

CHEMISTRY

A EUROPEAN JOURNAL

Supporting Information

© Copyright Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2013

A Fully Integrated Continuous-Flow System for Asymmetric Catalysis: Enantioselective Hydrogenation with Supported Ionic Liquid Phase Catalysts Using Supercritical CO₂ as the Mobile Phase

Ulrich Hintermair,^[a, b] Giancarlo Franciò,^[a] and Walter Leitner*^[a, c]

chem_201204159_sm_miscellaneous_information.pdf

1. High-pressure NMR experiments	2
2. High-pressure batch catalysis.....	2
3. High-pressure continuous-flow catalysis	2
4. Substrate volume expansion with subcritical CO ₂	4
5. Substrate extraction from EMIM NTf ₂ into scCO ₂	4
6. Hydrogenation kinetics of 1 using 3 in DCM	5
7. Stability of 3 in EMIM NTf ₂	5
8. Surface-analysis of SG100.....	6
9. Ageing of SILP catalysts based on 3 in EMIM NTf ₂ on SG100-500	6
10. Effect of additional ligand on 3 in EMIM NTf ₂ on SG100-500	9
11. Effect of additional ligand on hydrogenation performance of 3 in DCM.....	9
12. Hydrogenation kinetics of 1 using Rh-DuPHOS in DCM	10
13. Performance of SILP catalyst based on Rh-DuPHOS in EMIM NTf ₂ on SG100-500	10
14. Surface-deuteration of SG100.....	11
15. Performance of SILP catalyst based on 3 in 4-MBP NTf ₂ on SG100-500	11
16. Surface-analysis of SG170.....	12
17. Performance of SILP catalyst based on 3 in EMIM NTf ₂ on SG170-500	12
18. Surface-silylation of SG100.....	13
19. Performance of SILP catalyst based on 3 in EMIM NTf ₂ on SG100TMS	13
20. Surface-analysis of SGFLUO	14
21. Surface-analysis of SILP catalyst based on SGFLUO	14
22. Post-reaction analysis of SILP catalyst based on SGFLUO	15
23. Effect of trace water on hydrogenation performance of 3 in DCM	15
24. Post-reaction analysis of water scavenger.....	16

1. High-pressure NMR experiments

NMR spectra were recorded on a commercial BRUKER DPX-300 spectrometer equipped with a standard temperature control unit. High pressure measurements were performed in a 5 mm sapphire tube (id = 3.4 mm, V = 0.87 mL) glued (TEK Eccobond 104) into a titanium head connected to an electronic pressure reader (WIKA). The pre-heated, pressurized tube was equipped with a wide-bore spinner for improved heat transfer and manually lowered with a string into the magnet pre-heated to the required temperature. The sample was not unlocked but shimmed manually and data acquisition without spinning started with minimal delay. Spectra were automatically baseline and phase corrected and peaks integrated manually. Molar ratios were calculated from relative peak areas, and concentrations were obtained based on initial volumes of IL and CO₂, respectively.

2. High-pressure batch catalysis

Liquid phase high pressure reactions were conducted in 10 mL stainless steel autoclaves with sapphire windows and a magnetic stir bar. Periodical blank tests without catalyst confirmed negligible background activity under typical conditions. Prior to use, the autoclave was dried at 60 °C in HV and repeatedly filled with argon. The catalyst was weighed into a Schlenk flask inside a glovebox, solid substrate was added, and the mixture dissolved in the desired amount of solvent. The solution was quickly transferred into the autoclave via syringe against a counter-flow of argon. The reactor was sealed, heated to reaction temperature on a hot plate, CO₂ added (if needed), and catalysis started by addition of hydrogen overpressure. Gas uptake curves were recorded via an electronic pressure reader (WIKA) connected to LabVIEW (National Instruments). After the reaction the autoclave was cooled, carefully vented, and an aliquot of the content passed over silica to be analysed by chiral GC.

3. High-pressure continuous-flow catalysis

All continuous runs with scCO₂ flow were performed using the equipment described in detail in reference 44. Between the individual experiments, the setup typically remained under CO₂ pressure at 40 °C to prevent contamination and facilitate start-up. Prior to use, the LabVIEW regulation program was restarted to empty the internal cache. All gas feeds were checked for sufficient overpressure (at least 15 % above the operating pressure) and all lines opened until the last ball valve to the rig. Heating of the CO₂ dosing unit, the BPR, and the sample loop as well as data recording was started. If necessary, purified substrate was molten and filled into the reservoir via syringe under N₂.

The plug flow reactor (stainless steel tube, l = 13 cm, id = 0.7 cm), equipped with two ball valves, was closed on the downstream end and inserted into a glovebox. There it was filled with a stopper of dried glass wool (ca. 2 cm) and the height of the remaining empty tube measured with a dip stick. SILP catalyst was poured in (weighed from its stock container) and the reactor tapped to achieve even packing of the bed. The remaining height was measured again with the dip stick to yield the SILP bed volume by difference, and the catalyst fixed with another stopper of dried glass wool (ca. 1 cm). After cleaning the metal flange with a brush the reactor was closed with a wrench and taken out of

the glovebox. All connections were thoroughly tightened on a bench vice and the reactor mounted in the heated reaction rig.

