



Self-supported BINOL–Zn catalysts for heterogeneous enantioselective epoxidation of (*E*)- α,β -unsaturated ketones

Haiming Wang, Zheng Wang, Kuiling Ding*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, PR China

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ABSTRACT

A class of chiral self-supported catalysts prepared from bis-BINOL ligands and diethyl zinc were successfully applied in the heterogeneous enantioselective epoxidation of a range of (*E*)- α,β -unsaturated ketones, affording the corresponding epoxy ketones in high enantioselectivity. The self-supported catalysts were easily recovered from the reaction mixture and were reusable for several consecutive runs.

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The asymmetric epoxidation of α,β -enones is a useful approach to optically active epoxy ketones, which are versatile intermediates for the synthesis of many natural products or biologically active compounds.¹ Over several decades of development, a number of valuable catalytic methodologies have been established for efficient asymmetric induction,² mainly involving the use of chiral metal peroxides,³ asymmetric phase transfer catalysts,⁴ polyamino acid catalysts,⁵ chiral dioxiranes,⁶ or other organocatalysts.⁷ While excellent enantioselectivities have been achieved in many cases, the productivities of the catalysts were often not ideal, which necessitated fairly high loadings of the expensive chiral catalysts. Therefore, further development of recoverable chiral catalysts for the efficient asymmetric epoxidation of various enones is a highly desirable goal toward practical applications. To this end, our group have developed a series of reusable chiral BINOL–La–Ph₃PO^{3e,f} catalysts based on the self-supporting strategy,⁸ and demonstrated their excellent performance in the heterogeneous catalysis of the asymmetric epoxidation of α,β -unsaturated ketones.⁸ⁱ As an effort to develop cheaper and even more versatile self-supported catalysts for the titled reaction, we decided to investigate the catalytic potential of analogous systems based on other chiral metal complexes. The chiral BINOL–Zn catalyst reported by Minatti and Dötz appears attractive in this aspect.^{3c,d} Compared to the BINOL–La–Ph₃PO^{3e,f} system, BINOL–Zn prepared from BINOL⁹ and diethylzinc is a much less expensive catalyst, yet proved quite effective for the epoxidation of enones bearing either aryl- and/or alkyl-substituents, resulting in the corresponding products in good yields and ee values. In this Letter, we wish to report the preliminary results in the heterogeneous asymmetric catalysis of epoxidation of enones, using the in situ prepared chiral self-supported BINOL–Zn catalysts by taking the aggregating properties of BINOL–Zn complexes,¹⁰ with cumene hydroperoxide (CMHP) as the terminal oxidant.

As a preliminary test of the plausibility, the self-supported catalyst **L1**–Zn, readily prepared by reaction of the bis-BINOL ligand **L1**^{8e} (Chart 1) with diethyl zinc, was examined for the epoxidation using chalcone **1a** as a model substrate with CMHP as the oxidant. The addition of two molar equivalents of diethylzinc in hexane to a stirred solution of the bis-BINOL ligand **L1** in Et₂O resulted in immediate precipitation of a white amorphous solid of **L1**–Zn, which, after 10 min of stirring the mixture at room temperature, was isolated by filtration under argon. The resultant solid was virtually insoluble in all organic solvents (CH₂Cl₂, CHCl₃, THF, DMSO, toluene, diethyl ether, *t*-butyl methyl ether, 1,4-dioxane, ethyl

