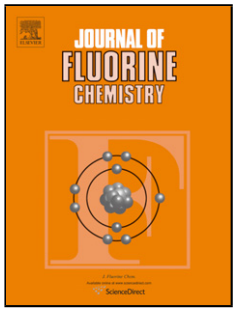

Title: New entry for fluorinated carbocycles: Unprecedented 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives

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New entry for fluorinated carbocycles: Unprecedented 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives

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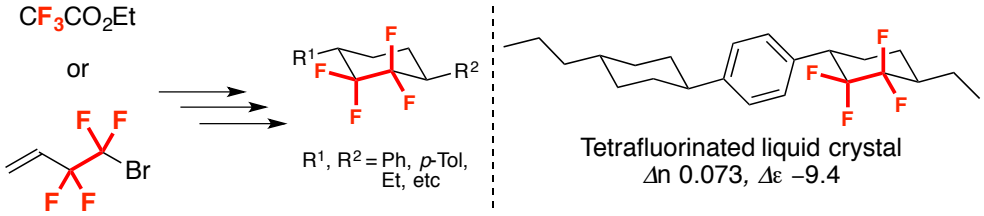
Graphical Abstract



Highlight

1. Synthetic methods for the preparation of tetrafluorinated cyclohexanes were established.
2. The methods involve a Pd-catalyzed formate reduction or a Barton-McCombie radical reduction as a key reaction
3. The tetrafluorinated cyclohexanes were found to have a large negative dielectric anisotropy.

Abstract:

The synthetic protocols for symmetrical/unsymmetrical 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane molecules were successfully established for the first time. Some of thus obtained tetrafluorinated cyclohexanes underwent recrystallization to afford *trans*-configured products preferentially. One of the unsymmetrical *trans*-disubstituted tetrafluorocyclohexanes, *trans*-1-ethyl-2,2,3,3-tetrafluoro-4-[4-(*trans*-4-*n*-propylcyclohex-1-yl)phenyl]cyclohexane, was found to possess a low birefringence Δn (0.073) and a large negative dielectric anisotropy $\Delta\varepsilon$ (–9.4) in a binary mixture system, which were very prominent as characteristics of LC molecules in VA-mode driving LC displays.

Keyword: Tetrafluoroethylenated cyclohexane, Homo-coupling, Pd-catalyzed regioselective formate reduction, Barton-McCombie radical reduction

1. Introduction

Many efforts have been devoted to the development of novel and efficient synthetic protocols for fluoroorganic molecules because introduction of a fluorine atom into organic substances can often bring about a significant improvement of their chemical and physical properties owing to the potent unique nature,[1] such as the largest electronegativity, the smallest van der Waals radius (147 pm) next to a hydrogen atom, and strong C–F bond energy (484 kJ mol^{-1}), etc. Among various organofluorine compounds, lowly fluorinated (≤ 3 fluorines) or highly fluorinated molecules (> 6 fluorines) have attracted an enormous interest due to their versatile utility in medicinal as well as in material fields so far, whereas little attention has been paid to the development of semi-fluorinated organic molecules containing 4–6 fluorine atoms. As the pioneering work, DiMagno *et al.* reported the first synthesis of hexafluoropropylene-containing (-$CF_2CF_2CF_2$- group) pyranose **1** in 1998 and found that the six fluorine atoms in the structure brought about drastic enhancement of cell membrane permeability, which was explained by a strong interaction with transport proteins, rather than non-fluorinated counterparts (Figure 1).[2]

Since the epoch-making report, extensive studies for the semi-fluorinated cyclic molecules, in particular cyclic molecules have been carried out in the world and several synthetic approaches have already been developed so far. For instance, Linclau and co-workers reported efficient and enantioselective synthetic methods for tetrafluoroethylene-containing (-CF_2CF_2- group) pyranose **2** and franoses **3**, **4**.[3] Also, Gouverneur *et al.* successfully developed new CF_2CF_2-containing *C*-nucleosides **5**.[4] As promising candidates for the sensitive photoswitching devices, $CF_2CF_2CF_2$-containing cyclopentene derivatives **6** have also been worthy of remark.[5]

Owing to the potent utility of such semi-fluorinated cyclic compounds,[6] our research group has also devoted a great deal of attention to the exploitation of the synthetic protocols for novel semi-fluorinated cyclic compounds. As novel synthetic applications of such cyclic compounds, we have also focused on the development of unprecedented liquid crystalline (LC) molecules having the cyclic fragments in the mesogenic core. Very recently, we succeeded in the synthesis of novel semi-fluorinated carbocycles[7] and it was proved that tricyclic organic molecules with the CF_2CF_2-containing cyclohexadiene scaffold as a part of mesogen possessed a large negative dielectric anisotropy in a host liquid-crystal, which would be one of the most desirable properties for the prominent vertical alignment (VA)-mode liquid-crystalline (LC) display devices.[8]

In order to further expand our research project on the development of much more efficient liquid

crystals having an unprecedented semi-fluorinated carbocycle fragment, our attention was subsequently directed towards novel CF_2CF_2-containing *cyclohexane* derivatives **7** and **8** that can be derived from commercially available fluorinated substances (Scheme 1): *symmetrical* 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives **7** can be synthesized from ethyl trifluoroacetate **9** (**Path A**) and the *unsymmetrical* derivatives **8** can be accessed from 4-bromo-3,3,4,4-tetrafluorobut-1-ene **10** (**Path B**). In this article, we would describe two types of novel synthetic approaches for unprecedented 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives as new entry for fluorinated carbocycles. In addition, results on the evaluation of LC properties, such as a birefringence (Δn) and dielectric anisotropy ($\Delta\varepsilon$), of tricyclic mesogenic molecules with a 1,1,2,2-tetrafluorocyclohexane moiety, would also be disclosed.

2. Results and discussion

*2.1. Synthesis of symmetrical 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane (**Path A**)*

Initially, we designed a synthetic pathway to *symmetrical* 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives (Scheme 2). To establish the synthetic approach, we started with a synthesis of 1,1,2,2-tetrafluoro-3,6-diphenylcyclohexane (**7a**), where Ar was phenyl (Ph) group in Scheme 2. Thus, reaction of ethyl trifluoroacetate (**9**) with phenylmagnesium bromide in THF at –78 °C during overnight, followed by acidic treatment, gave α,α,α-trifluoroacetophenone (**11a**) in 49% yield (Table 1).[9] Subsequent Mg(0)-promoted C–F bond cleavage of **11a**, which has been reported by Amii and Uneyama *et al.*, successfully gave rise to α,α-difluoro enol silane **12a** in good yield.[10] Mixing with $Cu(OTf)_2$ in acetonitrile at room temperature, the **12a** smoothly underwent homo-coupling reaction to afford 2,2,3,3-tetrafluoro-1,4-diphenylbutan-1,4-dione (**13a**) in 66% yield.[11] Exposing the **13a** under conditions of Horner-Wadsworth-Emmons reaction, the carbonyl functionality in **13a** was converted to α,β-unsaturated diester, *e.g.* **14a**, in 55% yield as a single (*2E*,*6E*)-isomer.[12] The diester moiety in **14a** were easily reduced by treating **14a** with diisobutylaluminium hydride (DIBAL-H) in CH_2Cl_2 at 0 °C for 3 h, leading to the tetrafluorinated 2,6-dien-1,8-diol derivative **15a** (66% yield), which was converted to the corresponding dicarbonate **16a** in 95% yield after the reaction with ethyl chloroformate ($ClCO_2Et$).

According to our previous report,[13] the allyl dicarbonate **16a** was subjected to Pd(0)-catalyzed formate reduction with $HCO_2^-NEt_3H^+$, *in situ* prepared from HCO_2H and Et_3N, in DMF at 80 °C for 2 h, leading to the desired terminal diene **17a**, the internal diene **18a,** and other isomers in an excellent yield as an inseparable mixture. Analyzing the diastereoselectivity (d.r.) of **17a** by NMR measurements, it was found to be approximately 1:1 ratio. Based on the results obtained, possible

reaction mechanism for the Pd(0)-catalyzed formate reduction of tetrafluorinated dicarbonate **16** can be explained as shown in Scheme 3. Thus, the reaction can be initiated by oxidative addition of **16** to a Pd center to generate π-allylpalladium species, which undergoes nucleophilic attack from formate towards the Pd center, giving rise to the corresponding π-allylpalladium complex, **Int-A** or **Int-B**. The **Int-B** having a large steric repulsion between an aryl group (Ar) and a phosphine ligand, may be easily interconverted to more stable **Int-A** with *trans*-configured ligands. It is also possible that a Pd metal would be closer to the γ-carbon attached with an Rf group than the α-carbon, like **Int-C**, owing to an extremely electron-withdrawing Rf group, though the γ-position is somewhat sterically hindered. Accordingly, subsequent evolution of CO_2 from the preferentially formed **Int-A** or **Int-C**, followed by hydride migration to γ-carbon and immediate reductive elimination of Pd(0), yields the corresponding γ-product **17** in a regioselective fashion.

With the obtained terminal diene **17a** in hand, we examined ring-closing metathesis (RCM)[14] using a Grubbs 2nd generation catalyst. On treating the mixture of **17a**, **18a**, and other isomers with a catalytic amount of Grubbs catalyst (5 mol%) in CH_2Cl_2 at room temperature for 5 days, only **17a** was subjected to the RCM reaction to provide the desired 4,4,5,5-tetrafluoro-3,6-diphenylcyclohex-1-ene (**19a**) in high yield as an inseparable diastereomeric mixture (*cis*/*trans* = 56/44). Finally, hydrogenation of **19a** under the standard reaction conditions proceeded smoothly to give the desired 1,1,2,2-tetrafluoro-3,6-diphenylcyclohexane **7a** in 83% yield. The NMR measurements made us note that **7a** was structurally well-characterized but still a mixture of diastereomers in a ratio of *cis*/*trans* = 56/44.

With this established synthetic protocol, we carried out the synthesis of novel tetrafluorinated carbocycles having other aromatic substituents, such as 4-$CH_3C_6H_4$ and 4-*n*-$C_3H_7C_6H_4$ group, as shown in Table 1. As a result, it was proved that the desired CF_2CF_2-containing cyclohexane derivatives **7b** and **7c** were successfully yielded in moderate efficiency. However, the **7b** and **7c** was also found to be a mixture of *cis*/*trans* isomers (*ca*. 1/1). To our great delight, it was proved that the *trans* isomers of **7b** and **7c** could be easily obtained in a pure form (*cis*/*trans* = <1/>99) after several recrystallization processes from hexane.

