 Supporting information

Catalysis in flow: Practical and selective aerobic oxidation of alcohols

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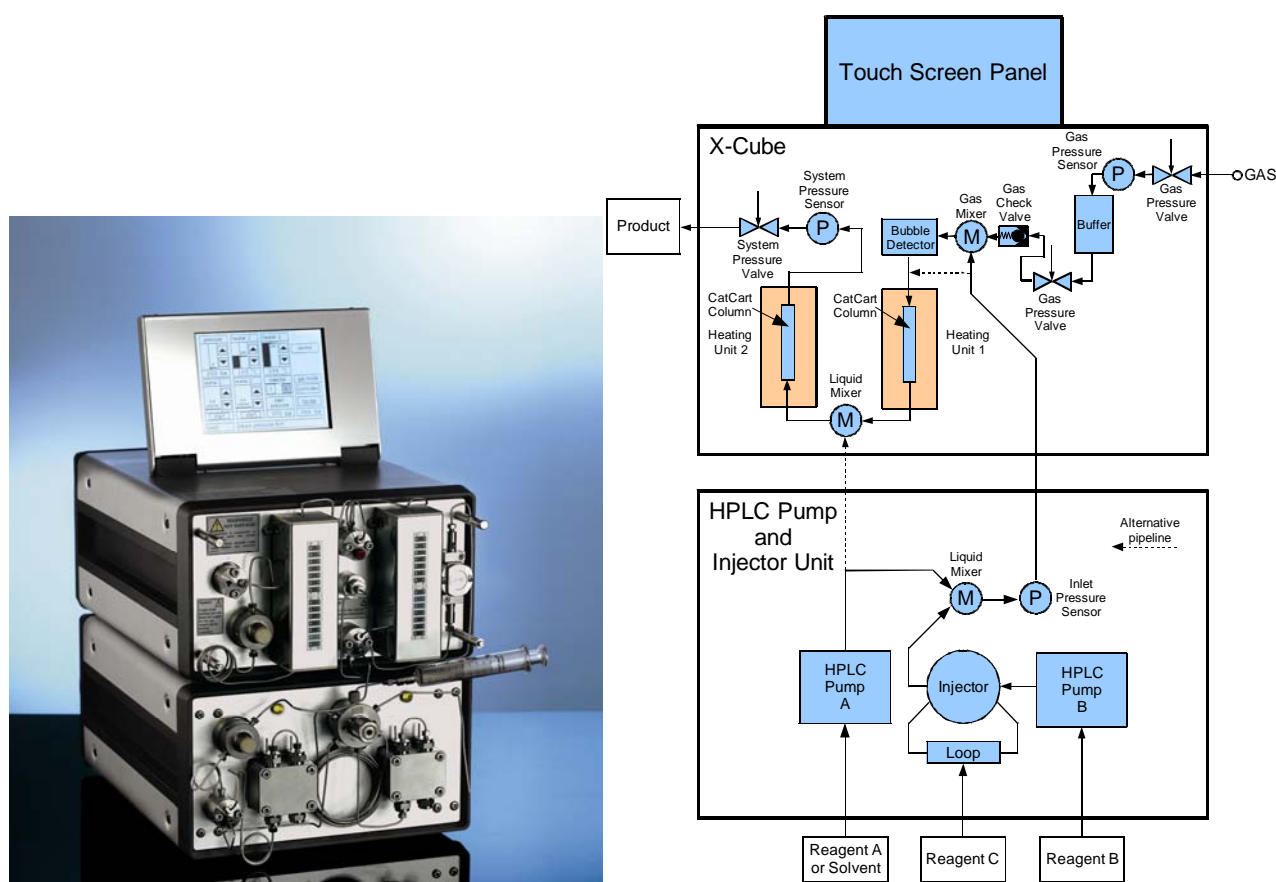*Development, Ramsgate Road, Sandwich CT13 9NJ, U.K.*

Figure S1. The X-cube reactor (left) and schematic diagram of its components (right).

Preparation of catalyst cartridge and calculation of residence time (τ): Using a CatCart Packer[TM], a

preweighed catalyst cartridge was packed with ca. 0.29 g of 5% Ru/Al_2O_3 (provided by Johnson Matthey plc),

selaed on either end with 8 μm filters. The cartridge was then reweighed to determine the precise amount of

catalyst loaded. It was then mounted in the X-Cube[TM], where it was filled with toluene. The cartridge was then

dismounted and reweighed to furnish the reaction volume (calculated from the weight and density of toluene).

