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Highly Diastereoselective Synthesis of α-Difluoromethyl Amines from *N-tert*-Butylsulfinyl Ketimines and Difluoromethyl Phenyl Sulfone

Jun Liu and Jinbo Hu*[a]

Abstract: The first highly efficient and stereoselective difluoromethylation of structurally diverse *N-tert*-butylsulfinyl ketimines has been achieved with an in situ generated $PhSO_2CF_2^-$ anion, which provides a powerful synthetic method for the preparation of a variety of structurally diverse homochiral α-difluoromethyl tertiary carbinamines, including α-difluoromethyl allylic amines and α-difluoromethyl propargylamines. The stereocontrol mode of the present diastereoselective difluoromethylation of ketimines was found to be different from that of other known fluoroalkylations of *N-tert*-butylsulfinyl aldimines, which suggests that a cyclic six-membered transition state may be involved in the reaction.

Keywords: amines · difluoromethylation · fluorine · ketimines · nucleophilic addition

Introduction

Chiral fluorinated amines are prevalent as a common motif in the design of new biologically important compounds, given the fact that the incorporation of a fluorine-containing group can tune the basicity of an amine functionality and thus enhance the bioavailability of a target drug molecule.[1] Therefore, chiral fluorinated amines have been the focus of numerous studies, and a number of strategies have been developed for their asymmetric synthesis, including the use of fluorination reagents and fluorinated building blocks.[2] Recently, diastereoselective nucleophilic fluoroalkylation of imines has attracted considerable attention as a promising method for the asymmetric synthesis of chiral fluorinated amines.[3,4] In this context, Ellman's *N-tert*-butylsulfinyl imines have been widely used in the asymmetric synthesis of fluorinated amines.[2c,4,5]

In 2001, Prakash et al. reported the first efficient synthesis of α-trifluoromethyl amines through diastereoselective nucleophilic trifluoromethylation of *N-tert*-butylsulfinyl aldimines, which opened up a new application of *N-tert*-butylsulfinyl imines for the synthesis of fluorinated amines.[4a] This methodology was then extended to the synthesis of α-trifluoromethyl allylic amines[4b] and α-trifluoromethylated vicinal ethylenediamines.[4c] (1*R*,1′*R*)-1,1′-(Anthracene-9,10-diyl)bis(2,2,2-trifluoroethanamine), a chiral diamine with low basicity, was also successfully synthesized by Estivill et al. using the same strategy.[4j] Not only did *N-tert*-butylsulfinyl imines readily undergo electrophilic reactions with the Ruppert–Prakash reagent (Me_3SiCF_3), but they also underwent the addition of fluorinated Reformatsky reagents to afford β-branched α,α-difluoro-β-amino esters.[4i]

Owing to the increasing importance of the CF_2H group in medicinal chemistry and drug discovery,[6] α-difluoromethyl amines have attracted broad interest during the past decade. Among the few known methods, stereoselective nucleophilic difluoromethylation of *N-tert*-butylsulfinyl imines is one of the most straightforward approaches for synthesizing α-difluoromethyl amines. Previously, we found difluoromethyl phenyl sulfone, $PhSO_2CF_2H$ (**1**), to be a versatile nucleophilic difluoromethylation reagent for the selective introduction of highly useful difluorinated moieties such as difluoromethyl (CF_2H), difluoromethylene ($-CF_2-$), and difluoromethylidene ($=CF_2$).[7] We successfully synthesized chiral α-difluoromethyl amines[4d] and α-difluoromethyl ethylenediamines[4g] by diastereoselective nucleophilic difluoromethylation of *N-tert*-butylsulfinyl aldimines using $PhSO_2CF_2H$ as a difluoromethylating agent. However, although significant progress has been made in the arena of difluoromethylation of *N-tert*-butylsulfinyl aldimines, the corresponding difluoromethylation of *N-tert*-butylsulfinyl ketimines has proved to be more challenging.[4h] The difficulty of nucleophilic fluoroalkylation of *N-tert*-butylsulfinyl ketimines can be attributed

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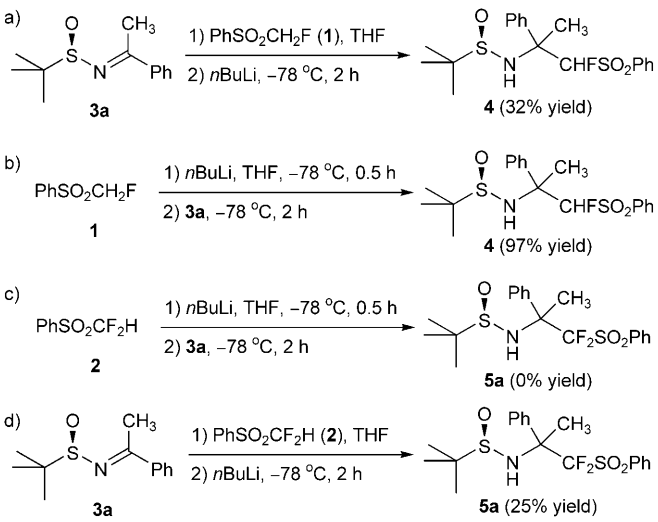
to the relatively low electrophilicity and possible aza-enolization of ketimines, as well as the relatively low thermal stability and nucleophilicity of fluorinated carbanions R_f^- (due to the "negative fluorine effect").[8]

In this paper, as part of our continuing effort to develop selective difluoromethylation methodologies, we wish to disclose the first highly diastereoselective difluoromethylation of structurally diverse *N*-*tert*-butylsulfinyl ketimines, which has enabled us to efficiently synthesize α-difluoromethyl allylic amines, α-difluoromethyl propargylamines, and other α-difluoromethyl tertiary carbinamines through a simple and reliable protocol.

Results and Discussion

Nucleophilic difluoromethylation of *N*-*tert*-butylsulfinyl ketimines: Previously, we discovered that pre-generation of the (phenylsulfonyl)fluoromethyl anion paved the way for the efficient monofluoromethylation of *N*-*tert*-butylsulfinyl ketimines (Scheme 1a and b).[4h] However, we found that a

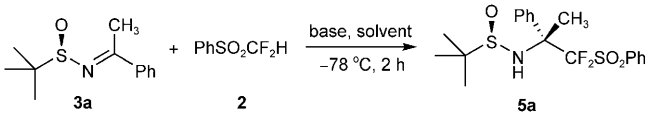


Scheme 1. Attempted difluoromethylation of ketimine **3a**.

similar pre-generation protocol did not work for the difluoromethylation of ketimine **3a** with the reagent $PhSO_2CF_2H$ (Scheme 1c), indicating that the lower thermal stability of the $PhSO_2CF_2^-$ anion does not allow for its pre-generation. Interestingly, when we attempted in situ generation of the $PhSO_2CF_2^-$ anion, we observed the formation of addition product **5a** in 25% yield (Scheme 1d).

We envisaged that if we could find an appropriate base to kinetically affect the deprotonation of $PhSO_2CF_2H$ rather than the unwanted aza-enolization of the ketimines at low temperature, nucleophilic difluoromethylation of *N*-*tert*-butylsulfinyl ketimines might be successfully accomplished. With this consideration in mind, we surveyed several bases (such as *n*BuLi, LiHMDS, NaHMDS, and KHMDS) using *N*-*tert*-butylsulfinyl ketimine **3a** as a model compound, and found that potassium hexamethyldisilazide (KHMDS) was the base of choice,[9] affording the nucleophilic addition product **5a** in 70% yield (Table 1, entries 1–4). This indicates that the basicity of KHMDS is appropriate for mediating this difluoromethylation reaction. Notably, in all cases the diastereoselectivity of the nucleophilic addition was excellent (d.r. = 99:1; see Table 1, entries 1–4).

Table 1. Survey of reaction conditions.[a]



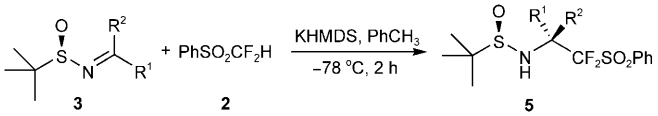
Entry	Base	Solvent	Molar ratio (**3a**/**2**/base)	Yield [%][b]	d.r.[c]
1	*n*BuLi	THF	1:1.2:1.3	25	99:1
2	LiHMDS	THF	1:1.2:1.3	12	99:1
3	NaHMDS	THF	1:1.2:1.3	29	99:1
4	KHMDS	THF	1:1.2:1.3	70	99:1
5	KHMDS	THF	1:1.2:1.2	59	99:1
6	KHMDS	THF	1.2:1:1.1	59	99:1
7[d]	KHMDS	THF/HMPA	1:1.2:1.3	55	28:72
8	KHMDS	$PhCH_3$	1:1.2:1.3	84	99:1
9	KHMDS	$PhCH_3/AlMe_3$	1:1.2:1.3	54	99:1
10	KHMDS	$PhCH_3$	1.5:1:1.2	77	99:1

[a] In all cases, a base was added to a mixture of **3a** and **2** in a solvent at −78 °C, and the reactions were usually complete in 2 h. [b] Yield of the isolated product. [c] Diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. [d] THF/HMPA = 6:1 (*v*/*v*).

Encouraged by these results, we further optimized the reaction conditions of this nucleophilic difluoromethylation, including the reactant ratios, solvents, and additives to further increase the chemical yield of the addition product **5a**. It turned out that toluene was the solvent of choice (Table 1). The optimal product yield (84%) was obtained when the reaction proceeded at −78 °C in toluene with a reactant ratio of **3a**/**2**/KHMDS = 1:1.2:1.3 (Table 1, entry 8). It should be noted that the opposite diastereoselectivity was observed when hexamethylphosphoric triamide (HMPA) was used as a co-solvent (Table 1, entry 7), indicating that the solvation of the potassium cation by HMPA can result in a different transition state mode of diastereoselective addition.