Fortunately, the *trans*-**7b** gave a single crystal suitable for X-ray crystallography, which was found to be monoclinic crystal with *P 1 2₁/a 1* space group and to contain twelve formula units in a unit

cell. The crystal structure and packing structures observed are shown in Fig. 2. The relative configuration of the preferentially crystalized **7b** was proved to be obviously *trans*-configuration at 3 and 6-positions (Fig. 2a). Viewing the packing structure of **7b**, the twelve molecules in a unit cell were tightly packed with multiple short contact between F···F with 290 pm as well as F···H of 260 pm, both of which are below the sum of van der Waals radii (Fig. 2b).[15]

Consequently, the synthetic approach for the unprecedented symmetrical 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives starting from commercially available fluorinated substance was successfully developed.

*2.2. Synthesis of unsymmetrical 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives (**Path B**)*

Our motivation was subsequently directed towards the development of *unsymmetrical* 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives, which would be more promising entries for versatile applications, like liquid crystals, etc. It is unfortunate, however, that the synthetic protocol shown in Scheme 2 is not applicable for construction of the unsymmetrical derivatives: it is necessary to exploit alternative synthetic approach to the unsymmetrical CF_2CF_2-containing cyclohexane derivatives.

As shown in Scheme 4, very recently, our group successfully developed the eight-step synthetic approach to unsymmetrical 1,4-disubstituted 5,5,6,6-tetrafluorocyclohexa-1,3-diene derivatives **21** through reductive coupling of **10** with aldehyde,[16] ozonolysis, Grignard reaction, Oxone® oxidation,[17] allylation, ring closing metathesis, hydrogenation, and the last dehydration of **20**.[8] To fulfill our goal, which is novel exploitation of synthetic route to the unsymmetrical 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives, we further examined a catalytic hydrogenation of cyclohexadiene derivative **21** as an initial attempt.

Thus, the **21a** dissolved in methanol was exposed under hydrogen atmosphere in the presence of a catalytic amount of Pd/C (10 mol%) and stirred at room temperature for 1 day. The catalytic hydrogenation underwent very smoothly to afford the desired unsymmetrical 1,1,2,2-tetrafluorocyclohexane derivatives **8a** in 96% yield. After NMR analyses, the **8a** was found to be obtained as a *cis*/*trans*-mixture (*cis*/*trans* = 70/30).

Several attempts to improve the ratio of *cis*/*trans* isomers, such as changing the reaction conditions

of hydrogenation, did not lead to a satisfactory result at all. This undesired stereoselectivity can be explained on the basis of the coordination pattern of alkene moieties to the Pd center. As illustrated in Scheme 5, the ***trans*-8a** can be obtained when two alkene moieties in **21a** coordinate to the different metal center of the Pd catalyst form an opposite direction, while the ***cis*-8a** can be produced in the hydrogen addition form the same direction *via* the simultaneous coordination of both alkenes to Pd center. Apparently, the former reaction is thermodynamicallly unfavorable than the latter, strongly indicating that a catalytic hydrogenation smoothly afforded **8a** with a *cis* selectivity.

In order to preferentially obtain the *trans*-isomers, we next designed an alternative approach, i.e. Barton-McCombie radical reduction of diol **20** (Scheme 6).

Thus, reaction of tetrafluorinated cyclohexan-1,4-diols **20a**–**c**, which were derived from the same starting substrate **10**,[8] with CS_2 in the presence of NaH in THF at room temperature, followed by the treatment of MeI, afforded the corresponding *S*,*S*-dimethyl bisxanthates. When the bisxanthates were submitted under reaction conditions of Barton-McCombie radical reduction,[18] they were smoothly converted to the corresponding reduction product, e.g. unsymmetrical 3,6-disubstituted tetrafluorocyclohexane derivatives **8a**–**c**, in good to high yields. In the radical reaction, the **8** were also found to obtain as a mixture of *cis* and *trans* isomers. After detailed investigations, the ratio of *cis*-/*trans*-**8** was proved to drastically change, depending on the substituents at 3 and 6 positions of **8**: the ratio of **8a** having two aryl substituents at the 3 and 6 positions was *cis*/*trans* = 74/26, while the ratio of the others, e.g. **8b** and **8c**, bearing one alkyl and one aryl substituents were *cis*/*trans* = 28/72 for **8b** and *cis*/*trans* = 13/87 for **8c**, respectively.

The *cis*/*trans*-selectivity in the radical reduction can be rationally understood by considering the reaction mechanism. Scheme 7 shows the possible reaction mechanism. Tributylstannyl radical (*Sn*•), generated from *n*-Bu_3SnH and Et_3B/O_2, attacks thiocarbonyl moiety in a bisxanthate to form a radical species **T1**. In all bisxanthates, a thiocarbonyl moieties neighboring aromatic substituent is preferentially subjected to a radical reaction, resulting in the formation of thermally stable benzyl radical **T1**. Subsequent H radical abstraction of the **T1** from *n*-Bu_3SnH gives the corresponding mono-reduction intermediate (**Int-D**), along with a generation of *Sn*•. The *Sn*• generated or remained in the mixture successively reacts with another xanthate moieties in **Int-D** to generate tertiary carbon radical **T2**. When R^2 is an aryl substituent, the radical intermediate is a resonance-stabilized radical **T2-Ar**, in which the radical carbon is sp^2-hybridized. Therefore, tin hydride (*Sn*H) preferentially comes close to the equatorial side, avoiding a large steric repulsion with axial substituents, to afford 3,6-disubstituted tetrafluorocyclohexanes in a *cis*-selective manner. In the case of R^2 = Et, on the other hand, the radical intermediate is not so stabilized because of the lack of resonance effect. Accordingly, **T2-Et$_{eq}$**, in which the ethyl group occupies the equatorial position, is more stable than **T2-Et$_{ax}$** with the ethyl group at the axial position, because of a steric

repulsion between the ethyl and axial substituents in **T2-Et$_{ax}$**. Therefore the radical reduction preferentially proceeds *via* **T2-Et$_{eq}$**, resulting in the preferential formation of a thermally stable ***trans*-8**.

In order to further prove the stereoselection in the reaction mechanism, we carried out density functional theory calculations at the B3LYP/6-311+G(d,p) levels of theory[19] for 3,6-diphenyl-1,1,2,2-tetrafluorocyclohexyl radical **T2-Ar** and 3-ethyl-6-phenyl-1,1,2,2-tetrafluorocyclohexyl radical **T2-Et**. In Fig 3-(a) and (b) are shown the most stable conformers for the above two radicals, and in addition their SOMOs are shown. As shown in (a), the unpaired electron at the benzylic position is delocalized along with the π electrons on the benzene ring, and electron clouds are equally oriented in both the benzene ring and the benzylic carbon. Electron lobes at the benzylic position are also equally oriented on the both equatorial and axial sides. Consequently, tin hydride preferentially approaches the radical from the equatorial side, avoiding the large repulsion between tin hydride and axial substituents, to produce *cis* isomer in a selective manner.

In sharp contrast, electron lobes at the tertiary radicalic carbon of two conformers in Fig (b), which are at almost the same energy level, is oriented more largely on the axial side rather than on the equatorial side. Then, the electron lobe of the tin hydride can overlap with the axially-oriented lobe more effectively than the equatorially-oriented one, resulting in the preferential formation of *trans* isomers.

Among the **8a**–**c** in hand, **8b** and **8c** were found to be successfully recrystallized from Et_2O/MeOH system, furnishing the *trans*-isomer in a pure form. The relative structures of ***trans*-8b** and ***trans*-8c** were determined by comparing not only their molecular polarity but also their spectral data to a structure-identified ***trans*-7b**.

Consequently, we successfully developed new fluorinated carbocycles, e.g. unsymmetrical 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives **8**. The unsymmetrical *trans*-configured cyclohexane scaffolds are widely known to be popular mesogenic structures, which are one of the most important segments in liquid-crystalline (LC) materials.[20]

2.3. Evaluation of LC properties of unsymmetrical 3,6-disubstituted 1,1,2,2-tetrafluoro-trans-cyclohexane derivatives

In our previous study,[8] we have disclosed tricyclic molecules **21b** and **21c** with 5,5,6,6-tetrafluorocyclohexa-1,3-diene motif exhibited a large negative dielectric anisotropy ($\Delta\varepsilon$), which is an important characteristic for the application to a vertical alignment (VA)-mode LC display. From the structural similarity, we envisioned that the present 3,6-disubstituted *trans*-1,1,2,2-tetrafluorocyclohexanes, *e.g.* ***trans*-8b** and ***trans*-8c**, presented here would become

novel structural motif with a large $\Delta\varepsilon$.

Measuring the thermodynamic behavior of ***trans*-8b** and ***trans*-8c** using differential scanning calorimeter and polarizing optical microscope, they did not exhibit any LC phase by direct phase transition from the crystalline to isotropic phase (Table 2), though the reported **21b** and **21c** showed nematic phase with a range of 4–12 °C.[21] However, it is in general that binary or multicomponent mixture systems with a host-material are employed in LC devices in a real world, meaning that the ***trans*-8b** and ***trans*-8c** without LC phases in a single molecule can be still candidates for a guest material. Therefore, we subsequently attempted evaluation of their physical properties, such as birefringence (Δn), and dielectric anisotropy ($\Delta\varepsilon$), in a binary mixture system containing ***trans*-8b** and ***trans*-8c** (10 wt%) and host material (90 wt%, MLC-6608 (Merck)). To estimate the properties for a single molecule, we calculated using an extrapolation technique from the results of a binary mixture system. In Table 3 are shown the observed Δn and $\Delta\varepsilon$ for the present ***trans*-8b** and ***trans*-8c** as well as the data for previously reported cyclohexa-1,3-diene analogues **21b** and **21c** as a comparison.

