New Antifungal 1,2,4-Triazoles with Difluoro(substituted sulfonyl)methyl Moiety

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New 1,2,4-triazoles (2) having a difluoro(substituted sulfonyl)methyl moiety were designed and synthesized *via* α,α-difluoro-α-(substituted thio)acetophenones (3). Compounds (2) showed potent antifungal activities against *C. albicans*, *C. krusei*, *A. flavus* and *A. fumigatus in vitro* and against *C. albicans in vivo* for oral and i.v. administrations. Especially, (−)-2a, (−)-2b and (−)-2d showed potent antifungal activities.

Key words antifungal; 1,2,4-triazole; difluoro(substituted sulfonyl)methyl derivative

In our previous paper,[1] we reported the preparation of the 1,2,4-triazole derivatives (**1**) with difluoro(heteroaryl)methyl moiety and their antifungal activities. The introduction of fluorine atoms enhanced their antifungal activities *in vitro* and some of them showed superior activities compared to those of fluconazole (FLCZ) and itraconazole (ITCZ) against *Candida albicans* (*C. albicans*), *Candida Krusei* (*C. Krusei*), *Trichophyton mentagrophytes* (*T. mentagrophytes*), and *Trichophyton rubrum* (*T. rubrum*), and equal to those of ITCZ against *Aspergillus fumigatus* (*A. fumigatus*) and *Aspergillus flavus* (*A. flavus*). The antifungal azole, which has a sulfonyl or sulfenyl moiety such as Sch42427[2] and R-102557,[3] were developed and showed excellent antifungal activities *in vivo.* We also reported that SSY726,[4] which has a sulfone moiety, showed excellent antifungal activities against *Candida* species *in vivo.*

Therefore, we designed new 1,2,4-triazole derivatives (**2**) with the difluoro(substituted sulfonyl)methyl moiety. In this paper, we describe the preparation of compounds (**2**) *via* key intermediates (**3**) and their antifungal activities.

Chemistry The key intermediates (**3**) were prepared by three routes. One route is the fluorination of acetophenones (**4**) by electrophilic fluorinating reagents (route A). The second route is the reaction of ethyl 2,2-difluoro-2-(substituted thio)acetate (**6**) with phenyllithiums (route B), and the third route is the reaction of α-chloro-α,α-difluoroacetophenone with mercaptans (route C).

3a—**e** and **3g**—**l** were prepared from the corresponding acetophenones (**5**) by route A as our previous paper.[5] However, the difluorination of **5n** (R=C_6H_5) and **5o** (R=4-CH_3–C_6H_4) did not proceed completely and a decomposition

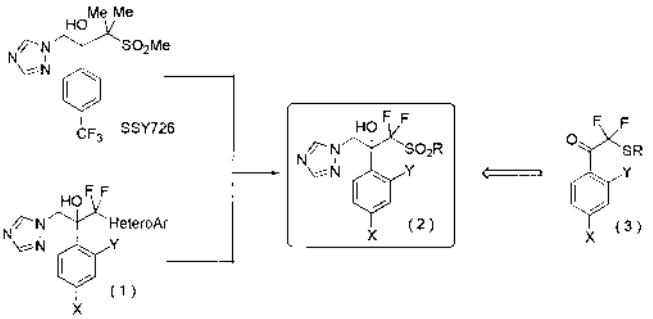
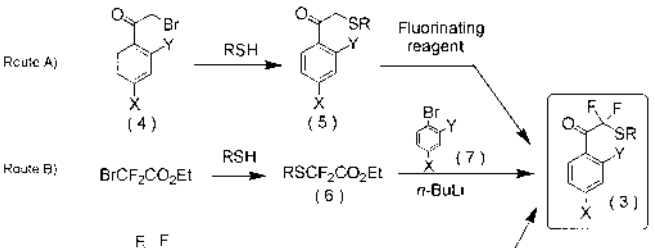


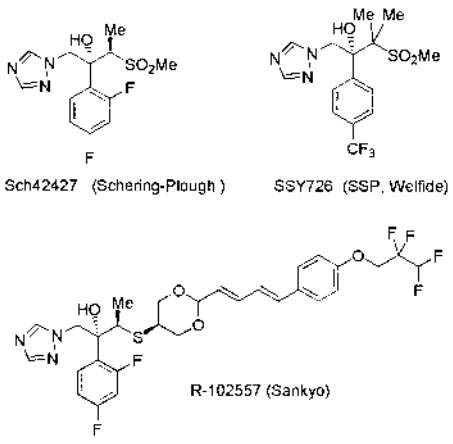
Chart 1



	X	Y	R
a	F	F	Me
b	F	F	Et
c	F	F	*n*-Pr
d	F	F	*cyclo*-Pr
e	F	F	*n*-Bu
f	F	F	*tert*-Bu
g	F	F	*n*-Pen
h	H	H	Me
i	F	H	Me

	X	Y	R
j	CF_3	H	Me
k	Cl	Cl	Me
l	F	F	$AcOCH_2CH_2$
m	F	F	$HOCH_2CH_2$
n	F	F	C_6H_5
o	F	F	4-CH_3-C_6H_4
p	F	F	$C_6H_5CH_2$
q	F	F	4-CH_3O-$C_6H_4CH_2$

Chart 2



Sch42427 (Schering-Plough) SSY726 (SSP, Welfide)

R-102557 (Sankyo)

Fig. 1

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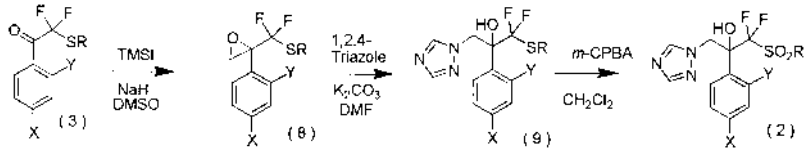
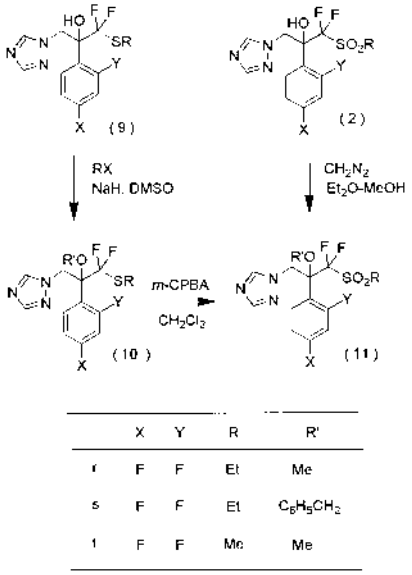


Chart 3



	X	Y	R	R'
r	F	F	Et	Me
s	F	F	Et	$C_6H_5CH_2$
t	F	F	Me	Me

Chart 4

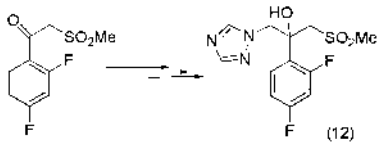


Chart 5

reaction was competed. The fluorination of **5f**, **5p** and **5q** did not proceed because of their degradation. Therefore, **3f** and **3n**—**q** were prepared from ethyl difluoro(substituted thio)acetate (**6**) by route B. **3h** was also prepared by route C, but attempt to prepare **3a** from route C by the methylthiolation of α-chloro-α,α-2′,4′-tetrafluoroacetophenone[6] was failed to give a complicated product, because the substitution reaction of the aromatic ring at the 2 and/or 4 position competed.

Compound **2** was prepared from the key intermediates (**3**) as shown in Chart 3.[7]

Compound **2m** was prepared from **9l** by hydrolysis followed by oxidation.

Compounds **10r** and **10s** were prepared from **9b** by alkylation. Also compounds **11r** and **11s** were prepared from **10r** and **10s** by oxidation, respectively. Compound **2a** was easily methylated by diazomethane to afford **11t** (Chart 4), because the acidity of the hydroxy proton is relatively high due to the strong electron withdrawing effect of the neighboring fluorine atoms.

A desfluoro analog of **2a** (**12**)[8] was prepared owing to comparing the activities.

Antifungal Activities The synthesized 1,2,4-triazole derivatives containing the difluoro(substituted sulfonyl)methyl moiety (**2a**—**q**, **11r**—**t**) and **12** were screened for their *in vitro* activities against *C. albicans*, *C. krusei*, *A. fumigatus* and *A. flavus*, and compared with those of FLCZ and ITCZ. The minimum inhibitory concentrations (MICs) are shown in Table 1.

The introduction of a bulky *tert*-Bu group (**2f**) or a hydroxy group into the ethyl group (**2m**) decrease the antifungal activities *in vitro.* The alkylation of the hydroxy group (**11r**—**t**) decreased the antifungal activities *in vitro.*

Table 1. Antifungal Activities of Compounds **2**, **11**, **12**, FLCZ and ITCZ *in Vitro*

Compounds	MIC (μg/ml)			
	C. albicans ATCC 90028	*C. krusei* ATCC 6258	*A. flavus* IFM 41935	*A. fumigatus* IFM 40808
2a	0.25	8	8	8
(−)-**2a**	0.125	4	4	4
(+)-**2a**	>64	>64	>64	>64
2b	0.125	1	4	4
(−)-**2b**	0.063	0.5	2	2
(+)-**2b**	>64	>64	>64	>64
2c	0.063	0.5	4	4
2d	0.125	2	4	4
(−)-**2d**	0.063	1	1	2
(+)-**2d**	>64	>64	>64	>64
2e	0.063	0.5	4	8
2f	2	>8	64	32
2g	0.031	0.5	4	8
2h	2	>64	>64	>64
2i	0.5	64	64	>64
(−)-**2i**	0.25	32	32	64
(+)-**2i**	>64	>64	>64	>64
2j	0.25	32	>64	>64
(−)-**2j**	0.125	16	>64	>64
(+)-**2j**	>64	>64	>64	>64
2k	0.25	2	8	32
(−)-**2k**	0.125	2	4	16
(+)-**2k**	>64	>64	>64	>64
2m	1	64	>64	>64
2n	1	16	>64	32
2o	0.063	4	8	1
2p	0.25	8	4	8
2q	0.125	2	4	4
11r	0.5	>64	64	>64
11s	>64	>64	>64	>64
11t	4	>64	>64	>64
12	8	>64	>64	>64
FLCZ	0.25	32	>64	>64
ITCZ	0.031	0.25	0.25	0.25

Compounds **2**, **12** and FLCZ, except for **2m**, were tested *in vivo* against *C. albicans* at the 4 times oral administrations after infection in Table 2.

The introduction of fluorine atoms enhanced the antifungal activities *in vitro* and *in vivo* (**2a**, **12**).

As phenyl substituents, the 2,4-difluoro (**2a**) and 2,4-dichloro (**2k**) derivatives showed superior activity to the un-

Table 2. *In Vivo* Antifungal Activities of Compounds **2**, **12** and FLCZ against *C. albicans* at the 4 Times Oral Administrations after Infection

Compounds	Dose (mg/kg)	Mean survival days (mean±S.D.)	No. of survivors on day 14/ tested mice
2a	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	5/5
	0.313	12.2±1.6***	2/5
(−)-**2a**	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	5/5
	0.313	13.8±0.4***	4/5
2b	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	4/5
	0.313	9.6±2.3***	0/5
(−)-**2b**	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	5/5
	0.313	11.4±2.4***	0/5
2c	5	14.0±0.0***	5/5
	1.25	12.6±1.9***	2/5
	0.313	3.8±0.8	0/5
2d	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	4/5
	0.313	13.2±1.8***	3/5
(−)-**2d**	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	5/5
	0.313	13.6±0.5***	2/5
2e	5	13.4±1.3***	4/5
	1.25	10.8±1.9***	1/5
	0.313	5.6±1.9	0/5
2f	5	11.4±2.4***	2/5
	1.25	8.8±3.2***	0/5
	0.313	3.8±0.8	0/5
2g	5	11.4±3.2**	2/5
	1.25	5.8±1.3	0/5
	0.313	5.0±2.5	0/5
2h	5	8.8±0.8***	0/5
	1.25	6.4±1.3**	0/5
2i	5	13.8±0.4***	3/5
	1.25	12.4±1.5***	1/5
	0.313	8.4±1.1***	0/5
2j	5	13.2±1.1***	3/5
	1.25	12.0±1.2***	0/5
	0.313	6.0±2.4*	0/5
2k	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	5/5
	0.313	10.2±2.4***	1/5
2n	5	5.0±1.6	0/5
2o	5	3.6±0.5	0/5
2p	5	4.6±1.5	0/5
2q	5	4.8±1.1	0/5
12	5	8.0±1.9**	0/5
FLCZ	5	13.0±1.2***	0/5
	1.25	10.6±2.3***	0/5
	0.313	6.2±1.8**	0/5
Control		3.4±0.6	0/10

Significantly different from the control by Kaplan Meire method (Cox mantel test). ***; $p<0.001$, **; $p<0.01$, *; $p<0.05$.

substituted (**2h**), 4-fluoro (**2i**), and 4-trifluoromethyl (**2j**) derivatives *in vitro* and *in vivo.* As substituent for R, the *in vitro* activities were increased in the order Me (**2a**)<Et (**2b**)<*n*-Pr (**2c**)<*n*-Bu (**2e**)<*n*-Pen (**2g**), but the *in vivo* activities were decreased in order Me (**2a**)≧Et (**2b**)>*n*-Pr (**2c**)>*n*-Bu (**2e**)>*n*-Pen (**2g**). We presume that the reason why the antifungal activities decrease according to alkyl chain length *in vivo* are due to their increase of hydrophobicity which caused a low absorption. Similarly, 4-methylphenyl (**2o**), benzyl (**2p**) and 4-methoxybenzyl (**2q**) derivatives showed excellent antifungal activities *in vitro* but showed very week antifungal activities *in vivo.* We postulate that the low *in vivo* activities of **2o**, **2p** and **2q** are also due to their hydrophobicity. *c*-Pr (**2d**) derivative showed excellent antifungal activities *in vitro* and *in vivo.*

