Supporting Information

Supercritical Carbon Dioxide as Reaction Medium for Selective Hydrogenation of Fluorinated Arenes

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Safety Warning

High-pressure experiments with compressed H_2 and CO_2 must be carried out only with appropriate equipment and under rigorous safety precautions.

Chemicals

Rh@Si-Dec was prepared according to a previously published paper.[1] CaO, Na_2CO_3, and all the organic substrates and used solvents were commercially available and used without further purification.

Reactors and reactor inlets

The catalytic tests involving $scCO_2$ were performed using an in-house engineered 30 mL autoclave (Alloy C-276, material No. 2.4819, T_{max} = 200°C, P_{max} = 400 bar), which was equipped with a Teflon inlet and a Teflon cap. (The actual volume including the upper part is 34 mL measured by CO_2 and the volume excluding the Teflon inlet, Teflon cap and magnetic stirrer is ca. 24.5 mL).

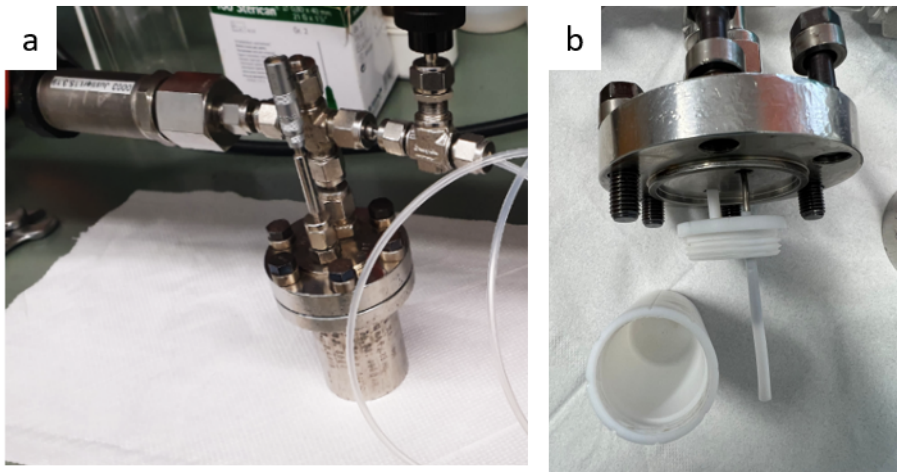


Figure S1. Picture of a) the 30 mL autoclave and b) the Teflon inlet with screw cap used for the catalytic reactions.

Synthesis of supported Rhodium nanoparticles

Synthesis of molecularly modifies silica supports (Si-R)

4 mmol of commercialized R-triethoxysilane (with R = n-decyl and perfluorodecyl) were added to a suspension of 5.0 g dehydroxylated SiO_2 in 30 mL anhydrous toluene. The reaction mixture was refluxed for 48 h under argon atmosphere at 130 °C. After cooling down, a phase separation was observed. The supernatant was removed carefully and filtered in a separate flask. The Si-R material was washed three times with anhydrous DCM and dried in vacuo at 40 °C for 6 h. The organic phases were combined and the solvent was removed under reduced pressure, in order to determine the quantity of alkyl-silane (R) not bound to the silica (Total alkyl-silane loading = theoretical loading - residual alkyl silane). Total alkylsilane loadings of ca. 0.5 mmol R/g SiO_2 were obtained using this method.

Synthesis of [Rh(allyl)$_3$]

The synthesis was accomplished according to a modified literature procedure.[2]

Synthesis of [$RhCl_3(THT)_3$]

Tetrahydrothiophene (2.2 mL, 24.9 mmol) was added dropwise to a suspension of Rhodium chloride hydrate (1 g, 3.8 mmol) in 50 mL methoxyethanol (dark red solution). The reaction mixture was refluxed overnight at 140 °C to obtain an orange/red solution. The mixture was put in the freezer (-25 °C) to cool down and an orange precipitate was formed overnight. 70 mL of distilled water was added to the solution, stirred violently then filtered over Büchner funnel. For recrystallization, 100 mL ethanol was added to the obtained crystals then heated under reflux at 90 °C until the ethanol boils and no more crystals appears. After cooling down, the mixture was put again in the freezer. After 48 h, the solvent was removed and the obtained crystals were dried under vacuum (1.6 g, 88.8% yield).

^{1}H NMR (299.6 MHz, $CDCl_3$) (Figure S11): δ (ppm) = 3.77 – 3.69 (m, 4H, S-CH2), 3.25 (m, 2H, S-CH_2), 2.90 – 2.82 (m, 6H, S-CH_2), 2.31 – 1.99 (m, 12H, CH_2-CH_2).

^{13}C NMR (75.3 MHz, $CDCl_3$) (Figure S12): δ (ppm) = 37.7 (s, S-CH_2), 37.1 (s, S-CH_2), 30.3 (s, CH_2-CH_2), 30.1 (s, CH_2-CH_2) ppm.

Synthesis of [Rh(allyl)$_3$]

A solution of [$RhCl_3(THT)_3$] (2.11 mmol, 1 g) suspended in 50 mL anhydrous diethylether was cooled down to -15 °C under vigorous stirring. Allyl magnesium chloride solution in THF (2 M, 6.70 mmol, 3.7 mL, 3.2 eq.) was diluted with 12 mL anhydrous THF then added dropwise (for $\approx$ 1 h) to the [RhCl3(THT)3] solution. The reaction mixture was stirred for 16 h at -15 °C, then filtered over celite and washed with diethylether (3 x10 mL). A yellow solution was obtained and dried under vacuum to remove the solvent. The residue was sublimated (25 °C, 30 °C, 40 °C, 50 °C) under high vacuum. [Rh(allyl)$_3$] was obtained as a bright yellow solid (0.3 g, 63% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) (Figure S13): δ (ppm) = 5.40 – 5.31 (m, 1H, CH), 3.98 (m, 2H, CH), 2.99 (d, J = 6.9 Hz, 2H, CH2), 2.77 (d, J = 6.7 Hz, 2H, CH_2), 2.61 (dd, J = 1.2 Hz, J = 11.6 Hz, 2H, CH_2), 1.62 (d, J = 11.2 Hz, 4H, CH2).

^{13}C NMR (100 MHz, CD_2Cl_2) (Figure S14): δ (ppm) = 100.5 (d, JC-Rh = 4.5 Hz, CH), 95.3 (d, JC-Rh = 4.3 Hz, CH), 48.3 (d, JC-Rh = 8.9 Hz, CH_2), 41.3 (d, JC-Rh = 9.2 Hz, CH_2) ppm.

Synthesis of Rh@Support

[Rh(allyl)$_3$] (11.30 mg, 0.05 mmol) was dissolved in 2 mL anhydrous DCM and added to a suspension of 500 mg Support (SiO_2, Si-R, SBA-15 or graphene) in 3 mL anhydrous DCM. The reaction mixture was

stirred for 1 h at room temperature under argon atmosphere and the support color changed from white to yellow/brown. The solvent was carefully removed under reduced pressure and the impregnated Support was transferred to an autoclave. The autoclave was pressurized with 50 bar H_2 (at r.t.) and heated to 100 °C for 18 h. A grey/black powder was obtained, indicating the formation of NPs. Theoretical metal loading = 0.1 mmol Rh/g Support.

Catalytic reactions

In a typical experiment, 5 mg of catalyst (1 wt.% Rh), CaO (typically 4.5 mol% as compared to the substrate) and the chosen mass of substrate were weighed in an antistatic weighing boat and transferred into a Teflon inlet. Covering one component with the others should be avoided. Finally, tetradecane was added as an internal standard directly into the Teflon inlet. The autoclave was first pressurized with 55 bar H_2 (controlled by a digital pressure meter), and then 12.3 g CO_2 ($\triangleq$ 0.5 g mL^{-1}) was added by gravimetric dosage using a balance and a high pressure compressor. Hereby it is important to control the gas flow rate in a very careful manner to avoid spreading the chemicals placed inside the Teflon inlet into the reactor parts. Purging of the pipes with the corresponding gas turned out to be important. The reaction mixture was heated to the reaction temperature while stirring at 500 rpm. After the reaction, the autoclave was cooled down in an ice bath and depressurized very slowly (ca. 45 min-60 min). The organic part inside the autoclave was extracted with acetone. (Sometimes, the gas phase was bubbled through 2 mL acetone solvent, which was cooled with a dry ice-acetone bath of -50 to -60°C to check if there was any organic residue in the CO_2 phase, this process usually lasted ca. 8 hours). Acetone solutions were analyzed separately by GC-FID and GC-MS. (There were nearly no organic compounds detected in the collected gas phase solution in all cases.). Selectivity and yields are given as average values with standard deviations from series of n experiments (n = 3 to 25).

The use of fresh well sealed Teflon inlets (see Figure S1 b) was found beneficial to avoid spreading material out of the container while pressurizing, as this may prevent catalyst and substrates from being in contact which might cause possible fluctuations in the reaction outcome. It is thus also advised to perform the flushing and depressurizing processes with extreme caution when using similar reactor setups to the one described here. We note that using reactors made from Hastelloy steel were found to be possible alternatives without the need for the Teflon inlets, albeit the formation of even small amounts of HF must be considered in appropriate safety measures.

Analytics

Gas chromatography (GC) was performed on a Shimadzu GC2030 equipped with an FID-detector. Gas chromatography coupled with a mass spectrometer (GC-MS) were performed on a Shimadzu QP2020. The determination of the yields was done by injecting the reaction mixture into the GC. The product identifications was achieved by injecting the pure products or by GC-MS.

Different conditions and equipment settings were used for the different substrates.

Parameters of GC-method used to analyze the conversion of substrates: 4-fluorophenol (**1**); 2,4-difluorophenol (**2**); 3-5-difluorophenol (**3**); 3,4,5-difluorophenol (**4**); 4-fluoroaniline N-Boc protected (**13**).

Stationary Phase (Column) from Agilent	RTX-1 (0.25 µm, 0.25 mm, 30 m)
Mobile Phase (Carrier Gas)	He
Flow Control Mode Linear Velocity	30 $cm \cdot sec^{-1}$
Injection Volume	1 µL
Injector Temperature	250 °C
Split Ratio	25
Temperature Program	90 °C for 5 min, then with 10 °C/min to 250 °C (keep constant for 15 min)
Detector Temperature	260 °C

Parameters of GC-method used to analyze the conversion of substrates: methyl-2-fluorobenzoate (**5**); methyl-4-fluorobenzoate (**6**); methyl-2,4-difluorobenzoate (**7**); methyl-2,4,5-trifluorobenzoate (**8**).

Stationary Phase (Column) from Agilent	RTX-170 (S51) (0.25 µm, 0.25 mm, 30 m)
Mobile Phase (Carrier Gas)	He
Flow Control Mode Linear Velocity	40 $cm \cdot sec^{-1}$
Injection Volume	0.5 µL
Injector Temperature	270 °C
Split Ratio	25
Temperature Program	50 °C to 130 °C (10 °C/min), then to 270 °C (25 °C/min), keep constant for 15 min
Detector Temperature	275 °C

Parameters of GC-method used to analyze the conversion of substrates: 4-fluorobenzoic acid (**9**); 4-fluorodiphenyl ether (**10**); 4-fluoroanisole (**11**); 4-fluoro-N-methylbenzamide (**12**).

Stationary Phase (Column) from Agilent	CP-WAX-52CB (0.25 µm, 0.25 mm, 30 m)
Mobile Phase (Carrier Gas)	He
Flow Control Mode Linear Velocity	50 $cm \cdot sec^{-1}$
Injection Volume	1 µL
Injector Temperatue	250 °C
Split Ratio	25
Temperature Program	50 °C to 250 °C (10 °C/min), keep constant for 15 min
Detector Temperature	260 °C

Solubility test

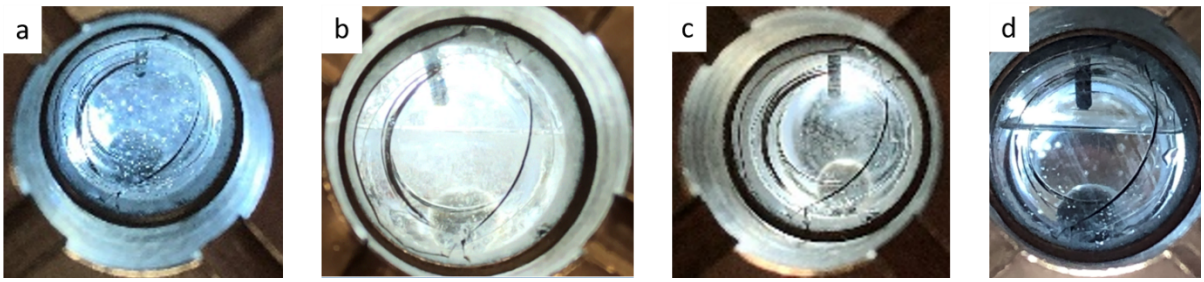


Figure S2. Taken snapshots from the window autoclave under reaction conditions (with 5 mg Rh@Si-Dec, 7 mg CaO and 22.4 mg 4-fluorophenol inside): (a) after flushing with 55 bar H_2, (b) after further flushing with 0.5 $g.mL^{-1}$ CO_2, (c) after heating to 80 °C, (d) after reaction at 80 °C for 1 h and cooling down to room temperature.

Catalysts characterization

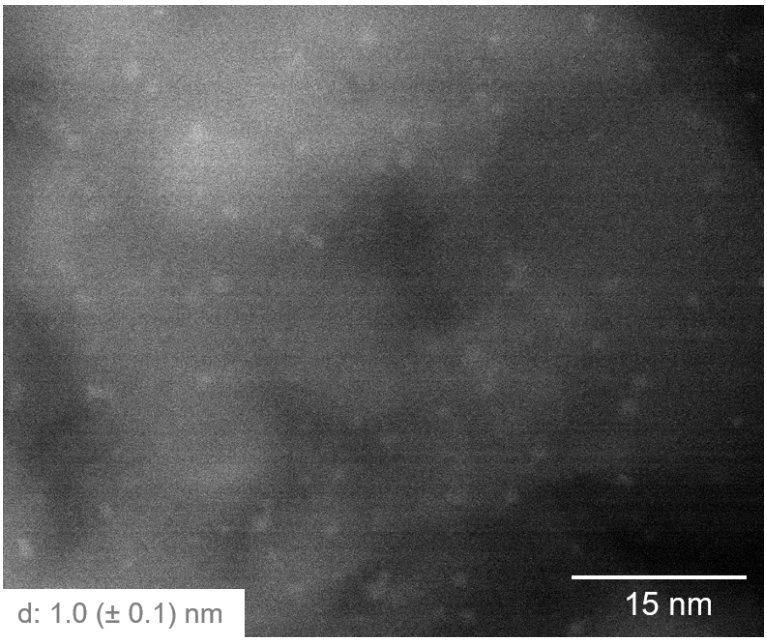


Figure S3. Transmission Electron Microscopy (TEM) image of Rh@SiO_2 with a mean particle size of 1.0 (±0.1) nm.

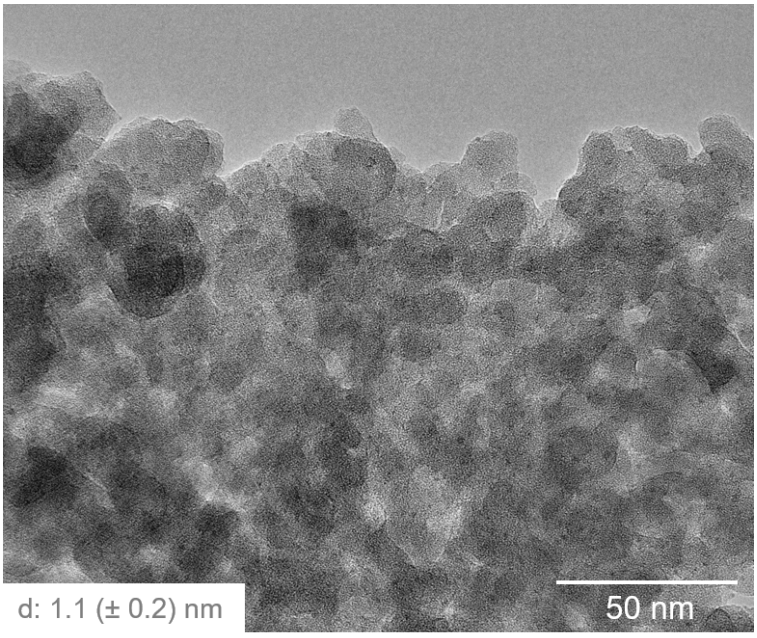


Figure S4. Transmission Electron Microscopy (TEM) image of Rh@Si-Fdec with a mean particle size of 1.1 (±0.2) nm.

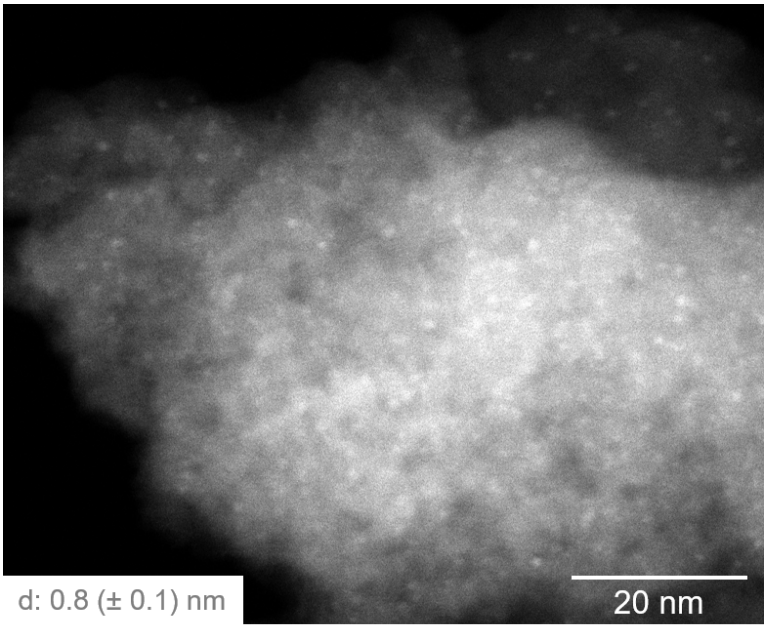


Figure S5. Scanning Transmission Electron Microscopy with High Annular Dark Field (STEM-HAADF) image of Rh@SBA-15 with a mean particle size of 0.8 (±0.1) nm.

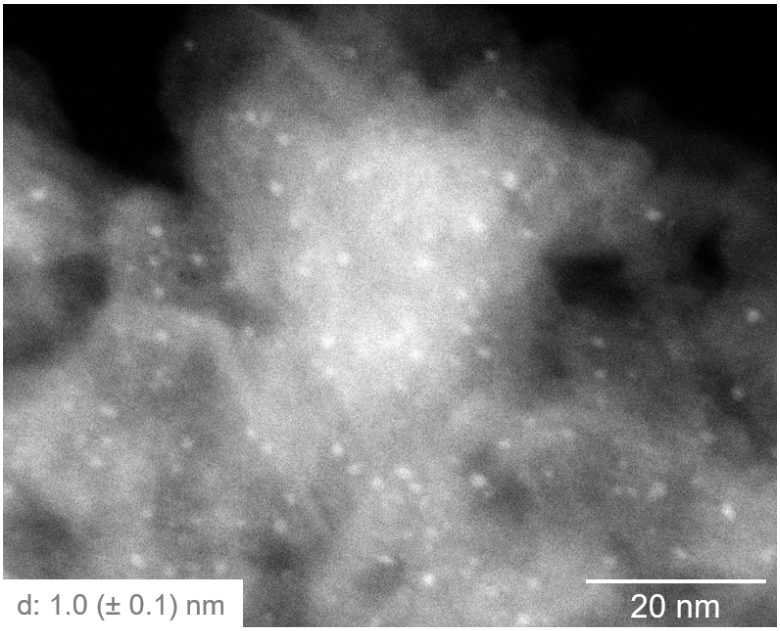


Figure S6. Scanning Transmission Electron Microscopy with High Annular Dark Field (STEM-HAADF) image of Rh@Graphene with a mean particle size of 1.0 (±0.1) nm.

