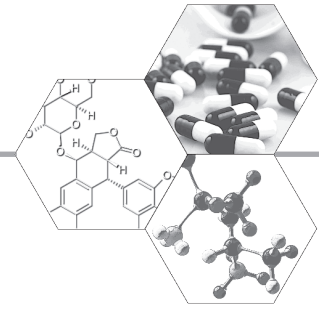


Synthesis of fluorinated chiral amines using *N-tert*-butylsulfinyl imines

Fluorinated chiral amines are highly important building blocks in medicinal chemistry since fluorine decreases the basicity of the amine functionality and, thus, improves the bioavailability of a drug molecule. Recently, stereoselective synthesis of fluorinated chiral amines based on the use of *N-tert*-butylsulfinyl imines has attracted much attention due to the high stereoselectivity, broad substrate scope and easy experimental handing. In this article, we summarize developments in the field over the last decade, including the synthesis of trifluoromethylated, difluoromethylated, *gem*-difluoromethylenated and monofluoromethylated chiral amines. Stereoselective synthesis of fluorinated chiral amines based on the use of *N-tert*-butylsulfinyl imines has been accomplished by two major strategies. One is the stereoselective addition or asymmetric reduction of fluorinated *N-tert*-butylsulfinyl imines and their derivatives. The other strategy is the asymmetric addition of fluorinated reagents to *N-tert*-butylsulfinyl imines, the development of which is lacking new efficient and atom-economic fluorinated reagents.

Fluorinated amines, especially chiral fluorinated amines, are important synthetic building blocks in drug design because of the minimal structural changes but maximal shifts in electron distribution caused by fluorine [1,2]. Furthermore, the basicity of amines (especially the β-fluorinated amines) can be tuned by fluorine or fluoroalkyl groups, thus increasing high bioavailability of a target drug [3–5]. Over the past three decades, efficient stereoselective synthesis of fluorinated amines has attracted much attention; such synthetic approaches are based mainly on the use of fluorinating reagents (e.g., diethylaminosulfur trifluoride and the hydrogen fluoride–pyridine complex) and fluorinated building blocks (e.g., fluorinated imidoyl halides and fluorinated α-imino esters and imines) [6–8]. In this context, diastereoselective synthesis of fluorinated amines using *N-tert*-butylsulfinyl imines has become one of the most important and widely used approaches. Although enantiopure *N-tert*-butylsulfinyl imines were firstly reported by García Ruano and co-workers in 1996 [9], their wide application in asymmetric synthesis was initiated by Ellman's seminal work on the practical preparation of *N-tert*-butylsulfinyl imines by condensation of optically pure *N-tert*-butylsulfinamide with aldehydes or ketones [10–18]. Furthermore, the easy recycling of the *tert*-butylsulfinyl chiral auxiliary group (by conversion back to enantiopure *tert*-butylsulfinamide) greatly improves the practicality and large-scale applications of *tert*-butylsulfinamide-based amine synthesis chemistry [19]. The fact that the *tert*-butylsulfinyl group activates the imine functional group (for the addition of many different classes of nucleophiles) and serves as a powerful chiral-directing group makes it highly attractive in the asymmetric synthesis of fluorinated chiral amines. In this article, we would like to summarize the stereoselective synthesis of fluorinated chiral amines based on the use of Ellman's *N-tert*-butylsulfinyl imines developed during the last decade, including the synthesis of trifluoromethylated, difluoromethylated, *gem*-difluoromethylenated and monofluoromethylated chiral amines.

Fluorinated chiral amines from fluorinated *tert*-butylsulfinyl imines & their derivatives

One of the useful methods for asymmetric synthesis of fluorinated chiral amines is based on the use of fluorinated enantiopure *tert*-butylsulfinyl imines and their derivatives as precursors [20]. It should be noted that the isolation and characterization of fluorinated enantiopure *tert*-butylsulfinyl imines are generally difficult due to their susceptibility to hydrolysis [21]. Therefore, in most cases, fluorinated *tert*-butylsulfinyl imines are generated *in situ* to react with various electrophiles [22,23].

In 2006, Lu and co-workers described the solvent-controlled asymmetric Strecker reactions with unstable trifluoromethyl sulfinimines **1**, and each diastereomer (**2** or **3**) of the α-trifluoromethyl α-cyano amines was obtained in good yield and with high diastereoselectivity

Jun Liu & Jinbo Hu†
†Author for correspondence
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China
Tel.: +86 215 492 5174
Fax: +86 216 416 6128
E-mail: jinbohu@mail.sioc.ac.cn

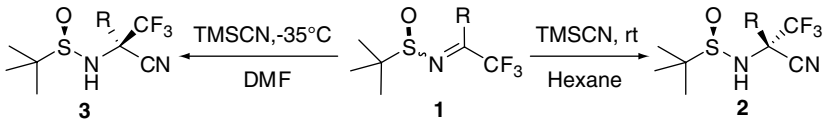
FLUORINATED AMINE
Amine compounds containing fluorine atom(s), with the fluorine substitution often on the β-position to the amino functionality

STEREOSELECTIVE SYNTHESIS
A chemical reaction (or reaction sequence) that produces the stereoisomeric (enantiomeric, diastereomeric or Z-/E-isomeric) products in unequal quantities

***N*-*TERT*-BUTYLSULFINYL IMINE**
A class of imine compounds that possess a (generally homochiral) *tert*-butylsulfinyl group on the nitrogen atom of imino group

Future science part of fsg

Table 1. Asymmetric Strecker reaction between CF_3-sulfinimines (1) and TMSCN.



3 1 2

Entry	Substrate	Hexane		DMF	
		Total yield (%)	*dr (2/3)*	*Total yield (%)*	*dr (2/3)*
1	R = Me	69	27:1	71	1:19
2	R = Et	77	7:1	76	1:10
3	R = *n*-C_6H_{13}	88	14:1	84	1:11
4	R = CH_2Bn	92	7:1	89	1:15
5	R = Ph	85	99:1	72	1:6
6	R = *p*-MeC_6H_4	87	11:1	69	1:7
7	R = *p*-$MeOC_6H_4$	89	14:1	78	1:9
8	R = *p*-ClC_6H_4	83	8:1	71	1:6

TMSCN: Trimethylsilyl cyanide.
Data from [21].

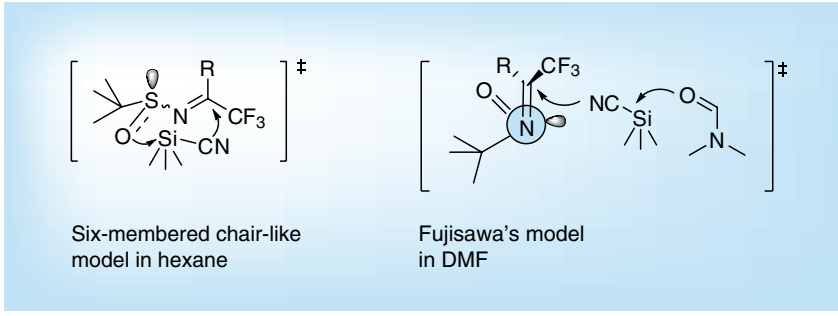
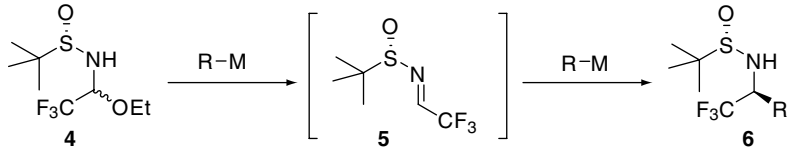


Figure 1. Different transition state models.

Table 2. Asymmetric addition reactions of Grignard reagents.



4 5 6

Entry	RM	Solvent	Product	dr [(S_s,*S*):(S_s,*R*)]	Yield (%)
1	MgBr	CH_2Cl_2	**6A**	22:1	77
2	MgBr	CH_2Cl_2	**6B**	11:1	81
3	MgBr	CH_2Cl_2	**6C**	5:1	98
4	MgBr	CH_2Cl_2	**6D**	>30:1	74
5	MgBr	CH_2Cl_2	**6E**	6:1	98
6	MgBr	THF	**6E**	3.5:1	97

Data from [22].

(Table 1) [21]. The authors rationalized the stereoselectivity using different models. The Strecker reaction in hexane may proceed via the six-membered chair-like model and the sulfinyl group-activated trimethyl cyanide (TMSCN) giving the (*S*, *Rs*)-isomer **2** as the predominant product. However, the Strecker reaction in DMF may undertake Fujisawa's model, in which DMF serves not only as a polar solvent but also as a Lewis base to active TMSCN. Therefore, (*R*, *Rs*)-isomer **3** was obtained as the major product **(Figure 1)**. Further deprotection and hydrolysis afforded α-trifluoromethyl α-amino acid [21].

Later, the addition of Grignard reagents to trifluoromethyl *tert*-butylsulfinimine–ethanol adducts was reported by Kuduk and co-workers **(Table 2)** [22]. In these reactions, sulfinamino acetals **4** served as stable precursors for the *in situ* generation of imines **5**, which underwent reactions with Grignard reagents to afford allyltrifluoromethylamines **6** in good yields and with moderate-to-excellent diastereoselectivity.

