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Convenient synthesis of fluorinated alkanes and cycloalkanes by hydrogenation of perfluoroalkylalkenes under ultrasound irradiation

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Abstract

Synthesis of several 1,4-disubstituted cyclohexanes, by hydrogenation of sterically hindered and electron poor perfluoroalkyl alkenes, was performed, at room temperature under hydrogen at atmospheric pressure. Hydrogenation was difficult to achieve without ultrasound whatever catalyst and pressure (from 1 to 120 bar) used. Coupling of ultrasonic irradiation with metallic catalysis dramatically increased the efficiency of hydrogenation of perfluoroalkyl alkenes.

Keywords: Ultrasound; Hydrogenation; Trifluoromethyl alkene; Pentafluoroethyl alkene; Cyclohexene

1. Introduction

Fluorine containing cyclohexanes are receiving a growing interest since their properties are relevant to different fields such as novel liquid crystalline materials [1,2] or fluorinated solvents [3]. Fluoroalkylcyclohexanes are also the key compounds for the determination of thermodynamic constants (ΔG°, ΔS°, ΔH° and A values) by the NMR study of conformational equilibria [4].

We chose to use hydrogenation of fluorinated alkenes for the last step of the synthesis. Reduction of alkenes is well known in the literature [5]. There is a trend over recent years to find catalysts and experimental conditions where the hydrogenation reactions take place at a high rate and with good selectivity under mild experimental conditions. It is straightforward to produce saturated alkanes using a large variety of precious metal catalysts, pressures and experimental conditions [6]. It is more difficult to obtain a high reactivity with electronically poor alkenes and fluorinated groups are strong electron withdrawing substituents. Recently, the application of ultrasound irradiation was investigated for the hydrogenation reaction. The use of ultrasound to promote organic reactions is well known [7,8] but its application to fluorine chemistry is less developed. Hydrogenation by this procedure was found to be highly efficient for increasing the yield and the hydrogenation rate in the case of non fluorinated olefins [9].

Generally, ultrasonic waves were used to activate the catalyst [10] under atmospheric hydrogen pressure before the reaction. The pre-sonochemically activated catalyst can be introduced into an autoclave to carry out the hydrogenation under various pressures. It was stated that sonochemical treatment produced highly dispersed metal on the surface of inert supports [11], but it was shown that pre-sonication in these conditions can also reduce the activity of the catalyst (Raney Nickel, Pd/C) [12]. However, Boudjouk et al. showed that the use of palladium catalyst and ultrasound during hydrogenation accelerated the reaction. Several olefins were hydrogenated in high yield at room temperature and atmospheric pressure. The authors concluded that sonication of the reaction mixture accelerates the reaction as if it was at reflux [13]. This is similar to the observations of Kitazume et al. [14]. They described the first hydrogenation of difluorinated acrylic acids or their benzyl esters which did not proceed under normal conditions. However, ultrasonically dispersed Pd/C in methanol had a marked effect on this hydrogenation. The corresponding

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saturated acids or esters were isolated in yields of 68–81% in 30 h.

A primary objective of this study was to perform a direct comparison between conventional (silently stirred) versus ultrasound mediated heterogeneous catalysis of trifluoromethyl or pentafluoroethyl alkenes.

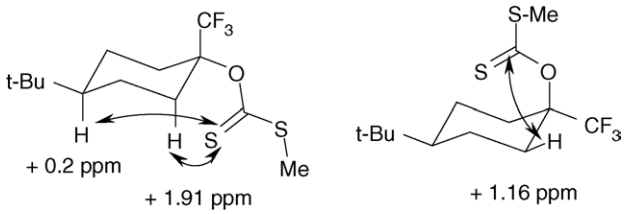
2. Results and discussion

The trifluoromethyl or the pentafluoroethyl groups were introduced with Ruppert's reagent [15] (trimethyltrifluoromethylsilane) or with its pentafluoro equivalent [16]. The addition of a catalytic amount of tetrabutylammonium fluoride to the mixture of 4-substituted cyclohexanone and the corresponding fluoroalkylsilane, promoted the nucleophilic transfer of the fluoroalkyl group, to give the intermediate trimethylsilylated ether. Desilylation of the intermediate with aqueous hydrochloric acid gave the trifluoromethylated alcohol **2** as a mixture of diastereoisomers (Scheme 1).

The stereochemistry of *cis* and *trans* isomers was attributed without ambiguity by chemical derivitisation of the alcohol into xanthate compounds [17]. The influence of the thiocarbonyl group upon the chemical shift of several protons of the alcohol in ^{1}H NMR allowed us to determine its spatial position and then the trifluoromethyl group's chemical shift too (Scheme 2). This substituent is more shielded in the equatorial position (−85.5 ppm) than in the axial position (−78.2 ppm). By analogy, we attributed the stereochemistry of all alcohols and alkanes.

This hypothesis was also confirmed for the alkane compounds: the trifluoromethyl signal of the *cis* isomer is a broad band due to a conformational equilibrium (Scheme 3) which is not observable on the narrow signal of the other diastereoisomer.

Dehydration of the alcohol adducts **2** was carried out following a modified literature procedure [18]. The addition of an excess of thionyl chloride to the mixture of alcohol and pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine gave the corresponding alkene derivatives **4**. The dehydration proceeds first with the formation of an intermediate chlorosulfite, which can be observed by ^{19}F NMR of the reaction mixture. The chloride can subsequently act as a base to promote the β-elimination process but the reaction is very slow and gives mainly to degradation products. We increased the yield by using an excess of pyridine and a catalytic amount of dimethylaminopyridine (DMAP) to accelerate the proton abstraction. All these results are summarized in Table 1.



Scheme 2.

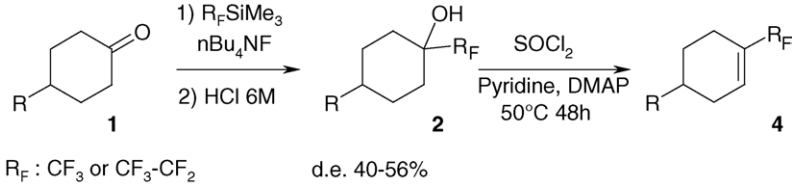
Scheme 3.

