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Light-fluorous TEMPO: reagent, spin trap and stable free radical

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ABSTRACT

The synthesis of two light-fluorous TEMPO derivatives is reported, along with their fluorous-organic solvent partition coefficients and their ESR spectra. Applications of the fluorous-TEMPO reagents in oxidation reactions and as radical traps are discussed.

1. Introduction

In recent years, the 'fluorous' concept has rapidly expanded and increased in popularity with many novel fluorous-tagged reagents reported and many reactions adapted to the fluorous biphase concept. There are now many excellent reviews of this emerging area.[1–5] In our own work in this area, we have previously reported the synthesis of fluorous-tagged reagents for the Mitsunobu reaction.[6]

We have recently turned our attention to the preparation and reactions of fluorous-tagged stable radicals. It occurred to us that stable nitroxyl radicals present considerable potential for modification for use either in fluorous media or by clean separation methods, such as by fluorous-organic liquid–liquid extraction or by fluorous solid-phase separation.

One of the most popular stable free radicals is 2,2,6,6-tetramethylpiperidine-1-oxyl or TEMPO **1**. For ease of use and reaction purification, there have been several reports of variously tagged TEMPO-type reagents for use in synthesis, including resin-bound[7] and polymer supported[8–10] TEMPO derivatives and an ionic liquid-based TEMPO system by Jiang and Ragauskas.[11,12] Concurrent with our own work, there have been two reports of heavy fluorous-based TEMPO derivatives: Pozzi and co-workers[13,14] have reported the preparation of a large and heavily fluorous-tagged (60.8%) heterocycle-linked TEMPO reagent **2** and Reiser and co-workers[15] similarly prepared a heterocycle-linked TEMPO **3** via a click reaction, albeit with lower fluorous content than the Pozzi system (Fig. 1).

2. Results and discussion

Herein, we report the synthesis, characterisation, properties and reactions of two smaller, amide—rather than heterocycle—linked fluorous-TEMPO reagents, **4** and **5** (Fig. 2), with a lighter fluorine content cf. the Pozzi and Reiser systems.[16] These were designed to be smaller, simpler and more easily prepared than any of the alternative TEMPO reagents and, with the incorporation of an extra amide function, should increase the fluorophilicity of the reagents. The compounds were prepared starting from 4-oxo-TEMPO **6**, itself prepared from 2,2,6,6-tetramethyl-4-oxopiperidine **7** by oxidation with Oxone® (Scheme 1).[17] With the aim of attaching two simple fluorous pony tails by a reductive-type amination approach, we next prepared the fluorous-amine **8** from the commercially available fluorous alcohol **9**, via tosylation,[18,19] azidation[20–22] and reduction with lithium aluminium hydride[20–22] (56% over three steps). Reductive amination gave the mono-tagged TEMPO **10**. All attempts at alkylation (using various bases and reaction temperatures) of this secondary amine failed. However, formation of the fluorous amide was to prove more successful. Starting from the same fluorous alcohol **9**, oxidation using Jones' reagent gave the carboxylic acid,[23] which was converted to the acid chloride with thionyl chloride and triethylamine. Amide formation proceeded in good yield to give the fluorous-TEMPO reagent **5**, in 16% overall yield over the five steps starting from **9**. Initially, the synthetic sequence was performed using two $CF_3(CF_2)_5$– fluorous pony tails;

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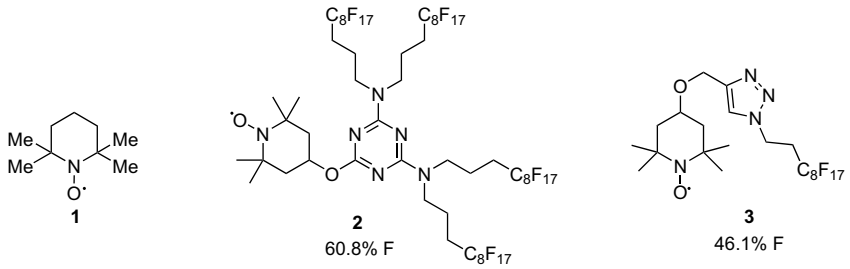


Figure 1. Recently reported heavy fluorous-TEMPO derivatives.

