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Nucleophilic difluoroalkylation of benzophenones, benzaldehydes and Schiff's bases by tetrafluoroethyl ether and difluoroacetamide

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ABSTRACT

From gem-difluoromethyl group of 1,1,2,2-tetrafluoroethyl ether and 2,2-difluoroalkylamide, proton can be removed by potassium bis(trimethylsilyl)amide in DMF, THF or toluene. The generated nucleophiles are then condensed with benzophenones, benzaldehydes or Schiff's bases to provide new fluorinated alcohols and amines. Some interesting solvent effects are also observed.

1. Introduction

Fluorine substitution often brings about unique changes in the property of the parent molecule when placed in appropriate positions. This is also true for perfluoroalkyl bearing compounds, the most important being trifluoromethyl group [1]. Such a profound improvement in the desired property is often attributed to their increased lipophilic character, lower surface tension, higher rigidity and electro negativity [2]. No wonder, many organofluorine compounds find increasing application as agrochemicals, drugs, surface active agents and materials for electronics because of these distinct properties. At present there is a lot of focus on fluorine containing bioactive compounds and the current estimate is that about 30% of newly introduced agrochemicals and 10% of 'block buster' drugs bear one or more fluorine atoms [3].

Carbon–carbon bond formation through C–H functionalization is central to synthetic organic chemistry for it provides atom economy in many synthetic sequences compared to the use of organometallics or metal mediated coupling reactions [4]. Moreover base catalyzed C–H functionalization is often preferred over use of organometallics for upscaling because less toxic effluent is generated in the former process. In the field of organofluorine chemistry also such a trend is but expected. For example, there had been continued attempts to functionalize C–H bond of fluoroform (CHF_3), as it is the cheapest raw material for the introduction of CF_3 anion in nucleophilic trifluoromethylation reaction. This method is an attractive option because CHF_3 is abundantly available as a by-product during the commercial production of difluorochloromethane, a standard raw material for Teflon production. However fluoroform as a precursor to CF_3 anion is beset with a few drawbacks. For example it is a greenhouse gas with subzero boiling point and is prone to decomposition in the presence of a base or upon conversion to an organometallic like CF_3Li through alpha elimination to give difluorocarbene [5]. Moreover, in spite of three electronegative fluorine atoms attached to the same carbon atom its p*K*a is rather high [6] compared to $CHCl_3$ and therefore requires very strong bases for deprotonation [7]. For these reasons, initial attempts to functionalize fluoroform through proton abstraction were not a great success. Electrochemical methods were explored to couple fluoroform with a good number of electrophiles but adaptability of the reaction condition in an organic chemistry laboratory is difficult and requires special equipment [8]. It was a great advancement when Russel and Roques demonstrated for the first time that common bases such as KH or *t*-BuOK could bring about deprotonation of CHF_3 and subsequent reaction with carbonyl compounds in good to excellent yields provided dimethylformamide (DMF) is used as a solvent [7c]. The pivotal role of DMF

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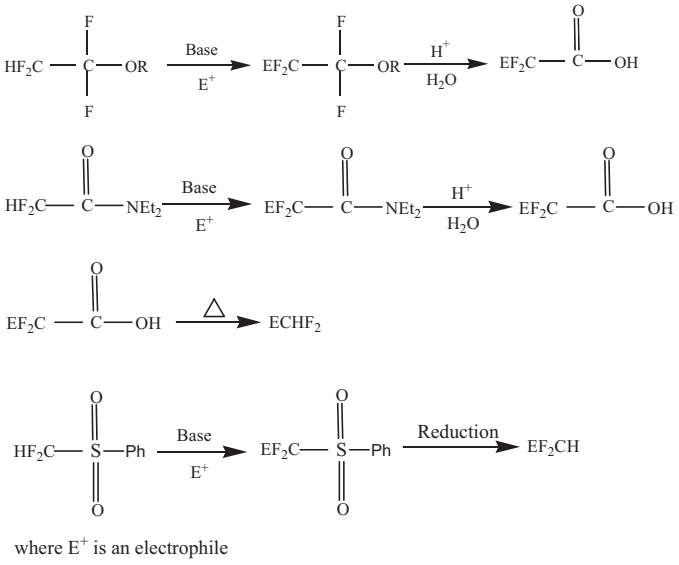
as a mediator in the above reaction was unequivocally demonstrated by the isolation of an intermediate [7a,9]. For well over 10 years DMF was considered an essential reservoir for CF_3 anion as the latter was thought to be unstable in the absence of DMF. However Prakash and coworkers dispelled this myth [10]. They found that fluoroform can be utilized for addition of $CF_3^{(-)}$ to B, C, Si and S electrophiles in common organic solvents such as THF or toluene [11].

Similar to trifluoromethyl function, difluoromethyl group (CHF_2) also brings about profound changes in the biological properties of the parent molecules. CHF_2 is considered to be isosteric and isopolar to the hydroxyl group and can involve in hydrogen bonding as a hydrogen donor [12]. This is exemplified by the recently introduced commercial agro chemicals and pharmaceuticals which bear this functionality [13]. Introduction of CHF_2 through deprotonation of CH_2F_2 is extremely difficult since CH_2F_2 is not sufficiently acidic [14]. The best way to accomplish this is to activate CH_2F_2 by an electronegative group like $-CF_2COOR$, $-CF_2CONR_2$ or $-CF_2SO_2Ph$ and their subsequent removal (Scheme 1) [15]. To the best of our knowledge, no attempt has been made to introduce difluoromethyl-carboxy or difluoromethyl amide by proton abstraction. All attempts so far tried were by indirect means. For instance, Dolbier [16] and Langlois [17] described use of (1,1-dimethylamino)2,2-difluroethene and ether of difluoroketene hemiaminal, respectively, as $-CF_2CONR_2$ or $-CF_2COOEt$ equivalent. Their use is restricted mostly to condensation with reactive aldehydes. Yet another similar reagent is difluoroenoxy silane [18] which has also found very limited application. To introduce difluoromethyl carboethoxy group, Reformatsky reagent from ethyl difluoroacetate and zinc (or any other heavy metal) has been used extensively for coupling with carbonyl compounds and imines [19]. It should be noted that however metal mediated reactions are not particularly ecofriendly and quite often involves circuitous route. The current popular reagent in this regard is HCF_2SO_2Ph developed by Prakash et al. [20]. In this case however removal of SO_2Ph is done under strong reducing condition which may be lethal to many functional groups. Therefore, there is a need to develop newer agents to introduce $-CHF_2$ group. We have chosen HCF_2CF_2OR (a precursor to CHF_2COOR) and CHF_2CONR_2 and describe here appropriate condition for removal of the proton (without the intervention of any heavy metal) and subsequent coupling with selected electrophiles.



Scheme 1. Proposed reaction sequence for introduction of CHF_2 into electrophiles.

2. Results and discussion

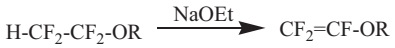
2.1. Reaction with benzophenones

Compounds with bi-functional moiety such as CHF_2CF_2OR (1) where R = phenyl (1a) or methyl (1b) are readily prepared both in the laboratory and in large scale by nucleophilic addition of phenol or methanol to tetrafluoroethylene (TFE) in the catalytic presence of the respective sodium salt [21a]. The other substrate CHF_2CONR_2 (2) is also obtained directly from TFE by a two-step reaction sequence [21a–c]. It may be noted that CF_2OR group in 1 can be easily converted to ester function in high yield by a variety of reagents and catalysts [21c,22]. Deprotonation and subsequent utilization of the anion generated from these compounds (1 or 2) as nucleophiles have not been attempted so far except for one patent literature where trialkylsilylchloride was used as an electrophile to form C–Si bond [23]. That attempt with CHF_2CF_2OR provided only a modest yield when R group was phenyl and poor yield when R was methyl. No reference could be found for the deprotonation of amide 2 or its analogues. A reasonable explanation for the paucity of literature in this regard is the instability of substrate 1 in the basic medium as the compound is susceptible to beta elimination of HF giving a stable enol–ether, Scheme 2 [24]. This present report is the first to demonstrate C–C bond formation through deprotonation of 1 or 2.

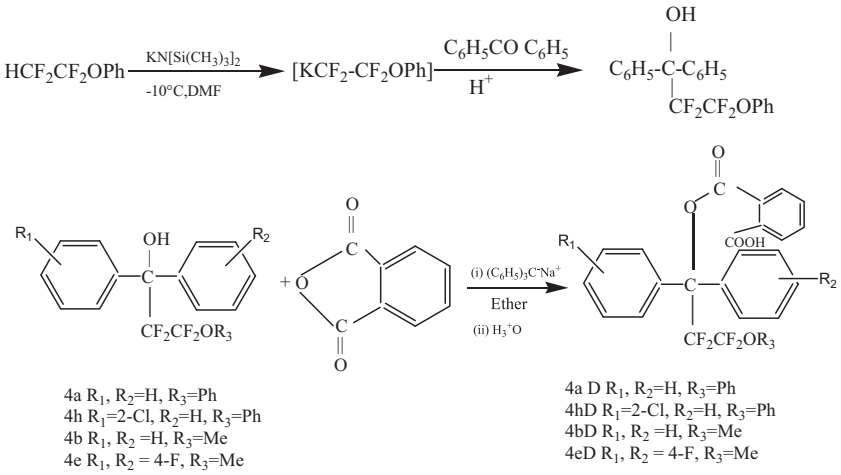
We initially tried a few bases to deprotonate 1a or 1b in the presence of electrophiles. Our preferred reagent was CHF_2CF_2–OPh as this compound has a higher boiling point than its methyl analogue and so handling becomes more convenient. We chose methyl *t*-butyl ether as the solvent and *n*-butyl lithium or lithium diisopropylamide as the base. In all these cases, enol–ether formation by HF elimination was the major pathway. When butyl lithium was used substitution of fluorine atom of the enol–ether by butyl group occurred as indicated by GC–MS. In the above cases one of the electrophiles namely acrylonitrile, ethyl acrylate, bromine or iodine was present in the medium but no expected addition occurred between the electrophiles and the generated nucleophile.

