

Multiphase Flow Systems for Selective Aerobic Oxidation of Alcohols Catalyzed by Bimetallic Nanoclusters

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Au–Pt and Au–Pd bimetallic nanoclusters that catalyzed the aerobic oxidation of alcohols during a once-through pass through gas–liquid–liquid–solid flow systems were developed. Alcohols were converted to aldehydes and ketones in benzotrifluoride (BTF)/water media by Au–Pt catalyst or to the corresponding methyl esters in methanol/water media by Au–Pd catalyst. The flow systems were superior to the batch systems in terms of both yield and selectivity.

Keywords: bimetallic cluster, oxidation, flow system, heterogeneous catalysis, alcohol

In synthesis, a flow system has several advantages over a batch system. Indeed, a flow system is crucial for large-scale industrial synthesis, high-throughput organic synthesis related to combinatorial library generation, and automation of multistep transformations [1]. Moreover, unique reactivity and selectivity are sometimes expected at a short residence time; a flow system is one of the methods for reaction integration (space integration) where, for example, unstable intermediates can be available [2]. While gas–solid, liquid–liquid, or liquid–solid biphasic conditions are common in flow systems, examples of gas–liquid–solid multiphase conditions are very rare. As for flow systems for aerobic oxidation of alcohols using heterogeneous catalysts, to the best of our knowledge, there are only a few reports of multiphase reactions in microreactor systems [3], capillary systems [4], and multichannel reactor systems [5], and only one report of a conventional packed flow system [6]. Moreover, there are several limitations in previous studies: immobilization of the catalyst was relatively difficult in the case of the microreactor, capillary, and multichannel systems [3–5].

Selective oxidation of alcohols is one of the most important transformations in organic synthesis. This is because the resulting carbonyl compounds possess higher energy and reactivity, allowing many types of carbon–carbon and other bond-forming reactions [7,8]. Although several metal-based oxidizing reagents have been developed, these protocols usually require stoichiometric amounts of metal oxidants, and thus a large amount of waste is formed in many cases [9]. Since Haruta's discovery, aerobic oxidation reactions catalyzed by gold nanoclusters have been widely investigated [10,11]. In particular, the selective oxidation of alcohols to the corresponding carbonyl compounds, such as aldehydes, carboxylic acids, and esters, catalyzed by gold-based bimetallic nanoclusters, is attractive in both industry and the laboratory [11,12].

We have been investigating aerobic oxidation reactions catalyzed by gold and gold-based bimetallic nanocluster catalysts, namely polymer incarcerated catalysts (PI catalysts) [13,14]. In a previous paper, we reported on the selective oxidation of alcohols to aldehydes and ketones catalyzed by novel carbon-black stabilized polymer-incarcerated gold/platinum bimetallic nanocluster catalysts (PI-CB/Au–Pt) and direct oxidative methyl ester formation from primary alcohols catalyzed by gold/palladium bimetallic nanocluster catalysts (PI-CB/Au–Pd) [15]. Here, we describe the application of these catalytic reactions to gas–liquid–solid multiphase flow systems.

The preparation of PI-CB bimetallic nanocluster catalysts is described in our previous paper [15a]. The gas–liquid–liquid–solid multiphase flow reactor was set up as shown in Figure 1. The catalysts were packed with an optimized amount of Celite in the glass column to prevent obstruction of the column by swelling of the catalysts. This was done because when the catalysts were packed without Celite, the column was obstructed and the reaction mixture could not pass through the column [16]. The reaction temperature was controlled by an aluminum heating block that fully covered the column. Molecular oxygen (1 atm), regulated by a mass flow controller, and an organic phase and an aqueous phase, which were regulated by conventional high performance liquid chromatography (HPLC) pumps, were introduced into the column simultaneously. The column had a head with three inlets. All the components were passed through the downflow column only once, and the resulting liquid was collected in a flask.

The efficiency of this flow system in the selective aerobic oxidation of alcohols was determined using 3-phenyl-1-propanol as a model substrate. Under basic conditions, in a benzotrifluoride (BTF)/water solvent system, PI-CB/Au–Pt oxidized 3-phenyl-1-propanol to 3-phenylpropionic acid selectively at lower temperature in the presence of a weaker base (Table 1, entries 1–3). In contrast, 3-phenyl-1-propanal was obtained under neutral conditions (entry 4), and after optimization of the reaction conditions (entries 5, 6), the yield of the desired aldehyde was improved to 81% while the yield of the carboxylic acid was only 1% (98% selectivity, entry 7). By controlling the residence time in the column (entry 7; 68.6 min) [17], the selectivity of the aldehyde was significantly improved. It should be noted that the activity of the catalyst inside the column was maintained and the yield and the selectivity were constant for

