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ARTICLE *in* GREEN CHEMISTRY · DECEMBER 2010

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Catalysis in flow: Practical and selective aerobic oxidation of alcohols to aldehydes and ketones

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Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X

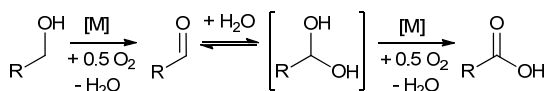
First published on the web Xth XXXXXXXXX 200X

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A safe, practical and selective process for the aerobic oxidation of alcohols to aldehydes and ketones has been developed using a Ru catalyst in a continuous flow reactor. Benzylic and allylic alcohols were oxidised selectively to their corresponding aldehydes and ketones, including substrates containing *N*- and *S*-heteroatoms. Rate of turnover is compatible with that previously reported, using batch or microchannel reactors, under optimised conditions. A preliminary kinetic model was derived, which is supported by experimental observations. Last but not least, tandem oxidation-olefination may be achieved without the need to isolate the alcohol intermediate/solvent switching.

A Introduction

Development of clean, selective and atom-efficient reactions is the new paradigm in organic synthesis, largely driven by a desire to reduce economic and environmental costs of chemical production.¹ Arguably, one of the most challenging reactions is the selective oxidation of alcohols to aldehydes and ketones – a process that is ubiquitous in organic chemistry, yet also one of the least efficient, engendering the development of a large number of methodologies.² In recent years, there has been substantial effort devoted to the replacement of stoichiometric oxidants with catalytic methodologies, in an attempt to improve the atom efficiency of the process.³



Scheme 1 Oxidation of primary alcohols by O₂.

One of the most attractive ways of oxidising an alcohol is to use O₂ as a terminal oxidant, where only H₂O is generated as a side-product (Scheme 1). Although there have been a number of heterogeneous catalysts reported to facilitate the process,⁴ there is a genuine concern that the process of mixing the catalyst, reactant and the gaseous oxidant can lead to explosive hazards, particularly if the reaction is performed on a large-scale in a batch reactor. In recent years, the emergence of flow chemistry⁵ provides a solution to the problem, and a number of systems can now be used to conduct these reactions safely. One way of minimising explosive risks is to employ an inert reaction medium, the most popular being supercritical CO₂, which has been employed successfully with supported Pd catalysts for the oxidation of alcohol.^{6-8,9} Very recently, the development of a continuous-flow tube reactor for the homogeneous Pd-catalysed aerobic oxidation of alcohols was also reported.¹⁰ These systems are very effective, but either require specialised equipment to generate and contain supercritical CO₂, or require extensive workup (product

extraction from reaction media/removal of additives), which may prevent their implementation on a large-scale.

In this paper, we will utilise commercially available catalyst and flow reactor for the selective oxidation of primary and secondary alcohols, delivering a practical synthesis of aldehyde and ketones that fulfils several criteria of green chemistry, exemplified by the following features:

1. Efficient mixing between gas-liquid-solid phases;
2. Good scope and chemoselectivity;
3. Easy to perform: employs commercially available catalyst and flow reactor;
4. Environmentally benign: does not require halogenated solvents, and only water is produced as a side-product;
5. Employs cheap oxidant (O₂) and heterogeneous catalyst (Ru/Al₂O₃). These, and the water side-product, can be easily removed from the product stream, thus affording an easy workup; and
6. Safe: does not involve hazardous reaction conditions or reagents.

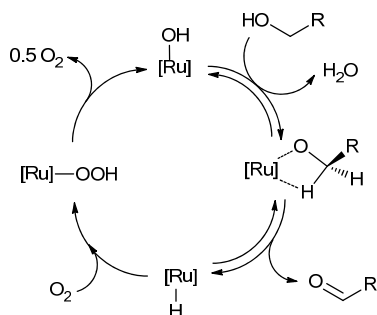
B Results and discussion

Choice of catalyst

There is a plethora of ruthenium catalysts reported for the oxidation of alcohols under aerobic conditions; ranging from monomeric complexes to metal clusters in different oxidation states, supported on a variety of materials.¹¹⁻¹⁵ In this work, Ru/Al₂O₃ was chosen as it is commercially available at a reasonable cost, thus accessible to most synthetic laboratories.

