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Dioxiranes – Highly Reactive Oxidants for Stereoselective Oxyfunctionalizations

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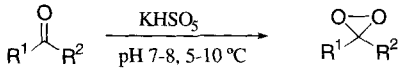
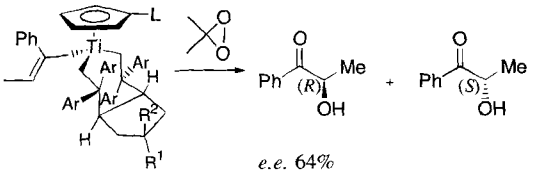
Dioxiranes, which are available through the reaction of a ketone with Caroate (Eq. 1), have gained prominence in organic synthesis as extremely useful, while mild and reactive oxidants.



(1)

Especially the widely employed dimethyldioxirane (DMD), which is isolated as acetone solution by codistillation [1], constitutes a most advantageous reagent for small scale (up to 10 mmol) oxidations. [2, 3] Despite its quite inexpensive and convenient preparation, [1a] the oxidation procedure with DMD is straightforward and simple: the dissolved substrate is treated with an appropriate amount of the standardized DMD solution and after completion of the reaction (monitored by thin-layer chromatography or NMR spectrocopy), generally no further work-up is required other than evaporation of the acetone solvent [4].

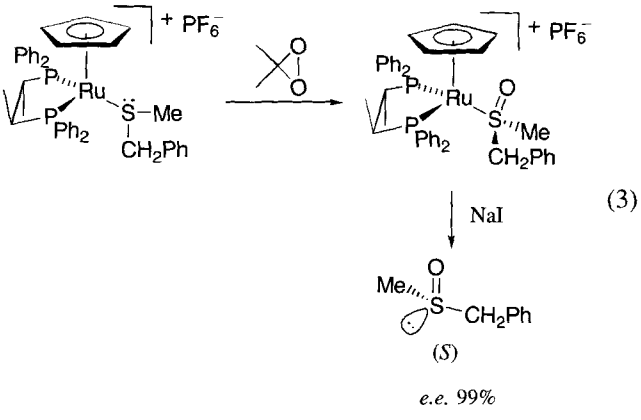
Numerous applications of DMD as diastereoselective epoxidizing agent have been reported [5] and generally DMD achieves higher diastereoselectivities than peracids [6], the frequently used alternative epoxidants. Thus, DMD is often the reagent of choice for highly diastereoselective oxidations of natural products to supply enantiomerically pure epoxides [7]. With chiral auxiliaries, which can be readily removed after the diastereoselective oxidation, a synthetic strategy has become available for enantioselective oxidations. For example, DMD was employed in the diastereoselective oxidation of optically *active titanium* enolates to afford α-hydroxy ketones in enantiomeric excesses of up to 64% (Eq. 2). More impressive, the DMD sulfoxidation of optically active ruthenium thioether



e.e. 64%

(2)

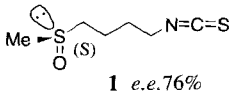
complexes results in high diastereo-selectivities, which are reflected in the enantioselectivity of the remaining sulfoxide after removal of the metal-functionalized chiral auxiliary (Eq. 3).



e.e. 99%

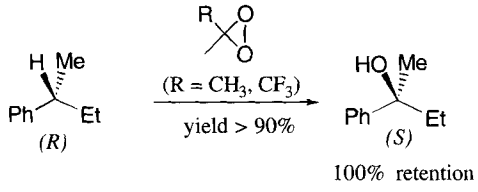
(3)

This synthetic sequence proved successful in the enantioselective preparation of the naturally occurring sulphoraphan (**1**), a sulfoxide contained in broccholi [8].



1 *e.e.*76%

Also of high synthetic value is the dioxirane-mediated oxygen insertion directly into CH bonds, which proceeds stereoselectively under complete retention of configuration (Eq. 4) [9]. Especially the more reactive – as compared to DMD – methyl(trifluoromethyl)dioxirane can be most successfully employed for selective oxyfunctionalizations of alkanes, a feature that is rarely exhibited by other non-metal oxidants. The reactivity order for the dioxirane CH insertions follows the expected primary-secondary-tertiary (PST) sequence [10].



(4)

Unfortunately, in view of volatility limitations, the isolation of dioxiranes by the destillation procedure is restricted to dimethyldioxirane and methyl(trifluoromethyl)dioxirane. Some further less volatile derivatives have been isolated by the salting-out extraction method [11], but with increasing size of the alkyl substituent, the concentrations of the dioxirane solution become impractically low to be synthetically useful. Hence, enantioselective oxygen transfer by optically active dioxiranes is confined to the *in situ modus operandi*, in which the substrate, the optically active ketone and Caroate are employed in a one-pot procedure. In fact, this concept of asymmetric oxygen transfer was already applied in the early developments of dioxirane chemistry, for which chiral-pool ketones (Figure 1) were chosen as catalyst in the *in situ*

