Synthesis of CF_3-substituted 1,2,3,4-tetrahydroisoquinolines and 1,2,3,6-tetrahydropyridines

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A three-step method for the preparation of CF_3-substituted 1,2,3,4-tetrahydroisoquinolines and 1,2,3,6-tetrahydropyridines has been suggested. The first step includes alkylation of isoquinoline or 4-methylpyridine at the nitrogen atom with the formation of salts, which are involved into the reaction with Grignard reagent or lithium triethylborohydride to give enamines. The enamines undergo nucleophilic trifluoromethylation upon the action of Me_3SiCF_3 under acidic conditions.

Key words: trifluoromethylation, amines, trimethyl(trifluoromethyl)silane.

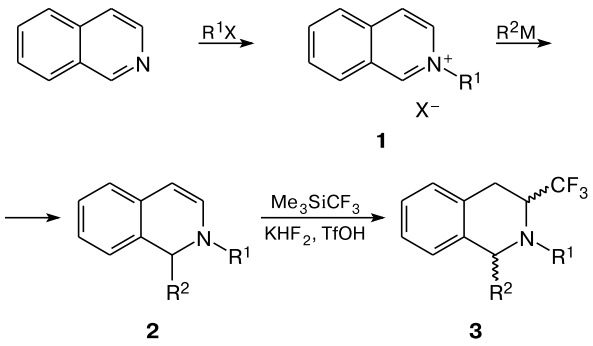
Amines containing trifluoromethyl group at the C_α atom are an important class of biologically active compounds.[1—4] The most efficient approaches to α-CF_3-substituted amines include nucleophilic addition[5] and 1,3-proton shift[6] reactions involving imines of trifluoroacetic aldehyde, as well as addition reactions of trifluoromethyl carbanion at the C=N bond of azomethine substrates[7,8] and iminium cations.[9]

Among different α-(trifluoromethyl)amines, 3-trifluoromethyl-1,2,3,4-tetrahydroisoquinolines are of special interest,[4] since they are selective inhibitors of phenylethanolamine-*N*-methyltransferase, the enzyme catalyzing the last step of biosynthesis of adrenalin. The earlier[4] described method for the synthesis of such compounds was based on the use of ethyl trifluoroacetate as a source of a CF_3 group, that required performing six and more steps. During preparation of this work, another approach has been reported, which included oxidative trifluoromethylation of 1,2,3,4-tetrahydroisoquinolines.[10]

In the present work, we suggest more simple three-step method for the synthesis of 3-CF_3-substituted 1,2,3,4-tetrahydroisoquinolines (Scheme 1). In the first step, isoquinoline is alkylated at the nitrogen atom. Then, isoquinolinium salt **1** is involved into the reaction with nucleophile (Grignard reagent or hydride anion) with the formation of enamine **2**, which can give the trifluoromethylation reaction with the formation of products **3**.

The trifluoromethylation reaction of enamines, recently developed in our group,[11,12] is carried out with the use of trimethyl(trifluoromethyl)silane upon the action of hydrofluoric acid, generated *in situ* from potassium hydrogen difluoride and trifluoromethanesulfonic acid[11] (Scheme 2). The mechanism of the reaction includes protonation of enamine **2** with hydrofluoric acid with subsequent reaction of the iminium cation with the silicon-containing reagent, which is activated by the hydrogen difluoride anion.

Scheme 1



The reaction of isoquinolinium salts **1** with Grignard reagents was performed in THF at the temperatures from −78 to 25 °C. Subsequent extraction with light petroleum allowed us to isolate enamines **2** in the individual state as light liquids. However, they are extremely sensitive to air oxygen, that makes difficult their isolation and handling. This was the reason that in some experiments enamines **2** were involved into the trifluoromethylation reaction without additional purification. The results obtained are given in Table 1.

The trifluoromethylation reaction leads to a mixture of isomers in approximately equal ratio even in the case of isopropyl-substituted enamines (see Table 1, entries *2* and *5*). Relative configuration of **3a** was established based on the NOESY data for the *trans*-isomer. Assignment for

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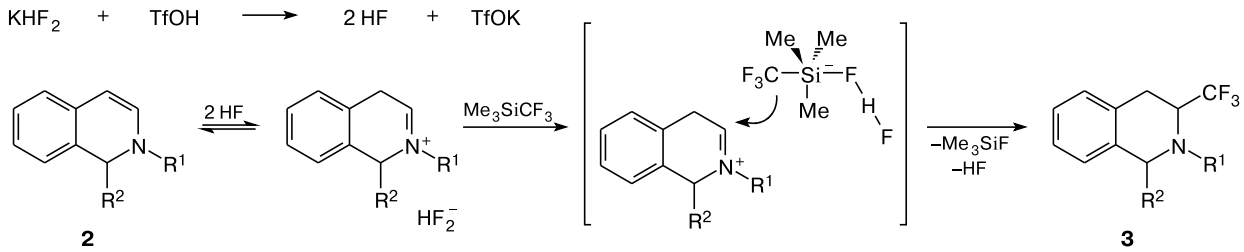
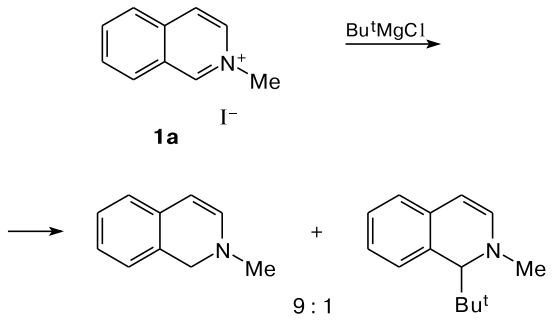
Scheme 2