The use of this catalyst for the selective oxidation of alcohols to carbonyl compounds was first proposed by Mizuno *et al.*,^{16, 17} where reactions were performed in a batch reactor using trifluorotoluene as a solvent, operating under a constant flow of O₂ with azeotropic removal of water. The active catalyst species is believed to be ruthenium hydroxide (Scheme 2), which reacts with the alcohol to generate a ruthenium-alkoxide species that dehydrogenates *via* a β-H elimination process. The insertion of a dioxygen molecule into the resultant Ru-H species forms an unstable peroxide

complex, which eliminates an oxygen atom to complete the catalytic cycle.¹⁷ Thus, the overall process consumes an oxygen atom and produces a water molecule as a by-product.



Scheme 2 Proposed catalytic cycle for Ru-catalysed oxidation of alcohol.

Description of flow reactor

Ru/Al₂O₃ has been previously employed as a catalyst in a compact multichannel reactor.¹⁸ The system consisted of five parallel mm-scaled square packed bed channels, each measuring 100 mm in length (*i.e.* 500 mm in total). As the reaction occurred in a two-phase flow along the length of the reactor, staged injection of oxygen was used to maintain a consistent amount of gas along the reaction bed. Although characteristics of the flow system were very well-defined, the generality of the system was not demonstrated, as only benzyl alcohol was examined as the substrate.

In this work, a commercially-available XCube™ reactor was employed, which has a smaller reaction volume (Figure 1).¹⁹ the catalyst is loaded in one or two cylindrical cartridges (each measuring 4 mm x 70 mm), which can be heated and pressurised. In a typical experiment, a solution of the alcohol (0.1-1 M in toluene) was delivered by a piston pump to a gas-mixer, where it was pre-mixed and saturated with the gaseous reactant (O₂ or air) before it was passed through the catalyst bed. A gas bubble detector maintains a 1:19 bubble-to-liquid ratio, thus the system is not subjected to gas-liquid mass transfer resistance, and the small reactor volume also ensures very little, if any, pressure drop. Residence times of up to 180 seconds may be achieved by controlling the flow rate (normally 1 mL/min), and the product stream can then be collected as separate fractions (for single-pass experiments), or, if desired, re-circulated in continuous flow until reaction is complete.

Using such a setup, a highly laminar flow regime operates in the reactor (calculated Reynold's number, $R_e = 0.5$). A liquid diffusivity of $5.2 \times 10^{-9} \text{ m}^2/\text{s}$ and a Peclet number (Pe_f) of 4.5 (see Supporting Information) suggest that mixing occurs mainly by molecular dispersion. The intrinsic large surface-to-volume ratio of the reactor should allow for efficient heat transfer, which is particularly important to prevent thermal runaway processes for these exothermic oxidation reactions. The oxidation of benzyl alcohol to benzaldehyde is calculated to be -187 kJ/mol. For the flow reactor operating at 1 mL/min with a 1 M solution of alcohol the generated heat was calculated to be 3.12 J/s. For a single pass conversion, this is significantly smaller (*ca.* $5.11 \times 10^{-2} \text{ J/s}$) than the heat needed to evaporate the toluene solvent

(4.59 J/s). With an extremely low adiabatic temperature rise ($\Delta T_{ad} = 1.8 \text{ }^\circ\text{C}$), the system operates essentially under isothermal conditions.²⁰

The small volume of the reactor ensures that even highly exothermic reactions, such as combustion of toluene, can be effectively contained. Under the maximum pressure of 25 bar, the amount of O₂ present in the system is only sufficient to generate -97.3 J of heat from this process, causing $\Delta T_{ad} = 77 \text{ }^\circ\text{C}$ and $\Delta P = 7.1 \text{ bars}$ (due to liberation of CO₂). Thus, the system can be considered as inherently safe for oxidation reactions.