Measuring the Δn for the binary mixture of ***trans*-8b** and ***trans*-8c** using Abbe's refractometer, equipped with a polarizer, the Δn were 0.13 for ***trans*-8b** and 0.073 for ***trans*-8c**, respectively. Indeed, the Δn values of ***trans*-8b** and ***trans*-8c** were much lower than those of **21b** and **21c**, which indicates that the switching partial mesogenic structure from tetrafluorocyclohexa-1,3-diene to tetrafluorocyclohexane moiety is significantly attributable to increasing the ordinary refractive indice. To ensure the change of the birefringence (Δn) depended on the mesogenic structure, therefore, we performed quantum chemical calculation[19] with a density functional theory at the B3LYP/6-311+G(d,p) levels of theory for ***trans*-8b**, **c**, together with the reported **21b, c**. It has been known that the Δn of the molecule mostly depends on the polarizability anisotropy ($\Delta\alpha$), which can explain the numerical relationship of the Δn for the most molecules.[22] The $\Delta\alpha$, obtained from DFT calculations, of **21b**, **c** were 47.16 Å^3 for **21b** and 35.00 Å^3 for **21c**, whereas the values for ***trans*-8b**, **c** were 32.41 Å^3 for ***trans*-8b** and 23.75 Å^3 for ***trans*-8c**. The results from DFT calculations clearly indicate that the changing mesogenic structure to tetrafluorocyclohexane unit contributes to effective decrease of the polarizability anisotropy. Moreover, comparing the Δn as well as $\Delta\alpha$ values between ***trans*-8b** and ***trans*-8c**, the both values for ***trans*-8c** were obviously smaller than those for ***trans*-8b**. Judging from these results, as a consequence, introducing less polar structures in a mesogenic core caused a decrease of the $\Delta\alpha$, resulting in a drastic decrease of the birefringence.

Similarly, the computational studies can be a powerful tool to expect dielectric anisotropy ($\Delta\varepsilon$) as well, since the $\Delta\varepsilon$ strongly depends on the molecular dipole moment (μ).[22] The dipole moment in short molecular axis ($\mu_\perp$) obtained from DFT calculation led us to figure out that ***trans*-8b**, **c** possessed a larger molecular dipole $\mu_\perp$, rather than the $\mu_\perp$ for the corresponding **21b**, **c**.

Comparing the values of $\mu_{\perp}$, it can be easily estimated a larger dielectric anisotropy ($\Delta\varepsilon$) in the present ***trans*-8b**, **c** than the corresponding **21**. In fact, the reported $\Delta\varepsilon$ for **21b**, **c** were –6.2 and –7.3, respectively, whilst more negative $\Delta\varepsilon$ were obtained in ***trans*-8b**, **c** (***trans*-8b**: –7.9, ***trans*-8c**: –9.4). These results suggest that change of a partial structure in the mesogen, from 5,5,6,6-tetrafluorocyclohexa-1,3-diene to 1,1,2,2-cyclohexane structure, induced a drastic enhancement of $\mu_{\perp}$, resulting in a larger $\Delta\varepsilon$. Comparing the $\Delta\varepsilon$ between ***trans*-8b** and ***trans*-8c**, it is likely to be important structural design that existence of less polar cyclohexane moiety in order to exploit larger negative dielectric molecules. Finally, It can be concluded that the switching the mesogenic structure from previously reported tetrafluorinated cyclohexadiene to the present tetrafluorocyclohexane moiety would be effective modification to give rise to the prominent LC molecules with a low birefringence and a large negative dielectric anisotropy,[23] which would be promising materials to produce LC display devices equipped with both a wide-viewing angle and a fast response properties.

3. Conclusions

In conclusion, we successfully developed unprecedented fluorinated carbocycles thus far, i.e. 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives, starting from commercially available fluorinated substances. Especially, we realized the development of effective synthetic protocols for symmetrical disubstituted derivatives **7** as well as unsymmetrical ones **8**. It was successful that, at first time, a determination of relative structure of 3,6-disubstituted tetrafluorocyclohexane moiety by single X-ray crystallography: it became clear that the disubstituted cyclohexane with *trans*-configuration. Similarly, among unsymmetrical tetrafluorocyclohexane derivatives **8** developed in this study, tetrafluorocyclohexane derivatives **8b** and **8c** with both ethyl and aromatic substituents were resolved into a single configuration by recrystallization processes, which were identified as a *trans*-configuration by comparing with spectral data of purely *trans*-analogue.

It was notable that the unsymmetrical ***trans*-8b** and **8c** were found to exhibit a low birefringence and a large negative dielectric anisotropy, which were evaluated by using extrapolation technique for the binary mixture with a host material. Comparing to the physical properties of the similar structure reported before, it was made clear that the present tetrafluorocyclohexane moiety in a mesogenic structure contributed to the lower birefringence as well as the larger dielectric anisotropy. We believe that these results and understandings obtained in this study would offer a rational design of novel LC molecules with a low birefringence as well as a large negative dielectric anisotropy, and be attributable to development of high-performance VA-mode LC display materials.

4. Experimental

4.1. General information

Infrared spectra (IR) were taken on a JASCO FT/IR 4100 type A spectrometer as a film on a NaCl plate. ^{1}H NMR (500.13 MHz, 400.13 MHz, 399.65 MHz) and ^{13}C NMR (125.75 MHz, 100.62 MHz, 100.40 MHz) spectra were measured with a Bruker DRX-500 NMR spectrometer, a Bruker AVANCE III 400 NMR spectrometer, and a JEOL JNM-AL400 NMR spectrometer in a chloroform-*d* ($CDCl_3$) solution with a tetramethylsilane (Me_4Si) as an internal standard. A JEOL JNM-EX90A (84.21 MHz, FT) spectrometer and a JEOL JNM-AL400 NMR spectrometer were used for determining the yield of the fluorine-containing products with hexafluorobenzene (C_6F_6) as an internal reference. ^{19}F NMR (376.05 MHz) spectra were measured with a JEOL JNM-AL400 spectrometer in a $CDCl_3$ solution containing $CFCl_3$ ($\delta F = 0$) as an internal standard. High resolution mass spectra (HRMS) were taken on a JEOL JMS-700 mass spectrometer by electron impact (EI), chemical impact (CI) and fast atom bombardment (FAB) methods

4.2. Materials

All chemicals were of reagent grade, and if necessary, were purified in the usual manner prior to use. Anhydrous tetrahydrofuran (THF) was purchased from Wako chemicals. Thin layer chromatography (TLC) was done on aluminium sheets coated with Merck silica gel $60F_{254}$ plates, and column chromatography was carried out using Wako-gel C-200 as adsorbent. The 1,4-diaryl-2,2,3,3-tetrafluorobutan-1,4-dione, **13a-c** could be prepared from the corresponding trifluoromethyl aryl ketones **11a-c**, according to the literature.[10,11] The synthetic procedures for 1,4-disubstituted 5,5,6,6-tetrafluorocyclohexa-1,3-diene (**20**) from **9**, as shown in Scheme 4, were described in the previous report.[8]

*4.3. General procedure for the synthesis of α□β-unsaturated ester **14***

In a three-necked round-bottomed flask were placed sodium hydride (60% dispersion in oil) (0.26 g, 6.5 mmol) in THF (10 mL) under argon atmosphere, and triethyl phosphonoacetate (1.3 g, 6.0 mmol) was added dropwise to the solution at 0 °C. The resultant homogeneous solution was stirred at that temperature for 0.5 h, followed by the addition of diketone (1.5 mmol). After completion of the addition of diketone, the whole was warmed up to room temperature and continuously stirred for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and extracted with AcOEt three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated using rotary evaporator under reduced pressure. The resulting crude product was purified by silica-gel column chromatography (Hexane:AcOEt = 5:1) to obtain the corresponding α□β-unsaturated diester **14**.

*4.3.1. Diethyl (2E,6E)-4,4,5,5-tetrafluoro-3,6-diphenylocta-2,6-diene-1,8-dioate (**14a**).*

Mp. 87–89 °C; ^{1}H NMR ($CDCl_3$): δ 1.02 (6H, t, J = 7.2 Hz, CH_3), 4.00 (4H, q, J = 7.2 Hz, CH_2),

6.50 (2H, s, vinyl-H), 7.19 (4H, d, J = 7.2 Hz, *ortho*-H in aromatic ring), 7.32–7.40 (6H, m, *meta*- and *para*-H in aromatic ring); ^{13}C NMR ($CDCl_3$): δ 13.6, 60.8, 115.3 (tt, J = 36.3, 256.2 Hz), 127.1 (m), 127.7, 128.7, 129.1, 132.3, 143.6 (t, J = 22.3 Hz), 164.3; ^{19}F NMR ($CDCl_3$): δ –108.77 (4F, s, CF_2CF_2); IR (KBr): ν 2982, 1734, 1374, 1230, 1139, 1027, 706 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{24}H_{23}F_4O_4$: 451.1532, found 451.1526.

*4.3.2. Diethyl (2E,6E)-4,4,5,5-tetrafluoro-3,6-bis(4-methylphenyl)octa-2,6-diene-1,8-dioate (**14b**).*
Mp. 75–77 °C; ^{1}H NMR ($CDCl_3$): δ 1.03 (6H, t, J = 6.8 Hz, CH_3), 2.33 (6H, s, CH_3), 3.99 (4H, q, J = 6.8 Hz, CH_2), 6.46 (2H, s, vinyl-H), 7.07 (4H, d, J = 8.0 Hz, Ar-H), 7.13 (4H, d, J = 8.0 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 13.6, 21.1, 60.6, 115.6 (tt, J = 35.5, 254.5 Hz), 126.8 (m), 128.3, 128.9, 129.3, 138.5, 143.8 (t, J = 22.2 Hz), 164.2; ^{19}F NMR ($CDCl_3$): δ –108.88 (4F, s, CF_2CF_2); IR (KBr): ν 2987, 1711, 1369, 1206, 1146, 1041, 905 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{26}H_{27}F_4O_4$: 479.1845, found 479.1851.

*4.3.3. Diethyl (2E,6E)-4,4,5,5-tetrafluoro-3,6-bis(4-n-propylphenyl)-octa-2,6-diene-1,8-dioate (**14c**).*
Mp. 61–63 °C; ^{1}H NMR ($CDCl_3$): δ 0.95 (6H, t, J = 7.2 Hz, CH_3), 1.00 (6H, t, J = 7.0 Hz, CH_3), 1.64 (4H, sext, J = 7.2 Hz, $CH_2CH_2CH_3$), 2.59 (4H, t, J = 7.2 Hz, CH_2), 3.98 (4H, q, J = 7.0 Hz, CH_2), 6.45 (2H, s, vinyl-H), 7.07 (4H, d, J = 7.6 Hz, Ar-H), 7.14 (4H, d, J = 7.6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 13.6, 13.8, 24.3, 37.8, 60.7, 115.3 (tt, J = 37.2, 255.4 Hz), 126.8 (m), 127.8, 129.0, 129.6, 143.3, 143.7 (t, J = 24.0 Hz), 164.5; ^{19}F NMR ($CDCl_3$): δ –108.91 (4F, s, CF_2CF_2); IR (KBr): ν 2982, 1734, 11374, 1230, 1139, 1027, 706 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{30}H_{35}F_4O_4$: 535.2471, found 535.2469.

