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Divergent Chemical Synthesis of Prolines Bearing Fluorinated One-Carbon Units at the 4-Position via Nucleophilic 5-*Endo*-*Trig* Cyclizations

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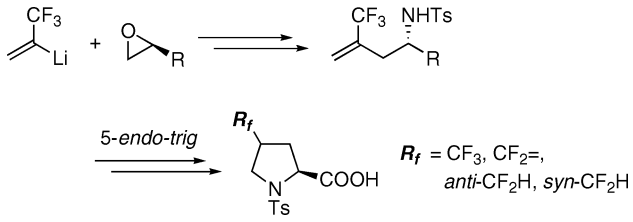

N-[3-(Trifluoromethyl)homoallyl]sulfonamides, prepared via ring opening of (*S*)-glycidyl ethers or 2-aryloxiranes with 1-(trifluoromethyl)vinyllithium, underwent intramolecular addition or S_N2'-type reaction in the normally disfavored 5-*endo*-*trig* fashion, leading to 2-substituted 4-(trifluoromethyl)- or 4-(difluoromethylene)pyrrolidines. Both α- and β-face-selective hydrogenation of the 4-difluoromethylene group afforded *syn*- and *anti*-4-(difluoromethyl)pyrrolidines, respectively. These sequences, followed by the oxidation of a 2-hydroxymethyl or 2-aryl group, successfully provided prolines with a trifluoromethyl, difluoromethylene, or difluoromethyl group at the 4-position, including optically active prolines.

Introduction

Proline is a unique amino acid with a rigid ring structure, which leads to its special role as a bending template in peptide chains.[1] Its secondary amine moiety with conformational constraint has allowed development of proline-based bioactive compounds,[2] ligands,[3] and organocatalysts.[4] 4-Substituted prolines, in particular, have found extensive use in this context,[5] well exemplified by (i) Spirapril[6] and Fosinopril,[7] angiotensin-converting enzyme (ACE) inhibitors, (ii) conformationally stabilized collagen triple helices,[8] and (iii) 4-hydroxyproline-based asymmetric organocatalysts.[9]

In the field of pharmaceuticals, agrochemicals, materials, and catalysts, introduction of fluorocarbon substituents has come into wide use as one of the most efficient methods for the modification of biological activity as well as physical and chemical properties.[10] Among fluorocarbon substituents, fluorinated one-carbon units are quite attractive:[11] (i) the incorpora-

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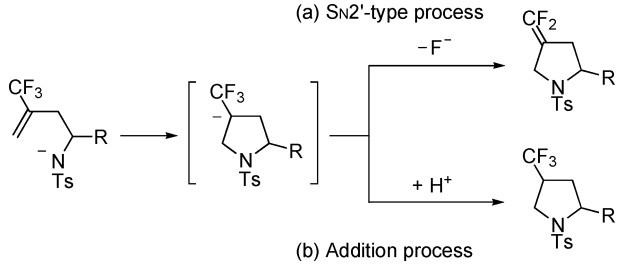
SCHEME 1. Nucleophilic 5-*Endo-Trig* Cyclizations of (3-CF_3-homoallyl)sulfonamides

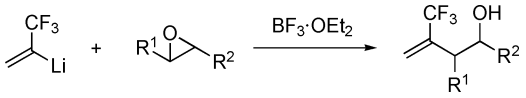


tion of a trifluoromethyl (CF_3) group into organic molecules increases lipophilicity and affects electron density,[12] (ii) a difluoromethyl (CF_2H) group has hydrogen bond donor ability without nucleophilicity and with high lipophilicity,[13] which makes it a special mimic of a hydroxy group,[14] and (iii) a difluoromethylene (CF_2═) group acts as a reactive site toward nucleophiles[15] and a potential isostere of carbonyl groups.[16]

Thus, prolines with such fluorinated substituents at the 4-position have importance in the design of molecules and, hence, immense potential. Recently, Goodman and Qing independently reported synthetic methods for 4-fluorocarbon-substituted prolines, with both methods starting from natural amino acids such as L-hydroxyproline and L-serine.[17,18] Their chemical synthesis based on non-natural starting materials is now a highly desirable goal.

In our recent studies, we have accomplished the construction of a pyrrolidine ring via nucleophilic 5-*endo-trig* cyclization of 2-trifluoromethyl-1-alkenes with a nitrogen functionality (Scheme 1).[19] *N*-[3-(Trifluoromethyl)homoallyl]sulfonamides underwent intramolecular S_N2'-type reaction under aprotic conditions to afford 4-difluoromethylene-substituted pyrrolidines (Scheme 1a), while protic conditions allowed nucleophilic addition, providing 4-trifluoromethyl-substituted pyrrolidines (Scheme 1b). This type of 5-*endo-trig* cyclization has been considered to be a geometrically disfavored process according to Baldwin's rules.[20] Such unique reactivity of 2-trifluoromethyl-1-alkenes is presumably due to the highly electrophilic double bond and the stabilized α-CF_3 carbanion intermediate, both of which are caused by the strong electron-withdrawing ability of the CF_3 group. Thus, both 4-difluoromethylene- and 4-trifluoromethyl-substituted pyrrolidines were selectively derived from the same sulfonamide precursor, depending on reaction in the presence or absence of a proton source.

SCHEME 2. Synthesis of 3-CF_3-Homoallyl Alcohols



We have also recently developed a synthetic method for 3-(trifluoromethyl)homoallyl alcohols via ring opening of substituted oxiranes with 1-(trifluoromethyl)vinyllithium in the presence of $BF_3{\cdot}OEt_2$, which allowed the synthesis of optically active homoallyl alcohols (Scheme 2).[21] The combination of the two processes, the oxirane ring opening and the 5-*endo-trig* cyclization, followed by introduction of a carboxy group at the 2-position, could provide 4-substituted proline derivatives in short steps, as outlined in Figure 1. The introduction of the carboxy group would be attained by oxidation of a hydroxymethyl or an aryl group, derived from the 2-substituent on the oxirane ring. The chirality of a commercially available, optically active glycidyl ether could be preserved in the sequence. A difluoromethylene substituent would be transformed to a difluoromethyl group by hydrogenation, where face-selective reactions could afford *anti*- or *syn*-4-(difluoromethyl)proline derivatives. On the basis of these considerations, we investigated synthetic methods for prolines bearing a fluorinated one-carbon unit at the 4-position.

We report a short chemical synthesis of proline derivatives bearing a fluorinated one-carbon unit, such as a trifluoromethyl, difluoromethylene, or difluoromethyl group, at the 4-position via (i) oxirane ring opening with 1-(trifluoromethyl)vinyllithium and (ii) nucleophilic 5-*endo-trig* cyclization of *N*-[3-(trifluoromethyl)homoallyl]sulfonamides.