compounds **3c—e** was made similarly based on the differences in the chemical shifts for the proton $CHCF_3$ in *trans*- and *cis*-isomers: for the *trans*-isomers, this proton is more downfield shifted (by ~0.4 ppm). The low stereoselectivity can be attributed to the placement of substituent R^2 in the pseudoequatorial position, that in the transition state does not lead to the repulsive interactions with the incoming CF_3 carbanion. We made an attempt to obtain an enamine containing a *tert*-butyl group, however, the reaction of salt **1a** with *tert*-butylmagnesium chloride predominantly leads to the reduction of the iminium salt and the yield of the target enamine does not exceed 10% (Scheme 3).

Scheme 3



Trifluoromethylation of enamine **4**, obtained by reduction of salt **5**, yielded an equimolar mixture of compounds **6** and **7** and expected product **8** in trace amounts, that was inferred from the ^1H and ^{19}F NMR spectra (Scheme 4). The initial step of this reaction includes generation of iminium cation **9**, which abstracts hydride anion from the starting enamine **4** with the formation of compound **7** and 2-methyl-4-phenylisoquinolinium cation, which reacts with the silicon-containing reagent giving rise to enamine **6**. To confirm the structure of enamine **6**, a sample of this compound was obtained by the reaction of iminium salt **5** with Me_3SiCF_3 in the presence of potassium fluoride.[13] At the same time, tetrahydroisoquinoline **7** was known earlier.[14]

It was also reasonable to apply the alkylation—nucleophilic addition—trifluoromethylation sequence for the synthesis of CF_3-substituted tetrahydropyridines. Thus, benzylation of 4-methylpyridine gives salts **10a**,**b** in quantitative yield, which were involved into the reaction with Grignard reagents with subsequent trifluoromethylation of the intermediate enamines to form tetrahydropyridines **11a**,**b** as a mixture of stereoisomers (Scheme 5). It should be noted that no products **12** are formed in the reaction mixture, which could have been obtained by protonation of enamines at the C(5) atom.

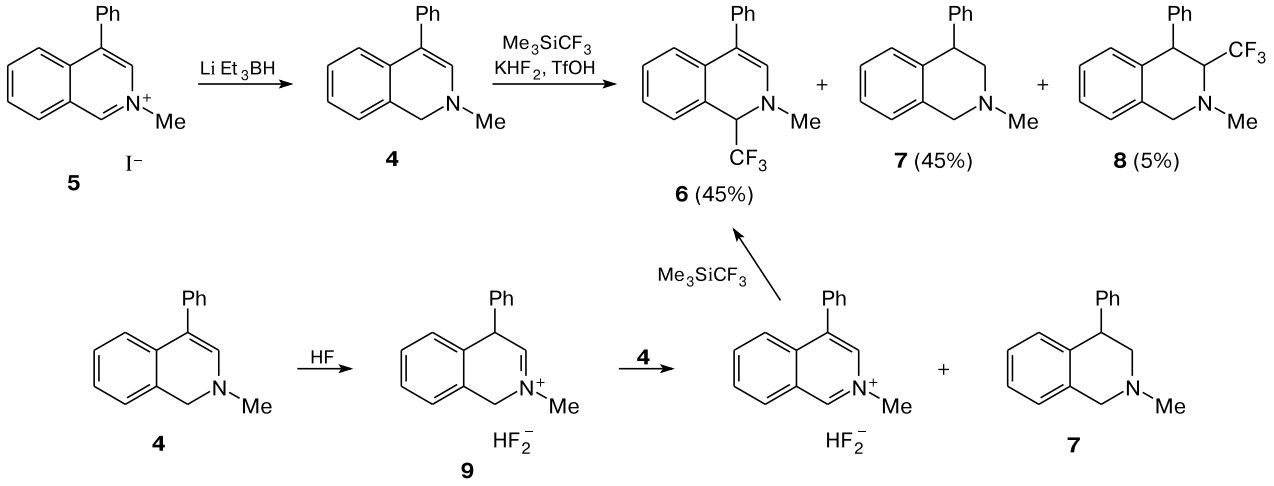
In conclusion, we suggested a simple method for the synthesis of CF_3-substituted 1,2,3,4-tetrahydroisoquinolines and 1,2,3,6-tetrahydropyridines using nucleophilic trifluoromethylation reaction under acidic conditions. The method gives products in moderate yields, however, availability of starting heterocyclic compounds makes this ap-