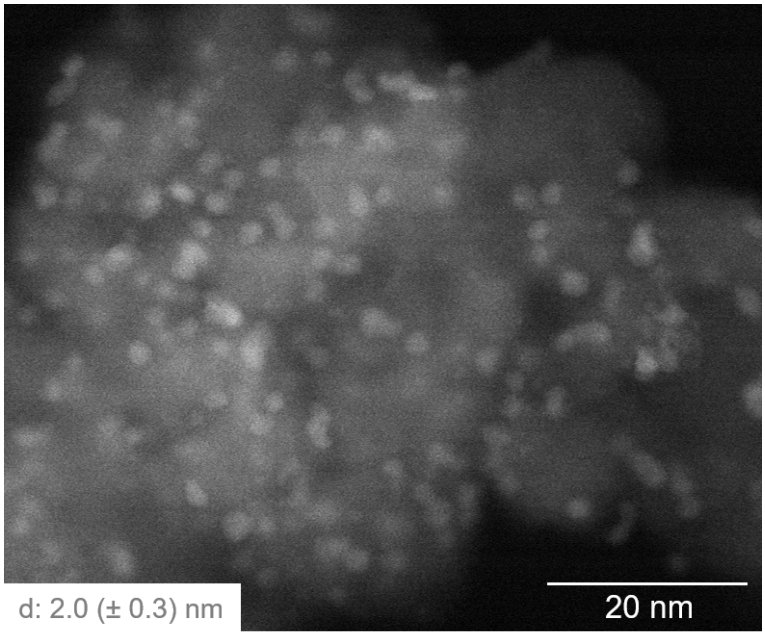


Figure S7. Scanning Transmission Electron Microscopy with High Annular Dark Field (STEM-HAADF) image of Rh@Al_2O_3 with a mean particle size of 2.0 (±0.3) nm.

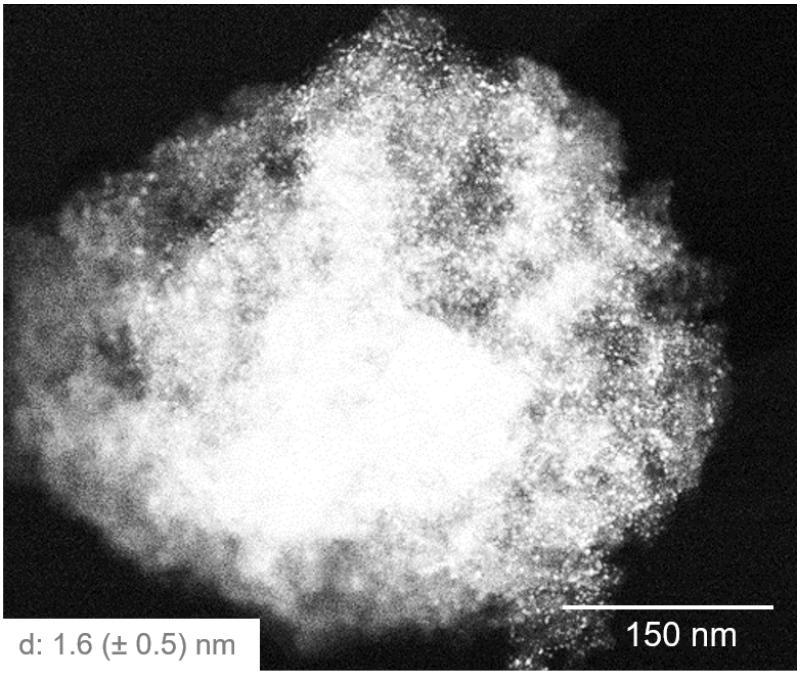


Figure S8. Scanning Transmission Electron Microscopy with High Annular Dark Field (STEM-HAADF) image of Rh@C with a mean particle size of 1.6 (±0.5) nm.

Table S1: BET and ICP-OES data for the different catalysts tested.

Entry	Catalyst	N_2 adsorption		NPs size [nm]	Rh loading by ICP [wt. %]
		BET Surface area [m^2/g]	Pore diameter [nm]		
1	Rh@SiO_2	453.0	7.0	1.2 ± 0.2	0.98
2	Rh@Si-Fdec	295.3	7.5	1.1 ± 0.2	0.81
3	Rh@Si-Dec	316.0	7.8	1.0 ± 0.1	0.90
4	Rh@SBA-15	708.6	4.9	0.8 ± 0.6	0.96
5	Rh@Graphene	1550.1	1.1	1.0 ± 0.1	0.98
6[a]	Rh@Al_2O_3	163.2	11.4	2.0 ± 0.2	-
7[a]	Rh@C	708.6	2.9	1.6 ± 0.5	-

[a]Commercial catalysts with 5 wt% Rh loading.

Table S2: Hydrogenation of 4-fluorophenol (**1**) in $scCO_2$ using different Rh@Support catalysts.

Catalyst	X (%)	S_{1a} (%)	Y (%)			
			1a	**1b**	**1c**	**1d**
none	0	-	0	0	0	0
Rh@Si-Fdec	91 ±9	50	45 ±5	26 ±4	9 ±1	10 ±1
Rh@SiO_2	>99	60 ±5	60 ±5	35 ±4	3 ±1	2
Rh@SBA-15	82 ±18	41 ±6	35 ±12	26 ±10	7 ±2	14 ±2
Rh@graphene	36 ±20	30 ±2	11 ±6	9 ±6	6 ±3	10 ±5
Rh@Al_2O_3[a]	98 ±1	26 ±2	26 ±2	41 ±2	12 ±1	19 ±1
Rh@C[a]	83 ±17	18 ±5	16 ±7	44 ±17	4 ±0	18 ±6

Reaction conditions: Catalyst (5 mg, $0.5 \cdot 10^{-3}$ mmol Rh), 4-fluorophenol (22.4 mg, 0.2 mmol, 400 eq.), $scCO_2$ (0.5 $g.mL^{-1}$, ≈ 12.5 g), CaO (7 mg), 55 bar H_2, 80 °C, 1 h, 500 rpm. X = conversion, S = selectivity, Y = yield, determined by GC-FID using tetradecane as an internal standard. [a]for 5 wt% Rh@Al_2O_3 and 5 wt% Rh@C, 112 mg (1 mmol) 4-fluorophenol and 35 mg CaO were used.

Synthetic approach evaluation

4-fuorocyclohexan-1-ol was selected as a target product for this evaluation. The selective hydrogenation approach we propose in this study was systematically compared to a typical conventional method. The detailed synthetic routes are shown in Figures S9 and S10. For both synthetic approaches, the starting point is a widely available and cheap commercial compound, which preparation is thus not included in the evaluation.

From the green chemistry principles, five parameters were chosen to rank the pathways, *i.e.* the number of steps (Steps), the atom economy (AE), the overall reaction yield (Y), the hazardous nature of the reagents (Safety) and the economical aspect (difference of value between the product and the starting substrate Eco).

The *AE* was determined using the following formula:

$$AE = \frac{total\ molecular\ weight\ of\ desired\ product}{total\ molecular\ weight\ of\ all\ reactants} \cdot 100$$

The *Safety* parameter was evaluated qualitatively by ranking the different pathways on a scale from one (= most hazardous) to five (= least hazardous) based on the hazardous nature[3] of the used chemicals as shown in Table S3.

The parameter *Eco* is based on the difference in price between the starting materials and the desired product. Our approach provides a better difference and the *Eco* parameter is set arbitrarily to 5. For the conventional pathway, the addition of value is still attractive, and *Eco* was thus set to 4.

Parameters *Y* and *Steps* are elucidated on Figures S9 and S10.

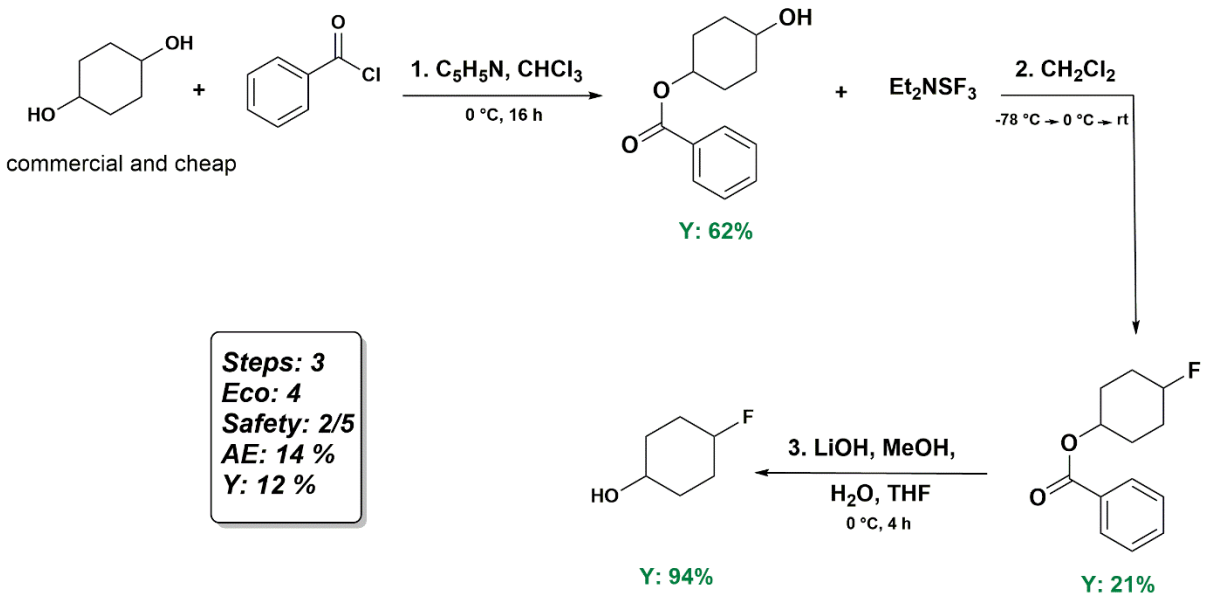


Figure S9. Conventional multistep synthesis pathway for 4-fluorocyclohexan-1-ol.[4]

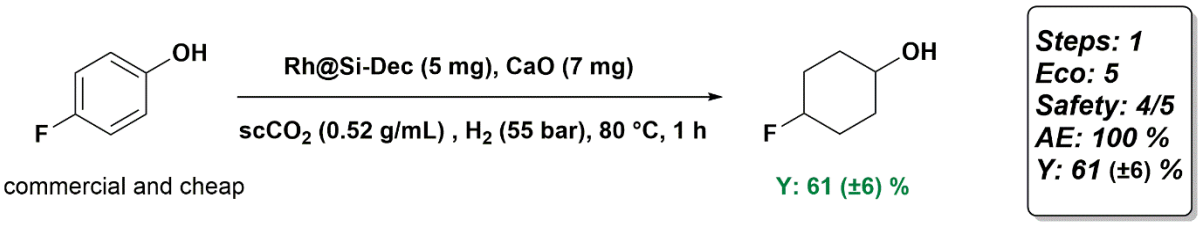


Figure S10. Selective hydrogenation of 4-fluorophenol to 4-fluorocyclohexan-1-ol, this work.

Table S3: Ranking of chemicals.

GHS ranking	
1	explosive, oxidizing, toxic, health hazard
2	harmful, flammable, environmental, corrosive (combination of 3 hazards)
3	harmful, flammable, environmental, corrosive (combination of 2 hazards)
4	harmful, flammable, environmental, corrosive (1 hazard)
5	-

Chemical	**CAS**	**Mw [g/mol]**	**Price [€/g]**	**GHS Hazard**
1,4-cyclohexanediol	556-48-9	116.16	0.48	Harmful
Benzoyl chloride	98-88-4	140.57	0.012	Toxic + Corrosive
pyridine	110-86-1	79.1	0.06	Toxic + Flammable
$CHCl_3$	67-66-3	119.38	-	Toxic
Et_2NSF_3	38078-09-0	161.19	32.8	Flammable + Corrosive
CH_2Cl_2	75-09-2	84.93	-	Toxic
LiOH	1310-65-2	23.95	0.8	Toxic + Corrosive
MeOH	67-56-1	32.04	-	Flammable + Harmful
THF	109-99-9	72.11	-	Flammable + Toxic + Harmful
4-fluorophenol	371-41-5	112.10	0.9	Harmful
4-fluorocyclohexanol	74058-19-8	118.15	642.40	***Product***

NMR characterization for the synthesized [$RhCl_3(THT)_3$] and [$Rh(allyl)_3$]

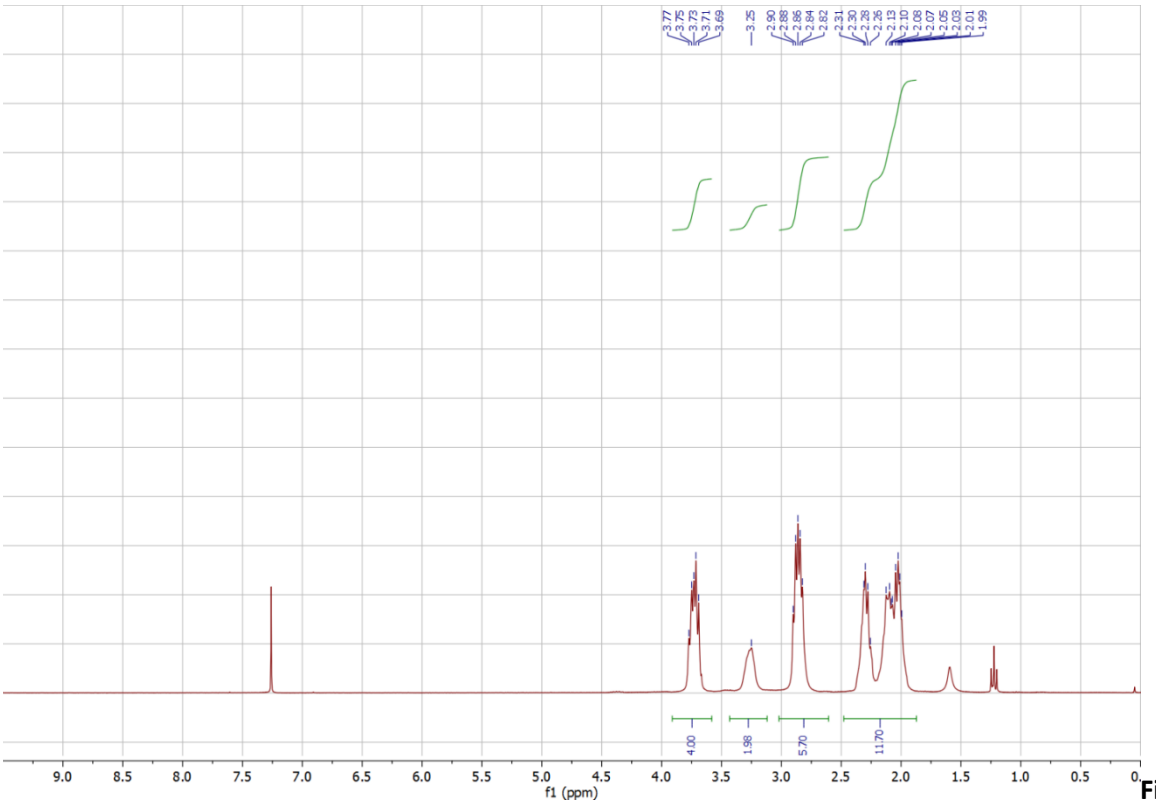


Figure S11. ^{1}H NMR spectrum of [$RhCl_3(THT)_3$] in $CDCl_3$ obtained using a 299.6 MHz spectrometer.

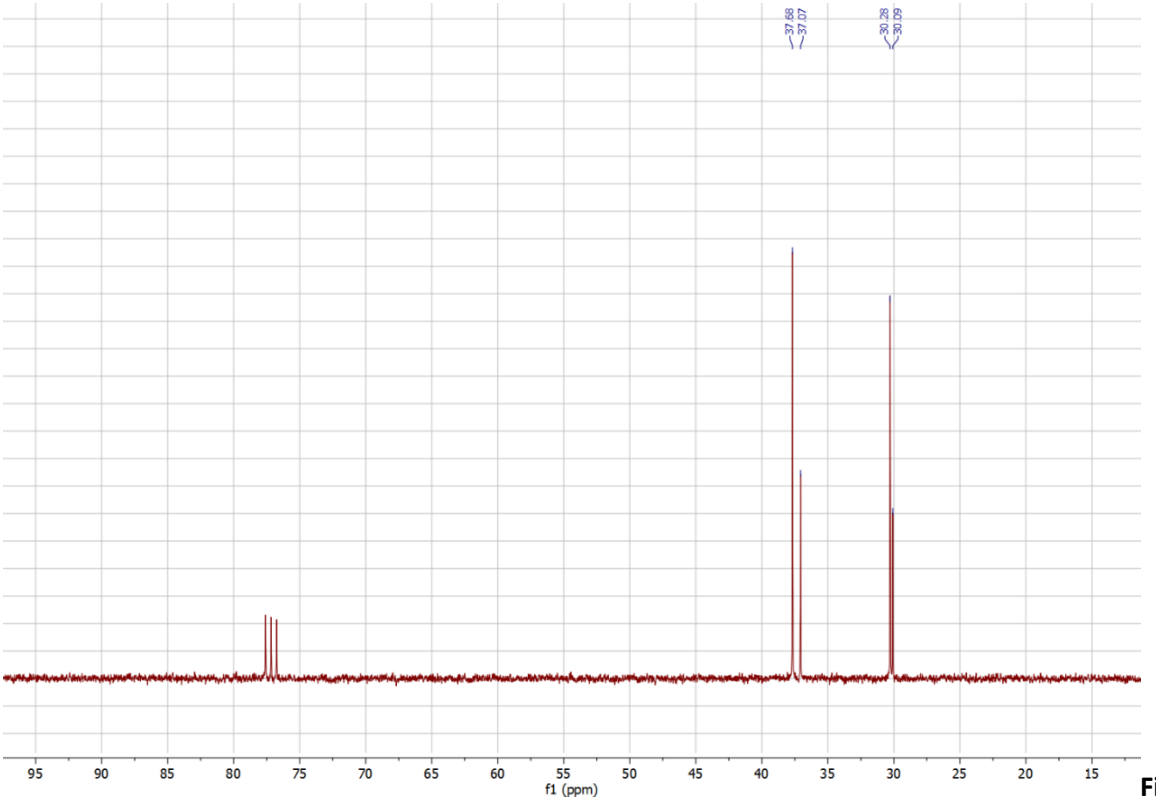
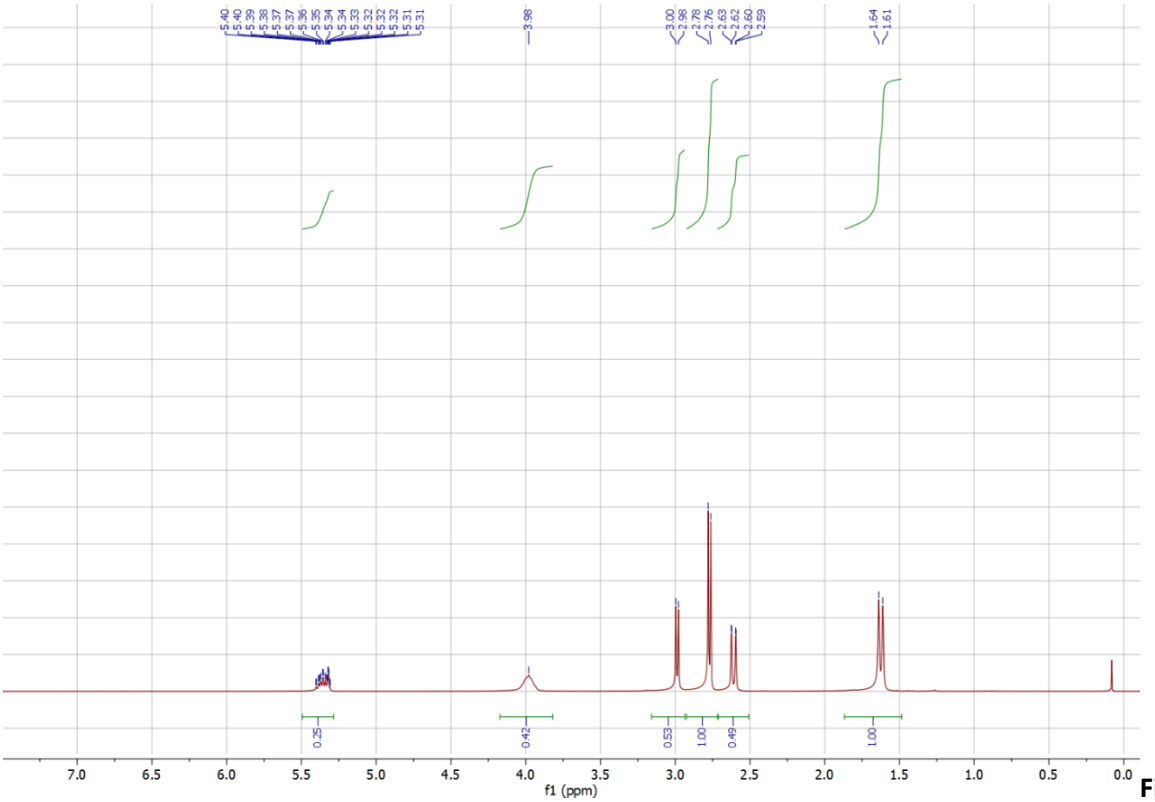
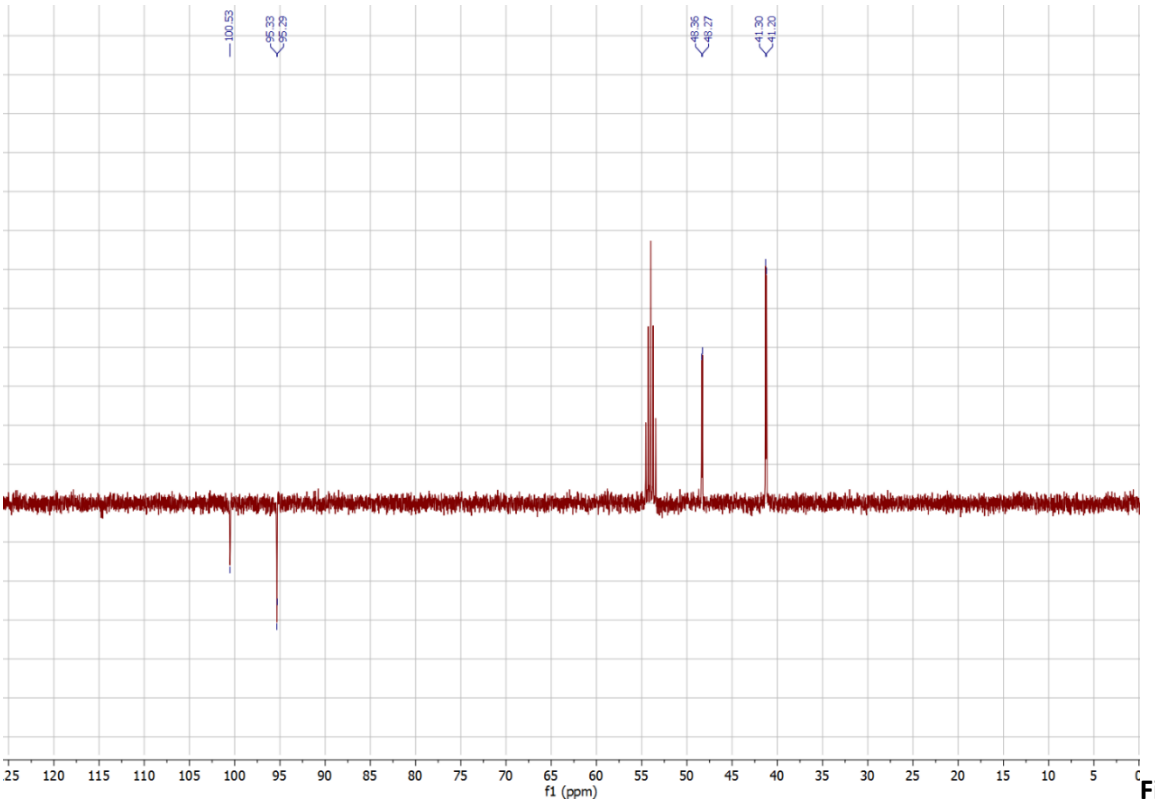


