Electronic Supplementary Material (ESI) for Green Chemistry.

Electronic Supporting Information

Optimization and sustainability assessment of a continuous flow Ru-catalyzed ester hydrogenation for an important precursor of a β2-adrenergic receptor agonist

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1. Materials and Methods

Solvents and chemicals were obtained from commercial suppliers and were used without any further purification unless otherwise noted.

1.1 Design of Experiments (DoE)

The data for the batch optimization was fitted to polynomial models in MODDE (version 12, Umetrics). The experimental data were fitted by using multiple linear regression (MLR). All main and interaction terms were fitted and then non-significant terms were removed. Summary of fit for all models. R^2 is a measure of how well the model fits the experimental data points. Q^2 measures how well the model predicts future data (should be greater than 0.1 for a significant model and greater than 0.5 for a good model). Reproducibility is a measure of experimental error.

1.2 High Field NMR

NMR spectra were recorded on a Bruker 300 MHz instrument. ^{1}H, ^{13}C and ^{19}F spectra were recorded at 300 MHz, 75 MHz and 282 MHz, respectively. The chemical shifts are relative to tetramethylsilane (TMS) and expressed in parts per million (ppm). Chemical shifts (δ) are reported in ppm downfield from TMS as the internal standard. The letters s, d, dd, t, tt, q, and m are used to indicate singlet, doublet, doublet of doublets, triplet, triplet of triplets, quadruplet, and multiplet respectively.

1.3 Benchtop NMR

Reaction monitoring and in-line NMR was accomplished by recording ^{19}F spectra using a low field benchtop 43 MHz NMR (Magritek, Spinsolve Ultra). All samples were measured directly without any dilution or addition of deuterated solvent.

1.4 Note of Caution

H_2 is extremely flammable. Care should be taken when operating pressurized equipment. A thorough safety assessment should be made before conducting any experiments.

2. Experimental Details

2.1 Batch Experiments

2.1.1 Experiments using Ru-MACHO

To a 15 mL glass vial were added Ru-MACHO and methanol (2.5 mL). The catalyst was dissolved by using an ultrasound bath. To the resulting solution were added ethyl 2,2-difluoro-2-phenylacetate **1** (1 g, 5 mmol) and α,α,α-trifluorotoluene (73 mg, 0.5 mmol) as an internal standard. Sodium methoxide (NaOMe) was added as a solution in methanol (25% w/w). The content of the vial was transferred to a 25 mL HEL batch autoclave containing a magnetic stirrer bar. The vessel was flushed with nitrogen three times. The reactor was heated and stirred at 600 rpm within a heating block for 10 minutes. The system was flushed three times with hydrogen gas. The reaction was stirred at 600 rpm for 1 h within the heating block. Subsequently, the reactor was removed from the heating block and cooled-down within a water bath. The reactor was flushed three times with nitrogen and then opened. The reaction mixture was transferred to a fresh glass vial. The reaction progress was determined by using ^{19}F NMR spectroscopy.

Table S1. Other solvents screened for the Ru-MACHO hydrogenation.

Entry	Solvent	Ester **1**	Alcohol **2**
1	THF	100	0
2	MeTHF	100	0
3	PhMe	45	55
4	tBuOH/PhMe	90	10

Standard reaction conditions: **1** (5 mmol scale) in solvent (2.5 mL) with stirring at 600 rpm for 1 h. 1 mol% cat. Conversion and product distribution were determined by integration of ^{19}F NMR.

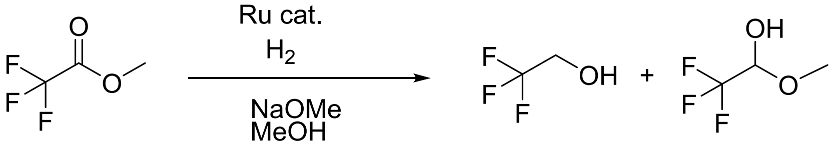
2.1.2 Experiments using Ru-MACHO-BH

Ru-MACHO-BH (57 mg, 97 µmol) was weighed into a 100 mL round bottom flask and sealed with a septum within a glovebox. The catalyst was dissolved in anhydrous methanol (50 mL) by using an ultrasound bath.

To a 15 mL glass vial were added stock catalyst solution (2 mL), ethyl 2,2-difluoro-2-phenylacetate (**1**) (1 g, 5 mmol), α,α,α-trifluorotoluene (73 mg, 0.5 mmol) as internal standard, and methanol (0.5 mL). The content of the vial was transferred to a 25 mL HEL batch autoclave containing a magnetic stirrer bar. The vessel was flushed with nitrogen three times. The reactor was heated and stirred at 600 rpm within a heating block for 10 minutes. The system was flushed three times with hydrogen gas. The reaction was stirred at 600 rpm for 1 h within the heating block. Subsequently, the reactor was removed from the heating block and cooled-down within a water bath. The reactor was flushed three times with nitrogen and then opened. The reaction mixture was transferred to a fresh glass vial. The progress of the reactions were determined by using ^{19}F NMR spectroscopy.

2.1.3 Experiments with Methyl Trifluoroacetate as Substrate

Table S2. Autoclave experiments using methyl trifluoroacetate as substrate.



5 **6** **7**

Exp.	Catalyst	T [°C]	p [bar]	c [M]	Base [eq]	Cat [mol%]	t [h]	Conv. **5** [%]	**6** [%]	**7** [%]
1	Ru-MACHO (**A**)	40	6	2	0.25	0.05	19	75	7	93
2	Ru-MACHO (**A**)	40	6	2	0.25	0.05	19	81	13	87
3	Ru-MACHO (**A**)	40	30	2	0.25	0.05	2	83	14	86
4	Ru-MACHO (**A**)	60	30	2	0.25	0.05	2	79	99	1
5	Ru-MACHO (**A**)	40	30	"neat"	0.25	0.05	2	89	6	94
6	Ru-SNS (**B**)	40	6	2	0.25	0.05	21	42	10	90
7	Ru-SNS (**B**)	40	6	2	0.25	0.05	21	38	7	93
8	Ru-SNS (**B**)	40	30	2	0.25	0.05	2	28	3	97

In 25 mL HEL autoclave batch vessels, 5 mL solution volume, 600 rpm stirring speed, conversion and yield measured by ^{19}F-NMR peak integration

2.2 Flow Experiments

2.2.1 Flow Procedure for the Optimization Experiments

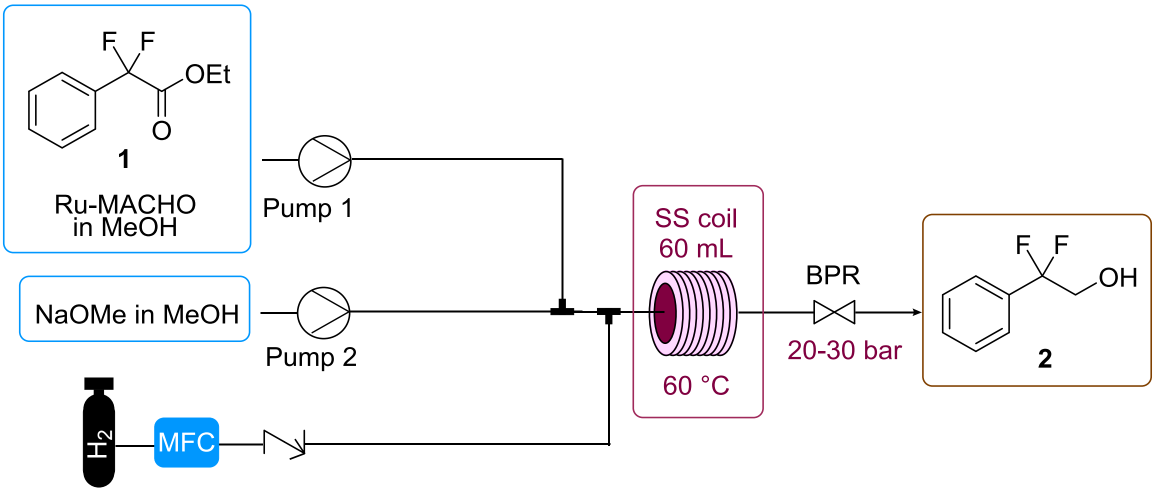
Feed Preparation

Feed 1: To a 5 mL volumetric flask were added Ru-MACHO, ethyl 2,2-difluoro-2-phenylacetate (**1**) (3.2 g, 16 mmol) and α,α,α-trifluorotoluene (230 mg, 1.6 mmol) as internal standard. Methanol was added to a fill volume of 5 mL. The resulting mixture was placed within an ultrasound bath until complete dissolution of the catalyst was observed. The solution was transferred to a 15 mL glass vial and 3 mL of methanol were added.

