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Trifluoroacetaldehyde: A useful industrial bulk material for the synthesis of trifluoromethylated amino compounds

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ABSTRACT

The synthesis of various trifluoromethylated amino compounds was studied using trifluoroacetaldehyde, an industrial bulk material, as a starting compound. One general application of trifluoroacetaldehyde is the preparation of trifluoroethylamino derivatives via reductive amination reaction. This synthesis includes the formation of the corresponding N,O-acetal intermediates followed by their reduction using $NaBH_4$ or 2-picoline borane complex, affording the target trifluoroethylamino compounds in moderate to good yields (47–87%).

Another general application of trifluoroacetaldehyde is the synthesis of chiral α-substituted trifluoroethylamino compounds. In this synthesis, trifluoroacetaldehyde was first converted into the chiral trifluoromethyl *tert*-butyl sulfinimine, which was subjected to 1,2-nucleophilic addition reactions across its C=N double bond. The addition of phenyllithium afforded α-(phenyl)trifluoroethylamino derivative in 83% yield and with 96% de. Allylation and Reformatsky reactions produced the corresponding α-substituted trifluoroethylamino derivatives in 82 and 58% yields and with 90 and 91% de, respectively.

1. Introduction

Trifluoroacetaldehyde has long been known as one of the most versatile CF_3-containing building blocks. The aldehyde is a highly reactive gaseous material with a boiling point of −18 °C; it polymerizes easily, and therefore is stored as a hydrate or a hemiacetal. Nevertheless, as reported in numerous publications, hydrate and hemiacetal forms can be directly used for many synthetic purposes without generating the free aldehyde [1], thus facilitating the synthetic use of trifluoroacetaldehyde.

In a previous study, we developed a catalytic process for the large-scale production of trifluoroacetaldehyde on the basis of vapor-phase oxidation of 2,2,2-trifluoroethanol [2]. This catalytic process had been proved quite durable for industrial manufacturing, making trifluoroacetaldehyde readily accessible and inexpensive.

One practical application of trifluoroacetaldehyde is in the preparation of trifluoromethylated amino compounds. α-Unsubstituted [3] and chiral α-substituted trifluoroethylamino compounds [4–6] have been extensively used in the design of new pharmaceuticals and agrochemicals (Fig. 1). Furthermore, chiral organic derivatives containing a trifluoromethyl group directly bound to the stereogenic carbon have recently been shown to undergo a self-disproportionation of enantiomers (SDE) [7] under achiral chromatography [8] and sublimation conditions [9]. However, almost all these studies have been conducted on α-hydroxycarboxylic acid derivatives. We expect that general methods for the preparation of α-substituted trifluoroethylamines will make these compounds readily available for SDE and pharmacological studies.

Several methods have been reported for the synthesis of trifluoroethylamino compounds, including the trifluoroethylation of amines using trifluoroethyl triflate [10], the substitution of trifluoroethylamine [11], and reductive amination using trifluoroacetaldehyde [12]. However, these methods often faced problems related to reagent toxicity (trifluoroethyl triflate) and poor reactivity (trifluoroethylamine). From this viewpoint, reductive amination is suitable for the preparation of trifluoroethylamino compounds.

α-Substituted trifluoroethylamino compounds have been synthesized through 1,2-nucleophilic addition reactions of trifluoroacetaldimines and related N,O-acetals [13], trifluoromethylation of imines [14], and reduction or isomerization of trifluoromethyl ketimines [15]. The 1,2-nucleophilic addition reactions, in which the starting material trifluoroacetaldimine was directly prepared by the reaction of trifluoroacetaldehyde hydrate or hemiacetal with an amine, have been well developed: various racemic and asymmetric reactions, including alkylation

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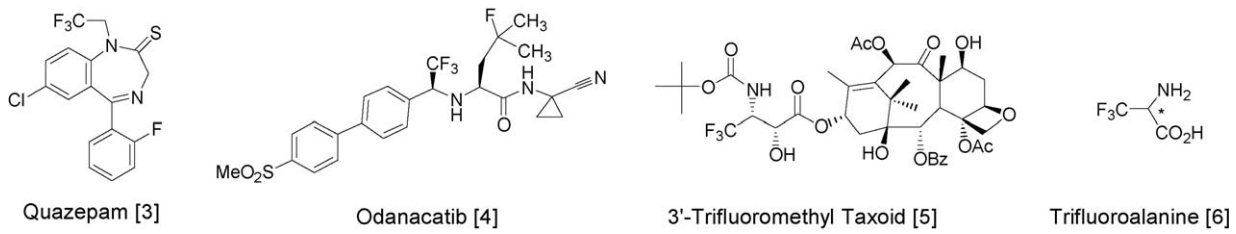


Fig. 1. Examples of viologically active trifluoromethylated amino compounds.

[16], allylation [17], Mannich reaction [18], and Reformatsky reactions [19], have been achieved successfully.

In this report, we discuss preparative aspects for the generalized synthesis of various trifluoromethylated amino compounds starting from trifluoroacetaldehyde. We also discuss the reactivity and physico-chemical properties of trifluoroacetaldehyde and related derivatives in detail to produce trifluoromethylated amino compounds in a reproducible and economical manner on a large scale.

2. Results and discussion

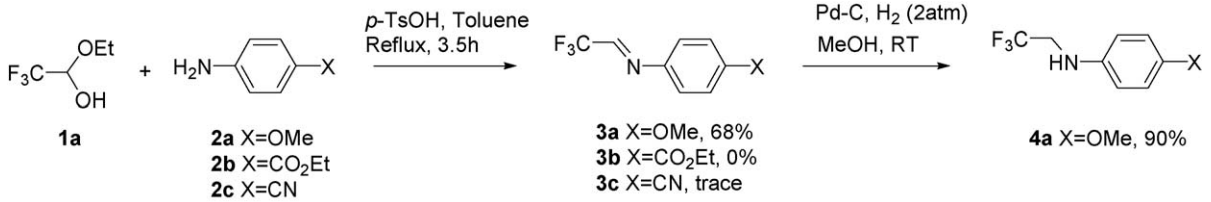
2.1. Synthesis of trifluoroethylamino compounds

Reductive amination is a well-established method for the preparation of alkylamines. However, its adaptation to trifluoroacetaldehyde has received little attention. First, we attempted to prepare trifluoroethylamino derivatives via reduction of trifluoroacetaldimine **3**, which was synthesized according to the conventional method [20]. Trifluoroacetaldimine **3a**, derived from *p*-anisidine **2a**, was easily reduced by catalytic hydrogenation using Pd–C catalyst to produce trifluoroethylamine **4a** in 90% yield (Scheme 1). However, the corresponding trifluoroacetaldimine **3b–c** was not obtained when this method was applied to anilines containing electron-withdrawing substituents. This dramatic difference in reactivity may be because the dehydration of the hemiaminal intermediate becomes less favorable in the presence of the strongly electron-withdrawing CF_3 group and the amine substituent. In addition, the resulting aldimine was expected to be extremely electrophilic and therefore unstable, producing various undesirable by-products.

