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Strategies for the synthesis of fluorinated liquid crystal derivatives from perbromofluoroaromatic systems

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ABSTRACT

The use of perbromofluorobenzene derivatives as starting materials for the synthesis of a variety of model liquid crystal systems by a combination of nucleophilic aromatic substitution, debromolithiation/trapping, dehydration and reduction processes is described.

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1. Introduction

Molecules that possess liquid crystalline properties are now widely used for many display applications in a range of electronic goods, such as television and laptop computer screens.[1–3] Indeed, it is now fair to say that televisions with flat-screen liquid crystal (LC) displays have, along with plasma systems, largely replaced cathode-ray tube based technologies. As LC-based display applications increase in performance (clarity, size, brightness, angle of view, low power consumption, fast response times, etc.), there exists a continuing need for the development of materials with liquid crystalline properties that can meet consumer demands for enhanced display technologies.

In general, molecules that exhibit liquid crystalline properties have narrow, elongated frameworks that may align along their linear axes, parallel to one another, towards a preferred direction in space.[4] The design of liquid crystalline molecules must take account of not only their general linear, rod-like shape but also the relative dipole moment and position of polar groups within the molecule, the overall molecular polarizability and the presence of any stereogenic centres. Recently, liquid crystalline molecules bearing fluorine-containing substituents,[4,5,6] termed superfluorinated materials (SFMs), have significantly contributed to the development of LC-based devices due to a number of factors including enhanced performance, increased longevity and the chemical robustness of appropriate liquid crystal formulations. Dielectrically positive LC molecules bear polar groups (F, CF_3) parallel to the longitudinal axis of the organic system, whereas dielectrically negative LC molecules bear polar groups that are perpendicular to the long axis. Both classes of LC molecule have a variety of uses in display technology and some examples of commercially important LC systems are shown in Fig. 1, where the molecular structures comprise of an aromatic polar, fluorine-containing 'head group', a rod-like, rigid core of cyclohexyl units and lipophilic alkyl 'tail' units.[2]

Synthesis of the fluorinated polar head group, usually a fluoroaromatic derivative, and attachment of the head group to the non-polar 'tail' of the LC molecule is perhaps the most challenging aspect of LC synthesis and is usually completed by a sequence of reactions involving displacement of hydrogen from mono- or di-fluorinated aromatic substrates by a combination of electrophilic substitution, palladium catalysed coupling and/or lithiation procedures.[4,7] Such strategies, however, may be limited by low regioselectivity, low yield and inconvenient reaction conditions and it is often difficult to access various isomers of all the polyfluoroaomatic structural units possible.

We decided to explore a complementary approach to the synthesis of LC molecules bearing fluoroaromatic polar head groups by using perbromofluoroaromatic derivatives as the starting materials. Such systems are, potentially, very susceptible towards nucleophilic

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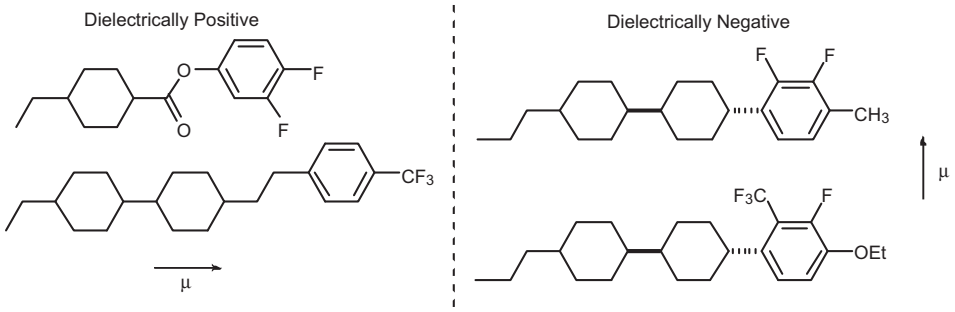
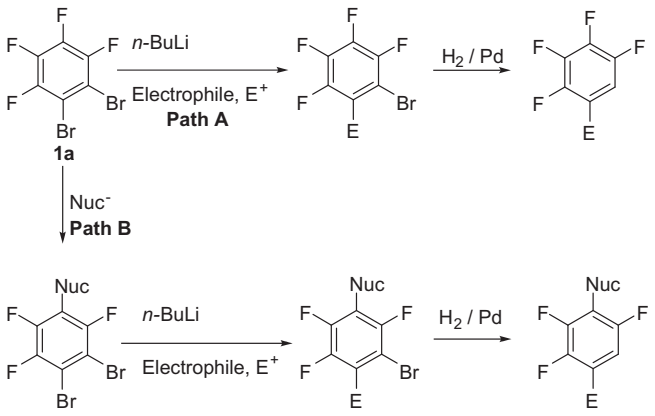


Fig. 1. Some commercially important liquid crystal systems.

attack due to the presence of a number of highly electron withdrawing substituents attached to the aromatic ring and the presence of carbon–bromine bonds offer opportunities for a variety of useful synthetic functionalisation procedures. In our initial experiments, we chose to develop strategies to both new and existing LC materials by using dibromotetrafluorobenzene systems **1a**–**c** as the starting materials. Sequences of debromolithiation and trapping with appropriate electrophiles, nucleophilic substitution and hydrogenation reactions could, in principle, give rise to many families of LC systems depending on the structure of the perhalogenated aromatic starting material, and this approach is shown in Scheme 1, where the envisaged use of 1,2-dibromotetrafluorobenzene **1a** as the starting material for LC synthesis is illustrated.



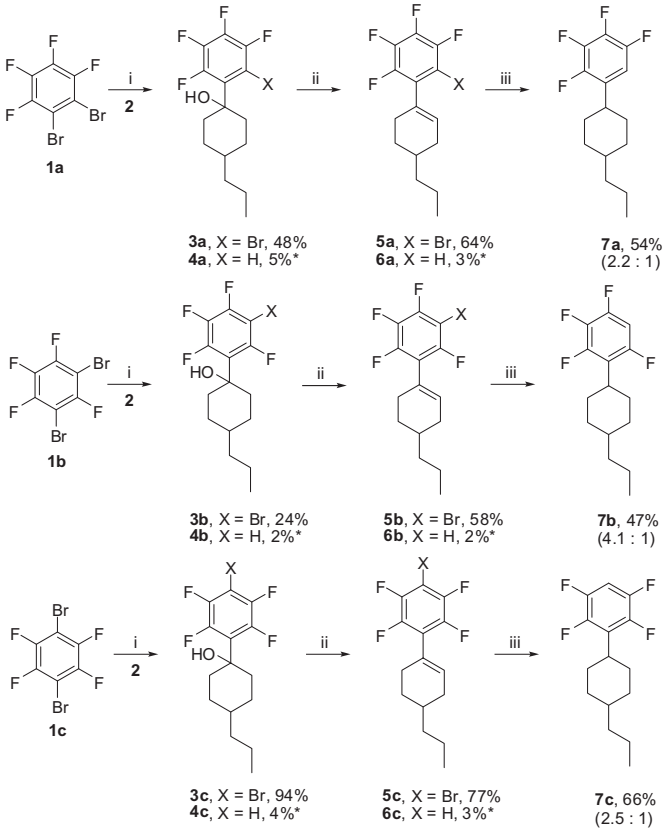
Scheme 1. General strategy for the synthesis of LC molecules from perbromofluorobenzene derivatives.

Whilst all three dibromotetrafluorobenzene systems **1a**–**c** (Scheme 2) have been known for some considerable time, it is perhaps surprising that a more comprehensive exploration of the reactivity of these potentially very useful polyfunctional aromatic synthetic scaffolds has not been developed to any great extent, although there are a few reports of reactions between these substrates and various nucleophilic species.[8–12]

In this paper, we discuss the synthesis of various model LC-type molecules using the synthetic strategy outlined in Scheme 1 and demonstrate the versatility of this approach for the preparation of new families of model LC molecules bearing various tetrafluoro- and trifluoro-aryl head groups.

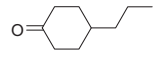
2. Results and discussion

In our initial investigations we sought to develop the synthesis of LC systems by debromolithiation/trapping as the first stage of the synthetic strategy (Path A, Scheme 1). Reaction of *n*-butyllithium with 1,2-dibromotetrafluorobenzene **1a** and subsequent trapping



Reagents and Conditions:
i, (a) *n*-BuLi, Et_2O, −78 °C; (b) **2**, −78 °C − rt; ii, *p*-TsOH, toluene, reflux; iii, H_2 (100 bar), Pd/C, 180 °C

2 =



* Not isolated; estimated yield by GCMS.

Scheme 2. Synthesis of model LC systems **7** from dibromotetrafluorobenzene systems **1a**–**c**.

of the corresponding lithiated species upon reaction with cyclohexanone derivative **2**, a model substrate for a linear LC 'tail' unit, gave the corresponding cyclohexanol derivative **3a** (Scheme 2). The alcohol was contaminated with small quantities (5% by GC/MS analysis) of the corresponding tetrafluoroaryl derivative **4a** arising from further debromolithiation and so the mixture **3a**/**4a** was used in the next synthetic stage without further purification. Dehydration of the alcohol mixture **3a**/**4a** using *p*-toluenesulfonic acid in toluene gave a corresponding alkene mixture **5a**/**6a**, which were not separated, and the mixture was reduced to give pure LC model system **7a** upon hydrogenation using a Pd/C catalyst and purification by column chromatography. The hydrogenation stage was

surprisingly difficult reflecting the effect of the electron withdrawing aromatic group on the alkene and high temperatures and pressures were required to deliver complete conversion to products. It was essential to optimize the hydrogenation reactions to completeness because the alkenes **5a**/**6a** were very difficult to separate from the liquid crystal type product **7a**. Analogous three-step processes using 1,3- and 1,4-dibromotetrafluorobenzene starting materials **1b** and **1c** gave the LC systems **7b** and **7c**, respectively (Scheme 2).

