ORGANIC LETTERS

2006
Vol. 8, No. 14
3013−3015

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

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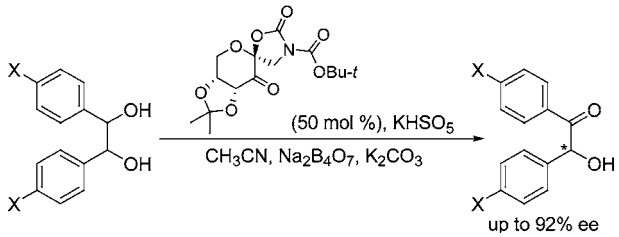
Received April 13, 2006

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 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, because dioxirane is normally obtained by the reaction of a suitable ketone and potassium monoperoxysulfate ($KHSO_5$), 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 the 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

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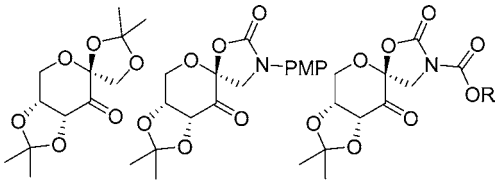
10.1021/ol060904a CCC: $33.50
Published on Web 06/16/2006



1 2 3 R = *t*-Bu 4 R = Et 5 R= Me

Figure 1. Ketone catalysts utilized for CH oxidation.

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 oxidation[7] with those of epoxidation of different alkene substrates, we found that these distinct TSs[3,8] achieve the closest resemblance of each other in the cases of CH oxidation and epoxidation of the terminal alkene (Figure 2):

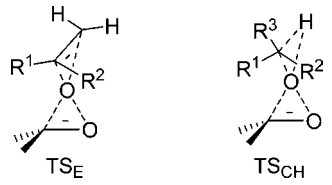


Figure 2. Transition states for the epoxidation of terminal alkene (TS_E) and the CH oxidation (TS_{CH}).

(1) Both TSs are asynchronous *spiro*; (2) in the terminal alkene cases (TS_E), the terminal CH_2 group is small and not differentiated in space (regarding the left and right sides of the forming oxirane plane), as 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. On the basis of this analysis, we hypothesized that the 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] On the basis of 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 also be good for CH oxidation of benzylic alcohols because 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 % of 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 a 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). On the basis of our preliminary screening, catalysts **3**−**5** are comparable in reactivity, whereas catalyst **3** always yields a 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 hydrobenzoins (≥76% ee, entries 5−9). However, the dependence of the enantioselectivity on the electronic nature of 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 hydrobenzoins 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, whereas 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), whereas the corresponding *meso* diol

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(7) As one reviewer pointed out, the most recent theoretic work by Sarzi-Amadé and co-workers described a perpendicular radicaloid transition state for this oxidation; however, as the authors conceded, such a mechanism cannot explain the high selectivity data obtained experimentally (ref 3d).

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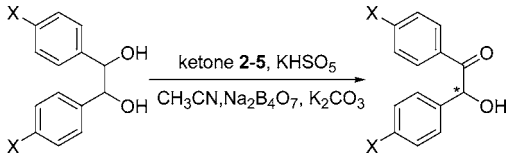
Table 1. Enantioselective C−H Oxidation of *vic*-Diols[a]



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

[a] Unless otherwise specified, all reactions were carried out with the diol (0.10 mmol), the ketone catalyst (0.05 mmol, 50 mol %) and Bu_4NHSO_4 (4 μmol) in CH_3CN (1.5 mL) and $Na_2B_4O_7$ (0.5 mL)/K_2CO_3 buffer at 0−5 °C. For asymmetrization of *meso*-diols, Oxone (0.15 mmol, in 1.0 mL of 4×10^{-4} M aq solution of Na_2EDTA) and K_2CO_3 (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 Na_2EDTA) and K_2CO_3 (0.58 mmol) were used. [b] Yield of isolated product after chromatography. [c] Determined by HPLC analyses. [d] Determined by comparison of the measured optical rotation with the reported data (ref 5). [e] 0.10 mmol (100 mol %) of catalyst was used. [f] Determined on the basis of its acetate. [g] The ee values of the remaining diols were not determined. [h] 0.20 mmol of Oxone and 0.72 mmol of K_2CO_3 were used. [i] Conversion.

gives a slightly inferior 87% value (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, and 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. On the basis of this and the theoretical work on the CH oxidations,[3a−c] the following TSs were proposed to account for these results (Figure 3).

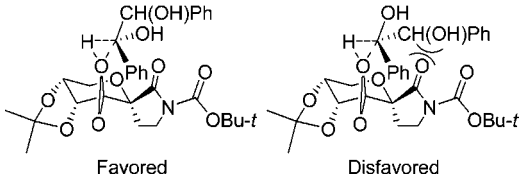


Figure 3. Transition states for the asymmetric CH oxidation.

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 directly 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 the *meso* substrate (from *S*,*R*) and the *S*-product for the racemic substrate (from *S*,*S*).

In summary, on the basis of the transition state analogy hypothesis, we have developed the first dioxirane-mediated highly enantioselective CH oxidation method with 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.

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

Supporting Information Available: Experimental procedures, NMR spectra for all new compounds, and HPLC analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060904A