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Stereoselective Synthesis of 3-Fluoro Azetidinones *via* the Condensation of 2-Fluoropropanethioate Lithium Enolate with Imines

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Abstract: *S*-Phenyl 2-fluoropropanethioate (**1**) was treated with lithium diisopropylamide in THF at -78 °C to give rise to the lithium enolate, which underwent stereoselective condensation with a variety of aldehyde imines (**2**) at room temperature to afford the corresponding *trans*-3-fluoro-3-methyl-2-azetidinone derivatives (**3**) in fair to good yields.

INTRODUCTION

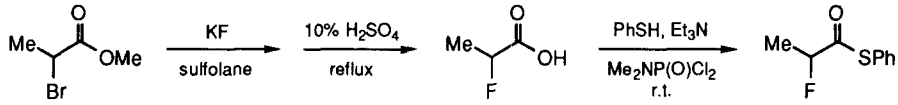
Since the discovery of the antibiotic activity of penicillin, thienamycin, and monobactams, a number of efforts have been made to develop efficient and stereoselective procedures for their preparations, many of which are based almost entirely upon the effective utilization of 2-azetidinone compounds as key intermediates.[1] According to the large volume of literature concerning with the synthesis of 2-azetidinones, the principal synthetic method for them is either the condensation reaction of ester enolates with imines[2] or the cycloaddition reaction of ketenes with imines.[3] The former ester enolate-imine condensation method has proved to be very useful for the construction, especially for diastereoselective or enantioselective construction, of the 2-azetidinone ring systems, as applied successfully to the synthesis of thienamycin or carbapenem antibiotics.[4]

In recent years, fluorine-containing 2-azetidinones have received increasing interest in the field of organic synthesis and bioorganic or biological chemistry, because they may be empolyed as building blocks for preparing fluorinated β-lactam antibiotics, carbohydrates, and amino acids, which often cause a unique and dramatic change in biological activities.[5] Although the literature has numerous reports on the synthesis of fluorine-containing 2-azetidinone derivatives,[6,7] only a few isolated examples deal with the preparation *via* the ester enolate-imine condensation method leading to 3-monofluorinated or 3,3-difluorinated 2-azetidinone compounds. For instance, Taguchi, *et al.* reported[6a] the synthesis of 3,3-difluoro-2-azetidinones by using the Reformatsky-type reaction of ethyl bromodifluoroacetate or methyl iododifluoroacetate with imines. Welch, *et al.* recently obtained the diastereomeric mixtures of 3-fluoro-2-azetidinone derivatives through the condensation reaction between the lithium enolate of 2,4,6-trimethylphenyl fluoroacetate and imines.[6b] Fujisawa, *et al.* demonstrated that the reaction of the triisopropoxytitanium enolate of *t*-butyl fluoroacetate with chiral imine proceeds in a highly stereoselective way to give optically active 3-fluoro-2-azetidinone.[6c]

As the control of stereochemistry is a central problem in organofluorine synthesis as well as in organic synthesis, it is of great importance to develop highly stereoselective methods for the synthesis of fluorinated compounds. In this paper, we would like to report that the lithium enolate of *S*-phenyl 2-fluoropropanethioate (**1**) reacts readily with a variety of aldehyde imines (**2**) at ambient temperature to produce stereoselectively the corresponding *trans*-3-fluoro-3-methyl-2-azetidinone derivatives (**3**) in fairly good yields.

RESULTS AND DISCUSSION

The starting thioester **1** was obtained according to such a three-step preparation as shown in Scheme 1. Thus, methyl 2-bromopropanoate was allowed to react with spray-dried potassium fluoride in tetramethylene sulfone (sulfolane) at 130 °C for 2.5 h, followed by distillation under reduced pressure to collect crude fluorinated methyl ester.[8,9] Hydrolysis of the crude ester with 10% sulfuric acid at reflux temperature for 1 h provided 2-fluoropropanoic acid in 52% overall yield. Thioesterification of this acid was readily made[10] by treating with benzenethiol and *N,N*-dimethylphosphoramidic dichloride[11] in the presence of triethylamine at room temperature for 2.5 h to give the desired *S*-phenyl thioester **1** in high yield.