Having failed with these bases we turned our attention to potassium bis-trimethylsilylamide (KHMDS) as the base and benzaldehyde as a substrate. The reaction did not provide any desired addition product in this reaction also but products from Cannizaro type reaction were obtained as major components of the mixture as revealed by GC analysis. However with benzophenone as the electrophile and DMF as the solvent, a new addition product was formed with 1a albeit in modest yield. By careful variation of temperature and mole proportion of the base with a limiting amount of benzophenone the reaction went up to 90% completion (Scheme 3). However, further increase of the amount of the base or change of temperature did not improve the yield. Since this was the best condition arrived at, 10 benzophenones having 1 or more electron withdrawing or donating substituents were tried and the results are compiled in Table 1. This table also includes representative reactions of methyl ether 1b or the amide 2 with a few benzophenones.

From the results, it is clear that the reaction is of general nature and not affected greatly by the electron donating or withdrawing power of the substituents in the phenyl ring in any position. However with 4,4′-dimethoxybenzophenone the starting ketone was recovered unchanged (entry 14, Table 1). Perhaps the nucleophilicity of the fluoro ether was too weak to attack the carbonyl group of dimethoxybenzophenone which has a reduced electrophilic character.



Scheme 2. Enol ether formation from tetrafluoroethyl ether.



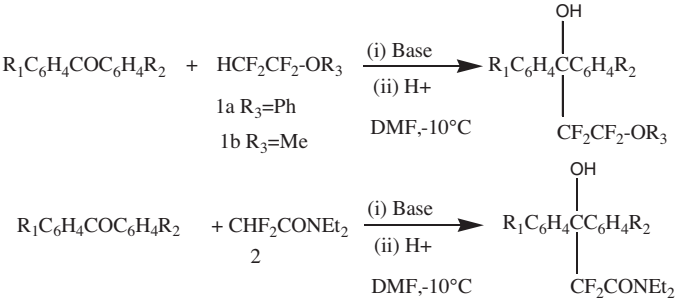
Scheme 3. Reaction of 1a with benzophenone and phthalate derivative formation.

The product in each reaction was contaminated with the unreacted starting materials. Isolation was done by careful column chromatography as the R_f values of the ketone and the addition product were either very close or sometimes merging. All the new compounds have been characterized by spectral data (IR and NMR). E.I. mass spectrum however presented some difficulty for interpretation. In none of the cases, the compounds gave molecular ion peak. Even under CI–MS condition (methane or isobutane) the highest peak observed was (M − OH) peak in most of the cases. In order to characterize the products unequivocally phthalate esters [25] were made for four of the tertiary alcohols (Scheme 3). The phthalate derivatives were characterized by IR and NMR. Single crystal X-ray was done for two of these esters (Figs. 1 and 2) and one amide (Fig. 3) to establish fully the structure of the newer compounds.

In several of the reactions with benzophenones, a peculiar phenomenon was observed when DMF was used as a solvent. We found progressive decrease of the product with respect to the starting ketone (3) and fluoro ether (1) as the time progressed. In order to understand this intriguing observation, we monitored the reaction at different time intervals using benzophenone, tetrafluoroethyl phenyl ether (1a) and KHMDS base. The results are presented in Table 2. It is obvious from the results that the reaction reverses as the time progresses and the best time to get maximum conversion and yield is between 1 and 10 min. Most likely the product is kinetically controlled and even with excess base, the intermediate is unstable in DMF and reverts to an equilibrium condition slowly.

In order to understand the influence of the other reaction parameters, a study was done using 1a and benzophenone. We varied the base, its proportion, the solvent and the temperature. The results are presented in Table 3. Some surprising results were

Table 1
Reaction of benzophenones with 1 or 2



Sl. no.	R_1	R_2	1a, 1b or 2	Extent of reaction in % after 0.5 h when 2 equiv. of base used at −10 °C	Isolated yield % in DMF	Isolated yield % in toluene
1	H	H	1a	90	56	96
2	H	H	1b	77	59	99
3	H	H	2	95	83	99
4	4-F	4-F	1a	89	67	76
5	4-F	4-F	1b	92	63	75
6	4-F	4-F	2	85	78	98
7	4-NO_2	H	1a	87	71	98
8	2-Cl	H	1a	90	72	83
9	2-Me	H	1a	85	70	99
10	3-Me	H	1a	81	70	90
11	4-Me	H	1a	80	65	94
12	4-CN	H	1a	66	51	98
13	2-Cl	H	2	90	73	95
14	4-OCH_3	4-OCH_3	1a	0	0	Not done

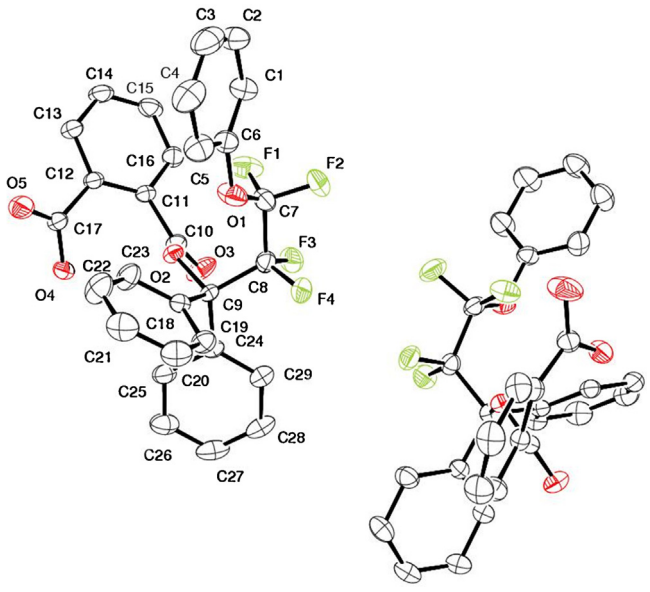


Fig. 1. ORTEP diagram and selected bond distances (A) of 4aD (CCDC 955789).

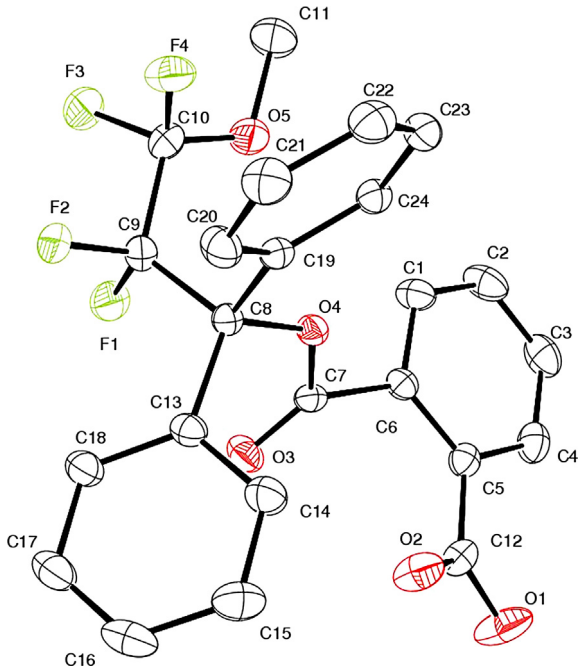


Fig. 2. ORTEP diagram and selected bond distances (A) of 4bD (CCDC 955790).

obtained. The reaction went to completion both in THF and toluene. The reaction went smoothly even at room temperature except for the formation of small amount of enol ether as an unwanted by-product without affecting the overall reaction since 1a was used in 1 mole excess. Third, by-products are formed when higher temperature was used. Using toluene as the solvent, the reaction proceeded well even at RT and all the benzophenones gave excellent isolated yield (last column in Table 1).

Some of the other features of the reaction are noteworthy. Even though *t*-BuOK is a good base to effect the reaction, KHMDS seems

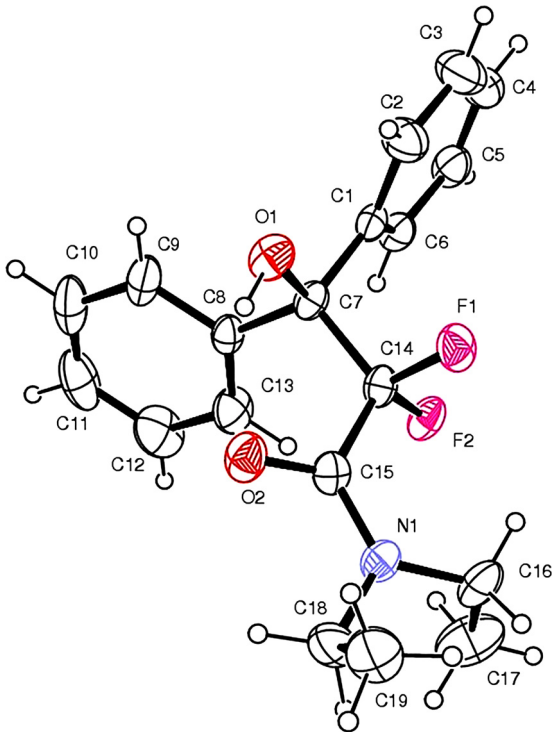
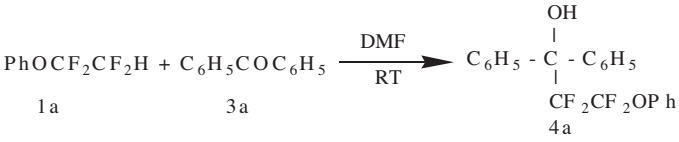


Fig. 3. ORTEP diagram and selected bond distances (A) of 4c (CCDC 955791).

