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α-Hydroxylation of 1,3-Dicarbonyl Compounds Catalyzed by Polymer-incarcerated Gold Nanoclusters with Molecular Oxygen

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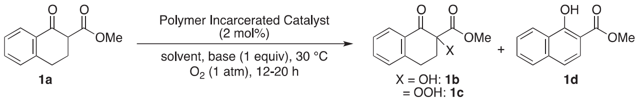
α-Hydroxylation of 1,3-dicarbonyl compounds was successfully catalyzed by carbon-stabilized polymer-incarcerated gold nanoclusters (PI/CB-Au). The reaction proceeded under mild conditions using molecular oxygen as oxidant with wide substrate scopes and the catalyst could be recovered and reused by a simple operation. The control experiments and the reaction monitoring revealed that α-peroxide compounds were reaction intermediates, and PI/CB-Au also catalyzed isomerization.

We have recently developed highly active gold nanocluster catalysts, which were immobilized on polystyrene-based polymer with a crosslinking moiety, namely polymer-incarcerated gold (PI-Au).[1–3] The catalysts have been used for various aerobic oxidations in organic synthesis, such as alcohols to aldehydes and ketones,[1,4] aldehydes to carboxylic acids,[5] alcohols to esters,[6,7] alcohols to amides,[8] hydroquinones to quinones,[9] and amines to imines.[10] This method has also been applied to the preparation of various metal nanocluster catalysts including bimetallic alloyed clusters and multifunctional catalysts.[11–17] In addition, we have demonstrated that incorporation of spherical hollow carbon black (ketjen black) during the catalyst preparation enhances the activity of the catalysts and the stability of metal nanoclusters by increasing the specific surface area to afford carbon-stabilized polymer-incarcerated metal nanoclusters (PI/CB-M).[18] Features of these catalysts are ease of use in liquid-phase organic transformations because of the high accessibility of organic molecules to the inside of amphiphilic polymer supports, availability in various types of oxidation reactions with molecular oxygen under ambient conditions (at room temperature under atmospheric conditions), reusability without metal leaching and loss of activity, and applicability for reaction integration[19] such as tandem reactions[6–8,16] and flow systems.[20,21]

Since Haruta and co-workers discovered gold nanocluster catalysts for carbon monoxide oxidation,[22–24] gold nanocluster catalysis has also been applied to various oxidative organic transformations, including synthesis of complex molecules.[25–32] However, only dehydrogenation reactions are possible with these catalysts under mild conditions and there are few examples of oxygenation reactions. Recently, Sakurai et al. demonstrated an oxygenation of benzyl ketones using Au:PVP as a homogeneous catalyst via a peroxo intermediate.[33]

The 1,3-dicarbonyl-2-hydroxy moiety is observed in various natural compounds, pharmaceutical compounds, and bioactive compounds, and α-hydroxylation of 1,3-dicarbonyl compounds, which is the most direct method to construct this motif, is a quite important transformation.[34] Many methods using molecular oxygen as an oxidant with Ce,[35–37] Cs,[38] Mn,[39,40] Pd,[41,42] and Fe[43] as homogeneous catalysts and photooxidation with sensitizers[44,45] have been developed. However, methods using reusable heterogeneous catalysts and gold catalysts have not been reported. Here, we show reusable heterogeneous gold-catalyzed α-hydroxylation of 1,3-dicarbonyl compounds using molecular oxygen as an oxidant under very mild conditions as one of the greenest methods for this transformation.

Table 1. Optimization of reaction conditions

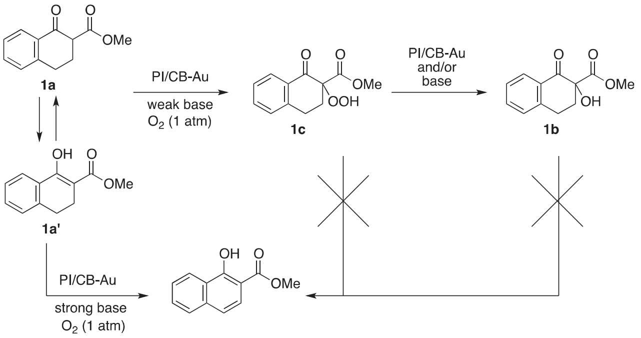


Entry	Catalyst	Base	Solvent	Yield/%[a]		
				1b	**1c**	**1d**
1	None	K_2CO_3	$MeCN/H_2O = 9/1$	7	nd	nd
2	PI/CB-Au	None	MeCN	62	16	nd
3	PI/CB-B	None	MeCN	nd	nd	nd
4	PI-Au	None	$MeCN/H_2O = 9/1$	nd	nd	14
5	PI/CB-Au	None	$MeCN/H_2O = 9/1$	59	12	nd
6	PI/CB-Au	None	$BTF/H_2O = 9/1$	54	nd	nd
7	PI/CB-Au	$KHCO_3$	MeCN	69	nd	Trace
8	PI/CB-Au	$KHCO_3$	$BTF/H_2O = 9/1$	71	nd	Trace
9	PI/CB-Au	$KHCO_3$	MeCN/MeOH = 9/1	**80**	nd	nd
10	PI/CB-Au	K_2CO_3	MeOH	11	nd	**56**

[a]Isolated yield.

