Electronic Supplementary Information (ESI)

# A methodical selection process for the development of ketones and esters as bio-based replacements for traditional hydrocarbon solvents

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## Materials and methods

### *Materials*

Methanesulfonic acid ≥99%, KSF montmorillonite, K10 montmorillonite, Nafion SAC-13, 2-butanone (MEK) ≥99%, toluene 99.9%, para-cymene 99.9%, triethylamine ≥99%, limonene 97%, methyl butyrate 99%, N-methyl pyrrolidinone 99%, ethyl isobutyrate 99%, 1-bromooctadecane ≥97%, 1-methylimidazole 99%, Nile red ≥99%, 4-nitroaniline ≥99%, and chloroform-d ($CDCl_3$, 99.8% D) were purchased from Sigma-Aldrich. H-BEA Zeolites were supplied by Clariant. ZSM-5 zeolites were supplied by RS Minerals. K30 montmorillonite was supplied by Fluka. Chlorobenzene ≥99% was purchased from Acros Organics. Tetrahydrofuran 99.9%, ethyl acetate ≥99%, and *N*,*N*-diethyl-4-nitroaniline were purchased from VWR. Methyl pivalate 99%, pinacolone 97%, *N*-methyl pyrrolidinone, dimethylformamide 99.9%, acetone ≥99%, ethyl acetate 99.9%, and sulfuric acid 95% d=1.83 were purchased from Fischer. QUANTOFIX® Peroxide 100 was purchased from Macherey-Nagel. Ames MPF 98/100 kits, 2-nitrofluorene and 4-nitroquinoline-N-oxide were purchased from Xenometrix. TA98 and TA100 were stored at -70 °C.

### *GC-MS analysis*

Gas chromatograph-mass spectrometry (GC-MS) was carried out on a Perkin Elmer Clarus 500 GC with a Clarus 560 S quadrupole mass spectrometer. The equipment was fitted with a ZB5-HT capillary column (30 m x 250 µm x 0.25 µm nominal, max temperature 430 °C). Helium was used as the carrier gas with flow rate of 1.0 mL/min, and a split ratio of 10:1. The injector temperature was 330 °C. The initial oven temperature was 50 °C which was held for 4 minutes. The temperature increased at a rate of 10 °C/min as far as 300 °C at which point it was held for 10 minutes. The Clarus 500 quadrupole mass spectrum was conducted in electron ionisation (EI) mode at 70 eV with the source temperature and the quadrupole both at 300 °C. The *m/z* mass scan was in the range of 40 to 640 *m/z*. The data was collected by the PerkinElmer enhanced TurboMass (Ver. 5.4.2) chemical software. Each GC-MS sample consisted of ~10 mg product mixture in 1.5 mL methanol or hexane as GC-MS solvent.

### *$^1$H NMR and $^{13}$C NMR analysis*

The $^1$H NMR and $^{13}$C NMR spectra were measured on a JEOL JNM-ECS 400 MHz spectrometer. 16 scans were used for $^1$H NMR analysis, and 256 scans were used for $^{13}$C NMR analysis. The NMR data were processed and analysed by ACD/NMR Processor Academic Edition software (Ver. 12.01).

### *UV vis. Analysis*

The UV vis. spectra were measured on a JENWAY, 6705 UV/Vis. spectrophotometer in quartz cuvettes at 25 °C.

### *GC-FID analysis*

An Agilent 6890N gas chromatograph with a flame ionisation detector (GC-FID), fitted with a ZB-5HT capillary column (30 m x 250 µm x 0.25 µm nominal, max temperature 400 °C) was used in this work. Helium was used as the carrier gas at a flow rate of 2.0 mL/min. The split ratio was 50:1. The initial oven temperature was 40 °C which was held for 5 minutes at which point it was increased at a rate of 10 °C/min to 250 °C. Injection temperature was 250 °C and the detector temperature was 250 °C.

