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Enantioselective epoxidation of α,β-unsaturated ketones using polymer-supported lanthanoid–BINOL complexes

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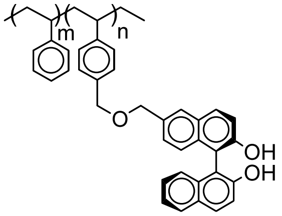
Abstract—The immobilization of chiral lanthanum and/or ytterbium complexes using polymer-support is described. The heterogeneous catalysts obtained promote the enantioselective epoxidation of α,β-unsaturated ketones affording the products in good yields with high enantiomeric excess. The catalysts were easily separated from the products by washing with ether and the recovered catalysts promote the enantioselective epoxidation reaction effectively maintaining the high level of enantioselectivity obtained during the first run. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Catalytic enantioselective epoxidation of α,β-unsaturated ketones offers a convenient procedure for the synthesis of epoxy ketones. A variety of catalytic systems employing polyamino acid catalysts,[1] asymmetric phase-transfer catalysts,[2] and chiral ligand–metal catalysts[3] have been developed. Recently the use of lanthanoid–BINOL complexes as catalysts for the catalytic enantioselective epoxidation of enones by hydroperoxides have been studied in great detail.[4] This catalytic system is applicable for both alkyl and aryl substituted enones giving the products in high yields with good enantioselectivity.

With the growing importance of polymer supported reagents and catalysts that offer methods to recover and reuse expensive chiral catalysts, considerable attention has been focused on the use of macromolecules, both soluble[5] and insoluble,[6] containing chiral 1,1′-bi-2-naphthol (BINOL) for the immobilization of a range of asymmetric catalysts. We have also reported the use of polymer[5h,7] and dendrimer[8] supported BINOL as the chiral ligand for the immobilization of AlLibis(binaphthoxide) catalyst. These immobilized catalysts promoted the asymmetric Michael addition of dibenzyl malonate to 2-cyclohexenone affording the product in high enantiomeric excess. The heterogeneous nature of these catalysts facilitated their recovery and reuse.

Herein we report the immobilization of enantioselective epoxidation catalysts using polymeric ligands containing BINOL. Using lanthanum and ytterbium complexes generated with sterically regular polymeric BINOL derivatives we have recently reported the epoxidation of chalcone **2** and benzalacetone **4**.[9] Contrary to our expectations the epoxidation catalysts afforded the products with lower enantioselectivities. Moreover yields and selectivities were found to decrease when attempts were made to reuse the catalysts. In search of better alternatives for this catalytic system we explored the use of polymer supported BINOL **1**[7] as a chiral ligand. Chalcone and benzalacetone were used as test substrates in this study.



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2. Results and discussion

Addition of La(O-*i*-Pr)$_3$ to a THF solution containing **1** resulted in a pale yellow precipitate. This precipitate **La-1** catalyzed the enantioselective epoxidation of **2**

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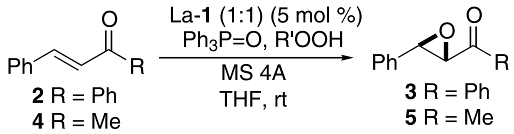
with cumene hydroperoxide (CMHP) in the presence of MS 4A. The product epoxide **3** was obtained in 30% yield with 65% e.e. after 22 h (Table 1, entry 1). The activity of the catalyst was greatly enhanced by the addition of 15 mol% of $Ph_3P{=}O$ and the product was obtained in 96% yield with 98% e.e. in 20 h (entry 2).[4d,4f] Although the catalyst requires longer reaction times, the chemical yield and the enantioselectivity offered are close to those obtained with the soluble parent catalysts.[4] The use of *tert*-butyl hydroperoxide (TBHP) as the oxidant afforded the product in 97% yield with 83% e.e. after 20 h (entry 3). Under similar conditions **4** was converted to the epoxide **5** in 86% yield with 82% e.e. after 18 h (entry 4). Addition of dry ether to the reaction mixture facilitated the separation of the catalyst and the reaction mixture. The clear supernatant solution was syringed out and the catalyst washed three times with ether followed by THF twice. The catalyst thus obtained as a dark brown solid was found to promote the epoxidation of **2**, however the product was obtained in 61% yield with 62% e.e. after 20 h (entry 5). While the exact reason for the decrease in activity is not clear at present, it could be in part due to the removal of the additive during washing by ether as the enantioselectivity obtained in the second run is comparable to that obtained in the absence of the additive (entry 1). In fact upon the addition of $Ph_3P{=}O$ during the second run the product was obtained in 88% yield with 85% e.e. although the reaction time was longer (entry 6). Addition of MS 4A during the second run did not have any impact on the yield and selectivity (entry 7). The observed results are consistent with a recent report by Inanaga et al. wherein the activity of the lanthanum complex of BINOL dropped drastically with aging.[4f]

