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Aerobic flow oxidation of alcohols in water catalyzed by platinum nanoparticles dispersed in an amphiphilic polymer†

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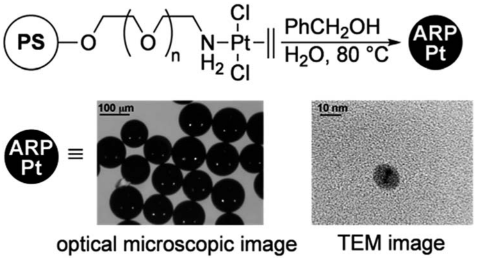
We have developed a technique for the aqueous aerobic flow oxidation of alcohols in a continuous-flow reactor containing platinum nanoparticles dispersed on an amphiphilic polystyrene–poly(ethylene glycol) resin (ARP-Pt). Various primary and secondary alcohols including aliphatic, aromatic and heteroaromatic alcohols were efficiently oxidized within 73 seconds in a flowing aqueous system at 100–120 °C under 40–70 bar of the system pressure to give the corresponding carboxylic acids and ketones, respectively, in up to 99% yield. Benzaldehydes could be also prepared selectively from benzyl alcohols by conducting the flow oxidation under the standard conditions in the presence of triethylamine. Moreover, a practical gram-scale synthesis of surfactants was realized in the aqueous aerobic continuous flow oxidation for 36–116 hours. This aerobic flow oxidation system provides a safe, clean, green, rapid and efficient practical method for oxidizing alcohols.

Introduction

Although the oxidation of alcohols to the corresponding carbonyl compounds is among the most fundamental and most important processes in organic chemistry, conducting the reaction in a safe and green manner remains a major challenge because conventional protocols for the oxidation of alcohols often require stoichiometric amounts of harmful and toxic oxidants, as well as the use of halogenated organic solvents.[1] Indeed, although a variety of heterogeneous catalysts that promote the aerobic oxidation of alcohols have been developed in the last decade,[2–4] there are only a few isolated reports on aerobic oxidations of less-active aliphatic alcohols.[5]

The development of organic transformations under conditions of continuous flow is becoming an increasingly important field of research in synthetic organic chemistry.[6] However, the catalytic aerobic oxidation of alcohols in continuous-flow systems with heterogeneous catalysts are yet immature.[7,8] Previously reported catalytic aerobic flow oxidations of alcohols were generally performed in toxic and/or explosive organic solvents.[7g–i,8b,9] In addition, the applicable substrates were usually limited to highly reactive (*e.g.*, benzylic) alcohols, and the reaction efficiency was not on a satisfactory level of practical synthetic processes.[7,8] Thus, it is not surprising that the continuous-flow systems for the aerobic oxidation of a wide range of alcohols (including less-active aliphatic alcohols), realizing safe, green, and efficient preparation of a variety of carbonyl compounds, would be an eagerly-awaited device.

We have previously developed novel supported palladium and platinum catalysts for the aerobic oxidation of alcohols in water.[3a–d] Dispersions of platinum nanoparticles in amphiphilic polystyrene–poly(ethylene glycol) resin (PS–PEG),[10] prepared by treatment of a PS–PEG resin-supported dichloro(ethene)platinum complex with benzyl alcohol (Scheme 1),[11] catalyze the aerobic oxidation of various alcohols, including less-reactive primary aliphatic alcohols, in water under mild conditions (oxygen or air at 1 atm, 60 °C, 8–36 h). Furthermore, the catalysts are stable and can be readily recycled.[3b,c] These findings prompted us to apply these catalysts in a continuous-flow system for the oxidation of alcohols. Here, we report the aerobic oxidation of a wide range of alcohols, including less-reactive primary aliphatic alcohols, in water in a continuous-flow reactor containing a PS–PEG resin dispersion of



Scheme 1 Preparation of ARP-Pt.

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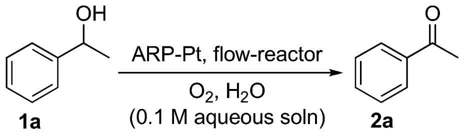
platinum nanoparticles (amphiphilic resin-supported nanoparticles of platinum (ARP-Pt)) (Scheme 1). Oxidation of various primary and secondary alcohols, including aliphatic, alicyclic, benzylic, and allylic alcohols, was achieved within 73 seconds of the residence time to give the corresponding carboxylic acids and ketones in up to 99% isolated yield with a practical level of the productivity (substrate concentration = 10–100 mM, flow rate = 0.6–0.8 mL min^{-1}). Moreover, >50 gram-scale synthesis of surfactants was realized *via* a continuous-flow of 116 h.