Table 1. Synthesis of 3-trifluoromethyl-1,2,3,4-tetrahydroisoquinolines **3**

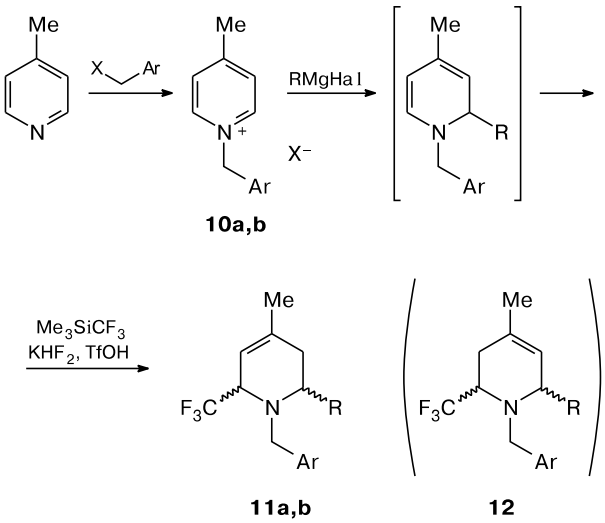
Entry	R^1	X	**1**	R^2M	**3**	R^2	*trans* : *cis*	Yield of **3**[a] (%)
1	Me	I	**1a**	MeMgI	**3a**	Me	1 : 1	50[b]
2	Me	I	**1a**	$Pr^iMgCl/LiCl$	**3b**	Pr^i	1 : 1	64[b]
3	Me	I	**1a**	$LiEt_3BH$	**3c**	H	—	17[c] (13)[b]
4	Me	I	**1a**	PhMgCl	**3d**	Ph	1.5 : 1	52[c]
5	PMB[d]	Cl	**1b**	$Pr^iMgCl/LiCl$	**3e**	Pr^i	1.3 : 1	54[b]

[a] The yield was calculated on two steps.
[b] Trifluoromethylation was performed with purified enamine.
[c] Trifluoromethylation was performed with unpurified enamine.
[d] PMB is *p*-methoxybenzyl.

Scheme 4



Scheme 5



10: Ar = Ph, X = Br (**a**); Ar = 4-$MeOC_6H_4$, X = Cl (**b**);
11: Ar = Ph, R = Ph, 57% yield, dr (ratio of diastereomers) = = 1.5 : 1 (**a**); Ar = 4-$MeOC_6H_4$, R = Me, 34% yield, dr = 1.3 : 1 (**b**).

proach competitive (as compared to the earlier described methods).

Experimental

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AM-300 or Bruker AM-200 spectrometers in $CDCl_3$. When NMR spectra of diastereomeric mixtures were described, the signals for two diastereomers were distinguished using the´ sign. Tetrahydrofuran was distilled over Na/benzophenone directly before use; DMF was distilled *in vacuo* over P_2O_5 and kept over molecular sieves 4 Å. Acetonitrile was first distilled over P_2O_5, then over CaH_2 and kept over molecular sieves 4 Å. Diethyl ether was distilled over $LiAlH_4$. 4-Phenylisoquinoline[15] and 4-methoxybenzyl chloride (PMBCl)[16] were obtained according to the known procedures. Other commercially available reagents were used as purchased.

2-Methylisoquinolinium iodide (1a).[17] Methyl iodide (1.69 mL, 27.2 mmol) was added to a solution of isoquinoline (2.80 g, 21.7 mmol) in diethyl ether (3.0 mL) under argon. The reaction flask was tightly capped and kept for 48 h at 35—40 °C. A precipitate formed was washed with diethyl ether (3×10 mL) and dried *in vacuo*. The yield was 5.29 g (90%), yellow crystals.

2-Methyl-4-phenylisoquinolinium iodide (5). Methyl iodide (310 μL, 4.98 mmol) was added to a solution of 4-phenylisoquinoline (452 mg, 2.20 mmol) in acetonitrile (4.5 mL) under argon at 0 °C. The mixture obtained was kept for 64 h at 35—40 °C. A precipitate formed was washed with diethyl ether (3×10 mL) and dried *in vacuo*. The yield was 711 mg (93%), light brown crystals, m.p. 179—180 °C. Found (%): C, 55.37; H, 3.93; N, 3.91. $C_{16}H_{14}IN$. Calculated (%): C, 55.35; H, 4.06; N, 4.03. ^1H NMR (300 MHz, $CDCl_3$), δ: 4.81 (s, 3 H, Me); 7.48—7.66 (m, 5 H, Ph); 7.89—7.99 (m, 1 H, Ar); 7.99—8.10 (m, 2 H, Ar); 8.44 (s, 1 H, Ar); 8.71 (d, 1 H, Ar, J = 8.2 Hz); 10.78 (s, 1 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 49.1, 125.2, 128.0, 129.3, 129.9, 130.0, 131.2, 131.4, 132.5, 134.0, 136.3, 137.1, 139.3, 149.0.

