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Thermocontrolled benzylimine–benzaldimine rearrangement over Nafion-H catalysts for efficient entry into α-trifluoromethylbenzylamines

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ABSTRACT

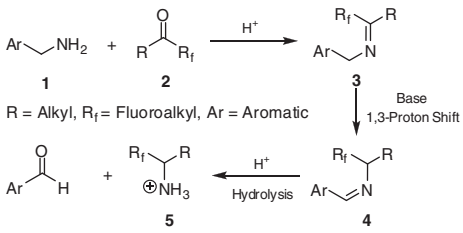
Nafion-H and Nafion SAC-13 are efficient solid Brønsted acid catalysts for the preparation of trifluoromethyl ketimines from benzylamines and trifluoromethylated ketones in high yields. A finely tuned benzylimine–benzaldimine rearrangement by facile 1,3-hydrogen shift has been achieved for the formation of fluorinated benzaldimines in high yields by careful optimization of reaction conditions including attempts under microwave conditions and a flow system. These α-trifluoromethylated benzaldimines are efficient precursors for pharmaceutically important α-trifluoromethylated benzylamines, accessed through their direct acid hydrolysis.

1. Introduction

Fluorinated bioactive molecules have garnered much attention in recent years due to the unique properties imparted by fluorine substitution.[1] In particular, α-trifluoromethylated amino compounds have become popular and indispensable building blocks in the synthesis and design of fungicides, pesticides, insecticides, selective antibacterial agents, enzyme inhibitors, and enzyme receptor antagonists or agonists.[2] Much of the interest associated with these precursors derives from the fact that α-trifluoromethylated amines may act as efficient isosteres to the carbonyl groups of amide bonds.[3] Trifluoromethyl substitution in bioactive amino compounds is a popular strategy to lower the basicity of the neighboring amino group and in turn, enhance the lipophilicity and metabolic stability of the parent C–H analog.[4] It increases their bioavailabilities by increasing their ability to cross membranes. It comes as no surprise that there have been a number of reported synthetic routes to these compounds.

One of the most commonly exploited methods is the reductive amination of trifluoromethylated carbonyl compounds usually through the use of chiral metal catalysts.[5] Other well known methods however, include the nucleophilic alkylation of trifluoromethyl imines,[6] various reductions, or ring opening reactions of fluorinated 1,2-oxazolidines[7] and nucleophilic additions of $TMSCF_3$ to nitrones and imines.[8] Within the last decade however, much of the synthetic work in this area has been focused on the base-catalyzed isomerization of trifluoromethylated imines pioneered by Soloshonok and co-workers.[9] Since more C–H acidic imine product is thermodynamically favored, the so called 'biomimetic reductive amination' approach exploits the electron withdrawing nature of the α-trifluoromethyl group that favors the irreversible formation of substituted benzaldimines **4** instead of benzylimines **3** from benzylamines **1** (Scheme 1).[10]

The reaction leads to the formation of a more stable imine and has even been shown to occur without the use of catalysts though only at higher temperatures.[11] The Schiff bases that result from such reactions can later be hydrolyzed under mildly acidic conditions to yield trifluoromethylated amines.[3a,b] However, while this is an important and elegant discovery, the methodology still



Scheme 1. Biomimetic reductive amination.

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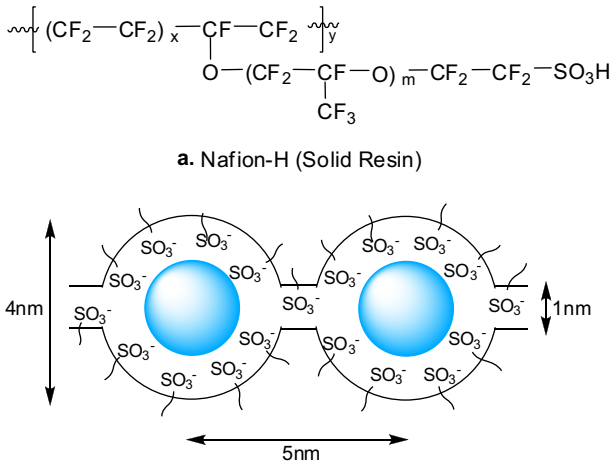


a. Nafion-H (Solid Resin)

b. Cluster Network-Model

Figure 1. Structure of Nafion®.