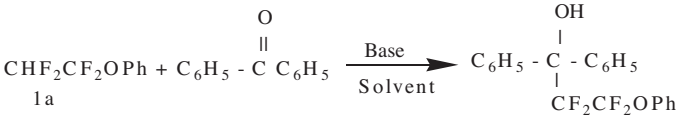
Table 2
Reaction of benzophenone with 1a at various time intervals.



Sl. no.	Time after completion of addition (min)	*1a (%)	*3a (%)	*4a (%)
1	1	20.8	1.1	69.7
2	5	11.3	1.7	75.7
3	22	26.7	3.8	56.3
4	85	45.9	19.9	18.8

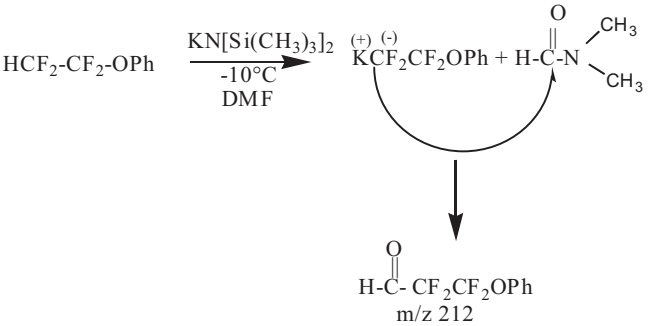
* Determined by GC based on weight %.

Table 3
Reaction of benzophenone with 1a under various reaction conditions.

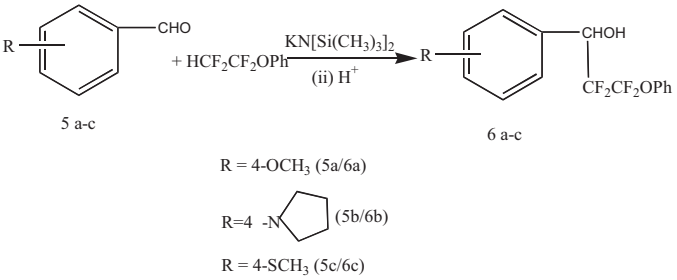


Sl. no.	Base (Equiv)	Solvent	Temp. RT	Maximum % conversion	Remarks
1	KHMDS (2)	DMF	RT	91	Reverses on longer reaction time
2	KHMDS (2)	DMF	60°	–	Many impurities formed
3	KHMDS (1)	DMF	RT	47	Reverses later
4	KHMDS (3)	DMF	RT	98	Reverses later
5	tBuOK (3)	DMF	RT	97	Reverses later
6	tBuOK (2)	THF	0 °C	93	No reversal
7	KHMDS (3)	THF	RT	99.8	No reversal
8	*t*-BuOK (2)	THF	RT	78	No reversal
9	KHMDS (2)	Toluene	RT	99	No reversal

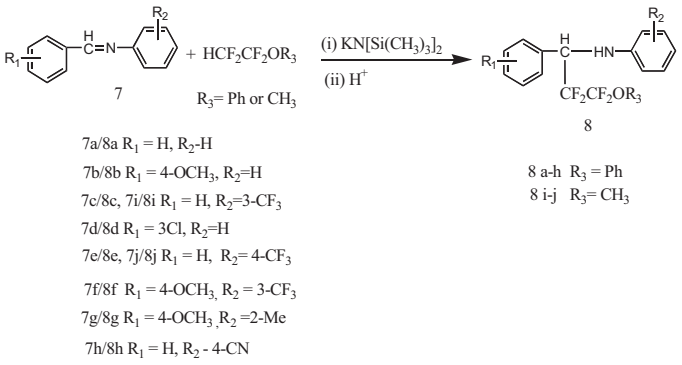
to be better in terms of yield when THF or toluene is used as a solvent. Perhaps this may be due to the differential solubility of the base in the medium. More importantly *the reaction does not reverse in toluene or THF.* A reasonable explanation can be offered. The anion of the product perhaps is more stable than the anion generated from 1a in less polar medium. While we observed evidence of intermediate aldehyde formation (Scheme 4) in DMF, the same was not detected in any of the reactions in toluene. Most likely as soon as the anion is generated, it undergoes addition reaction with benzophenone in toluene. In all the cases the reactions were complete at RT within 10 min in toluene thus



Scheme 4. Formation of aldehyde intermediate from 1a and base.

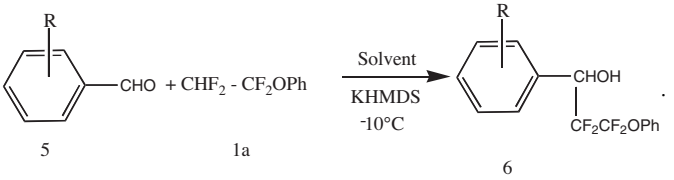


Scheme 5. Reaction of 1a with benzaldehydes.



Scheme 6. Reaction of 1a and 1b with Schiff's.

Table 4
Reaction of benzaldehydes with 1a.



Sl. no	R	Solvent	% Conversion	% Yield (isolated)
1	4-SCH_3	Toluene	51	32
2	4-pyrrolidine	Toluene	48	39
3	4-OCH_3	Toluene	45	25
4	4-OCH_3	DMF	11	Not attempted

making it more suitable for industrial application if a comparison is made with trifluoromethylation of similar substrates with fluoroform which requires cooling up to −40 °C [10].

This type of addition reaction was not successful however with enolisable ketone like acetophenone. Under these conditions self-condensation products resulted.

2.2. Reaction with benzaldehydes

Since right conditions for coupling of 1 or 2 with benzophenones were established, we reinvestigated the reaction of 1a with benzaldehydes. The reaction did not proceed at all in the desired direction when benzaldehyde or substituted benzaldehydes with electronegative or weakly electron donating substituents were employed. The reactions followed the same pattern of giving rise to competing Cannizaro reaction type products. However with electron donating groups such as *p*-methoxy, *p*-piperidino and *p*-methylthio the reaction provided products in modest yield (Scheme 5). Similar findings were observed in two previous studies of others also [7b,26]. Most likely, the aldehydes bearing electron donating substituents undergo slow Cannizaro reaction under these conditions and therefore open to attack by the generated nucleophile.

Unfortunately in spite of trying varied conditions the reaction did not go to completion (temperature, use of hexane-toluene mixture and use of higher proportion of base). The extent of the reaction and the isolated yield in each case (without accounting for respective benzaldehyde recovery) is collected in Table 4. While 6b could be isolated directly after column chromatography on neutral alumina, isolation of 6a and 6c was done only after the product mixture was treated with sodium borohydride in methanol to reduce the unreacted aldehyde to the corresponding alcohol and subjecting the resulting mixture to column chromatography. All the purified products were then characterized by IR, NMR, EI and CI mass spectra. X-ray was done for 6c to further confirm the structure (Fig. 4).

2.3. Reaction with Schiff's bases

To the best of our knowledge, earlier reports describing $CF_3^{(-)}$, $^{(-)}CF_2XR$ (where X = SO_2, S, Se or Te) addition did not provide any example with unactivated C=N as electrophiles [7,9,10,20]. This paper is perhaps the first to describe addition of 1a or 1b to a number of selected Schiff's bases derived from benzaldehydes. The scope of the reaction however is limited to aromatic amine and aromatic aldehyde based Schiff's bases. Attempts to bring about a reaction with benzophenone-aromatic amine derived Schiff's bases met with failure. Also aliphatic amines derived Schiff's bases provided complex product mixtures. Nevertheless, in spite of this limitation, the reaction provides a synthetic route for the formation of a few aromatic chiral amines as shown in Scheme 6.

Again to our utter surprise, the reaction did not consume the Schiff's base fully in spite of increased amount of base beyond two moles (Table 5). There was just only a marginal improvement in such attempts. Secondly the reaction proceeded only when DMF was the solvent. Neither in THF nor in toluene the reaction

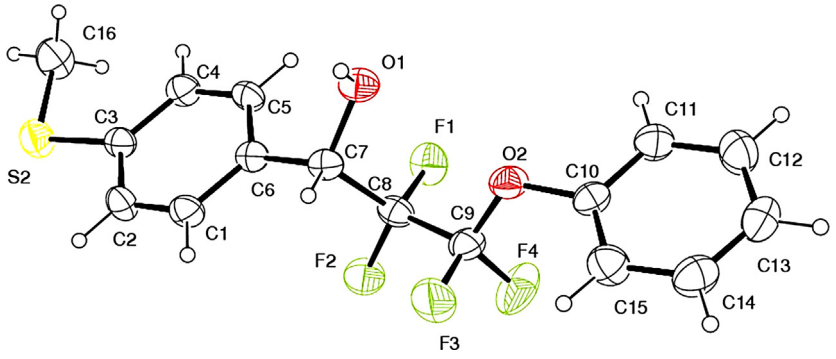
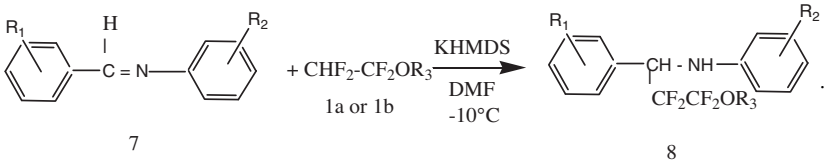


Fig. 4. ORTEP diagram and selected bond distances (A) of 6c (CCDC 1020926).

