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# Enantioselective Epoxidation of α,β-Enones by Electrophilic Activation with a BINOL–Zinc Catalyst

**Ana Minatti[a] and Karl Heinz Dötz*[a]**

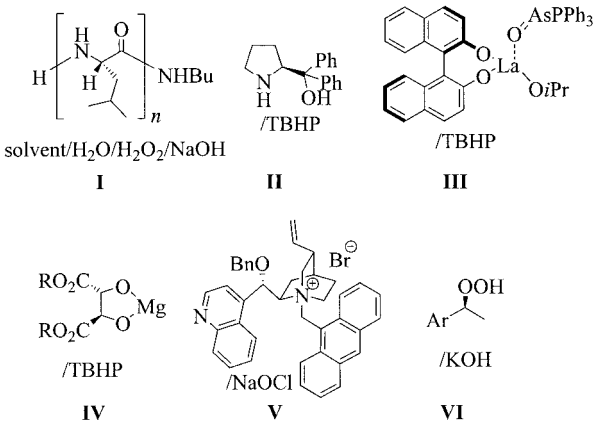
**Keywords:** Asymmetric catalysis / Enantioselectivity / Enones / Epoxidation / Zinc

The combination of BINOL and a dialkylzinc reagent $R_2Zn$ affords, in situ, a catalyst for homogeneous epoxidation of (*E*)-α,β-enones to the corresponding *trans*-epoxy ketones. *tert*-Butyl hydroperoxide (TBHP) and cumene hydroperoxide (CMHP) are effective terminal oxidants for this process. Enantiomeric excesses of up to 96 % can be achieved conveniently at room temperature. Mechanistic investigations point towards an electrophilic activation of the substrates by the chiral BINOL–zinc catalyst and a subsequent nucleophilic attack of the oxidant. This mechanistic proposal is supported additionally by a non-linear effect, the absolute product configuration as well as NMR studies.


## Introduction

The enantioselective synthesis of α,β-epoxy ketones is of major interest to organic synthesis in general and medicinal chemistry in particular as the resulting chiral compounds are versatile precursors to many natural products and pharmaceuticals.[1] Since the seminal work of Weitz and Scheffer on the epoxidation of electron-deficient alkenes,[2] several asymmetric variants of this reaction have been developed.[3] Juliá and Colonna were the first to report on the use of poly-L-alanine as a catalyst for the enantioselective epoxidation of chalcone.[4] Since then, a variety of valuable protocols based on poly(amino acid) catalysts (e.g. **I** in Scheme 1) have been established for a variety of α,β-enones.[5] Recently, even a monomeric proline-derived catalyst (**II**) has proved to be effective in the enantioselective epoxidation of enones.[6] Phase-transfer catalysis derived from Chinchona alkaloids (e.g. **V**) have also been found to catalyse the enantioselective epoxidation of a wide range of enones in the presence of, for example, sodium hypochlorite.[7] Another important contribution originated from the employment of optically pure hydroperoxides (**VI**).[8]

Nevertheless, a broad scope of developments can be found in the field of chiral ligand–metal peroxides for this enantioselective oxidative transformation. Enders et al. have reported that (*E*)-α,β-unsaturated ketones can be epoxidised in an enantioselective fashion using stoichiometric amounts of diethylzinc and (*R*,*R*)-*N*-methylpseudoephedrine, under oxygen (Scheme 2).[9] The initially formed chiral ethylzinc alkoxide is oxidised to the corresponding chiral ethylperoxyzinc alkoxide, which attacks the *si*-face of the enone in an oxa-Michael type addition to give the *trans*-epoxy ketone.




Scheme 1. Different strategies for the enantioselective epoxidation of α,β-unsaturated ketones.

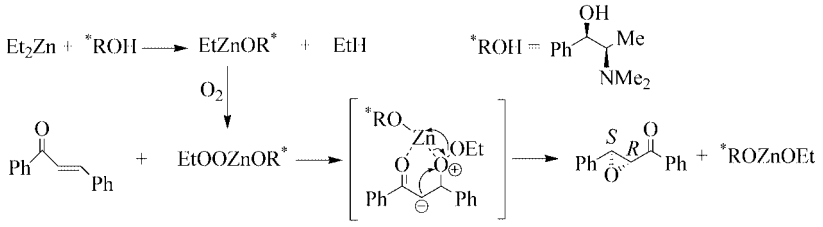
Later, Pu et al. employed a binaphthyl polymer as a chiral ligand, and by additional replacement of molecular oxygen by *tert*-butyl hydroperoxide (TBHP) turned the epoxidation into a catalytic process (Scheme 3).[10]

Shibasaki et al. introduced chiral lanthanide–BINOL catalysts (e.g. **III** in Scheme 1) and studied the effect of several additives on the course of the epoxidation reaction.[11] Finally, Jackson has developed the catalytic enantioselective epoxidation of aryl- and alkyl-substituted enones using tartrate-derived magnesium alkoxides (**IV** in Scheme 1).[12]

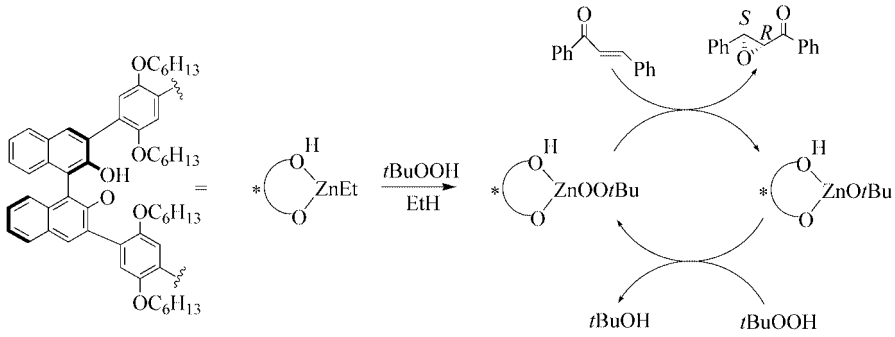
In a preliminary report, we have recently described a new method for the enantioselective epoxidation of α,β-enones with a chiral zinc–BINOL catalyst using *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CMHP) as the terminal oxidant.[13] In this paper, we wish to report the optimisation of this catalytic reaction and discuss its mech-

[a] Kekulé-Institut für Organische Chemie und Biochemie, Rheinische Friedrich-Wilhelms Universität Bonn, Gerhard-Domagk-Str. 1, 53112 Bonn, Germany
E-mail: doetz@uni-bonn.de



Scheme 2. Zinc-mediated aerobic enantioselective epoxidation in the presence of (*R*,*R*)-*N*-methylpseudoephedrine.