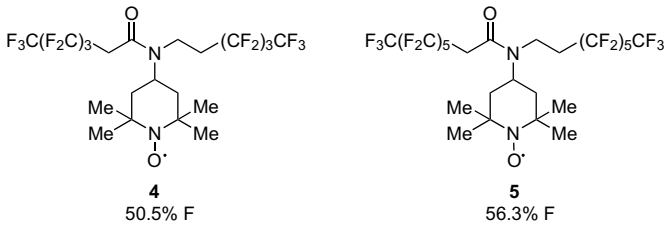
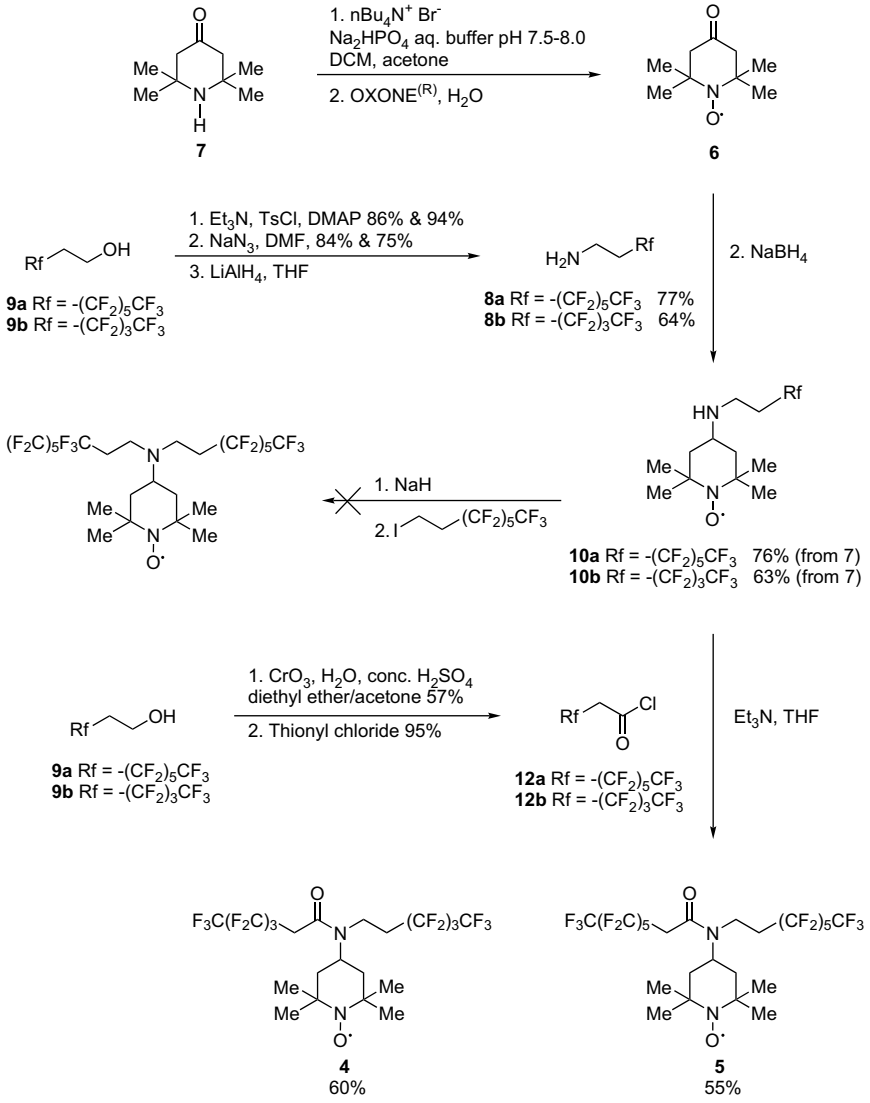


Figure 2. Light-fluorous TEMPO derivatives.

the sequence was later repeated with two shorter $CF_3(CF_2)_3$– pony tails to give **4**, which proved to be equally effective.

The partition coefficients for the two fluorous-TEMPO reagents were determined by stirring 25 mg of the fluorous-TEMPO in a mixture of 1 ml of an organic solvent and 1 ml of a fluorous solvent thermostated at 25 °C for 24 h, followed by separation and evaporation of each layer to determine the amount of fluorous-TEMPO within each layer (Satisfactory results could not be obtained using gas chromatography.). The results are presented in Table 1. These results were unsatisfactory for the concept of fluorous liquid–liquid extraction, with no solvent system showing anything close to the desired fluorous selectivity that would be



Scheme 1. Synthesis of light-fluorous TEMPO reagents.

Table 1
Partition coefficients for fluorous-TEMPO at 25 °C

Organic solvent	Fluorous solvent	Ratio (organic/fluorous)[a]	
		5 ($CF_3(CF_2)_{5-}$)	**4** ($CF_3(CF_2)_{3-}$)[b]
THF	FC-72[c]	92:8	—
THF	PFMC[d]	96:4	93:7
Toluene	FC-72	47:53	—
Toluene	PFMC	49:51	—
DCM	FC-72	39:61	76:24
DCM	PFMC	88:12	—
Methanol	FC-72	72:28	—
Methanol	PFMC	66:34	—
80% aq Methanol	FC-72	41:59	—
80% aq Methanol	PFMC	57:43	—

[a] After stirring at 25 °C for 24 h.
[b] The heavier fluorous compound **5** was prepared first and all partition coefficients obtained; only the best and worst biphasic solvent systems were selected and attempted for **4**.
[c] FC-72: perfluorohexane.
[d] PFMC: perfluoromethylcyclohexane.