Truong and co-workers reported the synthesis of a variety of optically enriched 1-aryl-2,2,2-trifluoroethylamine analogs **7** in moderate-to-good yields using 2-methyl-*N*-(2,2,2-trifluoro-ethylidene)propane-2-sulfinamide **5** as a key precursor **(Table 3)** [23]. The addition of phenyllithium to imine **5** appeared to have proceeded via a non-chelated transition-state model where phenyllithiun preferably added to the imine from the less-hindered face (derived from the most stable conformation of the imine) to afford the major diastereomer adduct (*Ss*,*S*)-**7a** [23]. It should be pointed out that recent studies have shown that the more stable conformation of the reacting *N-tert*-butylsulfinimines is the conformation where the N-S-O bonds are coplanar and the S-O bond lies away from the lone pair of the nitrogen atom [16,24–26].

Imine **5** was also subjected to the rhodium-catalyzed 1,2-addition of aryboronic acids affording optically enriched sulfinamides **8** in moderate-to-good yields and with good to excellent diastereoselectivies. The sense of the stereo-induction was explained by the non-chelated transition-state model, which was consistent with the addition of organolithium reagents. The chiral auxiliary group on sulfinamide **8** could be readily removed by acidic alcoholysis to provide the corresponding trifluoroethylamine analog **9 (Table 4)** [27].

The application of chiral trifluoromethyl α,β-unsaturated *N-tert*-butylsulfinyl ketimines in the asymmetric synthesis of trifluoromethylated

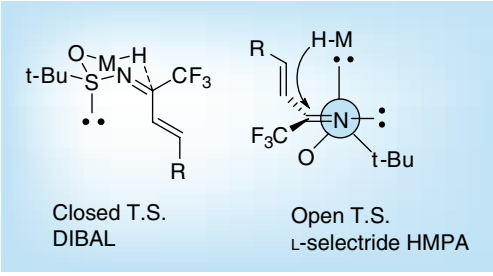


Figure 2. Different transition-state models.

allylic amines was demonstrated by Liu and coworkers [28]. Either diastereomer of the trifluoromethylated allylic amines was obtained in good yield and with excellent diastereoselectivity via the diastereoselective reduction of chiral trifluoromethyl α,β-unsaturated *N-tert*-butylsulfinyl ketimines **10** by diisobutylaluminium hydride (DIBAL-H) and L-selectride, respectively **(TABLE 5)** [28]. The reversal of the diastereofacial selectivity observed with different reducing agents could be explained by different transition states involved: a cyclic (closed) transition state in the reduction of DIBAL-H and an open transition state in the reduction of L-selectride **(FIGURE 2)** [28].

Chiral allylic primary amines **15** are potential dipeptide mimics, and their synthesis has been achieved through the efficient asymmetric reductive amination of fluoroenones **13 (TABLE 6)** [29]. Both diastereomers were obtained from the same chiral nonracemic sulfinyl imine by using different reducing agents. Moreover, neither the fluoroolefin geometry nor the presence of a chiral center on the C-terminal moiety affected the reduction selectivity [29]. The origins of different diastereoselectivities with different reducing agents (e.g., DIBAL-H and L-selectride) can be depicted with similar transition states, as shown in **FIGURE 2**.

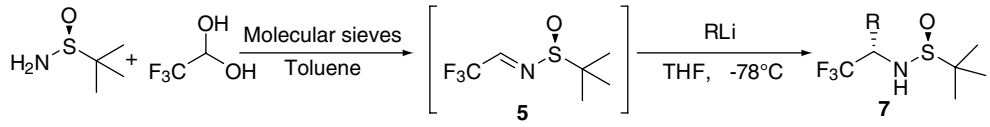
The synthesis of chiral fluorinated sulfinamides **14** was also achieved via diastereoselective addition of Grignard and organolithium reagents to *N*-(*tert*-butylsulfinyl)-α-fluoroenimines **16 (TABLE 7)** [30]. All organometallic reagents were added regioselectively at the imino carbon of α-fluoroenimines **16** to provide chiral allylamines in excellent yields and with diastereomeric ratios of up to 96:4. Enantiopure fluoroolefin dipeptide mimics could be obtained by acid-mediated removal of the sulfinyl group and simple chemical transformations.

Fluorinated chiral amines from nonfluorinated *tert*-butylsulfinimines & fluorinated reagents

The aforementioned asymmetric synthesis of fluorinated chiral amines was accomplished by using fluorinated *tert*-butylsulfinimines and their derivatives. However, most fluorinated *tert*-butylsulfinimines and their derivatives were easily hydrolyzed or decomposed during work-up and/or storage, limiting their large-scale applications. Another useful strategy for asymmetric synthesis of fluorinated chiral amines has been based on the stereoselective nucleophilic addition of fluoroalkylation reagents to nonfluorinated *tert*-butylsulfinimines. This direct nucleophilic

FLUOROALKYLATION
A chemical reaction (or reaction sequence) that introduces one or more fluorine-bearing alkyl group(s) into substrates

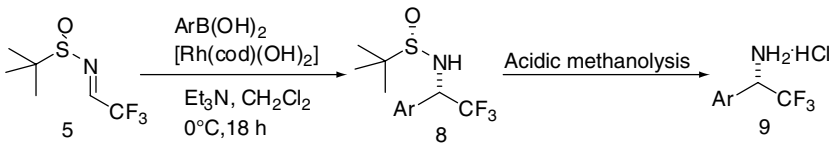
Table 3. Diastereoselective 1,2-addition of aryllithium reagents to imine 5.

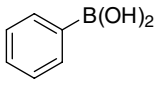
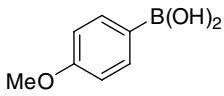
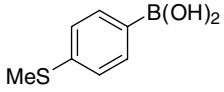
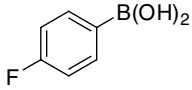
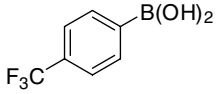
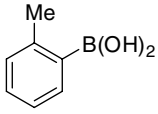
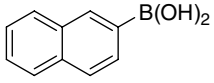
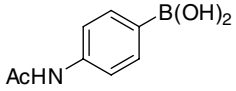
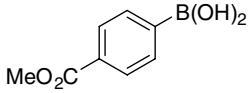
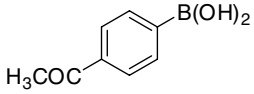


Entry	RLi	Product 7	Yield (%)	dr
1	PhLi*	**7a**	66	98:2
2	PhLi‡	**7a**	42	98:2
3	PhLi§	**7a**	58	96:4
4	4-MeOPhLi	**7b**	55	97:3
5	4-MeSPhLi	**7c**	53	98:2
6	4-FPhLi	**7d**	50	100:1
7	3,5-diFPhLi¶	**7e**	36	83:17
8	2-MePhLi	**7f**	40	99:1
9	Pyridin-2-yllithium	**7g**	15	98:2

*2.5 equiv of PhLi was used.
‡1.1 equiv of PhLi was used.
§Precomplexation of imine with $AlMe_3$ at 0°C, added to PhLi solution at -78°C.
¶Unoptimized conditions.
Data from [23].

Table 4. Rhodium-catalyzed diastereoselective 1,2-addition of arylboronic acids to imine 5.



Entry	$ArB(OH)_2$	Yield 8 (%)	de	Yield 9 (%)
1		72	90	90
2		73	81	92
3		55	93	94
4		75	93	92
5		58	>99	83
6		72	91	96
7		62	91	99
8		47	94	83
9		49	94	84
10		66	85	67

Data from [27].

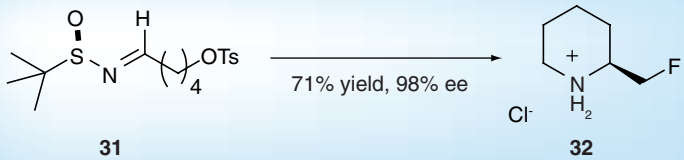


Figure 3. Synthesis of α-monofluoromethylated cyclic secondary amine 32.
Data from [44].

fluoroalkylation method was promoted by the development of a variety of fluoroalkylation reagents, such as Ruppert-Prakash reagent [(trifluoromethyl)trimethylsilane ($TMSCF_3$) and fluorinated sulfones, among others.

In 2001, Prakash and co-workers reported the first stereoselective synthesis of trifluoromethylated amines through nucleophilic trifluoromethylation of *N-tert*-butylsulfimines by using $TMSCF_3$ reagent **(Table 8)** [31]. Tetrabutylammonium triphenyldisilicate (TBAT) was applied as a hydrophobic fluoride initiator. The nucleophilic trifluoromethylation reaction can be applied to nonenolizable, enolizable, aromatic and heterocyclic imines alike, and the addition proceeded from the less hindered *Re* face of the imines to give the selective Cram products **18**, which can be transformed to the trifluoromethylated amines **19** [31].