Table 1
Synthesis of the fluorinated alkenes

R	R_F	Alcohol		Alkene	
		Product	Yield (%)[a]	Product	Yield (%)[b]
H	CF_3	**2a**	77	**4a**	50
Me	CF_3	**2b**	71	**4b**	77
Et	CF_3	**2c**	73	**4c**	57
*i*Pr	CF_3	**2d**	77	**4d**	72
Ph	CF_3	**2e**	89	**4e**	87
*t*Bu	CF_3	**2f**	68	**4f**	84
Me	C_2F_5	**2g**	86	**4g**	62
*i*Pr	C_2F_5	**2h**	84	**4h**	79

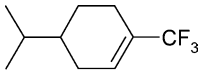
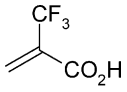
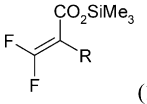
[a] Isolated yield based on the carbonyl compound **1**.
[b] Isolated yield based on the alcohol **2**.

Whilst the chemistry of perfluorinated alkenes is well established, alkenes with both alkyl and trifluoromethyl, or pentafluoroethyl substituents, are less common and only a few examples concerning their reactivity with hydrogen have been published [19,20]. In these reports, the reactions were performed under high pressure (100 bar) with palladium on charcoal as catalyst and during a long time, until the conversion of the alkenes was complete. But it was impossible to reproduce these results with our substrates; with this catalyst, we observed no reaction. Even with a wide range of catalysts and pressures from atmospheric to 120 bar, we were unable to perform the hydrogenation of the double bond in acceptable yields and the reactions were



Scheme 1.

Table 2
Activity data of hydrogenation with and without sonochemical treatment [((] under 1 bar hydrogen pressure at 25 °C

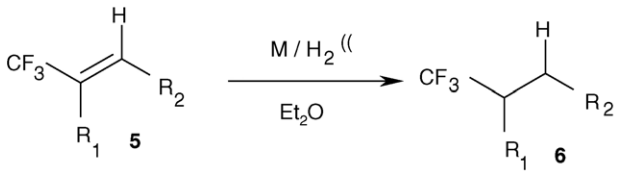
Entry	Substrate	Catalyst[a]	Time (h)	Conversion[d]	Yield %
1		5% Pd/C[b]	48	0	–
2		5% Pd/C ((	48	0	–
3		PtO_2[b]	48	10–98	51–64
4		PtO_2 ((	6	100	73
5	(**7d**)	PtO_2 ((c	24	40	–
6		((	72	0	–
7		PtO_2[b]	24	100	89
8		PtO_2 ((	6	100	96
9		PtO_2 ((c	6	100	–
10	(**8**)	5% Rh/Al_2O_3[b]	16	100	95
11		5% Rh/Al_2O_3 ((	2	100	97
12		5% Pd/C[b]	6	100	94
13		5% Pd/C ((	4	100	92
14		Ru^{II} ((	24	100	76
15	CF_3–$(CF_2)_7$–CH=CH_2 (**9**)	5% Pd/C ((	6	100	97
16	CF_3–CH=CH–CO_2–C_2H_5 (**10**)	5% Pd/C ((	6	100	88
17	 (**11**)	Pd/C ((e	30	100	68–81

[a] The ratio of the catalyst is from 1.5 to 5 mol%.
[b] Silent reaction.
[c] 1 h pre-sonication in hydrogen.
[d] Measured by ^{19}F NMR.
[e] Kitazume results, R = C_4H_9, C_5H_{11}, C_7H_{15}, C_9H_{19}, Bn [14].

scarcely reproducible (Table 2, entry 3). The deactivation of the double bond can be explained by two factors: the fluoroalkyl group is strongly electron withdrawing and the alkenes are also sterically hindered due to the cyclohexane ring.

We investigated the roles of ultrasound and of pretreatment of the catalyst with several metal catalysts. We also performed the hydrogenation with some other alkenes to study the substrate dependence of this reaction. The ultrasound assisted and conventional heterogeneous catalysis experiments were all performed at 25 ± 5 °C using a Schlenck tube reactor and 1 bar of hydrogen. The experiments were performed in a commercially available laboratory bath system ultrasonic generator. The reactions were followed by ^{19}F NMR observing the disappearance of the vinyl trifluoromethyl signal around −70 ppm with the concomitant formation and growth of the fluoroalkane compound's signals (Scheme 4, Table 2).

The ultrasound [((] enhanced the reactivity of the metal catalyst [Table 2, entry 3 (without ultrasound) versus 4 (with ultrasound), and 7 versus 8] for the hydrogenation reaction.



Scheme 4.

Regardless of the pretreatment procedure, a higher reaction rate was always observed under ultrasound compared with silent conditions (Table 2, entries 3, 7, 10 and 12) with any of the catalysts tested, and with all the substrates (Table 2, entries 4, 7, 15, 16). We also observed a higher reaction rate when the alkene bears a perfluoroalkyl group rather than two fluorine atoms (Table 2, entry 17). Most of our reactions were complete within 6 h which is five-fold faster than Kitazume's reactions [14] which is surprising: for two fluorine atoms directly linked to a double bond, the mesomeric donor effect should be more important than the inductive attractor effect. Basically catalytic hydrogenation rate is only slightly enhanced by the electronic effects and much more affected by the bulkiness of molecule [5]. In this case the molecules are less crowded and much electronically rich. The difference of reactivity is less comprehensible and the comparison with Kitazume's reaction has to be considered more carefully.

Ultrasound waves are commonly used to clean or erode the surface of solid materials. This phenomenon is due to the strength of the jets of solvent, hitting the surface itself, created by the collapse of the liquid phase. The ultrasonic treatment changes the catalyst morphology and particle size, thus it allows the production of a highly dispersed metal catalyst which shows a better reactivity than its initial homologue. With **8**, after pretreatment, we observed no difference with or without ultrasonic waves during the experiment (Table 2, entries 8 and 9); the ''cleaning effect'' of ultrasound is strong enough to explain the enhancement of

the reaction rate. However, the low performance observed with **7d** in the same conditions (Table 2, entry 5 versus 4) showed that the ultrasonic waves could act also during the reaction. The use of ultrasound during the reaction is substrate dependent.

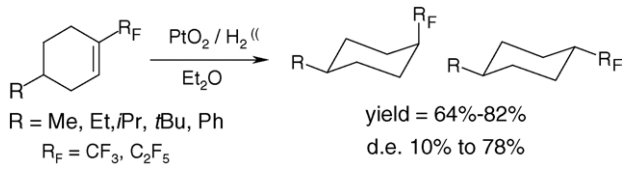
Commercially available, bath system instruments by virtue of their lower acoustic intensity (35 kHz, 30 W) are usually non cavitating. In our experiments; we did not observe the classical phenomenon of cavitation; we had no variation of the solution volume nor of colours. Thus we did not have the conditions required normally for this kind of experiment, so we cannot use the classical explanation of the mechanism by which ultrasound can enhance selectivity and activity in heterogeneous reacting systems [21].