The optimized reaction conditions (Table 1, entry 8) were then extended to a wide range of different *N*-*tert*-butylsulfinyl ketimines to examine the substrate scope of the reaction. As shown in Table 2, aromatic and heteroaromatic *N*-*tert*-butylsulfinyl methyl ketimines readily underwent the nucleophilic addition to provide the corresponding (phenylsulfonyl)difluoromethylated products in good yields with high diastereoselectivity (Table 2, entries 1–8). In the case of isopropyl methyl ketimine **3i**, we were still able to obtain the addition product **5i** in high yield with excellent diastereoselectivity (Table 2, entry 9). The nucleophilic addition to *N*-*tert*-butylsulfinyl ketimine **3j** gave only a 51% yield of product **5j**, probably due to the steric hindrance of the *tert*-butyl group (Table 2, entry 10). Furthermore, phenyl butyl ket-

Table 2. Diastereoselective (phenylsulfonyl)difluoromethylation of *N*-*tert*-butylsulfinyl ketimines **3**.[a]



3 **2** **5**

Entry	Ketimine	Yield [%][b]	d.r.[c]
1	R^1 = Ph, R^2 = CH_3 (**3a**)	84	99:1
2	R^1 = 4-$CF_3C_6H_4$, R^2 = CH_3 (**3b**)	80	99:1
3	R^1 = 4-$CH_3OC_6H_4$, R^2 = CH_3 (**3c**)	74	98:2
4	R^1 = 4-$CH_3C_6H_4$, R^2 = CH_3 (**3d**)	79	99:1
5	R^1 = 4-ClC_6H_4, R^2 = CH_3 (**3e**)	78	99:1
6	R^1 = 2-naphthyl, R^2 = CH_3 (**3f**)	73	98:2
7	R^1 = 2-furyl, R^2 = CH_3 (**3g**)	83	99:1
8	R^1 = 2-pyridyl, R^2 = CH_3 (**3h**)	80	99:1
9	R^1 = *i*Pr, R^2 = CH_3 (**3i**)	87	99:1
10	R^1 = *t*Bu, R^2 = CH_3 (**3j**)	51	99:1
11	R^1 = Ph, R^2 = *n*Bu (**3k**)	81	97:3
12	R^1 = Ph, R^2 = Et (**3l**)	85	97:3

[a] In all cases, KHMDS (1.3 equiv) was added to a mixture of **2** (1.0 equiv) and **3** (1.2 equiv) in $PhCH_3$ at −78 °C, and the reactions were usually complete in 2 h. [b] Yield of isolated analytically pure material with d.r. > 99:1. [c] Diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture.

imine **3k** and phenyl ethyl ketimine **3l** were also successfully (phenylsulfonyl)difluoromethylated in yields of 81% and 85%, respectively (Table 2, entries 11 and 12). In most cases, the good product yields and excellent diastereoselectivity of the nucleophilic addition reactions suggest that both the rate of deprotonation of **2** with KHMDS and the rate of nucleophilic addition of $PhSO_2CF_2^-$ anion to ketimines **3** are significantly faster than that of the unwanted base-mediated aza-enolization of ketimines **3**.

The absolute configuration of product **5k** was determined by its single-crystal X-ray structure (Figure 1, top), and the configurations of others were assigned by analogy. The stereocontrol mode of the present diastereoselective (phenylsulfonyl)difluoromethylation of ketimines can be predicted by envisaging a cyclic six-membered transition state in which the bulky *tert*-butyl group preferentially adopts an equatorial position (Figure 1, bottom). The observed diastereoselectivity mode is completely opposite to that of the nucleophilic fluoroalkylation of *tert*-butylsulfinyl aldimines,[4] but similar to our previous observation concerning the monofluoromethylation of *N*-*tert*-butylsulfinyl ketimines.[4h] This transition-state model is further supported by two pieces of experimental evidence: firstly, use of the coordinating solvent HMPA, which prevents complexation of the sulfinyl oxygen atom with the metal ion (i.e., K^+, Na^+, Li^+), resulted in an opposite diastereoselectivity (Table 1, entry 7); secondly, an apolar solvent such as toluene helped to improve the yield of the reaction (Table 1, entries 8, 10, and 11).

The obtained homochiral (phenylsulfonyl)difluoromethylated products **5** (as indicated in Table 2, d.r. > 99:1 after silica gel chromatography in all cases) could be conveniently converted into homochiral α-difluoromethyl tertiary carbinamines **6** in high yields by mild reductive desulfonylation with Mg/HOAc/NaOAc in a DMF-based system and acid-

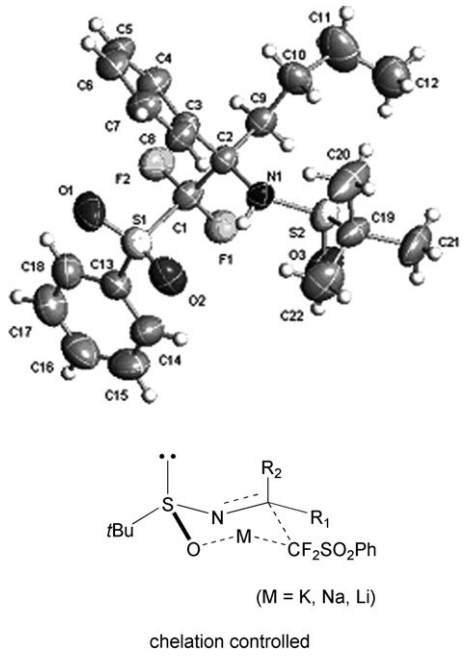
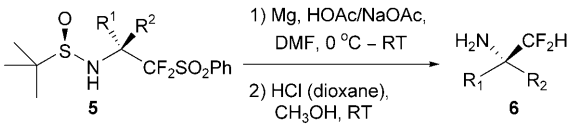


Figure 1. X-ray structure of product **5k** (top) and proposed transition state for chelation-controlled addition (bottom).

catalyzed alcoholysis (Scheme 2).[4h,10] It should be pointed out that these deprotection procedures have proved to be stereochemically reliable, incurring no loss of optical purity (for additional evidence, see Scheme 4).[4d,f–h] In addition, we

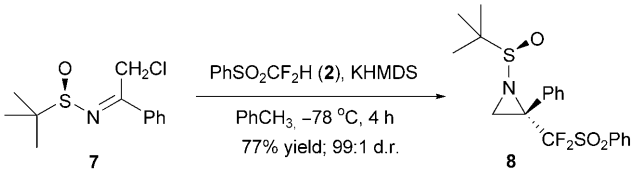


5 **6**

6a: R^1 = Ph, R^2 = CH_3 (82%)
6b: R^1 = 4-$CH_3OC_6H_4$, R^2 = CH_3 (87%)
6c: R^1 = 4-ClC_6H_4, R^2 = CH_3 (85%)
6d: R^1 = 2-naphthyl, R^2 = CH_3 (90%)
6e: R^1 = Ph, R^2 = C_2H_5 (82%)

Scheme 2. Preparation of α-difluoromethyl carbinamines **6**.

also extended this nucleophilic difluoromethylation to *N*-*tert*-butylsulfinyl α-chloro ketimine **7**. As shown in Scheme 3, α-chloro ketimine **7** readily reacted with the reagent $PhSO_2CF_2H$ in the presence of KHMDS, affording (phenylsulfonyl)difluoromethylated aziridine **8** in good yield



7 **8**

Scheme 3. Synthesis of chiral fluorinated aziridine **8**.

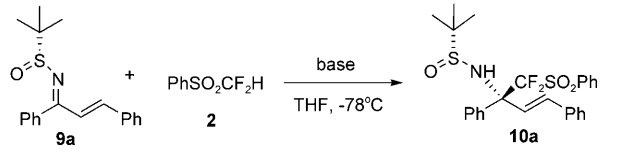
and with high diastereoselectivity through an addition–dechlorinative cyclization cascade reaction.

Nucleophilic difluoromethylation of α,β-unsaturated *N-tert*-butylsulfinyl ketimines: Allyllic amines are widely applied in medicinal chemistry and drug discovery, since a variety of synthetically and biologically important organic compounds can be obtained through the elaboration of their double bond.[11] However, although numerous synthetic endeavors have been undertaken towards the efficient preparation of nonfluorinated chiral allylic amines,[12] the synthesis of chiral α-fluoroalkyl allylic amines has been less well explored. The few known reports have been mostly based on the synthetic elaboration of chiral trifluoromethylated imines or their derivatives.[13] Another preparative method for chiral α-fluoroalkyl allylic amines is through a Julia-type methylenation–desulfonylation reaction of fluorinated β-amino sulfones.[14] Furthermore, the trifluoromethylation of unsaturated *N*-sulfinimines or *N*-tosyl imines can also afford chiral α-trifluoromethyl allylic amines, albeit in somewhat low yields.[4b,15] Compared with that of α-trifluoromethyl allylic amines, the asymmetric synthesis of α-difluoromethyl allylic amines is less well known, probably due to lower availability of difluoromethylated precursors and difluoromethylation reagents.[16]

Although α,β-unsaturated ketones have been widely used in organic synthesis,[17] α,β-unsaturated ketimines remain a relatively poorly studied class of compounds owing to their low chemical reactivity. Known conjugate additions of α,β-unsaturated ketimines are limited to nucleophiles such as dialkylzinc reagents[18a] and organocuprates.[18b] Moreover, instances of nucleophilic 1,2-addition of α,β-unsaturated ketimines are scarce, with the only example of which we are aware being the cyanation of α,β-unsaturated *N*-tosyl ketimine catalyzed by a nucleophilic N-heterocyclic carbene.[19] In our previous investigation, we found that because of the high electronegativity of the fluorine atom, difluorinated carbanions, regarded as "hard" nucleophiles, usually attack the carbonyl group and undergo 1,2-addition reactions with α,β-enones.[8b] Based on these results, we assumed that nucleophilic 1,2-addition of the (phenylsulfonyl)difluoromethyl anion ($PhSO_2CF_2^-$), generated in situ from $PhSO_2CF_2H$ and a base, to α,β-unsaturated *N-tert*-butylsulfinyl ketimines would proceed smoothly to afford the desired chiral α-difluoromethyl allylic amines.

Initially, we prepared a variety of α,β-unsaturated *N-tert*-butylsulfinyl ketimines **9** by $Ti(OEt)_4$-mediated condensation of *tert*-butylsulfinamide and the requisite α,β-unsaturated ketones, according to the reported protocol[18b] (see the Supporting Information). With these α,β-unsaturated ketimines **9** in hand, we next chose α,β-unsaturated *N-tert*-butylsulfinyl ketimine **9a** as a model compound to test the nucleophilic (phenylsulfonyl)difluoromethylation with $PhSO_2CF_2H$ (**2**). The results are summarized in Table 3. It should be mentioned that we found that the (phenylsulfonyl)difluoromethylation of **9a** could be achieved with THF as the solvent, which is more convenient to handle than toluene. Following initial deprotonation with lithium hexamethyldisilazide (LiHMDS), $PhSO_2CF_2H$ reacted with **9a** to afford the 1,2-addition product **10a** with good diastereoselectivity (d.r. 92:8), albeit in low yield (Table 3, entry 1). A subsequent screening of bases revealed that KHMDS provided a significant increase in yield (Table 3, entry 3). It turned out that *n*BuLi was not suitable for the reaction, probably due to its high nucleophilicity toward **9a** (Table 3, entry 5). To further improve the product yield, we then carefully examined the effect of reactant molar ratios on the chemical yield using KHMDS as the base. The best yield of product **10a** was obtained with a reactant molar ratio **9a**/**2**/KHMDS = 1.2:1:1.1 (Table 3, entry 10).

