2, 133.5, 142.9, 144.6 ppm; ^{19}F NMR: δ_F=90.0 ppm (d, $J_{F,H}$=9 Hz); elemental analysis: calcd (%) for $C_{16}H_{14}F_3NO_2S$: C 56.30, H 4.13, N 4.10; found: C 56.42, H 4.23, N 4.09.

13b: 5-Methyl-1-(4-methylbenzenesulfonyl)-3-(trifluoromethyl)indoline: Colorless crystals, yield 69%. IR (neat): $\tilde{\nu}$=3022, 2924, 2362, 1599, 1489, 1358, 1217, 1167, 912, 771, 748 cm^{-1}; ^1H NMR: δ=2.30 (s, 3H), 2.37 (s, 3H), 3.77–3.82 (m, 1H), 4.02 (dd, J=11.5, 5.6 Hz, 1H), 4.07 (dd, J=11.5, 11.5 Hz, 1H), 7.05 (s, 1H), 7.14 (d, J=8.3 Hz, 1H), 7.23 (d, J=8.0 Hz, 2H), 7.59 (d, J=8.3 Hz, 1H), 7.66 ppm (d, J=8.0 Hz, 2H); ^{13}C NMR: δ=20.9, 21.5, 44.4 (q, $J_{C,F}$=30 Hz), 49.4 (q, $J_{C,F}$=3 Hz), 114.9, 124.5 (q, $J_{C,F}$=2 Hz), 125.4 (q, $J_{C,F}$=279 Hz), 126.5, 127.3, 129.8, 130.8, 133.4, 133.9, 140.6, 144.4 ppm; ^{19}F NMR: δ_F=90.1 ppm (d, $J_{F,H}$=9 Hz); HRMS (FAB): m/z calcd for $C_{17}H_{17}F_3NO_2S$: 356.0932 $[M+H]^+$; found: 356.0947.

13c: 6-Chloro-1-(4-methylbenzenesulfonyl)-3-(trifluoromethyl)indoline: Colorless crystals, yield 71%. IR (neat): $\tilde{\nu}$=2920, 1601, 1481, 1358, 1267, 1161, 1117, 1090, 1074 cm^{-1}; ^1H NMR: δ=2.40 (s, 3H), 3.78–3.87 (m, 1H), 4.06 (dd, J=11.1, 5.1 Hz, 1H), 4.12 (dd, J=11.1, 9.8 Hz, 1H), 7.02 (dd, J=7.7, 1.9 Hz, 1H), 7.16 (d, J=7.7 Hz, 1H), 7.29 (d, J=7.6 Hz, 2H), 7.69 (d, J=7.6 Hz, 2H), 7.70 ppm (d, J=1.9 Hz, 1H); ^{13}C NMR: δ=21.6, 43.8 (q, $J_{C,F}$=30 Hz), 49.6 (q, $J_{C,F}$=3 Hz), 115.1, 124.1, 125.0 (q, $J_{C,F}$=279 Hz), 126.9, 127.2, 130.0, 133.2, 136.3, 144.0, 144.9, 149.8 ppm; ^{19}F NMR: δ_F=89.7 ppm (d, $J_{F,H}$=9 Hz); HRMS (FAB): m/z calcd for $C_{16}H_{14}ClF_3NO_2S$: 376.0386 $[M+H]^+$; found: 376.0381.

14: $Et_3N{\cdot}3HF$ (285 mg, 1.77 mmol) and NIS (364 mg, 1.62 mmol) were added to a solution of **12a** (226 mg, 0.704 mmol) in CH_2Cl_2 (3 mL) at −10°C. After the reaction mixture was stirred at −10°C for 2.5 h, aqueous $Na_2S_2O_3$ was added to quench the reaction. The organic materials were extracted with EtOAc (3×15 mL). The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=5:1) to give 1-(4-methylbenzenesulfonyl)-3-trifluoromethyl-1*H*-indole (**14**; 214 mg, 90%) as colorless crystals. IR (neat): $\tilde{\nu}$=3124, 3064, 2978, 1595, 1448, 1387, 1176, 1147, 1030, 912 cm^{-1}; ^1H NMR: δ=2.37 (s, 3H), 7.28 (d, J=8.5 Hz, 2H), 7.33 (dd, J=7.7, 7.7 Hz, 1H), 7.40 (dd, J=7.7, 7.7 Hz, 1H), 7.66 (d, J=7.7 Hz, 1H), 7.82 (d, J=8.5 Hz, 2H), 7.94 (q, $J_{H,F}$=1.4 Hz, 1H), 7.99 ppm (d, J=7.7 Hz, 1H); ^{13}C NMR: δ=21.6, 112.9 (q, $J_{C,F}$=37 Hz), 113.6, 120.1, 122.8 (q, $J_{C,F}$=266 Hz), 124.2, 125.6, 125.9, 126.1 (q, $J_{C,F}$=6 Hz) 127.1, 130.2, 134.6, 134.7, 145.9 ppm; ^{19}F NMR: δ_F=102.3 ppm (br s); HRMS (FAB): m/z calcd for $C_{16}H_{13}F_3NO_2S$: 340.0619 $[M+H]^+$; found: 340.0617.

15: A solution of Br_2 (52 mg, 0.32 mmol) in CCl_4 (0.3 mL) was added to a solution of **12a** (75 mg, 0.23 mmol) in CCl_4 (3 mL) at room temperature. After the reaction mixture was stirred at room temperature for 2.5 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. The organic materials were extracted with EtOAc (3×20 mL). The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on florisil (hexane/EtOAc=5:1) to give 3-bromodifluoromethyl-1-(4-methylbenzenesulfonyl)-1*H*-indole (**15**; 89 mg, 96%) as colorless crystals. IR (neat): $\tilde{\nu}$=3149, 3018, 2924, 1562, 1448, 1379, 1190, 1176, 958 cm^{-1}; ^1H NMR: δ=2.38 (s, 3H), 7.29 (d, J=8.6 Hz, 2H), 7.35 (dd, J=7.6, 7.6 Hz, 1H), 7.40 (dd, J=7.6, 7.6 Hz, 1H), 7.76 (d, J=7.6 Hz, 1H), 7.83 (d, J=8.6 Hz, 2H), 7.89 (s, 1H), 7.97 ppm (d, J=7.6 Hz, 1H); ^{13}C NMR: δ=21.6, 113.5, 114.3 (t, $J_{C,F}$=297 Hz), 120.1 (t, $J_{C,F}$=28 Hz), 120.6, 124.1, 124.2 (t, $J_{C,F}$=7 Hz), 125.2 (t, $J_{C,F}$=3 Hz), 125.8, 127.1, 130.2, 134.5, 134.8, 145.8 ppm; ^{19}F NMR: δ_F=121.9 ppm (br s); elemental analysis: calcd (%) for $C_{16}H_{12}BrF_2NO_2S$: C 48.01, H 3.02, N 3.50; found: C 48.18, H 3.18, N 3.27.

16: Me_3SiCl (39 mg, 0.36 mmol), water (3.2 mg, 0.18 mmol), and **12a** (72 mg, 0.23 mmol) were added to a solution of NaI (54 mg, 0.36 mmol) in CH_3CN (2 mL) at room temperature. The reaction mixture was stirred at room temperature for 10 h. The reaction was quenched with water (10 mL), and the organic materials were extracted with EtOAc (3×15 mL). The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=10:1) to give 3-difluoromethyl-1-(4-methylbenzenesulfonyl)-1*H*-indole (**16**; 69 mg, 96%) as colorless crystals. IR (neat): $\tilde{\nu}$=3114, 3022, 2968, 1595, 1568, 1446, 1373, 1219, 1174 cm^{-1}; ^1H NMR: δ=2.36 (s, 3H), 6.86 (t, $J_{H,F}$=55.6 Hz, 1H), 7.26 (d, J=8.4 Hz, 2H), 7.30 (dd, J=7.4, 7.4 Hz, 1H), 7.38 (dd, J=7.4, 7.4 Hz, 1H), 7.68 (d, J=7.4 Hz, 1H), 7.78 (t, $J_{H,F}$=2.4 Hz, 1H), 7.80 (d, J=8.4 Hz, 2H), 7.98 ppm (d, J=7.4 Hz, 1H); ^{13}C NMR: δ=21.6, 111.8 (t, $J_{C,F}$=235 Hz), 113.7, 116.6 (t, $J_{C,F}$=26 Hz), 120.4, 123.9, 125.5 (t, $J_{C,F}$=10 Hz), 125.6, 126.6, 127.0, 130.1, 134.8, 135.0, 145.6 ppm; ^{19}F NMR: δ_F=50.6 ppm (dd, $J_{F,H}$=56, 2 Hz); elemental analysis: calcd (%) for $C_{16}H_{13}F_2NO_2S$: C 59.80, H 4.08, N 4.36; found: C 59.83, H 4.18, N 4.14.