Figure S12. ^{13}C NMR spectrum of [$RhCl_3(THT)_3$] in $CDCl_3$ obtained using a 75.3 MHz spectrometer.



Figur

e S13. ^{1}H NMR spectrum of $[Rh(allyl)_3]$ in CD_2Cl_2 obtained using a 400 MHz spectrometer.

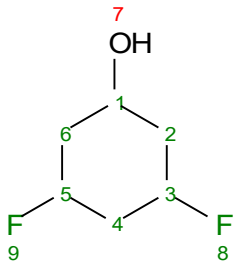


Figur

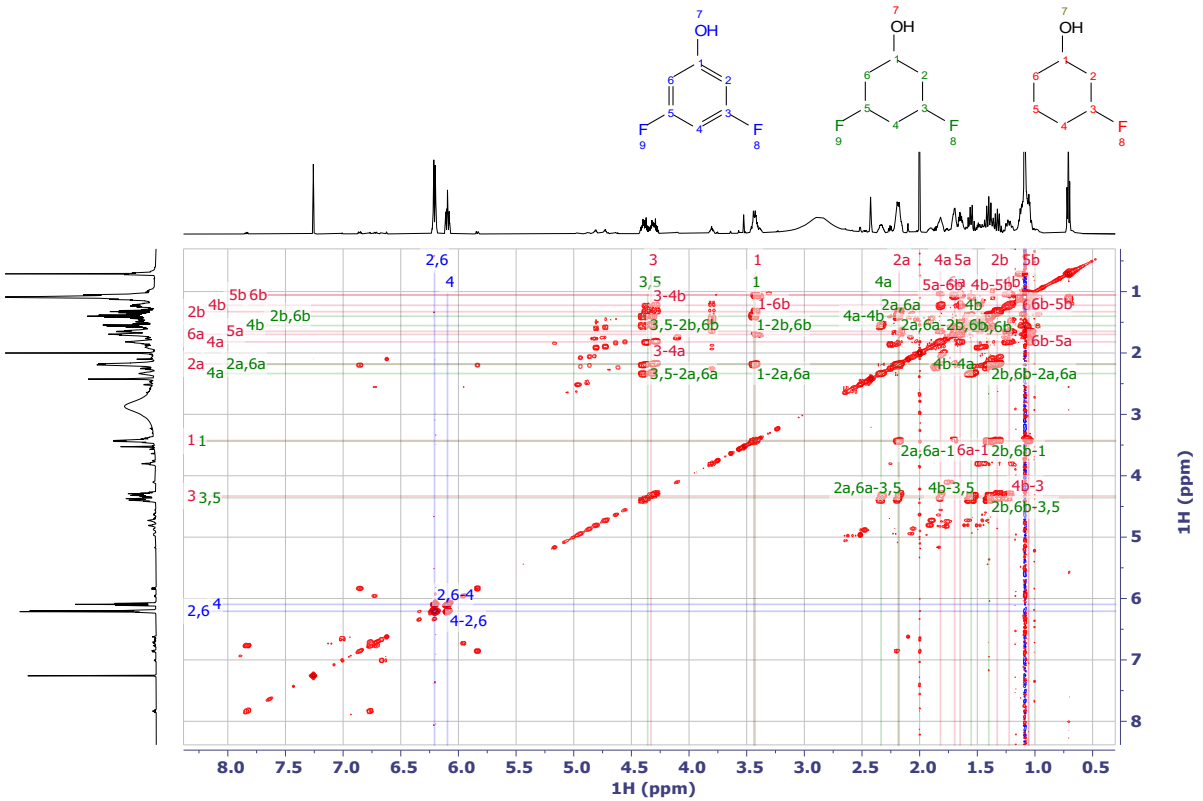
e S14. ^{13}C NMR spectrum of $[Rh(allyl)_3]$ in CD_2Cl_2 obtained using a 100 MHz spectrometer

NMR characterization for the synthesized products

3,5-difluoro-1-cyclohexanol (3a)

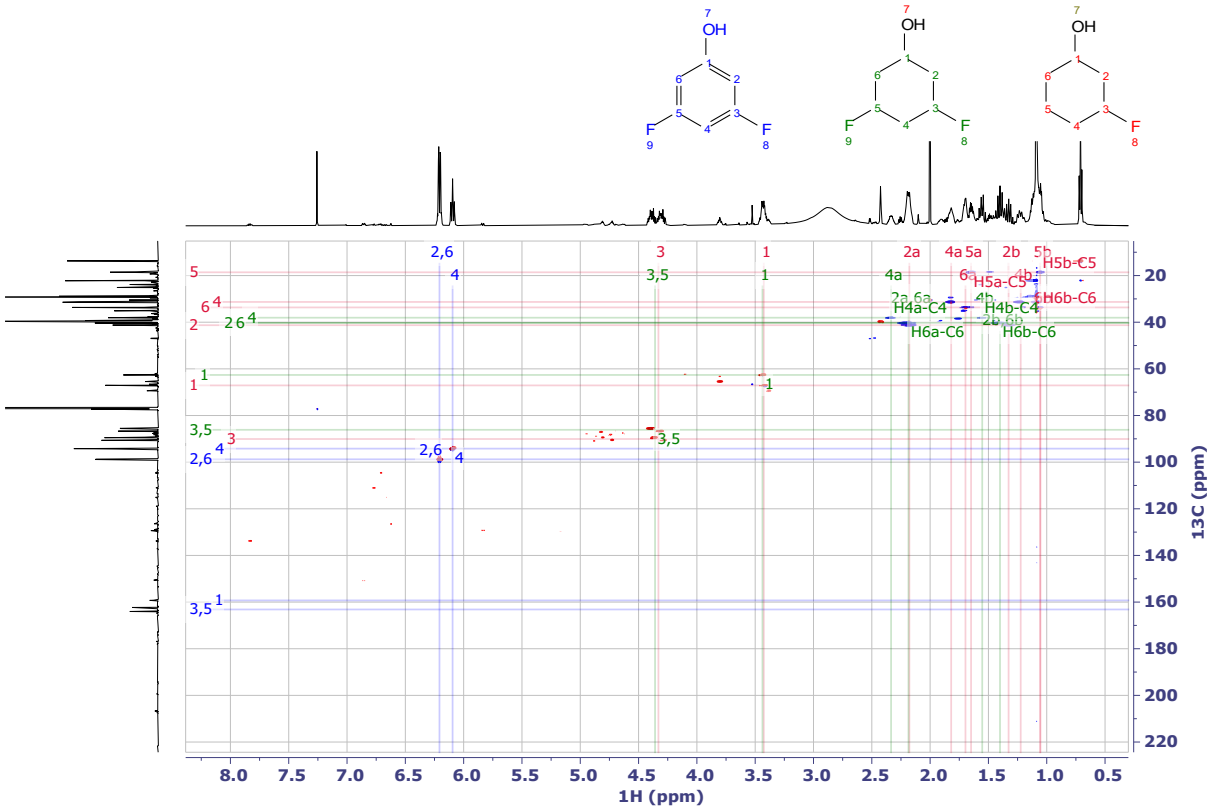


Atom	*δ* (ppm)	J	COSY	HSQC	HMBC	NOESY
1 C	62.61	15.00(8), 15.00(9)		1	2a, 2b, 3, 5, 6a, 6b	
H	3.44		2a, 2b, 6a, 6b	1	2, 3, 5, 6	2a, 3, 5, 6a
2 C	40.28			2a, 2b	1, 4a, 4b, 6a, 6b	
Ha	2.19		1, 2b, 3	2	1, 3, 4, 6	1, 3
Hb	1.40		1, 2a, 3	2	1, 3, 4, 6	
3 C	86.13	173.70(8), 16.70(9)		3	1, 2a, 2b, 4a, 4b, 5	
H	4.36	47.40(8F)	2a, 2b, 4a, 4b	3	1, 5	1, 2a, 4a
4 C	38.06	19.90(8), 19.90(9)		4a, 4b	2a, 2b, 6a, 6b	
Ha	2.33		3, 4b, 5	4	2, 3, 5, 6	3, 5
Hb	1.55		3, 4a, 5	4	2, 3, 5, 6	
5 C	86.13	16.70(8), 173.70(9)		5	1, 3, 4a, 4b, 6a, 6b	
H	4.36	47.40(9F)	4a, 4b, 6a, 6b	5	1, 3	1, 4a, 6a
6 C	40.28			6a, 6b	1, 2a, 2b, 4a, 4b	
Ha	2.19		1, 5, 6b	6	1, 2, 4, 5	1, 5
Hb	1.40		1, 5, 6a	6	1, 2, 4, 5	
7 O						
H						
8 F	-179.46	47.40(3H), 173.70(3), 16.70(5), 15.00(1), 19.90(4)				
9 F	-179.46	47.40(5H), 16.70(3), 173.70(5), 15.00(1), 19.90(4)				



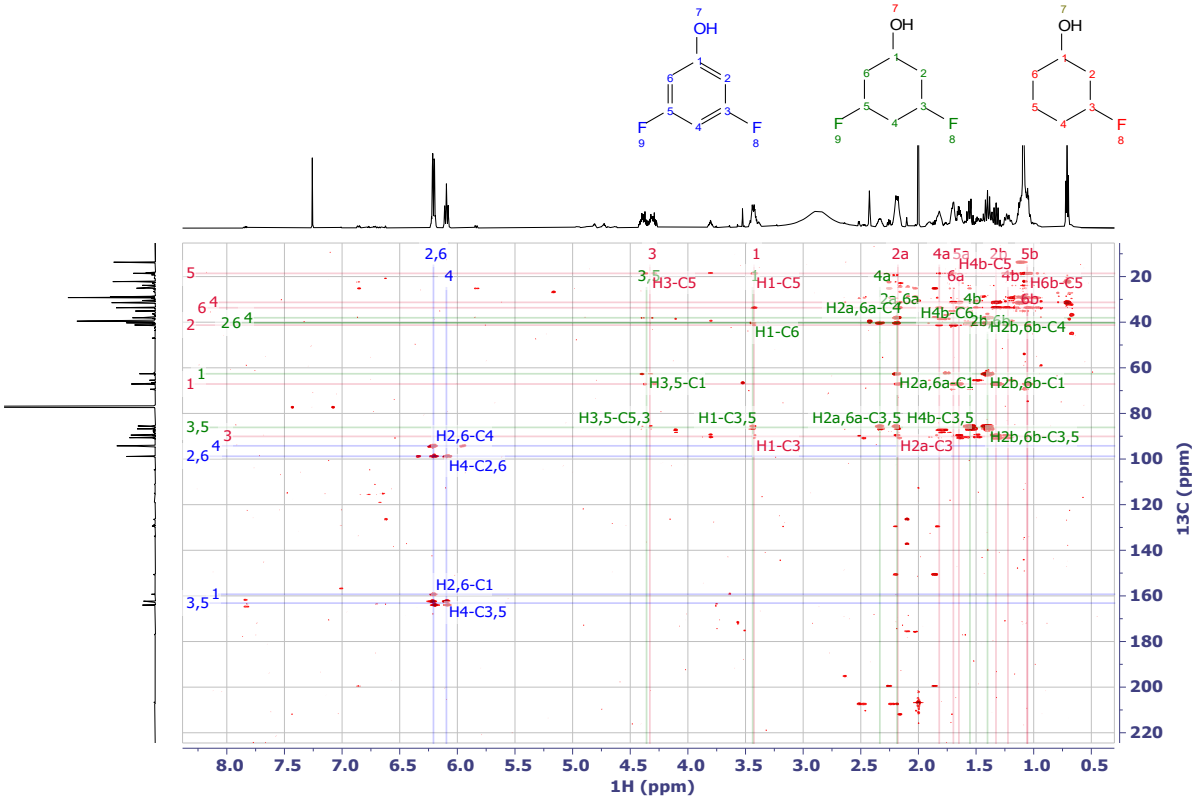
qiaqd10004.12.1.2rr — qiaqd10004 — CDCl3; 298.0 K; 20 mg; 5 mm — 1H (cosygpppqf) — AV600neo (cryoBBO) — 25.11.21 11:26:45

Figure S15. ^{1}H-^{1}H COSY spectrum of 3,5-difluorophenol and the corresponding hydrogenation products in $CDCl_3$ using a 600 MHz spectrometer.



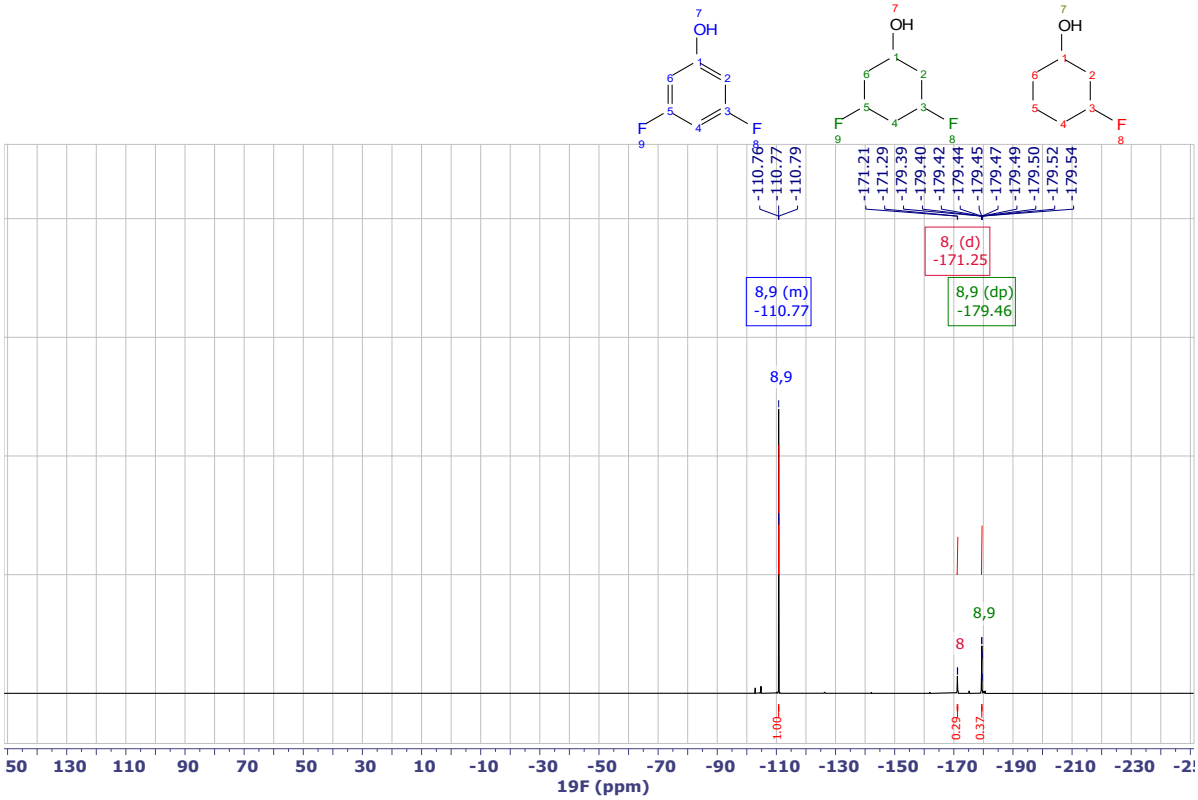
qiaqd10004.14.1.2rr — qiaqd10004 — CDCl3; 298.0 K; 20 mg; 5 mm — 1H-13C (hsqcedetgpsisp2.3) — AV600neo (cryoBBO) — 25.11.21 11:13:57

Figure S16. ^{1}H-^{13}C HSQC spectrum of 3,5-difluorophenol and the corresponding hydrogenation products in $CDCl_3$ using a 600 MHz spectrometer.