## Experimental procedures

### *Solubility tests using natural rubber*

Table S1. Natural rubber solubility test results for esters and ketones.

| Ester | Dissolution status | No. C (total) | No. C (carboxylate group) |
|---|---|---|---|
| Methyl acetate | Not dissolved | 3 | 2 |
| Ethyl acetate | Not dissolved | 4 | 2 |
| Methyl Propionate | Not dissolved | 4 | 3 |
| Isopropyl Acetate | Not dissolved | 5 | 2 |
| Propyl Acetate | Not dissolved | 5 | 2 |
| Ethyl Propionate | Not dissolved | 5 | 3 |
| Methyl Isobutyrate | Not dissolved | 5 | 4 |
| Methyl Butyrate | Dissolved | 5 | 4 |
| tert-Butyl Acetate | Not dissolved | 6 | 2 |
| sec-Butyl Acetate | Not dissolved | 6 | 2 |
| Isopropyl Propionate | Not dissolved | 6 | 3 |
| Ethyl Isobutyrate | Dissolved | 6 | 4 |
| Methyl Pivalate | Dissolved | 6 | 5 |

| **Ketone** | | | |
|---|---|---|---|
| Acetone | Not dissolved | 3 | n/a |
| 2-Butanone | Not dissolved | 4 | n/a |
| MIPK | Not dissolved | 5 | n/a |
| 2-Pentanone | Not dissolved | 5 | n/a |
| 3-Pentanone | Not dissolved | 5 | n/a |
| Pinacolone | Dissolved | 6 | n/a |

### *Synthesis of Poly (butyl acrylate-co-acrylic acid)*

In a 500 mL three-necked round-bottom flask, equipped with a condenser and an overhead stirrer, butyl acrylate (100 g) and acrylic acid (5 g) were mixed together with dibenzoylperoxide (0.382 g), and solvent (26.35 g). The mixture was then purged with nitrogen for at least 1 hour. The mixture was then heated to 70°C and stirred under a nitrogen atmosphere. Once an exothermic reaction was observed, solvent (219.54 g) was added dropwise. Finally, the mixture was aged at 80 °C for 4-6 hours until a conversion of at least 95 % was reached.

### *PSA preparation*

A pressure-sensitive adhesive composition was made from poly (butyl acrylate-co-acrylic acid). Poly (butyl acrylate-co-acrylic acid) (73.39 g, at a solid content of 27.25 %) was mixed with polyisocyanate (1.07 g, at a solid content of 75 %) and melamine resin (0.52 g, at a solid content of 58 %), dissolved in solvent. Subsequently, the solids content was reduced to 20 %. This composition was applied with a knife coater at a thickness of 25 µm onto a polyester film. The composition was dried to obtain a pressure-sensitive adhesive sheet.

### *Determination of Kamlet-Taft parameters*

The KT parameters were measured by dissolving *N*,*N*-diethyl-4-nitroaniline (NN) and 4-nitroaniline (NA) dyes in the test solvent (TS) and scanning on the UV vis. spectrophotometer to determine $\nu_{max}$ (NA) and $\nu_{max}$ (NA). $\pi^*$ and $\beta$ were then calculated using Equation S1 and S2 respectively.

Equation S1.
$$\pi^* = \frac{\nu_{max(NN)}[TS] - \nu_{max(NN)}[cyclohexane]}{\nu_{max(NN)}[DMSO] - \nu_{max(NN)}[cyclohexane]}$$

Equation S2. $$\beta = 0.74\frac{\nu_{Calculated}[TS] - \nu_{Observed}[TS]}{\nu_{Calculated}[DMSO] - \nu_{Observed}[DMSO]}$$

The $\nu_{Calculated}$ represents the $\nu_{max}$ predicted by a baseline of non-hydrogen-bonding solvents. Deviations from this baseline are proportional to $\beta$. Equation S3 shows baseline used in this work to find β was that which was determined by Sherwood.[1] R2 is shown in Equation S4.