17: KO*t*Bu (53 mg, 0.48 mmol) was added to a solution of **3** (106 mg, 0.432 mmol) in THF (3 mL) at 0°C. The reaction mixture was heated at reflux for 2 h, then phosphate buffer (pH 7, 10 mL) was added to quench the reaction. The organic materials were extracted with Et_2O (3×10 mL).

The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane) to give 3-difluoromethylene-2,3-dihydro-1-benzothiophene (**17**; 52 mg, 65%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3018, 1732, 1464, 1446, 1327, 1252, 1217, 1105, 982, 906 cm^{-1}; ^1H NMR: δ=4.04 (dd, $J_{H,F}$=4.1, 4.1 Hz, 2H), 7.06 (ddd, J=7.7, 7.7, 1.3 Hz, 1H), 7.13 (ddd, J=7.7, 7.7, 1.3 Hz, 1H), 7.16 (dd, J=7.7, 1.3 Hz, 1H), 7.38 ppm (dd, J=7.7, 1.3 Hz, 1H); ^{13}C NMR: δ=30.1 (d, $J_{C,F}$= 3 Hz), 94.2 (dd, $J_{C,F}$=26, 26 Hz), 122.1, 124.0 (dd, $J_{C,F}$=2, 2 Hz), 124.6, 128.3 (dd, $J_{C,F}$=3, 3 Hz), 131.5 (dd, $J_{C,F}$=3, 3 Hz), 142.7 (d, $J_{C,F}$=5 Hz), 152.0 ppm (dd, $J_{C,F}$=288, 288 Hz); ^{19}F NMR: δ_F=75.6 ppm (dt, $J_{F,F}$= 40 Hz, $J_{F,H}$=5 Hz, 1F), 78.4 (dt, $J_{F,F}$=40 Hz, $J_{F,H}$=5 Hz, 1F); elemental analysis: calcd (%) for $C_9H_6F_2S$: C 58.68, H 3.28; found: C 58.46, H 3.50.

18: K_2CO_3 (52 mg, 0.378 mmol) was added to a solution of **3** (97 mg, 0.39 mmol) in MeOH (3 mL) at room temperature. After the mixture was heated at reflux for 1 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. The organic materials were extracted with Et_2O (3×10 mL). The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane) to give 3-trifluoromethyl-2,3-dihydro-1-benzothiophene (**18**; 49 mg, 61%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3018, 1587, 1466, 1446, 1350, 1265, 1215, 1159, 1107 cm^{-1}; ^1H NMR: δ=3.49 (dd, J=12.0, 6.6 Hz, 1H), 3.59 (dd, J=12.0, 9.0 Hz, 1H), 4.12–4.20 (m, 1H), 7.08 (dd, J=7.6, 7.6 Hz, 1H), 7.21–7.25 (m, 2H), 7.34 ppm (d, J=7.6 Hz, 1H); ^{13}C NMR: δ=31.4 (q, $J_{C,F}$=3 Hz), 51.5 (q, $J_{C,F}$=28 Hz), 122.5, 124.6, 126.0, 126.2 (q, $J_{C,F}$=280 Hz), 129.5, 132.6, 142.7 ppm; ^{19}F NMR: δ_F=91.2 ppm (d, $J_{F,H}$=9 Hz); HRMS (FAB): calcd for $C_9H_8F_3S$: 205.0299 $[M+H]^+$; found: 205.0295.

Cyclization of **5** under aprotic conditions: NaH (60% dispersion in mineral oil; 52 mg, 1.3 mmol) was added to a solution of **5** (1.0 mmol) in DMF (10 mL) at 0°C. The reaction mixture was stirred at 0°C for 15 min and then at 120°C for 0.5–4 h. Phosphate buffer (pH 7, 20 mL) was added to quench the reaction, and the organic materials were extracted with EtOAc (3×10 mL). The combined extracts were washed with water and brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 3-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidines **19**.

19a: 4-Difluoromethylene-1-(4-methylbenzenesulfonyl)-2-phenylpyrrolidine: Colorless crystals, yield 91%. IR (neat): $\tilde{\nu}$=3064, 3032, 2927, 2866, 1782, 1350, 1273, 1219, 1161, 1093, 1058 cm^{-1}; ^1H NMR: δ=2.42 (s, 3H), 2.54 (br d, J=15.0 Hz, 1H), 2.66–2.74 (m, 1H), 4.13 (dm, J=14.5 Hz, 1H), 4.19 (dm, J=14.5 Hz, 1H), 4.95 (ddd, J=8.2, 3.1, 1.5 Hz, 1H), 7.22–7.31 (m, 7H), 7.57 ppm (d, J=8.3 Hz, 2H); ^{13}C NMR: δ=21.5, 33.9, 47.0 (d, $J_{C,F}$=4 Hz), 63.2, 85.4 (dd, $J_{C,F}$=25, 22 Hz), 126.2, 127.4, 127.7, 128.5, 129.6, 134.8, 140.8, 143.7, 149.8 ppm (dd, $J_{C,F}$=283, 283 Hz); ^{19}F NMR: δ_F=72.0 (dm, $J_{F,F}$=54 Hz, 1F), 74.5 ppm (d, $J_{F,F}$=54 Hz, 1F); elemental analysis: calcd (%) for $C_{18}H_{17}F_2NO_2S$: C 61.88, H 4.90, N 4.01; found: C 61.81, H 4.95, N 3.74.

19b: 2-(4-Bromophenyl)-4-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine: Colorless crystals, yield 79%. M.p.: 76–77°C; IR (neat): $\tilde{\nu}$=3026, 1782, 1489, 1350, 1275, 1219, 1163 cm^{-1}; ^1H NMR: δ=2.43 (s, 3H), 2.49 (br d, J=15.0 Hz, 1H), 2.67–2.74 (m, 1H), 4.13 (br d, J= 15.0 Hz, 1H), 4.16 (br d, J=15.0 Hz, 1H), 4.86 (dm, J=7.9 Hz, 1H), 7.11 (d, J=8.4 Hz, 2H), 7.26 (d, J=7.8 Hz, 2H), 7.40 (d, J=8.4 Hz, 2H), 7.57 ppm (d, J=7.8 Hz, 2H); ^{13}C NMR: δ=21.5, 33.9, 47.0 (d, $J_{C,F}$= 4 Hz), 62.6, 85.1 (dd, $J_{C,F}$=26, 24 Hz), 121.6, 127.3, 128.0, 129.7, 131.6, 134.6, 139.9, 143.9, 149.9 ppm (dd, $J_{C,F}$=285, 285 Hz); ^{19}F NMR: δ_F=72.4 (ddd, $J_{F,F}$=53 Hz, $J_{F,H}$=3, 3 Hz, 1F), 74.9 ppm (d, $J_{F,F}$=53 Hz, 1F); elemental analysis: calcd (%) for $C_{18}H_{16}BrF_2NO_2S$: C 50.48, H 3.77; N 3.27; found: C 50.49, H 3.93, N 3.15.