In an attempt to generate more stable complexes that would afford higher enantioselectivity for the epoxidation of **4** with TBHP**,** attention was focused on the ytterbium complex **Yb-1** obtained as a pale yellow solid by the reaction of **1** with $Yb(O\text{-}i\text{-}Pr)_3$ in a metal to ligand ratio of 2:3.[4b] Since water is known to be a good additive for this type of catalyst the epoxidation of **4** was performed in the presence of 4 equiv. of water with respect to ytterbium.[4b] The product was obtained in 62% yield with 86% e.e. after 23 h (Table 2, entry 1). In our previous report with polymeric BINOL ligands $Ph_3P{=}O$ was found to be more effective than water.[9] However, in the present study use of $Ph_3P{=}O$ (15 mol%) did not result in improvement and the product was obtained in 59% yield with 87% e.e. in 24 h (entry 2). Moreover, a decrease in the chemical yield and enan-

Table 1. Enantioselective epoxidation of enones catalyzed by polymer-supported La–BINOL complex



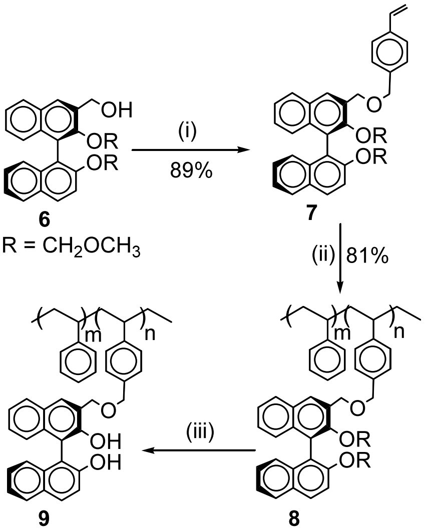
Entry	Substrate	$Ph_3P{=}O$ (mol%)	R′OOH	Time (h)	Yield (%)[a]	E.e. (%)[b]
1	**2**	–	CMHP	22	30	65
2	**2**	15	CMHP	20	96	98
3	**2**	15	TBHP	20	97	83
4	**4**	15	TBHP	18	86	82
5[c]	**2**	–	CMHP	20	61	62
6[c]	**2**	15	CMHP	67	88	85
7[d]	**2**	15	CMHP	67	91	84

[a] Isolated yields after column chromatography.
[b] Determined by HPLC analysis (Daicel Chiralcel OD column).
[c] Catalyst from entry 2 was reused.
[d] Catalyst from entry 2 was reused with MS 4A.

Table 2. Enantioselective epoxidation of **4** catalyzed by polymer-supported Yb–BINOL complex **Yb-1**

Entry	Additive		Time (h)	Yield of **5** (%)[b]	E.e. of **5** (%)[c]
	H_2O (equiv.)[a]	$Ph_3P{=}O$ (mol%)			
1	4	–	23	62	86
2	–	15	24	59	87
3[d]	–	15	38	49	82
4	4	15	20	58	91
5[d]	4	15	22	44	91

[a] Equivalents with respect to $Yb(O\text{-}i\text{-}Pr)_3$.
[b] Isolated yields after column chromatography.
[c] Determined by HPLC analysis (Daicel Chiralpak AD-H column).
[d] Catalyst reused after washing with ether and THF.