Table 5
Reaction of Schiff's bases with 1a or 1b



7 8

Sl. no.	R_1	R_2	R_3	Extent of reaction (%)	Isolated yield (%)
1	H	H	Ph	55	35
2	4-OCH_3	H	Ph	57	38
3	H	3-CF_3	Ph	90	70
4	3-Cl	H	Ph	45	23
5	H	4-CF_3	Ph	80	50
6	4-OCH_3	3-CF_3	Ph	60	40
7	4-OCH_3	2-CH_3	Ph	57	41
8	H	4-CN	Ph	77	58
9	H	3-CF_3	CH_3	70	49
10	H	4-CF_3	CH_3	80	61

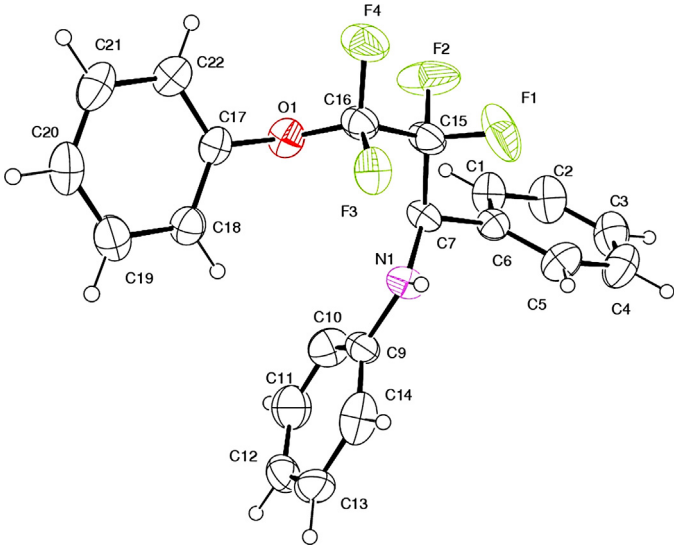


Fig. 5. ORTEP diagram and selected bond distances (A) of 8a (CCDC 1020925).

proceeded at all. The reason for such failure is very difficult to understand.

The products were isolated by column chromatography and characterized by spectral analyses. X-ray analysis (Fig. 5) was done for one of the amines (8a).

3. Conclusions

Appropriate conditions for the selective functionalization of C–H bond in difluoromethyl group in bifunctional compounds such as CHF_2CF_2OR or CHF_2CONR_2 have been found out. Further utilization of the intermediates to couple with benzophenones, benzaldehydes and Schiff's bases is also demonstrated for the first time.

4. Experimental

All chemicals were obtained either from Merck India or Sigma–Aldrich. 1,1,2,2-tetrafluoroethyl phenyl ether (1a) and 1, 1, 2, 2-tetrafluoroethyl methyl ether (1b) were prepared by the condensation of tetrafluoroethylene and phenol or methanol, respectively, in the presence of corresponding sodium salt as catalyst. Schiff's bases (7a to 7h) were prepared by the facile condensation of the respective benzaldehyde with anilines following the literature procedure [27] and recrystallized or distilled before use. The purity of Schiff's bases was more than 99.5% as determined by GC. *N,N*-diethyl difluoroacetamide (2) was prepared from difluoroacetyl fluoride and diethylamine [28]. DMF, THF and toluene were dried over 3A molecular sieves till the water content reduced below 200 ppm. ^1H, ^{19}F and ^{13}C NMR were recorded in Bruker A VIII 500 MHz spectrometer. For ^1H and ^{13}C TMS and for ^{19}F CFCl3 were used as internal standards. In ^{13}C NMR spectra, signals due to $-CF_2CF_2-$ groups were very weak. Only with increase in pulse delay time these signals could be recorded. Analyses in GC and GC–MS were performed in Agilent instruments 5973 and 6890, respectively. IR was recorded in Perkin-Elmer spectrum one FTIR spectrometer. Single crystal X-ray analyses were done in Bruker Apex-II X ray diffractometer. Crystallographic data (excluding structure factor) for the structures in this paper have been deposited with the Cambridge Crystallographic Data centre as supplementary publication numbers CCDC955789, 955790, 955791, 1020925 and 1020926. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2EZ, UK, (fax: +44 1223 336033 or deposit@ccdc.cam.ac.uk). Column chromatography where necessary was performed on silica gel for the isolation of pure product except for 6b for which neutral alumina was employed. Potassium *t* butoxide(*t* BuOK), potassium bis trimethylsilyl amide (KHMDS) or sodium hydride (NaH) were handled in a glove box for weighing. Solvents were transferred under minimum exposure to moisture.

4.1. Reaction of benzophenones with 1a, 1b or 2 and KHMDS in DMF

A three necked RB flask (25 mL) with a dropping funnel, an air condenser and inlet and outlet tubes for dry N_2 gas was cooled to $-10\ ^\circ C$ with ice salt mixture. One of the benzophenones (2 mmol) was dissolved in 2 mL of DMF and transferred under nitrogen atmosphere. 1a, 1b or 2 (4 mmol) was dissolved in 1 mL of DMF and added. A very slow stream of nitrogen was maintained in the case of reactions with 1b. KHMDS (0.798 g, 4 mmol) dissolved in 2 mL of DMF was added drop wise over a 5 min period while the contents were kept stirred. Different colour change occurred in all cases (violet in case of benzophenone) in the beginning but got discharged slowly. After about 15 min, water (3 mL), dil. H_2SO_4 (1 mL) and ether (10 mL) were added in that sequence. The contents were stirred at $-10\ ^\circ C$ for 5 min, brought to RT, the layers separated, water layer extracted with 2×10 mL of ether, all the organic layers combined, washed with dil. Sodium bicarbonate till

it was faintly acidic to pH paper and dried over anhydrous sodium sulfate. Upon evaporation of the solvent the crude mixture was chromatographed on silica gel using hexane-benzene. Isolated percentage yield of individual product is given in Table 1.

4.2. Reaction of benzophenones with 1a, 1b or 2 and KHMDS in THF or toluene

The above procedure was followed except that THF or toluene replaced (in volume quantity) DMF. The reaction was done at RT using a water bath as heat sink. Reaction was quenched with dil. H_2SO_4 10 min after the base was added. Extraction procedure similar to the one adopted in Section 4.1 was followed. The crude product contained only excess of 1a or 1b which was removed by evacuation at 1 mm Hg for 30 min keeping the temperature of flask at 90 °C (water bath). The products obtained were practically pure (>99% by GC).

4.3. Reaction of benzophenone with 1a under different experimental conditions

The experimental set-up and the procedure to start the reaction were same as in Section 4.1. Temperature, solvent, base and base quantities were varied as noted in Table 2 or Table 3. Samples (0.25 mL) were taken at regular time intervals and quenched immediately with dil. H_2SO_4. Extraction and analysis by GC were done to determine weight % of the product and the starting materials using precalibration with known weights of the respective pure compounds.

4.4. General procedure for the preparation of phthalate derivatives 4aD, 4bD, 4eD, 4hD

To a solution of the tertiary alcohol 4a, 4b, 4e or 4h (1 mmol) in 10 mL of dry ether was added freshly prepared triphenylmethyl-sodium [29] in ether until the blood red colour persisted. To this was added phthalic anhydride (1 mmol) and stirred for 2 h at RT. Water (10 mL) was added to quench the reaction, the ether layer was separated out and the water layer was poured into cracked ice and con. HCl. The precipitated solid was separated by filtration and air dried. This was recrystallized from chloroform–hexane (methanol was the solvent for recrystallization of 4hD). The products were obtained in 40–60% yield.

4.5. Reaction of benzaldehydes with 1a and KHMDS in toluene

The reaction vessel and the procedure used were as in Section 4.1. One of the benzaldehydes (2 mmol) was dissolved in toluene (2 mL) and introduced first followed by 1a (4 mmol) in toluene (2 mL) keeping the temperature at −10 °C. A solution of KHMDS (4 mmol) in toluene was added during a period of 5 min. The reaction was stopped after 15 min by the addition of dil. H_2SO_4. Extraction with ether and neutralization of ether layer, drying with anhydrous sodium sulfate and evaporation provided the crude product which contained the starting materials and the product. This mixture was chromatographed on neutral alumina using hexane–benzene eluent for 6b. The separated product was recrystallized from hexane before further analysis. To isolate 6a or 6c the respective mixtures were treated with 100 mg of $NaBH_4$ in 5 mL of methanol, stirred for 30 min at RT, solvent removed by applying vacuum and the residue chromatographed on silica gel. The solids obtained were practically pure for further analysis.

4.6. Reaction of Schiff's bases with 1a or 1b and KHMDS in DMF

In a similar reaction set up described for benzophenones in Section 4.1, Schiff's bases 7a–7h (2 mmol) were taken in 2 mL DMF and cooled to −10 °C. To this 1a or 1b (4 mmol) was added in 1 mL DMF. KHMDS (4 mmol) in 2 mL of DMF was added through the dropping funnel during a period of 5 min. Stirring was continued at the same temperature for a further period of 30 min after which 50% acetic acid was added till the solution became acidic. The contents were stirred for 5 min, cooled in ice water, 10% potassium hydroxide was added till it became basic (pH 9 by pH paper) extracted with ether (3 × 10 mL), ether layer combined and washed with water twice (5 mL each). The ether layer was dried, evaporated and the crude residue was chromatographed over silica gel to obtain the product. When solid product is obtained it is purified further by recrystallization, otherwise the product was evacuated at 60 °C/1 mm to remove any solvent before subjecting to further analysis.

4.7. 1,1-Diphenyl-2,2,3,3-tetrafluoro-3-phenoxypropan-1-ol (4a)

White crystalline solid, *m.p.* 64–65 °C.