Results and Discussion

Preparation of Tosylamide Cyclization Precursors 6. When (*S*)-glycidyl 4-(methoxy)benzyl (PMB) ether **(*S*)-2a** (99% ee)[22] was treated with 1-(trifluoromethyl)vinyllithium, generated in situ from bromotrifluoropropene **1** in the presence of $BF_3{\cdot}OEt_2$ at −100 °C, the corresponding partially protected diol **(*R*)-4a** was obtained in 82% yield with 99% ee (Scheme 3).[21] In this process, no racemization was observed. A similar ring opening of styrene oxide **2b** gave homoallylic alcohol **4b** in moderate yield. Homoallylic alcohols **4** were also prepared by the reaction of 2-(trifluoromethyl)allylsilane **3** with aldehydes.[23] Thus, homoallylic alcohol **4c** bearing a 2,4-dimethoxyphenyl group was obtained in 63% yield.[24]

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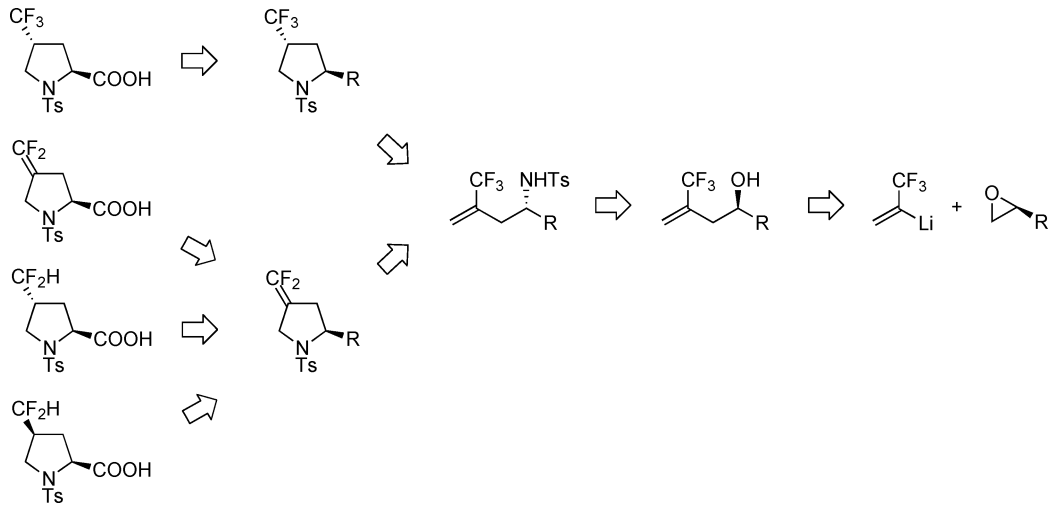
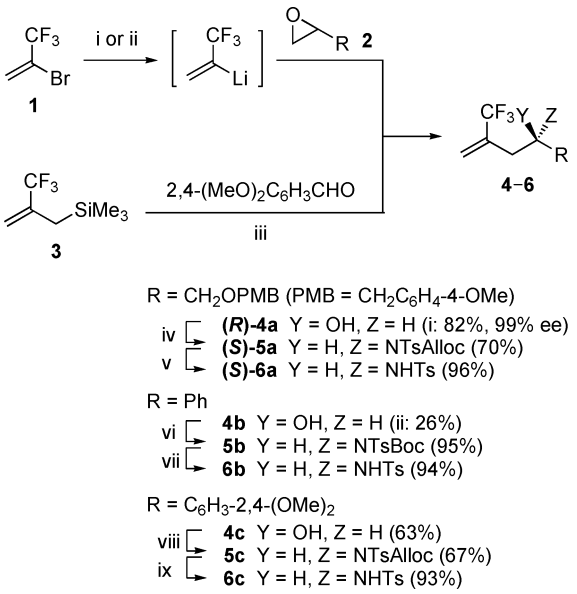


FIGURE 1. Synthetic strategy for 4-CF_3, CF_2═, or CF_2H-substituted prolines.

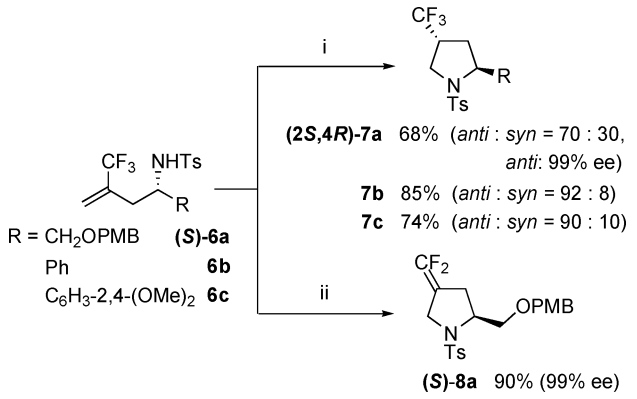
SCHEME 3. Preparation of Tosylamides 6[a]



[a] Reagents and conditions: (i) BF_3·OEt_2 (1.0 equiv), *n*-BuLi (1.0 equiv), −100 °C, 15 min, Et_2O; then **2a** (R = CH_2OPMB, 0.67 equiv), −100 °C, 15 min; (ii) *t*-BuLi (1.0 equiv), −100 °C, 0.5 h, Et_2O; then, BF_3·OEt_2 (1.0 equiv), 5 min; then, **2b** (R = Ph, 0.67 equiv), 15 min; (iii) 2,4-dimethoxybenzaldehyde (1.2 equiv), *n*-Bu_4NF (TBAF, 0.1 equiv), rt, 24 h, THF; (iv) CH_2═$CHCH_2OCONHTs$ (HNTsAlloc, 1.2 equiv), EtOCON═NCO_2Et (DEAD, 1.5 equiv), PPh_3 (1.5 equiv), 0 °C, 7 d, toluene;[26] (v) piperidine (3.0 equiv), $Pd(PPh_3)_4$ (2 mol %), rt, 1.5 h, MeCN; (vi) HNTsBoc (1.5 equiv), DEAD (2.0 equiv), PPh_3 (2.0 equiv), 0 °C, 10 h, THF; (vii) TFA (10 equiv), rt, 10 h, CH_2Cl_2; (viii) HNTsAlloc (1.5 equiv), DEAD (2.0 equiv), PPh_3 (2.0 equiv), rt, 10 h, THF; (ix) piperidine (4.0 equiv), $Pd(PPh_3)_4$ (2 mol %), rt, 10 h, MeCN.

The desired precursor sulfonamides were furnished as follows: Homoallylic alcohols **4a**−**c** were converted to the corresponding Alloc-protected tosylamides **5a** and **5c** or Boc-protected tosylamide **5b** by the Mitsunobu reaction.[25] Deprotection of the allyloxycarbonyl (Alloc) or *tert*-butoxycarbonyl (Boc) group was effected with piperidine and a palladium catalyst or trifluoroacetic acid to give tosylamides **6a**−**c** in excellent yield, respectively.

