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Synthetic Methods

Synthesis and Elaboration of All-*cis*-1,2,4,5-Tetrafluoro-3-Phenylcyclohexane: A Polar Cyclohexane Motif

Alastair J. Durie,[a] Tomoya Fujiwara,[a, b] Rodrigo Cormanich,[a] Michael Bühl,[a] Alexandra M. Z. Slawin,[a] and David O'Hagan*[a]

Abstract: A stereocontrolled synthesis of all-*cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane is developed as the first functionalised example of this polar cyclohexane motif. The dipolar nature of the ring, arising due to two 1,3-diaxial C–F bonds, is revealed in the solid-state (X-ray) structure. The orthogonal conformation of the aryl and cyclohexyl rings in all-*cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane, and in an *ortho*-nitro derivative, result in intramolecular $^{1h}J_{HF}$ and $^{2h}J_{CF}$ NMR couplings relayed through hydrogen bonding. The aryl group of all-*cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane is elaborated in different ways to demonstrate the versatility of this compound for delivering the motif to a range of molecular building blocks.

Selective fluorination of organic frameworks has long served the fine chemicals industries in tuning the properties of organic compounds to improve their performance.[1] Aryl/heteroaryl,[2] -F,[3] -CF_3[4] and -XCF_3[5] compounds are most commonly encountered in this context, leading to these motifs finding wide utility in pharmaceutical and agrochemical products.[6] However, aliphatic-ring motifs carrying fluorine atoms are also emerging as attractive compounds in structure–activity programs,[7] particularly as there has been a steady creativity and diversity in amenable syntheses and methodologies towards such small-ring aliphatic compounds in recent years.[8] We recently reported the synthesis and analysis of all-*cis*-1,2,4,5-tetrafluorocyclohexane **1**.[9] This compound was prepared by direct treatment of *cis*-diepoxide **2** with Deoxo-Fluor® (bis(2-methoxyethyl)aminosulfur trifluoride) or DAST (diethylaminosulfur trifluoride), to generate **1** in a single step. Cyclohexane **1** has some surprising properties for a small aliphatic fluorocarbon. It is a solid material at room temperature (m.p. = 107 °C), is amenable to X-ray structure analysis and it has a large calculated dipole moment of 5.2 D.[9] The polarity arises from the two 1,3-diaxial C–F bonds in the cyclohexane chair conformation, which is maintained on ring inversion. NMR spectroscopy in toluene indicates that the electropositive axial hydrogen atoms, on the opposite face to the fluorine atoms, are shielded and shifted ≈1.5 ppm in comparison with NMR spectroscopy performed in dichloromethane, indicating C–H···π(aryl) interactions between these hydrogen atoms and the aromatic ring of the solvent, and, thus, facial polarity of the cyclohexyl ring. This finding is consistent with a calculated electrostatic surface profile of **1** (B3LYP/6-311 + G(2d,p))[9] that demonstrates clear facial polarity, as illustrated in Figure 1. In view of these properties, it became an objective to prepare an analogue of **1** that could be functionalised to deliver building blocks and components for structural diversity in compound libraries. Herein, we report the synthesis and elaboration of phenyl derivative **3** as a molecular fragment containing the all-*syn*-1,2,4,5-tetrafluorocyclohexane motif, and we explore its potential as a building block by exemplifying a range of elaborations of the aryl ring.

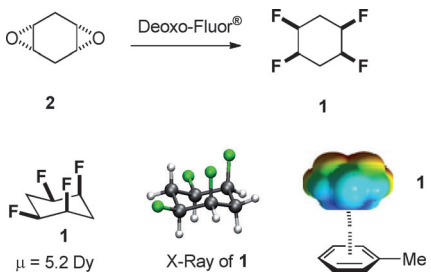

Figure 1. The synthesis of all-*cis*-tetrafluorocyclohexane **1**, with the crystal structure and the calculated electrostatic surface profile (B3LYP/6-311 + G(2d,p)). Red areas (−ve), blue areas (+ve).[9]

