

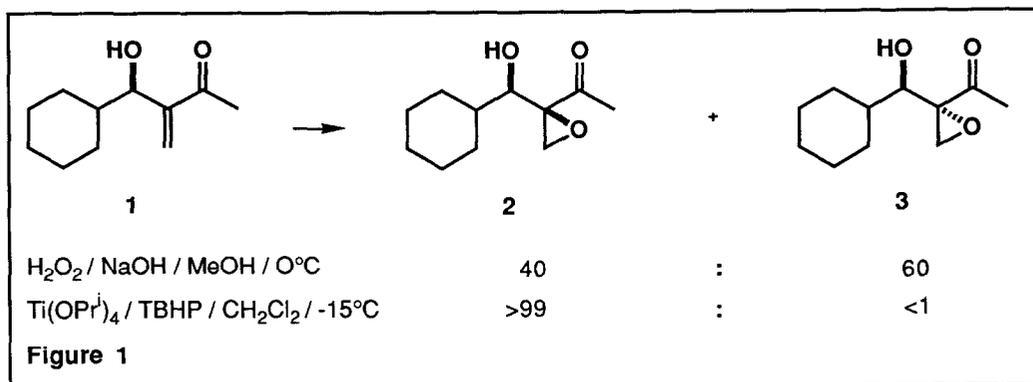
On the Metal-Catalysed Epoxidation of Electron-Deficient Olefins

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Abstract: The *SYN* diastereoselective epoxidation of β -hydroxyacrylates and cyclic β -hydroxyketones using the Sharpless titanium and vanadium catalysts is reported. The first kinetic resolution of these systems is also described.

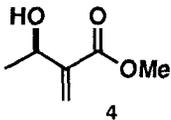
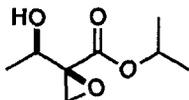
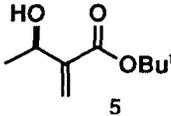
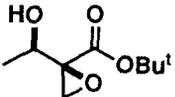
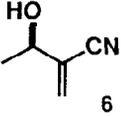
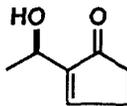
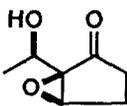
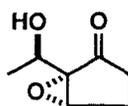
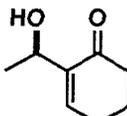
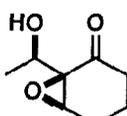
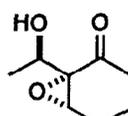
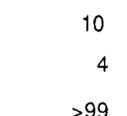
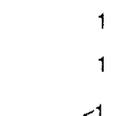
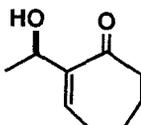
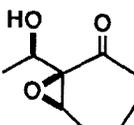
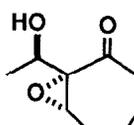
During some recent work ¹ directed towards the total synthesis of the diterpene antibiotics, clerocidin ² and terpenicin ³, we required the diastereocontrolled preparation of the *syn*-epoxy alcohol **2** from the β -hydroxyenone **1**. Although classical Weitz-Scheffer oxidation ⁴ proved to be non-diastereoselective, giving a roughly equal ratio of the *syn*- and *anti*-epoxides **2** and **3** respectively, Sharpless epoxidation ⁵ of hydroxyenone **1** afforded smoothly and exclusively the desired *syn*-epoxide **2** (Figure 1).



In view of the total lack of reactivity of titanium (IV) catalysts towards simple enones, this observation was highly unusual. This prompted a detailed study of this reaction, using various electron-deficient olefins, in order to delineate the structural features required in the starting material for its successful epoxidation. In this letter, we report on some of our results obtained using β -hydroxyacrylates (nitrile) as well as cyclic β -hydroxyenones as substrates. A mechanistic interpretation is proposed.

The starting materials for these studies were prepared easily and in good yields using published procedures. Substrates **4** - **6** were obtained following the method of Baylis and Hillman⁶, using 3-hydroxyquinuclidine as the catalyst. Compounds **7** - **9** were prepared by the Nozaki diethylaluminium iodide coupling⁷ reaction. The results of the epoxidation reactions, using various reagents, are collected in Table 1.

Table 1. Epoxidation of electron-deficient olefins

Entry	Substrate	Condition	Products	Yields		
1		A		81%		
2		A		78%		
3		A	No reaction			
4		A		>99	73%	
		B		<1		87%
5		A		>99	<1	82%
		B		10	1	91%
		C		4	1	70%
		D		>99	<1	92%
6		A		>99	<1	68%
		B		8	1	83%

A = $\text{Ti}(\text{OPr}^i)_4$ / TBHP / CH_2Cl_2 / -15°C . **B** = TBHP / MeOH / NaOH / 0°C . **C** = H_2O_2 / MeOH / NaOH / 0°C . **D** = $\text{VO}(\text{acac})_2$ / TBHP / CH_2Cl_2 / -15°C .

