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Enantioselective α-Hydroxylation by Modified Salen-Zirconium(IV)-Catalyzed Oxidation of β-Keto Esters

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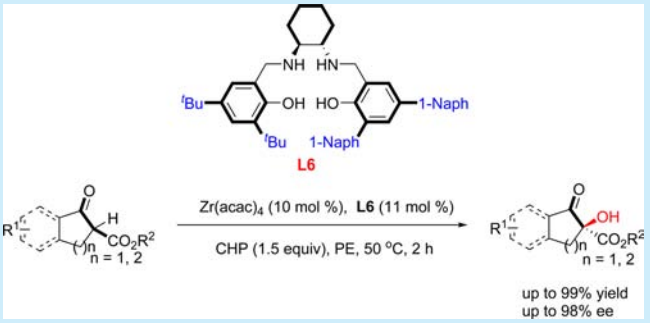
Supporting Information

ABSTRACT: The highly enantioselective α-hydroxylation of β-keto esters using cumene hydroperoxide (CHP) as the oxidant was realized by a chiral (1*S*,2*S*)-cyclohexanediamine backbone salen-zirconium(IV) complex as the catalyst. A variety of corresponding chiral α-hydroxy β-keto esters were obtained in excellent yields (up to 99%) and enantioselectivities (up to 98% ee). The zirconium-catalyzed enantioselective α-hydroxylation of β-keto esters was scalable, and the zirconium catalyst was recyclable. The reaction can be performed in gram scale, and corresponding chiral products were acquired in 95% yield and 99% ee.



Enantioenriched α-hydroxy β-keto esters are ubiquitous and important structural cores in a variety of biologically active natural products and pharmaceuticals, such as kjellmanianone,[1] hamigeran A,[2] and vindoline.[3] Particularly, the (*S*)-5-chloro-2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylic methyl ester has been widely used as the key synthetic intermediate for the preparation of Indoxacarb in the pesticide industry (Figure 1).[4] Therefore, extensive endeavors have been devoted

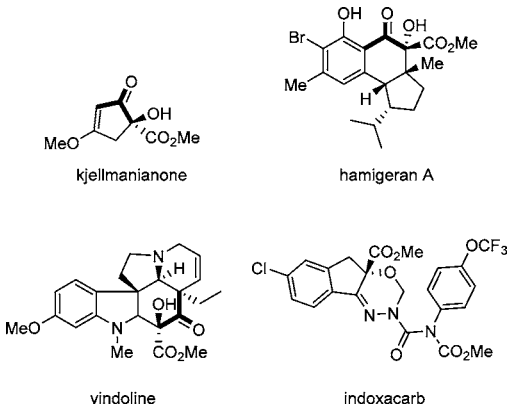


Figure 1. Biologically active molecules and drugs.

to the development of stereoselective synthesis of α-hydroxy β-keto esters.[5] The most convenient approach for accessing chiral α-hydroxy β-keto esters is the enantioselective α-hydroxylation of β-keto esters directly.

Although several methods using homogeneous organocatalyst have been reported, some problems remain unsolved in this area.[6] High catalyst loadings and harsh reaction conditions are required to achieve high yield and enantioselectivity. Subsequently, our group and others developed methods using phase transfer catalysts to improve the activity of catalyst,[7] whereas the peroxide oxidative and photosensitizer-mediated aerobic oxidative hydroxylation reactions have shown limited substrate scope.

In the past decades, an amount of transition-metal complexes catalyzed asymmetric α-hydroxylation of β-keto esters methods have been developed.[8] Several cases indicate a relatively wide substrate scope, such as cyclopentanones,[8b,d,f] cyclohexanones,[8b,d,f] cyclic 1,3-diesters,[8f] *N*-heterocycles,[8d] and acyclic ketoesters,[8b,d] when *N*-sulfonyloxaziridines or dimethyldioxiranes (DMDO) were used as oxidants. Feng's group reported another case that *N*,*N*′-dioxide magnesium ditriflate complex was used as the catalyst and peroxides were used as oxidant.[9] This method is more environment-friendly than previous work. However, the substrate scope was limited to 1-tetralone-derived β-keto esters/amides. According to these methodologies, excellent yields, and enantioselectivities were obtained for the substrates with bulky ester groups. Therefore, an efficient and novel enantioselective α-hydroxylation of β-keto esters with a broad substrate scope, especially for the substrates with smaller ester groups, is worthwhile to study.