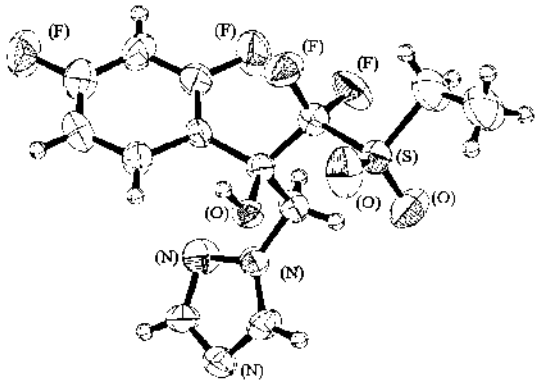


Fig. 2. ORTEP Drawing of (−)-**2b** (X-Ray Crystallography)

Table 3. *In Vivo* Antifungal Activities of Compounds (−)-**2** and FLCZ against *C. albicans* at a Single Oral Administration after Infection

Compounds	Dose (mg/kg)	Mean survival days (mean±S.D.)	No. of survivors on day 18/ tested mice
(−)-**2a**	5	17.7±0.9***	9/10
	1.25	16.6±1.3***	6/10
	0.313	10.6±2.4***	0/10
(−)-**2i**	5	12.4±1.8***	0/10
	1.25	10.4±1.6***	0/10
	0.313	6.0±1.8**	0/10
(−)-**2j**	5	13.7±2.1***	1/10
	1.25	12.4±1.5***	0/10
	0.313	6.9±1.4***	0/10
(−)-**2k**	5	18.0±0.0***	9/10
	1.25	12.6±1.5***	0/10
	0.313	8.3±1.2***	0/10
FLCZ	5	8.6±1.4***	0/5
	1.25	8.1±1.9***	0/5
	0.313	4.8±1.8*	0/5
Control		3.2±0.9	0/15

Significantly different from the control by Kaplan Meire method (Cox mantel test). ***; $p<0.001$, **; $p<0.01$, *; $p<0.05$.

Compounds (−)-**2a**, (−)-**2b**, (−)-**2d**, (−)-**2i**, (−)-**2j** and (−)-**2k** showed antifungal activities, but those of the (+)-form showed no significant activities. The absolute structure of (−)-**2b** is (*R*) as shown in Fig. 2.

Half lives of Sch42427 and SSY726 having methylsufonyl group were relatively long 13 and 44 h in rats, respectively. Therefore, the (−)-form of **2a**, **2i**, **2j** and **2k**, which have methylsulfonyl group, were tested *in vivo* against *C. albicans* for a single oral administration after infection (Table 3). (−)-**2a** and (−)-**2k** showed excellent activity at a single oral administration, and (−)-**2i** and (−)-**2j** showed superior activities to FLCZ. This suggest that half lives of (−)-**2a** and (−)-**2k** are long and they can be used in a tablet once a day or several days.

The (−)-form of **2a**, **2b**, **2d**, **2i** and **2k** were tested *in vivo* against *C. albicans* at the 4 times i.v. administrations after infection (Table 4). Their activities were excellent and superior

Table 4. *In Vivo* Antifungal Activities of Compounds (−)-**2** and FLCZ against *C. albicans* at the 4 Times i.v. Administrations after Infection

Compounds	Dose (mg/kg)	Mean survival days (mean±S.D.)	No. of survivors on day 14/ tested mice
(−)-**2a**	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	5/5
	0.313	14.0±0.0***	5/5
(−)-**2b**	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	5/5
	0.313	12.6±1.9***	3/5
(−)-**2d**	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	5/5
	0.313	14.0±0.0***	5/5
(−)-**2i**	5	13.6±0.9***	2/5
	1.25	11.8±1.1***	0/5
	0.313	10.6±1.6***	0/5
(−)-**2k**	5	14.0±0.0***	5/5
	1.25	14.0±0.0***	5/5
	0.313	12.2±1.8***	1/5
FLCZ	5	11.6±1.1***	0/5
	1.25	9.6±1.1***	0/5
	0.313	6.0±1.6**	0/5
Control		3.5±0.7	0/10

Significantly different from the control by Kaplan Meire method (Cox mantel test). ***; $p<0.001$, **; $p<0.01$, *; $p<0.05$.

to that of FLCZ. The water solubilities of (−)-**2a** and (−)-**2b** are 4.1 and 0.46 mg/ml, respectively. This result suggests that (−)-**2a** and (−)-**2b** can be used in a tablet and/or by injection.

Conclusion

New 1,2,4-triazoles (**2**) having a difluoro(substituted sulfonyl)methyl moiety were designed and synthesized *via* key intermediates (**3**). The introduction of fluorine atoms into the triazole antifungals enhanced their antifungal activities *in vitro* and *in vivo.* The (−)-form of **2** is the active form and the absolute configuration of (−)-**2b** is (*R*). Especially, (−)-**2a**, (−)-**2b** and (−)-**2d** showed potent activity against *C. albicans in vivo* for both oral and i.v. administrations. They are now undergoing further investigation.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus without correction. IR spectra were measured on a Nihon-bunko IR-810 spectrometer. ^{1}H-NMR spectra were recorded on a JOEL JNM-EX400 FT-NMR spectrometer in $CDCl_3$ using tetramethylsilane as a respective internal standard. ^{19}F-NMR spectra were recorded on a JOEL JNM-EX400 FT-NMR spectrometer in $CDCl_3$ with trifluoroacetic acid as an external standard. The following abbreviations are used: s=singlet, d=doublet, dd=doublet doublet, dt=doublet triplet, ddd=doublet doublet doublet, t=triplet, q=quartet, m=multiplet, br=broad. MS or high-resolution mass spectra (HRMS) were obtained on a JEOL JMS-DX303 or JEOL JMS-AX500 mass spectrometer. Optical rotations were determined on a Horiba SEPA-300 polarimeter. HPLC were performed on a Hitachi L-6000 pump equipped with a Hitachi L-4000 detector. Preparative HPLC were carried out on a Yamazen 800E pump equipped with an UV-10V detector. Column chromatography was carried out on silica gel (BW-80S Fuji-sirial). Resolution of (±)-**1** was carried out by preparative HPLC on CHIRALCEL OD (2 cm i.d.×25 cm) with pre-column CHIRALCEL OD (2 cm i.d.×5 cm) (Daicell Chemical Industries, Ltd.) and optical yields were measured by HPLC using CHIRALCEL OD (4.6 mm i.d.×250 mm) with pre-column CHIRALCEL OD (4.6 mm i.d.× 50 mm) (Daicell Chemical Industries, Ltd.).

General Procedure of Synthesis of 2-(Substituted thio)acetophenone (5) Mercaptans (50 mmol) was added to a solution of 2-haloacetophenone (**4**) (55 mmol) in dimethyl sulfoxide (DMSO) (150 ml) at room temperature with stirring. The mixture was stirred at room temperature for 15 h. After addition of water, the mixture was extracted with Et_2O. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 9 (v/v)] or distilled under reduced pressure to give **5**.

2′,4′-Difluoro-2-(methylthio)acetophenone (**5a**): Colorless oil. bp 126 °C/(14 mmHg). Yield 64%. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s), 3.73 (2H, d, J_{HF}=2.4 Hz), 6.86—6.91 (1H, m), 6.97—7.02 (1H, m), 7.98—8.04 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −25.5—−25.6 (1F, m), −27.4—−27.5 (1F, m). MS *m/z* (%): 202 (14, M^+), 141 (100). HRMS *m/z*: 202.0249 (Calcd for $C_9H_8F_2OS$: 202.0264). IR (neat) cm^{-1}: 1675.

2-(Ethylthio)-2′,4′-Difluoroacetophenone (**5b**): Colorless oil. bp 143 °C/ (13 mmHg). Yield 89%. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.3 Hz), 2.52 (2H, q, J=7.3 Hz), 3.78 (2H, d, J_{HF}=2.4 Hz), 6.86—6.91 (1H, m), 6.97—7.01 (1H, m), 7.96—8.02 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −25.5—−25.6 (1F, m), −27.5—−27.6 (1F, m). MS *m/z* (%): 216 (2, M^+), 141 (100). HRMS *m/z*: 216.0427 (Calcd for $C_{10}H_{10}F_2OS$: 216.0420). IR (neat) cm^{-1}: 1675.

2′,4′-Difluoro-2-(propylthio)acetophenone (**5c**): Colorless oil. bp 112 °C/ (5 mmHg). Yield 85%. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, dt, J=2.0, 7.3 Hz), 1.55—1.65 (2H, m), 2.47 (2H, dt, J=1.5, 7.3 Hz), 3.75 (2H, d, J_{HF}=2.0 Hz), 6.85—6.90 (1H, m), 6.95—7.00 (1H, m), 7.95—8.00 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −25.6—−25.7 (1F, m), −27.5—−27.6 (1F, m). MS *m/z* (%): 230 (15, M^+), 141 (100). HRMS *m/z*: 230.0558 (Calcd for $C_{11}H_{12}F_2OS$: 230.0577). IR (neat) cm^{-1}: 1675.

2-(Cyclopropylthio)-2′,4′-difluoroacetophenone (**5d**): Colorless oil. bp 123 °C/(3 mmHg). Yield 87%. ^{1}H-NMR ($CDCl_3$) δ: 0.50—0.54 (2H, m), 0.83—0.88 (2H, m), 1.82—1.88 (1H, m), 3.86 (2H, d, J_{HF}=2.4 Hz), 6.86—6.91 (1H, m), 6.97—7.02 (1H, m), 7.97—8.03 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −25.6—−25.7 (1F, m), −27.5—−27.6 (1F, m). MS *m/z* (%): 228 (18, M^+), 141 (100). HRMS *m/z*: 228.0415 (Calcd for $C_{11}H_{10}F_2OS$: 228.0421). IR (neat) cm^{-1}: 1680.

2-(Butylthio)-2′,4′-difluoroacetophenone (**5e**): Colorless oil. bp 123 °C/ (5 mmHg). Yield 85%. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz), 1.35—1.45 (2H, m), 1.50—1.60 (2H, m), 2.49 (2H, t, J=7.3 Hz), 3.75 (2H, d, J_{HF}=2.0 Hz), 6.85—6.90 (1H, m), 6.95—7.00 (1H, m), 7.95—8.00 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −25.5—−25.6 (1F, m), −27.4—−27.5 (1F, m). MS *m/z* (%): 244 (21, M^+), 141 (100). HRMS *m/z*: 244.0746 (Calcd for $C_{12}H_{14}F_2OS$: 244.0734). IR (neat) cm^{-1}: 1680.

2-(*tert*-Butylthio)-2′,4′-difluoroacetophenone (**5f**): Colorless oil. bp 125 °C/(5 mmHg). Yield 94%. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (9H, s), 3.88 (2H, d, J_{HF}=2.4 Hz), 6.86—6.91 (1H, m), 6.96—7.01 (1H, m), 7.91—7.97 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −25.7—−25.8 (1F, m), −27.9—−28.0 (1F, m). MS *m/z* (100): 244 (32, M^+), 141 (100). HRMS *m/z*: 244.0752 (Calcd for $C_{12}H_{14}F_2OS$: 244.0734). IR (KBr) cm^{-1}: 1680.

2′,4′-Difluoro-2-(pentylthio)-acetophenone (**5g**): Colorless oil. bp 137 °C/ (5 mmHg). Yield 81%. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz), 1.30—1.80 (6H, m), 2.49 (2H, t, J=7.3 Hz), 3.75 (2H, d, J_{HF}=2.4 Hz), 6.85—6.90 (1H, m), 6.95—7.00 (1H, m), 7.95—8.00 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −25.6—−25.7 (1F, m), −27.4—−27.5 (1F, m). MS *m/z* (%): 258 (23, M^+), 141 (100). HRMS *m/z*: 258.3291 (Calcd for $C_{13}H_{16}F_2OS$: 258.3283). IR (neat) cm^{-1}: 1680.

2-(Methylthio)acetophenone (**5h**): Colorless oil. bp 110 °C/(3 mmHg). Yield 73%. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s), 3.77 (2H, s), 7.48 (2H, t, J=7.3 Hz), 7.58 (1H, dd, J=1.5, 7.3 Hz), 7.98 (2H, dd, J=1.5, 7.3 Hz). MS *m/z* (%): 166 (19, M^+), 105 (100). HRMS *m/z*: 166.0440 (Calcd for $C_9H_{10}OS$: 166.0452). IR (neat) cm^{-1}: 1675.

4′-Fluoro-2-(methylthio)acetophenone (**5i**): Colorless oil. bp 112 °C/ (3 mmHg). Yield 73%. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s), 3.73 (2H, s), 7.10—7.15 (2H, m), 8.00—8.05 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −28.9 (1F, s). MS *m/z* (%): 184 (1, M^+), 123 (100). HRMS *m/z*: 184.0355 (Calcd for C_9H_9FOS: 184.0358). IR (neat) cm^{-1}: 1680.

2-(Methylthio)-4′-(trifluoromethy)acetophenone (**5j**): Colorless oil. bp 107 °C/(5 mmHg). Yield 66%. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 3.77 (2H, s), 7.75 (2H, d, J=7.8 Hz), 8.09 (2H, d, J=7.8 Hz). ^{19}F-NMR ($CDCl_3$) δ: 12.6 (3F, s). MS *m/z* (%): 234 (23, M^+), 173 (100). HRMS *m/z*: 234.0350 (Calcd for $C_{10}H_9F_3OS$: 234.0326). IR (neat) cm^{-1}: 1680.

