A Dramatic pH Effect Leads to a Catalytic Asymmetric Epoxidation

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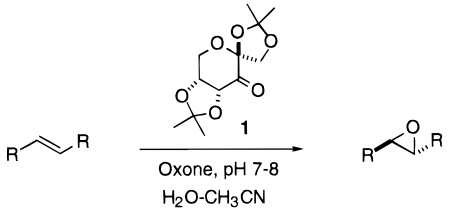
Chiral dioxiranes have appeared to be promising reagents for asymmetric epoxidations, particularly for *trans*-olefins bearing no allylic alcohol groups.[1−4] Recently, we reported a highly enantioselective epoxidation method of *trans* and trisubstituted olefins using a fructose-derived ketone **1** as catalyst and Oxone as oxidant (eq 1).[5] However, a drawback of our initial epoxidation



procedure was that an excess of ketone (3 equiv) was required in order to achieve a good conversion of substrate due to the rapid decomposition of the catalyst. Herein we wish to report a catalytic asymmetric epoxidation process, which results from our subsequent mechanistic studies.

Strict control of the reaction pH is critical for the efficiency of the epoxidation mediated by *in situ* generated dioxiranes. Typically, epoxidations are carried out at pH 7−8.[3,4,6] In certain cases, the optimal pH is within a narrow window of 7.8−8.0.[3c] Generally, the epoxidation efficiency drops dramatically with the increase of pH

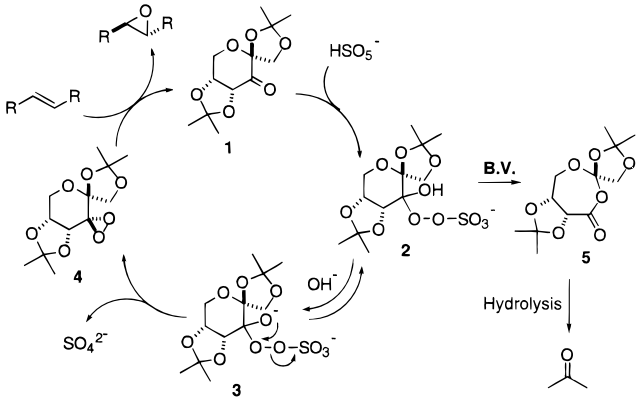


Figure 1. Reaction pathways of the epoxidation catalyzed by ketone **1**.

because of the rapid autodecomposition of Oxone at high pH.[3c,6a,7] In addition to the autodecomposition of Oxone, another potential problem for the epoxidation at high pH is that the uncatalyzed background reaction could be significant,[8] which is undesired for asymmetric epoxidations. In light of these two problems, our initial epoxidations were carried out at pH 7−8. At this pH, we found that ketone **1** decomposed very rapidly. Our results to date suggest that the Baeyer−Villiger reaction could be one of the major decomposition pathways for the catalyst (Figure 1), although no direct evidence has been obtained thus far. Further analysis of the reaction scheme shown in Figure 1 suggests that the competing Baeyer−Villiger reaction may be suppressed by raising the pH, since high pH favors the equilibrium toward intermediate **3**. This could consequently lead to a more efficient formation of dioxirane **4**.[9] We surmised that the above problems associated with high pH could possibly be overcome if the ketone catalyst is reactive enough to compete with these two processes. With this hope, we decided to carry out a systematic investigation of the pH effect on the epoxidation with ketone **1**.

We used *trans*-β-methylstyrene as a test substrate for the pH studies because of its simplicity for the determination of the conversion and enantiomeric excess by GC. In this case, 20% mole catalyst was used. The reaction was carried out at 0 °C (ice bath). The epoxidation reactions essentially stopped after 1.5 h at all pH's studied. The results with the 1.5 h reaction time are shown in Figure 2. Indeed, the pH showed a profound effect on the catalyst efficiency. The conversion of *trans*-β-methylstyrene to its epoxide increased more than 10-fold from a lower pH (7−8) (our initial epoxidation was carried out at this pH range) to a higher pH (>10), and the enantioselectivity remained high at higher pH (90−92% ee). In addition, the broad optimal pH range simplifies the experimental operation. The enhanced epoxidation efficiency could be due to the decrease of the

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(2) For general reviews on dioxiranes see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205−211. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187−1201. (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811−822.