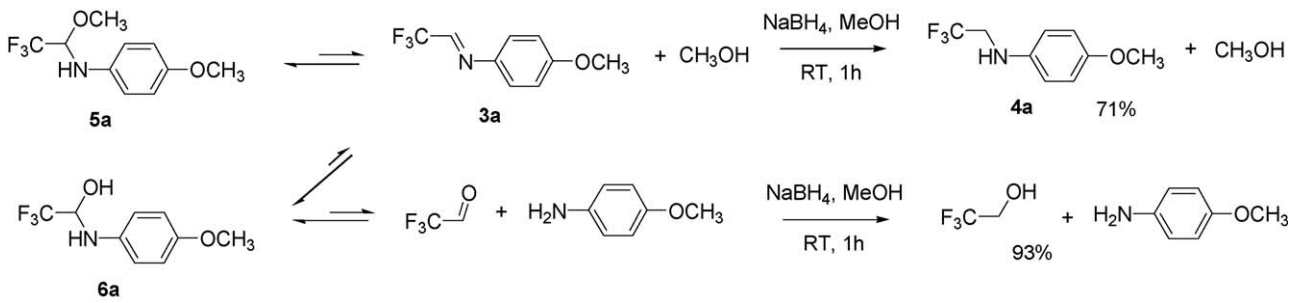
To overcome this obstacle, we examined a method that uses N,O-acetal or hemiaminal as a starting material instead of trifluoroacetaldimine. Thus, we prepared N,O-acetal **5a** [21] and hemiaminal **6a** [22] from *p*-anisidine and reduced them with $NaBH_4$. Reduction of N,O-acetal **5a** produced trifluoroethylamino derivative **4a** in 71% yield, while reduction of hemiaminal **6a** produced 2,2,2-trifluoroethanol almost quantitatively (Scheme 2).

The following mechanism is proposed to explain the observed difference in reactivity of the N,O-acetal and hemiaminal. The N,O-acetal was in equilibrium with trifluoroacetaldimine, which was reduced to the target trifluoroethylamino derivative by $NaBH_4$, thereby continuously shifting the equilibrium to the aldimine. On the other hand, the hemiaminal was in equilibrium with trifluoroacetaldehyde and trifluoroacetaldimine. The reduction of trifluoroacetaldehyde was faster under these conditions, leading to the formation of the corresponding 2,2,2-trifluoroethanol.

Several aniline derivatives possessing various substituents were examined to evaluate the scope of the reaction (Table 1). The N,O-acetal derivatives **5** without substituent and with an electron-donating substituent at the para- or meta-position were reduced by $NaBH_4$ in methanol (method A), affording the corresponding trifluoroethylamino derivatives **4** in yields ranging from 71 to 90%. This method was also applied to the N,O-acetal derivative with electron-donating substituent at ortho-position or with electron-withdrawing substituents and produced target trifluoroethylamino derivatives **4** in similar 58–80% yields. This reduction was performed using 2-picoline borane in acetic acid (method B) because the reaction did not proceed under the condition of method A (Table 1, Entry 4) and the acidic condition enables the equilibrium to shift to the trifluoroacetaldimine.

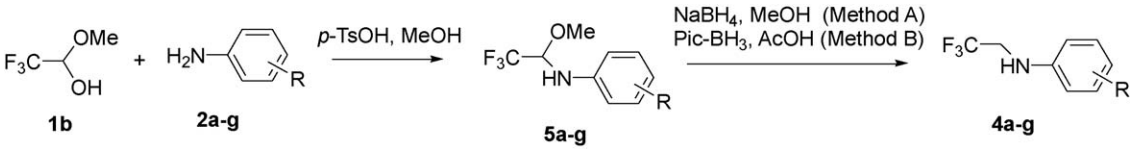


Scheme 1.



Scheme 2. A plausible mechanism for the different results of hydride reduction.

Table 1
Reductive amination reaction of trifluoroacetaldehyde hemiacetal with primary amines[a].

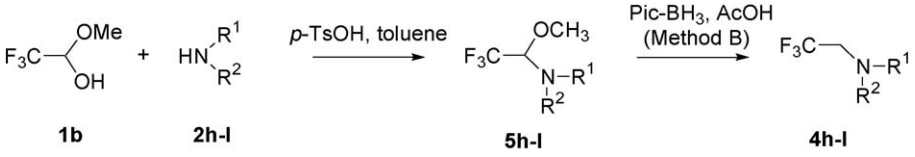


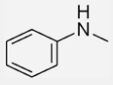
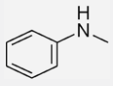
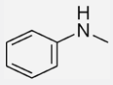
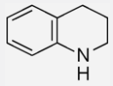
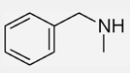
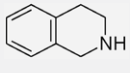
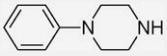
Entry	Amine		Yield, %[b] of **5**	Method	Yield, %[b] of **4**	Conditions
	#	R				
1	**2d**	H	91	A	71 (65)	Reflux, 0.25 h
2	**2a**	*p*-OMe	94	A	90 (85)	Reflux, 1 h
3	**2e**	*m*-OMe	68	A	87 (59)	Reflux, 1 h
4	**2f**	*o*-OMe	80	A	0[c]	Reflux, 0.5 h
5	**2f**	*o*-OMe	80	B	66 (53)	rt, 1 h
6	**2g**	*p*-Cl	88	B	79 (70)	rt, 0.5 h
7	**2b**	*p*-CO_2Et	84	B	80 (67)	Reflux, 0.5 h
8	**2c**	*p*-CN	81	B	58 (47)	Reflux, 0.5 h

[a] Preparation of N,O-acetals were carried out in MeOH in the presence of *p*-TsOH under reflux condition for 2 h.
[b] Isolated yield after chromatography. The values in parentheses are overall yields based on **2**.
[c] The starting material **5f** was recovered in 83% yield.

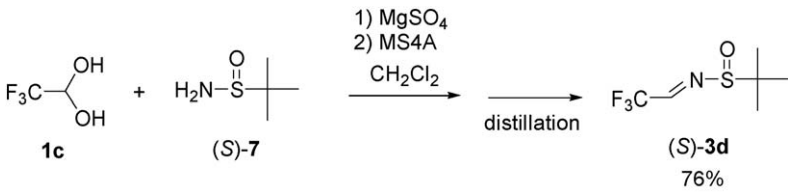
Next, the reductive amination reaction of secondary amines was examined (Table 2). When the mixture of a secondary amine and hemiacetal **1b** was heated in methanol in the presence of acid catalyst, the formation of N,O-acetal **5** was extremely slow and the starting materials were recovered almost intact (Table 2, Entry 1). On the other hand, when the reaction mixture was heated in toluene, aromatic and aliphatic secondary amines **2h**–**l** led to the expected N,O-acetals **5h**–**l**, which were isolated in good yields

Table 2
Reductive amination reaction of trifluoroacetaldehyde hemiacetal with secondary amines[a].