2′,4′-Dichloro-2-(methylthio)acetophenone (**5k**): Colorless oil. Yield 85%. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 3.86 (2H, s), 7.43 (1H, dd, J=2.0, 8.3 Hz), 7.55 (1H, d, J=2.0 Hz), 7.63 (1H, d, J=8.3 Hz). MS *m/z* (%): 234 (0.4, M^+), 173 (100). HRMS *m/z*: 233.9669 (Calcd for $C_9H_8Cl_2OS$: 233.9673). IR (neat) cm^{-1}: 1690.

2′,4′-Difluoro-2-(2-hydroxyethylthio)acetophenone (**5m**): Colorless oil.

Yield 72%. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (1H, br s), 2.73 (2H, t, J=5.9 Hz), 3.75 (2H, t, J=5.9 Hz), 3.84 (2H, d, J_{HF}=2.4 Hz), 6.87—6.93 (1H, m), 6.98—7.03 (1H, m), 7.98—8.04 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −24.7—−24.8 (1F, m), −27.3—−27.4 (1F, m). MS m/z (%): 214 (29, M^+-H_2O), 141 (100). HRMS m/z: 214.0258 (Calcd for $C_{10}H_8F_2OS$: 214.0264). IR (neat) cm^{-1}: 3425, 1675.

2′,4′-Difluoro-2-(phenylthio)acetophenone (**5n**): Colorless oil. Yield 81% ^{1}H-NMR ($CDCl_3$) δ: 4.15 (2H, s), 6.85—6.90 (1H, m), 6.95—7.00 (1H, m), 7.25—7.45 (5H, m), 7.85—7.89 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −27.7—−27.8 (1F, m), −30.0—−30.1 (1F, m). MS m/z (%): 264 (41, M^+), 141 (100). HRMS m/z: 264.0384 (Calcd for $C_{14}H_{10}F_2OS$: 264.0240). IR (neat) cm^{-1}: 1680.

2′,4′-Difluoro-2-[(4-methylphenyl)thio]acetophenone (**5o**): Colorless oil. Yield 99% ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, s), 4.15 (2H, s), 6.85—6.90 (1H, m), 6.95—7.00 (1H, m), 7.08 (2H, d, J=7.8 Hz), 7.25 (2H, d, J=7.8 Hz), 7.85—7.89 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −27.7—−27.8 (1F, m), −30.0—−30.1 (1F, m). MS m/z (%): 278 (46, M^+), 141 (100). HRMS m/z: 278.0587 (Calcd for $C_{15}H_{12}F_2OS$: 278.0577). IR (neat) cm^{-1}: 1680.

2-(Benzylthio)-2′,4′-difluoroacetophenone (**5p**): Colorless oil. Yield 68% ^{1}H-NMR ($CDCl_3$) δ: 3.63 (2H, s), 3.64 (2H, s), 6.82—6.87 (1H, m), 6.90—7.00 (1H, m), 7.27—7.34 (5H, m) , 7.92—7.98 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −30.7—−30.8 (1F, m), −32.5—−32.6 (1F, m). MS m/z (%): 278 (11, M^+), 141 (100). HRMS m/z: 278.0591 (Calcd for $C_{15}H_{12}F_2OS$: 278.0577). IR (neat) cm^{-1}: 1675.

2′,4′-Difluoro-2-[(4-methoxybenzyl)thio]acetophenone (**5q**): Colorless oil. Yield 33% ^{1}H-NMR ($CDCl_3$) δ: 3.63 (2H, s), 3.64 (2H, s), 3.79 (3H, s), 6.83 (2H, d, J=8.8 Hz), 6.82—6.87 (1H, m), 6.90—7.00 (1H, m), 7.23 (2H, d, J=8.8 Hz), 7.92—7.98 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −30.7—−30.8 (1F, m), −32.5—−32.6 (1F, m). MS m/z (%): 308 (7, M^+), 141 (100). HRMS m/z: 308.0678 (Calcd for $C_{16}H_{14}F_2O_2S$: 308.0682). IR (neat) cm^{-1}: 1675.

Preparation of 2-(2-Acetoxyethylthio)-2′,4′-difluoroacetophenone (5l) from 5m by Acetylation Acetic anhydride (0.60 g, 5.88 mmol) was added to a solution of 2′,4′-difluoro-2-[(2-hydroxyethyl)thio]acetophenone (**5m**) (1.14 g, 4.91 mmol) in pyridine (10 ml). The mixture was stirred at 50 °C for 3.0 h. The reaction mixture was evaporated under reduced pressure. The residue was diluted ether. The etheral solution was washed with aqueous saturated copper sulfate, water, brine, dried over magnesium sulfate and evaporated under reduced pressure. Distillation of crude product at 164 °C (3 mmHg) gave **5l** as a pale yellow oil (1.31 g, 97%). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s), 2.76 (2H, t, J=6.4 Hz), 3.84 (2H, d, J_{HF}=2.4 Hz), 4.25 (2H, t, J=6.4 Hz), 6.87—6.92 (1H, m), 6.98—7.03 (1H, m), 7.98—8.04 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −24.9—−25.0 (1F, m), −27.4—−27.5 (1F, m). MS m/z (%): 274 (5, M^+), 141 (100). HRMS m/z: 274.0470 (Calcd for $C_{12}H_{12}F_2O_3S$: 274.0476). IR (neat) cm^{-1}: 1675.

General Procedure for the Synthesis of Ethyl 2,2-Difluoro(substituted thio)acetate (6) NaH (55 mmol) was added to a solution of mercaptan (50 mmol) in DMSO (50 ml) at room temperature with stirring. After the mixture was stirred at the same temperature for 1 h, ethyl bromodifluoroacetate (55 mmol) was added to the solution at room temperature with stirring. The mixture was stirred at the same temperature for 15 h. After addition of aqueous NH_4Cl, the mixture was extracted with Et_2O. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 9 (v/v)] to give **6**.

Ethyl 2-(*tert*-Butylthio)-2,2-difluoroacetate (**6f**): Colorless oil. bp 55—56 °C/(3 mmHg). Yield 40%. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.3 Hz), 1.52 (9H, s), 4.35 (2H, q, J=7.3 Hz). ^{19}F-NMR ($CDCl_3$) δ: −3.4 (2F, s). MS m/z: 212 (0.6, M^+), 57 (100). HRMS m/z: 212.0661 (Calcd for $C_8H_{14}F_2O_2S$: 212.0682). IR (neat) cm^{-1}: 1770.

Ethyl 2,2-Difluoro-2-(phenylthio)acetate (**6n**): Colorless oil. bp 109 °C/(10 mmHg). Yield 48%. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.3 Hz), 4.24 (2H, q, J=7.3 Hz), 7.37—7.40 (2H, m), 7.41—7.46 (1H, m), 7.60—7.63 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −6.5 (2F, s). MS m/z : 232 (71, M^+), 159 (100). HRMS m/z: 232.0360 (Calcd for $C_{10}H_{10}F_2O_2S$: 232.0370). IR (neat) cm^{-1}: 1765.

Ethyl 2,2-Difluoro-2-[(4-methylphenyl)thio]acetate (**6o**): Colorless oil. Yield 47%. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.3 Hz), 2.38 (3H, s), 4.25 (2H, q, J=7.3 Hz), 7.20 (2H, d, J=8.3 Hz), 7.49 (2H, d, J=8.3 Hz). ^{19}F-NMR ($CDCl_3$) δ: −6.9 (2F, s). MS m/z (%): 246 (88, M^+), 173 (100). HRMS m/z: 246.0533 (Calcd for $C_{11}H_{12}F_2O_2S$: 246.0526). IR (neat) cm^{-1}: 1770.

Ethyl 2-(Benzylthio)-2,2-difluoroacetate (**6p**): Colorless oil. bp 116—117 °C/(3 mmHg). Yield 31%. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.3 Hz), 4.12 (2H, s), 4.30 (2H, q, J=7.3 Hz), 7.27—7.34 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: −7.3 (2F, s). MS m/z: 246 (4, M^+), 91 (100). HRMS m/z: 246.0523 (Calcd for $C_{11}H_{12}F_2O_2S$: 246.0526). IR (neat) cm^{-1}: 1770.

Ethyl 2,2-Difluoro-2-[(4-methoxybenzyl)thio]acetate (**6q**): Colorless oil. Yield 53%. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.3 Hz), 3.73 (3H, s), 4.08 (2H, s), 4.32 (2H, q, J=7.3 Hz), 6.86 (2H, d, J=8.8 Hz), 7.26 (2H, d, J=8.8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −7.3 (2F, s). MS m/z (%): 276 (7, M^+), 121 (100). HRMS m/z: 276.0609 (Calcd for $C_{12}H_{14}F_2O_3S$: 276.0632). IR (neat) cm^{-1}: 1765.

General Procedure of Synthesis of 2,2-Difluoro-2-(substituted thio)-acetophenone (3). (A) General Procedure *via* Fluorination A solution of **5** (50 mmol) in 1,1,2-trichloroethane (TCE) (10 ml) was added dropwise into the suspension of *N*-fluoro-2,4,6-trimethylpyridinium triflate (FP-T300) (150 mmol) and zinc bromide (25 mmol) in TCE (100 ml) for 10 min at 80 °C—100 °C. The mixture was stirred at 105 °C. After addition of water, the mixture was extracted with $CHCl_3$. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 9 (v/v)] or distilled under reduced pressure to give **3**.

2-(Methylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3a**): Colorless oil. bp 96 °C/(5 mmHg). Yield 82%. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 6.91—7.02 (2H, m), 7.95—8.01 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −9.4 (2F, d, J=15 Hz), −23.0—−23.1 (1F, m), −26.0—−26.1 (1F, m). MS m/z (%): 238 (1, M^+), 141 (100). HRMS m/z: 238.0062 (Calcd for $C_9H_6F_4OS$: 238.0076). IR (neat) cm^{-1}: 1700.

2-(Ethylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3b**): Colorless oil. bp 105 °C/(7 mmHg). Yield 85%. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.8 Hz), 2.92 (2H, q, J=7.8 Hz), 6.90—7.02 (2H, m), 7.95—8.01 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −6.4 (2F, d, J=14 Hz), −23.0—−23.1 (1F, m), −26.1—−26.2 (1F, m). MS m/z (%): 252 (0.3, M^+), 141 (100). HRMS m/z: 252.0229 (Calcd for $C_{10}H_8F_4OS$: 252.0232). IR (neat) cm^{-1}: 1715.

2-(Propylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3c**): Colorless oil. bp 102 °C/(4 mmHg). Yield 31%. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.3 Hz), 1.70—1.75 (2H, m), 2.87 (2H, t, J=7.3 Hz), 6.91—6.97 (1H, m), 6.98—7.02 (1H, m), 7.95—8.00 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −6.4 (2F, d, J=14 Hz), −23.1—−23.2 (1F, m), −26.1—−26.2 (1F, m). MS m/z (%): 266 (0.5, M^+), 141 (100). HRMS m/z: 266.0365 (Calcd for $C_{11}H_{10}F_4OS$: 266.0389). IR (neat) cm^{-1}: 1710.

2-(Cyclopropylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3d**): Colorless oil. bp 115 °C/(4 mmHg). Yield 72%. ^{1}H-NMR ($CDCl_3$) δ: 0.71—0.75 (2H, m), 0.99—1.04 (2H, m), 2.06—2.10 (1H, m), 6.91—7.02 (2H, m), 7.96—8.02 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −7.5 (2F, d, J=12 Hz), −23.0—−23.1 (1F, m), −26.0—−26.1 (1F, m). MS m/z (%): 264 (0.2, M^+), 141 (100). HRMS m/z: 264.0206 (Calcd for $C_{11}H_8F_4OS$: 264.0232). IR (neat) cm^{-1}: 1715.

2-(Butylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3e**): Colorless oil. bp 116 °C/(3 mmHg). Yield 24%. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.40—1.48 (2H, m), 1.64—1.71 (2H, m), 2.88 (2H, t, J=7.3 Hz), 6.91—7.02 (2H, m), 7.95—8.01 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −6.4 (2F, d, J=13 Hz), −23.1—−23.2 (1F, m), −26.1—−26.2 (1F, m). MS m/z (%): 280 (0.5, M^+), 141 (100). HRMS m/z: 280.0562 (Calcd for $C_{12}H_{12}F_4OS$: 280.0545). IR (neat) cm^{-1}: 1715.

2-(Pentylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3g**): Colorless oil. bp 132 °C/(4 mmHg). Yield 37%. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.45—1.80 (6H, m), 2.88 (2H, t, J=7.3 Hz), 6.91—7.02 (2H, m), 7.95—8.01 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −6.3 (2F, d, J=14 Hz), −23.0—−23.1 (1F, m), −26.1—−26.2 (1F, m). MS m/z (%): 294 (0.3, M^+), 141 (100). HRMS m/z: 294.3088 (Calcd for $C_{13}H_{14}F_4OS$: 294.3093). IR (neat) cm^{-1}: 1715.

2,2-Difluoro-2-(methylthio)acetophenone (**3h**): Colorless oil. bp 87 °C/(4 mmHg). Yield 82%. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 7.50 (2H, t, J=7.8 Hz), 7.65 (1H, dd, J=7.8, 1.5 Hz), 8.14 (2H, dd, J=7.8, 1.5 Hz). ^{19}F-NMR ($CDCl_3$) δ: −3.3 (2F, s). MS m/z (%): 202 (3, M^+), 105 (100). HRMS m/z: 202.0256 (Calcd for $C_9H_8F_2OS$: 202.0264). IR (neat) cm^{-1}: 1705.

2-(Methylthio)-2,2,4′-trifluoroacetophenone (**3i**): Colorless oil. bp 79 °C/(3 mmHg). Yield 45%. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 7.15—7.20 (2H, m), 8.15—8.20 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.9 (2F, s), −25.7 (1F, s). MS m/z (%): 220 (1, M^+), 123 (100). HRMS m/z: 220.0175 (Calcd for $C_9H_7F_3OS$: 220.0170). IR (neat) cm^{-1}: 1705.