Equation S3. $$y = 1.0025x + 3.4426$$

Equation S4. $$R^2 = 0.9945$$

***HSPiP software predictions***

HSPiP (4th Edition 4.1.04) is a computer modelling software which can predict the Hansen solubility parameters (HSPs) of an inputted molecule. HSPiP was employed to calculate the HSPs of the top four candidates, which are shown in Figure S1 in relation to other common solvents.

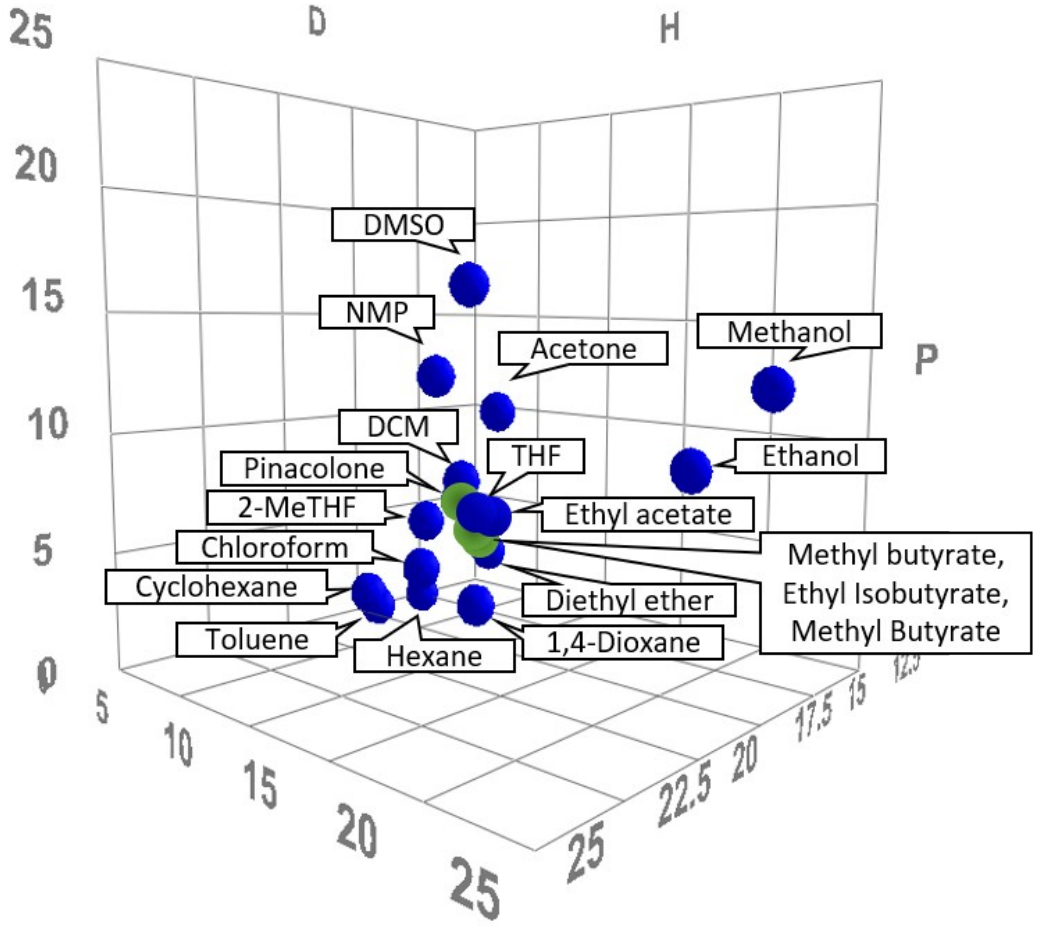


Figure S1. HSP maps showing the position of the top four candidates in relation to other common solvents.