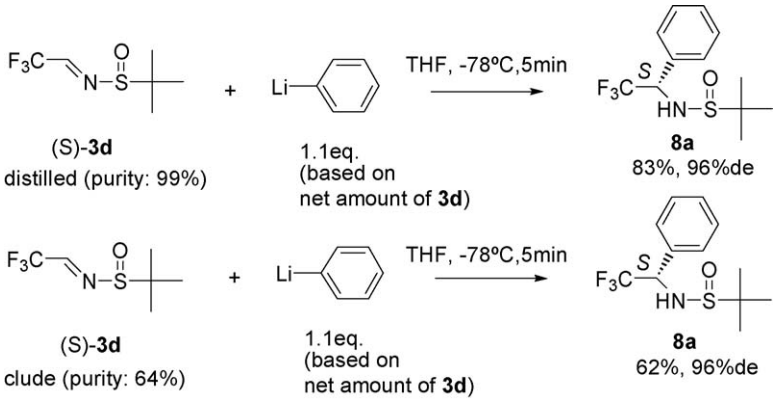


Entry	Amine		Yield, %[b] of **5**	Yield, %[b] of **4**	Conditions
1[c]	**2h**		Trace	–	–
2[d]	**2h**		68	0[e]	Reflux, 2 h
3	**2h**		68	72 (49)	rt, 1 h
4	**2i**		75	92 (69)	Reflux, 0.5 h
5	**2j**		68	79 (54)	rt, 0.5 h
6	**2k**		96	91 (87)	rt, 1 h
7	**2l**		83	96 (80)	Reflux, 0.5 h

[a] Preparation of N,O-acetals were carried out in toluene in the presence of *p*-TsOH under reflux condition for 3 h.
[b] Isolated yield after chromatography. The values in parentheses are overall yields based on **2**.
[c] Preparation of N,O-acetal was performed in MeOH in the presence of *p*-TsOH under reflux condition for 1 h.
[d] Reduction was performed using $NaBH_4$ in MeOH (method A).
[e] The starting material **5h** was recovered in 86% yield.



Scheme 3.



Scheme 4.

(68–96%). The obtained N,O-acetals **5h–l** were reduced using 2-picoline borane in acetic acid (method B) though the reduction did not occur under the condition of method A (Table 2, Entry 2). The corresponding trifluoroethylamino derivatives **4h–l** were isolated in yields ranging from 72 to 96%.

The synthesis of N,O-acetals from secondary amines had been reported previously but the electrochemical procedures developed by Fuchigami and Ichikawa were inconvenient [23]. The method described in this study offers substantially simpler and more operationally convenient [24] procedures for the generalized preparation of these N,O-acetals.

2.2. Synthesis of chiral α-substituted trifluoroethylamino compounds

Chiral α-substituted trifluoroethylamino compounds are of particular interest for the design and development of new pharmaceuticals. Therefore, the asymmetric synthesis of these derivatives is of great importance. These compounds are accessible from nucleophilic reactions using trifluoroacetaldimine starting materials that bear a chiral auxiliary at the amine site. In particular, Truong et al. have recently reported an effective asymmetric induction and an easy deprotection of the chiral auxiliary for trifluoromethyl *tert*-butyl sulfinimine **3d** [25,26]. Using the described literature method [25], we reacted trifluoroacetaldehyde hydrate **1c** with chiral *tert*-butane sulfinamide (*S*)-**7** in the presence of molecular sieves (MS4A) at 40 °C (Scheme 3). We monitored the condensation process by ^{19}F NMR analysis and noted the formation of by-products that were not mentioned previously. Therefore, we needed to modify the literature procedure to make it more reliable for large-scale synthesis.

Consequently, we conducted a series of experiments and found that compound **3d** was efficiently purified by vacuum distillation at a low temperature (40 °C, 0.6 kPa). This procedure allowed the preparation of highly chemically and enantiomerically pure (*S*)-**3d** in 76% overall yield.

Taking advantage of this highly chemically and enantiomerically pure sample, we examined the thermal stability of (*S*)-**3d**. We found that compound (*S*)-**3d** was relatively chemically stable below 60 °C and that its stereochemical integrity was not affected below 100 °C (Table 3).

With these data in hand, we studied the addition reactions of (*S*)-**3d** with phenyllithium (Scheme 4). The desired product **8a** was isolated in 83% yield (96% de). This yield was greater compared to the 64% yield (96% de) obtained using (*S*)-**3d** prepared according to the literature procedure. This result demonstrates the advantage of using our procedure to purify (*S*)-**3d**.

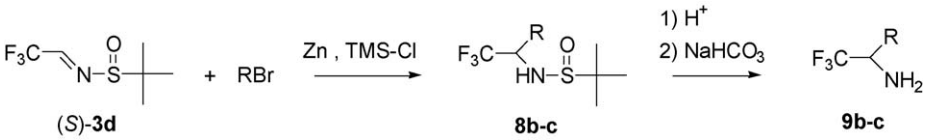
Next, we studied Zn-mediated allylation reactions using (*S*)-**3d** as a starting compound to demonstrate its applicability to generalized preparations of chiral α-substituted trifluoroethylamino compounds (Table 4). The reaction conducted in DMF gave target allylated product **8b** in 82% yield with high diastereoselectivity (90% de), while the reaction conducted in THF gave **8b** with substantially lower diastereoselectivity (43% de). Deprotection under acidic conditions followed by neutralization, afforded the allylated free amine in good yield. Following Mosher's method [27], we found that the major enantiomer had a *S* configuration from the ^{1}H NMR spectra of the corresponding (*R*)- and (*S*)-MTPA amides. This result suggests that this addition reaction may proceed through a non-chelated transition state (Scheme 5). The stereochemical outcome of Zn-mediated allylation reactions has been reported to be reversed depending on solvent choice for non-fluorinated chiral *tert*-butyl sulfinimines [28]. In contrast, the coordination ability of the nitrogen atom is substantially weakened in (*S*)-**3d** due to the electron-withdrawing CF_3 group. Therefore, the non-chelated transition state is preferred regardless of the solvent used.

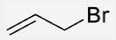
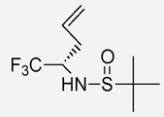
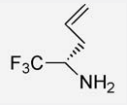
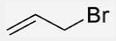
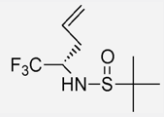
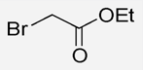
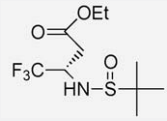
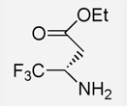
Table 3
Thermal stability of (*S*)-**3d**[a].

Entry	Temperature, °C	Chemical purity, %[b]	Optical purity, % ee[c]
1	Before heat	>99	>99
2	60	>99	>99
3	80	99	>99
4	100	86	>99

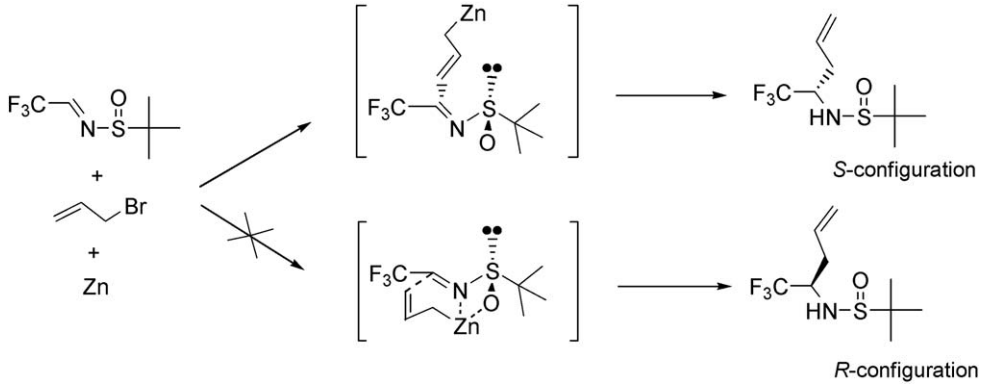
[a] (*S*)-**3d** (0.50 g) was placed in 20 ml Schlenk flask and heated for 6 h under N_2 atmosphere.
[b] Determined by ^{19}F NMR.
[c] Determined by chiral GC analysis.

Table 4
Zn-mediated addition reaction of (*S*)-**3d** with various nucleophiles.



