Straightforward synthesis of 1-alkyl-2-(trifluoromethyl)aziridines starting from 1,1,1-trifluoroacetone

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Abstract

An efficient and straightforward approach towards the synthesis of 1-alkyl-2-(trifluoromethyl)-aziridines starting from 1,1,1-trifluoroacetone via imination, α-chlorination, hydride reduction and ring closure, was developed. In addition, novel primary β-iodo amines were obtained by regioselective ring opening of these 2-(trifluoromethyl)aziridines using alkyl iodides, and their synthetic potential was demonstrated by converting them into novel α-CF_3-β-phenylethylamines upon treatment with lithium diphenylcuprate.

Introduction

In the past decade, organofluorine compounds have gained a lot of interest in organic and medicinal chemistry.[1] This is due to the fact that the incorporation of one or more fluorine atoms, for example as a trifluoromethyl group, often results in an improvement of the biological properties of bioactive compounds.[2] For this reason, fluorinated and trifluoromethylated compounds are increasingly used in the pharmaceutical and agrochemical industry.[3] The direct introduction of a fluorine atom or a trifluoromethyl group on heterocyclic compounds, however, is often problematic,[4] and therefore a building block approach can provide a useful alternative in some cases.

Aziridines are known to be excellent building blocks for the preparation of a large variety of nitrogen-containing compounds, and numerous synthetic approaches towards the preparation of aziridines have been described.[5] An interesting subclass of these three-membered rings is the class of 2-(trifluoromethyl)aziridines, and their preparation has been relatively well studied.[6] However,

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although the reactivity of non-activated aziridines is known to be different and often complementary to that of their activated counterparts,[7] only a few approaches towards the synthesis of non-activated 2-(trifluoromethyl)aziridines have been reported in the literature.[6h-k] In a first approach, 1-alkyl-2-(trifluoromethyl)aziridines have been obtained by ring closure of *N*-alkylamino alcohols using dichlorotriphenylphosphorane.[6h,6i] These *N*-alkylamino alcohols were synthesized through ring opening of (*S*)-3,3,3-trifluoropropylene oxide by the corresponding alkylamines. A drawback of this procedure involves the high cost of the optically pure starting material, and the preparation of racemic 3,3,3-trifluoropropylene oxide elongates this synthetic procedure substantially.[8] In a second approach, 1-alkyl-2-(trifluoromethyl)aziridines have been prepared by the reaction of (β-trifluoromethyl)vinyl diphenyl sulfonium triflate with different alkylamines.[6j] This (β-trifluoromethyl)vinyl diphenyl sulfonium triflate was synthesized starting from 3,3,3-trifluoro-2-bromopropene, which was converted by an addition-elimination reaction with thiophenol into phenyl β-(trifluoromethyl)vinyl sulfide.[9] Treatment of this sulfide with the expensive diphenyliodonium triflate results in (β-trifluoromethyl)vinyl diphenyl sulfonium triflate. The relatively high cost of diphenyliodonium triflate, however, represents an important drawback if large-scale preparations are desired. In a third approach, dimethylsulfonium methylide has been used to synthesize 1-(2-methoxy-1-phenylethyl)-2-(trifluoromethyl)aziridine.[6k] Despite the synthetic value of the above-described procedures, their application for large-scale approaches is less attractive from an economical point of view, hence the interest in short and straightforward alternatives. Therefore, a new and convenient approach towards 1-alkyl-2-(trifluoromethyl)aziridines is disclosed in this paper, starting from the commercially available and inexpensive 1,1,1-trifluoroacetone, known as a useful building block for fluorinated compounds.[10]

In addition, ring-opening reactions of these 1-alkyl-2-(trifluoromethyl)aziridines were evaluated in order to provide a new and selective approach towards CF_3-substituted nitrogen-containing target compounds. A number of ring-opening reactions of non-activated 2-(trifluoromethyl)aziridines have previously been studied,[11] involving proton-catalyzed ring-opening reactions and aziridinium ion formation through *N*-alkylation followed by ring opening. Complementary to these results, the regioselective ring opening by acetic acid and alkyl iodides was studied in this work, leading in the case of alkyl iodides to interesting novel primary β-iodo amines which can be used as precursors for the synthesis of a variety of compounds. As an example, new trifluorinated amphetamine derivatives were prepared through further elaboration of these β-iodo amines. Amphetamines are of pharmacological interest due to their stimulating or inhibiting effect on the central nervous system, their anti-inflammatory activity and their ability to inhibit several enzymes.[12] Although a few methods for the preparation of α-CF_3-β-phenylethylamines are known in the literature, i.e. through

reductive amination of 3-phenyl-1,1,1-trifluoropropan-2-one,[13] the addition of Grignard reagents to fluoral hemiacetal[14] and trifluoromethylation of enamines,[15] this particular methodology represents a new approach in that respect.