In all cases, the model LC systems **7a**–**c** were isolated as mixtures of two configurational isomers, resulting from the non-stereoselective hydrogenation of the precursor alkene derivatives **5**/**6**. The stereochemistries of the major and minor configurational isomers of **7a**–**c** were assigned by consideration of the NMR data.[13,14] The carbon NMR spectrum of the product isomer mixture was firstly fully assigned using HSQC and HMBC 2D NMR techniques. The HSQC spectrum was then used to assign clean (non-overlapping) splitting patterns in the proton NMR spectra through correlation with individual carbon atom environments. TOCSY 1D NMR also facilitated the correct assignment of signals in the proton NMR spectra to the major and minor isomers. The Karplus relationship indicates that a coupling of approximately 12 Hz is observed for two vicinal axial protons with a dihedral angle of 180° between them. In the ^{1}H NMR spectrum of, for example, LC model derivative **7c**, a triplet with a 12 Hz $^{3}J_{HH}$ coupling is observed for the proton attached to the C-1′ position found in both major (3.00 ppm) and minor (3.04 ppm) isomers suggesting that the benzene ring lies equatorially in both isomers. Different splitting patterns are, however, observed for the axial protons attached to the C-3′ position of the major and minor isomers. Three 12 Hz couplings (a quartet at 1.04 ppm) are observed for the major isomer suggesting that the propyl tail group lies equatorially, but only two (a triplet at 1.60 ppm) are observed for the minor isomer suggesting that the propyl group lies axially (Fig. 2).

Furthermore, the ^{19}F NMR spectrum of the LC model derivatives show two sets of signals corresponding to the major and minor isomers, allowing ratios of each isomer to be determined accurately by integration of peak intensities. For example, **7b** displays two sets of signals for both the F-5 fluorine atom (−117.7 and −118.0 ppm) and the F-3 fluorine atom (−135.8 and −136.0 ppm) and the peak integrals indicate the major:minor isomer ratio to be 4.1:1 (Fig. 3). Only one set of signals were observed for each of the fluorine atoms at the C-1 and C-2 positions and this may be due to the fact that they are located at sites more remote from the cyclohexane ring and, therefore, their electronic environments are unaffected by the isomeric configurations of the more remote atoms of the molecule.

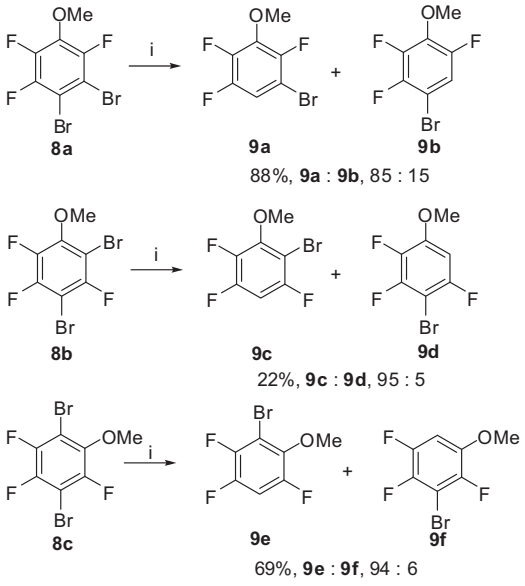
In all cases, the major isomers of the LC type systems **7a**–**c** are found to be the configurations with the C-1′ and C-4′ protons lying diaxially with the large aromatic head group and propyl tail-group lying equatorially, as would be expected.

Therefore, the strategy outlined in Scheme 1 can be used for the synthesis of LC systems bearing all three isomers of the tetrafluoroaryl head groups (Scheme 2) and, clearly, other tail groups could be attached to these head groups by reaction of an appropriate proprietary cyclohexanone derivative.

The incorporation of additional functionality attached to the polar fluoroaromatic head group may be achieved by reaction of the dibromotetrafluorobenzene systems **1a**–**c** with appropriate nucleophiles followed by debromolithiation, dehydration and hydrogenation procedures discussed above, following Path B (Scheme 1).

Reaction of the dibromotetrafluorobenzene derivatives **1a**–**c** with sodium methoxide following literature procedures[8,9] gave the corresponding methoxydibromoaryl systems **8a**–**c** as the major products, respectively, which were purified by column chromatography and the regioselectivity of these types of processes have been discussed previously.[12]

Reaction of **8a**–**c** with butyllithium could each lead to two possible lithiated species and, subsequently, two regioisomeric products upon trapping the carbanions with an appropriate electrophile. So, in order to establish the outcome of debromolithiation reactions of **8a**–**c** and the effects governing the regioselectivity of such processes, we reacted each system with *n*-butyllithium and trapped the resulting carbanions by hydrogen upon addition of ethanol/water and the results are shown in Scheme 3.



Reagents and conditions:
i, (a) *n*-BuLi, Et_2O, -78 °C; (b) EtOH, H_2O, rt.

Scheme 3. Debromolithiation and subsequent protonation of **8a**–**c**.

Reaction of **8a** with *n*-butyllithium and subsequent protonation gave a mixture of products **9a** and **9b** in the ratio 85:15 by ^{19}F NMR analysis of the crude product mixture, results consistent with previous observations.[8,9] Compounds **9a** and **9b** could not be separated by column chromatography and were characterized as a mixture, whereas anisoles **9c** and **9e** could be isolated as pure isomers. Confirmation of the identity of isomers **9c** and **9d** was provided through consideration of the ^{1}H NMR spectrum. The major isomer **9c** displays two $^{3}J_{HF}$ and one $^{4}J_{HF}$ couplings consistent with the structure proposed, whereas anisole **9d** has a single $^{3}J_{HF}$ coupling (ca. 10 Hz), one $^{4}J_{HF}$ coupling and one small $^{5}J_{HF}$ coupling.

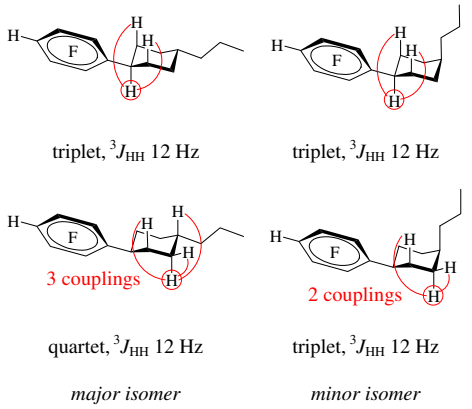


Fig. 2. Couplings between protons in major and minor isomers of **7c**.

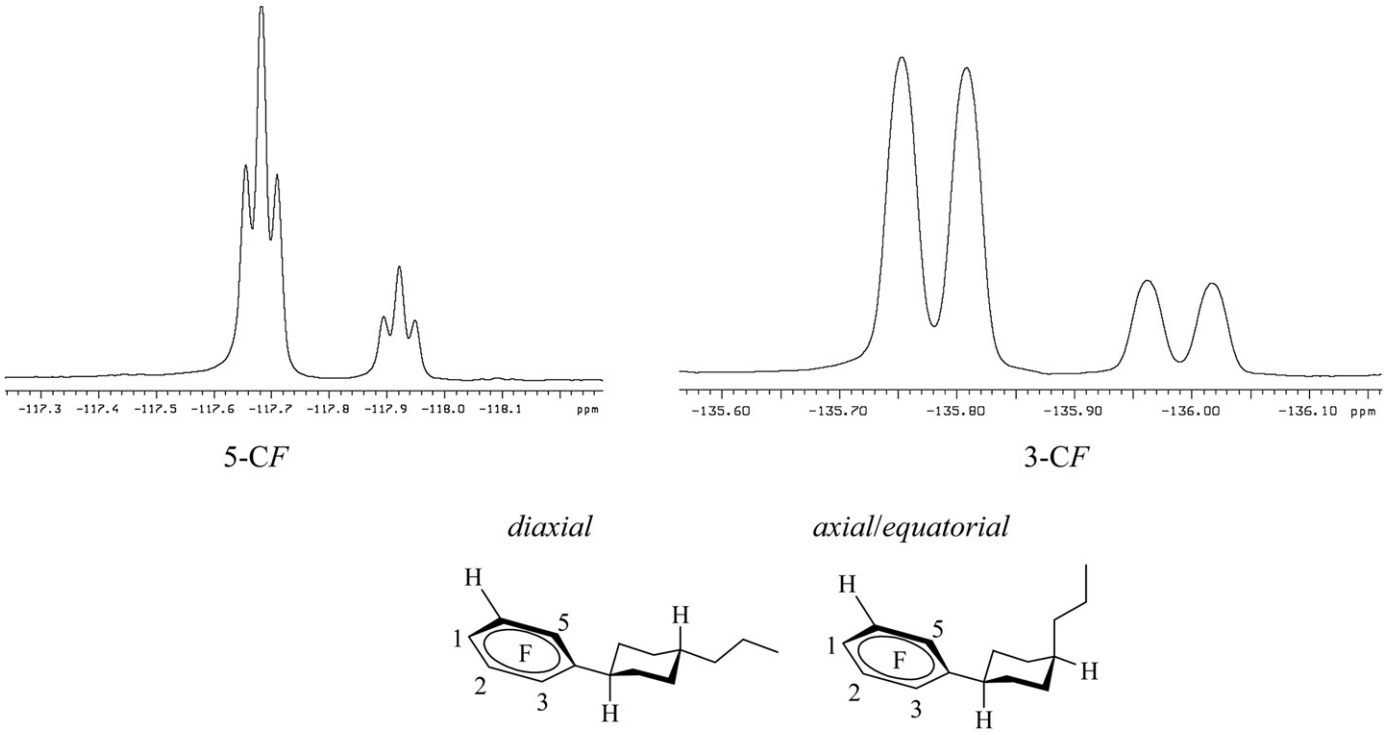


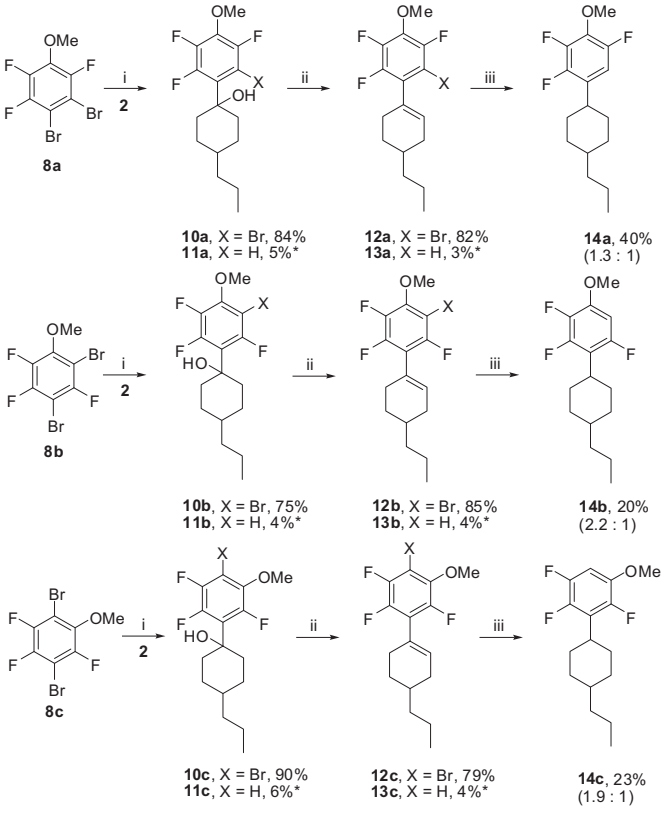
Fig. 3. Fluorine NMR signals arising from the two configurations of the LC system **7b**.