### *Ames test*

The experiment procedure was based on manufacturer's guidelines. TA98 and TA100 were tested at 6 different concentrations (0.16 mg/mL, 0.31 mg/mL, 0.63 mg/mL, 1.25 mg/mL, 2.5 mg/mL, 5 mg/mL) of each test solvent dissolved in DMSO, as well as a positive (2 μg/mL of 2-nitrofluorene (2-NF) and 0.1 μg/mL of 4-nitroquinoline-*N*-oxide (4-NQO)) control and a negative solvent control (DMSO). The bacterial strains were allowed to grow for 90 minutes in a medium containing enough histidine to conduct about two cell divisions. After exposure, the cultures were diluted in pH indicator medium without histidine and then aliquoted into 48 wells of a 384-well plate. After 48 hours at 37 °C, a colour change from purple to yellow was observed in wells containing bacteria which underwent reversion to $His^+$. The number of yellow wells were counted for each dose to obtain the average value. A spreadsheet which accompanies the Ames test kit generates the results and plots the graphs shown in Figure S2.

### *Determination of octanol/water partition coefficient (Log $P_{(o/w)}$)*

Determination of the log $P_{(o/w)}$ was done by the shake flask method. 1 mL each of octanol and water were mixed in a 2.5 mL vial. 60 μL of the test sample was added and the mixed was shaken for 30 seconds and allowed to stand for at least 1 hour. Samples (50 μL) were taken from both the aqueous and organic layers and dissolved in a standard GC solution (1 mL). The standard solution was made by adding cumene (20 μL) as internal standard (IS) to methanol (20 mL). GC-FID was run according to the method described. Log $P_{(o/w)}$ was obtained using Equation S5.

Equation S5.
$$Log\ P_{(o/w)} = \frac{Area(sample)_o Area(IS)_w}{Area(sample)_w Area(IS)_o}$$

### *Synthesis of 1-octadecyl-3-methylimidazolium bromide*

1-Methylimidazole (0.328 mL, 4.0 mmol) was added to the chosen solvent (4 mL) and heated to 50 °C. 1-Bromoctadecane (1.503 mL, 4.4 mmol) was added and conversion was monitored using $^1H$ NMR spectroscopy.

[1-octadecyl-3-methylimidazolium bromide] $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.23 (s, 1H), 7.20 (s, 1H), 4.28 (t, J = 7.2, 2H), 4.10 (s, 3H), 1.88 (quin, J = 7.6, 2H), 1.68 (s, 3H), 1.30-1.21 (bs, 30H), 0.84 (t, J = 6.9, 3H); $^{13}C$ NMR (400 MHz, $CDCl_3$): δ 138.62, 123.50, 121.75, 50.75, 37.25, 32.25,

30.25, 29.75, 29.25, 26.50, 23.00, 14.50; IR 3475, 3429, 3083, 3062, 2914, 2849, 1666, 1630, 1573, 1472, 863, 792, 715, 662.

### *Synthesis of esters by reactive distillation*

Alcohol (12 mL, 0.3 mol) and acid (0.1 mol) were added to a 50 mL two-necked round-bottomed flask equipped with a Dean-Stark apparatus and magnetic stirring bead and heated to reflux. Upon reaching reflux, catalyst was immediately added (440 mg for solid catalysts and 1.9 mmol liquid catalyst). Fresh alcohol was added via the second neck of the two-necked flask when 5 mL of an alcohol/water/ester mixture had distilled from the reaction mixture. The distillate was then released from the trap and this procedure was repeated until full conversion of the acid was achieved. Aliquots were removed from the reaction mixture at various time intervals and analysed by GC-FID. The relative peak areas of the chromatogram were used to assess conversion of the acid. Conversions are shown in Figure S3.