*4.4. General procedure for synthesis of allylic alcohol **15***
To a solution of α□β-unsaturated diester (0.40 mmol) in CH_2Cl_2 (5.0 mL) was added slowly diisobutylaluminium hydride (DIBAL-H, 1.0 M in hexane, 2.4 mL, 2.4 mmol) at 0 °C. After being stirred for 3 h, the reaction was quenched with saturated aqueous NH_4Cl solution (20 mL), and the whole was extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue was purified by silica-gel column chromatography (Hexane:AcOEt = 1:1) to give the corresponding allylic alcohol **15**.

*4.4.1. (2E,6E)-4,4,5,5-Tetrafluoro-3,6-diphenylocta-2,6-diene-1,8-diol (**15a**).*
Mp. 148–150 °C; ^{1}H NMR (Acetone-d_6): δ 3.90–4.05 (6H, m, CH_2OH), 6.41 (2H, t, J = 6.0 Hz, vinylic-H), 7.05–7.15 (4H, m, Ar-H), 7.30–7.38 (6H, m, Ar-H); ^{13}C NMR (Acetone-d_6): δ 59.4, 116.9 (tt, J = 36.5, 253.8 Hz), 128.7, 128.9, 130.8, 132.3 (t, J = 30 Hz), 134.0, 139.9; ^{19}F NMR ($CDCl_3$): δ –107.67 (4F, s, CF_2CF_2); IR (KBr): ν 3290, 2940, 1138, 1082, 1016, 709 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{20}H_{19}F_4O_2$: 367.1321, found 367.1325.

*4.4.2. (2E,6E)-4,4,5,5-Tetrafluoro-3,6-bis(4-methylphenyl)octa-2,6-diene-1,8-diol (**15b**).*
Mp. 127–129 °C; ^{1}H NMR ($CDCl_3$): δ 2.29 (6H, s, CH_3), 4.01 (4H, br s, CH_2OH), 4.20–4.40 (2H, m, OH), 6.35–6.45 (2H, m, vinylic-H), 6.95–7.10 (4H, m, Ar-H), 7.15–7.20 (4H, m, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.2, 59.6, 115.9 (tt, *J* = 35.5, 291.0 Hz), 128.7, 129.7, 129.9, 133.4 (t, *J* = 24.7 Hz), 136.6 (m), 138.1; ^{19}F NMR ($CDCl_3$): δ –107.83 (4F, s, CF_2CF_2); IR (KBr): ν 3348, 2920, 1430, 1138, 1088, 1040, 968 cm^{-1}; HRMS: calcd for $[M+Na]^+$ $C_{22}H_{22}F_4NaO_2$: 417.1454, found 417.1462.

*4.4.3. (2E,6E)-4,4,5,5-Tetrafluoro-3,6-bis(4-n-propylphenyl)-octa-2,6-diene-1,8-diol (**15c**).*
^{1}H NMR ($CDCl_3$): δ 0.96 (6H, t, *J* = 7.6 Hz, CH_3), 1.65 (4H, sext., *J* = 7.6 Hz, CH_2), 2.34 (2H, s, OH), 2.59 (4H, t, *J* = 7.6 Hz, CH_2), 4.02 (4H, br d, *J* = 6.4 Hz, CH_2OH), 6.37 (2H, t, *J* = 6.4 Hz, vinylic-H), 7.01 (4H, d, *J* = 8.4 Hz, Ar-H), 7.13 (4H, d, *J* = 8.4 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 13.9, 24.4, 37.8, 59.5, 116.3 (tt, *J* = 36.3, 255.4 Hz), 128.1, 129.8, 130.2, 133.4 (t, *J* = 23.1 Hz), 136.8 (m), 142.8; ^{19}F NMR ($CDCl_3$): δ –108.67 (4F, s, CF_2CF_2); IR (neat): ν 3347, 2960, 2872, 1457, 1219, 1081, 1021, 977 cm^{-1}; HRMS: calcd for $[M+Na]^+$ $C_{26}H_{30}F_4NaO_2$: 473.2080, found 473.2084.

*4.5. General procedure for synthesis of allylic dicarbonate **16***
The allylic alcohol (0.23 mmol) in CH_2Cl_2 (5.0 mL) was placed in a three-necked round-bottomed flask with stirrer bar under an argon atmosphere. To the solution was added ethyl chloroformate (1.15 mmol) at 0 °C, followed by adding pyridine (0.08 mL, 0.99 mmol). The reaction mixture was allowed to warm up to room temperature and stirred overnight. The resultant solution was quenched with saturated aqueous NH_4Cl solution, and separated the organic layer. The aqueous solution was washed with AcOEt twice and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated using rotary evaporator. The resulting mixture was purified by silica-gel column chromatography (Hexane:AcOEt = 1:1) to obtain the corresponding allylic dicarbonate **16**.

*4.5.1. Diethyl (2E,6E)-4,4,5,5-tetrafluoro-3,6-diphenylocta-2,6-diene-1,8-diyl dicarbonate (**16a**).*
Mp. 56–58 °C; ^{1}H NMR ($CDCl_3$): δ 1.29 (6H, t, *J* = 7.2 Hz, CH_2CH_3), 4.17 (4H, q, *J* = 7.2 Hz, CH_2CH_3), 4.50 (4H, d, *J* = 6.4 Hz, CH_2O), 6.36 (2H, t, *J* = 6.4 Hz, vinylic-H), 7.11–7.36 (10H, m, Ar-H); ^{13}C NMR ($CDCl_3$): δ 14.0, 63.9, 64.0, 115.3 (tt, *J* = 37.3, 254.6 Hz), 128.0, 128.4, 129.6, 131.8 (m), 132.1, 135.2 (t, *J* = 23.2 Hz), 154.6; ^{19}F NMR ($CDCl_3$): δ –108.72 (4F, s, CF_2CF_2); IR (KBr): ν 2987, 1748, 1252, 1139, 1092, 988, 791 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{26}H_{27}F_4O_6$: 511.1744, found 511.1735.

*4.5.2. Diethyl (2E,6E)-4,4,5,5-tetrafluoro-3,6-bis(4-methylphenyl)octa-2,6-diene-1,8-diyl dicarbonate (**16b**).*

^{1}H NMR ($CDCl_3$): δ 1.29 (6H, t, *J* = 6.8 Hz, CH_2CH_3), 2.35 (6H, s, CH_3), 4.17 (4H, q, *J* = 6.8 Hz, CH_2CH_3), 4.51 (4H, d, *J* = 6.2 Hz, CH_2O), 6.32 (2H, t, *J* = 6.2 Hz, vinylic-H), 7.00 (4H, d, *J* = 8.4 Hz, Ar-H), 7.14 (4H, d, *J* = 8.4 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 13.8, 20.8, 59.9, 63.8, 115.3 (tt, *J* = 37.2, 255.4 Hz), 128.6, 129.1, 129.4, 131.4 (m), 135.2 (t, *J* = 23.9 HZ), 138.1, 154.5; ^{19}F NMR ($CDCl_3$): δ –108.79 (4F, s, CF_2CF_2); IR (neat): ν 2984, 1613, 1446, 1345, 1140, 1094, 873 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{28}H_{31}F_4O_6$: 539.2057, found: 539.2058.

*4.5.3. Diethyl (2E,6E)-4,4,5,5-tetrafluoro-3,6-bis(4-n-propylphenyl)-octa-2,6-diene-1,8-diyl dicarbonate (**16c**).*

^{1}H NMR ($CDCl_3$): δ 1.03 (6H, t, *J* = 7.6 Hz, CH_2CH_3), 1.35 (6H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.73 (4H, sext., *J* = 7.6 Hz, $CH_2CH_2CH_3$), 2.67 (4H, t, *J* = 7.6 Hz, $CH_2CH_2CH_3$), 4.24 (4H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.61 (4H, d, *J* = 6.4 Hz, CH_2O), 6.44 (2H, t, *J* = 6.4 Hz, vinylic-H), 7.10 (4H, d, *J* = 8.0 Hz, Ar-H), 7.23 (4H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 13.6, 14.0, 24.1, 37.6, 64.00, 64.04, 115.4 (tt, *J* = 36.3, 254.5 Hz), 128.1, 129.4, 129.5, 131.6 (m), 135.4 (t, *J* = 24.0 Hz), 143.0, 154.7; ^{19}F NMR ($CDCl_3$): δ –108.91 (4F, s, CF_2CF_2); IR (neat): ν 2961, 1748, 1370, 1139, 1037, 1000, 791 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{32}H_{39}F_4O_6$: 595.2683, found: 595.2692.

4.6. General procedure for Pd(0)-catalyzed formate reduction

To a DMF solution of Pd(0) catalyst, prepared in *situ* by mixing $Pd_2(dba)_3{\cdot}CHCl_3$ (12 mg, 0.012 mmol) and PPh_3 (24 mg, 0.092 mmol), was added dicarbonate (0.23 mmol) at room temperature. After stirring of reaction mixture for 10 min at that temperature, a DMF solution of triethylammonium formate, prepared from formic acid (0.021 mL, 0.55 mmol) and triethylamine (0.090 mL, 0.64 mmol), was added to the reaction mixture, and the resultant was stirred at 80 °C for 2 h. The resultant solution was quenched with saturated aqueous NH_4Cl solution, and the whole was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated in *vacuo*. The residual crude product was purified by silica-gel column chromatography (Hexane:AcOEt = 10:1) to give the 4,4,5,5-tetrafluoroocta-1,7-diene **17** as a mixture of regioisomers.

*4.6.1. 4,4,5,5-Tetrafluoro-3,6-diphenylocta-1,7-diene (**17a**).*

Diastereomeric ratio **17a**:other isomers = 61:39; HRMS: calcd for $[M^+]$ $C_{20}H_{18}F_4$: 334.1345, found: 334.1353; [Terminal diene **17a**] ^{1}H NMR ($CDCl_3$): δ 3.90–4.10 (2H, m, allylic-H), 5.08–5.30 (4H, m, $CH=CH_2$), 6.13–6.25 (2H, m, $CH=CH_2$), 7.17–7.37 (10H, m, Ar-H); ^{19}F NMR ($CDCl_3$): δ –112.87 to –110.62 (4F, m, CF_2CF_2); [Internal diene **18a**] ^{1}H NMR ($CDCl_3$): δ 1.25 (6H, s, CH_3), 6.30–6.45 (2H, m, vinylic-H); ^{19}F NMR ($CDCl_3$): δ –112.87 to –110.17 (4F, m, CF_2CF_2).

