

Catalytic asymmetric epoxidation of α,β -unsaturated ketones using polymeric BINOL

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Abstract

The ability of the lanthanoid complexes generated with polymeric BINOL ligands in promoting the catalytic asymmetric epoxidation of chalcone and benzalacetone was explored. In the presence of additives like water and $\text{PPh}_3=\text{O}$ the catalysts afforded the product epoxides in good yield with modest enantioselectivity. The heterogeneous nature of these catalysts facilitates the recovery and reuse.

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1. Introduction

Catalytic asymmetric epoxidation of α,β -unsaturated ketones offers a convenient procedure for the synthesis of α,β -epoxy ketones. Since the first report by Julia et al. in 1980 [1], a variety of catalytic systems employing asymmetric phase transfer catalysts [2–6], polyaminoacid catalysts [7] and chiral ligand-metal catalysts [8–10] have been developed. Recently, we reported the catalytic asymmetric epoxidation of enones by hydroperoxides in the presence of lanthanoid–BINOL complexes [11–13]. This catalytic system is applicable to both alkyl and aryl

substituted enones giving the products in high yields with good enantioselectivity. The addition of triphenylphosphine oxide to the reaction mixture resulted in enhanced reaction rates and selectivities [14]. In a detailed mechanistic investigation using $\text{Ph}_3\text{As}=\text{O}$ as an additive, Shibasaki and co-workers proposed that La–BINOL– $\text{Ph}_3\text{As}=\text{O}$ complex derived from an equilibrating mixture of various oligomeric complexes could be the active species [15]. Additives like $\text{Ph}_3\text{P}=\text{O}$ and $\text{Ph}_3\text{As}=\text{O}$ bind strongly to the central lanthanum ion and facilitate the deoligomerization of the oligomeric species to the catalytically superior monomeric complex. In addition these ligands make the active sites sterically restricted thereby resulting in enhanced selectivity.

Recently we have been interested in the application of polymer enlarged BINOL as chiral ligand for the construction of multifunctional asymmetric catalysts [16,17]. The presence of large polymer architecture around the catalytic sites render enhanced stability and

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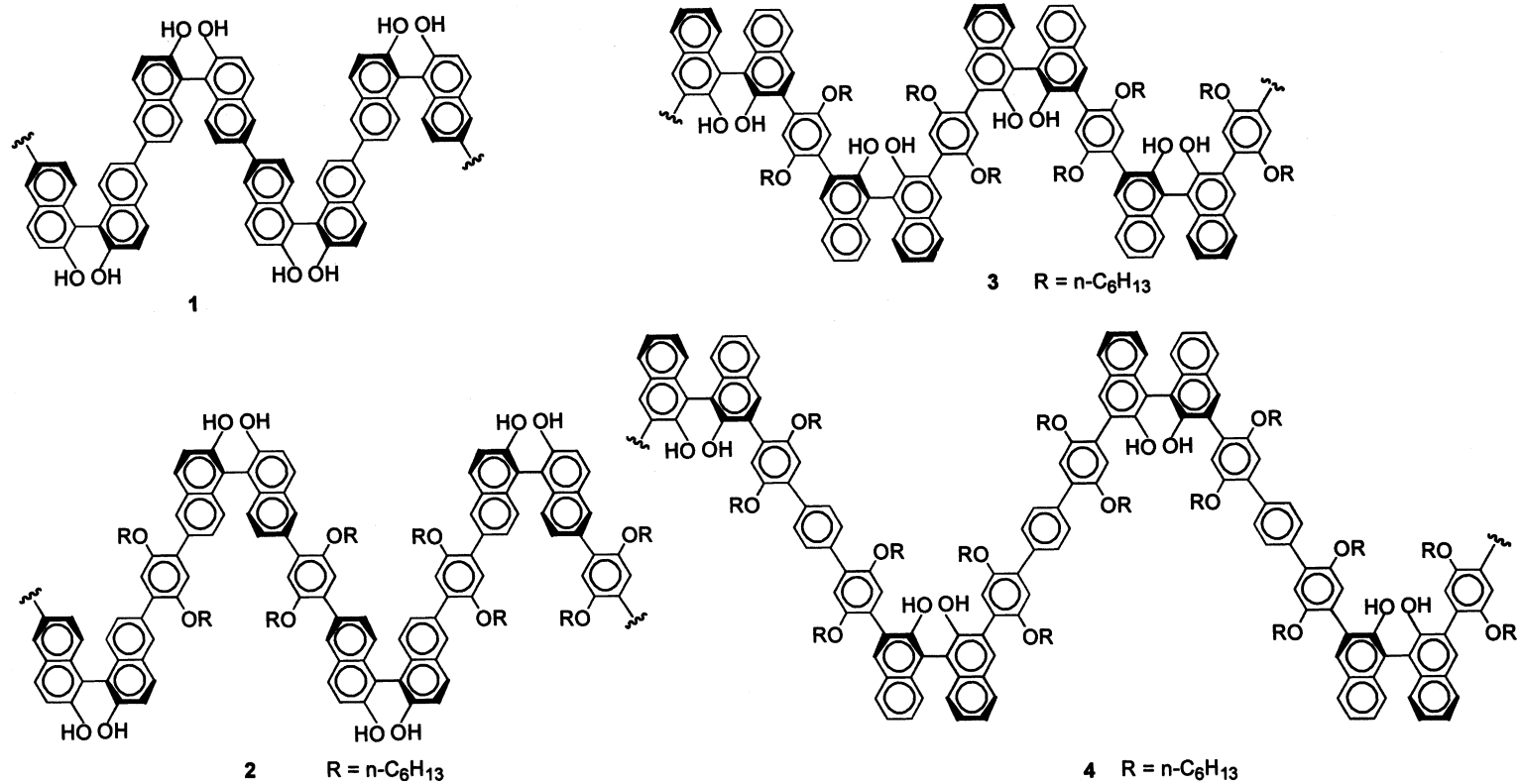


