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Tandem Oxidative Processes Catalyzed by Polymer-Incarcerated Multimetallic Nanoclusters with Molecular Oxygen

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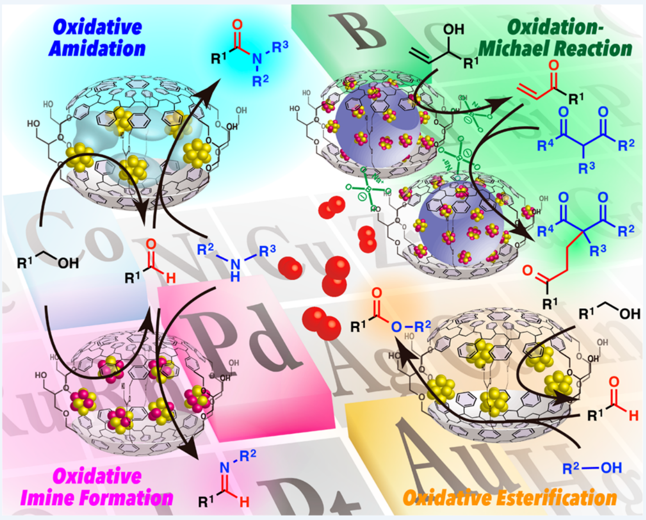

CONSPECTUS: Heterogeneous catalysis and one-pot tandem reactions are key for efficient and practical organic syntheses and for green and sustainable chemistry. Heterogeneous catalysts can be recovered and reused. These catalysts can be applied to efficient systems, such as continuous-flow systems. Tandem reactions often proceed via highly reactive but unstable intermediates. Tandem reactions do not require workup or much purification of the intermediate.

This Account summarizes recent developments that we have made in the field of multifunctional heterogeneous metal nanocluster catalysts for use in tandem reactions based on aerobic oxidation reactions as key processes. We constructed our heterogeneous metal nanoclusters via two important procedures—microencapsulation and cross-linking—using polystyrene-based copolymers with cross-linking moieties. These frameworks can efficiently stabilize small metal nanoclusters to maintain high catalytic activity without aggregation and leaching of nanoclusters. Aggregation and leaching are prevented by weak but multiple interactions between metal nanocluster surfaces and benzene rings in the copolymer as well as by the physical envelopment of cross-linked polymer backbones. Small nanoclusters, including multimetallic alloy clusters (nanoalloys), can be "imprisoned" into these cross-linked polymer composites. The term we use for these processes is polymer incarceration.

Direct oxidative esterifications were achieved with polymer-incarcerated (PI) Au nanocluster catalysts. Amides were synthesized from alcohols and amines under aerobic oxidative conditions with PI bimetallic nanocluster catalysts composed of Au and Fe-group metals that formed separated nanoclusters rather than alloys. Oxidative lactam formation from amino alcohols was also achieved. On the other hand, imines could be prepared selectively from alcohols and amines with PI Au−Pd bimetallic nanoclusters. We also achieved the integration of the aerobic oxidation of allylic alcohols and the following Michael reaction catalyzed by trimetallic PI catalysts containing Au−Pd alloy nanoclusters and tetraalkoxyborates as cross-linkers.

All of these heterogeneous catalysts could be recovered by simple operations and reused without significant loss of activity or any leaching of metals. We have demonstrated that the polymer incarceration method enables the simultaneous immobilization of several metals, with which we can achieve one-pot tandem oxidative processes using molecular oxygen as an oxidant within the multifunctional heterogeneous catalysts.

Suitable choices of metals and bimetallic structures are crucial for the reactivity and the selection of reaction pathways.

1. INTRODUCION

Aerobic oxidation of organic molecules is essential for various organic transformations as well as for energy production in biological systems, such as in respiration, and in our daily lives, such as in combustion and electrical power production. Ever since the dawn of time on the earth, plants have produced and accumulated molecular oxygen and organic compounds from carbon dioxide and water. Energy generated from reactions between molecular oxygen and organic compounds also enables us to construct complex molecules from simple compounds in biological systems. Because of the triplet nature of molecular oxygen, most organic molecules and molecular oxygen can coexist under ambient conditions in the absence of any catalysts or enzymes, in spite of their potentially enormous energy. The choice of catalyst (or enzyme) is the key to realizing selective oxidative processes. In general, metal-containing complexes or metalloenzymes are favored because metals can provide electrons one by one to molecular oxygen to control the oxidation state and process selectivity.

In nature, we see oxidation processes coupled with other catalytic systems in metalloenzymes or multienzyme complexes to realize tandem oxidative processes (TOPs), such as in Cu-containing amine oxidase and cellular metabolism.[1] In such elaborate systems, highly reactive, unstable, short-lifetime intermediates resulting from oxidation processes can be utilized in fully controlled cascade systems. In organic synthesis, carbonyl

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Scheme 1. Preparation of PI-Metal Nanoclusters and PICB Catalysts

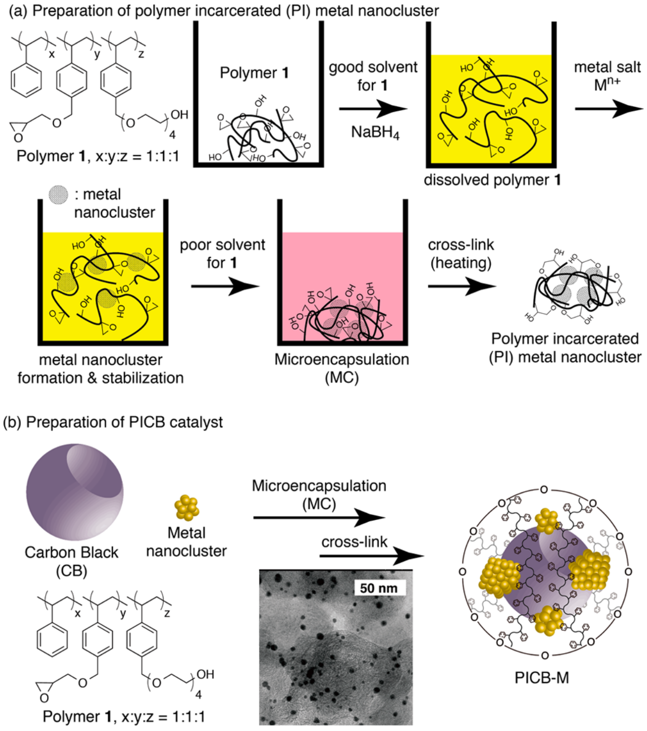
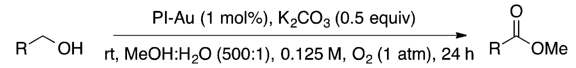


Table 1. Scope of Methyl Ester Formation



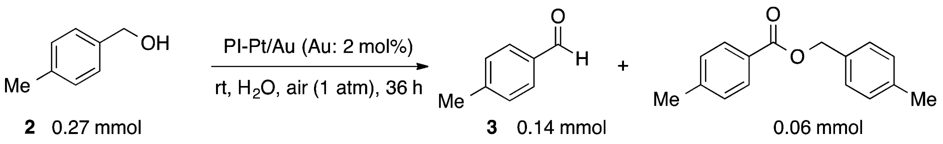
entry	R	conversion (%)[a]	yield (%)[a]
1	Ph	>99	95
2	4-MeOC_6H_4	>99	>99
3	4-BrC_6H_4	>99	92
4	4-$NO_2C_6H_4$	95	60
5	1-naphthyl	>99	95
6	Ph−CH═CH	>99	69
7	2-pyridyl	>99	>99
8	$PhCH_2CH_2CH_2$	12	10
9	CH_2═CH	>99	60[b]

[a]Determined by gas chromatography (GC). [b]Methyl 3-methoxypropionate was obtained.

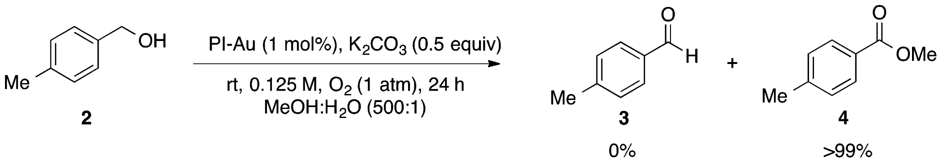
compounds such as aldehydes and ketones are key for both C−C bond formation reactions and functional group transformations. These highly reactive but relatively unstable compounds can be synthesized by oxidation of the corresponding alcohols, which are generally very stable and simple to use. Huang reported the first TOP in 1987 during the synthesis of carbon-14-labeled CI-933.[2] He conducted the oxidation of a primary alcohol using Dess−Martin periodinane in the presence of a Wittig reagent to obtain an unsaturated ester directly in a one-pot process. After this example, Taylor et al. developed TOPs extensively, including the oxidation of primary alcohols with MnO_2 as the oxidant.[3] These developments have shed light on the great potential of TOPs. A disadvantage, however, is the requirement of using stoichiometric amounts of oxidants. Thus, a TOP involving molecular oxygen, which is abundant in air, is highly desirable from the viewpoint of atom economy and green and sustainable chemistry.