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$$\text{residence time } (\tau) = \frac{reaction\ volume\ (mL)}{flow\ rate\ (mL/min)}$$

Reactor characterisation.

(a) Mass transfer. The Peclet number was calculated by using equation 1.

$$Pe_f = \frac{Ud_p}{\phi D_a} \qquad (1)$$

Where U = empty tube fluid velocity (m/s) (equation 2);

D_a = molecular dispersion (m^2/s).

d_p = particle size (m);

ϕ = voidage (equation 3).

$$U = \frac{F}{A} \qquad (2)$$

Where F = volumetric flow rate m^3/s (1mL/min = $1.7\cdot10^{-8}$m^3/s);

A = cross sectional area of reactor m^2 ($1.26\cdot10^{-5}$) .

$$\phi = \frac{v_\phi}{v_{total}} \qquad (3)$$

Where, v_{total} = total volume of void and pores in the reactor (m^3).

v_ϕ = interstitial volume (m^3)

v_{total} was obtained as a difference between dry and wet cartridge filled with catalyst. This value was *ca.* 0.74 mL. v_ϕ was obtained as a difference between v_{total} and pore volume. Pore volume depends on the amount of catalyst employed and was obtained from the cumulative pore volume per gram of catalyst (BET analysis). For one cartridge containing 0.29 g, pore volume is 0.22 mL and $\phi = 0.71$.

Physical properties of toluene as well as benzyl alcohol are present in Table S1.

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Table S1 Physical properties of toluene and benzyl alcohol.

Compound	Mw (mol/g)	T (K)	ρ (kg/m^3)	μ (Pa·s)	Heats of combustion (kJ/mol)	C_p (J/molK)
Toluene	92.14	363	802.39	3.01×10^{-4}	-3.91×10^3	183.83
Benzyl alcohol	108.14		995.12	12.84×10^{-4}		245.59
Benzaldehyde					-3.40×10^3	
H$_2$O						

Reynold's number was calculated from Equation 4

$$\text{Re} = \frac{\rho U d_p}{\mu \phi} \qquad (4)$$

Where, ρ = density (kg/m^3);

μ = dynamic viscosity of solvent (Pa·s);

Re = 0.5 (laminar flow regime in the reactor).

Hence, molecular dispersion D_a may be quantified by Equation 5.[1]

$$D_a = D_{AB} + \frac{U_f^2 d_p^2}{192 D_{AB}} \qquad (5)$$

D_{AB} – liquid diffusivity (m^2/s).

Liquid diffusivity can be calculated from the modified Wilke-Chang Equation 6.[2]

$$D_{AB} = 10 \cdot 10^{-15} \frac{Mw_{solvent}^{1/2} T}{\mu V_{solute}^{1/3} V_{solvent}^{1/3}} \qquad (6)$$

$Mw_{solvent}$ – molecular weight of solvent (g/mol);
V_{solute} – molecular volume of solute (cm^3/mol);
$V_{solvent}$ – molecular volume of solvent (cm^3/mol);
T – temperature (K).

From Equation 1, 5 and 6 we obtained the following values:

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[1] H. Scott Fogler, *Elements of chemical reaction engineering*; 4 ed.; Pearson education international: Boston, 2004.

[2] Reddy, K. A.; Doraiswamy, L. K. *Ind. Eng. Chem. Fund.* **1967**, *6*, 77.

Pe_f = 4.496
D_a = 4.1748·10^{-8} m^2/s
D_{AB} = 4.9929·10^{-9} m^2/s

(b) Generated heat. Thermodynamic net heat of reaction for the oxidation of benzyl alcohol by molecular oxygen was calculated from heats of formation of benzyl alcohol (BA), benzaldehyde (BAd), and H$_2$O from equation 7.

$$\Delta H_{net} = (H^f_{BAd} + H^f_{H_2O}) - H^f_{BA} = -187 \text{ kJ/mol} \quad \text{(eq. 7)}$$

Heats of formation can be obtained from the chemical database (DETHERM) and are presented in Table S1.

