Immobilization of a BINOLate–Titanium Catalyst by Use of Aggregation Phenomenon

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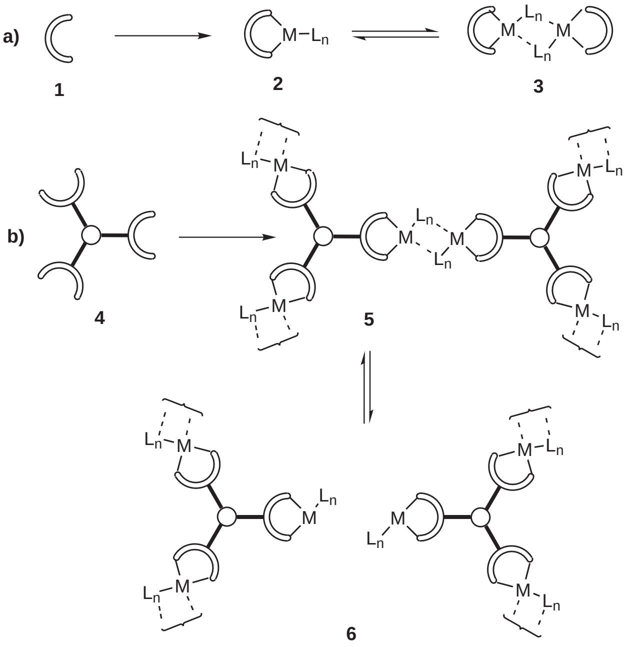
Abstract: Upon treatment with titanium tetraisopropoxide, tris-BINOL with a rigid aromatic tether forms an insoluble polymeric aggregate, which shows a catalytic activity in asymmetric addition of diethylzinc to aldehydes.

Key words: asymmetric catalysis, heterogeneous catalysis, Lewis acids, titanium, zinc

Heterogeneous catalysis offers the advantages of easy separation of the catalyst from the reaction mixture, possible recycling, and, in many cases, enhanced stability in comparison with the soluble analogue. The immobilization of asymmetric homogeneous catalysts is a current subject of intense research activity because sophisticated and expensive chiral ligand systems might become attractive for industrial applications by their heterogenization.[1] The most frequently used strategy of heterogenization is covalent binding of the catalyst or ligand of choice to organic or inorganic supports. Many homogeneous asymmetric catalysts have been immobilized onto organic polymers and inorganic supports such as silicas and zeolites. However, the activity of immobilized catalysts is often reduced with respect to their soluble analogues, due to diffusion problems or to the fact that the preferred conformation of the catalytic moiety cannot be adopted. New methods need to be developed for the heterogenization of homogeneous asymmetric catalysts.[2,3]

It is often observed that a catalyst complex **2** prepared from a chiral ligand **1** is in equilibrium with a dimeric aggregate **3** in solution (Scheme 1, a). When a complex is prepared from ligand **4** in which molecules of ligand **1** are linked with a polyvalent tether, the resulting complex is anticipated to form insoluble polymeric aggregate **5** (Scheme 1, b). The aggregate **5** might undergo partial dissociation in a reversible manner to generate active sites and exhibit a catalytic activity similar to that of a parent homogeneous catalyst while maintaining its heterogeneous state.

Titanium complexes of 1,1′-bi-2-naphthol (BINOL) and its derivatives have been employed as enantioselective chiral Lewis acid catalysts in a number of useful asymmetric processes.[4] They are known to form aggregates both in solution and solid state.[5] In the present study, we focus our attention on the heterogenization of BINOLate–Ti(O*i*-Pr)$_2$[6] based upon the approach presented in Scheme 1 (b). Herein, we wish to report the preparation of an immobilized chiral titanium complex from tris-BINOL ligand **9** as well as its application to asymmetric addition of diethylzinc to aldehydes.



Scheme 1 Immobilization of asymmetric catalysts by aggregation

Tris-BINOL **9** was synthesized in a convergent manner by joining three BINOL units with a rigid trivalent tether **7**[7] (Scheme 2). Treatment of a MOM-protected (*R*)-3-iodo-BINOL derivative **8** (3.2 equiv) and **7** in THF and Et$_3$N (3:1) in the presence of Pd(PPh$_3$)$_4$ (10 mol%) and CuI (20 mol%) afforded the corresponding coupling product in 91% yield. Removal of the protecting groups with Me$_3$SiBr in the presence of molecular sieves 4 Å[8] furnished **9** in 92% yield.