Since Haruta et al. pioneered the discovery of Au-nanocluster-catalyzed aerobic oxidation of carbon monoxide,[4] various aerobic oxidation processes with Au nanoclusters have been developed. Among them, oxidation of alcohols is a hot topic, and several excellent catalytic systems have been developed.[5] Although metal-nanocluster-catalyzed selective aldehyde formation from aerobic oxidation of alcohols is difficult because of overoxidation under basic and/or harsh conditions, we have succeeded in achieving selective aldehyde production using Au and its bimetallic nanoclusters immobilized in polystyrene-based copolymers with cross-linking moieties (**1**) by a method known as polymer incarceration (Scheme 1a).[6] This method is based on two key processes: microencapsulation and cross-linking of side chains in copolymers.[7] Polymer **1** and $NaBH_4$ are dissolved in a good solvent such as tetrahydrofuran (THF) or diglyme. Metal salts are added to the solution to form metal nanoclusters, which are stabilized by polymer **1**. A poor solvent such as hexane or Et_2O is added to cause precipitation of the microencapsulated metal nanoclusters. The precipitate is heated under neat conditions to afford an insoluble catalyst formed by cross-linking between alcohol and epoxy moieties in the polymer. The metal nanoclusters are stabilized by weak but multiple interactions between π electrons of the benzene rings in the copolymer and the surfaces of the metal nanoclusters and also by physical envelopment by the polymer backbone. In addition, when hollow-center spherical carbon black (CB) with a high specific surface area (Ketjen black) was used as a second support to make the polymer-incarcerated carbon black nanocomposite (PICB), a higher metal loading and retention of high reactivity were achieved because aggregation of the nanoclusters was prevented (Scheme 1b).[6a] Moreover, various bimetallic metal nanocluster

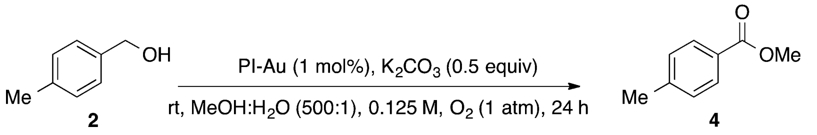
Scheme 2. Oxidative Esterification from an Alcohol



Scheme 3. Oxidative Methyl Esterification Using PI-Au



Scheme 4. Recovery and Reuse of PI-Au



* Collected catalysts heated to 170 °C for 4 h without solvent before use.

1st-4th: >97%, 5th: 92%, 6th: 90%, 7th: 86%
8th*: 97%, 9th: 95%, 10th: 74%, 11th*: 94%

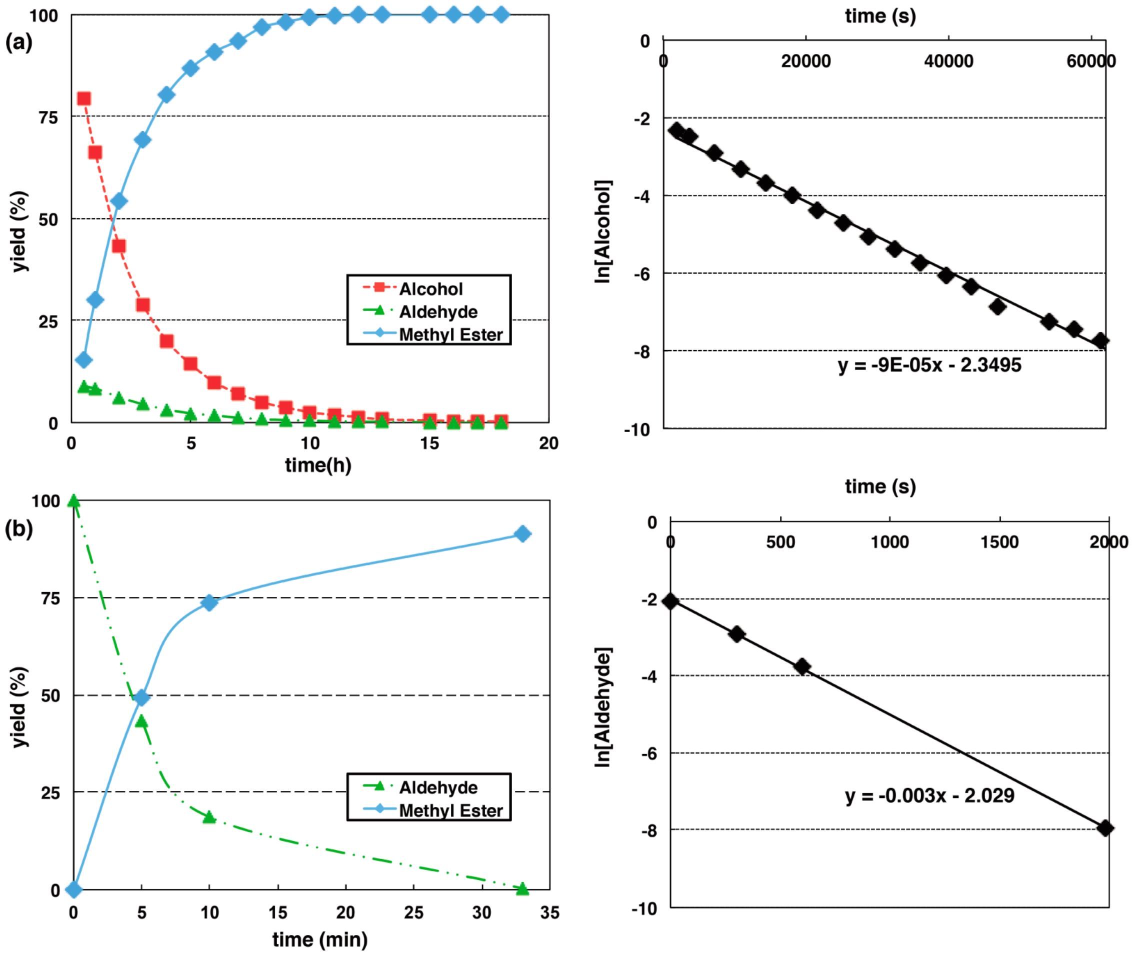


Figure 1. Reaction profiles of two oxidative esterifications: (a) from **2** to **4** via **3**; (b) from **3** to **4**. Reaction conditions: PI-Au = 1 mol % as Au, MeOH:H$_2$O = 500:1, [substrate]$_0$ = 0.125 M, P_{O_2} = 1 atm, T = 298 K. Left panels: reaction profiles. Right panels: plots based on the first-order rate equation for the consumption of (a) **2** and (b) **3**.

catalysts could be prepared readily using the polymer incarceration method. These catalysts showed characteristic reactivity and selectivity due to bimetallic effects.[8] Such flexible and secure immobilization means that substrates interact easily with the catalytic centers, and high reactivity, robustness, and reusability are achieved without the leaching of metals and aggregation of the nanoclusters. In this context, we used a TOP with molecular oxygen as the terminal oxidant and polymer-incarcerated metal (PI-metal) nanoclusters as multifunctional catalysts.

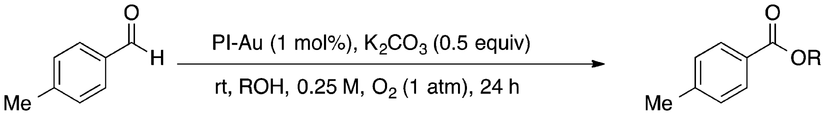
2. DIRECT OXIDATIVE ESTERIFICATION FROM TWO ALCOHOLS OR ALCOHOLS AND ALDEHYDES

2.1. Methyl Ester Formation.[9]

During an investigation of the aerobic oxidation of alcohols under air in the presence of a PI-Pt/Au catalyst, we found that in water an ester was obtained directly from a primary alcohol (Scheme 2). Christensen and co-workers have investigated aerobic oxidative methyl esterification from aldehydes or alcohols in methanol catalyzed by heterogeneous Au nanoclusters.[10] In their method, however, oxidative esterification from alcohols requires harsh conditions such as high temperature and pressurized conditions. Encouraged by our initial discovery that oxidative esterification from alcohols proceeds smoothly under mild conditions, we carried out direct oxidative esterification reactions with our PI-metal nanocluster catalysts.