2-(4-Methoxybenzyl)isoquinolinium chloride (1b).[18] 4-Methoxybenzyl chloride (7.62 μL, 5.60 mmol) was added to a solution of isoquinoline (631 μL, 5.33 mmol) in toluene (2.5 mL). The reaction mixture was refluxed for 1 h and cooled, toluene was evaporated *in vacuo*. The product was recrystallized from ethanol. The yield was 1.17 g (77%), light pink crystals.

1-Benzyl-4-methylpyridinium bromide (10a).[19] Benzyl bromide (837 mL, 7.00 mmol) was added to a solution of 4-picoline (565 μL, 7.00 mmol) in acetonitrile (0.7 mL). The mixture obtained was kept for 3 h at 45 °C. A precipitate formed was washed with diethyl ether (3×10 mL) and dried *in vacuo*. The yield was 1.73 g (99%), white crystals.

1-(4-Methoxybenzyl)-4-methylpyridinium chloride (10b). 4-Picoline (934 μL, 11.57 mmol) was added to PMBCl (788 μL, 5.79 mmol). The mass obtained was stirred for 3 h at 60 °C with a reflux condenser. The picoline excess was evaporated *in vacuo*, the residue was washed with diethyl ether (3×10 mL) and dried

in vacuo to obtain glassy hygroscopic compound (1.23 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.52 (s, 3 H, MeC); 3.69 (d, 3 H, OMe, J = 2.3 Hz); 6.12 (s, 2 H, CH_2); 6.75—6.81 (m, 2 H, Ar); 7.65 (d, 2 H, Ar, J = 8.2 Hz); 7.71 (d, 2 H, CH_{Py}, J = 6.2 Hz); 9.55 (d, 2 H, CH_{Py}, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 22.0, 55.3, 62.8, 114.7, 125.6, 128.6, 131.2, 144.2, 158.5, 160.5.

Reaction of isoquinolinium salts with Grignard reagents (general procedure).[20] Grignard reagent (1.5 mmol, a solution in THF for PhMgCl and Pr^iMgCl/LiCl or a solution in Et_2O for MeMgI) was added dropwise to a suspension of isoquinolinium salt **1** (1.0 mmol) and LiCl (64 mg, 1.5 mmol) in THF (2 mL) under argon at −78 °C. The temperature was increased to ~20 °C over 30 min and the mixture was kept for another 1.5 h at 25 °C. Methanol (0.2 mL, 5.0 mmol) was carefully added dropwise to the reaction mixture. The solvent was two third evaporated *in vacuo*, followed by extraction with pentane (3×5 mL). Combined extracts were concentrated *in vacuo*.

1,2-Dimethyl-1,2-dihydroisoquinoline (2a). The residue was distilled *in vacuo* to obtain colorless oil, 67%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.27 (d, 3 H, CHMe, J = 6.8 Hz); 2.96 (s, 3 H, NMe); 4.42 (q, 1 H, CHMe, J = 6.4 Hz); 5.22 (d, 1 H, NCHCH, J = 6.8 Hz); 5.98 (d, 1 H, NCH, J = 6.8 Hz); 6.86 (d, 2 H, Ar, J = 7.3 Hz); 6.91—7.16 (m, 2 H, Ar).

1-Isopropyl-2-methyl-1,2-dihydroisoquinoline (2b). The residue was distilled *in vacuo* to obtain colorless oil, 76%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.91 (d, 3 H, $CHMe_AMe_B$, J = 6.8 Hz); 1.00 (d, 3 H, $CHMe_AMe_B$, J = 6.8 Hz); 2.00—2.21 (m, 1 H, $CHMe_2$); 3.09 (s, 3 H, NMe); 4.08 (d, 1 H, Pr^iCH, J = 6.8 Hz); 5.23 (d, 1 H, NCHCH, J = 6.8 Hz); 6.16 (d, 1 H, NCH, J = 6.8 Hz); 6.81—6.96 (m, 2 H, Ar); 6.96—7.20 (m, 2 H, Ar).

2-Methyl-1-phenyl-1,2-dihydroisoquinoline (2d). The residue was recrystallized from hexane to obtain light brown crystals, 87%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.75 (s, 3 H, NMe); 5.27 (d, 1 H, NCHCH, J = 7.3 Hz); 5.42 (s, 1 H, PhCH); 6.22 (d, 1 H, NCHCH, J = 7.3 Hz); 6.77 (d, 1 H, Ar, J = 8.0 Hz); 6.86—7.00 (m, 2 H, Ar); 7.02—7.18 (m, 1 H, Ar); 7.24—7.50 (m, 5 H, Ar).

