ELECTRONIC SUPPORTING INFORMATION

A Sweet Flow: HMF Production and *in-situ* Valorization into Valuable Nitrile-Containing Compound via Telescopic Flow Chemistry

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Content

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S1. Catalytic performance for the synthesis of HMF from dehydration of fructose using Batch conditions.

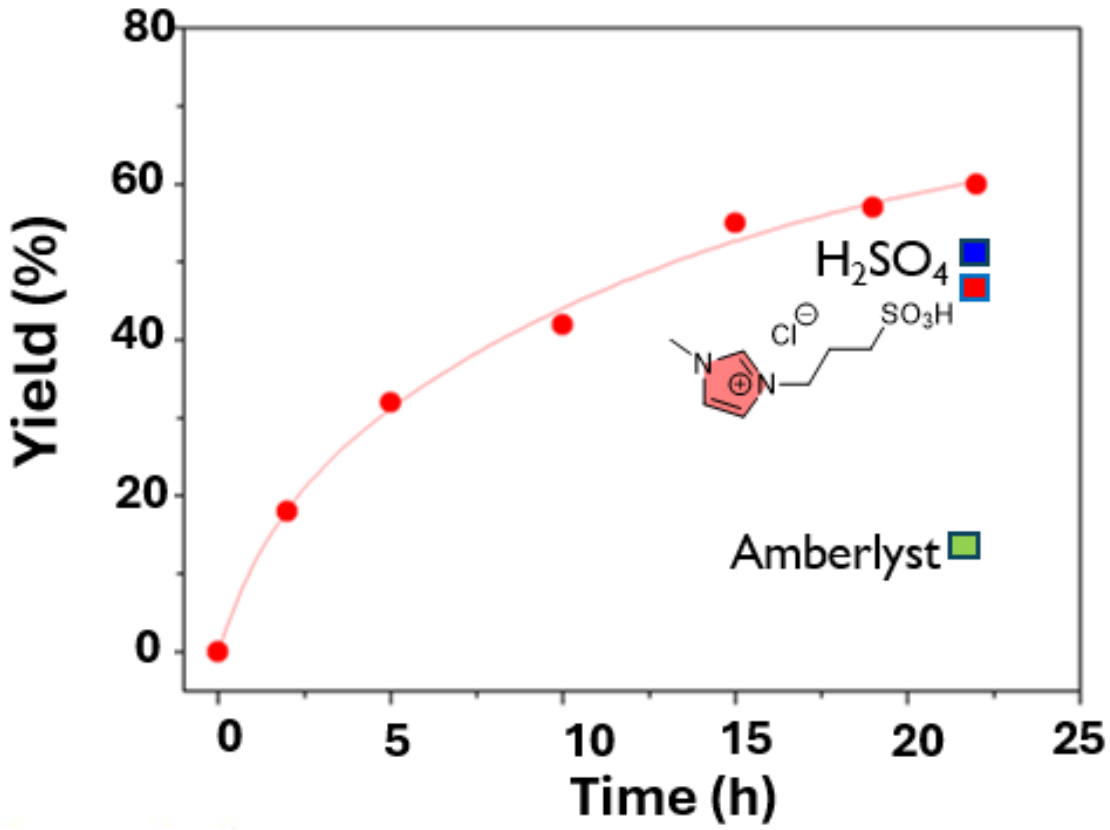


Fig. SI.1 Kinetic profile using 2-MeTHF: water (3:1) as the solvent. **Reaction conditions:** 1.250 g of fructose (6.94 mmol), 25 mL of dissolvent, 90°C, 450 rpm, 10 mol% cat TSIL-1. Blue square: yield obtained under same conditions using H_2SO_4 as catalyst instead of TSIL-1 at 24 h. Red square: yield obtained under same conditions using the **TSIL-2** as catalyst instead of **TSIL-1** at 24 h. Green square: yield obtained under same conditions using Amberlyst-15 as a catalyst instead of **TSIL-1** at 24 h.

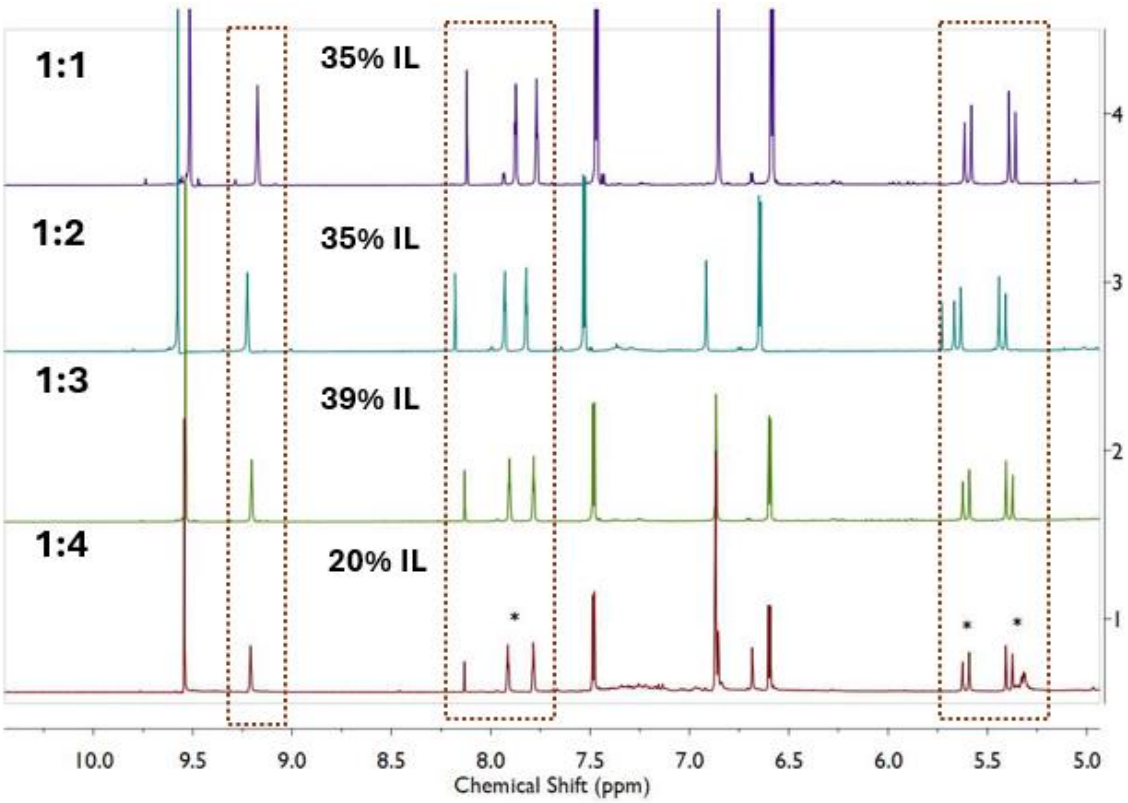


Fig. SI.2 ^{1}H-NMR (d_6-DMSO) of the extract obtained in the organic phase. The main signals assignable to the **TSIL-1** are highlighted together with the molar percentage related to the HMF signals relative to the mol of HMF.

