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Immobilization of asymmetric multifunctional catalysts on an insoluble polymer

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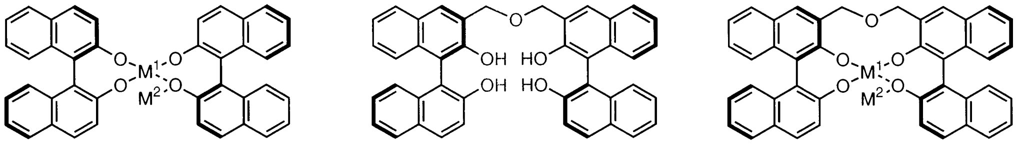
Abstract

Polymer-supported linked-BINOL was synthesized to immobilize asymmetric catalysts with two BINOL units. The advantage of the polymer-supported linked-BINOL over randomly polymer-supported BINOL was confirmed by asymmetric Michael reaction. A novel polymer-supported La–Zn-linked-BINOL complex afforded the Michael adduct in good yield and moderate ee. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric catalyst; asymmetric synthesis; solid-phase synthesis; Michael reaction; linked-BINOL.

Polymer-supported catalysts have various advantages over homogeneous catalysts in asymmetric synthesis, such as easy separation, reusability, stability and less toxicity of immobilized species. Numerous efforts have been devoted to develop polymer-supported asymmetric catalysts and several successful examples have been published so far.[1] However, no efficient method has been reported to immobilize asymmetric catalysts consisting of two or more chiral ligands per center metal. On the other hand, various highly efficient chiral catalysts constructed from



(*R*)-heterobimetallic complexes
M^1 = Al, M^2 = Li: Al-Li-BINOL (ALB) **1**
M^1 = Ga, M^2 = Li: Ga-Li-BINOL (GaLB) **2**

(*R*,*R*)-linked-BINOL **3**

(*R*,*R*)-linked-BINOL complexes
M^1 = Ga, M^2 = Li: Ga-Li-linked-BINOL **4**
M^1 = La, M^2 = H: La-linked-BINOL **5**
M^1 = La, M^2 = ZnEt: La-Zn-linked-BINOL **20**

Figure 1.

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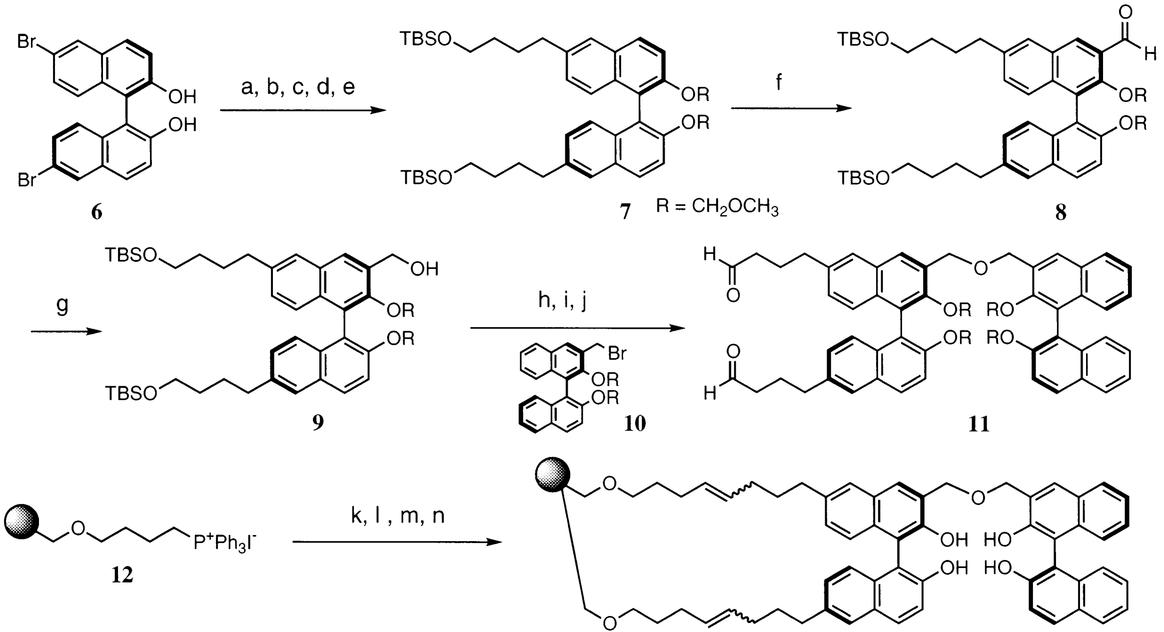
two chiral ligands, including our heterobimetallic multifunctional catalysts (Fig. 1, **1** and **2**),[2] are known in homogeneous asymmetric synthesis.[3] Therefore, the development of efficient methods to immobilize these catalysts is well desired. The main difficulty in achieving immobilization is summarized as follows. The classical random attachment of ligands onto a polymer often results in poor yield and/or ee of the products. The formation of desirable 1:2 (metal:ligand) species, essential for high enantiomeric induction, is partially prevented due to diluted distribution of the ligands on the polymer. If undesired 1:1 (metal:ligand) species catalyze the target reaction in lower selectivity, the ee of the product should become much lower than that obtained by the homogeneous counterpart.[4] To prepare this type of polymer-supported catalyst successfully, control of the relative spatial relationships between the ligands on the polymer seems to be necessary, which is by no means an easy task.