$TMSCF_3$ is also an efficient nucleophilic trifluoromethylating reagent for the direct preparation of trifluoromethylated vinical ethylenediamines **(Table 9)** [32]. The nucleophilic trifluoromethylation of α-amino *N-tert*-butylsulfinimines was achieved with $TMSCF_3$ and afforded high yield of the trifluoromethylated vinical ethylenediamines in high stereoselectivity, particularly in the case of imines derived from L-amino acids. The very high diastereoselectivity observed in the reaction suggests that both chiral centers present in the molecule induce the incoming nucleophile to the *Re* face of the imines [32]. While in the case of imine derived from D-amino acid, despite the fact that each chiral center directed the addition from a different face of the imine, the major diastereomer was obtained from the *Re* face attack of imine, indicating that the *tert*-butylsulfinyl group controlled the diasterofacial selectivity of the reaction [32].

With $TMSCF_3$ reagent, Prakash and co-workers also developed the asymmetric synthesis of trifluoromethylated allylic amines by highly diastereoselective addition to α,β-unsaturated *N-tert*-butylsulfinimines by using TBAT or tetramethylammonium fluoride (TMAF) as a fluoride initiator **(Table 10)** [33]. In this reaction, there is no 1,4-addition product obtained and the rationale for the high anti-Ellman products could be explained by Cram-Davis's open transition-state model [33].

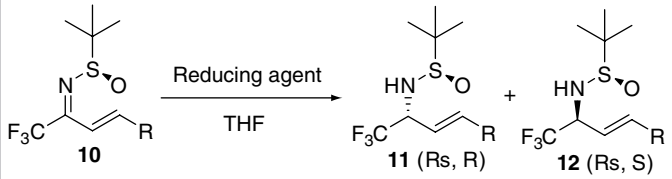
Fluorinated Reformatsky reagent was also found to readily react with *N-tert*-butylsulfinimines. Addition of the Reformatsky reagent **24** derived from ethyl bromodifluoroacetate to *N-tert*-butylsulfinimines produced

β-branched α,α-difluoro-β-amino esters **25** in moderate-to-good diastereomeric ratios (dr 80:20 to 95:5) **(TABLE 11)** [34]. The diastereomers were easily separated, and the resulting enantiopure protected β-amino esters were readily transformed to the corresponding acid, amide and amine derivatives as useful building blocks for medicinal chemistry applications.

Since 2003, difluoromethyl phenyl sulfone was extensively used as a versatile reagent for the selective transfer of difluoromethyl, difluoromethylene and difluoromethylidene building blocks [35–39]. In 2005, Li and Hu reported the first highly stereoselective and facile synthesis of α-difluoromethyl amines via nucleophilic difluoromethylation of *N*-(*tert*-butylsulfinyl)- aldimines with difluoromethyl-phenyl sulfone, followed by the convenient deprotection of both *tert*-butylsulfinyl and phenylsulfonyl groups **(TABLE 12)** [40]. The sense of diastereoselective induction can be depicted by a nonchelation-controlled addition step to give the Cram products **26**.

In 2007, Li and Hu reported the diastereoselective (phenylthio)difluoromethylation of *N*-(*tert*-butylsulfinyl)aldimines with the Me_3SiCF_2SPh reagent, which provides an alternative approach

Table 5. Diastereoselective reduction of 10 with DIBAL-H and L-selectride.



R	DIBAL-H 11 yield (%) (dr)	L-selectride 12 yield (%) (dr)
C_6H_5	99 (99:1)	99 (99:1)
4-$MeOC_6H_4$	98 (99:1)	92 (98:2)
4-MeC_6H_4	97 (>99:1)	95 (98:2)
4-ClC_6H_4	98 (99:1)	88 (99:1)
4-BrC_6H_4	97 (99:1)	96 (98:2)
2-$MeOC_6H_4$	97 (99:1)	96 (97:3)
3-BrC_6H_4	93 (97:3)	90 (99:1)
1-Naphthyl	96 (99:1)	94 (99:1)
2-Furyl	94 (>98:2)	97 (98:2)
$C_6H_5C{\equiv}C$	93 (> 96:4)	81 (95:5)
n-C_8H_{17}	87 (>99:1)	60 (96:4)
$C_6H_5(CH_2)_3$	81 (>99:1)	62 (99:1)

Data from [28].

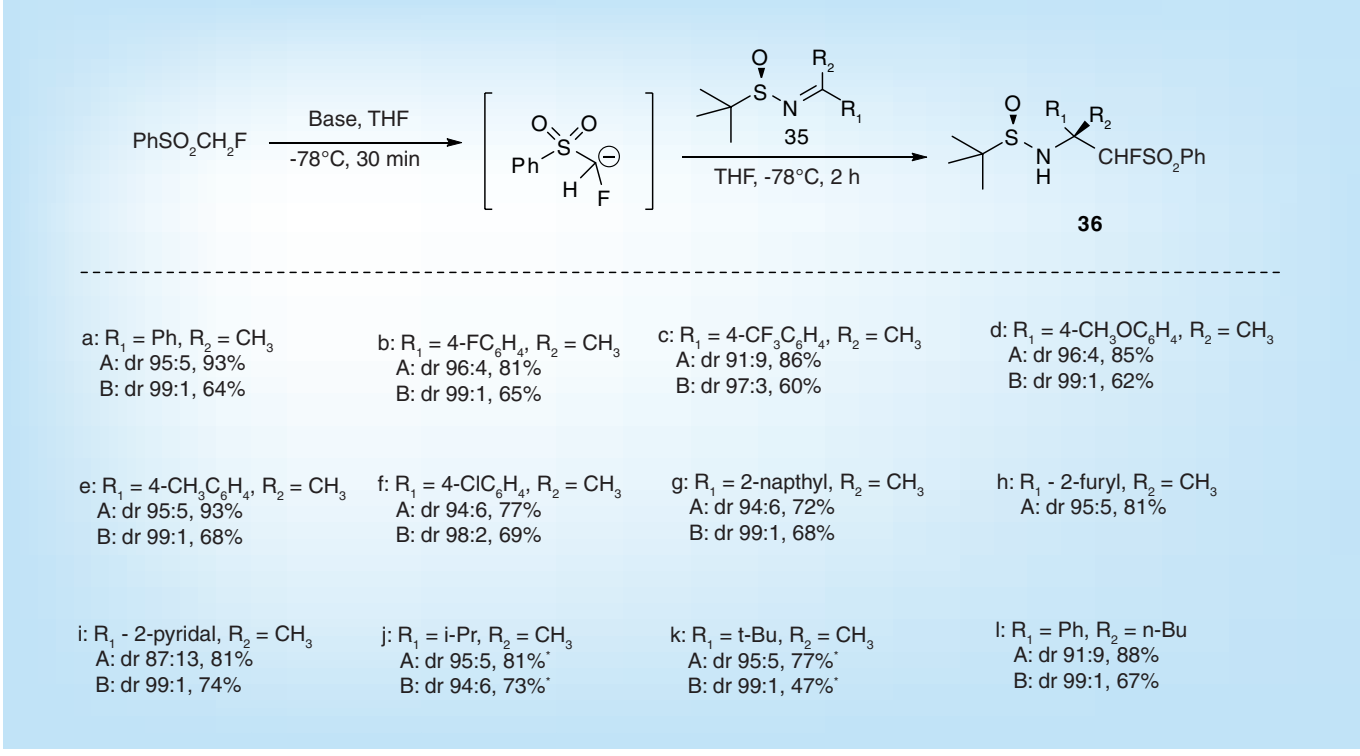


Figure 4. Diastereoselective monofluoromethylation of ketimines (35). Condition A: n-BuLi used as a base; condition B: KHMDS used as a base.
*Determined by ^{19}F NMR using $PhCF_3$ as internal standard.
Data from [46].

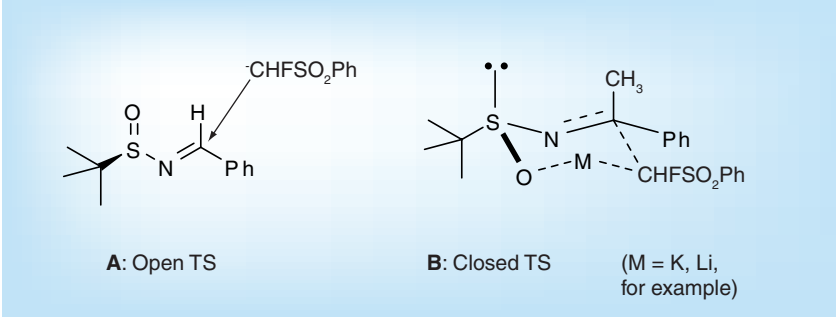
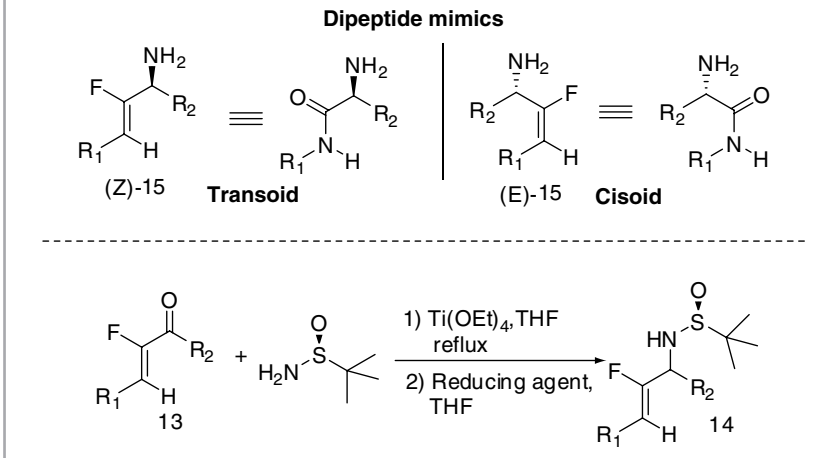
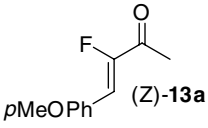
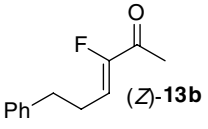
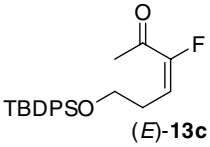
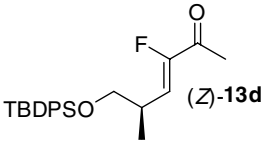


Figure 5. Different transition-state models.
Data from [46].