Reaction of isoquinolinium salts with lithium triethylborohydride (general procedure). A solution of $Li[HBEt_3]$ in THF (1 *M*, 1.25 mL, 1.25 mmol) was added dropwise to a suspension of isoquinolinium salt **1** (1.0 mmol) in THF (1 mL) under argon at −25 °C. The temperature was increased to ~20 °C over 30 min and the mixture was kept for another 1.5 h at 25 °C. The solvent was evaporated *in vacuo*, the residue was extracted with pentane (3×5 mL). Combined extracts were concentrated *in vacuo*.

1,2-Dimethyl-1,2-dihydroisoquinoline (2c). The residue was distilled *in vacuo* to obtain colorless oil, 53%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.78 (s, 3 H, NMe); 4.20 (s, 2 H, CH_2); 5.33 (d, 1 H, NCHCH, J = 7.3 Hz); 6.10 (d, 1 H, NCH, J = 7.3 Hz); 6.84—7.20 (m, 4 H, Ar).

Reaction of pyridinium salts with Grignard reagents (general procedure).[20] A solution of the corresponding Grignard reagent (1.5 mmol) was added dropwise to a suspension of pyridinium salt **5** (1.0 mmol) in diethyl ether (2 mL) under argon at −25 °C. The temperature was increased to ~20 °C over 30 min and the mixture was kept for another 1.5 h at 25 °C. A 30% aqueous NaOH (0.4 mL, 4.0 mmol) was carefully added dropwise to the reaction mixture obtained. The solvent was two third evaporated *in vacuo*, followed by extraction with pentane (3×5 mL). Combined extracts were concentrated *in vacuo*, the residue was used in further transformations without purification.

Trifluoromethylation reaction of enamines (general procedure). Potassium hydrogen difluoride (117 mg, 1.5 mmol), acetonitrile (2 mL), and DMF (232 μL, 3.0 mmol) were sequentially added to a enamine (1.0 mmol). Then, the mixture was cooled to 0 °C, followed by a dropwise addition of TfOH (142 μL, 1.6 mmol), and it was kept for 5 min at 0 °C with stirring. After addition of Me_3SiCF_3 (0.44 mL, 3.0 mmol), the cooling bath was removed and the reaction mixture was stirred for 18 h at ~20 °C. Saturated aq. Na_2CO_3 (0.5 mL) was added dropwise to the mixture obtained, which was stirred for 2 min, diluted with water (7 mL), and extracted with the ester—hexane (1 : 1) solvent mixture (3×5 mL). Combined extracts were filtered through Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to chromatography on silica gel.

1,2-Dimethyl-3-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (3a). Found (%): C, 62.72; H, 6.15; N, 6.14. $C_{12}H_{14}F_3N$. Calculated (%): C, 62.87; H, 6.16; N, 6.11. *cis*-Isomer, oil. Chromatography: hexane—EtOAc (25 : 1), R_f 0.25. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.46 (d, 3 H, $CHCH_3$, J = 7.0 Hz); 2.54 (s, 3 H, NMe); 2.96 (dd, 1 H, CH_AH_B, J = 15.7 Hz, J = 7.0 Hz); 3.05 (dd, 1 H, CH_AH_B, J = 15.7 Hz, J = 9.6 Hz); 3.13—3.28 (m, 1 H, $CHCF_3$); 3.92 (q, 1 H, $CHCH_3$, J = 7.0 Hz); 7.15—7.30 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 22.0, 25.9 (q, J = = 2.5 Hz); 44.1 (q, J = 1.4 Hz); 60.1, 62.3 (q, J = 28.4 Hz); 126.2, 126.5 (q, J = 282.0 Hz); 126.9, 128.1, 132.2, 140.0. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −75.9 (d, 3 F, J = 6.4 Hz). *trans*-Isomer, oil. Chromatography: hexane—EtOAc (25 : 1), R_f 0.19. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.49 (d, 3 H, $CHCH_3$, J = 6.8 Hz); 2.40 (s, 3 H, NMe); 2.90—3.02 (m, 2 H, CH_2); 3.46 (qdd, 1 H, $CHCF_3$, J = 7.7 Hz, J = 6.6 Hz, J = 6.6 Hz); 3.92 (q, 1 H, CHMe, J = 6.9 Hz); 7.10—7.29 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 19.7, 25.0 (q, J = 2.1 Hz); 38.8 (q, J = 1.4 Hz); 57.1, 58.3 (q, J = 27.8 Hz); 126.2, 126.6, 126.7 (q, J = 284.3 Hz); 128.2, 131.8, 139.1. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −73.1 (d, 3 F, J = 7.7 Hz).