Scheme 1. *Reagents and conditions*: (i) NaH, THF–DMF, 0°C, 30 min; then 4-vinyl-benzylchloride, rt, 24 h; (ii) styrene (4 equiv.), AIBN, toluene, 75°C, 56 h; (iii) HCl, THF, 0°C→ rt, 15 h.

tioselectivity was observed when the heterogeneous catalyst was reused (entry 3). Combined use of water and $Ph_3P{=}O$ afforded the product in 58% yield with 91% e.e. in 20 h (entry 4). Interestingly in the present system the reused catalyst maintained the high level of enantioselectivity obtained during the first cycle although a decrease in chemical yield was observed (entry 5). While $Ph_3P{=}O$ is required for higher reaction rates the presence of water is important for obtaining higher enantioselectivity and maintaining it in the case of reused catalyst.

In order to study the effect of the bulky polymer on the catalytic center another polymeric BINOL was prepared using the known 3-hydroxymethyl BINOL derivative **6**[4a] as shown in Scheme 1. Alcohol **6** was coupled to 4-vinylbenzylchloride by etherification to get the monomer **7**. Polymer **8** [Mw = 8548 (PDI = 1.5)] was then obtained by free radical co-polymerization of **7** with 4 equiv. of styrene. The protecting groups were finally removed by acid treatment to get polymer **9**.

Polymer **9** afforded the catalyst as a pale yellow solid upon treatment with Yb(O-*i*-Pr)$_3$ in THF in the presence of MS 4A. This catalyst was also found to be effective in promoting the enantioselective epoxidation of **4** with TBHP. The results are presented in Table 3. The product epoxide was obtained in 52% yield with 84% e.e. after 22 h with the use of water as additive (Table 3, entry 1). In the presence of both water and $Ph_3P{=}O$ as additives the catalyst afforded the product in 48% yield with 84% e.e. (entry 2). Since the oxygen atom of the ether linkage present in the polymer could also coordinate to the metal center the presence of both additives might make the complex crowded thereby reducing its activity. Thus with only $Ph_3P{=}O$ as additive the reaction afforded the product in 69% yield with 88% e.e. after 22 h (entry 3). When the catalyst was reused after washing with ether and THF the product was obtained in 48% yield with 85% e.e. (entry 4). Unlike the case of the **Yb-1** complex the reaction rate with **Yb-9** was found to be dependent on the amount of $Ph_3P{=}O$ used. When only half the amount of $Ph_3P{=}O$ (7.5 mol%) was used the reaction was much faster affording the product in 90% yield in 18 h with the enantioselectivity remaining unchanged (entry 5). Moreover, this catalyst maintained the enantioselectivity even upon being reused twice although the chemical yield was decreased on first reuse (entries 6 and 7). The fact that higher reactivity could be achieved even in the absence of water and with lower amounts of $Ph_3P{=}O$ suggests the positive influence of the bulky polymer on the catalytic activity.

Thus under all conditions the chiral La and Yb complexes generated with **1** or **9** as ligand were found to afford epoxides with high enantioselectivities. In addition these catalysts maintained high levels of enantioselectivities when attempts were made to reuse them.

Table 3. Enantioselective epoxidation of **4** catalyzed by polymer-supported Yb–BINOL complex **Yb-9**[a]

Entry	Additive		Time (h)	Yield of **5** (%)[c]	E.e. of **5** (%)[d]
	H_2O (equiv.)[b]	$Ph_3P{=}O$ (mol%)			
1	4	–	22	52	84
2	4	15	24	48	84
3	–	15	22	69	88
4[e]	–	15	22	48	85
5	–	7.5	18	90	88
6[e]	–	7.5	18	62	89
7[f]	–	7.5	36	60	88

[a] Metal to ligand ratio was 2:3.

