Published in final edited form as:

Org Lett. 2006 July 6; 8(14): 3013–3015. doi:10.1021/ol060904a.

Highly Enantioselective CH Oxidation of *vic*-Diols with Shi's Oxazolidinone Dioxiranes

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Abstract

Through an analogical study of the transition states of CH oxidation and asymmetric epoxidation of terminal alkenes, the first dioxirane-mediated catalytic highly enantioselective CH oxidation method was realized with the Shi's oxazolidinone ketone derivatives. Very good enantioselectivity (up to 92% ee) may be obtained for both asymmetrization of *meso vic*-diols and kinetic resolution of racemic *vic*-diols.

In the past decades, dioxirane has been shown to be a powerful and highly selective oxidant, demonstrating excellent chemoselectivity, regioselectivity, diastereoselectivity and enantioselectivity during the oxygen-transfer.¹ Moreover, since dioxirane is normally obtained by the reaction of a suitable ketone and potassium monoperoxydisulfate (KHSO₅), the oxidation may be carried out in a catalytic manner under in-situ conditions. One of the highlights of the dioxirane chemistry is its ability to oxidize *sp*³-hybridized CH bond with complete retention of configuration under mild conditions.^{2, 3} Although high regioselectivity and diastereoselectivity have been achieved in the CH bond oxidation, it is still a great challenge to achieve highly enantioselective CH oxidation by using optically active dioxiranes.^{1, 4} A few years ago, Adam and co-workers demonstrated the feasibility of enantioselective CH oxidation mediated by dioxirane with Shi's fructose-derived ketone **1** (Figure 1);⁵ however, the enantioselectivity obtained was only mediocre (<65% ee in most cases). Furthermore, ketone **1** is not stable under the reaction conditions, such that an excessive amount of ketone **1** (3 equiv) is required to achieve reasonable conversions. Herein we wish to report the first catalytic and highly enantioselective CH oxidation protocol for the oxidation of *vic*-diols.

Although ketone **1** is an excellent catalyst for the asymmetric epoxidation of *trans*- and trisubstituted alkenes,⁶ the asymmetric induction is considerably lower in CH bond oxidation.⁵ The reason for this is probably due to totally different steric requirements for these two oxidations. Through the comparison of the transition state (TS) of CH oxidation⁷ and those of epoxidation of different alkene substrates, we found that these distinct TS^{3, 8} achieve the closest resemblance of each other in the case of CH oxidation and epoxidation of terminal alkene (Figure 2): 1) Both TS are asynchronous *spiro*; 2) in the terminal alkene cases (TS_E), the terminal CH₂ group is small and not differentiated in space (regarding to the left and right sides of the forming oxirane plane); likewise is the hydrogen atom end of the CH bond (TS_{CH}); and 3) in both cases, the steric and/or electronic communications between the substrate and the dioxirane are mainly coming from the more substituted end. Based on this analysis, we hypothesized that ketone catalyst that induces high enantioselectivity in the epoxidation of terminal alkenes should also induce high enantioselectivity in CH bond oxidation.

Shi and co-workers have reported that oxazolidinone ketones **2** and **3** are very good catalysts for the asymmetric epoxidation of terminal alkenes such as styrenes.⁹ Based on the recent theoretic work on the origin of the enantioselectivity in this asymmetric epoxidation^{8d} and our above analogy, we reasoned that these catalysts should be also good for CH oxidation of benzylic alcohols, since in both cases there is a phenyl group to interact with dioxirane to direct the substrate approach.^{8d,9} By using a modified procedure, we synthesized the known ketones **2** and **3**, and the new derivatives **4** and **5**, and applied them for the asymmetric CH oxidation of some benzylic *vic*-diols. The results are collected in Table 1.

To our pleasure, ketone **2** indeed yields a much improved enantioselectivity in the asymmetrization of *meso*-hydrobenzoin, and an ee value of 70% was obtained with 1 equiv of the catalyst (Table 1, entry 1). For comparison, catalyst **1** yields only 45% ee of the product of this substrate.⁵ Ketone **3** is an even better catalyst for this oxidation, as a high ee value of 87% was obtained and only 50 mol % catalyst loading was necessary (entry 2). This is the first example of dioxirane-mediated asymmetric CH oxidation using a *catalytic* amount of the ketone catalyst. The remote substituent on the oxazolidinone ring was found to have subtle influence on the enantioselectivity of the reaction: With the size of R reduced from *t*-Bu to Et or Me, the enantioselectivity dropped slightly from 87% to 80% (entries 3 and 4). Based on our preliminary screening, catalysts **3–5** are comparable in reactivity, while catalyst **3** always yields slightly higher enantioselectivity than the other two.

Further study with catalyst **3** reveals that very good ee values may be obtained for the asymmetrization of various *meso*-4,4'-disubstituted hydrobenzoin ($\geq 76\%$ ee, entries 5–9). However, the dependence of the enantioselectivity on the electronic nature the *para* substituents that has been observed for catalyst **1**⁵ did not happen in the case of catalyst **3**.

