Advanced Synthesis & Catalysis

Very Important Publication

DOI: 10.1002/adsc.201500764

Quest for Efficient Catalysts based on Zinc *tert*-Butyl Peroxides for Asymmetric Epoxidation of Enones: C_2- *vs* C_1-Symmetric Auxiliaries

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Received: August 14, 2015; Revised: October 29, 2015; Published online: January 5, 2016

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500764.

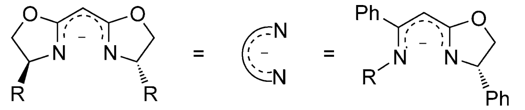
Abstract: Zinc *tert*-butyl peroxide-based catalysts for the asymmetric epoxidation of enones using *tert*-butyl hydroperoxide as an oxidant have been developed. A comparative study of chiral monoanioninc *N,N′*-bidentate ligands, C_2-symmetric bisoxazolinates and C_1-symmetric enaminooxazolinates, revealed excellent performance of C_1-symmetric auxiliary ligands on catalytic asymmetric epoxidation of enones (up to 96% yield, 91% *ee*).

Keywords: asymmetric catalysis; chiral auxiliaries; epoxidation of enones; ligand design; zinc

Asymmetric catalytic oxidation of olefins is a powerful tool to synthesize optically active epoxides, which are a common motif in many biologically important compounds and biosynthetic intermediates.[1] The highly enantioselective epoxidation of α,β-unsaturated ketones is of particular interest because it offers an efficient route to many useful enantioenriched products by selective functionalization of both carbonyl and epoxy groups. Over the last two decades, several methods have been developed to synthesize this type of chiral epoxide that use chiral metal complexes as well as organocatalysts.[2] Reported catalytic metal-mediated systems include complexes of Li,[3] Mg,[4] Zn,[5] Fe,[6] and lanthanides (e.g., La,[7] Sm,[8] and Yb[9]).

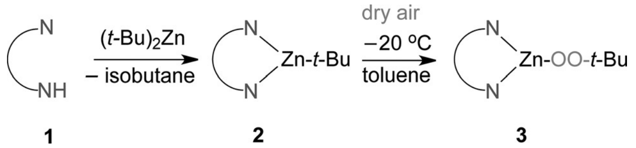
In terms of green and sustainable science, developing catalytic systems with non-toxic metals such as Zn is of great interest.[10] Nevertheless, despite continuous interest in this area, the well-defined Zn-catalyzed highly enantioselective epoxidation of enones remains elusive. In 1996, Enders et al.[11] reported the first stoichiometric asymmetric epoxidation of α,β-unsaturated ketones mediated by a Zn alkyl peroxide, which was generated *in situ* from Et_2Zn, (*R*,*R*)-*N*-methylpseudoephedrine and O_2. Under such conditions, *trans*-chalcone epoxidation was completed in 16 h with 61% *ee*. Since then, various structurally ill-defined Zn catalysts possessing a BINOL moiety in combination with *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CMHP) have been developed for the catalytic asymmetric epoxidation of a variety of enones, providing the corresponding epoxides in good yields and with very high enantiomeric excesses up to 96%.[5a–d]

In 2003, our group reported the first structurally authenticated Zn alkyl peroxides[12] and demonstrated that one of them, namely $[(BDI)ZnOOEt]_2$ (BDI = β-diketiminate ligand), exhibits high efficiency in the stoichiometric epoxidation of *trans*-chalcone.[12a] More recently, these findings were extended to a catalytic system with TBHP as an oxidant using $[(t\text{-}BuOO)Zn(ATI)]_2$ [ATI = (*S,S*)-*N,N′*-di-(1-phenylethyl)-aminotroponiminate] as a chiral catalyst. The *trans*-chalcone was oxidized within 4 h at 0 °C to the corresponding epoxide in 60% yield, but with low enantiomeric excess (29%).[5e] The latter studies[5e,12] provided the first structurally well-defined system for the epoxidation of *trans*-chalcone, so its further development is highly desirable. Here, we report the catalytic enantioselective epoxidation of various α,β-unsaturated ketones mediated by new Zn alkyl peroxides supported by monoanionic C_2- and much less common C_1-symmetric *N,N*-bidentate ligands.[13] Two C_2-symmetric bisoxazolinate ligands, **1a** and **1b**, and



1a, R = Ph
1b, R = *t*-Bu
1c, R = Ph
1d, R = 2,6-(i-Pr)$_2$C$_6$H$_3$

Figure 1. Selected C_2- and C_1-symmetric monoanionic ligands for asymmetric epoxidation.