For the reactor operating at 1 mL/min, with 1M alcohol loading, the generated heat flow is obtained as follows:
ΔQ_{net} = concentration of benzyl alcohol ·F ·ΔH_{net} = 3.12 J/s

For the fastest reaction at 1M alcohol achieved in full conversion in 45 min, the average single pass conversion is equalled to 0.02 (at residence time of 0.74 min). Hence, the average single pass generated heat flow is equalled to 5.11·10^{-2} J/s. This can be compared to the energy needed to evaporate the toluene. Heat of vaporisation of toluene, obtained from chemistry database, is equalled to 34kJ/mol. In 10 mL solution of 1M benzyl alcohol in toluene, there is 8M of toluene. Hence, at 1mL/min, it will be necessary 4.59 J/s of heat flow to evaporate completely toluene. This number is much greater than the heat obtained per average single pass conversion of alcohol.

Also adiabatic temperature rise (equation 8) can be calculated per average single pass conversion.

$$\Delta T_{ad} = \frac{\Delta H_{net}}{mole_{total} c_p} \quad \text{(eq. 8)}$$

Where, $mole_{total}$ – total moles of reactor content (Table S1)

c_p – average heat capacity of reactor content (Table S1)

If all heat is retained within the vessel due to loss of cooling capabilities, at full conversion of 1M benzyl alcohol, ΔT_{ad} = 108K. At single pass conversion ΔT_{ad} is only 1.8K.

(c) Combustion of toluene.

Overall reaction equation:

$C_7H_8 + 9 O_2 \rightarrow 7 CO_2 + 4H_2O$

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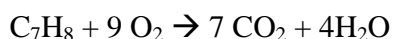
Heat of combustion ΔH_{rxn}(toluene) = -3910 kJ/mol, obtained from the chemical database (DETHERM).

At 25 bar pressure, the reactor cartridge contains 0.64 g (6.84 mmol) of toluene and 0.224 mmol of O_2 (total mole content in the cartridge is 7.06mmol and toluene/O_2 mole ratio is 0.93/0.3).

Assuming complete consumption of 0.224 mmol O_2 (limiting), 0.0248 mmol of toluene was converted to 0.174 mmol of CO_2. This corresponds to a pressure build up of 7.12 bar (calculated from ideal gas law at 363 K and 0.74 mL volume). The heat generated by this process Q = -3910·0.025 = -97.3 J.

The adiabatic temperature rise can be calculated from eq. 8. The average heat capacity (179 J/molK) for the cartridge content was calculated from the heat capacity of toluene (183.8 J/molK) and oxygen (30.4 J/molK) and their relative mole ratios (0.93/0.3), while total mole content in the cartridge was 7.06 mmol. Hence, ΔT_{ad} for the combustion of toluene is equalled to 77 K.

Synthesis and characterisation of unsaturated aldol product 15. Unsaturated aldol product **15** was prepared according to a literature procedure:[3] A mixture of hexanal (0.1045 g, 1 mmol), pyrrolidine (7 mg, 0.1 mmol) and benzoic acid (24 mg, 0.2 mmol) in toluene (5 mL) was stirred at 60 °C for 12 h. After cooling to ambient temperature, 0.1 mL sample was extracted, diluted to 1 mL and analysed by GC, while the rest of the sample was stripped of the solvent and subjected to NMR analysis.

Wittig olefination reaction. Dienoate **17** was prepared from cinnamyl alcohol as described in the main text. After filtration, the solvent was evaporated and the residue re-dissolved in $CDCl_3$ and subjected to NMR analysis (Figure S2).