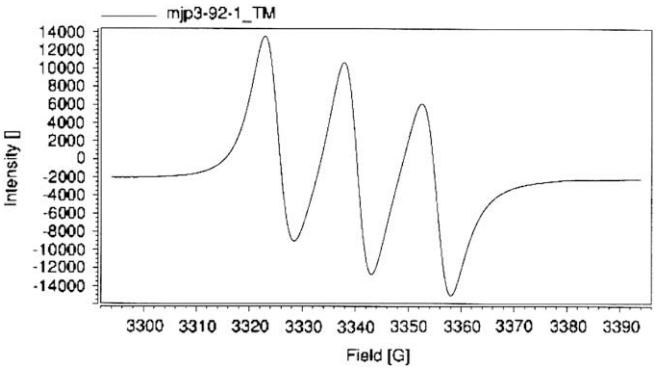
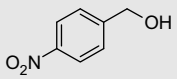
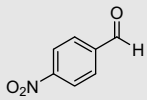
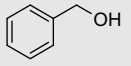
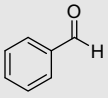
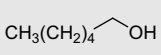
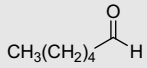
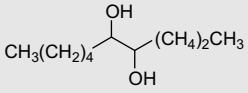
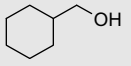
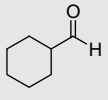
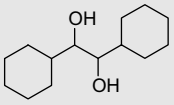
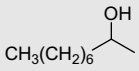
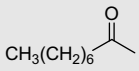
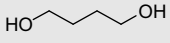
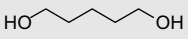
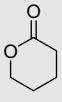
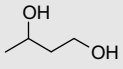
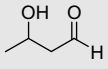


Figure 3. EPR spectrum of lighter fluorous-TEMPO, **4**.

Table 2
Oxidation reactions using fluorous-TEMPOs **4** and **5**

Entry	Starting material	Product	Method[a]	Lighter Rf-TEMPO **4**		Heavier Rf-TEMPO **5**	
				% Yield[b]	% Recovered fluorous-TEMPO[c]	% Yield[b]	% Recovered fluorous-TEMPO[c]
1			A	76	91	86 Recycle 1:89 Recycle 2:82	97 94 95
			B	65	89	—	—
2			A	89	94	—	—
			B	69	95	—	—
3			A	87[d]	94	91	94
			B	61	92		
			A			91[d]	94
4			A	89[d]	96	92	97
			B	75	93		
			A			97[d]	98
5			A	62	87	74	95
			B	—	94	—	—
6			A	71	89	—	—
			B	64	88	—	
7			A	73 (1:1.3 mixture Product/SM)	92	—	—
8			A	0	96	0	98
			B	0	97	0	89

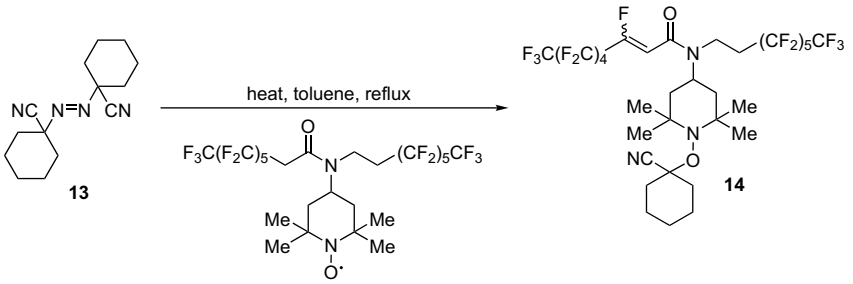
[a] Method A: alcohol (1 equiv), fluorous-TEMPO (0.03 equiv), 0.5 M KBr (0.3 equiv), NaOCl and $NaHCO_3$ (aq Buffer), 0 °C. Method B: alcohol (1 equiv), fluorous-TEMPO (0.1 equiv), Bu_4NBr (0.4 equiv), Oxone® (2.2 equiv), room temperature 22 °C.
[b] Purified and isolated yields. All compounds gave satisfactory spectroscopic and analytical data.
[c] Each reaction was purified using fluorous solid-phase extraction using fluorous silica: the organic material was first eluted using 10% water in methanol, followed by elution with 100% methanol to remove the fluorous-TEMPO.
[d] Pinacol-coupled products were obtained on one occasion; this could not be repeated.

necessary for satisfactory liquid–liquid extraction from reactions. Although compound **4** is considerably 'fluorous-light' with only 50% fluorine by weight, compound **5**, with 56% is closer to the general 'rule-of-thumb' of 60% fluorine content by weight for preferential solubility in a fluorous solvent.[1] This small difference in fluorine content is particularly obvious when comparing the partition coefficients for **4** and **5** between dichloromethane and FC-72: the greater fluorine content in **5** makes this preferentially (albeit moderately) soluble in the fluorous solvent, but the lower fluorine content of **4** now renders the molecule less fluorophilic and favours the organic solvent. Therefore, to utilise these light-fluorous TEMPO reagents, it would be necessary to use fluorous solid-phase extraction, as pioneered by Curran, employing fluorous silica.[24–26]

In order to demonstrate that we had indeed prepared a fluorous-TEMPO reagent, we next recorded the ESR spectrum of the two TEMPO reagents (Fig. 3). This revealed the same characteristic pattern as observed for the parent compound TEMPO, where the classic three line pattern is observed for a radical of spin $S=^1/_2$ adjacent and coupled to a spin $I=1$ nucleus (^{14}N) and values of $A_N=14.84$ G and $g=2.0057$. This is the first time that the EPR spectrum of a fluorous-TEMPO has been reported, definitely proving the radical nature of the compound. An identical spectrum was observed for **5**.

these results, despite many attempts. It is not known what caused these products to be formed and this is undergoing further investigation. However, it may be postulated that in the experimental procedure, the alcohol and fluorous-TEMPO are initially mixed and cooled to 0 °C before the addition of any other reagent or terminal oxidant. There is potential during this short period for the fluorous-TEMPO to abstract a hydrogen atom from the carbon bearing the alcohol (RCH_2OH) and then for two of these α-hydroxyradicals to dimerise to give the Pinacol-coupled product. The alcohol is not exposed to TEMPO alone in the second procedure B, and this may explain why the Pinacol product was never observed in this case.