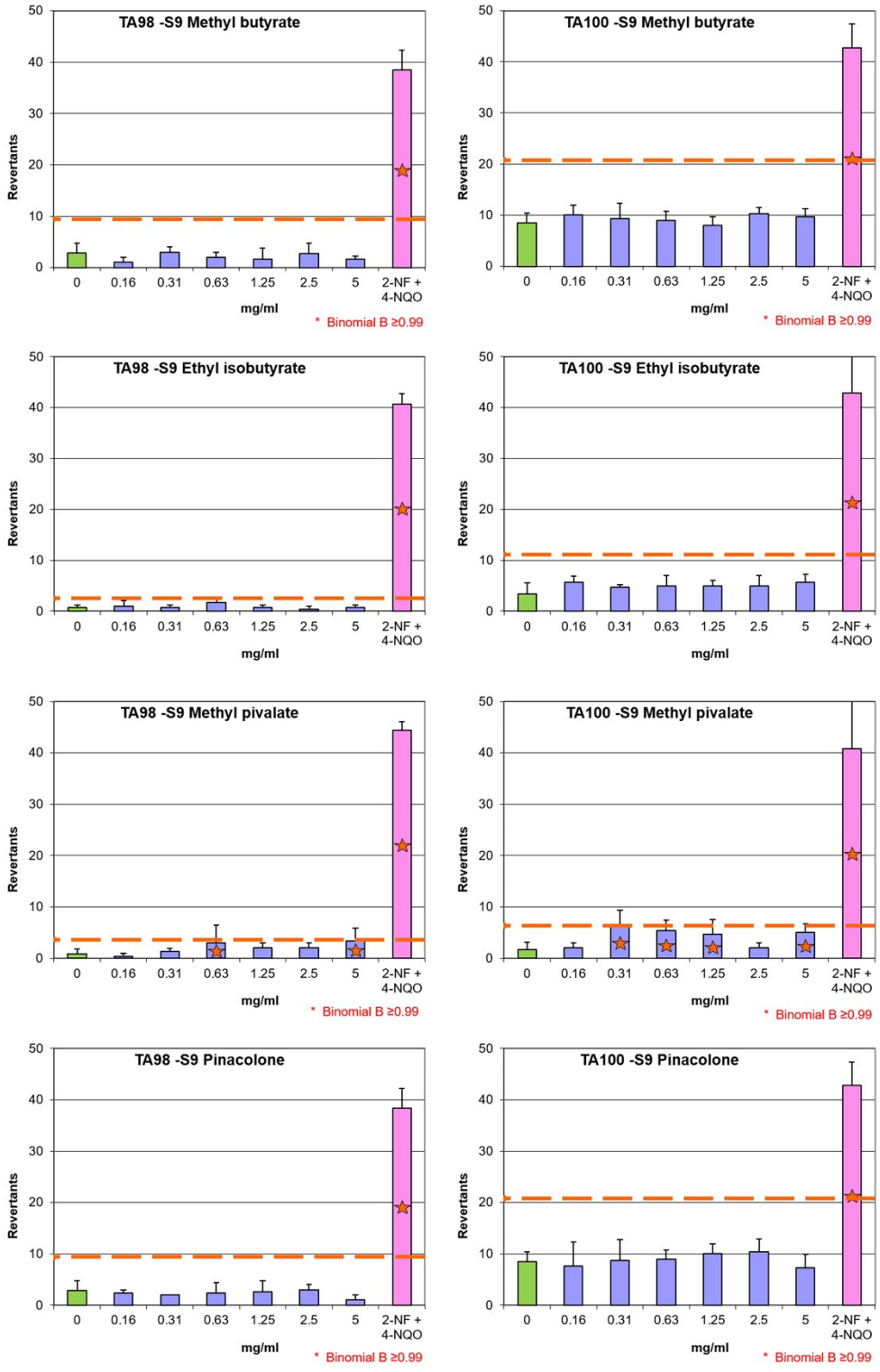



Figure S2. Ames test results at different concentrations of each test solvent in TA98 (left) and TA100 (right) bacterial strains.