In another study on the hydrogenation of allylic alcohols promoted by ultrasound with 5% Pd/C, Disselkamp et al. observed a 4.9-fold enhancement in reaction rate between noncavitating ultrasound hydrogenation compared to the silently stirred reaction which is significantly greater than the 37% increase in the surface area of the catalyst obtained by dispersion with ultrasound [22]. Thus catalyst dispersion alone cannot account for the observed rate enhancement. It should be noted that cavitation reactions compared to noncavitating yield a 3–35-fold enhancement in reaction rate.

The positive ultrasound effect can be explained by ultrasound induced catalyst morphology change and surface cleaning effects which reactivate the catalyst during the reaction, as well as by improvement of mass transfer. With pre-treated catalyst (Table 2, entry 3) the reaction rate slows after the beginning of the formation of the alkane. The ultrasonic waves applied during the reaction should enhance the rate of adsorption of the alkene, but mainly the rate of desorption of the product.

Experiments 13, 15 and 16 (Table 2) were also complete within 6 h with the use of Pd/C as catalyst. It should be noted that we observed a total lack of reactivity with the cyclohexene substrates using the same conditions (Table 2, entry 2). These last three fluorinated alkenes are less hindered showing the sensitivity of this catalyst to steric interactions and explaining the previous literature results [18,19].

Performing this procedure with other fluorinated alkenes, an enhancement of the initial reaction rate for all the substrates was shown (Scheme 5, Table 3). When the substituent was a phenyl group (Table 3, entry 6), we observed no regioselectivity with this catalyst whatever the hydrogenation conditions (silently stirred or ultrasonic).



Scheme 5.

Table 3
Catalytic hydrogenation of fluorinated alkenes at 25 °C using 4 mol% of PtO_2 as catalyst

Entry	R	R_F	Product	d.e. (%)[a]	Yield (%)[b]
1	H	CF_3	**7a**	–	97
2	Me		**7b**	20	64
3	Et		**7c**	18	80
4	*i*Pr		**7d**	10	73
5	Ph[c]		**7e**	14	93
6	*t*Bu		**7f**	14	71
7	Me	CF_3–CF_2	**7g**	78	77
8	*i*Pr		**7h**	56	82

[a] Measured by ^{19}F NMR.
[b] Isolated yield based on the alkene.
[c] The phenyl substituent is reduced in cyclohexyl group under these conditions. The 4-phenyl substituted compound (**7e′**) was obtained in 79% yield and 52% d.e. without ultrasound.

Selective reduction of the double bond was only obtained using Raney Nickel as catalyst. Previous experiments described in literature [12] showed lack of reactivity under ultrasonic waves with this catalyst, therefore we did not perform this last experiment under ultrasound.

The isolated yields did not totally reflect these results due to the volatility of some of these products. For all the cycloalkane compounds, we obtained a mixture of two diastereoisomers *cis* and *trans* in similar proportions to the diastereoisomeric excess (d.e.) obtained without ultrasound. The *cis* stereoisomer was always the major compound [23].

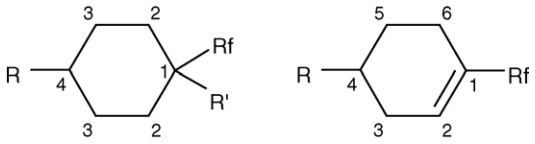
3. Conclusion

The results described here show unambiguously that the method was highly efficient for increasing the yield and the hydrogenation rate of electronically poor alkenes. The use of non cavitating ultrasonic waves during the course of the reaction is a promising way to promote the reactivity of the catalyst by the effect of the high dispersion of the metal as well as a rate enhancement for the desorption of the product around the catalyst, allowing a new molecule of substrate to react. We observed no evidence of a modification of the diastereoselectivity under these conditions.

4. Experimental

4.1. General

^1H NMR spectra were registrated on a Bruker AC300 (300 MHz) or AC200 (200 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AC300 (282 MHz) or AC200 (188 MHz) spectrometer using $CFCl_3$ as external standard. ^{13}C NMR were recorded on a Bruker AC300 (75 MHz) or AC200 (50 MHz) spectrometer. The numbers of the carbon atoms were given



Scheme 6.

following Scheme 6. Mass spectra were obtained on a HP MS 5989B spectrometer. The elementary analyses were performed at ICSN, (Gif sur Yvette, France). The Rf were determined from TLC on silica gel 60F254. Column chromatography was performed on silica gel, particle size 35–70 Å. The hydrogenation was performed under ultrasound with a laboratory cleaning device: Bioblock Scientific 88154, 35 kHz, 30 W. The CAS number and references are included for the known compounds. To our knowledge the other products are new.

4.1.1. Preparation of trifluoromethyl-substituted cyclohexanols: general procedure

A mixture of carbonyl compound (50 mmol) and (trifluoromethyl)trimethylsilane (60 mmol) in THF (50 mL) at room temperature was treated with a catalytic amount (ca. 0.5 mL) of TBAF (1.1 M in THF). The reaction mixture was stirred for 1 h. The resulting silyloxy compounds were then hydrolysed with aqueous HCl (6 M). After the reaction, the mixture was extracted with ether (3 × 50 mL) and the combinated organic phases were washed with a solution of sodium bicarbonate (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography and diastereoisomers were separated by this technique when it was possible; in such case, the melting point for each compound is given. Isolated yields and spectral data for all the prepared compounds are given below.

*4.1.1.1. 1-Trifluoromethyl-cyclohexan-1-ol [80768-55-4] [24] (**2a**).* 77% yield; white solid; mp 60–61 °C; flash chromatography was performed in dichloromethane, Rf: 0.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.6 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (m, 1H), 1.5–1.9 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2 (C_3), 25.0 (C_4), 29.8 (C_2), 72.6 (q, $^2J_{C–F}$ = 28.1 Hz, C_1), 126.3 (q, $^1J_{C–F}$ = 284 Hz, CF_3).

*4.1.1.2. 1-Trifluoromethyl-4-methylcyclohexan-1-ol (**2b**).* 71% yield; mixture (72/28) of *trans* and *cis* isomers; the diastereoisomers were partially separated by flash chromatography in dichloromethane, Rf: 0.5. White solid; mp 78–79 °C (*trans*) and 67–68 °C (mixture); spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −83.4 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, 3H, $^3J_{H–H}$ = 6.8 Hz), 1.2–1.4 (m, 2H), 1.5–1.7 (m, 3H), 1.75–1.90 (m, 3H), 2.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0 (CH_3), 26.9 (C_2), 27.0 (C_3), 27.4 (C_4), 72.4 (q, $^2J_{C–F}$ = 27.8 Hz, C_1), 126.5 (q, $^1J_{C–F}$ = 283 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.3 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, 3H, $^3J_{H–H}$ = 6.9 Hz), 1.2–1.4 (m, 3H), 1.50–1.70 (m, 3H), 1.75–2.05 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0 (CH_3), 28.6 (C_3), 29.8 (C_2), 31.6 (C_4), 72.4 (q, $^2J_{C–F}$ = 27.8 Hz, C_1), 126.5 (q, $^1J_{C–F}$ = 283 Hz, CF_3); IR (KBr) 3375, 2940, 2868 cm^{-1}; MS (CI CH_4) *m/z* 165 (5), 113 (66), 95 (100). Anal. Calcd. for $C_8H_{13}F_3O$: C, 52.7; H, 7.2. Found: C, 52.5; H, 7.2.

