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First highly enantioselective epoxidation of alkenes with aldehyde/Oxone®☆

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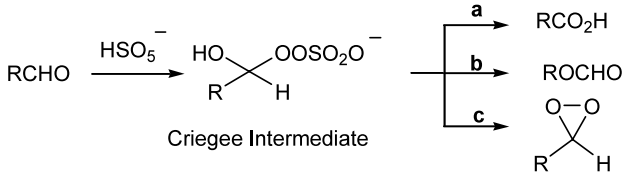
Abstract—Optically active aldehydes have been successfully used as catalysts for asymmetric epoxidations of unfunctionalized alkenes (ee up to 94%) by using Oxone® as the oxygen source. Experimental results indicate that the in-situ-generated aldehyde dioxirane is responsible for this catalytic activity.

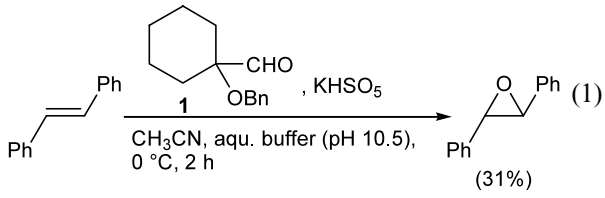
Ketone dioxiranes have been known for decades as excellent oxidants.[1] Through the efforts of recent years, chiral ketone dioxiranes have been shown to be prominent oxidants for asymmetric epoxidations.[2,3] They have also shown their potential in asymmetric C–H oxidations,[4] which is still a challenge of organic chemistry. In contrast, although substantiated in theoretical study,[5,6] aldehyde dioxiranes ($RHCO_2$), which have been involved in biological processes, still remain elusive. For example, the bioluminescent process of bacterial luciferase uses C4a-flavin hydroperoxide to react with an aldehyde to generate the corresponding dioxirane as the high-energy intermediate, which has not been isolated nor characterized.[6] So far the only known aldehyde dioxirane is dihydrodioxirane (H_2CO_2), but it was obtained from low temperature ozonolysis of ethene,[7] rather than from formaldehyde directly. Herewith we wish to report our preliminary results on asymmetric epoxidation by using optically active aldehydes and Oxone®, which, to the best of our knowledge, is the first direct evidence for the involvement of aldehyde dioxiranes.



Scheme 1. Possible reaction pathways of aldehyde.

Although ketone dioxirane may be readily prepared from Oxone® oxidation of a ketone, preparation of aldehyde dioxirane by this way was regarded as taboo. This is because aldehyde is reportedly prone to Oxone® oxidation to give the corresponding acid.[8] However, as shown in Scheme 1, this is only the major reaction pathway. Three reaction pathways may be envisaged when aldehyde is allowed to react with Oxone®, which rely on the Criegee intermediate. We reasoned that if both pathways **a** and **b** are inhibited, for example, through electronic effects,[9] then dioxirane formation is highly possible.

Recently we synthesized 1-benzyloxy cyclohexanecarbaldehyde (**1**) and found that it catalyzes the epoxidation of *trans*-stilbene (Eq. (1)). When 3 equiv. of **1** was used, 31% yield of the epoxide was obtained after 2 h of reaction, while under these conditions the background oxidation by Oxone® itself is negligible. The possible involvement of oxidative degradation product of **1** (such as cyclohexanone) as the actual catalyst in the present system was ruled out by NMR and GC–MS studies since neither cyclohexanone nor oxepan-2-one was found in the reaction mixture of **1** and Oxone® (Scheme 2).



(1)

Keywords: aldehyde dioxirane; enantioselective; alkene; epoxidation, Oxone®.

☆ Supplementary data associated with this article can be found at doi:10.1016/j.tetlet.2003.08.040

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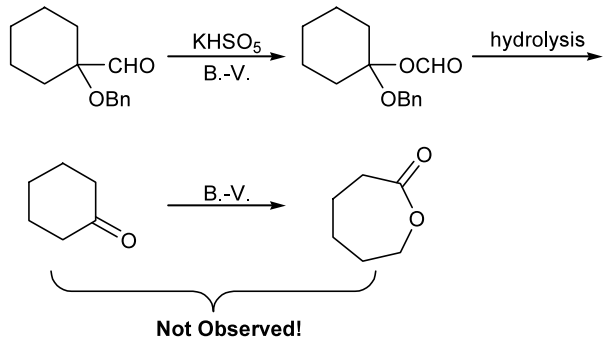
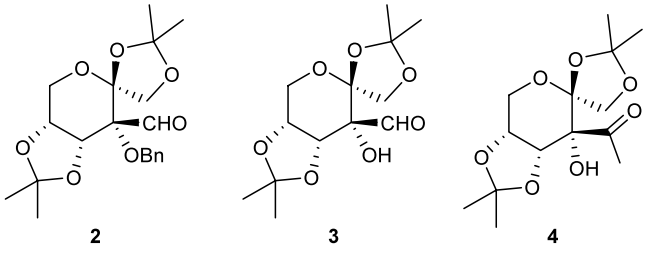


Scheme 2. Exclusion of cyclohexanone as the catalyst (B.-V. = Baeyer–Villiger oxidation).

