Supporting Information

Title: **The use of catalytic static mixers for continuous flow gas-liquid and transfer hydrogenations in organic synthesis**

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Reagents:

The reagents vinyl acetate, 3-nitroanisole and 2-chloro-nitrobenzene were obtained from TCI; the reagents allylbenzene, 3-bromo-nitrobenzene, and 2- and 4-nitroanisole were obtained from Fluka; the reagent azobenzene was obtained from British Drug Houses Ltd.; the reagents acetophenone, phenyl acetylene, benzylchloride, cinnamaldehyde, cinnamyl chloride, 4-nitrotoluene, 4-chloro styrene, 4-chloro-2-nitrobenzaldehyde and 3- and 4-chloro-nitrobenzene were obtained from Sigma Aldrich. The reagent *N*-butyl-1-phenylmethanimine was synthesised in our laboratory from benzaldehyde (Acros) and butylamine (Sigma Aldrich) using a procedure adapted from E.C. Border, V.L. Blair, P.C. Andrews, *Aust. J. Chem*. 2015, **68**, 844. The solvents ethyl acetate, ethanol and methanol were obtained from Merck KGaA. All reagents and solvents were used without further purification.

Analysis procedure:

Reaction conversions were calculated from ^{1}H NMR spectra, which were recorded on a Bruker AC-400 spectrometer in deuterated chloroform (from Cambridge Isotope Laboratories Inc.). The residual solvent peak at δ = 7.26 ppm was used as an internal reference. Product compositions were analysed by GC-FID and GC-MS. The GC-FID results were also used to confirm NMR conversions and to calculate GC-based yields. GC-mass spectra were obtained with a Perkin Elmer Clarus 600 GC mass spectrometer using electron impact ionization in the positive ion mode with an ionization energy of 70 eV. The gas chromatography was performed with a Perkin Elmer Elite-5MS GC column (30 m x 0.25 mm ID, 0.25 μm film thickness), with a temperature program of 40 °C for 2 minutes, then heating at 10 °C /min to 280 °C where the temperature was held for 4 minutes with a split ratio of 70, an injector temperature of 250 °C and the transfer line was set to 250 °C. Ultra high purity helium was used as the carrier gas with a flow rate of 0.7 ml/min. GC-FID analysis were performed on an Agilent 6850 Series II gas chromatograph with a split/splitless inlet and a detector temperature of 250 °C. Separation was done on a Grace BPX5 capillary column (25 m x 0.32 mm ID, 0.50 μm film thickness), with a temperature program of 40 °C for 2 minutes, then heating at 10 °C /min to 280 °C where the temperature was held for 4 minutes with a split ratio of 50 and an injector temperature of 200 °C. High purity helium was used as the carrier gas with a flow rate of 2.4 ml/min.

Calculation of CSM porosity:

The combined displacement volume of a CSM set, V_{CSM}, was determined by inserting them into a water filed tube of known dimensions and measuring the rise in water level. This was done in order to calculate the remaining reactor volume, V_R, and porosity of the CSM, ϕ.

$$\Phi = \frac{V_R}{n\left(\frac{\pi}{4}d^2l\right)} = \frac{\frac{\pi}{4}nd^2l - V_{CSM}}{\frac{\pi}{4}nd^2l} = 1 - \frac{4V_{CSM}}{\boldsymbol{\pi}nd^2l} \quad (S1)$$

Here, n is the number of identical catalytic tube sections, d is their diameter (6 mm ID), and l their length (15 cm). The physical data of the CSM sets is collated in Table 1 in the main text.

Reactor design and operation:

The reactor set-up consists of the reactor module, housing the CSMs (either Mk 1 module for four CSMs or Mk 2 module for twelve CSMs), a liquid feed line, including a liquid reagent pump, a gas feed line, and electronic process control and data logging.

The **Mk 1 reactor module** contains four parallel cylindrical reactor zones operated in series, each of which are made from 150 mm long 316 stainless steel tubing (Swagelok, 8 mm OD, 6 mm ID). The reactor body surrounding the SS tubing is made from aluminium and is covered by an outer heat insulating layer. The aluminium block is heated electrically using cartridge heaters and a PID controller. It contains five temperature probes (PT 100), situated before and after each reactor zone.