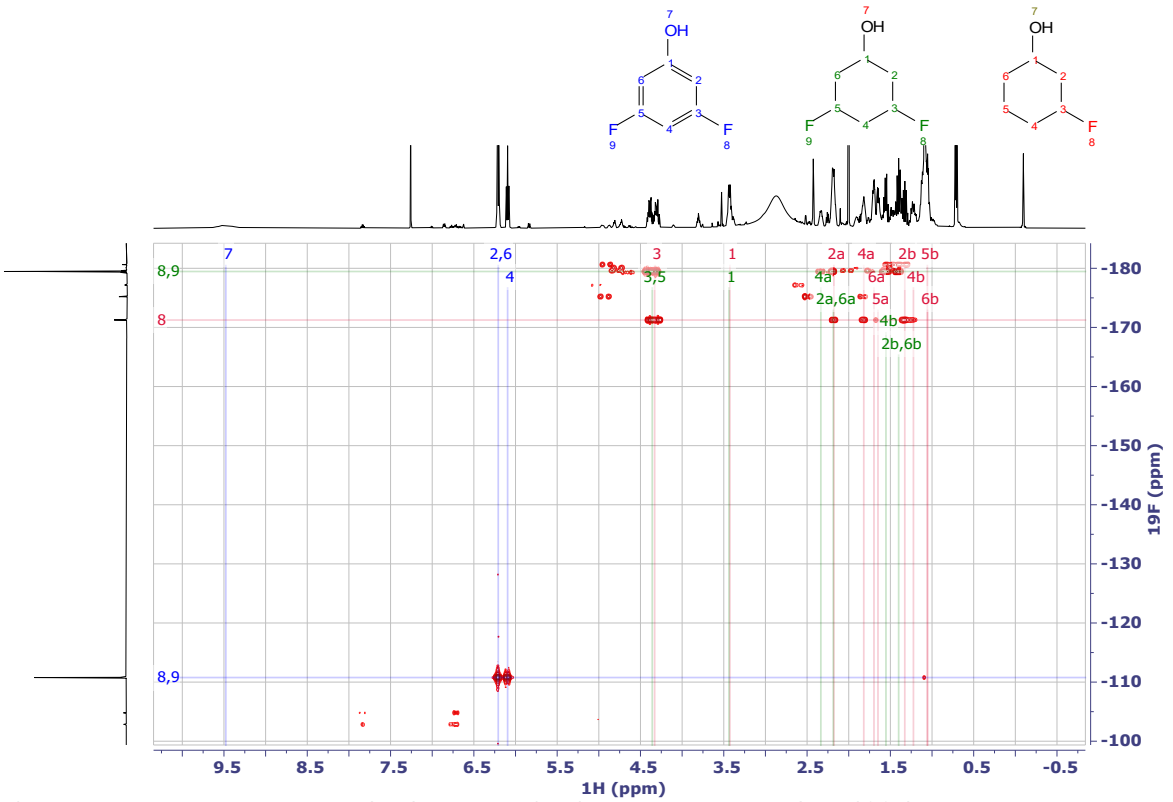
qiaqd10004.15.1.2rr — qiaqd10004 — CDCl3; 298.0 K; 20 mg; 5 mm — 1H-13C (hmbcetgpl3nd) — AV600neo (cryoBBO) — 25.11.21 12:06:35

Figure S17. ^{1}H-^{13}C HMBC spectrum of 3,5-difluorophenol and the corresponding hydrogenation products in $CDCl_3$ using a 600 MHz spectrometer.



qiaqd10004.17.1.1r — qiaqd10004 — CDCl3; 298.0 K; 20 mg; 5 mm — 19F (zg30) — AV600neo (cryoBBO) — 21/01/2022

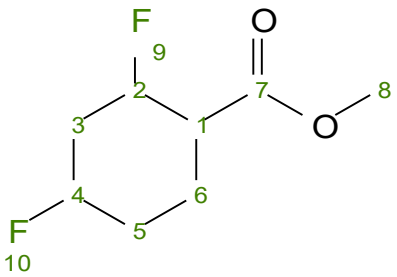
Figure S18. ^{19}F NMR spectrum of 3,5-difluorophenol and the corresponding hydrogenation products in $CDCl_3$ using a 600 MHz spectrometer.



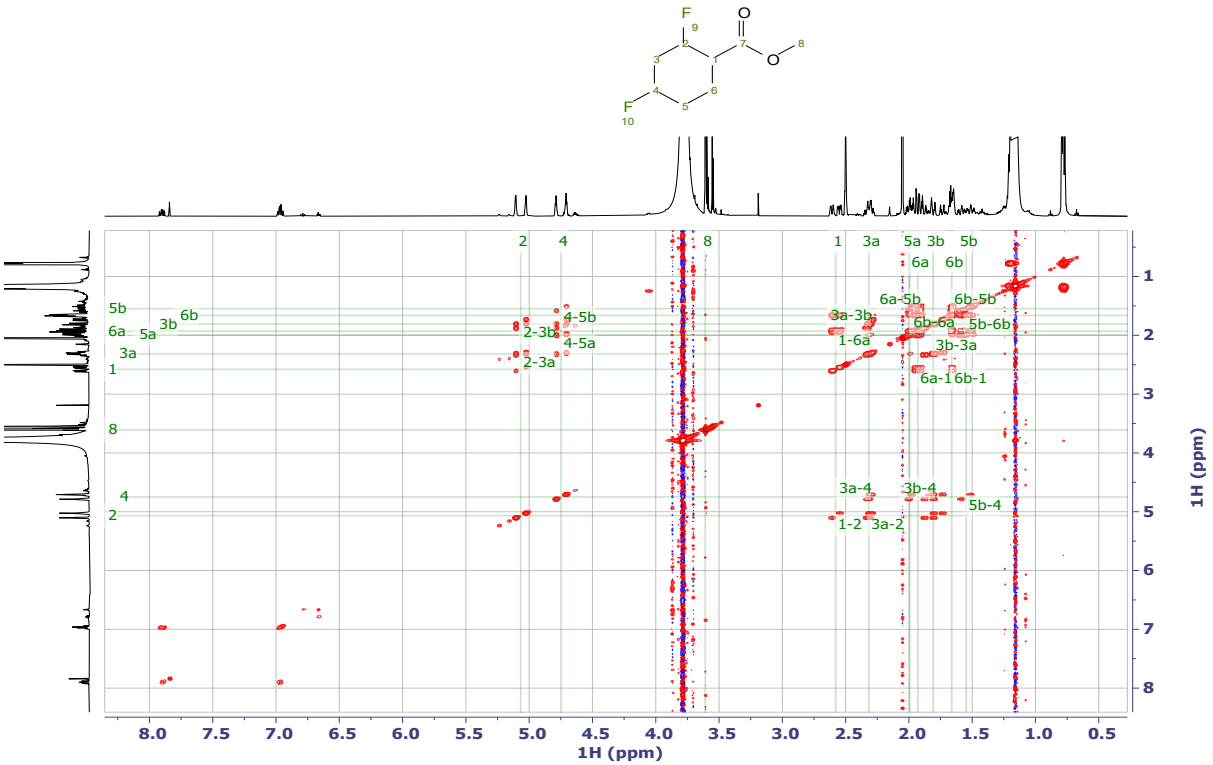
qiaqd10004_AV500as.14.1.2rr — QIA-QD-100-04 (7531) — 5 mm, CDCl3 + d6-DMSO, 70 mg — 1H-19F (cosygphfqfqn) @ 298.0 K — AV500as, BBFO —

Figure S19. ^{19}F-^{1}H COSY spectrum of 3,5-difluorophenol and the corresponding hydrogenation products in $CDCl_3$ + d6-DMSO using a 500 MHz spectrometer.

methyl 2,4-difluorocyclohexane-1-carboxylate (7a)

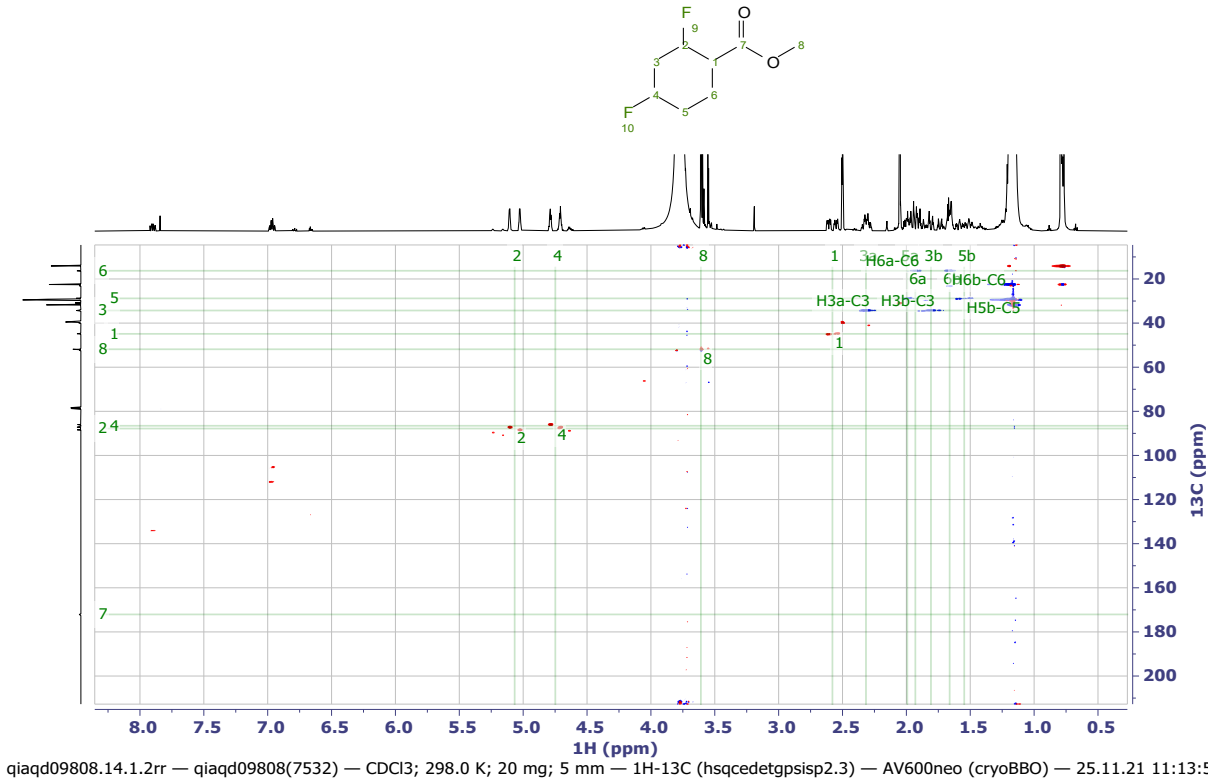


Atom	*δ* (ppm)	J	COSY	HSQC	HMBC
1 C	44.88	21.70(9)		1	3a, 5a, 5b, 6a, 6b
H	2.58	12.20(?), 4.10(?), 2.40(?)	2, 6a, 6b	1	5, 6, 7
2 C	87.81	175.10(9)		2	4, 6a, 6b
H	5.07	3.10(?), 3.10(?), 3.10(?)	1, 3a, 3b	2	4, 6, 7
3 C	34.30	20.10(9), 20.10(10)		3a, 3b	
Ha	2.32	16.00(?), 3.30(?), 3.10(?), 3.10(?)	2, 3b, 4	3	1, 5
Hb	1.81	43.10(9F), 43.10(10F), 16.00(?), 3.30(?), 3.30(?)	2, 3a, 4	3	
4 C	86.55	170.30(10)		4	2, 6a, 6b
H	4.75	3.20(?), 3.20(?), 3.20(?), 3.20(?)	3a, 3b, 5a, 5b	4	2, 6
5 C	28.80			5a, 5b	1, 3a, 6a, 6b
Ha	1.99		4, 5b, 6a, 6b	5	1
Hb	1.55		4, 5a, 6a, 6b	5	1
6 C	16.28	2.30(9), 2.30(10)		6a, 6b	1, 2, 4
Ha	1.93		1, 5a, 5b, 6b	6	1, 2, 4, 5, 7
Hb	1.66		1, 5a, 5b, 6a	6	1, 2, 4, 5, 7
7 C	172.08	1.80(9)			1, 2, 6a, 6b, 8
8 C	51.87			8	
H3	3.61			8	7
9 F	-187.66	1.80(7), 175.10(2), 21.70(1), 20.10(3), 2.30(6), 43.10(3b)			
10 F	-179.13	170.30(4), 20.10(3), 2.30(6), 43.10(3b)			



qiaqd09808.12.1.2rr — qiaqd09808(7532) — CDCl3; 298.0 K; 20 mg; 5 mm — 1H (cosygpppqf) — AV600neo (cryoBBO) — 21/01/2022

Figure S20. ^{1}H-^{1}H COSY spectrum of methyl 2,4-difluorocyclohexane-1-carboxylate in $CDCl_3$ using a 600 MHz spectrometer.



qiaqd09808.14.1.2rr — qiaqd09808(7532) — CDCl3; 298.0 K; 20 mg; 5 mm — 1H-13C (hsqcedetgpsisp2.3) — AV600neo (cryoBBO) — 25.11.21 11:13:5

Figure S21. ^{1}H-^{13}C HSQC spectrum of methyl 2,4-difluorocyclohexane-1-carboxylate in $CDCl_3$ using a 600 MHz spectrometer.

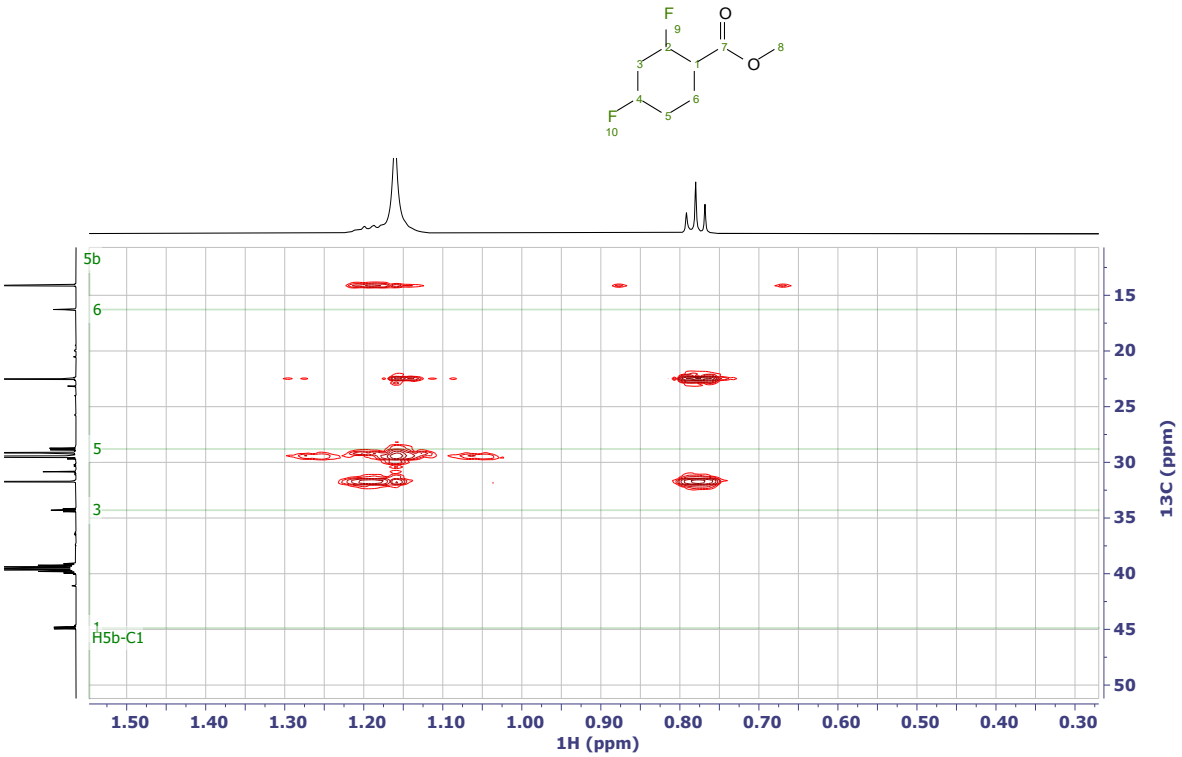
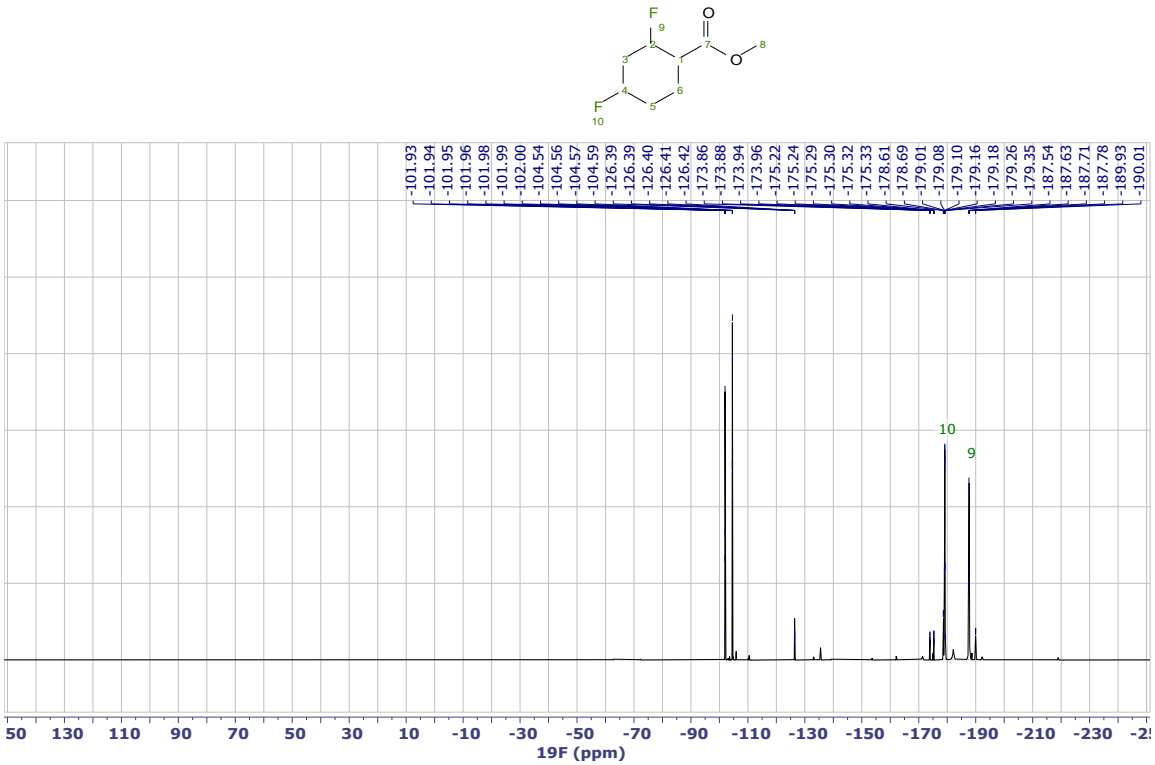
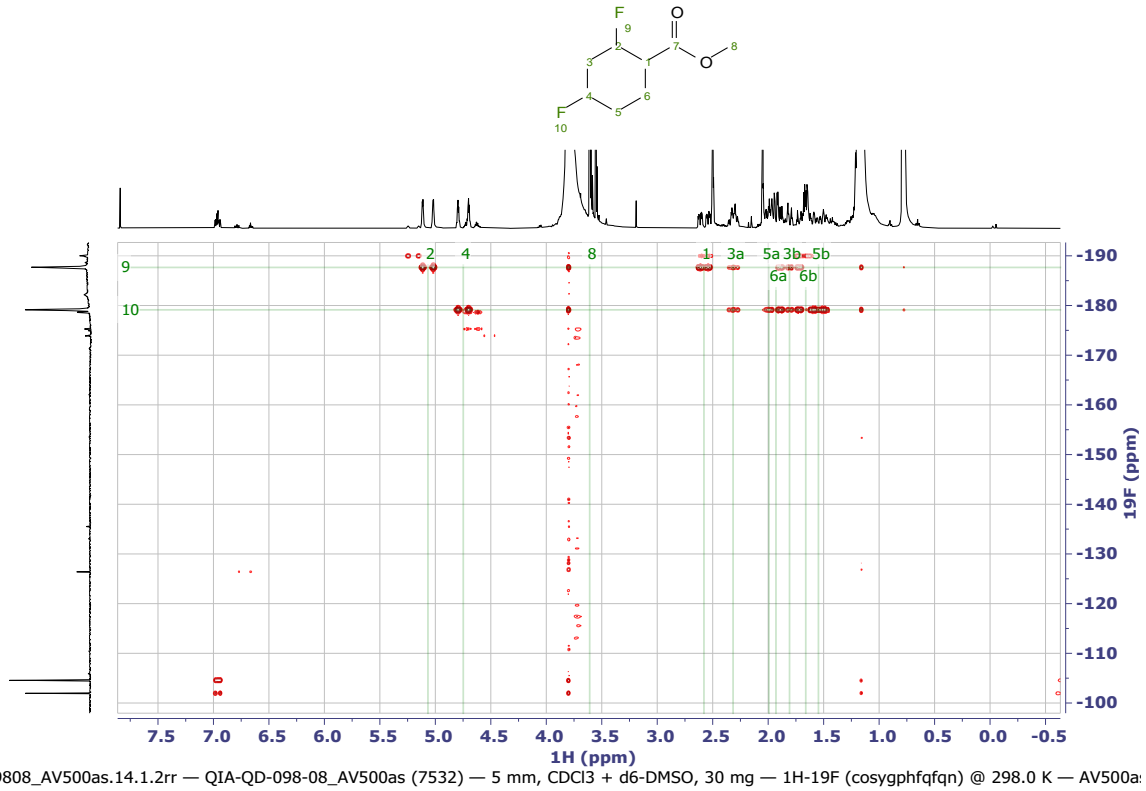


Figure S22. ^{1}H-^{13}C HMBC spectrum of methyl 2,4-difluorocyclohexane-1-carboxylate in $CDCl_3$ using a 600 MHz spectrometer.



qiaqd09808.17.1.1r — qiaqd09808 — CDCl3; 298.0 K; 20 mg; 5 mm — 19F (zg30) — AV600neo (cryoBBO) — 21/01/2022

Figure S23. ^{19}F NMR spectrum of methyl 2,4-difluorocyclohexane-1-carboxylate in $CDCl_3$ using a 600 MHz spectrometer.

