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Photochemical direct perfluoroalkylation of phenols

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ABSTRACT

A metal-free photochemical strategy for the direct aromatic perfluoroalkylation of phenols is reported. This operationally simple approach occurs at ambient temperature and under illumination by a fluorescent light bulb. The chemistry is driven by the ability of phenolate anions, transiently generated upon deprotonation of phenols, to directly reach an electronically excited state upon light absorption while successively triggering the formation of reactive radical species from perfluoroalkyl iodides. Preliminary mechanistic studies are reported.

1. Introduction

Fluorine-containing functional groups can profoundly alter the intrinsic properties of organic compounds. For this reason, incorporating perfluoroalkyl groups into aromatic scaffold is a chemical strategy often exploited in medicinal chemistry to modulate the biological activity of drug candidates.[1] Since 1957, over 150 fluorinated drugs have come to market (Fig. 1),[1a] justifying the profuse efforts made by the synthetic community to develop effective methodologies for directly incorporating perfluoroalkyl groups into aromatic compounds. To achieve this synthetic goal, cross-coupling methodologies that use stoichiometric amount of metals have been developed.[2] This approach requires that the fluorinated fragments are installed in place of halides or boronic acid derivatives. More recently, catalytic variants based on transition metals (especially copper and palladium) have been successfully realized.[3]

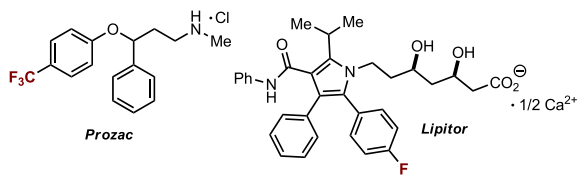

Fig. 1. Examples of major fluorinated drugs.

The direct functionalization of simple arenes, by avoiding the need for the pre-installation of a leaving group on the aromatics, provides a more straightforward approach. However, the direct introduction of perfluoroalkyl groups into a non-activated C–H bond of aromatic rings is a challenging transformation for which few strategies are available.[4] Typically, direct functionalization methodologies are based on radical reactivity. They capitalize upon the strongly electrophilic nature of the perfluoroalkyl radicals,[5] which are eager to react with arenes through the classical homolytic aromatic substitution (HAS) pathway.[6] Generating such radicals generally require harsh reaction conditions, including the use of high reaction temperature,[7a,b] stoichiometric amounts of radical initiators and/or metals,[7c–i] and potentially explosive oxidants.[7k–m] Recently, metal-based photoredox catalysis driven by visible light has been identified as a suitable approach to generate fluorinated radicals ($R_F^{\bullet}$) from perfluoroalkyl iodidies (R_FI, **1**, R_F indicates the perfluoroalkyl fragment) under mild reaction conditions (Scheme 1a).[8] In 2014, our research group developed an operationally simple strategy for the direct aromatic perfluoroalkylation of α-cyano arylacetates **I** that proceeded without the need for an external photosensitizer (Scheme 1b).[9] The metal-free process relied upon the formation of photon-absorbing electron donor-acceptor (EDA) complexes **II**,[10] generated in the ground-state upon association of R_FI with the electron-rich enolate, formed by deprotonating α-cyano arylacetates **I**. Visible light irradiation of the colored EDA complex **II** induced a single electron transfer (SET), allowing access to perfluoralkyl radicals under mild conditions. This served as the

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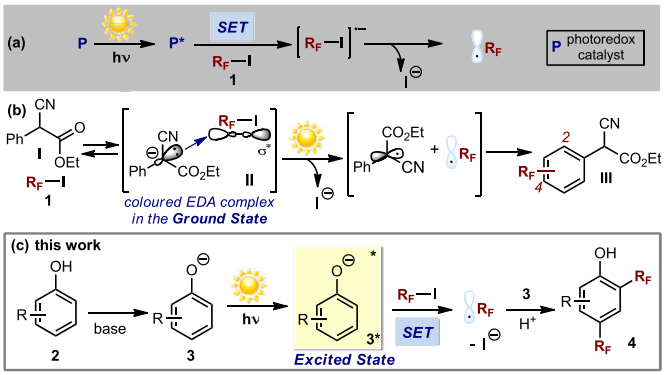
initiation step of a radical chain mechanism occurring trough a classical HAS pathway, and leading to product **III**.



Scheme 1. a & b: Previous photochemical strategies to generate perfluoroalkyl radicals ($R_F^{\cdot}$). c: the present metal-free strategy, which serves for the direct perfluoroalkylation of phenols **2** at ambient temperature.

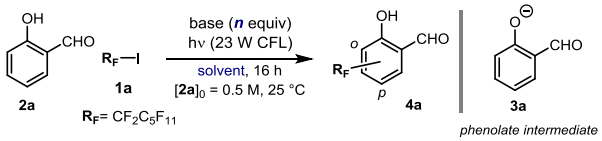
Herein, we describe a novel photochemical strategy for the direct perfluoroalkylation of phenols[11] with R_FI, which occurs under mild conditions, since it requires ambient temperature and illumination by a compact fluorescent light (CFL) bulb in order to proceed. The chemistry does not rely on the use of any external photoredox catalyst nor on the formation of ground-state EDA complexes to access radical reactivity patterns. Instead, the process is driven by the ability of phenolate anions **3**,[12] generated upon base-mediated deprotonation of phenols **2**, to directly reach an electronically excited state by light absorption while successively triggering the formation of the perfluoralkyl radicals from R_FI, **1** (Scheme 1c). Despite the propensity of excited phenolates to undergo a photo-induced electron ejection has been established in the 40's of the last century,[12,13] this mechanism has not found application in synthetic organic chemistry so far.

It is worth noting that, recently, Matsugi and co-workers developed a method for the direct perfluoroalkylation of phenols, which relied upon the use of stoichiometric amounts of a radical initiator while requiring a large excess of base (8 equiv of cesium carbonate) to deprotonate the phenols.[14] Our methodology, although is characterized by a similar reactivity, allows for a wider substrate scope. In addition, the systems are mechanistically distinguished by the way in which the perfluoroalkyl radical generation is achieved.

