A Chiral BINOL-Zinc Complex as a Novel Catalyst for the Enantioselective Epoxidation of α , β -Enones

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Abstract: First systematic studies on asymmetric epoxidation of electron-deficient α , β -enones with a simple zinc–BINOL catalyst in the presence of *tert*-butyl hydroperoxide and cumene hydroperoxide are described. The epoxidation proceeds in moderate to excellent yields with complete diastereoselectivity and high enantiomeric excesses by using enantiomerically pure BINOL. Different substituent effects are discussed.

Key words: enantioselective epoxidation, enones, BINOL, zinc, catalysis

The enantioselective synthesis of α , β -epoxy ketones is of major interest as the resulting chiral compounds are versatile precursors to many natural products and pharmaceuticals.¹ Juliá et al. were the first to report on the asymmetric epoxidation of chalcone using poly-L-alanine as a catalyst.² Although good enantio- and diastereoselectivities were observed, this method remained restricted to aryl-substituted α,β -unsaturated ketones. A crucial advancement was the involvement of a chiral ligand coordinated to the metal atom of a metal peroxide. Enders succeeded in generating a chiral zinc peroxide complex from the reaction of a chiral amino alcohol with diethylzinc under aerobic conditions.³ A stoichiometric amount of this metal complex was able to epoxidise a variety of (E)- α , β -unsaturated ketones with excellent yields, good enantioselectivities and complete diastereoselectivity. Later, Pu employed a binaphthyl polymer as chiral ligand, and through additional replacement of molecular oxygen by tert-butyl hydroperoxide (TBHP) turned the epoxidation into a catalytic process.^{2c,4} We were interested in studying the potential and efficiency of enantiopure BINOL in this reaction as to our knowledge no results have become available employing a simple zinc-BINOL complex in this type of epoxidation. Merely, lanthanide-BINOL complexes and the effect of several additives to the course of the epoxidation reaction have been extensively investigated.⁵ Still, unsubstituted BINOL is an attractive ligand since both enantiomers are commercially available. All reactions were carried out following the same experimental procedure.⁶ In a first set of experiments the solvent dependence of the epoxidation reaction was analysed using unsubstituted chalcone as a model substrate (Table 1).

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 Table 1
 Solvent Dependence of the Asymmetric Catalytic Epoxidation

$\begin{array}{c} 1) (R)-BINOL (20 \text{ mol}\%), \text{ solvent} \\ 2) ZnEt_2 (36 \text{ mol}\%), 0 °C, 15 \text{ min} \\ 3) \text{ oxidant (1.2 equiv), 0 °C } \rightarrow r.t., 12 \text{ h} \\ \end{array}$					
Entry So	olvent	Oxidant	Yield (%) ^a	ee (%) ^b	
1 CH	H ₂ Cl ₂	ТВНР	<5	_	
2 To	oluene	ТВНР	<5	_	
3 Et	₂ 0 7	ТВНР	80	47	
4 CH	H_2Cl_2	СМНР	95	5	
5 To	oluene	СМНР	95	71	
6 Et	₂ O	СМНР	99	68	
7° Et	₂ O	СМНР	99	67	
8 ^d Et	20	СМНР	99	76	

^a Only the *trans*-isomer is formed (de>99%), as determined from the

¹H NMR coupling constant of the vicinal protons on the oxirane ring.

^b Determined by HPLC analysis on a chiral stationary phase.⁸

^c 10 mol% (*R*)-BINOL, 18 mol% ZnEt₂. ^d 36 mol% ZnMe₂ instead of ZnEt₂.

Using TBHP as the terminal oxidant, diethyl ether is the solvent of choice in which the epoxide product could be isolated in reasonable amounts. Exclusively the trans-epoxide is formed in 80% yield with an ee of 47% (entry 3 in Table 1). Only traces of the product are detected in dichloromethane or toluene (entries 1, 2 in Table 1). The influence of the solvent on the observed chemical yields and enantiomeric excesses becomes more significant when switching to cumene hydroperoxide (CMHP). The solvent dependence of the chemical yield is completely canceled as nearly quantitative epoxidation is observed in the three chosen solvents. The extent of the asymmetric induction, however, varies strongly as the enantiomeric excess ranges from 71% and 68% in the case of toluene and diethyl ether to 5% in the case of dichloromethane (entries 4, 5, 6 in Table 1). Performing the reaction in diethyl ether with a reduced catalyst loading [10 mol% (R)-BINOL and 18 mol% ZnEt₂) did not have any negative influence on the results (entry 7 in Table 1). A remarkable increase of the enantiomeric excess up to 76% is detected in diethyl ether when dimethylzinc is employed instead of diethylzinc (entry 8 in Table 1). No epoxidation at all was