Finally, we investigated the potential use of the fluorous-TEMPO reagent as a radical trap. As a simple model system, we simply heated the radical initiator **13** in toluene in the presence of fluorous-TEMPO. After fluorous solid-phase extraction, the trapped radical-adduct **14** was isolated in 97% yield. Surprisingly, this product also showed elimination of a molecule of HF and the presence of an olefin in the product, which, from NMR, we believe to have been formed adjacent to the amide, although we cannot say for certain that this is not from the other fluorous pony tail.



Both fluorous-TEMPO reagents were used in a variety of oxidation reactions, initially with the heavier Rf-TEMPO **5** and later with the lighter Rf-TEMPO **4**. Two different methods were employed for the selective and high-yielding oxidation of primary alcohols to aldehydes and both methods gave good results. Both aromatic and aliphatic alcohols were oxidised in excellent yields to the aldehyde, with no-over oxidation to the carboxylic acid observed in any case. The fluorous-TEMPO **5** recovered from the oxidation of *p*-nitrobenzyl alcohol (Table 2, entry 1) was re-employed three additional times for the same reaction, with no loss of reaction yield and only small loss in %recovery of the fluorous-TEMPO on each occasion (ca. 10%). Double oxidation of the butane-1,4-diol (Table 2, entry 5) gave the cyclic lactone in 71% yield. The reagent could also be employed for the oxidation of secondary alcohols to ketones, albeit in lower yield (Table 2, entry 4). Finally, fluorous-TEMPO showed good selectivity for a primary alcohol over a secondary one (Table 2, entry 7). Given the remoteness of the fluorous pony tails from the radical centre, it was not surprising that similar yields for the oxidation reactions were obtained for both the lighter and heavier Rf-TEMPO reagents. Although the aldehydes obtained were known compounds, in addition to conventional characterisation methods, each aldehyde had its ^{19}F NMR spectrum recorded; in no case was any fluorine signal observed.

Although each reaction in Table 2 was highly reproducible, intriguingly, on two separate occasions with the heavier Rf-TEMPO reagent **5**, Pinacol coupling-type products were obtained on the attempted oxidation of hexanol (Table 2, entry 3) and cyclohexylmethanol (Table 2, entry 4). While the characterisation data are conclusive that the diols were indeed obtained (as a mixture of *d*/*l* and *meso* forms), it has been impossible to repeat

3. Conclusions

In conclusion, we have prepared two light-fluorous TEMPO reagents, characterised these as stable free radicals and employed them as effective reagents for both oxidation reactions and as a radical spin trap. The rapid synthesis of these compounds, their comparatively low molecular weight and ease of recycling via fluorous solid-phase purification give these fluorous-TEMPO reagents, we believe, a considerable advantage over alternative fluorous and solid-supported TEMPO reagents.

4. Experimental

4.1. General

Petroleum ether or petrol refers to the fraction boiling between 40 °C and 60 °C. Dichloromethane and xylene were distilled over calcium hydride. Diethyl ether, THF and toluene were distilled over sodium and benzophenone, which were used as indicators. All other solvents were obtained anhydrous and used directly in the reaction vessel. All reactions were carried out under an atmosphere of nitrogen unless otherwise stated using vacuum/nitrogen manifold. All glassware, syringes and needles were pre-dried in an oven (120–140 °C) and cooled in a nitrogen atmosphere prior to use. Stirring was by internal magnetic follower. All chemicals were purified by distillation or recrystallisation where appropriate. Commercially available compounds were generally used without further purification. All reactions were followed by TLC. Plates were visualised under UV light (at 254 nm) or by staining with acidic potassium permanganate followed by heating. Purification was by

flash chromatography or fluorous solid-phase separation. Infrared (IR) spectra were recorded in the range 4000–600 cm^{-1} with internal calibration. Spectra were recorded as KBr discs or as thin films between NaCl plates. Proton (^1H) NMR spectra were recorded at 270 or 400 MHz and carbon (^{13}C) NMR spectra at 75 or 100 MHz, respectively in deuterated solvents. Fluorine (^{19}F) NMR were recorded at 282 MHz. NMR chemical shifts (δ) are quoted in ppm (parts per million) relative to an internal standard ($CDCl_3$). Coupling constants, *J*, are quoted as experimentally observed. EPR spectra were run operating at X-band and at 292 K.

The preparation of the fluorous tosylates[18] and azides,[20–22] amines,[21,22] carboxylic acids and acid chlorides is given in Supplementary data.