Treatment of **9** with titanium tetraisopropoxide (3 equiv) in CH$_2$Cl$_2$ followed by addition of toluene and distillation of the solvents, to remove isopropyl alcohol liberated, gave **9**-[Ti(O*i*-Pr)$_2$]$_3$ as a dark orange amorphous solid. The solid was washed three times in toluene by centrifugation. Dissolution in toluene was negligibly small in the second and third wash. The yield of **9**-[Ti(O*i*-Pr)$_2$]$_3$ was estimated to be 75% from the recovery of the ligand **9** after hydrolysis of the solid.

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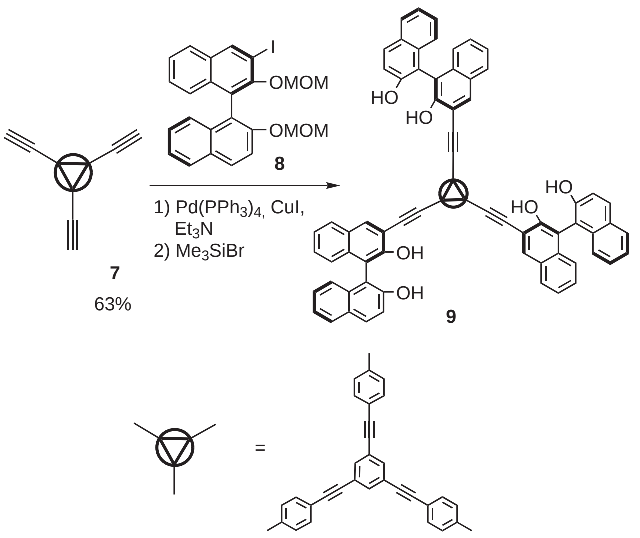


Scheme 2 Preparation of tris-BINOL **9**

Table 2 Asymmetric Ethylation of Aldehydes Catalyzed by **9**-[Ti(O*i*-Pr)$_2$]$_3$[a]

Entry	Aldehyde	Time (h)	Conversion (%)	ee (%)[b]
1	*p*-MeC$_6$H$_4$CHO	19	>98	74
2	*m*-ClC$_6$H$_4$CHO	24	>98	81
3	*m*-MeOC$_6$H$_4$CHO	20	>98	79
4	1-NaphCHO	22	95[c]	84
5	PhCH$_2$CH$_2$CHO	19	>98	79

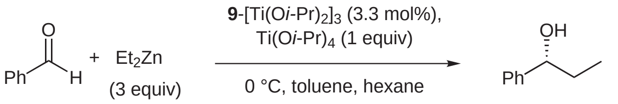
[a] Reactions were carried out under conditions similar to those of entry 1 in Table 1.
[b] Determined by chiral stationary phase HPLC (Chiralcel OD column).
[c] Isolated yield.

The activity of **9**-[Ti(O*i*-Pr)$_2$]$_3$ as a catalyst was examined in a prototypical diethylzinc addition to benzaldehyde (Table 1; R = Ph).[9] The solid catalyst was prepared by a procedure similar to that described above and stored under argon prior to use. Upon treatment of benzaldehyde with diethylzinc (3 equiv), titanium tetraisopropoxide (1 equiv), and 3.3 mol% of the catalyst **9**-[Ti(O*i*-Pr)$_2$]$_3$ suspended in toluene and hexane (73:27) at 0 °C, the ethylation reaction proceeded smoothly under the heterogeneous conditions to give (*R*)-1-phenylpropanol in 74% ee (Table 1, entry 1). The solid catalyst was recovered quantitatively by centrifugation. When twice as much solvent (toluene–hexane = 93:7) was used, a similar level of enantioselectivity and catalyst recovery was obtained albeit with considerable lowering in the reaction rate (entry 3). To gain information on the catalytic activity of **9**-[Ti(O*i*-Pr)$_2$]$_3$ in its solid form, control experiments were carried out in which a supernatant of a mixture of the titanium complex, titanium tetraisopropoxide (1 equiv), and diethylzinc (3 equiv) was used (entries 2 and 4). The reactions were slower and less selective, indicating the catalytic activity of the solid fraction of **9**-[Ti(O*i*-Pr)$_2$]$_3$.