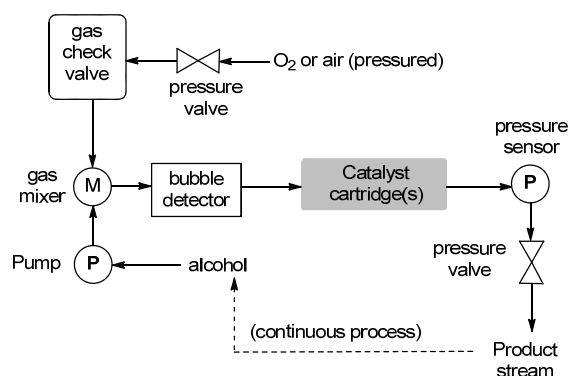


Fig. 1 General schematic of the XCube™ flow reactor.

Substrate scope

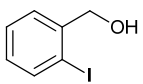
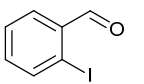
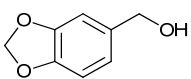
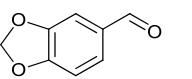
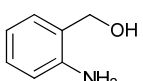
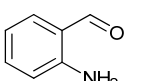
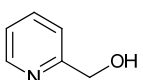
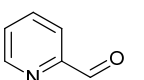
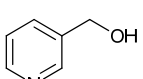
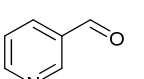
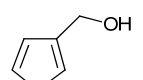
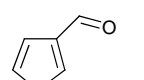
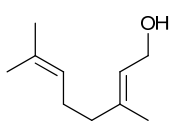
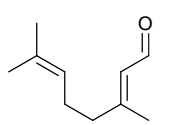
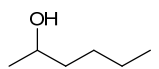
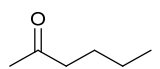
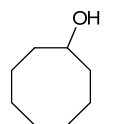
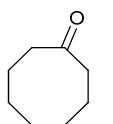
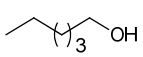
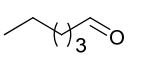
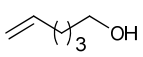
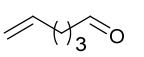
A number of primary and secondary alcohols were assessed to establish the scope of the system; the same reaction conditions were applied to provide comparison between the reactivity of the different substrates. The transformation of the benchmark substrate benzyl alcohol to benzaldehyde proceeded smoothly to completion in under an hour with >99% selectivity (Table 1, entry 1). Other benzylic alcohols also undergo similar transformation cleanly and selectively, including those containing bulky substituents and/or heteroatoms at the *ortho*-position (entries 2 and 3). The oxidation of 2-aminobenzyl alcohol, to 2-aminobenzaldehyde is particularly challenging, as the product is prone to self-condense to form imines. In this case, good conversion can be achieved with little side product formation (entry 4).

Most encouragingly, the catalyst remained robust in the presence of pyridyl and thienyl functional groups (entries 4-7), which are known to inhibit the catalyst in other systems, most notably: [RuCl₂(PPh₃)₃]/TEMPO,²¹ Ru deposited on TiO₂/O₂,²² and Au supported on ceria/air.²³ In the present system, although a longer reaction time was required for *N*-containing compounds, the reactions proceeded to completion with >95% selectivity.

Allylic alcohols such as cinnamyl alcohol and geraniol can be easily transformed into corresponding conjugated aldehydes (entries 8 and 9). In these cases, the C=C moiety remained intact, *i.e.* no epoxidation/hydrogenation products were detected. Oxidation of secondary alcohols to ketones can also be achieved: 2-phenylethanol was converted to acetophenone **10** in under an hour (entry 10), while the reaction of aliphatic 2-hexanol to 2-hexanone **11** was sluggish (entry 11). Conversely, oxidation of the sterically constrained

cyclooctanol to cyclooctanone **12** was achieved with 64% conversion (entry 12).