The synthesis of **3** (see Scheme 1) started with a Birch reduction of biphenyl **4** to generate diene **5**.[10] Treatment of **5** with *meta*-chloroperbenzoic acid (*m*CPBA) generated the *cis*-diepoxide, **6**, as the major diastereoisomer in a *cis*/*trans* ratio of 10:1. The minor diastereoisomer was readily removed by chromatography. Direct treatment of diepoxide **6** with DAST[11] or Deoxo-Fluor®[12] did not generate clean products, unlike the transformation of **2** into **1**. In view of this result, compound **6** was treated with $Et_3N{\cdot}3HF$[13] to give the two difluorohydrins, **7** and **8**, as a 1.6:1 mixture. These isomers could not be separated by chromatography; instead they were treated together

[a] Dr. A. J. Durie, Dr. T. Fujiwara, R. Cormanich, Prof. M. Bühl, Prof. A. M. Z. Slawin, Prof. D. O'Hagan
School of Chemistry
University of St Andrews
North Haugh, St Andrews KY169ST (United Kingdom)
E-mail: do1@st-andrews.ac.uk

[b] Dr. T. Fujiwara
Graduate School of Medicine and Pharmaceutical Sciences
University of Toyama
Sugitani, Toyama 930-0194 (Japan)

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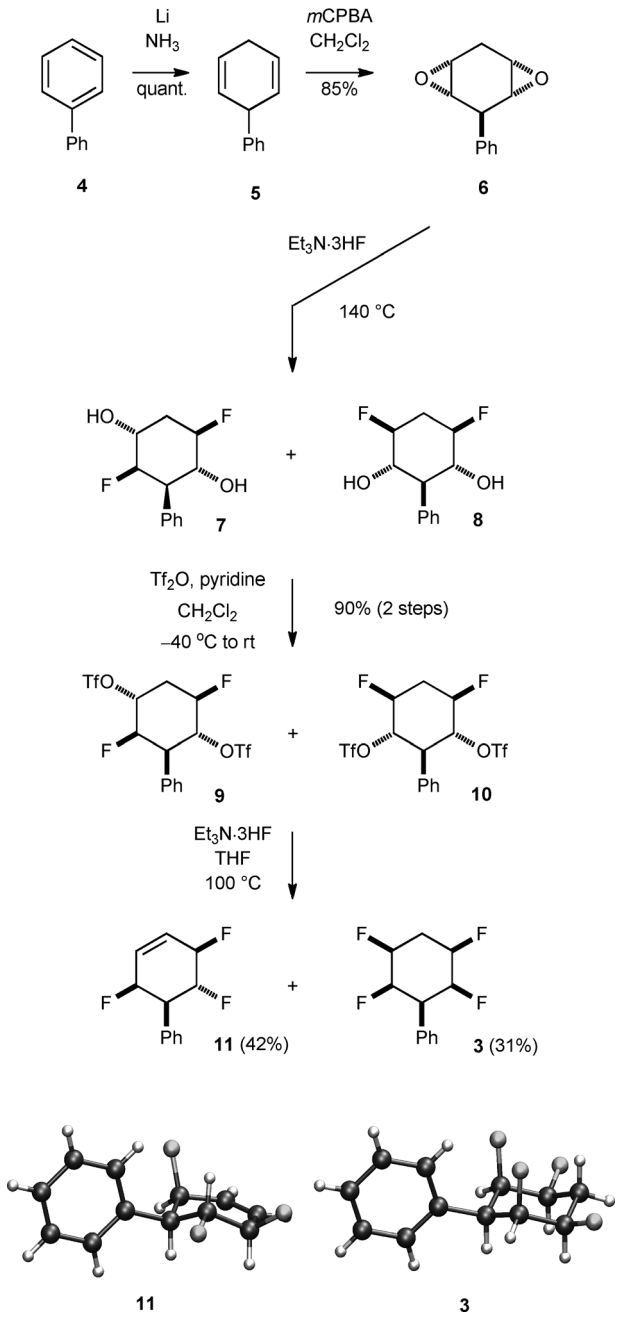


Scheme 1. Synthesis and X-ray structures of *cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane **3** and trifluorocyclohexene **11**. Tf_2O = triflic anhydride.

with triflic anhydride to generate a mixture of **9** and **10**. The ditriflate mixture was then treated with $Et_3N{\cdot}3HF$, at 100 °C, to give **11** and **3**, which could be separated by chromatography. Their structures and stereochemistry were confirmed by X-ray structure analysis. The structure and stereochemistry of **3** was consistent with expectation. However, in the case of product **11**, an elimination had occurred, accompanied by a retention of configuration of one of the original C–O bonds during its conversion to a C–F bond, most probably via a phenonium-ion intermediate.