Results and discussion

The ARP-Pt-catalyzed aerobic oxidation of alcohols in water was performed in a flow reactor (Fig. 1a).[12,13] The reactor was capable of producing controlled flow rates of up to 3.0 mL min^{-1} at temperatures of up to 200 °C and system pressures of up to 150 bar, while supplying a constant volume (5 vol%) of nanosize bubbles of O_2 to the continuously flowing solution through a gas mixer equipped with a titanium frit (pore size 50 nm).[14]

We selected 1-phenylethanol (**1a**) as a substrate for optimizing the conditions for the aerobic flow oxidation (Scheme 2). A 1.0 M aqueous solution of 1-phenylethanol (**1a**) was introduced into the reactor at a flow rate of 1.0 mL min^{-1}, and passed sequentially through two catalyst cartridges (internal diameter 4 mm, length 70 mm; Fig. 1b), each charged with ARP-Pt (0.17 mmol Pt for the two cartridges). Under these conditions, the total contact time of the solution with the catalyst was 44 seconds. Flow oxidation of **1a** at 25 °C and a system pressure of 30 bar gave 1-phenylethanone (**2a**) in 7% conversion (Fig. 2, entry 1A). Raising the temperature improved the conversion (entries 1A–D), and we were pleased to find that the aerobic oxidation proceeded smoothly in water at 100 °C to give 1-phenylethanone (**2a**) in 98% conversion within 44 seconds (entry 1D). Aerobic flow oxidation of **1a** at a system pressure of 30 bar was also examined at various temperatures with flow rates of 0.8 and 0.4 mL min^{-1}, corresponding to contact times of 55 and 110 seconds, respectively (entries 2A–D, 3A–D). At each temperature, the conversion of 1-phenylethanol was higher for the longer contact time. 1-Phenylethanol (**1a**) was quantitatively oxidized to 1-phenylethanone (>99%) at 100 °C within 55 seconds at a system pressure of 30 bar (entry 2D), although traces of unreacted **1a** could still be detected by GC/MS analysis. Complete conversion was observed at 100 °C and a contact time of 110 seconds (flow rate = 0.4 mL min^{-1}) (entry 3D).



Scheme 2 Continuous-flow aerobic oxidation of 1-phenylethanol to 1-phenylethanone.

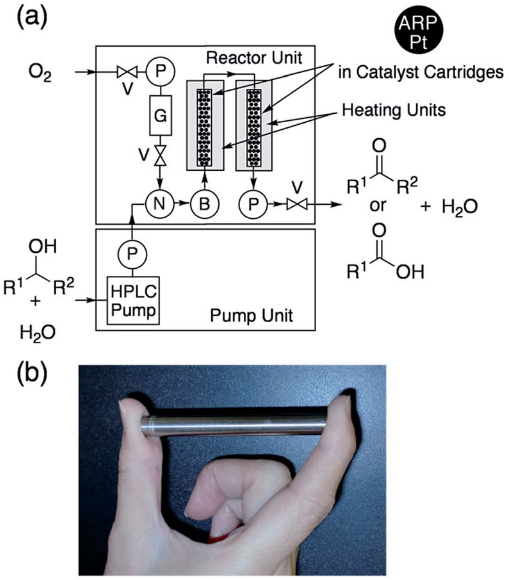
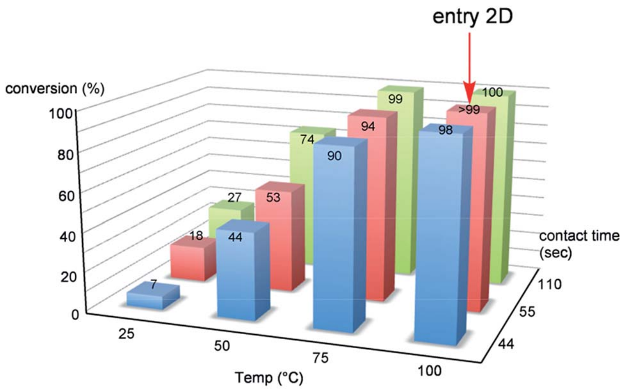


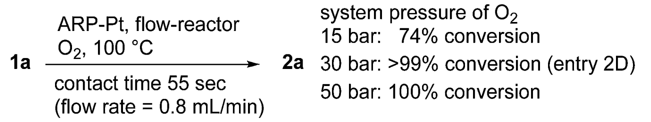
Fig. 1 (a) Schematic diagram of the flow-oxidation reactor. P: pressure sensor, G: gas buffer area, V: valve, N: nanobubble generator, B: bubble detector. (b) View of the catalyst cartridge.

