Aerobic oxidative esterification of alcohols catalyzed by polymer-incarcerated gold nanoclusters under ambient conditions†

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Environmentally benign aerobic oxidation of alcohols to methyl esters catalyzed by polymer-incarcerated gold nanoclusters (PI-Au) was developed and reactions proceeded under very mild conditions. The catalyst could be recovered by simple operations without significant loss of activity.

Environmentally benign organic synthesis making the most of resources and energy is required today, when the issues of global warming CO_2 emissions and shortage of natural resources are worsening. Esterification is one of the most important transformations in organic synthesis; esters are stable and can be easily transformed to many kinds of functional groups.[1] Methyl esters in particular are very useful from the viewpoints of atom economy and versatility for further transformations.

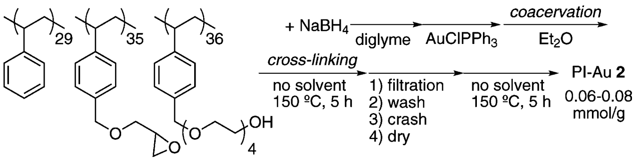
Esterification is traditionally a two-step procedure that includes synthesis of carboxylic acids or activated carboxylic acid derivatives such as acid anhydrides or acid chlorides.[2] While several facile and economical esterification reactions have been developed, these protocols usually require stoichiometric amounts of reagents, and thus a large amount of waste is formed. In this respect, direct oxidative esterification reactions from alcohols using molecular oxygen catalyzed by reusable heterogeneous catalysts under mild conditions, such as atmospheric pressure and room temperature, are an attractive and challenging subject for both organic synthesis and green chemistry.

Since the discovery of them by Haruta and coworkers, aerobic oxidation reactions catalyzed by gold nanoclusters have been widely investigated.[3,4] In particular, selective oxidation of alcohols to the corresponding carbonyl compounds such as aldehydes, carboxylic acids and esters catalyzed by gold nanoclusters is attractive for both industry and the laboratory, and has been extensively investigated recently,[4–6,8a,8d] and several gold nanocluster catalysts for aerobic oxidation of alcohols or aldehydes to esters have been reported. Although oxidation of aldehydes to esters proceeds under mild conditions,[7] examples starting from alcohols under mild conditions (atmospheric pressure and ambient temperature) were very limited.[8] Aerobic oxidation of alcohols to esters is divided into three steps: oxidation of alcohols to aldehydes; hemiacetal formation; and oxidation of hemiacetals to esters. Substantial mechanistic studies of esterification reactions from aldehydes using gold nanoclusters were recently performed by Christensen and coworkers.[7a,7b] They showed that oxidation of aldehydes to esters was much faster than that of alcohols to aldehydes.[7,9] However, they could not achieve quantitative comparison of these two steps because the first step required relatively harsh conditions.

Recently, we reported that gold nanocluster catalysts immobilized on polystyrene-based polymers with cross-linking moieties,[10] polymer-incarcerated gold nanocluster catalyst (PI-Au), were effective for aerobic oxidations of alcohols to ketones and aldehydes and hydroquinones to quinones under mild conditions.[11,12] Moreover, PI-Au can be reused several times with careful handling without loss of catalytic activity.

We now report selective aerobic oxidation of alcohols and aldehydes to the corresponding methyl esters catalyzed by PI-Au under mild conditions. The necessity of water for high activity and comparison of kinetic analysis between oxidation from alcohols to aldehydes and from aldehydes to esters is also described. To the best of our knowledge, this is the first example of aerobic oxidative methyl esterification from alcohols that proceeds at room temperature under atmospheric conditions.

PI-Au was prepared following the previously reported procedure (Scheme 1).[11] To examine the catalytic activity of PI-Au for an esterification reaction, oxidation of *p*-methylbenzyl alcohol was performed in methanol in the presence of a base under atmospheric oxygen conditions at room temperature (Table 1).



Scheme 1 Preparation of PI-Au.

First, bases were examined, and it was found that 0.5 equivalent of potassium carbonate (17.3 mg in 2 ml of MeOH) was enough to saturate the reaction mixture (Table 1, entries 1–4). Potassium carbonate was better than sodium methoxide (entry 4). In the absence of water, yield of the methyl ester dropped (entry 6), suggesting that water was essential as an activator.