2,2-Difluoro-2-(methylthio)-4′-(trifluoromethyl)acetophenone (**3j**): Colorless oil. bp 107 °C/(5 mmHg). Yield 60%. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 7.77 (2H, d, J=8.3 Hz), 8.25 (2H, d, J=8.3 Hz). ^{19}F-NMR ($CDCl_3$) δ: 12.3 (3F, s), −6.8 (2F, s). MS m/z (%): 270 (3, M^+), 173 (100). HRMS m/z: 270.0093 (Calcd for $C_{10}H_7F_5OS$: 270.0138). IR (neat) cm^{-1}: 1715.

2′,4′-Dichloro-2,2-difluoro-2-(methylthio)acetophenone (**3k**): Colorless

oil. Yield 72%. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 7.34 (1H, dd, J=8.3, 2.0 Hz), 7.53 (1H, d, J=2.0 Hz), 7.69 (1H, d, J=8.3 Hz). ^{19}F-NMR ($CDCl_3$) δ: −10.1 (2F, s). MS m/z (%): 270 (1, M^+), 173 (100). HRMS m/z: 269.9459 (Calcd for $C_9H_6Cl_2F_2OS$: 269.9485). IR (neat) cm^{-1}: 1725.

2-(2-Acetoxyethylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3l**): Colorless oil. bp 151 °C/(3 mmHg). Yield 45%. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 3.14 (2H, t, J=6.4 Hz), 4.31 (2H, t, J=6.4 Hz), 6.92—7.03 (2H, m), 7.94—7.99 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.4 (2F, d, J=15 Hz), −22.4—−22.5 (1F, m), −25.5—−25.6 (1F, m). MS m/z (%): 250 (11, M^+−AcOH), 141 (100). HRMS m/z: 250.0032 (Calcd for $C_{10}H_6F_4OS$: 250.0076). IR (neat) cm^{-1}: 1744,1712.

(B) General Procedure of Synthesis of 2,2-Difluoro-2-(substituted thio)acetophenone (3) *via* Lithiation A solution of *n*-BuLi (1.37 M solution in *n*-hexane; 20 mmol) was added to a solution of bromobenzene (**7**) (20 mmol) in Et_2O (100 ml) with stirring at −78 °C under Ar atmosphere. The mixture was stirred at the same temperature for 0.5 h. A solution of ethyl difluoroacetate (**6**) (20 mmol) in Et_2O (10 ml) was added to the solution with stirring at −78 °C and stirred at the same temperature for 1 h and at room temperature for 1 h. After addition of aqueous NH_4Cl, the mixture was extracted with AcOEt. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 8 (v/v)] to give **3**.

2-(*tert*-Butylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3f**): Colorless oil. Yield 68%. ^{1}H-NMR ($CDCl_3$) δ: 1.56 (9H, s), 6.72—7.01 (2H, m), 7.97—8.03 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −2.01 (2F, d, J=9 Hz), −23.2—−23.3 (1F, m), −26.4—−26.5 (1F, m). MS m/z: 280 (2, M^+), 57 (100). HRMS m/z: 280.0574 (Calcd for $C_{12}H_{12}F_4OS$: 280.0545). IR (neat) cm^{-1}: 1715.

2-(Phenylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3n**): Colorless oil. Yield 61%. ^{1}H-NMR ($CDCl_3$) δ: 6.90—7.00 (2H, m), 7.26—7.45 (2H, m), 7.46—7.48 (1H, m), 7.58—7.61 (2H, m), 7.91—7.97 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −4.4 (2F, d, J=14 Hz), −22.7—−22.8 (1F, m), −25.8—−25.9 (1F, m). MS m/z: 300 (9, M^+), 141 (100). HRMS m/z: 300.0228 (Calcd for $C_{14}H_8F_4OS$: 300.0232). IR (neat) cm^{-1}: 1710.

2-[(4-Methylphenyl)thio]-2,2,2′,4′-tetrafluoroacetophenone (**3o**): Colorless oil. Yield 66%. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 6.90—7.00 (2H, m), 7.19 (2H, d, J=8.3 Hz), 7.46 (2H, d, J=8.3 Hz), 7.92—7.98 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.0 (2F, d, J=14 Hz), −22.9—−23.0 (1F, m), −25.8—−26.0 (1F, m). MS m/z (%): 314 (18, M^+), 141 (100). HRMS m/z: 314.0403 (Calcd for $C_{15}H_{10}F_4OS$: 314.0389). IR (neat) cm^{-1}: 1660.

2-(Benzylthio)-2,2,2′,4′-tetrafluoroacetophenone (**3p**): Colorless oil. Yield 84%. ^{1}H-NMR ($CDCl_3$) δ: 4.12 (2H, s), 6.90—7.00 (2H, m), 7.26—7.35 (5H, m), 7.26—7.35 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −6.3 (2F, d, J=15 Hz), −22.8—−22.9 (1F, m), −25.8—−25.9 (1F, m). MS m/z: 314 (0.3, M^+), 141 (100). HRMS m/z: 314.0387 (Calcd for $C_{15}H_{10}F_4OS$: 314.0388). IR (neat) cm^{-1}: 1715.

2-[(4-Methoxybenzyl)thio]-2,2,2′,4′-tetrafluoroacetophenone (**3q**): Colorless oil. Yield 33%. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 4.09 (2H, s), 6.84 (2H, d, J=8.8 Hz), 6.89—7.00 (2H, m), 7.25 (2H, d, J=8.8 Hz), 7.92—7.98 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −6.3 (2F, d, J=14 Hz), −22.8—−22.9 (1F, m), −25.8—−26.0 (1F, m). MS m/z (%): 344 (3, M^+), 121 (100). HRMS m/z: 344.0474 (Calcd for $C_{16}H_{12}F_4O_2S$: 344.0494). IR (neat) cm^{-1}: 1710.

(C) Synthesis of 2,2-Difluoro-2-(methylthio)acetophenone (3h) *via* Methylthiolation Sodium methanethiolate (60 mmol) was added to a solution of 2-Chloro-2,2-difluoroacetophenone (50 mmol) in DMSO (150 ml) at room temperature with stirring. The mixture was stirred at room temperature for 15 h. After addition of water, the mixture was extracted with Et_2O. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 9 (v/v)] or distilled under reduced pressure to give **3h**. (yield 49%)

General Procedure for the Synthesis of 2-Aryl-2-[difluoro(substituted thio)methyl]oxirane (8) from 3 with Trimethylsulfoxonium Iodide (TMSI) TMSI (5.5 mmol) was added to a suspension of NaH (60% in oil; 6 mmol) in DMSO (30 ml) in tetrahydrofuran (THF) (10 ml). After stirring at room temperature for 1 h, the mixture was added to **3** (5 mmol) in THF (10 ml) at 0 °C with stirring. The mixture was stirred at the same temperature for 1 h. After addition of aqueous $NaHCO_3$, the mixture was extracted with AcOEt. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using *n*-hexane–AcOEt [9 : 1 (v/v)] to give **8**.

2-[Difluoro(methylthio)methyl]-2-(2,4-difluorophenyl)oxirane (**8a**): Colorless oil. Yield 46%. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 2.98—3.00 (1H, m), 3.48—3.50 (1H, m). 6.81—6.87 (1H, m), 6.89—6.95 (1H, m), 7.51—7.56 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −8.7 (1F, dd, J=9, 214 Hz), −9.5 (1F, dd, J=7, 214 Hz), −31.4—−31.5 (1F, m), −33.2—−33.3 (1F, m). MS m/z (%): 252 (5, M^+), 127 (100). HRMS m/z: 252.0259 (Calcd for $C_{10}H_8F_4OS$: 252.0232). IR (neat) cm^{-1}: 1270.

2-[Difluoro(ethylthio)methyl]-2-(2,4-difluorophenyl)oxirane (**8b**): Colorless oil. Yield 90%. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.3 Hz), 2.83—2.90 (2H, m), 2.97—3.00 (1H, m), 3.48—3.50 (1H, m). 6.81—6.90 (1H, m), 6.91—6.94 (1H, m), 7.51—7.55 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.6 (1F, dd, J=9, 214 Hz), −6.9 (1F, dd, J=7, 214 Hz), −31.4—−31.5 (1F, m), −33.2—−33.3 (1F, m). MS m/z (%): 266 (2, M^+), 127 (100). HRMS m/z: 266.0401 (Calcd for $C_{11}H_{10}F_4OS$: 266.0389). IR (neat) cm^{-1}: 1240.

2-(2,4-Difluorophenyl)-2-[difluoro(propylthio)methyl]oxirane (**8c**): Colorless oil. Yield 46%. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz), 1.58—1.69 (2H, m), 2.81 (2H, dt, J=2.0, 7.3 Hz), 2.98—3.00 (1H, m), 3.49—3.51 (1H, m). 6.81—6.87 (1H, m), 6.90—6.94 (1H, m), 7.51—7.57 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.5 (1F, dd, J=10, 214 Hz), −6.8 (1F, dd, J=7, 214 Hz), −31.5—−31.6 (1F, m), −33.2—−33.3 (1F, m). MS m/z (%): 280 (16, M^+), 155 (100). HRMS m/z: 280.0579 (Calcd for $C_{12}H_{12}F_4OS$: 280.0545). IR (neat) cm^{-1}: 1245.

2-[(Cyclopropylthio)difluoromethyl]-2-(2,4-difluorophenyl)oxirane (**8d**): Colorless oil. Yield 86%. ^{1}H-NMR ($CDCl_3$) δ: 0.65—0.70 (2H, m), 0.95—1.00 (2H, m), 2.00—2.10 (1H, m), 2.95—3.00 (1H, m), 3.45—3.50 (1H, m), 6.81—6.87 (1H, m), 6.89—6.95 (1H, m), 7.50—7.56 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −7.2 (1F, dd, J=12, 214 Hz), −8.0 (1F, dd, J=10, 214 Hz), −31.5—−31.6 (1F, m), −33.1—−33.2 (1F, m). MS m/z (%): 278 (2, M^+), 127 (100). HRMS m/z: 278.0392 (Calcd for $C_{12}H_{10}F_4OS$: 278.0389). IR (neat) cm^{-1}: 1230.

2-[(Butylthio)difluoromethyl]-2-(2,4-difluorophenyl)oxirane (**8e**): Colorless oil. Yield 61%. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz), 1.36—1.43 (2H, m), 1.57—1.65 (2H, m), 2.83 (2H, dt, J=2.0, 7.3 Hz), 2.85—3.00 (1H, m), 3.48—3.50 (1H, m). 6.80—6.87 (1H, m), 6.90—6.95 (1H, m), 7.50—7.57 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.6 (1F, dd, J=10, 214 Hz), −6.9 (1F, dd, J=14, 214 Hz), −31.5—−31.6 (1F, m), −33.2—−33.3 (1F, m). MS m/z (%): 294 (12, M^+), 155 (100). HRMS m/z: 294.0688 (Calcd for $C_{13}H_{14}F_4OS$: 294.0702). IR (neat) cm^{-1}: 1235.

2-[(*tert*-Butylthio)difluoromethyl]-2-(2,4-difluorophenyl)oxirane (**8f**): Colorless oil. Yield 98%. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.94—2.97 (1H, m), 3.38—3.40 (1H, m), 6.80—6.94 (2H, m), 7.50—7.57 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −4.18 (1F, dd, J=11, 211 Hz), −4.57 (1F, dd, J=7, 211 Hz), −31.7—−31.8 (1F, m), −33.0—−33.1 (1F, m). MS m/z: 294 (2, M^+), 57 (100). HRMS m/z: 294.0704 (Calcd for $C_{13}H_{14}F_4OS$: 294.0701). IR (neat) cm^{-1}: 1270.

2-[Difluoro(pentylthio)methyl]-2-(2,4-difluorophenyl)oxirane (**8g**): Colorless oil. Yield 67%. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz), 1.35—1.95 (6H, m), 2.83 (2H, dt, J=2.0, 7.3 Hz), 2.85—3.00 (1H, m), 3.48—3.50 (1H, m). 6.80—6.87 (1H, m), 6.90—6.95 (1H, m), 7.50—7.57 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.5 (1F, dd, J=10, 214 Hz), −6.9 (1F, dd, J=14, 214 Hz), −31.5—−31.6 (1F, m), −33.2—−33.3 (1F, m). MS m/z (%): 308 (9, M^+), 155 (100). HRMS m/z: 308.0861 (Calcd for $C_{14}H_{16}F_4OS$: 308.0858). IR (neat) cm^{-1}: 1235.

2-[Difluoro(methylthio)methyl]-2-phenyloxirane (**8h**): Colorless oil. Yield 95%. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 2.85—2.90 (1H, m), 3.45—3.47 (1H, m), 7.36—7.40 (3H, m), 7.53—7.56 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −0.4 (1F, d, J=215 Hz), −4.2 (1F, d, J=215 Hz). MS m/z (%): 216 (18, M^+), 133 (100). HRMS m/z: 216.0401 (Calcd for $C_{10}H_{10}F_2OS$: 216.0420). IR (neat) cm^{-1}: 1240.

2-[Difluoro(methylthio)methyl]-2-(4-fluorophenyl)oxirane (**8i**): Colorless oil. Yield 97%. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s), 2.85—2.90 (1H, m), 3.45—3.50 (1H, m), 7.05—7.10 (2H, m), 7.50—7.55 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.8 (1F, dd, J=6, 214 Hz), −6.3 (1F, dd, J=10, 214 Hz), −36.1 (1F, s). MS m/z (%): 234 (3, M^+), 61 (100). HRMS m/z: 234.0311 (Calcd for $C_{10}H_9F_3OS$: 220.0170). IR (neat) cm^{-1}: 1225.