We next examined the effect of the system pressure (15–50 bar) on the aerobic oxidation of 1-phenylethanol (**1a**) at 100 °C at a flow rate of 0.8 mL min^{-1} (Scheme 3). The flow oxidation of



	Column entry	A	B	C	D
Line entry	Temp / Contact time[a]	25 °C	50 °C	75 °C	100 °C
1	44 s	7	44	90	98
2	55 s	18	53	94	>99
3	110 s	27	74	99	100

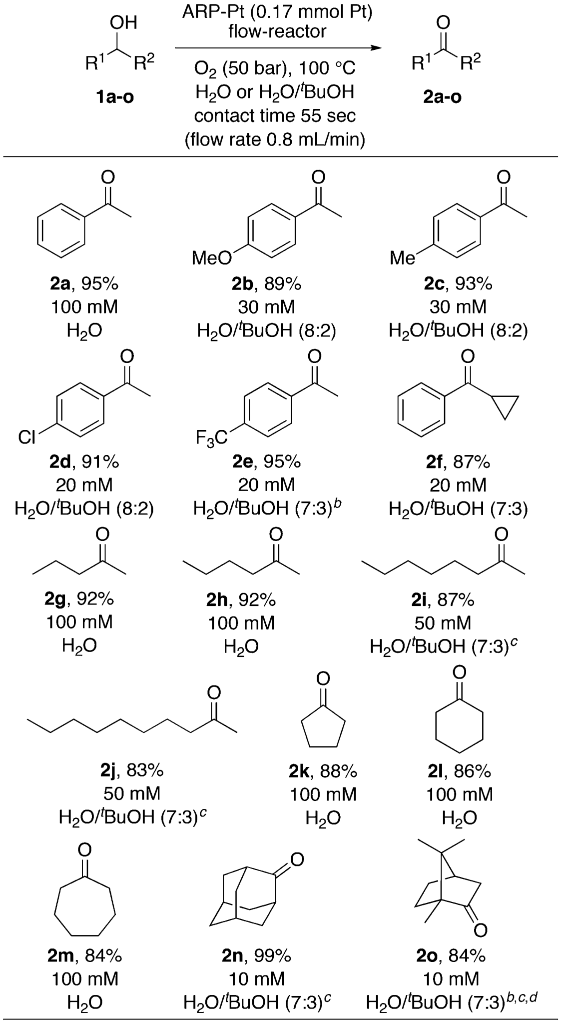
Fig. 2 Optimization of conditions for the aerobic oxidation of an aqueous solution of 1-phenylethanol (**1a**) in a flow reactor equipped with ARP-Pt cartridges. Top: three dimension bar graph. Bottom: table for the results. Reaction conditions: 0.1 M aq. 1-phenylethanol, APR-Pt (0.17 mmol Pt). O_2 (5 vol%) was introduced into the solution as nanosized bubbles at a system pressure of 30 bar (back pressure). The conversion (%) of 1-phenylethanol was determined by GC analysis. [a] 44 s: flow rate = 1.0 mL min^{-1}, 55 s: flow rate = 0.8 mL min^{-1}, 110 s: flow rate = 0.4 mL min^{-1}.



Scheme 3 Optimization of the pressure dependence.

1a at a system pressure of 15 bar provided **2a** in 74% conversion. When the system pressure increased to 50 bar, 1-phenylethanol (**1a**) was fully converted into 1-phenylethanone (**2a**) in 55 seconds.

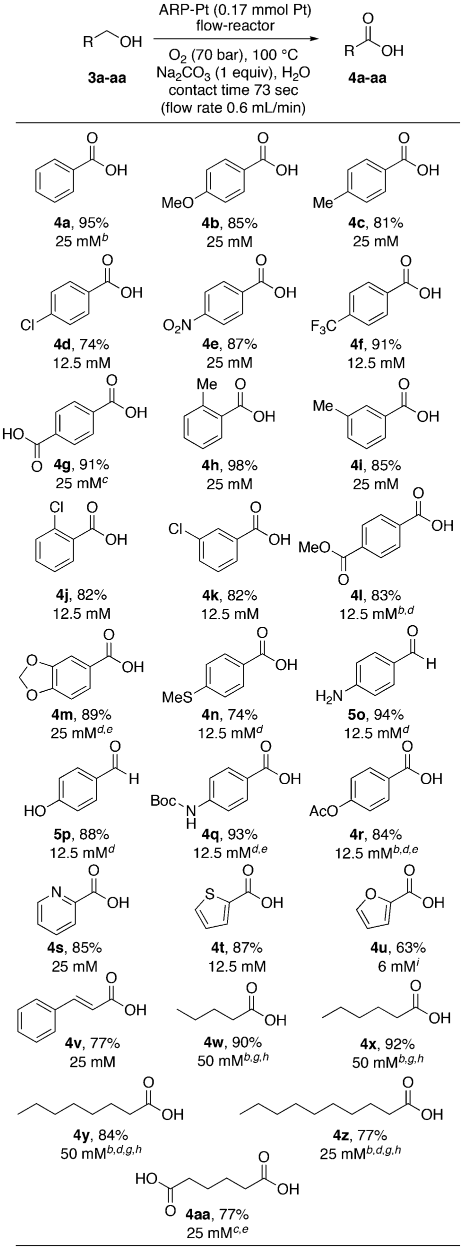
We then examined the aerobic flow oxidation of a range of benzylic and aliphatic secondary alcohols in water in the continuous-flow reactor containing ARP-Pt under the optimized conditions (Scheme 4). Oxidation of 1-phenylethanol (**1a**) under the optimal conditions (50 bar O_2, 100 °C, 0.8 mL min^{-1}; contact time = 55 s) gave a 95% isolated (100% conversion) yield of 1-phenylethanone (**2a**). 1-Phenylethanols bearing various *para* substituents, such as methoxy, methyl, chloro or trifluoromethyl, underwent aerobic flow oxidation in a mixture of water and *tert*-butyl alcohol (8 : 2 to 7 : 3)[15] at a system pressure of 50–70 bar to give the corresponding ketones **2b–e** in 91 to 95% isolated yield (100% conversion). Cyclopropyl(phenyl)methanol (**1f**) also underwent aerobic flow oxidation to give cyclopropyl(phenyl)methanone (**2f**) in 87% yield, without the formation of any ring-opening products. Aliphatic, acyclic and cyclic secondary alcohols **1g–n** were also fully oxidized (100% conversion) in water or a mixture of water and *tert*-butyl alcohol (7 : 3) at a system pressure of 50 bar with 55–73 seconds of contact time at 100–120 °C to give the corresponding ketones **2g–n** in 83–99% isolated yield. The flow oxidation of borneol (**1o**) proceeded efficiently at a system pressure of 70 bar to give camphor (**2o**) in 84% yield with 10% recovery of the starting alcohol.