19c: 4-Difluoromethylene-2-(furan-2-yl)-1-(4-methylbenzenesulfonyl)pyrrolidine: Colorless crystals, yield 74%. M.p.: 63–64°C; IR (neat): $\tilde{\nu}$= 3120, 3028, 2924, 2868, 1784, 1599, 1350, 1275, 1163, 1093 cm^{-1}; ^1H NMR: δ=2.40 (s, 3H), 2.64–2.68 (m, 2H), 3.99 (dm, J=13.4 Hz, 1H), 4.18 (dm, J=13.4 Hz, 1H), 5.09 (ddd, J=6.3, 4.1, 1.9 Hz, 1H), 6.24 (br d, J= 3.3 Hz, 1H), 6.25 (dd, J=3.3, 1.9 Hz, 1H), 7.18–7.19 (m, 1H), 7.23 (d, J= 8.3 Hz, 2H), 7.54 ppm (d, J=8.3 Hz, 2H); ^{13}C NMR: δ=21.5, 30.9 (dd, $J_{C,F}$=2, 2 Hz), 46.2 (dd, $J_{C,F}$=4, 1 Hz), 55.6, 85.6 (dd, $J_{C,F}$=26, 23 Hz), 107.6, 110.1, 127.2, 129.6, 134.8, 142.3, 143.5, 149.9 (dd, $J_{C,F}$=282, 282 Hz), 152.6 ppm; ^{19}F NMR: δ_F=71.8 ppm (ddd, $J_{F,F}$=55, $J_{F,H}$=3, 3 Hz, 1F), 74.4 (d, $J_{F,F}$=55 Hz, 1F); elemental analysis: calcd (%) for $C_{16}H_{15}F_2NO_3S$: C 56.63, H 4.46, N 4.13; found: C 56.45, H 4.45, N 3.86.

19d: 4-Difluoromethylene-2-hexyl-1-(4-methylbenzenesulfonyl)pyrrolidine: Colorless liquid, yield 82%. IR (neat): $\tilde{\nu}$=3026, 2956, 2927, 2858, 1782, 1348, 1217, 1163, 912 cm^{-1}; ^1H NMR: δ=0.89 (t, J=6.5 Hz, 3H), 1.21–1.46 (m, 10H), 2.06–2.16 (m, 2H), 2.43 (s, 3H), 3.83–3.90 (m, 1H), 3.96 (dm, J=14.7 Hz, 1H), 4.03 (dm, J=14.7 Hz, 1H), 7.31 (d, J=8.4 Hz, 2H), 7.70 ppm (d, J=8.4 Hz, 2H); ^{13}C NMR: δ=14.1, 21.5, 22.6, 25.7, 29.0, 30.2, 31.7, 35.4, 46.2 (d, $J_{C,F}$=3 Hz), 60.7, 85.9 (dd, $J_{C,F}$=25, 22 Hz), 127.3, 129.8, 135.1, 143.7, 149.9 ppm (dd, $J_{C,F}$=282, 282 Hz); ^{19}F NMR: δ_F=71.4 (ddd, $J_{F,F}$=56, $J_{F,H}$=3, 3 Hz, 1F), 74.2 ppm (d, $J_{F,F}$=56 Hz, 1F); elemental analysis: calcd (%) for $C_{18}H_{25}F_2NO_2S$: C 60.48, H 7.05, N 3.92; found: C 60.50, H 7.10, N 3.63.

19e: 3-Difluoromethylene-1-(4-methylbenzenesulfonyl)-4-phenylpyrrolidine: Colorless crystals, yield 65%. IR (neat): $\tilde{\nu}$=3030, 2924, 1774, 1597, 1495, 1350, 1271, 1163, 1093 cm^{-1}; ^1H NMR: δ=2.45 (s, 3H), 3.36 (ddd, J=9.5, 4.7, 1.4 Hz, 1H), 3.61 (dd, J=9.5, 7.7 Hz, 1H), 3,94–3.98 (m, 2H), 4.02 (dddd, J=13.2, 3.7, 1.4 Hz, $J_{H,F}$=3.7 Hz, 1H), 7.15 (d, J=6.8 Hz, 2H), 7.22–7.29 (m, 3H), 7.34 (d, J=8.1 Hz, 2H), 7.71 ppm (d, J=8.1 Hz, 2H); ^{13}C NMR: δ=21.5, 43.2, 47.2 (d, $J_{C,F}$=4 Hz), 56.2, 90.3 (dd, $J_{C,F}$= 23, 21 Hz), 126.9, 127.3, 127.9, 128.8, 129.8, 132.0, 139.9, 144.1, 150.8 ppm (dd, $J_{C,F}$=288, 288 Hz); ^{19}F NMR: δ_F=73.96 (ddd, $J_{F,F}$=48 Hz, $J_{F,H}$=3, 3 Hz, 1F), 76.1 ppm (d, $J_{F,F}$=48 Hz, 1F); elemental analysis: calcd (%) for $C_{18}H_{17}F_2NO_2S$: C 61.88, H 4.90, N 4.01; found: C 62.05, H 5.01, N 3.89.

19f: 3-Difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine: Colorless crystals, yield 83%. IR (neat): $\tilde{\nu}$=2924, 2864, 1782, 1348, 1269, 1161, 1093, 1072, 1039, 812 cm^{-1}; ^1H NMR: δ=2.45 (s, 3H), 2.44–2.48 (m, 2H), 3.30 (ddd, J=7.0, 7.0, 1.3 Hz, 2H), 3.79–3.82 (m, 2H), 7.36 (d, J= 8.1 Hz, 2H), 7.72 ppm (d, J=8.1 Hz, 2H); ^{13}C NMR: δ=21.5, 24.6, 46.5 (d, $J_{C,F}$=4 Hz), 48.0, 85.8 (dd, $J_{C,F}$=27, 22 Hz), 127.8, 129.8, 132.3, 144.0, 149.9 ppm (dd, $J_{C,F}$=285, 285 Hz); ^{19}F NMR: δ_F=71.6 (dm, $J_{F,F}$=55 Hz, 1F), 74.0 ppm (d, $J_{F,F}$=55 Hz, 1F); elemental analysis: calcd (%) for $C_{12}H_{13}F_2NO_2S$: C 52.74, H 4.79, N 5.13; found: C 52.83, H 4.88, N 4.87.

Cyclization of **5** under protic conditions: KOH powder (84 mg, 1.5 mmol) was added to a solution of **5** (0.3 mmol) in ethane-1,2-diol (3 mL) at room temperature. After the reaction mixture was stirred at 130°C for 10–20 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. The organic materials were extracted with EtOAc (3×20 mL), and the combined extracts were washed with water and brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 3-trifluoromethyl-1-(4-methylbenzenesulfonyl)pyrrolidines **20** as a mixture of *trans* and *cis* isomers.

20a: 1-(4-Methylbenzenesulfonyl)-2-phenyl-4-(trifluoromethyl)pyrrolidine: Colorless crystals, yield 85% (*trans*/*cis*=92:8). M.p.: 90–91°C; IR (neat): $\tilde{\nu}$=3030, 2983, 2881, 1452, 1400, 1348, 1157, 1120 cm^{-1}; ^1H NMR: *trans*: δ=2.05 (dd, J=8.6, 5.4 Hz, 2H), 2.44 (s, 3H), 2.88–3.06 (m, 1H), 3.50 (dd, J=10.5, 8.8 Hz, 1H), 3.85 (dd, J=10.5, 8.3 Hz, 1H), 4.94 (dd, J=5.4, 5.4 Hz, 1H), 7.23–7.48 (m, 7H), 7.67 ppm (d, J=8.2 Hz, 2H); *cis*: δ=2.42 (s, 3H), 2.48–2.53 (m, 2H), 2.58–3.68 (m, 1H), 3.58 (dd, J=11.5, 9.8 Hz, 1H), 3.96 (dd, J=11.5, 8.1 Hz, 1H), 4.71 (dd, J=9.3, 7.3 Hz, 1H), 7.23–7.48 (m, 7H), 7.54 ppm (d, J=8.2 Hz, 2H); ^{13}C NMR: *trans*: δ= 21.6, 34.8, 40.9 (q, $J_{C,F}$=29 Hz), 47.7, 62.6, 125.9, 126.1 (q, $J_{C,F}$=275 Hz), 127.5, 127.7, 128.6, 129.7, 134.2, 141.1, 143.9 ppm; ^{19}F NMR: *trans*: δ_F= 91.1 (d, $J_{F,H}$=8 Hz,); *cis*: δ_F=91.3 ppm (d, $J_{F,H}$=8 Hz); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79; found: C 58.43, H 5.00, N 3.59.