Table 1 Oxidation of alcohols using Ru/Al₂O₃ and O₂ under continuous flow.^a

Entry	Alcohol	Product ^b	t/h	Conv. ^c /%
1	PhCH ₂ OH	PhCHO	0.75	>99
2			1	>99
3			1	98
4			6	94 ^d
5			7	95
6			7	97
7			1	>99
8	Ph-CH=CH-CH ₂ OH	Ph-CH=CH-CHO	0.75	>99
9			2	>99
10	Ph-CH(OH)-CH ₃	Ph-C(=O)-CH ₃	1	>99
11			7	75 (91) ^e
12			7	64
13			7	87 ^f
14			7	65

^a Unless otherwise indicated, reactions were conducted in continuous recirculating mode, where a solution of the alcohol (0.1 M, 15 mL) was passed through a cartridge packed with 0.29 g of 5% Ru/Al₂O₃ under 5 bars of O₂ at 90 °C and a flow rate of 1 mL/min (residence time = 44 s).

^b Confirmed by ¹H NMR spectroscopy or GC, referenced to a genuine sample. Unless otherwise stated, selectivity >99%. ^c GC conversion, using o-xylene as an internal standard. ^d <10% unidentified side-product was observed. ^e Incorporating a desiccant cartridge. ^f Selectivity = 98%, 2% aldol product (*vide infra*).

Aliphatic primary alcohols are challenging substrates for this system. In the batch reactor, the addition of benzoquinone was required to suppress competitive over-oxidation to the

acid. Under continuous flow conditions, we were able to attain aldehyde products **13** and **14** from 1-hexanol and 5-hexen-1-ol, respectively, in moderate conversions, without the need for additives (entries 13 and 14).

Dioxygen was also replaced with zero-grade air (applied at 15 bars) for a few selected reactions (Table 2). No significant difference was observed for conversions of benzyl alcohol and 3-thienylmethanol (Table 2, entries 1 and 2 vs Table 1, entries 1 and 7). For slower reactions, such as oxidation of pyridyl alcohols and 1-hexanol (Table 2, entries 3-5 vs Table 1, entries 5, 6 and 12), rates of conversion were noticeably slower, although acceptable yields can still be achieved.

Table 2 Oxidation of alcohols using air as oxidant.^a

Entry	Alcohol	t/h	Conv./%
1	benzyl alcohol	1	>99
2	3-thienylmethanol	1	>99
3	2-pyridylmethanol	7	78
4	3-pyridylmethanol	7	70
5	1-hexanol	7	80

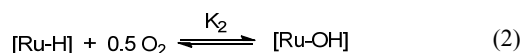
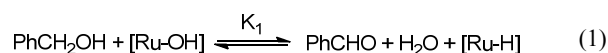
^a Reaction conditions are as stated in previous table, except O₂ was replaced by air (15 bar). Selectivity for the aldehyde was unchanged in these reactions.

At the end of each reaction, the collected solution was simply evaporated to furnish analytically pure product with >95% recovery in all cases. Nine of these product samples were subjected to ICP analysis (Supporting Information), none of which contained detectable level of metal residue (<0.003 ppm). Hence, catalyst leaching is not an issue.

Rate studies

Next, we examined effects of changing reaction parameters afforded by the reactor. Benzyl alcohol was selected as the model substrate so that our result can be compared to earlier systems.

Assuming that the overall rate is governed by the surface reactions, there are essentially two processes that operate in the catalytic system: (a) the conversion of benzyl alcohol to benzaldehyde with concomitant formation of a water molecule (eqn. 1), and (b) the regeneration of the active catalyst site by dioxygen (eqn. 2).



From these, a Mars-van Krevelen-type rate equation can be derived (eqn.3):²⁴

$$\text{rate} = A \frac{[\text{PhCH}_2\text{OH}][\text{O}_2]^{0.5} - [\text{PhCHO}][\text{H}_2\text{O}]/K_1K_2}{1 + [\text{O}_2]^{0.5}K_2} \quad (3)$$

where $A = k_1K_2[\text{cat}]_{\text{tot}}$, $[\text{cat}]_{\text{tot}}$ = total catalytic sites.