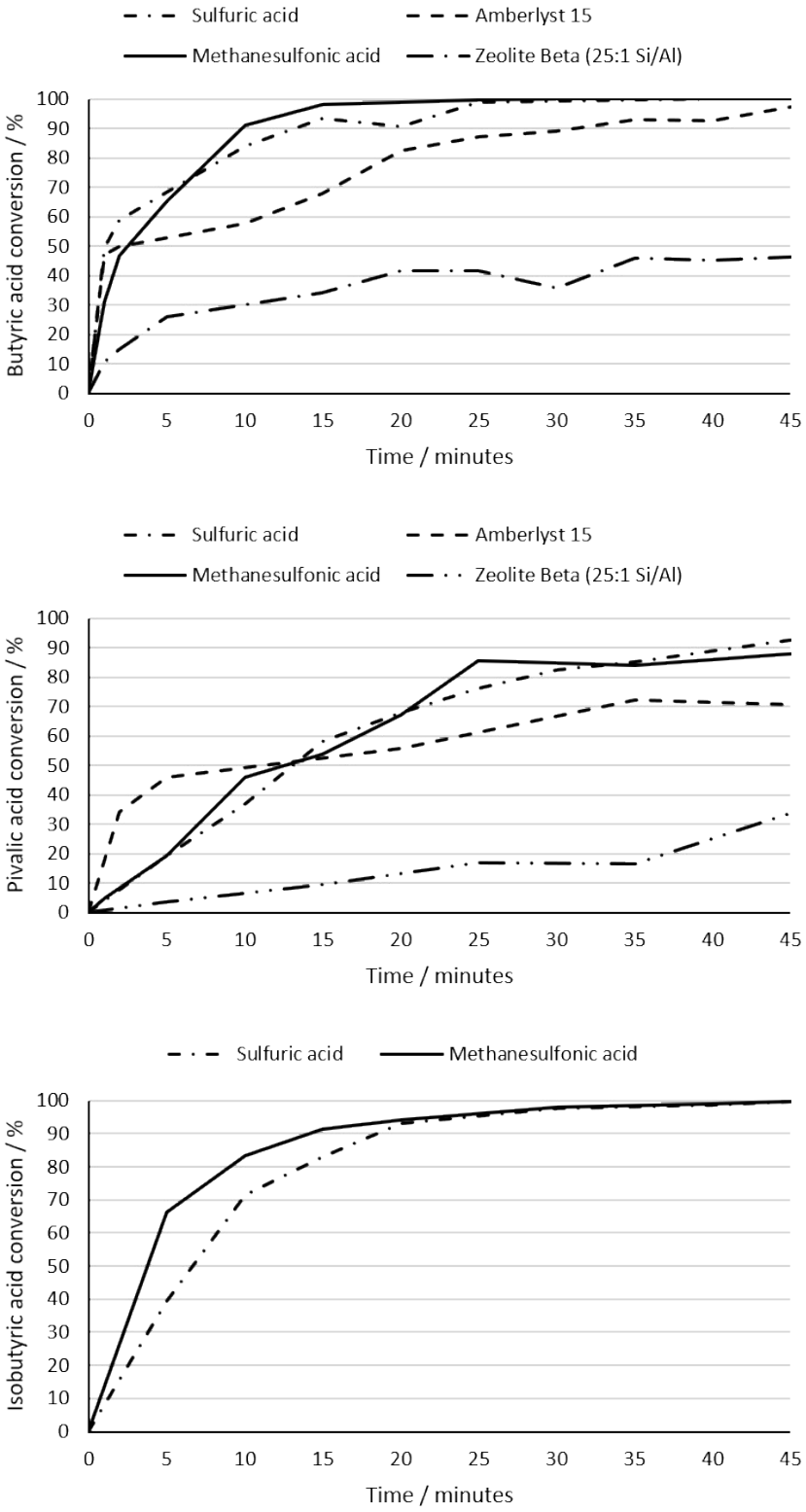



Figure S3. Conversion of butyric acid (top), pivalic acid (middle) and isobutyric acid (bottom) in a reactive distillation apparatus using different catalysts.