S2. FTIR-ATR spectra of the SILP containing DMSO.

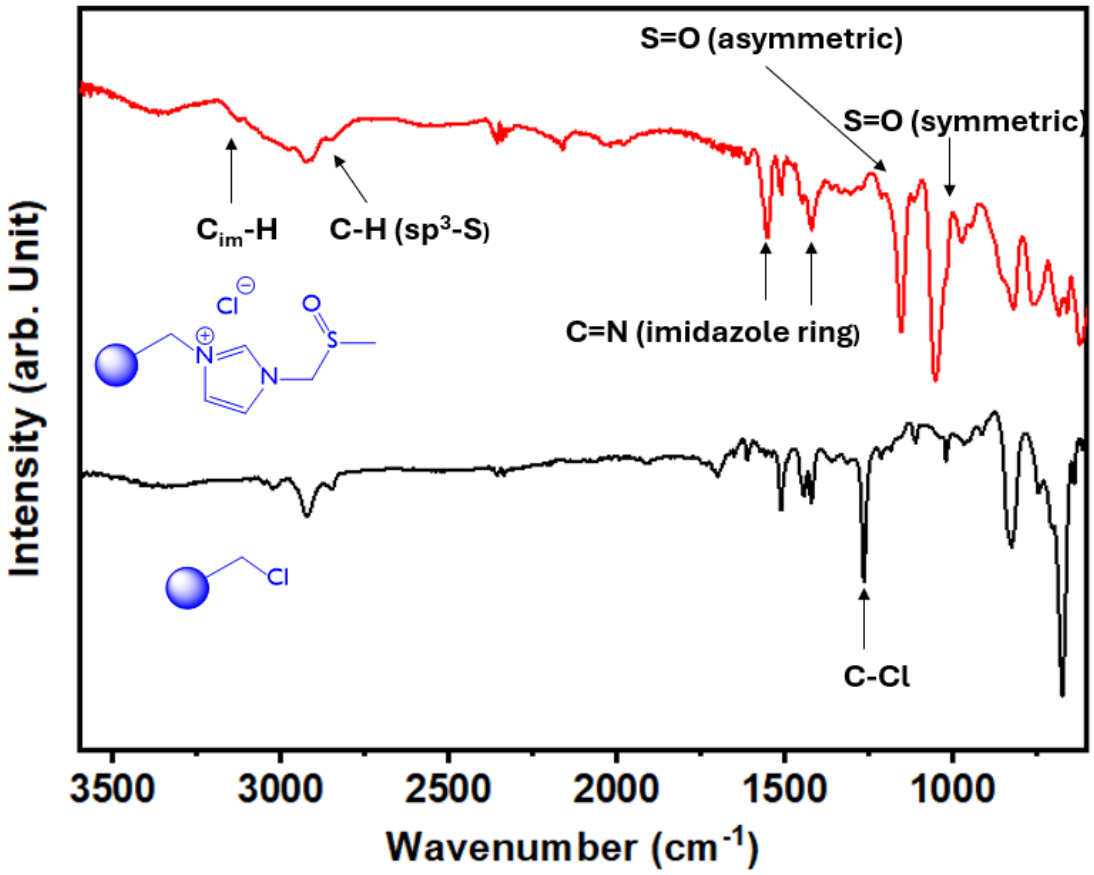


Fig. SI. 3. FTIR-ATR spectrum of TS-SILP-1 and PS-DVB resins containing DMSO and used as solid dissolvent in the dehydration of fructose into HMF.