observed when the reaction was conducted in tetrahydrofuran irrespective of the oxidating reagent in use. In order to compare the reactivity of TBHP and CMHP in the following studies the subsequent reactions were run in diethyl ether as solvent. The sensitivity of the reaction towards electronic modification of the substrate was investigated by changing the *para*-substituent X on the β -phenyl group (Table 2).

On the one hand, enhancing the electron-deficiency of the double bond with a substituent like R = Br results in an increase of the ee up to 71% and 72%, irrespective of whether TBHP or CMHP is used as an oxidant (entries 5, 6 in Table 2). Unexpectedly, this tendency is not sustained for the much more electron-withdrawing substituent $X = NO_2$ as the enantiomeric excesses decrease to 60% and 62%, respectively (entries 7, 8 in Table 2). On the other hand, rendering the unsaturated bond in the enone more electron-rich by replacing X = H for the electron-donating substituent X = OMe or even for a substituent with a slight positive inductive effect like X = Me causes a complete inhibition of the epoxidation (entries 1, 2 in Table 2). The possibility of increasing the enantiomeric excesses by performing the oxidation at lower temperatures was tested with *p*-Br-chalcone **1d** (Table 3).

 Table 2
 Asymmetric Catalytic Epoxidation of Substituted Chalcones

	1) (<i>R</i>)-BINOL (20 mol%), Et ₂ O 2) ZnEt ₂ (36 mol%),	
Ph	0 °C, 15 min 3) oxidant (1.2 equiv), 0 °C \rightarrow r.t., 12 h	Ph
x 1	х	2

Entry	Enone X ^c	Oxidant	Product ^d	Yield (%) ^a	ee (%) ^b
1	OMe 1a	TBHP/ CMHP	2a	-	-
2	Ме 1b	TBHP/ CMHP	2b	-	-
3	Н 1с	TBHP	2c	80	47
4	Н 1с	CMHP	2c	99	68
5	Br 1d	TBHP	2d	50	71
6	Br 1d	CMHP	2d	95	72
7	NO ₂ 1e	TBHP	2e	<10	60
8	NO ₂ 1e	CMHP	2e	86	62

^a trans-Isomer (de >99%).

^b Determined by HPLC analysis on a chiral stationary phase.⁸

° Ref.7

d Ref.8

When the temperature is slightly decreased from 0 °C to -5 °C the enantiomeric excess rises up to 80% while the yield still remains nearly quantitative (95%) (entry 2 in Table 3). Running the reaction at -10 °C affords the same enantiomeric excess as for 0 °C but with a lower yield (entry 3 in Table 3). A further lowering of the temperature to -20 °C is deleterious as both the enantiomeric excess and the chemical yield decrease significantly (entry 4 in Table 3). However, control experiments concerning the reaction time revealed a pronounced acceleration for CMHP as oxidant in comparison with TBHP. For example, standard epoxidations of 1d and chalcone were found to be completed after 2.5 and 4 hours, respectively. Additionally, alkyl-substituted olefins were investigated which have received only scant attention in this type of oxidation. The steric bulk at the enone was varied as different alkyl chains were introduced in the β -position (Table 4). For TBHP as an oxidant the asymmetric induction increases with the length of the alkyl chain. This tendency is reversed for CMHP as the enantiomeric excess decreases from 54% ee for R^1 = Me to 40% ee for R^1 = Pr (entries 2, 6 in Table 4). In general, the reactions with CMHP proceed in all cases with significantly higher chemical yields compared to TBHP. However, considering these tendencies the enantiomeric excesses measured for $R^1 = i$ -Pr do not match (entries 7, 8 in Table 4). A possible explanation for this phenomenon may be the conformational flexibility of R = i-Pr. A bulky substituent R^1 leads to high asymmetric induction only if R^1 is conformationally fixed as for R = t-Bu; both oxidants yield the epoxide in 80% ee (entries 9, 10 in Table 4). When using the sterically more hindered oxidant CMHP the yield is increased from <10% up to 73% (entry 10 in Table 4).