[b] Equivalents with respect to Yb(O-*i*-Pr)$_3$.

[c] Isolated yields after column chromatography.

[d] Determined by HPLC analysis (Daicel Chiralpak AD-H column).

[e] Catalyst was reused after washing with ether and THF.

[f] Third use of the catalyst.

3. Conclusion

To conclude, heterogeneous epoxidation catalysts were generated by the reaction of polymer supported BINOLs **1** or **9** with La(O-*i*-Pr)$_3$ or Yb(O-*i*-Pr)$_3$. These catalysts effectively promoted the enantioselective epoxidation of **2** and **4** affording the product epoxides in good yields with high enantioselectivity. In addition the catalysts could be reused after washing with ether and THF and were found to maintain high levels of enantioselectivity. The results obtained with this ligand system are much better compared to that obtained earlier with sterically regular polymeric BINOL.[9] Attempts to enhance the activity of these catalysts to obtain higher chemical yield and enantioselectivity are underway.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM-EX270 FT NMR system. IR spectra were recorded on Shimadzu FTIR 8300. Optical rotations were measured with a JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV–vis detector) using a mixture of *n*-hexane and *i*-PrOH as the eluent. Molecular weights of the polymers were determined by gel permeation chromatography (GPC) relative to polystyrene standards using SHODEX GPC KF 803L column. **2** and **4** were obtained from commercial sources. Chalcone was recrystallized from EtOH. Toluene solutions of anhydrous TBHP and anhydrous CMHP were prepared using literature procedures.[4a] All reactions were performed under an argon atmosphere. THF was freshly distilled from sodium benzophenone ketyl. MS 4A was dried in vacuum at 180°C for 3 h before use. Polymer **1** was prepared by the synthetic route reported by us earlier.[7]

4.2. Synthesis of (*R*)-3-(4-vinylbenzyloxy)methyl-2,2′-bis(methoxymethyloxy)-1,1′-binaphthalene 7

To an ice cooled solution of **6** (0.92 g, 2.27 mmol) in THF and DMF (15 mL+10 mL) was added NaH (133 mg, 3.35 mmol as 60% purity in oil) and the mixture stirred for 30 min. To this suspension was then added 4-vinyl benzylchloride (0.32 mL, 2.27 mmol). The mixture was allowed to warm to rt and stirred for 24 h. The reaction was quenched by addition of saturated NaCl solution. The product was extracted with ethyl acetate (20 mL×3) and dried over anhydrous Na$_2$SO$_4$. The crude product obtained upon evaporation of the solvent was subjected to flash chromatography (silica gel, *n*-hexane/ethyl acetate, 9/1) to get 1.06 g of the product **7** in 89% yield as a colorless pasty mass. $[\alpha]_D^{28}$ +50.2 (*c* 1.12, CHCl$_3$); IR (neat) 2896, 1591, 1238, 1147, 1008 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.82 (s, 3H), 3.14 (s, 3H), 4.53 (d, $J=5.4$ Hz, 1H), 4.61 (d, $J=5.4$ Hz, 1H), 4.73 (s, 2H), 4.90 (s, 2H), 4.99 (d, $J=6.9$ Hz, 1H), 5.09 (d, $J=6.9$ Hz, 1H), 5.22 (dd, $J=10.9$, 0.9 Hz, 1H), 5.72 (dd, $J=17.6$, 0.9 Hz, 1H), 6.67 (dd, $J=17.6$, 10.9 Hz, 1H), 7.41–7.15 (m, 11H), 7.55 (d, $J=9.1$ Hz, 1H), 7.84 (t, $J=9.1$ Hz, 1H), 7.93 (d, $J=9.1$ Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 55.9, 56.5, 68.1, 72.5, 94.8, 99.2, 113.7, 116.4, 120.6, 124.0, 124.8, 125.2, 125.4, 125.5, 125.9, 126.1, 126.5, 127.7, 127.8, 127.9, 128.2, 129.5, 129.7, 130.7, 131.6, 133.8, 136.4, 136.9, 137.7, 151.6, 152.6; FAB MS *m*/*z* 543 [M+Na]$^+$.