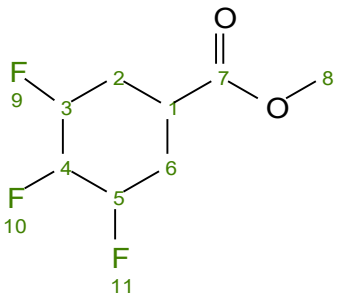


qiaqd09808_AV500as.14.1.2rr — QIA-QD-098-08_AV500as (7532) — 5 mm, CDCl3 + d6-DMSO, 30 mg — 1H-19F (cosygphfqfqn) @ 298.0 K — AV500a

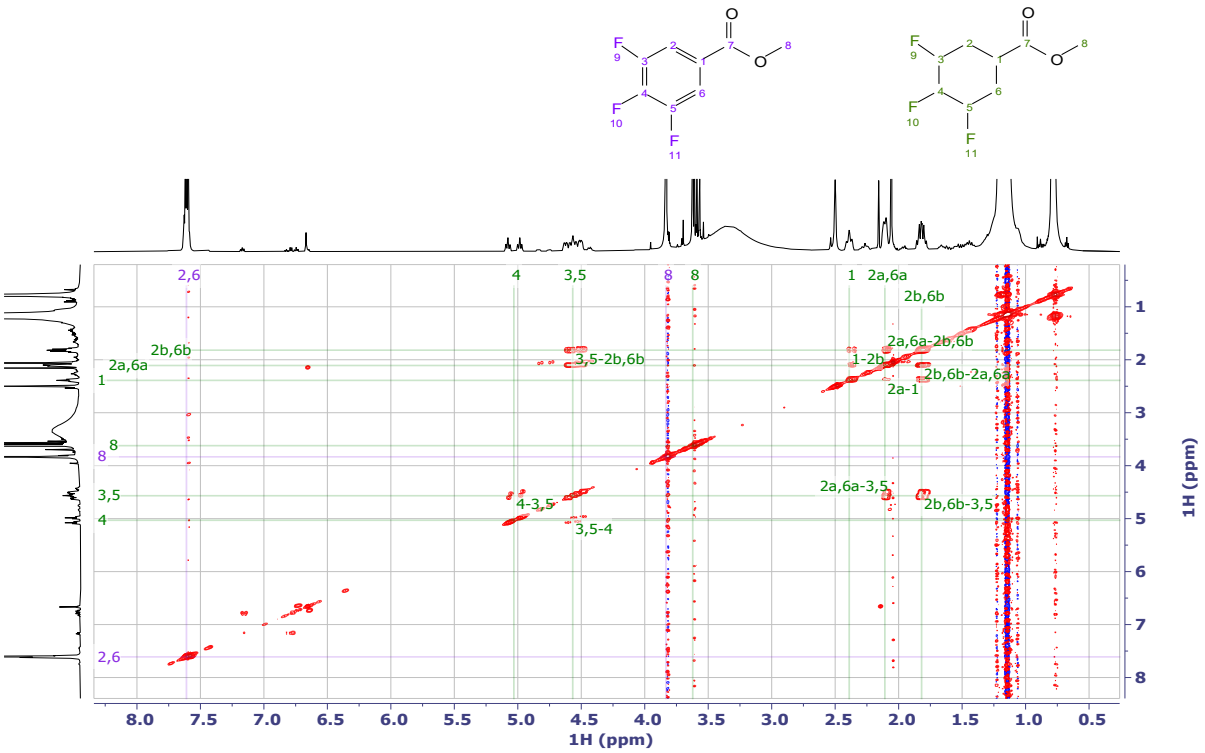
Figure S24. ^{19}F-^{1}H COSY spectrum of methyl 2,4-difluorocyclohexane-1-carboxylate in $CDCl_3$ + d6-DMSO using a 500 MHz spectrometer.

Atom	δ (ppm)	J	COSY	HSQC	HMBC
1 C	34.13	12.70(9), 12.70(11)		1	2a, 2b, 6a, 6b
H	2.39	13.20(?)	2a, 2b	1	2, 3, 5, 6, 7
2 C	26.78	21.50(9), 3.70(10)		2a, 2b	1, 3, 4, 6a, 6b
Ha	2.11		1, 2b, 3	2	1, 3, 4, 6
Hb	1.82		1, 2a, 3	2	1, 3, 4, 6, 7, 9
3 C	86.89	183.70(9), 18.20(10), 9.80(11)		3	1, 2a, 2b, 4
H	4.57	4.80(?), 12.60(?)	2a, 2b, 4	3	2, 4, 9, 10
4 C	87.88	17.60(9), 184.80(10), 17.60(11)		4	2a, 2b, 3, 5, 6a, 6b
H	5.03	9.90(?), 9.90(?)	3, 5	4	2, 3, 5, 6, 9, 10, 11

methyl 3,4,5-trifluorocyclohexane-1-carboxylate (8a)

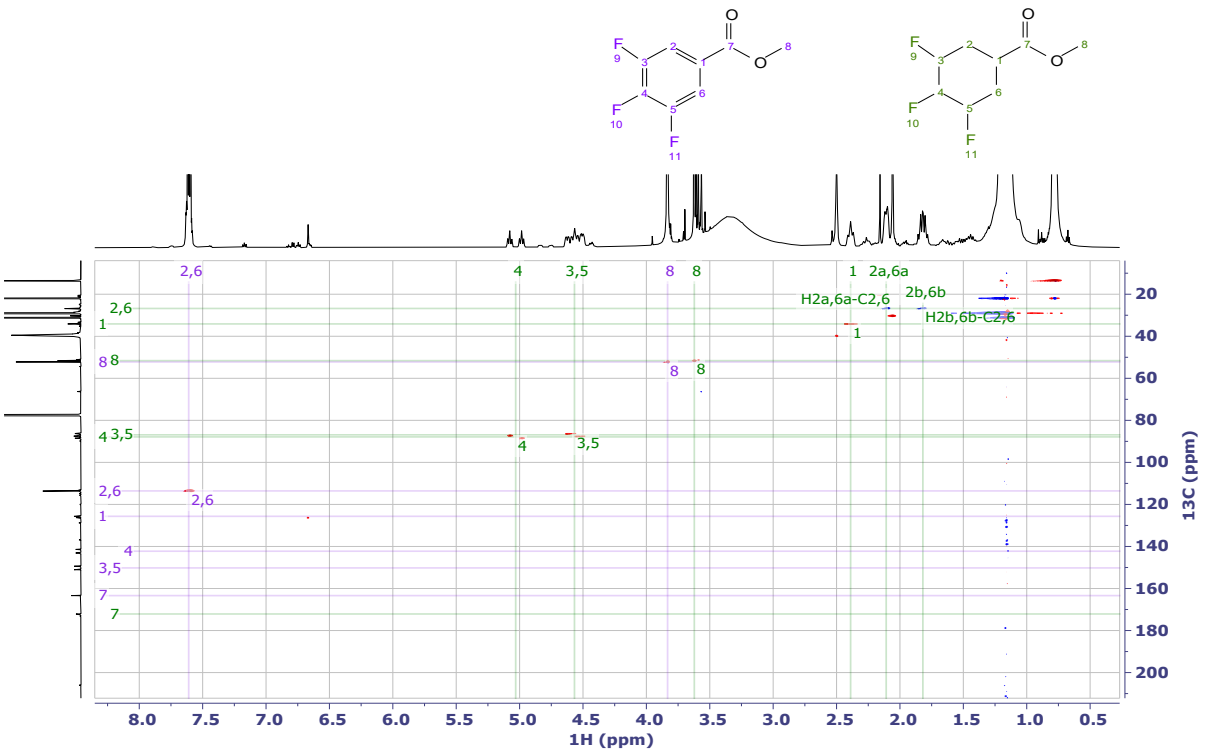


5 C	86.89	9.80(9), 18.20(10), 183.70(11)		5	1, 4, 6a, 6b
H	4.57	4.80(?), 12.60(?)	4, 6a, 6b	5	4, 6, 10, 11
6 C	26.78	3.70(10), 21.50(11)		6a, 6b	1, 2a, 2b, 4, 5
Ha	2.11		5, 6b	6	1, 2, 4, 5
Hb	1.82		5, 6a	6	1, 2, 4, 5, 7, 11
7 C	172.12	3.60(9), 3.60(11)			1, 2b, 6b, 8
8 C	51.59			8	
H3	3.62			8	7
9 F	-188.90	15.60(10), 3.60(7), 17.60(4), 183.70(3), 9.80(5), 12.70(1), 21.50(2)			2b, 3, 4
10 F	-218.91	15.60(9), 15.60(11), 184.80(4), 18.20(3), 18.20(5), 3.70(2), 3.70(6)			3, 4, 5
11 F	-188.90	15.60(10), 3.60(7), 17.60(4), 9.80(3), 183.70(5), 12.70(1), 21.50(6)			4, 5, 6b



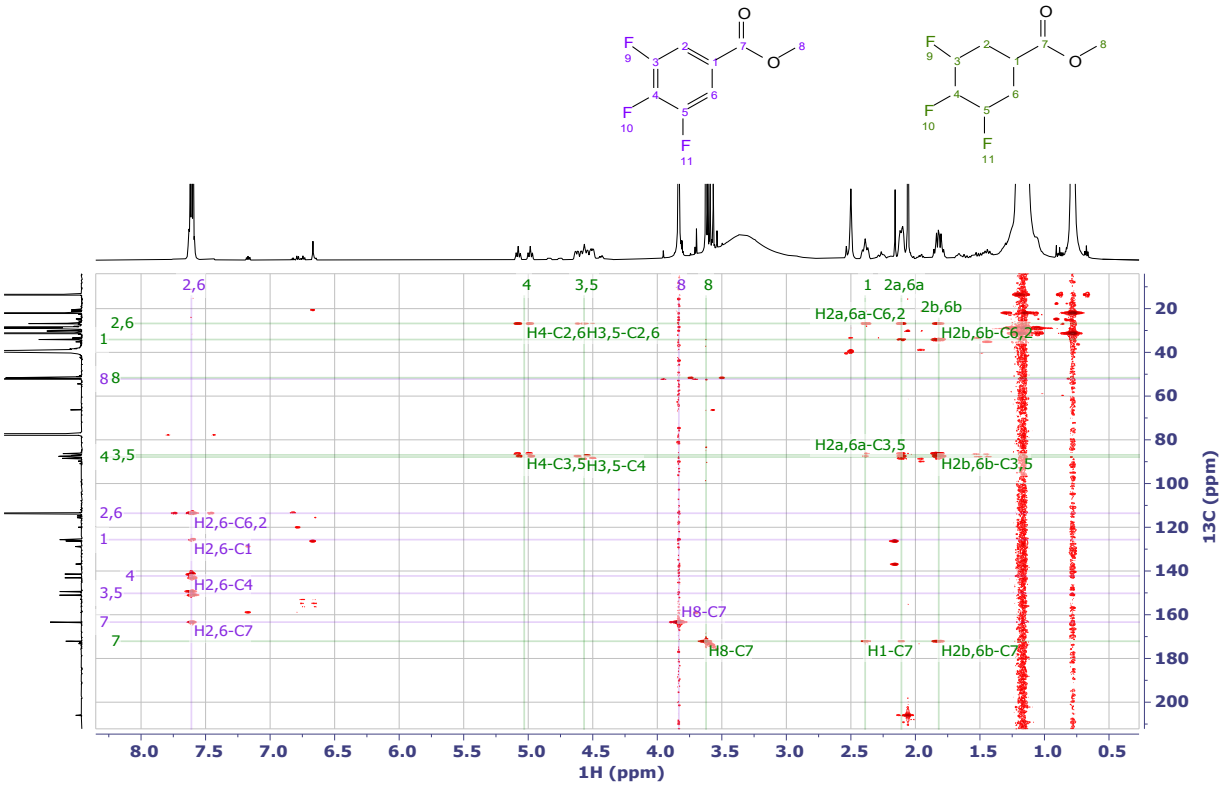
qiaqd09310.12.1.2rr — qiaqd09310 — CDCl3; 298.0 K; 20 mg; 5 mm — 1H (cosygpppqf) — AV600neo (cryoBBO) — 21/01/2022

Figure S25. ^{1}H-^{1}H COSY spectrum of methyl 3,4,5-trifluorobenzoate and methyl 3,4,5-trifluorocyclohexane-1-carboxylate in $CDCl_3$ using a 600 MHz spectrometer.



qiaqd09310.14.1.2rr — qiaqd09310 — CDCl3; 298.0 K; 20 mg; 5 mm — 1H-13C (hsqcedetgpsisp2.3) — AV600neo (cryoBBO) — 25.11.21 11:13:57

Figure S26. ^{1}H-^{13}C HSQC spectrum of methyl 3,4,5-trifluorobenzoate and methyl 3,4,5-trifluorocyclohexane-1-carboxylate in $CDCl_3$ using a 600 MHz spectrometer.



qiaqd09310.15.1.2rr — qiaqd09310 — CDCl3; 298.0 K; 20 mg; 5 mm — 1H-13C (hmbcetgpl3nd) — AV600neo (cryoBBO) — 25.11.21 12:06:35

Figure S27. ^{1}H-^{13}C HMBC spectrum of methyl 3,4,5-trifluorobenzoate and methyl 3,4,5-trifluorocyclohexane-1-carboxylate in $CDCl_3$ using a 600 MHz spectrometer.

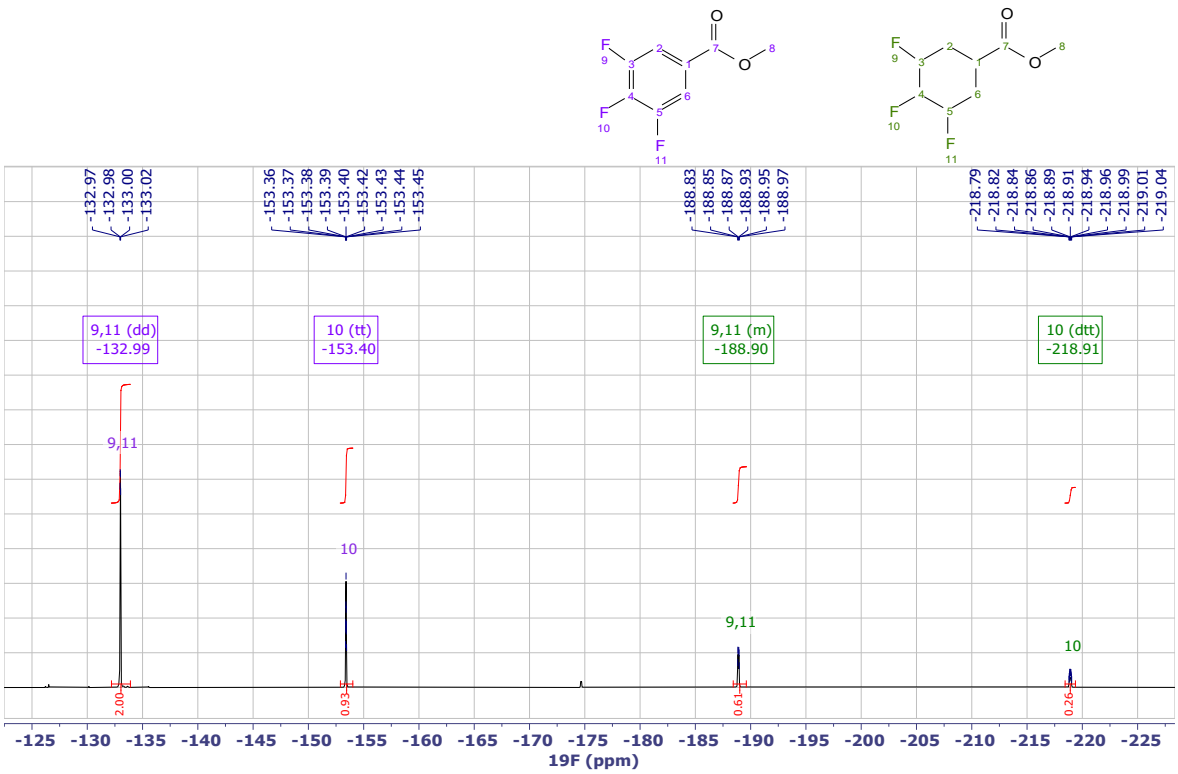
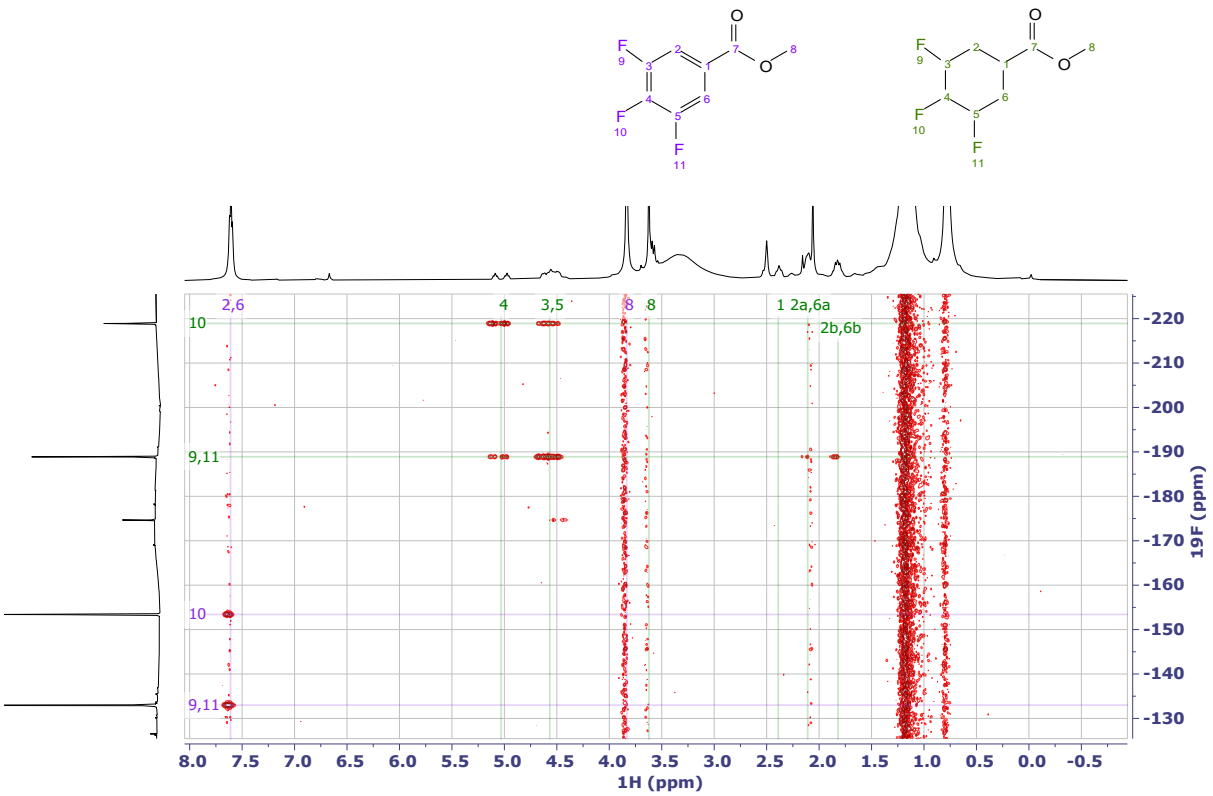


Figure S28. ^{19}F NMR spectrum of methyl 3,4,5-trifluorobenzoate and methyl 3,4,5-trifluorocyclohexane-1-carboxylate in $CDCl_3$ using a 600 MHz spectrometer.