The X-ray structure of **3** revealed some insights into the properties of this tetrafluorocyclohexane derivative. Notably, the phenyl ring, which lies equatorially, adopts an orientation parallel to the two diaxial C–F bonds. To assess the preference for this orientation, a rotational energy profile was calculated at the B3LYP/def2-TZVP level. This indicated that the solid-state structure adopts a conformation close to the energy minimum in the gas phase, and that the barrier to phenyl ring rotation is $\approx$4.0 kcal.mol^{-1} (see Figure 2). Examination of the molecular packing within the X-ray-derived unit cell reveals that there is an intermolecular interaction between the aryl ring of one molecule of **3** and the non-fluorous face of the cyclohexyl ring in a neighbouring molecule, indicative of an electrostatic···π interaction. This observation was reinforced by NMR experiments. In a similar manner to that previously shown for **1**, selected ^{1}H NMR signals of **3** show a very clear upfield shift in [D_8]toluene when compared with the spectrum obtained in $CDCl_3$ (Figure 3). In particular, the axial protons H2 and H4 display upfield shifts ($\Delta\delta \approx 1.1$ and $\Delta\delta \approx 1.0$ ppm, respectively) of around one ppm. The equatorial protons (H3 and H1 b) also experience upfield shifts in toluene of approximately half that magnitude ($\Delta\delta \approx 0.5$ ppm). Notably, the signal for the axial proton H1 a, which is situated on the fluorine face of the cyclohexane rings, does not shift significantly, indicating that the anisotropic influence of toluene is felt only on the lower electropositive face of the cyclohexane ring. Therefore, both X-ray crystallography and NMR spectroscopy indicate the facial polarity of this ring system. This comparative analysis was carried out for all compounds, **12**, **15**–**21** and **23**, and a consistent pattern was observed, in which the axial protons H2 and H4 in the tetrafluorocyclohexane ring systems became shifted upfield by $\approx$1.0 ppm in [D_8]toluene, relative to $CDCl_3$ (see Table in the Supporting Information).

The calculated minimum-energy conformer for **3** is not perfectly symmetrical, and has proximal *ortho*-H···F_{ax} distances of 2.22 and 2.70 Å. The former is particularly short,[14] with a H···F distance well within the van der Waals contact ($\approx$2.47 Å). This finding led us to explore the prospect of scalar NMR couplings transmitted through these contacts.[15] Thus, $^{1h}J_{HF}$ and $^{2h}J_{CF}$ coupling constants were calculated for the lowest-energy conformers of structure **3**. This study was extended to *ortho*-nitro derivative **12**, which has a significantly higher calculated barrier to rotation ($\approx$12 kcal mol^{-1}, see the Supporting Information), owing to the steric influence of the nitro group and the capacity for a hydrogen bond between the nitro group and the H1 axial hydrogen. This increase in restricted rotation should maximise intramolecular H···F coupling. The calculated $^{1h}J_{HF}$ and $^{2h}J_{CF}$ coupling constants are shown in Table 1. The experimental ^{1}H NMR data for **3** and **12** shows small J_{HF} couplings of $\approx$1 Hz, which are only observed when comparing the difference between the ^{1}H NMR and {^{19}F}^{1}H NMR spectra in each case. Theory suggests maximum values of $\approx$3.67 Hz. The magnitude of the experimental coupling is close to the value that might be found for a through bond $^5J_{HF}$ coupling, therefore, the F···H couplings do not convincingly suggest a $^{1h}J_{HF}$ coupling. However, the experimental $^{2h}J_{CF}$ couplings are much more convincing. Coupling constants in the ^{13}C NMR spectra for the *ortho*-C carbon atom of **3** (triplet, 2.4 Hz) and **12** (triplet, 7.3 Hz) are significant, suggesting coupling relayed through