Table 3. Optimization of reaction conditions.[a]

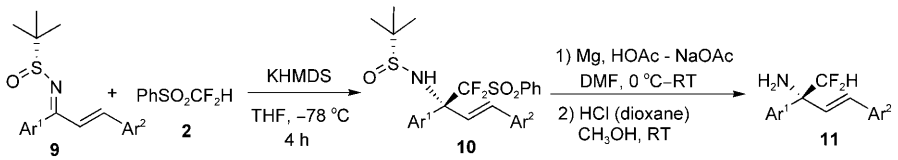


Entry	Base	Molar ratio (**9a**/**2**/base)	Yield [%][b]	d.r. (R_s,R)/(R_s,S)[c]
1	LiHMDS	1:1.2:1.3	23	92:8
2	NaHMDS	1:1.2:1.3	65	94:6
3	KHMDS	1:1.2:1.3	82	94:6
4	LDA	1:1.2:1.3	31	93:7
5	*n*BuLi	1:1.2:1.3	trace	–
6	KHMDS	1:1.1:1.2	77	94:6
7	KHMDS	1:1.5:1.6	69	92:8
8	KHMDS	1:2:2.2	88	94:6
9	KHMDS	1.1:1:1.1	86	95:5
10	KHMDS	1.2:1:1.1	91	95:5
11	KHMDS	1.5:1:1.1	76	94:6

[a] In all cases, base was added to a mixture of **2** and **9a** in THF at −78 °C, and the reactions were usually complete in 4 h. [b] Yield of isolated analytically pure material. [c] Diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture.

Having identified the optimal reaction conditions, the scope of this nucleophilic 1,2-addition reaction was investigated with various α,β-unsaturated *N-tert*-butylsulfinyl ketimines (Table 4). The reaction proved to be general and highly regioselective, with the $PhSO_2CF_2^-$ anion attacking the C=N double bond of α,β-unsaturated ketimines **9** to provide α-(phenylsulfonyl)difluoromethylated allylic sulfinamides **10**. In all cases, the α,β-unsaturated ketimines showed high reactivity towards reagent **2**, and the corresponding (phenylsulfonyl)difluoromethylated products **10** were obtained in good to excellent yields (77–97 %) and with high diastereoselectivities (d.r. 94:6–97:3). Electron-withdrawing or -donating substituents on the aryl rings of **9** did not exert a significant effect on the outcome of the diastereoselective nucleophilic (phenylsulfonyl)difluoromethylation. The present nucleophilic 1,2-addition of α,β-unsaturated ketimines **9** with **2** is remarkable, especially when compared with the previously reported nucleophilic trifluoromethylation of α,β-unsaturated *N-tert*-butylsulfinyl aldimines using $TMSCF_3$/TBAT or TMAF (TMS = trimethylsilyl; TBAT = tetrabutyl-

Table 4. Facile synthesis of α-difluoromethyl allylic amines **11**.[a]



Entry	Substrate **9**	**10** [%][b]	d.r. of **10** (R_s,R)/(R_s,S)[c]	**11** [%][d]
1	Ar^1=Ph, Ar^2=Ph (**9a**)	91	95:5	94
2	Ar^1=Ph, Ar^2=4-$MeOC_6H_4$ (**9b**)	82	94:6	92
3	Ar^1=4-$MeOC_6H_4$, Ar^2=Ph (**9c**)	90	97:3	92
4	Ar^1=4-$CF_3C_6H_4$, Ar^2=Ph (**9d**)	93	95:5	89
5	Ar^1=4-ClC_6H_4, Ar^2=Ph (**9e**)	96	96:4	90
6	Ar^1=Ph, Ar^2=4-FC_6H_4 (**9f**)	92	95:5	90
7	Ar^1=Ph, Ar^2=4-$CF_3C_6H_4$ (**9g**)	86	96:4	85
8	Ar^1=4-FC_6H_4, Ar^2=Ph (**9h**)	95	97:3	88
9	Ar^1=4-$CH_3C_6H_4$, Ar^2=Ph (**9i**)	94	96:4	90
10	Ar^1=Ph, Ar^2=4-$CH_3C_6H_4$ (**9j**)	92	95:5	86
11	Ar^1=Ph, Ar^2=2-furyl (**9k**)	80	94:6	82
12	Ar^1=Ar^2=4-$MeOC_6H_4$ (**9l**)	77	96:4	91

[a] In all cases, KHMDS was added to a mixture of **9** and **2** in THF at −78 °C, and the reactions were usually complete in 4 h. [b] Yield of isolated analytically pure material with d.r. > 99:1. [c] Diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. [d] Yield of the isolated product based on the amount of homochiral **10** used.

ammonium difluorotriphenylsilicate; TMAF = tetramethylammonium fluoride), which proceeded in lower yields.[4b]

The absolute configuration of product **10a** was determined by single-crystal X-ray structure analysis (Figure 2), and the configurations of **10b–l** were assigned by analogy.

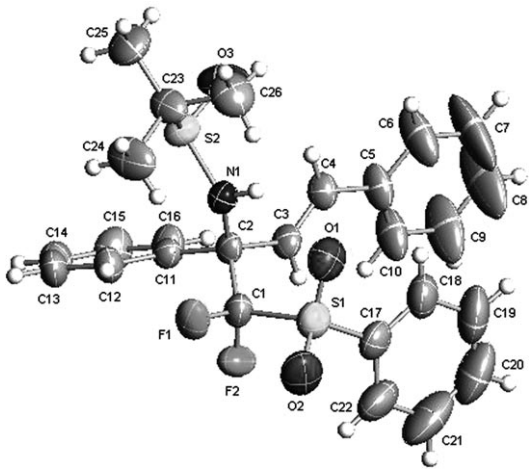
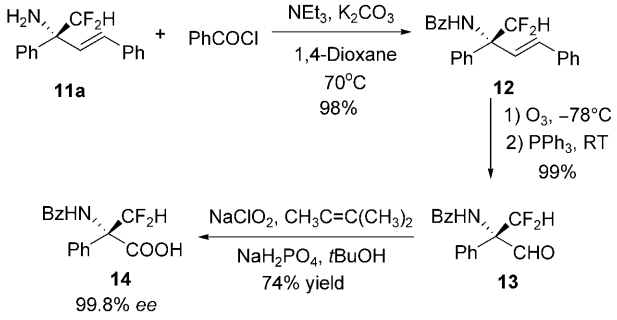


Figure 2. X-ray structure of product **10a**.

The sense of diastereoselective induction is consistent with a cyclic six-membered transition state, similar to that invoked in our previous mono- and difluoromethylation of *N-tert*-butylsulfinyl ketimines.[4h] Upon reductive desulfonylation with our previously developed Mg/HOAc/NaOAc system and acid-catalyzed alcoholysis,[4h,10] the α-(phenylsulfonyl)difluoromethyl allylic sulfinamides **10** were readily converted into the corresponding α-difluoromethyl allylic amines **11** in excellent yields (Table 4).

We also attempted to react other nucleophilic fluoroalkylating agents, such as $Me_3SiCF_2SO_2Ph$ and $PhSO_2CH_2F$, with α,β-unsaturated *N-tert*-butylsulfinyl ketimine **9a**. Although $Me_3SiCF_2SO_2Ph$ generated the $PhSO_2CF_2^-$ anion in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT),[10] it showed lower reactivity towards **9a**, and the 1,2-addition products were only obtained in 50% yield with modest diastereoselectivity (d.r. = 75:25), which is inferior to the results achieved with the present $PhSO_2CF_2H$/KHMDS system. In the case of $PhSO_2CH_2F$, which readily reacted with α,β-unsaturated ketones to afford a mixture of 1,2- and 1,4-addition products,[8b] the nucleophilic monofluoromethylation of **9a** afforded only 1,2-adducts in nearly quantitative yield.

Fluorinated α-amino acids are of particular importance in biological and peptide chemistry,[20] and have been shown to be irreversible inhibitors of pyridoxal phosphate-dependent enzymes.[1a] Much effort has been devoted to the synthesis of fluorinated α-amino acids, especially in a stereocontrolled manner.[13e,21] To demonstrate the synthetic utility of the present highly efficient difluoromethylation reaction, α-difluoromethyl allylic amine **11a** was further transformed to α-difluoromethyl α-amino acid **14** (Scheme 4). Firstly, the



Scheme 4. Synthesis of *N*-Bz-protected α-difluoromethyl α-amino acid **14**.

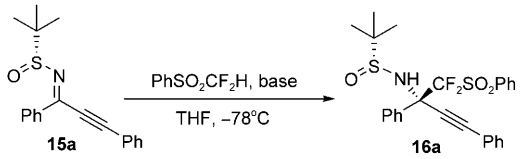
amino group of **11a** was protected with benzoyl chloride to afford benzamide derivative **12** in 98% yield. Ozonolysis of this *N*-Bz-protected amine in CH_2Cl_2 at −78 °C, followed by quenching with triphenylphosphine,[13e] gave the intermediate aldehyde **13**. Upon oxidation with sodium chlorite in *tert*-butyl alcohol in the presence of 2-methyl-2-butene and aqueous NaH_2PO_4,[22] compound **13** was converted into the

corresponding *N*-Bz-protected α-difluoromethyl α-amino acid **14** in good yield with no loss of stereochemical purity (with 99.8% *ee*). We found this two-step procedure to be more reliable than a one-step oxidation with $NaIO_4/RuCl_3$, which gave none of the desired product.

Nucleophilic difluoromethylation of α,β-acetylenic *N-tert*-butylsulfinyl ketimines: Propargylamines play an increasingly significant role in organic chemistry as both synthetic intermediates for the preparation of polyfunctional amino derivatives and biologically active compounds,[23] and their stereoselective synthesis is therefore attractive to synthetic organic chemists.[24,25] Although several different methods for the preparation of propargylamines have been disclosed in the literature, including metal-catalyzed addition of alkynes to enamines or imines[24] and asymmetric addition of alkynyl metal reagents to chiral sulfinylimines,[25] little synthetic effort has been reported so far about the synthesis of fluoroalkylated propargylamines, which are important building blocks for drug design and for the synthesis of bioactive target molecules.[26] In this context, we sought to extend our nucleophilic difluoromethylation strategy to the diastereoselective synthesis of α-difluoromethyl propargylamines through 1,2-addition of $PhSO_2CF_2H$ (**2**) to α,β-acetylenic *N-tert*-butylsulfinyl ketimines in the presence of a base.

Accordingly, α,β-acetylenic *N-tert*-butylsulfinyl ketimines **15** were first prepared in good yields from the commercially available (*Rs*)-*tert*-butylsulfinamide and α,β-acetylenic ketones[27] (see the Supporting Information). Firstly, α,β-acetylenic ketimine **15a** was chosen as a model compound to optimize the reaction conditions for the 1,2-addition with $PhSO_2CF_2H$. As shown in Table 5, we found that KHMDS, NaHMDS, and LiHMDS were all suitable for mediating this nucleophilic (phenylsulfonyl)difluoromethylation reaction (Table 5, entries 1–3), although the reaction with NaHMDS gave a slightly higher yield of product (Table 5, entry 2). After further optimization of the reactant ratio, an optimal yield of **16a** (91%) and high diastereoselectivity (d.r. = 98:2) were achieved when the reaction was allowed to proceed at −78°C for 2 h at a reactant molar ratio of **15a**/**2**/NaHMDS = 1.2:1:1.2 (Table 5, entry 7).