In the present system (essentially a differential batch recycle reactor), the dissolved [O₂] is kept constant over the course of the reaction and that equilibrium is achieved prior to contact with catalyst. Therefore, the rate of the reaction will

be dependent upon the parameters present in the numerator of eqn. 3, *i.e.* it will be expected to be accelerated by increasing the initial concentration of the alcohol, counteracted by the amount of benzaldehyde and water generated during the reaction.

The validity of the equation was tested by following the oxidation of benzyl alcohol at two different initial concentrations (0.1 and 0.2 M, fig. 2A). Under such dilute conditions, the reaction is pseudo-first order with respect to benzyl alcohol. The rate graphs showed that catalyst activity is reduced at higher concentration, denoting a catalyst deactivation process. By incorporating a desiccant cartridge (containing 1.7 g of MgSO_4) into the flow system, the effect can be removed (fig. 2B). Thus, the removal of water accumulated during the reaction has a beneficial effect. This is further illustrated by deploying the desiccant cartridge in the oxidation of 2-hexanol **11** (Table 1, entry 11), where the yield of 2-hexanone can be improved significantly from 75 to 91%.

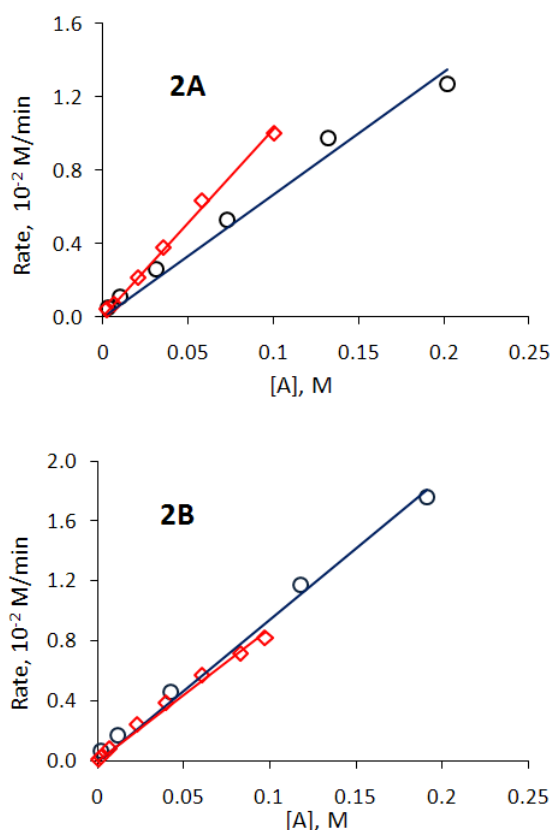


Fig. 2 Rate vs $[A]$ graphs at two different $[A]_0$ ($\Delta = 0.1$ and $\circ = 0.2$ M) in the absence (**2A**) and presence (**2B**) of a desiccant cartridge (MgSO_4), 5 bars of O_2 , $[A] = [\text{benzyl alcohol}]$.

Product inhibition was demonstrated at higher concentrations of alcohol (0.6 and 1 M). The addition of 0.41 M of benzaldehyde to 0.6 M of benzyl alcohol caused an overall decrease in its rate of reaction (fig. 3). Notably, the rate profile of the reaction initially emulated that exhibited by the reaction performed with 1 M of the alcohol, but began to deviate beyond 50% conversion, which is attributed to the difference in the amount of water present in the two systems.

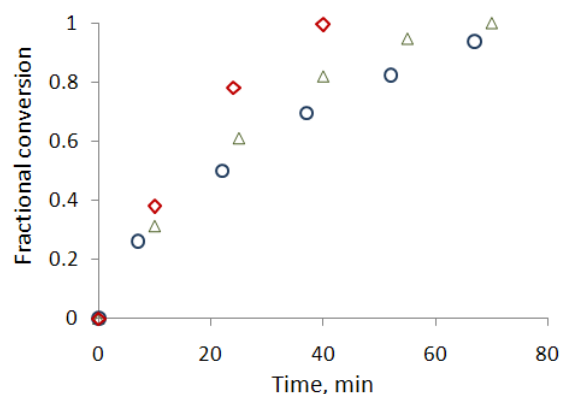


Fig. 3 Conversion graphs with 0.6M of $[A]_0$ (\diamond), 1M of $[A]_0$ (\circ), and 0.6M of $[A]_0 + 0.41\text{M}$ of benzaldehyde (Δ), 5 bars of O_2 .