Results and discussion

N-(1-Methyl-2,2,2-trifluoroethylidene)alkylamines **2** were prepared through condensation of 1,1,1-trifluoroacetone **1** with 3 equiv. of the corresponding alkylamines in diethyl ether in the presence of 0.5 equiv. of titanium(IV) chloride.[16] Subsequently, imines **2** were α-chlorinated using 1 equiv. of *N*-chlorosuccinimide (NCS) in cyclohexane upon reflux for 3 hours. Traditionally, carcinogenic carbon tetrachloride is used as a solvent for this type of transformations,[17] but could be replaced by cyclohexane in this case without altering the rate or yield of the reaction. Next to *N*-(1-chloromethyl-2,2,2-trifluoroethylidene)alkylamines **3**, the presence of the corresponding enamines[18] was observed as well (ratio: 9/1). Due to their hydrolytic instability, no attempts were made to obtain analytically pure samples of α,α,α-trifluoromethyl imines **2** and **3** through silicagel purification. However these imines **2** and **3** were obtained in a purity of at least 95 %. In the following step, *N*-(1-chloromethyl-2,2,2-trifluoroethylidene)alkylamines **3** were reduced by using 4 equiv. of sodium borohydride in methanol under reflux, yielding the corresponding β-chloro amines **4** in good overall yields (Scheme 1, Table 1). The spectral data obtained for compound **4a** were in full accordance with those reported in the literature.[11a] Attempted reductive cyclization of α-chloro imines **3** towards the desired 2-(trifluoromethyl)aziridines **5** using different reducing agents (e.g. 1 equiv. of $LiAlH_4$ in THF at 0°C or 1 equiv. of $LiBH_4$ in THF under reflux) did not lead to the desired conversion due to the reduced nucleophilicity of the nitrogen atom in amines **4**, caused by the strong electron-withdrawing effect of the trifluoromethyl substituent in α-position. Therefore, a strong base, such as lithium bis(trimethylsilyl)amide (LiHMDS), was shown to be necessary to affect ring closure of β-chloro amines **4**. In this way, several new 1-alkyl-2-(trifluoromethyl)aziridines **5** were obtained in high yields by treatment of α-CF_3-β-chloro amines **4** with 1.1 equiv. of LiHMDS in THF for 4 hours at room temperature (Scheme 1, Table 1). The spectral data obtained for compounds **5a** and **5e** were in full accordance with those reported in the literature,[9,11a] whereas aziridines **5b-d** have not been described before. Compared to known procedures for the preparation of 1-alkyl-2-(trifluoromethyl)aziridines, which either need expensive reagents or consist of multiple reaction steps, this short and efficient approach is based on the use of commercially available and relatively inexpensive resources and is therefore a suitable alternative for large-scale applications.

Scheme 1.

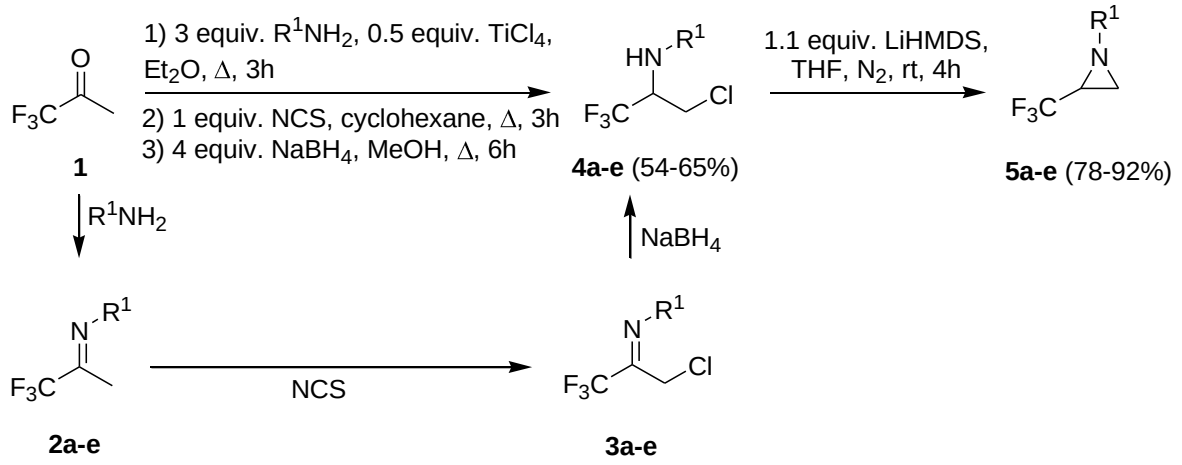

Table 1. Synthesis of *N*-alkyl-3-chloro-1,1,1-trifluoropropan-2-amines 4a-e and 1-alkyl-2-(trifluoromethyl)aziridines 5a-e

Compound	R^1	Yield[a]
4a	Bn	56%
4b	4-$ClC_6H_4CH_2$	54%
4c	4-$MeOC_6H_4CH_2$	58%
4d	n-Octyl	65%
4e	$(CH_2)_2C_6H_5$	63%
5a	Bn	92%
5b	4-$ClC_6H_4CH_2$	78%
5c	4-$MeOC_6H_4CH_2$	80%
5d	n-Octyl	83%
5e	$(CH_2)_2C_6H_5$	81%

[a] Yield after column chromatography (SiO_2).

With this novel and straightforward approach towards 2-(trifluoromethyl)aziridines **5** in hand, additional studies on the reactivity of these interesting building blocks were performed. As mentioned in the introduction, Katagiri and Karimova had already explored the reactivity of non-activated 2-(trifluoromethyl)aziridines towards a number of electrophiles and nucleophiles.[11] Complementary to these studies, ring-opening reactions with acetic acid and alkyl iodides were investigated in this work. The ring opening of 1-benzyl-2-(trifluoromethyl)aziridine **5a** to 2-benzylamino-3,3,3-trifluoropropyl acetate **6** using 5 equiv. of acetic acid in CH_2Cl_2 proceeded very sluggishly, as heating for 7 days at 60°C in a pressure vial was required to drive the reaction to completion, affording acetate **6** in 52% yield. Performing the reaction in acetic acid as a solvent appeared to be less successful, as it led to more formation of impurities. The ring opening with acetic acid had already briefly been explored in the literature, resulting in the conclusion that the acidity of

acetic acid is too weak to induce ring opening of 1-alkyl-2-(trifluoromethyl)aziridines, even after prolonged storage at 20°C.[11b] The rather drastic conditions required for the acetic acid-induced ring opening of aziridine **5a** to acetate **6** (Scheme 2) corroborate the previously described finding that the trifluoromethyl-substituted aziridine ring is quite inert towards electrophiles due to the strong electron-withdrawing effect of the CF_3-group,[11] but refute the conclusion that acetic acid is too weak to affect a ring-opening reaction.