Table 5. Optimization of reaction conditions.[a]



Entry	Base	Molar ratio (**15a**/**2**/base)	Yield of **16a** [%][b]	d.r.[c]
1	LiHMDS	1.2:1:1.1	86	98:2
2	NaHMDS	1.2:1:1.1	90	98:2
3	KHMDS	1.2:1:1.1	88	98:2
4	LDA	1.2:1:1.1	50	98:2
5	NaHMDS	1.1:1:1.1	88	98:2
6	NaHMDS	1:1.2:1.3	86	98:2
7	NaHMDS	1.2:1:1.2	91	98:2

[a] In all cases, base was added to a mixture of **2** and **15a** in THF at −78°C, and the reaction was usually complete in 2 h. [b] Yield of isolated analytically pure material with d.r. > 99:1. [c] Diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. LDA = lithium diisopropylamide.

Notably, among the three types of reactions studied between $PhSO_2CF_2H$ (**2**) and aza-enolizable ketimine **3a** (Table 1), α,β-unsaturated ketimine **9a** (Table 3), and α,β-acetylenic ketimine **15a** (Table 5), an appropriate base played a very important role. In the case of aza-enolizable ketimine **3a**, the product yield was most sensitive to the choice of base, and the reaction with KHMDS gave a much higher yield than those with NaHMDS or LiHMDS (Table 1, entries 2–4). It is likely that as the strongest base among Li-, Na-, and KHMDS, KHMDS is the best (among the three bases) to kinetically effect the deprotonation of $PhSO_2CF_2H$ and the subsequent nucleophilic (phenylsulfonyl)difluoromethylation, rather than the unwanted aza-enolization of the ketimine at low temperature. Since α,β-unsaturated ketimine **9a** and α,β-acetylenic ketimine **15a** are not aza-enolizable, it is reasonable to see that their reactions with reagent **2** were less sensitive to the choice of base (Table 3, entries 1–3; Table 5, entries 1–3). Indeed, the reaction between α,β-acetylenic ketimine **15a** and **2** gave very similar product yields (86–90%) when LiHMDS, NaHMDS, and KHMDS were applied (Table 5, entries 1–3).

The absolute configuration of **16a** was confirmed by single-crystal X-ray structure analysis (Figure 3), which indicated that the stereochemistry of this nucleophilic 1,2-addition was chelation-controlled and that the reaction proceeded through a similar cyclic six-membered transition state to that mentioned above in relation to the difluoromethylation of ketimines.

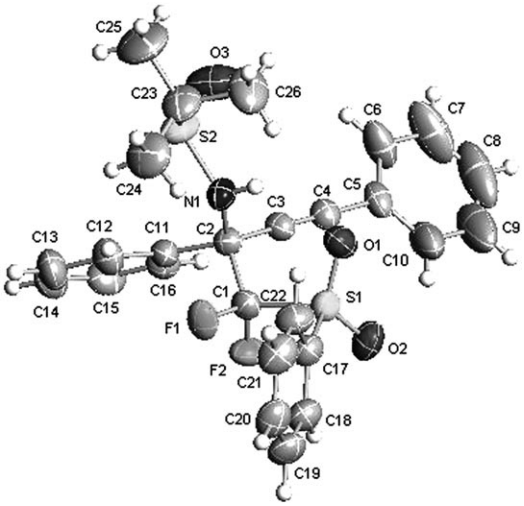
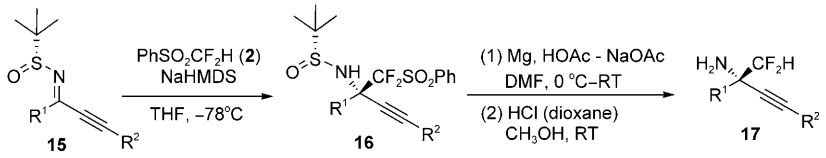


Figure 3. X-ray structure of product **16a**.

The scope of the reaction was explored with a variety of substrates to establish the generality of the process, and the results are summarized in Table 6. It turned out that, in the presence of NaHMDS, the difluoromethylating agent **2**

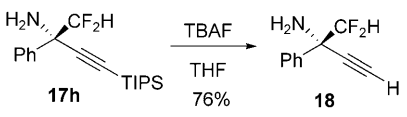
Table 6. Preparation of α-difluoromethyl propargylamines **17**.[a]



Entry	Ketimines **15**	**16** [%][b]	d.r. of **16**[c]	**17** [%][d]
1	$R^1=R^2=$Ph (**15a**)	91	98:2	96
2	$R^1=$Ph, $R^2=$4-$CH_3C_6H_4$ (**15b**)	94	98:2	95
3	$R^1=$4-$CH_3OC_6H_4$, $R^2=$Ph (**15c**)	86	95:5	93
4	$R^1=$4-ClC_6H_4, $R^2=$Ph (**15d**)	96	99:1	95
5	$R^1=$Ph, $R^2=$4-$CH_3OC_6H_4$ (**15e**)	93	98:2	92
6	$R^1=$4-$CH_3C_6H_4$, $R^2=$Ph (**15f**)	86	96:4	94
7	$R^1=$2-$CH_3OC_6H_4$, $R^2=$Ph (**15g**)	32	99:1	–
8	$R^1=$Ph, $R^2=$TIPS (**15h**)	83	99:1	93
9	$R^1=$Ph, $R^2=n$Bu (**15i**)	49	90:10	–
10	$R^1=$Ph, $R^2=CH_2CH_2$Ph (**15j**)	complex mixture	–	–
11	$R^1=t$Bu, $R^2=$Ph (**15k**)	trace	–	–

[a] In all cases, NaHMDS was added to a mixture of **15** and **2** in THF at −78 °C, and the reactions were usually complete in 2 h. [b] Yield of isolated analytically pure material with d.r. > 99:1. [c] Diastereomeric ratios were determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. [d] Yield of the isolated product based on the amount of homochiral **16** used. TIPS = triisopropylsilyl.

smoothly reacted with α,β-acetylenic *N-tert*-butylsulfinyl ketimines **15** to accomplish the 1,2-addition reaction. Good to excellent yields and high diastereoselectivities were observed with aryl rings present as both R_1 and R_2 (Table 6, entries 1–6), an exception being when a methoxy group was present at the *ortho* position of the aryl ring at R_1, in which case a relatively lower product yield, but still with excellent diastereoselectivity, was obtained, probably due to steric hindrance (Table 6, entry 7). The successful addition to α,β-acetylenic *N-tert*-butylsulfinyl ketimine **15h** demonstrates the promising functional group tolerance of the reaction (Table 6, entry 8). A moderate yield was obtained for the α,β-acetylenic ketimine **15i**, albeit with somewhat reduced diastereoselectivity (Table 6, entry 9) due to competitive base-assisted propargyl–allenyl isomerization.[27a] However, in the case of α,β-acetylenic ketimine **15j**, the nucleophilic 1,2-addition of $PhSO_2CF_2H$ was unsuccessful (Table 6, entry 10). Likewise, only a trace of the desired product was observed when sterically demanding ketimine **15k** was subjected to our optimized reaction conditions (Table 6, entry 11). It is clear that steric interaction significantly retards the nucleophilic 1,2-addition. Moreover, the nucleophilic 1,2-addition products **16** can be further converted into α-difluoromethyl propargylamines **17** in excellent yields after deprotection of both the *tert*-butylsulfinyl and phenylsulfonyl groups under mild conditions.[4h,10] Desilylation of **17h** by treatment with tetrabutylammonium fluoride (TBAF) in THF afforded the synthetically useful terminal acetylene **18** in 76% yield (as demonstrated in Scheme 5).



Scheme 5. Desilylation of α-difluoromethyl propargylamine **17h**.

Conclusion

We have developed the first efficient synthesis of α-difluoromethyl tertiary carbinamines, α-difluoromethyl allylic amines, and α-difluoromethyl propargylamines through diastereoselective nucleophilic difluoromethylations of *N-tert*-butylsulfinyl ketimines, α,β-unsaturated *N-tert*-butylsulfinyl ketimines, and α,β-acetylenic *N-tert*-butylsulfinyl ketimines with in situ generated $PhSO_2CF_2^-$ anion and an appropriate base (such as KHMDS). The kinetically preferred generation of the $PhSO_2CF_2^-$ anion and nucleophilic addition of the $PhSO_2CF_2^-$ anion to ketimines over the undesired aza-enolization of ketimines are the key factors for the success of these difluoromethylation reactions. The stereocontrol mode of the present diastereoselective difluoromethylation of ketimines is opposite to that of other known fluoroalkylations of *N-tert*-butylsulfinyl aldimines, but similar to that observed in our previous report concerning the monofluoroalkylation of ketimines, indicating a remarkable difference between the chemistry of ketimines and aldimines. Not only do our results represent a practically useful synthetic method for many potential applications, but the significantly different generation methods required for the (phenylsulfonyl)difluoromethyl anion (in situ generation) and the previously known (phenylsulfonyl)monofluoromethyl anion (pre-generation), as for the addition to *N-tert*-butylsulfinyl ketimines, also provide some new insights into the thermal stability and chemical reactivity of α-fluorinated carbanions.

Experimental Section

The *N-tert*-butylsulfinyl ketimines **3**[28] were prepared from the corresponding ketones according to the known condensation procedure in one step. Difluoromethyl phenyl sulfone **2**[29] was prepared according to known procedures. Unless otherwise mentioned, all chemicals were purchased from commercial sources. THF was freshly distilled over sodium. Silica gel (300–400 mesh) was used for column chromatography, and in most cases a petroleum ether/ethyl acetate combination was used as the eluent. All melting points are uncorrected. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on 400 MHz or 300 MHz NMR spectrometers. ^1H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at $\delta=0.0$ or to the signal of a residual protonated solvent: $CDCl_3$ $\delta=7.26$. ^{13}C NMR chemical shifts were determined relative to internal TMS at $\delta=0.0$. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at $\delta=0.0$. Chemical shifts are reported in ppm. Mass spectra were obtained on a Aglient 1100 mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in EI, ESI, or MALDI modes.

Typical procedure for stereoselective nucleophilic difluoromethylation of *N-tert*-butylsulfinyl ketimines 3 using difluoromethyl phenyl sulfone: Under an atmosphere of N_2, KHMDS (0.5 M solution in toluene; 2.6 mL, 1.3 mmol) was added dropwise to a solution of *N-tert*-butylsulfinyl ketimine **3** (1.0 mmol) and $PhSO_2CF_2H$ (230 mg, 1.2 mmol) in $PhCH_3$ (8 mL) at −78 °C. The reaction mixture was stirred vigorously at −78 °C for 2 h, and then saturated aqueous NaCl solution (10 mL) was added. The resulting mixture was extracted with Et_2O (3×10 mL), and the combined organic phases were dried over $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography to give product **5**.

