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Asymmetric epoxidation using hydrogen peroxide (H_2O_2) as primary oxidant

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Abstract

High enantioselectivities have been obtained for asymmetric epoxidation of olefins using a fructose-derived chiral ketone as catalyst and hydrogen peroxide as primary oxidant. © 1999 Elsevier Science Ltd. All rights reserved.

Dioxiranes, either isolated or generated in situ, have been shown to be extremely versatile epoxidation reagents (Scheme 1).[1–3] The reaction is rapid, mild, safe, and a variety of efficient protocols for this type of epoxidation have been developed. In nearly all cases, potassium peroxomonosulfate ($KHSO_5$) is used as oxidant.[4] Its effectiveness in the formation of dioxiranes is probably due to the fact that the sulfate moiety is a good leaving group, which facilitates the ring closure of intermediate **3** to form dioxirane **4** (Scheme 1). As close analogues of potassium peroxomonosulfate, arenesulfonic peracids generated from (arenesulfonyl)imidazole/H_2O_2/NaOH have also been shown to produce dioxiranes from acetone and trifluoroacetone as illustrated by ^{18}O-labeling experiments.[5] Nevertheless, the formation of dioxiranes using substantially different oxidants is largely unexplored. It is of particular interest whether oxidants with poorer leaving groups than sulfate are capable of generating dioxiranes. Herein we wish to report our preliminary studies in this area.

Among many oxidants, hydrogen peroxide (H_2O_2) is quite unique. It has a high active oxygen content and its reduction product is water.[6] We decided to test whether hydrogen peroxide itself, or its activated form, could serve as oxidants to produce dioxiranes. Our investigation started with *trans*-β-methylstyrene as substrate and chiral ketone **5** as catalyst (Eq. 1).[7] When a solution of the olefin (1 mmol), ketone **5** (0.3 mmol), hydrogen peroxide (30%, 0.5 mL, 5 mmol) in CH_3CN (2 mL)–buffer (AcOH–K_2CO_3; the buffer pH was adjusted to 10.3 by adding HOAc to 0.1 M K_2CO_3) (1 mL) was stirred at room temperature for 2 h, a 40% conversion was obtained. Analysis of the epoxide product using chiral GC (Chiraldex G-TA) showed 86% ee. The fact that the epoxide was formed with good enantioselectivity suggested that the dioxirane had indeed been formed. However, when the reaction was carried out in other solvents, such as DMF, THF, CH_2Cl_2, EtOH, or dioxane, instead of CH_3CN, only trace amounts of the epoxide

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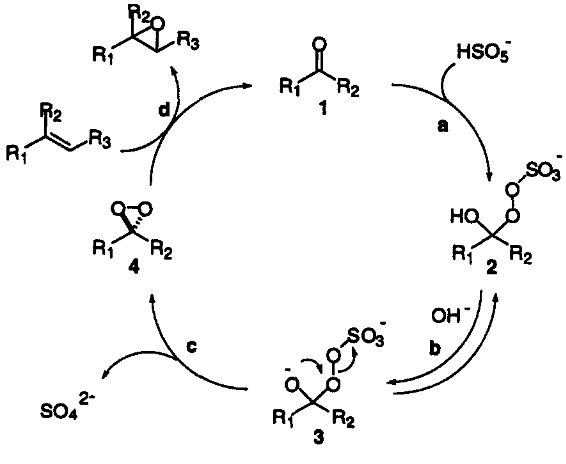
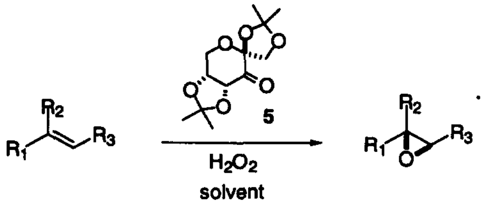


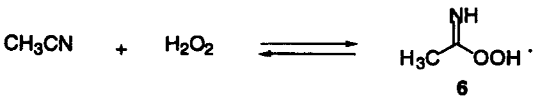
Scheme 1.

(<1%) were detected by GC, suggesting that hydrogen peroxide itself could not effectively generate the dioxirane and that CH_3CN acted as an activator. It is highly likely that in the case of CH_3CN, the actual oxidant responsible for the formation of the dioxirane was peroxyimidic acid **6** (Eq. 2).[8,9]

Encouraged by this initial result, we decided to further improve the reaction, primarily by varying the pH. The reaction was then investigated using different concentrations of K_2CO_3. As shown in Fig. 1, high conversion could be obtained when appropriate concentrations of K_2CO_3 were used, with over 90% ee obtained when $[K_2CO_3]$ was above 0.6 M (increasing the concentration of K_2CO_3 slightly increased the ee of the epoxide product). Further studies showed that this epoxidation system could also be extended to other substrates,[10] obtaining good yields and ees in each case (Table 1) (H_2O_2 provided similar enantioselectivities to Oxone). A control experiment showed that at 1.0 M K_2CO_3, only 1% conversion was obtained after 5 h stirring at 0°C in the absence of ketone. However, 61% conversion was obtained by addition of acetone under similar conditions, suggesting that dioxiranes could also be generated using ketones other than **5**.