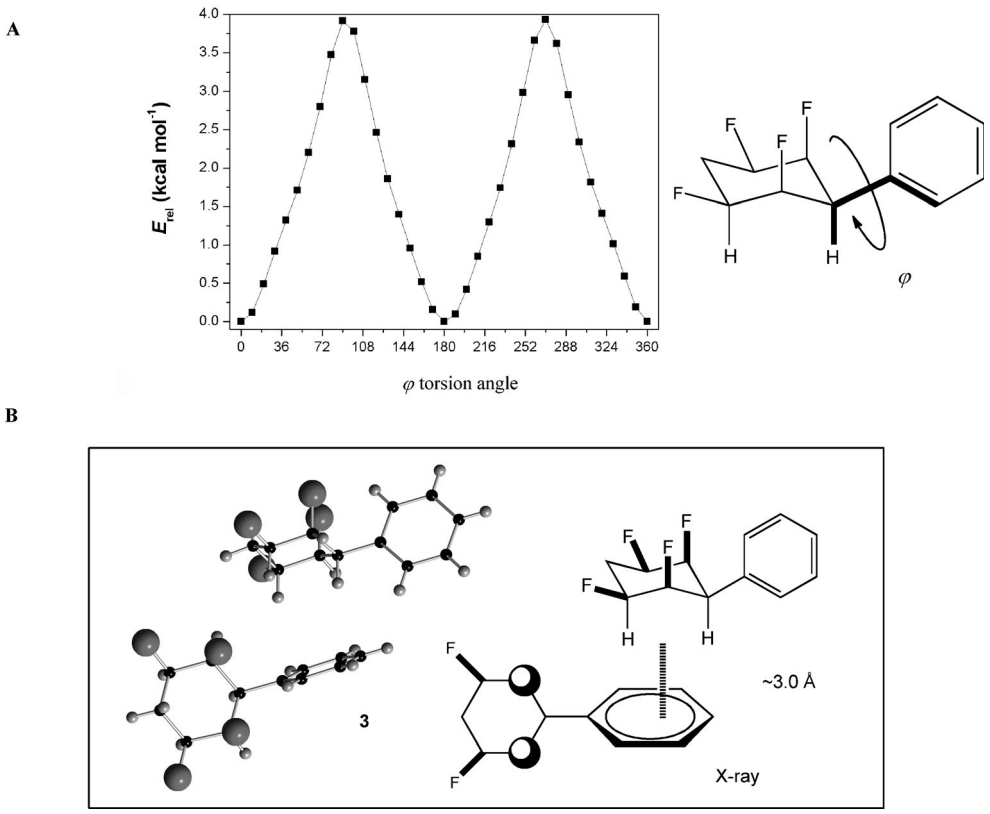


Figure 2.
A) Rotational energy profile of **3** around the C–Ph bond calculated at the B3LYP/def2-TZVP level. B) Crystal packing showing the interaction of two molecules of **3** in the solid state, indicative of an electrostatic interaction between the π system of the phenyl ring and the non-fluorous face of the cyclohexane ring.