2-[Difluoro(methylthio)methyl]-2-[4-(trifluoromethyl)phenyl]oxirane (**8j**): Colorless oil. Yield 99%. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s), 2.85—2.90 (1H, m), 3.50—3.52 (1H, m), 7.65 (2H, d, J=6.1 Hz), 7.67 (2H, d, J=6.1 Hz). ^{19}F-NMR ($CDCl_3$) δ: 12.9 (3F, s), −4.9 (1F, d, J=216 Hz), −9.1 (1F, d, J=216 Hz). MS m/z (%): 284 (28, M^+), 159 (100). HRMS m/z: 284.0291 (Calcd for $C_{11}H_9F_5OS$: 284.0294). IR (neat) cm^{-1}: 1240.

2-(2,4-Dichlorophenyl)-2-[difluoro(methylthio)methyl]oxirane (**8k**): Colorless oil. Yield 83%. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s), 3.03—3.05 (1H, m), 3.58—3.60 (1H, m), 7.30 (1H, dd, J=2.0, 8.8 Hz), 7.42 (1H, d, J=2.0 Hz), 7.54 (1H, d, J=8.8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −6.7 (1F, d, J=255 Hz), −7.5 (1F, d, J=255 Hz). MS m/z (%): 284 (6, M^+), 249 (100).

HRMS *m/z*: 283.9677 (Calcd for $C_{10}H_8Cl_2F_2OS$: 216.0420). IR (neat) cm^{-1}: 1245.

2-[[[2-(2,4-Difluorophenyl)-2-oxiranyl]difluoromethyl]thio]ethyl acetate (**8l**): Colorless oil. Yield 90%. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s), 2.95—3.00 (1H, m), 3.07 (2H, dd, J=1.0, 6.8 Hz), 3.48—3.51 (1H, m), 4.24 (2H, t, J=6.4 Hz), 6.82—6.88 (1H, m), 6.90—6.96 (1H, m), 7.50—7.56 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −4.3 (1F, dd, J=10, 211 Hz), −5.9 (1F, dd, J=5, 211 Hz), −31.1—−31.2 (1F, m), −33.1—−33.2 (1F, m). MS *m/z* (%): 324 (0.2, M^+), 205 (100). HRMS *m/z*: 324.0450 (Calcd for $C_{13}H_{12}F_4O_3S$: 324.0444). IR (neat) cm^{-1}: 1745, 1230.

2-(2,4-Difluorophenyl)-2-[difluoro(phenylthio)methyl]oxirane (**8n**): Colorless oil. Yield 49%. ^{1}H-NMR ($CDCl_3$) δ: 3.00—3.03 (1H, m), 3.50—3.52 (1H, m), 6.83—6.86 (1H, m), 6.87—7.00 (1H, m), 7.32—7.38 (3H, m), 7.39—7.44 (1H, m), 7.48—7.61 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.1 (1F, dd, J=10, 213 Hz), −6.3 (1F, dd, J=7, 213 Hz), −31.3—−31.4 (1F, m), −33.0—−33.2 (1F, m). MS *m/z*: 314 (0.2, M^+), 91 (100). HRMS *m/z*: 314.0364 (Calcd for $C_{15}H_{10}F_4OS$: 314.0388). IR (neat) cm^{-1}: 1270.

2-[Difluoro[(4-methylphenyl)thio]methyl]-2-(2,4-difluorophenyl)oxirane (**8o**): Colorless oil. Yield 52%. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 3.00—3.05 (1H, m), 3.45—3.50 (1H, m), 6.82—6.88 (1H, m), 6.90—6.96 (1H, m), 7.16 (2H, d, J=8.3 Hz), 7.44 (2H, d, J=8.3 Hz), 7.54—7.60 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −4.5 (1F, dd, J=10, 209 Hz), −5.5 (1F, dd, J=7, 210 Hz), −31.3—−31.4 (1F, m), −32.9—−33.0 (1F, m). MS *m/z* (%): 328 (74, M^+), 169 (100). HRMS *m/z*: 328.0533 (Calcd for $C_{16}H_{12}F_4OS$: 328.0545). IR (neat) cm^{-1}: 1270.

2-[(Benzylthio)difluoromethyl]-2-(2,4-difluorophenyl)oxirane (**8p**): Colorless oil. Yield 99%. ^{1}H-NMR ($CDCl_3$) δ: 2.97—3.00 (1H, m), 3.49—3.50 (1H, m), 4.07 (2H, s), 6.80—6.85 (1H, m), 6.86—6.92 (1H, m), 7.26—7.34 (5H, m), 7.50—7.55 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.2 (1F, dd, J=10, 213 Hz), −6.3 (1F, dd, J=10, 213 Hz), −31.2—−31.3 (1F, m), −33.0—−33.1 (1F, m). MS *m/z*: 328 (0.3, M^+), 91 (100). HRMS *m/z*: 328.0530 (Calcd for $C_{16}H_{12}F_4OS$: 328.0545). IR (neat) cm^{-1}: 1270.

2-[Difluoro[(4-methoxybenzyl)thio]methyl]-2-(2,4-difluorophenyl)oxirane (**8q**): Colorless oil. Yield 71%. ^{1}H-NMR ($CDCl_3$) δ: 2.97—3.00 (1H, m), 3.48—3.50 (1H, m), 3.78 (3H, s), 4.04 (2H, s), 6.80—6.85 (1H, m), 6.83 (2H, d, J=8.8 Hz), 6.86—6.93 (1H, m), 7.22 (2H, d, J=8.8 Hz), 7.45—7.55 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −5.3 (1F, dd, J=10, 214 Hz), −6.5 (1F, dd, J=5, 214 Hz), −31.3—−31.4 (1F, m), −33.1—−33.2 (1F, m). MS *m/z* (%): 358 (34, M^+), 121 (100). HRMS *m/z*: 358.0681 (Calcd for $C_{17}H_{14}F_4O_2S$: 358.0650). IR (neat) cm^{-1}: 1250.

General Procedure for the Synthesis of 1,1-Difluoro-1-(substituted thio)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (9) 1,2,4-Triazole (2.2 mmol) and K_2CO_3 (1.1 mmol) were added to a solution of **8** (2 mmol) in dimethylformamide (DMF) (30 ml). The mixture was warmed at 65 °C for 5 h. After addition of aqueous $NaHCO_3$, the mixture was extracted with AcOEt. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using $CHCl_3$–MeOH [98 : 2 (v/v)] as a mobile phase to give **9**.

Resolution of (±)-9 into (+)-9 and (−)-9 Compound (±)-**9** (50 mg) was subjected to preparative HPLC (CHIRALCEL OD with pre-column CHIRALCEL OD), using *n*-hexane–2-propanol [3 : 1 (v/v)] as a mobile phase. The more mobile isomer is (−)-**9** and the less mobile isomer is (+)-**9**. Their optical yields are measured by HPLC (CHIRALCEL OD with pre-column CHIRALCEL OD) using *n*-hexane–2-propanol [1 : 1 (v/v)] as a mobile phase (flow rate: 0.5 ml/min, column temperature: 21 °C).

2-(2,4-Difluorophenyl)-1,1-difluoro-1-(methylthio)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9a**): Colorless powder. mp 122.2 °C. Yield 72%. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s), 4.82 (1H, d, J=14.2 Hz), 5.28 (1H, d, J=14.2 Hz), 5.76 (1H, s), 6.71—6.75 (1H, m), 6.76—6.88 (1H, m), 7.71—7.77 (1H, m), 7.80 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −9.4 (1F, dd, J=25, 211 Hz), −11.8 (1F, dd, J=15, 211 Hz), −30.4—−30.5 (1F, m), −32.2—−32.3 (1F, m). MS *m/z* (%): 321 (1, M^+), 224 (100). HRMS *m/z*: 321.0546 (Calcd for $C_{12}H_{11}F_4N_3OS$: 321.0559). IR (KBr) cm^{-1}: 3100.

(+)-**9a**: Colorless powder, mp 154—156 °C, e.e. 99.2%, $[\alpha]_D^{25}$: 64.6° (c=0.5, acetone), retention time (min): 9.23.

(−)-**9a**: Colorless powder, mp 154—156 °C, e.e. 99.2%, $[\alpha]_D^{25}$: −65.0° (c=0.5, acetone), retention time (min): 8.80.

2-(2,4-Difluorophenyl)-1-(ethylthio)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9b**): Colorless powder. mp 110.7 °C. Yield 85%. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.3 Hz), 2.85 (2H, q, J=7.3 Hz), 4.82 (1H, d, J=14.2 Hz), 5.28 (1H, d, J=14.2 Hz), 5.71 (1H, s), 6.71—6.77 (1H, m), 6.82—6.88 (1H, m), 7.70—7.77 (1H, m), 7.81 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −5.9 (1F, dd, J=25, 214 Hz), −9.3 (1F, dd, J=12, 214 Hz), −30.5—−30.6 (1F, m), −32.3—−32.4 (1F, m). MS *m/z* (%): 336 (4, M^++1), 224 (100). HRMS *m/z*: 336.0820 (Calcd for $C_{13}H_{14}F_4N_3OS$: 336.0794). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{13}H_{13}F_4N_3OS$: C, 46.56; H, 3.91; N, 12.53. Found: C, 46.15; H, 3.87; N, 12.43.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-propylthio-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9c**): Colorless powder. mp 86.7 °C. Yield 32%. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz), 1.61—1.70 (2H, m), 2.80 (2H, t, J=7.3 Hz), 4.82 (1H, d, J=14.2 Hz), 5.28 (1H, d, J=14.2 Hz), 5.65 (1H, s), 6.70—6.77 (1H, m), 6.83—6.88 (1H, m), 7.70—7.77 (1H, m), 7.82 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −5.4 (1F, dd, J=25, 211 Hz), −8.7 (1F, dd, J=16, 211 Hz), −30.2—−30.3 (1F, m), −32.0—−32.1 (1F, m). MS *m/z* (%): 349 (1, M^+), 224 (100). HRMS *m/z*: 349.0887 (Calcd for $C_{14}H_{15}F_4N_3OS$: 349.0871). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{14}H_{15}F_4N_3OS$: C, 48.13; H, 4.33; N, 12.03. Found: C, 8.41; H, 4.34; N, 12.07.

1-(Cyclopropylthio)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9d**): Colorless powder. mp 102.1 °C. Yield 57%. ^{1}H-NMR ($CDCl_3$) δ: 0.65—0.70 (2H, m), 0.95—1.00 (2H, m), 2.00—2.05 (1H, m), 4.81 (1H, d, J=14.2 Hz), 5.28 (1H, d, J=14.2 Hz), 5.68 (1H, s), 6.70—6.75 (1H, m), 6.80—6.85 (1H, m), 7.70—7.75 (1H, m), 7.81 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −7.6 (1F, dd, J=24, 214 Hz), −10.1 (1F, dd, J=22, 214 Hz), −30.6—−30.7 (1F, m), −32.3—−32.4 (1F, m). MS *m/z* (%): 347 (4, M^+), 224 (100). HRMS *m/z*: 347.0710 (Calcd for $C_{14}H_{13}F_4N_3OS$: 347.0715). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{14}H_{13}F_4N_3OS$: C, 48.41; H, 3.77; N, 12.10; S, 9.23. Found: C, 48.62; H, 3.82; N, 12.09; S, 9.14.

1-(Butylthio)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9e**): Colorless powder. mp 77.1 °C. Yield 61%. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz), 1.36—1.41 (2H, m), 1.57—1.64 (2H, m), 2.82 (2H, t, J=7.3 Hz), 4.82 (1H, d, J=14.6 Hz), 5.28 (1H, d, J=14.6 Hz), 5.68 (1H, s), 6.71—6.77 (1H, m), 6.82—6.88 (1H, m), 7.70—7.77 (1H, m), 7.81 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −5.8 (1F, dd, J=25, 211 Hz), −9.0 (1F, dd, J=16, 211 Hz), −30.4—−30.6 (1F, m), −32.3—−32.4 (1F, m). MS *m/z* (%): 364 (1, M^++1), 224 (100). HRMS *m/z*: 364.1014 (Calcd for $C_{15}H_{18}F_4N_3OS$: 349.0871). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{15}H_{17}F_4N_3OS$: C, 49.58; H, 4.72; N, 11.56; S, 8.82. Found: C, 49.68; H, 4.77; N, 11.54; S, 8.82.

1-(*tert*-Butylthio)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9f**): Colorless powder. mp 142.7 °C. Yield 42%. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 5.28 (1H, d, J=14.7 Hz), 5.28 (1H, d, J=14.7 Hz), 5.78 (1H, s), 6.70—6.78 (1H, m), 6.81—6.86 (1H, m), 7.68—7.74 (1H,m), 7.77 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −1.9 (1F, dd, J=25, 211 Hz), −6.7 (1F, dd, J=17, 211 Hz), −30.1—−30.2 (1F, m), −32.6—−32.7 (1F, m). MS *m/z* (%): 363 (0.8, M^+), 224 (100). HRMS *m/z*: 363.1020 (Calcd for $C_{15}H_{17}F_4N_3OS$: 363.1028). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{15}H_{17}F_4N_3OS$: C, 49.58; H, 4.72; N, 11.56. Found: C, 49.80; H, 4.80; N, 11.70.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-(pentylthio)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9g**): Colorless powder. mp 59 °C. Yield 58%. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz), 1.17—1.80 (6H, m), 2.82 (2H, t, J=7.3 Hz), 4.82 (1H, d, J=14.6 Hz), 5.28 (1H, d, J=14.6 Hz), 5.68 (1H, s), 6.71—6.77 (1H, m), 6.82—6.88 (1H, m), 7.70—7.77 (1H, m), 7.81 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −5.8 (1F, dd, J=25, 211 Hz), −9.0 (1F, dd, J=16, 211 Hz), −30.4—−30.6 (1F, m), −32.3—−32.4 (1F, m). MS *m/z* (%): 378 (1, M^++1), 224 (100). HRMS *m/z*: 378.1242 (Calcd for $C_{16}H_{20}F_4N_3OS$: 378.1263). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{16}H_{19}F_4N_3OS$: C, 50.78; H, 5.33; N, 11.10; S, 8.47. Found: C, 50.92; H, 5.07; N, 11.13; S, 8.50.