Table 6. Diastereoselective reduction amination of α-fluoro α,β-unsaturated ketones 13.



Fluoroenone 13	Reducing agent (-78°C)	Product 14	Yield (%)	de
	DIBAL-H	(*Ss*,*S*,*Z*)-**14a**	79	97
	L-selectride	(*Ss*,*R*,*Z*)-**14a**	72	95
	DIBAL-H	(*Ss*,*S*,*Z*)-**14b**	57	96
	L-selectride	(*Ss*,*R*,*Z*)-**14b**	46	94
	DIBAL-H	(*Ss*,*S*,*E*)-**14c**	60	96
	L-selectride	(*Ss*,*R*,*E*)-**14c**	86	98
	DIBAL-H	(*R*,*Ss*,*S*,*E*)-**14d**	61	96
	L-selectride	(*R*,*Ss*,*R*,*E*)-**14d**	62	91

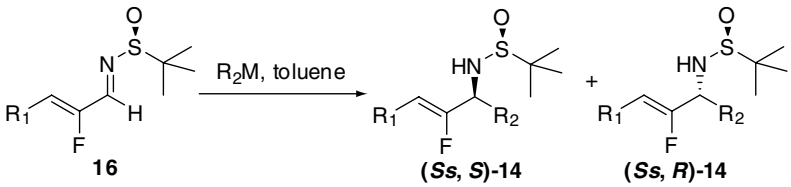
Data from [29].

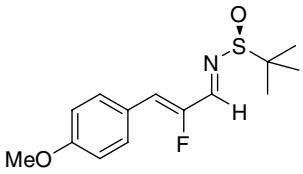
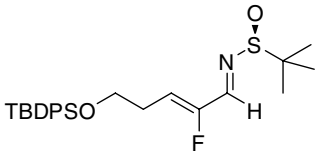
for the preparation of optically pure α-difluoromethyl amines **(Table 13)** [41]. Nucleophilic (phenylthio)difluoromethylation of *N*-(*tert*-butylsulfinyl)imines afforded the corresponding products in good yields and with high diastereoselectivity. The $PhSCF_2$-containing sulfinamides obtained could be further transformed into chiral 2,4-*trans*-disubstituted 3,3-difluoropyrrolidines through an intramolecular radical cyclization methodology [41].

α-monofluoromethyl amines have been extensively used as important building blocks in the design of many anticholinergic, antiemetic, antispastic drugs and enzyme inhibitors, given the fact that the fluorine atom lowers the basicity of amine functionality, decreases acute toxicity and increases the metabolic stability of a target drug [42,43]. The unprecedented nucleophilic monofluoromethylation of *N*-(*tert*-butylsulfinyl)imines using fluoromethyl phenyl sulfone was shown to be a highly stereoselective and convenient method for the synthesis of enantiopure α-monofluoromethyl amines **(Table 14)** [44]. The same methodology could also be used to synthesize homochiral α-monofluoromethylated cyclic secondary amine **32** by using tosylate-bearing *N*-*tert*-butylsulfinylimine **31 (Figure 3)** [44].

$PhSO_2CF_2H$ and $PhSO_2CH_2F$ were robust nucleophilic di- and mono-fluoromethylating agents, the application of which was extended to the highly diastereoselective synthesis of homochiral α-difluoromethylated and α-monofluoromethylated vicinal ethylenediamines through direct nucleophilic di- and monofluoromethylation of α-amino *N*-*tert*-butylsulfinimines **20 (Tables 15 & 16)** [45]. The excellent diastereoselectivity observed in the fluoroalkylation of imines **20** derived from the corresponding (*S*)-amino aldehyde indicated that both the *tert*-butylsulfinyl group and the dibenzylamino group induced the nucleophilic addition from the *Re* face of imines and the stereochemistry of the reactions was nonchelation controlled. The difluoromethylation of imine **20** derived from (*R*)-amino aldehyde gave the desired product with 95:5 diastereomeric ratio, which suggests that the *tert*-butylsulfinyl group (instead of the dibenzylamino group) dominated the stereochemical outcome of the addition products. Interestingly, moderate stereoselectivies (1.5:1 to 3.3:1) were observed in the case of monofluoromethylation of imines **20** during the formation of another neighboring stereogenic center (the fluorine-bearing carbon) **(Tables 15 & 16)** [45].

Table 7. Diastereoselective addition of organometallic reagents to α-fluoroenimines 16.



Substrate 16	R_2M	T (°C)	Time (h)	Additive	Yield (%)	dr
	PhMgBr	-30	2		95	10:90
	PhLi	-78	3		95	67:33
	MeMgBr	0	0.75	$AlMe_3$	82	6:94
	MeLi	-78	5		96	45:55
	i-PrMgCl	0	0.7		60	30:70
	i-PrLi	-78	1		98	60:40
	i-BuMgBr	0	0.7		27	30:70
	BnMgCl	0	1		94	30:70
	AllyMgBr	0	1		82	4:96
	VinylMgBr	0	0.5		95	33:67
	PhMgBr	0	1.5		90	14:86
	PhLi	-78	12		83	65:35
	MeMgBr	0	2.5	$AlMe_3$	84	10:90
	i-PrMgCl	0	0.75		41	49:51
	i-PrLi	-78	1		91	67:33
	i-BuMgBr	0	0.5		36	30:70
	BnMgCl	0	1.5		90	43:57
	AllyMgBr	0	0.75		91	8:92
	VinylMgBr	0	0.75		98	35:65

Data from [30].

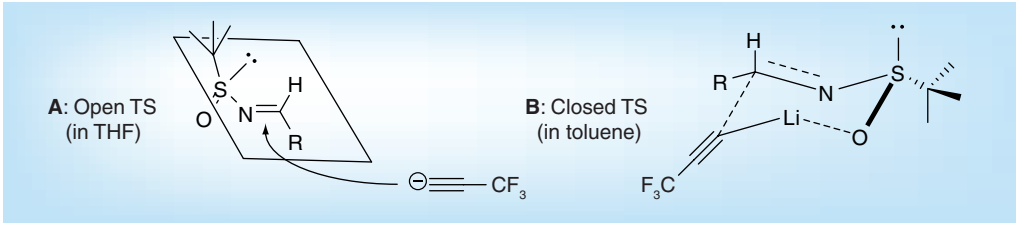


Figure 6. Different transition-state models.
Data from [47].

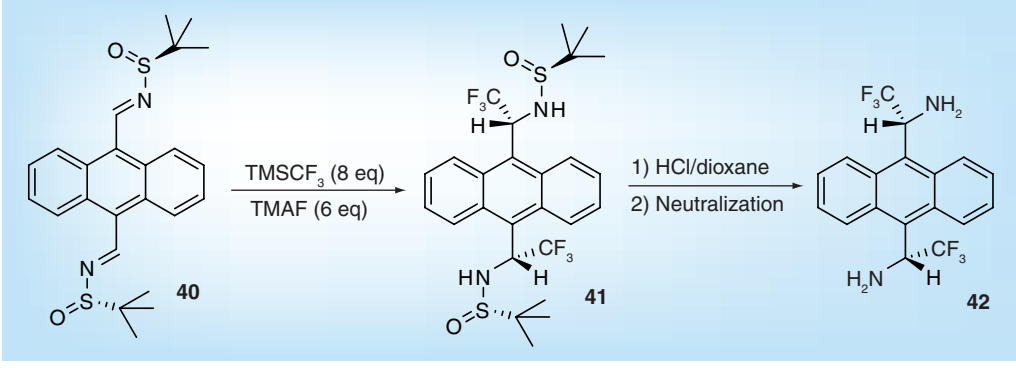
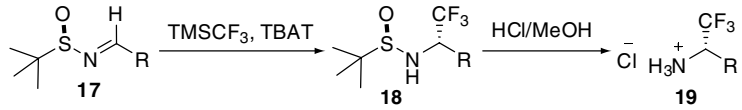


Figure 7. Synthesis of bistrifluoromethylated diamine (42).
Data from [48].