S3. NMR follow-up for the synthesis of HMF from fructose

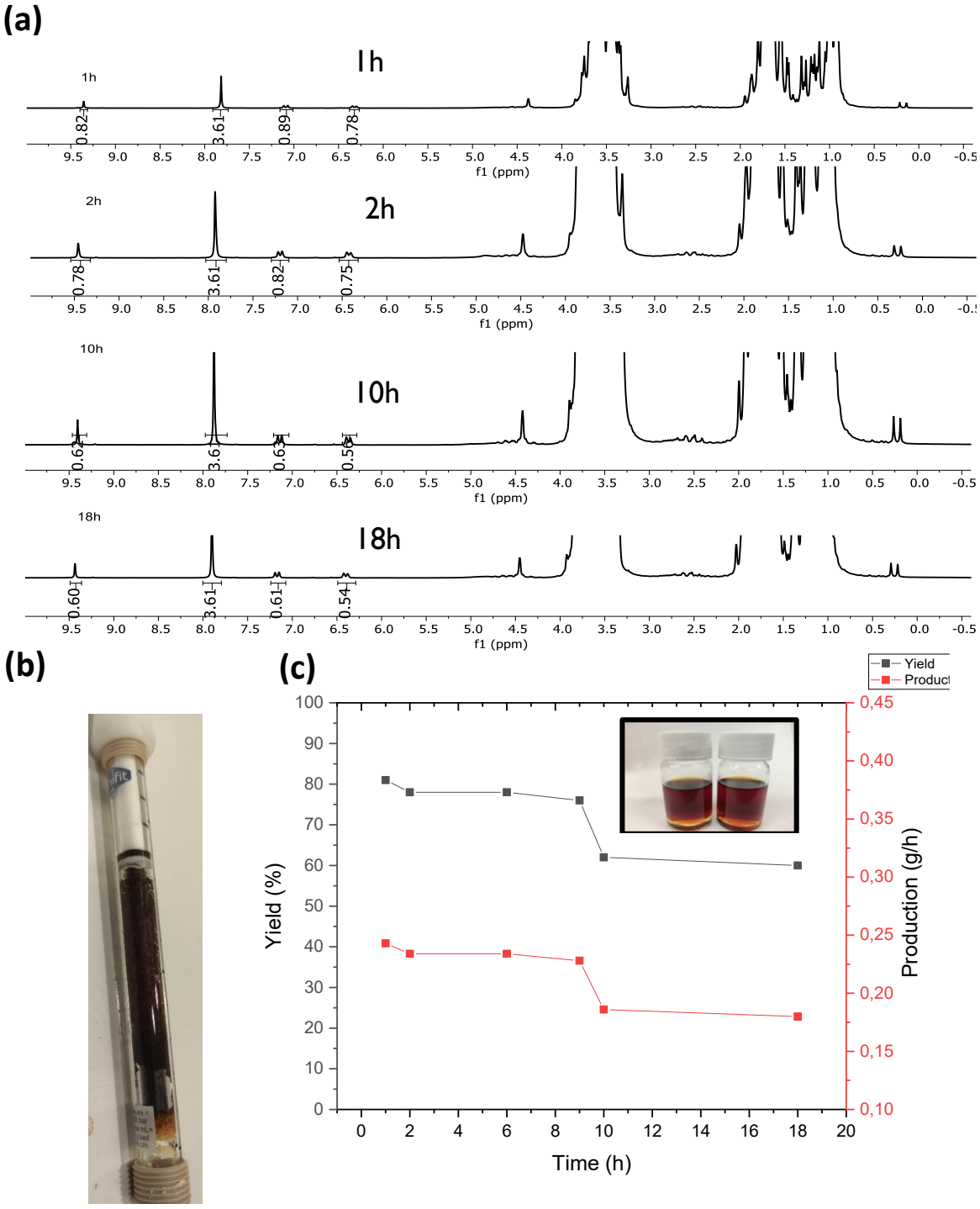


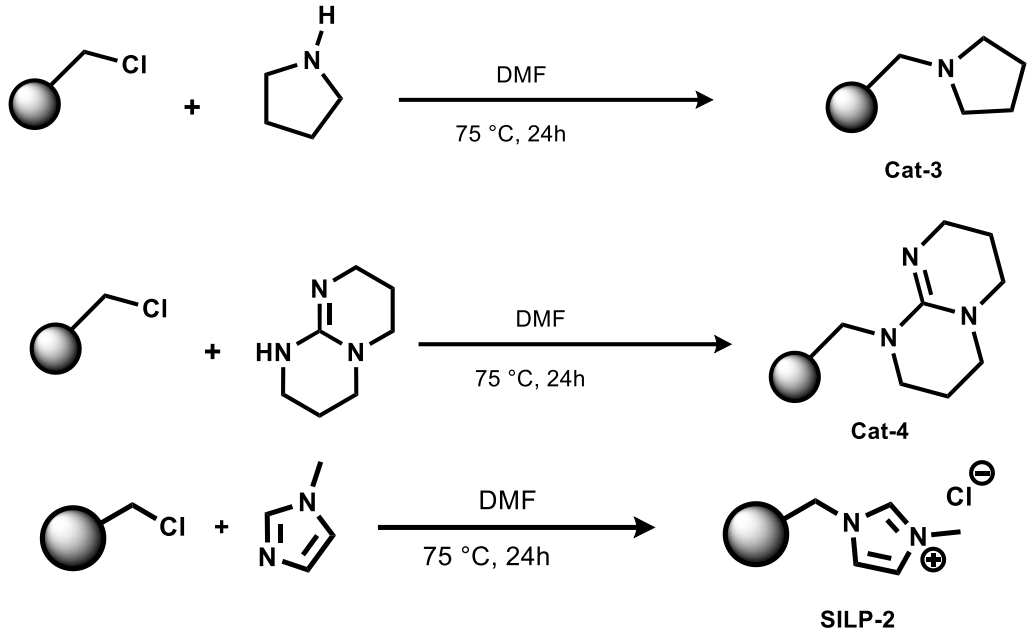
Fig. SI. 4. a) ^{1}H-NMR follow-up of the dehydration of fructose into HMF using $CHCl_3$ as internal standard by in-line NMR using Magritek Spinsolve 80 Ultra. b) appearance of the catalyst after performance of the flow reaction c) stability of the catalyst to produce HMF using fructose (10 wt%) T= 120ºC, 50 µL/min of water solution, 200 µL/min 2-MeTHF using a HPLC piston pumps

Table S1. Catalytic synthesis of HMF under flow conditions.

Reactor configuration	Catalyst	Solvent	T (°C)	Residence time (min)	HMF yield (%)	STY (g HMF/L min)	Ref.
Biphasic (DMC)							
flow tubular reactor system	HCl (0.23 M)	H_2O / DMC	200	1	87	159	[1]
Biphasic (MeTHF)							
Recirculated tubular reactor	HCl (28 mM)	H_2O / 2-MeTHF	150	360*	94	$2.81x10^{-3}$	[2]
Biphasic (MIBK)							
flow tubular reactor system	NbP / Amberlyst 36	H_2O / MIBK	150	140	58	1.16	[3]
Slug-flow capilar	$AlCl_3$ (40 mM)[a]	H_2O / MIBK	160	20	34	$4.53x10^{-2}$	[4]
Slug-flow microreactor	HCl (5 mol%)	DES[b] / MIBK	80	13	63	5.78	[5]
Fixed bed reactor	Amberlyst-15	H_2O / MIBK	120	5	34	$4.76x10^{-1}$	[6]
Micropacked bed reactor	HND-26	H_2O/MIBK	150	0.44	90	315	[7]
Biphasic (Water)							
Microreactor tubular	HCl (0.1 M)	H_2O/DMSO[c]	185	1	54	37.8	[8]
Fixed bed reactor	Amberlyst-15	H_2O/Acetone	110	**	92	**	[9]
Fixed bed reactor	Lewatit K2649	H_2O/Acetone	110	6.4	66	$7.22x10^{-1}$	[10]
Another disolvents/mixtures							
Fixed bed reactor	Resin DR-2030	DMSO	110	49***	82	3.46	[11]
Fixed bed reactor	Lewatit K2649	H_2O/HFIP[d]	95	80	76	$1.20x10^{-1}$	[12]
Fixed bed reactor	Amberlyst-70	H_2O/dioxane/MIBK	120	1.6	84	19.9	[13]
Fixed bed reactor	HCl (10 mol%)	H_2O/2-MeTHF/SILP-2	120	10	82	1.5	Our work

*The reaction was also performed with H_2O and H_2O/DMSO as solvents during the flow performance. Further reaction was also carried out with MIBK. ** Residence time was not available ***The residence time was estimated from data of flow and reactor volume [a]. The reaction was also performed with HCl as the homogeneous catalyst yielding 15% fructose conversion within 20 min (5.1% HMF yield). The mass balance was around 60% due to the formation of soluble unidentified products as well as humins. [b]. DES comprising Choline chloride and ethylene glycol in a 1:2 ratio. The 3:1 volume ratio of MIBK to DES was used for HMF extraction. [c] Extraction was performed with MIBK/2-butanol (70:30 in weight). The mixture of these solvents was introduced via the third fluidic port. [d]. HFIP means hexafluoroisopropanol. STY [g/L.min]= (g of HMF)/(reactor volume (L) x time (min))