1,1-Difluoro-1-(methylthio)-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9h**): Colorless powder. mp 135.8 °C. Yield 38%. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (3H, s), 4.82 (1H, d, J=14.7 Hz), 4.87 (1H, d, J=14.7 Hz), 6.03 (1H, s), 7.30—7.35 (3H, m), 7.55—7.58 (2H, m), 7.69 (1H, s), 7.88 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −8.7 (1F, d, J=211 Hz), −11.4 (1F, d, J=211 Hz). MS *m/z* (%): 285 (5, M^+), 188 (100). HRMS *m/z*: 285.0734 (Calcd for $C_{12}H_{13}F_2N_3OS$: 285.0748). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{12}H_{13}F_2N_3OS$: C, 50.52; H, 4.58; N, 14.73; S, 11.24. Found: C, 50.70; H, 4.56; N, 14.77; S, 11.34.

1,1-Difluoro-2-(4-fluorophenyl)-1-(methylthio)3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9i**): Colorless powder. mp 123.6 °C. Yield 70%. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 4.75 (1H, d, J=14.2 Hz), 4.88 (1H, d, J=14.2 Hz), 5.55 (1H, s), 7.00—7.05 (2H, m), 7.50—7.55 (2H, m), 7.81 (1H, s), 7.92 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −8.7 (1F, dd, J=7, 214 Hz), −6.7 (1F, dd, J=11, 214 Hz), −35.8 (1F, s). MS *m/z* (%): 303 (2, M^+), 206 (100). HRMS *m/z*: 303.0658 (Calcd for $C_{12}H_{12}F_3N_3OS$: 303.0653). IR (KBr) cm^{-1}: 3100.

Anal. Calcd for $C_{12}H_{12}F_3N_3OS$: C, 47.52; H, 3.99; N, 13.85. Found: C, 47.55; H, 4.13; N, 13.94.

1,1-Difluoro-1-(methylthio)-3-(1*H*-1,2,4-triazol-1-yl)-2-[4-(trifluoromethyl)phenyl]-2-propanol (**9j**): Colorless powder. mp 188.5 °C. Yield 37%. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s), 4.77 (1H, d, J=14.6 Hz), 4.93 (1H, d, J=14.6 Hz), 5.50 (1H, s), 7.61 (2H, d, J=8.3 Hz), 7.67 (2H, d, J=8.3 Hz), 7.87 (1H, s), 7.95 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: 12.9 (3F, s), −8.5 (1F, d, J=213 Hz), −9.3 (1F, d, J=213 Hz). MS *m/z* (%): 353 (5, M^++1), 256 (100). HRMS *m/z* 353.0583 (Calcd for $C_{13}H_{12}F_5N_3OS$: 353.0621). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{13}H_{12}F_5N_3OS$: C, 44.19; H, 3.42; N, 11.89. Found: C, 44.14; H, 3.57; N, 11.78.

2-(2,4-Dichlorophenyl)-1,1-difluoro-1-(methylthio)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9k**): Colorless powder. mp 143.5 °C. Yield 69%. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 4.86 (1H, d, J=14.7 Hz), 5.83 (1H, d, J=14.7 Hz), 5.97 (1H, s), 7.23 (1H, dd, J=2.0, 8.8 Hz), 7.32 (1H, d, J=2.0 Hz), 7.83 (1H, s), 7.90 (1H, d, J=8.8 Hz), 8.21 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −6.2 (1F, d, J=210 Hz), −8.6 (1F, d, J=210 Hz). MS *m/z* (%): 353 (10, M^+), 214 (100). HRMS *m/z*: 352.9952 (Calcd for $C_{12}H_{11}Cl_2F_2N_3OS$: 352.9968). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{12}H_{11}Cl_2F_2N_3OS$: C, 40.69; H, 3.13; N, 11.86; Cl, 20.02. Found: C, 40.78; H, 3.18; N, 11.86; Cl, 20.22.

(+)-**9k**: Colorless powder, mp 121—123 °C, e.e. 99.3%, $[\alpha]_D^{25}$: 85.0° (c=0.03, methanol), retention time (min): 27.48.

(−)-**9k**: Colorless powder, mp 120—123 °C, e.e. 99.1%, $[\alpha]_D^{25}$: −87.5° (c=0.02, methanol), retention time (min): 17.26.

2-[2-(2,4-Difluorophenyl)-1,1-difluoro-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propylthio]ethyl Acetate (**9l**): Colorless oil. Yield 38%. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s), 3.06 (2H, t, J=6.8 Hz), 4.24 (2H, dt, J=2.0, 6.4 Hz), 4.81 (1H, d, J=14.1 Hz), 5.28 (1H, d, J=14.1 Hz), 5.75 (1H, s), 6.71—6.77 (1H, m), 6.83—6.89 (1H, m), 7.71—7.77 (1H, m), 7.82 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −8.3 (1F, dd, J=15, 210 Hz), −8.7 (1F, dd, J=16, 210 Hz), −30.6—−30.8 (1F, m), −32.0—−32.1 (1F, m). MS *m/z* (%): 393 (0.4, M^+), 224 (100). HRMS *m/z*: 393.0788 (Calcd for $C_{15}H_{15}F_4N_3O_2S$: 393.0770). IR (neat) cm^{-1}: 1740, 3100.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-(phenylthio)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9n**): Colorless powder. mp 117.3 °C. Yield 51%. ^{1}H-NMR ($CDCl_3$) δ: 4.88 (1H, d, J=14.2 Hz), 5.30 (1H, d, J=14.2 Hz), 5.78 (1H, s), 6.71—6.77 (1H, m), 6.87—6.89 (1H, m), 7.32—7.37 (2H, m), 7.40—7.42 (1H, m), 7.53—7.56 (2H, m), 7.77—7.81 (1H, m), 7.83 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −4.5 (1F, dd, J=26, 206 Hz), −7.4 (1F, dd, J=16, 206 Hz), −30.5—−30.7 (1F, m), −32.2—−32.3 (1F, m). FAB-MS *m/z*: 384 ($M+H^+$). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{17}H_{13}F_4N_3OS$: C, 53.26; H, 3.42; N, 10.96. Found: C, 53.16; H, 3.69; N, 10.86.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-[(4-methylphenyl)thio]-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9o**): Colorless powder. mp 94.1 °C. Yield 49%. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 4.88 (1H, d, J=14.7 Hz), 5.29 (1H, d, J=14.7 Hz), 5.77 (1H, s), 6.70—6.77 (1H, m), 6.85—6.90 (1H, m), 7.16 (2H, d, J=8.3 Hz), 7.43 (2H, d, J=8.3 Hz), 7.76—7.81 (1H, m), 7.83 (1H, s), 8.08 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −4.8 (1F, dd, J=14, 207 Hz), −7.8 (1F, dd, J=14, 207 Hz), −30.5—−30.6 (1F, m), −32.2—−32.3 (1F, m). MS *m/z* (%): 397 (3, M^+), 224 (100). HRMS *m/z*: 397.0865 (Calcd for $C_{18}H_{15}F_4N_3OS$: 397.0872). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{18}H_{15}F_4N_3OS$: C, 54.40; H, 3.80; N, 10.57. Found: C, 54.54; H, 3.74; N, 10.82.

1-(Benzylthio)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9p**): Colorless powder. mp 107.7 °C Yield 34%. ^{1}H-NMR ($CDCl_3$) δ: 4.03 (1H, d, J=12.7 Hz), 4.07 (1H, d, J=12.7 Hz), 4.82 (1H, d, J=14.7 Hz), 5.28 (1H, d, J=14.7 Hz), 5.73 (1H, s), 6.70—6.76 (1H, m), 6.81—6.86 (1H, m), 7.24—7.32 (5H,m), 7.69—7.76 (1H,m), 7.80 (1H, s), 8.08 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −5.9 (1F, dd, J=25, 211 Hz), −8.7 (1F, dd, J=15, 211 Hz), −30.5—−30.7 (1F, m), −32.2—−32.3 (1F, m). MS *m/z* (%): 397 (1, M^+), 224 (100). HRMS *m/z*: 397.0849 (Calcd for $C_{18}H_{15}F_4N_3OS$: 397.0872). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{18}H_{15}F_4N_3OS$: C, 54.40; H, 3.80; N, 10.57. Found: C, 54.46; H, 3.83; N, 10.51.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-[(4-methoxybenzyl)thio]-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**9q**): Colorless powder. mp 109.5 °C. Yield 63%. ^{1}H-NMR ($CDCl_3$) δ: 3.78 (3H, s), 4.00 (1H, d, J=12.2 Hz), 4.04 (1H, d, J=12.2 Hz), 4.82 (1H, d, J=14.6 Hz), 5.28 (1H, d, J=14.6 Hz), 5.68 (1H, s), 6.70—6.74 (1H, m), 6.75—6.86 (1H, m), 6.82 (2H, d, J=8.8 Hz), 7.21 (2H, d, J=8.8 Hz), 7.69—7.75 (1H, m), 7.81 (1H, s), 8.08 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −6.0 (1F, dd, J=25, 211 Hz), −8.8 (1F, dd, J=15, 211 Hz), −30.6—−30.7 (1F, m), −32.2—−32.3 (1F, m). MS *m/z* (%): 427 (4, M^+), 121 (100). HRMS *m/z*: 427.0992 (Calcd for $C_{19}H_{17}F_4N_3O_2S$: 427.0978). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{19}H_{17}F_4N_3O_2S$: C, 53.39; H, 4.01; N, 9.83. Found: C, 53.45; H, 4.10; N, 9.82.

Preparation of 2-(2,4-Difluorophenyl)-1,1-difluoro-1-[(2-hydroxyethyl)thio]-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (9m) by Hydrolysis of 9l 1 N NaOH (11 ml) was added to a solution of **9l** (10 mmol) in dioxane (50 ml) at room temperature with stirring. After the mixture was stirred at the same temperature for 1 h. The mixture was stirred at the same temperature for 15 h. After addition of aqueous ammonium acetate, the mixture was extracted with Et_2O. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using $CHCl_3$ to give **9m**. Colorless oil. Yield 90%. ^{1}H-NMR ($CDCl_3$) δ: 3.00 (2H, t, J=5.8 Hz), 3.20 (1H, br s), 3.78 (2H, t, J=5.8 Hz), 4.83 (1H, d, J=14.6 Hz), 5.27 (1H, d, J=14.6 Hz), 6.07 (1H, s), 6.73—6.79 (1H, m), 6.85—6.87 (1H, m), 7.68—7.74 (1H, m), 7.76 (1H, s), 8.11 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −4.4 (1F, dd, J=28, 210 Hz), −7.9 (1F, dd, J=5, 210 Hz), −29.8—−29.9 (1F, m), −31.9—−32.0 (1F, m). MS *m/z* (%): 352 (0.5, M^++1), 224 (100). HRMS *m/z*: 352.0741 (Calcd for $C_{13}H_{14}F_4N_3O_2S$: 352.0743). IR (neat) cm^{-1}: 3100.

General Procedure for Alkylation of 9b NaH (11 mmol) was added to a solution of **9b** (10 mmol) in DMSO (50 ml) at room temperature with stirring. After the mixture was stirred at the same temperature for 1 h, alkyl halide (55 mmol) was added to the solution at room temperature with stirring. The mixture was stirred at the same temperature for 15 h. After addition of aqueous NH_4Cl, the mixture was extracted with Et_2O. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using $CHCl_3$ to give **10**.

1-[2-(2,4-Difluorophenyl)-3-(ethylthio-3,3-difluoro-2-methoxypropyl]-1*H*-1,2,4-triazole (**10r**): Colorless oil. Yield 68%. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.3 Hz), 2.75—2.85 (2H, m), 3.72 (3H, d, J=1.5 Hz), 5.05 (1H, d, J=14.7 Hz), 5.15 (1H, d, J=14.7 Hz), 6.80—6.90 (2H, m), 7.60—7.65 (1H, m), 7.79 (1H, s), 7.99 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −0.3 (1F, dd, J=37, 214 Hz), −1.3 (1F, dd, J=22, 214 Hz), −28.3—−28.4 (1F, m), −32.5—−32.6 (1F, m). MS *m/z* (%): 349 (2, M^+), 238 (100). HRMS *m/z*: 349.0891 (Calcd for $C_{14}H_{15}F_4N_3OS$: 349.0872). IR (neat) cm^{-1}: 1050.

1-[2-(Benzyloxy)-2-(2,4-difluorophenyl)-3-(ethylthio)-3,3-difluoropropyl]-1*H*-1,2,4-triazole (**10s**): Colorless oil. Yield 94%. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.7 Hz), 2.80—2.90 (2H, m), 4.93 (1H, d, J=10.3 Hz), 5.13 (1H, d, J=10.3 Hz), 5.18 (1H, d, J=15.6 Hz), 5.27 (1H, d, J=15.6 Hz), 6.75—6.85 (2H, m), 7.30—7.45 (5H, m), 7.60—7.65 (1H, m), 7.79 (1H, s), 7.94 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −0.2 (1F, dd, J=37, 214 Hz), −0.8 (1F, dd, J=22, 214 Hz), −28.3—−28.4 (1F, m), −32.4—−32.5 (1F, m). MS *m/z* (%): 426 (1, M^++1), 238 (100). HRMS *m/z*: 426.1252 (Calcd for $C_{20}H_{20}F_4N_3OS$: 426.1264). IR (KBr) cm^{-1}: 1070.