Fig. 1. Polymeric ligands used in catalytic asymmetric epoxidation.

altered reactivities. Employing chiral conjugated and sterically regular polymer containing BINOL [18–21], we recently reported the construction of air stable ALLibis(binaphthoxide) catalyst that was effective in promoting asymmetric Michael addition reaction and could be reused five times without loss in activity [16].

Encouraged by this result we then explored the role of these polymeric systems (**1–4**) (Fig. 1) in the catalytic asymmetric epoxidation of enones. These ligands differ largely in structure around the catalytic sites as a result of which would offer interesting variations in the activity of the catalyst. Ligand **3** has earlier been found to exhibit enhanced selectivity in the zinc complex catalyzed asymmetric epoxidation of enones due to a cooperative effect between the neighboring catalytic sites [10].

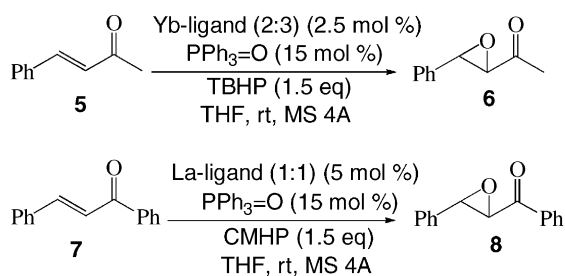
2. Experimental

2.1. Materials

The polymeric BINOL ligands were synthesized using procedures reported earlier [18–20]. Chalcone and benzalacetone were obtained from commercial sources. Chalcone was recrystallized from EtOH. Toluene solutions of anhydrous TBHP (*tert*-butyl hydroperoxide) and anhydrous CMHP (cumene hydroperoxide) were prepared using literature procedures [11]. 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.

2.2. Catalyst preparation

To a mixture of MS 4A (40 mg), ligand (0.015 mmol as a monomer in the case of ytterbium complex and 0.01 mmol as a monomer in the case of the lanthanum complex) and $\text{PPh}_3=\text{O}$ (8.3 mg, 15 mol% unless stated otherwise) was added dry THF (800 μl). After stirring the mixture for a few minutes Yb- or La-(O-^{*i*}Pr)₃ solution (100 μl , 0.01 mmol, 0.1 M in THF) was added in drops during which an orange precipitate was formed. The mixture was then warmed to 40 °C (unless mentioned otherwise) and stirred for an hour. The resulting suspension was then cooled to room temperature



Scheme 1.

and used as a catalyst for the asymmetric epoxidation of enones (Scheme 1).