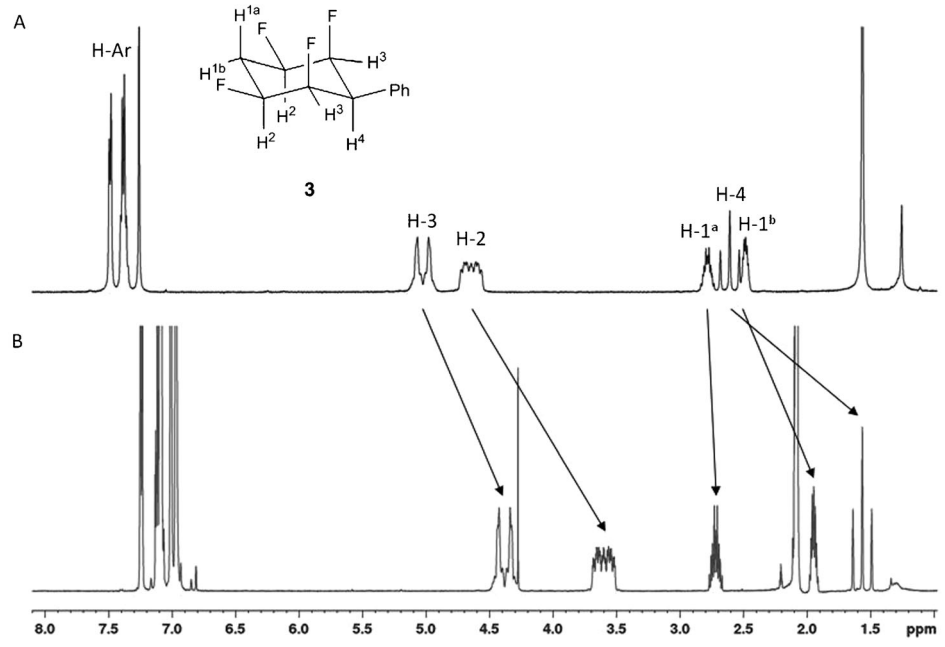


Figure 3.
A) shows the ^{1}H NMR spectrum of **3** in $CDCl_3$, and B) shows the ^{1}H NMR spectrum of **3** in [D_8]toluene There are significant upfield-shifted proton signals in toluene, consistent with a close interaction of the electropositive lower-face protons interacting with the aromatic solvent, and indicative of facial polarity of the tetrafluorocyclohexyl ring system.

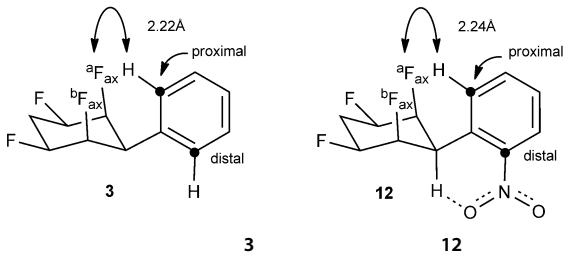
an intramolecular hydrogen bond. In the case of **12**, the experimental value (7.3 Hz) is very close to the average of the two expected theoretical coupling constants (13.4 Hz and 2.59 Hz), consistent with restricted rotation and a maximum value. There is no distal CF coupling observed experimentally, this is consistent with the theory calculations. For **3**, the experimental $^{2h}J_{CF}$ value (2.4 Hz) is a little smaller than the average $^{2h}J_{CF}$ value (3.86 Hz) predicted by theory, and is presumably reduced due to averaging associated with the more rapid aryl ring rotation. However, we conclude that for **3**, and certainly in the case of **12**, there are $^{2h}J_{CF}$ couplings (2.4 Hz and 7.3 Hz, respectively), which are consistent with scalar couplings relayed through short F···H contacts.

It became an objective to explore the derivatisation of **3** so that this motif could be elaborated in different synthetic directions. In the first instance, **3** was subjected to electrophilic aromatic substitution reactions. In particular, nitration was explored. Nitration under different reaction conditions[16] gave mixtures of *ortho*/*meta*/*para* products **12**–**14**, as summarised in Table 2. The regioselectivity varied in different solvents, but indicated that the tetrafluorocyclohexyl ring does not have a dominating *ortho*-/*para*-directing effect.

After the nitration reactions, the *ortho* isomer, **12**, was readily separated by chromatography from the *meta* and *para* isomers, **13** and **14**, which were recovered as a mixture. However, the *meta*/*para* isomer mixture could be efficiently reduced to the corresponding anilines, **15** and **16**, and these products were easily separated by chromatography (Scheme 2).

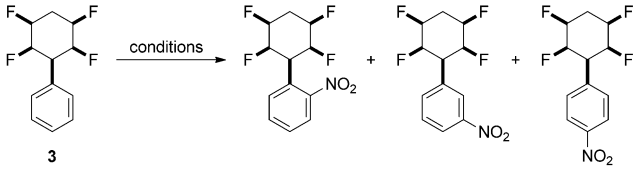
The *meta*- and *para*-anilines, **15** and **16**, were individually

Table 1. Calculated NMR spin–spin coupling constants (Hz) obtained for minimum-energy conformers of **3** and **12** (at the BHandH/EPR-III level), The $^{a}F\cdots H$ distances (Å) are the shortest calculated in each lowest-energy conformer. The dotted (●) *ortho* carbon atoms are those for which couplings to fluorine are reported in the Table.



	3	**12**
$^{1h}J(H_{proximal},{}^{a}F_{ax})$	2.54	1.91
$^{1h}J(H_{proximal},{}^{b}F_{ax})$	3.60	3.67
$^{5}J(H_{distal},{}^{a}F_{ax})$	−0.10	–
$^{5}J(H_{distal},{}^{b}F_{ax})$	0.25	–
$^{2h}J(C_{proximal},{}^{a}F_{ax})$	13.4	13.4
$^{2h}J(C_{proximal},{}^{b}F_{ax})$	2.41	2.59
$^{4}J(C_{distal},{}^{a}F_{ax})$	0.37	−0.01
$^{4}J(C_{distal},{}^{b}F_{ax})$	−0.74	−0.54

Table 2. The conditions and results of the nitration of **3**.