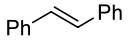
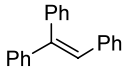
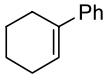
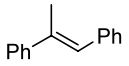
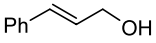
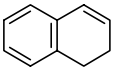
The intermediates formed by aldehyde and Oxone® that are capable of oxygen transfer are the Criegee intermediate and the aldehyde dioxirane (cf. Scheme 1). Since ketone dioxirane, rather than the Criegee intermediate, has been proved to be the active oxygen transfer reagent under similar conditions,[10] we favor the aldehyde dioxirane mechanism. Of course, more mechanistic scrutiny is still required to verify this.

On the basis of these findings, we explored the possibility of using optically active aldehyde dioxirane for asymmetric epoxidations. Chiral aldehydes **2** and **3** were designed and synthesized from fructose. The fructose backbone was selected because Shi et al. have shown that it is very effective in stereocontrol.[11] The results of asymmetric epoxidation of unfunctionalized alkenes by using aldehydes **2** and **3** as catalysts are summarized in Table 1. For comparison purpose the results of the corresponding ketone **4** are also included.



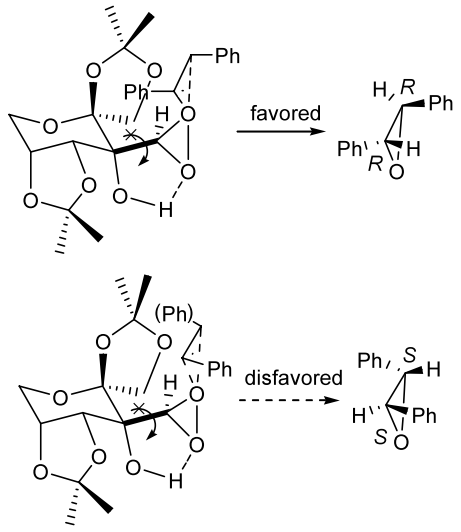
With *trans*-stilbene as the substrate, a 63.5% ee was obtained for the epoxide by using aldehyde **2** as the catalyst (entry 1). The ee value was greatly improved to 93.5% by using aldehyde **3** as catalyst, with also improved conversion of the substrate (entry 2).[12] In contrast, the corresponding ketone **4** only yielded 39% ee for the epoxide (entry 3). Under the same conditions, excellent ee values were obtained for triphenylethylene epoxide by using both aldehydes **2** (81% ee, entry 4) and **3** (92% ee, entry 5) as the catalyst, although the conversions were not so good. Again, much inferior enantioselectivity was obtained with ketone **4** as the catalyst (36% ee, entry 6). When 1-phenylcyclohexene and 1-methyl-*trans*-stilbene were used as substrates, ee values of 48% (entry 7) and 53% (entry 9) were obtained for aldehyde **2**, respectively. Similarly, aldehyde **3** also yielded higher enantioselectivity than aldehyde **2** for these substrates [67% (entry 9) and 82% (entry 10), respectively]. Aldehyde **3** also yielded a good enantioselectivity (70% ee, entry 11) for a prochiral allylic alcohol, while aldehyde **2** gave no conversion of this particular substrate (data not shown). A terminal alkene (entries 12 and 13) and a cyclic alkene (entries 14 and 15) produce low enantioselectivities with either aldehydes **2** or **3**, albeit with good conversions. It is clear from Table 1 that aldehyde **3** yields consistently better enantioselectivity than aldehyde **2**, except for the terminal and cyclic alkenes.

Table 1. Enantioselective epoxidation with chiral aldehydes **2** and **3** and ketone **4**[a]

Entry	Substrate	Catalyst	Convn. (%)[b]	ee (%)[c]	Config.[d]
1		**2**	16	63.5	(*R*,*R*)
2		**3**	54	93.5	(*R*,*R*)
3		**4**	31	39	(*R*,*R*)
4		**2**	8	81	(*R*)
5		**3**	8	92	(*R*)
6		**4**	4	36	(*R*)
7		**2**	28	48	(*R*,*R*)
8		**3**	12	67	(*R*,*R*)
9		**2**	8	53	(*R*,*R*)
10		**3**	8	82	(*R*,*R*)
11		**3**	14	70	(*R*, *R*)
12		**2**	50	18	(*S*)
13		**3**	36	18	(*S*)
14		**2**	>95	27	(1*S*, 2*R*)
15		**3**	>95	24	(1*S*, 2*R*)

