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Reusable nano-sized chiral bisoxazoline catalysts

Fumiyasu Ono,[b] Shuji Kanemasa[a,*] and Junji Tanaka[a]

[a]Institute for Materials Chemistry and Engineering, CREST of JST (Japan Science and Technology Agency), Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan

[b]Department of Molecular and Material Sciences, Graduate School of Engineering Sciences, Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan

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Abstract—The nano-sized gold particle-based chiral catalyst having two kinds of alkyl thiol spacers, one of which is substituted with the chiral bisoxazoline/copper(II) complex at the end, behaves as reusable homogeneous catalyst. This gold particle complex acts as nearly homogeneous catalyst in the ene reaction between 2-phenylpropene and ethyl glyoxylate in dichloromethane, while it undergoes dense aggregation when diluted with hexane so as to be separated by simple filtration. Thus, the catalyst can be recovered after the completion of reaction by the repeated sequences of solvent exchange, centrifugal treatment, and decantation, followed by the recharge of substrates, and the situation is ready for the second reaction.

Unlike homogeneous molecular catalysts, immobilized heterogeneous catalysts have a great synthetic advantage that these can be recovered through filtration after the completion of reaction and further can be reused for the next reaction. However, the limited mobility brings about a serious decrease of catalytic activity. Thus, the effective reuse of reactive catalysts has been achieved at the expense of catalytic activity.[1–4] This dilemma has remained unsolved.[5]

The authors have noticed that the metal complexes derived from nano-sized particles, the surface of which is modified with alkyl chains having a ligand at the terminus, would work as effective catalysts.[2–4] High synthetic advantage can be expected for such catalysts due to the mobility and immobility properties. They would act as nearly homogeneous catalysts at the stage of reaction in one solvent, and at the work-up stage they are aggregated in another solvent so that the catalysts can be separated through filtration from the products, which are soluble in the solvent. If the complex catalysts are stable enough to be isolated, repeated use of the catalysts may be attained. However, to the best of our knowledge, no precedent reports are known for such effective usage of nano-sized particle catalysts.

In this letter, we will report new types of nano-sized gold particle catalysts, which are modified with two alkyl chains, one with simple alkyl sulfides and the other with alkyl sulfides having copper(II) complexes of chiral bisoxazoline ligands **2**–**5** at the terminal (Fig. 1). These catalysts are highly dispersed in dichloromethane, but aggregate in hexane so that these can be separated from the solvent through simple filtration. Ene reactions between 2-phenylpropene and ethyl glyoxylate were catalyzed by the nano-sized complex catalysts **Au**-*n*/Cu(II) giving high yields of ene-reaction product with satisfactory enantioselectivity. Repeated use of the catalysts was performed without serious loss of catalytic activity.

Some examples are known for the heterogeneous chiral catalysts, which have been used in the catalyzed enantioselective ene reactions. Ene reaction between 2-phenylpropene and ethyl glyoxylate in the presence of the PEG-anchored (*R*)-BOX/Ph complex of $Cu(OTf)_2$ gave a satisfactory result for both yield and enantioselectivity.[6] Recently, Cu-exchanged zeolite Y modified by (*R*)-BOX/Ph ligand was examined in the same ene reaction, however, the recovered catalyst was much less reactive than the initial one showing a lower enantioselectivity in the second reaction (80–65% ee).[7]

Bisoxazoline ligands **2**–**5** were synthesized starting from diethyl methylmalonate (**6**). One typical example is shown for the synthesis of **5** in Scheme 1. Methylmalonate

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Keywords: Nano-sized particle; Chiral catalyst.

* Corresponding author. Tel.: +81 925837802; fax: +81 925837875; e-mail: kanemasa@cm.kyushu-u.ac.jp

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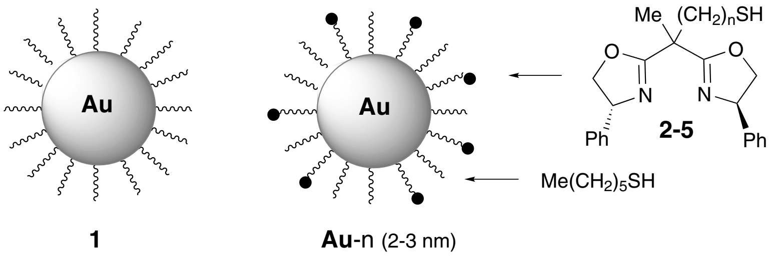
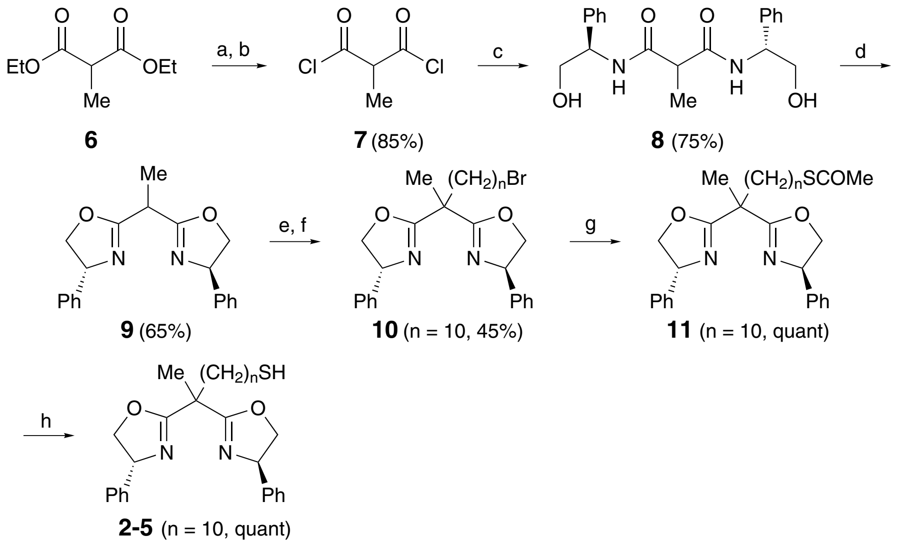