Several experiments using various amounts of water were performed. The excess water generated the carboxylic acid as a byproduct and deactivated the reaction (entries 7–10). On the other hand, the reaction proceeded sluggishly in the presence of a small amount of water (entry 16); methanol–water (500 : 1) was the most suitable solvent for this reaction (entry 12). The reaction almost reached completion under more concentrated

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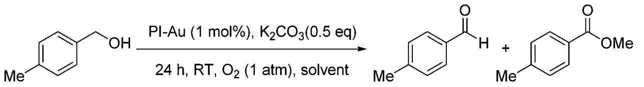
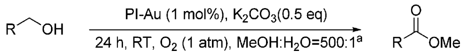
Table 1 Optimization of reaction conditions



Entry	Solvent	Conversion (%)[c]	Aldehyde (%)[c]	Ester (%)[c]
1[d]	MeOH (wet)[a]	>99	0	>99
2[e]	MeOH (wet)[a]	>99	0	>99
3	MeOH (wet)[a]	>99	0	>99
4[f]	MeOH (wet)[a]	86	12	63
5[g]	MeOH (wet)[a]	91	8	82
6	MeOH (dried)[a]	71	35	35
7	MeOH–H$_2$O 2 : 1[a]	57	22	18
8	MeOH–H$_2$O 10 : 1[a]	38	23	4
9	MeOH–H$_2$O 50 : 1[a]	92	5	85
10	MeOH–H$_2$O 100 : 1[a]	88	4	74
11	MeOH–H$_2$O 200 : 1[a]	>99	1	99
12	MeOH–H$_2$O 500 : 1[a]	>99	0	>99
13	MeOH–H$_2$O 500 : 1[b]	96	1	93
14[h]	MeOH–H$_2$O 500 : 1	97	1	86
15[i]	MeOH–H$_2$O 500 : 1	63	6	54
16	MeOH–H$_2$O 1000 : 1[a]	49	14	17

[a] 0.125 M. [b] 0.5 M, 5 h. [c] Determined by GC. [d] 1.0 eq. of K$_2$CO$_3$ was used. [e] 0.75 eq. of K$_2$CO$_3$ was used. [f] 0.1 eq. of K$_2$CO$_3$ was used. [g] NaOMe was used instead of K$_2$CO$_3$. [h] PI-Au (0.25 mol%), 0.5 M. [i] PI-Au (0.1 mol%), 1.25 M, K$_2$CO$_3$ (0.05 eq.).

Table 2 Substrate scope for aerobic esterifications



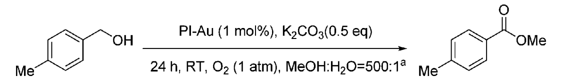
Entry	R	Conversion (%)[b]	Yield (%)[b]
1	Ph	>99	95
2	4-MeOC$_6$H$_4$	>99	>99
3	4-BrC$_6$H$_4$	>99	92
4	4-NO$_2$C$_6$H$_4$	95	60
5	1-Naphthyl	>99	95
6	2-Pyridyl	>99	>99
7	Ph–CH=CH–	>99	69
8	PhCH$_2$CH$_2$CH$_2$–	12	10
9	CH$_2$=CH–	>99	60[c]

[a] 0.125 M. [b] Determined by GC. [c] Methyl 3-methoxypropionate was obtained.

conditions in 5 h (entry 13). TON of PI-Au reached 540 over 24 h (entry 15). It is noted that leaching of gold was not observed by inductively coupled plasma (ICP) analysis.

Several examples of aerobic oxidative esterification catalyzed by PI-Au are summarized in Table 2. Aromatic alcohols containing both electron-donating and -withdrawing groups were converted to the corresponding methyl esters in good to high yields (Table 2, entries 1–5, 11). 2-Pyridyl methanol and cinnamyl alcohol were also transformed to the corresponding esters in high yields (entries 6 and 7). However, an aliphatic alcohol was not oxidized smoothly (entry 8). In the oxidation of allyl alcohol, further Michael addition of methanol to the ester occurred (entry 9).

Table 3 Recovery and reuse of catalyst

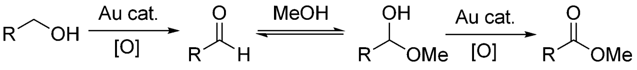


Run	Yield (%)[b]	Run	Yield (%)[b]
1	97	7	86
2	97	8[c]	97
3	97	9	95
4	>99	10	74
5	92	11[c]	94
6	90		

[a] 0.125 M. [b] Determined by GC. [c] Collected catalyst was heated at 170 °C for 4 h without solvent before using.