2. Results and discussion

Our initial explorations focused on the reaction between salicylaldehyde **2a** and perfluorohexyl iodide **1a** (Table 1). The experiments were conducted in CH_3CN under irradiation by a 23 W CFL lamp. Performing the reaction in the presence of a base such as 1,1,3,3-tetramethyl guanidine (TMG, 1 equiv), so as to favor the formation of the corresponding phenolate **3a**, provided both the *ortho* and *para* functionalized products **4a** in a roughly 5:1 ratio, along with the *ortho-para* bifunctionalized adduct *o,p*-**4a** (entry 1, total yield of 31%). Increasing the amount of TMG (2.5 equiv, entry 2) resulted in a higher reactivity (77% total yield), while the adduct *o,p*-**4a** was formed as the major product. A control experiment revealed how the careful exclusion of light completely suppressed the process, thus establishing the photochemical nature of the reaction (entry 3). In addition, we confirmed that the photochemical activity of the phenolate **3a**, formed in situ upon deprotonation of **2a**, was essential for reactivity, since in the absence of a base the starting substrates were completely recovered (entry 4). It is worth noting that, upon addition of TMG, the solution of salicylaldehyde **2a**, which was almost colorless, immediately turned to a bright yellow color, indicating the ability of the phenolate **3a** of absorbing in the visible spectral region (blue line in Fig. 2). Addition of the iodide **1a** did not bring about any appreciable change of the

Table 1
Reaction optimization[a]



Entry	Base (n)	Solvent	% Yield[b]	*o*-**4**	*p*-**4**	*o,p*-**4**%[c]
1	TMG (1)	CH_3CN	31	52%	9%	39%
2	TMG (2.5)	CH3CN	77	32%	8%	60%
3[d]	TMG (2.5)	CH_3CN	0	—	—	—
4	None	CH_3CN	0	—	—	—
5[e]	TMG (2.5)	CH_3CN	68	35%	6%	59%
6	KOH (2.5)	CH_3CN	0	—	—	—
7	$NaHCO_3$ (2.5)	CH_3CN	0	—	—	—
8	K_2CO_3(2.5)	CH_3CN	32	28%	0%	72%
9	Cs_2CO_3 (2.5)	CH_3CN	21	5%	0%	95%
10	TMG (2.5)	DCM	62	39%	13%	48%
11	TMG (2.5)	Toluene	36	32%	8%	60%
12	TMG (2.5)	DMF	65	28%	6%	68%
13	TMG (2.5)	MeOH	26	54%	30%	16%
14	TMG (2.5)	EtOAc	70	38%	11%	51%

[a] TMG: 1,1,3,3-tetramethylguanidine. Reactions performed on a 0.1 mmol scale using 3 equiv of **1a**, $[\mathbf{2a}]_0$=0.5 M, and a 23 W CFL bulb to illuminate the reaction vessel.

[b] Total yield determined by ^1H and ^{19}F NMR analysis using 1-fluoro-2-nitrobenzene as the internal standard.

[c] Percent distribution of the *para* (*p*-**4**), *ortho* (*o*-**4**) and *ortho*, *para* (*o,p*-**4**) functionalized products.

[d] Reactions performed *i*) in the dark, or *ii*) in air, or *iii*) in the presence of 2 equiv of TEMPO, were all completely inhibited.

[e] Reaction performed using a 300 W Xenon lamp, equipped with a cut-off filter at 385 nm.

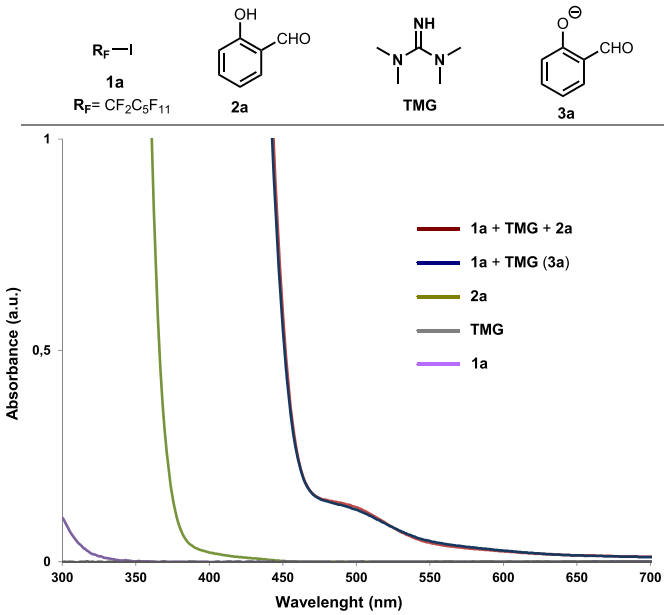


Fig. 2. Optical absorption spectra recorded in CH_3CN in quartz cuvettes (1 cm path) using a Shimadzu 2401 PC UV-visible spectrophotometer. [**2a**]=0.0025 M, [**1a**]=0.0075 M; [TMG]=0.00625 M. While the substrates **1a**, **2a**, and TMG are almost colorless, the formation of the phenolate anion **3a**, generated upon TMG addition, determines a strong bathochromic shift (blue line). Its combination with perfluorohexyl iodide **1a** does not lead to any appreciable change of the absorption spectrum (red line perfectly overlays the blue line).

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absorption spectrum (red line in Fig. 2, perfect overlap with the absorption of **3a**), which excluded the formation of an EDA complex ground-state association with the phenolate **3a**.

While further insights on the photo-activity[12] of the phenolate anion of type **3** are discussed in a following section of the manuscript, the observed reactivity deserves some comments. The product distribution is congruent with the ability of the phenolate intermediate **3a** of acting, by means of mesomeric effects, as a powerful electron releasing group, thus increasing the electronic density on both the *ortho* and *para* positions of the aromatic ring. This scenario is supported by the reactivity resonance parameter (σ_R) of the phenolate anion, derived from simple phenol, which is reported to be −0.60[15] (for comparison, an *N*,*N*-dimethyl amino substituent has a σ_R=−0.56). Mechanistically, the mesomeric effect within **3a** facilitates the trapping of the electrophilic perfluorohexyl radical through the classical HAS pathway,[6] which is generally characterized by a low level of regioselectivity.[7c,14]

We then conducted further control experiments to better understand the reactivity. The inhibition of the reaction observed under aerobic atmosphere was consonant with a radical mechanism occurring. This was further corroborated by the experiment conducted in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 2 equiv), since the product **4a** was not detected after prolonged exposure to light (entry 3 in Table 1). An additional experiment revealed how the use of a 300 W Xenon lamp, equipped with a cut-off filter at 385 nm, did not significantly alter the reaction efficiency (entry 5). This results is mechanistically relevant since it excluded a possible homolytic cleavage of the C—I bond in **1** (not feasible upon irradiation with such low-energy photons) as responsible for the $R_F^{\bullet}$ generation.