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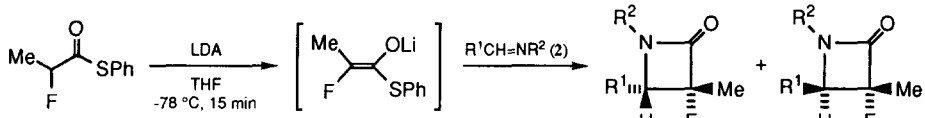
Scheme 1. Preparation of *S*-Phenyl 2-Fluoropropanethioate (**1**)

When the thus obtained thioester **1** was allowed to react with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78 °C for 15 min, followed by treatment with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) at the same temperature for 30 min, 1-(*t*-butyldimethylsilyl)oxy-2-fluoro-1-(phenylthio)-1-propene was obtained quantitatively as a mixture of the *E* and *Z* isomers (4 : 96). The stereochemistry of the predominant isomer was assigned as the *Z* configuration on the basis of relative comparison of its proton chemical shifts with those reported for the related fluorine-free ketene silyl acetals.[12] Thus, the intermediary lithium enolate of **1** was found to be generated stereoselectively with the *Z* configuration.[13]



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trans-**3** *cis*-**3**

Scheme 2. Condensation of the Lithium Enolate of **1** with Imines **2**

The condensation reaction of this enolate with *N*-benzylideneaniline (**2a**) (R^1 = R^2 = Ph) was first examined under various conditions, as shown in Scheme 2. Table 1 summarizes the results of these reactions. The enolate of **1** did not react with **2a** (1.0 equiv.) at low temperature (-78 °C), resulting in the quantitative recovery of the starting thioester (Entry 1). The reaction was not so much improved as expected even by use of

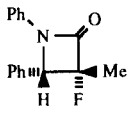
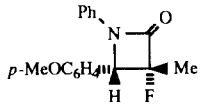
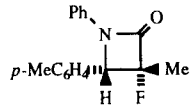
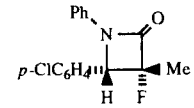
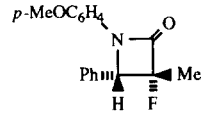
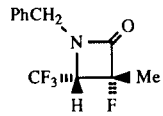
Table 1. Reaction of the Lithium Enolate of **1** with *N*-Benzylideneaniline (**2a**)

Entry	Imine **2a**/equiv.	Temp./°C	Time/h	Yield[a]/% of **3a**
1	1.0	-78	0.5	0
2	1.0	0	6.0	21
3	1.0	r.t.	4.0	53
4[b]	1.0	r.t.	4.0	23
5	1.0	r.t.	14.5	55
6	1.5	r.t.	4.0	73
7	1.5	r.t.	14.5	63
8	2.0	r.t.	14.5	61

[a] Yields refer to isolated product. [b] One equivalent of TMEDA was added prior to the reaction with **2a**.

higher reaction temperature (0 °C) and longer reaction period, *trans*-3-fluoro-3-methyl-1,4-diphenyl-2-azetidinone (**3a**) being produced only in 21% yield (Entry 2). The reaction performed at room temperature for 4.0 h (Entry 3) gave a 53% yield of **3a**, which was comparable to that obtained from the reaction at room temperature for 14.5 h (Entry 5). The addition of a coordinating solvent, such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA), was quite ineffective for the present reaction (Entry 4). The use of 1.5 equiv. of imine **2a** substantially increased the yield of the product. On treating the lithium enolate of **1** with 1.5 equiv. of **2a** in THF at ambient temperature for 4 h, the corresponding 2-azetidinone **3a** was given in 73% yield (Entry 6).

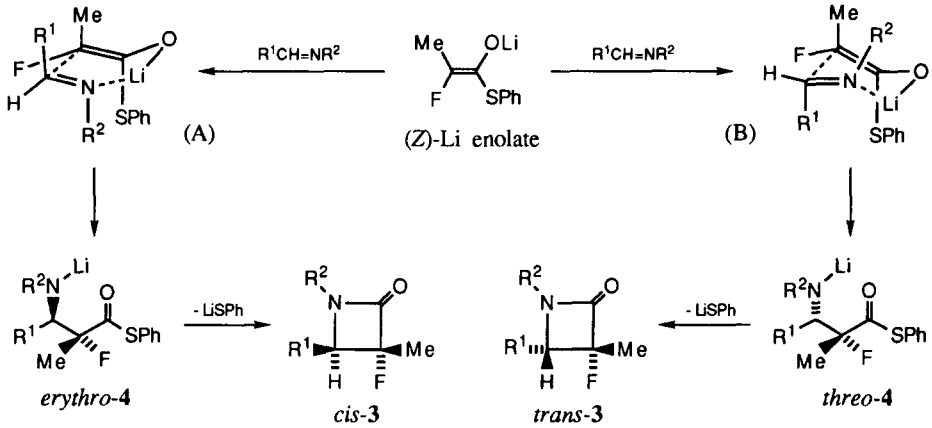
Table 2. Reaction of the Lithium Enolate of **1** with Various Imines **2**