We focus on developing enantioselective α-hydroxylation for a long time.[6b,c,e,7a,10] In order to overcome the challenges above, salen−metal complexes have been investigated in our groups recently. In the context of chiral ligand design, the salen-backbone has been considered as a privileged structure, which represents one of the most useful chiral controllers in many transition-metal-catalyzed reactions.[11] In this paper, a series of novel salen ligands with phenols as chelating units were

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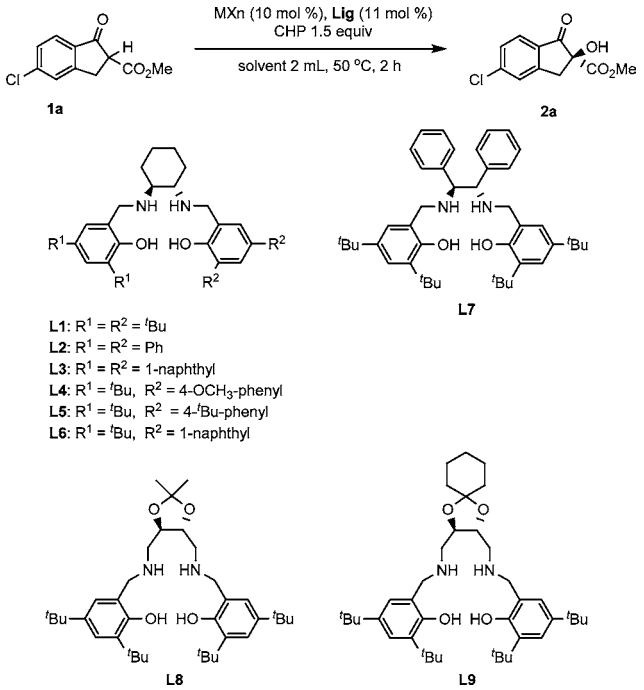
prepared from chiral diamine backbones. The modified salen-Zr(IV)-catalyzed enantioselective α-hydroxylation of β-keto esters with peroxide as an oxidant was developed.

Initially, chiral salen−transition metal complexes were used as the catalysts to promote the enantionselective α-hydroxylation of β-keto esters. 5-Chloro indanone carboxylic methyl ester **1a** served as a model substrate with easily accessible cumene hydroperoxide (CHP) as the oxidant in toluene at 50 °C. Using the **L1**−$CuCl_2$ or **L1**−$Mn(OAc)_2$ complex with a cyclohexanediamine-backbone salen ligand as the catalyst, moderate conversions and poor enatioselectivities were obtained (Table 1, entries 1 and 2). When the **L1**−$TiCl_4$ complex was used, a 60% conversion and 49% ee were obtained (Table 1, entry 3). To our delight, the combination of $Zr(acac)_4$ with **L1** afforded the desired product **2a** in 99% conversion and good enantioselectivity (90% ee) (Table 1, entry 4). The *tert*-butyl moiety of the chiral cyclohexanediamine ligand was revealed to impact the enantioselectivity of the α-hydroxylation significantly. When more sterically hindering aryls (**L2** or **L3**) were used instead of *tert*-butyls (**L1**), only moderate enantioselectivities were obtained (12% and 51% ee, respectively; Table 1, entries 5 and 6). Nevertheless, when one of the *tert*-butyl moieties on the phenol ring of **L1** was replaced by a variety of substituted phenyl groups (**L4** and **L5**), the good enantioselectivities were observed (78% and 79% ee, respectively; Table 1, entries 7 and 8). Unexpectedly, the combination of $Zr(acac)_4$ and ligand **L6** promoted the reaction to afford 99% conversion and 93% ee (Table 1, entry 9). In contrast, only using ligand **L6**, the racemic product **2a** was afforded in a 72% conversion (Table 1, entry 10). Although higher conversions can be obtained by the combination of $Zr(acac)_4$ and other kind chiral diamine ligands, only moderate enantioselectivities resulted (Table 1, entries 11−13). Especially, both **L8** and **L9**−Zr complexes gave racemic **2a** in 99% conversions (Table 1, entries 12 and 13). The conversions and enantioselectivities dropped dramatically when more polar solvents were used (Table 1, entries 14 and 15). When the petroleum ether was used as solvent, the ee can be further improved to 96% (Table 1, entry 16). When the reaction was performed in petroleum ether at room temperature, the conversion and enantioselectivity were slightly lower at 50 °C (Table 1, entry 17). The enantioselectivity declined slightly using heptane as the solvent (Table 1, entry 18). After further screening of oxidants, temperatures, and reaction times, the best conditions for α-hydroxylation included 11 mol % **L6** with 10 mol % of $Zr(acac)_4$, 1.5 equiv of CHP in petroleum ether at 50 °C.