By increasing the O_2 pressure from 5 to 25 bars,²⁵ the reaction rate was significantly enhanced (fig. 4), restoring the first-order rate of consumption of benzyl alcohol, therefore O_2 is integral to the kinetics of the reaction (eqn. 3). This result differs significantly from previous work by Mizuno *et al*, where O_2 was found to have no effect on the rate of reaction (zero order) when it was performed in a batch reactor.¹⁷ This could be due to the limited range of pressure examined (between 0.2-3 atm), which may not be sufficient for the effect to be discernable experimentally.

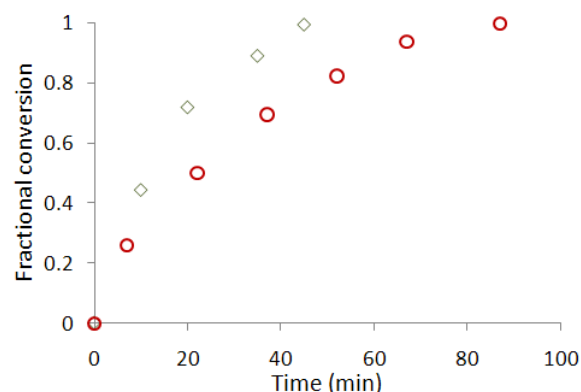


Fig. 4 Effect of increasing O_2 pressure. Reaction conditions: 1M of benzyl alcohol under 5 bars (\circ) and 25 bars (\diamond) of O_2 .

Although the selectivity of the reactions is $>99\%$ in most cases, a trace amount of the benzoic acid ($<1\%$) can often be detected in the reaction stream by GC, which is known to poison the catalyst.¹⁸ Indeed, the catalyst loses *ca.* 20% of its activity when it was reused in the oxidation of benzyl alcohol,²⁶ even though the selectivity of the reaction was maintained. However, catalytic activity can be restored by washing the supported catalyst with an aqueous NaOH solution.^{16, 18}

For comparison, the oxidation of 1-hexanol was also performed with and without added product (fig. 5). The conversion was clearly attenuated in the presence of added aldehyde (from 65% to *ca.* 40%), indicating that product inhibition is much more pronounced with this substrate. Furthermore, the formation of the aldol product **15** (Scheme 3) was detected as the reaction progressed by GC (verified by

independent synthesis), and it is possible that it can also inhibit catalyst activity.

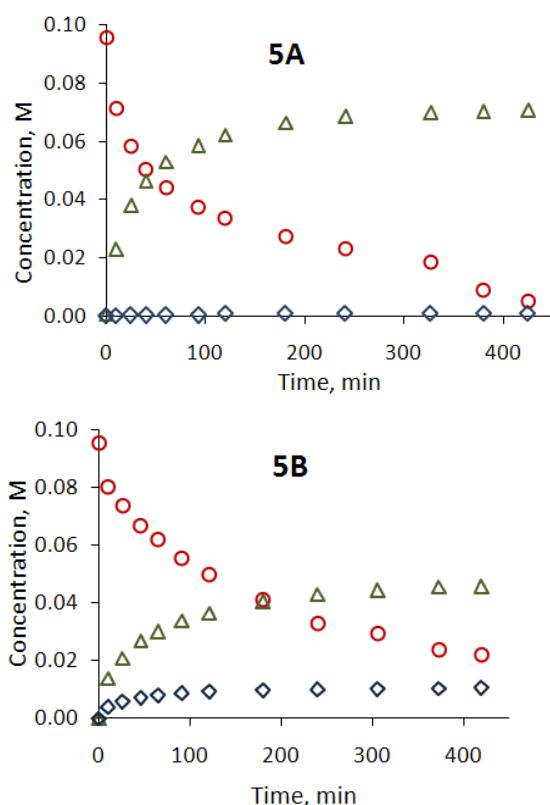
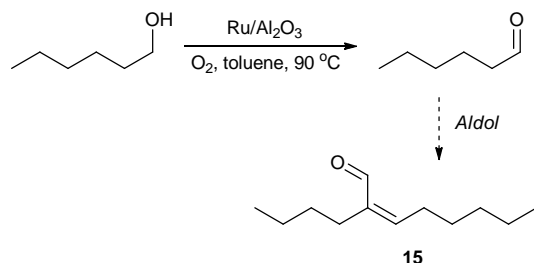