Entry	Imine (**2**)		Product (**3**)		Yield[a] %	Isomer ratio[b] *trans* : *cis*
1	PhCH=NPh	(**2a**)		(**3a**)	73	>97 : <3
2	*p*-$MeOC_6H_4CH$=NPh	(**2b**)		(**3b**)	55	>97 : <3
3	*p*-MeC_6H_4CH=NPh	(**2c**)		(**3c**)	58	>97 : <3
4	*p*-ClC_6H_4CH=NPh	(**2d**)		(**3d**)	76	97 : 3
5	PhCH=NC_6H_4OMe-*p*	(**2e**)		(**3e**)	44	>97 : <3
6	CF_3CH=NCH_2Ph	(**2f**)		(**3f**)	44	>97 : <3

[a] Yields are of pure products isolated by column chromatography. [b] Determined by ^{19}F NMR.

Thus, the present reaction conditions were applied to the condensation reactions with other aldehyde imines **2** to synthesize a variety of 2-azetidinone derivatives **3**. Table 2 compiles the yields and isomer ratios of the products, together with their structures of the preferentially formed isomer. Various imines **2b-e** derived from aromatic aldehydes underwent the condensation with the lithium enolate of **1** leading to the corresponding 2-azetidinones **3b-e** in fair to good yields. Particularly, the imines carrying an electron-donating substituent, **2b** and **2c**, gave relatively lower yields of the products (Entries 2 and 3 in Table 2). This is probably due to decreased electrophilicity of their imino functionality. The imine prepared from an aliphatic aldehyde, such as *N*-butylidenepropylamine, failed to react at all. In contrast, the imine from trifluoroacetaldehyde **2f** participated in the reaction with the enolate of **1** to afford 4-trifluoromethylated 2-azetidinone **3f** in 44% yield (Entry 6 in Table 2).

Significantly, all the condensation reactions led to the exclusive formation of the *trans*-isomers[14] of **3**. No *cis*-isomers were present in amounts detectable by ^{19}F NMR, except for the reaction of **2d**. It should be noted, to our knowledge, that these reactions provide us with a precious example of the diastereoselective synthesis of fluorinated 2-azetidinones *via* an ester enolate-imine condensation method. The stereochemical assignment of **3** was made straightforward by ^{1}H and ^{19}F NMR. The spectra of 2-azetidinones **3a-f** showed vicinal H-F couplings in a range of 2.6-4.0 Hz, which are in good agreement with those reported[6b] recently for *trans*-3-fluoro-2-azetidinone compounds. In addition, the two isomers of 4-(4-chlorophenyl)-3-fluoro-3-methyl-1-phenyl-2-azetidinone (**3d**) could be isolated in the reaction of the lithium enolate with **2d**, their configurations being determined unambiguously; the major isomer bearing a vicinal H-F coupling of 3.6 Hz was assigned to be *trans*, while the minor isomer having a coupling of 12.0 Hz was determined to be *cis*.



Scheme 3. Possible Mechanism for the Formation of **3**

The formation of the 2-azetidinone ring system from an ester enolate and an imine is generally assumed to be multistage. The present reaction using the thioester enolate can also be explained by a quite analogous mechanism (Scheme 3). Thus, the first step, the aldol-type addition of the enolate to the imine **2**, gives rise to an acyclic aldolate-like β-amino thioester intermediate **4**. In the second step, this intermediate may undergo ring-closure followed by elimination of the phenylthio group to furnish the azetidinone product **3**. During the C-C bond formation in the addition step, two new stereogenic centers are formed and the stereochemistry of the final product is determined. Several reports[15] disclose that this addition step may be reversible and thus loss of stereoselectivity takes place *via* a retro-aldolization process. However, occurrence of such a process seems to be unlikely in the present reaction, because our failure to detect the intermediately formed β-amino thioesters **4** strongly suggests that the first step is much slower than the second step, and is irreversible. Another possibility is considered that an isomerization between the *E* and *Z* enolates results in decreasing or reversing the stereoselectivity of the reaction. But it may be ruled out by the fact that treatment of the lithium enolate of **1** with TBSOTf, after being left for 1-2 h at room temperature, gave a 4 : 96 mixture of the *E* and *Z* isomers of the silylated ketene acetal.