In order to exclude any background reaction, i.e. the nonstereoselective epoxidation without a BINOL–zinc complex, two control experiments were performed: no epoxidation was observed in the absence of either diethylzinc or (R)-BINOL.

 Table 3
 Temperature Dependence of the Catalytic Epoxidation

Br	1) (<i>R</i>)- (20) 2) ZnE 0 °C 3) CMI Ph (1.2 1d	BINOL mol%), Et ₂ O t ₂ (36 mol%), , 15 min HP equiv), 12 h	O Ph
Entry	Temp (°C) ^a	Yield (%)	ee (%)
1	0	95	72
2	-5	95	80
3	-10	79	72
4	-20	51	64

^a The temperature is referred to as the temperature at which the enone and the CMHP are added. The temperature was held constant during the 12 h reaction time.

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Table 4 Asymmetric Epoxidation of Alkyl-Substituted Enones

p1	1) (F 0 2) Zi 3) 00	R)-BINOL (20 nEt ₂ (36 mol% kidant (1.2 equ	mol%), Et_2O b), 0 °C, 15 min uiv), 0 °C \rightarrow r.t.	, 12 h	
1	e Pn I			~ R' 0	>` Ph 2
Entry	Enone R ^{1c}	Oxidant	Product ^d	Yield (%) ^a	ee (%) ^b
1	Me 1f	ТВНР	2f	24	40
2	Me 1f	СМНР	2f	60	54
3	Et 1g	ТВНР	2g	28	48
4	Et 1g	СМНР	2g	79	50
5	Pr 1h	TBHP	2h	72	60
6	Pr 1h	CMHP	2h	78	40
7	<i>i-</i> Pr 1i	TBHP	2i	36	54
8	<i>i-</i> Pr 1i	СМНР	2i	75	40
9	<i>t-</i> Bu 1k	TBHP	2k	<10	80
10	<i>t</i> -Bu 1k	СМНР	2k	73	80

^a trans-Isomer (de >99%).

^b Determined by HPLC analysis on a chiral stationary phase.⁸

^c Ref.⁷

^d Ref.⁸

In summary, we have shown that the combination of enantiomerically pure BINOL and dialkylzinc provides an effective catalyst for the asymmetric epoxidation of α , β enones. This catalytic epoxidation proceeds with good enantiomeric excesses and complete diastereoselectivity, yielding exclusively the *trans*-isomer. A remarkable effect regarding the oxidant was observed and CMHP proves to be the oxidant of choice. Overall, the ease of conductance and the easy recovery of both commercially available BINOL-enantiomers render the described procedure an attractive protocol.

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- (6) Typical Procedure for the Asymmetric Epoxidation: (R)-BINOL (57 mg, 0.2 mmol) was dissolved in Et₂O (20 mL) in a 50 mL Schlenk flask equipped with a magnetic stirring bar under an inert atmosphere. After cooling to 0 °C with an ice-bath ZnEt₂ (0.33 mL, 0.36 mmol, 1.1 M solution in toluene) was added with stirring. After 15 min the α , β unsaturated ketone (1 mmol) and the oxidant (0.24 mL, 1.2 mmol, 5-6 M in decane in the case of TBHP; 0.22 mL, 1.2 mmol, 80% solution in cumene in the case of CMHP) were added, and the resulting mixture was allowed to warm to r.t. overnight. The reaction was quenched with aq sat. NaHSO₃ and extracted with EtOAc. The organic layer was washed with aq Na₂CO₃ and brine. The combined organic layers were dried over MgSO₄ and the solvent was evaporated in vacuo. The residue was purified by column chromatography (SiO₂: Macherey–Nagel type 60, 0.063–-0.2 mm). CH₂Cl₂ was used as eluent in all cases and remaining starting material and the α,β -epoxy-ketone were isolated in this sequence. As the last fraction (R)-BINOL was recovered almost quantitatively. The ee of the epoxides were determined by HPLC analysis on a stationary phase: Chiracel OD/OD-H column with n-hexane-2-propanol as eluent and 254 nm UV detector. The absolute configuration of the products has been assigned by comparison of optical rotation with literature values and the elution order of the two enantiomers on the HPLC column.
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