suffers significantly from several drawbacks, the most serious of which is its multi-step approach. Considerable improvement of this process has been achieved by various modifications including those with substrates and reaction conditions.[12]

The synthesis of trifluoromethylated imines as starting materials is not a trivial process and it was the focus of recent work in developing noticeably improved conditions.[13a] Afterward, the use of a base such as triethylamine during the second step requires careful neutralization and purification.[13b] Therefore, a need for cleaner and more efficient routes to these valuable products has emerged. Our attempts to improve the practical application of the biomimetic route to trifluoromethylated amines began by attempting to improve the way in which trifluoromethylated imines are synthesized.

2. Results and discussion

Most trifluoromethylated imines, as previously indicated, are synthesized through reactions catalyzed by acids such as *p*-toluenesulfonic acid. Therefore, we attempted to improve this process by instead choosing Nafion-H, a solid supported perfluoroalkanesulfonic acid resin as the Brønsted acid catalyst. Nafion® resins were first developed by Dupont and their remarkable properties led to their vast application as electrolyte membranes for electrochemical cells.[14] The acidic form, Nafion-H was prepared from its potassium salt by proton exchange and its application as an efficient solid acid catalyst in a wide range of organic reactions such as alkylations, acylations, nitrations, sulfonations, and isomerizations has been studied extensively by Olah and co-workers.[15] In chemical reactions, Nafion-H remains thermally stable up to 210 °C, chemically inert to many side reactions and can be easily recovered and recycled.[15,16]

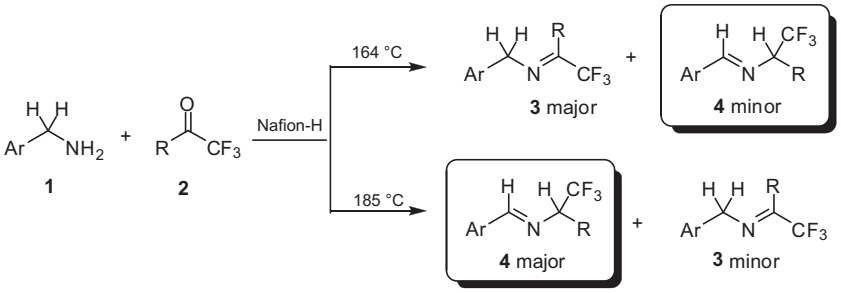
Nafion® is formed by the copolymerization of a perfluorinated vinyl ether comonomer possessing a sulfonated terminus with tetrafluoroethylene (TFE). Within the polymer's superstructure, the sulfonate groups tend to form aggregates or clusters creating channels through which cations can freely travel and it is this characteristic property that gives the polymer its high proton conductivity (Fig. 1).[17] These channels also play an important role in the remarkable acidic characteristics of Nafion®. In its acid form, the presence of so many electron withdrawing fluorine atoms within the polymer's backbone makes the acidity of Nafion-H comparable to that of concentrated sulfuric acid and in effect a solid superacid. At the same time, because the acid sites lie buried within the superstructure, bulk acidification of the solvent can largely be avoided.

The broad range of reactions catalyzed by Nafion-H not only demonstrates the efficacy and synthetic versatility of the polymer as a catalyst, but its many environmental benefits as well. Products of these reactions can simply be filtered from the polymer and isolated without the excessive use of hazardous solvents while, because of its high stability, the used polymer can be recovered, cleaned, and regenerated for recycling. Thus, instead of using a soluble organic Brønsted acid catalyst such as *p*-toluenesulfonic acid or trifluoromethanesulfonic acid, Nafion-H could be used as an effective catalyst for many reactions including imine synthesis that requires both strong acidities and higher temperatures.