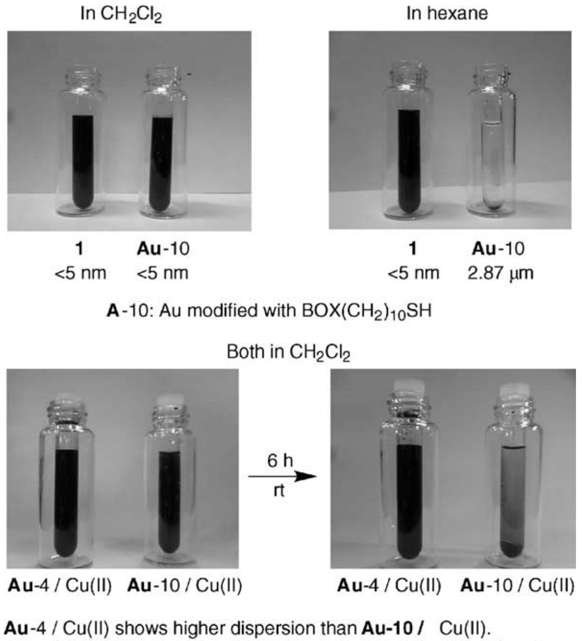
Figure 1. Au-modified chiral catalysts.



Scheme 1. Reagents and conditions: (a) KOH, H_2O–EtOH = 1:3 v/v, reflux, 4 h; (b) $SOCl_2$ (2.2 equiv), reflux, 3 h; (c) (*R*)-2-phenylglycinol (2 equiv), Et_3N (2 equiv), CH_2Cl_2, rt, 12 h; (d) MsCl (2 equiv), Et_3N (2 equiv), CH_2Cl_2, rt, 16 h; (e) *n*-BuLi (1.1 equiv), −78 °C, THF; (f) $Br(CH_2)_{10}Br$ (4 equiv), rt, 6 h; (g) MeCOSK (1.1 equiv), DMF, rt, 15 min; (h) NaOH, MeOH, rt, 15 min.

ester **6** was hydrolyzed with aqueous potassium hydroxide and chlorinated with thionyl chloride giving methylmalonyl chloride (**7**), which was then reacted with (*R*)-phenylglycinol to give bisamide **8**. Amide **8** was mesylated and cyclized into bisoxazoline **9**.[8] Deprotonation of **9** with butyllithium at −78 °C, followed by the alkylation with 1,10-dibromodecane, gave ω-bromodecanyl bisoxazoline **10**. Treatment of **10** with a potassium thioacetate led to thioacetate derivative **11**, which was then exposed to alkaline hydrolysis at room temperature for 15 min to give the target chiral ligand **5** in 19% of the total yield starting from **6**. Other chiral bisoxazoline ligands having C_4 **2** ($n = 4$), C_6 **3** ($n = 6$), and C_8 linkers **4** ($n = 8$) were similarly synthesized.

Hexanethiol-modified nanoparticle (diameter: 2–3 nm) **1**,[9] which was prepared by reduction of $HAuCl_4{\cdot}4H_2O$ with sodium borohydride in the presence of hexanethiol,[10] was treated with bisoxazoline **5** by stirring at room temperature for 24 h giving the hybrid chiral ligand **Au**-10, which contains 0.32 mmol/g of bisoxazoline ligand.[11,12] Although hexanethiol-modified gold particle **1** forms highly stabilized dispersion both in dichloromethane and hexane, bisoxazoline-modified particle **Au**-10 readily aggregates in hexane as less polar solvent (top two in Fig. 2). The size of particles included



Au-4 / Cu(II) shows higher dispersion than **Au-10 /** Cu(II).
Au-4 / Cu(II) keeps a high dispersion state even after centrifugal treatment (20,000 rpm, 10 min)

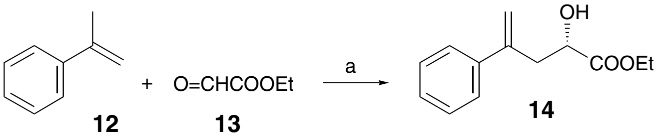
Figure 2. Dispersion and aggregation property of Au particles in different solvents.