General Procedure for the Synthesis of 1,1-Difluoro-1-(substituted sulfonyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (2) *m*-Chloroperbenzoic acid (*m*-CPBA) (25 mmol) was added to 2-(substituted thio)-2-propanol (**9**) (10 mmol) in CH_2Cl_2 (30 ml) at room temperature with stirring. The mixture was stirred at room temperature for 5 h. After addition of aqueous $Na_2S_2O_3$, the mixture was extracted with $CHCl_3$. The organic extract was washed with aqueous $Na_2S_2O_3$, water and brine, and dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using $CHCl_3$–MeOH [98 : 2 (v/v)] as a mobile phase to give **2**.

Resolution of (±)-2 into (+)-2 and (−)-2 Compound (±)-**2** (50 mg) was subjected to preparative HPLC (CHIRALCEL OD with pre-column CHIRALCEL OD), using *n*-hexane–2-propanol [3 : 1 (v/v)] as a mobile phase. Their optical yields are measured by HPLC (CHIRALCEL OD with pre-column CHIRALCEL OD) using *n*-hexane–2-propanol [1 : 1 (v/v)] as a mobile phase (flow rate: 0.5 ml/min, column temperature: 21 °C).

2-(2,4-Difluorophenyl)-1,1-difluoro-1-(methylsulfonyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2a**): Colorless powder. mp 104—105 °C, Yield 74%. ^{1}H-NMR ($CDCl_3$) δ: 3.23 (3H, s), 5.20 (1H, d, J=14.7 Hz), 5.35 (1H, d, J=14.7 Hz), 6.20 (1H, s), 6.75—6.90 (2H, m), 7.65—7.73 (1H, m), 7.76 (1H, s), 8.07 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −30.5—30.8 (1F, m), −31.0—−31.2 (1F, m), −31.5 (1F, dd, J=13, 254 Hz), −36.5 (1F, dd, J=29, 254 Hz). MS *m/z* (%): 354 (28, M^++1), 141 (100). HRMS *m/z*: 354.0546 (Calcd for $C_{12}H_{12}F_4N_3O_3S$: 354.0535). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{12}H_{11}F_4N_3O_3S$: C, 40.80; H, 3.14; N, 11.89; S, 9.07. Found: C, 40.93; H, 3.14; N, 11.93; S,9.10.

(+)-**2a**: Colorless powder, mp 102—103 °C, e.e. 99.5%, $[\alpha]_D^{25}$: 28.4° (c=0.125, acetone), retention time (min): 16.30.

(−)-**2a**: Colorless powder, mp 102—103 °C, e.e. 99.2%, $[\alpha]_D^{25}$: −28.0° (c=0.25, acetone), retention time (min): 15.62.

2-(2,4-Difluorophenyl)-1-(ethylsulfonyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2b**): Colorless powder. mp 126.3 °C. Yield 78%. ^{1}H-NMR

($CDCl_3$) δ: 1.49 (3H, t, J=7.7 Hz), 3.41 (2H, q, J=7.7 Hz), 5.19 (1H, d, J=14.7 Hz), 5.35 (1H, d, J=14.7 Hz), 6.11 (1H, s), 6.77—6.93 (2H, m), 7.65—7.74 (1H,m), 7.76 (1H, s), 8.07 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −30.4—30.6 (1F, m), −31.1—−31.3 (1F, m), −31.1 (1F, dd, J=14, 254 Hz), −35.0 (1F, dd, J=29, 254 Hz). MS m/z (%): 368 (39, M^++1), 274 (100). HRMS m/z: 368.0674 (Calcd for $C_{13}H_{14}F_4N_3O_3S$: 368.0706). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{13}H_{13}F_4N_3O_3S$: C, 42.51; H, 3.57; N, 11.44. Found: C, 42.69; H, 3.68; N, 11.39.

(+)-**2b**: Colorless powder, mp 131—132 °C, e.e. 100.0%, $[\alpha]_D^{25}$: 23.0° (c=0.1, acetone), retention time (min): 16.72.

(−)-**2b**: Colorless powder, mp 131—132 °C, e.e. 100.0%, $[\alpha]_D^{25}$: −20.0° (c=0.1, acetone), retention time (min): 26.00.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-(propylsulfonyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2c**): Colorless powder. mp 113.7 °C. Yield 68%. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7.3 Hz), 1.95—2.05 (2H, m), 3.33—3.36 (2H, m), 5.19 (1H, d, J=14.7 Hz), 5.34 (1H, d, J=14.7 Hz), 6.08 (1H, s), 6.75—6.80 (1H, m), 6.83—6.89 (1H, m), 7.67—7.78 (1H, m), 7.78 (1H, s), 8.07 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −31.1—−31.2 (1F, m), −31.8—−31.9 (1F, m), −32.3 (1F, dd, J=15, 254 Hz), −36.1 (1F, dd, J=29, 254 Hz). MS m/z (%): 382 (3, M^++1), 274 (100). HRMS m/z: 382.0974 (Calcd for $C_{14}H_{16}F_4N_3O_3S$: 382.0858). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{14}H_{15}F_4N_3O_3S$: C, 48.13; H, 4.33; N, 12.03. Found: C, 48.41; H, 4.34; N, 12.07.

1-(Cyclopropylsulfonyl)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2d**): Colorless powder. mp 153.3 °C Yield 76%. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.25 (2H, m), 1.40—1.45 (2H, m), 2.70—2.75 (1H, m), 5.20 (1H, d, J=14.7 Hz), 5.92 (1H, d, J=14.7 Hz), 5.92 (1H, s), 6.75—6.80 (1H, m), 6.85—6.90 (1H, m), 7.70—7.75 (1H, m), 7.80 (1H, s), 8.08 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −30.4 (1F, dd, J=18, 250 Hz), −30.5—−30.6 (1F, m), −31.4—−31.5 (1F, m), −33.6 (1F, dd, J=29, 250 Hz). MS m/z (%): 380 (0.9, M^++1), 274 (100). HRMS m/z: 380.0700 (Calcd for $C_{14}H_{14}F_4N_3O_3S$: 380.0692). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{14}H_{13}F_4N_3O_3S$: C, 44.33; H, 3.45; N, 11.08. Found: C, 44.20; H, 3.51; N, 11.06.

(+)-**2d**: Colorless powder, mp 130—132 °C, e.e. 100.0%, $[\alpha]_D^{25}$: 22.5° (c=0.1, acetone), retention time (min): 13.60.

(−)-**2d**: Colorless powder, mp 130—132 °C, e.e. 100.0%, $[\alpha]_D^{25}$: −24.5° (c=0.1, acetone), retention time (min): 19.00.

1-(Butylsulfonyl)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2e**): Colorless powder. mp 84.9 °C. Yield 32%. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7.3 Hz), 1.49—1.55 (2H, m), 1.89—1.97 (2H, m), 3.34—3.38 (2H, m), 5.19 (1H, d, J=14.2 Hz), 5.34 (1H, d, J=14.2 Hz), 6.06 (1H, s), 6.74—6.80 (1H, m), 6.84—6.89 (1H, m), 7.65—7.72 (1H, m), 7.78 (1H, s), 8.07 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −30.5—−30.6 (1F, m), −31.2—−31.3 (1F, m), −31.4 (1F, dd, J=14, 254 Hz), −35.4 (1F, dd, J=29, 254 Hz). MS m/z (%): 396 (3, M^++1), 274 (100). HRMS m/z: 396.1013 (Calcd for $C_{15}H_{18}F_4N_3O_3S$: 396.1019). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{15}H_{17}F_4N_3OS$: C, 45.57; H, 4.33; N, 10.63. Found: C, 45.60; H, 4.40; N, 10.58.

1-(*tert*-Butylsulfonyl)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2f**): Colorless powder. mp 155.1 °C. Yield 71%. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (9H, s), 5.17 (1H, d, J=14.2 Hz), 5.31 (1H, d, J=14.2 Hz), 5.66 (1H, s), 6.76—6.84 (1H, m), 6.86—6.89 (1H, m), 7.66—7.72 (1H, m), 7.79 (1H, s), 8.13 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −25.0 (1F, dd, J=24, 238 Hz), −26.1 (1F, dd, J=24, 238 Hz), −29.3—−29.4 (1F, m), −31.6—−31.7 (1F, m). MS m/z (%): 396 (3, M^++1), 274 (100). HRMS m/z: 396.0995 (Calcd for $C_{15}H_{18}F_4N_3O_3S$: 396.1019). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{15}H_{17}F_4N_3OS$: C, 45.57; H, 4.33; N, 10.63. Found: C, 45.79; H, 4.45; N, 10.56.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-(pentylsulfonyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2g**): Colorless powder. mp 78.2 °C. Yield 46%. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7.3 Hz), 1.17—1.90 (6H, m), 3.36—3.40 (2H, m), 5.19 (1H, d, J=14.2 Hz), 5.34 (1H, d, J=14.2 Hz), 6.06 (1H, s), 6.74—6.80 (1H, m), 6.84—6.89 (1H, m), 7.65—7.72 (1H, m), 7.78 (1H, s), 8.07 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −30.5—−30.6 (1F, m), −31.2—−31.3 (1F, m), −31.4 (1F, dd, J=14, 254 Hz), −35.4 (1F, dd, J=29, 254 Hz). MS m/z (%): 410 (2, M^++1), 274 (100). HRMS m/z: 410.1139 (Calcd for $C_{16}H_{20}F_4N_3O_3S$: 410.1161). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{16}H_{19}F_4N_3O_3S$: C, 46.94; H, 4.68; N, 10.26. Found: C, 46.710; H, 4.82; N, 10.13.

1,1-Difluoro-1-(methylsulfonyl)-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2h**): Colorless powder. mp 124.0 °C. Yield 46%. ^{1}H-NMR ($CDCl_3$) δ: 3.14 (3H, s), 4.92 (1H, d, J=14.2 Hz), 5.28 (1H, d, J=14.2 Hz), 6.2 (1H, s), 7.30—7.40 (3H, m), 7.50—7.56 (2H, m), 7.72 (1H, s), 7.91 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −30.7 (1F, d, J=256 Hz), −35.5 (1F, d, J=256 Hz). MS m/z (%): 318 (2, M^++1), 238 (100). HRMS m/z: 318.0711 (Calcd for $C_{12}H_{14}F_2N_3O_3S$: 318.0725). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{12}H_{13}F_2N_3O_3S$: C, 45.42; H, 4.13; N, 13.24. Found: C, 45.34; H, 4.23; N, 13.21.

1,1-Difluoro-2-(4-fluorophenyl)-1-(methylsulfonyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2i**): Colorless powder. mp 168.9 °C. Yield 33%. ^{1}H-NMR ($CDCl_3$) δ: 3.16 (3H, s), 4.86 (1H, d, J=14.2 Hz), 5.28 (1H, d, J=14.2 Hz), 6.00 (1H, s), 7.00—7.05 (2H, m), 7.45—7.50 (2H, m), 7.79 (1H, s), 7.88 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −8.7 (1F, dd, J=7, 256 Hz), −6.7 (1F, dd, J=11, 256 Hz), −35.8 (1F, s). MS m/z (%): 336 (1, M^++1), 256 (94), 123 (100). HRMS m/z: 336.0635 (Calcd for $C_{12}H_{13}F_3N_3O_3S$: 336.0630). IR (KBr) cm^{-1}: 3050. *Anal.* Calcd for $C_{12}H_{12}F_3N_3O_3S$: C, 42.98; H, 3.61; N, 12.53; S, 9.56. Found: C, 43.09; H, 3.63; N, 12.57; S, 9.56.

(+)-**2i**: Colorless powder, mp 103—106 °C, e.e. 99.0%, $[\alpha]_D^{25}$: 27.0° (c=0.1, methanol), retention time (min): 13.70.

(−)-**2i**: Colorless powder, mp 102—105 °C, e.e. 99.8%, $[\alpha]_D^{25}$: −31.0° (c=0.1, methanol), retention time (min): 20.23.

1,1-Difluoro-1-(methylsulfonyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-[4-(trifluoromethyl)phenyl]-2-propanol (**2j**): Colorless powder. mp 188.7 °C. Yield 53%. ^{1}H-NMR ($CDCl_3$) δ: 3.19 (3H, s), 3.56 (1H, s), 5.03 (1H, d, J=14.7 Hz), 5.25 (1H, d, J=14.7 Hz), 7.60 (2H, d, J=8.8 Hz), 7.66 (2H, d, J=8.8 Hz), 7.73 (1H, s), 8.06 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: 12.7 (3F, s), −31.4 (1F, d, J=254 Hz), −34.4 (1F, d, J=254 Hz). MS m/z (%): 386 (0.9, M^++1), 366 (7, M^+−F), 306 (100). HRMS m/z: 366.0504 (Calcd for $C_{13}H_{12}F_4N_3O_3S$: 366.0535). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{13}H_{12}F_5N_3O_3S$: C, 40.52; H, 3.14; N, 10.91. Found: C, 40.30; H, 3.09; N, 10.73.

(+)-**2j**: Colorless powder, mp 147—150 °C, e.e. 99.5%, $[\alpha]_D^{25}$: 20.5° (c=0.1, methanol), retention time (min): 13.20.

(−)-**2j**: Colorless powder, mp 153—154 °C, e.e. 99.5%, $[\alpha]_D^{25}$: −20.0° (c=0.1, methanol), retention time (min): 21.72.