Feed 2: NaOMe as a solution in methanol (25% w/w).

Flow Procedure

The flow setup (Scheme S1) consisted of two high pressure liquid chromatography (HPLC) pumps (Uniqsis) for introducing the liquid feeds. H_2 gas was introduced from a gas cylinder by using a calibrated mass flow controller (MFC, Bronkhorst EL-FLOW). Gas flow rates were measured in units of $mL_n\ min^{-1}$, where n represents measurement under standard conditions, i.e., $T_n = 0\ °C$, $P_n = 1.01$ bar. The two liquid feeds were mixed within an arrow-shaped mixer with integrated pressure sensor. The liquid stream was then combined with the gaseous stream using a Y-shaped three-way mixer. After mixing, a segmented (Taylor) flow regime could be observed. The mixer was connected to the reactor coil using fluoropolymer tubing (PFA, 0.8 mm inner diameter). A stainless steel (SS) reactor coil (60 mL, 1/8 in. OD, 1/16 in. ID) placed on an aluminum heating block within a glass dome was used. After exiting the reaction coil the reaction mixture passed through a short piece of fluoropolymer tubing followed by an adjustable back pressure regulator (BPR). A labeled picture of the setup is shown in Figure S1. Fractions of the liquid output were collected at 5 min intervals and used for analysis with ^{19}F NMR. For optimization experiments the liquid feed solutions were introduced over a 30 min time period. Methanol was used as a carrier solvent.



Scheme S1. Continuous flow scheme for the Ru-MACHO hydrogenation optimization experiments.

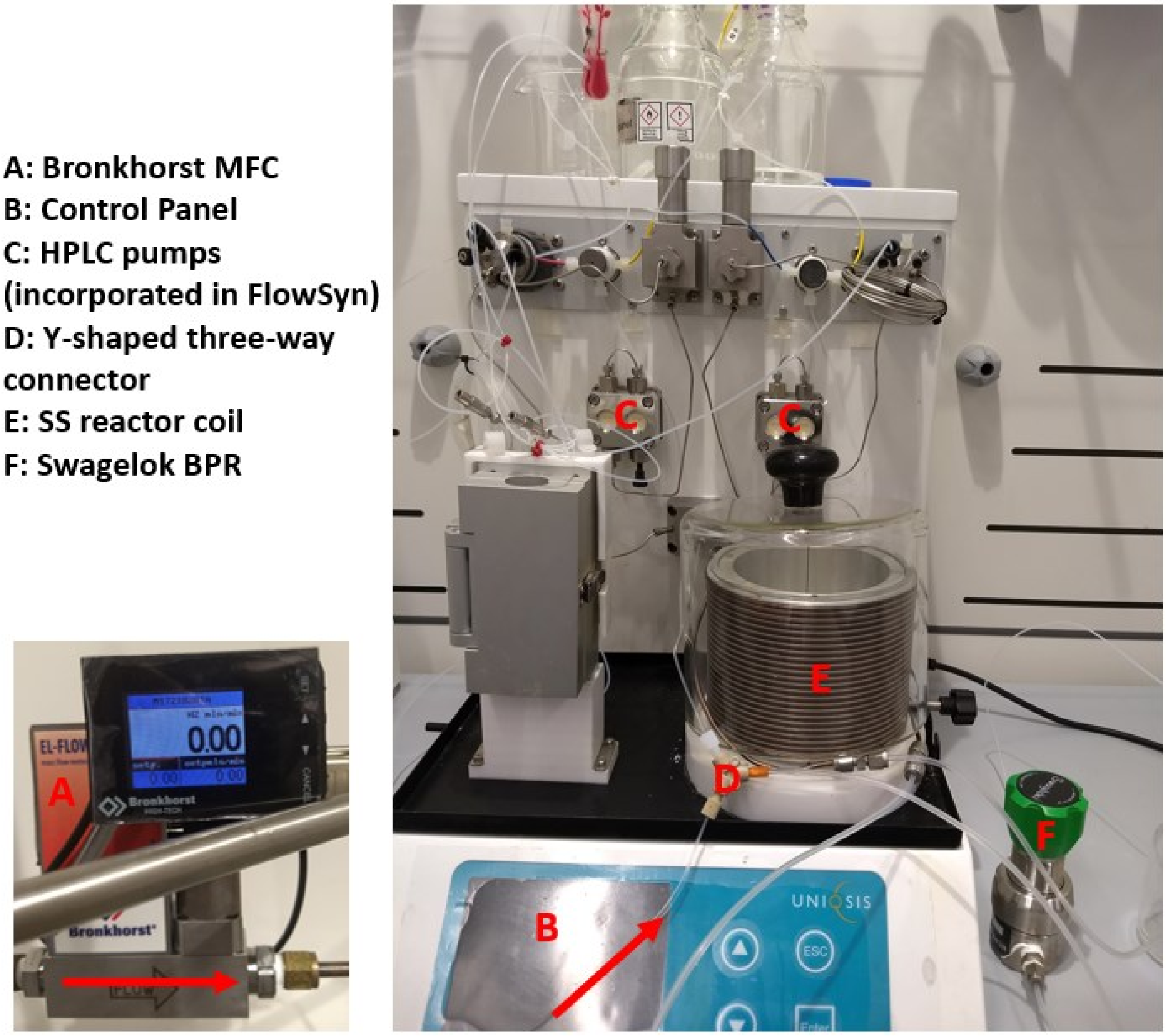

A: Bronkhorst MFC
B: Control Panel
C: HPLC pumps (incorporated in FlowSyn)
D: Y-shaped three-way connector
E: SS reactor coil
F: Swagelok BPR

Figure S1. Labeled continuous flow setup for the Ru-MACHO hydrogenation optimization experiments.