After purging all connections with CO₂, the reactor was pressurized with 120 bar CO₂ and purged at 100 – 200 mL_N min⁻¹ flow until regulation of pressure and flow had stabilized (30 – 60 minutes). Leak checks of both valves and connections were performed with soap water. The CO₂ flow was reduced to the desired value and 120 bar hydrogen pressure built up on the closed feed line. After H₂ had reached system pressure the desired flow was added to the feed to begin catalyst activation. During activation (typically one hour) the substrate dosing was tested to ensure proper start-up of the HPLC pump. The feed line was purged with a few mL of fresh liquid substrate to flush out potential gas bubbles from the line and the valves in the pump head. The line was closed and the pump started at 1 mL_N min⁻¹ until 100 – 120 bar pressure had been built up and remained stable after pump stop. The flow was lowered stepwise to 0.5, 0.1, and 0.05 mL_N min⁻¹ to ensure steady pressure build-up also at low piston velocities. When the pump was able to build up pressure at the desired reaction flow rate it was kept under overpressure ready for application. The reaction was started by switching on the pump and opening the ball valve to the equilibrated SCF flow, always with an overpressure of liquid substrate to avoid gas intrusion. The incubator was closed and left untouched to allow the balance-controlled substrate flow regulation to stabilise. Cooling traps (l = 20 cm, id = 2 cm) filled with glass beads (d = 1 mm) and distilled DCM (ca. 6 mL) collected non-volatiles from the effluent and allowed gases to vent to atmospheric pressure through an exhaust. The traps were changed periodically, the liquid content emptied into a tared flask, the glass beads and the trap washed twice with DCM, all fractions combined and the volatiles removed by rotary evaporation. The clear liquid residue was weighed and analysed by chiral GC for conversion and selectivity. The remaining sample was stored for further analysis (NMR or ICP-OES).

The reaction was stopped by closing substrate and hydrogen feeds, and the SILP catalyst was extracted with scCO₂ for at least 4 hours. The CO₂ flow was stopped and the BPR set to atmospheric pressure for ramped depressurization (3 bar min⁻¹). The ball valves of the reactor were closed, the BPR stopped and the rig switched to bypass to remain under CO₂ pressure. The reactor was dismantled, the upstream connector loosened and the SILP catalyst either recovered in air (storage or trace analysis) or in a glovebox (DRIFTS analysis or re-use in catalysis).

4. Substrate volume expansion with subcritical CO₂

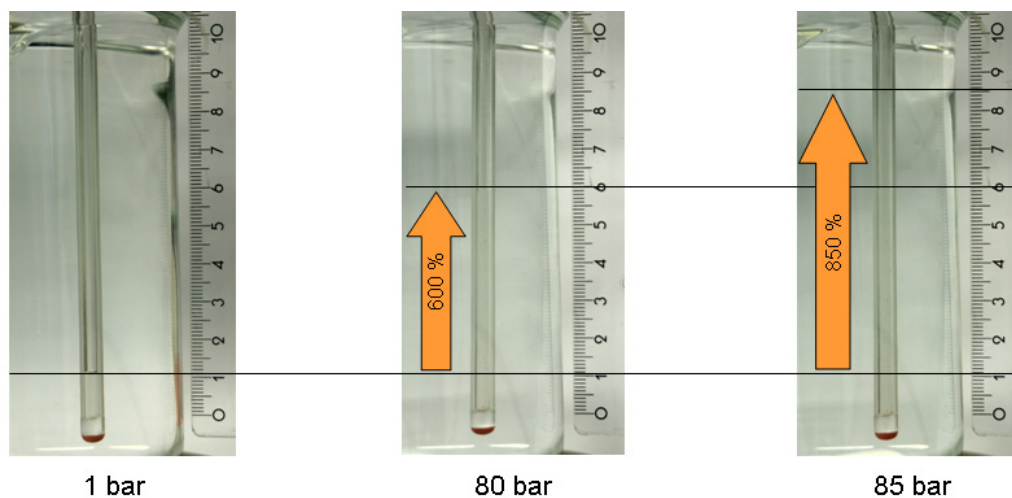


Figure S1: Volumetric expansion of 130 mg **1** with subcritical CO₂ in a 0.87 mL sapphire tube at 40 °C (± 0.2 °C) with increasing pressure (scale on the right in cm, lines indicate visually observed phase boundaries)

5. Substrate extraction from EMIM NTf₂ into scCO₂

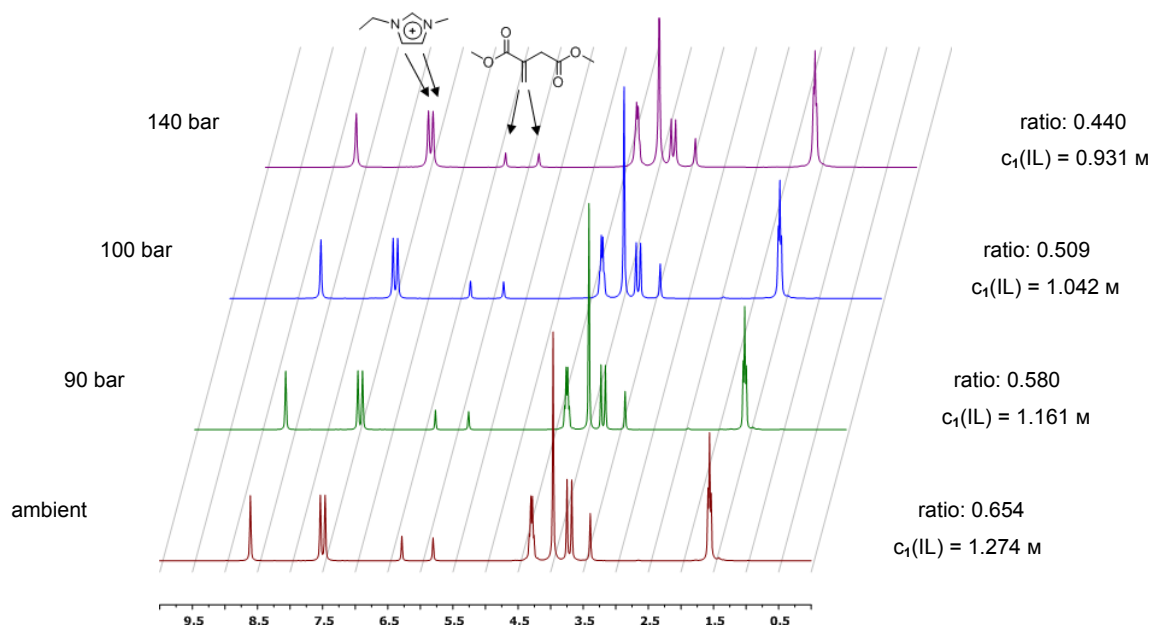


Figure S2: ¹H-NMR spectra of the liquid phase consisting of **1** and EMIM NTf₂ at 40 °C at various CO₂ pressures with integral ratios of the vinylic protons of **1** relative to the heterocyclic 4/5-protons of EMIM⁺ and concentrations of **1** in EMIM NTf₂ as calculated by difference