During the course of our experiments toward the synthesis of trifluoromethylated imines using Nafion-H, we found that reactions between aniline derivatives and trifluoromethylated ketones do in fact produce imines in quantitative yields. Surprisingly however, when the reaction was extended to benzylamines, the corresponding fluorinated imines were obtained along with a small amount of trifluoromethylated benzaldimines; the products identical to the ones obtained by the biomimetic 1,3-H shift mechanism. Further investigation revealed that a simple elevation in reaction temperature resulted in a significant enhancement in the yield of benzylidene-1-phenyl-2,2,2-trifluoroethylamine (**4**, Scheme 2). The reaction was carefully monitored at different conditions and the most suitable one for maximum conversion to the rearranged product with the least side reaction was found.

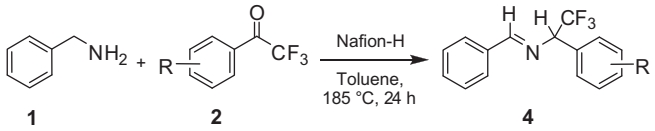
It is known that the presence of electron withdrawing groups in ketones dramatically increases their electrophilicity. Thus, despite the presence of a trifluoromethyl group in the substrate, the addition of another fluorine atom or a CF_3 group in the aryl ring also helps to significantly enhance the electrophilicity of the ketones and ultimately the reaction yields as reported earlier[18] (Table 1, entries 2, 4 and 7). Though we generally found high boiling solvents best suited to this methodology, the amount of solvent used in each reaction initially proved crucial. An excess of the solvent (toluene), led to a mixture of both the imines while a minimal amount (1 mL of toluene per mmol of the substrate) predominantly led to the formation of benzaldimine as the major product.

The aggregate-cluster model of Nafion-H (Fig. 1b) ensures, as mentioned, that acid sites are only found within the sub-structure of the catalyst's pockets and not throughout the solvent solution as

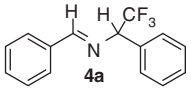
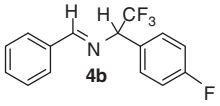
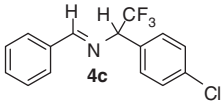
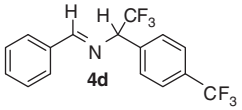
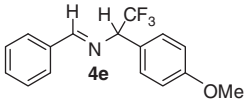
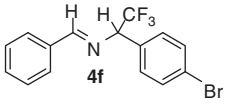
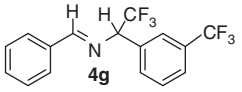


Scheme 2. Thermocontrolled synthesis of trifluoromethylated benzylimines and benzaldimines from trifluoromethylketones and benzylamines.

Table 1
Formation of trifluoromethylated benzylimines and their isomerization to benzaldimines catalyzed by Nafion-H



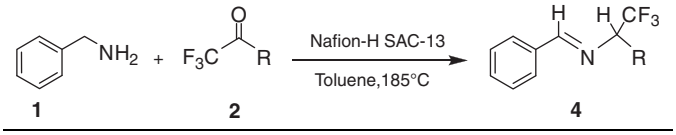
1 2 4

Entry	R	Product (**4**)	Yield (%)
1	H	 **4a**	54
2	4-F	 **4b**	68
3	4-Cl	 **4c**	36
4	4-CF_3	 **4d**	62
5	4-OMe	 **4e**	55
6	4-Br	 **4f**	58
7	3-CF_3	 **4g**	64

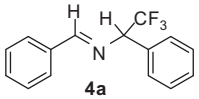
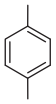
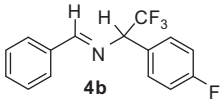
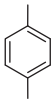
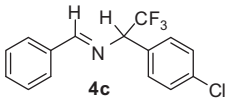
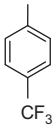
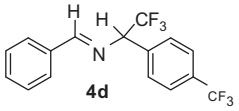
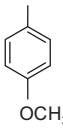
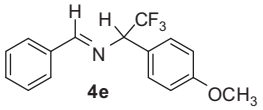
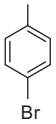
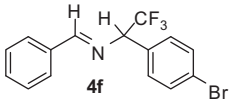
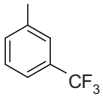
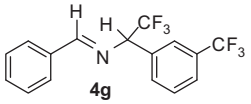
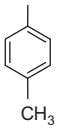
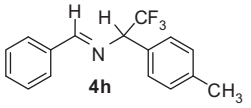
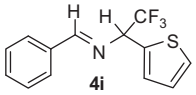
with other acids (so called high dilution effect). The present reaction therefore requires a higher concentration of the reaction mixture so that dilution effects can be minimized as more reactants are forced into the proximity of acid sites in the catalyst. Beyond the issue of access to the acid sites, inconsistencies in Nafion-H catalyzed reactions observed in some cases can be due to inconsistencies in the distribution and arrangement of reactants in these cluster pockets.