The **Mk 2 reactor module** contains twelve parallel cylindrical reactor zones operated in series, (diameter: 6 mm, length: 150 mm). The cylindrical reactor body is made from 316 SS and is shielded and insulated by an external housing. The module is heated by an electrical heating mantel in combination with a PID controller. It contains four temperature probes (PT 100), situated in one endplate of the reactor at turns 1, 3, 9 and 11.

Both reactor modules can be dismantled easily in order to facilitate change-over of the catalytic inserts. The reagent pump (Gilson 305 HPLC pump) supplies the substrate feed stream, which contains a solution of the starting material substrate, neat or in a solvent. The hydrogen gas is supplied from a hydrogen cylinder (G-type cylinder) and mixed with the liquid stream in a T-piece. The combined stream then flows through a liquid-gas disperser (Swagelok SS-4TF-90) before it enters the reactor. The pressure inside the reactor is regulated by a diaphragm back pressure regulator (BPR, Swagelok KBP1J0A4D5A20000), which is situated at the outlet of the reactor. After passing through the BPR, the hot effluent can optionally be cooled in a coil type heat exchanger, which is operated with room temperature water as the cooling fluid. The product stream is then collected in a bottle or flask for post processing and analysis. The following process control components are installed in the rig: safety pressure relief valve at reactor inlet (Swagelok, SS-4R3A); safety shut-down valve in the gas line (Bürkert, 2/2-way solenoid valve 6027 A03); two flash-back arrestors in the gas line (Witt 85-10) and three pressure sensors (Gilson 806 Manometric Module, GE UNIK 5000 Series, Impress IMP-G1003-SA4-BEV-00-000) measuring the pressure in the liquid line, gas line and at the inlet of the reactor (pL, pG, pR). The flow of gas in the hydrogen line is controlled using a Bronkhorst MFC F-201CV-500 mass flow controller which is measuring the normal gas flow rate, $\dot{V}_{G,N}$ (1 atm, 0 °C), from which the actual gas flow rate inside the reactor at reaction temperature and pressure, $\dot{V}_{G,R}$, can be calculated (see next paragraph). The mean residence time of the combined liquid and gas flow inside the reactor, τ, can then be calculated using:

$$\tau = \frac{V_R}{\dot{V}} = \frac{V_R}{\dot{V}_L + \dot{V}_{G,R}} \quad (S2)$$

Here, $\dot{V}_L$ is the liquid flow rate through the reactor. The reaction occurs at the solid-liquid interface of the catalytic inserts, inside the four/twelve reactor zones. The operation of the reactor system is controlled via a LabView™ interphase, which is also measuring temperature, pressure and gas flow rate data.

In order to demonstrate improvements of the new Mk2 design, a comparison between the Mk1 and Mk2 reactors was conducted for the hydrogenation of vinyl acetate using gaseous hydrogen and comparable operating conditions:

Mk1 reactor:
catalyst: Ni (cold sprayed); substrate: vinyl acetate
c = 2 mol/L; $\dot{V}_L$ = 0.5 ml/min, $\dot{V}_{G,R}$ = 2.5 mL/min, T = 140 °C, p = 22 bar, G/L = 5
conversion = **74%**

Mk2 reactor:
catalyst: Ni (cold sprayed); substrate: vinyl acetate
c = 2 mol/L; $\dot{V}_L$ = 1.0 ml/min, $\dot{V}_{G,R}$ = 5 mL/min, T = 120 °C, p = 20 bar, G/L = 5
conversion = **97%**

For twice the reactor throughput the Mk2 module achieved higher conversions at a lower reactor pressure than the Mk1 module, thus demonstrating its improved efficiency.