6. Hydrogenation kinetics of **1** using **3** in DCM

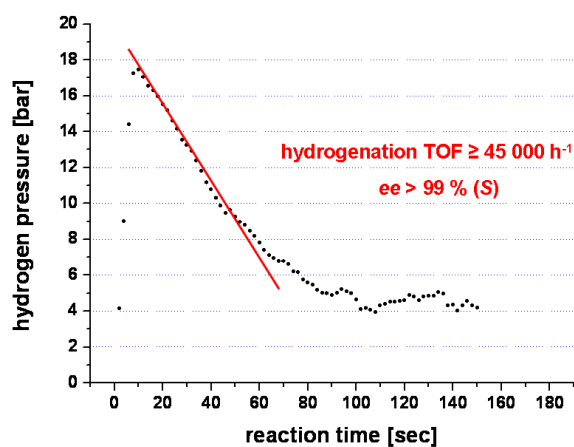


Figure S3: Gas uptake during the hydrogenation of **1** at 40 °C in 2 mL DCM with 5 μmol **3** at S/C = 1000 and 10 mL head-space

7. Stability of **3** in EMIM NTf₂

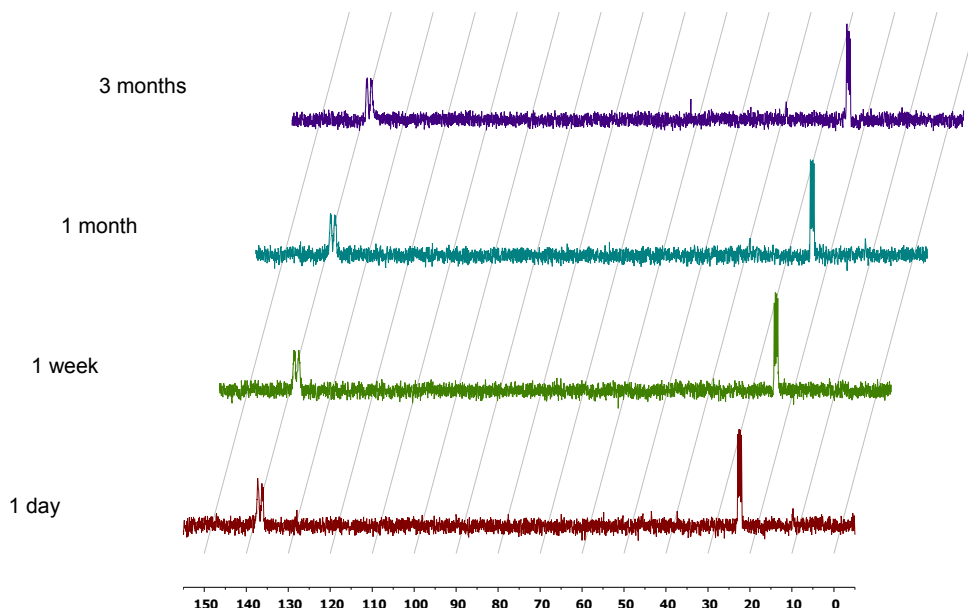


Figure S4: ^{31}P -NMR spectra of **3** in neat EMIM NTf₂ (7 mM) stored in a sealed NMR tube with external lock solvent under argon ($\delta = 136.6$ ppm (O₂NP-Rh), 22.5 ppm (C₃P-Rh). P-P couplings are not fully resolved due to poor shimming resulting from high solvent viscosity)

8. Surface-analysis of SG100

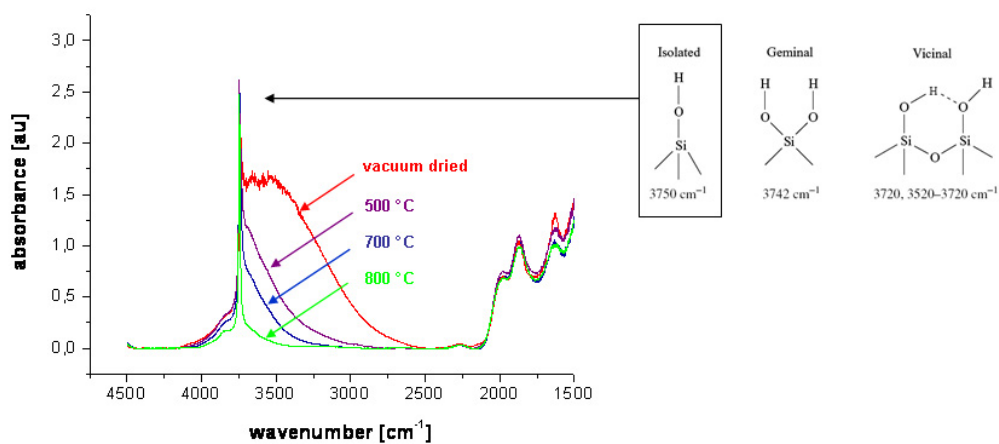


Figure S5: DRIFT spectra of SG100 after heating for 16 hours in vacuum to the temperature indicated with assignment of $\nu(\text{O-H})$ surface bands