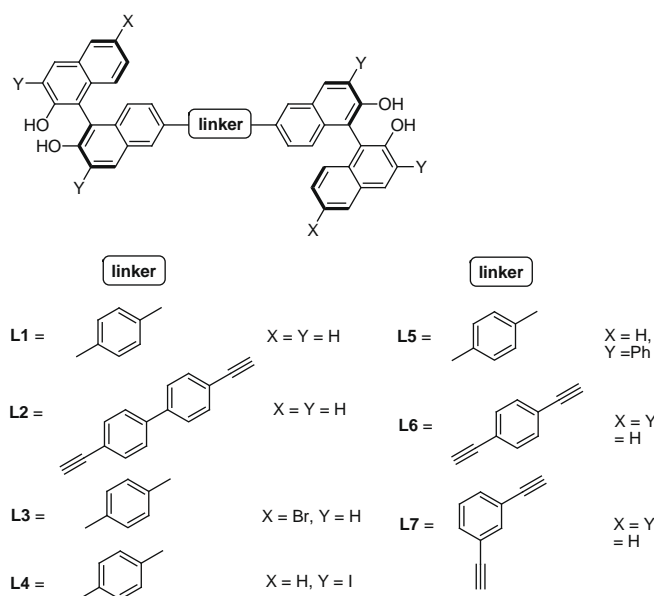


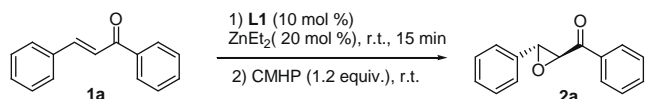
Chart 1. Bridged bis-binol ligands.

* Corresponding author.

E-mail address: kding@mail.sioc.ac.cn (K. Ding).

Table 1

Preliminary survey of reusability of self-supported catalyst **L1**/Zn for epoxidation of chalcone **1a**^a



Run	Time (min)	Yield ^b (%)	ee ^c (%)
1	30	99	78
2	45	99	82
3	45	78	85
4	45	42	85
5	60	54	88
6	90	54	85

^a Reactions were performed on 0.5-mmol scale of chalcone in Et₂O (2 mL) at room temperature.

^b The yield of isolated epoxide.

^c Determined by chiral HPLC.

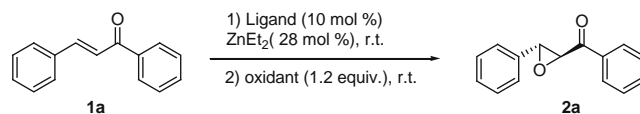
acetate, and 1,2-dichloroethane) tested, and thus fulfilling a basic prerequisite for heterogeneous catalysis. Indeed, charging a catalytic amount of the solid sequentially with chalcone and CMHP in Et₂O and stirring the mixture at rt for 30 min, afforded exclusively the *trans*-epoxidation product in nearly quantitative yield with an ee value of 78% (Table 1, entry 1). Upon completion of the reaction, the solid catalyst was readily recovered from the reaction mixture by filtration under argon. After recharging with the reactants and the solvent (Et₂O), the recovered catalyst was reused for several runs (Table 1, entries 2–6). Intriguingly, the ee values of the epoxidation product **2a** underwent a slight increase during successive recycling runs, whereas the reaction rate slowed down gradually, presumably as a result of partial catalyst inactivation. While the results were encouraging, a drawback was noted in that after prolonged standing (24 h) in diethyl ether the catalyst lost most of its activity for the epoxidation. Although the exact reason was unknown, it is plausible that on prolonged standing in Et₂O solution, the catalyst assembly may have undergone an irreversible change in structure, leading to the formation of a more stable but inactive species. In such a case, shortening the reaction time period seems to be crucial for the recycling of the catalyst.

Subsequently, we proceeded to optimize the conditions for the above epoxidation based on the screening of the effects of various reaction parameters, including the solvent dependence, catalyst composition, and loading, the nature of the terminal oxidant (for details, see Table S1 in Table S1 in Supplementary data). The reaction proceeded smoothly in Et₂O, but the enantioselectivity was only moderate (78% ee). On the other hand, the coordinating solvent 1,4-dioxane was found to considerably retard the reaction, affording the epoxidation product in poor yield (27%) after long reaction period (40 h). Nevertheless, the enantioselectivity was excellent in this case, giving an optimal value of 95% ee for the product among all the solvents tested. To reach an acceptable balance between the reactivity and enantioselectivity, we further tested the catalyst preparation in 1,4-dioxane. After the solvent was removed in vacuo, the solid residue **L1**/Zn was used in the epoxidation of chalcone in diethyl ether with CMHP as the oxidant. Gratifyingly, with this procedure the epoxidation product was obtained in good yield (76%) and excellent ee (94%) within a reasonable reaction period (7 h) (see Table S1 in Supplementary data). Further screening of the epoxidation conditions indicated that an **L1**/Et₂Zn ratio of 1:2.8 at a 10 mol % loading of **L1** (relative to chalcone) was the best catalyst composition, while CMHP turned out to be optimal among the tested oxidants.