4.3. Synthesis of the polymer-supported BINOL 8

To a toluene solution of **7** (0.6 g, 1.15 mmol in 2 mL) was added AIBN (0.053 g) and styrene (0.53 mL, 4.8 mmol). The solution was purged with argon thoroughly and polymerization was carried out at 75°C for 56 h. After cooling to rt the polymer was precipitated by addition to methanol. The precipitate was filtered, dissolved in CH$_2$Cl$_2$ and reprecipitated by addition to *n*-hexane. The white solid thus obtained was dried in vacuo at 50°C for 3 h to give the polymer **8** (0.857 g, 79% yield). $[\alpha]_D^{23}$ +30.3 (*c* 0.50, CHCl$_3$); Mw = 8548 [Mn = 5594, PDI = 1.5]; IR (neat) 2918, 1593, 1240, 1151, 1012 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.88 (br), 1.08 (br), 1.40 (br), 1.80 (br), 2.80 (br) 3.11 (br), 4.56 (br), 4.87 (br), 4.98 (br), 5.07 (br), 6.55 (br), 7.06 (br) 7.18 (br), 7.30 (br), 7.55 (br), 7.86 (br), 7.92 (br), 8.07 (br).

4.4. Removal of the protecting groups in 8

To an ice cooled solution of the polymer **8** (800 mg) in THF (2 mL) was added a THF solution of HCl (1 mL conc. HCl in 4 mL of THF). The solution was allowed to warm to rt. After being stirred for 15 h the solution was poured into water (50 mL). The product was extracted with CH$_2$Cl$_2$ and precipitated by addition to *n*-hexane twice. The precipitated polymer **9** was dried in vacuo at 50°C for 3 h (600 mg). $[\alpha]_D^{23}$ +15.0 (*c* 0.51, CHCl$_3$); IR (neat) 3030, 2918, 1596, 1099 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.88 (br), 1.08 (br), 1.42 (br), 1.77 (br), 4.54 (br), 4.82 (br), 5.03 (br), 6.54 (br), 7.03 (br), 7.26 (br), 7.84 (br).

4.5. Procedure for the enantioselective epoxidation of 2 catalyzed by polymer-supported La–BINOL complex La-1

MS 4A (100 mg), Ph$_3$P=O (21 mg, 15 mol%) and **1** (25 mg, 0.025 mmol as a monomer) were added to a dry reaction vessel and purged with argon. THF (0.5 mL) was then added at rt followed by La(O-*i*-Pr)$_3$ (0.25 mL, 0.1 M in THF, 0.025 mmol) in drops. The resulting pale yellow suspension was stirred for 1 h and anhydrous cumene hydroperoxide (0.3 mL, 1.5 equiv., 0.75 mmol, 2.6 M solution in toluene) was added. After being stirred for 10 min **2** (104 mg, 0.5 mmol) was added and the reaction was allowed to proceed at rt for 20 h during which the reaction mixture developed a dark brown color. Dry ether was then added and the brown solid was allowed to settle down. The supernatant solution was removed with a syringe and the catalyst washed with ether three times. The ether extract was quenched with saturated. aq. NH$_4$Cl, separated and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent under reduced pressure gave an oily residue, which was purified by flash chromatography (silica gel, *n*-hexane/ethyl acetate = 30/1) to give 108 mg of the epoxide **3** in 96% yield with 98% e.e. Enantiomeric excess was determined by chiral stationary phase HPLC (Daicel Chiralcel OD column, 1/49 *i*-PrOH/*n*-hexane, 1 mL/min, 254 nm, 16.0 min (major isomer) and 17.8 min (minor isomer)).