1-Isopropyl-2-methyl-3-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (3b). Found (%): C, 65.54; H, 7.07; N, 5.27. $C_{14}H_{18}F_3N$. Calculated (%): C, 65.35; H, 7.05; N, 5.44. *cis*-Isomer, oil. Chromatography: hexane—EtOAc (75 : 1), R_f 0.38. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.68 (d, 3 H, $CHMe_AMe_B$, J = 6.6 Hz); 1.22 (d, 3 H, $CHMe_AMe_B$, J = 6.6 Hz); 1.75 (septd, 1 H, $CHMe_2$, J = 8.5 Hz, J = 6.6 Hz); 2.57 (s, 3 H, NMe); 2.82—2.98 (m, 4 H, CH_2 + Pr^iCH + $CHCF_3$); 7.02—7.10 (m, 1 H, Ar); 7.14—7.29 (m, 3 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 20.7, 20.9, 26.5 (q, J = 2.9 Hz); 33.6, 48.7 (q, J = 1.0 Hz); 63.5 (q, J = 28.6 Hz); 74.5, 96.4, 126.3, 126.7 (q, J = 280.6 Hz); 127.1, 127.8, 128.7, 132.5, 138.7. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −77.04 (d, 3 F, J = 5.3 Hz). *trans*-Isomer, oil. Chromatography: hexane—EtOAc (75 : 1), R_f 0.21. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.04 (d, 3 H, $CHMe_AMe_B$, J = 6.6 Hz); 1.14 (d, 3 H, $CHMe_AMe_B$, J = 7.0 Hz); 2.02 (septd, 1 H, $CHMe_2$, J = 6.6 Hz, J = 2.2 Hz); 2.25 (s, 3 H, NMe); 2.88 (dd, 1 H, CH_AH_B, J = 10.0 Hz, J = 6.4 Hz); 2.96 (dd, 1 H, CH_AH_B, J = 10.0 Hz, J = 6.0 Hz); 3.19 (d, 1 H, Pr^iCH, J = 8.8 Hz); 3.38—3.55 (m, 1 H, $CHCF_3$); 7.08—7.21 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 20.4, 21.1, 24.3 (q, J = 2.0 Hz); 38.4 (q, J = 1.5 Hz); 57.8 (q, J = 29.0 Hz); 69.2, 96.5, 126.0, 126.6 (q, J = 282.5 Hz); 126.8, 128.1, 128.8, 132.9, 136.8. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −73.2 (s, 3 F).

2-Methyl-3-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (3c), oil. Chromatography: hexane—EtOAc (15 : 1), R_f 0.17. Found (%): C, 61.31; H, 5.59; N, 6.30. $C_{11}H_{12}F_3N$. Calculated (%):

C, 61.39; H, 5.62; N, 6.51. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.56 (q, 3 H, NCH_3, J = 1.1 Hz); 2.92 (dd, 1 H, $(F_3C)CHC\underline{H}_AH_B$, J = 16.0 Hz, J = 6.5 Hz); 3.10 (dd, 1 H, $(F_3C)CHCH_A\underline{H}_B$, J = 16.0 Hz, J = 6.5 Hz); 3.28 (qdd, 1 H, $C\underline{H}CF_3$, J = 7.9 Hz, J = 6.5 Hz, J = 6.5 Hz); 3.75 (d, 1 H, $NC\underline{H}_AH_B$, J = 15.2 Hz); 3.95 (d, 1 H, $NCH_A\underline{H}_B$, J = 15.2 Hz); 7.07—7.29 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 26.9 (q, J = 2.3 Hz); 43.9 (q, J = = 1.3 Hz); 54.1, 60.5 (q, J = 27.2 Hz); 126.3, 126.4, 126.9 (q, J = 285.4 Hz); 126.9, 128.0, 132.2, 134.8. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −73.0 (d, 3 F, J = 7.9 Hz).

