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Assembled catalysts of titanium and non-cross-linked chiral copolymers for an enantioselective carbonyl-ene reaction

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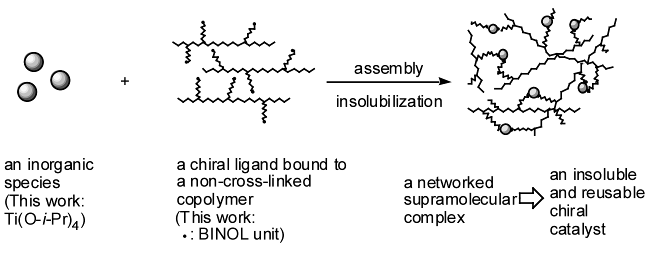
Abstract—New insoluble chiral catalysts were prepared from a self-assembly of $Ti(O\text{-}i\text{-}Pr)_4$ and non-cross-linked copolymers with (*R*)-binaphthol (BINOL) pendant groups. In the presence of one of the chiral catalysts, an enantioselective carbonyl-ene reaction proceeded at room temperature to give an adduct in 85% yield with 88% ee. This insoluble assembled catalyst was easily prepared and reusable. © 2002 Elsevier Science Ltd. All rights reserved.

Immobilization of chiral soluble catalysts is a challenging goal in recent organic chemistry.[1] This approach facilitates the separation of catalysts from the reaction mixtures by filtration, and enables their quantitative recovery and reuse. So far, cross-linked polystyrene resins and silica gels have been utilized as supports for immobilizing the catalysts. Unfortunately, their use often resulted in lower catalytic activity and/or enantioselectivity as compared with their soluble counterparts.[2] To overcome these drawbacks, it is worthwhile to present a novel methodology for creating insoluble and highly efficient catalysts from the standpoint of conceptional and practical significance.

We focused on a self-assembled process between non-cross-linked copolymer ligands and inorganic species for the preparation of highly active and insoluble catalysts: when the inorganic species were added to non-cross-linked copolymers with ligands, both substrates were self-assembled to afford insoluble materials. They were composed of networked and supramolecular complexes in which the copolymers were hooked together by the inorganic species. We envisioned that the complexes would act as highly reactive catalysts, because the copolymers and the inorganic species could construct effective catalytic sites with high affinity to substrates and reactants in the complexes. In fact, recently, we have reported a highly reactive catalyst, which was formed from phosphotungstic acid and an ammonium salt bound to poly(*N*-isopropylacrylamide).[3] The catalyst was insoluble in organic solvents and water, and thus, it was recoverable and reusable. The point to note is that only ppm molar equivalents of this catalyst worked efficiently for epoxidation of allylic alcohols; its turnover number was up to 35 000. Since this self-assembled catalyst exhibited great potentiality, we tried applying this concept to asymmetric synthesis (Scheme 1).[4] In this letter, we report development of new chiral catalysts by our methodology and their application to an asymmetric carbonyl-ene reaction.[5] It is noteworthy that one of the catalysts can be reused five times with retention of its activity and enantioselectivity.

Recently, Nakai and co-authors reported an excellent asymmetric carbonyl-ene reaction catalyzed by a bimetallic titanium complex, in which two binaphthols were bridged by μ-oxodititanium **1** (Fig. 1).[6a] They noted that the reaction of α-methylstyrene with methyl glyoxylate was carried out in the presence of 5 mole% of the titanium complex in CH_2Cl_2 at −30°C for 3 h to provide the corresponding product in 93% yield with 98% ee. We envisioned that this homogeneous catalyst



Scheme 1. Hypothesis of formation of a self-assembled complex for an insoluble and chiral catalyst.

Keywords: asymmetric reactions; ene reactions; polymer support; self-assembly; titanium and compounds.

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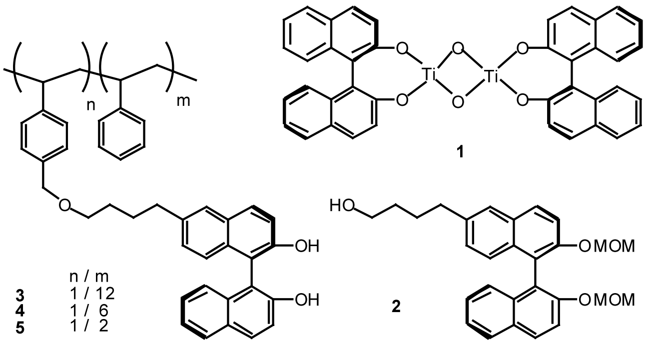