Having established the optimal reaction conditions of the procedure, we next shifted our attention to screen the structural ef-

Table 2

Screening of various bis-BINOL ligands in Zn-catalyzed heterogeneous epoxidation of chalcone **1a**^a



Entry	Ligand	Time (h)	Yield ^b (%)	ee ^c (%)
1	L1	5.5	76	91
2	L2	5	99	84
3	L3	4	82	89
4	L4	16	11	38
5	L5	19	93	10
6	L6	5	60	89
7	L7	5	88	88

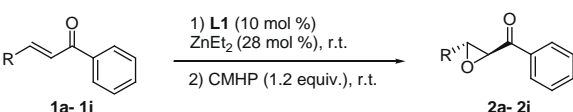
^a The catalysts were prepared in 1,4-dioxane (3 mL) followed by removal of the solvent in vacuo and the reactions were performed on 0.5-mmol scale of chalcone in Et₂O (2 mL) at room temperature.

^{b,c} See footnotes b and c in Table 1.

fects of a collection of bis-BINOL ligands **L1**–**L7**, featuring spacers with distinct shapes and/or sizes or bearing different substituents (X, Y) on the BINOL motifs (Chart 1). It was expected that such a difference in the geometry and/or substituent pattern on the bridging ligand skeleton should exert some effects on the catalysis of chalcone epoxidation, as a result of different microenvironment around the active sites in the resulting bis-BINOL/Zn assemblies.⁸ Indeed, under the above optimized conditions, wherein all the bis-BINOL/Zn catalysts were found insoluble in diethyl ether, wide variations in either the reactivity or the enantioselectivity were observed with different catalyst compositions, as summarized in Table 2. While increasing the length of the spacer to some extent seems to be beneficial for the catalytic reactivity (Table 2, entries 1, 2, and 6), introducing substituents other than H atoms at the 3,3'-positions of the BINOL motifs is obviously unfavorable for the catalysis, leading to a drastic degradation in product yield and/or ee values (Table 2, entries 4 and 5). These facts imply that the active species in the catalysis may be an aggregated multi nuclear Zn complex. Among all the catalysts tested, **L1**/Zn combination afforded the product with the highest ee value (91%), albeit in a slightly inferior yield as compared with some cases (entries 2, 3, and 7). In order to further highlight the advantage of this self-supported heterogeneous catalyst system, an analogous complex generated from (*R*)-BINOL and ZnEt₂ was examined in the epoxidation of chalcone under the same experimental conditions. Comparable yield (80%) and enantiomeric excess (95%) of the corresponding epoxide were obtained. Although the reaction mixture in this case appeared to remain turbid throughout the process, a significant amount of leached catalyst was observed in the filtrate. In fact, the catalytic activity of filtration-recovered BINOL/ZnEt₂ complex dramatically decreased on the consecutive reuses in the epoxidation (see Supplementary data, Table S2).

With these results in hand, we turned to examine the asymmetric epoxidation of various enones (**1a**–**i**) using **L1**/Zn as the heterogeneous catalyst.¹¹ As shown in Table 3, **L1**/Zn was quite versatile for the enones bearing either a β-aryl or alkyl substituent on the double bond. For the β-aryl substituted enones bearing electron-withdrawing groups, the corresponding epoxidation products were obtained in good to excellent yields with high ee values (Table 3, entries 2–6). Especially noteworthy is that the protocol could successfully be extended to the epoxidation of β-alkyl-substituted enones (Table 3, entries 7–9), which often constitute a challenging type of substrates for most catalytic protocols developed so far.

Table 3
Enantioselective heterogeneous epoxidation of α,β -unsaturated ketones with **L1**/Zn^a



Entry	R	Time (h)	Epoxide	Yield ^b (%)	ee ^c (%)
1	Ph	5.5	2a	76	91
2	4-ClC ₆ H ₅	4.5	2b	90	91
3	4-FC ₆ H ₅	4.5	2c	85	91
4	4-BrC ₆ H ₅	4.5	2d	99	91
5	4-NO ₂ C ₆ H ₅	4.5	2e	97	87
6	2-BrC ₆ H ₅	5	2f	81	90
7	Et	6	2g	73	81
8	n-Pr	6	2h	93	73
9	t-Bu	15	2i	61	93

^{a,b,c} See footnotes in Table 2.