IR (KBr) 3543, 1590, 1492, 1207, 1129, 1104, 748, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.36 (1*H*, s, OH), disappeared on D_2O shake), 6.95 (2*H*, d, *J* = 8 Hz, arom), 7.24 (1*H*, t, *J* = 8 Hz, arom), 7.30 to 7.42 (8*H*, m, arom) 7.72 (4*H*, d, *J* = 7.5 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 79.4 (t, *J* = 23 Hz, –C–OH) 115.6 (tt, *J* = 262 and 32 Hz, CF_2) 117.9 (tt, *J* = 278 and 33 Hz, CF_2) 121.6, 126.4, 127.4, 128, 128.2, 129.5, 140.1, 148.5 (all arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −115.0 (2F, s, (–C–CF_2–), −78.5 (2F, s, –CF_2–OPh).

EI–MS: 183 $(M - CF_2CF_2OPh)^+$.

CI–MS (methane): 359 $(M - OH)^+$, 337, 279.

4.8. Hydrogen 1,1-diphenyl-2,2,3,3-tetrafluoro-3-phenoxyprop-1-yl phthalate (4aD)

White crystalline solid, *m.p.* 156–158 °C.

IR (KBr) 3414, 1751, 1690, 1492, 1201, 1187, 1143, 1104, 748 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.5 (1*H*, br s, OH, disappeared on D_2O shake) 6.82 (2*H*, d, *J* = 8 Hz, arom) 7.13 (1*H*, m, arom) 7.20 (2*H*, m, arom) 7.32 to 7.39 (6*H*, m, arom) 7.57 (2*H*, m, arom) 7.7 (4*H*, d, *J* = 7.5 Hz, arom) 7.78 (1*H*, m, arom) 7.91 (1*H*, m, arom) [peaks at δ 7.57, 7.78 and 7.91 are due to phthalate ring].

^{13}C NMR (125 MHz, $CDCl_3$) δ 87.13(s, –C–O–phth) 121.5, 126.0, 127.7, 128.7, 129.1, 129.3, 129.5, 129.8, 131.5, 131.6, 131.7, 132.3, 135.3, 148.8 (all arom) 163.5 (C=O) 171.3 (C=O).

4.9. 1,1-(4,4′-Difluorodiphenyl)-2,2,3,3-tetrafluoro-3-phenoxypropan-1-ol (4d)

Colourless oil.

IR (film) 3567, 1604, 1508, 1187, 1129, 835, 791, 739 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.33 (1*H*, s, disappeared on D_2O shake, OH) 6.82 (2*H*, d, *J* = 8 Hz, arom) 6.92 (4*H*, m, arom) 7.1 (1*H*, m, arom) 7.17 (2*H*, m, arom) 7.51 (4*H*, dd, *J* = 9.0 and 5.5 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 78.9 (s, –C–OH) 115.4 (tt, *J* = 262 and 32 Hz)117.8 (tt, *J* = 278 and 33 Hz) 115.0 (d, *J* = 22 Hz, arom), 121.7 (s, arom), 126.6 (s, arom), 129.4 (d, *J* = 8 Hz, arom), 129.6 (s, arom), 135.8 (d, *J* = 3 Hz, arom), 148.5 (s, arom)162.6 (d, 246 Hz, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −115.2 (2F, s, –C–CF_2), −113.6 (2F, s, arom-F), −78.4 (2F, s, –CF_2OPh).

EI–MS: 219 $(M - CF_2CF_2OPh)^+$.

CI–MS (methane): 395 $(M - OH)^+$, 297.

4.10. 1-(2-Chlorophenyl)1-phenyl 2,2,3,3-tetrafluoro-3-phenoxypropan-1-ol (4h)

Colourless viscous oil.

IR (film) 3590, 1491, 1131, 755, 703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (1*H*, s, OH) 6.90 (2*H*, d, *J* = 8.0 Hz, arom) 7.10 (1*H*, m, arom) 7.12 to 7.23 (8*H*, m, arom) 7.39 (2*H*, m, arom) 7.97 (1*H*, d, *J* = 7.5 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 81.0 (s, –C–OH) 115.9 (tt, *J* = 265 and 33 Hz, $-CF_2$) 117.9 (tt, 277 and 32 Hz, $-CF_2$) 121.6, 126.16, 126.2, 127.7, 128, 128.2, 129.5, 129.7, 129.8, 132.4, 132.6, 137.8, 139.2, 149.0 (all arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −114.1 and −112.8 (2F, AB quartet, *J* = 270 Hz, C–CF_2) −78.3 (2F, s, CF_2OPh).

EI–MS: 219, 217 (1:3 ratio), $(M - CF_2CF_2OPh)^+$.

CI–MS (methane): 395, 393 (1:3 ratio), $(M - OH)^+$.

4.11. Hydrogen 1-(2-chlorophenyl)-1-phenyl-2,2,3,3–tetrafluoro-3-phenoxyprop-1-yl phthalate (4hD)

White crystals, *m.p.* 215–219 °C (decomp.).

IR (KBr) 3414, 3024, 1745, 1701, 1590, 1494, 1340, 1262, 1147, 1101, 762 cm^{-1}.

^1H NMR (500 MHz, CD_3OD) δ 6.97 (2*H*, d, *J* = 8 Hz, arom) 7.22 (1*H*, m, arom) 7.30 (3*H*, m, arom) 7.38 (4*H*, m, arom) 7.49 (1*H*, dt, *J* = 8.0 and 1.5 Hz, arom) 7.65 (5*H*, m, arom) 8.20 (1*H*, m, arom) 8.25 (1*H*, m, arom).

4.12. 1-(4-Nitrophenyl)1-phenyl-2,2,3,3-tetrafluoro-3-phenoxypropan-1-ol (4g)

Amber coloured oil.

IR (film) 3543, 3077, 1594, 1519, 1493, 1349, 1133, 748, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.65 (1*H*, s, OH) 6.95 (2*H*, d, *J* = 8 Hz, arom) 7.26 (1*H*, m, arom) 7.33 (2*H*, m, arom) 7.42 (3*H*, m, arom) 7.69 (2*H*, d, *J* = 8 Hz, arom) 7.90 (2*H*, d, *J* = 8 Hz, arom) 8.21 (2*H*, d, *J* = 8 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 79.2 (t, *J* = 24 Hz, –C–OH) 115.3 (tt, *J* = 270 and 25 Hz, $-CF_2$) 117.7 (tt, *J* = 277 and 33 Hz, $-CF_2$) 121.6, 123.0, 126.7, 127.0, 128.5, 128.6, 128.8, 129.6, 139.4, 146.8, 147.5, 148.5 (all aromatic).

^{19}F NMR (470 MHz, $CDCl_3$) δ −115.7 and −114.4 (2F, AB quartet = 272 Hz, –C–CF_2) −78.8 and −78.0 (2F, AB quartet, *J* = 141 Hz, $-CF_2OPh$).

EI–MS: 228 $(M - CF_2CF_2OPh)^+$.

4.13. 1, 1-Diphenyl-2,2,3,3-tetrafluoro-3-methoxypropan-1-ol (4b)

Colourless liquid.

IR (film) 3556, 2965, 1495, 1451, 1234, 1152, 1133, 1054, 748, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.46 (1*H*, s, –OH) 3.56 (3*H*, s, $-OCH_3$) 7.35 (6*H*, m, arom) 7.66 (4*H*, d, *J* = 7.5 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 51.2 (t, *J* = 6.9 Hz, OCH_3) 79.2 (t, *J* = 23 Hz, –C–OH) 115.3 (tt, *J* = 263 Hz and 32 Hz, $-CF_2$) 119.0 (tt, *J* = 275 Hz, 33 Hz, $-CF_2$) 127.4, 127.88, 128.05, 140.1 (all arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −115.1 (2F, s, C–CF_2) −84.5 (2F, s, CF_2OCH_3).

EI–MS: 183 $(M - CF_2CF_2OCH_3)^+$.

4.14. Hydrogen 1,1-diphenyl-2,2,3,3-tetrafluoro-3-methoxy prop-1-yl phthalate (4bD)

White crystalline solid, *m.p.* 183–85 °C.

IR (KBr) 3415, 2966, 2865, 1770, 1686, 1246, 1136, 753, 707 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.33 (3*H*, s, $-OCH_3$) 7.35 (6*H*, m, arom) 7.63 (6*H*, m, arom) 7.81 (1*H*, d, *J* = 7.5 Hz, arom) 7.92 (1*H*, d, *J* = 7.5 Hz, arom).

4.15. 1,1-(4,4′-Difluorodiphenyl)-2,2,3,3-tetrafluoro-3-methoxypropan-1-ol (4e)

Colourless oil.

IR (film) 3558, 2968, 2862, 1604, 1508, 1236, 1162, 835, 763 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.50 (1*H*, s, –OH), 3.57 (3*H*, s, $-OCH_3$) 7.05 (4*H*, m, arom) 7.59 (4*H*, dd, *J* = 8.5 and 5.5 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 51.2 (t, 6.9 Hz, $-OCH_3$) 78.7 (t, *J* = 23 Hz, –C–OH) 115.0 (tt, *J* = 262, 32 Hz, $-CF_2$) 118.9 (tt, *J* = 274, 33 Hz, CF_2), 114.8 (d, *J* = 22 Hz, arom) 129.3 (d, *J* = 6 Hz, arom) 135.6 (d, *J* = 3 Hz, arom) 162.9 (d, *J* = 243 Hz, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −115.3 (2F, s, –C–CF_2) −114.0 (2F, s, arom –C–F) −84.4 (2F, s, $-CF_2OCH_3$).