Keeping in mind these results combined with the *Z* configuration of the enolate of **1** as well as the *E* configuration[16] of most imines, we assume that the addition reaction is likely to proceed through a rigid cyclic chair- or boat-like transition state[17] with coordination of the imine **2** to the lithium ion of the enolate, as shown in Scheme 3. In the boat-like transition state (A), leading to the formation of the *cis*-2-azetidinone **3** *via erythro*-aldolate[18] intermediate **4**, an important 1,2-eclipsed nonbonded interaction can be observed between the methyl group of the enolate and the R^1 group of **2**. On the other hand, the chair-like transition state

(B) will scarcely have such destabilizing interactions and, therefore, is energetically more favorable than the transition state (A). Thus, the addition reaction between the enolate and imine **2** may occur through the chair-like transition state (B) to produce preferentially the *trans*-2-azetidinone **3**.

EXPERIMENTAL SECTION

General methods and materials. Melting points were obtained on a Shimadzu MM-2 micro melting point determination apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrophotometer. ^{1}H NMR spectra were measured with Hitachi R-24B (60 MHz) NMR and/or General Electric QE-300 (300 MHz) FT-NMR spectrometers in a $CDCl_3$ solution with tetramethylsilane as an internal reference. A Hitachi R-24F (56.466 MHz) NMR spectrometer was used for determining ^{19}F NMR spectra in a $CDCl_3$ solution with external CF_3COOH. Proton and fluorine chemical shifts, downfield from the corresponding references, are expressed positive in parts per million (ppm). Mass spectra (MS) were taken on a Hitachi M-80 or a Shimadzu QP-1000 GC mass spectrometer operating at an ionization potential of 70 eV. Column chroma-tography was carried out on silica gel C-200 (100-200 mesh, Wako Pure Chemical Industries, Tokyo) with the indicated solvents. All reactions were performed under an atmosphere of dry argon. THF and 1,2-di-methoxyethane were distilled from lithium aluminum hydride or benzophenone ketyl. Other solvents were freshly distilled prior to use. Aldehydes, except 4-chlorobenzaldehyde, were distilled (or vacuum-distilled) from calcium hydride and stored under argon. 4-Chlorobenzaldehyde was purified by recrystallization from hexane. *N,N*-Dimethylphosphoramidic dichloride[11] was commercially available from Tokyo Chemical Industry Co., Ltd. A 1.6 *M* hexane solution of butyllithium was purchased from Aldrich Chemical Co., Inc. All chemicals are of reagent grade and, if necessary, were purified by a conventional manner before use.

Preparation of 2-fluoropropanoic acid. In a three-necked flask, equipped with a magnetic stirrer, a thermometer, and a still head for distillation, were placed methyl 2-bromopropanoate (41.75 g, 250 mmol), spray-dried potassium fluoride (21.46 g, 370 mmol), and sulfolane (75 mL). The mixture was heated with stirring at 130 °C for 2.5 h, followed by distillation under the pressure of 50-100 mmHg at 130-150 °C to collect crude methyl 2-fluoropropanoate (23.02 g). The crude ester was mixed with 10% sulfuric acid (500 mL) and the mixture was refluxed for 1 h. After being cooled to room temperature, this mixture was made saturated with sodium chloride and then was subjected to extraction with diethyl ether (50 mL x 10). The ethereal extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated to leave a residual oil, which was distilled under reduced pressure to give pure 2-fluoropropanoic acid (11.96 g) in 52% overall yield. B.p. 86.0-87.0 °C (35 mmHg); IR (film) 3680-2783 (br s), 3003 (s), 2950 (m), 1740 (vs), 1470 (m), 1457 (m), 1380 (m), 1240 (m), 1125 (s), 1100 (s), 1049 (m), 826 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (dd, J = 7.3 and 23.0 Hz, 3H), 5.01 (dq, J = 48.0 and 7.3 Hz, 1H), 11.57 (s, 1H); ^{19}F NMR ($CDCl_3$) δ -106.0 (dq, J = 48.0 and 23.0 Hz, 1F).