SCHEME 4. 5-*Endo*-*Trig* Cyclization of Tosylamides 6[a]



[a] Reagents and conditions: (i) KOH (5.0 equiv for **6a**,**b** or 1.3 equiv for **6c**), 130 °C, 20 h, $(CH_2OH)_2$; (ii) NaH (1.2 equiv), 120 °C, 4 h, DMF.

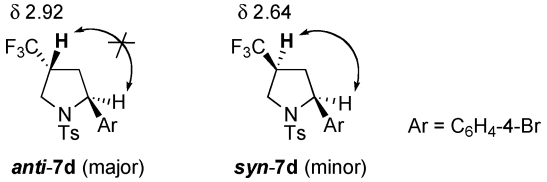
5-*Endo*-*Trig* Cyclization of Tosylamides 6. The cyclization of tosylamides **6a**−**c** obtained above was attempted by heating at 130 °C with an excess amount of KOH in ethylene glycol.[19] Nucleophilic addition proceeded in a 5-*endo*-*trig* fashion under protic conditions to afford pyrrolidines bearing a trifluoromethyl group at the 4-position with 2,4-*anti* stereoselectivity.[27] The results are summarized in Scheme 4.

Tosylamide **(*S*)-6a** cyclized to give pyrrolidine **(2*S*,4*R*)-7a** in 68% yield as a mixture of 2,4-*anti*/*syn* diastereomers (*anti*/

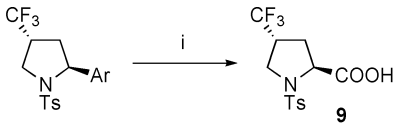
(25) Mitsunobu, O. *Synthesis* **1981**, 1.

(26) In the Mitsunobu reaction of **4a**, the yield of **5a** was improved by using toluene instead of THF as a solvent with a decrease in the amount of elimination product, a diene.

(27) The 2,4-*anti*/*syn* stereochemistry of the pyrrolidine ring was determined by a NOESY experiment on 2-(4-bromophenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (**7d**) as a representative example. A cross peak between the 2- and 4-protons was not observed in the major product, but in the minor product. As for the 4-proton of the pyrrolidine ring, the signal of the *anti*-isomer was observed at lower field (δ 2.92) than that of the *syn*-isomer (δ 2.64), with this spectral criterion confirming similar stereochemistry for **7a**−**c**.



SCHEME 5. Synthesis of 4-(Trifluoromethyl)proline 9[a]



Ar = Ph	**7b** (*anti* : *syn* = 92 : 8)	45% (*anti* : *syn* = 92 : 8)
C_6H_3-2,4-$(OMe)_2$	**7c** (*anti* : *syn* = 90 : 10)	72% (*anti* : *syn* = 90 : 10)

[a] Reagents and conditions: (i) $RuCl_3 \cdot nH_2O$ (2 mol %), $NaIO_4$ (11 equiv), rt, 4 d (for **7b**) or 6 h (for **7c**), $H_2O-CCl_4-CH_3CN$ (1.5:1:1).

syn = 70:30, *anti*: 99% ee) without racemization. Since phenyl-substituted tosylamide **6b** (R = Ph) exhibited better *anti* selectivity (*anti*/*syn* = 92:8) than that of alkyl-substituted precursor **6a**, we tried the cyclization of tosylamide **6c** bearing a 2,4-dimethoxyphenyl group, which could be more readily oxidized to a carboxy group. 4-(Trifluoromethyl)pyrrolidine **7c** was obtained in 74% yield with high diastereoselectivity (*anti*/*syn* = 90:10) in the 5-*endo*-*trig* cyclization of **6c**.

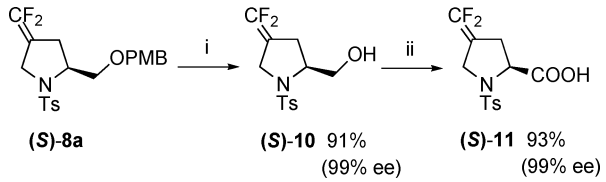
We also examined the S_N2'-type 5-*endo*-*trig* cyclization of tosylamide **6** under aprotic, basic conditions.[19] On treatment of tosylamide **(*S*)-6a** with 1.2 equiv of NaH at 120 °C in DMF, the corresponding pyrrolidine **(*S*)-8a** bearing a difluoromethylene group at the 4-position was obtained in 90% yield without racemization (Scheme 4). Thus, both trifluoromethylated and difluoromethylenated pyrrolidines **7** and **8** have been successfully constructed via addition reaction or S_N2'-type reaction, starting from a common precursor **6**.

Synthesis of 4-Trifluoromethyl-Substituted Proline 9. For the synthesis of prolines, the substituent at the 2-position should be oxidized to a carboxy group. Oxidation of the phenyl group in **7b** was examined with RuO_4, generated in situ from $NaIO_4$ and a catalytic amount of $RuCl_3$.[28] The reaction proceeded slowly to afford 4-trifluoromethyl-*N*-tosylproline **9** in 45% yield (Scheme 5). The 2,4-dimethoxyphenyl group in **7c** was oxidized with RuO_4 to improve the yield of the desired proline **9** up to 72%. This sequence provides the desired proline in only five steps from an oxirane with high 2,4-*anti* selectivity, which allows the synthesis of optically active 4-(trifluoromethyl)prolines.

Synthesis of 4-Difluoromethylene-Substituted Proline 11. The synthesis of (*S*)-4-difluoromethylene-*N*-tosylproline **(*S*)-11** was successfully effected via a two-step procedure: (i) deprotection of the PMB group in **(*S*)-8a** with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and (ii) conversion of the hydroxymethyl group to a carboxy group by TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)-catalyzed oxidation with $NaClO_2$,[29,30] both of which proceeded in excellent yield, albeit at a slow rate (Scheme 6). The optical purity of proline **(*S*)-11** was 99% ee, which shows that no racemization occurred during this sequence from the starting (*R*)-glycidol.[31]

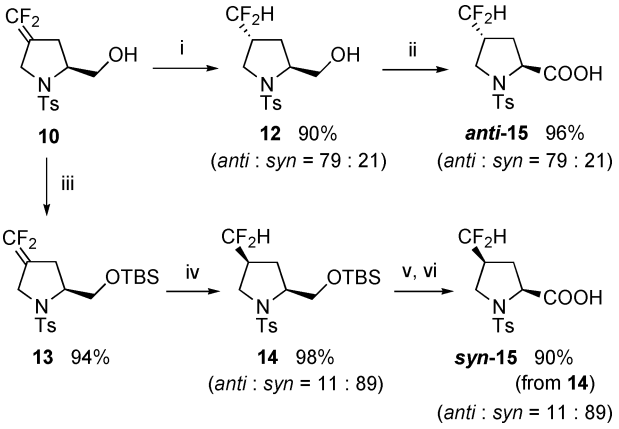
Synthesis of 4-Difluoromethyl-Substituted Proline 15. We then turned our attention to prolines bearing a 4-difluoromethyl group. Goodman and Qing reported hydrogenation of endocyclic double bonds in 4-(trifluoromethyl)pyrrolines and exocyclic

SCHEME 6. Synthesis of 4-(Difluoromethylene)proline 11[a]



[a] Reagents and conditions: (i) DDQ (1.3 equiv), rt, 2 d, CH_2Cl_2-MeOH (10:1); (ii) TEMPO (5 mol %), $NaClO_2$ (1.3 equiv), rt, 7 d, MeCN−pH 7 phosphate buffer (1.3:1).