Initial screening of metal nanocluster catalysts revealed that PI-Au appeared to be best for the oxidation of 4-methylbenzyl alcohol to the corresponding methyl ester in methanol with a base. The reaction proceeded smoothly in wet methanol but sluggishly in dry methanol. The amount of water in the methanol was key to control the reactivity and selectivity. Therefore, the effect of the ratio of water to methanol was examined. Excellent reactivity and selectivity were observed

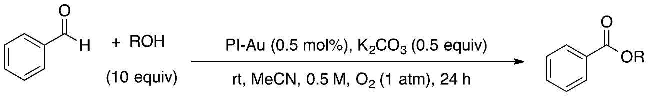
Scheme 5. Ethyl and Ethylene Glycol Ester Formation

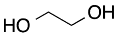
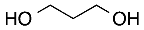
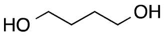
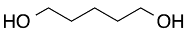
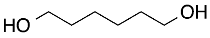
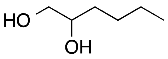
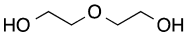
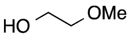
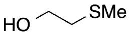
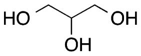
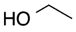
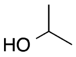


3

R=Et (**5**): 60%
R=HOCH$_2$CH$_2$(**6**): 85%

Table 2. Esterification of Diol Derivatives



Entry	Alcohol (R-OH)	Conversion (%)[a]	Yield (%)[b]
1		>99	95
2		86 (91)[c]	64 (74)[c]
3		25	20
4		7	4
5		14	9
6		40	32[d]
7		>99 (>99)[c]	65 (78)[c]
8		54 (99)[c]	48 (78)[c]
9		0	0
10		85 (91)[c]	25 (56)[c, e]
11		3	1
12		0	0

[a] Determined by GC analysis. [b] Isolated yields. [c] Conditions for the value in parentheses: 1 mol % PI-Au, 2 mL of the alcohol instead of acetonitrile as the solvent. [d] 1-Substituted monoester:2-substituted monoester = 18:14. [e] 1-Substituted monoester:2-substituted monoester = 50:6.

when the reaction was conducted using a methanol:water ratio of 500:1 (Scheme 3).

The scope of the direct oxidative esterification from alcohols was examined (Table 1). Benzylic alcohols, a heteroaromatic alcohol, and cinnamyl alcohol could be oxidized to the corresponding methyl esters in good to excellent yields (entries 1−7). An aliphatic primary alcohol was oxidized only sluggishly (entry 8). Allyl alcohol was converted to methyl 3-methoxypropionate as a result of subsequent Michael addition of methanol (entry 9).

The recovery and reuse of PI-Au was investigated (Scheme 4). The desired ester was obtained in excellent yield during the first four uses by simple filtration followed by drying. Because the yield dropped gradually during the following three uses, the collected catalyst was then heated to 170 °C for 4 h before the next use. This revived the catalytic activity, and the product again was obtained in excellent yield.

Two different kinetic behaviors of the oxidative esterification were analyzed: starting from 4-methylbenzyl alcohol (Figure 1a) and from 4-methylbenzaldehyde (Figure 1b). Both oxidations exhibited first-order kinetics, and the second oxidation (conversion of the aldehyde to the ester) was 30 times faster than the first oxidation (conversion of the alcohol to the aldehyde). The reactions that started from the carboxylic acid or the dimethyl acetal afforded no methyl ester, indicating that the reaction proceeds via a hemiacetal intermediate.

2.2. Monoesterification of Diol Derivatives.[11]

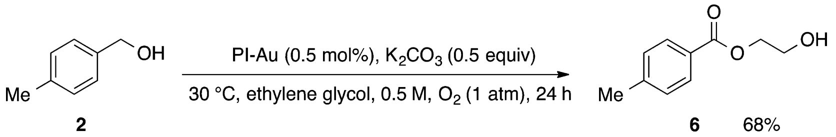
We also investigated the direct oxidative esterification using alcohols other than methanol (Scheme 5). When the oxidation of 4-methylbenzaldehyde was conducted in ethanol, a 60% yield of the ethyl ester was obtained. Ethylene glycol monoester was obtained in 85% yield in ethylene glycol.

We then commenced with an investigation of the esterification of benzaldehyde with 10 equiv of various diol derivatives in MeCN (Table 2). When the reaction was conducted with ethylene glycol, the desired ester was obtained in 83% yield (entry 1). Interestingly, the yield decreased gradually as the length of the alkyl chain between the two hydroxyl groups increased (entries 2−5). Comparison of the results for the reactions with 1,6-hexanediol (9% yield) and 1,2-hexanediol (32% yield) strongly supported this tendency (entries 5 and 6). Diethylene glycol and 2-methoxyethanol, which contain ethereal oxygen near the hydroxyl groups, also afforded the desired monoesters in good yields (entries 7 and 8). On the other hand, a sulfide-containing alcohol gave no conversion, probably because of too strong coordination of sulfur to the Au nanoclusters (entry 9). When a solvent amount of glycerol was used as the substrate, the reaction proceeded smoothly to afford a mixture of 1-substituted and 2-substituted monoesters (entry 10). Simple alcohols, such as ethanol and isopropanol, hardly afforded the desired esters (entries 11 and 12).

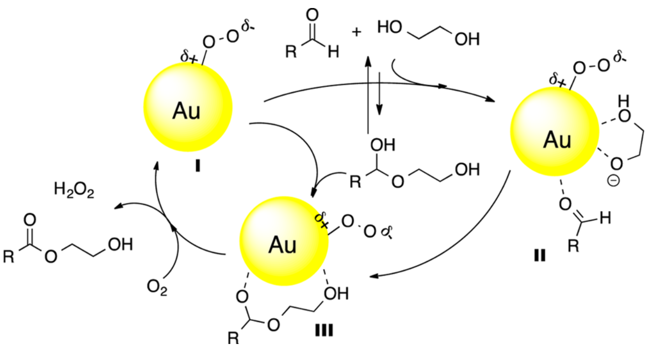
Ethylene glycol monoester was obtained from 4-methylbenzyl alcohol in good yield when a solvent amount of ethylene glycol was used (Scheme 6). When the cyclic acetal prepared from benzaldehyde and ethylene glycol was used as the starting material, no ester was obtained, even in ethylene glycol with PI-Au, K_2CO_3 and O_2. Haruta and co-workers and Tsukuda and co-workers have suggested that Au nanoclusters immobilized on polymers are sufficiently electron-rich to activate molecular oxygen on their surfaces, and subsequent alcohol absorption on Au nanoclusters could be facilitated by the presence of bases.[12]

Accordingly, we postulate the formation of intermediate **II**, in which both ethylene glycol and aldehyde are adsorbed on the same Au nanocluster (Scheme 7). Subsequent nucleophilic attack generates intermediate **III**, in which a hemiacetal intermediate is stabilized by multiple coordination of hydroxyl groups to the nanocluster surface. Another reaction pathway involving hemiacetal formation in the liquid phase followed by coordination to an activated Au nanocluster is also possible. However, no hemiacetal was detected by ^{1}H NMR analysis in the liquid phase. The remarkable reaction rate acceleration with 1,2- or 1,3-diol derivatives can be explained by the increased

Scheme 6. Ethylene Glycol Monoesterification from an Alcohol



Scheme 7. Possible Reaction Mechanism for Monoesterification



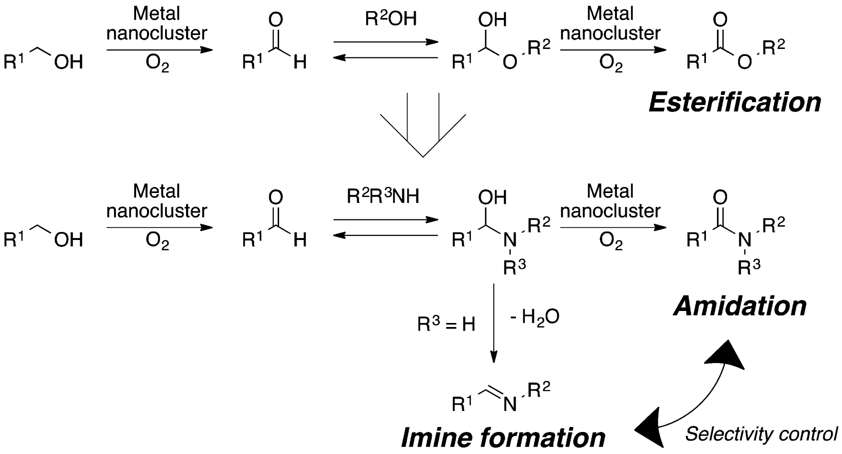
stability of their intermediates **III** due to multiple interactions between the hemiacetals and the Au nanocluster surface resulting from neighboring group participation.