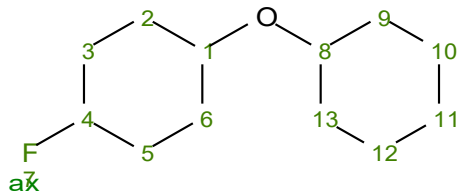


qiaqd09310_AV500as.14.1.2rr — QIA-QD-093-10_AV500as (7534) — 5 mm, CDCl3 + d6-DMSO, 30 mg — 1H-19F (cosygphfqfqn) @ 298.0 K — AV500a

Figure S29. ^{19}F-^{1}H COSY spectrum of methyl 3,4,5-trifluorobenzoate and methyl 3,4,5-trifluorocyclohexane-1-carboxylate in $CDCl_3$ + d6-DMSO using a 500 MHz spectrometer.

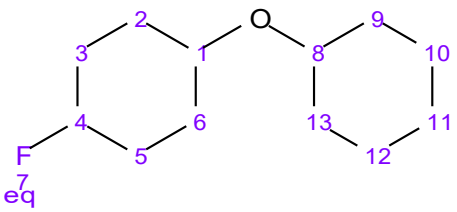
1-(cyclohexyloxy)-4-fluorocyclohexane (10a)

The desired compound is a mixture of 2 stereo isomers



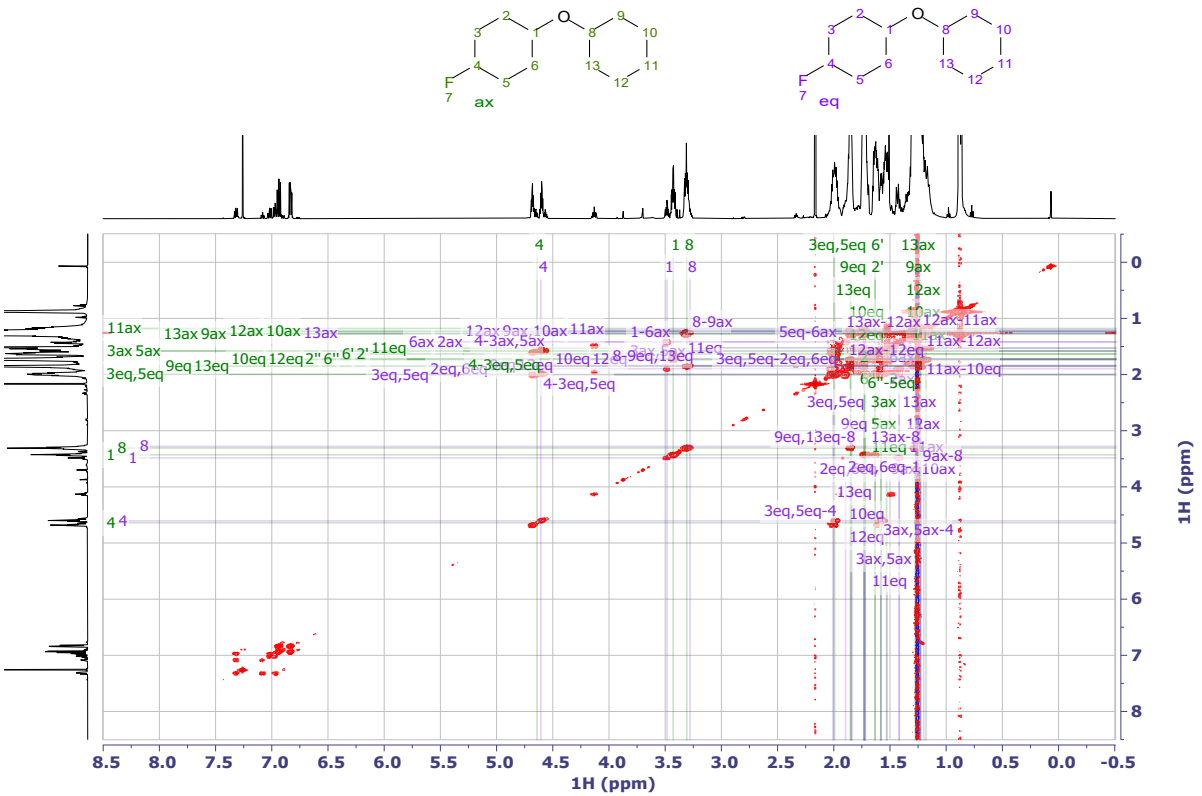
Atom	δ (ppm)	J	COSY	HSQC	HMBC	NOESY
1 C	72.01			1	2', 2'', 3ax, 3eq, 5ax, 5eq, 6', 6'', 8	
H	3.43	11.60(?), 8.00(?), 3.30(?), 3.30(?)	2', 2'', 6', 6''	1	3, 5, 8	2', 3ax, 5ax, 6', 8, 9eq, 13eq
2 C	27.95	4.60(7)		2', 2''	4	
H'	1.63		1, 2'', 3ax, 3eq	2	1, 3, 4	1, 4
H''	1.72		1, 2', 3ax, 3eq	2	1, 3, 4	
3 C	28.93	20.50(7)		3ax, 3eq	1, 2', 2'', 5eq	
Hax	1.58		2', 2'', 3eq, 4	3	1	1, 4
Heq	1.99		2', 2'', 3ax, 4	3	1, 4	4
4 C	89.39	169.60(7)		4	2', 2'', 3eq, 5eq, 6', 6''	
H	4.64	6.10(?), 6.10(?), 2.90(?), 2.90(?)	3ax, 3eq, 5ax, 5eq	4	2, 6	2', 3ax, 3eq, 5ax, 5eq, 6'
5 C	28.93	20.50(7)		5ax, 5eq	1	
Hax	1.58		4, 5eq, 6', 6''	5	1	1, 4
Heq	1.99		4, 5ax, 6', 6''	5	1, 3, 4	4
6 C	27.95	4.60(7)		6', 6''	4	
H'	1.63		1, 5ax, 5eq, 6''	6	1, 4	1, 4
H''	1.72		1, 5ax, 5eq, 6'	6	1, 4	
7 F	-178.85	169.60(4), 4.60(2), 4.60(6), 20.50(3), 20.50(5)				

Atom	δ (ppm)	J	COSY	HSQC	HMBC	NOESY
8 C	74.76			8	1, 9ax, 9eq, 10ax, 10eq, 12ax, 12eq, 13ax, 13eq	
H	3.31		9ax, 9eq, 13ax, 13eq	8	1, 9, 10, 12, 13	1, 9eq, 10ax, 12ax, 13eq
9 C	33.31			9ax, 9eq	8, 11ax, 11eq, 13eq	
Hax	1.27		8, 9eq, 10ax, 10eq	9	8, 11	
Heq	1.85		8, 9ax, 10ax, 10eq	9	8, 11, 13	1, 8
10 C	24.58			10ax, 10eq	8, 12ax, 12eq	
Hax	1.23		9ax, 9eq, 10eq, 11ax, 11eq	10	8, 11, 12	8
Heq	1.73		9ax, 9eq, 10ax, 11ax, 11eq	10	8, 11, 12	
11 C	25.96			11ax, 11eq	9ax, 9eq, 10ax, 10eq	
Hax	1.18		10ax, 10eq, 11eq, 12ax, 12eq	11	9, 13	
Heq	1.53		10ax, 10eq, 11ax, 12ax, 12eq	11	9, 13	
12 C	24.58			12ax, 12eq	8, 10ax, 10eq	
Hax	1.23		11ax, 11eq, 12eq, 13ax, 13eq	12	8, 10	8
Heq	1.73		11ax, 11eq, 12ax, 13ax, 13eq	12	8, 10	
13 C	33.31			13ax, 13eq	8, 9eq, 11ax, 11eq	
Hax	1.27		8, 12ax, 12eq, 13eq	13	8	
Heq	1.85		8, 12ax, 12eq, 13ax	13	8, 9	1, 8



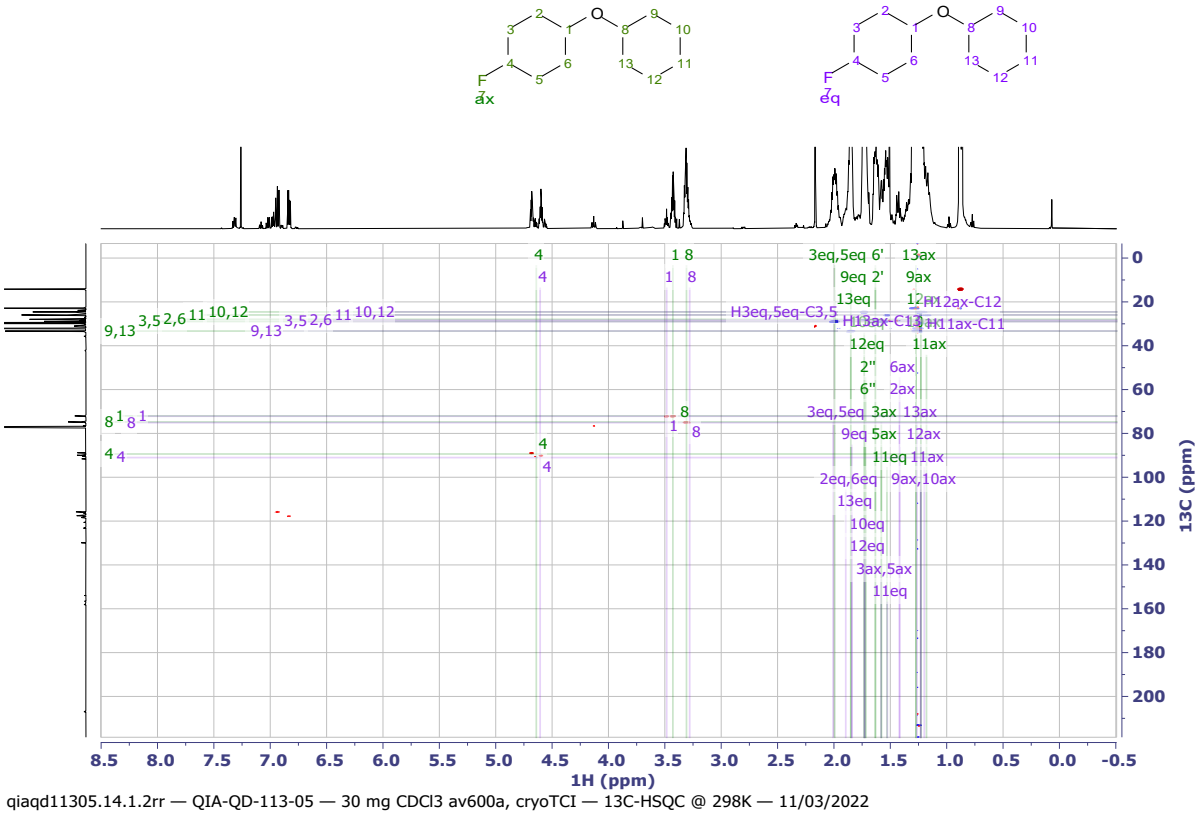
Atom	*δ* (ppm)	J	COSY	HSQC	HMBC	NOESY
1 C	72.15			1	2ax, 3ax, 3eq, 5ax, 5eq, 6ax, 8	
H	3.48	7.90(?), 7.90(?), 3.70(?), 3.70(?)	2ax, 2eq, 6ax, 6eq	1	3, 5, 8	2eq, 3ax, 5ax, 6eq, 8, 9eq, 13eq
2 C	28.38	8.10(7)		2ax, 2eq	4, 6ax	
Hax	1.42		1, 2eq, 3ax, 3eq	2	1, 4, 6	4
Heq	1.90		1, 2ax, 3ax, 3eq	2	4	1
3 C	28.99	20.10(7)		3ax, 3eq	1, 5eq	
Hax	1.58		2ax, 2eq, 3eq, 4	3	1, 4	1
Heq	2.01		2ax, 2eq, 3ax, 4	3	1	4
4 C	91.02	170.20(7)		4	2ax, 2eq, 3ax, 5ax, 6ax, 6eq	
H	4.61	48.90(?), 8.00(?), 8.00(?), 3.70(?), 3.70(?)	3ax, 3eq, 5ax, 5eq	4	2, 6	2ax, 3eq, 5eq, 6ax
5 C	28.99	20.10(7)		5ax, 5eq	1	
Hax	1.58		4, 5eq, 6ax, 6eq	5	1, 4	1
Heq	2.01		4, 5ax, 6ax, 6eq	5	1, 3	4
6 C	28.38	8.10(7)		6ax, 6eq	2ax, 4	
Hax	1.42		1, 5ax, 5eq, 6eq	6	1, 2, 4	4
Heq	1.90		1, 5ax, 5eq, 6ax	6	4	1
7 F	-178.37	8.10(2), 8.10(6), 20.10(3), 20.10(5), 170.20(4)				

Atom	δ (ppm)	J	COSY	HSQC	HMBC	NOESY
8 C	75.12			8	1, 9ax, 9eq, 10ax, 10eq, 12ax, 12eq, 13ax, 13eq	
H	3.28		9ax, 9eq, 13ax, 13eq	8	1, 10, 12	1, 9eq, 10ax, 12ax, 13eq
9 C	33.28			9ax, 9eq	11ax, 11eq, 13eq	
Hax	1.23		8, 9eq, 10ax, 10eq	9	8, 11	
Heq	1.84		8, 9ax, 10ax, 10eq	9	8, 11, 13	1, 8
10 C	24.56			10ax, 10eq	8, 12ax, 12eq	
Hax	1.23		9ax, 9eq, 10eq, 11ax, 11eq	10	8, 11, 12	8
Heq	1.73		9ax, 9eq, 10ax, 11ax, 11eq	10	8, 11, 12	
11 C	25.94			11ax, 11eq	9ax, 9eq, 10ax, 10eq	
Hax	1.20		10ax, 10eq, 11eq, 12ax, 12eq	11	9, 13	
Heq	1.53		10ax, 10eq, 11ax, 12ax, 12eq	11	9, 13	
12 C	24.56			12ax, 12eq	8, 10ax, 10eq	
Hax	1.23		11ax, 11eq, 12eq, 13ax, 13eq	12	8, 10	8
Heq	1.73		11ax, 11eq, 12ax, 13ax, 13eq	12	8, 10	
13 C	33.28			13ax, 13eq	9eq, 11ax, 11eq	
Hax	1.26		8, 12ax, 12eq, 13eq	13	8	
Heq	1.84		8, 12ax, 12eq, 13ax	13	8, 9	1, 8



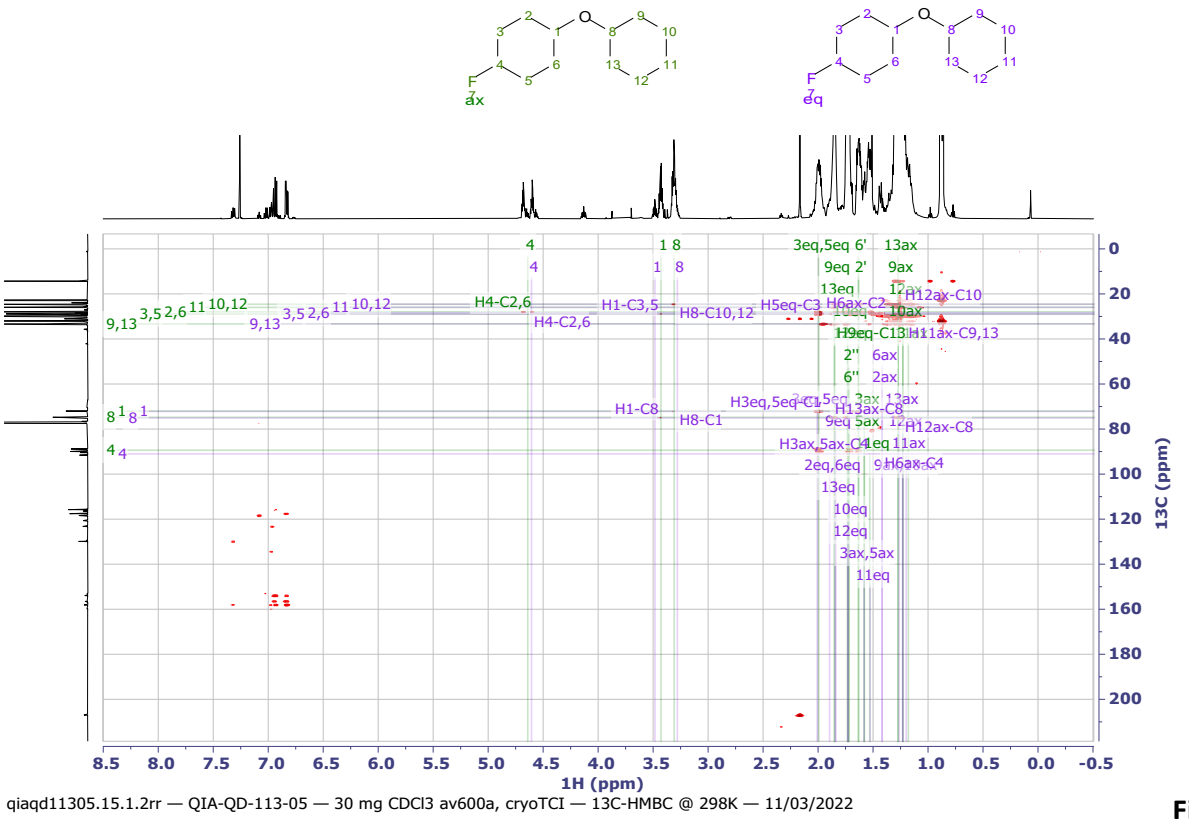
qiaqd11305.12.1.2rr — QIA-QD-113-05 — 30 mg CDCl3 av600a, cryoTCI — 1H COSY @ 298K — 11/03/2022

Figure S30. ^{1}H-^{1}H COSY spectrum of 1-(clohexyloxy)-4-fluorocyclohexane (ax and eq) in $CDCl_3$ using a 600 MHz spectrometer.



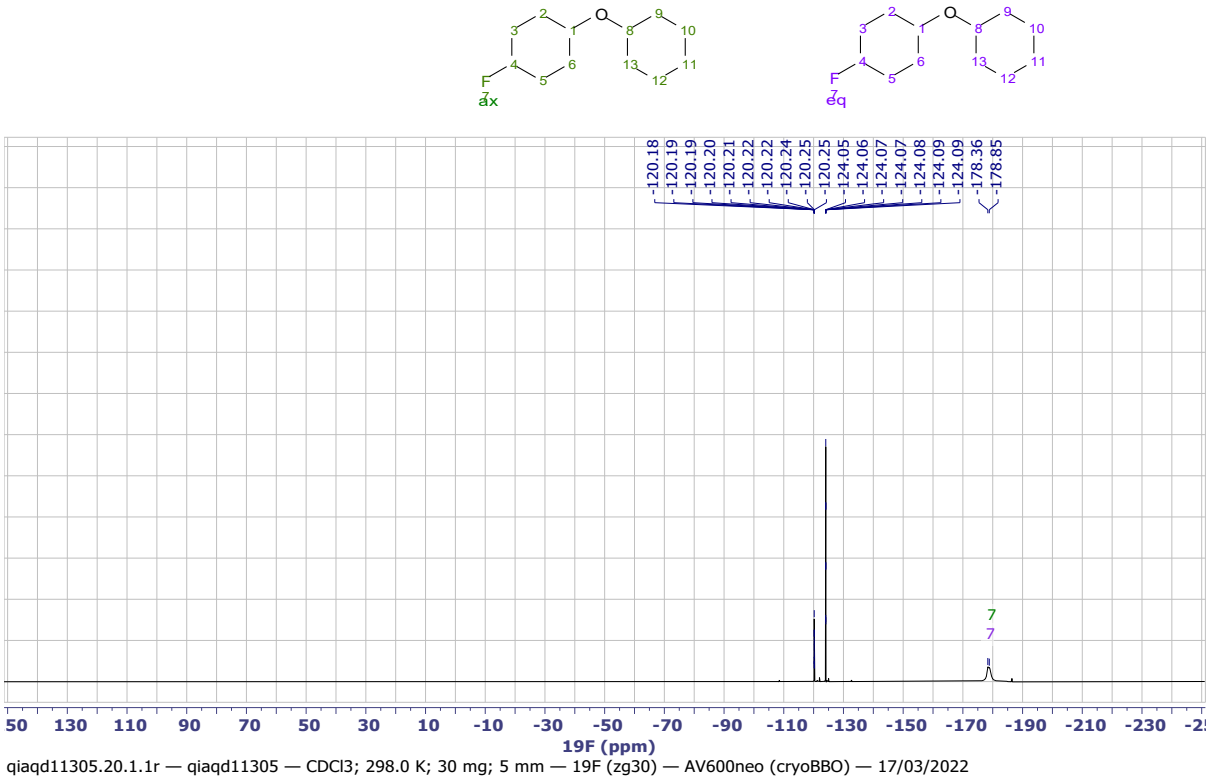
qiaqd11305.14.1.2rr — QIA-QD-113-05 — 30 mg CDCl3 av600a, cryoTCI — 13C-HSQC @ 298K — 11/03/2022

Figure S31. ^{1}H-^{13}C HSQC spectrum of 1-(clohexyloxy)-4-fluorocyclohexane (ax and eq) in $CDCl_3$ using a 600 MHz spectrometer.