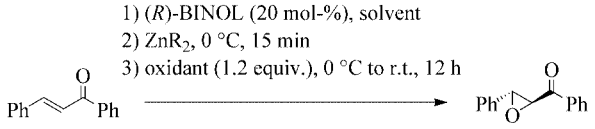


Scheme 3. Enantioselective epoxidation of enones catalysed by a chiral polybinaphthyl–zinc complex.

anistic background. Furthermore, a NMR spectroscopic study of the catalytically active species will be presented.

## Results and Discussion

In a first set of experiments the dependence of the epoxidation on various reaction parameters was analysed with chalcone as the model substrate (Scheme 4, Table 1). This includes the study of solvent dependence (Table 1, entries 1–7), catalyst loading (Table 1, entries 7–9), the nature of the diorganozinc species (Table 1, entries 10–12), and finally the nature of the terminal oxidant (Table 1, entries 13 and 14).



Scheme 4. Enantioselective catalytic epoxidation of chalcone.

Diethyl ether turned out to be the solvent of choice, as the reactions conducted in this solvent provided the best results both with TBHP (80% yield, 47% *ee*) as well as with CMHP (99% yield, 68% *ee*) as the terminal oxidant (Table 1, entries 4 and 7). The *trans*-epoxide was formed exclusively in all cases, rendering this reaction a completely diastereoselective process. The superiority of CMHP to

Table 1. Optimisation of reaction conditions for the epoxidation of chalcone.

| Entry | Solvent | Oxidant | $ZnR_2$ [mol-%] | Yield [%][a] | *de* [%][b] | *ee* [%][c,d] |
|---|---|---|---|---|---|---|
| 1 | THF | TBHP/CMHP | $ZnEt_2$ [36] | – | – | – |
| 2 | $CH_2Cl_2$ | TBHP | $ZnEt_2$ [36] | <5 | >99 | nd |
| 3 | toluene | TBHP | $ZnEt_2$ [36] | <5 | >99 | nd |
| 4 | $Et_2O$ | TBHP | $ZnEt_2$ [36] | 80 | >99 | 47 |
| 5 | $CH_2Cl_2$ | CMHP | $ZnEt_2$ [36] | 95 | >99 | 5 |
| 6 | toluene | CMHP | $ZnEt_2$ [36] | 95 | >99 | 71 |
| 7 | $Et_2O$ | CMHP | $ZnEt_2$ [36] | 99 | >99 | 68 |
| 8 | $Et_2O$ | CMHP | $ZnEt_2$ [18][e] | 99 | >99 | 67 |
| 9 | $Et_2O$ | CMHP | $ZnEt_2$ [9][f] | 99 | >99 | 58 |
| 10 | $Et_2O$ | CMHP | $ZnMe_2$ [36] | 99 | >99 | 76 |
| 11 | $Et_2O$ | CMHP | $ZnPh_2$ [36] | – | – | – |
| 12 | toluene | CMHP | $ZnPh_2$ [36] | – | – | – |
| 13 | $Et_2O$ | $H_2O_2$ | $ZnEt_2$ [36] | – | – | – |
| 14 | $Et_2O$ | *m*CPBA | $ZnEt_2$ [36] | –[g] | – | – |

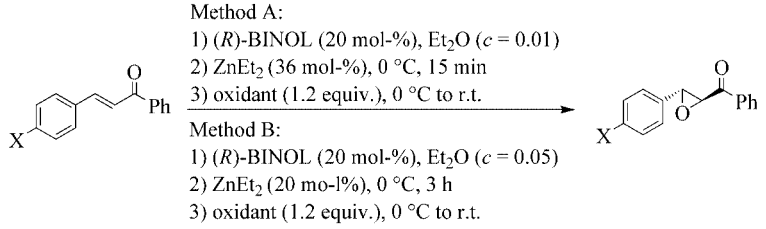
[a] Yield of epoxide isolated. [b] Only the *trans*-isomer is formed, as determined from the $^1H$ NMR coupling constant of the vicinal protons on the oxirane ring. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration of the major enantiomer was determined to be (2*S*,3*R*) by comparison of the optical rotation and HPLC retention times with those reported in the literature.[14] [e] 10 mol-% (*R*)-BINOL. [f] 5 mol-% (*R*)-BINOL. [g] Traces of (*E*)-β-benzoyloxystyrene were isolated.

TBHP was already noticeable in these early experiments as only traces of the product were detected in dichloromethane and toluene with TBHP (Table 1, entries 2 and 3) and nearly quantitative epoxidation was observed in dichloromethane, toluene and diethyl ether for CMHP (Table 1, entries 5–7). The extent of the asymmetric induction, however, varied strongly, as the enantiomeric excesses ranged from 71% and 68% in the case of toluene and diethyl ether, respectively, to 5% in the case of dichloromethane. No epoxidation at all was observed when the reaction was conducted in tetrahydrofuran, irrespective of the oxidising reagent in use (Table 1, entry 1). Performing the reaction in diethyl ether with half of the catalyst loading [10 mol-% (*R*)-BINOL and 18 mol-% $ZnEt_2$] did not have any negative influence on the result (Table 1, entry 8). However, a further decrease to 10 mol-% $ZnEt_2$ and 5 mol-% (*R*)-BINOL decreased the enantiomeric excess slightly to 58% (Table 1, entry 9). Variation of the diorganozinc species caused a remarkable increase of the enantiomeric excess up to 76% in diethyl ether when dimethylzinc was used (Table 1, entry 10). In contrast to the dialkylzinc species, which were employed as solutions, diphenylzinc was added as a solid to a solution of (*R*)-BINOL. No dissolution and therefore no epoxidation at all was observed in diethyl ether or toluene (Table 1, entries 11 and 12). Finally, hydrogen peroxide and *m*-chloroperbenzoic acid were tested as terminal oxidants. No epoxide formation was observed with either oxidant, although a small amount of the chalcone enol ester was isolated in the case of the peracid. The formation of this product can be explained by a Baeyer–Villiger oxidation of chalcone.[15]

The sensitivity of the reaction towards electronic modification of the substrate was investigated by changing the *para*-substituent X on the β-phenyl ring (Scheme 5, Table 2). Additionally, the epoxidation of each substrate was performed following two different methods A and B, which differ in the $ZnEt_2$/(*R*)-BINOL ratio (A: 1.8:1; B: 1:1) and concentration {A: *c* = 0.01 [mmol (*R*)-BINOL/mL $Et_2O$]; B: *c* = 0.05 [mmol (*R*)-BINOL/mL $Et_2O$]}.