2.2.2 Flow Procedure for the Long Run

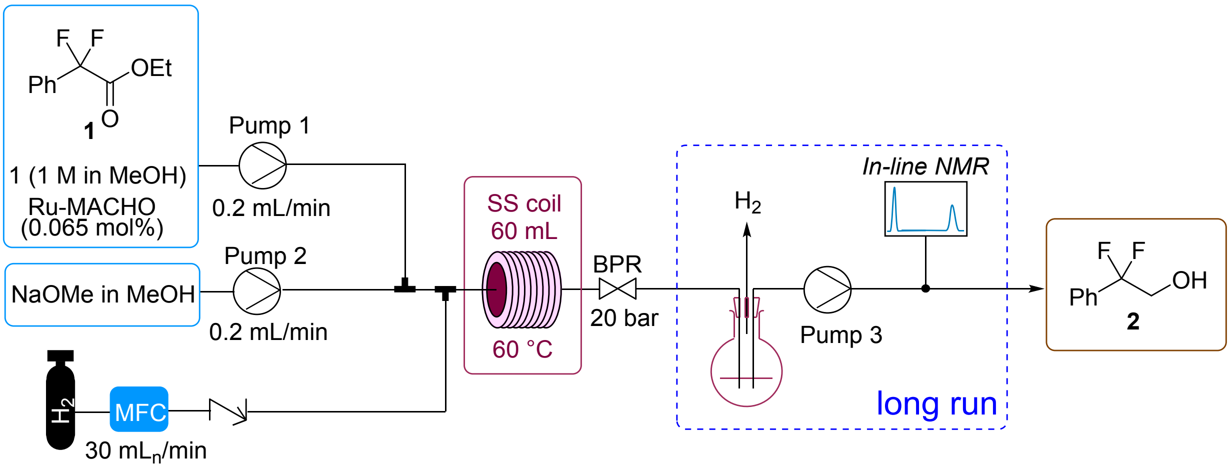
Feed Preparation

Feed 1: To a 50 mL volumetric flask were added Ru-MACHO (48 mg, 78 μmol), ethyl 2,2-difluoro-2-phenylacetate (**1**) (24.0 g, 120 mmol) and α,α,α-trifluorotoluene (1.8 g, 12.3 mmol) as internal standard. Anhydrous methanol was added to a fill volume of 50 mL and the solution was placed within an ultrasound bath until the catalyst was completely dissolved. The solution was then transferred to a 100 mL Duran bottle. Anhydrous methanol (10 mL) was added. The feed solution was kept under an argon atmosphere.

Feed 2: NaOMe as a solution in anhydrous methanol (25% w/w).

Flow Procedure

The continuous flow setup (Scheme S2) consisted of two HPLC pumps (Uniqsis) for introducing the two liquid feeds. Each liquid feed was pumped at 0.2 mL/min, corresponding to a total liquid flow rate of 0.4 mL/min. Hydrogen gas was introduced from a gas cylinder at 30 mL_n/min by using a calibrated mass flow controller (MFC, Bronkhorst EL-FLOW). The two liquid feeds were combined within an arrow-shaped mixer which contained an integrated pressure sensor. The liquid stream was then combined with the gas stream by using a Y-shaped three-way mixer. A segmented (Taylor) gas-liquid flow regime was observed. The mixer was connected to the reactor coil using fluoropolymer tubing (PFA, 0.8 mm inner diameter). For the reaction a stainless steel coil (60 mL, 1/8 in. OD, 1/16 in. ID), placed on an aluminium heating block and within a glass dome (Uniqsis FlowSyn), was heated to 60 °C. After exiting the reaction coil the reaction mixture passed through a short piece of fluoropolymer tubing and an adjustable back pressure regulator (BPR, Chemtrix, 20 bar). Afterwards the hydrogen was separated from the liquid phase by using a glass vial as a gas/liquid separator. After this separation, the reaction mixture was continuously pumped through a flow cell (0.8 mL internal volume, max. pressure 10 bar) using a HPLC pump (Knauer). ^{19}F NMR spectra were collected, approximately every 20 secs and >800 measurements. Labeled images of the setup are shown in Figure S2, including the incorporation of the in-line NMR.



Scheme S2. Continuous flow scheme for the Ru-MACHO hydrogenation long run.

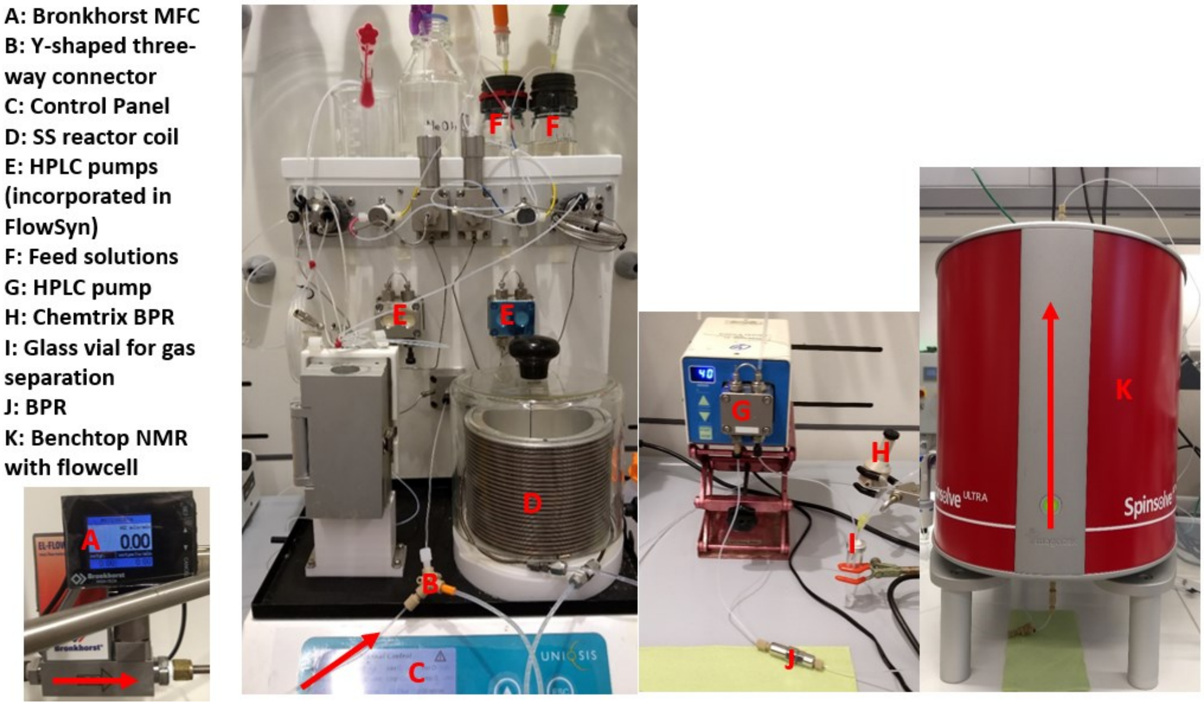

A: Bronkhorst MFC
B: Y-shaped three-way connector
C: Control Panel
D: SS reactor coil
E: HPLC pumps (incorporated in FlowSyn)
F: Feed solutions
G: HPLC pump
H: Chemtrix BPR
I: Glass vial for gas separation
J: BPR
K: Benchtop NMR with flowcell

Figure S2. Labeled flow setup for the long run of the Ru-MACHO hydrogenation.

Extraction Protocol

The fractions obtained during “steady-state” operation, which corresponded to an operating time of 220 min (88 mL, 88 mmol of substrate), were combined in a 250 mL round bottom flask. The solvent was evaporated under reduced pressure. Water (50 mL) was added and the product was extracted with ethyl acetate (50 mL) and a second time with ethyl acetate (20 mL). The combined organic phases were dried over sodium sulfate and filtered. The solvent was removed under reduced pressure to afford 2,2-difluoro-2-phenyl-2-ethanol (**2**) (13.7 g, 86 mmol, 98% yield). ^{1}H NMR (300.36 MHz, DMSO-d^{6}): δ = 7.64 - 7.45 (m, 5H), 5.78 - 5.68 (m, 1H), 4.00 - 3.85 (m, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d^{6}): δ = 135.2 (t, $^{2}J_{CF}$ =2 5.5 Hz), 130.18 (s), 128.54 (s), 125.69 (t, $^{3}J_{CF}$ = 6.2 Hz), 121.62 (t, $^{1}J_{CF}$ = 242.8 Hz), 64.27(t, $^{2}J_{CF}$ = 32.9 Hz) ppm. ^{19}F NMR (282 MHz, DMSO-d^{6}): δ = −103.74 (m) ppm.