4.2. 4-Oxo-2,2,6,6-tetramethylpiperidin-1-oxyl (6)[17]

A solution of 2,2,6,6-tetramethyl-4-piperidine (2 g, 12.9 mmol) and *n*-Bu_4N^+HBr (249 mg, 0.8 mmol) in dry CH_2Cl_2 (60 ml), acetone (80 ml) and Na_2HPO_4 aq buffer (60 ml) was cooled to 0 °C. The reaction mixture was treated, at 0 °C, with dropwise addition of a solution of Oxone® (15.8 g, 25.8 mmol) in water (90 ml) over 1 h, during which time the solution turned a deep red. The pH of the solution was monitored and kept at pH 7.5–8.0 by addition of 2 M KOH. The reaction mixture was stirred at 0 °C for 3 h before separating the two phases. The aqueous phase was further extracted with CH_2Cl_2 (2×50 ml). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to afford the *title compound* as a red crystalline solid (2.18 g, 12 mmol, 99%); found $[M+H]^+$ 171.1266; $C_9H_{16}NO_2+H$ requires 171.2383; ν_{max}/cm^{-1} (KBr disc) 2977 s, 2937 s, 2878 m (C–H), 1727 s (ketone), 1624 m, 1543 s, 1366 s (N–O•), 1315 s (N–O•) and 1234 s (N–O•); δ_C (75.5 MHz; $CDCl_3$) 207.2 (*C*=O) 53.1 (2×CH_2), 28.4 and 14.3 (4×CH_3); *m*/*z* (CI) 171 [$(MH)^+$, 8%], 170 [$(M)^+$, 12%] and 156 [$(MH-O)^+$, 100%]. ^1H NMR could not be recorded. Data in agreement with literature values.

4.3. General procedure for the formation fluorous primary amines[20–22]

A solution of lithium aluminium hydride in dry tetrahydrofuran was cooled to 0 °C under N_2 and a solution of an azide in dry tetrahydrofuran was added dropwise at 0 °C over 30 min; the reaction mixture was then stirred for a further 30 min at 0 °C. The reaction was then quenched, still at 0 °C, with the careful dropwise addition of saturated brine (10–30 ml) and diethyl ether (10–30 ml). The aluminium salts formed were filtered over Celite and the filtrate was separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 ml). The organic fractions were combined, washed with water (3×30 ml), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by fractional distillation.

*4.3.1. Preparation of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctylamine (**8a**)[20–22]*

Prepared according to the general procedure using lithium aluminium hydride (332 mg, 8.7 mmol), tetrahydrofuran (15 ml) and 8-azido-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctane (3.24 g, 8.3 mmol) to afford the *title compound* as a pale yellow oil (2.43 g, 6.7 mmol, 76.5%); found [M+H] 364.0387; $C_8H_6F_{13}N+H$ requires 364.1243; ν_{max}/cm^{-1} (thin film) 3410 w (NH_2), 2988 m (C–H), 1422 m (CF_3), 1266 s (CF_2), 1241 m (CF_2), 1209 m (CF_2), 1198 m (CF_2) and 1145 w (CF_2); δ_H (300 MHz; $CDCl_3$) 3.06 (2H, t, *J*=6 Hz, $CH_2CH_2NH_2$), 2.24 (2H, m, $CH_2CH_2NH_2$) and 1.11 (2H, br s, NH_2); δ_F (282.4 MHz; $CDCl_3$) −81.3 (3F, s, CF_3), −114.1 (2F, s, CF_2), −122.1 (2F, s, CF_2), −123.4 (2F, s, CF_2), −124.1 (2F, s, CF_2) and −126.6 (2F, s, CF_2); *m*/*z* (CI) 376 (80%), 364 [$(MH)^+$, $C_8H_6F_{13}N$, 26%] and 356 (34%). Data in agreement with literature values.

*4.3.2. Preparation of 3,3,4,4,5,5,6,6,6-nonafluorohexylamine (**8b**)[20–22]*

Prepared according to the general procedure using lithium aluminium hydride (718 mg, 18.9 mmol), tetrahydrofuran (50 ml) and 6-azido-1,1,1,2,2,3,3,4,4-nonafluorohexane (5.2 g, 18.0 mmol) to afford *title compound* as a pale yellow oil (3.1 g, 11.6 mmol, 64%); bp 90 °C at 750 mmHg; δ_H (300 MHz; $CDCl_3$) 3.06 (2H, t, *J*=6 Hz, $CH_2CH_2NH_2$), 2.25 (2H, m, $CH_2CH_2NH_2$) and 1.21 (2H, br s, NH_2); δ_C (100 MHz; $CDCl_3$) 68.3 (CH_2NH_2) and 34.8 ($CH_2CH_2NH_2$); δ_F (282.4 MHz; $CDCl_3$) −81.5 (3F, s, CF_3), −114.4 (2F, s, CF_2), −125.2 (2F, s, CF_2) and −126.5 (2F, s, CF_2). Data in agreement with literature values.

4.4. General procedure for the formation of acid chlorides

The carboxylic acid was heated to 60 °C, until the solid had melted, before being treated with dropwise addition of thionyl chloride. The reaction mixture was heated to reflux over 16 h before excess thionyl chloride was removed in vacuo. The acid chloride was employed in the next step immediately and without further purification, although a small amount was isolated to confirm acid chloride formation.