3. DIRECT OXIDATIVE AMIDE AND IMINE FORMATION FROM ALCOHOLS AND AMINES

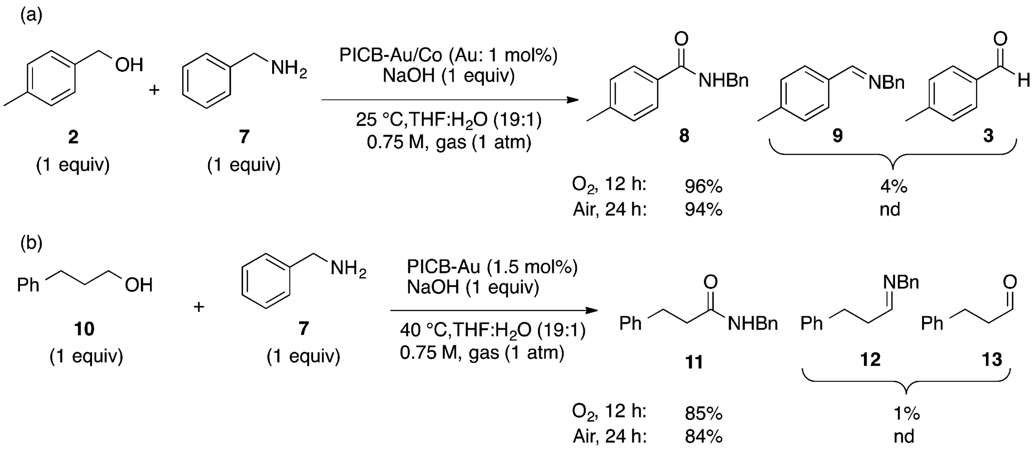
3.1. Amide Synthesis.[13]

Encouraged by the fruitful results of the direct oxidative esterification reactions, we next targeted direct oxidative amidation from amines and alcohols via hemiaminals as key intermediates (Scheme 8). Traditionally, an amide is synthesized from a carboxylic acid and an amine with a coupling reagent or using an activated carboxylic acid such as an acid chloride or an acid anhydride. This reaction requires stoichiometric amounts of reagents and the same amount of coproduct is formed as waste. Thus, more environmentally benign amidation reactions are highly desirable. Catalytic methods from aldehydes and amines under oxidative conditions or from alcohols and amines under dehydrogenative conditions have been developed as green methods.[14] Oxidative methods from alcohols and amines using Au nanocluster catalysts were reported by Ishida and Haruta and by Sakurai and co-workers, but these reactions were limited

Scheme 8. Oxidative Coupling of an Alcohol and an Amine



Scheme 9. Optimized Conditions for Oxidative Amidation



Scheme 10. Determination of the Reaction Pathway for Amidation

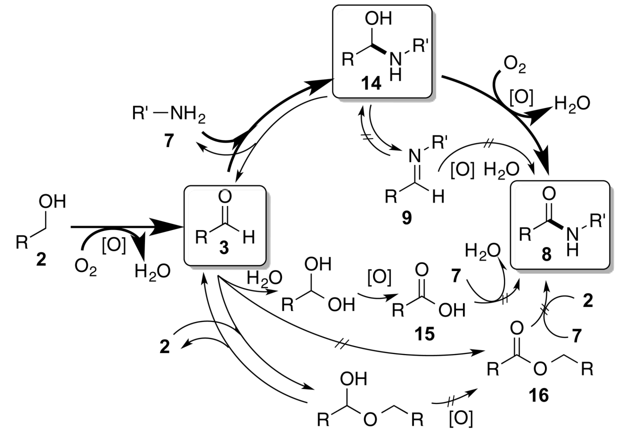
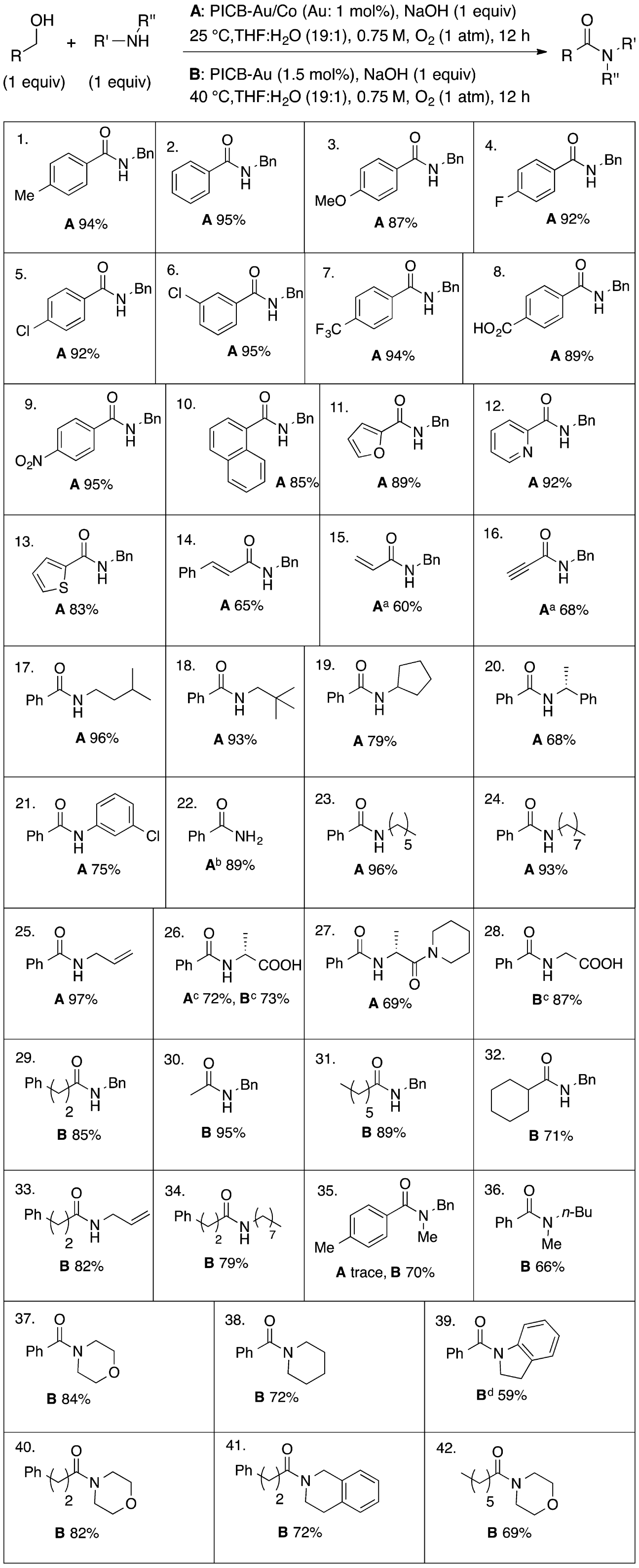


Table 3. Substrate Scope of Oxidative Amidation



[a] 2 equiv of the alcohol was used. [b] 6 equiv of aqueous NH_3 was used. [c] 2 equiv of NaOH in THF:H_2O (9:1) was used. [d] The reaction was performed at 60 °C.

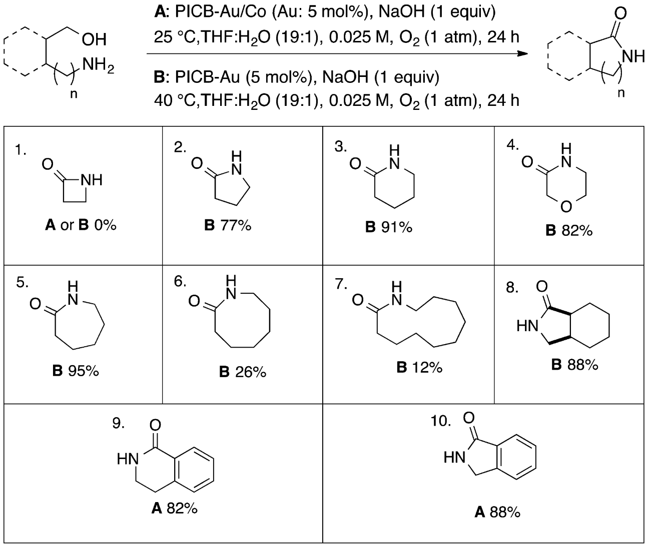
to only formylation.[15] We can expect various side reactions from alcohols and amines under aerobic oxidative conditions, and especially controlling the selectivity between amidation and imine formation would be very difficult (Scheme 8).