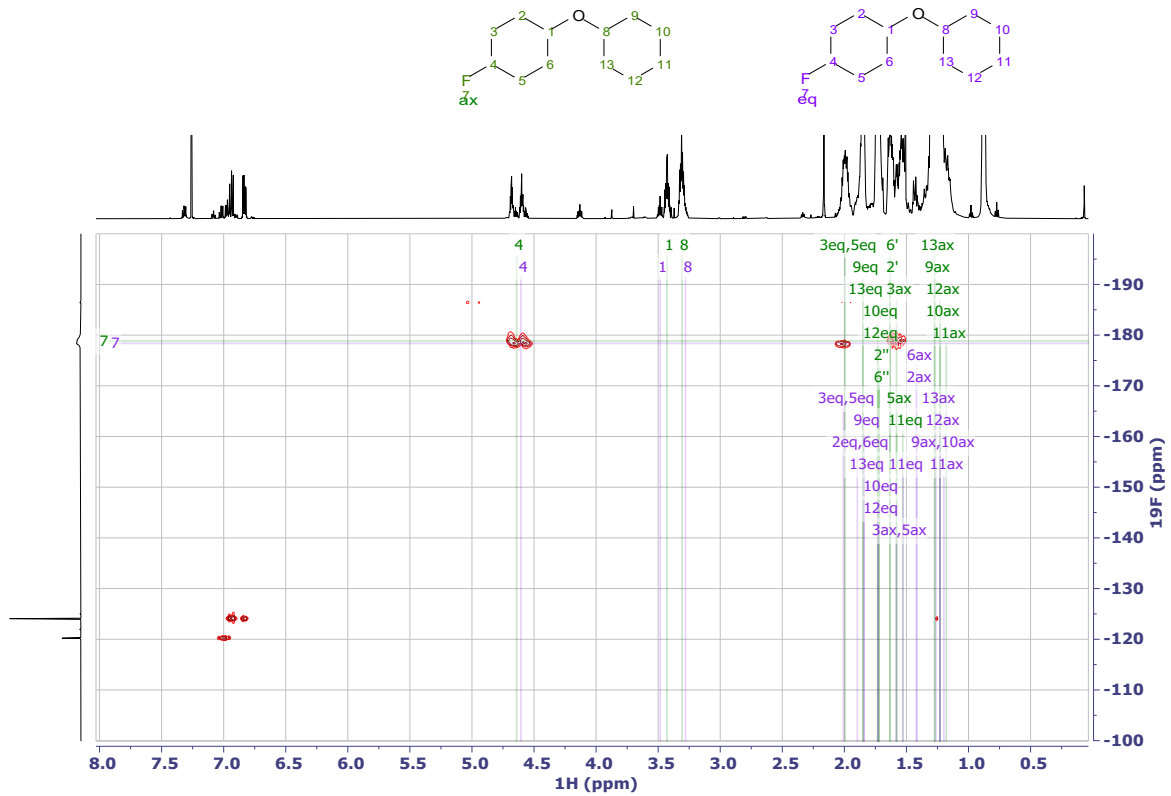
qiaqd11305.15.1.2rr — QIA-QD-113-05 — 30 mg CDCl3 av600a, cryoTCI — 13C-HMBC @ 298K — 11/03/2022

Figure S32. ^{1}H-^{13}C HMBC spectrum of 1-(clohexyloxy)-4-fluorocyclohexane (ax and eq) in $CDCl_3$ using a 600 MHz spectrometer.



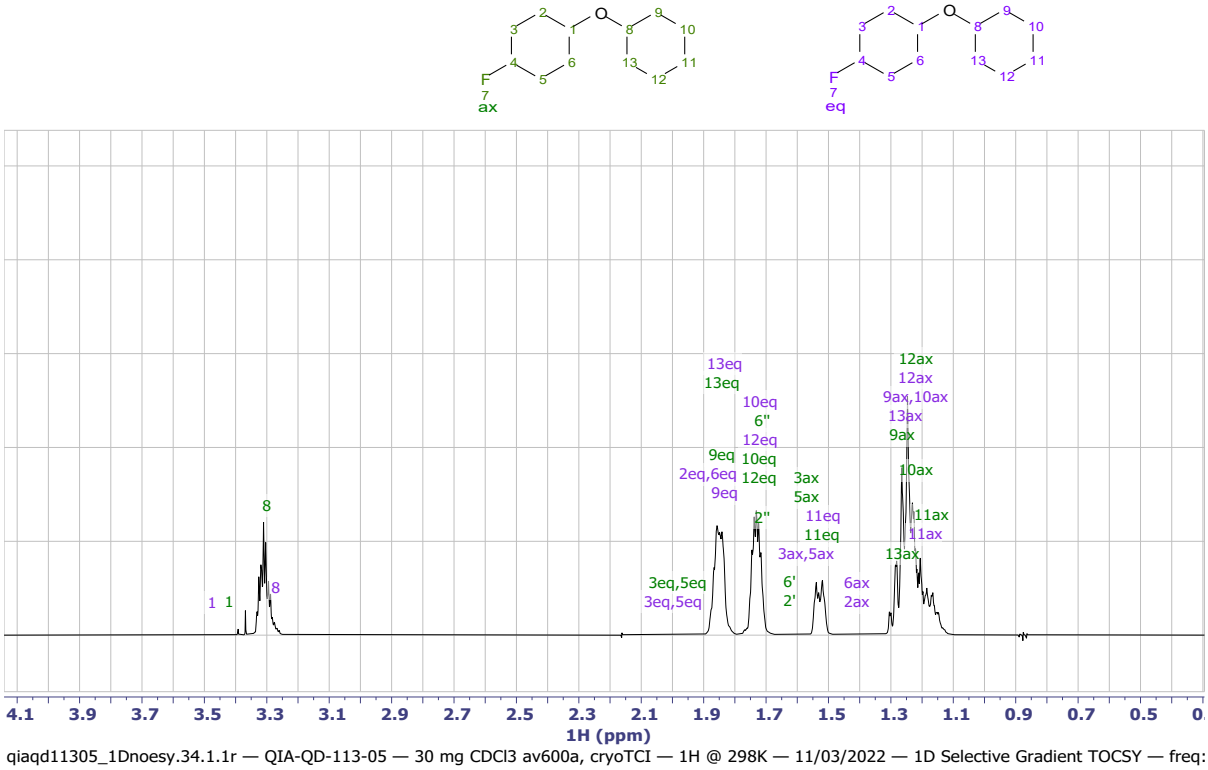
qiaqd11305.20.1.1r — qiaqd11305 — CDCl3; 298.0 K; 30 mg; 5 mm — 19F (zg30) — AV600neo (cryoBBO) — 17/03/2022

Figure S33. ^{19}F NMR spectrum of 1-(cyclohexyloxy)-4-fluorocyclohexane (ax and eq) in $CDCl_3$ using a 600 MHz spectrometer.



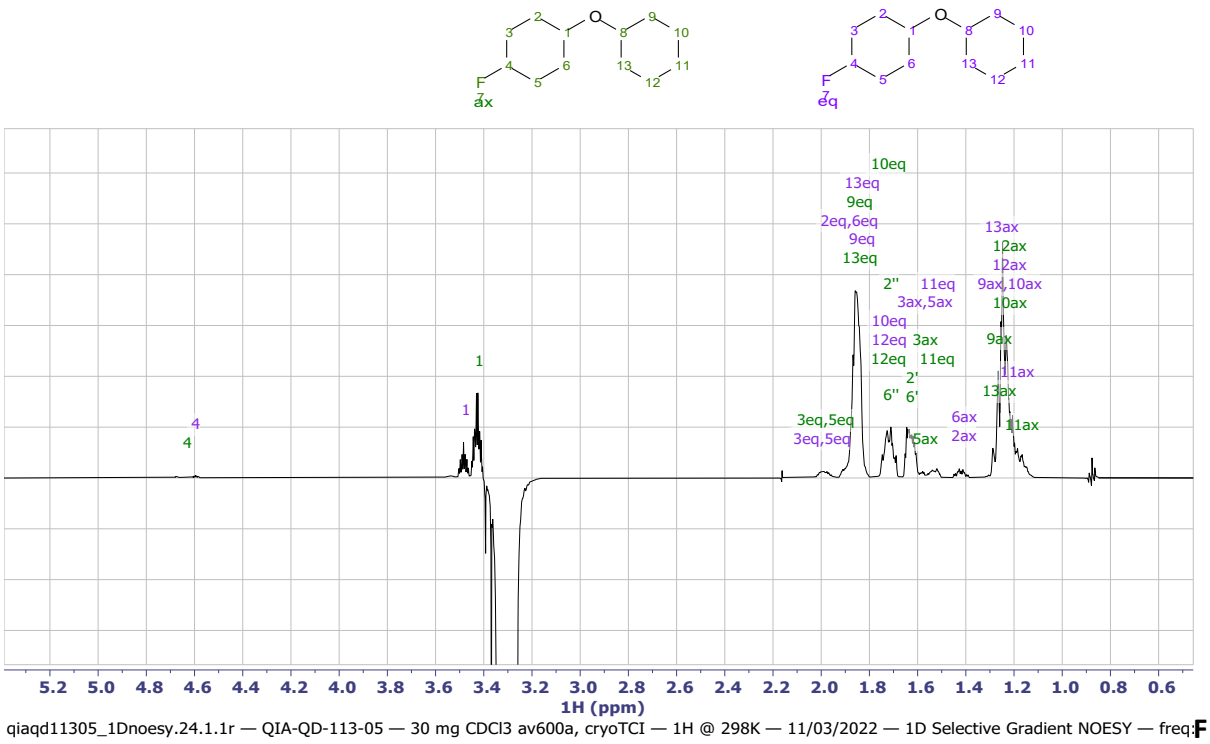
qiaqd11305_AV500as.14.1.2rr — QIA-QD-113-5_AV500as (7893) — 5 mm, CDCl3 30 mg — 1H-19F (cosygphfqfqn) @ 298.0 K — AV500as, BBFO — 11

Figure S34. ^{19}F-^{1}H COSY spectrum of 1-(cyclohexyloxy)-4-fluorocyclohexane (ax and eq) in $CDCl_3$ using a 500 MHz spectrometer.



qiaqd11305_1Dnoesy.34.1.1r — QIA-QD-113-05 — 30 mg CDCl3 av600a, cryoTCI — 1H @ 298K — 11/03/2022 — 1D Selective Gradient TOCSY — freq:

Figure S35. 1D ^{1}H TOCSY spectrum (freq: 3.331 ppm) of 1-(cyclohexyloxy)-4-fluorocyclohexane (ax and eq) in $CDCl_3$ using a 600 MHz spectrometer.

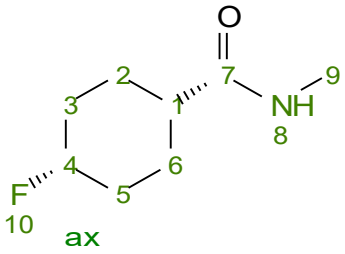


qiaqd11305_1Dnoesy.24.1.1r — QIA-QD-113-05 — 30 mg CDCl3 av600a, cryoTCI — 1H @ 298K — 11/03/2022 — 1D Selective Gradient NOESY — freq:

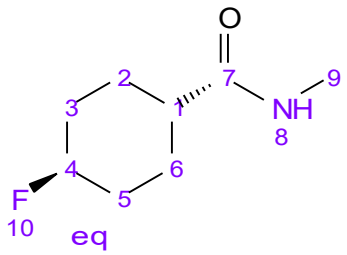
Figure S36. 1D ^{1}H NOESY spectrum (freq: 3.331 ppm) of 1-(cyclohexyloxy)-4-fluorocyclohexane (ax and eq) in $CDCl_3$ using a 600 MHz spectrometer.

4-fluoro-N-methylcyclohexane-1-carboxamide (12a)

The desired compound is a mixture of 2 stereo isomers



Atom	*δ* (ppm)	J	COSY	HSQC	HMBC	NOESY
1 C	44.27			1	2ax, 2eq, 3ax, 3eq, 5ax, 5eq, 6ax, 6eq, 9	
H	2.15	11.70(?), 11.70(?), 3.70(?), 3.70(?), 1.50(?)	2ax, 2eq, 6ax, 6eq	1	2, 3, 5, 6, 7	8
2 C	23.83	1.70(10)		2ax, 2eq	1, 3ax, 4, 5ax, 6ax, 6eq	
Hax	1.82		1, 2eq, 3ax, 3eq	2	1, 3, 4, 6, 7	
Heq	1.74		1, 2ax, 3ax, 3eq	2	1, 3, 4, 6, 7	
3 C	30.24	21.30(10)		3ax, 3eq	1, 2ax, 2eq	
Hax	1.51		2ax, 2eq, 3eq, 4	3	1, 2, 10	4
Heq	2.08		2ax, 2eq, 3ax, 4	3	1, 4, 10	4
4 C	87.96	168.30(10)		4	2ax, 2eq, 3eq, 5eq, 6ax, 6eq	
H	4.81	4.10(?), 4.10(?), 2.30(?), 2.30(?)	3ax, 3eq, 5ax, 5eq	4	2, 6, 10	3ax, 3eq, 5ax, 5eq
5 C	30.24	21.30(10)		5ax, 5eq	1, 6ax, 6eq	
Hax	1.51		4, 5eq, 6ax, 6eq	5	1, 2, 10	4
Heq	2.08		4, 5ax, 6ax, 6eq	5	1, 4, 10	4
6 C	23.83	1.70(10)		6ax, 6eq	1, 2ax, 2eq, 4	
Hax	1.82		1, 5ax, 5eq, 6eq	6	1, 2, 4, 5, 7	
Heq	1.74		1, 5ax, 5eq, 6ax	6	1, 2, 4, 5, 7	
7 C	175.81				1, 2ax, 2eq, 6ax, 6eq, 9	
8 N	-282.39					
H	5.61		9			1, 9
9 C	26.39			9		
H3	2.80	4.90(?)	8	9	1, 7	8
10 F	-184.71	21.30(3), 21.30(5), 1.70(2), 1.70(6), 168.30(4)			3ax, 3eq, 4, 5ax, 5eq	



Atom	δ (ppm)	J	COSY	HSQC	HMBC	NOESY
1 C	43.87	1.90(10)		1	2ax, 2eq, 3ax, 3eq, 5ax, 5eq, 6ax, 6eq, 9	
H	2.06	11.80(?), 11.80(?), 3.60(?), 3.60(?)	2ax, 2eq, 6ax, 6eq	1	2, 6, 7	8
2 C	27.08	11.40(10)		2ax, 2eq	1, 3ax, 3eq, 4	
Hax	1.58		1, 2eq, 3ax, 3eq	2	1, 3	4
Heq	1.93		1, 2ax, 3ax, 3eq	2	1	
3 C	31.75	19.20(10)		3ax, 3eq	2ax, 6ax	
Hax	1.47		2ax, 2eq, 3eq, 4	3	1, 2, 4	
Heq	2.15		2ax, 2eq, 3ax, 4	3	1, 2, 4	4
4 C	91.33	172.20(10)		4	3ax, 3eq, 5ax, 5eq	
H	4.50	10.40(?), 10.40(?), 4.50(?), 4.50(?)	3ax, 3eq, 5ax, 5eq	4	2, 6	2ax, 3eq, 5eq, 6ax
5 C	31.75	19.20(10)		5ax, 5eq		
Hax	1.47		4, 5eq, 6ax, 6eq	5	1, 4, 6	
Heq	2.15		4, 5ax, 6ax, 6eq	5	1, 4, 6	4
6 C	27.08	11.40(10)		6ax, 6eq	1, 4, 5ax, 5eq	
Hax	1.58		1, 5ax, 5eq, 6eq	6	1, 3	4
Heq	1.93		1, 5ax, 5eq, 6ax	6	1	
7 C	175.58	2.60(10)			1, 9	
8 N	-280.73					
H	5.65		9			1, 9
9 C	26.39			9		
H3	2.79		8	9	1, 7	8
10 F	-170.91	11.40(2), 19.20(3), 19.20(5), 11.40(6), 2.60(7), 172.20(4), 1.90(1)				

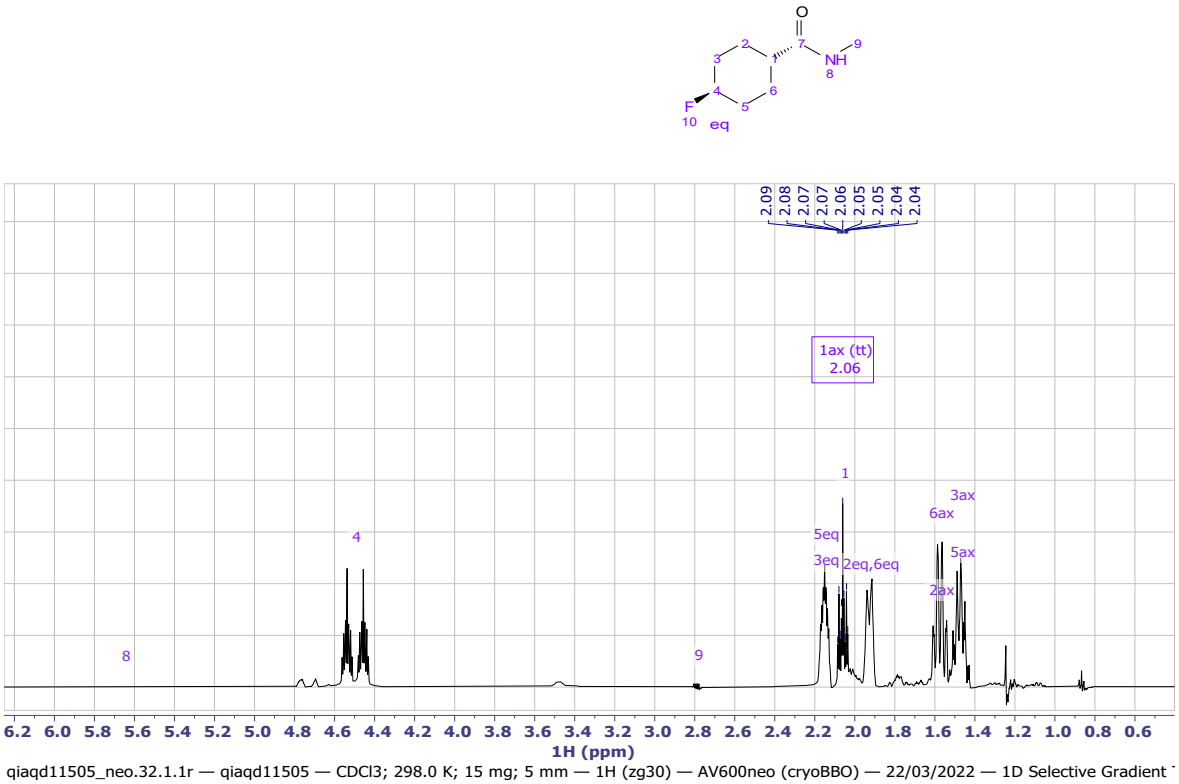


Figure S37. 1D ^{1}H TOCSY spectrum (freq: 4.524) of 4-fluoro-N-methylcyclohexane-1-carboxamide (eq) in $CDCl_3$.