20b: 2-(4-Bromophenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine: Separation of *cis* and *trans* isomers was achieved by column chromatography (hexane/EtOAc=5:1) to give *trans*-**20b** (70%) and *cis*-**20b** (6%) as colorless crystals. *trans*-**20b**: M.p.: 119–120°C; IR (neat): $\tilde{\nu}$=3030, 2910, 1489, 1400, 1350, 1163, 1122, 914 cm^{-1}; ^1H NMR: δ=2.01 (ddd, J=12.9, 7.2, 3.3 Hz, 1H), 2.08 (ddd, J=12.9, 9.9, 8.2 Hz, 1H), 2.45 (s, 3H), 2.86–2.99 (m, 1H), 3.47 (dd, J=10.6, 8.6 Hz, 1H), 3.85 (dd, J=10.6, 8.2 Hz, 1H), 4.83 (dd, J=8.2, 3.3 Hz, 1H), 7.17 (d, J=

8.5 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 7.45 (d, J=8.5 Hz, 2H), 7.65 ppm (d, J=8.1 Hz, 2H); ^{13}C NMR: δ=21.6, 34.8 (q, $J_{C,F}$=2 Hz), 40.8 (q, $J_{C,F}$=29 Hz), 47.8 (q, $J_{C,F}$=3 Hz), 62.1, 121.6, 126.0 (q, $J_{C,F}$=276 Hz), 127.5, 127.7, 129.8, 131.7, 134.0, 140.2, 144.1 ppm; ^{19}F NMR: δ_F=91.1 ppm (d, $J_{F,H}$=8 Hz); elemental analysis: calcd (%) for $C_{18}H_{17}BrF_3NO_2S$: C 48.23, H 3.82, N 3.12; found: C 48.04, H 3.84, N 2.87. *cis*-**20b**: IR (neat): $\tilde{\nu}$= 2960, 2910, 1489, 1404, 1360, 1271, 1161, 912 cm^{-1}; ^{1}H NMR: δ=1.99 (ddd, J=13.3, 11.0, 9.4 Hz, 1H), 2.44 (s, 3H), 2.52 (ddd, J=13.3, 7.5, 7.5 Hz, 1H), 2.58–2.71 (m, 1H), 3.58 (dd, J=11.5, 9.7 Hz, 1H), 3.94 (dd, J=11.5, 8.2 Hz, 1H), 4.65 (dd, J=9.4, 7.5 Hz, 1H), 7.14 (d, J=8.4 Hz, 2H), 7.27 (d, J=8.0 Hz, 2H), 7.40 (d, J=8.4 Hz, 2H), 7.54 ppm (d, J= 8.0 Hz, 2H); ^{13}C NMR: δ=21.6, 36.2, 41.6 (q, $J_{C,F}$=30 Hz), 48.5 (q, $J_{C,F}$= 3 Hz), 63.0, 121.7, 125.6 (q, $J_{C,F}$=276 Hz), 127.4, 128.2, 129.8, 131.6, 134.6, 139.7, 144.1 ppm; ^{19}F NMR: δ_F=91.2 ppm (d, $J_{F,H}$=8 Hz); elemental analysis: calcd (%) for $C_{18}H_{17}BrF_3NO_2S$: C 48.23, H 3.82, N 3.12; found: C 48.30, H 3.90, N 2.90.

20c: 2-(Furan-2-yl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine: Colorless liquid, yield 69% (*trans*/*cis*=83:17). IR (neat): $\tilde{\nu}$= 2958, 2925, 1599, 1348, 1271, 1159, 1120, 1011, 912 cm^{-1}; ^{1}H NMR: *trans*: δ=2.10 (ddd, J=12.6, 10.8, 8.2 Hz, 1H), 2.20 (ddd, J=12.6, 7.2, 1.9 Hz, 1H), 2.41 (s, 3H), 3.20–3.33 (m, 1H), 3.52 (dd, J=10.0, 8.4 Hz, 1H), 3.67 (dd, J=10.0, 8.8 Hz, 1H), 5.05 (br d, J=8.2 Hz, 1H), 6.28 (dd, J=3.2, 1.9 Hz, 1H), 6.30 (dm, J=3.2 Hz, 1H), 7.20 (dd, J=1.9, 0.9 Hz, 1H), 7.26 (d, J=8.3 Hz, 2H), 7.53 ppm (d, J=8.3 Hz, 2H); *cis*: δ=2.26–2.33 (m, 1H), 2.41 (s, 3H), 2.43–2.48 (m, 1H), 2.72–2.82 (m, 1H), 3.45 (dd, J= 10.5, 10.5 Hz, 1H), 3.94 (dd, J=10.5, 7.9 Hz, 1H), 4.96 (dd, J=8.0, 8.0 Hz, 1H), 6.27 (dd, J=3.2, 1.8 Hz, 1H), 6.31 (dm, J=3.2 Hz, 1H), 7.20–7.22 (m, 1H), 7.26 (d, J=8.3 Hz, 2H), 7.50 ppm (d, J=8.3 Hz, 2H); ^{13}C NMR: *trans*: δ=21.5, 31.5 (q, $J_{C,F}$=2 Hz), 41.7 (q, $J_{C,F}$=29 Hz), 46.7 (q, $J_{C,F}$=3 Hz), 56.2, 108.1, 110.2, 126.2 (q, $J_{C,F}$=275 Hz), 127.2, 129.6, 134.6, 142.2, 143.6, 152.9 ppm; ^{19}F NMR: *trans*: δ_F=90.9 ppm (d, $J_{F,H}$= 8 Hz); *cis*: δ_F=91.5 ppm (d, $J_{F,H}$=8 Hz); elemental analysis: calcd (%) for $C_{16}H_{16}F_3NO_3S$: C 53.48, H 4.49, N 3.90; found: C 53.52, H 4.65, N 3.72.

20d: 2-Hexyl-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine: Ethane-1,2-diol/THF=10:1 was used as solvent. Colorless liquid, yield 67% (*trans*/*cis*=77:23). IR (neat): $\tilde{\nu}$=2956, 2929, 2858, 1456, 1402, 1348, 1273, 1163, 914 cm^{-1}; ^{1}H NMR: *trans*: δ=0.89 (t, J=7.0 Hz, 3H), 1.25–1.53 (m, 9H), 1.60–1.68 (m, 1H), 1.75–1.83 (m, 2H), 2.44 (s, 3H), 2.89–3.02 (m, 1H), 3.24 (dd, J=10.5, 9.1 Hz, 1H), 3.65 (dd, J=10.5, 8.3 Hz, 1H), 3.70–3.78 (m, 1H), 7.33 (d, J=8.0 Hz, 2H), 7.71 ppm (d, J= 8.0 Hz, 2H); *cis*: δ=0.89 (t, J=7.0 Hz, 3H), 1.25–1.53 (m, 9H), 1.60–1.68 (m, 1H), 1.87–1.94 (m, 1H), 2.12 (ddd, J=12.8, 8.1, 8.1 Hz, 1H), 2.21–2.33 (m, 1H), 2.45 (s, 3H), 3.31 (dd, J=10.5, 8.8 Hz, 1H), 3.70–3.78 (m, 2H), 7.34 (d, J=8.0 Hz, 2H), 7.72 ppm (d, J=8.0 Hz, 2H); ^{13}C NMR: *trans*: δ=14.0, 21.4, 22.5, 25.8, 29.0, 30.0, 31.7, 35.8, 41.1 (q, $J_{C,F}$=29 Hz), 47.2 (q, $J_{C,F}$=2 Hz), 60.1, 126.2 (q, $J_{C,F}$=276 Hz), 127.4, 129.7, 134.0, 143.7 ppm; ^{19}F NMR: *trans*: δ_F=90.9 ppm (d, $J_{F,H}$=8 Hz); *cis*: δ_F= 91.5 ppm (d, $J_{F,H}$=8 Hz); elemental analysis: calcd (%) for $C_{18}H_{26}F_3NO_2S$: C 57.27, H 6.94, N 3.71; found: C 57.32, H 6.99, N 3.53.