*4.4.1. Preparation of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanoyl chloride (**12a**)*

Prepared according to the general procedure using 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanoic acid (1.00 g, 2.65 mmol) and thionyl chloride (1.57 g, 13.3 mmol) to afford *title compound* as a yellow oil (985 mg, 2.48 mmol, 94%), which was used immediately without further purification; found $[M-Cl]^+$ 361.0152; $C_8H_2ClF_{13}O$ requires 396.5352; ν_{max}/cm^{-1} (thin film) no broad –OH signal, 2954 m (C–H), 1809 s (acid chloride), 1408 m (CF_3), 1318 m (CF_2), 1251 s (CF_2), 1233 s (CF_2), 1203 (CF_2) and 1145 (CF_2); δ_H (300 MHz; $CDCl_3$) 3.73 (2H, t, *J*=18 Hz, CH_2COCl); δ_F (282.4 MHz; $CDCl_3$) −81.2 (3F, s, CF_3), −112.8 (2F, s, CF_2), −122.3 (2F, s, CF_2), −123.2 (2F, s, CF_2), −123.3 (2F, s, CF_2) and −124.0 (2F, s, CF_2).

*4.4.2. Preparation of 3,3,4,4,5,5,6,6,6-nonafluorohexanoyl chloride (**12b**)*

Prepared according to the general procedure using 3,3,4,4,5,5,6,6,6-nonafluorohexanoic acid (1.14 g, 4.10 mmol) and thionyl chloride (2.43 g, 20.5 mmol) to afford the *title compound* as a yellow oil (900 mg, 3.04 mmol, 74%) and which was used immediately without further purification; ν_{max}/cm^{-1} (thin film) no broad –OH signal, 2999 m (C–H), 1793 s (acid chloride), 1419 m (CF_3), 1353 s (CF_2), 1227 s (CF_2) and 1136 s (CF_2); δ_H (270 MHz; $CDCl_3$) 3.70 (2H, t, *J*=16.3 Hz, CH_2COCl); δ_F (282.4 MHz; $CDCl_3$) −81.4 (CF_3), −112.1 (CF_2), −124.2 (CF_2) and −126. 4 (CF_2).

4.5. General procedure for the formation of mono-alkylated TEMPO derivatives

A solution of 4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl in dry ethanol under nitrogen was treated with a fluorous pony tail containing amine[21,22] and stirred at room temperature over 3 days. The reaction mixture was then treated with sodium borohydride and stirred for a further 3 days at room temperature. The reaction mixture was quenched with diethyl ether/water (30 ml:30 ml) and stirred for 15 min. The aqueous phase was separated and extracted with diethyl ether (3×30 ml). The organic phases were combined, washed with water (3×30 ml), dried over $MgSO_4$, filtered and concentrated in vacuo. The red residue was purified by flash column chromatography (neutral aluminium oxide). The radical and also highly fluorinated nature of these compounds meant obtaining accurate NMR data was very difficult or impossible.

*4.5.1. 2,2,6,6-Tetramethyl-4-(3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′,8′-tridecafluorooctylamino)piperidin-1-oxyl (**10a**)*

Prepared according to the general procedure using 4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl (382 mg, 2.2 mmol), 3,3,4,4,5,5,6,6,7,7,-8,8,8-tridecafluorooctylamine (1.06 g, 2.9 mmol), sodium borohydride (128 mg, 3.4 mmol) and dry ethanol (10 ml) to afford the *title compound* as an orange/red solid (610 mg, 1.2 mmol, 52%); R_f 0.53 (4:1 [CH_2Cl_2/ether] plus 1% TEA); mp 86–88 °C (hexane); found $[M+H]^+$ 518.1570; $C_{17}H_{22}F_{13}N_2O+H$ requires 518.3617; ν_{max}/cm^{-1} (KBr) 3510 w (N–H), 3054 m, 2987 m (C–H), 1626 w, 1422 m (N–O˙), 1266 s (N–O•) and 1145 w (N–O•); δ_H could not be obtained; δ_C (100 MHz; $CDCl_3$) 55.3 C(2), 38.1 C(4), 32.2 C(1), 31.9 C(3), 29.9 C(5), 21.5 (*C*H$_3$), 20.1 (*C*H$_3$), 10.8 (*C*H$_3$) and 8.9 (*C*H$_3$); δ_F (282 MHz; $CDCl_3$) −81.07 (*C*F$_3$), −113.2 (*C*F$_2$), −121.4 (*C*F$_2$), −122.7 (*C*F$_2$), −124.0 (*C*F$_2$) and −126.5 (*C*F$_2$); *m*/*z* (CI) 518 $[(MH)^+$, 31%], 517 $[(M)^+$, 100%]; 501 $[(M-O)^+$, 27%].

*4.5.2. 2,2,6,6-Tetramethyl-4-(3′,3′,4′,4′,5′,5′,6′,6′,6′-nonafluorohexylamino)piperidin-1-oxyl (**10b**)*

Prepared according to the general procedure using 4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl (1.24 g, 7.3 mmol), 3,3,4,4,5,5,6,6,6-nonafluorohexylamine (2.5 g, 9.5 mmol), sodium borohydride (417 mg, 10.9 mmol) and dry ethanol (40 ml) to afford the *title compound* as a red/orange solid (1.68 g, 4.0 mmol, 55%); R_f 0.55 (4:1 [DCM/ether] plus 1% TEA); mp 81–82 °C (hexane); found $[M+H]^+$ 418. 5613, $C_{15}H_{22}F_9NO+H$ requires 418.3451; ν_{max}/cm^{-1} (KBr) 3296–3190 m (N–H), 2976 s, 2936 s, 2876 s (C–H), 1458 m (N–H), 1379 s (NO•), 1358 s (NO•), 1294 m (NO•), 1236 s (CF_2), 1221 s (CF_2) and 1134 s (CF_2); δ_H and δ_C could not be obtained; δ_F (282.4 MHz; $CDCl_3$) −81.9 (*C*F$_3$), −113.8 (*C*F$_2$), −125.0 (*C*F$_2$) and −126.4 (*C*F$_2$); *m*/*z* 418 $[(MH)^+$, 100%] and 401 $[(M-O)^+$, 65%].