SCHEME 7. Synthesis of 4-(Difluoromethyl)prolines 15[a]



[a] Reagents and conditions: (i) H_2 (1 atm), Pd/C (5%, 0.5 equiv), rt, 6 h, $CHCl_3$; (ii) TEMPO (5 mol %), NaBr (0.5 equiv), trichloroisocyanuric acid (5.0 equiv), $NaHCO_3$ (10 equiv), rt, 3 h, acetone−H_2O (4:1); (iii) TBSCl (1.5 equiv), TEA (2.0 equiv), DMAP (0.3 equiv), rt, 12 h, CH_2Cl_2; (iv) H_2 (1 atm), Pd/C (5%, 5 mol %), rt, 1 h, EtOH; (v) TBAF (1.2 equiv), rt, 1 h, THF; (vi) TEMPO (2 mol %), NaBr (0.2 equiv), trichloroisocyanuric acid (2.0 equiv), $NaHCO_3$ (6.0 equiv), rt, 3 h, acetone−H_2O (4:1).

double bonds in 4-(alkylidene)pyrrolidines, leading to the stereoselective formation of 4-substituted prolines.[17,18] On the basis of these observations, we pursued face-selective hydrogenation of the difluoromethylene group, exocyclic double bond in prolinol **10**.[32]

Hydrogenation of **10** was conducted in the presence of a palladium catalyst. Whereas the reaction in methanol afforded a 1:1 mixture of *anti*- and *syn*-4-(difluoromethyl)prolinols **12**, good *anti* selectivity (*anti*/*syn* = 79:21) was observed in a haloalkane solvent, such as dichloromethane and chloroform (Scheme 7). On the other hand, high *syn* selectivity (*anti*/*syn* = 11:89) was attained by protection of the hydroxy group in **10** as bulky TBS ether **13** prior to reduction, which gave *syn*-4-(difluoromethyl)pyrrolidine **14** as a major product.[33] Each face-selectivity can be explained by (i) chelation of the hydroxy group in **10** on the palladium surface (leading to the *anti* product) and (ii) a steric effect of the bulky silyl group of **13** (leading to the *syn* product). The desired *anti*-4-difluoromethyl-*N*-tosylproline ***anti*-15** was obtained by oxidation of ***anti*-12** with trichloroisocyanuric acid and a catalytic amount of TEMPO[29] in excellent yield. A similar oxidation procedure was also

(28) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(29) TEMPO-catalyzed oxidation using trichloroisocyanuric acid: (a) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041. (b) Luca, L. D.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999. TEMPO-catalyzed oxidation using $NaClO_2$: (c) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.

(30) Attempted TEMPO-catalyzed oxidation of **10** with trichloroisocyanuric acid was not successful due to affecting the difluromethylene moiety.

(31) Removal of the tosyl group on the nitrogen was achieved by photoinduced reduction of the benzyl ester derived from **11** in the presence of 1,5-dimethoxynaphthalene and ascorbic acid. Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.

(32) Although the reduction of a 4-(difluoromethylene)proline derivative was reported to give a single diastereomer in ref 18a, the reported ^1H and ^{13}C NMR data proved to be those of a diastereomer mixture. See also: Qiu, X.-L.; Qing, F.-L. *J. Org. Chem.* **2005**, *70*, 3826 and references therein.

applied to prolinol ***syn*-12**, derived from **14** by deprotection of the silyl group, to afford ***syn*-15**.

Conclusion

We have accomplished a divergent, chemical synthesis of *N*-protected prolines bearing a fluorocarbon moiety, such as a trifluoromethyl, difluoromethylene, or difluoromethyl group, at the 4-position from common tosylamide precursors. The combination of (i) oxirane ring opening with (trifluoromethyl)-vinyllithium and (ii) 5-*endo*-*trig* cyclization of *N*-(homoallyl)-sulfonamides has proven to be highly efficient to construct prolines bearing a trifluoromethyl or a difluoromethylene group, depending on protic or aprotic reaction media in (ii). Face-selective hydrogenation of the 4-difluoromethylene group in prolinol was achieved with or without protection of the 2-hydroxy group to afford *anti*- or *syn*-(difluoromethyl)proline derivatives. The results described herein provide a convenient access to prolines bearing fluorinated one-carbon units at the 4-position, which could find wide application in the design of new organocatalysts and the synthesis of the new fluorine-containing peptides.

Experimental Section

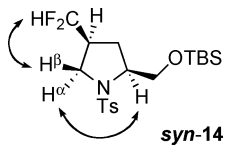
rel*-(2*R*,4*S*)-2-(2,4-Dimethoxyphenyl)-1-(4-methylbenzenesulfonyl)-4-(trifluoromethyl)pyrrolidine (7c).** To a solution of **6c** (88 mg, 0.21 mmol) in ethylene glycol (3 mL) was added KOH powder (15 mg, 0.27 mmol) at rt. After the reaction mixture was stirred at 130 °C for 20 h, phosphate buffer (pH 7, 10 mL) was added to quench the reaction. Organic materials were extracted with EtOAc (10 mL × 3), and the combined extracts were washed with water (10 mL × 3) and 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, 4:1) to give **7c** (65 mg, 74%, *anti*/*syn* = 90:10) as a colorless liquid. IR (neat): 3001, 2958, 2839, 1614, 1589, 1506, 1340, 1161, 1034 cm^{-1}. ^1H NMR: (anti*-7c**) δ 1.89−2.01 (2H, m), 2.44 (3H, s), 2.84−2.95 (1H, m), 3.42 (1H, dd, J = 9.8, 9.8 Hz), 3.75 (3H, s), 3.80 (3H, s), 3.84 (1H, dd, J = 9.8, 9.8 Hz), 5.11 (1H, d, J = 8.0 Hz), 6.40 (1H, s), 6.45 (1H, d, J = 8.4 Hz), 7.26 (1H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.0 Hz), 7.84 (2H, d, J = 8.0 Hz); (***syn*-7c**) δ 2.08 (2H, m), 2.41 (3H, s), 2.46 (1H, m), 3.55 (1H, dd, J = 9.9, 9.9 Hz), 3.62 (3H, s), 3.80 (3H, s), 3.95 (1H, dd, J = 9.9, 9.9 Hz), 4.86 (1H, dd, J = 7.6, 7.6 Hz), 6.28 (1H, s), 6.44 (1H, J = 8.4 Hz), 7.22 (2H, d, J = 8.1 Hz), 7.26 (1H, d, J = 8.4 Hz), 7.49 (2H, d, J = 8.1 Hz). ^{13}C NMR: (***anti*-7c**) δ 21.5, 33.3, 41.0 (q, J_{CF} = 29 Hz), 47.8, 55.1, 55.3, 58.7, 98.6, 103.5, 121.8, 126.2 (q, J_{CF} = 256 Hz), 127.4, 127.8, 129.6, 134.4, 143.6, 156.6, 160.5. ^{19}F NMR: (***anti*-7c**) δ_F 91.3 (d, J_{FH} = 8 Hz); (***syn*-7c**) δ_F 91.4 (d, J_{FH} = 8 Hz). HRMS (FAB): calcd for $C_{20}H_{23}F_3NO_4S$ ([M + H]$^+$) 430.1300, found 430.1284.