First, we chose ketoester **1a** as a model substrate for optimization of the reaction conditions (Table 1). The α-hydroxylation reaction hardly proceeded under basic conditions in the absence of any catalysts (Entry 1). When the PI-Au catalyst was used in the acetonitrile (MeCN)–water cosolvent system, only naphthol derivative **1d**, which was produced by a dehydrogenation reaction, was obtained (Entry 4). In contrast, when PI/CB-Au was used as a catalyst in MeCN–water, MeCN, or benzotrifluoride (BTF (=trifluoromethylbenzene))–water, a mixture of α-hydroxylated compound **1b** and peroxide compound **1c** was obtained in good yields (Entries 2, 5, and 6). Addition of potassium hydrogencarbonate ($KHCO_3$) improved the selectivity of **1b** (Entries 7–9) and the desired compound was obtained in 80% yield in the MeCN–MeOH cosolvent system (Entry 9). Interestingly, in the presence of K_2CO_3 in MeOH, **1d** was obtained as the major product (Entry 10).

To gain insight into the reaction pathway, we performed several control experiments. First, it was confirmed that carbon-stabilized polymer-incarcerated boron (PI-CB/B), prepared from sodium borohydride and a polymer,[16] could not mediate this oxidation reaction at all, either with or without base (Entry 3). Therefore, background reactions catalyzed by either carbon black or remaining boron species in the polymer can be rejected. Second, peroxide compound **1c** was quite stable in the solid state in air at room temperature (no decomposition occurred over two weeks); however, it was slowly converted to hydroxylated



Scheme 1. Proposed reaction pathway.

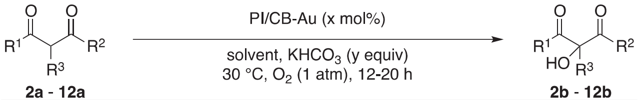
compound **1b** in MeCN at room temperature (12% after 12 h). Peroxide **1c** could be transformed to **1b** smoothly in the presence of the PI/CB-Au catalyst (50% after 12 h) and much smoother conversion was seen in the presence of both PI/CB-Au and the base (>95% after 12 h). In contrast, no transformation from either **1b** or **1c** to **1d** was observed in the presence of the base and/or PI/CB-Au.

Taking account of these control experiments, we propose the reaction pathway shown in Scheme 1. Keto form **1a** and enol form **1a′** of the substrate are held in equilibrium under the reaction conditions. When a weak base is used, the oxygenation reaction proceeds to afford peroxide **1c** in the presence of PI/CB-Au and molecular oxygen, followed by isomerization catalyzed by PI/CB-Au to give hydroxylated product **1b**. On the other hand, the dehydrogenative oxidation proceeds to afford naphthol **1d** in the presence of a strong base and PI/CB-Au. Compound **1d** cannot be obtained from **1c** or **1b** under any conditions.

We then examined the substrate scope using the PI/CB-Au catalyst under atmospheric oxygen. It was found that the best conditions of solvent systems and amount of base generally depended on the substrate, while MeCN–water and MeCN–MeOH cosolvent systems were similar (Table 2). Cyclic ketoesters could be converted to the desired hydroxylated products **2b** and **3b** (Chart 1) in good yields (Entries 1 and 2). Acyclic ketoesters were also oxidized to the corresponding hydroxylated compounds **4b**–**6b** in moderate yields (Entries 3–5). A ketoamide was oxidized to hydroxylated product **7b** with retention of the ratio of the diastereomers (Entry 6). Malonic ester derivatives also were oxidized smoothly to the corresponding hydroxylated compounds **8b**–**10b** (Entries 7–9). When reactive groups with a peroxy moiety were included in the starting materials, 1,2-dioxane intermediates **11e** and **12e** were also obtained (Entries 10 and 11).[46–48] A mixture of compounds **12b** and **12e** was converted to just **12b** in 71% yield by treatment with 1 equiv of triphenylphosphine.

The reaction profile in the oxidation of malonic ester **8a** using PI/CB-Au is shown in Figure 1. Initially, the fraction of peroxo intermediate **8c** increased, and **8c** was converted gradually to hydroxylated product **8b**. Judging from this result, the reaction speeds of the first and second steps are similar.