## Example LEL calculations

The below calculations show the LEL when density and molecular weight are also considered. A comparison between methyl pivalate and toluene is shown as an example.

- A container can hold 1 mole of an ideal gas and is currently full of air.
- Toluene and methyl pivalate are assumed to be ideal gases.
- The LEL of toluene (1.1%) allows 0.011 moles in the container before the risk of explosion.
- 0.011 moles of toluene = 1.012 g of toluene.
- 1.012 g of toluene = 1.168 mL of toluene

- The LEL of methyl pivalate (1.3%) allows 0.013 moles in the container before a risk of explosion.
- 0.013 moles of methyl pivalate = 1.510 g of methyl pivalate
- 1.510 g of methyl pivalate = 1.726 mL of methyl pivalate

1.726 mL methyl pivalate > 1.168 mL toluene, therefore a larger volume of liquid methyl pivalate can evaporate into the container before a risk of explosion.

## Flow diagram for the production of methyl butyrate and ethyl isobutyrate from glycerol

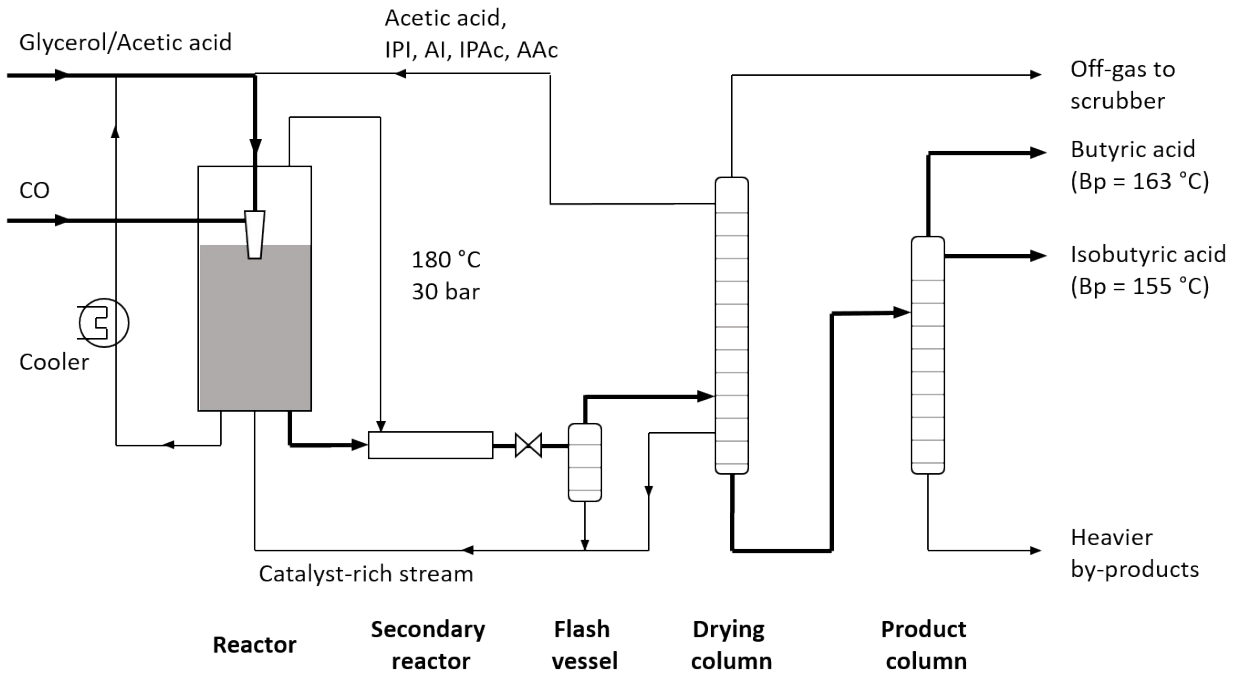
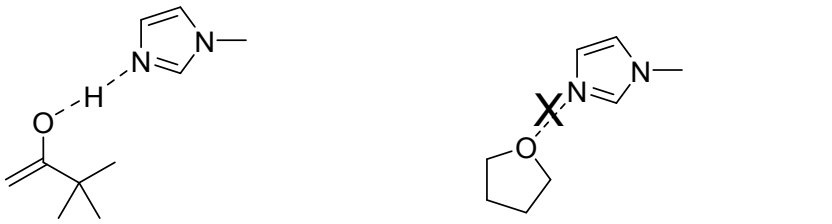