The results shown in Table 2 reveal that rendering the unsaturated bond in the enone more electron-rich by replacing X = H with OMe or even a substituent with only a slightly positive inductive effect, such as Me, causes a complete inhibition of the epoxidation (Table 2, entries 1 and 2). On the other hand, enhancing the electron-deficiency of the double bond with a substituent like Br resulted in an increase in the *ee* up to 71 and 72%, irrespective of whether TBHP or CMHP was used as oxidant (Table 2, entries 6 and 7). Unexpectedly, this tendency was not sustained for the much more electron-withdrawing group $NO_2$ − the enantiomeric excesses decreased to 60% and 62%, respectively (Table 2, entries 9 and 10). CMHP provided significantly higher yields than TBHP in all cases and increased the reaction rate, resulting in shorter reaction times. An exceptional increase of the enantiomeric excesses and acceleration of the reaction was found for the chalcone derivatives when the epoxidation was run under conditions B. After a reaction time of only one hour, complete epoxidation of all




Scheme 5. Enantioselective catalytic epoxidation of substituted chalcones.

Table 2. Enantioselective catalytic epoxidation of substituted chalcones.

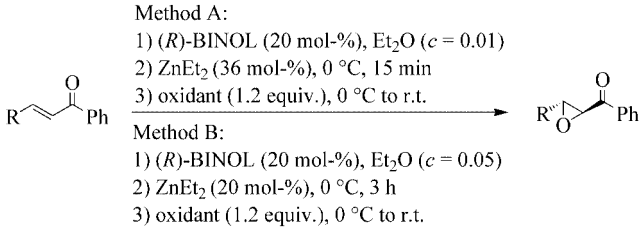
| Entry | Enone (X) | Method[a] | Oxidant | *t* [h] | Yield [%][b] | *de* [%][c] | *ee* [%][d,e] |
|---|---|---|---|---|---|---|---|
| 1 | **1** (OMe) | A | TBHP/CMHP | 12 | – | – | – |
| 2 | **2** (Me) | A | TBHP/CMHP | 12 | – | – | – |
| 3 | **3** (H) | A | TBHP | 12 | 80 | >99 | 47 |
| 4 | **3** (H) | A | CMHP | 4 | 99 | >99 | 68 |
| 5 | **3** (H) | B | CMHP | 1 | 99 | >99 | 90 |
| 6 | **4** (Br) | A | TBHP | 12 | 50 | >99 | 71 |
| 7 | **4** (Br) | A | CMHP | 2.5 | 95 | >99 | 72 |
| 8 | **4** (Br) | B | CMHP | 1 | 99 | >99 | 92 |
| 9 | **5** ($NO_2$) | A | TMHP | 12 | <10 | >99 | 60 |
| 10 | **5** ($NO_2$) | A | CMHP | 12 | 86 | >99 | 62 |
| 11 | **5** ($NO_2$) | B | CMHP | 1 | 99 | >99 | 76 |

[a] Method A: 20 mol-% (*R*)-BINOL, 36 mol-% $ZnEt_2$, 0 °C, 15 min, 1.2 equiv. oxidant, *c* = 0.01 [mmol (*R*)-BINOL/mL $Et_2O$]; Method B: 20 mol-% (*R*)-BINOL, 20 mol-% $ZnEt_2$, 0 °C, 3 h, 1.2 equiv. oxidant, *c* = 0.05 [mmol (*R*)-BINOL/mL $Et_2O$]. [b] Yield of epoxide isolated. [c] Only the *trans*-isomer is formed, as determined from the $^1H$ NMR coupling constant of the vicinal protons on the oxirane ring. [d] Determined by HPLC analysis on a chiral stationary phase. [e] The absolute configuration of the major enantiomer was determined to be (2*S*,3*R*) by comparison of the optical rotation and HPLC retention times with those reported in the literature.[14]

three substrates (**3**–**5**) was observed and the enantiomeric excesses of the corresponding epoxides were determined to be 90% (**3**), 92% (**4**) and 76% (**5**) (Table 2, entries 5, 8 and 11). This striking increase in *ee* renders protocol B the most convenient and efficient one.

This pronounced effect was also encountered when the present protocols were successfully extended to substrates bearing a β-alkyl substituent on the double bond (Scheme 6). The steric bulk at the enone was varied by introducing different alkyl chains (R) in the β-position (Table 3).




Scheme 6. Enantioselective catalytic epoxidation of alkyl-substituted enones.

When performing the epoxidations under conditions A with TBHP as 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% for R = Me to 40% for R = *n*Pr (Table 3, entries 2 and 8). As an exception, the *ee* obtained for R = *i*Pr does not follow this rule (Table 3, entries 10 and 11). A possible explanation for this phenomenon may be the conformational flexibility of *i*Pr. The bulky substituent *t*Bu is conformationally fixed and furnished an *ee* of 80%, irrespective of the oxidising reagent used (Table 3, entries 13 and 14). In general, the reactions with CMHP proceeded with significantly higher yields than with TBHP in all cases.

As expected, performing the epoxidations under conditions B led again to a significant improvement. The reaction times decreased from 12 h to 5 h (R = *t*Bu) or even 1.5 h (R = Me), the epoxides were isolated in very high yields (83–99%) and the enantiomeric excesses increased approximately up to 20% in every case (Table 3, entries 3, 6, 9, 12 and 15). The *t*Bu-substituted enone **10** provided the highest enantiomeric excess (96%).

The fact that the s-*cis* conformation of the enone moiety is a conformational prerequisite for a successful epoxidation was proven by the unreactivity of 2-cyclohexanone as a typical representative of an *s*-*trans*-enone.