Scheme 4 Scope of secondary alcohols for aerobic flow oxidation in water. Isolated yields are reported. [a] Isolated yield. [b] O_2 (70 bar). [c] Contact time 73 s (flow rate 0.6 mL min^{-1}), 120 °C. [d] NMR yield using an internal standard.

The scope of the reaction for various primary alcohols was also investigated under the aerobic flow oxidation conditions (Scheme 5). Aerobic flow oxidation of benzyl alcohol (**3a**) in water at 100 °C at a system pressure of 70 bar and a contact time of 73 seconds (flow rate = 0.6 mL min^{-1}) gave benzoic acid (**4a**) in 95% isolated yield (100% conversion). Various *para*-substituted benzyl alcohols bearing methoxy, methyl, chloro, nitro or trifluoromethyl groups underwent aerobic flow oxidation in the presence of one equivalent of sodium carbonate to give the corresponding *para*-substituted benzoic acids **4b–f** in 74–91% isolated yield (100% conversion). 1,4-Phenylenedimethanol (**3g**) was similarly converted into terephthalic acid (**4g**, 91%) in the presence of two equivalents of Na_2CO_3. Benzyl alcohols bearing methyl or chloro groups in the *ortho*- or *meta*-positions **3h–k** were tolerated and gave the corresponding benzoic acids **4h–k** in 74–98% isolated yield. Benzyl alcohols bearing an ester group (**3l**) or an ether group (**3m**) were oxidized in a mixture of water and *tert*-butyl alcohol (7 : 3)[15] at 120 °C to give the corresponding benzoic acids **4l** and **4m** without undergoing hydrolysis. [4-(Methylsulfanyl)phenyl]methanol (**3n**) was converted exclusively into 4-(methylsulfanyl)benzoic acid (**4n**) in 74% yield without oxidation of the sulfur atom.

Interestingly, the aerobic oxidation of 4-aminophenol (**3o**) and hydroquinone (**3p**) at a system pressure of 70 bar gave the corresponding benzaldehydes **5o** and **5p** in good yields without formation of the benzoic acids. It is possible that the catalytic activity of the platinum nanoparticles might have been reduced by coordination to the NH_2 and OH groups of the aniline and phenol derivatives, respectively.[16] In fact, protection of the hydroxy and amino groups with *tert*-butoxycarbonyl and acetyl groups, respectively, led to full conversion into the corresponding benzoic acids **4q** and **4r** in 93% and 84% yield, respectively. Aerobic oxidation of heteroaromatic primary alcohols (2-pyridyl-, 2-thienyl- and 2-furylmethanol) proceeded efficiently to give the corresponding carboxylic acids **4s–u** in 63–87% yield. Cinnamyl alcohol (**3v**) was also tolerated in the aerobic flow oxidation and gave cinnamic acid (**4v**) in 77% yield. It is noteworthy that the less-reactive primary aliphatic alcohols **3w–3aa** all underwent aerobic flow oxidation under similar conditions to give the corresponding acids **4w–4aa** in 77–92% isolated yield. When alcohols bearing terminal or internal