Calculation of hydrogen gas flow rate inside the reactor:

Since the mass flow controller operates on normal flow rate (flow rate under normal conditions, i.e. p = 1 atm, T = 0 °C, measured inside the mass flow controller), it is necessary to calculate the actual volumetric flow of hydrogen inside the reactor. To do so, the following equation was used:

$$\frac{\dot{V}_{G,R} \cdot p_R}{T_R \cdot Z_R} = \frac{\dot{V}_{G,N} \cdot p_N}{T_N \cdot Z_N} \qquad (S3)$$

Here $\dot{V}_{G,R}$, p_R, T_R, and Z_R are respectively the volumetric gas flow rate, pressure, temperature and compressibility factor of the hydrogen gas at the conditions inside the reactor, while $\dot{V}_{G,N}$, p_N, T_N, and Z_N are the values for the gas under normal conditions. For this equation, it is necessary to calculate the compressibility factor of hydrogen inside the reactor. For the temperature range used in our work, it can be assumed that this factor is only a function of pressure, not of temperature. The correlation between Z and p can be established by plotting the compressibility factor at 140 °C against pressures between 5 and 25 bar. Using equation S1; this gives the following expression of $\dot{V}_{G,R}$ with a R^2 value of 0.9999:

$$\dot{V}_{G,R} = \dot{V}_{G,N} \cdot \frac{T_R p_N e^{0.0005 \cdot p_R}}{T_N p_R Z_N} \qquad (S4)$$

The gas to liquid ratio can then be defined as:

$$\frac{G}{L} = \frac{\dot{V}_{G,R}}{\dot{V}_L} = \frac{\dot{V}_{G,N}}{\dot{V}_{tot} \cdot A - \dot{V}_{G,N}} \qquad (S5)$$

where $A = \frac{p_R T_N Z_N}{p_N T_R e^{0.0005 \cdot p_R}}$, $\dot{V}_L$ is the liquid flow rate and $\dot{V}_{tot} = \dot{V}_L + \dot{V}_{G,R}$.

Hydrogenation of benzyl cyanide using the Mk 2 configuration:

The hydrogenation of benzyl cyanide on *Pd-EP-2* and *Ni-CS-3* (see also main text, Table 2, entries 2.8 to 2.10) resulted in high selectivity towards the primary amine with only minor amounts of the undesired dimeric side product. Conversions of up to 86% could be achieved. The reduction of nitriles is a frequently occurring industrial operation and formation of secondary amine dimers are usually undesired. Scheme S1 shows the mechanism for hydrogenation of benzyl cyanide and Figure S1 shows a series of results from experiments on *Pd-EP-2* and *Ni-CS-3* at different reactor pressures and with different G/L.
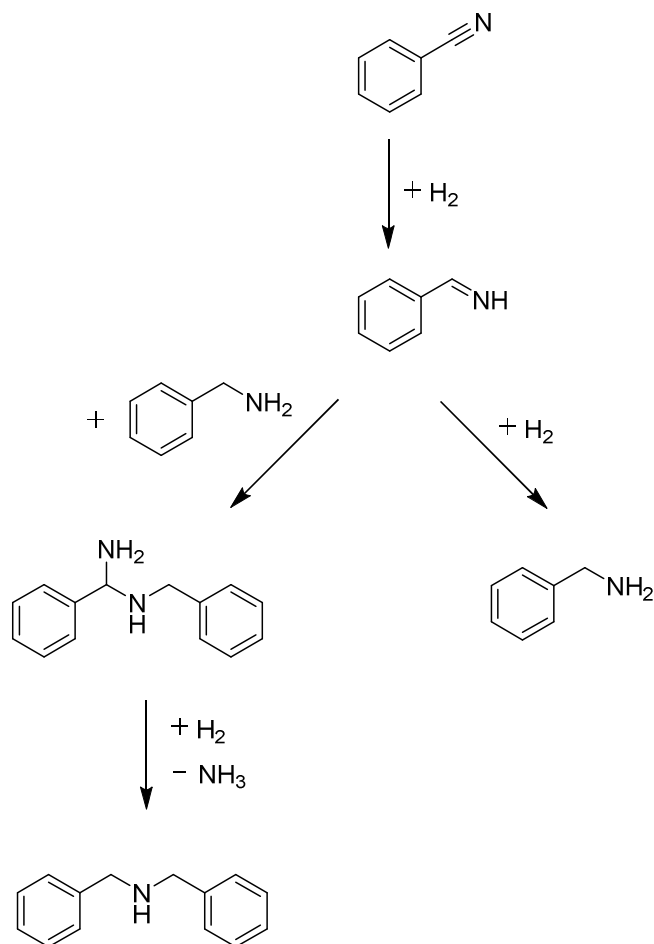
Scheme S1. Hydrogenation pathway of benzyl cyanide to benzylamine (primary amine) and dibenzylamine (dimer), adapted from: J. Barrault, Y. Pouilloux, *Catal. Today.* 1997, **37**, 137.
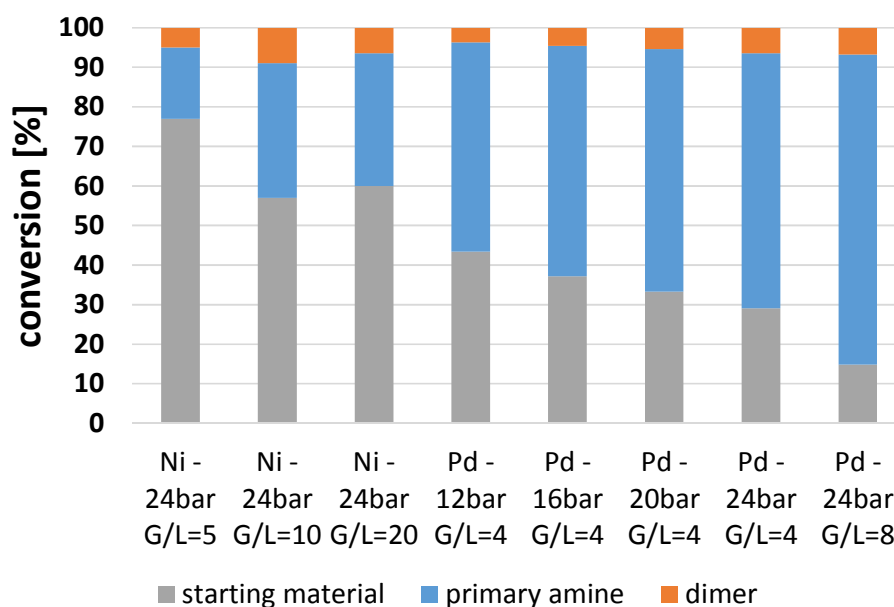
Figure S1. Hydrogenation of benzyl cyanide to benzylamine (primary amine) and dibenzylamine (dimer) using *Pd-EP-2* or *Ni-CS-3* in the Mk2 reactor.

Hydrogenation of cinnamaldehyde in ethanol using the Mk 2 configuration:

The hydrogenation of cinnamaldehyde was performed in the solvents EtOAc (see main text, Table 2 - entry 2.11, and Figure 6) or EtOH using *Pd-EP-2* or *Ni-CS-3*. While the reaction in EtOAc mainly yielded the three products hydrocinnamaldehyde (HCAL), hydrocinnamyl alcohol (HCOH) and cinnamyl alcohol (COH), using EtOH as a solvent under the same reaction conditions resulted in a series of additional coupling products with the solvent, EtOH, and subsequent hydrogenation break down products. These additional products were identified by GC-MS and are: cinnamaldehyde diacetal (CDA), cinnamyl ethylether (CEE), β-methyl styrene (MS), propylbenzene (PB), ethoxyallyl benzene (EAB) and allylbenzene (AB). Depending on catalyst and reaction pressure, the ratio of these products varied (see Figure S2). Scheme S2 shows the reaction pathways for the hydrogenation of cinnamaldehyde in EtOH.
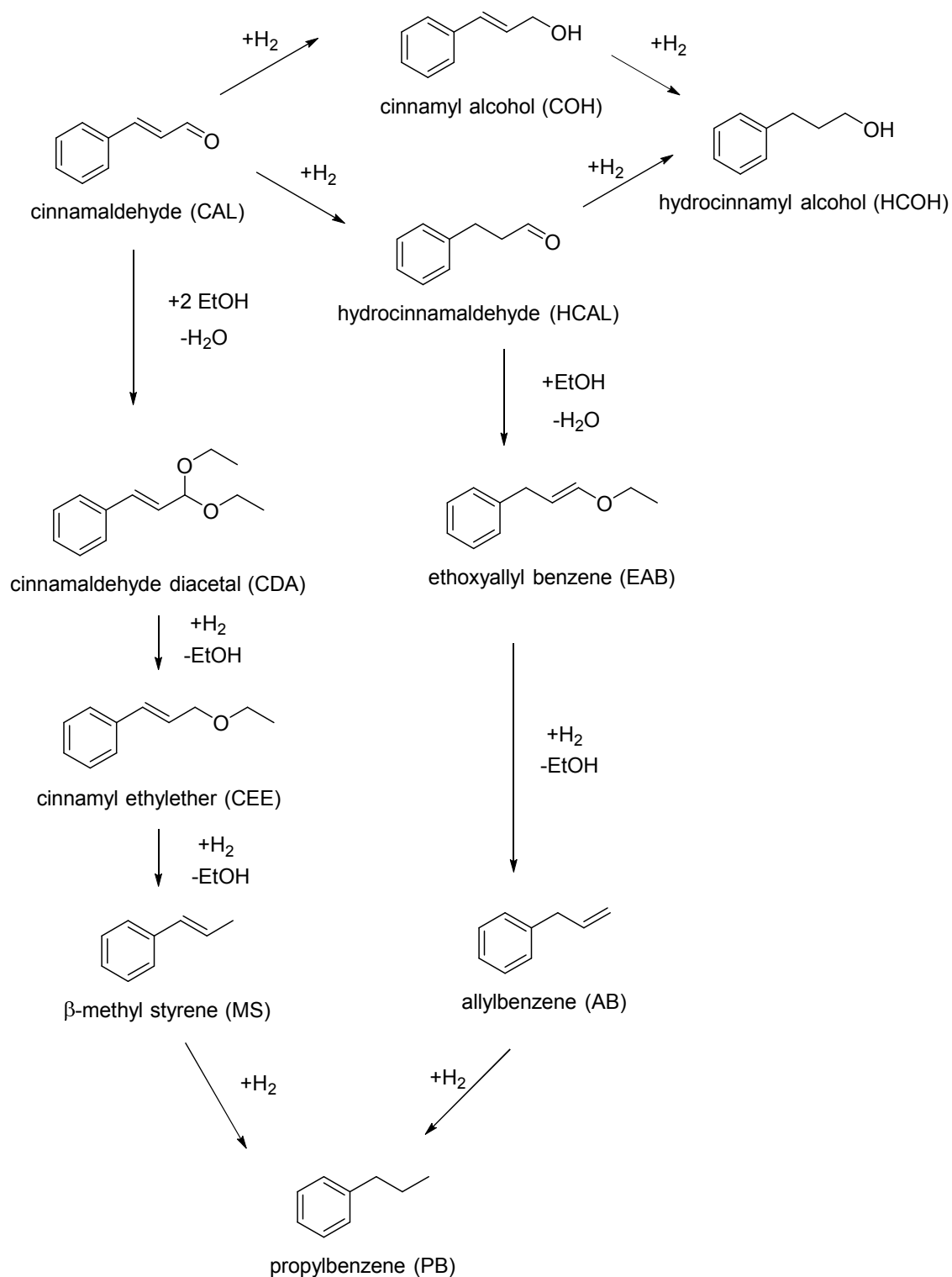
Scheme S2. Hydrogenation pathway of cinnamaldehyde to hydrocinnamyl alcohol in EtOH, including all identified side products and intermediates.
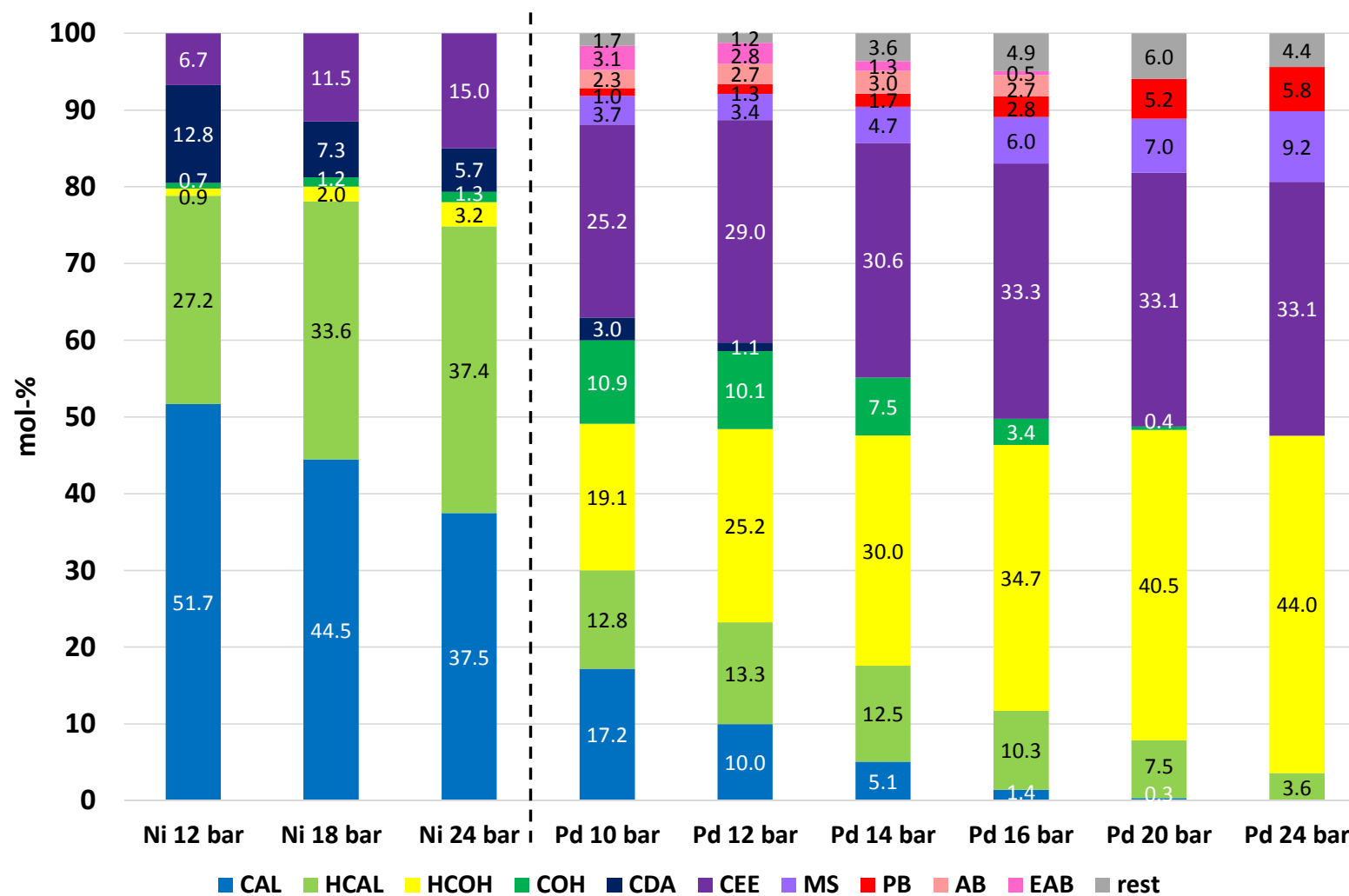
Figure S2. Hydrogenation of cinnamaldehyde in EtOH; product composition for different catalysts (Ni and Pd) and reactor pressures.