2.3 Identification of the Acid Side Product

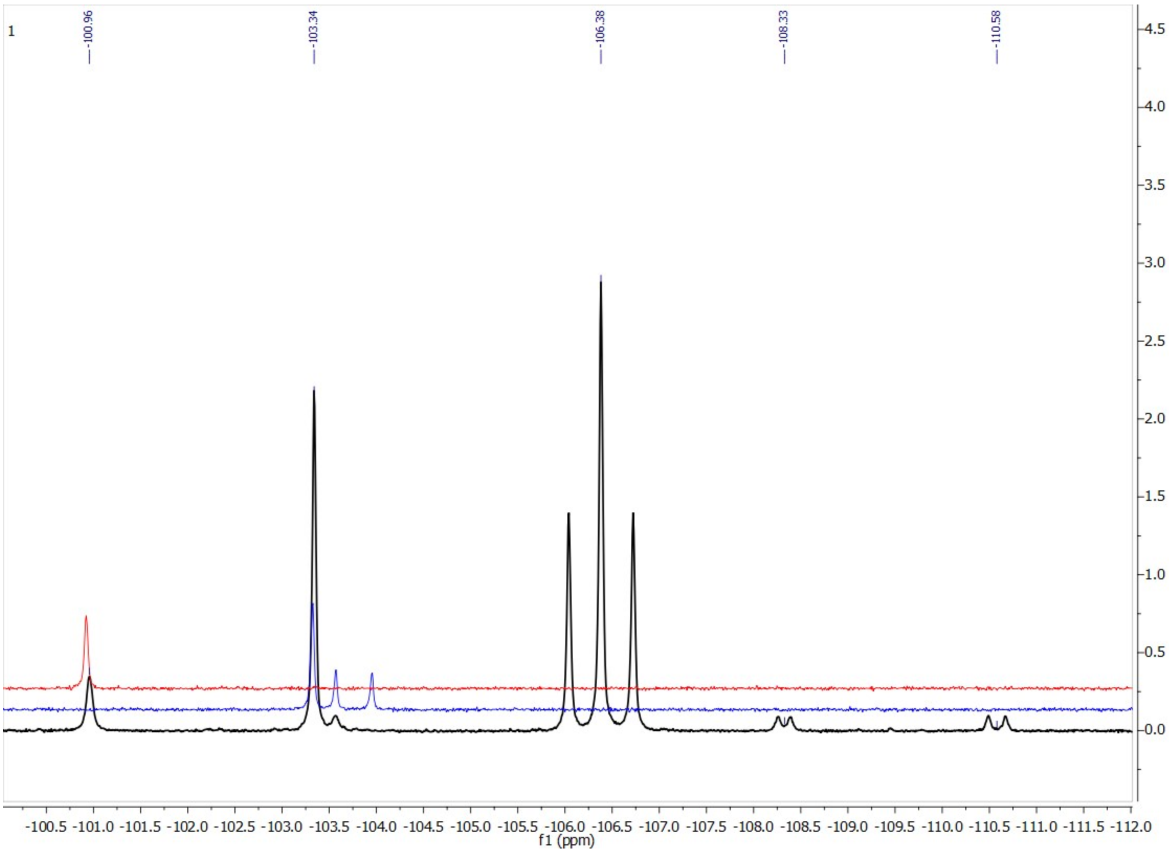


Figure S3. ^{19}F NMR to elucidate the acid side product **3**: The black spectrum is representative of a reaction mixture. The blue spectrum shows the methyl and ethyl ester (**1** and **5**) and the corresponding acid **3**. The red spectrum shows the acid in basic methanol solution, which overlaps with the peak corresponding with the side product in black at −100.96 ppm.

Table S3. Control experiments using acid **3** as starting material.

Exp.	NaOMe (equiv)	Acid **3** [%]	Product **2** [%]	Methyl ester **5** [%]
1	0.2	94	0	6
2	1.2	100	0	0

[a]0.4 mL/min total liquid flow rate, both liquid feeds were pumped at equal flow rates, 0.5 M acid **3**, 30 mL$_n$/min H$_2$ flow rate, 0.065 mol% catalyst loading, 60 °C temperature, 20 bar pressure. Reagents were introduced for 30 min then switched to carrier solvent.

2.4 DoE Analysis

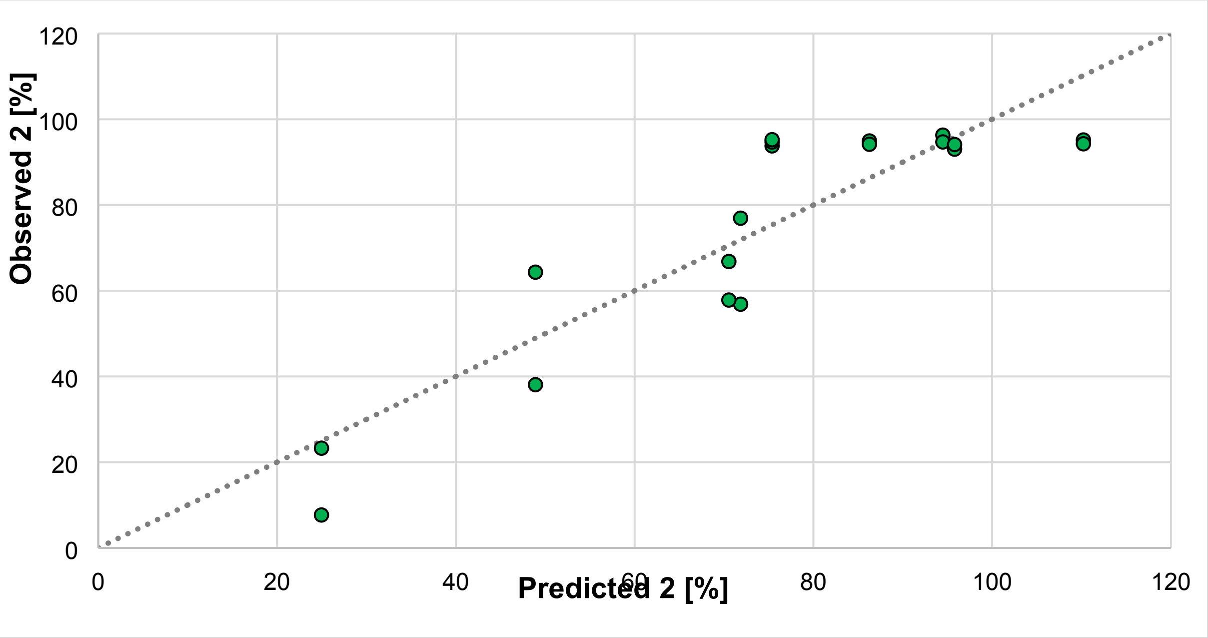


Figure S4. Observed versus predicted for alcohol **2** yield.