*4.6.2. 4,4,5,5-Tetrafluoro-3,6-bis(4-methylphenyl)octa-1,7-diene (**17b**).*

Diastereomeric ratio **17b**:other isomers = 62:38; [Terminal diene **17b**] ^{1}H NMR ($CDCl_3$): δ 2.30–

2.36 (6H, m, CH_3), 3.90–4.05 (2H, m, allylic-H), 5.07–5.25 (4H, m, $CH=CH_2$), 6.16 (2H, dt, J = 16.8, 8.4 Hz, $CH=CH_2$), 7.06–7.25 (8H, m, Ar-H); ^{19}F NMR ($CDCl_3$): δ –113.03 to –110.18 (4F, m); [Internal diene **18b**] ^1H NMR ($CDCl_3$): δ 1.26–1.59 (6H, m, CH_3), 2.36 (6H, s, CH_3), 6.28–6.40 (2H, m, vinylic-H); ^{19}F NMR ($CDCl_3$): δ –113.03 to –110.18 (4F, m, CF_2CF_2).

*4.6.3. 4,4,5,5-Tetrafluoro-3,6-bis(4-n-propylphenyl)octa-1,7-diene (**17c**).*

Diastereomeric ratio **17c**:other isomers = 64:36; HRMS: calcd for [M^+] $C_{26}H_{30}F_4$: 418.2284, found: 418.2283; [Terminal diene **17c**] ^1H NMR ($CDCl_3$): δ 0.89–0.98 (6H, m, CH_3), 1.53–1.69 (4H, m, CH_2), 2.54–2.61 (4H, m, CH_2), 3.88–4.10 (2H, m, allylic-H), 5.06–5.24 (4H, m, $CH=CH_2$), 6.13–6.36 (2H, m, $CH=CH_2$), 7.08–7.18 (8H, m, Ar-H); ^{19}F NMR ($CDCl_3$): δ –113.24 to –110.03 (4F, m, CF_2CF_2); [Internal diene **18c**] ^1H NMR ($CDCl_3$): δ 6.30–6.40 (2H, m, vinylic-H), ^{19}F NMR ($CDCl_3$): δ –114.24 to –109.68 (4F, m, CF_2CF_2).

*4.7. General procedure for ring-closing metathesis of diene **17***

To a solution of Grubbs 2nd generation catalyst (10 mg, 5 mol%, 0.011 mmol) in CH_2Cl_2 (5.0 mL) was added the diene **17** (0.23 mmol) at room temperature. The reaction mixture was stirred at room temperature for 5 days, then the solution was pass through silica-gel to give the crude solution. The solution was evaporated using rotary evaporator under high vacuum to afford the crude residue, which was purified by silica-gel column chromatography (Hexane:Benzene = 20:1) to yield the cyclic compound as a mixture of diastereoisomers.

*4.7.1. 4,4,5,5-Tetrafluoro-3,6-diphenylcyclohex-1-ene (**19a**).*

Diastereomeric ratio *cis*/*trans* = 56/44; HRMS: calcd for [M^+] $C_{18}H_{14}F_4$: 306.1032, found: 306.1026; [*cis* isomer] ^1H NMR ($CDCl_3$): δ 4.19–4.26 (2H, m, allylic-H), 5.99 (2H, brs, CH=CH), 7.28–7.43 (10H, m, Ar-H); ^{19}F NMR ($CDCl_3$): δ –123.76 to –123.06 (2F, m, CF_2), –115.59 to –114.87 (2F, m, CF_2); [*trans* isomer] ^1H NMR ($CDCl_3$): δ 5.89–5.91 (2H, m, CH=CH); ^{19}F NMR ($CDCl_3$); δ –128.19 to –127.45 (2F, m, CF_2), –124.26 to –123.41 (2F, m, CF_2).

*4.7.2. 4,4,5,5-Tetrafluoro-3,6-bis(4-methylphenyl)cyclohex-1-ene (**19b**).*

Diastereomeric ratio *cis*/*trans* = 51/49; [*cis* isomer] ^1H NMR ($CDCl_3$): δ 2.37 (6H, s, CH_3), 4.10–4.25 (2H, m, allylic-H), 5.95 (2H, brs, CH=CH), 7.10–7.30 (8H, m, Ar-H); ^{19}F NMR ($CDCl_3$): δ –123.70 to –123.03 (2F, m, CF_2), –115.56 to –114.85 (2F, m, CF_2); (The *trans* isomer could be obtained in a pure form after recrystallization.) [*trans* isomer] Mp. 163–165 °C; ^1H NMR ($CDCl_3$): δ 2.39 (6H, s, CH_3), 4.10–4.25 (2H, m, allylic-H), 5.82–5.88 (2H, m, CH=CH), 7.23 (8H, s, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.1, 47.3–48.0 (m), 115.6 (dddd, J = 245.5, 244.7, 37.2, 21.5 Hz), 127.7 (m), 129.2, 129.9, 130.2, 138.1; ^{19}F NMR ($CDCl_3$): δ –128.13 to –127.40 (2F, m, CF_2), –124.29 to –123.44 (2F, m, CF_2); IR (KBr): ν 1298, 1206, 1122, 1075, 861 cm^{-1}; HRMS: calcd for [M^+] $C_{20}H_{18}F_4$: 334.1345, found: 334.1337.

*4.7.3. 4,4,5,5-Tetrafluoro-3,6-bis(4-n-propylphenyl)cyclohex-1-ene (**19c**).*

Diastereomeric ratio *cis*/*trans* = 52/48; IR (neat): ν 3027, 2960, 2931, 2871, 1513, 1465, 1421, 1297, 1191, 1118, 1099 cm^{-1}; HRMS: calcd for $[M–H]^+$ $C_{24}H_{25}F_4$: 389.1892, found: 389.1902; [*cis* isomer] ^1H NMR ($CDCl_3$): δ 0.99 (6H, t, *J* = 7.34 Hz, CH_3), 1.60–1.75 (4H, m, $CH_2CH_2CH_3$), 2.60–2.68 (4H, m, $CH_2CH_2CH_3$), 4.15–4.30 (2H, m, allylic-H), 5.98 (2H, brs, CH=CH), 7.20–7.35 (8H, m, Ar-H); ^{19}F NMR ($CDCl_3$): δ –123.71 to –123.04 (2F, m, CF_2), –115.59 to –114.89 (2F, m, CF_2); [*trans* isomer] ^1H NMR ($CDCl_3$): δ 1.00 (6H, t, *J* = 7.42 Hz, CH_3), 5.85–5.95 (2H, m, CH=CH); ^{19}F NMR ($CDCl_3$): δ –128.11 to –127.44 (2F, m, CF_2), –124.30 to –123.54 (2F, m, CF_2).

*4.8. General procedure for preparation of cyclohexane **7***

To a suspension of Pd/C (24 mg) in MeOH (6.0 mL) was added the cyclohexene (**19**, 0.14 mmol) in AcOEt (1.0 mL) at room temperature. Then, the argon in the flask was replaced into gaseous hydrogen, and the whole was stirred at that temperature during overnight. The mixture was filtered, and thus obtained filtrate was concentrated in *vacuo*. The residue was purified by silica-gel column chromatography (Hexane:Benzene = 1:1) to afford the cyclohexane as a mixture of diastereomers.

*4.8.1. 2,2,3,3-Tetrafluoro-1,4-diphenylcyclohexane (**7a**).*

Diastereomeric ratio *cis*/*trans* = 56/44; IR (neat): ν 3096, 3065, 3034, 2964, 2878, 1602, 1584, 1498, 1456, 1262, 1228, 1168, 1103, 1082 cm^{-1}; HRMS: calcd for $[M^+]$ $C_{18}H_{16}F_4$: 308.1188, found: 308.1198; ^1H NMR ($CDCl_3$): δ 2.05–2.08 (1H, m, axial/equatorial-CH), 2.11–2.22 (2H, m, CH_2), 2.47–2.51 (1H, m, axial/equatorial-CH), 3.35–3.37 (1H, m, $CHCF_2$), 3.59–3.63 (1H, m, $CHCF_2$), 7.32–7.44 (10H, m, Ar-H); [*cis* isomer] ^{19}F NMR ($CDCl_3$): δ –113.16 (2F, d, *J* = 258.7 Hz, CF_2), –122.38 (2F, ddd, *J* = 17.7, 17.1, 258.7 Hz, CF_2); [*trans* isomer] ^{19}F NMR ($CDCl_3$): δ –125.08 to –124.92 (4F, m, CF_2CF_2).

*4.8.2. 2,2,3,3-Tetrafluoro-1,4-bis(4-methylphenyl)cyclohexane (**7b**).*

Diastereomeric ratio *cis*/*trans* = 51/49; The *trans* isomer could be obtained in a pure form after recrystallization. [*trans* isomer] Mp. 85–87 °C; ^1H NMR ($CDCl_3$): δ 1.95–1.98 (2H, m, CH_2), 2.03–2.12 (2H, m, CH_2), 2.34 (6H, brs, CH_3), 3.20–3.35 (2H, m, $CHCF_2$), 7.17 (4H, d, *J* = 8.39 Hz, Ar-H), 7.24 (4H, d, *J* = 8.39 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.0, 27.6, 46.3–46.9 (m), 116.9 (tt, *J* = 25.6, 256.2 Hz), 129.1, 131.8, 137.7, One carbon in the aromatic ring could not be detected by overlapping with other signals; ^{19}F NMR ($CDCl_3$): δ –125.11 to –125.06 (4F, m, CF_2CF_2); IR (KBr): ν 2920, 1516, 1284, 1214, 1104, 1072, 1014, 905, 811 cm^{-1}; HRMS: calcd for $[M^+]$ $C_{20}H_{20}F_4$: 336.1501, found: 336.1508.

