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Ketone-Directed Peracid Epoxidation

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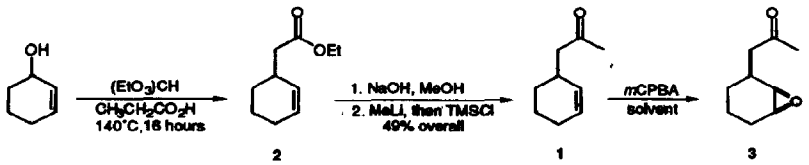
Abstract: Ketone carbonyl groups are shown to direct the epoxidation of cyclic alkenes with higher selectivity than that displayed by esters. An ^{18}O labelling study is used to show that a dioxirane intermediate is not involved in these reactions.

The ability of pre-existing functionality to direct the stereochemistry of organic transformations is of central importance in organic synthesis.[1] We have recently begun a study of the intramolecular dioxirane epoxidation reaction (Figure 1), as a method for effecting *ketone*-directed epoxidation.[2]

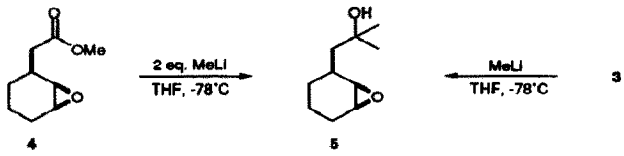
Figure 1: Intramolecular Dioxirane Epoxidation

As the first substrate to be tested, we prepared ketone **1**, where intramolecular epoxidation can occur only *syn*- to the side chain. As shown in Scheme 1, synthesis of **1** began with an orthoester Claisen rearrangement[3] of 2-cyclohexen-1-ol to give the ester **2**, followed by ester hydrolysis and conversion of the resulting acid to the corresponding methyl ketone.[4] In attempting to prepare a *syn*/*anti*- epoxide mixture for spectroscopic comparison purposes, we were surprised to find that standard peracid epoxidation of **1** in dichloromethane afforded a single epoxide **3** according to analysis of the crude ^1H NMR spectrum.



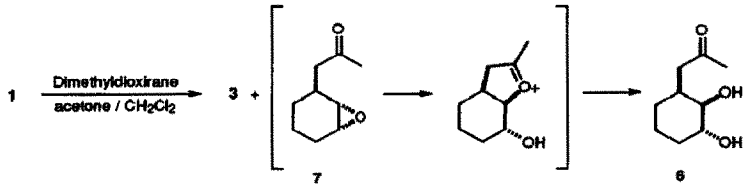
Scheme 1

Epoxide **3** was shown to possess the *syn*- relative stereochemistry by a correlation experiment (Scheme 2). Treatment of the known[5] *syn*-epoxy ester **4** with MeLi gave the tertiary alcohol **5**; the same compound (by ^1H and ^{13}C NMR) was also obtained from **3**.



Scheme 2

In contrast, epoxidation of **1** using isolated dimethyldioxirane[6] resulted in a 1:1 mixture of **3** and the diol **6**. Diol **6** possibly arises from facile opening of the *anti*-epoxide **7**, formed in a non-stereoselective intermolecular epoxidation, with neighbouring-group participation from the ketone carbonyl (Scheme 3).



Scheme 3

An obvious possible reason for the stereoselectivity of the peracid epoxidation of **1** is hydrogen bonding of the ketone carbonyl to the peracid hydroxyl. This is effectively the reverse of the well known mode of hydrogen bonding for hydroxyl-directed peracid epoxidation.[7] This explanation has been suggested for similar directing effects observed with basic carbonyl groups such as amides and carbamates (Figure 2); as expected on consideration of carbonyl basicity, esters give lower selectivity.[5,8] However, no evidence for the *anti*-epoxide **7** (or diol **6**) was observed for peracid epoxidation of **1** in a variety of solvents (dichloromethane, ether, methanol or *tert*-butanol), a list that includes protic solvents which would be expected to diminish hydrogen bonding between substrate and reagent.

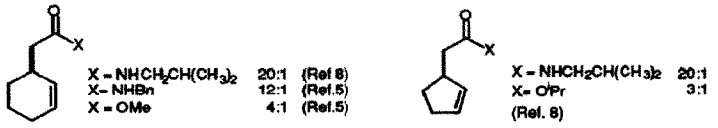
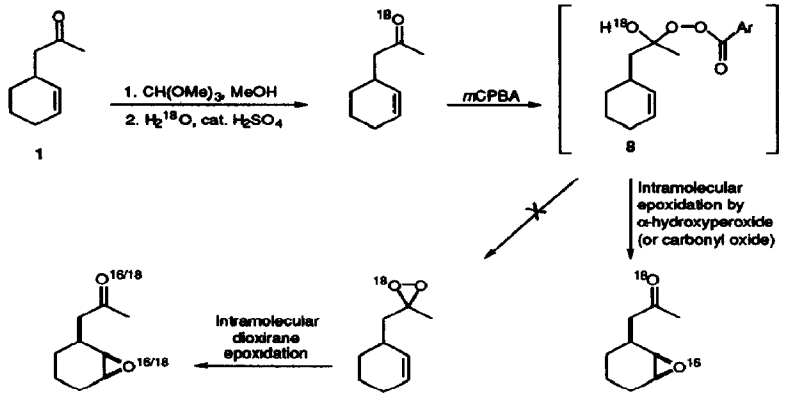