S4. FTIR-ATR spectra of the basic heterogeneous supported catalysts



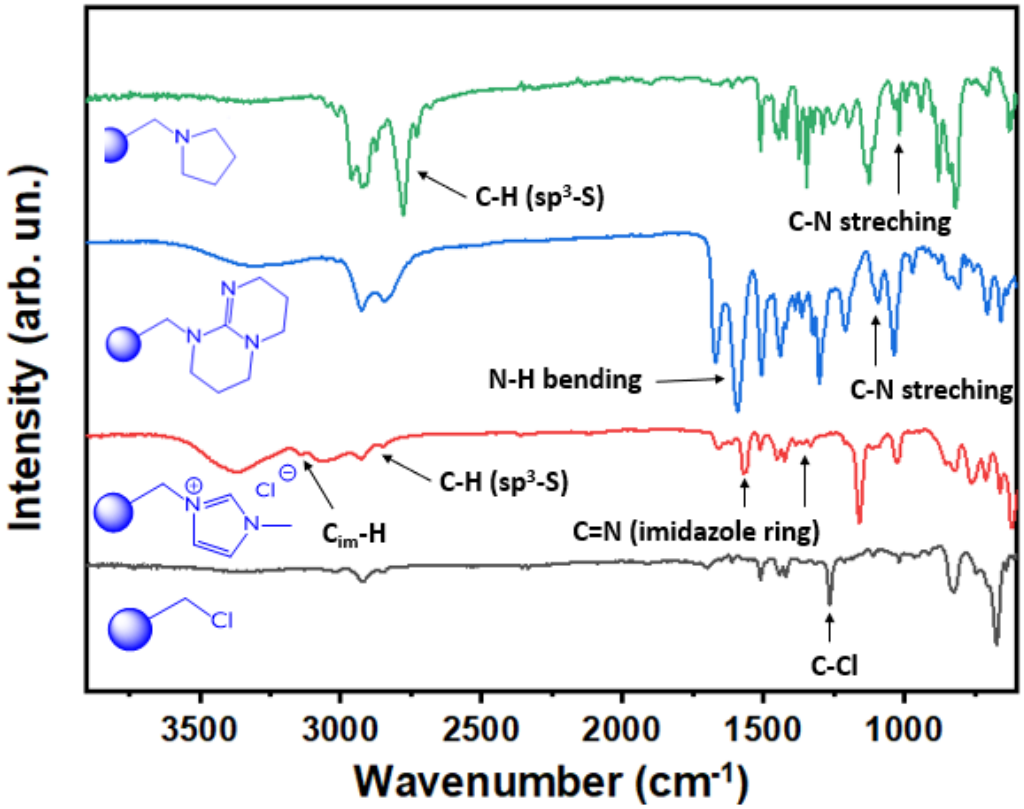
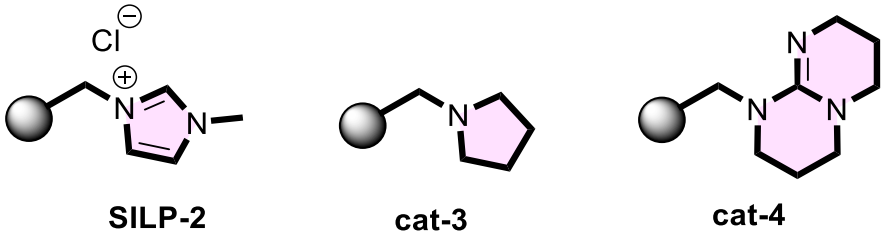


Fig. SI. 5. FTIR-ATR spectra of the heterogeneous supported catalysts used for the Knoevenagel condensation.

Table S2. Catalytic performance of basic SILPs in the Knoevenagel condensation of furfural with ethylcianoacetate.



SILP-2 **cat-3** **cat-4**

Entry	Catalyst	Yield (%)	Solvent
1	SILP-2	29	2-MeTHF
2	Cat-3	>92	2-MeTHF
3		99	DMC
4		>99	DMC:2-MeTHF [a]
5	Cat-4	78	2-MeTHF

Reaction conditions: 0.5 g of furfural (5.2 mmol), 1.7 eq of ethylcianoacetate, 5wt% basic catalyst, solvent (25 mL), 450 rpm, 24 h. [a]Ratio 1:1. Yield was calculated as the ratio of the integrations for the C=C bond proton and the aldehyde proton. Measurements were performed using a Bruker Avance 400 MHz NMR spectrometer ($CDCl_3$ as the solvent) with TMS as the internal reference standard.