*4.1.1.3. 1-Trifluoromethyl-4-ethylcyclohexan-1-ol (**2c**).* 73% yield; mixture (74/26) of *trans* and *cis* isomers; flash chromatography was performed in dichloromethane, Rf: 0.5. White solid; mp 51–52 °C (mixture); spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −83.4 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, $^3J_{H–H}$ = 7.2 Hz), 1.1–1.8 (m, 11H), 2.51 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (CH_3), 24.5 (CH_2), 24.7 (C_3), 27.1 (C_2), 34.6 (C_4), 72.5 (q, $^2J_{C–F}$ = 27.7 Hz, C_1), 126.5 (q, $^1J_{C–F}$ = 285 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.4 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, $^3J_{H–H}$ = 7.2 Hz), 1.1–1.8 (m, 11H), 2.70 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 (CH_3), 26.3 (C_3), 29.3 (CH_2), 29.6 (C_2), 38.6 (C_4), 72.6 (q, $^2J_{C–F}$ = 28.0 Hz, C_1), 126.4 (q, $^1J_{C–F}$ = 285 Hz, CF_3); IR (KBr) 3370, 2966, 2873 cm^{-1}; MS (CI CH_4) *m/z* 179 (6), 149 (54), 127 (58), 109 (100). Anal. Calcd. for $C_9H_{15}F_3O$: C, 55.1; H, 7.7. Found: C, 55.0; H, 7.75.

*4.1.1.4. 1-Trifluoromethyl-4-isopropylcyclohexan-1-ol (**2d**).* 77% yield; mixture (76/24) of *trans* and *cis* isomers; flash chromatography was performed in dichloromethane as eluent (Rf: 0.6). White solid; mp 57–58 °C (mixture); spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.2 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 6H, $^3J_{H–H}$ = 6.6 Hz), 1.21 (m, 1H), 1.3–2.1 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (CH_3), 25.3 (C_3), 28.1 (CH), 28.7 (C_2), 40.5 (C_4), 72.4 (q, $^2J_{C–F}$ = 27.7 Hz, C_1), 126.6 (q, $^1J_{C–F}$ = 285 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.3 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, 6H, $^3J_{H–H}$ = 6.6 Hz), 1.05 (m, 1H), 1.3–2.1 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7 (CH_3), 23.4 (C_3), 30.0 (C_2), 32.5 (CH), 43.0 (C_4), 72.5 (q, $^2J_{C–F}$ = 28.0 Hz, C_1), 126.4 (q, $^1J_{C–F}$ = 284 Hz, CF_3); IR (KBr) 3350, 2955, 2868 cm^{-1}; MS (CI CH_4) *m/z* 193 (17), 177 (48), 149 (100), 123 (59), 79 (74). Anal. Calcd. for $C_{10}H_{17}F_3O$: C, 57.1; H, 8.15. Found: C, 57.1; H, 8.2.

*4.1.1.5. 1-Trifluoromethyl-4-phenylcyclohexan-1-ol (**2e**).* 89% yield; mixture (77/23) of *trans* and *cis* isomers; flash chromatography was performed in dichloromethane as eluent (Rf: 0.4). White solid; mp 68–69 °C (*trans*) and 59–60 °C (mixture); spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.1 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (m, 2H), 1.90 (m, 4H), 1.98 (s, 1H, OH), 2.18

(m, 2H), 2.77 (m, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0 (C_3), 31.1 (C_2), 40.5 (C_4), 72.0 (q, $^2J_{C-F}$ = 27 Hz, C_1), 126.2 ($C_{4'}$), 126.7 (q, $^1J_{C-F}$ = 287 Hz, CF_3), 126.9 ($C_{2'}$), 128.5 ($C_{3'}$), 144.8 ($C_{1'}$); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.2 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6–2.1 (m, 9H), 2.56 (m, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7 (C_3), 30.1 (C_2), 43.2 (C_4), 72.0 (q, $^2J_{C-F}$ = 27 Hz, C_1), 126.3 ($C_{4'}$), 126.7 (q, $^1J_{C-F}$ = 287 Hz, CF_3), 126.8 ($C_{2'}$), 128.5 ($C_{3'}$), 146.1 ($C_{1'}$); IR (KBr) 3421, 3032, 2940, 2858, 1711, 785, 692 cm^{-1}; MS (EI) *m/z* 244 (34), 226 (85), 157 (100). Anal. Calcd. for $C_{13}H_{15}F_3O$: C, 63.9; H, 6.2. Found: C, 63.9; H, 6.1.

*4.1.1.6. 1-Trifluoromethyl-4-tertbutylcyclohexan-1-ol [120714-67-2] [25] (**2f**).* 68% yield; mixture (78/22) of *trans* and *cis* isomers. The diastereoisomers were separated by flash chromatography eluted in pentane/ether: 9/1 (Rf: 0.36 for the *trans* and 0.32 for the *cis* isomer) monitored by ^{19}F NMR to determine the purity each diastereoisomer. The *trans* isomer is isolated from the first fractions and after eluting some mixed fractions, the *cis* isomer is obtained at the end. The diastereoisomers were recrystallized in water/ethanol 7/2). White needles; mp 96–97 °C (*trans*) and 50–51 °C (*cis*); spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.2 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 9H), 1.07 (m, 1H), 1.32 (m, 2H), 1.51 (m, 2H), 1.70 (m, 2H), 2.10 (br s, 1H, OH), 2.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (q, $^4J_{C-F}$ = 1.5 Hz, C_3), 27.5 ($3CH_3$), 32.3 ($\underline{C}(CH_3)_3$), 33.3, (q, $^3J_{C-F}$ = 0.85 Hz, C_2), 46.2 (C_4), 72.2 (q, $^2J_{C-F}$ = 27.4 Hz, C_1), 126.9 (q, $^1J_{C-F}$ = 286 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.3 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.03 (m, 1H), 1.38 (m, 2H), 1.61 (m, 2H), 1.66 (br s, 1H, OH), 1.70 (m, 2H), 1.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 (C_3), 27.4 ($3CH_3$), 30.4 (q, $^3J_{C-F}$ = 1.4 Hz, C_2), 32.4 ($\underline{C}(CH_3)_3$), 47.2 (C_4), 72.2 (q, $^2J_{C-F}$ = 28 Hz, C_1), 126.9 (q, $^1J_{C-F}$ = 286 Hz, CF_3); IR (KBr) 3345, 2960, 2868 cm^{-1}; MS (CI CH_4) *m/z* 207 (12), 191 (59), 149 (100), 155 (8). Anal. Calcd. for $C_{11}H_{19}F_3O$: C, 58.9; H, 8.5. Found: C, 58.9; H, 8.6.