9. Ageing of SILP catalysts based on **3** in EMIM NTf₂ on SG100-500

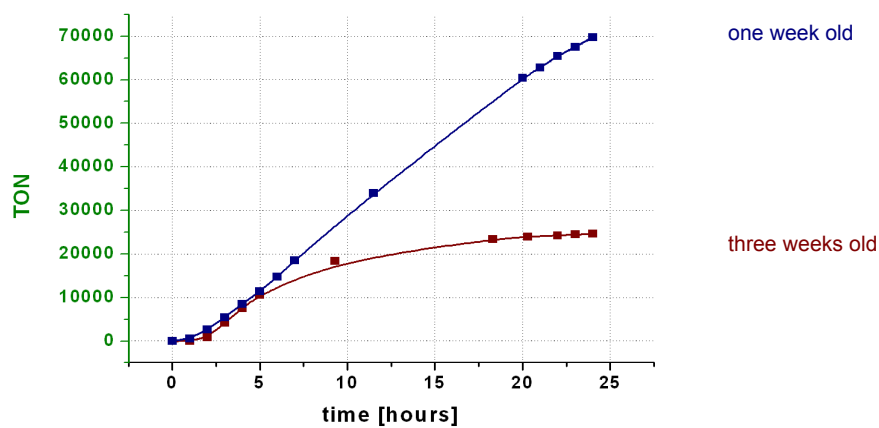


Figure S6: Cumulative TON curves of ~800 mg SILP catalyst based on **3** in EMIM NTf₂ ($\alpha = 0.35$) on SG100-500 of different age

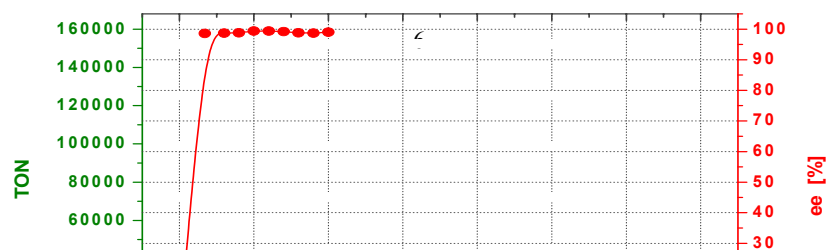


Figure S7. Cumulative TON (■) and *ee* (●) of 800 mg SILP catalyst based on **3** (1.3 μmol) in EMIM NTf₂ on SG100-500 (> 4 weeks old) in the continuous hydrogenation of **1** with scCO₂ flow at 40 °C and 120 bar ($V(\text{CO}_2) = 85 \text{ mL}_\text{N} \text{ min}^{-1}$, $V(\text{H}_2) = 10 \text{ mL}_\text{N} \text{ min}^{-1}$, $V(\text{1}) = 0.01 \text{ mL}_\text{N} \text{ min}^{-1} = 0.78 \text{ g h}^{-1}$)

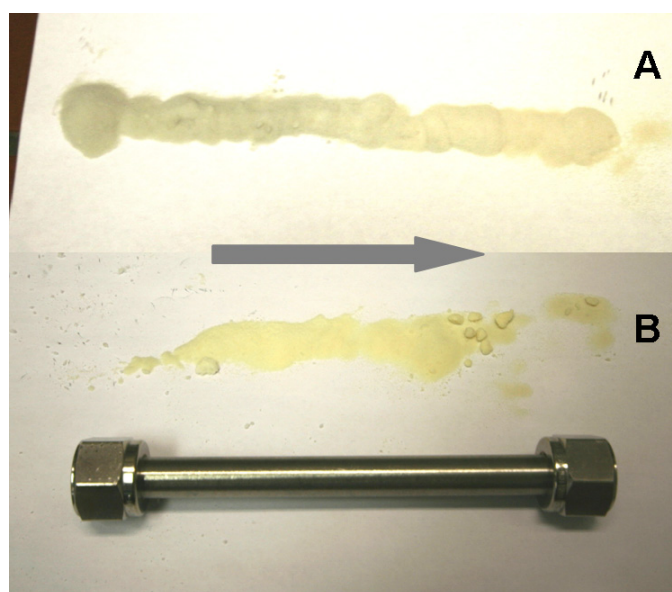


Figure S8. Photographs of SILP catalyst beds as recovered from the plug flow reactor (bottom, $l = 13 \text{ cm}$) after continuous-flow catalysis with scCO₂ (arrow indicates direction of the flow). A = slowly deactivated SILP catalyst (TON > 100 000, figure 8), B = quickly deactivated SILP catalyst (TON < 25 000, figure S7).

Table S1: ICP-OES elemental analysis of the SILP catalyst from figure S7 & S10B before and after application in continuous catalysis with scCO₂ (performed by MikroLab Kolbe, Mülheim an der Ruhr, Germany)

<i>3 in EMIM NTf₂ on SG100-500 ($\alpha = 0.35$)</i>	<i>carbon [%]</i>	<i>sulphur [%]</i>	<i>rhodium [ppm]</i>	<i>phosphorus [ppm]</i>
<i>as synthesised</i>	8.28	7.39	121	75
<i>after catalysis</i>	8.63	7.70	114	71

Table S2: ICP-OES elemental analysis of the SILP catalyst from figure 8 & S10A before and after application in continuous catalysis with scCO₂ (performed by MikroLab Kolbe, Mülheim an der Ruhr, Germany)

<i>3 in EMIM NTf₂ on SG100-500 ($\alpha = 0.35$)</i>	<i>carbon [%]</i>	<i>sulphur [%]</i>	<i>rhodium [ppm]</i>	<i>phosphorus [ppm]</i>
<i>as synthesised</i>	8.28	7.39	121	75
<i>after catalysis ^a</i>	11.59	7.64	86	50

^a Incomplete product extraction, as evidenced by ~30 % increased carbon content, suggests lower nominal Rh and P contents. Consistently, no rhodium was detected in any product fraction (detection limit 1 ppm).