Similarly, anisole **9e** shows two $^{3}J_{HF}$ and one $^{4}J_{HF}$ couplings and anisole **9f** displays one $^{3}J_{HF}$ and two $^{4}J_{HF}$ couplings, as would be expected. The results shown in Scheme 3 indicate that debromolithiation occurs in all cases predominantly at carbon–bromine sites with the greatest number of fluorine atoms that are *ortho* and *meta* to the site of debromolithiation, reflecting the enhanced electrophilicity of the bromine atoms at these positions.

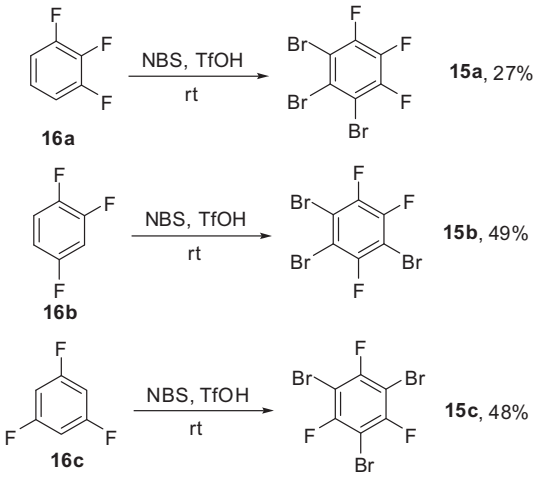
Since the debromolithiation reactions described above (Scheme 3) are sufficiently regioselective to allow the synthesis of various LC type systems, debromolithiation and trapping of **8a**–**c** gave predominantly **10a**–**c** as the major products, contaminated by minor quantities of **11a**–**c**, which were not purified at this stage. Subsequent processing, by similar reactions to those shown in Scheme 2, led to the methoxylated model LC systems **14a**–**c** as shown in Scheme 4. As in the synthesis of LC systems above, some debromination occurred in the lithiation step and so mixtures were carried through to the end of each sequence, allowing the isolation of pure LC type material **14a**–**c** at the final stage. Geometric isomers of each system **14a**–**c** were observed and characterized by NMR techniques, as described above.

We then sought to expand this methodology to the synthesis of LC systems from related tribromotrifluorobenzene **15a**–**c** starting materials. The three possible tribromotrifluorobenzene isomers **15a**–**c** were synthesised by perbromination of the corresponding trifluoraryl derivatives **16a**–**c** using *N*-bromosuccinimide in triflic acid at room temperature, by adapting related iodination methodology (Scheme 5).[15]

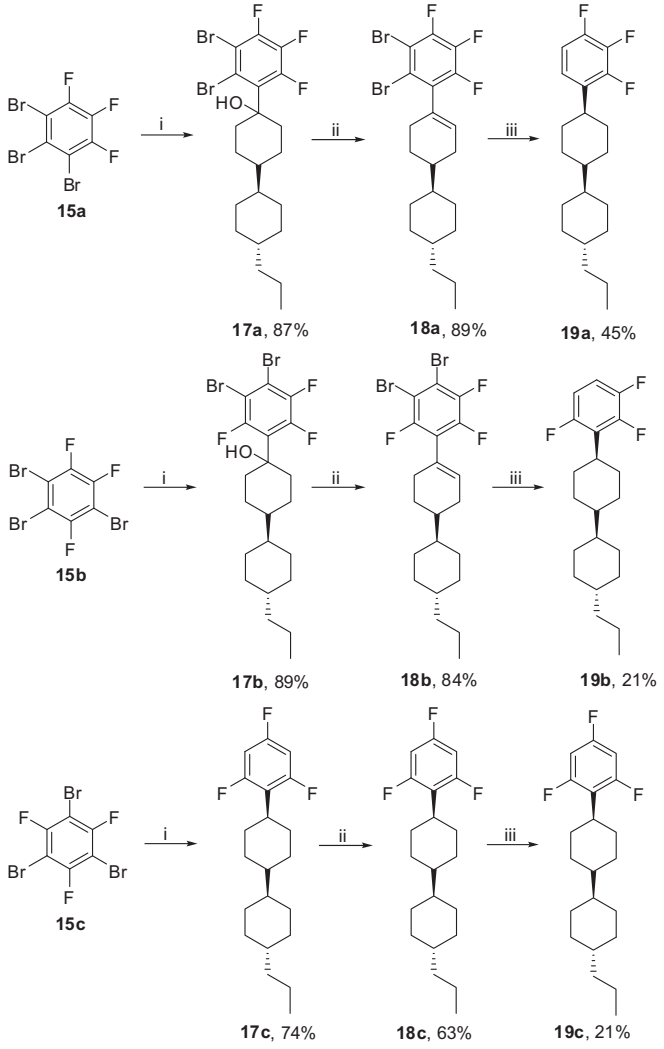
The strategy outlined above was utilized to synthesise various LC derivatives **19** proceeding via intermediate alcohol **17** and alkene **18** intermediates by a three step sequence as shown in Scheme 6. In these final experiments, a larger cyclohexanone derivative **20** was used as the lipophilic coupling partner and, here, we find that single geometric isomers may be isolated by recrystallisation of the crude product mixture for each model LC product. Again, debromolithiation occurs in **15a** and **15b** at carbon–bromine sites with the greatest number of *ortho* and *meta* fluorine atoms, reflecting the enhanced electrophilicity of the bromine atoms at these positions.



Scheme 4. Synthesis of methoxy-trifluoroaromatic LC systems **14a**–**c**.



Scheme 5. Synthesis of tribromotrifluorobenzene systems **15a**–**c**.



Reagents and Conditions:
i, (a) *n*-BuLi, Et_2O, −78 °C; (b) **20**, −78 °C – rt; ii, *p*-TsOH, toluene, reflux; iii, H_2 (100 bar), Pd/C, 180 °C

20 = O

Scheme 6. Synthesis of model LC systems **19a**–**c** from tribromotrifluorobenzene derivatives **15a**–**c**.

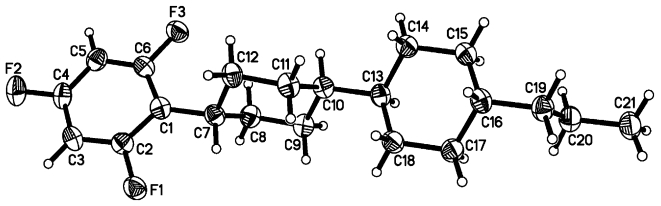


Fig. 4. X-ray crystal structure of bicyclohexylaryl **19c**.

The structure of the phenylbicyclohexyl derivative **19c** was confirmed by X-ray crystallography and we observe that all the tertiary hydrogens of the two cyclohexyl rings lie axially (Fig. 4) giving the structure the most 'rod-like' configuration, as would be expected.

Relatively few crystal structures of 4′,4-disubstituted bicyclohexyl derivatives have been reported and, indeed, the Cambridge Crystallographic Database[16] contains only 11 such compounds. In all reported structures, the substituents are in the equatorial positions of the bicyclohexyl system, similar to **19c**, but, in this case, the conformation of molecule **19c** is quite unusual. Most 4′,4-disubstituted bicyclohexyl structures show *s-trans* configurations around the central bond of the bicyclohexyl fragment with corresponding HCCH torsion angles of about 180°, but in one case, 4′-propen-1-yl-bicyclohexyl-4-carbonitrile,[17] this torsion angle is 71.2°, i.e., the cyclohexyl rings are almost perpendicular to each other. The conformation of molecule **19c** is similar where the central HCCH torsion angle is −73.1°.

3. Conclusions

We have outlined a general strategy for the synthesis of model liquid crystal systems **7a**–**c** from dibromotetrafluorobenzene **1a**–**c** starting materials. LC molecules bearing all three isomers of the tetrafluoroaryl unit can be synthesised from the appropriate starting material and additional functionality can be incorporated into the aromatic head group by nucleophilic aromatic substitution processes. Furthermore, we have developed methodology for the synthesis of tribromotrifluorobenzene systems **15a**–**c** and used these novel precursors for the synthesis of various model LC-type molecules **19a**–**c**. The use of this strategy for the synthesis of many families of LC systems bearing a range of isomeric fluoroaryl 'head' groups complements existing strategies for LC molecule synthesis, allowing the preparation of many novel SFM derivatives for liquid crystal display applications.

4. Experimental

4.1. General

All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem). All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian Mercury 400 NMR spectrometer operating at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25 m HP1 (methylsilicone) column. Elemental analyses were obtained on a Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040–0.063 mm) and TLC analysis was performed on silica gel TLC plates (Merck).

4.2. Synthesis of model liquid crystal systems with fluoroaryl head groups

4.2.1. General procedure. A solution of *n*-butyllithium (2.5 M in hexanes) in dry diethyl ether (10 mL) was added via a dropping funnel over 30 min to a solution of the dibromotetrafluoro- or tribromotrifluorobenzene derivative in dry diethyl ether (40 mL) cooled to −78 °C under an atmosphere of dry argon. The solution was stirred for 30 min and then the cyclohexanone derivative **2** or **20** was added dropwise over 30 min whilst maintaining a reaction temperature of −78 °C. The mixture was stirred for 2 h and water (10 mL) was added. The mixture was stirred for a further 15 min, allowed to warm to room temperature, poured into dilute HCl (30 mL) and the product extracted with diethyl ether (3×30 mL). The combined ether extracts were washed with water (100 mL) and dried ($MgSO_4$). The solvent was evaporated to leave the crude phenyl-4-propylcyclohexanol product, which was identified by GC/MS and used in the next stage without further purification.

A mixture consisting of the phenyl-4-propylcyclohexanol derivative, *p*-toluenesulfonic acid monohydrate (0.1 equiv) and toluene (30 mL) was heated to reflux for 6 h in a Dean and Stark vessel. After cooling, the solvent was evaporated and column chromatography with hexane as the eluent afforded the phenyl-4-propylcyclohexene derivative, which was identified by GC/MS and used in the next stage without further purification.