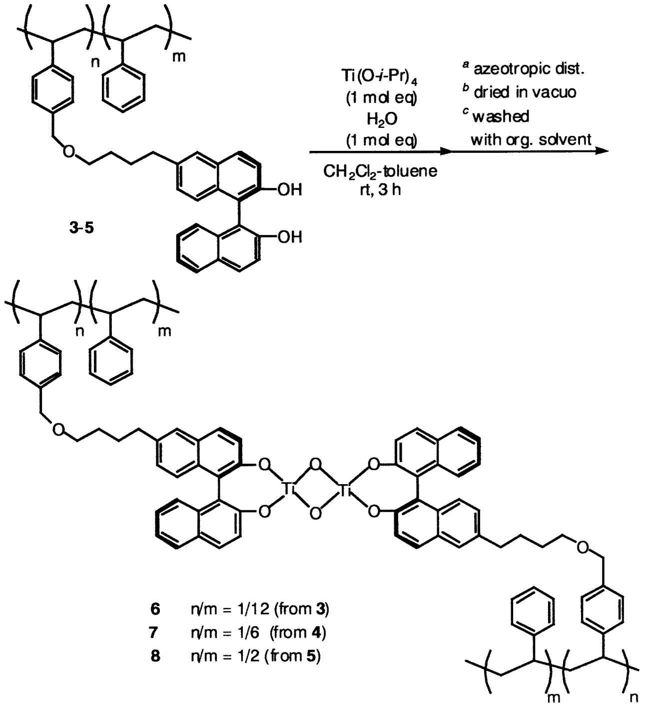
Figure 1.

would be applicable to the self-assembled and insoluble counterpart, wherein binaphthol moieties bound to non-cross-linked copolymer backbones would be cross-bridged by μ-oxodititanium. Therefore, we selected (*R*)-1,1′-bi-2-naphthol (BINOL) as a chiral ligand moiety. First, a titanium catalyst was made from poly(*N*-isopropylacrylamide) with (*R*)-BINOL. However, the carbonyl-ene reaction in the presence of this catalyst provided the corresponding product in low yield with poor ee. This result suggested that a component of the non-cross-linked copolymer backbones might affect the catalytic activity and enantioselectivity. Thus, after investigating several non-cross-linked copolymer backbones, we found the polystyrene copolymers **3**–**5** to be effective. These **3**–**5** were prepared from **2**[2j] via etherification with 4-vinylbenzyl chloride, random copolymerization with styrene, and deprotection of the methoxymethyl groups, successively. They were easily soluble polymers in CH_2Cl_2, and the ratio of n/m of **3**–**5** could be determined by ^1H NMR in $CDCl_3$.

With the chiral copolymers in hand, catalysts **6**–**8** were prepared by a self-assembly of **3**–**5**, Ti(O-*i*-Pr)$_4$, and H_2O based on Nakai's conditions for **1**[6a] (Scheme 2). Experimental procedure for the synthesis of **7** was as follows: To a solution of **4** (0.120 mmol as a BINOL unit) in CH_2Cl_2 (2.0 mL) was added a solution of Ti(O-*i*-Pr)$_4$ (0.120 mmol) in toluene (1.2 mL) and H_2O (0.120 mmol) in CH_2Cl_2 (12 mL). The solution was stirred at room temperature for 3 h to give reddish precipitates. The solvents were removed by azeotropic distillation at 110°C for 1 h, and evaporated at 110°C under reduced pressure for 1 h. The residue was dried in vacuo at room temperature for 14 h, and washed with Et_2O (2×2 mL) to give dark reddish lumps **7**. As predicted, **6**–**8** were insoluble in organic solvents such as CH_2Cl_2, THF, PhMe and Et_2O.

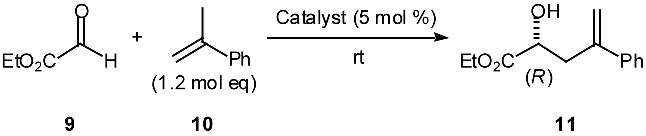
To survey the potency of complexes **6**–**8** as catalysts, we applied these catalysts to a catalytic enantioselective carbonyl-ene reaction (Table 1).[6] When the reaction of ethyl glyoxylate (**9**) and 1.2 mole equiv. of α-methylstyrene (**10**) was carried out with 5 mole% of **6**–**8** in CH_2Cl_2 at −30°C, the Nakai reaction conditions,[6a] only a trace amount of **11** was yielded. However, we were pleased to find that the reaction proceeded rather easily at room temperature to give **11** in moderate yield with modest ee (entries 1–3). It was found that the solvents influenced the enantioselectivity in this reaction (entries 2, 4–6). When diethyl ether was used as a solvent, **11** was obtained in 68% yield with 84% ee (entry 6), whereas CH_2Cl_2 and PhMe gave **11** with moderate ee, and THF afforded only a trace amount of **11**.[9] It is interesting that the highest enantioselectivity was achieved at room temperature by **7**.