4.1.2. Preparation of pentafluoroethyl-substituted cyclohexanols

The same procedure as that described to prepare the trifluoromethylated compounds was employed, using (pentafluoroethyl)trimethylsilane as perfluoroalkylating reagent.

*4.1.2.1. 1-Pentafluoroethyl-4-methylcyclohexan-1-ol (**2g**).* 86% yield; mixture (69/31) of *trans* and *cis* isomers; flash chromatography was performed in pentane/ether (9/1), Rf: 0.4. White solid; mp 55–56 °C (mixture); spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −78.7 (s, 3F), −126.2 (s, 2F); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, 3H, $^3J_{H-H}$ = 6.8 Hz), 1.2–1.5 (m, 2H), 1.5–2.0 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.1, 25.8, 26.3, 28.7, 73.4 (t, $^2J_{C-F}$ = 22.7 Hz), 115.1 (tq, $^1J_{C-F}$ = 260 Hz, $^2J_{C-F}$ = 34.8 Hz), 119.6 (qt, $^1J_{C-F}$ = 288 Hz, $^2J_{C-F}$ = 36.9 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −78.7 (s, 3F), −127.3 (s, 2F); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 3H, $^3J_{H-H}$ = 6.9 Hz), 1.2–1.5 (m, 3H), 1.5–2.0 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.0, 26.5, 29.8, 31.6, 73.3 (t, $^2J_{C-F}$ = 22.7 Hz), 115.1 (tq, $^1J_{C-F}$ = 260 Hz, $^2J_{C-F}$ = 34.8 Hz), 119.6 (qt, $^1J_{C-F}$ = 288 Hz, $^2J_{C-F}$ = 36.9 Hz); IR (KBr) 3416, 2976, 2884 cm^{-1}; MS (CI CH_4) *m/z* 249 (4), 215 (100), 195 (38). Anal. Calcd. for $C_9H_{13}F_5O$: C, 46.6; H, 5.7. Found: C, 46.7; H, 5.7.

*4.1.2.2. 1-Pentafluoroethyl-4-isopropylcyclohexan-1-ol (**2h**).* 84% yield; mixture (70/30) of *trans* and *cis* isomers; flash chromatography was performed in dichloromethane (Rf: 0.6). White solid; mp 47–48 °C (mixture); spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.8 (s, 3F), −125.3 (s, 2F); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.0–2.0 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 ($2CH_3$), 22.9 (C_3), 26.7 (CH), 27.6 (C_2), 39.8 (C_4), 73.3 (t, $^2J_{C-F}$ = 23.3 Hz, C_1), 115.3 (tq, $^1J_{C-F}$ = 260 Hz, $^2J_{C-F}$ = 34.5 Hz, CF_2), 119.6 (qt, $^1J_{C-F}$ = 288 Hz, $^2J_{C-F}$ = 36.9 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.7 (s, 3F), −127.3 (s, 2F); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.0–2.0 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7 ($2CH_3$), 23.5 (C_3), 30.0 (C_2), 32.5 (CH), 42.9 (C_4), 73.5 (t, $^2J_{C-F}$ = 22.3 Hz, C_1), 115.0 (tq, $^1J_{C-F}$ = 260 Hz, $^2J_{C-F}$ = 34.5 Hz, CF_2), 119.6 (qt, $^1J_{C-F}$ = 288 Hz, $^2J_{C-F}$ = 36.9 Hz, CF_3); IR (KBr) 3416, 2955, 2873 cm^{-1}; MS (CI CH_4) *m/z* 259 (6), 243 (100), 201 (26), 141 (10). Anal. Calcd. for $C_{11}H_{17}F_5O$: C, 50.8; H, 6.6. Found: C, 50.95; H, 6.6.

4.1.3. Dehydration of trifluoromethyl- and pentafluoroethyl-substituted cyclohexanols: general procedure

Pyridine (30 mmol) and $SOCl_2$ (30 mmol) were added successively at 0 °C to a solution of perfluoroalkylated alcohol (10 mmol) in THF (10 mL) with 50 mg of dimethylaminopyridine. The reaction mixture was warmed to 50 °C and stirred between 16 and 48 h (the reaction was followed by ^{19}F NMR). The mixture was then cooled to 0 °C and carefully poured onto saturated aqueous $CuSO_4$ at 0 °C. After extractions with ether (3 × 50 mL), the combinated organic phases were washed with 1 M HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by a short chromatography with pentane as eluant: Rf: 0.9 for all the alkenes excepted when R is a phenyl group (Rf: 0.7); and used directly for the hydrogenation.

*4.1.3.1. 1-Trifluoromethyl-cyclohexene [26] (**4a**).* 50% yield; colorless oil; ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.2 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6–1.8 (m, 4H),

2.0–2.2 (m, 4H), 6.34 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.5 (C_4, C_5), 21.9 (q, $^3J_{C-F}$ = 1.1 Hz, C_6), 24.3 (C_3), 124.0 (q, $^1J_{C-F}$ = 272 Hz, CF_3), 128.1 (q, $^2J_{C-F}$ = 29.7 Hz, C_1), 130.3 (q, $^3J_{C-F}$ = 6.0 Hz, C_2); IR (neat) 3031, 2920, 2878, 1680 cm^{-1}.

*4.1.3.2. 1-Trifluoromethyl-4-methylcyclohexene (**4b**).* 77% yield; colorless oil; ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.7 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, 3H, $^3J_{H-H}$ = 6.2 Hz), 1.3 (m, 1H), 1.7–2.3 (m, 6H), 6.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 (CH_3), 21.9 (C_6), 27.4 (C_5), 29.5 (C_3), 32.6 (C_4), 124.0 (q, $^1J_{C-F}$ = 271 Hz, CF_3), 127.9 (q, $^2J_{C-F}$ = 29.7 Hz, C_1), 129.7 (q, $^3J_{C-F}$ = 5.7 Hz, C_2); IR (neat) 3032, 2919, 2878, 1680 cm^{-1}; MS (CI CH_4) *m/z* 164 (23), 149 (36), 95 (100).