(1)



(2)

In summary, we have shown that dioxiranes could be generated in situ using a combination of nitriles and H_2O_2 as oxidant. Peroxyimidic acid **6** is postulated to be the active oxidant. A few appealing features of the current epoxidation system are worth mentioning. High yields and ees were obtained for a number of olefins. The epoxidation was carried out under mild conditions using inexpensive hydrogen peroxide as primary oxidant. Also, the amount of salts introduced and volume of solvent required were significantly reduced compared to our previous procedures using Oxone. In addition, the current study shows that

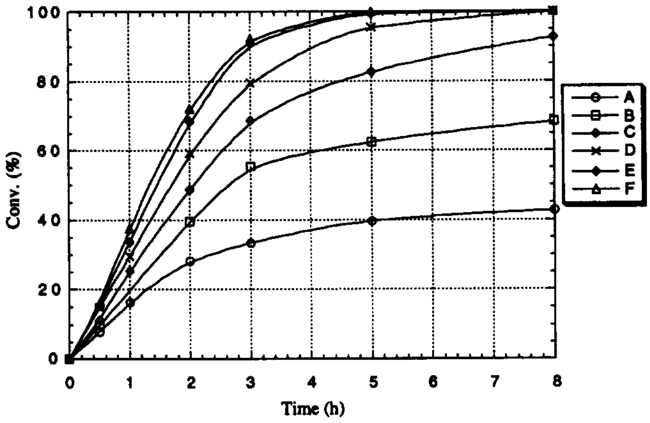
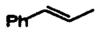
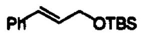
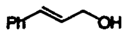
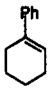
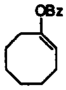


Figure 1. Plot of the conversion of *trans*-β-methylstyrene against time (h). The curves presented are: (A) 0.05 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.1), (B) 0.1 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.3), (C) 0.4 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.6), (D) 0.6 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.7), (E) 0.8 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.8), (F) 1.0 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.9). (The pH indicated above is the pH of the K_2CO_3 solution. The pH varied upon adding other reaction components as well as the reaction time. This variation became smaller when higher concentrations of K_2CO_3 were used)

Table 1
Asymmetric epoxidation of olefins catalyzed by ketone **5**[a]

Entry	Substrate	t (h)	Yield (%)[b]	ee (%)	Configuration[f]
1		7	84	92[c]	(*R*,*R*)[7b]
2		15	74	93[d]	(*R*,*R*)[7b]
3		18	55	89[e]	(*R*,*R*)[7c]
4		7	90	95[c]	(*R*,*R*)[7b]
5		7	75	93[e]	(*R*,*R*)[7d]

[a] All reactions were carried out at 0 °C (bath temperature) with substrate (1 mmol), ketone **5** (0.3 mmol), and H_2O_2 (3 mmol) in CH_3CN (2 mL) -1.0 M K_2CO_3 in 4 x 10^{-4} M of EDTA (1 mL) (the pH of K_2CO_3 solution was 11.9 and became 10.7 upon adding all the reaction components) except for entries 2 and 3 where 4 mmol of H_2O_2 used (for a detailed procedure see ref. 10). [b] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. [c] Enantioselectivity was determined by chiral GC (Chiraldex.G-TA). [d] Enantioselectivity was determined by chiral HPLC (Chiracel OD) after desilylation with TBAF. [e] Enantioselectivity was determined by chiral HPLC (Chiracel OD). [f] The absolute configuration was determined by comparing the measured optical rotations with the reported ones.

oxidants other than peroxysulfates could be used to generate dioxiranes. Investigations with other types of oxidants are currently underway.

Acknowledgements

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9. Asymmetric epoxidation also occurred when other nitriles such as CH_3CH_2CN, $CH_3CH_2CH_2CN$, *t*-BuCN and PhCN were used.
10. A representative epoxidation procedure (entry 1): To a solution of *trans*-β-methylstyrene (0.118 g, 1 mmol) and ketone **5** (0.077 g, 0.3 mmol) in CH_3CN (2 mL) was added a solution of 1.0 M K_2CO_3 in 4×10^{-4} M of EDTA (1 mL) followed by H_2O_2 (30%, 0.3 mL, 3 mmol) at 0°C. Upon stirring at 0°C for 7 h, the reaction mixture was quenched with hexane (5 mL), extracted with hexane, washed with saturated $Na_2S_2O_3$ and brine, dried (Na_2SO_4), filtered, concentrated, and purified by chromatography (silica gel was buffered with 1% Et_3N in hexane, using hexane:ether 1:0–50:1 as eluent) to afford the epoxide product as a colorless oil (0.113 g, 84% yield, 92% ee).