Entry	Substrate	Solvent	Product	Yield, %[a]	de, %[b]	Free amine	Yield, %[a]	Configuration
1		DMF		82	90		67 (55)	*S*[c]
2		THF		86	43	–	–	*S*
3		DMF		65	91		89 (58)	*S*[d]

[a] Isolated yield. The values in parentheses are overall yields based on (*S*)-**3d**.
[b] Determined by GC analysis.
[c] Speculated by ^{1}H NMR analysis using Mosher's method.
[d] Speculated by optical rotation.



Scheme 5. A plausible mechanism for stereocontrol.

In the Reformatsky reaction of (*S*)-**3d** with ethyl bromoacetate, the use of DMF as a solvent also produced the desired derivative **8c** with high diastereoselectivity (91% de). The optical rotation of the corresponding free amine **9c** ($[\alpha]_D^{25} = -19.4^\circ$) agreed with literature data for the (*S*)-enantiomer ($[\alpha]_D^{25} = -21.1^\circ$ [29]), indicating that this reaction also proceeded through similar mechanism that involves the non-chelated transition state.

In general, α-trifluoromethyl amino derivatives of high enantiomeric purity have been made available by methods developed by Bravo, Sorochinsky, and Soloshonok [30,31]. However, our developed procedures are more operationally convenient and can be reliably reproduced on a large scale. In addition, starting materials used in our approach are substantially more inexpensive; thus, they are attractive.

3. Conclusion

The method using an N,O-acetal intermediate followed by hydride reduction was proven to be general and efficient for synthesizing trifluoroethylamino compounds starting from trifluoroacetaldehyde. This method allows various trifluoroethylamino derivatives to be prepared in good yields from a wide range of amine derivatives, including primary and secondary amines substituted with electron-withdrawing and donating groups.

In regard to the synthesis of chiral α-substituted trifluoroethylamino compounds, trifluoromethyl *tert*-butyl sulfinimine was demonstrated to possess excellent properties as a precursor. Its 1,2-addition reactions with various nucleophiles were highly diastereoselective.

4. Experimental

Trifluoroacetaldehyde ethyl hemiacetal, trifluoroacetaldehyde methyl hemiacetal and trifluoroacetaldehyde hydrate used in this study were commercial products of Tosoh F-tech. 2-Picoline borane complex was obtained from Mitsui Chemical Company.

All other chemicals and solvents were purchased commercially and used without further purification.

The ^{1}H and ^{19}F NMR spectra were recorded on JEOL JNM-EX270 spectrometer or BRUCHER AVANCE 400 spectrometer. ^{1}H NMR spectra were obtained using chloroform-d or acetone-d6 as the solvent with tetramethylsilane as the internal standard. ^{19}F NMR

spectra were recorded in chloroform-d or acetone-d6 using $CFCl_3$ as the internal standard unless otherwise noted.

IR spectra were obtained on JASCO IR 810 spectrophotometer.

Mass spectra (EIMS and HRMS) were obtained with a JEOL JMX-DX 300 spectrometer with a direct inlet system at 70 eV. Mass spectra (ESI) were obtained with a Micromass LCT.

4.1. Preparation of N-(4-methoxyphenyl)trifluoroacetaldimine (3a) [20]

A round bottom flask equipped with a magnetic stirrer bar and a Dean-Stark trap was charged with 120 ml of toluene, *p*-anisidine (83 mmol), trifluoroacetaldehyde ethyl hemiacetal (94 mmol) and *p*-toluene sulfonic acid monohydrate (0.3 mmol) and then heated under reflux for 2 h. After cooled to room temperature, the reaction mixture was filtered and the solvent was removed *in vacuo*. The residue was distilled under a pressure of 0.4 kPa. Then **3a** (56 mmol, 68%) was obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.93 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 7.81 (q, J = 3.7 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.13 (d, J = 3.5 Hz).

4.2. Catalytic hydrogenation of trifluoroacetaldimine 3a

A stainless steel vessel equipped with a magnetic stirrer bar was charged with 20 g of toluene, **3a** (9.6 mmol) and 5% palladium on charcoal (96 mg). After sealed, a pressure of 0.2 MPa of hydrogen was applied and kept until its absorption ended. The reaction mixture was filtered and the solvent was removed *in vacuo*. The residue was distilled under a pressure of 0.3 kPa. Then **4a** (8.7 mmol, 90%) was obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (q, J = 9.1 Hz, 2H), 3.64–3.70 (brs, 1H), 3.73 (s, 3H), 6.63 (d, J = 9.2 Hz, 2H), 6.79 (d, J = 9.2 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.83 (d, J = 8.9 Hz).

4.3. Preparation of 2,2,2-trifluoro-1-(4-methoxypheylamino)ethanol (6a) [22]

A round bottom flask equipped with a magnetic stirrer bar was charged with 10 ml of diethyl ether, *p*-anisidine (18 mmol), trifluoroacetaldehyde ethyl hemiacetal (18 mmol) and molecular sieves 4 A (6.0 g). After stirred at room temperature for 3 h, the reaction mixture was filtered and the solvent was removed *in vacuo*. The crude hemiaminal was used without further purification.

^{19}F NMR (376 MHz, $CDCl_3$, internal standard C_6F_6) δ 80.06 (d, J = 4.7 Hz). EIMS m/z 203 $[M-H_2O]^+$ (59), 134 (100), 107 (34), 92 (26), 77 (43), 64 (24).

4.4. Reduction of hemiaminal 6a

A round bottom flask equipped with a magnetic stirrer bar was charged with 8 ml of methanol and **5a** (2.0 mmol). $NaBH_4$ (4 mmol) was added to the solution at room temperature and the mixture was stirred for 1 h. After the quench with 6N-HCl (4 ml), ^{19}F NMR analysis (internal standard method) and GC–MS analysis of the crude reaction mixture indicated the production of 2,2,2-trifluoroethanol (1.85 mmol, 93%).

^{19}F NMR (376 MHz, $CDCl_3$) δ −77.65 (d, J = 9.0 Hz); EIMS m/z 81 $[M-F]^+$ (3), 69 (9), 61 (20), 51 (15), 33 (26), 31 (100).

4.5. General procedure for the preparation of N,O-acetal from primary amines 5a–g [21]

A round bottom flask equipped with a magnetic stirrer bar and a condenser connected to a nitrogen source was charged with 10 ml of methanol, amine (4.1 mmol), trifluoroacetaldehyde methyl hemiacetal (16 mmol) and *p*-toluene sulfonic acid monohydrate (0.3 mmol) and then heated under reflux for 1 h. After cooled to room temperature, 10% aqueous $NaHCO_3$ (30 ml) was added. The mixture was extracted with ethyl acetate twice (30 ml), dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate afforded N,O-acetal **5a**–**g**.

4.5.1. N-(2,2,2-Trifluoro-1-methoxyethyl)-4-methoxyaniline (5a)

Oil. IR (neat): 3390, 2850, 1600, 1520, 1380, 1280, 1240, 1180, 1140, 900, 820, 780, 720, 650 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.47 (s, 3H), 3.76 (s, 3H), 4.02 (brs, 1H), 4.83–4.92 (m, 1H), 6.72–6.84 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.41 (d, J = 4.6 Hz); EIMS m/z 235 $[M]^+$ (93), 204 (48), 203 (19), 166 (100), 151 (28), 134 (34), 122 (25), 108 (15), 63 (10); HRMS (EI) Calcd for $C_{10}H_{12}F_3NO_2$: 235.0820. Found: 235.0823.