*4.8.3. 2,2,3,3-Tetrafluoro-1,4-bis(4-n-propylphenyl)cyclohexane (**7c**).*

Diastereomeric ratio *cis*/*trans* = 52/48; The *trans* isomer could be obtained in a pure form after

recrystallization. [*trans* isomer] Mp. 112–114 °C; ^{1}H NMR ($CDCl_3$): δ 0.96 (6H, t, J = 7.40 Hz, CH_3), 1.66 (4H, sext., J = 7.40 Hz, $CH_2CH_2CH_3$), 2.00–2.10 (2H, brs, axial/equatorial-CH), 2.10–2.20 (2H, m, axial/equatorial-CH), 2.55–2.65 (4H, m, $CH_2CH_2CH_3$), 3.20–3.40 (2H, brs, $CHCF_2$), 7.11 (4H, d, J = 6.8 Hz, Ar-H), 7.20 (4H, d, J = 6.8 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 14.0, 24.6, 27.8, 37.8, 46.6–47.3 (m), 117.2 (tt, J = 27.6, 256.0 Hz), 128.7, 129.3, 132.2, 142.6; ^{19}F NMR ($CDCl_3$): δ –125.03 to –125.09 (4F, m, CF_2CF_2); IR (KBr): 1655, 1542, 1076, 817 cm^{-1}; HRMS: calcd for [M^+] $C_{24}H_{28}F_4$: 392.2127, found: 392.2133.

*4.9. Typical procedure for the synthesis of cyclohexane **8a** in a catalytic hydrogenation protocol*

To a suspension of Pd/C (28 mg) in MeOH (10 mL) was added a pale yellow solid of diene[8] (**21a**, 0.10 g, 0.27 mmol) at room temperature. Then, the argon in the flask was replaced into gaseous hydrogen, and the whole was stirred at that temperature during overnight. The mixture was filtered through silica-gel, and thus obtained filtrate was concentrated in *vacuo*. The resultant colorless oil was purified by silica-gel column chromatography (Hexane:Benzene = 3:1) to give the corresponding cyclohexane **8a** (88 mg, 0.23 mmol) in 85% isolated yield as a colorless oil.

*4.9.1. 1-(4-Ethylphenyl)-2,2,3,3-tetrafluoro-4-(4-n-propylphenyl)cyclohexane (**8a**).*

Diastereomeric ratio: *cis*/*trans* = 60/40; IR (neat): ν 2963, 2932, 1516, 1177, 1108, 1077, 1012, 907 cm^{-1}; HRMS: calcd for [M^+] $C_{23}H_{26}F_4$: 378.1971, found: 378.1973; [*cis* isomer]: ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, t, J = 7.6 Hz, CH_3), 1.17 (3H, t, J = 7.6 Hz, CH_3), 1.54–1.58 (2H, m, CH_2), 1.94–2.01 (3H, m, CH_2 and CH), 2.30–2.42 (2H, m, CH_2), 2.49–2.60 (4H, m, CH_2 and CH_2), 3.46–3.55 (1H, m, CH), 7.07–7.29 (8H, m, Ar-H); ^{19}F NMR ($CDCl_3$): δ –122.77 to –121.99 (2F, m, CF_2), –113.17 (2F, d, ^{1}J = 248.6 Hz, CF_2); [*trans* isomer] ^{1}H NMR ($CDCl_3$): δ 0.89 (3H, t, J = 7.2 Hz, CH_3), 1.18 (3H, t, J = 7.2 Hz, CH_3), 3.22–3.24 (1H, m, CH), other signals cannot be assigned due to an extremely complicated spectrum; ^{19}F NMR ($CDCl_3$): δ –125.07 to –125.02 (4F, m, CF_2 and CF_2).

*4.10. Typical procedure for the synthesis of trans-cyclohexane **trans-8b** using a Barton-McCombie radical reduction*

Cyclohexan-1,4-diol[8] (0.16 g, 0.38 mmol) was added into a reaction flask placed sodium hydride (60% dispersion in oil, 0.15 g, 3.8 mmol), and the mixture was stirred at room temperature for 0.5 h. Then, CS_2 (0.23 mL, 3.8 mmol) was added to the reaction mixture and stirred at room temperature for 2 h. To the resultant solution was added a solution of MeI (0.23 mL, 3.8 mmol) in CH_2Cl_2 (5.0 mL) and the whole was stirred another 2 h. The reaction mixture was quenched with water and extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was dissolved in CH_2Cl_2 (2.4 mL) and *n*Bu_3SnH (0.40 mL, 1.5 mmol) was added into a flask at room temperature. After stirring at that temperature for 24 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4

and concentrated in *vacuo*. The resultant was purified by silica gel column chromatography (eluent: Hexane:AcOEt = 20:1) to obtain the corresponding cyclohexane **8b** as a mixture of diastereomers. The mixture was purified by recrystallization from MeOH/Et_2O three times to afford the *trans* isomer (38 mg, 99 □mol) in 25% isolated yield (*cis*/*trans* = 0/100).

*4.10.1. trans-1-Ethyl-2,2,3,3-tetrafluoro-4-[4-(trans-4-n-propylphenyl)phenyl]cyclohexane (**trans-8b**).*

Mp. 117–118 °C; ^{1}H NMR ($CDCl_3$): δ 1.01 (3H, t, *J* = 7.2 Hz, CH_3), 1.07 (3H, t, *J* = 7.6 Hz, CH_3), 1.38–1.48 (2H, m, CH_2), 1.72 (2H, sext., *J* = 7.6 Hz, CH_2), 1.77–1.90 (5H, m, CH and CH_2), 2.67 (2H, t, *J* = 7.6 Hz, CH_2), 3.20–3.31 (1H, m, CH), 7.29 (2H, d, *J* = 7.6 Hz, Ar-H), 7.41 (2H, d, *J* = 8.4 Hz, Ar-H), 7.54 (2H, d, *J* = 7.6 Hz, Ar-H), 7.60 (2H, d, *J* = 8.4 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 11.6, 13.9, 19.5, 24.5, 25.9 (d, *J* = 6.6 Hz), 27.5–27.6 (m, 1C for CH or CH_2 on cyclohexane), 37.7, 42.6 (t, *J* = 20.3 Hz), 46.7 (dt, *J* = 20.7, 1.9 Hz), 114.4–121.1 (m, 2C for CF_2CF_2), 126.88, 126.91, 128.9, 130.0, 133.7, 138.0, 140.8, 142.0; ^{19}F NMR ($CDCl_3$): δ –128.85 to –128.14 (1F, m, CF), –127.49 (1F, dd, *J* = 253.8, 24.3 Hz, CF), –125.68 to –125.60 (2F, m, CF_2); IR (KBr): ν 2975, 2935, 2875, 1497, 1283, 1184, 1143, 1119, 1011, 996 cm^{-1}; HRMS: calcd for [M^+] $C_{23}H_{26}F_4$: 378.1971, found: 378.1968.

*4.10.2. trans-1-Ethyl-2,2,3,3-tetrafluoro-4-[4-(trans-4-n-propylcyclohex-1-yl)phenyl]cyclohexane (**trans-8c**).* Mp. 95–96 °C; ^{1}H NMR ($CDCl_3$): δ 0.91 (3H, t, *J* = 7.4 Hz, CH_3), 1.03 (3H, t, *J* = 7.6 Hz, CH_3), 1.00–1.10 (2H, m, CH_2), 1.15–1.50 (9H, m, CH and CH_2 on cyclohexane), 1.80–2.10 (9H, m, CH and CH_2 on cyclohexane), 2.47 (1H, tt, *J* = 11.6, 3.4 Hz, CH), 3.10–3.25 (1H, m, CH), 7.19 (2H, d, *J* = 8.0 Hz, Ar-H), 7.24 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 12.0, 14.8, 19.8, 20.4, 26.3 (d, *J* = 7.4 Hz), 27.9, 33.9, 34.6, 37.4, 40.1, 43.0 (t, *J* = 20.3 Hz), 44.6, 47.0 (t, *J* = 19.8 Hz), 114.5–121.5 (m, 2C for CF_2CF_2), 127.2, 129.5, 132.7, 147.9; ^{19}F NMR ($CDCl_3$): δ –128.54 (1F, d, *J* = 251.6 Hz, CF), –127.55 (1F, dd, *J* = 251.6. 24.4 Hz, CF), –126.50 to –125.10 (2F, m, CF_2); IR (KBr): ν 2924, 2846, 1459, 1114, 826 cm^{-1}; HRMS: calcd for [M^+] $C_{23}H_{32}F_4$: 384.2440, found: 384.2445.

4.11. X-Ray crystallographic analysis

X-Ray analysis crystal data $C_{20}H_{20}F_4$, M=336.37, *a*=15.847(20) Å, □=31.72(5) Å, *c*=10.528(7) Å, *α*=90°, *β*=97.14(8)°, *γ*=90°, V=5250(11) Å^3, ρ_{calcd}=1.276 g/cm^3, *Z*=12. Intensities of 12481 reflections (R_{int}=0.058) were measured at 298.1 K with a Rigaku AFC7R using graphite monochromated Mo Kα radiation (λ=0.71069 Å, *θ*/2*θ* scan, *θ*≤30°). The structure was solved by direct method and refined by full matrix least squares against F2 in the anisotropic (H-atoms isotropic) approximation. All hydrogen atoms were located from the electron density difference synthesis and were included in the refinement in isotropic approximation. The refinement converged to wR_2=0.2294 and GOF=1.002 for 12485 independent reflections (R_1=0.0717, *I*>2σ(*I*)).

The number of refined parameters was 710. All calculations were performed using the CrystalStructure 3.8. Crystallographic data for this compound has been deposited with the Cambridge Crystallographic Data Centre, whose CCDC no. CCDC 1483305. Copy of the data can be obtained free of charge by applying to CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK (https://summary.ccdc.cam.ac.uk/structure-summary-form; email: deposit@ccdc.cam.ac.uk.

4.12. Computational studies

All calculations were carried out using the Gaussian09 program[19] package and density functional theory (DFT) method. We used the standard basis set, 6-311+G(d,p) levels of theory for the geometry optimizations.