In a second part, ring opening of 1-alkyl-2-(trifluoromethyl)aziridines **5a-c** with alkyl iodides towards β-iodo amines was investigated, as this approach has not been studied before (only chloride- and bromide-induced ring openings have been studied). At first, ring opening using 1 equiv. of benzyl bromide in acetonitrile was evaluated, which did not lead to complete conversion, even after 13 days of heating at reflux temperature. Attempts to accelerate the reaction, for example by replacing acetonitrile with a high-boiling solvent such as dimethylformamide and performing the reaction in acetonitrile under microwave irradiation, only resulted in complex mixtures. Finally, complete conversion was attained by treatment of 2-(trifluoromethyl)aziridines **5a-c** with 1 equiv. of benzyl iodide[19] at 100°C under neat conditions, affording 1,1,1-trifluoro-3-iodopropan-2-amines **7a-c** (Scheme 2, Table 2, Entries 1-3) in good yields. Detailed spectroscopic analysis ruled out the formation of the other regioisomers.[11a,20] It should be noted that the ring opening of non-activated aziridines by benzyl bromide in acetonitrile constitutes a highly efficient regio- and stereoselective approach towards the preparation of secondary β-bromo amines.[21] The observations made here once again confirm the reduced reactivity of CF_3-substituted 1-alkylaziridines with respect to electrophiles. In addition to benzyl iodide, ring opening of 2-(trifluoromethyl)aziridines **5a-b** by methyl iodide towards 1,1,1-trifluoro-3-iodopropan-2-amines **7d-e** (Scheme 2, Table 2, Entries 4-5) was attained in good yields by using 1 equiv. of methyl iodide in acetonitrile at 100°C for 3 days in a pressure vial (Scheme 2 Table 2). In an effort to improve the reaction rate, the amount of methyl iodide was increased to 5 equiv., which unfortunately resulted in the formation of benzyltrimethylammonium iodide as a side-product. It should be mentioned that β-iodo amines **7a-e** represent a novel class of compounds with unexplored synthetic potential.

As know from different literature reports, the ring opening of non-activated 2-alkylaziridines by alkyl iodides usually produces secondary β-iodo amines through ring opening of intermediate aziridinium salts at the substituted aziridine carbon atom under thermodynamic control.[22] In this case, however, ring opening of the aziridinium salts **10** by iodide proceeded regiospecifically towards primary β-iodo amines **7**, pointing to the conclusion that this transformation probably occurs under kinetic control. This change in regioselectivity can again be attributed to the strong electron-withdrawing property of

the CF_3-substituent, which prevents thermodynamic equilibration through recyclization of primary β-iodo amines **7** towards intermediate aziridinium salts **10**.

In order to demonstrate the synthetic potential of these novel 1,1,1-trifluoro-3-iodopropan-2-amines **7**, their coupling with benzene towards novel β-phenylethylamines, an interesting class of amphetamine derivatives, was evaluated. In a first approach, β-iodo amines **7a-b** were treated with phenylmagnesium chloride under various reaction conditions (2 equiv. of PhMgCl in THF or CH_2Cl_2 at -78°C, 0°C, room temperature or under reflux). Unfortunately, no desired β-phenylethylamines were formed, and even at low temperatures (-78°C) elimination products were observed. Another attempt involved a Negishi cross-coupling of β-iodo amines **7a-b** with iodobenzene. In accordance to literature procedures,[23] β-iodo amines **7a-b** were converted into the corresponding organozinc reagents using zinc, activated with catalytic iodine, in DMF. Subsequent Pd-catalysed cross-coupling of the zinc reagents with iodobenzene using 2.5 mol % of $Pd_2(dba)_3$ and 10 mol % of a precatalyst such as P(*o*-tol)$_3$ or SPhos, only resulted in complex mixtures. Finally, a successful synthesis of α-trifluoromethyl-β-phenylethylamines **8a-b** was accomplished by using a Gilman reagent such as lithium diphenylcuprate.[24] Thus, β-iodo amines **7a-b** were treated with 3 equiv. of lithium diphenylcuprate in diethyl ether at -78°C, and stirring at room temperature for 5 hours eventually afforded the desired 1,1,1-trifluoro-3-phenylpropan-2-amines **8a-b** (Scheme 2), which were purified by means of column chromatography on silica gel. In this way, 1,1,1-trifluoro-3-iodopropan-2-amines **7a-b** were applied for the formation of new trifluorinated amphetamine derivatives **8a-b**, demonstrating their synthetic potential. From a medicinal point of view, the introduction of an electron-withdrawing CF_3 group onto a β-phenylethylamino moiety can have a pronounced influence on the basicity of the nitrogen atom and hence on the pharmacological properties of these compounds. It should be mentioned that attempted direct conversion of aziridines **5** into the corresponding β-phenylethylamines upon treatment with 1.5 equiv. PhLi in THF or with 2 equiv. Ph_2CuLi in Et_2O was unsuccessful, resulting in full recovery of the starting material.

Scheme 2.