2-Methyl-1-phenyl-3-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (3d). Found (%): C, 70.32; H, 5.31; N, 4.75. $C_{17}H_{16}F_3N$. Calculated (%): C, 70.09; H, 5.54; N, 4.81. *cis*-Isomer, oil. Chromatography: hexane—EtOAc (30 : 1), R_f 0.33. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.59 (s, 3 H, NCH_3); 2.91 (dd, 1 H, $C\underline{H}_AH_B$, J = 15.4 Hz, J = 7.3 Hz); 3.04 (dd, 1 H, $CH_A\underline{H}_B$, J = 15.4 Hz, J = 5.5 Hz); 3.32 (m, 1 H, $C\underline{H}CF_3$); 4.62 (s, 1 H, $C\underline{H}$Ph); 6.80 (d, 1 H, Ar, J = 7.5 Hz); 7.16—7.42 (m, 8 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 27.7 (q, J = 2.5 Hz); 45.1 (q, J = = 1.5 Hz); 62.6 (q, J = 28.2 Hz); 68.2, 126.4 (q, J = 282.5 Hz); 126.5, 127.2, 127.3, 127.3, 127.5, 128.3, 128.6, 133.4, 138.9, 142.7. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −74.9 (d, 3 F, J = 7.5 Hz). *trans*-Isomer, oil. Chromatography: hexane—EtOAc (30 : 1), R_f 0.22. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.60 (q, 3 H, NCH_3, J = 1.8 Hz); 3.18 (dd, 1 H, $C\underline{H}_AH_B$, J = 16.6 Hz, J = 4.2 Hz); 3.45 (dd, 1 H, $CH_A\underline{H}_B$, J = 16.6 Hz, J = 5.9 Hz); 3.79 (m, 1 H, $C\underline{H}CF_3$); 4.97 (s, 1 H, $C\underline{H}$Ph); 6.91 (d, 1 H, Ar, J = 7.4 Hz); 7.15 (m, 1 H, Ar); 7.23 (m, 2 H, Ar); 7.38 (m, 5 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 27.7 (q, J = 1.7 Hz); 40.8 (q, J = 1.5 Hz); 58.3 (q, J = 25.9 Hz); 66.7, 126.3, 126.4, 127.5, 127.5 (q, J = 291.9 Hz); 128.4, 128.5, 128.6, 128.9, 130.6, 137.0, 144.2. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −68.0 (d, 3 F, J = 8.5 Hz).

1-Isopropyl-2-(4-methoxybenzyl)-3-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (3e), a mixture of two diastereomers (1.3 : 1), oil. Chromatography: hexane—EtOAc (20 : 1), R_f 0.33. Found (%): C, 69.65; H, 6.81; N, 3.71. $C_{21}H_{24}F_3NO$. Calculated (%): C, 69.40; H, 6.66; N, 3.85. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.66 (d, 3 H, $CH\underline{Me}_AMe_B$, J = 6.6 Hz); 1.00 (d, 3 H, $CHMe_A\underline{Me}_B$, J = 6.6 Hz); 1.10 (d, 3 H, $CH\underline{Me}'_AMe'_B$, J = 6.6 Hz); 1.25 (d, 3 H, $CHMe'_A\underline{Me}'_B$, J = 6.6 Hz); 1.80—1.96 (m, 1 H, $C\underline{H}Me_2$); 2.06—2.22 (m, 1 H, $C\underline{H}'Me_2$); 3.00—3.60 (m, 10 H, NCH_2 + NCH'_2 + CH_2 + CH'_2 + $CHCF_3$ + $CH'CF_3$); 3.86 (d, 1 H, $Pr^iC\underline{H}$, J = 13.2 Hz); 3.90 (s, 3 H, OCH'_3); 3.92 (s, 3 H, OCH_3); 4.07 (d, 1 H, $Pr^iC\underline{H}'$, J = 13.2 Hz); 6.96—7.06 (m, 4 H, 2 CH_{Ar} + 2 CH'_{Ar}); 7.17—7.28 (m, 4 H, 2 CH_{Ar} + 2 CH'_{Ar}); 7.30—7.46 (m, 8 H, 4 CH_{Ar} + 4 CH'_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 20.3, 20.7, 20.8, 24.2, 26.1 (q, J = 2.3 Hz); 31.6, 32.0, 51.6, 54.4, 54.8, 55.0, 55.2, 55.5, 62.8 (q, J = 28.8 Hz); 63.5, 65.9, 67.7, 113.5, 113.6, 125.7, 126.2, 126.6, 126.7 (q, J = 282.9 Hz); 126.8 (q, J = 281.9 Hz); 127.0, 127.9, 128.8, 129.0, 130.3, 130.7, 131.0, 131.4, 132.8, 132.9, 136.4, 139.0, 158.9, 159.0. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −71.4 (s, 3 F′); −77.0 (s, 3 F).