Compound 5a: 84% yield; white solid; m.p. 82–83 °C; d.r. > 99:1 (after silica gel chromatography, as detected by ^{19}F NMR spectroscopy), $[\alpha]_D^{27}=-63.06$ ($c=0.98$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.93$ (d, $J=7.5$ Hz, 2H), 7.72 (t, $J=7.5$ Hz, 1H), 7.54–7.62 (m, 4H), 7.34–7.40 (m, 3H), 5.28 (brs, 1H), 2.26 (s, 3H), 1.33 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-102.4$ (d, $J=234.9$ Hz, 1F), −103.6 ppm (d, $J=234.4$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.78$, 135.77, 135.4, 133.6, 130.5, 129.2, 129.1, 129.0, 128.2, 128.0, 120.7 (dd, $J=298.6$, 295.7 Hz), 65.8 (dd, $J=22.6$, 17.5 Hz), 57.2, 23.9, 22.7 ppm (d, $J=17.5$ Hz); IR (KBr): $\tilde{\nu}=3273$, 2979, 1451, 1340, 1166, 1070, 761, 538 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{23}F_2NO_3S_2$: C 54.92, H 5.58, N 3.37; found: C 54.64, H 5.79, N 3.24; MS (ESI): m/z: 416.2 [M^++1].

Compound 5b: 80% yield; white solid; m.p. 44–46 °C; d.r. > 99:1 (after silica gel chromatography, detected by ^{19}F NMR spectroscopy), $[\alpha]_D^{27}=-52.89$ ($c=1.24$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.93$ (d, $J=7.8$ Hz, 2H), 7.71–7.78 (m, 3H), 7.55–7.66 (m, 4H), 5.35 (brs, 1H), 2.28 (s, 3H), 1.34 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-62.0$ (s, 3F), −102.6 (d, $J=232.7$ Hz, 1F), −103.8 ppm (d, $J=240.3$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=139.9$, 135.6, 133.3, 131.2 (q, $J=32.9$ Hz), 130.5, 129.6, 129.3, 125.0 (q, $J=9.5$ Hz), 122.4, 120.3 (t, $J=296.4$ Hz), 65.7 (dd, $J=23.4$, 18.3 Hz), 57.4, 23.9, 22.8 ppm; IR (KBr): $\tilde{\nu}=3292$, 2964, 1451, 1330, 1078, 1017, 612 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{22}F_5NO_3S_2$: C 49.68, H 4.59, N 2.90; found: C 49.71, H 4.74, N 2.77; MS (ESI): m/z: 484.2 [M^++1].

Compound 5c: 74% yield; white solid; m.p. 36–38 °C; d.r. > 99:1 (after silica gel chromatography,), $[\alpha]_D^{27}=-66.33$ ($c=0.94$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.93$ (d, $J=7.8$ Hz, 2H), 7.72 (t, $J=7.5$ Hz, 1H), 7.57 (t, $J=7.5$ Hz, 2H), 7.49 (d, $J=6.9$ Hz, 2H), 6.88 (d, $J=9.3$ Hz, 2H), 5.21 (brs, 1H), 3.81 (s, 3H), 2.24 (s, 3H), 1.32 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-102.7$ (d, $J=229.0$ Hz, 1F), −103.7 ppm (d, $J=236.9$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=160.0$, 135.3, 133.7, 130.5, 130.4, 129.2, 127.4, 120.8 (t, $J=296.8$ Hz), 113.3, 65.5 (dd, $J=22.1$, 17.2 Hz), 57.1, 55.2, 24.1, 22.8 ppm; IR (KBr): $\tilde{\nu}=3291$, 2961, 1610, 1514, 1334, 1259, 1111, 1081, 597 cm^{-1}; MS (ESI): m/z: 446.0 [M^++1]; HRMS (ESI): m/z: calcd for $C_{20}H_{26}NO_4F_2S_2$ [M^++H]: 446.1283; found: 446.1265.

Compound 5d: 79% yield; white solid; m.p. 30–32 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{27}=-57.33$ ($c=0.91$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.93$ (d, $J=7.2$ Hz, 2H), 7.72 (t, $J=7.5$ Hz, 1H), 7.56 (t, $J=7.2$ Hz, 2H), 7.46 (d, $J=6.9$ Hz, 2H), 7.17 (d, $J=8.1$ Hz, 2H), 5.23 (brs, 1H), 2.35 (s, 3H), 2.24 (s, 3H), 1.32 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-102.4$ (d, $J=234.1$ Hz, 1F), −103.6 ppm (d, $J=237.2$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=139.1$, 135.3, 133.7, 132.73, 132.72, 130.4, 129.2, 128.98, 128.96, 128.8, 120.8 (t, $J=297.2$ Hz), 65.6 (dd, $J=22.6$, 17.5 Hz), 57.1, 23.9, 22.8, 21.1 ppm; IR (KBr): $\tilde{\nu}=3290$, 2960, 1450, 1335, 1111, 1082, 723, 595 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{25}F_2NO_3S_2$: C 55.92, H 5.87, N 3.26; found: C 55.84, H 6.16, N 3.13; MS (ESI): m/z: 430.2 [M^++1].

Compound 5e: 78% yield; white solid; m.p. 119–120 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{27}=-61.02$ ($c=0.92$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.93$ (d, $J=7.8$ Hz, 2H), 7.74 (t, $J=7.2$ Hz, 1H), 7.48–7.62 (m, 4H), 7.34 (d, $J=8.7$ Hz, 2H), 5.26 (brs, 1H), 2.24 (s, 3H), 1.32 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-102.6$ (d, $J=234.9$ Hz, 1F), −103.9 ppm (d, $J=235.2$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.5$, 135.4, 134.4, 133.4, 130.5, 129.3, 129.0, 128.3, 120.4 (t, $J=297.8$ Hz), 65.5 (dd, $J=22.6$, 17.5 Hz), 57.3, 23.9, 22.8 ppm; IR (KBr): $\tilde{\nu}=3289$, 2960, 1494, 1450, 1335, 1159, 1081, 721, 586 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{22}ClF_2NO_3S_2$: C 50.72, H 4.93, N 3.11; found: C 50.71, H 5.06, N 2.98; MS (ESI): m/z: 450.0 [M^++1].

Compound 5f: 73% yield; white solid; m.p. 70–72 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{28}=-99.67$ ($c=0.93$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=8.05$–8.08 (m, 1H), 7.92 (d, $J=7.8$ Hz, 2H), 7.77–7.87 (m, 3H), 7.64–7.72 (m, 2H), 7.48–7.57 (m, 4H), 5.33 (brs, 1H), 2.40 (s, 3H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-102.3$ (d, $J=235.5$ Hz, 1F), −103.3 ppm (d, $J=235.2$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.4$, 133.6, 133.2, 133.1, 132.6, 130.4, 129.4, 129.2, 128.6, 127.5, 127.4, 127.1, 126.4, 126.2, 120.9 (t, $J=295.6$ Hz), 66.0 (dd, $J=22.7$, 17.6 Hz), 57.2, 24.2, 22.8 ppm; IR (KBr): $\tilde{\nu}=3288$, 2960, 1334, 1159, 1110, 1079, 715, 593 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{25}F_2NO_3S_2$: C 59.33, H 5.41, N 3.01; found: C 59.07, H 5.59, N 2.85; MS (ESI): m/z: 466.2 [M^++1].

Compound 5g: 83% yield; white solid; m.p. 68–70 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{28}=-48.16$ ($c=0.98$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.95$ (d, $J=6.9$ Hz, 2H), 7.74 (t, $J=7.8$ Hz, 1H), 7.59 (t, $J=6.9$ Hz, 2H), 7.47–7.49 (m, 1H), 6.57 (d, $J=3.6$ Hz, 1H), 6.41–6.44 (m, 1H), 4.84 (brs, 1H), 2.14 (s, 3H), 1.26 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-103.1$ ppm (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=148.8$, 143.7, 135.4, 133.4, 130.6, 129.2, 120.4 (t, $J=298.0$ Hz), 111.9, 110.7, 62.4 (t, $J=21.1$ Hz), 56.9, 22.5, 21.6 ppm; IR (KBr): $\tilde{\nu}=3295$, 1451, 1331, 1110, 1068, 750, 580 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{21}F_2NO_4S_2$: C 50.36, H 5.22, N 3.45; found: C 50.12, H 5.36, N 3.43; MS (ESI): m/z: 406.0 [M^++1].

Compound 5h: 80% yield; white solid; m.p. 74–76 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{28}=-63.79$ ($c=0.91$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=8.66$–8.70 (m, 1H), 7.89 (d, $J=6.9$ Hz, 2H), 7.79 (td, $J=8.1$, 2.1 Hz, 1H), 7.65–7.74 (m, 2H), 7.54 (t, $J=7.8$ Hz, 2H), 7.32–7.37 (m, 1H), 6.11 (brs, 1H), 2.14 (s, 3H), 1.25 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-101.0$ (d, $J=234.4$ Hz, 1F), −102.6 ppm (d, $J=235.2$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=154.8$, 148.5, 136.6, 135.2, 133.7, 130.7, 129.1, 123.8, 122.7 (d, $J=2.4$ Hz), 121.3 (t, $J=298.6$ Hz), 64.4 (t, $J=19.7$ Hz), 56.9, 22.6, 20.8 ppm; IR (KBr): $\tilde{\nu}=3296$, 2962, 1592, 1450, 1334, 1154, 1076, 685, 537 cm^{-1}; MS (ESI): m/z: 417.2 [M^++1]; HRMS (MALDI): m/z: calcd for $C_{18}H_{23}N_2O_3F_2S_2$ [M^++H]: 417.1125; found: 417.1112.

Compound 5i: 97% yield; a liquid; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{27}=-48.49$ ($c=1.27$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=8.02$ (d, $J=7.8$ Hz, 2H), 7.73 (t, $J=6.9$ Hz, 1H), 7.59 (t, $J=7.8$ Hz, 2H), 4.27 (brs, 1H), 2.55–2.71 (m, 1H), 1.54 (s, 3H), 1.26 (s, 9H), 1.12 ppm (t, $J=6.6$ Hz, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-94.9$ (d, $J=239.2$ Hz, 1F), −95.9 ppm (d, $J=239.2$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.2$, 133.6, 130.7, 129.1, 122.9 (t, $J=292.8$ Hz), 66.0 (t, $J=17.8$ Hz), 57.0, 33.9, 22.7, 17.8 (dd, $J=10.5$, 6.3 Hz), 15.9 ppm (t, $J=4.1$ Hz); IR (KBr): $\tilde{\nu}=3315$, 2966, 1584, 1450, 1336, 1151, 1083, 905, 719, 593 cm^{-1}; MS (ESI): m/z: 382.2 [M^++1]; HRMS (ESI): m/z: calcd for $C_{16}H_{26}NO_3F_2S_2$ [M^++H]: 382.1324; found: 382.1318.