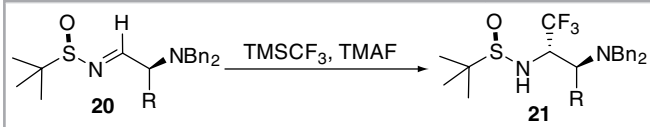
Table 8. Nucleophilic trifluoromethylation of sulfinylimines 17.

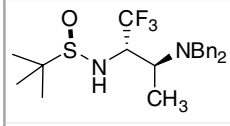
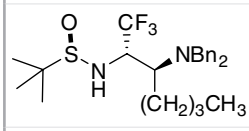
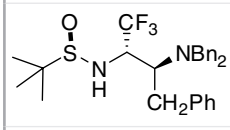
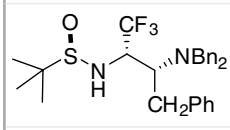
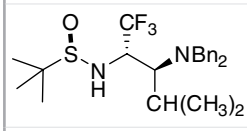
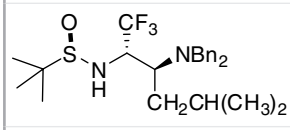
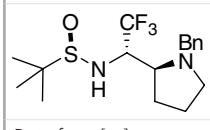


R	Yield (%)	dr
Ph	80	97:3
4-BrC_6H_4	90	>99:1
4-ClC_6H_4	95	>99:1
4-$CF_3C_6H_4$	84	95:5
2-pyridyl	95	99:1
3-pyridyl	92	99:1
2-furyl	85	97:3
2-naphthyl	83	96:4
9-anthryl	90	99:1
Cyclohexyl	88	99:1
t-Bu	75	99:1
CH_2CH_2Ph	84	90:10

Data from [31].

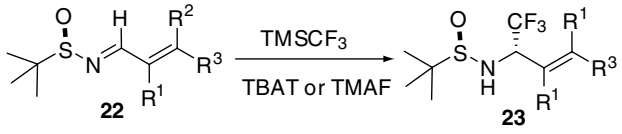
Table 9. Nucleophilic trifluoromethylation of α-amino *N*-tert-butylsulfinimines 20.

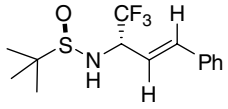
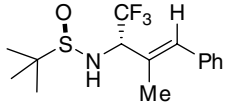
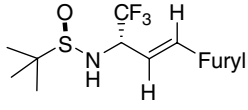
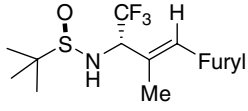
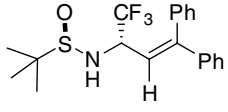
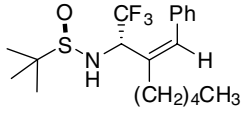
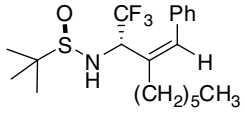
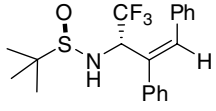


Product 21	Yield (%)	dr
	86	>99:1
	85	>99:1
	81	>99:1
	60	>80:20
	66	>99:1
	71	>99:1
	79	>99:1

Data from [32].

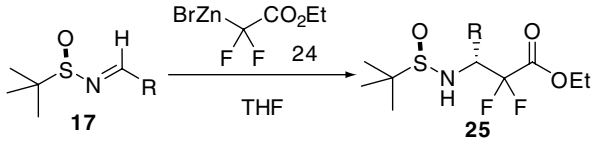
Table 10. Nucleophilic trifluoromethylation of α,β-unsaturated *N-tert*-butylsulfinimines 22.



Product 23	Yield (%)	dr
	55	90:10*
	73	>99:1*
	76	92:8*
	50	98:2*
	62	>99:1*
	82	90:10‡
	75	92:8‡
	62	93:7‡

*TBAT as the fluoride source.
‡TMAF as the fluoride source.
Data from [33].

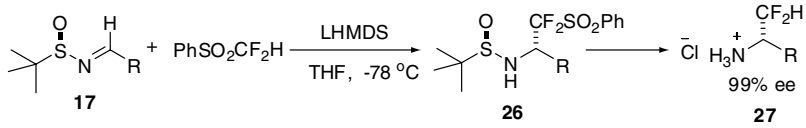
Table 11. Diastereoselective addition of 24 to chiral sulfinimines 17.



Substrate	Product	Yield (%)	dr
R = i-C_4H_9 (17a)	**25a**	51	81:19
R = n-C_3H_7 (17b)	**25b**	55	80:20
R = Ph (17c)	**25c**	82	90:10
R = c-C_6H_{11} (17d)	**25d**	81	87:13
R = 2-thiazolyl (17e)	**25e**	58	95:5

Data from [34].

Table 12. Stereoselective (phenylsulfonyl)difluoromethylation of chiral sulfinylimines 17.

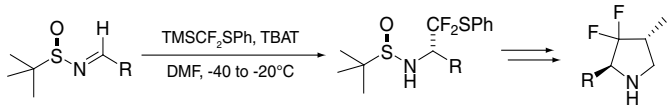


17 26 27

R	Yield (%)	dr
Ph	95	>99:1
4-MeOC6H4	96	>99:1
4-ClC6H4	95	>99:1
2-naphthyl	98	>99:1
2-furyl	90	>99:1
Et	95	>99:1
i-Pr	94	>99:1
t-Bu	85	>99:1

Data from [40].

Table 13. Stereoselective (phenylthio)difluoromethylation of sulfinylimines 17.

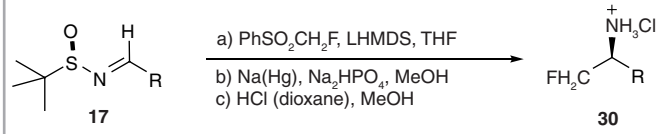


17 28 29

R	Yield (%)	dr
Ph	75	≥99:1
4-MeOC6H4	85	≥98:2
4-ClC6H4	89	≥99:1
2-naphthyl	85	≥98:2
2-furyl	72	≥98:2
iPr	75	≥99:1
c-C6H11	74	≥99:1
n-Pr	30	≥99:1
t-Bu	71	≥99:1
	58	≥99:1

Data from [41].

Table 14. Facile synthesis of α-monofluoromethyl amines 30.

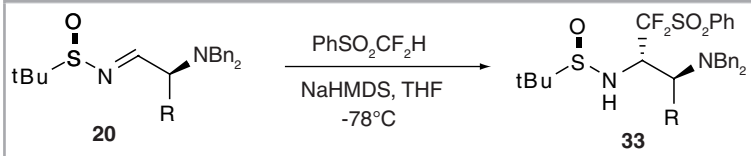


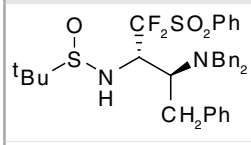
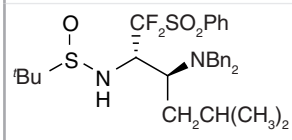
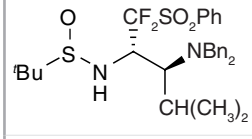
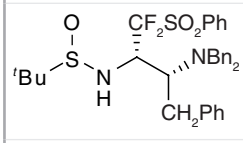
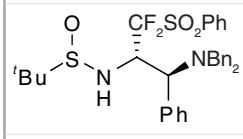
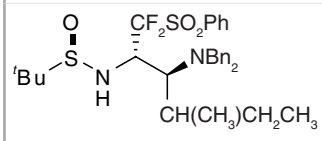
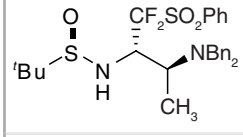
17 30

R	Yield (%)	dr
Ph	77	99:1
4-MeOC$_6$H$_4$	76	99:1
4-ClC$_6$H$_4$	73	99:1
2-naphthyl	74	99:1
4-Me$_2$NC$_6$H$_4$	75	98:2
2-furyl	71	99:1
t-Bu	73	99:1
i-Pr	70	99:1
n-Pr	70	99:1
CH$_2$CHMe$_2$	74	99:1

Data from [44].

Table 15. Difluoromethylation of α-amino *N-tert*-butylsulfinimines 20.



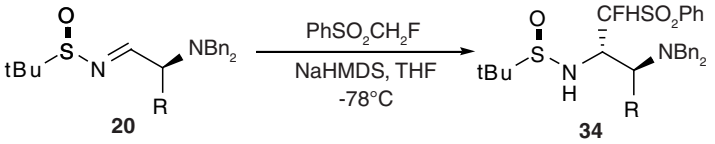
Product	Yield (%)	dr
	80	>99:1
	83	>99:1
	74	>99:1
	85	95:5
	73	>99:1
	83	>99:1
	95	>99:1

Data from [45].