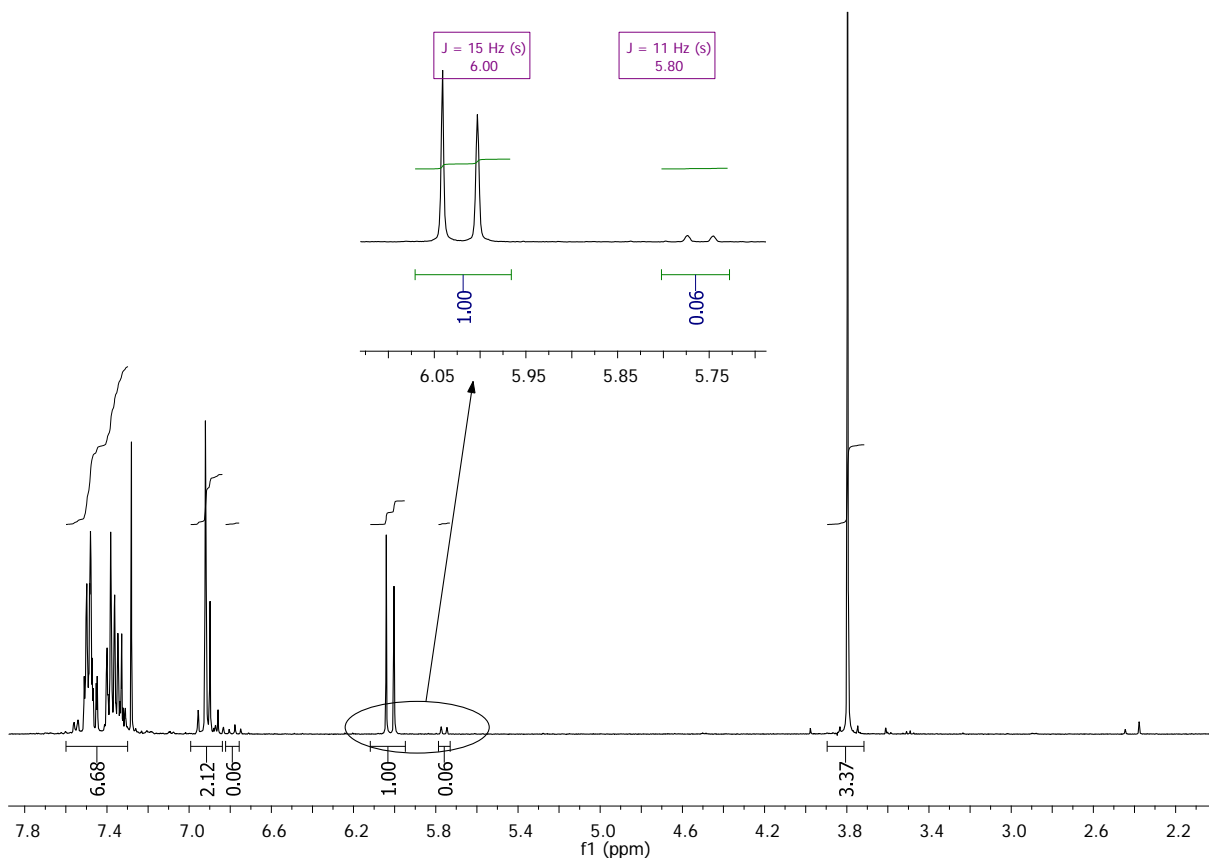[3] Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. *Synlett* **1999**, 450-452.

Figure S2 ^{1}H NMR spectrum of dienoate **17**.

By comparing the [1]*J*(HH) coupling constants of the alkene proton resonances, the *E,E : E,Z* ratio of **17** was found to be 1:17.[4]

Investigating leaching of Ru/Al$_2$O$_3$.

(a) **Sample preparation:** Oxidation of various alcohols was performed using standard conditions described in the main text. Upon completion, the solvent was evaporated and residue was re-dissolved in 2 mL of *aqua regia* and diluted to 10 mL. This sample was subjected to ICP analysis. Results are summarised in Table S2. In all cases, %Ru was found to be < 0.003 ppm.

Table S2 ICP analyses of %Ru contained in product samples.

Reaction No	Alcohol	Intensity	[Ru] ml/L (ppm)

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[4] ^{1}H NMR of the *E,E*-isomer: Takacs, J. M.; Jaber, M. R.; Clement, F.; Walters, C. *J. Org. Chem.* **1998**, *63*, 6757-6760. ^{1}H NMR of the *E,Z*-isomer: Mitsudo, T.; Takagi, M.; Zhang, S.-W.; Watanabe, Y. *J. Organomet. Chem.* **1992**, *423*, 405-414.

112	Hexanol	66.94175	0.001
115	Benzyl alcohol	-47.3378	-0.001
120	2-aminobenzylalcohol	-35.1462	-0.001
123	Piperonyl alcohol	-22.2291	0
130	2-hexanol	-66.5306	-0.001
134	1,2-hexanol	139.0454	0.003
135	Hexanol	57.25329	0.001
136	2-aminobenzylalcohol	-54.5334	-0.001
139	Benzyl alcohol	-74.4518	-0.002