Compound 5j: 51% yield; white solid; m.p. 101–103 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{27}=-74.10$ ($c=0.99$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=8.02$ (d, $J=7.8$ Hz, 2H), 7.72 (t, $J=7.2$ Hz, 1H), 7.59 (t, $J=7.8$ Hz, 2H), 4.75 (brs, 1H), 1.63 (s, 3H), 1.30 (s, 9H), 1.23 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-89.4$ (d, $J=248.2$ Hz, 1F), −95.7 ppm (d, $J=247.9$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.1$, 134.4, 130.8, 129.1, 122.9 (dd, $J=303.7$, 294.3 Hz), 70.5 (t, $J=18.8$ Hz), 57.1, 38.8 (d, $J=3.3$ Hz), 26.8, 23.0, 16.3 ppm (dd, $J=5.4$, 3.3 Hz); IR (KBr): $\tilde{\nu}=3329$, 2966, 1584, 1450, 1335, 1143, 1087, 717, 595 cm^{-1}; MS (ESI): m/z: 396.2 [M^++1]; HRMS (ESI): m/z: calcd for $C_{17}H_{28}NO_3F_2S_2$ [M^++H]: 396.1486; found: 396.1473.

Compound 5k: 81% yield; white solid; m.p. 124–125 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{27}=-20.86$ ($c=0.92$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.84$ (d, $J=7.2$ Hz, 2H), 7.67 (t, $J=7.5$ Hz, 1H), 7.48–7.60 (m, 4H), 7.38–7.47 (m, 3H), 5.58 (brs, 1H), 2.48–2.60 (m, 1H), 2.29–2.43 (m, 1H), 1.42 (s, 9H), 1.11–1.36 (m, 3H), 0.80 ppm (t, $J=7.2$ Hz, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-96.3$ (d, $J=228.4$ Hz, 1F), −101.4 ppm (d, $J=226.2$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.3$, 135.2, 135.0, 133.7, 130.5, 129.0, 128.6, 128.4, 127.5, 127.4, 121.1 (t, $J=303.3$ Hz), 67.8 (dd, $J=21.5$, 18.8 Hz), 57.9, 30.9, 24.3, 23.2, 22.4,

13.7 ppm; IR (KBr): $\tilde{\nu}$ = 3312, 2955, 1449, 1335, 1145, 1079, 709, 536 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{29}F_2NO_3S_2$: C 57.74, H 6.39, N 3.06; found: C 57.58, H 6.54, N 3.08; MS (ESI): *m/z*: 458.2 [M^++1].

Compound 5l: 85% yield; white solid; m.p. 32–33 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{27} = -18.49$ (*c* = 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.7 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.36–7.61 (m, 7H), 5.55 (brs, 1H), 2.57–2.72 (m, 1H), 2.35–2.51 (m, 1H), 1.42 (s, 9H), 0.69 ppm (t, *J* = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −96.3 (d, *J* = 225.1 Hz, 1F), −101.3 ppm (d, *J* = 230.7 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9, 134.85 (d, *J* = 1.2 Hz), 134.8 (d, *J* = 1.4 Hz), 133.6, 130.4, 129.0, 128.6, 128.4, 127.6, 127.5, 121.2 (t, *J* = 302.3 Hz), 68.1 (dd, *J* = 21.4, 17.8 Hz), 57.8, 24.3, 23.1, 7.0 ppm; IR (KBr): $\tilde{\nu}$ = 3312, 2982, 1450, 1336, 1147, 1082, 710, 593 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{25}F_2NO_3S_2$: C 55.92, H 5.87, N 3.26; found: C 55.77, H 6.09, N 3.20; MS (ESI): *m/z*: 430.2 [M^++1].

Typical procedure for stereoselective nucleophilic difluoromethylation of α,β-unsaturated *N*-*tert*-butylsulfinyl ketimines 9 using difluoromethyl phenyl sulfone: Under an atmosphere of N_2, KHMDS (0.5 M solution in toluene; 1.1 mL, 0.55 mmol) was added dropwise to a solution of α,β-unsaturated *N*-*tert*-butylsulfinyl ketimine **9a** (189 mg, 0.6 mmol) and $PhSO_2CF_2H$ (96 mg, 0.5 mmol) in THF (8 mL) at −78 °C. The reaction mixture was stirred vigorously at −78 °C for 4 h, and then saturated aqueous NaCl solution (5 mL) was added. The resulting mixture was extracted with Et_2O (3 × 10 mL), and the combined organic phases were dried over $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography (petroleum ether/EtOAc = 3:1 as eluent) to give product **10a** (229 mg, 91% yield).

Compound 10a: 91% yield; white solid; m.p. 168–170 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{23} = 22.68$ (*c* = 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.5 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.51–7.62 (m, 6H), 7.30–7.41 (m, 7H), 6.74 (d, *J* = 14.7 Hz, 1H), 5.56 (s, 1H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −101.7 (d, *J* = 226.9 Hz, 1F), −102.7 ppm (d, *J* = 229.2 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 136.2, 135.2, 133.9, 133.7, 130.5, 130.06 (d, *J* = 3.8 Hz), 129.5, 129.2, 128.6, 128.4, 128.2, 127.4, 125.4 (d, *J* = 2.2 Hz), 121.5 (dd, *J* = 304.0, 300.9 Hz), 71.3 (dd, *J* = 21.2, 17.3 Hz), 57.3, 22.9 ppm; IR (KBr): $\tilde{\nu}$ = 3320, 1498, 1448, 1333, 1191, 1145, 1084, 1068, 685 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{27}F_2NO_3S_2$: C 62.01, H 5.40, N 2.78; found: C 62.02, H 5.34, N 2.64; MS (ESI): *m/z*: 504.0 [M^++1].

Compound 10b: 82% yield; white solid; m.p. 79–81 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{24} = 12.19$ (*c* = 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.5 Hz, 2H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.51–7.62 (m, 4H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.32–7.40 (m, 3H), 7.27 (d, *J* = 16.2 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.57 (dd, *J* = 16.5, 1.5 Hz, 1H), 5.55 (s, 1H), 3.83 (s, 3H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −101.6 (d, *J* = 228.9 Hz, 1F), −102.6 ppm (d, *J* = 229.5 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 136.2, 135.1, 134.0, 130.5, 130.1, 130.05, 129.4, 129.2, 128.9, 128.7, 128.2, 123.07 (d, *J* = 2.5 Hz), 121.5 (dd, *J* = 304.4, 301.2 Hz), 114.0, 71.3 (dd, *J* = 21.3, 17.1 Hz), 57.3, 55.3, 23.0 ppm; IR (KBr): $\tilde{\nu}$ = 3316, 2958, 1608, 1513, 1449, 1336, 1250, 1143, 1076, 713 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{29}F_2NO_4S_2$: C 60.77, H 5.48, N 2.62; found: C 60.78, H 5.82, N 2.39; MS (ESI): *m/z*: 534.1 [M^++1].

Compound 10c: 90% yield; white solid; m.p. 88–90 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{24} = 13.37$ (*c* = 0.92, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.8 Hz, 2H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.46–7.59 (m, 6H), 7.27–7.43 (m, 4H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 17.4 Hz, 1H), 5.51 (s, 1H), 3.81 (s, 3H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −101.8 (d, *J* = 227.8 Hz, 1F), −102.9 ppm (d, *J* = 227.8 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 136.5, 136.3, 135.1, 134.0, 131.5 (d, *J* = 3.8 Hz), 130.5, 129.2, 128.6, 128.3, 127.4, 125.7 (d, *J* = 2.6 Hz), 125.5, 121.6 (t, *J* = 303.2 Hz), 113.5, 71.1 (dd, *J* = 21.4, 17.2 Hz), 57.2, 55.2, 23.0 ppm; IR (KBr): $\tilde{\nu}$ = 3317, 2959, 1608, 1512, 1449, 1335, 1259, 1143, 1073, 834, 597 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{29}F_2NO_4S_2$: C 60.77, H 5.48, N 2.62; found: C 60.58, H 5.74, N 2.55; MS (ESI): *m/z*: 534.1 [M^++1].

Compound 10d: 93% yield; white solid; m.p. 80–82 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{24} = 22.23$ (*c* = 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.5 Hz, 2H), 7.71–7.78 (m, 3H), 7.51–7.66 (m, 6H), 7.28–7.42 (m, 4H), 6.75 (d, *J* = 16.2 Hz, 1H), 5.62 (s, 1H), 1.36 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −63.3 (s, 3F), −101.8 (d, *J* = 230.1 Hz, 1F), −102.8 ppm (d, *J* = 230.1 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 137.6, 135.8, 135.4, 133.6, 131.6 (q, *J* = 32.6 Hz), 130.5, 129.3, 128.72, 128.69, 127.4, 125.1 (q, *J* = 3.7 Hz), 124.6 (d, *J* = 2.0 Hz), 122.4, 121.1 (t, *J* = 304.0 Hz), 119.7, 71.1 (dd, *J* = 21.3, 17.9 Hz), 57.6, 22.9 ppm; IR (KBr): $\tilde{\nu}$ = 3315, 1620, 1450, 1328, 1172, 1143, 1073, 1018, 582 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{26}F_5NO_3S_2$: C 56.73, H 4.58, N 2.45; found: C 56.68, H 4.73, N 2.35; MS (ESI): *m/z*: 572.0 [M^++1].

Compound 10e: 96% yield; white solid; m.p. 158–160 °C; d.r. > 99:1 (after silica gel chromatography). $[\alpha]_D^{24} = 15.31$ (*c* = 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.5 Hz, 2H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.50–7.60 (m, 6H), 7.28–7.41 (m, 6H), 6.71 (d, *J* = 15.9 Hz, 1H), 5.56 (s, 1H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −101.9 (d, *J* = 229.2 Hz, 1F), −102.9 ppm (d, *J* = 229.2 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2, 135.9, 135.8, 135.3, 133.7, 132.3, 131.4 (d, *J* = 3.9 Hz), 130.5, 129.3, 128.64, 128.59, 128.5, 127.4, 124.9 (d, *J* = 2.0 Hz), 121.3 (t, *J* = 301.0 Hz), 71.0 (dd, *J* = 21.3, 17.2 Hz), 57.4, 22.9 ppm; IR (KBr): $\tilde{\nu}$ = 3327, 1494, 1449, 1341, 1141, 1080, 720, 586 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{26}ClF_2NO_3S_2$: C 58.04, H 4.87, N 2.60; found: C 58.20, H 4.94, N 2.43; MS (ESI): *m/z*: 538.0 [M^++1].