Preparation of S-phenyl 2-fluoropropanethioate (1). To a stirred solution of 2-fluoropropanoic acid (1.85 g, 20 mmol) in 1,2-dimethoxyethane (110 mL) were added successively triethylamine (4.85 g, 48 mmol), *N,N*-dimethylphosphoramidic dichloride (3.89 g, 24 mmol), and benzenethiol (2.64 g, 24 mmol) at such a rate that the reaction temperature did not rise above 10 °C. After stirring at ambient temperature for 2.5 h, the mixture was poured into a cold 5% HCl solution and was extracted with chloroform (70 mL x 4). The organic extracts were dried over sodium sulfate, followed by filtration and concentration. The residue was chromatophraphed on a silica-gel column using hexane and benzene as eluents to afford *S*-phenyl 2-fluoropropanethioate (**1**) in 84% yield. M.p. 44.2-45.0 °C; IR (KBr) 3057 (w), 2937 (w), 1704 (vs), 1584 (w), 1482 (s), 1444 (s), 1373 (m), 1319 (m), 1148 (s), 1086 (s), 1068 (s), 1020 (m), 976 (vs), 870 (s), 743 (vs), 706

(s), 686 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (dd, J = 6.8 and 23.6 Hz, 3H), 5.03 (dq, J = 47.8 and 6.8 Hz, 1H), 7.32 (s, 5H); ^{19}F NMR ($CDCl_3$) δ -114.5 (dq, J = 47.8 and 23.6 Hz, 1F); MS *m/z* (rel. intensity) 184 (M^+, 45), 110 (100).

Preparation of imines (2). *N*-Benzylideneaniline (**2a**), *N*-(4-methoxybenzylidene)aniline (**2b**), *N*-(4-methylbenzylidene)aniline (**2c**), *N*-(4-chlorobenzylidene)aniline (**2d**), *N*-benzylidene-4-methoxyaniline (**2e**), *N*-(2,2,2-trifluoroethylidene)benzylamine (**2f**), and *N*-butylidenepropylamine were prepared according to the literature method.[19]

Reaction of the lithium enolate of S-phenyl 2-fluoropropanethioate (1) with t-butyldimethylsilyl trifluoromethanesulfonate. Lithium diisopropylamide was prepared by the reaction of diisopropylamine (0.222 g, 2.2 mmol) with a 1.6 *M* hexane solution of butyllithium (1.38 mL, 2.2 mmol) in THF (5.5 mL) at 0 °C for 0.5 h. To this solution was dropwise added a solution of **1** (0.368 g, 2.0 mmol) in THF (1 mL) at -78 °C. The mixture was stirred for 15 min at -78 °C and then TBSOTf (1.109 g, 4.2 mmol) was added to it. After stirring at -78 °C for 0.5 h, the reaction was quenched with an aqueous ammonium chloride solution and the resulting mixture was extracted with diethyl ether (25 mL x 4). The extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Thorough removal of volatile materials from the residue provided 1-(*t*-butyldimethylsilyl)oxy-2-fluoro-1-(phenylthio)-1-propene (0.584 g) quantitatively in an almost pure form. The isomer ratio of this silylated product was measured by ^{19}F and ^1H NMR as $E : Z$ = 4 : 96. IR (film) 3056 (w), 2954 (s), 2923 (s), 2858 (m), 1588 (w), 1485 (m), 1467 (m), 1446 (m), 1252 (s), 1191 (vs), 1172 (vs), 1088 (m), 1024 (m), 852 (vs), 840 (vs), 781 (s), 736 (s), 685 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 6H), 0.89 (s, 9H), 2.09 (d, J = 15.8 Hz, 3H) for the *Z* isomer, 2.14 (d, J = 16.2 Hz, 3H) for the *E* isomer, 7.18 (s, 5H); ^{19}F NMR ($CDCl_3$) δ -27.0 (d, J = 16.2 Hz, 1F) for the *E* isomer, -38.2 (d, J = 15.8 Hz, 1F) for the *Z* isomer.