2.3. Catalytic experiments

To the suspension of the catalyst stirred at room temperature were added the oxidant (0.3 mmol, 1.5 eq.) and the substrate (0.20 mmol). The reaction was allowed to proceed at room temperature and the progress monitored by thin layer chromatography. After being stirred for the mentioned period dry ether was added and the resulting suspension was centrifuged to separate the catalyst and the product. The supernatant solution was quenched with a saturated aqueous solution of ammonium chloride. The organic layer was separated and dried over anhydrous sodium sulfate. Purification and HPLC analyses were carried out using conditions reported earlier [11].

Table 1
Asymmetric epoxidation of **5** with TBHP catalyzed by Yb-ligand complex^a

Entry	Ligand	Additive (mol%)		Time (h)	Yield (%) ^b	ee (%) ^c
		H ₂ O	PPh ₃ =O			
1	1	–	–	18	84	34
2	2	–	–	22	91	49
3	3	–	–	20	47	39
4	4	–	–	18	51	41
5	2	5	–	24	73	50
6	2	–	15	24	86	71
7	2	5	15	18	59	63
8	2	–	75	18	76	72

^a The metal to ligand ratio was 2:3 and the catalyst was generated at 40 °C.

^b Isolated yields after column chromatography.

^c By HPLC analysis.

Table 2

Asymmetric epoxidation of chalcone with CMHP catalyzed by lanthanum complex of **2**

Entry	La: 2	Temperature ^a (°C)	Time (h) ^b	PPh ₃ =O (mol%)	Time (h) ^c	Yield (%)	ee (%)
1	2:3	RT	12	–	4	95	35
2	2:3	40	12	–	4	97	37
3	1:1	40	1	15	15	98	62
4	1:1	40	1	30	14	97	52
5	1:1	40	1	50	14	97	53
6	1:1	40	1	15 + 15 ^d	1.5	99	73

^a Temperature at which the catalyst was generated.^b Time required to generate the active catalyst.^c Reaction time.^d 15 mol% of the additive was added before the catalyst generation step and additional 15 mol% was added before the addition of substrates.

3. Results and discussion

The first system that we chose to study was the ytterbium complex catalyzed epoxidation of benzalacetone with TBHP. In our previous study [11,12], we observed that a 2:3 ratio of Yb(O-ⁱPr)₃ and the ligand gave higher ee than a ratio of 1:1. So the same ratio was maintained in this system also.

Among the ligands **1–4** screened in a preliminary test reaction, **2** offered the epoxide **6** in 91% yield with 49% ee (Table 1, entry 2). While ligand **1** was less selective, ligands **3** and **4** offered the product in low yields. Using ligand **2**, we then attempted to improve the selectivity by addition of H₂O [12] or PPh₃=O [14] as additive. Addition of water (5 M equivalents with respect to Yb) as additive to the preformed catalyst resulted in decreased chemical yield while maintaining comparable selectivity (Table 1, entry 5). With 15 mol% of PPh₃=O as additive, the selectivity was enhanced to a modest 71% ee (Table 1, entry 6). Combined use of both water and PPh₃=O afforded the product in 63% ee with 59% yield (Table 1, entry 7). Water was consistently found to have a deleterious effect both in terms of yield and selectivity. At the same time increasing the amount of PPh₃=O to 75 mol% resulted in a further decrease in chemical yield with comparable selectivity (Table 1, entry 8).

We then explored the asymmetric epoxidation of chalcone (**7**) with CMHP using a lanthanum complex generated with **2**. The complex with a metal ligand ratio of 2:3 afforded the product **8** in 95% yield and 35% ee (Table 2, entry 1). When the catalyst was formed at 40 °C the product was obtained in 97%

yield and 37% ee (Table 2, entry 2). Use of a 1:1 complex generated at 40 °C in the presence of 15 mol% of PPh₃=O as additive resulted in enhancement of selectivity to 62% ee (Table 2, entry 3). Consistent with the results of Shibasaki and co-workers [15] the catalyst obtained with a metal ligand ratio of 1:1 showed better reactivity although 15 mol% of the additive was required. Further increase in the additive concentration resulted in lower selectivity (Table 2, entries 4 and 5). Interestingly, the addition of 30 mol% of the PPh₃=O in two portions, before and after catalyst formation, resulted in enhanced reaction rate affording the product in 99% yield with 73% ee in 1.5 h (Table 2, entry 6).