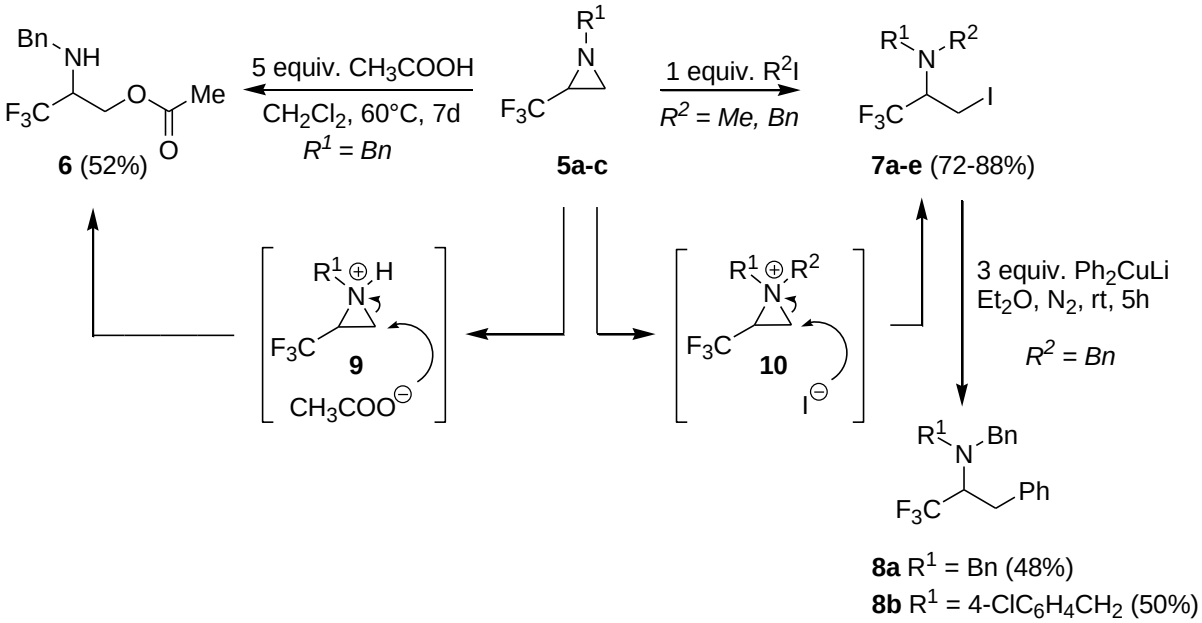

Table 2. Synthesis of 2-benzylamino-3,3,3-trifluoropropyl acetate 6 and *N*,*N*-dialkyl-1,1,1-trifluoro-3-iodopropan-2-amines 7

Entry	R^1	R^2	Reaction conditions[a]	Product (yield)
1	Bn	Bn	**A**	**7a** (74%)
2	4-$ClC_6H_4CH_2$	Bn	**A**	**7b** (88%)
3	4-$MeOC_6H_4CH_2$	Bn	**A**	**7c** (81%)
4	Bn	Me	**B**	**7d** (87%)
5	4-$ClC_6H_4CH_2$	Me	**B**	**7e** (72%)

[a] **A** = 1 equiv. BnI, neat, 100°C, 24h; **B** = 1 equiv. MeI, CH_3CN, 100°C, 3 d, pressure vial.

In conclusion, a novel and convenient method for the preparation of 1-alkyl-2-(trifluoromethyl)aziridines was developed using easily accessible and inexpensive resources, making it an economical approach for large-scale synthesis. Furthermore, additional information concerning the reactivity of these 2-(trifluoromethyl)aziridines was acquired by treatment of the latter with acetic acid and alkyl iodides. In the case of alkyl iodides, novel primary β-iodo amines were obtained through regioselective ring opening of intermediate aziridinium salts, which proved to be valuable precursors for the synthesis of novel α-trifluoromethyl-β-phenylethylamines, an interesting class of trifluorinated amphetamines derivatives.

Experimental part

^{1}H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded at 282 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and $CFCl_3$ as internal standard. Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000V) mass spectrometer. Electron impact (EI) mass spectra were recorded by using a HP 6890 GC coupled to a HP 5973 MSD (mass selective detector). IR spectra were measured with a Spectrum One FT-IR spectrophotometer. High resolution electron spray (ES) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of-Flight. Diethyl ether and tetrahydrofuran were dried over sodium benzophenone ketyl. Other solvents were used as received from the supplier. Melting points of crystalline compounds were measured with a Büchi 540 apparatus.

Synthesis of *N*-alkyl-3-chloro-1,1,1-trifluoropropan-2-amines 4 via *N*-(1-chloromethyl-2,2,2-trifluoroethylidene)alkylamines 3

General procedure: To an ice-cooled solution of 1,1,1-trifluoroacetone (0.09 mol, 1 equiv.) and the alkylamine (0.27 mol, 3 equiv.) in dry Et_2O (250 mL) was added dropwise a solution of $TiCl_4$ (0.05 mol, 0.5 equiv.) in dry petroleum ether (80 mL). After stirring for 3 hours under reflux, the reaction mixture was filtered over a pad of Celite® and washed with Et_2O (2 x 50 mL). Evaporation of the solvent under reduced pressure afforded *N*-(1-methyl-2,2,2-trifluoroethylidene)alkylamine **2** (purity >95% based on NMR). Subsequently, a solution of imine **2** (0.065 mol) and *N*-chlorosuccinimide (0.065 mol, 1 equiv.) in cyclohexane (200 mL) was heated under reflux for 3 hours. Afterwards, the resulting succinimide was filtered off and washed with cyclohexane (2 x 20 mL). Evaporation of the solvent *in vacuo* afforded the desired *N*-(1-chloromethyl-2,2,2-trifluoroethylidene)alkylamine **3** which occurs in equilibrium with a minor amount of *N*-alkyl-2-amino-1-chloro-3,3,3-trifluoropropenes (ratio: 9/1). To an ice-cooled solution of the crude mixture of imine **3** (0.06 mol, 1 equiv.) in MeOH (150 mL) was added $NaBH_4$ (0.06 mol, 1 equiv.) in small portions whilst stirring. Subsequently, the reaction mixture was heated under reflux for 4 hours, and every hour an extra equiv. of $NaBH_4$ (3 equiv. in total) was added in small portions. Afterwards, the reaction mixture was quenched by a saturated solution of NH_4Cl (75 mL), extracted with EtOAc (3 x 50 mL) and washed with brine (3 x 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-alkyl-3-chloro-1,1,1-trifluoropropan-2-amine **4**, which was purified by means of column chromatography on silicagel (hexane/EtOAc) in order to obtain an analytically pure sample**.**

N-(1-Chloromethyl-2,2,2-trifluoroethylidene)alkylamines **3** were obtained in high purity (>90% based on NMR, $CDCl_3$) and were used as such in the following step without prior purification. However, in order to confirm their structure, the spectral data of three derivatives are reported below. Despite several attempts, no conclusive mass spectra were obtained for these compounds due to their instability.