A solution of the alkene derivative in dry THF (5 mL) was added to palladium (30 wt % on carbon, 0.1 equiv). This was placed in an autoclave under 100 bar pressure of hydrogen at 180 °C for 7 days. The resulting cooled brown solution was filtered and solvent evaporated. Column chromatography on silica gel with hexane as the eluent afforded the model LC system, which was obtained as a mixture of two configurational isomers (major:minor) identified by NMR techniques, as described in the text.

4.3. Synthesis of 1,2,3,4-tetrafluoro-5-(4-propylcyclohexyl) benzene 7a from 1,2-dibromotetrafluorobenzene 1a

1,2-Dibromotetrafluorobenzene **1a** (6.16 g, 20.0 mmol), *n*-BuLi (8.00 mL, 20.0 mmol) and cyclohexanone **2** (2.80 g, 20.0 mmol) gave 1-(2-*bromo*-3,4,5,6-*tetrafluorophenyl*)-4-*propylcyclohexanol* **3a** (3.57 g, 48%) as a clear oil; *m*/*z* (EI^+) 370 ($[M]^+$, 2%), 368 ($[M]^+$, 2), 285 (34), 283 (34), 204 (48), 177 (38), 98 (53), 96 (38), 85 (48), 55 (51), 43 (100), 41 (47).

The alcohol **3a** (3.37 g, 9.13 mmol) and *p*-TsOH (0.15 g, 0.87 mmol) gave 1-*bromo*-2,3,4,5-*tetrafluoro*-6-(4-*propylcyclohex*-1-*enyl*)*benzene* **5a** (2.04 g, 64%) as a clear oil; *m*/*z* (EI^+) 352 ($[M]^+$, 19%), 350 ($[M]^+$, 19), 243 (47), 241 (44), 201 (100), 187 (45), 151 (65), 96 (73), 81 (98), 68 (64), 67 (70), 55 (49), 41 (47).

The alkene **5a** (1.91 g, 5.44 mmol) and Pd/C (0.17 g, 0.50 mmol) gave 1,2,3,4-*tetrafluoro*-5-(4-*propylcyclohexyl*)*benzene* **7a** (0.79 g, 54%) as a clear oil and as a mixture of isomers (2.2:1) (Found: C, 65.79; H, 6.73. $C_{15}H_{18}F_4$ requires: C, 65.68; H, 6.61%); R_f (hexane) 0.35; *major isomer*: δ_H 0.90 (3H, t, $^3J_{HH}$ 7.3, CH_3), 1.05–1.90 (13H, m, CH, CH_2), 2.81 (1H, tt, $^3J_{HH}$ 12.1, $^3J_{HH}$ 2.8, H-1′), 6.77–6.84 (1H, m, H-6); δ_C 14.5 (s, CH_3), 20.1 (s, CH_2CH_3), 30.1 (s, C-1′), 32.9 (s, C-2′), 33.3 (s, C-3′), 37.0 (s, C-4′), 39.7 (s, $CH_2CH_2CH_3$), 108.7 (ddd, $^2J_{CF}$ 19.1, $^3J_{CF}$ 4.9, $^3J_{CF}$ 3.5, C-6), 130.9 (dddd, $^2J_{CF}$ 13.8, $^3J_{CF}$ 5.8, $^3J_{CF}$ 3.8, $^4J_{CF}$ 1.1, C-5), 138.6 (dddd, $^1J_{CF}$ 250.4, $^2J_{CF}$ 17.1, $^2J_{CF}$ 13.1, $^3J_{CF}$ 3.4, C-2), 140.7 (dddd, $^1J_{CF}$ 251.4, $^2J_{CF}$ 18.1, $^2J_{CF}$ 12.1, $^3J_{CF}$ 4.2, C-3), 145.4 (dddd, $^1J_{CF}$ 243.4, $^2J_{CF}$ 10.0, $^3J_{CF}$ 3.4, $^4J_{CF}$ 1.6, C-1), 147.2 (dddd, $^1J_{CF}$ 245.4, $^2J_{CF}$ 9.9, $^3J_{CF}$ 3.8, $^4J_{CF}$ 2.3, C-4); δ_F −140.81 –to −140.88 (1F, m, F-1), −145.84 –to −145.90 (1F, m, F-4), −157.15 –to −157.21 (1F, m, F-2), −160.64 –to −160.72 (1F, m, F-3); *minor isomer*: δ_H 0.93 (3H, t, $^3J_{HH}$ 7.1, CH_3), 1.00–1.95 (13H, m, CH, CH_2), 2.80–2.90 (1H, m, H-1′), 6.80–6.85 (1H, m, H-6); δ_F −140.80 to −140.85 (1F, m, F-1), −145.61 to −145.69 (1F, m, F-4), −157.16 to −157.22 (1F, m, F-2), −160.65 to −160.71 (1F, m, F-3); *m*/*z* (EI^+) 274 ($[M]^+$, 82%), 189 (75), 176 (100), 163 (93), 81 (56), 55 (100), 43 (63), 41 (68).

4.4. Synthesis of 1,2,3,5-tetrafluoro-4-(4-propylcyclohexyl) benzene 7b from 1,3-dibromotetrafluorobenzene 1b

1,3-Dibromotetrafluorobenzene **1b** (6.16 g, 20.0 mmol), *n*-BuLi (8.00 mL, 20.0 mmol) and cyclohexanone **2** (2.80 g, 20.0 mmol)gave 1-(3-*bromo*-2,4,5,6-*tetrafluorophenyl*)-4-*propylcyclohexanol* **3b** (1.77 g, 24%) as a clear oil; *m*/*z* (EI^+) 370 ($[M]^+$, 6%), 368 ($[M]^+$, 6), 285 (82), 283 (85), 272 (59), 270 (58), 257 (55), 255 (55), 98 (90), 96 (77), 85 (69), 55 (79), 43 (100), 41 (68).

The alcohol **3b** (1.77 g, 4.79 mmol) and *p*-TsOH (0.08 g, 0.46 mmol) gave 1-*bromo*-2,3,4,6-*tetrafluoro*-5-(4-*propylcyclohex*-1-*enyl*)*benzene* **5b** (0.97 g, 58%) as a clear oil; *m*/*z* (EI^+) 352 ($[M]^+$, 24%), 350 ($[M]^+$, 25), 295 (77), 293 (84), 243 (82), 241 (77), 201 (51), 96 (68), 81 (100), 68 (86), 55 (55), 41 (51).

The alkene **5b** (0.82 g, 2.3 mmol) and Pd/C (0.07 g, 0.2 mmol) gave 1,2,3,5-*tetrafluoro*-4-(4-*propylcyclohexyl*)*benzene* **7b** (0.30 g, 47%) as a clear oil and as a mixture of isomers (4.1:1) (Found: C, 65.40; H, 6.54. $C_{15}H_{18}F_4$ requires C, 65.68; H, 6.61%); R_f (hexane) 0.42; *major isomer*: δ_H 0.90 (3H, t, $^3J_{HH}$ 7.3, CH_3), 1.05–2.00 (13H, m, CH, CH_2), 2.89 (1H, tt, $^3J_{HH}$ 12.0, $^3J_{HH}$ 3.9, H-1′), 6.69 (1H, dddd, $^3J_{HF}$ 10.1, $^3J_{HF}$ 10.1, $^4J_{HF}$ 6.1, $^5J_{HF}$ 2.5, H-6); δ_C 14.5 (s, CH_3), 20.1 (s, CH_2CH_3), 29.9 (s, C-2′), 31.0 (s, C-1′), 33.6 (s, C-3′), 36.8 (s, C-4′), 39.8 (s, $CH_2CH_2CH_3$), 100.7 (ddd, $^2J_{CF}$ 30.1, $^2J_{CF}$ 20.9, $^3J_{CF}$ 3.8, C-6), 119.8 (dddd, $^2J_{CF}$ 20.3, $^2J_{CF}$ 15.7, $^3J_{CF}$ 4.6, $^4J_{CF}$ 1.9, C-4), 137.4 (dddd, $^1J_{CF}$ 246.9, $^2J_{CF}$ 17.2, $^2J_{CF}$ 15.1, $^4J_{CF}$ 5.2, C-2), 148.8 (dddd, $^1J_{CF}$ 248.0, $^2J_{CF}$ 15.7, $^3J_{CF}$ 11.1, $^3J_{CF}$ 5.7, C-3), 150.2 (dddd, $^1J_{CF}$ 248.0, $^2J_{CF}$ 12.3, $^3J_{CF}$ 10.8, $^3J_{CF}$ 5.4, C-1), 155.5 (dddd, $^1J_{CF}$ 244.6, $^3J_{CF}$ 12.3, $^3J_{CF}$ 10.4, $^4J_{CF}$ 3.4, C-5); δ_F −117.70 to −117.78 (1F, m, F-5), −135.75 to −135.81 (1F, m, F-3), −137.21 to −137.29 (1F, m, F-1), −166.19 to −166.26 (1F, m, F-2); *minor isomer*: δ_H 0.94 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.00–2.00 (13H, m, CH, CH_2), 2.92 (1H, tt, $^3J_{HH}$ 12.9, $^3J_{HH}$ 3.7, H-1′), 6.65–6.70 (1H, m, H-6); δ_F −117.85 to −117.95 (1F, m, F-5), −135.95 to −136.08 (1F, m, F-3), −137.15 to −137.40 (1F, m, F-1), −166.10 to −166.35 (1F, m, F-2); *m*/*z* (EI^+) 274 ($[M]^+$, 53%), 231 (16), 189 (38), 177 (14), 176 (73), 169 (14), 163 (100), 82 (14), 70 (16), 69 (14), 55 (61), 43 (23), 41 (33).

4.5. Synthesis of 1,2,4,5-tetrafluoro-3-(4-propylcyclohexyl) benzene 7c from 1,4-dibromotetrafluorobenzene 1c

1,4-Dibromotetrafluorobenzene **1c** (3.08 g, 10.0 mmol), *n*-BuLi (4.00 mL, 10.0 mmol) and cyclohexanone **2** (1.40 g, 10.0 mmol) gave 1-(4-*bromo*-2,3,5,6-*tetrafluorophenyl*)-4-*propylcyclohexanol* **3c** (3.48 g, 94%); *m*/*z* (EI^+) 370 ($[M]^+$, 4%), 368 ($[M]^+$, 5), 285 (37), 283 (36), 99 (30), 98 (47), 96 (36), 85 (36), 55 (52), 43 (100), 41 (44), 28 (53).