(*S*)-4-Difluoromethylene-2-[(4-methoxybenzyloxy)methyl]-1-[(4-methylbenzene)sulfonyl]pyrrolidine [(*S*)-8a]. To a solution of **(*S*)-6a** (1.28 g, 2.89 mmol) in DMF (30 mL) was added NaH (55% dispersion in mineral oil; 151 mg, 3.47 mmol) at 0 °C. After being stirred for 10 min, the mixture was heated at 120 °C for 4 h. The reaction was quenched with phosphate buffer (pH 7, 40 mL), and organic materials were extracted with EtOAc (30 mL × 3). The combined extracts were washed with water (30 mL × 4) and 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, 2:1) to give **(*S*)-8a** (1.10 g, 90%) as a colorless liquid. $[\alpha]^{25}_D$ = −13.1 (*c* 1.0, $CHCl_3$). IR (neat): 2931, 2860, 1782, 1512, 1348, 1248, 1163, 1093, 1036, 816 cm^{-1}. ^1H NMR: δ 2.12−2.21 (1H, m), 2.41 (3H, s), 2.47 (1H, br d, J = 15.5 Hz), 3.38 (1H, dd, J = 9.4, 8.1 Hz), 3.63 (1H, dd, J = 9.4, 4.0 Hz), 3.79 (3H, s), 3.95 (1H, br d, J = 14.0 Hz), 3.99 (1H, br d, J = 14.0 Hz), 3.99−4.03 (1H, m), 4.43 (2H, s), 6.87 (2H, d, J = 8.3 Hz), 7.21 (2H, d, J = 8.3 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.68 (2H, d, J = 8.3 Hz). ^{13}C NMR: δ 21.4, 27.8, 46.9 (d, J_{CF} = 4 Hz), 55.1, 59.2, 71.6, 72.9, 85.6 (dd, J_{CF} = 25, 23 Hz), 113.7, 127.2, 129.1, 129.7, 129.9, 134.8, 143.8, 149.9 (dd, J_{CF} = 284, 284 Hz), 159.2. ^{19}F NMR: δ_F 71.3 (1F, d, J_{FF} = 55 Hz), 74.2 (1F, d, J_{FF} = 55 Hz). HRMS (FAB): calcd for $C_{21}H_{24}F_2NO_4S$ ([M + H]$^+$) 424.1394, found 424.1390. HPLC (*i*-PrOH−hexane, 1:30): retention time 20.4 min major peak, 22.7 min minor peak.

rel*-(2*R*,4*S*)-1-(4-Methylbenzenesulfonyl)-4-(trifluoromethyl)-proline (9).** To a suspension of $NaIO_4$ (457 mg, 2.14 mmol) in CH_3CN (1 mL) and H_2O (1.5 mL) were added a solution of **7c** (84 mg, 0.19 mmol) in CCl_4 (1.0 mL) and then $RuCl_3 \cdot H_2O$ (0.8 mg, 4 μmol) at rt. The reaction mixture was stirred for 6 h at rt, and then water was added to quench the reaction. Organic materials were extracted with Et_2O (15 mL × 3). The combined extracts were washed with aqueous NaOH (1 M, 15 mL × 3). The combined aqueous layer was brought to pH 3.0 with aqueous HCl (6 M) and extracted with Et_2O (30 mL × 3). After removal of the solvent under reduced pressure, **9** (47 mg, 72%, *anti*/*syn* = 90:10) was obtained as a colorless crystal. IR (neat): 3238, 2956, 2926, 1732, 1400, 1350, 1271, 1161, 1128, 1039 cm^{-1}. ^1H NMR: (anti*-9**) δ 2.13 (1H, ddd, J = 13.4, 9.2, 9.2 Hz), 2.34 (1H, ddd, J = 13.4, 8.0, 2.7 Hz), 2.46 (3H, s), 3.15 (1H, ddddq, J_{HF} = 8.0 Hz, J = 9.2, 8.0, 8.0, 8.0 Hz), 3.37 (1H, dd, J = 9.9, 8.0 Hz), 3.78 (1H, dd, J = 9.9, 8.0 Hz), 4.41 (1H, dd, J = 9.2, 2.7 Hz), 7.37 (2H, d, J = 8.4 Hz), 7.76 (2H, d, J = 8.4 Hz), 8.04 (1H, br s); (***syn*-9**) δ 2.27 (1H, ddd, J = 13.5, 8.9, 7.4 Hz), 2.46 (3H, s), 2.51 (1H, ddd, J = 13.5, 8.2, 8.2 Hz), 2.62−2.76 (1H, m), 3.45 (1H, dd, J = 11.4, 10.4 Hz), 3.77 (1H, dd, J = 11.4, 8.6 Hz), 4.47 (1H, dd, J = 8.2, 7.4 Hz), 7.37 (2H, d, J = 8.4 Hz), 7.79 (2H, d, J = 8.4 Hz), 8.04 (1H, br s). ^{13}C NMR: (***anti*-9**) δ 21.6, 30.0, 41.6 (q, J_{CF} = 30 Hz), 47.1, 59.9, 125.7 (q, J_{CF} = 276 Hz), 127.5, 130.0, 133.8, 144.5, 175.8. ^{19}F NMR: (***anti*-9**) δ_F 90.9 (d, J_{FH} = 8 Hz); (***syn*-9**) δ_F 91.5 (d, J_{FH} = 8 Hz). Anal. Calcd for $C_{13}H_{14}F_3NO_4S$: C, 46.29; H, 4.18; N, 4.15. Found: C, 46.38; H, 4.25; N, 3.89.

