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Chemo- and diastereoselectivities in the oxidation of cyclopentenols with dimethyldioxirane and methyl(trifluoromethyl)dioxirane †

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Abstract

A comparison of the diastereoselectivity and the chemoselectivity (epoxidation versus allylic oxidation) attained in the oxidation of cyclopentenols using dimethyldioxirane and methyl(trifluoromethyl)dioxirane is reported. The results indicate that with both dioxiranes diastereoselective epoxidation of allylic cyclopentenols is accompanied by competitive allylic oxidation to the corresponding enone; for the latter, a likely rationale is proposed. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: dioxiranes; allylic alcohols; epoxidation; diastereoselectivity; oxidation; chemoselectivity.

Epoxidations of allylic and homoallylic alcohols and of their derivatives with dioxiranes[1] represent a valuable tool in organic synthesis;[2] therefore, several studies have focused on assessing the levels of diastereoselectivity attainable using dimethyldioxirane (DMD) (**1a**)[1] and methyl(trifluoromethyl)dioxirane (TFD) (**1b**),[4] either in a solution of their ketone precursors [i.e. acetone and TFP (1,1,1-trifluoro-2-propanone)] or generated in situ.[1,5] When purely steric factors dictate the π-facial preference, DMD and TFD exhibit higher diastereoselectivities as epoxidizing agents with respect to *m*-CPBA; in general, it is found that protected (i.e. OH to OCH_3, OAc, etc.) allylic alcohols give rise to the corresponding *trans* epoxides preferentially.[5] Instead, in the epoxidation of unprotected allylic and homoallylic alcohols with isolated dioxiranes, the proper solvent choice[5a,b] can lead to *cis*-directed epoxidations, akin to the known results with peracids.[2] The latter diastereoselectivity-directing effect is ascribed to transition state (t.s.) stabilization by H-bonding of the substrate OH functionality with the incoming dioxirane.[5] This is in line with a phenomenon well established in peroxide reaction mechanisms.[6] A drawback of these hydroxy-directed diastereoselective epoxidations exists in competitive allylic oxidation to the

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† Dedicated to Professor Robert W. Murray, a distinguished colleague and a friend, on the occasion of his appointment as Professor Emeritus at University of Missouri, St. Louis, USA.

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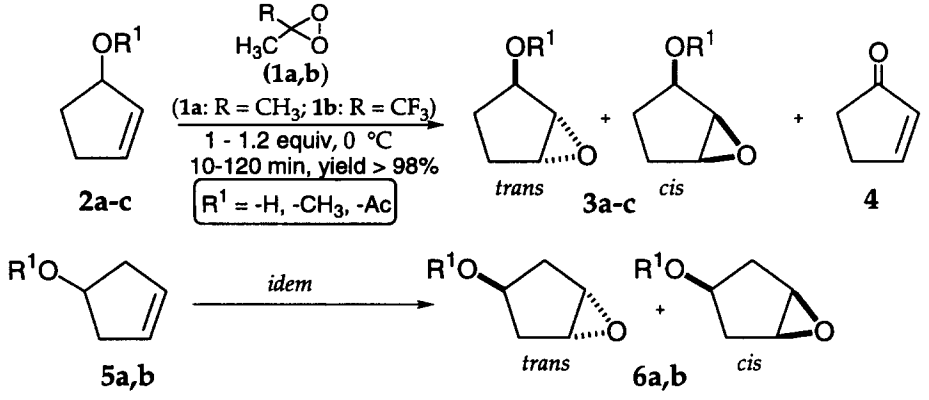
Table 1
Dioxirane oxidation of allylic and homoallylic cyclopentenols and derivatives[a]

Entry #	sub-strate	R^1	dioxi-rane	Solvent[b]	Reactn time (min)	conv. (%)[c]	diastereo-selectivity (syn:anti)[d]	epoxide: enone[d]
1	**2a**	H	DMD	*A*	55	92	53 : 47	70 : 30
2	**2a**	H	DMD	*B*	40	95	61 : 39	90 : 10
3	**2a**	H	TFD	*C*	10	95	70 : 30	66 : 34
4	**2b**	CH_3	DMD	*A*	90	54	20 : 80	95 : 5
5	**2b**	CH_3	DMD	*B*	75	60	30 : 70	95 : 5
6	**2b**	CH_3	TFD	*C*	20	70	8 : 92	98 : 2
7	**2c**	CH_3CO	DMD	*A*	150	60	30 : 70	—[e]
8	**2c**	CH_3CO	DMD	*B*	120	72	36 : 64	—[e]
9	**2c**	CH_3CO	TFD	*C*	30	56	38 : 62	—[e]
10	**5a**	H	DMD	*A*	70	96	54 : 46	—[e]
11	**5a**	H	TFD	*C*	18	85	78 : 22	—[e]
12	**5b**	CH_3	DMD	*A*	70	96	15 : 85	—[e]
13	**5b**	CH_3	TFD	*C*	18	85	2 : 98	—[e]