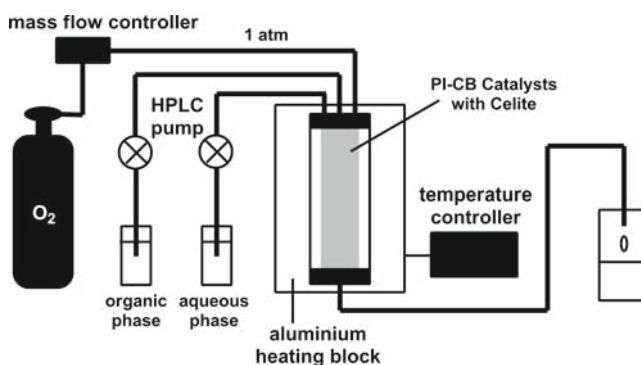
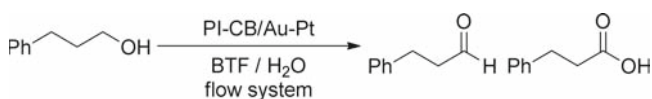


Figure 1. The gas–liquid–liquid–solid multiphase flow system

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Table 1. Selective oxidation of 3-phenylpropanol to 3-phenylpropanal catalyzed by PI-CB/Au-Pt


Conditions:

Organic phase: 0.108 M 3-phenyl-1-propanol in BTF

Aqueous phase: 0.324 M basic solution or pure water

 Column: ϕ 0.5 \times 5 cm (catalyst 100 mg, Celite 380 mg)

 O_2 rate: 120 mL/h (unless otherwise indicated)

Entry	Aqueous phase	Flow rate org./aq. (mL/h)	Temperature (°C)	Yield ^a (%)		
				Acid	Aldehyde	Alcohol
1	KOH aq.	0.84/0.84	60	90	4	2
2	KOH aq.	0.84/0.84	r.t.	86	n.d.	11
3	K ₂ CO ₃ aq.	0.84/0.84	r.t.	19	20	51
4	Pure water	0.84/0.84	60	2	29	62
5	Pure water	0.42/0.42	60	3	48	40
6 ^b	Pure water	0.42/0.42	60	n.d.	69	30
7 ^b	Pure water	0.21/0.21	80	1	81	17
8 ^{b,c}	Pure water	0.21/0.21	80	1	82	17
9 ^d	Pure water	0.21/0.21	80	1	59	35

n.d. = not detected.

^aDetermined by gas chromatography (GC) analyses (internal standard: anisole) recorded hourly, on average, over a period of 24 h.

^b O_2 rate: 60 mL/h.

^cResult after 216 h.

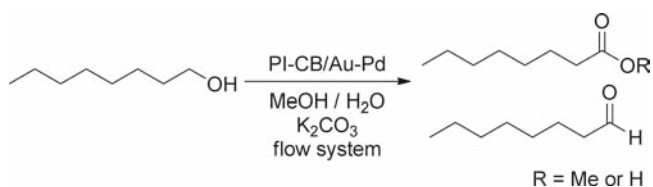
^d O_2 rate: 30 mL/h.

4 days. After 4 days, reactivity was decreased gradually, and it dropped to 60% conversion after 7 days. However, by washing with BTF (30 mL/h, 3 h), the reactivity was recovered and maintained for additional 2 days (entry 8) [18]. Lower oxygen flow rate gave lower conversion (entry 9). Behavior of each phase is still unclear; however, we assume that the liquid phases passed through swelled polymer layer of the catalyst and excess amount of oxygen (alcohol:oxygen is 1:118) prevented the liquid phases coming out from polymer layer to outside the catalyst.

The direct oxidative methyl ester formation reactions were also conducted in the flow system. Under basic conditions, in a MeOH/water solvent system, 1-octanol was oxidized to a mixture of methyl 1-octanoate and octanoic acid in the presence of PI-CB/Au-Pd catalyst (Table 2, entry 1). Interestingly, the ratio of the organic phase to the aqueous phase and the flow rate strongly affected the conversion and the selectivity of the products (entries 2–6). It was found that the 3:1 ratio of the organic phase/aqueous phase solvent system gave the best result (87% ester yield, 95% selectivity; entry 5, residence time: 37.6 min [17]). The catalytic activity was maintained for 11 days (entry 6) [18].