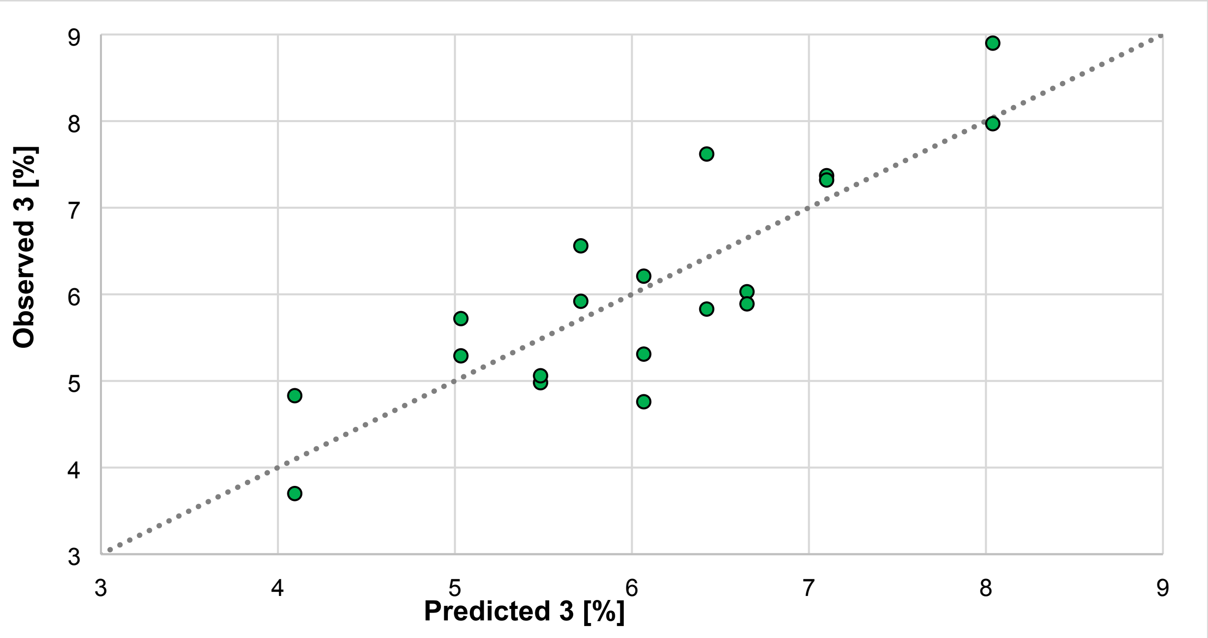


Figure S5. Observed versus predicted for acid side product **3** yield.

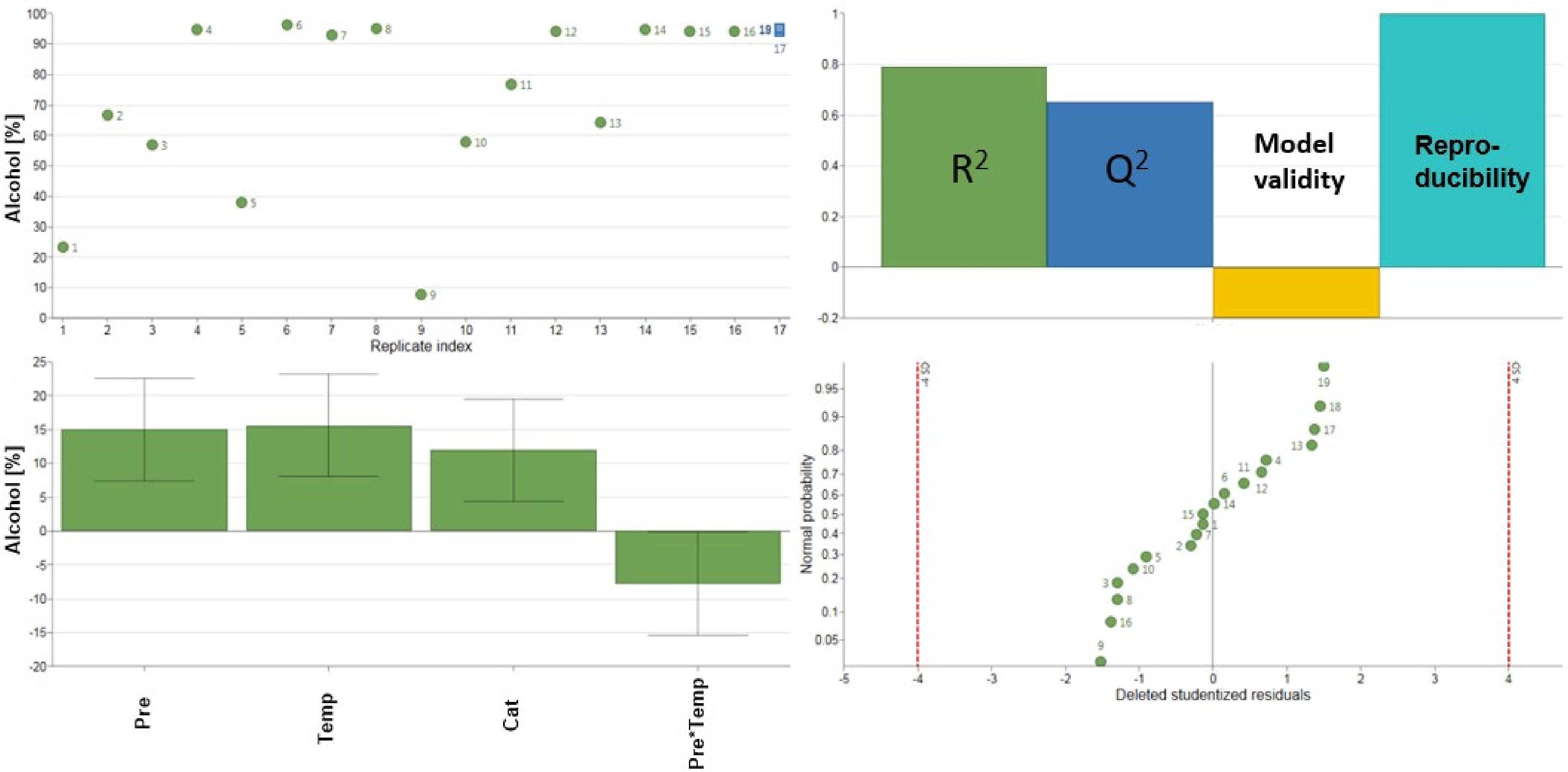


Figure S6. Summary of the model fit for product **2** yield. The top left shows the replicate index versus the alcohol **2** yield. The assessment of the model fit is shown with R^2, Q^2, model validity and reproducibility. Model validity can be low (negative) in very good models due to very good replicates. The bottom left shows all parameters that were identified to have a statistically significant influence on the product yield. The bottom right shows the statistical distribution of the residuals for the measured values.