A cycle of optimization studies did not bring about any improvement in the efficiency of the model perfluoroalkylation. Inorganic bases were not suitable for the reaction (entries 6–9). We also tested different solvents (entries 10–14). Although DCM, ethyl acetate, and DMF provided a good reactivity, none of them could parallel the performance offered by CH_3CN (entry 2).

With the best conditions in hand (CH_3CN, 2.5 equiv of TMG), we studied the evolution of the product formation during time (Fig. 3).

After an apparent induction period, the perfluoroalkylation became fast and the total yield of **4a** increased rapidly reaching a standstill at about 80% of conversion. To account for this reactivity profile, we propose that molecular oxygen (present in trace quantities despite the applied freeze-pump-thaw procedure) retards the initiation of the reaction by quenching the phenolate triplet state.[12d,13b] This is congruent with the complete loss of reactivity observed when running the reaction in air (Table 1, entry 3). As a final comment, the yield of the mono-perfluoralkylated products *o*-**4a** and *p*-**4a** reached a maximum to then decrease during the time. In contrast, the formation of the bifunctionalized adduct *o*,*p*-**4a** uniformly increased with the reaction progression, indicating that both *o*-**4a** and *p*-**4a** are reactive intermediates, which were continuously transformed into *o*,*p*-**4a**.

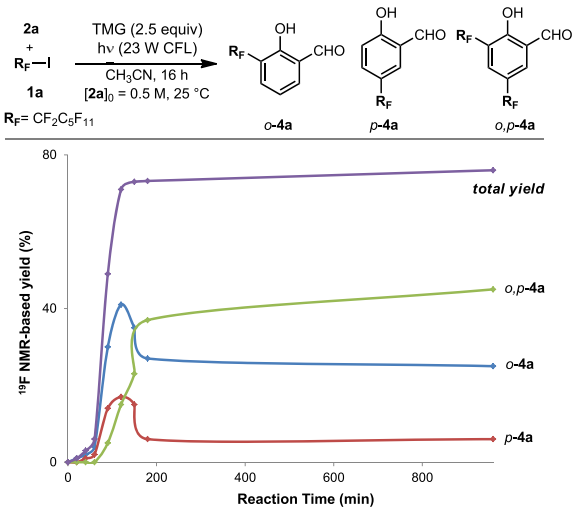

Fig. 3. Evolution of the product distribution during the reaction progress.

Next, we evaluated the synthetic potential of the photochemical perfluoroalkylation strategy, reacting differently substituted phenols with perfluorohexyl iodide **1a**. As shown in Fig. 4b, a variety of electron-withdrawing substituents at the *ortho*-position, including aldehyde, ester, bromine, and ketone moieties, was well tolerated. The resulting perfluoroalkylation took place with moderate regioselectivity, favoring the formation of the bi-functionalized *ortho*, *para*-adducts *o*,*p*-**4a**–**d**. Notably, the major positional isomers could be easily isolated by simple chromatography on silica gel, increasing the synthetic utility of the approach. In consonance with the classic HAS reactivity,[6] the use of a strongly electron-withdrawing nitro group greatly reduced the efficiency of the reaction, because of the reduced electron density on the arene (**4e**). As a limitation of the system (Fig. 4c), our attempts to react the unsubstituted phenol or a substrate bearing an electron donating methoxy moiety have met with failure (products **4f** and **4g**). Interestingly, the perfluoroalkylation of a *O*-methyl protected phenol did not proceed at all (**4h**), further highlighting the need for the phenolate formation in order for the photochemical reaction to occur.

Phenols bearing moderate electron-withdrawing group at the *para* position were also suitable substrates, affording the bifunctionalized *ortho*-adducts *o*,*o*′-**4i**–**j** in synthetically useful yield (Fig. 4d). The photochemical method was also useful to directly functionalize paracetamol, a widely prescribed pharmaceutical agent used as a mild analgesic. Albeit paracetamol bears a phenol moiety decorated with a weak electron-donating amide group, the corresponding product *o*,*o*′-**4k** was obtained in moderate yield using an excess of **1a** (6 equiv). Also an indanone derivative was a suitable substrate, the resulting adduct **4l** being obtained in moderate yield.

We also found that the system is amenable to the use of other perfluoralkyl iodides (Fig. 4e). We focused on a phenol adorned with two electron-withdrawing groups (*o*-ester and *p*-ketone), since the photochemical perfluoroalkylation led to the regioselective formation of the sole *ortho*-adducts in high chemical yield. In addition to the perfluorohexyl chain (product *o*-**4m**), either a shorter or a longer perfluorinated chain were installed in a fairly good yield to afford *o*-**4n** and *o*-**4o**, respectively. Notably, the trifluoromethyl moiety could be easily installed starting from CF_3I (*o*-**4p**).

We then evaluated the possibility of applying our photochemical perfluoroalkylation strategy to *meta*-aryl substituted phenols (Fig. 5a). The *ortho*-adduct *o*-**5a** was produced as the major isomer, while only a minor amount of the *ortho*-*para*-bifunctionalized compound was formed. This product distribution was probably dictated by steric effects of the *meta*-aryl substituent, which favored a single perfluoroalkylation event. Interestingly, the perfluoroalkylated adducts *o*-**5b**–**d** exhibited axial chirality.[16] This was due to the steric interactions between the *ortho*-methyl substituent on the pendant aryl moiety and the perfluoralkyl fragment, which precluded the possibility for the aryl–aryl single bond to freely rotate. Rotationally hindered biaryl axes are important stereogenic elements found in a number of natural products, chiral auxiliaries, and catalysts.[17] In particular, the antibiotic vancomycin contains three stable chiral axes, including one that features a tri-hydroxyl substituted bi-aryl system.[18]

The configurational stability of the chiral axis in *o*-**5b** was established by means of variable temperature (VT)-^{19}F NMR