The alcohol **3c** (3.48 g, 9.43 mmol) and *p*-TsOH (0.17 g, 0.99 mmol) gave 1-*bromo*-2,3,5,6-*tetrafluoro*-4-(4-*propylcyclohex*-1-*enyl*)*benzene* **5c** (2.55 g, 77%) as a clear oil; *m*/*z* (EI^+) 352 ($[M]^+$, 25%), 350 ($[M]^+$, 26), 295 (88), 293 (95), 243 (73), 241 (70), 201 (52), 151 (42), 96 (62), 81 (100), 68 (89), 55 (63), 41 (58).

The alkene **5c** (2.41 g, 6.8 mmol) and Pd/C (0.20 g, 0.7 mmol) gave 1,2,4,5-*tetrafluoro*-3-(4-*propylcyclohexyl*)*benzene* **7c** (1.24 g, 66%) as a clear oil and as a mixture of isomers (2.5:1) (Found: C, 65.39; H, 6.64. $C_{15}H_{18}F_4$ requires: C, 65.68; H, 6.61%); R_f (hexane) 0.25; *major isomer*: δ_H 0.91 (3H, t, $^3J_{HH}$ 7.3, CH_3), 1.04 (2H, dddd, $^2J_{HH}$ 13.0, $^3J_{HH}$ 13.0, $^3J_{HH}$ 12.0, $^4J_{HH}$ 3.1, H-3′), 1.20–1.90 (11H, m, CH, CH_2), 3.00 (1H, tt, $^3J_{HH}$ 12.3, $^3J_{HH}$ 3.7, H-1′), 6.87 (1H, tt, $^3J_{HF}$ 9.5, $^4J_{HF}$ 7.0, H-6); δ_C 14.5 (s, CH_3), 20.1 (s, CH_2CH_3), 30.8 (m, C-2′), 33.5 (s, C-3′), 35.9 (s, C-1′), 36.8 (s, C-4′), 39.8 (s, $CH_2CH_2CH_3$), 103.3 (t, $^2J_{CF}$ 22.8, C-6), 125.9 (t, $^2J_{CF}$ 16.3, C-3), 145.0 (dddd, $^1J_{CF}$ 244.6, $^2J_{CF}$ 13.4, $^3J_{CF}$ 7.2, $^4J_{CF}$ 3.8, C-2), 146.2 (dddd, $^1J_{CF}$ 247.0, $^2J_{CF}$ 15.9, $^3J_{CF}$ 10.5, $^4J_{CF}$ 3.8, C-1); δ_F −140.51 to −140.57 (2F, m, F-2), −143.90 to −143.98 (2F, m, F-1); *minor isomer*: δ_H 0.94 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.20–1.50 (4H, m, CH_2), 1.60 (2H, dddd, $^3J_{HH}$ 13.4, $^3J_{HH}$ 13.4, $^3J_{HH}$ 3.9, $^3J_{HH}$ 3.9, H-3′),

1.75–1.90 (5H, m, CH, CH_2), 2.01 (2H, ddd, $^2J_{HH}$ 12.9, $^3J_{HH}$ 12.9, $^3J_{HH}$ 12.9, H-2′), 3.03 (1H, tt, $^3J_{HH}$ 12.6, $^3J_{HH}$ 3.7, H-1′), 6.87 (1H, tt, $^3J_{HF}$ 9.5, $^4J_{HF}$ 7.0, H-6); δ_F −140.49 to −140.57 (2F, m, F-2), −144.10 to −144.30 (2F, m, F-1); *m*/*z* (EI$^+$) 274 ([M]$^+$, 70%), 231 (49), 189 (73), 176 (72), 169 (42), 163 (70), 67 (31), 55 (100), 43 (28), 41 (58).

4.6. Synthesis of 1,3,4-trifluoro-2-methoxy-5-(4-propylcyclohexyl)benzene 14a from 1,2-dibromo-3,4,6-trifluoro-5-methoxybenzene 8a

1,2-Dibromo-3,4,6-trifluoro-5-methoxybenzene **8a** (1.05 g, 3.28 mmol), *n*-BuLi (1.60 mL, 4.0 mmol) and cyclohexanone **2** (0.56 g, 4.00 mmol) gave 1-(2-*bromo*-3,5,6-*trifluoro*-4-*methoxyphenyl*)-4-*propylcyclohexanol* **10a** (1.50 g, 84%); *m*/*z* (EI$^+$) 382 ([M]$^+$, 23%), 380 ([M]$^+$, 23), 297 (89), 295 (95), 284 (82), 282 (84), 269 (47), 267 (45), 217 (33), 216 (100), 189 (49), 55 (83), 43 (69), 41 (64).

The alcohol **10a** (1.43 g, 3.75 mmol) and *p*-TsOH (0.07 g, 0.41 mmol) gave 1-*bromo*-2,4,5-*trifluoro*-3-*methoxy*-6-(4-*propylcyclohex*-1-*enyl*)*benzene* **12a** (1.13 g, 82%); *m*/*z* (EI$^+$) 364 ([M]$^+$, 21%), 362 ([M]$^+$, 23), 268 (64), 266 (64), 253 (33), 213 (36), 169 (38), 43 (58), 41 (100), 40 (41), 39 (35), 29 (74), 28 (47), 27 (51).

The alkene **12a** (1.41 g, 3.88 mmol) and Pd/C (0.14 g, 0.40 mmol) gave 1,3,4-*trifluoro*-2-*methoxy*-5-(4-*propyl*-*cyclohexyl*)*benzene* **14a** (0.44 g, 40%) as a clear oil and as a mixture of isomers (1.3:1) (Found: C, 67.26; H, 7.55. $C_{16}H_{21}F_3O$ requires C, 67.11; H, 7.39%); R_f (hexane) 0.35; *major isomer*: δ_H 0.90–1.02 (3H, m, CH_3), 1.05–1.90 (13H, m, CH, CH_2), 2.78 (1H, tt, $^3J_{HH}$ 12.1, $^3J_{HH}$ 3.0, H-1′), 3.95–4.02 (3H, m, OCH_3), 6.70–6.75 (1H, m, H-6); δ_C 14.2 (s, CH_3), 20.1 (s, CH_2CH_3), 30.1 (s, C-2′), 31.8 (s, C-1′), 33.4 (s, C-3′), 37.1 (s, C-4′), 39.7 (s, $CH_2CH_2CH_3$), 62.0 (m, OCH_3), 108.3 (ddd, $^2J_{CF}$ 21.5, $^3J_{CF}$ 5.4, $^4J_{CF}$ 3.4, C-6), 129.9 (dd, $^2J_{CF}$ 14.1, $^3J_{CF}$ 6.8, C-5), 135.3 (ddd, $^2J_{CF}$ 15.7, $^2J_{CF}$ 11.5, $^3J_{CF}$ 2.3, C-2), 144.6 (ddd, $^1J_{CF}$ 248.8, $^2J_{CF}$ 16.0, $^3J_{CF}$ 6.5, C-3), 145.6 (ddd, $^1J_{CF}$ 242.8, $^2J_{CF}$ 11.1, $^4J_{CF}$ 3.5, C-4), 151.4 (ddd, $^1J_{CF}$ 242.6, $^3J_{CF}$ 4.2, $^4J_{CF}$ 3.0, C-1); δ_F −134.96 to −135.02 (1F, m, F-1), −147.54 to −147.62 (1F, m, F-3), −152.67 to −152.75 (1F, m, F-4); *minor isomer*: δ_H 0.90–1.03 (3H, m, CH_3), 1.05–1.85 (13H, m, CH, CH_2), 2.80–2.85 (1H, m, H-1′), 3.99 (3H, s, OCH_3), 6.70–6.75 (1H, m, H-6); δ_F −135.03 to −135.09 (1F, m, F-1), −147.30 to −147.38 (1F, m, F-3), −152.67 to −152.73 (1F, m, F-4); *m*/*z* (EI$^+$) 286 ([M]$^+$, 76%), 201 (76), 188 (100), 175 (83), 173 (61), 145 (56), 55 (70), 43 (78), 41 (68), 29 (48).

4.7. Synthesis of 1,3,4-trifluoro-5-methoxy-2-(4-propylcyclohexyl)benzene 14b from 1,3-dibromo-2,4,5-trifluoro-6-methoxybenzene 8b

1,3-Dibromo-2,4,5-trifluoro-6-methoxybenzene **8b** (0.89 g, 2.78 mmol), *n*-BuLi (1.20 mL, 3.0 mmol) and cyclohexanone **2** (0.42 g, 3.00 mmol) gave 1-(3-*bromo*-2,5,6-*trifluoro*-4-*methoxyphenyl*)-4-*propylcyclohexanol* **10b** (0.80 g, 75%); *m*/*z* (EI$^+$) 382 ([M]$^+$, 54%), 380 ([M]$^+$, 58), 297 (73), 295 (100), 284 (73), 282 (83), 269 (64), 267 (88), 255 (51), 253 (55), 55 (78), 43 (58), 41 (64).

The alcohol **10b** (0.70 g, 1.84 mmol) and *p*-TsOH (0.03 g, 0.17 mmol) gave 1-*bromo*-2,4,5-*trifluoro*-6-*methoxy*-3-(4-*propylcyclohex*-1-*enyl*)*benzene* **12b** (0.56 g, 85%); *m*/*z* (EI$^+$) 364 ([M]$^+$, 72%), 362 ([M]$^+$, 75), 307 (79), 305 (84), 294 (68), 292 (71), 268 (86), 266 (100), 255 (93), 253 (86), 55 (66), 41 (68).

