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Selectively fluorinated cyclohexane building blocks: Derivatives of carbonylated all-*cis*-3-phenyl-1,2,4,5-tetrafluorocyclohexane

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Full Research Paper

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Abstract

Palladium catalysed carbonylation reactions using the *meta*- and *para*-iodo derivatives of all-*cis*-3-phenyl-1,2,4,5-tetrafluorocyclohexane (**4**) are illustrated as the start point for a variety of functional group interconversions. The resultant benzaldehyde and benzoic acids offer novel building blocks for further derivatisation and facilitate the incorporation of the facially polarised all-*cis*-1,2,4,5-tetrafluorocyclohexane motif into more advanced molecular scaffolds.

Introduction

Selectively fluorinated building blocks have proven invaluable in drug discovery [1] and agrochemical research programmes [2]. Most such building blocks possess aryl/heteroaryl-F, aryl/heteroaryl-(X)CF_3 or variants thereof, whereas selectively fluorinated aliphatics are much rarer. We have had a focus on introducing selectively fluorinated cyclohexane rings, to complement aromatic building blocks. In this context we have recently prepared the all-*cis*-tetrafluorocyclohexanes **2** and **3** [3,4] and also all-*cis*-hexafluorocyclohexane (**1**) [5] as shown in Figure 1. In the case of the hexafluorocyclohexane, the ring maintains a chair conformation and therefore there are three C–F bonds orientated triaxial, on one face of the ring. This gives rise to a large dipole moment (6.2 D) and a molecule which is among the most polar aliphatics known in organic chemistry. The all-*cis*-tetrafluorocyclohexanes **2** and **3** are also facially polarised because in the chair conformation, they always have two 1,3-diaxial C–F bonds on one face of the ring, and this results in ring systems also with large dipole moments (4.9 D for **2** and 5.2 D for **3**). The nature of these cyclohexanes, where the two faces are oppositely polarised, presents a unique property for

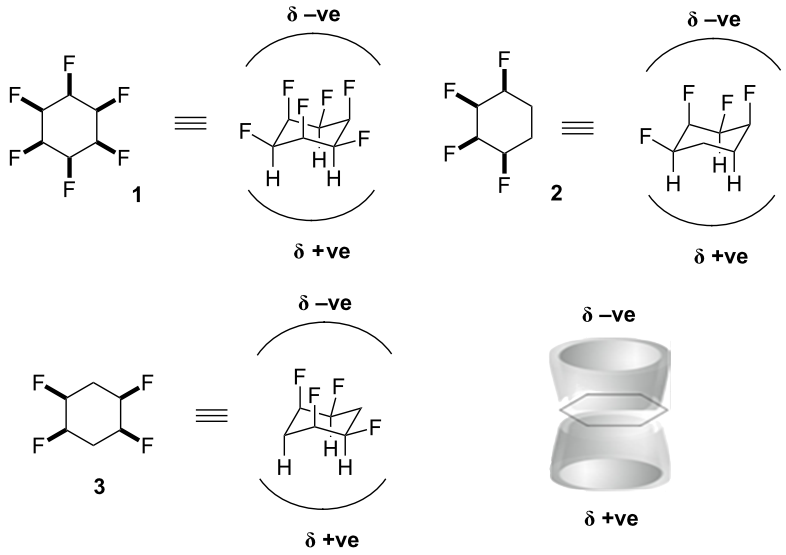


Figure 1: All *cis*-hexafluoro- **1** and tetrafluorocyclohexanes **2** and **3** result in facially polarised ring motifs with an electrostatically negative (δ –ve) fluorine face and an electrostatically positive (δ +ve) hydrogen face.

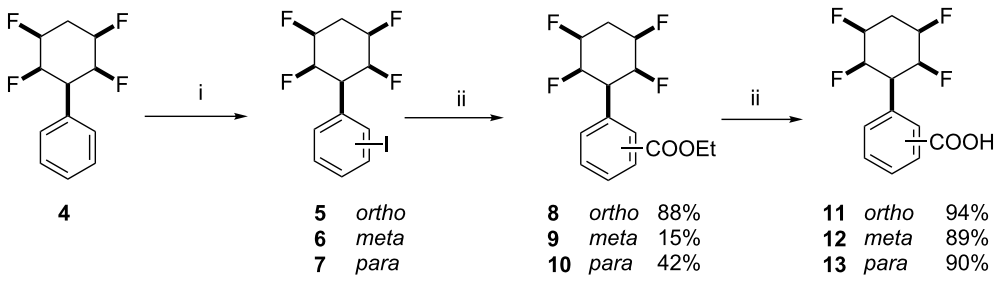
use in pharmaceuticals and agrochemicals discovery programmes.