_N_-(1-chloromethyl-2,2,2-trifluoroethylidene)benzylamine 3a

Brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (2H, s), 4.88 (2H, d, *J* = 1.7 Hz), 7.30-7.40 (5H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 30.54, 55.47, 119.32 (q, *J* = 278.8 Hz), 127.57, 127.74, 128.76, 137.05, 153.96 (q, *J* = 34.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ -72.32 (3F, s). IR (ATR, cm^{-1}): ν_{CN} = 1686; ν_{max} = 1454, 1339, 1194, 1116, 751, 699.

_N_-(1-chloromethyl-2,2,2-trifluoroethylidene)-(4-chlorobenzyl)amine 3b

Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (2H, s), 4.83 (2H, d, *J* = 1.7 Hz), 7.24-7.36 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 30.48, 54.54, 119.32 (q, *J* = 280.9 Hz), 128.74, 128.96, 133.23, 135.52, 154.14 (q, *J* = 34.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ -72.40 (3F, s). IR (ATR, cm^{-1}): ν_{CN} = 1636; ν_{max} = 1492, 1345, 1200, 1167, 1129, 1088, 1015, 833, 804.

_N_-(1-chloromethyl-2,2,2-trifluoroethylidene)-(4-methoxybenzyl)amine 3c

Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (3H, s), 4.17 (2H, s), 4.81 (2H, d, *J* = 1.1 Hz), 6.87-6.92 and 7.30-7.40 (4H, 2 × m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 30.39, 54.95, 55.17, 114.06, 119.23 (q, *J* = 280.4 Hz), 128.90, 128.99, 153.47 (q, *J* = 33.5 Hz), 158.99. ^{19}F NMR (282 MHz, $CDCl_3$): δ -72.33 (3F, s). IR (ATR, cm^{-1}): ν_{CN} = 1613; ν_{max} = 1513, 1247, 1168, 1130, 1087, 1033, 819.

_N_-alkyl-3-chloro-1,1,1-trifluoropropan-2-amines 4

3-Chloro-_N_-(4-chlorobenzyl)-1,1,1-trifluoropropan-2-amine 4b

Yellow oil. R_f = 0.28 (Petroleum ether/ EtOAc 95/5). Yield 54%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91 (1H, bs), 3.31-3.40 (1H, m), 3.63 (1H, d × d, *J* = 11.8, 6.6 Hz), 3.79 (1H, d × d, *J* = 11.8, 3.3 Hz), 3.90 and 3.97 (2H, 2 × (d × d), *J* = 13.5, 5.5, 5.0 Hz), 7.31-7.33 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 41.43 (d, *J* = 2.3 Hz), 50.82, 59.17 (q, *J* = 27.7 Hz), 125.23 (q, *J* = 284.6 Hz), 128.58, 129.51, 133.11, 137.33. ^{19}F NMR (282 MHz, $CDCl_3$): δ -72.88 (3F, d, *J* = 6.6 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3362; ν_{max} = 1492, 1274, 1162, 1090, 1015, 798, 688. MS (70 eV): m/z (%): 272/4 (M^++1, 100). HRMS (ES) calcd for $C_{10}H_{11}Cl_2F_3N$: 272.0221 $[M+H]^+$; Found: 272.0216.

3-Chloro-1,1,1-trifluoro-*N*-(4-methoxybenzyl)propan-2-amine 4c

Yellow oil. R_f = 0.22 (Petroleum ether/ EtOAc 95/5). Yield 58%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88 (1H, bs), 3.34-3.40 (1H, m), 3.63 (1H, d × d, *J* = 11.6, 6.6 Hz), 3.77 (1H, d × d, *J* = 11.6, 3.9 Hz), 3.81 (3H, s), 3.86 and 3.94 (2H, 2 × d, *J* = 13.2 Hz), 6.86-6.91 and 7.23-7.35 (4H, 2 × m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 41.34 (CH_2Cl, d, *J* = 2.3 Hz), 50.88, 54.97, 58.83 (q, *J* = 27.7 Hz), 113.75, 125.30 (q, *J* = 283.8 Hz), 129.37, 130.75, 158.92. ^{19}F NMR (282 MHz, $CDCl_3$): δ -72.84 (3F, d, *J* = 6.6 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3358; ν_{max} = 2838, 1513, 1247, 1165, 1121, 1033, 830. GC-MS (EI): m/z (%): 267 (M^+, 15), 266 (19), 236 (7), 136 (7), 121 (100).

***N*-(3-Chloro-1,1,1-trifluoropropan-2-yl)octan-1-amine 4d**

Yellow oil. R_f = 0.26 (Petroleum ether/ EtOAc 99/1). Yield 65%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86-0.90 (2H, m), 0.88 (3H, t, *J* = 6.8 Hz), 1.23-1.35 (8H, m), 1.45-1.56 (2H, m), 2.67-2.81 (2H, m), 3.27-3.38 (1H, m), 3.61 (1H, d × d, *J* = 11.6, 6.6 Hz), 3.79 (1H, d × d, *J* = 11.6, 3.3 Hz). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.96, 22.62, 26.94, 29.21, 29.36, 30.16, 31.79, 41.42 (d, *J* = 3.5 Hz), 48.21, 60.73 (q, *J* = 27.7 Hz), 125.26 (q, *J* = 284.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ -73.34 (3F, d, *J* = 6.6 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3320; ν_{max} = 1467, 1270, 1148, 1120, 688. GC-MS (EI): m/z (%): 259 (M^+, 1), 160 (100).