Recently, we have succeeded in developing a novel linked-BINOL **3** (Fig. 1), which bears an asymmetric environment similar to that constructed by two BINOLs around a center metal.[5a] We envisioned that the use of one linked-BINOL instead of two BINOLs makes a standard anchoring approach possible and facilitates the immobilization of asymmetric catalysts which require two BINOL units for high enantiomeric induction. In this paper we wish to report our efforts toward this direction—synthesis of polymer-supported linked-BINOL and evaluation of its asymmetric environment by asymmetric Michael reaction catalyzed by an La-linked-BINOL complex.[5b]

On the basis of precedent reports concerning polymer-supported binaphthyl ligands,[6] we designed linked-BINOL **13** possessing a spacer at the 6,6′-position to avoid adverse effects of the

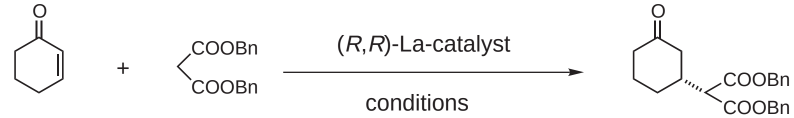


Scheme 1. Synthesis of polymer-supported linked-BINOL **13**. *Reagents and conditions*: (a) CH_3OCH_2Cl, *i*-Pr_2NEt, CH_2Cl_2, rt, 90%; (b) $CH_2{=}CHCH_2CH_2MgBr$, $PdCl_2dppf$ (4 mol%), THF, 50°C; (c) 9-BBN, THF, rt; (d) aq. NaOH, 30% H_2O_2, rt; (e) TBSCl, imidazole, DMF, rt, 71% (four steps); (f) *t*-BuLi, THF, −78°C; then DMF, 68%; (g) $NaBH_4$, THF, CH_3OH, 0°C; (h) NaH, THF, DMF; **10**, rt, 57% (two steps); (i) $Bu_4N^+F^-$, THF, rt; (j) PCC, MS 4 Å, CH_2Cl_2, rt, 69% (two steps); (k) LHMDS, THF, rt; (l) **11** (0.25 mol equiv.), THF, −10°C to rt; (m) acetaldehyde (capping); (n) $TsOH{\cdot}H_2O$, CH_2Cl_2, CH_3OH, 40°C

spacer on the asymmetric environment. Compound **13** has a sufficiently long (C_8) and flexible spacer so that the ligand part would be positioned far away from the polymer backbone. It should be mentioned that the spacer part does not contain an ester or amide functionality, which often interacts strongly with Lewis acidic center metals to affect the asymmetric environment in undesirable manner. The synthetic route towards **13** is shown in Scheme 1. Starting from 6,6′-Br-BINOL **6**, **11** was prepared in ten steps. The aldehyde **11** was attached to resin **12**, which was prepared from Merrifield resin following the literature procedure,[7] by a Wittig reaction. After checking complete consumption of **11** by TLC analysis, excess acetaldehyde was added to quench the remaining ylide. Following the removal of the MOM group by treatment of the resin with a catalytic amount of $TsOH{\cdot}H_2O$ in CH_2Cl_2 at 40°C, the polymer-supported linked-BINOL **13** was obtained (loading 0.24 mmol/g based on mass balance).

