ChemComm

COMMUNICATION

RSCPublishing

View Article Online View Journal | View Issue

Cite this: Chem. Commun., 2013, 49, 9917

Received 13th August 2013, Accepted 3rd September 2013

DOI: 10.1039/c3cc46204h

www.rsc.org/chemcomm

A heterogeneous layered bifunctional catalyst for the integration of aerobic oxidation and asymmetric C–C bond formation[†]

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The design and synthesis of a heterogeneous bifunctional chiral catalyst for the sequential aerobic oxidation–asymmetric Michael reactions between primary allylic alcohols and dibenzyl malonate are described. Interestingly, we found that layering bimetallic nanoparticles over the organocatalyst, within the chiral composite material, is crucial for catalytic activity.

The *in situ* generation and elaboration of highly reactive/unstable compounds in reactions is a crucial concept in organic synthesis. This concept allows chemists to take advantage of the high chemical reactivity of the compounds when isolation of the desired intermediates is impossible.¹ Thus, methods to carry out two or more transformations in one reaction pot are highly desirable. A well-established method is the tandem oxidation process (TOP)² and recently, one-pot organo-catalytic reactions that introduce chirality into the final product are gaining much attention.^{3–5} On the other hand, heterogeneous catalysts have attracted much attention in the field of catalysis due to the advantages that they offer, such as ease of handling, and their industrial applications.⁶ To the best of our knowledge, there are no reported examples of a heterogeneous bifunctional chiral catalyst for an asymmetric TOP with molecular oxygen as the terminal oxidant.

Our group has established a method for immobilizing metal nanoparticles (NPs) onto a polymer support and we have already demonstrated that these polymer-incarcerated (PI) metal catalysts effectively facilitate aerobic oxidations, reductions, coupling reactions and other C–C bond formations with little to no leaching of metal from the polymer support.^{7–9} Furthermore, the activity of the PI metal catalysts was shown to be very high and comparable or, in some cases, superior to that of the original homogeneous metal catalysts when small metal NPs were formed and immobilized.^{10,11} Recently, we succeeded in catalyzing several TOPs with oxygen as the terminal oxidant.^{12–15} In these TOPs, the reaction intermediate was either a ketone or an aldehyde generated *in situ*, *via* the aerobic oxidation of the corresponding secondary or primary alcohol.

We were interested in whether metal NPs could be immobilized together with a chiral moiety to form a heterogeneous bifunctional chiral catalyst that could be used in an asymmetric TOP with oxygen as the terminal oxidant. The concept of bifunctional catalysis is best exemplified in nature with multienzyme complexes, where the spatial arrangement of enzymes within such complexes is optimized such that a neighboring enzyme within the same complex preferentially transforms the intermediate produced by another enzyme.¹⁶⁻¹⁸ We envisioned a heterogeneous bifunctional chiral catalyst that would mimic enzymes by providing a confined environment¹⁹ for catalysis to take place, thereby offering the advantage of rate enhancement for the asymmetric TOP. In addition, the facile separation of catalysts from the product and the prevention of probable undesired interactions between the two catalysts in a completely homogeneous system are possible *via* immobilization (Fig. 1).^{20–22}



Fig. 1 Preventing undesired interactions between catalysts.

Herein, we report a novel layered heterogeneous bifunctional chiral catalyst consisting of metal NPs and a chiral Jørgensen–Hayashi-type organocatalyst (OC) supported on different polymers. This catalyst could be applied to the integration of aerobic oxidation of primary allylic alcohols to the corresponding α , β -unsaturated aldehydes and asymmetric 1,4-Michael addition of a malonate to these newly generated aldehydes.

We began the investigation by screening several Jørgensen-Hayashi-type OCs and co-monomers²³ and immobilizing the most suitable one (1) with acrylamides *via* suspension copolymerization with optimized amounts of *N-tert*-butylacrylamide (3), *N*,*N'*-methyl-enebismethacrylamide (4) and dimethyl 2,2'-azobis(2-methyl-propionate) (V-601 initiator) to form polymer beads 5 containing the OCs (Fig. 2a).²³ The beads exhibited activity for the

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Fig. 2 Fabrication procedure for (a) polymer-supported OC (5); (b) PI(Au/Pd)– CO catalyst (6); (c) IOC/PI/CB–Au/Pd catalyst (7). Blue represents the layer containing OC 1 while red represents the layer containing Au–Pd alloy NPs.

asymmetric Michael reaction between *trans*-cinnamaldehyde and dibenzyl malonate, affording the desired product in quantitative yield with >90% ee under our optimized reaction conditions.²³ We chose acrylamides as co-monomers after taking into account commercial availability, hydrophilicity and ease of handling of the resulting beads.²³