We compared the results of the above flow systems with those of the batch systems [15a] (Table 3). In the case of selective oxidation to an aldehyde, the batch system gave a higher yield (92% in 9 h) than the flow system (81% in 68.6 min); however, the selectivity of the flow system (98%) was higher than that of the batch system (92%). On the other hand, in the case of direct oxidative ester formation, the flow system showed much higher yield and selectivity (87% yield, 95% selectivity in 37.6 min) than the batch system (78% yield, 90% selectivity in 24 h). These results showed the advantages of flow systems, because overoxidation could be prevented by controlling the residence time in the column. In addition, space-time yield of flow systems was about 5–10 times higher than that of batch systems, which showed high productivity of flow systems.

These flow systems for aerobic oxidation could be used for various alcohols (Table 4). Primary aliphatic alcohols (entries 1–4) and primary benzyl alcohols (entries 5–10) were smoothly converted to the corresponding aldehydes (conditions A, B,

Table 2. Direct oxidative methyl ester formation from 1-octanol catalyzed by PI-CB/Au-Pd


Conditions:

Organic phase: 0.108 M 1-octanol in MeOH

 Aqueous phase: 0.324 M K₂CO₃ aq.

 Column: ϕ 0.5 \times 5 cm (catalyst 100 mg, Celite 380 mg)

 O_2 rate: 120 mL/h

Entry	Flow rate org./aq. (mL/h)	Temperature (°C)	Yield ^a (%)			
			Ester	Acid	Aldehyde	Alcohol
1	0.42/0.42	r.t.	13	11	2	77
2	0.42/0.42	60	48	24	2	25
3	0.42/0.21	60	86	8	n.d.	2
4	0.42/0.168	60	89	4	n.d.	4
5	0.42/0.14	60	87	3	n.d.	8
6 ^b	0.42/0.14	60	89	1	Trace	9
7	0.42/0.105	80	78	3	Trace	16

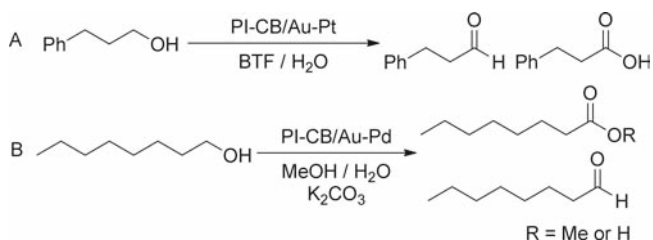
n.d. = not detected.

^aDetermined by GC analyses (internal standard: anisole) recorded hourly, on average, over a period of 24 h.

^bResult after 264 h.

or C) and esters (conditions E or F) in high yields. Secondary alcohols (entries 11–16) were also oxidized to the corresponding ketones in excellent yields (condition D). In most cases, the flow systems were superior to the batch systems in terms of both yield and selectivity.

In summary, we have developed multiphase flow systems for the selective aerobic oxidation of alcohols and direct oxidative methyl ester formation reactions with PI-CB catalysts. Notably, the PI-CB catalysts have sufficient activity in the flow systems, and substrates can be converted to the desired products in good to excellent yields by a single pass through the column. This is

Table 3. Comparison of flow systems and batch systems for aerobic oxidation


Reaction	System	Yield ^a (%)			Selectivity ^b	Space-time yield (μmol/cm ³ /h)
		Ester	Acid	Aldehyde		
A	Flow ^c	–	1	81	99/1	4.79
	Batch ^d	–	8	90	92/8	0.958
B	Flow ^e	87	3	n.d.	97/3	9.93
	Batch ^f	78	7	n.d.	92/8	0.813

n.d. = not detected.

^aDetermined by GC analyses (internal standard: anisole) recorded hourly, on average, over a period of 24 h.

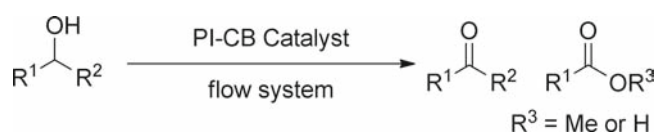
^bReaction A: aldehyde/acid. Reaction B: ester/acid.

^cFlow system; Table 1, entry 7. Residence time: 68.6 min. 17% of alcohol was recovered.

^dBatch system; 2 mol% catalyst, BTF/H₂O = 2/1, r.t., 9 h. 1% of alcohol was recovered.

^eFlow system; Table 2, entry 5. Residence time: 37.6 min. 8% of alcohol was recovered.

^fBatch system; 1 mol% catalyst, MeOH/H₂O = 1/2, 3 eq. K₂CO₃, r.t., 24 h. 13% of alcohol was recovered.