*4.1.3.3. 1-Trifluoromethyl-4-ethylcyclohexene (**4c**).* 57% yield; colorless oil; ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 3H, $^3J_{H-H}$ = 7.4 Hz), 1.2–2.3 (m, 9H), 6.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 (CH_3), 22.1 (C_6), 27.5, 28.7, 30.7 (C_3, C_5, CH_2), 34.4 (C_4), 124.2 (q, $^1J_{C-F}$ = 271 Hz, CF_3), 128.2 (q, $^2J_{C-F}$ = 29.7 Hz,C_1), 129.9 (q, $^3J_{C-F}$ = 5.7 Hz, C_2); IR (neat) 2955, 2920, 2863, 1680 cm^{-1}; MS (CI CH_4) *m/z* 178 (18), 163 (33), 149 (68), 109 (100).

*4.1.3.4. 1-Trifluoromethyl-4-isopropylcyclohexene (**4d**).* 72% yield; colorless oil; ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.9 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, 3H, $^3J_{H-H}$ = 6.7 Hz), 0.95 (d, 3H, $^3J_{H-H}$ = 6.7 Hz), 1.2–2.3 (m, 8H), 6.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4 (CH_3), 19.7 (CH_3), 22.8 (C_6), 25.1 (C_3), 28.0 (C_5), 32.0 (CH), 39.2 (C_4), 124.2 (q, $^1J_{C-F}$ = 271 Hz, CF_3), 128.2 (q, $^2J_{C-F}$ = 29.7 Hz, C_1), 130.3 (q, $^3J_{C-F}$ = 5.7 Hz, C_2).

*4.1.3.5. 1-Trifluoromethyl-4-phenylcyclohexene (**4e**).* 87% yield; Rf: 0.7. White solid; mp 42–43 °C; ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.8 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5–2.5 (m, 6H), 2.84 (m, 1H), 6.46 (s, 1H), 7.1–7.4 (m 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7 (C_6), 28.7 (C_3), 32.3 (C_5), 39.1 (C_4), 124.0 (q, $^1J_{C-F}$ = 272 Hz, CF_3), 126.5 ($C_{4'}$), 126.8 ($C_{2'}$), 128.1 (q, $^2J_{C-F}$ = 30.0 Hz, C_1), 128.6 ($C_{3'}$), 130.0 (q, $^3J_{C-F}$ = 5.6 Hz, C_2); IR (KBr) 3063, 3021, 2924, 1675, 785, 692 cm^{-1}; MS (EI) *m/z* 226 (27), 104 (100). Anal. Calcd. for $C_{13}H_{13}F_3$: C, 69.0; H, 5.8. Found: C, 69.0; H, 5.9.

*4.1.3.6. 1-Trifluoromethyl-4-tertbutylcyclohexene (**4f**).* 81% yield; colorless oil; ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.8 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.2–2.3 (m, 7H), 6.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0 (C_3), 23.4 (C_6), 26.0 (C_5), 27.0 ($3CH_3$), 32.1 ($\underline{C}(CH_3)_3$), 43.2 (C_3), 124.1 (q, $^1J_{C-F}$ = 272 Hz, CF_3), 128.0 (q, $^2J_{C-F}$ = 29.7 Hz, C_1), 130.7 (q, $^3J_{C-F}$ = 5.9 Hz, C_2); IR (neat) 2965, 2858, 1680 cm^{-1}; MS (CI CH_4) *m/z* 206 (7), 191 (15), 149 (100), 135 (62). Anal. Calcd. for $C_{11}H_{17}F_3$: C, 64.1; H, 8.3. Found: C, 63.9; H, 8.2.

*4.1.3.7. 1-Pentafluoroethyl-4-methylcyclohexene (**4g**).* 62% yield; colorless oil; ^{19}F NMR (188 MHz, $CDCl_3$) δ −84.4 (s, 3F), −116.1 (d, 1F, $^2J_{F-F}$ = 265 Hz), −119.1 (d, 1F, $^2J_{F-F}$ = 265 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (d, 3H, $^3J_{H-H}$ = 6.1 Hz), 1.2–2.2 (m, 7H), 6.32 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3 (CH_3), 22.6 (C_6), 27.3 (C_4), 29.9 (C_5), 33.2 (C_3), 113.4 (tq, $^1J_{C-F}$ = 252 Hz, $^2J_{C-F}$ = 37.6 Hz, CF_2), 119.3 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 39.4 Hz, CF_3), 126.8 (t, $^2J_{C-F}$ = 21.3 Hz, C_1), 133.0 (q, $^3J_{C-F}$ = 8.9 Hz, C_2); IR (neat) 2950, 2873, 1670 cm^{-1}.

*4.1.3.8. 1-Pentafluoroethyl-4-isopropylcyclohexene (**4h**).* 79% yield; colorless oil; ^{19}F NMR (282 MHz, $CDCl_3$) δ −84.4 (s, 3F), −115.8 (d, 1F, $^2J_{F-F}$ = 264 Hz), −119.2 (d, 1F, $^2J_{F-F}$ = 264 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3H, $^3J_{H-H}$ = 6.8 Hz), 0.93 (d, 3H, $^3J_{H-H}$ = 6.8 Hz), 1.2–1.4 (m, 2H), 1,53 (m, 1H), 1.8–2.3 (m, 5H), 6.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4 (CH_3), 19.7 (CH_3), 23.4 (C_6), 25.4 (C_3), 28.6 (C_5), 32.0 (CH), 39.1 (C_4), 113.4 (tq, $^1J_{C-F}$ = 252 Hz, $^2J_{C-F}$ = 37.7 Hz, CF_2), 119.4 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 39.7 Hz, CF_3), 127.0 (t, $^2J_{C-F}$ = 21.5 Hz, C_1), 133.4 (q, $^3J_{C-F}$ = 8.5 Hz, C_2); IR (neat) 2960, 2868, 1665 cm^{-1}; MS (CI CH_4) *m/z* 243 (34), 223 (100), 203 (86). Anal. Calcd. for $C_{11}H_{15}F_5$: C, 54.5; H, 6.2. Found: C, 54.6; H, 6.2.

4.1.4. Reduction of perfluoroalkylated alkenes: general procedure

In a Schlenck tube PtO_2 (5% mol) in ether (10 mL) was sonicated under hydrogen 30 min prior to the addition of a solution of alkene (2 mmol) in ether (10 mL). The mixture was hydrogenated at room temperature for 6 h, under ultrasound. The solution was then filtered and concentrated. All the alkenes were purified by flash chromatography eluted with pentane (Rf $\geq$ 0.9). It was not possible to separate the mixture of diastereoisomers.