3-Chloro-1,1,1-trifluoro-*N*-(2-phenylethyl)propan-2-amine 4e

Yellow oil. R_f = 0.36 (Petroleum ether/EtOAc 95/5). Yield 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.75-2.88 (2H, m), 2.95-3.07 and 3.17-3.24 (2H, 2 × m), 3.33-3.41 (1H, m), 3.57 (1H, d × d, *J* = 11.6, 7.2Hz), 3.76 (1H, d × d, *J* = 11.6, 3.9 Hz). 7.19-7.33 (5H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 36.46, 41.26 (d, *J* = 2.3 Hz), 49.24, 60.62 (q, *J* = 27.7 Hz), 125.14 (q, *J* = 283.8 Hz), 126.25, 128.41, 128.58, 139.06. ^{19}F NMR (282 MHz, $CDCl_3$): δ -73.30 (3F, d, *J* = 6.6 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3350; ν_{max} = 1454, 1266, 1123, 1087, 749, 698. GC-MS (EI): m/z (%): 251 (M^+, 0.1), 216 (1), 160 (100).

Synthesis of 1-alkyl-2-(trifluoromethyl)aziridines 5

General procedure: In a flame-dried flask, *N*-alkyl-3-chloro-1,1,1-trifluoropropan-2-amine **4** (0.05 mol, 1 equiv.) was dissolved in dry THF (100 mL) under nitrogen atmosphere. The resulting mixture was then cooled to 0°C and LiHMDS (1.1 equiv., 1M in THF) was added dropwise *via* a syringe. After stirring at room temperature for 4 hours, the reaction mixture was quenched with a saturated solution of NH_4Cl (50 mL), extracted with EtOAc (3 x 25 mL) and washed with brine (3 x 25 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-alkyl-2-

(trifluoromethyl)aziridine **5**, which was purified by means of column chromatography on silicagel (hexane/EtOAc) to obtain an analytically pure sample.

1-(4-Chlorobenzyl)-2-(trifluoromethyl)aziridine 5b

Yellow oil. R_f = 0.28 (Petroleum ether/EtOAc 95/5). Yield 83%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (1H, d, *J* = 6.1 Hz), 2.09-2.17 (2H, m), 3.46 and 3.53 (2H, 2 × d, *J* = 13.8 Hz), 7.25-7.32 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 30.04, 37.40 (q, *J* = 39.2 Hz), 62.65, 123.98 (q, *J* = 272.3 Hz), 128.59, 129.24, 133.27, 135.92. ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -70.93 (3F, d, *J* = 5.3 Hz). IR (ATR, cm^{-1}): ν_{max} = 1492, 1284, 1138, 1088, 1016, 803. MS (70 eV): m/z (%): 236/8 (M^++1, 100). HRMS (ES) calcd for $C_{10}H_{10}ClF_3N$: 236.0454 $[M+H]^+$; Found: 236.0451.

1-(4-Methoxybenzyl)-2-(trifluoromethyl)aziridine 5c

Yellow oil. R_f = 0.25 (petroleum ether/EtOAc 95/5). Yield 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (1H, d, *J* = 5.5 Hz), 2.07-2.15 (2H, m), 3.44 and 3.50 (2H, 2 × d, *J* = 13.8 Hz), 3.78 (3H, s), 6.85-6.89 and 7.21-7.26 (4H, 2 × m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.83, 37.19 (q, *J* = 29.2 Hz), 55.24, 62.83, 113.93, 124.24 (q, *J* = 272.3 Hz), 129.32, 129.46, 159.16. ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -71.52 (3F, d, *J* = 4.0 Hz). IR (ATR, cm^{-1}): ν_{max} = 1613, 1513, 1284, 1243, 1135, 1032, 811. MS (70 eV): *m/z* (%): 232 (M^++1, 100). HRMS (ES) calcd for $C_{11}H_{13}F_3NO$: 232.0949 $[M+H]^+$; Found: 232.0953.

1-Octyl-2-(trifluoromethyl)aziridine 5d

Light-yellow oil. R_f = 0.29 (Petroleum ether/EtOAc 98/2). Yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85-0.90 (2H, m), 0.88 (3H, t, *J* = 6.3 Hz), 1.23-1.39 (8H, m), 1.50 (1H, d, *J* = 6.6 Hz), 1.54-1.61 (2H, m), 1.91-1.99 (1H, m), 2.07 (1H, d, *J* = 3.3 Hz), 2.16-2.25 and 2.38-2.47 (2H, 2 × m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 14.05, 22.62, 27.06, 29.15, 29.33, 29.44, 30.04 (d, *J* = 2.3 Hz), 31.78, 37.32 (q, *J* = 39.2 Hz), 60.59, 124.21 (q, *J* = 272.3 Hz).^{19}F NMR (282 MHz, $CDCl_3$): δ –71.16 (3F, d, *J* = 5.3 Hz). IR (ATR, cm^{-1}): ν_{max} = 1405, 1286, 1155, 1089, 700, 658. GC-MS (EI): m/z (%): 223 (M^+, 0.54); (M^+-CH_2CH_3, 8); (M^+-$(CH_2)_2CH_3$, 26); (M^+-$(CH_2)_4CH_3$, 34); (M^+-$CH_2)_6CH_3$, 100). HRMS (ES) calcd for $C_{11}H_{21}F_3N$: 224.1626 $[M+H]^+$; Found: 224.1626.