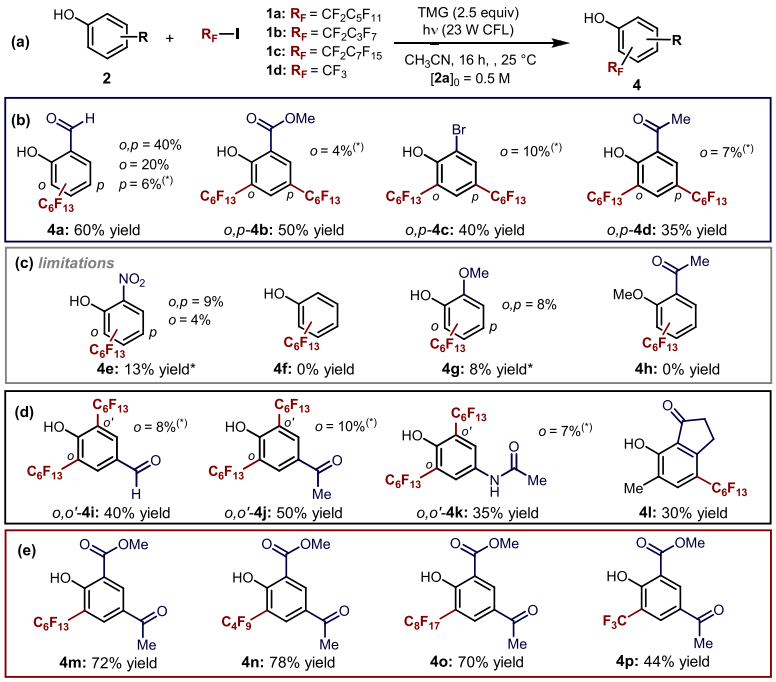

Fig. 4. Metal-free photochemical aromatic perfluoroalkylation of substituted phenols. The yields refer to the major isolated regioisomeric compounds; for **4a**, since two positional isomers could be isolated by chromatography, individual yields are also given. [*]^{19}F NMR yields of the minor positional isomers, as inferred by analysis of the crude reaction. (**a**) General conditions: reactions performed on a 0.2 mmol scale using 3 equiv of perfluoroalkyl iodides **1**, 2.5 equiv of TMG, 0.4 mL of MeCN and a 23 W CFL bulb; an acidic work-up (HCl 1N) is required to isolate the products. For the synthesis of compounds **4c**, **4i**, **4j**, and **4k**, 6 equiv of **1** have been used. (**b**) Scope of the perfluorohexylation of *o*-substituted phenols. (**c**) Limitations of the system. (**d**) Perfluorohexylation of *p*-substituted phenols and of an indanone derivative. (**e**) Scope of the perfluoroalkylating agents.

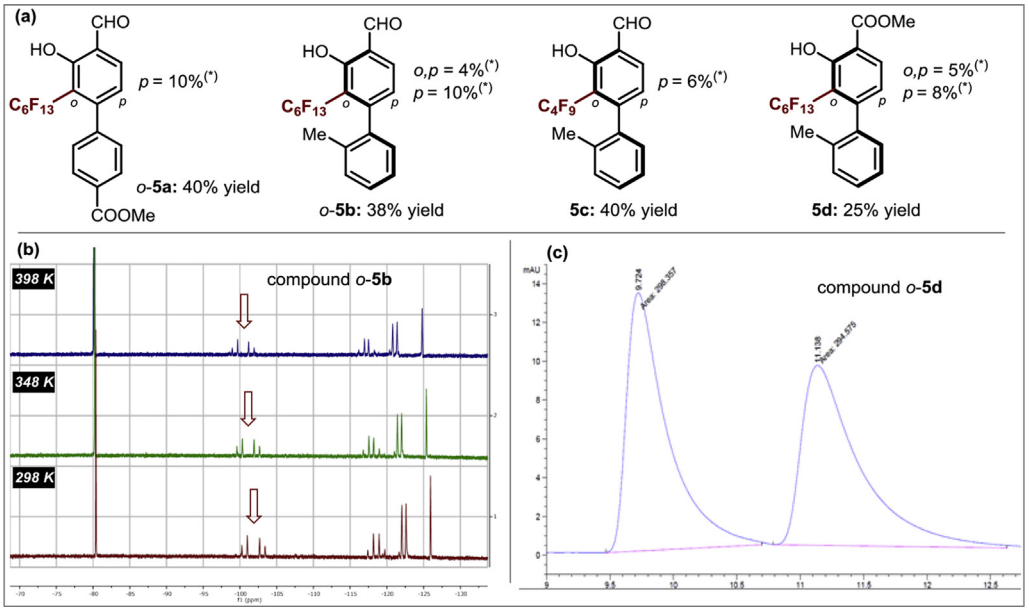

Fig. 5. (**a**) Metal-free photochemical aromatic perfluoroalkylation of biaryl phenols. The yields refer to the major isolated regioisomeric compounds. [*]^{19}F NMR yields of the minor positional isomers, as inferred by analysis of the crude reaction. (**b**) (VT)-^{19}F NMR studies (376 MHz) of *o*-**5b** in dimethyl sulfoxide-d_6. Red spectrum: 298 K; green spectrum: 348 K; blue spectrum: 398 K. The red arrows identify the diastereotopic CF_2 signals. (**c**) Chromatographic trace of the two enantiomers of *o*-**5d** (chiral stationary phase column: IC-3; eluent: hexane/dichloromethane 98:2; flux: 0.5 mL/min).

analyses, conducted in dimethyl sulfoxide-d_6. The presence of the axial stereogenic element rendered the two fluorine nuclei of the CF_2 group adjacent to the arene diastereotopics (Fig. 5b). Even at a temperature as high as 398 K, we could not observe coalescence of the diastereotopic CF_2 signals, which confirmed the high stability of the chiral axis against rotation. In addition, we found that a perfluorobutyl fragment was bulky enough to block the rotation between the two aromatic systems (product *o*-**5c**). A bi-aryl phenol bearing an ester substituent was also a suitable substrate, since compound *o*-**5d** was isolated in a moderate yield. In this case, the configurational stability of the chiral axis has allowed the separation of the atropoisomers by HPLC analysis on a chiral stationary phase (Fig. 5c). All our attempts to perform an enantioselective variant of the process, i.e. a dynamic kinetic resolution of the biaryl

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atropisomers via photochemical perfluoroalkylation driven by a chiral phase transfer catalyst or a chiral base, have met with failure.[19]

2.1. Mechanistic considerations

Our initial explorations, detailed in Table 1, indicated that the photochemical activity of the phenolate **3a**, formed in situ upon deprotonation of **2a**, was essential for reactivity. To further examine the possible implication of the phenolate within the photochemical regime, we investigated the photo-physical behaviour of the intermediate **3a**, prepared by dissolving salicylaldehyde **2a** in a freshly distilled solution of TMG.[20] Fig. 6a shows the absorption spectrum of **3a**. More importantly, we have recorded the emission spectra of **3a** upon excitation at 460 nm (Fig. 6b, maximum emission at 490 nm). A series of Stern-Volmer quenching studies was performed, which revealed that perfluorohexyl iodide **1a** effectively quenched the excited state of **3a**.