We then commenced with an investigation using a stoichiometric mixture of 4-methylbenzyl alcohol and benzylamine as substrates. The reaction proceeded at room temperature under atmospheric oxygen to almost full conversion in the presence of 1 equiv of NaOH with PICB-Au, although the selectivity for amide **8** was only 45%. Extensive screening of metals found that bimetallic catalysts of Au and an Fe-group metal (Fe, Ni, Co) showed excellent selectivity toward amides. In particular, PICB-Au/Co, prepared from a mixture of 1 equiv of $AuClPPh_3$ and 1 equiv of $CoCl_2$, gave the desired amide in >95% yield (Scheme 9a). The reaction also proceeded cleanly under atmospheric air to afford amide **8** selectively. On the other hand, when aliphatic alcohol **10** was used as a substrate, the reaction proceeded sluggishly with the PICB-Au/Co catalyst despite high selectivity for amide **11**. We found that at a slightly elevated temperature PICB-Au afforded the desired amide **11** in high yield (Scheme 9b).

We then tried to confirm the reaction pathway by conducting various control experiments (Scheme 10). Neither 4-methylbenzoic acid (**15**), *N*-(4-methylbenzylidene)benzylamine (**9**), nor 4-methylbenzyl 4-methylbenzoate (**16**) as the starting material gave the desired amide by reaction with amine **7** under the optimized conditions. Furthermore, ester **16** was not observed in any case. On the other hand, when 4-methylbenzaldehyde (**3**) was used instead of alcohol **2**, the desired amide was obtained, as well as imine **9**, with almost 1 to 1 selectivity. From these experimental results, we postulate that hemiaminal **14** is a key intermediate in the reaction pathway of oxidative amidation (Scheme 10).

With two different sets of optimized conditions in hand, we examined the scope of the oxidative amidation from alcohols and amines (Table 3). Conditions A (PICB-Au/Co at 25 °C) were generally suitable for combinations of activated primary alcohols (e.g., benzylic, cinnamyl, allylic, and propargylic alcohols) and primary amines (entries 1−27). Benzylic alcohols, including aromatic rings with both electron-donating and electron-withdrawing groups and heteroaromatic rings, underwent oxidation to afford the desired amides in good to excellent yields. The reactions with aqueous ammonia and protecting-group-free amino acids, in particular, are highlighted (entries 22 and 26). On the other hand, conditions B (PICB-Au at 40 °C) were appropriate for amidation when using aliphatic alcohols or secondary amines (entries 29−42). Amidations using amino acids proceeded well under conditions B (entries 26 and 28).

Table 4. Scope of Lactam Synthesis



Carbon−carbon double and triple bonds are tolerated (entries 14−16, 25, and 33).

3.2. Lactam Synthesis.[16]

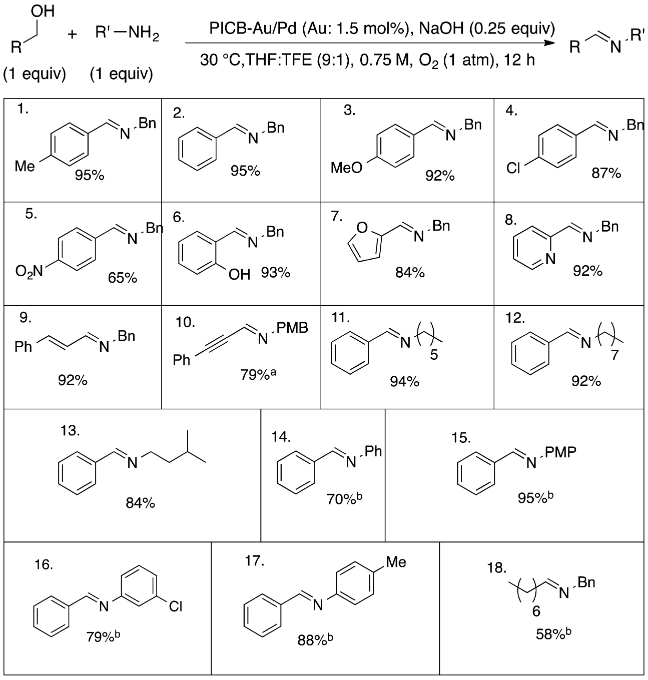
We also investigated the synthesis of lactams from amino alcohols. Using a slight modification of reaction conditions B (dilute conditions), we obtained the desired lactams in excellent yields from amino alcohols (Table 4). Five- to seven-membered heterocycles were obtained, and polymerization was avoided (entries 2−5). *β*-Lactam formation, however, did not proceed under our reaction conditions (entry 1). Lactams with rings containing eight or more members were obtained, albeit in lower yields (entries 6 and 7). Bicyclic structures were also obtained (entries 8−10). Conditions A were suitable in the case of benzylic alcohols (entries 9 and 10).

3.3. Imine Formation.[17]

Next, we were interested in the direct oxidative synthesis of imines from alcohols and amines. Green methods for catalytic imine formation from alcohols and amines via dehydrogenation or aerobic oxidation have been reported; however, most of them require relatively harsh conditions, and no mention of the recyclability of catalysts has been made.[18]

We first investigated the reaction of benzylic alcohol **2** with benzylamine **7** in the presence of the PICB-Au catalyst and NaOH in anhydrous THF. Amide **8** was obtained as the major product in 42% yield, with a 38% yield of the aldehyde and a 15% yield of the desired imine (Scheme 11). PICB-Au/Pd suppressed the amide formation, and aldehyde **3** was obtained in 83% yield (Scheme 11). After extensive screening of solvents and cosolvent systems, we found that a mixture of THF and 2,2,2-trifluoroethanol (TFE) gave excellent imine selectivity with the PICB-Au/Pd catalyst (Scheme 11). Analytically pure imine as judged by ^{1}H and ^{13}C NMR analysis could be obtained in most of the cases after just filtration of the catalyst, aqueous washing, evaporation, and removal of unreacted starting materials by high vacuum.

Table 5. Scope of Oxidative Imine Formation



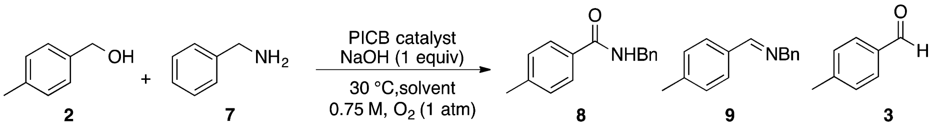
[a]In THF:TFE (4:1) at 40 °C. [b]In THF:TFE (4:1) at 60 °C. TFE = trifluoroethanol.

The scope of the direct oxidative imine formation was examined (Table 5). Benzylic alcohols and heteroaromatic rings afforded the desired imines in good to excellent yields (entries 1−8). Activated alcohols containing carbon−carbon double and triple bonds afforded the desired imines with preservation of the unsaturated moieties (entries 9 and 10). Aliphatic primary amines and aniline derivatives were also obtained (entries 11−17). An aliphatic primary alcohol could be oxidized to the corresponding imine without isomerization to an enamine (entry 18).

3.4. Recovery and Reuse of the Catalysts

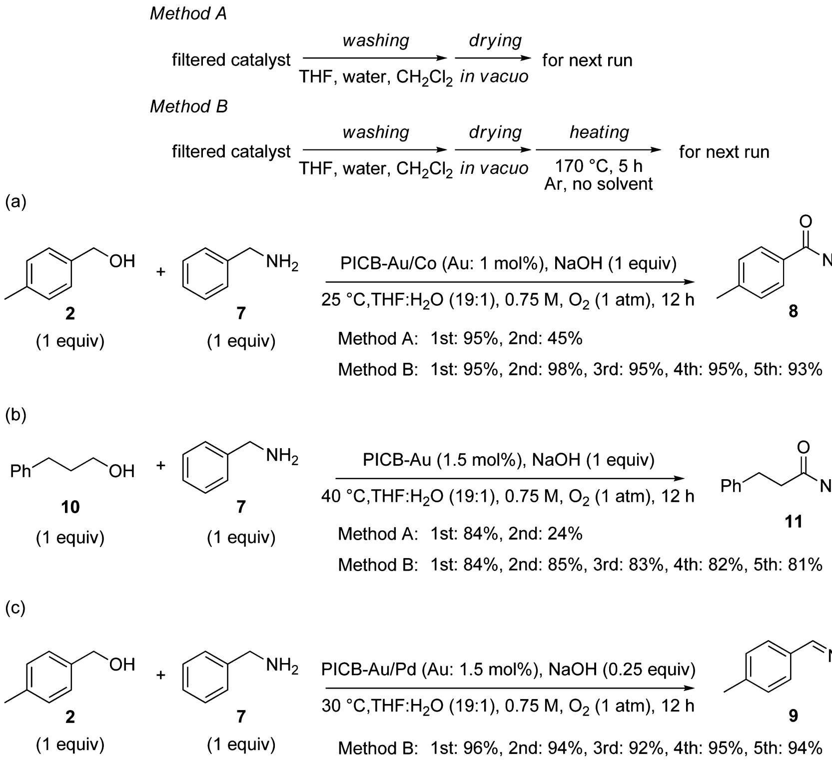
The recovery and reuse of the catalysts was studied. A once-used catalyst was collected after simple filtration and drying in vacuum (method A) and then used a second time for the oxidative amidation. However, the yields for both benzylic and aliphatic alcohols decreased significantly (Scheme 12a,b). When method B was used for catalyst recovery, the yields could be maintained for a further four uses in both cases (Scheme 12a,b).