Extension of the above asymmetric alkylation reaction to other aldehydes also gave relatively high enantioselectivity (Table 2). Of these, the reaction of 1-naphthaldehyde exhibited the highest ee of 84% (entry 4). The catalyst was also used successfully in the reaction of an aliphatic aldehyde without a decrease in enantioselectivity (entry 5).[10]

The reuse of the polymeric aggregate catalyst was examined in the asymmetric ethylation of aldehydes (Table 3). The reuse experiments were carried out in a flask

Table 1 Asymmetric Ethylation of Benzaldehyde Catalyzed by **9**-[Ti(O*i*-Pr)$_2$]$_3$



Entry	Catalyst (μmol/mL)[a]	Time (h)	Conversion (%)	ee (%)[b]	Recovery (%)[c]
1	1.5	20	>98	74	98
2[d]	1.5	20	83	58	–
3	0.75	67	>98	74	99
4[d]	0.75	67	39	40	–

[a] The amount (mmol) of the catalyst suspended in 1 mL of solvents (toluene–hexane = 73:27 for entries 1 and 2 and 93:7 for entries 3 and 4).
[b] Determined by chiral stationary phase HPLC (Chiralcel OD column).
[c] Recovery of the solid catalyst.
[d] The reaction was carried out after removing solid fraction of the catalyst by centrifugation.

Table 3 Reuse of **9**-[Ti(O*i*-Pr)$_2$]$_3$ in Asymmetric Ethylation of Aldehydes[a]

Entry	Aldehyde	Cycle	Time (h)	Conversion (%)	ee (%)[b]
1	PhCHO	1	18	>98	72
2	PhCHO	2	18	>98	75
3	PhCHO	3	18	>98	75
4	PhCHO	4	18	>98	75
5	PhCHO	5	18	>98	74
6	PhCHO	6	18	>98	74
7	1-NaphCHO	1	22	95[c]	84
8	1-NaphCHO	2	22	97[c]	80
9	1-NaphCHO	3	22	98[c]	84

[a] Reactions were carried out as described in the text under the conditions similar to that of entry 1 in Table 1.
[b] Determined by chiral stationary phase HPLC.
[c] Isolated yield.

equipped with a filter. The solid catalyst was separated from the product by filtration and used in the subsequent cycle. For the reaction of benzaldehyde, the catalyst maintained its activity even after six cycles without lowering of the enantioselectivity (entries 1–6). The recycled catalyst was also used effectively for 1-naphthaldehyde (entries 7–9).

In summary, we have developed a new method for the immobilization of BINOLateTi(O*i*-Pr)$_2$ by utilizing an aggregation phenomenon. Upon treatment with titanium tetraisopropoxide, tris-BINOL **9** formed an insoluble polymeric aggregate, which exhibited a catalytic activity in asymmetric ethylation of aldehydes. The catalyst tolerated recycled uses at least six times, suggesting the potential of the present method of immobilization based on an aggregation phenomenon.

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(10) **Typical Experimental Procedure (Table 2, Entry 4).**
To a solution of tris-BINOL **9** in CH_2Cl_2 (0.08 M) in a Schlenk flask at r.t. under argon atmosphere was added titanium tetraisopropoxide (3 equiv). The resulting dark orange suspension was stirred for 1 h. After addition of toluene, the mixture was concentrated by distillation of the solvents under atmospheric pressure. The residue was washed three times with toluene by centrifugation under argon and vacuum dried to give **9**-[Ti(O*i*-Pr)$_2$]$_3$, which was stored in an argon-filled glovebox prior to use. To a suspension of **9**-[Ti(O*i*-Pr)$_2$]$_3$ (27 mg, 0.015 mmol) in toluene (7.2 mL) and hexane (1.3 mL) at 0 °C under argon atmosphere was added titanium tetraisopropoxide (0.13 g, 0.46 mmol). The resulting suspension was sonicated for 15 min at 0 °C. To this at 0 °C was added diethylzinc (1.0 M in hexane) (1.4 mL, 1.4 mmol) and the mixture was stirred for 20 min. To the resulting mixture was added 1-naphthaldehyde (72 mg, 0.46 mmol). After being stirred at 0 °C for 22 h, the reaction mixture was filtered in a glovebox under argon atmosphere. The filtrate was poured into aq 1 N HCl, extracted three times with EtOAc, and washed with aq 5% $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 15% EtOAc in hexane) to give 81 mg (95% yield) of (*R*)-1-naphthyl-1-propanol (74% ee). Enantioselectivity was determined by HPLC analysis using a Chiralcel OD column (10% *i*-PrOH in hexane, 0.8 mL/min); t_R = 11.8 min (minor *S* enantiomer), 22.5 min (major *R* enantiomer). The absolute structure of the product was determined by comparing the retention time with that of an authentic sample prepared by asymmetric ethylation using (*R*)-BINOL as a ligand.[9]