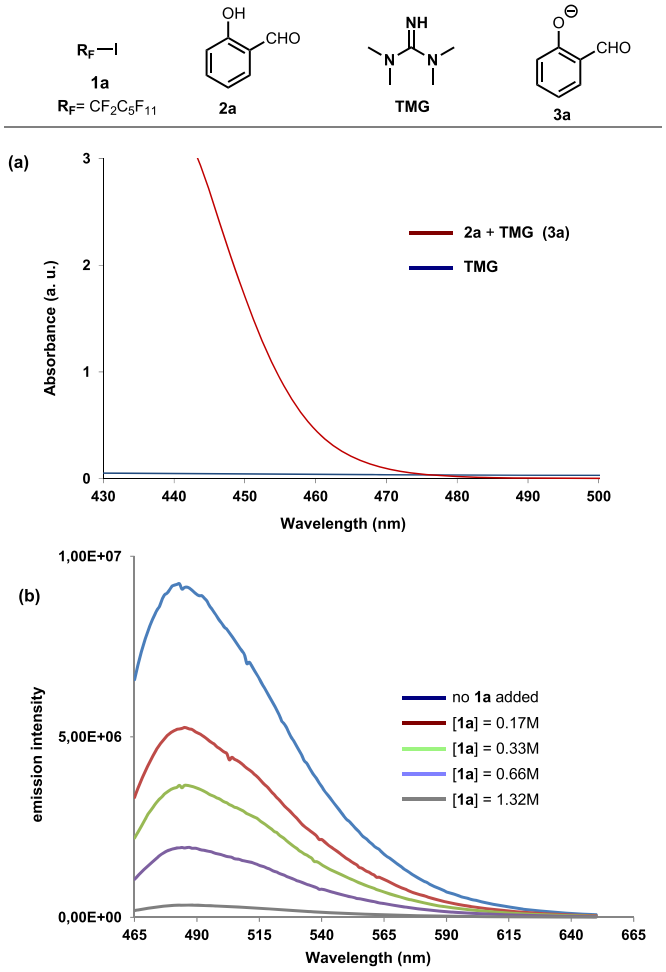

Fig. 6. (**a**) Optical absorption spectra of neat TMG (blue line) and of the phenolate **3a** in neat TMG ([**3a**]=0.007 M, red line). (b) Quenching of the phenolate **3a** emission ([**3a**]= $7\cdot10^{-3}$ M in TMG, excitation at 460 nm) in the presence of increasing amounts of perfluorohexyl iodide **1a**.

On the basis of these observations, we propose a radical chain mechanism, which follows a classical HAS pathway[6] (Fig. 7). The reaction is initiated by the photochemical activity of the phenolate anion of type **3**, formed by deprotonation of the phenol **2**. Upon light absorption, **3** can reach an electronically excited state (**3***)

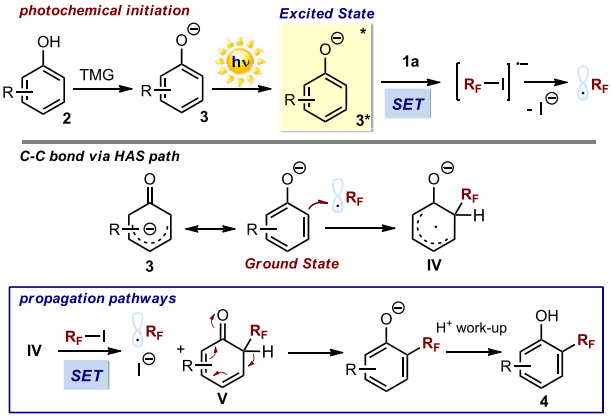

Fig. 7. Proposed mechanism: exploiting the dichotomous reactivity profile of phenolates **3** in the ground- and excited-states. For simplicity, only the *ortho*-alkylation pathway is shown.

triggering the formation of the electron-deficient radical $R_F^{\bullet}$ through the reductive cleavage of the perfluorohexyl iodide C—I bond via a single electron transfer (SET) mechanism. Consistently with a SET pathway, the model reaction was strongly inhibited when performed in the presence of 0.2 equiv of a redox trap such as 1,4-dinitrobenzene (30% yield, 16 h). $R_F^{\bullet}$ is then trapped by the ground-state phenolate **3** to form the new C—C bond. The mesomeric effect of the phenolate anion facilitates the C—C bond formation leading to the cyclohexadienyl radical **IV**. As for the chain propagation step, **IV** is oxidized by R_FI through a SET mechanism to give the cyclohexadienyl intermediate **V** along with $R_F^{\bullet}$ and the iodide anion. **V** is eventually deprotonated to form the final product **4** (upon acidic work-up).

3. Conclusions

In summary, we have developed a direct and effective way to install perfluoroalkyl and trifluoromethyl groups within the aromatic ring of substituted phenols. The reaction protocol is operationally simple, conducted at ambient temperature with readily available substrates and reagents, and using household CFL bulbs as the light source. The chemistry is driven by the ability of phenolate anions to act as photosensitizers upon excitation by simple light irradiation, and to trigger the formation of perfluoroalkyl radicals under mild conditions.