2-(2,4-Dichlorophenyl)-1,1-difluoro-1-(methylsulfonyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2k**): Colorless powder. mp 146.7 °C. Yield 91%. ^{1}H-NMR ($CDCl_3$) δ: 3.23 (3H, s), 5.21 (1H, d, J=14.6 Hz), 5.99 (1H, d, J=14.6 Hz), 6.40 (1H, s), 7.23 (1H, dd, J=2.0, 8.8 Hz), 7.35 (1H, d, J=2.0 Hz), 7.81 (1H, s), 7.83 (1H, d, J=8.8 Hz), 8.16 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −29.0 (1F, d, J=248 Hz), −32.3 (1F, d, J=248 Hz). MS m/z (%): 386 (1, M^++1), 306 (100). HRMS m/z: 385.9921 (Calcd for $C_{12}H_{12}Cl_2F_2N_3O_3S$: 385.9944). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{12}H_{11}Cl_2F_2N_3O_3S$: C, 37.32; H, 2.87; N, 10.88; Cl, 18.36. Found: C, 37.43; H, 2.91; N, 10.91; Cl, 18.00.

(+)-**2k**: Colorless powder, mp 165—167 °C, e.e. 100.0%, $[\alpha]_D^{25}$: 30.2° (c=0.04, methanol), retention time (min): 25.91.

(−)-**2k**: Colorless powder, mp 165—167 °C, e.e. 96.9%, $[\alpha]_D^{25}$: −29.5° (c=0.1, methanol), retention time (min): 22.51.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-[(2-hydroxyethyl)sulfonyl]-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2m**): Colorless powder. mp 77—80 °C. Yield 14%. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (2H, t, J=5.4 Hz), 4.20—4.25 (2H, m), 5.19 (1H, d, J=14.2 Hz), 5.35 (1H, d, J=14.2 Hz), 6.15 (1H, s), 6.75—6.79 (1H, m), 6.80—6.89 (1H, m), 7.64—7.70 (1H, m), 7.81 (1H, s), 8.06 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −30.8—−30.9 (2F, m), −31.2 (1F, dd, J=13, 252 Hz), −36.8 (1F, dd, J=33, 252 Hz). MS m/z (%): 384 (1, M^++1), 274 (100). HRMS m/z: 384.0627 (Calcd for $C_{13}H_{14}F_4N_3O_4S$: 384.0641). IR (neat) cm^{-1}: 3100. *Anal.* Calcd for $C_{13}H_{13}F_4N_3O_4S$: C, 40.73; H, 3.42; N, 10.96. Found: C, 40.51; H, 3.45; N, 10.96.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-(phenylsulfonyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2n**) Colorless powder. mp 123.4 °C. Yield 49%. ^{1}H-NMR ($CDCl_3$) δ: 5.27 (1H, d, J=14.7 Hz), 5.36 (1H, d, J=14.7 Hz), 6.71—6.77 (1H, m), 6.83—6.88 (1H, m), 7.59—7.63 (2H, m), 7.70—7.82 (2H, m), 7.81 (1H, s), 7.97—8.00 (2H, m), 8.10 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −29.3 (1F, dd, J=11, 253 Hz), −30.0—−30.1 (1F, m), −30.2 (1F, dd, J=25, 253 Hz), −31.1—−31.2 (1F, m). MS m/z (%): 416 (1, M^++1), 274 (100). HRMS m/z: 416.0718 (Calcd for $C_{17}H_{14}F_4N_3O_3S$: 416.0691). IR (neat) cm^{-1}: 3100. *Anal.* Calcd for $C_{17}H_{13}F_4N_3O_3S$: C, 49.16; H, 3.15; N, 10.12. Found: C, 49.23; H, 3.15; N, 10.11.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-[(4-methylphenyl)sulfonyl]-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2o**): Colorless powder. mp 108.9 °C. Yield 63%. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s), 5.26 (1H, d, J=14.7 Hz), 5.36 (1H, d, J=14.7 Hz), 5.80 (1H, s), 6.71—6.77 (1H, m), 6.82—6.88 (1H, m), 7.40 (2H, d, J=8.3 Hz), 7.68—7.74 (1H, m), 7.81 (1H, s), 7.85 (2H, d, J=8.3 Hz), 8.11 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −30.0 (1F, dd, J=21, 249 Hz), −30.1—−30.3 (1F, m), −30.8 (1F, dd, J=19, 249 Hz), −31.4—−31.6 (1F, m). MS m/z (%): 430 (0.5, M^++1), 274 (100). HRMS m/z:

430.0833 (Calcd for $C_{18}H_{16}F_4N_3O_3S$: 430.0863). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{18}H_{15}F_4N_3O_3S$: C, 50.35; H, 3.52; N, 9.79. Found: C, 50.43; H, 3.60; N, 9.88.

1-(Benzylsulfonyl)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2p**): Colorless powder. mp 138.6 °C Yield 64%. ^{1}H-NMR ($CDCl_3$) δ: 4.59 (1H, d, J=13.2 Hz), 4.64 (1H, d, J=13.2 Hz), 5.23 (1H, d, J=14.7 Hz), 5.35 (1H, d, J=14.7 Hz), 6.19 (1H, s), 6.74—6.79 (1H, m), 6.84—6.89 (1H, m), 7.42 (5H, s), 7.68—7.75 (1H, m), 7.79 (1H, s), 8.07 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −38.5 (1F, dd, J=14, 253 Hz), −41.9 (1F, dd, J=17, 253 Hz), −38.4—−38.7 (1F, m), −39.0—−39.1 (1F, m). MS *m/z* (%): 430 (1, M^++1), 274 (52), 91 (100). HRMS *m/z*: 430.0834 (Calcd for $C_{18}H_{16}F_4N_3O_3S$: 430.0863). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{18}H_{15}F_4N_3O_3S$: C, 50.35; H, 3.52; N, 9.79. Found: C, 50.51; H, 3.69; N, 9.81.

2-(2,4-Difluorophenyl)-1,1-difluoro-1-[(4-methoxyphenyl)methylsulfonyl]-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2q**): Colorless powder. mp 79.0 °C. Yield 37%. ^{1}H-NMR ($CDCl_3$) δ: 3.81 (3H, s), 4.53 (1H, d, J=13.4 Hz), 4.59 (1H, d, J=13.4 Hz), 5.22 (1H, d, J=14.7 Hz), 5.35 (1H, d, J=14.7 Hz), 6.17 (1H, s), 6.74—6.80 (1H, m), 6.84—6.90 (1H, m), 6.93 (2H, d, J=8.3 Hz), 7.34 (2H, d, J=8.3 Hz), 7.68—7.74 (1H, m), 7.80 (1H, s), 8.09 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −30.3—−30.5 (1F, m), −30.6 (1F, dd, J=14, 254 Hz), −30.9—−31.2 (1F, m), −34.0 (1F, dd, J=27, 254 Hz). MS *m/z* (%): 459 (0.2, M^+), 121 (100). HRMS *m/z*: 459.0903 (Calcd for $C_{19}H_{17}F_4N_3O_4S$: 459.0876). IR (KBr) cm^{-1}: 3100. *Anal.* Calcd for $C_{19}H_{17}F_4N_3O_4S$: C, 49.67; H, 3.73; N, 9.15; S, 6.98. Found: C, 49.59; H, 3.82; N, 9.15.

1-[2-(2,4-Difluorophenyl)-3-(ethylsulfonyl)-3,3-difluoro-2-methoxypropyl]-1*H*-1,2,4-triazole (**11r**): Colorless oil. Yield 78%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7.3 Hz), 3.17—3.23 (2H, m), 3.74 (3H, d, J=1.2 Hz), 5.16 (1H, d, J=15.6 Hz), 5.32 (1H, d, J=15.6 Hz), 6.78—6.90 (2H, m), 7.53—7.60 (1H, m), 7.78 (1H, s), 8.06 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −25.3 (1F, dd, J=30, 248 Hz), −26.8 (1F, dd, J=16, 248 Hz), −28.0—−28.1 (1F, m), −31.2—−31.3 (1F, m). MS *m/z* (%): 382 (0.5, M^++1), 288 (100). HRMS *m/z*: 382.0834 (Calcd for $C_{14}H_{16}F_4N_3O_3S$: 382.0848). IR (KBr) cm^{-1}: 1050.

1-[2-(Benzyloxy)-2-(2,4-difluorophenyl)-3-ethylsulfonyl-3,3-difluoropropyl]-1*H*-1,2,4-triazole (**11s**): Colorless powder. mp 117.3 °C. Yield 33%. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.7 Hz), 3.15—3.21 (2H, m), 5.05 (1H, d, J=9.8 Hz), 5.10 (1H, d, J=9.8 Hz), 5.30 (1H, d, J=15.6 Hz), 5.47 (1H, d, J=15.6 Hz), 6.80—6.90 (2H, m), 7.34—7.41 (3H, m), 7.45—7.47 (2H, m), 7.58—7.62 (1H, m), 7.80 (1H, s), 8.04 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −25.3 (1F, dd, J=30, 248 Hz), −26.8 (1F, dd, J=16, 248 Hz), −27.6—−27.8 (1F, m), −31.0—−31.1 (1F, m). MS *m/z* (%): 458 (0.5, M^++1), 364 (12, M^+-SO_2Et), 258 (100). HRMS *m/z*: 364.1046 (Calcd for $C_{18}H_{14}F_4N_3O$: 364.1072). IR (KBr) cm^{-1}: 1050. *Anal.* Calcd for $C_{20}H_{19}F_4N_3O_3S$: C, 52.51; H, 4.19; N, 9.19. Found: C, 52.48; H, 4.22; N, 9.08.

Preparation of 1-[2-(2,4-Difluorophenyl)-3-methoxy-3-(methylsulfonyl)]-1*H*-1,2,4-triazole (11t) Diazomethane (0.29 M/l in Et_2O; 10 ml) was added to a solution of 2-(2,4-difluorophenyl)-2,2-difluoro-3-(methylsulfonyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**2a**) (0.3 mmol) in MeOH (10 ml) with stirring at 0 °C. The mixture was stirred at room temperature for 12 h, and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 8 (v/v)] to give **11t**. Yield 82%. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.03 (3H, s), 3.75 (3H, s), 5.18 (1H, d, J=15.6 Hz), 5.32 (1H, d, J=15.6 Hz), 6.79—6.84 (1H, m), 6.85—6.91 (1H, m), 7.53—7.59 (1H, m), 7.78 (1H, s), 8.07 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −25.4 (1F, dd, J=30, 248 Hz), −27.1 (1F, dd, J=15, 248 Hz), −27.9—−28.2 (1F, m), −31.1—−31.2 (1H, m). FAB-MS *m/z*: 368 (M^++1). MS *m/z* (%) 368 (0.6, M^++1), 288 (100). HRMS *m/z*: 368.0712 (Calcd for $C_{13}H_{14}F_4N_3O_3S$: 368.0706). IR (KBr) cm^{-1}: 1400.

Synthesis of 2-(2,4-Difluorophenyl)-3-(methylsulfonyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-propanol (12) **12** was prepared from 2′,4′-difluoro-2-(methylthio)acetophenone.[8] Colorless powder. mp 149.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.86 (3H, s), 3.42 (1H, d, J=15.1 Hz), 3.84 (1H, d, J=15.1 Hz), 4.62 (1H, d, J=14.7 Hz), 4.88 (1H, d, J=14.7 Hz), 5.49 (1H, s), 6.83—6.92 (2H, m), 7.50—7.57 (1H, m), 7.87 (1H, s), 8.04 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −32.1—−32.2 (1F, m), −33.6—−33.8 (1F, m). MS *m/z* (%): 318 (3, M^++1), 121 (100). HRMS *m/z*: 318.0704 (Calcd for $C_{12}H_{14}F_2N_3O_3S$: 318.0725). IR (KBr) cm^{-1}: 3100. *Anal.* calcd. For $C_{12}H_{13}F_2N_3O_3S$: C, 45.42; H, 4.13; N, 13.24. Found: C, 45.63; H, 4.17; N, 13.48.

***In Vitro* Antifungal Activities** The MICs of the compounds were determined by the National Committee for Clinical Laboratory Standards (NCCLS) guideline M27-A[9] broth microdilution method for yeasts and by the NCCLS guideline M38-P[10] for filamentous fungi. The compounds were dissolved in DMSO (final concentration of DMSO: 1%), and were tested at different concentrations (from 8 to 0.016 μg/ml). *C. albicans* (ATCC 90028) and *C. krusei* (ATCC 6258) for yeast strains, and *A. flavus* (IFM 41935) and *A. fumigatus* (IFM 40808) for filamentous fungi strains were used. The MICs were measured after 48 h incubation at 35 °C.

***In Vivo* Antifungal Activities** The therapeutic effect of the compounds of single or four-day repeated oral administration on a mouse model of systemic infection with *C. albicans* was investigated in comparison with that of FLCZ. Systemic candidosis was induced in four-week-old male ICR mice, and five or ten mice per group were used. Mice were infected intravenously by inoculation of *C. albicans* IFM 40009 suspension (3×10^6 cells/mouse) into the lateral tail vein. The compounds and FLCZ were dissolved in 20% polyethylene glycol 200 (doses were 5, 1.25 and 0.313 mg/kg/day), and were administered orally or i.v. 1 h after the challenge once or daily for 4 consecutive days. The therapeutic effect was presented as the duration of survival days until days 14 or 18 after infection, and were compared with control group. The significantly difference from control were obtained by Kaplane-Miere method (cox-mantel test).

X-Ray Crystallographic Analysis of (−)-2a Diffraction measurments were performed on a RAXIS-RAPID diffractometer using the graphite monochromated Cu-$K\alpha$ radiation (λ=1.54178 Å). The crystal data are as follows: $C_{13}H_{13}O_3N_3F_3S$, F.W.=367.32, orthorhombic, space group $P2_12_12_1$, a=13.3423(5) Å, b=20.1496(9) Å, c=11.7259(4) Å, V=3152.4(2) Å^3, Z=8. A total of 31618 reflections were measured, of which 5622 unique (R_{int}=0.066) reflections were used for analysis. The final R-factor and weighted R-factor were 0.042 and 0.040, respectively. The structure was solved by the direct methods using SHELX86,[11] and expanded using Fourier techniques.[12] All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.

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