4.5.2. Ethyl 4-[(2,2,2-trifluoro-1-methoxyethyl)amino]benzoate (5b)

Solid, mp 101 °C. IR (KBr): 3325, 1710, 1610, 1600, 1540, 1320, 1300, 1260, 1180, 1150, 1130, 1090, 770 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (t, J = 7.1 Hz, 3H), 3.49 (s, 3H), 4.34 (q, J = 7.1 Hz, 2H), 4.63 (brd, J = 10.1, 1H), 5.04–5.13 (m, 1H), 6.78 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.7 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.44 (d, J = 4.3 Hz); EIMS m/z 277 $[M]^+$ (30), 245 (47), 208 (94), 200 (100), 176 (40); Anal. Calcd for $C_{12}H_{14}F_3NO_3$: C, 51.99; H, 5.09; N, 5.05. Found: C, 52.07, H, 5.10, N, 5.14.

4.5.3. 4-[(2,2,2-Trifluoro-1-methoxyethyl)amino]benzonitrile (5c)

Solid, mp 100–101 °C. IR (KBr): 3360, 3340, 2230, 1620, 1540, 1340, 1280, 1260, 1180, 1140, 1080, 980, 830 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.50 (s, 3H), 4.70 (brd, 1H), 4.99–5.08 (m, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.53, d, J = 8.7 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.31 (d, J = 4.3 Hz); EIMS m/z 230 $[M]^+$ (34), 199 (39), 161 (100), 129 (68), 102 (35); Anal. Calcd for $C_{10}H_9F_3N_2O$: C, 52.18; H, 3.94; N, 12.17. Found: C, 52.52, H, 4.01, N, 12.33.

4.5.4. N-(2,2,2-Trifluoro-1-Methoxyethyl)aniline (5d)

Oil. IR (neat): 3400, 2950, 1610, 1520, 1505, 1380, 1280, 1260, 1190, 1150, 900, 850, 760, 720, 700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.48 (s, 3H), 4.23–4.26 (brs, 1H), 4.97–5.06 (m, 1H), 6.75–7.29 (m, 5H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.49 (d, J = 4.6 Hz); EIMS m/z 205 $[M]^+$ (39), 174 (39), 136 (100), 104 (42), 93 (23), 77 (31), 51 (10); HRMS (EI) Calcd for $C_9H_{10}F_3NO$: 205.0714. Found: 205.0719.

4.5.5. N-(2,2,2-Trifluoro-1-methoxyethyl)-3-methoxyaniline (5e)

Oil. IR (neat): 3370, 3000, 2950, 2850, 1720, 1620, 1530, 1500, 1470, 1380, 1310, 1280, 1260, 970, 880, 840, 770, 710, 690 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.48 (s, 3H), 3.79 (s, 3H), 4.25–4.29 (brs, 1H), 4.96–5.05 (m, 1H), 6.31–6.46 (m, 3H), 7.12–7.18 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.50 (d, J = 4.5 Hz); EIMS m/z 235 $[M]^+$ (61), 204 (51), 203 (19), 166 (100), 134 (29), 123 (13), 107 (20), 92 (13), 77 (12); HRMS (EI) Calcd for $C_{10}H_{12}F_3NO_2$: 235.0820. Found: 235.0822.

4.5.6. N-(2,2,2-Trifluoro-1-methoxyethyl)-2-methoxyaniline (5f)

Oil. IR (neat): 3420, 3000, 2950, 2850, 1740, 1610, 1520, 1460, 1380, 1330, 1280, 1260, 1230, 1180, 1140, 1090, 980, 900, 780, 740, 720 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.45 (d, 3H), 3.87 (s, 3H), 4.90–5.08 (m, 2H), 6.77–6.93 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.38 (d, J = 4.3 Hz); EI-MS m/z 235 $[M]^+$ (81), 204 (49), 203 (27), 166 (68), 134 (100), 121 (28), 120 (23), 92 (14), 77 (20); HRMS (EI) Calcd for $C_{10}H_{12}F_3NO_2$: 235.0820. Found: 235.0810.

4.5.7. 4-Chloro-N-(2,2,2-trifluoro-1-methoxyethyl)aniline (5g)

Oil. IR (neat): 3400, 2950, 1605, 1510, 1500, 1280, 1255, 1190, 1150, 110 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.48 (s, 3H), 4.26 (brd,

1H), 4.93 (m, 1H), 6.72 (d, J = 8.9, 2H), 7.21 (d, J = 8.7 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.40 (d, J = 4.4 Hz); EIMS m/z 239 $[M]^+$ (31), 208 (34), 170 (100), 155 (12), 138 (66), 127 (25), 111 (39), 107 (10), 75 (34), 63 (25); HRMS (EI) Calcd for $C_9H_9ClF_3NO$: 239.0352. Found: 239.0337.

4.6. General procedure for the preparation of N,O-acetal from secondary amines 5h–l

A round bottom flask equipped with a magnetic stirrer bar and a condenser connected to a nitrogen source was charged with 25 ml of toluene, amine (4.1 mmol), trifluoroacetaldehyde methyl hemiacetal (16 mmol) and p-toluene sulfonic acid monohydrate (0.15 mmol) and then heated under reflux for 2 h. After cooled to room temperature, 10% aqueous $NaHCO_3$ (30 ml) was added and extracted with ethyl acetate twice (30 ml). The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate afforded N,O-acetal **5h–l**.

4.6.1. N-(2,2,2-Trifluoro-1-methoxyethyl)-N-methylaniline (5h)

Oil. IR (neat): 3000, 2950, 2830, 1610, 1510, 1460, 1410, 1350, 1320, 1300, 1280, 1220, 1180, 1150, 1120, 1080, 1040, 1010, 950, 870, 810, 760, 720, 700, 640 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.92 (s, 3H), 3.34 (s, 3H), 5.08–5.14 (q, 1H), 6.87–7.33 (m, 5H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.99 (d, J = 4.9 Hz); EIMS m/z 219 $[M]^+$ (27), 188 (40), 150 (100), 106 (13), 77 (20); HRMS (EI) Calcd for $C_{10}H_{12}F_3NO$: 219.0871. Found: 219.0873.

4.6.2. N-(2,2,2-Trifluoro-1-methoxyethyl)-1,2,3,4-tetrahydroquinoline (5i)

Oil. IR (neat): 2950, 2930, 1610, 1510, 1310, 1270, 1150, 750 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.81–2.04 (m, 2H), 2.75–2.89 (m, 2H), 3.17–3.26 (m, 1H), 3.40 (s, 3H), 3.44–3.53 (m, 1H), 5.22 (q, J = 5.2, 1H), 6.71–6.78 (m, 2H), 7.02–7.11 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.77 (d, J = 5.2 Hz); EIMS m/z 245 $[M]^+$ (36), 214 (22), 176 (100); HRMS (EI) Calcd for $C_{12}H_{14}F_3NO$: 245.1027. Found: 245.1044.

4.6.3. N-(2,2,2-Trifluoro-1-methoxyethyl)-N-methylbenzylamine (5j)

Oil. IR (neat): 2970–2850, 1505, 1460, 1290, 1180–1120, 1060 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.51 (s, 3H), 3.85 (d, J = 13.9, 1H), 3.85 (d, J = 14.0, 1H), 4.20 (q, J = 5.6, 1H), 7.24–7.38 (m, 5H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.95 (d, J = 5.0 Hz); EIMS m/z 233 $[M]^+$ (1), 164 (56), 91 (100); HRMS (EI) Calcd for $C_{11}H_{14}F_3NO$: 233.1027. Found: 233.1021.