Once the optimized conditions were established, the scope of substrates was examined, and the results are summarized in Scheme 1. The nonsubstituted indanone carboxylic methyl ester **2b** gave similar results as **2a** (99% yield, 94% ee). The enantioselectivities slightly fluctuated for 5- or 6-halogen-substituted substrates (87%−94% ee, **2c**−**2e**). But a much lower ee value was acquired by a 4-halogen-substituted one (80% ee, **2f**). When electron-donating groups were introduced into the aromatic ring, good results and ee values were observed (up to 98% ee) (**2g**−**2i**). Surprisingly, the enantioselectivity declined to 84% when two methoxy groups were in the benzene ring (**2j**). Besides investigating the substituent effects of the aromatic ring, various ester groups were also examined. To our delight, most ester groups can be tolerated in this transformation. Interestingly, the yields and ee values of corresponding products were slightly decreased with more hindered substituents in the ester side of the substrates (80%−91% yield, 82−94% ee, **2k**−**2r**), which were very different from previous results.[8c,f] The substrates with smaller ester groups worked better than the bigger ones. It was noteworthy that the cyclopentanone-derived β-keto ester **1s** also worked well and a desirable product **2s** was generated (82% yield, 90% ee). However, the enantioselectivity dramatically declined for 1-tetralone-derived β-keto ester **1t** (only 9% ee). Unfortunately, the reaction failed to occur for acyclic substrate **1u**.

To demonstrate the utility of this reaction, we scaled up the reaction to the gram scale. After treatment with 5 mmol of **1a**

Table 1. Optimization of the Reaction Conditions[a]



entry	MX_n	Lig	solv	conv (%)[b]	ee (%)[c]
1	$CuCl_2$	**L1**	toluene	56	2
2	$Mn(OAc)_2$	**L1**	toluene	68	7
3	$TiCl_4$	**L1**	toluene	60	−49
4	$Zr(acac)_4$	**L1**	toluene	99	90
5	$Zr(acac)_4$	**L2**	toluene	99	12
6	$Zr(acac)_4$	**L3**	toluene	99	51
7	$Zr(acac)_4$	**L4**	toluene	99	79
8	$Zr(acac)_4$	**L5**	toluene	99	78
9	$Zr(acac)_4$	**L6**	toluene	99	93
10[d]	–	**L6**	toluene	72	0
11	$Zr(acac)_4$	**L7**	toluene	99	80
12	$Zr(acac)_4$	**L8**	toluene	99	1
13	$Zr(acac)_4$	**L9**	toluene	99	1
14	$Zr(acac)_4$	**L6**	THF	51	74
15	$Zr(acac)_4$	**L6**	MeOH	82	70
16[e]	$Zr(acac)_4$	**L6**	PE	99	96
17[f]	$Zr(acac)_4$	**L6**	PE	95	95
18	$Zr(acac)_4$	**L6**	heptane	99	94

[a]All reactions were performed at 0.1 mmol scale. [b]The conversion was determined by HPLC. [c]Determined by HPLC on chiral stationary phase. [d]Reaction performed at 5 °C for 12 h. [e]PE = petroleum ether, mixture of hexane and pentane, boiling range 60−90 °C. [f]Reaction performed at room temperature for 4 h.