*4.1.4.1. Trifluoromethyl-cyclohexane (401-75-2) (**7a**).* 97% yield; colorless oil; spectral data: ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.6 (d, $^3J_{F-H}$ = 8.9 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1–1.4 (m, 5H), 1.6–2.0 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0 (C_3), 25.1 (q, $^3J_{C-F}$ = 2.5 Hz, C_2), 25.6 (C_4), 42.0 (q, $^2J_{C-F}$ = 26.3 Hz, C_1), 127.8 (q, $^1J_{C-F}$ = 278 Hz, CF_3).

*4.1.4.2. 1-Trifluoromethyl-4-methylcyclohexane (13127-02-1) [27] (**7b**).* 64% yield; mixture (60/40) of *cis* and *trans* isomers; colorless oil; spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.8 (d, $^3J_{F-H}$ = 8.9 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, 3H, $^3J_{H-H}$ = 6.4 Hz), 1.1–2.0 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (Me), 20.3 (q, $^3J_{C-F}$ = 2.3 Hz, C_2), 27.5 (C_4), 30.2 (C_3), 40.8 (q, $^2J_{C-F}$ = 26.3 Hz, C_1), 128.1 (q, $^1J_{C-F}$ = 279 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.3 (d, $^3J_{F-H}$ = 8.9 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 3H, $^3J_{H-H}$ = 7.2 Hz),

1.1–2.0 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2 (Me), 25.0 (q, $^3J_{C-F}$ = 2.8 Hz, C_2), 31.9 (C_4), 33.5 (C_3), 41.7 (q, $^2J_{C-F}$ = 26.3 Hz, C_1), 127.1 (q, $^1J_{C-F}$ = 279 Hz, CF_3).

*4.1.4.3. 1-Trifluoromethyl-4-ethylcyclohexane (**7c**).* 80% yield; mixture (59/41) of *cis* and *trans* isomers; colorless oil; spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.8 (d, $^3J_{F-H}$ = 7.6 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 3H, $^3J_{H-H}$ = 7.4 Hz), 1.1–2.0 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (CH_3), 20.5 (C_2), 24.7 (CH_2), 28.0 (C_3), 34.8 (C_4), 40.9 (q, $^2J_{C-F}$ = 25.9 Hz, C_1), 128.1 (q, $^1J_{C-F}$ = 279 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.3 (d, $^3J_{F-H}$ = 7.6 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 3H, $^3J_{H-H}$ = 7.4 Hz), 1.1–2.0 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 (CH_3), 24.7 (C_2), 29.6 (CH_2), 31.2 (C_3), 38.6 (C_4), 42.1 (q, $^2J_{C-F}$ = 26.2 Hz, C_1), 127.9 (q, $^1J_{C-F}$ = 279 Hz, CF_3).

*4.1.4.4. 1-Trifluoromethyl-4-isopropylcyclohexane (30129-17-0) (**7d**).* 73% yield; mixture (55/45) of *cis* and *trans* isomers; colorless oil; spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.8 (d, $^3J_{F-H}$ = 8.9 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6H, $^3J_{H-H}$ = 6.7 Hz), 1.2–2.0 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5 ($2CH_3$), 21.4 (q, $^3J_{C-F}$ = 2.45 Hz, C_2), 26.0 (C_3), 28.0 (CH), 40.0 (q, $^2J_{C-F}$ = 25.9 Hz, C_1), 40.8 (C_4), 128.3 (q, $^1J_{C-F}$ = 279.6 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.5 (d, $^3J_{F-H}$ = 8.9 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 6H, $^3J_{H-H}$ = 6.7 Hz), 1.2–2.0 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7 ($2CH_3$), 25.2 (q, $^3J_{C-F}$ = 2.45 Hz, C_2), 28.2 (C_3), 32.6 (CH), 42.1 (q, $^2J_{C-F}$ = 26.2 Hz, C_1), 43.3 (C_4), 127.9 (q, $^1J_{C-F}$ = 278.8 Hz, CF_3).

*4.1.4.5. 1-Trifluoromethyl-4-cyclohexylcyclohexane (**7e**).* 93% yield; mixture (57/43) of *cis* and *trans* isomers; colorless oil; spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.9 (d, $^3J_{F-H}$ = 11.4 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9–1.5 (m, 10H), 1.5–2.2 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (q, $^3J_{C-F}$ = 2.5 Hz, C_2), 25.7 (C_3), 26.6 ($C_{4'}$), 26.6 ($C_{2'}$), 30.7 ($C_{3'}$), 37.5 ($C_{1'}$), 39.2 (C_4), 40.2 (q, $^2J_{C-F}$ = 25.9 Hz, C_1), 128.3 (q, $^1J_{C-F}$ = 279 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.4 (d, $^3J_{F-H}$ = 7.6 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9–1.5 (m, 10H), 1.5–2.2 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3 (q, $^3J_{C-F}$ = 2.7 Hz, C_2), 26.8 ($C_{4'}$,$C_{2'}$), 28.4 (C_3), 30.2 ($C_{3'}$), 42.3 (q, $^2J_{C-F}$ = 26.4 Hz, C_1), 42.7 ($C_{1'}$), 43.0 (C_4), 127.9 (q, $^1J_{C-F}$ = 279 Hz, CF_3); MS (CI CH_4) *m/z* 233 (49), 215 (100), 85 (26).

*4.1.4.6. 1-Trifluoromethyl-4-phenylcyclohexane (**7e′**).* This compound was prepared without ultrasound, using Raney Nickel as hydrogenation catalyst: 79% yield; mixture (76/24) of *cis* and *trans* isomers; colorless oil; Spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.0 (d, $^3J_{F-H}$ = 8.9 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6–1.9 (m, 8H), 2.30 (m, 1H), 2.72 (m, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (q, $^3J_{C-F}$ = 2.3 Hz, C_2), 29.0 (C_3), 37.8 (q, $^2J_{C-F}$ = 25.4 Hz, C_1), 41.0 (C_4), 126.0 ($C_{4'}$), 127.0 ($C_{2'}$), 127.8 (q, $^1J_{C-F}$ = 278 Hz, CF_3), 128.4 ($C_{3'}$), 145.8 ($C_{1'}$); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.2 (d, $^3J_{F-H}$ = 7.6 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 4H), 1.95 (m, 1H), 2.05 (m, 4H), 2.54 (m, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3 (q, $^3J_{C-F}$ = 2.7 Hz, C_2), 32.5 (C_3), 41.6 (q, $^2J_{C-F}$ = 26.5 Hz, C_1), 43.5 (C_4), 126.3 ($C_{4'}$), 126.7 ($C_{2'}$), 127.8 (q, $^1J_{C-F}$ = 278 Hz, CF_3), 128.5 ($C_{3'}$), 146.3 ($C_{1'}$). Anal. Calcd. for $C_{13}H_{15}F_3$: C, 68.4; H, 6.6. Found: C, 68.35; H, 6.6.