Reaction of the lithium enolate of S-phenyl 2-fluoropropanethioate (1) with various imines (2). The reaction of the lithium enolate of **1** with *N*-benzylideneaniline (**2a**) was described as the typical procedure. To a THF solution of lithium diisopropylamide (2.2 mmol) was gradually added a solution of **1** (0.368 g, 2.0 mmol) in THF (1 mL) at -78 °C under argon. After stirring for 15 min at the same temperature, a solution of **2a** (0.543 g, 3.0 mmol) in THF (1 mL) was dropwise added to the reaction mixture. The whole was stirred for 4 h at room temperature and then poured into a cold aqueous ammonium chloride solution. The resultant mixture was extracted with diethyl ether (25 mL x 3) and with chloroform (25 mL x 2). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with hexane-benzene (1:2) and benzene to furnish analytically pure product **3a** (0.373 g) in 73% yield.

trans-3-Fluoro-3-methyl-1,4-diphenyl-2-azetidinone (3a). M.p. 154.3-154.7 °C; IR (KBr) 3032 (w), 2988 (w), 1744 (vs), 1600 (m), 1498 (s), 1460 (m), 1391 (s), 1366 (m), 1206 (m), 1149 (m), 1114 (s), 1080 (w), 1050 (m), 1027 (w), 960 (w), 898 (w), 843 (w), 825 (w), 766 (m), 750 (s), 683 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77 (d, J = 22.0 Hz, 3H), 4.97 (d, J = 3.6 Hz, 1H), 7.0-7.4 (m, 5H), 7.31 (s, 5H); ^{19}F NMR ($CDCl_3$) δ -82.5 (dq, J = 3.6 and 22.0 Hz, 1F); MS *m/z* (rel. intensity) 255 (M^+, 0.9), 136 (100). HRMS (EI) Found: *m/z* 255.1068. Calcd for $C_{16}H_{14}FNO$: M, 255.1060.

trans-3-Fluoro-4-(4-methoxyphenyl)-3-methyl-1-phenyl-2-azetidinone (3b). Eluted with hexane-ethyl acetate (5:1); 55% yield; m.p. 111.7-113.2 °C; IR (KBr) 3006 (w), 2973 (w), 2925 (w), 2845 (w), 1753 (vs), 1618 (s), 1600 (s), 1587 (m), 1500 (vs), 1469 (m), 1452 (m), 1425 (w), 1385 (vs), 1339 (m), 1308 (s), 1293 (s), 1251 (vs), 1215 (m), 1203 (m), 1172 (s), 1124 (vs), 1083 (m), 1053 (w), 1020 (s), 954 (m), 840 (s), 816 (s), 785 (m), 757 (vs), 740 (m), 683 (s), 670 (w), 650 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (d, J = 21.8 Hz,

3H), 3.72 (s, 3H), 4.89 (d, J = 4.0 Hz, 1H), 6.80 (ABq, J = 9.2 Hz, 2H), 7.0-7.3 (m, 2H and 5H); ^{19}F NMR ($CDCl_3$) δ -83.0 (dq, J = 4.0 and 21.8 Hz, 1F); MS *m/e* (rel. intensity) 285 (M^+, 1.8), 166 (100). HRMS (EI) Found: *m/z* 285.1164. Calcd for $C_{17}H_{16}FNO_2$: M, 285.1165.

trans-3-Fluoro-3-methyl-4-(4-methylphenyl)-1-phenyl-2-azetidinone (3c). Eluted with hexane-ethyl acetate (10:1); 58% yield; m.p. 138.2-139.4 °C; IR (KBr) 3030 (w), 2973 (m), 2918 (m), 2857 (w), 1740 (vs), 1601 (s), 1492 (s), 1465 (m), 1410 (w), 1376 (vs), 1311 (m), 1300 (m), 1206 (m), 1180 (m), 1160 (s), 1117 (s), 1077 (s), 1049 (m), 806 (s), 768 (m), 751 (vs), 731 (s), 683 (s), 651 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (d, J = 22.0 Hz, 3H), 2.32 (s, 3H), 4.93 (d, J = 2.6 Hz, 1H), 7.14 (s, 4H and 5H); ^{19}F NMR ($CDCl_3$) δ -82.6 (dq, J = 2.6 and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 269 (M^+, 4.2), 150 (100). HRMS (EI) Found: *m/z* 269.1200. Calcd for $C_{17}H_{16}FNO$: M, 269.1216.