(*S*)-4-Difluoromethylene-2-hydroxymethyl-1-(4-methylbenzenesulfonyl)pyrrolidine [(*S*)-10]. To a solution of **(*S*)-8a** (141 mg, 0.333 mmol) in CH_2Cl_2 (1.5 mL) and MeOH (0.15 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 98 mg, 0.43 mmol) at rt. After being stirred for 2 d, the reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (hexane−EtOAc, 2:1) to give **(*S*)-10** (92 mg, 91%) as a pale yellow liquid. $[\alpha]^{25}_D$ = +45.5 (*c* 1.0, $CHCl_3$). IR (neat): 3529, 2954, 2924, 2854, 1782, 1344, 1271, 1161 cm^{-1}. ^1H NMR: δ 2.23−2.31 (1H, m), 2.39 (1H, br d, J = 14.5 Hz), 2.45 (3H, s), 2.52 (1H, br s), 3.65 (1H, dd, J = 11.5, 5.8 Hz), 3.70 (1H, dd, J = 11.5, 4.7 Hz), 3.79−3.86 (1H, m), 3.96 (1H, br d, J = 14.1 Hz), 4.08 (1H, br d, J = 14.1 Hz), 7.35 (2H, d, J = 7.9 Hz), 7.73 (2H, d, J = 7.9 Hz). ^{13}C NMR: δ 21.5, 27.5, 47.5 (d, J_{CF} = 3 Hz), 61.8, 64.4, 84.9 (dd, J_{CF} = 23, 23 Hz), 127.5, 130.0, 133.7, 144.3, 149.9 (dd, J_{CF} = 283, 283 Hz). ^{19}F NMR: δ_F 71.7 (1F, ddd, J_{FF} = 54 Hz, J_{FH} = 3, 3 Hz), 74.4 (1F, dd, J_{FF} = 54 Hz, J_{FH} = 1 Hz). HRMS (FAB): calcd for $C_{13}H_{16}F_2NO_3S$ ([M + H]$^+$) 304.0820, found 304.0828. The ee value was determined to be 99% by HPLC

(33) The 2,4-*anti*/*syn* stereochemistry of the pyrrolidine ring was determined by a NOESY experiment on TBS protected prolinol **14** as a representative example. Cross peaks between the 2-proton and the 5α-proton and between the 5β-proton and the difluoromethyl proton were observed as shown below.



***syn*-14**

(*i*-PrOH−hexane, 1:10, retention time 12.9 min major peak, 10.9 min minor peak).

(*S*)-4-Difluoromethylene-1-(4-methylbenzenesulfonyl)proline [(*S*)-11]. To a solution of **(*S*)-10** (144 mg, 0.475 mmol) in CH_3CN (4.8 mL) and phosphate buffer (pH 7, 3.6 mL) were added 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 3.7 mg, 24 μmol) and $NaClO_2$ (80%; 70 mg, 0.62 mmol). The reaction mixture was stirred for 7 d at rt. After aqueous HCl (1 M, 2 mL) was added to the mixture, organic materials were extracted with Et_2O (10 mL × 4). The combined extracts were washed with aqueous Na_2CO_3 (10%, 10 mL × 2), and then the combined aqueous layer was acidified with concd aqueous HCl (2 mL). Organic materials were extracted by Et_2O (10 mL × 3). The combined extracts were washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, **(*S*)-11** (141 mg, 93%) was obtained as a colorless liquid. $[\alpha]^{25}_D = -13.7$ (*c* 1.0, $CHCl_3$). IR (neat): 3228, 2927, 2879, 1783, 1724, 1350, 1275, 1161, 1095, 1063, 771 cm^{-1}. ^1H NMR: δ 2.45 (3H, s), 2.70−2.75 (2H, m), 4.04−4.12 (2H, m), 4.53 (1H, ddd, J = 8.4, 4.1, 1.6 Hz), 7.35 (2H, d, J = 8.1 Hz), 7.62 (1H, br s), 7.75 (2H, d, J = 8.1 Hz). ^{13}C NMR: δ 21.5, 29.6, 46.5 (d, J_{CF} = 3 Hz), 60.2, 84.6 (dd, J_{CF} = 25, 25 Hz), 127.4, 130.0, 134.5, 144.4, 150.1 (dd, J_{CF} = 286, 286 Hz), 175.6. ^{19}F NMR: δ_F 73.1 (1F, d, J_{FF} = 52 Hz), 75.5 (1F, d, J_{FF} = 52 Hz). HRMS (FAB): calcd for $C_{13}H_{14}F_2NO_4S$ ($[M + H]^+$) 318.0613, found 318.0601. The ee value was determined to be 99% by HPLC (*i*-PrOH−hexane, 1:10, retention time 12.0 min major peak, 9.1 min minor peak).

Benzyl 4-(Difluoromethylene)pyrrolidine-2-carboxylate (16). After a solution of benzyl 4-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine-2-carboxylate (37 mg, 90 μmol), 1,5-dimethoxynaphthalene (8.8 mg, 47 μmol), and ascorbic acid (49 mg, 280 μmol) in H_2O (1.1 mL) and EtOH (19 mL) was degassed with argon, the solution was irradiated with high-pressure Hg lamp at rt for 2 h through a Pyrex tube. Aqueous HCl (1 M, 1 mL) was added, and the solvent was removed under reduced pressure. Aqueous HCl (1 M, 5 mL) was added to the residue, and the aqueous solution was washed with Et_2O (5 mL). After the aqueous layer was brought to alkaline pH with concd aqueous Na_2CO_3 (5 mL), organic materials were extracted by Et_2O (5 mL × 3). The combined extracts were washed with brine (5 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, **16** (8.0 mg, 35%) was obtained as a colorless liquid. IR (neat): 3035, 2925, 2856, 1783, 1743, 1265, 1219, 1186, 771 cm^{-1}. ^1H NMR: δ 1.92 (1H, br s), 2.58−2.64 (1H, m), 2.78−2.85 (1H, m), 3.56 (1H, br d, J = 13.7 Hz), 3.74 (1H, br d, J = 13.7 Hz), 3.93 (1H, dd, J = 7.6, 6.0 Hz), 5.18 (2H, s), 7.32−7.41 (5H, m). ^{13}C NMR: δ 30.3, 45.5, 60.3, 67.0, 88.0, 128.2, 128.5, 128.7, 135.4, 149.7 (dd, J_{CF} =128, 128 Hz), 173.3. ^{19}F NMR: δ_F 71.7 (1F, dq, J_{FF} = 59 Hz, J_{FH} = 3 Hz), 72.9 (1F, dq, J_{FF} = 59 Hz, J_{FH} = 3 Hz). HRMS (FAB): calcd for $C_{13}H_{14}F_2NO_2$ ($[M + H]^+$) 254.0993, found 254.0985.