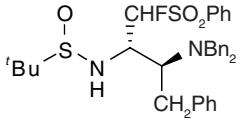
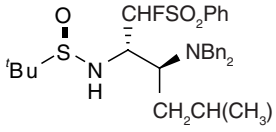
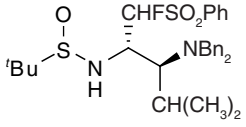
Although the stereoselective fluoroalkylations of *N-tert*-butylsulfinyl aldimines have been successfully accomplished to afford chiral α-fluoroalkyl amines (as mentioned above), the efficient and stereoselective synthesis of α-fluoroalkyl tertiary carbinamines by nucleophilic fluoroalkylation of ketimines is more difficult. The first highly diastereoselective synthesis of α,α-dibranched monofluoromethyl amines was achieved by Hu and co-workers via monofluoromethylation of *N-tert*-butylsulfinyl ketimines using the pregenerated fluoro(phenylsulfonyl)methyl anion **(Figure 4)** [46]. The pregeneration of $PhSO_2CHF^-$ anion from the $PhSO_2CH_2F$ and a base played a key role in the reaction, and the thermal stability, good nucleophilicity and relatively weak basicity of the $PhSO_2CHF^-$ anion accounted for the overall chemical outcome of the reaction. The stereocontrol mode of the current diastereoselective monofluoromethylation of ketimines was opposite to the other known nucleophilic fluoroalkylation of *N-tert*-butylsulfinyl aldimines **(Figure 5A)**, which suggests that a cyclic six-membered (closed) transition state is involved in the reaction **(Figure 5B)** [46].

N-tert-butylsulfinimines were also subjected to the 1,2-additions of trifluoromethylacetylide (prepared from lithium diisopropylamide [LDA] and the 2-bromo-3,3,3-trifluoropropene, *in situ*) to give homochiral trifluoromethylated propargylamines [47]. In the case of *N-tert*-butylsulfinyl aldimines **(Table 17)**, the diastereoselectivity

Table 16. Monofluoromethylation of α-amino *N-tert*-butylsulfinimines 20.



20 34

Product	Yield (%)	dr	Isomeric ratio
	99	>99:1	1.5:1
	97	>99:1	2.2:1
	87	>99:1	3.3:1

Data from [45].

could be tuned by the use of a polar or nonpolar solvent **(Figure 6)**; while the addition of trifluoromethylacetylide to *N-tert*-butylsulfinyl ketimines and the subsequent significant improvement of the diastereoselectivity was achieved through the use of $AlMe_3$ as an adductive **(Table 18)** [47].

The bis(trifluoromethylation) of imine **40** with $TMSCF_3$ (using TMAF as initiator) was also found to be successful, and both trifluoromethyl groups were added to the *Si* face of the imine *E*-bonds, giving (S_s,S_s)-*N*,*N*′-(*1R*,*1R*′)-1,1′-(anthracene-9,10-diyl)-bis(2,2,2-trifluoroethane-1,1-diyl)-bis(2-methylpropane-2-sulfinamide) **(41)** as a single isomer **(Figure 7)** [48]. Hydrolysis of **41** followed by neutralization afforded bis(trifluoromethylated) diamine **42**.

The electron-withdrawing trifluoromethyl group greatly reduces the donating ability of the electron lone pairs on the nitrogen atoms, thus decreasing the basicity of the amine and increasing the acidity of the corresponding ammonium salts.

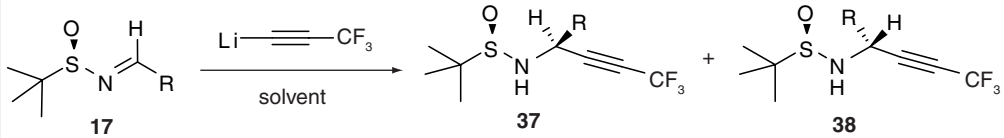
Future perspective

Significant progress has been made in the development of stereocontrolled synthesis of fluorinated chiral amines, the majority of which have been accomplished based on chiral auxiliaries, especially on Ellman's *N-tert*-butylsulfinyl imines. These synthetic methodologies provide a simple and efficient way to get access to a variety of structurally diverse fluorinated chiral amines, which are highly useful for developments in medicinal chemistry. As discussed above, fluorinated chiral amines have been designed as potential peptidomimetics **(Table 6)** [29], tripeptides [34] and 2-oxa-1-imidazolidinyl derivatives [32], among others [1–8]. It should be noted that, although catalytic enantioselective monofluoromethylation of *in situ*-generated imines (from α-amido sulfones) under the combination of fluorobis(phenylsulfonyl)methane chemistry with a Mannich-type reaction was recently reported [49], the enantioselective synthesis of tri- and di-fluoromethylated chiral amines via nucleophilic fluoroalkylation still remains a challenging task. Considerable attention should be focused on the organocatalytic or metallocatalytic enantioselective synthesis of fluorinated chiral amines in the coming years.

Acknowledgements

The authors would like to thank the National Natural Science Foundation of China (20825209, 20832008, 20772144) and the Chinese Academy of Sciences (Hundreds-Talent Program and Knowledge Innovation Program) for their financial support of this work.

Table 17. 1,2-addition of lithium trifluoromethylacetylide to aldimines 17.



17 37 38

R	In toluene		In THF	
	Yield (%)	*dr (37/38)*	*Yield (%)*	*dr (37/38)*
Et	79	86:14	69	7:93
iPr	85	87:13	72	8:92
Pr	76	91:9	67	6:94
iBu	85	99:1	76	11:89

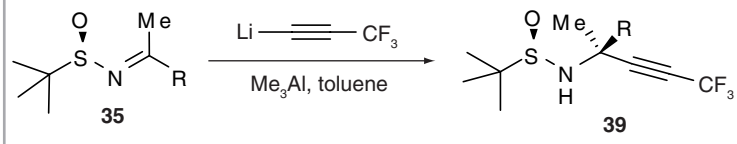
Data from [47].

Financial & competing interests disclosure

The authors would like to thank the National Natural Science Foundation of China (20825209, 20832008, 20772144) and the Chinese Academy of Sciences (Hundreds-Talent Program and Knowledge Innovation Program) for their financial support to this work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Table 18. 1,2-Addition of lithium trifluoromethylacetylide to ketimines 35.



R	Yield (%)	dr
iPr	88	94:6
iBu	83	93:7
Et	69	>99:1
Ph	31	>99:1

Data from [47].

Executive summary

- The stereoselective synthesis of fluorinated chiral amines based on the use of Ellman's *N-tert*-butylsulfinyl imines has been accomplished by two major strategies.
- One is the stereoselective addition or asymmetric reduction of fluorinated *tert*-butylsulfinimines and their derivatives. The unstability of fluorinated *tert*-butylsulfinimines limits the scope of their applications.
- The other strategy is the asymmetric addition of fluorinated reagents to *tert*-butylsulfinyl imines, the development of which is lacking new efficent and atom-economic fluorinated reagents.
- These highly useful synthetic methodologies provide powerful tools for the synthesis of optically pure fluorinated amines, amino acids and peptides, and promise to find many applications in the future for medicinal chemistry.

Bibliography

Papers of special note have been highlighted as:
▪▪ of considerable interest

1 Welch JT, Eswarakrishnan S. *Fluorine in Bioorganic Chemistry*. Wiley, NY, USA (1991).

2 Ojima I, McCarthy JR, Welch JT. *Biomedical Frontiers of Fluorine Chemistry*. ACS, Washington, DC, USA (1996).

3 Bégué JP, Bonnet-Delpon D. *Bioorganic and Medicinal Chemistry of Fluorine*. Wiley, Hoboken, NJ, USA (2008).

4 van Niel MB, Collins I, Beer MS *et al.* Fluorination of 3-(3-(piperidin-1-yl) propyl) indoles and 3-(3-(piperazin-1-yl)propyl) indoles gives selective human 5-HT_{1D} receptor ligands with improved pharmacokinetic profiles. *J. Med. Chem.* 42(12), 2087–2104 (1999).

5 Rowley M, Hallett DJ, Goodacre S *et al.* 3-(4-fluoropiperidin-3-yl)-2-phenylindoles as high affinity, selective, and orally bioavailable H5-HT_{2a} receptor antagonists. *J. Med. Chem.* 44(10), 1603–1614 (2001).

6 Welch JT, Eswarakrishnan S. Fluorinated amines. In: *Fluorine in bioorganic Chemistry*. Wiley, NY, USA (1991).

7 Fustero S, Sanz-Cervera JF, Aceña JL, Sánchez-Roselló M. Nitrogen-containing organofluorine derivatives: an overview. *Synlett* 4, 525–549 (2009).

8 Kukhar VP, Soloshonok VA. *Fluorine-containing Amino Acids*. Wiley, NY, USA (1995).

9 Carcía Ruano JL, Fernández, I, del Prado Catalina M, Cruz AA. Asymmetric aziridinination by reaction of chiral *N*-sulfinylimines with sulfur ylides: stereoselectivity improvement by use of *tert*-butylsulfinyl group as chiral auxiliary. *Tetrahedron: Asymmetry* 7(12), 3407–3414 (1996).

10 Liu G, Cogan DA, Ellman JA. Catalytic asymmetric synthesis of *tert*-butanesulfinamide. Application to the asymmetric synthesis of amines. *J. Am. Chem. Soc.* 119(41), 9913–9914 (1997).

11 Ellman JA, Owens TD, Tang TP. *N-tert*-butanesulfinyl imines: versatile intermediates for the asymmetric synthesis of amines. *Acc. Chem. Res.* 35(11), 984–995 (2002).