20e: 1-(4-Methylbenzenesulfonyl)-3-phenyl-4-(trifluoromethyl)pyrrolidine: Yield 57% (*trans*/*cis*=72:28). *trans*-**20e**: Colorless crystals; m.p.: 84–86°C; IR (neat): $\tilde{\nu}$=3032, 2956, 1599, 1348, 1265, 1163, 1113, 1028, 663 cm^{-1}; ^{1}H NMR: δ=2.48 (s, 3H), 2.96 (dddq, J=8.4, 8.4, 8.4 Hz, $J_{H,F}$= 8.4 Hz, 1H), 3.33–3.43 (m, 3H), 3.64 (dd, J=9.3, 8.4 Hz, 1H), 3.70 (dd, J=10.7, 8.8 Hz, 1H), 7.16 (d, J=7.7 Hz, 2H), 7.24–7.33 (m, 3H), 7.38 (d, J=7.9 Hz, 2H), 7.74 ppm (d, J=7.9 Hz, 2H); ^{13}C NMR: δ=21.6, 44.3, 47.4 (q, $J_{C,F}$=3 Hz), 49.5 (q, $J_{C,F}$=28 Hz), 54.8, 126.1 (q, $J_{C,F}$=279 Hz), 127.0, 127.7, 127.8, 129.0, 129.9, 132.5, 139.2, 144.2 ppm; ^{19}F NMR: δ_F= 91.4 ppm (d, $J_{F,H}$=9 Hz); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79, found: C 58.82, H 5.19, N 3.73. *cis*-**20e**: Colorless crystals; m.p. 96–97°C; IR (neat): $\tilde{\nu}$=3032, 2960, 1599, 1400, 1348, 1281, 1163, 1120, 1049 cm^{-1}; ^{1}H NMR: δ=2.48 (s, 3H), 3.00 (dddq, J=8.5, 8.5, 8.5 Hz, $J_{H,F}$=8.5 Hz, 1H), 3.56–3.75 (m, 5H), 7.08–7.10 (m, 2H), 7.24–7.26 (m, 3H), 7.40 (d, J=8.0 Hz, 2H), 7.79 ppm (d, J=8.0 Hz, 2H); ^{13}C NMR: δ=21.6, 43.9, 46.4 (q, $J_{C,F}$=3 Hz), 46.9 (q, $J_{C,F}$=27 Hz), 52.5, 125.3 (q, $J_{C,F}$=280 Hz), 127.5, 127.7, 128.1, 128.5, 130.0, 133.5, 136.2, 144.1 ppm; ^{19}F NMR: δ_F=96.5 ppm (d, $J_{H,F}$=9 Hz); elemental analysis: calcd (%) for $C_{18}H_{18}F_3NO_2S$: C 58.53, H 4.91, N 3.79; found: C 58.70, H 5.04, N 3.73.

Cyclization of **7**: KO*t*Bu (20.4 mg, 0.18 mmol) was added to a solution of **7** (0.14 mmol) in THF (2 mL) at room temperature. The reaction mixture was heated at reflux for 2.5–6 h, then phosphate buffer (pH 7, 10 mL) was added to quench the reaction. The organic materials were extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography (hexane/EtOAc=10:1) to give 3-difluoromethylene-2,3,4,5-tetrahydrofurans **21**.

21a: 4-Difluoromethylene-3,3-dimethyl-2-phenyl-2,3,4,5-tetrahydrofuran: Colorless liquid, yield 80%. IR (neat): $\tilde{\nu}$=3032, 2970, 2931, 2850, 1766, 1466, 1271, 1226, 1030, 723, 700 cm^{-1}; ^{1}H NMR: δ=0.74 (s, 3H), 1.31 (s, 3H), 4.42 (ddd, J=12.3 Hz, $J_{H,F}$=4.7, 4.1 Hz, 1H), 4.52 (s, 1H), 4.67 (ddd, J=12.3 Hz, $J_{H,F}$=2.8, 2.8 Hz, 1H), 7.30–7.36 ppm (m, 5H); ^{13}C NMR: δ=21.9, 22.6, 43.7 (dd, $J_{C,F}$=4, 3 Hz), 65.0 (d, $J_{C,F}$=4 Hz), 90.6, 97.9 (dd, $J_{C,F}$=18, 18 Hz), 126.7, 127.8, 127.9, 136.8, 149.2 ppm (dd, $J_{C,F}$=287, 284 Hz); ^{19}F NMR: δ_F=67.6 (d, $J_{F,F}$=66 Hz, 1F), 75.4 ppm (d, $J_{F,F}$=66 Hz, 1F); HRMS (FAB): m/z calcd for $C_{13}H_{15}F_2O$: 225.1091 $[M+H]^+$; found: 225.1107.

21b: 4-Difluoromethylene-1-phenyl-2-oxaspiro[4.4]nonane: Colorless liquid, yield 70%. IR (neat): $\tilde{\nu}$=3032, 2956, 2870, 1765, 1454, 1265, 1217, 1051, 985, 729, 702 cm^{-1}; ^{1}H NMR: δ=0.76–0.81 (m, 1H), 1.40–1.50 (m, 3H), 1.59–1.67 (m, 2H), 1.86 (ddd, J=13.6, 8.3, 8.3 Hz, 1H), 2.09 (ddd, J=13.6, 8.8, 6.7 Hz, 1H), 4.46 (ddd, J=12.1 Hz, $J_{H,F}$=4.1, 3.5 Hz, 1H), 4.65 (ddd, J=12.1 Hz, $J_{H,F}$=2.9, 2.9 Hz, 1H), 4.66 (s, 1H), 7.29–7.36 ppm (m, 5H); ^{13}C NMR: δ=24.9, 25.6, 34.2 (d, $J_{C,F}$=2 Hz), 34.3, 54.3 (d, $J_{C,F}$=4 Hz), 65.6 (d, $J_{C,F}$=4 Hz), 90.1, 99.1 (dd, $J_{C,F}$=19, 17 Hz), 127.3, 127.9, 127.9, 137.4, 148.9 ppm (dd, $J_{C,F}$=286, 283 Hz); ^{19}F NMR: δ_F=68.2 (d, $J_{F,F}$=65 Hz, 1F), 74.7 ppm (dd, $J_{F,F}$=65 Hz, $J_{F,H}$=4 Hz, 1F); HRMS (FAB): m/z calcd for $C_{15}H_{17}F_2O$ 251.1247 $[M+H]^+$; found: 251.1271.

21c: 4-Difluoromethylene-3,3-dimethyl-2-(2-phenylethyl)-2,3,4,5-tetrahydrofuran: Colorless liquid, yield 87%. IR (neat): $\tilde{\nu}$=3028, 2956, 2927, 2854, 1768, 1496, 1456, 1277, 1227, 1027, 698 cm^{-1}; ^{1}H NMR: δ=1.02 (s, 3H), 1.17 (s, 3H), 1.63–1.81 (m, 2H), 2.63 (ddd, J=13.6, 10.0, 6.8 Hz, 1H), 2.91 (ddd, J=13.6, 10.4, 5.2 Hz, 1H), 3.42 (dd, J=10.0, 2.4 Hz, 1H), 4.25 (ddd, J=12.4 Hz, $J_{H,F}$=4.4, 4.0 Hz, 1H), 4.47 (ddd, J=12.4 Hz, $J_{H,F}$=2.8, 2.8 Hz, 1H), 7.17–7.31 ppm (m, 5H); ^{13}C NMR: δ=20.8, 22.7 (d, $J_{C,F}$=4 Hz), 30.8, 33.3, 42.5 (d, $J_{C,F}$=3 Hz), 64.9 (d, $J_{C,F}$=4 Hz), 88.3, 98.3 (dd, $J_{C,F}$=18, 18 Hz), 125.9, 128.4, 128.4, 142.0, 149.1 ppm (dd, $J_{C,F}$= 286, 283 Hz); ^{19}F NMR: δ_F=67.3 (d, $J_{F,F}$=66 Hz, 1F), 75.1 ppm (d, $J_{F,F}$= 66 Hz, 1F); HRMS (FAB): m/z calcd for $C_{15}H_{19}F_2O$ 253.1404 $[M+H]^+$; found: 253.1384.