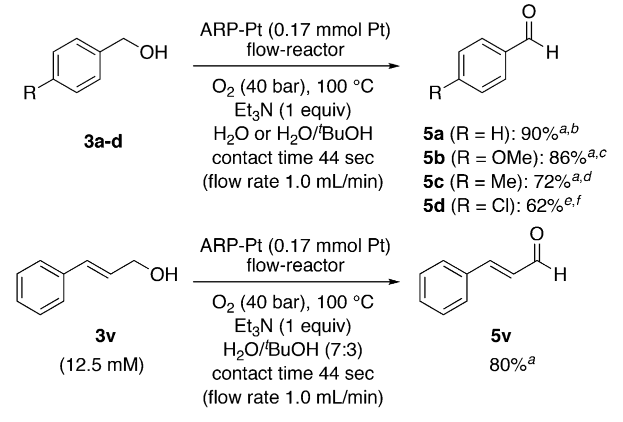
Scheme 5 Aerobic flow oxidation of primary alcohols in water. [a]Isolated yield. [b]Without Na_2CO_3. [c]Na_2CO_3 (2 equiv.) was used. [d]In $H_2O/^tBuOH$ (7 : 3). [e]At 120 °C. [f]The yield was determined by ^1H NMR with an internal standard. [g]Contact time 55 s (flow rate 0.8 mL min^{-1}). [h]O_2 (50 bar). [i]Contact time 88 s (flow rate 0.5 mL min^{-1}).

alkyne groups were used as substrates, the aerobic flow oxidation was sluggish, possibly because the reaction was inhibited by strong coordination of the alkyne to the platinum species.

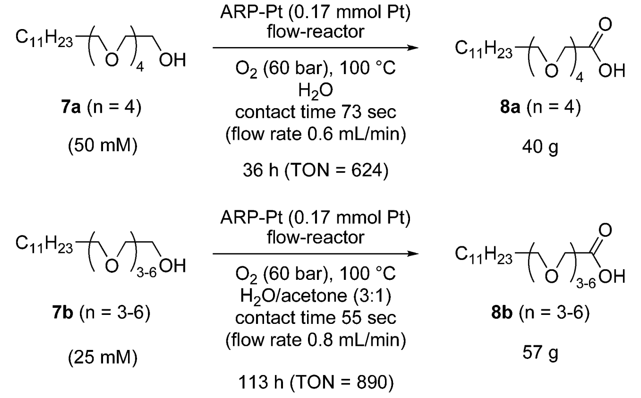
As mentioned above, aerobic flow oxidation of 4-aminophenol (**3o**) and hydroquinone (**3p**) gave the corresponding benzaldehydes **5o** and **5p** exclusively. These results prompted us to explore the conditions for the selective oxidation of primary alcohols to aldehydes. We were pleased to find that aerobic flow oxidation of benzyl alcohol (**3a**) in the presence of one equivalent of triethylamine at 100 °C and a system pressure of 40 bar with a contact time of 44 seconds (flow rate = 1.0 mL min^{-1}) gave benzaldehyde (**5a**) in 90% yield with no formation of benzoic acid (Scheme 6).[17] The oxidation of aldehydes to carboxylic acids is suppressed by deactivation of the platinum nanoparticles by the amine.

In the presence of triethylamine, (4-methoxyphenyl)methanol (**3b**) and (4-methylphenyl)methanol (**3c**) were converted into benzaldehydes **5b** and **5c**, respectively, in 86 and 72% yield without formation of the carboxylic acids.[17] When (4-chlorophenyl)methanol was subjected to the flow-reaction conditions, 4-chlorobenzaldehyde was obtained as the major product in 62% yield, together with 14% of the carboxylic acid **4d** (14%). Cinnamyl alcohol (**3v**) was also tolerated and it gave cinnamaldehyde (**5v**) in 80% yield as the sole product. However, oxidation of aliphatic alcohols in the presence of triethylamine was sluggish and gave low conversions of the alcohols.

To demonstrate the practical utility of this process, we performed a gram-scale oxidation of oligo(ethylene glycol) monododecyl ethers **7** in the aqueous aerobic flow oxidation system to give the corresponding dodecyl{oligo(oxyethylene)}acetic acids.[18] A 0.05 M aqueous solution of tetra(ethylene glycol) dodecyl ether (**7a**; $n = 4$) was introduced into the flow reactor containing ARP-Pt cartridges (0.17 mmol Pt for the two catalyst cartridges) and subjected to flow oxidation at 100 °C and 60 bar at a flow-rate of 0.6 mL min^{-1} (contact time 73 s) for 26 hours. The collected aqueous eluent was freeze dried to give 40 g (100%) of the desired detergent carboxylic acid **8a** ($n = 4$) with a high catalyst turnover number (TON = 624) (Scheme 7). Detergent **8a** was obtained in a highly pure state without further purification. The flow oxidation of a 0.25 M aqueous solution of a mixture of oligo(ethylene glycol) ethers **7b** (n = 3–6) also proceeded efficiently under similar conditions at a flow-rate of 0.8 mL min^{-1} (contact time 55 s) for 113 hours to give 57 g of **8b** (n = 3–6) at a TON of 890 (100% conversion). These results showed that the catalytic activity was retained during the continuous flow oxidation at 100 °C for long period (113 hours).