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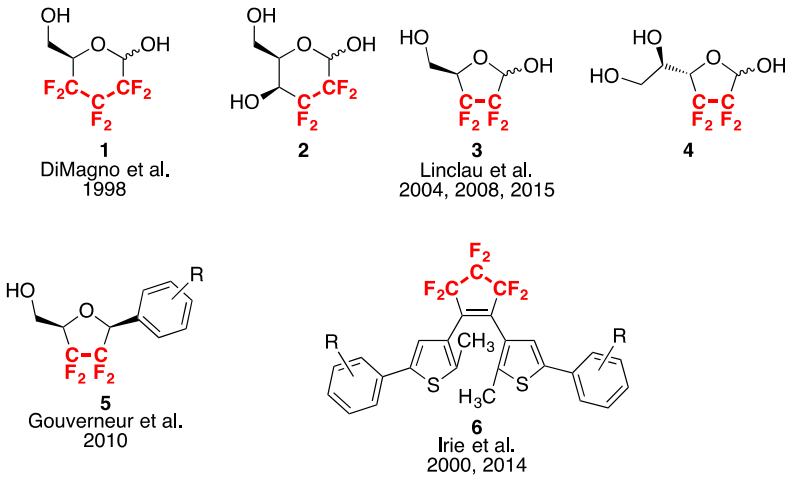


Fig. 1. Various semi-fluorinated cyclic materials

(a)

(b)

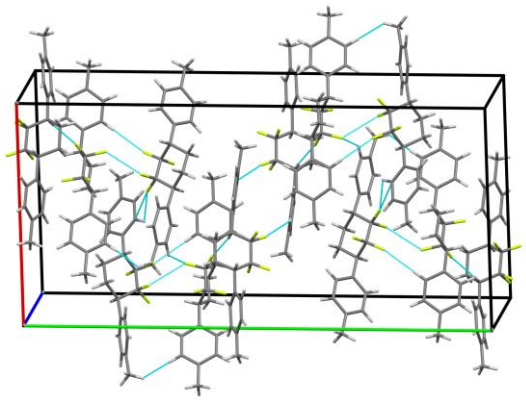


Fig. 2 (a) Crystal structure and (b) Packing structure of *trans*-**7b**. Color legend: C, gray; H, light gray; F, light green. Light blue line: short contact below the sum of van der Waals radii.

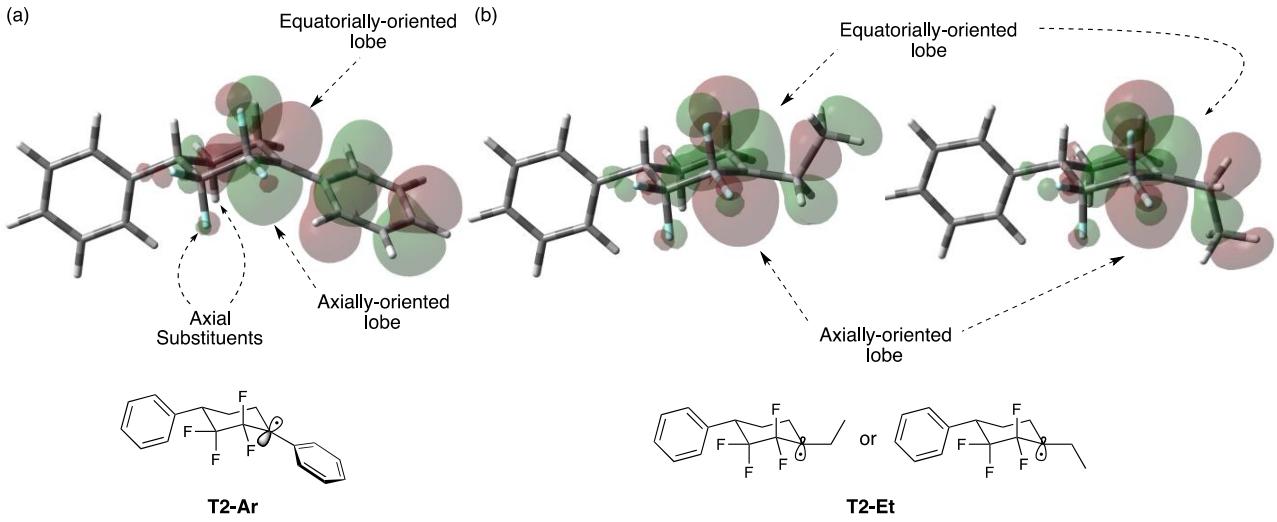
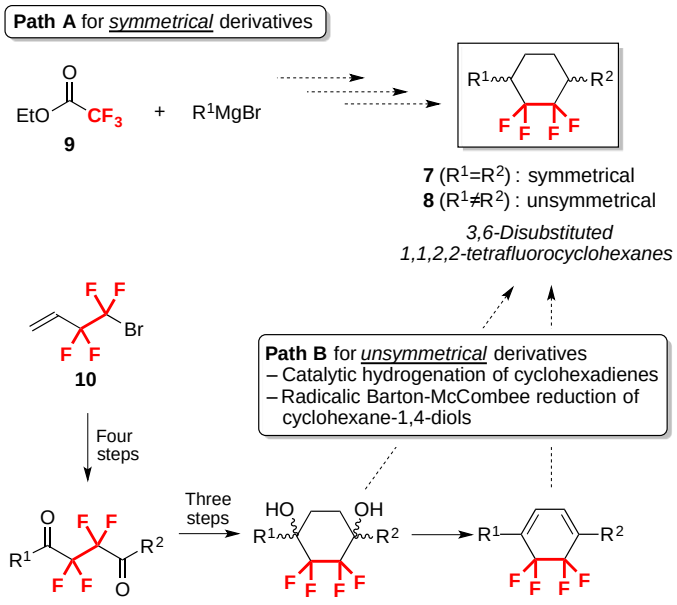
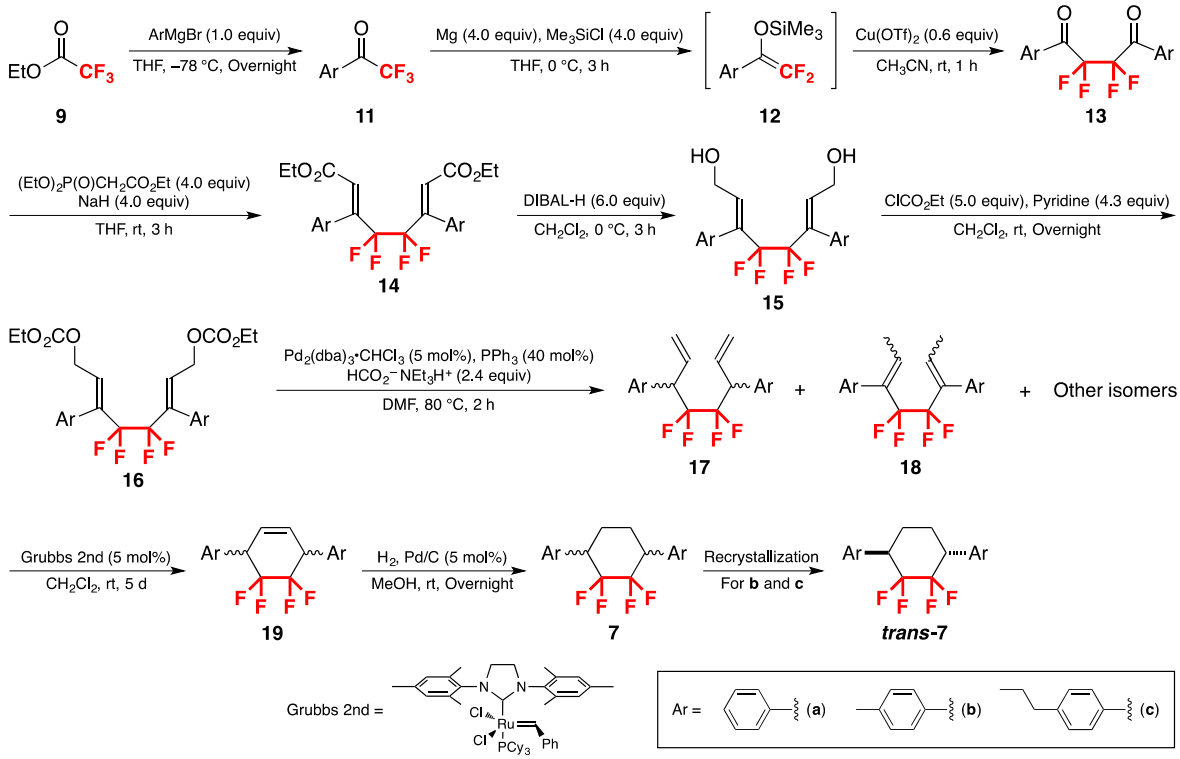


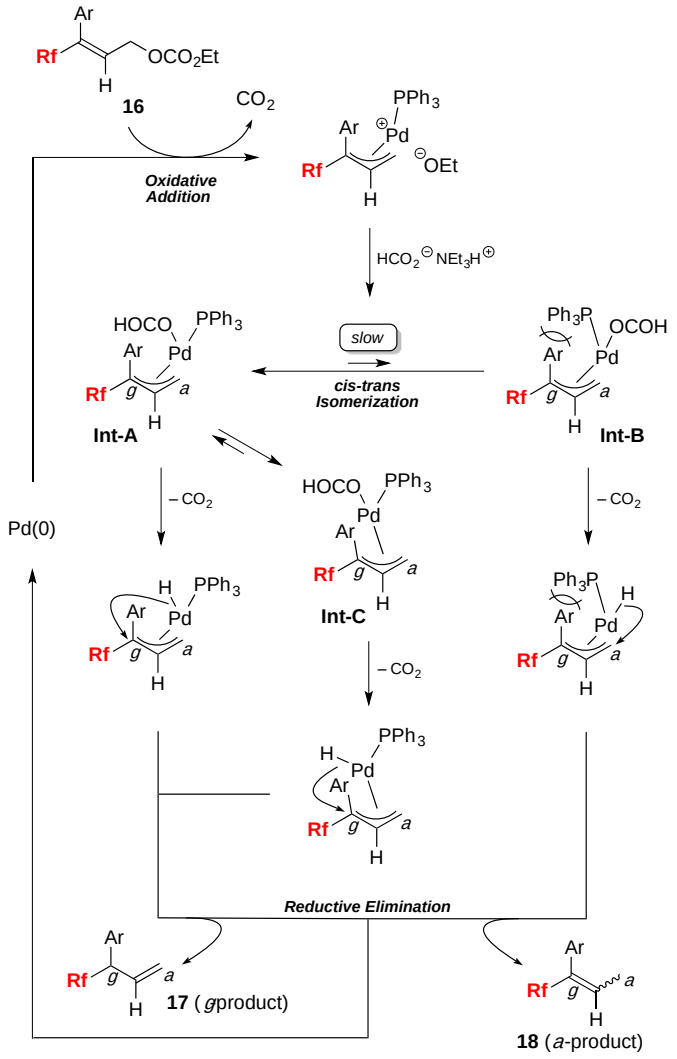
Fig. 3. SOMOs of 3,6-diphenyl-1,1,2,2-tetrafluorocyclohexyl and 3-ethyl-6-phenyl-1,1,2,2-tetrafluorocyclohexyl radicals