10. Effect of additional ligand on **3** in EMIM NTf₂ on SG100-500

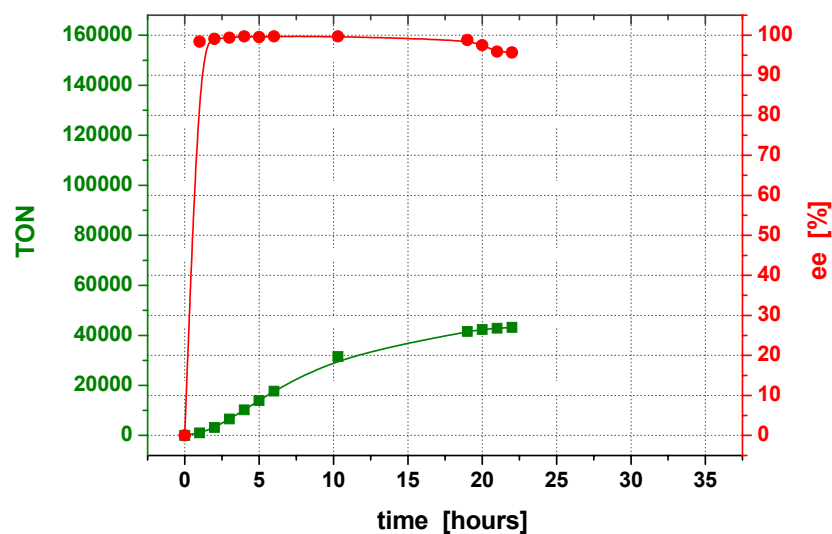


Figure S9. Cumulative TON (■) and *ee* (●) of 800 mg SILP catalyst based on **3** (1.3 μmol) plus 1-Naphthyl-QUINAPHOS (1.3 μmol) in EMIM NTf₂ on SG100-500 in the continuous hydrogenation of **1** with scCO₂ flow at 40 °C and 120 bar ($V(\text{CO}_2) = 85 \text{ mL}_N \text{ min}^{-1}$, $V(\text{H}_2) = 10 \text{ mL}_N \text{ min}^{-1}$, $V(\mathbf{1}) = 0.01 \text{ mL}_N \text{ min}^{-1} = 0.78 \text{ g h}^{-1}$)

11. Effect of additional ligand on hydrogenation performance of **3** in DCM

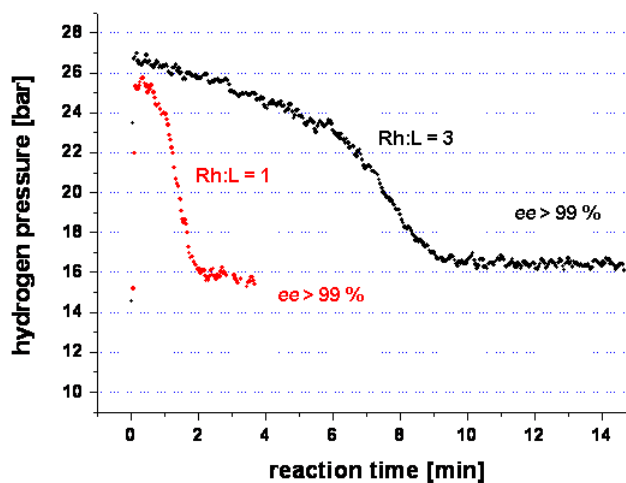


Figure S10: Gas uptake during the hydrogenation of **1** at 40 °C in 2 mL DCM with 5 μmol Rh with various eq. of 1-Naphthyl-QUINAPHOS (L) at S/Rh = 1000 and 10 mL headspace

12. Hydrogenation kinetics of **1** using Rh-DuPHOS in DCM

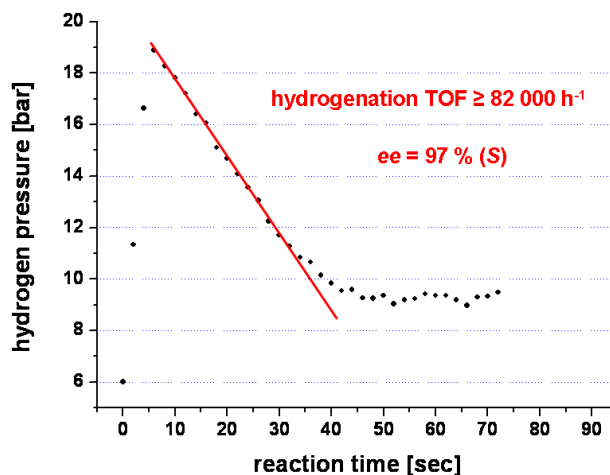


Figure S11: Gas uptake during the hydrogenation of **1** at 40 °C in 2 mL DCM with 5 μmol [Rh(cod)(*all*-*R*-MeDUPHOS)] NTf₂ at S/C = 1000 and 10 mL headspace