Synthesis of 2-benzylamino-3,3,3-trifluoropropyl acetate 6

In a 20 mL pressure vial, 1-alkyl-2-(trifluoromethyl)aziridine **5a** (0.5 mmol, 1 equiv.) and CH_3COOH (5 mmol, 5 equiv.) were dissolved in CH_2Cl_2 (3 mL), after which the reaction mixture was stirred for 7 days at 60°C. Afterwards, the reaction mixture was neutralised by means of a saturated solution of

$NaHCO_3$, poured into water (4 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation of the solvent afforded 2-benzylamino-3,3,3-trifluoropropyl acetate **6**, which was purified by means of column chromatography on silicagel (hexane/EtOAc) to obtain an analytically pure sample (25% yield, 33 mg)**.**

Light-yellow oil. R_f = 0.21 (Petroleum ether/EtOAc 90/10). Yield 25%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (1H, bs), 2.06 (3H, s), 3.29-3.39 (1H, m), 3.90 and 4.01 (4H, 2 × d, *J* = 13.2 Hz), 4.22 (1H, d × d, *J* = 12.1 Hz, 4.4 Hz), 4.29 (1H, d × d, *J* = 12.1 Hz, 5.5 Hz), 7.26-7.35 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.70, 51.66, 57.27 (q, *J* = 27.7 Hz), 61.12 (CH_2O), 125.70 (q, *J* = 283.8 Hz), 127.47, 128.20, 128.55, 139.06, 170.57. ^{19}F NMR (282 MHz, $CDCl_3$): δ -73.00 (3F, d, *J* = 6.6 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3359; ν_{CO} = 1745; ν_{max} =1226, 1133, 1047, 739, 698. MS (70 eV): m/z (%): 262 (M^++1, 100). HRMS (ES) calcd for $C_{12}H_{15}F_3NO_2$: 262.1055 $[M+H]^+$; Found: 262.1047.

Synthesis of *N*-alkyl-*N*-benzyl-1,1,1-trifluoro-3-iodopropan-2-amines 7a-c

General procedure: A mixture of 1-alkyl-2-(trifluoromethyl)aziridine **5** (6 mmol, 1 equiv.) and benzyl iodide[19] (6 mmol, 1 equiv.) was heated at 100°C under neat conditions for 24 h, affording β-iodo amine **7** in 72-88% yield. This compound was purified by recrystallisation from absolute EtOH or by means of column chromatography on silicagel (hexane) to obtain an analytically pure sample.

***N*,*N*-Dibenzyl-1,1,1-trifluoro-3-iodopropan-2-amine 7a**

White crystals. Recrystallisation from absolute EtOH; Mp = 94.8°C. Yield 32%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30-3.46 (3H, m), 3.72 and 3.99 (4H, 2 × d, *J* = 13.2 Hz), 7.25-7.37 and 7.44-7.47 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ -2.92, 53.96, 60.43 (q, *J* = 25.4 Hz), 125.56 (q, *J* = 294.2 Hz), 127.52, 128.36 and 129.45, 137.79. ^{19}F NMR (282 MHz, $CDCl_3$): δ -67.14 (3F, d, *J* = 7.9 Hz). IR (ATR, cm^{-1}): ν_{max} = 1238, 1144, 1109, 1090, 748, 697. MS (70 eV): m/z (%): 420 (M^++1, 100). HRMS (ES) calcd for $C_{17}H_{18}F_3IN$: 420.0436 $[M+H]^+$; Found: 420.0414.

***N*-Benzyl-*N*-(4-chlorobenzyl)-1,1,1-trifluoro-3-iodopropan-2-amine 7b**

White crystals. Recrystallisation from absolute EtOH; Mp = 70.3°C. Yield 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.26-3.45 (3H, m), 3.70 and 3.95 (2H, 2 × d, *J* = 13.2 Hz), 3.70 and 3.97 (2H, 2 × d, *J* = 13.8 Hz), 7-27-7.44 and 7.44-7.47 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ -3.00, 53.35, 54.02, 60.58 (q, *J* = 25.4 Hz), 125.44 (q, *J* = 293.1 Hz), 127.64, 128.42, 128.53, 129.46, 130.76, 133.28, 136.34, 137.55. ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -67.88 (3F, d, *J* = 7.9 Hz). IR (ATR, cm^{-1}): ν_{max} = 2852, 1490, 1260,

1235, 1164, 1144, 1088, 1100, 1074, 695. MS (70 eV): m/z (%): 454/6 (M^++1, 100). HRMS (ES) calcd for $C_{17}H_{17}ClF_3IN$: 454.0046 $[M+H]^+$; Found: 454.0055.

***N*-Benzyl-1,1,1-trifluoro-3-iodo-*N*-(4-methoxybenzyl)propan-2-amine 7c**

Light-yellow oil. R_f = 0.29 (Petroleum ether/EtOAc 98/2). Yield 34%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30-3.45 (3H, m), 3.81 (3H, s), 3.65 and 3.98 (2H, 2 × d, *J* = 13.2 Hz), 3.69 and 3.92 (2H, 2 × d, *J* = 13.8 Hz), 6.86-6.89, 7-25-7.36 and 7.44-7.47 (9H, 3 × m). ^{13}C NMR (75 MHz, $CDCl_3$): δ -2.72, 53.38, 53.67, 55.22, 60.28 (q, *J* = 25.4 Hz), 113.70, 125.56 (q, *J* = 293.1 Hz), 127.46, 128.36, 129.38, 129.67, 130.69, 138.02, 159.02. ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -67.76 (3F, d, *J* = 7.9 Hz). IR (ATR, cm^{-1}): ν_{max} = 1511, 1241, 1164, 1143, 1105, 1036, 738, 698. MS (70 eV): m/z (%): 450 (M^++1, 100). HRMS (ES) calcd for $C_{18}H_{20}F_3INO$: 450.0542 $[M+H]^+$; Found: 450.0539.