12 Ellman JA. Application of *tert*-butanesulfinamide in the asymmetric synthesis of amines. *Pure Appl. Chem.* 75(1), 39–46 (2003).

13 Senanayake CH, Krishnamurthy D, Lu ZH, Han Z, Gallon E. Enantiopure sulfoxides and sulfinamides: recent developments in their stereoselective synthesis and application to asymmetric synthesis. *Aldrichim. Acta* 38(3), 93–103 (2005).

14 Daniel M, Stockman RA. Chiral nonracemic sulfinimines: versatile reagents for asymmetric synthesis. *Tetrahedron* 62(38), 8869–8905 (2006).

15 Lin GQ, Xu MH, Zhong YW, Sun XW. An advance on exploring *N-tert*-butanesulfinyl imines in asymmetric synthesis of chiral amines. *Acc. Chem. Res.* 41(7), 831–840 (2008).

16 Ferreira F, Botuha C, Chemla F, Pérez-Luna A. *tert*-butanesulfinimines: structure, synthesis and synthetic applications. *Chem. Soc. Rev.* 38(4), 1162–1186 (2009).

17 Liu G, Cogan DA, Owens TD, Tang TP, Ellman JA. Synthesis of enantiomerically pure *N-tert*-butanesulfinyl imines (*tert*-butanesulfinimines) by the direct condensation of *tert*-butanesulfinamide with aldehydes and ketones. *J. Org. Chem.* 64(4), 1278–1284 (1999).

18 Huang Z, Zhang M, Wang Y, Qin Y. $KHSO_4$-mediated condensation reaction of *tert*-butanesulfinamide with aldehydes. preparation of *tert*-butanesulfinyl aldimines. *Synlett* 8, 1334–1336 (2005).

19 Wakayama M, Ellman JA. Recycling the *tert*-butanesulfinyl group in the synthesis of amines using *tert*-butanesulfinamide. *J. Org. Chem.* 74(7), 2646–2650 (2009).

20 Fustero S, Sanz-Cervera JF, Aceña JL, Sánchez-Roselló M. Nitrogen-containing organofluorine derivatives: an overview. *Synlett* 4, 525–549 (2009).

21 Wang H, Zhao XM, Li YH, Lu L. Solvent-controlled asymmetric strecker reaction: stereoselective synthesis of α-trifluoromethylated α-amino acids. *Org. Lett.* 8(7), 1379–1381 (2006).

22 Kuduk SD, Di Marco CN, Pitzenberger SM, Tsou N. Asymmetric addition reactions of Grignard reagents to chiral 2-trifluoromethyl *tert*-butyl(Ellman) sulfinimine-ethanol adducts. *Tetrahedron Lett.* 47(14), 2377–2381 (2006).

23 Truong VL, Menard MS, Dion I. Asymmetric synthesis of 1-aryl-2,2,2- trifluoroethylamines via diastereoselective 1,2-addition of arylmetals to 2-methyl-*N*-(2,2,2-trifluoroethylidene)propane-2-sulfinamide. *Org. Lett.* 9(4), 683–685 (2007).

24 Bharatam PV, Uppal P, Amita, Kaur D. Theoretical investigation on the conformational preferences of sulfinimines. *J. Chem. Soc. Perkin Trans.* 2(1), 43–50 (2000).

25 Bharatam PV, Amita, Kaur D. Theoretical studies on the S–N interaction in sulfinamides. *J. Phys. Org. Chem.* 15(4), 197–203 (2002).

26 Ferreira, F, Audouin, M, Chemla F. Stereoselective access to enantiopure *cis*-ethynylaziridines. *Chem. Eur. J.* 11(18), 5269–5278 (2005).

▪▪ **Explanations of the stereochemical outcome of the reactions are mostly those proposed by the original authors. However, new insights may be obtained by applying the recently reported result that the more stable conformation of the reacting sulfinimines is the conformation where the N-S-O bonds are coplanar and the S-O bond lies away from the lone pair of the nitrogen atom.**

27 Truong VL, Pfeiffer JY. Rhodium-catalyzed diastereoselective 1,2-addition of arylboronic acids to chiral trifluoroethyl imine. *Tetrahedron Lett.* 50(14), 1633–1635 (2009).

28 Liu ZJ, Liu JT. Asymmetric synthesis of either diastereomer of trifluoromethylated allylic amines by the selective reduction of trifluoromethyl α,β-unsaturated *N-tert*-butanesulfinyl ketoimines. *Chem. Commun.* 41, 5233–5235 (2008).

29 Dutheuil G, Couve-Bonnaire S, Pannecoucke X. Diastereomeric fluoroolefins as peptide bond mimics prepared by asymmetric reductive amination of α-fluoroenones. *Angew. Chem. Int. Ed.* 46(8), 1290–1292 (2007).

30 Pierry C, Zoute L, Jubault P *et al.* Diastereocontrolled addition of organometallic reagents to *S*-chiral *N*-(*tert*-butanesulfinyl)-α-fluoroenimines. *Tetrahedron Lett.* 50(3), 264–266 (2009).

31 Prakash GKS, Mandal M, Olah GA. Stereoselective nucleophilic trifluoromethylation of *N*-(*tert*-butanesulfinyl)imines by using trimethyl(trifluoromethyl)silane. *Angew. Chem. Int. Ed.* 40(3), 589–590 (2001).

32 Prakash, GKS, Mandal M. Stereoselective synthesis of trifluoromethylated vicinal ethylenediamines with α-amino *N-tert*-butanesulfinimines and $TMSCF_3$. *J. Am. Chem. Soc.* 124(23), 6538–6539 (2002).

33 Prakash GKS, Mandal M, Olah GA. Asymmetric synthesis of trifluoromethylated allylic amines using α,β-unsaturated *N-tert*-butanesulfinimines. *Org. Lett.* 3(18), 2847–2850 (2001).

34 Staas DD, Savage KL, Homnick CF, Tsou NN, Ball RG. Asymmetric synthesis of α,α-difluoro-β-amino acid derivatives from enantiomerically pure *N-tert*-butylsulfinimines. *J. Org. Chem.* 67(23), 8276–8279 (2002).

35 Prakash GKS, Hu J, Olah GA. Preparation of tri- and difluoromethylsilianes via an unusual magnesium metal-mediated reductive tri- and difluoro- methylation of chlorosilanes using tri- and difluoromethyl sulfides, sulfoxides, and sulfones. *J. Org. Chem.* 68(11), 4457–4463 (2003).

36 Prakash GKS, Hu J, Mathew T, Olah GA. Difluoromethyl phenyl sulfone as a selective difluoromethylene dianion equivalent: one-pot stereoselective synthesis of anti-2,2-difluoropropane-1,3-diols. *Angew. Chem. Int. Ed.* 42(42), 5216–5219 (2003).

37 Prakash GKS, Hu J, Wang Y, Olah GA. Difluoromethyl phenyl sulfone, a difluoromethylidene equivalent: use in the synthesis of 1,1-difluoro-1-alkenes. *Angew. Chem. Int. Ed.* 43(39), 5203–5206 (2004).

38 Prakash GKS, Hu J, Wang Y, Olah GA. Nucleophilic difluoromethylation of primary alkyl halides using difluoromethyl phenyl sulfone as a difluoromethyl anion equivalent. *Org. Lett.* 6(23), 4315–4317 (2004).

39 Prakash GKS, Hu J, Wang Y, Olah GA. Convenient synthesis of difluoromethyl alcohols from both enolizable and non-enolizable carbonyl compounds with difluoromethyl phenyl sulfone. *Eur. J. Org. Chem.* 11, 2218–2223 (2005).

40 Li Y, Hu J. Facile synthesis of chiral α-difluoromethyl amines from *N*-(*tert*-butylsulfinyl)aldimines. *Angew. Chem. Int. Ed.* 44(36), 5882–5886 (2005).

41 Li Y, Hu J. Stereoselective difluoromethylenation using Me_3SiCF_2SPh: synthesis of chiral 2,4-disubstituted 3,3-difluoropyrrolidines. *Angew. Chem. Int. Ed.* 46(14), 2489–2492 (2007).

42 Grunewald GL, Caldwell TM, Li Q *et al.* Synthesis and biochemical evaluation of 3-fluoromethyl-1,2,3,4-tetrahydroisoquinolines as selective inhibitors of phenylethanolamine *N*-methyl-transferase versus the α_2-adrenoceptor. *J. Med. Chem.* 42(18), 3588–3601 (1999).

43 Silverman RB, Nanavati SM. Selective inhibition of γ-aminobutyric acid aminotransferase by (*3r,4r*),(*3s,4s*)- and (*3r,4s*),(*3s,4r*)-4-amino-5-fluoro-3-phenylpentanoic acids. *J. Med. Chem.* 33(3), 931–936 (1990).

44 Li Y, Ni C, Liu J *et al.* Stereoselective nucleophilic monofluoromethylation of *N*-(*tert*-butanesulfinyl) imines using fluoromethyl phenyl sulfone. *Org. Lett.* 8(8), 1693–1696 (2006).