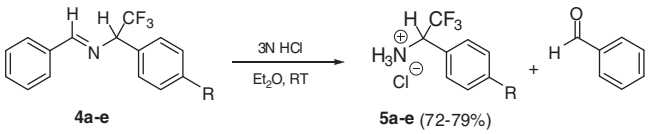
In order to have greater accessibility to more acid sites and further improve and enhance the reaction conditions, we examined Nafion-H SAC-13, a catalyst derived from Nafion-H with a varied morphology and its synthetic potential in the present protocol has also been explored. First reported by Harmer and coworkers in 1996, Nafion-H SAC-13 is a silica supported form of the solid Nafion-H.[19,20] By immobilizing Nafion-H on a silica matrix, Harmer and his group found that the surface area of the catalyst could be improved almost tenfold. This provides for greater accessibility to acidic sites and, in our experiments, further yield improvements and even greater selectivity. We found in fact, that using Nafion-H SAC-13 led to the formation of trifluoromethylated benzaldimines cleanly and, in some cases, as the sole product making purification rather easier. When the reaction has been expanded to a variety of trifluoromethylated acetophenones, the corresponding trifluoromethylated benzaldimines were obtained in good to excellent yields (Table 2)[21] further establishing the profound catalytic effect of Nafion-H SAC-13 on this reaction. The reactions carried out using both the unsubstituted and 4-fluoro substituted 1,1,1-trifluoroacetophenone in the absence of catalyst resulted in much lower

Table 2
Synthesis of trifluoromethylated benzylimines and their isomerization to benzaldimines using Nafion-H SAC-13



1 2 4

Entry	R	Time (h)	Product (**4a–i**)	Yield (%)
1		24	 **4a**	82
2	 F	24	 **4b**	80
3	 Cl	24	 **4c**	94
4	 CF_3	24	 **4d**	73
5	 OCH_3	48	 **4e**	83
6	 Br	24	 **4f**	66
7		24	 **4g**	92
8	 CH_3	48	 **4h**	71
9		48	 **4i**	50



4a-e
R = H, F, Cl, CF_3, OCH_3

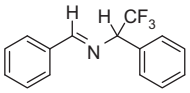
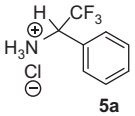
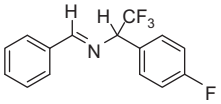
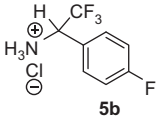
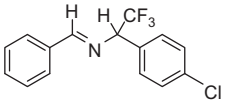
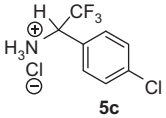
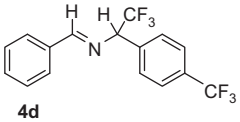
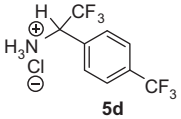
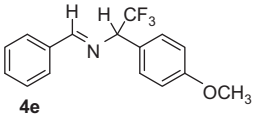
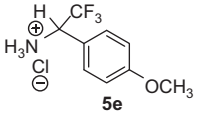
5a-e (72-79%)

Scheme 3. Hydrolysis of trifluoromethylated benzaldimines (**4a–e**) to 1,1,1-trifluoro-2-phenylethylamines (**5a–e**).

yields (47%, 56%, respectively) of the benzaldimine product further manifesting the influence of the catalyst.