EI–MS: 219 $(M - CF_2CF_2OCH_3)^+$.

4.16. Hydrogen 1,1-(4,4'-difluorodiphenyl)-2,2,3,3-tetrafluoro-3-methoxyprop-1-yl phthalate (4eD)

White crystalline solid, *m.p.* 167–69 °C (decomp.).

IR (KBr) 3414, 1767, 1697, 1509, 1247, 839, 830 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.38 (3*H*, s, OCH_3) 7.06 (4*H*, m, arom) 7.59 to 7.69 (6*H*, m, arom) 7.84 (1*H*, dd, *J* = 7.5 and 1.5 Hz, arom) 7.88 (1*H*, dd, *J* = 7.5 and 1.5 Hz, arom).

4.17. N,N-*Diethyl 3,3-(diphenyl)-3-hydroxy-2,2-difluoropropanamide (4c)*

White solid, *m.p.* 116.5–117.5 °C.

IR (KBr) 3411, 2972, 1639, 1452, 1085, 742, 702 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (3*H*, t, *J* = 7.5 Hz, $-CH_3$) 1.30 (3*H*, t, *J* = 7.0 Hz, $-CH_3$) 3.38 (2*H*, q, *J* = 7.5 Hz, $-CH_2-$) 3.58 (2*H*, q, *J* = 7.0 Hz, $-CH_2-$) 5.6 (1*H*, s, OH) 7.28 to 7.36 (6*H*, m, arom) 7.52 (4*H*, d, *J* = 7.5 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1 ($-CH_3$) 14.33 (-CH_3) 42.0 ($-CH_2-$) 42.38 (t, *J* = 6.5 Hz, $-CH_2-$) 80.5 (t, *J* = 23 Hz, –C–OH) 115.4 (t, *J* = 268 Hz, $-CF_2$) 127.5, 127.68, 127.77, 141.4 (all arom), 163.8 (t, *J* = 29 Hz, –C=O).

^{19}F NMR (470 MHz, $CDCl_3$) δ −103.0 ($-CF_2CO$).

EI–MS: 183 $(M - CF_2CONEt_2)^+$.

CI–MS (methane): 334 $(MH)^+$, 316 $(M - OH)^+$.

HRMS: 356.1441 calculated mass for $C_{19}H_{21}NO_2F_2Na$ is 356.1438.

4.18. N,N-*Diethyl 3,3-(4,4′-difluorodiphenyl)-3-hydroxy-2,2-difluoropropanamide (4f)*

Colorless viscous oil.

IR (film) 3416, 3081, 2981, 2940, 1646, 1603, 1508, 1233, 1163, 1067, 835, 626 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 1.12 (3*H*, t, *J* = 7.0 Hz, $-CH_3$) 1.27 (3*H*, t, *J* = 7.0 Hz, $-CH_3$) 3.35 (2*H*, q, *J* = 7.0 Hz, $-CH_2-$) 3.55 (2*H*, q, *J* = 7.0 Hz, $-CH_2-$) 5.62 (1*H*, s, –OH) 6.99 (4*H*, m, arom) 7.44 (4*H*, dd, *J* = 10 and 5 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 12.11 (CH_3) 14.32 (CH_3) 42.1 (CH_2) 42.4 (t, *J* = 6.5 Hz, $-CH_2$) 79.96 (t, *J* = 22 Hz, –C–OH) 114.7 (d, *J* = 21 Hz, arom) 115.14 (t, *J* = 265 Hz, $-CF_2$), 129.36 (d, *J* = 8 Hz, arom), 137.1 (s, arom), 162.3 (d, *J* = 246 Hz, arom –C–F) 163.6 (t, *J* = 28 Hz, –C=O).

^{19}F NMR (470 MHz, $CDCl_3$) δ −114.7 (2F, s, arom F) −103.1 (2F, s, $-CF_2CO$).

EI–MS: 219 ($M - CF_2CONEt_2$)$^+$.

CI–MS (methane): 370(MH)$^+$, 352($M - OH$)$^+$.

4.19. 1-(2-Methylphenyl)-1-phenyl-2,2,3,3-tetrafluoro-3-phenoxypropan-1-ol (4i)

Colourless oil.

IR (film) 3564, 3063, 1492, 1192, 1127, 1050, 746, 736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (3*H*, s, CH_3) 3.19 (1*H*, s, –OH) 7.07 (2*H*, d, *J* = 7.5 Hz, arom) 7.18 (1*H*, m, arom), 7.27 (1*H*, t, *J* = 7.5 Hz, arom) 7.30 to 7.40 (7*H*, m, arom) 7.60 (2*H*, d, *J* = 6 Hz, arom), 8.05 (1*H*, m, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −115.3 and −112.5 (2F, AB quartet, *J* = 269 Hz, –C–CF_2) −78.2 (2F, s, $-CF_2OPh$).

EI–MS: 197 ($M - CF_2CF_2OPh$)$^+$, 119, 105, 91, 77, 65.

CI–MS (isobutane): 373 ($M - OH$)$^+$, 197.

4.20. 1-(3-Methylphenyl)-1-phenyl-2,2,3,3-tetrafluoro-3-phenoxypropan-1-ol (4j)

Colourless oil.

IR (film) 3571, 3062, 2923, 1591, 1492, 1321, 1192, 1128, 1050, 736 cm^{-1}.

^{1}H NMR: (500 MHz $CDCl_3$) δ 2.39 (3*H*, s, $-CH_3$) 3.34 (1*H*, s, OH), 6.94 (2*H*, d, *J* = 8 Hz, arom) 7.17 (1*H*, d, 8 Hz, arom) 7.21 to 7.42 (7*H*, m, arom) 7.49(1*H*, d, *J* = 8 Hz, arom) 7.52 (1*H*, bs, arom). 7.70 (2*H*, d, *J* = 8 Hz, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −115.1 and −114.9 (2F, AB quartet, *J* = 272 Hz, –C–CF_2) −78.5 (2F, s, CF_2–OPh).

EI–MS: 197 ($M - CF_2CF_2OPh$)$^+$, 119, 105, 77, 65.

CI–MS (isobutane) 373 ($M - OH$)$^+$, 197.

4.21. 1-(4-Methylphenyl)-1-phenyl-2,2,3,3-tetrafluoro-3-phenoxypropan-1-ol (4k)

Colourless oil.

IR (film) 3569, 3062, 3027, 1591, 1492, 1192, 1126, 749, 736 cm^{-1}.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 2.39 (3*H*, s, CH_3) 3.34 (1*H*, s, OH) 6.96 (2*H*, d, *J* = 8 Hz, arom) 7.17 to 7.43 (8*H*, m, arom) 7.59 (2*H*, d, *J* = 8 Hz, arom) 7.71 (2*H*, d, *J* = 7.5 HZ, arom).

^{19}F NMR: (470 MHz, $CDCl_3$) δ −115.45 and −114.75 (2F, AB quartet, *J* = 274 Hz –C–CF_2) −78.4 (2F, s, CF_2–OPh).

EI–MS: 197 ($M - CF_2CF_2OPh$)$^+$, 119, 105, 77.

CI–MS (isobutane) 373($M - OH$)$^+$, 197.

4.22. 1-(4-Cyanophenyl)-1-phenyl-2,2,3,3-tetrafluoro-3-phenoxypropan-1-o1 (4 l)

Solid, *m.p.* 98–100 °C.

IR (film) 3413, 3065, 2232, 1591, 1492, 1198, 1129, 809, 698 cm^{-1}.

^{1}H NMR: δ 3.51 (1*H*, s, –OH) 6.93 (2*H*, d, *J* = 8 Hz, arom) 7.23 to 7.44 (6*H*, m, arom) 7.64 to 7.69 (4*H*, m, arom) 7.82 (2*H*, d, *J* = 8.5 Hz, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −115.8 and −114.5 (2F, AB quartet, *J* = 275 Hz, –C–CF_2) −78.9 and −78.0 (2F, AB quartet, *J* = 140 HZ, –CF_2OPh).

EI–MS: 208 ($M - CF_2CF_2OPh$)$^+$, 130, 102, 77.

CI–MS (isobutane): 458 ($M + C_4H_9$)$^+$, 402 ($M + H$)$^+$, 208.

4.23. N,N-*Diethyl 3-(2-chlorophenyl)-3-phenyl-2,2-difluoro-3-hydroxypropanamide (4 m)*

Solid, *m.p.* 97–99 °C.

IR (KBr) 3391, 2980, 1644, 1454, 1162, 1079, 744, 713, 660 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (3*H*, t, *J* = 7 Hz, $-CH_3$), 1.31 (3*H*, t, *J* = 7 Hz, $-CH_3$) 3.44 to 3.53 (3*H*, m, $-CH_2-$) 3.64 to 3.72 (1*H*, m, $-CH_2-$) 5.79 (1*H*, s, OH) 7.24 to 7.29 (2*H*, m, arom) 7.33 to 7.39 (4*H*, m, arom) 7.40 to 7.44 (2*H*, m, arom) 7.46 to 7.49 (1*H*, m, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −107.0 and −99.3 (AB quartet, *J* = 290 Hz, $-CF_2-CO$).

EI–MS: 332 ($M - Cl$)$^+$, 219, 217 (ratio 1:3, $M - CF_2CONEt_2$)$^+$ 151, 139, 100.

CI–MS (isobutane): 406, 408 (ratio 3:1, $M + K$)$^+$ 368 and 370 (ratio 3:1, $M + H$)$^+$.

HRMS: 390.1064 calculated for $C_{19}H_{20}NO_2F_2NaCl$ is 390.1048.

4.24. 1-(4-Methoxyphenyl)-2,2,3,3-tetrafluoro-3-phenoxypropan -1-ol (6a)

Solid, *m.p.* 67–69 °C.