4.6.4. N-(2,2,2-Trifluoro-1-methoxyethyl)-1,2,3,4-tetrahydroisoquinoline (5k)

Oil. IR (neat): 2950, 2850, 1280, 1170, 1150, 1110 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.86 (t, J = 5.8, 2H), 2.98–3.07 (m, 1H), 3.14–3.22 (m, 1H), 3.47 (s, 3H), 3.83 (d, J = 15.0 Hz, 1H), 4.03 (d, J = 15.0 Hz, 1H), 4.25 (q, J = 5.6 Hz, 1H), 7.00–7.15 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.78 (d, J = 5.4 Hz); EIMS m/z 245 $[M]^+$ (27), 244 (22), 214 (23), 176 (100); HRMS (EI) Calcd for $C_{12}H_{14}F_3NO$: 245.1027. Found: 245.1011.

4.6.5. N-(2,2,2-Trifluoro-1-methoxyethyl)-N′-phenylpiperazine (5l)

Oil. IR (neat): 2950, 2900, 2830, 1605, 1505, 1460, 1280, 1240, 1180, 1160, 1140, 1020, 760, 690 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.90–2.97 (m, 2H), 3.03–3.12 (m, 2H), 3.15–3.20 (m, 4H), 3.51 (s, 3H), 4.12 (q, J = 5.5 Hz, 1H), 6.85–7.00 (m, 3H), 7.24–7.31 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.96 (d, J = 5.3 Hz); EIMS m/z 274 $[M]^+$ (100), 259 (23), 243 (31), 205 (69), 132 (27), 105 (43), 104 (25); HRMS (EI) Calcd for $C_{13}H_{17}F_3N_2O$: 274.1293. Found: 274.1298.

4.7. General procedure for the reduction method A

A round bottom flask equipped with a magnetic stirrer bar and a condenser connected to a nitrogen source was charged with 3 ml of methanol and N,O-acetal **5** (1.0 mmol). $NaBH_4$ (2.0 mmol) was added and the mixture was heated under reflux for 1 h. After that MeOH was removed under reduced pressure. The residue was quenched with water (10 ml), extracted with ethyl acetate twice (20 ml). The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate afforded trifluoroethylamino compounds **4**.

4.7.1. N-(2,2,2-Trifluoroethyl)-4-methoxyaniline (4a)

Oil. IR (neat): 3400, 1520, 1470, 1440, 1390, 1330, 1280, 1240, 1160, 1120, 1040, 950, 820, 730, 670, 640 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.66–3.75 (m, 2H), 3.66–3.75 (brs, 1H), 3.75 (s, 3H), 6.64–6.68 (m, 2H), 6.79–6.83 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.83 (d, J = 8.9 Hz); EIMS m/z 205 $[M]^+$ (98), 190 (100), 170 (12), 162 (13), 136 (74), 121 (16), 120 (15), 92 (10); HRMS (EI) Calcd for $C_9H_{10}F_3NO$: 205.0714. Found: 205.0708.

4.7.2. N-(2,2,2-Trifluoroethyl)aniline (4d)

Oil. IR (neat): 3420, 1610, 1520, 1450, 1400, 1340, 1280, 1260, 1160, 830, 760, 700, 670, 620 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.71–3.81 (m, 2H), 3.91 (brs, 1H), 6.67–7.27 (m, 5H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.87 (d, J = 8.8 Hz); EIMS m/z 175 $[M]^+$ (46), 106 (100), 104 (15), 77 (34), 51 (11); HRMS (EI) Calcd for $C_8H_8F_3N$: 175.0609. Found: 175.0601.

4.7.3. N-(2,2,2-Trifluoroethyl)-3-methoxyaniline (4e)

Oil. IR (neat): 3440, 2950, 1620, 1610, 1520, 1505, 1265, 1220, 1170 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.70–3.90 (m, J = 9.0 Hz, 2H), 3.78 (s, 3H), 3.95 (brs, 1H), 6.23–6.46 (m, 3H) 7.12 (t, J = 8.3 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.80 (d, J = 8.9 Hz); EIMS m/z 205 $[M]^+$ (60), 136 (100), 108 (11); HRMS (EI) Calcd for $C_9H_{10}F_3NO$: 205.0714. Found: 205.0729.

4.8. General procedure for the reduction method B

A round bottom flask equipped with a magnetic stirrer bar and a condenser connected to a nitrogen source was charged with 2.5 ml of acetic acid and N,O-acetal **5** (1.0 mmol). 2-Picoline borane complex (1.2 mmol) was added at room temperature and the mixture was stirred for 0.5 h. After the quench with 6N-HCl (10 ml) and the neutralization with $NaHCO_3$, the mixture was extracted with ethyl acetate twice (20 ml). The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate afforded trifluoroethylamino compounds **4**.

4.8.1. Ethyl 4-[(2,2,2-trifluoroethyl)amino]benzoate (4b)

Solid, mp 94–95 °C. IR (KBr): 3380, 1695, 1605, 1540, 1520, 1275, 1250, 1180, 1150, 770 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ1.37 (t, J = 7.1), 3.79–389 (m, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.37 (brs, 1H), 6.67 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.72 (d, J = 8.8 Hz); EIMS m/z 247 $[M]^+$ (53), 202 (100), 178 (22), 150 (26); Anal. Calcd for $C_{11}H_{12}F_3NO_2$: C, 53.44; H, 4.89; N, 5.67. Found: C, 53.54, H, 4.94, N, 5.75.

4.8.2. 4-[(2,2,2-Trifluoroethyl)amino]benzonitrile (**4c**)

Solid, mp 116–118 °C. IR (KBr): 3360, 3165–2955, 2215, 1605, 1530, 1350, 1295, 1275, 1260, 1155, 1125, 950, 825, 670, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (qd, J = 8.8, 6.8 Hz, 2H), 4.78 (brt, J = 6.2 Hz, 1H), 6.71 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.56 (d, J = 8.8 Hz); EIMS m/z 200 $[M]^+$ (26), 131 (100), 102 (24), 75 (16), 69 (23), 64 (14), 51 (16).

4.8.3. N-(2,2,2-Trifluoroethyl)-2-methoxyaniline (**4f**)

Oil. IR (neat): 3440, 2950, 2850, 1610, 1605, 1520, 1500, 1400, 1280–1260, 1220, 1165, 1060, 960, 830, 770, 695 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.72–3.79 (m, 2H), 3.78 (s, 3H), 3.94 (brs, 1H), 6.23–6.43 (m, 3H), 7.09–7.18 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.72 (d, J = 9.0 Hz); EIMS m/z 205 $[M]^+$ (100), 190 (54), 162 (33), 136 (87), 121 (51), 120 (67), 115 (9), 93 (16), 77 (21), 65 (23), 52 (21).

4.8.4. 4-Chloro-N-(2,2,2-trifluoroethyl)aniline (**4g**)

Oil. IR (neat): 3430, 1605, 1505, 1330, 1290, 1270, 1250, 1180, 1165, 1120, 1090, 950, 820, 675, 505 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.68–3.80 (m, 2H), 3.94 (brs, 1H), 6.62 (d, J = −8.9 Hz, 2H,), 7.17 (d, J = 9.1, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.79 (d, J = 8.8 Hz); EIMS m/z 211 (9), 209 $[M]^+$ (28), 142 (31), 140 (100), 111 (16), 105 (16), 77 (22), 75 (27), 69 (14), 63 (14), 50 (18).