(3) For examples of *in situ* generation of dioxiranes see: (a) Corey, P. F.; Ward, F. E. *J. Org. Chem.* **1986**, *51*, 1925−1926. (b) Yang, D.; Wong, M. K.; Yip, Y. C. *J. Org. Chem.* **1995**, *60*, 3887−3889 and references cited therein. (c) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391−1407 and references cited therein.

(4) For examples of asymmetric epoxidation mediated by chiral ketones see: (a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155−156. (b) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831−5834. (c) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L *Tetrahedron* **1995**, *51*, 3587−3606. (d) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491−492. (e) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311−11312.

(5) Tu, Y.; Wang, Z-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, 118, 9806−9807.

(6) (a) Edwards, J. O.; Pater, R. H.; Curci, R.; DiFuria, F. *Photochem. Photobiol.* **1979**, *30*, 63−70. (b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758−4760. (c) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670−2673.

(7) (a) Ball, L. D.; Edwards, J. O. *J. Am. Chem. Soc.* **1956**, *78*, 1125−1129. (b) Montgomery, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 7820−7821.

(8) It has been observed that the epoxidation can occur with Oxone in the absence of a ketone catalyst at pH 11.0 using CH_2Cl_2, MeOH, and water as solvents: Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett.* **1994**, *35*, 1577−1580.

(9) (a) There is a report showing that the catalytic efficiency of cyclohexanone for the oxidation of pyridine with Oxone is maximized at a slightly higher pH (8.5). The data suggest that at this pH the Baeyer−Villiger process of cyclohexanone is minimized; see: Gallopo, A. R.; Edwards, J. O. *J. Org. Chem.* **1981**, *46*, 1684−1688. (b) There is also a report suggesting that the Baeyer−Villiger reaction might become significant at high pH values (pH > 11); see ref 6a.

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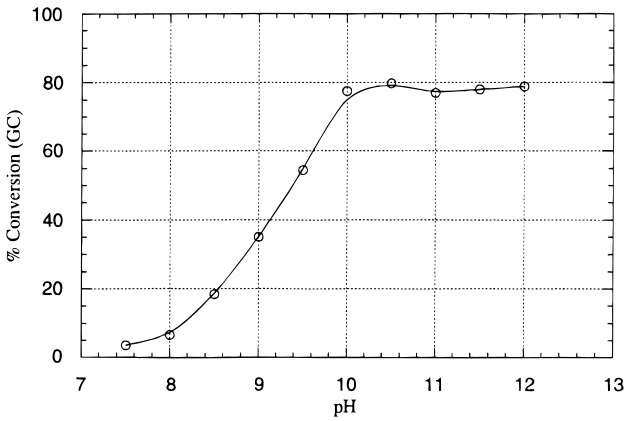
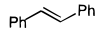
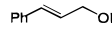
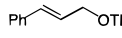
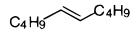
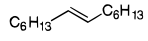
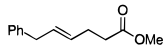
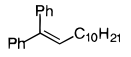


Figure 2. Plot of the conversion of *trans*-β-methylstyrene against pH (for details see the text and the Supporting Information).

Table 1. Catalytic Asymmetric Epoxidation of Representative Olefins Catalyzed by Ketone 1[a]

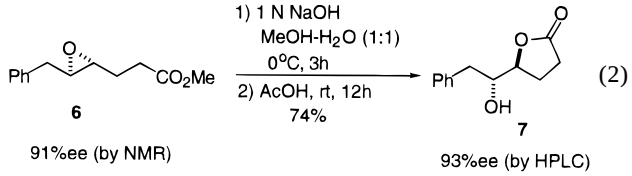
Entry	Substrate	Ketone/ Substrate	Yield[b] (%)	ee (%)	Config.[h]
1[c]		0.3	75	97[d]	(+)-(R,R)[10a]
2		0.3	93	92[e] (91.7[g])	(+)-(R,R)[10a]
3		0.3	70	90[e]	(+)-(R,R)[10a]
4		0.3	87	94[e]	(+)-(R,R)[10a]
5		0.2	70	91[f]	(+)-(R,R)[10b]
6		0.2	88	93[f]	(+)-(R,R)[i]
7		0.3	76	91[e]	(+)-(R,R)[10c]
8[c]		0.3	66	93.5[d]	(+)-(R)[10d]

