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Solvent Tuning of Diastereoselectivity in Dimethyldioxirane Epoxidation Reactions[1]

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Abstract: Diastereoselectivity in the epoxidation of cyclohex-2-en-1-ol shows a remarkable solvent dependence. In some solvent systems the substrate OH group apparently can provide a *cis* selectivity through H-bonding.

Dioxiranes are remarkably versatile oxidation reagents. Their use as epoxidation reagents has reached particular prominence. The reaction is rapid, requires simple workup, and, with the appropriate substrates, is stereospecific[2]. There are a number of reports describing diastereoselectivity in dioxirane epoxidations[3-8]. In some cases this stereoselectivity is attributed to steric factors in the substrates[3,7]. Where several different dioxiranes have been used for the epoxidations, preferential *trans* epoxidation is attributed to steric factors in the dioxirane[5]. In one study of allylic alcohol epoxidations[4] it was found that only low diastereoselectivity could be observed in dimethyldioxirane epoxidations. Furthermore, the diasteroselectivity showed no temperature dependence. The authors concluded[4] that the hydroxyl group does not exert the type of hydrogen bonding influence in these epoxidations that it does in peracid reactions[9]. When the allylic alcohol is located in a larger ring system high *trans* diastereoselectivity is obtained, as in the case of *(Z)*-cyclooct-2-en-1-ol[6]. Danishefsky and coworkers have made great use of the pronounced diastereoselctivity of dimethyldioxirane epoxidation of glycals in the synthesis of 1,2-anhydro sugars[8]. In a particularly revealing observation[8a] they have noted that use of a solvent system consisting of acetone/methylene chloride (6:1) gives a far higher *cis* diastereoselectivity than use of acetone alone. The mixed solvent system was used in the hope that it would provide greater opportunity for the hydroxyl group to exert the desired *cis* stereoselectivity.

We have been studying the effect of solvent on dimethyldioxirane epoxidation and insertion reactions[10,11]. The epoxidation of cyclohex-2-en-1-ol **1** has been studied in a variety of solvents at room temperature. The reaction gives the *cis* **2c** and *trans* **2t** epoxides as well as cyclohex-2-en-1-one **3** (Eq. 1, R=OH). The latter product arises from the insertion of an O atom into the C-1 methine C-H bond[2,4]. The ratio of diastereomers, as well as the distribution between epoxide and enone products, is dependent on the solvent used (Table 1). The epoxide diastereoselectivity shows a pronounced dependence on solvent. The epoxide distribution obtained is essentially tunable depending on solvent choice. Use of a solvent consisting of methanol/acetone (90:10) gives an epoxide distribution of 2:1 in favor of the *trans* isomer, while use of

CCl_4/acetone (95:5) solvent gives almost exclusively *cis* epoxide[12]. The epoxide/enone ratio is also solvent dependent[13].

When derivatives of **1** are exposed to a similar change of epoxidation solvent the effect on epoxide diastereoselectivity is only slight (Table 1). These results suggest that the OH group in **1** is able to exert an H-bonding effect favoring *cis* selectivity. We interpret the solvent influence on this selectivity as arising from the relative ease of achieving this directing effect. Thus in the solvent system giving the highest *cis* selectivity (CCl_4/acetone, 95:5), the presence of the CCl_4 must dilute the association between the dioxirane and acetone such that the intramolecular H-bonding effect is more competitive. The other solvent effects shown in Table 1

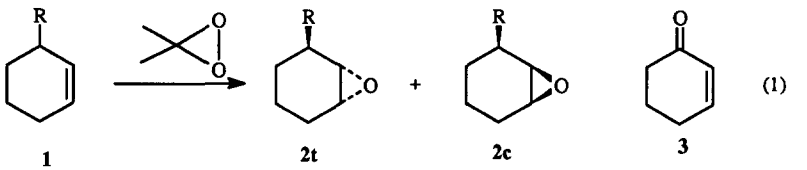
Table 1 Diastereoselectivity in Dimethyldioxirane Epoxidations[a]

R	Solvent System	(%)	Epoxides (%) trans/cis	Epoxides/Enone (%)	Conversion (%)
-OH	Acetone	(100)	54/46	46/54	94
	CH_2Cl_2/Acetone	(50:50)	43/57	65/35	94
	CH_2Cl_2/Acetone	(90:10)	22/78	84/16	89
	CH_2Cl_2/Acetone	(97: 3)	18/82	89/11	77
	MeOH/Acetone	(90:10)	66/34	75/25	100
	$CHCl_3$/Acetone	(90:10)	88/12	88/12	100
	CCl_4/Acetone	(90:10)	15/85	52/48	87
	CCl_4/Acetone	(95: 5)	6/94	59/41	86
$-OSi(CH_3)_3$	Acetone	(100)	87/13	95/5	100
	CH_2Cl_2/Acetone	(50:50)	89/11	94/6	95
	CCl_4/Acetone	(90:10)	99/ 1	90/10	60
$-O-\overset{O}{\overset{\|}{C}}-CH_3$	Acetone	(100)	66/34		86
	CH_2Cl_2/Acetone	(50:50)	64/36		84
	CCl_4/Acetone	(90:10)	65/35		25
$-\overset{O}{\overset{\|}{C}}-OCH_3$	Acetone	(100)	55/45		97
	CH_2Cl_2/Acetone	(50:50)	58/42		95
	CCl_4/Acetone	(90:10)	68/32		56

a) Reactions performed at RT; substrate/DMD ratio (1:1); conversion was determined by GLC analysis at 60 min.

can be explained in a similar fashion. When the solvent system leads to greater association with the OH group in **1**, such as in the CH_3OH/acetone system, then there is less opportunity for the OH to influence *cis* selectivity and the *trans* isomer predominates. The distribution in the absence of this directing influence is apparently determined largely by steric effects[14]. These results indicate that dioxirane epoxidations can be influenced by intramolecular H-bonding from OH groups in the same manner as are peracid epoxidations[15]. In the dioxirane case choice of a suitable solvent discloses this influence.

Equation 1



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12. We have shown that continued dilution of the acetone solution of the dioxirane with CCl_4 beyond that shown in the table leads to increasing amounts of the *cis* isomer. However the solutions become so dilute that measurement of the isomer distribution by GLC becomes imprecise.
13. We are presently carrying out studies on the dependence of the rate of the insertion reaction on the nature of the α substituent. The results will be reported separately.
14. Results of work on the influence of steric effects on the epoxide distribution will be published separately.
15. We have observed a similar, but less pronounced, solvent effect in the dimethyldioxirane epoxidation of 3-methylcyclohex-2-en-1-ol. This work will be published separately.

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