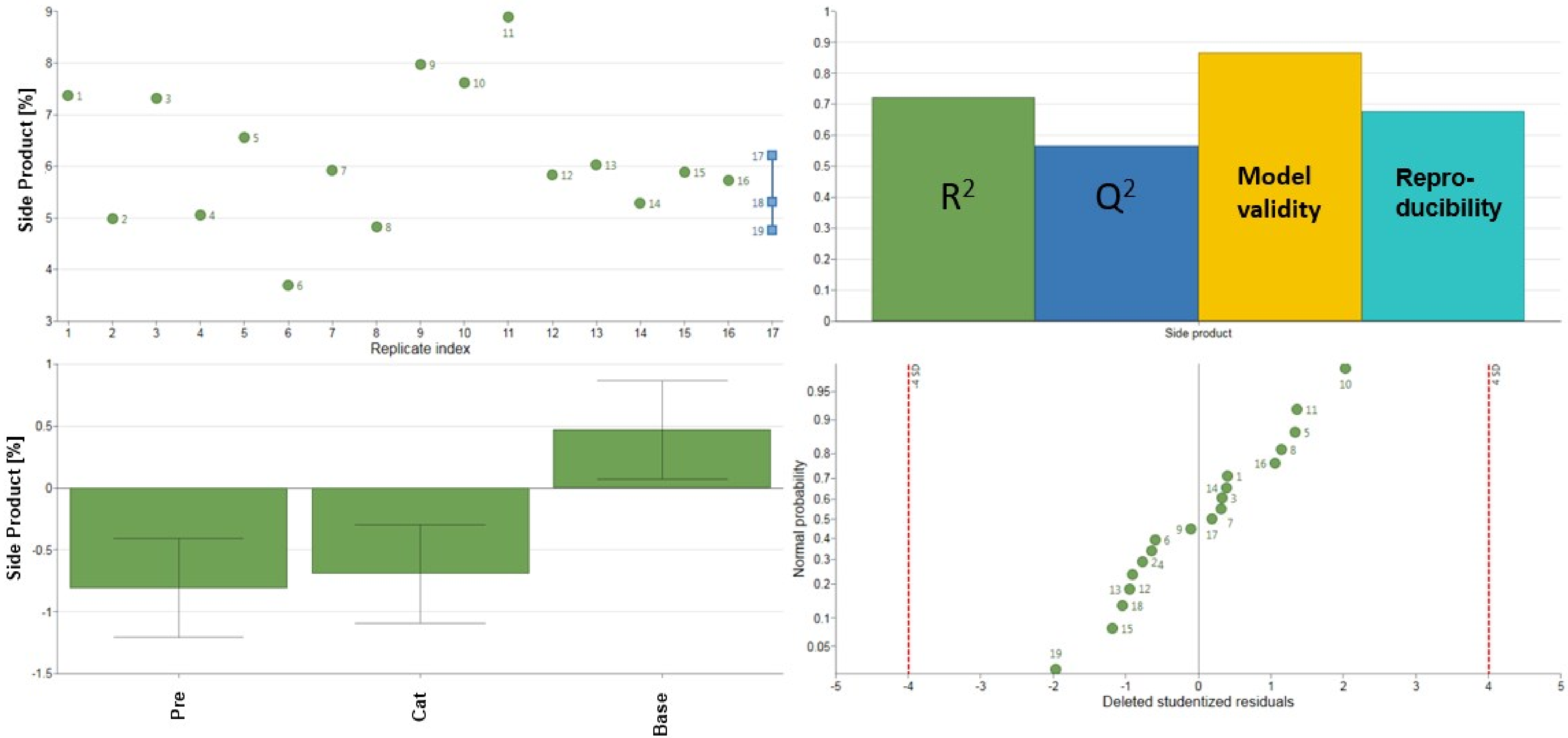


Figure S7. Summary of the model fit for acid side product (**3**) yield. The top left shows the replicate index versus the side product (**3**) yield. The assessment of the model fit is shown with R^2, Q^2, model validity and reproducibility. The bottom left shows all parameters that were identified to have a statistically significant influence on the side product yield. The bottom right shows the statistical distribution of the residuals for the measured values.

2.5 Data Ru-MACHO-BH

Table S4. Results from the experiments using Ru-MACHO-BH as catalyst.[a]

Entry	Temperature [°C]	Pressure [bar]	Cat. loading [mol%]	Base [eq]	Conc. [mol/L]	Conv. [%]	Alcohol [%]
1	50	20	0.076	0	2	0	0
2	50	20	0.076	0.2	2	>99	98

[a]Reaction conditions: 5 mmol of **1,** 2.5 mL of MeOH, stirring at 600 rpm for 1 h. Conversion and product formation determined by ^{19}F NMR.

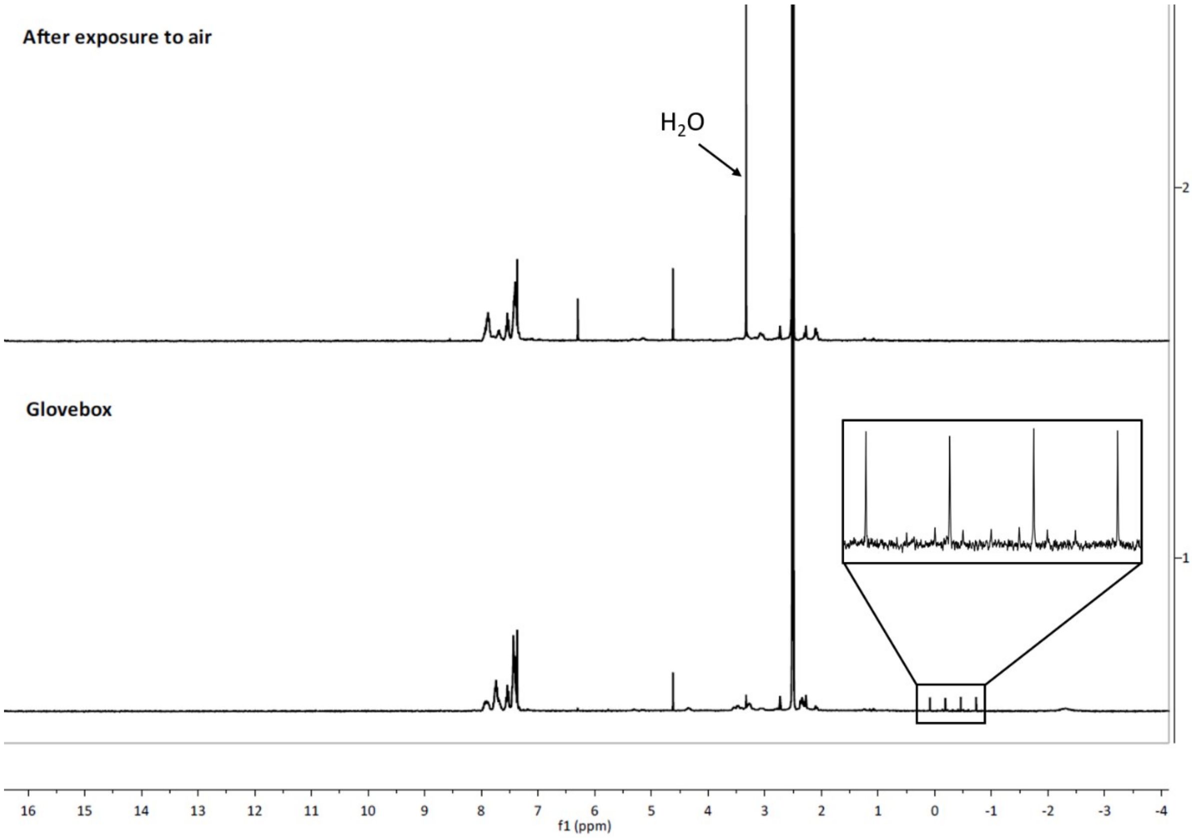


Figure S8. Comparison of ^1H NMR spectra for Ru-MACHO-BH in DMSO-d^6 before and after exposure to air. At 3.33 ppm the peak corresponding to water is visible, which is clearly much larger after exposure to air. Between −0.73 ppm and 0.08 ppm the signal corresponding to protons connected to a boron atom are assigned because of the specific coupling pattern to ^{10}B and ^{11}B. This signal disappears after exposure to air, which implies that the borane group has been hydrolyzed.

3. Green Metrics

$$\%\,Yield = \frac{moles\ of\ product}{moles\ of\ limiting\ reactant} \cdot 100$$

$$\%\,Conversion = 100 - \frac{final\ mass\ of\ limiting\ reactant}{initial\ mass\ of\ limiting\ reactant} \cdot 100$$

$$\%\,Selectivity = \frac{\%\,yield}{\%\,conversion} \cdot 100$$

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

$$E = \frac{mass\ of\ total\ waste}{mass\ of\ product}$$

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \cdot 100$$

$$Process\ mass\ intensity\ = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$E\ factor = \frac{total\ mass\ of\ waste}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \cdot 100$$

3.1 Amounts and quantities used for Green Metrics Calculations

Table S5. Values used for the assessment of the green metrics for the Ru-MACHO flow protocol.