IR (KBr): 3453, 2936, 2840, 1613, 1515, 1492, 1190, 1118, 789, 739 cm^{-1}.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 2.61 (1*H*, d, *J* = 4.5HZ, –OH) 3.82 (3*H*, s, OCH_3) 5.21 (1*H*, ddd, *J* = 18, 9, 4.5 Hz, –CH) 6.93 (2*H*, m, arom) 7.16 (2*H*, d, *J* = 7.5 Hz, arom) 7.26 (1*H*, m, arom) 7.35 (2*H*, m, arom) 7.44 (2*H*, d, *J* = 8.5 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 55.3 (s, $-OCH_3$), 71.9 (q, *J* = 27 and 22.5 Hz, –CH) 113.9 (s, arom), 114.2 (tt, *J* = 260 and 32 Hz, $-CF_2$) 117.8 (tt, *J* = 262 and 32 Hz, $-CF_2$), 121.8 (s, arom), 126.5 (s, arom), 126.9 (s, arom), 129.4 (s, arom), 129.6 (s, arom) 148.8 (s, arom) 160.3 (s, arom). Signals of $-CF_2$ were very weak.

^{19}F NMR (470 MHz, $CDCl_3$) δ −128.2 and −123.1 (2F, AB quartet, *J* = 267 Hz, –C–CF_2) −83.6 (2F, s, $-CF_2-OPh$).

EI–MS: 330 (M)$^+$, 137 ($M - CF_2CF_2OPh$)$^+$, 109, 94, 77.

CI–MS (isobutane): 331 ($M + H$)$^+$ 330, 313 ($M - OH$)$^+$.

4.25. 1-(4-Pyrrolidinophenyl)-2,2,3,3-tetrafluoro-3-phenoxypropan-1-ol (6b)

Solid, *m.p.* 128–130 °C.

IR (KBr): 3497, 3070, 2976, 2838, 1618, 1526, 1491, 1191, 1112, 778, 739 cm^{-1}.

^{1}H NMR: (500 MHz, $CDCl_3$) δ, 2.00 (4*H*, m, –C–CH_2) 2.41 (1*H*, d, *J* = 4.5 Hz, –OH) 3.29 (4*H*, m, N–CH_2) 5.14 (1*H*, ddd, *J* = 16, 9, 4.5 Hz, CH) 6.56 (2*H*, m, arom) 7.18 (2*H*, d, *J* = 8 Hz, arom) 7.25 (1*H*, m, arom), 7.36 (4*H*, m, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5 (s, C–CH_2–CH_2–C), 47.6 [–$N(CH_2)_2$], 72.39 (dd, *J* = 26 and 22 Hz, CH) 111.4 (s, arom), 121.1 (s, arom), 121.9 (s, arom), 126.4 (s, arom), 129.1 (s, arom), 129.5 (s, arom), 148.6 (s, arom) 149.0 (s, arom). CF_2 groups gave too weak signals.

^{19}F NMR (470 MHz, $CDCl_3$) δ −128.2 and −123.0 (2F, AB Quartet, *J* = 268 Hz, CF_2–C) −83.63 (2F, s, $-CF_2-OPh$).

EI–MS: 369 (M)$^+$, 176 ($M - CF_2CF_2OPh$)$^+$.

CI–MS (isobutane): 408 ($M + K$)$^+$, 370 ($M + H$)$^+$, 352 ($M - OH$)$^+$.

4.26. 1-(4-Methylthiophenyl)-2,2,3,3-tetrafluoro-3-phenoxypropan-1-ol (6c)

Solid, *m.p.* 92–93 °C.

IR (KBr) 3480, 1492, 1197, 1090, 1017, 783, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (3*H*, s, S–CH_3) 2.67 (1*H*, d, *J* = 4.5 Hz, –OH) 5.22 (1*H*, ddd, *J* = 15.5, 10.5, 5 Hz, –CH) 7.16 (2*H*, d, *J* = 8 Hz, arom) 7.26 (3*H*, m, arom), 7.36 (2*H*, m, arom) 7.42 (2*H*, d, *J* = 8 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5 (s, S–CH_3) 72.0 (dd, *J* = 26 and 23 Hz, –CH) 121.8 (s, arom), 126.1 (s, arom), 126.6 (s, arom) 128.5 (s, arom) 129.6 (s, arom) 131.3 (s, arom) 140.2 (s, arom), 148.8 (s, arom). CF_2 signals too weak to record.

^{19}F NMR (470 MHz, $CDCl_3$) δ −128.3 and −122.7 (AB quartet, J = 268 Hz, –C–CF_2), −83.54 (2F, s, CF_2–OPh).

EI–MS: 346 $(M)^+$ 153 $(M - CF_2CF_2OPh)^+$, 109, 77.

CI–MS (isobutane): 403 $(M + C_4H_9)^+$, 385 $(M + K)^+$, 347 $(M + H)^+$, 329 $(M - OH)^+$.

4.27. N-*Phenyl-1-phenyl-2,2,3,3-tetrafluoro-3-phenoxypropylamine (8a)*

Solid, *m.p.* 93–94.5 °C.

IR (KBr) 3408, 3059, 3034, 1605, 1515, 1496, 1184, 1102, 749, 691 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (1*H*, s, –NH) 5.20 (1*H*, dd, J = 17.5 and 8 Hz, –CH) 6.68 (2*H*, d, J = 8 Hz, arom) 6.77 (1*H*, t, J = 7.5 Hz, arom) 7.09 (2*H*, d, J = 8 Hz, arom) 7.19 (2*H*, m, arom) 7.28 (1*H*, m, arom) 7.33 to 7.45 (5*H*, m, arom) 7.54 (2*H*, d, J = 7.5 Hz, arom).

^{19}F NMR: (470 MHz, $CDCl_3$) δ −125.7, −117.6 (AB quartet, J = 268 Hz, C–CF_2) −83.7 and −82.5 (AB quartet, J = 142 Hz, CF_2OPh).

EI–MS: 375 $(M)^+$, 182 $(M - CF_2CF_2OPh)^+$ 104, 77.

CI–MS (isobutane): 376 $(M + H)^+$.

HRMS: 376.1316 calculated mass for $C_{21}H_{18}NOF_4$ is 376.1325.

4.28. N-*Phenyl-1-(4-methoxyphenyl)-2,2,3,3-tetrafluoro-3-phenoxypropylamine (8b)*

Colourless oil.

IR (film) 3424, 3058, 2838, 1603, 1513, 1491, 1251, 1183, 1115, 1029, 749, 690 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (3*H*, s, OCH_3) 4.57 (1*H*, d, J = 7.5 Hz, NH, partially disappears on D_2O shake) 5.16 (1*H*, m, CH, collapses to dd, J = 17 and 9 Hz upon D_2O shake) 6.69 (2*H*, d, J = 8 Hz, arom) 6.77 (1*H*, t, 7.5 Hz, arom) 6.96 (2*H*, m, arom) 7.11 (2*H*, d, J = 8 Hz, arom) 7.18 (2*H*, t, J = 7.5 Hz) 7.28 (1*H*, m, arom) 7.37 (2*H*, m, arom) 7.46 (2*H*, d, J = 8 Hz, arom).

^{19}F NMR: (470 MHz, $CDCl_3$) δ −125.3 and −117.6 (AB quartet, J = 268 Hz, C–CF_2) −83.7 and −82.4 (AB quartet, J = 143 Hz, CF_2–OPh).

EI–MS: 405 $(M)^+$, 212 $(M - CF_2CF_2OPh)^+$, 77.

CI–MS (isobutane): 406 $(M + H)^+$.

4.29. N-*(3-Trifluoromethyl phenyl)-1-phenyl 2,2,3,3-tetrafluoro-3-phenoxypropylamine (8c)*

Colourless oil.

IR (film): 3440, 3036, 2926, 1617, 1599, 1492, 1343, 1187, 1123, 1017, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.83 (1*H*, d, J = 8 Hz, NH), 5.23 (1*H*, m, –CH, collapses to dd, J = 17.5 and 8.5 Hz on D_2O shake), 6.83 (1*H*, dd, J = 8.0 and 2.5 Hz, arom) 6.93 (1*H*, s, arom), 7.02 (1*H*, d, J = 7.5 Hz, arom), 7.10 (2*H*, d, J = 8 Hz, arom) 7.29 (2*H*, m, arom) 7.38 (2*H*, m, arom) 7.44 (3*H*, m, arom), 7.55 (2*H*, d, J = 7.5 Hz, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −124.7, −118 (AB quartet, J = 275 Hz, –CF_2–C–) −83.74, −82.6 (AB quartet, J = 150 Hz, –CF_2OPh) −62.99 (s, CF_3)

EI–MS: 443 $(M)^+$, 424 $(M - F)^+$, 250 $(M - CF_2CF_2 - OPh)^+$, 172, 145, 77.

CI–MS (isobutane): 444 $(M + H)^+$.

4.30. N-*Phenyl-1-(3-chlorophenyl)-2,2,3,3-tetrafluoro-3-phenoxy-propylamine (8d)*

Colourless oil.

IR (film) 3435, 3059, 2926, 2853, 1602, 1509, 1491, 1299, 1194, 1120, 771, 749, 690 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (1*H*, d, J = 7.5 Hz, –NH), 5.20 (1*H*, dt, J = 18 and 8.0 Hz, respectively, –CH), 6.68 (2*H*, d, J = 8.0 Hz, arom) 6.82 (1*H*, t, J = 7.5 Hz, arom) 7.11 (2*H*, d, J = 8 Hz, arom) 7.21 (2*H*, m, arom) 7.30 (1*H*, m, arom) 7.38 (4*H*, m, arom) 7.45 (1*H*, d, J = 7.0 Hz, arom) 7.58 (1*H*, s, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −125.54, −116.87 (AB quartet, J = 276 Hz, –C–CF_2), −83.82 and −82.4 (AB quartet, J = 147 Hz, –CF_2–OPh).