Scheme 1. One-pot procedure for the synthesis of our catalysts.

two electronically and sterically asymmetric enaminooxazolinates with C_1-symmetry, **1c** and **1d**, were selected to study the factors affecting the title reaction (Figure 1).

The new Zn *tert*-butyl peroxides were prepared by a slightly modified version of the previously reported two-step procedure.[12a] The corresponding *N,N*-proligands were treated with 1 equiv. of (t-Bu)$_2$Zn in toluene for 2 h at room temperature, then the resulting alkylzinc complexes **2a–d** were exposed to dry air at −20 °C (Scheme 1) to give Zn *tert*-butyl peroxides **3a–d** (Figure 2).

Initially, *trans*-chalcone **4a** was used as a model substrate to investigate the catalytic activities of Zn *tert*-butyl peroxides **3a–d** generated *in situ*. A catalytic amount of the Zn *tert*-butyl peroxide at −60 °C was added to a mixture of *trans*-chalcone and TBHP[14] in toluene. The mixture was then warmed to 0 °C to afford the 2*S*,3*R* isomer of epoxy chalcone.[15] The alkyl peroxides **3a–d** exhibited high activities in the benchmark epoxidation reaction (Table 1). After 1 h, the epoxy chalcone was formed in high yield in the reactions catalyzed by the enaminooxazolinate complexes **3c** and **3d** (up to 96%) and with slightly lower conversion (80%) in the case of bisoxazolinate catalysts **3a** and **3b**. Strikingly, the most sterically hindered catalyst **3d** showed the highest activity and was the most active catalyst of the oxazolinate **3b** and enaminooxazolinate **3d** catalysts bearing sterically demanding substituents (68% *ee*; Table 1, entries 2 and 4), whereas the less hindered catalyst **3c** gave the lowest enantioselectivity (32% *ee*; Table 1, entry 3). These observations indicate that both the symmetry of the auxiliary ligand (i.e., C_1 *vs* C_2) and electronic factors arising from the characteristics of the ligand backbone have minor effects on the enantioselectivities in the studied reactions, whereas the steric environment in close proximity to the coordinating center seems to be crucial.

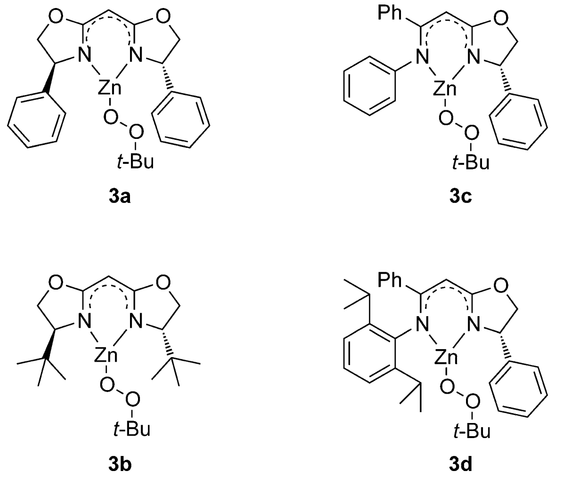
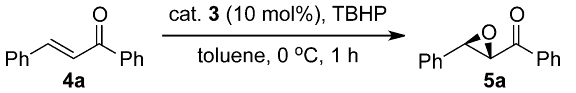


Figure 2. Schematic representation of Zn *tert*-butyl peroxides **3a–d**.

Table 1. Catalytic enantioselective epoxidation of *trans*-chalcone.[a]

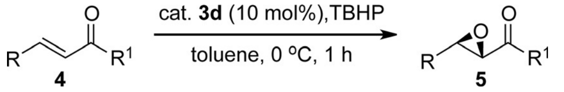


Entry	Catalyst **3**	Conversion [%][b]	*ee* [%][c,d]
1	**3a**	80	54
2	**3b**	80	68
3	**3c**	90	32
4	**3d**	96	68

[a] The reaction was performed with 10 mol% **3**, 0.1 mmol *trans*-chalcone and 1.2 equiv. TBHP at 0 °C for 1 h.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.
[d] The absolute configuration was assigned to be (2*S*,3*R*) based on optical rotation reported.