***rel*-(2*R*,4*S*)-4-Difluoromethyl-2-hydroxymethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (*anti*-12).** To a solution of **10** (19.2 mg, 63 μmol) in $CHCl_3$ (5 mL) was added Pd/C (5%, 67 mg, 32 μmol). The mixture was stirred under H_2 (1 atm) at rt for 6 h. The mixture was filtered through a pad of Celite. Removal of the solvent under reduced pressure gave **12** (90% NMR yield, *anti*/*syn* = 79:21) as a pale yellow liquid. IR (neat): 3521, 2952, 2881, 1597, 1398, 1336, 1155, 1087, 1024, 665 cm^{-1}. ^1H NMR: δ 1.67 (1H, ddd, J = 12.9, 8.8, 8.8 Hz), 1.95−2.00 (1H, m), 2.46 (3H, s), 2.71 (1H, br s), 2.71−2.84 (1H, m), 3.16 (1H, dd, J = 10.1, 8.2 Hz), 3.61−3.73 (3H, m), 3.80 (1H, dd, J = 10.9, 2.9 Hz), 5.38 (1H, ddd, J_{HF} = 56.1, 56.1 Hz, J = 4.8 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.74 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 21.4, 28.5, 41.0 (t, J_{CF} = 8 Hz), 48.5 (t, J_{CF} = 4 Hz), 61.0, 65.2, 116.1 (t, J_{CF} = 240 Hz), 127.6, 129.9, 133.3, 144.2. ^{19}F NMR: δ_F 40.5 (1F, ddd, J_{FF} = 285 Hz, J_{FH} = 56, 14 Hz), 41.4 (1F, ddd, J_{FF} = 285 Hz, J_{FH} = 56, 12 Hz). HRMS (FAB): calcd for $C_{13}H_{18}F_2NO_3S$ ($[M + H]^+$) 306.0977, found 306.0966.

***rel*-(2*R*,4*S*)-4-Difluoromethyl-1-(4-methylbenzenesulfonyl)proline (*anti*-15).** To a solution of **12** (19.8 mg, 65 μmol, *anti*/*syn* = 79:21) in acetone (2 mL) were added a solution of aqueous $NaHCO_3$ (15%, 0.6 mL), NaBr (3.6 mg, 35 μmol), TEMPO (0.56 mg, 3.6 μmol), and trichloroisocyanuric acid (82 mg, 0.35 mmol). After the mixture was stirred for 3 h at rt, the reaction was quenched with H_2O (5 mL). Organic materials were extracted with Et_2O (5 mL × 3). The combined extracts were washed with aqueous NaOH (1 M, 5 mL × 3). The combined aqueous layer was brought to pH 3.0 with aqueous HCl (6 M) and extracted with Et_2O (30 mL × 3). After removal of the solvent under reduced pressure, **15** (19.8 mg, 96%, *anti*/*syn* = 79:21) was obtained as colorless crystals. IR (neat): 3534, 2954, 2924, 2852, 1732, 1340, 1159, 1090, 1034 cm^{-1}. ^1H NMR: δ 1.98 (1H, ddd, J = 13.3, 9.5, 9.2 Hz), 2.30 (1H, ddd, J = 13.3, 6.8, 2.8 Hz), 2.46 (3H, s), 2.81−2.93 (1H, m), 3.29 (1H, dd, J = 10.0, 8.2 Hz), 3.69 (1H, dd, J = 10.0, 8.0 Hz), 4.38 (1H, dd, J = 9.2, 2.8 Hz), 5.60 (1H, td, J_{HF} = 55.3 Hz, J = 4.4 Hz), 7.37 (2H, d, J = 8.5 Hz), 7.76 (2H, d, J = 8.5 Hz), 8.20 (1H, br s). ^{13}C NMR: δ 21.8, 30.2 (t, J_{CF} = 3 Hz), 41.7 (t, J_{CF} = 22 Hz), 47.4 (t, J_{CF} = 5 Hz), 60.2, 115.8 (t, J_{CF} = 241 Hz), 127.7, 130.2, 134.3, 144.6, 176.2. ^{19}F NMR: δ_F 40.2 (1F, ddd, J_{FF} = 287 Hz, J_{FH} = 55, 13 Hz), 41.0 (1F, ddd, J_{FF} = 287 Hz, J_{FH} = 55, 11 Hz). HRMS (FAB): calcd for $C_{13}H_{16}F_2NO_4S$ ($[M + H]^+$) 320.0768, found 320.0742.

2-[(*tert*-Butyldimethylsilyloxy)methyl]-4-difluoromethylene-1-(4-methylbenzenesulfonyl)pyrrolidine (13). To a solution of **10** (81 mg, 0.27 mmol) in CH_2Cl_2 (3 mL) were added *t*-$BuMe_2SiCl$ (61 mg, 0.41 mmol), NEt_3 (54 mg, 0.54 mmol), and 4-dimethylaminopyridine (DMAP, 10 mg, 0.08 mmol) at rt. The reaction mixture was stirred at rt for 3 h. The reaction was quenched with water (10 mL), and organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine (10 mL) 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 **13** (105 mg, 94%) as a colorless liquid. IR (neat): 2954, 2929, 2858, 1782, 1350, 1271, 1163, 1093, 837, 777, 665 cm^{-1}. ^1H NMR: δ 0.04 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 2.14−2.22 (1H, m), 2.44 (3H, s), 2.49 (1H, br d, J = 15.3 Hz), 3.56 (1H, dd, J = 10.1, 7.1 Hz), 3.75 (1H, dd, J = 10.1, 3.6 Hz), 3.92−3.98 (2H, m), 4.01 (1H, br d, J = 13.8 Hz), 7.32 (2H, d, J = 8.2 Hz), 7.72 (2H, d, J = 8.2 Hz). ^{13}C NMR: δ −5.6, −5.6, 18.1, 21.5, 25.7, 27.4, 47.2 (d, J_{CF} = 4 Hz), 61.1, 65.5, 86.1 (dd, J_{CF} = 26, 22 Hz), 127.3, 129.8, 135.1, 143.8, 149.9 (dd, J_{CF} = 284, 284 Hz). ^{19}F NMR: δ_F 70.7 (1F, ddddd, J_{FF} = 57 Hz, J_{FH} = 3, 3, 3, 3 Hz), 73.6 (1F, dd, J_{FF} = 56 Hz, J_{FH} = 2 Hz). HRMS (FAB): calcd for $C_{19}H_{30}F_2NO_3SSi$ ($[M + H]^+$) 418.1684, found 418.1683.