22a: NaOMe (19 mg, 0.36 mmol) was added to a solution of **8a** (80 mg, 0.29 mmol) in DMF (3 mL) at 0°C. After the reaction mixture was stirred at 100°C for 10 h, phosphate buffer (pH 7, 20 mL) was added to quench the reaction. The organic materials were extracted with EtOAc (3×20 mL). The combined extracts were washed with water and brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=5:1) to give 4-difluoromethylene-2-phenyl-2,3,4,5-tetrahydrothiophene (**22a**; 51 mg, 82%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3064, 3030, 2912, 1765, 1267, 1219, 1049 cm^{-1}; ^{1}H NMR: δ=2.72–2.78 (m, 1H), 3.06 (dd, J=13.7, 5.7 Hz, 1H), 3.63 (d, J=13.6 Hz, 1H), 3.69 (d, J= 13.6 Hz, 1H), 4.52 (dd, J=8.4, 5.7 Hz, 1H), 7.26 (t, J=7.3 Hz, 1H), 7.33 (dd, J=7.3, 7.3 Hz, 2H), 7.38 ppm (d, J=7.3 Hz, 2H); ^{13}C NMR: δ=30.2 (d, $J_{C,F}$=2 Hz), 38.5 (d, $J_{C,F}$=2 Hz), 51.8, 90.0 (dd, $J_{C,F}$=22, 22 Hz), 127.3, 127.6, 128.6, 140.6, 150.3 ppm (dd, $J_{C,F}$=284, 284 Hz); ^{19}F NMR: δ_F=71.7 (ddd, $J_{F,F}$=54 Hz, $J_{F,H}$=3, 3 Hz, 1F), 72.6 ppm (dd, $J_{F,F}$=54 Hz, $J_{F,H}$= 4 Hz, 1F); HRMS (FAB): m/z calcd for $C_{11}H_{11}F_2S$: 213.0550 $[M+H]^+$; found: 213.0564.

22b: 4-Difluoromethylene-2-hexyl-2,3,4,5-tetrahydrothiophene (**22b**) was prepared by the method described for **22a** by using **8b** (80 mg, 0.28 mmol), NaOMe (20 mg, 0.37 mmol) in DMF (3 mL) at 100°C for 15 h. Purification by column chromatography (hexane/EtOAc=50:1) gave **22b** (47 mg, 75%) as a colorless liquid. IR (neat): $\tilde{\nu}$=2956, 2926, 2854, 1765, 1267, 1201, 1047, 912 cm^{-1}; ^{1}H NMR: δ=0.88 (t, J=7.1 Hz,

3H), 1.22–1.41 (m, 8H), 1.50–1.59 (m, 1H), 1.60–1.68 (m, 1H), 2.27–2.34 (m, 1H), 2.78 (dm, J=14.3 Hz, 1H), 3.31–3.37 (m, 1H), 3.45 (dm, J=12.9 Hz, 1H), 3.48 ppm (dm, J=12.9 Hz, 1H); ^{13}C NMR: δ=14.0, 22.6, 28.6, 28.8 (d, $J_{C,F}$=1 Hz), 29.1, 31.7, 36.1, 36.4 (dd, $J_{C,F}$=2, 2 Hz), 48.8, 89.8 (dd, $J_{C,F}$=21, 21 Hz), 150.4 ppm (dd, $J_{C,F}$=283, 283 Hz); ^{19}F NMR: δ_F=70.6 (dm, $J_{F,F}$=56 Hz, 1F), 72.2 ppm (d, $J_{F,F}$=56 Hz, 1F); elemental analysis: calcd (%) for $C_{11}H_{18}F_2S$: C 59.97, H 8.23; found: C 59.84, H 8.21.

23a: K_2CO_3 (47 mg, 0.34 mmol) was added to a solution of **8a** (87 mg, 0.32 mmol) in MeOH (3 mL) at room temperature. After the reaction mixture was heated at reflux for 2 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. The organic materials were extracted with EtOAc (3×20 mL). The combined extracts were washed with water and brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=20:1) to give 2-phenyl-4-trifluoromethyl-2,3,4,5-tetrahydrothiophene (**23a**; >98:2 mixture, 66 mg, 90%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3064, 3020, 2945, 2875, 1381, 1267, 1215, 1151, 1107 cm^{-1}; ^{1}H NMR: δ=2.35 (ddd, J=13.3, 6.2, 6.2 Hz, 1H), 2.53 (ddd, J=13.3, 8.0, 7.1 Hz, 1H), 3.05–3.15 (m, 2H), 3.23–3.30 (m, 1H), 4.64 (dd, J=7.1, 6.2 Hz, 1H), 7.26 (t, J=7.4 Hz, 1H), 7.34 (dd, J=7.4, 7.4 Hz, 2H), 7.41 ppm (d, J=7.4 Hz, 2H); ^{13}C NMR: δ=31.2 (q, $J_{C,F}$=2 Hz), 39.4 (q, $J_{C,F}$=1 Hz), 46.0 (q, $J_{C,F}$=27 Hz), 50.8, 127.0 (q, $J_{C,F}$=277 Hz), 127.4, 127.4, 128.6, 141.6 ppm; ^{19}F NMR: δ_F=91.8 ppm (d, $J_{F,H}$=8 Hz); HRMS (FAB): m/z calcd for $C_{11}H_{12}F_3S$ 233.0612 $[M+H]^+$; found: 233.0625.

23b: 2-Hexyl-4-trifluoromethyl-2,3,4,5-tetrahydrothiophene (**23b**) was prepared by the method described for **23a** by using **8b** (81 mg, 0.29 mmol) and K_2CO_3 (43 mg, 0.31 mmol) in MeOH (3 mL) for 1 h. Purification by column chromatography (hexane/EtOAc=50:1) gave **23b** (92:8 mixture, 56 mg, 82%) as a colorless liquid. IR (neat): $\tilde{\nu}$=2956, 2927, 2873, 2856, 1380, 1269, 1161, 1111 cm^{-1}; ^{1}H NMR: δ=0.88 (t, J=7.1 Hz, 3H), 1.23–1.65 (m, 10H), 1.98–2.03 (m, 1H), 2.19 (ddd, J=12.9, 8.4, 7.0 Hz, 1H), 2.91–3.05 (m, 3H), 3.37–3.43 ppm (m, 1H); ^{13}C NMR: δ=14.0, 22.5, 28.4, 29.0, 30.2 (q, $J_{C,F}$=3 Hz), 31.7, 36.5 (q, $J_{C,F}$=2 Hz), 37.7, 46.0 (q, $J_{C,F}$=27 Hz), 47.4, 127.1 ppm (q, $J_{C,F}$=277 Hz); ^{19}F NMR: δ_F=91.8 (d, $J_{F,H}$=9 Hz); HRMS (FAB): m/z calcd for $C_{11}H_{19}F_3NaS$ 263.1057 $[M+Na]^+$; found: 263.1046.

24: KH (30% dispersion in mineral oil; 50 mg, 0.37 mmol) was added to a solution of **10** (83 mg, 0.23 mmol) in DMF (3 mL) at 0°C. After being stirred at 0°C for 1 h, the reaction mixture was heated at 110°C for 3 h. Phosphate buffer (pH 7, 20 mL) was added to quench the reaction, and the organic materials were extracted with EtOAc (3×20 mL). The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=5:1) to give diethyl 4-difluoromethylene-2-phenylcyclopentane-1,1-dicarboxylate (**24**; 60 mg, 77%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3032, 2983, 1772, 1730, 1456, 1367, 1269, 1221, 1036 cm^{-1}; ^{1}H NMR: δ=0.94 (t, J=7.1 Hz, 3H), 1.25 (t, J=7.1 Hz, 3H), 2.71 (dm, J=16.4 Hz, 1H), 2.82 (dm, J=16.8 Hz, 1H), 2.92–2.99 (m, 1H), 3.34 (dm, J=16.8 Hz, 1H), 3.71 (dq, J=10.7, 7.1 Hz, 1H), 3.90 (dq, J=10.7, 7.1 Hz, 1H), 4.05 (dd, J=7.9, 5.8 Hz, 1H), 4.18 (dq, J=10.7, 7.1 Hz, 1H), 4.26 (dq, J=10.7, 7.1 Hz, 1H), 7.19–7.28 ppm (m, 5H); ^{13}C NMR: δ=13.5, 13.9, 31.7, 33.2, 49.6, 61.2, 61.7, 65.1, 87.1 (dd, $J_{C,F}$=23, 22 Hz), 127.3, 128.1, 128.2, 139.8, 150.4 (dd, $J_{C,F}$=281, 281 Hz), 168.9, 171.0 ppm; ^{19}F NMR: δ_F=71.7 (dm, $J_{F,F}$=58 Hz, 1F), 71.9 ppm (dm, $J_{F,F}$=58 Hz, 1F); elemental analysis: calcd (%) for $C_{18}H_{20}F_2O_4$: C 63.90, H 5.96; found: C 63.74, H 5.89.