13. Performance of SILP catalyst based on Rh-DuPHOS in EMIM NTf₂ on SG100-500

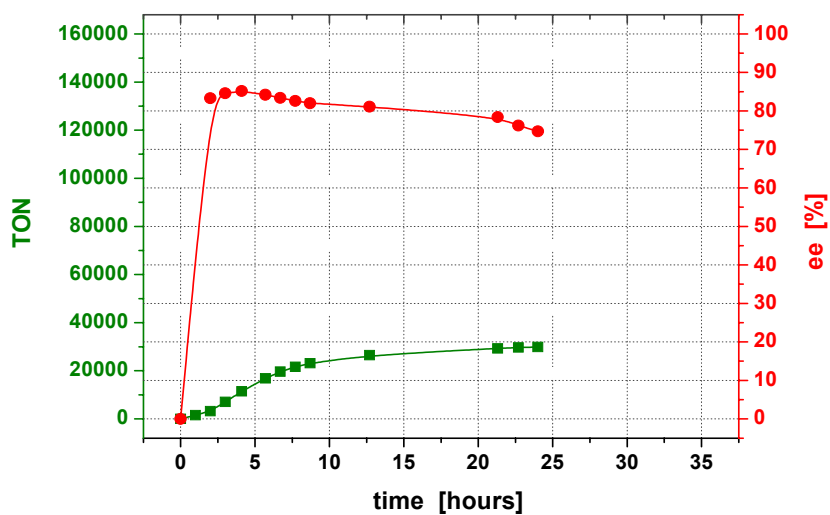


Figure S12: Cumulative TON (■) and *ee* (●) of 750 mg freshly prepared SILP catalyst based on [Rh(cod)(*all*-*R*-MeDUPHOS)] NTf₂ (1.2 μmol) in EMIM NTf₂ on SG100-500 in the continuous hydrogenation of **1** with scCO₂ flow at 40 °C and 120 bar ($V(\text{CO}_2) = 85 \text{ mL}_\text{N} \text{ min}^{-1}$, $V(\text{H}_2) = 10 \text{ mL}_\text{N} \text{ min}^{-1}$, $V(\textbf{1}) = 0.01 \text{ mL}_\text{N} \text{ min}^{-1} = 0.78 \text{ g h}^{-1}$)

14. Surface-deuteration of SG100

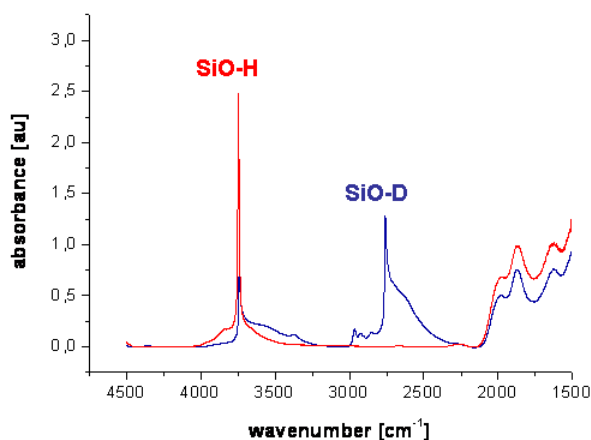


Figure S13: DRIFT spectra of SG100-800 and deuterated SG100-500. The difference between 3750 cm^{-1} for SiO-H and 2760 cm^{-1} for SiO-D is consistent with an increase of the reduced mass from 0.94 to 1.78 upon isotope exchange.

15. Performance of SILP catalyst based on **3** in 4-MBP NTf_2 on SG100-500

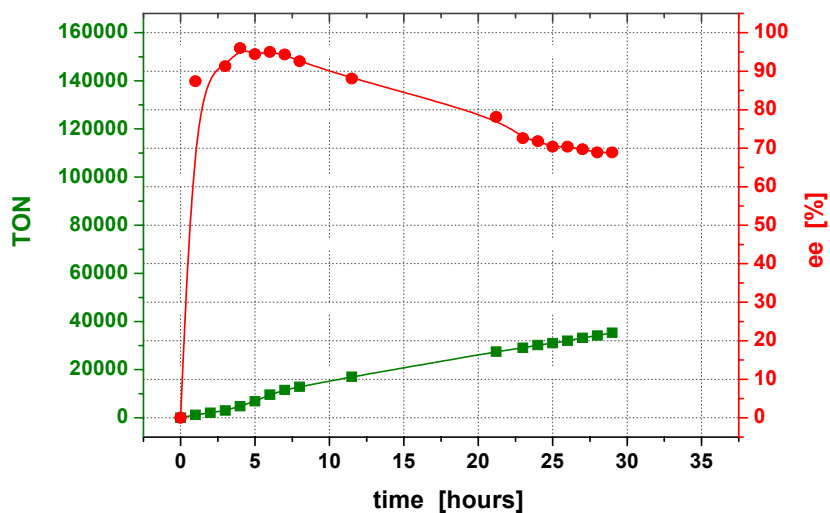


Figure S14: Cumulative TON (■) and *ee* (●) of 840 mg freshly prepared SILP catalyst based on **3** (1.4 μmol) in 4-MBP NTf_2 on SG100-500 in the continuous hydrogenation of **1** with scCO_2 flow at 40 $^\circ\text{C}$ and 120 bar ($V(\text{CO}_2) = 85 \text{ mL}_\text{N} \text{ min}^{-1}$, $V(\text{H}_2) = 10 \text{ mL}_\text{N} \text{ min}^{-1}$, $V(\textbf{1}) = 0.01 \text{ mL}_\text{N} \text{ min}^{-1} = 0.78 \text{ g h}^{-1}$)

16. Surface-analysis of SG170

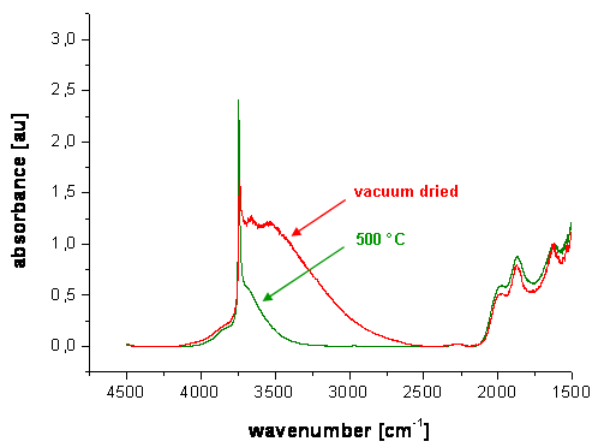


Figure S15: DRIFT spectra of SG170 before and after heating to 500 °C for 16 hours in vacuum