4.6. General procedure for the formation of di-fluorous-tagged TEMPO derivatives

A solution of the mono-alkylated TEMPO derivative in dry THF was cooled to 0 °C under N_2, treated with dry triethylamine and stirred at 0 °C for 15 min. The reaction mixture was treated with the perfluorinated-acid chloride and stirred at 0 °C for 3 h. The reaction mixture was then warmed to room temperature and quenched with water (25 ml) and diethyl ether (25 ml) and stirred vigorously for 10 min. The aqueous mixture was separated and extracted with diethyl ether (3×50 ml). The organic phases were combined, washed with water (3×50 ml), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash neutral alumina column chromatography. The radical and also highly fluorinated nature of these compounds meant obtaining accurate NMR data was very difficult or impossible.

*4.6.1. 2,2,6,6-Tetramethyl-4-(3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′-tridecafluorooctyl)-(3″,3″,4″,4″,5″,5″,6″,6″,7″,7″,8″,8″,8″-tridecafluorooctan)amide piperidin-1-oxyl (**5**)*

Prepared according the general procedure using 2,2,6,6-tetramethyl-4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctylamino)piperidin-1-oxyl (600 mg, 1.16 mmol), 3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanoyl chloride (460 mg, 1.16 mmol), triethylamine (117 mg, 1.16 mmol) and dry THF (10 ml) to afford the *title compound* as an orange/red solid (818 mg, 0.93 mmol, 55%); R_f 0.42 (4:1 [DCM/ether] plus 1% TEA); mp 48–49 °C (petrol); ν_{max}/cm^{-1} (KBr disc) 2979 w, 2899 w, 1702 m, 1639 s (amide), 1436 m, 1365 m, 1294 m (CF_3), 1236 s (CF_3), 1221–1159 br, s (8×CF_2), 1144 s (CF_2) and 1114 s (CF_2); δ_H could not be obtained; δ_C (100 MHz; $CDCl_3$) 161.9 (*C*H$_2$*C*ON), 57.7 (*C*HN), 34.1 (*C*H$_2$CO), 33.9 (CH$_2$*C*H$_2$N), 30.5 (*C*H$_2$CHN), 30.3 (*C*H$_2$CHN), 28.2 (*C*H$_2$CH$_2$N), 21.8 (*C*H$_3$), 19.6 (*C*H$_3$), 11.9 (*C*H$_3$) and 11.8 (*C*H$_3$); δ_F (282.4 MHz; $CDCl_3$) −81.1 (*C*F$_3$), −112.7 (*C*F$_2$), −118.6 (*C*F$_2$), −121.5 (*C*F$_2$), −124.3 (*C*F$_2$) and −126.5 (*C*F$_2$); *m*/*z* (EI) 877 $(M+H)^+$, 100%) and 857 $(M+H, -F)^+$, 58%). Found C 33.37, H 2.22, N 2.15, F 56.28%. $C_{25}H_{23}F_{26}N_2O_2$ requires C, 34.22; H, 2.64; F, 56.30; N, 3.19; O, 3.65% (sample was very difficult to dry, hence the slight discrepancy).

*4.6.2. 2,2,6,6-Tetramethyl-4-(3′,3′,4′,4′,5′,5′,6′,6′,6′-nonafluorohexyl)-(3″,3″,4″,4″,5″,5″,6″,6″,6″-nonafluorohexan)amide piperidin-1-oxyl (**4**)*

Prepared according to the general procedure using 2,2,6,6-tetramethyl-4-(3,3,4,4,5,5,6,6,6-nonafluorohexylamino)piperidin-1-oxyl (900 mg, 2.16 mmol), 3,3,4,4,5,5,6,6,6-nonafluorohexanoyl chloride (639.8 mg, 2.158 mmol), triethylamine (217.9 mg, 2.158 mmol) and dry THF (15 ml) to afford *title compound* as an orange solid (802 mg, 1.29 mmol, 60%); R_f 0.63 (4:1 [DCM/ether] plus 1% TEA); mp 84 °C; δ_H could not be obtained; δ_C 162.7 (C1′), 56.3 (C4), 36.1 (C2′), 35.3 (C1″), 30.9 and 30.5 (C3 and C5), 27.4 (C2″), 21.8 (CH_3), 19.5 (CH_3), 12.1 (CH_3), 11.8 (CH_3); δ_F (282 MHz, $CDCl_3$) −81.1 (CF_3), −119.8 (CF_2), −124.3 (CF_2), −125.4 (CF_2); *m*/*z* (EI) 677.1 $[(M)^+$, 27%], 657.1 $[(M-HF)^+$, 48%]. Found C, 38.16; H, 3.30; N, 4.00; F, 48.71%. $C_{21}H_{23}F_{18}N_2O_2$ requires C, 37.23; H, 3.42; F, 50.48; N, 4.14% (sample was very difficult to dry, hence the slight discrepancy).