To gain insight into the mechanism of this epoxidation reaction, we next investigated the possible existence of nonlinear effects using BINOL of different degrees of optical purity (Figure 1).[16]

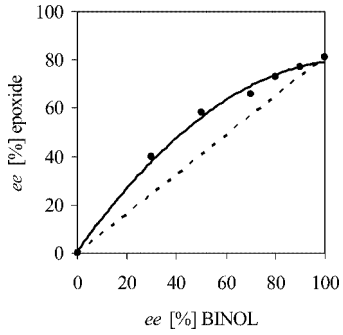



Figure 1. Asymmetric amplification in the epoxidation of chalcone at $c$ = 0.05 catalysed by the Zn–BINOL catalyst generated in situ.

Within experimental error, asymmetric amplification was observed for the epoxidation of chalcone under conditions B. This correlation points towards the preferential formation of heterodimeric or -oligomeric zinc BINOLate complexes, which are less reactive than the monomeric ones.

Two striking differences between our experimental data and the results obtained in the zinc-mediated enantioselective epoxidations by Enders[9a,9b] and Pu[10] prompted us to

Table 3. Enantioselective catalytic epoxidation of alkyl-substituted enones.

| Entry | Enone (R) | Method[a] | Oxidant | *t* [h] | Yield [%][b] | *de* [%][c] | *ee* [%][d,e] |
|---|---|---|---|---|---|---|---|
| 1 | **6** (Me) | A | TBHP | 12 | 24 | >99 | 40 |
| 2 | **6** (Me) | A | CMHP | 12 | 60 | >99 | 54 |
| 3 | **6** (Me) | B | CMHP | 1.5 | 99 | >99 | 68 |
| 4 | **7** (Et) | A | TBHP | 12 | 28 | >99 | 48 |
| 5 | **7** (Et) | A | CMHP | 12 | 79 | >99 | 50 |
| 6 | **7** (Et) | B | CMHP | 2.5 | 99 | >99 | 73 |
| 7 | **8** (*n*Pr) | A | TBHP | 12 | 72 | >99 | 60 |
| 8 | **8** (*n*Pr) | A | CMHP | 12 | 78 | >99 | 40 |
| 9 | **8** (*n*Pr) | B | CMHP | 4 | 90 | >99 | 64 |
| 10 | **9** (*i*Pr) | A | TBHP | 12 | 36 | >99 | 54 |
| 11 | **9** (*i*Pr) | A | CMHP | 12 | 75 | >99 | 40 |
| 12 | **9** (*i*Pr) | B | CMHP | 1.5 | 90 | >99 | 68 |
| 13 | **10** (*t*Bu) | A | TBHP | 12 | <10 | >99 | 80 |
| 14 | **10** (*t*Bu) | A | CMHP | 12 | 73 | >99 | 80 |
| 15 | **10** (*t*Bu) | B | CMHP | 5 | 83 | >99 | 96 |

[a] Method A: 20 mol-% (*R*)-BINOL, 36 mol-% $ZnEt_2$, 0 °C, 15 min, 1.2 equiv. oxidant, $c$ = 0.01 [mmol (*R*)-BINOL /mL $Et_2O$]; Method B: 20 mol-% (*R*)-BINOL, 20 mol-% $ZnEt_2$, 0 °C, 3 h, 1.2 equiv. oxidant, $c$ = 0.05 [mmol (*R*)-BINOL/mL $Et_2O$]. [b] Yield of epoxide isolated. [c] Only the *trans*-isomer is formed, as determined from the $^1H$ NMR coupling constant of the vicinal protons on the oxirane ring. [d] Determined by HPLC analysis on a chiral stationary phase. [e] The absolute configuration of the major enantiomer was determined to be (2*S*,3*R*) by comparison of the optical rotation and HPLC retention times with those reported in the literature.[14]

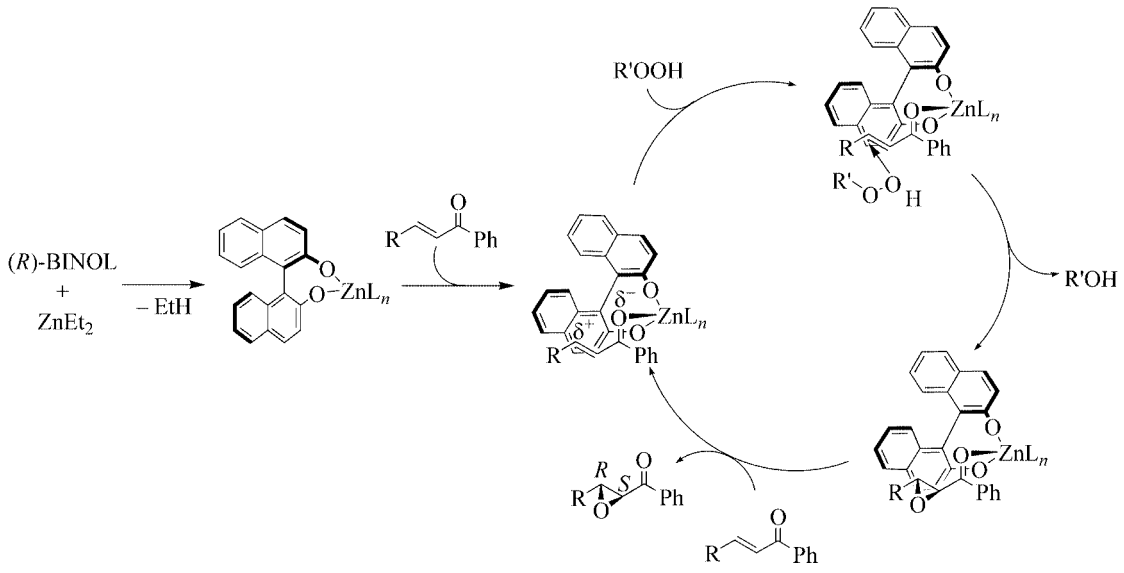



Figure 2. Proposed catalytic cycle for the enantioselective epoxidation with the Zn–(*R*)-BINOL catalyst.

suggest a different reaction mechanism to the commonly stated one (Schemes 2 and 3).

Pu obtained (2*R*,3*S*)-configured epoxy ketones when using (*R*)-binaphthol polymeric zinc complexes and both Enders and Pu have reported the successful epoxidation of enones bearing an electron-donating group at the *para*-position on the β-phenyl ring. As a consequence, we postulate the mechanism depicted in Figure 2 for the enantioselective epoxidation of enones catalysed by a zinc (*R*)-BINOLate complex.