17. Performance of SILP catalyst based on **3** in EMIM NTf₂ on SG170-500

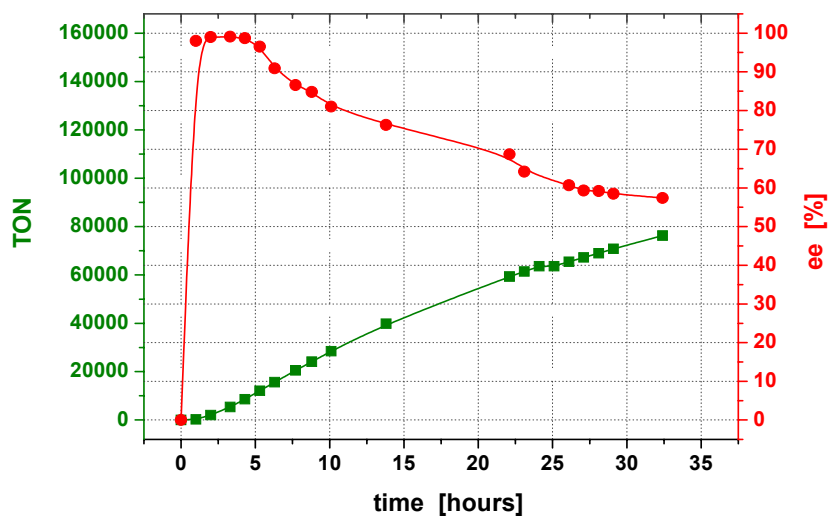


Figure S16. Cumulative TON (■) and ee (●) of 0.6 g SILP catalyst based on **3** (1.4 μmol) in EMIM NTf₂ on SG170-500 in the continuous hydrogenation of **1** with scCO₂ flow at 40 °C and 120 bar ($V(\text{CO}_2) = 85 \text{ mL}_N \text{ min}^{-1}$, $V(\text{H}_2) = 10 \text{ mL}_N \text{ min}^{-1}$, $V(\text{1}) = 0.01 \text{ mL}_N \text{ min}^{-1} = 0.78 \text{ g h}^{-1}$)

18. Surface-silylation of SG100

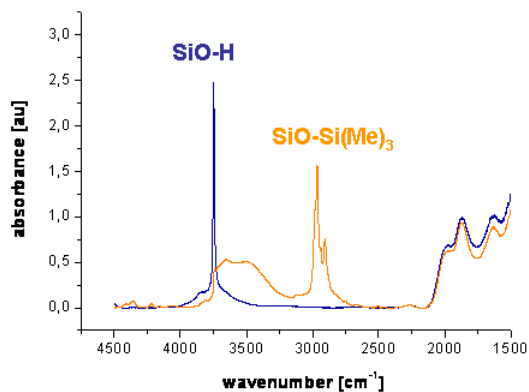


Figure S17: DRIFT spectra of SG100-800 before and after silylation with imidazole-TMS (SG100TMS)

19. Performance of SILP catalyst based on **3** in EMIM NTf₂ on SG100TMS

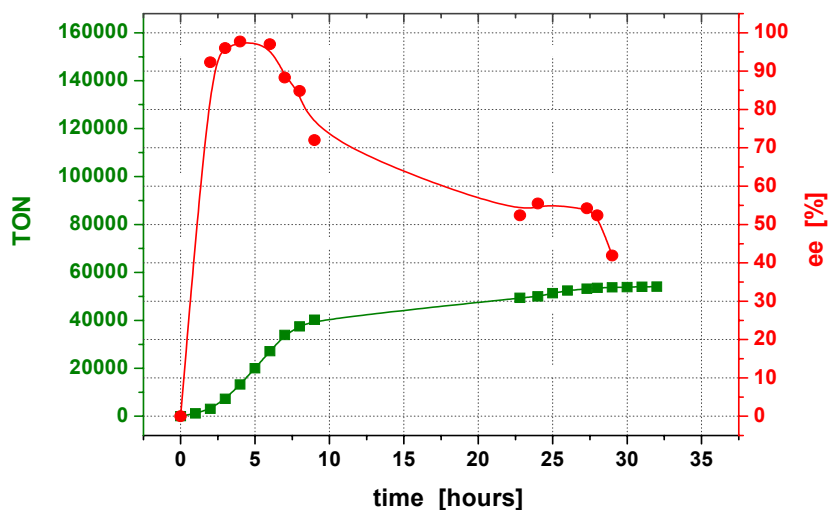


Figure S18: Cumulative TON (■) and *ee* (●) of 1 g freshly prepared SILP catalyst based on **3** (0.7 μmol) in EMIM NTf₂ on SG100TMS in the continuous hydrogenation of **1** with scCO₂ flow at 40 °C and 120 bar ($V(\text{CO}_2) = 85 \text{ mL}_N \text{ min}^{-1}$, $V(\text{H}_2) = 10 \text{ mL}_N \text{ min}^{-1}$, $V(\text{1}) = 0.01 \text{ mL}_N \text{ min}^{-1} = 0.78 \text{ g h}^{-1}$)

20. Surface-analysis of SGFLUO

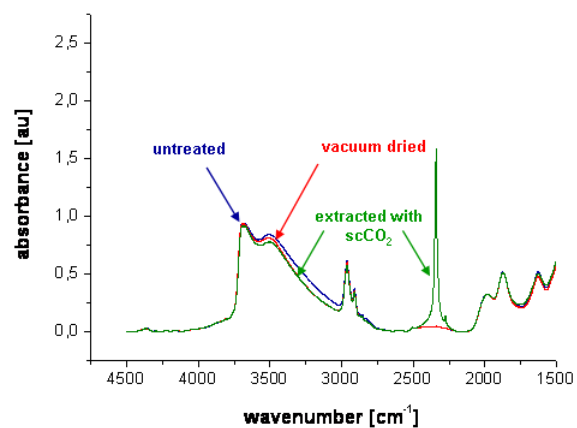


Figure S19: DRIFT spectra of SGFLUO as synthesized, after drying in HV, and after scCO₂ extraction (physically entrapped CO₂ visible at 2340 cm⁻¹)