4. Experimental section

4.1. General information

All reactions were set up under an argon atmosphere in oven-dried glassware using standard Schlenk techniques, unless otherwise stated. Synthesis grade solvents were used as purchased and the reaction mixtures were deoxygenated by three cycles of freeze-pump-thaw. Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (35–70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were employed, using UV light as the visualizing agent and an acidic mixture of *para*-anisaldehyde or basic aqueous potassium permanganate ($KMnO_4$) stain solutions, and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator. The ^1H and ^{13}C NMR spectra were recorded at 400 MHz or 500 MHz for ^1H and at 100 MHz or 125 MHz for ^{13}C, respectively. The chemical shifts (δ) for ^1H and ^{13}C are given in parts per million relative to residual

signals of the solvents ($CHCl_3$ @ 7.26 ppm ^1H NMR, 77.0 ppm ^{13}C NMR). Coupling constants are given in Hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; bs, broad signal. Mass spectra (high and low resolution) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on a Bruker Maxis Impact (QTOF) or Waters Micromass LCT-Premier (TOF) in Electrospray Ionization (ESI) by direct infusion. Optical rotations Optical rotations were measured on a Polarimeter Jasco P-1030 and are reported as follows: $[\alpha]_D$ rt (c in g per 100 mL, solvent). UV–vis measurements were carried out on a Shimadzu UV-2401PC spectrophotometer equipped with photomultiplier detector, double beam optics and D_2 and W light sources. The emission spectra were recorded in a Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with photomultiplier detector, double monochromator and 350 W xenon light source. Cut-off and band-pass photochemical experiments have been performed using a 300 W xenon lamp (*Asashi* Spectra Co., Ltd.) to irradiate the reaction mixture. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated.

4.2. General procedures for the light-driven perfluoroalkylation of phenols

A 10 mL Schlenk tube was charged with the appropriate phenol **2** (0.2 mmol), acetonitrile (0.4 mL, 0.5 M referring to **2**), perfluoroalkyl iodide **1** (0.6 mmol, 3 equiv) and *N*,*N*,*N*′,*N*′-tetramethylguanidine (0.063 mL, 0.5 mmol, 2.5 equiv). The reaction mixture was thoroughly degassed via 3 cycles of freeze pump thaw, and the vessel was refilled with argon, sealed, and positioned approximately 5 cm away from a household full spectrum 23 W compact fluorescent light (CFL). For the preparation of the trifluoromethylated phenol **4p**, the trifluoroiodomethane (0.6 mmol, 15 mL, gas) was added via gas syringe at −196 °C (nitrogen bath) after freeze pump thaw of the reaction mixture.

After stirring for the indicated time, the reaction was diluted with DCM, quenched with aqueous HCl 1 M solution and extracted 3 times with DCM. The organic phase was then dried and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the title compounds **4** and **5**.

4.3. Characterization of products

*4.3.1. 2-Hydroxy-3,5-bis(perfluorohexyl)benzaldehyde (o,p-**4a**).* The title compound was isolated in 40% yield as a colorless oil by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.25 hexane/ethyl acetate 20:1). The characterization of compound (*o*,*p*-**4a**) matches with the data reported in the literature.[13] ^1H NMR (400 MHz, $CDCl_3$) δ 12.20 (s, 1H), 10.02 (s, 1H), 8.03 (d, J=2.28 Hz, 1H), 7.93 (d, J=2.29 Hz, 1H); ^{19}F NMR decoupled ^1H (376 MHz, $CDCl_3$) δ −81.00 (m, 6F), −109.42 (t, J=14.61 Hz, 2F), −110.75 (t, J=14.42 Hz, 2F), −121.47 (m, 4F), −121.88 (m, 4F), −122.88 (m, 4F), −126.26 (m, 4F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.72, 163.31, 136.70, 134.6, 121.34, 120.65 (t, J=26.26 Hz), 118.56 (t, J=24.13 Hz). HRMS calculated for $C_{19}H_3F_{26}O_2$ (M−H): 756.9723, found: 756.9735.

*4.3.2. 2-Hydroxy-3-(perfluorohexyl)-benzaldehyde (o-**4a**).* The title compound was isolated in 20% yield as a colorless oil by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.33 hexane/ethyl acetate 20:1). The characterization of the compound matches with the data reported in the literature.[13] ^1H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H), 9.96 (s, 1H), 7.83–7.72 (m, 2H), 7.16 (t, J=7.8 Hz, 1H); ^{19}F NMR decoupled ^1H (376 MHz, $CDCl_3$) δ −80.88 (m, 3F), −109.03 (t, J=28.95 Hz, 2F), −121.48 (m, 2F), −121.88 (m, 2F), −122.82 (m, 2F), −126.21 (m, 2F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.75, 161.21, 138.49, 136.82 (t, J=8.4 Hz), 121.84, 121.65, 119.82; HRMS calculated for $C_{13}H_4F_{13}O_2$ (M−H): 439.0009, found: 439.0016.

*4.3.3. Methyl 2-hydroxy-3,5-bis(perfluorohexyl)benzoate (o,p-**4b**).* The title compound was isolated in 50% yield as a white solid by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.30 hexane/ethyl acetate 24:1). ^1H NMR (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 8.30 (d, J=2.08 Hz, 1H), 7.87 (d, J=2.00 Hz, 1H), 4.05 (s, 3H); ^{19}F NMR decoupled ^1H (376 MHz, $CDCl_3$): δ −80.92 (m, 6F), −109.22 (t, J=14.60 Hz, 2F), −110.68 (t, J=14.30 Hz, 2F), −121.47 (m, 4F), −121.95 (m, 4F), −122.89 (m, 4F), −126.27 (m, 4F).^{13}C NMR (100 MHz, $CDCl_3$) δ 164.44, 163.29, 133.70, 133.31, 119.59 (t, J=26.04 Hz), 118.12 (t, J=23.87 Hz), 114.36, 53.55. HRMS calculated for $C_{20}H_6F_{26}NaO_3$ (M+Na): 810.9794, found: 810.9824.

*4.3.4. 2-Bromo-4,6-bis(perfluorohexyl)phenol (o,p-**4c**).* The title compound was isolated in 40% yield as a colorless oil by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.35 hexane/ethyl acetate 24:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.67 (s, 1H). ^{19}F NMR decoupled ^1H (376 MHz, $CDCl_3$) δ −80.96 (m, 6F), −109.15 (t, J=14.67 Hz, 2F), −110.54 (t, J=14.41 Hz, 2F), −121.52 (m, 4F), −121.89 (m, 4F), −122.90 (m, 4F), −126.28 (m, 4F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.33, 134.66, 128.13, 122.36 (t, J=25.88 Hz), 116.73 (t, J=24.12 Hz), 113.28. HRMS calculated for $C_{18}H_2BrF_{26}O$ (M−H): 806.8879, found: 806.8883.