Compound 10f: 92% yield; white solid; m.p. 98–100 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{24} = 21.39$ (*c* = 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.8 Hz, 2H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.50–7.61 (m, 6H), 7.34–7.41 (m, 4H), 7.06 (t, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 16.2 Hz, 1H), 5.56 (s, 1H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −101.9 (d, *J* = 228.7 Hz, 1F), −102.9 (d, *J* = 226.9 Hz, 1F), −113.6–113.7 ppm (m, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9 (d, *J* = 246.6 Hz), 135.6, 135.3, 133.8, 133.6, 132.4 (d, *J* = 3.0 Hz), 130.5, 130.0 (d, *J* = 3.5 Hz), 129.6, 129.3, 129.0 (d, *J* = 8.2 Hz), 128.3, 125.3, 121.4 (t, *J* = 304.2 Hz), 115.5 (d, *J* = 21.5 Hz), 71.4 (dd, *J* = 21.3, 17.3 Hz), 57.4, 23.0 ppm; IR (KBr): $\tilde{\nu}$ = 3320, 2984, 1604, 1513, 1449, 1328, 1235, 1144, 1061, 713, 572 cm^{-1}; MS (ESI): *m/z*: 522.0 [M^++1]; HRMS (MALDI): *m/z*: calcd for $C_{26}H_{26}NO_3F_3S_2Na$ [M^++Na]: 544.1198; found: 544.1226.

Compound 10g: 86% yield; white solid; m.p. 85–87 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{24} = 18.80$ (*c* = 0.93, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.2 Hz, 2H), 7.49–7.79 (m, 10H), 7.33–7.42 (m, 3H), 6.91 (d, *J* = 15.9 Hz, 1H), 5.59 (s, 1H), 1.36 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −62.9 (s, 3F), −102.2 (d, *J* = 229.8 Hz, 1F), −103.2 ppm (d, *J* = 228.9 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 135.4, 135.3, 133.6, 133.3, 130.5, 130.05, 130.02, 129.9 (q, *J* = 32.1 Hz), 129.7, 129.3, 128.4, 127.6, 125.5 (q, *J* = 3.7 Hz), 122.8, 121.3 (dd, *J* = 303.6, 300.6 Hz), 71.6 (q, *J* = 21.7, 17.5 Hz), 57.4, 22.9 ppm; IR (KBr): $\tilde{\nu}$ = 3318, 1616, 1450, 1326, 1168, 1144, 1068, 1017, 713, 600 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{26}F_5NO_3S_2$: C 56.73, H 4.58, N 2.45; found: C 56.40, H 4.69, N 2.27; MS (ESI): *m/z*: 572.1 [M^++1].

Compound 10h: 95% yield; white solid; m.p. 82–84 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25} = 12.82$ (*c* = 0.93, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.8 Hz, 2H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.51–7.61 (m, 6H), 7.28–7.41 (m, 4H), 7.05 (t, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 16.2 Hz, 1H), 5.56 (s, 1H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −101.9 (d, *J* = 229.5 Hz, 1F), −102.9 (d, *J* = 227.2 Hz, 1F), −111.89 to −111.96 ppm (m, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2 (d, *J* = 248.8 Hz), 137.1, 136.0, 135.3, 133.8, 132.1 (dd, *J* = 8.4, 4.3 Hz), 130.5, 129.6, 129.3, 128.6, 128.5, 127.4, 125.2 (d, *J* = 2.1 Hz), 121.3 (t, *J* = 301.1 Hz), 115.2 (d, *J* = 21.4 Hz), 71.0 (q, *J* = 21.3, 17.1 Hz), 57.4, 22.9 ppm; IR (KBr): $\tilde{\nu}$ = 3317, 2961, 1604, 1509, 1450, 1336, 1143, 1075, 838, 595 cm^{-1}; MS (ESI): *m/z*: 522.1 [M^++1]; HRMS (MALDI): *m/z*: calcd for $C_{26}H_{26}NO_3F_3S_2Na$ [M^++Na]: 544.1198; found: 544.1196.

Compound 10i: 94% yield; white solid; m.p. 173–174 °C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25} = 18.00$ (*c* = 0.94, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.5 Hz, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.43–7.58 (m, 6H), 7.27–7.30 (m, 4H), 7.16 (d, *J* = 8.1 Hz,

2H), 6.73 (d, $J=18.9$ Hz, 1H), 5.53 (s, 1H), 2.35 (s, 3H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-101.7$ (d, $J=227.2$ Hz, 1F), -102.8 ppm (d, $J=228.7$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 139.5, 136.5, 136.2, 135.1, 133.9, 130.6, 130.5, 129.9 (d, $J=3.8$ Hz), 129.2, 128.9, 128.5, 128.3, 127.4, 125.6 (d, $J=2.7$ Hz), 121.3 (t, $J=303.6$ Hz), 71.2 (q, $J=21.3$, 16.9 Hz), 57.3, 23.0, 21.1 ppm; IR (KBr): $\tilde{\nu}=3325$, 2975, 1449, 1339, 1141, 1075, 725, 595 cm^{-1}; MS (ESI): m/z: 518.0 [M^++1]; HRMS (MALDI): m/z: calcd for $C_{27}H_{29}NO_3F_2S_2Na$ [M^++Na]: 540.1449; found: 540.1441.

Compound 10j: 92% yield; white solid; m.p. 83–85°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25}=15.53$ ($c=1.01$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.91$ (d, $J=7.8$ Hz, 2H), 7.71 (t, $J=7.5$ Hz, 1H), 7.51–7.62 (m, 4H), 7.26–7.45 (m, 6H), 7.17 (d, $J=8.1$ Hz, 2H), 6.68 (d, $J=16.2$ Hz, 1H), 5.55 (s, 1H), 2.37 (s, 3H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-101.5$ (d, $J=229.8$ Hz, 1F), -102.6 ppm (d, $J=$ 228.9 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=138.4$, 136.7, 135.2, 133.97, 133.92, 133.3, 130.5, 130.0 (d, $J=3.8$ Hz), 129.4, 129.3, 129.2, 128.2, 127.3, 124.3 (d, $J=2.1$ Hz), 121.5 (t, $J=304.1$ Hz), 71.3 (q, $J=21.2$, 17.3 Hz), 57.3, 22.9, 21.2 ppm; IR (KBr): $\tilde{\nu}=3315$, 2959, 1514, 1449, 1336, 1143, 1077, 713, 572 cm^{-1}; MS (ESI): m/z: 518.0 [M^++1]; HRMS (MALDI): m/z: calcd for $C_{27}H_{29}NO_3F_2S_2Na$ [M^++Na]: 540.1449; found: 540.1452.

Compound 10k: 80% yield; white solid; m.p. 167–169°C, d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25}=-33.93$ ($c=0.94$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.89$ (d, $J=8.1$ Hz, 2H), 7.71 (t, $J=$ 8.1 Hz, 1H), 7.56–7.61 (m, 2H), 7.50 (t, $J=7.8$ Hz, 2H), 7.33–7.40 (m, 4H), 7.21 (d, $J=15.6$ Hz, 1H), 6.59 (d, $J=16.2$ Hz, 1H), 6.41–6.47 (m, 2H), 5.57 (s, 1H), 1.35 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=$ -101.8 (d, $J=227.5$ Hz, 1F), -103.6 ppm (d, $J=229.5$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=151.7$, 142.7, 134.9, 133.9, 133.7, 130.5, 130.1 (d, $J=4.1$ Hz), 129.5, 129.1, 128.2, 124.8 (d, $J=1.5$ Hz), 123.4 (d, $J=3.8$ Hz), 121.4 (dd, $J=304.6$, 300.8 Hz), 111.6, 110.8, 71.1 (dd, $J=21.8$, 17.1 Hz), 57.4, 22.9 ppm; IR (KBr): $\tilde{\nu}=3341$, 1449, 1340, 1145, 1071, 770, 604, 539 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{25}F_2NO_4S_2$: C 58.40, H 5.11, N 2.84; found: C 58.41, H 5.36, N 2.75; MS (ESI): m/z: 494.0 [M^++1].

Compound 10l: 77% yield; white solid; m.p. 84–87°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25}=4.09$ ($c=1.08$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.91$ (d, $J=7.5$ Hz, 2H), 7.71 (t, $J=7.8$ Hz, 1H), 7.44–7.58 (m, 6H), 7.29 (d, $J=16.5$ Hz, 1H), 6.83–6.93 (m, 4H), 6.55 (d, $J=15.9$ Hz, 1H), 5.50 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.34 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-101.8$ (d, $J=227.8$ Hz, 1F), -102.8 ppm (d, $J=227.8$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 160.2, 159.8, 135.9, 135.1, 134.1, 131.4 (d, $J=3.9$ Hz), 130.4, 129.1, 128.9, 128.6, 125.7, 123.3 (d, $J=2.6$ Hz), 121.6 (t, $J=300.1$ Hz), 113.9, 113.5, 71.0 (dd, $J=21.5$, 17.2 Hz), 57.2, 55.2, 55.1, 22.9 ppm; IR (KBr): $\tilde{\nu}=3317$, 2959, 1608, 1513, 1449, 1335, 1255, 1176, 1143, 1074, 828, 686, 597 cm^{-1}; MS (ESI): m/z: 564.1 [M^++1]; HRMS (MALDI): m/z: calcd for $C_{28}H_{31}NO_5F_2S_2Na$ [M^++Na]: 586.1504; found: 586.1506.

Typical procedure for stereoselective nucleophilic difluoromethylation of α,β-acetylenic *N-tert*-butylsulfinyl ketimines 15 using difluoromethyl phenyl sulfone: Under an atmosphere of N_2, NaHMDS (2 M solution in THF; 0.3 mL, 0.6 mmol) was added dropwise to a solution of α,β-unsaturated *N-tert*-butylsulfinyl ketimine **15a** (186 mg, 0.6 mmol) and $PhSO_2CF_2H$ (96 mg, 0.5 mmol) in THF (8 mL) at −78°C. The reaction mixture was stirred vigorously at −78°C for 2 h, and then saturated aqueous NaCl solution (5 mL) was added. The resulting mixture was extracted with Et_2O (3×10 mL), and the combined organic phases were dried over $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography (petroleum ether/EtOAc = 4:1 as eluent) to give product **16a** (228 mg, 91% yield).