To evaluate the utility of polymer-supported linked-BINOL **13**, we investigated the Michael reaction of **15** with **14** catalyzed by an La-linked-BINOL complex. The polymer-supported La-linked-BINOL complex **17** was prepared in a similar manner to the homogeneous La-linked-BINOL complex **5**.[5b,8] Although the chemical yield was relatively low (45%), moderate ee was achieved (66%) using **17** (Table 1, entry 2). The advantage of the polymer-supported linked-BINOL over randomly polymer-supported BINOL is apparent, when comparing this result (66% ee) with that obtained using the catalyst prepared from 2 equiv. of polymer-supported BINOL (27% ee, Ref. 4). To improve the reactivity and selectivity, we tried using DME as solvent instead of THF. In the homogeneous case, La-linked-BINOL complex **5** afforded the best results when using DME instead of THF (4°C, 72 h, yield 98%, >99% ee, Ref. 5b). Unfortunately, the reactivity of **17** in DME became very low: the Michael product **16** was obtained only in 56% yield despite the use of 50 mol% catalyst, although a better ee (78%) was

Table 1
Catalytic asymmetric Michael reaction promoted by La-linked-BINOL complexes

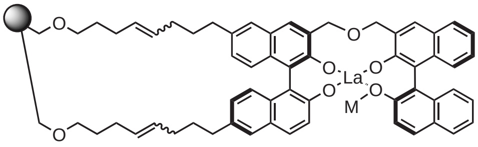


14 **15** **16**

Entry	Cat.[a] (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ee (%)
1[b]	**5** (10)	THF	0	45	53	85
2	**17** (20)	THF	rt	72	45	66
3	**17** (50)	DME	rt	87	56	78
4	**18** (20)	THF	rt	45	72	66

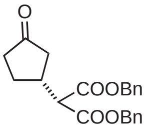
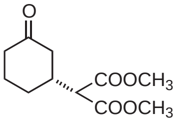
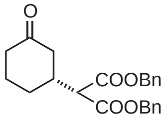
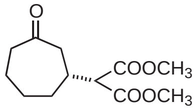
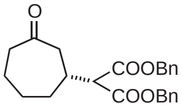
[a] **5**: homogeneous La-linked-BINOL; **17**: polymer-supported La-linked-BINOL; **18**: polymer-supported La–Zn-linked-BINOL.

[b] The result was reported in Ref. 5b.



M = H: catalyst **17**, M = ZnEt: catalyst **18** achieved (entry 3). With less catalyst loading, a further decrease in the chemical yield was observed. The low reactivity is due to the property of DME against polystyrene beads. The polymer was not swollen sufficiently in DME, and so the substrates did not interact well with the catalyst on the polymer. After many trials, we were pleased to find that a novel heterobimetallic La–Zn-linked-BINOL complex, prepared by adding 1.0 equiv. of Et_2Zn to La-linked-BINOL, was effective for the present heterogeneous reaction. Polymer-supported La–Zn-linked-BINOL **18** afforded **16** in good yield (72%) and moderate ee (66%) (entry 4). In fact, the La–Zn-linked-BINOL complex also promoted the Michael reaction efficiently in the homogeneous phase (Table 2). An Et-Zn moiety was used for the first time as a Brønsted base in our heterobimetallic asymmetric catalysis.[9] We believe that this finding opens up the possibility of developing new types of asymmetric reactions by utilizing the mild and selective reactivity of Zn species.