*4.3.5. 1-(2-Hydroxy-3,5-bis(perfluorohexyl)phenyl)ethan-1-one (o,p-**4d**).* The title compound was isolated in 35% yield as a colorless oil by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.30 hexane/ethyl acetate 15:1).^1H NMR (500 MHz, $CDCl_3$) δ 13.55 (s, 1H), 8.14 (d, J=1.66 Hz, 1H), 7.90 (d, J=1.67 Hz, 1H), 2.75 (s, 3H); ^{19}F NMR decoupled ^1H (376 MHz, $CDCl_3$) δ −80.89 (m, 6F), −109.25 (t, J=14.51 Hz, 2F), −110.64 (t, J=14.67 Hz, 2F), −121.38 (m, 4F), −121.87 (m, 4F), −122.86 (m, 4F), −126.25 (m, 4F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.26, 164.32, 134.31, 133.61, 120.51, 119.11 (t, J=26.03 Hz), 118.90 (t, J=23.83 Hz); HRMS calculated for $C_{20}H_6F_{26}NaO_2$ (M+Na): 794.9845, found: 794.9878.

*4.3.6. 4-Hydroxy-3,5-bis(perfluorohexyl)benzaldehyde (o,o′-**4i**).* The title compound was isolated in 40% yield as a white solid by chromatography using a gradient eluent of hexane/DCM (R_f=0.3 hexane/DCM 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.22 (s, 2H); ^{19}F NMR decoupled ^1H (376 MHz, $CDCl_3$): δ −80.89 (t, J=9.9 Hz, 6F), −108.25 (t, J=14.5 Hz, 4F), −121.38 (m, 4F), −121.74 (m, 4F), −122.79 (m, 4F), −126.21 (m, 4F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.16, 158.37, 135.09, 129.46, 118.12 (t, J=23.0 Hz). HRMS calculated for $C_{19}H_3F_{26}O_2$ (M−H): 756.9723, found: 756.9749.

*4.3.7. 1-(4-Hydroxy-3,5-bis(perfluorohexyl)phenyl)ethan-1-one (o,o′-**4j**).* The title compound was isolated in 50% yield as a white solid by chromatography using a gradient eluent of hexane/DCM (R_f=0.35 hexane/DCM 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 2H), 2.62 (s, 3H). ^{19}F NMR decoupled ^1H (376 MHz, $CDCl_3$): δ −80.97 (t, J=10.0 Hz, 6F), −108.19 (t, J=14.6 Hz, 4F), −121.45 (m, 4F), −121.81 (m, 4F), −122.85 (m, 4F), −126.28 (m, 4F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.27, 157.50, 133.90 (t, J=8.0 Hz), 130.12, 117.41 (t, J=22.9 Hz), 26.26; HRMS calculated for $C_{20}H_5F_{26}O_2$ (M−H): 770.9880, found: 770.9875.

*4.3.8. N-(4-Hydroxy-3,5-bis(perfluorohexyl)phenyl)acetamide (o,o′-**4k**).* The title compound was isolated in 35% yield as a white solid by chromatography using a gradient eluent of hexane/DCM (R_f=0.40 hexane/DCM 2:1). ^1H NMR (400 MHz, acetonitrile-d_3); δ 8.55 (s, 1H), 7.98 (s, 2H), 2.06 (s, 3H); ^{19}F NMR (376 MHz,

acetonitrile-d_3): δ −81.70 (m, 6F), −107.84 (t, J=14.8 Hz, 4F), −121.77 (m, 4F), −122.33 (m, 2F), −123.30 (m, 4F), −126.7 (m, 4F); ^{13}C NMR (101 MHz, acetonitrile-d_3): δ 170.03, 150.53, 133.85, 126.05−123.98 (m), 119.38 (t, J=22.0 Hz), 24.15; HRMS calculated for $C_{20}H_6F_{26}NO_2$ (M−H): 785.9989, found: 785.9983.

*4.3.9. 7-Hydroxy-6-methyl-4-(perfluorohexyl)-2,3-dihydro-1H-inden-1-one (p-**4l**).* The title compound was isolated in 30% yield as a yellow solid by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.35 hexane/ethyl acetate 24:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.48 (s, 1H), 3.36−3.12 (m, 2H), 2.82−2.70 (m, 2H), 2.29 (s, 3H); ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): δ −80.86 (m, 3F), −108.61 (m, 2F), −121.67 (m, 4F), −122.84 (m, 2F), -126.18 (m, 2 F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 209.88, 158.97, 152.17, 137.27 (t, J=7.2 Hz), 124.62, 122.72, 116.86 (t, J=25.0 Hz), 35.85, 25.38, 14.37. HRMS calculated for $C_{16}H_8F_{13}O_2$ (M−H): 479.0322, found: 479.0325.

*4.3.10. Methyl 5-acetyl-2-hydroxy-3-(perfluorohexyl)benzoate (o-**4m**).* The title compound was isolated in 72% yield as a white solid by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.3 hexane/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.31 (s, 1H), 4.04 (s, 3H), 2.61 (s, 3H); ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): δ −80.95 (t, J=10.0 Hz, 3F), −108.97 (t, J=14.3 Hz, 2F), −121.18 (m, 2F), −121.90 (m, 2F), −122.85 (m, 2F), −126.22 (m, 2F); ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.74, 169.94, 164.09, 135.43 (t, J=8.4 Hz), 134.89, 128.30, 117.53 (t, J=23.8 Hz), 113.78, 53.39, 26.33. HRMS calculated for $C_{16}H_8F_{13}O_4$ (M−H): 511.0220, found: 511.0218.

*4.3.11. Methyl 5-acetyl-2-hydroxy-3-(perfluorobutyl)benzoate (o-**4n**).* The title compound was isolated in 78% yield as a yellow solid by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.35 hexane/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.14 (s, 1H), 8.67 (d, J=2.3 Hz, 1H), 8.30 (d, J=2.3 Hz, 1H), 4.03 (s, 3H), 2.60 (s, 3H); ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): δ −81.12 (m, 3F), −109.21 (t, J=13.7 Hz, 2F), −122.11 (m, 2F), −126.06 (m, 2F); ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.72, 169.93, 164.06, 135.37 (t, J=8.4 Hz), 134.88, 128.29, 117.39 (t, J=23.7 Hz), 113.75, 53.35, 26.25. HRMS calculated for $C_{14}H_8F_9O_4$ (M−H): 411.0284, found: 411.0292.