Compound 16a: 91% yield; white solid; m.p. 150–151°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25}=-122.60$ ($c=0.98$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.00$ (d, $J=8.1$ Hz, 2H), 7.81–7.87 (m, 2H), 7.29–7.71 (m, 11H), 5.65 (s, 1H), 1.34 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-101.0$ (d, $J=229.2$ Hz, 1F), -105.5 ppm (d, $J=$ 228.9 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.3$, 134.0, 132.9, 132.0, 130.6, 129.8, 129.7, 129.1, 128.1, 128.0, 121.5, 119.0 (dd, $J=302.2$, 298.5 Hz), 92.8, 82.9 (d, $J=5.2$ Hz), 64.2 (t, $J=22.4$ Hz), 57.5, 22.8 ppm; IR (KBr): $\tilde{\nu}=3303$, 2980, 2227, 1490, 1449, 1331, 1146, 1083, 715, 582 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{25}F_2NO_3S_2$: C 62.26, H 5.02, N 2.79; found: C 62.12, H 4.98, N 2.82; MS (ESI): m/z: 502.2 [M^++1].

Compound 16b: 94% yield; white solid; m.p. 130–132°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25}=-119.81$ ($c=1.03$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.00$ (d, $J=7.5$ Hz, 2H), 7.81–7.87 (m, 2H), 7.66 (d, $J=7.2$ Hz, 1H), 7.38–7.55 (m, 7H), 7.13 (d, $J=8.4$ Hz, 2H), 5.61 (s, 1H), 2.36 (s, 3H), 1.33 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-99.9$ (d, $J=229.8$ Hz, 1F), -104.4 ppm (d, $J=229.8$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=140.2$, 136.1, 134.9, 133.9, 132.8, 131.4, 130.7, 130.5, 129.9, 129.7, 128.9, 119.9 (dd, $J=302.2$, 297.7 Hz), 119.2, 93.9, 83.1 (d, $J=5.2$ Hz), 65.1 (t, $J=21.6$ Hz), 58.3, 23.6, 22.4 ppm; IR (KBr): $\tilde{\nu}=3306$, 2980, 2230, 1510, 1450, 1331, 1146, 1087, 715, 579 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{27}F_2NO_3S_2$: C 62.89, H 5.28, N 2.72; found: C 62.83, H 5.37, N 3.03; MS (ESI): m/z: 516.1 [M^++1].

Compound 16c: 86% yield; white solid; m.p. 166–167°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25}=-107.22$ ($c=0.94$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.00$ (d, $J=8.1$ Hz, 2H), 7.74 (d, $J=$ 7.5 Hz, 2H), 7.48–7.69 (m, 5H), 7.28–7.38 (m, 3H), 6.91 (d, $J=9.3$ Hz, 2H), 5.58 (s, 1H), 3.82 (s, 3H), 1.33 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-100.1$ (d, $J=226.7$ Hz, 1F), -104.5 ppm (d, $J=227.8$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=160.6$, 135.3, 134.1, 132.0, 131.3, 130.6, 129.1, 128.1, 124.6, 121.5, 119.2 (t, $J=297.7$ Hz), 113.4, 92.5, 83.3 (d, $J=5.2$ Hz), 63.8 (t, $J=22.6$ Hz), 57.4, 55.2, 22.8 ppm; IR (KBr): $\tilde{\nu}=$ 3275, 2232, 1607, 1511, 1338, 1259, 1145, 1083, 839, 598 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{27}F_2NO_4S_2$: C 61.00, H 5.12, N 2.63; found: C 60.72, H 5.26, N 2.50; MS (ESI): m/z: 532.0 [M^++1].

Compound 16d: 96% yield; white solid; m.p. 69–70°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25}=-105.87$ ($c=0.97$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.99$ (d, $J=7.8$ Hz, 2H), 7.77 (d, $J=9.0$ Hz, 2H), 7.67 (t, $J=6.9$ Hz, 1H), 7.50–7.61 (m, 4H), 7.29–7.41 (m, 5H), 5.62 (s, 1H), 1.33 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-100.1$ (d, $J=$ 224.5 Hz, 1F), -104.5 ppm (d, $J=230.4$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=136.1$, 135.4, 133.8, 132.1, 131.6, 131.3, 130.6, 129.3, 129.2, 128.3, 128.2, 121.2, 118.9 (dd, $J=302.2$, 298.5 Hz), 93.1, 82.5 (d, $J=$ 5.2 Hz), 63.9 (t, $J=224.5$ Hz), 57.6, 22.8 ppm; IR (KBr): $\tilde{\nu}=3273$, 2234, 1491, 1340, 1146, 1089, 757, 586, 539 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{24}ClF_2NO_3S_2$: C 58.26, H 4.51, N 2.61; found: C 57.99, H 4.67, N 2.49; MS (ESI): m/z: 536.0 [M^++1].

Compound 16e: 93% yield; white solid; m.p. 142–143°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{27}=-129.62$ ($c=1.09$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.00$ (d, $J=7.5$ Hz, 2H), 7.80–7.87 (m, 2H), 7.66 (t, $J=7.8$ Hz, 1H), 7.48–7.55 (m, 4H), 7.38–7.43 (m, 3H), 6.85 (d, $J=9.0$ Hz, 2H), 5.62 (s, 1H), 3.82 (s, 3H), 1.33 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-99.8$ (d, $J=225.0$ Hz, 1F), -104.3 ppm (d, $J=$ 229.3 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=160.3$, 135.3, 134.1, 133.6, 133.2, 130.6, 129.9, 129.7, 129.1, 128.1, 119.1 (t, $J=302.2$ Hz), 113.8, 113.6, 93.0, 81.7 (d, $J=5.2$ Hz), 64.3 (t, $J=22.3$ Hz), 57.5, 55.3, 22.8 ppm; IR (KBr): $\tilde{\nu}=3273$, 2978, 2233, 1608, 1512, 1450, 1333, 1145, 1095, 1025, 714, 580 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{27}F_2NO_4S_2$: C 61.00, H 5.12, N 2.63; found: C 60.95, H 5.03, N 2.49; MS (ESI): m/z: 532.1 [M^++1].

Compound 16f: 86% yield; white solid; m.p. 67–69°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{27}=-107.13$ ($c=1.03$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.00$ (d, $J=7.8$ Hz, 2H), 7.47–7.74 (m, 7H), 7.29–7.39 (m, 3H), 7.21 (d, $J=8.1$ Hz, 2H), 5.60 (s, 1H), 2.37 (s, 3H), 1.33 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-99.9$ (d, $J=$ 230.7 Hz, 1F), -104.4 ppm (d, $J=225.0$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=139.9$, 135.3, 134.1, 132.1, 130.6, 129.9, 129.8, 129.1, 128.9, 128.2, 121.6, 119.2 (dd, $J=301.7$, 297.2 Hz), 92.6, 83.2 (d, $J=5.2$ Hz), 64.1 (t, $J=24.5$ Hz), 57.5, 22.8, 21.1 ppm; IR (KBr): $\tilde{\nu}=3277$, 2233, 1449, 1341, 1145, 1088, 758, 595, 539 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{27}F_2NO_3S_2$: C 62.89, H 5.28, N 2.72; found: C 62.60, H 5.40, N 2.48; MS (ESI): m/z: 516.2 [M^++1].

Compound 16g: 32% yield; white solid; m.p. 170–172°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{26} = 13.66$ ($c = 1.02$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 9.6$ Hz, 1H), 7.88 (d, $J = 8.1$ Hz, 2H), 7.58–7.69 (m, 3H), 7.35–7.54 (m, 6H), 7.11 (t, $J = 7.8$ Hz, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 6.51 (s, 1H), 3.92 (s, 3H), 1.22 ppm (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -94.7$ (d, $J = 229.0$ Hz, 1F), −101.5 ppm (d, $J = 231.2$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 158.3, 135.1, 134.5, 132.6, 132.1, 131.6, 130.9, 129.6, 129.2, 128.6, 121.8, 121.7, 121.4, 120.5 (t, $J = 304.5$ Hz), 112.9, 93.7, 82.5 (d, $J = 5.2$ Hz), 66.5 (dd, $J = 26.4$, 21.4 Hz), 57.2, 56.4, 22.9 ppm; IR (KBr): $\tilde{\nu} = 3339$, 2953, 2224, 1584, 1493, 1342, 1245, 1138, 1084, 977, 757, 585 cm^{-1}; MS (ESI): m/z: 532.0 [M^++1]; HRMS (MALDI): m/z: calcd for $C_{27}H_{27}NO_4F_2S_2Na$ [M^++Na]: 554.1242; found: 554.1243.

Compound 16h: 83% yield; gummy liquid; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{27} = -30.32$ ($c = 0.92$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (d, $J = 7.8$ Hz, 2H), 7.79–7.86 (m, 2H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.55 (t, $J = 7.8$ Hz, 2H), 7.38–7.45 (m, 3H), 1.30 (s, 9H), 1.09–1.27 ppm (m, 21H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -98.8$ (d, $J = 224.2$ Hz, 1F), −100.3 ppm (d, $J = 228.4$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 135.5$, 134.1, 133.5, 130.7, 129.8, 129.44, 129.40, 128.3, 119.4 (t, $J = 301.5$ Hz), 99.2, 96.5, 64.8 (t, $J = 23.0$ Hz), 57.5, 23.0, 18.8, 11.4, 11.1 ppm; IR (KBr): $\tilde{\nu} = 3287$, 2945, 2867, 1450, 1345, 1146, 883, 714, 578 cm^{-1}; MS (ESI): m/z: 582.2 [M^++1]; HRMS (MALDI): m/z: calcd for $C_{29}H_{41}NO_3F_2SiS_2Na$ [M^++Na]: 604.2157; found: 604.2169.

Compound 16i: 49% yield; white solid; m.p. 88–90°C; d.r. > 99:1 (after silica gel chromatography), $[\alpha]_D^{25} = -70.79$ ($c = 0.92$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.97$ (d, $J = 8.1$ Hz, 2H), 7.69–7.81 (m, 3H), 7.58 (t, $J = 7.5$ Hz, 2H), 7.35–7.42 (m, 3H), 5.47 (s, 1H), 2.31–2.38 (m, 2H), 1.55–1.65 (m, 2H), 1.42–1.51 (m, 2H), 1.31 (s, 9H), 0.93 ppm (t, $J = 7.5$ Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -100.3$ (d, $J = 227.6$ Hz, 1F), −103.5 ppm (d, $J = 228.7$ Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 136.1, 135.1, 134.2, 131.3, 130.6, 130.4, 129.9, 128.7, 120.0 (t, $J = 301.5$ Hz), 95.6, 74.8 (d, $J = 5.2$ Hz), 64.7 (t, $J = 21.6$ Hz), 58.1, 30.7, 23.6, 22.8, 19.6, 14.3 ppm; IR (KBr): $\tilde{\nu} = 3277$, 2962, 2239, 1449, 1340, 1137, 1087, 713, 582 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{29}F_2NO_3S_2$: C 59.85, H 6.07, N 2.91; found: C 60.29, H 6.12, N 3.18; MS (ESI): m/z: 582.2 [M^++1].

X-ray crystallographic analysis: CCDC-756004 (**5k**), 781706 (**10a**), and 781707 (**16a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The X-ray crystallographic analysis was perfomed by using a Rigaku FCR diffractometer.

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