A Mild and Efficient Epoxidation of Olefins Using *in Situ* Generated Dimethyldioxirane at High pH

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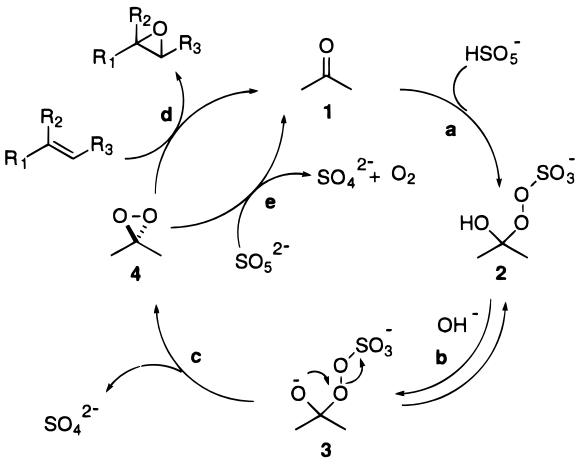
Epoxides are important synthetic intermediates,[1] and epoxidation of olefins provides a powerful strategy for their construction.[2] Dioxiranes, either isolated or generated *in situ* (Scheme 1), have been shown to be extremely versatile epoxidation reagents.[3−5] The reaction is rapid, mild, and safe, and a variety of efficient protocols for this type of epoxidation have been developed. Due to the concern for the autodecomposition of Oxone at high pH, the reaction pH for most of the epoxidations mediated by *in situ* generated dioxiranes have generally been controlled at 7 to 8[5] with few exceptions.[5f]

During our studies on chiral ketone mediated asymmetric epoxidations,[6] we found that the catalytic efficiency for certain chiral ketones were highly pH dependent and that high pH was actually beneficial in these cases.[6b,c] In a subsequent comparison study, we also found that the epoxidation of β-methylstyrene mediated by acetone displayed a similar behavior under the reaction conditions (homogeneous organic solvent/water system).[6c] In this case, the substrate conversion increased from 3 to 90% within the same reaction time when the apparent pH changed from 7.5 to 12. The enhanced epoxidation efficiency of acetone at higher pH could be due to the fact that the high pH favored the formation of oxy-anion intermediate **3** and led to more efficient generation of dimethyldioxirane (the step from **3** to **4** could be the rate-determining step). Considering that the basic reaction conditions would also be very attractive for the synthesis of acid-sensitive epoxides,[7] we thought that this acetone-mediated epoxidation at high pH could provide a valuable epoxidation procedure. We therefore decided to undertake a survey of various olefins to ascertain the generality of the reaction.

Scheme 1



The epoxidation was carried out at apparent pH 10.5−11.5 (precise control of pH was unnecessary in most cases). As shown in Table 1, the epoxidation method appears to be relatively general and effective with substrates containing terminal, *trans*, *cis*, and trisubstituted olefins. Furthermore, a wide variety of functional groups are compatible with the basic reaction conditions; acetylenes, allyl silanes, allyl chlorides, alcohols, esters, ketals, and TBS ethers are all unaffected by the reaction. The conversions of many substrates were greater than 95% as judged by the ^{1}H NMR spectra of the crude reaction mixtures. Side oxidations were also minimal, as only a trace (<5%) of allylic oxidation was seen in the reaction of allylic alcohols (Table 1, entries 5 and 6). Substrates containing hydroxy groups were also epoxidized in good yield even in the absence of acetone. For olefins without hydroxy groups, acetone was required for the epoxidation (for a detailed study on this topic, see ref 6e). The epoxidations of electron-deficient olefins were not efficient under the current reaction conditions. For example, only 21% conversion was obtained for ethyl *trans*-cinnamate. The low efficiency could be due to the fact that the dimethyldioxirane generated was converted back to acetone by Oxone via pathway **e** (Scheme 1), as

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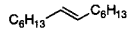
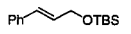
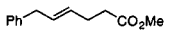
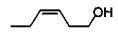
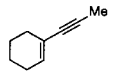
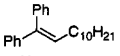
Table 1. Epoxidation of Olefins with *in situ* Generated Dimethyldioxirane at High pH[a]

Entry	Substrate	Reaction time (h)	Yield[b] (Conv.) (%)
1		4	67 (79)[6c]
2		4	77 (89)[6c]
3		4	91 (>95)[6c]
4		2	72 (>95)[6c]
5		2	67 (>95)[6c]
6		2	79 (>95)[6c]
7		2	80 (>95)[6c]
8		1.5	92 (>95)[6c]
9		2	77 (>95)[6c]
10		2	85 (94)[6c]
11		4	84 (>95)[6c]
12		4	86 (>95)[6c]
13		4	90 (>95)[8]
14		4	66 (>95)[6c]
15		4	50 (>95)[9]
16		2	98 (>95)[6c]
17		2	84 (>95)[6c]
18		1.5	88 (>95)[10]
19		4	72 (>95)[6c]
20		4	75 (>95)[6c]

[a] For detailed reaction conditions, see the Experimental Section. [b] Epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. For leading references for these epoxides, see: refs 6c and 8−10.

the epoxidation was slower when the electron-deficient olefins were used as substrates.