The zinc (*R*)-BINOLate complex formed in situ acts solely as a Lewis acid and activates the enone function for nucleophilic attack by complexing the carbonyl functionality. The final configuration of the obtained epoxy ketone (2*S*,3*R*) suggests that the (*R*)-BINOLate complex blocks the *si*-face of the enone (Figure 3).

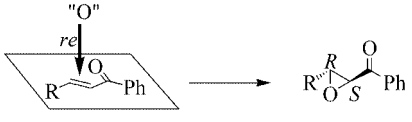



Figure 3. Face-selectivity in the enantioselective epoxidation with the Zn–(*R*)-BINOL catalyst.

This observation is in complete agreement with the general rule for (*R*)-binaphthyl metal complexes interacting with carbonyl functionalities.[17] For the present oxidation, Lewis acidic activation by the zinc catalyst renders the β-carbon atom of the vinylogous substrate positively charged. This electrophilic position can then be attacked by the weakly nucleophilic hydroperoxide, which transfers an oxygen atom within the chiral environment to yield the (2*S*,3*R*)-epoxy ketone and the corresponding alcohol (Figure 4).

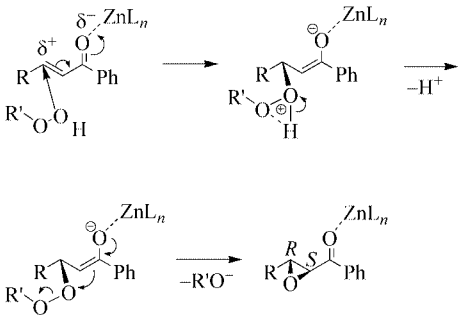



Figure 4. Proposed mechanism for the oxygen transfer.

The resulting epoxy ketone is readily displaced by another enone molecule to close the overall catalytic cycle as, due to the conjugated system, the carbonyl oxygen of the enone displays a higher electron density than the carbonyl oxygen of the epoxy ketone.

Our control experiments rule out background reactions like the epoxidation in the absence of $ZnEt_2$ or (*R*)-BINOL. The inertness of *p*-OMe- or *p*-Me-substituted chalcone derivatives can be rationalised by considering that these enones undergo electronic stabilisation through the arene donor substituent, which decreases their Michael acceptor character. Thus, the nucleophilicity of the peroxides is not sufficient to initiate oxidation. The acceleration of the reaction rate and the increased yields observed for CMHP as terminal oxidant reflects the better leaving-group character of $PhMe_2CO^-$ as compared to $t$BuO$^-$ [p$k_a$($t$BuOH, DMSO) = 29.4; p$k_a$($PhMe_2COH$, DMSO) = 14.3].[18]

The formation of a "white precipitate" was observed upon mixing one equivalent of (*R*)-BINOL with one equivalent of $ZnEt_2$ solution (conditions B).[19] A simple stoichiometric experiment proved this species to be the catalytically active species, or at least the immediate precatalyst, as

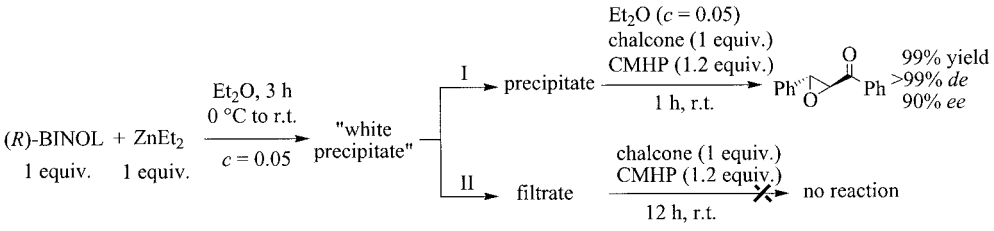
  

filtering the precipitate off and performing an epoxidation with the solid resulted in complete conversion and formation of the epoxy ketone in 99% yield, >99% *de* and 90% *ee* (Scheme 7, case I). No reaction, however, was observed when the filtrate was used instead (Scheme 7, case II).

$^1$H NMR spectroscopic experiments were undertaken to visualise the chemical reaction between (*R*)-BINOL and $ZnEt_2$. A comparison of the NMR spectra before and after the addition of one equivalent of $ZnEt_2$ (solution in toluene) to a solution of (*R*)-BINOL in $CDCl_3$ reveals that the hydroxy protons ($\delta$ = 5.1 ppm) have disappeared [Figure 5, parts a) and b)]. Interestingly, spectrum b) shows very broad signals, which suggests the formation of zinc (*R*)-BINOLate aggregates. This is in agreement with the observation that the solution in the NMR tube turned very viscous until a white gel was formed. Simple shaking of the NMR probe, however, caused the solution to turn clear again, and the recorded NMR spectrum c) reveals sharp signals again, indicating efficient deaggregation.

A comparison of the aromatic section of the $^1$H NMR spectra of a) and c) (Figure 6) suggests the formation of a $C_2$-symmetric complex present in b) characterised by only six multiplets (corresponding to 2 H atoms each); the multiplet fine-structures are identical to those of the parent (*R*)-BINOL signals. The coordination of diethylzinc to (*R*)-BINOL with concomitant loss of ethane is supported by both the missing OH signals and the distinct upfield shift of the aromatic protons ($6.47 < \delta < 7.91$ ppm) compared to those in free (*R*)-BINOL ($7.16 < \delta < 7.95$ ppm), which is most noticeable for $H^3$, $H^4$ and $H^8$, as expected for zinc–BINOLate chelation.

Based on these results, we conclude a pronounced role of a BINOL–Zn catalyst, readily generated in situ from $ZnR_2$ and BINOL as a white precipitate when both components are mixed in a 1:1 ratio. This complex, even when present in minor amounts, is suggested to dominate the kinetic activation of the enone carbonyl group and, thus, the enantioselective oxidation pathway. The role of the alkyl hy-




Scheme 7. Reactivity of the "white precipitate".