[a] All reactions were carried out at 0 °C for 4 h with the substrate (1.0 mmol), catalyst (3.0 equiv.), Bu_4NHSO_4 (0.008 equiv.) in CH_3CN (3.0 mL) and 0.05 M $Na_2B_4O_7$ in 4×10^{-4} M aq. Na_2EDTA (1.0 mL). Aq. Oxone® (1.38 equiv.) and aq. K_2CO_3 (5.8 equiv.) in 4×10^{-4} M aq. Na_2EDTA (0.65 mL) and) were added to maintain pH 10.5. [b] Determined by ^1H NMR, error limit ≤5%. [c] Determined by chiral HPLC (Chiralcel OD-H or OB-H), error limit ≤2%. [d] Determined by comparing the measured optical rotations with reported ones.

The observed enantioselectivity may be explained in terms of the favored *spiro* transition states,[13] as shown for aldehyde **3** in Scheme 3. The lower dioxirane oxygen atom is sterically hindered for the oxygen transfer by the two nearby acetal functionalities and electronically deactivated by the hydrogen bonding. Thus, the upper oxygen atom is favored for oxygen transfer. In the disfavored transition state, the phenyl group of the *trans*-stilbene interacts with the dioxolane ring of the dioxirane, while in the favored one such steric encumbrance is absent and, therefore, a high enantioselectivity is obtained. The favored transition state will



Scheme 3. Favored and disfavored transition states of the oxygen transfer for the dioxirane of aldehyde **3**.

generate the (*R*,*R*) enantiomer, as the experimental results confirmed. It should be pointed out that the hydrogen bonding is also helpful in fixing the conformation of the dioxirane by limiting the rotation of the carbon–carbon bond (dark-marked in Scheme 3) so that energy difference between the favored and disfavor transition states ($\Delta\Delta G^{\neq}$) is maximized and, therefore, enantioselectivity is improved. In aldehyde **2**, although the large benzyl group helps limit the free rotation of the carbon–carbon bond, the conformation of the dioxirane becomes more flexible since there is no such hydrogen bonding and inferior enantioselectivity is observed. As for ketone **4**, the methyl group will unfavorably interact with the dioxolane ring if it also adopts similar transition states as aldehyde **3**. Apparently, the hydrogen bonding is not forming in this case and low enantioselectivity is obtained.

It should be pointed out that asymmetric epoxidation with *acyclic* chiral ketones is still a challenge in dioxirane chemistry (less than 20% ee has been obtained;[14] we improved it ca. 40% ee with ketone **4**), despite the fact that cyclic chiral ketones have been established as efficient catalysts for asymmetric epoxidations. In contrast, chiral aldehydes, which must be acyclic, may offer opportunity in overcoming this difficulty, as our preliminary results show. Furthermore, mechanistically the reaction should be catalytic, although the catalytic efficiency of these aldehydes is still low at this moment.

In summary, we developed the first highly enantioselective epoxidation protocol with optically active aldehydes as the catalysts. Aldehyde dioxirane is proposed as the active oxygen transfer reagent. We are currently working on the reaction mechanism and the improvement of the catalytic efficiency of the aldehydes.

Acknowledgements

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9. The inhibition of pathway **a** is known, although it has not been explored for dioxirane formation. For example, when anisaldehyde is oxidized by Oxone®, only low yield of the acid could be obtained (cf. Ref. 8).
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12. **General epoxidation procedure**: To a stirred solution of *trans*-stilbene (0.018 g, 0.1 mmol) and aldehyde **3** (0.086 g, 0.3 mmol) in CH_3CN (3.0 mL) were added tetrabutyl ammonium sulfate (3 mg, 8 μmol) and the buffer (0.05 M $Na_2B_4O_7$ in 4×10^{-4} M aqueous Na_2EDTA, 1.0 mL) at 0°C. A solution of Oxone® (0.085 g, 0.138 mmol) in aqueous Na_2EDTA (4×10^{-4} M, 0.65 mL) and an aqueous solution of K_2CO_3 (0.080 g, 0.58 mmol) in water (0.65 mL) were added dropwise simultaneously through syringe over a period of 2 h. After stirring for additional 2 h the reaction mixture was quenched by addition of hexane and water. Then the reaction mixture was extracted with hexane (3×10 mL), dried over $MgSO_4$ and evaporated to give the crude product. A conversion of 54% of the starting material with an ee value of 93.5% for the epoxide were achieved as indicated by ^{1}HNMR and HPLC analyses, respectively.
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