Addition of ether followed by centrifugal separation enabled the recovery of the catalyst from the product. On reuse the recovered catalysts were found to promote the asymmetric epoxidation reactions. While comparable chemical yields were obtained the enantioselectivities were slightly lower (53% ee in the case of ytterbium complex catalyzed epoxidation of **5** and 62% ee in the case of the lanthanum complex catalyzed epoxidation of **7**).

4. Conclusion

To conclude, sterically regular polymeric BINOL derivatives were used as chiral ligands to generate epoxidation catalysts using Yb-(O-ⁱPr)₃ or La-(O-ⁱPr)₃. These heterogeneous catalysts were found to promote the epoxidation of **5** and **7**, respectively. In the presence of PPh₃=O as additive, ligand **2** was found

to be effective affording the products in high yield with good selectivity. In addition these catalysts could easily be recovered from the reaction mixture and reused.

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References

- [1] S. Julia, J. Masana, J.C. Vega, *Angew. Chem. Int. Ed. Engl.* 19 (1980) 929.
- [2] S. Arai, H. Tsuge, M. Oku, M. Miura, T. Shioiri, *Tetrahedron* 58 (2002) 1623.
- [3] B. Lygo, P.G. Wainwright, *Tetrahedron* 55 (1999) 6289.
- [4] G. Macdonald, L. Alcaraz, N.J. Lewis, R.J.K. Taylor, *Tetrahedron Lett.* 39 (1998) 5433.
- [5] S. Arai, M. Oku, M. Miura, T. Shioiri, *Synlett.* (1998) 1201.
- [6] S. Arai, H. Tsuge, T. Shioiri, *Tetrahedron Lett.* 39 (1998) 7563.
- [7] M.J. Porter, S.M. Roberts, J. Skidmore, *Bioorg. Med. Chem.* 7 (1999) 2145.
- [8] D. Enders, J. Zhu, G. Raabe, *Angew. Chem. Int. Ed. Engl.* 35 (1996) 1725.
- [9] C.L. Elston, R.F.W. Jackson, S.J.F. Macdonald, P.J. Murray, *Angew. Chem. Int. Ed. Engl.* 36 (1997) 410.
- [10] H.-B. Yu, X.-F. Zheng, Z.-M. Lin, Q.-S. Hu, W.-S. Huang, L. Pu, *J. Org. Chem.* 64 (1999) 8149.
- [11] M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* 119 (1997) 2329.
- [12] S. Watanabe, Y. Kobayashi, T. Arai, H. Sasai, M. Bougauchi, M. Shibasaki, *Tetrahedron Lett.* 39 (1998) 7353.
- [13] S. Watanabe, T. Arai, H. Sasai, M. Bougauchi, M. Shibasaki, *J. Org. Chem.* 63 (1998) 8090.
- [14] K. Daikai, M. Kamaura, J. Inanaga, *Tetrahedron Lett.* 39 (1998) 7321.
- [15] T. Nemoto, T. Ohshima, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* 123 (2001) 2725.
- [16] T. Arai, Q.-S. Hu, X.-F. Zheng, L. Pu, H. Sasai, *Org. Lett.* 2 (2000) 4261.
- [17] D. Jayaprakash, H. Sasai, *Tetrahedron: Asymmetry* 12 (2001) 2589.
- [18] Q.-S. Hu, X.-F. Zheng, L. Pu, *J. Org. Chem.* 61 (1996) 5200.
- [19] Q.-S. Hu, W.-S. Huang, D. Vitharana, X.-F. Zheng, L. Pu, *J. Am. Chem. Soc.* 119 (1997) 12454.
- [20] L. Pu, *Chem. Rev.* 98 (1998) 2405.
- [21] L. Pu, *Chem. Eur. J.* 5 (1999) 2227.