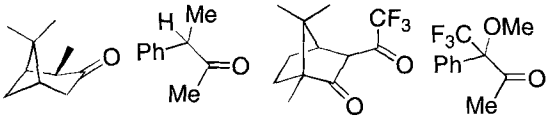
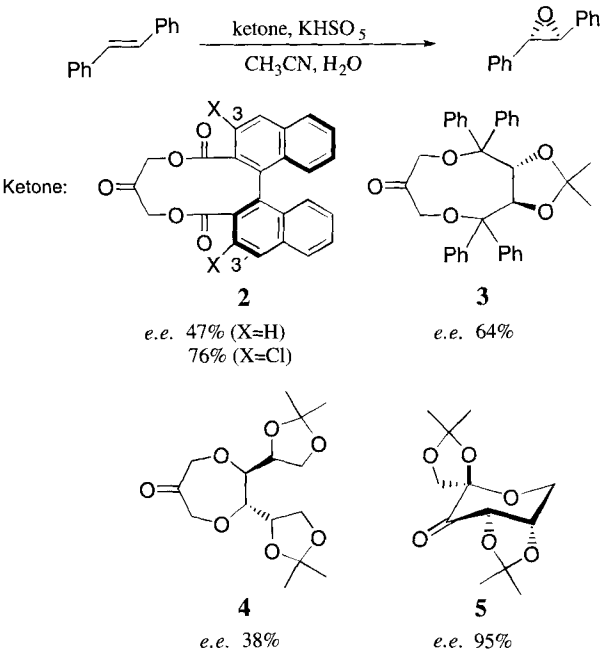


Fig. 1 Chiral pool ketones employed in the *in situ modus*

procedure. Expectedly, only moderate enantiomeric excesses (up to 20%) were achieved in the asymmetric epoxidations with such dioxiranes, *in situ* generated in a biphasic solvent mixture (e.g. CH_2Cl_2/H_2O). Solubility problems of the ketone and substrate may be overcome by the use of acetonitrile [12] or dioxane [15] as cosolvent with water. Indeed, such practical improvements have recently paved the way for impressive enantioselective dioxirane epoxidations with C_2-symmetric ketones as asymmetric catalyst.

The advantage of C_2-symmetric ketones as chiral precursoris for optically active dioxiranes is the fact that the two dioxirane oxygen atoms are homotopic, whereas they are diastereomerically differentiated for dioxiranes which are not C_2-symmetric. Hence, for the former, high enantioselectivities may be readily achieved in the oxygen transfer through sterically controlled approach of the prochiral substrate (olefin in the case of epoxidations) to either face of the *C_2-symmetric* dioxirane to produce the same epoxide configuration rather than through mere preferential blocking of one of the oxygen atoms in the *centro-chiral* dioxirane derived from the chiral pool ketone in Figure 1.

The success of this concept is illustrated in Eq. 5 with the C_2-symmetric ketones **2**–**5** (strictly applied, the fructose-derived ketone **5** is not genuinely C_2-symmetric) as precursors to optically active dioxiranes in the epoxidation of *trans*-stilbene. Of these enantioselective catalysts, the first example was the axial-chiral, binaphthalene-derived ketone **2** (X=H) [13] which managed to epoxidize *trans*-stilbene in an enantiomeric excess (*e.e.*) of 47% [13]. A significant improvement to an *e.e.* value of 76% was achieved by placing sterically demanding substituents in the 3 and 3' positions of the binaphthalene-derived ketone **2** (X=Cl) [14]. The C_2-symmetric, TADDOL-derived ketone **3** as dioxirane precursor gave an *e.e.* value of 64% in the *in situ* epoxidation of *trans*-stilbene15, but instead of the usual Caroate oxygen source, the persulfonic acid route was employed [16]. Unfortunately, the readily available mannitol-derived C_2-symmetric ketone **4** gave an enantiomeric excess of only 38% in the epoxidation of *trans*-stilbene under the standard conditions. The hitherto highest asymmetric inductions were obtained by employing the fructose-derived ketone **5** [17]. The stilbene epoxidation with this ketone proceeded in the *in situ* modus in a very high enantioselectivity with an *e.e.* value of 95% (Eq. 5). Even some nonaromatic, prochiral olefins have been epoxidized in impressive *e.e.* values (>90%), a feature which is rarely met by alternative oxidants. The difficulty with the latter ketone is that it does not persist the oxidation conditions and non-catalytic amounts must be employed to achieve practical conversions. Consequently, the C_2-symmetric binaphthalene-derived ketones **2** are to date the best choice, which in the *in situ modus operandi* afford *e.e.* values >90% for a variety of prochiral olefins.



(5)

These latest advances in the enantioselective epoxidation by dioxiranes promise a tremendous potential for asymmetric synthesis. Thus, with ketones that combine improved persistence under the oxidation conditions with high enantioselectivity in the oxygen transfer by the corresponding dioxirane, the *in situ* dioxirane route should provide a valuable strictly nonmetallic, catalytic enantioselective oxidation method even for large-scale applications. The future challenge in this promising research area will definitely include the search for easily accessible, optically active, C_2-symmetric ketones, which are readily transformed to the respective dioxiranes, are persistent under the oxidation conditions, and provide high asymmetric induction.

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