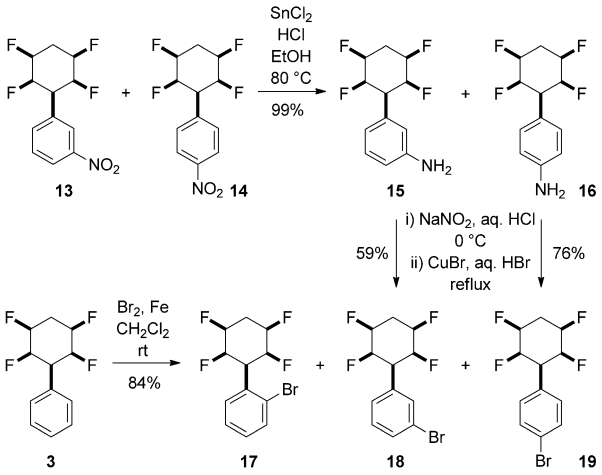


Entry	Conditions	Yield [%][a]	Ratio[b] **12/13/14**
1	$(NH_4)_2Ce(NO_3)_6$ (2 equiv), H_2SO_4/CH_2Cl_2, rt, 3.5 h	96[c]	1.0:1.2:1.9
2	NH_4NO_3 (2 equiv), $(CF_3CO)_2O/CH_2Cl_2$, rt to reflux, 6 h	96	1.7:1.0:1.4
3	HNO_3 (20 equiv), H_2SO_4/CH_2Cl_2, rt, 2 h	98	1.8:1.0:1.6
4	HNO_3 (20 equiv), $H_2SO_4/PhNO_2$, rt, 2 h	96	1.0:1.0:2.0
5	HNO_3 (20 equiv), $H_2SO_4/MeNO_2$, rt, 2.5 h	99	1.0:1.1:2.0

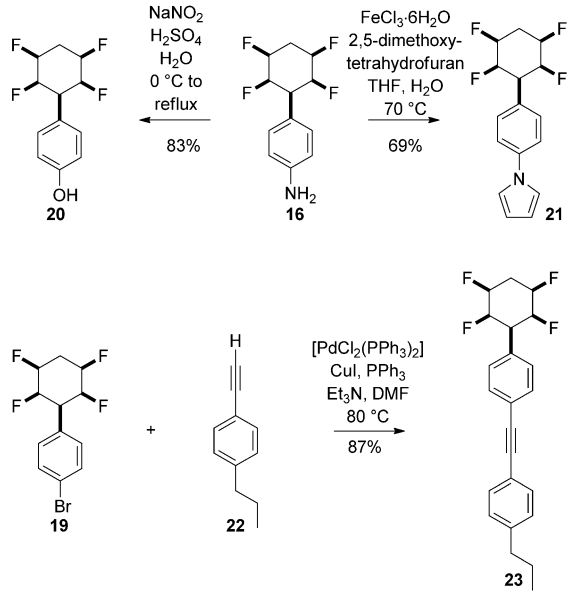
[a] Combined yield of **12**–**14**. [b] Determined by ^{19}F NMR spectroscopy of the product mixture. [c] Contains a trace amount of the dinitrated derivative.

converted to the corresponding bromides, **18** and **19**, under Sandmeyer conditions. Direct bromination of **3** with bromine in the presence of iron gave a similar regioselectivity to that of nitration. The *ortho* isomer, **17**, was readily separated from the *meta* and *para* isomers, **18** and **19**. However, it was not possible to separate **18** and **19** by chromatography. Therefore, the preparation of **18** and **19** was most conveniently achieved by means of the Sandmeyer reaction protocol starting from **15** and **16**, respectively.

A Sandmeyer reaction of *para*-aniline **16** using water as a nucleophile generated the corresponding phenol **20**. *Para*-aniline



Scheme 2. Synthesis of the amino and bromo derivatives of tetrafluorophenylcyclohexane **3**.