[a] All reactions were carried out at 0 °C (bath temperature) with substrate (1 equiv), ketone (0.2−0.3), Oxone (1.38 equiv), and K_2CO_3 (5.8 equiv) in (1.5:1) CH_3CN−0.05 M $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aqueous EDTA; the reactions were stopped after 1.5 h (see text). [b] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. [c] Carried out in 2.5:1 CH_3CN−0.05 M $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aqueous EDTA. [d] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [e] Enantioselectivity was determined by ^1H NMR shift analysis of the epoxide products directly with Eu(hfc)$_3$. [f] The epoxide was opened (NaOMe−MeOH), and the resulting alcohol was converted to its acetate; enantioselectivity was determined by ^1H NMR shift analysis of the resulting acetate with Eu(hfc)$_3$. [g] Enantioselectivity was determined by chiral GC (Chiraldex γ-TA column). [h] The absolute configurations were determined by comparing the measured optical rotations with the reported ones. [i] Absolute configuration (*R*,*R*) assumed by analogy with entry 5.

Baeyer−Villiger reaction and the increase of the nucleophilicity of Oxone.

Encouraged by this result, we investigated the generality of this catalytic system with a variety of olefins. The epoxidation was carried out at pH 10.5, which can be conveniently achieved by adding K_2CO_3. The results (Table 1) show that this catalytic process can be extended to other olefins, and the enantioselectivities are slightly improved compared to the earlier conditions.[5] It is also worth noting that the amount of Oxone used in this catalytic process is actually decreased compared to the previous epoxidation conditions,[11] which indicates that ketone **1** is sufficiently reactive to compete with the autodecomposition of Oxone.[12]

The chiral epoxides prepared by the current method should be synthetically useful. For example, epoxide **6** (entry 7) can be readily converted to the hydroxyllactone **7** by one pot saponification and acidification without the loss of ee (eq 2).[13] This type of lactone is an important fragment in many natural products.[14]



(2)

In summary, we have found that pH has a dramatic effect on the epoxidation efficiency of ketone catalyst **1**. As a result, a catalytic asymmetric epoxidation process has been developed. The enantioselectivity is very high in many of the cases studied. Since both ketone **1** and Oxone are readily available, the current epoxidation process has a high potential for practical use. Future efforts will be devoted to further understanding of the factors involved in this epoxidation reaction and enhancing the enantioselectivity by optimizing reaction conditions and designing new ketone catalysts.

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Supporting Information Available: The NMR spectral, GC, and HPLC data for the determination of the enantiomeric excess of the formed epoxides, the characterization data of the epoxides in Table 1, and detailed epoxidation procedures (14 pages).

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(10) (a) See ref 5 and references cited therein. (b) Tanner, D.; Birgersson, C.; Gogoll, A. *Tetrahedron* **1994**, *50*, 9797−9824. (c) The epoxide was converted to lactone **7** (eq 2), which has a known configuration; see ref 16c. (d) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130−3136.

(11) In the literature, a large excess of Oxone (>5 equiv) is often used to achieve good conversions of olefins.

(12) Under these conditions the epoxidation in the absence of the ketone catalyst is negligible within 1.5 h reaction time.

(13) (a) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105−2106. (b) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106−2108.

(14) (a) Pougny, J. R. *Tetrahedron Lett.* **1984**, *25*, 2363−2366. (b) Cooper, R. D.; Jigajinni, V. B.; Wightman, R. H. *Tetrahedron Lett.* **1984**, *25*, 5215−5218. (c) Wright, A. E.; Schäfer, M.; Midland, S.; Munnecke, D. E.; Sims, J. J. *Tetrahedron Lett.* **1989**, *30*, 5699−5702. (d) Koert, U. *Synthesis* **1995**, 115−132.