Nafion-H based acids promote thermocontrolled chemoselectivity in these reactions. Interestingly, 1,3-proton shift was shown to occur under simple thermal conditions and we were able to

Table 3
1,1,1-Trifluoro-2-phenylethylamines (**5a**–**e**) obtained by the hydrolysis of trifluoromethylated benzaldimines (**4a**–**e**)

Entry	Benzaldimines (**4a**–**e**)	1,1,1-Trifluoro-2-phenylethylamines (**5a**–**e**)	Yield (%)
1	 **4a**	 **5a**	77
2	 **4b**	 **5b**	74
3	 **4c**	 **5c**	79
4	 **4d**	 **5d**	77
5	 **4e**	 **5e**	72

detect the presence of benzaldimine products at temperatures well below 185 °C. As the reaction mixtures were heated from room temperature, we were able to observe the initial formation of the imine **3** and its subsequent conversion to the rearranged isomer by ^{19}F NMR spectroscopy. After carefully monitoring the formation of the ketimine and its rearrangement to the benzaldimine at various stages of the reaction, it became evident that the rate-determining step in the reaction is the initial imine formation.

Substituent-effects in these reactions could, once again, be clearly observed as electron deficient acetophenones generally reacted faster than the electron rich ones. However, even in instances where the use of longer reaction time was required, reactions still went essentially to completion with good yields. Afterward, the isolated products may be further converted into the synthetically valuable, fluorinated benzylamines by previously established mineral acid hydrolysis (Scheme 3). This particular transformation was carried out on a selected number of trifluoromethylated benzaldimines and the corresponding benzylamine hydrochloride salts were obtained in good yields (Table 3).

As observed from the enhancement of yield and selectivity of the benzaldimines upon change in solid acid morphology (Nafion-H to Nafion-H SAC 13), the role of the acid catalyst and accessibility of more acidic sites is further manifested. Thus elevated heating may serve to merely ensure reaction completion in a more timely fashion.

3. Conclusion

In conclusion, Nafion-H and its silica supported form (Nafion-H SAC 13) act as effective Brønsted acid catalysts in the one-pot synthesis of trifluoromethylated benzaldimines from trifluoromethylated ketones and benzylamines. Easy separation of the catalysts and purification of the products in good yields as well as general applicability to a variety of ketones and benzylamines are the main features of the reaction. The products are used as important precursors for trifluoromethylated benzylamines and efficient synthons in the design of many fluorinated amino compounds in the pharmaceutical and industrial arena.

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21. *Typical procedure for the synthesis of substituted imines:* A solution of 2,2,2-trifluoroacetophenone **2a** (2 mmol, 0.348 g) in toluene (1 mL) was taken in a pressure tube containing 0.10 g of Nafion-H SAC 13. To this mixture, a solution of benzylamine (**1a**, 3 mmol, 0.321 g) in toluene (1 mL) was slowly added with stirring. The mixture was supplemented with another 1 mL of toluene, closed and heated slowly to 185 °C. The reaction was then monitored by ^{19}F NMR and GC–MS. Upon completion, the mixture was allowed to cool to room temperature, 50 mL of dichloromethane was added and the mixture was filtered. The filtrate was then concentrated under vacuum and purified by flash column chromatography using a mixture of *n*-hexane and ethyl acetate (9:1). The solvent was removed in a rotary evaporator and the product benzylidene-1-phenyl-2,2,2-trifluoroethylamine 4a, was obtained as a pale yellow oil (0.432 g, 82%).