The alkene **12b** (0.81 g, 2.23 mmol) and Pd/C (0.10 g, 0.30 mmol) gave 1,3,4-*trifluoro*-5-*methoxy*-2-(4-*propyl*-*cyclohexyl*)*benzene* **14b** (0.13 g, 20%) as a clear oil and as a mixture of isomers (2.2:1) (Found: C, 67.39; H, 7.44. $C_{16}H_{21}F_3O$ requires: C, 67.11; H, 7.39%); R_f (hexane) 0.40; *major isomer*: δ_H 0.90 (3H, t, $^3J_{HH}$ 7.3, CH_2CH_3), 1.00–1.95 (13H, m, CH, CH_2), 2.86 (1H, tt, $^3J_{HH}$ 12.0, $^3J_{HH}$ 3.8, H-1′), 3.84 (3H, s, OCH_3), 6.45 (1H, ddd, $^3J_{HF}$ 11.6, $^4J_{HF}$ 6.8, $^5J_{HF}$ 2.2, H-6); δ_C 14.5 (s, CH_2CH_3), 20.1 (s, CH_2CH_3), 30.4 (s, C-2′), 31.2 (s, C-1′), 33.7 (s, C-3′), 36.9 (s, C-4′), 39.8 (s, $CH_2CH_2CH_3$), 56.6 (s, OCH_3), 96.8 (dd, $^2J_{CF}$ 30.2, $^3J_{CF}$ 3.1, C-6), 115.5 (ddd, $^2J_{CF}$ 20.6, $^2J_{CF}$ 16.3, $^3J_{CF}$ 2.3, C-2), 138.4 (ddd, $^1J_{CF}$ 242.4, $^2J_{CF}$ 16.1, $^4J_{CF}$ 4.5, C-4), 146.7 (ddd, $^2J_{CF}$ 13.1, $^3J_{CF}$ 9.2, $^3J_{CF}$ 5.3, C-5), 150.0 (ddd, $^1J_{CF}$ 245.4, $^2J_{CF}$ 13.1, $^3J_{CF}$ 11.1, C-3), 156.0 (ddd, $^1J_{CF}$ 241.4, $^3J_{CF}$ 11.1, $^4J_{CF}$ 3.8, C-1); δ_F −118.98 to −119.04 (1F, m, F-1), −138.77 to −138.83 (1F, m, F-4), −165.69 to −165.76 (1F, m, F-3); *minor isomer*: δ_H 0.94 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3), 1.00–1.95 (13H, m, CH, CH_2), 2.89 (1H, tt, $^3J_{HH}$ 12.8, $^3J_{HH}$ 3.8, H-1′), 3.85 (3H, s, OCH_3), 6.45 (1H, ddd, $^3J_{HF}$ 11.6, $^4J_{HF}$ 6.8, $^5J_{HF}$ 2.2, H-6); δ_F −119.24 to −119.32 (1F, m, F-1), −138.96 to −139.03 (1F, m, F-4), −165.70 to −165.76 (1F, m, F-3); *m*/*z* (EI$^+$) 286 ([M]$^+$, 82%), 202 (49), 201 (90), 188 (100), 175 (87), 173 (31), 145 (36), 55 (50), 43 (50), 41 (44).

4.8. Synthesis of 1,2,4-trifluoro-5-methoxy-3-(4-propylcyclohexyl)benzene 14c from 1,4-dibromo-2,3,5-trifluoro-6-methoxybenzene 8c

1,4-Dibromo-2,3,5-trifluoro-6-methoxybenzene **8c** (1.70 g, 5.31 mmol), *n*-BuLi (2.10 mL, 5.30 mmol) and cyclohexanone **2** (0.74 g, 5.28 mmol) gave 1-(4-*bromo*-2,3,6-*trifluoro*-5-*methoxyphenyl*)-4-*propylcyclohexanol* **10c** (1.82 g, 90%); *m*/*z* (EI$^+$) 382 ([M]$^+$, 58%), 380 ([M]$^+$, 62), 297 (82), 295 (100), 284 (84), 282 (99), 269 (64), 267 (66), 98 (61), 96 (69), 81 (64), 55 (92), 43 (75), 41 (76).

The alcohol **10c** (2.30 g, 6.04 mmol) and *p*-TsOH (0.10 g, 0.71 mmol) gave 1-*bromo*-2,3,5-*trifluoro*-6-*methoxy*-4-(4-*propylcyclohex*-1-*enyl*)*benzene* **12c** (1.74 g, 79%); *m*/*z* (EI$^+$) 364 ([M]$^+$, 59%), 362 ([M]$^+$, 61), 321 (78), 319 (79), 307 (88), 305 (92), 268 (95), 266 (100), 255 (73), 253 (75), 182 (55), 169 (44), 55 (60), 41 (64).

The alkene **12c** (2.02 g, 5.56 mmol) and Pd/C (0.21 g, 0.6 mmol) gave 1,2,4-*trifluoro*-5-*methoxy*-3-(4-*propyl*-*cyclohexyl*)*benzene* **14c** (0.37 g, 23%) as a clear oil and as a mixture of isomers (1.9:1) (Found: C, 67.35; H, 7.55. $C_{16}H_{21}F_3O$ requires C, 67.11; H, 7.39%); R_f (hexane) 0.40; *major isomer*: δ_H 0.90 (3H, t, $^3J_{HH}$ 7.3, CH_2CH_3), 1.05–2.10 (13H, m, CH, CH_2), 2.97 (1H, tt, $^3J_{HH}$ 12.5, $^3J_{HH}$ 3.7, H-1′), 3.82 (3H, s, OCH_3), 6.64 (1H, ddd, $^3J_{HF}$ 11.2, $^4J_{HF}$ 7.7, $^4J_{HF}$ 7.7, H-6); δ_C 14.5 (s, CH_3), 20.1 (s, CH_2CH_3), 30.3 (s, C-2′), 30.8 (s, C-1′), 33.6 (s, C-3′), 36.8 (s, C-4′), 39.8 (s, $CH_2CH_2CH_3$), 56.7 (s, OCH_3), 99.6 (dd, $^2J_{CF}$ 22.7, $^3J_{CF}$ 2.2, C-6), 124.7 (dd, $^2J_{CF}$ 17.1, $^2J_{CF}$ 15.9, C-3), 142.7 (ddd, $^1J_{CF}$ 236.7, $^2J_{CF}$ 13.8, $^3J_{CF}$ 8.1, C-2), 143.8 (dd, $^2J_{CF}$ 16.8, $^3J_{CF}$ 8.4, C-5), 146.3 (ddd, $^1J_{CF}$ 241.9, $^2J_{CF}$ 6.9, $^4J_{CF}$ 3.5, C-1), 146.5 (ddd, $^1J_{CF}$ 242.3, $^3J_{CF}$ 3.8, $^4J_{CF}$ 3.1, C-4); δ_F −141.64 to −141.71 (1F, m, F-4), −142.40 to −142.46 (1F, m, F-2), −149.67 to −149.75 (1F, m, F-1); *minor isomer*: δ_H 0.93 (3H, t, $^3J_{HH}$ 7.1, CH_2CH_3), 1.00–2.10 (13H, m, CH, CH_2), 3.01 (1H, tt, $^3J_{HH}$ 12.5, $^3J_{HH}$ 3.7, H-1′), 3.82 (3H, s, OCH_3), 6.64 (1H, ddd, $^3J_{HF}$ 11.2, $^4J_{HF}$ 7.7, $^4J_{HF}$ 7.7, H-6); δ_F −141.78 to −141.85 (1F, m, F-4), −142.39 to −142.45 (1F, m, F-2), −149.90 to −149.97 (1F, m, F-1); *m*/*z* (EI$^+$) 286 ([M]$^+$, 77%), 188 (76), 175 (85), 173 (44), 170 (100), 145 (65), 67 (44), 55 (72), 43 (64), 41 (67), 29 (51).

4.9. Synthesis of 4′-propyl-4-(2,3,4-trifluoro-phenyl)-bicyclohexyl 19a from 1,2,3-tribromo-4,5,6-trifluoro-benzene 15a

1,2,3-Tribromo-4,5,6-trifluoro-benzene **15a** (1.37 g, 3.72 mmol), *n*-BuLi (1.50 mL, 3.70 mmol) and cyclohexanone **20** (0.82 g, 3.69 mmol) gave 4-(2,3-*dibromo*-4,5,6-*trifluoro*-*phenyl*)-4′-*propyl*-*bicyclohexyl*-4-*ol* **17a** (1.66 g, 86%); *m*/*z* (EI$^+$) 514 ([M]$^+$, 1%), 512 ([M]$^+$, 1%), 510 ([M]$^+$, 1%), 83 (35), 81 (42), 69 (84), 67 (50), 55 (100), 43 (43), 41 (88).

The alcohol **17a** (1.50 g, 2.93 mmol) and *p*-TsOH (0.05 g, 0.29 mmol) gave 4-(2,3-*dibromo*-4,5,6-*trifluoro*-*phenyl*)-4′-*propyl*-*bicyclohexyl*-3-*ene* **18a** (1.32 g, 89%); *m*/*z* (EI$^+$) 496 ([M]$^+$, 12%), 494 ([M]$^+$, 23%), 492 ([M]$^+$, 12%), 182 (44), 83 (46), 69 (100), 67 (58), 55 (91), 43 (41), 41 (88).

The alkene **18a** (1.70 g, 3.44 mmol) and Pd/C (0.14 g, 0.40 mmol), following recrystallisation from THF/hexanes, gave 4′-*propyl*-4-(2,3,4-*trifluoro*-*phenyl*)-*bicyclohexyl* **19a** (0.52 g, 45%) as a white solid; mp 56.5–58.0 °C (Found: C, 74.57; H, 8.70. $C_{21}H_{29}F_3$ requires

C, 74.52; H, 8.64%); R_f (hexane) 0.25; δ_H 0.91 (3H, t, $^3J_{HH}$ 7.3, CH_3), 0.99–1.25 (10H, m, CH_2), 1.35–1.90 (11H, m, CH, CH_2), 2.79 (1H, tt, $^3J_{HH}$ 12.3, $^3J_{HH}$ 3.0, H-4′), 6.85–6.92 (2H, m, H-5,6); δ_C 14.6 (s, *C*H$_3$), 20.3 (s, *C*H$_2$CH$_3$), 30.3 (s), 30.3 (s), 33.3 (s), 33.8 (s), 37.3 (s), 37.9 (s), 40.1 (s), 43.0 (s), 43.6 (s), 111.6 (dd, $^2J_{CF}$ 16.7, $^3J_{CF}$ 3.8, C-5), 120.8 (ddd, $^3J_{CF}$ 7.6, $^3J_{CF}$ 5.7, $^4J_{CF}$ 4.3, C-6), 132.0 (ddd, $^2J_{CF}$ 12.2, $^3J_{CF}$ 3.6, $^4J_{CF}$ 1.4, C-1), 140.0 (ddd, $^1J_{CF}$ 249.9, $^2J_{CF}$ 16.4, $^2J_{CF}$ 15.2, C-3), 149.5 (dd, $^1J_{CF}$ 247.0, $^2J_{CF}$ 9.6, C-2), 149.6–149.7 (m, C-4); δ_F −139.25 to −139.31 (1F, m, F-4), −140.94 to −141.01 (1F, m, F-2), −161.82 to −161.89 (1F, m, F-3); *m*/*z* (EI$^+$) 338 ([M]$^+$, 49%), 158 (65), 145 (65), 125 (41), 83 (100), 81 (56), 69 (76), 67 (46), 55 (68), 41 (54).