With an efficient catalyst for the asymmetric epoxidation of *trans*-chalcone in hand, we started to evaluate the substrate scope of this reaction using various α,β-unsaturated ketones with different substitution patterns, including a diketone (Table 2). The most active C_1-symmetric catalyst **3d** was selected for further studies. Enones **4b–g** were all oxidized in excellent yields under the reaction conditions studied. The introduction of a strong electron-withdrawing group such as a nitro moiety at the *para*-position of the aromatic ring on the carbonyl side of the enone resulted in a marked increase in enantioselectivity (89% *ee*) and excellent yield (98%) of oxazolinate **3b** and enaminooxazolinate **3d** catalysts (Table 2, entry 2). Conversely, an electron-donating *para*-OMe group on the same aromatic ring decreased both the selectivity and yield to 56% and 85%, respectively (Table 2, entry 3). Substituting the aromatic ring of the olefin side of the enone with an electron-withdrawing halogen (*para*-

Table 2. Catalytic enantioselective epoxidation of α,β-unsaturated ketones.[a]



Entry	R	R^1	5	Yield [%][b]	*ee* [%][c]
1	C_6H_5	C_6H_5	**5a**	96	68
2	C_6H_5	4-$NO_2C_6H_4$	**5b**	98	89
3	C_6H_5	4-$OMeC_6H_4$	**5c**	85	56
4	4-BrC_6H_4	C_6H_5	**5d**	97	81
5	4-MeC_6H_4	C_6H_5	**5e**	98	71
6[d]	*i*-Pr	C_6H_5	**5f**	90	21
7[e]	(CO)C_6H_5	C_6H_5	**5g**	80	91

[a] Reaction was performed with 10 mol% **3d**, 0.1 mmol enone and 1.2 equiv. TBHP at 0 °C for 1 h.

[b] Yield after column chromatography.

[c] The *ee* value was determined by chiral HPLC. The absolute configuration was assigned to be (2*S*,3*R*) based on optical rotation reported.

[d] The 2*R*,3*S* isomer was obtained.

[e] Reaction was performed at −20 °C.

bromo) or an electron-donating *para*-Me group led to the same yields as in the cases of **5a** and **5b**. While the reaction yields were constant, the bromo and Me substituents caused the enantioselectivities to decrease to 81% and 71% *ee*, respectively (Table 2, entries 4 and 5). Moreover, the *ee* decreased to 21% for aliphatic (*i*-Pr) enone **4f**. These results suggest that electron-deficient enones could be epoxidized asymmetrically and efficiently under the studied reaction conditions. For example, *trans*-1,2-dibenzoylethylene gave an excellent enantioselectivity (91% *ee*).

To confirm the structure of the catalytic species, we isolated a single crystal of the most efficient catalyst **3d** from the reaction system outlined in Scheme 1 and subjected it to single-crystal X-ray diffraction.[16] The molecular structure of **3d** consists of a dinuclear aggregate with monomeric **3d** units joined by the μ$_2$-bridging oxygen atoms of the *t*-BuOO groups (Figure 3). Dimeric **3d** has C_2 crystallographic symmetry and distorted tetrahedral geometry about the Zn centers. The average peroxo O−O bond length is 1.479 Å and the Zn−N bond lengths vary from 1.962(8) to 1.970(7) Å. All these distances are similar to the corresponding bond lengths found for Zn μ$_2$-alkyl peroxide complexes supported by *N*,*N*,-bidentate ligands.[12a,13,17]

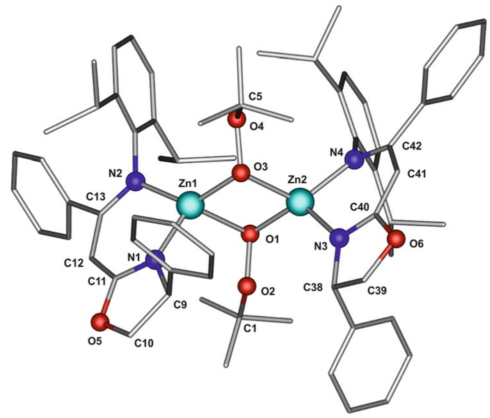
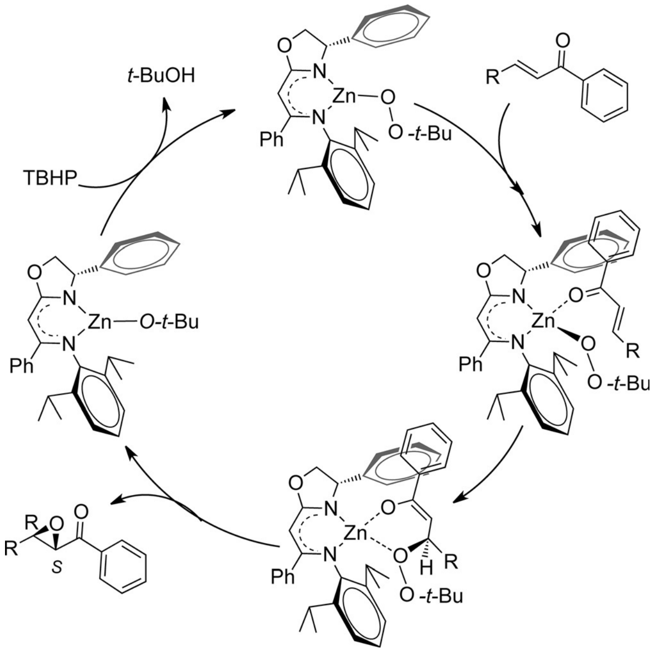