Fig. 5 Reaction profiles for the oxidation of 1-hexanol (0.1 M) under 5 bars of O₂ in the absence (**5A**) and presence (**5B**) of added hexanal (0.08 M, normalised): 1-hexanol (○), hexanal (Δ) and aldol product (◇).



Scheme 3 Competitive formation of aldol product.

With the limited data in hand, preliminary fitting to eqn. 3 revealed that K_2 is approximately two orders of magnitude smaller than K_1 for the oxidation of benzyl alcohol, *i.e.* the formation of benzaldehyde is a much more favourable process than the regeneration of the active catalyst site. This suggests that the catalyst surface is largely populated by Ru-H species. Since the regeneration of catalyst is not substrate-dependent, the difference in reactivity between benzyl alcohol and hexanol can be attributed entirely to the difference in K_1 . This, and other related aspects of the reaction, will be delineated in our future work.

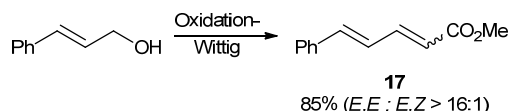
Under these conditions (1 M benzyl alcohol and 25 bars of O₂), 44% conversion to benzaldehyde can be obtained in 10 min (fig. 4), corresponding to a TOF of 97 h⁻¹. This compares favourably with that reported using the compact multichannel

reactor under similar conditions (60 h⁻¹).¹⁸ As complete conversion to benzaldehyde can be achieved in 45 min, corresponding to a space-time-yield of 974 g L⁻¹ h⁻¹. This is substantially better than the result obtained with the Pd-catalysed process utilising a sc-CO₂ reactor (reported STY of >100 g L⁻¹ h⁻¹).⁷

Tandem oxidation-Wittig reactions

By performing reactions in a flow reactor, the product is obtained as a solution in toluene, which can be isolated simply by evaporating the solvent. However, more commonly, aldehydes and ketones are transformed into further compounds. As a workup procedure is not necessary, this can improve the atom-economy of the process by allowing reactions to be performed in tandem. This was demonstrated by performing oxidation-Wittig reactions in a telescoped synthesis. Previously, a one-pot procedure utilising Ru/Al₂O₃ and a Wittig reagent had been reported for the synthesis of α,β -unsaturated esters from primary alcohols,²⁷ where mixtures of the alcohol, catalyst and Wittig reagent were refluxed in toluene under an O₂ atmosphere for 12–24 h, and the final product was purified by column chromatography.

In the present work, methyl (triphenylphosphoranylidene)-acetate was added to a solution of cinnamaldehyde collected from the flow reactor. When the olefination was complete, the resultant triphenylphosphine oxide was scavenged using Merrifield resin.²⁸ Following filtration and evaporation, the dienoate **17** can be isolated in 85% yield, predominantly as the *E,E*-isomer (Scheme 4). The overall procedure, including product isolation, can be achieved in a matter of hours. Crucially, the catalyst can be recovered uncontaminated and regenerated, if so desired.



Scheme 4 Telescoped oxidation-Wittig olefination reactions: (i) Ru/Al₂O₃, O₂, 90 °C, 1 h; (ii) Ph₃P=CHCO₂Me, 3 h.