Table 2. Substrate scope



Entry	Product	x	y	Solvent	Yield/%[a]
1	**2b**	3	0.5	$MeCN/H_2O = 10/1$	79
2	**3b**	3	1	MeCN/MeOH = 10/1	75
3	**4b**	2	1	$BTF/H_2O = 10/1$	49
4	**5b**	4	2	$MeCN/H_2O = 10/1$	46
5	**6b**	5	2	$MeCN/H_2O = 10/1$	48
6	**7b**	5	2	$MeCN/H_2O = 10/1$	69
7	**8b**	3	1	$MeCN/H_2O = 10/1$	72
8	**9b**	3	0.5	$MeCN/H_2O = 10/1$	71
9	**10b**	4	0.2	$MeCN/H_2O = 10/1$	62
10	**11b (11e)**	5	2	$MeCN/H_2O = 10/1$	40 (6)[b]
11	**12b (12e)**	4	1.5	$MeCN/H_2O = 10/1$[c]	44 (31)[b]

[a] Isolated yield. [b] Yield of compound **e**. Compounds **e** and **b** cannot be separated and the ratio of **b** and **e** was determined by ^1H NMR analysis. [c] 20 mol % of $NaB(OMe)_4$ was used. BTF: benzotrifluoride.

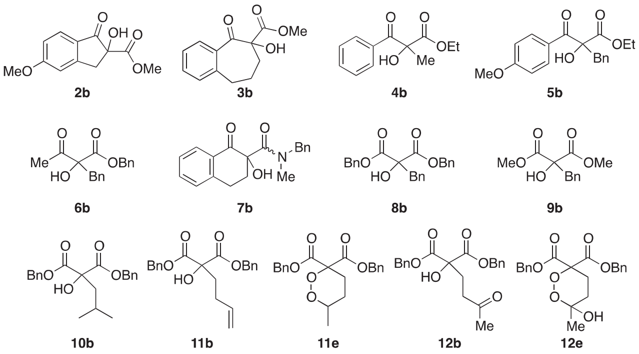


Chart 1. Structures of products.

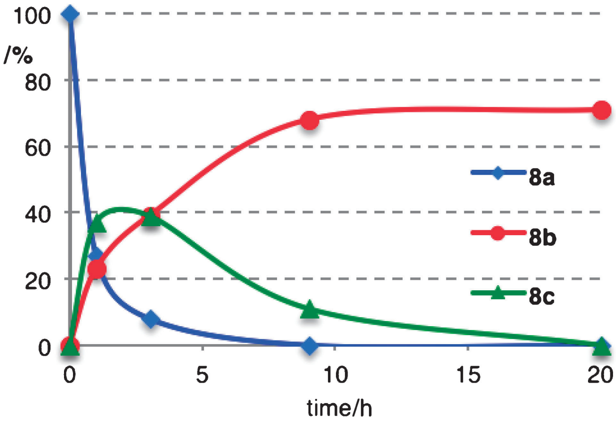
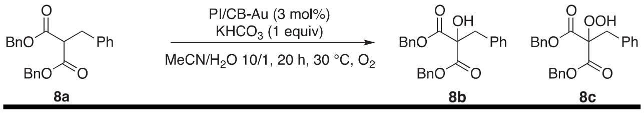


Figure 1. Reaction profile of the oxidation reaction using PI/CB-Au.

Recovery and reuse of the catalyst was examined using malonic ester **8a** as the substrate (Table 3). The PI/CB-Au catalyst could be recovered by simple filtration. In the second and third runs, conversion of **8a** was complete, but peroxo intermediate **8c** remained. These results indicate that the recovered catalyst retains activity for the first step; however, activity for the second step decreased a little during recycling. In other words, the metal nanocluster catalyst is important for both

Table 3. Recovery and reuse of the catalyst



Run	**8b**/%	**8c**/%
1	72	0
2	55	11
3	62	9

the first and second steps. The deactivation of the PI/CB-Au catalyst is presumably caused by adsorption of small amounts of solvents or organic compounds on the nanocluster surface. We tried to regenerate the recovered catalyst by heating; however, this treatment was not effective in this case.[1,8,12]

In conclusion, we have demonstrated that PI/CB-Au catalyzed α-hydroxylation of 1,3-dicarbonyl compounds. The reaction proceeded under mild conditions using molecular oxygen as oxidant, and the catalyst could be recovered by a simple operation. The control experiments and reaction monitoring revealed that α-peroxide compounds were intermediates and that the polymer-incarcerated gold nanocluster also catalyzed isomerization to the hydroxylated compounds. This catalytic system satisfies criteria for green sustainable chemistry, and a new class of heterogeneous gold nanocluster catalyzed oxygenation reaction has been developed.

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