1-Benzyl-4-methyl-2-phenyl-6-trifluoromethyl-1,2,3,6-tetrahydropyridine (11a), a mixture of two diastereomers (1.5 : 1), oil. Chromatography: hexane—EtOAc (30 : 1), R_f 0.38. Found (%): C, 72.40; H, 6.19; N, 4.14. $C_{20}H_{20}F_3N$. Calculated (%): C, 72.19; H, 6.08; N, 4.23. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.85 (s, 3 H, Me); 1.98 (s, 3 H, Me′); 2.11 (dd, 1 H, $C\underline{H}_AH_B$, J = 16.3 Hz, J = 3.7 Hz); 2.29 (dd, 1 H, $C\underline{H}_A'H_B$, J = 16.9 Hz, J = 3.7 Hz); 2.44 (dd, 1 H, $CH_A\underline{H}_B$, J = 16.3 Hz, J = 11.7 Hz); 2.63 (dd, 1 H, $CH_A\underline{H}_B'$, J = 16.1 Hz, J = 11.7 Hz); 3.32 (d, 1 H, $PhC\underline{H}_AH_B$, J = 13.9 Hz); 3.55—3.72 (m, 2 H, $PhCH_A\underline{H}_B$ + CF_3CH); 3.87 (d, 1 H, $PhC\underline{H}_AH_B'$, J = 15.4 Hz); 3.96—4.07 (m, 2 H, $PhCH_A\underline{H}_B'$ + PhCH′); 4.12—4.24 (m, 1 H, CF_3CH'); 4.57 (dd, 1 H, PhCH, J = 11.7 Hz, J = 3.7 Hz); 5.56 (s, 2 H, =CH + + =CH′); 7.15—7.72 (m, 20 H, 10 CH_{Ar} + 10 CH_{Ar}'). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 23.1, 24.0, 27.6, 39.7, 50.8, 56.3 (q, J = 2.2 Hz); 56.6, 58.9 (q, J = 28.8 Hz); 60.0 (q, J = 28.8 Hz); 60.9, 112.9, 114.6 (q, J = 2.2 Hz); 126.0 (q, J = 283.1 Hz); 126.6 (q, J = 283.1 Hz); 126.1, 127.2, 127.3, 127.6, 127.7, 127.8, 128.2, 128.2, 128.3, 128.6, 128.7, 129.5, 137.1, 138.8, 139.5, 140.8, 141.2, 144.8. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −72.7 (d, 3 F′, J = 8.5 Hz); −75.5 (d, 3 F, J = 8.5 Hz).

1-(4-Methoxybenzyl)-2,4-dimethyl-6-trifluoromethyl-1,2,3,6-tetrahydropyridine (11b), a mixture of two diastereomers (1.5 : 1), oil. Chromatography: hexane—EtOAc (25 : 1), R_f 0.31. Found (%): C, 64.32; H, 6.71; N, 4.73. $C_{16}H_{20}F_3NO$. Calculated (%): C, 64.20; H, 6.73; N, 4.68. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.05 (d, 3 H, $CHC\underline{H}_3$, J = 6.6 Hz); 1.27 (d, 3 H, $CHC\underline{H}_3'$, J = 6.6 Hz); 1.81 (s, 6 H, =CMe + =CMe′); 1.72—2.24 (m, 4 H, $CHC\underline{H}_2$ + $CHC\underline{H}_2'$); 2.92—3.05 (m, 1 H, $MeC\underline{H}$); 3.26 (d, 1 H, $NC\underline{H}_AH_B$, J = 13.2 Hz); 3.33—3.53 (m, 1 H, $CF_3C\underline{H}$); 3.66—3.98 (m, 5 H, $MeC\underline{H}'$ + $CF_3C\underline{H}'$ + $NCH_A\underline{H}_B$ + $NC\underline{H}_A\underline{H}_B'$); 3.83 (s, 6 H, OMe + OMe′); 5.38 (s, 1 H, CH); 5.47 (s, 1 H, CH′); 6.83—6.93 (m, 4 H, 2 H_{Ar} + 2 H_{Ar}'); 7.25—7.35 (m, 4 H, 2 H_{Ar} + 2 H_{Ar}'). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 18.5, 21.5, 23.6, 23.9, 32.4, 33.6, 48.7 (q, J = 2.3 Hz); 49.4, 49.6, 55.2, 59.1 (q, J = 28.8 Hz); 59.8, 60.6 (q, J = 28.8 Hz); 112.3, 113.1, 113.6, 126.0 (q, J = 282.5 Hz); 126.1 (q, J = 282.5 Hz); 129.4, 129.8, 131.2, 131.6, 137.8, 139.7, 158.7, 158.8. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −72.8 (d, 3 F′, J = 8.5 Hz); −75.3 (d, 3 F, J = 8.5 Hz).

2-Methyl-4-phenyl-1-trifluoromethyl-1,2-dihydroisoquinoline (6). Potassium fluoride (82 mg, 1.5 mmol) and Me_3SiCF_3 (221 μL, 1.5 mmol) were added to a solution of salt **5** (347 mg, 1 mmol) in DMF (2 mL). The suspension obtained was stirred for 4 h at ~20 °C, followed by a dropwise addition of saturated aq. Na_2CO_3 (0.5 mL), the stirring was continued for another 2 min, then, the mixture was diluted with water (7 mL) and extracted with the diethyl ether—hexane (1 : 1) solvent mixture (3×5 mL). Combined extracts were filtered through Na_2SO_4 and concentrated *in vacuo*. The yield was 91%, light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.24 (s, 3 H, NMe); 4.92 (q, 1 H, $CHCF_3$, J = 7.3 Hz); 6.41 (s, 1 H, NCH); 7.25—7.46 (m, 5 H, Ar); 7.47—7.57 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 42.4, 63.5 (q, J = 29.9 Hz); 112.6, 120.6, 122.3, 125.8, 125.9 (q, J = 292.5 Hz); 126.4, 128.6, 128.7, 129.2, 129.3, 133.9, 134.9, 138.4. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −76.2 (d, 3 F, J = 7.9 Hz).

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