Compounds **1–3** are unfunctionalised and not amenable to derivatisation, and therefore we started to explore the chemistry of all-*cis*-3-phenyl-1,2,4,5-tetrafluorocyclohexane (**4**) [6], to access derivatives carrying this ring motif. In that context it has been demonstrated that **4** can be elaborated in a relatively straightforward manner by mainstream reactions of electrophilic aromatic substitution [7]. This extended to the synthesis of cyclohexane substituted (*S*)-L-phenylalanines with orthogonal protecting groups suitable for their incorporation into peptides [8]. In this paper it is demonstrated that palladium mediated carbonylation of the aryl iodinated derivatives **5–7** forms the basis of a diversity of new products which may prove attractive as building blocks for structure activity studies in bioactive research projects.

Results and Discussion

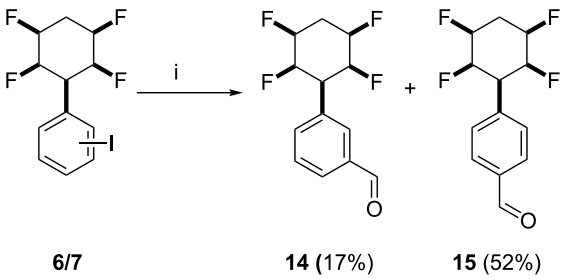
A key reaction for this programme involved the carbonylation of aryl iodides **5**, **6** and **7** which are derived by HIO_4 treatment of all-*cis*-3-phenyl-1,2,4,5-tetrafluorocyclohexane (**4**). The *ortho* isomer **5** was separated from the *meta* and *para* isomers **6** and **7**, the latter of which were recovered as a mixture as previously reported [8]. Palladium catalysed carboxylation [9] was explored with aryl iodides **5** or **6**/**7** as a mixture, and these gave the corresponding ethyl esters **8** and **9**/**10**, respectively. The *meta* and *para* esters **9** and **10** were easily separated by chromatography. Hydrolysis of esters **8**–**10** using trifluoroacetic acid (TFA) or 6 M HCl in dioxane [10] gave the corresponding benzoic acids **11**, **12**, and **13** as illustrated in Scheme 1.

Direct palladium catalysed formylation of aryl iodides **6**/**7** as a mixture was explored using $Pd(PPh_3)_4$, Bu_4SnH and CO [11]. This generated benzaldehyde derivatives **14** and **15** in a 1:3



Scheme 1: Preparation of benzoic acids **11–13**; i. $HIO_4{\cdot}2H_2O$ (50%), AcOH, H_2SO_4, I_2, H_2O, 70 °C 24 h, 92%.; ii. $Pd(OAc)_2$, Ph_3P,Et_3N, EtOH, CO (1 atm), 80 °C, 16 h. iii. HCl (6 M), 1,4-dioxane, 70 °C, 24 h or TFA/H_2O (9:1), 100 °C, 24 h.

ratio, respectively, which could be separated by column chromatography. The reaction is illustrated in Scheme 2. The structure of aldehyde **15** was confirmed by X-ray structure analysis and is shown in Figure 2.



Scheme 2: Synthesis of benzaldehyde derivatives **14** and **15**: i. $Pd(PPh_3)_4$, Bu_3SnH, THF, CO (1 atm), 50 °C, 2–3 h, 70%.

Transformations of benzaldehyde **15** were explored. For example McMurry coupling [12] of **15** gave a mixture of stilbene isomers **16**. Direct hydrogenation of the mixture afford dihydrostilbene **17** as a crystalline solid, a structure which was confirmed by X-ray crystallography and is shown in the inset in Scheme 3. Aldehyde **15** could also be converted to styrene **18** in