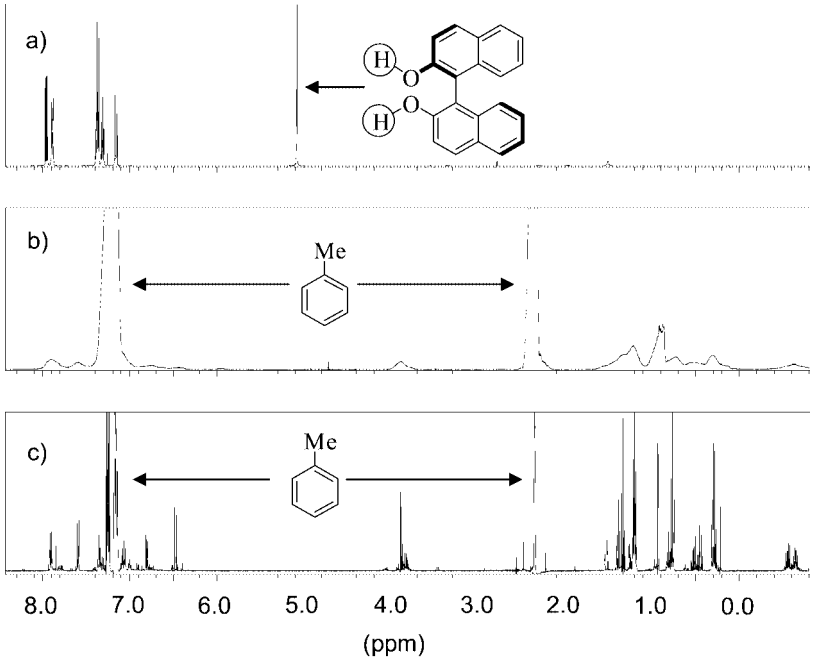



Figure 5. $^1$H NMR spectrum of (*R*)-BINOL ($CDCl_3$) (a), $^1$H NMR spectrum of (*R*)-BINOL + 1 equiv. $ZnEt_2$ ($CDCl_3$, toluene) white precipitate (b), and $^1$H NMR spectrum of (*R*)-BINOL + 1 equiv. $ZnEt_2$ ($CDCl_3$, toluene) clear solution (c).

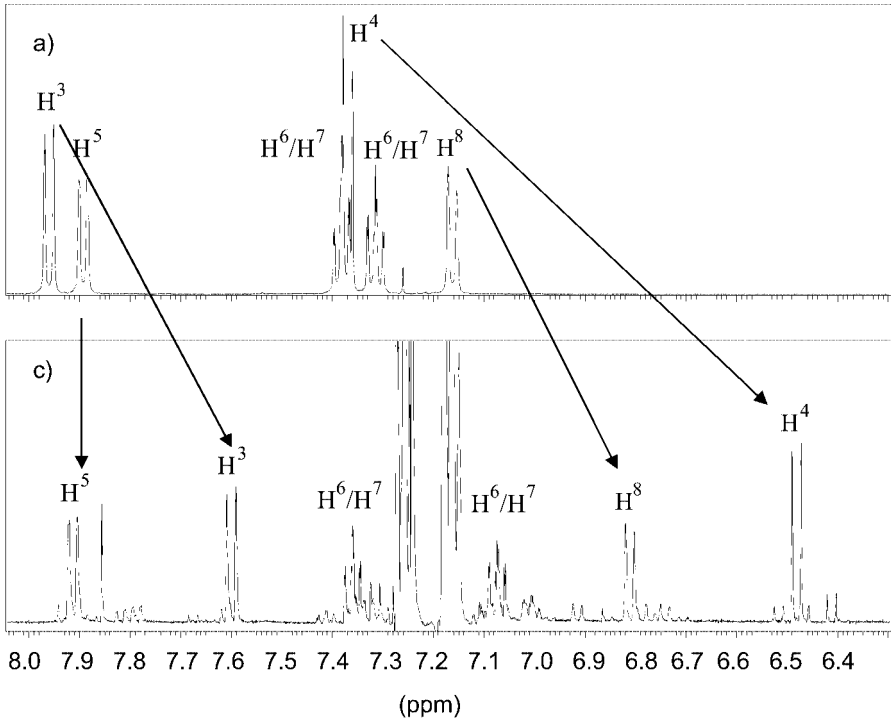



Figure 6. Enlarged aromatic sections of the $^1$H NMR spectra labeled a) and c) in Figure 5.

droperoxide is characterised by a nucleophilic attack at the β-carbon atom of the enone.

## Conclusions

In summary, we have demonstrated that the combination of enantiomerically pure BINOL and a dialkylzinc reagent provides an effective catalyst for the enantioselective epoxidation of α,β-enones. Under optimised conditions, the catalytic epoxidation proceeds for a variety of enones in very high yields, with excellent enantiomeric excesses up to 96% and complete diastereoselectivity, yielding exclusively the *trans*-epoxide. The efficiency of the reaction depends on the nature of the oxidant, and CMHP proved to be the oxidant of choice. Since both (*R*)- and (*S*)-BINOL, are commercially available, either enantiomer of the resulting epoxides is accessible. The ease of performance, the commercial availability of all reagents and the easy recovery of the chiral ligand render the described procedure an attractive synthetic methodology.

## Experimental Section

**General Remarks:** All reactions were carried out using standard Schlenk techniques under an inert atmosphere. Solvents were dried and purified by conventional methods prior to use. Diethyl ether ($Et_2O$), tetrahydrofuran (THF) and toluene were freshly distilled from benzophenone ketyl radical under argon. Dichloromethane was distilled from $CaH_2$ under argon. Column chromatography was performed with silica gel 60 (0.063–0.2 mm). Optical rotations [$c$ = g/100 mL] were measured on a Perkin–Elmer 431 polarimeter. $^1$H and $^{13}$C NMR spectra were recorded on a 300 MHz spectrometer. The chemical shifts are reported in ppm relative to TMS. GC-MS was performed with a Hewlett–Packard 5890 Series-II Gas Chromatograph with 5972 Series-Mass Selective Detector, using an HP-5 column. All yields given refer to isolated yields. The diastereomeric ratio of the epoxides was determined by $^1$H NMR analysis of the crude reaction mixtures. The enantiomeric excess of the epoxides was determined by HPLC on a chiral stationary phase (Chiracel OD/OD-H column with *n*-hexane/2-propanol as eluent and a 254 nm UV detector). The absolute configurations of the epoxides were assigned by comparison of their optical rotation with literature values and the elution order of the two enantiomers on the HPLC column. (*R*)-BINOL, (*S*)-BINOL, $ZnEt_2$, TBHP, CMHP and chalcone were used as commercial reagents without further purification. The epoxidations were allowed to proceed until the substrates had been totally consumed, as monitored by TLC, or until no further consumption was observed. The syntheses of some of the α,β-enones have been described previously: **1**,[20] **2**,[21] **4**,[21] **5**,[20] **6**,[22] **7**,[9b] **8**,[9b] **9**,[9b] **10**.[23]