S5. Reduction of HMF into BHMF using $NaBH_4$ at room temperature

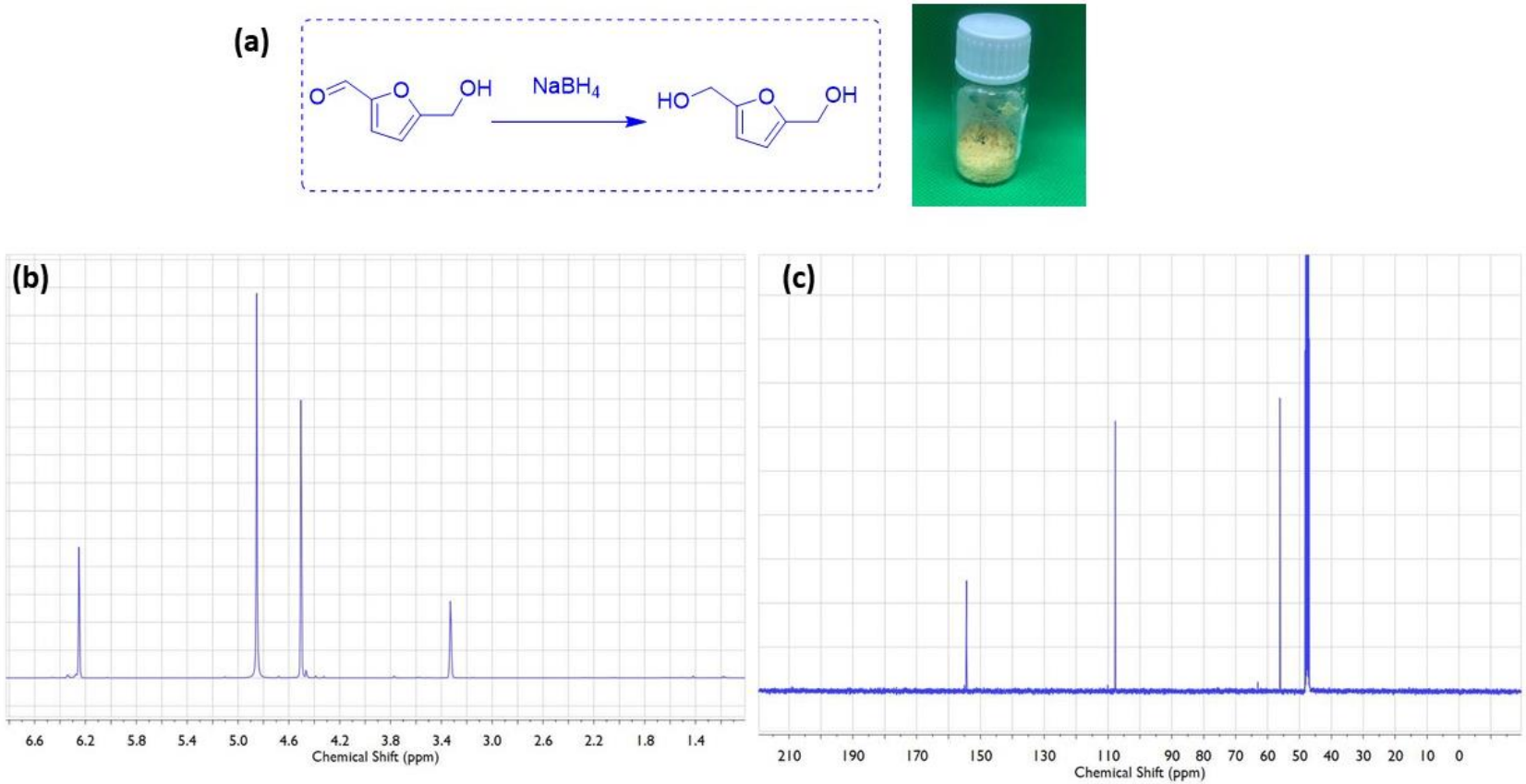


Fig. SI. 6. a) Schematic representation and appearance of the reduction of HMF into BHMF b) ^{1}H NMR and c)^{13}C NMR spectra. Measurements were performed using a Bruker Avance 400 MHz NMR spectrometer ($CDCl_3$ as the solvent) with TMS as the internal reference standard.The singlet peak at 3.3 ppm correspond to MeOH from the reaction solvent.

S6. Typical NMR spectra for samples 1 and 15 in the synthesis of_ethyl (E)-2-cyano-3-(5-(hydroxymethyl) furan-2-yl) acrylate

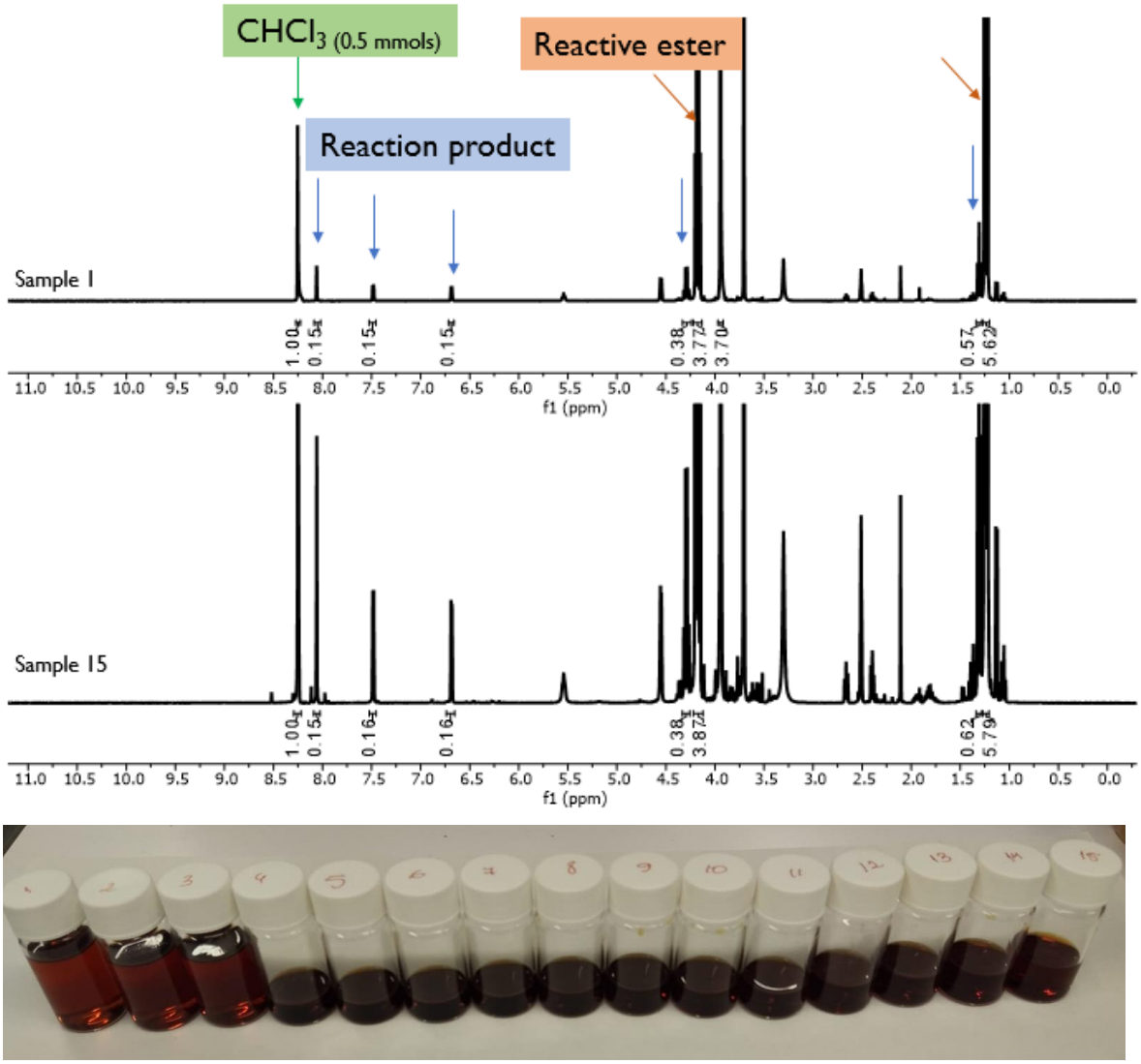


Fig. SI. 7. NMR spectra for samples 1 and 15 showing the in-line spectrum for ethyl (E)-2-cyano-3-(5-(hydroxymethyl)furan-2-yl)acrylate and the collected samples. The NMR spectra acquisition was performed by using $CDCl_3$ as internal standard in an in-line NMR using Magritek Spinsolve 80 Ultra