Scheme 11. Optimization of the Conditions for Imine Synthesis



	8	9	3
PICB-Au (1 mol%), THF	42%	15%	38%
PICB-Au/Pd (Au:1 mol%), THF	6%	6%	83%
PICB-Au/Pd (Au: 1.5 mol%), THF:TFE (9:1)	0%	95%	trace

Scheme 12. Recovery and Reuse Experiments



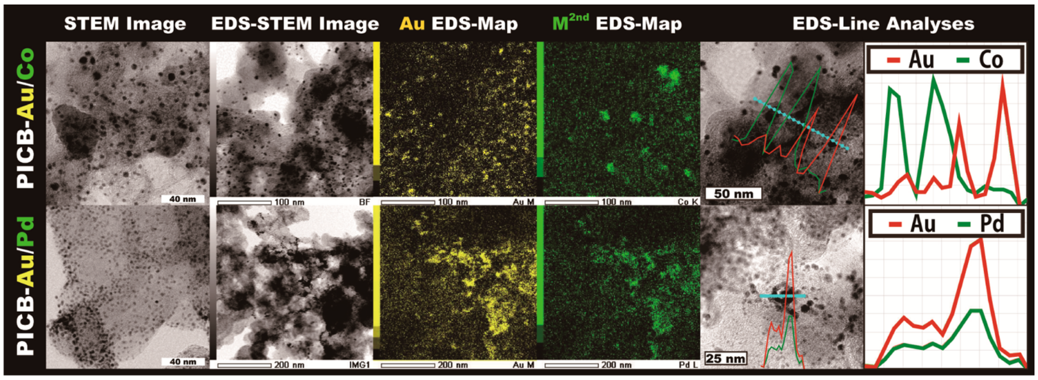


Figure 2. STEM and EDS images.

This recovery method was also effective in the oxidative formation of imines using PICB-Au/Pd (Scheme 12c).

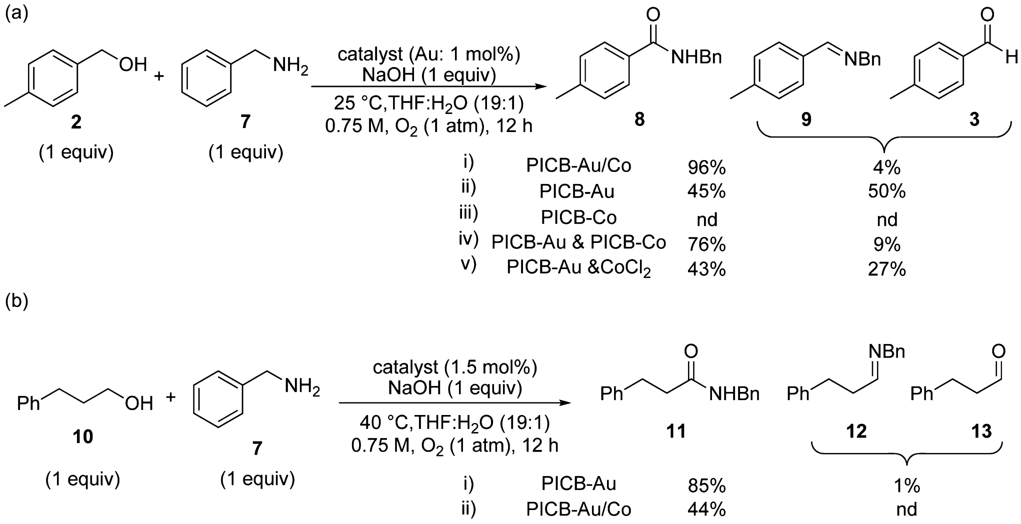
3.5. Structure of the Catalysts: Effect of Metal Combinations on Selecting Reaction Pathways

We could achieve selection of the reaction pathway from amines and alcohols toward amides or imines by changing the combination of metals forming the nanoclusters. We carried out detailed analyses of the morphologies of the bimetallic catalysts by scanning transmission electron microscopy (STEM) and energy-dispersive spectroscopy (EDS). Small nanoclusters (2–4 nm) were observed in both the PICB-Au/Co and PICB-Au/Pd catalysts (Figure 2). EDS mapping revealed that Au and Co existed in different positions but in close proximity to the polymer matrixes. On the other hand, Au and Pd existed in exactly the same position, indicating alloy formation (Figure 2). EDS line analysis corroborated this interpretation (Figure 2).

To determine the effect of Co in the reaction, several control experiments were conducted (Scheme 13). PICB-Co showed no activity for the oxidation (Scheme 13a, iii). When a mixture of PICB-Au and PICB-Co was used for an activated alcohol (benzylic alcohol), moderate selectivity toward the amide was obtained (Scheme 13a, iv). On the other hand, PICB-Au with $CoCl_2$ gave low reactivity (Scheme 13a, v). When PICB-Au/Co was used for the reaction of a nonactivated alcohol (aliphatic alcohol), a lower yield than that obtained with PICB-Au was achieved, but there was good amide selectivity (Scheme 13b, ii). Combining these experimental results, we postulated two main roles of Co in the oxidative amidation: (1) control of the oxidation ability due to the presence of Co particles in the polymer matrix in order to keep the concentration of aldehyde low and to suppress imine formation; (2) facilitation of hemiaminal formation or suppression of imine formation.

The selectivity of PICB-Au/Pd in favor of the imine can be explained by electronic effects of the alloy surface. The more electropositive nature of Pd compared with Au results in strong Lewis acid sites on the surface of the alloy nanoclusters,[8a] which

Scheme 13. Control Experiments



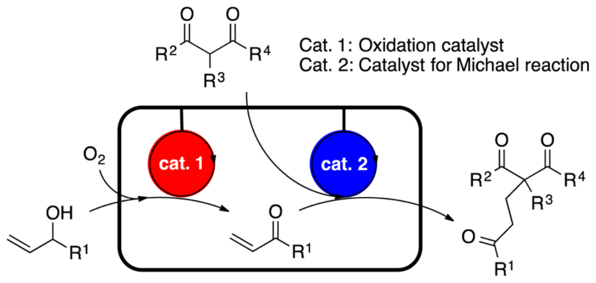
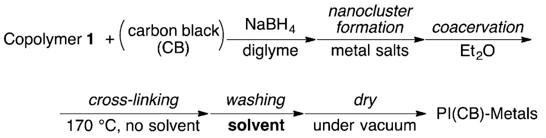


Figure 3. TOP in the confined environment of a bifunctional heterogeneous catalyst.

Table 6. Preparation of Boron-Containing Catalysts



entry	metal salt(s)	solvent	catalyst
1	$AuClPPh_3$	H_2O, THF, DCM	PI-Au
2	$AuClPPh_3$	DCM	PI-Au/B
3	none	DCM	PI-B
4	none	DCM	PICB-B
5	$AuClPPh_3$, $Pd(OAc)_2$	DCM	PICB-Au/Pd/B
6	$AuClPPh_3$, $[RuCl_2(p\text{-cymene})]_2$	DCM	PICB-Au/Ru/B

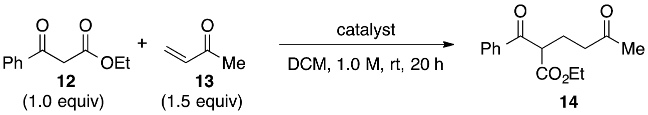
facilitates dehydration of the hemiaminal intermediates in cooperation with the acidic property of TFE as the solvent.

4. SEQUENTIAL AEROBIC OXIDATION−MICHAEL ADDITION CATALYZED BY POLYMER-INCARCERATED AU/PD ALLOY NANOCLUSTERS WITH BORON[19]

4.1. Tetraalkoxyborate Catalyst Derived from $NaBH_4$ for the Michael Reaction

Enzymes and multienzyme complexes can realize multistep cascade reactions in confined reaction environments.[1b] We were interested in constructing enzyme-like multifunctional immobilized catalysts where two distinct organic transformations could proceed: for example, a TOP for aerobic oxidation of allylic alcohols and a subsequent Michael addition reaction (Figure 3).