Figure S4. Flow diagram for the production of methyl butyrate and ethyl isobutyrate from glycerol.

## Stabilisation of the enol form of pinacolone by 1-methylimidazole




Hydrogen-bond stabilisation of 1-methylimidazole by pinacolone

No hydrogen-bond stabilisation of 1-methylimidazole by THF

Figure S5. Proposed hydrogen-bond stabilisation of 1-methylimidazole with the enol form of pinacolone.

## Proposed mechanism of radical formation resulting in chain termination in ethyl isobutyrate

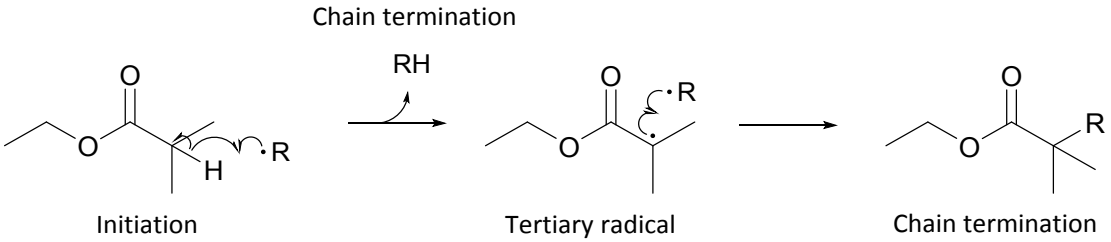



Figure S6. Mechanism of radical formation and chain termination in ethyl isobutyrate.

## Toxicity and ecotoxicity information

Table S2. Publicly available toxicity and ecotoxicity data for the four candidates in comparison with toluene.

| Solvent | Ames test | Rat (oral) $LD_{50}$ / mg $kg^{-1}$ | *Tetrahymena pyriformis* $IGC_{50}$ (48 hr) / mg $L^{-1}$ | Fathead minnow $LC_{50}$ (96 hr) / mL $L^{-1}$ |
|---|---|---|---|---|
| Methyl butyrate | Pass | 6,378* | 1,800 | 111* |
| Ethyl isobutyrate | Pass | 7,150* | 2,168 | 56* |
| Methyl pivalate | Pass | 2,664* | 2,214 | 143* |
| Pinacolone | Pass | 611 | 2,772 | 87 |
| Toluene | Pass[2] | 636 | 52 | 34 |

Ames test data (except toluene) have been obtained in this work. All other data have been obtained from the U.S. Environmental Protection Agency's T.E.S.T software.[3] Those values marked with a star (*) are predicted using the "Consensus" QSAR method (see ref. 2 weblink for information on this QSAR method), while those without a star are experimental and are form part of the T.E.S.T. software training set on which predictions are based.

## References

[1] J. Sherwood, Bio-Based Solvents for Organic Synthesis, PhD Thesis, University of York, **2013**.
[2] R. P. Bos, R. M. E. Brouns, R. van Doorn, J. L. G. Theuws, P. T. Henderson, *Mutat. Res. Toxicol.* **1981**, *88*, 273–279.
[3] US EPA, "Toxicity Estimation Software Tool (TEST)," can be found under https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test, **n.d.**