Typical procedure for the hydrolysis of substituted imines: Benzylidene-1-phenyl-2,2,2-trifluoroethylamine **4a** (1 mmol, 0.2723 g) was first dissolved in 2 mL of diethyl ether and placed in a small vial. Hydrochloric acid (3 N, 5 mL) was slowly added after which the vial was closed and stirred for 24 h. Upon completion (as determined by TLC) the reaction mixture was added to ice water (10 mL) and then washed with diethyl ether (2 × 30 mL). The excess acid was removed by adding aqueous sodium hydroxide (3 N) till the solution turned slightly basic. The solution was the concentrated under vacuum to obtain the hydrochloride salt of 2,2,2-trifluoro-1-phenylethylamine **5a**. All products were characterized by spectral analysis and by comparing the spectral data (for known compounds) with those of the authentic samples products.[5a,6b,10]

Spectral data of benzylidene-1-(phenyl)-2,2,2-trifluoroethyl-amine (**4a**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (q, 1H, J = 7.63 Hz), 7.349–7.47 (m, 6H), 7.56 (d, 2H, J = 7.50 Hz), 7.83 (dd, 2H, J_1 = 1.70 Hz, J_2 = 7.90 Hz), 8.37 (s, 1H); ^{13}C NMR (1 00 MHz, $CDCl_3$): δ 75.07 (q, J = 28.23 Hz), 124.67 (q, J = 280.76 Hz), 128.57, 128.65, 128.79, 128.91, 128.98, 131.66, 134.98, 135.31, 165.81; ^{19}F NMR (376.1 MHz, $CFCl_3$): δ −74.35 (d, 3F, J = 7.63 Hz).

Benzylidene-1-(4-fluorophenyl)-2,2,2-trifluoroethylamine (**4b**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.82 (q, 1H, J = 7.50 Hz), 7.12 (t, 2H, J = 8.70 Hz), 7.48 (m, 3H), 7.59 (dd, 2H, J = 5.60 Hz, J = 8.6 Hz), 7.88 (dd, 2H, J_1 = 1.50 Hz, J_2 = 8.00 Hz), 8.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.37 (q, J = 28.60 Hz), 115.55 (d, J = 21.6 Hz), 124.50 (q, J = 280.60 Hz), 128.70, 128.81, 130.46 (d, 1H, J = 8.2 Hz), 130.79, 131.79, 135.18, 163.00 (d, J = 247.70 Hz), 166.02; ^{19}F NMR (376.1 MHz, $CFCl_3$): δ −113.29 (d, 1F, J = 9.16 Hz), -74.63 (d, 3F, J = 7.63 Hz); HRMS (EI) for: $C_{15}H_{11}F_4N$ calcd 281.0828, found 281.0813.

Benzylidene-1-(4-chlorophenyl)-2,2,2-trifluoroethylamine (**4c**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (q, 1H, J = 7.40 Hz), 7.41 (m, 7H), 7.82 (dd, 2H, J_1 = 1.60 Hz, J_2 = 8.00 Hz), 8.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.56 (q, J = 28.60 Hz), 124.51 (d, J = 281.20 Hz), 128.85, 128.94, 128.97, 130.22, 131.99, 133.55, 135.04, 135.25, 166.30; ^{19}F NMR (376.1 MHz, $CFCl_3$): δ −74.51 (d, 3F, J = 7.63 Hz); HRMS (EI) for: $C_{15}H_{11}ClF_3N$ calcd 297.0532, found 297.0520.

Benzylidene-1-(4-trifluoromethylphenyl)-2,2,2-trifluoroethyl-amine (**4d**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (q, 1H, J = 7.40 Hz), 7.47 (m, 3H), 7.68 (dd, 4H, J_1 = 8.30 Hz, J_2 = 25.50 Hz), 7.84 (dd, 2H, J_1 = 1.50 Hz, J_2 = 8.00 Hz), 8.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.71 (q, J = 28.80 Hz), 123.89 (q, J = 272.30 Hz), 124.14 (q, J = 261.40 Hz), 125.48, 125.52, 128.74, 128.87, 129.21, 131.11 (q, J = 32.50 Hz), 131.97, 134.99, 138.77, 166.52; ^{19}F NMR (376.1 MHz, $CFCl_3$): δ −63.25 (s, 3F), −74.29 (d, 3F, J = 7.60 Hz).