Scheme 6 Selective synthesis of aldehydes by aerobic flow oxidation of alcohols on ARP-Pt in the presence of Et_3N. [a]Isolated yield. [b]**3a** (25 mM), H_2O. [c]**3b** (25 mM), $H_2O/^tBuOH$ (8 : 2). [d]**3c** (12.5 mM), $H_2O/^tBuOH$ (8 : 2), O_2 (60 bar). [e]NMR yield using an internal standard. [f]**3d** (15 mM), $H_2O/^tBuOH$ (7 : 3).



Scheme 7 Gram-scale syntheses of surfactants **8** by aerobic aqueous flow oxidation of alcohols **7**.

Conclusions

We have developed a technique for the aqueous aerobic flow oxidation of alcohols in a continuous-flow reactor containing platinum nanoparticles dispersed on a PS–PEG resin (ARP-Pt). Various primary and secondary alcohols were efficiently oxidized within 73 seconds in the flowing aqueous system at 100–120 °C and 40–70 bar to give the corresponding carboxylic acids and ketones, respectively. Benzaldehydes were prepared selectively from benzyl alcohols by conducting the flow oxidation under the standard conditions in the presence of triethylamine. Moreover, a practical gram-scale synthesis of surfactants was realized in the aqueous aerobic flow system. This aerobic flow oxidation system provides a safe, clean, green and efficient practical method for oxidizing alcohols. Further investigations on practical applications of the technique are underway in our laboratory.

Experimental section

General

All chemicals were commercially available and used without further purification. Water was deionized with a Millipore system as a Milli-Q grade. An X-Cube™ reactor system was purchased from ThalesNano Nanotechnology Inc, Hungary. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a JEOL JNM-A500 or JNM-ECS 400. GC analysis was carried out on a Hewlett Packard 4890 system. Mass spectra were recorded on a JEOL AccuTOF GC JMS-T100GC equipped with Agilent 6890N GC (GC TOF-MS), a JEOL AccuTOF JMS-T100LC (ESI TOF-MS), or a JEOL JMS-777V (EI and FAB-MS). ICP analysis was performed on a LEEMAN LABS Profile plasma spectrometer.

General information for the X-Cube reactor

The picture and the schematic diagram of the X-Cube reactor are shown in Fig. S1.† The X-Cube system consists of 3 units; (1) the pump unit having two built-in HPLC pumps which can provide up to 3 mL min^{-1} liquid flow; (2) the reactor unit including two heating units (up to 200 °C) equipped with the catalyst cartridges (ϕ 4 × 70 mm) and gas mixer system; (3) the touch screen panel where the reaction conditions (flow rate, system pressure, and temperature) can be controlled and monitored. The stainless steel tubing has an inner diameter of 500 mm. The system can be pressurized up to 150 bar. In the nanobubble generator part, a constant volume (5 vol%) of the gas passed through a titanium frit (pore size 50 nm) is provided as nano bubbles to the solution.

Preparation of the catalyst cartridges and calculation of the contact time

A preweighed catalyst cartridge was packed with ARP-Pt (300 mg, 0.085 mmol Pt)[3b,c] with water and sealed on either end with 8 mm filters. After wetting the cartridge with H$_2$O, the wet catalyst cartridge was weighed. The reaction volume was determined from the weight difference between the dry and the wet cartridges. The reaction volume was 0.36 mL. According to eqn (1), when the flow rate was set as 1.0 mL min^{-1}, the contact time per one cartridge was 22 second.

$$\text{Contact time (s)} = \frac{\text{reaction volume (mL)} \times 60}{\text{flow rate (mL min}^{-1}\text{)}} \tag{1}$$

Typical procedure for the catalytic aerobic flow oxidation of secondary alcohols in water

An aqueous solution of 1-phenylethanol (**1a**, 100 mM) was pumped into the X-Cube reactor system installed with two catalyst cartridges (300 mg × 2; total 0.17 mmol Pt) at a flow rate of 0.8 mL min^{-1}. The oxidation was conducted at 100 °C under 50 bar of the system pressure. The resulting solution was collected for 1 h (48 mL) and extracted with Et$_2$O three times. The combined organic phase was dried over Na$_2$SO$_4$ and the solvent was removed by evaporation to afford acetophenone (**2a**, 548 mg, 95% yield).