Table 7. Catalyst Screening for the Michael Reaction



entry	catalyst (mol %)	yield (%)[a]
1	PI-Au (Au:5)	<5
2	PI-Au/B (Au:2, B:46)	>95
3	PI-B (B:5)	>95
4[b]	PICB-B (B:5)	>95
5−13[b]	second to 10th uses of recovered catalyst in entry 4	93 to >95

[a]Determined by ^1H NMR analysis. [b]THF was used as the solvent.

We first investigated the Michael addition reaction of the 1,3-dicarbonyl compound **12** with vinyl ketone **13** in the presence of various PI catalysts prepared by the procedures shown in Table 6. When PI-Au prepared by the standard procedure (Table 6, entry 1) was used, no reaction took place (Table 7, entry 1). Interestingly, the catalyst prepared without aqueous washing (Table 6, entry 2) afforded full conversion to the Michael adduct **14** (Table 7, entry 2). Careful analysis revealed that a considerable amount of boron was contained in this catalyst. Furthermore, the Michael reaction proceeded in the presence of PI-B without Au nanoclusters (Table 6, entry 3; Table 7, entry 3). In light of the reports about Michael reactions catalyzed by tetraalkoxyborate complexes derived from sodium borohydride,[20] the real active species should be a similar borate complex formed from alkoxy moieties in polymers and sodium borohydride. ^{11}B cross-polarization magic-angle-spinning NMR experiments confirmed the existence of tetraalkoxyborate complexes in the immobilized catalysts. A PICB-B catalyst containing CB gave excellent results in THF (Table 6, entry 4; Table 7, entry 4). This catalyst could be recovered by simple filtration and reused 10 times without significant loss of activity (Table 7, entries 5−13)

4.2. Sequential Aerobic Oxidation−Michael Addition Reaction Catalyzed by Bifunctional Heterogeneous Catalysts

We next carried out the sequential aerobic oxidation−Michael reaction from allylic alcohol **15** and keto ester **12** using

Scheme 14. Recyclability of Catalysts

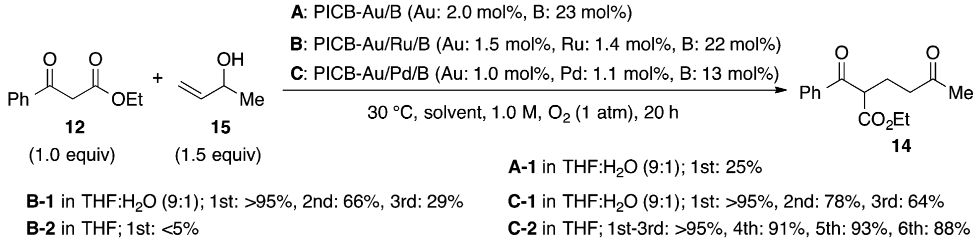
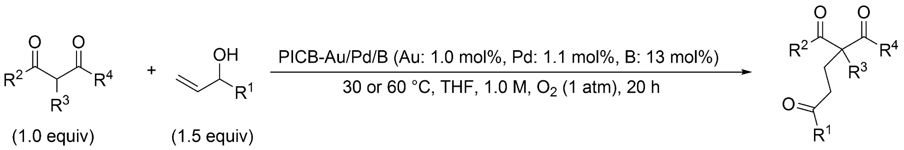
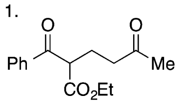
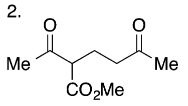
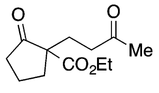
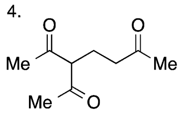
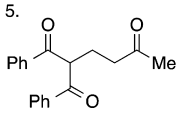
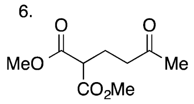
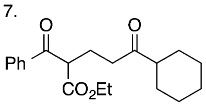
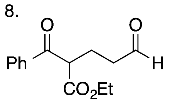
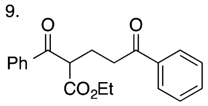
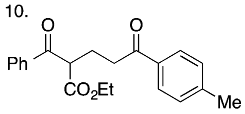
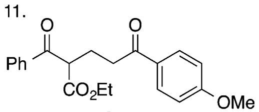
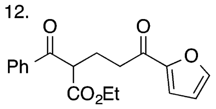
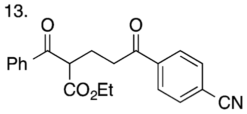
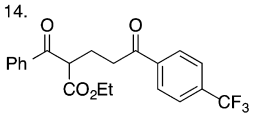


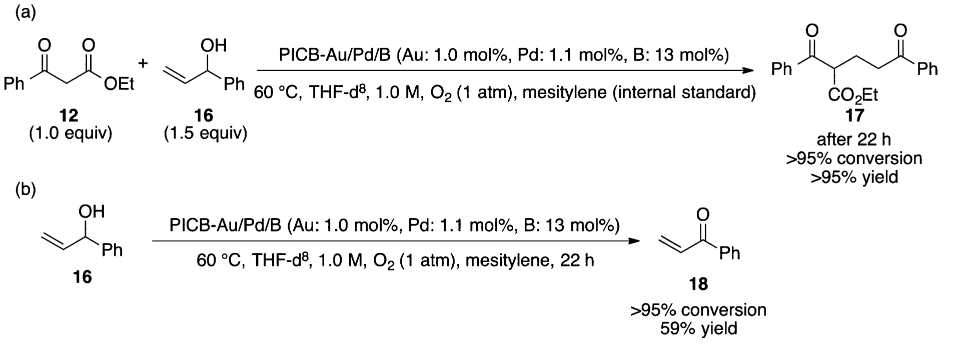
Table 8. Substrate Scope for the Oxidation−Michael Addition Reaction



1.  30 °C, 95% (>95%)[a]	2.  30 °C, 98%	3.  30 °C, 97%	4.  30 °C, 82%
5.  30 °C, 86%	6.  60 °C[b], 88%	7.  60 °C[c], 87%	8.  30 °C, 83%
9.  60 °C[c], 95%	10.  60 °C[c], 94%	11.  30 °C[c], 89%	
12.  60 °C[c], 93%	13.  60 °C[c], 98%	14.  60 °C[c], 98%	

[a]The reaction was conducted under air (atm.). [b]2.0 equiv of alcohol was used. [c]1.1 equiv of alcohol was used.

Scheme 15. Advantage of the TOP



PICB-M/B as bifunctional catalysts. The PICB-Au/B catalyst afforded the desired Michael adduct **14** in low yield (Scheme 14A-1). We screened various bimetallic nanoclusters and found that PICB-Au/Ru/B and PICB-Au/Pd/B gave excellent results in a THF−water cosolvent system (Scheme 14B-1,C-1). We then studied the recovery and reuse of these catalysts; the yield of **14** gradually dropped in both cases (Scheme 14B-1,C-1). Because of the aqueous reaction conditions, leaching of boron

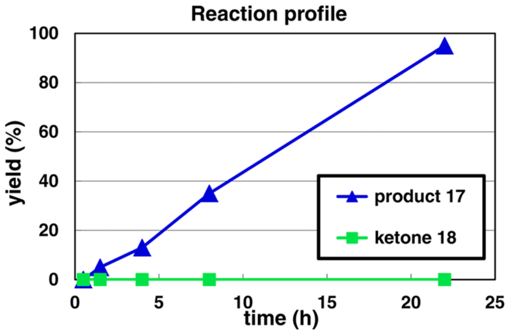
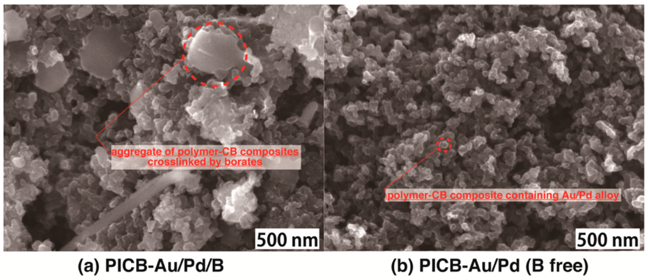


Figure 4. Time course of the oxidation–Michael reaction.