Scheme 3. Elaboration of the tetrafluorophenylcyclohexane motifs **16** and **19**.

16 was also treated under Paal–Knorr conditions[17] to generate pyrrole **21**. A Sonogoshira reaction with *para*-bromide **19** and alkyne **22** generated the coupled product **23** in an efficient reaction. These elaborations of aniline **16** and arylbromide **19** are illustrated in Scheme 3.

In conclusion, aryl **3** has been introduced as a novel organofluorine motif with unique structural and polar properties, and its chemical elaboration into a variety of derivatives has been demonstrated, exemplifying its utility as a building block for fine chemical discovery programmes.

Experimental Section

All-*cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane (3) and 3,4,6-trifluoro-5-phenylcyclohexene (11)

$Et_3N{\cdot}3HF$ (9.50 mL, 57.9 mmol, 8.0 equiv) was added to a solution of diepoxide **6** (1.36 g, 7.24 mmol, 1.0 equiv) in dried THF (2 mL) at room temperature. After stirring at 130 °C under argon atmosphere for 40 h, the mixture was cooled to room temperature and was poured into saturated aqueous sodium bicarbonate (200 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (4×100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2/EtOAc = 1:2:2) to give a mixture of difluorohydrins **7** and **8** (1.51 g, 91%, **7**/**8** = ca. 1.6:1) as a colourless powder.This mixture of **7** and **8** was dissolved in dried CH_2Cl_2 (50 mL) under an argon atmosphere. Pyridine (2.14 mL, 26.4 mmol, 4.0 equiv) and trifluoromethanesulfonic anhydride (3.33 mL, 19.8 mmol, 3.0 equiv) were added to the solution at −40 °C and the mixture was allowed to warm to room temperature. After stirring for 21 h, the mixture was filtered through a small pad of silica gel (petroleum ether/CH_2Cl_2/EtOAc = 1:1:1) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2/diethyl ether = 8:4:1) to give a mixture of ditriflates **9** and **10** (3.20 g, 98%, **9**/**10** = ca. 1.6:1) as a colourless powder.$Et_3N{\cdot}3HF$ (21.0 mL, 130 mmol, 20 equiv) was added to a solution of this mixture of ditriflates **9** and **10** in dried THF (5 mL) at room temperature. After stirring at 100 °C under argon atmosphere for 60 h, the mixture was cooled to room temperature and was poured into saturated aqueous sodium bicarbonate (300 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (4×90 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified three times by silica gel chromatography (petroleum ether/diethyl ether = 1:1, petroleum ether/CH_2Cl_2 = 3:2, and petroleum ether/diethyl ether = 2:1, respectively) to give (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-1,2,4,5-tetrafluoro-3-phenylcyclohexane **3** (471 mg, 31%) and (3*RS*,4*SR*,5*SR*,6*SR*)-3,4,6-trifluoro-5-phenylcyclohexene **11** (579 mg, 42%).

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Keywords: aromatic transformations · cyclohexane · fluorinations · organofluorine compounds · polar organic motifs

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Synthetic Methods

*A. J. Durie, T. Fujiwara, R. Cormanich, M. Bühl, A. M. Z. Slawin, D. O'Hagan**

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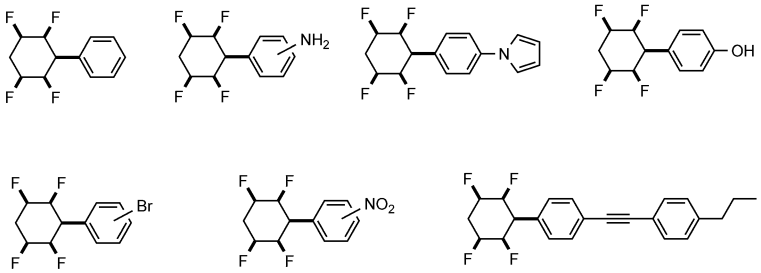
Synthesis and Elaboration of All-*cis*-1,2,4,5-Tetrafluoro-3-Phenylcyclohexane: A Polar Cyclohexane Motif



A stereocontrolled synthesis of all-*cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane is developed as the first functionalised example of this polar cyclohexane motif. The dipolar nature of the cyclohexane ring is explored and the aryl ring is elaborated in different ways to demonstrate its versatility as a molecular building block (see figure).