*4.1.4.7. 1-Trifluoromethyl-4-tertbutylcyclohexane (13127-04-3) [28] (**7f**).* 71% yield; mixture (57/43) of *cis* and *trans* isomers; colorless oil; spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.1 (d, $^3J_{F-H}$ = 11.4 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 9H), 1.0–2.3 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (C_3), 27.4 ($3CH_3$), 24.6 (q, $^3J_{C-F}$ = 2.1 Hz, C_2), 32.5 ($C(Me)_3$), 47.2 (C_4), 36.5 (q, $^2J_{C-F}$ = 25.2 Hz, C_1), 126.9 (q, $^1J_{C-F}$ = 281 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.3 (d, $^3J_{F-H}$ = 7.6 Hz, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 9H), 1.0–2.3 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9. (C_3), 27.5 ($3CH_3$), 32.4 ($C(Me)_3$), 25.4 (q, $^3J_{C-F}$ = 2.5 Hz, C_2), 47.4 (C_4), 42 (q, $^2J_{C-F}$ = 26.3 Hz, C_1), 127.9 (q, $^1J_{C-F}$ = 278.2 Hz, CF_3).

*4.1.4.8. 1-Pentafluoroethyl-4-methylcyclohexane (**7g**).* 77% yield; mixture (88/12) of *cis* and *trans* isomers; colorless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −82.3 (s, 3F), −121.1 (d, 2F, $^3J_{F-H}$ = 15.3 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, 3H, $^3J_{H-H}$ = 7.1 Hz), 1.2–2.2 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7 (CH_3), 19.3 (td, $^3J_{C-F}$ = 4.1 Hz, $^4J_{C-F}$ = 1.4 Hz, C_2), 27.0 (C_4), 30.5 (C_3), 39.3 (t, $^2J_{C-F}$ = 20.6 Hz, C_1), 116.7 (tq, $^1J_{C-F}$ = 254 Hz, $^2J_{C-F}$ = 36.0 Hz, CF_2), 119.6 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 37.3 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −82.2 (s, 3F), −122.0 (d, 2F, $^3J_{F-H}$ = 14.5 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, 3H, $^3J_{H-H}$ = 7.1 Hz), 1.2–2.2 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3 (CH_3), 24.4 (td, $^3J_{C-F}$ = 4.2 Hz, $^4J_{C-F}$ = 1.4 Hz, C_2), 31.9 (C_4), 33.9 (C_3), 39.8 (t, $^2J_{C-F}$ = 20.6 Hz, C_1), 116.5 (tq, $^1J_{C-F}$ = 253 Hz, $^2J_{C-F}$ = 36.1 Hz, CF_2), 119.6 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 37.3 Hz, CF_3); MS (EI) *m/z* 216 (100); MS HR Calcd. for $C_9H_{13}F_5$: 216.0937. Found: 216.0937.

*4.1.4.9. 1-Pentafluoroethyl-4-isopropylcyclohexane (**7h**).* 82% yield; mixture (78/22) of *cis* and *trans* isomers; colorless oil; spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.5 (s, 3F), −120.4 (d, 2F, $^3J_{F-}$

$_H$ = 16.5 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.2–2.2 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4 (td, $^3J_{C-F}$ = 3.8 Hz, $^4J_{C-F}$ = 1.4 Hz, C_2), 20.7 (CH_3), 26.6 (C_3), 27.1 (CH), 38.6 (t, $^2J_{C-F}$ = 20.6 Hz, C_1), 40.5 (C_4), 116.9 (tq, $^1J_{C-F}$ = 254 Hz, $^2J_{C-F}$ = 36.1 Hz, CF_2), 119.6 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 37.3 Hz, CF_3); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.2 (s, 3F), −122.1 (d, 2F, $^3J_{F-H}$ = 15.2 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.2–2.2 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6 (CH_3), 24.6 (td, $^3J_{C-F}$ = 4.2 Hz, $^4J_{C-F}$ = 1.4 Hz, C_2), 28.5 (C_3), 32.7 (CH), 40.2 (t, $^2J_{C-F}$ = 20.7 Hz, C_1), 43.3 (C_4), 116.5 (tq, $^1J_{C-F}$ = 253 Hz, $^2J_{C-F}$ = 36.1 Hz, CF_2), 119.6 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 37.3 Hz, CF_3); MS (CI CH_4) *m/z* 243 (83), 225 (77), 205 (100), 183 (68), 163 (20), 159 (20). Anal. Calcd. for $C_{11}H_{17}F_5$: C, 54.1; H, 7.0. Found: C, 54.0; H, 6.9.

*4.1.4.10. 2-Trifluoromethylpropanoïc acid [381-97-5] [29] (**8**).* 96% yield; colorless oil; spectral data ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.5 (s, 3F); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, 3H, $^3J_{H-H}$ = 7.2 Hz), 3.26 (sep, 1H, $^3J_{H-H}$ = 7.7 Hz), 8.9 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8 (q, $^3J_{C-F}$ = 2.8 Hz, C_3), 44.4 (q, $^2J_{C-F}$ = 29.1 Hz, C_2), 124.6 (q, $^1J_{C-F}$ = 279.3 Hz, CF_3), 173.8 (q, $^3J_{C-F}$ = 2.8 Hz, C_1).

*4.1.4.11. 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluorodecane [77117-48-7] [30] (**9**).* 97% yield; colorless oil; spectral data: ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.8, −117.4, −122.8, −123.7, −124.5, −127.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H, $^3J_{H-H}$ = 7.5 Hz), 2.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.24 (t, ^3J = 5.3 Hz); 24.54 (tr, J = 23.4 Hz).

*4.1.4.12. Ethyl-4,4,4-trifluorobutanoate [371-26-6] [31] (**10**).* 88% yield; colorless oil; spectral data: ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.8 (t, ^3J = 9.4 Hz, 3F); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, $^3J_{H-H}$ = 6.7 Hz), 2.4–2.7 (m, 4H), 4.18 (q, 3H, $^3J_{H-H}$ = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 61.0, 126.4 (q, $^1J_{C-F}$ = 279.3 Hz), 170.8.

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