**General Procedures for the Enantioselective Epoxidation of α,β-Enones. A:** (*R*)-BINOL (57 mg, 0.2 mmol) was dissolved in the corresponding solvent (20 mL) in a 50-mL Schlenk flask equipped with a magnetic stirring bar under an inert atmosphere. After cooling to 0 °C in an ice-bath, $ZnEt_2$ (0.33 mL, 0.36 mmol, 1.1 M solution in toluene) was added whilst 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 warmed to room temperature overnight. The reaction was quenched with aq. sat. $NaHSO_3$ and extracted with EtOAc and the organic layer was washed with aq. $Na_2CO_3$ and brine. The combined organic layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by column chromatography. $CH_2Cl_2$ was used as eluent in all cases, and re-

maining starting material and the α,β-epoxy ketone were isolated in this sequence. (*R*)-BINOL was recovered almost quantitatively as the last fraction.

**B:** (*R*)-BINOL (57 mg, 0.2 mmol) was dissolved in $Et_2O$ (4 mL) in a 50-mL Schlenk flask equipped with a magnetic stirring bar under an inert atmosphere. After cooling to 0 °C in an ice-bath, $ZnEt_2$ (0.18 mL, 0.2 mmol, 1.1 M solution in toluene) was added whilst stirring. After 3 h the complete precipitation of an amorphous white solid was observed and α,β-unsaturated ketone (1 mmol) and CMHP (0.22 mL, 1.2 mmol, 80% solution in cumene) were added; stirring of the reaction mixture at room temperature was maintained for the indicated time. The reaction was quenched with aq. sat. $NaHSO_3$ and extracted with EtOAc. The organic layer was washed with aq. $Na_2CO_3$ and brine. The combined organic layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by column chromatography. $CH_2Cl_2$ was used as eluent in all cases and remaining starting material and the α,β-epoxy ketone were isolated in this sequence. (*R*)-BINOL was recovered almost quantitatively as the last fraction.

**(*E*)-Phenyl-(3-phenyloxiran-2-yl)methanone:**[24] $^1$H NMR (300 MHz, $C_6D_6$): $\delta$ = 4.04 (d, $J$ = 1.8 Hz, 1 H, $H_\beta$), 4.06 (d, $J$ = 1.8 Hz,1 H, $H_\alpha$), 6.97–7.15 (m, 8 H), 7.81 (m, 2 H) ppm. GCMS: $m/z$ = 224 [$M^+$], 207 [$M^+$ – OH], 105 [$C_7H_5O^+$]. HPLC (Chiracel OD, *n*-hexane/2-propanol, 95:5, 0.7 mL min$^{-1}$): $t_R$ = 15.17 min (2*S*,3*R*-enantiomer, major), $t_R$ = 16.35 min (2*R*,3S-enantiomer, minor), 90% *ee*. $[\alpha]_D^{26}$ = +207.7 ($c$ = 0.78, $CH_2Cl_2$). Literature value for the other enantiomer (2*R*,3*S*): $[\alpha]_D^{26}$ = –130.0 ($c$ = 1.1, $CH_2Cl_2$, *ee* = 61%).[9b]

**(*E*)-[3-(*p*-Bromophenyl)oxiran-2-yl]phenylmethanone:**[25] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 3.95 (d, $J$ = 1.8 Hz, 1 H, $H_\beta$), 4.15 (d, $J$ = 1.8 Hz, 1 H, $H_\alpha$), 7.14 (d, $J$ = 8.5 Hz, 2 H), 7.37–7.55 (m, 5 H), 7.90 (d, $J$ = 7 Hz, 2 H) ppm. GCMS: $m/z$ = 302 [$C_{15}H_{11}{}^{79}BrO_2{}^+$], 286 [$C_{15}H_{11}{}^{79}BrO_2{}^+$ – O], 105 [$C_7H_5O^+$]. HPLC (Chiracel OD-H, *n*-hexane/2-propanol, 90:10, 0.4 mL min$^{-1}$): $t_R$ = 27.08 min (2*S*,3*R*-enantiomer, major), $t_R$ = 29.12 min (2*R*,3S-enantiomer, minor), 90% *ee*. $[\alpha]_D^{26}$ = +137.2 ($c$ = 1.22, $CH_2Cl_2$).

**(*E*)-[3-(*p*-Nitrophenyl)oxiran-2-yl]phenylmethanone:**[26] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.11 (d, $J$ = 1.8 Hz, 1 H, $H_\beta$), 4.17 (d, $J$ = 1.8 Hz, 1 H, $H_\alpha$), 7.29 (d, $J$ = 9 Hz, 1 H), 7.44 (t, $J$ = 8 Hz, 4 H), 7.91 (d, $J$ = 7 Hz, 2 H), 8.16 (d, $J$ = 8.9 Hz, 2 H) ppm. GCMS: $m/z$ = 269 [$M^+$], 165 [$M^+$ – $C_7H_5O^+$], 105 [$C_7H_5O^+$]. HPLC (Chiracel OD-H, *n*-hexane/2-propanol, 75:25, 0.5 mL min$^{-1}$): $t_R$ = 31.38 min (2*S*,3*R*-enantiomer, major), $t_R$ = 34.37 min (2*R*,3S-enantiomer, minor), 76% *ee*. $[\alpha]_D^{26}$ = +156.8 ($c$ = 0.98, $CH_2Cl_2$). Literature value for the other enantiomer (2*R*,3*S*): $[\alpha]_D^{25}$ = –274.0 ($c$ = 2.0, $CH_2Cl_2$, *ee* = 99%).[27]