S7. The illustrative Knoevenagel condensation of HMF and OBMF with malononitrile

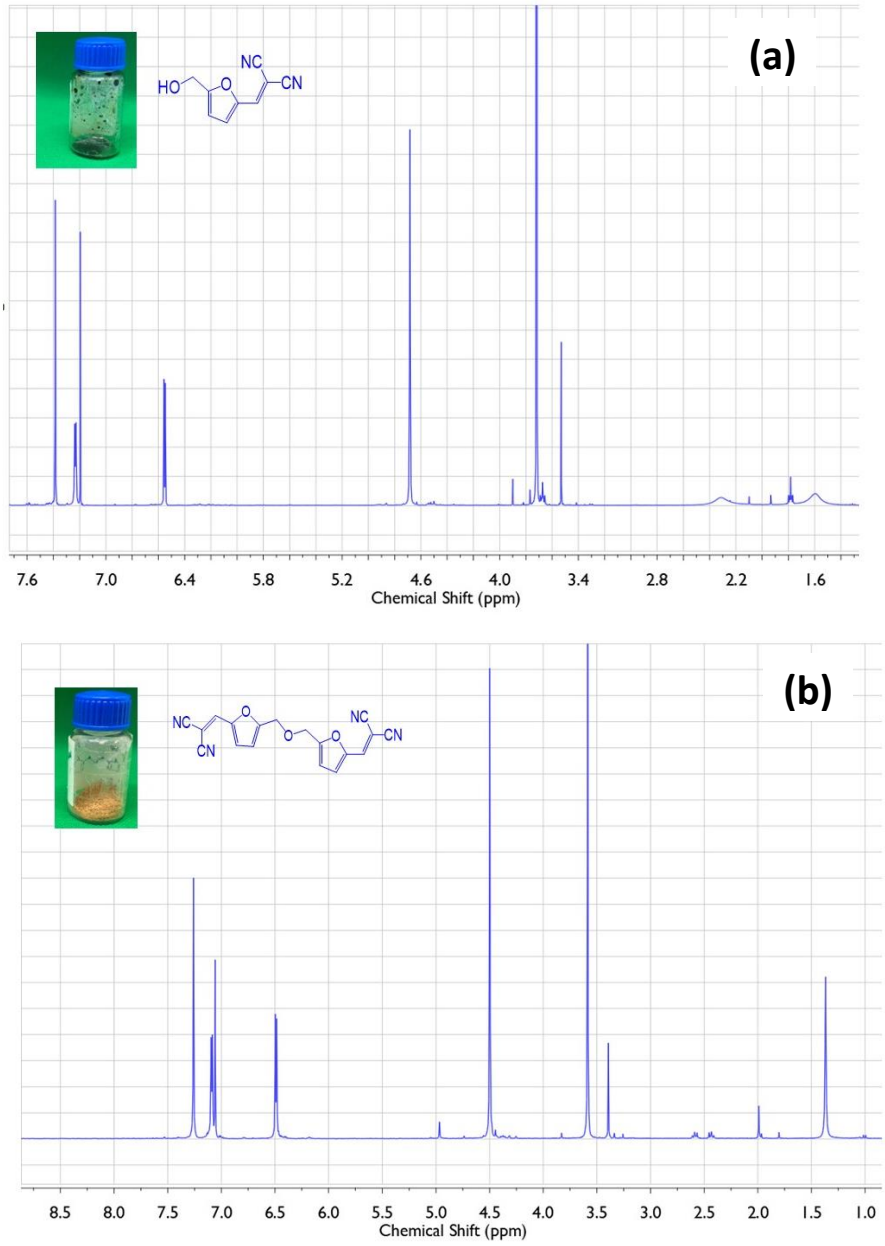


Fig. SI. 8. NMR spectrum and physical appearance of the products of the Knoevenagel condensation of HMF (a) and OBMF (b) with malononitrile. Measurements were performed using a Bruker Avance 400 NMR spectrometer ($CDCl_3$ as the solvent) with TMS as the internal reference standard

S8. Purificaton of ethyl-2-cyano-3-(5-(hydroxymethyl) furan-2-yl) acrylate

The ethyl-2-cyano-3-(5-(hydroxymethyl)furan-2-yl)acrylate obtained from the condensation of 5-hydroxymethylfurfural and ethylcianoacetate was crystallized simply by partial removal of the solvent (DMC/MeTHF) and then left in room temperature. The solid was then filtered off. A brownish solid was obtained which was further dried at 50°C in vacuum. No presence of ethylcianoacetate was observed either in HPLC nor NMR.