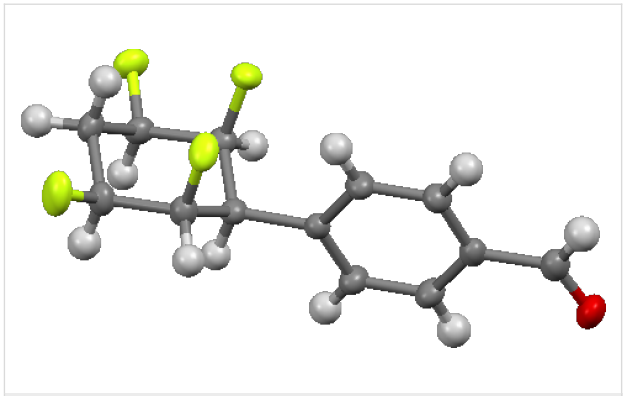
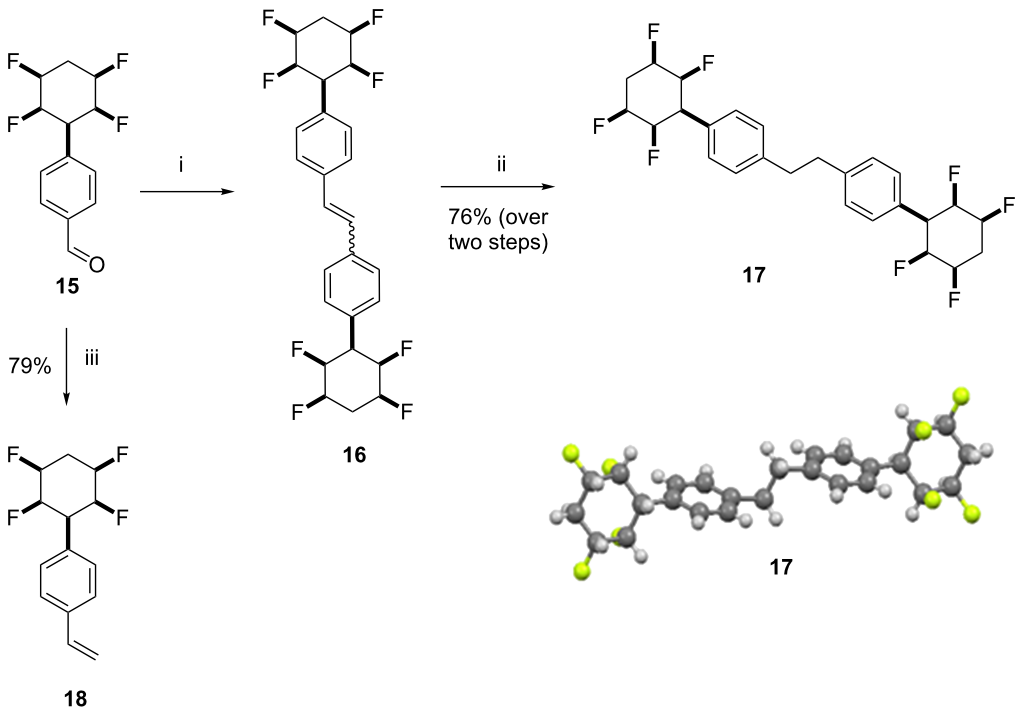


Figure 2: X-ray structure of aldehyde **15**. CCDC number 1432193.

good yield using the Simmons–Smith method [13] as illustrated in Scheme 3.

For further elaboration, aldehyde **15** was reduced with $NaBH_4$ in good yield to generate the corresponding benzyl alcohol **19** [14]. Iodination of **19** to generate **20** with HI in chloroform [15] proved superior (95% yield) to the more classical Appel protocol which gave low yields in our hands. Nucleophilic substitution with the resultant benzyl iodide **20** using azide gave the corresponding benzyl azide **21** in good yield [16]. Chlorination to generate **23** was accomplished by treatment with mesyl



Scheme 3: Olefination reactions of **15** and the X-ray structure of **17** (CCDC number 1432194): i. Zn, $TiCl_4$, THF, 0 °C to reflux, 12 h; ii. Pd/C, H_2, EtOAc, 20 °C, 16 h, 76% over 2 steps. iii. Zn, CH_2I_2, $TiCl_4$, THF, 0 °C to 20 °C, 12 h; 79%.