Conclusions

A new flow system (differential batch reactor) has been described for the selective oxidation of alcohols to aldehydes and ketones. Reactions were achieved by using commercially available Ru/Al₂O₃ and toluene as a solvent. A variety of primary and secondary alcohols can be converted to their corresponding carbonyl compounds in good yields and excellent selectivity, with the exception of primary aliphatic alcohols, which gave only moderate conversions. For certain reactions, oxygen can be replaced with air without noticeable decrease in catalyst activity.

A global rate equation was derived to model the behaviour of the system. The product and by-product (water) can exert an inhibitory effect on the reaction rate, which can be compensated by increasing the oxygen pressure.

The system can be operated safely even at high pressures of oxygen, and compares very favourably with other flow reactors in terms of turnover rate and space-time-yield.

Another advantage of the current system is the ease of workup; analytically pure product can be obtained in high yields simply by evaporating the solvent, or used directly in another process without contaminating the catalyst/reagent. This was demonstrated by a telescoped oxidation-Wittig reaction, which was achieved with high yield and selectivity.

Experimental Section

Starting materials were procured commercially and used without purification. Reactions were performed in reagent-grade toluene. Conversion of alcohol to product was monitored using a HP6890 gas chromatography system fitted with a SPB-5 column (30 m x 0.2 mm x 0.8 µm). The percentage of conversion/selectivity was determined by comparing with known standards, using a calibration plot for product and reactant, against o-xylene as an internal standard. The identity of all product was further verified by recording their ¹H NMR spectra in CDCl₃ using a Bruker Avance NMR spectrometer at 400 MHz. ICP analyses (%Ru) were performed using a Perkin Elmer 2000 DV ICP-OE spectrometer. SEM images were recorded with a JEOL JSM840A microscope, fitted with an Oxford Instruments INCA energy dispersive analytical system (EDS) for elemental X-ray analysis and digital image capture.

Commercially-available Ru/Al₂O₃ (5 wt%) was provided by Johnson Matthey plc. BET surface area and mean pore size of the catalyst were obtained by low-temperature N₂ adsorption studies at 77 K using a Micromeritics Tristar 3000 instrument. It was found to have a surface area of 129 m²g⁻¹ with a mean pore size of 0.75 cm³ g⁻¹. The mean pore diameter = 85 nm. The mean particle size was found to be 100 µm.

Typical experimental procedure for the oxidation of alcohols.

Using an X-CubeTM, a solution of the alcohol in toluene (0.1/0.2M, 15 mL, or 0.6/1M, 10 mL), containing o-xylene (0.05M of 0.5 M) as an internal standard, was introduced into a heated cartridge containing 5 wt. Ru/Al₂O₃ (0.29 g) at 90 °C, under 5 or 25 bars of O₂. The solution was re-circulated continuously, and the conversion was monitored by GC analysis. Upon completion, the solution was evaporated to afford the corresponding aldehyde/ketone with >90% recovery. The purity and identity of the product was verified by ¹H NMR spectroscopy.

Procedure for tandem oxidation-Wittig reactions.

A 0.1M solution of the aldehyde was generated from the corresponding alcohol using the procedure described above, until complete conversion was indicated by GC. Methyl (triphenylphosphoranylidene)acetate (1.2 eq.) was added in one portion, and stirred at room temperature until all aldehyde has been consumed (TLC, 3 h). Merrifield resin (1 g/2 mmol of acetate used) and KI (2.5 eq.) were added to the reaction mixture and stirred for 2 h at room temperature, to remove any remaining traces of the phosphorus reagent/by product. The insoluble material was removed by filtration through a short pad of silica gel, which was washed repeatedly with Et₂O. The combined filtrate was evaporated to give analytically pure product **17**. ¹H NMR spectrum recorded of

the residue is given in the Supporting Information.

Acknowledgements

This work is funded by an EPSRC grant, co-sponsored by Pfizer (EP/G027544/1). We are grateful to Johnson Matthey plc for the provision of supported metal catalysts for this project.

Notes and references

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