Supporting information

Catalysis in flow: Practical and selective aerobic oxidation of alcohols

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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™, a preweighed catalyst cartridge was packed with ca. 0.29 g of 5% Ru/Al₂O₃ (provided by Johnson Matthey plc), sealed 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™, 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).
residence time \( \tau = \frac{\text{reaction volume (mL)}}{\text{flow rate (mL/min)}} \)

Reactor characterisation.

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

\[
\text{Pe}_f = \frac{U d_p}{\phi D_a} \quad (1)
\]

Where \( U \) = empty tube fluid velocity (m/s) (equation 2);
\( D_a \) = molecular dispersion (m²/s);
\( d_p \) = particle size (m);
\( \phi \) = voidage (equation 3).

\[
U = \frac{F}{A} \quad (2)
\]

Where \( F \) = volumetric flow rate m³/s (1mL/min = 1.7 \times 10^{-8} \text{m}^3/\text{s});
A = cross sectional area of reactor m² (1.26 \times 10^{-5}) .

\[
\phi = \frac{v_\phi}{v_{\text{total}}} \quad (3)
\]

Where, \( v_{\text{total}} \) = total volume of void and pores in the reactor (m³).
\( v_\phi \) = interstitial volume (m³)

\( v_{\text{total}} \) was obtained as a difference between dry and wet cartridge filled with catalyst. This value was ca. 0.74 mL.
\( v_\phi \) was obtained as a difference between \( v_{\text{total}} \) 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.
Table S1 Physical properties of toluene and benzyl alcohol.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mw (mol/g)</th>
<th>T (K)</th>
<th>ρ (kg/m³)</th>
<th>μ (Pa·s)</th>
<th>Heats of combustion (kJ/mol)</th>
<th>Cp (J/molK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>92.14</td>
<td>363</td>
<td>802.39</td>
<td>3.01 x 10^{-4}</td>
<td>-3.91 x 10^3</td>
<td>183.83</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>108.14</td>
<td>995.12</td>
<td>12.84 x 10^{-4}</td>
<td></td>
<td>245.59</td>
<td></td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-3.40 x 10^3</td>
<td></td>
</tr>
<tr>
<td>H₂O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reynold’s number was calculated from Equation 4

\[
Re = \frac{\rho U d_p}{\mu \phi}
\]  

Where, \( \rho \) = density (kg/m³); \( \mu \) = 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

\[
D_a = D_{AB} + \frac{U_f d_p^2}{192 D_{AB}}
\]  

\( D_{AB} \) – liquid diffusivity (m²/s).

Liquid diffusivity can be calculated from the modified Wilke-Chang Equation 6.2

\[
D_{AB} = 10 \cdot 10^{-15} \frac{Mw_{solvent}^{1/2} T}{\mu \sqrt[1/3]{V_{solvent}}}
\]  

\( Mw_{solvent} \) – molecular weight of solvent (g/mol);
\( V_{solvent} \) – molecular volume of solvent (cm³/mol);
\( T \) – temperature (K).

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

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\( Pe_f = 4.496 \)
\( D_s = 4.1748 \times 10^{-8} \text{ m}^2/\text{s} \)
\( D_{AB} = 4.9929 \times 10^{-9} \text{ m}^2/\text{s} \)

**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.

\[
\Delta H_{net} = \left( H_f^{BAd} + H_f^{H_2O} \right) - H_f^{BA} = -187 \text{ kJ/mol} \quad \text{(eq. 7)}
\]

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:

\[
\Delta Q_{net} = \text{concentration of benzyl alcohol} \cdot F \cdot \Delta H_{net} = 3.12 \text{ J/s}
\]

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 \( 5.11 \times 10^{-2} \) 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.

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

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, \( \Delta T_{ad} = 108 \text{K} \). At single pass conversion \( \Delta T_{ad} \) is only 1.8K.

**c) Combustion of toluene.**

Overall reaction equation:

\[
\text{C}_7\text{H}_8 + 9 \text{O}_2 \rightarrow 7 \text{CO}_2 + 4\text{H}_2\text{O}
\]
Heats of combustion $\Delta H_{\text{rxn}}$ (toluene) = -3910 kJ/mol, obtained from the chemical database (DETERM). 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 7.06 mmol 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 buildup of 7.12 bar (calculated from ideal gas law at 363 K and 0.74 mL volume). The heat generated by this process $Q = -3910 \times 0.025 = -97.3$ 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, $\Delta T_{\text{ad}}$ for the combustion of toluene is equalled to 77 K.

**Synthesis and characterization 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).

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By comparing the $^1J_{(HH)}$ 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>
<thead>
<tr>
<th>Reaction No</th>
<th>Alcohol Intensity [Ru] ml/L (ppm)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Substance</th>
<th>Value</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>112</td>
<td>Hexanol</td>
<td>66.94175</td>
<td>0.001</td>
</tr>
<tr>
<td>115</td>
<td>Benzyl alcohol</td>
<td>-47.3378</td>
<td>-0.001</td>
</tr>
<tr>
<td>120</td>
<td>2-aminobenzylalcohol</td>
<td>-35.1462</td>
<td>-0.001</td>
</tr>
<tr>
<td>123</td>
<td>Piperonyl alcohol</td>
<td>-22.2291</td>
<td>0</td>
</tr>
<tr>
<td>130</td>
<td>2-hexanol</td>
<td>-66.5306</td>
<td>-0.001</td>
</tr>
<tr>
<td>134</td>
<td>1,2-hexanol</td>
<td>139.0454</td>
<td>0.003</td>
</tr>
<tr>
<td>135</td>
<td>Hexanol</td>
<td>57.25329</td>
<td>0.001</td>
</tr>
<tr>
<td>136</td>
<td>2-aminobenzylalcohol</td>
<td>-54.5334</td>
<td>-0.001</td>
</tr>
<tr>
<td>139</td>
<td>Benzyl alcohol</td>
<td>-74.4518</td>
<td>-0.002</td>
</tr>
</tbody>
</table>