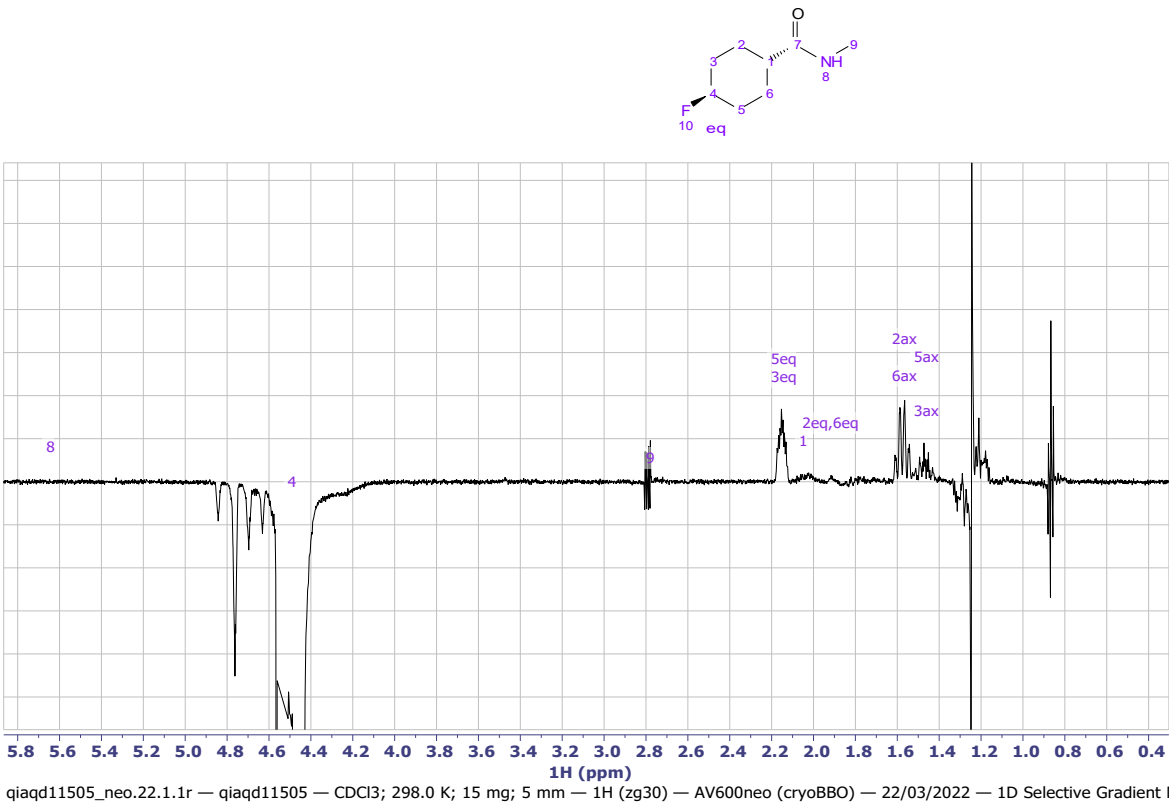
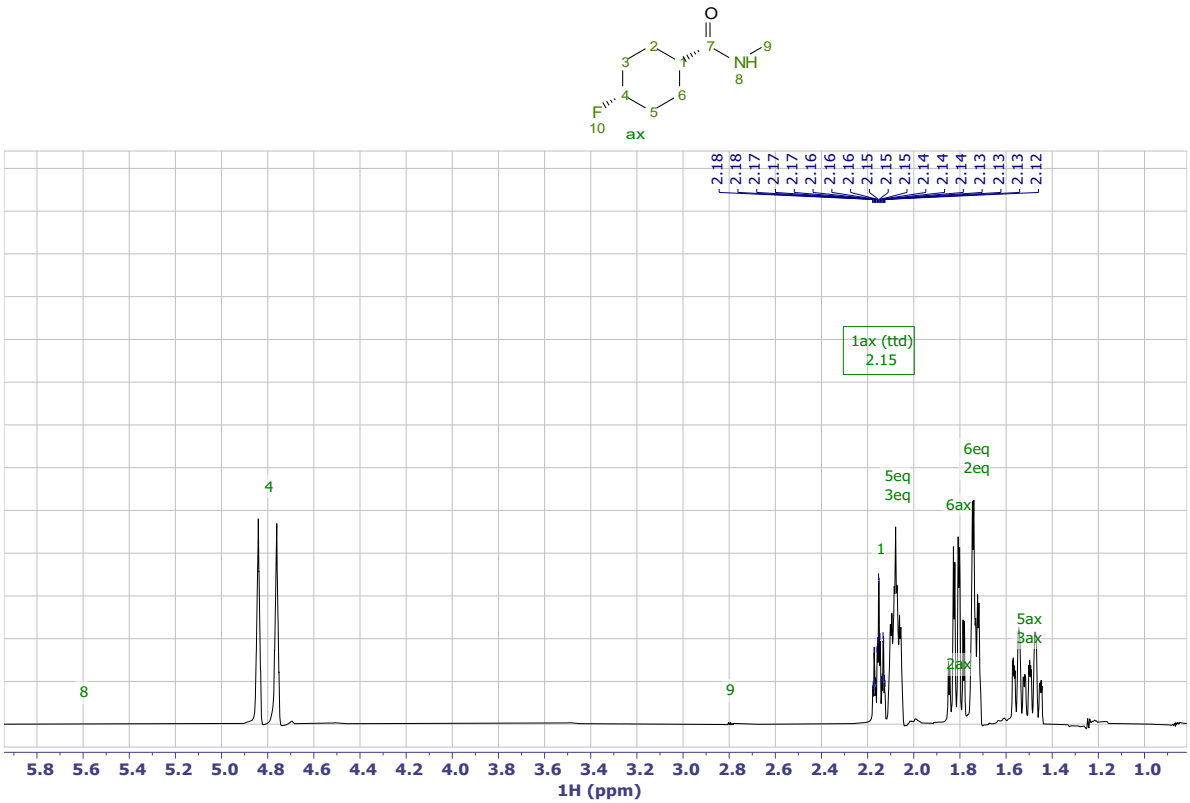
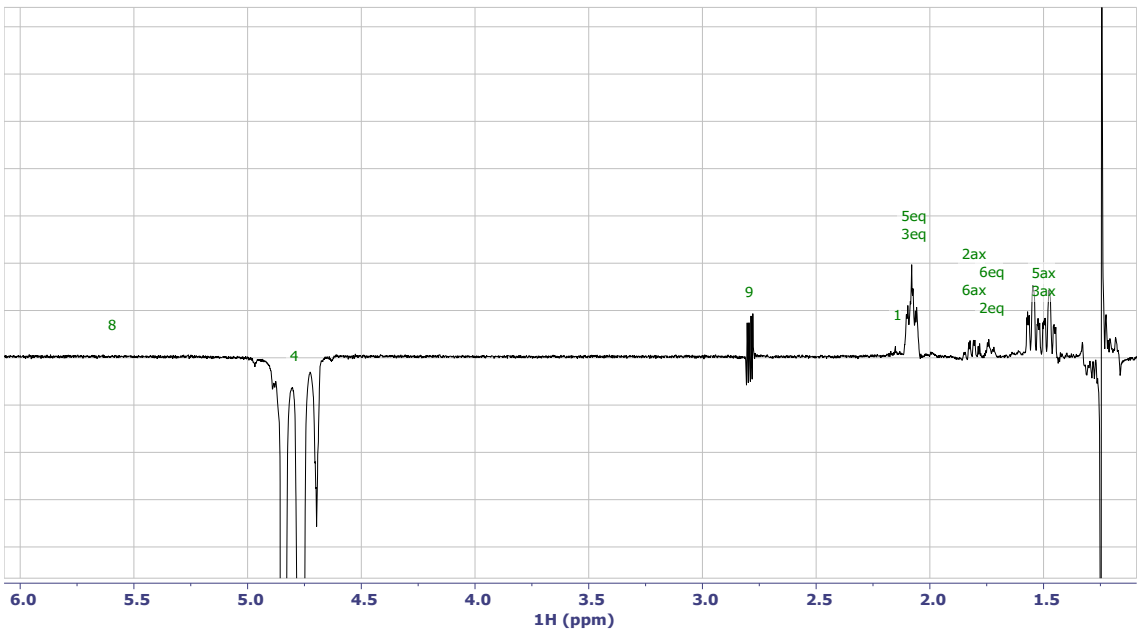


Figure S38. 1D ^{1}H NOESY spectrum (freq: 4.524) of 4-fluoro-N-methylcyclohexane-1-carboxamide (eq) in $CDCl_3$.



qiaqd11505_neo.31.1.1r — qiaqd11505 — CDCl3; 298.0 K; 15 mg; 5 mm — 1H (zg30) — AV600neo (cryoBBO) — 22/03/2022 — 1D Selective Gradient

Figure S39. 1D ^{1}H TOCSY spectrum (freq: 4.827) of 4-fluoro-N-methylcyclohexane-1-carboxamide (ax) in $CDCl_3$.



qiaqd11505_neo.21.1.1r — qiaqd11505 — CDCl3; 298.0 K; 15 mg; 5 mm — 1H (zg30) — AV600neo (cryoBBO) — 22/03/2022 — 1D Selective Gradient I

Figure S40. 1D ^{1}H NOESY spectrum (freq: 4.828) of 4-fluoro-N-methylcyclohexane-1-carboxamide (ax) in $CDCl_3$.

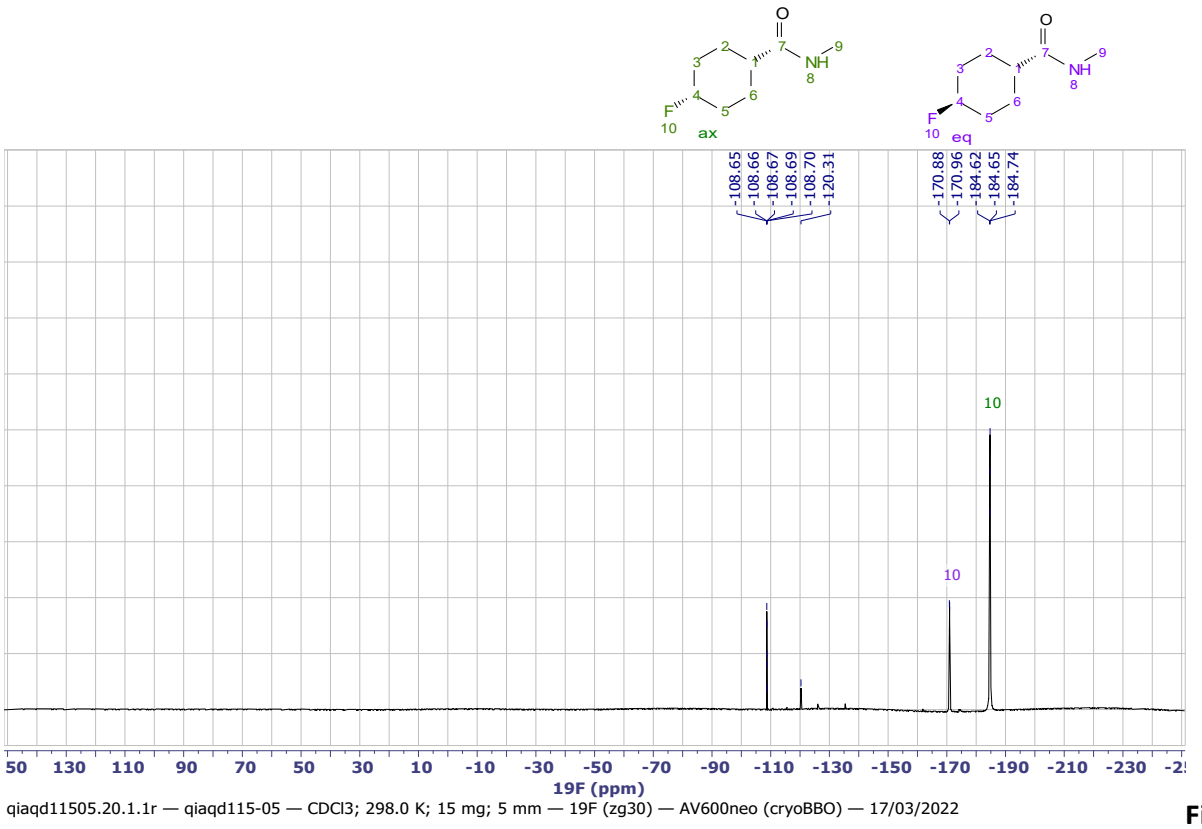
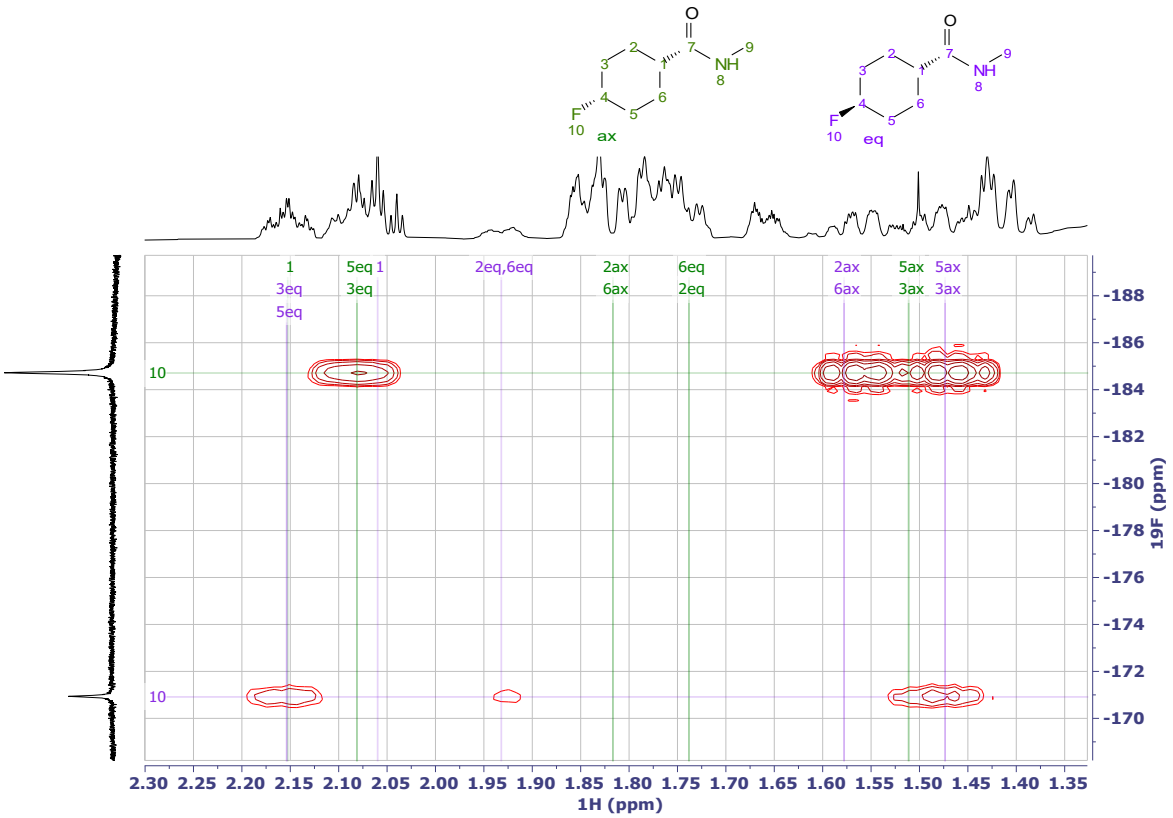


Figure S41. ^{19}F spectrum of 4-fluoro-N-methylcyclohexane-1-carboxamide (ax and eq) in $CDCl_3$ using a 600 MHz spectrometer.



qiaqd11505_AV500as.14.1.2rr — QIA-QD-115-05_AV500as (7895) — 5 mm, CDCl3 15 mg — 1H-19F (cosygphfqfqn) @ 298.0 K — AV500as, BBFO — 11

Figure S42. ^{19}F-^{1}H spectrum of 4-fluoro-N-methylcyclohexane-1-carboxamide (ax and eq) in $CDCl_3$ using a 500 MHz spectrometer.

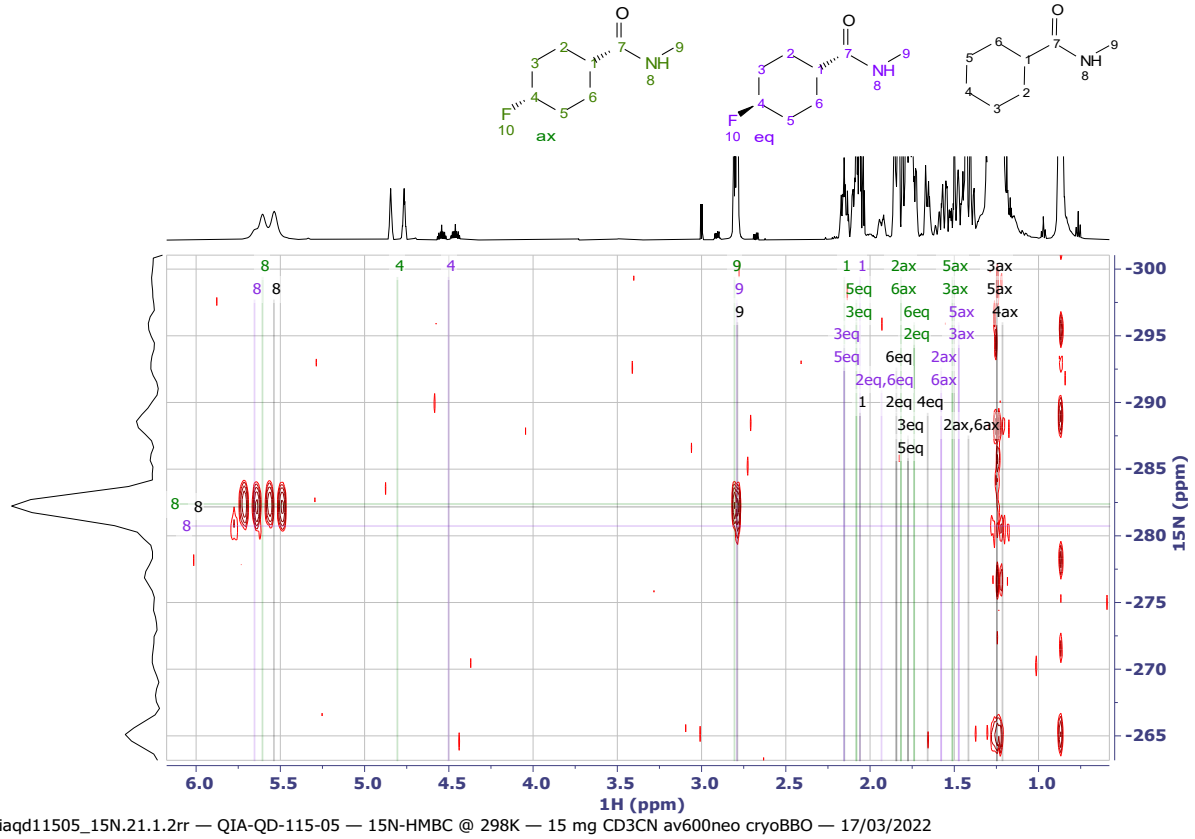


Figure S43. ^{1}H-^{15}N HMBC spectrum of 4-fluoro-N-methylcyclohexane-1-carboxamide (ax and eq) and N-methylcyclohexanecarboxamide in CD_3CN using a 600 MHz spectrometer.

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1 S. Kacem, M. Emondts, A. Bordet, W. Leitner, *Catal. Sci. Technol.* 2020, **10**, 8120-8126.

2 K. D. John, J. L. Eglin, K. V. Salazar, R. T. Baker, A. P. Sattelberger, D. Serra, L. M. White, *Tris(Allyl)Iridium and -Rhodium, Vol. 36*, Inorganic Syntheses, 2014.

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