Synthesis of *N*-alkyl-1,1,1-trifluoro-3-iodo-*N*-methylpropan-2-amines 7d-e

General procedure: In a 20 mL pressure vial, 1-alkyl-2-(trifluoromethyl)aziridine **5** (2 mmol, 1 equiv.) and MeI (2 mmol, 1 equiv.) were dissolved in acetonitrile (6 mL). After stirring for 3 days at 100°C, the solvent was removed *in vacuo*, affording *N*-alkyl-1,1,1-trifluoro-3-iodo-*N*-methylpropan-2-amine **7**, which was purified by means of column chromatography on silicagel (hexane) to obtain an analytically pure sample.

***N*-Benzyl-1,1,1-trifluoro-3-iodo-*N*-methylpropan-2-amine 7d**

Light-yellow oil. R_f = 0.34 (Hexane). Yield 12%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (3H, s), 3.28-3.48 (3H, m), 3.85 and 3.96 (2H, 2 x d, *J* = 13.8 Hz), 7.24-7.46 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ -1.72, 35.78, 59.37, 66.29 (q, *J* = 25.4 Hz), 125.26 (q, *J* = 295.4 Hz), 127.41, 128.42, 128.86, 138.66. ^{19}F NMR (282 MHz, $CDCl_3$): δ -68.55 (3F, d, *J* = 7.9 Hz). IR (ATR, cm^{-1}): ν_{max} = 1712, 1454, 1251, 1163, 1105, 1075, 734, 698. MS (70 eV): m/z (%): 344 (M^++1, 20). HRMS (ES) calcd for $C_{11}H_{14}F_3IN$: 344.0123 $[M+H]^+$; Found: 344.0106.

***N*-(4-Chlorobenzyl)-1,1,1-trifluoro-3-iodo-*N*-methylpropan-2-amine 7e**

Yellow oil. R_f = 0.34 (Hexane). Yield 10%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (3H, s), 3.26-3.44 (3H, m), 3.81 and 3.92 (2H, 2 × d, *J* = 13.8 Hz), 7.30 and 7.39 (4H, 2 × d, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ -1.80, 35.58, 58.63, 66.25 (q, *J* = 25.8 Hz), 125.15 (q, *J* = 293.1 Hz), 128.51, 130.04, 133.01, 137.09. ^{19}F NMR (282 MHz, $CDCl_3$): δ -68.01 (3F, d, *J* = 6.6 Hz). IR (ATR, cm^{-1}): ν_{max} = 1490, 1321, 1252, 1163, 1104,

1076, 1014, 837, 804. MS (70 eV): m/z (%): 378/80 (M^++1, 45). HRMS (ES) calcd for $C_{11}H_{13}ClF_3IN$: 377.9733 $[M+H]^+$; Found: 377.9724.

Synthesis of *N,N*-dialkyl-1,1,1-trifluoro-3-phenylpropan-2-amines 8

A suspension of CuI (3 mmol, 3 equiv.) in dry Et_2O was cooled to -78°C and PhLi (6 equiv., 1.8 M in dibutyl ether) was slowly added to the solution under nitrogen atmosphere *via* a syringe. After stirring for 30 min at -78°C, a solution of *N*-benzyl-1,1,1-trifluoro-3-iodopropan-2-amine **7** (1 mmol) in dry Et_2O was added at -78°C, and the resulting suspension was further stirred for 5 hours at room temperature. Afterwards, the reaction mixture was quenched with a saturated solution of NH_4Cl (10 mL), filtered through a pad of Celite® and washed with Et_2O (2 x 10 mL). The filtrate was poured into H_2O (15 mL), extracted with Et_2O (3 x 10 mL), and the combined organic layers were washed with a saturated solution of NH_4Cl (15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent under reduced pressure afforded *N,N*-dialkyl-1,1,1-trifluoro-3-phenylpropan-2-amine **9**, which was purified by means of column chromatography on silica gel (hexane) in order to obtain an analytically pure sample.

***N,N*-Dibenzyl-1,1,1-trifluoro-3-phenylpropan-2-amine 8a**

Colourless oil. R_f = 0.30 (Hexane). Yield: 48%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.96-2.99 (2H, m), 3.42-3.56 (1H, m), 3.73 and 3.88 (4H, 2 × d, *J* = 13.8 Hz), 6.59-6.63 (2H, m), 6.96-7.48 (13H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 32.52, 53.85, 59.86 (q, *J* = 24.6 Hz), 126.55, 127.06, 127.38, 127.61 (q, *J* = 281.9 Hz), 128.22, 128.74, 129.51, 138.55, 140.91. ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -68.52 (3F, d, *J* = 7.9 Hz). IR (ATR, cm^{-1}): ν_{max}= 1454, 1247, 1165, 1140, 1101, 744, 697. MS (70 eV): *m/z* (%): 370 (M^+ +1, 100). HRMS (ES) calcd for $C_{23}H_{23}F_3N$: 370.1783 $[M+H]^+$; Found: 370.1779.

***N*-Benzyl-*N*-(4-chlorobenzyl)-1,1,1-trifluoro-3-phenylpropan-2-amine 8b**

Colourless oil. R_f = 0.25 (Hexane). Yield: 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.90-3.01 (2H, m), 3.39-3.52 (1H, m), 3.68 and 3.81 (2H, 2 × d, *J* = 13.8 Hz), 3.71 and 3.87 (2H, 2 × d, *J* = 13.8 Hz), 6.93-7.41 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.52, 53.25, 53.83, 59.99 (q, *J* = 24.6 Hz), 127.24, 127.58 (q, *J* = 291.1 Hz), 127.84, 128.31, 128.37, 128.77, 129.49, 130.02, 130.59, 137.09, 137.34, 138.31. ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -68.62 (3F, d, *J* = 7.9 Hz). IR (ATR, cm^{-1}): ν_{max}= 1491, 1455, 1247, 1141, 1097, 747, 698. MS (70 eV): *m/z* (%): 404/6 (M^+ +1, 100). HRMS (ES) calcd for $C_{23}H_{22}ClF3N$: 404.1393 $[M+H]^+$; Found: 404.1389.

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