[a]All reactions routinely run at 0 °C, with dioxirane to substrate molar ratio ca. 1.2 to 1. [b]Solvent: (*A*) acetone; (*B*) CH_2Cl_2/acetone ca. 1:1; (*C*) CCl_4 [ketone-free solutions of dioxirane **1b**, ref. 4c]. [c]As determined (±2%) by GC (SPB-1, 0.25 μm film thickness, 30 m × 0.25 mm ID, capillary column); GC yields > 95% in all cases. [d]As determined by GC (±2%) and by ^1H NMR analysis (±5%) based on integration of characteristic signals. [e]No enone was detected.

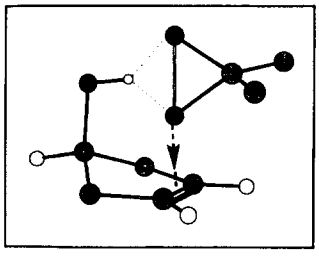
corresponding enone; especially allylic cyclohexenols display a marked tendency towards competitive allylic oxidation instead of the expected epoxidation.[5a–e]



In order to gain more insight into this aspect, we have now applied both dioxiranes to a limited series of allylic and homoallylic cyclopentenol derivatives. Representative results are shown in Table 1.

Dimethyldioxirane (**1a**) (ca. 0.1 M in acetone) was prepared as described;[1,3] ketone-free 0.5–0.8 M methyl(trifluoromethyl)dioxirane (**1b**) solutions in CCl_4 were obtained by following a protocol already reported in detail.[4] Substrates **2a–c** and **5a,b** were synthesized by standard literature procedures;[7] to these, dioxiranes **1a,b** were applied in the isolated form.[8] Inspection of data in Table 1 confirms that several effects are at play in determining the observed diastereoselectivities. For OH protected substrates **2b**, **2c**, and **5b**, which epoxidation cannot be affected by H-bonding effects, the *trans* epoxide is

dominant (entries 4–9, 12–13) using both dioxiranes. Apparently, similar selectivities are displayed in spite of the higher reactivity of TFD with respect to DMD; this is in line with previous observations regarding violation of the reactivity–selectivity principle (RSP) in dioxirane chemistry.[1a] Here, given the characteristics of the simple substrates chosen, general steric effects[1,5] and allylic strain arguments[5b–d] do not appear to be controlling the π-facial selectivity. Instead, it is likely that the stereochemistry is largely determined by repulsive dipole–dipole interactions between the existing OCH_3 functionality and the incoming dioxirane, leading to dominant *anti* attack.[1,5] Indeed, almost exclusive *anti* selectivity is observed for the oxidation of methyl ethers **2b** and **5b** with ketone-free[4c] TFD in CCl_4 (entry 6 and 13), a situation where the said dipole–dipole interaction can act undisturbed by the interference of polar solvent species (i.e. acetone, TFP). Analogous to established precedents,[1a] in **2c** attractive secondary dipolar interaction of the dioxirane with the strong C=O dipole of the acetoxy group (favoring *syn* attack) might be envisaged to intervene; this could act to mitigate the (otherwise favored) *anti* selectivity in CCl_4, an apolar solvent (entry 9). For unprotected allylic alcohols such as **2a**, dipole interactions in the t.s. can also take the form of cooperative H-bonding with the dioxirane oxygens, in analogy with a well documented phenomenon in peroxide reaction mechanisms.[6]



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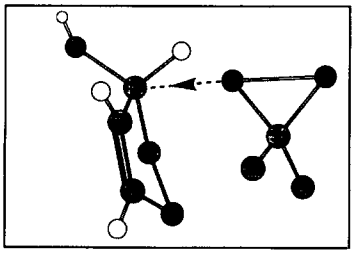
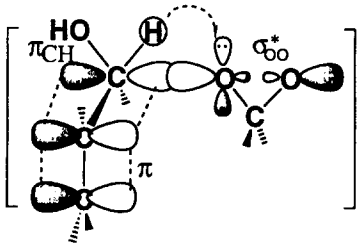