Role	Chemical	Mass (g)	Volume (mL)	MW	Density (g/mL)	Mol
Reaction						
Reactant	Ethyl 2,2-difluoro-2-phenyl-acetate (**1**)	17.6		200.18		0.0880
Reactant	H_2	0.59		2.00		0.297
Catalyst	Ru-MACHO (**A**)	0.0347				
Reagent	NaOMe	0.957				
Solvent	MeOH	69.7	88.0		0.792	
	Reaction total	88.8				
Work-up						
Solvent	EtOAc	66.6	70		0.902	
Solvent	H_2O	44.7	50		1.00	
	Work-up total	108.2				
	Reaction and work-up total	197				
Product						
Product	2,2-Difluoro-2-phenylethanol (**2**)	13.7				0.0866

Table S6. Values used for the assessment of the green metrics for the $LiAlH_4$ reduction. Based on procedure in ref (1).

Role	Chemical	Mass (g)	Volume (mL)	MW	Density (g/mL)	Mol
Reaction						
Reactant	Ethyl 2,2-difluoro-2-phenyl-acetate (**1**)	15.0		200.18		0.0749
Reactant	$LiAlH_4$	3.12		38.0		0.0822
Solvent	THF	95.1	107		0.889	
	Reaction total	113.4				
Work-up						
Chemical	L-(+)-tartaric acid	25.0				
Solvent	H_2O		272		1.00	
Solvent	MTBE	133	180		0.740	
	Work-up total	452				
	Reaction and work-up total	565.4				
Product						
Product	2,2-Difluoro-2-phenylethanol (**2**)	11.0				0.0694

Table S7. Values used for the assessment of the green metrics for the $NaBH_4$ reduction. Based on procedure in ref (2).

Role	Chemical	Mass (g)	Volume (mL)	MW	Density (g/mL)	Mol
Reaction						
Reactant	Ethyl 2,2-difluoro-2-phenyl-acetate (**1**)	1.46		200.18		0.00729
Reactant	$NaBH_4$	0.276		38.0		0.00730
Solvent	MeOH	19.8	25.0		0.792	
	Reaction total	21.5				
Work-up						
Chemical	NH_4Cl	3.28				
Solvent	EtOAc	46.0	50.0		0.902	
Solvent	H_2O	53.0	53.0		1.00	
	Work-up total	102.2				
	Reaction and work-up total	106.5				
Product						
Product	2,2-Difluoro-2-phenylethanol (**2**)	0.934				0.00591

Table S8. Values used for the assessment of the green metrics for the synthesis of Ru-MACHO (**A**). Based on procedure in ref 3.

Role	Chemical	Mass (kg)	MW	Mol
Reaction				
Reactant	Carbonylchloro-hydridotris(triphenylphosphine)ruthenium(II) (**E**)	72.0	952.40	75.6
Reactant	Bis[(2-diphenylphosphino)ethyl]ammonium chloride (**D**)	42.0	477.95	87.9
Reactant	NaOH	10.5	40.0	262
Solvent	PhMe	294		
	Reaction total	419		
Work-up				
Solvent	H_2O	84		
Solvent	PhMe	216		
	Work-up total	300		
	Reaction and work-up total	719		
Product				
Product	Ru-MACHO (**A**)	38.8		63.9

4. References

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2) M.-T. Hsieh, K.-H. Lee, S.-C. Kuo and H.-C. Lin, *Adv. Syn. Catal.*, 2018, **360**, 1605-1610.

3) W. Kuriyama, T. Matsumoto, O. Ogata, Y. Ino, K. Aoki, S. Tanaka, K. Ishida, T. Kobayashi, N. Sayo and T. Saito, *Org. Process Res. Dev.*, 2012, **16**, 166–171.

5. NMR Spectra

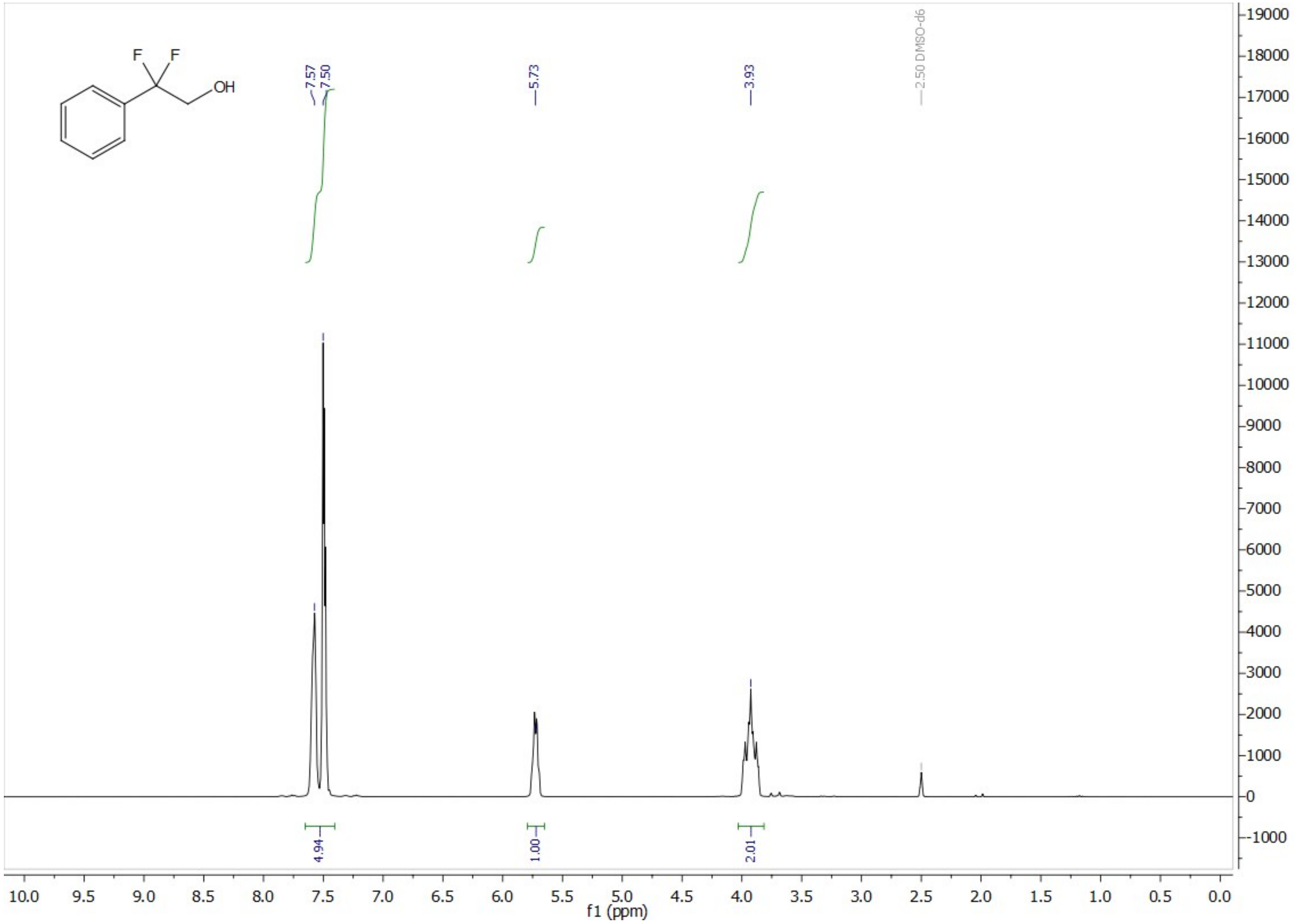

Figure S9. ^{1}H NMR spectrum of 2,2-difluoro-2-phenylethanol (**2**).