Figure 3. Molecular structure of **3d**; hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): O1−O2 = 1.485(8), O3−O4 1.473(8), Zn1−O1 2.077(6), Zn1−O3 1.951(6), Zn2−O1 1.969(6), Zn2−O3 2.041(6), Zn1−N1 1.962(8), Zn1−N2 1.970(7), Zn2−N3 1.968(8), Zn2−N4 1.963(7).



Scheme 2. Proposed catalytic cycle for the enantioslective epoxidation of enones.

In Scheme 2 we propose a catalytic cycle for the enantioselective epoxidation of enones mediated by the Zn *t*-Bu peroxide and TBHP as oxidant. In our previous study involving the related zinc alkyl peroxide catalytic system, the diffusion ordered spectroscopy experiments revealed that the catalyst most likely existed as a monomeric species in solution,[5e] so we assume that under the reaction conditions the monomeric form (N,N′)ZnOO-*t*-Bu acts as the true catalyst. In the first step the carbonyl oxygen of the enone is being coordinated to the metal center followed by a nucleophilic attack of oxygen[18] from the *si*-side of the activated enone, which affords 2*S*,3*R* epoxide as the major product. The cycle is completed by exchange of the O-*t*-Bu ligand in the resulting alkoxide (N,N′)ZnO-*t*-Bu moiety with *tert*-butyl peroxide originating from TBHP.

In summary, useful insights to allow further development of catalytic systems for the epoxidation of enones mediated by Zn alkyl peroxides have been presented. An appropriate choice of C_2-symmetric bisoxazolinate and C_1-symmetric enaminooxazolinate auxiliaries showed that the steric effects of the substituents in close proximity of the binding site had a major influence on the enantioselectivities of the studied reactions. The most active and selective C_1-symmetric enaminooxazolinate gave epoxides of both aliphatic and aromatic enones in excellent yields and with good enantioselectivities; for example, up to 96% yield and 91% *ee* for aromatic enones. Thus, the data show that C_2 symmetry is not a requirement for obtaining high enantioselectivity. We believe that our results will enable the rational development of new efficient and environmentally benign catalysts for the asymmetric epoxidation of enones.

Experimental Section

General Procedure

(t-Bu)$_2$Zn (0.01 mmol) was added to a Schlenk flask containing a solution of pro-ligand **1** (0.01 mmol) in toluene (0.5 mL) under inert conditions at –60 °C. The resulting solution was stirred at room temperature for 2 h. The Zn complex **2** generated *in situ* was exposed to dry air at –20 °C for 1 h to afford Zn alkyl peroxide **3**. To the resulting solution of **3** cooled at –60 °C was added a toluene solution of TBHP (4 M, 0.12 mmol) followed by enone (0.1 mmol) in toluene (1 mL). The reaction was warmed to 0 °C within 10 min, then stirred for 1 h. Volatile solvents were removed under high vacuum. The crude product was dissolved in diethyl ether (5 mL), and filtered through a pad of silica gel. The resulting residue was further purified by silica-gel column chromatography (hexane:ethyl acetate 9:1) to give the desired epoxy products **5**.

Acknowledgements

We acknowledge the European Union and Regional Development Fund within a project of Foundation for Polish Science (MPD/2010/13; A. R. K.) and the National Science Centre (grant DEC-2012/04A/ST5/00595; I. J., J. L.) for financial support.

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[14] In our standard epoxidation study, TBHP was found to be the optimal oxidant, whereas CMHP was less efficient and using H_2O_2 lead to ill-defined products (all these issues require further investigations and will be published in due course).

[15] Using the *R* isomer of **1d** under the same catalytic conditions provided the 2*R*,3*S* epoxy chalcone with 68% *ee*. When 5 mol% of **3d** was used, the *ee* remained the same, however the conversion was reduced to 40%. We have also observed reduced *ee* and reaction rate when Et_2Zn was used as Zn source.

[16] CCDC 1063927 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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[18] The electron-rich substrate (*E*)-(3-chloroprop-1-en-1-yl)benzene did not epoxidize under these conditions.