(a) PICB-Au/Pd/B (b) PICB-Au/Pd (B free)

Figure 5. SEM analysis of PICB catalysts.

took place. Although the PICB-Au/Ru/B catalyst showed no activity at all in anhydrous THF (Scheme 14B-2), PICB-Au/Pd/B performed well for the tandem reaction even under anhydrous conditions and withstood six cycles of recovery and reuse while maintaining high activity (Scheme 14C-2).

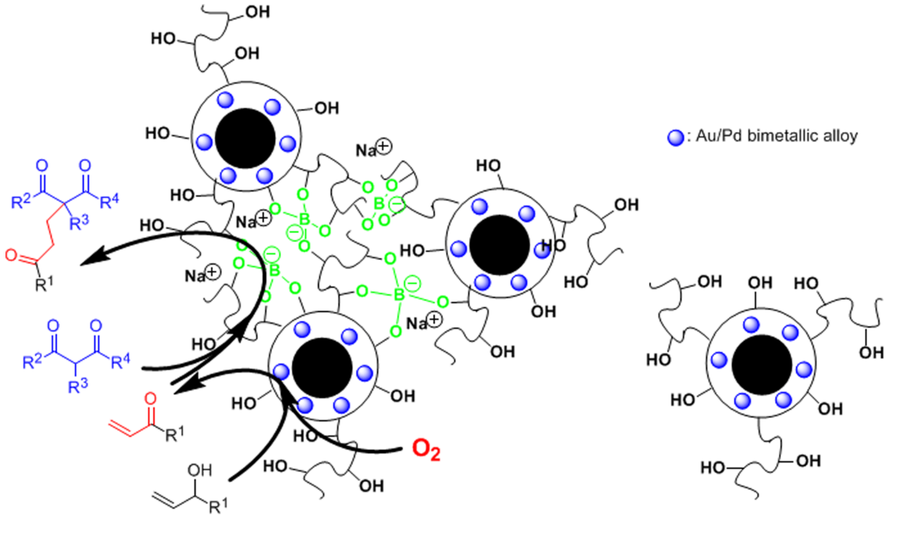
We examined the scope of the sequential oxidation–Michael addition reaction using PICB-Au/Pd/B (Table 8). Mixtures of allylic alcohols and various β-keto esters afforded the desired products in excellent yields (entries 1–3). 1,3-Diketones gave Michael adducts in high yields (entries 4 and 5). A malonate also reacted at a slightly elevated temperature to afford the desired product (entry 6). When bulky alcohols with high molecular weight were employed, the use of 1.1 equiv of the alcohol was sufficient to obtain the desired product in excellent yield (entries 7, 9–14). Allylic alcohol could react to afford the desired aldehyde in high yield (entry 8). We also confirmed that the reaction proceeded smoothly even under atmospheric air (entry 1).

The time course of the tandem reaction was studied using ^{1}H NMR spectroscopy (Scheme 15a). The yield of the product increased linearly throughout, but we could not detect α,β-unsaturated ketone **18** (Figure 4). On the other hand, when the oxidation of allylic alcohol **16** was conducted under the same reaction conditions, only a 59% yield of **18** was obtained despite full conversion of **16** (Scheme 15b). This was due to side reactions such as polymerization. We were therefore able to clearly show the advantage of our TOP in the aerobic oxidation–Michael reaction.

4.3. Structure of the Bifunctional Catalyst

The structures of PICB catalysts were analyzed by scanning electron microscopy (SEM). CB has a hollow spherical structure with a diameter of 45 nm. We found that an equivalent weight mixture of CB and copolymer **1** led to a sphere with a diameter of 55 nm; copolymer **1** was adsorbed on and spread over the surface of CB uniformly. An almost identical structure was observed for the PICB-Au/Pd catalyst after immobilization of Au/Pd alloy followed by aqueous washing (Figure 5b). On the other hand, PICB-Au/Pd/B gave a distinct structure in which uneven and large (>100 nm) spheres were involved (Figure 5a).

These large spheres may represent aggregates of polymer–CB units inter-cross-linked with borate derived from $NaBH_4$ and hydroxy moieties of the polymer (Figure 6a). The Brunauer–Emmett–Teller surface area based on the adsorption/desorption isotherm supported this structural difference. The boron-free catalyst, PICB-Au/Pd, had a larger surface area (56.4 m^2/g) than PICB-Au/Pd/B (19.1 m^2/g). Two distinct reactions were catalyzed by the different parts within the nanosized confined environment composed of self-assembled frameworks. Aerobic oxidation proceeded on the bimetallic alloy clusters in the polymer–CB units, and the resulting α,β-unsaturated ketone might react immediately, catalyzed by borate that inter-cross-links these nanocomposites (Figures 5a and 6a).



(a) PICB-Au/Pd/B (BET surface area: 19.1 m^2/g) (b) PICB-Au/Pd (BET surface area: 56.4 m^2/g)

Figure 6. Models of (a) PICB-Au/Pd/B and (b) PICB-Au/Pd.

5. CONCLUSION

Gold and multimetallic nanoclusters immobilized on a polystyrene-based copolymer, termed polymer-incarcerated metal nanoclusters, can be applied to tandem oxidative processes based on the aerobic oxidation of alcohols. Different types of multifunctional heterogeneous catalysts containing gold nanoclusters were developed, depending on the intended purposes. These catalysts possess various advantages and features. (1) The polymer support swells in some solvents to provide good diffusion of substrates between solid and liquid phases. (2) Molecular oxygen is used as the oxidant. (3) Highly reactive and unstable intermediates resulting from oxidation can be used. (4) Multimetallic structures, such as combinations of metal species and microscopic morphologies (alloy or distinct clusters), are key for the reactivity and selectivity of reaction pathways. (5) The catalysts can be recovered and reused without loss of activity, aggregation, and leaching of metal nanoclusters. These heterogeneous catalysts can be prepared through self-assembly of different components: polymer, CB, metal salts, and reductant. Their nanosized morphology is somewhat fuzzy; however, it is well-organized on the micrometer scale.

Although this dual nature results from simple and ingenious techniques, namely, microencapsulation and polymer incarceration, it is highly beneficial for the construction of multifunctional catalysts for TOP. Mechanistic studies and structural analyses of these catalysts are ongoing in order to construct guidelines for how metals should be combined to obtain the desired selectivity and reactivity. Further sophisticated design of functionality in a heterogeneous catalyst for more complicated tandem oxidative processes could lead to the creation of a "nanofactory", where multiple catalysts located in nanoscale reaction environments will produce more complex molecules, perhaps exceeding multienzyme complexes.

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Notes

The authors declare no competing financial interest.

Biographies

Hiroyuki Miyamura was born in 1982 in Saitama, Japan. He received his B.S. degree in Pharmaceutical Sciences in 2004 from The University of Tokyo. In 2006 and 2009, he received his M.Sc. and Ph.D. degrees, respectively, at the same university under the supervision of Professor S. Kobayashi. In 2009, just after receiving his Ph.D. degree, he was appointed Assistant Professor in the Department of Chemistry at The University of Tokyo. During the period 2006−2009, he received the Japan Society for the Promotion of Science (JSPS) Fellowship for Japanese Junior Scientists. In 2010, he was the winner of the Reaxys Ph.D. Prize. His current research interests include multifunctional heterogeneous catalysis, metal nanocluster catalysis, and reaction integration, such as tandem reactions and flow synthesis.

Shū Kobayashi studied at the University of Tokyo, receiving his Ph.D. in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as an assistant professor, he was promoted to lecturer and then associate professor at Science University of Tokyo (SUT). In 1998, he moved to the Graduate School of Pharmaceutical Sciences at the University of Tokyo as a full professor. In 2007, he was appointed to his current position as a professor of organic chemistry in the Department of Chemistry, Faculty of Science, the University of Tokyo, and is now head of the department. He has held various visiting professorships, including ones at Université Louis Pasteur, Strasbourg (1993), Kyoto University (1995), Nijmegen University (1996), Philipps University of Marburg (1997), and Université Paris-Sud (2010). Professor Kobayashi has wide-ranging research interests that include the development of new synthetic methods and novel catalysts, organic reactions in water, solid-phase synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry. He has held numerous named lectureships and is a recipient of many prestigious awards, including the Chemical Society of Japan Award for Young Chemists (1991), Ciba-Geigy Research Foundation Award (1994), Springer Award in Organometallic Chemistry (1997), IBM Science Award (2001), Organic Reactions Lecturer (2002), Nagoya Silver Medal (2002), Mitsui Chemical Catalysis Science Award (2005), JSPS Prize (2005), the Arthur C. Cope Scholar Award from the American Chemical Society (2006), Howard Memorial Lecturer (2006), C. S. Hamilton Award (2007), Merck-Cambridge Lecturer (2007), Humboldt Research Award (2013), and Green Chemistry Minister of Education Award (2013).

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