The catalyst could be recovered by simple filtration and washing with water and MeOH. It could be reused several times without significant loss of activity (Table 3, runs 1–4). Catalysts with decreased activity after repeated use were also revived by heating at 170 °C for 4 h (runs 8 and 11).

This esterification was divided into three steps: oxidizing alcohols to aldehydes; hemiacetal formation; and second oxidation to form methyl esters (Scheme 2). Kinetic analysis was performed by using *p*-methylbenzyl alcohol or *p*-tolualdehyde under the optimized conditions in Table 1. An aliquot reaction mixture was taken by microsyringe and analyzed by GC at each time step (Fig. 1a and 1b). According to these results, each step was a first-order reaction and the second step was 30 times faster than the first step (Fig. 1a-inset and 1b-inset). Moreover, no hemiacetal formation was observed from the mixture of an aldehyde and a base in d-MeOH/D$_2$O by NMR measurement (see ESI†). Therefore, hemiacetal formation and the following rapid oxidation to esters are considered to occur within the interior of the solid catalyst.



Scheme 2

In summary, we have developed aerobic oxidative esterification reactions of alcohols using a polymer-incarcerated gold nanocluster catalyst. While most of the reported esterification reactions of alcohols mediated by gold nanoclusters require harsh conditions such as elevated temperature and pressurized conditions, it is noteworthy that the reactions proceeded under very mild conditions such as atmospheric pressure and room temperature. Moreover, catalysts could be reused several times by simple operations. Thus PI-Au-catalyzed aerobic oxidative methyl esterification reactions have advantages in terms of energy efficiency and green chemistry. We also examined kinetic measurements and revealed that oxidation of hemiacetal to ester is much faster than oxidation of alcohol to aldehyde. Further mechanistic study, especially on hemiacetal formation and the following rapid oxidation inside the PI-Au, is now in progress.

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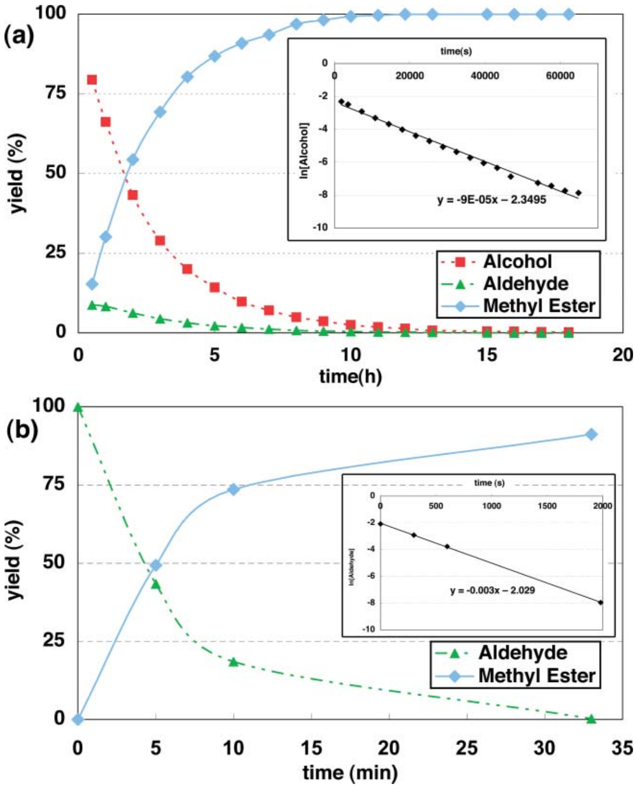

Fig. 1 Reaction conditions: PI-Au = 1 mol% as Au, MeOH–H$_2$O = 500 : 1, [Substrate]$_0$ = 0.125 M, P_{O_2} = 1 atm, T = 298 K. (a) Reaction profile of aerobic oxidation of 4-methylbenzyl alcohol to 4-methyl methylbenzoate *via* 4-methyl benzaldehyde; (a-inset) plot of first-order rate equation for consumption of 4-methylbenzyl alcohol. (b) Reaction profile of aerobic oxidation of 4-methyl benzaldehyde; (b-inset) plot of first-order rate equation for consumption of 4-methylbenzyl alcohol.

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