Typical procedure for the catalytic aerobic flow oxidation of primary alcohols in water

An aqueous solution of *p*-methoxybenzyl alcohol (**3b**, 25 mM) in the presence of Na$_2$CO$_3$ (25 mM) was pumped into the X-Cube reactor system installed with two catalyst cartridges (ARP-Pt: 300 mg × 2; total 0.17 mmol Pt) at a flow rate of 0.6 mL min^{-1}. The aerobic flow oxidation was conducted at 100 °C under 70 bar of the system pressure. The resulting solution was collected for 32 min (19 mL) and acidified by addition of 5% HCl aq. until the pH of the solution became 3–4. The resulting precipitate was collected by filtration, washed with water, and dried under vacuum to afford a white solid (**4b**, 62 mg, 85% yield).

Typical procedure for the selective synthesis of aldehydes

A solution of *p*-anisic alcohol (**3b**, 25 mM) in the presence of Et$_3$N (25 mM) in a mixture of H$_2$O and ^{t}BuOH (8 : 2) was pumped into the X-Cube reactor system installed with two catalyst cartridges (ARP-Pt: 300 mg × 2; total 0.17 mmol Pt) at a flow rate of 1.0 mL min^{-1}. The flow oxidation was conducted at 100 °C under 40 bar of the system pressure. The resulting solution was collected for 18 min (17.7 mL) and extracted with EtOAc (20 mL × 4). The combined organic phase was washed with brine (20 mL × 3) and dried over Na_2SO_4. After removal of the solvent by evaporation, a colorless oil was obtained in 86% yield (*p*-anisic aldehyde, **5b**, 52 mg).

Typical procedure for gram-scale synthesis of the surfactant 8

An aqueous solution of tetraethylene glycol dodecyl ether (**7a**) (0.05 M) was pumped into an X-Cube reactor system installed with two catalyst cartridges (ARP-Pt: 300 mg × 2: total 0.017 mmol Pt) at a flow rate of 0.6 mL min^{-1}. The oxidation was conducted at 100 °C under 60 bar of the system pressure. After the continuous flow for 36 h, 1290 mL of the product solution was collected. The resulting solution was concentrated under freeze-dry conditions to afford **8a** (white solid, 40 g).

Acknowledgements

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7 For examples of flow-aerobic oxidation of alcohols with heterogeneous catalysts. Early examples for ref. 7*a*–*e* only described the *partial* oxidation of benzyl alcohol to benzaldehyde under continuous flow conditions in scCO$_2$: (*a*) G. Jenzer, T. Mallat and A. Baiker, *Catal. Lett.*, 2001, **73**, 5–8 (conversion of benzyl alcohol = 13.5% in scCO$_2$ at 100 °C, 100 bar); (*b*) D. V. Bavykin, A. A. Lapkin, S. T. Kolaczkowski and P. K. Plucinski, *Appl. Catal., A*, 2005, **288**, 175–184 (conversion of benzyl alcohol = 25% in toluene at 115 °C, 8 bar); (*c*) Z. Hou, N. Theyssen, A. Brinkmann and W. Leitner, *Angew. Chem., Int. Ed.*, 2005, **44**, 1346–1349 (conversion of benzyl alcohol = 50% in scCO$_2$ at 80 °C, 132 bar); (*d*) M. Caravati, J.-D. Grunwaldt and A. Baiker, *Appl. Catal., A*, 2006, **298**, 50–56 (conversion of benzyl alcohol = 70% in scCO$_2$–toluene at 80 °C, 150 bar); (*e*) Z. Hou, N. Theyssen, A. Brinkmann, K. V. Klementiev, W. Grünert, M. Bühl, W. Schmidt, B. Spliethoff, B. Tesche, C. Weidenthalar and W. Leitner, *J. Catal.*, 2008, **258**, 315–323 (conversion of benzyl alcohol = 41% in scCO$_2$ at 60 °C, 150 bar); (*f*) The flow reaction was limited to the aerobic oxidation of vanilly alcohol to vaniline: A. L. Tarasov, L. M. Kustov, A. A. Bogolyubov, A. S. Kiselyov and V. V. Semenov, *Appl. Catal., A*, 2009, **366**, 227–231 (conversion of vanillyl alcohol = 100% in aq. NaOH at 80 °C); ref. 7*g* and *h* described the flow aerobic oxidation of the various primary and secondary alcohols was achieved in *halogenated* organic solvents (1,2-dichloroethane and benzotrifluoride). However the productivity of the desired carbonyl compounds was *very low* due to the slow solvent flow ([substrate] = 0.1 M, solution rate rate: 0.1–0.4 mL h^{-1}); (*g*) N. Wang, T. Matsumoto, M. Ueno, H. Miyamura and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2009, **48**, 4744–4746 (the typical oxidation: conversion of benzyl alcohol = >99% (yield of benzaldehyde 92%) at 50 °C, [substrate] = 0.1 M in 1,2-dichloroethane, solution flow rate = 0.1 mL h^{-1}); (*h*) K. Kaizuka, K.-Y. Lee, H. Miyamura and S. Kobayashi, *J. Flow Chem.*, 2012, **1**, 1–4 (yield of benzaldehyde from benzyl alcohol = 99% at 80 °C, [substrate] = 0.11 M in benzotrifluoride–H$_2$O, solution flow rate = 0.42 mL h^{-1}); (*i*) The flow system was limited to the aerobic oxidation of benzyl alcohol to benzaldehyde. In order to complete the conversion of benzyl alcohol, the substrate solution containing co-oxidant, TEMPO must be circulated in the flow system for hours: D. Obermayer, A. M. Balu, A. A. Remero, W. Goessler, R. Luque and C. O. Kappe, *Green Chem.*, 2013, **15**, 1530–1537 (circulated flow run for 1 h: conversion of benzyl alcohol = 98% in the presence of 10 mol% TEMPO at 120 °C, [substrate] = 0.1 M in *n*-heptane–dioxane (2 : 1), solution flow rate = 0.22 mL min^{-1}, 35 bar of O$_2$).