4.10. Synthesis of 4′-propyl-4-(2,3,6-trifluoro-phenyl)-bicyclohexyl 19b from 1,2,4-tribromo-3,5,6-trifluoro-benzene 15b

1,2,4-Tribromo-3,5,6-trifluoro-benzene **15b** (2.41 g, 6.54 mmol), *n*-BuLi (2.60 mL, 6.5 mmol) and cyclohexanone **20** (1.44 g, 6.48 mmol) gave 4-(3,4-*dibromo*-2,5,6-*trifluoro*-*phenyl*)-4′-*propyl*-*bicyclohexyl*-4-*ol* **17b** (2.96 g, 89%); *m*/*z* (EI$^+$) 514 ([M]$^+$, 2%), 512 ([M]$^+$, 4%), 510 ([M]$^+$, 2%), 178 (60), 81 (59), 69 (94), 67 (61), 55 (100), 43 (53), 41 (66).

The alcohol **17b** (2.80 g, 5.47 mmol) and *p*-TsOH (0.09 g, 0.52 mmol) gave 4-(3,4-*dibromo*-2,5,6-*trifluoro*-*phenyl*)-4′-*propyl*-*bicyclohexyl*-3-*ene* **18b** (2.03 g, 84%); *m*/*z* (EI$^+$) 496 ([M]$^+$, 20%), 494 ([M]$^+$, 39%), 492 ([M]$^+$, 20%), 123 (84), 81 (65), 69 (100), 67 (93), 55 (98), 43 (57), 41 (79).

The alkene **18b** (2.50 g, 5.06 mmol) and Pd/C (0.17 g, 0.50 mmol), following recrystallisation from THF/hexanes, gave 4′-*propyl*-4-(2,3,6-*trifluoro*-*phenyl*)-*bicyclohexyl* **19b** (0.36 g, 21%) as a white solid; mp 86.5–88.0 °C (Found: C, 74.27; H, 8.63. $C_{21}H_{29}F_3$ requires: C, 74.52; H, 8.64%); R_f (hexane) 0.30; δ_H 0.89 (3H, t, $^3J_{HH}$ 7.3, CH_3), 0.98–1.36 (12H, m, CH_2), 1.73–1.90 (11H, m, CH, CH_2), 2.95 (1H, tt, $^3J_{HH}$ 12.0, $^3J_{HH}$ 4.0, H-4′), 6.74 (dddd, $^3J_{HF}$ 9.4, $^3J_{HH}$ 9.4, $^4J_{HF}$ 3.9, $^4J_{HF}$ 2.1, H-5), 6.92 (ddd, $^3J_{HF}$ 9.0, $^3J_{HH}$ 9.0, $^4J_{HF}$ 4.9, H-4); δ_C 14.6 (s, CH_3), 20.2 (s, *C*H$_2$CH$_3$), 30.2 (s), 30.4 (s), 31.1 (s), 33.8 (s), 33.6 (s), 37.8 (s), 40.0 (s), 42.7 (s), 43.6 (s), 110.6 (ddd, $^2J_{CF}$ 26.3, $^3J_{CF}$ 6.7, $^3J_{CF}$ 4.3, C-4), 113.9 (dd, $^2J_{CF}$ 19.6, $^3J_{CF}$ 10.4, C-5), 124.4 (dd, $^2J_{CF}$ 20.1, $^2J_{CF}$ 14.8, C-1), 147.6 (ddd, $^1J_{CF}$ 242.5, $^2J_{CF}$ 14.4, $^4J_{CF}$ 3.4, C-3), 149.2 (ddd, $^1J_{CF}$ 247.1, $^2J_{CF}$ 13.9, $^3J_{CF}$ 10.1, C-2), 156.8 (ddd, $^1J_{CF}$ 242.3, $^3J_{CF}$ 7.7, $^4J_{CF}$ 2.9, C-6); δ_F −119.33 to −119.52 (1F, m, F-6), −137.82 to −137.95 (1F, m, F-2), −143.3 to −143.4 (1F, m, F-3); *m*/*z* (EI$^+$) 338 ([M]$^+$, 29%), 212 (20), 171 (21), 158 (39), 145 (41), 82 (100), 69 (54), 67 (33), 55 (47), 41 (36).

4.11. Synthesis of 4′-propyl-4-(2,4,6-trifluoro-phenyl)-bicyclohexyl 19c from 1,3,5-tribromo-2,4,6-trifluoro-benzene 15c

1,3,5-Tribromo-2,4,6-trifluoro-benzene **15c** (1.18 g, 3.20 mmol), *n*-BuLi (1.30 mL, 3.20 mmol) and cyclohexanone **20** (0.71 g, 3.20 mmol) gave 4-(3,5-*dibromo*-2,4,6-*trifluoro*-*phenyl*)-4′-*propyl*-*bicyclohexyl*-4-*ol* **17c** (1.20 g, 74%); *m*/*z* (EI$^+$) 514 ([M]$^+$, 1%), 512 ([M]$^+$, 2%), 510 ([M]$^+$, 1%), 178 (87), 97 (80), 83 (87), 81 (71), 69 (100), 55 (94), 41 (73).

The alcohol **17c** (1.11 g, 2.17 mmol) and *p*-TsOH (0.03 g, 0.17 mmol) gave 4-(3,5-*dibromo*-2,4,6-*trifluoro*-*phenyl*)-4′-*propyl*-*bicyclohexyl*-3-*ene* **18c** (0.67 g, 63%); *m*/*z* (EI$^+$) 496 ([M]$^+$, 10%), 494 ([M]$^+$, 19%), 492 ([M]$^+$, 10%), 123 (48), 83 (42), 81 (50), 69 (100), 67 (71), 55 (90), 41 (80).

The alkene **18c** (1.20 g, 2.43 mmol) and Pd/C (0.11 g, 0.30 mmol), following recrystallisation from THF/hexanes, gave 4′-*propyl*-4-(2,4,6-*trifluoro*-*phenyl*)-*bicyclohexyl* **19c** (0.17 g, 21%) as a white solid; mp 88.0–89.0 °C (Found: C, 74.28; H, 8.64. $C_{21}H_{29}F_3$ requires: C, 74.52; H, 8.64%); R_f (hexane) 0.30; δ_H 0.89 (3H, t, $^3J_{HH}$ 7.3, CH_3), 0.97–1.36 (12H, m, CH_2), 1.73–1.84 (11H, m, CH, CH_2), 2.88 (1H, tt, $^3J_{HH}$ 11.7, $^3J_{HH}$ 3.8, H-4′), 6.58 (2H, t, $^3J_{HF}$ 8.8, H-3); δ_C 14.6 (s, CH_3), 20.2 (s, *C*H$_2$CH$_3$), 30.2 (s), 30.5 (s), 31.3 (s), 33.8 (s), 34.9 (s), 37.8 (s), 40.0 (s), 42.8 (s), 43.6 (s), 100.2–100.3 (m, C-3), 118.5 (td, $^2J_{CF}$ 18.6, $^4J_{CF}$ 4.8, C-1), 160.8 (dt, $^1J_{CF}$ 245.3, $^3J_{CF}$ 16.3, C-4), 161.7 (ddd, $^1J_{CF}$ 264.4, $^3J_{CF}$ 14.9, $^3J_{CF}$ 13.1, C-2); δ_F −111.05 to −111.13 (2F, m, F-2), −113.12 to −113.27 (1F, m, F-4); *m*/*z* (EI$^+$) 338 ([M]$^+$, 30%), 158 (93), 145 (97), 83 (63), 82 (53), 81 (59), 69 (100), 67 (43), 55 (82), 41 (63).

4.12. Debromolithiation/protonation of 8a–c

4.12.1. General procedure. A solution of *n*-butyllithium (2.5 M in hexanes) in dry diethyl ether (5 mL) was added via a dropping funnel over 0.5 h to a solution of the anisole **8** in dry diethyl ether (10 mL) at −78 °C under an atmosphere of dry argon. The solution was stirred for 6 h and then quenched slowly with ethanol (7.5 mL) followed by water (7.5 mL). The mixture was stirred for 0.5 h, allowed to warm to room temperature, poured into water (30 mL) and extracted with diethyl ether (3×30 mL). The combined extracts were washed with water (100 mL) and dried ($MgSO_4$).

4.13. 1-Bromo-2,4,5-trifluoro-3-methoxybenzene 9a and 1-bromo-2,3,5-trifluoro-4-methoxybenzene 9b

n-Butyllithium (0.90 mL, 2.50 mmol) and **8a** (0.71 g, 2.22 mmol) gave 1-*bromo*-2,4,5-*trifluoro*-3-*methoxybenzene* **9a** and 1-*bromo*-2,3,5-*trifluoro*-4-*methoxybenzene* **9b** (0.47 g, 88%) as a yellow oil and as a mixture of isomers in the ratio 85:15 by ^{19}F NMR analysis; *found for* **9a**:[18] δ_H 4.05 (3H, s, OCH_3), 7.04–7.12 (1H, m, H-6); δ_C 62.1 (s, *O*CH$_3$), 103.2 (ddd, $^2J_{CF}$ 21.4, $^3J_{CF}$ 10.0, $^4J_{CF}$ 4.6, C-1), 113. 7 (d, $^2J_{CF}$ 21.8, C-6), 138.7 (ddd, $^2J_{CF}$ 15.7, $^2J_{CF}$ 11.5, $^3J_{CF}$ 2.6, C-3), 143.9 (ddd, $^1J_{CF}$ 251.1, $^2J_{CF}$ 14.6, $^3J_{CF}$ 4.2, C-4), 147.6 (ddd, $^1J_{CF}$ 248.9, $^2J_{CF}$ 12.0, $^4J_{CF}$ 3.9, C-5), 149.4 (ddd, $^1J_{CF}$ 244.9, $^3J_{CF}$ 3.5, $^4J_{CF}$ 3.5, C-2); δ_F −126.10 to −126.23 (1F, m F-2), −140.05 to −140.12 (1F, m, F-5), −151.73 to −151.81 (1F, m, F-4); *found for* **9b**:[18] δ_H 4.03 (3H, s, OCH_3), 7.08–7.18 (1H, m, H-6); δ_C 62.3 (s, OCH_3), 101.8 (ddd, $^2J_{CF}$ 20.0, $^3J_{CF}$ 11.2, $^3J_{CF}$ 1.5, C-1), 114.6 (dd, $^2J_{CF}$ 23.7, $^3J_{CF}$ 3.4, C-6), 137.5 (ddd, $^2J_{CF}$ 15.1, $^2J_{CF}$ 12.1, $^3J_{CF}$ 2.0, C-4), 145.1 (ddd, $^1J_{CF}$ 253.3, $^2J_{CF}$ 15.4, $^3J_{CF}$ 6.5, C-3), 145.9 (ddd, $^1J_{CF}$ 245.3, $^2J_{CF}$ 13.8, $^4J_{CF}$ 3.8, C-2), 151.4 (ddd, $^1J_{CF}$ 260.8, $^3J_{CF}$ 4.2, $^4J_{CF}$ 4.2, C-5); δ_F −133.02 to −133.13 (1F, m, F-5), −133.32 to −133.41 (1F, m, F-2), −148.78 to −148.86 (1F, m, F-3). *m*/*z* (EI$^+$) 242 ([M]$^+$, 97%), 240 ([M]$^+$, 100), 227 (60), 225 (62), 199 (86), 197 (88), 130 (43), 118 (60), 99 (88), 80 (38), 68 (34).