Figure 2: *Syn:anti* epoxide ratios for peracid epoxidation in dichloromethane

An alternative explanation for the high stereoselectivity involves the possibility of addition of the peracid to the carbonyl group (Scheme 4). This is identical to the first step of the Baeyer-Villiger reaction, a process which does not generally occur for simple acyclic ketones (*e.g.* acetone) with *m*CPBA due to the poor migratory aptitude of the primary alkyl group.[9] Indeed, acetone has been shown to react with peracetic acid to provide a species capable of alkene epoxidation;[9] this intermediate was postulated to be either the carbonyl oxide or the dioxirane. As indicated in Scheme 4, the dioxirane mechanism can be tested by ^{18}O labelling of the ketone carbonyl. Assuming little or no stereocontrol in the addition to the carbonyl group, the ^{18}O label would be expected to be distributed equally between the two diastereotopic oxygens of the dioxirane, either of which is capable geometrically of being transferred intramolecularly to the alkene. A dioxirane mechanism would therefore distribute the ^{18}O label between the ketone and epoxide groups in the

product. We therefore carried out the peracid epoxidation using ketone bearing ^{18}O label in the carbonyl group, prepared as shown in Scheme 4. No transfer of ^{18}O label to the ring epoxide was observed by ^{13}C NMR or mass spectrometric analysis.[10] The observed stereoselectivity is therefore probably due to intramolecular epoxidation by α-hydroxy peroxide intermediate **8**, or by a carbonyl oxide.



Scheme 4

The *syn*-selectivity observed for epoxidation of ketone **1** seems to be general for cyclic ketones of this type (Figure 3).[11] Comparison to the literature data in Figure 2 shows that selectivity is usually lower than for amides, but in all cases higher than for the isosteric ester. Interestingly, use of ether as solvent results in higher selectivity than with dichloromethane, the reverse of the situation for hydroxyl-directed epoxidation.[12]

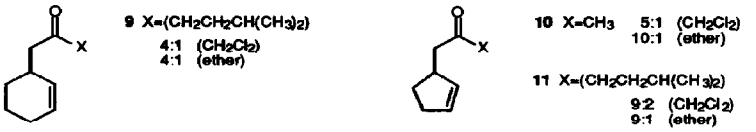
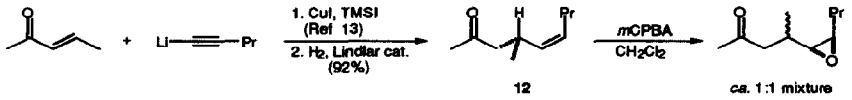


Figure 3: *Syn:anti* epoxide ratios for *m*CPBA epoxidation of ketones

In a typical experiment, *m*CPBA (Aldrich; 50%, 1.2-2 equiv.) was added to a solution of the alkene (0.43 mmol) in ether (1 ml) at room temperature. When reaction was complete (as judged by TLC), powdered sodium sulfite was added until the mixture was neutral to Merck peroxide indicator paper. The mixture was diluted with the organic reaction solvent and the aqueous phase extracted three times. The combined organics were washed successively with water, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give the crude product which was analysed by ^1H NMR. For compound **9**, the ratio was determined by integral of the epoxide protons (at *ca.* 3.2 ppm) relative to the diol protons (at *ca.* 3.6 ppm), assuming that the diol was derived from the *anti*-epoxide. Since diol can also be formed by direct hydrolysis of the *syn*-isomer, these ratios represent a lower limit to the selectivity. For compounds **10** and **11**, the ratio was determined by integration of the epoxide protons (both appeared at *ca.* 3.4 ppm for the *syn*-isomer; for the *anti*-isomer, they were separate at *ca.* 3.4 ppm and 3.2 ppm). Flash chromatography afforded the pure *syn*-epoxide in good yield (> 60%). A correlation experiment similar to that shown in Scheme 2 was used as proof of stereochemistry in all cases.

We have briefly examined the peracid epoxidation of acyclic substrates. The *Z*-ketoalkene **12**, prepared as shown in Scheme 5, was chosen since it has the same tether length and position of chiral centre as in **1**. Alkene **12** should have a marked ground-state conformational preference due to $A_{1,3}$ strain,[14] and intramolecular epoxidation would therefore be expected to occur stereoselectively. However, treatment of **12** with *m*CPBA provided essentially a 1:1 mixture of diastereomeric epoxides. Presumably, the extra conformational freedom about the alkene-chiral centre bond for compound **12** relative to **1** allows intermolecular peracid epoxidation to predominate over any intramolecular process. Less surprisingly, *m*CPBA epoxidation of the *E*-isomer of **12**[15] also provided a 1:1 mixture of diastereomeric products.



Scheme 5

This lack of stereoselectivity in the peracid epoxidation of acyclic substrates provides a great incentive for study of the intramolecular dioxirane epoxidation process, currently underway.

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References and Notes

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