4.6. Procedure for the enantioselective epoxidation of 4 catalyzed by polymer-supported Yb–BINOL complex Yb-1

4.6.1. First cycle. MS 4A (50 mg) and **1** (18.8 mg, 0.018 mmol as a monomer) were added to a dry reaction vessel and purged with argon. THF (0.5 mL) was then added at rt followed by Yb(O-*i*-Pr)$_3$ (0.25 mL, 0.05 M in THF, 0.0125 mmol) in drops. The resulting pale yellow suspension was stirred for 1 h and H_2O (0.1 mL, 0.5 M in THF) was added followed by $Ph_3P{=}O$ (10 mg, 15 mol%) and anhydrous TBHP (0.09 mL, 1.5 equiv., 0.375 mmol, 4.8 M solution in toluene). After being stirred for 10 min **4** (37.5 mg, 0.25 mmol) was added and the reaction was allowed to proceed at rt. After 20 h dry ether was added and the brown solid was allowed to settle down. The supernatant solution was removed with a syringe and the catalyst washed with ether three times. The ether extract was quenched with saturated. aq. NH_4Cl, separated and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oily residue that was purified by flash chromatography (silica gel, *n*-hexane/CH_2Cl_2 = 1/10) to give 23 mg the epoxide **5** in 58% yield with 91% e.e. Enantiomeric excess was determined by chiral stationary phase HPLC analysis (Daicel Chiralpak AD-H column, 1/49 *i*-PrOH/*n*-hexane, 0.6 mL/min, 254 nm, 21.3 min (minor isomer) and 24.6 min (major isomer)).

4.6.2. Reuse of the catalyst. The brown solid obtained at the end of the reaction was suspended in dry THF followed by the addition of H_2O (0.1 mL, 0.5 M in THF) and $Ph_3P{=}O$ (10 mg, 15 mol%). After being stirred for 10 min anhydrous TBHP (0.09 mL, 1.5 equiv., 0.37 mmol, 4.8 M solution in toluene) and **4** (37.5 mg, 0.25 mmol) were added and reaction was allowed to proceed at rt for 22 h. Dry ether was added to separate the product and the catalyst repeatedly washed with ether. The ether extract after quenching and purification by flash chromatography afforded 18 mg of **5** in 44% yield and 91% e.e.

4.7. Procedure for the enantioselective epoxidation of 4 catalyzed by polymer-supported Yb–BINOL complex Yb-9

4.7.1. First cycle. MS 4A (100 mg) and **9** (37.5 mg, 0.037 mmol as a monomer) were weighed into a dry reaction vessel and purged with argon. THF (0.5 mL) was then added at rt followed by Yb(O-*i*-Pr)$_3$ (0.5 mL, 0.05 M in THF, 0.025 mmol) in drops. The resulting pale yellow suspension was stirred for 1 h and $PPh_3{=}O$ (10 mg, 7.5 mol%) was added followed by anhydrous TBHP (0.18 mL, 1.5 equiv., 0.75 mmol, 4.8 M solution in toluene). After being stirred for 10 min **4** (73 mg, 0.5 mmol) was added and the reaction was allowed to proceed at rt. After 18 h dry ether was added and the brown solid was allowed to settle down. The supernatant solution was removed with a syringe and the catalyst washed with ether three times. The ether extract was quenched with saturated. aq. NH_4Cl, separated and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oily residue that was purified by flash chromatography (silica gel, *n*-hexane/CH_2Cl_2 = 1/10) to give 73 mg of **5** in 90% yield with 88% e.e. Enantiomeric excess was determined by chiral stationary phase HPLC analysis.

4.7.2. Reuse of the catalyst. The brown solid obtained at the end of the reaction was suspended in dry THF followed by the addition of $Ph_3P{=}O$ (10 mg, 7.5 mol%). After being stirred for 10 min anhydrous TBHP (0.18 mL, 1.5 equiv., 0.75 mmol, 4.8 M solution in toluene) and **4** (73 mg, 0.5 mmol) were added and reaction was allowed to proceed at rt for 18 h. Dry ether was added to separate the product and the catalyst repeatedly washed with ether. The ether extract after quenching and purification by flash chromatography afforded 50 mg of **5** in 62% yield and 89% e.e.

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