rel*-(2*R*,4*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-4-difluoromethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (14).** To a solution of **13** (75 mg, 0.18 mmol) in EtOH (3 mL) was added Pd/C (5%, 19 mg, 9.0 μmol). The mixture was stirred under H_2 (1 atm) at rt for 1 h. The mixture was filtered through a pad of Celite. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane−EtOAc, 5:1) to give **14** (73 mg, 98%, *anti*/*syn* = 11:89) as a colorless liquid. IR (neat): 2954, 2929, 2858, 1348, 1254, 1161, 1090, 1036, 835 cm^{-1}. ^1H NMR: (syn*-14**) δ 0.08 (6H, s), 0.89 (9H, s), 1.92 (1H, ddd, J = 13.4, 8.6, 6.1 Hz), 2.00 (1H, ddd, J = 13.4, 8.0, 8.0 Hz), 2.02−2.12 (1H, m), 2.44 (3H, s), 3.30 (1H, dd, J = 11.7, 8.6 Hz), 3.56 (1H, dd, J = 11.7, 7.5 Hz), 3.72−3.79 (2H, m), 3.84 (1H, dd, J = 9.9, 3.0 Hz), 5.69 (1H, ddd, J_{HF} = 56.3, 56.3 Hz, J = 5.6 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz); (***anti*-14**) δ 0.08 (6H, s), 0.89 (9H, s), 2.02−2.12 (2H, m), 2.44 (3H, s), 2.78−2.89 (1H, m), 3.11 (1H, dd, J = 9.7, 8.6 Hz), 3.66 (1H, dd, J = 9.7, 6.5 Hz), 3.72−3.79 (3H, m), 5.43 (1H, ddd, J_{HF} = 57.8, 57.8 Hz, J = 5.2 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz). ^{13}C NMR: (***syn*-14**) δ −5.5, −5.4, 18.2, 21.5, 25.8, 28.4 (dd, J_{CF} = 5, 3 Hz), 41.8 (t, J_{CF} = 22 Hz), 49.0 (dd, J_{CF} = 7, 4 Hz), 60.8, 65.8, 116.5 (t, J_{CF} = 241 Hz), 127.4, 129.9, 134.8, 143.8. ^{19}F

NMR: (***syn*-14**) δ_F 41.8 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 11 Hz), 42.9 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 12 Hz). HRMS (FAB): calcd for $C_{19}H_{32}F_2NO_3SSi$ ($[M + H]^+$) 420.1840, found 420.1853.

***rel*-(2*R*,4*R*)-4-Difluoromethyl-2-hydroxymethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (*syn*-12).** To a solution of **14** (86 mg, 0.20 mmol, *anti*/*syn* = 11:89) in THF (3 mL) was added TBAF (1 M in THF; 0.25 mL, 0.25 mmol) at rt. The reaction mixture was stirred at rt for 1 h. The reaction was quenched with water (10 mL), and organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine (10 mL) 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 **12** (56 mg, 90%, *anti*/*syn* = 11:89) as a colorless liquid. IR (neat): 3521, 2954, 2885, 1597, 1338, 1219, 1157, 1089, 1026, 771 cm^{-1}. ^1H NMR: δ 1.75−1.86 (1H, m), 1.93−2.12 (2H, m), 2.46 (3H, s), 2.89 (1H, br s), 3.39 (1H, dd, J = 11.8, 8.6 Hz), 3.58 (1H, dd, J = 11.8, 7.8 Hz), 3.61−3.73 (2H, m), 3.87 (1H, br d, J = 10.5 Hz), 5.69 (1H, ddd, J_{HF} = 56.2, 56.2 Hz, J = 5.4 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.74 (2H, d, J = 8.0 Hz). ^{13}C NMR: δ 21.5, 28.7, 41.0 (t, J_{CF} = 22 Hz), 49.2 (t, J_{CF} = 4 Hz), 61.8, 64.8, 116.2 (t, J_{CF} = 240 Hz), 127.5, 130.1, 133.6, 144.3. ^{19}F NMR: δ_F 41.7 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 11 Hz), 42.7 (1F, ddd, J_{FF} = 286 Hz, J_{FH} = 56, 12 Hz). HRMS (FAB): calcd for $C_{13}H_{18}F_2NO_3S$ ($[M + H]^+$) 306.0975, found 306.0978.

***rel*-(2*R*,4*R*)-4-Difluoromethyl-1-(4-methylbenzenesulfonyl)-proline (*syn*-15).** To a solution of **12** (54 mg, 0.18 mmol, *anti*/*syn* = 11:89) in acetone (2 mL) was added a solution of aqueous $NaHCO_3$ (15%, 0.6 mL), NaBr (4 mg, 0.03 mmol), and TEMPO (0.56 mg, 3.6 μmol) and then trichloroisocyanuric acid (82 mg, 0.35 mmol). After the mixture was stirred for 3 h at rt, the reaction was quenched with water (5 mL). Organic materials were extracted with Et_2O (5 mL × 3), and the combined extracts were washed with aqueous NaOH (1 M, 15 mL × 3). The combined aqueous layer was brought to pH 3.0 with aqueous HCl (6 M) and extracted with Et_2O (30 mL × 3). After removal of the solvent under reduced pressure, **15** (57 mg, 100%, *anti*/*syn* = 11:89) was obtained as a colorless crystal. IR (neat): 3546, 3220, 2964, 1733, 1340, 1219, 1161, 1035 cm^{-1}. ^1H NMR: δ 2.19 (1H, ddd, J = 13.5, 6.4, 6.1 Hz), 2.35 (1H, ddd, J = 13.5, 9.0, 8.8 Hz), 2.41−2.50 (1H, m), 2.46 (3H, s), 3.47 (1H, dd, J = 11.1, 6.5 Hz), 3.54 (1H, dd, J = 11.1, 7.6 Hz), 4.32 (1H, dd, J = 9.0, 6.1 Hz), 5.79 (1H, ddd, J_{HF} = 56.1, 56.1 Hz, J = 6.0 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.78 (2H, d, J = 8.0 Hz), 8.20 (1H, br s). ^{13}C NMR: δ 21.8, 30.4 (t, J_{CF} = 3 Hz), 42.3 (t, J_{CF} = 22 Hz), 48.3 (t, J_{CF} = 4 Hz), 60.0, 116.1 (t, J_{CF} = 240 Hz), 127.9, 130.3, 133.9, 144.8, 176.3. ^{19}F NMR: δ_F 40.9 (1F, ddd, J_{FF} = 287 Hz, J_{FH} = 56, 11 Hz), 42.3 (1F, ddd, J_{FF} = 287 Hz, J_{FH} = 56, 13 Hz). Anal. Calcd for $C_{13}H_{15}F_2NO_4S$: C, 48.90; H, 4.73; N, 4.39. Found: C, 48.99; H, 4.85; N, 4.12.

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Supporting Information Available: Experimental procedures and spectroscopic data of compounds **(*R*)-4a**, **4b**, **4c**, **(*S*)-5a**, **5b**, **5c**, **(*S*)-6a**, **6b**, **6c**, **(2*R*,4*S*)-7a**, **7b**, and **7d**; copies of ^1H spectra of compounds **4c**, **(*S*)-5a**, **5c**, **(*S*)-6a**, **(2*R*,4*S*)-7a**, **7c**, **(*S*)-8a**, **(*S*)-10**, **(*S*)-11**, ***anti*-12**, ***syn*-12**, **13**, **14**, ***anti*-15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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