21. Surface-analysis of SILP catalyst based on SGFLUO

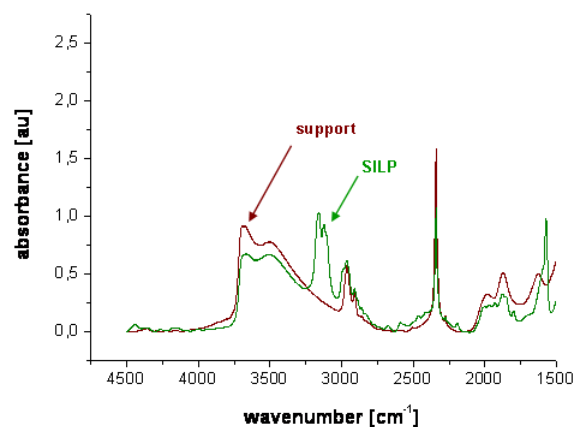


Figure S20: DRIFT spectra of pre-treated SGFLUO support and its SILP catalyst with EMIM NTf₂ (physically entrapped CO₂ visible at 2340 cm⁻¹)

22. Post-reaction analysis of SILP catalyst based on SGFLUO

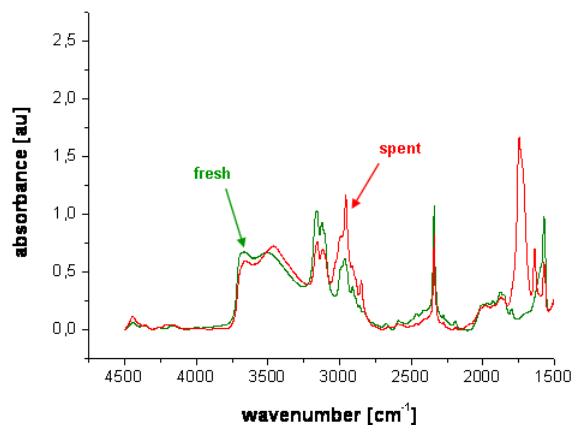


Figure S21: DRIFT spectra of SILP catalyst based on SGFLUO as synthesized and as recovered after catalysis (figure 10) (new bands around 3000 cm^{-1} and 1700 cm^{-1} arise from adsorbed **1** and **2**)

23. Effect of trace water on hydrogenation performance of **3** in DCM

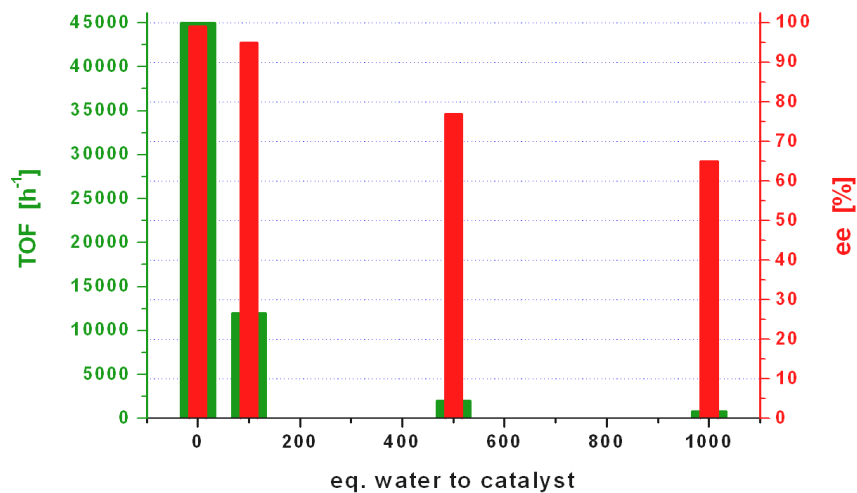


Figure S22: TOF and enantioselectivity of the hydrogenation of **1** with **3** pre-activated with H_2 in the presence of D_2O for 30 min, all at $40\text{ }^\circ\text{C}$ in 2 mL DCM with $5\text{ }\mu\text{mol}$ **3** at $\text{S/C} = 1000$ and 25 bar H_2 (no deuterium incorporation in **2** was observed)

24. Post-reaction analysis of water scavenger

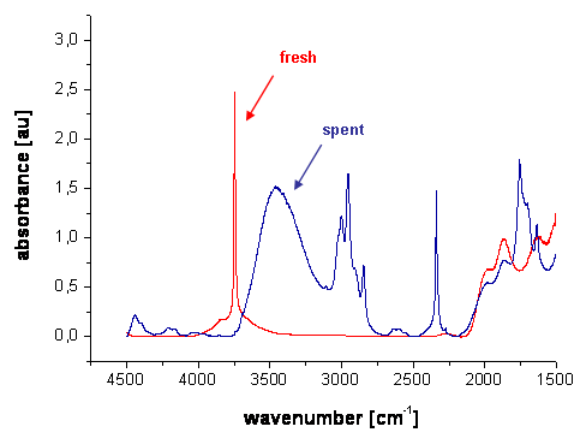


Figure S23: DRIFT spectra of SG100-800 before and after use as upstream water scavenger in catalysis (figure 11). Besides CO₂ (2340 cm⁻¹) and **1** & **2** (~3000 cm⁻¹ / ~1700 cm⁻¹) water is clearly visible on the surface around 3400 cm⁻¹