25: NaH (60% dispersion in mineral oil; 10.6 mg, 0.265 mmol) was added to a solution of **11** (54 mg, 0.21 mmol) in DMF (3 mL) at 0°C. After being stirred at 0°C for 1 h, the reaction mixture was heated at 100°C for 3 h. Phosphate buffer (pH 7, 20 mL) was added to quench the reaction, and the organic materials were extracted with EtOAc (3×20 mL). The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/EtOAc=5:1) to give 4-difluoromethylene-2-phenylcyclopentane-1,1-dicarbonitrile (**25**; 31 mg, 61%) as a colorless liquid. IR (neat): $\tilde{\nu}$=3033, 2935, 2360, 2332, 1772, 1498, 1271, 1078 cm^{-1}; ^{1}H NMR: δ=2.95 (ddm, J=15.8, 7.5 Hz, 1H), 3.04 (ddm, J=15.8, 11.3 Hz, 1H), 3.16 (dm, J=15.6 Hz, 1H), 3.37 (dm, J=15.6 Hz, 1H), 3.72 (dd, J=11.3, 7.5 Hz, 1H), 7.42–7.48 ppm (m, 5H); ^{13}C NMR: δ=28.4, 38.4 (d, $J_{C,F}$=3 Hz), 41.5, 54.4, 83.3 (dd, $J_{C,F}$=27, 23 Hz), 113.4, 114.6, 128.0, 129.2, 129.6, 133.0, 151.5 ppm (dd, $J_{C,F}$=285, 285 Hz); ^{19}F NMR: δ_F=76.0 (dm, $J_{F,F}$=49 Hz, 1F), 76.3 ppm (dm, $J_{F,F}$=49 Hz, 1F); elemental analysis: calcd (%) for $C_{14}H_{10}F_2N_2$: C 68.85, H 4.13, N 11.47; found: C 68.83, H 4.21, N 11.37.

Acknowledgements

We are grateful to Central Glass Co., Ltd. for financial support and Tosoh F-Tech, Inc. for a generous gift of 2-bromo-3,3,3-trifluoroprop-1-ene.

[1] a) J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734; b) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, R. C. Thomas, *J. Chem. Soc. Chem. Commun.* **1976**, 736; c) J. E. Baldwin, R. C. Thomas, L. Kruse, L. Silberman, *J. Org. Chem.* **1977**, *42*, 3846.

[2] J. Ichikawa, Y. Wada, M. Fujiwara, K. Sakoda, *Synthesis* **2002**, 1917, and references therein.

[3] For recent reports, see: a) J. Ichikawa, G. Lapointe, Y. Iwai, *Chem. Commun.* **2007**, 2698; b) J. J. Caldwell, D. Craig, *Angew. Chem.* **2007**, *119*, 2685; *Angew. Chem. Int. Ed.* **2007**, *46*, 2631; c) J. J. Caldwell, D. Craig, S. P. East, *ARKIVOC* **2007**, *XII*, 67; d) J. Clayden, D. W. Watson, M. Helliwell, M. Chambers, *Chem. Commun.* **2003**, 2582; e) R. Naitoh, Y. Nakamura, E. Katano, Y. Nakamura, E. Okada, M. Asaoka, *Heterocycles* **2004**, *63*, 1009; f) P. Auvray, P. Knochel, J. F. Normant, *Tetrahedron Lett.* **1985**, *26*, 4455; for recent reports on the cyclization of allenes, see: g) H. Ohno, Y. Kadoh, T. Tanaka, *Org. Lett.* **2006**, *8*, 947; h) M. A. Chowdhury, H.-U. Reissig, *Synlett* **2006**, 2383.

[4] For a recent review, see: a) D. W. Knight in *Progress in Heterocyclic Chemistry, Vol. 14* (Eds.: G. W. Gribble, T. L. Gilchrist), Pergamon, Amsterdam, **2002**, chap. 2; for recent reports, see: b) A. D. Jones, A. L. Redfern, D. W. Knight, I. R. Morgan, A. C. Williams, *Tetrahedron* **2006**, *62*, 9247; c) N. S. Karanjule, S. D. Markad, V. S. Shinde, D. D. Dhavale, *J. Org. Chem.* **2006**, *71*, 4667.

[5] For recent reports, see: a) A. J. Clark, C. P. Dell, J. M. McDonagh, J. Geden, P. Mawdsley, *Org. Lett.* **2003**, *5*, 2063; b) C. Chatgilialoglu, C. Ferreri, M. Guerra, V. Timokhin, G. Froudakis, T. Gimisis, *J. Am. Chem. Soc.* **2002**, *124*, 10765; for recent reviews, see: c) H. Ishibashi, *Chem. Rec.* **2006**, *6*, 23; d) H. Ishibashi, T. Sato, M. Ikeda, *Synthesis* **2002**, 695; e) A. F. Parsons, *C. R. Acad. Sci.* **2001**, *4*, 391.

[6] a) J. Ichikawa, H. Fukui, Y. Ishibashi, *J. Org. Chem.* **2003**, *68*, 7800, and references therein; b) J.-P. Bégué, D. Bonnet-Delpon, M. H. Rock, *J. Chem. Soc. Perkin Trans. 1* **1996**, 1409.

[7] a) T. Mori, J. Ichikawa, *Chem. Lett.* **2004**, *33*, 1207; b) T. Mori, Y. Iwai, J. Ichikawa, *Chem. Lett.* **2005**, *34*, 778.

[8] a) *Organofluorine Chemistry: Principles and Commercial Applications* (Eds: R. E. Banks, B. E. Smart, J. C. Tatlow), Plenum Press, New York, **1994**; b) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.

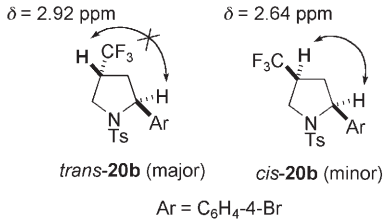
[9] R. Plantier-Royon, C. Portella, *Carbohydr. Res.* **2000**, *327*, 119.

[10] *Biomedical Frontiers of Fluorine Chemistry* (Eds: I. Ojima, J. R. McCarthy, J. T. Welch), American Chemical Society, Washington, D.C., **1996**.

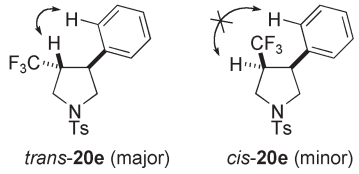
[11] a) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 1626; b) S. Kaneko, T. Yamazaki, T. Kitazume, *J. Org. Chem.* **1993**, *58*, 2302, and references therein; for a review, see: c) J. T. Welch, *Tetrahedron* **1987**, *43*, 3123.

[12] a) G. Wang, K. Sakthivel, V. Rajappan, T. W. Bruice, K. Tucker, P. Fagan, J. L. Brooks, T. Hurd, J. M. Leeds, P. D. Cook, *Nucleosides Nucleotides Nucleic Acids* **2004**, *23*, 317; b) S. Marcotte, B. Gerard, X. Pannecoucke, C. Feasson, J.-C. Quirion, *Synthesis* **2001**, 929, and references therein.