4.8.5. N-(2,2,2-Trifluoroethyl)-N-methylaniline (**4h**)

Oil. IR (neat): 1610, 1510, 1380, 1170, 1150, 1100, 1000, 980, 830, 760, 700, 670 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.86 (q, J = 8.1, 2H), 6.79–6.83 (m, 3H), 7.24–7.29 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −70.91 (d, J = 9.0 Hz); EIMS m/z 189 $[M]^+$ (47), 120 (100), 105 (13), 104 (12), 77 (17).

4.8.6. N-(2,2,2-Trifluoroethyl)-1,2,3,4-tetrahydroquinoline (**4i**)

Oil. IR (neat): 2935, 2850, 1605, 1500, 1460, 1350, 1265, 1205, 1140, 1110, 1065, 1020, 800, 750, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98–1.92 (m, 2H), 2.76 (t, J = 6.4 Hz, 2H), 3.38 (t, J = 5.6, 2H), 3.78 (q, J = 9.1 Hz, 2H), 6.67 (t, J = 8.0, 2H), 6.96 (dd, J = 7.6, 1.4 Hz, 1H), 7.06 (td, J = 7.8, 1.6, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −70.70 (d, J = 9.1 Hz); EIMS m/z 215 $[M]^+$ (59), 146 (100).

4.8.7. N-(2,2,2-Trifluoroethyl)-N-methylbenzylamine (**4j**)

Oil. IR (neat): 2800, 1500, 1460, 1410, 1320, 1270, 1150, 1130, 1100, 1050, 750, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.04 (q, J = 9.6 Hz, 2H), 3.72 (s, 2H), 7.24–7.34 (m, 5H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −69.29 (t, J = 9.5 Hz); EIMS m/z 203 $[M]^+$ (30), 134 (41), 126 (23), 91 (100); HRMS (EI) Calcd for $C_{10}H_{12}F_3N$: 203.0922. Found: 203.0932.

4.8.8. N-(2,2,2-Trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (**4k**)

Oil. IR (neat): 3070, 2960, 2800, 1430, 1270, 1140, 1125, 1100, 1055, 1030, 945, 845, 800, 745, 720, 700, 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.89 (t, J = 5.6, 2H), 2.96 (t, J = 5.6, 2H), 3.13 (q, J = 9.5, 2H), 3.86 (s, 2H), 6.98–7.00 (m, 1H), 7.07–7.13 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −69.70 (d, J = 9.5 Hz); EIMS m/z 215 $[M]^+$ (74), 214 (100), 146 (37), 104 (87).

4.8.9. N-(2,2,2-Trifluoroethyl)-N′-phenylpiperazine (**4l**)

Solid. IR (KBr): 2850, 2830, 1610, 1515, 1460, 1320, 1270, 1170, 1150, 1105, 760, 690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.83 (t, 4H), 3.03 (q, J = 9.6 Hz, 2H), 3.21 (t, 4H), 6.84–6.94 (m, 3H), 7.23–7.30 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −69.41 (d, J = 9.6 Hz); EIMS m/z 244 $[M]^+$ (100), 132 (19), 106 (24), 105 (65); Anal. Calcd for $C_{12}H_{15}F_3N_2$: C, 59.01; H, 6.19; N, 11.47. Found: C, 59.04, H, 6.23, N, 11.72.

4.9. Preparation of trifluoromethy (S)-tert-butyl sulfinimine ((S)-**3d**) [25]

A round bottom flask equipped with a magnetic stirrer bar and a condenser connected to a nitrogen source was charged with 1800 ml of dichloromethane, (*S*)-*tert*-butane sulfinamide (*S*)-**7** (0.83 mol), trifluoroacetaldehyde hydrate **1c** (0.91 mol) and $MgSO_4$ (0.60 mol) and heated at 40 °C for 4 h. After cooled to room temperature, $MgSO_4$ was removed by filtration. To the filtrate, molecular sieves 4 A (500 g) was added and heated again for 8 h. After that, molecular sieves were removed by filtration and washed with dichloromethane (600 ml). The solvent was removed *in vacuo*. The residue was distilled under a pressure of 0.6 kPa. Then (*S*)-**3d** (0.63 mol, 76%) was obtained as colorless oil. The chemical purity of (*S*)-**3d** was determined by ^{19}F NMR analysis with benzotrifluoride as internal standard. The optical purity was determined by chiral GC (Inertcap CHIRAMIX) analysis after (*S*)-**3d** (0.25 mmol) was mixed with excess amount (11 mmol) of MeOH to be converted into the N,O-acetal form.

Oil. IR (neat): 2985, 2970, 2930, 1480, 1460, 1370, 1335, 1285, 1170, 1155, 1100, 870, 735, 515, 455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 7.99 (q, J = 3.6 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −70.60 (d, J = 3.5 Hz); EIMS m/z 145 $[M-C_4H_8]^+$ (1), 144 (2), 69 (7), 57 (100), 41 (83).

4.10. General procedure for the reaction of (S)-**3d** with phenyllithium

A flame-dried Schlenk flask equipped with a magnetic stirrer bar was charged with 3 ml of THF and bromobenzen (5.0 mmol) and then cooled to −78 °C. After 1.65 M n-butyllithium hexane solution (2.5 ml, 4.1 mmol) was added, the solution was stirred at −78 °C for 1 h. Then a cooled (−78 °C) solution of (*S*)-**3d** (3.8 mmol) in THF was transferred to the mixture via cannula. The resulting mixture was aged at −78 °C for 5 min and transferred to a cooled (0 °C) saturated aqueous NH_4Cl. The aqueous layer was extracted three times with ethyl acetate. The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (3:1) afforded **8a** as colorless oil.

4.10.1. (S)-2-Methyl-N-[(1S)-2,2,2-trifluoro-1-phenyl]propane-2-sulfinamide (**8a**)

Oil. IR (neat): 3200, 2965–2870, 1460, 1365, 1265, 1170, 1125, 1070, 905, 760, 700, 635, 585; ^1H NMR (400 MHz, acetone-d6) δ 1.15 (s, 9H), 5.02–5.10 (m, J = 8.0 Hz, 1H), 5.40 (d, J = 8.0, 1H), 7.41–7.46 (m, 3H), 7.59–7.61 (m, 2H); ^{19}F NMR (376 MHz, acetone-d6) δ −73.20 (d, J = 7.9 Hz); EIMS m/z 223 $[M-C_4H_8]^+$ (10), 159 (20), 140 (12), 109 (21), 57 (100), 41 (41).

Deprotection of **8a** was performed according to the literature procedure [25]. The optical rotation of corresponding amine salt ($[\alpha]_D^{23}$: +15.6°; c 1.0, MeOH) agreed with literature data, indicating *S* configuration of **8a**.

4.11. General procedure for the allylation reaction of (S)-**3d**

A Schlenk flask equipped with a magnetic stirrer bar was charged with 2 ml of solvent, (*S*)-**3d** (0.91 mmol), allyl bromide (1.2 mmol) and zinc powder (1.2 mmol) and then cooled to 0 °C. After a drop of trimethylsilyl chrolide was added, resulting mixture was aged at 0 °C for 3 h and transferred to a cooled (0 °C) saturated aqueous NH_4Cl. The aqueous layer was extracted three times with ethyl acetate. The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (1:4) afforded **8b**.