45 Liu J, Li Y, Hu J. Stereoselective synthesis of di- and monofluoromethylated vicinal ethylenediamines with di- and monofluoromethyl sulfones. *J. Org. Chem.* 72(8), 3119–3121 (2007).

46 Liu J, Zhang L, Hu J. Stereoselective monofluoromethylation of *N-tert*-butylsulfinyl ketimines using pregenerated fluoro(phenylsulfonyl) methyl anion. *Org. Lett.* 10(23), 5377–5380 (2008).

47 Chen XY, Qiu XL, Qing FL. Asymmetric synthesis of trifluoromethylated propargylamines via 1,2-addition of trifluoromethylacetylide to *N-tert*-butanesulfinyl imines. *Tetrahedron* 64(10), 2301–2306 (2008).

48 Estivill C, Mendizabal J, Virgili A, *et al.* Preparation of (1R,1′R)-1,1′-(anthracene-9,10-diyl)*bis*(2,2,2-trifluoroethanamine): a chiral diamine with low basicity. *Tetrahedron* 65(1), 171–176 (2009).

49 Mizuta S, Shibata N, Goto Y, Furukawa T, Nakamura S, Toru T. Cinchona alkaloid – catalyzed enantioselective monofluoromethylation reaction based on fluorobis – (phenylsulfonyl)methane chemistry combined with a Mannich-type reaction. *J. Am. Chem. Soc.* 129(20), 6394–6395 (2007).

Following the publication of the Mini-Review by Jinbo Hu *et al.* 'Synthesis of fluorinated chiral amines using *N-tert*-butylsulfinyl imines, published in the August 2009 issue of *Future Medicinal Chemistry* (*Future Med. Chem.* 1[5], 875–888 [2009]), it has been brought to our attention that:

- The footnote of Table 1 was incorrectly printed as: TMSCN: Trimethyl cyanide. Data from [15]. This should have read: TMSCN: Trimethylsilyl cyanide. Data from [21].

- A sentence on page 877 was incorrectly printed as:

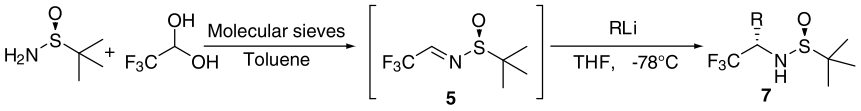
"Chiral allylic primary amines **15** are potential dipeptide mimics, and their synthesis has been achieved through the efficient asymmetric reductive amination of fluoroenones **13 (FIGURE 2)** [29]."

This should have read:

"Chiral allylic primary amines **15** are potential dipeptide mimics, and their synthesis has been achieved through the efficient asymmetric reductive amination of fluoroenones **13 (TABLE 6)** [29]."

- Table 3 was incorrectly printed as:

Table 3. Diastereoselective 1,2-addition of aryllithium reagents to imine 5.

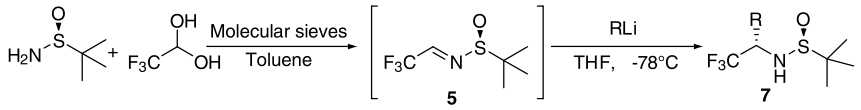


Entry	RLi	Product 7	Yield (%)	dr
1	RLi	**7a**	66	98:2
2	PhLi*	**7a**	42	98:2
3	PhLi‡	**7a**	58	96:4
4	4-MeOPhLi	**7b**	55	97:3
5	4-MeSPhLi	**7c**	53	98:2
6	4-FPhLi	**7d**	50	100:1
7	3,5-diFPhLi§	**7e**	36	83:17
8	2-MePhLi	**7f**	40	99:1
9	Pyridin-2-yllithium	**7g**	15	98:2

**2.5 equiv of PhLi was used.*
‡1.1 equiv of PhLi was used.
§Precomplexation of imine with $AlMe_3$ at 0°C, added to PhLi solution at -78°C. Unoptimized conditions.
Data from [23].

This should have read:

Table 3. Diastereoselective 1,2-addition of aryllithium reagents to imine 5.

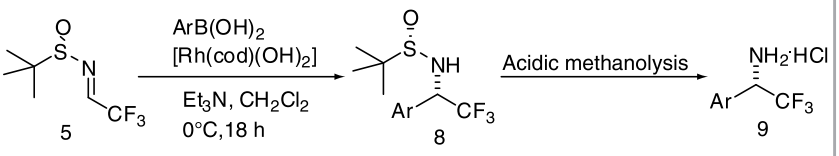


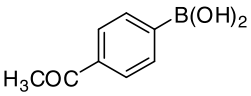
Entry	RLi	Product 7	Yield (%)	dr
1	PhLi*	**7a**	66	98:2
2	PhLi‡	**7a**	42	98:2
3	PhLi§	**7a**	58	96:4
4	4-MeOPhLi	**7b**	55	97:3
5	4-MeSPhLi	**7c**	53	98:2
6	4-FPhLi	**7d**	50	100:1
7	3,5-diFPhLi¶	**7e**	36	83:17
8	2-MePhLi	**7f**	40	99:1
9	Pyridin-2-yllithium	**7g**	15	98:2

**2.5 equiv of PhLi was used.*
‡1.1 equiv of PhLi was used.
§Precomplexation of imine with $AlMe_3$ at 0°C, added to PhLi solution at -78°C.
¶Unoptimized conditions.
Data from [23].

- Table 4 row 10 was incorrectly printed as:

Table 4. Rhodium-catalyzed diastereoselective 1,2-addition of arylboronic acids to imine 5.

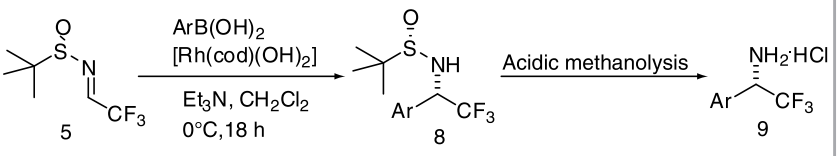


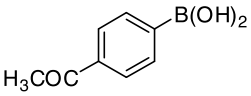
Entry	$ArB(OH)_2$	Yield 8 (%)	de	Yield 9 (%)
10		66	85	86

Data from [27].

This should have read:

Table 4. Rhodium-catalyzed diastereoselective 1,2-addition of arylboronic acids to imine 5.



Entry	$ArB(OH)_2$	Yield 8 (%)	de	Yield 9 (%)
10		66	85	67

Data from [27].

- Table 5 row 10 was incorrectly printed as:

Table 5. Diastereoselective reduction of 10 with DIBAL-H and L-selectride.

R	DIBAL-H 11 yield (%) (dr)	L-selectride 12 yield (%) (dr)
	93 (> 96:4)	81 (95:5)

Data from [21].

This should have read:

Table 5. Diastereoselective reduction of 10 with DIBAL-H and L-selectride.

R	DIBAL-H 11 yield (%) (dr)	L-selectride 12 yield (%) (dr)
$C_6H_5C{\equiv}C$	93 (> 96:4)	81 (95:5)

Data from [28].

- The footnote of Figure 4 should have read: "Figure 4. Diastereoselective monofluoromethylation of ketimines (35). Condition A: n-BuLi used as a base; condition B: KHMDS used as a base. *Determined by ^{19}F NMR using $PhCF_3$ as internal standard. Data from [46]."

- A sentence on page 885–886 was incorrectly printed as:

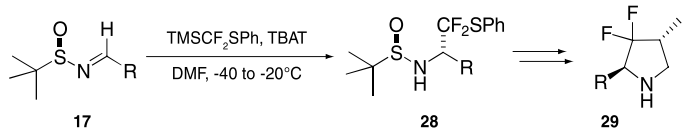
"In the case of *N-tert*-butylsulfinyl aldimines, the diastereoselectivity could be tuned by the use of a polar or nonpolar solvent **(FIGURES 6 & 7)**; while the addition of trifluoromethylacetylide to *N-tert*-butylsulfinyl ketimines and the subsequent significant improvement of the diastereoselectivity was achieved through the use of $AlMe_3$ as an adductive **(TABLE 18)** [47]."

This should have read:

"In the case of *N-tert*-butylsulfinyl aldimines **(TABLE 17)**, the diastereoselectivity could be tuned by the use of a polar or nonpolar solvent **(FIGURE 6)**; while the addition of trifluoromethylacetylide to *N-tert*-butylsulfinyl ketimines and the subsequent significant improvement of the diastereoselectivity was achieved through the use of $AlMe_3$ as an adductive **(TABLE 18)** [47]."

- Table 13 was incorrectly printed. It should have read:

Table 13. Stereoselective (phenylthio)difluoromethylation of sulfinylimines 17.



17 28 29

R	Yield (%)	dr
Ph	75	≥99:1
4-MeOC6H4	85	≥98:2
4-ClC6H4	89	≥99:1
2-naphthyl	85	≥98:2
2-furyl	72	≥98:2
iPr	75	≥99:1
c-C6H11	74	≥99:1
n-Pr	30	≥99:1
t-Bu	71	≥99:1
	58	≥99:1

Data from [41].

The authors and editors of *Future Medicinal Chemistry* would like to sincerely apologize for any inconvenience or confusion this may have caused our readers.