Table 2
Catalytic asymmetric Michael reaction promoted by homogeneous (*R*,*R*)-La–Zn-linked-BINOL complex **20**[a]

					
Time (h)	87	72	72	72	72
Yield (%)	92	99	86	70	83
Ee (%)	80	96	83	93	89

[a] Conditions: enone (1 equiv.), malonate (1 equiv.), (*R*,*R*)-La–Zn-linked-BINOL 10 mol%, THF, 4°C. Ee's were determined by HPLC analysis, see Ref. 5b.

In summary, we have synthesized a new polymer-supported linked-BINOL. The advantage of polymer-supported linked-BINOL over randomly polymer-supported BINOL was confirmed by the catalytic asymmetric Michael reaction: a much higher ee (up to 78% vs 27%) of the Michael adduct was achieved when polymer-supported linked-BINOL was used. It is worth noting that moderate to good ees (up to 78%) were achieved for the first time with a polymer-supported asymmetric catalyst which essentially needs two chiral ligand units. In addition, a novel La–Zn-linked-BINOL complex—a new entry to heterobimetallic asymmetric complexes—was developed during the investigation to improve the reactivity of the polymer-supported La-linked-BINOL complex. We believe that the polymer-supported linked-BINOL can be applied to various useful chiral catalysts with two BINOL units other than La complexes. However, it is apparent that the present polymer-supported linked-BINOL is still unsatisfactory, compared with its homogeneous analogue. Moreover, the recovery of the metal complex itself has not yet been fully achieved,[10] although the recovery and reuse of the ligand was performed easily. Further optimizations of polymer-supported linked-BINOL, in combination with its application to other Lewis acidic complexes, are now under investigation by our group.

Acknowledgements

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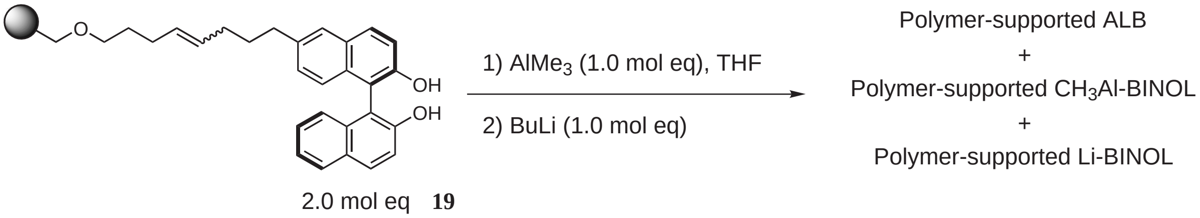

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8. *General Procedure*: After the polymer-supported linked-BINOL (414 mg, ca. 0.1 mmol) was washed with anhydrous THF (10 mL×2), it was swollen with THF (1.5 mL). La(O-*i*-Pr)$_3$ (0.2 M in THF, 0.4 mL, 0.08 mmol) was added and the mixture was shaken gently (300 rpm) at room temperature. After 12 h, THF was removed by filtration and the resin was washed with THF (5 mL×2). THF (1.4 mL), dibenzyl malonate **15** (100 μL, 0.4 mmol) and cyclohexenone **14** (40 μL, 0.41 mmol) were added successively and the mixture was shaken at room temperature. After 72 h, the product in THF was collected by filtration, and the resin was washed with THF (10 mL×2). The combined organic layers were evaporated and the residue was purified by flash column chromatography (SiO_2, hexane/acetone 8/1) to afford **16** (yield 45%, 66% ee). The recovered resin was treated with $TsOH{\cdot}H_2O$, washed with CH_2Cl_2, CH_3OH, and Et_2O, and then dried in vacuo. The recovered ligand on resin was reused at least five times without loss of activity. In the case of La–Zn-linked-BINOL, Et_2Zn (1.0 M in hexane, 1.0 equiv. to La-linked-BINOL complex) was added to La-linked-BINOL resin in THF before adding **15**.
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10. We tried to reuse the recovered resin as catalyst without treating with $TsOH{\cdot}H_2O$. However, the ee decreased to 40–50% in the second cycle.