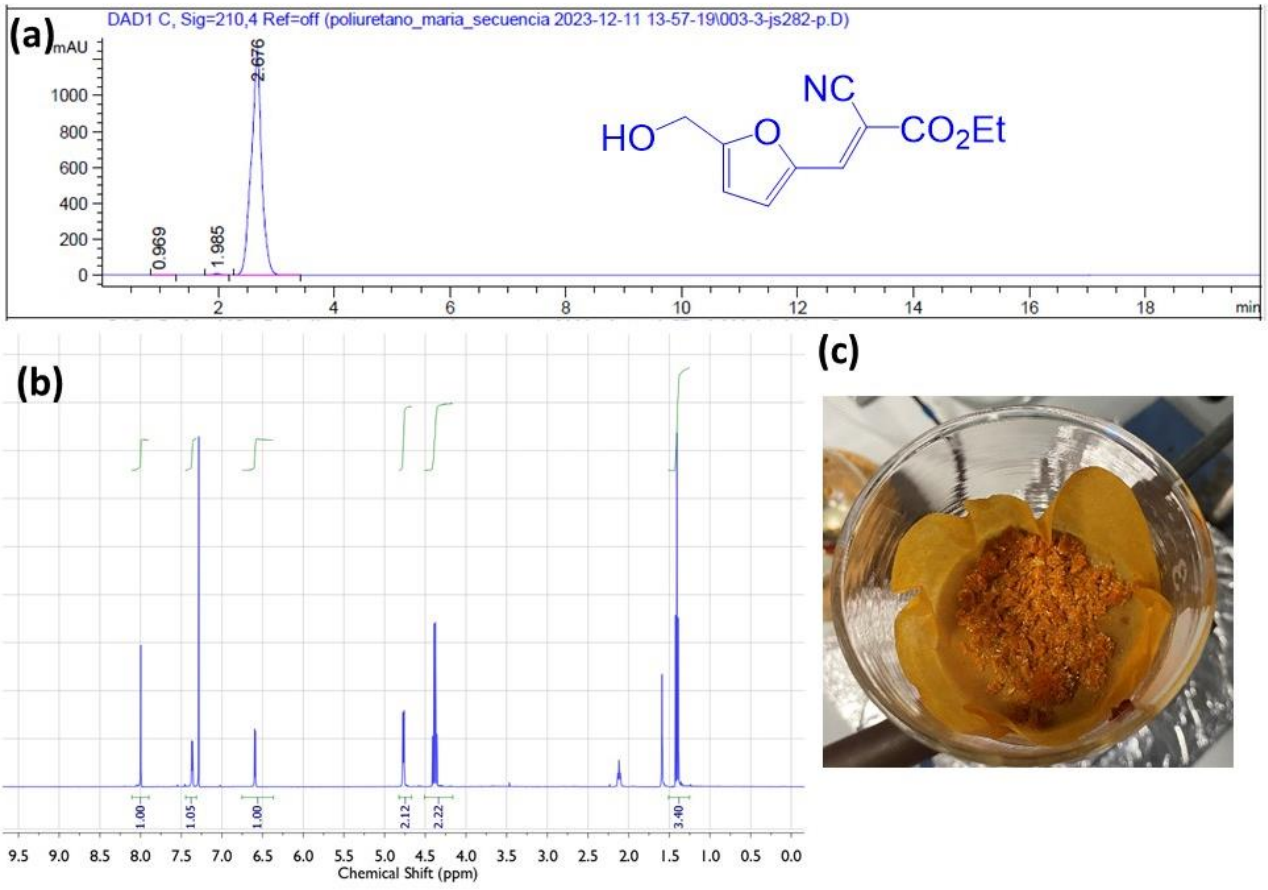


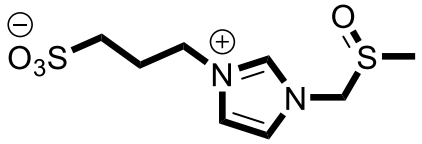
Fig. SI. 9. (a) HPLC chromatogram (b) ^{1}H-NMR and (c) appearance of the solid obtained of the condensation of HMF with ethylcianoacetate after purification. Measurements were performed using a Bruker Avance 400 NMR spectrometer ($CDCl_3$ as the solvent) with TMS as the internal reference standard

S9. Experimental methodology

S9.1 Synthesis of Task Specific Ionic Liquid (TSIL) and Supported Ionic Liquid Phases (SILPs)

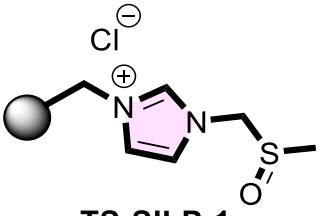
S9.1.1 Synthesis of catalysts for the dehydration of fructose

Synthesis of of TSIL-1: The synthesis and characterization was performed as reported in [14] with slight modifications. To a solution of 1-((methylsulfinyl)methyl)-1H-imidazole (7, 5.0 g, 34.2 mmol) in acetonitrile (50 mL, 952 mmol) heated at 35 ºC under nitrogen, 1,3-propanesultone (4.5 g, 36 mmol) was added slowly. The resulting mixture was stirred at 35 ºC for 48 h. After this time, the reaction mixture was cooled at room temperature. The obtained precipitated solid was filtered, washed with toluene:MeOH (1:1) (2 x 30 mL) and dried in vacuum to obtain a corresponding product as a white solid (7.9 g, 29.7 mmol, 86.7% yield).



TSIL-1

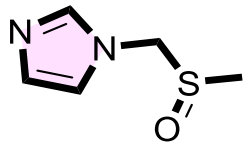
Synthesis of TS-SILP-1: 1 g of (chloromethyl)polystyrene (5.5 meq/g Cl, macroporous) was suspended in DMF, and subsequently, 2 eq of chloro(methylsulfinyl)methane was added. The mixture is heated to 80°C for 24 h with gentle stirring. After 24 h, the solid product was filtered off and washed with DMF (5 × 50 mL), MeOH (3 × 50 mL) and H_2O (2 × 50 mL), and dried under vacuum. FTIR spectrum is shown in Fig. SI.3. Loading: 2.78 meq IL/g.



TS-SILP-1

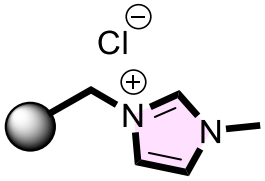
Synthesis of ImDMSO (Precursor for SILP-1): The synthesis and characterization was performed as reported in [1]. In a balloon, 50 g (730 mmol) of Imidazole and 117 g (840 mmol) of K_2CO_3 are placed. Four vacuum/N_2 cycles are done. Under a N_2 atmosphere, the temperature is raised to 120 ºC and left for 30 min with stirring. The temperature is lowered to 90ºC and 250 mL (3.8 mol) of dry ACN are added. It is kept at reflux for 2 hours and then the temperature is lowered to 0ºC. 112g of chloro(methylsulfinyl)methane (767 mmol) are added drop by drop, maintaining the temperature at 0 ºC. After the addition, the temperature is allowed to increase to RT and left stirring for 24 h. Once 24 h have elapsed,

48 g (730 mmol) of KOH are added and left stirring at RT under N_2 for 2 days. After this time the reaction is terminated. Once the reaction is finished, the crude oil is filtered. The solvent is evaporated and 50 mL of toluene and 25mL of ACN are added. They are heated to 70ºC. 50 mL of AcOEt are added and allowed to crystallize. The corresponding product was obtained by crystallization (toluene (50 mL)/acetonitrile (25 mL)/ethyl acetate (50 mL)) as an orange solid (89.5 g, 621 mol, 85% of yield). The crystals are washed with 25 mL Et_2O. 85 g (89.5 mmol) of crystallized ImdDMSO (85% yield) are obtained.



ImDMSO

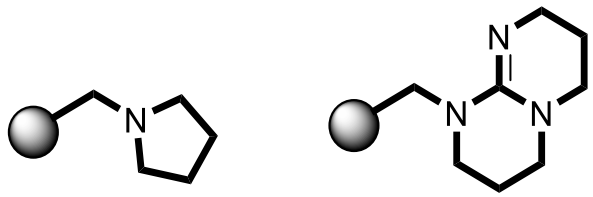
Synthesis of **SILP-2**: 5 g of (Chloromethyl)polystyrene (5.5 meq/g Cl, macroporous), are suspended in a mixture of 6.77 g of N-methylimidazole (3.00 eq. mol) and 25 mL of DMF. The mixture is heated to 75°C for 24 hours with gentle stirring to prevent the support abrasion. After 24 h, the solid product is filtered off, washed with methanol (5 × 50 mL) and diethyl ether (3 × 50 mL), and dried under vacuum



SILP-2

S9.1.2 Synthesis of catalysts for the Knoevenagel condensation

Synthesis of basic catalysts: Different heterogeneous basic catalysts based on (chloromethyl)polystyrene (5.5 meq/g Cl, macroporous) resins were prepared using either or pyrrolidine (**cat-3**) or TBD (**cat-4**). The typical synthetic protocol is reported as follows: 1g of (chloromethyl)polystyrene (5.5 meq/g Cl, macroporous) is suspended in DMF, and subsequently, 3 eq of the corresponding amine (Pyrrolidine or TBD) are added. The mixture is heated to 75°C for 24 h with gentle stirring to prevent the support abrasion. After 24 h, the solid is filtered off, washed thoroughly with methanol (5 × 50 mL) and diethyl ether (3 × 50 mL), and dried under vacuum.



cat-3 cat-4

S9.2 Characterization of the catalysts

FTIR spectra were obtained by using a spectrometer (JASCO FT/IR-6200) equipped with an ATR (MIRacle single-reflection ATR diamond/ZnS) accessory at 4 cm^{-1} of resolution in the range of 4000 and 600 cm^{-1} spectral range. Elemental analysis was carried out in a TruSpec Micro CHNSO de Leco and a CHN628 with an additional module of S de LECO. The elemental analyses for the selected materials tested in this research are shown in **Table S3**.