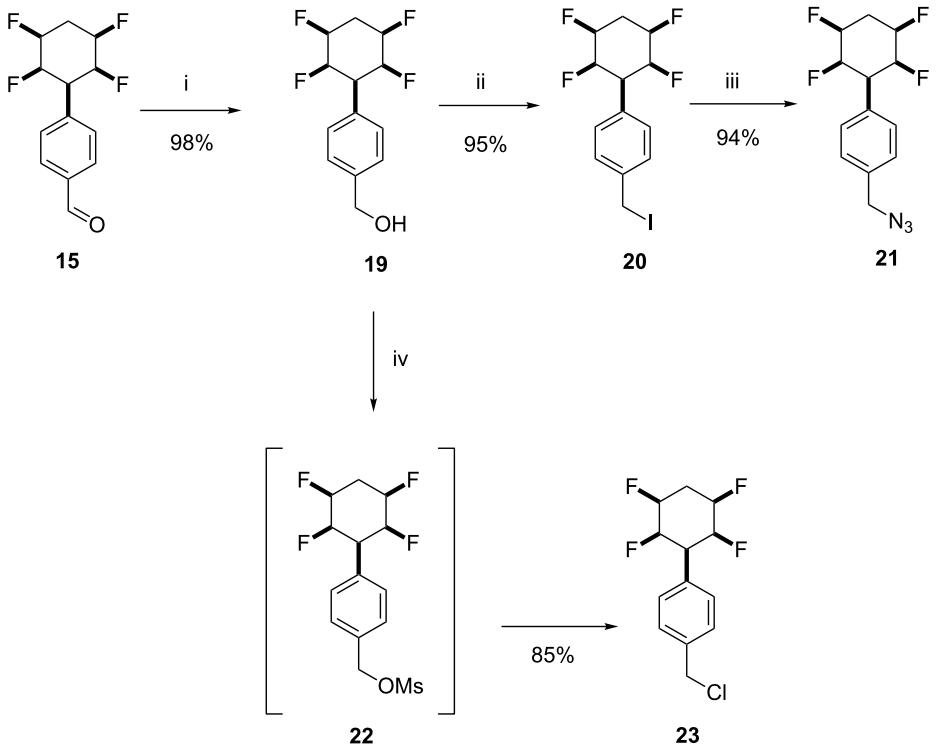
chloride/Et_3N in a one pot protocol, presumably via mesylate **22**, as illustrated in Scheme 4 [17].

Reduction of benzyl azide **21** to generate amine **27** as its hydrochloride salt was achieved by a Staudinger reduction in good yield [18]. Azide **21** was also amenable to a 'click' reaction, in this case with the acetylenic protected amino acid **24** [19]. This gave the 1,2,3-triazol linked adduct **25** which could be fully deprotected to generate the free amino acid hydrochloride **26** as illustrated in Scheme 5.

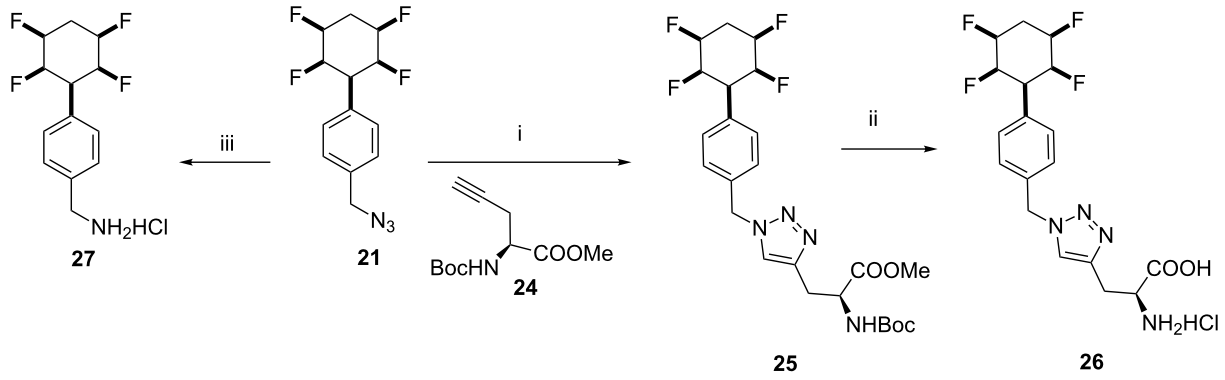
The reactions described above were equally amenable to the *meta*-benzaldehyde **14**, as illustrated in Scheme 6.