We then proceeded to incorporate Au-Pd bimetallic alloy NPs with polymer beads 5 to form a heterogeneous bifunctional chiral catalyst. In one of our previous TOP reports, PI Au-Pd alloy NPs with carbon black as a secondary support (PI/CB-Au/Pd) demonstrated high activity for the aerobic oxidation of secondary allylic alcohols to the corresponding α,β -unsaturated ketones,¹⁴ and we expected similar activity for primary allylic alcohols. We examined the effect of the ratio of Au: Pd on the aerobic oxidation of cinnamyl alcohol to trans-cinnamaldehyde and determined that a 1:1 ratio was the best, and that Au or Pd alone was not efficient.²³ The styrene-based copolymer with cross-linking moieties 2 that is used during the fabrication of PI heterogeneous catalysts^{10,12-14} was employed for the incorporation of Au-Pd alloy NPs and beads 5. Polymer beads 5 were added to polymer 2, followed by the addition of Au and Pd salts for the formation of bimetallic alloy NPs (Fig. 2b). After coacervation and cross-linking of polymer 2,10 we obtained the PI(Au/Pd)-coated OC (PI(Au/Pd)-CO) 6. We expected polymer 2 to form a coating around polymer beads 5, assisted by the interactions between the polar moieties found on each polymer, such that the alloy NPs would be in the outer layer of this two-layered heterogeneous catalyst, while the OC would exist in the inner layer. Simultaneously, we also prepared another two-layered heterogeneous bifunctional chiral catalyst, where the placement of NPs and the OC was reversed. This was accomplished by first preparing the PI/CB-Au/Pd catalyst based on a method established by us in our previous work¹⁴ and then coating it with the polyacrylamide that contains OC 1 via pseudo suspension copolymerization to form an immobilized-organocatalyst-coated (IOC) PI/CB-Au/Pd catalyst (IOC/PI/CB-Au/Pd) 7 (Fig. 2c). The target mole ratio of Au to OC was 1:5 in both cases.

Next, we investigated the activity of these catalysts when applied to our model reaction for the desired asymmetric TOP, with cinnamyl alcohol and dibenzyl malonate as the model substrates (Table 1). The aerobic oxidation of cinnamyl alcohol to the corresponding *trans*-cinnamaldehyde would be catalyzed by Au–Pd alloy NPs and the *trans*-cinnamaldehyde intermediate

Table 1 Optimization of conditions for the asymmetric TOP

ОН			CO ₂ Bn	n	catalyst AcOH (20 mol%)		* 00-Bn	
Ph 2 8	Ph 8a (2 eq)				EtOH/H ₂ O (1 30 °C, O ₂	:1, C = 0.25 M) (1 atm), 24 h	Ph 10a C	O ₂ Bn
Entry	Catalyst	(m	nol%)			Conv. ^{<i>a</i>} (%)	Yield ^b (%) ee^{c} (%)
1	6 (Au =	1, 1	Pd = 1,	OC = 5)	76	nd	91
2	7 (Au =	1, 1	Pd = 1,	OC = 5)	nr	_	_
3	PI/CB-A	u/F	d (Au,	Pd = 1	8 1 (5)	39	nd	85
4	6 (Au =	2, 1	Pd = 2,	OC = 1	0)	97	75	90

^{*a*} Conversion of **9** based on ¹H NMR analysis (nr = no reaction). ^{*b*} Isolated yield (nd = not determined). ^{*c*} Determined by chiral HPLC analysis after oxidation to the corresponding methyl ester.

would then undergo an asymmetric 1,4-Michael addition, facilitated by OC-containing polymer beads 5, to afford the desired asymmetric adduct. Our initial screening revealed that only PI(Au/Pd)–CO **6** demonstrated catalytic activity and satisfactory conversion of dibenzyl malonate was observed (entry 1). It was a challenge to determine the best reaction conditions for the asymmetric TOP, as some reaction conditions that are suitable for the first step may not be so for the second step. Fortunately, having water as a co-solvent did not pose any problem for the aerobic oxidation and in fact, might have promoted the aerobic oxidation.^{15,24,25} Interestingly, we observed that the aerobic oxidation of the allylic alcohols proceeded smoothly even in the presence of acetic acid that is required to accelerate the OC-catalyzed 1,4-Michael addition;²⁶ aerobic oxidation is usually difficult under acidic conditions.²⁷

On the other hand, the reaction did not proceed with catalyst 7 (entry 2), suggesting that the layering order of catalysts within the composite structure affects its ability to facilitate this tandem reaction. As a control, we also performed the reaction using the PI/CB-Au/Pd heterogeneous catalyst and the homogeneous OC 1 (entry 3), and we found that the conversion was poor and the enantioselectivity decreased slightly.

After further optimization using catalyst **6**, we adopted the conditions shown in entry 4 of Table 1 as the optimized conditions.²³ It should be noted that no leaching of Au or Pd was detected under these reaction conditions.²⁸

To demonstrate the generality of this novel layered heterogeneous bifunctional chiral catalyst, we attempted the reaction using the optimized conditions with cinnamyl alcohol analogues as substrates (Table 2). The catalyst could be applied to a variety of substrates including aliphatic allylic alcohols and heteroatom-containing allylic alcohols. The yields ranged from moderate to excellent with high enantioselectivity observed for many substrates.