4.11.1. (S)-2-Methyl-N-[(1S)-2,2,2-trifluoro-1-(propen-2-yl)ethyl]propane-2-sulfinamide (**8b**)

Solid. IR (KBr): 3175, 3165, 2985–2870, 1645, 1475, 1435, 1365, 1275, 1230, 1170, 1115, 1065, 990, 920, 855, 700, 600; ^{1}H NMR (400 MHz, acetone-d6) δ 1.19 (s, 9H), 2.49–2.59 (m, 2H), 3.83–3.91 (m, 1H), 5.04 (d, J = 9.2 Hz, 1H), 5.12–5.25 (m, 2H), 5.87–5.97 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.25 (d, J = 6.4 Hz); EIMS m/z 187 $[M-C_4H_8]^+$ (2), 57 (100), 41 (43); HRMS (ESI) Calcd for $C_9H_{17}F_3NOS$ $[M+H]^+$: 244.0983. Found: 244.0966.

4.12. Reformatsky reaction of (S)-3d

A Schlenk flask equipped with a magnetic stirrer bar was charged with 20 ml of DMF, (*S*)-**3d** (10 mmol), ethyl bromoacetate (13 mmol) and zinc powder (13 mmol) and then cooled to 0 °C. After two drops of trimethylsilyl chrolide in DMF were added, resulting mixture was aged at 0 °C for 5 h and transferred to a cooled (0 °C) saturated aqueous NH_4Cl (50 ml). The aqueous layer was extracted three times with ethyl acetate. The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (3:2) afforded **8c** as colorless oil.

4.12.1. (S)-2-Methyl-N-[(1S)-2,2,2-trifluoro-1-(ethoxycarbonylmethyl)ethyl]propane-2-sulfinamide (**8c**)

Oil. IR (neat): 3205, 2985–2875, 1740, 1475, 1370, 1345, 1275, 1230, 1195, 1170, 1125, 1070, 1025, 940, 885, 660; ^{1}H NMR (400 MHz, acetone-d6) δ 1.16 (s, 9H), 1.24 (t, J = 7.0, 3H), 2.77 (dd, J = 16.0, 9.4 Hz, 1H), 2.85 (dd, J = 16.0, 4.2 Hz, 1H), 4.11–4.20 (m, 2H), 4.23–4.34 (m, 1H), 5.27 (d, J = 10.0 Hz, 1H); ^{19}F NMR (376 MHz, acetone-d6) δ −74.83 (d, J = 7.8 Hz); EIMS m/z 233 $[M-C_4H_8]^+$ (5), 57 (100), 41 (52); HRMS (ESI) Calcd for $C_{10}H_{19}F_3NO_3S$ $[M+H]^+$: 290.1038. Found: 290.1039.

4.13. General procedure for deprotection

A flask equipped with a magnetic stirrer bar was charged with 27 ml of diisopropyl ether, **8** (6.5 mmol) and ethanol (37 mmol) and then cooled to 0 °C. After the addition of acetyl chloride (19 mmol), the mixture was aged at 0 °C for 5 h. Then the mixture was condensed *in vacuo*. The residue was dissolved with 15 ml of water and washed with dichloromethane. Then $NaHCO_3$ (8.9 mmol) was added to the aqueous layer and extracted twice with 8 ml of dichloromethane (veratrol was used as an extraction solvent for **9b**). The organic layer was dried over $MgSO_4$ and distilled under reduced pressure with Kugel–Rohr apparatus.

4.13.1. (1S)-2,2,2-Trifluoro-1-(propen-2-yl)ethylamine (**9b**)

Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (brs, 2H), 2.15–2.24 (m, 1H), 2.47–2.54 (m, 1H), 3.23–3.28 (m, 1H), 5.17–5.23 (m, 2H), 5.78–5.85 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.93 (d, J = 7.4 Hz); EIMS m/z 139 $[M]^+$ (1), 98 (100), 78 (24), 48 (16); HRMS (ESI) Calcd for $C_5H_9F_3$ N $[M+H]^+$: 140.0687. Found: 140.0690; $[\alpha]_D^{25}$ −17.5° (c 0.5, $CHCl_3$).

4.13.2. Ethyl (3S)-3-amino-4,4,4-trifluorobutylate (**9c**)

Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2, 3H), 1.55 (brs, 2H), 2.44 (dd, J = 16.0, 10.0, 1H), 2.72 (dd, J = 16.0, 3.2, 1H), 3.73 (brs, 1H), 4.20 (q, J = 7.1, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.40 (d, J = 7.2 Hz); EIMS m/z 165 $[M-HF]^+$ (15), 140 (26), 116 (36), 98 (100), 93 (38), 70 (34), 43 (89); $[\alpha]_D^{25}$ −19.4° (c 1.0, $CHCl_3$).

4.14. General procedure for preparation of Mosher's MTPA amide

A Schlenk flask equipped with a magnetic stirrer bar was charged with 2 ml of dichloromethane, amine **9b** (0.24 mmol), diisopropylethylamine (0.36 mmol), α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.29 mmol). The mixture was stirred at room temperature for 1 h. After cooled in an ice bath, aqueous 1 M NH_4Cl (2 ml) was added. The organic layer was dried over $MgSO_4$ and condensed *in vacuo*. The residue was chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (8:2) afforded MTPA amide.

4.14.1. N-[(1S)-2,2,2-Trifluoro-1-(propen-2-yl)ethyl]-(S)-α-methoxy-α-(trifluoromethyl)phenylacetamide

Yield 74%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28–2.34 (m, 1H), 2.52–2.58 (m, 1H), 3.47 (q, J = 1.6, 3H), 4.66–4.77 (m, 1H), 4.99 (dq, J = 17.2, 1.3 Hz, 1H), 5.05 (dq, J = 10.4, 1.2 Hz, 1H), 5.56–5.66 (m, 1H), 6.70 (d, J = 9.6, 1H), 7.37–7.42 (m, 3H), 7.50–7.53 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.98 (d, J = 7.4 Hz, 3F), −69.62 (s, 3F); EIMS m/z 355 $[M]^+$ (1), 189 (100), 175 (45), 170 (42), 119 (32), 105 (92), 91 (39), 77 (54); HRMS (ESI) Calcd for $C_{15}H_{15}F_6$ N O_2 $[M+H]^+$: 356.1085. Found: 356.1119.

4.14.2. N-[(1S)-2,2,2-Trifluoro-1-(propen-2-yl)ethyl]-(R)-α-methoxy-α-(trifluoromethyl)phenylacetamide

Yield 74%. Solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35–2.43 (m, 1H), 2.58–2.64 (m, 1H), 3.36 (q, J = 1.3, 3H), 4.68–4.80 (m, 1H), 5.19 (dq, J = 5.6, 1.5 Hz, 1H), 5.22 (bs, 1H), 5.69–5.79 (m, 1H), 6.97 (d, J = 9.6, 1H), 7.40–7.42 (m, 3H), 7.48–7.50 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.82 (d, J = 7.4 Hz, 3F), −69.59 (s, 3F); EIMS m/z 355 $[M]^+$ (1), 189 (100), 175 (48), 170 (45), 119 (34), 105 (97), 91 (42), 77 (57); HRMS (ESI) Calcd for $C_{15}H_{15}F_6$ N O_2 $[M+H]^+$: 356.1085. Found: 356.1085.

The negative $\delta^S-\delta^R$ value for the allyl protons on ^{1}H NMR indicates *S* configuration of 1-(trifluoromethyl)but-3-enylamino moiety.

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