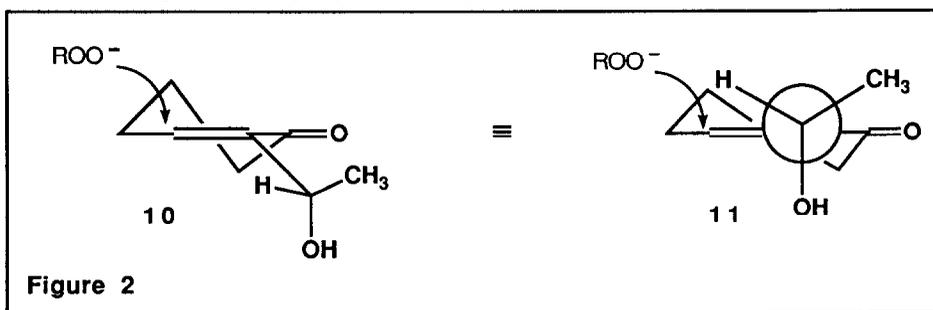
In all cases, except entry 3 where no reaction took place, **epoxidation using the Sharpless catalyst resulted solely in the formation of the *syn*-epoxide** in high yields. When a methyl ester was employed (Entry 1), epoxidation was accompanied by transesterification. This side-reaction could be easily suppressed by employing the corresponding *t*-butyl ester (Entry 2). Interestingly, base-catalysed oxidation (condition C) of the β -hydroxyester **5** failed to give the expected epoxide. Only the product, resulting from the addition of methanol onto the double bond, could be isolated, though in poor yields.

The fate of the acyclic and cyclic β -hydroxyenones under alkaline epoxidising conditions differs markedly. Indeed, base-catalysed epoxidation of acyclic β -hydroxyenones gives a mixture of *syn*- and *anti*-epoxides with a slight *anti*-preference (Figure 1). **In sharp contrast, Weitz-Scheffer epoxidation of cyclic β -hydroxyenones afforded mostly the *syn*-epoxide.** This selectivity is dependent not only upon the reaction conditions but also never reaches ⁸ the exquisite preference displayed by the titanium catalysed reaction ⁹ (condition A).

Although the Sharpless epoxidation proceeds smoothly when β -hydroxyenones and β -hydroxyacrylates are employed as substrates (though more slowly than with the corresponding allylic alcohols) **no reaction is observed with the corresponding nitrile** (Entry 3) and only starting material is recovered. Similarly, **blocking the hydroxyl function totally inhibits the epoxidation reaction.** Clearly, initial coordination of the titanium complex with the hydroxyl group is necessary for subsequent reaction to ensue.

It has been shown that the titanium-catalysed epoxidations of 1,1-disubstituted allylic alcohols were highly erythro selective ¹⁰. The carbonyl oxygen of the β -hydroxyenones and β -hydroxyacrylates appears to be involved in these reactions and somehow enhances the *syn* selectivity ¹¹.

In the case of cyclic systems, the high diastereoselectivity obtained using alkaline epoxidation conditions can be rationalised by invoking two factors: the stereoelectronic bias for axial attack on a cyclic enone ¹² and a preferred ground state conformation of the allylic alcohol portion ¹³, as shown in diagrams 10 and 11 (Figure 2). Synergistic interaction between these two effects could then explain the high *syn*-selectivity which is observed.



Interestingly, kinetic resolution of hydroxyenone **1** [$\text{Ti}(\text{OPri})_4$ / (+) - DET / TBHP / -15°C] leads to optically active epoxide **2** (23% ee). The recovered starting material was also optically active (22% ee). Although these enantiomeric excesses are relatively low, they are the first

reported examples of the Sharpless asymmetric epoxidation of β -hydroxyenones. The synthetic utility of these epoxidations appears particularly attractive and is being actively investigated in this laboratory.

In summary, we have shown for the first time that Sharpless epoxidation of acyclic and cyclic electron-deficient olefins could be realised efficiently, leading to the *syn*-epoxides with high diastereocontrol. A free hydroxyl group and a carbonyl function - but not a nitrile - are necessary for reaction to occur. Asymmetric epoxidation was also successfully performed though the ee are, so far, moderate.

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- 8 For a similar observation, see: Marson, C. M.; Benzie, D. W. M.; Hobson, A. D.; Adams, H.; Bailey, N. A. *J. Chem. Soc. Chem. Commun.*, **1990**, 1516.
- 9 Remarkably, VO(acac)₂/TBHP catalysed epoxidation of the same β -hydroxyenones also provides the *syn*-epoxyalcohol as a single diastereoisomer. The oxidation of other electron-deficient olefins using various metal catalysts will be reported elsewhere.
- 10 Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1981**, *103*, 6237.
- 11 It is possible that a six-membered titanium chelate, involving both the hydroxyl and carbonyl oxygen atoms, is implicated in these reactions. Intramolecular oxygen transfer, *via* a boat-like transition state may then lead to the observed *syn*-epoxide. However, it must be remembered that these titanium alkoxides are dynamic systems so that such an intermediate may not be the most reactive species in the mixture.
- 12 Wu, Y. D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.*, **1987**, *109*, 5560.
- 13 Such a conformation will place the C-OH bond in a position suitable for its antibonding orbital to overlap with the π -system of the C-C double bond. This orbital arrangement should facilitate nucleophilic attack onto the enone π system.

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