**(*E*)-(3-Methyloxiran-2-yl)phenylmethanone:**[28] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.52 (d, $J$ = 5.5 Hz, 3 H, $CH_3$), 3.46 (dq, $J$ = 5.5, 2 Hz, 1 H, $H_\beta$), 3.96 (d, $J$ = 2 Hz, 1 H, $H_\alpha$), 7.31–7.75 (m, 3 H), 7.95–8.11 (m, 2 H) ppm. GCMS: $m/z$ = 161 [$M^+$ – H], 146 [$M^+$ – O], 105 [$C_7H_5O^+$]. HPLC (Chiracel OD, *n*-hexane/2-propanol, 90:10, 0.4 mL min$^{-1}$): $t_R$ = 17.47 min (2*S*,3*R*-enantiomer, major), $t_R$ = 18.58 min (2*R*,3*S*-enantiomer, minor), 68% *ee*. $[\alpha]_D^{26}$ = +9.5 ($c$ = 0.78, $CHCl_3$). Literature value for the other enantiomer (2*R*,3*S*): $[\alpha]_D^{25}$ = –10.0 ($c$ = 0.6, $CHCl_3$, *ee* = 63%).[6]

**(*E*)-(3-Ethyloxiran-2-yl)phenylmethanone:**[9b] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.09 (t, $J$ = 7.4 Hz, 3 H. $CH_3$), 1.69–1.90 (m, 2 H, $CH_2$), 3.15 (m, 1 H, $H_\beta$), 4.04 (d, $J$ = 2.0 Hz, 1 H, $H_\alpha$), 7.47–7.65 (m, 3 H), 8.02 (m, 2 H) ppm. GCMS: $m/z$ = 176 [$M^+$], 147 [$M^+$ – $C_2H_5$], 131 [$M^+$ – $C_2H_5O$], 105 [$C_7H_5O^+$]. HPLC (Chiracel OD, *n*-hexane/2-propanol, 90:10, 0.5 mL min$^{-1}$): $t_R$ = 12.47 min (2*S*,3*R*-enantiomer, major), $t_R$ = 13.37 min (2*R*,3S-enantiomer, minor), 73% *ee*. $[\alpha]_D^{26}$ = –7.8 ($c$ = 0.94, $CH_2Cl_2$). Literature value for the other enantiomer (2*R*,3*S*): $[\alpha]_D^{26}$ = +13.8 ($c$ = 1.4, $CH_2Cl_2$, *ee* = 91%).[9b]

**(*E*)-Phenyl-(3-propyloxiran-2-yl)methanone:**[9b] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.01 (t, $J$ = 7.4 Hz, 3 H, $CH_3$), 1.48–1.83 (m, 4 H, $CH_2CH_2$), 3.15 (m, 1 H, $H_\beta$), 4.03 (d, $J$ = 2 Hz, 1 H, $H_\alpha$), 7.47–7.65 (m, 3 H), 8.01 (m, 2 H) ppm. GCMS: $m/z$ = 189 [$M^+$ – H], 147 [$M^+$ – $C_3H_7$], 131 [$M^+$ – $C_3H_7O$], 105 [$C_7H_5O^+$]. HPLC (Chiracel OD, *n*-hexane/2-propanol, 90:10, 0.5 mL min$^{-1}$): $t_R$ = 11.88 min (2*S*,3*R*-enantiomer, major), $t_R$ = 12.60 min (2*R*,3S-enantiomer, minor), 64% *ee*. $[\alpha]_D^{26}$ = –1.3 ($c$ = 0.9, $CH_2Cl_2$). Literature value for the other enantiomer (2*R*,3*S*): $[\alpha]_D^{26}$ = +1.7 ($c$ = 1.0, $CH_2Cl_2$, *ee* = 76%).[10]

**(*E*)-(3-Isopropyloxiran-2-yl)phenylmethanone:**[9b] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.07 (d, $J$ = 6.7 Hz, 3 H, $CH_3$), 1.10 (d, $J$ = 6.7 Hz, 3 H, $CH_3$), 1.79 (m, 1 H, CH), 2.96 (dd, $J$ = 6.7 Hz, 2.0 Hz, 1 H, $H_\beta$), 4.07 (d, $J$ = 2.0 Hz, 1 H, $H_\alpha$), 7.47–7.64 (m, 3 H), 8.02 (m, 2 H) ppm. GCMS: $m/z$ = 189 [$M^+$ – H], 174 [$M^+$ – O], 147 [$M^+$ – $C_3H_7$], 105 [$C_7H_5O^+$]. HPLC (Chiracel OD, *n*-hexane/2-propanol, 90:10, 0.5 mL min$^{-1}$): $t_R$ = 11.08 min (2*S*,3*R*-enantiomer, major), $t_R$ = 12.18 min (2*R*,3S-enantiomer, minor), 68% *ee*. $[\alpha]_D^{26}$ = –21.9 ($c$ = 1.2, $CH_2Cl_2$). Literature value for the other enantiomer (2*R*,3*S*): $[\alpha]_D^{26}$ = +32 ($c$ = 1.3, $CH_2Cl_2$, *ee* = 92%).[10]

**(*E*)-(3-*tert*-Butyloxiran-2-yl)phenylmethanone:**[29] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.02 [s, 9 H, $C(CH_3)_3$], 2.94 (d, $J$ = 2.2 Hz, 1 H, $H_\beta$), 4.09 (d, $J$ = 2.2 Hz, 1 H, $H_\alpha$), 7.45–7.60 (m, 3 H), 7.97–8.01 (m, 2 H) ppm. GCMS: $m/z$ = 204 [$M^+$], 189 [$M^+$ – $CH_3$], 173 [$M^+$ – $CH_3O$], 147 [$M^+$ – $C_4H_9$], 105 [$C_7H_5O^+$]. HPLC (Chiracel OD, *n*-hexane/2-propanol, 90:10, 0.4 mL min$^{-1}$): $t_R$ = 12.38 min (2*S*,3*R*-enantiomer, major), $t_R$ = 14.23 min (2*R*,3S-enantiomer, minor), 96% *ee*. $[\alpha]_D^{26}$ = –18.0 ($c$ = 1.3, $CHCl_3$). Literature value for the other enantiomer (2*R*,3*S*): $[\alpha]_D^{26}$ = +14 ($c$ = 0.36, $CH_2Cl_2$, *ee* = 64%).[10]

**(*E*)-β-Benzoyloxystyrene:**[30] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 6.51 (d, $J$ = 12.76 Hz, 1 H, $H_\beta$), 7.17 (m, 1 H), 7.26 (m, 2 H), 7.32 (m, 2 H), 7.41 (m, 2 H), 7.53 (m, 1 H), 8.01 (d, $J$ = 12.76 Hz, 1 H, $H_\alpha$), 8.07 (m, 2 H) ppm. GCMS: $m/z$ = 224 [$M^+$], 105 [$C_7H_5O^+$].

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