4.14. 2-Bromo-1,4,5-trifluoro-3-methoxybenzene 9c

n-Butyllithium (2.00 mL, 5.00 mmol) and anisole **8b** (1.54 g, 4.81 mmol) and column chromatography on silica gel with diethyl ether as the eluent gave 2-*bromo*-1,4,5-*trifluoro*-3-*methoxybenzene* **9c**[19] (0.26 g, 22%) as a clear oil; δ_H 4.02 (3H, s, OCH_3), 6.77 (ddd, $^3J_{HF}$ 10.0, $^3J_{HF}$ 8.2, $^4J_{HF}$ 6.5, H-6); δ_C 61.8 (s, OCH_3), 99.8 (ddd, $^2J_{CF}$ 23.2, $^3J_{CF}$ 4.6, $^4J_{CF}$ 1.4, C-2), 100.2 (dd, $^2J_{CF}$ 28.6, $^2J_{CF}$ 22.4, C-6), 141.6 (ddd, $^1J_{CF}$ 248.1, $^3J_{CF}$ 14.3, $^4J_{CF}$ 4.9, C-1), 147.3 (ddd, $^2J_{CF}$ 10.3, $^3J_{CF}$ 4.8, $^3J_{CF}$ 3.6, C-3), 150.4 (ddd, $^1J_{CF}$ 250.3, $^2J_{CF}$ 14.2, $^3J_{CF}$ 13.1, C-5), 154.8 (ddd, $^1J_{CF}$ 242.7, $^2J_{CF}$ 15.3, $^4J_{CF}$ 3.5, C-4); δ_F −108.71 to −108.79 (1F, m, F-1), −134.47 to −134.58 (1F, m, F-4), −157.50 to −157.98 (1F, m, F-5). *m*/*z* (EI$^+$) 242 ([M]$^+$, 100%), 240 ([M]$^+$, 95), 227 (70), 225 (67), 199 (90), 197 (82), 130 (79), 118 (68), 99 (89), 81 (64).

4.15. 3-Bromo-1,2,5-trifluoro-4-methoxybenzene 9e

n-Butyllithium (2.30 mL, 5.75 mmol) and anisole **8c** (1.80 g, 5.63 mmol), after column chromatography on silica gel with diethyl ether as the eluent, gave 3-*bromo*-1,2,5-*trifluoro*-4-*methoxybenzene* **9e**[19] (0.93 g, 69%) as a clear oil; δ_H 3.93 (3H, s, OCH_3), 6.97 (1H, ddd,

$^3J_{HF}$ 10.9, $^3J_{HF}$ 10.9, $^4J_{HF}$ 7.5, H-6); δ_C 61.8 (s, OCH_3), 105.2 (dd, $^2J_{CF}$ 25.2, $^2J_{CF}$ 22.3, C-6), 107.0 (ddd, $^2J_{CF}$ 18.9, $^3J_{CF}$ 4.6, $^3J_{CF}$ 2.4, C-3), 142.4 (dd, $^2J_{CF}$ 14.4, $^3J_{CF}$ 3.8, C-4), 145.0 (ddd, $^1J_{CF}$ 246.0, $^2J_{CF}$ 14.9, $^4J_{CF}$ 4.3, C-2), 146.2 (ddd, $^1J_{CF}$ 249.4, $^2J_{CF}$ 15.2, $^3J_{CF}$ 12.1, C-1), 151.1 (ddd, $^1J_{CF}$ 248.7, $^3J_{CF}$ 10.2, $^4J_{CF}$ 3.5, C-5); δ_F −138.61 to −138.71 (1F, m, F-2), −132.82 to −132.93 (1F, m, F-1), −130.93 to −130.84 (1F, m, F-5); *m*/*z* (EI^+) 242 ($[M]^+$, 100%), 240 ($[M]^+$, 93), 227 (74), 225 (70), 199 (75), 197 (71), 130 (40), 118 (47), 99 (63), 81 (37).

4.16. Synthesis of tribromotrifluorobenzene derivatives 15a–c

4.16.1. General procedure. Triflic acid (15 mL) was added slowly to a cooled (0 °C) and stirred mixture consisting of the trifluorobenzene derivative **16** (1.0 equiv) and NBS (3.1 equiv). The solution was allowed to warm to room temperature, stirred for 72 h and poured into ice water (50 mL). The aqueous solution was extracted with DCM (3×30 mL) and the organic extracts were dried ($MgSO_4$), evaporated and the residue recrystallised from ethanol/water to provide the tribromo-trifluoroaromatic product.

4.17. 1,2,3-Tribromo-4,5,6-trifluoro-benzene 15a

1,2,3-Trifluorobenzene **16a** (1.32 g, 10 mmol) and *N*-bromosuccinimide (5.70 g, 32 mmol) gave 1,2,3-*tribromo*-4,5,6-*trifluorobenzene* **15a** (0.99 g, 27%) as a white solid; mp 70.5–72.0 °C (lit.[20] mp 67 –69 °C) (Found: C, 19.33. $C_6Br_3F_3$ requires: C, 19.54%); δ_C 110.0 (d, $^2J_{CF}$ 24.5, C-3), 123.1–123.2(m, C-2), 139.6 (dt, $^1J_{CF}$ 258.7, $^2J_{CF}$ 17.3, C-5), 148.5 (ddd, $^1J_{CF}$ 251.9, $^2J_{CF}$ 11.8, $^3J_{CF}$ 4.3, C-4); δ_F −117.70 (2F, d, $^3J_{FF}$ 21.1, F-4), −153.65 (1F, t, $^3J_{FF}$ 21.1, F-5); *m*/*z* (EI^+) 372 ($[M]^+$, 20%), 370 ($[M]^+$, 56), 368 ($[M]^+$, 56), 366 ($[M]^+$, 19), 210 (44), 208 (42), 129 (71), 110 (30), 98 (29), 79 (100).

4.18. 1,2,4-Tribromo-3,5,6-trifluoro-benzene 15b

1,2,4-Trifluorobenzene **16b** (2.64 g, 20 mmol) and *N*-bromosuccinimide (10.68 g, 60 mmol) gave 1,2,4-*tribromo*-3,5,6-*trifluoro-benzene* **15b** (3.61 g, 49%) as a clear oil (Found: C, 19.55. $C_6Br_3F_3$ requires: C, 19.54%); δ_C 99.2 (dd, $^2J_{CF}$ 27.9, $^2J_{CF}$ 22.0, C-4), 108.8 (dd, $^2J_{CF}$ 25.6, $^3J_{CF}$ 4.9, C-2), 113.7 (ddd, $^2J_{CF}$ 20.7, $^3J_{CF}$ 1.6, $^3J_{CF}$ 1.1, C-1), 145.8 (A of ABMX, $^1J_{CF}$ 235.5, C-5/6), 148.0 (B of ABMX, $^1J_{CF}$ 251.6, C-5/6), 153.2 (ddd, $^1J_{CF}$ 246.8, $^3J_{CF}$ 4.2, $^4J_{CF}$ 3.1, C-3); δ_F −95.48 (X of ABMX, $^5J_{FF}$ 10.0, $^4J_{FF}$ 6.4, F-3), −124.54 (A of ABMX, $^3J_{FF}$ 22.5, $^5J_{FF}$ 10.0, F-6), −124.97 (B of ABMX, $^3J_{FF}$ 22.5, $^4J_{FF}$ 6.4, F-5); *m*/*z* (EI^+) 372 ($[M]^+$, 52%), 370 ($[M]^+$, 90), 368 ($[M]^+$, 100), 366 ($[M]^+$, 78), 289 (73), 210 (88), 208 (83), 129 (88), 110 (76), 79 (100).

4.19. 1,3,5-Tribromo-2,4,6-trifluoro-benzene 15c

1,3,5-Trifluorobenzene **16c** (2.64 g, 20 mmol) and *N*-bromosuccinimide (10.68 g, 60 mmol) gave 1,3,5-*tribromo*-2,4,6-*trifluorobenzene* **15c** (3.54 g, 48%) as a white solid; mp 98.0–99.0 °C (lit.[19] mp 94–95 °C) (Found: C, 19.54. $C_6Br_3F_3$ requires: C, 19.54%); δ_C 94.8 (td, $^2J_{CF}$ 27.1, $^4J_{CF}$ 5.1, C-1), 156.3 (dt, $^1J_{CF}$ 248.5, $^3J_{CF}$ 5.8, C-2); δ_F −95.79 (s); *m*/*z* (EI^+) 372 ($[M]^+$, 13%), 370 ($[M]^+$, 38), 368 ($[M]^+$, 38), 366 ($[M]^+$, 12), 210 (26), 208 (27), 129 (44), 110 (30), 98 (22), 81 (22), 79 (100).

4.20. X-ray crystallography

The single crystal X-ray data for **19c** were collected on a Rigaku R-AXIS IP Spider diffractometer at 120 K using graphite monochromated Mo Kα radiation(λ=0.71073 Å). The structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were found in the difference Fourier maps and refined isotropically. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 784207.

Crystal data for **19c**: $C_{21}H_{29}F_3$, *M*=338.44, triclinic, space group *P*−1, *a*=5.3626(3), *b*=7.0644(4), *c*=24.8576(10)Å, α=90.32(3), β=95.03(3), γ=108.57(3)°, *U*=888.68(8) Å,[3] *F*(000)=364, *Z*=2, D_c=1.265 mg/m^3, μ=0.093 mm^{-1}, 11,121 reflections collected, 3830 unique data (R_{merg}=0.0577). Final $wR_2(F^2)$=0.1433 for all data (334 refined parameters), conventional $R_1(F)$=0.0560 for 2723 reflections with $I \geq 2\sigma$, GOF=1.033.

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