4.7. General procedure for the determination of partition coefficients

The fluorous-TEMPO reagent (25 mg) was dissolved in the organic solvent (1 ml) and the fluorous solvent (1 ml) added in a small sample vial. The vial was placed in a thermostatic bath at 25 °C and the mixture was stirred vigorously for 24 h. After this time, the two layers were carefully separated and concentrated in vacuo. The residue remaining in each flask was weighed to give the amount of fluorous-TEMPO in each layer. Each system was repeated twice for accuracy.

4.8. Typical experimental procedure for oxidation reaction

4.8.1. Method A: general procedure for the mild oxidation of alcohols using fluorous-TEMPO and NaOCl

A solution of the alcohol (1 equiv, typically 0.5–1 mmol) in CH_2Cl_2 was cooled to 0 °C and treated with a solution of fluorous-TEMPO (0.03 equiv) in CH_2Cl_2. The reaction mixture was stirred at 0 °C for 5 min before being treated with a 0.5 M solution of KBr (0.3 equiv) and NaOCl solution buffered with $NaHCO_3$. The reaction mixture was stirred at 0 °C for 1 h before being allowed to warm to room temperature over 20 min. The aqueous phase was separated and extracted with CH_2Cl_2 (3×10 ml). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by fluorous silica column chromatography, eluting first with 10% water in methanol to remove the organic reaction components, followed by 100% methanol to obtain the recycled Rf-TEMPO.

4.8.2. Method B: general procedure for the mild oxidation of alcohols using fluorous-TEMPO and oxone®

A solution of the alcohol (1.0 equiv, typically 0.5–1 mmol) and Bu_4NBr (0.4 equiv) in dry toluene was treated with a 0.1 M solution of fluorous-TEMPO (0.1 equiv) in dry toluene and oxone® (2.2 equiv) and stirred at room temperature for 8–48 h. After TLC showed complete conversion the solvent was removed in vacuo and the residue was suspended between CH_2Cl_2 and water (10 ml, 1:1). The aqueous phase was separated and extracted with CH_2Cl_2 (3×10 ml). The organic phases were combined, washed with water (15 ml), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by fluorous silica column chromatography, eluting first with 10% water in methanol to remove the organic reaction components, followed by 100% methanol to obtain the recycled Rf-TEMPO.

4.9. 3′,3′,4′,4′,5′,5′,6′,6′,6′-Nonafluorohexanoic acid [1-(1-cyano-cyclohexyloxy)-2,2,6,6-tetramethylpiperidin-4-yl]-(3″,3″,4″,4″,5″,5″,6″,6″,6″-nonafluorohexyl)-amide (14)

Dry toluene (5 ml) was degassed using N_2 for 30 min. The dry toluene was treated with 3′,3′,4′,4′,5′,5′,6′,6′,6′-nonafluorohexanoic acid (1-hydroxyl-2,2,6,6,-tetramethylpiperidin-4-oxyl)-(3″,3″,4″,4″,5″,5″,6″,6″,6″-nonafluorohexyl)-amide (150 mg, 0.221 mmol) and heated to reflux temperature. This solution was then treated with portionwise additions of azobis(cyanocyclohexane) (5×21.5 mg, 5×0.0884 mmol) over 5 h, at reflux temperature. The reaction mixture was then heated at reflux temperature for 24 h. The reaction mixture was then cooled to room temperature and the toluene was removed in vacuo. The residue was purified by flash fluorous silica column chromatography, eluted with 100% methanol, to afford the *title compound* as a white/creamy solid (169 mg, 0.215 mmol, 97%) mp 102–104 °C; found 788.1976 (M+Na), $C_{28}H_{32}F_{17}N_3O$+Na requires 788.2121; ν_{max}/cm^{-1} 2981, 2880, 1654 (C=C), 1632 (CON), 1433 (CF), 1246 (CF), 1217–1167 (br, CF), 1138; δ_H (400 MHz; $CDCl_3$) 6.22 (1H, d, *J*=46 Hz, CF=C*H*), 4.82 (2H, br s, $NCH_2CH_2CF_2$), 3.98 (1H, t, *J*=17.6 Hz, NC*H*), 3.59 (2H, t, *J*=3.5 Hz, $NCH_2CH_2CF_2$), 2.42 (2H, m, $NCHCH_2$-amide side), 2.12 (2H, d, *J*=8.9 Hz, $NCHCH_2$), 1.82 (4H, br m, $COCN(CH_2)_5$), 1.57 (6H, br m, $COCN(CH_2)_5$), 1.32 (6H, s, 2×CH_3), 1.24 (6H, s, 2×CH_3); δ_C (100 MHz; $CDCl_3$) 161 C(1), 136 C(3), 108 C(2), 78 C(5), 49 C(6), 45 C(13+14), 35 C(4), 32 C(9+11), 29 C(7+8), 23 C(17), 22 C(15+16) and 20 C(10+12); δ_F (376 MHz; $CDCl_3$) −81.3 (CF_3), −81.9 (CF_3), −115.7 (CF_2), −120.5 (CF_2), −125.5 (CF_2), −127.3 (CF_2), −127.8 (CF_2).

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Supplementary data

Experimental procedures for compounds **6**, **8a** and **b**, **12a** and **b** and **14**, together with copies of spectra for compounds **4**, **5**, **10a** and **10b** and **14**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.078.

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