In view of the persistent insolubility of the **L1**/Zn assembly in the reaction systems, the heterogeneous nature of the catalysis and the catalyst reuse were examined in the epoxidation of chalcone **1a** (Table 4). The catalyst, prepared by mixing **L1** with Et₂Zn in 1,4-dioxane followed by removal of the solvent, washing with diethyl ether and drying in vacuo, was isolated as an amorphous white solid. X-Ray powder diffraction analysis confirmed the amorphous nature of the solid, whereas SEM images revealed that the solid was composed of micrometer-sized noncrystalline particles. While the epoxidation proceeded smoothly in the presence of the **L1**/Zn solid, the inactivity of the filtrate was consistent with the heterogeneous nature of the catalysis. After completion of the reaction, the solid catalyst **L1**/Zn was separated from the reaction mixture by filtration under argon. The inductively coupled plasma (ICP) spectroscopic analysis of the liquid phase showed that no detectable zinc (<1 ppm) was leached into the solution. The recovered solid catalyst was recharged with diethyl ether, chalcone, and CMHP for the next run. The catalyst was reused for five consecutive runs, however, with notable decrease in reactivity after the second run for unknown reasons. Increasing the catalyst loading led to an enhancement in both reactivity and enantioselectivity during catalyst recycle.

In summary, we have developed a class of chiral self-supported bis-BINOL–Zn catalysts, which demonstrated good enantioselectivity and versatility in the heterogeneous catalysis of epoxidation of enones. The procedure is operationally simple and the catalyst could be easily recovered and reused several times. Further exploration on the potential application of self-supporting strategy in other catalytic reactions is underway in this laboratory.

Table 4
Recovery and reuse of the heterogeneous catalyst **L1**/Zn in the epoxidation of **1a**^a

Run	Time (h)	Yield ^b (%)	Ee ^c (%)
1 ^a	5.5	76	91
2	5.5	80	92
3	9.5	54	86
4	9.5	38	69
5	24	42	54
1 ^d	3	99	90
2	3	99	93
3	3	89	91
4	3	63	84
5	20	81	72

^{a,b,c} See footnotes in Table 2.

^d The loadings of **L1** and Et₂Zn were 15 mol % and 42 mol %, respectively, relative to **1a**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.151.

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- Typical procedure for the asymmetric epoxidation: To a Schlenk tube containing a stirred solution of ligand **L1** (32.4 mg, 0.05 mmol) in 1,4-

dioxane (3 mL) was added dropwise a solution of ZnEt₂ (0.14 mL, 0.14 mmol, 1.0 M solution in hexane) under argon. The resulted white turbid mixture was stirred at rt for 15 min, followed by removal of the solvent under reduced pressure. The residual white solid was charged with Et₂O (2 mL) and chalcone **1a** (104 mg, 0.5 mmol), and the resultant mixture was stirred at rt for 5 min before addition of CMHP (0.11 mL, 0.6 mmol, 80% solution in cumene). The mixture was stirred at rt for a period of time indicated in Table 4. The reaction process was monitored by TLC. After the reaction, the solid was isolated from the mixture by filtration under argon, washed twice with Et₂O, and recharged with Et₂O (2 mL), chalcone **1a** (104 mg, 0.5 mmol) and CMHP (0.11 mL, 0.6 mmol, 80% solution in cumene) for the next run. The combined filtrate was quenched with aq NaHSO₃ (5 mL), extracted with

EtOAc (3 × 10 mL), and the combined organic phase was washed with aq Na₂CO₃ and brine, and dried with MgSO₄. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (20:1) as eluent to give the epoxide **2a** as a white solid (85 mg, 76% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.00 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.42–7.36 (m, 5H), 4.31 (d, *J* = 1.8 Hz, 1H), 4.07 (d, *J* = 1.8 Hz, 1H). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL Chiralpak OB-H, hexane/2-propanol = 60:40, flow rate = 0.5 mL/min, 20 °C, λ = 254 nm; retention time: 22.2 min (major), 27.8 min (minor); 91% ee); [α]_D²⁰ +199.1 (*c* 0.58 in CH₂Cl₂) [lit.^{3d} [α]_D²⁶ +207.7 (*c* 0.78 in CH₂Cl₂) for 2*S*, 3*R* enantiomer with 90% ee].