We have demonstrated that the order of the layers of catalysts for this heterogeneous bifunctional chiral catalyst is crucial for its catalytic activity (Table 1). IOC/PI/CB-Au/Pd catalyst 7, in which the bimetallic alloy NPs are in the inner layer and the OC is in the outer layer, gave no reaction (Table 1, entry 2). A possible reason would be that the OC, which contains an amine moiety, deactivated the bimetallic alloy NPs during the fabrication of the catalyst. From our control experiment, we confirmed that the unsupported OC has a deactivating effect on the bimetallic alloy NPs (entry 3). However, some activity was still observed in the case of the latter as compared to the zero activity of the former (entry 2), which suggests poisoning of the bimetallic alloy NPs *via* some kind of coordination by

Table 2 Substrate scope

R + 8 (2 eq)		CO ₂ Bn	PI(Au/Pd)-0 AcOl	CO 6 (2 mol% Au) H (20 mol%)	* 00 Pr	
		CO ₂ Bn ⁻ 9	EtOH/H ₂ O (1:1, C = 0.25 M) 30 °C, O ₂ (1 atm), 24 h		R 10 CO ₂ Bn	
Entry	8	R		Yield ^a (%)	ee^{b} (%)	
1	8a	Ph		75	90	
2	8b	p-Me-	C_6H_4	79	91	
3	8c	p-Me0	$D-C_6H_4$	66	87	
4	8d	p-F-C	$_{5}H_{4}$	80	91	
5	8e	p-Cl-C	C_6H_4	83	91	
6	8f	$p-O_2N$	$-C_6H_4$	35	86	
7	8g	<i>p</i> -Ph-0	C_6H_4	56	91	
8	8ĥ	2-Nap	hthyl	61	74	
9	8i ^c	Me	-	34	83	
10	8j	2-Thie	enyl	42	87	

^{*a*} Isolated yield. ^{*b*} Determined by chiral HPLC analysis after oxidation to the corresponding methyl ester for **10a–10h** and **10j**, and direct analysis for **10i**. ^{*c*} 4 equivalents of **8i** was used.

acrylamides²⁹ during fabrication of the composite catalyst, and highlights the importance of microscopic structural differences between catalysts resulting from layering order. We were able to remove all these undesired interactions between the NPs and the OC by arranging the catalysts in the manner described in Fig. 2b to form PI(Au/Pd)–CO catalyst **6**.

Scanning transmission electron microscopy (STEM) and energy-dispersive X-ray spectroscopy (EDS) analyses of catalyst **6** revealed that while Au and Pd were found at the same positions, indicating the presence of an alloy structure, Si was found at distinct and separate locations from Au/Pd within the same polymer particle (Fig. 3a). EDS line analysis of the clusters within the polymer also suggests that where Au and Pd exist, Si does not.²³ Regions with Si indicate the presence of the OC and we believe that the results of this EDS analysis reinforce the notion that undesired interactions between bimetallic alloy NPs and OC were removed using our strategy and catalyst preparation. Furthermore, similar analyses of inactive catalyst 7 revealed that Au, Pd and Si were all found at the same sites within the catalyst (Fig. 3b), indicating that some kind of interaction may exist between OC and bimetallic alloy NPs, causing the composite catalyst to become inactive.

In summary, we have developed a novel heterogeneous bifunctional chiral catalyst by coating a polymer-supported OC with a styrene-based copolymer that can immobilize and incarcerate Au–Pd alloy NPs. Undesired interactions between OC and NPs were



Fig. 3 (a) PI(Au/Pd)–CO 6 (above). (b) IOC/PI/CB–Au/Pd 7 (below). From left to right: STEM image, mapping of Au, mapping of Pd, mapping of Si. Note: pink = Au, green = Pd and orange = Si.

avoided using this strategy. The order of the two layers containing the respective catalysts was crucial and it determined the catalytic activity of the composite catalyst for the asymmetric TOP. Good yield and excellent enantioselectivity were observed for many substrates, demonstrating the effectiveness of this catalyst, and offering proof of concept for this novel method for preparing a heterogeneous bifunctional chiral catalyst. This preparation method may be applied to other catalytic systems where undesired interactions between two types of catalysts must be avoided.

This work was partially supported by a Grant-in-Aid for Scientific Research from JSPS, MEXT (Japan) and JST. T. Yasukawa thanks JSPS for the Research Fellowship for Young Scientists. We thank Mr Noriaki Kuramitsu (The University of Tokyo) for STEM and EDS analyses.

This communication is dedicated to Professor Irina Petrovna Beletskaya for her great contributions to metalcatalyzed reactions.

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