[13] V. J. Lee in *Comprehensive Organic Synthesis*, *Vol. 4* (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, p. 69.
[14] C. Leriche, X. He, C. T. Chang, H. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 6348, and references therein.
[15] R. Nadano, Y. Iwai, T. Mori, J. Ichikawa, *J. Org. Chem.* **2006**, *71*, 8748, and references therein.
[16] J. Ichikawa, T. Mori, Y. Iwai, *Chem. Lett.* **2004**, *33*, 1354.
[17] B. Jiang, Q.-F. Wang, C.-G. Tang, M. Xu, *Tetrahedron Lett.* **2001**, *42*, 4083.
[18] T. Yamazaki, N. Ishikawa, *Chem. Lett.* **1984**, 521.
[19] R. Nadano, J. Ichikawa, *Synthesis* **2006**, 128.
[20] O. Mitsunobu, *Synthesis* **1981**, 1.
[21] T. Tsunoda, F. Ozaki, S. Ito, *Tetrahedron Lett.* **1994**, *35*, 5081.
[22] For a report on 3-(methylene)indolines, see: J. Barluenga, F. J. Fañanás, R. Sanz, Y. Fernández, *Chem. Eur. J.* **2002**, *8*, 2034.
[23] For recent reports on 3-(trifluoromethyl)indoline derivatives, see: a) N. Shibata, H. Fujimoto, S. Mizuta, S. Ogawa, Y. Ishiuchi, S. Nakamura, T. Toru, *Synlett* **2006**, 3484; b) B. Dolenský, J. Kvíčala, O. Paleta, *J. Fluorine Chem.* **2005**, *126*, 745; c) H. A. Schenck, P. W. Lenkowski, I. Choudhury-Mukherjee, S.-H. Ko, J. P. Stables, M. K. Patel, M. L. Brown, *Bioorg. Med. Chem.* **2004**, *12*, 979; d) V. A. Petrov, *J. Fluorine Chem.* **2000**, *106*, 25.
[24] For recent reports on 3-(trifluoromethyl)indoles, see: a) Y.-Q. Fang, M. Lautens, *Org. Lett.* **2005**, *7*, 3549; b) T. Konno, J. Chae, T. Ishihara, H. Yamanaka, *J. Org. Chem.* **2004**, *69*, 8258, and references therein; c) I. Choudhury-Mukherjee, H. A. Schenck, S. Cechova, N. Pajewski, J. Kapur, J. Ellena, D. S. Cafiso, M. L. Brown, *J. Med. Chem.* **2003**, *46*, 2494; d) I. Rodrigues, D. Bonnet-Delpon, J.-P. Bégué, *J. Org. Chem.* **2001**, *66*, 2098, and references therein.
[25] a) T. Fukuyama, M. Cheung, C.-K. Jow, Y. Hidai, T. Kan, *Tetrahedron Lett.* **1997**, *38*, 5831; b) T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373.
[26] G. Alvernhe, A. Laurent, G. Haufe, *Synthesis* **1987**, 562.
[27] S. Irifune, T. Kibayashi, Y. Ishii, M. Ogawa, *Synthesis* **1988**, 366.
[28] To our knowledge, there are no reports on 3-(difluoromethyl)indoles; for recent reports on 2-(difluoromethyl)indoles, see: a) F. Ge, Z. Wang, W. Wan, J. Hao, *Synlett* **2007**, 447; b) see reference [24b].
[29] a) R. D. Chambers, *Fluorine in Organic Chemistry*, Antony Rowe, Chippenham, **1973**, p. 1; b) B. E. Smart in *Organofluorine Chemistry: Principles and Commercial Applications* (Eds.: R. E. Banks, B. E. Smart, J. C. Tatlow), Plenum Press, New York, **1994**, p. 57; c) A. D. Allen, T. T. Tidwell in *Advances in Carbocation Chemistry*, *Vol. 1* (Ed.: X. Creary), Jai Press, Greenwich, **1989**, p. 1.
[30] For recent reports on 3-trifluoromethyl-2,3-dihydrobenzothiophenes, see: a) E. Okada, N. Tsukushi, N. Shimomura, *Synthesis* **2000**, 237; b) M. Yoshimatsu, T. Sugimoto, N. Okada, S. Kinoshita, *J. Org. Chem.* **1999**, *64*, 5162; c) E. Okada, R. Masuda, M. Hojo, N. Imazaki, H. Miya, *Heterocycles* **1992**, *34*, 103.
[31] For recent reports on 3-(difluoromethylene)pyrrolidines, see: a) J. Ichikawa, R. Nadano, N. Ito, *Chem. Commun.* **2006**, 4425; b) X.-L. Qiu, F.-L. Qing, *J. Org. Chem.* **2005**, *70*, 3826; c) A. Kamal, P. S. M. M. Reddy, D. R. Reddy, E. Laxman, Y. L. N. Murthy, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5699; d) X.-L. Qiu, F.-L. Qing, *Synthesis* **2004**, 334; e) X.-L. Qiu, F.-L. Qing, *J. Org. Chem.* **2002**, *67*, 7162.
[32] For recent reports on 3-(trifluoromethyl)pyrrolidines, see: a) T. Llamas, R. G. Arrayás, J. C. Carretero, *Synthesis* **2007**, 950; b) V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, I. V. Martynov, *Russ. Chem. Bull.* **2005**, *54*, 2851; c) C. Brule, J.-P. Bouillon, C. Portella, *Tetrahedron* **2004**, *60*, 9849; d) X.-L. Qiu, F.-L. Qing, *J. Org. Chem.* **2003**, *68*, 3614; e) X.-L. Qiu, F.-L. Qing, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2052; f) J. R. Del Valle, M. Goodman, *Angew. Chem.* **2002**, *114*, 1670; *Angew. Chem. Int. Ed.* **2002**, *41*, 1600; g) P.-H. Liang, L.-W. Hsin, C.-Y. Cheng, *Bioorg. Med. Chem.* **2002**, *10*, 3267.
[33] The 2,4-*trans*/*cis* stereochemistry of the pyrrolidine ring was determined by a NOESY experiment on 2-(4-bromophenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (**20b**) as a representative example. A cross-peak between the C2 and C4 protons was observed in the minor product, but not in the major product. As for the C4 proton of the pyrrolidine ring, the signal of the *trans* isomer was observed at lower field ($\delta = 2.92$ ppm) than that of the *cis* isomer ($\delta = 2.64$ ppm), which allowed assignment of the configuration of the other stereoisomers **20a**, **20c** and **20d**.



[34] The 3,4-*trans*/*cis* stereochemistry of 1-(4-methylbenzenesulfonyl)-3-phenyl-4-(trifluoromethyl)pyrrolidine (**20e**) was determined by a NOESY experiment. A cross-peak between the C4 proton of the pyrrolidine ring and the *ortho* protons of the 3-phenyl group was observed in the major product, but not in the minor product.



[35] For a recent review on the *gem*-dialkyl effect, see: M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735.
[36] For recent reports on 3-(difluoromethylene)tetrahydrofurans, see: a) A. Gautier, G. Garipova, C. Salcedo, S. Balieu, S. R. Piettre, *Angew. Chem.* **2004**, *116*, 6089; *Angew. Chem. Int. Ed.* **2004**, *43*, 5963; b) S. Marcotte, B. Gérard, X. Pannecoucke, C. Feasson, J.-C. Quirion, *Synthesis* **2001**, 929; c) P. J. Serafinowski, C. A. Brown, *Tetrahedron* **2000**, *56*, 333; d) see reference [9].
[37] For a recent report on 3-(difluoromethylene)tetrahydrothiophenes, see: M. H. Lim, H. O. Kim, H. R. Moon, M. W. Chun, L. S. Jeong, *Org. Lett.* **2002**, *4*, 529.
[38] For recent reports on 3-(trifluoromethyl)tetrahydrothiophenes, see: a) R. Huisgen, E. Langhals, K. Polborn, K. Karaghiosoff, *Helv. Chim. Acta* **2004**, *87*, 1426; b) X. Zhang, F.-L. Qing, *J. Org. Chem.* **2002**, *67*, 1016; c) R. Huisgen, X. Li, H. Giera, E. Langhals, *Helv. Chim. Acta* **2001**, *84*, 981.
[39] For recent reports on (difluoromethylene)cyclopentane derivatives, see: a) H. Yuan, R. B. Silverman, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1651; b) Y. Pan, J. Qiu, R. B. Silverman, *J. Med. Chem.* **2003**, *46*, 5292; c) A. Saito, M. Okada, Y. Nakamura, O. Kitagawa, H. Horikawa, T. Taguchi, *J. Fluorine Chem.* **2003**, *123*, 75.
[40] J. R. Henry, L. R. Marcin, M. C. McIntosh, *Tetrahedron Lett.* **1989**, *30*, 5709.
[41] P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85.

Received: September 26, 2007
Published online: January 18, 2008