The kinetic resolution of racemic hydrobenzoin was also studied with catalyst **3**. Again, improved enantioselectivity was observed as compared with catalyst **1**. For example, with **3** as catalyst, an ee value of 87% was obtained for the product of *rac*-hydrobenzoin, while the reported result with catalyst **1** was only 65% ee.⁵ In most cases, the racemic substrates yield better enantioselectivities of the products than their *meso* counterparts (entries 10–15). For example, the fluoro-substituted racemic diol generates an ee value of 90% for the product (entry 12), while the corresponding *meso* diol gives slightly inferior 87% (entry 7). Racemic 4,4'-dicyanohydrobenzoin produces the highest ee value of 92% (entry 15). The low conversion obtained in this case was probably due to the low solubility of this substrate in such a reaction medium.⁵

In the asymmetrization of *meso*-diols, the *R*-configured α -hydroxy ketones were obtained as the major products, while in the kinetic resolution of racemic diols, the *S*-configured ones were obtained (Table 1). The results indicate that in both cases, the *S*-configured center is preferably oxidized. According to the recent theoretical work on the asymmetric epoxidation of *cis*-alkenes with ketone **3**,^{8d} the phenyl group has to be aligned roughly parallel with the oxazolidinone ring to lower the energy of the transition state. Based on this and the theoretical work on the CH oxidations,^{3a–c} the following TS were proposed to account for these results (Figure 3).

When the substrate is using its *S*-configured center to approach the dioxirane, the favored TS may be achieved (Figure 3, left), as the smaller hydroxy group will interact direct with the oxazolidinone ring. If the *R*-configured center is used, then the large secondary alcohol group will have to interact with the oxazolidinone ring (Figure 3, right), which will cause the energy of the TS to increase. Therefore, the *S*-configured center will be preferably oxidized to generate the *R*-product for *meso* substrate (from *S,R*) and *S*-product for the racemic substrate (from *S,S*).

In summary, based on the transition state analogy hypothesis, we have developed the first dioxirane-mediated highly enantioselective CH oxidation method with the Shi's oxazolidinone ketone catalyst **3**. Although the catalytic efficiency of the ketone is still to be improved, very good enantioselectivity may be obtained for both asymmetrization of *meso vic*-diols and kinetic resolution of racemic *vic*-diols. These new results demonstrate the potential of chiral dioxiranes in highly enantioselective CH oxidations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The authors thank the NIH-MBRS program (Grant No. S06 GM 08194) for the generous financial support of this project.

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Figure 1.
Ketone Catalysts Utilized for CH Oxidation

Figure 2.
Transition States for the Epoxidation of Terminal Alkene (TS_E) and the CH Oxidation (TS_{CH})

Figure 3.
Transition States for the Asymmetric CH Oxidation

Enantioselective C-H Oxidation of *vic*-Diols^a

Table 1

entry	diol		catalyst	time (h)	yield (%) ^b	ee (%) ^c	con-fig ^d
	X	config					
1	H	<i>meso</i>	2 ^e	1.5	60	70	<i>R</i>
2	H	<i>meso</i>	3	1.8	80	87	<i>R</i>
3	H	<i>meso</i>	4	1.8	90	80	<i>R</i>
4	H	<i>meso</i>	5	1.3	85	80	<i>R</i>
5	Me	<i>meso</i>	3	1.5	85	77	<i>R</i>
6	OMe	<i>meso</i>	3	1.8	60	76	<i>R</i>
7	F	<i>meso</i>	3	1.8	65	87	<i>R</i>
8	Cl	<i>meso</i>	3	1.8	80	77 ^f	<i>R</i>
9	Br	<i>meso</i>	3	1.8	74	76 ^f	<i>R</i>
10	H	<i>rac</i>	3	1.5	48	87 ^g	<i>S</i>
11	Me	<i>rac</i>	3	1.3	42	85 ^g	<i>S</i>
12	F	<i>rac</i>	3	1.3	45	90 ^g	<i>S</i>
13	Cl	<i>rac</i>	3	1.3	38	84 ^{f,g}	<i>S</i>
14	Br	<i>rac</i>	3	1.3	40	84 ^{f,g}	<i>S</i>
15	CN ^h	<i>rac</i>	3	2.0	10 ⁱ	92 ^g	<i>S</i>

^aUnless otherwise specified, all reactions were carried out with the diol (0.10 mmol), the ketone catalyst (0.05 mmol, 50 mol %) and Bu₄NHSO₄ (4 μmol) in CH₃CN (1.5 mL) and Na₂B₄O₇ (0.5 mL) / K₂CO₃ buffer at 0–5 °C. For asymmetric oxidation of *meso*-diols, Oxone® (0.15 mmol, in 1.0 mL of 4 × 10^{−4} M aq solution of Na₂EDTA) and K₂CO₃ (0.63 mmol) were used; for kinetic resolution of *rac*-diols, Oxone® (0.12 mmol, in 1.0 mL of 4 × 10^{−4} M aq solution of Na₂EDTA) and K₂CO₃ (0.58 mmol) were used.

^bYield of isolated product after chromatography.

^cDetermined by HPLC analyses.

^dDetermined by comparison the measured optical rotation with the reported data (ref 5).

^e0.10 mmol (100 mol %) catalyst was used.

^fDetermined based on its acetate.

^gThe ee values of the remaining diols were not determined.

^h0.20 mmol of Oxone® and 0.72 mmol of K₂CO₃ were used.