Benzylidene-1-(4-methoxyphenyl)-2,2,2-trifluoroethylamine (**4e**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 4.75 (q, 1H, J = 7.70 Hz), 6.92 (d, 2H, J = 8.90 Hz), 7.44 (m, 5H), 7.83 (dd, 2H, J_1 = 1.60 Hz, J_2 = 8.00 Hz), 8.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 55.29, 74.45 (q, J = 28.50 Hz), 113.98, 124.75 (q, J = 280.80 Hz), 127.09, 128.66, 128.77, 129.91, 131.61, 135.39, 159.97, 165.54; ^{19}F NMR (376.1 MHz, $CFCl_3$): δ −74.68 (d, 3F, J = 7.63 Hz); HRMS (EI) for: $C_{16}H_{14}F_3NO$ calcd 293.1027, found 293.1034.

Benzylidene-1-(4-bromophenyl)-2,2,2-trifluoroethylamine (**4f**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 (q, 1H, J = 7.40 Hz), 7.46 (m, 7H), 7.82 (dd, 2H, J_1 = 1.60 Hz, J_2 = 8.10 Hz), 8.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.46 (q, J = 28.60 Hz), 123.11, 124.28 (q, J = 283.60 Hz), 128.70, 128.82, 130.38, 131.74, 131.84, 133.91, 135.08, 166.20; ^{19}F NMR (376.1 MHz, $CFCl_3$): δ −74.51 (d, 3F, J = 7.63 Hz); HRMS (EI) for: $C_{15}H_{11}BrF_3N$ calcd 341.0027, found 341.0026.

Benzylidene-1-(p-tolyl)-2,2,2-trifluoroethylamine (**4g**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 4.74 (q, 1H, J = 7.60 Hz), 7.17 (d, 2H, J = 7.90 Hz), 7.39 (m, 5H), 7.80 (dd, 2H, J_1 = 1.60 Hz, J_2 = 7.90 Hz), 8.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.26, 74.77 (q, J = 28.40 Hz), 124.92 (q, J = 280.80 Hz), 128.75, 128.87, 129.42, 131.71, 132.17, 135.50, 138.91, 165.76; ^{19}F NMR (376.1 MHz, $CFCl_3$): δ −74.38 (d, 3F, J = 7.63 Hz); HRMS (EI) for: $C_{16}H_{14}F_3N$ calcd 277.1078, found 277.1082.

Benzylidene-1-(3-trifluoromethylphenyl)-2,2,2-trifluoroethyl-amine (**4h**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.83 (q, 1H, J = 7.40 Hz), 7.46 (m, 4H), 7.62 (d, 1H, J = 7.80 Hz), 7.78 (d, 1H, J = 7.70 Hz), 7.85 (m, 3H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.96 (q, J = 28.70 Hz), 124.09 (q, J = 272.30 Hz), 124.38 (q, J = 269.20 Hz), 125.80 (m), 125.97 (q, J = 3.70 Hz), 128.91, 129.07, 129.27, 131.16 (q, J = 32.51 Hz), 132.34, 132.49, 135.17, 136.09, 166.76; ^{19}F NMR (376.1 MHz, $CFCl_3$): δ −69.10 (s, 3F), -74.45 (d, 3F, J = 7.40 Hz); HRMS (EI) for: $C_{16}H_{11}F_6N$ calcd 331.0796, found 331.0790.

Benzylidene-1-(2-thiophenyl)-2,2,2-trifluoroethylamine (**4i**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (q, 1H, J = 7.20 Hz), 7.04 (dd, 1H, J_1 =3.60 Hz, J_2 = 5.10 Hz), 7.19 (d, 1H, J = 3.60 Hz), 7.35 (dd, 1H, J_1 = 1.20 Hz, J_2 = 5.10 Hz), 7.45 (m, 3H), 7.83 (dd, 2H, J_1 = 1.50 Hz, J_2 = 8.10 Hz), 8.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.59 (q, J = 30.00 Hz), 123.98 (q, J = 280.80 Hz), 126.66, 126.74, 126.93, 128.68, 128.89, 131.88, 134.98, 136.26, 166.34; ^{19}F NMR (376.1 MHz, $CFCl_3$): δ −74.95 (d, 3F, J = 7.63 Hz); HRMS (EI) for: $C_{13}H_{10}F_3NS$ calcd 269.0486, found 269.0480.