Table S3. Elemental analysis and loading of the basic resins.

Catalyst	%N	%C	%H	Loading (meq/g)* Real	Loading (meq/g) Theoretical
Cat-3	7.176	82.138	8.7301	4.99	4.59
Cat-4	8.647	55.524	7.3883	3.11	3.87
SILP-2	13.419	61.693	7.1712	3.17	3.50
TS-SILP-1	7.790	20.03	2.8102	2.78	2.66

**The loading was calculated as follows: Loading = [(%WN/100) / MN] x [1000/ nN], where WN is the % mass fraction of nitrogen, MN=14.007 g·mol^{-1}, and nN is the number of nitrogen atoms per functional site.*

S9.3 Synthesis in Batch of HMF from dehydration of fructose

In a typical experiment, D-fructose (1.25 g) was dissolved in 25 mL of an H_2O/2-MeTHF mixture and magnetically stirred (450 rpm). The reaction was carried out at 90 °C in a H_2O/THF mixture under reflux, with a condenser fitted to prevent evaporation of the more volatile THF component. Once the temperature was stabilized, 10 mol% of the catalyst was added, and the reaction was allowed to proceed for different time intervals. Typical appearance of a brown reddish was indicative of HMF formation. Reaction products were identified by ^{1}H NMR (Bruker Avance 400 MHz, using $CDCl_3$ as solvent) and HPLC by comparison with authentic standards. The carbon mass balance ranged between 90–99% in all cases. Replicate experiments showed a reproducibility within approximately 2%.

S9.4 Synthesis in Flow of HMF from dehydration of Fructose

The continuous flow reaction system utilized a Vapourtec R400 flow system, comprising essential components including the 'R-4 Flow Reactor Heater' module and the 'R2S Pumping Module' equipped with two peristaltic pumps. In the experiment, an aqueous solution of

fructose (10-20%) with an 10% mol the of HCl with respect to fructose was continuously pumped at a rate of 0.05 $mL.min^{-1}$ using a peristaltic pump. Simultaneously, 2-Me-THF was pumped at a flow rate of 0.20 $mL.min^{-1}$ using another peristaltic pump. These streams were combined in a T-mixer. The reaction took place inside a column reactor containing the catalyst, reactor volume of 2.5 mL, at a temperature of 120°C and a pressure of 5 bar, resulting in a residence time of 10 min. The reacted mixture was collected in a vial for subsequent phase separation and product reuse. For the stability test, an autosampler was integrated into the system to automate sample collection at regular intervals of every 2 h. This ensured consistent and timely sampling throughout the duration of the stability test, allowing for accurate monitoring of the reaction over time. The conversion and selectivity to the products were determined using ^{1}H NMR spectroscopy (Magritek Spinsolve 80 Ultra) and using $CDCl_3$ as the internal standard. The carbon mass balance ranged between 90-99% in all cases. Replicate experiments showed a reproducibility within approximately 5%.

S9.5. Synthesis in Batch of furfural derivatives by using Knoevenagel Condensation

In a typical procedure, furfural (0.5 g, 0.0052 mol) and ethyl cyanoacetate (1.7 equiv) were dissolved in 25 mL of 2-MeTHF (0.21 M) and magnetically stirred (450 rpm). The reaction was carried out at 70 °C in a H_2O/THF mixture under reflux, with a condenser fitted to prevent evaporation of the more volatile THF component. Once the temperature was stabilized, 5 wt% of the catalyst was added, and the mixture was stirred for 24 h. The reaction progress and product formation were monitored by ^{1}H NMR spectroscopy (Bruker Avance 400 MHz, $CDCl_3$ as solvent, TMS as internal standard). Replicate experiments showed a reproducibility within ca. 3.2%.

S9.6 Synthesis in Flow of furfural derivatives by using Knoevenagel Condensation

The continuous flow system used was homemade and comprised of an HPLC pump, while the reactor was an OMNIFIT® Labware brand. Depending on the desired reaction conditions, the reactor was immersed in a preheated water bath, and the various fractions were collected manually. A solution in desired solvent of furfural (1.25 M) and malononitrile (1.0 eq. mol) was prepared at room temperature and then flowed at a rate of 250 µL/min through the reactor with a volume of 2.75 mL (residence time: 11 min). The reactor was filled with 1.0 g of immobilized pyrrolidine (cat-3) and immersed in a water bath. Another aldehyde from biomass were also evaluated (HMF and OBMF). Identification of Knoevenagel product was performed by using ^{1}H-NMR (Bruker Avance 400 MHz ($CDCl_3$ as the solvent) with TMS as the internal reference standard).

S9.7 Coupling HMF production with Knoevenagel condensation using a flow system

The continuous flow reaction system utilized a Vapourtec R400 flow system, comprising essential components including the 'R-4 Flow Reactor Heater' module, the 'R2S Pumping Module' equipped with two peristaltic pumps, and the 'R2C Pumping Module' featuring two HPLC-type pumps. Additionally, an autosampler was integrated into the system to enable

automated sample collection. All modules and systems were remotely controlled via a UA-OPC communication protocol, facilitated by Python-developed software.

In the experiment, an aqueous solution of fructose (15%) with 10% mol of HCl was continuously pumped at a rate of 0.05 mL.min^{-1} using a peristaltic pump. Simultaneously, 2-Me-THF was pumped at a flow rate of 0.20 mL.min^{-1} using another peristaltic pump. These streams were combined in a T-mixer. The reaction took place inside a column reactor with a volume of 3.06 mL, containing the catalyst, at a temperature of 120°C and a pressure of 5 bar. This configuration yielded a residence time of 12.2 min. Following reaction completion, the resultant mixture, comprised of two distinct phases, underwent separation using a Zaiput gas-liquid separator device. The aqueous phase was collected, while the organic phase was directed to the subsequent reaction stage. Concurrently, a solution containing DMC and ethyl cyanoacetate (1.25 M) was introduced at a flow rate of 0.20 mL.min^{-1}. These streams were mixed within a T-mixer. Subsequently, the reaction ensued within a column reactor with a volume of 7.5 mL, housing the catalyst (1.0 g, cat-3), operating at a temperature of 70°C and a pressure of 8 bar, thereby yielding a residence time of 18.7 min. The conversion and selectivity were calculated via flow ^{1}H NMR spectroscopy (Magritek Spinsolve 80 Ultra), seamlessly integrated into the system for direct analysis.

S10. References

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