II



III

Of course, this H-bonding effect promotes *syn* π-facial selectivity and can become so significant as to effectively overturn the trend for *anti* attack. Hence the *cis* epoxide becomes predominant, but it never becomes the exclusive diastereomer formed (entries 1–3); indeed a maximum dr of 70:30 is reached for ketone-free TFD in apolar CCl_4 (entry 3). Notice that the latter system is devoid of interfering H-bonding acceptors (i.e. TFP or acetone), thus it is particularly suited to optimize cooperative H-bonding. This *syn*-directing H-bonding effect must also be responsible for the prevailing *cis*-diastereoselectivity observed for homoallylic alcohol **5a**. In fact, molecular models show that, in a favored conformation of **5a**,[9] the OH functionality is placed as to establish effective H-bonds with either peroxide oxygen of the dioxirane; the latter is seen to attack the C=C bond in the preferred spiro arrangment,[1,10] as presented in t.s. ***I***.

As stated in the introduction, our interest in the cyclic substrates **2a–c** was also aimed at probing the chemoselectivity in terms of epoxidation versus enone formation. The latter transformation represents *O*-insertion into allylic C–H, obviously forming the carbonyl via *gem*-diol $C(OH)_2$ [or via hemiacetal $C(OH)(OCH_3)$]. As for the *O*-insertion into C–H bonds of alkanes,[1a,11] also for the dioxirane transformation of alcohols into carbonyls ample evidence (including the application of radical probes)[12] now exists that allow one to rule out a radical pathway.[13] It is recognized[5d] that a convincing mechanistic rationale is not available so far for this unusual aspect of dioxirane reactivity. We propose herein that this phenomenon can be rationalized in general terms starting with the established model for dioxirane *O*-insertion into C–H bonds first advanced by Bach et al.[10a] on the ground of high-level computations. In the related FMO analysis,[10,11] electrophilic attack is directed along the peroxide *O–O* bond axis towards the relevant carbon atom of the substrate; the dioxirane electrophilic oxygen approaches a filled C–H fragment orbital containing both a carbon 2*p* and a hydrogen atom 1*s* orbital. An extension of this model

to the allylic oxidation case at hand is shown in ***II***; here, t.s. stabilization can take place by the secondary orbital interaction presented in ***III***, in a fashion similar to allylic S_N2. For allylic alcohols such as **2a**, this t.s. stabilization could prompt oxidation at allylic C–H to compete significantly with the otherwise favored epoxidation (entries 1–3). Clearly, the competition is significantly less for *O*-insertion into C–H of the corresponding allylic ether **2b** (entries 4–6); it can be completely suppressed by the adoption of an electron-withdrawing protecting group, i.e. the acetyl in **2c** (entries 7–9). Cooperative t.s. effects favoring epoxidation might also act to suppress allylic oxidation to carbonyl for substrates **2b,c** and **5b** (Table 1).

In summary, results herein and the existing literature[1,5] suggests that, besides steric effects, a number of factors determine the diastereoselectivity and the competitive enone formation in the dioxirane oxidation of cyclic allylic alcohols and derivatives. For instance, it has been recently reported[5d] that, on passing from isolated DMD (in acetone) to the more reactive TFD (in TFP), enone formation no longer competes with epoxidation in the oxidation of allylic cyclohexenols. On the other hand, our results show that enone formation becomes again significant even using TFD in the oxidation of the conformationally less flexible cyclopentenol **2a** (entry 3).

Acknowledgements

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with the corresponding epoxycyclopentanols (**6a**); *inter alia*, in their ^{1}H NMR (500 MHz, $CDCl_3$) spectra, *trans*-**6b** and *cis*-**6b** present distinct OCH_3 resonances at δ 3.23 and 3.20, respectively. $\{^1H\}^{13}C$ NMR (125 MHz, $CDCl_3$): *trans*-**6b**, δ 77.6, 55.8, 54.0, 33.9; *cis*-**6b**, δ 80.5, 58.1, 57.3, 34.5. Signal assignments were confirmed by simulated spectra (ACD/Labs™/HNMR Predictor 3.0; Advanced Chemistry Development, Inc.; Toronto, Canada). (b) Steyn, R.; Sable, H. Z. *Tetrahedron* **1971**, *27*, 4429. (c) Bloodworth, A. J.; Eggelte, H. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1375. (d) Langstaff, E. J.; Moir, P. Y.; Bannard, R. A. B.; Casselmann, A. A. *Can. J. Chem.* **1968**, *46*, 3649.

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