*4.3.12. Methyl 5-acetyl-2-hydroxy-3-(perfluorooctyl)benzoate (o-**4o**).* The title compound was isolated in 70% yield as a yellow solid by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.35 hexane/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.16 (s, 1H), 8.69 (d, J=2.2 Hz, 1H), 8.31 (d, J=2.2 Hz, 1H), 4.04 (s, 3H), 2.61 (s, 3H);^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$) δ −80.86 (t, J=10.0 Hz, 3F), −108.92 (t, J=14.1 Hz, 2F), −121.09 (m, 2F), −121.82 (m, 6F), −122.79 (m, 2F), −126.20 (m, 2F); ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.75, 169.94, 164.10, 135.44 (t, J=8.4 Hz), 130.18, 128.43, 128.30, 113.78, 53.40, 26.35; HRMS calculated for $C_{18}H_8F_{17}O_4$ (M−H): 611.0157, found: 611.0167.

*4.3.13. Methyl 5-acetyl-2-hydroxy-3-(trifluoromethyl)benzoate (o-**4p**).* The title compound was isolated in 44% yield as a white solid by chromatography using a gradient eluent of hexane/ethyl acetate (R_f=0.35 hexane/ethyl acetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.03 (s, 1H), 8.66 (d, J=2.2 Hz, 1H), 8.38 (d, J=2.7 Hz, 1H), 4.04 (s, 3H), 2.61 (s, 3H); ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): δ −63.37 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.83, 169.81, 163.20, 134.44, 133.10 (t, J=5.0 Hz), 128.16, 122.77 (q, J=273.1 Hz), 119.37 (q, J=32.5 Hz), 113.63, 53.35, 26.38. HRMS calculated for $C_{11}H_8F_3O_4$ (M−H): 261.0380, found: 261.0384.

*4.3.14. Methyl 4′-formyl-3′-hydroxy-2′-(perfluorohexyl)-[1,1′-biphenyl]-4-carboxylate (o-**5a**).* The title compound was isolated in 40% yield as a colorless oil by chromatography using a gradient eluent of hexane/toluene (R_f=0.35 hexane/toluene 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.17 (s, 1H), 9.98 (s, 1H), 8.05 (d, J=8.5 Hz, 2H), 7.74 (d, J=7.9 Hz, 1H), 7.28 (d, J=8.4 Hz, 2H), 6.87 (d, J=7.9 Hz, 1H), 3.95 (s, 3H); ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): δ −80.91 (m, 3F), −100.59 (m, 2F), −118.88 (m, 2F), −122.11 (m, 2F), −122.78 (m, 2F), −126.22 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.96, 166.68, 161.97, 151.23, 144.80, 136.25, 129.61, 128.73, 127.76, 123.54, 120.4; 52.40; HRMS calculated for $C_{21}H_{10}F_{13}O_4$ (M−H): 573.0377, found: 573.0376.

*4.3.15. 3-Hydroxy-2′-methyl-2-(perfluorohexyl)-[1,1′-biphenyl]-4-carbaldehyde (o-**5b**).* The title compound was isolated in 38% yield as a yellow oil by chromatography using a gradient eluent of hexane/toluene (R_f=0.3 hexane/toluene 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.20 (s, 1H), 9.99 (s, 1H), 7.75 (d, J=7.9 Hz, 1H), 7.38−7.17 (m, 3H), 7.04 (dd, J=7.4, 3.0 Hz, 1H), 6.86 (d, J=7.9 Hz, 1H), 2.08 (s, 3H); ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): δ −101.49 (m, 3F), −104.79 (dd, J=722.1, 282.2 Hz 2F), −118.95 (dd, J=581.7, 292.2 Hz, 2F), −122.17 (m, 2F), −122.80 (m, 2F), −126.22 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.11, 162.39, 152.25, 139.81 (d, J=3.0 Hz), 136.55, 134.91 (d, J=3.9 Hz), 129.55, 128.04, 127.50, 124.93, 123.81, 120.26, 115.78 (t, J=21.3 Hz), 20.12; HRMS calculated for $C_{20}H_{10}F_{13}O_2$ (M−H): 529.0479, found: 529.0468.

*4.3.16. 3-Hydroxy-2′-methyl-2-(perfluorobutyl)-[1,1′-biphenyl]-4-carbaldehyde (o-**5c**).* The title compound was isolated in 40% yield as a yellow oil by chromatography using a gradient eluent of hexane/toluene (R_f=0.25 hexane/toluene 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.19 (s, 1H), 9.99 (s, 1H), 7.75 (d, J=7.9 Hz, 1H), 7.40−7.09 (m, 3H), 7.04 (dd, J=7.4, 2.9 Hz, 1H), 6.86 (d, J=7.9 Hz, 1H), 2.08 (s, 3H); ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): δ −81.03 (m, 3F), −102.90 (dd, J=718.5, 286.2 Hz, 2F), −119.45 (dd, J=593.8, 293.0 Hz, 2F), −126.32 (m, 2F); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.10, 162.32, 152.24, 139.80, 136.54, 134.92, 129.55, 128.03, 127.51, 124.93, 123.80, 120.24, 115.70, 20.15; HRMS calculated for $C_{18}H_{10}F_9O_2$ (M−H): 429.0543, found: 429.0555.

*4.3.17. Methyl 3-hydroxy-2′-methyl-2-(perfluorohexyl)-[1,1′-biphenyl]-4-carboxylate (o-**5d**).* The title compound was isolated in 25% yield as a yellow oil by chromatography using a gradient eluent of hexane/toluene (R_f=0.25 hexane/toluene 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.91 (s, 1H), 8.02 (d, J=8.2 Hz, 1H), 7.31−7.10 (m, 3H), 7.05−6.96 (m, 1H), 6.69 (d, J=8.2 Hz, 1H), 4.01 (s, 3H), 2.05 (s, 3H); ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): δ −80.92 (t, J=10.0 Hz, 3F), −102.75 (dd, J=693.7, 279.6 Hz, 2F), −119.50 (dd, J=565.0, 287.7 Hz, 2F), −122.18 (m, 2F), −122.76 (m, 2F), −126.25 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.41, 162.08, 150.91, 140.27, 135.03, 132.96, 129.44, 127.78, 127.66, 124.85, 122.89, 121.62, 112.57, 52.99, 20.13; HRMS calculated for $C_{21}H_{12}F_{13}O_3$ (M−H): 559.0584, found: 559.0593.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.02.034.

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