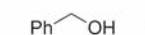


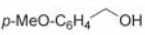





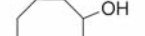

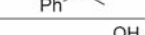
Table 4. Selective aerobic oxidation of alcohols catalyzed by bimetallic nanostructures using flow systems

Conditions:

Organic phase: 0.108 M

Aqueous phase: 0.324 M

Column: ϕ 0.5 \times 5 cm (catalyst 100 mg, Celite 380 mg)A: PI-CB/Au-Pt, BTF/H₂O (0.21/0.21 mL/h), O₂ 60 mL/h, 80 °CB: PI-CB/Au-Pt, BTF/H₂O (0.42/0.42 mL/h), O₂ 60 mL/h, 60 °CC: PI-CB/Au-Pt, BTF/H₂O (0.42/0.42 mL/h), O₂ 60 mL/h, 80 °CD: PI-CB/Au-Pt, BTF/KOH aq. (0.42/0.42 mL/h), O₂ 300 mL/h, 60 °CE: PI-CB/Au-Pd, MeOH/K₂CO₃ aq. (0.42/0.14 mL/h), O₂ 120 mL/h, 60 °CF: PI-CB/Au-Pd, MeOH/K₂CO₃ aq. (0.42/0.105 mL/h), O₂ 120 mL/h, 60 °C

Entry	ROH	Condition	Yield ^a (%)		
			Ester	Acid	Aldehyde/ ketone
1		A	–	1	81
2		E	84	9	1
3		A	–	3	83
4		E	86	8	n.d.
5		B	–	n.d.	99
6		F	97	2	n.d.
7		B	–	quant.	n.d.
8		F	quant.	n.d.	n.d.
9		C	–	97	2
10		F	93	n.d.	4
11		D	–	–	98
12		D	–	–	92
13		D	–	–	88
14		D	–	–	83
15		D	–	–	97
16		D	–	–	96

quant. = quantitative

n.d. = not detected.

^aDetermined by GC analyses (internal standard: anisole) recorded hourly, on average, over a period of 24 h.

an advantage of multistep continuous-flow systems. In addition, to the best of our knowledge, this is the first example of aerobic oxidative methyl ester formation from alcohols using flow systems. Using the flow systems, we could control the residence time in the column and achieve higher reactivity and selectivity than those achieved in batch systems. We believe that this methodology may be applicable to other aerobic oxidation reactions, multistep continuous-flow system reactions, and industrial-scale syntheses.

Experimental Section

1. Oxidation of 3-phenyl-1-propanol by PI-CB/Au-Pt (Table 1, entry 7). PI-CB/Au-Pt (100 mg, Au 0.1198 mmol/g, Pt 0.1764 mmol/g) and Celite (380 mg) were packed in the glass column (ϕ 0.5 \times 5 cm). The reaction temperature was kept at 80 °C by an aluminum heating block. Molecular oxygen (1 atm), regulated by a mass flow controller (60 mL/h), and an organic phase (0.108 M 3-phenyl-1-propanol in BTF, 0.21 mL/h) and pure water (0.21 mL/h), which were regulated by conventional HPLC pumps, were introduced into the column simultaneously. The column had a head with three inlets. All the compounds were passed through the downflow column only once and the resulting liquid was collected in a flask. Yields were determined by GC analysis using anisole as an internal standard (3-phenylpropionic acid: 1%, 3-phenyl-1-propanol: 81%, 3-phenyl-1-propanol: 17%).

2. Direct Oxidative Methyl Ester Formation from 1-octanol by PI-CB/Au-Pd (Table 2, entry 5). PI-CB/Au-Pd (100 mg, Au 0.1933 mmol/g, Pd 0.2167 mmol/g) and Celite (380 mg) were packed in the glass column (ϕ 0.5 \times 5 cm). The reaction temperature was kept at 60 °C by an aluminum heating block. Molecular oxygen (1 atm), regulated by a mass flow controller (120 mL/h), and an organic phase (0.108 M 1-octanol in MeOH, 0.42 mL/h) and an aqueous phase (0.324 M K₂CO₃ aq., 0.14 mL/h), which were regulated by conventional HPLC pumps, were introduced into the column simultaneously. The column had a head with three inlets. All the compounds were passed through the downflow column only once and the resulting liquid was collected in a flask. After neutralization with hydrochloric acid and separation of the organic phase and the aqueous phase, yields were determined by GC analysis using anisole as an internal standard (methyl 1-octanoate: 87%, 1-octanoic acid: 3%, 1-octanal: not detected, 1-octanol: 8%).

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16. Details of ratio of catalysts and Celite are shown in Supporting Information.
17. Details of determination of the residence time are shown in Supporting Information.
18. Details of reaction profiles are shown in Supporting Information.