8 Aerobic flow oxidation of aliphatic alcohols with heterogeneous catalysts is still limited, see: (*a*) A. O. Chapman, G. R. Akien, N. J. Arrowsmith, P. Licence and M. Poliakoff, *Green Chem.*, 2010, **12**, 310–315 (The aerobic flow oxidation of aliphatic alcohols was performed under flow conditions in scCO$_2$. But the substrate scope was limited [*eg.* for the oxidation of 1-octanol: yield of 1-octanal = 80%, yield of 1-octanoic acid = 18%; for the oxidation of 2-octanaol: yield of 2-octanone = 34% in scCO$_2$ at 130 °C, 100 bar]); (*b*) N. Zotova, K. Hellgardt, G. H. Kelsall, A. S. Jessiman and K. K. Hii, *Green Chem.*, 2010, **12**, 2157–2163 (The flow oxidation required the *recirculation* of the reaction solution in the flow system for hours to complete the reaction. [*e.g.* the oxidation of 1-haxanol: 87% yield of 1-hexanal, [substrate condition] = 0.1 M in toluene, solution rate rate: 1 mL min^{-1}, circulating reaction for 7 hour at 90 °C, 5 bar of O$_2$]). See also ref. 7*h* (81–98% yield of the aldehydes in BFT–water at 60–90 °C, 1 atm).

9 Organic solvents containing a high concentration of oxygen (air) often causes explosion, and halogenated solvents are highly toxic. For a recent review, see: P. Patnaik, *A Comprehensive Guide to Hazardous Properties of Chemical Substances*, Wiley, New Jersey, 3rd edn, 2007.

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11 The average diameter of the Pt nano particles of ARP-Pt = 5.9 ± 0.75 nm; see ref. 3*c*.

12 A commercially available X-Cube™ flow reactor system (ThalesNano Nanotechnology Inc.) was used as a base equipment. For details, see http://www.thalesnano.com and also the ESI.† See also ref. 6*m*.

13 For recent studies for organic transformations using the X-Cube™ flow systems, see: (*a*) C. Csajági, B. Borcsek, K. Niesz, I. Kovács, Z. Székelyhidi, Z. Bajkó, L. Ürge and F. Darvas, *Org. Lett.*, 2008, **10**, 1589–1592; (*b*) C. Csajági, G. Szatzker, E. R. Töke, L. Ürge, F. Darvas and L. Poppe, *Tetrahedron: Asymmetry*, 2008, **19**, 237–246; (*c*) N. Glansnov, S. Findenig and C. O. Kappe, *Chem.–Eur. J.*, 2009, **15**, 1001–1010; (*d*) J. Sedelmeier, S. V. Ley and I. R. Baxendale, *Green Chem.*, 2009, **11**, 683–685; (*e*) P. Falus, Z. Boros, G. Hornyánszky, J. Nagy, F. Darvas, L. Ürge and L. Poppe, *Tetrahedron Lett.*, 2011, **52**, 1310–1312; (*f*) D. Cantillo,

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15 Because of low solubility of the resulting carbonyl compounds in water, the continuous flow stream was blocked without addition of *tert*-butyl alcohol. We used a mixture of water and *tert*-butyl alcohols (8 : 2–7 : 3) to solve the blocking issue. A mixture of water–alcohols is greener than organic solvents. See the evaluation of water–alcohols for greenness: C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927–934.

16 J. N. Kuhn, C.-K. Tsung, W. Huang and G. A. Somorjai, *J. Catal.*, 2009, **265**, 209–215.

17 When the flow oxidation of **3a–c** and **3v** in the presence of triethylamine was conducted at a system pressure of 70 bar, the aldehydes were obtained exclusively without formation of the carboxylic acids. Therefore the system pressure did not affect the selectivity for formation of aldehydes.

18 The target compounds **8** are known as a potential alternative to perfluoro carbon detergents for fine electronic devices.