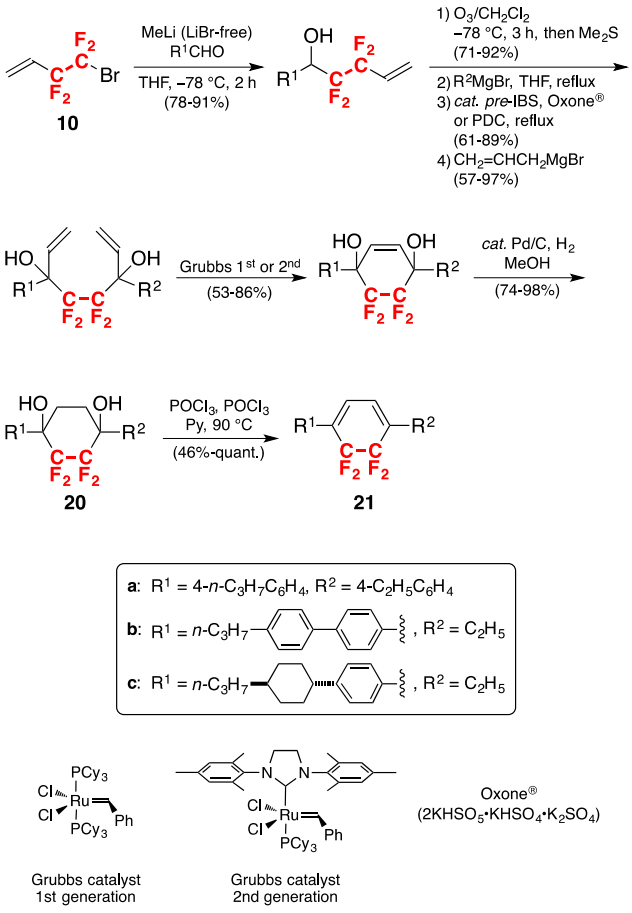
Scheme 1. Synthetic approaches to unprecedented 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives



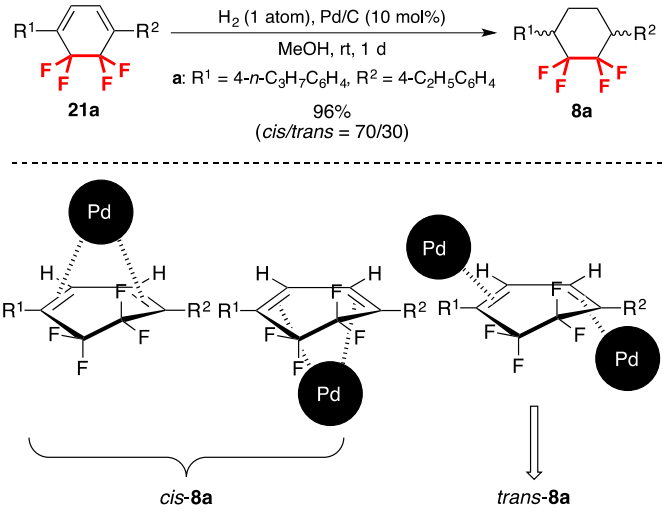
Scheme 2. Synthetic route to symmetrical 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives



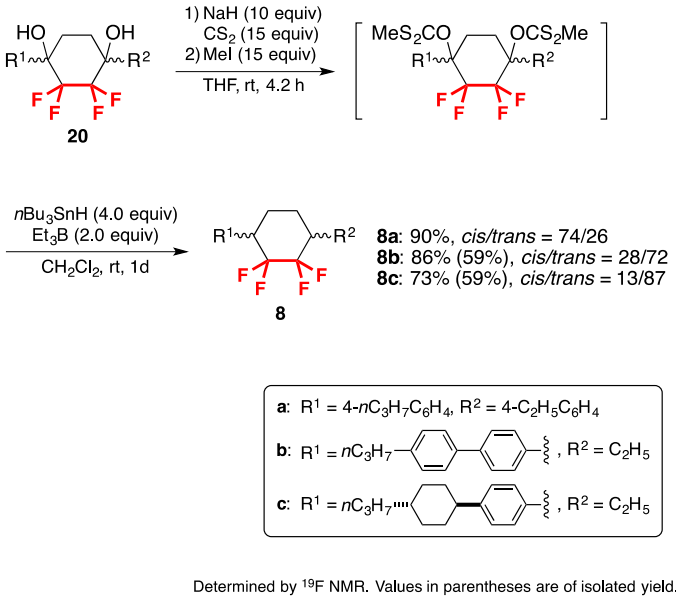
Scheme 3. Possible reaction mechanism for γ-selective formate-reduction of fluorinated allylic dicarbonate **16**



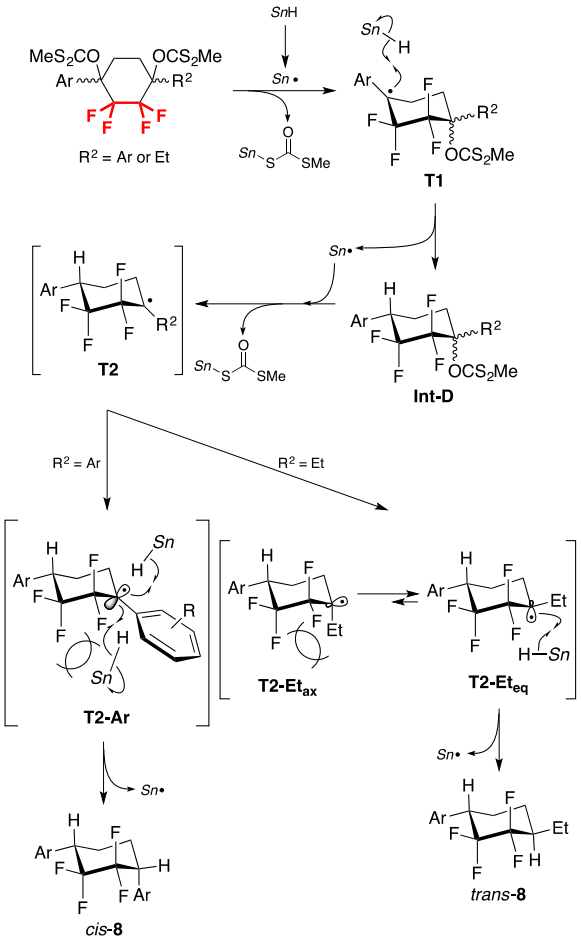
Scheme 4. Previous work: an easy access to various tetrafluoroethylenated cyclohexadienes



Scheme 5. Catalytic hydrogenation of **21a** to unsymmetrical tetrafluorocyclohexane derivative **8a** and the reasonable explanation on the stereoselectivity.



Scheme 6. Alternative approach to unsymmetrical tetrafluorocyclohexanes **8** through Barton-McCombie radical reduction.



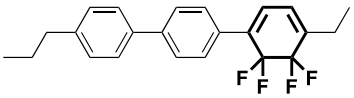
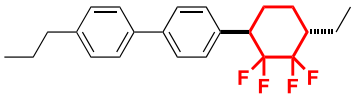
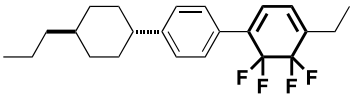
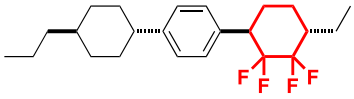
Scheme 7. Possible reaction mechanism for a radical reduction of bisxanthate.

Table 1. Results of the synthesis of symmetrical 3,6-disubstituted 1,1,2,2-tetrafluorocyclohexane derivatives **7**

Ar	Yield[a]/%								
	11	**12**[b]	**13**	**14**	**15**	**16**	**17** [**17**/other isomers][c, d]	**19**[e] [*cis*/*trans*][e]	**7** [*cis*/*trans*][f]
Ph (**a**)	49	80	66	55	66	95	95 [61/39]	89 [56/44]	83 [56/44]
4-$CH_3C_6H_4$(**b**)	67	85	50	71	83	90	90 [62/38]	74 [51/49]	75 [51/49]→[<1/>99]
4-*n*-$C_3H_7C_6H_4$ (**c**)	81	98	53	75	43	93	72 [64/36]	70 [52/48]	91 [52/48]→[<1/>99]

[a] Unless otherwise noted, isolated yields are shown. [b] Yields are determined by ^{19}F NMR analysis. [c] Isomeric ratios are determined by ^{19}F NMR. [d] Diastereomeric ratio in **15** was approximately 1:1. [e] Isolated yields based on the terminal diene **15**. [f] Diastereomeric ratio are determined by ^{19}F NMR. [g] Diastereomeric ratio obtained after several recrystallization process using hexane as a solvent.

Table 2. Evaluation of LC properties in a binary mixture system

	Fluorine-containing molecule /Phase transition sequence[a] and temperature [°C]	Δn[b] ($\Delta\alpha$[Å^3][c])	$\Delta\varepsilon$[b] (μ[D][c])
21b	 /Cr 106 N 110 I	0.25 (47.16)	−6.2 (3.68)
***trans*-8b**	 /Cr 117 I	0.13 (32.41)	−7.9 (3.91)
21c	 /Cr 65 N 77 I	0.15 (35.00)	−7.3 (3.67)
***trans*-8c**	 /Cr 102 I	0.073 (23.75)	−9.4 (3.81)

[a]Estimated using POM and DSC. Heating rate: 1.0 °C min^{-1}. Abbreviations, Cr: crystalline; N: Nematic; I: isotropic phase. [b]Measured by extrapolation technique from a binary mixture system with MLC-6608 (Merck). The physical parameters for MLC-6608 employed as host material are as follows: Δn (25 °C) = 0.0818, $\varepsilon_\perp$ = 7.1, $\varepsilon_\parallel$ = 3.3, $\Delta\varepsilon$ = −3.8. Δn: birefringence; $\Delta\varepsilon$: dielectric anisotropy; η: shear viscosity. [c]Vacuum dipole moments in a long molecular axis calculated from DFT theory at B3LYP/6-311+G(d,p) levels of theory. Unit of the polarizability was converted from a. u. to Å^3 using the factor 0.1482. $\Delta\alpha$: polarizability anisotropy calculated from $[\alpha_{xx}-(\alpha_{yy}+\alpha_{zz})/2]$