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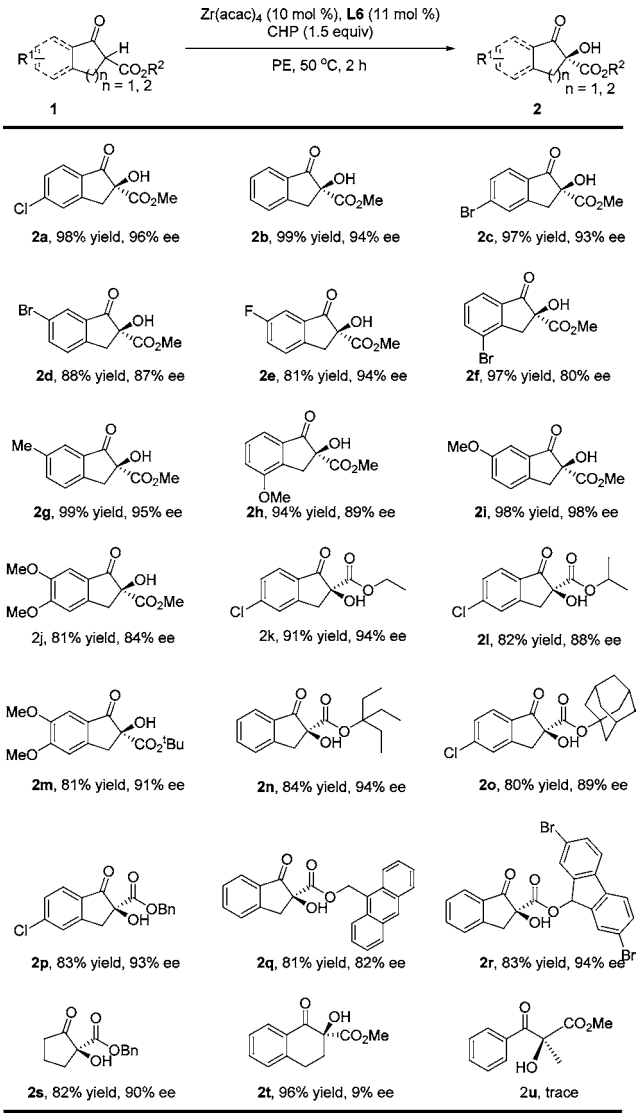
Scheme 1. Enantioselective α-Hydroxylation of β-Keto Esters[a]

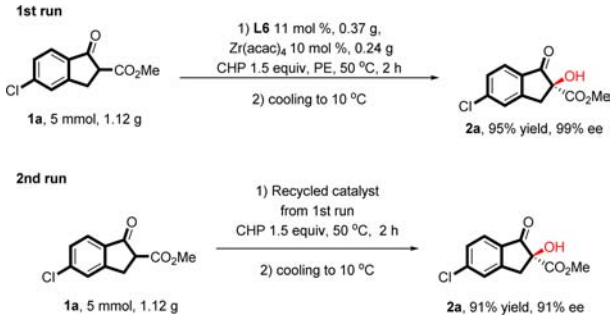


[a]The absolute configuration was determined by comparison with the optical rotation of an authentic sample.[8b]

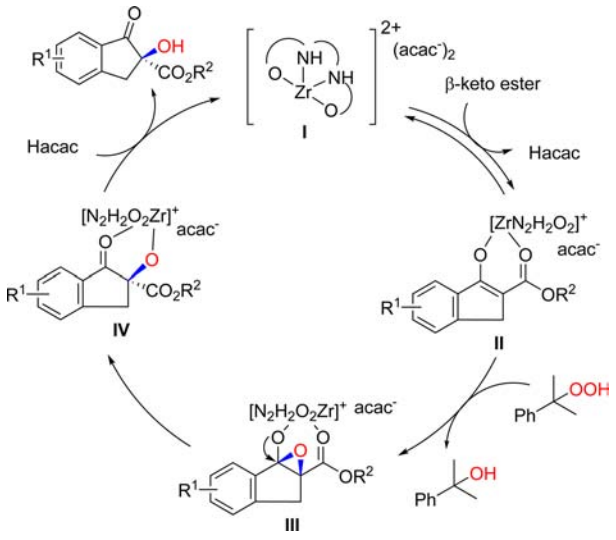
(1.12 g) under the standard conditions, the mixture was cooled to 10 °C for filtering to obtain solid **2a** in 95% yield (1.14 g) and 99% ee. When the recycled salen-Zr(IV) catalyst was used in the second round, a slight deactivation of the catalyst was observed and a lower yield and enantioselectivity were acquired (91% yield, 91% ee) (Scheme 2).