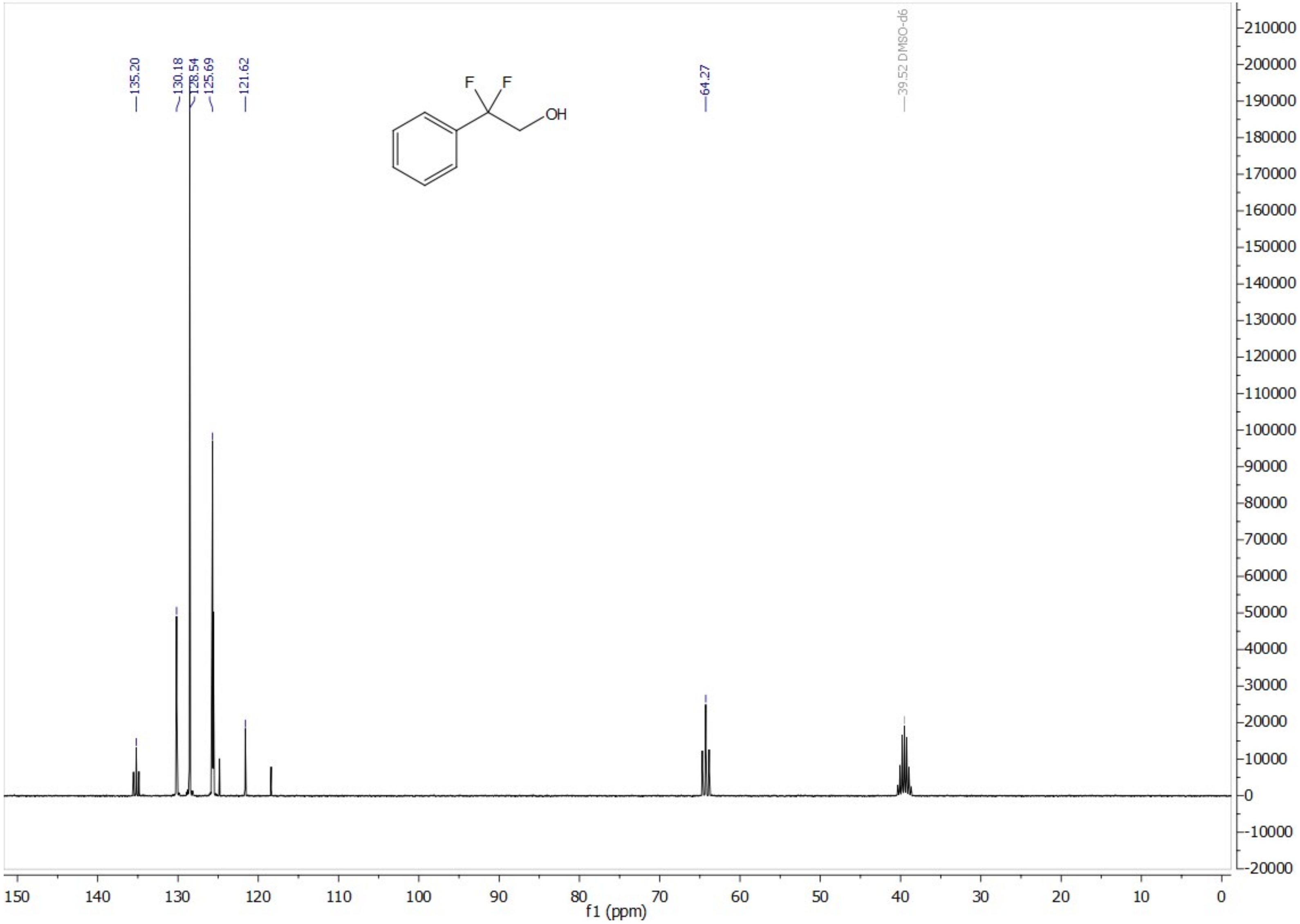

Figure S10. ^{13}C NMR spectrum of 2,2-difluoro-2-phenylethanol (**2**).

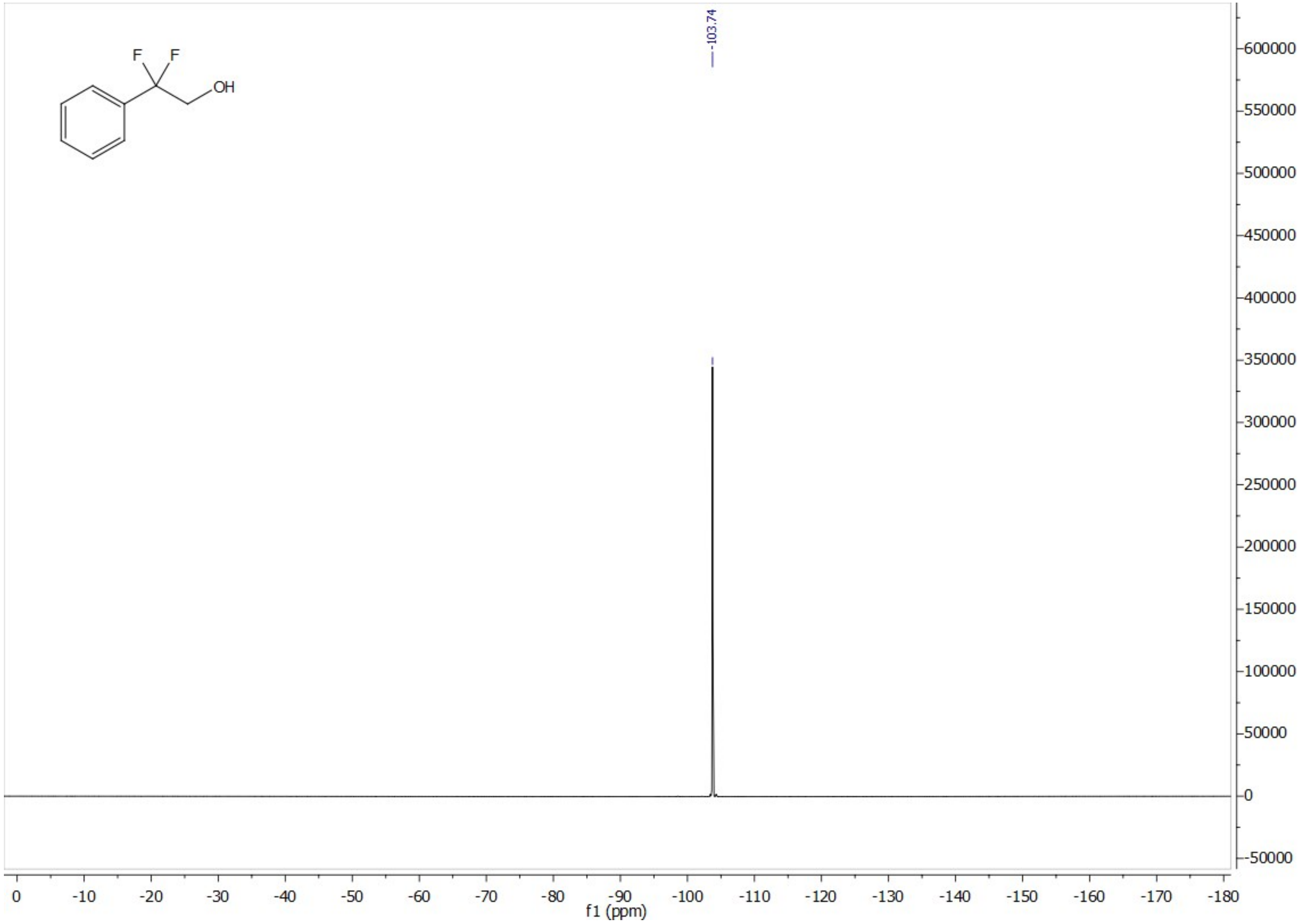

Figure S11. ^{19}F NMR spectrum of 2,2-difluoro-2-phenylethanol (**2**).