The olefin reactivity and solubility are two important factors affecting the epoxidation. Upon screening solvent systems, we found that CH_3CN−dimethoxymethane (2:1) produced the best combination of dioxirane reactivity and substrate solubility although other solvents such as alcohols, dioxane, DME, dimethoxymethane, DMF, and CH_3CN were also good for many substrates. For less reactive substrates, the epoxidation could be enhanced by adding Oxone over longer periods of time (4 h). For substrates which were less soluble in the reaction system (such as entries 8, 12, and 18 in Table 1), the epoxidation could be boosted by using more organic solvent. The experimental procedure presented provides the most general procedure possible. In many cases, less Oxone is needed to achieve complete conversion. The reactions presented in Table 1 were run on a small scale (1 mmol). To further illustrate the usefulness of this epoxidation, the epoxidations of two selected olefins (*trans*-stilbene and 1-phenylcyclohexene) were carried out on a multigram scale (see Experimental Section). In each case the epoxidation also worked well.

In conclusion, we report a highly efficient epoxidation procedure utilizing the *in situ* generated dimethyldioxirane at high pH. The method is exceedingly mild and can be used to prepare acid labile epoxides. We believe this procedure is easy to carry out and will provide a highly attractive epoxidation method since it is safe and economical.

Experimental Section

The general experimental information is similar to that recently described.[6c]

General Epoxidation Procedure for Table 1. To a mixture of the olefin (1 mmol) and tetrabutylammonium hydrogen sulfate (0.015 g, 0.04 mmol) in CH_3CN−dimethoxymethane (2:1) (4−8 mL), acetone (2.2 mL, 30 mmol), and 0.1 M solution of K_2CO_3 (2 mL) were added Oxone (1.84 g, 3 mmol in 8 mL 4×10^{-4} M EDTA solution) and K_2CO_3 (1.84 g, 13.3 mmol in 8 mL of H_2O) separately either by syringe pump or addition funnel over the indicated time. After the addition of Oxone was complete, the reaction mixture was extracted with hexanes or methylene chloride (3×25 mL). The combined extracts were washed with brine and dried (Na_2SO_4). Upon removal of solvent under reduced pressure the crude product was purified by flash column chromatography with silica gel (buffered with 1% Et_3N) as the stationary phase.

***trans*-Stilbene Oxide.** To a 5 L three-necked flask equipped with a mechanical stirrer was added *trans*-stilbene (18.02 g, 100 mmol), CH_3CN−dimethoxymethane (1.17 L, 2/1 v/v), 0.1 M aqueous K_2CO_3 (330 mL), acetone (220 mL, 3 mol), and tetrabutylammonium hydrogen sulfate (1.5 g). The pH was adjusted to 10.5 by the dropwise addition of glacial acetic acid. Oxone (92.2 g, 150 mmol) in 330 mL of 4×10^{-4} M EDTA and K_2CO_3 (92.2 g, 667 mmol) in 330 mL of H_2O were added separately via addition funnels over 2 h. The reaction mixture was extracted with hexanes (3×1.5 L), washed with brine (1×1L), dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel buffered with 1% Et_3N) (hexanes) to yield *trans*-stilbene oxide as a white solid (17.00 g, 86.7%).

1-Phenylcyclohexene Oxide. To a 5 L three-necked flask equipped with a mechanical stirrer was added 1-phenylcyclohexene (15.82 g, 100 mmol), CH_3CN−dimethoxymethane (400 mL, 2/1 v/v), 0.1 M aqueous K_2CO_3 (200 mL), acetone (220 mL, 3 mol), and tetrabutylammonium hydrogen sulfate (1.5 g). The pH was adjusted to 10.5 by the dropwise addition of glacial acetic acid. Oxone (184 g, 300 mmol) in 660 mL of 4×10^{-4} M EDTA and K_2CO_3 (184 g, 1.33 mol) in 660 mL of H_2O were added separately via addition funnels over 2 h. The reaction mixture was extracted with hexanes (3×1.5 L), washed with brine (1×1L), dried (Na_2SO_4), concentrated, and filtered through a bed of silica gel (buffered with 1% Et_3N) (hexane/ether, 10/1 v/v) to yield 1-phenylcyclohexene oxide as a colorless oil (14.48 g, 83.1%).

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