Furthermore, **7** was found to be recoverable and reusable (Table 2): when the reaction of **9** and 1.2 mole equiv. of **10** was performed in the presence of 20 mole% of **7** at room temperature for 72 h, **11** was given in 85% yield with 88% ee (entry 1).[10] The catalyst was reused



Scheme 2.

Table 1. Surveying potency of complexes **6**–**8** as chiral catalysts for an enantioselective carbonyl-ene reaction



Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]	ee (%)[b]
1	**6**	CH_2Cl_2	48	49	49
2	**7**	CH_2Cl_2	60	55	58
3	**8**[c]	CH_2Cl_2	14	87	56
4	**7**	THF	60	Trace	N.D.[d]
5	**7**	PhMe	60	56	59
6	**7**	Et_2O	60	68	84

[a] Isolated yield after purification by column chromatography.

[b] Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALPAK AS.

[c] Compound **11** was obtained in 26% yield with 36% ee by reused **8** which was recovered after the reaction in entry 3.[7]

[d] N.D., not determined.

Table 2. Recyclable catalysis promoted by **7**

$$\mathbf{9} \quad + \quad \underset{(1.2\ \text{mol eq})}{\mathbf{10}} \quad \xrightarrow[\text{Et}_2\text{O, rt, 72 h}]{\text{Catalyst } \mathbf{7}\ (20\ \text{mol \%})} \quad (R)\text{-}\mathbf{11}$$

Entry	Catalyst	Yield (%)	ee (%)
1	1st use	85	88[a]
2	2nd use	83	88
3	3rd use	79	87
4	4th use	77	85
5	5th use	86	81

[a] $[\alpha]_D^{26}$ −20.1 ($CHCl_3$, *c* 0.75) (lit. $[\alpha]_D^{20}$ −22.2 ($CHCl_3$, *c* 1.9, 96.3% ee).[8]

without further treatment after recovery by filtration. In the repeated use of the recovered catalyst, **11** was obtained in 83% yield with 88% ee (entry 2). Again, the recovered catalyst was reused; that is, the third, fourth and fifth reactions afforded **11** in 79% yield with 87% ee, in 77% yield 85% ee, and in 86% yield with 81% ee, respectively (entries 3–5).[11]

A scanning electron microscope (SEM) study was made to obtain further information on the catalyst (Fig. 2). Complex **7** was treated with gold vapor by a sputter coating method. The SEM picture showed the presence of many prominences, which were approximately 1–10 μm in length. The surface of **7** is now being investigated to clarify the structure and recognition mechanism.

In conclusion, we have developed new chiral catalysts prepared from a self-assembly of $Ti(O\text{-}i\text{-}Pr)_4$, H_2O and binaphthol moieties bound to non-cross-linked copolymers. A catalytic enantioselective carbonyl-ene reaction using the catalyst resulted in the corresponding product in 85% yield with 88% ee. The catalyst was reusable five times with retention of its activity and enantioselectivity. While some drawbacks in terms of reactivity still remain, the asymmetric reaction can be carried out at room temperature. Since the reaction system itself exhibited great possibility and could be promoted by ppm molar equivalents of catalysts, applications to other enantioselective reactions are currently under study.

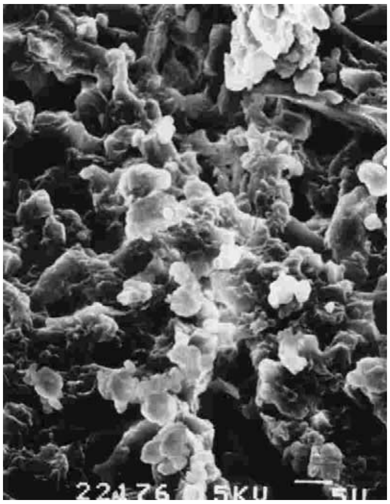


Figure 2. A scanning electron micrograph (SEM) of **7**; scale bar: 5 μm.

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10. Experimental procedure for the asymmetric carbonyl-ene reaction catalyzed by the self-assembled and reusable catalyst **7**: To a suspension of **7** (0.060 mmol as one catalyst unit) in Et_2O (2 mL) was added a solution of **9**[12] (0.30 mmol) and **10** (0.36 mmol) in dist Et_2O (0.30 mL) at room temperature under argon atmosphere. The reaction suspension was stirred for 72 h. After Et_2O (10 mL) was added to the reaction suspension, the supernatant was filtered under argon atmosphere. Addition of Et_2O and filtration was carried out one more time. The residue (catalyst) can be used as a reusable catalyst. The filtrate was evaporated, and purified by flash column chromatography (eluent: AcOEt/hexane (1/15)) to give **11** in 85% yield with 88% ee.
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