A possible mechanism is proposed in Scheme 3.[8d,9] Herein, the catalytic cycle was initiated by the formation of activated electron-rich zirconium(IV) enolate complex **II**, with the acac- as the counterion. Then the CHP attacked the olefin moiety following by the O−O bond cleavage of the peroxide to afford the zirconium coordinated epoxide intermediate **III**. After electrophilic addition, a rearrangement occurred in the epoxide intermediate **III** to form alkoxide complex **IV**. The product was released after protonation. The transition state is proposed in Figure 2. The *Re*-face of the enolate intermediate was effectively shielded by the sterically bulky 1-naphthyl groups on the benzene ring of the catalyst. Thus, the CHP could only attack the enolate from the *Si*-face.

Scheme 2. Gram-Scale Reaction of β-Keto Ester 1a



Scheme 3. Possible Zr-Catalyzed Route for α-Hydroxylation



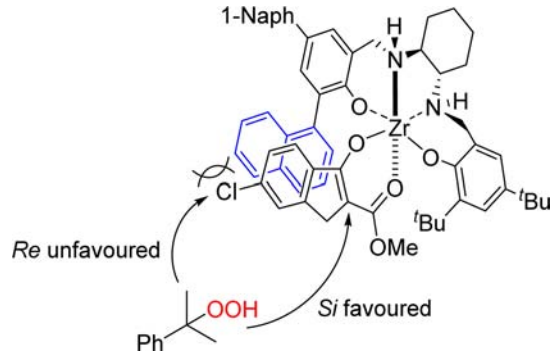


Figure 2. Proposed transition state for asymmetric induction.

For a comprehensive understanding of the transformation, preliminary density functional theory (DFT) calculations have been used to rationalize the stereoselectivity-related transition states (see Supporting Information for computational details). As shown in Figure 3, the transition state $\mathbf{TS}_S$ was from the *Si*-face peroxide attack, which could give an (*S*)-configurated product. While the $\mathbf{TS}_R$ derived from the *Re*-face peroxide attack could yield an (*R*)-configurated one. Both of the transition states featured O−O bond cleavage of the peroxide. According to the calculated results, the energy of $\mathbf{TS}_S$ was 3.2 kcal/mol lower than the $\mathbf{TS}_R$. This suggested that the formation of the (*S*)-configurated product was more favorable, which was in line with experimental observation. To further access the origin of the stereoselectivity, the energy decomposition

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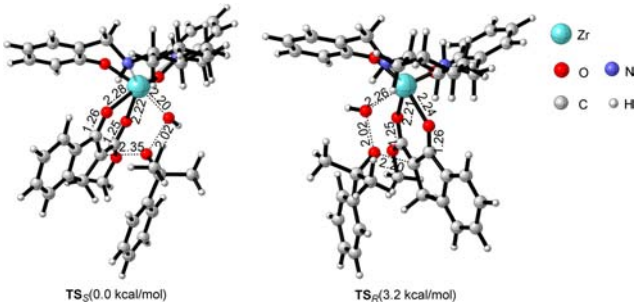

Figure 3. Optimized transition state structures (distances in Å) and their relative free energies.

analysis[12] was applied for the two transition states. The results indicated that the relative stability of $\mathbf{TS}_S$ could be ascribed to the smaller deformation of the peroxide unit and stronger interaction between the peroxide moiety and the remaining part of $\mathbf{TS}_S$.

In conclusion, this work describes modified salen−Zr(IV)-catalyzed α-hydroxylation of β-keto esters in high yields and enantioselectivities using CHP as the oxidant. The modified salen−Zr(IV) catalyst, containing a tetradentate ligand with two distinct bulky benzene rings and a chiral cyclohexanediamine core, could control the stereoselectivity of α-hydroxylation efficiently, especially for the substrates with smaller ester groups, which were difficult to achieve before.[8b] The α-hydroxy β-keto esters were acquired up to 98% ee. Even if the reaction scale was increased to 1.12 g, a good yield and enantioselectivity could also be obtained. When the catalyst was used in the second round, a slight deactivation of the catalyst was observed. The transition-metal catalyst dually functioned in coordination and enantioinduction to the substrate simultaneously. It provided an alternative and competitive method to organocatalyzed α-hydroxylation of β- keto ester.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03554.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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