Conclusion

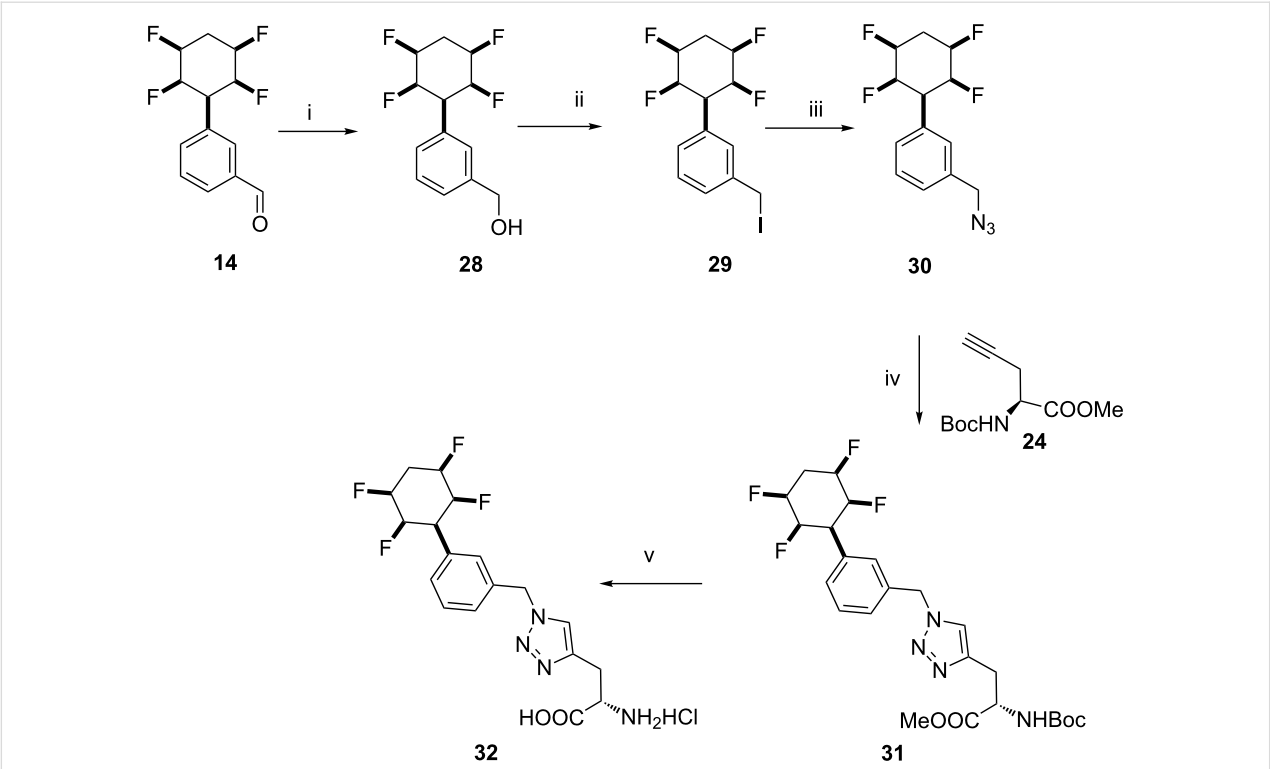
In summary it is demonstrated that the all-*cis*-1,2,4,5-tetrafluorocyclohexane motif has been incorporated in a range of products prepared from aryl iodides **5**–**7**. These derivatives derive from aryl carboxylation or carbonylation, and complement those that can be prepared directly by electrophilic aromatic substitution of phenyl derivative **4**. This chemistry



Scheme 4: Reactions from aldehyde **15**: i. $NaBH_4$, THF, 20 °C, 1 h, 98%.; ii. HI (57%), $CHCl_3$, 30 h, 95%; iii. Bu_4NN_3, acetone/H_2O (4:1), 20 °C, 3 h, 94%; iv. MsCl, Et_3N, DCM, −78 °C to 20 °C, 85%.



Scheme 5: Reactions of benzyl azide **21**; i. **24**, $Cu(OAc)_2$, Na ascorbate, *t*-BuOH, H_2O, 20 °C, 16 h, 72%; ii. HCl (6 M), 1,4-dioxane, 80 °C, 48 h, 96%; iii. Ph_3P, THF/H_2O (10:1), then HCl, rt, 1 h, 74%.



Scheme 6: Reactions of aldehyde **14**: i. $NaBH_4$, THF, rt, 1 h, 98%.; ii. HI (57%), $CHCl_3$, 30 h, 94%; iii. Bu_4NN_3, acetone/H_2O (4:1), rt, 3 h, 91%; iv. **24**, $Cu(OAc)_2$, Na ascorbate, *t*-BuOH, H_2O, rt, 12 h, 81%; v. HCl (6 M), 1,4-dioxane, 70 °C, 48 h, 94%.

should more readily facilitate the exploration of the properties and potential of the all-*cis*-1,2,4,5-tetrafluorocyclohexane motif in a diversity of research programmes.

Supporting Information

Supporting Information File 1

Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-287-S1.pdf]

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