EI–MS: 411, 409 (ratio 1:3, $M)^+$ 218, 216 (ratio 1:3, $M - CF_2CF_2OPh)^+$ 104, 77, 65.

CI–MS (isobutane): 412, 410 (ratio 1:3, $M + H)^+$.

4.31. N-*(4-Trifluoromethylphenyl)-1-phenyl-2,2,3,3-tetrafluoro-3-phenoxypropylamine (8e)*

Colourless oil.

IR (film) 3445, 3070, 1618, 1532, 1492, 1329, 1190, 1111, 1066, 1017, 824, 744 cm^{-1}.

^{1}H NMR:(500 MHz, $CDCl_3$) δ 4.92 (1*H*, d, J = 8 Hz, NH) 5.22 (1*H*, dt, J = 17.5 and 8.5 Hz, respectively), 6.70 (2*H*, d, J = 8.5 Hz, arom) 7.07 (2*H*, d, J = 8 Hz, arom) 7.29 (1*H*, m, arom) 7.37 (2*H*, m, arom) 7.42 (5*H*, m, arom) 7.52 (2*H*, d, J = 7 Hz, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −125.1 −117.78 (AB quartet, J = 276 Hz, –CF_2–C–) −83.38, −82.64 (AB quartet, J = 147 Hz, –CF_2–OPh) −61.4 (s, CF_3).

EI–MS: 443 $(M)^+$, 424 $(M - F)^+$, 250 $(M - CF_2CF_2OPh)$ 172, 145, 77

CI–MS (isobutane): 444 $(M + H)^+$.

4.32. N*(3-Trifluoromethylphenyl)-1-(4-methoxyphenyl) 2,2,3,3-tetrafluoro-3-phenoxypropyl amine (8f)*

Colourless oil.

IR (film): 3438, 3073, 2934, 2841, 1614, 1514, 1252, 1181, 1122, 1027, 786, 738 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (3*H*, s, OCH_3) 4.79 (1*H*, d, J = 8 Hz, NH), 5.19 (1*H*, dt, 17.0 and 8.5 Hz, respectively, –CH–) 6.83 (1*H*, d, J = 8.5 Hz, arom) 6.94 (1*H*, s, arom) 6.98 (2*H*, d, J = 8.5 Hz, arom) 7.03 (1*H*, d, J = 7.5 Hz, arom) 7.13 (2*H*, d, J = 8.0 Hz, arom) 7.28 (2*H*, m, arom) 7.38 (2*H*, d, J = 7.5 Hz, arom) 7.47 (2*H*, d, J = 8.5 Hz, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −124.82, −118.1 (AB quartet, J = 275 Hz, –CF_2–C–), −83.60, -82.6 (AB quartet, J = 147 Hz, –CF_2OPh) −62.87 (s, CF_3).

EI–MS: 473 $(M)^+$, 280 $(M - CF_2CF_2OPh)^+$, 205, 172, 145, 77.

CI–MS (isobutane): 474 $(M + H)^+$, 313 $(M - NH - C_6H_4 - CF_3)^+$.

4.33. N-*(2-Methyphenyl)-1-(4-methoxyphenyl)-2,2,3,3-tetrafluoro-3-phenoxypropylamine (8g)*

Colourless oil.

IR (film) 3452, 3018, 2960, 2933, 1608, 1589, 1513, 1491, 1193, 1117, 1027, 748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (3*H*, s, CH_3) 3.86 (3*H*, s, OCH_3), 4.59 (1*H*, d, J = 7.5 Hz, NH) 5.26 (1*H*, dt, J = 16 Hz, 7.5 Hz, respectively, –C–H) 6.60 (1*H*, d, J = 8.5 Hz, arom) 6.75 (1*H*, t, J = 7.0 Hz, arom) 7.00 (2*H*, m, arom) 7.09 (1*H*, m, arom) 7.15 (3*H*, m, arom) 7.31 (1*H*, m, arom) 7.41 (2*H*, m, arom) 7.52 (2*H*, d, J = 8.5 Hz, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −125.7, −116.7 (AB quartet, J = 275 Hz, –C–CF_2-), −83.50, −82.17 (AB quartet, J = 146 Hz, CF_2OPh).

EI–MS: 419 $(M)^+$, 226 $(M - CF_2CF_2OPh)^+$ 205, 118, 91, 77.

CI–MS (isobutane): 420 $(M + H)^+$.

4.34. N-*(4-Cyanophenyl)1-phenyl-2,2,3,3-tetrafluoro 3-phenoxypropylamine (8h)*

Solid, *m.p.* 134–137 °C.

IR (KBr) 3364, 3074, 2924, 2216, 1604, 1523, 1201, 737 cm^{-1}.

^1H NMR (500 MHz $CDCl_3$) δ 5.09 (1*H*, d, *J* = 8.0 Hz, NH) 5.22 (1*H*, dt, *J* = 17 and 8.5 Hz, respectively, –CH) 6.68 (2*H*, d, *J* = 7 Hz, arom) 7.07 (2*H*, d, *J* = 8 Hz, arom) 7.29 (1*H*, m, arom) 7.37 (2*H*, m, arom) 7.45 (5*H*, m, arom) 7.51 (2*H*, d, *J* = 7.0 Hz, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −124.7, −118.7 (AB quartet, *J* = 276 Hz, –C–CF_2) −83.9 and −82.7 (AB quartet, *J* = 148 Hz, –CF_2OPh).

EI–MS: 400 $(M)^+$, 207 $(M - CF_2CF_2OPh)^+$, 129, 102, 77.

CI–MS (isobutane): 457 $(M + C_4H_9)^+$, 401 $(M + H)^+$.

4.35. N-*(3-Trifluoromethylphenyl)-1-phenyl-2,2,3,3-tetrafluoro-3-methoxypropylamine (8i)*

Colourless oil.

IR (film): 3444, 3036, 2968, 2869, 1616, 1524, 1345, 1200, 1123, 1037, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.68 (3*H*, s, OCH_3) 4.74 (1*H*, d, *J* = 7.5 Hz, NH), 5.04 (1*H*, dt, *J* = 17 and 8.0 Hz, respectively, –CH) 6.75 (1*H*, d, *J* = 8.5 Hz, arom) 6.88 (1*H*, s, arom) 7.00 (1*H*, d, *J* = 7.5 Hz, arom) 7.24 (1*H*, t, *J* = 8.0 Hz, arom) 7.41 (3*H*, m, arom) 7.48 (2*H*, d, *J* = 7.5 Hz, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 51.2 (t, *J* = 6.75 Hz, OCH_3) 58.6 (dd, *J* = 27 and 21 Hz, –CH), 110.1 (q, *J* = 3.8 Hz, arom) 114.6 (tt, *J* = 255 and 33 Hz, –CF_2) 115 (q, *J* = 3.6 Hz, arom) 116.3 (s, arom), 118.6 (tt, *J* = 252, 32 Hz, -CF_2) 124.1 (q, *J* = 271 Hz, –CF_3) 128.4 (s, arom), 128.7 (s, arom), 128.9 (s, arom) 129.7 (s, arom) 131.8 (q, *J* = 32 Hz, arom C–CF_3) 134.1 (s, arom) 146 (s, arom).

^{19}F NMR (470 MHz, $CDCl_3$) δ −125.4, −117.5 (AB quartet, *J* = 275 Hz, –C–CF_2) −90.2, −88.6 (AB quartet, *J* = 145 Hz, CF_2–OCH_3), −62.9 (s, CF_3).

EI–MS: 381 $(M)^+$, 250 $(M - CF_2CF_2OCH_3)^+$, 172, 145.

CI–MS (isobutane): 382 $(M + H)^+$.

4.36. N-*(4-Trifluoromethylphenyl)-1-phenyl-2,2,3,3-tetrafluoro-3-methoxypropylamine (8j)*

Colourless oil.

IR (film): 3445, 3032, 2967, 2868, 1619, 1532, 1330, 1111, 1066, 825, 731 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.69 (3*H*, s, OCH_3), 4.89 (1*H*, bd, NH), 5.06 (1*H*, m, –CH), 6.66 (2*H*, d, *J* = 7.5 Hz, arom), 7.42 (5*H*, m, arom), 7.49 (2*H*, m, arom).

^{13}C NMR (125 MHz, $CDCl_3$) δ 51.2 (t, *J* = 6.9 Hz, OCH_3), 58.4 (dd, *J* = 26.5 and 21 Hz, –CH), 112.8 (s, arom), 114.5 (tt, *J* = 255 and 33 Hz, CF_2) 118.7 (tt, *J* = 251 and 32 Hz, CF_2) 120.3 (q, *J* = 32 Hz, arom C–CF_3) 124.8 (q, *J* = 269 Hz, CF_3) 126.7 (q, *J* = 3.8 Hz, arom) 128.5 (s, arom), 128.7 (s, arom), 129.0 (s, arom) 133.9 (s, arom), 148.3 (s, arom).

^{19}F NMR: (470 MHz, $CDCl_3$) δ −125.5, −117.5 (AB quartet, *J* = 276 Hz, –C–CF_2) −90.2, −88.6 (AB quartet, *J* = 147 Hz, –CF_2–OCH_3) −61.31 (s, CF_3).

EI–MS: 381 $(M)^+$, 250 $(M - CF_2CF_2OCH_3)^+$, 172, 145.

CI–MS (isobutane): 382 $(M + H)^+$.

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