trans-4-(4-Chlorophenyl)-3-fluoro-3-methyl-1-phenyl-2-azetidinone (3d). Eluted with hexane-benzene (1:2) and benzene; 76% yield; m.p. 153.9-154.9 °C; IR (KBr) 3032 (w), 2978 (w), 1748 (vs), 1600 (s), 1492 (s), 1467 (m), 1416 (m), 1377 (vs), 1297 (w), 1205 (m), 1161 (m), 1112 (s), 1083 (s), 1057 (m), 1014 (m), 850 (m), 806 (s), 789 (m), 751 (vs), 733 (s), 685 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.69 (d, J = 22.0 Hz, 3H), 4.97 (d, J = 3.6 Hz, 1H), 7.2-7.3 (m, 4H and 5H); ^{19}F NMR ($CDCl_3$) δ -82.4 (dq, J = 3.6 and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 291 (M^++2, 1.7), 289 (M^+, 5.2), 170 (100). HRMS (EI) Found: *m/z* 289.0668. Calcd for $C_{16}H_{13}ClFNO$: M, 289.0671.

cis-4-(4-Chlorophenyl)-3-fluoro-3-methyl-1-phenyl-2-azetidinone (3d). Eluted with hexane-benzene (1:2); ^{1}H NMR ($CDCl_3$) δ 1.06 (d, J = 23.6 Hz, 3H), 5.12 (d, J = 12.0 Hz, 1H), 7.2-7.3 (m, 4H and 5H); ^{19}F NMR ($CDCl_3$) δ -71.8 (dq, J = 12.0 and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 291 (M^++2, 1.7), 289 (M^+, 5.2), 170 (100).

trans-3-Fluoro-1-(4-methoxyphenyl)-3-methyl-4-phenyl-2-azetidinone (3e). Eluted with hexane-ethyl acetate (5:1); 44% yield; m.p. 147.2-148.4 °C; IR (KBr) 3062 (w), 3017 (w), 2968 (w), 2930 (w), 2835 (w), 1742 (vs), 1593 (w), 1518 (s), 1450 (s), 1403 (m), 1368 (m), 1322 (w), 1306 (s), 1250 (vs), 1212 (s), 1164 (s), 1120 (vs), 1031 (vs), 962 (m), 843 (vs), 829 (s), 808 (vs), 767 (m), 700 (s), 667 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.77 (d, J = 22.0 Hz, 3H), 3.36 (s, 3H), 4.90 (d, J = 3.4 Hz, 1H), 6.69 and 7.18 (ABq, J = 8.4 and 8.4 Hz, 2H and 2H), 7.26 (s, 5H); ^{19}F NMR ($CDCl_3$) δ -82.3 (dq, J = 3.4 and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 285 (M^+, 10), 149 (100). HRMS (EI) Found: *m/z* 285.1165. Calcd for $C_{17}H_{16}FNO_2$: M, 285.1166.

trans-1-Benzyl-3-fluoro-3-methyl-4-(trifluoromethyl)-2-azetidinone (3f). Eluted with hexane-chloroform (1:1); 44% yield; IR (film) 3053 (w), 3011 (w), 2975 (w), 2922 (w), 1780 (vs), 1601 (w), 1583 (w), 1496 (w), 1451 (m), 1440 (m), 1400 (vs), 1380 (s), 1350 (m), 1289 (vs), 1175 (vs), 1111 (s), 1084 (s), 1070 (s), 952 (m), 940 (m), 860 (m), 831 (m), 735 (m), 694 (vs), 666 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (d, J = 22.0 Hz, 3H), 3.65 (dq, J = 3.0 and 5.8 Hz, 1H), 3.96 (d, J = 13.4 Hz, 1H), 4.71 (d, J = 13.4 Hz, 1H), 7.0-7.5 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 8.0 (dd, J = 5.8 and 13.5 Hz, 3F), -85.9 (dqq, J = 3.0, 13.5, and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 261 (M^+, tr), 91 (100). HRMS (CI) Found: *m/z* 262.0848. Calcd for $C_{12}H_{11}F_4NO$: M+H, 262.0855.

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