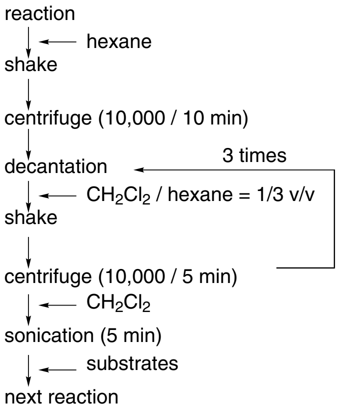
in the high dispersion was smaller than 5 nm, but that of **Au**-10 in hexane was estimated to be ca. 3 μm.[13] Copper(II) triflate complex derived from **Au**-4 in dichloromethane was stable enough to keep high dispersion at least 6 h at room temperature, but the complex of **Au**-10 was readily converted into dense aggregation under similar conditions (bottom two in Fig. 2), indicating that the dispersion degree of copper(II) complex catalysts of **Au**-*n* depends upon the length of the spacer.

Copper(II) triflate complex prepared from **Au**-4 was successfully applied to the enantioselective ene reaction between 2-phenylpropene (**12**) and ethyl glyoxylate (**13**) (Scheme 2). The typical procedure is as follows: A mixture of **12**, **13**, and **Au**-4·Cu(OTf)$_2$ (10 mol % each) in dichloromethane was stirred at room temperature for 5 h. After the reaction is complete (checked by TLC), hexane is added (hexane/CH$_2$Cl$_2$ = 3:1 v/v) and shaken well. The resulting aggregation was centrifuged (10,000 rpm/10 min) and the upper clear solution was separated by decantation. The residue was washed with the combined solvent of hexane/CH$_2$Cl$_2$ and centrifugal separation was applied. After this washing and separation procedure was repeated three times, the extract and washings were combined and evaporated to give ethyl 4-phenyl-4-pentenoate (**14**) as the ene reaction product in 99% yield with an enantioselectivity of 86% ee.[14] A comparable result was obtained in the same reaction in the presence of the molecular catalyst derived from BOX/Ph ligand and copper(II) triflate.[15]

On the other hand, the residue including the catalyst was dissolved in dichloromethane. A clear solution is obtained through sonication for 5 min and the resulting catalyst solution could be reused for the second reaction. This procedure was repeated five times as shown in Scheme 2. Although yields of the ene product **14** gradually decreased in the late reactions, enantioselectivity remained.

A variety of hybrid chiral ligands **Au**-4, **Au**-6, **Au**-8, and **Au**-10 having spacers of different chain lengths were converted into copper(II) triflate complexes and used in the ene reactions between **12** and **13** (Scheme 3). As apparent by comparison of the results shown in Scheme 3, the copper(II) complex derived from **Au**-4, having the shortest spacer of *n* = 4, showed the most effective catalytic activity and recyclic utility. Probably, **Au**-4·copper(II) complex shows the highest dispersion, and hence the minimized aggregation in dichloromethane solution, since the complex parts are buried in an array





recycle	yield/%	ee %
0	99	86
1	94	84
2	90	85
3	87	84
4	80	84

a: **Au**-4 / Cu(OTf)$_2$ (10 mol% each), CH$_2$Cl$_2$, rt, 5 h.

Scheme 2.

$$\mathbf{12} + \mathbf{13} \xrightarrow{a} \mathbf{14}$$

a: **Au**-n / Cu(OTf)$_2$ (10 mol% each), CH$_2$Cl$_2$, rt

	Au-4		**Au**-6		**Au**-8		**Au**-10	
recycle	time/h	yield/% (% ee)	time/h	yield/% (% ee)	time/h	yield/% (% ee)	time/h	yield/% (% ee)
0	5	99 (86)	9	95 (85)	11	97 (85)	16	93 (85)
1	10	99 (84)	20	98 (86)	20	90 (86)	20	80 (85)
2	13	94 (85)	20	73 (85)	20	55 (84)	20	39 (86)
3	24	92 (86)						

Scheme 3.

of neighboring hexanethiol ligands. However, this complex shows the effective aggregation in hexane solution to make large sized particles, which are separable by filtration. This indicates that the size matching of the spacers included in the chiral ligand and the aggregation-inhibiting hexanethiol ligands is essential to attain the homogeneous reusable catalysts.

In conclusion, we have succeeded to develop a new type of gold particle-based chiral copper(II) complex catalyst, which works as almost homogeneous catalyst in the ene reaction between 2-phenylpropene and ethyl glyoxylate in dichloromethane. When the reaction is over, the catalyst can be separated simply by dilution with hexane and centrifugal treatment.

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13. Size of the particles in solution was determined by dynamic light scattering analysis (DLS).
14. Ene reaction was carried out in a centrifuge tube in open air. Stirring was made by a magnetic stirring bar.
15. Although the reaction between **12** and **13** under the catalysis of the BOX/Ph·Cu(OTf)$_2$ complex (10 mol %) was previously reported (20 h at rt, **14**: 66% (80% ee)), [7] we have reexamined in the present work: 4 h at rt, **14**: quant (86% ee).